ELSEVIER

Tetrahedron

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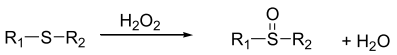
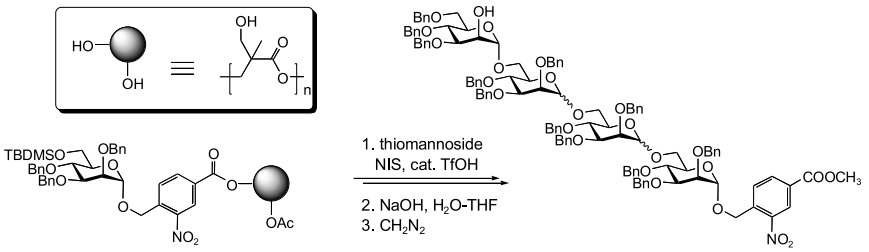
Contents

REPORT

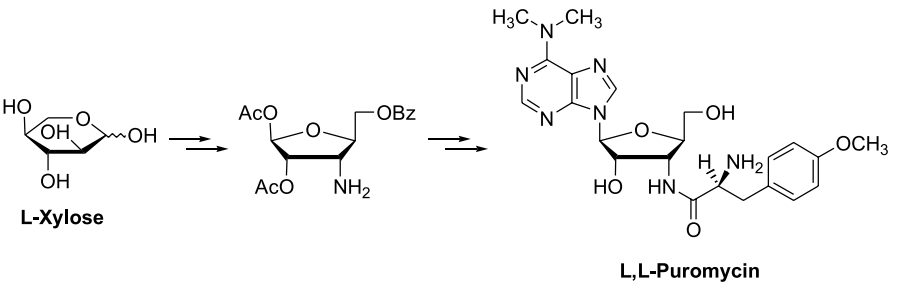


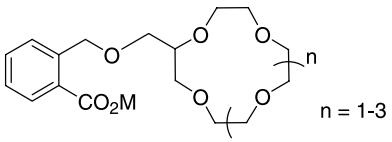
The oxidation of sulfides to sulfoxides by hydrogen peroxide has been reviewed. The report contains 120 references, 14 tables and 16 schemes and 6 figures.

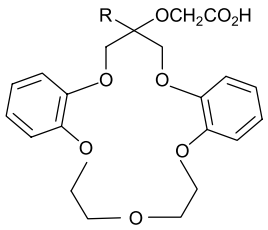
ARTICLES



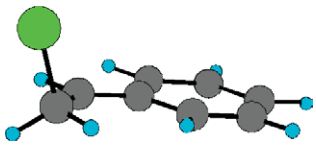
The syntheses of linear and branched di-, tri- and tetramannosides on a commercially available hyperbranched polyester as a soluble, high loading support are described.



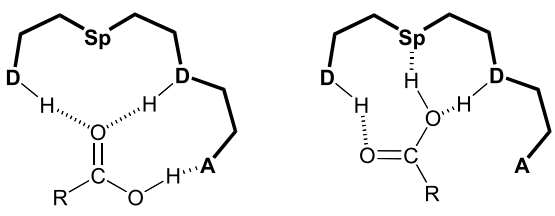


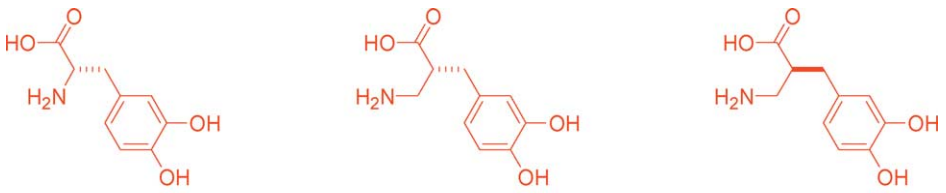


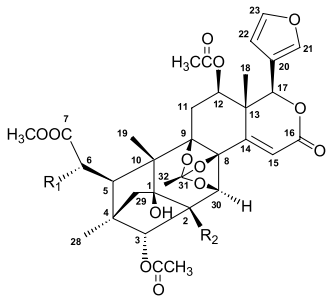
Enhanced Na^+ selectivity in competitive solvent extraction of alkali metal cations when R = H is replaced by decyl is attributed to increased Na^+ binding caused by orientation of the functional sidearm over the crown ether cavity.

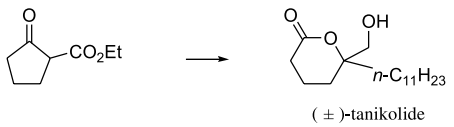


Density functional computations were carried out with the objective of quantifying the interactions of bromine and chlorine atoms with neighboring cationic centers in a series of 1-aryl-2-haloethyl cations. Analyses of structural changes and bonding interactions between the positive center and the halogen gave rise to linear correlations with σ^+ values. Electron-donating groups diminished bridging and electron-withdrawing groups enhanced bridging.

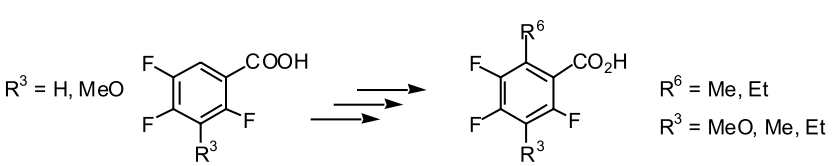


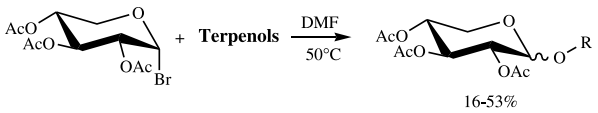


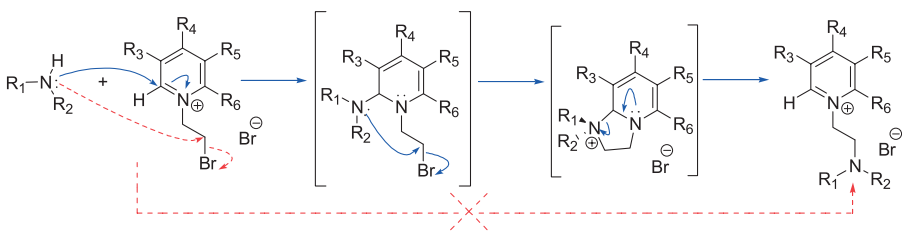


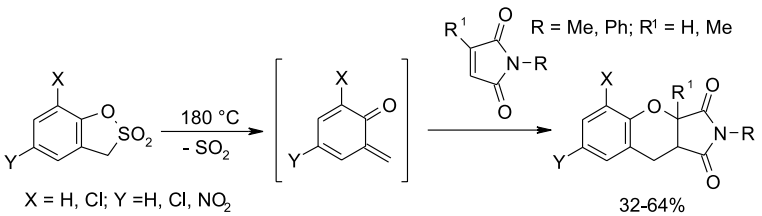


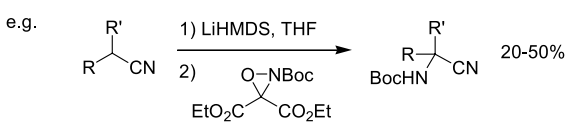
Route A: 4 steps, 76% overall yield
Route B: 4 steps, 85% overall yield

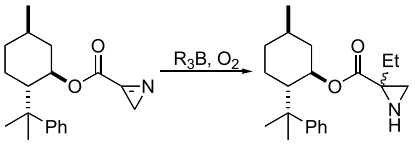




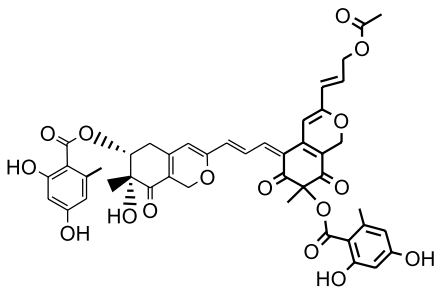


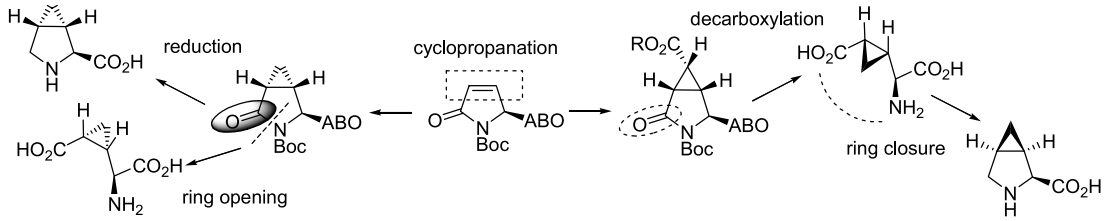


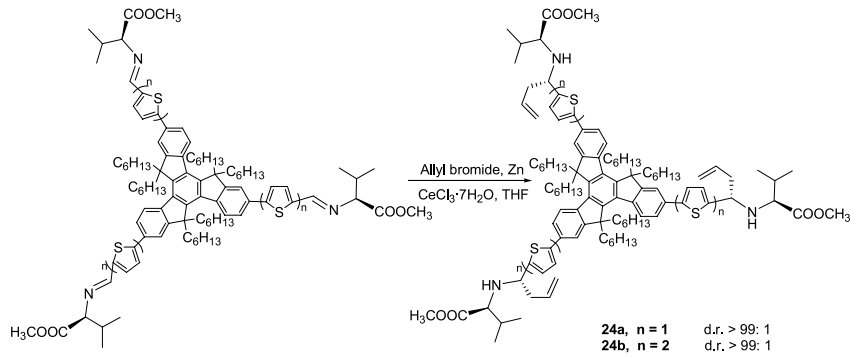


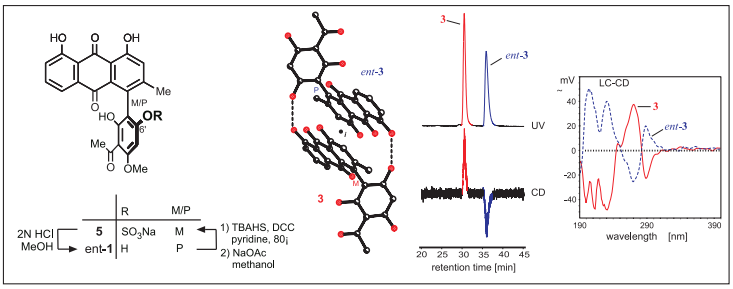


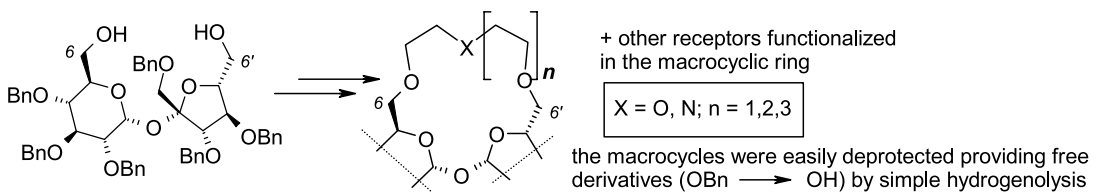
Two novel dimeric azaphilones named rutilins A and B, together with known compounds, entonaemin A, rubiginosins A and B were isolated from the methanolic extract of the stromata of the fungus *Hypoxylon rutilum*.

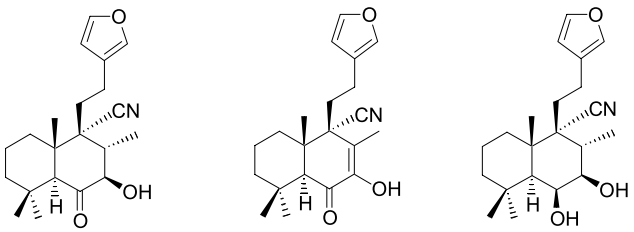


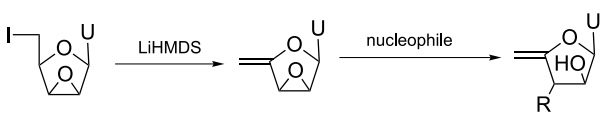


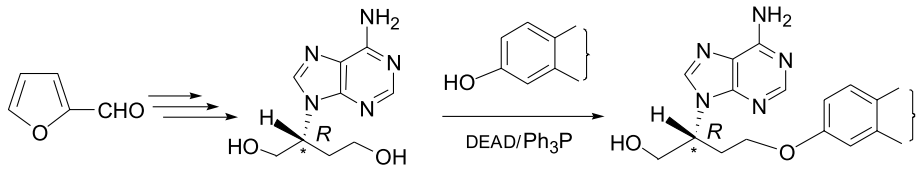




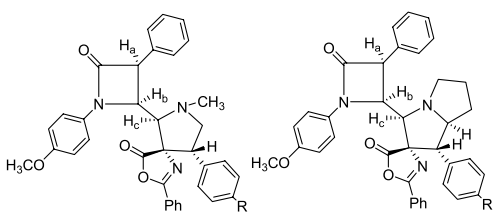


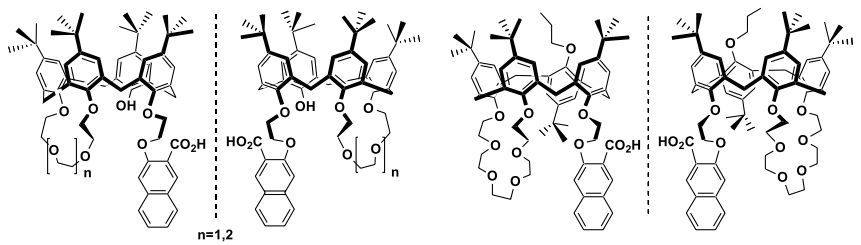


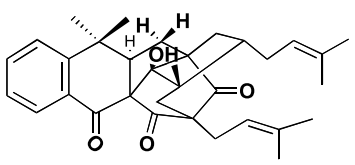




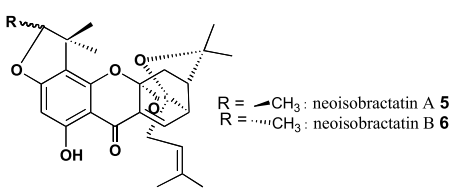
An efficient synthetic strategy for chiral acyclic nucleoside analogues containing both the phenoxy components of some bioactive natural compounds and adenine base was achieved.

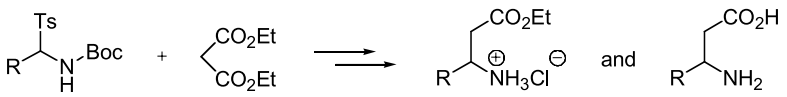






garcibracteatone **1**





OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

In the roots from *Bulbine frutescens* (center), phenylanthraquinones like knipholone (right formula, R=H, R′=Me) co-occur together with their unprecedented sulfated analogues, like, *e.g.*, knipholone 6′-*O*-sulfate (left formula, R=SO_3Na, R′=Me); unexpectedly, the latter exhibits an opposite axial configuration. Most of these compounds are not enantiomerically pure in nature, as analyzed by HPLC-CD coupling (left and right bottom), and only the racemic portion gives rise to crystals suited for an X-ray structure analysis (center).

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Oxidation of sulfides to sulfoxides. Part 2: Oxidation by hydrogen peroxide

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Contents

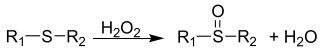
1. Introduction

The increasing interest and applications of sulfoxides have stimulated investigations on new methodologies of sulfoxide synthesis.

Organic sulfoxides are useful synthetic intermediates for the construction of various chemically and biologically active molecules. They often play an important role as therapeutic agents such as anti-ulcer (proton pump inhibitor),[1–7] antibacterial, antifungal, anti-atherosclerotic,[8–14] anthelmintic,[15,16] antihypertensive,[17] and cardiotonic agents,[18,19] as well as psychotonics[20–22] and vasodilators.[23]

The oxidation of sulfides is the most straightforward method for the synthesis of sulfoxides. There are a lot of reagents available for the oxidation of sulfides, but many of them cause over-oxidation to sulfones. Therefore, the conditions of the reaction, that is, time, temperature and the relative amount of oxidants, have to be controlled to avoid forming side products of the oxidation.

Recently, the oxidation of sulfides to sulfoxides by hydrogen peroxide has proved to be one of the most attractive methods (Scheme 1). This review is intended to survey the recent literature and to focus on new methods of sulfide oxidation by hydrogen peroxide.



Scheme 1.

Over the past few years, the importance of hydrogen peroxide and its derivatives as oxidising agents has grown considerably. In contrast to other oxidising agents, hydrogen peroxide is the most attractive from an environmental

Keywords: Oxidation; Sulfides; Sulfoxides; Hydrogen peroxide.
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viewpoint. It is an ideal waste-avoiding oxidant, since water is the only theoretical by-product, and is very attractive as an oxidant for liquid-phase reactions, thanks to its solubility in water and many organic solvents.[24,25] Moreover, aqueous hydrogen peroxide solution shows safety in storage, operation and transportation, is easy available on the market and is relatively cheap.[26,27] Hydrogen peroxide alone, without any organic solvents and catalysts, however, has to be used in a controlled manner, due to the possibility of an over-oxidation reaction.[28]

The oxidation of sensitive sulfides by hydrogen peroxide usually proceeds under relatively mild conditions and, in many cases, only a small excess of H_2O_2 is required.[28–30]

Hydrogen peroxide, either alone or in the presence of catalysts, in various solvents under neutral, acid or alkaline conditions, is known to oxidise aromatic or aliphatic sulfides to the corresponding sulfoxides with high yields. It is noteworthy that dialkyl sulfides are more easily oxidised than diaryl sulfides.[31]

Dialkyl sulfides were shown to be oxidised with an excess of hydrogen peroxide in an alcoholic solvent at room temperature, even in the absence of any catalyst. Oxidation of diaryl sulfides can be achieved by the use of H_2O_2 with various catalysts. A lot of transition metal (Ti, Mo, Fe, V, W, Re, Ru and Mn) compounds have been used as catalysts for the selective oxidation of sulfides with H_2O_2.[32–36]

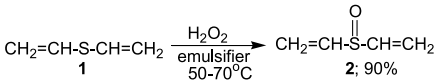
By the use of transition metal catalysts, selective transformation of a protochiral to a chiral sulfoxide is possible. The use of a chiral ligand with a transition metal, such as Ti, V or Mn in the presence of hydrogen peroxide has been reported in numerous methodologies.

It has been found that some metals (Ti and V) incorporated in a zeolitic framework are able to catalyse the oxidation of sulfides under mild conditions.[27,37–39]

2. Oxidation of sulfides by hydrogen peroxide in various solvents

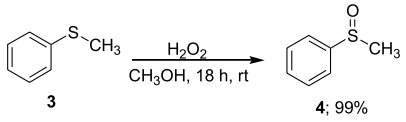
Gazdar and Smiles initiated the oxidation of sulfides to the corresponding sulfoxides by the use of hydrogen peroxide. In their experiments, acetone and acetic acid were chosen as the solvents. Since that time, many sulfoxides were obtained by the use of their procedure (Table 1).[40–51]

Addition of emulsifier in the oxidation of unsaturated sulfide **1** gives the corresponding sulfoxide **2** with high yield (Scheme 2).[38]



Scheme 2.

Drabowicz et al. observed that the use of methanol instead of acetone as the solvent in the case of thioanisole (**3**) oxidation by H_2O_2 to give the sulfoxide **4** speeds up the reaction time from 24 to 18 h (Scheme 3).[52,53]



Scheme 3.

The time of the oxidation reaction in methanol as the solvent was, however, relative long and many functional groups in the sulfides were easily destroyed.[54]

In 1998, Ravikumar et al.[55] reported the transformation of various sulfides into sulfoxides by H_2O_2 in hexafluoro-2-propanol (HFIP) as the solvent (Table 2).

Table 2. Oxidation of sulfides R_1SR_2 by 30% H_2O_2 in HFIP[55]

Entry	R_1	R_2	t (min)	Yield (%)
1	C_2H_5	$F_3CC{=}CHC_6H_5$	5	98
2	i-C_3H_7	i-C_3H_7	20	97
3	n-C_4H_9	n-C_4H_9	5	92
4	C_6H_5	C_2H_5	5	97
5	C_6H_5	$CH{=}CH_2$	15	94
6	C_6H_5	$CH_2{=}CHCH_2$	5	99
7	C_6H_5	$cyclo$-C_3H_5	5	93
8	C_6H_5	C_6H_5	5	99
9	$C_6H_5CH_2$	$C_6H_5CH_2$	5	98
10			5	82

The results presented in Table 2 indicate that the oxidation reactions in HFIP proceed smoothly with excellent yields of sulfoxides. Unfortunately, the HFIP is poisonous, expensive and volatile which severely restrict its use in practical organic synthesis.

Table 1. Oxidation of sulfides R_1SR_2 to $R_1S(O)R_2$ by H_2O_2 in acetone or acetic acid

Entry	R_1	R_2	Solvent	Yield (%)	References
1	CH_3	CH_2CONH_2	CH_3COCH_3	81	45
2	CH_3	CH_2CN	CH_3COCH_3	54	45
3	C_2H_5	C_2H_5	CH_3COOH	80–90	42
4	$ClCH_2CH_2$	$ClCH_2CH_2$	CH_3COOH	75	44
5	i-C_5H_{11}	i-C_5H_{11}	CH_3COCH_3	80–90	40
6	$CH_2{=}CHCH_2$	C_6H_5	CH_3COOH	64	47
7	CH_2COOH	CH_2COOH	CH_3COCH_3	75	40
8	$cyclo$-C_5H_{11}	$cyclo$-C_5H_{11}	CH_3COOH	77	46
9	$C_6H_5CH_2$	CH_3	CH_3COCH_3	77	45
10	$C_6H_5CH_2$	C_6H_5	CH_3COCH_3	64	48
11	$C_6H_5CH_2$	$C_6H_5CH_2$	CH_3COOH	~87	50

Recently, a new convenient and selective oxidation method of some alkyl phenyl sulfides to the corresponding sulfoxides was reported by Xu et al.[54] A large number of sulfides were tested in an oxidation by 30% aqueous H_2O_2 at room temperature in phenol as a solvent (Table 3). This system is highly efficient and selective for the oxidation of various sulfides (Table 3) within a short reaction time and the authors found that the functional groups, even the highly reactive carbonyl, were unaffected.

Table 3. Oxidation of sulfides R_1SR_2 by 30% aqueous H_2O_2 in phenol[54]

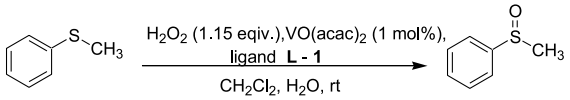
Entry	R_1	R_2	t (min)	Yield (%)
1	n-C_4H_9	n-C_4H_9	0.5	97
2	CH_3COCH_2	C_6H_5	0.8	95
3	C_6H_5	CH_3	0.5	99
4	C_6H_5	C_2H_5	0.5	97
5	C_6H_5	$CH(CH_3)C_2H_4OH$	0.5	98
6	C_6H_5	$CH_2CH_2COOC_2H_5$	1.5	97
7	C_6H_5	C_6H_5	4	99
8	$C_6H_5CH_2$	C_6H_5	4.5	97
9		$C_6H_5CH_2$	0.5	93

3. Oxidation of sulfides to sulfoxides by hydrogen peroxide in the presence of catalysts

3.1. Vanadium catalysts

During recent years, the chemistry of vanadium complexes has attracted considerable attention due to the possible applications of these compounds as catalysts for the oxidation of various sulfides.[56–59] Vanadium compounds such as ammonium metavanadate (NH_4VO_3),[59] vanadium pentoxide (V_2O_5),[38,59,60] sodium metavanadate ($NaVO_3$),[59,61] and vanadium(IV) acetylacetonate [$(CH_3COCH_2COCH_2)_2$-VO][59,61–65] have been generally applied in this process. By the use of these catalysts, oxidation of the sulfides **5**, **7** and **9** to the corresponding sulfoxides **6**, **8** and **10** occurs smoothly with good yield under mild conditions (Scheme 4).

Vanadium(IV) compounds with various chiral ligands **L-1** to **L-10** (Fig. 1) play an important role in the synthesis of a wide range of chiral sulfoxides.[66] A vanadium(IV)–Schiff base **L-1** (Fig. 1) complex was successfully applied for the first time in 1995 by Bolm and Bienewald for the oxidation of thioanisole (**3**) to the corresponding sulfoxide **4** by the use of H_2O_2 with good enantioselectivity and under relative mild conditions (Scheme 5).[67]



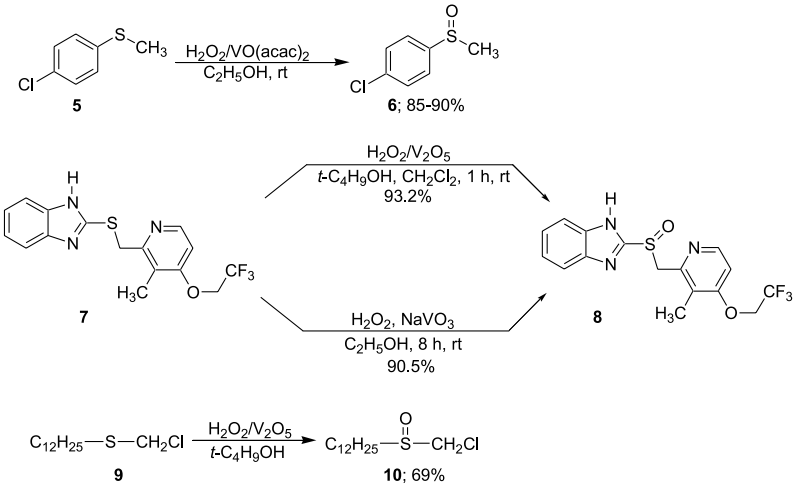
Scheme 5.

This complex was prepared in situ from $VO(acac)_2$ and the appropriate Schiff base ligand **L-1** (3-*tert*-butyl-5-nitro-salicylidene derivative), which was obtained from salicyl-aldehyde and β-amino alcohol.[56,65,67–71]

Since 1995, vanadium(IV)–Schiff base complexes were modified by introducing an additional element of chirality into the salicylic aldehyde moiety in order to increase the selectivity of the sulfide oxidation. Thus, binaphthyl-derived ligand **L-2**[72] and biphenyl-derived ligand **L-5**,[56] afforded the methyl phenyl sulfoxide **4** in 78 and 86% ee, respectively (Table 4).

In the case of ligand **L-5**, a small enhancement of enantioselectivity was additionally observed when, into the oxidation, a slight amount of methanol was applied (compare entries 6 with 8 and 7 with 9 in Table 4).[56] Investigations on methyl phenyl sulfide **3** oxidation have shown that introducing iodine atoms on the Schiff base ligand **L-8** and additional supporting of its complex on silica give the best enantioselectivity (Table 4, entry 14).[58]

The results presented in Table 4 indicated that the enantioselectivity of sulfoxide **4** could also be improved by decreasing the reaction temperature using ligands **L-3**, **L-4**, **L-5** and **L-7** (compare entries 2 with 3, 4 with 5, 6 with 7 and 8 with 9). Moreover, gradual addition of the oxidant enhances the enantioselectivity of sulfoxidation (compare entries 15 with 16 and 17 with 18).



Scheme 4.

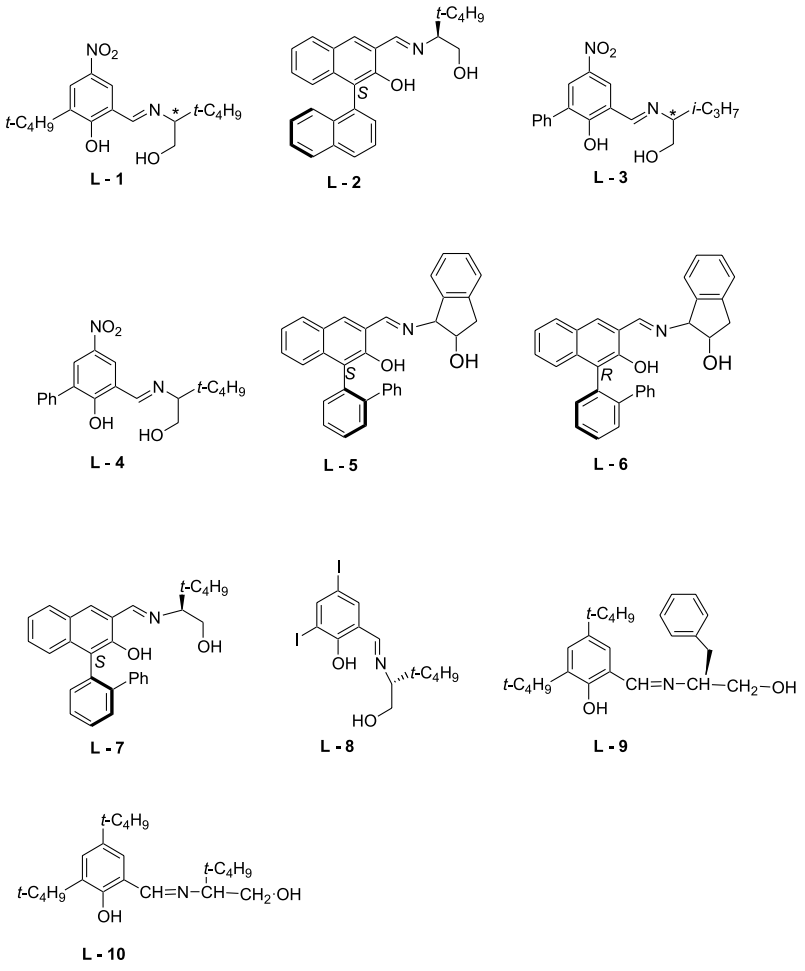


Figure 1. Schiff base ligands used in the preparation of vanadium complexes.

3.2. Rhenium catalysts

Several rhenium compounds have been investigated as catalysts for the oxidation of sulfides to the corresponding sulfoxides. It is beyond doubt that, from an industrial point of view, the rhenium compounds are very attractive due to their non-toxicity, ease of storage and operation, air stability and resistance to autoxidation reactions.[37]

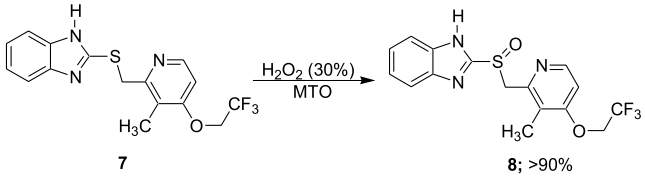
Methyltrioxorhenium (MTO) (catalyst **C-1**) (Fig. 2) is known as a versatile oxygen-transfer catalyst for the oxidation of various sulfides by H_2O_2.[73–77] MTO was

Table 4. Selected results of thioanisole oxidation in the presence of chiral Schiff base–vanadium(IV) complexes and aqueous H_2O_2 in dichloromethane

Entry	Ligand	Temperature (°C)	Yield (%)	ee (%)	References
1	**L-2**	0	92	78	72
2	**L-3**	Room temperature	80	58	65
3	**L-3**	0	90	75	65
4	**L-4**	Room temperature	78	62	65
5	**L-4**	0	74	73	65
6	**L-5**	Room temperature	88	77	56
7	**L-5**	0	83	86	56
8	**L-5**	Room temperature	84[a]	78	56
9	**L-5**	0	81[a]	88	56
10	**L-6**	Room temperature	77	32	56
11	**L-7**	Room temperature	72	71	56
12	**L-7**	0	72	74	56
13	**L-7**	0	71[a]	83	56
14	**L-8**	0	81	90	58
15	**L-9**	1–20	60[b]	27[b]	71
16	**L-9**	1–20	93[c]	39[c]	71
17	**L-10**	1–20	82[b]	40[b]	71
18	**L-10**	1–20	61[c]	47[c]	71

[a] Reaction run in the presence of 10 μl CH_3OH.
[b] Fast addition of hydrogen peroxide.
[c] Gradual addition of hydrogen peroxide.

reported to have a high solubility in water and also in most of the organic solvents (chloroform, dichloromethane, methanol, ethanol and acetonitrile). Application of **C-1** in the oxidation of the sulfide **7** in methanol as the solvent allowed the synthesis of lansoprazole (**8**) – an anti-ulcer drug with high yield (>90%) and excellent purity (99.95%) (Scheme 6).[37]



Scheme 6.

In 1998, Gunaratne et al.[78] reported the use of the rhenium(V) catalysts **C-1** to **C-4** (Fig. 2) for the oxidation of sulfides by a urea–hydrogen peroxide (1:1) adduct (UHP). The oxidation was carried out in various solvents such as chloroform, dichloromethane and acetonitrile.

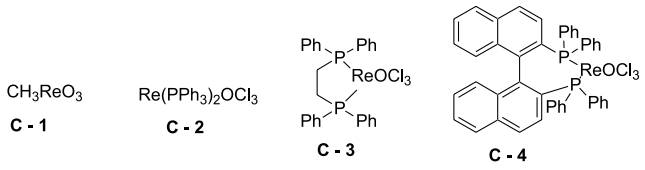
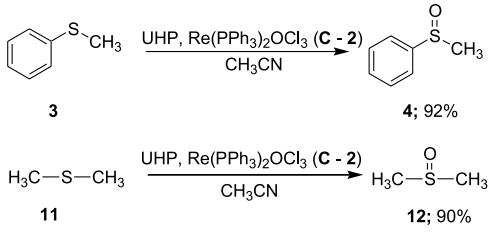


Figure 2. Rhenium catalysts.

It was found that the use of catalyst **C-2** in the oxidation of sulfides **3** and **11** to **4** and **12**, respectively, limits sulfone formation (Scheme 7). It was also observed that the rate of the oxidation reaction was very slow in chloroform and dichloromethane, but increased dramatically in acetonitrile. A similar solvent effect was observed in the MTO (**C-1**)-catalysed oxidation of methyl phenyl sulfide **3** with UHP. The authors concluded that the dialkyl sulfide **11** is more easily oxidised than the alkyl aryl sulfide **3** in the presence of the catalyst **C-2**.[78] In both cases, however, the yields of the corresponding sulfoxides were very high (Scheme 7).

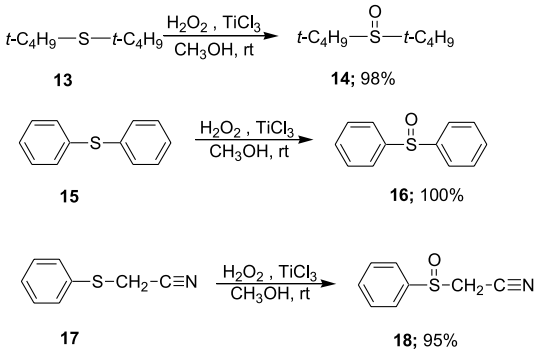


Scheme 7.

Studies of methyl benzyl sulfide and methyl phenyl sulfide (**3**) oxidation indicated that the structures of the catalysts play an important role in the oxidation of sulfides. In these processes, catalyst **C-3** was less active than **C-2**, whereas catalyst **C-4** speeds up the reaction time in both of the sulfides, in comparison to catalyst **C-2**.[78]

3.3. Titanium catalysts

Much effort has been devoted to the development of efficient titanium catalysts for the oxidation of sulfides into the corresponding sulfoxides. Titanium trichloride ($TiCl_3$) was successfully used as a catalyst for the hydrogen peroxide oxidation of sulfides **13**, **15**, **17** by Japanese workers in 1981.[79] The oxidation reactions were carried out in methanol at room temperature with a time shorter than 20 min. The dialkyl **14**, diaryl **16** and alkyl aryl **18** sulfoxides were obtained with excellent yields of 98, 100 and 95%, respectively (Scheme 8).



Scheme 8.

In recent decades, much work has been done in the discovery of new Ti-containing zeolites as catalysts for the selective oxidation of sulfides into sulfoxides. A wide range of these catalysts such as TS-1,[29,31,66,80,81] TS-2,[29,82] Ti-β,[30,31,83] Ti-MCM-41 (Ti-M41),[84,85] Ti-HMS,[30] and Ti-MMM[86] show good catalytic properties in a range of mild selective oxidations of sulfides by the use of aqueous hydrogen peroxide.

Titanium silicate TS-1 as a commercial oxidation catalyst is used in the reactions of relatively small molecules,[30,87,88] while Ti-β and Ti-mesoporous materials can be applied for the oxidation of bulkier sufides.[30,31]

Hulea et al.[31] compared the activity of Ti-β zeolite with TS-1. Both catalysts were tested in the hydrogen peroxide oxidation of various dialkyl and diaryl sulfides at 30 °C (Table 5).

The results presented in Table 5 indicate that TS-1 and Ti-β have the same high activity towards the oxidation of small-sized substrates such as diethyl sulfide. It was also found that Ti-β was more active than TS-1 in the oxidation of hindered molecules, such as di-*n*-butyl sulfide and diphenyl sulfide, due to its bigger pore diameter.[31]

Application of TS-1 as the catalyst for the oxidation of various alkyl methyl sulfides was also studied by Robinson et al.[80] It was found that, the more hindered the sulfides, the less the sulfones were formed (Table 6).

Oxidations of alkyl and aryl methyl sulfides by dilute hydrogen peroxide (26%) in acetone on TS-1 and TS-2 as catalysts were investigated by Reddy et al.[39] It was found

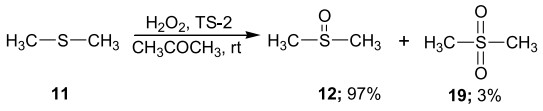
Table 5. Oxidation of various sulfides R_1SR_2 by H_2O_2 on TS-1 and Ti-β as catalysts[31]

Entry	R_1	R_2	Catalyst	Solvent	Conversion towards sulfoxide (%)
1	C_2H_5	C_2H_5	TS-1	*t*-C_4H_9	42.5
2	C_2H_5	C_2H_5	TS-1	CH_3OH	97.1
3	*n*-C_4H_9	*n*-C_4H_9	TS-1	*t*-C_4H_9	20.5
4	C_6H_5	C_6H_5	TS-1	CH_3OH	5.1
5	C_2H_5	C_2H_5	Ti-β	*t*-C_4H_9	99.0
6	C_2H_5	C_2H_5	Ti-β	CH_3OH	98.2
7	*n*-C_4H_9	*n*-C_4H_9	Ti-β	*t*-C_4H_9	77.2
8	*n*-C_4H_9	*n*-C_4H_9	Ti-β	CH_3OH	89.0
9	*sec*-C_4H_9	*sec*-C_4H_9	Ti-β	*t*-C_4H_9	14.1
10	C_6H_5	C_6H_5	Ti-β	*t*-C_4H_9	18.5
11	C_6H_5	C_6H_5	Ti-β	CH_3OH	37.6

Table 6. Oxidation of R_1SR_2 by H_2O_2 with TS-1[80]

Entry	R_1	R_2	Conversion (%)	Selectivity (%)	
				Sulfoxide	Sulfone
1	*n*-C_4H_9	CH_3	52.1	79.3	20.7
2	*i*-C_4H_9	CH_3	49.5	88.9	11.1
3	*sec*-C_4H_9	CH_3	47.8	90.4	9.6
4	*t*-C_4H_9	CH_3	51.7	93.8	6.2

that, oxidation of dimethyl sulfide **11** to the sulfoxide **12** on TS-2 proceed with high yield (97%) and only 3% of the sulfone **19** was formed (Scheme 9).

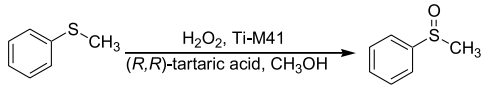


Scheme 9.

Under the same reaction conditions other sulfides such as diethyl, methyl phenyl and ethyl phenyl sulfide gave the sulfoxides with lower yields (85, 78 and 75%, respectively).

The results of sulfide oxidation on TS-1 and TS-2 indicated that better yields of the sulfoxides were achieved for alkyl sulfides than for aryl methyl sulfides. Moreover, when TS-1 was used in place of TS-2 as the catalyst, similar yields were obtained, except that a longer reaction time was required.

Oxidation of the sulfide **3** by H_2O_2 on Ti-MCM-41(Ti-M41) in various solvents and with or without a chiral modifier, (*R*,*R*)-tartaric acid was studied by Iwamoto et al.[85] They observed that, when methanol was used as the solvent in the oxidation of thioanisole (**3**) without the chiral modifier, the sulfoxide **4** was obtained with a yield of 28 and 9% ee. Application of (*R*,*R*)-tartaric acid allowed the sulfoxide **4** synthesis with a much higher yield (94%) and enantioselectivity (18%) (Scheme 10).



Scheme 10.

The oxidation of methyl phenyl sulfide in the presence of (*R*,*R*)-tartaric acid was explored in various solvents (Table 7). The results indicated that the polarity of the solvent had an influence on the asymmetric oxidation of sulfide **3**.

Table 7. Solvent influence on enantioselectivity of methyl phenyl sulfide (**3**) oxidation over Ti-M41 in the presence of tartaric acid at room temperature[31]

Entry	Solvent	Yield (%)	ee (%)
1	CH_3CN	66	1
2	THF	58	1
3	$(C_2H_5)_2O$	22	1
4	$(CH_3)_2CO$	63	1
5	CH_2Cl_2	53	12
6	$ClCH_2CH_2Cl$	50	11
7	*n*-C_6H_{14}	43	9

The experimental data (Table 7) show that a trace of enantioselectivity was found in CH_3CN, THF, $(C_2H_5)_2O$ and $(CH_3)_2CO$ as the solvents, while, in CH_2Cl_2, $ClCH_2$-CH_2Cl and *n*-hexane, some improvement was observed.

Kagan et al.[89] reported for the first time the use of titanium tetra-isopropoxide [Ti(O*i*-Pr)$_4$] and diethyl tartrate as catalysts in the asymmetric oxidation of sulfides by hydrogen peroxide in 1984.

Fraile and co-workers[29] supported Ti(O*i*-Pr)$_4$ on silica and then treated this catalyst (**C-5**) with (*R*)-tartaric acid or diethyl (*R*)-tartrate. The catalysts obtained in this manner (**C-6** and **C-7**) (Fig. 3) were found to be a highly suited to the oxidation of sulfides into the corresponding sulfoxides by H_2O_2 and *tert*-butyl hydroperoxide (TBHP) (Table 8).

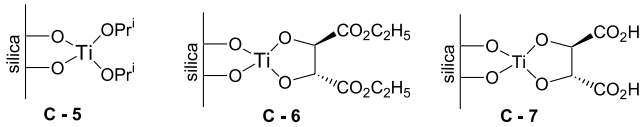


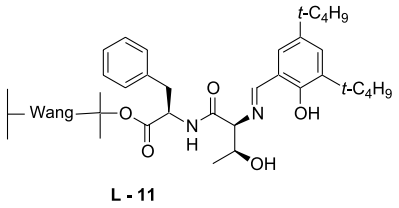
Figure 3. Titanium catalysts.

Table 8. Selected results of sulfide R_1SR_2 oxidation by H_2O_2 and TBHP in the presence of **C-5** to **C-7** as catalysts[29]

Entry	Catalyst	Oxidant	R_1	R_2	t (h)	Yield (%)	
						Sulfoxide	Sulfone
1	**C-5**	H_2O_2	p-$CH_3C_6H_4$	CH_3	3	75	12
2	**C-5**	TBHP	p-$CH_3C_6H_4$	CH_3	0.5	59	20
3	**C-6**	H_2O_2	p-$CH_3C_6H_4$	CH_3	3.5	84	1
4	**C-6**	TBHP	p-$CH_3C_6H_4$	CH_3	4	83	7
5	**C-7**	H_2O_2	p-$CH_3C_6H_4$	CH_3	4.5	95	1
6	**C-7**	TBHP	p-$CH_3C_6H_4$	CH_3	4	82	9
7	**C-7**	H_2O_2	n-C_4H_9	n-C_4H_9	4	100	0
8	**C-7**	H_2O_2	CH_3	t-C_4H_9	24	94	3
9	**C-7**	H_2O_2	C_6H_5	$C_6H_5CH_2$	24	93	1
10	**C-7**	H_2O_2	C_6H_5	C_6H_5	24	94	3

It was observed that the oxidation of methyl *p*-tolyl sulfide was faster in the presence of TBHP, but the formation of the sulfone was smaller in the case of oxidation by H_2O_2 (compare entries 1 with 2, 3 with 4 and 5 with 6). The best chemical yield and selectivity were achieved by the use of catalyst **C-7**.

In 2001, Green and co-workers[90] reported a new efficient protocol for the oxidation of various alkyl aryl sulfides by aqueous hydrogen peroxide with a titanium–ligand complex supported on Wang resin (**L-11**) (Fig. 4).



L - 11

Figure 4. Schiff base ligand used for the preparation of titanium complexes.

These authors synthesised several sulfoxides with a very good conversion of the sulfides into the sulfoxides with moderate enantioselectivity (Table 9).

Table 9. Oxidation of alkyl aryl sulfides R_1SR_2 by H_2O_2 with titanium–ligand complex on Wang resin (**L-11**) in CH_2Cl_2[90]

Entry	R_1	R_2	Conversion towards sulfoxide (%)	ee (%)
1	C_6H_5	CH_3	100	64
2	C_6H_5	C_2H_5	96	64
3	C_6H_5	C_3H_7	90	57
4	4-$CH_3OC_6H_4$	CH_3	85	63
5	4-ClC_6H_4	CH_3	90	58
6	4-BrC_6H_4	CH_3	70	53
7	4-$O_2NC_6H_4$	CH_3	61	64
8	4-NCC_6H_4	CH_3	90	45
9	$C_{10}H_7$	CH_3	87	72

3.4. Molybdenum catalysts

Several molybdenum compounds are known as selective catalysts for the oxidation of various sulfides. Molybdenum salts such as molybdyldiacetylacetonate $[MoO_2(acac)_2]$,[91] hexacarbonylmolybdenum $[Mo(CO)_6]$ and molybdenum peroxide $[MoO_5]$ are widely used as catalysts for the oxidation of sulfides by H_2O_2.[38,92–94]

Sulfoxide **21**, one of the main intermediates in pantoprazole (anti-ulcer agent) synthesis, was prepared[95] via the oxidation of sulfide **20** [5-(difluoromethoxy)-2-{[(3-methoxy-4-chloro-2-pyridinyl)-methyl]thio}-1*H*-benzimidazole] by H_2O_2 in the presence of ammonium molybdate with very good yield (~83%) (Scheme 11).

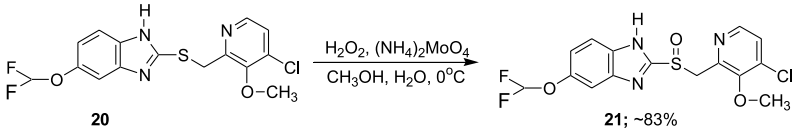
The substitution of Si^{4+} ions in an Al-free silicalite framework with Mo^{5+} ions gives a very efficient catalytic system for the oxidation of sulfides. The interest in these catalysts has increased in recent decades.[96–99]

Raghavan and co-workers[81] have reported a hydrothermal synthesis of Al-free Mo-silicalite-1 (MoS-1) with Si/Mo (mole) ratios in the range 80–300 and its selective oxidation properties towards sulfoxides.

This catalyst (MoS-1) was found to be active for the chemoselective oxidation of various sulfides into the corresponding sulfoxides by 30% H_2O_2 without the generation of sulfones. It is important to note that both aliphatic and aromatic sulfides were smoothly and efficient oxidised (Table 10).

Table 10. Selected results of sulfide R_1SR_2 oxidation into corresponding sulfoxides by 30% H_2O_2 in the presence of MoS-1 catalyst[81]

Entry	R_1	R_2	t (h)	Selectivity towards sulfoxide (%)
1	CH_3	CH_3	2	94
2	CH_3	C_6H_5	3	90
3	n-C_4H_9	n-C_4H_9	3	93
4	C_6H_5	C_6H_5	8	75
5	$C_6H_5CH_2$	$C_6H_5CH_2$	3	85



Scheme 11.

Molybdenum(VI) (oxo diperoxo)-pyridine-*N*-oxide (**C-8**) and molybdenum(VI) (oxo diperoxo)-pyrazole (**C-9**) (Fig. 5) complexes coated on silica gel were investigated by Batigalhia and co-workers[100] as an oxidation system for the conversion of aliphatic and aromatic sulfides into the corresponding sulfoxides (Table 11).

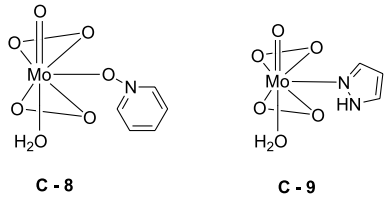
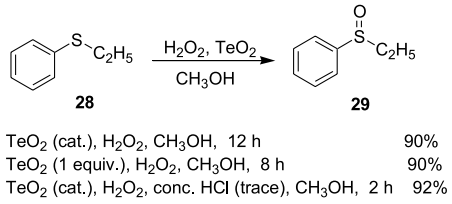


Figure 5. Molybdenum catalysts.

It was observed that, during sulfide **28** oxidation to **29**, an increase in the catalyst amount of up to 1 equiv shortened the reaction time and that the addition of a small quantity of concentrated HCl (1/100 molar ratio to sulfide) speeded up the reaction (Scheme 13).



Scheme 13.

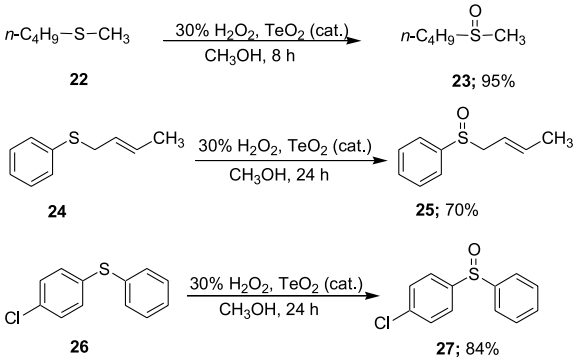
Table 11. Oxidation of various sulfides R_1SR_2 by H_2O_2 with complexes **C-8** and **C-9** supported on silica[100]

Entry	R_1	R_2	Complex **C-8**		Complex **C-9**	
			Yield of sulfoxide (%)	*t* (h)	Yield of sulfoxide (%)	*t* (h)
1	CH_3COCH_2	CH_3	92	9	86	6
2	CH_3COCH_2	C_6H_5	88	7	74	5
3	C_6H_5	CH_3	97	23	92	12
4	4-BrC_6H_4	CH_3	96	11	95	7
5	$C_6H_5CH_2$	C_6H_5	97	13	97	6
6	*p*-$CH_3C_6H_4COCH_2$	C_2H_5	97	6	87	4
7		C_6H_5	91	15	90	11

The experimental data collected in Table 11 indicate that, by the use of complexes **C-8** and **C-9**, the synthesis of different sulfoxides was achieved in high yield. Moreover, it is noteworthy that the carbonyl group was not affected.

3.5. Tellurium catalysts

The complex H_2O_2–TeO_2 was described as a remarkably selective agent for the oxidation of sulfides into the corresponding sulfoxides.[101–105] In 1990, Kim et al.[101] investigated the oxidation of various sulfides by the use of this catalytic system. The obtained results indicated that both aromatic and aliphatic sulfides **22**, **24** and **26** are transformed into the sulfoxides **23**, **25** and **27**, respectively, with high yield at room temperature (Scheme 12). The oxidation of aliphatic sulfides **22**, however, proceeds much more smoothly and in a shorter reaction time than the aromatic derivatives **24** and **26**.[101]



Scheme 12.

3.6. Tungsten catalysts

Tungsten catalyst systems such as the peroxotungsten complex [$WO(O_2)_2$, HMPT/H_2O],[106] tungstic oxide (WO_3),[107] tungstic acid [H_2WO_4],[108] hexacarbonyltungsten [$W(CO)_6$],[109] phosphotungstenic acid [$H_3(P(W_3O_{10})_4)\cdot H_2O$],[110] [$C_5H_5N(n\text{-}C_{16}H_{33})]_3PO_4[W(O)(O_2)_2]_4$,[111] Na_2WO_4 and other tungsten complexes with various quaternary ammonium salts as phase-transfer catalysts[112–115] are used for the oxidation of sulfides.

Sato et al.[26] have investigated the oxidation of sulfides into the corresponding sulfoxides by H_2O_2 in the presence or absence of Na_2WO_4, $C_6H_5PO_3H_2$ and a phase-transfer catalyst (PTC = $[CH_3(n\text{-}C_8H_{17})_3N]HSO_4$) (Table 12).

The results presented in Table 12 show that the susceptibility of the sulfides to H_2O_2 is highly dependent on the structure of the sulfides.

The oxidation of dialkyl sulfides and alkyl aryl sulfides was found to be efficient without a tungsten catalyst (entries 1 and 4), whilst, in the case of diaryl sulfides, the oxidation reaction proceeded with a high yield only in the presence of the catalyst (entry 8).

Thakur et al.[116] found a new tungsten heterogeneous catalytic system (WO_3–30% H_2O_2) which can catalyse efficiently the asymmetric oxidation of various sulfides in the presence of cinchona alkaloids such as hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether [$(DHQD)_2$–PYR] with high yields and with good enantioselectivity (Table 13).[116]

Table 12. Sulfide R_1SR_2 oxidation into sulfoxides by H_2O_2 in the presence or absence of Na_2WO_4, $C_6H_5PO_3H_2$ and PTC[26]

Entry	R_1	R_2	Na_2WO_4, $C_6H_5PO_3H_2$, PTC, mmol (S/C)[a]	H_2O_2 (equiv)	Temperature (°C)	t (h)	Yield of sulfoxide (%)
1	CH_3	C_6H_5	—	1.0	35	18	99
2	CH_3	C_6H_5	—	1.1	0	9	39
3	CH_3	C_6H_5	0.005	1.1	0	9	94
4	n-C_4H_9	n-C_4H_9	—	1.0	35	18	99
5	n-C_4H_9	n-C_4H_9	—	1.1	0	9	31
6	n-C_4H_9	n-C_4H_9	0.005	1.1	0	9	93
7	C_6H_5	C_6H_5	—	2.5	50	12	2
8	C_6H_5	C_6H_5	0.005	1.2	25	3	61

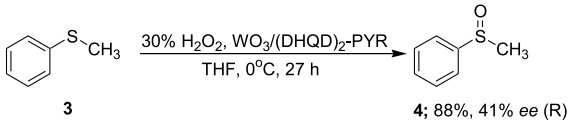
[a] Substrate/catalysts molar ratio.

Table 13. Oxidation of sulfide R_1SR_2 by H_2O_2 in the presence of WO_3–cinchona alkaloids at 0 °C[116]

Entry	R_1	R_2	t (h)	Yield of sulfoxide (%)	ee (%)
1	C_6H_5	CH_3	49	88	59 (*R*)
2	C_6H_5	C_2H_5	44	82	51 (*R*)
3	C_6H_5	i-C_3H_7	44	83	45 (*R*)
4	C_6H_5	n-C_4H_9	40	90	35 (*R*)
5	C_6H_5	C_6H_{11}	36	78	46 (*R*)
6	C_6H_5	$C_6H_5CH_2$	24	88	61 (*R*)
7	p-$CH_3C_6H_4$	CH_3	44	81	44 (*R*)
8	p-$CH_3C_6H_4$	C_2H_5	46	86	43 (*R*)
9	p-$CH_3C_6H_4$	$C_6H_5CH_2$	34	85	65 (*R*)

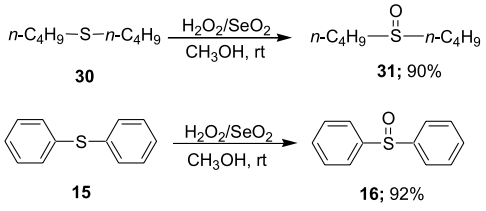
The data collected in Table 13 demonstrate that the oxidation of sulfides possessing benzyl as the R_2 group (entries 6 and 9) proceeded with the best enantioselectivity.

The oxidation of phenyl benzyl sulfide by the use of WO_3–cinchona alkaloids as the catalyst was tested in various solvents such as THF, CH_3OH, CH_2Cl_2, $CHCl_3$ and CH_3CN. The best yield of methyl phenyl sulfoxide **4** was achieved in THF (Scheme 14).



3 **4**; 88%, 41% *ee* (R)

Scheme 14.



Scheme 15.

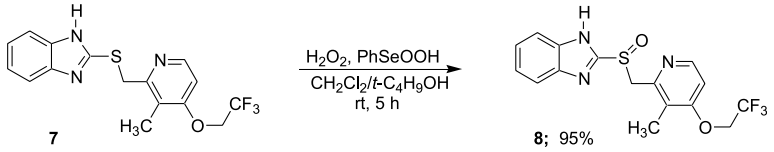
3.7. Selenium catalysts

Some selenium compounds are known to be efficient catalysts for the preparation of different sulfoxides. The use of selenium dioxide as a catalyst for the selective oxidation of the sulfides **15** and **30** to the corresponding sulfoxides by hydrogen peroxide in methanol as the reaction medium was disclosed by Drabowicz et al.[102] Sulfoxides **16** and **31** were obtained with high yields (92 and 90%, respectively) (Scheme 15).

The application of benzeneselenic acid (PhSeOOH) as a catalyst for the oxidation of (2[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]-thio]-1*H*-benzimidazole) **7** by 35% hydrogen peroxide allowed the synthesis of sulfoxide **8** with excellent yield (95%). The reaction was carried out in a mixture of dichloromethane and *t*-butanol as the solvents at a temperature of 15–20 °C[117] (Scheme 16).

3.8. Iron catalysts

Iron complexes for sulfide oxidation have not been widely studied, in contrast to the other complexes mentioned in this paper. Recently, however, research attention has focused on iron complexes such as $[Fe(acac)_3]$[118] and $[Fe_2O(pb)_4(H_2O)_2](ClO_4)_4]$ (pb = (−)4,5-pinene-2,2′-bipyridine)[119] used for asymmetric sulfide oxidation. Iron complexes have a bigger advantage over many of the other catalysts



7 **8**; 95%

Scheme 16.

Table 14. Oxidation of sulfides R_1SR_2 by H_2O_2 in the presence of various iron Schiff base complexes[118]

Entry	R_1	R_2	Ligand	Yield of sulfoxide (%)	ee (%)
1	C_6H_5	CH_3	**L-12**	27	26 (*S*)
2	C_6H_5	CH_3	**L-13**	15	13 (*S*)
3	C_6H_5	CH_3	**L-14**	27	23 (*S*)
4	C_6H_5	CH_3	**L-15**	30	55 (*S*)
5	C_6H_5	CH_3	**L-16**	36	59 (*S*)
6	C_6H_5	C_2H_5	**L-16**	30	44 (*S*)
7	C_6H_5	$C_6H_5CH_2$	**L-16**	40	27 (*S*)
8	2-$C_{10}H_7$	CH_3	**L-16**	44	70 (−)
9	*p*-$NO_2C_6H_4$	CH_3	**L-16**	21	90 (*S*)

due to their non-toxicity and commercial availability and they are relatively cheap.[118] Legros and Bolm[118] studied the iron-catalysed asymmetric oxidation of alkyl aryl sulfides. The experiments were carried out in dichloromethane for 16 h at room temperature, using H_2O_2 as the oxidising agent in the presence of various iron(III)–Schiff base complexes (**L-12** to **L-16**) (Fig. 6) (Table 14).

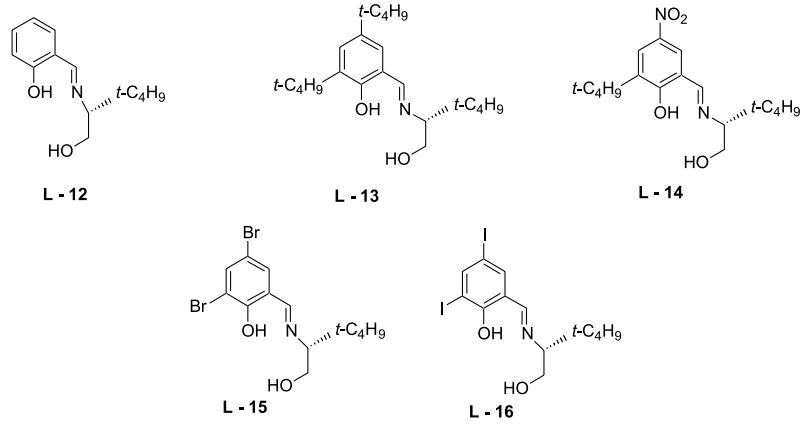


Figure 6. Schiff base ligands used for the preparation of iron complexes.

The data presented in Table 14 indicate that the sulfides can be oxidised into the corresponding chiral sulfoxides with good enantioselectivity (entry 9) and moderate yields under experimental conditions.

to autoxidation reactions. Moreover, transition metal catalysts provide a valuable tool for the synthesis of both aromatic and aliphatic sulfoxides. The oxidation can be carried out even with molecules containing highly reactive chemical groups, that is, carbonyl, hydroxyl and unsaturated bonds, with good results. It is also noteworthy that a number of important chiral sulfoxides and biologically active molecules are already prepared by the use of the previously mentioned catalysts with high yield and purity. Generally, much work has been undertaken on sulfide oxidation with H_2O_2, but we believe that more attention should still be paid to the improvement of the described processes.

4. Conclusions

As mentioned in this and our previous review,[120] the importance of sulfoxides as biologically active molecules has grown considerably and, therefore, many studies towards the selection of oxidising agents for sulfide oxidation have been carried out. In contrast to many other oxidising agents like hypochlorites, bromites, potassium permanganate and potassium chromate, hydrogen peroxide is the most attractive due to its safety in storage, operation, and transportation and also from an economical point of view. It is readily available on the market and is relatively cheap. A number of new, atom-efficient and waste-free methods for sulfoxide synthesis are presented in this survey. Recently, numerous new methods for sulfide oxidation by H_2O_2 in the presence of transition metals as catalysts have been developed. As presented in our article, many of these catalysts show good catalytic properties, non-toxicity, safety in storage and operation, air stability and resistance

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Biographical sketch

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Oligosaccharide synthesis on a soluble, hyperbranched polymer support via thioglycoside activation

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Abstract—The synthesis of linear and branched di-, tri- and tetramannosides on a commercially available hyperbranched polyester as a soluble, high loading support is described. Glycosylation products were isolated in 26–63% yield as mixtures of anomers after total hydrolytic degradation of the polymer. All polymer-bound intermediates were purified through simple extraction or precipitation. Solution-phase NMR and MALDI-TOF were used to monitor the progress of the reaction directly on the hyperbranched polymer support.

1. Introduction

The development of insoluble polymeric supports[1] to facilitate the purification of synthetic intermediates has dramatically streamlined the synthesis of natural and unnatural molecules.[2] However, the lower kinetic reactivity of polymer-supported substrates, which depends greatly on the swelling characteristics of the polymer–substrate conjugate, impedes the routine application of solution-phase synthetic procedures to the solid phase. The use of highly-crosslinked, macroporous supports that do not require swelling for reactivity,[3] and insoluble resins grafted with soluble linear[4] or dendritic polymers,[5] partially circumvents these kinetic impediments. Similarly, the solubility of non-crosslinked polymers, such as linear polystyrene (PS) and poly(ethylene glycol) (PEG),[6] permits supported reactions to be performed in solution. However, the practical utility of many of these linear supports is limited by low loading capacities. Dendrimers[7] and hyperbranched polymers[8] possess an $(x-1)n+1$ ($n=$ degree of polymerization) number of terminal groups for an AB_x-type repeat unit. Accordingly, polyamidoamine (PAMAM),[9] carbosilane,[10] polyglycerol,[11] and dye-conjugated[12] dendrimers have been employed as high-loading, soluble supports for organic synthesis.[13] The utility of dendrimer-based supports is severely limited by the high cost of their synthesis. However, a perfectly branched dendrimer architecture is not absolutely required for efficacy as a high loading support. For example, hyperbranched polymers are highly branched polymers that are prepared in a single synthetic step with degrees of branching that are typically less than 50%. Therefore, these imperfect analogs may serve as practical, low cost alternatives to dendrimers (Fig. 1). Despite the tremendous potential of these readily accessible materials to serve as inexpensive, high-loading dendritic supports, they have received only limited attention as synthetic[14] or catalyst[15] supports.

Although the preparation of peptides[16] and nucleotides[17] on solid phase has become routine, oligosaccharide synthesis on polymer supports[18] remains problematic due to the structural complexity of oligosaccharides and difficulties associated with glycosyl bond formation. However, recent success in the automation of solid-phase oligosaccharide

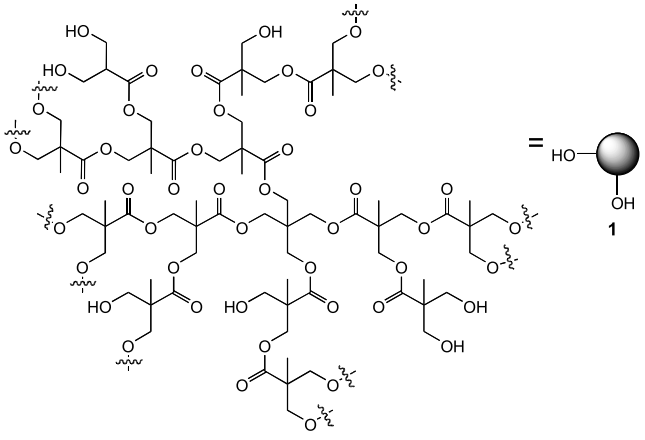

Figure 1. The hyperbranched polymer (Boltorn™).

Keywords: Carbohydrates; Glycosylations; Polymers; Dendrimers; Solid-phase.
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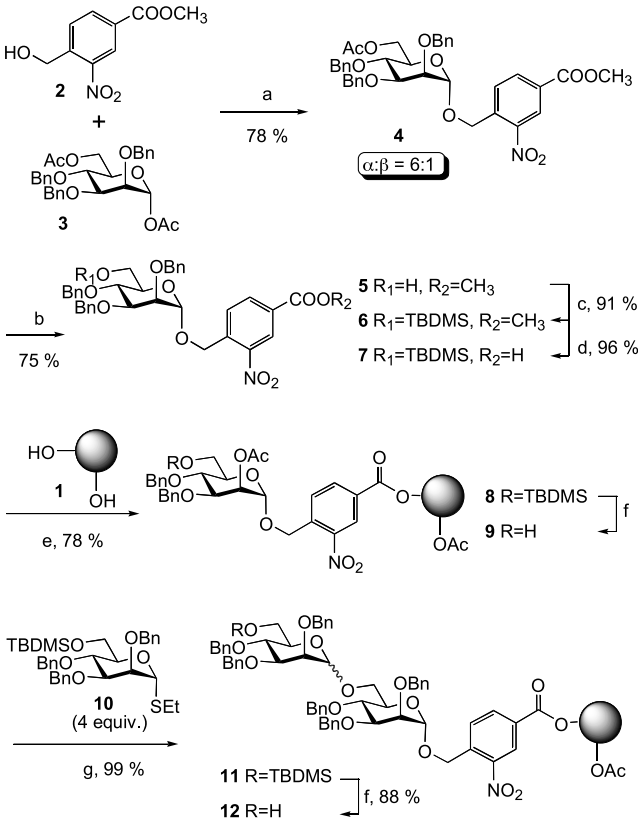
synthesis bodes well for the development of a routine solid-phase approach to these molecules.[19] In a preliminary communication,[20] we demonstrated that the synthesis of disaccharides via thioglycoside activation[21] could be performed using this hyperbranched polymer as a support. We report herein the extension of this approach to the preparation of linear and branched di-, tri- and tetrasaccharides. This paper focuses on hyperbranched polymer supported assembly of oligomannosides[22,23] because of their important role as a structural constituent of *N*-glycans.[24]

2. Results and discussion

The hyperbranched polymer support employed in this study is constructed via an acid-catalyzed polymerization of dimethylolpropionic acid in the presence of pentaerythritol as a central core (Fig. 1, commercially available as Boltorn™ H-50).[25] This support exhibits several properties that facilitate purification and analysis of polymer-bound intermediates: (1) the polymer-bound intermediates tend to exhibit high solubility in most aprotic solvents but very low solubility in methanol, from which they can be quantitatively precipitated. Although purification by size exclusion chromatography (SEC) remains as a potential purification method, we found that precipitation was much more expedient, especially on preparative scale. (2) Direct mass spectral analysis of the polymer-bound disaccharides can be achieved by photolytic release of the disaccharide from the support with the MALDI-TOF laser. (3) The support undergoes rapid hydrolytic degradation to water-soluble materials thereby permitting product purification by extraction. This method typically provides more efficient cleavage from the support than photolysis of the 2-nitrobenzyl linkage. (4) The high intrinsic loading capacity of Boltorn™ H-50 polymer (8.8 mmol/g OH-groups; nominal M_w = 14,500, pdi = 2.0) permits relatively large amounts of substrates per gram of polymer support to be immobilized.

2.1. O-6 Glycoside bond

2.1.1. Preparative scale synthesis of a supported disaccharide. The 2-nitrobenzyl alcohol photolabile linker (**2**)[26] was glycosylated with 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-mannose (**3**)[27] affording the mannoside **4** (α:β = 6:1) in 78% yield (Scheme 1). The anomers could not be separated and were carried through the rest of the synthesis as a mixture. Deprotection of the 6-*O*-acetyl group with potassium carbonate in methanol–THF followed by silylation with TBDMSCl/Et_3N afforded the methyl ester **6**. Subsequent hydrolysis in a biphasic mixture of THF and aqueous KOH provided the carboxylic acid **7**, which was coupled to the Boltorn H-50 polyester (**1**) using EDCI in THF–pyridine. After an extractive aqueous work-up, the polymer-mannoside conjugate **8** was desilylated with excess HF·pyridine and glycosylated with the thioethyl donor **10**[28] affording polymer-supported disaccharide **11** (99% for both steps, loading level: 0.59 mmol/g).[29] Desilylation with HF–pyridine provided multigram quantities of the polymer-acceptor conjugate **12** in 88% yield (loading level: 0.64 mmol/g).[29b]

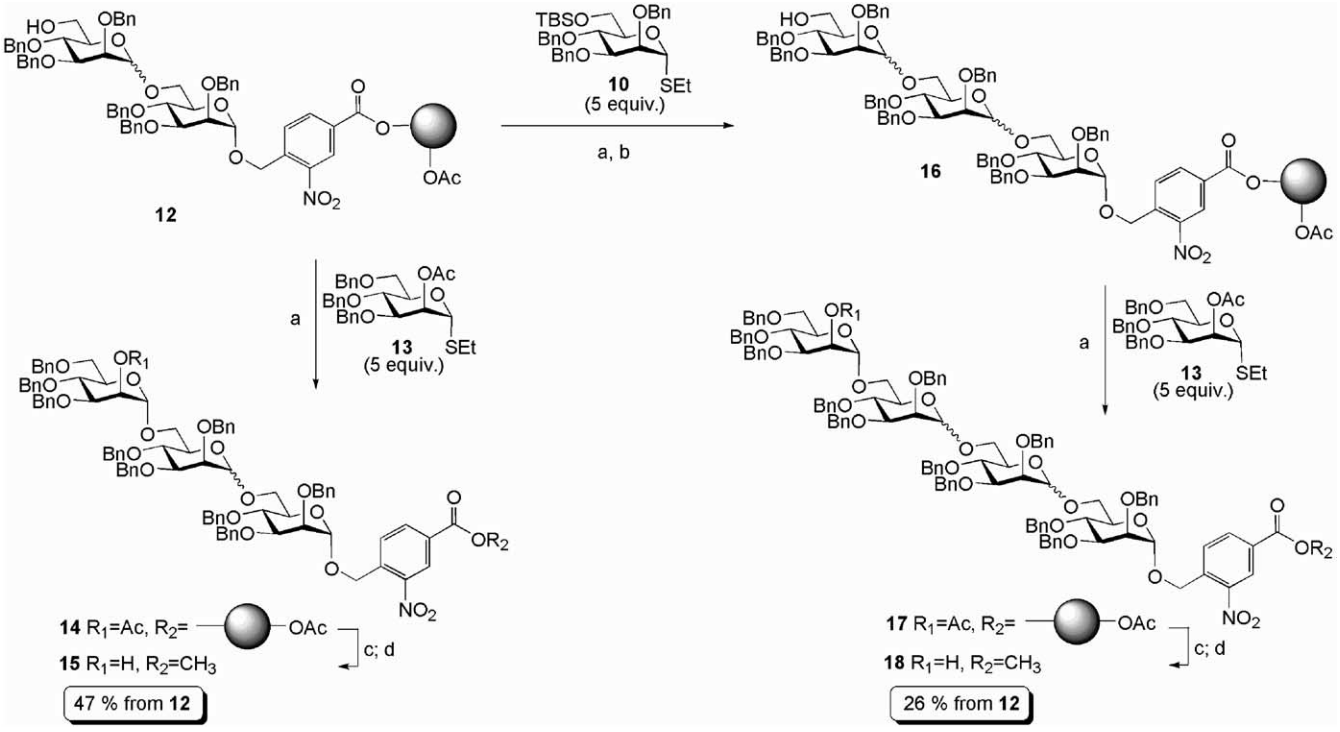


Scheme 1. Reagents and conditions: (a) $BF_3 \cdot OEt_2$, CH_2Cl_2, 0 °C; (b) K_2CO_3, MeOH–THF; (c) TBDMSCl, cat. DMAP, Et_3N, CH_2Cl_2; (d) NaOH, THF–H_2O, then dil H_2SO_4; (e) EDCI, cat. DMAP, THF–pyridine, then CH_3COCl; (f) HF–pyridine, THF; (g) NIS, cat. TfOH, CH_2Cl_2, −40 °C.

2.1.2. Synthesis of linear tri- and tetrasaccharides. Linear tri-and tetrasaccharides were prepared from **12** by an iterative glycosylation–deprotection sequence (Scheme 2). Glycosylation of **12** with 5 equiv of the thioethyl glycoside donor **13**[30] using *N*-iodosuccinimide (NIS) and cat. trifluoromethanesulfonic acid (TfOH) in acetonitrile at −40 °C followed by precipitation into methanol afforded polymer-bound trisaccharide **14**. Hydrolytic degradation of the support with NaOH in H_2O–THF at 65 °C and treatment with diazomethane[31] afforded the trisaccharide **15** as a mixture of anomers in 47% yield after chromatographic purification. Similarly, treatment of **12** with the activated thioglycoside **10**, silyl deprotection with HF–pyridine, and further glycosylation of trisaccharide **16** with **13** afforded the tetrasaccharide **18** in 26% isolated yield as a mixture of anomers following hydrolytic liberation of the product from the polymer support. The complexity of the NMR spectra of the oligosaccharide products **15** and **18** did not allow the ratios of the individual anomers to be determined. However, in the case of **15** small amounts of pure trisaccharides were obtained and their gate-decoupled ^{13}C NMR spectra were consistent with α,α,α (δ 98.4 ($^1J_{C-H}$ = 168.5 Hz), 100.7 ($^1J_{C-H}$ = 171.7 Hz), 102.4 ($^1J_{C-H}$ = 164.5 Hz)) and α,β,α (δ 98.4 ($^1J_{C-H}$ = 173.4 Hz), 98.5 ($^1J_{C-H}$ = 156.8 Hz), 100.2 ($^1J_{C-H}$ = 173.4 Hz)) configurations.[32]

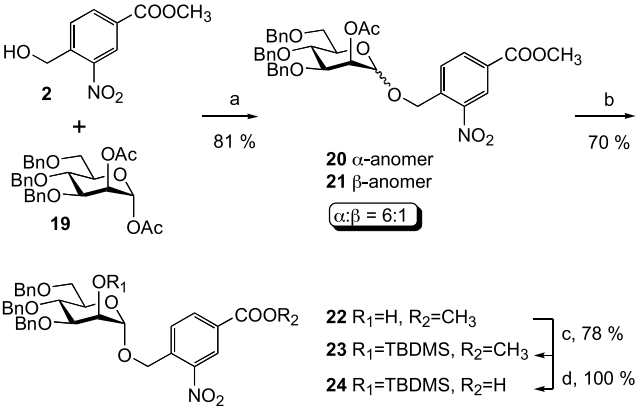
2.2. O-2 Glycoside bond: disaccharide synthesis

Mannose–mannose α-glycosidic bonds in *N*-glycans occur

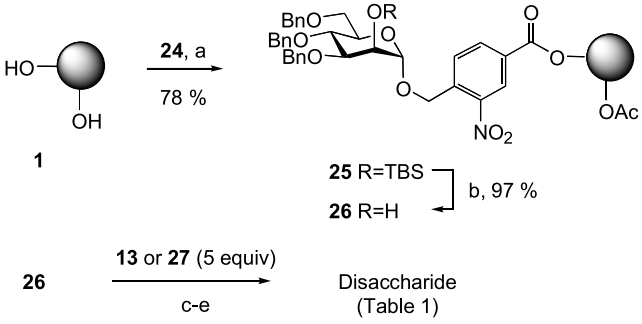


Scheme 2. Reagents and conditions: (a) NIS-cat. TfOH, CH_3CN, −40 °C; (b) HF·pyridine, THF; (c) NaOH, THF–H_2O, 65 °C, then dil H_2SO_4; (d) CH_2N_2, ether.

most often at C-6, C-2 and more rarely at C-3 hydroxyl groups.[23] Accordingly, disaccharides were elaborated from C-2 on the hyperbranched polymer support. The 2-nitrobenzyl linker-mannose conjugate (**24**) was prepared from 1,2-di-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-mannose[33] (**19**) via a $BF_3 \cdot OEt_2$-promoted glycosylation with linker alcohol **2** as shown in Scheme 3. The acetyl protected mannoside was formed as a mixture of two anomers (**20**, **21**) in a 6:1 ratio. It is noteworthy that hydrolysis of the acetoxy group in β-anomer **21** proceeded much slower than for α-anomer **20**, presumably a consequence of the increased steric bulk of the β-substituent. Therefore, selective hydrolysis of the α-anomer **20** provided **22** in 70% isolated yield as a single anomer, along with 7% of recovered **21**. The β-configuration of **21** was confirmed by gate-decoupled ^{13}C NMR (δ 99.4, $^1J_{C-H} = 155.3$ Hz).[32] Silylation of the 2-hydroxyl group in **22** with TBDMSOTf and lutidine[34] followed by saponification of the methyl ester provided the carboxylic acid **24**, which was coupled with EDCI to the Boltorn™ H-50 (**1**) polymer support in 86% yield (loading level: 0.64 mmol/g).[29b] Deprotection of the axial 2-OTBDMS group in the product (**25**) proved to be significantly more difficult in comparison with the 6-OTBDMS analog **11**, most likely for steric reasons (Scheme 4). Accordingly, exposure to a large excess of HF–pyridine in THF at reflux was required to achieve 95% deprotection of the TBDMS groups. Fortuitously, the factors responsible for hindering C-2 desilylation did not impede glycosylation of the C-2 hydroxyl group in the polymer-bound acceptor **26**. Accordingly, glycosylation of **26** with donors **13** and **27**[35] provided disaccharides **28** in 41% and **29** in 63% isolated yield as pure α-anomers (Scheme 4, Table 1).

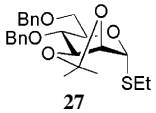
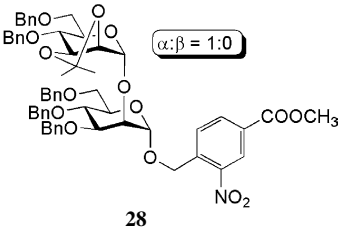
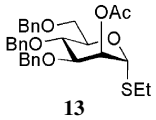
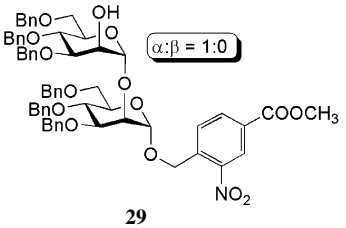


Scheme 3. Reagents and conditions: (a) $BF_3 \cdot OEt_2$, CH_2Cl_2, 0 °C; (b) K_2CO_3, MeOH–THF (from **20**; **21** was recovered in 7% isolated yield); (c) TBDMSOTf, 2,6-lutidine, CH_2Cl_2; (d) NaOH, THF–H_2O, then dil H_2SO_4.



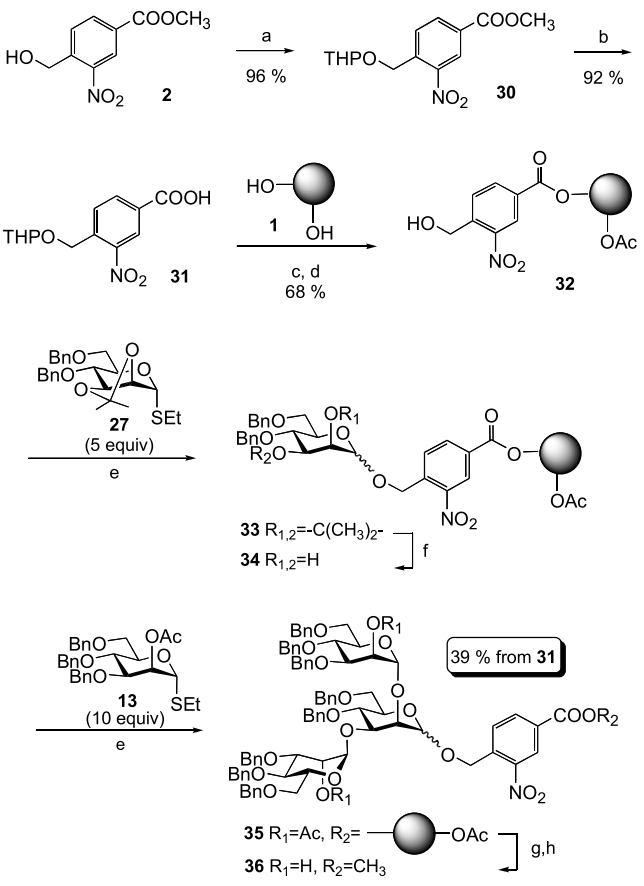
Scheme 4. Reagents and conditions: (a) EDCI, cat. DMAP, THF–pyridine, then excess CH_3COCl; (b) HF·pyridine, THF, 65 °C; (c) NIS-cat. TfOH, CH_3CN, −40 °C; (d) KOH, THF–H_2O, 65 °C, then dil H_2SO_4; (e) CH_2N_2, ether.

Table 1. Disaccharides extended from C-2 (Scheme 4)

Donor	Disaccharide	Yield (%)
 **27**	 **28**	63
 **13**	 **29**	41

2.3. Synthesis of 2,3-branched trisaccharides

The synthesis of 2,3-branched oligosaccharides was addressed using 2,3-isopropylidene thioethyl donor **27** as a protected branching unit (Scheme 5). Accordingly, polymer-supported linker **32**, prepared by EDCI mediated coupling of 3-nitro-4-(tetrahydropyran-2-yloxymethyl)benzoic acid, **31**, to the Boltorn™ H-50 polymer (loading 1.36 mmol/g)[29b] and acid-catalyzed THP deprotection, was glycosylated with the glycosyl donor **27**. Cleavage of the 2,3-isopropylidene protecting group in **33** with 1,3-propanedithiol–trifluoroacetic acid (TFA) followed by simultaneous glycosylation at O-2 and O-3 with donor provided supported trisaccharide **35** after precipitation with methanol. Release of the product by treatment with aqueous KOH and methylation with diazomethane afforded branched trisaccharide **36** as a mixture of anomers in 39% overall yield from **32**, after chromatographic purification. The ratios of the individual anomers could not be determined due to the complexity of the ^{1}H NMR spectrum of **36**. However, inspection of the gate-decoupled ^{13}C NMR spectrum[32] revealed that α,α,α-stereoisomer was the major constituent of the mixture.



Scheme 5. Reagents and conditions: (a) DHP, cat. TsOH, CH_2Cl_2; (b) KOH, H_2O–THF, then dil H_2SO_4; (c) EDCI, cat. DMAP, THF–pyridine, then excess CH_3COCl; (d) cat. HCl, MeOH–CH_2Cl_2; (e) NIS-cat. TfOH, CH_3CN, −40 °C; (f) $HS(CH_2)_3SH$, TFA, CH_2Cl_2; (g) KOH, THF–H_2O, 65 °C, then dil H_2SO_4; (h) CH_2N_2, ether.

3. Conclusion

This work demonstrates the potential for hyperbranched polymers to serve as high loading, soluble supports for multistep synthesis of large, complex molecules. We prepared linear and branched di-, tri-, and tetrasaccharides on the hyperbranched polyester Boltorn™ H-50 as a soluble support in good yields on a preparative scale. Boltorn polyester shares numerous advantageous characteristics with linear polymers previously used as soluble supports. For example, separation from soluble by-products and excess of reagents can be accomplished by simple precipitation from a poor solvent (methanol).[36] The high solubility of all protected intermediates in most organic solvents ensured that synthetic protocols and analytical techniques used for conventional chemistry (solution ^{1}H and ^{13}C NMR and MALDI-TOF MS) could be applied to the supported reactions and intermediates with minimal changes, and specialized equipment was not required. In contrast to the traditional linear soluble supports, the high loading capacity (theoretically 8.8 mmol/g) and low cost (commercially available at US$ 5/kg) allows economical, large scale preparations to be possible. As a potential drawback, the base-labile nature of the polyester backbone limits the range of reactions and conditions applicable to Boltorn polymer supports. However, the preparation of new, more chemically robust hyperbranched polymers from readily available starting materials should remedy this problem.

4. Experimental

4.1. General

THF was distilled from sodium/benzophenone ketyl; CH_3CN, CH_2Cl_2 and pyridine were distilled from calcium hydride; methanol was dried over 3 Å molecular sieves. Chromatographic separations were performed on silica gel 60 (230–400 mesh, 60 Å) using the flash technique in the indicated solvents as mobile phase. TLC was performed on silica gel 60-F_{254} plates. Visualization of the compounds was accomplished by UV-detection (254 nm) or staining with 10% H_2SO_4. The solvents used for extraction and

column chromatography were removed on a rotary evaporator (40 mm Hg). All glycosylation reactions were performed under anhydrous conditions under an argon atmosphere. The precipitated polymers were centrifuged in an Eppendorf centrifuge at 5000 rpm for time sufficient to achieve complete precipitation (5–60 min). NMR spectra were recorded at Bruker DPX-250, AC-300, DPX-400 and DRX-500 spectrometers, referenced to the residual deuterated solvent peaks and the chemical shifts expressed with respect to tetramethylsilane (TMS). MALDI-TOF mass spectra were recorded using 2,3-dihydrobenzoic acid as matrix in THF. Elemental analyzes were obtained at Atlantic Microlabs, Norcross, GA. All samples for elemental analysis were dried for 16 h in vacuum over P_2O_5 at 56 °C (refluxing acetone).

4.1.1. 4-Methoxycarbonyl-2-nitrobenzyl 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α/β-D-mannopyranoside (4). Methyl 4-hydroxymethyl-2-nitrobenzoate **2** (3.51 g, 6.6 mmol, 1 equiv) and **3** (1.52 g, 7.2 mmol, 1.09 equiv) and were dissolved in dry CH_2Cl_2 (12 mL). The solution was cooled in an ice bath and $BF_3 \cdot OEt_2$ (4.1 mL, 4.68 g, 33 mmol, 5 equiv) were added. After stirring at 0 °C for 6 h, the solution was diluted with CH_2Cl_2 (50 mL), washed with water (50 mL), saturated $NaHCO_3$ solution (2×100 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$) and the solvent was evaporated. The acetate **4** (3.54 g, 5.1 mmol, 78%) was obtained as a pale yellow foam after column chromatography (toluene/ether, 6:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.07 (s, 3H), 3.78–3.85 (m, 2H), 3.92–4.05 (m, 5H), 4.14–4.39 (m, 2H), 4.60–5.19 (m, 9H), 7.54 (d, J=8.1 Hz, 1H), 8.24 (dd, J=8.1, 1.7 Hz, 1H), 8.70 (d, J=1.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 52.6, 63.3, 65.6, 70.7, 71.8, 72.2, 74.3, 74.3, 75.1, 79.5, 97.9, 125.8, 127.5–129.2 (multiple carbons), 130.5, 133.9, 137.8, 138.0, 138.2, 147.1, 164.6, 170.7. Anal. Calcd for $C_{38}H_{39}NO_{11}$: C, 66.56; H, 5.69; N, 2.04. Found: C, 66.82; H, 5.69; N, 2.10.

4.1.2. 4-Methoxycarbonyl-2-nitrobenzyl 2,3,4-tri-*O*-benzyl-α/β-D-mannopyranoside (5). The acetate **4** (7.17 g, 10.5 mmol, 1 equiv) was dissolved in a mixture of THF (15 mL) and methanol (45 mL) and cooled in an ice bath. Finely powdered K_2CO_3 (2.77 g, 20 mmol, 1.90 equiv) was added and the mixture stirred for 1 h 15 min. The solution was acidified with 10% aqueous H_2SO_4 (5 mL), the organic solvents were removed and the organic material was extracted in ethyl acetate (100 mL). The organic layer was washed with saturated $NaHCO_3$ solution (2×50 mL), brine (30 mL), dried ($MgSO_4$) and evaporated. The alcohol **5** (5.06 g, 7.88 mmol, 75%) was obtained as pale yellow foam after column chromatography (hexane/ethyl acetate, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96 (broad s, 1H), 3.75–3.81 (m, 2H), 3.85–4.08 (m, 8H), 4.61–5.09 (m, 8H), 7.08–7.43 (m, 15H), 7.30–7.48 (m, 15H), 7.61 (d, J=8.1 Hz, 1H), 8.23 (dd, J=8.1, 1.5 Hz, 1H), 8.69 (d, J=1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.7, 62.1, 65.8, 72.3, 72.9, 72.9, 74.5, 74.5, 75.2, 79.5, 98.4, 125.8, 127.5, 127.5–129.2 (multiple carbons), 130.5, 134.0, 137.9, 138.1, 138.2, 138.2, 147.1, 164.6. Anal. Calcd for $C_{36}H_{37}NO_{10}$: C, 67.17; H, 5.79; N, 2.18. Found: C, 67.44; H, 5.91; N, 1.93.

4.1.3. 4-Methoxycarbonyl-2-nitrobenzyl 2,3,4-tri-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-α/β-D-mannopyranoside (6). To a solution of **5** (2.46 g, 3.8 mmol, 1 equiv) in dry CH_2Cl_2 (10 mL) and Et_3N (2.8 mL), DMAP (50 mg, 0.4 mmol, 0.11 equiv) and TBDMSCl (0.60 g, 4.0 mmol, 1.05 equiv) were added in succession and the solution stirred for 4 h. The mixture was diluted with ethyl acetate (50 mL), washed successively with water (30 mL), 5% H_2SO_4 (3×30 mL), saturated $NaHCO_3$ solution (2×30 mL), brine (20 mL), dried ($MgSO_4$) and evaporated. After column chromatography (hexane/ethyl acetate, 7:1), **6** (2.63 g, 3.5 mmol, 91%) was obtained as a yellow foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.13 (s, 6H), 0.94 (s, 9H), 3.63–3.67 (m, 1H), 3.91–4.01 (m, 3H), 4.02–4.06 (m, 5H), 4.70–5.16 (m, 8H), 7.24–7.36 (m, 15H), 7.69 (d, J=8.1 Hz, 1H), 8.29 (dd, J=8.1, 1.3 Hz, 1H), 8.75 (d, J=1.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.77, −4.73, 18.2, 26.3, 53.2, 63.8, 65.9, 72.8, 72.9, 73.1, 74.6, 75.1, 75.4, 80.0, 98.2, 126.3, 128.1–128.8 (multiple carbons), 129.1, 130.9, 134.5, 138.7, 138.8, 139.0, 139.2, 147.6, 165.2. Anal. Calcd for $C_{42}H_{51}NO_{10}Si$: C, 66.56; H, 6.78; N, 1.85. Found: C, 66.60; H, 6.63; N, 1.74.

4.1.4. 4-Oxycarbonyl-2-nitrobenzyl 2,3,4-tri-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-α/β-D-mannopyranoside (7). Solution of **6** (2.63 g, 3.47 mmol, 1 equiv) in THF (30 mL) was mixed with freshly prepared 2 M aqueous KOH solution (30 mL). The mixture was stirred for 6 h, then acidified with 10% H_2SO_4 (pH=3) and extracted with ethyl acetate (3×30 mL), washed with water (5×30 mL), dried ($MgSO_4$) and evaporated. The carboxylic acid **7** (2.48 g, 3.33 mmol, 96%) was obtained as pale yellow foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.13 (s, 6H), 0.94 (s, 9H), 3.63–3.67 (m, 1H), 3.91–4.01 (m, 3H), 4.02–4.06 (m, 5H), 4.70–5.16 (m, 8H), 7.24–7.36 (m, 15H), 7.69 (d, J=8.1 Hz, 1H), 7.80 (broad s, 1H), 8.29 (dd, J=8.1, 1.3 Hz, 1H), 8.75 (d, J=1.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.83, −4.73, 18.2, 26.3, 53.2, 63.8, 65.9, 72.8, 74.7, 73.1, 75.2, 75.3, 75.7, 89.9, 98.1, 126.3, 128.1–128.8 (multiple carbons), 129.1, 130.9, 134.5, 138.7, 138.8, 139.0, 139.2, 147.5, 168.9. Anal. Calcd for $C_{41}H_{49}NO_{10}Si$: C, 66.20; H, 6.64; N, 1.88. Found: C, 66.47; H, 6.64; N, 1.71.

4.1.5. 4-Methoxycarbonyl-2-nitrobenzyl 6-(6-(3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-2,3,4-tri-*O*-benzyl-α/β-D-mannopyranosyl)-2,3,4-tri-*O*-benzyl-α/β-D-mannopyranoside (15). A. To a solution of **7** (2.30 g, 3.09 mmol, 1 equiv), Boltorn H-50 polymer **1** (1.41 g, 12.4 mmol OH-groups, 4 equiv) and DMAP (42 mg, 0.34 mmol, 0.11 equiv) in dry pyridine (3.7 mL) and dry THF (4.8 mL), EDCI (0.65 g, 3.40 mmol, 1.10 equiv) was added and the mixture stirred for 16 h. It was then cooled in an ice bath and acetyl chloride (0.83 mL, 0.92 g, 11.7 mmol, 3.78 equiv) was added dropwise. The mixture was warmed up to room temperature and stirred for additional 8 h, poured in water (100 mL) and extracted with ethyl acetate (2×30 mL). The combined organic extracts were washed with 10% H_2SO_4 (2×30 mL), saturated $NaHCO_3$ solution (2×30 mL), brine (30 mL), dried ($MgSO_4$) and evaporated, affording **8** (4.20 g, 2.60 mmol, 84%, loading level: 0.62 mmol/g) as pale yellow foam.

B. A solution of **8** from the previous step in THF (25 mL) was then treated with HF·pyridine (0.83 g, 8.33 mmol,

3.19 equiv) and the solution stirred for 16 h. The solution was diluted with ethyl acetate (50 mL) and washed with water (50 mL), 10% H_2SO_4 (2×20 mL) and saturated $NaHCO_3$ solution (2×20 mL). After drying ($MgSO_4$) and evaporation, **9** (3.80 g) was obtained as a pale yellow foam. This material was used directly for the next step.

C. The polymer-immobilized acceptor **9** (3.80 g, 2.61 mmol, 1 equiv) and the thioethyl glycoside **10** (6.09 g, 10.40 mmol, 4 equiv) were dissolved in dry CH_2Cl_2 (10 mL). After a clear solution had formed, the flask was cooled to −40 °C. NIS (2.56 g, 11.40 mmol, 4.40 equiv) was added, followed by TfOH (90 μL, 156 mg, 1.04 mmol, 0.40 equiv). After stirring for 30 min at −40 °C, the mixture was diluted with CH_2Cl_2 (50 mL), washed with 10% $NaHSO_3$ solution (100 mL), saturated $NaHCO_3$ solution (50 mL), brine (10 mL), dried ($MgSO_4$) and concentrated in vacuum. The crude polymer was dissolved in CH_2Cl_2 (10 mL) and precipitated out of methanol (250 mL). After decanting of the supernatant, rinsing with methanol (3×10 mL) and drying in vacuum, the disaccharide **11** (4.36 g, mmol, 99%, loading level: 0.59 mmol/g) was obtained as a pale yellow foam.

D. From **11** (4.22 g, 2.57 mmol, 1 equiv), dissolved in THF (20 mL) and HF·pyridine (0.57 g, 5.66 mmol, 2.20 equiv), **12** (3.52 g, mmol, 88%, loading level: 0.64 mmol/g) was obtained as a yellow foam following the procedure (Part B) for preparation of **9**.

E. The glycosyl acceptor **12** (156 mg, 0.1 mmol, 1 equiv) and the glycosyl donor **13** (0.27 g, 0.5 mmol, 5 equiv) were dissolved in dry CH_3CN (0.6 mL). After stirring at room temperature for 15 min, the mixture was cooled to −40 °C. NIS (135 mg, 0.6 mmol, 6 equiv) and TfOH (2 μL, 3.4 mg, 0.022 mmol, 0.20 equiv) were added in succession. After stirring for 20 min at −40 °C, the reaction mixture was diluted with ethyl acetate (5 mL) and washed with 10% $NaHSO_3$ solution (5 mL), saturated $NaHCO_3$ solution (5 mL) and brine (2 mL). After drying ($MgSO_4$) and concentrating in vacuum, the polymer-immobilized trisaccharide **14** (194 mg) was purified by dissolving in CH_2Cl_2 (0.5 mL) and precipitating out of methanol (15 mL), decanting the supernatant, rinsing with methanol (3× 3 mL) and drying under high vacuum.

F. The immobilized trisaccharide **14** was heated at reflux in a mixture of THF (2 mL) and 2 M aqueous NaOH solution (2 mL) for 16 h. H_2SO_4 (10%) was added (pH=3) and the product was extracted into ethyl acetate (3×5 mL). The combined organic extracts were washed with water (5× 10 mL), brine (5 mL), dried ($MgSO_4$) and evaporated. The crude product was dissolved in diethyl ether (2 mL) and an excess of freshly prepared diazomethane solution in diethyl ether was added dropwise until the evolution of N_2 had ceased. The excess of diazomethane was destroyed by dropwise addition of glacial acetic acid. The ether solution was washed with saturated $NaHCO_3$ solution (2×5 mL), brine (5 mL), dried ($MgSO_4$) and evaporated. The trisaccharide **15** (73 mg, 0.047 mmol, 47%) was obtained as a pale yellow foam after chromatography on silica gel (hexane/ethyl acetate, 2:1). MALDI-TOF MS: *m/z* calcd for $C_{90}H_{93}NNaO_{20}$ $(M+Na)^+$: 1530.62, found: 1525.8. Anal. Calcd for $C_{90}H_{93}NO_{20}$: C, 71.65; H, 6.21; N, 0.93. Found: C, 71.25; H, 6.27; N, 0.97.

A small portion of the product was chromatographically separated into two fractions. The (α,α,α)-trisaccharide: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.89 (broad s, 1H), 3.63–4.03 (m, 22H), 4.12–4.17 (m, 1H), 4.51–4.96 (m, 22H), 5.03–5. 15 (m, 3H), 7.25–7.49 (m, 45H), 7.58 (d, J=8.1 Hz, 1H), 8. 23 (dd, J=8.1, 1.5 Hz, 1H), 8.66 (d, J=1.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 53.2, 66.2, 67.0, 68.1, 68.9, 69. 4, 71.5, 71.6, 71.8, 72.7, 72.9, 73.3, 73.8, 74.3, 74.5, 74.7, 74.7, 74.9, 75.1, 75.3, 75.5, 75.5, 75.7, 79.7, 80.2, 82.7, 98. 4 ($^1J_{C-H}$=168.5 Hz), 100.7 ($^1J_{C-H}$=171.7 Hz), 102.4 ($^1J_{C-H}$=164.5 Hz), 126.4, 128.0–128.9 (multiple carbons), 130.9, 134.5, 138.4–139.2 (multiple carbons), 147.4, 165.2.

The (α,β,α)-trisaccharide: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1. 89 (broad s, 1H), 3.63–4.03 (m, 22H), 4.12–4.17 (m, 1H), 4. 51–4.96 (m, 22H), 5.03–5.15 (m, 3H), 7.25–7.49 (m, 45H), 7.59 (d, J=8.0 Hz, 1H), 8.22 (dd, J=8.0, 1.3 Hz, 1H), 8.70 (d, J=1.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 53.2, 60. 8, 66.1, 67.4, 67.5, 68.4, 69.3, 71.6, 71.8, 71.9, 72.0, 72.8, 73.1, 73.5, 73.8, 74.7, 74.8, 74.9, 75.1, 75.4, 75.4, 75.6, 75. 6, 80.0, 80.0, 80.2, 98.4 ($^1J_{C-H}$=173.4 Hz), 98.5 ($^1J_{C-H}$= 156.8 Hz), 100.2 ($^1J_{C-H}$=173.4 Hz), 126.3, 127.9–128.9 (multiple carbons), 130.1, 134.5, 138.4–138.8 (multiple carbons), 147.8, 165.2.

4.1.6. 4-Methoxycarbonyl-2-nitrobenzyl 6-(6-(6-(3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-2,3,4-tri-*O*-benzyl-α/β-D-mannopyranosyl)-2,3,4-tri-*O*-benzyl-α/β-D-mannopyranosyl)-2,3,4-tri-*O*-benzyl-α/β-D-mannopyranoside (18). From the glycosyl acceptor **12** (321 mg, 0.2 mmol, 1 equiv) and the glycosyl donor **10** (0.68 g, 1 mmol, 5 equiv) in dry CH_3CN (1 mL), following the procedure for preparation of compound **14**, polymer-supported, 6-*O*-TBDMS-protected trisaccharide (432 mg) was obtained as a pale yellow foam after precipitation from methanol (30 mL, containing five drops Et_3N), decanting of the supernatant, washing with methanol (3×2 mL) and drying in vacuum. The polymer was treated with HF·pyridine (0.5 mL, 0.5 g, 5.0 mmol, 2.50 equiv) in THF (3 mL), following the procedure for compound **12**. From the glycosyl acceptor **16** (obtained as described above, 0.1 mmol, 1 equiv) and the glycosyl donor **13** (0.54 g, 1 mmol, 5 equiv) in dry CH_3CN (1 mL), following the procedure for preparation of **14**, the polymer-supported tetrasaccharide **17** (534 mg) was obtained as a pale yellow foam after precipitation into methanol (30 mL), decanting of the supernatant, rinsing with methanol (3×2 mL) and drying in vacuum. From **17** (536 mg), following the general procedure for compound **15**, the tetrasaccharide (mixture of anomers) **18** (100 mg, 0.52 mmol, 26%) was obtained as a pale yellow foam after chromatography on silicagel (hexane/ethyl acetate, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (broad s, 1H), 3.05–4.05 (m, 33H), 4.22–5.13 (m, 33H), 6.94–7.32 (m, 60H), 7.42 (m, 1H), 8.11 (m, 1H), 8.68 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 53.2, 66.8–82.0 (multiple carbons), 98.4, 98.5, 98.9, 102.2, 126.4, 127.8–128.8 (multiple carbons), 129.3, 134.4, 138.7–139.0 (multiple carbons), 147.8, 165.2. MALDI-TOF MS: *m/z* calcd for $C_{117}H_{121}NNaO_{25}$ $(M+Na)^+$: 1962.81, found

1957.6. Anal. Calcd for $C_{117}H_{121}NO_{25}$: C, 72.39; H, 6.28; N, 0.72. Found: C, 72.55; H, 6.19; N, 0.82.

4.1.7. 4-Methoxycarbonyl-2-nitrobenzyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α/β-D-mannopyranoside (20, 21). From **19** (4.74 g, 22.4 mmol, 1.20 equiv) and **2** (10.0 g, 18.7 mmol, 1 equiv), activated with $BF_3 \cdot OEt_2$ (6.0 mL, 6.92 g, 48.8 mmol, 2.61 equiv) in dry CH_2Cl_2 (30 mL), **20** and **21** (10.4 g, 15.1 mmol, 81%, α/β 6:1) were obtained as pale yellow foam after column chromatography (toluene/ether, 5:1) as described for compound **4**. The major anomer (**20**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.22 (s, 3H), 3.77 (m, 1H), 3.82–3.85 (m, 3H), 3.97–4.03 (m, 5H), 4.08 (m, 1H), 4.55–4.82 (m, 8H), 4.92 (d, $J=10.7$ Hz, 1H), 5.00–5.06 (m, 2H), 5.19 (m, 1H), 5.34 (s, 1H), 5.49 (m, 1H), 7.23–7.40 (m, 15H), 7.79 (d, $J=8.1$ Hz, 1H), 8.32 (dd, $J=8.1$, 1.7 Hz, 1H), 8.77 (d, $J=1.7$ Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 53.2, 66.3, 67.0, 69.1, 72.4, 72.7, 74.0, 74.6, 75.7, 78.2, 98.2, 126.4, 128.1–128.9 (multiple carbons), 129.2, 131.1, 134.7, 138.2, 138.6, 138.7, 147.5, 165.2, 170.9. Anal. Calcd for $C_{38}H_{39}NO_{11}$: C, 66.56; H, 5.73; N, 2.04. Found: C, 6.47; H, 5.47; N, 1.97.

4.1.8. 4-Methoxycarbonyl-2-nitrobenzyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranoside (22) and 4-methoxycarbonyl-2-nitrobenzyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-mannopyranoside (21 recovered). Following the procedure for compound **5**, acetate deprotection of the mixture of **20** and **21** (10.4 g, 15.2 mmol, 1 equiv) with K_2CO_3 (2.10 g, 15 mmol, 1 equiv) in dry THF (15 mL) and dry methanol (50 mL) after 1 h 45 min afforded **22** (6.83 g, 10.6 mmol, 70%) as a pale yellow foam after column chromatography (hexane/ethyl acetate, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (broad s, 1H), 3.60–3.72 (m, 2H), 3.85 (m, 2H), 3.92 (s, 3H), 4.04 (s, 1H), 4.46 (d, $J=9.4$ Hz, 1H), 4.47 (d, $J=12.2$ Hz, 1H), 4.58 (d, $J=12.1$ Hz, 1H), 4.68 (s, 2H), 4.77 (d, $J=10.7$ Hz, 1H), 4.77 (d, $J=10.7$ Hz, 1H), 4.90–5.06 (m, 3H), 7.13–7.32 (m, 15H), 7.65 (d, $J=8.1$ Hz, 1H), 8.19 (dd, $J=8.1$, 1.7 Hz, 1H), 8.63 (d, $J=1.7$ Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 53.2, 66.3, 68.7, 69.1, 72.2, 72.6, 74.0, 74.5, 75.7, 80.3, 99.8, 126.4, 128.0–129.0 (multiple carbons), 129.3, 131.1, 134.5, 138.2, 138.5, 138.8, 147.7, 165.2. Anal. Calcd for $C_{36}H_{37}NO_{10}$: C, 67.17; H, 5.79; N, 2.18. Found: C, 67.08; H, 5.93; N, 2.11.

Unreacted **21** (0.70 g, 1.1 mmol, 7%) was recovered as a pale yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 3H), 3.46 (m, 1H), 3.64–3.74 (m, 3H), 3.84–3.92 (m, 5H), 4.43–4.85 (m, 9H), 4.92 (m, 1H), 5.06 (d, $J=19.2$ Hz, 1H), 5.28 (d, $J=19.2$ Hz, 1H), 5.69 (d, $J=3.4$ Hz, 1H), 7.14–7.30 (m, 15H), 7.84 (d, $J=10.2$ Hz, 1H), 8.22 (dd, $J=10.2$, 2.0 Hz, 1H), 8.65 (d, $J=2.0$ Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 53.2, 68.3, 68.5, 69.3, 72.1, 74.0, 74.7, 75.7, 76.2, 80.6, 99.4, 126.2, 128.1–128.9 (multiple carbons), 129.3, 130.8, 134.7, 138.0, 138.6, 139.6, 147.1, 165.3, 170.1.

4.1.9. 4-Oxycarbonyl-2-nitrobenzyl 3,4,6-tri-*O*-benzyl-2-*O*-*tert*-butyldimethylsilyl-α-D-mannopyranoside (24). A. 4-Methoxycarbonyl-2-nitrobenzyl 3,4,6-tri-*O*-benzyl-2-*O*-*tert*-butyldimethylsilyl-α-D-mannopyranoside (**23**)

To a solution of **22** (6.0 g, 9.3 mmol, 1.00 equiv) in dry CH_2Cl_2 (45 mL), 2,6-lutidine (2.1 mL, 1.93 g, 19 mmol, 2.04 equiv) were added, followed by dropwise addition of TBSOTf (2.6 mL, 2.99 g, 11.3 mmol, 1.22 equiv). After 5 h, the solution was diluted with CH_2Cl_2 (150 mL), washed with 10% aqueous H_2SO_4 (100 mL), saturated $NaHCO_3$ solution (2×150 mL), brine (50 mL), dried ($MgSO_4$) and evaporated. After column chromatography (hexane/ethyl acetate, 6:1), **23** (5.5 g, 7.25 mmol, 78%) was obtained as a yellow foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.49 (s, 3H), −0.43 (s, 3H), 0.77 (s, 9H), 3.45–4.00 (m, 10H), 4.38–4.84 (m, 9H), 4.99 (d, $J=9.3$ Hz, 1H), 7.03–7.58 (m, 15H), 7.57 (d, $J=8.1$ Hz, 1H), 8.07 (dd, $J=8.1$, 1.6 Hz, 1H), 8.54 (d, $J=1.6$ Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.88, −1.28, 18.6, 26.2, 53.1, 66.3, 69.7, 70.2, 72.8, 73.5, 73.7, 74.9, 75.5, 80.2, 101.2, 126.3, 127.8–128.8 (multiple carbons), 129.3, 131.0, 134.5, 138.8, 139.0, 139.0, 147.7, 165.2.

B. 4-Oxycarbonyl-2-nitrobenzyl 3,4,6-tri-*O*-benzyl-2-*O*-*tert*-butyldimethylsilyl-α-D-mannopyranoside (**24**)

Following the procedure for compound **7**, from **23** (3.60 g, 4.75 mmol, 1.00 equiv) dissolved in THF (23 mL) and 2 M aqueous KOH solution (23 mL) after stirring for 4 h, **24** (3.53 g, 4.75 mmol, 100%) was obtained as a pale yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.14 (s, 3H), 0.19 (s, 3H), 0.97 (s, 9H), 3.80–4.20 (m, 10H), 4.57–5.02 (m, 9H), 5.18 (d, $J=9.3$ Hz, 1H), 7.23–7.47 (m, 15H), 7.77 (d, $J=8.2$ Hz, 1H), 8.26 (dd, $J=8.2$, 1.5 Hz, 1H), 8.69 (d, $J=1.5$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.25, −3.92, 18.7, 26.3, 66.5, 69.7, 70.2, 72.9, 73.5, 73.7, 75.0, 75.6, 80.1, 101.1, 126.8, 128.0–128.9 (multiple carbons), 129.3, 130.5, 134.9, 138.5, 138.7, 138.9, 139.9, 147.7, 168.5. Anal. Calcd for $C_{41}H_{49}NO_{10}Si$: C, 66.20; H, 6.64; N, 1.88. Found: C, 66.00; H, 6.72; N, 1.87.

4.1.10. 4-Methoxycarbonyl-2-nitrobenzyl 2-(4,6-di-*O*-benzyl-2,3-*O*-isopropylidene-α-D-mannopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (28). Following the procedure for compound **8**, the carboxylic acid **24** (1.33 g, 1.79 mmol, 1.00 equiv) and Boltorn H-50 polymer (0.82 g, 7.16 mmol, 4.00 equiv) were coupled in dry pyridine (2 mL) and dry THF (7 mL) using EDCI (0.38 g, 1.97 mmol, 1.10 equiv) and DMAP (0.02 g, 0.18 mmol, 0.10 equiv). The polymer was then capped with acetyl chloride (0.51 mL, 0.71 g, 7.16 mmol, 400 mol%). The polymer-immobilized product **25** (2.30 g, 1.54 mmol, 86%) was obtained as a pale yellow foam after the usual work-up and precipitation from methanol (50 mL), decanting of the supernatant, rinsing with methanol (3×5 mL) and drying in high vacuum. To a solution of **25** (1.83 g, 1.24 mmol, 1.00 equiv) in THF (7 mL), HF·pyridine (0.76 g, 7.7 mmol, 6.21 equiv) was added and the solution stirred for 12 h at reflux. After cooling to room temperature, the mixture was diluted with ethyl acetate (75 mL) and washed with water (50 mL), 10% aqueous H_2SO_4 (2×50 mL), saturated $NaHCO_3$ solution (2×50 mL) and brine (50 mL). After drying ($MgSO_4$) and evaporation, **26** was obtained as a pale yellow foam (1.46 g, 1.15 mmol, 94%, loading level: 0.79 mmol/g). The glycosylation-cleavage procedure used compounds **14** and **15** was applied using 2 M aqueous KOH solution. From glycosyl acceptor **26** (126 mg, 0.1 mmol, 1.00 equiv) and glycosyl donor **27** (222 mg, 0.5 mmol,

5.00 equiv), **28** (63 mg, 0.063 mmol, 63%) was isolated after column chromatography (hexanes/ethyl acetate, 3:1) as a pale yellow foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 (s, 3H), 1.53 (s, 3H) 3.49–3.80 (m, 7H), 3.90–3.98 (m, 6H), 4.18 (s, 1H), 4.30–4.38 (m, 2H), 4.49–4.55 (m, 5H), 4.65–5.04 (m, 6H), 5.14 (d, J=1.8 Hz), 5.40 (s, 1H), 7.15–7.35 (m, 25H), 7.60 (d, J=8.1 Hz, 1H), 8.17 (dd, J=8.1, 1.7 Hz, 1H), 8.68 (d, J=1.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.9, 28.5, 53.1, 66.1, 69.2, 69.5, 70.1, 72.7, 73.0, 73.1, 73.8, 73.8, 74.4, 74.4, 75.0, 75.6, 76.3, 76.3, 79.0, 79.6, 99.4 ($^1J_{C-H}$=173.1 Hz), 99.4 ($^1J_{C-H}$=173.1 Hz), 109.7, 126.2, 127.7–128.7 (multiple carbons), 128.9, 134.5, 138.6–138.7 (multiple carbons), 147.3, 165.3. Anal. Calcd for $C_{59}H_{63}NO_{15}$: C, 69.06; H, 6.19; N, 1.37. Found: C, 68.66; H, 6.31; N, 1.36.

4.1.11. 4-Methoxycarbonyl-2-nitrobenzyl 2-(3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (29). The glycosylation-cleavage procedure for compounds **14** and **15** was applied using 2 M aqueous KOH. From glycosyl acceptor **26** (126 mg, 0.1 mmol, 1.00 equiv) and glycosyl donor **13** (268 mg, 0.5 mmol, 5.00 equiv), **29** (44 mg, 0.041 mmol, 41%) was isolated after column chromatography (hexanes/ethyl acetate, 2:1) as a pale yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (broad s, 1H), 3.65–3.95 (m, 15H), 4.03–4.14 (m, 2H), 4.65–4.80 (m, 14H), 5.06–5.13 (m, 3H), 7.12–7.33 (m, 30H), 7.58 (d, J=8.1 Hz, 1H), 8.17 (dd, J=8.1, 1.7 Hz, 1H), 8.65 (d, J=1.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.1, 66.2, 68.9, 69.5, 69.6, 72.1, 72.6, 72.9, 73.1, 73.8, 73.8, 74.8, 75.0, 75.3, 75.4, 75.6, 79.6, 80.4, 99.4 ($^1J_{C-H}$=172.4 Hz), 101.6 ($^1J_{C-H}$=172.0 Hz), 126.3, 127.8–128.8 (multiple carbons), 128.9, 128.9, 134.5, 138.4–138.7 (multiple carbons), 147.7, 165.3. Anal. Calcd for $C_{63}H_{65}NO_{15}$: C, 70.31; H, 6.09; N, 1.30. Found: C, 70.26; H, 6.23; N, 1.31.

4.1.12. Methyl 4-((tetrahydro-2[*H*]-pyran-2-yl)-oxymethyl)-3-nitrobenzoate (30). To a suspension of methyl 4-hydroxymethyl benzoate (**2**) (10.56 g, 50 mmol, 1.00 equiv) in dry dichloromethane (20 mL), 2,3-dihydro-4[*H*]-pyrane (9.12 mL, 8.42 g, 100 mmol, 2.00 equiv) was added, followed by *p*-toluenesulfonic acid monohydrate (0.19 g, 1 mmol, 0.02 equiv). After 15 min, the clear solution formed was diluted with dichloromethane (150 mL), washed with saturated $NaHCO_3$ solution (50 mL), dried ($MgSO_4$) and the solvent was evaporated in vacuum. The THP ether **30** (14.21 g, 96%) was obtained as a pale yellow oil after chromatography on silicagel (hexane/ethyl acetate, 5:1 containing 0.5% Et_3N). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.48–1.85 (m, 8H), 3.44–3.50 (m, 1H), 3.73–3.79 (m, 1H), 3.82 (s, 3H), 4.68–4.72 (m, 1H), 4.87 (d, J=16.1 Hz, 1H), 5.10 (d, J=16.1 Hz, 1H), 7.87 (d, J=8.1 Hz, 1H), 8.20 (dd, J=8.2, 1.5 Hz, 1H), 8.60 (d, J=1.5 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 19.8, 25.7, 30.8, 53.0, 62.9, 66.1, 99.3, 126.1, 129.4, 130.6, 134.4, 140.4, 147.6, 165.3. HR-QTOF-MS: m/z calcd for $C_{14}H_{17}NNaO_6$ $(M+Na)^+$318.0954, found 318.0952.

4.1.13. 4-((Tetrahydro-[2*H*]-pyran-2yl)-oxymethyl)-3-nitrobenzoic acid (31). A solution of **30** (3.51 g, 11.9 mmol, 100 mol%) in THF (50 mL) was mixed with 2 M aqueous KOH solution (50 mL) and the two-phase mixture was stirred vigorously for 6 h at room temperature. The mixture was acidified with 10% aqueous H_2SO_4 (pH=4), extracted with ethyl acetate (3×30 mL), washed with water (5×50 mL), brine (30 mL), dried ($MgSO_4$) and the solvent was evaporated to afford **31** (3.08 g, 92%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.51–1.82 (m, 7H), 3.50–3.57 (m, 1H), 3.77–3.81 (m, 1H), 4.74–4.76 (m, 1H), 4.91 (d, J=16.4 Hz, 1H), 5.16 (d, J=16.4 Hz, 1H), 7.93 (d, J=8.2 Hz, 1H), 8.26 (dd, J=8.2, 1.7 Hz, 1H), 8.69 (d, J=1.7 Hz, 1H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 19.8, 25.7, 30.8, 53.0, 62.9, 66.1, 99.3, 126.1, 129.4, 130.6, 134.4, 140.4, 147.6, 165.3. HR-QTOF-MS: m/z calcd for $C_{13}H_{15}NNaO_6$ $(M+Na)^+$304.0797, found 304.0782.

4.1.14. 4-Methoxycarbonyl-2-nitrobenzyl 2-(3,4,6-tri-*O*-benzyl-D-mannopyranosyl)-3-(3,4,6-tri-*O*-benzyl-D-mannopyranosyl)-4,6-di-*O*-benzyl-D-mannopyranoside (36). The carboxylic acid **31** (2.97 g, 10.5 mmol, 1.00 equiv), Boltorn H-50 polymer (**1**) (4.72 g, 42 mmol, 4.00 equiv) and DMAP (130 mg, 1.1 mmol, 0.11 equiv) were dissolved in dry pyridine (15 mL) and dry THF (20 mL). EDCI (2.20 g, 11.5 mmol, 1.10 equiv) was added and the reaction mixture was stirred for 16 h. The mixture was cooled in an ice bath and acetyl chloride (2.85 mL, 3.14 g, 40 mmol, 3.81 equiv) was added dropwise. The reaction was warmed to room temperature with stirring for 8 h, poured into water (100 mL) and extracted with ethyl acetate (2×30 mL). The combined organic extracts were washed with 10% H_2SO_4 (2×30 mL), saturated $NaHCO_3$ solution (2×30 mL), brine (30 mL), dried ($MgSO_4$) and the solvent was evaporated to afford the THP-protected polymer-immobilized linker, which was used directly for the next step. THP-protected **32** was dissolved in CH_2Cl_2 and methanol (40 mL each) and concd HCl (2 mL) was added. After stirring for 4 h, saturated aqueous $NaHCO_3$ solution was added (pH=8). The organic solvents were removed on rotary evaporator and the product was extracted in ethyl acetate (3×30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The polymer-immobilized alcohol **32** (5.27 g, 68%, loading level: 1.36 mmol/g) was obtained as a pale yellow foam after dissolving the crude polymer in dichloromethane (10 mL) and precipitation into methanol (150 mL), decanting of the supernatant, rinsing with methanol (3×10 mL), and drying in high vacuum. From the polymer-supported linker **32** (73.5 mg, 0.1 mmol, 1.00 equiv) and the glycosyl donor **27** (0.23 g, 0.5 mmol, 5.00 equiv) in dry CH_3CN (0.6 mL), following the procedure for preparation of **14**, the monosaccharide **33** (110 mg) was obtained as a pale yellow foam after precipitation from methanol (15 mL, containing five drops of Et_3N), decanting of the supernatant, rinsing with methanol (3×2 mL), and drying in high vacuum. To **33** (110 mg, 0.1 mmol, 1.00 equiv) dissolved in dry CH_2Cl_2 (1 mL), 1,3-propanedithiol (100 μL, 108 mg, 0.5 mmol, 5.00 equiv) and TFA (30 μL, 44 mg, 0.39 mmol, 3.90 equiv) were added and the solution was stirred overnight. Excess Et_3N (60 μL) was used to quench the acid and the solution was concentrated. The diol **34** was obtained by precipitation into methanol (30 mL), decanting of the supernatant, rinsing with methanol (3×2 mL) and drying in high vacuum. The product was directly applied into the next step. Following the procedure for preparation of **14**, the glycosylation of the diol **34** and the glycosyl donor

13 (0.54 g, 1 mmol, 10.00 equiv) in dry CH_3CN (0.7 mL) was accomplished using NIS (0.27 g, 1.2 mmol, 12.00 equiv) and TfOH (10 μL, 17 mg, 0.1 mmol, 100 mol%). The polymer-immobilized trisaccharide **35** was obtained as a pale yellow foam after precipitation into methanol (15 mL), decanting of the supernatant, rinsing with methanol (3×2 mL) and drying in high vacuum. Following the procedure for compound **15**, the trisaccharide (mixture of anomers) **36** (56 mg, 0.039 mmol, 39%) was obtained as a pale yellow foam after chromatography on silicagel (hexane/ethyl acetate, 2:1). The major anomer (α,α,α): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.00 (broad s, 2H), 3.75–5.26 (m, 58H), 7.28–7.37 (m, 40H), 7.75–8.00 (m, 1H), 8.07–8.23 (m, 1H), 8.72–8.78 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 53.2, 66.2, 66.4, 68.3, 69.1, 69.1, 69.3, 69.6, 69.7, 72.1, 72.1, 72.4, 72.5, 72.7, 73.8, 73.9, 74.0, 74.7, 74.7, 74.9, 75.2, 75.4, 75.5, 76.3, 80.3, 80.6, 99.1 ($^1J_{C-H}$=174.8 Hz), 99.2 ($^1J_{C-H}$=174.8 Hz), 99.9 ($^1J_{C-H}$=170.8 Hz), 126.3, 128.1–129.2 (multiple carbons), 130.7, 134.7, 137.9–139.3 (multiple carbons), 147.1, 165.3. MALDI-TOF MS: *m/z* calcd for $C_{80}H_{87}NNaO_{20}$ $(M+Na)^+$: 1440.57, found 1441.30; *m/z* calcd for $C_{80}H_{87}NKO_{20}$ $(M+K)^+$: 1456.68, found 1457.27. Anal. Calcd for $C_{80}H_{87}NO_{20}$: C, 70.27; H, 6.18; N, 0.99. Found: C, 70.04; H, 6.33; N, 0.89.

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Synthesis of L,L-puromycin

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Abstract—L,L-Puromycin, a diastereomer of the natural peptidyl nucleoside antibiotic puromycin, has been synthesized from L-xylose in 13 steps.

1. Introduction

Puromycin is a peptidyl nucleoside antibiotic produced by *Streptomyces alboniger* that inhibits peptidyl transfer in both prokaryotic and eukaryotic ribosomes.[1] A number of natural peptidyl nucleoside antibiotics share similar properties with puromycin, among, which the recently discovered cystocin (Fig. 1).[2] Widely used as a basic tool in biochemistry and cell biology, puromycin has been evaluated as an antimicrobial and antitumor agent with disappointing results. Major drawbacks of puromycin include (1) the lack of selectivity toward prokaryotic cells; (2) the nephrotoxicity of the metabolite puromycin aminonucleoside (PAN);[3] (3) the rapid occurrence of bacterial resistance.[4]

In order to improve both selectivity and toxicity profile of puromycin, a number of analogs have been synthesized and evaluated.[5] Although non-nephrotoxic analogs have been described, the selectivity issue has never been solved. Interestingly, protein synthesis is required for the expression of the anthrax lethal toxin cytotoxicity, and puromycin has shown complete protection against anthrax lethal toxin-induced cytolysis in vitro.[6] These observations suggest that puromycin-like agents may be particularly useful in anti-anthrax therapy, being potentially able to exert their effect through a triple mechanism of action: inhibition of the synthesis of the toxin, inhibition of the expression of the toxin and the more general bacteriostatic effect.

Previous studies on carbocyclic analogs of puromycin indicated that analogs in which the nucleoside base has the non-natural L-configuration may be competitive inhibitors of peptidyl transferase, as opposed to natural isomers that act as substrates causing termination of the growing peptide.[5d] In an effort to investigate this unusual mechanism of action and in view of the potential of puromycin analogs as biological tools as well as pharmaceutical agents, we decided to synthesize L,L-puromycin **1**, that is, the diastereomer of natural puromycin in which the nucleoside

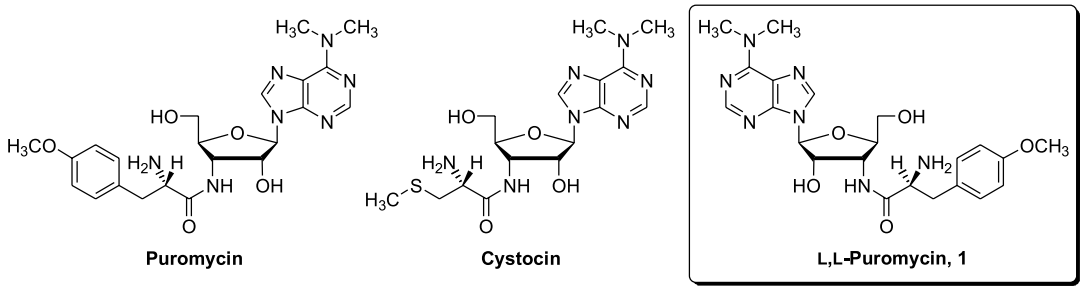

Figure 1. Structures of natural aminoacyl nucleosides and L,L-puromycin **1**.

Keywords: L-Nucleoside; Peptidyl nucleoside antibiotic.
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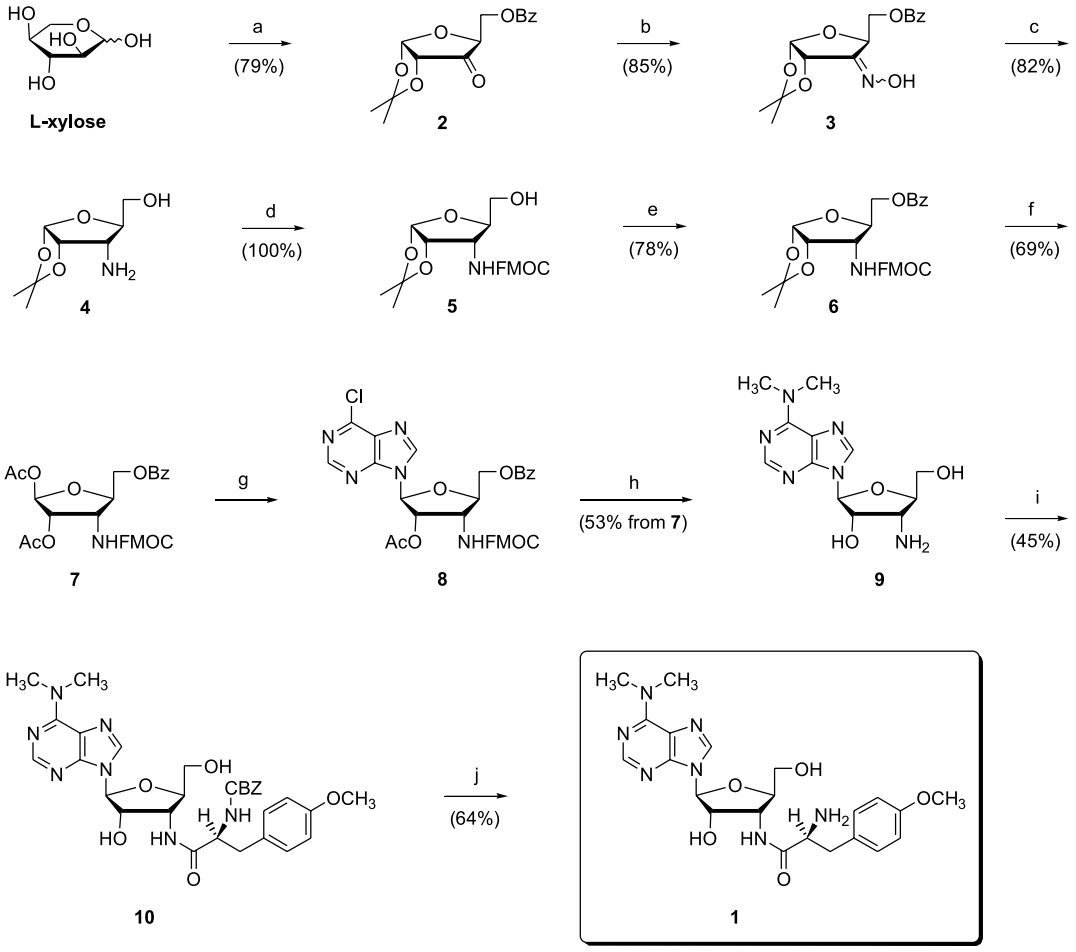

Scheme 1. Synthesis of L,L-puromycin. Reagents and conditions: (a) Four steps, Ref. 8; (b) $H_2NOH\cdot HCl$, Py, 55 °C, overnight; (c) LAH, THF, 0 °C to reflux, 3 h, then rt overnight; (d) FMOC-OSu, $NaHCO_3$, 1:1 acetone/H_2O, rt, 1 h; (e) BzCl, Py, CH_2Cl_2, rt, 1 h; (f) AcOH, H_2SO_4, rt, 24 h, then Ac_2O, Py, rt, 4 h; (g) silylated 6-chloropurine, TMSOTf, MeCN, 0 °C to rt, overnight; (h) 40% aq Me_2NH, rt, 24 h; (i) [*N*-CBZ-L-*O*-methyltyrosine, ethyl chlorocarbonate, Et_3N], DMF, 0–5 °C, 24 h; (j) H_2, 10% Pd/C, AcOH, rt, 10 min.

moiety has the unnatural L configuration and the amino acid retains the natural L configuration.

2. Results and discussion

2.1. Synthesis

In devising our synthetic route, we examined previously reported syntheses of natural puromycin. In the first total synthesis by Baker et al.[7] puromycin was synthesized from D-xylose in 21 steps with very low overall yield. More recently, a much more efficient procedure was reported by Robins et al.[5l] However, this procedure employs adenosine as starting material, which represents a problem in the synthesis of the L-isomer, due to the commercial unavailability of suitable amounts of L-adenosine. Drawbacks of other published methods include the introduction of the amino functionality via hazardous azides.[5m] More attractive to our purpose was the published synthesis of a D-3′-amino-3′-deoxyribose by reduction of an oxime prepared from D-xylose.[5f]

Thus L-xylose, the starting material of our synthesis, was converted to ketone **2** in four steps according to published procedures (Scheme 1).[8] Treatment of ketone **2** with hydroxylamine hydrochloride in pyridine afforded a mixture of oximes **3** in 3:2 isomeric ratio, as shown by NMR of the crude reaction mixture. Although no stereochemical assignment was attempted, the major isomer is assumed to be the syn, as in the case of the reported D-5-*O*-carbonate analogs.[5f] Oximes **3** were reduced to the 3-amino-3-deoxyribose derivative **4**. As previously described,[5f] the reduction proceeds with high stereoselectivity, giving mainly the 3-α amino group with less than 10% (by NMR) of the β-isomer. Protection of **4** as the fluorenylmethylcarbamate was easily achieved to give **5**, which was benzoylated to fully protected compound **6**. Carefully controlled acetolysis/acetylation of isopropylidene **6** gave almost exclusively the β-diacetate **7**. Vorbrüggen glycosidation[9] of **7** produced the protected nucleoside **8**. The reaction proceeded cleanly and a simple extractive work-up was found sufficient to obtain a crude **8** that was pure enough for the next step. ^{1}H NMR of the crude mixtures of both **7** and **8** showed only minor anomeric peaks possibly belonging to the α-isomers (although in the case of **8** the presence of minor amounts of N^7 glycosylation product cannot be excluded). The predominance of the β-anomer is expected on the basis of participation of the 2-acetyl group in acid catalysis and is supported by ^{1}H NMR

by the lack of coupling between H-1 and H-2, typical of a trans geometry. Treatment of **8** with a 40% aqueous solution of dimethylamine allowed the simultaneous removal of the three different protecting groups and substitution of the 6-chlorine to give L-PAN **9**. The obtainment of pure **9** is important for toxicological studies, since its natural D-counterpart is responsible for the nephrotoxicity associated with puromycin. TLC monitoring of the reaction qualitatively shows that the FMOC group is cleaved in a few minutes, as shown by the rapid formation of dibenzofulvene, followed by the hydrolysis of the 5- and 2-ester functionalities, whereas the ring substitution takes several hours to complete. The nucleoside **9** is less polar than expected from the presence of two hydroxyl and one amino group and can be carefully purified by silica gel flash chromatography. It can also be recrystallized from hot ethanol,[7a] to give a dry powder that loses much of its solubility in many solvents. Comparison of physical and spectroscopic properties of **9** with the known D-isomer PAN definitely proved the correct stereochemical assignment of the anomeric position. Particularly, the specific optical rotation of **9** in water ($[\alpha]_D^{27}$ +25.45) correlated well with the reported value for the D-isomer ($[\alpha]_D^{25}$ −24.6).[7a] Reaction of **9** with the mixed anhydride obtained by treating *N*-benzyloxycarbonyl-L-*O*-methyltyrosine with ethyl chloroformate[7a] gave protected L,L-puromycin **10**. Deprotection was easily achieved by catalytic hydrogenation on Pd/C in acetic acid[7a] to afford the target compound **1**.

2.2. Microbiological evaluation

In preliminary studies, the antimicrobial activities of L,L-puromycin **1** and L-PAN **9** were evaluated on strains of *B. subtilis* and *B. cereus*. The latter is genetically similar to *B. anthracis* and a safer model for the study of potential anti-anthrax agents. Both compounds were found inactive, with MIC >100 μg/mL. The MIC of puromycin was 3.13 μg/mL against both strains. At this concentration, puromycin was also bactericidal.

3. Summary and conclusion

In conclusion, we have described the synthesis of L,L-puromycin, non-natural diastereomer of the potent translation inhibitor puromycin. Our synthesis proceeds via the versatile intermediate L-puromycin amino nucleoside **9**, which can be easily coupled with a number of natural and non-natural amino acids to produce a series of analogs in a procedure of general applicability. The synthesis and biological evaluation of a series of analogs are currently in progress.

4. Experimental

4.1. General

All the reactions were carried out under a positive pressure of argon and monitored by TLC on Uniplates (silica gel) purchased from Analtech Co. All the reagents and anhydrous solvents were purchased from commercial sources and used without further purification except where noted. Chromatographic purifications were performed on flash silica gel (particle size 40–63 μm) purchased from Silicycle or TLC grade silica gel (particle size 5–15 μm) purchased from Sorbent Technologies. All solvents for chromatographic purifications were HPLC grade. Melting points were determined on a Barnstead Mel-Temp and are uncorrected. ^{1}H NMR spectra were recorded on a Varian 400 MHz spectrometer with Me_4Si as an internal standard and signals are represented as s (singlet), d (doublet), t (triplet), m (multiplet), or combinations of the above. Anomeric protons have been assigned by one- or two-dimensional homocorrelation experiments as needed. UV spectra were obtained on a BECKMAN DU-650 spectrophotometer. Optical rotations were measured on a Rudolph Research Analytical Autopol IV digital polarimeter. Elemental analyses were performed by Atlantic Microlabs Inc. Norcross, GA.

4.2. Experimental procedures

4.2.1. 5-*O*-Benzoyl-1,2-*O*-isopropylidene-α-L-*erythro*-pentofuranose-3-ulose oxime (3). A mixture of **2** (3.22 g, 11.0 mmol), and hydroxylamine hydrochloride (5.00 g, 71.6 mmol) in anhydrous pyridine (20 mL) was stirred overnight in a 55 °C oil bath. The volatiles were then evaporated under reduced pressure, water (15 mL) and dichloromethane (15 mL) were added to the residue and the organic phase was separated. The aqueous layer was extracted with dichloromethane (4×15 mL), and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated. The resulting oil was dissolved in ethyl acetate and purified by tlc-grade silica gel flash column chromatography (1:4 ethyl acetate/hexanes) to give syn/anti mixture **3** as a white solid (2.91 g, 85%). R_f 0.35 (1:3 ethyl acetate/hexanes); mp 125–127 °C; $[\alpha]_D^{26}$ −170.64 (*c* 0.69, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.04–8.00 (m, 0.8H), 7.98–7.96 (m, 1.2H), 7.95 (s, 0.4H, D_2O exchangeable), 7.93 (s, 0.6H, D_2O exchangeable), 7.60–7.55 (m, 1H), 7.47–7.42 (m, 2H), 6.08 (d, $J_{1,2}$=2.5 Hz, 0.6H, anomeric), 6.04 (d, $J_{1,2}$=4.3 Hz, 0.4H, anomeric), 5.40 (ddd, J=3.0, 2.3, 1.6 Hz, 0.6H), 5.37 (dd, J=4.3, 1.4 Hz, 0.4H), 5.13 (ddd, J=5.5, 2.7, 1.4 Hz, 0.4H), 5.12 (dd, J=4.3, 1.4 Hz, 0.6H), 4.79 (dd, J=11.7, 3.2 Hz, 0.6H), 4.69 (dd, J=12.9, 7.3 Hz, 0.4H), 4.61 (dd, J=11.7, 2.3 Hz, 0.6H), 4.44 (dd, J=12.1, 5.3 Hz, 0.4H), 1.55 (s, 1.2H), 1.52 (s, 1.8H), 1.46 (s, 1.8H), 1.45 (s, 1.2H); ^{13}C NMR ($CDCl_3$): δ 166.3, 166.0, 158.0, 156.9, 133.6, 133.3, 130.2, 129.7, 129.4, 128.5, 128.4, 114.2, 113.7, 105.0, 104.7, 78.3, 75.9, 75.3, 73.4, 65.2, 64.2, 27.7, 27.4, 27.2, 27.1; Mass [(M+H)$^+$] 308. Anal. Calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.76; H, 5.62; N, 4.51.

4.2.2. 3-Amino-3-deoxy-1,2-*O*-isopropylidene-α-L-ribofuranose (4). Lithium aluminum hydride (1.0 M sol. in tetrahydrofuran, 22.6 mL, 22.6 mmol) was added to a stirring ice-cold solution of **3** (2.80 g, 9.1 mmol) in tetrahydrofuran (50 mL). The reaction was refluxed for 3 h, then stirred at rt overnight. Ethyl acetate (10 mL) was then added to quench the reaction, and the mixture was loaded onto a tlc-grade silica gel flash column and eluted with 1:12 methanol/dichloromethane to afford **4** as a yellow syrup (1.4 g, 82%). R_f 0.06 (1:12 methanol/dichloromethane); $[\alpha]_D^{23}$ −47.67 (*c* 1.46, $CHCl_3$); ^{1}H NMR

($CDCl_3$): δ 5.77 (d, $J_{1,2}=3.7$ Hz, 1H, anomeric), 4.45 (t, $J=4.2$ Hz, 1H), 3.88 (dd, $J=11.6$, 3.6 Hz, 1H), 3.75 (dd, $J=11.6$, 3.5 Hz, 1H), 3.71 (dt, $J=9.5$, 3.7 Hz, 1H), 3.18 (dd, $J=9.4$, 4.7 Hz, 1H), 1.82–1.71 (m, 3H, D_2O exchangeable), 1.52 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 111.4, 103.6, 81.1, 80.1, 59.6, 53.6, 26.1, 25.9; Mass [$(M+H)^+$] 190. Anal. Calcd for $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40. Found: C, 51.00; H, 7.99; N, 7.17.

4.2.3. 3-Deoxy-3-fluorenylmethylcarbonylamino-1,2-*O*-isopropylidene-α-L-ribofuranose (5). *N*-(9-Fluorenylmethoxycarbonyloxy) succinimide (7.49 g, 22.2 mmol) was added portionwise to a stirred suspension of **4** (2.00 g, 10.6 mmol) and sodium bicarbonate (8.88 g, 105.7 mmol) in acetone (50 mL) and water (50 mL). The mixture was stirred for 1 h at rt, then solvents were concentrated under reduced pressure to half volume and the residue was extracted with ethyl acetate (3×100 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The compound was purified by tlc-grade silica gel flash column chromatography (dichloromethane to 1:49 methanol/dichloromethane) to give **5** as a white solid (4.35 g, 100%). R_f 0.43 (1:19 methanol/dichloromethane); mp 118–120 °C; $[\alpha]_D^{24}$ −34.33 (*c* 0.60, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.80–7.77 (m, 2H), 7.62–7.58 (m, 2H), 7.45–7.40 (m, 2H), 7.36–7.32 (m, 2H), 5.87 (d, $J_{1,2}=3.7$ Hz, 1H, anomeric), 5.30 (d, $J=8.8$ Hz, 1H), 4.64 (t, $J=4.4$ Hz, 1H), 4.48 (d, $J=6.5$ Hz, 2H), 4.22 (t, $J=6.5$ Hz, 1H), 4.07 (dt, $J=9.1$, 5.0 Hz, 1H), 3.87 (d, $J=13.2$ Hz, 1H), 3.69 (dd, $J=13.2$, 2.0 Hz, 1H), 2.79 (br s, 1H, D_2O exchangeable), 1.56 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 156.6, 143.6, 143.5, 141.3, 127.8, 127.0, 124.9, 124.8, 120.0, 120.0, 112.6, 103.9, 80.0, 78.8, 67.1, 60.4, 52.8, 47.1, 26.4, 26.3; Mass [$(M+Na)^+$] 434, [$(2M+Na)^+$] 845. Anal. Calcd for $C_{23}H_{25}NO_6\cdot 0.4\ CH_2Cl_2$: C, 62.18; H, 5.77; N, 3.09. Found: C, 62.44; H, 5.75; N, 3.23.

4.2.4. 5-*O*-Benzoyl-3-deoxy-3-fluorenylmethylcarbonylamino-1,2-*O*-isopropylidene-L-ribofuranose (6). Benzoyl chloride (1.5 mL, 12.9 mmol) was added to a stirring ice-cold solution of **5** (4.35 g, 10.6 mmol) and anhydrous pyridine (1.9 mL, 23.5 mmol) in anhydrous dichloromethane (50 mL). The mixture was stirred for 1 h at rt, then treated with 10% hydrochloric acid (20 mL). The organic layer was separated and washed with water (20 mL), a saturated solution of sodium bicarbonate (20 mL) and brine (20 mL), then dried over magnesium sulfate and filtered. The filtrate was directly loaded onto a tlc-grade silica gel column and eluted with dichloromethane, then (1:19 methanol/dichloromethane) to give **6** as a white solid (4.25 g, 78%). R_f 0.71 (1:19 methanol/dichloromethane); mp 71–73 °C; $[\alpha]_D^{24}$ −51.15 (*c* 0.33, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.07 (d, $J=7.4$ Hz, 2H), 7.77 (d, $J=7.4$ Hz, 2H), 7.61–7.58 (m, 2H), 7.56–7.51 (m, 1H), 7.44–7.38 (m, 4H), 7.35–7.30 (m, 2H), 5.88 (d, $J_{1,2}=3.5$ Hz, 1H, anomeric), 5.25 (d, $J=9.2$ Hz, 1H), 4.73 (dd, $J=12.3$, 2.4 Hz, 1H), 4.65 (t, $J=4.3$ Hz, 1H), 4.41 (d, $J=7.0$ Hz, 2H), 4.33 (dd, $J=12.3$, 5.6 Hz, 1H), 4.24–4.18 (m, 2H), 4.15–4.09 (m, 1H), 1.59 (s, 3H), 1.37 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.2, 155.9, 143.7, 143.6, 141.2, 133.0, 129.7, 128.3, 127.7, 127.0, 125.0, 124.9, 120.0, 119.9, 112.6, 104.2, 78.5, 77.5, 67.0, 63.5, 54.2, 47.1, 26.6, 26.3; Mass [$(M+H)^+$] 516. Anal. Calcd for $C_{30}H_{29}NO_7$: C, 69.89; H, 5.67; N, 2.72. Found: C, 69.62; H, 5.65; N, 2.70.

4.2.5. 5-*O*-Benzoyl-3-deoxy-1β,2-diacetyl-3-fluorenylmethylcarbonylamino-L-ribofuranose (7). Sulfuric acid (0.45 mL, 8.4 mmol) was added to a suspension of **6** (4.20 g, 8.2 mmol) in glacial acetic acid (60 mL) and anhydrous dichloromethane (5 mL). The mixture was stirred at rt for 36 h. The resulting solution was then heated to 55 °C for 2 h. Upon cooling to rt, acetic anhydride (10.4 mL, 110.0 mmol) and pyridine (2.3 mL, 28.4 mmol) were added, and the resulting solution was stirred at rt for 4 h. The volatiles were evaporated in vacuo, and the residue was dissolved in dichloromethane (400 mL) and washed with a saturated solution of sodium bicarbonate (2×100 mL), water (100 mL), and brine (100 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated, and purified by tlc-grade silica gel flash chromatography (1:99 methanol/dichloromethane) to give **7** as a white solid (3.15 g, 69%). R_f 0.46 (1:49 methanol/dichloromethane); mp 136–138 °C; $[\alpha]_D^{24}$ −15.90 (*c* 1.76, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.10–8.06 (m, 2H), 7.80–7.76 (m, 2H), 7.61–7.53 (m, 3H), 7.44–7.39 (m, 4H), 7.35–7.29 (m, 2H), 6.13 (s, 1H, anomeric), 5.13 (d, $J=4.5$ Hz, 1H), 4.96 (d, $J=9.6$ Hz, 1H), 4.81 (dt, $J=9.4$, 4.7 Hz, 1H), 4.71 (dd, $J=12.0$, 2.2 Hz, 1H), 4.50–4.48 (m, 2H), 4.32–4.18 (m, 3H), 2.17 (s, 3H), 1.93 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 169.4, 168.9, 166.0, 155.7, 143.5, 143.4, 141.2, 133.2, 129.6, 128.3, 127.7, 127.0, 124.8, 124.7, 119.9, 97.5, 80.4, 75.4, 66.9, 63.6, 51.3, 47.0, 20.7, 20.7; Mass [$M+Na]^+$582. Anal. Calcd for $C_{31}H_{29}NO_9$: C, 66.54; H, 5.22; N, 2.50. Found: C, 66.79; H, 5.25; N, 2.67.

4.2.6. 9-(2-*O*-Acetyl-5-*O*-benzoyl-3-deoxy-3-fluorenylmethylcarbonylamino-L-ribofuranosyl)-6-chloropurine (8). A mixture of 6-chloropurine (1.24 g, 8.0 mmol) and ammonium sulfate (60 mg, 0.5 mmol) in 1,1,1,3,3,3-hexamethyldisilazane (50 mL) was refluxed for 4 h, then the solvent was removed in vacuo at 40 °C. A solution of **7** (3.08 g, 5.5 mmol) in anhydrous acetonitrile (50 mL) was added to the residual solid. The resulting solution was cooled to 0 °C and trimethylsilyl triflate (1.45 mL, 8.0 mmol) was added, and the reaction was stirred at rt overnight. The resulting solution was diluted to 400 mL with dichloromethane and added to an ice-cold saturated solution of sodium bicarbonate. The organic phase was separated and the aqueous layer was extracted with dichloromethane (100 mL). The combined organic layers were washed with brine (50 mL), dried over magnesium sulfate, filtered, and concentrated to crude **8** (3.22 g, 89%), which was used in the following step without further purification. R_f 0.20 (1:49 methanol/dichloromethane); mp 113–115 °C; UV (MeOH) λ_{max} 264.5, 300.0; ^1H NMR ($CDCl_3$): δ 8.68 (s, 1H), 8.17 (s, 1H), 7.95 (d, $J=7.2$ Hz, 2H), 7.77 (d, $J=6.8$ Hz, 2H), 7.60–7.53 (m, 3H), 7.42–7.28 (m, 6H), 6.02 (s, 1H, anomeric), 5.70 (d, $J=5.7$ Hz, 1H), 5.39 (dd, $J=15.8$, 9.0 Hz, 1H), 5.22 (d, $J=9.0$ Hz, 1H), 4.83 (d, $J=12.3$ Hz, 1H), 4.56–4.52 (m, 2H), 4.43 (dd, $J=11.0$, 3.6 Hz, 1H), 4.37–4.33 (m, 1H), 4.24–4.16 (m, 1H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 169.7, 166.1, 155.7, 152.2, 151.5, 150.7, 144.3, 143.5, 143.4, 141.3, 133.4, 132.2, 129.5, 128.4, 127.8, 127.8, 127.1, 124.8, 124.7,

120.0, 89.1, 80.7, 75.5, 66.9, 62.9, 51.4, 47.1, 20.7; Mass $[MH]^+$654.

4.2.7. 9-(3-Amino-3-deoxy-L-ribofuranosyl)-6-dimethylaminopurine (L-PAN, 9). A suspension of **8** (1.50 g, 2.3 mmol) in 40% aqueous solution of dimethylamine (50 mL) and methanol (10 mL) was stirred at rt for 24 h. The suspension was concentrated under reduced pressure to 20 mL, then washed with ether (3×50 mL). The combined organic extracts were extracted with water (20 mL). The combined aqueous extracts were concentrated in vacuo and co-evaporated with ethanol (20 mL). The residual yellow oil was dissolved in methanol and tlc-grade silica gel was added, then the solvent was evaporated to leave a residue that was loaded on a short tlc-grade silica gel column and eluted with 1:12 methanol/dichloromethane) to afford **9** as a white solid (400 mg, 59%). R_f 0.18 (1:9 methanol/dichloromethane); mp 212–214 °C; $[\alpha]_D^{27}$ +25.45 (*c* 0.20, H_2O); UV (H_2O) λ_{max} 267.5 (ε 19,240, pH 2), 275.0 (ε 18,860, pH 7), 275.0 (ε 19,260, pH 11); ^{1}H NMR (DMSO-d_6): δ 8.42 (s, 1H), 8.22 (s, 1H), 5.95 (d, $J_{1',2'}$= 2.5 Hz, 1H, anomeric), 5.81 (br s, 1H, D_2O exchangeable), 5.15 (t, J=5.4 Hz, 1H, D_2O exchangeable), 4.24–4.21 (m, 1H), 3.76–3.71 (m, 2H), 3.62–3.55 (m, 1H), 3.46 (dd, J= 7.0, 5.5 Hz, 1H), 3.34 (s, 6H), 1.69 (br s, 2H, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 154.2, 151.8, 149.6, 138.0, 119.6, 89.1, 85.5, 74.9, 60.8, 52.4, 38.0; Mass $[MH]^+$295. Anal. Calcd for $C_{12}H_{18}N_6O_3\cdot 0.5H_2O$: C, 48.38; H, 6.50; N, 27.08. Found: C, 48.45; H, 6.15; N, 26.77.

4.2.8. 9-[3*N*-(*N*-Benzyloxycarbonyl-*p*-methoxy-L-phenylalanyl)amino]-3-deoxy-L-ribofuranosyl)-6-dimethylaminopurine (*N*-benzyloxycarbonyl-L,L-puromycin, 10). Ethyl chloroformate (75 μL, 0.78 mmol) was added to an ice-cold solution of *N*-benzyloxycarbonyl-*p*-methoxy-L-phenylalanine (250 mg, 0.76 mmol) and triethylamine (0.11 mL, 0.79 mmol) in anhydrous dimethylaformamide (2 mL), and the resulting mixture was stirred at 0 °C for 10 min. In the mean time, a suspension of **9** (200 mg, 0.68 mmol) and triethylamine (0.16 mL, 1.15 mmol) in dimethylformamide (3 mL) was warmed until dissolution, then rapidly cooled down in ice bath, and the first mixture was added. The reaction was sealed and left in the refrigerator at 1–5 °C for 24 h. The resulting mixture was concentrated in vacuo, then treated with 1:1 methanol/water (20 mL). The precipitate was filtered and dried to give a crude that was purified by silica gel flash chromatography (1:19 methanol/dichloromethane) to give **10** as a white solid (185 mg, 45%). R_f 0.4 (1:19 methanol/dichloromethane); mp 226–228 °C; $[\alpha]_D^{23}$ +22.58 (*c* 0.33, MeOH); UV (MeOH) λ_{max} 275.5; ^{1}H NMR (DMSO-d_6): δ 8.47 (s, 1H), 8.24 (s, 1H), 8.13 (d, J=7.2 Hz, 1H, D_2O exchangeable), 7.51 (d, J=8.6 Hz, 1H, D_2O exchangeable), 7.34–7.20 (m, 7H), 6.83 (d, J=7.2 Hz, 2H), 6.11 (d, J=3.7 Hz, 1H, D_2O exchangeable), 6.01 (s, 1H, anomeric), 5.26 (t, J=4.8 Hz, 1H, D_2O exchangeable), 4.94 (s, 2H), 4.54–4.45 (m, 2H), 4.32–4.25 (m, 1H), 4.05–4.01 (m, 1H), 3.74–3.72 (m, 4H), 3.57–3.51 (m, 1H), 3.35 (s, 6H), 3.02–2.96 (m, 1H), 2.70–2.63 (m, 1H); ^{13}C NMR (DMSO-d_6): δ 172.1, 157.8, 155.9, 154.3, 151.9, 149.7, 137.9, 137.0, 130.2, 130.0, 128.3, 127.7, 127.4, 119.6, 113.5, 89.3, 83.4, 73.2, 65.2, 60.9, 56.5, 54.9, 50.4, 36.9, 35.5, 35.0; Mass $[MH]^+$606. Anal. Calcd for $C_{30}H_{35}N_7O_7\cdot 2H_2O$: C, 56.15; H, 6.13; N, 15.28. Found: C, 55.78; H, 6.27; N, 14.93.

4.2.9. L,L-Puromycin (1). A suspension of **10** (90 mg, 0.15 mmol) and 10% palladium over carbon (45 mg, 0.04 mmol) in glacial acetic acid (9 mL) was hydrogenated at atmospheric pressure for 10 min. The reaction was filtered through Celite washing with methanol and concentrated to dryness. The residual yellow oil was dissolved in 1 mL of hot ethanol and neutralized with 100 μL of triethylamine. Standing in refrigerator at 0 °C overnight allowed **1** to crystallize as a white solid (45 mg, 64%). R_f 0.6 (1:9 methanol/dichloromethane); mp 203–204 °C; $[\alpha]_D^{24}$ +21.30 (*c* 0.30, MeOH); UV (H_2O) λ_{max} 268.0 (ε 22,030, pH 2), 274.5 (ε 21,960, pH 7), 275.0 (ε 22,290, pH 11); ^{1}H NMR (DMSO-d_6): δ 8.46 (s, 1H), 8.23 (s, 1H), 8.04 (br s, 1H, D_2O exchangeable), 7.15 (d, J= 8.6 Hz, 2H), 6.85 (d, J=8.6 Hz, 2H), 6.19 (d, J=5.1 Hz, 1H, D_2O exchangeable), 5.97 (d, $J_{1',2'}$=1.5 Hz, 1H, anomeric), 5.19 (t, J=5.5 Hz, 1H, D_2O exchangeable), 4.50–4.44 (m, 2H), 3.96–3.92 (m, 1H), 3.72 (s, 3H), 3.56–3.49 (m, 1H), 3.44–3.36 (m, 1H), 3.35 (s, 6H), 3.32 (br s, 2H, D_2O exchangeable), 2.92 (dd, J=13.5, 3.7 Hz, 1H), 2.66–2.68 (m, 1H), 2.59 (dd, J=13.5, 8.4 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 174.8, 157.8, 154.3, 151.9, 149.6, 138.0, 130.4, 130.3, 119.6, 113.6, 89.5, 83.7, 73.2, 61.0, 56.2, 55.0, 49.9, 39.8 38.5, 37.9; Mass $[MH]^+$472. Anal. Calcd for $C_{22}H_{29}N_7O_5\cdot H_2O$: C, 53.98; H, 6.38; N, 20.03. Found: C, 54.31; H, 6.08; N, 20.09.

4.3. Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) tests

Broth microdilution minimum inhibitory concentration (MIC) testing was performed with puromycin, L,L-puromycin **1** and L-PAN **9** for potential microbiological activity against *B. anthracis*. MIC testing was performed using *B. subtilis* ATCC 6633 as a control strain and *B. cereus* ATCC 10987, an organism that has been shown to be genetically similar to *B. anthracis*. The dihydrochlorides of compounds **1** and **9** were dissolved in purified water and diluted in Mueller-Hinton broth supplemented with 25 mg/L of calcium and 12.5 mg/L of magnesium (CSMHB) for in vitro microbiologic testing using two-fold dilutions ranging from concentrations of 100–0.04 μg/mL. MIC testing was performed in triplicate for each dilution series according to guidelines of the National Committee for Clinical Laboratory Standards (NCCLS) for *S. aureus*.[10] The bacterial inoculum used in the study was prepared by inoculating the organisms into separate test tubes containing 5 mL of CSMHB and incubating the suspension at 35 °C overnight until visually turbid. These actively growing cultures were photometrically matched to a 0.5 McFarland turbidity standard. The adjusted culture was diluted with CSMHB to yield a final inoculum of approximately 10^5–10^6 organisms/mL. Sterile CSMHB (50 μL) was delivered into each well in sterile 96 well microdilution trays. Then, 50 μL of the agent to be tested was introduced into the first well of each of three rows in the tray and serially two-fold diluted in each of the remaining rows. The bacterial inoculum (50 μL) was introduced into each well so that each well in the tray contained a total volume of 100 μL. Positive (for growth of the organism) and negative (for initial sterility of the broth)

controls were assessed. After inoculation, all microdilution plates were sealed and incubated at 35 °C for 18 h. The MIC was defined as the lowest concentration of the agent that completely inhibited growth of the microorganism as detected by the unaided eye. Minimum bactericidal testing (MBC) testing was determined in duplicate by subculturing from all nonturbid wells. Using a calibrated pipet, 20 μL was subcultured in duplicate, plated onto antibiotic-free Mueller-Hinton agar plates, and incubated at 35 °C for 24 h. The MBC was defined as the lowest antibiotic concentration that decreased the final inoculum by $\geq$99.9%. Since the MIC values were greater than 100 μg/mL for **1** and **9**, MBC testing was performed only for puromycin.

MIC and MBC were interpreted based on the lowest value obtained from the traditional or intermediate concentration range.

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Side arm participation in lariat ether carboxylate-alkali metal cation complexes in solution

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Abstract—Lariat ether carboxylic acids of structure $CECH_2OCH_2C_6H_4$–2-CO_2H with crown ether (CE) ring sizes of 12-crown-4, 15-crown-5 and 18-crown-6 are prepared and converted into alkali metal–lariat ether carboxylate complexes. Absorptions for the diastereotopic benzylic protons in the ^1H NMR spectra of the complexes in $CDCl_3$ are utilized to probe the extent of side arm interaction with the crown ether-complexed metal ion as a function of the crown ether ring size and identity of the alkali metal cation.

1. Introduction

For more than three decades, macrocyclic polyether compounds (crown ethers) have been synthesized and utilized in alkali and alkaline earth metal cation determinations due to their superior binding ability for these metal ions.[1] Attachment of a side arm with potential metal ion coordination sites produces complexing agents called lariat ethers.[2] Such lariat ethers are designed to enhance the cation binding ability or selectivity of crown ethers by providing the potential of three-dimensional complexation, thereby mimicking the dynamic complexation processes exhibited by natural macrocyclic ionophores. When the side arm contains an acidic group, a proton-ionizable lariat ether is produced in which the ligand provides not only a polyether binding site for metal ion complexation, but also the requisite anion for formation of an electroneutral complex.[3] Such proton-ionizable lariat ethers exhibit markedly enhanced solvent extraction of alkali and alkaline earth metal cations and their transport across liquid membranes compared to non-ionizable analogs when the source aqueous solutions contain metal chlorides, nitrates and sulfates.[4]

Side arm participation in metal ion complexation by lariat ethers has been demonstrated in solid-state structures and inferred by increased stability constants in solution compared with corresponding crown ether ligands.[2] More convincing evidence for side arm participation in metal ion complexation by lariat ethers in solution was provided by ^{13}C NMR relaxation time (T_1) measurements.[5] In these studies, the mobility of carbons within dialkyl and alkyl aryl ether-containing side arms of non-ionizable lariat ethers was reduced when a complex was formed.

Some time ago, we designed and synthesized the lariat ether phosphonic acid monoethyl ester **1** with a 15-crown-5 ring (Scheme 1) and prepared from this proton-ionizable lariat ether the lithium, sodium, and potassium lariat ether phosphonate monoethyl ester complexes.[6] In $CDCl_3$, the ^1H NMR signals for the benzylic protons were broadened singlets for the lithium and potassium salts. However, the signal for the benzylic protons in the sodium salt was an AB quartet. The differences between the proton NMR spectra for the sodium salt on the one hand and the lithium and potassium salts on the other are readily interpretable in terms of the relationship between the diameters of the polyether cavity (1.7–2.2 Å) and lithium (1.20 Å), sodium (1.90 Å), and potassium (2.66 Å) cations. Thus, Na^+ is of an appropriate size to bind tightly within the polyether cavity. Simultaneous coordination of the phosphonate function markedly restricts the mobility of the side group and the diastereotopic benzylic protons in the sodium complex.

To explore the influence of ring size variation upon such side arm participation, the series of lariat ether carboxylic acids **2**–**4** (Scheme 1) has been prepared. In this series, the crown ether ring size is systematically varied from 12-crown-4 to 15-crown-5 to 18-crown-6. Five alkali metal carboxylate salts were produced from each of these three proton-ionizable lariat ethers and their ^1H NMR spectra in deuteriochloroform were determined to assess the level of side arm participation. Results of this study are now reported.

Keywords: Proton-ionizable lariat ether; Metal ion complexation.
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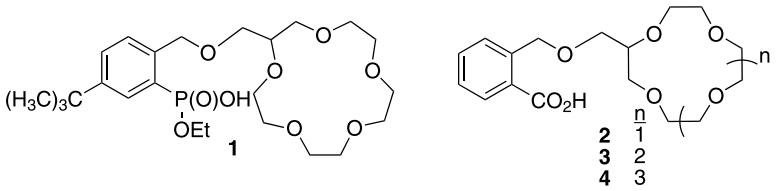


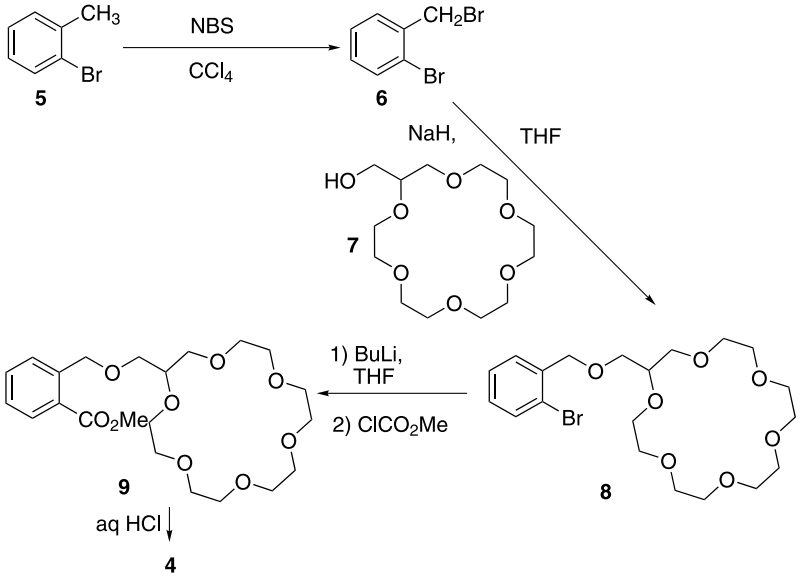
Scheme 1. Structures of a lariat ether phosphonic acid monoethyl ester **1** and lariat ether carboxylic acids **2**–**4**.

2. Results and discussion

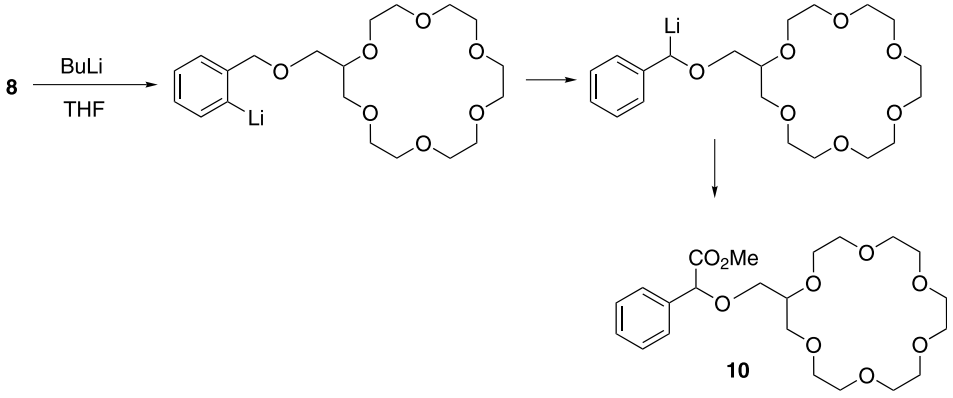
2.1. Synthesis of lariat ether carboxylic acids

For the original preparative approach to lariat ether carboxylic acids **2**–**4**, the 18-crown-6 compound **4** was the target, as illustrated in Scheme 2. Bromination of 2-bromotoluene (**5**) with NBS in CCl_4 gave 2-bromobenzyl bromide (**6**) in 84% yield. Reaction of **6** with the sodium alkoxide of hydroxymethyl-18-crown-6 (**7**) in THF gave key intermediate **8**. However, when **8** was treated with *n*-BuLi in THF at −78 °C followed by quenching with methyl chloroformate, problems were encountered. While it appeared that some of the desired methyl benzoate crown ether **9** was formed, a by-product was produced in an approximately equal amount. Thin layer chromatographic analysis showed two compounds with very similar R_f values. The IR spectrum of the mixture exhibited two strong carbonyl stretching absorptions of equal intensity. One absorption at 1756 cm^{-1} was consistent with an aliphatic ester, while the other absorption at 1736 cm^{-1} corresponded to the aromatic ester carbonyl group of **9**. Although no attempt was made to separate the two products, these observations together with the ^1H NMR spectrum of the mixture led to the conclusion that the two compounds were structural isomers. It is postulated that the undesired product is the structural isomeric ester **10** resulting from a transmetallation reaction of the initially formed aryllithium compound (Scheme 3).

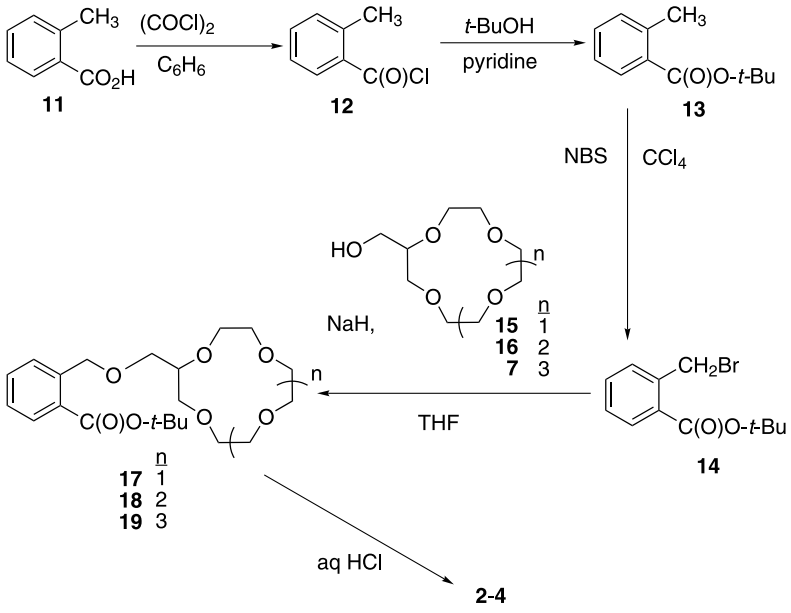
The successful preparative route to lariat ether carboxylic



Scheme 2. Initial synthetic scheme for preparation of lariat ether carboxylic acid **4**.



Scheme 3. Rationalization for formation of a second isomeric 18-crown-6 ester.



Scheme 4. Synthetic scheme for preparation of lariat ether carboxylic acids **2**–**4**.

acids **2**–**4** is shown in Scheme 4. Reaction of 2-methylbenzoic acid (**11**) with oxalyl chloride in benzene gave a quantitative yield of the corresponding acid chloride **12**. Reaction of **12** and *t*-BuOH gave *t*-butyl ester **13**. Benzylic bromination of **13** with NBS in CCl_4 provided a 61% yield of *t*-butyl 2-bromomethylbenzoate (**14**). Coupling of **14** with the sodium alkoxides derived from hydroxymethyl-12-crown-4 (**15**), hydroxymethyl-15-crown-5 (**16**) and hydroxymethyl-18-crown-6 (**7**) in THF gave lariat ether esters **17**–**19** in 68, 81, and 90% yields, respectively. (A model study performed with methyl 2-bromomethylbenzoate showed competing attack of the sodium alkoxide derived from (hydroxymethyl)cyclohexanol at both the benzylic and carbonyl carbons. To suppress the latter, the *t*-butyl ester **14** was utilized for reaction with the (hydroxymethyl)crown ethers **15**, **16**, and **7**.) Acidic hydrolysis gave the lariat ether carboxylic acids **2**–**4** in 96, 86, and 89% yields, respectively.

Table 1. Chemical shift (δ) the chemical shift difference ($\Delta\upsilon$) data for diastereotopic, benzylic protons of the lariat ether carboxylic acids **2**–**4** and their alkali metal carboxylate salts in $CDCl_3$

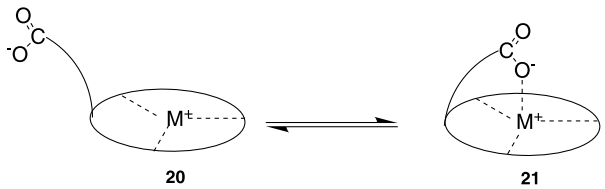
Compound	δ (ppm)[a]	$\Delta\upsilon$ (Hz)[b]
2	4.91	[c]
Li^+	4.73	[d]
Na^+	4.85	11.4
K^+	4.80	32.8
Rb^+	4.81	[d]
Cs^+	4.82	[d]
3	4.93	[c]
Li^+	4.85	[c]
Na^+	4.89	15.9
K^+	4.92	31.3
Rb^+	4.91	25.7
Cs^+	4.93	18.2
4	4.94	[d]
Li^+	4.92	[d]
Na^+	4.84	45.9
K^+	4.89	56.9
Rb^+	4.94	63.2
Cs^+	4.96	21.5

[a] Chemical shift for the singlet or the average chemical shift for the benzylic protons in the AB pattern.
[b] Calculated based upon the center of gravity for the AB quartet.
[c] Absorption was a sharp singlet.
[d] Absorption was a broad singlet.

2.2. NMR spectroscopic studies

Chemical shift (δ) and chemical shift difference ($\Delta\upsilon$) data for the AB quartets exhibited by the diastereotopic benzylic protons in lariat ether carboxylic acids **2**–**4** and their alkali metal carboxylate salts in $CDCl_3$ are presented in Table 1. The chemical shift values for the AB quartets were based on calculations for the center of gravity.[7]

It is readily evident from the data presented in Table 1 that the ^{1}H NMR absorptions for the benzylic protons in the lariat ether carboxylate salts exhibit a strong dependence on the identity of the alkali metal cation and the crown ether ring size. This dependence can be rationalized using the conformational equilibrium shown in Scheme 5. In structure **20**, the pendant carboxylate group does not interact with the polyether-bound metal ion. Rotation about the single bonds in the side arm is facile and the diastereotopic benzylic protons are magnetically equivalent, leading to a singlet absorption in the ^{1}H NMR spectrum. In structure **21**, the carboxylate group coordinates with the polyether-bound metal ion. This restricts the side arm and the diastereotopic benzylic protons are non-equivalent producing an AB



Scheme 5. Depiction of lariat ether carboxylates in which the ionized side arm is: (a) conformationally mobile in **20**; and (b) conformationally restricted due to its interaction with the polyether-complexed metal ion in **21**.

pattern in the ^{1}H NMR spectrum. The greater is the carboxylate–metal ion interaction in **21**, the more this form will contribute to the equilibrium mixture. A greater proportion of conformer **21** will produce greater restriction of the side arm in the 'averaged' structure for the equilibrium. This will enhance the level of non-equivalency for the diastereotopic benzylic protons and result in a larger chemical shift difference, $\Delta\upsilon$.

For crown ethers with 12-crown-4, 15-crown-5 and 18-crown-6 rings, averaged cavity sizes are 1.44, 1.84, and 2.90 Å, respectively.[8] For the alkali metal cations, the diameters for Li^+, Na^+, K^+, Rb^+, and Cs^+ are 1.56, 1.96, 2.66, 2.98, and 3.30 Å, respectively.[8]

For the lariat ether carboxylates derived from **2**, the cavity of 12-crown-4 is too small to accommodate even the smallest alkali metal cation. Therefore, perching[9] complexes would be formed with the alkali metal cation located somewhat above the plane of the crown ether oxygens. The chemical shift differences recorded in Table 1 reveal little restriction of the side arm for the lithium, rubidium, and cesium carboxylates. However, ^{1}H NMR absorptions for the benzylic protons in the sodium and potassium carboxylate salts exhibit pronounced AB patterns. The larger $\Delta\upsilon$ value for the potassium carboxylate salt indicates greater side arm restriction than in the sodium carboxylate complex. It is envisioned that the potassium ion perches on the crown ether ring and interacts with both the carboxylate terminus and the dialkyl ether oxygen in the side arm.

Although Li^+ can form a nesting[9] complex, the other alkali metal cations are too large to fit within the 15-crown-5 cavity of lariat ether carboxylates obtained from **3**. For the Li^+ complex, the benzylic proton absorption is a sharp singlet, revealing a conformationally mobile side arm. The $\Delta\upsilon$ values in Table 1 show that the side arm restriction increases as the metal ion is varied $Na^+ < Cs^+ < Rb^+ < K^+$. This ordering indicates that K^+ is the most appropriate size to perch on the polyether oxygens, while interacting with both the carboxylate and ether oxygens in the side arm.

For the carboxylates derived from lariat ether **4**, Li^+, Na^+, and K^+ can all form nesting complexes, with formation of perching complexes for Rb^+ and Cs^+. The broadened singlet observed for the benzylic protons in the complex with Li^+, shows a slight conformational restriction of the side arm. From the data in Table 1, it is seen that the $\Delta\upsilon$ values for the AB quartets increase as the alkali metal cation is varied in the order $Cs^+ < Na^+ < K^+ < Rb^+$. Once again the cation with the greatest side arm restriction in the complex is that in which the metal ion can perch on the oxygens of the polyether ring and interact with both the carboxylate and ether oxygens in the side arm.

3. Conclusions

For the alkali metal carboxylates obtained from lariat ether carboxylic acids **2**–**4**, the complexes with the greatest side arm restrictions are those in which the metal ion is large enough to perch on the crown ether oxygens yet small enough to interact well with the ether and carboxylate oxygens in the side arm.

4. Experimental

4.1. General

Melting points were determined with a Fisher-Johns melting point apparatus. ^{1}H and ^{13}C NMR spectra were obtained with an IBM AF-200 or AF-300 spectrometer. Spectra were taken in $CDCl_3$ and chemical shifts are reported in parts per million (ppm) downfield from TMS. IR spectra were obtained with a Perkin-Elmer 1600 Series FT-IR spectrophotometer and are given in wave numbers (cm^{-1}).

THF was distilled from sodium metal. Pyridine was dried over KOH pellets and *t*-BuOH was distilled from CaH_2.

Hydroxymethyl-12-crown-4 (**15**), hydroxymethyl-15-crown-4 (**16**) and hydroxymethyl-18-crown-6 (**7**) were prepared by reported procedures.[10,11]

4.1.1. 2-Bromobenzyl bromide (6). 2-Bromotoluene (10.00 g, 59 mmol) was dissolved in CCl_4 (100 mL) followed by addition of NBS (10.41 g, 59 mmol) and a catalytic amount of benzoyl peroxide. The mixture was stirred at reflux for 6 h. The mixture was allowed to cool to room temperature and was filtered. The filtrate was washed with water and dried over Na_2SO_4. Removal of the solvent in vacuo gave a light yellow liquid, which was distilled under vacuum (bp 80–85 °C/0.85 Torr, literature[12] bp 120–123 °C/16 Torr) to give 12.39 g (84%) of **6** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 4.54 (s, 2H), 7.10 (d of t, 1H), 7.23 (d of t, 1H), 7.38 (d of d, 1H), 7.51 (dd, 1H).

4.1.2. Bromo-2-(oxymethyl-18-crown-6)methylbenzene (8). A solution of hydroxymethyl-18-crown-6 (**7**) (1.50 g, 5.10 mmol) in THF (10 mL) was added dropwise to a flask containing NaH (0.31 g of 60% dispersion in mineral oil, 7.65 mmol). The mixture was stirred for 5 min at room temperature and a solution of bromide **6** (1.40 g, 5.10 mmol) in THF (10 mL) was added dropwise over a 10 min period. The mixture was stirred overnight at room temperature and the solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 and the solution was dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel with CCl_4/EtOAc (1:1) as eluent to give 1.83 g (77%) of **8** as a colorless, viscous oil. ^{1}H NMR ($CDCl_3$): δ 3.62–3.74 (m, 25H), 4.60 (s, 2H), 7.14 (d of t, 1H), 7.30 (d of t, 1H), 7.50 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 69.93, 70.64, 70.76, 70.83, 71.56, 72.32, 72.50, 78.33, 122.40, 127.22, 128.70, 128.8, 132.31. Anal. Calcd for $C_{18}H_{27}O_6Br$: C, 51.56; H, 6.49. Found: C, 51.44; H, 6.46.

4.1.3. 2-Methylbenzoyl chloride (12). *o*-Toluic acid (5.00 g, 36.7 mmol) was suspended in dry benzene (30 mL) and oxalyl chloride (9.32 g, 73.4 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 14 h under nitrogen. The solvent and excess of oxalyl chloride were evaporated in vacuo to

provide a quantitative yield of **12** as a pale green oil. IR (neat): 1770 (C=O) cm^{-1}.

4.1.4. *tert*-Butyl 2-methylbenzoate (13).[13] Pyridine (8.9 mL, 110 mmol) and *t*-BuOH (10.4 mL, 110 mmol) were added to a flask containing acid chloride **12** (5.67 g, 36.7 mmol). Upon stirring the solution overnight at room temperature, a white precipitate formed. After addition of CH_2Cl_2, the resulting solution was washed with water and 5% aq HCl. The organic layer was dried over Na_2SO_4 and the solvent was evaporated in vacuo. The residue was passed through a short column of alumina with petroleum ether as eluent to give 6.02 g (85%) of ester **13** as a colorless oil. IR (neat): 1718 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.59 (s, 9H), 2.57 (s, 3H), 7.18–7.24 (m, 2H), 7.33 (d of d, 1H), 7.83 (d of d, 1H).

4.1.5. *tert*-Butyl 2-(bromomethyl)benzoate (14).[14] To a solution of ester **13** (1.68 g, 8.76 mmol) in CCl_4 (20 mL) was added NBS (1.81 g, 10.52 mmol) and benzoyl peroxide (0.20 g). The solution was irradiated for 2 h with a 500 watt tungsten lamp, allowed to cool to room temperature and washed with water. The organic layer was dried over $MgSO_4$ and evaporated in vacuo to provide a viscous oil. Chromatography on silica gel with CCl_4 as eluent gave **14** (1.46 g, 61%) as a colorless, viscous oil. ^1H NMR ($CDCl_3$): δ 1.62 (s, 9H), 4.93 (s, 2H), 7.29–7.48 (m, 3H), 7.87 (d of d, 1H).

4.1.6. *tert*-Butyl 2-[(oxymethyl-12-crown-4)methyl]-benzoate (17). A solution of hydroxymethyl-12-crown-4 (**15**) (0.41 g, 2.00 mmol, dried at 90 °C under high vacuum for 24 h) in THF (10 mL) was added to a flask containing NaH (0.09 g, 2.2 mmol, 60% dispersion in mineral oil). After stirring the mixture for 10 min, a solution of ester **14** (0.54 g, 2.00 mmol) in THF (10 mL) was added. The mixture was stirred for 5 h at room temperature and the solvent was evaporated in vacuo. To the residue were added CH_2Cl_2 and water. The organic layer was dried over $MgSO_4$, concentrated, and chromatographed on deactivated alumina with EtOAc as eluent to yield **17** (0.55 g, 68%) as a colorless oil. IR (neat): 1705 (C=O), 1134 (C–O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.58 (s, 9H), 3.50–4.00 (m, 17H), 4.91 (s, 2H), 7.25–7.90 (m, 4H). Anal. Calcd for $C_{21}H_{32}O_7$: C, 63.60; H, 8.14. Found: C, 63.42; H, 7.83.

4.1.7. 2-[Oxymethyl-12-crown-4)methyl]benzoic acid (2). To ester **17** (0.55 g, 1.40 mmol) was added 6 N HCl (5 mL) and the mixture was stirred at room temperature under nitrogen for 3 h. The acidic solution was made basic (pH ~ 12) with 20% aq NaOH. The basic solution was extracted with CH_2Cl_2 (3×10 mL) and acidified to pH 1 with 6 N HCl. The acidic solution was extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give **2** (0.45 g, 96%) as a pale yellow oil. IR (neat): 2864 (COOH), 1715 (C=O), 1136 (C–O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.40–3.95 (m, 17H), 4.92 (s, 2H), 6.70 (br s, 1H), 7.35 (t, 1H), 7.55 (m, 2H), 7.99 (d, 1H). ^{13}C NMR ($CDCl_3$): δ 70.07, 70.18, 70.51, 70.93, 70.93, 71.49, 71.56, 76.57, 77.00, 77.42, 78.48, 127.20, 127.63, 127.75, 130.15, 131.36, 132.93, 140.80, 171.44. Anal. Calcd for $C_{17}H_{24}O_7$: C, 59.96; H: 7.11. Found: C, 59.95; H, 7.23.

4.1.8. *tert*-Butyl 2-[(oxymethyl-15-crown-5)methyl]-benzoate (18). By the procedure recorded above for preparation of **17**, hydroxymethyl-15-crown-5 (**16**) (0.50 g, 2.00 mmol, dried at 80 °C under high vacuum for 24 h) was reacted with ester **14** to give **18** (0.71 g, 81%) as a colorless oil. IR (neat): 1706 (C=O), 1134 (C–O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.58 (s, 9H), 3.60–3.88 (m, 21H), 4.91 (s, 2H), 7.20–7.90 (m, 4H). Anal. Calcd for $C_{23}H_{36}O_8$: C, 62.71; H, 8.23. Found: C, 62.92; H, 7.96.

4.1.9. 2-[Oxymethyl-15-crown-5)methyl]benzoic acid (3). By the procedure given above for the preparation of **2**, ester **18** (0.71 g, 1.60 mmol) was hydrolyzed to provide **3** (0.53 g, 86%) as a pale yellow oil. IR (neat): 2870 (COOH), 1713 (C=O), 1119 (C–O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.55–3.95 (m, 21H), 4.93 (s, 2H), 6.70 (br s, 1H), 7.35 (t, 1H), 7.55 (t, 1H) 7.65 (t, 1H), 8.05 (d, 1H). ^{13}C NMR ($CDCl_3$): δ 70.08, 70.36, 70.53, 70.69, 71.03, 71.09, 71.25, 76.57, 77.00, 77.42, 78.55, 126.88, 127.02, 127.37, 127.69, 131.00, 131.15, 132.75, 141.06, 170.93. Anal. Calcd for $C_{19}H_{28}O_8$: C, 59.39; H, 7.34. Found: C, 59.44; H, 7.26.

4.1.10. *tert*-Butyl 2-[(oxymethyl-18-crown-6)methyl]-benzoate (19). A solution of hydroxymethyl-18-crown-6 (**7**) (0.89 g, 2.96 mmol, dried at 80 °C under high vacuum for 24 h) in THF (10 mL) was added to a flask containing NaH (0.14 g, 3.55 mmol, 60% dispersion in mineral oil). After the mixture was stirred for 5 min, a solution of ester **14** (0.80 g, 2.95 mmol) in THF (10 mL) was added. The mixture was stirred for 5 h at room temperature and the solvent was evaporated in vacuo. To the residue, CH_2Cl_2 and water were added. The organic layer was dried over $MgSO_4$, concentrated, and chromatographed on silica gel with CH_2Cl_2/MeOH (10:1) as eluent to give **19** (1.26 g, 89%) as a viscous, colorless oil. IR (neat): 1710 (C=O), 1126 (C–O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.59 (s, 9H), 3.61–3.86 (m, 25H), 4.91 (s, 2H), 7.30 (d of t, 1H), 7.48 (d of t), 7.65 (d of t), 7.86 (d of d, 1H). Anal. Calcd for $C_{25}H_{40}O_9$: C, 61.97; H, 8.32. Found: C, 62.20; H, 8.16.

4.1.11. 2-[Oxymethyl-18-crown-6)methyl]benzoic acid (4). By the procedure given above for the preparation of **2**, ester **19** (0.71 g, 1.60 mmol) was hydrolyzed to provide **4** (0.53 g, 86%) as a pale yellow oil. IR (neat): 2850 (OH); 1712 (C=O), 1125 (C–O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.65–3.74 (m, 22H), 3.83–3.86 (m, 3H), 7.35 (d of t, 1H), 7.53 (d of t, 1H), 7.64 (d of d, 1H), 8.02 (d of t, 1H) 10.90 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 69.59, 70.41, 70.54, 70.66, 70.75, 71.35, 71.40, 76.57, 77.00, 77.42, 78.13, 127.00, 127.64, 128.12, 131.06, 132.46, 140.57, 170.71. Anal. Calcd for $C_{21}H_{32}O_9$: C, 58.87, H, 7.53. Found: C, 58.92; H, 7.48.

4.2. ^1H NMR investigations of lariat ether carboxylic acids and their alkali metal carboxylates

Lariat ether sodium, potassium, rubidium, and cesium carboxylates were produced by stirring **2–4** with an excess of the alkali metal carbonate in $CDCl_3$ at room temperature followed by filtration with the filtrate passing directly into the NMR tube. The lithium lariat ether carboxylates were prepared by reaction of solutions of **2–4** in THF with 1 equiv of *n*-BuLi in THF at −78 °C. The THF was

evaporated in vacuo. After addition of $CDCl_3$, the resultant solutions were transferred to NMR tubes.

^1H NMR spectra of **2–4** and their alkali metal carboxylate salts in $CDCl_3$ were measured at 300 MHz. Chemical shift values were determined to be independent of the sample concentration. The chemical shift differences were calculated for the AB quartets based on the center of gravity.[7] The coupling constants J_{AB} for all observed doublets were approximately 12 Hz, which is consistent with normal bond angles for a tetrahedral methylene group.

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Structures of *sym*-(R)dibenzo-16-crown-5-oxyacetic acids and their alkali metal cation binding

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Abstract—To provide insight into the influence of geminal group (R) variation in *sym*-(R)dibenzo-16-crown-6-oxyacetic acids upon their selectivity in alkali metal cation separations by solvent extraction and liquid membrane transport, studies have been conducted for R = hydrogen and decyl in homogeneous solutions by ^{1}H NMR spectroscopy and titration calorimetry and in the solid state.

1. Introduction

Attachment of a side arm with potential metal ion binding sites to a crown ether (macrocyclic polyether)[1,2] gives a lariat ether.[3] Proton-ionizable lariat ethers[4] are crown ethers with a pendant acidic group (e.g., carboxylic acid,[5] phosphonic acid,[6] phosphonic acid monoalkyl ester,[6–8] hydroxamic acid,[9] sulfonic acid, and *N*-(X)sulfonyl carboxamide[10,11]). Compared with neutral crown and lariat ethers, proton-ionizable lariat ethers have an important advantage that transfer of a metal ion into an organic medium in a separation process does not require concomitant transport of an aqueous phase anion.[12] This factor is of immense importance for potential practical applications in which hydrophilic aqueous phase anions, such as chloride, nitrate or sulfate, would be involved.

Reaction of bisphenols with metal hydroxides in aqueous solvents provides a convenient synthesis of dibenzocrown ethers containing a three-carbon bridge with a hydroxyl group on the central carbon.[13] Such dibenzocrown ether alcohols may be transformed into lariat ether carboxylic acids, such as **1**–**3** (Fig. 1).[12,14,15] Incorporation of a lipophilic group into lariat ether carboxylic acid **4** prevents loss of the lariat ether carboxylates from the organic layer into a contacting highly alkaline aqueous phase during solvent extraction.[16]

To study the influence of structural variation within proton-ionizable lariat ethers upon selectivity for competitive solvent extraction of alkali and alkaline earth metal cations, the effect of changing the lipophilic group attachment site was probed.[17] Thus, compounds **1**–**3** are structural isomers with a common dibenzo-16-crown-5-oxyacetic acid unit. Lipophilic groups are attached to the side arm, the two benzo groups, and a polyether ring carbon in lariat ether carboxylic acids **1**–**3**, respectively. Although all three ligands exhibited Na^+ selectivity (as would be predicted for a 16-crown-5 ring) in competitive extractions of five alkali metal cation species from aqueous solutions into chloroform, the Na^+ selectivity of **3** was much higher than those for structural isomers in **1** and **2**. It was proposed that the geminal lipophilic group in **3** is directed away from the polar polyether ring which orients the pendent carboxylic acid group directly over the crown ether cavity.[17] Thus, the enhanced Na^+ selectivity of **3** was attributed to preorganization of the binding site.[18]

The validity of this rationalization is now probed with dibenzo-16-crown-5-oxyacetic acid (**4**) and *sym*-(decyl)dibenzo-16-crown-5-oxyacetic acid (**5**) in homogeneous solutions by NMR spectroscopy and titration calorimetry and in the solid state.

2. Results and discussion

2.1. Alkali metal cation binding by lariat ether carboxylates derived from 4 and 5

It has been demonstrated that the Na^+ selectivity of lariat

Keywords: Proton-ionizable lariat ethers; Metal ion binding.
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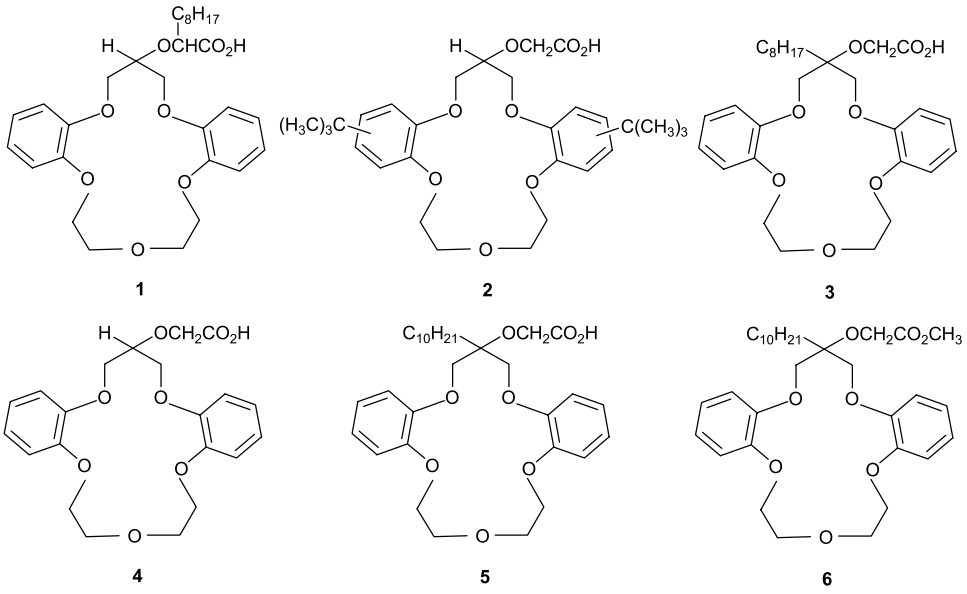


Figure 1. Structures of lariat ether carboxylic acids and ester.

ether carboxylic acid **3**, which has a geminal octyl group, in competitive solvent extraction of five alkali metal cation species from aqueous solution into chloroform is significantly greater than those for **1** and **2**, which have hydrogens geminal to the oxyacetic acid side arms.[17] However, such competitive experiments do not reveal if this increased selectivity results from: (i) enhanced Na^+ complexation; (ii) poorer complexation of the other alkali metal cation species; or (iii) a combination of both factors.

To provide greater insight into alkali metal cation complexation by such lariat ether carboxylic acids, isothermal titration calorimetry experiments were performed with the corresponding lariat ether carboxylates in homogeneous solution. To avoid complication from both deprotonation and metal ion binding events, the titration solutions contained sufficient tetrabutylammonium hydroxide to quantitatively convert the lariat ether carboxylic acids into the corresponding lariat ether carboxylates. Association constants and the enthalpies and entropies for 1:1 complexation of the five different alkali metal cation species by the lariat ether carboxylates of **4** and **5** in methanol are presented in Table 1.

From the relationship between the metal ion diameter and the cavity of a 16-crown-5 ring, strongest complexation of Na^+ by **4** and **5** is anticipated. As can be seen, the association constants for complexation of alkali metal cations by the carboxylate form of **4** decrease in order $Na^+ > K^+ > Rb^+ > Li^+$, Cs^+. (The heat generated in titrations of Li^+ and Cs^+ was too low for reliable data to be obtained.) Association constants for complexation of alkali metal cations by the carboxylate form of **5** decrease in the order $Na^+ \gg K^+ > Rb^+ > Li^+$, Cs^+, with the heat generated in titration of Li^+ and Cs^+ being too low for reliable data to be obtained. Although the log K_{ass} values for complexation of K^+ and Rb^+ show only small changes in going from the carboxylate form of **4** to the carboxylate form of **5**, the log K_{ass} value for Na^+ increases by 0.75. These data clearly establish that the greater Na^+ selectivity observed in competitive solvent extraction of alkali metal cations from aqueous solutions into chloroform by lariat ether carboxylic acid **3** than by **1** and **2** results from enhanced Na^+ complexation, rather than from poorer complexation of the other alkali metal cations.

2.2. Solid-state structures of lariat ether carboxylic acids 4 and 5

The three-carbon bridge in a 16-crown-5 ring presents conformational possibilities not found in crown ethers with only two-carbon bridges. Limiting conformations for the three carbons and the two attached oxygen atoms in dibenzo-16-crown-5-oxyacetic acids are shown in Figure 2.

Table 1. Association constants and enthalpies and entropies of complexation of alkali metal cation complexation by the tetrabutylammonium lariat ether carboxylates of **4** and **5** in methanol at 20.00 °C

	Li^+	Na^+	K^+	Rb^+	Cs^+
Tetrabutylammonium dibenzo-16-crown-5-oxyacetate (from **4**)					
log K_{ass}	IH[a]	3.99±0.03[b]	3.47±0.01	2.70±0.13	IH[a]
ΔH (kcal/mol)		−2.68±0.02	−5.00±0.02	−7.07±0.20	
ΔS (cal/mol-deg)		9.2±0.6	−0.8±0.01	−11.3±0.6	
Tetrabutylammonium *sym*-(decyl)dibenzo-16-crown-5-oxyacetate (from **5**)					
log K_{ass}	IH[a]	4.68±0.01	3.42±0.01	2.63±0.03	IH[a]
ΔH (kcal/mol)		−2.48±0.01	−3.31±0.01	−3.89±0.22	
ΔS (cal/mol-deg)		13.1±0.3	4.6±0.1	−1.0±0.1	

[a] Insufficient heat generated for reliable data to be obtained.
[b] Error limits calculated by curve fitting by the MicroCal software.

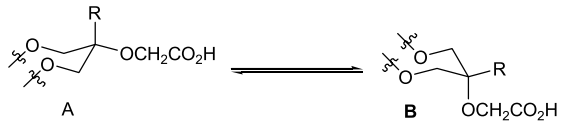


Figure 2. Limiting conformations of the three-carbon bridge in *sym*-(R) dibenzo-16-crown-5-oxyacetic acids.

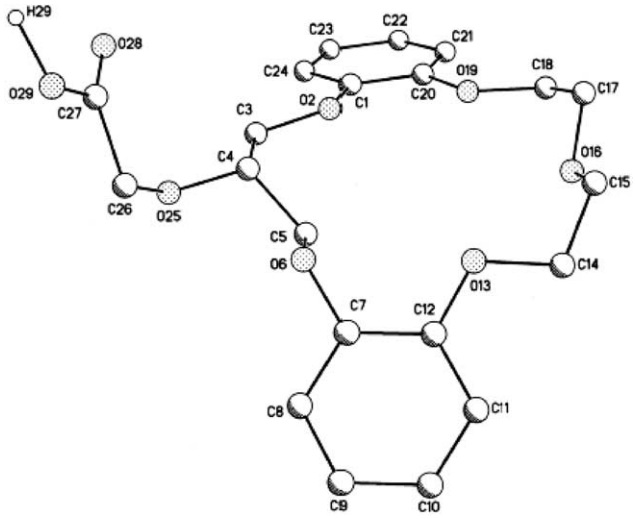


Figure 3. Solid-state structure and numbering scheme for *sym*-dibenzo-16-crown-5-oxyacetic acid.

In structure A, the oxyacetic acid side arm is in a pseudoequatorial position and the R group is pseudoaxial. Conformational inversion produces the right-hand structure B in which R is pseudoequatorial and the oxyacetic acid group is pseudoaxial. When R is hydrogen, the larger oxyacetic acid group prefers the pseudoequitorial position, favoring structure A. On the other hand, when R is an alkyl group, it is larger and prefers to be pseudoequatorial. This places the oxyacetic acid group in a pseudoaxial position favoring structure B. In B, the functional side arm may be oriented over the crown ether cavity, which preorganizes the binding site for metal ion complexation and increases the binding and selectivity for the metal ion that is best accommodated by the crown ether cavity. To evaluate the validity of this conformational analysis, solid-state structures have been determined for lariat ether carboxylic acids **4** and **5**.

A ball-and-stick representation showing the atom numbering scheme for the solid-state structure of lariat ether carboxylic acid **4** is presented in Figure 3. As can be seen, the oxyacetic acid group is in a pseudoequatorial position. Molecules of **4** are linked together by intermolecular hydrogen bonds (Fig. 4). The oxyacetic acid group points away from the polyether cavity of the molecule toward the polyether framework in another unit cell with H29 forming a hydrogen bond with O16A of that molecule. The hydrogen bond data are: H29···O16A = 1.68 Å and O29···O16A = 2.73 Å with the angle O29–H29–O16A = 141°.

In contrast, the presence of the geminal decyl group in **5** causes the oxyacetic acid group to be oriented in a pseudoaxial position with the carboxylic acid function oriented over the crown ether cavity (Fig. 5). Interestingly, the carboxylic acid groups of two molecules of **5** form dimers (Fig. 6, with the decyl groups truncated to methyl groups for clarity), which are related by centers of inversion. The hydrogen bond data are: H29···O28A = 1.66 Å and O29···O28A = 2.65 Å with the angle O29–H29–O28A = 145°.

The solid-state structures of **4** and **5** are consistent with the conformational analysis shown in Figure 2 in which lariat ether carboxylic **4** is represented by Structure A and **5** by Structure B. Thus, a geminal alkyl group serves to orient the functional side in a pseudodoaxial position. This preorganizes the binding site and increasing binding for the alkali metal cation best accommodated within the 16-crown-5 cavity. This is consistent with the increased Na^+ selectivity observed in competitive alkali metal cation extraction by lariat ether carboxylic acid **3** compared with **1** and **2**.

2.3. Solution structures of lariat ether carboxylic acids 4 and 5

To compare structures for lariat ether carboxylic acids **4** and **5** in solution with those found in the solid state (vide infra), ^{1}H NMR spectroscopy was employed. Variation of the substituent geminal to the oxyacetic acid side arm was found to affect their ^{1}H NMR spectra (Fig. 7). Particularly interesting is the separation of signals for the diastereotopic protons of the crown ether portion of the molecule (Fig. 8), which is evident in the spectra of **5** in some solvents, but not in the spectra of **4**.

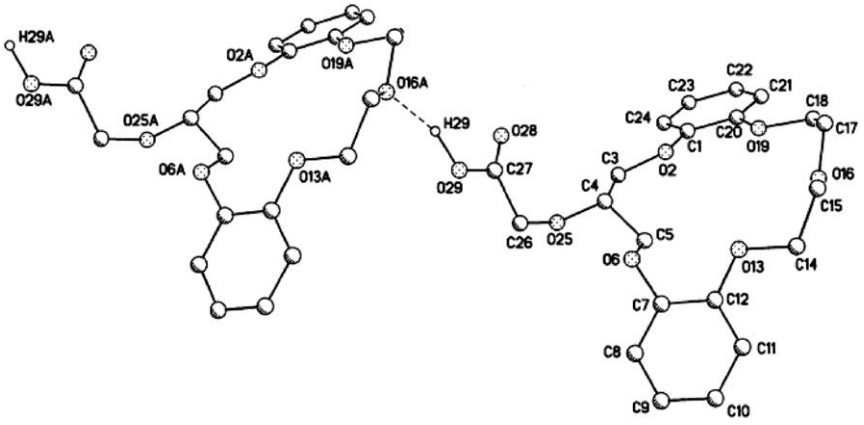


Figure 4. Intermolecular hydrogen bonding of *sym*-dibenzo-16-crown-5-oxyacetic acid in the solid state.

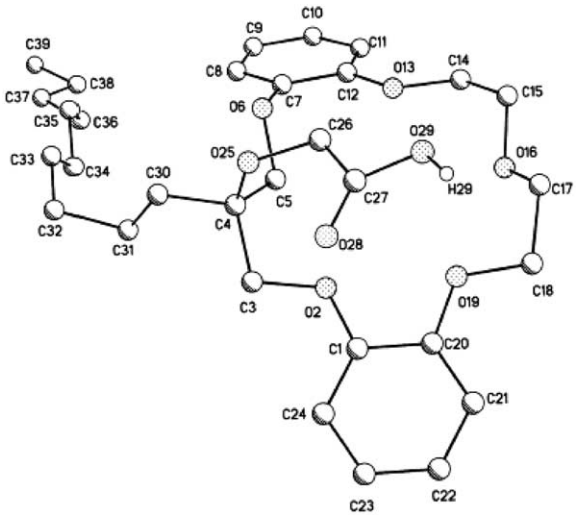


Figure 5. Solid-state structure and numbering scheme for *sym*-(decyl) dibenzo-16-crown-5-oxyacetic acid.

A single set of signals observed in a spectrum is due to a fast conformational exchange and arises from the weight-averaged conformation, which results from averaging of all conformations of a compound in solution with respect to their populations. Recently,[19,20] we demonstrated that analysis of differences in chemical shifts ($\Delta\delta$) for the diastereotopic protons in the crown ether portion of a lariat ether molecule, especially for those remote to the side arm attachment site, can provide insight into the orientation of the side arm. Significant $\Delta\delta$ values observed for those 'remote' diastereotopic protons revealed appreciably different environments for the H_A and H_B protons, which is consistent with close proximity of the side arm to the crown ether unit.

From the ^{1}H NMR spectral data for **5** presented in Table 2, it can be seen that the $\Delta\delta$ values for the remote protons attached to C7 and C8 are solvent-dependent, revealing changes in the weight-averaged conformation with solvent variation. From the changes in these $\Delta\delta$ values, it is evident

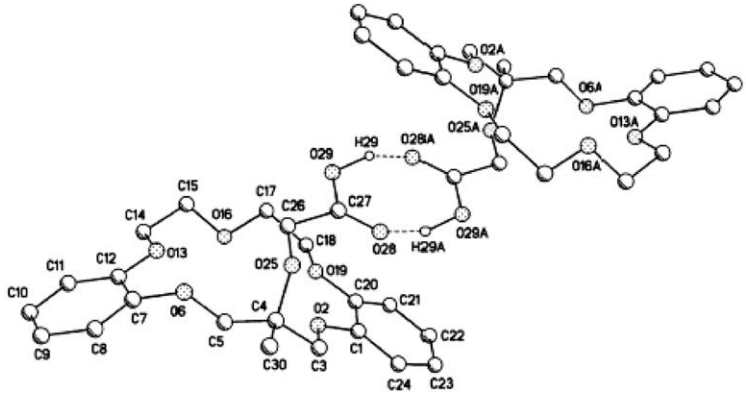


Figure 6. Intermolecular hydrogen bonding of *sym*-(decyl)dibenzo-16-crown-5-oxyacetic acid in the solid state.

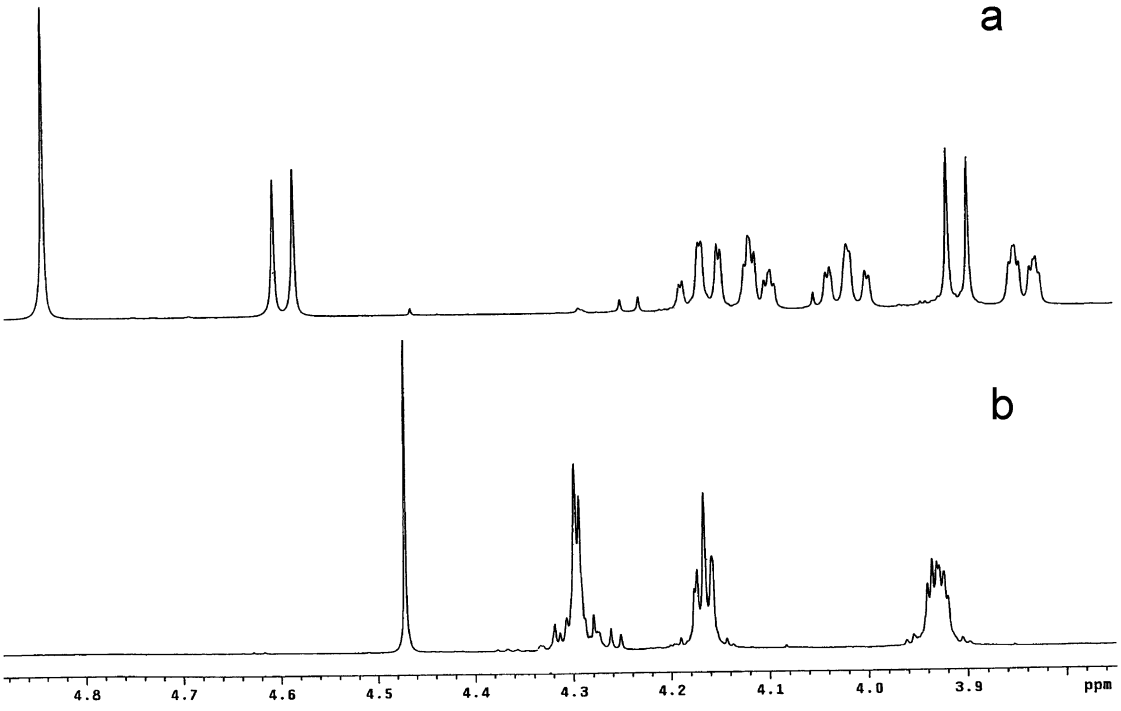
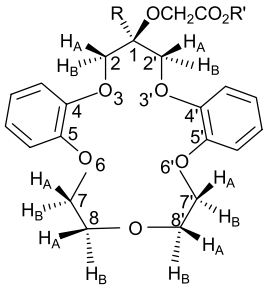


Figure 7. Portions of the 500 MHz spectra for (a) *sym*-(decyl)dibenzo-16-crown-5-oxyacetic acid (**5**) and (b) *sym*-dibenzo-16-crown-5-oxyacetic acid (**4**) in $CDCl_3$.



	R	R'
4	H	H
5	$C_{10}H_{21}$	H
6	$C_{10}H_{21}$	CH_3

Figure 8. Numbering scheme for diastereotopic crown ether ring hydrogens in *sym*-(R)dibenzo-16-crown-5-oxyacetic acids **4** and **5** and ester **6**.

that the contribution of conformations with the side arm located over the crown ether unit decreases as the polarity and hydrogen bond acceptor ability of the solvent are increased, becoming negligible in DMSO-d_6. Participation of the carboxylic acid group in stabilizing conformations with the side arm located over the crown ether cavity is supported by comparison of the $\Delta\delta$ values in $CDCl_3$ for lariat ether carboxylic acid **5** and its methyl ester **6** (Table 2). For **6**, in which the side arm cannot function as a hydrogen bond donor, no differentiation is evident for the remote protons attached to C7 and C8.

To probe the nature of the hydrogen bonding present in solutions of **5** in $CDCl_3$, ^{1}H NMR spectra were recorded at different concentrations. No difference was observed in the ^{1}H NMR spectra for 0.050 and 0.0020 M solutions of **5** in $CDCl_3$ (see Figure S1 in the Supplementary data). This reveals that the hydrogen bonding is intramolecular, rather than the intermolecular hydrogen bonding found in the solid-state structure of **5** (Fig. 6). Examination of CPK space-filling models suggests that the intramolecular hydrogen bonding is interaction of the carboxylic acid group proton with O6 (Fig. 8).

No separation was observed in the signals for the diastereotopic protons in the crown ether portion of the molecule in the ^{1}H NMR spectra of lariat ether carboxylic acid **4** in any of the four solvents studied. Therefore, conformations with the side arm located over the crown ether cavity are concluded to be absent in appreciable amounts for solutions of **4**. Interestingly, some broadening of signals was observed in the ^{1}H NMR spectrum of **4** in $CDCl_3$ upon dilution of the solution (see Figure S2 in the Supplementary data). This indicates some type of intermolecular association of **4**, which may be similar to that observed in its solid-state structure (Fig. 4).

Thus, results of the ^{1}H NMR studies for lariat ether carboxylic acids **4** and **5** in solution with respect to orientation of the functional side arm relative to the crown ether cavity are the same as those found in their solid-state structures. However, in solvents with poor hydrogen bond acceptor ability and low polarity, **5** exhibits intramolecular hydrogen bonding, rather than the intermolecular hydrogen bonding found in the solid state. In polar solvents with good hydrogen accepting ability, neither intramolecular nor intermolecular hydrogen bonding was evident for **5**.

3. Conclusions

For *sym*-(R)dibenzo-16-crown-6-oxyacetates, isothemal titration calorimetry in methanol reveals that log K_{ass} for Na^+ complexation increased by 0.69 kcal/mole in going R=H to decyl; whereas the binding of K^+ and Rb^+ remained nearly constant. Thus, introduction of a decyl group geminal to the oxyacetate side arm substantially enhances the Na^+ binding and selectivity. In solid-state structures for the corresponding lariat ether carboxylic acids, the functional side arm points away from the crown ether cavity in **4**, but is oriented over the crown ether portion of the molecule in **5**. In solvents of poor hydrogen bond acceptor ability and low polarity, ^{1}H NMR results reveal proximity of the functional side arm to the remote portion of the crown ether ring in **5**, but not in **4**. Thus, introduction of the decyl geminal group preorganizes the binding site in the ligand and enhances complexation of that alkali metal cation which provides the best fit with the crown ether cavity.

4. Experimental

The ^{1}H NMR spectra were taken at 23 °C with a Varian Unity INOVA spectrometer at 499.7 MHz. Chemical shifts are reported in ppm (δ) downfield from TMS. For the isothermal titration calorimetry measurements, a MicroCal MCS ITC instrument was utilized. Reagent-grade methanol was dried over and distilled from magnesium. Tetrabutylammonium hydroxide (TBAOH, 1.0 M) in methanol was obtained from Aldrich.

4.1. Synthesis

Lariat ether carboxylic acids **4** and **5** and lariat ether ester **6** were prepared by reported procedures.[5,17]

Table 2. Selected ^{1}H NMR data for *sym*-(decyl)dibenzo-16-crown-5-oxyacetic acid (**5**) and methyl *sym*-(decyl)dibenzo-16-crown-5-oxyacetate (**6**)

Compound	Solvent	δ		$\Delta\delta 8_{AB}$[a]	δ		$\Delta\delta 7_{AB}$[a]
		8-H_A	8-H_B		7-H_A	7-H_B	
5	C_6D_6	3.86	3.30	0.56	3.73	3.52	0.21
5	$CDCl_3$	4.02	3.84	0.18	4.17	4.11	0.06
5	$CD_3C(O)CD_3$	3.95	3.87	0.08	4.15		ND[b]
5	$CD_3S(O)CD_3$	3.81		ND	4.08		ND
6	$CDCl_3$	3.95		ND	4.15		ND

[a] $\Delta\delta_{AB}=\delta H_A-\delta H_B$.
[b] ND, not definable.

4.2. Determination of alkali metal cation binding by lariat ether carboxylates by isothermal titration calorimetry

The calorimeter measured the heat generated when a 40 mM solution of the alkali metal chloride and 5.0 mM TBAOH in methanol was titrated into a thermostatically controlled solution of the ligand (4.0 mM) and TBAOH (5.0 mM) in methanol at 25.00 °C.[21] At the beginning of each titration run, the calorimeter was allowed to automatically monitor the baseline and start the injections when the cell temperature had stabilized. A total of 50 4.5-μL injections were made in a titration run with elapsed times of 250 s of between injections. MicroCal software[22] was utilized to fit the titration data and calculate the association constant and enthalpy and entropy of metal ion complexation.

4.3. Solid-state structure determination for lariat ether carboxylic acids 4 and 5

Suitable crystals for structure determination of **4** and **5** were crystallized from aqueous EtOH and CH_2Cl_2-hexanes, respectively. Crystal and intensity data were collected using a Nicolet R3 automated diffractometer using graphite monochromated Mo Kα radiation ($\lambda=0.71073$ Å). Data for **4** were collected at 123(3) K because the structure was badly disordered, while the data for **5** were collected at room temperature. The crystallographic data are summarized in Table 3. Both structures were solved using SHELXTL[23] and were refined and displayed using the program package SHELXTL PC.[24]

Both structures were solved using direct methods. The crystal data for **4** (Table 3) indicated that the structure was likely disordered. With only two molecules present in the unit cell, the symmetry of space group $Pmn2_1$ requires that the molecule must contain a mirror plane. Since it is impossible for **4** to contain a mirror plane, disorder was present. Initial attempts to solve the structure using room temperature data verified the presence of disorder. To properly resolve the disorder, intensity data were collected at 123(3) K. The disorder was resolved and Figure 3 shows the solid-state structure of one orientation of **4**. The disordered structure consists of the two enantiomers superimposed with atoms O25, C27, and H29 lying on a mirror plane and being common to both isomers. Hydrogen atom positions with the exception of H29 were calculated. The hydrogen atoms bonded to aliphatic carbon atoms were allowed to ride on their neighboring carbons during refinement, while those bonded to aromatic carbons were not refined. The position for the acid hydrogen H29 was obtained from a difference map and the hydrogen atom was allowed to ride on its neighboring oxygen atom. The two benzo groups were refined as rigid bodies. All non-hydrogen atoms were refined anisotopically.

For compound **5**, positions for hydrogen atoms bonded to carbon atoms of the ring and the acid group and the first four atoms of the decyl chain were calculated. The position of the acid hydrogen was obtained from a difference map. All of the hydrogen atoms were allowed to ride on their neighboring heavy atoms during the refinement process. The thermal motions of the last six carbon atoms of the decyl chain were large and several of the carbon atoms were disordered, so no attempt was made to assign hydrogen atoms to those carbon atoms. Disorder of C33, C35 and C37 was resolved, but Figure 5, for clarity, includes only one atom of each disordered pair. All of the non-hydrogen atoms except disordered C33 and C35–C39 were refined anisotropically.

CIF files for compounds **4** and **5** have been deposited with CCDC with identification numbers 260638 and 260637, respectively.

Table 3. Crystallographic data for lariat ether carboxylic acids **4** and **5**

	4	**5**
Formula	$C_{21}H_{24}O_8$	$C_{31}H_{44}O_8$
FS (g mol^{-1})	404.40	544.66
Temperature (K)	123(3)	293(3)
Crystal system	Orthorhombic	Monoclinic
Space group	$Pmn2_1$	$P2_1/n$
a (Å)	18.913(11)	17.874(6)
b (Å)	4.5480(10)	8.266(3)
c (Å)	11.155(8)	20.848(8)
β (°)	90.00	99.32(3)
Volume (Å^3)	959.5	3040
Z	2	4
μ (mm^{-1})	0.108	0.085
ρ calc. (g cm^{-1})	1.400	1.190
Crystal size (mm)	0.5×0.4×0.3	0.45×0.35×0.25
2θ Range (°)	4.24–60.12	4.62–45.08
Reflections collected	1520	4125
Unique reflections	1520 ($R_{int}=0.0$)	3978 ($R_{int}=0.0200$)
Reflections ($I>2\sigma(I)$)	1219	2237
Number of parameters	235	339
Goodness-of-fit on F^2	1.056	0.999
R ($I>2\sigma(I)$)	$R1=0.0401$, $wR^2=0.1001$	$R1=0.0736$, $wR^2=0.2004$
wR^2 (all data)	$R1=0.0525$, $wR^2=0.1124$	$R1=0.1238$, $wR^2=0.2352$
Extinction correction	0.003(4)	0.002(2)
Largest difference peak and hole, e Å^{-3}	0.156, −0.175	0.347, −0.203

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.06.095

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Computational studies of benzyl-substituted halonium ions

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Abstract—Density functional computations were carried out whose objectives were to quantify the interactions of chlorine and bromine with neighboring cationic centers in a series of 1-aryl-2-haloethyl cations. Analysis of structural changes and bonding interactions gave rise to linear correlations with σ^+ values of the aryl substituents. Electron-donating groups diminished bridging and electron-withdrawing groups gave rise to stronger bridging.

1. Introduction

Halonium ions, involving iodine, bromine or chlorine, are well-documented species formed as intermediates in various chemical processes, for example, in the electrophilic addition of halogens to alkenes.[1] The electrophilic addition of halogens to unsymmetrical alkenes can lead to carbocations in which the cationic center is stabilized by partial halogen bridging, or to dipole-stabilized carbocations, resulting in restricted rotation about the C=C bond.[2] For example, calculations have established that the cationic center–bromine distance increases with weaker bridging in alkyl substituted unsymmetrical bromonium ions.[3] Stabilization of the halogen-substituted cationic center by conjugation with vinyl or aryl substituents might be expected to further reduce the extent of halogen bridging. Density functional theory and ab initio calculations have shown that halogen bridging in vinyl stabilized chloronium and bromonium ions is weaker than in alkyl substituted analogs.[4] Bromonium ion bridging was stronger than chloronium ion bridging in vinyl-stabilized systems,[4] as expected from previous experimental[5] and computational[6] studies.

The addition of bromine to aryl-substituted alkenes has been studied experimentally in solution, mainly with substituted styrenes and stilbenes.[7] These addition reactions generally show lower stereoselectivities (*anti* addition) than bromine addition to alkyl-substituted alkenes. Phenyl ring substituents affect stereoselectivities and electron donating *para* substituents show lower stereoselectivities in styrene derivatives.[8] Rate studies of bromine addition to ring-substituted styrenes were consistent with the intermediacy of benzylic carbocations[9] on the basis of Hammett correlations. Stereochemical studies of bromine addition to *cis*- and *trans*-β-methylstyrene in acetic acid were interpreted as involving intimate bromocarbocation bromide ion pairs.[10] Rate studies of bromine addition to 4-substituted stilbenes in solution were interpreted as involving competing bridged and unbridged bromocationic intermediates[11] although other interpretations envision intermediates with variable degrees of bridging.[12,13]

In light of the variety of structural possibilities for aryl-substituted β-bromocarbocations and the smaller number of studies available for chlorine substituted cations it was of interest to extend our earlier DFT computational study[4a] to include the structures and energies of halomethyl substituted benzyl cations: Ar–CH(+)–CH_2-X. Because this study involved both chlorine and bromine a comparison of variable bridging interactions was possible. The extent of bridging was assessed by comparing C^+–C–X bond angles and bond index values between halogens (X) and the cationic center. In addition, potential energy plots revealed the relative energies of bridged versus classical ions. Computations were carried out in vacuo to assess the importance of intrinsic interactions. The affect of solvation on geometry and relative stability in selected cases was probed using continuum methodology.

2. Computational methods

All structures were fully optimized by analytical gradient using the Gaussian 98[14] suites. Density functional (DFT)

Keywords: Bridged ions; Bromonium ions; Chloronium ions; Hammett correlations.
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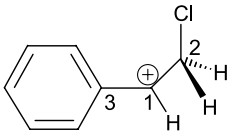
calculations used the exchange potentials of Becke[15a] and the correlation functional of Lee, Yang and Parr.[15b] Frequencies were computed by analytical methods. Reported enthalpies were corrected for zero-point energy differences (ZPVE) (unscaled)[16] and thermal effects at 298.150 K. Conformational searches involved systematic changes (12–20° increments) in the C–C–C–X dihedral angles followed by full optimizations of the maxima and minima. All stationary points gave rise to the correct number of imaginary frequencies. Curves for conformational plots and Hammett plots were fitted using MicrosoftWord Excel routines.

3. Results and discussion

3.1. 2-Chloro-1-phenylethyl cation (1)



1

A plot of the conformational energy versus dihedral angle Cl–C_2–C_1–C_3 for 2-chloro-1-phenylethyl cation **1** at the B3LYP/6-31+G(d) level was used to locate maxima and minima (Fig 1).

The structures 2, 3, 4 and 5 were subjected to full optimization and normal coordinate analysis at the B3LYP/6-311+G(d) level. Relative enthalpies and geometric features are listed in Table1.

Representations of the four 2-chloro-1-phenylethyl cation stationary points based on fully optimized structures are shown in Figure 2. Numbering used for these structures is also shown, with carbon 1 representing the carbocationic center. Figure 2 shows ion **4** conformation with dihedral angle Cl–C_2–C_1–C_3=106.5°. This structure corresponds to the geometry expected for a chloronium ion, that is, chlorine is positioned to bridge to the cationic center on C_1. Figure 2 also shows a higher energy minimum conformation **2** with chlorine C_3 eclipsed: Cl–C_2–C_1–C_3=0.0°. The carbon framework of this molecule is planar and the geometry about the carbocationic center C_1 is planar, with angles adding to 360°. An analogous minimum enthalpy eclipsed conformation was observed for 4-chlorobutenyl [4] (Fig. 3).

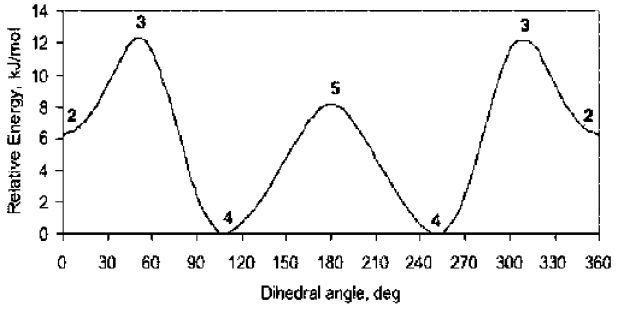


Figure 1. Dependence of relative energy of **1** with dihedral angle Cl–C_2–C_1–C_3: B3LYP/6-31+G(d).

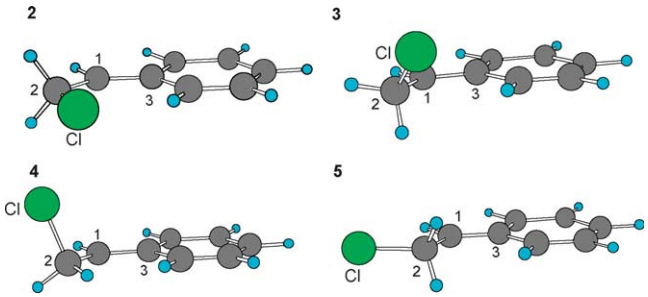
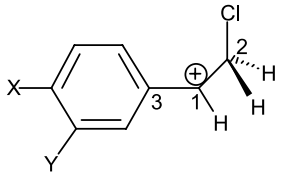


Figure 2. 2-Chloro-1-phenylethyl cation stationary points taken from Figure 1 and optimized at the B3LYP/6-311+G(d) level.

The localized representation of the cation in Figure 3 as well as cations described herein are as shown for convenience as these cations are all delocalized to some extent.

The data in Table 1 show that the Cl–C_2–C_1 bond angle decreases on rotation about the C_1–C_2 bond from a maximum value of 121.6° in conformer **2** to a minimum value of 101.6° in the chloronium ion **4**. The chlorine–carbocationic center C_1 distance also decreases and reaches a minimum value of 256 pm in **4**. The planar geometry about C_1 in **4** suggests that the chlorine bridging is relatively weak. Further evidence for chlorine bridging was obtained by correlations of the Cl–C_2–C_1 bond angle as well as Wiberg bond index (BI)[17] values with electronic properties of phenyl substituents in **1**.

3.2. 2-Chloro-1-arylethyl cations 6



6

Optimizations were carried out for a series of 2-chloro-1-arylethyl cations **6** at the B3LYP/6-31+G(d) computational level. The computed structures are minima and correspond to chloronium ion conformations as judged by the Cl–C_2–C_1–C_3 dihedral angles. Important structural parameters are shown in Table 2 along with substituent constants.[18] The Cl–C_2–C_1 bond angle decreases from a value of 106.5° for the *p*-amino substituent to 98.7° for the 5,6-dinitro substituents. Since a smaller Cl–C_2–C_1 bond angle is expected with stronger halogen bridging, this trend correlates with reduced stabilization of the carbocationic center C_1 by the ring containing electron withdrawing substituents. A Hammett plot of the bond angles with σ/σ^+ substituent constants (Fig. 4, data from Table 2) shows an acceptable correlation (R^2=0.964) and ρ=−2.86.

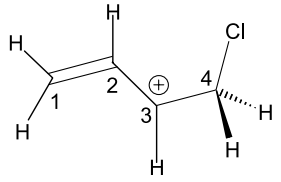


Figure 3. 4-Chlorobutenyl cation: Cl–C_4–C_3–C_2 eclipsed conformation.

Table 1. Relative enthalpies and structural parameters of stationary points of **1**: B3LYP/6-311+G(d)

Conformation	Cl–C_2–C_1–C_3[a]	ΔH[b]	Cl–C_2–C_1[c]	Cl–C_2[d]	Cl–C_1[e]	ν_i, cm^{-1}
2	0.0	4.90	121.6	178	284	
3	49.8[f]	9.42	114.5	180	277	89.9
4	106.5[g]	0.00	101.6	182	256	
5	180.0	4.05	112.8	179	273	62.9

[a] Dihedral angle, deg.
[b] kJ mol^{-1} at 298.15 K.
[c] Bond angle, deg.
[d] Bond length, pm.
[e] Interatomic distance, pm.
[f] Enantiomeric conformation at $D=310.2°$.
[g] Enantiomeric conformation at $D=253.5°$.

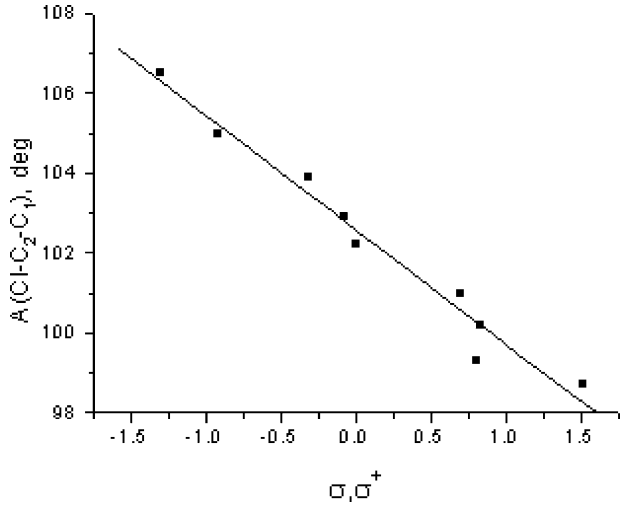


Figure 4. Correlation of Cl–C_2–C_1 bond angle with substituent constants in **6**: B3LYP/6-31+G(d).

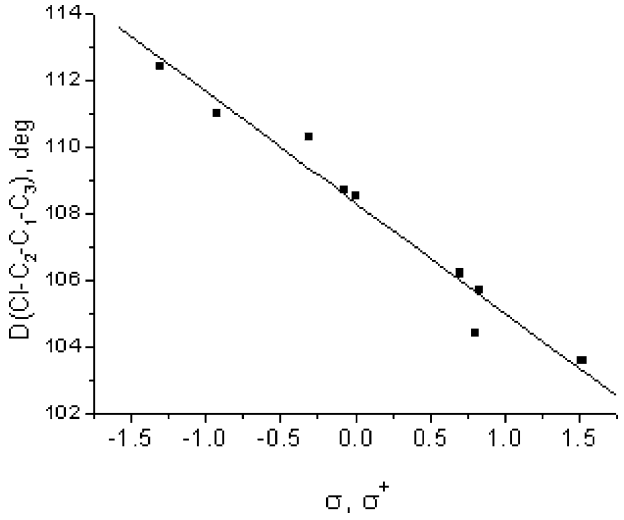


Figure 5. Dihedral angle Cl–C_2–C_1–C_3 variation with substituent constants in **6**.

Chlorine–C_2 bond lengths are constant in **6** at 182 pm for cations (181 pm for X=OH). The chlorine–C_1 interatomic distances in **6** vary from 265 to 251 pm with the smaller values corresponding to electron-withdrawing ring substituents. This correlates with stronger chlorine bridging as stabilization of the carbocationic center C_1 by the substituted ring decreases.

Dihedral angles Cl–C_2–C_1–C_3 vary from 112.4° for the electron-donating amino substituent to a value of 103.6° for the electron-withdrawing 5,6-dinitro substituents. Thus as the importance of chlorine bridging increases with greater substituent electron-withdrawal, chlorine–C_2 bonds become more parallel to the carbocationic-ring pi system. A plot of dihedral angle Cl–C_2–C_1–C_3 as a function of substituent constants shows a linear correlation (Fig. 5, $R^2=0.962$).

Table 2 shows the variation of Wiberg BI's for the Cl···C_1 and Cl···C_2 bonds in **6**. The bond index for the Cl···C_1 bond increases with electron-withdrawing capacity of ring substituents, as indicated by σ or σ^+ constants. There is a simultaneous decrease in the bond index for the Cl···C_2 bond with increasing ring substituent electron withdrawal. These variations in bond index are consistent with increased chlorine bridging resulting from decreased stabilization of

Table 2. Structural parameters for **6**: B3LYP/6-31+G(d)

Y=H, X=	σ[a,b]	A(Cl–C_2–C_1)[c]	D(Cl–C_2–C_1–C_3)[d]	Wiberg BI Cl···C_1	Wiberg BI Cl···C_2
NH_2	−1.3[a]	106.5	112.4	0.0598	0.983
OH	−0.92[a]	105.0	111.0	0.0779	0.981
CH_3	−0.31[a]	103.9	110.3	0.0924	0.978
F	−0.07[a]	102.9	108.7	0.105	0.976
H	0.0	102.2	108.5	0.115	0.974
CN	0.70[b]	101.0	106.2	0.131	0.969
NO_2	0.81[b]	99.3	104.4	0.157	0.965
NO	0.83[a,19]	100.2	105.7	0.142	0.967
Y=X=NO_2	0.71[e]	98.7	103.6	0.164	0.963

[a] σ^+ values.
[b] σ_p values.
[c] Bond angle, deg.
[d] Dihedral angle, deg.
[e] σ_m value; $\sigma_p+\sigma_m=1.52$.

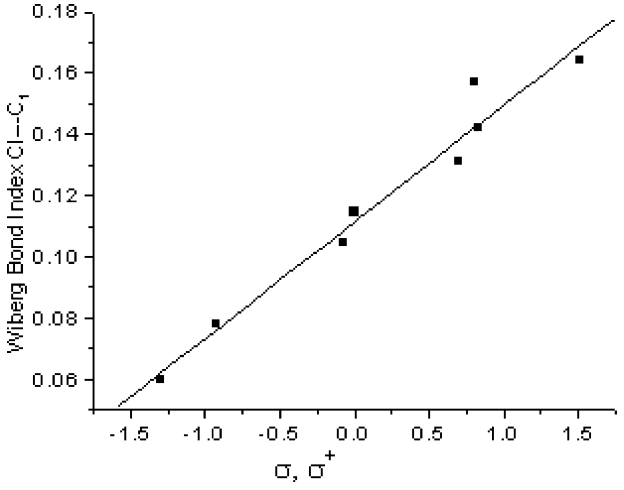


Figure 6. Variation of Wiberg bond index for Cl···C_1 with substituent constants.

the carbocationic center C_1 as a consequence of ring substituent electron withdrawal. Figure 6 shows the linear correlation ($R^2=0.966$) between Wiberg BI of Cl···C_1 and substituent constants. The above data refer to free cations in vacuum. The chloronium ion **4** was also optimized at the B3LYP/6-31+G(d) level in a dielectric continuum corresponding to that of CCl_4 (dielectric constant, DC=2.228)[20] and to DMSO (DC=46.7). Structural and relative enthalpy data for **4** in solvents are compared with vacuum data in Table 3.

The Cl–C_2–C_1 bond angle for the chloronium ion **4** increases with increasing polarity of the medium, going from 102.2° in vacuum to 103.4° in CCl_4 (DC=2.228), to 104.7° in DMSO (DC=46.7). There is a concurrent increase in the Cl···C_1 interatomic distance consistent with a decreased bridging interaction with the carbocationic center as a result of stabilization of the cation by solvation. Furthermore, the Cl–C_2–C_1–C_3 dihedral angle also increases with decreased chlorine bridging. Decreased bridging interaction of Cl with C_1 is also reflected in smaller values of the Wiberg BI, decreasing from 0.115 to 0.079 in vacuum and in DMSO, respectively. Thus, it appears that stabilization of the cation by resonance or by solvation decreases the degree of bridging by chlorine. Chloronium ion enthalpies decrease markedly in more polar media as shown in Table 3. The degree of bridging interaction by chlorine is still relatively small, however. This is shown by the low values of Wiberg BI in Table 3, as

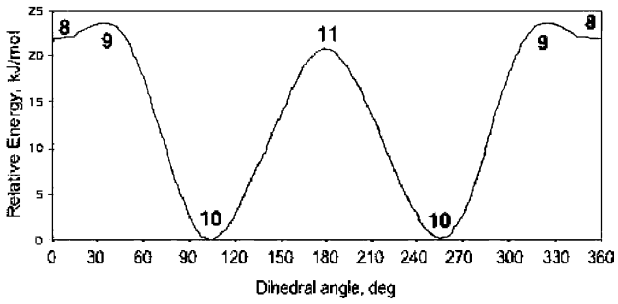
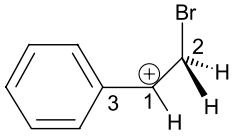


Figure 7. Variation of relative energy with conformation in **7**: B3LYP/6-31+G(d,p); LAN2LDZ.

well as by structural parameters. For example, in DMSO the geometry about C_1 is planar, with angles to adjacent hydrogen and carbons adding to 360°. Planarity about C_1 appears to correlate with weak bridging by halogen.

3.3. 2-Bromo-1-phenylethyl cation 7



7

Conformational stationary points were determined for the 2-bromo-1-phenylethyl cation **7** using DFT calculations at the B3LYP/6-31+G(d,p); LANL2DZ level (Fig. 7). As with the chlorine analog **1**, two conformational minima **8** and **10** and two conformational transition states **9** and **11** were located in the Br–C_2–C_1–C_3 dihedral angle region 0 to 180°. Further refinement led to relative enthalpies and structural parameters as shown in Table 4 for stationary points determined by B3LYP/6-311+G(d) optimizations.

That the significant stabilization of conformation **10** corresponds to an unsymmetrically bridged bromonium ion is evident from ΔH data in Table 4 and the deep minimum at ca. 104° in Figure 7. It is notable that conformation **10** is considerably more stabilized than the analogous chloronium ion **4** (cf. Table 1). The greater degree of bridging by bromine in **10** than by chlorine in **4** is further supported by the smaller Br–C_2–C_1 bond angle versus the Cl–C_2–C_1 angle (98.7 vs 101.6°, respectively). Also, the interatomic Br···C_1 distance in **10** is minimal relative to alternate conformations (Table 4). These

Table 3. Structural parameters and relative enthalpies for **4** optimized in solvents[a]

Solvent	ΔH[b]	D(Cl–C_2–C_1–C_3)[c]	A(Cl–C_2–C_1)[d]	Cl···C_1[e]	Wiberg BI, Cl···C_1
Vacuum	0.0	108.5	102.2	258	0.115
CCl_4	83.9	111.9	103.4	259	0.097
DMSO	179.0	116.0	104.7	262	0.079

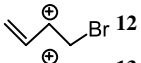
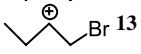
[a] B3LYP/6-31+G(d).
[b] $\Delta(H_{vac}-H_{sol})$, kJ/mol.
[c] Dihedral angle.
[d] Bond angle, deg.
[e] Interatomic distance, pm.

Table 4. Relative enthalpies and structural parameters for stationary points of **7**: B3LYP/6-311+G(d)

Conformation	Br–C_2–C_1–C_3[a]	ΔH[b]	Br–C_2[c]	Br–C_1[d]	Br–C_2–C_1[e]	ν_i, cm^{-1}
8	0.0	19.72[f]	194	302	123.4	
9	37.5	19.74[g]	196	298	119.2	31.0
10	103.7	0.0	199	264	98.7	
11	180.0	16.10	195	288	113.5	82.3

[a] Dihedral angle, deg.
[b] kJ mol^{-1} at 298.15 K.
[c] Bond length, pm.
[d] Interatomic distance, pm.
[e] Bond angle, deg.
[f] Relative $\Delta G=18.5$[b] kJ mol^{-1}.
[g] Relative $\Delta G=25.0$[b] kJ mol^{-1}.

Table 5. Wiberg bond index: Br···C^+ for conformations of **7** and reference cations

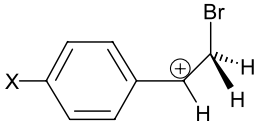
Structure	Wiberg BI[a] Br···C^+	NBO charge[14b] at C^+
8	0.051	0.146
9	−0.016	0.157
10	0.169	0.108
11	0.030	0.176
 **12**	0.336[b]	0.0046[b]
 **13**	0.688[b]	−0.095[b]

[a] Calculated at B3LYP/6-311+G(d) level for **8**–**11**.
[b] Calculated at B3LYP/6-31+G(d) level.

structural differences are expected since bromine is known to be a better bridging atom than chlorine.[6,21–24] due to its greater polarizability and larger C–halogen bond length.

Further evidence that conformation **10** corresponds to the bridged bromonium ion is based on Wiberg BI values and cationic charges for stationary point conformations of **7** shown in Table 5 along with two reference cations **12** and **13**. Thus, the Wiberg bond index corresponding to the Br···C^+ interaction is larger in conformation **10** corresponding to the bromonium ion than in the other stationary point conformations **8**, **9**, and **11**. The reference bromonium ion **13** shows a much larger index for the corresponding interaction, due to lack of additional stabilization by phenyl as in **10**. Cation **12** has a smaller index than **13** due to additional stabilization by the vinyl group. The comparison of calculated positive charge at the carbocationic centers of conformations **8**–**11** further supports bridging in **10**. The smallest charge occurs with the bromonium ion **10**, presumably because of stabilization by bromine.

3.4. 2-Aryl-1-bromoethyl cations 14



14

Optimizations were carried out for a series of *p*-substituted 2-phenyl-1-bromoethyl cations **14** at the B3LYP/6-31+G(d) computational level. The data refer to cations in vacuum in the lowest energy conformation. Important structural parameters are shown in Table 6 including Wiberg bond index data and atomic charges on C_1.

Bond angle Br–C_2–C_1 in Table 6 decreases with increasing electron-withdrawal by the *p*-substitutent, reaching the value of 94.7° for the *p*-nitro group. Figure 8 shows a good linear correlation of the bond angle with substituent constants ($R^2=0.956$). This trend is that expected for stronger bridging by bromine, and the correlation with increasing electron-withdrawal by the aryl group shows that decreased stabilization of the carbocationic center C_1 by the aryl group is compensated by stronger bridging by bromine. This effect is similar to that observed for chlorine (vide supra), although bridging by bromine is stronger than that by chlorine as expected. For example, the bond angle for the *p*-nitro substituent is 94.7° (Table 6) compared with 99.3° with chlorine bridging (Table 2). This interpretation is strengthened by the monotonic increase of Wiberg bond index values for Br···C_1 with increasing electron-withdrawal by the aryl group in **14**. A linear correlation of Wiberg Br···C_1 bond index with substituent constants is shown in Figure 9 ($R^2=0.952$).

Table 6. Structural parameters for **14**

14 X=	σ[a,b]	A(Br–C_2–C_1)[c]	D(Br–C_2–C_1–C_3)[d]	Wiberg BI[e] Br···C_1	Wiberg BI[e] Br···C_2	C_1 NBO charge[14b]
NH_2	−1.3[a]	105.3	102.5	0.075	0.955	−0.0056
OH	−0.92[a]	102.8	102.1	0.107	0.950	0.0264
F	−0.07[a]	99.9	101.4	0.150	0.942	0.0483
H	0.0	98.8	101.7	0.167	0.939	0.0587
CN	0.70[b]	97.4	101.8	0.191	0.934	0.0536
NO_2	0.81[b]	94.7	99.8	0.235	0.927	0.0558

[a] σ^+ values.
[b] σ_p values.
[c] Bond angle, deg.
[d] Dihedral angle, deg.
[e] Wiberg bond index.[17]

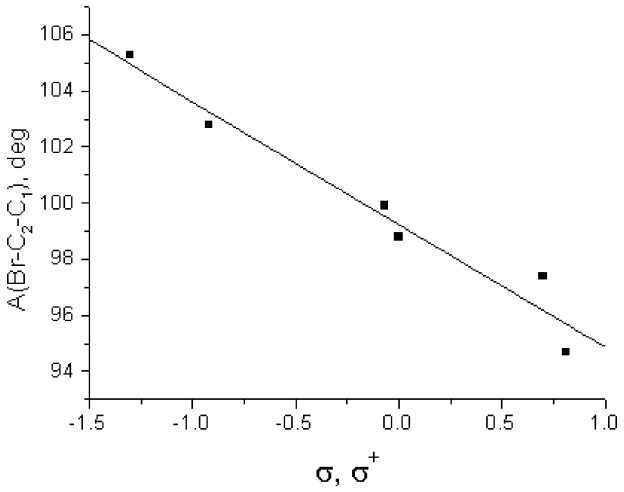


Figure 8. Br–C_2–C_1 bond angle variation with substituent constants in **14**.

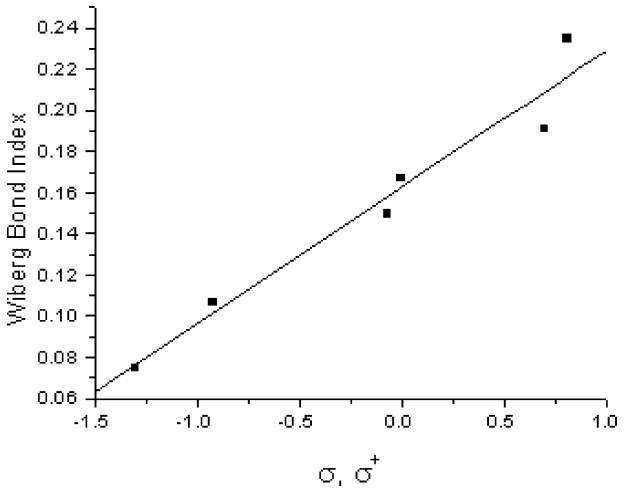


Figure 9. Variation of Wiberg bond index for Br···C_1 with substituent constants.

A decrease in Wiberg bond index for the Br···C_2 bond is seen with increasing electron-withdrawal by the aryl group. Increased bridging weakens the Br–C_2 bond. Halogen bridging depends on double bond substitution[1c] and for strongly electron-donating ring substituents it has been proposed that bromination involves β-bromocarbocations.[25] Kinetic studies of bromination of substituted styrenes and stilbenes in methanol have been interpreted as involving carbocations and/or bromonium ions formed by competitive pathways.[1c,7,25,26] The data for free ions **14** are more simply explained by a series of cations with varying degrees of bromine bridging. Although bridging interactions appear to be weak, as judged by planarity about C_1, the sequence of Wiberg BI values (Table 6) are indicative of some degree of bonding interaction between Br and C_1.

Optimizations of the bromonium ion **10** were carried out at the B3LYP/6-31+G(d,p); LANL2DZ computational level in a dielectric continuum corresponding to CCl_4 (DC= 2.228) and to DMSO (DC=46.7). The results are compared with vacuum data in Table 7. In going from vacuum to media of increasing polarity the Br–C_2–C_1 bond angle in **10** is seen to increase.

In addition, the Br–C_2–C_1–C_3 dihedral angle concurrently increases and the Br···C_1 interatomic distance increases. These changes parallel similar changes in the cation **4** (Table 3). Increasing stabilization of the dissociated cation by a polar medium decreases the degree of halogen bridging in both **10** and **4**. Decreased interaction between Br and the electron-deficient π-system in polar media is further demonstrated by smaller values of the Wiberg BI in Table 7. Corresponding values of the Wiberg bond index for the chlorine-substituted cations are smaller than bromine-substituted cations in vacuum and in solvents (see Tables 2 and 3). Differences in structural detail between these systems and cations studied experimentally may be expected. In the absence of a counterion,[27] and with possible specific solvation effects, the halogen may provide additional stabilization by partial bridging with C_1. Increasing polarity of the medium has a large stabilizing effect on the relative energy of the systems.

The electronic properties of *p*- (and *m*-) phenyl substituents affect the geometry of halomethyl benzyl cations. Substituents affect stereoselectivity and chemoselectivity (when nucleophilic solvents can compete with bromide ion) in the bromination of styrenes and stilbenes[1c]. Bromination of ring-substituted styrenes in acetic acid[10] and in methanol[26] is completely regioselective[1c], with the nucleophilic solvent moiety adding to the benzyl carbon. This is consistent with the weakly bridged cations computed in this work. Ring substituents exert a marked effect on stereochemistry. For example, in the bromination of *trans*-β-methylstyrenes in dichloromethane the extent of *anti*-addition of Br_2 increased from 63% for the 4-OMe substituent to 100% for the 3,5-$(CF_3)_2$ substituted olefin[26]. This was attributed to an unbridged carbocation intermediate in the former case, and to a bromonium ion intermediate in the latter case. The structures of variable-bridged carbocations, examined by the computational data in this study are consistent with the results obtained in the experimental studies. For further

Table 7. Structural parameters and relative enthalpies for **10** in vacuum and in solvents

Solvent	ΔH^a	D(Br–C_2–C_1–C_3)[b,c]	A(Br–C_2–C_1)[b,d]	Br···C_1[b,e]	Wiberg BI[f], Br···C_1
Vacuum	0.0	104.0	99.4	267	0.166
CCl_4	97.1	105.4	101.1	270	0.134
DMSO	174.7	108.6	103.2	274	0.107

[a] $\Delta H_{vac} - \Delta H_{sol}$, kJ mol^{-1}.
[b] B3LYP/6-31+G(d,p); LANL2DZ.
[c] Dihedral angle, deg.
[d] Bond angle, deg.
[e] Interatomic distance, pm.
[f] B3LYP/6-31+G(d).

discussion and references to the nature of intermediates in the bromination of olefins see, for example, Refs. 7 and 1c.

4. Summary

In summary, detailed computational analyses of the 2-chloro- and 2-bromo-1-phenylethyl cations as well as ring-substituted cations were carried out. Energies and structural parameters for the free cations were determined as a function of conformation and substitution on the phenyl rings. Our results reveal subtleties in structure and energy associated with halogen bridging in a more systematic way than has been hitherto reported. Weakly bridged halonium ions were found as stationary point minima with bromine showing stronger bridging than chlorine. Evidence for bridging involved analysis of structural parameters, bond angles, interatomic distances and dihedral angles, in addition to relative energies and Wiberg bond index values. These parameters were shown to be sensitive to other stabilizing interactions of the cations, including the electronic properties of phenyl ring substituents. In dielectric continua corresponding to carbon tetrachloride and dimethyl sulfoxide, stabilization of the cations decreases the degree of halogen-cationic interactions and markedly lowers the energies of the cations. These results support a model involving variable bridging by chlorine and bromine in free cations. Strongly bridged halonium ion species are to be expected only in structures derived solely from double bonds substituted with alkyl groups.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.06.091

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Participation of host 'spacer' atoms in carboxylic acid binding: implications for amino acid recognition

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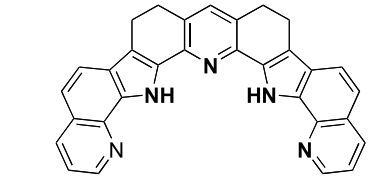
Abstract—Chiral 4,4′-diamido-2,2′-biimidazoles were synthesized and found to bind *N*-Boc protected amino acids in $CDCl_3$. The biimidazole that features (*R*)-tetrahydrofurfuryl units discriminates between *N*-Boc-L-Ser ($K_{assoc} = 120\ M^{-1}$) and its non-natural D-enantiomer ($270\ M^{-1}$). X-ray diffraction and computational analyses show that members of this receptor class adopt a cleft-like conformation, presenting a donor-spacer-donor-acceptor H-bonding array. Complexes of such biimidazoles with the –COOH unit of amino acids are stabilized by direct involvement of what is nominally a 'spacer' atom, unlike other D-Sp-D-A hosts.

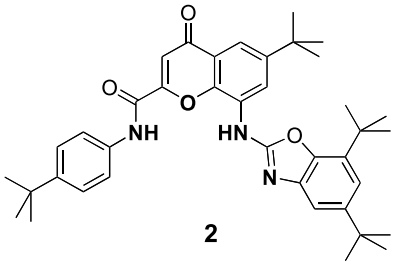
1. Introduction

Biological recognition of amino acids is accomplished by macromolecules with binding sites that are complementary to their designated substrates. Each of the aminoacyl-*t*RNA synthetases, for example, presents a unique array of functional groups and hydrophobic surfaces to detect differences in the structures of amino acid side chains.[1] Selectivity arises from a combination of noncovalent interactions like hydrogen bonding and van der Waals contacts. Individually, such interactions are generally weak; cumulatively, several such interactions can be relatively strong. Complexes of synthetic hosts and amino acid guests[2] can therefore be quite robust if stabilized by multiple H-bonds, particularly in nonpolar solvents.[3–5]

In the design of artificial receptors for carboxylic acids, the donor-spacer-donor-acceptor arrays present in **1**[6] and **2**[7] offer several advantages. Binding occurs according to mode *A*, which places the most acidic proton of the guest close to the H-bond **A**cceptor, while the lone pair electrons of the carbonyl O are 'saturated' with hydrogen bonds from the **D**-H units.[8] Nitrogen or oxygen spacer atoms (**Sp**) help maintain receptor rigidity via intramolecular D-H···Sp interactions, but are not expected to directly bind to a carboxylic acid guest. As part of a program to evaluate the supramolecular chemistry of biheterocycles,[9] the present paper examines the factors that drive recognition between the –COOH unit of amino acids and D-Sp-D-A receptors. Comparing a new set of 2,2′-biimidazoles to other cleft-shaped hosts, we find that the spacer group can play an active role in the recognition process. This result calls into question the assumption that mode *A* is always operative, and may have practical consequences for the design of enantioselective sensors and chiral stationary phases.[10]



1



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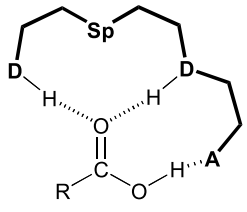

mode *A*

Keywords: Biimidazole; Amino acid recognition; Hydrogen bonding; DFT.
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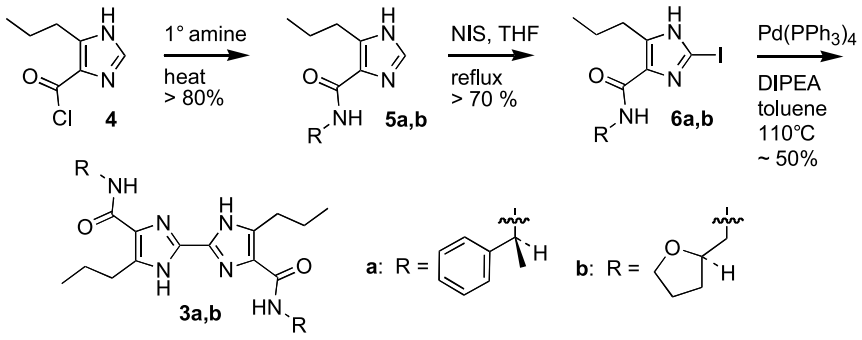

Scheme 1.

2. Results and discussion

Biimidazoles **3** were prepared by adapting previously described procedures,[9b] as shown in Scheme 1. Molecular diversity was provided by treating acid chloride **4** separately with (*S*)-α-methylbenzylamine and (*R*)-tetrahydrofurfurylamine; these arms were chosen for their potential to participate in π interactions[11] or H-bonds with aromatic or polar amino acids, respectively. Products **3a** and **3b** were judged to be enantiomerically pure by chiral HPLC (CH_3CN–H_2O gradient, monitoring 295 nm) and by ^1H NMR ($CDCl_3$, 500 MHz).

A solid-state structure was obtained for an achiral diastereomer of **3a** (Fig. 1).[12] As observed in other biimidazole diamides,[9b] *meso*-**3a** adopts an anti conformation in which the imidazole rings are nearly coplanar. Assuming that a planar orientation is retained in solution, two essentially identical chiral clefts (with N*H*···*H*N ≈ 4.2 Å) are available to bind carboxylic acid guests.

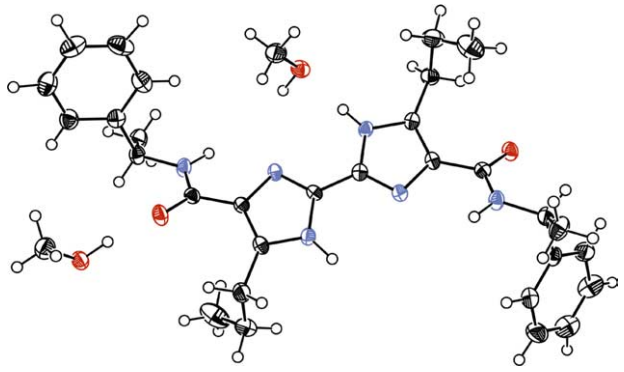

Figure 1. Structure of *meso*-**3a**·$(CH_3OH)_2$ in the crystal.

Computational modeling[13,14] of several biimidazole conformations and tautomers reveals that the anti structure observed in the crystal minimizes steric congestion while maximizing intramolecular N–H···N hydrogen bonding. Both the amide N*H* groups and the imidazole N and N*H* are involved in this stabilizing intramolecular interaction. The syn conformer, in its various tautomeric forms, disrupts the network of intramolecular hydrogen bonding and replaces these stabilizing interactions with steric clashes between adjacent N*H* atoms, increasing the energy anywhere from 5.6 to 21.3 kcal/mol (see the Supplementary data).

Table 1 shows the association constants, derived from ^1H NMR titrations in $CDCl_3$,[15] for **3a** and **3b** with both enantiomers of two different *N*-Boc amino acids. Downfield chemical shifts in the amide N*H* protons of the receptors occurred with increasing amino acid concentration, consistent with H-bond donation to the guests. Control experiments using an esterified amino acid (*N*-Boc-L-Phe-OMe) established that guest binding takes place largely at the –COOH group; although *N*-Boc-L-Phe is bound relatively strongly by **3a** ($K_{assoc} = 100\ M^{-1}$), *N*-Boc-L-Phe-OMe induced negligible shifts in the ^1H resonances of the same receptor ($K_{assoc} \approx 0\ M^{-1}$).

Table 1. Binding constants K_{assoc} (M^{-1})[a] for chiral biimidazoles with amino acid derivatives in $CDCl_3$ at 23 °C

Complex	K_{assoc}
3a·*N*-Boc-L-Phe, -D-Phe	100, 65
3a·*N*-Boc-L-Ser, -D-Ser	<60, 65
3b·*N*-Boc-L-Phe, -D-Phe	65, 65
3b·*N*-Boc-L-Ser, -D-Ser	120, 270

[a] Values represent averages of at least two replicate titrations, rounded to the nearest ±5 M^{-1}. Errors in individual fits were ≤15%.

Participation of the imidazole NH groups in guest binding could not be established from the experiments described above, because the heterocycle N*H* signals disappeared upon addition of the amino acids in Table 1. However, complexes of 'half biimidazoles' **5a** and **5b** were significantly less robust than those formed from the corresponding full receptors; K_{assoc} for **5a**·*N*-Boc-L-Phe and **3a**·*N*-Boc-L-Phe in $CDCl_3$ were 15 and 100 M^{-1}, respectively, while **5b**·*N*-Boc-D-Ser and **3b**·*N*-Boc-D-Ser had values of 80 and 270 M^{-1}. That the imidazole N*H* groups make a significant contribution, two possible amino acid binding modes were examined with DFT computational methods.[13,14] Using receptor **3b** for illustration, Figure 2a shows an interaction analogous to mode *A* described above. Alternatively, the carboxylic acid proton can interact with the imidazole nitrogen (Fig. 2b), an atom which is several orders of magnitude more basic than the ethereal oxygen. To highlight the direct involvement of so-called spacer atoms in such complexes, we describe them as occurring by mode *S*.

Although all of the complexes listed in Table 1 are weak, modest enantioselectivity was observed between **3b** and the *N*-Boc-serines. This result is difficult to rationalize within the context of mode *A*, which places the stereogenic α carbon of the amino acid far from the chiral arm of the receptor. Both the relatively high K_{assoc} values and degree of

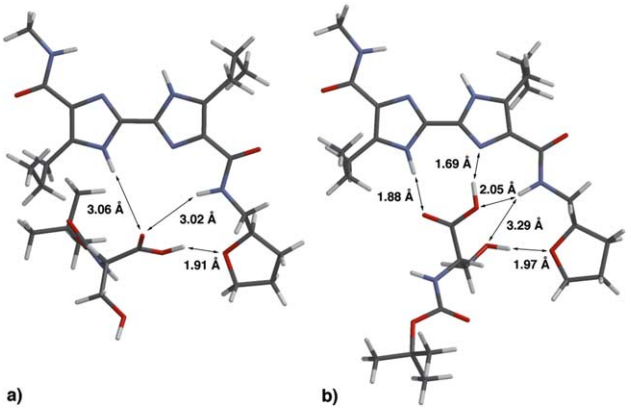

Figure 2. Model complexes of **3b**·*N*-Boc-L-Ser, optimized at the BOP/DNP level of theory. (a) Mode *A*; (b) Mode *S*. Binding energies are given in Table 2.

stereodifferentiation are better explained if complexation occurs predominantly by mode *S*,[16] which allows a tetrahydrofuranyl ring in **3b** to accept a hydrogen bond from the $-CH_2OH$ side chain. Computational studies of serine complexes predict small enhancements (-2 to -3 kcal/mol) in binding energies for **3b** relative to **3a**, consistent with weak $O–H_{Ser}\cdots O_{\mathbf{3b}}$ interactions (Table 2).

Unlike biimidazole **3b**, the groups Sp and A in molecule **1** are electronically similar (i.e., both are nitrogen atoms from substituted pyridines). As such, this host allows for more direct assessment of the geometric factors that influence guest binding, divorced from effects arising from differences in the basicities of the groups Sp and A. Gas phase calculations indicate that *N*-Boc-L/D-Phe and *N*-Boc-L/D-Ser prefer to associate with **1** via traditional mode *A*, with the intrinsic helicity of the host giving rise to small energy differences between complexes of enantiomers (Table 2). However, calculations using acetic acid as a model guest show that mode *S* can be competitive with mode *A* as the binding cleft of the host becomes less concave. Parent **1** favors mode *A* over mode *S* by -5.9 kcal/mol, largely because its 'pinched' binding pocket prevents host–guest coplanarity in mode *S* (Fig. 3a). Removal of a bridging methylene group yields the hypothetical **1**-pent, which features a greater N*H*···*H*N separation and a mode *A* bias of just -2.7 kcal/mol (Fig. 3b). This analysis was extended to determine the optimal placement of donor pyrroles and spacer/acceptor pyridine, in the absence of a receptor scaffold. In Figure 3c, the heterocycles were allowed to move independently of each other, with the single constraint that the three host nitrogen atoms and the carboxyl carbon of the acid guest remain planar. Under these conditions, mode *S* is favored by 0.7 kcal/mol. At the opposite extreme, the tiny cleft in receptor **2** (calcd N*H*···*H*N <3 Å) precludes approach of acid guests in mode *S*.

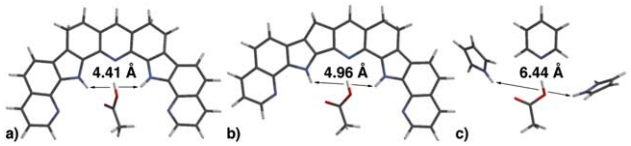

Figure 3. Comparison of acetic acid complexes derived from (a) **1**, (b) model receptor **1**-pent, and (c) their 'free floating' donor–acceptor fragments. As the D*H*···*H*D distance increases (from (a) to (c)), the O–C═O unit of the guest becomes more nearly coplanar with the D-'Sp'-D atoms.

3. Conclusions

For receptors with D-Sp-D-A topology, binding of carboxylic acids may occur at 'spacer' atoms with good accessibility/basicity. If close contact between the stereogenic centers of a chiral receptor and chiral analyte is desired (e.g., as a means to enantioselective recognition), the binding pocket of the host should be carefully engineered to control the preference for mode *A* or mode *S*.

4. Experimental

4.1. (*S*)-5-Propyl-1*H*-imidazole-4-carboxylic acid (1-phenylethyl)amide (5a)

Under N_2, a stirring mixture of freshly prepared acid chloride **4**[9b] (0.92 g, 5.3 mmol) and neat (*S*)-α-methylbenzylamine (4.2 mL, 33 mmol) was warmed with a heat gun for 15 min. Upon cooling, the green-gold syrup was dissolved in 100 mL of EtOAc, and the precipitated hydrochloride salt was filtered off. The filtrate was evaporated and purified by flash column chromatography on silica gel using EtOAc as the eluent to afford 1.25 g (92%) of the product as a viscous brown oil. TLC (EtOAc): $R_f=0.32$; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, $J=7.2$ Hz, 3H), 1.57 (d, $J=6.9$ Hz, 3H), 1.64 (m, 2H), 3.01 (m, 2H), 5.25 (m, $J=7.2$ Hz, 1H), 7.20–7.38 (m, 6H), 7.45 (d, $J=7.2$ Hz, 1H), 10.21 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 22.6, 26.9, 48.4, 126.0, 127.2, 128.6, 129.7, 132.5, 136.2, 143.8, 163.1; Anal. Calcd for $C_{15}H_{19}N_3O\cdot0.5(H_2O)$: C 67.64, H 7.57, N 15.78. Found: C 67.99, H 7.51, N 15.46.

4.2. (*R*)-5-Propyl-1*H*-imidazole-4-carboxylic acid (tetrahydrofuran-2-ylmethyl)amide (5b)

Under N_2, a biphasic stirring mixture of acid chloride **4**[9b] (1.55 g, 9.8 mmol), (*R*)-tetrahydrofurfurylamine (1.00 g,

Table 2. Calculated binding energies (kcal/mol) for complexes of amino acid derivatives

Complex	Mode *A*	Mode *S*
1·*N*-Boc-L-Phe, -D-Phe	−8.2, −7.3	+0.1, −2.3
1·*N*-Boc-L-Ser, -D-Ser	−9.1, −11.7	−5.3, −6.1
3a·*N*-Boc-L-Phe, -D-Phe	ND,[a] ND[a]	−7.1, −5.7
3a·*N*-Boc-L-Ser, -D-Ser	ND,[a] ND[a]	−7.8, −7.6
3b·*N*-Boc-L-Phe, -D-Phe	−4.5, ND	−7.3, −7.1
3b·*N*-Boc-L-Ser, -D-Ser	−4.6, ND	−9.5, −10.4

[a] The α-methylbenzyl groups of receptor **3a** lack classical H-bond acceptor atoms like O or N. See Ref. 11. ND, not determined.

9.9 mmol), and *N*,*N*-diisopropylethylamine (6.8 mL) was warmed with a heat gun for 10 min. Upon cooling, the top layer was decanted away, and the bottom layer was treated with 100 mL of EtOAc. The precipitated hydrochloride salt was removed by filtration, and the filtrate was evaporated. Flash column chromatography on silica gel using EtOAc–MeOH (9:1, v:v) as the eluent provided 1.89 g (81%) of the product as a yellow oil which solidified upon standing. Mp 98–100 °C; TLC (EtOAc–MeOH, 9:1) R_f=0.31; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J=7.2 Hz, 3H), 1.64 (m, 3H), 1.85–2.05 (m, 3H), 2.98 (t, J=7.2 Hz, 2H), 3.37 (m, 1H), 3.60 (m, 1H), 3.75 (q, J=6.9 Hz, 1H), 3.88 (q, J=6.3 Hz, 1H), 4.06 (m, 1H), 7.44 (s, 1H), 7.53 (t, 1H), 11.76 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.6, 22.6, 25.7, 26.9, 28.6, 42.5, 68.0, 77.8, 129.5, 133.0, 136.2, 164.2; Anal. Calcd for $C_{12}H_{19}N_3O_2$: C 60.74, H 8.07, N 17.71. Found: C 60.58, H 8.06, N 17.34.

4.3. (*S*)-2-Iodo-5-propyl-1*H*-imidazole-4-carboxylic acid (1-phenylethyl)amide (6a)

Reaction of **5a** (1.02 g, 4.0 mmol) with *N*-iodosuccinimide (95%; 1.10 g, 4.6 mmol) under conditions previously described[9b] afforded 1.07 g (70%) of iodide **6a** as a light yellow oil after flash column chromatography on silica gel using EtOAc as the eluent. TLC (EtOAc): R_f=0.61; ^{1}H NMR ($CDCl_3$) δ 0.79 (t, J=7.5 Hz, 3H), 1.51 (m, 2H), 1.54 (d, J=6.9 Hz, 3H), 2.85 (m, 2H), 5.21 (m, J=7.2 Hz, 1H), 7.15–7.35 (m, 5H), 7.45 (d, J=8.1 Hz, 1H), 11.62 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 22.4, 26.9, 48.5, 81.4, 126.0, 127.2, 128.5, 133.5, 141.4, 143.3, 162.0.

4.4. (*R*)-2-Iodo-5-propyl-1*H*-imidazole-4-carboxylic acid (tetrahydrofuran-2-ylmethyl)amide (6b)

Reaction of **5b** (1.08 g, 4.6 mmol) with *N*-iodosuccinimide (95%; 1.19 g, 5.0 mmol) under conditions previously described[9b] afforded 1.60 g (97%) of iodide **6b** as a faintly yellow syrup. TLC (EtOAc): R_f=0.49; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J=7.5 Hz, 3H), 1.63 (m, 3H), 1.85–2.05 (m, 3H), 2.97 (t, J=7.5 Hz, 2H), 3.35 (m, 1H), 3.59 (m, 1H), 3.79 (m, 1H), 3.91 (m, 1H), 4.12 (m, 1H), 7.37 (s, 1H), 8.68 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 22.6, 25.7, 26.9, 28.8, 42.7, 68.0, 77.9, 81.3, 133.6, 140.9, 162.7.

4.5. (*S*,*S*)-5,5′-Dipropyl-1*H*,1′*H*-[2,2′]biimidazolyl-4,4′-dicarboxylic acid bis[(1-phenylethyl)amide] (3a)

Homocoupling of **6a** (1.00 g, 2.6 mmol) using tetrakis-(triphenylphosphine)palladium(0) (0.12 g, 0.10 mmol) under conditions previously described[9b] afforded 0.36 g (54%) of biimidazole **3a** as a tan solid after flash column chromatography on silica gel using CH_2Cl_2–EtOAc (2:1, v:v) as the eluent. Mp 165 °C dec.; TLC (CH_2Cl_2–EtOAc, 2:1) R_f=0.36; ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J=7.0 Hz, 6H), 1.58 (d, J=6.5 Hz, 6H), 1.68 (m, J=7.5 Hz, 4H), 3.04 (m, 4H), 5.27 (m, J=7.5 Hz, 2H), 7.23–7.37 (m, 12H), 9.96 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 13.6, 22.1, 22.2, 26.9, 48.4, 125.9, 127.1, 128.5, 130.7, 135.7, 137.6, 143.2, 162.6; UV/vis (CH_2Cl_2): λ_{max} (ε M^{-1} cm^{-1})=291 (32,000), 299 (33,000), 314 (19,000); Anal. Calcd for $C_{30}H_{36}N_6O_2$: C 70.29, H 7.08, N 16.39. Found: C 70.39, H 7.30, N 16.20.

4.6. *meso*-5,5′-Dipropyl-1*H*,1′*H*-[2,2′]biimidazolyl-4,4′-dicarboxylic acid bis[(1-phenylethyl)amide] (*meso*-3a)

The reactions described above (Scheme 1, **4**→**3**) were repeated using racemic α-methylbenzylamine instead of (*S*)-α-methylbenzylamine. Product *meso*-**3a** was isolated as a tan solid after flash column chromatography on silica gel using CH_2Cl_2–EtOAc (2:1, v:v) as the eluent. TLC (CH_2Cl_2–EtOAc, 2:1) R_f=0.43; ^{1}H NMR (CD_3OD) δ 0.94 (t, J=7.5 Hz, 6H), 1.55 (d, J=7.0 Hz, 6H), 1.68 (m, 4H), 2.98 (m, 4H), 5.17 (m, J=7.0 Hz, 2H), 7.23–7.40 (m, 12H); ^{13}C NMR (CD_3OD) δ 14.0, 22.7, 24.0, 27.8, 127.1, 128.2, 129.6, 139.4, 145.2; Anal. Calcd for $C_{30}H_{36}N_6O_2$: C 70.29, H 7.08, N 16.39. Found: C 70.15, H 7.11, N 16.48.

4.7. (*R*,*R*)-5,5′-Dipropyl-1*H*,1′*H*-[2,2′]biimidazolyl-4,4′-dicarboxylic acid bis[(tetrahydrofuran-2-ylmethyl) amide] (3b)

Homocoupling of **6b** (1.60 g, 4.4 mmol) using tetrakis-(triphenylphosphine)palladium(0) (0.20 g, 0.17 mmol) under conditions previously described[9b] afforded 0.47 g (45%) of biimidazole **3b** as a white crystalline solid after flash column chromatography on silica gel using EtOAc–MeOH (9:1, v:v) as the eluent. Mp >260 °C; TLC (EtOAc–MeOH, 9:1) R_f=0.54; ^{1}H NMR ($CDCl_3$) δ 0.99 (t, J=7.5 Hz, 6H), 1.62 (m, 2H), 1.72 (m, J=7.5 Hz, 4H), 1.92 (m, 4H), 2.01 (m, 2H), 3.07 (t, J=7.5 Hz, 4H), 3.26 (m, 2H), 3.73 (m, 2H), 3.79 (q, J=6.0 Hz, 2H), 3.88 (q, J=7.0 Hz, 2H), 4.08 (m, 2H), 7.40 (t, J=7.0 Hz, 2H), 10.28 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.6, 25.8, 27.0, 28.8, 42.6, 78.2, 130.9, 135.8, 137.3, 163.4; UV/vis (CH_2Cl_2): λ_{max} (ε M^{-1} cm^{-1})=290 (29,000), 298 (31,000), 313 (18,000); Anal. Calcd for $C_{24}H_{36}N_6O_4$: C 61.00, H 7.68, N 17.78. Found: C 60.89, H 7.82, N 18.05.

4.8. ^{1}H NMR binding studies

A sample of **3a** or **3b** was dissolved in 1.0 mL of $CDCl_3$ such that its concentration was near 0.01 M, then the solution was transferred to an NMR tube. Solid amino acid was added to a concentration of approximately 0.005 M, the tube was vigorously shaken, and a proton NMR spectrum was acquired. Successive additions of amino acid were made, and spectra recorded, until [amino acid] was at least five times [biimidazole]. During several titrations with **3a**, aryl proton peaks obscured the amide N*H* resonances, preventing their use in derivations of K_{assoc}. In these cases, chemical shifts of the benzylic C*H* were followed instead. Control experiments confirmed that using data for either the amide N*H* or benzylic C*H* gave the same K_{assoc} values within $\pm$5 M^{-1}. Binding curves (i.e., plots of $\delta_{NH/CH}$ vs [amino acid]) were fit using the program WinEQNMR.[15]

During ^{1}H NMR titration with *N*-Boc-L-Phe, the benzylic C*H* nuclei of biimidazole **3a** experienced a small upfield shift ($\Delta\delta$=−0.015 ppm) which was not observed with any other amino acids in Table 1. This phenomenon was examined using computational methods (see the Supplementary data).

^{1}H NMR titrations were also performed for **3a** and **3b** with *N*-Boc-L/D-Pro, but a reliable association constant could

only be derived in one case (**3a**·*N*-Boc-D-Pro, $K_{assoc}=30\ M^{-1}$). Binding curves for **3a**·L-Pro and **3b**·L/D-Pro were not strictly hyperbolic, but instead featured an initial region in which δ_{NH} moved upfield. Exclusion of these 'inverted' regions from the curve fits allowed for calculation of K_{assoc} values, but with errors of >20%. The anomalous binding curves may reflect the presence of competing equilibria involving weakly self-associated biimidazole oligomers.[9] A ^{1}H NMR dilution experiment[17] using **3b** in $CDCl_3$, in which the chemical shift of the imidazole N*H* was monitored as a function of [**3b**], gave $K_{dimer}=25\ M^{-1}$.

4.9. Computational methods

Preliminary geometry optimizations were performed using Gaussian 03[18] with a restricted Hartree–Fock (RHF) wave function and a 3-21G basis set.[19] These structures were subsequently refined using the density functional theory[20] package DMol3[13] with the Becke–Tsuneda–Hirao gradient-corrected exchange-correlation functional[14] (BOP) and a double numerical plus polarization (DNP) basis set.

To avoid overwhelming the available computational resources, truncated models of host–guest complexes involving **3** were necessary and involved replacing the chiral arm of the distal amide with a methyl group. Several initial host–guest geometries, including those with secondary H-bonding to the guest Boc group, were evaluated in an effort to probe all relevant regions of the potential energy surface, because algorithms for the systematic conformational search of such complex systems were not available.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.06.096

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12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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Preparation of both enantiomers of β^2-(3,4-dihydroxybenzyl)-β-alanine, higher homologues of Dopa ☆

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Abstract—β^2-(3,4-Dihydroxybenzyl)-β-alanine [β^2-Homo-Dopa, **1**] is a novel β-amino acid homologue of Dopa, the most successful therapeutic agent in the treatment of Parkinson's disease. Enantioenriched (*R*)-**1** and (*S*)-**1** were obtained via the diastereoselective alkylation of enantiopure pyrimidinone (*R*)- and (*S*)-**3**, chiral derivatives of β-alanine, with veratryl iodide. The major diastereomeric products (2*S*,5*R*)-**4** and (2*R*,5*S*)-**4** were hydrolyzed with 57% HBr, and the desired β-amino acids were purified by silica gel chromatography. Alternatively, enantioenriched (*R*)- and (*S*)-**1** were prepared by means of the highly diastereoselective alkylation (3,4-dimethoxybenzyl iodide) of open-chain β-aminopropionic acid derivatives (*R*,*R*,*S*)-**8** and (*S*,*S*,*R*)-**8** containing the chiral auxiliary α-phenylethylamine. Finally, nearly enantiopure (*R*)- and (*S*)-**1** were obtained by resolution of racemic *N*-benzyloxycarbonyl-2-(3,4-dibenzyloxybenzyl)-3-aminopropionic acid, *rac*-**12**, with (*R*)- or (*S*)-α-phenylethylamine, followed by catalytic hydrogenolysis.

1. Introduction

Several hydroxylated derivatives of the twenty proteinogenic α-amino acids present relevant biological activity on their own. Salient examples include 4-hydroxyproline, 5-hydroxylysine, and 3,4-dihydroxyphenylalanine (Dopa). In particular, Parkinson's disease is associated with a low neurotransmitter dopamine level in the body, and it is treated with L-Dopa. Indeed, the Monsanto process for the large-scale production of L-Dopa became the first successful asymmetric protocol carried out in industry,[2] and was recently recognized with the Nobel Prize granted to its leader W. S. Knowles.[3] Academic interest in the asymmetric synthesis of L-Dopa and derivatives continues to this day.[4]

β-Amino acids are not as ubiquitous as their α-analogues, but have attracted extraordinary interest in recent years,[5] owing to their presence in numerous natural products,[6] and as precursors of β-lactams[7] and unnatural β-peptides.[8]

In this context, the enantioselective preparation of β-amino acid analogues of L-Dopa is a highly attractive goal in view of their potential as brain neurotrasmitters[9] and biologically relevant metal chelators.[10] Basically, β-amino acid homologues of L-Dopa are possible with the benzylic side chain in the 2- or 3-position; that is, β^2-homoDopa or β^3-homoDopa (Fig. 1a).[11] Interestingly, in 1998, Steglich and co-workers[12] reported the isolation of a novel β-amino acid from mushroom *Cortinarius violaceus*, which is regioisomeric to L-Dopa (Fig. 1b).

Very recently, Mazaleyrat and co-workers[13] reported the synthesis of terminally protected (*S*)-β^3-homoDopa, from L-Dopa by means of the Arndt-Eistert homologation protocol. In the present paper, we describe our work directed to the enantioselective preparation of (*R*)- and (*S*)-β^2-homoDopa.

2. Results and discussion

For the enantioselective preparation of β-amino acid (*R*)-β^2-homoDopa, (*R*)-**1**, we chose the general method developed by Juaristi et al.[14,15] employing pyrimidinone (*S*)-**2**, as outlined in Scheme 1.

Preliminary examination of the alkylation reaction was carried out on the racemic 2-isopropyl-pyrimidinone analogue *rac*-**3**, that was prepared according to the described procedure[16] (Scheme 2). In the event, generation

☆ See Ref. 1.

Keywords: β-Amino acids; Diastereoselective alkylation; Resolution; Dopa homologues.
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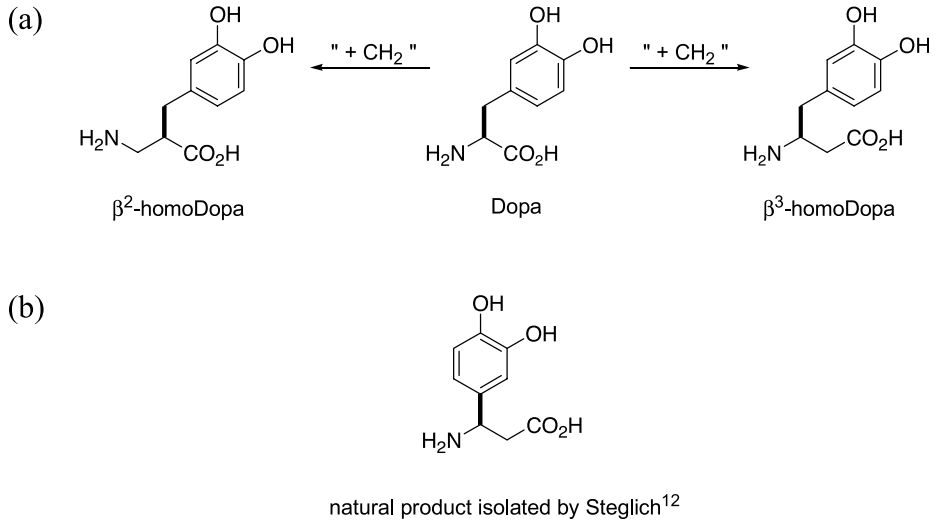
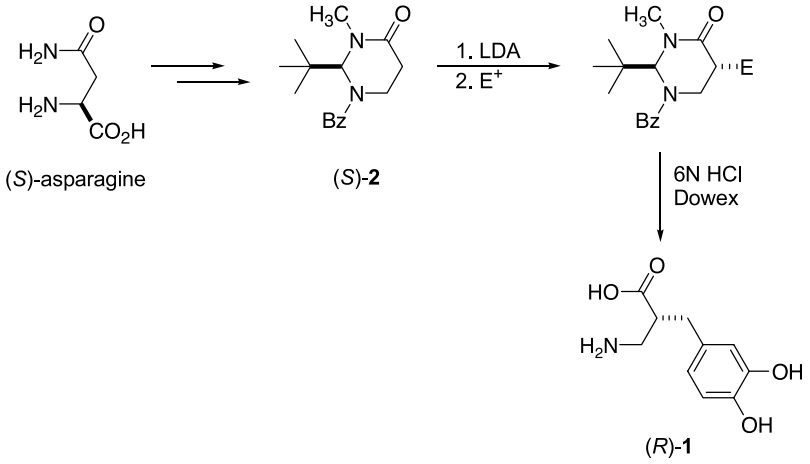


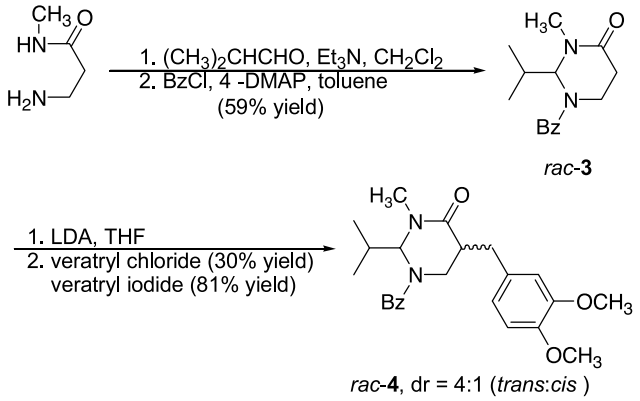
Figure 1. β-Amino acid analogues of Dopa.



Scheme 1.

of enolate *rac*-**3**-Li with LDA and subsequent addition of veratryl chloride as electrophile afforded the expected product *rac*-**4** as a 4:1 mixture of the trans- and cis-diastereomers, respectively, in a low 30% yield (Scheme 2).

In order to improve the yield of the alkylation reaction, veratryl iodide[17] was next used as electrophile. As it can be appreciated in Scheme 2, the desired product *rac*-**4** was

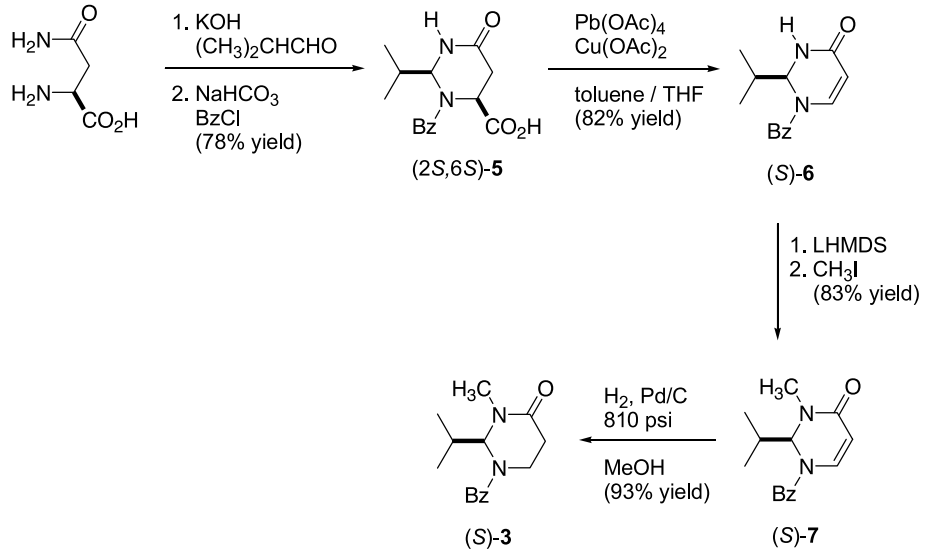


Scheme 2.

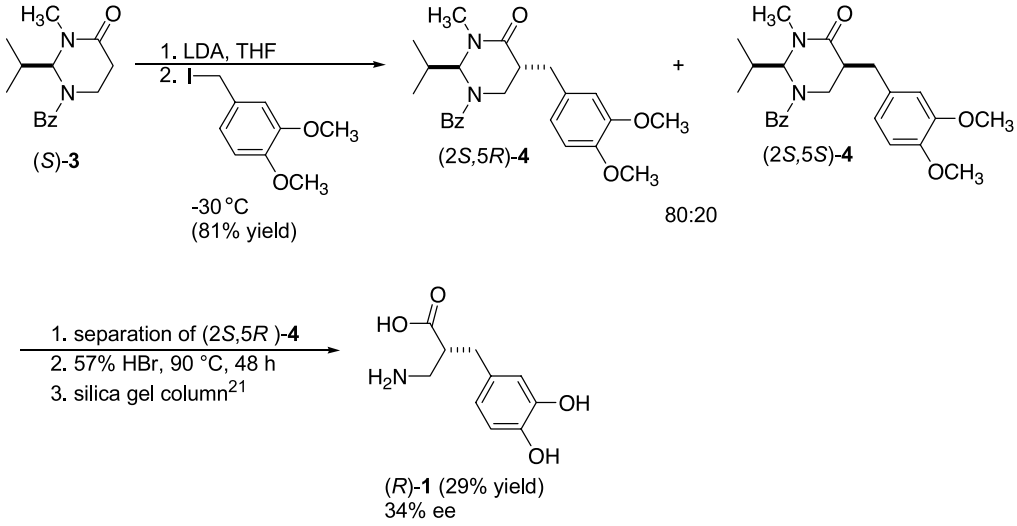
obtained in 81% yield, as a 4:1 trans:cis diastereomeric mixture. (The diastereomeric ratio was determined by integration of suitable signals in ^{1}H NMR spectra, or by means of HPLC analysis). The trans configuration was assigned to the major product based on literature precedent,[14–16] and confirmed by NOE experiments. The substantial predominance of the trans isomer can be ascribed to the quasi-axial orientation of the isopropyl group[16] (as a consequence of allylic $A^{1,3}$-strain[18]) that causes steric hindrance during electrophilic approach to the *syn* face of the enolate (*S*)-**3**-Li.

The preparation of enantiopure (*R*)-β^2-(3,4-dihydroxybenzyl)-β-alanine, (*R*)-**1**, required of the alkylation of enantiopure pyrimidinone (*S*)-**3**, that was synthesized from (*S*)-asparagine following a slightly modified literature procedure.[1] (Scheme 3).

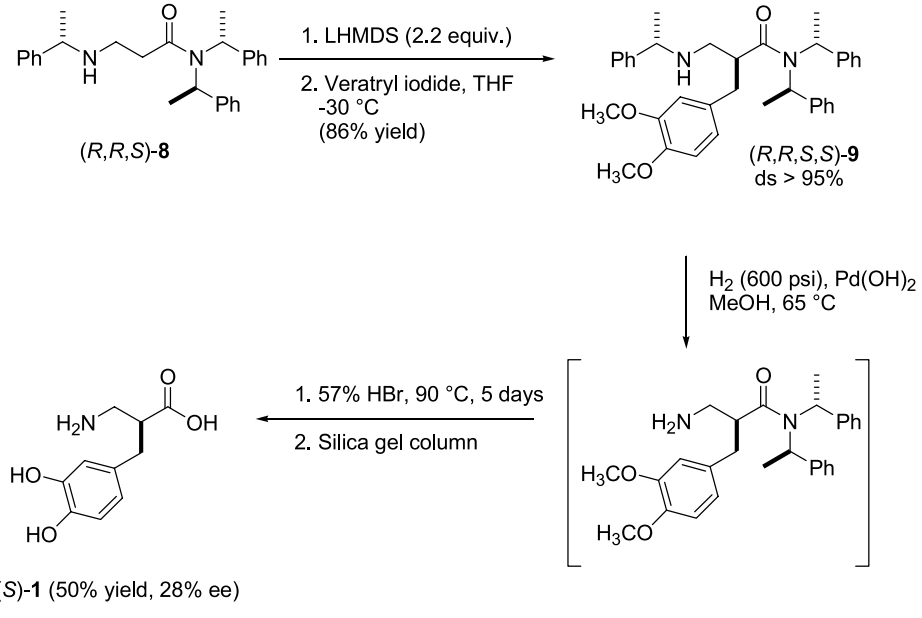
As anticipated, the alkylation reaction of (*S*)-**3**-Li with veratryl iodide proceeded in a higher 81% yield, affording diastereomeric (2*S*,5*R*)-**4** and (2*S*,5*S*)-**4** in a 4:1 ratio, respectively. These products were separated by flash chromatography,[19] and then the major unlike[20] isomer was hydrolyzed with 57% HBr to give the expected β-amino



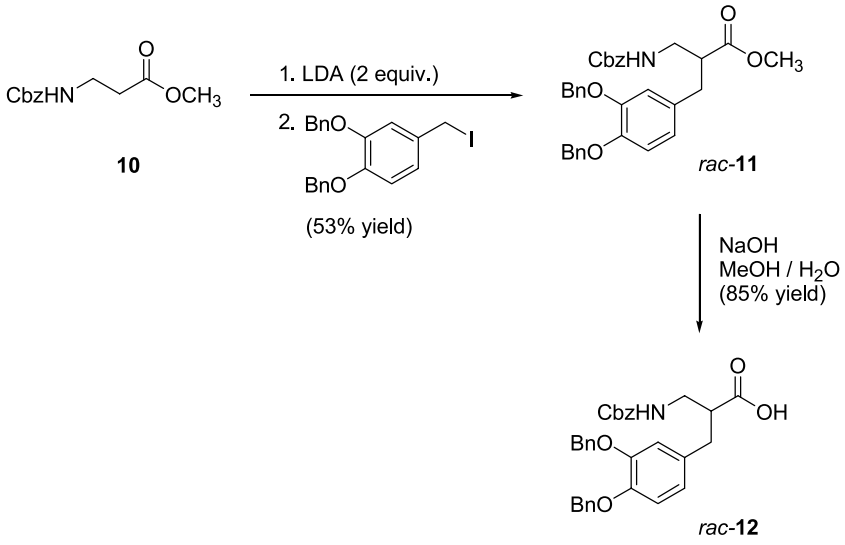
Scheme 3.



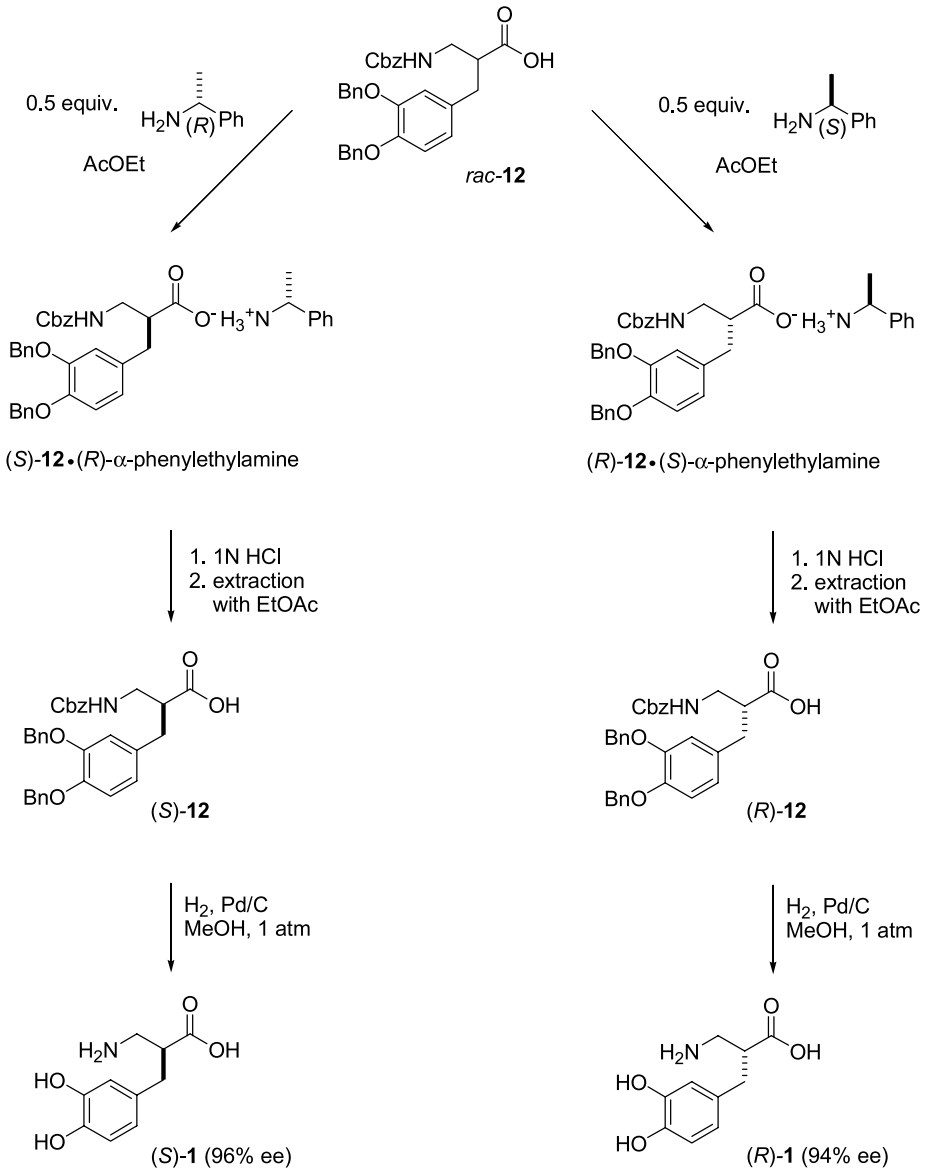
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

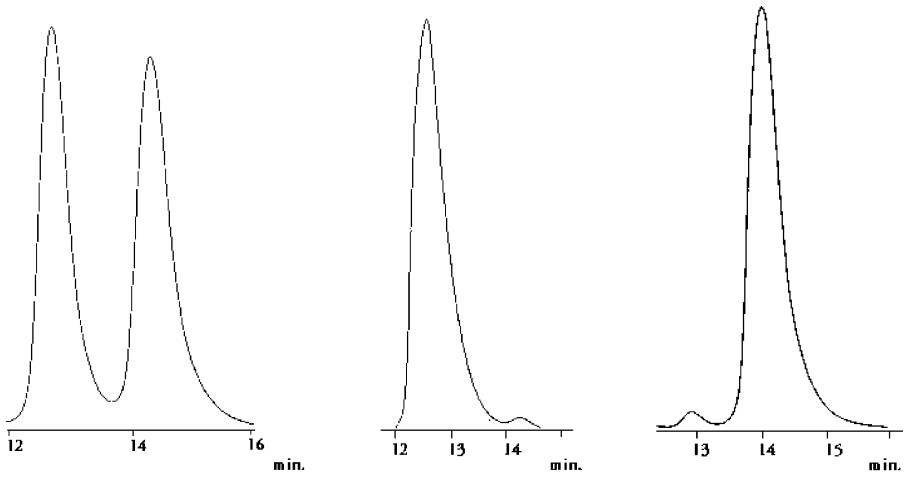


Figure 2. The enantiomeric purity of (*R*)-β^2-homoDopa and (*S*)-β^2-homoDopa, (*R*)- and (*S*)-**1**, was established by HPLC on a Chirobiotic T column (λ= 210 nm, elution system: methanol–water, 70:30).

acid (*R*)-**1** in 29% yield. Unfortunately, and in contrast with other alkylated analogues,[14–16] the acid hydrolysis of (2*S*,5*R*)-**4** proceeded with significant racemization: chiral phase HPLC analysis showed the isolated β-amino acid of only 34% ee (Scheme 4).

By the same token, enantiomer (*S*)-**1** was prepared from (*R*)-**3** via its alkylation with veratryl iodide (80% yield) followed by hydrolysis with 57% HBr (32% yield, 34.5% ee). Isolation of the free β-amino acid (*S*)-**1** was achieved by means of silica gel chromatography, according to the general protocol described recently.[21]

An alternative method for the enantioselective synthesis of β^2-amino acids involves the diastereoselective alkylation of open-chain chiral derivatives of β-aminopropionic acid (β-alanine) containing the (*R*)- or (*S*)-α-phenylethylamine auxiliary.[22] In particular, *C*-alkylation of the lithium dianion derived from (*R*,*R*,*S*)-**8** has been shown to proceed with high diastereoselectivity to afford as the main product the diastereoisomer produced from addition on the *Si* face of the enolate.[23] In the system of interest, treatment of (*R*,*R*,*S*)-**8**-Li_2 with 3,4-dimethoxybenzyl iodide proceeded in 86% yield and higher than 95% diastereoselectivity to give (*R*,*R*,*S*,*S*)-**9**, which was hydrogenolyzed (H_2, $Pd(OH)_2$, 600 psi) and hydrolyzed (57% HBr) to provide (*S*)-**1** (50% yield for the last two steps). Unfortunately, chiral phase HPLC analysis evidenced partial racemization during hydrolysis since the isolated (*S*)-β^2-homoDopa, (*S*)-**1**, presented a low 28% ee (Scheme 5).

Similar observations were recorded in the preparation of (*R*)-**1** by means of highly diastereoselective alkylation of enantiomeric substrate (*S*,*S*,*R*)-**8**[23] with 3,4-dimethoxybenzyl iodide (veratryl iodide) followed by hydrogenolysis and hydrolysis, as described in Scheme 5 for enantiomeric (*S*)-**1**.

In view of the low enantiomeric purities in the samples of (*R*)- and (*S*)-**1** obtained by the two routes depicted in Schemes 4 and 5, we decided to explore the resolution of racemic β^2-homoDopa (*rac*-**1**) with α-phenylethylamine as resolving agent.[22a,24] To this end, the *N*-protected methyl ester of β-aminopropionic acid (**10**) was alkylated with 3,4-dibenzyloxybenzyl iodide to give *rac*-**11** which was saponified with sodium hydroxyde in methanol and water (Scheme 6).

Two samples of racemic β^2-homoDopa carboxylic acid derivative *rac*-**12** were treated separately with half equivalent of (*R*)- and (*S*)-α-phenylethylamine, respectively. In each case, the precipitated salt was recrystallized (three times, EtOAc–hexane, 2:8) to constant values of optical rotation and melting point. When (*R*)-α-phenylethylamine was used, the recovered β^2-homoDopa corresponded to the (*S*) enantiomer (96% ee) whereas the use of (*S*)-α-phenylethylamine afforded (*R*)-β^2-homoDopa (94% ee). This means that the diastereomeric salt that precipitates is of unlike relative configuration (Scheme 7 and Fig. 2).

In summary, enantioenriched (ee = 28–35%) β^2-homoDopa was obtained via highly diastereoselective alkylation of chiral substrates (*R*)- or (*S*)-**3** and (*R*,*R*,*S*)- or (*S*,*S*,*R*)-**8** (Schemes 4 and 5, respectively). Unfortunately, these approaches suffered of partial racemization during acid hydrolysis of the alkylated derivatives. Nearly enantiopure (*R*)- and (*S*)-β^2-homoDopa were obtained via classical resolution of racemic β-aminopropionic acid derivative *rac*-**12** with (*R*)- and (*S*)-α-phenylethylamine (Scheme 7).

3. Experimental

3.1. General

Flasks, stirring bars, and hypodermic needles used for the generation and reactions of organolithiums were dried for ca. 12 h at 120 °C and allowed to cool in a desiccator over anhydrous $CaSO_4$. Anhydrous solvents were obtained by distillation from benzophenone/ketyl radical.[25] *n*-Butyllithium was titrated according to the method of Juaristi et al.[26]

TLC: Merck DC-F_{254} plates, detection UV light, iodine vapour, or ninhydrine spray. Flash chromatography:[19] Merk silica gel (0.040–0.063 mm). Melting points: Melt Temp apparatus, not corrected. ^{1}H NMR spectra: Jeol Eclipse-400 (400 MHz), Bruker Ultra Shield (300 MHz), Jeol GSX-270 (270 MHz) spectrometers; ^{13}C NMR spectra: Jeol Eclipse-400 (100 MHz), and Bruker Ultra Shield (75 MHz). Chemical shifts δ in ppm relative to Me_4Si as internal reference, coupling constants in J (Hz). Mass spectra were obtained in a Hewlett-Packard HP-5986 instrument. High-resolution mass spectra (HR-MS) were obtained at Instituto de Química, UNAM, México. HPLC: Waters 600 provided with UV/Vis detector and a μporasil™ column, hexane/EtOAc (70:30) eluent, 1 mL/min flow and Chirobiotic T column, MeOH/H_2O (1:1) eluent, 1 mL/min.

3.2. Route 1: diastereoselective alkylation of pyrimidinones (*R*)- and (*S*)-3

3.2.1. *rac*-1-Benzoyl-2-isopropyl-3-methylperhydropyrimidin-4-one, *rac*-3. In a dry 250-mL round-bottom flask provided with magnetic stirrer and addition funnel, was placed 9.5 g (69 mmol) of *N*-methyl β-aminopropionamide and suspended in 70 mL of dry CH_2Cl_2. To the resulting mixture was added dropwise 19 mL (117 mmol) of triethylamine and then 11 mL (117 mmol) of isobutyraldehyde before heating to reflux for 4 h with water removal (Dean-Stark trap). The precipitate of triethylamine hydrochloride was removed by filtration, and the filtrate was concentrated to dryness, redissolved in toluene, and treated with 7.5 g (61 mmol, 0.8 equiv) of 4-DMAP and 8.9 mL (76 mmol, 1.1 equiv) of benzoyl chloride. The reaction mixture was heated to reflux for 4 h, the precipitate that formed was removed by filtration, and the filtrate was concentrated in a rotary evaporator. The crude product was purified by flash chromatography[19] using hexane–ethyl acetate (1:1) as eluent to give 10.5 g (59% yield) of *rac*-**3** as a white solid, mp 100–101 °C. ^{1}H NMR (DMSO-d_6, 100 °C, 400 MHz) δ 0.95 (d, J=6.8 Hz, 3H), 0.99 (d, J=6.8 Hz, 3H), 2.34 (dh, J_1=9.0 Hz, J_2=6.8 Hz, 1H), 2.44 (ddd, J_1=17.6 Hz, J_2=6.8 Hz, J_3=5.1 Hz, 1H), 2.52 (ddd, J_1=17.6 Hz, J_2=6.8 Hz, J_3=5.1 Hz, 1H), 2.92 (s, 3H), 3.58 (ddd, J_1=13.6 Hz, J_2=7.6 Hz, J_3=7.6 Hz, 1H), 3.86 (br s, 1H), 5.15 (br s, 1H), 7.47 (m, 5H). ^{13}C NMR (DMSO-d_6, 100 °C, 100 MHz) δ 19.2, 30.4, 33.2, 35.5, 40.2, 74.6, 127.1, 128.9, 130.2, 136.2, 167.4, 170.2. Anal. Calcd for $C_{15}H_{20}N_2O_2$ C, 69.20; H, 7.74; N, 10.76. Found: C, 69.49; H, 7.86; N, 10.95.

3.2.2. 1-Benzoyl-(2*S*)-isopropyl-(6*S*)-carboxyperhydropyrimidin-4-one, (2*S*,6*S*)-5. The literature procedure[1,27] was followed with 30.0 g (0.2 mol) of (*S*)-asparagine monohydrate, 13.2 g (0.2 mol) of 85% KOH, and 42.0 mL (0.4 mol) of isobutyraldehyde to give 45.5 g (78.4% yield) of (2*S*,6*S*)-**5**, mp 175–177 °C (lit.[27] mp 177–178 °C). $[\alpha]_D^{25}$ −150.0 (*c* 1, MeOH), [lit.[27] $[\alpha]_D^{25}$ −156 (*c* 1, MeOH)].

3.2.3. 1-Benzoyl-(2*S*)-isopropyl-2,3-dihydro-4(1H)-1,3-pyrimidin-4-one, (*S*)-6. According to the literature procedure,[1,27] 10.1 g (34.8 mmol) of (2*S*,6*S*)-**5** was decarboxylated with 27.0 g (52.2 mmol, 1.5 equiv) of lead tetraacetate and 2.0 g (12 mmol) of copper diacetate. The desired product was obtained in 75% yield (6.4 g), mp 152–154 °C (lit.[16] mp 154–156 °C). $[\alpha]_D^{25}$ +509 (*c* 1, $CHCl_3$), [lit.[16] $[\alpha]_D^{25}$ +517 (*c* 1, $CHCl_3$)].

3.2.4. 1-Benzoyl-(2*S*)-isopropyl-3-methyl-2,3-dihydro-4(H)-1,3-pyrimidin-4-one, (*S*)-7. In a 250-mL flask provided with magnetic stirrer and nitrogen atmosphere, was placed 5.0 g (20.5 mmol) of (*S*)-**6** and 150 mL of dry THF. The resulting solution was cooled to −78 °C before the dropwise addition of 20.5 mL (20.5 mmol) of 1 M LHMDS. Stirring was continued for 2 h at −78 °C and then methyl iodide (1.9 mL, 30.8 mmol) was added. The temperature was allowed to raise to 25 °C and the reaction mixture was stirred at this temperature for 3 h, before quenching with aq. satd NH_4Cl. The product was extracted with two 200-mL portions of EtOAc, dried over anhyd. Na_2SO_4, and concentrated in the rotary evaporator. The expected product, (*S*)-**7**, was obtained after purification by flash chromatography (hexane–EtOAc, 1:1) as a white solid (4.4 g, 83% yield). mp 99–100 °C (lit.[15] mp 103–104 °C). $[\alpha]_D^{25}$ +497 (*c* 1, $CHCl_3$), [lit.[15] $[\alpha]_D^{25}$ +510 (*c* 1, $CHCl_3$)].

3.2.5. 1-Benzoyl-(2*S*)-isopropyl-3-methyl-perhydropyrimidin-4-one, (*S*)-3. The literature procedure[1] was followed with 2.0 g (7.7 mmol) of unsaturated heterocycle (*S*)-**7**, to give 1.9 g (94% yield) of saturated derivative (*S*)-**3**, as a white solid with mp 98–100 °C (lit.[15] mp 101–102 °C). $[\alpha]_D^{25}$ +28.0 (*c* 1, $CHCl_3$), [lit.[15] $[\alpha]_D^{25}$ +21.0 (*c* 1, $CHCl_3$)].

3.3. General procedure for the alkylation of perhydropyrimidinones 3

A round-bottom flask provided with magnetic stirrer, dry nitrogen atmosphere, and cooling bath (−20 °C) was loaded with 0.06 mL (0.42 mmol, 1.1 equiv) of diisopropylamine and 20 mL of dry THF. Butyllithium (0.16 mL of 2.3 N hexane solution, 0.38 mmol, 1.0 equiv) was added dropwise and the resulting solution was stirred at −20 °C for 20 min. The reaction flask was then cooled to −78 °C before the addition of 0.38 mmol (100 mg, 1.0 equiv) of heterocycle **3**. The reaction mixture was stirred at −78 °C for 1 h and then 0.76 mmol (211 mg, 2.0 equiv) of the electrophile was added. The temperature was allowed to raise to −30 °C and the reaction mixture was stirred at this temperature for 17 h, before quenching with aq. satd NH_4Cl. The product was extracted with two 40-mL portions of EtOAc, dried over anhyd. Na_2SO_4, and concentrated in the rotary evaporator.

3.3.1. *rac-trans*- and *rac-cis*-1-Benzoyl-5-(3,4-dimethoxy) benzyl-2-isopropyl-3-methyl-perhydropyrimidin-4-one, *rac*-4. The general procedure for the alkylation reaction of *rac*-**3** (200 mg, 0.77 mmol) with 422 mg (1.5 mmol, 2 equiv) of veratryl iodide was followed. The expected product, *rac*-**4**, was obtained as a pale-yellow oil (256 mg, 81% yield) after purification by flash chromatography (hexane–EtOAc, 1:1). ^{1}H and ^{13}C NMR spectroscopy show a 4:1 mixture of the trans and cis isomers, respectively. MS (20 eV): *m*/*z* 411 (M+1), 410, 367, 245, 151, 105, 85, 83, 71, 57, 45. HRMS (FAB) calcd for $C_{24}H_3N_2O_2$ (M^++H) 411.2284; found: 411.2296.

3.3.2. Major isomer, *rac-trans*-4. Colorless oil, ^{1}H NMR (DMSO-d_6, 120 °C, 400 MHz) δ 0.89 (d, J=6.15 Hz, 3H), 0.97 (d, J=6.15 Hz, 3H), 2.35 (m, 1H), 2.51 (m, 1H), 2.86

(m, 1H), 2.97 (s, 3H), 3.02 (m, 1H), 3.5 (m, 2H), 3.66 (s, 3H), 3.69 (s, 3H), 5.12 (br, 1H), 6.50–6.72 (m, 3H), 7.28–7.44 (m, 5H). ^{13}C NMR (DMSO-d_6, 120 °C, 100 MHz) δ 19.4, 33.4, 36.0, 36.4, 40.9, 44.4, 56.7, 56.8, 75.0, 114.0, 115.0, 121.9, 127.4, 128.9, 130.3, 132.5, 136.2, 148.7, 149.9, 170.0, 170.2.

3.3.3. Minor isomer, *rac-cis*-4. Colorless oil, ^{1}H NMR (DMSO-d_6, 120 °C, 400 MHz) δ 0.79 (d, J=7.0 Hz, 3H), 0.90 (d, J=7.0 Hz, 3H), 1.88 (m, 1H), 2.75 (m, 1H), 2.86 (br, 1H), 2.92 (s, 3H), 2.96 (m, 1H), 3.20 (m, 1H), 3.69 (s, 3H), 3.70 (s, 3H), 3.79 (m, 1H), 5.15 (br, 1H), 6.62–6.78 (m, 3H), 7.29–7.43 (m, 5H). ^{13}C NMR (DMSO-d_6, 120 °C, 100 MHz) δ 18.7, 19.2, 33.4, 34.9, 35.6, 42.3, 43.5, 56.8, 57.0, 73.8, 114.2, 115.1, 122.1, 127.0, 129.0, 130.2, 132.0, 135.9, 149.0, 150.0, 169.6, 170.2.

3.3.4. 1-Benzoyl-(2*S*)-isopropyl-(5*R*)-(3,4-dimethoxybenzyl)-3-methyl-perhydropyrimidin-4-one, (2*S*,5*R*)-4. The general alkylation procedure was followed with 500 mg (1.9 mmol) of (*S*)-**3** and 1.05 mg (3.8 mmol, 2.0 equiv) of veratryl iodide. Following purification of the crude product by flash chromatography (hexane–EtOAc, 1:1), the alkylated product (654 mg, 83% yield) was isolated as a 4:1 mixture of (2*S*,5*R*)-**4** and (2*S*,5*S*)-**4**. These diastereoisomers were separated by flash chromatography (CH_2Cl_2–EtOAc, 9:1).

(2*S*,5*R*)-**4**. Colorless oil, 521 mg (66% yield), $[\alpha]_D^{25}$ −86.9 (*c* 0.8, $CHCl_3$), ^{1}H NMR (DMSO-d_6, 120 °C, 400 MHz) δ 0.89 (d, J=6.15 Hz, 3H), 0.97 (d, J=6.15 Hz, 3H), 2.35 (m, 1H), 2.51 (m, 1H), 2.86 (m, 1H), 2.97 (s, 3H), 3.02 (m, 1H), 3.5 (m, 2H), 3.66 (s, 3H), 3.69 (s, 3H), 5.12 (br, 1H), 6.50–6.72 (m, 3H), 7.28–7.44 (m, 5H).^{13}C NMR (DMSO-d_6, 120 °C, 100 MHz) δ 19.4, 33.4, 36.0, 36.4, 40.9, 44.4, 56.7, 56.8, 75.0, 114.0, 115.0, 121.9, 127.4, 128.9, 130.3, 132.5, 136.2, 148.7, 149.9, 170.0, 170.2. MS (20 eV): *m*/*z* 410 (M^+), 367, 245, 151, 105, 85, 57, 45. HRMS (FAB) calcd for $C_{24}H_3N_2O_4$ (M^++H) 411.2284; found 411.2302.

(2*S*,5*S*)-**4**. Colorless oil, 123 mg (16% yield), $[\alpha]_D^{25}$ −23.5 (*c* 0.75, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 120 °C, 400 MHz) δ 0.79 (d, J=7.0 Hz, 3H), 0.90 (d, J=7.0 Hz, 3H), 1.88 (m, 1H), 2.75 (m, 1H), 2.86 (br, 1H), 2.92 (s, 3H), 2.96 (m, 1H), 3.2 (m, 1H), 3.69 (s, 3H), 3.70 (s, 3H), 3.79 (m, 1H), 5.15 (br, 1H), 6.62–6.78 (m, 3H), 7.29–7.43 (m, 5H). ^{13}C NMR (DMSO-d_6, 120 °C, 100 MHz) δ 18.7, 19.2, 33.4, 34.9, 35.6, 42.3, 43.5, 56.8, 57.0, 73.8, 114.2, 115.1, 122.1, 127.0, 129.0, 130.2, 132.0, 135.9, 149.0, 150.0, 169.6, 170.2. MS (20 eV): *m*/*z* 411 (M^+), 410, 367, 245, 151, 105, 85, 57, 45. HRMS (FAB) calcd for $C_{24}H_3N_2O_4$ (M^++H) 411.2284; found 411.2281.

3.3.5. 1-Benzoyl-(2*R*)-isopropyl-(5*S*)-(3,4-dimethoxybenzyl)-3-methyl-perhydropyrimidin-4-one, (2*R*,5*S*)-4. The general alkylation procedure was followed with 150 mg (0.57 mmol) of (*R*)-**3** and 320 mg (1.15 mmol, 2.0 equiv) of veratryl iodide. After purification of the crude product by flash chromatography (hexane–EtOAc, 1:1), the alkylated product (189 mg, 80% yield) was isolated as a 4:1 mixture of (2*R*,5*S*)-**4** and (2*R*,5*R*)-**4**. These diastereoisomers were separated by flash column chromatography (CH_2Cl_2–EtOAc, 9:1).

(2*R*,5*S*)-**4**. Colorless oil, 150 mg (64% yield), $[\alpha]_D^{25}$ +93 (*c* 1, $CHCl_3$). ^{1}H and ^{13}C NMR spectra were identical to those recorded for enantiomeric (2*S*,5*R*)-**4**. MS (20 eV): *m*/*z* 410 (M^+), 367, 245, 151, 105, 85, 57, 45. HRMS (FAB) calcd for $C_{24}H_3N_2O_4$ (M^++H) 411.2284; found 411.2285.

(2*R*,5*R*)-**4**. Colorless oil, 45 mg (15% yield) $[\alpha]_D^{25}$ +23.0 (*c* 1, $CHCl_3$). ^{1}H and ^{13}C NMR spectra were identical to those recorded for enantiomeric (2*S*,5*S*)-**4**. MS: *m*/*z* 411 (M^+), 410, 367, 245, 151, 105, 85, 57, 45. HRMS (FAB) calcd for $C_{24}H_3N_2O_4$ (M^++H) 411.2284; found 411.2291.

3.4. General procedure for the acid hydrolysis of the α-alkylated perhydropyrimidinones

An ampoule was loaded with 150 mg (0.36 mmol) of the alkylated pyrimidinone (**4**) and 3 mL of 48% HBr. The sealed ampoule was heated to 90 °C for 48 h, allowed to cool to ambient temperature, and the reaction mixture was extracted with three 30 mL portions of CH_2Cl_2. The aqueous phase was concentrated at reduced pressure and the residue (amino acid hydrobromide) was purified by silica gel column chromatography[21] with CH_2Cl_2/MeOH/AcOH (90:10:1) eluent.

3.4.1. (*rac*)-2-(3,4-Dihydroxybenzyl)-3-aminopropionic acid, *rac*-1. The general procedure for hydrolysis was followed with 150 mg (0.36 mmol) of *rac*-**4** to give 44 mg (32% yield) of *rac*-**1** as a yellowish foam. ^{1}H NMR (D_2O, 400 MHz) δ 2.67–3.18 (m, 5H), 6.54–6.74 (m, 3H). ^{13}C NMR (D_2O, 100 MHz) δ 34.8, 39.7, 44.5, 116.6, 117.0, 121.7, 130.1, 143.1, 144.2, 176.4. MS: *m*/*z* 211 (M^+), 191, 183, 167, 149, 71.

3.4.2. (*R*)-2-(3,4-Dihydroxybenzyl)-3-aminopropionic acid, (*R*)-1. The general procedure for hydrolysis was followed with 500 mg (1.21 mmol) of (2*S*,5*R*)-**4** to give 75 mg (29% yield) of (*R*)-**1** as a yellowish foam, $[\alpha]_D^{25}$ −7.0 (*c* 1, MeOH). Chiral phase HPLC (Chirobiotic T column, λ=210 nm, elution system: MeOH–water, 70:30) showed this material to present 34% ee. ^{1}H and ^{13}C NMR spectra were identical with those recorded for *rac*-**1**. HRMS (FAB) calcd for $C_{10}H_{14}NO_4$ (M^++H) 212.0923; found 212.0926.

3.4.3. (*S*)-2-(3,4-Dihydroxybenzyl)-3-aminopropionic acid, (*S*)-1. The general procedure for hydrolysis was followed with 300 mg (0.73 mmol) of (2*R*,5*S*)-**4** to give 49 mg (32% yield) of (*S*)-**1** as a yellowish foam, $[\alpha]_D^{25}$ +6.8 (*c* 1, MeOH). Chiral phase HPLC (Chirobiotic T column, λ=210 nm, elution system: MeOH–water, 70:30) showed this material to present 34.5% ee. ^{1}H and ^{13}C NMR spectra were identical with those recorded for *rac*-**1**. HRMS (FAB) calcd for $C_{10}H_{14}NO_4$ (M^++H) 212.0923; found 212.0922.

3.5. Route 2: diastereoselective alkylation of β-aminopropionic acid derivatives (*R*,*R*,*S*)- and (*S*,*S*,*R*)-8

3.5.1. *N*,*N*-Bis-[(*S*)-1-phenylethyl]-3-{[(*R*)-1-phenylethyl]amino}propanamide, (*S*,*S*,*R*)-8. A mixture of 3.0 g (10.7 mmol) of *N*,*N*-bis-[(*S*)-1-phenylethyl]prop-2-enamide[23] and 1.95 g (16.1 mmol) of (*R*)-1-phenylethylamine was dissolved in 130 mL of ethanol, and the resulting mixture was heated to reflux for 36 h. Solvent removal at

reduced pressure and purification by flash column chromatography[19] (hexane–EtOAc, 7:3) afforded 3.9 g (92% yield) of (*S*,*S*,*R*)-**8** as a yellow oil. $[\alpha]_D^{25}$ − 99.2 (*c* 1, $CHCl_3$), ^{1}H NMR (DMSO-d_6, 100 °C, 300 MHz) δ 1.20 (d, J=6.5 Hz, 3H), 1.64 (d, J=7.1 Hz, 6H), 2.28 (m, 1H), 2.44 (m, 1H), 2.62 (m, 2H), 3.65 (q, J=6.5 Hz, 1H), 5.05 (q, J=7.0 Hz, 2H), 7.0–7.25 (m, 15H). ^{13}C NMR (DMSO-d_6, 120 °C, 100 MHz) δ 19.6, 24.5, 36.7, 44.4, 54.2, 58.1, 127.2, 127.3, 127.4, 128.2, 128.5, 128.8, 142.6, 172.5. MS (20 eV): *m*/*z* 401 (M^++H), 295, 191, 120, 105. HRMS (FAB) calcd for $C_{27}H_{33}N_2O$ (M^++H) 401.2593; found: 401.2584.

3.6. General procedure for the alkylation of (*R*,*R*,*S*)-8 and (*S*,*S*,*R*)-8

To a solution of 0.2 g (0.5 mmol) of **8** in 30 mL of dry THF, under nitrogen atmosphere and at −78 °C, was added dropwise 1.1 mL of LHMDS (1 M solution in hexane, 2.2 equiv). The resulting solution was stirred at −78 °C for 1 h before the slow addition of 153 mg of veratryl iodide (5.5 mmol, 1.1 equiv) diluted in 10 mL of dry THF. The reaction mixture was allowed to warm to −30 °C and stirred at this temperature for 4 h. The reaction was quenched with 2 mL of saturated NH_4Cl and the product was extracted with three 10 mL portions of EtOAc. The organic extracts were combined, dried with anhyd. Na_2SO_4, filtered, and concentrated. The product was purified by flash column chromatography[19] (hexane–EtOAc, 8:2).

3.6.1. (2*S*)-*N*,*N*-Bis-[(*R*)-1-phenylethyl]-2-(3,4-dimethoxybenzyl)-3-{[(*S*)-1-phenylethyl]-amino}propanamide, (*R*,*R*,*S*,*S*)-9. The general procedure was followed with 3.0 g (7.5 mmol) of (*R*,*R*,*S*)-**8** and 2.3 g (11.25 mmol) of veratryl iodide. The desired product (3.5 g, 86% yield) was obtained as a slightly yellow oil, in greater than 98% ds. $[\alpha]_D^{25}$ +70.1 (*c* 1, $CHCl_3$), ^{1}H NMR (DMSO-d_6, 100 °C, 300 MHz) δ 1.24 (d, J=6.5 Hz, 3H), 1.24–1.27 (br, 6H), 2.55 (m, 1H), 2.65 (m, 2H), 2.75 (m, 1H), 2.88 (br, 1H), 3.28 (m, 1H), 3.66 (m, 1H), 3.75 (s, 6H), 6.6–7.4 (m, 18 H). ^{13}C NMR (DMSO-d_6, 100 °C, 75 MHz) δ 17.9, 23.1, 36.1, 44.7, 50.0, 52.9, 55.6, 55.8, 57.0, 113.1, 114.4, 121.1 125.7, 126.9, 127.4, 132.4, 145.6, 147.5, 148.8, 173.5. MS (20 eV): *m*/*z* 551 (M^++H), 445, 269, 151, 120, 105. HRMS (FAB) calcd for $C_{36}H_{43}N_2O_3$ (M^++H) 551.3274; found: 551.3278.

3.6.2. (2*R*)-*N*,*N*-Bis-[(*S*)-1-phenylethyl]-2-(3,4-dimethoxybenzyl)-3-{[(*R*)-1-phenylethyl]-amino}propanamide, (*S*,*S*,*R*,*R*)-9. The general procedure was followed with 3.0 g (7.5 mmol) of (*S*,*S*,*R*)-**8** and 2.3 g (11.25 mmol) of veratryl iodide. The desired product (3.4 g, 82% yield) was obtained as a slightly yellow oil, in greater than 98% ds. $[\alpha]_D^{25}$ − 69.7 (*c* 1, $CHCl_3$). ^{1}H and ^{13}C NMR spectra were identical to those recorded for enantiomeric (*R*,*R*,*S*,*S*)-**9**. HRMS (FAB) calcd for $C_{36}H_{43}N_2O_3$ (M^++H) 551.3274; found: 551.3287.

3.7. General procedure for the hydrolysis of 9

In a hydrogenation flask was placed 2.2 g (4.0 mmol) of **9**, 440 mg of 20% $Pd(OH)_2$, 40 mL of methanol, and 10 drops of acetic acid. The flask was pressurized to 600 psi of hydrogen and stirred at 60 °C for 12 h. The reaction mixture was filtered over Celite and concentrated at reduced pressure to give 1.8 g (~100% yield) of debenzylated amine (Scheme 5), which was transferred to a hydrolysis tube and dissolved in 18 mL of 48% HBr. The tube was sealed and heated to 90 °C for 5 days. The reaction mixture was extracted with CH_2Cl_2 (3×100 mL) and the aqueous phase was concentrated to afford the crude product **1** which was purified as described in Section 3.2.

3.7.1. (*R*)-2-(3,4-Dihydroxybenzyl)-3-aminopropionic acid, (*R*)-1. The general procedure for hydrolysis was followed with 600 mg (1.1 mmol) of (*S*,*S*,*R*,*R*)-**9** to give 120 mg (52% yield) of (*R*)-**1** as a yellow foam, $[\alpha]_D^{25}$ −4.5 (*c* 1, MeOH). Chiral phase HPLC (Chirobiotic T column, λ=210 nm, elution system methanol–water, 70:30) showed this material to present 24% ee. ^{1}H and ^{13}C NMR spectra were identical with those recorded for (*R*)-**1** in Section 3.2. HRMS (FAB) calcd for $C_{10}H_{14}NO_4$ (M^++H) 212.0923; found 212.0929.

3.7.2. (*S*)-2-(3,4-Dihydroxybenzyl)-3-aminopropionic acid, (*S*)-1. The general procedure for hydrolysis was followed with 600 mg (1.1 mmol) of (*R*,*R*,*S*,*S*)-**9** to give 115 mg (50% yield) of (*S*)-**1** as a yellow foam, $[\alpha]_D^{25}$ +4.2 (*c* 1, MeOH). Chiral phase HPLC (Chirobiotic T column, λ=210 nm, elution system methanol–water, 70:30) showed this material to present 28% ee. ^{1}H and ^{13}C NMR spectra were identical with those recorded for (*S*)-**1** in Section 3.2. HRMS (FAB) calcd for $C_{10}H_{14}NO_4$ (M^++H) 212.0923; found 212.0919.

3.8. Route 3: via the resolution of racemic 12

3.8.1. *N*-Benzyloxycarbonyl-3-aminopropionic acid methyl ester, 10. To a solution of 10.0 g (112 mmol) of β-aminopropionic acid in 112 mL of 1 N NaOH was added at 0 °C 17.6 mL (21.0 g, 123 mmol) of benzyl chloroformate and additional (30–40 mL) 1 N NaOH to maintain a basic pH in the reaction mixture. The temperature was allowed to reach ambient temperature and the reaction mixture was stirred at this temperature overnight. Side products were removed by extraction with two 100-mL portions of EtOAc, and then the aqueous phase was acidulated with 6 N HCl to pH=2.0. The precipitate that formed was filtered and the filtrate was extracted with three 200-mL portions of EtOAc. The precipitate and the organic layers were combined, dried with anhyd. Na_2SO_4, and concentrated in the rotary evaporator. The residue was redissolved in MeOH and 4 drops of conc. HCl were added. The mixture was heated to reflux for 20 min. and then concentrated again at reduced pressure to give a colorless oil that was purified by flash chromatography[19] (hexane–EtOAc, 1:1) to give 22.7 g (86% yield) of the desired product **10**. ^{1}H and ^{13}C NMR spectra were similar to those reported in the literature:[28] ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.51 (t, J=6.05 Hz, 2H), 3.42 (m, 2H), 3.64 (s, 3H), 5.06 (s, 2H), 5.51 (br, 1H), 7.30 (m, 5H). ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 34.3, 36.6, 51.8, 66.7, 128.1, 128.5, 136.6, 156.4, 172.8.

3.8.2. *N*-Benzyloxycarbonyl-2-(3,4-dibenzyloxybenzyl)-3-aminopropionic acid methyl ester, *rac*-11. In a 500-mL flask provided with magnetic stirrer an nitrogen atmosphere was placed 2.6 mL (18.5 mmol) of diisopropylamine and

30 mL of dry THF. The resulting solution was cooled to −20 °C before the addition of 8.4 mL (16.9 mmol) of 2.02 M *n*-BuLi in hexane. Stirring was continued for 20 min and then the temperature was lowered to −78 °C before the slow addition of 2.0 g (8.43 mmol) of **10** in 100 mL of dry THF. The resulting suspension was stirred at −78 °C for 1 h and then 3.99 g (9.27 mmol) of 3,4-dibenzyloxybenzyl iodide in 50 mL of dry THF was added dropwise. The reaction mixture was stirred for 5 h at −78 °C and then quenched with 25 mL of saturated NH_4Cl, extracted with three 150-mL portions of EtOAc. The organic layers were combined, dried with anhyd. Na_2SO_4, and concentrated in the rotary evaporator. The crude product was purified by flash chromatography[19] (hexane–EtOAc, 9:1) to give 2.4 g (53% yield) of *rac*-**11** as a white solid, mp 80–82 °C. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.72 (m, 1H), 2.86 (m, 2H), 3.32 (m, 2H), 3.58 (s, 3H), 5.09 (s, 2H), 5.12 (s, 2H), 5.14 (s, 2H), 6.68–6.86 (m, 3H), 7.24–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 35.4, 41.8, 47.3, 51.9, 66.9, 71.3, 71.4, 115.2, 115.9, 121.8, 127.4, 127.5, 127.9, 128.3, 128.6, 128.6, 147.8, 148.9, 156.4, 174.7. MS (20 eV): *m*/*z* 539 (M^+), 431, 340, 181, 108, 91. Anal. Calcd for $C_{33}H_{33}NO_6$: C, 73.45; H, 6.16; N, 2.60. Found: C, 73.13; H, 6.00; N, 2.65.

3.8.3. *N*-Benzyloxycarbonyl-2-(3,4-dibenzyloxybenzyl)-3-aminopropionic acid, *rac*-12. In a 100-mL flask provided with magnetic stirrer was placed 2.3 g (4.3 mmol) of *rac*-**11** and 40 mL of methanol. The resulting solution was treated with 683 mg (17.2 mmol) of NaOH dissolved in the minimum amount of water. The reaction mixture was stirred at ambient temperature for 48 h, and then concentrated in a rotary evaporator. The residue was redissolved in 100 mL of EtOAc, washed with two 100-mL portions of 1 N HCl and then with 100 mL of aq saturated sodium and potassium tartrate. The organic phase was dried with anhyd. Na_2SO_4 and concentrated in a rotary evaporator. The product was recrystallized from EtOAc–hexane (2:8) to give 1.9 g (85% yield) of *rac*-**12** as a white solid, mp 108–110 °C. ^{1}H NMR ($CDCl_3$, 60 °C, 300 MHz) δ 2.73 (m, 1H), 2.96 (m, 2H), 3.42 (m, 2H), 5.11 (s, 4H), 5.13 (s, 2H), 6.70–6.88 (m, 3H), 7.27–7.45 (m, 5H). ^{13}C NMR ($CDCl_3$, 60 °C, 75 MHz) δ 35.4, 42.0, 47.3, 67.3, 72.0, 72.1, 116.2, 117.1, 122.3, 127.7, 127.8, 128.0, 128.2, 128.4, 128.7, 128.8, 131.8, 136.7, 137.8, 137.8, 148.6, 149.5, 156.9, 170.8, 178.0. MS (20 eV): *m*/*z* 525 (M^+), 417, 326, 181, 91, 79. Anal. Calcd for $C_{32}H_{31}NO_6$ C, 73.13; H, 5.94; N, 2.66. Found: C, 73.10; H, 6.09; N, 2.67.

3.8.4. *N*-Benzyloxycarbonyl-(2*R*)-(3,4-dibenzyloxybenzyl)-3-aminopropionic acid, (*R*)-12. In a 50-mL Erlenmeyer flask was placed 0.8 g (1.5 mmol) of *rac*-**12** and 5.0 mL of EtOAc. The resulting solution was heated to reflux and then 0.1 mL (0.76 mmol, 0.5 equiv) of (*S*)-α-phenylethylamine was added. The resulting mixture was allowed to stand at ambient temperature for 15 h upon which a precipitate was formed, mp 147–149 °C. This solid material was recrystallized twice from EtOAc to give a white solid with mp 154–155 °C, $[\alpha]_D^{25}$ −6.3 (*c* 1, MeOH), $[\alpha]_{Hg365}^{25}$ −17.9 (*c* 1, MeOH). This solid was dissolved in 50 mL of EtOAc, extracted with two 50-mL portions of 1 N HCl, and washed with aqueous saturated sodium and potassium tartrate solution. The organic phase was dried with anhyd. Na_2SO_4 and concentrated in a rotary evaporator. Product (*R*)-**12** was recrystallized from EtOAc–hexane (2:8) to give 335 mg (42% yield, 84% of theoretical yield) of a white solid, mp 112–114 °C. ^{1}H and ^{13}C NMR spectra were identical to those described above for *rac*-**12**. Anal. Calcd for $C_{32}H_{31}NO_6$: C, 73.13; H, 5.94; N, 2.66. Found: C, 72.97; H, 6.15; N, 2.65.

3.8.5. *N*-Benzyloxycarbonyl-(2*S*)-(3,4-dibenzyloxybenzyl)-3-aminopropionic acid, (*S*)-12. The same procedure described above for the isolation of (*R*)-**12** was followed, only that (*R*)-α-phenylethylamine was used. The unlike diastereomeric salt (see discussion in the main text) presented the following physical properties: mp 154–155 °C, $[\alpha]_D^{25}$ +7.0 (*c* 1, MeOH), $[\alpha]_{Hg365}^{25}$ +18.0 (*c* 1, MeOH). The liberated carboxylic acid (*S*)-**12** was obtained in 44% yield (355 mg, 88% of theoretical yield) and presented the following physical properties: mp 112–114 °C. ^{1}H and ^{13}C NMR spectra were identical to those recorded for *rac*-**12**. Anal. Calcd for $C_{32}H_{31}NO_6$ C, 73.13; H, 5.94; N, 2.66. Found: C, 73.12; H, 6.25; N, 2.54.

3.8.6. (*R*)-2-(3,4-Dihydroxybenzyl)-3-aminopropionic acid, (*R*)-1. In a hydrogenation flask provided with magnetic stirrer was placed 300 mg (0.57 mmol) of (*R*)-**12** and 30 mL of methanol. The resulting solution was treated with 30 mg of 10% palladium on charcoal and the flask was pressurized to 1 atm of hydrogen. The reaction mixture was filtered over Celite and concentrated in a rotary evaporator to give 96 mg (80% yield) of (*R*)-**1** as a yellow foam, $[\alpha]_D^{25}$ −24.5 (*c* 1, MeOH). ^{1}H and ^{13}C NMR spectra were identical with those recorded for (*R*)-**1** in Section 3.2. Chiral phase HPLC (Chirobiotic T column, λ=210 nm, elution system methanol–water, 70:30) showed this material to be 94% ee. HRMS (FAB) calcd for $C_{10}H_{14}NO_4$ (M^++H) 212.0923; found 212.0925.

3.8.7. (*S*)-2-(3,4-Dihydroxybenzyl)-3-aminopropionic acid, (*S*)-1. The same procedure described above for the hydrogenolysis of (*R*)-**12** was followed, with 300 mg (0.57 mmol) of (*S*)-**12** and 20 mg of 10% palladium on charcoal. Free β-amino acid (*S*)-**1** (112 mg, 93% yield) was obtained as a yellow foam, $[\alpha]_D^{25}$ +23.5 (*c* 1, MeOH). Chiral phase HPLC (Chirobiotic T column, λ=210 nm, elution system methanol–water, 70:30) showed this material to be 96% ee (Fig. 2). ^{1}H and ^{13}C NMR spectra were identical with those recorded for (*S*)-**1** in Section 3.2. HRMS (FAB) calcd for $C_{10}H_{14}NO_4$ (M^++H) 212.0923; found 212.0918.

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Xyloccensins Q–V, six new 8,9,30-phragmalin *ortho* ester antifeedants from the Chinese mangrove *Xylocarpus granatum*

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Abstract—Six new 8,9,30-phragmalin *ortho* esters, named xyloccensins Q–V (**3–8**), have been isolated from the stem bark of a Chinese mangrove *Xylocarpus granatum*, and their structures were elucidated on the basis of spectroscopic data and chemical means. The absolute stereochemistry of these compounds and xyloccensins O–P (**1–2**), revised as enantiomeric to all the phragmalins reported so far, was determined by application of the modified MTPA Mosher ester method and circular dichroism analysis. Both xyloccensins P and Q exhibited potent antifeedant activity against the third instar larvae of *Mythimna separata* (Walker) at a concentration of 500 ppm.

1. Introduction

The family Meliaceae has proven to produce a variety of chemically unique antifeedant limonoids, such as azadirachtin[1] from the neem tree *Azadiracha indica* and harrisonin[2] from *Harrisonnia abyssinica*. Previous investigations on the seeds of two Meliaceae plants of mangrove, *X. granatum* and *X. moluccensis*, uncovered eleven limonoids, xyloccensins A–K.[3] In a continuing search for potential drug leads from Chinese tropical mangrove plants, we have recently, reported the isolation and identification of three novel mexicanolides, named xyloccensins L–N,[4] and two unique 8,9,30-phragmalin *ortho* esters, named xyloccensins O–P (**1–2**),[5] from the stem bark of *X. granatum*. Furthermore, a reinvestigation of the same plant result in the discovery of the other six 8,9,30-phragmalin *ortho* esters, namely xyloccensins Q–V (**3–8**). The absolute stereochemistry of these compounds and xyloccensins O–P, enantiomeric to all the phragmalins reported so far, was determined by application of the modified MTPA Mosher ester method and circular dichroism analysis. Here, we present the isolation, stereostructure elucidation and antifeedant activities of these compounds.

Keywords: Absolute stereochemistry; 8,9,30-Phragmalin *ortho* ester; *Xylocarpus granatum*; Antifeedant activity.
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2. Results and discussion

2.1. Isolation

The EtOH extract of the dried stem bark of *X. granatum* was concentrated and partitioned between water and petroleum ether. The aqueous layer was further extracted with ethyl acetate to give a brown gum, which was separated by silica gel chromatography and repetitive reversed-phase HPLC to afford xyloccensins Q–V (**3–8**).

2.2. Structural elucidation of xyloccensin Q–V (3–8)

Xyloccensin Q (**3**), a colorless crystal, had a molecular formula of $C_{35}H_{40}O_{16}$ established by HR-ESIMS spectrum (*m/z* 717.2395, calcd for $[M+H]^+$ 717.2394). The ^1H (Table 1) and ^{13}C NMR data (Table 2) of **3** indicated the presence of the following functional groups: a methoxy (δ_H 3.81s, δ_C 53.6q), two hydroxyls [δ_H 3.49s, 3.87s], an *ortho*acetate (δ_H 1.70s, δ_C 16.6q, 120.1s) and three acetyl groups (δ_H 1.52s, δ_C 19.8q, 170.2s; δ_H 1.99 s, δ_C 21.8q, 170.0s; δ_H 2.22s, δ_C 21.0q, 169.3s), together with a β-furyl ring [δ_H 6.65 (dd, $J=2.0$, 1.0 Hz), 7.54 (br s) 7.62 (br s); δ_C 111.1d, 122.5s, 142.8d, 144.3d]. Its UV, IR and NMR spectra were very similar to those of xyloccensin P (**2**)[5] isolated from the same plant, with the exception for the absence of an acetyl group (δ_H 2.09s, δ_C 21.6q, 168.8s, 2-OAc in **2**) and the presence of one more hydroxyl (δ_H 3.87s). It was indicated that 2-acetoxy group in **2** was replaced by a hydroxyl. Moreover, the position of this

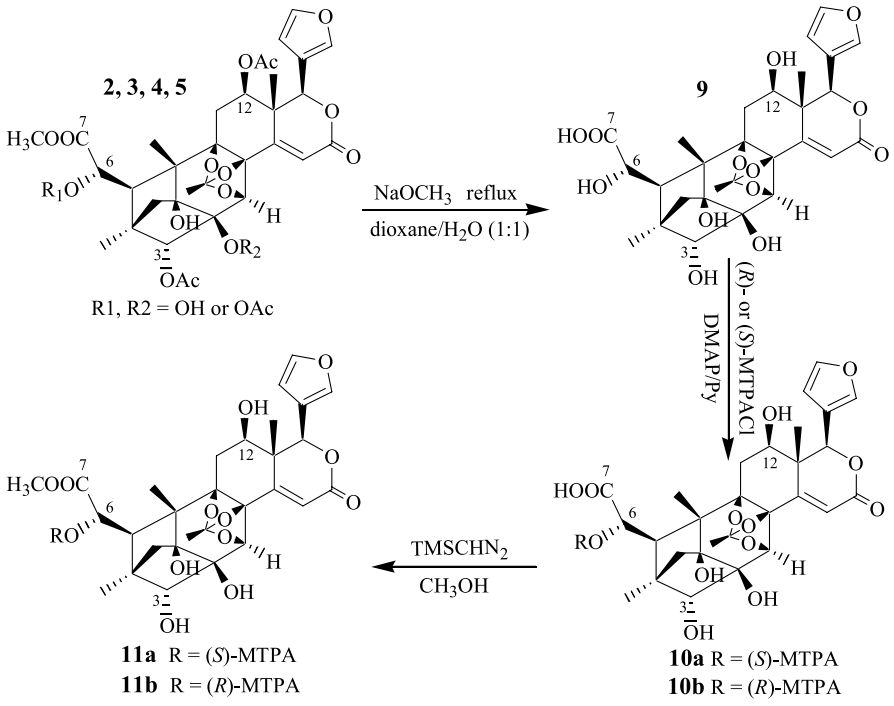
Table 1. ^{1}H NMR (500 MHz) data for xyloccensin Q–V (**3**–**8**) in acetone-d_6

No.	3	4	5	6	7	8
2				3.09; dd; 12.0; 4.0		
3	4.80; s	4.77; s	5.14; s	5.27; d; 12.0	4.80; s	5.23; s
5	2.53; br s	2.38; br s	2.33; br s	2.48; br s	2.22; d; 10.5	2.22; d; 10.5
6α					3.18; dd; 17.0; 1.0	3.15; dd; 17.0; 1.0
6β	6.24; br s	4.95; dd; 4.0; 1.0	5.19; d; 4.0	4.88; dd; 4.0; 1.0	2.52; dd; 17.0; 10.5	2.53; dd; 17.0; 10.5
11α	2.03[a]	2.04[a]	2.01[a]	2.01[a]	2.04[a]	2.04[a]
11β	2.33; dd, 14.0; 4.5	2.36; dd, 14.0; 4.5	2.39; dd, 14.0; 4.5	2.39; dd; 14.0; 4.5	2.33; dd, 14.0; 4.5	2.33; dd, 14.0; 4.5
12α	4.99; dd; 14.0; 4.5	4.89; dd; 14.0; 4.5	4.92; dd; 14.0; 4.5	4.92; dd; 14.0; 4.5	4.83; dd; 14.0; 4.5	4.83; dd; 14.0; 4.5
15	6.89; s	6.86; s	6.53; s	6.65; s	6.89; s	6.57; s
17	5.90; s	5.94; s	5.93; s	5.96; s	5.95; s	5.93; s
18	1.59; s	1.59; s	1.59; s	1.59; s	1.58; s	1.59; s
19	1.28; s	1.53; s	1.53; s	1.47; s	1.30; s	1.31; s
21	7.54; br s	7.50; br s	7.51; br s	7.50; br s	7.48; br s	7.50; br s
22	6.65; dd; 2.0; 1.0	6.63; dd; 2.0; 1.0	6.63; dd; 2.0; 1.0	6.63; dd; 2.0; 1.0	6.63; dd; 2.0; 1.0	6.64; dd; 2.0; 1.0
23	7.62; br s	7.61; br s	7.61; br s	7.61; br s	7.60; br s	7.61; br s
28	0.92; s	0.92; s	0.91; s	0.93; s	0.73; s	0.72; s
$29_{pro\text{-}R}$	2.16; d; 11.0	2.28; d; 10.0	2.37; d; 11.0	2.35; d; 10.5	2.18; d; 11.5	2.18; d; 11.5
$29_{pro\text{-}S}$	1.71; dd; 11.0; 1.0	1.62; dd; 10.0; 1.5	1.69; dd; 11.0; 1.0	1.38; dd; 10.5; 1.5	1.75; dd; 11.5; 1.5	1.75; dd; 11.5; 1.5
30	5.11; s	5.07; s	5.38; s	4.95; d; 4.0	5.15; s	5.39; s
2-OAc			2.08; s			2.08; s
3-OAc	1.99; s	1.98; s	1.98; s	1.95; s	2.01; s	2.00; s
6-OAc	2.22; s					
12-OAc	1.52; s	1.52; s	1.52; s	1.52; s	1.52; s	1.52; s
7-OMe	3.81; s	3.82; s	3.81; s	3.80; s	3.75; s	3.74; s
1-OH	3.49; s	3.48; s	3.35; s	3.43; s	3.48; s	3.36; s
2-OH	3.87; s	3.82; s			3.85; s	
6-OH		5.22; d; 4.5	5.00; d; 4.5	5.23; d; 4.5		
Ortho esters						
31						
32	1.70; s	1.69; s	1.71; s	1.67; s	1.69; s	1.70; s

[a] Overlapped by the solvent of acetone-d_6 without designating multiplicity.

Table 2. ^{13}C NMR (125 MHz) data for xyloccensin Q–V (**3**–**8**) in acetone-d_6

No.	3	4	5	6	7	8
1	84.7; s	84.7; s	84.8; s	82.7; s	84.8; s	84.8; s
2	76.0; s	76.1; s	84.5; s	45.8; d	76.1; s	84.4; s
3	86.4; d	86.7; d	86.6; d	78.8; d	86.2; d	86.1; d
4	45.0; s	44.8; s	45.1; s	46.8; s	45.0; s	45.4; s
5	46.1; d	46.6; d	46.0; d	46.5; d	41.5; d	40.9; d
6	71.9; d	71.2; d	71.1; d	71.3; d	33.4; t	33.4; t
7	172.7; s	176.9; s	176.9; s	177.0; s	175.5; s	175.5; s
8	84.9; s	84.9; s	85.0; s	82.9; s	84.9; s	84.9; s
9	87.6; s	87.9; s	87.1; s	88.0; s	87.4; s	86.6; s
10	49.0; s	48.8; s	49.5; s	49.5; s	48.0; s	48.8; s
11	33.0; t	33.1; t	33.2; t	33.1; t	33.1; t	33.3; t
12	69.0; d	69.4; d	69.5; d	69.6; d	69.3; d	69.3; d
13	43.7; s	43.7; s	43.7; s	43.6; s	43.7; s	43.7; s
14	153.9; s	154.1; s	154.0; s	154.6; s	154.1; s	153.9; s
15	125.0; d	124.8; d	124.5; d	124.3; d	124.9; d	124.8; d
16	163.8; s	163.8; s	163.6; s	163.9; s	163.9; s	163.6; s
17	79.4; d	79.2; d	79.4; d	79.2; d	79.3; d	79.5; d
18	15.0; q	15.0; q	15.0; q	14.9; q	14.9; q	14.9; q
19	16.5; q	17.5; q	17.5; q	17.4; q	14.8; q	14.8; q
20	122.5; s	122.5; s	122.4; s	122.6; s	122.6; s	122.4; s
21	142.8; d	142.8; d	142.7; d	142.7; d	142.7; d	142.8; d
22	111.1; d	111.1; d	111.1; d	111.1; d	111.1; d	111.1; d
23	144.3; d	144.3; d	144.3; d	144.3; d	144.4; d	144.4; d
28	15.9; q	15.8; q	15.8; q	15.9; q	15.7; q	15.6; q
29	41.2; t	41.3; t	41.6; t	44.7; t	40.0; t	40.3; t
30	78.8; d	78.9; d	74.9; d	75.4; d	79.0; d	75.1; d
2-OAc			21.6; q			21.6; q
			168.9; s			169.0; s
3-OAc	21.8; q	21.8; q	21.8; q	21.8; q	21.8; q	21.7; q
	170.0; s	170.0; s	170.9; s	170.7; s	170.8; s	170.9; s
6-OAc	21.0; q					
	169.3; s					
12-OAc	19.8; q	20.0; q	20.0; q	20.0; q	20.0; q	20.0; q
	170.2; s	170.2; s	170.7; s	170.6; s	170.1; s	170.7; s
7-OMe	53.6; q	53.0; q	53.0; q	52.9; q	52.4; q	52.5; q
Ortho esters						
31	120.1; s	120.1; s	120.5; s	120.3; s	120.3; s	120.7; s
32	16.6; q	16.6; q	16.5; q	16.7; q	16.6; q	16.5; q



Scheme 1. Modified Mosher's method to determine the absolute stereochemistry of C-6 in xyloccensins P–S (**2**–**5**).

hydroxyl was reconfirmed to be at C-2 by the HMBC correlation from it to the carbon of C-2. By the same way, another hydroxyl (δ_H 3.49s) was determined to be at C-1. In addition, treatment of **2** and **3** with sodium methoxide, respectively, afforded the same compound **9** (Scheme 1), indicating that they had the same absolute stereochemistry. From these results, the structure of **3** was identified as 2-deacetyl xyloccensin P, named xyloccensin Q.

The relative structure of **3** was also confirmed with the help of X-ray crystallographic analysis. A computer-generated perspective drawing of the final X-ray model of **3** was given in Figure 1. The result demonstrated that **3** was a new type of phragmalin, consisting of eight rings, designated as A_1, A_2, B, C, D, E, F and G (Chart 1). The two five-carbocyclic rings (A_1 and A_2) and the two dioxolane rings (F and G), adopted the envelope conformations. The two six carbocyclic rings, B and C, appeared as chairs. The unsaturated δ-lactone ring D exhibited a half-chair conformation and the furan ring E was planar. Rings A_1/B, A_2/B, B/C, B/F, B/G

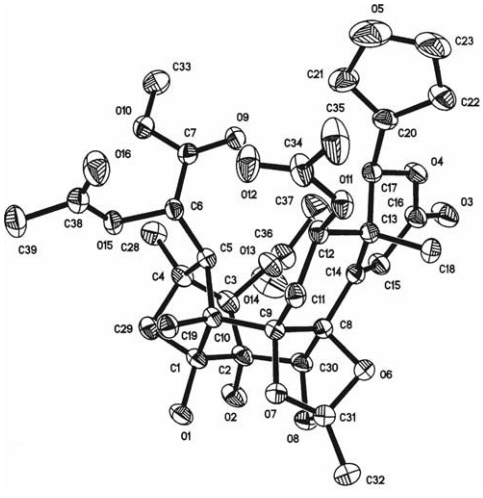
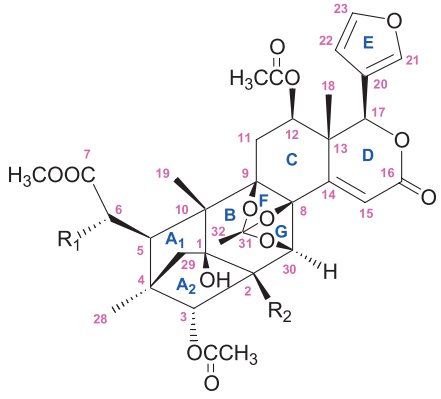


Figure 1. Perspective drawing of the X-ray structure of xyloccensin Q (**3**).



1:	R_1=$OCOCH_3$	R_2=H
2:	R_1=$OCOCH_3$	R_2=$OCOCH_3$
3:	R_1=$OCOCH_3$	R_2=OH
4:	R_1=OH	R_2=OH
5:	R_1=OH	R_2=$OCOCH_3$
6:	R_1=OH	R_2=H
7:	R_1=H	R_2=OH
8:	R_1=H	R_2=$OCOCH_3$

Chart 1. Structures of compounds **1**–**8**.

and C/F were all *cis*-fused. The *ortho*acetate group was bridged at positions of C-8, 9 and 30. The whole shape of the molecule looked like a basket.

Xyloccensin R (**4**) was isolated as colorless crystals. The HR-ESIMS spectrum (*m/z* 675.2273, calcd for $[M+H]^+$ 675.2289) showed that **4** had the molecular formula of $C_{33}H_{38}O_{15}$. The NMR data of **4** were almost the same as those of **3**, except for the absence of an acetyl group (δ_H 2.22s, δ_C 21.0q, 169.3s, 6-OAc in **3**) and the presence of one more hydroxyl [δ_H 5.22 (d; $J=4.5$ Hz)]. It was indicated that 6-acetoxy group in **3** was replaced by a hydroxyl. This result was further confirmed by the ^1H–^1H COSY correlation observed in **4** from the proton of this hydroxyl to H-6 and the HMBC correlation from the same proton to the carbon of an oxygenated methine at δ_C 71.2 (C-6). Treatment of **3** and **4** with sodium methoxide, respectively, afforded the same compound **9** (Scheme 1). Therefore, the structure of **4** was identified as 6-deacetyl xyloccensin Q, named xyloccensin R.

Xyloccensin S (**5**) was isolated as a white powder. The HR-ESIMS spectrum (*m/z* 717.2406, calcd for $[M+H]^+$ 717.2394) showed that **5** had the same molecular formula as **3**. The NMR data of **5** were almost the same as those of xyloccensin P, (**2**), isolated from the same plant, except for the absence of an acetyl group (δ_H 2.22s, δ_C 21.0q, 169.3s, 6-OAc in xyloccensin P) and the presence of one more hydroxyl [δ_H 5.00 (d; $J=4.5$ Hz)]. It was indicated that 6-acetoxy group in xyloccensin P was replaced by a hydroxyl. This result was further confirmed by the ^1H–^1H COSY correlation observed in **5** from the proton of this hydroxyl to H-6 and the HMBC correlation from the same proton to the carbon of an oxygenated methine at δ_C 71.1 (C-6). Treatment of **2** and **5** with sodium methoxide, respectively, gave the same compound **9** (Scheme 1). Therefore, the structure of **5** was identified as 6-deacetyl xyloccensin P, named xyloccensin S.

Xyloccensin T (**6**), a white powder, had a molecular formula of $C_{33}H_{38}O_{14}$ established by HR-ESIMS spectrum (*m/z* 659.2330, calcd for $[M+H]^+$ 659.2339). The UV, IR and NMR spectra of **6** were very similar to those of xyloccensin O (**1**),[5] isolated from the same plant. It was revealed that **6** had the same phragmalin nucleus as xyloccensin O. However, an acetyl signal at δ_H 2.21s and δ_C 169.3s, 21.0q (6-OAc in xyloccensin O) disappeared, whereas one more hydroxyl signal at δ_H 5.23 (d; $J=4.5$ Hz) (Table 1) appeared. The 6-acetoxy group in xyloccensin O was replaced by a hydroxyl, which was further confirmed by the ^1H–^1H COSY correlation observed in **6** from the proton of this hydroxyl to H-6 and the HMBC correlation from the same proton to the carbon of an oxygenated methine at δ_C 71.3 (C-6) (Fig. 2). Moreover, the relative stereochemistry of **6** was established as that of xyloccensin O by the NOE correlations: H-5/H_3-28, H-5/H-17, H-5/H-30, H-17/H-12, H-17/H-21, H-17/H-30, H_3-19/H-6, H_3-19/H-11β, OH-1/H-3, OH-1/H_3-32, H-11β/H-6 (Fig 3). Based on these results, the structure of **6** was identified as 6-deacetyl xyloccensin O, named xyloccensin T.

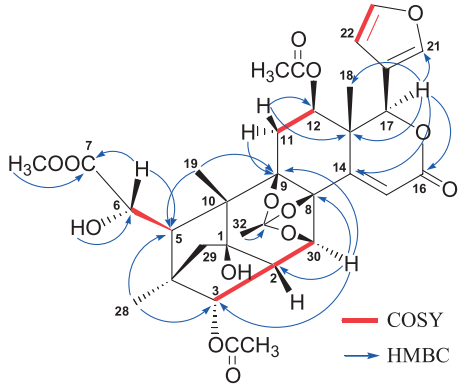


Figure 2. Selected ^1H–^1H COSY and HMBC correlations for xyloccensin T (**6**).

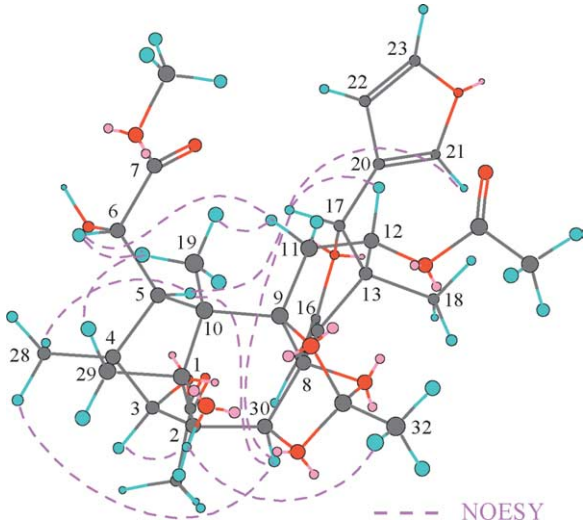


Figure 3. Significant NOE correlations for xyloccensin T (**6**).

Xyloccensin U (**7**) was isolated as a white powder. HR-ESIMS spectrum (*m/z* 659.2344, calcd for $[M+H]^+$ 659.2339) showed that it had the same molecular formula as **6**. The NMR data of **7** were almost the same as those of **6**, except for the remarkable difference of a hydroxyl [δ_H 3.85s in **7** and 5.23 (d; $J=4.5$ Hz, 6-OH) in **6**]. The above evidence suggested that **7** was the positional isomer of **6** and the only difference between the two molecules was the differently substituted position of a hydroxyl. The HMBC correlation observed in **7** from the proton of this hydroxyl (δ_H 3.85s) to the C-2 revealed that it was connected to the C-2. Moreover, The relative structure of **7** elucidated by the NOESY correlations (H-5/H_3-28, H-5/H-17, H-5/H-30, H-17/H-12, H-17/H-21, H-17/H-30, H_3-19/H-6, H_3-19/H-11β, OH-1/H-3, OH-1/H_3-32, H-11β/H-6) was the same as that of **6**. Consequently, the structure of **7** was identified as 2-hydroxyl-6-deoxy xyloccensin T, named xyloccensin U.

Xyloccensin V (**8**), a white powder, had a molecular formula of $C_{35}H_{40}O_{15}$ established by HR-ESIMS spectrum (*m/z* 701.2422, calcd for $[M+H]^+$ 701.2445). The NMR data of **8** were similar to those of **7**, except for the absence of a hydroxyl (δ_H 3.85s, 2-OH in **7**) and the presence of one more acetyl group (δ_H 2.08s and δ_C 169.0s, 21.6q, 2-OAc in **8**). It was indicated that 2-hydroxyl in **7** was replaced by an acetoxy group. The NOE correlations

(H-5/H_3-28, H-5/H-17, H-5/H-30, H-17/H-12, H-17/H-21, H-17/H-30, H_3-19/H-6, H_3-19/H-11β, OH-1/H-3, OH-1/H_3-32, H-11β/H-6) established that **8** had the same relative stereochemistry as **7**. Based on these results, the structure of **8** was characterized as 2-acetyl xyloccensin T, named xyloccensin V.

2.3. Absolute stereochemistry of xyloccensins P–S (2–5) by the modified Mosher's method

Alkaline hydrolysis of xyloccensins P–S (**2**–**5**) with sodium methoxide, respectively, yielded the same compound (**9**) (see Scheme 1). It was suggested that the absolute stereochemistry of those compounds was the same. As reported in our previous published paper[5] and mentioned above, the relative structures of xyloccensins P–S had been established by single-crystal X-ray diffraction and spectroscopic experiments. Obviously, if the chirality of one carbon in those compounds was determined, the absolute stereochemistry of all carbons in xyloccensins P–S was established unambiguously.

From the relative structures of compounds **2**–**5** (Chart 1), it was found that xyloccensins R and S (**4**, **5**) had a secondary alcohol at C-6, respectively. To determine the absolute stereochemistry of this chiral center, using NMR spectroscopy, the modified Mosher's method[6] was employed. The chiral derivatizing agents used in the esterification reaction were (*R*)- and (*S*)-α-methoxy-α-(trifluoromethyl) phenylacetyl chloride [(*R*)- and (*S*)-MTPACl]. Unfortunately, when compounds **4** and **5** were treated with (*R*)- and (*S*)-MTPACl under the catalysis of (dimethylamino)pyridine (DMAP), respectively, no reluctant esterified products yielded for the low reactivity of MTPACl with the 6-OH of the above two compounds. However, when compound **9**, the alkaline hydrolytic product of xyloccensins P–S, was treated with (*R*)- and (*S*)-MTPACl under the catalysis of DMAP at room temperature, respectively, to our surprising, only its 6-(*S*)- and 6-(*R*)-MTPA esters produced selectively. HPLC separation furnished compounds **10a** and **10b**. Treatment of **10a** and **10b** with excess (trimethylsilyl) diazomethane ($TMSCHN_2$) in the mixture of anhydrous hexane and methanol, respectively, produced the desired 7-methylate derivatives **11a** and **11b** (Scheme 1).

The absolute configuration at C-6 was determined by application of the modified Mosher's method for **11a** and **11b** (Fig. 4). The $\Delta\delta$ value ($\delta_S-\delta_R$) of H_3-7-OMe (+0.185) showed positive, while those of H-5 (−0.039), H_3-19 (−0.228), H_3-28 (−0.098), H_2-29 (−0.200, −0.021), H-30 (−0.036) and H_3-32 (−0.031) were negative, thus, suggesting the 6*S*-configuration in compound **9**. Therefore, the absolute stereochemistry of all the carbons of compound **9** and xyloccensins P–S (**2**–**5**) was elucidated as shown in Figure 4.

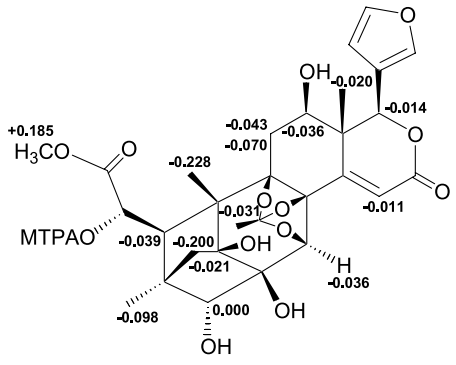


Figure 4. $\Delta\delta$ values [$\Delta\delta$ (ppm)$=(\delta_S-\delta_R)$] obtained for the 6-(*S*)- and 6-(*R*)-MTPA esters (**11a** and **11b**, respectively) of the 7-methylate of compound **9**.

2.4. Absolute stereochemistry of xyloccensins O–V (1–8) by CD analysis

Xyloccensins O–V (**1**–**8**) are 8,9,30-phragmalin *ortho* esters with two main intramolecular chromophores. One is a furan ring and another is an α,β-unsaturated δ-lactone. Both are connected through the chiral center of C-17. The absolute stereochemistry of C-17 in these compounds was further examined using CD analysis. The CD spectrum of **3**, detected in the solvent of acetonitrile of chromatographic grade, exhibited two positive Cotton effects at 217 ($\Delta\varepsilon=+18.4$) and 264 nm ($\Delta\varepsilon=+3.1$), respectively, (Fig. 5A). Taking into account the position and intensity, the first Cotton effect was related to the $\pi\rightarrow\pi^*$ transition of the furan ring chromophore, while the second Cotton effect was resulted from the $n\rightarrow\pi^*$ transition of the α, β-unsaturated δ-lactone. Compared the CD spectrum of **3** to that of khayanolide C[7] [212 ($\Delta\varepsilon=+1.8$), 245 ($\Delta\varepsilon=-4.3$) and 358 nm ($\Delta\varepsilon=-0.7$)], a rearranged phragmalin having the same intramolecular chromophores connected through C-17 with a *R* configuration, it was found that the second Cotton effect corresponding to the $n\rightarrow\pi^*$ transition of the α, unsaturated δ-lactone was opposite. Consequently, the absolute configuration at C-17 of **3** was enantiomeric to that of khayanolide C and assigned as S unambiguously. This result was also identical to that determined by the combination of single-crystal X-ray diffraction and modified Mosher's method mentioned above.

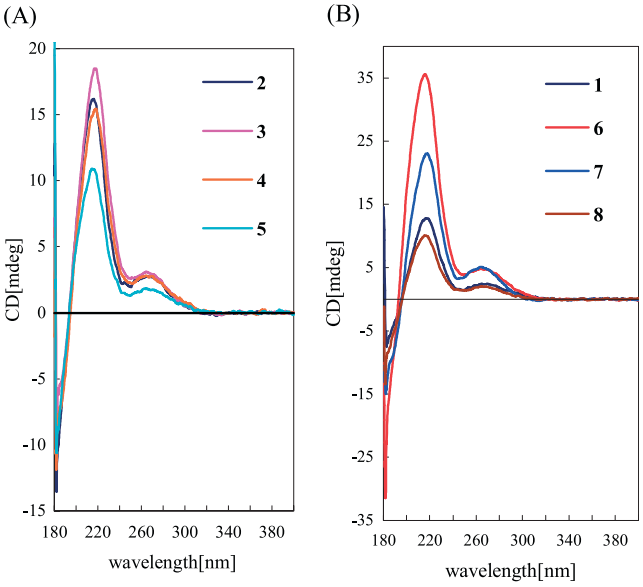


Figure 5. (A) CD spectra of xyloccensins P(**2**), Q(**3**), R(**4**), S(**5**). (B) CD spectra of xyloccensins O(**1**), T(**6**), U(**7**), V(**8**).

By using the same method, the absolute stereochemistry of compounds **1**, **2**, **4**–**8** (Fig. 5A and B) was elucidated as the same as that of compound **3**.

2.5. Antifeedant activity of xyloccensins O–V

The antifeedant activity of the isolated compounds **1**–**8**, was tested with a conventional leaf disk method against the third instar larvae of *Mythimna separata* (Walker). Compounds **2** and **3** were strongly active at a concentration of 500 ppm, with 50 ppm corresponding to a concentration of ca. 1 μg/leaf·cm^2, whereas other compounds showed weak activity.

3. Conclusion

Xyloccensins Q–V, highly oxidized 8,9,30-phragmalin *ortho* esters, were isolated from the Chinese mangrove *X. granatum*. The absolute stereochemistry of xyloccensins O–V was determined by the combination of X-ray crystallographic data, NOESY correlations, the modified MTPA Mosher ester method and CD analysis. To the best of our knowledge, xyloccensins O–V are enantiomeric to all the phragmalins reported so far. Xyloccensins P and Q exhibited potent antifeedant activity against the third instar larvae of *M. separata* at a concentration of 500 ppm. This study also demonstrated that *X. granatum* is a new source for the production of limonoids with novel carbon framework.

4. Experimental

4.1. General procedure

NMR spectra were recorded in acetone-d_6 and pyridine-d_5 using a Bruker AV-500 spectrometer (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) with tetramethylsilane as the internal standard. UV spectra were obtained on a Beckman DU-640 UV spectrophotometer and IR spectra recorded on a Perkin-Elmer FT-IR 1760X spectrophotometer. Electrospary ionization (ESI)-MS spectra were measured on a Bruker APEX II spectrometer in positive or negative ion mode. Optical rotations were recorded on a POLAPTRONIC HNQW5 automatic high-resolution polarimeter (Schmidt and Haensch Co. Ltd) and CD spectra obtained on a JASCO *J*-810 circular dichroism spectrometer. Preparative HPLC was carried out on ODS columns (250×10 mm i.d., YMC) with a Waters 996 photodiode array detector, and X-ray data on a Bruker Smart 1000 CCD system diffractometer. For CC, silica gel (200–300 mesh) (Qingdao Mar. Chem. Ind. Co. Ltd) and octadecylsilyl silica gel (80–100 μm) (Unicorn) were used.

4.2. Plant material

X. granatum was collected in July 2001 from Sanya of Hainan Province, southern China. The identification of the plant was performed by Prof. Yongshui Lin, Laboratory of Marine Biology, South China Sea Institute of Oceanology, Chinese Academy of Sciences. A voucher sample (NO. GKLMMM-002) is kept in the Herbarium of South China Sea Institute of Oceanology.

4.3. Extraction and isolation

The dried stem bark (2.3 kg) of *X. granatum* was extracted with hot 95% ethanol. The extract was concentrated under reduced pressure, followed by suspension in water. After defatting with petroleum ether, the aqueous layer was further extracted with ethyl acetate. The ethyl acetate extract (80 g) was chromatographed on silica gel column and eluted using chloroform–methanol system (100:0–2:1) to yield 120 fractions. Fractions 6–11 (5 g) were combined and further purification with preparative HPLC (YMC-Pack ODS-5-A, 250×20 mm i.d., acetonitrile–water 35:65–45:55) yielded xyloccensins Q (**3**, 60 mg), R (**4**, 22 mg), S (**5**, 20 mg), T (**6**, 16 mg), U (**7**, 8 mg), V (**8**, 6 mg).

4.3.1. Xyloccensin Q (3). A colorless crystal; mp 150–152 °C; $[\alpha]_D^{25}$ +75 (*c* 1.3, MeCN); UV (MeCN) λ_{max} 213.5 nm; IR (KBr) ν_{max} 3600–3210, 2985, 1740–1715 cm^{-1}; ^{1}H and ^{13}C NMR (see Tables 1 and 2); ESI-MS *m/z* 739 [M+ Na]$^+$; HR-ESIMS *m/z* 717.2395 [calcd for $C_{35}H_{41}O_{16}$ [M+H]$^+$, 717.2395].

4.3.2. Xyloccensin R (4). A colorless crystal; mp 184–186 °C; $[\alpha]_D^{25}$ +61 (*c* 0.1, MeCN); UV (MeCN) λ_{max} 214.7 nm; IR (KBr) ν_{max} 3600–3200, 2985, 1740–1710 cm^{-1}; ^{1}H and ^{13}C NMR (see Tables 1 and 2); ESI-MS *m/z* 697 [M+ Na]$^+$; HR-ESIMS *m/z* 675.2273 [calcd for $C_{33}H_{39}O_{15}$ [M+H]$^+$, 675.2289].

4.3.3. Xyloccensin S (5). A white powder; mp 174–176 °C; $[\alpha]_D^{25}$ +42 (*c* 0.2, MeCN); UV (MeCN) λ_{max} 213.5 nm; IR (KBr) ν_{max} 3600–3200, 2985, 1740–1710 cm^{-1}; ^{1}H and ^{13}C NMR (see Tables 1 and 2); ESI-MS *m/z* 739 [M+ Na]$^+$; HR-ESIMS *m/z* 717.2406 [calcd for $C_{35}H_{41}O_{16}$ [M+H]$^+$, 717.2395].

4.3.4. Xyloccensin T (6). Colorless crystals; mp 145–147 °C; $[\alpha]_D^{25}$ +28 (*c* 0.8, MeCN); UV (MeCN) λ_{max} 212.4 nm; IR (KBr) 3600–3200, 2985, 1740–1715 cm^{-1}; ^{1}H and ^{13}C NMR (see Tables 1 and 2); ESI-MS *m/z*: 659 [M+H]$^+$, 681 [M+Na]$^+$; HRESI-MS *m/z*: 659.2330, [calcd for $C_{33}H_{39}O_{14}$ [M+H]$^+$, 659.2340].

4.3.5. Xyloccensin U (7). A white powder; mp 142–144 °C; $[\alpha]_D^{25}$ +22 (*c* 0.2, MeCN); UV (MeCN) λ_{max} 212.4 nm; IR (KBr) 3600–3200, 2985, 1740–1715 cm^{-1}; ^{1}H and ^{13}C NMR (see Tables 1 and 2); ESI-MS *m/z*: 659 [M+H]$^+$, 681 [M+Na]$^+$; HRESI-MS *m/z*: 659.2344, [calcd for $C_{33}H_{39}O_{14}$ [M+H]$^+$, 659.2340].

4.3.6. Xyloccensin V (8). A white powder; mp 131–133 °C; $[\alpha]_D^{25}$ +5 (*c* 0.5, MeCN); UV (MeCN) λ_{max} 214.7 nm; IR (KBr) 3600–3200, 2985, 1740–1710 cm^{-1}; ^{1}H and ^{13}C NMR (see Tables 1 and 2); ESI-MS *m/z*: 723 [M+Na]$^+$; HRESI-MS *m/z*: 701.2422, [calcd for $C_{35}H_{41}O_{15}$ [M+H]$^+$, 701.2445].

4.4. Preparation of compounds 11a and 11b [(*R*)- and (*S*)-MTPA ester] from xyloccensins P–S (2–5)

Xyloccensins Q (**3**) (10 mg) was treated with excess sodium methoxide (150 mg) and refluxed in the mixture of dioxane and water (1:1) for 6 h. The reaction mixture was partitioned

between the water and ethyl acetate. Then the ethyl acetate layer was neutralized with acetic acid and concentrated under reduced pressure. The residue was applied to the preparative HPLC (YMC-Pack ODS S-5 μ, 250×10 mm i.d.) to afford compound **9** [methanol–acetonitrile–water–acetic acid (26:6:67.75:0.25), t_r=49.5 min, 6 mg]. By the same method, xyloccensins P, R and S provided compound **9**, respectively.

A half portion of resultant compound **9** (11 mg) was transferred into a clean NMR tube and dried completely under the vacuum of an oil pump. Deuterated pyridine (0.5 mL), (*S*)-MTPA chloride (15 μL) and DMAP (5 mg) were added into the NMR tube immediately under a N_2 gas stream, and the NMR tube was shaken carefully to mix the sample and MTPA chloride evenly. The reaction NMR tube was permitted to stand at room temperature and monitored every 1 h by ^{1}H NMR spectrum. The reaction was completed after 2 h. Then the reaction mixture was concentrated and applied to the preparative HPLC (YMC-Pack ODS S-5μ, 250×10 mm i.d.) to afford the (*S*)-MTPA derivative of **9** [**10a**, methanol–acetonitrile–water–acetic acid (37:22:40.5:0.5), t_r=47.1 min, 6 mg]. In the same manner described for **10a**, another portion of compound **9** was reacted in a second NMR tube with (*R*)-MTPA chloride (15 μL) and DMAP (5 mg) at room temperature for 2 h using deuterated pyridine (0.5 mL) as the solvent, followed by HPLC (YMC-Pack ODS S-5μ, 250×10 mm i.d.) to afford the (*R*)-MTPA derivative of **9** [**10b**, methanol–acetonitrile–water–acetic acid (37:20:42.5:0.5), t_r= 46.6 min, 7 mg]. Then treatment of dried compounds **10a** and **10b** with excess $TMSCHN_2$ (0.5 mL each) in the mixture of anhydrous hexane and methanol (1:1) and stirred at room temperature overnight, followed by preparative HPLC (YMC-Pack ODS S-5μ, 250×10 mm i.d.), respectively, gave compounds **11a** [methanol–acetonitrile–water–acetic acid (37:28:34.5:0.5), t_r=33.4 min, 4 mg] and **11b** [methanol–acetonitrile–water–acetic acid (37:26:36.5:0.5), t_r=34.5 min, 5 mg].

4.4.1. Compound 9. A white powder; ^{1}H NMR (pyridine-d_5): 8.09 (br s, H-21), 7.56 (br s, H-23), 7.31 (s, H-15), 6.96 (br s, H-22), 6.79 (s, H-17), 5.29 (s, H-30), 4.90 (d, J= 14.0 Hz, H-12), 4.82 (s, H-6), 4.24 (s, H-3), 3.17 (br s, H-5), 2.86 (d, J=10.0 Hz, H-29$_{pro\text{-}R}$), 2.83 (dd, J=13.5, 3.3 Hz, H-11β), 2.56 (t, J=13.5 Hz, H-11α), 2.09 (d, J=10.5 Hz, H-29$_{pro\text{-}S}$), 2.04 (s, 3H, H_3−28), 1.89 (s, 3H, H_3-18), 1.77 (s, 3H, H_3-32), 1.56 (s, 3H, H_3-19); ^{13}C NMR (pyridine-d_5): 85.2 (C-1), 77.9(C-2), 88.1 (C-3), 44.8 (C-4), 45.1 (C-5), 72.3 (C-6), 178.9 (C-7), 85.3 (C-8), 88.9 (C-9), 49.3 (C-10), 37.9 (C-11), 66.2 (C-12), 45.2 (C-13), 155.2 (C-14), 124.2 (C-15), 165.0 (C-16), 80.5 (C-17), 14.0 (C-18), 16.8 (C-19), 123.0 (C-20), 142.5 (C-21), 111.6 (C-22), 143.1 (C-23), 17.8 (C-28), 41.7 (C-29), 80.3 (C-30), 119.2 (C-31), 16.8 (C-32); ESI-MS *m/z*: 575 $[M-H]^-$.

4.4.2. Compound 10a. A white powder; ^{1}H NMR[8] (pyridine-d_5): 8.03 (br s, H-21), 7.58 (br s, H-23), 7.30 (s, H-15), 6.96 (br s, H-22), 6.68 (s, H-17), 6.07 (s, H-6), 5.24 (s, H-30), 4.97 (dd, J=13.0, 4.0 Hz, H-12), 4.26 (s, H-3), 4.04 (H_3-MTPA-OMe), 3.36 (s, H-5), 2.81 (dd, J=13.5, 3.0 Hz, H-11β), 2.52 (t, J=13.5 Hz, H-11α), 2.20 (d, J= 10.5 Hz, H-29$_{pro\text{-}R}$), 2.01 (d, J=10.5 Hz, H-29$_{pro\text{-}S}$), 1.85 (s, 3H, H_3−18), 1.71 (s, 3H, H_3-32), 1.59 (s, 3H, H_3-19), 1.17 (s, 3H, H_3-28); ESI-MS *m/z*: 815 $[M+Na]^+$.

4.4.3. Compound 10b. White powder; ^{1}H NMR[8] (pyridine-d_5): 8.03 (br s, H-21), 7.57 (br s, H-23), 7.33 (s, H-15), 6.94 (br s, H-22), 6.68 (s, H-17), 6.20 (s, H-6), 5.31 (s, H-30), 4.97 (dd, J=13.0, 4.0 Hz, H-12), 4.28 (s, H-3), 3.58 (H_3-MTPA-OMe), 3.40 (s, H-5), 2.91 (dd, J=13.5, 3.0 Hz, H-11β), 2.55 (t, J=13.5 Hz, H-11α), 2.51 (d, J=10.5 Hz, H-29$_{pro\text{-}R}$), 2.06 (d, J=10.5 Hz, H-29$_{pro\text{-}S}$), 1.85 (s, 3H, H_3-18), 1.74 (s, 3H, H_3-32), 1.71 (s, 3H, H_3-19), 1.45 (s, 3H, H_3-28); ESI-MS *m/z*: 815 $[M+Na]^+$.

4.4.4. Compound 11a. A white powder; ^{1}H NMR (pyridine-d_5): 8.02 (br s, H-21), 7.88 (d, J=4.5 Hz, OH-3), 7.79 (d, 2H, J=7.5 Hz, MTPA-H-2, 6), 7.66 (br s, H-23), 7.50 (t, 1H, J=7.5 Hz, MTPA-H-4), 7.46 (t, 2H, J= 7.5 Hz, MTPA-H-3, 5), 7.27 (s, H-15), 6.96 (br s, H-22), 6.42 (s, H-17), 6.33 (d, J=5.0 Hz, OH-12), 5.89 (s, H-6), 5.76 (br s, OH-2), 5.22 (s, H-30), 4.64 (d, J=14.0 Hz, H-12), 4.24 (d, J=4.5 Hz, H-3), 3.99 (br s, OH-1), 3.82 (s, 3H, H_3-7-OMe), 3.68 (s, 3H, H_3-MTPA-OMe), 3.16 (s, H-5), 2.70 (dd, J=13.5, 3.0 Hz, H-11β), 2.52 (t, J= 13.5 Hz, H-11α), 2.12 (d, J=10.5 Hz, H-29$_{pro\text{-}R}$), 2.02 (d, J=10.5 Hz, H-29$_{pro\text{-}S}$), 1.89 (s, 3H, H_3-18), 1.71 (s, 3H, H_3-32), 1.29 (s, 3H, H_3-19), 1.08 (s, 3H, H_3-28); ^{13}C NMR (pyridine-d_5): 84.9 (C-1), 77.4 (C-2), 87.1 (C-3), 45.1 (C-4), 44.4 (C-5), 74.8 (C-6), 170.1 (C-7), 84.6 (C-8), 87.7 (C-9), 48.9 (C-10), 37.6 (C-11), 66.0 (C-12), 44.2 (C-13), 154.5 (C-14), 124.4 (C-15), 164.4 (C-16), 80.6 (C-17), 13.7 (C-18), 16.5 (C-19), 121.0 (C-20), 142.3 (C-21), 111.4 (C-22), 143.0 (C-23), 15.9 (C-28), 40.7 (C-29), 79.9 (C-30), 118.9 (C-31), 16.4 (C-32), 53.0 (C-7-OMe), 130.1 (MTPA-C-1), 127.4 (MTPA-C-2, 6), 128.6 (MTPA-C-3, 5), 129.3 (MTPA-C-4), ND[9] (MTPA-C-7), 166.3 (MTPA-C-8), ND[9] (MTPA-CF_3), 56.1 (MTPA-OMe); ESI-MS *m/z*: 807 $[M+H]^+$, 829 $[M+Na]^+$.

4.4.5. Compound 11b. A white powder; ^{1}H NMR (pyridine-d_5): 8.02 (br s, H-21), 7.87 (d, J=4.5 Hz, OH-3), 7.77 (d, 2H, J=7.5 Hz, MTPA-H-2, 6), 7.66 (br s, H-23), 7.51 (t, 1H, J=7.5 Hz, MTPA-H-4), 7.49 (t, 2H, J= 7.5 Hz, MTPA-H-3, 5), 7.28 (s, H-15), 6.96 (br s, H-22), 6.43 (s, H-17), 6.34 (d, J=5.0 Hz, OH-12), 6.01 (s, H-6), 5.78 (br s, OH-2), 5.26 (s, H-30), 4.68 (d, J=14.0 Hz, H-12), 4.24 (d, J=4.5 Hz, H-3), 4.17 (br s, OH-1), 3.64 (s, 3H, H_3-7-OMe), 3.45 (s, 3H, H_3-MTPA-OMe), 3.20 (s, H-5), 2.78 (dd, J=13.5, 3.0 Hz, H-11β), 2.56 (t, J= 13.5 Hz, H-11α), 2.32 (d, J=10.5 Hz, H-29$_{pro\text{-}R}$), 2.05 (d, J=10.5 Hz, H-29$_{pro\text{-}S}$), 1.91 (s, 3H, H_3-18), 1.72 (s, 3H, H_3-32), 1.59 (s, 3H, H_3-19), 1.17 (s, 3H, H_3-28); ^{13}C NMR (pyridine-d_5): 85.0 (C-1), 77.6 (C-2), 87.3 (C-3), 45.3 (C-4), 44.6 (C-5), 75.1 (C-6), 170.2 (C-7), 85.0 (C-8), 87.9 (C-9), 49.2 (C-10), 37.8 (C-11), 66.2 (C-12), 44.3 (C-13), 154.7 (C-14), 124.6 (C-15), 164.6 (C-16), 80.7 (C-17), 13.9 (C-18), 16.8 (C-19), 122.9 (C-20), 142.5 (C-21), 111.6 (C-22), 143.2 (C-23), 15.8 (C-28), 40.8 (C-29), 80.2 (C-30), 119.2 (C-31), 16.6 (C-32), 53.0 (C-7-OMe), 131.1 (MTPA-C-1), 128.5 (MTPA-C-2, 6), 129.0 (MTPA-C-3, 5), 130.4 (MTPA-C-4), ND[9] (MTPA-C-7), 166.3 (MTPA-C-8), ND[9] (MTPA-CF_3), 55.5 (MTPA-OMe); ESI-MS *m/z*: 807 $[M+H]^+$, 829 $[M+Na]^+$.

4.5. X-ray Crystal Data for Xyloccensin Q (3)

All measurements were made on a Bruker Smart 1000 CCD system diffractometer with graphite monochromated Mo Kα radiation $\lambda=0.71073$ Å at 293 K. Crystal data: orthorhombic, $C_{35}H_{40}O_{16}$, space group $P2_12_12_1$ with $a=12.9405(16)$ Å, $b=13.0548(15)$ Å, $c=20.344(3)$ Å, $V=3436.8(8)$ Å^3, $Z=4$, $D_{calcd}=1.385$ g/cm^3, $m=0.110$ mm^{-1} and $F(000)=1512$. Crystal size: $0.50\times0.50\times0.43$ mm^3. Independent reflections: 4197 with $R_{int}=0.0195$. Observed reflections: 4193 with $[I\geq4\sigma(I)]$. The structure was solved by direct methods (SHELXS-97) and refined using full-matrix least-squares difference Fourier techniques. All non-hydrogen atoms were refined anisotropically, and all hydrogen atoms were placed in idealized positions and refined as riding atoms with the relative isotropic parameters. The final agreement factors of $R_1=0.0353$ and $wR_2=0.0889$ $[I\geq2\sigma(I)]$. Crystallographic data (excluding structure factors) for **3** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 249551. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1233 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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8. Detected in the mixture of MTPACl [(*R*)- or (*S*)-] and DMAP. The aromatic proton signals of the MTPA fragment of **10a** and **10b** are overlapped with that of the reacting reagents.
9. ND: not detected for the split and low intensity caused by C–F coupling.

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Two efficient four-step routes to marine toxin tanikolide

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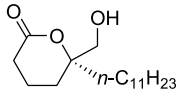
Abstract—We have presented two facile four-step syntheses of (±)-tanikolide from ethyl 2-oxocyclopentanecarboxylate. The overall chemical yields of the two sequences reached as high as 76 and 85%, respectively. The first strategy involved alkylation, Baeyer–Villiger reaction, saponification, and reduction/lactonization. The second approach for synthesizing tanikolide took advantage of the same intermediate, the alkylated ketoester **2**, which was converted to the target molecule in such three steps as deethoxycarbonylation, hydroxymethylation, and Baeyer–Villiger reaction. Our strategies are advantageous because of their high yields and suitability for the preparation of **1** in multigram or larger quantities.

1. Introduction

As a wellspring of drugs and drug leads, natural products have been one of the most rewarding scientific research areas for decades. In particular, marine natural products, perpetually provided by the oceans, have gained increasing popularity owing to their various distinct structures and bioactivities. Gerwick and co-workers[1] reported in 1999, the isolation and structural elucidation of (*R*)-(+)-tanikolide, a brine-shrimp toxic and antifungal metabolite native to the marine cyanobacterium *Lyngbya majuscula* collected from Tanikeli Island. The biological assays of this new toxin demonstrated an LD_{50} of 3.6 μg/mL against brine shrimp and 9.0 μg/mL against the snail. Moreover, a 13-mm diameter inhibition zone (100 μg/disk) was observed when (*R*)-(+)-tanikolide was tested with the fungus *Candida albicans*.[1] Due to the presence of a tertiary carbon center in the δ-lactone framework and the unique bioactivity, the synthesis of tanikolide has aroused considerable interests from the synthetic community.[2] Ogasawara accomplished an enantioselective synthesis of (*R*)-(+)-tanikolide in 12 steps from a known 1,2-enediol bis-silyl ether, where a kinetic resolution based on a ruthenium-promoted catalytic asymmetric hydrogen transfer reaction was utilized as a key step.[2a] It was the remarkable optically active allene strategy that enabled Nelson to realize the asymmetric total synthesis of (*R*)-(+)-tanikolide in six steps from propargyl alcohol.[2b] Afterwards, two different nine-step approaches to the synthesis of tanikolide in the racemic form were achieved by Chen[2c] and Krauss,[2d] respectively; both of the syntheses featured the use of a dihydroxylation and a Grignard addition. The powerful ring closing metathesis (RCM) transformation has found successful applications in forming the δ-lactone framework of tanikolide.[2e,f] More recently, Koumbis and co-workers[2g] accomplished a 10-step enantioselective synthesis of (*R*)-(+)-tanikolide starting from *D*-erythrose, a useful chiron.



(*R*)-(+)-tanikolide

Even nowadays, formulating a highly efficient synthetic strategy for constructing biosignificant natural products remains a tremendous challenge. The chemical community is more willing than ever to show concern for '(reaction) step economy' in organic synthesis. In our case, a suitable cyclopentanone derivative was envisioned as an excellent starting point to develop synthetic avenues to tanikolide with high efficacy. We now wish to provide a full account of our findings regarding the syntheses of this new marine toxin.[3]

Keywords: Tanikolide; Syntheses; Marine natural product.
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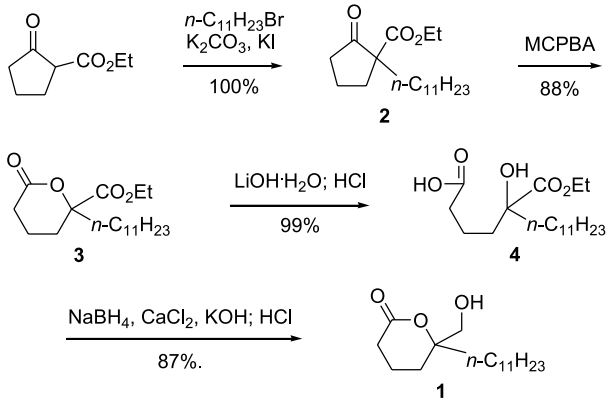
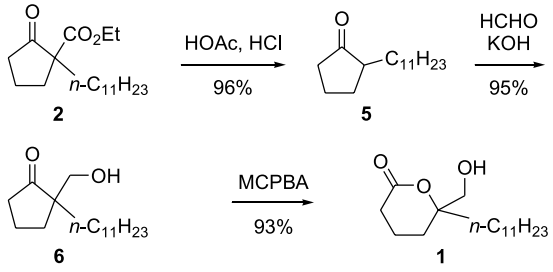
2. Results and discussion

We have developed two shorter and more efficient syntheses of tanikolide (**1**). Our first synthesis,[2h] as outlined in Scheme 1, commenced from the commercially available ethyl 2-oxocyclopentanecarboxylate, which was alkylated[4a–c] with 1-bromoundecane in the presence of K_2CO_3 and KI in refluxing anhydrous acetone for 20 h to furnish the known intermediate[4d] **2** in 100% yield. Baeyer–Villiger oxidation of **2** under typical conditions[5] (MCPBA, $NaHCO_3$, anhydrous $CHCl_3$, rt) led to lactone **3** (88%), in which the monooxygenated tertiary carbon center was in place. With **3** in hand, selective reduction of the ethoxycarbonyl group in the presence of the lactone moiety was attempted. Mild reduction with $NaBH(OAc)_3$ effected no reaction at all. Treatment of **3** with excess $NaBH_4$ in ethanol at rt for 30 min gave a ring-opened dihydroxyester, which indicated that the lactone carbonyl was actually more reactive toward borohydride reduction than the ethoxycarbonyl moiety. If the above reaction mixture was heated at reflux for 1 h, a triol was formed as a result of extensive reduction. After several unfruitful trials, we resorted to a different strategy that involved effecting the reduction at a later stage. Saponification[6] of **3** with $LiOH\cdot H_2O$ in THF/H_2O (1:1) at −2 °C for 4 h followed by acidification with 6 M HCl generated the hydroxydiacid monoester **4** in almost quantitative yield (99%). Under the reaction conditions, the ethoxycarbonyl group was kept intact because of steric hindrance. Finally, monoester **4** was treated with the $NaBH_4/CaCl_2$/KOH reduction system[7] to afford, after lactonization during the acidic workup with 6 M HCl, tanikolide (**1**) in good yield (87%). No reaction took place when $NaBH_4/CaCl_2$ (i.e., in the absence of KOH) or $NaBH_4$ alone was used instead. The spectroscopic data of our synthetic sample of tanikolide (**1**) were in accord with those reported previously.[1,2]



Scheme 1.

Next, an alternative, convenient approach for synthesizing tanikolide emerged that took advantage of the same intermediate **2** but avoided the step of calcium borohydride (generated in situ from $NaBH_4$ and $CaCl_2$) reduction in basic (KOH) media. Deethoxycarbonylative hydrolysis of **2** in refluxing concentrated HCl–HOAc (5:3, v/v) for 2 days cleanly afforded 2-(*n*-undecyl)cyclopentanone[8] (**5**) in 96% yield (Scheme 2). Upon treatment of **5** in methanol with formalin (105 mol%) and KOH (110 mol%) at 0 °C for 2 h,



Scheme 2.

selective hydroxymethylation at C-2 took place to produce aldol **6** with a quaternary carbon center in excellent yield (95%, based on consumed **5**).[9] For this step, longer reaction time proved detrimental to the outcome by allowing the formation of the bis-and tris-hydroxymethylation byproducts. Under the same Baeyer–Villiger oxidation conditions as for **2**, the desired ring expansion was effected to transform **6** into (±)- tanikolide (**1**) in 93% yield.

3. Conclusion

In summary, we have presented two facile four-step syntheses of (±)-tanikolide from ethyl 2-oxocyclopentanecarboxylate. The features of the current work are as follows. (i) The overall chemical yields of the two sequences reached as high as 76 and 85%, respectively. (ii) The first strategy involved alkylation, Baeyer–Villiger reaction, saponification, and reduction/lactonization. Each step proceeds in better than 87% yield. In addition, the net result of the last two steps (i.e., saponification and reduction/lactonization) is an efficient reduction of the ethoxycarbonyl of **3** while keeping the lactone carbonyl intact. The alternative in situ protection (LDA)–reduction ($LiAlH_4$) strategy[10] worked with the analogues of **2** (though the chemical yields were not so impressive, ranging from 53[10c] to 64%[10b]) and should presumably also do with **3**, but no doubt is difficult to scale up. (iii) The second approach for synthesizing tanikolide took advantage of the same intermediate **2** but avoided the step of borohydride reduction in basic media. The alkylated ketoester **2** was converted to the target molecule (**1**) in such three steps as deethoxycarbonylation, hydroxymethylation, and Baeyer–Villiger reaction. (iv) Our strategies are advantageous because of their high yields and suitability for the preparation of **1** in multigram or larger quantities.

4. Experimental

4.1. General

Melting points were determined on an XT-4 apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ (^1H at 300 MHz and ^{13}C at 75.47 MHz) using TMS as the internal standard. Column chromatography was performed on silica gel. Acetone and $CHCl_3$ were distilled over P_2O_5 and CaH_2, respectively, prior to use. IR, MS, and elemental analyses were conducted by the Analytical Laboratory at Shanghai Institute of Organic Chemistry.

4.2. Ethyl 2-oxo-1-(*n*-undecyl)cyclopentanecarboxylate (2)

In a dried 50-mL three-necked round-bottomed flask fitted with a condenser and an addition funnel were placed K_2CO_3 (4.01 g, 29.0 mmol) and KI (0.68 g, 4.1 mmol). A solution of ethyl 2-oxocyclopentanecarboxylate (1.90 mL, 12.8 mmol) in anhydrous acetone (30 mL) was added via the addition funnel. After 10 min, a solution of 1-bromoundecane (2.88 mL, 12.9 mmol) in acetone (8 mL) was added and the mixture was rapidly brought to reflux by heating in an oil bath. After 20 h, the resultant mixture was cooled to rt, diluted with Et_2O (50 mL), and filtered. The filtrate was concentrated at the reduced pressure, diluted with ether, washed in succession with water and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (SiO_2, petroleum ether–EtOAc, gradient, 100:1 to 60:1) to give **2** (3.97 g, 100%) as a pale yellow oil: IR λ_{max} 1725, 1747 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, $J=6.6$ Hz, 3H), 1.20–1.32 (m, 21H), 1.53–1.56 (m, 1H), 1.86–2.00 (m, 4H), 2.22–2.28 (m, 1H), 2.37–2.55 (m, 2H), 4.12–4.20 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.0, 19.6, 22.6, 24.7, 29.3, 29.3, 29.5, 29.6, 29.8, 31.8, 32.6, 33.8, 38.0, 60.5, 61.2, 171.0, 215.1; (only 18 peaks shown in the spectrum); EI-MS: *m/z* (%) 310 (M^+), 157 (61), 156 (100), 110 (100), 97 (64), 67 (58), 55 (93), 43 (85), 41 (80). Anal. Calcd for $C_{19}H_{34}O_3$: C, 73.50; H, 11.04. Found: C, 73.57; H, 11.36.

4.3. 5-Ethoxycarbonyl-5-(*n*-undecyl)-δ-valerolactone (3)

A solution of **2** (3.836 g, 12.36 mmol) in anhydrous $CHCl_3$ (100 mL) was treated with $NaHCO_3$ (1.922 g, 22.88 mmol) and MCPBA (70%, 4.288 g, 17.39 mmol). The mixture was stirred at rt for 20 h, diluted with saturated aqueous $NaHCO_3$ solution (120 mL), vigorously stirred for 15 min, and extracted with CH_2Cl_2. The combined organic layers were washed in succession with water and brine, dried over Na_2SO_4, filtered, and evaporated at the reduced pressure. The yellowish residue was chromatographed (SiO_2, petroleum ether–EtOAc, gradient, 20:1 to 10:1) to give **3** (3.53 g, 88%) as a colorless oil: IR (film) λ_{max} 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, $J=6.6$ Hz, 3H), 1.19–1.34 (m, 19H), 1.61–2.21 (m, 8H), 2.43–2.64 (m, 2H), 4.23–4.31 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.1, 17.0, 22.6, 22.8, 28.6, 29.2, 29.2, 29.4, 29.4, 29.5, 30.4, 31.8, 38.6, 61.8, 86.0, 170.2, 171.9 (only 18 peaks shown in the spectrum); EI-MS: *m/z* (%) 326 (M^+), 253 (100), 225 (44), 97 (22), 71 (22), 57 (35), 55 (76), 43 (57), 41 (46). Anal. Calcd for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 70.04; H, 10.58.

4.4. 2-Hydroxy-2-(*n*-undecyl)hexanedioic acid 1-ethyl ester (4)

To a cold (−2 °C) mixture of **3** (220 mg, 0.674 mmol) and THF/H_2O (1:1, 8 mL) was added $LiOH\cdot H_2O$ (32.5 mg, 0.774 mmol). The mixture was stirred for 4 h at −2 °C, made acidic (pH=2–3) with 6 M HCl, and extracted with $CHCl_3$. The combined organic layers were dried ($MgSO_4$), and the volatiles were evaporated to give **4** as a solid mass (230 mg, 99%). The crude product was sufficiently pure and used directly in the next reaction. Chromatography (SiO_2, petroleum ether–EtOAc, gradient, 3:1 to 1:1) furnished the analytical sample of **4** as a colorless solid: mp 71–72 °C; ^1H NMR ($CDCl_3$) δ 0.88 (t, $J=6.8$ Hz, 3H), 1.00–1.15 (m, 2H), 1.25–1.33 (m, 19H), 1.44–1.50 (m, 2H), 1.61–1.82 (m, 4H), 2.33–2.39 (m, 2H), 3.28 (br s, 1H), 4.25 (q, $J=7.2$ Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.2, 18.8, 22.6, 23.3, 29.3, 29.4, 29.4, 29.6 (very strong), 31.8, 33.8, 38.3, 39.2, 61.9, 77.2, 176.6, 179.3 (only 17 peaks shown in the spectrum). Anal. Calcd for $C_{19}H_{36}O_5$: C, 66.24; H, 10.53. Found: C, 66.32; H, 10.51.

4.5. 2-(*n*-Undecyl)cyclopentanone (5)

To a mixture of **2** (1.998 g, 6.44 mmol) in HOAc (15 mL) was added concentrated HCl (25 mL). The mixture was rapidly brought to reflux by heating in an oil bath. After 48 h the volatiles were evaporated at the reduced pressure. The residue was diluted with saturated aqueous $NaHCO_3$ solution and extracted with ether. The combined organic layers were washed in succession with saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated to give **5** (1.47 g, 96%) as a pale yellow oil: IR (film) λ_{max} 1741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, $J=$ 7.2 Hz, 3H), 1.21–1.38 (m, 19H), 1.45–1.58 (m, 1H), 1.69–1.84 (m, 2H), 1.94–2.10 (m, 2H), 2.14 (td, $J=9.8$, 1.2 Hz, 1H), 2.18–2.25 (m, 1H), 2.30 (dt, $J=18$, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.7, 22.6, 27.5, 29.3, 29.5, 29.6, 29.6, 29.6, 29.6, 29.6, 29.6, 31.9, 38.2, 49.2, 220.2; EI-MS: *m/z* (%) 238 (M^+), 238 (15), 156 (25), 97 (21), 84 (100), 83 (16), 55 (16), 43 (12), 41 (17). EI-HRMS: Calcd for $C_{16}H_{30}O$ 238.2297. Found: 238.2282.

4.6. 2-(Hydroxymethyl)-2-(*n*-undecyl)cyclopentanone (6)

To a mixture of **5** (223 mg, 0.935 mmol) and KOH (58 mg, 1.0 mmol) in MeOH (2.5 mL) at 0 °C was slowly added formalin (containing 37% HCHO, 80 mg, 0.98 mmol). The mixture was stirred at 0 °C for 2 h, and the pH was adjusted to 6–7 with 1 M HCl. The volatiles were evaporated under the reduced pressure. The residue was diluted with EtOAc, washed in succession with saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography (SiO_2, petroleum ether–EtOAc, gradient, 10:1 to 6:1) to give recovered **5** (139 mg, 62%) and **6** (90 mg, 36%, or 95% based on consumed **5**). **6**: IR (film) λ_{max} 3435, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, $J=6.6$ Hz, 3H), 1.08–1.35 (m, 18H), 1.35–1.55 (m, 2H), 1.86–1.99 (m, 4H), 2.24–2.40 (m, 2H), 2.72 (br s, 1H, OH), 3.48 (d, $J=11.1$ Hz, 1H), 3.64 (d, $J=11.1$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 19.1, 22.6, 24.0, 29.3, 29.4, 29.5, 29.5, 29.6, 30.2, 30.5, 31.8, 32.4, 38.8, 53.4, 65.6, 224.7; EI-MS: *m/z* (%) 269 (M+1, 96), 114 (100), 96 (38), 95 (26), 68 (27), 55 (31),43 (28), 41 (43). MALDI-HRMS: Calcd for $C_{17}H_{32}NaO_2$ (M+ Na) 291.2300. Found: 291.2295.

4.7. Tanikolide (1)

Method A (*Prepared from* **4**). A mixture of KOH (130 mg, 2.32 mmol), $CaCl_2$ (516 mg, 4.65 mmol) and **4** (200 mg, 0.580 mmol) in anhydrous EtOH (10 mL) was cooled to 0 °C, then $NaBH_4$ (176 mg, 4.65 mmol) was added in one portion. The reaction mixture was stirred for 26 h at rt, cooled to 0 °C, made acidic (pH=ca. 1) with 6 M HCl, evaporated, diluted with water, saturated with solid NaCl,

and extracted with $CHCl_3$. The combined organic layers were dried ($MgSO_4$), set aside for 14 h, and concentrated. The residue was chromatographed (SiO_2, petroleum ether–EtOAc, 1:1) to provide **1** (144 mg, 87%) as a colorless oil.

Method B (*Prepared from* **5**). A solution of **5** (62 mg, 0.23 mmol) in anhydrous $CHCl_3$ (3 mL) was treated with $NaHCO_3$ (29 mg, 0.34 mmol) and MCPBA (70%, 86 mg, 0.35 mmol). The mixture was stirred at rt for 4 h, diluted with saturated aqueous $NaHCO_3$ solution, vigorously stirred for 15 min, and extracted with CH_2Cl_2. The combined organic layers were washed in succession with water and brine, dried over $MgSO_4$, filtered, and concentrated at the reduced pressure. The residue was chromatographed (SiO_2, petroleum ether–EtOAc, 1:1) to provide **1** (61 mg, 93%) as a colorless oil: IR (film) λ_{max} 3424, 1721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, $J=6.6$ Hz, 3H), 1.21–1.33 (m, 18H), 1.61–1.97 (m, 6H), 2.46–2.51 (m, 2H), 2.78 (br s, 1H, OH), 3.55 (dd, $J=12.0$, 2.1 Hz, 1H), 3.66 (dd, $J=12.0$, 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 16.5, 22.5, 23.2, 26.5, 29.2, 29.3, 29.4, 29.4, 29.5, 29.6, 29.8, 31.7, 36.7, 67.1, 86.5, 172.2; EI-MS: *m*/*z* (%) 253 (M−31, 90), 225 (43), 129 (26), 71 (32), 57 (48), 55 (70), 43 (100), 41 (60). Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.79; H, 11.34. Found: C, 71.64; H, 10.98.

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Synthesis of mono- and di-substituted 2,4,5-trifluorobenzoic acid synthons, key precursors for biologically active 6-fluoroquinolones

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Abstract—In the search for new potent antiparasitical fluoroquinolones, a QSAR analysis by molecular connectivity led to the design of R^5 (Me or Et)/R^8 (MeO, Me or Et)-substituted analogs of the most powerful antibacterial or antiparasitical fluoroquinolones known so far. Unfortunately, the synthetic schemes that were elaborated in literature for 3- and 3,6-di-substituted 2,4,5-trifluorobenzoic acids, the key precursors of the target R^5/R^8-substituted 6-fluoroquinolones, led in our hands to poor yields and/or to inextricable mixtures of derivatives. This led us to reinvestigate the key alkylation steps of the 2,4,5-trifluorophenyl-oxazoline synthons and the subsequent deprotection of their oxazoline into acid with the aim of optimising the syntheses of 3- and 3,6-di-substituted 2,4,5-trifluorobenzoic acids, which constitute the entries to our target derivatives.

1. Introduction

Several quinolones and more particularly fluoroquinolones are widely used as antibacterial and antimycobacterial drugs to treat various infectious diseases.[1–7] A few fluoroquinolones were also shown to display antiparasitical activities against *Toxoplasma gondii* and *Plasmodium falciparum* that are responsible of toxoplasmosis and malaria, respectively. The first quinolone which showed antibacterial activities was nalidixic acid which was isolated in 1962.[8] Since then, more than ten thousands of quinolones have been patented, and the successive chemical modifications improved considerably their potency and spectrum of activity [for reviews, see Refs. 9–20] and parasitical responses.[21–24] Quinolones are bactericidal by interfering with bacterial DNA topoisomerases II (DNA gyrase) and IV, which are enzymes involved in DNA replication, decatenation, recombination and repair.[13,25–27] This inhibition results from formation of a strong ternary complex between the quinolone and the DNA/DNA gyrase duplex, which traps the enzyme on DNA.[9,28,29] There are clues that quinolones act on similar targets located within the apicoplast of the *T. gondii* and *P. falciparum* parasites and through similar pathways, although no definitive evidence has been provided up to now. However, the spread of multidrug-resistant bacterial and *P. falciparum* strains has highlighted the need to develop new antibacterial and antiparasitical drugs.[7,16,30]

The most active quinolones share common features which are (i) a bicyclic quinolone structure or a naphthyridone one (the quinolone carbon atom in position 8 (see Fig. 1a) has been replaced by nitrogen), (ii) an alkyl (ethyl, cyclopropyl, 2-fluoroethyl) or aryl (2,4-difluorophenyl) in position 1 as R^1, (iii) a hydrogen in position 2, (iv) a carboxylic acid in position 3, (v) a carbonyl in position 4, and (vi) a five or six-membered *N*-heterocycle or azabicycle in position 7. Other chemical modifications at any of the 1 to 4 positions have resulted in much less active compounds. These structural features are conserved in fluoroquinolones which contain a fluorine atom in position 6 as R^6. These derivatives are among the most active quinolones which display further a much broader spectrum of activity.[10,15,17] The most often used, relatively safe and well-tolerated quinolones as antibacterials are indeed 6-fluoroquinolones which include norfloxacin, ofloxacin, ciprofloxacin, levofloxacin, moxifloxacin (MXFX), and gatifloxacin (GTFX). These two latter derivatives with grepafloxacin (GPFX) and trovafloxacin (TVFX) (GPFX and TVFX were taken off from the market more or less shortly after launch) account for among the most powerful antiparasitical fluoroquinolones known so far (for their chemical structure, see Fig. 1b).[21,22] If a huge number of (fluoro)quinolones differing by the nature of

Keywords: Fluoroquinolone; Antiparasitical; Plasmodium; *Toxoplasma gondii*.
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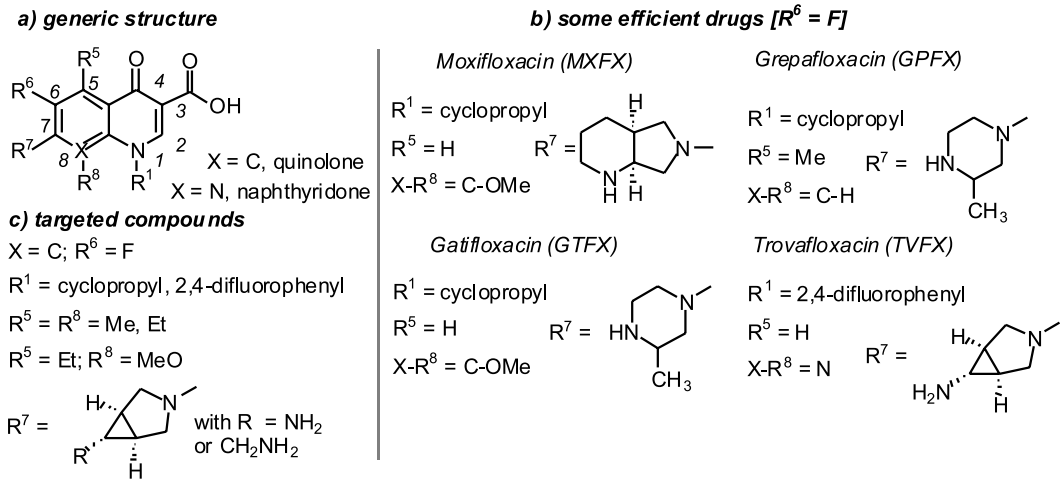


Figure 1. Chemical structure of (a) generic quinolones, (b) selected highly active antibacterial and antiparasitical 6-fluoroquinolones, and (c) our targeted R^5/R^8-substituted 6-fluoroquinolones.

the R^7 substituent were elaborated enabling the establishment of structure/antibacterial,[31] antituberculosis,[32] or antiparasitical relationships,[21,23,24] only a limited number of R^5 or/and R^8 substituted 6-fluoroquinolones are known, probably due to the difficult access to the precursors of these derivatives. Although R^5 or/and R^8-substituted 6-fluoroquinolones have been the focus of intensive search, R^5 or R^8 substitutions are restricted to F, Cl, Br, NH_2, Me, MeO, EtO, MeS, OH, F_2CHO, or CF_3O.[33–39] R^5- and R^8-substituted 6-fluoroquinolones are also scarce and R^5/R^8 substitutions are limited to Me/F, Me/Cl, Me/Me, Me/OMe, Cl/Me, NH_2/F, NH_2/Cl, NH_2/Me, NHMe/Me, NMe_2/Me, NH_2/OMe, NH_2/OEt.[33,34,36,40–42]

In the search for new potent antiparasitical fluoroquinolones, a QSAR analysis by molecular connectivity of a series of quinolones active against *T. gondii* was performed.[21,23] This analysis led to the design of R^5- and R^8-substituted 6-fluoroquinolones which were predicted to display higher or at least comparable biological activities to those of already known fluoroquinolones. Among the virtual computer designed, potentially active derivatives, we selected those presented in Figure 1c. They are R^5-(Me or Et)-substituted analogs of MXFX or GTFX (wherein R^5 is H and R^8 is OMe) or R^5/R^8-substituted analogs of GPFX (wherein R^5 is Me and R^8 is H). Their structure combines also the R^7 substituent found in TVFX. Unfortunately, the synthetic schemes that were elaborated in literature for the access of R^5- and/or R^8-substituted 6-fluoroquinolones starting from the oxazoline synthons **2** or **5** (see retrosynthetic pathway in Fig. 2), when applied for the preparation of the target derivatives shown in Figure 1c, led in our hands to poor yields and/or to inextricable mixtures of derivatives. This led us to reinvestigate the key alkylation steps of position 3 and 6 in the oxazoline synthons **2** and **5**, and the subsequent deprotection of their oxazoline into the acid function with the aim of optimising the syntheses of derivatives **9** and **10** which constitute the entries to our target derivatives shown in Figure 1c.

2. Results and discussion

2.1. Alkylation (Scheme 1A and B)

When oxazoline **2** was reacted with 1 equiv of LDA then with excess methyl iodide, as described in literature,[33] we obtained a 67% conversion of **2** into its 3-Me-derivative **5a**. However, separation of **5a** from the starting material was most difficult to achieve. To avoid this time-consuming separation and to optimise formation of derivative **5a**,**b**, we investigated alkylation of oxazoline **2** using increasing

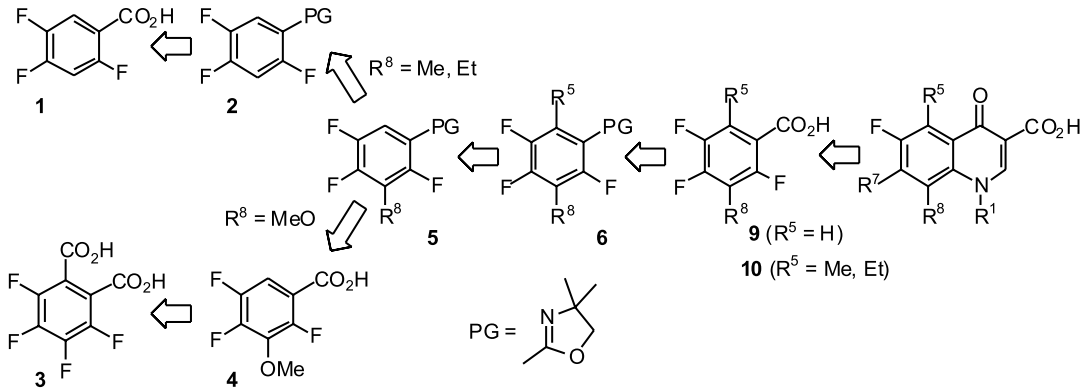
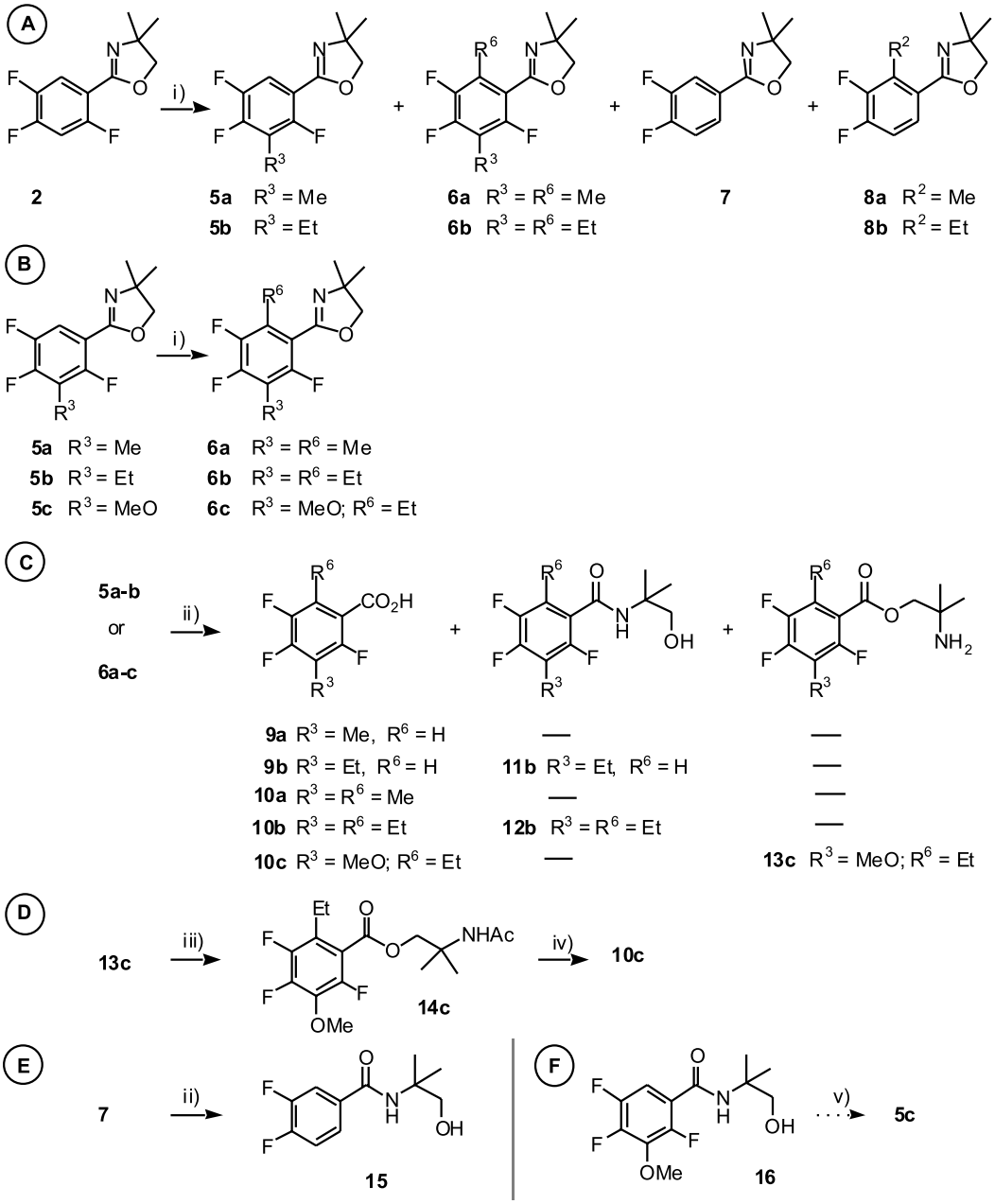


Figure 2. Retrosynthetic pathway to the targeted R^5/R^8-substituted 6-fluoroquinolones.



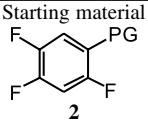
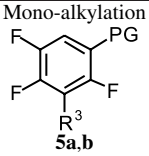
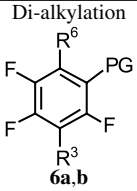
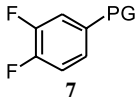
Scheme 1. (A) to (D): synthetic pathway to mono- and di-substituted 2,4,5-trifluorobenzoic acids. (A): alkylation of 2-(2,4,5-trifluorophenyl)-4,4-dimethyl-oxazoline **2**. (B): Alkylation of 2-(3-substituted-2,4,5-trifluorophenyl)-4,4-dimethyl-oxazoline **5a–c**. (C): Acid hydrolysis of the oxazolines **5a**,**b** and **6a–c**. (D): conversion of ester **13c** into acid **10c**. (E): Acid hydrolysis of the oxazoline **7** into amide **15**. (F): Chemical structure of **16**, precursor of **5c**. (i) LDA, THF, −78 °C then RI, −78 °C to rt: (ii) aq HCl (see text and Table 3), reflux; (iii) Ac_2O, pyridine; (iv) aq NaOH, rt; (v) (a) $CHCl_3$, $SOCl_2$, (b) aq NaOH, rt.

amounts of LDA in THF at −78 °C (Scheme 1A)[†] followed by the action of excess methyl or ethyl iodide. Work-up and column chromatography of the crude reaction mixtures led us to show that the reaction issue depended drastically on the LDA:**2** molar ratio. The issues of these reactions with the formation of, among others, the expected R^3-alkylated trifluoro derivatives **5a**,**b**, the R^3- and R^6-dialkylated trifluoro species **6a**,**b**, the difluoro derivative **7** and its alkylated analogs **8a**,**b** (vide infra), and the relative proportions of these derivatives in the crude reaction mixture determined by means of ^{19}F NMR are collected in Table 1.

Our data indicate that much higher conversion levels of **2** into **5a** could be obtained when increasing the amount of LDA equivalents from 1 to 1.7–1.9 (entries 2 and 3). For 1.9 LDA equivalents however, one observes the formation of the 3,6-dimethylated trifluoro species **6a** (16%, entry 3) and traces of by-products among which we could isolate and identify the difluoro derivative **7** and its methylated analogue **8a** (see entry 3). Similar results were obtained when oxazoline **2** was reacted with 2 equiv of LDA, then with excess ethyl iodide, though much lower amounts of 3,6-diethylated trifluoro species **6b** were detected (entry 4).

[†] The R^3 and R^6 groups in the chemical structures shown in Scheme 1 and Tables 1–3 are featuring the R^8 and R^5 substituents in the target 6-fluoroquinolones, respectively.

Table 1. Alkylation on 2-(2,4,5-trifluorophenyl)-4,4-dimethyl-oxazolines by alkyl halides

Entry	RI	LDA:**2** molar ratio	Relative mol%[a]				
			Starting material  **2**	Mono-alkylation  **5a**,**b**	Di-alkylation  **6a**,**b**	 **7**	Other **8a**,**b**
1	MeI	1.05	33	67	0	0	0
2	MeI	1.35–1.72	7–10	90–93	0	0	0
3	MeI	1.90	<1	82	16	<1	<1
4	EtI	2.00	0	96	2	2	0
5	EtI	2.10	0	71	16	5	8[b]
6	EtI	2.65–2.75	0	40–46	17–20	12–16	22–28[c]
7	EtI	7.9	0	0	0	~25[d]	[e]

[a] As determined by ^{19}F NMR of the crude reaction mixture; PG represents the oxazolinyl group.
[b] Compound **8b** and three unidentified compounds.
[c] Compound **8b** and four unidentified compounds.
[d] Major compound.
[e] Complex mixture.

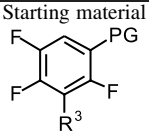
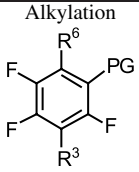
The use of higher amounts of LDA equivalents led to a subsequent decrease of the proportion of mono-alkylated species **5b** but this decrease was not compensated by the formation of the diethylated trifluoro species **6b** (see entries 5–7). These conditions favoured mostly formation of by-products, the major compound in the complex mixture being the difluoro derivative **7** (entry 7).

Our results indicate further that the 3,6-di-alkyl substituted compounds **6a**,**b** are not attainable cleanly and in good yields from **2** using a one-pot reaction. These compounds are best obtained by repeating the alkylation procedure on the isolated 3-alkylated species **5a**,**b** (Scheme 1B). Table 2 presents the results of the alkylation reaction of **5a**,**b** and of their 3-methoxy-analog **5c**. By contrast to the alkylation of the position 3, a large excess of LDA was needed to obtain high conversion levels of alkylation of position 6. Fortunately, the use of such large excesses of LDA did not led to by-products. Complete conversion of the starting material was however not obtained. The lower conversion levels of **5b** and **5c** into **6b** and **6c**, respectively, as compared with those of **5a** into **6a** are most likely related to steric effects of the alkyl iodide. Indeed, the use of the more powerful ethyl trifluoromethanesulfonate-alkylating agent did not improve the conversion levels of **5b** into **6b** (data not shown).

All products were unambiguously and fully characterised by ^{1}H, ^{19}F, and DEPT ^{13}C NMR. That mono-alkylation took place on position 3 was unequivocally attested by comparing the spectra of **5a**,**b** with those of the starting material and with those reported in literature for **5a**.[33,43] Thus, the ^{1}H NMR spectra of **5a**,**b** display the expected pattern for the sole aromatic H-6 proton (triplet of doublet at 7.51 ppm and doublet of doublet of doublet at 7.40 ppm for **5a** and **5b**, respectively, due to characteristic $^{3}J_{H-F}$ and $^{4}J_{H-F}$ couplings), and for the methyl (a triplet at 2.24 ppm due to the two $^{4}J_{H-F}$ couplings) or ethyl group (a triplet at 1.10 ppm and a quadruplet 2.62 ppm), respectively. The ^{13}C resonance of the quaternary aromatic C-3 carbon (at 116.4 and 122.5 ppm for **5a** and **5b**, respectively) adjacent to two fluorine atoms appears as a doublet of doublet with $^{2}J_{C-F}$ coupling constants in the 17–24 Hz range, as expected.[44] The ^{19}F NMR confirms the presence of three fluorine resonances, each being a doublet of doublet due to ^{3}J, ^{4}J and/or $^{5}J_{F-F}$ couplings.

The structure of the 3,6-di-alkylated Me/Me or Et/Et derivatives **6a**,**b** is attested by the absence of aromatic ^{1}H resonances, the presence of the expected patterns of the two alkyl moieties in both their ^{1}H and ^{13}C NMR spectra, and the presence of the characteristic three fluorine resonances in their ^{19}F NMR spectra.

Table 2. Alkylation of 2-(3-substituted-2,4,5-trifluorophenyl)-4,4-dimethyl-oxazolines by alkyl halides

Entry	R^3	RI	LDA:**5a–c** molar ratio	Relative mol%[a]	
				Starting material 	Alkylation 
8	Me	MeI	3.3	16	84
9	Me	MeI	3.6	5	95
10	Et	EtI	7.0	25	75
11–16	MeO	EtI	5.9 to 10.4	23±3	77±3

[a] As determined by ^{19}F NMR of the crude reaction mixture; PG represents the oxazolinyl group.

The difluoro oxazoline by-product **7** obtained in the course of alkylation of compound **2** could be identified and purified after hydrolysis into its benzamide **15** (see Scheme 1E). The presence in its ^{19}F, ^{13}C and ^{1}H NMR spectra of, respectively, (i) two ^{19}F doublets (integrating each for one fluorine) with a high coupling constant (20.6 Hz) characteristic of a $^{3}J_{F-F}$,[44] (ii) two ^{13}C–F doublets of doublet (due to $^{1}J_{C-F}$ of 250–255 Hz and $^{2}J_{C-F}$ of 12–13 Hz), and three aromatic ^{13}C–H resonances (one doublet and two doublets of doublet due to $^{3,4}J_{C-F}$ couplings), and (iii) a ^{1}H pattern in the aromatic region integrating for one proton at 7.18 ppm (H_5) and two protons at 7.50 ppm (H_2 and H_6) supports strongly the proposed structure for **15** and, consequently, for **7**.

Concerning by-products **8a**,**b** which are the methylated/ethylated analogue of **7**, respectively, only **8a** was purified and **8b** was identified by analogy in the mixture. The ^{19}F NMR spectrum of **8a** exhibits the characteristic ^{19}F pattern of the two C–F bonds in ortho ($^{3}J_{F-F}=20.6$ Hz) on the benzene ring measured for **7**. The ^{1}H NMR spectrum of **8a** affirmed the presence of unaffected oxazoline moiety, of only one aromatic methyl substituent in ortho to a F-atom (doublet at 2.52 ppm, $^{4}J_{H-F}=2.9$ Hz) and of two H-aromatic protons. The ortho location of these two protons on the benzene ring (and, consequently, of the methyl moiety on the C-2 position) is further confirmed by the typical high $^{3}J_{H-H}$ coupling constant of 8.7 Hz.

2.2. Oxazoline deprotection (Scheme 1C)

Deprotection of oxazolines **5a**,**b** and **6a–c** into acids **9a**,**b** and **10a–c**, respectively, was accomplished by treatment of the oxazolinyl derivatives with aqueous acidic media as described in literature.[33,45,46] However, the issue of this treatment depended on the presence/absence of a substituent on the C-6 position and on the acidic conditions used, the oxazolinyl moiety being hydrolysed to give the desired acid **9** or **10**, or a mixture of acid **9** or **10** and amide **11** or **12**, or even and unexpectedly the ester **13**. Though quite unusual, hydrolysis of aromatic oxazolines into amides or esters was already reported.[36,45,47] Formation of esters, such as **13c**, was observed only in the case of the methoxy derivative **6c**, its corresponding acid **10c** being obtained indirectly by acetylation of **13c** with acetic anhydride and subsequent alkaline hydrolysis of resulting hydrolysis of resulting **14c** (Scheme 1D).[36]

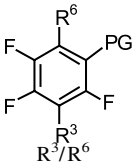
The issue of hydrolysis with the acidic conditions used was more carefully checked in the case of the ethyl-substituted derivatives **5b** and **6b**. As shown in Table 3, hydrolysis of the monoethyl derivative **5b** when performed with 1 N HCl under reflux gave a mixture of acid **9b** and amide **11b**. The acid **9b** was obtained in high yield when **5b** was refluxed in 6 N HCl for 8 h. By contrast, hydrolysis of the diethyl derivative **6b** when performed with 6 N HCl under reflux, even for 14 h, led to the amide **12b** as sole compound. More drastic conditions (12 N HCl) were needed to obtain the acid **10b** from **12b**.

Formation of acid, amide or ester was attested by IR, ^{1}H, ^{19}F, and ^{13}C NMR. The acid structure is confirmed by (i) the presence of a ν(C=O) vibration at 1700–1710 cm^{-1} and a ^{13}C resonance at 162–170 ppm in their IR and ^{13}C spectra, respectively, which are characteristic of a C(O)OH function, and (ii) the absence of the characteristic oxazoline ^{1}H and ^{13}C signals of their respective starting material.

The $C(O)OCH_2C(Me)_2NH_2$ amino-ester sequence in **13c** and the $C(O)NHC(Me)_2CH_2OH$ amido-alcool sequence in **11b** was proven by comparing (i) the ^{1}H and ^{13}C resonances of the OCH_2 group which appears more downfield for **13c** (singlet at 4.06 and 75.2 ppm, respectively) than for **11b** (singlet at 3.60 and 70.0 ppm, respectively), and (ii) the ^{13}C resonance of the quaternary carbon which appears more upfield for **13c** (49.4 ppm) than for **11b** (56.5 ppm), as expected, all values being further in line with literature.[48] Amido-alcool **11b** (and **16** from which **5c** is obtained,[33] Scheme 1F) displays for the NH proton a ^{1}H signal which is likely a doublet (J of 13.9 Hz) owing to space ^{1}H–^{19}F spin–spin interactions with the fluorine in ortho as a result of an intramolecular N–H···F hydrogen bond.[49–52] This is further supported by the fact that the NH proton of **15** (which has no fluorine in *ortho*) appears as a singlet.

It is further noticeable that the amido-alcool **12b** displays ^{1}H and ^{13}C chemical shifts for the CH_2O group of the amido-alcool sequence (at 3.91 and 51.0 ppm, respectively) that differ quite substantially from those measured for the amido-alcool derivatives **11b**, **15**, and **16** (at 3.60–3.70 and 69–71 ppm, respectively), the ^{1}H and ^{13}C chemical shifts for the adjacent $NC(Me)_2$ unit being very similar and in line with literature.[53,54] IR spectrum of **12b** confirmed unambiguously the amide linkage ν(C=O) at 1641 cm^{-1}.

Table 3. Deprotection of the oxazolinyl moiety

Starting compound	Conditions		Products % yield[a]		
	HCl (N)	Time (h)[b]	Acid **9** or **10**	Amide **11** or **12**	Ester **13**
Et/H (**5b**)	1	6	28	36	0
Et/H (**5b**)	6	8	82	2[c]	0
Et/Et (**6b**)	6	14	nd	73	0
MeO/Et (**6c**)	1	6	0	0	98

[a] Purified compound unless otherwise indicated.
[b] Stirring under reflux.
[c] Estimated by ^{19}F NMR.

3. Conclusion

With the aim of optimising the syntheses of 3- and 3,6-disubstituted 2,4,5-trifluorobenzoic acids, which constitute the entries to R^5/R^8-substituted 6-fluoroquinolones, our reinvestigation of the key alkylation steps of the 2,4,5-trifluorophenyl-oxazoline synthons led us to show that monoalkylation was cleanly performed with a high conversion into the 3-substituted 2,4,5-trifluorophenyl-oxazoline when using 1.7–1.9 LDA equivalents. Our results indicated further that the 3,6-dialkyl substituted compounds are best obtained by repeating the alkylation procedure on the isolated 3-mono-alkylated species. Concerning the deprotection of the oxazoline into the acid function, this step required more drastic conditions (12 N HCl, 12 h) than those reported in literature in order to avoid the intermediary formation of amides.

4. Experimental

4.1. Generalities

Alkylation reactions were conducted under an anhydrous nitrogen atmosphere using dry THF and reagents. Anhydrous THF was prepared by standard methods. Column chromatography purifications were carried out on Silica Gel 60 (E. Merck, 70–230 mesh). The purity of all new compounds was checked by thin-layer chromatography (TLC) and NMR. TLC analyses were performed on precoated Silica Gel F254 plates (E. Merck) with detection by UV. Melting points, determined with a Electrothermal model 3100 apparatus, are uncorrected. The ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded with a Brucker AC 200 spectrometer at 200, 50.3, and 188.3 MHz, respectively. Chemical shifts (δ) are given in ppm relative to the signal indirectly (i) to $CHCl_3$ (δ 7.27) for ^{1}H, (ii) to $CDCl_3$ (δ 77.16) for ^{13}C and (iii) to $CFCl_3$ (δ 0.0) for ^{19}F. Concerning the description of the NMR spectra, the atoms are depicted as C_x, H_y, and F_z according to their standard nomenclature numbering. IR spectra were realized on a Spectrum BX Perkin Elmer FTIR as KBr disk. Electron-spray ionization mass spectra (ESI MS) in positive/negative mode were recorded on a Finnigan MAT TSQ 7000 apparatus equipped with an atmospheric pressure ionization source. The high resolution mass spectrometry analyses were performed by the 'Service Commun de Spectrométrie de Masse', at the Institut de Chimie des Substances Naturelles, Gif sur Yvette, France.

4.1.1. Reagents and starting materials. 2,4,5-Trifluorobenzoic acid **1** and 3,4,5,6-tetrafluoro-phthalic acid **3** were purchased from Lancaster, thionyl chloride from Fluka, and acetic anhydride, 2-amino-2-methyl-propan-1-ol, 2.5 M *n*-BuLi in hexane, diisopropylamine, iodoethane, 2.0 M iodomethane in *tert*-butyl methyl ether, and oxalyl chloride from Aldrich.

2-(2,4,5-Trifluorophenyl)-4,4-dimethyl-oxazoline **2** was synthesized from 2,4,5-trifluoro-benzoic acid **1**, as described in literature.[33] Its NMR data, which were only described succinctly in literature and limited to ^{1}H NMR, are given in detail hereafter: ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 6H, CH_3), 4.09 (s, 2H, OCH_2), 6.95 (td, 1H, H_3, $^3J_{H-F}$=10.0 Hz, $^4J_{H-F}$=6.4 Hz), 7.72 (ddd, 1H, H_6, $^3J_{H-F}$=10.6 Hz, $^4J_{H-F}$=8.9, 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 28.2 (2 CH_3), 68.0 (CMe_2), 79.0 (CH_2O), 106.7 (dd, C_3, $^2J_{C-F}$=28.0, 21.0 Hz), 112.9 (ddd, C_1, $^2J_{C-F}$=12.8 Hz, $^3J_{C-F}$=6.0 Hz, $^4J_{C-F}$=4.2 Hz), 118.9 (d, C_6, $^2J_{C-F}$=22.2 Hz), 146.4 (ddd, C_5, $^1J_{C-F}$=245.9 Hz, $^2J_{C-F}$=12.9 Hz, $^4J_{C-F}$=3.6 Hz), 151.8 (dt, C_4, $^1J_{C-F}$=257.2 Hz, $^2J_{C-F}$=$^3J_{C-F}$=14.6 Hz), 156.7 (dd, C_2, $^1J_{C-F}$=255.6 Hz, $^3J_{C-F}$=8.7 Hz), 157.2 (dt, C=N, $^3J_{C-F}$=6.3 Hz); ^{19}F NMR ($CDCl_3$) δ −109.8 (dd, 1F, F_2, $^5J_{F-F}$=15.8 Hz, $^4J_{F-F}$=7.2 Hz), −128.9 (dd, 1F, F_4, $^3J_{F-F}$=22.0 Hz, $^4J_{F-F}$=7.2 Hz), −142.5 (dd, 1F, F_5, $^3J_{F-F}$=22.0 Hz, $^5J_{F-F}$=15.8 Hz).

2,4,5-Trifluoro-3-methoxy-benzoic acid **4** was prepared from 3,4,5,6-tetrafluoro-phthalic acid **3** according to the procedure described in references.[35,55] This acid **4** was used for the synthesis of compound 2-(2,4,5-trifluoro-3-methoxy-phenyl)-4,4-dimethyl-oxazoline, **5c**, which was performed using the same two-step experimental procedure than that applied for **2**.[33] Briefly, a mixture of 3.28 g (15.9 mmol) of 2,4,5-trifluoro-3-methoxy-benzoic acid **4**, 2.00 mL (22.8 mmol) of oxalyl chloride and 5 drops of DMF was stirred at room temperature for 24 h. The oily material obtained after evaporation under reduced pressure was redissolved in CH_2Cl_2 (20 mL) and added dropwise to 9.0 mL (94.2 mmol) of 2-amino-2-methyl-propan-1-ol in CH_2Cl_2 (15 mL) cooled at 0 °C. The resulting mixture was then stirred at room temperature for 48 h. After filtration, the organic phase was successively washed with water, 5% Na_2CO_3 aq solution, water, then 5% $KHSO_4$ aq solution. After drying over Na_2SO_4 and filtration, the solvent was evaporated affording 4.30 g (15.5 mmol, 97%) of the amido-alcool **16** as an oil [R_f=0.30 (7:3 hexane/AcOEt, UV); ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 6H, CH_3), 3.68 (d, 2H, OCH_2, $^3J_{H-H}$=6.1 Hz), 4.04 (d, 3H, OCH_3, $^5J_{H-F}$=0.9 Hz), 4.11 (t, 1H, OH, $^3J_{H-H}$=6.1 Hz), 6.74 (d, 1H, NH, $^5J_{H-F}$=13.1 Hz), 7.55 (ddd, 1H, H_6, $^3J_{H-F}$=10.6 Hz, $^4J_{H-F}$=8.6, 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 23.1 (2 CH_3), 55.9 (CMe_2), 61.7 (t, OCH_3, $^4J_{C-F}$=3.5 Hz), 69.1 (CH_2OH), 110.7 (dd, C_1, $^2J_{C-F}$=21.0 Hz, $^3J_{C-F}$=2.7 Hz), 118.4 (ddd, C_6, $^2J_{C-F}$=13.2 Hz, $^3J_{C-F}$=6.2, 3.7 Hz), 137.6 (ddd, C_3, $^2J_{C-F}$=17.6, 11.3 Hz, $^3J_{C-F}$=2.2 Hz), 145.7 (ddd, C_4, $^1J_{C-F}$=256.0 Hz, $^2J_{C-F}$=15.4 Hz, $^3J_{C-F}$=5.5 Hz), 146.9 (ddd, C_5, $^1J_{C-F}$=247.0 Hz, $^2J_{C-F}$=11.4 Hz, $^4J_{C-F}$=2.9 Hz), 149.6 (dt, C_2, $^1J_{C-F}$=246.0 Hz, $^3J_{C-F}$=$^4J_{C-F}$=3.5 Hz), 161.4 (t, C=O, $^3J_{C-F}$=$^4J_{C-F}$=1.3 Hz); ^{19}F NMR ($CDCl_3$) δ −133.6 (dd, 1F, F_2, $^5J_{F-F}$=13.8 Hz, $^4J_{F-F}$=8.9 Hz), −139.7 (dd, 1F, F_5, $^3J_{F-F}$=20.6 Hz, $^5J_{F-F}$=13.8 Hz), −146.5 (dd, 1F, F_4, $^3J_{F-F}$=20.6 Hz, $^4J_{F-F}$=8.9 Hz)]. The amido-alcohol **16** (4.30 g, 15.5 mmol) in $CHCl_3$ (30 mL) was then reacted with 3.4 mL (47 mmol) of $SOCl_2$ overnight at room temperature. After precipitation with Et_2O and filtration, the solid was dissolved in a NaOH aq solution (pH 8) and extracted with CH_2Cl_2. The organic layer was then dried over Na_2SO_4, filtrated, and evaporated giving 2.56 g (9.9 mmol, 65%) of the oxazoline **5c** as a colorless oil: R_f=0.80 (7:3 hexane/AcOEt, UV); ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 6H, 2 CH_3), 3.92 (t, 3H, OCH_3, $^5J_{H-F}$=1.1 Hz), 3.96 (s, 2H, OCH_2), 7.26 (ddd, 1H, H_6, $^3J_{H-F}$=10.5 Hz, $^4J_{H-F}$=8.5, 6.1 Hz); ^{13}C NMR ($CDCl_3$) δ 28.1 (2 CH_3), 62.0 (t, OCH_3, $^4J_{C-F}$=3.5 Hz), 67.9 (CMe_2), 78.8 (CH_2O), 110.6 (dd, C_1, $^2J_{C-F}$=11.0 Hz, $^3J_{C-F}$=2.4 Hz),

112.3 (ddd, C_6, $^2J_{C-F}=11.0$ Hz, $^3J_{C-F}=7.7$, 4.0 Hz), 138.5 (ddd, C_3, $^2J_{C-F}=15.6$, 11.2 Hz, $^3J_{C-F}=2.8$ Hz), 146.0 (ddd, C_4, $^1J_{C-F}=255.4$ Hz, $^2J_{C-F}=15.0$ Hz, $^3J_{C-F}=5.1$ Hz), 146.7 (ddd, C_5, $^1J_{C-F}=245.5$ Hz, $^2J_{C-F}=11.4$ Hz, $^4J_{C-F}=3.6$ Hz), 151.0 (dt, C_2, $^1J_{C-F}=257.6$ Hz, $^3J_{C-F}=^4J_{C-F}=3.3$ Hz), 157.2 (dt, C=N, $^3J_{C-F}=5.9$ Hz, $^4J_{C-F}=^5J_{C-F}=2.4$ Hz); ^{19}F NMR ($CDCl_3$) δ −129.2 (dd, 1F, F_2, $^5J_{F-F}=13.1$ Hz, $^4J_{F-F}=9.6$ Hz), −140.8 (dd, 1F, F_5, $^3J_{F-F}=21.0$ Hz, $^5J_{F-F}=13.1$ Hz), −146.7 (dd, 1F, F_4, $^3J_{F-F}=21.0$ Hz, $^4J_{F-F}=9.6$ Hz).

4.2. Alkylation reaction

4.2.1. General procedure: synthesis of 2-(3-methyl-2,4,5-trifluoro-phenyl)-4,4-dimethyl-oxazoline (5a). A solution of 1.0 mL (7.1 mmol) of diisopropylamine in 8 mL of dry THF cooled at −78 °C was treated dropwise with 3.0 mL of 2.0 M *n*-BuLi (6.0 mmol; 1.72 equiv) in hexane and stirred for 30 min. To this LDA solution was added a solution of 800 mg (3.49 mmol) of **2** in 4 mL of dry THF, and the solution was stirred for 1 h at −78 °C. A 2.0 M iodomethane solution in *tert*-butyl methyl ether (4.8 mL, 9.6 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was treated with water and extracted with ethyl acetate. The organic phase was washed with 5% $KHSO_4$, water, 5% Na_2CO_3. dried over $MgSO_4$ and concentrated. The residue was purified by chromatography (97:3 hexane/ethyl acetate) to give 793 mg (3.26 mmol, 93%) of **5a** as a colorless oil. $R_f=0.40$ (4:1 hexane/AcOEt, UV); ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 6H, $NCCH_3$), 2.24 [t, 3H, CH_3 (R^3)], $^4J_{H-F}=2.1$ Hz), 4.07 (s, 2H, CH_2O), 7.51 (td, 1H, H_6, $^3J_{H-F}=$ $^4J_{H-F}=9.7$, 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 7.2 [CH_3 (R^3)], 28.1 ($NCCH_3$), 67.9 (CMe_2), 78.7 (CH_2O), 111.8 (ddd, C_6, $^2J_{C-F}=13.9$ Hz, $^3J_{C-F}=6.6$, 4.0 Hz), 115.1 (ddd, C_1, $^2J_{C-F}=21.2$ Hz, $^3J_{C-F}=3.3$ Hz, $^4J_{C-F}=1.8$ Hz), 116.4 (dd, C_3, $^2J_{C-F}=$ 23.2, 17.4 Hz), 146.2 (ddd, C_5, $^1J_{C-F}=245.2$ Hz, $^2J_{C-F}=13.5$ Hz, $^4J_{C-F}=3.7$ Hz), 150.5 (ddd, C_4, $^1J_{C-F}=$ 252.9 Hz, $^2J_{C-F}=14.3$ Hz, $^3J_{C-F}=8.4$ Hz), 155.3 (ddd, C_2, $^1J_{C-F}=255.0$ Hz, $^3J_{C-F}=6.6$ Hz, $^4J_{C-F}=2.6$ Hz), 157.4 (dt, C=N, $^3J_{C-F}=4.0$ Hz, $^4J_{C-F}=^5J_{C-F}=$ 2.0 Hz); ^{19}F NMR ($CDCl_3$) δ −114.5 (dd, 1F, F_2, $^5J_{F-F}=15.8$ Hz, $^4J_{F-F}=8.9$ Hz), −132.8 (dd, 1F, F_4, $^3J_{F-F}=22.0$ Hz, $^4J_{F-F}=8.9$ Hz), −142.9 (dd, 1F, F_5, $^3J_{F-F}=22.0$ Hz, $^5J_{F-F}=15.8$ Hz).

4.2.2. Synthesis of 2-(3-ethyl-2,4,5-trifluoro-phenyl)-4,4-dimethyl-oxazoline (5b). Compound **5b** was obtained likewise by stirring **2** (301 mg, 1.31 mmol) with LDA prepared in situ (1.05 mL of 2.5 M *n*-BuLi (2.6 mmol) and 0.50 mL (3.6 mmol) of diisopropylamine in 10 mL of dry THF), then adding 0.42 mL (5.3 mmol) of neat iodoethane. Work-up followed by chromatography (97:3 hexane/ethyl acetate) afforded 324 mg (1.26 mmol, 96%) of **5b** as a colorless oil: $R_f=0.55$ (4:1 hexane/AcOEt, UV); ^{1}H NMR ($CDCl_3$) δ 1.10 (t, 3H, CH_3CH_2, $^3J_{H-H}=7.5$ Hz), 1.27 (s, 6H, $NCCH_3$), 2.62 (q, 2H, CH_3CH_2, $^3J_{H-H}=7.5$ Hz), 3.97 (s, 2H, CH_2O), 7.40 (ddd, 1H, H_6, $^3J_{H-F}=10.4$ Hz, $^4J_{H-F}=$ 9.0, 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 13.6 (CH_3CH_2), 16.3 (CH_3CH_2), 28.1 ($NCCH_3$), 67.9 (CMe_2), 78.7 (CH_2O), 112.1 (ddd, C_6, $^2J_{C-F}=13.9$ Hz, $^3J_{C-F}=6.6$, 4.4 Hz), 115.3 (ddd, C_1, $^2J_{C-F}=21.2$ Hz, $^3J_{C-F}=3.5$ Hz, $^4J_{C-F}=1.7$ Hz), 122.5 (dd, C_3, $^2J_{C-F}=22.5$, 17.0 Hz), 146.3 (ddd, C_5, $^1J_{C-F}=245.2$ Hz, $^2J_{C-F}=13.9$ Hz, $^4J_{C-F}=3.7$ Hz), 150.3 (ddd, C_4, $^1J_{C-F}=252.9$ Hz, $^2J_{C-F}=14.1$ Hz, $^3J_{C-F}=$ 8.8 Hz), 155.0 (ddd, C_2, $^1J_{C-F}=250.7$ Hz, $^3J_{C-F}=7.0$ Hz, $^4J_{C-F}=2.6$ Hz), 157.5 (dt, C=N, $^3J_{C-F}=6.2$ Hz, $^4J_{C-F}=$ $^5J_{C-F}=1.8$ Hz); ^{19}F NMR ($CDCl_3$) δ −116.7 (dd, 1F, F_2, $^5J_{F-F}=15.8$ Hz, $^4J_{F-F}=8.3$ Hz), −134.9 (dd, 1F, F_4, $^3J_{F-F}=22.0$ Hz, $^4J_{F-F}=8.3$ Hz), −142.6 (dd, 1F, F_5, $^3J_{F-F}=22.0$ Hz, $^5J_{F-F}=15.8$ Hz).

4.2.3. Synthesis of 2-(3,6-dimethyl-2,4,5-trifluoro-phenyl)-4,4-dimethyl-oxazoline (6a). The general alkylation procedure when applied to 322 mg (1.32 mmol) of **5a** in 5 mL of THF, LDA prepared from 2.40 mL of 2.5 M *n*-BuLi (4.8 mmol) with 0.90 mL (6.4 mmol) of diisopropylamine in 5 mL of dry THF, then 6.50 mL (13.0 mmol) of 2 M iodomethane in *tert*-butyl methyl ether, afforded after work-up and column chromatography (97:3 hexane/ethyl acetate) 324 mg (1.26 mmol, 95%) of **6a** as a colorless oil: $R_f=0.60$ (4:1 hexane/AcOEt, UV); ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 6H, $NCCH_3$), 2.09 [t, 3H, CH_3 (R^3)], $^4J_{H-F}=1.7$ Hz), 2.20 (d, 3H, CH_3 (R^6), $^4J_{H-F}=$ 2.3 Hz), 4.01 (s, 2H, CH_2O); ^{13}C NMR ($CDCl_3$) δ 7.0 (td, CH_3 (R^3), $^3J_{C-F}=3.6$ Hz, $^4J_{C-F}=1.8$ Hz), 11.3 (dt, CH_3 (R^6), $^3J_{C-F}=4.4$ Hz, $^4J_{C-F}=2.2$ Hz), 28.2 ($NCCH_3$), 68.1 (CMe_2), 79.0 (CH_2O), 112.6 (dd, C_3, $^2J_{C-F}=23.4$, 17.9 Hz), 113.2 (dt, C_1, $^2J_{C-F}=17.9$ Hz, $^3J_{C-F}=^4J_{C-F}=3.8$ Hz), 124.4 (ddd, C_6, $^2J_{C-F}=16.5$ Hz, $^3J_{C-F}=3.5$, 1.3 Hz), 145.4 (ddd, C_5, $^1J_{C-F}=242.0$ Hz, $^2J_{C-F}=13.4$ Hz, $^4J_{C-F}=$ 3.8 Hz), 149.9 (ddd, C_4, $^1J_{C-F}=250.0$ Hz, $^2J_{C-F}=15.0$ Hz, $^3J_{C-F}=9.7$ Hz), 154.6 (ddd, C_2, $^1J_{C-F}=247.0$ Hz, $^3J_{C-F}=$ 7.9 Hz, $^4J_{C-F}=3.1$ Hz), 157.1 (m, C=N); ^{19}F NMR ($CDCl_3$) δ −120.6 (dd, 1F, F_2, $^5J_{F-F}=15.1$ Hz, $^4J_{F-F}=$ 6.2 Hz), −136.1 (dd, 1F, F_4, $^3J_{F-F}=21.0$ Hz, $^4J_{F-F}=$ 6.2 Hz), −146.0 (dd, 1F, F_5, $^3J_{F-F}=21.0$ Hz, $^5J_{F-F}=$ 15.1 Hz).

4.2.4. Synthesis of 2-(3,6-diethyl-2,4,5-trifluoro-phenyl)-4,4-dimethyl-oxazoline (6b). The general alkylation procedure when applied to LDA prepared in situ from 6.6 mL of 2.5 M *n*-BuLi (16.5 mmol) in hexane, and 3.0 mL (21.7 mmol) of diisopropylamine in 15 mL of dry THF, 605 mg (2.35 mmol) of **5b** in 8 mL of THF, then to 2.0 mL (25.0 mmol) of neat iodoethane afforded after work-up and chromatography (97:3 hexane/ethyl acetate) 513 mg (1.80 mmol, 76%) of compound **6b** as a colorless oil: $R_f=0.60$ (4:1 hexane/AcOEt, UV); ^{1}H NMR ($CDCl_3$) δ 1.17 (t, 6H, CH_3CH_2, $^3J_{H-H}=7.5$ Hz), 1.39 (s, 6H, $NCCH_3$), 2.70 (bq, 4H, 2 CH_2, $^3J_{H-H}=7.5$ Hz), 4.10 (s, 2H, CH_2O); ^{13}C NMR ($CDCl_3$) δ 13.7 [CH_3CH_2 (R^3)], 14.6 [CH_3CH_2 (R^6)], 16.0 (bd, CH_3CH_2, (R^3), $^3J_{C-F}=1.8$ Hz), 20.0 (bd, CH_3CH_2, (R^6), $^3J_{C-F}=1.8$ Hz), 28.1 ($NCCH_3$), 68.2 (CMe_2), 79.1 (CH_2O), 113.0 (dt, C_1, $^2J_{C-F}=18.3$ Hz, $^3J_{C-F}=^4J_{C-F}=3.8$ Hz), 118.9 (dd, C_3, $^2J_{C-F}=22.7$, 17.6 Hz), 130.7 (dd, C_6, $^2J_{C-F}=15.9$ Hz, $^3J_{C-F}=2.4$ Hz), 145.3 (ddd, C_5, $^1J_{C-F}=242.6$ Hz, $^2J_{C-F}=13.2$ Hz, $^4J_{C-F}=$ 3.7 Hz), 149.7 (ddd, C_4, $^1J_{C-F}=250.3$ Hz, $^2J_{C-F}=14.8$ Hz, $^3J_{C-F}=10.1$ Hz), 154.4 (ddd, C_2, $^1J_{C-F}=247.4$ Hz, $^3J_{C-F}=$ 8.2 Hz, $^4J_{C-F}=3.1$ Hz), 157.0 (d, C=N, $^3J_{C-F}=1.2$ Hz); ^{19}F NMR ($CDCl_3$) δ −122.5 (dd, 1F, F_2, $^5J_{F-F}=15.1$ Hz, $^4J_{F-F}=6.2$ Hz), −138.0 (dd, 1F, F_4, $^3J_{F-F}=21.3$ Hz, $^4J_{F-F}=6.2$ Hz), −148.2 (dd, 1F, F_5, $^3J_{F-F}=21.3$ Hz, $^5J_{F-F}=15.1$ Hz).

4.2.5. Synthesis of 2-(6-ethyl-2,4,5-trifluoro-3-methoxyphenyl)-4,4-dimethyl-oxazoline (6c). The general alkylation procedure when applied to LDA prepared in situ from 35.4 mL of 2.5 M *n*-BuLi (88.5 mmol) with 16.2 mL (116 mmol) of diisopropylamine in 120 mL of dry THF, and **5c** (3.26 g, 12.6 mmol), then to 12.5 mL (156 mmol) of neat iodoethane, gave after work-up and chromatography (95:5 hexane/ethyl acetate) 2.37 g (8.24 mmol, 65%) of **6c** as a colorless oil: R_f=0.50 (85:15 hexane/AcOEt, UV); ^{1}H NMR ($CDCl_3$) δ 1.10 (q, 3H, CH_3CH$_2$,, $^3J_{H-H}$=7.5 Hz), 1.33 (s, 6H, NCCH$_3$), 2.64 (qd, 2H, CH$_3$CH_2, $^3J_{H-H}$=7.5 Hz, $^4J_{H-F}$=2.1 Hz), 3.91 (s, 3H, OCH$_3$), 4.04 (s, 2H, OCH$_2$); ^{13}C NMR ($CDCl_3$) δ 14.6 (*C*H$_3$CH$_2$), 19.7 (CH$_3$*C*H$_2$), 28.0 (NC*C*H$_3$), 61.9 (OCH$_3$), 68.2 (*C*Me$_2$), 79.1 (CH$_2$O), 113.3 (dt, C$_1$, $^2J_{C-F}$=16.1 Hz, $^3J_{C-F}$=$^4J_{C-F}$=4.6 Hz), 126.5 (d, C$_6$, $^2J_{C-F}$=16.1 Hz), 135.5 (ddd, C$_3$, $^2J_{C-F}$=15.6, 11.5 Hz, $^3J_{C-F}$=2.5 Hz), 145.4 (ddd, C$_4$, $^1J_{C-F}$=252.9 Hz, $^2J_{C-F}$=15.7 Hz, $^3J_{C-F}$=6.2 Hz), 145.7 (ddd, C$_5$, $^1J_{C-F}$=243.3 Hz, $^2J_{C-F}$=11.0 Hz, $^4J_{C-F}$=3.7 Hz), 150.0 (dt, C$_2$, $^1J_{C-F}$=249.2 Hz, $^3J_{C-F}$=$^4J_{C-F}$=3.7 Hz), 156.4 (C=N); ^{19}F NMR ($CDCl_3$) δ −134.5 (dd, 1F, F$_2$, $^5J_{F-F}$=12.4 Hz, $^4J_{F-F}$=6.9 Hz), −145.9 (dd, 1F, F$_5$, $^3J_{F-F}$=21.0 Hz, $^5J_{F-F}$=12.7 Hz), −149.3 (dd, 1F, F$_4$, $^3J_{F-F}$=21.0 Hz, $^4J_{F-F}$=6.9 Hz).

4.3. By-products

4.3.1. 4,4-Dimethyl-2-(3,4-difluoro-2-methyl-phenyl)-oxazoline (8a). The title compound was isolated by chromatographic purification (97:3 hexane/AcOEt) of the reaction mixture obtained when the methylation of **2** was performed with 1.9 equiv of LDA: R_f=0.45 (4:1 hexane/AcOEt, UV); ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 6H, NCCH$_3$), 2.52 (d, 3H, CH$_3$, $^4J_{H-F}$=2.9 Hz), 4.07 (s, 2H, CH$_2$), 7.00 (q, 1H, H$_5$, $^3J_{H-Fr4e}$∼$^4J_{H-F}$∼$^3J_{H-H}$∼8.7 Hz), 7.51 (ddd, 1H, H$_6$, $^3J_{H-H}$=8.7 Hz, $^4J_{H-F}$=5.2 Hz, $^5J_{H-F}$=2.0 Hz); ^{19}F NMR ($CDCl_3$) δ −134.7 (d, 1F, F$_4$, $^3J_{F-F}$=20.6 Hz), −140.6 (d, 1F, F$_3$, $^3J_{F-F}$=20.6 Hz).

4.3.2. 2-(3,4-Difluoro-phenyl)-4,4-dimethyl-oxazoline (7). The title compound was identified as its deprotected compound 3,4-difluoro-*N*-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide **15**. This derivative was isolated after acid hydrolysis (1 N HCl for 6 h) of a mixture containing **5b** and **7** which resulted from the ethylation of **2** with >2 equiv of LDA, and chromatographic purification (silica gel; 9:1 to 3:2 hexane/AcOEt). R_f=0.10 (7:3 hexane/AcOEt, UV); ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 6H, NCCH$_3$), 3.65 (s, 2H, CH$_2$O), 6.32 (br s, 1H, NH), 7.18 (m, 1H, H$_5$), 7.50 (m, 2H, H$_2$ and H$_6$); ^{13}C NMR ($CDCl_3$) δ 24.5 (NC*C*H$_3$), 56.6 (*C*Me$_2$), 70.5 (CH$_2$O), 116.9 (dd, C$_2$, $^2J_{C-F}$=18.5 Hz, $^3J_{C-F}$=1.3 Hz), 117.5 (d, C$_5$, $^2J_{C-F}$=17.9 Hz), 123.5 (dd, C$_6$, $^3J_{C-F}$=7.2 Hz, $^4J_{C-F}$=3.9 Hz), 132.1 (t, C$_1$, $^3J_{C-F}$=$^4J_{C-F}$=4.4 Hz), 150.3 (dd, C$_3$, $^1J_{C-F}$=250.5 Hz, $^2J_{C-F}$=13.0 Hz), 152.6 (dd, C$_4$, $^1J_{C-F}$=254.2 Hz, $^2J_{C-F}$=12.6 Hz), 166.2 (C=O); ^{19}F NMR ($CDCl_3$) δ −133.0 (d, 1F, F$_4$, $^3J_{F-F}$=20.6 Hz), −136.5 (d, 1F, F$_3$, $^3J_{F-F}$=20.6 Hz).

4.4. General procedure for the NMR analysis of the crude reaction mixture

The alkylation reaction was performed in the same way as described above for the LDA:**2** and LDA:**5a–c** ratios indicated in Tables 1 and 2, respectively. After hydrolysis and evaporation of the solvent, the residue was extracted with ethyl acetate. The organic phase was washed with water, dried, and concentrated. The residue was then dissolved in $CDCl_3$ for ^{1}H and ^{19}F NMR spectra recording. The ^{19}F chemical shifts of **2**, **5**, **6**, **7** and **8** were used for the identification of the compounds present in the crude mixture and the relative percentages of each of these compounds were calculated by integrating its ^{19}F resonances with respect to the overall integration.

4.5. Hydrolysis of the oxazoline derivatives

4.5.1. Hydrolysis of 5a and synthesis of 3-methyl-2,4,5-trifluoro-benzoic acid (9a). A suspension of compound **5a** (64 mg, 0.24 mmol) in 10 mL 3 N HCl was refluxed for 8 h. The reaction mixture was then extracted with 3×20 mL CH_2Cl_2. The organic phase was extracted with 1 N NaOH (3×20 mL). After acidification of the combined aqueous phases to pH 1 with 6 N HCl, extraction with CH_2Cl_2 (3×30 mL), the organic phase was washed with water until neutrality, dried (Na_2SO_4), filtrated, and concentrated leading to 42 mg (0.22 mmol, 92%) of **9a** as a white solid: R_f=0.60 (84:14:2 CH_2Cl_2/MeOH/$H_2$0, UV); ^{1}H NMR ($CDCl_3$) δ 2.29 (t, 3H, CH$_3$, $^4J_{H-F}$=2.1 Hz), 7.70 (td, 1H, H$_6$, $^3J_{H-F}$=$^4J_{H-F}$=9.5, 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 7.7 (CH$_3$), 113.1 (m, C$_6$), 117.0 (d, C$_1$, $^2J_{C-F}$=20.6 Hz), 117.4 (dd, C$_3$, $^2J_{C-F}$=24.1, 17.2 Hz), 146.5 (ddd, C$_5$, $^1J_{C-F}$=246.7 Hz, $^2J_{C-F}$=13.8 Hz, $^4J_{C-F}$=3.4 Hz), 152.9 (ddd, C$_4$, $^1J_{C-F}$=256.6 Hz, $^2J_{C-F}$=13.8 Hz, $^3J_{C-F}$=8.0 Hz), 157.5 (ddd, C$_2$, $^1J_{C-F}$=259.9 Hz, $^3J_{C-F}$=8.0 Hz, $^4J_{C-F}$=2.3 Hz), 168.1 (C=O); ^{19}F NMR ($CDCl_3$) δ −112.7 (dd, 1F, F$_2$, $^5J_{F-F}$=16.2 Hz, $^4J_{F-F}$=11.7 Hz), −127.5 (dd, 1F, F$_4$, $^3J_{F-F}$=22.0 Hz, $^4J_{F-F}$=11.7 Hz), −141.9 (dd, 1F, F$_5$, $^3J_{F-F}$=22.0 Hz, $^5J_{F-F}$=16.2 Hz); ESI-MS (negative mode): 189.3 $(M-H)^-$ in agreement with the mass calculated for M=$C_8H_5F_3O_2$ (190.02).

4.5.2. Hydrolysis of 5b and synthesis of 3-ethyl-2,4,5-trifluoro-benzoic acid (9b) and 3-ethyl-2,4,5-trifluoro-*N*-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide (11b).

4.5.2.1. 3-Ethyl-2,4,5-trifluoro-benzoic acid (9b). A suspension of **5b** (940 mg, 3.66 mmol) in 10 mL of 6 N HCl was stirred under reflux for 8 h. Work-up as described for **9a** led to 645 mg (3.01 mmol, 82%) of acid **9b** as a white solid. ^{19}F NMR of the organic phase resulting from CH_2Cl_2 extraction of the reaction mixture showed the presence of 2% mol of benzamide **11b** (see below) besides acid **9b**. R_f 0.65 (84:14:2 CH_2Cl_2/MeOH/$H_2$0, UV); ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3H, CH$_3$, $^3J_{H-H}$=7.5 Hz), 2.78 (q, 2H, CH$_2$, $^3J_{H-H}$=7.5 Hz), 7.71 (td, 1H, H$_6$, $^3J_{H-F}$=$^4J_{H-F}$=9.4, 6.7 Hz), 11.70 (s, 1H, COOH); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH$_3$), 16.5 (CH$_2$), 113.3 (ddd, C$_6$, $^2J_{C-F}$=12.1 Hz, $^3J_{C-F}$=5.9, 4.0 Hz), 117.2 (dt, C$_1$, $^2J_{C-F}$=20.5 Hz, $^3J_{C-F}$=$^4J_{C-F}$=2.0 Hz), 123.4 (dd, C$_3$, $^2J_{C-F}$=22.5, 17.0 Hz), 146.6 (ddd, C$_5$, $^1J_{C-F}$=246.6 Hz, $^2J_{C-F}$=13.7 Hz, $^4J_{C-F}$=3.5 Hz), 152.8 (ddd, C$_4$, $^1J_{C-F}$=256.9 Hz, $^2J_{C-F}$=13.9 Hz, $^3J_{C-F}$=9.0 Hz), 157.4 (ddd, C$_2$, $^1J_{C-F}$=260.5 Hz, $^3J_{C-F}$=7.5 Hz, $^4J_{C-F}$=2.4 Hz), 168.8 (C=O); ^{19}F NMR ($CDCl_3$) δ −114.9 (dd, 1F, F$_2$, $^5J_{F-F}$=15.8 Hz, $^4J_{F-F}$=11.7 Hz), −129.4 (dd, 1F, F$_4$, $^3J_{F-F}$=22.0 Hz, $^4J_{F-F}$=11.7 Hz), −141.5 (dd, 1F, F$_5$, $^3J_{F-F}$=22.0 Hz, $^5J_{F-F}$=15.8 Hz).

4.5.2.2. 3-Ethyl-2,4,5-trifluoro-*N*-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide (11b). Hydrolysis of **5b** (418 mg, 1.62 mmol) when performed with 1 N HCl during 6 h at reflux and work-up as described above afforded acid **9b** (94 mg, 0.46 mmol, 28%). Evaporation of the organic phase after extraction with 1 N NaOH and chromatography of the residue (9:1 to 3:2 hexane/AcOEt) led to the title compound **11b** (160 mg, 0.58 mmol, 36%) as a colorless liquid: R_f=0.30 (7:3 hexane/AcOEt, UV); ^{1}H NMR ($CDCl_3$) δ 1.16 (t, 3H, CH_3CH$_2$, $^3J_{H-H}$=7.5 Hz), 1.35 (s, 6H, NCCH$_3$), 2.68 (q, 2H, CH$_3$CH_2, $^3J_{H-H}$=7.5 Hz), 3.60 (s, 2H, OCH_2), 4.59 (s, 1H, OH), 6.91 (d, 1H, NH, $^5J_{H-F}$=13.9 Hz), 7.60 (td, 1H, H$_6$, $^3J_{H-F}$=$^4J_{H-F}$=9.4, 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 13.8 (*C*H$_3$CH$_2$), 16.4 (CH$_3$*C*H$_2$), 24.3 (NC*C*H$_3$), 56.5 (*C*Me$_2$), 70.0 (CH$_2$OH), 116.1 (ddd, C$_6$, $^2J_{C-F}$=21.0 Hz, $^3J_{C-F}$=3.7, 1.8 Hz), 117.9 (dt, C$_1$, $^2J_{C-F}$=14.3 Hz, $^3J_{C-F}$=$^4J_{C-F}$=4.6 Hz), 122.1 (dd, C$_3$, $^2J_{C-F}$=25.8, s17.4 Hz), 147.1 (ddd, C$_5$, $^1J_{C-F}$=246.3 Hz, $^2J_{C-F}$=13.5 Hz, $^4J_{C-F}$=2.9 Hz), 150.6 (ddd, C$_4$, $^1J_{C-F}$=254.0 Hz, $^2J_{C-F}$=14.3 Hz, $^3J_{C-F}$=9.9 Hz), 154.3 (ddd, C$_2$, $^1J_{C-F}$=243.7 Hz, $^3J_{C-F}$=7.0 Hz, $^4J_{C-F}$=2.6 Hz), 162.2 (d, C=O, $^3J_{C-F}$=3.6 Hz); ^{19}F NMR ($CDCl_3$) δ −121.1 (dd, 1F, F$_2$, $^5J_{F-F}$=16.5 Hz, $^4J_{F-F}$=8.9 Hz), −133.8 (dd, 1F, F$_4$, $^3J_{F-F}$=22.0 Hz, $^4J_{F-F}$=8.9 Hz), −141.2 (dd, 1F, F$_5$, $^3J_{F-F}$=22.0 Hz, $^5J_{F-F}$=16.5 Hz).

4.5.2.3. Hydrolysis of 6b into 3,6-diethyl-2,4,5-trifluoro-*N*-(2-hydroxy-1,1-dimethyl-ethyl)-benzamide (12b). A suspension of **6b** (270 mg, 0.95 mmol) in 6 mL of 6 N HCl was refluxed for 12 h. The aqueous phase was extracted with CH_2Cl_2. The organic phase was then dried (Na_2SO_4), filtrated, and concentrated leading to 208 mg (0.69 mmol, 73%) of **12b** as a white solid: R_f=0.65 (4:1 hexane/AcOEt, UV); mp=125–127 °C; IR (KBr, cm^{-1}): 3246 (NH), 3060 (OH), 1641 (C=O), 1563 (CNH), 1464 (NH); ^{1}H NMR ($CDCl_3$) δ 1.18 and 1.20 (t, t, 3H, 3H, CH_3CH$_2$, $^3J_{H-H}$=7.5 Hz), 1.48 (s, 6H, NCCH$_3$), 2.71 (bq, 4H, CH$_3$CH_2, $^3J_{H-H}$=7.5 Hz), 3.91 (s, 2H, CH$_2$O), 5.78 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.0 [*C*H$_3$CH$_2$ (R^3)], 15.1 [*C*H$_3$CH$_2$ (R^6)], 16.2 [CH$_3$*C*H$_2$ (R^3)], 20.2 [CH$_3$*C*H$_2$ (R^6)], 25.2 (NC*C*H$_3$), 51.0 (CH$_2$O), 55.3 (*C*Me$_2$), 119.0 (dd, C$_3$, $^2J_{C-F}$=23.2, 17.4 Hz), 121.0 (dt, C$_1$, $^2J_{C-F}$=18.7 Hz, $^3J_{C-F}$=$^4J_{C-F}$=2.9 Hz), 129.3 (dd, C$_6$, $^2J_{C-F}$=15.5 Hz, $^3J_{C-F}$=4.2 Hz), 145.7 (ddd, C$_4$, $^1J_{C-F}$=249.6 Hz, $^2J_{C-F}$=14.8 Hz, $^3J_{C-F}$=10.1 Hz), 149.2 (ddd, C$_5$, $^1J_{C-F}$=243.2 Hz, $^2J_{C-F}$=13.2 Hz, $^4J_{C-F}$=3.7 Hz), 152.6 (ddd, C$_2$, $^1J_{C-F}$=243.0 Hz, $^3J_{C-F}$=8.1 Hz, $^4J_{C-F}$=3.3 Hz), 163.6 (C=O); ^{19}F NMR ($CDCl_3$) δ −125.7 (dd, 1F, F$_2$, $^5J_{F-F}$=15.1 Hz, $^4J_{F-F}$=5.5 Hz), −139.0 (dd, 1F, F$_4$, $^3J_{F-F}$=21.3 Hz, $^4J_{F-F}$=5.5 Hz), −147.7 (dd, 1F, F$_5$, $^3J_{F-F}$=21.3 Hz, $^5J_{H-F}$=15.1 Hz); ESI-MS (positive mode): 303.7 (M)$^+$ in agreement with the mass calculated for M=$C_{15}H_{20}F_3NO_2$ (303.32).

4.5.2.4. Hydrolysis of 12b into 3,6-diethyl-2,4,5-trifluoro-benzoic acid (10b). A suspension of 76 mg (0.25 mmol) of **12b** in 5 mL of 12 N HCl was refluxed for 24 h. The reaction mixture was made basic with 10 N NaOH, then washed with CH_2Cl_2 (recovery of 48 mg of starting material 64%). The aqueous phase acidified with 12 N HCl was extracted with CH_2Cl_2. The organic phase was then washed with water until neutrality, dried (Na_2SO_4), filtrated, concentrated giving 21 mg (0.09 mmol, 36%) of acid **10b** as a white solid: R_f=0.70 (CH_2Cl_2/MeOH/H$_2$0 84/14/2 UV); ^{1}H NMR ($CDCl_3$) δ 1.22 and 1.24 (t, t, 3H, 3H, CH_3CH$_2$, $^3J_{H-H}$=7.5 Hz), 2.71 (bq, 2H, CH$_3$CH_2, $^3J_{H-H}$=7.5 Hz), 2.83 (qd, 2H, CH$_3$CH_2, $^3J_{H-H}$=7.5 Hz, $^4J_{H-F}$=2.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0 [*C*H$_3$CH$_2$ (R^3)], 14.9 [*C*H$_3$CH$_2$ (R^6)], 16.3 [CH$_3$*C*H$_2$ (R^3)], 20.4 [CH$_3$*C*H$_2$ (R^6)], 116.0 (m, C$_1$), 119.6 (dd, C$_3$, $^2J_{C-F}$=22.4, 17.8 Hz), 130.7 (d, C$_6$, $^2J_{C-F}$=16.1 Hz), 145.7 (ddd, C$_5$, $^1J_{C-F}$=242.0 Hz, $^2J_{C-F}$=13.2 Hz, $^4J_{C-F}$=3.5 Hz), 150.5 (dt, C$_4$, $^1J_{C-F}$=253.0 Hz, $^2J_{C-F}$=$^3J_{C-F}$=10.2 Hz), 154.3 (ddd, C$_2$, $^1J_{C-F}$=250.0 Hz, $^3J_{C-F}$=5.7 Hz, $^4J_{C-F}$=2.3 Hz), 169.5 (C=O); ^{19}F NMR ($CDCl_3$) δ −121.3 (dd, 1F, F$_2$, $^5J_{F-F}$=14.4 Hz, $^4J_{F-F}$=7.6 Hz), −135.6 (dd, 1F, F$_4$, $^3J_{F-F}$=21.3 Hz, $^4J_{F-F}$=7.6 Hz), −147.2 (dd, 1F, F$_5$, $^3J_{F-F}$=21.3 Hz, $^5J_{F-F}$=14.4 Hz); ESI-MS (negative mode): 231.40 (M−H)$^-$, 187.07 (M–H–CO$_2$)$^-$ in agreement with the mass calculated for M=$C_{11}H_{11}F_3O_2$ (232.18); high resolution ESI-MS (negative mode): 231.0645 (M−H)$^-$, in agreement with the mass calculated for (M−H)$^-$=$C_{11}H_{10}F_3O_2$ (231.0633).

4.5.2.5. Hydrolysis of 6a into 3,6-dimethyl-2,4,5-trifluoro-benzoic acid (10a). A suspension of **6a** in 12 N HCl was stirred under reflux for 36 h. Work-up as described for **10b** led to **10a** whose NMR data are identical to those reported in literature.[33]

4.5.2.6. Hydrolysis of 6c into (2-amino-2-methyl-propyl) 6-ethyl-2,4,5-trifluoro-3-methoxy-benzoate (13c). A suspension of **6c** (770 mg, 2.68 mmol) in 10 mL of 1 N HCl was stirred under reflux for 6 h. After extraction with CH_2Cl_2, the organic phase was dried (Na_2SO_4), filtrated, and concentrated to give 556 mg (1.63 mmol, 61%) of **13c** (as its HCl salt) as a white solid. The remaining aqueous phase was made basic with NaOH aq solution and was extracted by CH_2Cl_2, which, after work-up, gave another crop of 305 mg (1.0 mmol, 37%) of **13c** as its NH$_2$ form: mp=162–163 °C; IR (KBr, cm^{-1}): 1706 (C=O), 1469 and 1413 (CO); ^{1}H NMR ($CDCl_3$) δ 1.13 (bt, 9H, CH$_3$), 2.65 (qd, 2H, CH$_3$CH_2, $^3J_{H-H}$=7.5 Hz, $^4J_{H-F}$=2.1 Hz), 3.95 (s, 3H, OCH$_3$), 4.06 (s, 2H, OCH$_2$); ^{13}C NMR ($CDCl_3$) δ 14.9 (*C*H$_3$CH$_2$), 19.9 (CH$_3$*C*H$_2$), 27.1 (NC*C*H$_3$), 49.4 (*C*Me$_2$), 62.1 (t, OCH$_3$, $^4J_{C-F}$=3.5 Hz), 75.2 (OCH$_2$), 117.1 (dt, C$_1$, $^2J_{C-F}$=15.7 Hz, $^3J_{C-F}$=$^4J_{C-F}$=4.0 Hz), 125.8 (dd, C$_6$, $^2J_{C-F}$=16.1 Hz, $^3J_{C-F}$=2.2 Hz), 135.7 (ddd, C$_3$, $^2J_{C-F}$=15.9, 11.3 Hz, $^3J_{C-F}$=2.4 Hz), 145.7 (ddd, C$_4$, $^1J_{C-F}$=253.9 Hz, $^2J_{C-F}$=15.9 Hz, $^3J_{C-F}$=6.0 Hz), 145.9 (ddd, C$_5$, $^1J_{C-F}$=244.4 Hz, $^2J_{C-F}$=11.0 Hz, $^4J_{C-F}$=3.6 Hz), 149.5 (dt, C$_2$, $^1J_{C-F}$=249.6 Hz, $^3J_{C-F}$=$^4J_{C-F}$=4.0 Hz), 163.9 (dd, C=O, $^3J_{C-F}$=2.9 Hz, $^4J_{C-F}$=1.5 Hz); ^{19}F NMR ($CDCl_3$) δ −134.8 (dd, 1F, F$_2$, $^5J_{F-F}$=12.4 Hz, $^4J_{F-F}$=6.9 Hz), −145.1 (dd, 1F, F$_5$, $^3J_{F-F}$=20.6 Hz, $^5J_{F-F}$=12.4 Hz), −148.4 (dd, 1F, F$_4$, $^3J_{F-F}$=20.6 Hz, $^4J_{F-F}$=6.9 Hz).

Compound **13c** (as its HCl salt): ^{1}H NMR ($CDCl_3$) δ 1.13 (t, 3H, CH_3CH$_2$, $^3J_{H-H}$=7.5 Hz), 1.46 (s, 6H, NCCH$_3$), 2.65 (bq, 2H, CH$_3$CH_2, $^3J_{H-H}$=7.5 Hz), 3.98 (s, 3H, OCH$_3$), 4.37 (s, 2H, OCH$_2$); ^{19}F NMR ($CDCl_3$) δ −133.0 (dd, 1F, F$_2$, $^5J_{F-F}$=12.6 Hz, $^4J_{F-F}$=7.9 Hz), −145.0 (dd, 1F, F$_5$, $^3J_{F-F}$=20.6 Hz, $^5J_{F-F}$=12.4 Hz), −147.4 (dd, 1F, F$_4$, $^3J_{F-F}$=20.6 Hz, $^4J_{F-F}$=7.9 Hz).

4.6. Synthesis of 6-ethyl-2,4,5-trifluoro-3-methoxy-benzoic acid (10c)

A mixture of **13c** as its HCl salt (365 mg, 1.07 mmol), pyridine (0.40 mL, 4.90 mmol) in 5 mL of acetic anhydride was stirred at 60 °C for 6 h. After cooling, water was added and the mixture was extracted with Et_2O. The combined organic phases were washed to neutrality, dried (Na_2SO_4), filtrated, and concentrated leading to 335 mg (0.96 mmol, 90%) of 2-acetylamino-2-methylpropyl 6-ethyl-2,4,5-trifluoro-3-methoxy-benzoate **14c** as an oil: R_f=0.65 (1:4 hexane/AcOEt, UV); ^{1}H NMR ($CDCl_3$) δ 1.07 (t, 3H, CH_3CH$_2$, $^3J_{H-H}$=7.5 Hz), 1.30 (s, 6H, NCCH$_3$), 1.84 (s, 3H, CH$_3$C=O), 2.59 (qd, 2H, CH$_3$CH_2, $^3J_{H-H}$=7.5 Hz, $^4J_{H-F}$=2.0 Hz), 3.92 (s, 3H, OCH$_3$), 4.43 (s, 2H, OCH$_2$), 6.07 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.0 (*C*H$_3$CH$_2$), 20.7 (CH$_3$*C*H$_2$), 23.8 [*C*H$_3$C(O)], 24.1 (NC*C*H$_3$), 53.1 (*C*Me$_2$), 62.0 (t, OCH$_3$, $^4J_{C-F}$=3.3 Hz), 69.7 (OCH$_2$), 117.0 (dt, C$_1$, $^2J_{C-F}$=15.7 Hz, $^3J_{C-F}$=$^4J_{C-F}$=4.1 Hz), 125.6 (dd, C$_6$, $^2J_{C-F}$=16.1 Hz, $^3J_{C-F}$=2.2 Hz), 135.6 (ddd, C$_3$, $^2J_{C-F}$=15.9, 11.4 Hz, $^3J_{C-F}$=2.4 Hz), 145.5 (ddd, C$_4$, $^1J_{C-F}$=254.0 Hz, $^2J_{C-F}$=15.9 Hz, $^3J_{C-F}$=6.2 Hz), 145.8 (ddd, C$_5$, $^1J_{C-F}$=244.1 Hz, $^2J_{C-F}$=10.6 Hz, $^4J_{C-F}$=4.0 Hz), 149.3 (dt, C$_2$, $^1J_{C-F}$=248.5 Hz, $^3J_{C-F}$=$^4J_{C-F}$=4.0 Hz), 170.7 (C(O)O), 174.5 (C(O)N); ^{19}F NMR ($CDCl_3$) δ −135.1 (dd, 1F, F$_2$, $^5J_{F-F}$=12.4 Hz, $^4J_{F-F}$=6.9 Hz), −145.1 (dd, 1F, F$_5$, $^3J_{F-F}$=20.6 Hz, $^5J_{F-F}$=12.4 Hz), −148.4 (dd, 1F, F$_4$, $^3J_{F-F}$=20.6 Hz, $^4J_{F-F}$=6.9 Hz).

Hydrolysis of **14c** (335 mg, 0.96 mmol) was performed in 5 mL of 1 N NaOH under reflux for 5 h. After cooling, the aqueous phase was made acidic with 12 N HCl and extracted with CH_2Cl_2. After drying over Na_2SO_4, the organic phase was filtrated and concentrated affording 200 mg (0.85 mmol, 89%) of **10c** as a white solid: R_f=0.70 (84:14:2 CH_2Cl_2/MeOH/H_2O, UV); mp=79–80 °C; IR (KBr, cm^{-1}): 1707 (C=O), 1469, 1413, 1244; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H, CH_3CH$_2$, $^3J_{H-H}$=7.5 Hz), 2.81 (qd, 2H, CH$_3$CH_2, $^3J_{H-H}$=7.5 Hz, $^4J_{H-F}$=2.3 Hz), 4.03 (t, 3H, OCH$_3$, $^5J_{H-F}$=1.0 Hz); ^{13}C NMR ($CDCl_3$) δ 14.9 (*C*H$_3$CH$_2$), 20.1 (CH$_3$*C*H$_2$), 62.3 (t, OCH$_3$, $^4J_{C-F}$=3.5 Hz), 115.9 (dt, C$_1$, $^2J_{C-F}$=14.3 Hz, $^3J_{C-F}$=$^4J_{C-F}$=4.1 Hz), 126.7 (dd, C$_6$, $^2J_{C-F}$=16.2 Hz, $^3J_{C-F}$=1.7 Hz), 136.0 (ddd, C$_3$, $^2J_{C-F}$=15.7, 11.3 Hz, $^3J_{C-F}$=2.6 Hz), 146.1 (ddd, C$_5$, $^1J_{C-F}$=244.1 Hz, $^2J_{C-F}$=10.8 Hz, $^4J_{C-F}$=4.0 Hz), 146.4 (ddd, C$_4$, $^1J_{C-F}$=255.1 Hz, $^2J_{C-F}$=15.7 Hz, $^3J_{C-F}$=6.4 Hz), 150.7 (dt, C$_2$, $^1J_{C-F}$=253.6 Hz, $^3J_{C-F}$=$^4J_{C-F}$=4.0 Hz), 169.8 (d, C=O, $^3J_{C-F}$=1.5 Hz); ^{19}F NMR ($CDCl_3$) δ −133.2 (dd, 1F, F$_2$, $^5J_{F-F}$=12.4 Hz, $^4J_{F-F}$=8.3 Hz), −144.7 (dd, 1F, F$_5$, $^3J_{F-F}$=20.6 Hz, $^5J_{F-F}$=12.4 Hz), −146.8 (dd, 1F, F$_4$, $^3J_{F-F}$=20.6 Hz, $^4J_{F-F}$=8.3 Hz); ESI-MS (negative mode): 233.4 (M−H)$^-$, 189.4 (M−H–CO$_2$)$^-$ in agreement with the mass calculated for M=$C_{10}H_9F_3O_3$ (234.2); high resolution ESI-MS (negative mode): 233.0413 (M−H)$^-$ in agreement with the mass calculated for (M−H)$^-$=$C_{10}H_8F_3O_3$ (233.0426).

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DMF promoted xylosylation of terpenols

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Abstract—The glycosidation of 2,3,4-triacetyl-1-bromo-α-D-xylopyranose with various terpenols occurs at 50 °C in DMF without the requirement of any additive. The decisive role of DMF as solvent on the coupling efficiency is highlighted.

1. Introduction

The progressive changeover of the chemical industry to renewable instead of fossil feedstocks is ineluctable. In this context, the use of cheap and abundant carbohydrates is of great interest,[1] their transformation into biodegradable surfactants being one possibility for their valorisation.[2] As the lipophilic moiety of the surfactants, it would be of interest to use renewable materials such as terpenols. Over the last past years, we have been involved in the valorization of pentoses, which are easily extracted from wheat straw and bran.[3] Consequently, we envisaged to carry out the glycosydation of a D-xylose derivative with terpenols by variations of the Koenigs–Knorr methodology.[4] To the best of our knowledge, such couplings have never been reported using pentose derivatives, while modifications of the Koenigs–Knorr procedure have been used for the coupling of tetra-*O*-protected-glucosyl bromides with terpenols.[5]

2. Results and discussion

The Koenigs–Knorr method was attempted with tri-*O*-acetylxylosyl bromide **1**. This substrate was obtained in two steps via the acetylation of D-xylose and the reaction of the corresponding peracetylated compound with a solution of HBr in acetic acid in 70–75% overall yield.[6–10]

This compound has already been documented in various papers[6–15] but without specification of the configuration of the C-1 center,[6] or with either a rather arbitrarily α-[9–11] or β-[7,8] stereochemistry of the bromine atom, and also with various melting points[10,13,15] and optical rotations.[10,13,15] In fact, we observed that our compound is rapidly decomposed on the bench and should be stored at low temperature, and that best yields were obtained with new solutions of HBr. It has been reported that the α-bromide is more stable than the β-bromide,[13] and, for our compound, we assumed the α-stereochemistry on the basis of the value of $J_{1,2}=4.0$ Hz of the doublet at $\delta=6.58$ ppm, this coupling constant corresponding to an equatorial/axial arrangement of the two vicinal hydrogens.

The reaction of **1** with (±)-citronellol in the presence of $AgBF_4$ and collidine in anhydrous CH_2Cl_2 at 0 °C[16] led to the expected β-D-xyloside **2** in only 14% yield (Table 1, entry 1). Variations of the experimental conditions were then attempted in order to improve the efficiency of the process. In DMF at 50 °C with Ag_2CO_3 as both base and

Table 1. Reaction of **1** with (±)-citronellol[a]

Entry	Additive (equiv)	Solvent	**2**, Yield %[b]	α/β[c]
1[d]	$AgBF_4$ (1.1)+collidine (1.1)	CH_2Cl_2	14	0:100
2	Ag_2CO_3 (0.5)	DMF	21	17:83
3	K_2CO_3 (0.5)	DMF	22	38:62
4	$AgBF_4$ (1)	DMF	19	30:70
5	NaBr (1)	DMF	46	45:55
6	NaI (2)	DMF	42	45:55
7		DMF	53	41:59
8		CH_2Cl_2	Traces	
9		THF	<5	40:60
10		Pyridine	Traces	

[a] Conditions: **1** (0.6 mmol), citronellol (1.5 mmol), additive (as indicated), solvent (1.0 mL), 50 °C, 16 h.
[b] Isolated yield.
[c] Ratio determined by ^{1}H NMR.
[d] Reaction at 0 °C for 18 h.

Keywords: Glycosylation; Xylosylation; Terpenols; Acid sensitive compounds.
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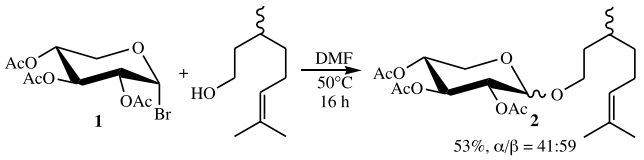
metal halophile, a 17/83 mixture of α- and β- anomers was obtained in 21% yield (entry 2). The use of K_2CO_3 or $AgBF_4$ instead of Ag_2CO_3 afforded similar yields (entries 3 and 4). The glycosydation in DMF was improved to 42–46% yield in the presence of NaBr or NaI (entries 5 and 6) but, surprisingly, the best yield was reached over 16 h[17] in the absence of any additive (entry 7, Eq. 1). The very low amounts of **2** obtained in CH_2Cl_2, THF and pyridine under similar conditions (entries 8–10) highlighted the decisive role of DMF on the efficiency of the coupling. Experiment carried out with (−)-citronellol under conditions of entry 7 led to a mixture of the two corresponding diastereoisomers.



(1)

Recently, ^{1}H NMR studies by Nishida et al. have allowed to demonstrate the formation of a kind of Vilsmeier–Haack intermediate between glycosyl bromides and DMF.[18] An ^{1}H NMR spectra of **1** in DMF-d_7 showed a doublet at 6.86 ppm (J=3.8 Hz), which disappeared with time. According to Nishida et al., this signal would be due to the formation of sensitive *O*-[tri-*O*-acetylxylosyl]-methylene-*N*,*N*-dimethylammonium bromide. We suggest that the glycosylation occurs, at least in part, via the reaction of this adduct with the alcohol and that HBr is neutralized by DMF.

The above results led us to use the conditions of Table 1, entry 7, for the glycosidation of **1** with other terpenols (Table 2). Similar yields have been obtained with (+)-menthol and (−)-borneol (entries 1 and 2), while primary and secondary allylic alcohols afforded lower yields (entries 3–5). No glycosidation of **1** was observed with a tertiary allylic alcohol such as linalol.

3. Conclusion

DMF can have a key role in the glycosidation of 2,3,4-triacetyl-1-bromo-α-D-xylopyranose with primary and secondary alcohols; modest yields, even from sensitive alcohols, can be obtained in this solvent in the absence of any additive.

Table 2. Xylosylation of terpenols[a]

Entry	Terpenol	Products	Yield %[b]	α/β[c]
1	(+)-Menthol	**3**	45	44:56
2	(−)-Borneol	**4**	42	34:66
3	Nerol	**5**	34	42:58
4	Geraniol	**6**	36	40:60
5	(−)-Carveol	**7**	16	43:57

[a] Conditions: **1** (0.6 mmol), terpenol (1.5 mmol), DMF (1.0 mL), 50 °C, 16 h.
[b] Isolated yield.
[c] Ratio determined by ^{1}H NMR.

4. Experimental

4.1. General methods

All reagents used were commercially available and with high purity grade. (−)-Carveol was a mixture of epimers at C(1). TLC were achieved with Silica Gel $60F_{254}$ (E. Merck). Column chromatographies were conducted over silica gel 63–200 μm (SDS). Melting points were measured on a Büchi Schmelzpunktbestimmungsapparat. NMR spectroscopies were performed with a Bruker Avance DRX 500 apparatus. FT-IR spectra were recorded on Avatar 320 FT-IR as KBr pellets or films. $[\alpha]_D^{20}$ were measured with a Perkin Elmer 241 Polarimeter. Mass spectra using electrospray ionization were performed with a Q-TOF micro from micromass.

4.1.1. 1,2,3,4-Tetraacetyl-D-xylopyranose. Acetyl chloride (3.0 mL, 42 mmol) was added dropwise to a solution at 0 °C of xylose (1.0 g, 6.7 mmol) in dichloromethane (25 mL) and pyridine (2.6 mL, 32 mmol). The mixture was allowed to stir overnight, and then quenched with water (50 mL). The organic layer was washed with 2 M HCl (2×50 mL), saturated $NaHCO_3$ (50 mL), water (50 mL), and dried over $MgSO_4$. The removing of the solvent under reduced pressure afforded a yellow paste (2.1 g, 97%, α/β=88/12). R_f 0.61 (1:1 petroleum ether/EtOAc). IR (KBr): ν 2961, 1756. ^{1}H NMR ($CDCl_3$): δ 6.26 (d, 0.88H, $J_{1,2}$=3.6 Hz, H-1α), 5.72 (d, 0.12H, $J_{1,2}$=6.9 Hz, H-1β), 5.47 (t, 0.88H, $J_{2,3,4}$=9.8 Hz, H-3α), 5.21 (t, 0.12H, $J_{2,3,4}$=8.2 Hz, H-3β), 5.03 (m, 2H, H-2α, H-4α, H-2β, H-4β), 4.16 (dd, 0.12H, $J_{4,5a}$=5.0 Hz, $J_{5a,5b}$=12.2 Hz, H-5aβ), 3.94 (dd, 0.88H, $J_{4,5a}$=5.9 Hz, $J_{5a,5b}$=11.2 Hz, H-5aα), 3.72 (t, 0.88H, $J_{4,5b,5a}$=10.9 Hz, H-5bα), 3.53 (dd, 0.12H, $J_{4,5b}$=8.5 Hz, $J_{5a,5b}$=12.0 Hz, H-5bβ), 2.10 (m, 12H, acetyls). ^{13}C NMR: δ 170.1, 169.7 (2), 169.0 (carbonyls), 91.9 (C-1β), 89.1 (C-1α), 70.9 (C-3β), 69.4 (C-2β), 69.2 (2) (C-3α, C-2α), 68.6 (C-4α), 68.2 (C-4β), 62.7 (C-5β), 60.6 (C-5α), 21.0, 20.8, 20.7, 20.6, 20.5, 20.4 (acetyls). ESHRMS: calcd for $C_{13}H_{18}O_9Na^+$: 341.0849; found: 341.0820.

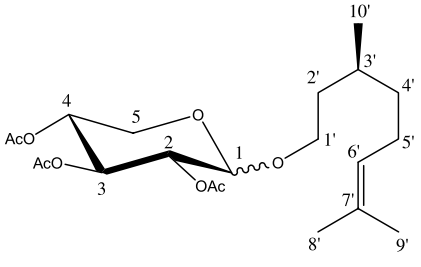
4.1.2. 2,3,4-Triacetyl-1-bromo-α-D-xylopyranose (1).[6–10] 1,2,3,4-Tetraacetyl-D-xylopyranose (4.1 g, 12.8 mmol) was dissolved in dichloromethane (40 mL) and HBr (33% w/v in AcOH) was added dropwise at 0 °C. After 1 h, the reaction was allowed to stir overnight at room temperature. Dichloromethane (60 mL) was added and the reaction was quenched with ice water (100 mL). The organic layer was washed twice with saturated aq. $NaHCO_3$ (100 mL), saturated aq. NaCl (100 mL) and dried over $MgSO_4$. After removing dichloromethane under reduced pressure, the crude product was dissolved in hot diethyl ether (minimum) and crystallized with petroleum ether (150 mL). The product was obtained as light brown crystals (3.3 g, 75%). Mp 75–82 °C (decomposition); lit. 83–85 °C[9]; 97–98 °C[10]; 96–97 °C[13]; 101–102 °C[15]. $[\alpha]_D^{20}$ +192 (*c* 0.87, $CHCl_3$); lit. +215 ($CHCl_3$)[9]; lit. +183 (*c* 2.5 $CHCl_3$)[10]; +206 (*c* 2.3 $CHCl_3$)[13]; +211.9 ($CHCl_3$)[15]. R_f 0.70 (4:1 petroleum ether/EtOAc). IR (KBr): ν 1754. ^{1}H NMR ($CDCl_3$): δ 6.58 (d, 1H, $J_{1,2}$=4.0 Hz, H-1), 5.56 (t, 1H, $J_{2,3,4}$=10.0 Hz, H-3), 5.04 (ddd, 1H, $J_{4,5a}$=5.5 Hz, $J_{3,4}$=9.5 Hz, $J_{4,5b}$=10.5 Hz, H-4), 4.77 (dd, 1H, $J_{1,2}$=4.3 Hz, $J_{2,3}$=10.0 Hz, H-2), 4.06 (dd, 1H, $J_{4,5a}$=6.0 Hz, $J_{5a,5b}$=11.2 Hz, H-5a), 3.88 (t, 1H, $J_{4,5b,5a}$=

10.7 Hz, H-5b), 2.08 (m, 9H, acetyls). ^{13}C NMR: δ 170.0, 169.9 (carbonyls), 87.7 (C-1), 71.0 (C-2), 69.7 (C-3), 68.2 (C-4), 62.7 (C-5), 20.9, 20.8 (2) (acetyls). ESHRMS: calcd for $C_{11}H_{15}O_7BrNa^+$: 360.9899; found: 360.9897. Due to the instability of the product, it should be noted that this signal was not always observed.

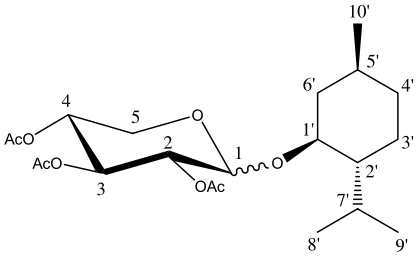
4.2. General method for xylosylation

2,3,4-Triacetyl-1-bromo-α-D-xylopyranose (0.6 mmol) and alcohol (1.5 mmol) were dissolved in anhydrous DMF (1.0 mL) and kept under Ar at 50 °C for 16 h. EtOAc (20 mL) was added and the organic layer was washed with saturated $NaHCO_3$ (20 mL) and water (20 mL), then dried over $MgSO_4$. The mixture was filtered, CH_2Cl_2 (5 mL) and pyridine (2.2 mmol, 0.18 mL) were added. $ClCOCH_3$ (1.8 mmol, 0.13 mL) was added dropwise at 0 °C and the mixture was stirred for 1 h. CH_2Cl_2 (5 mL) was added, the mixture was successively washed with water (10 mL), HCl 2 M (2×10 mL), saturated aq. $NaHCO_3$ (10 mL) and water (10 mL). The organic phase was dried over $MgSO_4$, filtered, then purified by silica gel column chromatography (9:1 then 4:1 petroleum ether/EtOAc). The products were obtained as a mixture of two anomers.

4.2.1. (3′*S*)-3′,7′-Dimethyloct-6′-enyl 2,3,4-triacetyl-D-xylopyranoside (2). Colourless oil. Yield=53%; α/β=41/59. $R_f\alpha$ 0.45; $R_f\beta$ 0.34 (4:1 petroleum ether/EtOAc). IR (KBr): ν 2927, 1755. ^{1}H NMR ($CDCl_3$): δ 5.48 (t, 0.41H, $J_{2,3,4}$=9.7 Hz, H-3α), 5.16 (t, 0.59H, $J_{2,3,4}$=8.5 Hz, H-3β), 5.09 (m, 1H, H-6′), 4.99 (m, 0.41H, H-1α), 4.94 (m, 1.59H, H-4α, H-2β, H-4β), 4.79 (dd, 0.41H, $J_{2,1}$=3.4 Hz, $J_{2,3}$=9.9 Hz, H-2α), 4.47 (d, 0.59H, $J_{1,2}$=6.9 Hz, H-1β), 4.12 (dd, 0.59H, $J_{4,5a}$=5.1 Hz, $J_{5a,5b}$=11.8 Hz, H-5aβ), 3.87 (m, 0.59H, H-1′aβ), 3.77 (m, 0.41H, H-5aα), 3.73 (m, 0.82H, H-1′aα, H-5bα), 3.49 (m, 0.59H, H-1′bβ), 3.44 (m, 0.41H, H-1′bα), 3.37 (m, 0.59H, H-5bβ), 2.05 (m, 9H, acetyls), 2.04 (m, 1H, H-5′a), 1.68 (s, 3H, H-8′), 1.66 (m, 1H, H-2a′), 1.60 (m, 3H, H-9′), 1.55 (m, 1H, H-3′), 1.41 (m, 1H, H-2′b), 1.34 (m, 1H, H-4′a), 1.21 (m, 1H, H-5′b), 1.16 (m, 1H, H-4′b), 0.88 (m, 3H, H-10′). ^{13}C NMR: δ 170.4, 170.3, 170.2, 170.1, 170.0, 169.5 (carbonyls), 131.4, 131.3 (C-7′), 124.8, 124.7 (C-6′), 100.9 (C-1β), 95.7 (C-1α), 71.7 (C-3β), 71.3 (C-2α), 71.0 (C-2β), 69.9 (C-3α), 69.6 (C-4α), 69.1 (C-4β), 68.1 (C-1′β), 66.9 (C-1′α), 62.1 (C-5β), 58.4 (C-5α), 37.2 (2) (C-4′), 36.5, 36.3 (C-2′), 29.7, 29.4 (C-3′), 25.8 (C-8′), 25.6, 25.5 (C-5′), 20.7 (4), 20.6 (2) (acetyls), 19.6, 19.4 (C-10′), 17.7 (C-9′). ESHRMS: calcd for $C_{21}H_{34}O_8Na^+$: 437.2151; found: 437.2159.

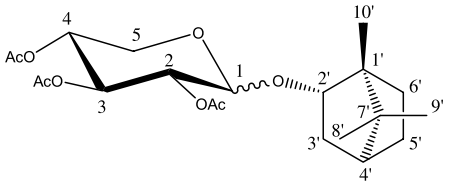


4.2.2. (1′*S*,2′*R*,5′*S*)-2′-(Prop-2-yl)-5′-methylcyclohexyl 2,3,4-triacetyl-D-xylopyranoside (3). White paste. Yield=45%; α/β=44/56. $R_f\alpha$ 0.49; $R_f\beta$ 0.39 (4:1 petroleum ether/EtOAc). IR (KBr): ν 2956, 1747. ^{1}H NMR ($CDCl_3$): δ 5.45 (t, 0.44H, $J_{2,3,4}$=9.8 Hz, H-3α), 5.17 (m, 0.56H, H-1α, H-3β), 4.96 (m, 1.56H, H-4α, H-2β, H-4β), 4.77 (dd, 0.44H, $J_{1,2}$=3.9 Hz, $J_{2,3}$=10.3 Hz, H-2α), 4.52 (d, 0.56H, $J_{1,2}$=7.4 Hz, H-1β), 4.14 (dd, 0.56H, $J_{5a,4}$=5.5 Hz, $J_{5a,5b}$=11.8 Hz, H-5aβ), 3.75 (m, 0.88H, H-5α), 3.38 (dt, 0.44H, $J_{1',6'}$=4.0 Hz, $J_{6',1',2'}$=10.6 Hz, H-1′α), 3.33 (m, 0.56H, H-5bβ), 3.30 (m, 0.56H, H-1′β), 2.24 (m, 0.44H, H-7′α), 2.15 (m, 0.56H, H-6′aβ), 2.08 (m, 0.56H, H-7′β), 2.05 (m, 19.8H, acetyls), 1.84 (m, 0.44H, H-6′aα), 1.65 (m, 0.88H, H-4′aα, H-3′aα), 1.63 (m, 0.56H, H-4′aβ), 1.61 (m, 0.56H, H-3′aβ), 1.37 (m, 0.56H, H-5′β), 1.35 (m, 0.44H, H-2′α), 1.30 (m, 0.44H, H-5′α), 1.22 (m, 0.56H, H-2′β), 1.06 (m, 0.56H, H-6′bβ), 0.95 (d, 1.32H, $J_{7',8'}$=7.0 Hz, H-8′α), 0.94 (m, 1H, H-3′b), 0.89 (m, 3H, H-10′), 0.88 (m, 1.68H, H-8′β), 0.83 (m, 0.44H, H-4′bα), 0.80 (m, 1H, H-6′bα, H-4′bβ), 0.77 (d, 1.32H, $J_{7,9}$=7.0 Hz, H-9′α), 0.75 (d, 1.68H, $J_{7',9'}$=7.1 Hz, H-9′β). ^{13}C NMR: δ 170.3 (2), 170.0 (2), 169.8, 169.3 (carbonyls), 102.3 (C-1β), 92.6 (C-1α), 82.3 (C-1′β), 77.3 (C-1′α), 72.1 (C-3β), 71.5 (C-2β), 71.1 (C-2α), 69.5 (2) (C-3α, C-4α), 69.0 (C-4β), 62.2 (C-5β), 58.6 (C-5α), 48.2 (C-2′β), 47.4 (C-2′α), 43.0 (C-6′β), 40.0 (C-6′α), 34.2 (C-4′α), 34.1 (C-4′β), 31.6 (C-5′β), 31.2 (C-5′α), 25.3 (C-7′α), 24.9 (C-7′β), 22.7 (C-3′β), 22.5 (C-3′α), 22.2 (C-10′β), 22.1 (C-10′α), 21.1 (C-8′α), 21.0 (C-8′β), 20.8 (3), 20.7 (2), 20.5 (acetyls), 15.8 (C-9′β), 14.9 (C-9′α). ESHRMS: calcd for $C_{21}H_{34}O_8Na^+$: 437.2151; found: 437.2148.

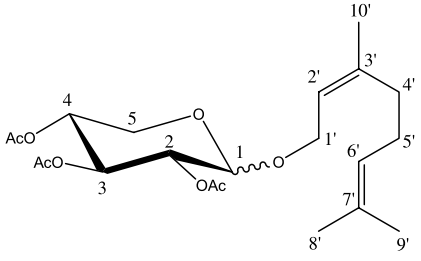


4.2.3. (1′*S*,2′*S*,4′*S*)-1′,7′,7′-Trimethylbicyclo[2.2.1]hept-2′-yl 2,3,4-triacetyl-D-xylopyranoside (4). White paste. Yield=42%; α/β=34/66. $R_f\alpha$ 0.42; $R_f\beta$ 0.32 (4:1 petroleum ether/EtOAc). IR (KBr): ν 2953, 1751. ^{1}H NMR ($CDCl_3$): δ 5.50 (t, 0.34H, $J_{2,3,4}$=9.8 Hz, H-3α), 5.16 (t, 0.66H, $J_{2,3,4}$=8.5 Hz, H-3β), 5.04 (d, 0.34H, $J_{1,2}$=3.7 Hz, H-1α), 4.94 (m, 1.66H, H-4α, H-2β, H-4β), 4.76 (dd, 0.34H, $J_{1,2}$=3.7 Hz, $J_{2,3}$=10.1 Hz, H-2α), 4.47 (d, 0.66H, $J_{1,2}$=6.7 Hz, H-1β), 4.12 (dd, 0.66H, $J_{4,5a}$=4.9 Hz, $J_{5a,5b}$=11.7 Hz, H-5aβ), 3.99 (d, 0.66H, $J_{2',3'}$=8.8 Hz, H-2′β), 3.76 (dd, 0.34H, $J_{4,5a}$=6.1 Hz, $J_{5a,5b}$=10.6 Hz, H-5aα), 3.76 (m, 0.34H, H-2′α), 3.69 (t, 0.34H, $J_{4,5b,5a}$=10.8 Hz, H-5bα), 3.34 (dd, 0.66H, $J_{4,5b}$=8.9 Hz, $J_{5a,5b}$=11.8 Hz, H-5bβ), 2.18 (m, 0.34H, H-3′aα), 2.13 (m, 0.66H, H-3′aβ), 2.10 (m, 0.34H, H-6′aα), 2.08 (m, 9H, acetyls), 1.90 (m, 0.34H, H-6′bα), 1.72 (m, 2H, H-5′), 1.66 (m, 1H, H-4′), 1.20 (m, 1.32H, H-6′β), 1.11 (m, 0.34H, H-3′bα), 0.91 (m, 0.66H, H-3′bβ), 0.86 (s, 1.98H, H-10′β), 0.85 (s, 1.98H, H-8′β), 0.84 (2s, 3H, H-8′α H-9′β), 0.83 (s, 1.02H, H-9′α), 0.80 (s, 1.02H, H-10′α). ^{13}C NMR: δ 170.5, 170.3 (2), 170.2, 170.0, 169.4 (carbonyls), 99.1 (C-1β), 97.2 (C-1α), 85.5 (C-2′α), 82.7 (C-2′β), 71.5 (C-2α), 71.4 (C-3β), 70.9 (C-2β), 69.9 (C-3α), 69.8 (C-4α), 69.0 (C-4β), 62.0 (C-5β), 58.6 (C-5α), 49.7 (C-7′α), 49.1 (C-7′β), 48.0 (C-1′β), 47.8 (C-1′α), 45.1

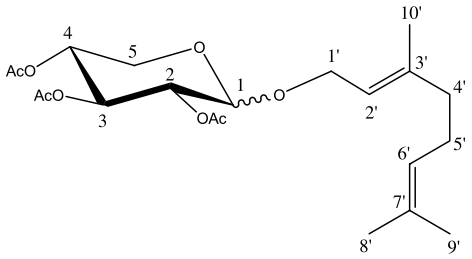
(C-4′α), 45.0 (C-4′β), 37.0 (C-3′α), 35.9 (C-3′β), 28.5 (C-5′β), 28.4 (C-5′α), 26.6 (C-6′α), 26.5 (C-6′β), 21.0, 20.9 (3), 20.8 (2) (acetyls), 19.8 (C-8′), 19.0 (C-9′β), 18.9 (C-9′α), 13.8 (C-10′α), 13.5 (C-10′β). ESHRMS: calcd for $C_{21}H_{32}O_8Na^+$: 435.1995; found: 435.2012.



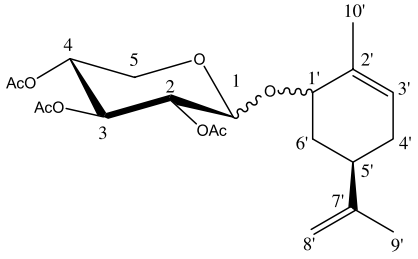
4.2.4. (2′*Z*)-3′,7′-Dimethyloct-2′,6′-dienyl 2,3,4-triacetyl-D-xylopyranoside (5). Colourless oil. Yield=34%; α/β=42/58. $R_f\alpha$ 0.39; $R_f\beta$ 0.31 (4:1 petroleum ether/EtOAc). IR (KBr): ν 2933, 1754. ^{1}H NMR ($CDCl_3$): δ 5.49 (t, 0.42H, $J_{2,3,4}$=9.8 Hz, H-3α), 5.28 (m, 1H, H-2′), 5.16 (t, 0.58H, $J_{2,3,4}$=8.7 Hz, H-3β), 5.07 (m, 1H, H-6′), 5.01 (d, 0.42H, $J_{1,2}$=3.6 Hz, H-1α), 4.94 (m, 1H, H-4α, H-4β), 4.91 (dd, 0.58H, $J_{1,2}$=6.9 Hz, $J_{2,3}$=8.6 Hz, H-2β), 4.81 (dd, 0.42H, $J_{1,2}$=3.6 Hz, $J_{2,3}$=10.2 Hz, H-2α), 4.51 (d, 0.58H, $J_{1,2}$=6.9 Hz, H-1β), 4.22 (dd, 0.58H, $J_{1'a,2'}$=5.6 Hz, $J_{1'a,1'b}$=12.0 Hz, H-1′aβ), 4.13 (m, 1.58H, H-1′aα, H-1′bβ, H-5aβ), 4.01 (dd, 0.42H, $J_{1'a,1'b}$=11.8 Hz, $J_{1'b,2'}$=7.6 Hz, H-1′bα), 3.78 (dd, 0.42H, $J_{4,5a}$=6.0 Hz, $J_{5a,5b}$=10.8 Hz, H-5aα), 3.65 (t, 0.42H, $J_{4,5b,5a}$=10.8 Hz, H-5bα), 3.34 (dd, 0.58H, $J_{4,5b}$=8.9 Hz, $J_{5a,5b}$=11.7 Hz, H-5bβ), 2.07 (m, 4H, H-4′, H-5′), 2.05 (m, 9H, acetyls), 1.76 (s, 3H, H-10′), 1.68 (s, 3H, H-8′), 1.60 (s, 3H, H-9′). ^{13}C NMR: δ 170.4 (2), 170.3, 170.2, 170.0, 169.6 (carbonyls), 142.0 (C-3′β), 141.8 (C-3′α), 132.3 (C-7′), 123.7 (C-6′), 120.5 (C-2′β), 120.4 (C-2′α), 99.2 (C-1β), 94.5 (C-1α), 71.7 (C-3β), 71.1 (C-2α), 71.0 (C-2β), 69.8 (C-3α), 69.7 (C-4α), 69.1 (C-4β), 65.1 (C-1′β), 64.0 (C-1′α), 62.1 (C-5β), 58.4 (C-5α), 32.3 (C-4′), 26.8 (C-5′β), 26.7 (C-5′α), 25.8 (C-8′), 23.7 (C-10′β), 23.6 (C-10′α), 20.9 (6) (acetyls), 17.8 (C-9′). ESHRMS: calcd for $C_{21}H_{32}O_8Na^+$: 435.1995; found: 435.1994.



4.2.5. (2′*E*)-3′,7′-Dimethyloct-2′,6′-dienyl 2,3,4-triacetyl-D-xylopyranoside (6). Colourless oil. Yield=36%; α/β=40/60. $R_f\alpha$ 0.38; $R_f\beta$ 0.28 (4:1 petroleum ether/EtOAc). IR (KBr): ν 2930, 1754. ^{1}H NMR ($CDCl_3$): δ 5.52 (t, 0.4H, $J_{2,3,4}$=9.9 Hz, H-3α), 5.30 (m, 1H, H-2′), 5.19 (t, 0.6H, $J_{2,3,4}$=8.6 Hz, H-3β), 5.11 (m, 1H, H-6′), 5.04 (d, 0.40H, $J_{1,2}$=3.6 Hz, H-1α), 4.97 (m, 1.6H, H-4α, H-2β, H-4β), 4.84 (dd, 0.4H, $J_{1,2}$=3.6 Hz, $J_{2,3}$=10.2 Hz, H-2α), 4.53 (d, 0.6H, $J_{1,2}$=6.9 Hz, H-1β), 4.27 (dd, 0.6H, $J_{1'a,2'}$=6.2 Hz, $J_{1'a,1'b}$=12.0, Hz, H-1′aβ), 4.17 (m, 1.6H, H-1′aα, H-1′bβ, H-5aβ), 4.07 (dd, 0.4H, $J_{1'b,2'}$=7.5 Hz, $J_{1'a,1'b}$=12.0 Hz, H-1′bα), 3.80 (dd, 0.4H, $J_{4,5a}$=5.9 Hz, $J_{5a,5b}$=10.8 Hz, H-5aα), 3.68 (t, 0.4H, $J_{4,5b,5a}$=10.8 Hz, H-5bα), 3.36 (dd, 0.6H, $J_{4,5b}$=8.9 Hz, $J_{5a,5b}$=11.8 Hz, H-5bβ), 2.09 (m, 4H, H-4′, H-5′), 2.07 (m, 9H, acetyls), 1.71 (s, 3H, H-8′), 1.68 (s, 3H, H-10′), 1.63 (s, 3H, H-9′). ^{13}C NMR: δ 170.4, 170.3, 170.2 (2), 170.0, 169.6 (carbonyls), 142.0 (C-3′β), 141.8 (C-3′α), 131.9 (C-7′), 123.9 (C-6′), 119.5 (C-2′), 99.1 (C-1β), 94.5 (C-1α), 71.7 (C-3β), 71.2 (C-2α), 71.0 (C-2β), 69.8 (C-3α), 69.6 (C-4α), 69.1 (C-4β), 65.2 (C-1′β), 64.3 (C-1′α), 62.2 (C-5β), 58.4 (C-5α), 39.7 (C-4′), 26.4 (C-5′), 25.8 (C-8′), 17.8 (C-9′), 17.8 (6) (acetyls), 16.6 (C-10′α), 16.5 (C-10′β). ESHRMS: calcd for $C_{21}H_{32}O_8Na^+$: 435.1995; found: 435.1985.



4.2.6. (1′*RS*,5′*R*)-2′-Methyl-5′-(prop-1-en-2-yl)cyclohex-2′-enyl 2,3,4-triacetyl-D-xylopyranoside (7). The product was obtained as a mixture of two (1′)-epimers. Colourless oil. Yield=16%; α/β=43/57. $R_f\alpha$ 0.41; $R_f\beta$ 0.32 (4:1 petroleum ether/EtOAc). IR (KBr): ν 2922 (alkyl), 1754 (ester). ^{1}H NMR ($CDCl_3$): δ 5.60 (m, 1H, H-3′), 5.50 (m, 0.43H, H-3α), 5.16 (m, 1H, H-1α, H-3β), 4.94 (m, 1.57H, H-4α, H-2β, H-4β), 4.80 (m, 0.43H, $J_{1,2}$=3.7 Hz, $J_{2,3}$=10.4 Hz, H-2α), 4.71 (m, 2H, H-8′), 4.64 (m, 0.57H, H-1β), 4.13 (m, 0.57H, H-5aβ), 3.94 (m, 1H, H-1′), 3.80 (m, 0.86H, H-5α), 3.37 (m, 0.57H, H-5bβ), 2.17 (m, 3H, H-5′ and H-4′ or H-6′), 2.06 (m, 9H, acetyls), 1.90 (m, 6H, H-9′, H-10′), 1.50 (m, 2H, H-4′ or H-6′). ^{13}C NMR: δ 170.5, 170.4, 170.2, 170.0, 169.5 (carbonyls), 149.4, 149.3, 148.8, 148.7 (C-2′), 134.6, 134.4, 131.9 (C-7′), 127.4, 126.8, 125.2, 125.0 (C-3′), 109.4, 109.3, 109.2, 108.8 (C-8′), 102.6, 98.2 (C-1β), 98.0, 93.8 (C-1α), 79.4, 76.9 (C-1′β), 80.9, 74.6 (C-1′α), 72.0, 71.6 (C-3β), 71.5, 71.3 (C-2α), 71.2, 70.9 (C-2β), 69.8, 69.6 (C-3α, C-4β), 69.1, 68.9 (C-4α), 62.2, 61.8 (C-5β), 58.8, 57.8 (C-5α), 40.8, 40.5, 35.2, 34.9 (C-5′), 36.4, 35.0, 33.9, 32.1, 30.7 (C-4′, C-6′), 21.6, 21.1, 20.5 (C-9′, C-10′), 21.0, 20.9, 20.8, 20.7 (acetyls). ESHRMS: calcd for $C_{21}H_{30}O_8Na^+$: 433.1838; found: 433.1841.



Acknowledgements

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An unusual substitution reaction directed by an intramolecular re-arrangement

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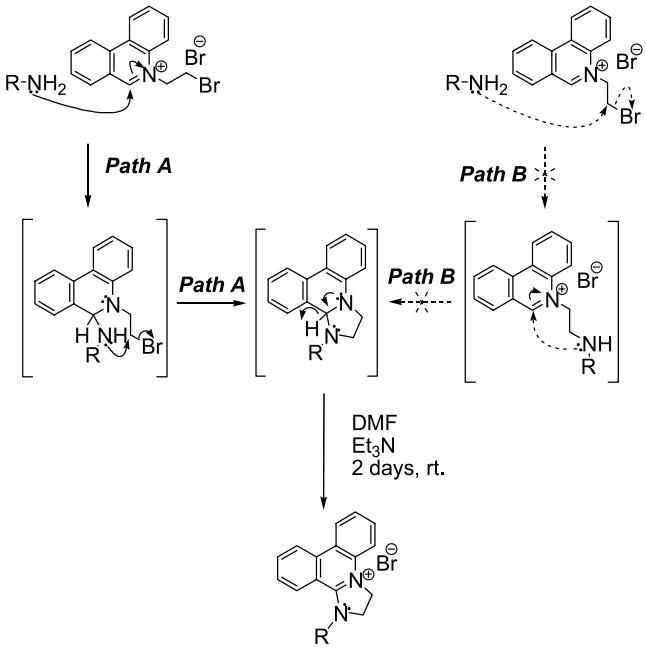
Abstract—Secondary amines and thiols undertake a substitution reaction on the side chain of 2-bromoethyl-pyridinium derivatives 'directed' by an intramolecular re-arrangement. Experimental investigations strongly indicate that the reaction is initiated by an alpha addition of the nucleophile onto the iminium moiety of the N-heteroaromatic cation, followed by a cyclisation and an oxidative ring opening. This novel substitution process is able to occur with less reactive nucleophiles that would not undergo conventional substitution with 'isolated' bromoethyl moieties.

1. Introduction

It is almost impossible to imagine a biological process that does not involve a heterocyclic compound.[1] Heterocycles also form the building blocks of many important pharmaceuticals.[2] One of the reasons for the widespread use of heterocyclic compounds in nature as well as in the pharmaceutical industry is their implication in a wide range of reaction types allowing subtle structural modification.[3–5] Therefore, investigations working towards the understanding of the reactivity of heterocyclic compounds is of great practical significance. Efficient syntheses leading to N-heteroaromatic cations are especially interesting as they often form the framework of DNA intercalating agents and have anticancer properties.[6,7] In this respect, molecules containing a phenanthridinium core are one important subset of heteroaromatic cations.[8–11]

Recently, we have discovered a flexible methodology allowing the ring extension of *N*-heterocyclic cations.[12] Specifically, we found that a primary amine reacted with 2-bromoethyl-phenanthridinium leading to the corresponding dihydro-imidazo-phenanthridinium derivative (DIP) via a nucleophilic addition followed by a cyclisation and an in-situ oxidation step (Path A, Scheme 1).

Evidence strongly suggesting Path A as a mechanism was confirmed by isolation of intermediates demonstrating the alpha addition step. The alternative pathway, (Path B, Scheme 1), was ruled out when experiments highlighted the poor reactivity of the 2-bromoethyl side chain, as well the necessity for a disfavoured 5-*endo*-trig-cyclisation.[12,13]



Scheme 1. The cascade reaction leading to the Dihydro-Imidazo-Phenanthridinium DIP derivative.[12] Note that the hydride loss could also be viewed as two consecutive electron transfers and a proton loss.

Keywords: *N*-Heterocyclic; Substitution; Intramolecular re-arrangement; Mechanism; Phenanthridinium.
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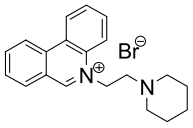
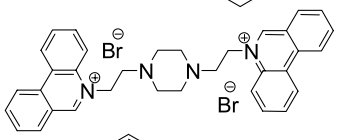
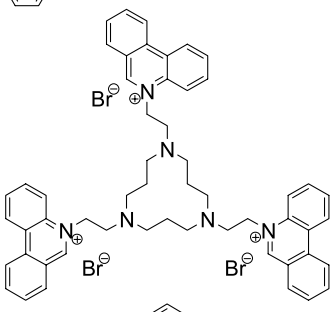
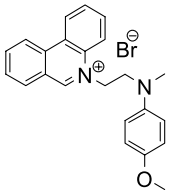
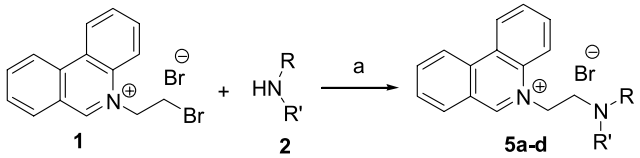
Table 1. Products and yields

Entry	Structure **5**	Secondary amine **2**	Yield %
5a		Piperidine	71
5b		Piperazine	73
5c		1,5,9-Triaza-cyclododecane	93
5d		*p*-Methoxy methyl aniline	77

Following the discovery of this useful one-pot-methodology, we were interested in utilising nucleophiles other than primary amines: for example, what would be the result if a nucleophile with only one available valence is used with the same reaction conditions? Herein, we report a surprising reaction that allows substitution of the bromo-ethyl side chain via a 'directed' cyclisation process with secondary amines and thiol-derivatives.

2. Results and discussion

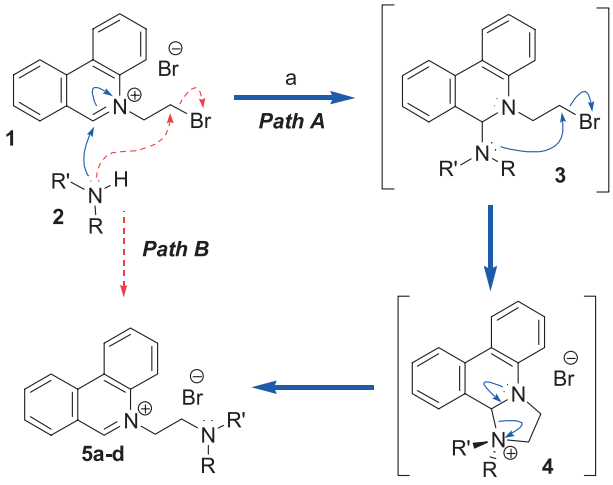
Under mild reaction conditions, the starting material 2-bromoethyl-phenanthridinium bromide **1** reacts with a series of secondary amines **2** to give the corresponding 2-aminoethyl-phenanthridinium bromide derivatives **5a–d** (Scheme 2 and Table 1).



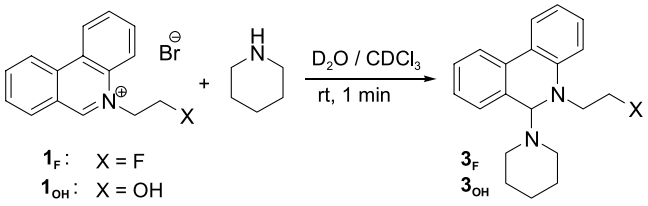
Scheme 2. Reagents and conditions: (a) DMF, Et_3N, N_2, rt, 48 h.

Upon initial inspection, this result seems to be in direct contradiction with the previously published Path A mechanism shown in Scheme 1, which states that direct bromine substitution on the side chain of molecule **1**, that is, Path B, does not take place.[12] Nevertheless, another pathway, avoiding direct substitution could also explain the formation of substituted products **5a–d** (Path A, Scheme 3). This intricate mechanism would involve an alpha addition on the iminium moiety of molecule **1**, followed by a ring cyclisation and a retro-5-*endo*-trig ring opening leading to re-oxidation of the heterocyclic middle ring.

Strong arguments in favour of Path A mechanism of Scheme 3 were obtained in the course of our experiments. Firstly, the reactivity of the iminium moiety of starting material **1** was assessed by reacting piperidine with the fluoro- and hydroxyl analogues of molecule **1** (respectively, $\mathbf{1}_F$ and $\mathbf{1}_{OH}$, Scheme 4). These two analogues, with their iminium moiety assumed to be as reactive as the one of molecule **1** (this assumption was made on the basis of DFT



Scheme 3. The two possible mechanistic pathways leading to **5a–d**. Reagents and conditions: (a) DMF, Et_3N, N_2, rt, 48 h.



Scheme 4. NMR phase transfer experiment with fluoro and hydroxyl analogue of molecule **1**.

calculations),[14] have the advantage of being unable to undertake the cyclisation of the hypothetic second step of Path A (Scheme 3). For reason of simplicity, and in order to evaluate how quickly the alpha addition step takes place, the reaction was undertaken in a biphasic system with D_2O/$CDCl_3$; this was done in practice in a NMR tube, where $\mathbf{1}_F$ or $\mathbf{1}_{OH}$ were partitioned between the organic and aqueous layers. Upon addition of piperidine, a white precipitate appears instantaneously in the D_2O layer and shifts towards the bottom $CDCl_3$ layer where ^1H and ^{13}C NMR measurements were used to characterize the corresponding alpha adduct $\mathbf{3}_F$ or $\mathbf{3}_{OH}$ (Scheme 4), analogues of intermediate **3** (Scheme 3).

The efficiency of the alpha addition step was also realised by isolating and analysing the D_2O layer during an identical NMR phase transfer reaction: following the addition of piperidine to the biphasic system, no starting material could be detected after only 1 min of reaction time.

This NMR phase transfer experiment highlights the high reactivity of the iminium moiety of starting material **1**. Moreover, other examples of alpha addition of secondary amines onto N-heteroaromatic cations like phenanthridinium,[15,16] isoquinolinium[17] and pyridinium[18,19] systems are also reported to lead to stable products.

Secondly, further support for the involvement of the central aromatic ring in the substitution reaction of Scheme 3 was obtained by UV absorption spectroscopy measurements. The absorption was measured between 200 and 500 nm and the λ_{max} determined to be at ca. 320 nm. If the reaction proceeds via Path A, the UV absorption of the de-aromatized intermediates (**3** and **4**), at this wavelength, should be different from both the starting material **1** and the final product **5**. Subsequently, the UV absorption was continuously monitored at 320 nm over a period of 12 h. On addition of the piperidine to a solution of starting material **1**, the absorbance drops instantly from 0.75 to 0.50 (formation of intermediates **3** and **4**) and rises back slowly to 0.75 due to the formation of final product **5** (Fig. 1).

This data allow us to conclude that the intermediate is present for at least 2 h. Therefore, in a subsequent reaction, a UV spectrum of the starting material was taken between 200 and 500 nm, and compared with both the UV spectrum of the intermediate after 30 min and the final product after 12 h reaction time (Fig. 2). The difference in absorbance between the intermediate and the starting material confirms the de-aromatisation process involved in the proposed mechanism of Path A.

Lastly, the hypothetical Path B depicted in Scheme 3, is not consistent with the observation that compound **5d** can be

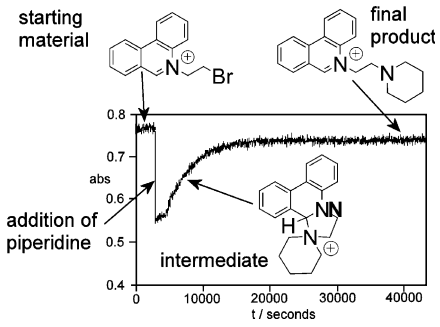


Figure 1. Absorbance at 320 nm versus time showing the formation of **5** from the reaction of **1** with piperidine highlighting the de-aromatisation/re-aromatisation process expected for Path A.

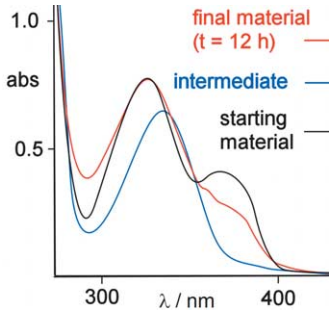
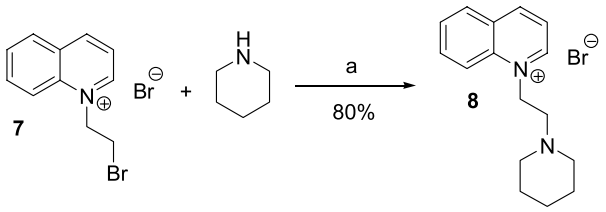


Figure 2. The alpha adduct intermediate(s) **3** and/or **4** can be observed by UV spectroscopy. λ_{max} for the starting and final material is ca. 320 nm.

synthesized. This is because, under the mild reaction conditions implemented (Scheme 3), it seems unlikely that the weakly nucleophilic aromatic amine *p*-methoxy-methylaniline is capable of performing a direct substitution on the ethyl-bromine side chain of starting material **1** (Path B). On the contrary, in the synthesis of **5d** via Path A, the ethyl-bromine side chain substitution of the corresponding aromatic amine intermediate **3** (Scheme 3) would be favoured entropically by the formation of a five-membered ring. Therefore, to test the reactivity of the ethyl-bromine side chain of **1** on its own, *p*-methoxy-methylaniline was added to a DMF solution of 1,2-dibromoethane, using the same reaction conditions as for the synthesis of **5a–d**. Under these mild conditions, no substitution on this bromoethyl-analogue of **1** could be detected by TLC. The same test was repeated with 2-bromoethyl-trimethyl-ammonium bromide, with identical outcome. Therefore, assuming that those two bromoethyl derivatives have reactivity similar to the bromoethyl side chain of staring material **1**, the isolation of final molecule **5d** is not likely to occur via Path B. This result also highlights the more effective substitution reaction of Path A allowing somewhat weaker nucleophiles to ultimately undergo this substitution reaction. Consequently, the alpha addition step of Path A can be seen as a 'directing step' helping the side chain substitution leading to **5**.

In order to examine the generality of the reaction to other N-heteroaromatic cations with an available alpha position, the reaction was also attempted using 2-bromoethyl-quinoline **7** to obtain with good yield the corresponding 2-aminoethyl-quinolinium derivative **8** (Scheme 5).

In this context, it is interesting to note that the



Scheme 5. Reaction on quinolinium system. Reagents and conditions: (a) DMF, Et_3N, N_2, rt, 48 h.

functionalization of N-heteroaromatic systems with a 2-aminoethyl side chain is often encountered in DNA intercalators where the resulting tertiary amine is either used as a spacer in bis-intercalating agents,[20–24] or used for structural/solubility/charge reasons.[25–29]

In addition, the substitution reaction of 2-bromoethyl-phenanthridinium **1** was also successful with thiol-derivatives. The nucleophile *p*-methoxybenzyl mercaptan leads to the corresponding substituted 2-mercaptoethyl-phenanthridinium derivative **9** in good yield (Scheme 6).

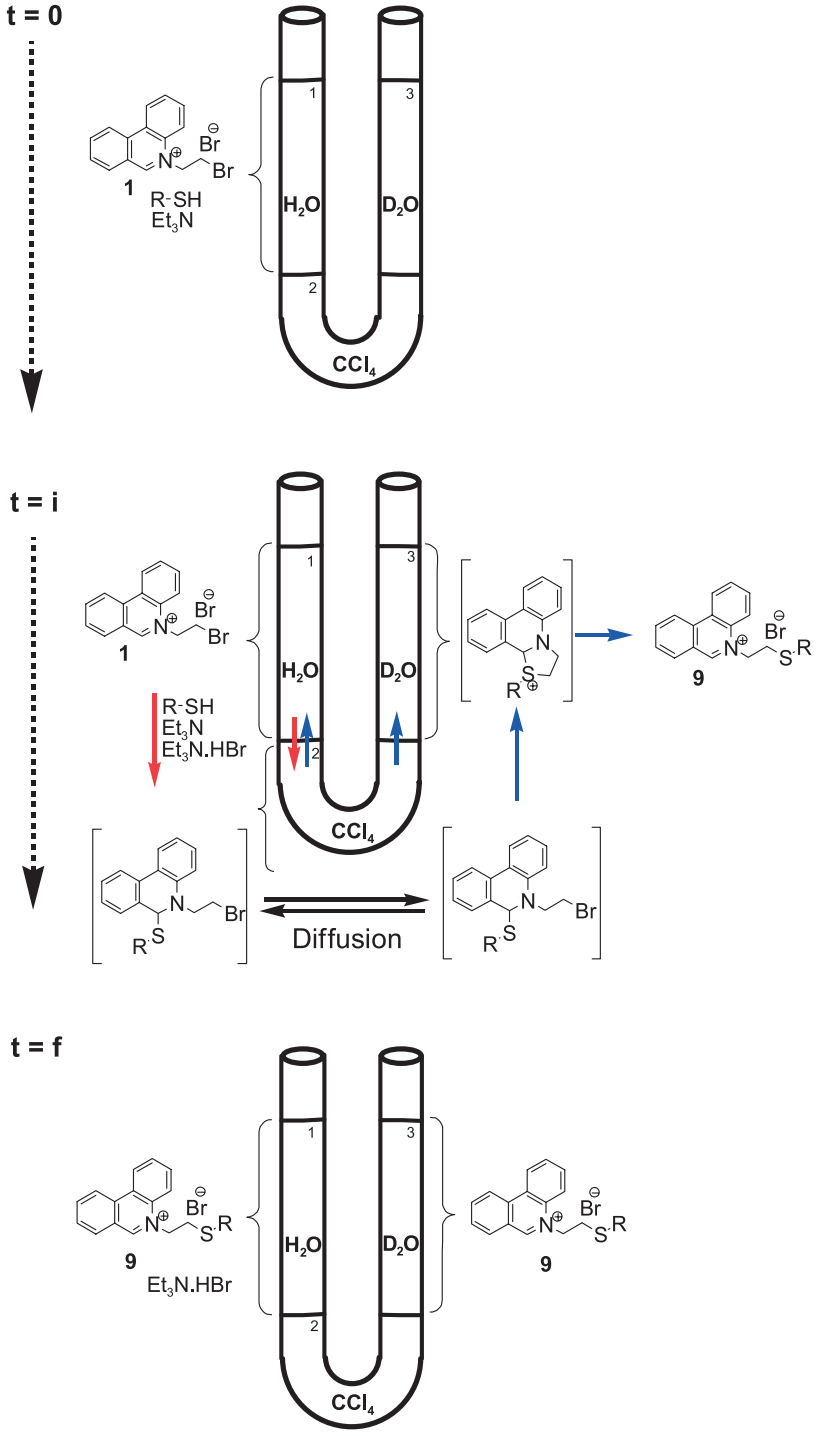
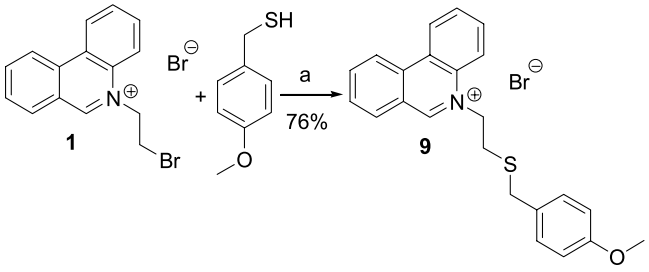


Figure 3. Phase transfer reaction in a 'U-Tube' highlighting the existence of an organic soluble intermediate. R = *p*-methoxybenzyl.



Scheme 6. Substitution reaction with a thiol derivative. Reagents and conditions: DMF, Et_3N, N_2, rt, 48 h.

Moreover, indirect proof of the alpha adduct intermediates could be obtained, using a phase transfer reaction in a 'U-tube' (Fig. 3). In this experiment, a 'U-tube' containing CCl_4 in the bottom (compartment 2, Fig. 3), was filled with water in one side (compartment 1, Fig. 3) and D_2O in the other (compartment 3, Fig. 3). Molecule **1** was added to compartment 1, followed by *p*-methoxybenzyl mercaptan and triethylamine. The organic layer of compartment 2 was gently stirred with a small magnet, taking care not to exchange any water from compartment 1 with D_2O from compartment 3. After 48 h, the deuterated solution of compartment 3 was analyzed by ^1H and ^{13}C NMR spectroscopy, and final molecule **9** was characterized. It is unlikely that the cationic starting material **1** nor the cationic final product **9** could diffuse from one aqueous medium to the other through the organic medium. Therefore, the occurrence of molecule **9** in compartment 3 can be best explained by the formation of an intermediate soluble in the organic phase, being able to diffuse between the two aqueous layers. Furthermore, the exchange of water between the two opposite layers (i.e., D_2O with H_2O and vice versa) was not observed during the NMR experiments and acts as a further control.

Consequently, the substitution of **1** by thiol-derivatives is also believed to be 'directed' by a similar re-arrangement as Path A of Scheme 3, that is: an alpha addition forming an intermediate soluble in organic solvent, followed by a five-membered ring cyclisation and an oxidative ring opening leading to the final material **9**, which is soluble in aqueous solution.

3. Conclusions

We have described the mechanism of a new type of nucleophilic substitution on 2-bromoethyl-pyridinium-like-cations. The substitution appears to be 'directed' by an initial alpha addition step on the iminium moiety, followed by a five-membered ring cyclisation and a re-aromatisation process via an oxidative C–N bond breakage. This intricate substitution was shown to be more effective than conventional types of nucleophilic substitution. In further work, we intend to examine the reaction of secondary amines with the 3-bromopropyl-pyridinium framework whereby any substitution taking place is also likely to occur via a similar re-arrangement requiring the formation of a six-membered ring intermediate. We will also examine the reaction pathways outlined here using theoretical methods.

4. Experimental

4.1. General

All reactions were carried out using oven-dried glassware under a nitrogen atmosphere using standard Schlenk line techniques. Commercial starting materials and solvents were used as supplied, without further purification. ^1H and ^{13}C NMR were recorded using a Bruker DPX 400 spectrometer operating at 400 and 100 MHz, respectively. Chemical shifts (δ) are given in ppm relative to residual solvent peak. Coupling constants (J) are given in Hz. Infrared spectral analysis were performed on a JASCO 410 spectrophotometer, using a KBr disc unless otherwise stated; peaks are quoted in wave numbers (cm^{-1}) and their relative intensity are reported as follows: s = strong, m = medium, w = weak. Mass spectra were obtained using a JEOL JMS 700 spectrometer operating, in FAB, EI, CI or ES mode. Microanalyses were performed on a CE-440 elemental analyzer. Melting points were determined on a digital IA9000 series melting point apparatus, using capillary tubes. UV spectrums were recorded on a Shimadzu UV-310PC UV–VIS–NIR Scanning Spectrophotometer.

Definitions of abbreviations: DMF, dimethylformamide; DIP, dihydro-imidazo-phenanthridinium bromide; TEA, triethylamine; rt, room temperature.

4.2. Synthesis and analytical data

4.2.1. General procedure for the synthesis of 2-bromoethyl-pyridinium derivative (1 and 7). Phenanthridine or quinoline (30.3 mmol) was dissolved in 1,2-dibromoethane (114.2 g; 52 mL; 608 mmol) and stirred at 90 °C for a week. During that time, any precipitate formed was recovered by filtration. After each filtration, the precipitate was rinsed with an additional 5 mL of 1,2-dibromoethane and the mother liquor stirred at 90 °C until the next filtration. The reaction was deemed to be complete when no more precipitate formed. The precipitates were combined and washed thoroughly with ethyl acetate to give **1** or **7**.

4.2.1.1. 2-Bromoethyl-phenanthridinium bromide (1). Product **1** (10.55 g; 28.8 mmol) was recovered as a beige powder in a 95% yield; mp: 234–235 °C (dec); ^1H NMR (D_2O, 400 MHz): δ 9.81 (s, 1H), 8.72 (d, 1H, J=7.2 Hz), 8.63 (d, 1H, J=7.2 Hz), 8.37 (d, 1H, J=7.2 Hz), 8.26 (d, 1H, J=7.2 Hz), 8.18 (t, 1H, J=7.2 Hz), 7.98 (t, 1H, J=7.2 Hz), 7.90 (m, 2H), 5.37 (t, 2H, J=5.8 Hz), 4.05 (t, 2H, J=5.8 Hz); ^{13}C NMR (D_2O, 100 MHz): δ 155.27 (CH), 139.03 (CH), 135.59 (C), 133.18 (CH), 132.78 (C), 132.58 (CH), 130.85 (CH), 130.72 (CH), 126.57 (C), 125.13 (CH), 123.32 (C), 123.00 (CH), 118.91 (CH), 58.87 (CH_2), 29.41 (CH_2); IR (KBr, cm^{-1}): 2947 (w), 1620 (m), 763 (s), 717 (m); MS (ES): 288.1 (M–Br) (100), 206.2 (8). Anal. Calcd for $C_{15}H_{13}NBr_2$: C, 49.32; H, 3.59; N, 3.84. Found: C, 49.15; H, 3.48; N, 3.76.

4.2.1.2. 2-Bromoethylquinolinium bromide (7). Product **4** (9.10 g; 28.7 mmol) was recovered as a beige powder in a 95% yield; mp: 289–290 °C (dec); ^1H NMR (D_2O, 400 MHz): δ 9.24 (d, 1H, J=8.4 Hz), 9.12 (d, 1H,

J=8.4 Hz), 8.87 (d, 1H, J=8.4 Hz), 8.33 (d, 1H, J=8.4 Hz), 8.20 (t, 1H, J=8.4 Hz), 7.98 (m, 2H), 5.41 (t, 2H, J=5.8 Hz), 4.05 (t, 2H, J=5.8 Hz); ^{13}C NMR (D_2O, 100 MHz): δ 149.80 (C), 149.20 (CH), 138.08 (C), 136.66 (CH), 131.43 (CH), 130.68 (CH), 130.55 (CH), 121.59 (CH), 118.08 (CH), 58.59 (CH_2), 29.28 (CH_2); IR (KBr, cm^{-1}): 3437 (s), 3045 (w), 2981 (m), 2947 (m), 1624 (s), 1599 (m), 1585 (m), 1525 (s), 1489 (w), 1450 (m), 1400 (m), 1363 (s), 1242 (s), 1126 (m), 1161 (m), 1144 (m), 1049 (w), 874 (w), 816 (m), 800 (m), 775 (s); MS (FAB): 237 (M–Br) (98), 236 (100), 209.9 (2), 172 (2), 156 (12), 129.1 (6), 107.2 (2), 89.5 (2), 72.7 (1), 59.9 (1). Anal. Calcd for $C_{11}H_{11}NBr_2$: C, 41.67; H, 3.49; N, 4.42. Found: C, 41.75; H, 3.50; N, 4.51.

4.2.2. General procedure for the synthesis of 2-aminoethyl-pyridinium derivative (5a–d; 8) and 2-thioethyl-pyridinium derivative (9). 2-Bromoethyl-pyridinium **1** or **7** (1.9 mmol) was dissolved in 20 mL DMF. Secondary amine or thiol derivative (2.1 mmol) and TEA (0.576 mg; 795 μL; 5.7 mmol) were added successively to the stirred solution. After stirring for 48 h at rt under nitrogen, the final product and TEA hydrobromide salt were precipitated from the solution by adding diethyl ether (40 mL) and were recovered by filtration. The precipitate was washed thoroughly with ethyl acetate and then triturated twice with 0.5 mL of water to get rid of the TEA salt. The residue was dried by successive diethyl ether addition/suction cycles to obtain **5a–d**; **8** or **9**.

4.2.2.1. 5-(2-Piperidin-1-yl-ethyl)-phenanthridinium bromide (5a). Product **5a** was obtained as a pale yellow powder in a 71% yield; mp: 167–168 °C (dec); ^{1}H NMR (D_2O, 400 MHz): δ 9.80 (s, 1H), 8.90 (d, 1H, J=7.2 Hz), 8.83 (d, 1H, J=8.4 Hz), 8.41 (d, 1H, J=8 Hz), 8.28 (m, 2H), 7.99 (m, 3H), 5.15 (t, 2H, J=7.2 Hz), 3.04 (t, 2H, J=7.2 Hz), 2.56 (m, 4H), 1.50 (m, 4H), 1.41 (m, 2H); ^{13}C NMR (D_2O, 100 MHz): δ 154.63 (CH), 147.71 (C), 138.61 (CH), 136.45 (C), 135.35 (C), 132.72 (CH), 132.47 (CH), 130.67 (CH), 126.56 (CH), 125.11 (CH), 123.83 (C), 123.04 (CH), 119.06 (CH), 56.40 (CH_2), 54.87 (CH_2), 54.18 (CH_2), 25.11 (CH_2), 23.42 (CH_2); IR (KBr, cm^{-1}): 3448 (s), 2923 (m), 2852 (w), 2794 (w), 2360 (w), 1628 (s), 1535 (w), 1506 (w), 1454 (m), 1352 (w), 1257 (w), 1161 (w), 1122 (w), 1036 (w), 769 (s); MS (FAB): 291.2 (M–Br) (100); 273.1 (4), 206.1 (7), 193 (7), 154 (92), 137 (60), 136 (60), 112.3 (45), 98.4 (16), 89.5 (11), 77.6 (5), 56.9 (2), 52 (2). Anal. Calcd for $C_{20}H_{23}N_2Br$: C, 64.69; H, 6.24; N, 7.54. Found: C, 64.17; H, 6.10; N, 7.58.

4.2.2.2. Piperazine diethyl-phenanthridinium bromide (5b). Product **5b** was obtained as a yellow powder in a 73% yield; mp: 260–261 °C (dec); ^{1}H NMR (D_2O, 400 MHz): δ 9.80 (s, 2H), δ 8.95 (d, 2H, J=8.0 Hz), δ 8.88 (d, 2H, J=8.0 Hz), δ 8.42 (d, 2H, J=8.0 Hz), δ 8.33 (d, 2H, J=8.0 Hz), δ 8.29 (t, 2H, J=8.0 Hz), δ 8.01 (m, 6H), δ 5.14 (t, 4H, J=6.8 Hz), δ 3.05 (t, 4H, J=6.8 Hz), δ 2.57 (s, 8H); ^{13}C NMR (D_2O, 100 MHz): δ 155.94 (CH), δ 138.46 (CH), δ 134.63 (C), δ 133.28 (CH), δ 133.07 (C), δ 132.41 (CH), δ 130.89 (CH), δ 130.54 (CH), δ 126.03 (C), δ 125.48 (CH), δ 123.66 (CH), δ 120.19 (CH), δ 55.43 (CH_2), δ 55.08 (CH_2), δ 52.95 (CH_2); IR (KBr, cm^{-1}): 3430.74 (s), 2923 (w), 2360 (w), 1626 (s), 1456 (m), 1261 (w), 1026 (w), 758 (w); MS (FAB): 498.4 (M–2Br) (60), 318.2 (30), 292.1 (50), 249.1 (80), 206.1 (70), 154.0 (100), 136.0 (80), 112.3 (35), 56.9 (30). Anal. Calcd for $C_{34}H_{34}N_4Br_2$: C, 62.01; H, 5.20; N, 8.51. Found: C, 62.30; H, 5.45; N, 8.51.

4.2.2.3. Triazacyclododecane triethyl phenanthridinium bromide (5c). Product **5c** was obtained as a yellow-orange powder in a 93% yield; ^{1}H NMR (CD_3OD, 400 MHz): δ 9.93 (s, 3H), 8.99 (t, 6H, J=8.8 Hz), 8.45 (d, 3H, J=8.0 Hz), 8.42 (d, 3H, J=6.8 Hz), 8.30 (t, 3H, J=7.6 Hz), 8.00 (m, 6H), 7.85 (t, 3H, J=7.6 Hz), 5.02 (m, 6H), 2.57 (m, 6H), 1.41 (m, 12H), 0.05 (m, 6H); ^{13}C NMR (CD_3OD, 100 MHz): δ 156.53 (CH), 140.11 (CH), 136.93 (C), 135.00 (C), 134.23 (CH), 133.95 (CH), 132.28 (CH), 132.19 (CH), 128.13 (C), 126.71 (CH), 125.14 (C), 124.85 (CH), 121.43 (CH), 57.57 (CH_2), 53.34 (CH_2), 49.39 (CH_2), 23.25 (CH_2); IR (KBr, cm^{-1}): 3430.74 (s), 2923 (w), 2360 (w), 1626 (s), 1456 (m), 1261 (w), 1026 (w), 758 (w); MS (FAB): 498.4 (M–2Br) (60), 318.2 (30), 292.1 (50), 249.1 (80), 206.1 (70), 154.0 (100), 136.0 (80), 112.3 (35), 56.9 (30). Anal. Calcd for $C_{54}H_{57}N_6Br_3$: C, 62.98; H, 5.58; Br, 23.28; N, 8.16. Found: C, 63.08; H, 4.51; N, 8.10.

4.2.2.4. 5-{2-[(4-Methoxy-phenyl)-methyl-amino]-ethyl}phenanthridinium bromide (5d). Product **5d** was obtained as brown powder in a 77% yield; mp: 66–67 °C; ^{1}H NMR (D_2O, 400 MHz): δ 9.42 (s, 1H), δ 8.71 (d, 1H, J=7.6 Hz), δ 8.58 (d, 1H, J=7.6 Hz), δ 8.34 (d, 1H, J=7.6 Hz), δ 8.13 (t, 1H, J=7.6 Hz), δ 8.03 (m, 2H), δ 7.95 (t, 1H, J=7.6 Hz), δ 7.82 (t, 1H, J=7.6 Hz), δ 6.10 (d, 2H, J=8.8 Hz), δ 5.89 (d, 2H, J=8.8 Hz), δ 5.17 (m, 2H), δ 3.97 (m, 2H), δ 3.20 (s, 3H), δ 2.87 (s, 3H); ^{13}C NMR (D_2O, 100 MHz): δ 155.16 (CH), δ 151.02 (C), δ 142.00 (C), δ 138.21 (CH), δ 134.85 (C), δ 132.31 (CH), δ 132.11 (C), δ 130.45 (CH), δ 129.94 (CH), δ 126.11 (C), δ 124.61 (CH), δ 122.92 (C), δ 122.29 (CH), δ 119.07 (CH), δ 115.46 (CH), δ 113.90 (CH), δ 55.59 (CH_2), δ 55.09 (CH_3), δ 50.00 (CH_2), δ 37.59 (CH_3); MS (FAB): 342.2 (M–Br) (100), 327.2 (10), 218.1 (5), 206.1 (13), 164.1 (75), 133.1 (30), 120.2 (4). Anal. Calcd for $C_{23}H_{23}BrN_2O$: C, 65.25; H, 5.48; N, 6.62. Found: C, 65.28; H, 5.60; N, 6.58.

4.2.2.5. 1-(2-Piperidin-1-yl-ethyl)-quinolinium bromide (8). Product **8** was obtained as a brown powder in an 80% yield; mp: 220–221 °C (dec); ^{1}H NMR (D_2O, 400 MHz): δ 9.20 (d, 1H, J=7.6 Hz), 9.06 (d, 1H, J=8.4 Hz), 8.32 (t, 2H, J=7.6 Hz), 8.20 (t, 1H, J=8.2 Hz), 7.97 (d, 1H, J=8.2 Hz), 7.94 (d, 1H, J=8.4 Hz), 5.14 (t, 2H, J=7.4 Hz), 3.03 (t, 2H, J=7.4 Hz), 2.58 (m, 4H), 1.53 (m, 4H), 1.41 (m, 2H); ^{13}C NMR (D_2O, 100 MHz): δ 149.40 (CH), 148.57 (CH), 138.42 (C), 136.55 (CH), 131.37 (CH), 130.69 (C), 130.45 (CH), 122.03 (CH), 118.17 (CH), 56.57 (CH_2), 54.57 (CH_2), 54.14 (CH_2), 25.04 (CH_2), 23.39 (CH_2); IR (KBr, cm^{-1}): 3448 (s), 2923 (m), 2852 (w), 2794 (w), 2360 (w), 1628 (s), 1535 (w), 1506 (w), 1454 (m), 1352 (w), 1257 (w), 1161 (w), 1122 (w), 1036 (w), 769 (s); MS (FAB): 241.1 (M–Br) (100), 156 (73), 140 (15), 112.3 (33). Anal. Calcd for $C_{16}H_{21}N_2Br$: C, 59.82; H, 6.59; N, 8.72. Found: C, 59.70; H, 6.62; N, 8.70.

4.2.2.6. 5-[2-(4-Methoxy-benzylsulfanyl)-ethyl]phenanthridinium bromide (9). Product **9** was obtained as a pale yellow powder in a 76% yield; mp: 182–183 °C (dec);

^{1}H NMR (CD_3OD, 400 MHz): δ 9.91 (s, 1H), δ 9.08 (t, 2H, J=8.0 Hz), δ 8.85 (d, 1H, J=8.0 Hz), δ 8.47 (t, 1H, J=8.0 Hz), δ 8.37 (m, 1H), δ 8.15 (t, 1H, J=8.0 Hz), δ 8.11 (m, 2H), δ 6.80 (d, 2H, J=8.8 Hz), δ 6.33 (d, 2H, J=8.8 Hz), δ 5.17 (t, 2H, J=6.0 Hz), δ 4.90 (t, 2H, J=6.0 Hz), δ 3.69 (s, 3H), δ 3.56 (s, 2H); ^{13}C NMR (CD_3OD, 100 MHz): δ 161.8 (C), δ 156.84 (C), δ 140.00 (CH), δ 137.21 (C), δ 134.41 (CH), δ 133.77 (CH), δ 132.07 (CH), δ 131.96 (CH), δ 131.31 (C), δ 130.96 (CH), δ 128.00 (C), δ 126.72 (CH), δ 125.21 (CH), δ 124.74 (CH), δ 120.76 (CH), δ 114.96 (CH), δ 58.90 (CH_2), δ 55.92 (CH_3), δ 36.97 (CH_2), δ 31.70 (CH_2); IR (KBr, cm^{-1}): 3435 (s), 1626 (s), 1533 (w), 1510 (s), 1450 (m), 1304 (w), 1248 (s), 1174 (w), 1030 (s), 829 (s), 764 (s); MS (FAB): 360.0 (M–Br) (70), 309.0 (20), 290.0 (15), 238.0 (5), 206.0 (10), 179 (7), 155.0 (100), 136.0 (50), 121.1 (50), 108.2 (20), 89.5 (12). Anal. Calcd for $C_{23}H_{22}$-NOSBr: C, 62.72; H, 5.03; N, 3.18. Found: C, 62.72; H, 5.01; N, 3.78.

4.2.3. 2-Fluoroethyl-phenanthridinium bromide ($\mathbf{1_F}$). 2-Fluoroethyltosylate was prepared: 2-Fluoroethanol (1 g; 15.6 mmol) dissolved in dry pyridine (15 mL) under nitrogen. The solution was stirred at 0 °C and *p*-toluene sulfonyl chloride (6.5 g; 34.1 mmol) was added slowly to the solution over a period of 30 min, keeping the temperature below 5 °C. The solution was then stirred at 0 °C for another 4 h before quenching by slow addition of ice (15 g) then water (20 mL). Ethyl acetate (50 mL) was added, the organic layer separated and washed with water. Excess pyridine was removed by washing the organic layer with a 1 M HCl solution until the aqueous layer became acidic. The excess tosyl chloride was removed by washing the organic layer with an aqueous solution of Na_2CO_3 (pH$\approx$10). The organic layer was then washed with brine, dried over $MgSO_4$ and concentrated under vacuum to obtain 2-fluoroethyltosylate (3.29 g; 15 mmol) as an oil in a 96% yield; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81 (d, 2H, J=8.0 Hz), 7.38 (d, 2H, J=8.0 Hz), 4.65 (t, 1H, J=4.2 Hz), 4.53 (t, 1H, J=4.2 Hz), 4.32 (t, 1H, J=4.2 Hz), 4.25 (t, 1H, J=4.2 Hz), 2.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.53 (C), 133.05 (C), 130.32 (CH), 128.37 (CH), 81.78 (CH_2), 80.06 (CH_2), 68.91 (CH_2), 68.70 (CH_2), 22.05 (CH_3); MS (EI): 218.2 (M+1) (50), 185.2 (8), 155.1 (100), 139.1 (5), 107.1 (8), 91.1 (100), 65.1 (30), 63.1 (10). Phenanthridine (690 mg; 3.84 mmol) was added to a solution of 2-fluoroethyltosylate (1.68 g; 7.68 mmol) in DMF (10 mL) and stirred at 100 °C for 48 h. The solution was then concentrated to a brown oil and precipitated by addition of acetone (10 mL) followed by diethyl ether (60 mL). The precipitate was recovered by filtration, washed with diethyl ether and dried under vacuum to obtain the tosylate salt of $\mathbf{1_F}$ (1.52 g; 3.84 mmol) as an off white powder in a quantitative yield. Finally, the tosylate salt was passed through an anionic exchange column (Dowex 1X-850) preloaded with a saturated NaBr solution and flushed with distilled water. The compound was eluted with distilled water. The resulting aqueous solution was washed twice with ethyl acetate before being concentrated under vacuum to obtain $\mathbf{1_F}$ (1.12 g; 3.68 mmol) as a pale yellow powder in a 96% yield; mp: 239–240 °C (dec); ^{1}H NMR (D_2O, 400 MHz): δ 9.80 (s, 1H), 8.79 (d, 1H, J=8.0 Hz), 8.71 (d, 1H, J=8.0 Hz), 8.36 (d, 1H, J=8.0 Hz), 8.29 (d, 1H, J=8.4 Hz), 8.21 (t, 1H, J=7.2 Hz), 8.01 (t, 1H, J=7.2 Hz), 7.94 (m, 2H), 5.40 (t, 1H, J=4.4 Hz), 5.33 (t, 1H, J=4.4 Hz), 5.12 (t, 1H, J=4.4 Hz), 5.00 (t, 1H, J=4.4 Hz); ^{13}C NMR (D_2O, 100 MHz): δ 155.22 (CH), 138.89 (CH), 135.09 (C), 133.08 (C), 132.96 (CH), 132.60 (CH), 130.85 (CH), 130.70 (CH), 126.20 (C), 124.88 (CH), 123.37 (C), 122.79 (CH), 119.18 (CH), 82.08 (CH_2), 80.39 (CH_2), 58.17 (CH_2), 57.98 (CH_2); IR (KBr, cm^{-1}): 3404 (m), 1534 (m), 1460 (m), 1447 (m), 1371 (m), 1265 (s), 1165 (s), 1048 (s), 1031 (s), 764 (s), 718 (m); MS (FAB): 226.2 (M–Br) (100), 199.2 (10), 180.1 (25), 101.4 (20); MS (FAB): 226.2 (M–Br) (100), 199.2 (10), 180.1 (25), 101.4 (20). Anal. Calcd for $C_{15}H_{13}BrFN$: C, 58.84; H, 4.28; N, 4.57. Found: C, 59.00; H, 4.23; N, 4.45.

4.2.4. 2-Hydroxyethyl-phenanthridinium bromide ($\mathbf{1_{OH}}$). Phenanthridine (2 g; 11.17 mmol) was added to a solution of 2-bromoethanol (3.2 mL; 44.8 mmol). The reaction mixture was refluxed for 4 h under N_2. After cooling, crystallisation was aided by the addition of ether. After 2 h, the crystals were recovered by filtration and washed with ether to produce $\mathbf{1_{OH}}$ (3.10 g; 10.13 mmol) as a beige powder in a 90% yield; mp: 239–240 °C (dec); ^{1}H NMR (D_2O, 400 MHz): δ 9.71 (s, 1H), 8.81 (d, 1H, J=8.0 Hz), 8.74 (d, 1H, J=8.0 Hz), 8.37 (d, 1H, J=8.0 Hz), 3.32 (d, 1H, J=8.0 Hz), 8.22 (t, 1H, J=8.0 Hz), 7.97 (m, 3H), 5.11 (t, 2H, J=5.0 Hz), 4.14 (t, 2H, J=5.0 Hz); ^{13}C NMR (D_2O, 100 MHz): δ 156.71 (CH), 140.70 (CH), 136.62 (C), 134.88 (CH), 134.68 (CH), 132.81 (CH), 127.93 (C), 126.75 (C), 125.09 (C), 124.65 (CH), 121.33 (CH), 62.31 (CH_2), 61.19 (CH_2); IR (KBr, cm^{-1}): 3232 (s), 1624 (s), 1581 (w), 1535 (m), 1446 (s), 1423 (m), 1346 (m), 1261 (s), 1157 (s), 1084 (s), 1033 (s), 899 (s), 867 (m), 756 (s), 717 (s), 609 (s); MS (ES): 224.1 (M–Br) (100), 222.1 (25), 210.1 (10), 206.1 (40), 194.1 (8), 193.1 (18), 182.1 (10), 181.1 (80), 180.1 (100). Anal. Calcd for $C_{15}H_{14}BrNO$: C, 59.23; H, 4.64; N, 4.60. Found: C, 59.10; H, 4.73; N, 4.52.

4.2.5. 5-(2-Fluoroethyl)-6-piperidin-1-yl-5,6-dihydrophenanthridine ($\mathbf{3_F}$). In an NMR tube, $\mathbf{1_F}$ (10 mg; 0.032 mmol) was dissolved in D_2O (0.6 mL). $CDCl_3$ (0.6 mL) was added followed by 2 equiv of piperidine (6.30 μL; 5.4 mg; 0.064 mmol) used both as a reactant and as a base. The NMR tube was energetically shaken for 1 min to allow the phase transfer process to occur. A ^{1}H and ^{13}C NMR spectrum as well as an MS of the bottom organic layer was taken, characterising $\mathbf{3_F}$; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (d, 1H, J=8.0 Hz), 7.76 (d, 1H, J=8.0 Hz), 7.31 (t, 1H, J=7.2 Hz), 7.22 (t, 1H, J=7.2 Hz), 7.15 (t, 1H, J=8.0 Hz), 7.05 (d, 1H, J=8.0 Hz), 6.75 (t, 2H, J=7.2 Hz), 4.97 (s, 1H), 4.75 (m, 1H), 4.60 (m, 1H), 3.90 (m, 1H), 3.80 (m, 1H), 2.20 (m, 4H), 1.30 (m, 4H), 1.15 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.35 (C), 139.72 (C), 131.65 (C), 129.14 (CH), 127.21 (CH), 126.35 (CH), 123.76 (CH), 123.26 (CH), 122.44 (CH), 121.70 (CH), 120.51 (C), 111.16 (CH), 83.47 (CH), 82.70 (CH_2), 82.19 (CH_2), 81.03 (CH_2), 80.51 (CH_2), 50.06 (CH_2), 48.63 (CH_2), 26.29 (CH_2); MS (EI+): 311.37 (M+1) (3), 292.38 (M–F) (4), 241.2 (15), 226.3 (100), 195.2 (20), 179.2 (40), 152.2 (15), 84 (100).

4.2.6. 2-(6-Piperidin-1-yl-6*H*-phenanthridin-5-yl)-ethanol ($\mathbf{3_{OH}}$). In an NMR tube, $\mathbf{1_{OH}}$ (10 mg; 0.033 mmol) was dissolved in D_2O (0.6 mL). $CDCl_3$ (0.6 mL) was added

followed by 2 equiv of piperidine (6.50 μL; 0.066 mmol) used both as a reactant and as a base. The NMR tube was energetically shaken for 1 min to allow the phase transfer process to occur. A ^{1}H and ^{13}C NMR spectrum as well as an MS of the bottom organic layer was taken, characterising $\mathbf{3}_{OH}$; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85 (d, 1H, J=7.6 Hz), 7.81 (dd, 1H, J=7.6, 1.2 Hz), 7.37 (dt, 1H, J=7.6, 1.2 Hz), 7.26 (dt, 1H, J=7.6, 1.6 Hz), 7.16 (dt, 1H, J=7.6, 1.6 Hz), 7.02 (d, 1H, J=7.6 Hz), 6.77 (dt, 1H, J=7.6, 1.2 Hz), 6.68 (d, 1H, J=7.6 Hz), 4.84 (s, 1H), 4.17 (dd, 1H, J=15.6, 2.0 Hz), 4.01 (t, 1H, J=11.2 Hz), 3.60 (d, 1H, J=11.2 Hz), 3.31 (ddd, 1H, J=15.6, 11.2, 2 Hz), 2.25 (m, 4H), 1.45 (m, 4H), 1.18 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.14 (C), 131.73 (C), 129.20 (CH), 128.23 (CH), 127.69 (CH), 126.21 (CH), 125.30 (C), 123.14 (CH), 122.13 (CH), 119.63 (C), 117.16 (CH), 111.27 (CH), 80.35 (CH), 59.28 (CH_2), 57.54 (CH_2), 48.10 (CH_2), 25.01 (CH_2), 23.87 (CH_2); MS (CI+): 307.41 (M–1) (2), 281.39 (4), 240.29 (1), 226.30 (2), 224.29 (2), 196.25 (1), 180.22 (3), 103.2 (10), 86.2 (100), 52.1 (35).

4.2.7. UV spectroscopy determination of the substitution reaction intermediate(s) 6-(2-bromoethyl)-5-(2-piperidin-1-yl-ethyl)-5,6-dihydro-phenanthridine (3) and/or piperidinium-1,2,3,12*b*-tetrahydro-imidazo[1,2-*f*]phenanthridine bromide (4). Starting material **1** (37 mg; 0.1 mmol) was dissolved in 100 mL water. Ten millilitre aliquot was diluted by 10 to obtain a 0.1 mM stock solution. One millilitre of the stock solution was transferred to a UV cell and the UV spectrum of the starting material **1** measured between 200 and 500 nm. Two λ_{max} can be observed at 320 and 361 nm. At 320 nm, the absorption of the starting material **1** was recorded every 40 s, and after 1 h, piperidine (10 μL; 0.01 μmol) added. UV absorption measurements were carried on for 12 h, characterizing the slow transformation of the intermediate(s) into the final material **3a**. After this reaction time, a UV scan was also undertaken between 200 and 500 nm, characterizing the final product **3a** without intermediate. Subsequently, using the same reaction conditions, a UV spectrum of the intermediate was measured after 30 min reaction time between 200 and 500 nm and compared with the UV spectrum of both the starting material **1** and the final material **3a**.

4.2.8. U-tube experiment: formation of 5-[2-(4-methoxybenzylsulfanyl)-ethyl] phenanthridinium bromide (9) via a necessary organic soluble intermediate. In a U-tube, containing a layer of CCl_4 (1 mL) with 10 mg of $MgSO_4$, was added a layer of H_2O (1 mL) in one harm and a layer of D_2O (1 mL) in the other harm. In the H_2O compartment, was added starting material **1** (12.6 mg; 0.034 mmol) followed by *p*-methoxybenzyl mercaptan (4.7 μL; 0.03 mmol) and triethylamine (4.7 μL; 0.04 mmol). A white precipitate appears instantaneously in the H_2O compartment. The phase transfer was assisted by gently stirring the inter-phase with the tip of a Pasteur pipette before sealing the two extremity of the U-tube with parafilm. The underneath organic layer was gently stirred with a small magnet for 48 h, taking care not to contaminate the D_2O compartment with H_2O. The D_2O layer was analyzed by ^{1}H NMR spectroscopy and final molecule **9** was cleanly characterized, along with some triethylamine.

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Generation of *ortho*-quinone methides upon thermal extrusion of sulfur dioxide from benzosultones

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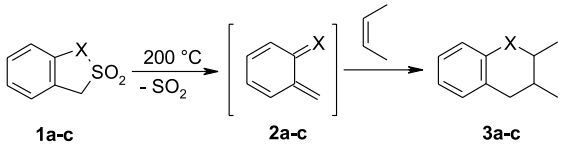
Abstract—3*H*-1,2-Benzoxathiole 2,2-dioxides (benzosultones) undergo thermal extrusion of sulfur dioxide to form *ortho*-quinone methides that enter Diels–Alder reaction with maleimides to form chroman 2,3-dicarboxylic acid derivatives.

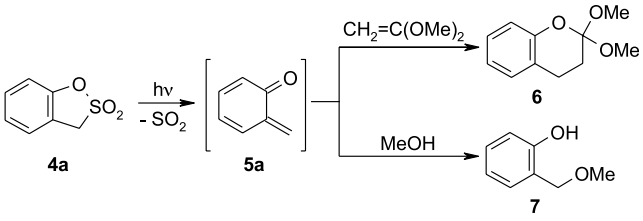
1. Introduction

Thermal extrusion of sulfur dioxide from 1,3-dihydrobenzo[c]thiophene 2,2-dioxides (**1a**) and 1,3-dihydro-2,1-benzisothiazole 2,2-dioxides (benzosultams, **1b**) is a well established method for the generation of the corresponding quinodimethanes (*ortho*-xylylenes, **2a**)[1] and quinonemethyleneimines (aza-*ortho*-xylylenes, **2b**).[2] These reactive intermediates enter Diels–Alder reactions leading to tetrahydronaphthalenes (**3a**) and 1,2,3,4-tetrahydroquinolines (**3b**), respectively (Scheme 1). There is also one report concerning the synthesis of thiochromans (**3c**) via addition of thioquinone methide (**2c**) generated via thermal extrusion of SO_2 from 1,2-benzodithiole 2,2-dioxide (**1c**).[3]



Scheme 1.

In the only report dealing with an application of the analogous oxygen derivative **4a**, namely the sultone of 2-hydroxytoluene-α-sulfonic acid, as a precursor of *o*-quinone methide **5a**, extrusion of SO_2 upon photochemical irradiation has been described.[4] The intermediate **5a** was trapped in a [4+2] cycloaddition with 1,1-dimethoxyethene leading to 2,2-dimethoxychroman (**6**) (Scheme 2). Such decomposition in methanol led to *o*-hydroxybenzyl methyl ether (**7**) formed via addition of a nucleophile to intermediate **5a**. However, no experimental details of these reactions were given.



Scheme 2.

The chemistry of *ortho*-quinone methides has been recently reviewed by Van De Water and Pettus.[5] These reactive intermediates play an important role in numerous biological processes.[6] Thermal reactions were used for the generation of *o*-quinone methides from such heterocycles as chromans,[7,8] 4*H*-1,3-benzodioxins,[9] 1,2-benzoxazines.[10] Thermal extrusion of SO_2 from 4,4-bis(trifluoromethyl)-4*H*-benzo-1,3,2-dioxathiin 2-oxide leading to the corresponding quinone methide has also been described.[11]

2. Results and discussion

In the present study we report our results on the thermal extrusion of sulfur dioxide from 3*H*-1,2-benzoxathiole 2,2-dioxides (benzosultones, **4**). Benzosultones can be easily obtained from 2-hydroxytoluene-α-sulfonic acid upon treatment with phosphorus oxychloride.[12]

Keywords: *o*-Quinone methide; Diels–Alder; Cycloaddition; Cheletropic extrusion; Chroman.
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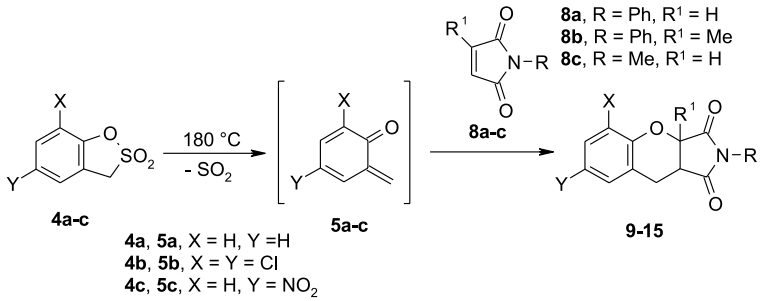

Scheme 3.

Table 1

Product	X	Y	R	R^1	Yield (%)
9	H	H	Ph	H	37
10	H	H	Ph	Me	32
11	H	H	Me	H	64
12	Cl	Cl	Ph	H	58
13	Cl	Cl	Ph	Me	32
14	H	NO_2	Ph	H	41
15	H	NO_2	Ph	Me	40

Heating of benzosultone **4a** with *N*-phenylmaleimide (NPMI, **8a**) (1:1 mixture) in boiling 1,2-dichlorobenzene (180 °C) led to the formation of a mixture of products. MS analysis of the crude reaction mixture revealed the presence of products with molecular mass corresponding to dimers and trimers of methylene quinone, as well as the expected [4+2] cycloadduct **9**. Using a two- or three-fold excess of the NPMI, the amount of these by-products was diminished and the cycloadduct **9** was formed in 37% yield. The reactions of benzosultones **4b** and **4c** proceeded in a similar way (Scheme 3, Table 1).

In reactions of quinonemethides **5** with 2-methyl-*N*-phenylmaleimide (**8b**) two regioisomeric products can be formed (Fig. 1). GC–MS analysis of the crude reaction mixture revealed the formation of only one product with a molecular mass corresponding to the expected cycloaddition product. The structure of these adducts was deduced from the ^{1}H NMR spectra. The spectra of compounds **10**, **13**, and **15** revealed the presence of an ABX system corresponding to 3a-methyl substituted derivatives. The alternative structures **16** would show an AB system of protons at C-9 and a singlet of hydrogen at C-3a position.

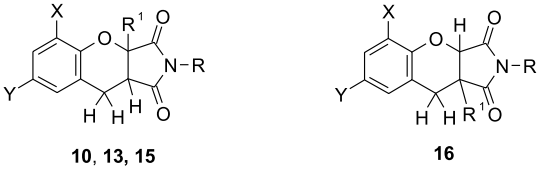

Figure 1.

Attempts to trap the generated quinone methides **5a–c** with other dienophiles were unsuccessful. When the sultones **4** were thermolysed in the presence of dimethyl maleate and fumarate, and 2,3-dimethyl-*N*-phenylmaleimide, GC–MS analysis showed only trace amounts of chromane-2,3-dicarboxylates or the corresponding imide, but their isolation proved impossible. Similarly, in the reaction with 2-phenoxyethyl vinyl ether, an electron rich alkene, no cycloaddition product was formed. In all of these instances large amounts of dimers and trimers of *o*-quinone methide were formed.

In summary, we describe a novel method for the synthesis of practically unknown chroman-2,3-dicarboxylic acid derivatives. The synthesis was performed under neutral conditions. In the only known report[13] chroman-2,3-dicarboxylates were obtained via addition of dimethyl fumarate to *ortho*-quinone methides generated by a thermal elimination of water from 2-hydroxybenzyl alcohols.

3. Experimental

3.1. General remarks

Melting points are uncorrected. ^{1}H and ^{13}C NMR and spectra were obtained with Varian Mercury 400 BB instrument with TMS as internal standard. Coupling constants *J* are given in Hz. IR were obtained using a Perkin–Elmer 2000 FTIR instrument. Mass spectra (electron impact, 70 eV) were obtained on AMD 604 (AMD Intectra GmbH, Germany) instrument. HRMS were measured in the presence of perfluorokerosene as the reference compound. Column chromatography was performed using silica gel 240–400 mesh (Merck).

3.2. Starting materials

Starting benzosultones **4a** and **4b** were obtained from the corresponding 2-hydroxybenzyl alcohols following the known procedure.[12]

3.2.1. 3*H*-1,2-Benzoxathiole 2,2-dioxide (4a). Colorless crystals. Mp 86–88 °C (lit.,[14] mp 86–87 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.50 (s, 2H), 7.10 (d, J=8.2 Hz, 1H),

7.20 (dd, $J=8.2$, 7.6 Hz, 1H), 7.33 (d, $J=7.4$ Hz, 1H), 7.40 (dd, $J=7.6$, 7.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.2, 112.5, 119.3, 124.7, 125.8, 130.4, 151.0. IR (KBr, cm^{-1}) ν: 2999, 2945, 1477, 1463, 1364, 1213. MS (*m*/*z*, %): 170 (M^+, 88), 106 (69), 78 (100).

3.2.2. 5,7-Dichloro-3*H*-1,2-benzoxathiole 2,2-dioxide (4b). Colorless crystals. Mp 139–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.56 (s, 2H), 7.24 (d, $J=1.4$ Hz, 1H), 7.43 (d, $J=1.4$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.0, 119.3, 120.2, 121.5, 124.1, 130.8, 146.2. IR (KBr, cm^{-1}) ν: 3091, 2995, 2943, 1585, 1459, 1400, 1368, 1209, 1163. MS (*m*/*z*, %): 238 (M^+, 46), 174 (100), 146 (38), 111 (38), 75 (24). HRMS calcd for $C_7H_4O_3S^{35}Cl_2$: 237.9258. Found 237.9262. Elemental analysis calcd for $C_7H_4SO_3Cl_2$ (239.07): C, 35.17; H, 1.69. Found: C, 35.18; H, 1.93.

3.2.3. 5-Nitro-3*H*-1,2-benzoxathiole 2,2-dioxide (4c). To the solution of benzosultone (**4a**, 0.85 g, 5 mmol) in concentrated sulfuric acid (10 mL) sodium nitrate (0.43 g, 5 mmol) was added in one portion at 5–10 °C. The reaction mixture was stirred for 15 min at room temperature and then poured into ice. The solid was separated, washed with water, dissolved in dichloromethane and dried with $MgSO_4$. After evaporation of the solvent product was recrystallized from hexane–ethyl acetate (2:1).

Yield 0.86 g (80%). Colorless crystals. Mp 144–146 °C. (Lit.,[14] mp 148–150 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.64 (s, 2H), 7.26–7.30 (m, 1H); 8.31–8.37 (m, 2H). ^{13}C NMR (100 MHz): δ 50.0, 113.2, 120.4, 122.0, 126.7, 144.3, 154.8. IR (KBr, cm^{-1}): ν 3114, 2947, 1593, 1531, 1475, 1380, 1342, 1210. MS (*m*/*z*, %): 215 (M^+, 44), 151 (100), 135 (4), 121 (2), 93 (7), 79 (10), 74 (2), 65 (7).

3.3. Cycloaddition of *ortho*-quinonemethides (general procedure)

Benzosultone **4a–c** (1 mmol) and maleimide **8a–c** (3 mmol) were refluxed in 1,2-dichlorobenzene (5 mL) for 2 h. After cooling, the reaction mixture was subjected to column chromatography. The solvent was eluted with hexane–ethyl acetate (50:1) and then the product was eluted with hexane–ethyl acetate (5:1). The following compounds were obtained.

3.3.1. 2-Phenyl-9,9a-dihydro-3a*H*-chromeno[2,3-*c*]pyrrole-1,3-dione (9). Colorless crystals. Mp 147–149 °C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$]: δ 3.04 (dd, $J=15.1$, 4.8 Hz, 1H), 3.07 (dd, $J=15.1$, 7.0 Hz, 1H), 3.77 (ddd, $J=8.7$, 7.0, 4.8 Hz, 1H), 5.29 (d, $J=8.7$ Hz, 1H), 6.95–7.05 (m, 4H), 7.20–7.24 (m, 2H), 7.31–7.50 (m, 3H). ^{13}C NMR [100 MHz, $(CD_3)_2SO$]: δ 24.3, 41.3, 73.9, 117.6, 123.1, 125.4, 126.6, 128.2, 128.5, 128.6, 129.0, 131.6, 153.4, 173.2, 176.5. IR (KBr, cm^{-1}): ν 3042, 1721, 1708, 1585, 1486, 1405, 1228, 1201. MS (*m*/*z*, %): 279 (M^+, 100), 251 (5), 186 (14), 160 (26), 159 (12), 132 (35), 131 (83), 103 (6), 93 (41), 77 (11). HRMS calcd for $C_{17}H_{13}NO_3$: 279.0895. Found: 279.0896. Elemental analysis calcd for $C_{17}H_{13}NO_3$ (279.30): C, 73.11; H, 4.69; N, 5.02. Found: C, 72.99; H, 4.90; N, 4.97.

3.3.2. 3a-Methyl-2-phenyl-9,9a-dihydro-3a*H*-chromeno-[2,3-*c*]pyrrole-1,3-dione (10). Colorless crystals. Mp 137–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.85 (s, 3H), 3.09 (dd, $J=14.8$, 6,7 Hz, 1H), 3.22 (dd, $J=14.8$, 2.8 Hz, 1H), 3.32 (dd, $J=6.7$, 2.8 Hz, 1H); 6.95–7.42 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.7, 25.3, 48.1, 79.3, 118.3, 123.6, 124.4, 126.2, 128.4, 128.7, 128.8, 129.1, 131.2, 153.61, 175.2, 175.4. IR (KBr, cm^{-1}): ν 2965, 1717, 1595, 1494, 1485, 1396, 1234. MS (*m*/*z*, %): 293 (M^+, 66), 265 (4), 201 (11), 200 (28), 187 (18), 174 (50), 173 (14), 172 (13), 146 (24), 144 (11), 107 (15), 93 (8), 91 (26), 77 (27), 63 (13). HRMS calcd for $C_{18}H_{15}NO_3$: 293.1052. Found: 293.1052. Elemental analysis calcd for $C_{18}H_{15}NO_3$ (293.32): C, 73.71; H, 5.15; N, 4.78. Found: C, 72.92; H, 5.55; N, 4.77.

3.3.3. 2-Methyl-9,9a-dihydro-3a*H*-chromeno[2,3-*c*]pyrrole-1,3-dione (11). Colorless crystals. Mp 97–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.93 (s, 3H); 3.02 (dd; $J=15.0$, 4.7 Hz, 1H), 3.09 (dd, $J=15.0$, 4.9 Hz, 1H), 3.47 (ddd; $J=8.7$, 4.7, 4.9 Hz, 1H), 5.05 (d, $J=8.7$ Hz, 1H), 6.99 (dd, $J=8.4$, 7.3 Hz, 1H), 7.03 (d, $J=8.4$ Hz, 1H), 7.12 (d, $J=7.2$ Hz, 1H), 7.20 (dd, $J=7.3$, 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.7, 25.0, 41.7, 73.5, 118.2, 123.6, 124.5, 128.5, 128.7, 153.5, 173.9, 176.8. IR (KBr, cm^{-1}) ν: 2959, 1702, 1484, 1435, 1384, 1343, 1322, 1284, 1225. MS (*m*/*z*, %): 217 (M^+, 56), 200 (5), 199 (2), 189 (2), 186 (23), 160 (32), 132 (30), 131 (100), 111 (6), 91 (2), 77 (24). HRMS calcd for $C_{12}H_{11}NO_3$: 217.0739. Found 217.0761. Elemental analysis calcd for $C_{12}H_{11}NO_3$ (217.22): C, 66.34; H, 5.11; N, 6.45. Found: C, 66.40; H, 5.24; N 6.24.

3.3.4. 5,7-Dichloro-2-phenyl-9,9a-dihydro-3a*H*-chromeno[2,3-*c*]pyrrole-1,3-dione (12). Colorless crystals. Mp 212–214 °C. ^{1}H NMR [400 MHz, $(CD_3)_2CO$]: δ 3.19–3.24 (m, 2H), 3.91 (ddd, $J=8.7$, 6.3, 5.6 Hz, 1H), 5.48 (d, $J=8.7$ Hz, 1H), 7.14–7.17 (m, 2H), 7.29–7.33 (m, 1H), 7.39–7.48 (m, 4H). ^{13}C NMR [100 MHz, $(CD_3)_2CO$]: δ 25.3, 41.9, 75.7, 124.4, 127.4, 128.0, 128.2, 129.0, 129.4, 129.7, 129.9, 132.9, 149.5, 172.8, 176.3. IR (KBr, cm^{-1}) ν: 3062, 1718, 1598, 1462, 1401, 1185. MS (*m*/*z*, %): 351 (11, $M^+ +4$), 349 (64, $M^+ +2$), (100, M^+), 329 (3), 319 (3), 257 (5), 255 (7), 230 (17), 228 (26), 202 (30), 201 (49), 200 (49), 199 (68), 173 (14), 165 (18), 136 (7), 93 (86). HRMS calcd for $C_{17}H_{11}NO_3^{35}Cl_2$: 347.0116. Found: 347.0118. Elemental analysis calcd for $C_{17}H_{11}NO_3Cl_2$ (348.19): C, 58.64; H, 3.19; N, 4.02. Found: C, 58.82; H, 3.42; N, 4.04.

3.3.5. 5,7-Dichloro-3a-methyl-2-phenyl-9,9a-dihydro-3a*H*-chromeno[2,3-*c*]pyrrole-1,3-dione (13). Colorless crystals. Mp 144–146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.90 (s, 3H), 3.05 (dd, $J=15.0$, 6.7 Hz, 1H), 3.25 (dd, $J=15.0$, 3.1 Hz, 1H), 3.34 (dd, $J=6.7$, 3,1 Hz, 1H), 7.04–7.09 (m, 3H), 7.29 (d, $J=2.2$ Hz, 1H), 7.34–7.45 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 25.2, 47.3, 80.2, 124.4, 126.0, 126.2, 127.3, 128.4, 128.9, 129.0, 129.2, 130.9, 148.1, 174.0, 174.4. IR (KBr, cm^{-1}): ν 3063, 2963, 1716, 1575, 1501, 1461, 1390, 1225. MS (*m*/*z*, %): 361 (M^+, 100), 344 (4), 269 (6), 268 (13), 242 (23), 241 (6), 240 (4), 214 (13), 212 (2), 187 (61), 174 (2), 159 (3), 149 (2), 143 (7), 119 (4), 115 (6), 93 (37), 77 (5). HRMS calcd for $C_{18}H_{13}NO_3^{35}Cl_2$: 361.0272. Found: 361.0270. Elemental analysis calcd for $C_{18}H_{13}NO_3Cl_2$ (362.21): C, 59.69; H, 3.62; N, 3.87. Found: C, 59.80; H, 3.77; N, 3.88.

3.3.6. 7-Nitro-2-phenyl-9,9a-dihydro-3a*H*-chromeno[2,3-*c*]pyrrole-1,3-dione (14). Colorless crystals. Mp 139–141 °C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$]: δ 3.20 (dd, J=15.5, 5.8 Hz, 1H), 3.24 (dd, J=15.5, 7.3 Hz, 1H), 3.80 (ddd, J=8.5, 7.3, 5.8 Hz, 1H), 5.43 (d, J=8.5 Hz, 1H), 7.16–7.23 (m, 2H); 7.29–7.35 (m, 1H); 7.34–7.51 (m, 5H). ^{13}C NMR [400 MHz, $(CD_3)_2SO$]: δ 23.4, 42.7, 74.2, 124.3, 128.7, 125.5, 126.8, 127.8, 128.9, 129.0, 131.5, 142.3, 170.0, 172.3, 175.7. IR (KBr, cm^{-1}): ν 3077, 1722, 1709, 1594, 1514, 1401, 1343, 1242, 1182. MS (*m*/*z*, %): 324 (M^+, 100), 306 (5), 294 (6), 279 (5), 232 (4), 205 (15), 177 (43), 176 (68), 160 (9), 130 (20), 119 (16), 77 (14). HRMS calcd for $C_{17}H_{12}N_2O_5$: 324.0746. Found: 324.0757.

3.3.7. 3a-Methyl-7-nitro-2-phenyl-9,9a-dihydro-3a*H*-chromeno[2,3-*c*]pyrrole-1,3-dione (15). Colorless crystals. Yield 40%. Mp 155–156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.88 (s, 3H), 3.14 (dd, J=7.3, 15.9 Hz, 1H), 3.40 (dd, J=3.0, 15.9 Hz, 1H), 3.45 (dd, J=3.0, 7.3 Hz, 1H), 7.04–7.13 (m, 3H), 7.32–7.45 (m, 3H), 8.09–8.15 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.7, 23.9, 46.4, 79.7, 118.7, 123.8, 124.6, 124.7, 126.0, 129.0, 129.2, 130.8, 143.2, 158.4, 173.7, 174.1. IR (KBr, cm^{-1}): ν 1704, 1485, 1436, 1284, 1225. MS (*m*/*z*, %): 338 (91, M^+), 321 (11), 308 (8), 293 (7), 245 (7), 219 (33), 191 (21), 190 (36), 176 (100), 144 (24), 130 (16), 121 (14), 93 (52). HRMS calcd for $C_{18}H_{14}N_2O_5$: 338.0903. Found: 338.0931. Elemental analysis calcd for $C_{18}H_{14}N_2O_5$ (338.32): C, 63.90; H, 4.17; N, 8.28. Found: C, 63.82; H, 4.14; N, 7.93.

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Electrophilic amination of enolates with oxaziridines: effects of oxaziridine structure and reaction conditions

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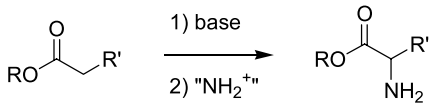
Abstract—A range of *N*-alkoxycarbonyl- and *N*-carboxamido-oxaziridines has been prepared to test the effects of oxaziridine structure on yields of enolate amination product. Side-products arising from reaction of aldehyde-derived oxaziridines with base were identified, while a ketone-derived oxaziridine afforded moderate yields of amination product with stabilised carbanions.

1. Introduction

The electrophilic amination of enolates provides a conceptually simple and powerful approach to α-amino carbonyl compounds, important structural motifs in many biologically significant molecules (Scheme 1).[1] A variety of useful reagents have been developed for this reaction, including haloamines, hydroxylamine derivatives, azides, nitroso compounds and azodicarboxylates.[1a] However, there are currently limitations or drawbacks to all of these reagents, as some (e.g., haloamines, hydroxylamine derivatives) give only moderate yields and have limited scope,[1a] whilst others (azides, nitroso compounds, azodicarboxylates) require additional synthetic manipulations of the initial product in order to obtain the desired α-amino carbonyl compound. Very few directly deliver nitrogen bearing a synthetically useful protecting group.[1a,c]



Scheme 1.

Oxaziridines are well known as electrophilic oxidising agents and in particular *N*-sulfonyl oxaziridines have been widely exploited for the oxidation of a variety of nucleophiles.[2] However, structural modification of the oxaziridine, most notably the nitrogen substituent, can result in useful reagents for the electrophilic amination of nucleophiles. Indeed a number of examples of oxaziridine-mediated enolate amination have been reported. The use of *N*–H oxaziridines in this reaction was first described by Schmitz[3] for a limited range of highly stabilised enolates. This chemistry was recently further developed by Page, who reported asymmetric amination of enolates using enantiopure camphoryl or fenchyl *N*–H oxaziridines.[4] Good yields and moderate stereoselectivity were obtained in some cases, but the reaction was rather substrate-specific. In addition, ester and nitrile units in the substrate were usually hydrolysed (and in some cases decarboxylated). Collet and co-workers have demonstrated that *N*-alkoxycarbonyl oxaziridines (e.g., **1**) can also be used to aminate enolates, although the yields were low due to competing aldol reaction with the aldehyde co-product (Scheme 2).[5] Asymmetric variants of this work have been published by Enders,[6] using enantiopure α-silylketones, and by our group, using *N*-menthyloxycarbonyl oxaziridine **2**, albeit with low to moderate levels of stereoselectivity.[7] In addition, preliminary results in our group indicated that the aldol side reaction could be minimised by incorporation of an *ortho*-cyano group on the aromatic 3-substituent of *N*-carboxamido-oxaziridines **3**.[8]

In view of the extremely high synthetic value of the enolate amination process, we considered that attempts to improve the reaction yields by variation of oxaziridine structure and the reaction conditions would be a very worthwhile endeavour. In this paper, we report our efforts in this area,

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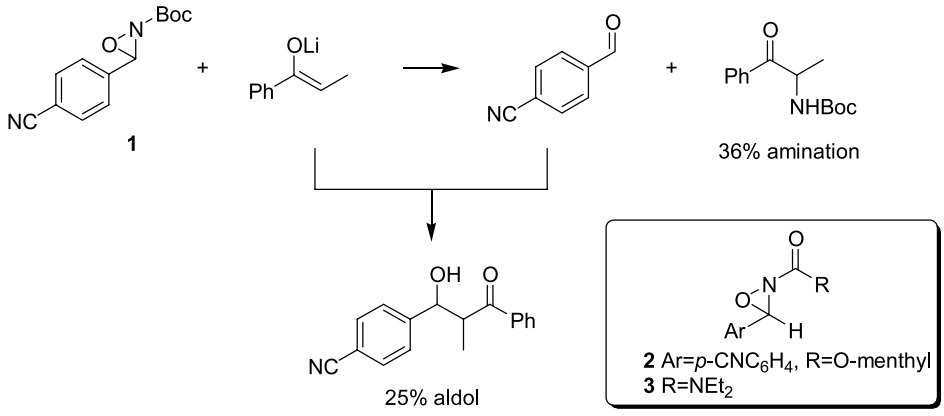


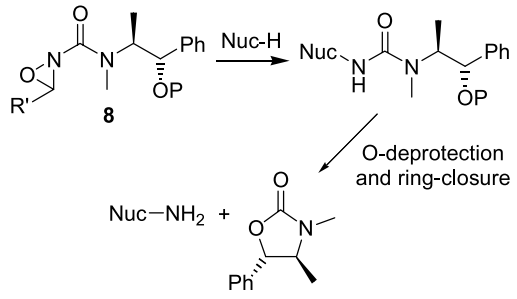
Scheme 2.

including the synthesis of several novel *N*-alkoxycarbonyl- and *N*-carboxamido-oxaziridines for this purpose.

2. Results and discussion

2.1. Oxaziridine synthesis

Our aforementioned earlier work had indicated that structural modification of the oxaziridine offered a means to improve the efficiency of amination. In order to probe these effects more deeply, a range of reagents **3**–**8** (Fig. 1) was synthesised, based on the *N*-alkoxycarbonyl- and *N*-carboxamido-oxaziridines **1** and **3**. The *o*-cyanophenyl substituted oxaziridine **3b** was of particular interest for further study as it had shown promise for reducing the amount of aldol side reaction,[8] and the *p*-chlorophenyl analogue **3a** was prepared for comparison purposes. A separate study had shown that the 3,3-disubstituted oxaziridine **4** was a highly efficient reagent for amination of sulfides,[9] and it was anticipated that it may also prove useful for amination of enolates. The ultimate aim of this research was to develop reagent-controlled asymmetric amination, and although the ester groups of oxaziridine **4** provide a useful handle for introduction of chirality, chiral analogues of this reagent would be likely to give low stereoselectivity as the ring carbon is not a stereocentre. Other non-identically 3,3-disubstituted oxaziridines **5** and **6**, and a mono-ester substituted oxaziridine **7**, were therefore targeted. In addition, a pseudoephedrine-derived oxaziridine **8** was synthesised in an attempt to address the main drawback of *N*-carboxamido-oxaziridines, namely that the aminated products contain a urea linkage that is potentially difficult to cleave. It was proposed that this auxiliary might enable cleavage of the urea via intramolecular nucleophilic attack of the hydroxyl group (Scheme 3). This auxiliary would also allow further investigation of asymmetric enolate amination. It was envisaged that the poor stereoinduction obtained with menthyloxycarbonyl oxaziridine **2**[7] could be improved by using enantiopure *N*-carboxamido-oxaziridines such as **8**, due to increased conformational restriction about the *N*-carbonyl bond relative to the *O*-carbonyl bond in **2**.



Scheme 3.

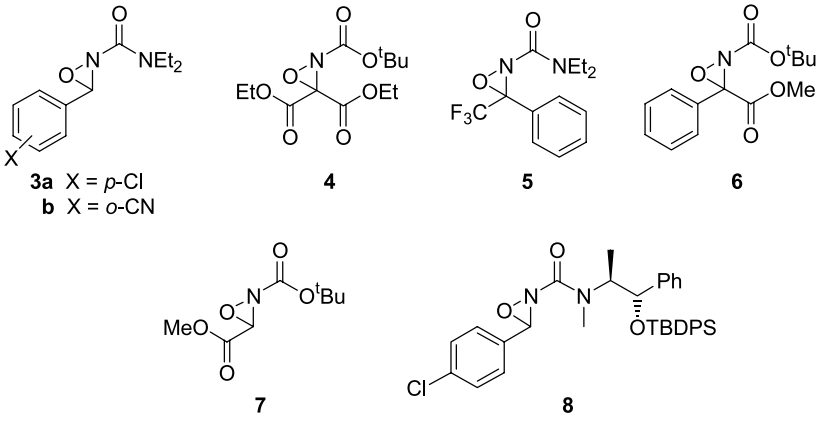
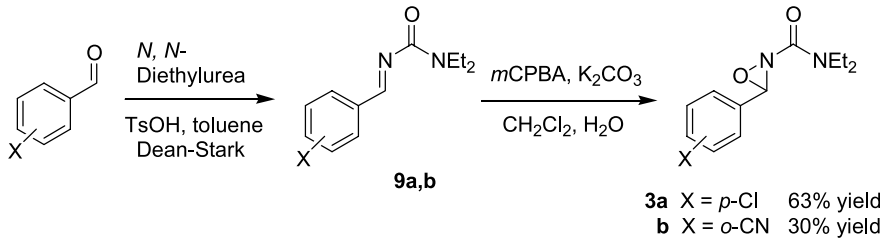


Figure 1.

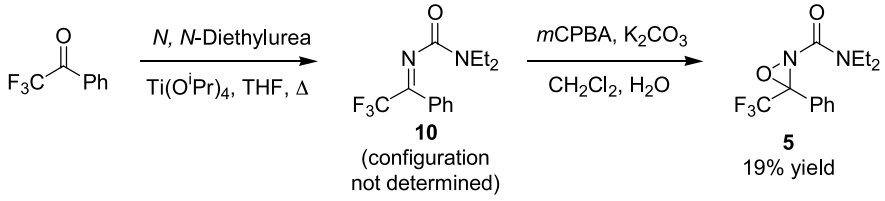


Scheme 4.

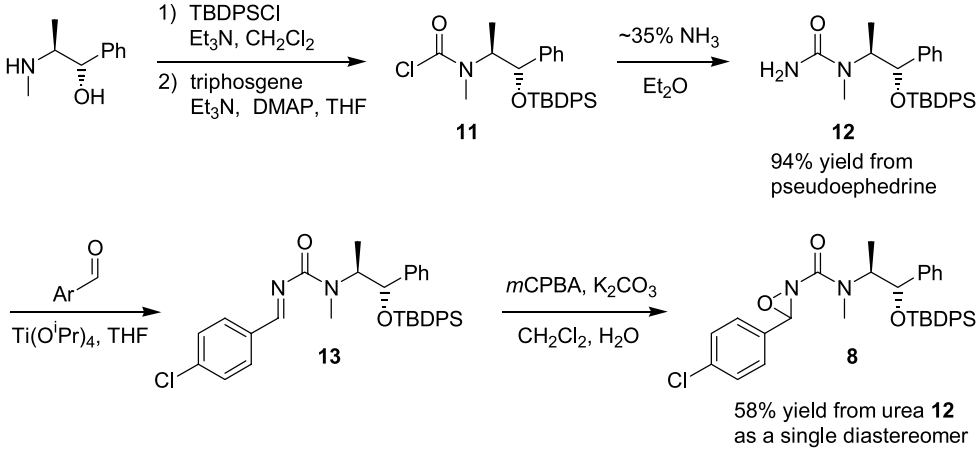
Synthesis of the requisite *N*-carboxamido-oxaziridines **3** was achieved by direct condensation of the appropriate urea and carbonyl compound, followed by oxidation of the resulting imines **9** (Scheme 4). For the imine oxidation, we preferred to use *m*CPBA/K_2CO_3 rather than the experimentally less convenient *m*CPBA/BuLi protocol employed in our preliminary work.[8] The TsOH-catalysed condensation failed to provide other *N*-carboxamido-imines **10** and **13**, required for synthesis of oxaziridines **5** and **8**, respectively, but a milder approach utilising titanium (IV) isopropoxide as a Lewis acid catalyst and water scavenger proved successful (Schemes 5 and 6). This procedure had previously only been reported for in situ formation of imines, as part of a reductive amination.[10]

The ketomalonate-derived oxaziridine **4** was prepared according to the published procedure,[9] involving an aza-Wittig imine synthesis. This approach is suitable for many *N*-alkoxycarbonylimines, but for unstable compounds the high temperatures required can prove too harsh. An alternative approach, involving elimination from an α-bromo amine, has been reported for a variety of unstable imines,[11] and is attractive as the reaction can be carried out at low temperature and the imine purified by simple filtration to remove $Et_3N{\cdot}HBr$. This procedure is particularly suitable for making α-carbonyl imines, such as **16** and **18**, as these can then be derived from readily available and inexpensive amino acid derivatives (Schemes 7 and 8). The bromide **15** required for synthesis of methyl glycinate-derived oxaziridine **7** was prepared from glycine derivative **14** (Scheme 7). Subsequent elimination with triethylamine was achieved at low temperature and the cold crude imine **16** rapidly transferred and filtered via cannula and sinter into a pre-prepared *m*CPBA/*n*-BuLi solution. The yield of oxaziridine **7** was extremely low, presumably due to the inefficiency of the transfer/filtration procedure, which allowed the sensitive imine to warm considerably above −78 °C. Some attempts were made to improve the yield of this route, but this was hindered due to the bromide and imine intermediates being unstable (the imine in particular could not be detected at room temperature). It was envisaged that a one-pot elimination–oxidation might be possible, with the basic conditions required for oxidation potentially also carrying out the elimination. However treatment of the bromide **15** with 2.5 equiv of *m*CPBA/*n*-BuLi solution failed to deliver any oxaziridine. Other attempts including the use of anhydrous K_2CO_3 with subsequent addition of *m*CPBA were also unsuccessful.

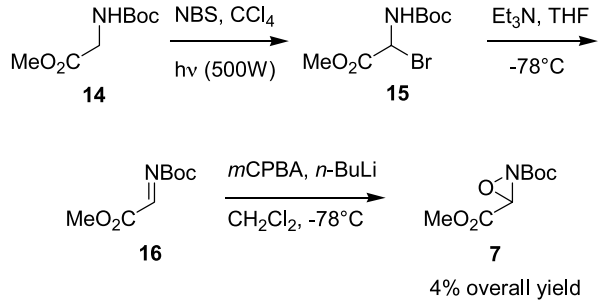
The same approach was utilised for synthesis of the methyl phenylglycinate-derived oxaziridine **6** (Scheme 8). In this



Scheme 5.



Scheme 6.



Scheme 7.

case the imine **18** proved to be significantly more stable and could be purified by silica chromatography. In fact the imine was formed directly from *N*-BOC methyl phenylglycinate **17** in the bromination reaction. The reaction afforded a 5:3 mixture of imine and starting material, with approximately quantitative yield based on recovered starting material, and although no attempts were made to optimise this reaction it is likely that the yield could be improved by extension of the reaction time and/or addition of extra NBS. Oxidation using the simple *m*CPBA/K_2CO_3 procedure afforded the oxaziridine **6** in high yield.

2.2. Structural information

N-Alkoxycarbonyl and *N*-carboxamido-oxaziridines having two different ring carbon substituents exist as equilibrium mixtures of cis and trans isomers, which can interconvert by inversion at nitrogen (e.g., $\Delta G^{\ddagger} = 18.3$ kcal mol^{-1} for oxaziridine **1**).[5] This process is slow on the NMR timescale, such that distinct signals can be observed for the two isomers. The cis–trans ratio depends on the relative steric influence of the two carbon substituents, and if there is a large difference in size the oxaziridine can exist exclusively in the trans form. In these cases, the nitrogen atom is in effect thermodynamically configurationally stable, with its configuration directly determined by that of the ring carbon stereocentre. This is clearly of significance when attempting asymmetric amination using chiral oxaziridines.

The cis–trans ratios of oxaziridines **3**–**8** are shown in Table 1. Clearly oxaziridine **4** can only exist as one isomer, but oxaziridines **3a** and **3b** are also observed in almost exclusively one isomeric form (presumably trans) in solution. A single stereoisomer was also observed in the ^{1}H and ^{19}F NMR spectra of oxaziridine **5**. X-ray crystallography showed the carboxamido and trifluoromethyl groups *trans* to each other (Fig. 2), and this is presumably also the form present in solution. In contrast, mixtures of isomers were observed for oxaziridines **6** and (surprisingly) **7** with the major isomer presumably as shown. The ^{1}H NMR spectrum of pseudoephedrine-derived oxaziridine **8** also showed two sets of resonances in a 2:1 ratio (in $CDCl_3$), but for this reagent there are three potential causes of the isomerism: invertomers (cis–trans isomers), rotamers (about the exocyclic nitrogen–carbonyl bond) and diastereomers (two possible configurations of the ring carbon). Comparison with the other aldehyde-derived *N*-carboxamido-oxaziridines (>98:2 ratio) suggests that the observed 2:1 ratio is unlikely to be caused by invertomers. Diastereomers were also ruled out as the isomeric ratio was found to be dependent on solvent, changing to a 1:1 ratio in toluene-d_6. This therefore indicated that the isomerism was due to rotamers, and that the oxaziridine **8** was formed as a single diastereomer, the relative configuration of which was not assigned.

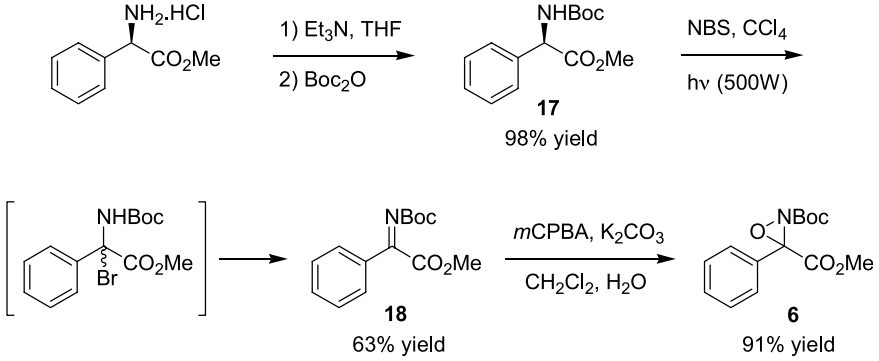
Table 1. cis–trans isomerism of oxaziridines

Entry	Oxaziridine	trans:cis[a]
1	**3a**	>98:2
2	**3b**	>98:2
3	**4**	—
4	**5**	>98:2
5	**6**	71:29
6	**7**	69:31
7	**8**	>98:2

[a] Ratio determined by integration of peaks in the ^{1}H NMR spectrum.

2.3. Amination of *t*-butyl acetate

With several oxaziridines in hand, we were particularly interested in investigating their use in amination of ester enolates, since this would lead to a direct synthesis of protected amino acids. Preliminary results had suggested that the *o*-cyanophenyl substituted oxaziridine **3b** could virtually eliminate formation of the aldol product on amination of *t*-butyl acetate.[8] Thus addition of **3b** to the enolate derived from *t*-butyl acetate and LDA at −78 °C, followed by gradual warming to room temperature prior to quenching and work-up was reported to afford 55% yield of α-amino ester **19** and only 7% yield of aldol product **20b**. However, in further investigations we found difficulty in obtaining such high yields of **19**, and discovered that the nature of the aqueous work-up for this reaction was crucial:



Scheme 8.

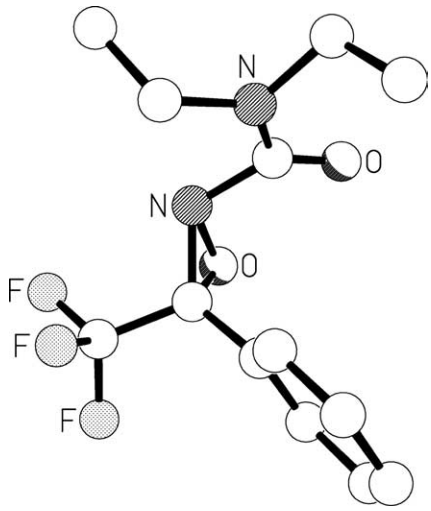
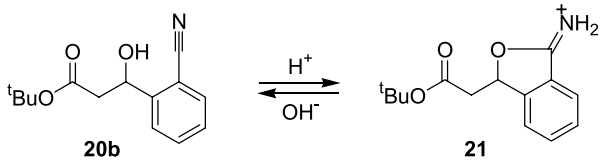


Figure 2. X-ray crystal structure of oxaziridine **5**.

the observed amount of aldol product was low only when an aqueous acid work-up was used. When the reaction was repeated and the acid wash omitted from the work-up procedure, a 1:1 ratio of α-amino ester **19** and aldol product **20b** was observed in the ^{1}H NMR spectrum of the crude product and 33% isolated yield of α-amino ester **19** was obtained (Scheme 9). This was comparable to the result obtained with the *p*-chlorophenyl substituted oxaziridine **3a**, which produced a 4:3 ratio of α-amino ester **19** and aldol product **20a**, with 24% yield of the α-amino ester **19**. Therefore, the *ortho*-cyano substituent in **3b** does not appear significantly to affect the ratio of **19**:**20** in the amination reaction.

Further study of the reaction involving oxaziridine **3b** indicated that the aldol product **20b** had been extracted into the acidic aqueous layer during work-up of the original experiment, and that this compound could in fact be recovered by basifying the aqueous layer with saturated aqueous $NaHCO_3$ (to pH∼8), followed by extraction with dichloromethane. A possible explanation for the acid-mediated removal of the aldol product **20b** could involve reversible formation of a cyclic imino ether **21** via intramolecular nucleophilic attack of the hydroxyl group on the *ortho*-cyano substituent (Scheme 10). This compound is likely to be sufficiently basic to be protonated by 1 M HCl, causing it to be washed into the aqueous layer (pK_a values:[12] HCl = −2.2; PhC(OH)(=NH_2^+) = −2.0). On neutralisation this could undergo the reverse reaction,



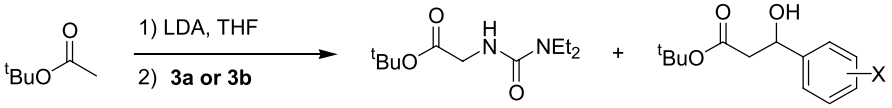
20b **21**

Scheme 10.

regenerating **20b**. When the corresponding *p*-cyanobenzaldehyde aldol product (prepared from the reaction of the enolate of *tert*-butyl acetate with *p*-cyanobenzaldehyde) was subjected to the same work-up procedure, no washing out was observed, supporting involvement of this intramolecular interaction of the hydroxyl and *ortho*-cyano groups.

It therefore appears that the *ortho*-substituent actually has little or no effect in preventing the aldol reaction, although it may be useful in allowing easy separation of the amination and aldol products. In order to further probe the effect of oxaziridine substituents on the yield of amination product, other oxaziridines were also tested with the enolate derived from *t*-butylacetate and LDA. These proved even less successful than **3**. Thus, 3-phenyltrifluoromethyloxaziridine **5** (11% **19** along with significant amounts of iminoaldol product and unreacted **5** in the ^{1}H NMR spectrum of the crude mixture) gave lower yields than **3**, while 3-alkoxycarbonyl oxaziridines **6** and **7** gave no observable amination product. Yields were also low with ketomalonate-derived oxaziridine **4**.

In view of the disappointing lack of improvement on changing the oxaziridine, we decided to focus on modification of the reaction conditions. The *p*-chlorophenyl substituted oxaziridine **3a**, which could be synthesised in high yield from inexpensive starting materials, was selected for further study (Table 2). Use of LiHMDS as base gave a very similar result to the above reaction using LDA. A∼1:1 crude ratio of amination and aldol products (**19** and **20a**) was formed, with 22% yield of amination (entry 2). Switching to NaHMDS had a significant effect on the reaction (entries 3–5). With 1 equiv of oxaziridine very little amination was observed (entry 3), but 2 equiv gave 30% yield of α-amino ester **19** with very little aldol product **20a** detectable (entry 4). Use of 3 equiv of oxaziridine had no extra benefit, again giving 30% yield of amination product (entry 5). Potassium and magnesium counterions did not have the same effect. Use of KHMDS with 2 equiv of oxaziridine **3a** afforded a 1:1 ratio of amination and aldol

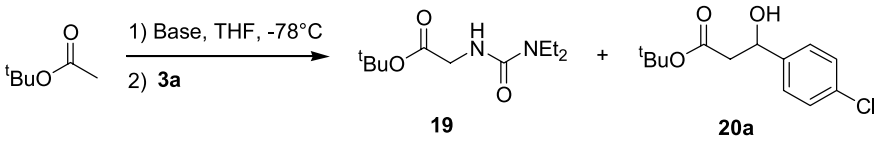


19 **20a** X = *p*-Cl
b X = *o*-CN

Oxaziridine **3a** -> ~4:3 **19** : **20a**; 24% yield **19**.
Oxaziridine **3b** -> ~1:1 **19** : **20b**; 33% yield **19**.

Scheme 9.

Table 2.



Entry	Base[a]	**19**/**20a**[b]	Yield of **19**[c] (%)
1	LDA	4:3	24
2	LiHMDS	1:1	22
3	NaHMDS	—	<5
4	NaHMDS (2 equiv **3a**)	<5% **20a**	30
5	NaHMDS (3 equiv **3a**)	<5% **20a**	30
6	KHMDS (2 equiv **3a**)	1:1	n.d.
7	LDA/$MgBr_2$	1:1	11
8	^{t}BuLi	1:1	15

[a] Using 1 equiv of base, *t*-butyl acetate and oxaziridine **3a** unless otherwise stated.
[b] Approximate ratio measured by integration of the (C=O)CH_2 peaks in the ^{1}H NMR spectrum of the crude product.
[c] Yield based on *t*-butyl acetate.

products, but only in low yield (entry 6), and a similar result was observed for the magnesium enolate, formed by transmetallation of the lithium enolate with magnesium bromide (entry 7). The effect of using non-amide bases was also studied, but deprotonation with ^{t}BuLi produced the same 1:1 ratio of amination and aldol products, and in lower yield than LDA (entry 8). In addition to the results in Table 2, the use of sodium hydride, sodium *t*-butoxide and butylmagnesium diisopropylamide was studied, but these bases resulted in little or no observable amination product being formed.

The observation that NaHMDS gave only trace amounts of aldol product suggests that the mechanism may involve an intermediate hemiaminal **22** that is stabilised by the sodium counterion (Scheme 11). This explanation is analogous to that proposed for α-hydroxylation using *N*-sulfonyl oxaziridines, in which formation of the imino-aldol product could be minimised by using sodium or potassium counterions (Scheme 11).[13]

The reason that 2 equiv of oxaziridine were required in order to obtain any α-amino ester **19** when using NaHMDS was initially not clear. Presumably, the first equivalent of oxaziridine was consumed by side reactions and the second then underwent the amination reaction to some extent. A more detailed analysis of this reaction and its side products was carried out in order to clarify the process. This revealed that amide **23** was formed in ~19% yield based on oxaziridine, along with an imino-aldol product **24** which was detected in the crude mixture in a ~3:1 ratio of **19**:**24** based on integration of the (C=O)CH_2 peaks in the ^{1}H NMR spectrum (Fig. 3).

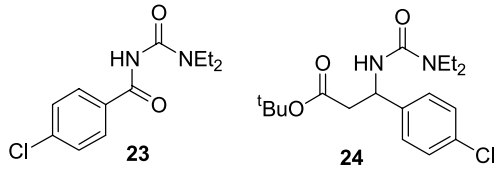
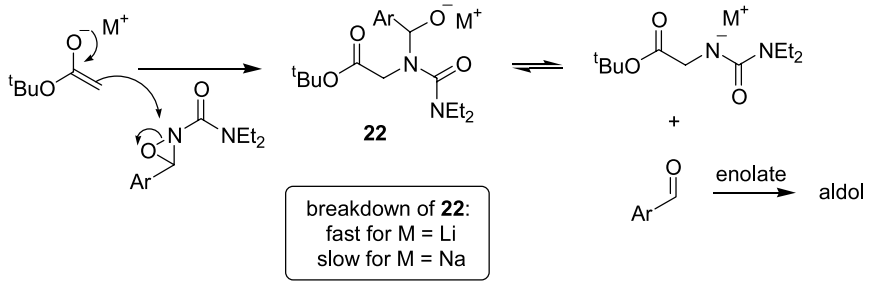
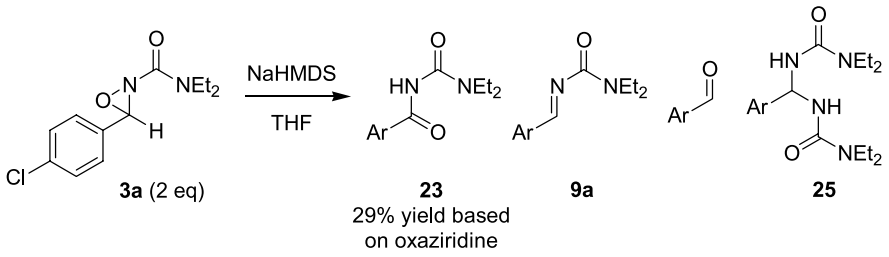


Figure 3.

It had previously been reported that ring deprotonation of oxaziridines could afford amide products[14] so the production of amide **23** in the amination reaction suggested that this process could be occurring here. This could have been carried out by the enolate, but also possibly by NaHMDS, which may have been present in the reaction mixture due to incomplete or reversible[15] deprotonation of the ester (pK_a of *t*-butyl acetate in DMSO=30.3; pK_a of HMDS in DMSO=30)[16]. In order to test this theory, direct reaction of oxaziridine **3a** and NaHMDS was carried out. Reaction of 3 equiv of oxaziridine with NaHMDS in THF at −78 °C demonstrated that approximately 2 equiv were consumed by the base to produce a mixture of amide **23**, imine **9a**, *p*-chlorobenzaldehyde and diaminal **25**. A preparative repeat of this reaction using 2 equiv of oxaziridine and



Scheme 11.



Scheme 12.

allowing the reaction to warm to room temperature before quenching, as in the amination procedure, afforded 29% yield of the amide **23** (Scheme 12). It is significant that oxaziridine **3a** reacts with NaHMDS at −78 °C, as no reaction of this oxaziridine with the enolate derived from *t*-butyl acetate and LDA was observed when the amination reaction was quenched at this temperature. This indicates that reaction of oxaziridine **3a** with NaHMDS is faster than with the enolate, and therefore if deprotonation of the ester is reversible, oxaziridine decomposition via reaction with NaHMDS is likely to be a significant problem. The presence of the imino-aldol side product **24** in the amination reaction indicated that imine **9a** must be formed in the reaction and therefore that there is some O-transfer occurring. However, no oxidation of the enolate was observed, so the most likely candidate for oxidation is the NaHMDS, which was indeed shown to produce imine on reaction with oxaziridine as described above.

In view of the potential problems of amide bases, amine-free methods were sought and an obvious candidate was Rathke's anion **26** (lithio *t*-butyl acetate). This could be synthesised according to the literature procedure[17] by deprotonation of *t*-butyl acetate with LDA in hexane, followed by evaporation of the solvent and diisopropylamine.

Reaction between this species and oxaziridine **3a** in dichloromethane (Scheme 13) afforded a 7:10:4 mixture of α-amino ester **19**, aldol **20a** and imino-aldol **24** products (~22% yield of α-amino ester **19**), along with small amounts of amide **23**. Performing the reaction in toluene, tetrahydrofuran, ether or acetonitrile resulted in less clean reactions, with a smaller proportion of α-amino ester **19** observable in the ^{1}H NMR spectra of the crude reaction mixtures. The use of Rathke's anion therefore offered no improvement over the original procedure.

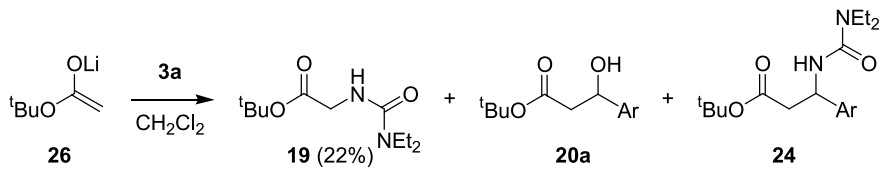
Some of the modified procedures described above were also carried out with the *ortho*-cyano substituted oxaziridine **3b**. Amination of *t*-butyl acetate using NaHMDS as base again afforded no observable aldol product **20b**, but in this case 33% yield of α-amino ester **19** was obtained using only 1 equiv of oxaziridine **3b**. The addition of a second equivalent of oxaziridine had little effect on the reaction, giving 31% yield of α-amino ester **19**. This could be accounted for by a change in the relative reactivity of the oxaziridine with NaHMDS and the enolate: if oxaziridine **3b** reacts with the enolate faster than its reaction with NaHMDS, this would remove the need for 2 equiv of oxaziridine. As stated previously, oxaziridine **3a** reacts with NaHMDS but not the enolate at −78 °C. In contrast, oxaziridine **3b** does react with the enolate derived from *t*-butyl acetate and LDA at −78 °C, as demonstrated by quenching the reaction at this temperature. Therefore, in the amination procedure using NaHMDS as base, at least some of oxaziridine **3b** can react with the enolate rather than NaHMDS at the initial reaction temperature (−78 °C).

Reaction of oxaziridine **3b** with Rathke's anion in dichloromethane gave a slightly improved reaction compared to the *p*-chloro analogue **3a**. The crude product contained an 11:8:5 mixture of α-amino ester **19**, aldol product **20b** and imino-aldol product **24b**, and ~30% yield of α-amino ester **19** was obtained.

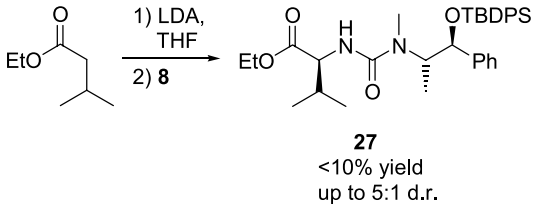
Overall, in spite of some promising results regarding prevention of the aldol reaction by use of NaHMDS, the efficiency of amination of *t*-butyl acetate could not be improved to any significant extent over that initially obtained using LDA. At this stage, it was decided to investigate whether other substrates might be aminated more successfully with these oxaziridines. The initial modification to the substrate simply involved examining amination of a propionate rather than an acetate. However, the reaction of ethyl propionate with oxaziridines **3a** or **3b** using LDA as base gave very low yields of amination (<10%), along with small amounts of tentatively identified imino-aldol and aldol products.

2.4. Attempted asymmetric amination of an ester enolate with 8 and subsequent cleavage of the pseudoephedrine auxiliary

Despite the low yields in amination of ester enolates, we decided to investigate the use of chiral oxaziridine **8**. If this



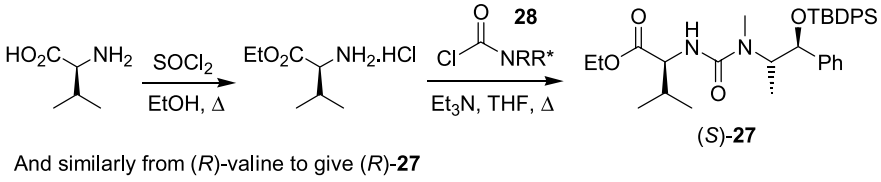
Scheme 13.



Scheme 14.

occurred with high levels of diastereocontrol, this would compensate for the low chemical yields thus far obtained. Ethyl isovalerate was chosen as the test substrate for asymmetric amination as this had given the best stereoselectivity in previous work with the *N*-menthyloxycarbonyl oxaziridine **2**.[7] However, initial reaction of the pseudoephedrine-derived oxaziridine **8** with this substrate was again low yielding (Scheme 14). Partial purification could be achieved by flash chromatography but the products could not be separated from closely running impurities. Comparison of ^{1}H NMR spectra and HPLC traces with those of authentic samples indicated a reasonable degree of selectivity towards formation of (*S*)-amino ester **27** (up to ~5:1), but the impurities prevented accurate quantification of the diastereoselectivity.

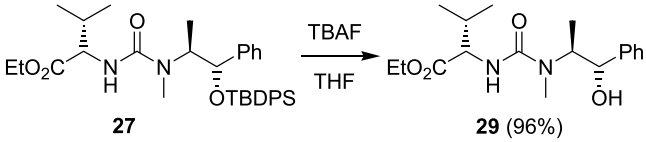
The authentic samples of both diastereomers of the amination product **27** were synthesised in two steps from (*S*)- and (*R*)-valine in 86 and 78% yield, respectively (Scheme 15). The products could be discriminated by HPLC and some analytically useful differences in the ^{1}H NMR spectra (NCH_3 and (C=O)C*H* peaks).



Scheme 15.

The reason for the low yield in this initial amination reaction was unclear, but it was thought that steric interactions between the bulky enolate and oxaziridine could potentially have been the cause. However, amination of the smaller ethyl propionate with pseudoephedrine-derived oxaziridine **8** again proceeded in low yield.

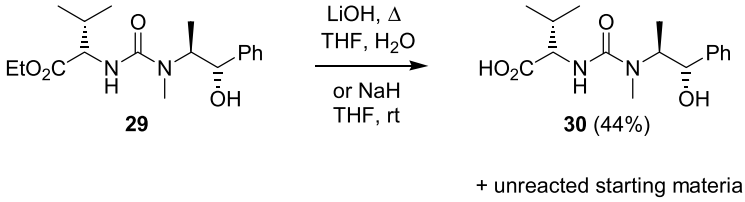
In spite of the poor results obtained on reaction of pseudoephedrine-derived oxaziridine **8** with enolates, study of the auxiliary cleavage in the aminated products **27** was still of interest. It was envisaged that this might be possible via an intramolecular cyclisation of the deprotected alcohol (cf. Scheme 3). The TBDPS protecting group was readily and quantitatively removed to give the free alcohol **29** using tetrabutylammonium fluoride (Scheme 16), but no spontaneous cyclisation was observed under the reaction conditions.



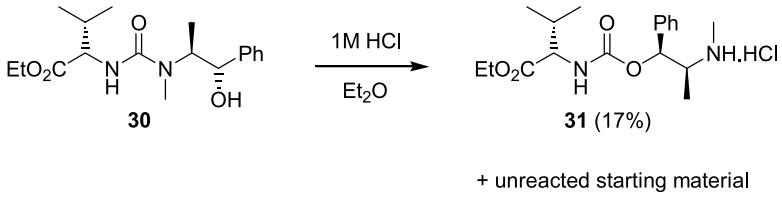
Scheme 16.

Many attempts were made to induce selective intramolecular cleavage of the urea in **29** without success. For instance, basic conditions led to hydrolysis of the amino ester function to afford **30** before any cleavage of the urea was observed (Scheme 17), and the use of Lewis acids ($NiCl_2$ in EtOH; $Ti(O^iPr)_4$ in THF) gave no reaction. Heating **29** in 1 M aqueous hydrochloric acid produced small amounts of the ring-closed oxazolidinone, although the desired amino ester could not be isolated and had presumably been hydrolysed to the amino acid. Interestingly, treatment of **30** with 1 M HCl in diethyl ether afforded small amounts of a rearranged carbamate product **31** along with unreacted starting material (Scheme 18). This structure was confirmed by X-ray crystallography (Fig. 4).

Formation of **31** might suggest that the desired nucleophilic attack of the hydroxyl group on the urea had occurred, but that the 'wrong' nitrogen had subsequently been eliminated. However, a study of the literature[18] revealed that the usual mechanism of urea hydrolysis actually proceeds via an isocyanate intermediate. For the unsymmetrical pseudoephedrine urea **29**, only one isocyanate intermediate can potentially form, as the pseudoephedrine nitrogen does not have the necessary proton for isocyanate formation in that direction (Scheme 19). The isocyanate could then be intercepted by the pseudoephedrine hydroxyl group to give the rearranged product, which precipitates out of the reaction mixture as its hydrochloride salt **31**.



Scheme 17.



Scheme 18.

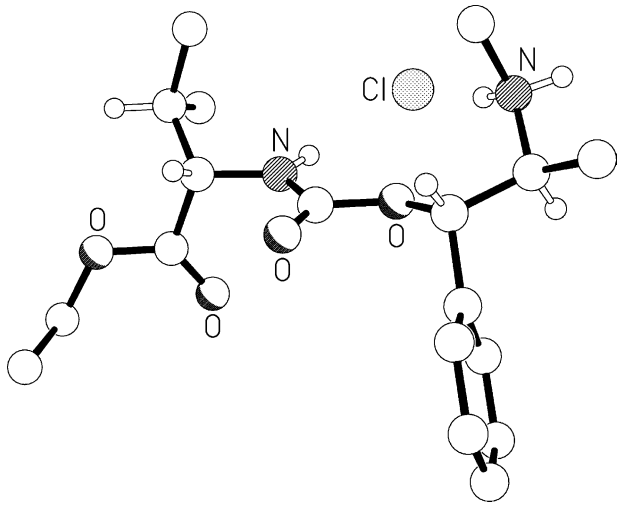


Figure 4. X-ray crystal structure of **31**.

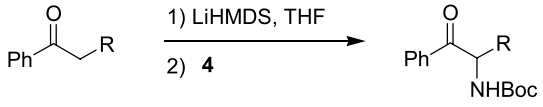
2.5. Amination of more acidic substrates

Because incomplete or reversible deprotonation had been identified as a key issue when using NaHMDS as base with esters, it was proposed that the use of more acidic substrates may improve the amination reaction. *i*-Propyl phenylacetate (pK_a of *t*-butyl phenylacetate in DMSO=23.6[16]) was selected first. Equimolar reaction of this substrate, NaHMDS and oxaziridine **3a** gave only trace amounts of amination product along with side products consistent with reaction of NaHMDS and the oxaziridine (including amide **23** and an imino-aldol product). Complete deprotonation of the substrate would have been expected prior to addition of the oxaziridine and this therefore suggests that the deprotonation may be reversible, with 'internal return' of the originally removed proton by the complexed HMDS occurring on addition of the oxaziridine.[15] The equilibrium is presumably pulled in this direction due to a more rapid reaction of the oxaziridine with NaHMDS than with the enolate.

Ketones are generally more acidic than their corresponding esters and so the amination of propiophenone (pK_a in DMSO=24.4)[16] was examined. However, no amination product could be isolated from the reaction of this substrate with oxaziridine **3a** using either LDA (1 equiv **3a**) or NaHMDS (2 equiv **3a**) as base. However, modest yields of amination product were obtained using the ketomalonate-derived oxaziridine **4** with this substrate class (Table 3).

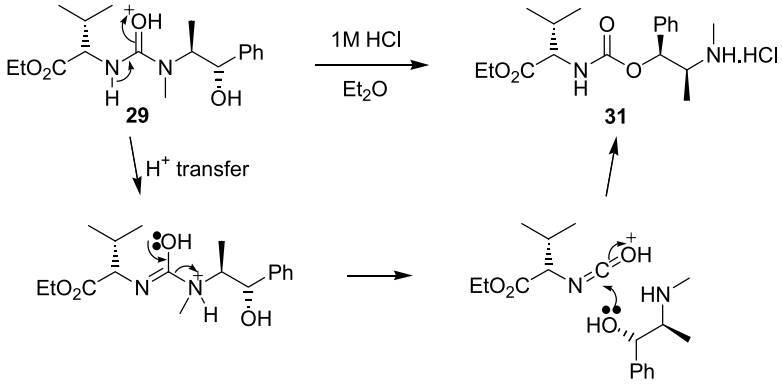
With this substrate class, the opportunity was also taken to examine the use of boron and titanium enolates. The boron enolate was prepared using Bu_2BOTf and DIPEA according to a literature procedure,[19] but gave no amination product on reaction with 1 equiv of oxaziridine **3a**. The titanium enolate, derived using $TiCl_4$ and Bu_3N,[20] again afforded no amination product but instead gave clean conversion to the α-chloro ketone **33** in 84% yield (Scheme 20). The full scope of this procedure was not determined, although deoxybenzoin could also be chlorinated efficiently (86% yield of α-chloro ketone **34**).

Table 3.

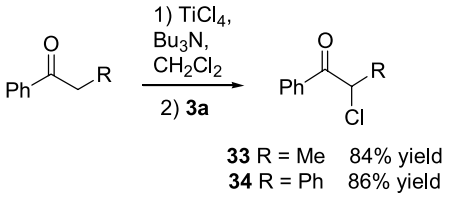


Entry		R	Yield of **32**[a] (%)
1	**a**	H	21
2	**b**	Me	31
3	**c**	Ph	15

[a] Using 1 equiv of LiHMDS, substrate and oxaziridine **4**.



Scheme 19.



Scheme 20.

A similar reaction had recently been reported for α-chlorination of silyl enol ethers, giving comparable yields for the above substrates (Scheme 21).[21] In this procedure the silyl enol ether had been treated with pyridine and $TiCl_2(O^iPr)_2$, followed by *t*-butyl hydroperoxide. It is likely that this reaction and the oxaziridine-mediated α-chlorination would proceed by analogous mechanisms, due to the similarity of the two processes, and two potential mechanisms had been proposed for the literature reaction (Scheme 21). The first involved oxidation of chloride to an electrophilic chlorine species, which then reacted with the silyl enol ether to give the product. The second proposal involved formation of a titanium enolate and reaction with *t*-butylhydroperoxide followed by attack of chloride anion.

An attempt to develop enantioselective chlorination using pseudoephedrine-derived oxaziridine **8** was unsuccessful, affording racemic α-chloro ketone **33** in low yield. Mechanistically this suggests involvement of an electrophilic chlorine species, as some enantioselectivity might be expected if the reaction proceeded via oxidation of the substrate by the oxaziridine.

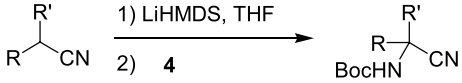
The Page group had achieved most success with their *N*–H oxaziridines when aminating nitrile stabilised carbanions.[4] However, attempted amination of ethyl phenyl cyanoacetate using oxaziridine **3a** and either LiHMDS or NaHMDS as base gave none of the desired product, instead affording ketoacetate **35** and cyano-imine adduct **36** (Scheme 22). These likely originate from oxidation of the enolate as shown, although no mechanistic studies were carried out. The reason for this apparent switch in chemoselectivity from the reaction with *t*-butyl acetate could be a combination of steric and electronic factors. As amination is sensitive to the size of substituents on the oxaziridine ring,[5] it might also be expected to be less favourable when using large nucleophiles such as trisubstituted enolates. In addition, the softer nature of this highly stabilised enolate may also favour the oxidation pathway. Collet had calculated[5] on a model oxaziridine that the nitrogen was almost neutral, whilst the oxygen had a partial negative charge of 0.26 e^-. Electrostatic repulsion between the anionic enolate and oxygen atom might therefore favour the amination pathway, but this effect would be less significant for softer nucleophiles. It is relevant to note that Collet's *N*-alkoxycarbonyl oxaziridines gave exclusive amination with hard enolates, but mixtures of amination and oxidation products on reaction with the softer sulfides, phosphines and amines, and exclusive oxidation on reaction with silyl enol ethers.[5]

In reactions of oxaziridines with sulfides, we have shown that the use of ketone-derived oxaziridines can favour transfer of nitrogen over oxygen.[9] We therefore tested the above nitrile substrate with the 3,3-disubstituted oxaziridine **4**. Pleasingly, this did prove more successful, with moderate yields obtained for range of nitriles with 1 equiv of oxaziridine **4** (Table 4). Additionally, we were able to aminate substituted malonate anions (Table 5), albeit in low yields. Simple unsubstituted malonates (dimethyl- or diethylmalonate) afforded impure products due to competing diamination. However, it is notable that, in contrast to the aminations of the same anions reported by Page using NH-oxaziridines, no hydrolysis/decarboxylation was observed. The use of 1.5 equiv of oxaziridine **4** had mixed results, increasing the yield of α-amino ester in some examples (up to 70% yield, e.g., Table 4, entry 6), but reducing the yield for others.

2.6. Reaction with silyl enol ethers

Given the problems encountered with the base-sensitivity of

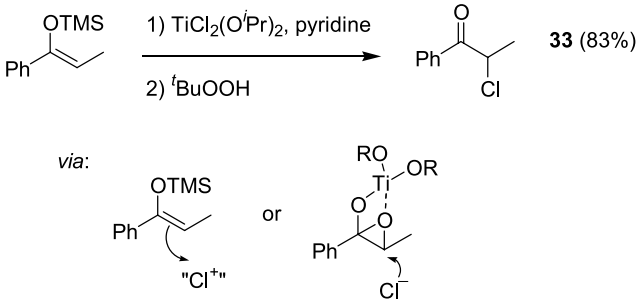
Table 4.



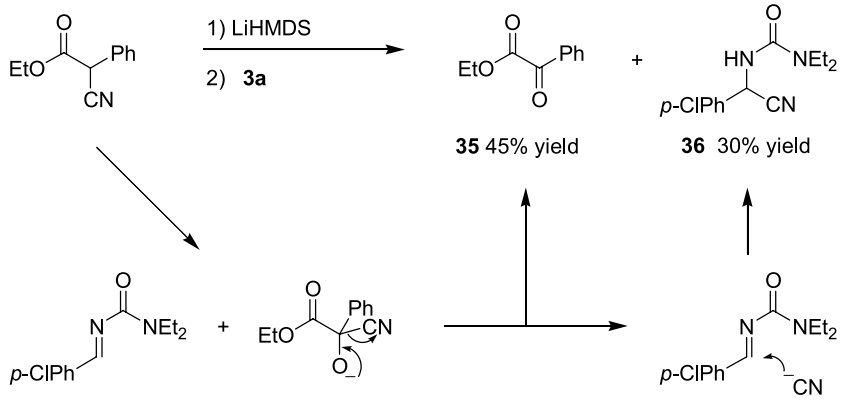
37

Entry		R	R′	Yield of **37**[a] (%)
1	**a**	C_6H_5	H	45
2	**b**	*p*-$MeOC_6H_4$	H	20
3	**c**	*p*-ClC_6H_4	H	46
4	**d**	EtO_2C	H	33
5	**e**	$^tBuO_2C$	H	20
6	**f**	EtO_2C	Ph	50 (70%)[b]

[a] Using 1 equiv of LiHMDS, substrate and oxaziridine **4**.
[b] 1.5 equiv oxaziridine **4** employed.

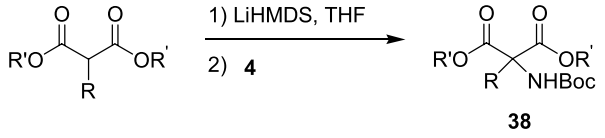


Scheme 21.



Scheme 22.

Table 5.



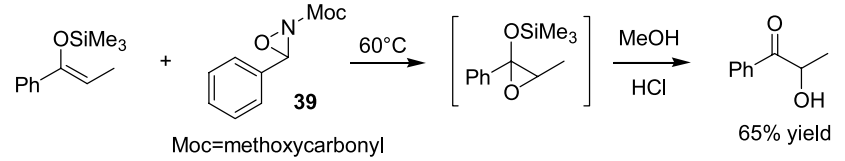
Entry		R	R′	Yield of **38**[a] (%)
1	**a**	Me	Me	30
2	**b**	Me	Et	22

[a] Using 1 equiv of LiHMDS, substrate and oxaziridine **4**.

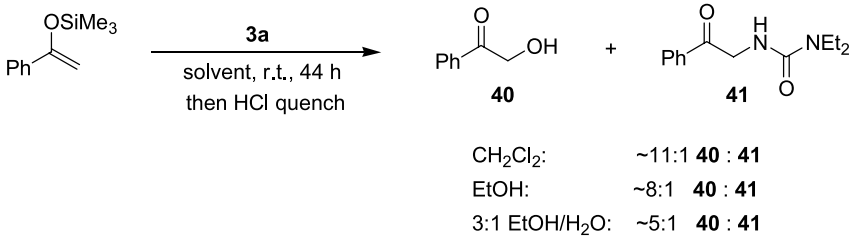
the oxaziridine reagents, the use of neutral reaction conditions with silyl enol ethers as substrates was an attractive possibility. Collet had reported that reaction of the TMS enol ether of propiophenone with *N*-alkoxycarbonyl oxaziridine **39** gave oxidation but no amination of the substrate (Scheme 23, solvent not reported).[5]

When we carried out the similar reaction of acetophenone TMS enol ether with oxaziridine **3a** in dichloromethane, this was also found to be selective for oxidation, but in this case a small amount of amination product **41** could also be detected (~11:1 oxidation to amination, Scheme 24). Study of the reaction between oxaziridines and sulfides had demonstrated that the use of more polar solvents could increase the ratio of amination to oxidation.[22] This same effect was also observed on the reaction of acetophenone TMS enol ether with oxaziridine **3a** (Scheme 24). Thus, performing the reaction in ethanol afforded a ~8:1 mixture of oxidation and amination products, and this ratio could be further improved to ~5:1 by using a 3:1 ethanol/water solvent mixture. Although the amount of amination had been increased, the reaction was still selective for oxidation and in the latter case only ~60% of the oxaziridine reacted, presumably due to competing hydrolysis of the TMS enol ether. Potential origins of the solvent polarity effect have been discussed in the previously reported study of sulfimidation, involving preferential stabilisation by high polarity solvents of the more polar amination transition state compared to that of oxidation.[22]

Examination of other oxaziridines in this reaction was also carried out. Reaction of acetophenone TMS enol ether with ketomalonate-derived oxaziridine **4** or 3-methoxycarbonyl oxaziridine **7** in ethanol gave improved ratios of oxidation–amination products (~1.8:1 and ~2.8:1 **40**:**41**, respectively), but conversion was less clean with substantial amounts of decomposition products also being formed. 3-Methoxycarbonyl 3-phenyl oxaziridine **6** gave very little reaction even after 44 h at room temperature, but that which had occurred was selective for oxidation, and no amination could be detected. These results indicate that there is



Scheme 23.



Scheme 24.

potential for optimisation of the amination pathway by further structural modifications to the oxaziridine, although a considerable improvement is required.

3. Conclusions

We have successfully prepared a structurally diverse range of novel oxaziridines and tested these in the amination of enolates. With aldehyde-derived *N*-carboxamido-oxaziridine **3a**, the use of a sodium base was found to reduce the amount of aldol side-product. For *ortho*-cyanophenyl-oxaziridine **3b**, the aldol side-product was found to be removed from the reaction mixture by washing with acid, probably by intramolecular cyclisation of the aldol hydroxyl group onto the nitrile. While these new reagents and conditions disappointingly did not improve the isolated yield of the amination product, they provide useful ways of facilitating isolation and purification of the amination product. A chiral oxaziridine **8** allowed us to test the concept of a novel 'self-cleaving' amino alcohol protecting group, and appeared to offer promising diastereoselectivity in ester enolate amination, but yields were again low. In a further study with aldehyde-derived oxaziridine **3a**, products derived from deprotonation of the oxaziridine ring were identified, suggesting that ketone-derived oxaziridines may be worthy of investigation. However, ketomalonate-derived oxaziridine **4** afforded significant amination yields only for relatively stabilised carbanions. Despite the lack of success in improving the enolate amination yields, the study has revealed interesting and useful information about the process, and the work has led to development of other methodology that may be of wider value: for example, the $Ti(O^iPr)_4$-mediated synthesis of *N*-carboxamido-imines and the alpha-chlorination of ketones. Moreover, the novel oxaziridines prepared are now available for other processes such as heteroatom transfer to amine and sulfide nucleophiles, which are synthetically useful in themselves.[9]

4. Experimental

4.1. General details

Diethyl ether and tetrahydrofuran were distilled before use from sodium-benzophenone ketyl, and dichloromethane from calcium hydride. Other solvents and reagents were purified according to standard procedures where appropriate. Solutions of butyllithium were titrated against diphenylacetic acid before use. Reaction temperatures were recorded as bath temperatures. Flash chromatography was performed using BDH F_{254} silica gel. Analytical thin layer chromatography was performed on pre-coated Merck silica gel 60 F_{254} glass backed plates and visualised by ultraviolet light and potassium permanganate, anisaldehyde, ceric ammonium nitrate or ninhydrin stains as appropriate. NMR analyses were performed on Bruker 250, 300, 400 or 500 MHz instruments in $CDCl_3$; chemical shifts are quoted in ppm relative to TMS (as referenced to residual $CHCl_3$ $\delta_H=7.26$ or $CDCl_3$ $\delta_C=77.0$ ppm), with coupling constants quoted in Hertz. Infrared analyses were recorded as a thin film (produced from evaporation of a dichloromethane solution) unless otherwise stated, on NaCl plates using a Mattson Satellite FTIR spectrometer from 4000 to 600 cm^{-1}. Mass spectrometry was carried out under CI (ammonia reagent gas) or FAB conditions using a Micromass Autospec-Q spectrometer at the Imperial College Mass Spectrometry Service. Where compounds contain chlorine, the peaks quoted refer to ^{35}Cl-containing isotopes. Elemental analysis was carried out by Mr. Stephen Boyer at the University of North London. Optical rotation measurements were performed on an Optical Activity Polarimeter and the reported $[\alpha]_D$ values are given in 10^{-1}deg cm^2 g^{-1}. X-ray crystal structures were obtained at the Imperial College Crystallography Service.[31]

4.2. Synthesis of oxaziridines

4.2.1. Synthesis of *N*-carboxamido-oxaziridines.

4.2.1.1. General procedures for preparation of *N*-diethylcarboxamido benzaldimines 9. *Method A*. A solution of *N*,*N*-diethylurea (1.0 equiv), aldehyde (1.0 equiv) and $TsOH\cdot H_2O$ (catalyst) in toluene under nitrogen was heated at reflux under Dean–Stark conditions. After the reaction was complete it was cooled to room temperature and evaporated to afford the crude imine **9**.

Method B. To *N*,*N*-diethylurea (1.0 equiv) and aldehyde (1.0 equiv) in THF (4 ml/mmol) under nitrogen was added titanium (IV) isopropoxide (1.2 equiv). After stirring at room temperature until completion of the reaction, water was added and the mixture extracted with ethyl acetate (×2). The combined organics were washed with water (×2), dried over $MgSO_4$, filtered and evaporated to afford the crude imine **9**.

Imine **9a**. *Method A*. *N*,*N*-Diethylurea (3.6 g, 30 mmol), *p*-chlorobenzaldehyde (4.3 g, 30 mmol) and $TsOH\cdot H_2O$ (50 mg) in toluene (60 ml) were allowed to react according to the above procedure for 19 h to afford the crude imine **9a** (7.5 g) as a brown oil with a 9:1 imine–aldehyde ratio by ^1H NMR, δ_H (250 MHz, $CDCl_3$) 8.98 (1H, s, N=CH), 7.83 (2H, d, $J=8.4$ Hz, Ar-H), 7.41 (2H, d, $J=8.4$ Hz, Ar-H), 3.59 (2H, q, $J=7.0$ Hz, NCH_2), 3.47 (2H, q, $J=7.0$ Hz, NCH_2), 1.20 (3H, t, $J=7.0$ Hz, NCH_2CH_3), 1.15 (3H, t, $J=7.0$ Hz, NCH_2CH_3).

Method B. *N*,*N*-Diethylurea (232 mg, 2.0 mmol), *p*-chlorobenzaldehyde (282 mg, 2.0 mmol) and titanium (IV) isopropoxide (0.72 ml, 2.4 mmol) were allowed to react according to the above procedure for 20 h to afford crude imine **71a** (467 mg) as a pale yellow oil with a 10:1 imine–aldehyde ratio.

Imine **9b**. *Method A*. *N*,*N*-Diethylurea (1.5 g, 13 mmol), *o*-cyanobenzaldehyde (1.7 g, 13 mmol) and $TsOH\cdot H_2O$ (50 mg) in toluene (40 ml) were allowed to react according to the above procedure for 5 h to afford the crude imine **9b** (3.0 g) as a dark brown oil, δ_H (250 MHz, $CDCl_3$) 9.27 (1H, s, N=CH), 8.08–7.60 (4H, m, Ar-H), 3.69 (2H, q, $J=7.1$ Hz, NCH_2), 3.52 (2H, q, $J=7.1$ Hz, NCH_2), 1.25 (3H, t, $J=7.1$ Hz, NCH_2CH_3), 1.19 (3H, t, $J=7.1$ Hz, NCH_2CH_3.

4.2.1.2. General procedure for preparation of 2-diethylcarboxamido-3-aryloxaziridines 3. To a solution of the crude imine **9** (1.0 equiv) in CH_2Cl_2 (4 ml/mmol) and

saturated aqueous K_2CO_3 (4 ml/mmol) was added *m*CPBA (70–75%, ~3.0 equiv) in CH_2Cl_2 (4 ml/mmol). The mixture was vigorously stirred until completion of the reaction and worked up by addition of water. This was extracted with CH_2Cl_2 (×2) and the combined organics dried over $MgSO_4$, filtered, evaporated and purified by flash chromatography (5–25% EtOAc in petrol) to afford the oxaziridine **3**.

2-(Diethylcarboxamido)-3-(p-chlorophenyl)oxaziridine **3a**. Crude *p*-chlorobenzaldimine **9a** (7.5 g), prepared by the Dean–Stark method, was reacted according to the above procedure for 5 h to afford the oxaziridine **3a** (4.9 g, 63% from aldehyde) as a low-melting solid, ν_{max} (film)/cm^{-1} 2977, 2935, 2875, 1703 (br), 1601, 1495, 1428, 1382, 1269, 1091, 738; δ_H (250 MHz, $CDCl_3$) 7.43 (2H, d, J=8.9 Hz, Ar-H), 7.40 (2H, d, J=8.9 Hz, Ar-H), 5.18 (1H, s, oxaziridine-H), 3.63 (1H, dq, J=14.3 Hz, 7.1, NCH_AH_B), 3.53 (1H, dq, J=14.3, 7.1 Hz, NCH_AH_B), 3.40 (1H, qd, J=7.1, 3.6 Hz, NCH_AH_B), 3.39 (1H, qd, J=7.1, 3.6 Hz, NCH_AH_B), 1.19 (6H, t, J=7.1 Hz, NCH_2CH_3); δ_C (62.5 MHz, $CDCl_3$) 160.8, 136.7, 131.6, 129.3, 128.9, 77.5, 42.0, 41.9, 14.4, 12.7; MS (EI+) *m*/*z* 254 (M^+). Found: $[M]^+$, 254.0819, $C_{12}H_{15}N_2O_2Cl$ requires 254.0822.

Similar reaction using crude *p*-chlorobenzaldimine **9a** (467 mg) prepared by the titanium isopropoxide method afforded the oxaziridine **3a** (340 mg, 67% from aldehyde).

2-(Diethylcarboxamido)-3-(o-cyanophenyl)oxaziridine **3b**. Crude *o*-cyanobenzaldimine **9b** (3.0 g), prepared by the Dean–Stark method, was reacted according to the above procedure for 3 h to afford the oxaziridine **3b** (0.97 g, 30% from aldehyde) as a pale yellow oil, ν_{max} ($CHCl_3$ solution)/cm^{-1} 2972, 2937, 2361, 2228, 1698, 1601, 1430, 1271; δ_H (250 MHz, $CDCl_3$) 7.68–7.46 (4H, m, Ar-H), 5.52 (1H, s, oxaziridine-H), 3.56 (1H, dq, J=14.4, 7.2 Hz, NCH_AH_B), 3.50 (1H, dq, J=14.4, 7.2 Hz, NCH_AH_B), 3.34 (1H, qd, J=7.0, 1.7 Hz, NCH_AH_B), 3.33 (1H, qd, J=7.0, 1.7 Hz, NCH_AH_B), 1.14 (3H, t, J=7.0 Hz, NCH_2CH_3), 1.12 (3H, t, J=7.2 Hz, NCH_2CH_3); δ_C (67 MHz, $CDCl_3$) 160.0 (C), 136.4 (C), 133.2 (CH), 133.1 (CH), 130.7 (CH), 128.4 (CH), 116.3 (C), 112.7 (C), 74.8 (CH), 42.1 (CH_2), 42.0 (CH_2), 14.4 (CH_3), 12.6 (CH_3); MS (EI+) *m*/*z* 245 (M^+, 3.48%). Found: $[M]^+$, 245.1174, $C_{13}H_{15}N_3O_2$ requires 245.1164. Found: C, 63.46; H, 6.23; N, 16.99. $C_{13}H_{15}N_3O_2$ requires C, 63.66; H, 6.16; N, 17.13%.

2-(Diethylcarboxamido)-3-phenyl-3-(trifluoromethyl)oxaziridine **5**. To *N*,*N*-diethylurea (232 mg, 2.0 mmol) and trifluoroacetophenone (280 µl, 2.0 mmol) in THF (4 ml) under nitrogen was added titanium (IV) isopropoxide (720 µl, 2.4 mmol). After stirring at reflux for 6 h, water (20 ml) was added and the mixture extracted with ethyl acetate (2×20 ml). The combined organics were washed with water (2×20 ml), dried over $MgSO_4$, filtered and evaporated to afford the crude imine **10** as a yellow oil. To a solution of the crude imine **10** in CH_2Cl_2 (10 ml) and saturated aqueous K_2CO_3 (10 ml) was added *m*CPBA (50–55%, 2.0 g, ~6.0 mmol) in CH_2Cl_2 (10 ml). After stirring at room temperature for 5 h, water (40 ml) was added and the mixture extracted with CH_2Cl_2 (2×40 ml). The combined organics were dried over $MgSO_4$, filtered, evaporated and purified by flash chromatography (5–10% EtOAc in petrol) to afford the oxaziridine **5** (107 mg, 19% from ketone) as a white crystalline solid, mp 95–96 °C; ν_{max}/cm^{-1} 3414, 2981, 1720, 1428, 1333, 1268, 1205, 1166, 957, 725, 697; δ_H (250 MHz, $CDCl_3$) 7.65–7.35 (5H, m, Ar-H), 3.58 (1H, dq, J=14.4, 7.2 Hz, NCH_AH_B), 3.31 (1H, dq, J=14.1, 7.1 Hz, NCH_AH_B), 3.18 (1H, dq, J=14.4, 7.2 Hz, NCH_AH_B), 2.84 (1H, dq, J=14.1, 7.1 Hz, NCH_AH_B), 1.23 (3H, t, J=7.2 Hz, NCH_2CH_3), 0.62 (3H, t, J=7.1 Hz, NCH_2CH_3); δ_C (62.9 MHz, $CDCl_3$) 155.9 (C), 131.2 (CH), 128.4 (CH), 127.9 (CH), 124.8 (C), 121.2 (CF_3, q, J=280 Hz), 80.6 (C_{ring}, q, J=39 Hz), 41.3 (CH_2), 41.2 (CH_2), 13.5 (CH_3), 12.0 (CH_3); δ_F (235 MHz, $CDCl_3$) −79.5 (CF_3); *m*/*z* (CI, NH_3) 306 ($[M+NH_4]^+$, 43%), 289 ($[M+H]^+$, 11). Found: $[M+NH_4]^+$, 306.1426. $C_{13}H_{19}N_3O_2F_3$ requires 306.1429. Structure confirmed by X-ray crystallography (recrystallisation from EtOAc/petrol).[31]

4.2.1.3. Synthesis of (1*S*,2*S*)-(+)-pseudoephedrine-derived oxaziridine 8. *O-TBDPS-N-chlorocarbonyl-(1S,2S)-pseudoephedrine* **11**. To a solution of (1*S*,2*S*)-(+)-pseudoephedrine hydrochloride (4.0 g, 20 mmol) in CH_2Cl_2 (40 ml) under nitrogen was added TBDPSCl (5.45 ml, 21 mmol) and triethylamine (5.85 ml, 42 mmol). After stirring at room temperature for 24 h diethyl ether (8 ml) was added and after 10 min the mixture was filtered. The filtrate was evaporated to afford the crude *O*-TBDPS pseudoephedrine (9.88 g) as a white oily solid, δ_H (250 MHz, $CDCl_3$) 7.74–7.12 (15H, m, Ar-H), 4.61 (1H, d, J=6.7 Hz, PhCH), 2.83 (1H, dq, J=6.7, 6.4 Hz, NCH), 2.25 (3H, s, NCH_3), 1.02 (9H, s, $C(CH_3)_3$), 0.78 (3H, d, J=6.4 Hz, $NCHCH_3$).

To a solution of the crude *O*-TBDPS pseudoephedrine (8.09 g, 16.4 mmol, assuming 100% yield) in THF (50 ml) under nitrogen was added triethylamine (3.2 ml, 22.9 mmol) and 4-dimethylaminopyridine (50 mg). After cooling to 0 °C, triphosgene (1.94 g, 6.55 mmol) was added in one portion. After stirring for 30 min at 0 °C and 10 min at room temperature, water (100 ml) was cautiously added and the solution extracted into ethyl acetate (3×50 ml). The combined organics were washed with brine (50 ml), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give the crude title compound **11** as a pale yellow viscous oil (8.48 g). This was of sufficient purity for further reaction but could be purified by flash chromatography (5% EtOAc in petrol) to provide an analytically pure sample as a colourless oil, $[\alpha]_D^{19}$ +78.5 (*c* 0.93, $CHCl_3$); ν_{max}/cm^{-1} 3071, 2933, 1738, 1427, 1293, 1242, 1106, 823, 703, 612, 504; δ_H (300 MHz, $CDCl_3$, 2 rotamers a and b in 9:5 ratio) 7.71–7.18 (15H, m, Ar-H), 4.76–4.50 (2H, m, NCH and PhCH), 2.63 (3H, s, NCH_3 a), 2.54 (3H, s, NCH_3 b), 1.03 (9H, s, $C(CH_3)_3$ b), 1.01 (9H, s, $C(CH_3)_3$ a), 0.91 (3H, d, J=6.9 Hz, $NCHCH_3$ b), 0.86 (3H, d, J=6.8 Hz, $NCHCH_3$ a); δ_C (75.4 MHz, $CDCl_3$, 2 rotamers with some superposition of peaks) 150.3 (C), 150.0 (C), 140.8 (C), 140.5 (C), 136.1 (CH), 136.0 (CH), 134.8 (CH), 133.4 (C), 132.9 (C), 132.8 (CH), 129.7 (CH), 129.6 (CH), 129.5 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.6 (CH), 127.5 (CH), 76.4 (CH), 61.2 (CH), 59.9 (CH), 33.2 (CH_3), 31.0 (CH_3), 26.9 (CH_3), 19.2 (C), 14.3 (CH_3), 14.2 (CH_3); *m*/*z* (CI, NH_3) 483 ([M+

$NH_4]^+$, 87%), 466 ($[M+H]^+$, 20). Found: $[M+NH_4]^+$, 483.2231. $C_{27}H_{36}N_2O_2SiCl$ requires 483.2235.

O-TBDPS-N-carboxamido-(1S,2S)-pseudoephedrine **12**. To a solution of the crude carbamoyl chloride **11** (1.81 g, 3.5 mmol, assuming 100% yield) in diethyl ether (30 ml) was added ~35% aqueous ammonia solution (40 ml). The ammonia solution was replenished periodically until the reaction was complete as evidenced by thin layer chromatography. The mixture was separated and the aqueous layer re-extracted with diethyl ether (2×30 ml). The combined organics were washed with brine (30 ml), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. Flash chromatography (20–100% EtOAc in petrol) afforded the title compound **12** (1.47 g, 94% from pseudoephedrine hydrochloride) as a colourless viscous glass, $[\alpha]_D^{19}$ +67.9 (*c* 1.12, $CHCl_3$); ν_{max}/cm^{-1} 3347, 3204, 2931, 2235, 1659, 1599, 1488, 1404, 1107, 910, 823, 703, 611, 504; δ_H (250 MHz, $CDCl_3$) 7.68–7.14 (15H, m, Ar-H), 4.72 (2H, br s, NH_2), 4.55 (1H, d, J=7.6 Hz, PhCH), 4.30 (1H, br m, NCH), 2.36 (3H, br s, NCH_3), 0.98 (9H, s, $C(CH_3)_3$), 0.82 (3H, d, J=6.8 Hz, NCHCH_3); δ_C (75.4 MHz, $CDCl_3$, 1 aromatic CH not found) 159.6 (C), 141.1 (C), 135.8 (CH), 135.8 (CH), 133.4 (C), 132.7 (C), 129.5 (CH), 129.3 (CH), 127.8 (CH), 127.4 (CH), 127.2 (CH), 127.1 (CH), 77.0 (CH), 56.7 (CH), 28.4 (CH_3), 26.8 (CH_3), 19.0 (C), 14.1 (CH_3); *m/z* (CI, NH_3) 447 ($[M+H]^+$, 100%). Found: $[M+H]^+$, 447.2466. $C_{27}H_{35}N_2O_2Si$ requires 447.2468.

2-(N-Methyl-N-((1′S,2′S)-1′-TBDPSO-1′-phenyl-2′-propyl) carboxamido)-3-(p-chlorophenyl)oxaziridine **8**. To a solution of the urea **12** (915 mg, 2.05 mmol) and *p*-chlorobenzaldehyde (290 mg, 2.05 mmol) in THF (10 ml) was added titanium (IV) isopropoxide (750 μl, 2.46 mmol). After stirring at room temperature under nitrogen for 16 h, water (40 ml) was added and the mixture extracted with ethyl acetate (2×60 ml). The combined organics were washed with water (2×40 ml), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to afford the crude imine **13** (1.1 g) as a colourless viscous oil with a 8:1 imine–aldehyde ratio, δ_H (250 MHz, $CDCl_3$, 2 rotamers a and b in 2:5 ratio) 8.83 (1H, s, N=CH a), 8.52 (1H, s, N=CH b), 7.84–7.00 (19H, m, Ar-H), 5.00–4.80 (1H, br m, NCH), 4.70 (1H, d, J=8.3 Hz, PhCH a), 4.62 (1H, d, J=5.4 Hz, PhCH b), 2.88 (3H, s, NCH_3 b), 2.72 (3H, s, NCH_3 a), 1.05 (3H, d, J=7.0 Hz, NCHCH_3 b), 0.96 (9H, s, $C(CH_3)_3$ b), 0.94 (9H, s, $C(CH_3)_3$ a), 0.89 (3H, d, J=7.0 Hz, NCHCH_3 a).

To a solution of the crude imine **13** (1.1 g, 2.05 mmol, assuming 100% yield) in CH_2Cl_2 (15 ml) and saturated aqueous K_2CO_3 (12 ml) was added *m*CPBA (70–75%, 1.5 g, ~6.0 mmol) in CH_2Cl_2 (10 ml). After stirring at room temperature for 5 h, water (60 ml) was added and the mixture extracted with CH_2Cl_2 (2×30 ml). The combined organics were dried over $MgSO_4$, filtered, evaporated and purified by flash chromatography (3–7% EtOAc in petrol) to afford the oxaziridine **8** (700 mg, 58% from urea **12**) as a white foam, $[\alpha]_D^{22}$ −4.2 (*c* 2.16, $CHCl_3$); ν_{max}/cm^{-1} 3071, 2932, 2858, 2248, 1692, 1602, 1427, 1242, 1090, 824, 702; δ_H (300 MHz, $CDCl_3$, 2 rotamers a and b in ~1:2 ratio) 7.71–6.82 (19H, m, Ar-H), 5.06 (1H, s, oxaziridine-H a), 5.03 (1H, s, oxaziridine-H b), 5.06–4.90 (1H, m, NCH b), 4.72–4.64 (2H, m, PhCH a and NCH a), 4.48 (1H, d, J=7.3 Hz, PhCH b), 2.85 (3H, s, NCH_3 b), 2.72 (3H, s, NCH_3 a), 1.00 (9H, s, $C(CH_3)_3$ a), 0.98–0.92 (12H, m, $C(CH_3)_3$ b and NCHCH_3 b), 0.89 (3H, d, J=6.6 Hz, NCHCH_3 a); δ_C (75.4 MHz, $CDCl_3$, 2 rotamers with some superposition of peaks) 161.7 (C), 161.6 (C), 141.0 (C), 140.7 (C), 136.1 (CH), 136.0 (CH), 133.6 (C), 133.1 (C), 132.8 (C), 131.8 (C), 131.6 (C), 130.8 (C), 129.8 (CH), 129.5 (CH), 129.3 (CH), 128.8 (CH), 128.7 (CH), 128.0 (CH), 127.8 (CH), 127.5 (CH), 127.3 (CH), 127.2 (CH), 127.1 (CH), 77.7 (CH), 77.1 (CH), 76.8 (CH), 76.3 (CH), 57.6 (CH), 57.3 (CH), 29.3 (CH_3), 27.0 (CH_3), 26.9 (CH_3), 19.3 (C), 19.2 (C), 15.1 (CH_3), 14.1 (CH_3), 13.6 (CH_3); *m/z* (FAB) 585 ($[M+H]^+$, 0.6%). Found: C, 70.0; H, 6.28; N, 4.74. $C_{34}H_{37}N_2O_3SiCl$ requires C, 69.8; H, 6.37; N, 4.79%.

4.2.2. Synthesis of *N*-Boc oxaziridines. *N*-Boc oxaziridines **1**[5] and **4**[9] were prepared according to literature procedures.

N-Boc -3-Methoxycarbonyloxaziridine **7**. A mixture of methyl *N*-Boc glycinate **14** (0.9 ml, 6.0 mmol) and NBS (1.08 g, 6.0 mmol) in CCl_4 (12 ml) under nitrogen was irradiated with a 500 W bulb (distance ~10 cm) for 1 h (temperature of solution kept below 30 °C using a water bath). The reaction was filtered and evaporated to afford the crude bromide **15** as a yellow oil, δ_H (250 MHz, $CDCl_3$) 6.35 (1H, br d, J=10.6 Hz, CH), 6.00 (1H, br d, J=10.6 Hz, NH), 3.85 (3H, s, CH_3), 1.47 (9H, s, $C(CH_3)_3$). To the crude bromide **15** in THF (6 ml) at −78 °C under nitrogen was added triethylamine (0.70 ml, 5.0 mmol) and the reaction stirred for 30 min at −78 °C to afford a crude imine solution **16**.Meanwhile, to a solution of purified *m*CPBA (0.43 M in CH_2Cl_2, 12.7 ml, 5.5 mmol) at −78 °C under nitrogen was slowly added *n*-BuLi (2.5 M in hexanes, 2.1 ml, 5.3 mmol) and the reaction stirred for 30 min. The cold crude imine solution **16** was then quickly filtered under nitrogen into the *m*CPBA solution. After stirring for 2 h at −78 °C, the reaction was allowed to warm to −50 °C then quenched with saturated aqueous sodium bicarbonate solution (20 ml). The layers were separated and the aqueous layer re-extracted with CH_2Cl_2 (2×20 ml). The combined organics were dried over $MgSO_4$, filtered, evaporated and purified by flash chromatography (10–20% EtOAc in petrol, then recolumned using 100% CH_2Cl_2) to afford oxaziridine **7** (36 mg, 4%) as a colourless oil, ν_{max}/cm^{-1} 2982, 1773, 1752, 1444, 1373, 1251, 1152, 1019, 846; δ_H (250 MHz, $CDCl_3$, mixture of cis and trans isomers in a ratio of 31:69) 4.64 (1H, s, oxaziridine-H cis), 4.63 (1H, s, oxaziridine-H trans), 3.86 (3H, s, CH_3), 1.51 (9H, s, $C(CH_3)_3$); δ_C (101 MHz, $CDCl_3$, cis and trans isomers) 164.6 (C), 164.5 (C), 158.8 (C), 157.5 (C), 86.5 (C), 85.8 (C), 71.3 (CH), 71.2 (CH), 53.4 (2×CH_3), 27.7 (CH_3), 27.6 (CH_3); *m/z* (CI, NH_3) 221 ($[M+NH_4]^+$, 44%). Found: $[M+NH_4]^+$, 221.1131.$C_8H_{17}N_2O_5$ requires 221.1137.

4.2.2.1. Synthesis of methyl phenylglycinate-derived oxaziridine 6. *Methyl (R)-N-Boc-phenylglycinate* **17**.[23] To a suspension of methyl phenylglycinate hydrochloride (1.0 g, 5 mmol) in THF (40 ml) at 0 °C under nitrogen was added triethylamine (0.73 ml, 5.2 mmol). After stirring at room temperature for 15 min, Boc anhydride (1.64 g, 7.5 mmol) was added. After a further 2 h the reaction was filtered, evaporated and purified by flash chromatography

(15% EtOAc in petrol) to afford *N*-Boc phenylglycine methyl ester **17** (1.3 g, 98%) as a white solid, δ_H (250 MHz, $CDCl_3$) 7.38–7.32 (5H, m, Ar-H), 5.53 (1H, br, NH), 5.32 (1H, br d, $J=7.3$ Hz, CH), 3.72 (3H, s, CH_3), 1.43 (9H, s, $C(CH_3)_3$). Consistent with literature.[23]

Methyl N-Boc-α-iminophenylacetate **18**. A mixture of methyl (*R*)-*N*-Boc-phenylglycinate 17 (1.12 g, 4.2 mmol) and NBS (0.98 g, 5.5 mmol) in CCl_4 (12 ml) under nitrogen was irradiated with a 500 W bulb (distance ~10 cm) for 2 h (temperature of solution kept below 30 °C using a water bath). The reaction was filtered and evaporated to afford a ~5:3 mixture of imine **18**: starting material **17**. Flash chromatography (50–80% CH_2Cl_2 in petrol) afforded the imine 18 (0.70 g, 63%) as a colourless oil, ν_{max}/cm^{-1} 2981, 1744, 1719, 1632, 1249, 1217, 1153, 1020; δ_H (250 MHz, $CDCl_3$) 7.76 (2H, br d, $J=7.3$ Hz, Ar-H), 7.47–7.27 (3H, m, Ar-H), 3.81 (3H, s, CH_3), 1.45 (9H, s, $C(CH_3)_3$); δ_C (62.9 MHz, $CDCl_3$) 164.8 (C), 162.4 (C), 160.4 (C), 132.8 (CH), 132.2 (C), 129.0 (CH), 128.6 (CH), 83.0 (C), 52.7 (CH_3), 27.9 (CH_3); *m/z* (CI, NH_3) 264 ($[M+H]^+$, 63%). Found: $[M+H]^+$, 264.1233.$C_{14}H_{18}NO_4$ requires 264.1236.

N-Boc-3-methoxycarbonyl-3-phenyloxaziridine **6**. To a solution of the imine 18 (607 mg, 2.3 mmol) in CH_2Cl_2 (20 ml) and saturated aqueous K_2CO_3 (20 ml) was added *m*CPBA (50–55%, 2.4 g, ~6.9 mmol) in CH_2Cl_2 (20 ml). After stirring at room temperature for 2 h, water (80 ml) was added and the mixture extracted with CH_2Cl_2 (2×60 ml). The combined organics were dried over $MgSO_4$, filtered, evaporated and purified by flash chromatography (50–60% CH_2Cl_2 in petrol) to afford the oxaziridine **6** (584 mg, 91%) as a colourless oil, ν_{max}/cm^{-1} 3065, 2982, 1769, 1763, 1453, 1372, 1246, 1150, 1015, 852, 697; δ_H (250 MHz, $CDCl_3$, mixture of cis and trans isomers in a ratio of 29:71) 7.55–7.23 (5H, m, Ar-H), 3.73 (3H, s, CH_3 cis), 3.70 (3H, s, CH_3 trans), 1.41 (9H, s, $C(CH_3)_3$ cis), 0.97 (9H, s, $C(CH_3)_3$ trans); δ_C (62.9 MHz, $CDCl_3$, cis and trans isomers with some signals superimposed, 1 aromatic CH not found) 164.8 (C), 164.4 (C), 157.4 (C), 156.1 (C), 130.6 (CH), 130.3 (CH), 128.1 (CH), 127.9 (CH), 127.5 (C), 127.4 (CH), 126.9 (CH), 85.2 (C), 84.8 (C), 80.9 (C), 80.6 (C), 52.9 (2×CH_3), 27.1 (CH_3), 26.6 (CH_3); *m/z* (CI, NH_3) 297 ($[M+NH_4]^+$, 100%). Found: $[M+NH_4]^+$, 297.1439.$C_{14}H_{21}N_2O_5$ requires 297.1450.

4.3. Reactions with enolates

4.3.1. Amination using racemic aldehyde-derived oxaziridines 3.

4.3.1.1. Typical procedure: reaction of *t*-butyl acetate with oxaziridine 3a using LDA as base (Table 2, entry 1). To a solution of diisopropylamine (52 µl, 0.37 mmol) in THF (0.5 ml) at 0 °C under nitrogen was added *n*-BuLi (2.38 M in hexanes, 156 µl, 0.37 mmol). After stirring for 30 min the reaction was cooled to −78 °C and *t*-butyl acetate (50 µl, 0.37 mmol) in THF (0.75 ml) added dropwise. After a further 1 h at −78 °C, oxaziridine **3a** (94 mg, 0.37 mmol) in THF (0.75 ml) was added and the reaction allowed to slowly warm to room temperature over 3 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (6 ml) and extracted with CH_2Cl_2 (3×8 ml). The combined organics were dried over $MgSO_4$, filtered and evaporated to afford a crude mixture of amino ester **19** and aldol product **20a** (~4:3 according to ^1H NMR analysis), plus other side products including diethyl urea and amide **23**. Flash chromatography (10–30% EtOAc in petrol) afforded *t*-butyl *N*-(diethylcarboxamido)glycinate **19** (20 mg, 24%) as white needles.

t-Butyl N-(diethylcarboxamido)glycinate **19**. Mp 143–145 °C; ν_{max} ($CHCl_3$ solution)/cm^{-1} 3168, 2927, 2855, 1721, 1614, 1467, 1452, 1215, 1075; δ_H (250 MHz, $CDCl_3$) 4.88–4.78 (1H, br m, NH), 3.93 (2H, d, $J=4.9$ Hz, $NHCH_2$), 3.28 (4H, q, $J=7.2$ Hz, NCH_2CH_3), 1.46 (9H, s, $C(CH_3)_3$), 1.15 (6H, t, $J=7.2$ Hz, NCH_2CH_3); δ_C (67 MHz, $CDCl_3$) 170.5 (C), 156.8 (C), 81.7 (C), 43.2 (CH_2), 41.2 (2×CH_2), 27.9 (3×CH_3), 13.7 (2×CH_3); MS (EI+) *m/z* 231 (M^+H, 20.5%), 175 (M−*t*Bu, 60.4%). Found: $[M+H]^+$, 231.1712. $C_{11}H_{23}N_2O_3$ requires 231.1708.

t-Butyl 3-(p-chlorophenyl)-3-hydroxypropionate **20a**.[24] Isolated as a colourless oil, δ_H (250 MHz, $CDCl_3$) 7.30 (4H, s, Ar-H), 5.04 (1H, dd, $J=7.0$, 5.8 Hz, CH), 3.60 (1H, br s, OH), 2.62–2.60 (2H, m, CH_2), 1.44 (9H, s, $C(CH_3)_3$); *m/z* (CI, NH_3) 274 ($M+NH_4]^+$, 11%), 257 ($[M+H]^+$, 17). Consistent with literature.[24]

Similar reactions with other bases and conditions afforded **19** and **20a** in the yields indicated in Table 2.

4.3.1.2. Reaction of *t*-butyl acetate with oxaziridine 3b using LDA as base. Similar reaction of *t*-butyl acetate (91 µl, 0.67 mmol), oxaziridine **3b** (165 mg, 0.67 mmol) and LDA (prepared from diisopropylamine (103 µl, 0.73 mmol) and *n*-BuLi (2.4 M in hexanes, 290 µl, 0.70 mmol)) using $NaHCO_3/CH_2Cl_2$ work-up gave a mix of amino ester **19** and aldol product **20b** (~1:1). Flash chromatography (10–30% EtOAc in petrol) afforded amino ester **19** (51 mg, 33%) and aldol **20b** (38 mg, 23%).

t-Butyl 3-(o-cyanophenyl)-3-hydroxypropionate **20b**. Isolated as a colourless oil, ν_{max}/cm^{-1}: 3294, 2979, 2932, 2361, 2331, 2224, 1767, 1726, 1686, 1469, 1368; δ_H (250 MHz, $CDCl_3$): 7.30 (1H, d, $J=7.2$ Hz, ArH), 7.53–7.39 (2H, m, ArH), 7.33 (1H, d, $J=7.2$ Hz, ArH), 5.76 (1H, d, $J=6.0$ Hz, C*H*OH), 2.74–2.71 (2H, m, CH_2CO_2t-Bu), 1.39 (9H, s, *t*-Bu); δ_C (62.5 MHz, $CDCl_3$):168.7, 167.4, 146.2, 132.1, 129.3, 129.0, 123.9, 121.6, 81.5, 79.2, 41.2, 27.9; *m/z* (EI) 247 (M^+5%). Found M^+, 247.1207 $C_{14}H_{17}NO_3$ requires: M, 247.1208.

The same procedure using water as the quench, followed by extraction with CH_2Cl_2 (×3) and sequential washing with saturated aqueous $NaHCO_3$, 1 M HCl and brine removed almost all the aldol product **20b**. This could be recovered by basifying the acid wash to pH ~8 with $NaHCO_3$ followed by extraction with CH_2Cl_2.

4.3.1.3. Reaction of oxaziridine 3a with NaHMDS. To NaHMDS (1.04 M in THF, 183 µl, 0.19 mmol) in THF (1 ml) at −78 °C under nitrogen was added oxaziridine **3a** (97 mg, 0.38 mmol) and the reaction allowed to warm to room temperature over 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 ml), extracted with CH_2Cl_2 (3×7 ml) and the organics dried over $MgSO_4$ and evaporated to afford a complex mixture of products

including amide **23**, imine **9a**, aldehyde and diaminal **25**. Flash chromatography (0–30% EtOAc in cyclohexane) afforded the amide **23** (28 mg, 29% based on oxaziridine).

N-(Diethylcarboxamido)-p-chlorobenzamide **23**. Isolated as a colourless oil, ν_{max}/cm^{-1} 3429, 2976, 1692, 1656, 1478, 1260, 1091, 1014, 755; δ_H (250 MHz, $CDCl_3$) 8.64 (1H, br s, NH), 7.79 (2H, d, $J=8.4$ Hz, Ar-H), 7.41 (2H, d, $J=8.4$ Hz, Ar-H), 3.40 (4H, q, $J=7.1$ Hz, NCH_2CH_3), 1.21 (6H, t, $J=7.1$ Hz, NCH_2CH_3); δ_C (62.9 MHz, $CDCl_3$) 166.3 (br C), 153.7 (br C), 138.8 (C), 131.7 (C), 129.4 (CH), 128.8 (CH), 42.2 (br CH_2), 13.3 (br CH_3); *m/z* (LC–MS, ES+) 255 ($[M+H]^+$, 100%). Found: $[M+H]^+$, 255.0898. $C_{12}H_{16}N_2O_2Cl$ requires 255.0900.

Aminal **25**. Not isolated cleanly-tentatively assigned based on the following data: δ_H (400 MHz, $CDCl_3$) 7.37 (2H, d, $J=8.5$ Hz, Ar-H), 7.27 (2H, d, $J=8.5$ Hz, Ar-H), 6.40 (2H, d, $J=7.9$ Hz, NH), 6.18 (1H, t, $J=7.9$ Hz, CH), 3.31 (4H, dq, $J=14.4$, 7.2 Hz, $NCH_AH_BCH_3$), 3.24 (4H, dq, $J=14.4$, 7.2 Hz, $NCH_AH_BCH_3$), 1.26 (12H, t, $J=7.2$ Hz, NCH_2CH_3); *m/z* (LC–MS, ES+) 355 ($[M+H]^+$, 100%), 239 (40).

4.3.1.4. Iminoaldol products 24a and 24b. These were not isolated in pure form, but were tentatively identified as by-products in the reaction between *tert*-butyl acetate/NaHMDS and oxaziridines **3a** and **3b**, respectively, from the following data:

Compound **24a**. δ_H (250 MHz, $CDCl_3$) 7.30–7.22 (4H, m, Ar-H), 5.82 (1H, br d, $J=7.8$ Hz, NH), 5.25 (1H, dt, $J=7.8$, 5.5 Hz, CH), 3.29 (4H, q, $J=7.2$ Hz, NCH_2CH_3), 2.74 (2H, d, $J=5.5$ Hz, CH_2), 1.34 (9H, s, $C(CH_3)_3$), 1.16 (6H, t, $J=7.2$ Hz, NCH_2CH_3); *m/z* (CI, NH_3) 355 ($[M+H]^+$, 100%), 299 (37). Found: $[M+H]^+$, 355.1791. $C_{18}H_{28}N_2O_3Cl$ requires: 355.1788.

Compound **24b**. δ_H (250 MHz, $CDCl_3$) 7.65–7.28 (4H, m, Ar-H), 6.01 (1H, d, $J=6.3$ Hz, NH), 5.44 (1H, apparent q, $J=6.4$ Hz, CH), 3.28 (4H, q, $J=7.2$ Hz, NCH_2CH_3), 2.85 (1H, dd, $J=15.0$, 6.7 Hz, CH_AH_B), 2.80 (1H, dd, $J=15.0$, 6.0 Hz, CH_AH_B), 1.33 (9H, s, $C(CH_3)_3$), 1.15 (6H, t, $J=7.2$ Hz, NCH_2CH_3); *m/z* (CI, NH_3) 346 ($[M+H]^+$, 100%), 290 (51). Found: $[M+H]^+$, 346.2141. $C_{19}H_{28}N_3O_3$ requires 346.2131.

4.3.1.5. Reaction of Rathke's anion 26 with 2-(diethylcarboxamido)-3-(*p*-chlorophenyl)oxaziridine 3a. Similar reaction of Rathke's anion **28** (60 mg, 0.49 mmol) and oxaziridine **3a** (125 mg, 0.49 mmol) in CH_2Cl_2 (3 ml) gave a crude mixture of amino ester **19**, aldol **20a** and imino-aldol **24** (~7:10:4), plus other side products including diethylurea and amide **23**. Flash chromatography (10–30% EtOAc in petrol) afforded semi-purified amino ester **19** (~10:3:1 with amide **23** and imino-aldol product **24**, 37 mg, ~22%).

4.3.2. Asymmetric amination using enantiopure oxaziridine 8.

4.3.2.1. Amination of ethyl isovalerate with oxaziridine 8. To a solution of diisopropylamine (55 µl, 0.39 mmol) in THF (0.5 ml) at 0 °C under nitrogen was added *n*-BuLi (2.5 M in hexanes, 150 µl, 0.37 mmol). After stirring for 30 min the reaction was cooled to −78 °C and ethyl isovalerate (52 µl, 0.35 mmol) in THF (0.5 ml) added dropwise. After a further 1 h at −78 °C, oxaziridine **8** (94 mg, 0.37 mmol) in THF (0.5 ml) was added. After stirring for 4 h at −78 °C, the reaction was allowed to slowly warm to room temperature over 2 h, quenched with saturated aqueous $NaHCO_3$ (5 ml) and extracted with CH_2Cl_2 (3×8 ml). The combined organics were dried over $MgSO_4$, filtered and evaporated to afford a complex mixture of products. The aminated product **27** could not be separated from co-running impurities by flash chromatography (5–15% EtOAc in petrol), but comparison of ^1H NMR and HPLC traces with authentic samples, after partial purification, indicated some selectivity towards formation of the (*S*)-stereocentre (dr ~5:1).

4.3.2.2. Synthesis of authentic diastereomeric amination products. *Ethyl N-(N-methyl-N-((1′S,2′S)-1′-TBDPSO-1′-phenyl-2′-propyl)carboxamido)-(S)-valinate* (()-**27**). To a suspension of (*S*)-(+)-valine (585 mg, 5.0 mmol) in ethanol (5 ml) at −5 °C under nitrogen was added dropwise thionyl chloride (0.95 ml, 13.0 mmol). After heating to reflux for 4 h the reaction was allowed to cool and evaporated to afford (*S*)-(+)-valine ethyl ester hydrochloride (878 mg, 97%) as an off-white solid, δ_H (250 MHz, DMSO-d_6) 8.41 (2H, br s, NH_2), 4.32–4.11 (2H, m, CH_3CH_2O), 3.86 (1H, d, $J=4.8$ Hz, NCH), 2.16 (1H, m, $(CH_3)_2CH$), 1.23 (3H, t, $J=7.0$ Hz, CH_3CH_2O), 0.97 (3H, d, $J=7.1$ Hz, $(CH_3)_2CH$), 0.93 (3H, d, $J=7.1$ Hz, $(CH_3)_2CH$). Consistent with literature.[25]

To (*S*)-(+)-valine ethyl ester hydrochloride (205 mg, 1.13 mmol) in THF (3 ml) at 0 °C under nitrogen was added triethylamine (315 µl, 2.26 mmol). After stirring for 5 min carbamoyl chloride **11** (526 mg, 1.13 mmol) in THF (2 ml) was added. After heating to 55 °C for 20 h the reaction was allowed to cool to room temperature and a white solid removed by filtration. The filtrate was purified by flash chromatography (5–20% EtOAc in petrol) to afford the title compound (*S*)-**27** (580 mg, 89%) as a colourless viscous oil, $[\alpha]_D^{20}$ +40.5 (*c* 3.9, $CHCl_3$); ν_{max}/cm^{-1} 3445, 3071, 2963, 2858, 2241, 1732, 1651, 1504, 1372, 1312, 1262, 1192, 1111, 823, 737, 505; δ_H (250 MHz, $CDCl_3$) 7.65–7.12 (15H, m, Ar-H), 4.94 (1H, d, $J=7.7$ Hz, NH), 4.67–4.52 (2H, m, PhC*H*C*H*), 4.38 (1H, dd, $J=7.7$, 4.7 Hz, ^iPrCH), 4.22–4.10 (2H, m, CH_3CH_2O), 2.46 (3H, s, NCH_3), 2.15–1.98 (1H, m, $(CH_3)_2CH$), 1.24 (3H, t, $J=7.1$ Hz, CH_3CH_2O), 0.97 (9H, s, $C(CH_3)_3$), 0.93–0.86 (6H, m, $(CH_3)_2CH$), 0.80 (3H, d, $J=6.5$ Hz, $NCHCH_3$); δ_C (75.4 MHz, $CDCl_3$, 1 aromatic CH not found) 172.8 (C), 157.6 (C), 141.5 (C), 135.7 (CH), 133.2 (C), 132.9 (C), 129.2 (CH), 128.9 (CH), 127.6 (CH), 127.4 (CH), 127.1 (CH), 127.0 (CH), 126.7 (CH), 77.0 (CH), 60.4 (CH_2), 58.2 (CH), 55.5 (CH), 31.0 (CH), 28.0 (CH_3), 26.6 (CH_3), 18.8 (C), 18.4 (CH_3), 17.8 (CH_3), 14.2 (CH_3), 13.8 (CH_3); *m/z* (CI, NH_3) 575 ($[M+H]^+$, 19%). Found: $[M+H]^+$, 575.3290. $C_{34}H_{47}N_2O_4Si$ requires 575.3305.

Ethyl N-(N-methyl-N-((1′S,2′S)-1′-TBDPSO-1′-phenyl-2′-propyl)carboxamido)-(R)-valinate ((*R*)-**27**). The above procedure using (*R*)-(−)-valine (118 mg, 1.0 mmol) afforded (*R*)-(−)-valine ethyl ester hydrochloride

(185 mg, 100%) as an off-white solid, δ_H (250 MHz, $CDCl_3$) 8.87 (2H, br s, NH_2), 4.37–4.19 (2H, m, CH_3CH_2O), 3.90 (1H, d, $J=4.8$ Hz, NCH), 2.49 (1H, m, $(CH_3)_2CH$), 1.31 (3H, t, $J=7.0$ Hz, CH_3CH_2O), 1.20–1.09 (6H, m, $(CH_3)_2CH$). Further reaction of (*R*)-(−)-valine ethyl ester hydrochloride (180 mg, 0.97 mmol) afforded the title compound (*R*)-**27** (420 mg, 78%) as a colourless viscous oil, $[\alpha]_D^{20}$ +37.3 (*c* 3.8, $CHCl_3$); ν_{max}/cm^{-1} 3438, 3071, 2963, 2858, 2242, 1731, 1650, 1503, 1372, 1311, 1262, 1195, 1111, 921, 823, 735, 703, 612; δ_H (250 MHz, $CDCl_3$) 7.65–7.10 (15H, m, Ar-H), 4.88 (1H, d, $J=7.7$ Hz, NH), 4.72–4.55 (1H, br m, PhCHC*H*), 4.50 (1H, d, $J=7.9$ Hz, PhC*H*CH), 4.43 (1H, dd, $J=7.7$, 4.7 Hz, ^{i}PrCH), 4.22–4.10 (2H, m, CH_3CH_2O), 2.34 (3H, s, NCH_3), 2.15–1.95 (1H, m, $(CH_3)_2CH$), 1.25 (3H, t, $J=7.0$ Hz, CH_3CH_2O), 0.93 (9H, s, $C(CH_3)_3$), 0.89 (3H, d, $J=6.9$ Hz, $(CH_3)_2CH$), 0.86 (3H, d, $J=6.9$ Hz, $(CH_3)_2CH$), 0.77 (3H, d, $J=6.6$ Hz, NCHCH_3); δ_C (62.9 MHz, $CDCl_3$, 3 aromatic CH not found) 172.8 (C), 157.7 (C), 141.6 (C), 135.7 (CH), 133.4 (C), 133.0 (C), 129.3 (CH), 129.1 (CH), 127.7 (CH), 127.2 (CH), 126.8 (CH), 77.0 (CH), 60.5 (CH_2), 58.1 (CH), 55.8 (CH), 31.4 (CH), 28.1 (CH_3), 26.6 (CH_3), 18.9 (C), 18.5 (CH_3), 17.7 (CH_3), 14.2 (CH_3), 14.0 (CH_3); *m/z* (CI, NH_3) 575 ($[M+H]^+$, 100%). Found: $[M+H]^+$, 575.3312. $C_{34}H_{47}N_2O_4Si$ requires 575.3305.

4.3.2.3. Attempted cleavage of the pseudoephedrine auxiliary. *Ethyl N-(N-methyl-N-((1′S,2′S)-1′-hydroxy-1′-phenyl-2′-propyl)carboxamido)-(S)-valinate* **29**. To a solution of TBDPS protected carboxamido valinate (*S*)-**27** (98 mg, 0.17 mmol) in THF (1.5 ml) was added 1 M TBAF in THF (0.3 ml, 0.3 mmol). After stirring at room temperature for 90 min, water (4 ml) was added and extracted with ether (2×5 ml). The organics were dried over $MgSO_4$, evaporated and purified by flash chromatography (2–5% MeOH in CH_2Cl_2) to afford the free-hydroxy carboxamido valinate **29** (55 mg, 96%) as a colourless viscous oil, $[\alpha]_D^{24}$ +56.0 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} 3323, 2966, 1733, 1632, 1518, 1454, 1394, 1314, 1260, 1191, 1028, 759, 702; δ_H (300 MHz, $CDCl_3$) 7.36–7.27 (5H, m, Ar-H), 5.24 (1H, d, $J=8.2$ Hz, NH), 4.52 (1H, dd, $J=8.5$, 5.1 Hz, PhC*H*CH), 4.40 (1H, dd, $J=8.4$, 4.8 Hz, ^{i}PrCH), 4.29–4.15 (4H, m, PhCHC*H*, OH, CH_3CH_2O), 2.82 (3H, s, NCH_3), 2.15 (1H, m, $(CH_3)_2CH$), 1.29 (3H, t, $J=7.1$ Hz, CH_3CH_2O), 1.00–0.92 (9H, m, $(CH_3)_2CH$ and NCHCH_3); δ_C (75.4 MHz, $CDCl_3$) 173.2 (C), 159.9 (C), 142.3 (C), 128.3 (CH), 127.6 (CH), 126.6 (CH), 76.8 (CH), 61.0 (CH_2), 58.5 (CH), 58.2 (CH), 31.2 (CH), 30.0 (CH_3), 19.0 (CH_3), 17.9 (CH_3), 15.1 (CH_3), 14.2 (CH_3); *m/z* (CI, NH_3) 337 ($[M+H]^+$, 100%). Found: $[M+H]^+$, 337.2123. $C_{18}H_{29}N_2O_4$ requires 337.2127.

N-(N-Methyl-N-((1′S,2′S)-1′-hydroxy-1′-phenyl-2′-propyl) carboxamido)-(S)-valine **30**. *Method A*. To a solution of free-hydroxy carboxamido valinate **29** (25 mg, 0.07 mmol) in THF (0.5 ml) and water (3 drops) was added lithium hydroxide monohydrate (3 mg, 0.07 mmol). After stirring at room temperature for 20 h the reaction mixture was partitioned between water (2 ml) and ether (4 ml). TLC analysis of the organic layer showed unreacted starting material **29**. The aqueous layer was acidified to pH∼2 with 2 M HCl and re-extracted with ether (4 ml). This organic layer was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to afford **30** as a colourless viscous oil (10 mg, 44%), $[\alpha]_D^{27}$ +40.0 (*c* 0.2, $CHCl_3$); ν_{max}/cm^{-1} 3377, 2966, 2606, 2248, 1723, 1611, 1525, 1396, 1203, 732; δ_H (250 MHz, $CDCl_3$) 7.36–7.26 (5H, m, Ar-H), 5.61 (1H, br d, $J=8.6$ Hz, NH), 4.52 (1H, d, $J=9.1$ Hz, PhCH), 4.29 (1H, dd, $J=8.6$, 5.2 Hz, ^{i}PrCH), 4.13 (1H, m, PhCHC*H*), 2.84 (3H, s, NCH_3), 2.22 (1H, m, $(CH_3)_2CH$), 1.08–0.90 (9H, m, NCHCH_3 and $(CH_3)_2CH$); δ_C (62.9 MHz, $CDCl_3$) 175.6 (C), 161.0 (C), 141.6 (C), 128.5 (CH), 127.9 (CH), 126.7 (CH), 76.3 (CH), 59.1 (CH), 58.7 (CH), 30.4 (CH), 29.6 (CH_3), 19.4 (CH_3), 18.0 (CH_3), 15.3 (CH_3); *m/z* (CI, NH_3) 309 ($[M+H]^+$, 10%). Found: $[M+H]^+$, 309.1812. $C_{16}H_{25}N_2O_4$ requires 309.1814.

Method B. To a solution of free-hydroxy carboxamido valinate **29** (30 mg, 0.09 mmol) in THF (0.5 ml) at 0 °C under nitrogen was added sodium hydride (60% w/w in mineral oil, 4 mg, 0.1 mmol). After stirring at room temperature for 20 h the reaction mixture was evaporated and partitioned between water (2 ml) and CH_2Cl_2 (4 ml). TLC analysis of the organic layer showed unreacted starting material **29**. The aqueous layer was acidified to pH∼2 with 2 M HCl and re-extracted with CH_2Cl_2 (4 ml). This organic layer was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to afford **30** as a colourless viscous oil (12 mg, 44%), analytically identical to that derived from method A.

Ethyl N-(((1′S,2′S)-2′-methylamino-1′-phenyl-1′-propyl) alkoxycarbonyl)-(S)-valinate hydrochloride **31**. To a sample of crude free-hydroxy carboxamido valinate **29**, derived from TBDPS protected carboxamido valinate **27** (166 mg, 0.29 mmol) without chromatographic purification, was added 1 M HCl in ether (2 ml, 2 mmol). After stirring under nitrogen at room temperature for 20 h, a white precipitate had formed which was removed by filtration and recrystallised from ethyl acetate to afford **31** (18 mg, 17%) as white needles, mp 145 °C (decomp.), $[\alpha]_D^{29}$ +31.6 (*c* 0.095, $CHCl_3$); ν_{max}/cm^{-1} 3372, 2967, 2736, 2459, 1729, 1529, 1467, 1375, 1270, 1233, 1209, 1095, 1028, 702; δ_H (250 MHz, $CDCl_3$) 9.94 and 9.72 (2H, 2×br, NH_2), 7.46–7.30 (5H, m, Ar-H), 6.39 (1H, d, $J=9.2$ Hz, NH), 5.47 (1H, d, $J=9.7$ Hz, PhCH), 4.20–4.00 (3H, m, ^{i}PrCH, CH_3CH_2O), 3.85–3.65 (1H, br m, PhCHC*H*), 2.67 (3H, br s, NCH_3), 2.30–2.10 (1H, m, $(CH_3)_2CH$), 1.24 (3H, d, $J=6.8$ Hz, NCHCH_3), 1.16 (3H, t, $J=7.0$ Hz, CH_3CH_2O), 1.02 (3H, d, $J=6.7$ Hz, $(CH_3)_2CH$), 1.00 (3H, d, $J=6.7$ Hz, $(CH_3)_2CH$); δ_C (62.9 MHz, $CDCl_3$) 171.4 (C), 154.6 (C), 136.3 (C), 129.2 (CH), 128.9 (CH), 127.1 (CH), 75.3 (CH), 60.9 (CH_2), 59.5 (CH), 57.1 (CH), 31.1 (CH), 27.1 (CH_3), 19.1 (CH_3), 17.8 (CH_3), 14.1 (CH_3), 12.3 (CH_3); *m/z* (CI, NH_3) 337 ($[M+H]^+$, 58%). Found: $[M+H]^+$, 337.2116. $C_{18}H_{29}N_2O_4$ requires 337.2127. The structure was confirmed by X-ray crystallography.[31]

The filtrate was shown by ^{1}H NMR to be predominantly unreacted free-hydroxy carboxamido valinate **27**.

4.3.3. Aminations using oxaziridine 4 (Tables 3–5).

4.3.3.1. General procedure. To a stirred solution of LiHMDS (1.0 M in hexanes, 0.22 ml, 0.22 mmol) in THF (1 ml) at −78 °C was added substrate (0.22 mmol) dropwise. After 30 min oxaziridine (65 mg, 0.22 mmol) in

THF (1 ml) was added dropwise. The reaction mixture was stirred at −78 °C for ca. 20 h before allowing to warm to room temperature. The reaction was quenched by the addition saturated aqueous NH_4Cl and CH_2Cl_2. The organic layer was further washed twice with saturated aqueous NH_4Cl, then dried (Na_2SO_4) and concentrated in vacuo. The product was then purified by flash chromatography.

4.3.3.2. Product data. *2-[N-(tert-Butylcarbonyl)amino] acetophenone* **32a**[27] (Table 3, entry 1). Using the above procedure followed by flash column chromatography (petrol–ethyl acetate 10:1) yielded the title compound (10.8 mg, 21%) as a white solid, mp 56.8–57.4 °C; δ_H (300 MHz, $CDCl_3$) 7.98 (2H, d, J=7.3 Hz, C*H*), 7.63 (1H, t, J=7.4 Hz, C*H*), 7.51 (2H, t, J=7.6 Hz, C*H*), 5.57 (1H, brd s, N*H*), 4.68 (2H, d, J=4.3 Hz, CH_2), 1.50 (9H, s, $(CH_3)_3$).

2-N-Boc-Amino-1-phenyl-1-propanone **32b**[28] (Table 3, entry 2). Using the above procedure followed by flash column chromatography (petrol–ethyl acetate 10:1) yielded the title compound (17 mg, 31%) as a white solid, mp 80.3–81.0 °C; δ_H (300 MHz, $CDCl_3$) 8.00 (2H, d, J=7.4 Hz, CH), 7.62 (1H, t, J=7.4 Hz, CH), 7.51 (2H, t, J=7.6 Hz, CH), 5.58 (1H, br s, NH), 5.32 (2H, app t, J=6.9 Hz, CH), 1.48 (9H, s, $(CH_3)_3$), 1.42 (3H, d, J=6.9 Hz, CH_3).

N-(2-Oxo-1,2-diphenyl-ethyl)-carbamic acid tertbutyl ester **32c**[29] (Table 3, entry 3). Using the above procedure followed by flash column chromatography yielded the title compound (10.2 mg, 15%) as a white solid, δ_H (300 MHz, $CDCl_3$) 7.98 (2H, d, J=7.4 Hz, CH), 7.52 (1H, t, J=7.3 Hz, CH), 7.26–7.44 (2H, m, CH), 6.29 (1H, d, J=7.6 Hz, CH), 6.04 (1H, d, J=7.6 Hz, NH), 1.45 (9H, s, $(CH_3)_3$).

(Cyano-phenyl-methyl)-carbamic acid tert-butyl ester **37a** (Table 4, entry 1). Using the above procedure followed by flash column chromatography (petrol–ethyl acetate 10:1) yielded the title compound (22.9 mg, 45%) as a white solid, mp 110.9–112.8 °C; ν_{max}(film)/cm^{-1} 3325, 2978, 1692; δ_H (300 MHz, $CDCl_3$) 7.44 (5H, m, ArC*H*), 5.82 (1H, d, J= 7.2 Hz, N*H*), 5.16 (1H, brd s, C*H*), 1.50 (9H, s, $(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 154.5 (C), 133.8 (C), 129.9 (CH), 129.7 (CH), 127.3 (CH), 118.1 (CN), 81.9 (C), 46.5(CH), 28.6 ($(CH_3)_3$); *m/z* (CI) 250 (M+NH_4), 233 (M+H). Found MH^+233.1282 $C_{13}H_{17}N_2O_2$ requires 233.1290.

[Cyano-(4-methoxy-δ-phenyl)-methyl]-carbamic acid tert-butyl ester ester **37b** (Table 4, entry 2). Using the above procedure followed by flash column chromatography (petrol–ethyl acetate 10:1) yielded the title compound (11.8 mg, 20%) as a white solid, mp 119.5–121.8 °C; ν_{max}(film)/cm^{-1} 3560, 3537, 2979, 2934, 2248, 1695, 1513; δ_H (300 MHz, $CDCl_3$) 7.41 (2H, d, J=8.6 Hz, ArC*H*), 6.95 (2H, d, J=8.7 Hz, ArC*H*), 5.73 (1H, brd d, J=7.3 Hz, N*H*), 5.07 (1H, brd s, 1H, C*H*), 3.84 (3H, s, OCH_3), 1.49 (9H, s, $(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 160.4 (C), 154.1 (C), 128.4 (C*H*), 125.5 (C), 117.9 (CN), 114.6 (CH), 81.5 (C), 55.4 (OCH_3), 45.7 (CH), 28.2 ($(CH_3)_3$); *m/z* (CI) 280 (M+NH_4), 263 (M+H). Found (M+NH_4), 280.1665. $C_{14}H_{22}N_3O_3$ requires 280.1661.

[(4-Chloro-phenyl)-cyano-methyl]-carbamic acid tert-butyl ester **37c** (Table 4, entry 3). Using the above procedure followed by flash column chromatography (petrol–ethyl acetate 10:1) yielded the title compound (26.8 mg, 46%) as a white solid, mp 143.8–144.7 °C; ν_{max}(film)/cm^{-1} 3432, 3055, 2988, 2306, 1721; δ_H (300 MHz, $CDCl_3$) 7.42–7.43 (4H, m, ArC*H*), 5.80 (1H, brd d, 1H, J=6.9 Hz, N*H*), 5.24 (1H, brd d, J=6.9 Hz, C*H*), 1.49 (9H, s, $(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 154.1 (C), 135.5 (C), 132.0 (C), 129.4 (CH), 128.2 (CH), 117.3 (CN), 81.7 (C), 45.4 (CH), 28.2 ($(CH_3)_3$); *m/z* (CI) 284 (M+NH_4), 267 (M+H). Found MH^+267.0903. $C_{13}H_{15}N_2O_2Cl$ requires 267.0900.

tert-Butoxycarbonylaminocyano acetic acid ethyl ester ester **37d** (Table 4, entry 4). Using the above procedure followed by flash column chromatography (petrol–ethyl acetate 10:1) yielded the title compound (16.5 mg, 33%) as a white solid, mp 69.8–72.0 °C; ν_{max}(film)/cm^{-1} 3344, 2985, 2932, 2254, 1753, 1684; δ_H (300 MHz, $CDCl_3$) 5.47 (1H, brd d, J=6.6 Hz, N*H*), 5.23 (1H, d, J=7.9 Hz, C*H*), 4.37 (3H, q, J=7.1 Hz, CH_2), 1.48 (9H, s, $(CH_3)_3$) 1.37 (3H, t, J=7.1 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 163.6 (C), 154.1 (C), 114.4 (CN), 82.0 (C), 64.1 (CH_2), 44.7 (CH), 28.1 ($(CH_3)_3$) 13.9 (CH_3); *m/z* (CI) 246 (M+NH_4), 229 (M+H). Found MH^+229.1186. $C_{10}H_{17}N_2O_4$ requires 229.1188.

The same reaction with 1.5 equiv **4** gave **37d** (13.1 mg, 26%) as a white solid and the diaminated species (14.1 mg 18%) as a white solid, mp 125–127 °C. Diaminated (di-*tert*-butoxycarbonylamino)cyano acetic acid ethyl ester, ν_{max}(film)/cm^{-1} 3323, 3272, 2980, 2929, 1764, 1698, 1685; δ_H (300 MHz, $CDCl_3$) 6.43 (2H, brd s, $(NH)_2$), 4.44 (2H, q, J=7.1 Hz, CH_2CH_3), 1.47 (9H, s, $(CH_3)_3$), 1.37 (3H, t, J=7.1 Hz, CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 162.9 (C), 153.4 (C), 114.1 (CN), 82.7 (C), 65.3 (CH_2), 62.4 (C), 28.5 ($(CH_3)_3$) 14.1 (CH_3); *m/z* (CI) 361 (M+NH_4), 344 (M+H). Found MH^+344.1810. $C_{15}H_{26}N_3O_6$ requires 344.1822.

tert-Butoxycarbonylaminocyano acetic acid tert-butyl ester **37e** (Table 4, entry 5). Using the above procedure followed by flash column chromatography (petrol–ethyl acetate 10:1) yielded the title compound (11.6 mg, 20%) as an oil; ν_{max}(film)/cm^{-1} 3352, 2981, 2934, 2254, 1815, 1749, 1722, 1152; δ_H (300 MHz, $CDCl_3$) 5.37 (1H, s, N*H*), 5.16 (1H, d, J=7.9 Hz, C*H*), 1.55 (9H, s, $(CH_3)_3$) 1.49 (9H, s, $(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 162.2 (C), 154.0 (C), 114.7 (CN), 86.0 (C), 81.8 (C), 45.1 (CH) 28.1 ($(CH_3)_3$), 27.7 ($(CH_3)_3$); *m/z* (CI) 274 (M+NH_4), 257 (M+H). Found M+NH_4 274.1760. $C_{12}H_{24}N_3O_4$ requires 274.1767.

tert-Butoxycarbonylaminocyanophenyl acetic acid ethyl ester **37f** (Table 4, entry 6). Using the above procedure but using 1.5 equiv oxaziridine (95 mg, 0.33 mmol) followed by flash column chromatography (petrol–ethyl acetate 10:1) yielded the title compound (46.9 mg, 70%) as an oil; ν_{max}(film)/cm^{-1} 3416, 3060, 2983, 2937, 2253, 1754, 1721, 1481, 1286; δ_H (300 MHz, $CDCl_3$) 7.67 (2H, br s, C*H*), 7.45–7.46 (3H, m, C*H*), 5.75 (1H, br s, N*H*), 4.29 (2H, q, J=7.2 Hz, CH_2), 1.46 (9H, s, $(CH_3)_3$) 1.25 (3H, t, J=7.2 Hz); δ_C (75 MHz, $CDCl_3$, 323 K) 165.4 (C), 160.9 (C), 133.6 (C), 129.9 (CH), 129.2 (CH), 125.9 (CH), 116.2 (CN), 82.2 (C), 64.1 (CH_2) 61.4 (C), 28.1 ($(CH_3)_3$) 13.6 (CH_3); *m/z* (CI) 322 (M+NH_4), 305 (M+H). Found MH^+305.1511. $C_{16}H_{21}N_2O_4$ requires 305.1501.

Dimethyl-2-[(tert-butyloxycarbonyl)amino]methylmalonate **38a** (Table 5, entry 1). Using the above procedure (anion stirred with the oxaziridine for 4 h) followed by flash column chromatography (petrol–ethyl acetate 10:1) yielded the title compound (17.2 mg, 30%) as an oil; ν_{max}(film)/cm^{-1} 3432, 2978, 2957, 1746, 1720, 1288; δ_H (300 MHz, $CDCl_3$) 5.94 (1H, s, N*H*), 3.79 (6H, s, (OCH_3)$_2$), 1.75 (3H, s, CH_3), 1.44 (9H, s, (CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 167.6 (C), 152.1 (C), 78.6 (C), 61.1 (C), 51.6 (OCH$_3$)$_2$) 26.4 ((CH$_3$)$_3$), 19.9 (CH$_3$); *m/z* (CI) 279 (M+NH$_4$), 262 (M+H). Found MH$^+$262.1302. $C_{11}H_{20}NO_6$ requires 262.1290.

Diethyl-2-[(tert-butyloxycarbonyl)amino]methylmalonate **37f** (Table 5, entry 2). Using the above procedure followed by flash column chromatography (petrol–ethyl acetate 10:1) yielded the title compound (13.8 mg, 22%) as an oil, ν_{max}(film)/cm^{-1} 3432, 2980, 2939, 1741, 1721, 1283; δ_H (300 MHz, $CDCl_3$) 5.91 (1H, s, N*H*), 4.25 (4H, q, J=7.0 Hz, (OCH_2CH$_3$)$_2$), 1.74 (3H, s, CH_3), 1.44 (9H, s, (CH_3)$_3$) 1.27 (6H, t, J=7.0 Hz, (OCH$_2$CH_3)$_2$); δ_C (75 MHz, $CDCl_3$) 167.8 (C), 152.8 (C), 79.2 (C), 61.9 (C), 61.3 (CH$_2$), 27.2 (CH$_3$)$_3$), 20.4 (CH$_3$), 12.9 (CH$_3$); *m/z* (CI) 307 (M+NH$_4$), 290 (M+H). Found M+NH$_4$ 290.1596. $C_{13}H_{24}NO_6$ requires 290.1604.

4.3.4. α-Chlorination of titanium enolates. *α-Chloropropiophenone* **33**.[21] To a solution of propiophenone (70 μl, 0.52 mmol) in CH_2Cl_2 (2 ml) at −78 °C under nitrogen was added titanium tetrachloride (70 μl, 0.64 mmol) followed by tributylamine (175 μl, 0.74 mmol). After stirring for 30 min oxaziridine **3a** (150 mg, 0.59 mmol) in CH_2Cl_2 (1 ml) was added. The reaction was allowed to warm to room temperature over 2.5 h, quenched with saturated aqueous NH_4Cl (15 ml), and extracted with CH_2Cl_2 (3×10 ml). The combined organics were dried over $MgSO_4$, filtered, evaporated and purified by flash chromatography (5% EtOAc in petrol) to afford α-chloropropiophenone **33** (74 mg, 84%) as a yellow oil, δ_H (250 MHz, $CDCl_3$) 8.00–7.95 (2H, m, Ar-H), 7.60–7.41 (3H, m, Ar-H), 5.24 (1H, q, J=6.7 Hz, CH), 1.71 (3H, d, J=6.7 Hz, CH_3); *m/z* (CI, NH_3) 186 ([M+NH$_4$]$^+$, 95%). Consistent with literature.[21]

Similar reaction of propiophenone (18 μl, 0.13 mmol) with oxaziridine **8** (~95%, 90 mg, 0.15 mmol) afforded α-chloropropiophenone **33** (3 mg, 13%), analytically identical to above. HPLC analysis (Chiralcel-OD, 0.5 ml/min, 1% ^{i}PrOH in hexane) showed racemic product.

α-Chlorodeoxybenzoin **34**.[21] Reaction of deoxybenzoin (99 mg, 0.5 mmol) as above afforded α-chlorodeoxybenzoin **346** (100 mg, 86%) as a white solid, δ_H (250 MHz, $CDCl_3$) 8.02–7.30 (10H, m, Ar-H), 6.36 (1H, s, CH); *m/z* (CI, NH_3) 248 ([M+NH$_4$]$^+$, 100%). Consistent with literature.[21]

4.3.5. Reaction of ethyl phenylcyanoacetate with 2-(diethylcarboxamido)-3-(*p*-chlorophenyl)oxaziridine 3a using LiHMDS as base. Reaction of ethyl phenylcyanoacetate (36 μl, 0.20 mmol), oxaziridine **3a** (51 mg, 0.20 mmol) and LiHMDS (1 M in hexanes, 200 μl, 0.20 mmol) followed by flash chromatography (4–40% EtOAc in petrol) afforded ethyl phenylketoacetate **35** (16 mg, 45%) and α-cyano-*N*-diethylcarboxamido-*p*-chlorobenzylamine **36** (16 mg, 30%).

Ethyl phenylketoacetate **35**.[26] Isolated as a colourless oil, δ_H (250 MHz, $CDCl_3$) 8.01 (2H, m, Ar-H), 7.66 (1H, tt, J=7.3, 1.6 Hz, Ar-H), 7.51 (2H, m, Ar-H), 4.45 (2H, q, J=7.1 Hz, OCH_2CH$_3$), 1.42 (3H, t, J=7.1 Hz, OCH$_2$CH_3). Consistent with lit.[26]

α-Cyano-N-diethylcarboxamido-p-chlorobenzylamine **36**. Isolated as an off-white solid, ν_{max}/cm^{-1} 3315, 2977, 2933, 1637, 1518, 1492, 1282, 1094, 826; δ_H (250 MHz, $CDCl_3$) 7.48–7.36 (4H, m, Ar-H), 6.10 (1H, d, J=8.6 Hz, CH), 5.03 (1H, br d, J=8.6 Hz, NH), 3.34–3.19 (4H, m, NCH_2CH$_3$), 1.14 (6H, t, J=7.2 Hz, NCH$_2$CH_3); δ_C (101 MHz, $CDCl_3$) 155.1 (C), 135.2 (C), 133.0 (C), 129.4 (CH), 128.3 (CH), 118.2 (C), 45.3 (CH), 41.4 (CH$_2$), 13.7 (CH$_3$); *m/z* (CI, NH_3) 283 ([M+NH$_4$]$^+$, 97%), 266 ([M+H]$^+$, 100). Found: [M+H]$^+$, 266.1066. $C_{13}H_{17}N_3OCl$ requires 266.1060.

4.3.6. Reaction of acetophenone-trimethylsilylenol ether with oxaziridine 3a. A solution of acetophenone TMS enol ether (80 μl, 0.39 mmol) and oxaziridine **1a** (90 mg, 0.35 mmol) in ethanol (0.4 ml) was stirred at room temperature under nitrogen. After 44 h, 1 M HCl (2 ml) was added and extracted with CH_2Cl_2 (2×2 ml). The organics were dried over $MgSO_4$, filtered and evaporated to afford a crude mixture of amino ester **41** and hydroxy ketone **40** (~1:8). α-Hydroxyacetophenone **40** was isolated as a white solid, δ_H (250 MHz, $CDCl_3$) 7.92 (2H, m, Ar-H), 7.63 (1H, m, Ar-H), 7.50 (2H, m, Ar-H), 4.88 (2H, d, J=4.7 Hz, CH_2), 3.53 (1H, t, J=4.7 Hz, OH). Consistent with literature.[30] Amidoketone **41** was not isolated in pure form, but was identified by the following data: δ_H (250 MHz, $CDCl_3$) includes 5.54 (1H, br m, NH), 4.82 (2H, d, J=4.2 Hz, CH_2); *m/z* (CI, NH_3) 235 ([M+H]$^+$, 100%). Found: [M+H]$^+$, 235.1447. $C_{13}H_{19}N_2O_2$ requires 235.1447.

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Lewis acid-catalyzed asymmetric radical additions of trialkylboranes to (1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl-2*H*-azirine-3-carboxylate

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Abstract—The asymmetric addition of alkyl radicals to (1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl-2*H*-azirine-3-carboxylate (**1**) yielding the corresponding 2-alkylaziridine-2-carboxylates has been investigated. High diastereoselectivities and good yields were obtained in the addition of primary alkyl radicals to azirine **1**, while secondary radicals gave a lower dr. The influence of Lewis acids was also investigated; 10 mol% of CuCl were found to increase the dr.

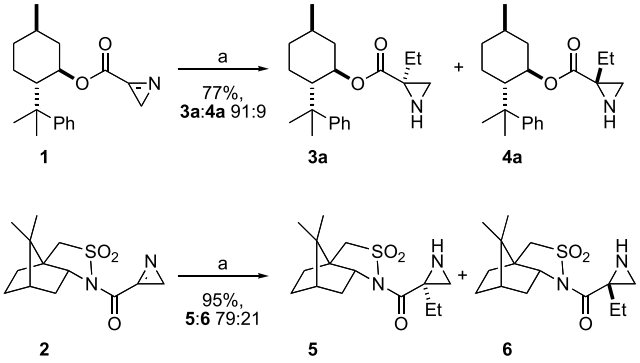
1. Introduction

The asymmetric addition of carbon nucleophiles to imines is an important route to chiral amines and has been employed in the synthesis of various amino acids and alkaloids.[1] In the search for new, efficient and general methods to generate enantiopure amines, radical addition to imine derivatives, particularly oxime ethers and hydrazones, has become an interesting alternative.[2,3] In this respect, it has recently been shown that 2*H*-azirines are promising alternative alkyl radical acceptors,[4] yielding aziridines, a class of compounds that has received much recent attention.[5]

There are two common methods to induce stereoselectivity in intermolecular alkyl radical additions to imines, either by use of a chiral Lewis acid or by a chiral auxiliary.[2,3,6] A large number of Lewis acids have previously been investigated in order to increase selectivities and reactivities in radical reactions.[6,7] However, difficulties experienced when studying the asymmetric addition of organolithiums[8] and the hetero Diels–Alder reaction using azirines as substrates and various chiral Lewis acids to mediate the reactions indicated the difficulties associated with this approach.[9] In contrast, it was shown that 8-phenylmenthyl-2*H*-azirine-3-carboxylate undergoes highly diastereoselective aza-Diels–Alder reactions under Lewis acid activation.[9,10] Prompted by these results we decided to investigate the use of chiral auxiliaries in the asymmetric addition of alkyl radical addition to azirines, and herein detail our results.[11]

2. Results and discussion

Azirine carboxylates **1** and **2**, having as auxiliaries 8-phenylmenthyl and Oppolzers sultam, respectively, were selected as substrates for initial screening in the radical addition reaction (Scheme 1). Initial studies were conducted using Et_3B/O_2 as radical initiator; in this reaction Et_3B is believed to function as an initiator and Lewis acid.[12,13] Using these reaction conditions azirine **1** gave **3a**:**4a** in excellent dr (91:9) and good yield (77%), while **2** afforded **5**:**6** in only modest dr (79:21) but high yield (95%).



Scheme 1. (a) Et_3B (5 equiv), EtI (10 equiv) O_2, CH_2Cl_2, −105 °C.

Keywords: Azirines; Asymmetric radical addition; Chiral auxiliaries.
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Consequently azirine **1** was chosen as substrate for further investigations.

Optimization of the reaction conditions showed that the highest diastereoselectivity was obtained in CH_2Cl_2 or Et_2O, dr 91:9 in both solvents, and CH_2Cl_2 was chosen for further studies. The dependence of the temperature on the dr was then evaluated (Table 1).

Table 1. Influence of temperature on diastereoselectivity[a]

Entry	Temperature (°C)	Yield[b] (%)	dr[c] **3a**:**4a**
1	−105	77	91:9
2	−78	76	88:12
3	−40	72	85:15
4	−20	80	72:28
5	0	70	66:34
6	rt	65	55:45

[a] Reaction conditions: azirine **1** (1 equiv), EtI (10 equiv), Et_3B (5 equiv), O_2 (5 mL), CH_2Cl_2, 5 min.
[b] Isolated yield.
[c] Determined by HPLC.

As expected the highest dr was obtained at −105 °C (entry 1), but the selectivity decreased only slightly for temperatures up to −40 °C (entries 2, 3). With temperatures at and above −20 °C the dr fell dramatically, giving almost a 1:1 mixture at rt (entries 4–6).

The addition of other alkyl radicals was then attempted. This could potentially be realized by an iodine atom-transfer process in which the desired radical ($R^{\cdot}$) is generated from an initiator, such as Et_3B/O_2, and R–I to give EtI and the corresponding alkyl radical ($R^{\cdot}$).[14] A requirement in this process is that the generated radical ($R^{\cdot}$) is more stable then $Et^{\cdot}$, shifting the equilibrium towards addition of the desired radical ($R^{\cdot}$). To test the feasability of this protocol, three secondary and tertiary alkyl iodides were selected for an initial screening (Table 2).

Table 2. Effect of alkyl iodides on the addition of ethyl radical to **1**[a]

Entry	RI	Yield[b] (%)	dr[c] **3a**:**4a**
1	*i*-PrI	58	94:6
2	*t*-BuI	62	93:7
3	*c*-$C_6H_{11}I$	71	94:6
4	*c*-$C_6H_{11}I$[d]	82	89:11

[a] Reaction conditions: azirine **1** (1 equiv), RI (10 equiv), Et_3B (5 equiv), O_2 (5 mL), CH_2Cl_2, −105 °C, 5 min.
[b] Isolated yield of **3a**:**4a**.
[c] Determined by HPLC.
[d] Freshly distilled *c*-$C_6H_{11}I$ was used.

The reaction of azirine **1** with *i*-PrI, *t*-BuI and *c*-$C_6H_{11}I$ in the presence of Et_3B/O_2 gave selective addition of only the ethyl radical, furnishing **3a**,**4a** in moderate to good yields and high diastereoselectivity (entries 1–3). Considering that the radical transfer rate can be slow at low temperatures and that all starting material was consumed after 5 min at −105 °C, these observations are understandable.[4,15] Interestingly, the dr obtained in these reactions were somewhat higher compared to a reaction without an added alkyl iodide (compare Table 2, entries 1–3 with Table 1, entry 1). Commercially available alkyl iodides are stabilized with metallic copper, the salts of which are well known to act as Lewis acids.[16] When the reaction was repeated with freshly distilled *c*-$C_6H_{11}I$ the dr dropped, supporting the notion of Cu-salts acting as Lewis acids (entry 4).

Consequently, it was decided to investigate the influence of Lewis acids on the radical addition reaction (Table 3). Strong Lewis acids such as $BF_3\cdot OEt_2$ and $SnCl_4$ were found to cause instant decomposition of azirine **1**. Weaker Lewis acids were therefore, selected; initially five different Lewis acids were investigated (entries 2–6). Catalytic amounts of AgOTf and CuCl increased the dr, giving aziridine **2a** in moderate yields (entries 2 and 3), while treatment with $Cu(OTf)_2$ significantly decreased the dr (entry 4). Neither $In(OTf)_3$ nor $YbCl_3$ altered the diastereoselectivity, but caused dramatically lowered yields (entries 5 and 6). The use of Lewis acids lowered the yield in all reactions and unreacted **1** was present in all reaction mixtures, as judged by TLC. As a result the reaction time was increased to 60 min in the subsequent experiments. Three Cu(I) salts were evaluated to investigate the importance of the counter ion (entries 7–9). Lower yields were obtained in all cases, compared to the uncatalyzed reaction. The selectivities for the $(CuOTf)_2\cdot$ PhMe and CuI catalyzed reactions were lower compared to the uncatalyzed one, while the dr in the reaction promoted by CuCl was higher. This suggests that the Lewis acid not only influences the dr but also decreases the reactivity of **1** to various extents. We have previously shown that $MgBr_2\cdot OEt_2$ and $ZnCl_2\cdot OEt_2$ are excellent catalysts for the hetero Diels–Alder reaction with **1**.[9,10] In the present reaction, however, they gave inferior results.

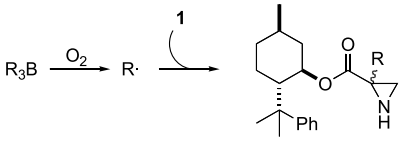
Table 3. Influence of Lewis acids on the radical addition to azirine **1**[a]

Entry	Reaction time (min)	Lewis acid/ equiv	Yield[b] (%)	dr[c] **3a**:**4a**
1	5	—	81	91:9
2	5	AgOTf/0.1	52	96:4
3	5	CuCl/0.1	53	96:4
4	5	$Cu(OTf)_2$/0.1	54	75:25
5	5	$In(OTf)_3$/0.1	16	90:10
6	5	$YbCl_3$/0.1	28	90:10
7	60	CuCl/0.1	69	96:4
8	60	CuI/0.1	58	91:9
9	60	$(CuOTf)_2\cdot$ ⊜ PhMe/0.1	61	92:8

[a] Reaction conditions: azirine **1** (1 equiv), Et_3B (3 equiv), Lewis acid, O_2 (5 mL), CH_2Cl_2, −105 °C.
[b] Isolated yield.
[c] Determined by HPLC.

From the results in Table 2 it is evident that the atom-transfer technique is not applicable to the addition of alkyl moieties, other than ethyl, to **1**. To circumvent this drawback it was decided to investigate the use of other boranes in the addition reaction (Scheme 2).[17]

A requirement in the alkyl radical addition to **1** is the use of 3 equiv of Et_3B. Attempts with 0.5 and 2 equiv of Et_3B gave only trace amounts of aziridines **3a**:**4a**. Trialkylboranes coordinated to a donor atom such as oxygen or nitrogen, as is the case in the present reaction, might be less inclined to react with O_2 to generate alkyl radicals, and consequently the formation of radicals from such species might be retarded. The necessity for excessive amounts of Et_3B is consistent with a mechanism in which the trialkylborane



Scheme 2. Addition of trialkylboranes to azirine **1**.

plays multiple roles: as Lewis acid, radical initiator, and terminator.[4,18] Consequently, it would be valuable if a radical initiator carrying less than three R-groups could be applied. B-Alkyl catecholboranes have been used as radical sources in reactions with enones, vinyl sulfones and in direct allylations.[19] Disappointingly, attempts with B-propyl catecholborane as a radical initiator only gave decomposition of azirine **1**, which might be due to the increased Lewis activity of the borane compared to Et_3B. By the same reasoning boranes with N- or S- ligands can be expected to give similar results. As a result, it was decided to investigate the use of various trialkylboranes in the radical addition to azirine **1** and the reults are summarized in Table 4.[20]

In order to further evaluate the influence of Lewis acid activation, all reactions were run in the presence and the absence of catalytic amounts of CuCl. As shown previously, addition of CuCl to azirine **1** prior to addition of Et_3B increased the dr, but lowered the yield (entries 1, 2). Addition of *n*-Bu_3B, gave **3b**:**4b** in good dr that remained unchanged upon addition of CuCl, while the yield increased significantly (entries 3, 4). With the more stable radicals formed from triallylborane, *i*-Pr_3B and *s*-Bu_3B the corresponding aziridines **3c**:**4c**, **3d**:**4d**, and **3e**:**4e** (4 diastereomers) were obtained in modest to good yields, but poor selectivities (entries 5–10). Finally, $(C_6H_{11}CH_2CH_2)_3B$ and (2-methylallyl)$_3B$ were employed to find out if primary radicals generally give higher selectivities than secondary ones in this reaction. This gave aziridines **3f**:**4f** and **3g**:**4g**, respectively, in moderate to good yield and dr (entries 11, 13). In both cases the addition of CuCl increased the dr, but resulted in lower yields with $(C_6H_{11}CH_2CH_2)_3B$ (entries 12, 14).

The relative stereochemistry of the newly formed stereocenter in the addition reactions was analyzed as follows. Compound **3a** and **5**, the major diastereomers from the addition of Et_3B to **1** and **2**, respectively, were separated. Compound **5** was then recrystallized and the absolute configuration of the quaternary aziridine carbon was determined to be (*S*) by X-ray measurements (Fig. 1).[11]

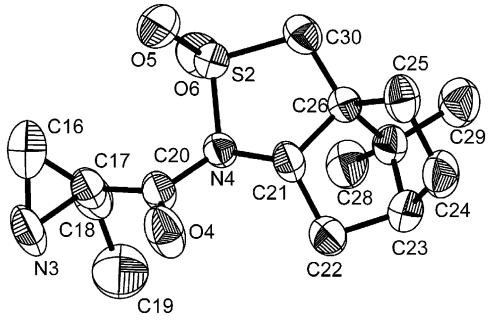
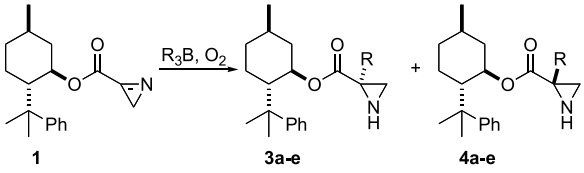


Figure 1. One of the four molecules of **5** in the asymmetric unit. Thermal ellipsoids are drawn at a 50% probability level.

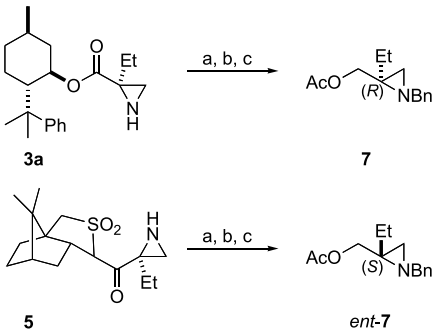
The absolute stereochemistry of **3a** was then deduced as follows. Reduction of aziridine **3a** with $LiAlH_4$ followed by benzylation and acetylation gave compound **7** (Scheme 3).

Table 4. Addition of various alkyl radicals to azirine **1**[a]



Entry	Reaction time (min)	R_3B	Lewis acid/equiv	Products	Yield[b] (%)	Ratio[c]
1	5	Et_3B	—	**3a**:**4a**	81	91:9
2	60	Et_3B	CuCl/0.1	**3a**:**4a**	69	96:4
3	5	*n*-Bu_3B	—	**3b**:**4b**	69	87:13
4	60	*n*-Bu_3B	CuCl/0.1	**3b**,**4b**	81	88:12
5	5	(allyl)$_3B$[d]	—	**3c**:**4c**	72	59:41
6	60	(allyl)$_3B$[d]	CuCl/0.1	**3c**:**4c**	85	66:34
7	5	*i*-Pr_3B[d]	—	**3d**:**4d**	51	49:51
8	60	*i*-Pr_3B[d]	CuCl/0.1	**3d**:**4d**	63	61:39
9	5	*s*-Bu_3B	—	**3e**:**4e**[e]	43	50:50
10	60	*s*-Bu_3B	CuCl/0.1	**3e**:**4e**[e]	63	55:45
11	5	$(C_6H_5CH_2CH_2)_3B$[d]	—	**3f**:**4f**	56	72:28
12	60	$(C_6H_5CH_2CH_2)_3B$[d]	CuCl/0.1	**3f**:**4f**	28	83:17
13	5	(2-methylallyl)$_3B$[d]	—	**3g**:**4g**	71	78:22
14	60	(2-methylallyl)$_3B$[d]	CuCl/0.1	**3g**:**4g**	71	83:17

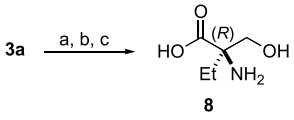
[a] Reaction conditions: azirine **1** (1 equiv), R_3B (3 equiv), Lewis acid, O_2 (5 mL), CH_2Cl_2, −105 °C.
[b] Isolated yield.
[c] Determined by HPLC.
[d] R_3B not isolated and >3 equiv were used.
[e] Four stereoisomers formed.



Scheme 3. (a) $LiAlH_4$, Et_2O, −78 °C→rt, 2 h; (b) BnBr, K_2CO_3, MeCN, reflux; (c) Ac_2O, DMAP, CH_2Cl_2, 0 °C→rt, 3 h, yield over three steps: **7**: 63%, *ent*-**7**: 86%.

Treatment of **5** under identical reaction conditions resulted in a compound that upon comparison with **7** by chiral HPLC and optical rotation proved to be *ent*-**7**. Thus, the absolute configuration of the quaternary carbon in aziridine **3a** is (*R*).

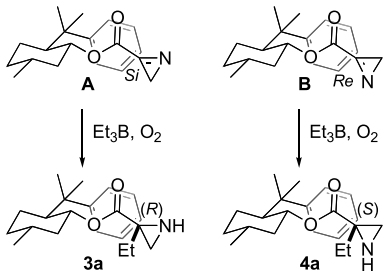
This assignment was also confirmed by chemical correlation (Scheme 4). Hydrolysis[21] of the aziridine moiety in **3a** gave the corresponding amino alcohol, which was benzoylated followed by hydrolysis of the ester moiety to give (*R*)-(+)-C^{α}-ethyl serine (**8**), the analytical data of which was in good agreement with literature data.[22]



Scheme 4. (a) $HClO_4$, THF/H_2O, 80 °C, 10 h; (b) BzCl, Et_3N, DMAP, CH_2Cl_2, rt, 3 h; (c) KOH, hydroquinone, $EtOH/H_2O$, 80 °C, 14 h, yield over three steps: 51%.

It is likely that trialkylborane plays an important role for the stereoselectivity obtained in radical addition to azirine **1**. In contrast to the hetero Diels–Alder reaction with azirine **1**, requiring stoichiometric amounts of a chelating Lewis acid to obtain high diastereoselectivity,[10] good selectivity was observed in the present study in the absence of with Et_3B. Spectroscopic investigations of conjugate radical additions to α,β-unsaturated carbonyl compounds suggest a complexation of the organoborane to the C=O oxygen prior to addition of the radical.[23] It has also been shown that Lewis acids such as $BF_3{\cdot}OEt_2$ can catalyze reactions with 2*H*-azirines, indicating the possibility of coordination to the azirine nitrogen.[24] Thus, the mode of complexation of the trialkylborane to azirine **1** is not obvious.

8-Phenylmenthyl derivatives similar to azirine **1** adopt s-*cis* (**A**) or s-*trans* (**B**) conformations as depicted in Scheme 5.[25] Assuming that these structures are relevant for the present study, then a monodentate Lewis acid is expected, for steric and electronic reasons, to favor s-*trans* conformer (**B**). Addition to this conformer would preferentially take place to the *Re* face of the C=N bond, affording the (*S*) stereochemistry at the newly formed stereocenter. Similarly, a chelating Lewis acid would be expected to preferentially react through structure **A**, thus, affording an adduct having (*R*) stereochemistry. As has been shown (vide supra), the (*R*) aziridine is obtained as the major diastereomer in Et_3B/O_2



Scheme 5.

initiated ethyl radical additions to azirine **1**, indicating that these simple models are not applicable to the present study. The stereochemical outcome in the addition to azirine **2** can be rationalised in analogy to similar reactions with glyoxylic oxime ethers.[13]

3. Conclusion

We have shown that radical addition to azirine **1** afford the corresponding aziridine in modest to excellent dr. The use of catalytic amounts of CuCl was found to increase the dr, although the effect on the yield varied. The scope of the reaction, in terms of varying the trialkylborane used in the additions, has been investigated.

4. Experimental.[26]

4.1. General methods

4.1.1. General procedure for alkyl radical additions to azirine 1 in the presence of an alkyliodide. *Method A*. To **1** (17 mg, 0.058 mmol) in CH_2Cl_2 (2 mL) at −105 °C was added EtI (46 μL, 0.58 mmol) and Et_3B (288 μL, 0.29 mmol, 1 M solution in hexanes) followed by O_2 (5 mL). After 5 min the reaction was quenched by addition of $NaHCO_3$ (1 mL aqueous satd). The resultant mixture was filtered through an Extrelute® NT3 tube and eluted with CH_2Cl_2 (15 mL), EtOAc (15 mL) and CH_2Cl_2 (15 mL), The combined organic phases were concentrated and flash chromatographed (pentane/EtOAc 1:0→4:1) to give **3a**:**4a** (15 mg, 77%, 91:9) as an oil.

4.1.2. General procedure for alkyl radical additions to azirine 1 without an alkyliodide. *Method B*. To **1** (17 mg, 0.058 mmol) in CH_2Cl_2 (2 mL) at −105 °C was added Et_3B (172 μL, 0.17 mmol, 1 M solution in hexanes) and O_2 (5 mL). After 5 min the reaction was quenched by addition of $NaHCO_3$ (1 mL aqueous satd). The resultant mixture was filtered through an Extrelute® NT3 tube eluted with CH_2Cl_2 (15 mL), EtOAc (15 mL) and CH_2Cl_2 (15 mL). The combined organic phases were concentrated and flash chromatographed (pentane/EtOAc 1:0→4:1) to give **3a**:**4a** (15.2 mg, 81%, 91:9) as an oil.

4.1.3. General procedure for alkyl radical additions to azirine 1 in the presence of Lewis acid. *Method C*. To **1** (17 mg, 58 μmol) in CH_2Cl_2 at −105 °C was added CuCl (0.61 mg, 6 μmol). The resultant mixture was stirred for 10 min before Et_3B (172 μL, 172 μM, 1 M in hexanes) was

added followed by O_2 (5 mL). After stirring for 60 min at −105 °C the reaction was quenched by addition of $NaHCO_3$ (1 mL aqueous satd). This mixture was filtered through an Extrelut® NT3 tube eluting with CH_2Cl_2 (15 mL), EtOAc (15 mL) and CH_2Cl_2 (15 mL). The combined organic phases were and concentrated and flash chromatographed (pentane/EtOAc 1:0→4:1) to give **3a**:**4a** (12.9 mg, 69%, 96:4) as a pale oil.

4.2. Data for compounds

4.2.1. (2*S*)-(1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl) cyclohexyl 2-ethylaziridine-2-carboxylate (3a). Prepared according to method A, B or C to give **3a**:**4a** as a colorless oil; dr was determined by HPLC: (Zorbax Rx-SIL, hexane/*i*-PrOH 99.5:0.5, 1.1 mL/min) R_t **4a** = 19.5 min, R_t **3a** = 23.0 min.

Analytical data for **3a**: R_f 0.38 (pentane/EtOAc 4:1); $[\alpha]_D^{25}$ + 7.4 (*c* 1.0, CH_2Cl_2); δ_H ($CDCl_3$, 400 MHz) 7.37–7.24 (4H, m, Ph), 7.23–7.14 (1H, m, Ph), 4.80 (1H, dt, *J* = 12.1, 3.5 Hz, C*H*O), 2.10 (1H, m, C*H*CMe$_2$Ph) 1.87–1.77 (3H, m, C*H*$_2$N, C*H*HCHMe), 1.73–1.57 (3H, m, C*H*HMe, CHMeC*H*H, C*H*HCHCMe$_2$Ph) 1.52–1.41 (2H, m, CH*H*Me, C*H*Me), 1.29 (3H, s, Me), 1.18 (3H, s, Me), 1.13 (1H, dt, *J* = 12.9, 3.3 Hz, CH*H*CHMe), 1.01–0.79 (9H, m, CH$_2$*Me*, CH*Me*, CH*H*CHCMe$_2$Ph, CHMeCH*H*, N*H*); δ_C ($CDCl_3$, 100 MHz) 172.7, 151.8, 128.1, 125.2, 125.1, 75.6, 50.3, 41.5, 39.4, 39.1, 34.5, 33.9, 31.3, 29.1, 26.4, 24.5, 23.7, 21.7, 9.9; IR (neat) 2964, 2926, 1714, 1193, 1093 cm^{-1}; HRMS (FAB+) calcd for $C_{21}H_{32}NO_2$ (M+H) 330.2433, found 330.2432.

4.2.2. (2*S*)-(1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl) cyclohexyl 2-butylaziridine-2-carboxylate (3b). Prepared according to method B or C to give **3b**:**4b** as a colorless oil; dr was determined by HPLC: (Zorbax Rx-SIL, hexane/*i*-PrOH 99.5:0.5, 1.1 mL/min) R_t **4b** = 15.6 min, R_t **3b** = 17.6 min.

Analytical data for **3b**: R_f 0.38 (pentane/EtOAc 4:1); $[\alpha]_D^{25}$ + 9.2 (*c* 0.39, CH_2Cl_2); δ_H ($CDCl_3$, 400 MHz) 7.32–7.24 (4H, m, Ph), 7.20–7.15 (1H, m, Ph), 4.85 (1H, dt, *J* = 10.6, 4.3 Hz, C*H*O), 2.10 (1H, dt, *J* = 11.9, 3.3 Hz, C*H*HCHCMe$_2$Ph), 1.86–1.77 (3H, m, C*H*$_2$N, C*H*HCHMe), 1.73–1.66 (1H, m, CC*H*H), 1.62–1.41 (4H, m, CCH*H*, CHMeC*H*H, C*H*HCHCMe$_2$Ph, C*H*Me), 1.28 (3H, s, Me), 1.18 (3H, s, Me), 1.33–1.10 (5H, m, CH*H*CHMe, CHMeCH*H*, CH*H*CMe$_2$Ph, CCH$_2$C*H*$_2$), 0.98–0.76 (9H, m, CH*Me*, C*H*$_2$Me, CH$_2$*Me*, N*H*); δ_C ($CDCl_3$, 125 MHz) 172.8, 151.9, 128.1, 125.2, 125.0, 75.7, 50.2, 41.4, 39.4, 38.3, 34.5, 33.9, 31.3, 31.1, 29.2, 27.8, 26.4, 23.6, 22.7, 21.7, 14.0; IR (neat) 2954, 2927, 1715, 1094 cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{36}NO_2$ (M+H) 358.2746, found 358.2747.

4.2.3. (2*S*)-(1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl) cyclohexyl 2-allylaziridine-2-carboxylate (3c) and (2*R*)-(1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-allylaziridine-2-carboxylate (4c). Prepared according to method B or C to give **3c**:**4c** as a colorless oil; dr was determined by HPLC: (Zorbax Rx-SIL, hexane/*i*-PrOH 99.5:0.5, 1.1 mL/min) R_t **4c** = 15.3 min, R_t **3c** = 18.7 min.

Analytical data for **3c**: R_f 0.34 (pentane/EtOAc 4:1); $[\alpha]_D^{25}$ + 5.1 (*c* 0.49, CH_2Cl_2); δ_H ($CDCl_3$, 500 MHz) 7.31–7.25 (4H, m, Ph), 7.19–7.15 (1H, m, Ph), 5.71–5.62 (1H, m, C*H*CH$_2$), 5.03–4.97 (2H, m, CHC*H*$_2$), 4.86 (1H, dt, *J* = 10.6, 4.4 Hz, C*H*O), 2.18 (1H, dd, *J* = 14.7, 6.6 Hz, C*H*HCH=CH$_2$), 2.11 (1H, m, C*H*CMe$_2$Ph), 1.87–1.76 (3H, m, C*H*HCHMe, CHMeC*H*H, C*H*HN), 1.70 (1H, br d, *J* = 12.8 Hz, CH*H*N), 1.64 (1H, dd, *J* = 14.7, 6.6 Hz, CH*H*CH=CH$_2$), 1.52–1.43 (2H, m, C*H*Me, C*H*HCHCMe$_2$Ph), 1.28 (3H, s, Me), 1.20–1.11 (1H, m, CH*H*CHMe), 1.18 (3H, s, Me), 0.97–0.85 (3H, m, CHMeCH*H*, CH*H*CHCMe$_2$Ph, N*H*), 0.88 (3H, d, *J* = 7.1 Hz, CH*Me*); δ_C ($CDCl_3$, 125 MHz) 172.5, 151.9, 133.8, 128.1, 125.2, 125.1, 117.2, 75.9, 50.3, 41.5, 39.4, 37.5, 35.2, 34.5, 33.2, 31.3, 29.5, 26.4, 23.3, 21.7; IR (neat) 2957, 2924, 1714, 1094 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{32}NO_2$ (M+H) 342.2433, found 342.2432.

Analytical data for **4c**: R_f 0.41 (pentane/EtOAc 4:1); $[\alpha]_D^{25}$ + 29.9 (*c* 0.38, CH_2Cl_2); δ_H ($CDCl_3$, 500 MHz) 7.33–7.25 (4H, m, Ph), 7.18–7.14 (1H, m, Ph), 5.73–5.63 (1H, m, C*H*CH$_2$), 5.06–4.97 (2H, m, CHC*H*$_2$), 4.94 (1H, dt, *J* = 10.6, 4.4 Hz, C*H*O), 2.24–2.16 (1H, m, C*H*HCH=CH$_2$), 2.07 (1H, m, C*H*HN), 1.93 (1H, br dd, *J* = 14.3, 6.6 Hz, CH*H*N), 1.79 (1H, m, CH*H*CH=CH$_2$), 1.74–1.68 (2H, m, C*H*HCHCMe$_2$Ph, C*H*HCHMe), 1.64 (1H, app dt, *J* = 12.8, 2.9 Hz, C*H*CMe$_2$Ph), 1.50–1.41 (1H, m, N*H*), 1.32 (3H, s, Me), 1.20 (3H, s, Me), 1.10 (1H, m, CHMeC*H*H), 1.05–0.96 (1H, m, C*H*Me), 0.99 (1H, m, CH*H*CHMe), 0.92–0.82 (2H, m, CHMeCH*H*, CH*H*CHCMe$_2$Ph), 0.87 (3H, d, *J* = 6.6 Hz, CH*Me*); δ_C ($CDCl_3$, 125 MHz) 172.8, 151.4, 134.0, 128.2, 125.4, 125.3, 117.2, 76.1, 50.1, 41.8, 39.7, 37.4, 35.0, 34.4, 31.9, 31.3, 28.2, 26.7, 25.3, 21.7; IR (neat) 2959, 2924, 1716, 1093 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{32}NO_2$ (M+H) 342.2433, found 342.2444.

4.2.4. (2*S*)-(1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl) cyclohexyl 2-isopropylaziridine-2-carboxylate (3d) and (2*R*)-(1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-isopropylaziridine-2-carboxylate (4d). Prepared according to method B or C to give **3d**:**4d** as a colorless oil; dr was determined by HPLC: (Zorbax Rx-SIL, hexane/*i*-PrOH 99.5:0.5, 1.1 mL/min) R_t **4d** = 10.1 min, R_t **3d** = 12.3 min.

Analytical data for **3d**: R_f 0.48 (pentane/EtOAc 4:1); $[\alpha]_D^{25}$ + 26.6 (*c* 0.55, CH_2Cl_2); δ_H ($CDCl_3$, 500 MHz) 7.31–7.24 (4H, m, Ph), 7.20–7.16 (1H, m, Ph), 4.88 (1H, dt, *J* = 11.0, 4.4 Hz, C*H*O), 2.10 (1H, m, C*H*CMe$_2$Ph), 1.85–1.77 (2H, m, C*H*HN, C*H*Me), 1.72–1.61 (3H, m, CH*H*N, CHMeC*H*H, C*H*HCHCMe$_2$Ph), 1.54–1.44 (2H, m, C*H*Me$_2$, C*H*HCHMe), 1.28 (3H, s, Me), 1.18 (3H, s, Me), 1.15 (1H, m, N*H*), 0.95 (1H, m, CH*H*CHMe), 0.95–0.85 (1H, m, CHMeCH*H*), 0.88 (6H, d, *J* = 7.0 Hz, CH*Me*$_2$), 0.76 (1H, m, CH*H*CHCMe$_2$Ph), 0.67 (3H, d, *J* = 7.0 Hz, CH*Me*); δ_C ($CDCl_3$, 125 MHz) 172.8, 151.8, 128.1, 125.2, 125.1, 75.6, 50.2, 42.2, 41.5, 39.4, 34.5, 31.9, 31.3, 29.0, 27.4, 26.5, 23.8, 21.7, 19.4, 16.8; IR (neat) 2962, 2925, 1715, 1185, 1091 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{34}NO_2$ (M+H) 344.2590, found 344.2588.

Analytical data for **4d**: R_f 0.57 (pentane/EtOAc 4:1); $[\alpha]_D^{25}$ + 24.3 (*c* 0.35, CH_2Cl_2); δ_H ($CDCl_3$, 500 MHz)

7.32–7.26 (4H, m, Ph), 7.19–7.15 (1H, m, Ph), 4.92 (1H, dt, $J=10.6$, 4.4 Hz, C*H*O), 2.09 (1H, m, C*H*CMe$_2$Ph), 1.85–1.75 (2H, m, C*H*HN, C*H*Me), 1.70 (1H, m, CHMeC*H*H), 1.65 (1H, m, CH*H*N), 1.52–1.42 (1H, m, C*H*HCHCMe$_2$Ph), 1.45 (1H, m, C*H*Me$_2$), 1.38 (1H, m, C*H*HCHMe), 1.31 (3H, s, Me), 1.19 (3H, s, Me), 1.11 (1H, m, N*H*), 0.99 (1H, m, CH*H*CHMe), 0.92–0.82 (1H, m, CH*H*CHCMe$_2$Ph), 0.88 (3H, d, $J=6.6$ Hz, Me), 0.84 (3H, d, $J=7.0$ Hz, Me), 0.82 (3H, d, $J=7.0$ Hz, CH*Me*), 0.76 (1H, m, CHMeCH*H*); δ_C ($CDCl_3$, 125 MHz) 172.6, 151.5, 128.2, 125.3, 125.2, 75.9, 49.9, 42.4, 41.8, 39.7, 34.5, 31.3, 29.9, 28.3, 27.8, 26.7, 25.1, 21.7, 18.7, 18.2; IR (neat) 2961, 2925, 1718, 1183, 1094 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{34}NO_2$ (M+H) 344.2590, found 344.2593.

4.2.5. (2*R*)-(1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl) cyclohexyl 2-sec-butylaziridine-2-carboxylate (3e) and (2*R*)-(1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-sec-butylaziridine-2-carboxylate (4e). Prepared according to method B or C to give **3d**:**4d** as a colorless oil; dr was determined by HPLC: (Zorbax Rx-SIL, hexane/*i*-PrOH 99.5:0.5, 1.1 mL/min) R_t **4e**=9.6 min and 10.0, R_t **3e**=12.6 min.

Analytical data for **3e**, mixture of the two diastereomers, not separable by preparative HPLC: R_f 0.53 (pentane/EtOAc 4:1); δ_H ($CDCl_3$, 500 MHz) 7.31–7.24 (4H, m), 7.21–7.17 (1H, m), 4.88 (1H, m), 2.08 (1H, m), 1.85–1.73 (2H, m), 1.71–1.64 (2H, m), 1.53 (1H, m), 1.51–1.44 (1H, m), 1.44–1.36 (1H, m), 1.35–1.20 (2H, m), 1.28 (3H, br s), 1.18 (3H, br s), 1.16–1.10 (1H, m), 0.96–0.82 (9H, m), 0.77–0.71 (3H, m); δ_C ($CDCl_3$, 125 MHz) 172.7, 172.6, 151.74, 151.68, 128.1, 125.2, 125.1, 75.63, 75.57, 50.19, 50.16, 42.3, 41.8, 41.5, 41.4, 39.46, 39.50, 36.0, 35.3, 34.51, 34.50, 32.0, 31.9, 31.3, 28.8, 28.6, 26.8, 26.54, 26.51, 24.35, 24.29, 24.1, 21.7, 16.2, 14.2, 12.4, 12.0; IR (neat) 2961, 2926, 1716, 1185, 1094 cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{36}NO_2$ (M+H) 358.2746, found 358.2741.

Analytical data for **4e**, two minor diastereomers still containing small amounts of the other isomer after preparative HPLC, first peak: R_f 0.64 (pentane/EtOAc 4:1); δ_H ($CDCl_3$, 500 MHz) 7.32–7.25 (4H, m), 7.19–7.15 (1H, m), 4.91 (1H, m), 2.07 (1H, m), 1.82 (1H, m), 1.65 (1H, m), 1.52–1.33 (5H, m), 1.30 (3H, br s), 1.19 (3H, br s), 1.17–1.04 (2H, m), 0.98 (1H, app q, $J=11.8$ Hz), 0.92–0.83 (10H, m), 0.77 (1H, m); δ_C ($CDCl_3$, 125 MHz) 172.3, 151.4, 128.2, 125.4, 125.2, 75.9, 49.8, 42.1, 41.8, 39.7, 36.1, 34.4, 31.3, 31.0, 28.0, 26.8, 25.7, 25.5, 21.7, 15.6, 12.2; IR (neat) 2962, 2926, 1714, 1181, 1094 cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{36}NO_2$ (M+H) 358.2746, found 358.2758.

Analytical data **4e**, second peak: R_f 0.64 (pentane/EtOAc 4:1); δ_H ($CDCl_3$, 500 MHz) 7.32–7.25 (4H, m), 7.20–7.15 (1H, m), 4.91 (1H, m), 2.07 (1H, m), 1.82 (1H, m), 1.74–1.60 (2H, m), 1.52–1.33 (5H, m), 1.30 (3H, br s), 1.19 (3H, br s), 1.17–1.05 (2H, m), 0.98 (1H, app q, $J=11.6$ Hz), 0.92–0.82 (10H, m,), 0.77 (1H, m); δ_H ($CDCl_3$, 125 MHz) 172.3, 151.4, 128.2, 125.4, 125.2, 75.9, 49.8, 42.1, 41.8, 39.7, 36.1, 34.4, 31.3, 31.0, 28.0, 26.8, 25.7, 25.5, 21.7, 15.6, 12.2; IR (neat) 2962, 2927, 1178, 1093 cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{36}NO_2$ (M+H) 358.2746, found 358.2742.

4.2.6. (2*S*)-(1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl) cyclohexyl 2-(2-cyclohexylethyl) aziridine-2-carboxylate (3f) and (2*R*)-(1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-(2-cyclohexylethyl)aziridine-2-carboxylate (4f). Prepared according to method B or C to give **3f**:**4f** as a colorless oil; dr was determined by HPLC: (Zorbax Rx-SIL, hexane/*i*-PrOH 99.5:0.5, 1.1 mL/min) R_t **4f**=12.0 min, R_t **3f**=13.6 min.

Analytical data for **3f**: R_f 0.48 (pentane/EtOAc 4:1); $[\alpha]_D^{25}+$ 10.3 (*c* 0.73, CH_2Cl_2); δ_H ($CDCl_3$, 500 MHz) 7.30–7.24 (4H, m), 7.19–7.15 (1H, m), 4.84 (1H, dt, $J=10.7$, 4.1 Hz), 2.12 (1H, m), 1.87–1.79 (3H, m), 1.75–1.62 (6H, m), 1.59–1.41 (3H, m), 1.31 (s, 3H), 1.23–1.06 (7H, m), 1.21 (3H, s), 0.99–0.80 (6H, m), 0.91 (3H, d, $J=6.6$ Hz); δ_C ($CDCl_3$, 125 MHz) 172.8, 151.8, 128.1, 125.2, 125.1, 75.7, 50.3, 41.5, 39.4, 38.4, 37.7, 34.5, 33.9, 33.3, 33.14, 33.07, 31.3, 29.2, 28.8, 26.7, 26.4, 26.34, 26.31, 23.6, 21.7; IR (neat) 2920, 2851, 1715, 1201, 1094 cm^{-1}; HRMS (FAB+) calcd for $C_{27}H_{42}NO_2$ (M+H) 412.3216, found 412.3216.

Analytical data for **4f**: R_f 0.53 (pentane/EtOAc 4:1); $[\alpha]_D^{25}+$ 15.3 (*c* 0.40, CH_2Cl_2); δ_H ($CDCl_3$, 500 MHz) 7.31–7.26 (4H, m), 7.19–7.15 (1H, m), 4.92 (1H, dt, $J=10.7$, 4.4 Hz), 2.05 (1H, m), 1.80 (1H, m), 1.74–1.59 (9H, m), 1.50–1.38 (3H, m), 1.32 (s, 3H), 1.35–1.05 (6H, m), 1.21 (3H, s), 1.02–0.79 (6H, m), 0.87 (3H, d, $J=6.6$ Hz); δ_H ($CDCl_3$, 125 MHz) 173.0, 151.3, 128.2, 125.4, 125.3, 75.6, 50.1, 41.8, 39.8, 38.5, 37.8, 34.4, 33.39, 33.36, 33.3, 33.2, 31.3, 27.6, 26.8, 26.7, 26.42, 26.35, 26.3, 25.9, 21.7; IR (neat) 2924, 2852, 1092 cm^{-1}; HRMS (FAB+) calcd for $C_{27}H_{42}NO_2$ (M+H) 412.3216, found 412.3216.

4.2.7. (2*S*)-(1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl) cyclohexyl 2-(2-methylallyl)aziridine-2-carboxylate (3g) and (2*R*)-(1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-(2-methylallyl)aziridine-2-carboxylate (4g). Prepared according to method B or C to give **3g**:**4g** as a colorless oil; dr was determined by HPLC: (Zorbax Rx-SIL, hexane/*i*-PrOH 99.5:0.5, 1.1 mL/min) R_t **4g**= 15.3 min, R_t **3g**=16.9 min.

Analytical data for **3g**: R_f 0.44 (pentane/EtOAc 4:1); $[\alpha]_D^{25}+$ 38.2 (*c* 0.92, CH_2Cl_2); δ_H ($CDCl_3$, 400 MHz) 7.32–7.27 (4H, m, Ar), 7.19–7.14 (1H, m, Ar), 4.81 (1H dt, $J=10.8$, 4.3 Hz, C*H*O), 4.72 (1H, s, =C*H*H), 4.62 (1H, s, =CH*H*), 2.15–2.04 (2H, m, C*H*CMe$_2$Ph, C*H*HC(Me)CH$_2$), 1.85–1.77 (3H, m, CH*H*C(Me)CH$_2$, C*H*HN, C*H*Me), 1.72–1.67 (1H, m, CH*H*N), 1.66 (3H, s, C(*Me*)CH$_2$), 1.55–1.40 (3H, m, CHMeC*H*H, C*H*HCHCMe$_2$Ph, C*H*HCHMe), 1.27 (3H, s, Me), 1.17 (3H, s, Me), 1.16–1.07 (2H, m, N*H*, CH*H*CHMe), 0.96–0.84 (2H, m, CHMeCH*H*, CH*H*CHCMe$_2$Ph), 0.87 (3H, d, $J=6.5$ Hz, CH*Me*); δ_C ($CDCl_3$, 125 MHz) 172.7, 152.0, 142.3, 128.1, 125.2, 125.1, 111.5, 76.2, 50.2, 41.1, 39.4, 38.4, 37.0, 34.5, 33.4, 31.2, 29.3, 26.4, 23.5, 23.5, 21.7; IR (neat) 2957, 2923, 1716, 1217, 1093 cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{34}NO_2$ (M+H) 356.2590, found 356.2592.

Analytical data for **4g**: R_f 0.52 (pentane/EtOAc 4:1); $[\alpha]_D^{25}+$ 23.5 (*c* 0.31, CH_2Cl_2); δ_H ($CDCl_3$, 500 MHz) 7.33–7.27 (4H, m, Ar), 7.20–7.14 (1H, m, Ar), 4.89 (1H, dt, $J=10.8$, 4.5 Hz, C*H*O), 4.76 (1H, s, =C*H*H), 4.66 (1H, s, =CH*H*),

2.15–1.97 (3H, m, $CHCMe_2Ph$, C*H*HC(Me)CH_2, CH*H*C(Me)CH_2), 1.83–1.77 (2H, m, C*H*HN, C*H*Me), 1.70–1.60 (2H, m, C*H*HN, C*H*HCHCMe_2Ph), 1.68 (3H, s, C(*Me*)CH_2), 1.53–1.40 (2H, m, C*H*HCHMe, m, CHMeC*H*H), 1.31 (3H, s, Me), 1.19 (3H, s, Me), 1.14–0.80 (4H, m, N*H*, CHMeC*H*H, CH*H*CHCMe_2Ph, CH*H*CHMe), 0.87 (3H, d, $J=6.5$ Hz, CH*Me*); δ_C ($CDCl_3$, 125 MHz) 172.7, 151.4, 142.3, 128.2, 125.4, 125.3, 111.5, 76.3, 50.0, 41.5, 39.7, 38.7, 36.9, 34.4, 32.7, 31.3, 27.9, 26.7, 25.5, 23.6, 21.7; IR (neat) 2960, 2924, 1174 cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{34}NO_2$ (M+H) 356.2590, found 356.2591.

4.2.8. Aziridine 5. Prepared according to method A to give **5**:**6** as crystals; dr was determined by HPLC: (Zorbax Rx-SIL, hexane/*i*-PrOH 95:5, 1.1 mL/min) R_t **5**=12.3 min, R_t **6**=18.2 min.

Analytical data for **5**: R_f 0.42 (pentane/EtOAc 1:1); mp 151–152 °C (from EtOH/H_2O); $[\alpha]_D^{25}$ −13.2 (*c* 1.0, CH_2Cl_2); δ_H ($CDCl_3$, 400 MHz) 3.90 (1H, dd, $J=7.6$, 4.5 Hz, C*H*NSO_2), 3.44 (2H, AB q, $J=13.8$ Hz, CH_2SO_2), 2.64–2.54 (1H, m, C*H*HCHN), 2.22 (1H, br s, N*H*), 2.07 (1H, A-part of AB dq, $J=14.6$, 7.3 Hz, C*H*HMe), 1.98–1.89 (5H, m, C*H*CMe_2, C*H*HCHN, CH_2N, CHCH_2C*H*H), 1.49–1.35 (3H, m, CHCH_2CH*H*, CHCH_2), 1.35–1.28 (1H, B-part of AB dq, 1H, $J=14.6$, 7.3 Hz, CH*H*Me), 1.19 (3H, s, Me), 0.98 (3H, s, Me), 0.95 (3H, t, $J=7.5$ Hz, CH_2*Me*); δ_C ($CDCl_3$, 100 MHz) 173.5, 77.2, 65.2, 52.9, 48.5, 47.9, 44.5, 43.1, 38.1, 32.7, 27.2, 26.6, 20.4, 19.9, 9.8; IR (neat) 3294, 2955, 1678, 1328, 1200, 1136 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{25}N_2O_3S$ (M+H) 313.1586, found 313.1588.

4.2.9. ((*S*)-1-Benzyl-2-ethylaziridin-2-yl)methyl acetate (7). To **3a** (25.4 mg, 77 μmol) in MeCN (15 mL) was added K_2CO_3 (32 mg, 230 μmol) and BnBr (28 μL, 230 μmol) and the resultant mixture was heated to reflux. After 5 h the mixture was cooled to rt and H_2O was added. The phases were separated and the aqueous phase extracted with Et_2O. The combined organic phases were washed with H_2O, dried ($MgSO_4$) and concentrated. Flash chromatography (pentane/EtOAc 1:0→10:1) of the residue gave the corresponding benzylated aziridine (25.6 mg, 80%) as a colorless oil, which was used directly in the next step.

To the material from above (25.6 mg, 61 μmol) in Et_2O (5 mL) at −78 °C was added $LiAlH_4$ (183 μL, 183 μmol, 1M in THF) dropwise. After warming to rt for 1.5 h the reaction was quenched by addition of H_2O (7 μL), 15% aqueous NaOH (7 μL) and H_2O (21 μL). After stirring the resultant mixture for 15 min $MgSO_4$ was added and the slurry was filtered. Concentration gave a crude product that was used in the next step without further purification.

To the crude reaction mixture from above in CH_2Cl_2 (5 mL) at 0 °C was added DMAP (18.0 mg, 148 μmol) and Ac_2O (18.6 μL, 197 μmol). After stirring at rt for 3 h the reaction was quenched by addition of H_2O (1 mL). The resultant mixture was filtered through an Extrelut® NT3 tube eluting with CH_2Cl_2 (15 mL), EtOAc (15 mL) and CH_2Cl_2 (15 mL). Removal of the solvents and flash chromatography (pentane/EtOAc 1:0→1:1) gave **7** (11.1 mg, 79% over two steps) as a colorless oil.

Comparison of retention times between **7** and *ent*-**7** was performed by HPLC: (Chiralcel OJ, hexane/*i*-PrOH 99:1, 0.7 mL/min) R_t **7**=26.5 min, R_t *ent*-**7**=24.6 min.

Analytical data for **7**: R_f 0.18 (pentane/EtOAc 4:1); $[\alpha]_D^{25}$ −5.9 (*c* 0.58, CH_2Cl_2); δ_H ($CDCl_3$, 500 MHz, mixture of *N*-invertomers) 7.42–7.21 (10H, m, Ar), 4.42 (1H, d, $J=$ 12.4 Hz, C*H*HO), 4.17 (2H, AB q, $J=11.8$, 4.8 Hz, CH_2O), 3.89 (1H, d, $J=12.4$ Hz, CH*H*O), 3.73 (4H, m, CH_2Ph, CH_2Ph), 2.06 (3H, s, *Me*CO), 1.94 (C*H*HN1H, s), 1.91 (3H, s, *Me*CO), 1.89 (1H, s, C*H*HN), 1.84 (1H, m, C*H*HMe), 1.70 (1H, m, C*H*HMe), 1.62 (1H, m, CH*H*Me), 1.43 (1H, s, CH*H*N), 1.42 (1H, m, CH*H*Me), 1.34 (1H, s, CH*H*N), 1.03 (3H, t, $J=7.3$ Hz), 0.94 (3H, t, $J=7.3$ Hz); δ_C ($CDCl_3$, 125 MHz) 170.92, 170.88, 139.9, 139.8, 128.3, 127.59, 127.57, 126.7, 68.7, 62.6, 56.8, 56.0, 42.5, 42.4, 37.6, 37.3, 28.3, 20.9, 20.6, 19.6, 11.0, 9.5; IR (neat) 2970, 1740, 1235, 1097, 1034 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{20}NO_2$ (M+H) 234.1494, found 234.1498.

4.2.10. ((*R*)-1-Benzyl-2-ethylaziridin-2-yl)methyl acetate (*ent*-7). *Ent*-**7** was prepared in analogy with **7** starting from **5** and was spectroscopically identical to **7**. Comparison of retention times between **7** and *ent*-**7** was performed by HPLC: (Chiralcel OJ, hexane/*i*-PrOH 99:1, 0.7 mL/min) R_t *ent*-**7**=24.6 min.

Additional analytical data for *ent*-**7**; $[\alpha]_D^{25}$ +8.3 (*c* 0.56, CH_2Cl_2); HRMS (FAB+) calcd for $C_{14}H_{20}NO_2$ (M+H) 234.1494, found 234.1489.

4.2.11. (*R*)-(+)-C^{α}-Ethyl serine (8). $[\alpha]_D^{25}$ +2.9 (*c* 0.90, 5 N HCl); δ_H (1 N DCl/D_2O, 400 MHz) 3.89 (1H, d, $J=$ 12.1 Hz, C*H*HOH), 3.61 (1H, d, $J=12.1$ Hz, CH*H*OH), 1.79 (1H, m, C*H*HMe), 1.63 (1H, m, CH*H*Me), 0.86 (3H, br t, $J=7.1$ Hz, CH_2*Me*).

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Dimeric azaphilones from the xylariaceous ascomycete *Hypoxylon rutilum*

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Dedicated to the memory of Professor Dr. Wilfried A. König.

Abstract—Fractionation of the methanolic extract of the stromata of *Hypoxylon rutilum* (Xylariaceae, Ascomycetes) resulted in the isolation of two novel dimeric azaphilones named rutilins A and B, together with the known compounds, entonaemin A, and rubiginosins A and B. Their structures were elucidated by 2D NMR, HR-MS, IR and UV spectroscopy. Rutilins A and B are presumably synthesized via specific biogenic aldol condensations of mitorubrinol acetate moieties with rubiginosins A and B, respectively. The resulting dimeric azaphilone scaffold of the rutilins is unprecedented in nature.

1. Introduction

The Xylariaceae is one of the largest and most important groups of ascomycetes, and they also show a remarkable diversity with respect to the production of unique secondary metabolites.[1] Recent studies showed that classical morphology of the Xylariaceae agrees well with the occurrence of characteristic secondary metabolites, as well as with the molecular phylogeny of these organisms.[2–5] In this context, HPLC profiling studies have repeatedly resulted in new taxonomic evidence, but on the other hand, they also facilitated the discovery of several novel natural products. For instance, the fruit-bodies (stromata) of the genus *Hypoxylon*, which are frequently encountered on wood, have proved to be a rich source for various types of azaphilone pigments. Those can be divided into three main subgroups; (i) the mitorubrin-like metabolite family (mitorubrins,[6] rubiginosins[7] and hypomiltin[8]) where an orsellinic acid moiety is attached to the bicyclic azaphilone backbone by an ester bond; (ii) the daldinins,[9,10] constituting *spiro*-tricyclic derivatives of the azaphilone core, and (iii) the cohaerins[11] and multiformins,[12] which have a third ring system attached by a C–C bond to the bicyclic system. All of these compounds are preferably located in granules that are embedded in waxy tissue directly beneath the stromatal surface and/or surrounding perithecia (Fig. 3). They may remain stable for over 200 years in herbarium specimens,[11] and comprise up to 10% of the dried total stromatal biomass in particular *Hypoxylon* spp., suggesting a high biological significance.[8] Colors of these pigments in 10% KOH are highly species-consistent and constitute important criteria in modern taxonomy. Morphologically rather similar species in *Hypoxylon* can be discriminated well by comparing the colors of the aforementioned pigment granules in addition to microscopic characters.[13,14] For instance, *Hypoxylon rutilum* Tul. and C. Tul. and *H. julianii* L. E. Petrini are the only European members of the genus that have scarlet to dark orange red granules (rather than the bright orange granules encountered in their relatives). A HPLC-based profiling study had revealed apparently specific metabolites in their stromatal extracts that were presumably identical with these coloring matters,[14] but their identity remained unclear. Recently, *H. rutilum* was encountered in sufficient quantities for detailed studies. From its MeOH extract, two novel dimeric azaphilones named rutilins A and B (**1**–**2**) were isolated, together with three known compounds, entonaemin A (**3**),[15] and rubiginosins A and B (**4**–**5**).[7] Further congeners, such as orsellinic acid and mitorubrinol acetate, were also detected in the extract but not isolated in a pure state, since analytical HPLC using authentic standards[8,14] had revealed their identity (Fig. 1).

Keywords: Fungi; *Hypoxylon rutilum*; Rutilin; Dimeric azaphilones; Xylariaceae.
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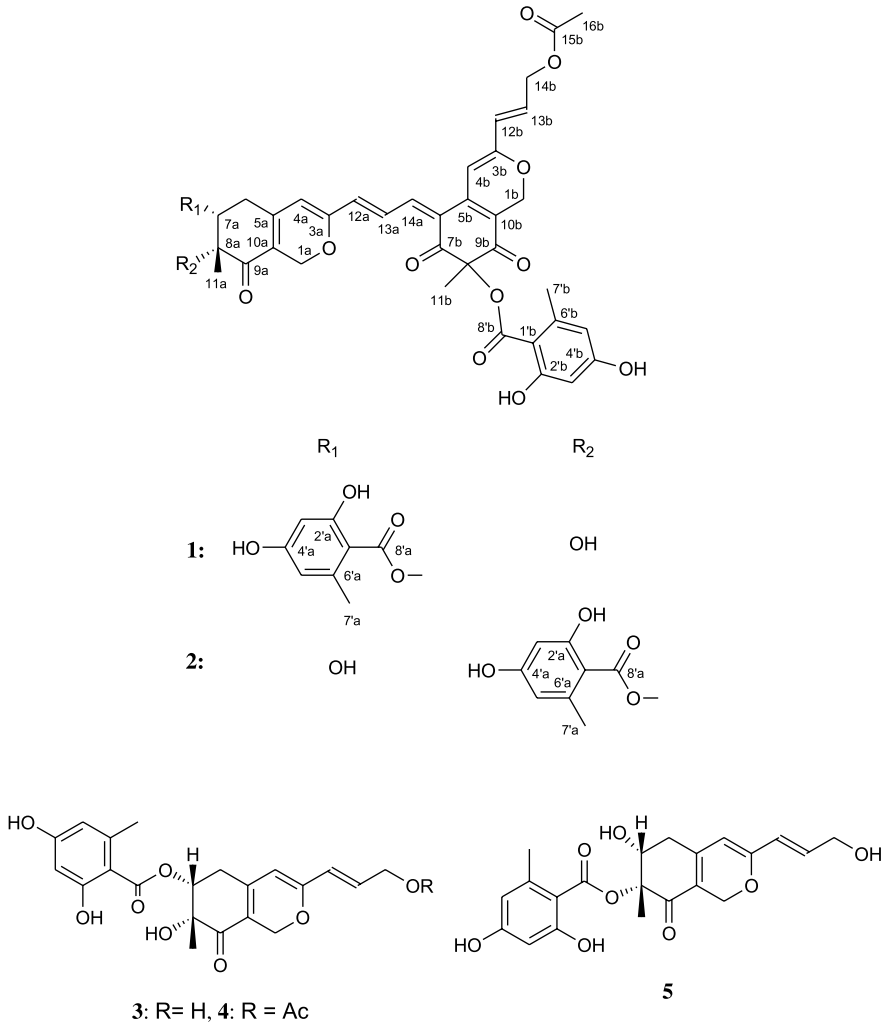


Figure 1. Structures of **1**–**5**.

2. Results and discussion

The methanolic extract of *H. rutilum* was condensed under reduced pressure and low temperature. Sephadex LH-20, silicagel column chromatography, followed by further purification using preparative HPLC led to the isolation of five compounds (**1**–**5**).

Rutilin A (**1**) was isolated as dark red powder. Upon FABMS, the compound exhibits a molecular ion peak at *m/z* 825 $[M+H]^+$. High resolution FABMS indicated the molecular formula as $C_{44}H_{40}O_{16}$. Initial analysis of the ^1H and ^{13}C NMR data (Table 1) revealed that it was an almost symmetrical molecule consisting of two moieties that could be only distinguished by minor differences in the observed NMR data, including five methyl groups, eleven olefinic protons, four methylenes, three conjugated ketones (δ_C 196.6, 193.8, 189.1; corresponding to γ_{max} 1648 cm^{-1} by IR), three ester (δ_C 171.6, 170.6, 170.4) and four phenolic carbons. Interpretation of 2D NMR data allowed for the assignment of two subunits, one of which (the 'a' unit) has identical spectral data to those of **3**, except for the side chain at C-3a position.[7] The other (the 'b' unit) could be mitorubrinol acetate derivative as inferred from a comparison of its spectral data with those in the literature. It differs only from the presence of a methylene at C-1b and the absence of a proton at C-6b.[6,7,15] The two subunits were further elaborated by interpretation of the HMBC and NOESY spectra (Fig. 2). The spectral data of the side chain at C-3b resembled those of **4**,[7] which connected to C-3b by HMBC correlations between H-12b and C-3b, and between H-4b and C-12b. Furthermore, H-14a was correlated with C-5b and C-7b, suggesting that the 'a' unit (i.e., **3**) was attached to C-6b of unit 'b'. Strong NOESY correlations between H-12a/H-4a and H-14a, and H-4b/H-14a and H-12b supported the proposed structure. The relative configuration of **1** was established from its NOESY spectrum (Fig. 2), in which H-7a correlated with H-11a, indicating that H-7a and Me-8a were β-face. It is conceivable that the dimer (**1**) is synthesized via a biogenic aldol condensation of the aldehyde corresponding to entonaemin A (**3**) with dihydromitorubrinol acetate as proposed in Scheme 1.[16] Initially, the secondary hydroxyl group of **3** may be oxidized to form an aldehyde group (**6**). Then, the addition of a carbon C-6b to the carbonyl C-14a followed by elimination of one water molecule could result in the formation of **1**.

Rutilin B (**2**) possesses a molecular formula ($C_{44}H_{40}O_{16}$) identical to that of rutilin A. Its spectral data resemble those

Table 1. ^{1}H and ^{13}C NMR data for rutilins A and B (**1–2**) (acetone)

Position	Compound **1**		Compound **2**	
	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
1a	5.06 (dd, 1.7, 12.9) 4.91 (br d, 12.9)	64.5	5.04 (d, 13.2) 4.89 (d, 13.2)	64.6
3a		158.9		158.6
4a	5.95 (s)	112.0	5.93 (s)	112.1
5a		146.4		145.9
6a	3.17 (d, 19.5) 2.95 (overlapped)	32.3	2.97 (br d, 18.7) 2.77 (dd, 4.1, 18.7)	34.9
7a	5.66 (t, 3.3)	77.8	4.84 (br d, 4.64)	71.9
8a		75.1		87.6
9a		196.6		191.7
10a		117.9		118.2
11a	1.44 (s)	23.6	1.76 (s)	19.7
12a	6.87 (d, 14.8)	138.6	6.86 (d, 15.1)	138.8
13a	8.00 (dd, 11.8, 14.8)	130.2	7.95 (dd, 12.1, 15.1)	130.0
14a	7.60 (d, 11.8)	141.8	7.59 (d, 12.1)	141.8
1′a		105.3		106.7
2′a		166.4		165.3
3′a	6.21 (d, 2.5)	101.6	6.22 (d, 2.5)	101.9
4′a		164.1		163.1
5′a	6.24 (d, 2.5)	112.7	6.28 (d, 2.5)	112.3
6′a		144.8		144.9
7′a	2.24 (s)	24.4	2.53 (s)	24.5
8′a		171.6		169.4
8a-OH	4.60 (s)			
2′a-OH	11.51 (s)		10.88 (s)	
4′a-OH	9.46 (s)		9.05 (s)	
1b	5.13 (d, 13.7) 4.99 (d, 13.7)	64.7	5.13 (d, 13.8) 4.99 (d, 13.8)	64.7
3b		161.0		161.0
4b	6.37 (s)	100.6	6.37 (s)	100.6
5b		144.2		144.2
6b		127.8		127.7
7b		193.8		193.8
8b		86.7		86.7
9b		189.1		189.1
10b		116.2		116.1
11b	1.72 (s)	22.6	1.71 (s)	22.6
12b	6.39 (m)	125.6	6.39 (d, 15.7)	125.6
13b	6.54 (td, 5.2, 15.7)	132.6	6.54 (td, 5.2, 15.7)	132.6
14b	4.75 (d, 5.2)	63.9	4.76 (d, 5.2)	63.9
15b		170.6		170.6
16b	2.09 (s)	20.7	2.08 (s)	20.7
1′b		104.6		104.7
2′b		166.4		166.3
3′b	6.22 (d, 2.5)	101.6	6.24 (d, 2.5)	101.7
4′b		163.5		163.9
5′b	6.36 (d, 2.5)	112.7	6.38 (d, 2.5)	112.7
6′b		144.7		145.5
7′b	2.64 (s)	24.2	2.64 (s)	24.2
8′b		170.4		170.3
2′b-OH	10.80 (s)		10.79 (s)	
4′b-OH	9.30 (s)		9.27 (s)	

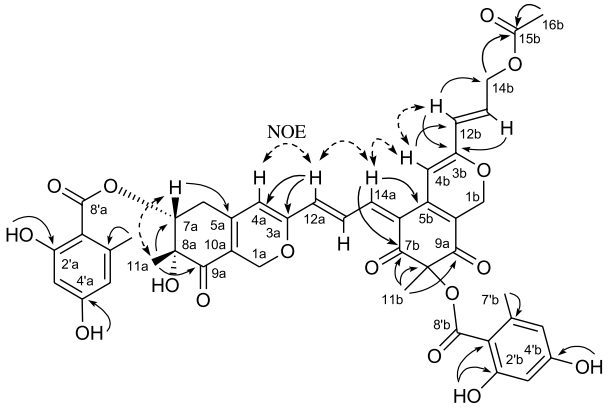
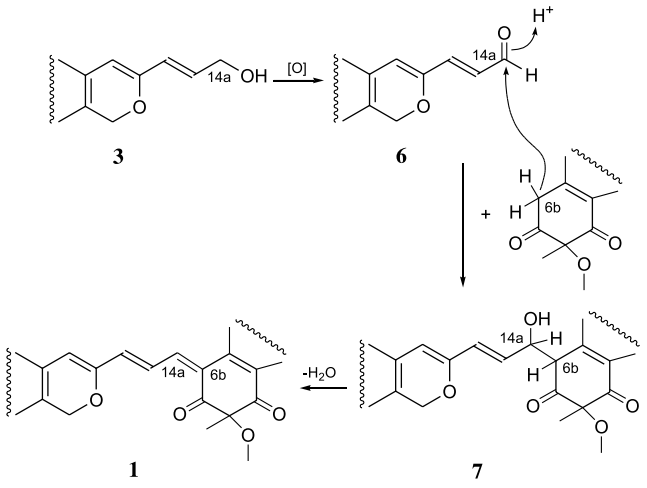


Figure 2. Important HMBC (arrows) and NOESY correlations of **1**.

of **1**, except for notable differences in its NMR data of subunit (a). Analysis of its 2D NMR led to establish subunit (a) as rubiginosin B, which was also isolated from another related species (*H. rubiginosum*).[7] Thus, **2** was determined to be a dimeric azaphilone, composed of a rubiginosin B (**5**) and a mitorubrinol acetate moiety. Compound **2** was also detected by HPLC in the freshly prepared methanolic extract of the fungus. Thus, **2** is a natural product. The absolute configurations of C-8 of rutilins A–B remain to be clarified.

To the best of our knowledge, this is the first report on the isolation and structural elucidation of real dimeric azaphilones, which result from condensation of two monomeric moieties and hence show an unique and unprecedented carbon skeleton. The only previously reported fungal



Scheme 1. Proposed biosynthetic pathway of **1**.

metabolite containing two independent azaphilone moieties is entonaemin C from the xylariaceous *Entonaema splendens*, which was published without any spectral data. However, in this molecule, the linkage between two monomers was proposed to have occurred via an oxygen atom.[17]

Analytical HPLC of the granules of *H. rutilum* (Fig. 3), carefully detached from the stromatal interior under a dissecting microscope, revealed extraordinary high amounts of **1** and **2** as compared to their monomeric congeners (**3–5**) in the crude extract. Extracts prepared from waxy tissue surrounding perithecia as well as the crude extract from the entire stromata (see Fig. 3 in Ref. 14 and yields of **1–5** in Section 3) revealed relatively large amounts of **3–5** and rather low quantities of rutilins. These results suggest that the monomers are distributed in the entire tissue surrounding the perithecia beneath the surface of the fruit-bodies, while the characteristic scarlet colors of the granules are due to accumulation of rutilins. The fact that these compounds were not detected in various *Hypoxylon* spp., including those that contain **3–5** as major components, suggest the occurrence of specific enzymatic reactions in *H. rutilum* and *H. julianii*.[8,14] Nonetheless, the biogenetic enzymes for azaphilones in *Hypoxylon* in general (and those for the rutilins in particular) remain to be characterized. Studies on their biological activities and possible chemo-ecological functions of the rutilins are currently under way. From our ongoing studies, which are so far based on over 2000 specimens, manifold further unprecedented metabolites may be expected in the near future.

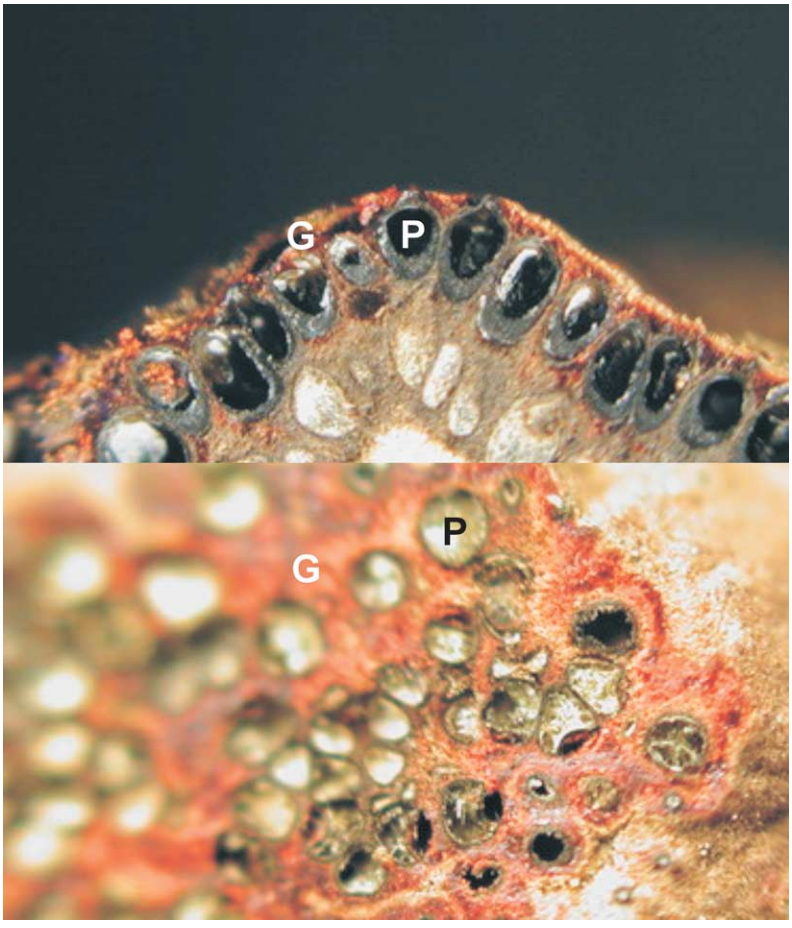


Figure 3. The pigments located in the scarlet or dark red orange colored granules (**G**) surrounding perithecia (**P**) in the fruit-bodies of the wood-inhabiting ascomycete *H. rutilum* (Xylariaceae). Section (above) and view from above after removal of stromatal surface (below).

3. Experimental

3.1. General

NMR spectra were recorded on a Varian Unity 600 (600 MHz for ^{1}H NMR and 150 MHz for ^{13}C NMR) in acetone-d_6. Mass spectra were recorded on a JEOL JMS AX-500 spectrometer. IR spectra were measured on a Perkin Elmer Spectrum One FT-IR spectrometer. UV spectra were obtained on a Shimadzu UV-1650PC in MeOH. Optical rotations were measured on a JASCO DIP-1000 polarimeter in MeOH. Preparative HPLC was performed on a Shimadzu liquid chromatograph LC-10AS with RID-10A and SPD-10A detectors using a Waters 5 SL-II column (10×250 mm, Nacalai Tesque, Japan). Analytical HPLC was performed using previously described systems,[8,14] taking the data obtained in the course of these studies into account.

3.2. Fungal material

Stromata of *H. rutilum* were collected and identified by M. S. from a partly decorticated trunk of *Fagus* in the vicinity of Wuppertal, Germany, on June 17, 2004. A voucher specimen (STMA 04108B) is deposited at the Fuhlrott-Museum, Wuppertal.

3.3. Extraction and isolation

The air-dried stromata were detached from the substrate and extracted with 2×500 ml MeOH at rt for each 30 min in an ultrasonic bath. The extracts were combined, filtered and evaporated to dryness. This crude extract (2.34 g from 24 g of dry biomass) was subjected to Sephadex LH-20 column chromatography using $CHCl_3$/MeOH 1:1 (400 ml) as solvent system to obtain nine fractions. The first four fractions were discarded. Fraction 5 (802 mg) was further chromatographed on a SiO_2 column (28×600 mm); mobile phase $CHCl_3$/EtOAc 1:1 (500 ml) to afford **4** (168.9 mg). Fractions 6 (89.1 mg), 8 (78.9 mg) and 9 (47.6 mg) were also purified by SiO_2 column (20×800 mm), $CHCl_3$/EtOAc 1:1 (300 ml) to give **1** (6 mg), **2** (4.5 mg), **3** (17.3 mg), and **5** (14.7 mg), respectively. Fraction 7 (53.5 mg) was treated in a similar manner as described above, followed by preparative HPLC, (hexane/EtOAc 1:5, 250 ml) to yield **1** (4 mg), t_R=20 min and **2** (7.3 mg), t_R=33 min.

3.3.1. Rutilin A (1). $[\alpha]_D^{20}$ −61.9 (*c* 1.01, MeOH); IR(KBr) ν_{max} cm^{-1}: 3322, 1717, 1648, 1624, 1582, 1519 cm^{-1}; UV λ_{max} nm (log ε): 456 (4.1), 306 (4.2), 263 (4.4), 227 (4.4), 215 (4.4); HR-FABMS *m/z* 825.2397 [Calcd for $C_{44}H_{41}O_{16}$ $(M+H)^+$, 825.2395]; ^{1}H NMR and ^{13}C NMR are listed in Table 1.

3.3.2. Rutilin B (2). $[\alpha]_D^{20}$ −26.4 (*c* 1.01, MeOH); IR(KBr) ν_{max} cm^{-1}: 3334, 1718, 1648, 1624, 1580, 1518 cm^{-1}; UV λ_{max} nm (log ε): 460 (4.6), 307 (4.4), 262 (4.6), 226 (4.5), 215 (4.6); HR-FABMS *m/z* 825.2392 [Calcd for $C_{44}H_{41}O_{16}$ $(M+H)^+$, 825.2395]; ^{1}H NMR and ^{13}C NMR are listed in Table 1.

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Novel stereocontrolled approach to conformationally constrained analogues of L-glutamic acid and L-proline via stereoselective cyclopropanation of 3,4-didehydro-L-pyroglutamic ABO ester

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Abstract—A new stereocontrolled approach to L-(carboxycyclopropyl)glycines (L-CCGs) and 3,4-methano-L-prolines, conformationally constrained analogues of L-glutamic acid and L-proline, respectively, was developed using a 3,4-didehydro-L-pyroglutamate derivative as a common chiral template. The unsaturated L-pyroglutamate derivative employed in this work is a novel chiral synthon in which the carboxyl functionality is protected as a 2,7,8-trioxabicyclo[3.2.1]octyl group (ABO ester). Stereospecific cyclopropanation of the olefin using diazomethane followed by appropriate functional group interconversion gave L-CCG-III and *trans*-3,4-methano-L-proline with complete stereocontrol. Synthesis of other diastereomers of L-CCG and *cis*-3,4-methano-L-proline was accomplished by alteration of the 3,4-methanoglutamic acid framework via carboxycyclopropanation of the olefin with sulfur ylide and subsequent Barton decarboxylation reaction of the original γ-carboxyl group included in the pyroglutamate skeleton.

1. Introduction

L-Glutamic acid is the most widely used α-amino acid in asymmetric synthesis because of its versatility as a chiral starting material and its availability at low cost.[1] Among a wide variety of chiral synthons derived from L-glutamic acid, L-pyroglutamic acid, easily prepared by the intramolecular dehydration of L-glutamic acid, occupies an important place in the field of natural product synthesis.[2] For the functionalization at the 3- or 3,4-positions of the lactam ring, it is necessary to employ 3,4-didehydropyroglutamic acid derivatives. Although there are some reports concerning the reactivity of the unsaturated pyroglutamates,[3] they could not be used as a chiral template due to their tendency to racemize and isomerize via a double-bond shift. For example, Ezquerra and co-workers reported the first trapping reaction of the olefin with cyclopentadiene where the Diels–Alder adduct was obtained only in 50% ee.[3b] To circumvent the above problems, the corresponding pyroglutaminol derivatives are often employed as the chiral template; however, the procedure necessitates the reduction of the carboxyl group and its regeneration after the desired modification has been completed.

In an effort to overcome the problems encountered by the above approaches, we opted to explore an alternative chiral template involving the unsaturated pyroglutamate skeleton. Recently, Lajoie and co-workers have developed a new methodology for the synthesis of a wide range of nonproteinogenic α-amino acids based on the elaboration of a chiral serine aldehyde in which Corey's 2,6,7-trioxabicyclo[2.2.2]octyl group (OBO ester)[4] was used as a protective group for the carboxylic acid.[5] The bulky OBO moiety was found to reduce the acidity of the α-proton allowing several transformations without racemization and to induce high diastereoselectivity in the addition reactions performed on the aldehyde moiety.

In the present work, we adopted a 2,7,8-trioxabicyclo[3.2.1]octyl group (ABO ester)[6] as a protective group for the carboxyl functionality of the unsaturated pyroglutamate derivative because the pyroglutamic ABO ester is easier to prepare than the corresponding OBO ester. During the course of our investigation, synthesis of an unsaturated L-pyroglutamic OBO ester has been published;[7] however, the overall yield of the olefin from the starting L-pyroglutamic acid was very low (8.4%) and the reaction of the olefin was limited to Michael additions. In our preliminary communication,[8] we demonstrated an efficient synthesis of a 3,4-didehydropyroglutamic ABO ester **1** (49.8% overall yield) and its reactions, such as catalytic hydrogenation, Diels–Alder reaction, cyclopropanation, dihydroxylation,

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and Michael addition, which were found to proceed with excellent π-facial diastereoselectivity to the olefin without loss of enantiomeric purity at the α-position. As part of our ongoing development of the unsaturated orthopyroglutamate methodology for the asymmetric synthesis of unusual amino acids, we report herein a full account of the synthesis of L-(carboxycyclopropyl)glycines (L-CCGs) and 3,4-methano-L-prolines, the conformationally restricted analogues of L-glutamic acid and L-proline, respectively, via stereoselective cyclopropanation of 3,4-didehydro-L-pyroglutamic ABO ester **1**. Recently, considerable interest has been drawn to such conformationally constrained α-amino acids containing a cyclopropyl ring in their structure on account of their diverse biological activities.[9] In particular, L-CCGs are recognized as useful pharmacological tools for analyzing glutamate neurotransmitter systems.[10]

2. Results and discussion

2.1. Synthetic strategy

Since the first synthesis of racemic CCG-I by Ohfune and co-workers,[11] several enantioselective syntheses of L-CCGs have been reported mainly on the basis of cyclopropanation of chiral olefinic precursors,[12] where an appropriate choice of the geometrical isomer of the olefin or the starting olefin itself was necessary depending upon the desired diastereomer of CCGs. On the other hand, the first synthetic 3,4-methano-L-proline was obtained as a mixture of *cis* and *trans* isomers by Fujimoto and co-workers via addition of carbene to the corresponding dehydroproline derivative.[13] Later, several synthetic methods leading to the 3,4-methanoproline have appeared in the literature;[14] however, most of them were not enantioselective and gave a mixture of *cis* and *trans* isomers. To our knowledge, there are only two enantioselective routes to *cis*-3,4-methano-L-proline using chiral cyclopropane derivatives as starting materials.

This paper presents a novel stereocontrolled approach to L-CCGs and 3,4-methano-L-prolines from a common chiral olefinic precursor **1** as outlined in Figure 1. In general, an unsaturated lactam such as compound **1** can become a precursor only to L-CCG-III and *trans*-3,4-methano-L-proline because the cyclopropanation of the olefin is expected to occur exclusively from *trans* to the resident substituent at the 5-position (path A). The present strategy enables an alteration of the 3,4-methanoglutamic acid framework by carboxycyclopropanation of the olefin to introduce a new γ-carboxyl group into the cyclopropane ring as in path B followed by decarboxylation of the original γ-carboxyl group included in the pyroglutamate skeleton. Consequently, it becomes possible to obtain L-CCG-IV and *cis*-3,4-methano-L-proline, which can be formally accessible via *cis*-selective cyclopropanation of the olefin, from the *endo* adduct. Furthermore, it is feasible to obtain L-CCG-II, an extended derivative of CCGs, provided the corresponding *exo* adduct can be isolated in pure form. Usually, the extended form of CCGs can not be secured from the cyclopropanation of the cyclic olefin.

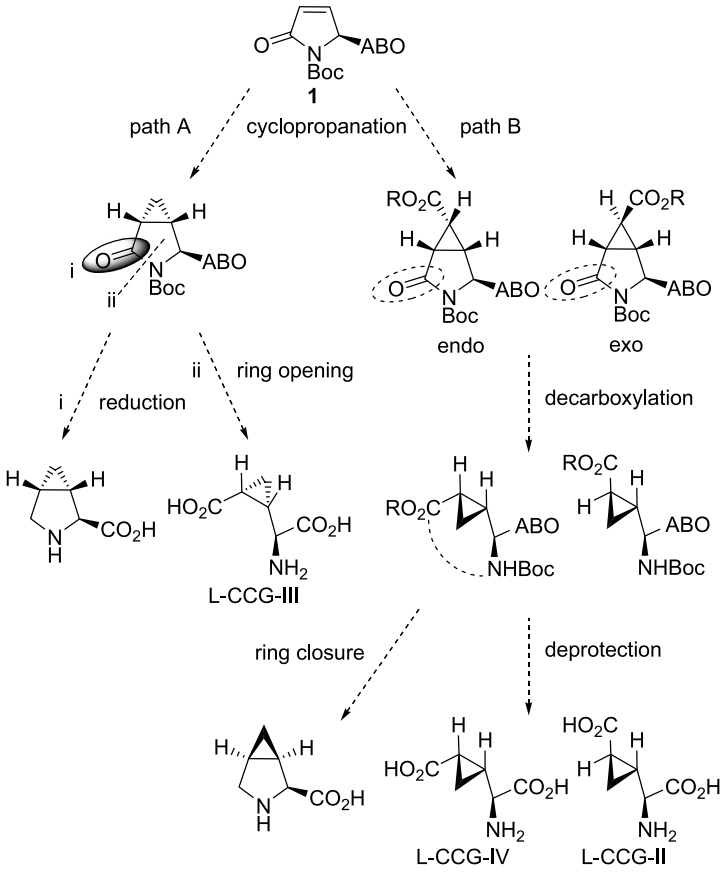
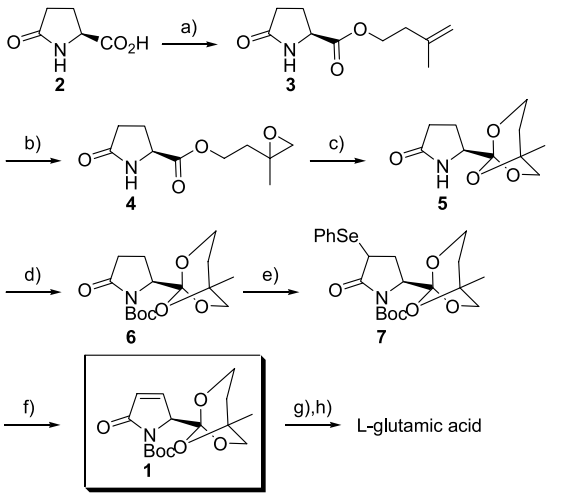


Figure 1. Stereocontrolled approach to L-CCGs and 3,4-methano-L-prolines.

2.2. Synthesis of unsaturated orthopyroglutamate 1

Construction of the 2,7,8-trioxabicyclo[3.2.1]octane (ABO) skeleton relied on zirconocene-catalyzed rearrangement of the epoxy ester toward the ortho ester reported by Wipf and co-workers.[6] According to the procedure shown in Scheme 1, the epoxy ester **4** was prepared from L-pyroglutamic acid **2** via condensation with 3-methyl-3-buten-1-ol in the presence of 1,3-dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-dimethylaminopyridine (DMAP) followed by epoxidation with 3-chloroperoxybenzoic acid (*m*CPBA). The obtained epoxy ester **4** was then treated with zirconocene catalyst, prepared in situ from zirconocene dichloride and silver perchlorate, to give an ABO ester **5**. Since the epoxidation of the chiral olefin **3** was non-stereoselective, the orthopyroglutamate **5** was obtained as a 1:1 mixture of diastereomers. In Scheme 1, only one enantiomeric form of the ABO skeleton is depicted for clarity. After protection of the amide proton with a *tert*-butoxycarbonyl (Boc) group, the orthopyroglutamate **6** was converted to a 3,4-didehydro-L-pyroglutamic ABO ester **1** using the well-established procedure involving phenylselenenylation and oxidative deselenenylation by hydrogen peroxide. The unsaturated orthopyroglutamate **1** was isolated in 49.8% yield based on the starting L-pyroglutamic acid (six steps) as a colorless crystalline solid, which was stable at room temperature for several months.

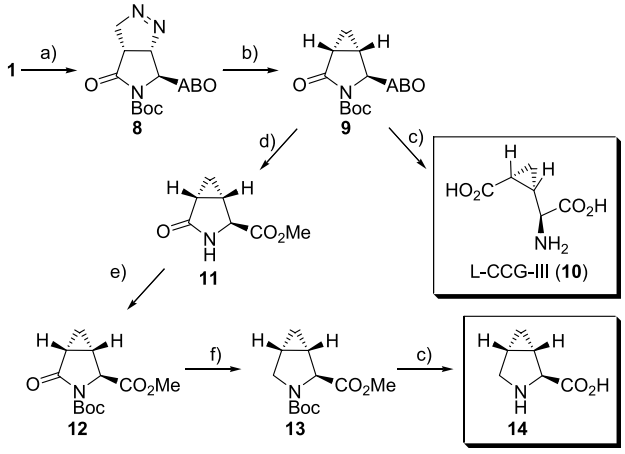


Scheme 1. Preparation of 3,4-didehydro-L-pyroglutamic ABO ester (**1**). Reagents and conditions: (a) $CH_2{=}C(Me)CH_2CH_2OH$, DCC, DMAP, CH_2Cl_2, quant; (b) *m*CPBA, CH_2Cl_2, 0 °C; (c) Cp_2ZrCl_2, $AgClO_4$, CH_2Cl_2; (d) $(tert\text{-}BuOCO)_2O$, DMAP, MeCN, 60% (three steps); (e) $NaN(SiMe_3)_2$, PhSeCl, DMPU–THF, −78 °C; (f) 30% H_2O_2, THF, 83% (two steps); (g) H_2, 10% Pd/C, MeOH; (h) 1 M HCl reflux; then Dowex 50W-X8, 77% (two steps).

In order to evaluate the chiral integrity at the α-position of the unsaturated orthopyroglutamate **1**, the olefin **1** was hydrogenated in the presence of 10% palladium on carbon followed by acidic hydrolysis in refluxing 1 M HCl to give L-glutamic acid in 77% yield. The enantiomeric purity of the obtained L-glutamic acid was found to be >99% ee by HPLC analysis using a chiral stationary column (MCIGEL CRS10W), suggesting that no racemization at the α-position occurred during the chemical transformations shown in Scheme 1.

2.3. Synthesis of L-CCG-III (10) and *trans*-3,4-methano-L-proline (14)

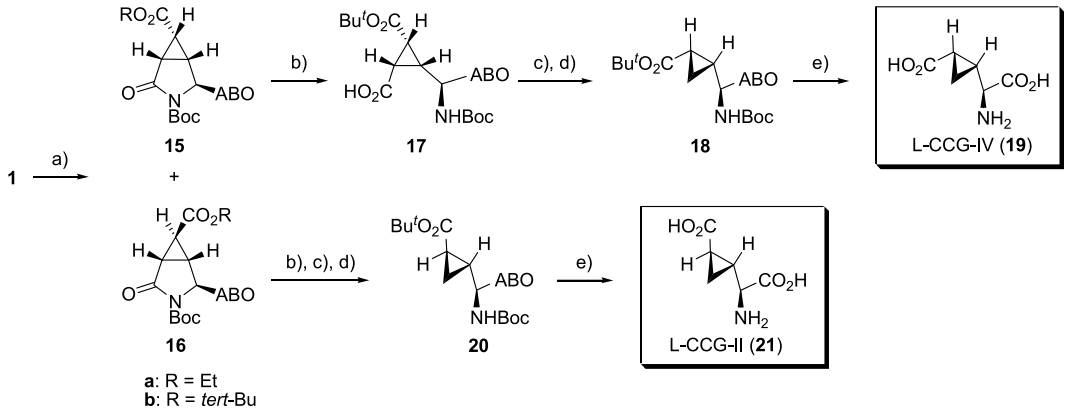
The synthetic course of (2*S*,1′*S*,2′*R*)-(carboxycyclopropyl) glycine (L-CCG-III, **10**) and *trans*-3,4-methano-L-proline (**14**) based on stereospecific cyclopropanation of the unsaturated orthopyroglutamate **1** is illustrated in Scheme 2. First of all, we investigated direct cyclopropanation of the unsaturated lactam **1** using a sulfoxonium ylide[15] as an alkylidene transfer reagent; however, the desired cycloadduct **9** could be obtained in only 32% yield. The cyclopropanation of the olefin **1** was next carried out by 1,3-dipolar cycloaddition of diazomethane followed by photolysis of the resultant pyrazoline **8** in the presence of benzophenone as a photosensitizer,[5b] affording the cycloadduct **9** in 61% yield. We could not detect the corresponding *cis* adduct in the reaction mixture, suggesting that exclusive addition of diazomethane to the olefin **1** opposite to the bulky ABO group occurred. In this case, the $Pd(OAc)_2$-catalyzed cycloaddtion of diazomethane to the olefin **1** gave no cycloadduct.



Scheme 2. Preparation of L-CCG-III (**10**) and *trans*-3,4-methano-L-proline (**14**). Reagents and conditions: (a) CH_2N_2, ether; (b) Hg-lamp (400 W), benzophenone, MeCN, 0 °C, 64% (two steps); (c) 1 M HCl reflux; then Dowex 50W-X8, **10**: 61%, **14**: 89%; (d) HCl–MeOH, 0 °C; (e) $(tert\text{-}BuOCO)_2O$, DMAP, MeCN, 56% (two steps); (f) BH_3–THF, 64%. ABO= 5-methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl.

Acidic hydrolysis of the cyclopropane derivative **9** in refluxing 1 M HCl and subsequent ion exchange operation afforded 61% yield of enantiomerically pure (>99% ee) L-CCG-III (**10**) in a single step, where ring-opening of the lactam skeleton, deprotection of the *N*-Boc group, and regeneration of the carboxyl functionality from the ABO ester occurred simultaneously. The stereochemistry of L-CCG-III (**10**) was determined by comparison of the ^1H NMR spectrum and specific rotation with the reported data.[12d]

To access the *trans*-3,4-methano-L-proline (**14**), we next investigated the chemoselective reduction of the lactam carbonyl moiety. Several attempts to reduce directly the carbonyl group of the bicyclic lactam **9** by borane or $LiEt_3BH$ were unsuccesfull. We eventually found that the corresponding methyl ester **12**, prepared by methanolysis of the ABO ester **9** followed by reprotection with the Boc group, underwent chemoselective reduction by borane–THF



Scheme 3. Preparation of L-CCG-II (**21**) and L-CCG-IV (**19**). Reagents and conditions: (a) $Me_2S{=}CHCO_2R$, DMSO, **15a**: 56%, **16a**: 40%, **15b**: 54%, **16b**: 29%; (b) 1 M LiOH, THF; (c) 4-methylmorpholine, $ClCO_2Bu^i$, THF; then 2-mercaptopyridine *N*-oxide, Et_3N, THF; (d) *tert*-BuSH, W-lamp (100 W), **18**: 85% (three steps), **20**: 51% (three steps); (e) 1 M HCl reflux; then Dowex 50W-X8, **19**: 86%, **21**: 84%. ABO=5-methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl.

to afford 3,4-methanoproline derivative **13** in 63% yield. Deprotection of compound **13** in refluxing 1 M HCl followed by treatment with Dowex 50W-X8 gave enantiomerically pure (>99% ee) *trans*-3,4-methano-L-proline (**14**) in 89% yield; and the structure was also confirmed by ^{1}H NMR data and specific rotation.[13]

The present protocol provides an extremely facile and straightforward approach to L-CCG-III and *trans*-3,4-methano-L-proline with unprecedented complete stereocontrol.

2.4. Synthesis of L-CCG-IV (19) and L-CCG-II (21)

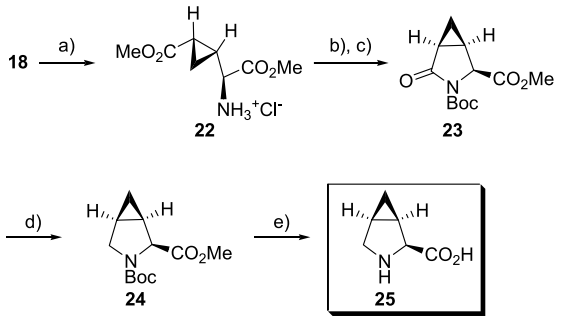
Scheme 3 shows the synthetic course of (2*S*,1′*R*,2′*S*)-(carboxycyclopropyl)glycine (L-CCG-IV, **19**) and (2*S*,1′*R*,2′*R*)-(carboxycyclopropyl)glycine (L-CCG-II, **21**) via alteration of the 3,4-methanoglutamic acid framework by a combination of carboxycyclopropanation of the olefin with sulfur ylides[16] and Barton decarboxylation reaction. When a solution of the unsaturated pyroglutamate **1** and ethyl dimethylsulfuranylideneacetate[17] in dimethyl sulfoxide was stirred at room temperature overnight, a mixture of *endo* and *exo* adducts, **15a** and **16a**, respectively, was obtained in a 57:42 ratio. Similar treatment of the olefin **1** with *tert*-butyl dimethylsulfuranylideneacetate[18] slightly improved the *endo* selectivity, giving a 67:33 mixture of **15b** and **16b**. This stereochemical outcome observed in the conjugate addition of sulfur ylides toward the unsaturated lactam **1** can be rationalized by considering a synclinal-like transition state proposed by Meyers and co-workers.[19] We also investigated the cyclopropanation using ethyl and *tert*-butyl diazoacetate in the presence or absence of a catalytic amount of $Pd(OAc)_2$; however, the expected cycloadducts could not be detected in the reaction mixture. The reason for the lower reactivity of the diazoacetates compared to diazomethane itself is probably due to the steric hindrance. Several efforts to obtain either diastereomer as a major product utilizing thermodynamic equilibration of the two products by treatment with a weak base or kinetic protonation of the corresponding enolate were unsuccessful. While the addition of the sulfur ylides across the carbon–carbon double bond is stereospecific, we could not obtain either an *endo* or *exo* adduct as a major product with overwhelming selectivity.

With the basic and nucleophilic reaction conditions employed in the succeeding processes in mind, only the *tert*-butyl ester derivatives **15b** and **16b** were adopted in this synthesis. The obtained *endo* and *exo* adducts **15b** and **16b** were chromatographically separable and were isolated in 54 and 29% yields, respectively. The chemoselective ring-opening of the lactam **15b** was carried out with 1 M LiOH to give crude carboxylic acid **17**. The acid **17** was then subjected to Barton decarboxylation reaction[20] using mercatopyridine *N*-oxide as a derivatizing reagent of the carboxyl group to afford fully protected (carboxycyclopropyl)glycine derivative **18** in 85% yield for the three steps. Finally, deprotection of compound **18** in refluxing 1 M HCl followed by the standard ion exchange operation afforded 86% yield of enantiomerically pure (99% ee) L-CCG-IV (**19**).

In order to obtain the corresponding extended form, similar treatment of the *exo* adduct **16b**, even though it was obtained as a minor product in the carboxycyclopropanation reaction, was carried out and afforded L-CCG-II (**21**) in 43% yield based on the adduct **16b** (four steps). The structures of L-CCG-IV (**19**) and L-CCG-II (**21**) were established by comparing their physical and spectral data with those reported in the literature.[12d]

2.5. Synthesis of *cis*-3,4-methano-L-proline (25)

Since the *cis*-3,4-methano-L-proline (**25**) is regarded as a cyclic analogue of L-CCG-IV (**19**), it is reasonable to employ a common precursor to these amino acids. There has been only one enantioselective route to *N*-Boc derivatives of L-CCG-IV and *cis*-3,4-methano-L-proline from a common key intermediate.[14b] In this work, we planned to prepare the methanoproline **25** via intramolecular cyclization of compound **18**, the precursor of L-CCG-IV, as shown in Scheme 4. Treatment of compound **18** with dry hydrogen chloride in methanol gave a crude dimethyl ester of L-CCG-IV as the hydrochloride salt **22**. The obtained hydrochloride **22** was neutralized to effect intramolecular cyclization reaction and subsequent protection of the resultant pyroglutamate derivative with the Boc group afforded 3,4-methano-L-pyroglutamate **23** in 40% yield based on compound **18** (three steps). According to the procedure for the synthesis of *trans*-3,4-methanoproline (**14**), the bicyclic



Scheme 4. Preparation of *cis*-3,4-methano-L-proline (**25**). Reagents and conditions: (a) HCl–MeOH, 0 °C; (b) aqueous $NaHCO_3$–THF; (c) (*tert*-$BuOCO)_2O$, DMAP, MeCN, 40% (three steps); (d) BH_3–THF, 31%; (e) 1 M HCl reflux; then Dowex 50W-X8, 70%.

lactam **23** was converted to the corresponding *cis*-3,4-methano-L-proline (**25**) via chemoselective reduction of the lactam carbonyl group followed by the standard deprotection protocol. The structure and enantiomeric purity (>99% ee) of the final product **25** were determined by comparison of their ^1H NMR data and the specific rotation with those reported.[13]

3. Conclusion

In this paper, we have demonstrated a novel approach to some pharmacologically important cyclopropane amino acids, such as L-CCGs and 3,4-methano-L-prolines, via stereoselective cyclopropanation of 3,4-didehydro-L-pyroglutamic ABO ester **1**.

Among the four possible diastereomers of L-CCGs, two folded and one extended forms, L-CCG-III, -IV, and -II, respectively, were prepared from a common starting olefin **1** in a stereodivergent way using a combination of cyclopropanation with diazomethane or sulfur ylides and Barton decarboxylation reaction. The *trans*- and *cis*-3,4-methano-L-prolines, which are considered to be cyclic derivatives of the folded L-CCGs, were also prepared from the precursors of L-CCG-III and -IV, respectively.

As expected, the ABO group serves as an efficient protective group, which completely prevents racemization at the α-position. Furthermore, the bulky ABO group provides steric hindrance that limits the approach of reagents from the β-face of the olefin, thus realizing stereospecific cyclopropanation. The ABO moiety can resist various reaction conditions employed in the present work and is amenable to regeneration of the carboxyl functionality through acidic treatment in the final stage of the synthetic processes.

4. Experimental

4.1. General

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were measured at 400 and 100 MHz, respectively. All chemical shifts are reported as δ values (ppm) relative to residual chloroform (δ_H 7.26), sodium 3-(trimethylsilyl)[2,2,3,3-D_4]propionate (δ_H 0.00), or the central peak of deuteriochloroform (δ_C 77.0). High-resolution mass spectra (HRMS) were determined using perfluorokerosene as an internal standard. Optical rotations were measured on a HORIBA SEPA-200 polarimeter. Solvents and reagents were of commercial grade and were purified if necessary.

4.1.1. (5*S*)-2-Pyrrolidone-5-carboxylic acid 3-methyl-3-butenyl ester (3). To a solution of 1,3-dicyclohexylcarbodiimide (DCC, 12.3 g, 59.7 mmol), 4-dimethylaminopyridine (DMAP, 610 mg, 5.00 mmol) and 3-methyl-3-buten-1-ol (5.17 g, 60.1 mmol) in dichloromethane (150 mL) was added L-pyroglutamic acid (**2**, 6.45 g, 50.0 mmol) at 0 °C and the reaction mixture was stirred at room temperature overnight. After removal of the precipitated 1,3-dicyclohexylurea, the filtrate was washed with saturated aqueous NH_4Cl and concentrated. The residue was dissolved in ether and extracted several times with water. The combined aqueous extracts were evaporated and the residue was dissolved in chloroform. The organic layer was dried over $MgSO_4$ and concentrated to give quantitative yield of the title compound **3** (9.85 g, 50.0 mmol) as an oil. ^1H NMR ($CDCl_3$) δ 1.75 (s, 3H), 2.17–2.51 (m, 6H), 4.21–4.32 (m, 3H), 4.73 (br s, 1H), 4.82 (br s, 1H), 6.15 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 21.4, 24.1, 28.5, 35.8, 54.9, 62.4, 111.7, 140.5, 171.6, 177.9. HRMS (EI, 70 eV) *m/z* 197.1052 (M^+, calcd for $C_{10}H_{15}NO_3$ 197.1031).

4.1.2. (5*S*)-1-*tert*-Butoxycarbonyl-5-(5-methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl)-2-pyrrolidone (6). To a solution of 3-chloroperoxybenzoic acid (*m*CPBA, 13.0 g, 75.0 mmol) in dichloromethane (150 mL) was added a solution of ester **3** (9.85 g, 50.0 mmol) in dichloromethane (50 mL) at 0 °C and the reaction mixture was stirred for 4 h. After removal of the solvent, the residue was chromatographed on silica gel (chloroform/methanol=90:10) to give epoxide **4** (10.7 g) in quantitative yield. Although the obtained epoxide **4** was still contaminated with 3-chlorobenzoic acid, the sample could be used in the next step without further purification.

To a suspension of bis(cyclopentadienyl)zirconium dichloride (1.47 g, 5.03 mmol) and $AgClO_4$ (1.10 g, 5.31 mmol) in dichloromethane (60 mL) was added a solution of the obtained crude epoxide **4** in dichloromethane (40 mL) and the mixture was stirred for 2 days. After addition of saturated aqueous $NaHCO_3$, the insoluble materials were filtered off. The filtrate was washed with brine, dried over $MgSO_4$, and concentrated to afford crude orthopyroglutamate **5**.

The obtained orthoester **5** was then treated with di-*tert*-butyl dicarbonate (13.2 g, 60.6 mmol) and DMAP (6.20 g, 50.8 mmol) in acetonitrile (80 mL) at room temperature for 1.5 h. After removal of the solvent, the residue was extracted with ethyl acetate. The organic layer was washed successively with aqueous $KHSO_4$ and brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate=50:50) to afford 9.40 g (60%, three steps) of the title compound **6** as an oil. ^1H NMR ($CDCl_3$) δ 1.34 and 1.35 (2s, 3H), 1.43–1.48 (m, 1H), 1.51 (s, 9H), 1.98–2.35 (m, 4H), 2.74–2.84 (m, 1H), 3.45–3.49 (m, 1H), 3.85–3.91 (m,

1H), 3.97–4.14 (m, 2H), 4.44 and 4.48 (2d, $J=9$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 19.2 and 19.6, 21.2, 27.1 and 27.2, 31.2, 33.05 and 33.08, 57.9 and 58.5, 58.75 and 58.83, 72.9 and 73.2, 78.5 and 78.6, 81.59 and 81.61, 119.6 and 119.7, 149.09 and 149.12, 174.6. HRMS (EI, 30 eV) *m/z* 313.1525 (M^+, calcd for $C_{15}H_{23}NO_6$ 313.1556).

4.1.3. (5*S*)-1-*tert*-Butoxycarbonyl-5-(5-methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl)-5*H*-2-pyrrolinone (1). A solution of 1 M sodium bis(trimethylsilyl)amide in THF (61 mL, 61 mmol) was treated with *N*,*N*′-dimethylpropyleneurea (8.2 mL, 68 mmol) at 0 °C under an argon atmosphere for 20 min, cooled to −78 °C, and treated with a solution of compound **6** (7.90 g, 25.2 mmol) in THF (50 mL). After 0.5 h, a solution of phenylselenenyl chloride (5.30 g, 27.7 mmol) in THF (50 mL) was added and the mixture was stirred for 2 h. The reaction was quenched with saturated aqueous NH_4Cl and the mixture was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and the solvent was evaporated to give 3-phenylseleno-2-pyrrolidone derivative **7**.

To a solution of the obtained crude phenylselenide **7** in THF (300 mL) was added dropwise 30% H_2O_2 (15 mL, 132 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 2 h. The mixture was extracted with ethyl acetate and the organic layer was washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel. Elution with a mixture of hexane and ethyl acetate (50:50) afforded 6.48 g (83%, two steps) of the title compound **1** as a colorless solid, mp 110–112 °C. ^{1}H NMR ($CDCl_3$) δ 1.34 and 1.35 (2s, 3H), 1.43–1.48 (m, 1H), 1.52 (s, 9H), 1.99 and 2.08 (2m, 1H), 3.45 and 3.47 (2d, $J=2$ Hz, 1H), 3.84–4.1 (m, 3H), 4.97 and 5.03 (2dd, $J=2$, 2 Hz, 1H), 6.11 (m, 1H), 7.19 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 21.6 and 21.7, 27.7 and 27.8, 33.6, 59.4 and 59.5, 63.3 and 63.9, 73.4 and 73.5, 79.1 and 79.5, 82.6 and 82.7, 117.9 and 118.0, 127.3, 146.1, 149.1, 169.8. HRMS (EI, 30 eV) *m/z* 312.1447 [$(M+1)^+$, calcd for $C_{15}H_{22}NO_6$ 312.1485].

4.1.4. (1*R*,4*S*,5*S*)-3-*tert*-Butoxycarbonyl-4-(5-methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl)-3-azabicyclo[3.1.0]hexan-2-one (9). To a solution of olefin **1** (3.11 g, 10 mmol) in ether (50 mL) was added an excess ethereal solution of diazomethane (ca. 8.3 equiv) at 0 °C and the mixture was stirred at room temperature in the dark for 3.5 h. The reaction was quenched by addition of anhydrous $CaCl_2$ and, after filtration, evaporation of the solvent gave very unstable pyrazoline derivative **8** (3.53 g).

An acetonitrile solution (500 mL) of the obtained pyrazoline **8** in the presence of benzophenone (1.87 g, 10.3 mmol) was irradiated with a 400 W medium-pressure mercury lamp at 0 °C under an argon atmosphere for 20 min. After removal of the solvent, the crude product was purified by flash column chromatography on silica gel (hexane/ethyl acetate=50:50) to afford the title compound **9** (2.09 g, 64%) as an oil. ^{1}H NMR ($CDCl_3$) δ 0.65–0.69 (m, 1H), 1.08–1.13 (m, 1H), 1.35 and 1.37 (2s, 3H), 1.45–1.50 (m, 1H), 1.47 and 1.48 (2s, 9H), 1.93–2.14 (m, 3H), 3.47–3.51 (m, 1H), 3.88–4.13 (m, 3H), 4.38 and 4.42 (2s, 1H). ^{13}C NMR ($CDCl_3$) δ 10.8, 12.0 and 12.3, 20.2, 21.7 and 21.8, 27.8, 33.8, 59.4 and 59.5, 60.0, 73.6 and 73.8, 79.0 and 79.3, 82.3, 119.3, 150.3, 174.3. HRMS (EI, 70 eV) *m/z* 326.1604 [$(M+1)^+$, calcd for $C_{16}H_{24}NO_6$ 326.1648].

4.1.5. (2*S*,1′*S*,2′*R*)-2-(Carboxycyclopropyl)glycine (10, L-CCG-III). A mixture of compound **9** (318 mg, 0.978 mmol) and 1 M HCl (30 mL) was heated to reflux for 3 h. The cooled solution was washed with chloroform and concentrated to dryness. The residue was submitted to ion-exchange column chromatography on Dowex 50W-X8 and elution with 1 M NH_4OH to give the ammonium salt of compound **10**. The salt was then dissolved in water and the solution was acidified to pH 3 with 1 M HCl. The precipitated solids were collected by filtration and recrystallized from water–acetone to give the title compound **10** (95.0 mg, 61%) as colorless crystals, mp 205–207 °C (lit.[12d] mp 192–197 °C dec). $[\alpha]_D^{23}$ +20.7 (*c* 0.54, H_2O) (lit.[12d] $[\alpha]_D^{22}$ +20.8 (*c* 0.52, H_2O)). ^{1}H NMR (D_2O) δ 1.37 (ddd, $J=6$, 6, 7 Hz, 1H), 1.52 (ddd, $J=6$, 9, 9 Hz, 1H), 1.77 (dddd, $J=7$, 8, 9, 11 Hz, 1H), 1.99 (ddd, $J=6$, 8, 9 Hz, 1H), 4.21 (d, $J=11$ Hz, 1H).

4.1.6. (1*R*,4*S*,5*S*)-3-*tert*-Butoxycarbonyl-4-methoxycarbonyl-3-azabicyclo[3.1.0]hexan-2-one (12). A solution of compound **9** (534 mg, 1.64 mmol) in methanol (40 mL) was cooled in an ice bath and a slow stream of HCl was introduced with stirring to saturation. After being stirred at room temperature for 3 h, the solution was concentrated and the residue was extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give crude methyl pyroglutamate derivative **11** (187 mg).

The obtained ester **11** was treated with di-*tert*-butyl dicarbonate (640 mg, 2.94 mmol) and DMAP (310 mg, 2.54 mmol) in acetonitrile (20 mL) at room temperature overnight. After removal of the solvent, the residue was extracted with ethyl acetate. The organic layer was washed successively with aqueous $KHSO_4$ and brine, dried over $MgSO_4$, and concentrated to give 233 mg (56%, two steps) of the title compound **12** as an oil. ^{1}H NMR ($CDCl_3$) δ 0.84 (ddd, $J=4$, 4, 5 Hz, 1H), 1.24 (ddd, $J=5$, 8, 9 Hz, 1H), 1.45 (s, 9H), 1.95 (ddd, $J=4$, 6, 8 Hz, 1H), 2.06 (dddd, $J=1$, 4, 6, 9 Hz, 1H), 3.79 (s, 3H), 4.51 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 12.0, 14.9, 20.4, 27.8, 52.7, 60.2, 83.4, 149.5, 170.6, 172.6. HRMS (EI, 70 eV) *m/z* 255.1107 (M^+, calcd for $C_{12}H_{17}NO_5$ 255.1124).

4.1.7. (1*S*,2*S*,5*R*)-3-*tert*-Butoxycarbonyl-2-methoxycarbonyl-3-azabicyclo[3.1.0]hexane (13). To a solution of compound **12** (83.0 mg, 0.325 mmol) in THF (10 mL) was added a 1 M solution of borane in THF (1 mL, 1 mmol) under an argon atmosphere and the mixture was stirred at room temperature overnight. The reaction was quenched by addition of methanol and, after being stirred for 1 h, the mixture was diluted with dichloromethane. The organic layer was then dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/ethyl acetate=50:50) to afford the title compound **13** (50.0 mg, 64%) as an oil. ^{1}H NMR ($CDCl_3$) δ 0.319 (ddd, $J=5$, 9, 9 Hz, 1H), 0.742 (ddd, $J=5$, 7, 15 Hz, 1H), 1.39 and 1.44 (2s, 9H), 1.49–1.56 (m, 1H), 1.57–1.62 (m, 1H), 3.54 (d, $J=2$ Hz, 1H), 3.58 (d, $J=4$ Hz, 1H), 3.74

and 3.75 (2s, 3H), 4.27 and 4.39 (2s, 1H). ^{13}C NMR ($CDCl_3$) δ 8.84 and 9.13, 14.9 and 15.4, 18.9 and 19.8, 28.3 and 28.4, 48.3 and 48.4, 52.0 and 52.1, 60.9 and 61.5, 80.0, 154.7 and 155.2, 172.7 and 172.9. HRMS (EI, 70 eV) *m/z* 241.1314 (M^+, calcd for $C_{12}H_{19}NO_4$ 241.1313).

4.1.8. (2*S*,3*S*,4*R*)-3,4-Methanoproline (14). A mixture of compound **13** (255 mg, 1.06 mmol) and 1 M HCl (26 mL) was heated to reflux for 3 h. The cooled solution was washed with chloroform and concentrated to dryness. The residue was submitted to ion-exchange column chromatography on Dowex 50W-X8 and elution with 1 M NH_4OH to give the title compound **14** (120 mg, 89%) as colorless crystals (water–acetone), mp 263–265 °C (lit.[13] mp 245–250 °C). $[\alpha]_D^{20}$ −94.8 (*c* 0.5, H_2O) (lit.[13] $[\alpha]_D^{20}$ −94 (*c* 1.0, H_2O)). ^{1}H NMR (D_2O) δ 0.38–0.42 (m, 1H), 0.93–0.99 (m, 1H), 1.80–1.86 (m, 1H), 1.99–2.04 (m, 1H), 3.45 (d, *J*=11 Hz, 1H), 3.58 (dd, *J*=4, 12 Hz, 1H), 4.13 (s, 1H).

4.1.9. (1*S*,4*S*,5*R*,6*R*)-3,6-Di-*tert*-butoxycarbonyl-4-(5-methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl)-3-azabicyclo-[3.1.0]hexan-2-one (15b) and (1*S*,4*S*,5*R*,6*S*)-isomer (16b). A solution of olefin **1** (5.07 g, 16.3 mmol) and *tert*-butyl dimethylsulfuranylideneacetate (5.70 g, 32.4 mmol) in DMSO (100 mL) was stirred at room temperature overnight. The mixture was diluted with ethyl acetate, washed with brine, and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel (hexane/ethyl acetate=50:50) to give compound **16b** (1.99 g, 29%) as colorless crystals, mp 173–178 °C. ^{1}H NMR ($CDCl_3$) δ 1.35 and 1.37 (2s, 3H), 1.43 (s, 9H), 1.47 (s, 9H), 1.57–1.67 (m, 1H), 1.71 (dd, *J*=3, 3 Hz, 1H), 2.00–2.14 (m, 1H), 2.41 (d, *J*=3 Hz, 1H), 2.45 and 2.47 (2d, *J*=3 Hz, 1H), 3.46–3.51 (m, 1H), 3.88–4.13 (m, 3H), 4.44 and 4.48 (2s, 1H). ^{13}C NMR ($CDCl_3$) δ 20.0 and 20.3, 21.7, 25.6, 27.7, 27.9, 28.4 and 28.5, 33.7, 59.3 and 59.4, 59.6 and 59.9, 73.6 and 73.8, 79.2 and 79.4, 81.8, 82.7 and 82.8, 118.8, 149.5, 168.7 and 168.8, 171.3. HRMS (EI, 70 eV) *m/z* 426.2128 [$(M+1)^+$, calcd for $C_{21}H_{32}NO_8$ 426.2169].

Further elution with a mixture of hexane and ethyl acetate (50:50) afforded the compound **15b** (3.75 g, 54%) as an oil. ^{1}H NMR ($CDCl_3$) δ 1.31 and 1.32 (2s, 3H), 1.36 (s, 9H), 1.42 (s, 9H), 1.45–1.47 (m, 1H), 1.94–2.08 (m, 2H), 2.19–2.27 (m, 2H), 3.45–3.46 (m, 1H), 3.83–4.09 (m, 3H), 4.51 and 4.54 (2s, 1H). ^{13}C NMR ($CDCl_3$) δ 18.9 and 19.1, 21.4, 24.7, 25.9 and 26.0, 27.4 and 27.5, 27.6, 33.5, 56.9 and 57.4, 59.1 and 59.3, 73.2 and 73.5, 77.2, 78.8 and 79.1, 81.4 and 81.8, 118.9 and 119.0, 149.0, 166.1 and 166.2, 170.3. HRMS (EI, 70 eV) *m/z* 425.2050 (M^+, calcd for $C_{21}H_{31}NO_8$ 425.2056).

4.1.10. (2*S*,1′*R*,2′*S*)-*N*-*tert*-Butoxycarbonyl-2-((*tert*-butoxycarbonyl)cyclopropyl)glycine ABO ester (18). To a solution of compound **15b** (2.37 g, 5.58 mmol) in THF (60 mL) was added a solution of 1 M aqueous LiOH (20 mL) and the mixture was stirred at room temperature overnight. The solution was then acidified to pH 4 with 10% aqueous citric acid and extracted with chloroform. The organic layer was dried over $MgSO_4$ and concentrated to give compound **17** (2.47 g) in quantitative yield.

To a solution of the obtained acid **17** (912 mg, 2.06 mmol) in THF (40 mL) were added 4-methylmorpholine (250 mg, 2.47 mmol) and isobutyl chloroformate (337 mg, 2.47 mmol) at −15 °C under an argon atmosphere. After 5 min, a solution of 2-mercaptopyridine *N*-oxide (326 mg, 2.56 mmol) and triethylamine (259 mg, 2.56 mmol) in THF (20 mL) was added and the mixture was stirred in the dark for 1 h. After removal of the precipitated triethylamine hydrochloride, the filtrate was concentrated and the residue was chromatographed on silica gel in the dark. Elution with a mixture of hexane and ethyl acetate (50:50) gave quantitative yield (1.14 g) of the corresponding ester, which was very unstable and used immediately in the next step.

A solution of the obtained ester and 2-methyl-2-propanethiol (1.88 g, 20.8 mmol) in THF (40 mL) was irradiated with a 100 W tungsten lamp at room temperature under an argon atmosphere for 1 h. After removal of the solvent, the residue was extracted with ethyl acetate, washed successively with 0.1 M aqueous $NaHCO_3$, 0.5 M aqueous $KHSO_4$, and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/ethyl acetate=70:30) to afford the title compound **18** (701 mg, 85%, three steps) as an oil. ^{1}H NMR ($CDCl_3$) δ 0.86–0.91 (m, 1H), 1.16–1.22 (m, 1H), 1.35 and 1.36 (2s, 3H), 1.40–1.42 (dd, *J*=4, 4 Hz, 1H), 1.45 (s, 18H), 1.60–1.70 (m, 2H), 1.99–2.08 (m, 1H), 3.44–3.50 (m, 1H), 3.82–3.88 (m, 1H), 3.99–4.08 (m, 2H), 4.26 (br s, 1H), 4.85 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 10.4, 20.3 and 20.4, 21.8, 21.9, 28.2, 28.3, 33.8, 51.4, 59.1 and 59.2, 73.7, 73.9, 78.9, 79.9, 119.6, 155.4, 171.4. HRMS (EI, 70 eV) *m/z* 399.2257 (M^+, calcd for $C_{20}H_{33}NO_7$ 399.2291).

4.1.11. (2*S*,1′*R*,2′*S*)-2-(Carboxycyclopropyl)glycine (19, L-CCG-IV). A mixture of compound **18** (219 mg, 0.549 mmol) and 1 M HCl (30 mL) was heated to reflux for 3 h. The cooled solution was washed with chloroform and concentrated to dryness. The residue was submitted to ion-exchange column chromatography on Dowex 50W-X8 and elution with 1 M NH_4OH to give the ammonium salt of compound **19**. The salt was then dissolved in water and the solution was acidified to pH 3 with 1 M HCl. The precipitated solids were collected by filtration and recrystallized from water–acetone to give the title compound **19** (75.0 mg, 86%) as colorless crystals, mp 180–182 °C (lit.[12d] mp 178–180 °C). $[\alpha]_D^{22}$ +103.7 (*c* 0.2, H_2O) (lit.[12d] $[\alpha]_D^{26}$ +103.4 (*c* 0.5, H_2O)). ^{1}H NMR (D_2O) δ 1.13 (ddd, *J*=6, 6, 7 Hz, 1H), 1.29 (ddd, *J*=6, 9, 9 Hz, 1H), 1.66 (dddd, *J*=7, 9, 9, 10 Hz, 1H), 2.02 (ddd, *J*=6, 9, 9 Hz, 1H), 3.83 (d, *J*=10 Hz, 1H).

4.1.12. (2*S*,1′*R*,2′*R*)-*N*-*tert*-Butoxycarbonyl-2-((*tert*-butoxycarbonyl)cyclopropyl)glycine ABO ester (20). According to the procedure for the preparation of compound **18**, ring-opening of lactam **16** (504 mg, 1.14 mmol) followed by the Barton decarboxylation reaction afforded 51% (three steps) yield of the title compound **20** (233 mg) as an oil. ^{1}H NMR ($CDCl_3$) δ 0.86–0.91 (m, 1H), 0.96–1.02 (m, 1H), 1.20–1.26 (m, 1H), 1.35 and 1.37 (2s, 3H), 1.42 (s, 9H), 1.43 (s, 9H), 1.51–1.62 (m, 2H), 1.99–2.08 (m, 1H), 3.45–3.51 (m, 1H), 3.67–3.73 (m, 1H), 3.84–3.91 (m, 1H), 4.01–4.09 (m, 2H), 4.65–4.76 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 10.9, 19.5 and 19.7, 21.8, 28.1, 28.3, 29.6, 33.8, 54.8, 59.3,

73.9 and 74.0, 79.0 and 79.1, 79.5, 79.9, 119.6, 155.9, 173.3. HRMS (EI, 70 eV) *m/z* 400.2335 [$(M+1)^+$, calcd for $C_{20}H_{34}NO_7$ 400.2341].

4.1.13. (2*S*,1′*R*,2′*R*)-2-(Carboxycyclopropyl)glycine (21, L-CCG-II). According to the procedure for the preparation of compound **19**, hydrolysis and deprotection of compound **20** (293 mg, 0.734 mmol) gave the title compound **21** (98.0 mg, 84%) as colorless crystals (water–acetone), mp 265–270 °C dec (lit.[12d] mp 255–258 °C dec). $[\alpha]_D^{23}$ −20.0 (*c* 0.1, H_2O) (lit.[12d] $[\alpha]_D^{25}$ −20.2 (*c* 0.51, H_2O)). ^1H NMR (D_2O) δ 1.04 (ddd, $J=5$, 7, 9 Hz, 1H), 1.21 (ddd, $J=5$, 5, 9 Hz, 1H), 1.67 (dddd, $J=4$, 7, 9, 9 Hz, 1H), 1.80 (ddd, $J=4$, 5, 9 Hz, 1H), 3.39 (d, $J=9$ Hz, 1H).

4.1.14. (1*S*,4*S*,5*R*)-3-*tert*-Butoxycarbonyl-4-methoxycarbonyl-3-azabicyclo[3.1.0]hexan-2-one (23). A solution of compound **18** (1.32 g, 3.31 mmol) in methanol (300 mL) was cooled in an ice bath and a slow stream of HCl was introduced with stirring to saturation. After being stirred at room temperature overnight, the solution was concentrated and the residue was dissolved in water. The aqueous layer was washed with chloroform and concentrated to give quantitative yield of crude methyl ester **22**.

The obtained ester was then dissolved in a mixture of water (100 mL) and THF (100 mL) and the pH was adjusted to 8 by adding $NaHCO_3$. After being stirred at room temperature overnight, the mixture was extracted with ethyl acetate and the organic layer was dried over $MgSO_4$ and concentrated to give a crude lactam (372 mg). The obtained lactam was then treated with di-*tert*-butyl dicarbonate (631 mg, 2.89 mmol) and DMAP (297 mg, 2.43 mmol) in acetonitrile (30 mL) at room temperature overnight. After removal of the solvent, the residue was extracted with ethyl acetate. The organic layer was washed successively with aqueous $KHSO_4$ and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate=50:50) to give 341 mg (40%, three steps) of the title compound **23** as an oil. ^1H NMR ($CDCl_3$) δ 0.98 (ddd, $J=5$, 8, 9 Hz, 1H), 1.14 (ddd, $J=5$, 6, 6 Hz, 1H), 1.37 (s, 9H), 2.02 (ddd, $J=4$, 6, 9 Hz, 1H), 2.12 (dddd, $J=4$, 6, 6, 8 Hz, 1H), 3.72 (s, 3H), 4.61 (d, $J=6$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 8.8, 14.6, 21.2, 27.7, 52.4, 58.5, 83.4, 149.1, 169.8, 172.4. HRMS (EI, 70 eV) *m/z* 255.1107 (M^+, calcd for $C_{12}H_{17}NO_5$ 255.1101).

4.1.15. (1*R*,2*S*,5*S*)-3-*tert*-Butoxycarbonyl-2-methoxycarbonyl-3-azabicyclo[3.1.0]hexane (24). According to the procedure for the preparation of compound **13**, reduction of lactam **23** (341 mg, 1.34 mmol) afforded the title compound **24** (101 mg, 31%) as an oil. ^1H NMR ($CDCl_3$) δ 0.62 (m, 1H), 0.72 (m, 1H), 1.35 and 1.40 (2s, 9H), 1.56–1.61 (m, 1H), 1.77–1.83 (m, 1H) 3.49–3.58 (m, 2H), 3.71 and 3.72 (2s, 3H), 4.30 and 4.34 (2d, $J=5$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 8.26 and 8.38, 15.8 and 16.5, 19.7 and 20.6, 28.1 and 28.3, 49.7, 51.8 and 51.9, 60.3 and 60.5, 80.0 and 80.1, 154.2, 171.8. HRMS (EI, 70 eV) *m/z* 241.1314 (M^+, calcd for $C_{12}H_{19}NO_4$ 241.1355).

4.1.16. (2*S*,3*R*,4*S*)-3,4-Methanoproline (25). According to the procedure for the preparation of compound **14**, hydrolysis and deprotection of compound **24** (101 mg, 0.419 mmol) gave the title compound **25** (37.0 mg, 70%) as colorless crystals (water–acetone), mp 224–230 °C (lit.[13] mp 235–245 °C). $[\alpha]_D^{20}$ −130 (*c* 0.12, H_2O) (lit.[13] $[\alpha]_D^{20}$ −131 (*c* 0.1, H_2O)). ^1H NMR (D_2O) δ 0.508 (ddd, $J=4$, 5, 6 Hz, 1H), 0.804 (ddd, $J=6$, 7, 8 Hz, 1H), 1.83–1.89 (m, 1H), 2.01–2.05 (m, 1H), 3.51 (d, $J=2$ Hz, 2H), 4.32 (d, $J=5$ Hz, 1H).

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Novel highly fluorescent dendritic chiral amines: synthesis and optical properties

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Abstract—An efficient approach to dendritic chiral amines through the allylation of optically active imines bearing chiral auxiliaries were developed. The addition of allylic zinc catalyzed by $CeCl_3 \cdot 7H_2O$ to chiral imines derived from 2-thiophenecarboxaldehyde and α-amino acid esters conveniently and efficiently afforded the corresponding homoallylic amines with excellent diastereoselectivity. Such addition reactions employing diimines or triimines of the polycyclic aromatic derivatives also produced the chrial multiallylic dendritic amines with the similar diastereoselectivity. The investigation of their photophysical properties including UV–vis absorption and fluorescence spectra as well as circular dichroism (CD) indicated that it did not affect the absorption of the precursors to induce the chiral auxiliaries; however, that the whole molecules exhibited the obvious CD behaviors.

1. Introduction

Metal-mediated allylation reactions of imines to the corresponding homoallylic amines have been developed as one of the most important conversion for the carbon–carbon bond formation.[1–5] Its convenient experimental procedure and wide applicability provide synthetically useful intermediates for preparing nitrogen-containing natural and bioactive compounds including amino sugar, β-amino acids, γ-amino acids and β-lactams.[6–8] In the past decades, various metals including zinc, tin, bismuth, indium, and samarium have been employed to such asymmetric allylation of chiral imines.[9,10] A number of optically active primary homoallylic amines were prepared in high diastereoselectivities through such reactions.[11–13] The chiral auxiliary compounds usually include optically active phenylethylamine, various α-amino acid esters as well as amino alcohols. For instance, zinc mediated allylation of chiral imines using methyl (*S*)-valinate as the chiral auxiliary catalyzed by Lewis acids afforded chiral homoallylic amines with excellent diastereoselectivity.[14–16] The chiral auxiliary groups are subsequently removed to afford the corresponding allylic-functionalized optical amines, which are readily converted into β-amino acids or γ-amino acids after ozonolysis or other oxidation.[9,17,18] Therefore, such allylic reactions have exhibited more widely application to asymmetric synthesis of functional optical amine molecules.

Dendrimers have become a subject of intense research in recent years owing to their unique structures and properties. Various applications of dendrimers have been developed using their unique characters.[19,20] Optically active derivatives of dendrimers with chiral ligands have exhibited broad applications in asymmetric catalysis and chiral recognization.[21–24] There is much interest in the development of dendrimers as efficient molecular sensors that selectively respond to specifically detected molecules. The light harvesting effects, one of the unique properties of dendrimers, make dendrimers exhibit much more sensitive fluorescence responses than corresponding small molecules.[25–29] A variety of chiral luminescent dendrimers have shown enantioselective responses when treated with chiral quenchers or enhancers. Their properties responding differently to the circularly polarized lights can be potentially used as chiral sensors to recognize the enantiomers of chiral molecules.

Among various chiral dendrimers, optically pure dendritic chiral amines have attracted considerable interest because they are easily modified to acquire a series of chiral dendrimers with various structures.[30–33] These optically pure chiral dendrimers could be considerably applied in asymmetric catalysis. The fluorescence of these dendrimers is probably enantioselectively quenched by some special chiral molecules, so these dendrimers exhibit the potential

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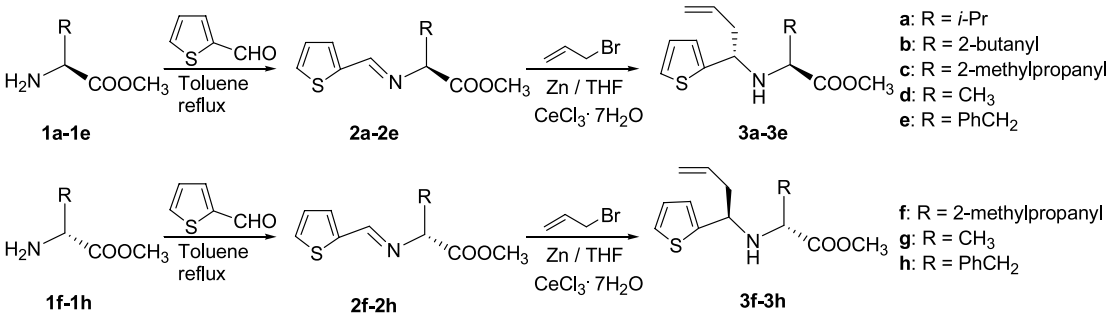


Scheme 1. Asymmetric addition of allyl zinc bromide to the chiral imines.

use for enantioselective sensors. Although dendritic chiral amines have such significant potential applications, there are still great challenges to synthesize these dendrimers with high enantioselectivity.

In this contribution, we developed a facile approach to a kind of novel dendritic chiral amines with high optical activity. They were readily prepared through the diastereoselectivity of zinc-mediated allylation of dendritic imines bearing (*S*)-valine methyl ester as the chiral auxiliary under mild conditions. These chiral dendrimers containing multiple modifiable groups could be used to build the potential enantioselective sensors for recognition of chiral molecules.

2. Results and discussion

To understand the diastereoselectivity of the allylic reaction of dendritic truxene deriavatives with multi-imine groups, we systematically investigated the zinc-mediated asymmetric allylation of chiral imines bearing α-amino acid methyl esters as auxiliaries derived from 2-thiophenealdehyde (Scheme 1). The chiral imines were prepared by the condensation of 2-thiophenecarboxaldehyde and α-amino acid methyl esters. The mixture was stirred in refluxing toluene and ^{1}H NMR spectra in situ were employed to monitor the reaction process. After 10 h, the signal of aldehyde group disappeared to indicate the completion of conversion. The crude imines were obtained after removal of the solvents under vacuum in almost quantitative yield, and used in the following allylic reaction immediately. The allylic reactions were performed on 1 mmol of imine reacted with 1.2 equiv of allylbromide and 1.5 equiv of zinc powder in the presence of 0.1 equiv of $CeCl_3 \cdot 7H_2O$.

Table 1. Asymmetric addition of allyl zinc bromide to the chiral imines

Entry	Amine	Yield (%)[a]	Config.[b]	d.r.[c]
1	**3a**	84	(*S*,*S*)	>99:1
2	**3b**	83	(*S*,*S*)	>99:1
3	**3c**	85	(*S*,*S*)	>99:1
4	**3d**	80	(*S*,*S*)	>99:1
5	**3e**	88	(*S*,*S*)	>99:1
6	**3f**	86	(*R*,*R*)	>99:1
7	**3g**	82	(*R*,*R*)	>99:1
8	**3h**	79	(*R*,*R*)	>99:1

[a] Total isolated yield from aldehyde.
[b] Configuration was assigned by comparison ^{1}H NMR with data in literature.[14,15]
[c] The diastereomeric ratios were determined by ^{1}H NMR of the crude reaction mixtures.

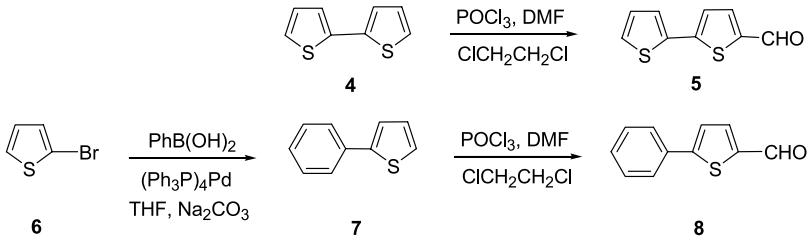
The reaction proceeded smoothly in THF solution at room temperature under nitrogen atmosphere. The decrease of ^{1}H NMR peak belonging to imine group could be used to detect the reaction process.

The results of asymmetric addition of allylzinc bromide to the chiral imines were presented in Table 1. Firstly, (*S*)-valine methyl ester was selected as the chiral auxiliary to investigate the asymmetric allylation (entry 1). The Zn-mediated allylic reaction in the presence of $CeCl_3 \cdot 7H_2O$ was completed after 4 h affording (*S*,*S*)-**3a** with excellent diastereoselectivity (d.r.>99:1). To further confirm our results, we also investigated such allylation reaction using the Al–$TiCl_4$ system.[34] The mixture of (*S*,*S*)-**3a** and (*S*,*R*)-**3a** were obtained with 86:14 diastereomeric ratio. They were obviously identified in 300 MHz ^{1}H NMR spectra. The $CHCO_2CH_3$ showed characteristic protons absorption at 2.98 (d, 1H) and 3.70 (s, 3H) for (*S*,*S*)-**3a**, and 3.10 (d, 1H) and 3.57 (s, 3H) for (*S*,*R*)-**3a**, respectively. The diastereoisomeric ratio was obtained by ^{1}H NMR spectrum of the crude reaction mixture.[14,15,30] According to the same process, the homoallylic amines (*S*,*S*)-**3b**–**3e** were also achieved with excellent stereoselectivity in good yields (entries 2–5).

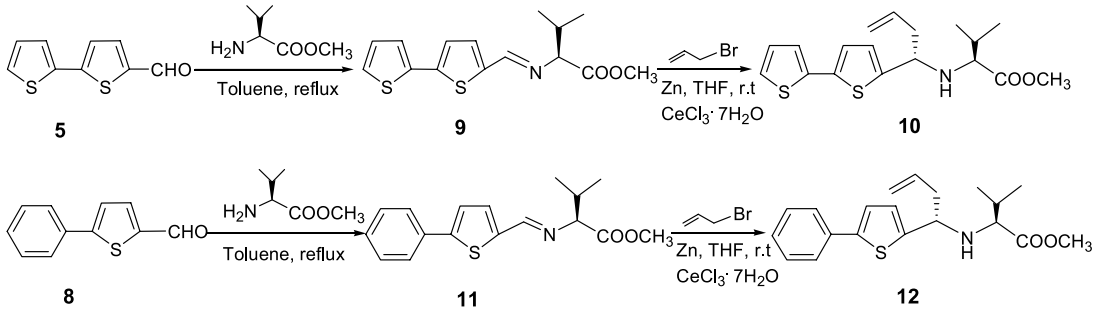
Subsequently, (*R*)-α-amino acid esters **1f**–**1h** derived from the corresponding D-α-amino acid were introduced as chiral auxiliaries. The same procedures were employed to prepare the homoallylic amines (*R*,*R*)-**3f**–**3h** (entries 6–8). Since both optically pure L-α-amino acid and D-α-amino acid are commercially available, it was emerged as a convenient route to synthesize homoallylic chiral amines and their derivatives.

For the stereochemical mechanism,[15,34] the diastereoselective delivery was described as following model using (*S*)-valine methyl ester as the chiral auxiliary. The $CeCl_3$ acted as both Lewis acid and Lewis base. The cerium atom was chelated with both nitrogen atom of the imine group and oxygen atom of the ester group, and the zinc atom of allylzinc bromide was coordinated with chlorine atom of $CeCl_3$. The bulky *i*-Pr group shielded one face of imine and allowed the addition to occur only from the *si* face through a cyclic six-membered transition state, affording (*S*,*S*) diastereoisomer.[16,17] The similar delivery was assumed that should occur in the allylation of (*R*)-**2f**–**2h** affording (*R*,*R*)-**3f**–**3h**.

The results indicated that the zinc-mediated allylation of



Scheme 2. Synthesis of aldehyde derivatives of thiophene.



Scheme 3. Asymmetric addition of allyl zinc bromide to the chiral imines.

chiral imines was applied to the preparation of optically pure homoallylic amines. Its excellent stereoselectivity was a synthetically useful feature, and did not depend upon the steric bulk of the R groups. The configuration of the newly formed chiral center could be estimated from the configuration of the auxiliary. Another useful feature of the reaction was a broad functional group tolerance. Many functional groups, including ester, hydroxyl, and amino groups, remained unchanged under the applied reaction conditions. Moreover, the auxiliaries were easily removed and the homoallylic chiral amines were converted into other functional amines with maintenance of chiral characters.

Two aldehyde derivatives of thiophene were prepared for further investigation of the asymmetric allylation of chiral imines. The corresponding homoallylic amines (*S*,*S*)-**10** and (*S*,*S*)-**12** were afforded with excellent diastereoselectivities in good yields. The mixture of (*S*,*S*)-**10** and (*S*,*R*)-**10** (75:25) was also obtained. The C*H*CO_2CH_3 showed characteristic protons absorption at 3.07 (d, 1H) and 3.71 (s, 3H) for (*S*,*S*)-**10**, and 3.13 (d, 1H) and 3.59 (s, 3H) for (*S*,*R*)-**10**.

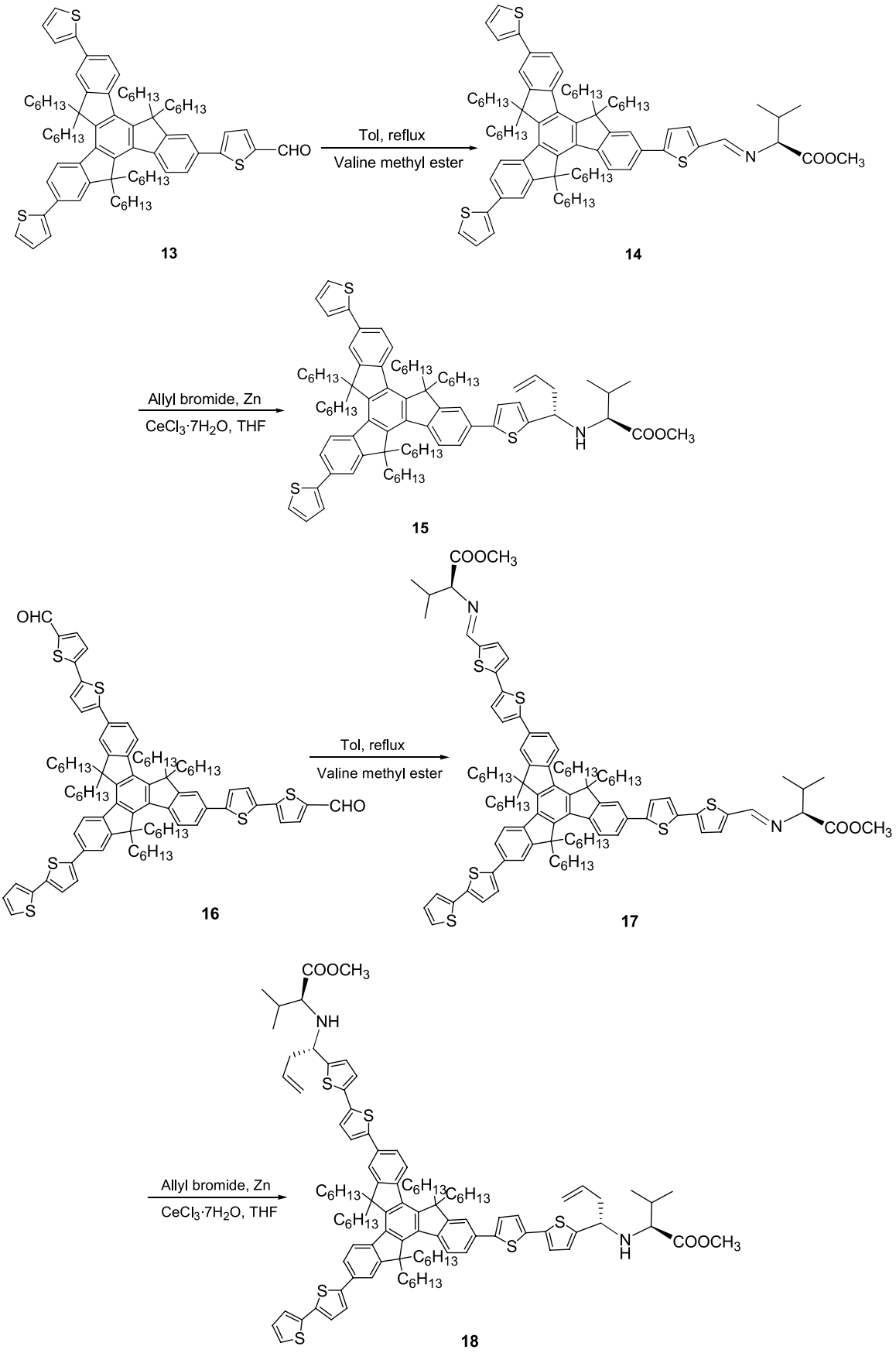
Owing to the satisfactory diastereoselectivities obtained by the Zn-mediated allylation procedure, we also investigated the allylation of dendritic imines (Scheme 2). Firstly, the asymmetric allylation was performed on dendritic imine carrying one chiral imine group to afford dendritic amine **15**. The mixture of (*S*,*S*)-**15** and (*S*,*R*)-**15** (64:36) were prepared using the Al–$TiCl_4$ system. The C*H*CO_2CH_3 showed characteristic protons absorption at 3.14 (d, 1H) and 3.75 (s, 3H) for (*S*,*S*)-**15**, and 3.21 (d, 1H) and 3.64 (s, 3H) for (*S*,*R*)-**15**, respectively. The diastereoisomeric ratio (>99:1) was obtained from the ^{1}H NMR analysis (Scheme 3).

Secondly, the allylation of dendritic imine containing two chiral imine groups also gave dendritic amine **18** and **21** in excellent results. They all exhibited the same characteristic protons signals of C*H*CO_2CH_3 at δ (ppm) 3.11 (d, 2H) and 3.74 (s, 6H). They were determined with (*S*,*S*,*S*,*S*) configuration. Finally, (*S*,*S*,*S*,*S*,*S*,*S*)-**24a** and **24b** were successfully obtained by the allylation to the dendritic amines bearing three chiral auxiliaries simultaneously. They showed proton signals of C*H*CO_2CH_3 at δ (ppm) 3.14 (d, 3H) and 3.75 (s, 9H) for **24a**, and at 3.12 (d, 3H) and 3.74 (s, 9H) for **24b**, respectively. Such asymmetric allylation of chiral imines provided a powerful method to construct multi-chiral centres simultaneously. To our best knowledge, this was the first example to effectively synthesize optically pure dendritic homoallylic amines through asymmetric allylation of imines (Scheme 4).

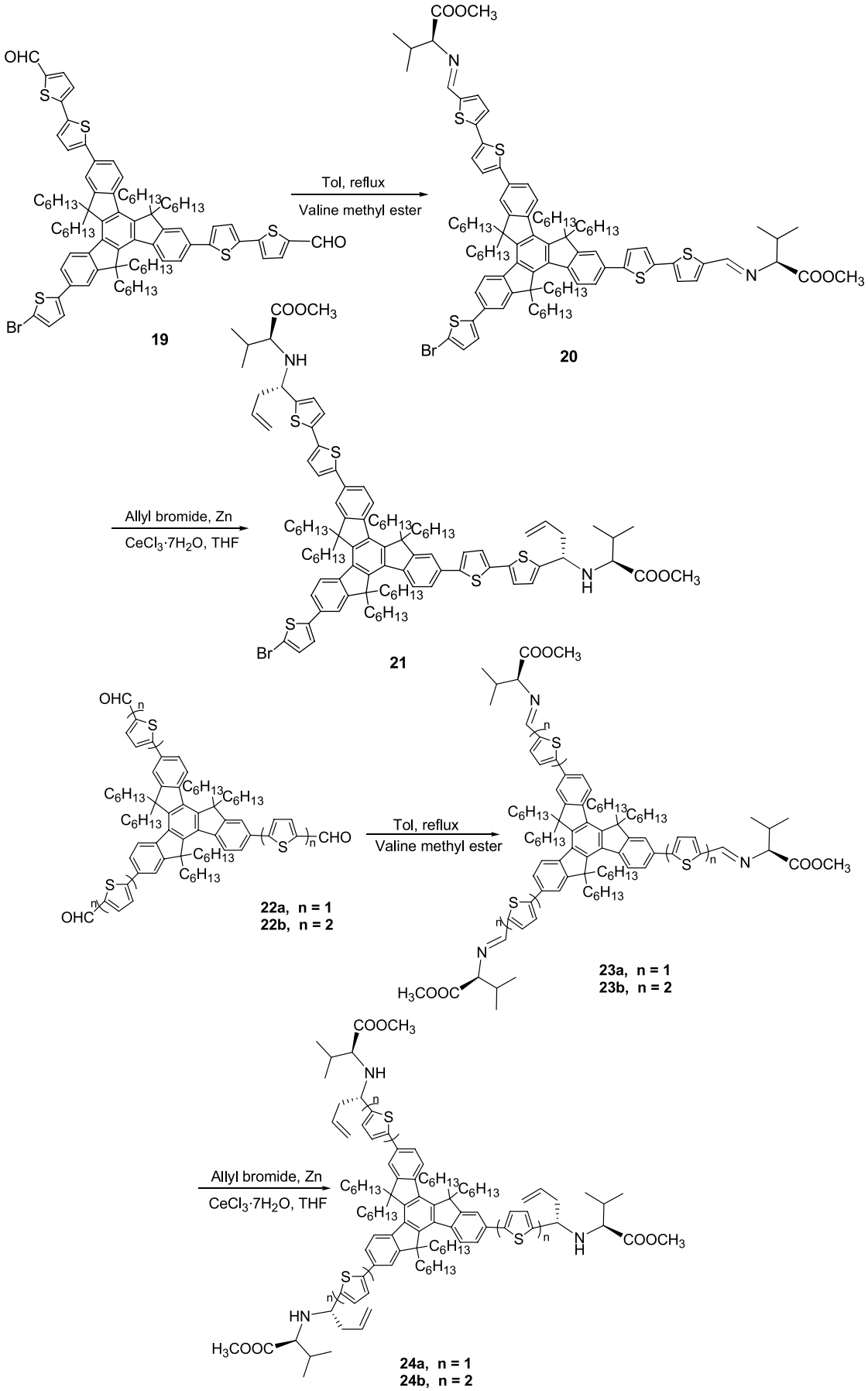
2.1. Optical properties

The UV–vis absorption and photoluminescence (PL) spectra of **15**, **18**, **21**, **24a**, and **24b** were measured in dilute THF solution. Normally, polycyclic aromatics show very strong π–π^* electron absorption band in the UV–visible region, which progressively red-shifts with increase of effective conjugation length. The solution concentration of all compounds was about 1.0×10^{-5} M. The absorption spectra of **15**, **18**, **21**, **24a**, and **24b** in THF solution showed strong π–π^* electron transition band from conjugated skeleton as shown in Figure 1. The absorption peaks showed obvious red-shift with increase of thiophene rings. The absorption behaviors peaked at 343 nm for **15**, at 348 nm for **24a**, at 371 nm for **21**, 386 nm for **18**, and at 388 nm for **24b**. The results indicated that the chiral amine groups did not affect the effective conjugation length of the corresponding compounds.

The PL spectra of these five compounds in dilute THF solution were shown in Figure 2. Well-defined structured emission peaks of all compounds were observed. The emission peaks of **15** and **24a** were largely overlapped and the same to **18**, **21**, and **24b**. The absorption and the photoluminescence spectra of **15**, **18**, **21**, **24a**, and **24b** exhibited slight changes in comparison with ones of their



Scheme 4. Synthesis of dendritic homoallylic chiral amines.



Scheme 4 (*continued*)

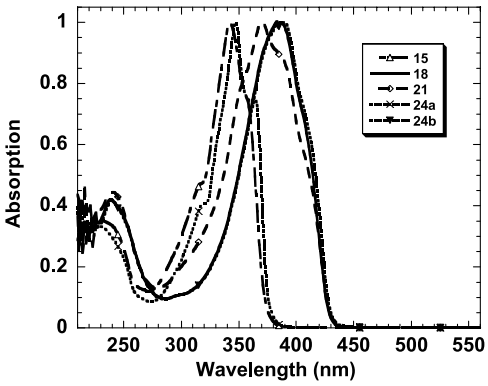


Figure 1. Absorption spectra of homoallylic dendritic chiral amines in solutions.

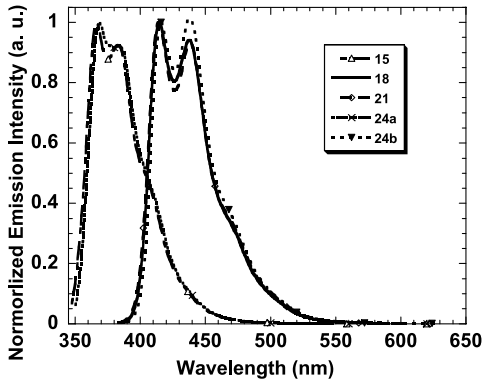


Figure 2. Photoluminescence spectra of homoallylic dendritic chiral amines in solutions.

corresponding full conjugated aromatic skeleton.[35,36] Fluorescence quantum yields (Φ_f) of **15**, **18**, **21**, **24a**, and **24b** in dilute THF solutions were measured by using 9,10-diphenylanthracene as the standard. The values were 0.55 for **15**, 0.53 for **18**, 0.42 for **21**, 0.49 for **24a**, and 0.43 for **24b**, respectively.

2.2. The circular dichroism properties

We also investigated the circular dichroism properties of these chiral dendritic compounds. The circular dichroism (CD) spectra of the derivatives of (*S*)-valine obtained in dilute THF solutions were shown in Figure 3. For the comparison, we also studied the CD spectra of (*S*)-valine in aqueous solution. It exhibited the positive Condon effect and the λ_{max} appeared at 202 nm, which was contributed to n-π^* electronic transition of carboxyl group. The CD spectra of (*S*)-valine methyl ester also gave positive band with λ_{max} at 212 nm. In comparison with (*S*)-valine, CD spectra of **3a** with λ_{max} at 221 nm exhibited obvious red-shift, which was contributed to that thiophene group made the energy of electronic transition of carbonyl group decrease. In addition, a weak vibrational circular dichroism band resolved at 251 nm was contributed to π–π^* electronic transition of thiophene. It was also shown that molar ellipticity ([θ]) of **3a** increased sharply in comparison with **1a** due to the introduction of thiophene.

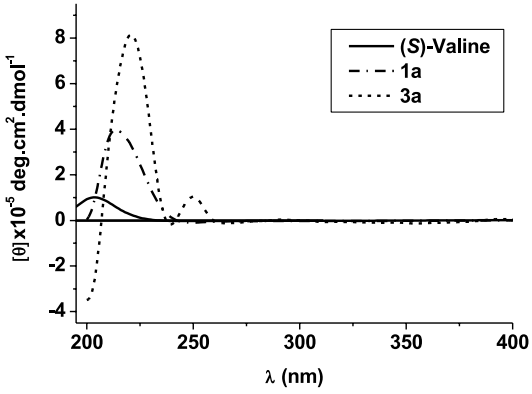


Figure 3. Circular dichroism spectra of (*S*)-valine and its derivatives.

The CD spectra of the homoallylic dendritic chiral amines obtained in THF solutions were shown in Figure 4. The CD behaviors of **15** exhibited two negative bands. One broad band from 280 to 380 nm was contributed to π–π^* electron transition of the conjugated aromatic skeleton. The other band belonged to n-π^* electronic transition of the carbonyl group. The CD behaviors of **18** and **21** were similar to **15**. But **24a**, and **24b** showed slightly different CD behaviors from **15**, **18** and **21**. The band at low wavelength contributed to the carbonyl group also exhibited a small red-shift compared with compound **3a**, which was caused by the large aromatic core. The CD absorption spectra of **15**, **18**, **21**, **24a**, and **24b** all showed different the Condon effect from **3a** owing to the influence of the full conjugated aromatic core.

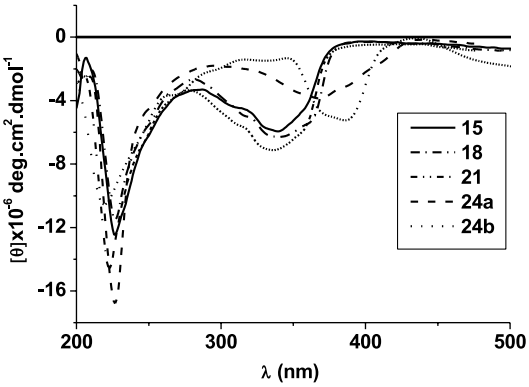


Figure 4. Circular dichroism spectra of homoallylic dendritic chiral amines.

3. Conclusion

In conclusion, the asymmetric allylation of imines bearing chiral auxiliary groups were investigated under very mild conditions to afford homoallylic amines in high yields with excellent enantioselectivities. The systematic investigation on the diastereoselectivity of the reaction showed that the configurations of the newly formed chiral center were altered by simply changing the configuration of the auxiliary group. The reaction was firstly applied to the allylic addition to multi chiral imine groups beared on dendrimers to synthesize homoallylic dendritic chiral amines. The UV–vis absorption and emission spectra of these dendritic chiral amines were quite similar to their corresponding precursors. But they exhibited the interesting circular dichroism (CD) behaviors. These homoallylic dendritic chiral amines

exhibited characteristic properties, which indicated they could be possibly used as enantioselective fluorecent sensors. Further modification of these dendritic chiral amines is in progress.

4. Experimental

4.1. General methods

Melting points were recorded on a Yanaco MP-500 micro melting point apparatus. Optical rotations were obtained on a PerkinElmer Model 341LC. The ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer in $CDCl_3$ solution with TMS as the internal standard. MALDI/TOF (Matrix assisted laser desorption ionization/Time-of-flight) MS spectra were recorded in Bruker BIFLEX III. Elemental analyzes were carried out on Elementar Vario EL (Germany). UV–vis spectra were recorded on PerkinElmer Lambda 35 UV/VIS Spectrometer. Photoluminescence spectra were carried out on PerkinElmer LS 55 Luminescence Spectrometer. The purification of the products was conducted by flash column chromatography on silica gel (200–300 mesh). The organometallic allylation reactions were performed in dried apparatus in nitrogen atmosphere. THF were freshly dried and distilled over Na before using.

Fluorescence quantum yields (Φ_f) of the samples in THF solutions were measured by using 9,10-diphenylanthracene (Φ_f=0.93) in toluene with a concentration lower than 1×10^{-5} M) as standards. Values are calculated according to Eq. 1, where Φ_{unk} is the fluorescence quantum yield of the sample, Φ_{std} is the fluorescence quantum yield of the standard. I_{unk} and I_{std} are the integrated emission intensities of the sample and the standard, respectively. A_{unk} and A_{std} are the absorbance of the sample and the standard at the excitation wavelength, respectively, and η_{unk} and η_{std} are the refractive indexes of the corresponding solutions (pure solvents were assumed).

$$\Phi_{unk} = \Phi_{std}(I_{unk}/A_{unk})(A_{std}/I_{std})(\eta_{unk}/\eta_{std})^2 \quad (1)$$

4.2. General procedure for the preparation of homoallylic amines

4.2.1. General procedure for the preparation of imine. The mixture of 2-thiophenecarboxaldehyde (112 mg, 1 mmol) and (*S*)- or (*R*)-α-amino acid methyl ester (131 mg, 1 mmol) was refluxed in toluene for 10 h. The crude imine was obtained after removing the solvent under vacuum in almost quantitative yield and in pure state inferred by ^{1}H NMR analysis. The imines were immediately used in the subsequent allylation reaction without further purification.

4.2.2. General procedure for the allylation of imines mediated by zinc. To a suspension of Zn powder (0.13 g, 1 mmol) in anhydrous THF (3 mL), stirred magnetically at room temperature, was added $CeCl_3\cdot7H_2O$ (0.037 g, 0.1 mmol) and then a solution of the imine (1 mmol) and allyl bromide (182 mg, 1.5 mmol) in THF (3 mL) was added under nitrogen. Then the mixture was stirred vigorously at room temperature for 4 h. The reaction was inspected by ^{1}H NMR analyzes until the imine was converted completely. After the reaction was quenched with saturated aqueous ammonium chloride solution, the product was extracted with dichloromethane. The combined organic solutions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude product. The crude product was purified by flash silica gel column chromatography employing a mixture of ethyl acetate and petroleum (V/V=1/15) as eluant. Pure (*S*,*S*)-**3a** was obtained as colorless oil with 84% total yield from aldehyde.

(*S*,*S*)-**3a**. $[\alpha]_D^{20}$ −82.8 (*c* 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.25–6.85 (m, 3H, Ar-*H*), 5.76–5.70 (m, 1H, C*H*=CH_2), 5.12 and 5.09 (2d, *J*=15.6, 9.2 Hz, 2H, CH=CH_2), 3.82 (dd, *J*=6.0, 7.6 Hz, 1H, C*H*NH), 3.70 (s, 3H, $CHCO_2CH_3$), 2.97 (d, *J*=6.1 Hz, 1H, $CHCO_2CH_3$), 2.47–2.37 (m, 2H, $CH_2CH{=}CH_2$), 1.87–1.82 (m, 1H, $(CH_3)_2CH$), 0.89 and 0.87 (2d, *J*=6.7, 6.6 Hz, 6H, $(CH_3)_2CH$). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 175.8, 148.6, 134.7, 126.1, 124.4, 124.2, 118.0, 64.2, 56.5, 51.3, 44.5, 31.7, 19.4, 18.4. EI-MS (*m*/*e*): 226 ($[M-C_3H_5]^+$, 100%), 166; ESI-MS (*m*/*e*): 268.1 $(M+1)^+$.

(*S*,*S*)-**3b**. 83% total yield, $[\alpha]_D^{20}$ −77.2 (*c* 1.1, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.20–6.86 (m, 3H, Ar-*H*), 5.77–5.69 (m, 1H, C*H*=CH_2), 5.16–5.09 (m, 2H, CH=CH_2), 3.84 (dd, *J*=5.7, 7.9 Hz, 1H, C*H*NH), 3.71 (s, 3H, $CHCO_2CH_3$), 3.06 (d, *J*=6.1 Hz, 1H, $CHCO_2CH_3$), 2.49–2.38 (m, 2H, $CH_2CH{=}CH_2$), 1.62–1.52 (m, 2H, CH_3CH_2), 1.16–1.11 (m, 1H, CH_3CH), 0.85–0.80 (m, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 175.8, 148.5, 134.7, 126.1, 124.5, 124.2, 118.0, 63.2, 56.6, 51.2, 44.5, 38.5, 25.2, 15.7, 11.4. EI-MS (*m*/*e*, %): 240 ($[M-C_3H_5]^+$, 100), 180, 137; ESI-MS (*m*/*e*): 282.1 $(M+1)^+$.

(*S*,*S*)-**3c**. 85% yield, $[\alpha]_D^{20}$ −46.7 (*c* 1.3, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.21–6.86 (m, 3H, Ar-*H*), 5.80–5.69 (m, 1H, C*H*=CH_2), 5.16–5.09 (m, 2H, CH=CH_2), 3.88 (dd, *J*=5.6, 8.0 Hz, 1H, C*H*NH), 3.70 (s, 3H, $CHCO_2CH_3$), 3.23 (dd, *J*=5.6, 8.4 Hz, 1H, $CHCO_2CH_3$), 2.49–2.37 (m, 2H, $CH_2CH{=}CH_2$), 1.84–1.77 (m, 1H, $(CH_3)_2CH$), 1.45–1.33 (m, 2H, $(CH_3)_2CHCH_2$), 0.86 (d, *J*=6.8 Hz, 3H, CH_3), 0.74 (d, *J*=6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 176.7, 148.5, 134.6, 126.1, 124.5, 124.2, 118.0, 57.0, 56.4, 51.5, 44.4, 43.2, 24.6, 23.0, 21.9; ESI-MS (*m*/*e*): 282.3 $(M+1)^+$.

(*S*,*S*)-**3d**. 80% yield, $[\alpha]_D^{20}$ −8.0 (*c* 0.5, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.21–6.88 (m, 3H, Ar-*H*), 5.82–5.71 (m, 1H, C*H*=CH_2), 5.18–5.09 (m, 2H, CH=CH_2), 3.95 (dd, *J*=5.6, 8.0 Hz, 1H, C*H*NH), 3.71 (s, 3H, $CHCO_2CH_3$), 3.30 (q, *J*=7.2 Hz, 1H, $CHCO_2CH_3$), 2.52–2.38 (m, 2H, $CH_2CH{=}CH_2$), 1.24 (d, *J*=7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 176.5, 148.5, 134.5, 126.3, 124.4, 124.1, 118.2, 56.4, 53.9, 51.7, 44.4, 19.6. EI-MS (*m*/*e*): 240 $(M+1)^+$, 198 ($[M-C_3H_5]^+$, 100%), 138; ESI-MS (*m*/*e*): 240.2 $(M+1)^+$.

(*S*,*S*)-**3e**. 88% yield, $[\alpha]_D^{20}$ −35.9 (*c* 0.9, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$, ppm) 7.25–6.76 (m, 8H, Ar-*H*), 5.74–5.65 (m, 1H, C*H*=CH_2), 5.11 and 5.07 (2d, *J*=9.6, 15.6 Hz, 2H, CH=CH_2), 3.91 (dd, *J*=6.0, 7.6 Hz, 1H,

C*H*NH), 3.61 (s, 3H, $CHCO_2CH_3$), 3.48 (t, $J=6.8$ Hz, 1H, $CHCO_2CH_3$), 2.91 and 2.89 (2d, $J=5.2$, 5.6 Hz, 1H, $PhCH_2$), 2.48–2.35 (m, 2H, $CH_2CH=CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) 175.2, 148.2, 137.1, 134.5, 129.2, 128.2, 126.6, 126.2, 124.4, 124.2, 118.1, 59.9, 56.3, 51.5, 44.2, 40.1; ESI-MS (*m/e*): 316.1 $(M+1)^+$.

(*R*,*R*)-**3f**. 86% yield, $[\alpha]_D^{20}$ +55.6 (*c* 1.1, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$, ppm): 7.20–6.86 (m, 3H, Ar-*H*), 5.80–5.69 (m, 1H, $CH=CH_2$), 5.17–5.09 (m, 2H, $CH=CH_2$), 3.89 (dd, $J=5.6$, 8.0 Hz, 1H, C*H*NH), 3.70 (s, 3H, $CHCO_2CH_3$), 3.23 (dd, $J=6.0$, 8.4 Hz, 1H, $CHCO_2CH_3$), 2.49–2.37 (m, 2H, $CH_2CH=CH_2$), 1.84–1.77 (m, 1H, $(CH_3)_2CH$), 1.45–1.33 (m, 2H, $(CH_3)_2CHCH_2$), 0.86 (d, $J=6.4$ Hz, 3H, CH_3), 0.74 (m, $J=6.4$ Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 176.7, 148.5, 134.6, 126.1, 124.5, 124.2, 118.0, 57.0, 56.4, 51.5, 44.4, 43.2, 24.6, 23.0, 21.9. EI-MS (*m/e*): 240 ($[M-C_3H_5]^+$, 100%), 180, 137.

(*R*,*R*)-**3g**. 82% yield, $[\alpha]_D^{20}$ +5.8 (*c* 0.5, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$, ppm): 7.22–6.87 (m, 3H, Ar-*H*), 5.82–5.71 (m, 1H, $CH=CH_2$), 5.19–5.09 (m, 2H, $CH=CH_2$), 3.94 (dd, $J=5.6$, 8.0 Hz, 1H, C*H*NH), 3.71 (s, 3H, $CHCO_2CH_3$), 3.30 (q, $J=7.2$ Hz, 1H, $CHCO_2CH_3$), 2.52–2.38 (m, 2H, $CH_2CH=CH_2$), 1.25 (d, $J=7.1$ Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 176.5, 148.5, 134.5, 126.3, 124.4, 124.2, 118.2, 56.5, 53.9, 51.7, 44.4, 19.6. EI-MS (*m/e*): 198 ($[M-C_3H_5]^+$, 100%), 137.

(*R*,*R*)-**3h**. 79% yield, $[\alpha]_D^{20}$ +29.8 (*c* 1.2, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$, ppm): 7.25–6.76 (m, 8H, Ar-*H*), 5.74–5.65 (m, 1H, $CH=CH_2$), 5.13–5.06 (m, 2H, $CH=CH_2$), 3.91 (dd, $J=5.6$, 7.8 Hz, 1H, C*H*NH), 3.61 (s, 3H, $CHCO_2CH_3$), 3.48 (t, $J=6.8$ Hz, 1H, $CHCO_2CH_3$), 2.91 and 2.87 (2d, $J=4.8$, 5.6 Hz, 1H, $PhCH_2$), 2.48–2.35 (m, 2H, $CH_2CH=CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 175.2, 148.2, 137.1, 134.5, 129.2, 128.2, 126.6, 126.2, 124.4, 124.2, 118.1, 59.9, 56.3, 51.5, 44.2, 40.1; ESI-MS (*m/e*): 316.1 $(M+1)^+$.

4.2.3. General procedure for the preparation of two diastereoisomers of homoallylic amines using Al–$TiCl_4$ system. Into a mixture of imine **2a** (675 mg, 3 mmol) and aluminum powder (81 mg, 3 mmol) in dry THF (6 mL) were successively added allyl bromide (1.09 g, 9 mmol) and $TiCl_4$ (28 mg, 0.15 mmol) at room temperature. After being stirred for 12 h, the mixture was poured into 5% aqueous sodium hydroxide and extracted with dichloromethane. After purification by column chromatography, (*S*,*S*)-**3a** and (*S*,*R*)-**3a** were obtained, respectively.[34]

4.2.4. General procedure for the preparation of aldehyde derivatives of thiophene. *General procedure for the Suzuki coupling reaction*.[35,36] To a solution of 2-bromothiophene **6** (815 mg, 5.0 mmol) and benzeneboronic acid (915 mg, 7.5 mmol) in 75 mL of THF was added $Pd(PPh_3)_4$ (173 mg, 0.15 mmol), and 7 mL of 2 M aqueous Na_2CO_3 solution. The mixture was heated to reflux for 15 h and then was poured into a saturated solution of ammonium chloride and extracted with ethyl acetate (50 mL×3). The combined organic phase was washed with brine (5 mL) and dried over Na_2SO_4. After the solvents were evaporated under vacuum, the residue was purified by flash column chromatography using petroleum ether as eluent to give pale yellow solid. *Compound* **7**. 90% yield, ^1H NMR (200 MHz, $CDCl_3$, ppm): 7.64–7.05 (m, 8H, Ar-*H*). ^{13}C NMR (50 MHz, $CDCl_3$, ppm): 128.9, 127.9, 127.4, 125.9, 124.8, 123.0, 29.7. EI-MS (*m/e*): 160 $(M+1)^+$(100%).

General procedure for the Vilsmeier reaction.[37] To a solution of DMF (365 mg, 5 mmol) in dry dichloroethane (10 mL), $POCl_3$ (765 mg, 5 mmol) was added into a round-bottomed flask under nitrogen atmosphere. A solution of **4** (830 mg, 5 mmol) in dry dichloroethane (50 mL) was added, then the mixture was refluxed for 8 h. After cooling to room temperature, 1 M sodium acetate was added to neutrality and the mixture was stirred vigorously for 0.5 h. The solution was extracted with dichloromethane (50 mL× 5), and the organic phase was dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by chromatography employing a mixture of ethyl acetate and petroleum (V/V=1/15) as the eluant. Pure **5** was obtained as a pale yellow solid. 87% yield, ^1H NMR (300 MHz, $CDCl_3$, ppm): 9.86 (s, C*H*O), 7.67–7.06 (m, 5H, Ar-*H*). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 182.5, 147.1, 141.6, 137.3, 135.9, 128.3, 127.1, 126.1, 124.2. EI-MS (*m/e*): 194 $(M+1)^+$(100%).

Compound **8**. 84% yield, ^1H NMR (300 MHz, $CDCl_3$, ppm): 9.90 (s, C*H*O), 7.75–7.40 (m, 7H, Ar-*H*). ^{13}C NMR ((75 MHz, $CDCl_3$, ppm): 182.8, 147.1, 142.4, 137.4, 133.0, 129.4, 129.2, 126.4, 124.1. EI-MS (*m/e*): 188 $(M+1)^+$(100%).

4.2.5. Synthesis of homoallylic chiral amines from aldehyde derivatives of thiophene. Homoallylic chiral amines **10** and **12** were obtained as a colorless oil employing the general procedure of the allylation of imines. *Compound* **10**. 93% yield, $[\alpha]_D^{20}$ −109.2 (*c* 0.66, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.25–7.11 (m, 5H, Ar-*H*), 5.81–5.71 (m, 1H, $CH=CH_2$), 5.18–5.11 (m, 2H, $CH=CH_2$), 3.81–3.71 (m, 1H, C*H*NH), 3.71 (s, 3H, $COOCH_3$), 3.07 (d, 1H, $J=8.0$ Hz, CH-$COOCH_3$), 2.52–2.41 (m, 2H, CH_2–$CH=CH_2$), 1.94–1.85 (m, 1H, $CH(CH_3)_2$), 0.94–0.90 (m, 6H, $CH(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 175.7, 147.9, 137.9, 136.0, 134.5, 127.6, 125.1, 123.9, 123.1, 122.8, 118.2, 64.2, 56.8, 51.3, 44.3, 31.7, 19.4, 18.5; ESI-MS (*m/e*): 349.9 $(M+1)^+$(100%). HRMS (EI) for $C_{18}H_{23}NO_2S_2$, calcd 349.11702, found 349.11784.

Compound **12**. 91% yield, $[\alpha]_D^{20}$ −88.6 (*c* 0.50, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.59–6.83 (m, 7H, Ar-*H*), 5.80–5.70 (m, 1H, $CH=CH_2$), 5.18–5.11 (m, 2H, $CH=CH_2$), 3.83–3.72 (m, 1H, C*H*NH), 3.72 (s, 3H, $COOCH_3$), 3.08 (d, 1H, $J=8.0$ Hz, CH–$COOCH_3$), 2.51–2.41 (m, 2H, CH_2–$CH=CH_2$), 1.94–1.85 (m, 1H, $CH(CH_3)_2$), 0.94–0.90 (m, 6H, $CH(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 175.8, 148.3, 142.8, 134.6, 128.8, 127.1, 125.5, 122.1, 118.1, 64.2, 56.9, 51.3, 44.4, 31.7, 29.6, 19.4, 18.5; ESI-MS (*m/e*): 343.9 $(M+1)^+$(100%). Anal. Calcd for $C_{20}H_{25}NO_2S$: C, 69.93; H, 7.34; N, 4.08. Found: C, 69.88; H, 7.42; N, 3.95.

4.2.6. Synthesis of homoallylic dendritic chiral amines. The same procedure was applied as well in the synthesis of

optically pure dendritic amines. The reaction was usually completed in 24 h to give **15**, **18**, **21**, **24a**, and **24b** as yellow powder.

Compound **15**. 86% yield, mp 44.0–45.2 °C, $[\alpha]_D^{20}$ −33.3 (*c* 0.05, CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 8.37–6.91 (m, 17H, Ar-*H*), 5.87–5.77 (m, 1H, C*H*=CH_2), 5.20 and 5.13 (2d, *J*=18.4, 18.4 Hz, 2H, CH=CH_2), 3.86 (dd, *J*=5.6, 6.6 Hz, 1H, C*H*NH), 3.75 (s, 3H, $CHCO_2CH_3$), 3.14 (d, *J*=5.9 Hz, 1H, $CHCO_2CH_3$), 2.98–2.95 (m, 6H, $C_5H_{11}CH_2$), 2.58–2.48 (m, 2H, CH_2CH=CH_2), 2.13–2.11 (m, 6H, $C_5H_{11}CH_2$), 1.96–1.91 (m, 1H, $(CH_3)_2CH$), 0.99–0.84 (m, 42H, CH_2 and $(CH_3)_2CH$), 0.61–0.47 (m, 30H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 175.8, 154.4, 148.0, 144.9, 143.3, 139.7, 139.5, 138.0, 137.9, 134.6, 132.7, 132.4, 128.1, 125.6, 124.9, 124.5, 124.1, 123.7, 122.8, 122.0, 119.3, 118.7, 118.2, 64.3, 56.9, 55.7, 51.3, 44.5, 37.0, 31.8, 31.4, 29.4, 23.9, 22.2, 19.3, 18.6, 13.8, 13.7. MALDI-TOF MS: Calcd for $C_{85}H_{113}NO_2S_3$: 1275.8. Found: 1275.7 (M^+). Anal. Calcd for $C_{85}H_{113}NO_2S_3$: C, 79.95; H, 8.92; N, 1.10; S, 7.53. Found: C, 79.78; H, 8.70; N, 0.83; S, 7.61.

Compound **18**. 82% yield, mp 73.0–74.5 °C, $[\alpha]_D^{20}$ −72.5 (*c* 0.12, CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 8.38–6.82 (m, 22H, Ar-*H*), 5.85–5.74 (m, 2H, C*H*=CH_2), 5.18 and 5.15 (2d, *J*=15.6, 8.8 Hz, 4H, CH=CH_2), 3.82 (dd, *J*=5.6, 8.0 Hz, 2H, C*H*NH), 3.74 (s, 6H, $CHCO_2CH_3$), 3.11 (d, *J*=5.6 Hz, 2H, $CHCO_2CH_3$), 3.00–2.93 (m, 6H, $C_5H_{11}CH_2$), 2.55–2.42 (m, 4H, CH_2CH=CH_2), 2.17–2.10 (m, 6H, $C_5H_{11}CH_2$), 1.94–1.89 (m, 2H, $(CH_3)_2CH$), 1.01–0.83 (m, 48H, CH_2 and $(CH_3)_2CH$), 0.62–0.56 (m, 30H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 175.8, 154.4, 148.1, 145.1, 143.6, 139.7, 138.0, 137.1, 136.4, 136.2, 134.5, 132.2, 127.8, 125.2, 124.9, 124.6, 124.1, 123.7, 123.5, 122.7, 118.9, 118.2, 64.3, 56.9, 55.7, 51.4, 44.4, 37.1, 31.8, 31.4, 29.4, 23.9, 22.2, 19.4, 18.5, 13.8. MALDI-TOF MS: Calcd for $C_{107}H_{136}N_2O_4S_6$: 1704.9. Found: 1813.0 ($[M+Ag]^+$). Anal. Calcd for $C_{107}H_{136}N_2O_4S_6$: C, 75.30; H, 8.03; N, 1.64; S, 11.27. Found: C, 75.38; H, 8.08; N, 1.57; S, 11.16.

Compound **21**. 74% yield, mp 62.1–63.5 °C, $[\alpha]_D^{20}$ −43.1 (*c* 0.07, CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 8.38–6.82 (m, 19H, Ar-*H*), 5.85–5.75 (m, 2H, C*H*=CH_2), 5.19 and 5.15 (2d, *J*=16.0, 9.2 Hz, 4H, CH=CH_2), 3.83 (dd, *J*=6.0, 7.8 Hz, 2H, C*H*NH), 3.74 (s, 6H, $CHCO_2CH_3$), 3.11 (d, *J*=6.0 Hz, 2H, $CHCO_2CH_3$), 2.97–2.93 (m, 6H, $C_5H_{11}CH_2$), 2.56–2.42 (m, 4H, CH_2CH=CH_2), 2.13–2.07 (m, 6H, $C_5H_{11}CH_2$), 1.96–1.88 (m, 2H, $(CH_3)_2CH$), 0.97–0.84 (m, 48H, CH_2 and $(CH_3)_2CH$), 0.62–0.55 (m, 30H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 175.8, 154.4, 148.2, 145.2, 143.2, 140.1, 139.7, 138.0, 137.1, 136.2, 134.5, 132.3, 131.7, 130.9, 125.2, 124.1, 123.8, 123.5, 123.0, 118.9, 118.2, 111.1, 64.3, 56.9, 55.8, 51.4, 44.4, 37.0, 31.8, 31.4, 29.4, 23.9, 22.2, 19.4, 18.5, 13.8. MALDI-TOF MS: Calcd for $C_{103}H_{133}BrN_2O_4S_5$: 1700.8. Found: 1701.8 ($[M+H]^+$). Anal. Calcd for $C_{107}H_{136}N_2O_4S_6$: C, 72.63; H, 7.87; N, 1.64; S, 9.41. Found: C, 72.38; H, 7.85; N, 1.45; S, 9.32.

Compound **24a**. 58% yield, mp 39.2–40.6 °C, $[\alpha]_D^{20}$ −129.0 (*c* 0.1, CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$, ppm) 8.35–6.91 (m, 15H, Ar-*H*), 5.87–5.77 (m, 3H, C*H*=CH_2), 5.20 and 5.16 (2d, *J*=18.8, 10.8 Hz, 6H, CH=CH_2), 3.86 (dd, *J*=6.8, 6.9 Hz, 3H, C*H*NH), 3.75 (s, 9H, $CHCO_2CH_3$), 3.14 (d, *J*=5.9 Hz, 3H, $CHCO_2CH_3$), 2.98–2.94 (m, 6H, $C_5H_{11}CH_2$), 2.56–2.50 (m, 6H, CH_2CH=CH_2), 2.14–2.05 (m, 6H, $C_5H_{11}CH_2$), 1.96–1.91 (m, 3H, $(CH_3)_2CH$), 0.99–0.83 (m, 54H, CH_2 and $(CH_3)_2CH$), 0.62–0.57 (m, 30H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 175.8, 154.3, 147.9, 144.9, 143.4, 139.5, 137.9, 134.6, 132.7, 125.6, 124.8, 123.6, 122.0, 118.7, 118.1, 64.3, 56.9, 55.7, 51.3, 44.4, 37.0, 31.8, 31.4, 29.4, 23.9, 23.6, 22.6, 22.2, 19.3, 18.6, 14.1, 13.8. MALDI-TOF MS: Calcd for $C_{105}H_{147}N_3O_6S_3$: 1642.1. Found: 1643.1 ($[M+H]^+$). Anal. Calcd for $C_{105}H_{147}N_3O_6S_3$: C, 76.74; H, 9.01; N, 2.56; S, 5.85. Found: C, 76.70; H, 8.79; N, 2.38; S, 5.66.

Compound **24b**. 60% yield, mp 59.9–61.5 °C, $[\alpha]_D^{20}$ −24.6 (*c* 0.07, CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 8.38–6.82 (m, 21H, Ar-*H*), 5.85–5.75 (m, 3H, C*H*=CH_2), 5.18 and 5.15 (2d, *J*=16.0, 9.2 Hz, 6H, CH=CH_2), 3.83 (dd, *J*=5.6, 6.6 Hz, 3H, C*H*NH), 3.74 (s, 9H, $CHCO_2CH_3$), 3.12 (d, *J*=6.0 Hz, 3H, $CHCO_2CH_3$), 2.99–2.93 (m, 6H, $C_5H_{11}CH_2$), 2.56–2.44 (m, 6H, CH_2CH=CH_2), 2.17–2.10 (m, 6H, $C_5H_{11}CH_2$), 1.96–1.90 (m, 3H, $(CH_3)_2CH$), 0.97–0.85 (m, 54H, CH_2 and $(CH_3)_2CH$), 0.62–0.56 (m, 30H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 175.8, 154.4, 148.1, 145.1, 143.2, 139.8, 138.0, 137.1, 136.2, 134.5, 132.2, 125.2, 124.9, 124.1, 123.7, 123.5, 122.7, 118.9, 118.2, 64.3, 56.9, 55.8, 51.3, 44.4, 37.1, 31.8, 31.4, 29.4, 23.9, 22.2, 19.4, 18.5, 13.8. MALDI-TOF MS: Calcd for $C_{117}H_{153}N_3O_6S_6$: 1888.0. Found: 1889.0 ($[M+H]^+$). Anal. Calcd for $C_{105}H_{147}N_3O_6S_3$: C, 74.36; H, 8.16; N, 2.22; S, 10.18. Found: C, 74.35; H, 8.22; N, 2.11; S, 10.15.

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The first 6′-*O*-sulfated phenylanthraquinones: isolation from *Bulbine frutescens*, structural elucidation, enantiomeric purity, and partial synthesis

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Dedicated to Professor W. Steglich and Professor E. Dagne, discoverers of the first phenylanthraquinone

Abstract—From the roots of *Bulbine frutescens*, the first sulfated phenylanthraquinones were isolated, together with their known sulfate-free analogs. Their structures were elucidated by spectroscopic and chiroptical methods, by acid hydrolysis or by partial synthesis. The new compounds have the usual stereo-orientation at the biaryl axis (i.e., with the acetyl portion above the anthraquinone plane) except for sodium *ent*-knipholone 6′-*O*-sulfate (and thus, also its hydrolysis product, *ent*-knipholone), which exhibit an opposite axial configuration. We also describe the first stereoanalysis of natural phenylanthraquinones, some of which were found to be not enantiomerically pure, some even near-racemic. We furthermore, report on the first X-ray structure analysis of a phenylanthraquinone, viz. 4′-*O*-demethylknipholone.

1. Introduction

Bulbine frutescens (L.) Wild (Asphodelaceae) is an ornamental plant widely grown in Botswana, while it is used for the treatment of various ailments, particularly for wound healing, in other Southern African countries.[1] Previous work on this plant yielded knipholone (**1**), 4′-*O*-demethylknipholone-4′-β-D-glucopyranoside (**2**), and gaboroquinones A and B,[2] of which compounds **1** and **2** showed remarkable antiplasmodial activities.[2,3] Other knipholone-related phenylanthraquinones with antiplasmodial activity have also been isolated from *B. capitata* and *B. abyssinica*,[3–6] making *Bulbine* species attractive plants for the search for further new metabolites.

We therefore, reinvestigated *B. frutescens*, especially with respect to the polar fractions as detected on TLC, which showed the presence of four unidentified metabolites. In this paper, we report on the isolation and structural elucidation of as yet unprecedented *O*-sulfated phenylanthraquinones, viz. compounds **5**–**8**, along with the corresponding non-sulfated 'parent compounds', **1**–**4**. The absolute configurations at the biaryl axes of the new sulfated phenylanthraquinones were established by CD spectroscopy, by comparison of both the sulfates and of their desulfated hydrolysis products with the authentic sulfate-free parent analogs, revealing that all these natural products have the same (preferential) absolute stereo-orientation—except for compound **5**: it has the constitution of an as yet unknown 6′-*O*-sulfate of knipholone, but its absolute configuration is opposite,[7] since its hydrolysis product is *ent*-knipholone (*ent*-**1**), not knipholone (**1**) itself. This, and the fact that the crystal structure of 4′-*O*-demethylknipholone (**3**), that is, the first X-ray structure analysis in this class of natural products, established that particular sample to be racemic, raised the question of enantiomeric purities of all these axially chiral biaryls. For this purpose, the first enantiomer analysis of phenylanthraquinones was developed, by chromatography on a chiral phase, showing that the biarylic compounds isolated here show largely divergent enantiomeric ratios.

Keywords: *Bulbine frutescens*; Sulfated phenylanthraquinones; Axial chirality; Enantiomeric resolution; LC–CD coupling; Crystal structure.
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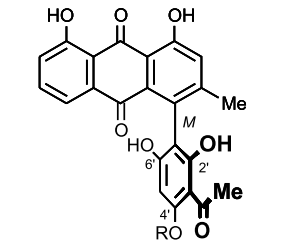

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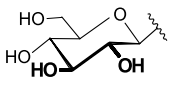
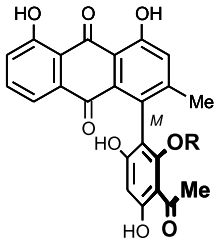
1	Me
2	



	R
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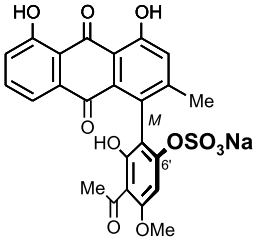
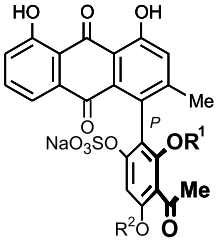
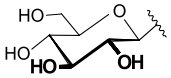
4	Me



5



	R^1	^{2} R
6	H	
7	H	H
8	Me	H

2. Results and discussion

Flash chromatography of the organic extract (129 g) of the roots of *B. frutescens* followed by TLC comparison (SiO_2, $CHCl_3$/MeOH, 4:1) with authentic samples of phenylanthraquinones revealed the presence of four unidentified metabolites in the polar fractions (100% EtOAc to 20% MeOH in EtOAc), whilst TLC (SiO_2, $CHCl_3$/MeOH, 96:4) of the relatively nonpolar fractions (20% EtOAC to 50% EtOAc in petroleum ether) showed the presence of 4′-*O*-demethylknipholone (**3**) and isoknipholone (**4**), in addition to the previously isolated[2] compounds knipholone (**1**) and 4′-*O*-demethylknipholone-4′-β-D-glucopyranoside (**2**). Gel permeation chromatography of the polar fractions on Sephadex LH-20 ($CHCl_3$/MeOH, 1:1) followed by PTLC ($CHCl_3$/MeOH, 4:1) and repeated Sephadex LH-20 purification ($CHCl_3$/MeOH, 2:1) afforded four new compounds.

The EIMS of the first compound gave a molecular ion at *m/z* 434 corresponding to the molecular formula $C_{23}H_{16}O_8$ suggesting the presence of an isomer of knipholone (**1**). This was, at first sight, in agreement with the ^{1}H NMR spectrum of **1**, which showed three proton signals at δ 12.02, 12.52, and 13.87 characteristic of chelated hydroxyl groups, a three-proton ABC system (δ 7.53, dd, J=7.6, 1.1 Hz; 7.72, dd, J=8.2, 7.7 Hz; 7.27, dd, J=8.3, 1.2 Hz) typical of proton signals at positions 5-, 6-, and 7-, and proton signals at 7.27, 2.20, 2.67, and 3.98 characteristic of proton signals at H-2, C-3 methyl, acetyl methyl, and methoxy at C-4′, respectively. The above ^{1}H NMR spectral data closely resembled those of knipholone (**1**)[8] except that the signal characteristic of the proton at C-5′ in **1** (δ 6.24, s) was shifted downfield to δ 7.30.

An acetone solution of the compound, at room temperature, was transformed to knipholone within a few hours (according to NMR and by co-TLC with authentic sample), with the simultaneous liberation of a white precipitate, suggesting that the compound contained a readily hydrolyzable oxygen functional group. Possible substituents included an *O*-alkyl or an *O*-glycoside, but these functional groups were clearly ruled out since, they would be seen in both, the ^{1}H and in the ^{13}C NMR spectrum. Therefore, it had to be a heteroatom containing functionality such as an *O*-sulfate or an *O*-phosphate group. The white precipitate referred to above was found to contain the elements sodium and sulfur by EDX analysis (see Section 4 and Supporting information), hinting at the existence of a sulfate group, most probably as the sodium salt. The identity of the white solid as sodium sulfate was confirmed by standard tests (white precipitate with aqueous $BaCl_2$) and later by FABMS.

The co-occurrence of sulfated and non-sulfated phenolic compounds in higher plants has been reported mainly for flavonoids.[9–20] The only sulfated anthraquinones that have so far been isolated from plants, are 'emodin-1(or 8)-monoglucoside sulfate' and emodin dianthrone diglucoside sulfate from *Rumex pulcher*,[21] and sulfemodin 8-*O*-β-D-glucoside from *Rheum emodi*.[22]

Sulfated natural products are usually isolated as their K^+ salts,[23] but other cations such as sodium and calcium have also been reported.[13,15,17,20]

Different from the above mentioned EIMS analysis, which had apparently delivered the spectrum of the sulfate-free compound, HRFABMS gave *m/z* 536.0394 (calcd for $C_{24}H_{17}O_{11}SNa$ 536.0389), while LRFABMS showed significant ions at 513 and 433 indicating the loss of sodium and sulfate portions, respectively, and a peak observed at *m/z* 80 confirmed the presence of an *O*-sulfate moiety in the sample. IR spectroscopy gave further support for the presence of a sulfate residue by showing strong bands at 1280, 1026, and 780 cm^{-1} similar to the literature values 1250 cm^{-1} (S=O), 1030 cm^{-1} (C–O–S) and 800 cm^{-1} (S–O) observed in sulfated flavonoids.[24–27] The presence of sodium was further noted from the yellow color obtained by flame assay. Furthermore, the ^{13}C NMR spectrum of the acetylphloroglucinol moiety of the phenylanthraquinone as compared to that of knipholone[8] showed downfield shift values of 7.1, 0.1, and 3.7 ppm, for carbons C-1′, C-3′, and C-5′, respectively, whilst C-6′ experienced an upfield shift of 3.6 ppm (Table 1). These carbon shifts were attributed to the presence of an *O*-sulfate group; this phenomenon had also been observed in sulfated flavonoids.[14,15,19,20,26] The shifts suggested that the sulfate group was most likely located at C-6′. This conclusion was supported by HMBC, which showed interactions of the 2′-OH proton to C-1′,

Table 1. ^{13}C NMR spectral data of the new compounds **5–8** in comparison to those of **1–4**

Compound	1	2	3	4	5	6	7	8
C-1	161.7	163.7	162.1	159.8	162.8	162.8	162.6	163.3
C-2	124.6	125.7	124.4	125.9	124.8	124.8	125.2	125.4
C-3	151.6	153.1	151.4	151.9	152.9	152.7	153.7	153.2
C-4	128.5	129.6	128.7	126.5	129.5	129.1	130.1	129.7
C-5	119.3	120.3	119.1	120.1	119.8	119.8	120.2	120.4
C-6	137.4	138.1	137.3	137.3	137.6	137.6	138.0	138.1
C-7	123.3	124.4	123.4	124.2	123.5	123.5	123.9	124.0
C-8	161.1	163.0	161.5	159.4	162.1	162.1	162.4	162.5
C-9	192.5	194.4	192.0	192.7	193.6	193.6	194.1	194.1
C-10	181.9	183.9	181.9	183.0	182.2	182.2	182.6	183.1
C-11	134.4	136.1	134.2	134.3	135.2	135.1	135.8	135.9
C-12	115.5	116.9	115.4	115.5	115.9	116.0	116.5	116.5
C-13	114.7	116.1	114.5	115.0	114.9	114.9	115.4	115.5
C-14	131.6	133.2	131.3	132.3	131.9	131.9	132.6	133.0
C-1′	104.7	110.4	104.0	103.4	111.8	113.1	110.7	117.6
C-2′	163.3	164.0	161.4	165.5	163.1	162.6	163.3	159.8
C-3′	107.3	106.9	105.8	110.0	107.2	107.6	107.1	111.2
C-4′	162.4	162.7	161.2	163.0	162.2	159.7	161.7	165.4
C-5′	91.2	95.4	94.5	100.3	94.9	98.5	99.5	105.2
C-6′	161.9	161.9	160.7	162.0	158.3	157.6	158.5	159.4
Ar-CH_3	20.4	21.0	20.4	21.4	20.9	20.9	21.5	21.7
3′-$COCH_3$	32.6	33.6	32.5	31.6	32.9	33.3	33.1	31.7
3′-$COCH_3$	202.3	205.0	202.6	203.5	204.1	204.8	204.7	204.5
2′-OCH_3	—	—	—	60.7	—	—	—	61.0
4′-OCH_3	55.6	—	—	—	55.7	—	—	—
C-1″	—	102.3	—	—	—	101.5	—	—
C-2″	—	74.8	—	—	—	74.2	—	—
C-3″	—	78.5	—	—	—	78.1	—	—
C-4″	—	78.7	—	—	—	78.3	—	—
C-5″	—	71.2	—	—	—	71.1	—	—
C-6″	—	62.6	—	—	—	62.7	—	—

C-2′, and C-3′, whilst NOESY correlations were observed between the *O*-methyl group and both, H-5′ and the methyl group of the acetyl substituent at C-3′. Therefore, the new compound was deduced to have the constitution **5** shown in Figure 1.

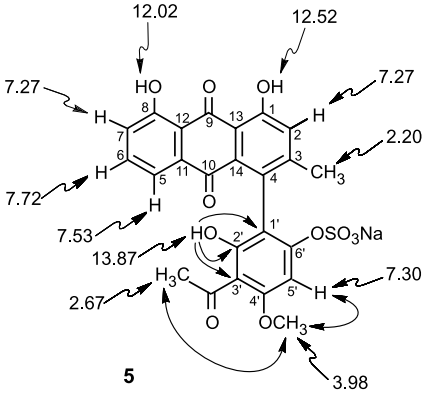


Figure 1. ^{1}H NMR chemical shifts as well as selected HMBC (single arrows) and NOESY (double arrows) correlations of **5**.

As with all phenylanthraquinones isolated so far, compound **5** is optically active due to the presence of a rotationally hindered biaryl axis. Its absolute configuration was established by comparison of the circular dichroism (CD) spectrum of compound **5** with that of the sulfate-free analog, knipholone (**1**). Surprisingly, the CD spectra of compounds **5** and **1** were found to be opposite to each other (Fig. 2). To exclude that this phenomenon might be due to the presence of the sulfate ester group and in order to get additional support for the constitution of **5**, the new sulfated compound was hydrolyzed (see Section 4) to yield knipholone (92%), but indeed with the opposite axial configuration (i.e., *ent*-**1**), as evidenced from its still opposite CD spectrum (Fig. 2). This proved that, as compared to **1**, compound **5** has a different stereo-orientation at the axis (although for formal reasons, it is likewise *M*-configured[7]).

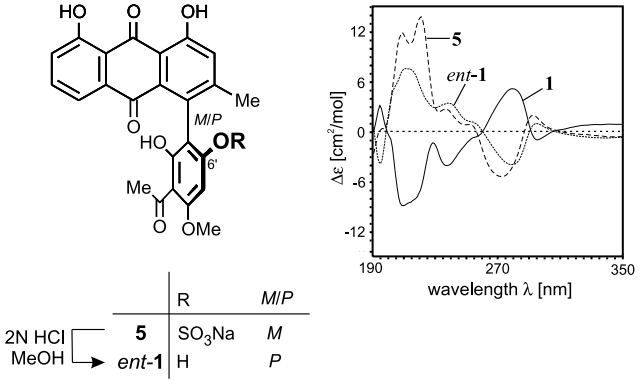


Figure 2. Comparison of the CD spectra of compound **5** and its hydrolysis product, *ent*-**1**, with the CD curve of authentic knipholone (**1**).

The FABMS (negative mode) of the second compound showed characteristic ion peaks at *m/z* 684 [M·$^-$], 661 [M−Na]$^-$, 581 [661-SO_3]$^-$, and 419 [581-Gluc+H]$^-$ corresponding to the molecular formula $C_{29}H_{25}O_{16}SNa$. Once again, as expected, the chemical shifts in the ^{1}H NMR (Fig. 3a) spectrum were in good agreement with those published for 4′-*O*-demethylknipholone-4′-β-D-glucopyranoside[2] except for the proton signal at H-5′, which resonated at a lower field (*δ* 7.51, Fig. 3a) compared to *δ*

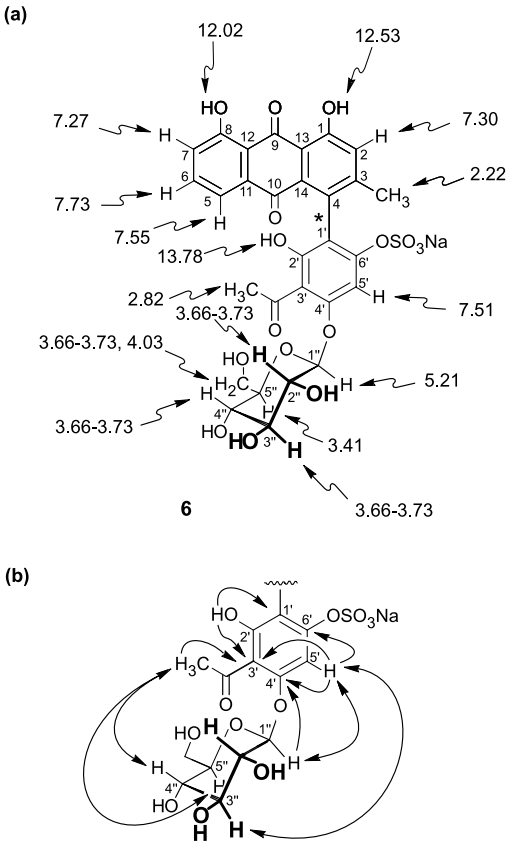


Figure 3. Diagnostically significant ^{1}H NMR data (a) as well as HMBC (single arrows) and NOESY (double arrows) interactions (b) of compound **6**.

6.38 in 4′-*O*-demethylknipholone-4′-β-D-glucopyranoside (**2**). The ^{13}C NMR data as compared to those of **2** (Table 1) showed that while carbons C-1′, C-3′ and C-5′ were shifted downfield by 2.7, 0.7, and 3.1 ppm, respectively, C-6′ underwent an upfield shift by 4.3 ppm. The chelated OH group at C-2′ revealed HMBC interactions to carbons C-1′ and C-3′; H-5′ gave correlations to C-3′, C-4′, and C-6′ (Fig. 3b). Furthermore, NOESY experiments displayed interactions between H-5′ and both, H-1″ and H-3″, whilst the methyl group of the acetyl function showed interactions to H-4″ and H-5″. The sulfate moiety was therefore, unequivocally deduced to be located on the oxygen at C-6′, so that the new compound had the constitution **6** as shown in Figure 3.

The third compound exhibited an ion peak at *m*/*z* 522 in the negative FABMS and its formula was deduced to be $C_{23}H_{15}O_{11}SNa$. The spectrum also showed significant ion peaks at *m*/*z* 499 and 419, indicative of the loss of sodium and sulfate ions, respectively. Mild acid hydrolysis of the compound afforded a product whose chromatographic and spectroscopic properties (co-TLC, co-HPLC, ^{1}H and ^{13}C NMR) were identical to those of 4′-*O*-demethylknipholone (**3**). The ^{1}H NMR spectrum displayed characteristic proton signals similar to those observed for 4′-*O*-demethylknipholone[5] except for the proton at H-5′, which resonated downfield at δ 7.20 as compared to δ 6.11 in 4′-*O*-demethylknipholone. Like for compounds **5** and **6**, the ^{13}C NMR spectrum revealed significant downfield shifts for the *ortho* carbons at C-1′ (6.7 ppm) and C-5′ (5.0 ppm), and the *para* carbon C-3′ (1.3 ppm), and an upfield shift for the *ipso* carbon C-6′ (2.2 ppm). Although, the ^{1}H NMR spectrum showed proton signals characteristic of chelated OH groups at C-2′ (13.28 ppm) and C-4′ (10.02 ppm), these did not give long-range HMBC correlations to C-1′, C-2′, C-3′, C-4′ and C-5′, which would have excluded either positions C-2′ or C-4′ to be the site of the sulfate group. However, NOESY experiments revealed interactions between the acetyl methyl and both 2′-OH and 4′-OH, whilst the proton signal at H-5′ showed correlations to 4′-OH. Thus, together with the aforementioned significant downfield and upfield shifts in ^{13}C NMR, unambiguously assigned the sulfate substituent to be located at C-6′ (see Fig. S2, Supporting information). Therefore, the new compound was deduced to have the constitution **7**.

The fourth compound was assigned the molecular formula $C_{24}H_{17}O_{11}SNa$ from negative FABMS, which displayed a molecular ion peak at *m*/*z* 536 [M·$^{-}$]. The spectrum also revealed a peak at *m*/*z* 513 indicating the loss of the sodium ion. Acid hydrolysis yielded a compound whose chromatographic and spectroscopic data were fully identical to those observed for isoknipholone.[4] The ^{1}H NMR spectrum displayed a downfield shift of H-5′ from 6.22 in isoknipholone[4] to 7.39 in the new compound and in ^{13}C NMR, significant downfield shifts were observed for the *ortho* carbons C-1′ (14.2 ppm) and C-5′ (4.9 ppm) and for the *para* carbon C-3′ (1.2 ppm), whilst an upfield shift was found for the *ipso* carbon C-6′ (2.6 ppm). HMBC experiments indicated correlations between the hydroxyl group at C-4′ and C-3′, C-4′, and C-5′, whereas the *O*-methyl group showed correlation to C-2′. Furthermore, NOESY measurements displayed interactions of the methoxy group to both the aryl methyl group (at C-3) and the aryl acetyl (at C-3′). The above data suggested that the sulfate moiety was located at position C-6′ (see Fig. S3, Supporting information) and thus, the new compound had the structure **8**.

Compounds **5**–**8** were all isolated and identified as sodium salts. They were observed to be highly polar, with R_f values of 0.08, 0.05, and 0.06 in $CHCl_3$/MeOH (9:1) for **5**, **7**, and **8**, and of 0.1 in $CHCl_3$/MeOH (4:1) for **6**, as compared to their sulfate-free analogs, which had R_f values of 0.8, 0.5, 0.7, and 0.6 for **1**, **3**, **4**, and **2**, respectively.

Compounds **6**–**8** were all found to be optically active due to the presence of the rotationally hindered biaryl axis and were thus, configurationally stable. Their absolute configurations were determined, as already described for **5**, by CD comparison with their sulfate-free analogs **2**, **3**, and **4**, respectively (see Fig. S4, Supporting information). Different from **5** (whose axial configuration was opposite to that of knipholone, **1**, see Fig. 2), **6**–**8** all had the same stereoorientation as **2**–**4**.

A solution of sodium 4′-*O*-demethylknipholone 6′-*O*-sulfate (**7**) in acetone slowly generated crystals of quality sufficient for an X-ray structure analysis, a lucky circumstance because no crystal structure analysis had so far succeeded in the field of phenylanthraquinones. This crystal structure analysis gave rise to two surprises: firstly, the compound that had crystallized out was not compound **7**,

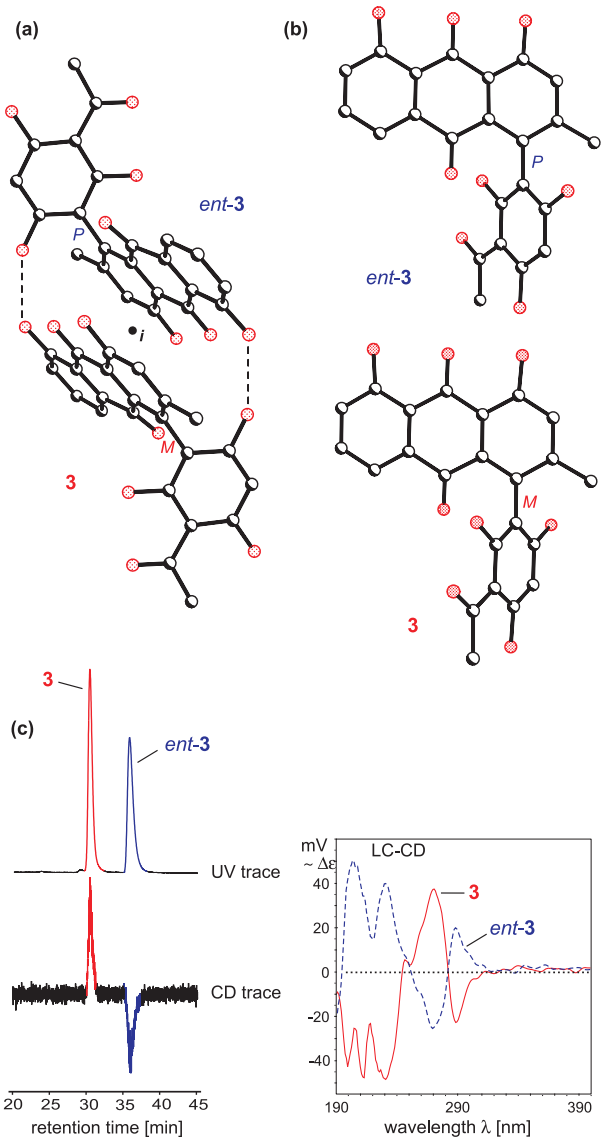


Figure 4. Racemic 4′-*O*-demethylknipholone (*rac*-**3**): crystal structure showing, both, the *M*- and the *P*-enantiomers, **3** and *ent*-**3**, in their relative orientation to each other in the crystal (a) and 'isolated' from each other, for reasons of clarity (the solvent molecule, acetone, has been omitted) (b); enantiomeric resolution on a chiral HPLC phase (Chiracel OD-H) with UV and CD detection (both monitored at 277 nm), and full CD spectra of the two enantiomers of **3** measured online, right from the peaks (c); *i*=centre of inversion.

but the sulfate-free 'parent compound', 4′-*O*-demethylknipholone (**3**, see Fig. 4), indicating that even under the mild conditions of crystallization, sulfate hydrolysis had taken place and that this slow hydrolysis was apparently a good precondition for the formation of suitable crystals. It is generally known that sulfate ester bonds are highly labile and among flavonoids it has been observed that some compounds spontaneously hydrolyze upon standing in methanol.[14,15] The second surprise was that **3** had crystallized in a racemic form, although, as described above, compound **7** had been optically active and had shown a significant CD spectrum, indicating that possibly the natural product **7** had not been enantiomerically pure, but only enantiomer-enriched. Even more remarkably, in the case of knipholone itself the *M*-enantiomer **1** prevails for the isolated sulfate-free compound and the other enantiomer for the sulfate **5** (for formal reasons likewise to be denoted as *M*[7]); the large portion of racemic material in the case of **7** had now—besides the slow formation of the product (see above)—been another favorable circumstance for the improved crystallization properties of the hydrolyzed material, **3**.

The presence of racemic or near-racemic material warranted the availability of an analytical method for the determination of the enantiomeric ratios of all these natural products. This was achieved by chromatography on a chiral OD-H phase (see Section 4), indeed showing the crystalline material to be fully racemic (Fig. 4, exact values measured experimentally: 51.3% *M* and 48.7% *P*), while the mother liquor displayed a slight enrichment (54.1:45.9) in favor of the *M*-enantiomer.

The enantiomer analysis on the chiral phase then also proved to be applicable to the resolution of the other isolated phenylanthraquinones, showing that indeed only two of them were atropisomerically pure [4′-*O*-demethylknipholone-4′-β-D-glucopyranoside, **2** (95:5)] or nearly pure [4′-*O*-demethylknipholone, **3** (93:7)], while knipholone (**1**) proved to be a 60:40 *M* to *P* mixture and isoknipholone (**4**) was even virtually racemic (52:48, see Table 2).

Exemplarily for knipholone, the analytical resolution of the naturally occurring *M* to *P* mixture on the chiral phase was successfully extended to a semi-preparative scale, to give enantiomerically pure *M* (1.2 mg; 100:0, *M* to *P*) and a *P*-rich fraction (0.5 mg; 6:94, *M* to *P*). The pure *M*-knipholone gave an optical rotation $[\alpha]_D^{20}$ +81 (*c* 0.09, MeOH) almost identical to the value initially reported for knipholone, $[\alpha]_D^{20}$ +80 (*c* 0.01, MeOH), by Dagne and Steglich.[8] With this first $[\alpha]_D$ of a provenly enantiomerically pure sample of *M*-knipholone, determined as +81, it was then possible to deduce the enantiomeric composition of the above *M* to *P* mixture from the measured optical rotation of +22 (*c* 0.04, MeOH), to be 64:36, which is reasonably close to the chromatographically measured value of 60:40. Similarly, the enantiomerically nearly pure *P* isolated (6:94, *M* to *P*) was observed to have $[\alpha]_D^{20}$ −59 (*c* 0.03, MeOH; calcd er.: 13:87 *M* to *P*).[28] For compounds **2**–**4**, the sulfates **6**–**8** and their respective hydrolysis products, however, the $[\alpha]_D$ values were not as reliable and reproducible as those obtained for knipholone—a problem typical of strongly colored compounds,[29] showing once again the value of now having the chromatography on a chiral phase available for the analysis of enantiomeric ratios.

Unfortunately, the sulfates **5**–**8** themselves were not amenable to HPLC analysis on a chiral phase due to their highly polar nature so that they could be analyzed only via their hydrolyzed products (see Table 2). Note, however, that possibly some or even all the sulfates, **5**–**8**, lose their enantiomeric purities during hydrolysis (either by spontaneous hydrolysis during isolation or chemically using 2 N HCl). This becomes evident for the sulfated glycoside **6**: since in this case, due to the presence of the chiral glucose portion, the rotational isomers are diastereomers, NMR clearly reveals that the hydrolysis product of **6**, viz.

Table 2. Results of the enantiomeric analysis of phenylanthraquinones

Compound	Enantiomeric ratios	
	M (%)	*P* (%)
Knipholone (**1**)	60	40
4′-*O*-Demethylknipholone-4′-*O*-β-D-glucopyranoside (**2**)	95	5
4′-*O*-Demethylknipholone (**3**)	93	7
Isoknipholone (**4**)	52	48
ent-Knipholone[a]	42	58
4′-*O*-Demethylknipholone-4′-*O*-β-D-glucopyranoside[a]	58	42
4′-*O*-Demethylknipholone[a]	51	49
Isoknipholone[a]	52	48

[a] Obtained by acid hydrolysis of the respective sulfates, **5**–**8**.

compound **2**, is a near 1:1 mixture of atropisomers (see Table 2 and Supporting information) consistent with the chiral phase analysis, whereas the respective sulfate precursor, compound **6**, and also the genuine, isolated **2** are clearly one species each, according to ^{1}H NMR (see Supporting information).

The most remarkable stereochemical relationship is that between knipholone (**1**) and its sulfate, **5**: although, constitutionally, they only differ by the (easily hydrolyzable) sulfate group, they belong to (preferentially) opposite stereochemical series, so that one has to expect that the (as such nearly enantiomerically pure) sulfate **5** upon hydrolysis would always diminish the enantiomeric purity of the (opposite-configured) 'parent' knipholone—to the best of our knowledge a unique case in natural product chemistry.

For a further confirmation of structure, one of the novel phenylanthraquinone sulfates was synthesized from its sulfate-free analog (Fig. 5). Thus, reaction of *ent*-**1** with tetrabutylammonium hydrogensulfate (TBAHS, 4 equiv) and dicyclohexylcarbodiimide (DCC, 20 equiv) in pyridine at 80 °C (15 min),[30] followed by cation exchange to give the sodium salt, yielded sodium *ent*-knipholone 6′-*O*-sulfate (**5**, 61%). Since knipholone itself had already been prepared by an atropo-enantiodivergent total synthesis,[31] the partial synthesis of its 6′-*O*-sulfate simultaneously constitutes a formal total synthesis of the sulfated natural product, **5**.

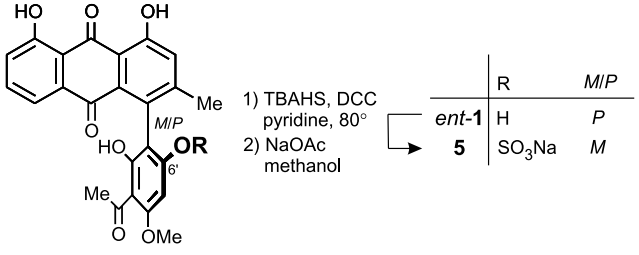


Figure 5. Reaction conditions for the partial synthesis of the sulfate **5**.

Due to the in part high antimalarial activities of knipholone and its analogs,[3] the new isolated phenylanthraquinones **5**–**8** were submitted to in vitro antiplasmodial tests against the chloroquine resistant strain K1 of *Plasmodium falciparum.* Compound **7** showed weak activity, while the other three were not active even at the highest concentration tested (5.0 μg/mL) (Table 3). The sulfate-free compound isoknipholone (**4**), however, which was tested for the first time in this paper, was found to have considerable antiplasmodial activity in vitro, comparable to that of knipholone anthrone,[3] thus, being the compound with the as yet highest activity among the phenylanthraquinones previously tested (Table 3). This made it interesting to examine its cytotoxic effects on mammalian cells, which were fortunately found to be much weaker, by a factor of >360. None of the above compounds showed any activity in vitro against *Trypanosoma brucei rhodesiense* (causes African sleeping sickness) or *Trypanosoma cruzi* (pathogen of the South American Chagas' disease).

3. Conclusion

From the polar fraction of *B. frutescens* roots, the first *O*-sulfated phenylanthraquinones have been discovered, occurring as the respective sodium salt with the sulfate substituent at the 6′-position of the acetyl phloroglucinol moiety. Chiroptical analysis of these four new compounds revealed that three of them, viz. sodium 4′-*O*-demethylknipholone-4′-β-D-glucopyranoside 6′-*O*-sulfate (**6**),

Table 3. Biological activities of **4**–**8** against *P. falciparum* (K1 strain), *T. brucei rhodesiense*, and *T. cruzi* and cytotoxicities against rat skeletal myoblast cells (L6)

Compound	IC_{50} (μg/mL)			
	P. falciparum	*T. cruzi*	*T. brucei rhodesiense*	*Cytotoxicity*
Standard	0.0461[a]	0.26[b]	0.0029[c]	nd[d]
4	0.12	14.4	9.94	43.5
5	>5	>90	56.3	nd[d]
6	>5	>90	25.5	nd[d]
7	4.13	>90	56.7	nd[d]
8	>5	>90	53.8	nd[d]

[a] Chloroquine.
[b] Benznidazole.
[c] Melarsoprol.
[d] Not determined.

sodium 4′-*O*-demethylknipholone 6′-*O*-sulfate (**7**), and sodium isoknipholone 6′-*O*-sulfate (**8**), exhibited the same main stereo-orientation at the biaryl axis as their sulfate-free analogs, **2**–**4**. The configurations of sodium *ent*-knipholone 6′-*O*-sulfate (**5**) and its hydrolysis product, *ent*-knipholone, by contrast, were observed to be opposite to that of knipholone (**1**). Enantiomeric analysis of compounds **1**–**4** and the hydrolysis products of **5**–**8**, achieved successfully by chromatography on a chiral OD-H HPLC phase, indicated that all these compounds were not enantiomerically pure. For the first time in the field of natural phenylanthraquinones, an X-ray structure analysis is reported in this paper, viz. for 4′-*O*-demethylknipholone (**3**). The sulfated phenylanthraquinones **5**–**8** showed no significant activity against the test organisms, *P. falciparum*, *T. cruzi*, and *T. brucei. rhodesiense*, while the sulfate-free compound isoknipholone (**4**) was found to possess a good antiplasmodial in vitro activity with essentially no cytotoxicity.

4. Experimental

4.1. General

Melting points were determined on a Griffin melting point instrument and are uncorrected. Optical rotations were measured on a JASCO P-1030 polarimeter using a thermostated cell (20 °C, 10-cm cell). UV–vis spectra were performed on a Shimadzu UV-2101PC spectrometer. CD spectra were recorded on a J-715 spectropolarimeter (JASCO Deutschland, Gross-Umstadt, Germany) at room temperature using a 0.05-cm standard cell and spectrophotometric grade MeOH, and are reported in $\Delta\varepsilon$ in cm^2/mol at the given wavelength λ (nm). Stereoanalytical separations were carried out on a chiral stationary phase employing a Chiralcel OD-H HPLC column (dimensions: 4.6×250 mm; particle size: 5 μm) from Daicel Chemical Industries Ltd (Tokyo, Japan). For HPLC-CD coupling experiments, the J-715 CD spectrometer was equipped with a PU-1580 pump (JASCO), a LG-980-02S ternary gradient unit, a 7725i Rheodyne injector valve, an ERC-7215 UV detector hyphenated to a J-715 spectropolarimeter with a 5 mm standard flow cell, and the Borwin chromatographic software (JASCO Deutschland). IR spectra were carried out on a Perkin-Elmer 2000 FT-IR spectrometer. ^1H and ^{13}C NMR were obtained on a Bruker Avance 300, 400 and DMX 600 (300, 400 and 600 MHz) instruments using CD_3COCD_3 as the solvent. FABMS was carried out, in the negative mode, with a Finnigan MAT 90 instrument using 3-nitrobenzylalcohol as the matrix. Flash chromatography was carried out using columns packed with silica gel 60 (particle size 0.040–0.063 mm). Gel filtration was achieved using Sephadex LH-20. Preparative TLC plates (0.5 mm thick) were prepared using either silica gel 60 $HF_{254+366}$ (Merck, Germany) or silica gel 60 PF_{254} containing $CaSO_4$ (Merck, Germany) on 20×20 cm glass plates. Spots were detected under UV light.

4.2. Plant material

The roots of *B. frutescens* were harvested from the chemistry experimental garden at the University of Botswana in September 2003. Voucher specimens have been deposited at the Herbarium, Biological Sciences, University of Botswana (code BA 205) and at the Herbarium Bringmann, University of Würzburg (code 60).

4.3. Extraction and isolation

Dried powdered roots (1.8 kg) were soaked in CH_2Cl_2/MeOH (1:1) for 24 h followed by MeOH for 30 min. The two extracts, combined and freed of solvent, yielded an organic extract (129 g), which was subjected to flash chromatography eluted first with petroleum ether and then with increasing amounts of ethyl acetate. Fractions (about 250 mL each) were collected as follows: fraction 1 (100% petroleum ether), fractions 2–4 (20% EtOAc), fraction 5 (50% EtOAc), fraction 6 (100% EtOAc), fraction 7 (10% MeOH/EtOAc), fraction 8 (20% MeOH/EtOAc). Fractions 6–8 were combined since they contained the same compounds according to TLC.

Fractions 6–8 (33 g) were applied to Sephadex LH-20 ($CHCl_3$/MeOH, 1:1) giving six fractions, of which fractions 3–6 were submitted to PTLC ($CHCl_3$/MeOH, 4:1) each yielding four bands. Repeated chromatography on Sephadex LH-20 ($CHCl_3$/MeOH, 2:1) of bands 1 and 2 afforded sodium 4′-*O*-demethylknipholone-4′-β-D-glucopyranoside 6′-*O*-sulfate (**6**, 22 mg) and sodium 4′-*O*-demethylknipholone 6′-*O*-sulfate (**7**, 43 mg). However, in most cases bands 3 and 4 were not well resolved so they were combined and subjected to PTLC (EtOAc/MeOH, 2:1) giving sodium *ent*-knipholone 6′-*O*-sulfate (**5**, 21 mg) and sodium isoknipholone 6′-*O*-sulfate (**8**, 5 mg).

A portion of fraction 5 (500 mg) was subjected to chromatography on Sephadex LH-20 ($CHCl_3$/MeOH, 2:1) followed by PTLC ($CHCl_3$/MeOH, 95:5) giving 4′-*O*-demethylknipholone-4′-β-D-glucopyranoside (**2**, 8 mg; $[\alpha]_D^{20}$ +8 (*c* 0.04, MeOH); 95:5 *M* to *P*; lit.[2] $[\alpha]_D^{25}$ −218; note: the value has apparently been a mistake; the sample has been remeasured, showing $[\alpha]_D^{20}$ +36, (*c* 0.06, MeOH)) and 4′-*O*-demethylknipholone (**3**, 4 mg; $[\alpha]_D^{20}$ +113 (*c* 0.04, MeOH); 93:7 *M* to *P*; lit.[5] $[\alpha]_D$ +104). Like in the case of their sulfated analogs, knipholone and isoknipholone were isolated as a mixture, which was successfully separated by PTLC (*n*-hexane/acetone, 2:1) yielding knipholone (**1**, 95 mg; $[\alpha]_D^{20}$ +22 (*c* 0.04, MeOH); 60:40 *M* to *P*; lit.[8] $[\alpha]_D^{22}$ +80) and isoknipholone (**4**, 11 mg; $[\alpha]_D^{20}$ −12 (*c* 0.06, MeOH); 52:48 *M* to *P*; lit.[4] $[\alpha]_D^{24}$ +33.3).

4.3.1. Sodium *ent*-knipholone 6′-*O*-sulfate (5). Red amorphous powder: mp 182–184 °C (dec); $[\alpha]_D^{20}$ −4 (*c* 0.05, MeOH); UV–vis (MeOH): λ_{max} 431 (log ε 4.22), 343 (log ε 3.96), 285 (log ε 4.62), 256 (log ε 4.64), 225 (log ε 4.85); CD (MeOH): $\Delta\varepsilon_{209}$+11.9, $\Delta\varepsilon_{221}$+13.8, $\Delta\varepsilon_{237}$+2.7, $\Delta\varepsilon_{252}$+0.8, $\Delta\varepsilon_{273}$−5.4, $\Delta\varepsilon_{293}$+1.9; IR (KBr): ν_{max} 3541, 3475, 3414, 2924, 1616, 1460, 1372, 1280, 1107, 1026, 780 cm^{-1}; ^1H NMR (300 MHz, CD_3COCD_3): δ 2.20 (s, 3H, CH_3-3), 2.67 (s, 3H, CH_3CO), 3.98 (s, 3H, CH_3O), 7.27 (s, 1H, H-2), 7.27 (dd, *J*=8.3, 1.2 Hz, 1H, H-7), 7.30 (s, 1H, H-5′), 7.53 (dd, *J*=7.6, 1.1 Hz, 1H, H-5), 7.72 (dd, *J*=8.2, 7.7 Hz, 1H, H-6), 12.02 (s, 1H, 8-OH), 12.52 (s, 1H, 1-OH), 13.87 (s, 1H, 2′-OH); ^{13}C NMR (150 MHz, CD_3COCD_3): δ, see Table 1; MS (EI): *m/z* (%)=434 (100) [M−$NaSO_3$+H],

419 (66); MS (FAB): *m/z* (%)=536 (32) [M·$^-$], 513 (100) [M−Na]$^-$, 433 (40) [513-SO_3]$^-$, 80 (7) [SO_3]$^-$; MS (FAB) exact mass calcd for $C_{24}H_{17}O_{11}SNa$: 536.0389; found 536.0394.

4.3.2. Sodium 4′-*O*-demethylknipholone-4′-β-D-glucopyranoside 6′-*O*-sulfate (6). Orange-red colored amorphous powder: mp 201–203 °C (dec); $[\alpha]_D^{20}$ −16 (*c* 0.05, MeOH); UV–vis (MeOH): λ_{max} 433 (log ε 3.41), 340 (log ε 3.20), 279 (log ε 3.83), 256 (log ε 3.86), 220 (log ε 4.01); CD (MeOH): $\Delta\varepsilon_{195}$+1.2, $\Delta\varepsilon_{209}$−16.2, $\Delta\varepsilon_{221}$−18.5, $\Delta\varepsilon_{296}$+7.8, $\Delta\varepsilon_{292}$−3.1; IR (KBr): ν_{max} 3418, 1622, 1383, 1279, 1246, 1076, 1050, 1026, 776, 611 cm^{-1}; ^{1}H NMR (600 MHz, CD_3COCD_3): δ 2.22 (s, 3H, CH_3-3), 2.82 (s, 3H, CH_3CO), 3.41 (m, 1H, H-5″), 3.66–3.73 (m, 4H, CH_2OH), 4.03 (m, 1H, CH_2OH), 5.21 (d, *J*=7.4 Hz, 1H, H-1″), 7.27 (dd, *J*=8.3 Hz, 1H, H-7), 7.30 (s, 1H, H-2), 7.51 (s, 1H, H-5′), 7.55 (dd, *J*=7.5 Hz, 1H, H-5), 7.73 (t, *J*=8.0 Hz, 1H, H-6), 12.02 (s, 1H, 8-OH), 12.53 (s, 1H, 1-OH), 13.78 (s, 1H, 2′-OH); ^{13}C NMR (150 MHz, CD_3COCD_3): δ, see Table 1; MS (FAB): *m/z* (%)=684 (6) [M·$^-$], 661 (13) [M−Na]$^-$, 581 (4) [661-SO_3]$^-$, 419 (4) [581-Gluc+H]$^-$; MS (FAB) exact mass calcd for $C_{29}H_{25}O_{16}SNa$: 684.0758; found 684.0769.

4.3.3. Sodium 4′-*O*-demethylknipholone 6′-*O*-sulfate (7). Red amorphous powder: mp 161–163 °C (dec); $[\alpha]_D^{20}$ +67 (*c* 0.06, MeOH); UV–vis (MeOH): λ_{max} 430 (log ε 4.34), 288 (log ε 4.75), 255 (log ε 4.74), 225 (log ε 4.96); CD (MeOH): $\Delta\varepsilon_{220}$−27.4, $\Delta\varepsilon_{270}$+13.5, $\Delta\varepsilon_{292}$−3.6; IR (KBr): ν_{max} 3549, 3467, 3416, 2918, 1623, 1458, 1425, 1367, 1280, 1086, 1048, 1022, 781 cm^{-1}; ^{1}H NMR (600 MHz, CD_3COCD_3): δ 2.23 (s, 3H, CH_3-3), 2.69 (s, 3H, CH_3CO), 7.20 (s, 1H, H-5′), 7.28 (d, *J*=6.6 Hz, 1H, H-7), 7.29 (s, 1H, H-2), 7.56 (dd, *J*=7.5, 0.5 Hz, 1H, H-5), 7.74 (d, *J*=8.0 Hz, 1H, H-6), 10.02 (s, 1H, 4′-OH), 12.03 (s, 1H, 8-OH), 12.53 (s, 1H, 1-OH), 13.28 (s, 1H, 2′-OH); ^{13}C NMR (150 MHz, CD_3COCD_3): δ, see Table 1; MS (FAB): *m/z* (%)=522 (31) [M·$^-$], 499 (85) [M−Na]$^-$, 419 (41) [499-SO_3]$^-$; MS (FAB) exact mass calcd for $C_{23}H_{15}O_{11}SNa$: 522.0231; found 522.0227.

4.3.4. Sodium isoknipholone 6′-*O*-sulfate (8). Red amorphous powder: mp 105–108 °C (dec); $[\alpha]_D^{20}$ −27 (*c* 0.03, MeOH); UV–vis (MeOH): λ_{max} 427 (log ε 3.26), 338 (log ε 3.00), 285 (log ε 3.68), 255 (log ε 3.83), 205 (log ε 4.02); CD (MeOH): $\Delta\varepsilon_{215}$−1.8, $\Delta\varepsilon_{251}$+2.4, $\Delta\varepsilon_{294}$−0.3; IR (KBr): ν_{max} 3541, 3467, 3416, 2923, 1618, 1417, 1384, 1265, 1107, 1026, 622 cm^{-1}; ^{1}H NMR (600 MHz, CD_3COCD_3): δ 2.26 (s, 3H, CH_3-3), 2.65 (s, 3H, CH_3CO), 3.39 (s, 3H, CH_3O), 7.30 (dd, *J*=8.4, 1.1 Hz, 1H, H-7), 7.32 (s, 1H, H-2), 7. 39 (s, 1H, H-5′), 7.58 (dd, *J*=7.6 Hz, 1H, H-5), 7.77 (dd, *J*=8.3, 7.5 Hz, 1H, H-6), 13.25 (s, 1H, 4′-OH); ^{13}C NMR (150 MHz, CD_3COCD_3): δ, see Table 1; MS (FAB): *m/z* (%)=536 (5) [M·$^-$], 513 (23) [M−Na]$^-$; MS (FAB) exact mass calcd for $C_{24}H_{17}O_{11}SNa$: 536.0389; found 536.0394.

4.4. Energy dispersive X-ray (EDX) analysis

The white inorganic substance originating in the hydrolysis of phenylanthraquinone sulfates was analyzed by using an environmental scanning electron microscope (ESEM) fitted with an EDX analysis system (EDAX 3.10 with an ultra thin window). The sample, mounted on aluminum pin type mounts (3 mm) using a carbon tape, was examined under low vacuum using a Phillips XL 30 ESEM microscope fitted with a tungsten filament and a gaseous secondary electron detector.

4.5. Acid hydrolysis

Compounds **5**–**8** (1.1, 1.2, 1.3, and 1.0 mg, respectively) were dissolved in MeOH (2 mL each) and mixed with 2 N HCl (5 mL). The mixture was stirred at room temperature for 30 min, after which the sulfate-free phenylanthraquinones were extracted with EtOAc (3×5 mL), purified on a small Sephadex LH-20 column ($CHCl_3$/MeOH, 2:1), and analyzed by TLC and ^{1}H NMR: *ent*-knipholone (*ent*-**1**, 0.8 mg, 1.8 μmol, 92%), 4′-*O*-demethylknipholone (**3**, 0.9 mg, 2.1 μmol, 90%), isoknipholone (**4**, 0.7 mg, 1.6 μmol, 90%). Acid hydrolysis of sodium 4′-*O*-demethylknipholone-4′-β-D-glucopyranoside 6′-*O*-sulfate (**6**), subsequent extraction with EtOAc (8×5 mL), and TLC indicated the presence of two compounds, which were separated on a small silica gel column (SiO_2, $CHCl_3$/MeOH, 96:4 then 90:10) delivering 4′-*O*-demethylknipholone (**3**, 0.2 mg, 0.48 μmol, 36%) and 4′-*O*-demethylknipholone-4′-β-D-glucopyranoside (**2**, 0.5 mg, 0.86 μmol, 51%), the latter being identical to the authentic compound **2** except for the peak doubling in NMR (see Fig. S2, Supporting information) showing the presence of diastereomers, as evident also by analysis on a chiral phase (Table 2). The aqueous layer was concentrated and tested with $BaCl_2$.

4.6. Resolution of atropisomers

Solutions of compounds **1**, **2**, **3**, and **4** (0.5 mg each) in MeOH (500 μL each) were resolved by HPLC on a Chiralcel OD-H column (4.6 mm×250 mm, 5 μm), with an isopropanol/*n*-hexane gradient under the following conditions: flow 0.5 mL/min; 0–10 min: isopropanol/*n*-hexane 10:90, 10–40 min: isopropanol/*n*-hexane 50:50, giving the following retention times: for **1** [t_R=31.5 min for (*M*)-**1**, t_R=33.9 min for (*P*)-**1**], for **2** [t_R=36.2 min for (*M*)-**2**, t_R=34.4 min for (*P*)-**2**], for **3** [t_R=35.5 min for (*M*)-**3**, t_R=42.4 min for (*P*)-**3**], for **4** [t_R=20.4 min for (*M*)-**4**, t_R=24.1 min for (*P*)-**4**]; the peaks were analyzed stereochemically by HPLC–CD coupling.

4.7. Partial synthesis of sodium *ent*-knipholone 6′-*O*-sulfate (5)

A solution of *ent*-**1** (5.0 mg, 11.5 μmol) in pyridine (2 mL) was treated under nitrogen with TBAHS (15.6 mg, 45 μmol) and DCC (47.5 mg, 230 μmol) and stirred at 80 °C for 15 min. After cooling to room temperature, pyridine was removed by repeated addition of toluene and evaporation of the solvent mixture. The reaction medium was diluted with MeOH (2 mL) and filtered several times through Celite to remove the dicyclohexylurea precipitate. Conversion of the TBA salt to the respective sodium salt was performed by addition of a saturated solution of NaOAc (2 mL) in MeOH, after which the mixture was purified by repeated PTLC ($CHCl_3$/MeOH, 4:1) giving sodium *ent*-knipholone 6′-*O*-sulfate (**5**, 3.6 mg, 6.7 μmol, 61%). The synthetic product

proved to be identical in all respects with natural sodium *ent*-knipholone 6′-*O*-sulfate (**5**).

4.8. Biological experiments

Antiparasitic activities against the pathogens *P. falciparum*, *T. cruzi*, and *T. brucei rhodesiense*, as well as cytotoxicities (rat skeletal myoblast L-6 cells) were assessed as described earlier.[32]

4.9. X-ray crystallographic data

The X-ray data were collected from shock-cooled, oil coated crystals on a BRUKER SMART-APEX diffractometer with a D8-goniometer equipped with a low-temperature device in ω-scan mode at 173(2) K,[33] using graphite-monochromated Mo K_α radiation ($\lambda = 0.71073$ Å). The structure was integrated with SAINT[34] and a semiempirical absorption correction (SADABS)[35] was applied. The structure was solved by direct methods (SHELXS97)[36] and refined by full-matrix least-squares methods against F^2 (SHELXL97).[37]

Crystallographic data (excluding structure factors) for the structure in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 242760. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.06.055

Copies of the ^{1}H and ^{13}C NMR spectra for **5**, **6**, **7**, and **8**. ^{1}H NMR spectra for **2** (as isolated from the plant and as obtained by acid hydrolysis of the respective sulfate **6**), and synthetic **5**. EDX graph of white precipitate. ^{1}H NMR shifts as well as HMBC and NOESY correlations of compounds **7** and **8**. CD spectra of compounds **6–8** in comparison to their sulfate-free analogs, **2–4**.

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Macrocyclic receptors containing sucrose skeleton

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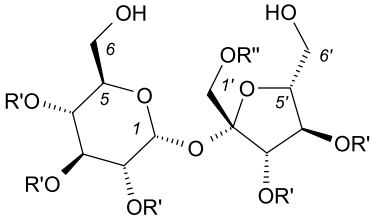
Abstract—Crown ether analogues with incorporated sucrose unit were prepared by reaction of 1′,2,3,3′,4,4′-hexa-*O*-benzylsucrose with polyethylene ditosylates in up to 52% yield. Stability constants of their complexes with Li^+, Na^+, K^+, NH_4^+ were determined by the NMR titration method. The macrocycles were also tested as catalysts in the enantioselective Michael reaction, but with little success (ee up to only 22%). The macrocycle containing nitrogen in the ring was also prepared in good yield. All prepared macrocycles were easily converted into the free sucrose crowns (H_2/Pd/C) without destroying the (very labile) glycosidic bond. The crystal structure of the selected receptor was determined.

1. Introduction

Sucrose (**1**) represents of a cheap raw material and is available in more than 100 million tons per year; most of it being consumed on the food market. This disaccharide is also a subject of interest for many laboratories, which apply it in chemical synthesis. For example, it maybe used for the preparation of bio-degradable polymers and surfactants,[1] or applied as a chiral matrix for the synthesis of complex natural products.[2,3] The very high purity of commercially available sucrose allows the use of this compound as a source of chirality for chemical synthesis without any additional purification.



1. R' = R" = H; **2.** R' = Bn, R" = H
3. R' = Bn, R" = BOM; **4.** R' = R" = Bn

As a part of an on-going program, we elaborated a convenient route to 2,3,3′,4,4′-penta-*O*-benzyl-sucrose[4] (**2**), a convenient starting material for the preparation of analogues modified at the terminal positions. The primary hydroxyl group in **2** can be differentiated, allowing the preparation of a number of sucrose derivatives, which—after removing the benzyl protecting groups—can be obtained in a free form.[3] Also, the diol **3** was prepared readily from **2**.[5] Recently, we prepared in high overall yield (48%) even more convenient dihydroxylated sucrose derivative: the hexa-*O*-benzylated diol **4**.[6]

2. Results and discussion

Easy access to the diol **4** opened the possibility for the preparation of the crown ether analogues with incorporated sucrose unit, in which the C-6 and C-6′ positions are connected via a heteroatomic bridge (Fig. 1).

Recently we synthesized several such derivatives (**5a–9a**)[6,7] albeit in moderate yields (ca. 12% for **5a** up to 31% for **9a**) by reaction of the diol **4** with the corresponding polyethylene ditosylates. By the improved procedure reported here, these yields are now improved up to 52%. The important feature of this methodology lies in the easy deprotection of the macrocycles without destroying the very labile glycosidic bond. Simple hydrogenolysis removes the benzyl protecting groups and allows to obtain the free compounds, further isolated as peracetates **5b–11b**.

The structure of one of these derivatives—**7b**—was assigned by X-ray analysis. The numbering scheme and overall conformation of **7b** is shown in Figure 2. The

Keywords: Sucrose; Chiral receptors; Crown ether analogues.
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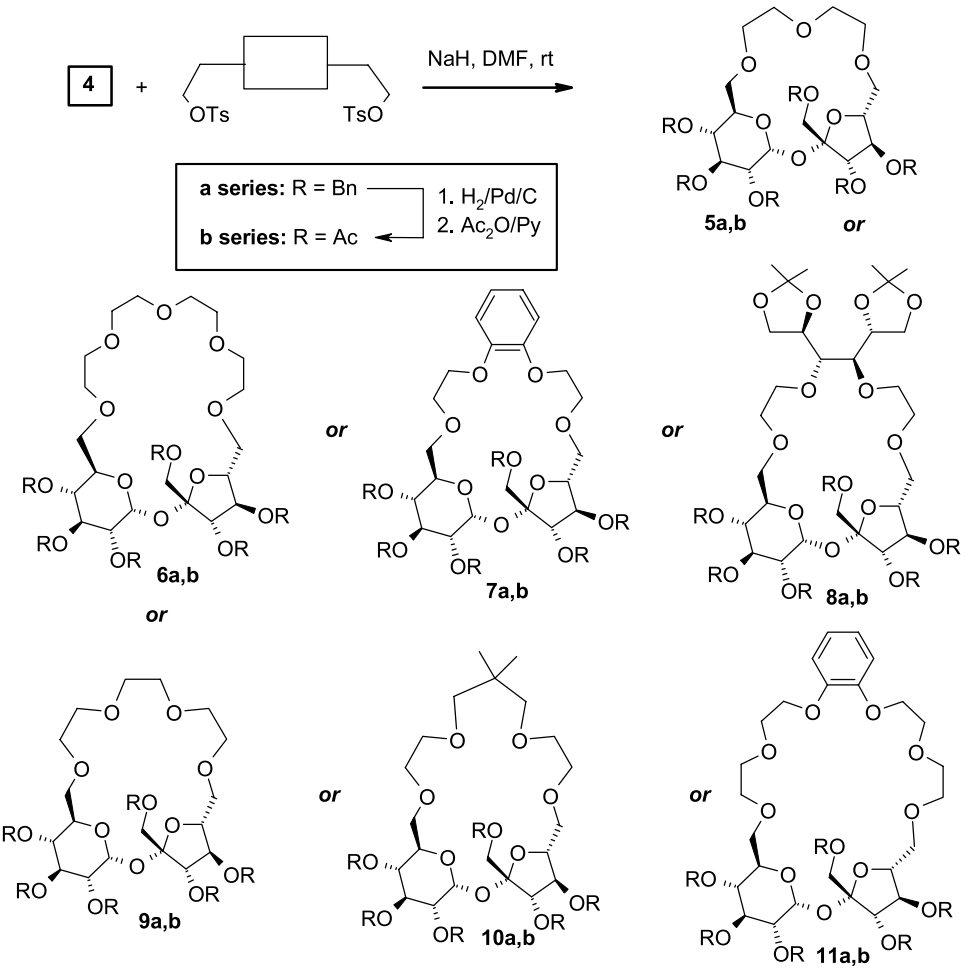


Figure 1. Preparation of sucrose-based crown ether analogues.

asymmetric part of the crystal consists of two symmetry independent molecules A and B. The sucrose units of both molecules are very similar. The Cremer and Pople ring-puckering parameters[8,9] Q, θ and ϕ (calculated using program PUCK2[10]) for glucopyranoid rings of molecules A and B [0.581(7) Å, 6.6(7)°, 309(6)° and 0.583(7) Å, 5.8(6)°, 312(6)°] indicate the typical $^4C_1$(D)-chair conformation and for the furanoid rings the q_2 and ϕ_2 parameters

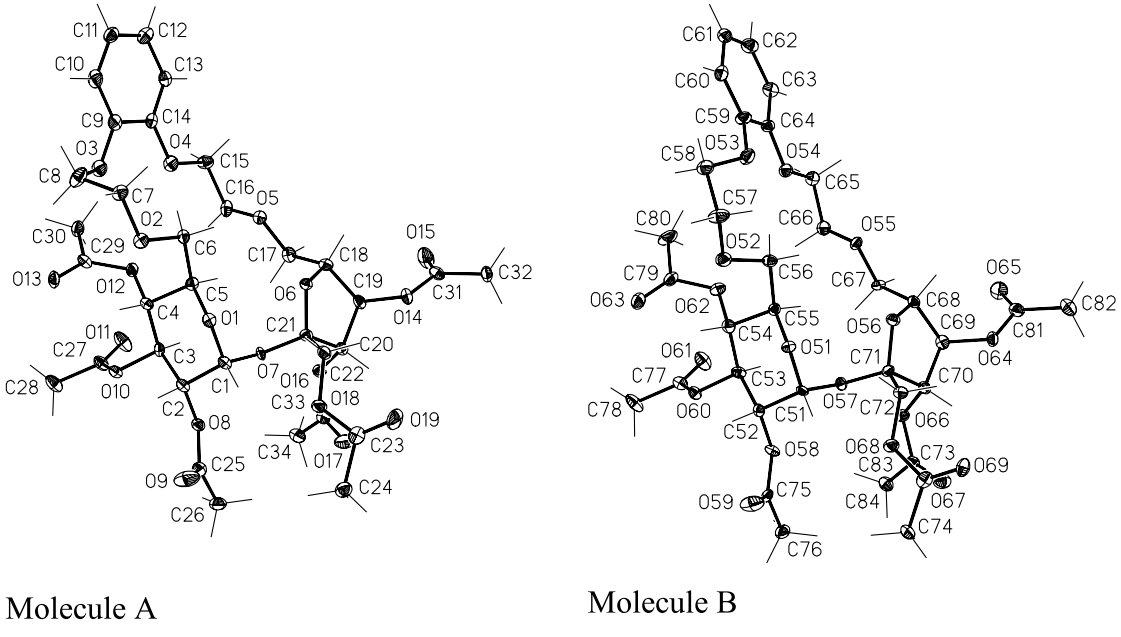


Figure 2. X-ray structure of compound **7b**.

Table 1. Selected torsion angles (°)

	Molecule A (i=0)	Molecule B (i=50)
C(5+i)–O(1+i)–C(1+i)–O(7+i)	56.4(7)	58.6(7)
C(1+i)–O(1+i)–C(5+i)–C(6+i)	−171.3(5)	−169.3(5)
O(1+i)–C(5+i)–C(6+i)–O(2+i)	−68.7(6)	−75.0(6)
C(7+i)–O(2+i)–C(6+i)–C(5+i)	−163.6(5)	169.1(6)
C(6+i)–O(2+i)–C(7+i)–C(8+i)	93.9(7)	77.4(8)
O(2+i)–C(7+i)–C(8+i)–O(3+i)	−66.7(8)	−67.0(9)
C(9+i)–O(3+i)–C(8+i)–C(7+i)	−89.6(8)	175.1(6)
C(8+i)–O(3+i)–C(9+i)–C(14+i)	151.1(6)	−146.1(7)
O(3+i)–C(9+i)–C(14+i)–O(4+i)	−7.2(9)	8.9(9)
C(15+i)–O(4+i)–C(14+i)–C(9+i)	178.5(6)	−175.5(6)
C(14+i)–O(4+i)–C(15+i)–C(16+i)	170.2(6)	−174.5(6)
O(4+i)–C(15+i)–C(16+i)–O(5+i)	−76.7(7)	−67.0(7)
C(17+i)–O(5+i)–C(16+i)–C(15+i)	−163.1(5)	−160.8(5)
C(16+i)–O(5+i)–C(17+i)–C(18+i)	179.7(5)	179.9(5)
O(5+i)–C(17+i)–C(18+i)–O(6+i)	67.3(7)	68.9(7)
C(21+i)–O(6+i)–C(18+i)–C(17+i)	93.6(6)	95.9(6)
C(18+i)–O(6+i)–C(21+i)–O(7+i)	−99.6(6)	−94.7(6)
C(1+i)–O(7+i)–C(21+i)–O(6+i)	−86.5(6)	−88.7(6)
C(21+i)–O(7+i)–C(1+i)–O(1+i)	63.2(7)	65.2(7)

[0.259(7), 142(2) and 0.218(6), 14(2)] indicate the ^{18}E-envelope [with the C(18) atom in the apex] and the $^{71}T_{70}$ twist conformations, respectively.

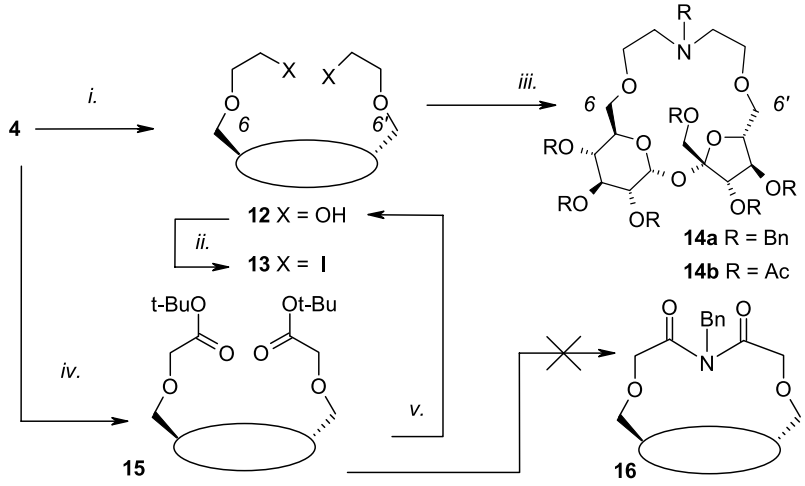
This difference has rather a minor influence on the crown ring conformation. The respective torsion angles listed in Table 1, which characterize this part of molecules have very similar values. On the other hand, the molecules A and B have different conformations near the aromatic ring. The C(9)–O(3)–C(8)–C(7) and C(59)–O(53)–C(58)–C(57) torsion angles are equal −89.6(8) and 175.1(6)°, and the C(8)–O(3)–C(9)–C(14) and C(58)–O(53)–C(59)–C(64) are equal 151.1(6) and −146.1(7)°, respectively.

The starting material for the preparation of the aza-analogue **14a**—the diol **12**—was synthesized by two different routes from **4** (Scheme 1). The first involved double allylation followed by cleavage of the double bonds with OsO_4/$NaIO_4$ and subsequent reduction. The second was based on the reaction of the diol **4** with *t*-butyl bromoacetate and reduction of the resulting diester **15** with $LiAlH_4$. The second method afforded diol **12** in higher yield (66 vs 49%). Surprisingly, reaction of diol **4** with methyl bromoacetate did not afford any diester. Compound **14a** was easily converted into the peracetylated analogue **14b** by simple hydrogenolysis followed by acetylation.

Reaction of **15** with benzylamine, which would provide the direct precursor of **14**-imide **16**—was unsuccessful. Also trans-esterification of **15** into dimethyl ester (which should react with benzylamine more readily than **15**) under various conditions failed.

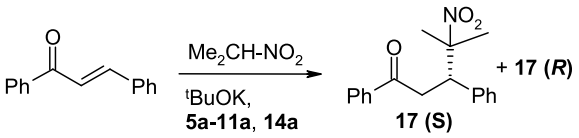
The 1,4-addition of nucleophiles to α,β-unsaturated ketones catalyzed by chiral crown ethers may provide the corresponding adducts in high optical purity. One such reaction is the addition of 2-nitropropane to chalcone leading to 1,4-adducts **17**. When such catalysts based on simple sugar were used, the optical purity of **17** amounted to 95%.[11] We tested our analogues in such a process, however, with no success. Optical purities of product **17** in the reaction catalyzed by sucrose crowns were very low and did not exceed 22% (see Table 2).

The stability constants of complexes formed can be easily determined by NMR titration;[12] the results obtained for



Scheme 1. (i) a. AllBr, NaH, DMF, 3 h, rt, 95%; b. OsO_4, $NaIO_4$, THF/H_2O (1:1) then $NaBH_4$, 52%; (ii) a. MsCl, Et_3N, DMAP, CH_2Cl_2, b. NaI, acetone, reflux, 6 h, 69%; (iii) $BnNH_2$, $NaCO_3$, CH_3CN, 50 h, reflux, 73%; (iv) $BrCH_2CO_2^tBu$, 50% NaOH, toluene, Bu_4NBr, 69%; (v) $LiAlH_4$, THF, 95%.

Table 2. Base-catalyzed 1,4-addition of 2-nitropropene to chalcone catalyzed by sucrose crowns



Catalyst	Chemical yield %	**17**% ee
5a	88	15 (***S***)
6a	88	22 (***S***)
7a	77	13 (***S***)
8a	56	9 (***R***)
9a	85	17 (***S***)
10a	9	16 (***S***)
14a	66	17 (***S***)

sucrose receptors are shown in Table 3. The stability constants are rather moderate; they depend on the cavity of the macrocycle, but do not depend on the counter ion as can be noticed for compound **7a** (entry 2; Table 3). The highest values were noted for complexes of **5a** with sodium and potassium and the aza-analogue **14a** for potassium cation.

The stability constants of complexes of sucrose receptors were low. First (most likely) reason results from a distorted crown structure of sucrose macrocycles described here. Second one is a consequence of a sugar unit being part of a macrocycle. It is reported, that the complexing abilities of monosaccharide based crown ethers strongly depend on the configuration of a sugar. For example, mannose derived receptor **18** forms strong complex with *t*butylammonium thiocyanate ($K_a = 39{,}000\ M^{-1}$), while analogous complex of macrocycle **19**—differing only in configuration at the C-3 atom of the sugar skeleton—is very weak ($K_a < 50\ M^{-1}$ see Fig. 3).[13]

3. Conclusion

The sucrose macrocycles—analogues of the crown ethers—are easily prepared from 'sucrose diol', which has the C6 and C6′ positions free and the other hydroxyl groups protected as benzyl ethers. These macrocyclic derivatives are easily converted into the free analogues by simple hydrogenation. The complexing properties of the 'crowns' studied are rather moderate. The highest stability constant with potassium ion was measured for compound **5a** and **14a** having a 16-membered ring.

Application of such sucrose-derived macrocycles as catalysts in enantioselective Michael reaction was not successful.

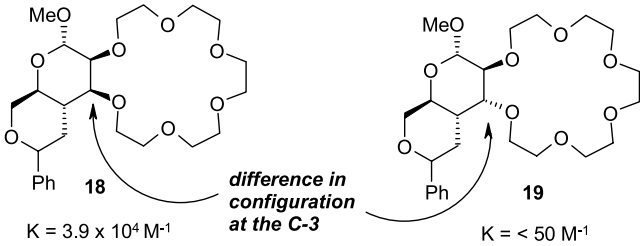


Figure 3. Complexes of sugar derived macrocycles with *t*-bytulammonium thiocyanate.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded with a Varian Mercury 400 BB (for **10b**), or a Bruker DRX 500 spectrometers for solutions in $CDCl_3$ (internal Me_4Si). NMR titration of macrocycles with thiocyanates (and KPF_6) was performed with a Varian Gemini 2000 BB spectrometer in acetone-d_6 according to a standard methodology.[12,14] Most of the proton resonances were assigned by the ^{1}H–^{1}H- and the carbon resonances in **5b** by the ^{1}H–^{13}C- correlations. Mass spectra (ESI) were recorded with PE SCIEX API 365, or Mariner PerSeptive Biosystems apparatus. Optical rotations were measured with a Digital Jasco polarimeter DIP-360 for solutions in chloroform ($c = 1$) at room temperature. Column chromatography was performed on silica gel (Merck, 70–230 or 230–400 mesh). THF was distilled from potassium prior to use. For chromatography purposes a fraction of mineral oil with a boiling point in range 70–90 °C was used as mixture of hexanes. All solutions were dried over anhydrous sodium sulfate.

X-ray data of **7b** were collected at low temperature using an Oxford Cryosystem device on a Kuma KM4CCD κ-axis diffractometer with graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). The crystal was positioned at 65 mm from the CCD camera. 612 frames were measured at 0.75° intervals with a counting time of 20 s. Accurate cell parameters were determined and refined by least-squares fit of 3900 the strongest reflections. The data were corrected for Lorentz and polarization effects. No absorption correction was applied. Data reduction and analysis were carried out with the Oxford Diffraction (Poland) Sp. z o.o. programs. The structure was solved by direct methods

Table 3. Stability constants of 1:1 complexes (calculated from the shift of the H-1 signal) of 'crown sucroses' with cations (compound **6a** formed complexes of different stoichiometry); measured in acetone-d_6

	Compound	LiSCN	NaSCN	KSCN	NH_4SCN
1.	**5a**	<5	250	258	17
2.	**7a**		31	57[a]	9
3.	**7b**		9	12	<5
4.	**8a**		19	18	
5.	**9a**	7	60	66	25
6.	**10a**		14	<5	
7.	**14a**	50		234	125

[a] $K = 63\ M^{-1}$ with KPF_6.

Table 4. Crystal data and structure refinement

Empirical formula	$C_{34}H_{44}O_{19}$
Formula weight	756.69
T/K	100(2)
λ/Å	0.71073
Crystal system	Monoclinic
Space group	$P2_1$
a/Å	17.645(19)
b/Å	8.957(10)
c/Å	22.74(3)
β/°	92.370(10)
V/Å^3	3591(7)
Z	4
D_c/mg m^{-3}	1.400
μ/mm^{-1}	0.115
F(000)	1600
Crystal size/mm	0.25×0.17×0.10
θ range for data collection/°	3.34–28.54
Ranges of h,k,l	−23→22, −8→11, −30→29
Reflections collected	25,113
Independent reflections (R_{int})	11,423 (0.0816)
Data/parameters	11,423/968
GOF(F^2)	1.097
Final R_1/wR_2 indices ($I>2\sigma_I$)	0.0837/0.2093
Extinction coefficient	0.0123(15)
Largest diff. peak/hole (e Å^{-3})	0.330/−0.331

(program SHELXS97[15]) and refined by the full-matrix least-squares method on all F^2 data using the SHELXL97[16] program. Non-hydrogen atoms were refined with anisotropic displacement parameters; hydrogen atoms were included from geometry of molecules and $\Delta\rho$ maps. During the refinement their parameters were fixed. Crystal data are given in Table 4, together with refinement details.

Crystallographic data for the structures reported in this paper (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 272641. Copies of this information may be obtained free of charge from the Director, CCDC, 12 UNION Road, Cambridge 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

4.2. Synthesis of the diol 4

This compound was prepared from 1′,2,3,3′,4,4′-hexa-*O*-benzyl-6,6′-dichloro-6,6′-dideoxysucrose according to Ref. 6 by substitution of both 6,6′chlorine atoms with acetates using 5 equiv of Bu_4NOAc (75% yield) followed by hydrolysis of acetates under Zemplen conditions.

We have found that Bu_4NOAc can be replaced with sodium acetate without significant decrease of the yield of 6,6′-diacetate, although the time of this substitution is much longer. Thus, to a solution of 1′,2,3,3′,4,4′-hexa-*O*-benzyl-6,6′-dichloro-6,6′-dideoxysucrose (400 mg) in DMF (100 mL) anhydrous sodium acetate (2 g) was added and the mixture was stirred at 100–110 °C for 20 days. After cooling it was poured into the water (150 mL) and the product was extracted with ether (3×100 mL) to afford diacetate **4-Ac** in (290 mg, 69%).

4.3. General procedure for the preparation of macrocycles 5a–11a

To a solution of **4** (0.66 g, 0.75 mmol) in dry DMF (25 mL), sodium hydride (50% suspension in mineral oil, 110 mg ca. 2.25 mmol) and a catalytic amount of imidazole (30 mg) were added under an argon atmosphere and the mixture was stirred for 20 min at room temperature. The corresponding ditosylate (0.98 mmol) in DMF (15 mL) was then added dropwise over 30 min, and stirring was continued for 12 h. The excess of hydride was then carefully decomposed with water and the products were extracted with ethyl acetate. The organic phase was washed with water, dried, concentrated and the products **5a–11a** were isolated by column chromatography (eluent: hexane–ethyl acetate).

This preparation essentially followed the procedure applied recently by us, except the solvent. When the reaction was performed in THF the yields of macrocycles were low.[6] However, changing the solvent to dry DMF increased the yields significantly.

- Compound **6a**, 35% (after column chromatography with hexane/ethyl acetate, 2:1 to 1:1). Previously reported yield: 12%.
- Compound **7a**, 48% (after column chromatography with hexane/ethyl acetate, 2:1, then HPLC with hexane/ethyl acetate, 5:2). Previously reported yield: 15%.
- Compound **9a**, 52% (after column chromatography with hexane/ethyl acetate, 3:2). Previously reported yield: 31%.

4.3.1. 1′,2,3,3′,4,4′-Hexa-*O*-benzyl-6,6′-*O*-(5,5-dimethyl-3,7-dioxanonan-1,9-di-yl)-sucrose (10a). (Eluent: hexane/ethyl acetate, 4:1, then HPLC). Colorless oil, $[\alpha]_D$ +37.4. IR (film) ν 3031, 2868, 1454, 1092, 1028, 736, 698 cm^{-1}; ^{1}H NMR δ: 5.66 (d, $J_{1,2}$=3.5 Hz, 1H, H-1), 0.86, 0.83 (2× s, 2×3H, 2×CH_3). ^{13}C NMR δ: 138.9, 138.72, 138.67, 138.47, 138.40, 138.3 (6×C_q benzyl), 104.1 (C-2′), 89.4 (C-1), 83.4, 82.02, 81.99, 79.9, 79.7, 77.8 and 70.82 (C-2,3,3′,4,4′,5,5′), 76.6, 76.4, 75.4, 74.7, 73.3, 72.65, 72.57, 72.55, 71.7 (double intensity), 71.0, 70.78, 70.75, 70.73, 69.6 (C-1′,6,6′, 6×OCH_2Ph and 6×–OCH_2– from the macrocyclic ring) 36.1 (CMe_2), 22.3, 22.1 (2× CH_3). *m/z*: 1061 [M($C_{63}H_{74}O_{13}$)+Na^+]. Anal. Calcd for $C_{63}H_{74}O_{13}$: C, 72.81; H, 7.18. Found: C, 72.8; H, 7.2%.

4.3.2. 1′,2,3,3′,4,4′-Hexa-*O*-benzyl-6,6′-*O*-(1,2-diphenoxy-3-oxapentylidene)-sucrose (11a). (Eluent: hexane/ethyl acetate, 1:1, then HPLC. Colorless oil, $[\alpha]_D$ +40.2. IR (film) ν 2918, 2869, 1498, 1454, 1257, 1127, 1091, 1028, 738, 698 cm^{-1}; ^{1}H NMR δ: 5.65 (d, $J_{1,2}$=3.6 Hz, 1H, H-1). ^{13}C NMR δ: 149.18, 149.13 (2×C from –C_6H_4–), 139.0, 138.7, 138.4, 138.34, 138.26, 138.0 (6×C_q benzyl), 121.6 (double intensity), 115.0, 114.7 (4×C from –C_6H_4–), 104.2 (C-2′), 89.4 (C-1), 83.4, 81.9, 81.8, 79.9, 79.5, 77.9 and 71.08 (C-2,3,3′,4,4′,5,5′), 75.4, 74.7, 73.3, 72.59, 72.58, 72.49, 71.8, 71.7, 71.1, 70.95, 70.92, 70.5, 69.84, 69.80, 69.7, 69.5, 69.4 (C-1′,6,6′, 6×OCH_2Ph and 8×–OCH_2– from macrocyclic ring). *m/z*: 1155 [M($C_{68}H_{76}O_{15}$)+Na^+]. Anal. Calcd for $C_{68}H_{76}O_{15}$: C, 72.07; H, 6.76. Found: C, 72.3; H, 6.6%.

4.4. General procedure for deprotection of macrocycles; synthesis of pearacetetas 5b–11b and 14b

To a solution of the appropriate perbenzylated derivative (0.4 mmol) in ethanol (7 mL), ethyl acetate (7 mL), and water (0.1 mL), 10% Pd/C (20 mg) was added, and the mixture was hydrogenolyzed for 24 h under standard conditions. Solvents were removed in vacuum, the residue was suspended in pyridine (5 mL), to which acetic anhydride (2 mL) and DMAP (ca. 30 mg) were added and the mixture was stirred at room temperature for 2 h. Products were isolated by column chromatography.

4.4.1. 1′,2,3,3′,4,4′-Hexa-*O*-acetyl-6,6′-*O*-(3-oxapentan-1,5-diyl)-sucrose (5b). (Eluent: ethyl acetate). White, amorphous solid, $[\alpha]_D$ +26.8; ^{1}H NMR δ: 5.55 (dd, $J_{3',4'}=7.1$ Hz, $J_{4',5'}=7.1$ Hz, 1H, H-4′), 5.54 (d, $J_{1,2}=3.6$ Hz, 1H, H-1), 5.48 (d, 1H, H-3′), 5.43 (dd, $J_{3,4}=9.6$ Hz, $J_{2,3}=10.2$ Hz, 1H, H-3), 4.93 (dd, $J_{4,5}=10.3$ Hz, 1H, H-4), 4.92 (dd, 1H, H-2), 4.40–4.20 (m, 1H, H-5), 4.17–4.13 (m, 1H, H-5′), 4.09 (d, $J_{A,B}=11.7$ Hz, 1H, H-1′of AB) 4.04–4.01 (m, 2H, both H-6′), 4.00 (d, 1H, second H-1′ of AB), 3.73–3.52 (m, 10H, both H-6 and 4×CH_2O), 2.24, 2.125, 2.124, 2.11, 2.09, 2.02 (6×s, 6×3H, 6×$COCH_3$). ^{13}C NMR δ: 170.3, 170.2, 170.10, 170.06, 169.86, 169.82 (6×CO), 102.5 (C-2′), 89.5 (C-1), 79.8 (C-5′), 76.1 (C-4′), 76.0 (C-3′), 72.7 (C-6′), 72.5 (C-6), 70.44, 70.41, 70.25 (double intensity, 4×CH_2O), 70.22 (C-2), 69.8 (C-3), 69.7 (C-5), 69.5 (C-4), 63.8 (C-1′), 20.9, 20.7, 20.65, 20.64, 20.60, 20.56 (6×COCH_3). HRMS: 687.2132 [$C_{28}H_{40}O_{18}Na$ (M+Na^+) requires: 687.2107]. Anal. Calcd for $C_{28}H_{40}O_{18}$: C, 50.60; H, 6.07. Found: C, 50.8; H, 5.9%.

4.4.2. 1′,2,3,3′,4,4′-Hexa-*O*-acetyl-6,6′-*O*-(5,5-dimethyl-3,7-dioxanonan-1,9-diyl)-sucrose (10b). (Eluent: hexane/ethyl acetate, 1:1). Pale yellow oil, $[\alpha]_D$ +43.3. IR (film) ν 2955, 2872, 1750, 1370, 1224, 1097, 1038 cm^{-1}; ^{1}H NMR δ: 5.66 (d, $J_{1,2}=3.6$ Hz, 1H, H-1), 5.47–5.38 (m, 3H, H-3, H-3′, H-4′), 5.11 (dd, $J_{3,4}=9.8$ Hz, $J_{4,5}=9.8$ Hz, 1H, H-4), 4.88 (dd, $J_{2,3}=10.4$ Hz, 1H, H-2), 2.19, 2.10, 2.08, 2.06, 2.05, 2.01 (6×s, 6×3H, 6×$COCH_3$), 0.88, 0.86 (2×s, 2×3H, 2×CH_3). ^{13}C NMR δ: 170.22, 170.18, 170.02, 169.98, 169.93, 169.62 (6×CO), 103.3 (C-2′), 89.5 (C-1), 80.8, 75.7, 74.9, 70.3, 69.9, 69.5 and 69.1 (C-2,3,3′,4,4′,5,5′), 76.1, 75.9, 71.2 (double intensity), 71.0, 70.8, 70.6, 69.6, 63.1 (C-1′,6,6′ and 6×–OCH_2– from macrocyclic ring), 35.9 (*C*Me_2), 22.3, 22.2 (2×CH_3), 20.76, 20.72, 20.65, 20.61, 20.52 (double intensity, 6×COCH_3). HRMS: 773.2822 [$C_{33}H_{50}O_{19}Na$ (M+Na^+) requires: 773.2839]. Anal. Calcd for $C_{33}H_{50}O_{19}$: C, 52.80; H, 6.71. Found: C, 53.0; H, 6.5%.

4.4.3. 1′,2,3,3′,4,4′-Hexa-*O*-acetyl-6,6′-*O*-(1,2-diphenoxy-3-oxapentylidene)-sucrose (11b). (Eluent: hexane/ethyl acetate, 1:1). Colorless oil, $[\alpha]_D$ +46.6. IR (film) ν 2924, 2874, 1750, 1371, 1245, 1223, 1040 cm^{-1}; ^{1}H NMR δ: 6.92–6.86 (m, 4H, –C_6H_4–), 5.66 (d, $J_{1,2}=3.8$ Hz, 1H, H-1), 2.2, 2.09, 2.08, 2.05, 2.00, 1.99 (6×s, 6×3H, 6×$COCH_3$). ^{13}C NMR δ: 170.16, 170.15, 170.0 (double intensity), 169.9, 169.7 (6×CO), 149.1, 149.0, 121.5 (double intensity), 114.5, 114.4 (aromatic from macrocyclic ring), 103.6 (C-2′), 89.7 (C-1), 80.6, 75.9, 75.2, 70.4, 69.94, 69.7 and 69.1 (C-2,3,3′,4,4′,5,5′), 71.5, 71.4, 71.0, 70.9, 70.6, 69.86 (double intensity), 69.81, 69.3, 69.2, 63.1 (C-1′,6,6′ and 8×–OCH_2– from macrocyclic ring), 20.72, 20.67, 20.63 (double intensity), 20.57, 20.54 (6×COCH_3). HRMS: 867.2926 [$C_{38}H_{52}O_{21}Na$ (M+Na)$^+$ requires: 867.2893]. Anal. Calcd for $C_{38}H_{52}O_{21}$: C, 50.02; H, 6.20. Found: C, 49.8; H, 6.2%.

4.4.4. 1′,2,3,3′,4,4′-Hexa-*O*-acetyl-6,6′-(3-azabenzyl-penta-1,5-di-yl)-sucrose (14b). (Eluent: hexane/ethyl acetate, 2:3–1:2). Yellowish oil, $[\alpha]_D$ +28.1. IR (film) ν 2929, 1748, 1643, 1370, 1224, 1046 cm^{-1}; ^{1}H NMR [Signals from two conformers in ratio 1.72 (a-major) to 1 (b-minor)] δ: 5.64 (d, $J_{1,2}=3.6$ Hz, 1H, H-1, b), 5.57 (d, $J_{1,2}=3.5$ Hz, 1H, H-1, a), 2.22 (a), 2.20 (b), 2.12 (a), 2.112 (b), 2.107 (a), 2.104 (a+b), 2.90 (a), 2.072 (b), 2.067 (a), 2.063 (b), 2.01 (b), 2.00 (a), 1.96 (b) (7×s, 6×3H, 6×$COCH_3$ from a and 7×s, 6×3H, 6×$COCH_3$ from b). ^{13}C NMR δ: 170.9 (a), 170.7 (b), 170.07 (b), 170.06 (a), 170.00 (b), 169.98 (a), 169.93 (a), 169.90 (double intensity, 2×a), 169.88 (double intensity, 2×b), 169.81 (b), 169.77 (b), 169.67 (a) (7×CO from a and 7×CO from b), 103.7 (C-2, a), 103.4 (C-2, b), 90.0 (C-1′, a), 89.6 (C-1, b), 81.0 (a), 80.0 (b), 76.4 (a), 76.3 (b), 76.0 (a), 75.1 (b), 70.4 (b), 70.28 (a), 70.1 (b), 69.7 (a), 69.57 (a), 69.4 (b), 69.3 (b), 69.2 (a) (C-2,3,3′,4,4′,5,5′ from a and C-2,3,3′,4,4′,5,5′ from b), 71.4 (a), 71.2 (a+b), 70.94 (a), 70.91 (b), 70.8 (b), 70.26 (b), 69.51 (a), 62.9 (a), (C-1′,6,6′ and 3× –OCH_2– from macrocyclic ring from a and 5× –CH_2– from b), 50.0 (NCH_2–, b), 49.4 (NCH_2–, a), 47.2 (NCH_2–, a), 46.5 (NCH_2–, b). HRMS: 728.2407 [$C_{30}H_{43}O_{18}NNa$ (M+Na)$^+$ requires: 728.2372]. Anal. Calcd for $C_{30}H_{43}O_{18}N$: C, 51.06; H, 6.17; N, 1.98. Found: C, 51.3; H, 6.1; N, 2.0%.

4.4.5. 6,6′-Bis-(*O*-2-hydroxyethyl)-1′,2,3,3′,4,4′-hexa-*O*-benzylsucrose (12). *Method A*. 1′,2,3,3′,4,4′-Hexa-*O*-benzylsucrose (**4**) was converted into the diallyl ether as described previously[17] in 95% yield. Thus, obtained 6,6′-di-*O*-allyl-1′,2,3,3′,4,4′-hexa-*O*-benzylsucrose (0.974 g, 1.0 mmol) was dissolved in THF (13 mL) and H_2O (13 mL), to which $NaIO_4$ (1.3 g, 6.0 mmol) was added followed by OsO_4 (70 μL of a ~2% solution in toluene). The resulting mixture was stirred at room temperature for 1.5 h and then partitioned between water (100 mL) and ether (80 mL). The organic phase was collected, dried, concentrated and the residue was dissolved in CH_2Cl_2 (10 mL) and MeOH (10 mL). The solution was cooled to −78 °C, $NaBH_4$ (0.6 g) was added in several portions, the mixture was stirred for 1 h at −78 °C, and 2 h at room temperature. Water (40 mL) was added and product was extracted with CH_2Cl_2 (50 mL). The organic layer was dried, concentrated, and the crude product was purified by column chromatography (hexane/ethyl acetate, 1:1–2:3) to afford the title compound **12** (0.508 g, 0.5 mmol, 52%; 49% overall from **4**) as a pale yellow oil, $[\alpha]_D$ +44.3. IR (film) ν 2916, 2866, 1454, 1086, 1072, 736, 697 cm^{-1}; ^{1}H NMR δ: 6.12 (d, $J_{1,2}=4.0$ Hz, 1H, H-1). ^{13}C NMR δ: 139.2, 138.8, 138.3, 138.2, 137.98, 137.95 (6×C_q benzyl), 103.8 (C-2′), 87.8 (C-1), 83.4, 82.0, 79.02, 78.95 (double intensity), 77.1 and 70.6 (C-2,3,3′,4,4′,5,5′), 75.2, 74.6, 73.4, 73.1, 73.0, 72.9 (double intensity), 72.3, 71.9 (C-1′,6,6′, 6×OCH_2Ph), 68.49, 68.47, 61.69, 61.66 (4×CH_2 from 2-hydroxyethyl). *m*/*z*: 993.5 [M($C_{58}H_{66}O_{13}$)+Na^+]. Anal: Calcd for

$C_{58}H_{66}O_{13}\times\frac{1}{2}H_2O$: C, 71.07; H, 6.89. Found: C, 71.0; H, 7.1%.

Method B. 1′,2,3,3′,4,4′-Hexa-*O*-benzylsucrose (0.15 g, 0.170 mmol) was dissolved in toluene (15 mL), to which a 50% aqueous solution of sodium hydroxide (15 mL) and tetrabutylammonium bromide (0.01 g, 0.03 mmol) were added. Then *tert*-butyl bromoacetate (0.15 mL) was added dropwise and the mixture was stirred vigorously at room temperature for 4 h. Water (30 mL) and toluene (15 mL) were added to the mixture, and the organic layer was separated, washed with water (10 mL) and brine (10 mL), dried and concentrated. Purification of the crude product by column chromatography (hexane/ethyl acetate, 7:1) afforded compound **15** as colorless oil (0.13 g, 0.117 mmol, 69%), $[\alpha]_D$ +30.7; ^{1}H NMR δ: 5.7 (d, $J_{1,2}$= 3.64 Hz, 1H, H-1), 1.50 (s, 9H, *tert*-butyl), 1.49 (s, 9H, *tert*-Bu). ^{13}C NMR (125 MHz) δ: 169.4, 169.2 (2×CO), 139.0, 138.8, 138.4, 138.3, 138.2, 138.0 (6×C_q benzyl), 104.6 (C-2′), 90.1 (C-1), 83.8, 82.4, 81.9, 79.7 (double intensity), 77.4, 70.6 (C-2,3,3′,4,4′,5,5′), 81.3, 81.2 (2×C, C_q *tert*-butyl) 75.4, 74.7, 73.4, 72.9, 72.7, 72.5, 72.3, 71.2 (6×O*C*H$_2$Ph, 2×*C*H$_2$COO), 28.1 (6×CH$_3$). *m/z*=1133.4 [M($C_{66}H_{78}O_{15}$)+Na$^+$]. Anal. Calcd for $C_{66}H_{78}O_{15}\times H_2O$: C, 70.21; H, 7.09. Found: C, 70.2; H, 7.1%.

Compound **15** (0.126 g, 0.114 mmol) was dissolved in dry THF (45 mL), to which a suspension of $LiAlH_4$ (0.09 g, 2.368 mmol) in THF (15 mL) was added. The mixture was stirred at room temperature for 3 h and the excess of hydride was decomposed by careful addition of water. Then it was partitioned between water (75 mL) and diethyl ether (60 mL). The layers were separated and the aqueous phase was extracted with diethyl ether (2×60 mL). The extracts were combined, washed with water (30 mL), dried and the solvents were removed in vacuum to give product **14** (0.105 g, 0.108 mmol, 95%; 66% overall from **4**) identical in all respects with the material prepared in Method A.

4.4.6. 6,6′-Bis-(*O*-2-iodoethyl)-1′,2,3,3′,4,4′-hexa-*O*-benzylsucrose (13). Compound **12** (0.300 g, 0.31 mmol) was dissolved in CH_2Cl_2 (25 mL) containing triethylamine (3 mL) and DMAP (ca. 7 mg) and cooled to 0 °C. Mesyl chloride (0.073 mL, 0.9 mmol) was added, the reaction mixture was stirred for 15 min at 0 °C, 1 h at room temperature, and then partitioned between water (70 mL) and CH_2Cl_2 (100 mL). The organic layer was washed with water (50 mL), dried, concentrated, and the residue was dissolved in acetone (25 mL). Sodium iodide (1.3 g, 8.6 mmol) was added and the mixture was stirred under reflux for 6 h. Acetone was removed under reduced pressure, and the residue was partitioned between ethyl acetate (70 mL) and water (70 mL). The organic phase was washed with water (50 mL), dried, concentrated and the residue was purified by column chromatography (hexane/ethyl acetate, 5:1) to give **13** (0.253 g, 0.21 mmol, 69%) as a brown oil, $[\alpha]_D$ +29.2. IR (film) ν 2921, 2867, 1454, 1090, 1074, 1027, 735, 697 cm^{-1}; ^{1}H NMR δ: 5.71 (d, $J_{1,2}$= 3.6 Hz, 1H, H-1). ^{13}C NMR δ: 138.8, 138.7, 138.3, 138.20, 138.17, 137.9 (6×C_q benzyl), 104.7 (C-2′), 90.2 (C-1), 83.9, 82.3, 81.9, 79.8, 79.6, 77.4 and 70.6 (C-2,3,3′,4,4′,5,5′), 75.5, 74.9, 73.4, 73.0, 72.47, 72.42, 72.2, 72.0, 71.8, 71.1, and 69.2, 2.78, 2.69 (C-1′,6,6′, 6×O*C*H$_2$Ph and 4× –CH$_2$). *m/z*: 1213.2 [M($C_{58}H_{64}O_{11}I_2$)+Na$^+$]. Anal. Calcd for $C_{58}H_{64}O_{11}I_2+2H_2O$: C, 56.78; H, 5.26. Found: C, 56.8; H, 5.5%.

4.4.7. 1′,2,3,3′,4,4′-Hexa-*O*-benzyl-6,6′-(3-azabenzyl-penta-1,5-di-yl)-sucrose (14a). Compound **13** (0.48 g, 0.41 mmol) was dissolved in acetonitrile (25 mL), to which benzylamine (45 μL, 0.18 mmol) and Na_2CO_3 (0.15 g) were added. The reaction mixture was stirred under reflux for 50 h concentrated and the residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was separated, washed with water (30 mL), dried, and concentrated, and the product was isolated by column chromatography (hexane/ethyl acetate, 2:1–1:1) as a pale yellow oil (0.306 g, 0.29 mmol, 73%), $[\alpha]_D$ +28.7. IR (film) ν 2921, 2866, 1453, 1091, 1073, 1027, 734, 697 cm^{-1}; ^{1}H NMR δ: 5.44 (d, $J_{1,2}$=3.3 Hz, 1H, H-1). ^{13}C NMR δ: 139.5, 138.8, 138.7, 138.6, 138.3, 138.00, 137.98 (7×C from benzyl), 104.2 (C-2′), 90.1 (C-1), 84.9, 83.7, 81.6, 80.01, 71.98, 79.5, and 70.95 (C-2,3,3′,4,4′,5,5′), 75.4, 74.8, 73.4, 73.2, 72.7, 72.2 (double intensity), 71.7, 71.1, 70.7, 69.1, 60.4, 53.6, 53.2 (C-1′,6,6′, 7×O*C*H$_2$Ph and 4× –CH$_2$–). *m/z*: 1042.5 [M($C_{65}H_{71}O_{11}N$)+Na$^+$].

4.5. Reaction of chalcone with 2-nitropropane catalyzed by sucrose crown ether analogues[†]

Chalcone (200 mg, 0.96 mmol), 2-nitropropane (0.2 mL), and the appropriate crown analogue **5a**–**10a** and **14a** (0.067 mmol) were dissolved in dry toluene (5 mL). Potassium *tert*-butoxide (40 mg, 0.37 mmol) was added and the mixture was stirred at room temperature for 2 days. Then it was partitioned between water (25 mL) and ethyl acetate (25 mL), the organic phase was separated, washed with brine and water, dried and concentrated. The crude product **17** was isolated by column chromatography (hexane/ethyl acetate, 9:1). The optical purity of the adduct **17** was determined by comparison of the $[\alpha]_D$ value with the analogous data of the pure enantiomer.[18] The results are shown in Table 3.

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Transformations of hispanolone. Novel Michael adducts with in planta activity against rice blast

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Abstract—Two novel Michael adducts 9α-cyano-15,16-epoxy-7β-hydroxylabda-13(16),14-dien-6-one (**2**) and 9α-cyano-15,16-epoxy-7-hydroxylabda-7,13(16),14-trien-6-one (**3**) and the reduction product of **2**, 9α-cyano-15,16-epoxy-6β,7β-dihydroxylabda-13(16),14-diene (**4**), were synthesized from the naturally occurring labdane diterpene hispanolone (**1**). Compounds **2**–**4** exhibited in planta activity against the pathogenic rice blast fungus *Magnaporthe grisea*.

1. Introduction

The filamentous ascomycete fungus *Magnaporthe grisea* (Herbert) Barr (anamorph *Pyricularia grisea*=*P. oryzae*), the causal agent of the leaf spot disease known as rice blast, is a pathogen of over fifty different grass species including economically important crops such as rice, wheat, and barley.[1] Rice blast is a serious disease of cultivated rice in most rice growing nations (ca. 85 countries worldwide) and losses in excess of 50% of the global annual crop yield can be attributed directly to this pathogenic fungus.[2] In mature rice plants the fungus prevents maturation of the rice grains by attacking the panicle (the inflorescence that holds the rice grain). Infection of the panicle is known as 'neck blast' and can ultimately lead to total crop loss.[1,2] As part of an ongoing screening programme of both natural products and their semi-synthetic derivatives for in planta inhibition of pathogenic fungal infection we have identified two novel Michael adducts, 9α-cyano-15,16-epoxy-7β-hydroxylabda-13(16),14-dien-6-one (**2**) and 9α-cyano-15,16-epoxy-7-hydroxylabda-7,13(16),14-trien-6-one (**3**), of the naturally occurring labdane diterpene hispanolone (**1**), which exhibited in planta inhibition of rice blast. 9α-Cyano-15,16-epoxy-6β,7β-dihydroxylabda-13(16),14-diene (**4**), the reduction product of **2**, was also active against rice blast. The synthesis of **2**–**4** from **1** is outlined in Scheme 1.

2. Results and discussion

Hispanolone was first isolated from *Ballota hispanica*[3] and has subsequently been isolated from other Lamiaceae sp.[4–7] including the endemic southern African medicinal plant *B. africana*.[8] Hispanolone is an abundant constituent of this latter plant and can be readily dehydrated to afford hispanone (**5**). Hispanolone and hispanone have proved to be useful precursors for the semi-syntheses of a number of related diterpenes[9–12] and we recently, converted **1** into 6β-hydroxy-15,16-epoxylabda-8,13(16),14-trien-7-one (**6**), the enantiomer of a diterpene metabolite previously isolated from *B. aucheri*.[13] It was en route to **6** that we serendipitously prepared **2** and the minor compounds **3**, **7** and **8** (Scheme 1).

An acetone extract of air-dried *B. africana* leaves was concentrated in vacuo and the resultant solution adsorbed onto HP-20 polystyrene resin. Subsequent gradient elution (acetone/water) of this resin afforded **1** in a substantially enhanced yield (1.5%) compared to that previously obtained from this plant (0.8%).[8] Facile dehydration of **1** with iodine in refluxing anhydrous benzene gave **5** as pale yellow needles.[13] The treatment of **5** with manganic acetate [$Mn(OAc)_3$] in refluxing anhydrous benzene[13,14] gave a

Keywords: Labdane diterpene; Hispanolone; Michael adduct; Rice blast.
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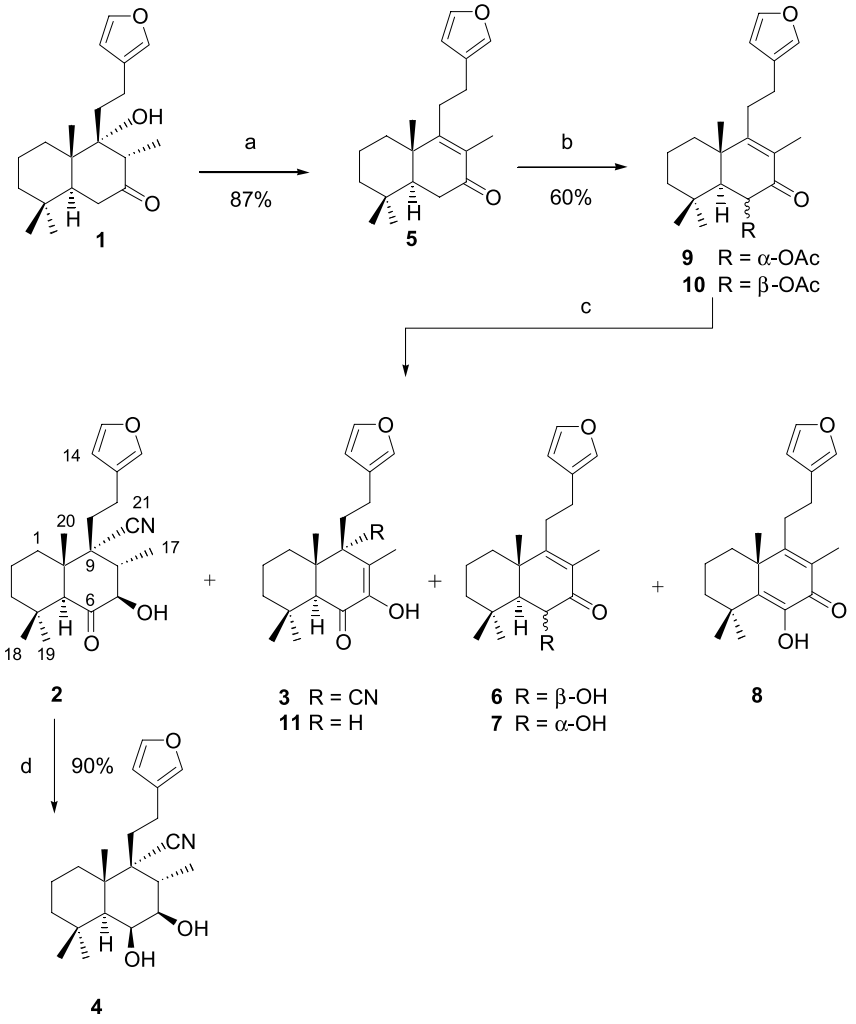


Scheme 1. (a) I_2, C_6H_6, reflux; (b) $Mn(OAc)_3$, C_6H_6, reflux; (c) KCN, EtOH (95%); (d) LAH, THF, reflux.

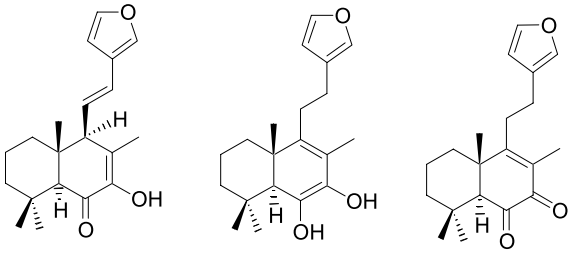
5:2 ratio of 6α-acetoxy- and 6β-acetoxyhispanone (**9** and **10**, respectively), in 60% overall isolated yield. Unfortunately, we were unable to improve the yields of **9** and **10** using the recently published method of Demir et al., in which the addition of up to 10% acetic acid to the reaction mixture was reported to enhance the manganic acetate mediated α′-acetoxylation of α,β-unsaturated enones in benzene.[15] Nonetheless, our preparation of **9** and **10** from **5** constitutes a significant improvement in the yield (19%) of these compounds achieved by Rodríguez and co-workers for this transformation.[9]

Our initial attempts at converting **10** to the *B. aucheri* metabolite (**6**), via saponification with ethanolic KOH, did not yield the desired product and instead gave **7** (4%) and the two diosphenols **8** (26%) and **11** (30%). We have previously isolated **8** as a minor product from Vedejs' oxidation of hispanone.[13] The ^{1}H NMR data and optical rotation of **11** ($[\alpha]_D+2$) were compatible with those reported for dihydro-7-hydroxyhedychenone ($[\alpha]_D+1$).[16] Compound **11** is the Δ^{11} hydrogenation product of 7-hydroxyhedychenone (**12**), a furanolabdane diterpene previously isolated from the rhizomes of *Hedychium*

Table 1. ^{1}H (400 MHz, $CDCl_3$), ^{13}C (100 MHz, $CDCl_3$) data for compound **11**

Carbon	δ_C ppm (mult.)	δ_H ppm (mult., int., *J*/Hz)
1	38.4 (t)	1.15 (1H, m), 1.81 (1H, d, 12.9)
2	18.0 (t)	1.48 (2H, m)
3	43.0 (t)	1.18 (1H, m), 1.40 (1H, d, 15)
4	32.5 (s)	
5	62.4 (d)	2.10 (1H, s)
6	195.2 (s)	
7	143.9 (s)	
8	126.4 (s)	
9	53.9 (d)	2.17 (1H, br d, 6.9)
10	43.6 (s)	
11	28.2 (t)	1.68 (2H, m)
12	27.1 (t)	2.49 (1H, m)
		2.65 (1H, m)
13	124.5 (s)	
14	110.9 (d)	6.29 (1H, s)
15	143.0 (d)	7.37 (1H, s)
16	138.9 (d)	7.25 (1H, s)
17	13.58 (q)	1.92 (3H, s)
18	33.4 (q)	1.17 (3H, s)
19	21.5 (q)	1.13 (3H, s)
20	14.8 (q)	0.84 (3H, s)
7-OH		6.22 (1H, s)

spicatum.[16] Sharma et al.,[16] provided limited ^{1}H NMR data of **11** acquired at 60 MHz and the fully assigned ^{1}H and ^{13}C NMR data of **11**, prepared from the saponification of **10**, are accordingly presented in Table 1.



Interestingly, the saponification of the 6α-acetoxy epimer (**9**) with ethanolic KOH afforded the same three products in similar yields suggesting that the enediol (**13**) is a possible precursor of **7** and **11**. The formation of **8** is more difficult to rationalise as this transformation possibly involves initial oxidation of either **6** or **7** to give the diketone **14**. Although no diketone was evident amongst the reaction products an autooxidative transformation of either **6** or **7** to **14** is supported by evidence for the facile α-oxidation of ketones in aerated ethanolic KOH solutions.[17] Subsequent keto–enol tautomerism of **14** would afford the conjugated enol **8**.

The results of the unsuccessful KOH saponification of **9** and **10** prompted us to investigate other ester hydrolyses and we accordingly applied a milder KCN mediated hydrolysis procedure to **9** and **10** (Scheme 1).[18] Semi-preparative HPLC separation of the reaction products from this hydrolysis gave the unexpected Michael adduct (**2**) as the major product (45%) together with three minor products **3** (9%), **7** (1%) and **8** (2%). Both **9** and **10** gave the same product mixture, thus making prior separation of the epimers unnecessary.

The incorporation of a nitrile moiety into the diterpene skeleton of **2** was supported firstly by the molecular formula ($C_{21}H_{29}NO_3$) established from HRFABMS data and secondly from a nitrile stretching absorption (ν_{max} 2228 cm^{-1}) in the IR spectrum of **2**. The nitrile functionality was positioned at C-9 (δ_C 53.4) from the three bond HMBC correlations (Fig. 1) observed between neighbouring protons and the nitrile carbon (C-21, δ_C 120.3). HMBC data were similarly instrumental in confirming the 1,2-transposition of the carbonyl moiety,

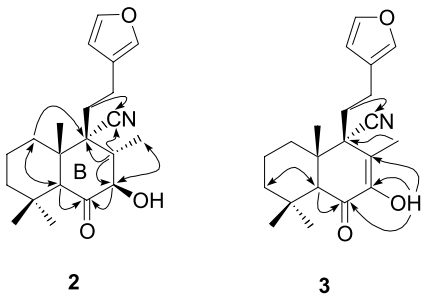


Figure 1. Key HMBC correlations used to establish the structure of ring B in compounds **2** and **3**.

originally at C-7 in **9** and **10**, to C-6 in **2** (Fig. 1). The singlet attributed to H-5 (δ_H 2.73) together with the doublet and the doublet of quartets assigned, respectively, to the H-7 (δ_H 3.92) and H-8 (δ_H 1.87) resonances in the ^{1}H NMR spectrum of **2** further supported the substitution pattern proposed for ring B. The *trans* diaxial relationship between H-7 and H-8 was confirmed from the coupling constant ($J_{7,8}$ = 10.8 Hz) and a NOESY correlation between the α-axial proton H-7 and both H-5 and the protons of the α-equatorial methyl substituent at C-8. The α-axial orientation of the nitrile moiety at C-9 was proposed from NOESY correlations between the C-11 methylene protons (δ_H 1.54 and 1.98) and both the H-8 methine proton and the protons of the angular methyl group at C-10 (δ_H 0.89). The ^{1}H and ^{13}C NMR data of **2**, assigned from exhaustive 2D NMR experiments, are presented in Table 2.

Table 2. ^{1}H (400 MHz, $CDCl_3$), ^{13}C (100 MHz, $CDCl_3$) data for compounds **2** and **3**

	2		**3**	
Carbon	δ_C ppm (mult.)	δ_H ppm (int., mult., *J*/Hz)	δ_C ppm (mult.)	δ_H ppm (int., mult., *J*/Hz)
1	35.2 (t)	1.75 (2H, br t, 6.2)	35.1 (t)	1.80 (2H, m)
2	18.1 (t)	1.61 (2H, m)	17.8 (t)	1.60 (2H, m)
3	41.6 (t)	1.28 (1H, m), 1.38 (1H, m)	41.9 (t)	1.32 (1H, m) 1.45 (1H, m)
4	32.7 (s)		32.8 (s)	
5	59.7 (d)	2.73 (1H, s)	58.6 (d)	2.75 (1H, s)
6	209.0 (s)		193.6 (s)	
7	77.3 (s)	3.92 (1H, br d, 10.8)	145.0 (s)	
8	47.1 (d)	1.87 (1H, dq, 10.8, 6.5)	120.0 (s)	
9	53.4 (s)		46.0 (s)	
10	47.0 (s)		52.5 (s)	
11	31.6 (t)	1.54 (1H, m), 1.98 (1H, m)	31.6 (t)	1.85 (1H, m), 1.99 (1H, m)
12	24.6 (t)	2.70 (2H, m)	24.7 (t)	2.82 (m)
13	123.6 (s)		123.6 (s)	
14	110.5 (d)	6.27 (1H, d, 0.9)	110.5 (d)	6.29 (1H, d, 0.9)
15	143.2 (d)	7.36 (1H, t, 1.6)	143.3 (d)	7.38 (1H, t, 1.6)
16	138.8 (d)	7.26 (1H, br s)	138.8 (d)	7.28 (1H, br s)
17	14.7 (q)	1.42 (3H, d, 6.5)	12.6 (q)	2.01 (3H, s)
18	32.3 (q)	1.02 (3H, s)	33.4 (q)	1.24 (3H, s)
19	22.1 (q)	1.30 (3H, s)	21.5 (q)	1.16 (3H, s)
20	15.8 (q)	0.89 (3H, s)	15.7 (q)	1.00 (3H, s)
21	120.3 (s)		119.5 (s)	
7-OH		3.71 (1H, br d, 3.0)		6.46 (br s)

The mechanism for the formation of **2** is of interest and appears to involve an initial Michael addition of a cyanide nucleophile with re facial selectivity to the α,β-unsaturated ketone in either **9** or **10**, followed by a 1,2-carbonyl transposition through a classic Lobry de Bruyn-van Ekenstein rearrangement of an α-hydroxy carbonyl group. This rearrangement inhibits reversal of the Michael addition with loss of the cyanide. It is unclear at which stage hydrolysis of the acetate occurs.

The structure of the nitrile-containing minor metabolite (**3**) was established by recourse to 2D NMR data and comparison of the IR and the ^{1}H and ^{13}C NMR data (Table 2) of this compound with those of **2**. Eight of the nine degrees of unsaturation implied by the molecular formula of

3 ($C_{21}H_{27}NO_3$) were attributed to the nitrile moiety, the furanolabdane skeleton and the carbonyl functionality (δ_C 193.6). The single remaining double bond equivalent was assigned to a tetra-substituted olefin from the chemical shifts of two vinylic quaternary carbons (δ_C 125.0 and 140.0) in the ^{13}C NMR spectrum of **3** (Table 2). Key HMBC correlations (Fig. 1) positioned the carbonyl moiety at C-6 and confirmed that this group was conjugated with a Δ^7-enolic olefin. An X-ray structural analysis of **3** (Fig. 2) unequivocally confirmed the C-9α position of the nitrile substituent proposed from a NOESY correlation between the C-11 methylene protons (δ_H 1.85 and 1.99) and the C-20 methyl protons (δ_H 1.00).

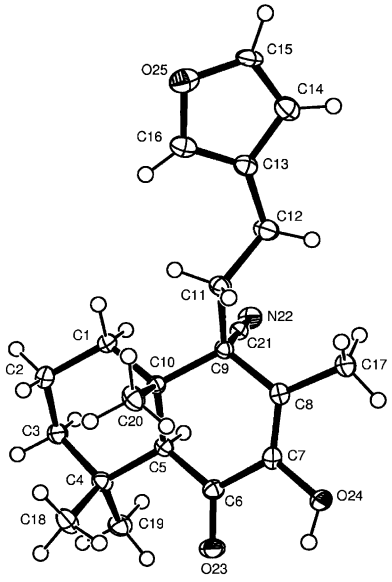


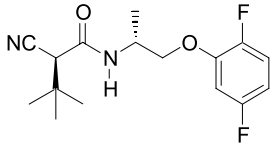
Figure 2. A view of a molecule of 9α-cyano-15,16-epoxy-7-hydroxylabda-7,13(16),14-trien-6-one (**3**) from the crystal structure showing the numbering scheme employed. Anisotropic atomic displacement ellipsoids for the non-hydrogen atoms are shown at the 50% probability level.[19]

Preliminary in vitro screening of **2** against a panel of plant diseases suggested that this compound possessed potential anti-fungal activity. In an attempt to obtain further analogues of **2** for in planta screening against several pathogenic plant fungi, the diol nitrile **4** was prepared by LAH reduction of **2**. The β-axial assignment of the secondary alcohol moiety at C-6 followed from the small coupling constants ($J_{5,6}=1.6$ Hz and $J_{6,7}=3.1$ Hz) between the H-6 proton (δ_H 4.28) and H-5 (δ_H 1.44) and between H-6 and H-7 (δ_H 3.53).

Table 3. One day protectant percent disease control of compounds **2**, **3** and **4** against *M. grisea* and *P. recondita*

Compound	Concentration (ppm)	% Control of *M. grisea*	% Control of *P. recondita*
2	200	90	80
	50	33	22
	12.5	21	22
3	200	91	—
4	200	83	56
	50	29	22
	12.5	13	0
Tebuconazole	25	63	100
Azoxystrobin	50	99	99
	25	99	100
	12.5	99	100

Compounds **2**–**4** all exhibited significant control of rice blast (*M. grisea*) at a concentration of 200 ppm in initial in planta screens. Interestingly, **2** also exhibited an 80% control of wheat brown rust fungus *Puccinia recondita* f.sp. *tritici* at this concentration. Unfortunately, the ability of both **2** and **4** to prevent the infection of plants by *M. grisea* or *P. recondita* declined with dilution. This trend was not observed in the commercial fungicide (e.g., azoxystrobin) control experiments (Table 3). A paucity of **3** prevented the acquisition of similar dose response data for this compound.



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Compounds possessing both a nitrile functionality and activity against rice blast are not unprecedented. The nitrile (**15**) and a series of related analogues exhibited excellent control of rice blast disease in outdoor field trials.[20,21] Interestingly, the role of **15** in the control of *M. grisea* infection has been linked to this compound's ability to inhibit the enzyme scytalone dehydratase (SD) necessary for the biosynthesis of fungal melanin in rice blast.[20] The production of fungal melanin facilitates the penetration of the rice leaf by *M. grisea* and therefore, enhances infection of the plant by this pathogenic fungus. The SD inhibition of **2**, **3** and **4**, if any, is unknown.

3. Conclusion

The abundant furanolabdane diterpene metabolite hispanolone **1**, isolated from the endemic South African plant *B. africana*, continues to provide a suitable starting point for the semi-synthesis of a number of bioactive diterpene compounds. In this paper the semi-synthesis of **2** and **3**, arising from a novel tandem Michael addition/Lobry de Bruyn–van Ekenstein rearrangement of both 6α and 6β-acetoxy analogues (**9** and **10**) of dehydrohispanolone **5**, is described. Both **2** and **3** and the reduction product of **2**, diol nitrile **4**, exhibited >80% inhibition of the pathogenic plant fungus, *M. grisea* (rice blast) at a concentration of 200 ppm.

4. Experimental

Diaion HP-20 polystyrene beads (supplied by Supelco) and Kieselgel 60 (230–400 mesh) were used for initial chromatographic separations. Semi-preparative HPLC was performed using a Whatman's Partisil 10 column (10 mm i.d., length 50 cm). Optical rotations were measured using a Perkin-Elmer 141 polarimeter at the sodium *D* line (598 nm). IR spectra were recorded on a Perkin Elmer Spectrum 2000 FT-IR spectrometer with the compounds as films (neat) on NaCl discs. The NMR spectra were acquired on a Bruker AVANCE 400 MHz spectrometer using

standard pulse sequences. Chemical shifts are reported in ppm, referenced to residual solvent resonances ($CDCl_3$ δ_H 7.25, δ_C 77.0), and coupling constants are reported in Hz. HRFABMS data were obtained on a JEOL SX102 spectrometer.

4.1. Isolation of hispanolone (1) from *B. africana*

Aerial parts of *B. africana* were collected 40 kms south west of Grahamstown, South Africa in November 2003. Air-dried leaves (250 g) were steeped in Me_2CO (3.5 L) for 3 days, the Me_2CO solution concentrated in vacuo, decolourised with activated charcoal (20 g), adsorbed onto HP-20 beads and eluted sequentially with aliquots (1.5 L) of 40 and 60% aqueous acetone. The fraction eluted with 60% aqueous acetone was diluted with H_2O (1.5 L) and allowed to stand at 4 °C for 4 days to afford **1** (3.82 g, 1.52%) as white crystalline plates (acetone/water); mp 133–135 °C, lit.[3] 142–144 °C; $[\alpha]_D^{32}$ −18.8 (*c* 6.35, $CHCl_3$), lit.[3] −17.6; IR, ^1H and ^{13}C NMR data consistent with published values.[3,8]

4.2. Dehydration of 1 and α-acetoxylation of hispanone (5)

The procedures for the dehydration of **1** to give **5** and the subsequent α-acetoxylation of **5** to give the epimeric acetates **9** and **10** have been previously reported.[13]

4.3. Saponification of 9 and 10

A solution of **9** (163 mg, 0.46 mmol) in EtOH (30 mL) and 1.5 M KOH (5.0 mL) was heated at 70 °C for 1 h. The reaction mixture was cooled, 1.0 M HCl (10.0 mL) added and the EtOH removed in vacuo to give a cloudy suspension that was extracted with CH_2Cl_2 (3×15 mL). The organic phases were combined, washed with 5% aqueous $NaHCO_3$ (10 mL), dried (anhydrous $MgSO_4$) and concentrated to give a yellow oil (106 mg). Column chromatography (4:1 hexane/EtOAc) and normal phase semi-preparative HPLC of the oil (19:1 hexane/EtOAc) gave **7** (7 mg, 4%),[13] (**8**, 45 mg, 30%)[13] and **11** (38 mg, 26%). The saponification procedure was repeated on **10** (58 mg, 0.16 mmol) and the same products **7**, **8** and **11** were obtained in similar yields (6, 39 and 38%).

4.3.1. 11,12-Dihydro-7-hydroxyhedychenone (11). Yellow oily solid; $[\alpha]_D^{25}$ +2 (*c* 0.89, $CHCl_3$), lit.[16] +0.7; IR ν_{max} 3382 (br), 2930, 2863, 1692, 1615, 1615, 1471, 1385, 1026, 874, 774 cm^{-1}; ^1H and ^{13}C NMR data presented in Table 1; EIMS *m/z* (rel. int.) 316 [M^+] (6), 301 (100), 283 (43), 255 (17), 229 (12), 192 (17), 175 (12), 161 (26), 133 (14), 96 (11); HRFABMS *m/z* 317.2116 (calcd for $C_{20}H_{29}O_3$ [$(M+H)^+$], 317.2117).

4.4. KCN mediated hydrolysis of 9 and 10

A solution of a 5:2 mixture of **9** and **10** (152 mg, 0.4 mmol) and KCN (70 mg, 1.08 mmol) in 95% EtOH (3 mL) was refluxed (24 h). The ethanol was removed in vacuo, and the white residue taken up in water (5 mL) and extracted with EtOAc (3×5 mL). The organic fractions were combined, dried (anhydrous $MgSO_4$) and concentrated to give a pale yellow oil (150 mg) that after normal phase HPLC (9:1 hexane/EtOAc) gave **2** (65 mg, 45%), **3** (14 mg, 9%), **7** (2 mg, 1%)[13] and **8** (3 mg, 2%).[13]

4.4.1. 9α-Cyano-15,16-epoxy-7β-hydroxylabda-13(16), 14-dien-6-one (2). White amorphous solid; $[\alpha]_D$ +53 (*c* 0.80, $CHCl_3$), IR ν_{max} 3469, 2980, 2874, 2228, 1715, 1464, 1366, 1046, 874, 780 cm^{-1}; ^1H and ^{13}C NMR data see Table 2; EIMS *m/z* (rel. int.) 343 [M^+] (6), 326 (17), 314 (5), 262 (8), 182 (21), 139 (29), 121 (25), 95 (100), 67 (46); HRFABMS *m/z* 344.2226 (calcd for $C_{21}H_{30}NO_3$ [$(M+H)^+$], 344.2226).

4.4.2. 9α-Cyano-15,16-epoxy-7-hydroxylabda-7,13(16), 14-trien-6-one (3). White needles (from benzene/hexane); mp 138–139 °C; $[\alpha]_D$ −44 (*c* 0.73, $CHCl_3$); IR ν_{max} 3397 (br), 2927, 2863, 2351, 2222, 1683, 1456, 1386, 1122, 876, 792 cm^{-1}; ^1H and ^{13}C NMR data see Table 2; EIMS *m/z* (rel. int.) 341 [M^+] (13), 326 (100), 243 (12), 167 (15), 95 (17), 81 (19), 67 (15), 55 (11); HRFABMS *m/z* 341.1992 (calcd for $C_{21}H_{27}NO_3$ [$(M)^+$], 341.1990).

4.5. LAH reduction of 2

A solution of $LiAlH_4$ (3.6 mg, 0.038 mmol) and **2** (13 mg, 0.03 mmol) in dry THF (4 mL) was refluxed (5 h), cooled and acidified. The solvent was removed in vacuo and the residue taken up in EtOAc (5 mL), washed with H_2O (3× 2 mL), dried (anhydrous $MgSO_4$) and concentrated to yield a yellowish oil (17 mg). Subsequent purification with normal phase HPLC (4:1 hexane/EtOAc) yielded **4** (13 mg, 0.038 mmol, 98%).

4.5.1. 6,7-Hydroxy-9-carbonitrile-15,16-epoxylabda-13(16),14-dienol (4). Colourless oil; $[\alpha]_D^{19}$ +37 (*c* 0.5, $CHCl_3$); IR ν_{max} 3437, 2928, 2859, 2852, 2221, 1365, 1160, 1023, 871, 784 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.03 (3H, m, H_3-18 or H_3-19); 1.25 (3H, m, H_3-19 or H_3-18); 1.26 (3H, m, H_3-20); 1.27 (3H, m, H_3-17); 1.28 (1H, m, H-3a); 1.40 (1H, m, H-3b); 1.44 (1H, d, J=1.6 Hz, H-5); 1.53 (1H, dd, J=6.4, 2.7 Hz, H-11a); 1.55 (1H, m, H-2a); 1.60 (2H, m, H_2-1), 1.66 (1H, m, H-2b); 1.96 (1H, ddd, J= 14.4, 12.5, 6.9 Hz, H-11b); 2.11 (1H, m, H-8); 2.65 (2H, m, H_2-12); 3.53 (1H, dd, J=10.9, 3.5 Hz, H-7); 4.28 (1H, dd, J=3.1, 1.7 Hz, H-6); 6.27 (1H, d, J=1.8 Hz, H-14); 7.24 (1H, br s, H-16); 7.35 (1H, t, J=1.5 Hz, H-15); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.2 (q, C-17); 17.1 (q, C-20); 18.6 (t, C-2); 24.5 (q, C-18 or C-19); 24.6 (t, C-12); 31.7 (t, C-11); 33.4 (q, C-19 or C-18); 34.4 (s, C-4); 37.6 (t, C-1); 38.0 (d, C-8); 41.9 (s, C-10); 43.0 (t, C-3); 51.2 (d, C-5); 54.1 (s, C-9); 69.6 (d, C-6); 74.3 (d, C-7); 110.6 (d, C-14); 121.4 (s, C-21); 124.0 (s, C-13); 138.7 (d, C-16); 143.0 (d, C-15); HRFABMS *m/z* 345.2304 (calcd for $C_{21}H_{31}NO_3$ [$(M+H)^+$], 345.2304).

4.6. In planta test methods

For evaluations in 1 day protectant tests, samples of the compounds were dissolved in acetone at 2000 ppm, then diluted in acetone to 500 and 125 ppm. Samples were then brought to final concentrations of 200, 50 and 12.5 ppm by addition of 9 volumes of milli-Q water containing 110 ppm Triton X-100. Applications were made in 20 mL spray

volumes using a turntable sprayer equipped with two Spraying Systems Co. 1/4JAUPM-SS nozzles with 4010055 fluid caps and a spray pressure of 206 kPa.

Inoculation of plants was done by spraying suspensions of 5×10^5–6×10^6 conidia per mL, depending on the pathogen, 1 day after application. Conidial suspensions were prepared with de-ionized water containing 3 drops of Tween-20 per 100 mL of suspension. Inoculated plants were placed in a dew room (99–100% relative humidity, 20 °C) overnight to allow infection. The plants were then moved to either a greenhouse or growth chamber at a suitable temperature, daylength and humidity for expression of the disease.

Evaluation of disease control were made 6 days after inoculation in the case of *M. grisea* and 7 days after inoculation in the case of *P. recondite*, by visual estimation of disease severity. Percent disease control was calculated from disease severity ratings by the calculation: $\%DC=(1-\%DS_{trt}/\%DS_{untrt})\times100$, where %DC is percent disease control; $\%DS_{trt}$ is the observed percent disease severity for treated plants; and $\%DS_{untrt}$ is the observed percent disease severity for untreated controls.

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19. X-ray analysis of **3**. Intensities were recorded from a cubic fragment using Φ- and ω-scans on a Nonius Kappa CCD diffractometer employing Mo K_α-radiation with the crystal cooled to 113(2) K in a nitrogen stream. Crystal data for **3**: $C_{21}H_{27}NO_3$, $M=341.44$, monoclinic, space group $P2_1$ (no. 4), $a=6.2718(1)$ Å, $b=14.6696(2)$ Å, $c=9.7782(2)$ Å, $\beta=103.735(1)°$, $V=873.92(3)$ Å^3, $Z=2$, $D_c=1.298$ Mg/m^3, μ(Mo K_α)$=0.086$ mm^{-1}, $F(000)=368$. A total of 3700 reflections were collected, of which 3410 were observed [$I>2\sigma(I)$]. The structure was solved by direct methods and refined on F^2 using all data, with non-hydrogen atoms treated anisotropically. All H atoms were located but were added in idealised positions in a riding model. The final R factors were $R_1=0.0385$ (all data), 0.0334 (observed data), $wR_2=0.0846$ (all data), 0.0816 (observed data) for 231 parameters. Crystallographic data (excluding structure factors) for this compound have been deposited at the Cambridge Crystallographic Data Centre as supplementary material no. 262101.
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3′-Selective modification of a 4′,5′-didehydro-5′-deoxy-2′,3′-epoxyuridine using nucleophiles

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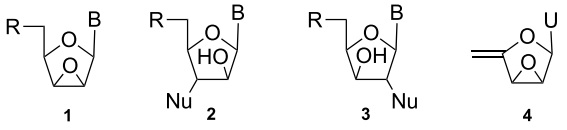
Abstract—1-(2,3-Anhydro-5-deoxy-4,5-didehydro-α-L-*erythro*-pent-4-enofuranosyl)uracil **4** was obtained by the treatment of 5′-iodo-2′,3′-epoxyuridine **5** with LiHMDS in excellent yield. The pyrimidine nucleoside **4** possesses quite unique vinyl epoxide moiety within the molecules. The reactions of **4** with a variety of nucleophiles gave 3′-substituted pyrimidine nucleosides without the formation of the corresponding 2′-substituted isomers. In the case of NaN_3 or PhSH, the corresponding 5′-adduct was obtained as a minor product together with the expected 3′-adduct.

1. Introduction

Chemical modification of nucleosides has been very important for the synthesis of biologically active compounds such as anti-viral agents[1] and synthetic oligonucleotide probes.[2] A number of modifications of the sugar moiety in nucleosides have been carried out up to now. Especially, a wide variety of attempts have been made to devise novel methodologies to functionalize the 2′- and 3′-sites of nucleosides in connection with AZT, a potent anti-HIV agent. 2′,3′-Anhydro-β-D-lyxofuranosyl pyrimidine nucleosides (**1**) first synthesized by Fox et al.,[3] are useful key intermediates for the 2′- or 3′-modified pyrimidine nucleoside analogues. A large number of reactions of **1** with a variety of nucleophiles have been investigated.[4,5] However, a limitation to these methods is the poor regio-control of 2′- or 3′-addition of nucleophiles. Usually, 3′-adducts (**2**) were obtained as major products together with minor 2′-adducts (**3**). Although a few reports indicated that 3′-adducts (**2**) were obtained selectively[5], the yields of the 3′-adducts were very low and the existence of unisolable 2′-adducts (**3**) was suspected. Previously, we have reported the reaction of **1** (R = OH, or OR′) with $AlMe_3$ with a view to the regioselective 2′-attack of the methyl group by the cyclic coordination effect of $AlMe_3$ between 5′- and epoxide-oxygen, while a mixture of the 3′- and 2′-adduct (**2** and **3**) was obtained[6] as well as other reported results.[4]

In order to develop an entirely regioselective nucleophilic attack toward the epoxide moiety of 2′,3′-anhydro nucleosides, we expected the use of a conjugated epoxide with a double bond such as **4** would lead to a better result. Here we would like to report the synthesis of 1-(2,3-anhydro-5-deoxy-4,5-didehydro-α-L-*erythro*-pent-4-enofuranosyl)uracil (**4**) and its application to the regioselective synthesis of 3′-adducts (**2**).[7]



2. Results and discussion

The synthesis of 4′,5′-didehydro-5′-deoxy-2′,3′-epoxyuridine (**4**) was achieved by treatment of 5′-iodo-2′,3′-epoxyuridine (**5**)[3c] with *t*-BuOK, an appropriate non-nucleophilic base, at room temperature (64%), while the use of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as a base gave a complex mixture. After optimization of the reaction conditions, we finally found the use of LiHMDS, a bulky and totally non-nucleophilic base, in DMF at 0 °C gave **4** in 92% yield (Scheme 1).

Therefore, the reaction of **4** using a variety of nucleophiles was investigated. We first carried out the reaction of **4** with

Keywords: Nucleophile; Nucleoside; Adduct.
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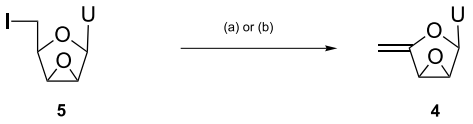
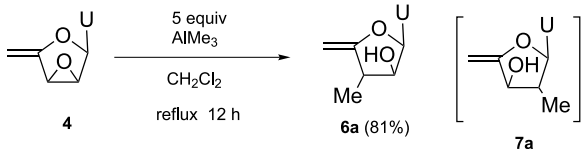


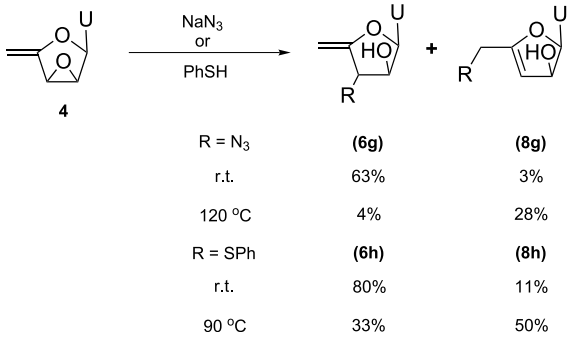
Scheme 1. Synthesis of 1-(2,3-anhydro-5-deoxy-4,5-didehydro-α-L-*erythro*-pent-4-enofuranosyl)uracil **4** from **5**. Reactant and condition: (a) *t*-BuOK, DMF, rt (64%) or (b) LiHMDS, DMF, 0 °C, Ar (92%).

5 equiv of $AlMe_3$ in CH_2Cl_2 under reflux conditions. The regioselective nucleophilic addition of a methyl group to epoxide proceeded on the 3′-position and the 3′-adduct (**6a**) was obtained as the sole product in 81% isolated yield and the isomeric 2′-adduct (**7a**) and other by-products were not detected in the reaction mixture (Scheme 2). To ascertain the generality of this regioselective reaction, treatment of **4** with various nucleophiles was investigated. The results are summarized in Table 1. When MeONa was used as a nucleophile, reflux conditions were required for completion of the reaction. On the other hand, all other additions were achieved at room temperature (entries 3–8). Reactions using $BnNH_2$, $AlMe_3$, MeONa and NaN_3 proceeded without an additional base (entries 1–3, and 7). In the case of BzOH, BzSH and PhSH, Et_3N was employed as a base (entries 5, 6, and 9). When NaH was employed as a base instead of Et_3N for the reaction of BzOH, a lowering of the yield of **6e** and a remaining of the starting material **4** were observed. The reaction of BzOH was very slow (168 h) and the corresponding arabinofuranosyl derivative (**6e′**) was formed as a by-product based upon the hydrolysis of (**6e**), although the 3′-addition of BzSH was completed within 48 h because of the high nucleophilicity.



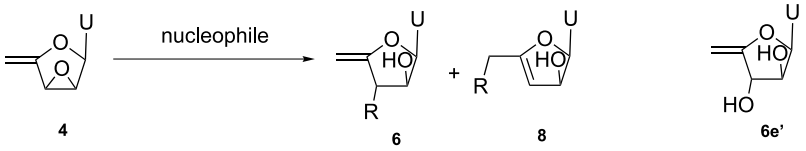
Scheme 2. Reaction of **4** with $AlMe_3$.

Next, we investigated the reaction of **4** with NaN_3 in DMF at room temperature. Similar to the other reactions (entries 1–6), 3′-adduct (**6g**) was afforded as a major product together with 5′-adduct (**8g**),[8] formed by the nucleophilic addition onto the 5′-position of **4** as a side product (3%) (Scheme 3 and Table 1, entry 7). When this reaction was carried out at 120 °C, the 5′-adduct (**8g**) was afforded as a major product (28%) along with 3′-adduct (**6g**) as a minor product (4%) (Scheme 3). In addition, a similar tendency was observed in the reaction of **4** with PhSH (Scheme 3 and Table 1, entry 8). In these reactions, formation of a 2′-adduct (**7**) was never observed as well as in other reactions of **4** with nucleophiles (entries 1–6). Usually, the 3′-cation is more stable than the 2′-cation owing to the electron-withdrawing effect of the 1′-uracil moiety of 2′,3′-epoxyuridine derivatives (**1**) and the formation of 3′-adduct (**2**) was superior to the formation of 2′-adduct (**3**), although the effect is not enough to perform the regioselective 3′-nucleophilic addition. On the other hand, the 3′-position of **4** is the allylic position and it is obvious that the 3′-cation is strongly stabilized by the conjugation with the 4′,5′-double bond as an allylic cation (Fig. 1). Therefore, regioselective nucleophilic addition onto the 3′-position occurred readily and the 3′-adduct (**6**) was obtained regioselectively. In the reaction with a comparatively soft nucleophile such as NaN_3 or PhSH, 5′-adduct (**8**) was also formed as a by-product.[9,10]



Scheme 3. Reaction of **4** with NaN_3 or PhSH.

Table 1. Nucleophilic addition to **4**



Entry	Nucleophile	Additional base	Solvent	Temperature	*T* (h)	R	Yield (%)[a]		
							Product	**6**	**8**
1	$AlMe_3$	—	CH_2Cl_2	reflux	12	Me	**a**	81	nd[b]
2	MeONa	—	MeOH	reflux	6	OMe	**b**	80	nd[b]
3	$BnNH_2$	—	CH_2Cl_2	rt	24	NHBn	**c**	81	nd[b]
4	$CH_2(CO_2Me)_2$	MeONa	MeOH	rt	12	$CH(CO_2Me)_2$	**d**	69	nd[b]
5	BzOH	Et_3N	CH_2Cl_2	rt	168	OBz	**e**	61	nd[b]
6	BzSH	Et_3N	CH_2Cl_2	rt	48	SBz	**f**	52	nd[b]
7	NaN_3	—	DMF	rt	3	N_3	**g**	63	3
8	PhSH	Et_3N	—	rt	1	SPh	**h**	80	11

[a] Isolated yield after chromatographic separation.
[b] Not detectable.

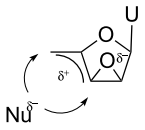
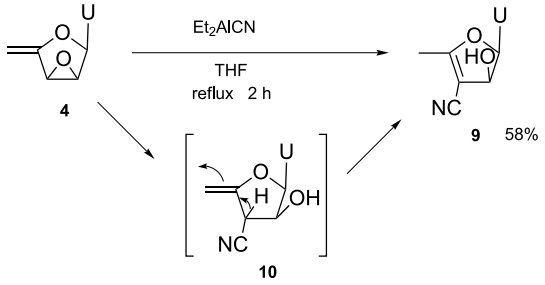


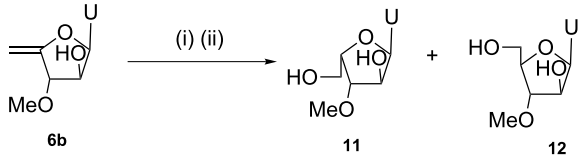
Figure 1.

It was noteworthy that the use of Et_2AlCN as a nucleophile provided 3′,4′-unsaturated-3′-adduct (**9**) as the sole product via isomerization of the 3′-adduct (**10**) because of the efficient activation of 3′-hydrogen of **10** by the strong electron-withdrawing cyano group after regular nucleophilic attack of the cyano anion onto the 3′-position of **4** (Scheme 4).



Scheme 4. Reaction of **4** with Et_2AlCN.

Usually, the 5′-hydroxy group of nucleosides is supposed to be important for biological activity, while 3′-adducts (**6**) do not possess the 5′-hydroxy group. So we investigated the conversion method of the olefin of **6** to a hydroxymethyl group. The hydroboration reaction of **6b** should be applicable to the introduction of the 5′-hydroxy group. The reaction of **6b** with BH_3–THF at room temperature, followed by H_2O_2–NaOH treatment, gave only undesirable α-isomer (**11**). When the reaction was heated at reflux temperature, the desired β-isomer (**12**) was afforded as a minor product (17%) together with corresponding α-isomer (**11**) (53%) (Scheme 5). As the reason for this isomer ratio, it was indicated that the steric hindrance effect of the 3′-methoxy group was more effective than that of the uracil ring. At present, we are unable to determine the underlying cause of this stereoselectivity.



Scheme 5. 5′-Hydroxylation reaction of **6b**: (i) BF_3–THF, THF, reflux (ii) H_2O_2, NaOH.

3. Conclusion

We have shown a simple synthetic method of 1-(2,3-anhydro-5-deoxy-4,5-didehydro-β-D-*erythro*-pent-4-enofuranosyl)uracil (**4**) and mild and efficient regioselective method for the conversion of **4** to 3′-substituted pyrimidine nucleosides (**6**), (**9**), (**11**) and (**12**) without the formation of the corresponding 2′-substituted derivatives. The reaction is general for a variety of nucleophiles and the simplicity of this method makes it an attractive new tool for synthesis of various sugar modified pyrimidine nucleosides.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded on a JEOL EX 400 spectrometer or a JEOL GX 270 spectrometer (^1H: 400 or 270 MHz, ^{13}C: 100 MHz). Chemical shifts (δ) are given in ppm relative to residual solvent or tetramethylsilane as an internal standard. Low and high-resolution mass spectra were taken on a JEOL JMS-SX 102 or JMS-D300 machine. Melting points were determined on a Yanagimoto micro-melting-point apparatus and were corrected. IR spectra were recorded on a Perkin Elmer model 1600 FT-IR spectrophotometer. UV spectra were obtained from EtOH solution on a Shimazu UV-260 spectrophotometer. All reagents were commercially available and used without further purification. Compounds known in the literature were characterized by comparison of their ^1H NMR data with the previously reported data.

4.1.1. 1-(2,3-Anhydro-5-deoxy-4,5-didehydro-α-L-*erythro*-pent-4-enofuranosyl)uracil (4). To a stirred solution of **5**[3c] (336 mg, 1.0 mmol) in dry DMF (20 ml) was added 1.0 M THF solution of $LiN[(CH_3)_3Si]_2$ (2.2 ml, 2.2 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 4 h at 0 °C and the mixture was evaporated in vacuo at room temperature. The residue was diluted with water and neutralized with saturated NH_4Cl and extracted with AcOEt. The organic solution was evaporated in vacuo and the residue was subjected to silica gel column chromatography (benzene/AcOEt 3:1) to afford **4** (192 mg, 92%) as a white foam.

MASS *m/z* (relative intensity): 208 (M^+, 43%), 112 ($B^+ + 1$, 18%), 97 (S^+, 100%). ^1H NMR ($CDCl_3$) δ: 8.71 (1H, br s, N^3–H), 7.50 (1H, d, $J=8.3$ Hz, 6-H), 6.39 (1H, s, 1′-H), 5.76 (1H, d, $J=8.3$ Hz, 5-H), 4.74 (1H, d, $J=2.4$ Hz, 5′-Ha), 4.59 (1H, d, $J=2.4$ Hz, 5′-Hb), 4.23 (1H, d, $J=2.9$ Hz, 2′-H), 4.05 (1H, d, $J=2.9$ Hz, 3′-H). ^{13}C NMR ($CDCl_3$) δ: 162.84 (4-C), 154.34 (4′-C), 150.30 (2-C), 140.75 (6-C), 102.80 (5-C), 95.95 (5′-C), 81.79 (1′-C), 56.52 (2′-C), 54.56 (3′-C). HRMS *m/z* calcd for $C_9H_8N_2O_4$: 208.0484. Found: 208.0473.

4.1.2. 1-(3,5-Dideoxy-3-methyl-β-D-*threo*-pent-4-enofuranosyl)uracil (6a). To a stirred solution of **4** (48 mg, 0.23 mmol) in dry CH_2Cl_2 (10 ml) was added 1.0 M hexane solution of $AlMe_3$ (1.20 ml, 1.20 mmol) at room temperature under argon atmosphere. The reaction mixture was refluxed for 12 h and the mixture was partitioned between $CHCl_3$ (30 ml) and water (30 ml). The aqueous layer was filtered using a Celite cake and the filtrate was concentrated in vacuo. The residue was subjected to silica gel column chromatography ($CHCl_3$/MeOH 10:1) to afford **6a** (42 mg, 81%) as a white foam.

MASS *m/z* (relative intensity): 224 (M^+, 2%), 113 (S^+ and $B^+ + 2$, 14%), 112 ($B^+ + 1$, 14%), 95 (100%). ^1H NMR (DMSO-d_6) δ: 11.35 (1H, br s, N^3–H), 7.31 (1H, d, $J=8$.

3 Hz, 6-H), 6.26 (1H, d, J=4.9 Hz, 1′-H), 5.77 (1H, d, J=4.9 Hz, 2′-OH), 5.58 (1H, d, J=8.3 Hz, 5-H), 4.32 (1H, d, J=1.5 Hz, 5′-Ha), 4.03 (1H, t, J=4.9 Hz, 2′-H), 4.01 (1H, d, J=1.5 Hz, 5′-Hb), 2.68 (1H, q, J=6.8 Hz, 3′-H), 1.15 (3H, d, J=6.8 Hz, 3′-CH_3). ^{13}C NMR (DMSO-d_6) δ: 163.93 (4-C), 163.15 (4′-C), 150.47 (2-C), 141.47 (6-C), 100.86 (5-C), 85.17 (5′-C), 82.40 (1′-C), 74.36 (2′-C), 41.99 (3′-C), 16.60 (3′-CH_3). Anal. Calcd for $C_{10}H_{12}N_2O_4$ (M_w=224.21): C, 53.57; H, 5.39; N, 12.49. Found: C, 53.30; H, 5.42; N, 12.23.

4.1.3. 1-(5-Deoxy-3-*O*-methyl-β-D-*threo*-pent-4-enofuranosyl)uracil (6b). To a stirred solution of **4** (13 mg, 0.06 mmol) in dry MeOH (5 ml) was added 28% MeOH solution of sodium methoxide (0.06 ml, 0.30 mmol) at room temperature under argon atmosphere. The reaction mixture was refluxed for 6 h and the mixture was neutralized with AcOH. The solvent was evaporated in vacuo. The residue was subjected to silica gel column chromatography ($CHCl_3$/MeOH 20:1) to afford **6b** (12 mg, 80%). Residue was recrystallized from MeOH (colorless solid).

Mp: 166–167 °C. MASS m/z (relative intensity): 240 (M^+, 1%), 111 (B^+, 100%). ^{1}H NMR (DMSO-d_6) δ: 11.47 (1H, br s, N^3–H), 7.41 (1H, d, J=8.0 Hz, 6-H), 6.29 (1H, d, J=3.4 Hz, 1′-H), 6.07 (1H, d, J=2.9 Hz, 2′-OH), 5.74 (1H, d, J=8.0 Hz, 5-H), 4.67 (1H, s, 5′-Ha), 4.43 (1H, s, 5′-Hb), 4.21 (1H, br s, 2′-H), 4.13 (1H, br s, 3′-H), 3.42 (3H, s, 3′-OCH_3). ^{13}C NMR (DMSO-d_6) δ: 163.16 (4-C), 157.49 (4′-C), 150.31 (2-C), 141.60 (6-C), 100.62 (5-C), 88.07 (5′-C), 86.70 (1′-C), 83.96 (3′-C), 72.15 (2′-C), 55.76 (3′-OCH_3). Anal. Calcd for $C_{10}H_{12}N_2O_5$ (M_w=240.21): C, 50.00; H, 5.04; N, 11.66. Found: C, 50.07; H, 5.04; N, 11.52.

4.1.4. 1-(3-Benzylamino-3,5-dideoxy-β-D-*threo*-pent-4-enofuranosyl)uracil (6c). To a stirred solution of **4** (137 mg, 0.66 mmol) in dry CH_2Cl_2 (5 ml) was added benzylamine (3.60 ml, 32.9 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred for 24 h and the mixture was concentrated in vacuo. The residue was subjected to silica gel column chromatography ($CHCl_3$/MeOH 30:1) to afford **6c** (169 mg, 81%). Residue was recrystallized from AcOEt (colorless solid).

Mp: 153–155 °C. MASS m/z (relative intensity): 315 (M^+, 5%), 297 (M^+-H_2O, 4%), 224 (M^+-CH_2Ph, 6%), 203 (S^++1, 12%), 186 (S^+-H_2O, 58%), 91 ($PhCH_2^+$, 100%). IR (KBr) cm^{-1}: 3395.9, 1685.7. ^{1}H NMR (DMSO-d_6) δ: 11.41 (1H, br s, N^3–H), 7.27–7.42 (6H, m, Ph-H and 6-H), 6.48 (1H, d, J=3.4 Hz, 1′-H), 5.80 (1H, d, J=4.3 Hz, 2′-OH), 5.65 (1H, d, J=7.8 Hz, 5-H), 4.52 (1H, s, 5′-Ha), 4.21 (1H, br s, 2′-H), 4.19 (1H, s, 5′-Hb), 3.88 (1H, d, J=10 Hz, 3′-$NHCH_2$), 3.78 (1H, d, J=10 Hz, 3′-$NHCH_2$), 3.54 (1H, br s, 3′-H), 2.80 (1H, br s, 3′-NH). Anal. Calcd for $C_{16}H_{17}N_3O_4$ (M_w=315.33): C, 60.94; H, 5.43; N, 13.33. Found: C, 60.94; H, 5.46; N, 13.17.

4.1.5. 1-(3,5-Dideoxy-3-di(methoxycarbonyl)methyl-β-D-*threo*-pent-4-enofuranosyl)uracil (6d). To a stirred solution of dimethyl malonate (1.28 ml, 11.19 mmol) in dry MeOH (5 ml) was added 28% MeOH solution of sodium methoxide (1.08 ml, 5.60 mmol) at room temperature under argon atmosphere. The mixture was added to a stirred solution of **4** (291 mg, 1.40 mmol) in dry MeOH (5 ml) at room temperature under argon atmosphere. The reaction mixture was stirred for 12 h and the mixture was neutralized with AcOH. The solvent was evaporated in vacuo and the residue was diluted with water and extracted with AcOEt. The organic solution was dried over $MgSO_4$ and the solvent was evaporated in vacuo and residue was subjected to silica gel column chromatography ($CHCl_3$/MeOH 30:1) to afford **6d** (331 mg, 69%) as a white foam.

MASS m/z (relative intensity): 340 (M^+, 5%), 322 (M^+-H_2O, 100%), 228 (S^+-1, 38%), 211 ($M^+-CH(CO_2Me)_2+2$, 80%). ^{1}H NMR ($CDCl_3$) δ: 9.01 (1H, br s, N^3–H), 7.33 (1H, d, J=8.3 Hz, 6-H), 6.39 (1H, d, J=4.8 Hz, 1′-H), 5.69 (1H, d, J=8.3 Hz, 5-H), 4.86 (1H, d, J=4.8 Hz, 2′-H), 4.60 (1H, d, J=2.4 Hz, 5′-Ha), 4.10 (1H, d, J=2.4 Hz, 5′-Hb), 3.79 (6H, s, $CH_3\times2$), 3.74 (1H, br s, 3′-H), 3.71 (1H, br s, 2′-OH), 3.35–3.43 (1H, m, 3′-$CH(CO_2Me)_2$). HRMS m/z calcd for $C_{14}H_{16}N_2O_8$: 340.0897. Found: 340.0907.

4.1.6. 1-(3-*O*-Benzoyl-5-deoxy-β-D-*threo*-pent-4-enofuranosyl)uracil (6e). To a stirred solution of **4** (107 mg, 0.51 mmol) in dry CH_2Cl_2 (5 ml) was added benzoic acid (188 mg, 1.54 mmol) and Et_3N (0.21 ml, 1.54 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred for 168 h at room temperature and the solvent was evaporated in vacuo. The residue was diluted with water and extracted with AcOEt and the organic solution was dried over $MgSO_4$ and the solvent was evaporated in vacuo. The residue was subjected to silica gel column chromatography ($CHCl_3$/MeOH 50:1) to afford **6e** (103 mg, 61%) (white foam) and **6e′** (12 mg, 10%) (white foam), respectively.

Compound **6e**. MASS m/z (relative intensity): 330 (M^+, 0.7%), 312 (M^+-H_2O, 13%), 218 (S^+-1, 18%), 208 ($M^+-OCOPh+1$, 19%), 201 (S^+-H_2O, 7%), 105 (PhCO, 100%). IR (KBr) cm^{-1}: 3424.3, 1686.7. ^{1}H NMR ($CDCl_3$) δ: 10.46 (1H, br s, N^3–H), 7.98 (2H, d, J=7.3 Hz, Ph-*o*), 7.32–7.51 (4H, m, Ph-*m* and *p* and 6-H), 6.51 (1H, d, J=3.4 Hz, 1′-H), 5.75 (1H, br s, 3′-H), 5.62 (1H, d, J=8.3 Hz, 5-H), 5.17 (1H, br s, 2′-OH), 4.80 (2H, br s, 2′-H and 5′-Ha), 4.66 (1H, d, J=2.4 Hz, 5′-Hb). HRMS m/z calcd for $C_{16}H_{14}N_2O_6$: 330.0852. Found: 330.0843.

Compound **6e′**. MASS m/z (relative intensity): 226 (M^+, 51%), 208 (M^+-H_2O, 13%), 115 (S^+, 100%). IR (KBr) cm^{-1}: 3383.9, 1686.8. ^{1}H NMR ($CDCl_3$) δ: 10.83 (1H, br s, N^3–H), 7.98 (1H, d, J=8.1 Hz, 6-H), 6.62 (1H, d, J=2.9 Hz, 1′-H), 5.58 (1H, d, J=8.1 Hz, 5-H), 4.81 (1H, br s, 2′-H), 4.72 (1H, d, J=2.7 Hz, 5′-Ha), 4.63 (1H, br s, 3′-H), 4.55 (1H, d, J=2.7 Hz, 5′-Hb). FABHRMS m/z calcd for $C_9H_{11}N_2O_5$: 227.0668. Found: 227.0664.

4.1.7. 1-(3-Benzoylthio-3,5-dideoxy-β-D-*threo*-pent-4-enofuranosyl)uracil (6f). To a stirred solution of **4** (169 mg, 0.81 mmol) in dry CH_2Cl_2 (5 ml) was added thiobenzoic acid (0.29 ml, 2.44 mmol) and Et_3N (0.34 ml, 2.44 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred for 2 days at room temperature and the solvent was evaporated in vacuo. The residue was subjected to silica gel column chromatography ($CHCl_3$/MeOH 45:1) to afford **6f** (145 mg, 52%) as a white foam.

MASS *m/z* (relative intensity): 346 (M^+, 4%), 328 ($M^+ - H_2O$, 3%), 209 ($M^+ - SCH_2Ph$, 5%), 105 (PhCO, 100%), 77 (Ph, 48%). IR (KBr) cm^{-1}: 3425.2, 1683.6. ^1H NMR ($CDCl_3$) δ: 9.64 (1H, br s, N^3–H), 7.93 (2H, d, $J=7.3$ Hz, Ph-*o*), 7.58–7.64 (1H, m, Ph-*p*), 7.44–7.49 (3H, m, Ph-*m* and 6-H), 6.40 (1H, d, $J=3.4$ Hz, 1′-H), 5.65 (1H, d, $J=7.8$ Hz, 5-H), 4.71 (1H, d, $J=1.9$ Hz, 5′-Ha), 4.60–4.67 (3H, m, 3′-H, 2′-H and 2′-OH), 4.44 (1H, d, $J=2.4$ Hz, 5′-Hb). HRMS *m/z* calcd for $C_{16}H_{14}N_2O_5S_1$: 346.0623. Found: 346.0610.

4.1.8. 1-(3-Azido-3,5-dideoxy-β-D-*threo*-pent-4-enofuranosyl)uracil (6g) and 1-(5-azido-3,5-dideoxy-β-D-*glycero*-pent-4-enofuranosyl)uracil (8g). To a stirred solution of **4** (122 mg, 0.59 mmol) in dry DMF (10 ml) was added sodium azido (57 mg, 0.88 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred for 3 h at room temperature and the mixture was concentrated in vacuo. The residue was subjected to silica gel column chromatography (benzene/AcOEt 2:1) to give **6g** (93 mg, 63%) as the first fraction (white foam) and **8g** (5 mg, 3%) as the second fraction (white foam).

Compound **6g**. IR (KBr) cm^{-1}: 2104 (N_3). MASS *m/z* (relative intensity): 251 (M^+, 2%), 209 ($M^+ - N_3$, 14%), 167 (100%), 112 ($B^+ + 1$, 39%). ^1H NMR (DMSO-d_6) δ: 11.44 (1H, br s, N^3–H), 7.36 (1H, d, $J=8.3$ Hz, 6-H), 6.29 (1H, d, $J=4.4$ Hz, 2′-OH), 6.24 (1H, d, $J=4.4$ Hz, 1′-H), 5.61 (1H, d, $J=8.3$ Hz, 5-H), 4.69 (1H, d, $J=2.4$ Hz, 5′-Ha), 4.63 (1H, br s, 3′-H) 4.41 (1H, d, $J=2.4$ Hz, 5′-Hb), 4.09 (1H, br s, 2′-H). Anal. Calcd for $C_9H_9N_5O_4$ ($M_w=251.20$): C, 43.03; H, 3.61; N, 27.88. Found: C, 43.13; H, 3.67; N, 27.64.

Compound **8g**. IR (KBr) cm^{-1}: 2105 (N_3). MASS *m/z* (relative intensity): 251 (M^+, 12%), 209 ($M^+ - N_3$, 4%), 167 (100%), 113 ($B^+ + 2$, 44%). ^1H NMR (DMSO-d_6) δ: 11.42 (1H, br s, N^3–H), 7.32 (1H, d, $J=8.0$ Hz, 6-H), 6.42 (1H, d, $J=6.8$ Hz, 1′-H), 5.62 (1H, d, $J=8.0$ Hz, 5-H), 5.57 (1H, d, $J=4.9$ Hz, 2′-OH), 5.29 (1H, d, $J=1.5$ Hz, 3′-H), 4.88–4.91 (1H, m, 2′-H), 4.09 (2H, s, 5′-H×2). ^{13}C NMR (DMSO-d_6) δ: 163.32 (4-C), 154.29 (4′-C), 150.53 (2-C), 142.37 (6-C), 103.89 (5′-C), 100.82 (5-C), 86.02 (1′-C), 70.68 (3′-C), 46.45 (2′-C). HRMS *m/z* calcd for $C_9H_9N_5O_4$: 251.0662. Found: 251.0655.

4.1.9. 1-(3,5-Dideoxy-3-phenylthio-β-D-*threo*-pent-4-enofuranosyl)uracil (6h) and 1-(3,5-dideoxy-5-phenylthio-β-D-*glycero*-pent-4-enofuranosyl)uracil (8h). To a stirred solution of **4** (110 mg, 0.53 mmol) in Et_3N (10 ml) was added thiophenol (82 μl, 0.80 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred for 1 h at room temperature and the solvent was evaporated in vacuo and a small amount of the remaining Et_3N was removed as the toluene azetrope. The residue was subjected to silica gel column chromatography ($CHCl_3$/MeOH 150:1) to give **6h** (134 mg, 80%) as the first fraction (white foam) and **8h** (19 mg, 11%) as the second fraction (white foam).

Compound **6h**. MASS *m/z* (relative intensity): 318 (M^+, 58%), 206 ($S^+ - 1$, 100%), 112 ($B^+ + 1$, 16%). ^1H NMR ($CDCl_3$) δ: 11.04 (1H, br s, N^3–H), 7.23–7.50 (6H, m, 6-H and 3′-SPh), 6.37 (1H, d, $J=2.9$ Hz, 1′-H), 5.46 (1H, d, $J=8.3$ Hz, 5-H), 5.38 (1H, d, $J=4.4$ Hz, 2′-OH), 4.80–4.82 (1H, m, 2′-H), 4.61 (1H, d, $J=2.0$ Hz, 5′-Ha), 4.23 (1H, br s, 3′-H), 4.21 (1H, d, $J=2.0$ Hz, 5′-Hb). ^{13}C NMR ($CDCl_3$) δ: 165.99 (4-C), 157.96 (4′-C), 149.91 (2-C), 142.95 (6-C), 132.63 (SPh-C), 129.25 (SPh-C), 128.17 (SPh-C), 100.41 (5-C), 88.06 (1′-C), 87.41 (5′-C), 74.24 (2′-C), 53.50 (3′-C). Anal. Calcd for $C_{15}H_{14}N_2O_4S_1$ ($M_w=318.35$): C, 56.59; H, 4.43; N, 8.80. Found: C, 56.34; H, 4.49; N, 8.78.

Compound **8h**. MASS *m/z* (relative intensity): 318 (M^+, 33%), 209 ($M^+ - SPh$, 50%), 206 ($S^+ - 1$, 7%), 123 ($PhSCH_2^+$, 100%), 112 ($B^+ + 1$, 9%). ^1H NMR ($CDCl_3$) δ: 10.75 (1H, br s, N^3–H), 7.23–7.47 (6H, m, 6-H and 3′-SPh), 6.46 (1H, d, $J=6.4$ Hz, 1′-H), 5.51 (1H, d, $J=8.3$ Hz, 5-H), 5.16 (2H, br s, 2′-H and 3′-H), 4.58 (1H, d, $J=3.9$ Hz, 2′-OH), 3.66 (2H, s, 5′-H×2). ^{13}C NMR ($CDCl_3$) δ: 165.22 (4-C), 156.88 (4′-C), 150.48 (2-C), 143.00 (6-C), 134.83 (SPh-C), 130.53 (SPh-C), 129.07 (SPh-C), 127.15 (SPh-C), 102.27 (3′-C), 100.74 (5-C), 86.91 (1′-C), 71.88 (2′-C), 31.46 (5′-C). Anal. Calcd for $C_{15}H_{14}N_2O_4S_1$ ($M_w=318.35$): C, 56.59; H, 4.43; N, 8.80. Found: C, 56.30; H, 4.40; N, 8.72.

4.1.10. 1-(3-Cyano-3,5-dideoxy-β-D-*glycero*-pent-3-enofuranosyl)uracil (9). To a stirred solution of **4** (296 mg, 1.42 mmol) in dry THF (10 ml) was added 1.0 M toluene solution of Et_2AlCN (14 ml, 14 mmol) under argon atmosphere. The reaction mixture was refluxed for 2 h. EtOH was added and the mixture was stirred for 30 min and the solvent was evaporated in vacuo. The residue was diluted with water and extracted with AcOEt and the organic solution was dried over $MgSO_4$ and the solvent was evaporated in vacuo. The residue was subjected to silica gel column chromatography ($CHCl_3$/MeOH 30:1) to afford **9** (193 mg, 58%). Residue was recrystallized from acetone and AcOEt (colorless solid).

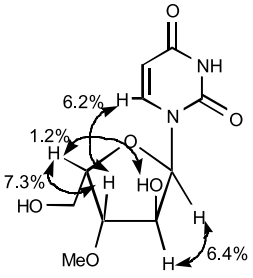
Mp: 219–222 °C. MASS *m/z* (relative intensity): 235 (M^+, 29%), 217 ($M^+ - H_2O$, 9%), 192 ($M^+ - H_2O$–CN+1, 6%), 123 ($S^+ - 1$, 38%), 113 ($B^+ + 2$, 100%). IR (KBr) cm^{-1}: 3426.6, 3196.6, 2218.0 (CN), 1697.9, 1671.7, 1653.5. ^1H NMR (DMSO-d_6) δ: 11.53 (1H, br s, N^3–H), 7.44 (1H, d, $J=7.8$ Hz, 6-H), 6.66 (1H, d, $J=7.3$ Hz, 1′-H), 6.23 (1H, d, $J=5.9$ Hz, 2′-OH), 5.65 (1H, d, $J=7.8$ Hz, 5-H), 5.07–5.11 (1H, m, 2′-H), 2.15 (3H, s, 5′-CH_3). Anal. Calcd for $C_{10}H_9N_3O_4$ ($M_w=235.20$): C, 51.07; H, 3.86; N, 17.87. Found: C, 51.27; H, 3.93; N, 17.68.

4.1.11. 1-(3-*O*-Methyl-α-L-*xylo*-furanosyl)uracil (11) and 1-(3-*O*-methyl-β-D-*arabino*-furanosyl)uracil (12). To a stirred solution of **6b** (30 mg, 0.125 mmol) in dry THF (10 ml) was added 1 M THF solution of BH_3–THF (0.625 ml, 0.625 mmol) at 0 °C under argon atmosphere and the reaction mixture was stirred for 1 h at 0 °C. One molar THF solution of BH_3–THF (1.625 ml, 1.625 mmol) was added to the reaction mixture and the reaction mixture was refluxed for 17 h. After cooling to room temperature, H_2O and 3 N NaOH (0.125 ml, 0.375 mmol) and 30% H_2O_2 (0.12 ml, 1.25 mmol) was added to the reaction mixture. The reaction mixture was stirred for 6 h at room temperature. After acidification with AcOH, the reaction mixture was washed with saturated NaCl and the aqueous layer was extracted with THF. The organic solution was

combined and dried over Na_2SO_4. The solvent was removed in vacuo and the mixture was analyzed by the ^1H NMR (17% of the **12** was detected). The crude mixture was purified by silica gel column chromatography ($CHCl_3$/MeOH 15:1) to give **11** (53%).

Compound **11**. FABMASS *m/z* (relative intensity): 259 ($M^+ + 1$, 7%), 154 (100%). ^1H NMR (DMSO-d_6) δ: 11.25 (1H, br s, N^3–H), 7.41 (d, $J=8.2$ Hz, 6-H), 5.92 (1H, d, $J=3.6$ Hz, 1′-H), 5.76 (1H, d, $J=4.5$ Hz, 2′-OH), 5.55 (1H, d, $J=8.2$ Hz, 5-H), 4.72 (1H, t, $J=5.5$ Hz, 5′-OH), 4.28–4.34 (1H, m, 3′-H), 4.21–4.25 (1H, m, 2′-H), 3.74–3.76 (1H, m, 4′-H), 3.48–3.63 (2H, m, 5′-H×2), 3.36 (3H, s, 3′-OCH_3). NOE experiment, 4′-H/3′-H (7.3%), 4′-H/2′-OH (1.2%), 3′-H/6-H (6.2%) and 1′-H/2′-H (6.4%). FABHRMS *m/z* calcd for $C_{10}H_{15}N_2O_6$: 259.0930. Found: 259.0938.

Compound **12**. ^1H NMR (DMSO-d_6) δ: 11.28 (1H, br s, N^3–H), 7.60 (d, $J=8.2$ Hz, 6-H), 5.90 (1H, d, $J=4.5$ Hz, 1′-H), 5.76 (1H, d, $J=5.1$ Hz, 2′-OH), 5.57 (1H, d, $J=8.2$ Hz, 5-H), 5.08 (1H, t, $J=5.7$ Hz, 5′-OH), 4.12–4.16 (1H, m, 2′-H), 3.79–3.84 (1H, m, 3′-H), 3.66–3.68 (1H, m, 4′-H), 3.58–3.61 (2H, m, 5′-H×2), 3.34 (3H, s, 3′-OCH_3). FABHRMS *m/z* calcd for $C_{10}H_{15}N_2O_6$: 259.0930. Found: 259.0943.



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10. Detailed results for the reaction mechanism will be reported in due course.

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Highly enantioselective synthesis and potential biological activity of chiral novel nucleoside analogues containing adenine and naturally phenol derivatives

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Abstract—This paper described an efficient synthetic strategy for chiral acyclic nucleoside analogues containing both the phenoxy components of some bioactive natural compounds and a heterocyclic base. The phenoxy components with adenine moiety were incorporated into the chiral acyclic nucleoside analogues through two key synthetic tactics. Chiron 5-(*R*)-menthyloxy-2(5*H*)-furanone **5** was obtained in good yield from the cheap starting material furfural via a valuable synthetic route. The asymmetric Michael addition of **5** with adenine and the subsequent reduction reaction afforded the key chiral intermediate, 2-(*R*)-(9′-adeninyl)-1,4-butanediol **8**. The absolute configuration of **8** was established by X-ray crystallography. The intermolecular dehydration reaction between 2-(9′-adeninyl)-1,4-butanediol **8** and phenoxy components **9** on treatment with diethyl azodicarboxylate and triphenylphosphine was carried out to give the chiral acyclic nucleoside analogues **1a**–**1e**. The regioselectivity of the reaction was established by NMR methods, especially through ^{13}C NMR shifts and NOE effect observed in the target molecule **1c**, as well as by HMBC/HMQC experiments. The target compounds were tested for inhibition of cytopathogenicity against different cancer cells and exhibited potential anticancer activity.

1. Introduction

It is well known that the phenoxy group is an important component of some bioactive compounds for their biologic properties.[1] For example, the flavan derivatives[2] as new aromatase inhibitors have been considered as a result of the modulation of flavonoids, which are natural products extensively distributing in the plant kingdom. An appropriately fashioned hybrid drug of galdanamycin and estradiol would offer the ability to induce a selective degradation of the estrogen receptor (ER).[3] Several adenosine nucleosides, such as the antibiotics aristeromycin[4] and neplanocin A[5] (as inhibitor *S*-adenosyl-L-homocyseine hydrolase), are obtained from natural products. Despite of the progress that has been made in this field, efficient synthesis of chiral acyclic nucleoside analogues **1a**–**1e**, which contains both the phenoxy components of some bioactive natural compounds and a heterocyclic base, has not been reported.

Our approach to use a synthetic strategy in which the phenoxy components and the adenine moiety could be incorporated into chiral acyclic nucleoside analogues through two key synthetic tactics: (i) preparation of 2-(*R*)-(9′-adeninyl)-1,4-butanediol **8** by the asymmetric Michael addition of chiron, (5)-(*R*)-(−)-menthyloxy-2(5*H*)-furanone **5** with adenine and subsequent reduction reaction; and (ii) the intermolecular dehydration reaction occurring between the 2-(9′-adeninyl)-1,4-butanediol **8** and phenoxy (acidic) components **9** on treatment with diethyl azodicarboxylates (DEAD) and triphenylphosphine under mild conditions[6]. Herein, we report our results on the efficient synthesis of the target chiral acyclic nucleoside analogues containing the phenoxy components of some bioactive natural compounds (Fig. 1).

2. Results and discussion

The synthesis of enantiopure 5-(*R*)-(−)-menthyloxy-2(5*H*)-furanone **5** was conveniently achieved starting from 5-hydroxy-2(5*H*)-furanone **3** as shown in Scheme 1. The photooxidation of furfural **2** was probably the most suitable method for the preparation of **3**.[7,8] The improved photosynthetic procedure using 95% C_2H_5OH as a the solvent at room temperature provided 5-hydroxy-2(5*H*)-furanone in good yield.[7] Epimeric mixture of 5-menthyloxy-2(5*H*)-furanone **4** was readily available through acetalization of the

Keywords: Asymmetric synthesis; Enantiopure; Chiral acyclic nucleoside analogue; Phenoxy and adenine components; Potential anticancer activity.
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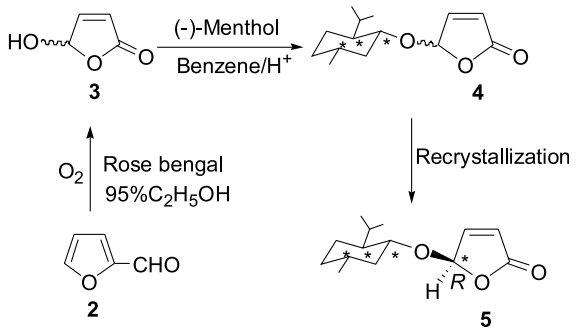
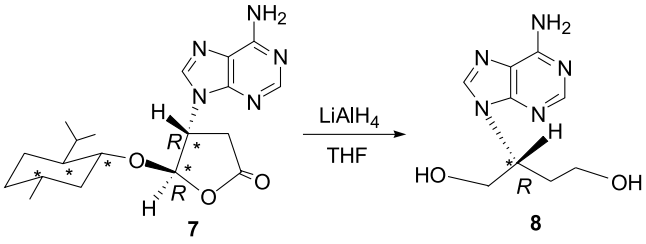


Scheme 1. The synthesis of enantiomerically pure 5-(*R*)-(−)-menthyloxy-2(5*H*)-furanone **5**.

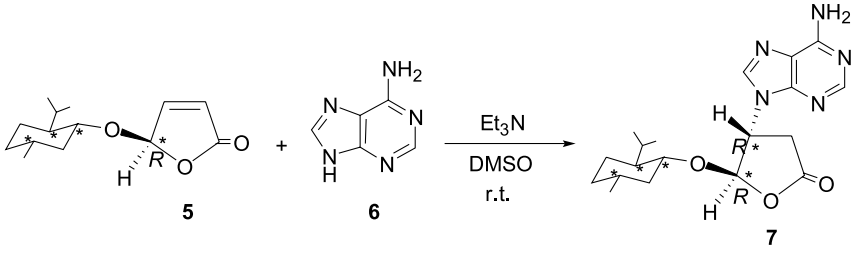
resulting 5-hydroxy-2(5*H*)-furanone with (−)-menthol in refluxing benzene in the presence of a catalytic amount of condensed sulfuric acid.[7,9]

Asymmetric Michael addition of heterocyclic bases with 5-(*R*)-(−)-menthyloxy-2(*5H*)-furanone **5** was studied originally in our laboratory.[7] Basic condition was one of the most important factors for the successful reaction to acquire the main N-9 alkylation product (Scheme 2). The reaction of **5** and adenine **6** in the presence of triethylamine afforded 5-(*R*)-(−)-menthyloxy-4-(*R*)-(9′-adeninyl)-butyrolactone **7** via the asymmetric addition. The important factor was the selection of solvent. Because of the low solubility of adenine, DMSO was chosen as the suitable solvent. The base **6** was dissolved in DMSO at 40 °C, and then triethylamine was added at room temperature. Purification of the products was another key factor. The remaining chiron **5** was washed with petroleum, and the adduct was extracted using acetone due to the solubility difference between the chiron and the product. The optically pure compound **7** was obtained in 64% yield with ≥98% ee by column chromatography. The chemical structures of chiral products were established by element analysis, IR, UV, ^{1}H NMR, ^{13}C NMR, MS and X-ray crystallography.[7]

As outlined in Scheme 3, 5-(*R*)-(−)-menthyloxy-4-(*R*)-(9′-adeninyl)-butyrolactone **7** was reduced by $LiAlH_4$ in a suspension of THF to give the enantiopure functionalized compound, 2-(*R*)-(9′-adeninyl)-1,4-butanediol **8** in good yield with ≥98% ee. The chemical structure of **8** was readily confirmed by the spectroscopic data. The stereochemistry and configuration of the molecule were further confirmed by its X-ray crystallography as shown in Figure 2 (CCDC 273580).



Scheme 3. The synthesis of enantiomerically pure 2-(*R*)-(9′-adeninyl)-1,4-butanediol **8**.



Scheme 2. The synthesis of enantiomerically pure **7**.

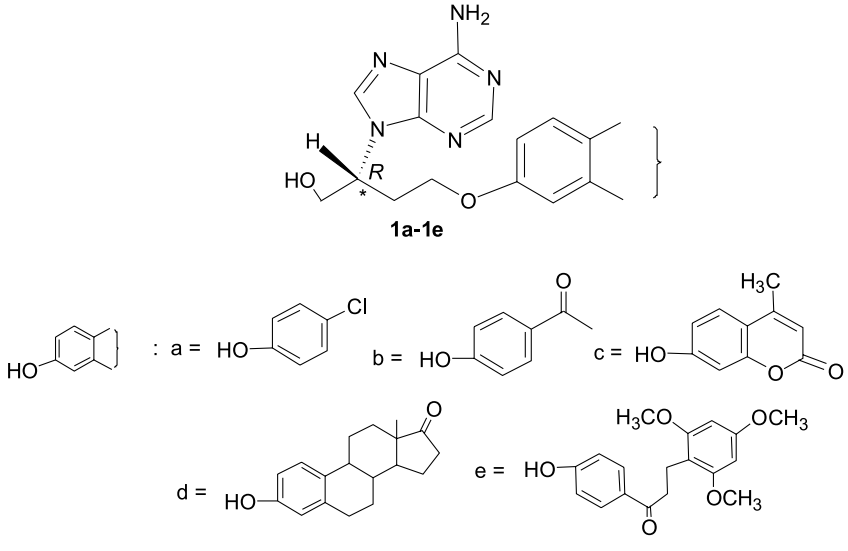


Figure 1. The structures of target molecules.

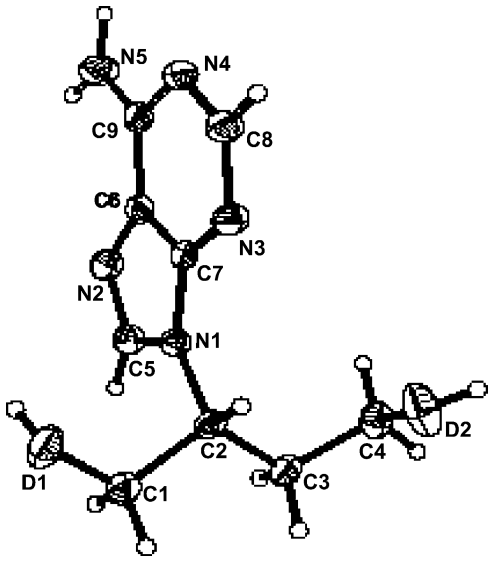
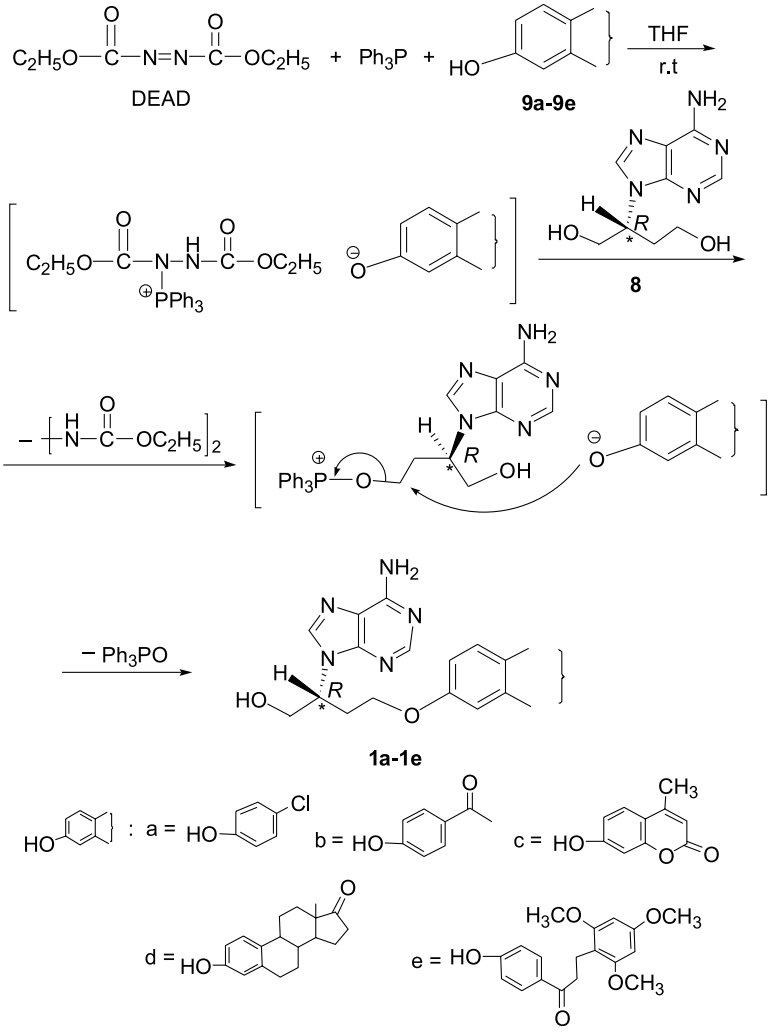


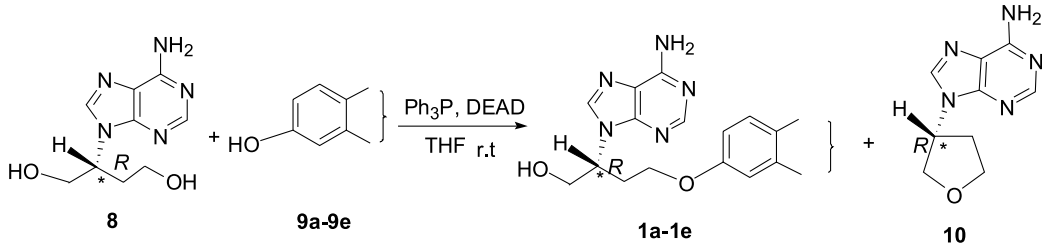
Figure 2. ORTEP drawing of the molecule **8**.

The development of mild methods for the synthesis of phenoxy ethers has recently gained increased attention, mainly due to their important roles in natural and unnatural pharmacologically antibiotics and other biologically active compounds.[10] The formation of the C–O bond in ethers can usually be realized by the dehydration of alcohols using sulfuric acid as the catalyst, but this process is not suitable for the synthesis of unsymmetrical ethers partly due to the low selectivity and strong sensitivity of the substrates. The reaction of alcohols and acidic components such as phenoxy group takes place easily to form the condensation products in the presence of organic dehydrating reagents such as the diethyl azodicarboxylate(DEAD)/triphenylphosphine(Ph_3P) system under mild conditions.[6] The condensation reaction of 2-(*R*)-(9′-adeninyl)-1,4-butanediol **8** with different phenoxy components **9a–9e** was proceeded to afford the corresponding chiral acyclic nucleoside analogues **1a–1e** as shown in Scheme 4. The dehydrating behavior of different phenoxy compounds **9** with alcohol **8** could be explained on the basis of a reaction mechanism including the phenoxy compound as an acidic component and the alcohol containing adenine moiety **8** as a nucleophilic reagent. At first, the adduct of DEAD and Ph_3P by the protonation supported from phenoxy compound was formed as a dipolar system and subsequently the elimination of 1,2-dicarbethoxyhydrazine was easily carried out by the nucleophilic reaction of **8** to afford a new zwitterion. Finally, the target molecules, chiral acyclic nucleoside analogues **1a–1e** were obtained through the nucleophilic substitution of the anion of



Scheme 4. The synthetic route to chiral acyclic nucleoside analogues **1a–1e**.

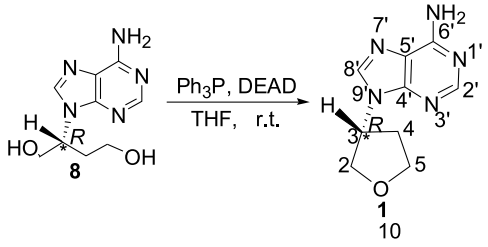
Table 1. Etherification of chiral compond **8** with phenoxy components **9** in the presence of DEAD and Ph_3P[a]



Entry	**1** Yield[b] (mg) (%)	**10** Yield[b] (mg) (%)	**8** Recovered[b] (mg)
1 (**1a**)	130 (43)	86 (42)	22
2 (**1b**)	112 (44)	46 (22)	56
3 (**1c**)	198 (52)	Trace[c]	Trace[c]
4 (**1d**)	251 (75)	—	Trace[c]
5 (**1e**)	279 (53)	Trace[c]	Trace[c]

[a] The etherification was carried out at room temperature for 1–3 days using 1.0 mmol of **8**, 1.2 mmol of **9**, 1.2 mmol of DEAD, 1.2 mmol of Ph_3P in THF.
[b] Yield after flash chromatography based on the amount of **8**.
[c] It was checked by TLC to show the traces of **8**, **9**, and **10**, but did not obtain the pure compounds after the separation by flash chromatography.

phenoxy compound and elimination of triphenylphosphine oxide. The results were summarized in Table 1. The dehydration of alcohol **8** with **9a**–**9e** afforded the corresponding ethers **1a**–**1e** in 43–75% FC yields. When the reactions of **8** with **9a**–**9b** were performed, the corresponding ethers were achieved in 43–44% FC yields (Table 1, entries 1, 2) along with the self-etherification product **10** (Scheme 5) in 42 and 22% FC yields, as well as recovering 22 and 56 mg of starting material **8**, respectively. The unsymmetrical etherification of **8** with **9c** and **9e** gave the corresponding ethers **1c** and **1e** in 52 and 53% FC yields, respectively, (Table 1, entries 3, 5). At the same time, the traces of **8**, **9** and **10** were found by checking TLC, which were not obtained after flash chromatography. The result of the dehydration of alcohol **8** with **9d** under the same condition gave **1d** in 75% FC yield (Table 1, entry 4). Obviously, the aim of our present study would be to propose further groundwork for any future applications on the unsymmetric etherification to the synthesis of more complex molecules containing similar chiral acyclic and cyclic nucleoside skeleton.



Scheme 5. The intramolecular dehydration of 2-(*R*)-(9′-adeninyl)-1,4-butanediol **8**.

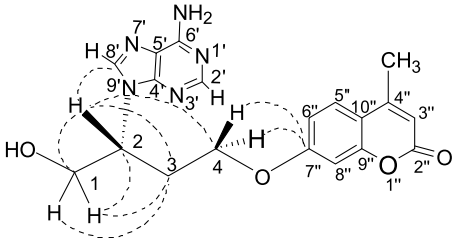


Figure 3. Relevant $^{1}H/^{13}C$ HMBC correlations for structural identification of compound **1c**.

The stereochemistry of the nucleoside **1c** was elucidated by HMQC and HMBC experiment as shown in Figures 3, 4, and 5 as well as Table 2. The result described that H-4 was correlated only with C-2, C-3 and C-7″, which proved the

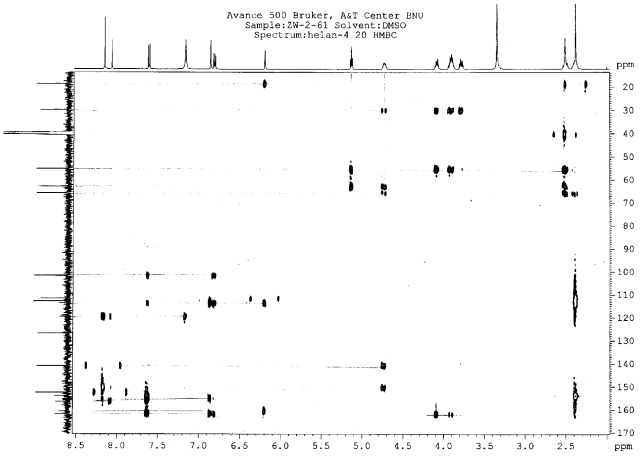


Figure 4. The 500 MHz HMBC spectrum of compound **1c**.

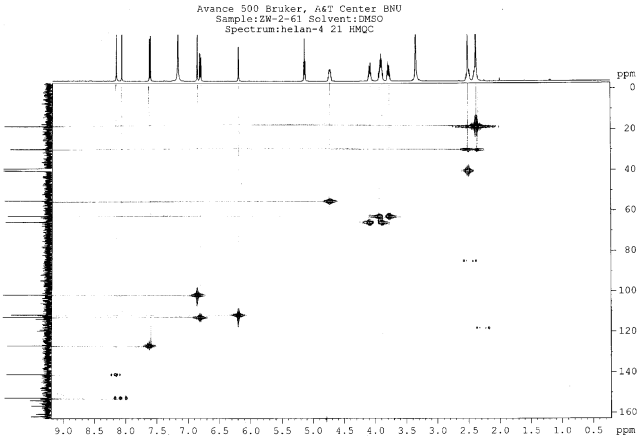


Figure 5. The 500 MHz HMQC spectrum of compound **1c**.

Table 2. ^{1}H NMR, ^{13}C NMR data and HMQC, HMBC correlations for **1c**[a]

Position	δ_H (mult. J in Hz)	δ_C (mult.)	HMQC	HMBC
1	3.77–3.81 (m), 388–3.94 (m)	62.9	C-1	C-3, C-2
2	4.73–4.75 (m)	55.3	C-2	C-1, C-3, C-4, C-8′
3	2.40–2.42 (m), 2.47–2.51 (m)	29.8	C-3	C-1, C-2, C-4
4	3.88–3.94 (m), 4.07–4.11 (m)	65.8	C-4	C-2, C-3, C-7″
2′	8.08 (s)	152.5	C-2′	C-4′, C-5′
4′		155.1	C-4′	
5′		119.5	C-5′	C-10, C-7, C-4
6′		150.2	C-6′	
8′	8.16 (s)	141.0	C-8′	C-5′
2″		161.8	C-2″	
3″	6.20 (s)	111.6	C-3″	C–CH_3
4″		156.4	C-4″	
5″	7.26 (d, 8.8)	126.8	C-5″	C-8″, C-10″
6″	6.82 (d, 8.8)	112.8	C-6″	C-7″, C-8″
7″		160.6	C-7″	
8″	6.87 (s)	101.7	C-8″	C-6″, C-7″, C-9″
9″		153.8	C-9″	
10″		113.6	C-10″	
CH_3	2.37 (s)	18.6	C–CH_3	H-3″
OH	5.13 (t, 5.5)			C-2
NH_2	7.16 (s)			C-5′

[a] ^{1}H NMR and ^{13}C NMR spectra were measured at 500 and 125 MHz, respectively. Couling constants (in parentheses) are given in Hz.

ether bond formed between C-4 and C-7″. The long-range correlations of H-2 with C-8′, C-1, C-3, and C-4, respectively, were observed and demonstrated that target molecule **1c** was the N-9′ regioisomer as shown in Figure 3.

Compounds **1a**, **1b**, **1c**, and **1d** were tested for inhibition of cytopathogenicity against different cancer cells such as the colon cancer HCT-8 cell, the cervical cancer HELA cell, the pulmonary cancer A549 cell and the skin cancer A431 cell in pharmacological primary screen model as shown in Table 3. In comparison to the target molecules against the different types of cancer cells, **1d** exhibited higher anticancer activity against skin cancer A431 cell and pulmonary cancer A549 cell. These results probably provided a valuable research route to look for novel types of chiral acyclic nucleoside analogues with new biological activities.

3. Conclusion

An efficient synthetic strategy for chiral acyclic nucleoside analogues containing both the phenoxy components of some bioactive natural compounds and a heterocyclic base was achieved through two key synthetic tactics. One was the asymmetric Michael addition of the chiron 5-(*R*)-(−)-menthyloxy-2(5*H*)-furanone **5** with adenine and the subsequent reduction reaction, which provided the key chiral intermediate, 2-(*R*)-(9′-adeninyl)-1,4-butanediol **8**. The other was the intermolecular dehydration reaction between chiral **8** and phenoxy components **9** to form the target compounds **1**. The enantiopure acyclic nucleoside analogues exhibited potential anticancer activity.

4. Experimental

4.1. General

Infrared spectra were recorded on a Fourier 170-sx spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker-500 MHz spectrometer and the chemical shifts were expressed in δ-values using TMS as the internal standard. Mass spectra were determined with a Finnegan GC2000/TRACE TM/MS mass spectrometer. Microanalyses were performed on a Perkin-Elemer 240-C elemental analyzer. Melting point was determined on a XT Digital melting-point apparatus with microscope and uncorrected. All chemical reagents were commercially available and treated with standard methods before use. Solvents were dried in a routine way and redistilled.

4.2. Synthesis of 2-(*R*)-(9′-adeninyl)-1,4-butanediol (8)

To a solution of 6 mmol $LiAlH_4$ in dry THF (20 mL) was added **7** (2 mmol) in dry THF (40 mL) under nitrogen atmosphere. The reaction mixture was stirred for 12–24 h until **7** had been consumed. Saturated Na_2SO_4 solution was added to decompose excess $LiAlH_4$, followed by addition of ethanol (20 mL). Then the mixture was filtered, washed with ethanol. The combined organic layer was dried and concentrated in vacuum and purified by flash chromatography to afford 368 mg (82%) of **8** as colorless crystals. Mp 181.3–181.7 °C; $[\alpha]_D^{20}+41.6$ (c 1.0, CH_3OH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.02–2.04 (1H, m, H-3), 2.09–2.15 (1H, m, H-3), 3.20–3.23 (1H, m, H-4), 3.31–3.33 (1H, m, H-4), 3.68–3.72 (1H, m, H-1), 3.84–3.88 (1H, m, H-1), 4.60 (1H, t, $J_{HO-CH_2}=5.28$ Hz, OH), 4.62–4.64 (1H, m, H-2), 5.03 (1H, t, OH), 7.19 (2H, s, NH_2), 8.11 (2H, s, H-8′, 2′); ^{13}C NMR (125 MHz, DMSO-d_6) δ 33.4 (C-3), 55.1 (C-2), 57.6 (C-4), 62.8 (C-1), 119.3 (C-5′), 141.1 (C-8′), 150.0 (C-6′), 152.4 (C-2′), 156.2 (C-4′); IR (KBr, cm^{-1}): 3426 (br OH), 1648, 1599, 1575, 1484. Anal. Calcd for $C_9H_{13}N_5O_2$: C, 48.42; H, 5.87; N, 31.37. Found: C, 48.37; H, 5.89; N, 31.11.

Table 3. Inhibitory ratio (IR)[a] and corresponding inhibitory concentrations (IC_{50})[b] of chiral acyclic nucleoside analogues on the cytopathogenicity of different cancer cells, in pharmacological primary screen model

Compound	Colon cancer HCT-8 cell IR/IC_{50} (μg/mL)	Cervical cancer HELA cell IR/IC_{50} (μg/mL)	Pulmonary cancer A549 cell IR/IC_{50} (μg/mL)	Skin cancer A431 cell IR/IC_{50} (μg/mL)
1a	9.5/50	7.6/50	23.9/50	58.8/4.10
1b	23.7/50	−1.5/50	31.6/50	78.1/12.0
1c	43.5/61.7	33.0/>50	39.2/>50	42.4/53.1
1d	84.9/9.5	79.3/16.1	82.7/16.8	80.5/5>IC_{50}<50

[a] Inhibitory ratio (IR) was obtained through the use of the concentration of 50 μg/mL.
[b] Inhibitory concentrations (IC_{50}) were determined through the use of an established MTTmethod[11,12] and represent the average of duplicate determinations.

4.3. General procedure for the preparation of (1a–1e)

To a mixture of compound **8** (1 mmol), ROH **9** (1.2 mmol), Ph_3P (1.2 mmol) in 1 mL THF, DEAD (1.2 mmol) in THF (0.5 mL) was added dropwise. The solution was stirred at room temperature under N_2 atmosphere for 1–3 days. The solvent was removed in vacuum and the crude product was obtained and further purified by flash chromatography to afford the target compounds **1a**–**1e**.

4.3.1. 2-(*R*)-(9′-Adeninyl)-4-(4″-chlorophenoxy)-butan-1-ol (1a). One hundred and thirty milligrams, yield 43%; mp 185.7–186.3 °C; $[\alpha]_D^{20}+80.0$ (*c* 1.0, DMSO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.34–2.37 (1H, m, H-3), 2.44–2.49 (1H, m, H-3), 2.44–2.49 (2H, m, H-1), 3.88–3.95 (2H, m, H-4), 4.70–4.73 (1H, m, H-2), 5.11 (1H, t, OH), 6.83 (2H, d, $J=9.0$ Hz, H-2″, 6″), 7.16 (2H, s, NH_2), 7.26 (2H, d, $J=9.0$ Hz, H-3″, 5″), 8.08 (1H, s, H-2′), 8.15 (1H, s, H-8′); ^{13}C NMR (125 MHz, DMSO-d_6) δ 30.0 (C-3), 55.2 (C-2), 62.8 (C-1), 65.3 (C-4), 116.6 (C-2″, 6″), 119.4 (C-5′), 124.7 (C-4″), 129.6 (C-3″, 5″), 141.0 (C-8′), 150.1 (C-6′), 152.5 (C-2′), 156.3 (C-4′), 157.6 (C-1″); IR (KBr, cm^{-1}): 3442 (br OH), 1678, 1605, 1492; HRMS (FAB^+) *m/z* calcd for $C_{15}H_{17}ClN_5O_2$ $(M+H)^+$334.1071, found 334.1070.

4.3.2. 2-(*R*)-(9′-Adeninyl)-4-(4″-acetophenyl)-butan-1-ol (1b). One hundred and twelve milligrams, yield 44%; mp 233.8–235.0 °C; $[\alpha]_D^{20}+85.9$ (*c* 1.0, DMSO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.09 (3H, s, CH_3), 2.37–2.40 (1H, m, H-3), 2.50–2.51 (1H, m, H-3), 3.76–3.79 (1H, m, H-1), 3.86–3.92 (2H, m, H-1, 4), 4.03–4.06 (1H, m, H-4), 4.72–4.75 (1H, m, H-2′), 5.14 (1H, t, OH), 6.89 (2H, d, $J=8.8$ Hz, H-2″,6″), 7.21 (2H, s, NH_2), 7.86 (2H, d, $J=8.8$ Hz, H-3″,5″), 8.08 (1H, s, H-2′), 8.17 (1H, s, H-8′); ^{13}C NMR (125 MHz, DMSO-d_6) δ 26.8 (CH_3), 30.0 (C-3), 55.2 (C-2), 62.8 (C-1), 65.3 (C-4), 114.7 (C-2″,6″), 119.0 (C-5′), 130.4 (C-4″), 130.8 (C-3″,5″), 141.0 (C-8′), 150.1 (C-6′), 152.4 (C-2′), 156.2 (C-4′), 162.6 (C-1″), 196.7 (C=O); IR (KBr, cm^{-1}): 3307 (br OH), 1677 (C=O). Anal. Calcd for $C_{17}H_{19}N_5O_3$: C, 59.81; H, 5.61; N, 20.51. Found: C, 59.22; H, 5.80; N, 20.02.

4.3.3. 2-(*R*)-(9′-Adeninyl)-4-[7″-(4″-menthylumbelliferonyl)]-butan-1-ol (1c). One hundred and ninety three milligrams, yield 52%; mp 202.3–202.4 °C; $[\alpha]_D^{20}+85.6$ (*c* 0.9, DMSO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.37 (3H, s, CH_3), 2.40–2.42 (1H, m, H-3), 2.47–2.51 (1H, m, H-3), 3.77–3.81 (1H, m, H-1), 3.88–3.94 (2H, m, H-1, 4), 4.07–4.11 (1H, m, H-4), 4.73–4.75 (1H, m, H-2), 5.13 (1H, t, OH), 6.20 (1H, s, H-3″), 6.82 (1H, d, $J=8.8$ Hz, H-6″), 6.87 (1H, s, H-8″), 7.16 (2H, s, NH_2), 7.26 (1H, d, $J=8.8$ Hz, H-5″), 8.08 (1H, s, H-2′), 8.16 (1H, s, H-8′); ^{13}C NMR (125 MHz, DMSO-d_6) δ 18.6 (CH_3), 29.8 (C-3), 55.3 (C-2), 62.9 (C-1), 65.8 (C-4), 101.7 (C-8″), 111.6 (C-3″), 112.8 (C-6″), 113.6 (C-10″), 119.5 (C-5′), 126.8 (C-5″), 141.0 (C-8′), 150.2 (C-6′), 152.5 (C-2′), 153.8 (C-9″), 155.1 (C-4′), 156.4 (C-4″), 160.6 (C-7″), 161.8 (C-2″); IR (KBr, cm^{-1}): 3424 (br OH), 1711 (C=O); HRMS (FAB^+) *m/z* calcd for $C_{19}H_{20}N_5O_4$ $(M+H)^+$382.1515, found 382.1514.

4.3.4. 2-(*R*)-(9′-Adeninyl)-4-(3″-estronyl)-butan-1-ol (1d). Two hundred and fifty one milligrams, yield 75%; mp 242.4–244.5 °C; $[\alpha]_D^{20}+141.1$ (*c* 0.9, DMSO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.82 (3H, s, H-18″), 2.43–2.46 (2H, m, H-3), 2.75–2.78 (2H, m, H-16″), 3.70–3.77 (2H, m, H-4), 3.87–3.91 (2H, m, H-1), 4.69–4.71 (1H, m, H-2), 5.11 (1H, t, OH), 6.48 (1H, s, H-4″), 6.57 (1H, dd, $J=2.5$, 8.6 Hz, H-2″), 7.11 (1H, d, $J=8.6$ Hz, H-1″), 7.20 (2H, s, NH_2), 8.10 (1H, s, H-2′), 8.15 (1H, s, H-8′); ^{13}C NMR (125 MHz, DMSO-d_6) δ 14.0 (C-18″), 29.5 (C-3), 55.3 (C-2), 62.8 (C-1), 64.7 (C-4), 112.6 (C-4″), 114.6 (C-2″), 119.2 (C-5′), 126.6 (C-1″), 132.3 (C-10″), 137.8 (C-5″), 141.0 (C-8′), 150.1 (C-6′), 152.5 (C-2′), 156.6 (C-4′), 220.2 (C-17″); IR (KBr, cm^{-1}): 3437 (br OH), 1732 (C=O); HRMS (FAB^+) *m/z* calcd for $C_{27}H_{34}N_5O_3$, $(M+H)^+$476.2662, found 476.2650.

4.3.5. 2-(*R*)-(9′-Adeninyl)-4-[4″-(2‴,4‴,6‴-trimethoxyldihydrochalcony1)]-butan-1-ol (1e). Two hundred and seventy nine milligrams, yield 53%; mp 100.1–102.0 °C; $[\alpha]_D^{20}+12.0$ (*c* 0.2, DMSO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.36–2.41 (1H, m, H-3), 2.48–2.51 (1H, m, H-3), 2.74–2.77 (2H, m, H-β), 2.88–2.91 (2H, m, H-α), 3.73 (6H, s, 2× OCH_3), 3.76 (3H, s, OCH_3), 3.78–3.79 (1H, m, H-1), 3.88–3.90 (2H, m, H-1,4), 4.03–4.06 (1H, m, H-4), 4.71–4.73 (1H, m, H-2), 5.14 (1H, t, OH), 6.21 (2H, s, H-3‴,5‴), 6.89 (2H, d, $J=8.8$ Hz, H-3″,5″), 7.18 (2H, s, NH_2), 7.86 (2H, d, $J=8.8$ Hz, H-2″,6″), 8.08 (1H, s, 2′), 8.17 (1H, s, H-8′); ^{13}C NMR (125 MH_Z, DMSO-d_6) δ 18.8 (C-β), 30.0 (C-3), 38.5 (C-α), 55.2 (C-2), 55.6 (OCH_3), 56.1 (OCH_3), 62.8 (C-1), 65.3 (C-4), 91.2 (C-3‴,5‴), 109.0 (C-1‴), 114.7 (C-3″, 5″), 129.9 (C-1″), 130.6 (C-2″, 6″), 141.0 (C-8′), 150.2 (C-6′), 152.5 (C-2′), 156.4 (C-4′), 158.7 (C-2‴, 6‴), 159.8 (C-4‴), 162.5 (C-4″), 198.8 (C=O); IR (KBr, cm^{-1}): 3437 (br OH), 1670 (C=O); HRMS (FAB^+) *m/z* calcd for $C_{27}H_{32}N_5O_6$, $(M+H)^+$522.2353, found 522.2348.

4.3.6. 3-(*R*)-(9′-Adeninyl)-tetrahydrofuran(10). Mp 202.3–203.1 °C; $[\alpha]_D^{20}-2.2$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.29–2.30 (1H, m, H-4), 2.47–2.50 (1H, m, H-4), 3.84–3.89 (1H, m, H-5), 3.96–3.97 (2H, m, H-2, 5), 4.08–4.11 (1H, m, H-2), 5.15–5.19 (1H, m, H-3), 7.25 (2H, s, NH_2), 8.14 (1H, s, H-2′), 8.15 (1H, s, H-8′); ^{13}C NMR (125 MHz, DMSO-d_6) δ 32.3 (C-4), 54.4 (C-3), 67.0 (C-5), 72.2 (C-2), 119.3 (C-5′), 139.3 (C-8′), 149.8 (C-6′), 152.8 (C-2′), 156.4 (C-4′); IR (KBr, cm^{-1}): 3341.9, 3180.9, 1652.0. Anal. Calcd for $C_9H_{11}N_5O$: C, 52.67; H, 5.40; N, 34.13. Found: C, 52.78; H, 5.30; N, 33.59.

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A novel access to highly functionalised β-lactams by regio- and stereoselective 1,3-dipolar cycloaddition reaction

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Abstract—A highly regio- and stereoselective synthesis of novel spiro pyrrolidines/pyrrolizidines containing β-lactam and oxazolone moieties under two different conditions is achieved using [3+2] cycloaddition methodology in moderate to good yield.

1. Introduction

cis-Substituted-4-formyl-2-azetidinones are versatile building blocks[1] that can serve not only for the synthesis of β-lactam antibiotics including monolactams, carbapenems, carbacephems and isooxacephems[2] but also for the preparation of other useful non-β-lactam synthetic targets such as β-substituted aspartic acid derivatives and isoserines. In recent years several natural β-lactams have been shown to exhibit high antibacterial activity. 1,3,4-Trisubstituted β-lactams were found to be new, potent cholesterol absorption inhibitors,[3] human cylomegalonims, protease inhibitors[4] and thrombin inhibitors.[5]

Spiro compounds represent an important class of naturally occurring compounds characterized highly pronounced biological properties.[6–9] The most developed protocol for the synthesis of these compounds depends on the cycloaddition to an exocyclic bond. Furthermore, oxazolone heterocycles are found in a large number of polycyclic compounds with high biological activity and there has been large number of examples of these *N,O*-heterocycles being used as key building blocks in the total synthesis of natural and unnatural compounds.

Recently, the intermolecular 1,3-dipolar cycloaddition reaction of nitrones containing β-lactam derivaties with alkenes has been reported.[10] In connection with this, we wish to report on the synthesis of substituted spiropyrrolidines containing β-lactam and oxazolone moieties through 1,3-dipolar cycloaddition reaction of azomethine ylide generated through decarboxylative route. Having decided to extend the study of β-lactam in the dipolar cycloaddition, we adopted the decarboxylative route and were successful in synthesizing a series of spiro compounds containing oxazolone and β-lactam moieties in moderate to good yield, through two different sets of conditions.

2. Results and discussion

The synthesis began with the known *cis*-4-formyl-2-azetidinone and various *p*-substituted arylidene oxazolones as starting materials, which were prepared according to literature procedures.[11,12] The azomethine ylide generated from the secondary acyclic and cyclic amino acids (sarcosine and proline) with *cis*-4-formyl-2-azetidinone by two different methods:

(i) Refluxing in toluene using Dean-Stark apparatus.

(ii) Using camphor sulphonic acid (CSA) as catalyst in refluxing toluene readily undergoes [3+2] cycloaddition with (*Z*) 2-phenyl-4-arylidene-5-(4*H*)-oxazolones to yield novel spiro cycloadducts 1-*N*-methyl-2-[1″-*N*-(*p*-methoxyphenyl)-3″-phenylazetidine-2″-one]spiro[3.4′]-(2′-phenyloxazol-5′-one)-4-arylpyrrolidine **4a–e** and 2-[1″-*N*-(*p*-methoxyphenyl)-3″-phenylazetidine-2″-onespiro [3.4′]-(2′-phenyloxazol-5′-one)-4-arylpyrrolizidines **7a–e** in moderate to good yield (Table 1, Schemes 1 and 2).

The cycloadducts were characterized by spectral and elemental analysis. The ^{1}H NMR spectrum of **4a** showed well separated doublets for H_A and H_C protons at δ 5.06 and

Keywords: Cycloaddition; β-Lactam; Azomethine ylide.
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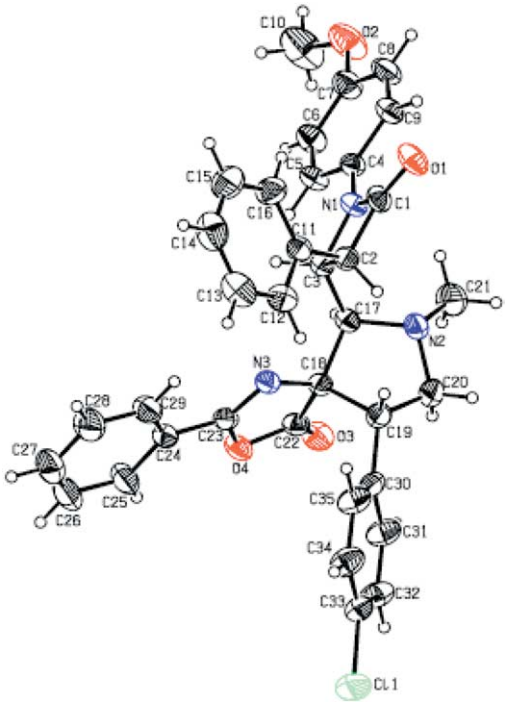
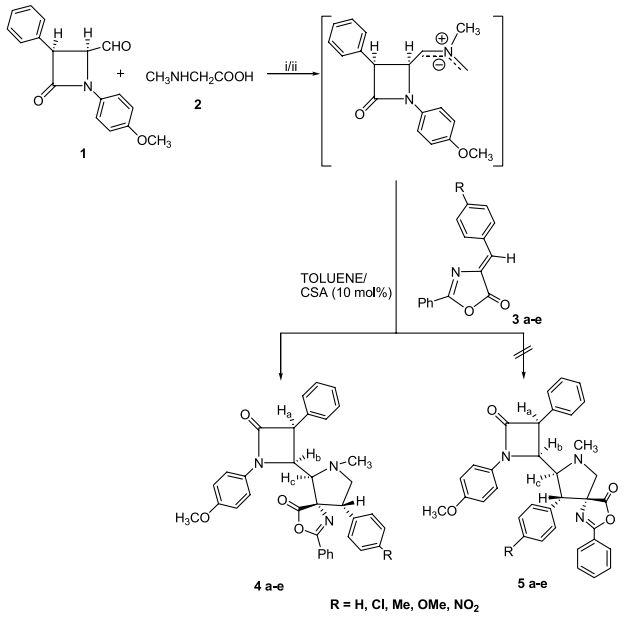


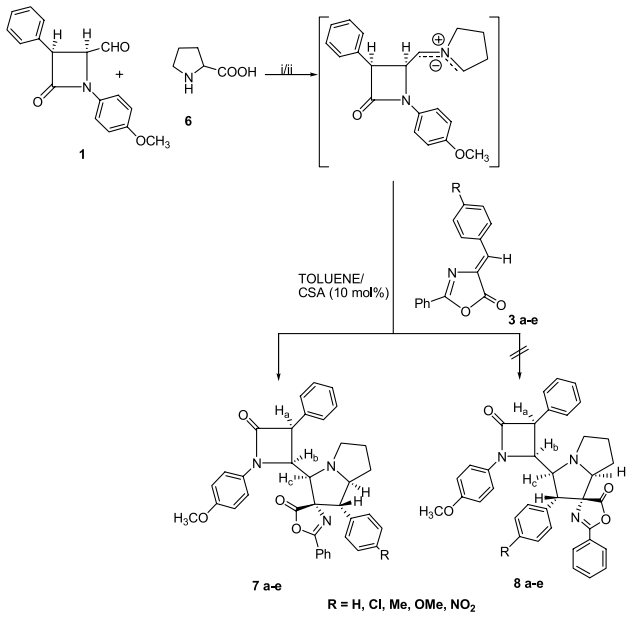
Figure 1. ORTEP diagram of **4b**.



Scheme 1. Reagents and conditions: (i) Reflux in toluene at 120 °C, 3 h; (ii) CSA (10 mol%) in toluene at 120 °C, 2 h.

4.01, respectively. The H_B proton resonates as doublet of doublet at δ 4.17 (J=7.9, 5.6 Hz). The multiplet for benzylic proton appeared in the region δ 3.95–3.98. The ^{13}C NMR spectrum of **4a** showed peaks at δ 161.13 and 178.59 ppm for the amide carbonyl and oxazolone ring carbonyl carbon, respectively. The structure of **4b** was further confirmed by X-ray analysis (Fig. 1).

To extend the scope of the reaction, we have investigated the reaction of azomethine ylide generated from cyclic secondary amino acid, proline.



Scheme 2. Reagents and conditions: (i) Reflux in toluene at 120 °C, 2 h; (ii) CSA (10 mol%) in toluene at 120 °C, 2 h.

Table 1. Cycloaddition of sarcosine and *cis*-4-formyl-2-azetidinone with 4-arylidene-2-phenyloxazol-5-one under two different conditions

Entry	Yield %	
	In toluene[a]	CSA (10 mol%) in toluene[b]
4a R=H	20	75
4b R=Cl	35	80
4c R=Me	28	78
4d R=OMe	18	70
4e R=NO_2	45	90

[a] Reaction time in toluene for **4a–e** was 60–72 h at 120 °C.
[b] Reaction time in CSA (10 mol%)/toluene for **4a–e** was 1–2 h at 120 °C.

The cycloadducts were characterized by spectral and elemental analysis. The ^{1}H NMR spectrum of **7a** showed a doublet of doublet for the H_B proton at δ 4.27. The doublets at δ 5.16 and 4.17 corresponds to the H_A and H_C protons, respectively. The methylene protons of the pyrrolizidine ring system showed a multiplet in the region δ 1.8–2.9. The benzylic proton showed a doublet at δ 4.05. The ^{13}C NMR spectrum of **7a** exhibits two peaks at δ 152.13 and at 180.09 ppm for the carbonyl carbon of the β-lactam ring and oxazolone carbonyl carbons, respectively. The stereochemistry of the ring junction proton of the products **7a–e** obtained was corroborated to the X-ray structure of the similar type of compounds[13].

Table 2. Cycloaddition of proline and *cis*-4-formyl-2-azetidinone with 4-arylidene-2-phenyloxazol-5-one under two different conditions

Entry	Yield %	
	In toluene[a]	CSA (10 mol%) in toluene[b]
7a R=H	28	70
7b R=Cl	30	85
7c R=Me	27	73
7d R=OMe	15	67
7e R=NO_2	37	88

[a] Reaction time in toluene for **7a–e** was 48–60 h at 120 °C.
[b] Reaction time in CSA (10 mol%)/toluene for **7a–e** was 1–1.5 h at 120 °C.

In the above reactions the time and yield were studied under two different conditions: it was found that the use of toluene alone gave poor yield with the reaction time ranging from 48–72 h. In order to increase the yield of the cycloadducts, CSA (10 mol%) was used as a catalyst. Changing the solvent to the lower boiling benzene or higher boiling *o*-dichlorobenzene resulted in poor yield of the cycloaddition product. Switching to a more polar solvent (propionitrile or *N*-methylpyrrolidinone) resulted in no cycloadduct after heating for several days and only the starting materials were recovered (Table 2).

In conclusion, the present study provides the first insight into the manner, in which the *cis*-4-formyl-2-azetidinone undergoes 1,3-dipolar cycloaddition through decarboxylation route with various para substituted arylidene oxazolones. In addition, in all the cases the reaction has been shown to be highly stereo- and regioselective providing the synthetically feasible novel entry into various types of substituted spiro pyrrolidines and pyrrolizidines containing oxazolone and β-lactam units.

3. Experimental

3.1. General

All melting points are uncorrected. IR spectra were recorded on a SHIMADZU FT-IR 8300 instrument. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on a JEOL 400 spectrometer at 400 and 100 MHz, respectively. Mass spectra were recorded on a JEOL DX 303 HF spectrometer. Elemental analysis were carried out on a Perkin–Elmer 240 B instrument.

3.2. Representative procedure for the synthesis of spiropyrrolidine/pyrrolizidine cycloadducts

(i) A solution of *cis*-4-formyl-2-azetidinones (1 mmol), sarcosine/proline (1 mmol) and (*Z*) 2-phenyl-4-arylidene-5-(4*H*)-oxazolone (1 mmol) was refluxed in toluene using Dean–Stark apparatus. The completion of the reaction was evidenced by TLC analysis. The solvent was then removed in vacuo. The crude was then subjected to column chromatography using petroleum ether/ethylacetate (8:2) as eluent.

(ii) A solution of *cis*-4-formyl-2-azetidinones (1 mmol), sarcosine/proline (1 mmol), 4-arylidene-2-phenyl-oxazol-5-one (1 mmol) and CSA (10 mol%) was refluxed in toluene using Dean–Stark apparatus. The completion of the reaction was evidenced by TLC analysis. The solvent was then removed in vacuo. The crude was then subjected to column chromatography using petroleum ether/ethylacetate (8:2) as eluent.

3.2.1. 1-*N*-Methyl-2-[1″-*N*-(*p*-methoxyphenyl)-3″-phenyl azetidine-2″-one]spiro[3.4′]-(2′-phenyloxazol-5′-one)-4-phenyl pyrrolidine (4a). As a white solid (4.1 g, 75%), mp 245 °C; IR (KBr): 1739, 1647 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.60–6.65 (19H, m, Ph), 5.16 (1H, dd, $J=11.0$, 7.3 Hz, C*H*Ph), 5.08 (1H, d, $J=5.2$ Hz, CH_APh), 4.15 (1H, dd, $J=11.0$, 9.8 Hz, NCH_2), 4.07 (1H, dd, $J=8.0$, 5.2 Hz, CH_B), 3.85 (1H, d, $J=8.0$ Hz, CH_C), 3.75 (3H, s, OCH_3), 3.43 (1H, dd, $J=9.8$, 7.3 Hz, NCH_2), 2.35 (3H, s, NCH_3); δ_C (100 MHz, $CDCl_3$) 179.72, 168.73, 163.32, 157.53, 156.69, 143.00, 142.27, 141.60, 140.56, 137.51, 136.94, 136.57, 134.36, 133.23, 132.52, 131.73, 130.81, 129.23, 128.15, 127.72, 125.26, 124.69, 123.03, 120.97, 120.64, 120.05, 117.73, 115.25, 69.76, 59.90, 59.61, 57.25, 54.72, 48.53, 43.85, 40.73, 26.89, 22.53 ppm; Mass *m/z*: 557 (M^+). Anal. Calcd for $C_{35}H_{31}N_3O_4$: C, 75.40; H, 5.56; N, 7.54. Found: C, 75.66; H, 5.74; N, 7.25.

3.2.2. 1-*N*-Methyl-2-[1″-*N*-(*p*-methoxyphenyl)-3″-phenyl azetidine-2″-one]spiro[3.4′]-(2′-phenyloxazol-5′-one)-(4-*p*-chlorophenyl)pyrrolidine (4b). As a white solid (4.7 g, 80%), mp 267 °C; IR (KBr): 1740, 1645 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.48–6.88 (18H, m, Ph), 5.18 (1H, dd, $J=11.1$, 7.3 Hz, C*H*Ph), 5.10 (1H, d, $J=5.4$ Hz, CH_APh), 4.21 (1H, dd, $J=11.1$, 9.5 Hz, NCH_2), 4.00 (1H, dd, $J=8.1$, 5.4 Hz, CH_B), 3.65 (1H, d, $J=8.1$ Hz, CH_C), 3.62 (3H, s, OCH_3), 3.38 (1H, dd, $J=9.5$, 7.3 Hz, NCH_2), 2.41 (3H, s, NCH_3); δ_C (100 MHz, $CDCl_3$) 178.32, 162.25, 157.03, 156.56, 156.45, 135.89, 134.29, 133.13, 130.25, 129.26, 128.87, 128.73, 128.65, 128.57, 128.04, 127.24, 126.24, 126.08, 125.93, 124.62, 118.56, 114.87, 114.76, 79.85, 67.97, 62.09, 57.56, 56.80, 51.95, 43.32 ppm; Mass *m/z*: 593 ($M^+ + 2$), 591 (M^+). Anal. Calcd for $C_{35}H_{30}N_3O_4Cl$: C, 71.01; H, 5.08; N, 7.10. Found: C, 70.71; H, 5.37; N, 7.21.

3.2.3. 1-*N*-Methyl-2-[1″-*N*-(*p*-methoxyphenyl)-3″-phenyl-azetidine-2″-one]spiro[3.4′]-(2′-phenyloxazol-5′-one)-(4-*p*-methylphenyl)pyrrolidine (4c). As a white solid (4.4 g, 78%), mp 256 °C; IR (KBr): 1741, 1645 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.55–6.68 (18H, m, Ph), 5.10 (1H, dd, $J=11.1$, 7.2 Hz, C*H*Ph), 4.96 (1H, d, $J=5.2$ Hz, CH_APh), 4.23 (1H, dd, $J=11.1$, 9.6 Hz, NCH_2), 3.85 (1H, dd, $J=8.1$, 5.2 Hz, CH_B), 3.67 (1H, d, $J=8.1$ Hz, CH_C), 3.62 (3H, s, OCH_3), 3.41 (1H, dd, $J=9.6$, 7.2 Hz, NCH_2), 2.61 (3H, s, CH_3), 2.45 (3H, s, NCH_3); δ_C (100 MHz, $CDCl_3$) 180.13, 167.25, 161.16, 157.05, 152.46, 141.76, 141.58, 140.68, 140.13, 138.69, 134.75, 129.70, 129.26, 129.00, 128.38, 128.04, 127.56, 127.31, 124.58, 123.62, 123.12, 121.70, 120.15, 119.90, 117.83, 116.72, 70.12, 59.15, 58.75, 56.13, 53.73, 46.73, 45.15, 40.53, 26.49, 23.57, 20.53 ppm; Mass *m/z*: 571 (M^+). Anal. Calcd for $C_{36}H_{33}N_3O_4$: C, 75.66; H, 5.78; N, 7.35. Found: C, 75.85; H, 5.56; N, 7.55.

3.2.4. 1-*N*-Methyl-2-[1″-*N*-(*p*-methoxyphenyl)-3″-phenyl-azetidine-2″-one]spiro[3.4′]-(2′-phenyloxazol-5′-one)-(4-*p*-methoxyphenyl)pyrrolidine (4d). As a white solid (4.1 g, 70%), mp 250 °C; IR (KBr): 1743, 1643 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.63–6.60 (18H, m, Ph), 5.12 (1H, dd, $J=11.0$, 7.3 Hz, C*H*Ph), 4.78 (1H, d, $J=5.3$ Hz, CH_APh), 4.20 (1H, dd, $J=11.0$, 9.6 Hz, NCH_2), 3.91 (1H, dd, $J=8.0$, 5.3 Hz, CH_B), 3.72 (1H, d, $J=8.0$ Hz, CH_C), 3.67 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 3.58 (1H, dd, $J=9.6$, 7.3 Hz, NCH_2), 2.40 (3H, s, NCH_3); δ_C (100 MHz, $CDCl_3$) 182.01, 170.77, 160.31, 141.84, 141.60, 140.23, 139.92, 139.56, 135.69, 132.36, 129.77, 129.68, 128.00, 127.63, 120.33, 117.23, 115.90, 115.78, 68.16, 58.93, 58.12, 57.15, 57.13, 54.16, 46.68, 46.15, 41.58, 27.89, 24.56 ppm; Mass *m/z*: 587 (M^+). Anal. Calcd for $C_{36}H_{33}N_3O_5$: C, 73.59; H, 5.62; N, 7.15. Found: C, 73.77; H, 5.42; N, 7.34.

3.2.5. 1-*N*-Methyl-2-[1″-*N*-(*p*-methoxyphenyl)-3″-phenyl-azetidine-2″-one]spiro[3.4′]-(2′-phenyloxazol-5′-one)-(4-*p*-nitrophenyl)pyrrolidine (4e). As a pale yellow solid (5.1 g, 90%), mp 259 °C; IR (KBr): 1742, 1645 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.59–6.81 (18H, m, Ph), 5.11 (1H, dd, $J=11.0$, 7.4 Hz, C*H*Ph), 4.98 (1H, d, $J=5.2$ Hz, CH_APh), 4.18 (1H, dd, $J=11.0$, 9.8 Hz, NCH_2), 3.92 (1H, dd, $J=8.1$, 5.2 Hz, CH_B), 3.67 (1H, d, $J=8.1$ Hz, CH_C), 3.65 (3H, s, OCH_3), 3.48 (1H, dd, $J=9.8$, 7.4 Hz, NCH_2), 2.40 (3H, s, NCH_3); δ_C (100 MHz, $CDCl_3$) 178.15, 169.83, 164.16, 154.32, 139.12, 135.83, 132.76, 131.07, 130.10, 129.85, 128.01, 127.71, 127.36, 127.15, 125.89, 125.72, 123.66, 120.89, 120.70, 120.35, 119.95, 119.76, 118.27, 115.94, 70.15, 58.93, 58.75, 58.15, 53.71, 49.56, 44.76, 41.32, 28.75, 23.76 ppm; Mass *m/z*: 602 (M^+). Anal. Calcd for $C_{35}H_{30}N_4O_6$: C, 69.77; H, 4.98; N, 9.30. Found: C, 69.98; H, 5.21; N, 9.11.

3.2.6. 2-[1″-*N*-(*p*-Methoxyphenyl)-3″-phenyl-azetidine-2″-onespiro[3.4′]-(2′-phenyloxazol-5′-one)-4-phenyl-pyrrolizidine (7a). As a white solid (4.0 g, 70%), mp 190 °C; IR (KBr): 1741, 1647 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38–6.75 (19H, m, Ph), 5.10 (1H, d, $J=10.4$ Hz, C*H*Ph), 5.00 (1H, d, $J=6.0$ Hz, CH_APh), 4.23 (1H, dd, $J=8.1$, 6.0 Hz, CH_B), 4.15 (1H, d, $J=8.1$ Hz, CH_C), 3.65 (3H, s, OCH_3), 3.20–1.85 (7H, m, pyrrolizidine); δ_C (100 MHz, $CDCl_3$) 182.56, 170.09, 163.37, 141.26, 141.09, 140.25, 137.00, 136.94, 134.07, 128.00, 127.81, 126.69, 126.50, 125.73, 125.02, 124.88, 124.23, 121.59, 121.42, 120.32, 120.00, 115.89, 110.84, 80.05, 64.00, 57.02, 53.03, 52.91, 43.94, 40.53, 36.84 ppm; Mass *m/z*: 583 (M^+). Anal. Calcd for $C_{37}H_{33}N_3O_4$: C, 76.16; H, 5.66; N, 7.20. Found: C, 76.37; H, 5.86; N, 7.01.

3.2.7. 2-[1″-*N*-(*p*-Methoxyphenyl)-3″-phenylazetidine-2″-one-spiro[3.4′]-(2′-phenyloxazol-5′-one)-(4-*p*-chloro-phenyl) pyrrolizidine (7b). As a white solid (5.2 g, 85%), mp 195 °C; IR (KBr): 1743, 1645 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.48–6.83 (18H, m, Ph), 5.15 (1H, d, $J=10.4$ Hz, C*H*Ph), 4.96 (1H, d, $J=5.8$ Hz, CH_APh), 4.28 (1H, dd, $J=8.2$, 5.8 Hz, CH_B), 4.18 (1H, d, $J=8.2$ Hz, CH_C), 3.68 (3H, s, OCH_3), 3.18–1.78 (7H, m, pyrrolizidine); δ_C (100 MHz, $CDCl_3$) 180.07, 172.23, 162.25, 143.00, 140.79, 138.47, 138.39, 138.27, 137.22, 136.81, 135.00, 131.47, 130.03, 129.55, 127.00, 123.52, 123.36, 123.09, 122.27, 122.12, 120.00, 118.29, 116.07, 114.69, 114.42, 78.54, 63.79, 58.89, 53.93, 50.06, 42.27, 39.07, 37.82 ppm; Mass *m/z*: 619 ($M^+ +2$), 617 (M^+). Anal. Calcd for $C_{37}H_{32}N_3O_4Cl$: C, 71.96; H, 5.19; N, 6.81. Found: C, 72.15; H, 4.98; N, 7.03.

3.2.8. 2-[1″-*N*-(*p*-Methoxyphenyl)-3″-phenylazetidine-2″-onespiro[3.4′]-(2′-phenyloxazol-5′-one)-(4-*p*-methyl-phenyl) pyrrolizidine (7c). As a white solid (4.3 g, 73%), mp 205 °C; IR (KBr): 1740, 1642 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.63–6.75 (18H, m, Ph), 5.10 (1H, d, $J=10.2$ Hz, C*H*Ph), 5.01 (1H, d, $J=5.9$ Hz, CH_APh), 4.20 (1H, dd, $J=8.0$, 5.9 Hz, CH_B), 4.12 (1H, d, $J=8.0$ Hz, CH_C), 3.72 (3H, s, OCH_3), 2.32 (3H, s, CH_3), 3.05–1.79 (7H, m, pyrrolizidine); δ_C (100 MHz, $CDCl_3$) 179.11, 161.92, 156.81, 152.17, 133.86, 133.41, 133.19, 132.89, 131.51, 131.21, 129.94, 129.72, 129.15, 128.80, 128.35, 127.29, 127.14, 126.83, 126.12, 118.61, 118.35, 114.92, 114.47, 112.15, 80.23, 69.07, 62.57, 59.12, 56.98, 56.32, 55.91, 28.54, 27.93, 20.92 ppm; Mass *m/z*: 597 (M^+). Anal. Calcd for $C_{38}H_{35}N_3O_4$: C, 76.38; H, 5.86; N, 7.03. Found: C, 76.60; H, 5.65; N, 7.21.

3.2.9. 2-[1″-*N*-(*p*-Methoxyphenyl)-3″-phenylazetidine-2″-onespiro[3.4′]-(2′-phenyloxazol-5′-one)-(4-*p*-methoxy-phenyl) pyrrolizidine (7d). As a white solid (4.1 g, 67%), mp 198 °C; IR (KBr): 1741, 1647 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.83–6.75 (18H, m, Ph), 5.12 (1H, d, $J=10.3$ Hz, C*H*Ph), 5.08 (1H, d, $J=5.6$ Hz, CH_APh), 4.35 (1H, dd, $J=8.0$, 5.6 Hz, CH_B), 4.23 (1H, d, $J=8.0$ Hz, CH_C), 3.71 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 3.15–1.82 (7H, m, pyrrolizidine); δ_C (100 MHz, $CDCl_3$) 182.00, 175.76, 160.09, 158.93, 157.78, 152.54, 152.42, 140.60, 135.97, 133.33, 131.52, 129.81, 129.14, 128.76, 127.47, 127.04, 126.59, 126.35, 123.60, 122.07, 120.00, 119.60, 119.00, 114.82, 112.90, 76.82, 57.61, 55.23, 52.72, 43.04, 37.53, 34.27 ppm; Mass *m/z*: 613 (M^+). Anal. Calcd for $C_{38}H_{35}N_3O_5$: C, 74.39; H, 5.71; N, 6.85. Found: C, 74.59; H, 5.90; N, 6.63.

3.2.10. 2-[1″-*N*-(*p*-Methoxyphenyl)-3″-phenyl-azetidine-2″-onespiro[3.4′]-(2′-phenyloxazol-5′-one)-(4-*p*-nitro-phenyl) pyrrolizidine (7e). As a pale yellow solid (5.5 g, 88%), mp 189 °C; IR (KBr): 1745, 1648 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.48–6.56 (18H, m, Ph), 5.11 (1H, d, $J=10.4$ Hz, C*H*Ph), 5.02 (1H, d, $J=5.6$ Hz, CH_APh), 4.26 (1H, dd, $J=8.0$, 5.6 Hz, CH_B), 4.17 (1H, d, $J=8.0$ Hz, CH_C), 3.60 (3H, s, OCH_3), 3.12–1.80 (7H, m, pyrrolizidine); δ_C (100 MHz, $CDCl_3$) 183.75, 173.82, 162.04, 156.77, 156.24, 155.73, 152.00, 147.49, 147.25, 147.00, 146.92, 144.33, 142.37, 137.19, 136.40, 134.88, 130.35, 129.75, 129.00, 128.11, 125.36, 123.10, 122.88, 119.72, 116.60, 108.35, 75.29, 63.21, 51.63, 51.45, 50.00, 46.22, 35.60, 33.90 ppm; Mass *m/z*: 628 (M^+). Anal. Calcd for $C_{37}H_{32}N_4O_6$: C, 70.70; H, 5.09; N, 8.92. Found: C, 70.92; H, 4.91; N, 9.13.

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Facile synthesis and optical resolution of inherently chiral fluorescent calix[4]crowns: enantioselective recognition towards chiral leucinol

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Abstract—A series of tri-*O*-alkylated inherently chiral fluorescent calix[4]crowns in the cone conformations and a series of tetra-*O*-alkylated inherently chiral fluorescent calix[4]crowns in the partial cone conformations have been synthesized. By condensing with chiral auxiliary (*S*)-BINOL, the resulting diastereomers could be separated via preparative TLC. We found that the size of the crown moiety effected the separation of the diastereomers. Further, removal of the BINOL unit by hydrolysis furnished pairs of enantiomers with optical purity. Moreover, we found that a tetra-*O*-alkylated inherently chiral fluorescent calix[4]crown-6 in the partial cone conformation **6c** showed considerable enantioselective recognition capability towards chiral leucinol.

1. Introduction

Chiral calixarenes have attracted increasing attention in recent years due to their potential as enantioselective artificial receptors and asymmetric catalysts.[1] Besides the direct introduction of the chiral residues to the calixarene backbones, there is an alternative chiral source to the inherently chiral calixarenes from the asymmetric array of achiral residues on the calixarene skeletons. In spite of the ever-increasing reports on the synthesis of inherently chiral calix[4]arenes, their optical resolution is usually realized by HPLC method.[2] Only in two cases where the optical resolution were achieved via conventional column chromatography on silica gel.[3] Due to the difficulty of obtaining optically pure inherently chiral calix[4]arenes, so far there have been few reports regarding their recognition and catalysis properties.[2h,3a]

Among chemosensory systems, the fluorescence method has a great advantage because of its simple instrumentation, high selectivity and direct visual perception even in very dilute solutions.[4] In 1998, Takashi et al. reported the first example of a tri-*O*-alkylated inherently chiral fluorescent calix[4]arene (ABBH type), which was resolved by chiral HPLC (Chiralcel OD column). Its excimer fluorescence increased up to two-fold by the addition of, for example, L-alanine methyl ester or L-phenylglycinol, but no enantioselective discrimination was observed.[2h]

Recently, we have reported the synthesis of tri-*O*-alkylated racemic inherently chiral calix[4]crown-4 acids by the *O*-monoalkylation of 1,2-calix[4]crown-4. The optical resolution was achieved through their esterification using (*S*)-BINOL followed by diastereomer separation via preparative TLC.[5] To introduce the carboxylic group onto the calix[4]arene skeleton we used ethyl bromoacetate as the alkylating agent, followed by a hydrolysis to furnish. The carboxylic group may be further, condensed with the axial chiral auxiliary (*S*)-BINOL. It occurred to us that if methyl 3-(2-bromoethoxy)-naphthalene-2-carboxylate, as the fluorescent moiety bearing a potential carboxylic group, is introduced, the whole calixarene molecule may be endowed with fluorescent chirality. In addition, the crown ether moiety may be enlarged for suitable accommodation to some potential species. Herein, we report the synthesis of the tri-*O*-alkylated and tetra-*O*-alkylated inherently chiral fluorescent calix[4]crowns in the cone and partial cone conformations. The optical resolution was, in some cases, readily realized by the separation of the diastereomers derived from (*S*)-BINOL via preparative TLC and the subsequent removal of the BINOL unit. The recognition properties towards chiral aminoalcohols of the enantiopure inherently chiral calix[4]crowns were measured and the results showed that calix[4]crown-6 derivative had a

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ca. 2:1 bias for the enantioselective recognition capability towards chiral leucinol.

2. Results and discussion

2.1. Synthesis and optical resolution of tri-*O*-alkylated inherently chiral fluorescent calix[4]crowns in the cone conformations

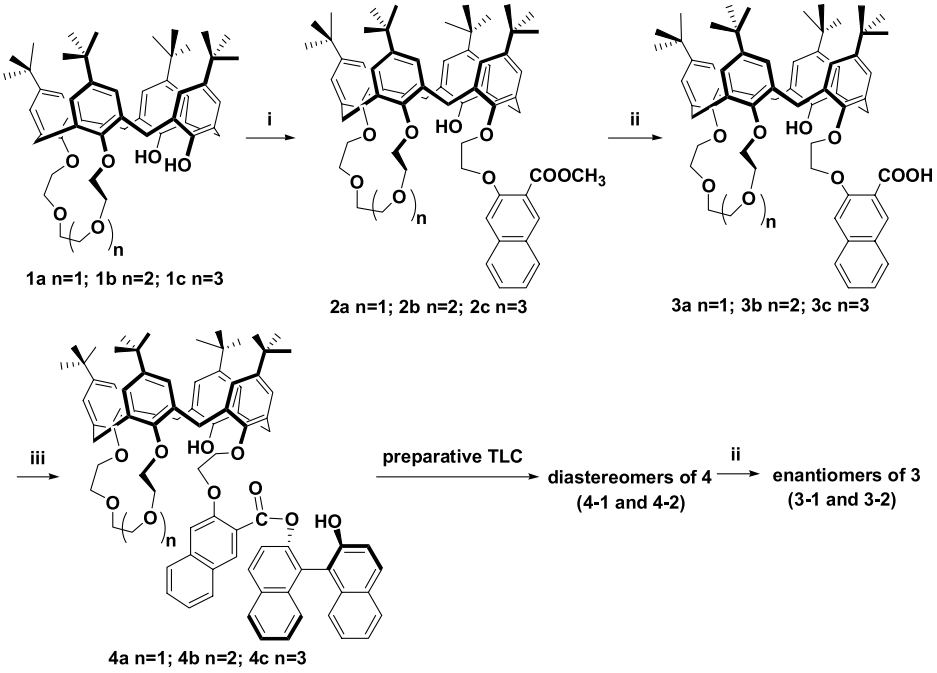
The reaction pathway is depicted in Scheme 1. The reaction of 1,2-calix[4]crown ethers **1**[6] with 1.2 equiv of methyl 3-(2-bromoethoxy)-naphthalene-2-carboxylate in the presence of 1 equiv of Cs_2CO_3 in dry DMF at 60 °C under nitrogen gave the racemic calix[4]crown ethers **2** in moderate yields. The absence of symmetry in tri-*O*-alkylated compounds **2** can be deduced from the complexity of their NMR spectra. In the ^{1}H NMR spectrum, in principle the signals for the ArCH_2Ar protons are supposed to appear as four pairs of doublets and those for the *tert*-butyl groups as four singlets. Yet in some cases (OCH_2CH_2O) they are obscured by other signals or overlapped with each other due to the lower dispersion of the ^{1}H scale. The ^{13}C NMR spectra show carbon signals close to that expected. Signals for the ArCH_2Ar carbons all appear around 31 ppm, indicating they adopt cone conformations.[7]

To confirm the presence of both enantiomers, the ^{1}H NMR spectra of **2** were also measured in the presence of excess (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Pirkle's reagent). As expected, several signals split into 1:1 ratios, the most significant splitting being the protons of the phenolic OH, CO_2CH_3 and *tert*-butyl groups, as shown for the typical compound **2b** in Figure 1.

The structure of **2b** was also unequivocally proven by a single crystal X-ray determination (Fig. 2). In the solid state, **2b** adopts a distorted cone conformation, which is defined by the angles, which the aromatic rings make with the plane of the four bridging methylene carbon atoms. The interplanar angles are 136.2° for the phenolic ring and 135.5° for its opposite ring, respectively, both rings being tilted so that their *tert*-butyl groups are pitched away from the calix cavity. Yet for the naphthalene-containing ring and its opposite ring, the interplanar angles are 99.6 and 84.4°, respectively, indicating the *tert*-butyl group of the latter aromatic ring is pitched slightly towards the calix cavity and the two aromatic rings are almost parallel to each other.

Compounds **2** were hydrolyzed to furnish the carboxylic acid derivatives **3** whose structures were confirmed from relevant spectroscopic data. Compounds **3**, which possess a carboxylic group, was reacted with the axial chiral auxiliary (*S*)-BINOL in the presence of DCC and DMAP in CH_2Cl_2 at room temperature to afford **4** as a pair of diastereomeric mixture. For the crown-4 and crown-5 derivatives **4a** and **4b**, TLC analysis showed two discrete spots after one or two runs of developing (petroleum ether–AcOEt = 8:3). Yet unfortunately, for the crown-6 derivatives **4c** the two spots were overlapped with each other even after several times of developing using diverse eluting solvents. It seems that increasing the size or the elasticity of the crown ether moiety has a detrimental influence upon the diastereomer separation. Using preparative TLC, we successfully separated the diastereomeric mixture **4a** to **4a–1** and **4a–2** while **4b** to **4b–1** and **4b–2** in ca. 1:1 ratios (de > 99% by HPLC analysis).

The ^{1}H NMR spectra of the isolated diastereomers show much difference as those of the typical **4a–1** and **4a–2**. For **4a–1**, four of the eight ArH protons are obscured by the signals of Naph-H, with other four protons appear as a pair



Scheme 1. Reagents and conditions: (i) methyl 3-(2-bromoethoxy)-naphthalene-2-carboxylate, Cs_2CO_3, DMF, 60 °C; (ii) 10% Me_4NOH, THF, reflux; (iii) (*S*)-BINOL, DCC, DMAP, CH_2Cl_2, rt **4–1** denotes the fractions of lower polarity from preparative TLC; **4–2** denotes that of higher polarity from preparative TLC. **3–1** and **3–2** were derived from **4–1** and **4–2**, respectively.

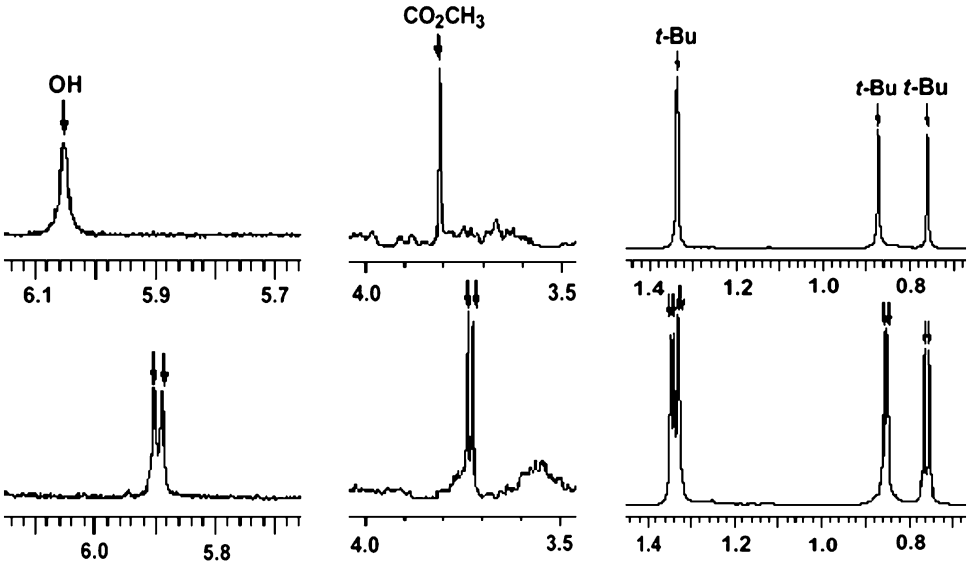


Figure 1. Partial ^{1}H NMR spectrum of **2b** in the absence (upper) and the presence (lower) of Pirkle's reagent. The three regions are plotted in different scales.

of doublets at 6.64 and 6.62 ppm and a pair of doublets at 6.49 and 6.45 ppm. Yet for **4a–2**, the signals for ArH protons appear as a pair of doublets at 7.20 and 7.17 ppm, a pair of doublets at 7.12 and 7.08 ppm, a pair of doublets at 6.65 and 6.60 ppm and a singlet at 6.47 ppm. The OH signal of **4a–1** appears at 5.93 ppm compared with that of **4a–2** appearing at 5.89 ppm. For the signals of the $ArCH_2Ar$ methylene protons, **4a–1** gives four pairs of doublets at 4.51, 4.44, 4.37, 4.29, 3.33, 3.24, 3.16 and 3.10 ppm while **4a–2** gives four pairs of doublets at 4.50, 4.48, 4.40, 4.22, 3.28, 3.24, 3.18 and 3.17 ppm. In addition, the signals for OCH_2CH_2O protons demonstrate quite different splitting pattern too. This phenomena may be attributed to the interaction between binaphthyl moiety and calix[4]arene inherent chirality, the existence of the outer chirality of (*S*)-BINOL distorting the diastereomeric calix[4]arene backbones to different degrees. It is obvious that the structural differences of the diastereomers **4–1** and **4–2** result in the differential physical properties (polarity) that facilitate the separation on column chromatography.

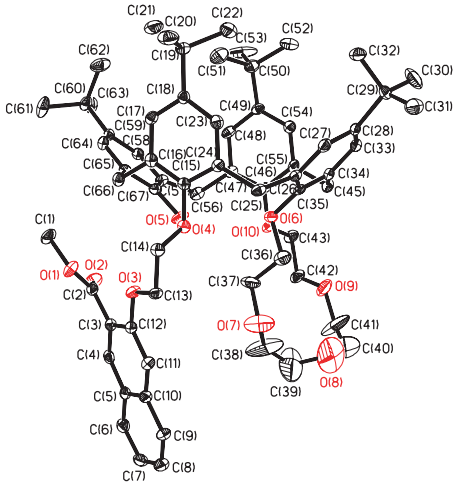


Figure 2. Molecular structure of **2b**. The hydrogen atoms are omitted for clarity.

The isolated **4–1** and **4–2** were hydrolyzed under alkaline conditions to give optically pure **3–1** and **3–2**, respectively, without the possibility of racemization. Their CD spectra are in mirror image relationship for each pair of enantiomers (Fig. 3).

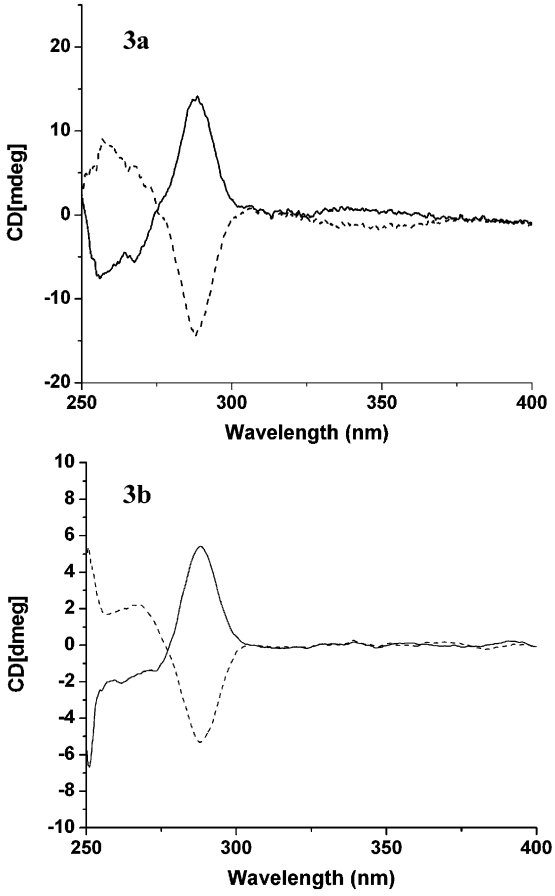
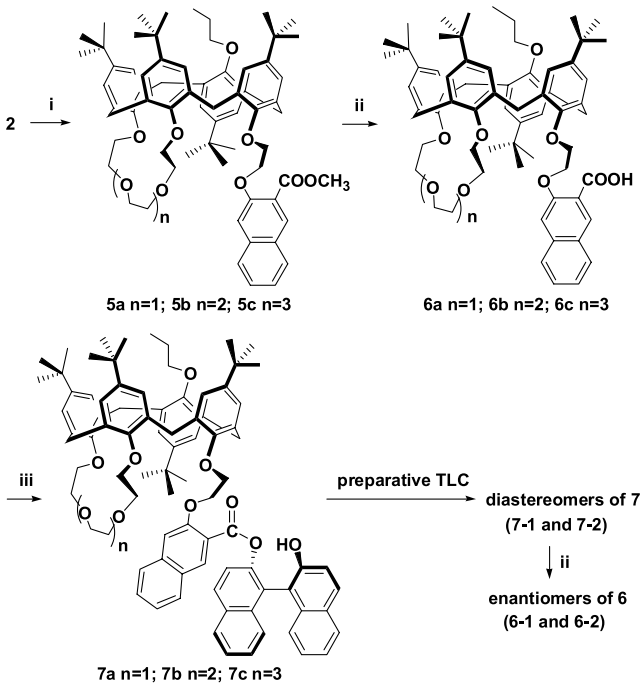


Figure 3. CD spectra (CH_2Cl_2, 25 °C) of the enantiomers **3a** (left) and **3b** (right) (the solid lines and the dotted lines denote **3–1** and **3–2**, respectively).



Scheme 2. Reagents and conditions: (i) ^{n}PrI, Cs_2CO_3, DMF, 70 °C; (ii) 10% Me_4NOH, THF, reflux; (iii) (*S*)-BINOL, DCC, DMAP, CH_2Cl_2, rt **7–1** denotes the fractions of lower polarity from preparative TLC; **7–2** denotes that of higher polarity from preparative TLC. **6–1** and **6–2** were derived from **7–1** and **7–2**, respectively.

2.2. Synthesis and optical resolution of tetra-*O*-alkylated inherently chiral fluorescent calix[4]crowns in the partial cone conformation

From the above results, attempt to separate the tri-*O*-alkylated calix[4]crown-6 diastereomeric mixture **4c** in the cone conformation by preparative TLC method was failed. Yet we are interested in inherently chiral calix[4]arene with the crown-6 moiety, which is likely to be a prerequisite for anchoring $-NH_3^+$ group of the primary ammonium cation into its crown ether cavity via N–H···O hydrogen bonds.[2g,8] Fortunately, after trial and test, we found that the tetra-*O*-alkylated calix[4]crown-6 diastereomers adopting the partial cone conformations could be successfully optically resolved via preparative TLC.

The reaction pathway is depicted in Scheme 2. The tri-*O*-alkylated cone conformers **2** were reacted with 10 equiv of ^{n}PrI in the presence of 15 equiv of Cs_2CO_3 in dry DMF at 70 °C for 1 day to yield the tetra-*O*-alkylated partial cone conformers **5**. In the ^{1}H NMR spectra, only two pairs of doublets arising from $ArCH_2Ar$ methylene protons are observed. Signals for other $ArCH_2Ar$ protons being obscured by that of the polyether chains. In the ^{13}C NMR spectra, two of the $ArCH_2Ar$ carbon signals appear at ca. 38 ppm and the other two at ca. 31 ppm. Because in the reaction of **2**, only the unsubstituted phenolic ring can rotate freely and the other three are immobilized by the substituents, we can deduce the partial cone conformations adopted by **5**.[7] The rationale for the conformational change from cone to partial cone may be attributed to the template effect of Cs^+, under which the alkylation of the tri-*O*-alkylated **2** has to occur from the opposite side of the lower rim to avoid steric hindrance, furnishing tetra-*O*-alkylated products **5** in the partial cone conformations.[2d,f,3b,9]

Hydrolizing **5** afforded **6**, which were then reacted with (*S*)-BINOL to furnish **7** as a pair of diastereomers. For the calix[4]crown-4 and calix[4]crown-5 derivatives **7a** and **7b**, TLC analysis showed one spot or two overlapped spots after several runs of developing using diverse eluting solvents. Yet interestingly, for the calix[4]crown-6 diastereomers **7c** two discrete spots were observed. From the above results, there are opposite crown ether size effects upon the diastereomer separation of the cone conformers to the partial cone conformers. Using preparative TLC, we successfully separated the diastereomeric mixture **7c** to **7c–1** and **7c–2** in ca. 1:1 ratios (de>99% by HPLC analysis). The ^{1}H NMR spectra of the isolated diastereomers show remarkable differences as Figure 4.

The isolated **7c–1** and **7c–2** were hydrolyzed under alkaline conditions to give optically pure **6c–1** and **6c–2**, respectively, without the possibility of racemization. Their CD spectra are in mirror image relationship for each other of the enantiomers (Fig. 5). It is interesting that on similar concentration, the CD value of the calix[4]crown-6 partial cone conformer **7c** is much lower than that of the calix[4]crown-4 and calix[4]crown-5 cone conformers.

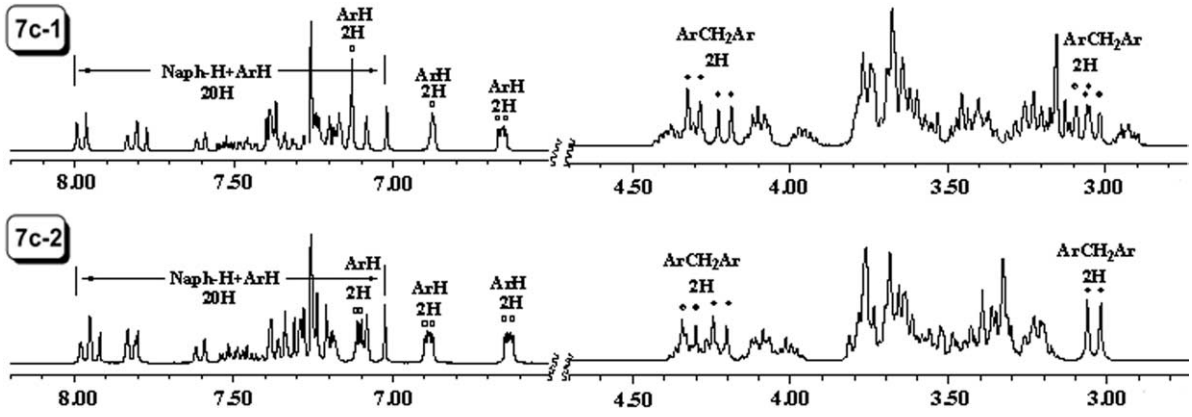


Figure 4. Partial ^{1}H NMR spectra of the isolated diastereomers **7c–1** and **7c–2** (signals for the OCH_2CH_2O and four $ArCH_2Ar$ protons are not annotated, the latter being overlapped with the former).

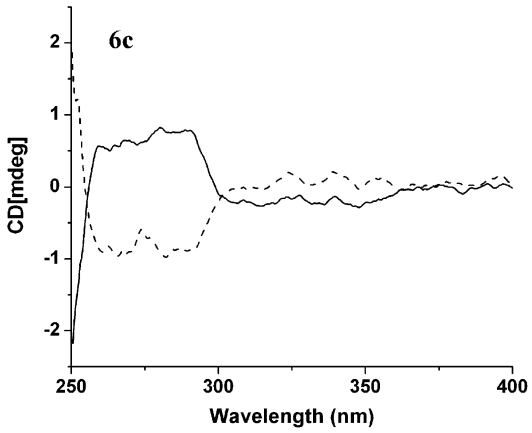


Figure 5. CD spectra (CH_2Cl_2, 25 °C) of the enantiomer **6c** (the solid lines and the dotted lines denote **6c–1** and **6c–2**, respectively).

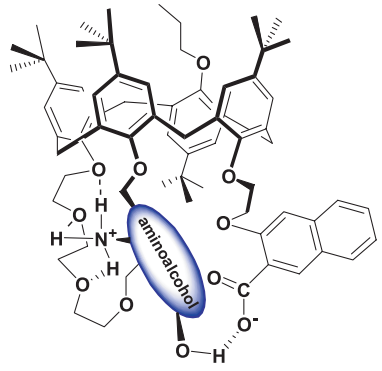


Figure 6. Proposed recognition mode of a inherently chiral calix[4]crown-6 towards a chiral aminoalcohol.

2.3. Preliminary study on the recognition property of inherently chiral fluorescent calix[4]crowns

The optically resolved inherently chiral fluorescent calix[4] arenes comprise a crown ether moiety and a carboxylic group as recognition sites while a naphthyl group linked as fluorophore. So, we envision that these fluorescent receptors could be utilized for chiral recognition. As a result, the recognition property of the fluorescent enantiomers **6c–1** and **6c–2** bearing the crown-6 moiety towards chiral aminoalcohols were investigated. The proposed recognition mode is shown in Figure 6.

The fluorescence experiments were carried out in CH_2Cl_2, and the fluorescent spectra of **6c–1** and **6c–2** were characterized by the maximum emission wavelength at 393 nm along with 340 nm as excitation wavelength.[10] We first, examined the recognition property of the partial cone conformer **6c–1** towards chiral leucinol and found that the fluorescence intensity of **6c–1** (10^{-5} M) decreased to 19.3% of the primal value upon the addition of 700 equiv D-Leucinol, yet decreased to 38.8% of the primal value upon the addition of the same amount L-leucinol. From the fluorescence titration experiments, the association constant (K_a) of the 1:1 complex formation were estimated to be 50 M^{-1} for D-leucinol, and 143 M^{-1} for L-leucinol according to the Stern–Volmer plot (Fig. 7).[11] The results indicated that **6c–1** has enantioselective recognition capability towards chiral leucinol.

We further, measured the fluorescence behaviour of the enantiomer **6c–2** in the presence of chiral leucinol, and found that there was a mirror image relationship of the fluorescence change between **6c–1** and **6c–2**. This confirmed that the observed different fluorescence change between the two enantiomers of leucinol is indeed due to the enantioselective recognition by the fluorescent host. Such unusually enantioselective recognition might make the inherently chiral fluorescent calix[4]crown-6 **6c** to be a practical fluorescent sensor for chiral leucinol. Moreover, they are also potentially useful for the combinatorial screening of the catalysts for the asymmetric synthesis of chiral leucinol.[12]

We also examined the recognition property of **6c** towards chiral 2-amino-3-methyl-1-butanol and 2-amino-1-butanol. The results showed that no significant fluorescence changes of **6c** were observed. In the cases of the calix[4]crown-4 acid **3a** and the calix[4]crown-5 acid **3b** in the cone conformations, the fluorescence changes in the presence of chiral leucinol are much slighter than those of the calix[4]crown-6 acid **6c**. This demonstrated that the crown-6 moiety in **6c** is important for the chiral recognition of aminoalcohol.

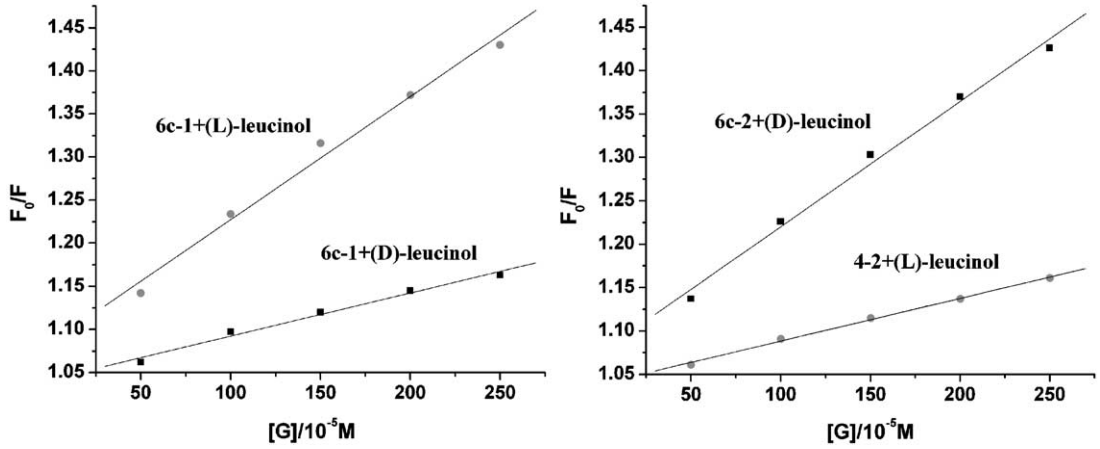


Figure 7. Stern–Volmer plot of **6c–1** and **6c–2** (10^{-5} M in CH_2Cl_2, 25 °C) in the presence of chiral leucinol.

3. Conclusion

We have synthesized a series of tri-*O*-alkylated and tetra-*O*-alkylated inherently chiral fluorescent calix[4]crowns in the cone and partial cone conformations, respectively. Meanwhile, we have developed a convenient access to optically pure inherently chiral fluorescent calix[4]crowns. Moreover, we found that the inherently chiral fluorescent calix[4]crown-6 in the partial cone conformation **6c–1** and **6c–2** showed considerable enantioselective recognition capability towards chiral leucinol. This could make them to be practical enantioselective fluorescent sensors for chiral leucinol.

4. Experimental

4.1. General

Melting points were determined on an electrothermal melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained at 300.13 and 75 MHz ($CDCl_3$, with TMS as internal standard), respectively. MALDI-TOF MS were recorded with CCA (2-cyano-4′-hydroxycinamic acid) as the matrix. NaH (80% in oil, Merck) was washed twice with petroleum ether (30–60 °C) and stored under nitrogen. All other chemicals were reagent grade and stored over 3 Å molecular sieves before use. Preparative TLC was self-made using silica gel HF_{254} (10–40 μm) with CMC as adhesive. Column chromatography was performed on silica gel (200–300 mesh). 1,2-Calix[4]crown-4 **1a** and 1,2-calix[4]crown-5 **1b** were synthesized according to the literature.[6]

4.1.1. 27,28-Dihydroxy-*p*-*tert*-butylcalix[4]-(25,26)-crown-6, cone conformer (1c). To a suspension of *p*-*tert*-butylcalix[4]arene (5 g, 7.7 mmol) in dry DMF (500 mL) was added NaH (924 mg, 5.0 equiv) and the reaction mixture was stirred at room temperature under nitrogen for 1 h. Then pentaethylene glycol ditosylate (1.2 equiv) was added and the mixture was stirred at 60 °C for 24 h. Methanol (40 mL) was added dropwise to destroy the excess of NaH. After removal of the solvent under reduced pressure, the residue was partitioned between 10% HCl (300 mL) and CH_2Cl_2 (2×300 mL). The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (SiO_2, petroleum ether–acetone 9:1) to give **1c** as a white solid. Yield 74%. Mp 195–197 °C (CH_2Cl_2/CH_3OH). ^{1}H NMR: δ 8.56 (s, 2H, O*H*), 6.97–6.87 (m, 8H, Ar*H*), 4.48 (d, J=12.7 Hz, 1H, ArCH_2Ar), 4.40 (d, J=13.0 Hz, 2H, ArCH_2Ar), 4.28 (d, J=13.7 Hz, 1H, ArCH_2Ar), 4.36–3.65 (m, 20H, polyether chain), 3.30 (d, J=13.3 Hz, 2H, ArCH_2Ar), 3.28 (d, J=13.0 Hz, 2H, ArCH_2Ar), 1.18 and 1.07 (2s, 18H each, C(CH_3)$_3$). ^{13}C NMR: δ 151.8, 149.0, 146.1, 142.0, 133.7, 133.6, 128.6, 127.7, 125.8, 125.8, 125.1, 125.1 (Ar*C*), 74.8, 71.4, 71.0, 70.9, 70.7 (O*C*H$_2$*C*H$_2$O), 34.0, 33.8 (*C*(CH$_3$)$_3$), 32.5, 31.8, 31.2 (Ar*C*H$_2$Ar), 31.6, 31.3 (C(*C*H$_3$)$_3$). MALDI-TOF MS: *m*/*z* 850.4 (M^+), 873.4 ([M+Na]$^+$), 889.4 ([M+K]$^+$). Anal. Calcd for $C_{54}H_{74}O_8$: C, 76.20; H, 8.76. Found: C, 76.21; H, 8.80.

4.2. Reaction of compound 1 with methyl 3-(2-bromoethoxy)-naphthalene-2-carboxylate. General procedure

A stirred mixture of **1** (2.7 mmol), methyl 3-(2-bromoethoxy)-naphthalene-2-carboxylate (371 mg, 1.2 equiv) and Cs_2CO_3 (326 mg, 1.0 equiv) in dry DMF (200 mL) was heated at 60 °C for 24 h. Then 2 mL 10% HCl was added to quench the reaction. After removal of the solvent under reduced pressure, the residue was partitioned between H_2O and CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography to give **2** as white solids.

4.2.1. 25-[(2-Methoxycarbonyl-naphthal-3-oxy)ethoxy]-28-hydroxy-*p*-*tert*-butylcalix[4]-(26,27)-crown-4, cone conformer (2a). Column chromatography (SiO_2, petroleum ether–AcOEt 5:1). Yield 62%. Mp 216–218 °C (CH_2Cl_2/CH_3OH). ^{1}H NMR: δ 8.29 (s, 1H, Naph-*H*), 7.82 (d, J=8.1 Hz, 1H, Naph-*H*), 7.75 (d, J=8.2 Hz, 1H, Naph-*H*), 7.52 (t, J=6.9 Hz, 1H, Naph-*H*), 7.38 (t, J=7.1 Hz, 1H, Naph-*H*), 7.29 (s, 1H, Naph-*H*), 7.15 and 7.14 (2s, 1H each, Ar*H*), 7.09 and 7.04 (2s, 1H each, Ar*H*), 6.62 and 6.58 (2s, 1H each, Ar*H*), 6.47 (s, 2H, Ar*H*), 5.87 (s, 1H, O*H*), 4.51 (d, J=12.4 Hz, 1H, ArCH_2Ar), 4.47 (d, J=11.8 Hz, 1H, ArCH_2Ar), 4.40 (d, J=12.7 Hz, 1H, ArCH_2Ar), 4.24 (d, J=13.3 Hz, 1H, ArCH_2Ar), 4.35–3.32 (m, 16H, OCH_2-CH_2O), 3.79 (s, 3H, COOCH_3), 3.27 (d, J=13.4 Hz, 2H, ArCH_2Ar), 3.19 (d, J=10.7 Hz, 1H, ArCH_2Ar), 3.16 (d, J=11.8 Hz, 1H, ArCH_2Ar), 1.34, 1.33, 0.87 and 0.78 (4s, 9H each, C(CH_3)$_3$). ^{13}C NMR: δ 166.9 (*C*O$_2$CH$_3$), 154.7, 153.6, 151.2, 150.7, 150.4, 145.9, 145.8, 145.3, 141.2, 136.0, 136.0, 135.8, 132.69, 132.67, 132.1, 132.0, 131.6, 129.4, 128.6, 128.3, 128.1, 127.7, 126.6, 125.7, 125.7, 125.4, 125.1, 125.1, 124.8, 124.7, 124.6, 124.4, 122.5, 107.7 (Naph-*C* and Ar*C*), 75.3, 73.2, 72.5, 71.3, 70.1, 69.7, 69.1, 67.7 (O*C*H$_2$*C*H$_2$O), 52.3 (CO$_2$*C*H$_3$), 34.2, 33.8, 33.8, 33.6 (*C*(CH$_3$)$_3$), 31.8, 31.7, 31.0 (C(*C*H$_3$)$_3$), 31.5, 31.1, 30.9, 30.3 (Ar*C*H$_2$Ar). MALDI-TOF MS: *m*/*z* 1013.4 ([M+Na]$^+$), 1029.4 ([M+K]$^+$). Anal. Calcd for $C_{64}H_{78}O_9$: C, 77.54; H, 7.93. Found: C, 77.57; H, 7.92.

4.2.2. 25-[(2-Methoxycarbonyl-naphthal-3-oxy)ethoxy]-28-hydroxy-*p*-*tert*-butylcalix[4]-(26,27)-crown-5, cone conformer (2b). Column chromatography (SiO_2, petroleum ether–AcOEt 5:1). Yield 51%. Mp 95–97 °C. ^{1}H NMR: δ 8.27 (s, 1H, Naph-*H*), 7.82 (d, J=8.1 Hz, 1H, Naph-*H*), 7.73 (d, J=8.2 Hz, 1H, Naph-*H*), 7.52 (t, J=7.0 Hz, 1H, Naph-*H*), 7.38 (t, J=7.0 Hz, 1H, Naph-*H*), 7.27 (s, 1H, Naph-*H*), 7.14 (2s, 2H, Ar*H*), 7.10 and 7.04 (2d, J=2.3 Hz, 1H each, Ar*H*), 6.59 (s, 2H, Ar*H*), 6.45 and 6.43 (2d, J=2.4 Hz, 1H each, Ar*H*), 6.05 (s, 1H, O*H*), 4.56 (d, J=12.9 Hz, 1H, ArCH_2Ar), 4.44 (d, J=12.6 Hz, 1H, ArCH_2-Ar), 4.41 (d, J=13.2 Hz, 1H, ArCH_2Ar), 4.34 (d, 1H, J=12.7 Hz, ArCH_2Ar), 4.23–3.27 (m, 20H, OCH_2CH_2O), 3.81 (s, 3H, COOCH_3), 3.25 (d, J=13.4 Hz, 2H, ArCH_2Ar), 3.18 (d, J=12.7 Hz, 1H, ArCH_2Ar), 3.16 (d, J=12.7 Hz, 1H, ArCH_2Ar), 1.34 (s, 18H, C(CH_3)$_3$), 0.87 and 0.76 (2s, 9H each, C(CH_3)$_3$). ^{13}C NMR: δ 167.0 (*C*O$_2$CH$_3$), 154.6, 153.7, 151.4, 150.9, 150.7, 145.9, 145.8, 145.1, 141.0, 136.1, 135.9, 135.7, 132.6, 132.5, 132.2, 131.9, 131.8, 129.4, 128.6, 128.3, 128.2, 127.7, 126.5, 125.8, 125.6, 125.4, 125.1, 125.0, 124.9, 124.8, 124.6, 124.5, 122.6, 107.6 (Naph-*C* and Ar*C*), 76.3, 73.3, 72.0, 71.8, 70.9, 70.4, 69.8,

69.3, 68.3, 67.6 (O*C*H_2*C*H_2O), 52.3 (CO_2*C*H_3), 34.2, 33.8, 33.7, 33.6 (*C*(CH_3)$_3$), 31.8, 31.7, 31.0 (C(*C*H_3)$_3$), 31.3, 30.7, 30.7 (Ar*C*H_2Ar). MALDI-TOF MS: *m/z* 1057.5 ([M+Na]$^+$), 1073.4 ([M+K]$^+$). Anal. Calcd for $C_{66}H_{82}O_{10}$: C, 76.56; H, 7.98. Found: C, 76.56; H, 8.08.

4.2.3. 25-[(2-Methoxycarbonyl-naphthal-3-oxy)ethoxy]-28-hydroxy-*p-tert*-butylcalix[4]-(26,27)-crown-6, cone conformer (2c). Column chromatography (SiO_2, petroleum ether–acetone 7:1). Yield 47%. Mp 144–146 °C (CH_2Cl_2/CH_3OH). ^{1}H NMR: δ 8.27 (s, 1H, Naph-*H*), 7.82 (d, *J*=8.2 Hz, 1H, Naph-*H*), 7.74 (d, *J*=8.2 Hz, 1H, Naph-*H*), 7.52 (t, *J*=7.1 Hz, 1H, Naph-*H*), 7.38 (t, *J*=7.5 Hz, 1H, Naph-*H*), 7.30 (s, 1H, Naph-*H*), 7.14 (2s, 2H, Ar*H*), 7.08 and 7.04 (2d, *J*=1.6 Hz, 1H each, Ar*H*), 6.57 (s, 2H, Ar*H*), 6.52 (s, 2H, Ar*H*), 5.67(s, 1H, O*H*), 4.49 (d, *J*=12.8 Hz, 1H, ArC*H*$_2$Ar), 4.23 (d, *J*=12.9 Hz, 1H, ArC*H*$_2$Ar), 4.57–3.19 (m, 26H, ArC*H*$_2$Ar and OC*H*$_2$C*H*$_2$O), 3.78 (s, 3H, CO_2C*H*$_3$), 3.26 (d, *J*=13.7 Hz, 2H, ArC*H*$_2$Ar), 3.22 (d, *J*=14.3 Hz, 1H, ArC*H*$_2$Ar), 3.15 (d, *J*=12.7 Hz, 1H, ArC*H*$_2$Ar), 1.34, 1.33, 0.85 and 0.81 (4s, 9H each, C(C*H*$_3$)$_3$). ^{13}C NMR: δ 166.9 (*C*O_2CH$_3$), 154.7, 153.6, 151.2, 150.9, 150.6, 145.9, 145.7, 145.4, 141.4, 136.0, 135.9, 135.8, 132.7, 132.6, 132.2, 132.1, 131.7, 129.4, 128.6, 128.6, 128.4, 127.7, 126.5, 125.7, 125.6, 125.2, 125.1, 125.0, 124.8, 124.79, 124.77, 124.5, 122.6, 107.7 (Naph-*C* and Ar*C*), 74.8, 73.4, 71.6, 71.4, 70.7, 70.6, 70.4, 70.3, 70.0, 69.6, 69.4, 67.7 (O*C*H$_2$*C*H$_2$O), 52.2 (CO_2*C*H$_3$), 34.1, 33.8, 33.7, 33.7 (*C*(CH_3)$_3$), 31.8, 31.7, 31.0 (C(*C*H$_3$)$_3$), 31.5, 30.7 (Ar*C*H$_2$Ar). MALDI-TOF MS: *m/z* 1101.7 ([M+Na]$^+$), 1117.7 ([M+K]$^+$). Anal. Calcd for $C_{68}H_{86}O_{11}$: C, 75.66; H, 8.03. Found: C, 75.59; H, 8.02.

4.3. Hydrolysis of compounds 2. General procedure

Compounds **2** (1.2 mmol) in THF (100 mL) were treated with aqueous 10% tetramethylammonium hydroxide solution (5.0 equiv, 5.45 mL) at reflux temperature for 12 h. After removal of the solvent, 10% HCl (40 mL) was added. The aqueous solution was extracted with CH_2Cl_2 (2×40 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The residue was crystallized from CH_2Cl_2/CH_3OH to give corresponding products **3** as white solids.

4.3.1. 25-[(2-Carboxy-naphthal-3-oxy)ethoxy]-28-hydroxy-*p-tert*-butylcalix[4]-(26,27)-crown-4, cone conformer (3a). Yield 75%. Mp 242–244 °C (CH_2Cl_2/CH_3OH). ^{1}H NMR: δ 8.69 (s, 1H, Naph-*H*), 7.92 (d, *J*=8.2 Hz, 1H, Naph-*H*), 7.79 (d, *J*=8.2 Hz, 1H, Naph-*H*), 7.59 (t, *J*=7.3 Hz, 1H, Naph-*H*), 7.46 (t, *J*=7.6 Hz, 1H, Naph-*H*), 7.36 (s, 1H, Naph-*H*), 7.16 and 7.05 (2d, *J*=1.9 Hz, 1H each, Ar*H*), 7.11 and 7.10 (2d, *J*=2.0 Hz, 1H each, Ar*H*), 6.70 and 6.64 (2d, *J*=1.8 Hz, 1H each, Ar*H*), 6.47 and 6.45 (2s, 1H each, Ar*H*), 5.80 (s, 1H, O*H*), 4.50 (d, *J*=12.5 Hz, 1H, ArC*H*$_2$Ar), 4.45 (d, *J*=12.7 Hz, 1H, ArC*H*$_2$Ar), 4.39 (d, *J*=12.7 Hz, 1H, ArC*H*$_2$Ar), 4.19 (d, *J*=13.4 Hz, 1H, ArC*H*$_2$Ar), 4.63–3.52 (m, 16H, OC*H*$_2$-C*H*$_2$O), 3.32 (d, *J*=13.6 Hz, 1H, ArC*H*$_2$Ar), 3.27 (d, *J*=13.1 Hz, 1H, ArC*H*$_2$Ar), 3.19 (d, *J*=12.5 Hz, 1H, ArC*H*$_2$-Ar), 3.18 (d, *J*=12.8 Hz, 1H, ArC*H*$_2$Ar), 1.34 (s, 18H, C(C*H*$_3$)$_3$), 0.91 and 0.76 (2s, 9H each, C(C*H*$_3$)$_3$). ^{13}C NMR: δ 166.1 (*C*O_2), 153.8, 153.4, 151.4, 150.6, 149.8, 146.3, 146.0, 145.3, 141.5, 136.4, 135.9, 135.6, 135.3, 132.9, 131.93, 131.88, 131.5, 129.6, 129.3, 129.1, 128.4, 128.0, 126.6, 125.8, 125.7, 125.5, 125.4, 125.3, 125.2, 124.78, 124.76, 124.7, 119.7, 107.8 (Naph-*C* and Ar*C*), 75.2, 72.8, 71.9, 71.6, 69.6, 69.4, 68.7, 68.3 (O*C*H$_2$*C*H$_2$O), 34.2, 33.9, 33.8, 33.6 (*C*(CH_3)$_3$), 31.8, 31.7, 31.0, 31.0 (C(*C*H$_3$)$_3$), 30.3 (Ar*C*H$_2$Ar). MALDI-TOF MS: *m/z* 998.5 ([M+Na]$^+$), 1015.5 ([M+K]$^+$). Anal. Calcd for $C_{63}H_{76}O_9$: C, 77.43; H, 7.84. Found: C, 77.27; H, 7.84.

4.3.2. 25-[(2-Carboxy-naphthal-3-oxy)ethoxy]-28-hydroxy-*p-tert*-butylcalix[4]-(26,27)-crown-5, cone conformer (3b). Yield 76%. Mp 209–211 °C (CH_2Cl_2/CH_3OH). ^{1}H NMR: δ 8.70 (s, 1H, Naph-*H*), 7.91 (d, *J*=8.1 Hz, 1H, Naph-*H*), 7.77 (d, *J*=8.2 Hz, 1H, Naph-*H*), 7.58 (t, *J*=7.2 Hz, 1H, Naph-*H*), 7.45 (t, *J*=6.9 Hz, 1H, Naph-*H*), 7.36 (s, 1H, Naph-*H*), 7.13 and 7.11 (2d, *J*=2.3 Hz, 1H each, Ar*H*), 7.08 and 7.03 (2d, *J*=2.4 Hz, 1H each, Ar*H*), 6.63 and 6.62 (2d, *J*=2.3 Hz, 1H each, Ar*H*), 6.45 and 6.44 (2s, 1H each, Ar*H*), 5.97 (s, 1H, O*H*), 4.49 (d, *J*=12.8 Hz, 1H, ArC*H*$_2$Ar), 4.41 (d, *J*=13.0 Hz, 1H, ArC*H*$_2$Ar), 4.36 (d, *J*=12.5 Hz, 1H, ArC*H*$_2$Ar), 4.33 (d, *J*=12.8 Hz, 1H, ArC*H*$_2$Ar), 4.69–3.47 (m, 20H, OC*H*$_2$-C*H*$_2$O), 3.27 (d, *J*=13.7 Hz, 1H, ArC*H*$_2$Ar), 3.17 (d, *J*=12.4 Hz, 1H, ArC*H*$_2$Ar), 3.21 (d, *J*=12.7 Hz, 2H, ArC*H*$_2$-Ar), 1.33, 1.32, 0.90 and 0.75 (4s, 9H each, C(C*H*$_3$)$_3$). ^{13}C NMR: δ 165.9 (*C*O_2), 153.7, 153.4, 151.5, 150.7, 150.5, 146.2, 145.9, 145.3, 141.3, 136.3, 135.8, 135.5, 135.5, 132.7, 132.1, 131.7, 131.6, 129.5, 129.3, 129.2, 128.3, 128.0, 126.5, 125.9, 125.6, 125.5, 125.3, 125.3, 125.1, 125.0, 124.8, 124.7, 119.5, 107.8 (Naph-*C* and Ar*C*), 76.3, 72.8, 71.7, 71.6, 70.7, 70.40, 70.37, 69.7, 68.9, 68.8 (O*C*H$_2$*C*H$_2$O), 34.2, 33.8, 33.8, 33.6 (*C*(CH_3)$_3$), 31.8, 31.7, 31.0, 31.0 (C(*C*H$_3$)$_3$), 31.5, 31.1, 30.7 (Ar*C*H$_2$Ar). MALDI-TOF MS: *m/z* 1043.4 ([M+Na]$^+$), 1059.3 ([M+K]$^+$). Anal. Calcd for $C_{65}H_{80}O_{10}$: C, 76.44; H, 7.90. Found: C, 76.62; H, 7.93.

4.3.3. 25-[(2-Carboxy-naphthal-3-oxy)ethoxy]-28-hydroxy-*p-tert*-butylcalix[4]-(26,27)-crown-6, cone conformer (3c). Yield 72%. Mp 197–199 °C (CH_2Cl_2/CH_3OH). ^{1}H NMR: δ 8.71 (s, 1H, Naph-*H*), 7.93 (d, *J*=8.1 Hz, 1H, Naph-*H*), 7.80 (d, *J*=8.2 Hz, 1H, Naph-*H*), 7.61 (t, *J*=7.3 Hz, 1H, Naph-*H*), 7.47 (t, *J*=7.6 Hz, 1H, Naph-*H*), 7.40 (s, 1H, Naph-*H*), 7.13 (s, 2H, Ar*H*), 7.10 and 7.04 (2d, *J*=1.6 Hz, 1H each, Ar*H*), 6.66 (s, 2H, Ar*H*), 6.52 and 6.51 (2s, 1H each, Ar*H*), 5.73 (s, 1H, O*H*), 4.49 (d, *J*=12.6 Hz, 1H, ArC*H*$_2$Ar), 4.46 (d, *J*=12.8 Hz, 2H, ArC*H*$_2$-Ar), 4.76–3.35 (m, 24H, OC*H*$_2$C*H*$_2$O), 4.19 (d, *J*=13.1 Hz, 1H, ArC*H*$_2$Ar), 3.32 (d, *J*=13.2 Hz, 1H, ArC*H*$_2$Ar), 3.27 (d, *J*=12.8 Hz, 1H, ArC*H*$_2$Ar), 3.23 (d, *J*=12.7 Hz, 1H, ArC*H*$_2$Ar), 3.18 (d, *J*=12.8 Hz, 1H, ArC*H*$_2$Ar), 1.34 (s, 18H, C(C*H*$_3$)$_3$), 0.92 and 0.80 (2s, 9H each, C(C*H*$_3$)$_3$). ^{13}C NMR: δ 166.0 (*C*O_2), 153.8, 153.4, 151.4, 150.4, 150.3, 146.2, 146.0, 145.5, 141.6, 136.3, 135.8, 135.4, 135.3, 133.1, 132.1, 132.0, 131.6, 129.7, 129.3, 129.2, 128.3, 128.2, 126.6, 125.8, 125.6, 125.4, 125.31, 125.29, 125.2, 125.1, 124.8, 124.7, 119.6, 107.8 (Naph-*C* and Ar*C*), 75.1, 72.8, 71.7, 71.5, 70.8, 70.6, 70.4, 70.3, 70.1, 69.6, 69.5, 69.0 (O*C*H$_2$*C*H$_2$O), 34.1, 33.9, 33.8, 33.6 (*C*(CH_3)$_3$), 31.7, 31.6, 31.0, 31.0 (C(*C*H$_3$)$_3$), 30.7 (Ar*C*H$_2$Ar). MALDI-TOF MS: *m/z* 1087.3 ([M+Na]$^+$), 1103.3 ([M+K]$^+$). Anal. Calcd for $C_{67}H_{84}O_{11}$: C, 75.53; H, 7.95. Found: C, 75.17; H, 7.94.

4.4. Condensation of compounds 3 with the chiral auxiliary (*S*)-BINOL. General procedure

Compounds **3** (0.55 mmol), (*S*)-BINOL (173 mg, 1.1 equiv), DCC (227 mg, 2.0 equiv) and DMAP (14 mg, 0.2 equiv) in CH_2Cl_2 (50 mL) were stirred at room temperature for 2 days. After filtering off the insoluble DCU, CH_2Cl_2 was evaporated and 5 mL AcOEt was added. The remaining insoluble DCU was again removed by filtration and the solvent was evaporated.

4.4.1. 25-[(2-(*S*)-Binaphthoxycarbonyl-naphthal-3-oxy) ethoxy]-28-hydroxy-*p-tert*-butylcalix[4]-(26,27)-crown-4, cone conformer (4a). Firstly, the crude products were purified via column chromatography (SiO_2, petroleum ether–AcOEt 9:2), then the diastereomeric mixture was subjected to preparative TLC (petroleum ether–AcOEt 8:3) to give **4a–1** and **4a–2** as white solids.

Compound **4a–1**. Yield 20%. Mp 142–144 °C. ^{1}H NMR: δ 7.91 (d, J=8.2 Hz, 1H, Naph-*H*), 7.85 (d, J=7.6 Hz, 1H, Naph-*H*), 7.79 (d, J=8.9 Hz, 1H, Naph-*H*), 7.69 (d, J=8.9 Hz, 1H, Naph-*H*), 7.61 (d, J=8.4 Hz, 1H, Naph-*H*), 7.52–7.09 (m, 17H, Naph-*H* and Ar*H*), 6.63 and 6.62 (2s, 1H each, Ar*H*), 6.49 and 6.44 (2d, J=2.1 Hz, 1H each, Ar*H*), 5.93 (s, 1H, O*H*), 4.51 (d, J=13.2 Hz, 1H, ArC*H*$_2$-Ar), 4.44 (d, J=12.5 Hz, 1H, ArC*H*$_2$Ar), 4.37 (d, J=13.0 Hz, 1H, ArC*H*$_2$Ar), 4.28 (d, J=13.1 Hz, 1H, ArC*H*$_2$-Ar), 4.36–2.78 (m, 16H, OC*H*$_2$C*H*$_2$O), 3.33 (d, J=13.2 Hz, 1H, ArC*H*$_2$Ar), 3.24 (d, J=13.2 Hz, 1H, ArC*H*$_2$Ar), 3.16 (d, J=12.6 Hz, 1H, ArC*H*$_2$Ar), 3.10 (d, J=12.8 Hz, 1H, ArC*H*$_2$Ar), 1.39, 1.35, 0.88 and 0.77 (4s, 9H each, C(C*H*$_3$)$_3$). ^{13}C NMR: δ 164.1 (*C*O$_2$), 154.8, 153.5, 152.2, 150.8, 150.6, 150.2, 148.4, 145.9, 145.8, 145.2, 141.4, 136.2, 136.1, 135.8, 133.9, 133.4, 133.3, 132.7, 132.2, 132.2, 131.6, 131.6, 130.5, 130.1, 129.9, 128.9, 128.8, 128.5, 128.3, 128.2, 128.0, 127.2, 127.0, 126.7, 126.3, 125.9, 125.8, 125.7, 125.7, 125.6, 125.2, 125.1, 124.8, 124.8, 124.6, 124.6, 124.2, 123.4, 122.9, 122.9, 120.4, 118.5, 114.1, 107.1 (Naph-*C* and Ar*C*), 75.3, 72.9, 72.4, 71.1, 70.0, 69.3, 68.8, 67.2 (O*C*H$_2$*C*H$_2$O), 34.2, 33.9, 33.8, 33.6 (*C*(CH$_3$)$_3$), 31.9, 31.7, 31.0, 31.0 (C(*C*H$_3$)$_3$), 31.5, 30.6, 30.3 (Ar*C*H$_2$Ar). MALDI-TOF MS: m/z 1267.4 ([M+Na]$^+$), 1283.4 ([M+K]$^+$). Anal. Calcd for $C_{83}H_{88}O_{10}$: C, 80.03; H, 7.12. Found: C, 79.92; H, 7.15.

Compound **4a–2**. Yield 19%. Mp 141–143 °C. ^{1}H NMR: δ 7.94 (d, J=8.2 Hz, 1H, Naph-*H*), 7.85 (d, J=8.7 Hz, 2H, Naph-*H*), 7.78 (d, J=8.9 Hz, 1H, Naph-*H*), 7.63 (d, J=8.2 Hz, 1H, Naph-*H*), 7.54–7.19 (m, 12H, Naph-*H*), 7.20 and 7.17 (2d, J=2.4 Hz, 1H each, Ar*H*), 7.14 (s, 1H, Naph-*H*), 7.12 and 7.08 (2d, J=2.4 Hz, 1H each, Ar*H*), 6.99 (s, 1H, Naph-*H*), 6.65 and 6.60 (2d, J=2.3 Hz, 1H each, Ar*H*), 6.47 (s, 2H, Ar*H*), 5.89 (s, 1H, O*H*), 4.50 (d, J=13.0 Hz, 1H, ArC*H*$_2$Ar), 4.48 (d, J=12.8 Hz, 1H, ArC*H*$_2$Ar), 4.40 (d, J=12.6 Hz, 1H, ArC*H*$_2$Ar), 4.22 (d, 1H, J=13.4 Hz, ArC*H*$_2$Ar), 4.45–3.09 (m, 16H, OC*H*$_2$C*H*$_2$O), 3.28 (d, J=13.8 Hz, 1H, ArC*H*$_2$Ar), 3.24 (d, J=13.7 Hz, 1H, ArC*H*$_2$-Ar), 3.18 (d, J=13.1 Hz, 1H, ArC*H*$_2$Ar), 3.17 (d, J=12.5 Hz, 1H, ArC*H*$_2$Ar), 1.39, 1.37, 0.89 and 0.77 (4s, 9H each, C(C*H*$_3$)$_3$). ^{13}C NMR: δ 164.3 (*C*O$_2$), 154.7, 153.6, 151.9, 151.2, 150.7, 150.4, 148.3, 145.9, 145.8, 145.2, 141.3, 136.2, 136.1, 135.8, 133.8, 133.4, 133.1, 132.7, 132.2, 132.1, 132.0, 131.6, 130.7, 130.3, 129.6, 129.0, 128.8, 128.5, 128.3, 128.2, 128.0, 127.3, 127.2, 126.9, 126.4, 126.1, 125.9, 125.7, 125.7, 125.5, 125.1, 125.0, 124.8, 124.8, 124.7, 124.6, 124.2, 123.6, 122.7, 122.6, 120.6, 118.4, 114.1, 107.4 (Naph-*C* and Ar*C*), 75.3, 73.1, 72.6, 71.2, 70.2, 69.8, 69.3, 67.6 (O*C*H$_2$*C*H$_2$O), 34.2, 33.9, 33.8, 33.6 (*C*(CH$_3$)$_3$), 31.84, 31.78, 31.1, 31.0 (C(*C*H$_3$)$_3$), 31.6, 31.2, 30.7, 30.3 (Ar*C*H$_2$Ar). MALDI-TOF MS: m/z 1267.5 ([M+Na]$^+$), 1283.5 ([M+K]$^+$). Anal. Calcd for $C_{83}H_{88}O_{10}$: C, 80.03; H, 7.12. Found: C, 79.90; H, 7.21.

4.4.2. 25-[(2-(*S*)-Binaphthoxycarbonyl-naphthal-3-oxy) ethoxy]-28-hydroxy-*p-tert*-butylcalix[4]-(26,27)-crown-5, cone conformer (4b). Firstly, the crude products were purified via column chromatography (SiO_2, petroleum ether–AcOEt 9:2), then the diastereomeric mixture was subjected to preparative TLC (petroleum ether–AcOEt 8:3) to give **4b–1** and **4b–2** as white solids.

Compound **4b–1**. Yield 23%. Mp 147–149 °C. ^{1}H NMR: δ 7.92 (d, J=8.0 Hz, 1H, Naph-*H*), 7.88 (d, J=9.3 Hz, 1H, Naph-*H*), 7.85 (d, J=9.2 Hz, 1H, Naph-*H*), 7.61 (d, J=8.3 Hz, 1H, Naph-*H*), 7.56 (d, J=8.9 Hz, 1H, Naph-*H*), 7.53–7.11 (m, 16H, Naph-*H* and Ar*H*), 6.78 (s, 1H, Naph-*H*), 6.64 and 6.60 (2d, J=2.4 Hz, 1H each, Ar*H*), 6.46 and 6.41 (2d, J=2.4 Hz, 1H each, Ar*H*), 6.11 (s, 1H, O*H*), 4.59 (d, J=13.2 Hz, 1H, ArC*H*$_2$Ar), 4.50 (d, J=13.5 Hz, 1H, ArC*H*$_2$Ar), 4.40 (d, J=12.7 Hz, 1H, ArC*H*$_2$Ar), 4.33 (d, J=12.4 Hz, 1H, ArC*H*$_2$Ar), 4.50–2.97 (m, 23H, ArC*H*$_2$Ar and OC*H*$_2$C*H*$_2$O), 3.32 (d, J=13.6 Hz, 1H, ArC*H*$_2$Ar), 1.40, 1.36, 0.89 and 0.76 (4s, 9H each, C(C*H*$_3$)$_3$). ^{13}C NMR: δ 164.0 (*C*O$_2$), 154.5, 153.7, 152.1, 151.3, 150.8, 150.6, 148.1, 145.9, 145.9, 145.0, 141.2, 136.2, 135.9, 135.7, 133.8, 133.3, 132.6, 132.5, 132.4, 132.2, 131.8, 131.7, 130.7, 130.2, 129.9, 129.0, 128.7, 128.5, 128.3, 128.2, 128.1, 127.2, 127.1, 126.8, 126.3, 126.0, 125.8, 125.7, 125.6, 125.6, 125.2, 125.0, 124.9, 124.9, 124.7, 124.5, 124.3, 123.6, 122.8, 122.5, 120.9, 118.6, 114.2, 107.0 (Naph-*C* and Ar*C*), 76.5, 73.2, 72.0, 71.6, 71.0, 70.2, 69.4, 69.0, 68.2, 67.5 (O*C*H$_2$*C*H$_2$O), 34.2, 33.9, 33.8, 33.6 (*C*(CH$_3$)$_3$), 31.9, 31.7, 31.0, 31.0 (C(*C*H$_3$)$_3$), 31.3, 30.9, 30.7, 30.3 (Ar*C*H$_2$Ar). MALDI-TOF MS: m/z 1311.6 ([M+Na]$^+$), 1327.5 ([M+K]$^+$). Anal. Calcd for $C_{85}H_{92}O_{11}$0.5 H_2O: C, 78.61; H, 7.22. Found: C, 78.39; H, 7.41.

Compound **4b–2**. Yield 23%. Mp 151–153 °C. ^{1}H NMR: δ 7.93 (d, J=8.2 Hz, 1H, Naph-*H*), 7.87 (d, J=9.0 Hz, 2H, Naph-*H*), 7.74(d, J=8.9 Hz, 1H, Naph-*H*), 7.61 (d, J=8.1 Hz, 1H, Naph-*H*), 7.54–7.12 (m, 15H, Naph-*H* and Ar*H*), 7.11 and 7.09 (2d, J=2.4 Hz, 1H each, Ar*H*), 6.89 (s, 1H, Naph-*H*), 6.59 (s, 2H, ArH), 6.45 (s, 2H, Ar*H*), 5.91 (s, 1H, O*H*), 4.53 (d, J=13.0 Hz, 1H, ArC*H*$_2$Ar), 4.45 (d, J=12.6 Hz, 1H, ArC*H*$_2$Ar), 4.36 (d, J=12.7 Hz, 1H, ArC*H*$_2$-Ar), 4.42–3.16 (m, 24H, ArC*H*$_2$Ar and OC*H*$_2$C*H*$_2$O), 3.26 (d, J=12.1 Hz, 1H, ArC*H*$_2$Ar), 1.39, 1.37, 0.88 and 0.77 (4s, 9H each, C(C*H*$_3$)$_3$). ^{13}C NMR: δ 164.2 (*C*O$_2$), 154.6, 153.7, 151.9, 151.3, 150.8, 150.8, 148.2, 145.8, 145.8, 145.1, 141.2, 136.3, 136.0, 135.7, 133.7, 133.3, 132.9, 132.5, 132.17, 132.15, 132.0, 131.7, 130.7, 130.3, 129.6, 129.0, 128.7, 128.5, 128.4, 128.3, 128.0, 127.2, 127.2, 126.9, 126.3, 126.1, 125.9, 125.64, 125.62, 125.4, 124.99, 124.96, 124.9, 124.84, 124.82, 124.7, 124.2, 123.6, 122.7, 122.5, 120.7, 118.4, 114.2, 107.2 (Naph-*C* and Ar*C*), 76.2,

73.2, 71.8, 70.9, 70.4, 69.7, 69.2, 68.3, 67.5 (O*C*H_2*C*H_2O), 34.2, 33.9, 33.7, 33.6 (*C*(CH_3)$_3$), 31.9, 31.8, 31.0, 31.0 (C(*C*H_3)$_3$), 31.3, 30.8, 30.6 (Ar*C*H_2Ar). MALDI-TOF MS: *m/z* 1311.4 ($[M+Na]^+$), 1327.4 ($[M+K]^+$). Anal. Calcd for $C_{85}H_{92}O_{11}$: C, 79.16; H, 7.19. Found: C, 79.09; H, 7.26.

4.5. Hydrolysis of compounds 4. General procedure for optically pure enantiomers 3

Compounds **4–1** or **4–2** (100 mg, 0.08 mmol) in THF (10 mL) was treated with aqueous 10% tetramethylammonium hydroxide solution (5.0 equiv, 0.44 mL) at reflux temperature for 12 h. After removal of the solvent, 10% HCl (10 mL) was added. The aqueous solution was extracted with CH_2Cl_2 (2×10 mL). The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (SiO_2, petroleum ether–AcOEt 3:1–1:1) to give optically pure compound **3–1** or **3–2**, respectively, as a white solid without recrystallization. The enantiomers have the spectroscopic data identical to those of the corresponding racemates **3**.

Compound **3a–1**. Yield 82%. $[\alpha]_D^{25}$ −28 (*c* 0.5, $CHCl_3$).

Compound **3a–2**. Yield 81%. $[\alpha]_D^{25}$ +28 (*c* 0.5, $CHCl_3$).

Compound **3a–1** and **3a–2** have same Mp 138–140 °C.

Compound **3b–1**. Yield 77%. $[\alpha]_D^{25}$ −12 (*c* 0.5, $CHCl_3$).

Compound **3b–2**. Yield 80%. $[\alpha]_D^{25}$ +12 (*c* 0.5, $CHCl_3$).

Compound **3b–1** and **3b–2** have same Mp 131–133 °C.

4.6. Alkylation of the tri-*O*-alkylated calixcrowns in cone conformer to the tetra-*O*-alkylated calixcrowns in partial cone conformer. General procedure

Compounds **3** (1.8 mmol), ^{n}PrI (10 equiv) and Cs_2CO_3 (8.8 g, 15 equiv) in dry DMF (100 mL) were stirred at 70 °C for 1 day. Then 20 mL 10% HCl was added to quench the reaction. After removal of the solvent under reduced pressure, the residue was partitioned between H_2O and CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography to give **5** as white solids.

4.6.1. 25-[(2-Methoxycarbonyl-naphthal-3-oxy)ethoxy]-28-propoxy-*p-tert*-butylcalix[4]-(26,27)-crown-4, partial cone conformer (5a). Column chromatography (SiO_2, petroleum ether–AcOEt 8:1). Yield 73%. Mp 218–220 °C (CH_2Cl_2/CH_3OH). ^{1}H NMR: δ 8.30 (s, 1H, Naph-*H*), 7.82 (d, *J*=8.0 Hz, 1H, Naph-*H*), 7.73 (d, *J*=8.2 Hz, 1H, Naph-*H*), 7.52 (t, *J*=6.9 Hz, 1H, Naph-*H*), 7.38 (t, *J*=8.0 Hz, 1H, Naph-*H*), 7.30 (s, 1H, Naph-*H*), 7.27 and 7.14 (2d, *J*=2.4 Hz, 1H each, Ar*H*), 7.10 and 7.08 (2d, *J*=2.4 Hz, 1H each, Ar*H*), 6.89 and 6.88 (2d, *J*=2.6 Hz, 1H each, Ar*H*), 6.70 and 6.69 (2d, *J*=2.4 Hz, 1H each, Ar*H*), 4.49–4.45 (m, 2H, OCH_2CH_2O), 4.37 (d, *J*=12.4 Hz, 1H, ArCH_2Ar), 4.28–4.19 (m, 2H, OCH_2CH_2O), 4.15 (d, *J*=12.5 Hz, 1H, ArCH_2Ar), 3.86 (s, 3H, CO_2CH_3), 4.03–3.46 (m, 16H, OCH_2CH_2O and ArCH_2Ar), 3.28 (t, *J*=7.7 Hz, 2H, ArOC$H_2$$CH_2$$CH_3$), 3.13 (d, *J*=12.6 Hz, 1H, ArCH_2Ar), 3.07 (d, *J*=12.5 Hz, 1H, ArCH_2Ar), 1.64–1.51 (m, 2H, ArOCH_2C$H_2$$CH_3$), 1.35 and 1.32 (2s, 9H each, C(CH_3)$_3$), 1.07 (s, 18H, C(CH_3)$_3$), 0.74 (t, *J*=7.4 Hz, 3H, ArOCH_2-CH_2CH_3). ^{13}C NMR: δ 167.0 (*C*O_2), 155.5, 154.7, 153.7, 153.0, 152.7, 145.3, 144.2, 144.0, 143.1, 136.1, 135.5, 135.1, 133.5, 133.1, 133.0, 132.7, 132.6, 132.3, 132.2, 128.7, 128.2, 128.0, 127.7, 127.0, 126.5, 126.2, 125.8, 125.79, 125.77, 125.5, 125.2, 124.4, 122.3, 108.1 (Naph-*C* and Ar*C*), 73.6, 72.7, 72.3, 71.6, 70.6, 69.5, 68.4, 67.7, 66.8 (O*C*H_2*C*H_2O and ArO*C*$H_2$$CH_2$$CH_3$), 52.2 ($CO_2$*C*$H_3$), 38.1, 38.0, 30.9, 30.2 (Ar*C*H_2Ar), 34.1, 34.0, 33.8 (*C*(CH_3)$_3$), 31.8, 31.7, 31.42, 31.40 (C(*C*H_3)$_3$), 23.8 (ArOCH_2*C*H_2-CH_3), 10.2 (ArOC$H_2$$CH_2$*C*$H_3$). MALDI-TOF MS: *m/z* 1055.5 ($[M+Na]^+$), 1071.5 ($[M+K]^+$). Anal. Calcd for $C_{67}H_{84}O_9$: C, 77.87; H, 8.19. Found: C, 77.60; H, 8.17.

4.6.2. 25-[(2-Methoxycarbonyl-naphthal-3-oxy)ethoxy]-28-propoxy-*p-tert*-butylcalix[4]-(26,27)-crown-5, partial cone conformer (5b). Column chromatography (SiO_2, petroleum ether–AcOEt 6:1). Yield 62%. Mp 197–199 °C (CH_2Cl_2/CH_3OH). ^{1}H NMR: δ 8.28 (s, 1H, Naph-*H*), 7.81 (d, *J*=8.0 Hz, 1H, Naph-*H*), 7.73 (d, *J*=8.1 Hz, 1H, Naph-*H*), 7.52 (t, *J*=6.9 Hz, 1H, Naph-*H*), 7.37 (t, *J*=8.0 Hz, 1H, Naph-*H*), 7.31 (s, 1H, Naph-*H*), 7.28 and 7.21 (2d, *J*=2.5 Hz, 1H each, Ar*H*), 7.08 and 7.06 (2d, *J*=2.5 Hz, 1H each, Ar*H*), 6.90 and 6.86 (2d, *J*=2.4 Hz, 1H each, Ar*H*), 6.67 and 6.61 (2d, *J*=2.4 Hz, 1H each, Ar*H*), 4.59–4.44 (m, 2H, OCH_2CH_2O), 4.29 (d, *J*=12.6 Hz, 1H, ArCH_2Ar), 4.22 (d, *J*=13.0 Hz, 1H, ArCH_2Ar), 4.30–4.10 (m, 2H, OCH_2-CH_2O), 4.05–3.94 (m, 2H, OCH_2CH_2O), 3.86 (s, 3H, CO_2CH_3), 3.82–3.35 (m, 18H, OCH_2CH_2O and ArCH_2Ar), 3.32 (t, *J*=7.7 Hz, 2H, ArOC$H_2$$CH_2$$CH_3$), 3.12 (d, *J*=12.8 Hz, 1H, ArCH_2Ar), 3.05 (d, *J*=12.7 Hz, 1H, ArCH_2-Ar), 1.68–1.53 (m, 2H, ArOCH_2C$H_2$$CH_3$), 1.38, 1.32, 1.08 and 1.04 (4s, 9H each, C(CH_3)$_3$), 0.76 (t, *J*=7.4 Hz, 3H, ArOC$H_2$$CH_2CH_3$). ^{13}C NMR: δ 167.0 (*C*O_2), 155.3, 154.7, 153.6, 153.5, 153.1, 145.1, 144.2, 143.8, 143.2, 136.1, 135.8, 135.0, 133.8, 132.9, 132.8, 132.60, 132.55, 132.2, 131.9, 128.6, 128.2, 127.6, 127.6, 127.5, 126.5, 126.1, 126.1, 125.6, 125.5, 125.44, 125.40, 124.3, 122.3, 108.0 (Naph-*C* and Ar*C*), 73.9, 73.1, 71.57, 71.55, 71.5, 70.8, 70.7, 70.5, 69.3, 68.6, 67.6 (O*C*H_2*C*H_2O and ArO*C*$H_2$$CH_2$-$CH_3$), 52.2 ($CO_2$*C*$H_3$), 38.0, 37.8, 31.3, 30.8 (Ar*C*H_2Ar), 34.1, 34.0, 33.8, 33.7 (*C*(CH_3)$_3$), 31.8, 31.7, 31.44, 31.42 (C(*C*H_3)$_3$), 23.8 (ArOCH_2*C*H_2CH_3), 10.3 (ArOC$H_2$$CH_2$-*C*$H_3$). MALDI-TOF MS: *m/z* 1099.5 ($[M+Na]^+$), 1115.4 ($[M+K]^+$). Anal. Calcd for $C_{69}H_{88}O_{10}$: C, 76.92; H, 8.23. Found: C, 76.69; H, 8.26.

4.6.3. 25-[(2-Methoxycarbonyl-naphthal-3-oxy)ethoxy]-28-propoxy-*p-tert*-butylcalix[4]-(26,27)-crown-6, partial cone conformer (5c). Yield 63%. Mp 78–79 °C (CH_2Cl_2/CH_3OH). ^{1}H NMR: δ 8.28 (s, 1H, Naph-*H*), 7.82 (d, *J*=8.0 Hz, 1H, Naph-*H*), 7.73 (d, *J*=8.2 Hz, 1H, Naph-*H*), 7.53 (t, *J*=7.0 Hz, 1H, Naph-*H*), 7.39 (t, *J*=8.0 Hz, 1H, Naph-*H*), 7.26 (s, 1H, Naph-*H*), 7.28 and 7.20 (2d, *J*=2.5 Hz, 1H each, Ar*H*), 7.09 and 7.08 (2d, *J*=2.5 Hz, 1H each, Ar*H*), 6.90 and 6.87 (2d, *J*=2.5 Hz, 1H each, Ar*H*), 6.66 and 6.64 (2d, *J*=2.5 Hz, 1H each, Ar*H*), 4.56–4.45 (m, 2H, OCH_2CH_2O), 4.31 (d, *J*=12.5 Hz, 1H, ArCH_2Ar), 4.21 (d, *J*=12.4 Hz, 1H, ArCH_2Ar), 4.28–4.08 (m, 3H, OCH_2-CH_2O), 3.86 (s, 3H, CO_2CH_3), 3.85–3.16 (m, 25H, ArOC$H_2$$CH_2$$CH_3$, ArC$H_2$Ar and OC$H_2CH_2$O), 3.12 (d,

J=12.7 Hz, 1H, ArCH_2Ar), 3.03 (d, J=12.7 Hz, 1H, ArCH_2Ar), 1.68–1.54 (m, 2H, ArOCH$_2$CH_2CH$_3$), 1.37, 1.33, 1.06 and 1.05 (4s, 9H each, C(CH_3)$_3$), 0.70 (t, J=7.4 Hz, 3H, ArOCH$_2$CH$_2$CH_3). ^{13}C NMR: δ 166.9 (CO_2), 155.3, 154.7, 153.6, 153.0, 152.9, 145.3, 144.2, 143.9, 143.2, 136.0, 135.7, 135.5, 133.3, 133.0, 132.9, 132.7, 132.4, 132.2, 132.1, 128.7, 128.4, 127.7, 127.6, 127.3, 126.4, 126.3, 126.1, 125.7, 125.5, 125.4, 125.3, 124.4, 122.3, 107.8 (Naph-*C* and Ar*C*), 73.9, 72.1, 71.6, 70.8, 70.7, 70.6, 70.5, 70.42, 70.38, 70.3, 69.9, 69.1, 67.7 (OCH$_2$CH$_2$O and ArOCH$_2$CH$_2$CH$_3$), 52.2 (CO_2CH$_3$), 38.1, 37.9, (ArCH$_2$-Ar), 34.1, 34.0, 33.8, 33.7 (C(CH$_3$)$_3$), 31.8, 31.7, 31.4 (C(CH$_3$)$_3$), 31.0, 30.7 (ArCH$_2$Ar), 23.8 (ArOCH$_2$CH$_2$CH$_3$), 10.2 (ArOCH$_2$CH$_2$CH$_3$). MALDI-TOF MS: *m*/*z* 1143.6 ([M+Na]$^+$), 1159.6 ([M+K]$^+$). Anal. Calcd for $C_{71}H_{92}O_{11}$: C, 76.04; H, 8.27. Found: C, 76.05; H, 8.51.

4.7. Hydrolysis of compounds 5. Refer to the general hydrolysis procedure of compounds 2.

4.7.1. 25-[(2-Carboxyl-naphthal-3-oxy)ethoxy]-28-propoxy-*p*-*tert*-butylcalix[4]-(26,27)-crown-4, partial cone conformer (6a). Column chromatography (SiO_2, petroleum ether–AcOEt 3:1–1:1). Yield 82%. Mp 133–135 °C. ^{1}H NMR: δ 8.58 (s, 1H, Naph-*H*), 7.88 (d, J=8.0 Hz, 1H, Naph-*H*), 7.74 (d, J=8.2 Hz, 1H, Naph-*H*), 7.56 (t, J=6.9 Hz, 1H, Naph-*H*), 7.42 (t, J=8.1 Hz, 1H, Naph-*H*), 7.32 (s, 1H, Naph-*H*), 7.26 and 7.18 (2d, J=2.4 Hz, 1H each, Ar*H*), 7.08 and 7.02 (2d, J=2.4 Hz, 1H each, Ar*H*), 6.91 and 6.90 (2d, J=2.5 Hz, 1H each, Ar*H*), 6.73 and 6.72 (2d, J=2.7 Hz, 1H each, Ar*H*), 4.57–4.37 (m, 4H, OCH_2CH_2O), 4.32 (d, J=12.4 Hz, 1H, ArCH_2Ar), 4.15 (d, J=12.5 Hz, 1H, ArCH_2Ar), 4.02–3.54 (m, 16H, OCH_2CH_2O and ArCH_2Ar), 3.25–3.08 (m, 2H, ArOCH_2CH$_2$CH$_3$), 3.08 (d, J=13.5 Hz, 1H, ArCH_2Ar), 3.04 (d, J=13.1 Hz, 1H, ArCH_2Ar), 1.51 (sextet, J=7.7 Hz, 2H, ArOCH$_2$CH_2CH$_3$), 1.41, 1.28, 1.072 and 1.070 (4s, 9H each, C(CH_3)$_3$), 0.67 (t, J=7.4 Hz, 3H, ArOCH$_2$CH$_2$CH_3). ^{13}C NMR: δ 166.4 (CO_2), 155.4, 153.9, 153.4, 152.6, 152.4, 145.5, 144.7, 144.2, 143.3, 136.4, 135.4, 135.0, 134.9, 133.5, 133.2, 133.1, 133.0, 132.3, 131.9, 129.2, 128.9, 128.3, 127.6, 127.2, 126.6, 126.5, 125.90, 125.86, 125.8, 125.4, 125.3, 125.0, 120.1, 107.9 (Naph-*C* and Ar*C*), 73.5, 72.8, 72.3, 71.0, 69.7, 68.3, 67.9, 66.4 (OCH$_2$CH$_2$O and CH$_2$CH$_2$CH$_3$), 38.4, 38.3, 30.5, 30.3 (ArCH$_2$Ar), 34.10, 34.07, 33.8, 33.8 (C(CH$_3$)$_3$), 31.9, 31.6, 31.4, 31.3 (C(CH$_3$)$_3$), 23.6 (CH$_2$-CH$_2$CH$_3$), 10.1 (CH$_2$CH$_2$CH$_3$). MALDI-TOF MS: *m*/*z* 1041.7 ([M+Na]$^+$), 1057.7 ([M+K]$^+$). Anal. Calcd for $C_{66}H_{82}O_9$: C, 77.77; H, 8.11. Found: C, 77.61; H, 8.25.

4.7.2. 25-[(2-Carboxyl-naphthal-3-oxy)ethoxy]-28-propoxy-*p*-*tert*-butylcalix[4]-(26,27)-crown-5, partial cone conformer (6b). Yield 71%. Mp 220–222 °C (CH_2Cl_2/CH_3OH). ^{1}H NMR: δ 8.64 (s, 1H, Naph-*H*), 7.88 (d, J=8.2 Hz, 1H, Naph-*H*), 7.76 (d, J=8.2 Hz, 1H, Naph-*H*), 7.57 (t, J=7.1 Hz, 1H, Naph-*H*), 7.43 (t, J=7.1 Hz, 1H, Naph-*H*), 7.37 (s, 1H, Naph-*H*), 7.24 (s, 2H, Ar*H*), 7.06 and 7.02 (2d, J=2.4 Hz, 1H each, Ar*H*), 6.92 and 6.87 (2d, J=2.4 Hz, 1H each, Ar*H*), 6.69 and 6.64 (2d, J=2.3 Hz, 1H each, Ar*H*), 4.76–4.69 (m, 1H, OCH_2CH_2O), 4.52–4.46 (m, 1H, OCH_2CH_2O), 4.41–4.34 (m, 1H, OCH_2CH_2O), 4.21–4.14 (m, 1H, OCH_2CH_2O), 4.28 (d, J=12.9 Hz, 1H, ArCH_2Ar), 4.23 (d, J=13.9 Hz, 1H, ArCH_2Ar), 4.06–3.38 (m, 20H, OCH_2CH_2O and ArCH_2Ar), 3.32–3.19 (m, 2H, CH_2CH$_2$CH$_3$), 3.11 (d, J=13.0 Hz, 1H, ArCH_2Ar), 3.06 (d, J=12.8 Hz, 1H, ArCH_2Ar), 1.60–1.48 (m, 2H, CH$_2$CH_2-CH$_3$), 1.40, 1.30, 1.09 and 1.05 (4s, 9H each, C(CH_3)$_3$), 0.72 (t, J=7.4 Hz, 3H, CH$_2$CH$_2$CH_3). ^{13}C NMR: δ 166.1 (CO_2), 155.3, 153.8, 153.5, 153.3, 152.6, 145.2, 144.7, 144.0, 143.3, 136.4, 135.6, 135.2, 134.7, 133.1, 133.0, 132.8, 132.7, 131.9, 131.8, 129.2, 129.1, 128.3, 127.7, 127.2, 126.6, 126.4, 126.1, 125.7, 125.63, 125.61, 125.4, 125.1, 119.6, 108.1 (Naph-*C* and Ar*C*), 73.8, 73.1, 71.6, 71.4, 71.0, 70.8, 70.7, 70.5, 69.3, 69.0, 68.7 (OCH$_2$CH$_2$O and CH$_2$-CH$_2$CH$_3$), 38.1, 38.1, 31.1, 30.8 (ArCH$_2$Ar), 34.1, 34.0, 33.8, 33.7 (C(CH$_3$)$_3$), 31.8, 31.6, 31.4, 31.4 (C(CH$_3$)$_3$), 23.7 (CH$_2$CH$_2$CH$_3$), 10.3 (CH$_2$CH$_2$CH$_3$). MALDI-TOF MS: *m*/*z* 1085.3 ([M+Na$^+$]), 1101.2 ([M+K$^+$]). Anal. Calcd for $C_{68}H_{86}O_{10}$: C, 76.80; H, 8.15. Found: C, 76.63; H, 8.13.

4.7.3. 25-[(2-Carboxyl-naphthal-3-oxy)ethoxy]-28-propoxy-*p*-*tert*-butylcalix[4]-(26,27)-crown-6, partial cone conformer (6c). Yield 85%. Mp 240–242 °C (CH_2Cl_2/CH_3OH). ^{1}H NMR: δ 8.62 (s, 1H, Naph-*H*), 7.89 (d, J=8.1 Hz, 1H, Naph-*H*), 7.76 (d, J=8.1 Hz, 1H, Naph-*H*), 7.58 (t, J=6.9 Hz, 1H, Naph-*H*), 7.44 (t, J=7.1 Hz, 1H, Naph-*H*), 7.31 (s, 1H, Naph-*H*), 7.25 and 7.22 (2d, J=2.4 Hz, 1H each, Ar*H*), 7.07 and 7.05 (2d, J=2.4 Hz, 1H each, Ar*H*), 6.92 and 6.89 (2d, J=2.4 Hz, 1H each, Ar*H*), 6.69 and 6.68 (2d, J=2.5 Hz, 1H each, Ar*H*), 4.70–4.63 (m, 1H, OCH_2CH_2O), 4.54–4.48 (m, 1H, OCH_2CH_2O), 4.43–4.36 (m, 1H, OCH_2CH_2O), 4.23–4.13 (m, 1H, OCH_2CH_2O), 4.34 (d, J=12.5 Hz, 1H, ArCH_2Ar), 4.20 (d, J=12.3 Hz, 1H, ArCH_2Ar), 3.92–3.30 (m, 24H, ArCH_2Ar and OCH_2-CH_2O), 3.08 (d, J=14.3 Hz, 1H, ArCH_2Ar), 3.03 (d, J=12.5 Hz, 1H, ArCH_2Ar), 3.02 (t, J=8.1 Hz, 2H, ArOCH_2-CH$_2$CH$_3$), 1.59–1.44 (m, 2H, ArOCH$_2$CH_2CH$_3$), 1.39, 1.31, 1.07 and 1.06 (4s, 9H each, C(CH_3)$_3$), 0.58 (t, J=7.5 Hz, 3H, ArOCH$_2$CH$_2$CH_3). ^{13}C NMR: δ 166.0 (CO_2), 155.2, 153.7, 153.3, 152.7, 152.4, 145.4, 144.7, 144.1, 143.3, 136.3, 135.5, 135.2, 135.0, 133.3, 133.2, 133.0, 132.7, 132.2, 132.0, 129.2, 129.1, 128.2, 127.4, 127.3, 126.50, 126.47, 126.3, 125.8, 125.4, 125.4, 125.4, 125.1, 119.7, 107.8 (Naph-*C* and Ar*C*), 73.8, 71.9, 71.0, 70.7, 70.5, 70.4, 69.8, 69.3, 68.6 (OCH$_2$CH$_2$O and ArOCH$_2$CH$_2$CH$_3$), 38.3 (ArCH$_2$Ar), 34.1, 34.0, 33.8, 33.7 (C(CH$_3$)$_3$), 31.8, 31.6, 31.34, 31.30 (C(CH$_3$)$_3$), 30.7, 30.6 (ArCH$_2$Ar), 23.6 (ArOCH$_2$CH$_2$CH$_3$), 10.0 (ArOCH$_2$CH$_2$CH$_3$). MALDI-TOF MS: *m*/*z* 1129.3 ([M+Na]$^+$), 1145.2 ([M+K]$^+$). Anal. Calcd for $C_{70}H_{90}O_{11}$: C, 75.92; H, 8.19. Found: C, 75.69; H, 8.14.

4.8. Condensation of compounds 6 with the chiral auxiliary (*S*)-BINOL. Refer to the general condensation procedure of the cone conformers 2

4.8.1. 25-[(2-(*S*)-Binaphthoxycarbonyl-naphthal-3-oxy)ethoxy]-28-propoxy-*p*-*tert*-butylcalix[4]-(26,27)-crown-6, partial cone conformer (7c). Firstly, the crude products were purified via column chromatography (SiO_2, petroleum ether–AcOEt 9:2), then the diastereomeric mixture was subjected to preparative TLC (petroleum ether–AcOEt 8:3) to give **7c–1** and **7c–2** as white solids.

Compound **7c–1**. Yield 23%. Mp 128–130 °C. ^{1}H NMR: δ 7.98 (d, J=8.8 Hz, 2H, Naph-*H*), 7.82 (d, J=9.2 Hz, 1H,

Naph-*H*), 7.79 (d, $J=9.3$ Hz, 1H, Naph-*H*), 7.60 (d, $J=8.1$ Hz, 1H, Naph-*H*), 7.55–7.17 (m, 13H, Naph-*H* and Ar*H*), 7.13 (s, 2H, Ar*H*), 7.08 (s, 1H, Naph-*H*), 7.02 (s, 1H, Naph-*H*), 6.88 (s, 2H, Ar*H*), 6.66 and 6.65 (2d, $J=2.5$ Hz, 1H each, Ar*H*), 5.31 (s, 1H, O*H*), 4.43–4.31 (m, 2H, OCH_2CH_2O), 4.30 (d, $J=12.2$ Hz, 1H, $ArCH_2Ar$), 4.21 (d, $J=12.6$ Hz, 1H, $ArCH_2Ar$), 4.13–4.05 (m, 2H, OCH_2CH_2O), 3.99–3.90 (m, 1H, OCH_2CH_2O), 3.80–2.90 (m, 25H, OCH_2CH_2O, $ArCH_2Ar$ and $CH_2CH_2CH_3$), 3.07 (d, $J=12.7$ Hz, 1H, $ArCH_2Ar$), 3.04 (d, $J=12.5$ Hz, 1H, $ArCH_2Ar$), 1.67–1.57 (m, 2H, $CH_2CH_2CH_3$), 1.39 and 1.35 (2s, 9H each, $C(CH_3)_3$), 1.06 (s, 18H, $C(CH_3)_3$), 0.71 (t, $J=7.4$ Hz, 3H, $CH_2CH_2CH_3$). ^{13}C NMR: δ 164.6 (CO_2), 155.3, 154.7, 153.7, 152.9, 152.8, 152.0, 148.3, 145.2, 144.2, 143.9, 143.2, 136.1, 135.8, 135.7, 133.8, 133.4, 133.3, 133.2, 132.99, 132.97, 132.6, 132.2, 132.2, 132.1, 130.7, 130.3, 129.0, 128.7, 128.6, 128.3, 128.0, 127.6, 127.4, 127.3, 127.2, 126.9, 126.3, 126.2, 126.2, 126.1, 125.8, 125.7, 125.6, 125.40, 125.38, 124.7, 124.3, 123.6, 123.0, 122.4, 120.5, 118.5, 114.1, 107.3 (Naph-*C* and Ar*C*), 73.9, 72.1, 71.2, 70.8, 70.6, 70.4, 70.3, 70.2, 69.9, 69.1, 67.4 (OCH_2CH_2O and $CH_2CH_2CH_3$), 38.1, 38.0 ($ArCH_2Ar$), 34.2, 34.0, 33.8, 33.7 ($C(CH_3)_3$), 31.8, 31.8, 31.4 ($C(CH_3)_3$), 30.8, 30.7 ($ArCH_2Ar$), 23.8 ($CH_2CH_2CH_3$), 10.2 ($CH_2CH_2CH_3$). MALDI-TOF MS: *m/z* 1397.1 ($[M+Na]^+$), 1413.1 ($[M+K]^+$). Anal. Calcd for $C_{90}H_{102}O_{12}$: C, 78.57; H, 7.47. Found: C, 78.74; H, 7.83.

Compound **7c–2**. Yield 23%. Mp 128–130 °C. ^1H NMR: δ 7.96 (d, $J=8.6$ Hz, 1H, Naph-*H*), 7.94 (d, $J=9.1$ Hz, 1H, Naph-*H*), 7.82 (d, $J=6.8$ Hz, 1H, Naph-*H*), 7.81 (d, $J=9.2$ Hz, 1H, Naph-*H*), 7.60 (d, $J=8.0$ Hz, 1H, Naph-*H*), 7.54–7.18 (m, 13H, Naph-*H* and Ar*H*), 7.11 and 7.09 (2d, $J=2.4$ Hz, 1H each, Ar*H*), 7.08 (s, 1H, Naph-*H*), 7.02 (s, 1H, Naph-*H*), 6.89 and 6.88 (2d, $J=2.5$ Hz, 1H each, Ar*H*), 6.64 and 6.63 (2d, $J=2.5$ Hz, 1H each, Ar*H*), 4.32 (d, $J=12.6$ Hz, 1H, $ArCH_2Ar$), 4.22 (d, $J=12.7$ Hz, 1H, $ArCH_2Ar$), 4.38–3.18 (m, 30H, OCH_2CH_2O, $ArCH_2Ar$ and $CH_2CH_2CH_3$), 3.04 (d, $J=12.7$ Hz, 2H, $ArCH_2Ar$), 1.70–1.56 (m, 2H, $CH_2CH_2CH_3$), 1.35, 1.32, 1.06 and 1.05 (4s, 9H each, $C(CH_3)_3$), 0.72 (t, $J=7.4$ Hz, 3H, $CH_2CH_2CH_3$). ^{13}C NMR: δ 164.5 (CO_2), 155.3, 154.6, 153.7, 152.9, 152.6, 152.0, 148.3, 145.3, 144.2, 143.9, 143.3, 136.1, 135.7, 135.6, 133.7, 133.4, 133.3, 133.04, 133.01, 132.95, 132.6, 132.2, 132.1, 132.0, 130.5, 130.3, 123.0, 128.7, 128.5, 128.3, 128.0, 127.6, 127.4, 127.3, 127.3, 126.9, 126.28, 126.25, 126.17, 126.16, 125.7, 125.58, 125.56, 125.4, 125.3, 124.7, 124.3, 123.6, 123.1, 122.4, 120.6, 118.5, 114.2, 107.4 (Naph-*C* and Ar*C*), 74.0, 72.1, 71.0, 70.7, 70.7, 70.6, 70.4, 70.4, 70.1, 69.9, 69.0, 67.3 (OCH_2CH_2O and $CH_2CH_2CH_3$), 38.1, 37.8 ($ArCH_2Ar$), 34.1, 34.0, 33.8, 33.7 ($C(CH_3)_3$), 31.74, 31.69, 31.39, 31.38 ($C(CH_3)_3$), 30.9, 30.7 ($ArCH_2Ar$), 23.8 ($CH_2CH_2CH_3$), 10.2 ($CH_2CH_2CH_3$). MALDI-TOF MS: *m/z* 1397.0 ($[M+Na]^+$), 1413.0 ($[M+K]^+$). Anal. Calcd for $C_{90}H_{102}O_{12}$: C, 78.57; H, 7.47. Found: C, 78.73; H, 7.89.

4.9. Hydrolysis of 7c to furnish optically pure enantiomers 6c. Refer to the general procedure for optically pure enantiomers 3

Compound **6c–1**. Yield 80%. $[\alpha]_D^{25}$ +28 (*c* 0.5, $CHCl_3$).

Compound **6c–2**. Yield 82%. $[\alpha]_D^{25}$ −28 (*c* 0.5, $CHCl_3$).

Compound **3a–1** and **3a–2** have same Mp 93–95 °C.

4.10. Crystallographic data for 2b

Crystallographic data for **2b** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-270016. The data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223/336 033; e-mail: deposit@ccdc.cam.ac.uk].

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Further rearranged prenylxanthones and benzophenones from *Garcinia bracteata*

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Abstract—New rearranged polyprenylxanthones, namely garcibracteatone, neoisobractatins A and B, and xerophenone C were isolated from the leaves and bark of a vietnamese *Garcinia*, *Garcinia bracteata*, together with 5-*O*-methylxanthone V_1, bracteaxanthones I and II, and the known nemorosonol and simple xanthones. Neoisobractatins A and B exhibit a significant cytotoxic activity on KB cells. A biogenetic hypothesis is proposed, which explains the possible origin of these so-called cage-xanthanoids.

1. Introduction

In continuation of our preliminary investigations on the leaves of *Garcinia bracteata* Wu ex Li (Clusiaceae)[1] we isolated from the bark of the plant new prenylxanthones, garcibracteatone **1**, xerophenone C **2**, 5-*O*-methylxanthone V_1 **3**, together with the known nemorosonol **4**,[2,3] and 10-*O*-methylmacluraxanthone.[4] From the leaves of the plant, neoisobractatins **5** and **6**, bracteaxanthones I **7**, and II **8**, and the known macluraxanthone,[5] cudraxanthone R[6] and gerontoxanthone I,[7] were isolated. In this paper, we report the isolation, structure elucidation and biological evaluation on KB cells culture of the new compounds. A hypothetic mechanism is formulated to explain the biogenesis of the tetraprenylbenzophenones **1**, **2**, and **4** in the plant, and of the triprenylxanthones **5** and **6**, which are new examples of the so-called cage-xanthanoids.[8–10]

2. Results and discussion

2.1. Isolation

Dried and powdered leaves were extracted with EtOAc then EtOH as previously described.[1] Bark of the plant was extracted by the same method. Both extracts were chromatographed on silica gel, and compounds **1**–**4** and 10-*O*-methylmacluraxanthone were isolated from the EtOAc extract of the bark. Compounds **5**–**8**, macluraxanthone, cudraxanthone R, and gerontoxanthone I were isolated from the EtOAc extract of the leaves. The structures of **1**–**8** have been determined by a combination of ^{1}H, ^{13}C, and 2D NMR techniques. X-ray analysis of the diastereoisomer **5** gives its relative configuration.

2.2. Structure elucidation

Compound **4** was first isolated and compared to nemorosonol, which was previously isolated from *Clusia nemorosa*, and re-isolated in the present work from *G. bracteata*. The NMR data and HMBC correlations were identical.[2,3] So compound **4** is nemorosonol.

Garcibracteatone (**1**), gave a molecular peak at *m/z* 500 (EIMS) corresponding to the molecular formula $C_{33}H_{40}O_4$. The IR spectrum indicated the presence of three ketone functions at 1739, 1708, and 1675 cm^{-1}. The ^{13}C NMR spectrum allows to number 33 carbons of which seven signals correspond to methyl substituents, eight methine of which four are aromatic and two olefinic, 13 quaternary carbons of which three are keto groups, and five methylene carbons (Table 1). In the HMBC NMR spectrum, the presence of two isoprenyl chains was deduced from the observation of a broad triplet of 2H at 5.02 ppm (H-12, H-22) correlating with two methylene signals at 2.28 (d, CH_2-11) and at 2.25 (H_A-21) and 2.10 (H_B-21) (Table 1). Four aromatic protons coupling together correspond to a

Keywords: Clusiaceae; *Garcinia bracteata*; Garcibracteatone; Xerophenone C; Neoisobractatins; Nemorosonol; Bracteaxanthones; Xanthones; Benzophenones.
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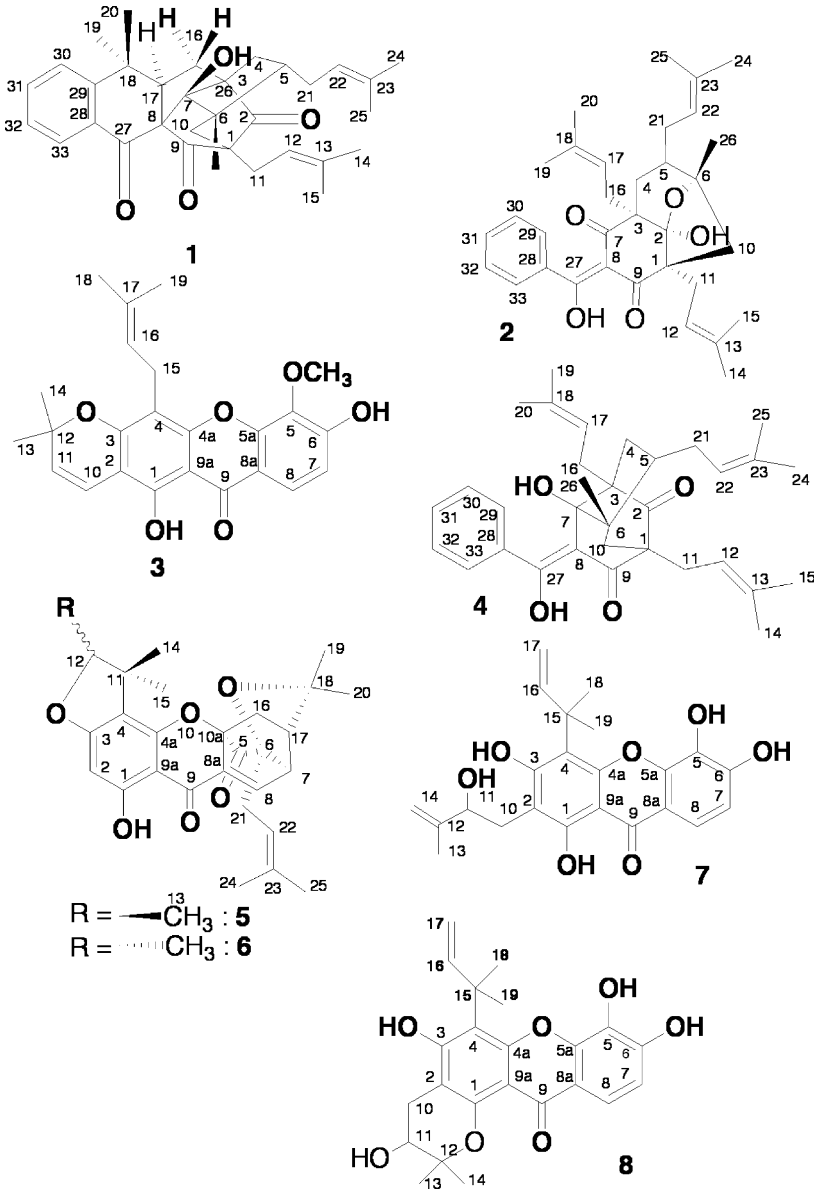


disubstituted aromatic ring. These data and the observation of other correlations lead to a nemorosonol-type structure with only two isoprenyl chains, and a possible rearrangement of the third one. In COSY and HMBC spectra, correlations between H-30 and C-18, which couples itself with CH_3-19 and CH_3-20, between H-17, C-8, and C-18, lead us to propose for compound **1** the structure of garcibracteatone as indicated. The relative configuration of (**1**) is possibly similar to the nemorosonol one (**4**) of which the relative configuration is known, all the stereocenters being determined except C-17 (see after), NOESY experiments show correlations between CH_3-20 and OH-7, CH_3-19, and H-17. Biogenetically, it can be hypothetized that garcibracteatone comes from nemorosonol **4**, also isolated from the plant, by a cycloaddition involving carbons C-17 and C-18 on one hand, C-28 and C-29/C-8 and C-27 on the other hand, followed by oxidation of the enol (Scheme 1).

Xerophenone C (**2**) gave a peak $[M]^{+\cdot}$ at *m/z* 518 (EIMS), which matched the molecular formula $C_{33}H_{42}O_5$. The presence of the unsubstituted phenylketone/enol was shown by a peak at *m/z* 105, $C_6H_5CO^+$, and by five aromatic protons in the NMR spectrum. The ^1H NMR spectrum in $CDCl_3$ shows unresolved signals. In pyridine-d_5, all the signals are well resolved, which lead us to suppose the presence of tautomeric forms (Table 1). The presence of three isoprenyl chains was deduced from the observation of three vinyl protons at 5.94 ppm (H-12), 5.85 (H-17), and 5.07 (H-22), correlating in COSY with three methylenes and six methyls, respectively. The ^{13}C NMR spectrum allows to number 33 carbons of which five CH_2 (three for the three isoprenyl chains, one isolated CH_2 and the last one connected to a CH), seven methyls, nine CH, and 12 quaternary carbons (Table 1). HMBC correlations allow to connect the quaternary carbons with the isoprenyl chains. This product is very close to xerophenones A and B isolated from *Clusia portlandiana*,[11,12] the only difference being a double bond between C-22 and C-23, instead of C-23 and C-24. NOESY experiments show correlations between H-5 and CH_2-16, meaning that H-5 has the same orientation that the isoprenyl chain in C-3, between H-29/

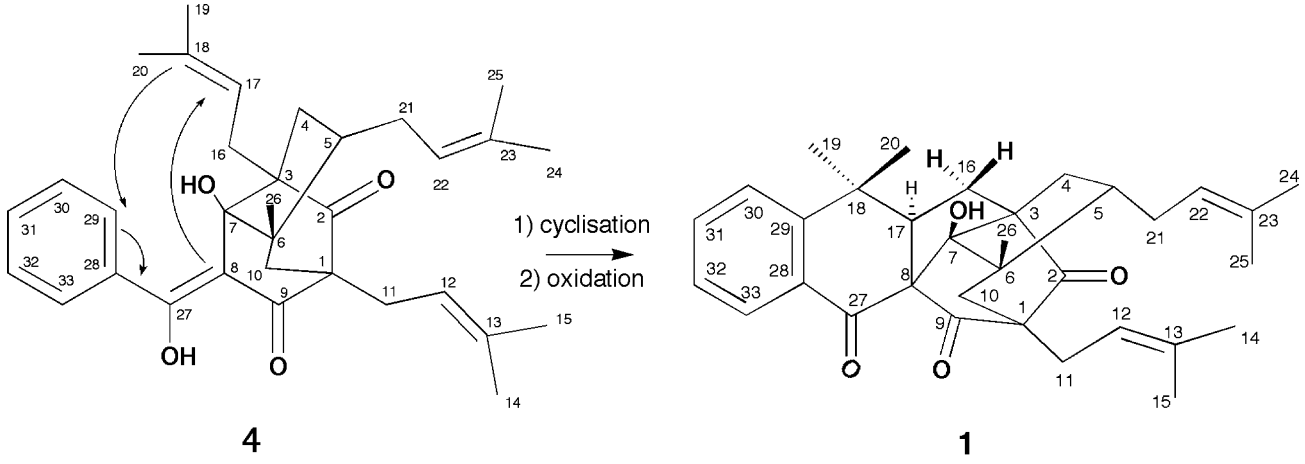
Table 1. ^{1}H and ^{13}C NMR data of benzophenones **1** ($CDCl_3$) and **2** (pyridine-d_5)

Position	**1**[a]			**2**[b]		
	^{1}H	^{13}C	HMBC	^{1}H	^{13}C	HMBC
1		63.3			59.8	
2		213.4			105.7	
3		70.3			54.3	
4	1.60 m	32.6	2, 3, 5, 6	1.45 m	35.4	3, 7, 21
	2.00 m		2, 3, 5, 7	2.32 m		2, 3, 5, 6, 16
5	1.85 m	57.0		1.70 m	41.9	
6		47.6			81.5	
7		91.9			203.4	
8		69.3			111.4	
9		203.5			198.6	
10	1.60 m	47.6	1, 5, 6, 7, 9, 26	1.96 d (13)	41.9	1, 2, 5, 6, 9, 11, 26
	1.80 m		1, 5, 6, 9, 26	2.54 d (13)		1, 2, 5, 6, 9, 11
11	2.28 2H d (7.5)	25.2	1, 9, 10, 12, 13	3.02 2H d (6.5)	35.9	1, 2, 9, 10, 12, 13
12	5.02 br t	119.0	14	5.94 t (7)	122.2	11, 14, 15
13		134.3			132.5	
14	1.64 3H s	25.9	12, 13, 15	1.74 3H s	26.1	12, 13, 15
15	1.56 3H s	17.9	12, 13, 14	1.61 3H s	17.8	12, 13, 14
16	2.00 m	29.1	2, 3, 17, 18	3.19 2H d (6.5)	26.4	2, 3, 4, 7, 17, 18
	2.20 m		2, 3, 17, 18			
17	2.63 dd (8, 10)	56.8	7, 8, 9, 16, 18, 19, 20	5.85 t (6.5)	123.7	19, 20
18			37.3		133.1	
19	1.31 3H s	26.2	17, 18, 20, 29	1.74 3H s	26.1	17, 18, 20
20	0.96 3H s	29.8	17, 18, 19, 29	1.71 3H s	17.8	17, 18, 19
21	2.10 m	33.1	22, 23	1.53 m	28.9	
	2.25 m		22, 23	2.11 m		
22	5.02 br t	123.1		5.07 t (7)	122.7	21, 24, 25
23		132.4		2.5		
24	1.68 3H, s	25.9	22, 23, 25	1.69 3H s	25.7	22, 23, 25
25	1.62a 3H s	18.1	22, 23, 24	1.51 3H s	17.6	22, 23, 24
26	1.49 3H s	18.6	5, 6, 7, 10	1.47 3H s	25.2	5, 6, 10
27		200.3			193.4	
28		136.4			138.3	
29		150.3		7.83 d (7)	128.9	27, 31, 33
30	7.32 d (9)	123.5	18, 28	7.41 m	128.0	28, 32
31	7.54 dd (9, 9)	133.7	29, 33	7.41 m	131.5	29, 33
32	7.32 dd (9, 9)	126.9	28, 30	7.41 m	128.0	28, 30, 33
33	7.67 d (9)	126.6	29, 31	7.83 d (7)	128.9	27, 29, 31
OH-7	3.10		3, 7			

[a] $CDCl_3$.
[b] Pyridine-d_5.

H-33 and H-11 and H-12, meaning that there is an hydrogen bond between CO-9 and OH-27 as observed for xerophenone A.[11,12] We give it the trivial name of xerophenone C (**2**).

Isolated from the leaves, neoisobractatins A (**5**) and B (**6**), gave a major peak in FABMS at *m/z* 465 $[MH]^+$, which matched the pseudomolecular formula $C_{28}H_{33}O_6$. In the ^{1}H NMR spectrum, the presence of additional methyl signals led to the conclusion that the product was a mixture of diastereoisomers. Re-chromatography on a graphite column allowed the isolation of the two separate diastereoisomers **5** and **6**, one only crystallizing in heptane. The ^{1}H and ^{13}C



Scheme 1.

Table 2. ^{1}H and ^{13}C NMR data of neoisobractatins **5** and **6** ($CDCl_3$)

Position	**5**		**6**	
	^{1}H	^{13}C	^{1}H	^{13}C
1		166.0		166.0
2	5.98 s	92.3	5.99 s	92.3
3		168.5		168.5
4		114.1		114.1
4a		155.2		155.2
5		199.8		199.8
6		79.4		79.2
7	3.76 dd (4, 7)	44.8	3.76 dd (4, 7)	44.8
8	7.21 d (7)	134.1	7.21 d (7)	134.1
8a		134.8		134.8
9		177.2		177.2
9a		101.8		101.8
10a		83.7		83.7
11		43.4		43.4
12	4.47 q (6)	91.2	4.50 q (6)	91.2
13	1.39 d (6)	14.2	1.38 d (6)	14.3
14	1.36 3H s	20.7	1.21 3H s	21.0
15	1.45 3H s	25.5	1.57 3H s	25.5
16	1.88 dd (10, 14)	33.0	1.88 dd (10, 14)	33.0
	2.48 d (14)		2.49 d (14)	
17	2.19 dd (5, 10)	42.3	2.21 dd (4, 10)	42.5
18		83.7		83.7
19	1.37 3H s	26.7	1.36 3H s	26.7
20	1.39 3H s	29.6	1.39 3H s	29.6
21	2.07 dd (8, 14)	30.2	2.09 dd (8, 14)	30.2
	2.48 m		2.49 m	
22	5.04 t (7)	117.3	5.03 t (7)	117.3
23		136.3		136.3
24	1.62 3H s	18.1	1.61 3H s	18.1
25	1.74 3H s	25.8	1.73 3H s	25.8
OH-1	12.7 s		12.7 s	

NMR spectra of both **5** and **6** were superimposable (except two methyls) and very close to those of isobractatin and 1-*O*-methylneobractatin, with a similar dihydrofurane substituted ring and a chelated hydroxy group as in isobractatin on one part, and a sequence CH_2–CH–CH–CH= as in 1-*O*-methylneobractatin on the other part, which led us to propose that compounds **5** and **6** are new and correspond to neoisobractatin. The differences are observed in the ^{13}C NMR spectrum for carbons C-13, C-14, and in the ^{1}H NMR for CH_3-14 and CH_3-15 (Table 2). The two products are stereoisomers on C-12, each stereoisomer being isolated as a racemic mixture and we call them neoisobractatins A (**5**) and B (**6**).

The structure of **5** isolated from the mixture **5** and **6** is confirmed by single-crystal X-ray structure analysis. Compound **5** crystallizes in the centrosymmetric space group *P*-1 of the triclinic system, implying that in the solid state neoisobractatin A is racemic. The depicted enantiomer (C12, S) (Fig. 1) can be directly compared to isobractatin.[1] The left moieties of the molecules are identical, with the same intramolecular hydrogen bond observed between the hydroxyl group O1–H and the oxygen atom O9 (distances O1···O9 = 2.563 Å, H_{O1}···O9 = 1.84 Å, angle O–H–O = 146.3°). Although, the right moieties look nearly similar, they are very different with respect to CO-5 position.

Many xanthones have been isolated from leaves and bark of the plant. All of them have a UV spectrum characteristic of a 1,3,5,6-tetraoxygenated xanthone chromophore. Macluraxanthone,[5] 10-*O*-methylmacluraxanthone,[4] cudraxanthone R,[6] and gerontoxanthone I[7] have been identified by comparison with the literature NMR data.

The molecular formula $C_{24}H_{24}O_6$ of compound **3** is derived from its EIMS (*m*/*z* 408 $[M]^{+\cdot}$) and HREIMS. The UV spectrum is characteristic of a 1,3,5,6-tetraoxygenated xanthone. The IR spectrum indicated the presence of a conjugated ketone at 1649 cm^{-1} and OH absorptions at 3516 cm^{-1}. NMR data show that **3** possesses a xanthone skeleton, with a chelated OH at C-1, a prenyl substituent in position 4, and a dimethylpyran ring. The data are quite similar to that of xanthone V_1 isolated from *Vismia guineensis*,[13] except the presence of a methoxyle. NOESY correlations between the prenyl chain in C-4 and methoxyl allows to attach this methoxy at C-5 (Tables 3 and 4). This product is a *O*-methyl derivative of xanthone V_1 and is named 5-*O*-methylxanthone V_1 **3**.

Two other xanthones isolated from the leaves present spectral data characteristic of a 1,3,5,6-tetraoxygenated

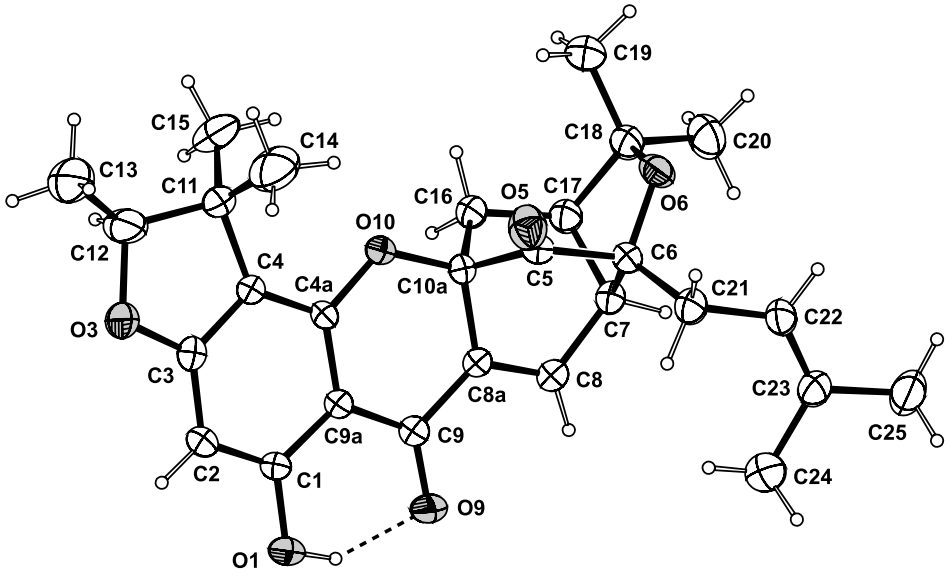


Figure 1. ORTEP diagram of compound **5**.

Table 3. ^{1}H NMR data of xanthones **3**, **7**, and **8**

Position	**3**[a]	**7**[b]	**8**[b]
7	6.99 d (9)	6.96 d (9)	6.88 d (9)
8	7.92 d (9)	7.60 d (9)	7.56 d (9)
10	6.75 d (10)	2.83 dd (8, 14)	2.57 dd (8, 17)
		3.16 dd (2, 14)	2.90 dd (5, 17)
11	5.62 d (10)	4.39 br d (8)	3.80 br t
13	1.48 3H s	1.86 s	1.34 s
14	1.48 3H s	5.03 s	1.42 s
		4.83 s	
15	3.52, 2H, d (7)		
16	5.23, t (7)	6.57 dd (10, 18)	6.64 dd (10, 18)
17		4.88 d (10)	5.25 d (10)
		5.03 d (18)	5.43 d (18)
18	1.69 s 3H	1.75 3H s	1.80 3H s
19	1.86 s 3H	1.75 3H s	1.80 3H s
OH-1	13.2 s	14.07 s	
OCH_3-5	4.13 s 3H		

[a] $CDCl_3$.
[b] Acetone-d_6.

xanthone with a 1,1-dimethylallyl group located at C-4 as in gerontoxanthone I isolated from the same plant. Compounds **7** and **8** exhibit in mass spectrometry the same molecular weight at *m/z* 412 corresponding to $C_{23}H_{24}O_7$, which is confirmed by HREIMS. 1D- and 2D NMR experiments show for compound **7** a five carbon chain with a 2H *exo* methylene at 4.83 and 5.03 ppm (singlets), and a CHOH at 78.3 ppm coupling with a CH_2 at 23.1 ppm (Tables 3 and 4). Compound **7** is thus a new molecule named bracteaxanthone I. For compound **8**, NMR data show that the *exo* methylene disappear, and that the C-12 is cyclised on the –OH on C-1 (Tables 3 and 4). This compound is a new molecule named bracteaxanthone II **8**.

2.3. Biological activity

Compounds **1**–**8** were evaluated against KB cell lines (Table 5). Many compounds are active, the most interesting being compounds neoisobractatins A **5** and B **6**, as for 1-*O*-methylneobractatin previously isolated from the leaves of the same plant.[1]

Table 4. ^{13}C NMR data for compounds **3**, **7**, and **8**

Position	**3**[a]	**7**[b]	**8**[b]
1	158.2	161.1	155.4
2	104.8	111.0	106.6
3	156.0	165.2	160.1
4	114.8	114.7	113.4
4a	154.5	156.0	nd
5	133.9	134.6	135.9
5a	149.8	148.9	147.0
6	154.0	153.2	151.9
7	112.5	114.7	114.9
8	121.8	118.0	118.6
8a	107.6	114.7	118.6
9	180.5	182.5	176.2
9a	102.9	104.1	nd
10	115.8	23.1	28.5
11	127.4	78.3	70.4
12	78.2	148.9	79.6
13	28.4	19.4	21.5
14	28.4	111.4	27.1
15	21.7	43.0	43.4
16	122.3	154.0	153.3
17	131.9	108.0	112.8
18	18.1	29.9	29.4
19	25.9	29.9	29.4
OCH_3	61.8		

[a] $CDCl_3$.
[b] Acetone-d_6.

Table 5. Cytotoxicity on KB cells

Compound	KB (IC_{50} μg/mL)
AcOEt leaf extract	4
AcOEt trunk bark extract	15
Garcibracteatone **1**	4.2
Xerophenone C **2**	0.8
5-*O*-methylxanthone V_1 **3**	0.9
Nemorosonol **4**	0.9
Neoisobractatin A **5**	0.14
Neoisobractatin B **6**	0.16
Bracteaxanthone I **7**	Inactive
Bracteaxanthone II **8**	Inactive

3. Experimental

3.1. General

Optical rotations at 20° were measured on a Perkin-Elmer 241 polarimeter. IR spectra were recorded on a Perkin-Elmer Spectrum BX FT-IR spectrometer and UV on a Varian Cary 100 spectrometer; EIMS were recorded on a Automass ThermoFinnigan. The NMR spectra were recorded on a Bruker AC-250 and AC 300 or AM 400. CC was performed using silica gel Merck H60. Compounds **5** and **6** have been purified by HPLC on Hypercarb column (5μ, 10×150 mm), (CH_2Cl_2/AcOEt 3:1, 3 mL/mn), using a Waters equipment with a 600 E pump Autoinjector and a 996 photodiode array detector.

3.2. Plant material

Leaves and bark of *G. bracteata* were collected at Pà Co, Mai Chau, Hoa Binh province, 150 km west of Hanoi, North Vietnam, in September 1999. Identification was provided by one of us (A.G.) and Nguyen Huu Hien (Institute of Ecology, NCST, Hanoi). Voucher specimens (VN 578) are deposited in the Herbarium of the Institute of Ecology and Biological Resources, NCST, Hanoi, Vietnam.

3.3. Extraction and isolation

The dried ground leaves of *G. bracteata* (2.88 kg) were extracted in a Soxhlet at room temperature with EtOAc and the extract was evaporated under vacuum (62 g, yield 2. 15%). Repeated column chromatography on silica gel afforded, (from heptane/EtOAc to EtOAc/MeOH), the previously isolated isobractatin, bractatin, 1-*O*-methylisobractatin, 1-*O*-methylbractatin, 1-*O*-methylneobractatin, 1-*O*-methyl-8-methoxy-8,8a-dihydro-bractatin,[1] macluraxanthone, gerontoxanthone I, cudraxanthone R, and four new compounds, bracteaxanthones I **3** (0.040 g, Et_2O/cyclohexane 6:4) and II **4** (0.015 g, CH_2Cl_2/MeOH 9.5:0.5), and neoisobractatins A **5** and B **6** (0.025 and 0.025 g, respectively, heptane/EtOAc 9:1, then HPLC on Hypercarb column).

The dried ground trunk bark of *G. bracteata* (1.9 kg) was extracted in a Soxhlet at room temperature with EtOAc and

the extract was evaporated under vacuum (60 g, yield 3.1%). Repeated column chromatography on silica gel afforded (from CH_2Cl_2 to MeOH) 25 fractions. Further purifications by CC on silica gel afforded the known 10-*O*-methylmacluraxanthone, nemorosonol, and three new compounds, garcibracteatone **1** (0.270 g), 5-*O*-methylxanthone V_1 **3** (0.083 g) and xerophenone C **2** (0.048 g).

3.3.1. Garcibracteatone 1. White crystals, mp 168–169 °C; $[\alpha]_D^{25}$ −1 (*c* 1.00, $CHCl_3$); UV (MeOH) λ_{max} (log ε): 253 (4.05), 202 (4.53); IR ($CHCl_3$) ν_{max} 1739, 1708, 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) see Table 1; ^{13}C NMR ($CDCl_3$, 75 MHz) see Table 1; EIMS *m/z* 500 (20) $[M]^{+\cdot}$, 199 (80), 95 (60), 69 (100), 55 (80); HREIMS *m/z* 500.2927 (calcd for $C_{33}H_{40}O_4$, 500.2942).

3.3.2. Xerophenone C 2. Whitish crystals, mp 145–146 °C; $[\alpha]_D^{25}$ +105.7 (*c* 1.00, $CHCl_3$); UV (MeOH) λ_{max} (log ε): 284 (4.16), 246 (4.05), 203 (4.53); IR ($CHCl_3$) ν_{max} 1670, 1587, 1570 cm^{-1}; ^1H NMR (pyridine-d_5, 250 MHz) see Table 1; ^{13}C NMR (pyridine-d_5, 75 MHz) see Table 1; EIMS *m/z* 518 (10) $[M]^{+\cdot}$, 147 (12), 105 (65), 69 (100), 55 (15); HREIMS *m/z* 518.3032 (calcd for $C_{33}H_{42}O_5$, 518.3035).

3.3.3. 5-*O*-Methylxanthone V_1 3. Amorphous powder; UV (MeOH) λ_{max} (log ε): 336 (4.18), 281 (4.60); IR ($CHCl_3$) ν_{max} 3516, 1650, 1609, 1587 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) see Tables 3 and 4; ^{13}C NMR ($CDCl_3$, 75 MHz) see Tables 3 and 4; EIMS *m/z* 408 (100) $[M]^{+\cdot}$, 393 (100), 365 (15); HREIMS *m/z* 408.1573 (calcd for $C_{24}H_{24}O_6$, 408.1580).

3.3.4. Neoisobractatins A 5 and B 6 (mixture). Yellow crystals, mp (mixture) 182–183 °C; UV (MeOH) λ_{max} (log ε): 334 (4.21), 259 (3.80); IR ($CHCl_3$) ν_{max} 1751, 1639 cm^{-1}; ^1H NMR of **5** and **6** ($CDCl_3$, 250 MHz) see differences in Table 2; ^{13}C NMR ($CDCl_3$, 75 MHz), see differences in Table 2; HRFABMS $[MH]^+$ 465.2269 (**5**), 465.2264 (**6**) (calcd for $C_{28}H_{33}O_6$, 465.2277).

X-ray structure analysis of neoisobractatin A **5**. *Crystal data*. Small yellow crystal of $0.10\times0.13\times0.26$ mm^3 grown from a mixture of heptane. C_{28} H_{32} O_6, M_w=464.54, mp 182–183 °C. Triclinic system, space group *P*-1, *Z*=2, *a*=7.948(6) Å, *b*=10.282(6) Å, *c*=15.393(8) Å, α=90.93(3)°, β=101.96(4)°, γ=99.87(3)°, *V*=1210.7 $Å^3$, d_c=1.274 g cm^{-3}, *F*(000)=496, λ(Cu Kα)=1.5418 Å, μ=0.721 mm^{-1}, decay: 7%. Data were measured with a Nonius-CAD4 diffractometer, up to θ=68° ($-9\le h\le 9$, $-12\le k\le 12$, l:0–18). 4465 data were collected leading to 4265 unique reflections, of, which 2334 were considered as observed having $I\ge 2\sigma(I)$. The structure was solved by direct methods using program SHELXS86[14] and refined by full-matrix least-squares, based upon unique F^2 with program SHELXL93.[15] The hydrogen atoms, located in difference Fourier maps, were fitted at theoretical positions and assigned an isotropic displacement parameter equivalent to 1.2 that of the bonded atom. Thus, refinement converged to $R1(F)$=0.0764 for the 2334 observed reflections and $wR2(F^2)$=0.2460 for all the 4285 data with a goodness-of-fit *S* factor of 1.028. The residual electron density was found between −0.40 and 0.36 e $Å^{-3}$. In the crystal packing, only van der Waals contacts are observed. Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 235853. Copies can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

3.3.5. Bracteaxanthone I 7. Amorphous powder; UV (MeOH) λ_{max} (log ε): 330 (4.14), 254 (4.50); IR ($CHCl_3$) ν_{max} 1626, 1659 cm^{-1}; ^1H NMR (acetone-d_6, 250 MHz) see Tables 3 and 4; ^{13}C NMR (acetone-d_6, 75 MHz) see Tables 3 and 4; EIMS *m/z* 412 (18) $[M]^{+\cdot}$, 341 (100), 285 (90), 273 (50), 153 (25), 71 (50), 69 (55), 55 (70); HREIMS *m/z* 412.1523 (calcd for $C_{23}H_{24}O_7$, 412.1522).

3.3.6. Bracteaxanthone II 8. Amorphous powder; UV (MeOH) λ_{max} (log ε): 317 (3.98), 290 (3.92), 252 (4.40); IR ($CHCl_3$) ν_{max} 1629, 1602 cm^{-1}; ^1H NMR (acetone-d_6, 250 MHz) see Tables 3 and 4; ^{13}C NMR (acetone-d_6, 75 MHz) see Tables 3 and 4; EIMS *m/z* 412 (100) $[M]^{+\cdot}$, 397 (90), 285 (90), 341 (33), 325 (33), 285 (35), 55 (90); HREIMS *m/z* 412.1531 (calcd for $C_{23}H_{24}O_7$, 412.1522).

3.4. KB cytotoxicity assay

Experiments were performed in 96-well microtiter plates (2×10^5 cells mL^{-1}). Cell growth was estimated by colorimetric assay based on conversion of tetrazolium dye (MTT) to a blue formazan product using live mitochondria.[16] Eight determinations were performed for each concentration. Control growth was estimated at 16 determinations. Optical density at 570 nm corresponding to solubilized formazan was read for each well on a Titertek Multiskan MKII.

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New access to racemic β^3-amino acids

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Abstract—A general simple procedure having the potential for large scale preparations of racemic β^3-amino acids has been developed. The procedure involves base-catalyzed Michael-type addition of sodium diethyl malonate to *N*-Boc-α-amidoalkyl-*p*-tolyl sulfones in tetrahydrofuran. Hydrolysis of the adducts by refluxing with 6 M aqueous hydrochloric acid affords β^3-amino acid hydrochlorides in high yield and excellent purity.

1. Introduction

In recent years, there has been increased interest in β-amino acids due mainly to the fact that the corresponding oligomers, the β-peptides, display a high tendency towards the formation of secondary structures including helices, sheets, and reverse turns.[1] Furthermore, some representatives of β^3-amino acids are found in nature in free form or as components of naturally occurring biologically active peptides.[2] In this respect, several methods for the synthesis of racemic β-amino acids have been developed.[3] Recently, stereoselective syntheses of β-amino acids have been the subject of a series of review articles.[4–6] The effective route to enantiopure β^3-amino acids by 1,3-dipolar cycloaddition has been also recently described by Mapp and co-workers.[7] The wide implementation of numerous stereoselective methods into synthetic practice, especially for large scale production, is, however, hampered by the use of expensive reagents and/or often multistep procedures. Fortunately, it has been well established that β-amino acid/ester racemates can be easily resolved using a variety of techniques including enzymatic or chemical resolution.[8]

In a search for a simple, effective, and economic approach to racemic β^3-amino acids, which could be applicable especially for multigram scale, we have focused our attention on Michael-type addition of sodium diethyl malonate to *N*-Boc imines.

2. Results and discussion

Nucleophilic addition to *N*-Boc imines generated in situ from α-amidoalkyl-*p*-tolyl(phenyl)sulfones by base-induced elimination has been nowadays the subject of extensive studies.[9] The easily available *N*-Boc imines can be considered as natural precursors of primary amines because the Boc group can function both as C=N bond activator and be easily detached once nucleophilic addition has been attained. We found that *N*-Boc-α-amidoalkyl-*p*-tolyl sulfones **1** readily underwent base induced elimination and the *N*-Boc imines **2** thus formed reacted smoothly with sodium diethyl malonate to give the respective adducts **3a–h** in high yields (Scheme 1).

The reaction was carried out at room temperature by adding 1 equiv of diethyl malonate to the suspension of 2 equiv of sodium hydride and 1 equiv of the sulfone **1** in tetrahydrofuran. The strongly exothermic process was moderated by occasional cooling with cold water. Crude adducts **3a–h** obtained by quenching the reaction mixture with aqueous ammonium chloride followed by extraction with dichloromethane were spectroscopically pure (NMR). They could be directly used for subsequent hydrolysis without additional purification.

Upon refluxing with 6 M (ca. 20%) hydrochloric acid for 1 h the adducts **3a–h** were transformed into β^3-amino acid hydrochlorides **4a–h** by amino group deprotection, hydrolysis, and decarboxylation (Scheme 2).

Aqueous solutions of **4a–h** decolorized with active charcoal, evaporated to dryness, washed with ether and dried over phosphorus pentoxide afforded pure, crystalline β^3-amino acid hydrochlorides **4a–h** in excellent yields (see Table 1) and analytical purity.

Keywords: Michael-type addition; *N*-Boc imines; Diethyl malonate.
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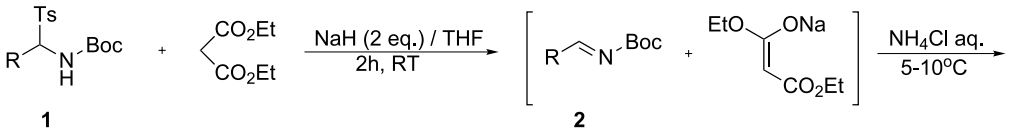
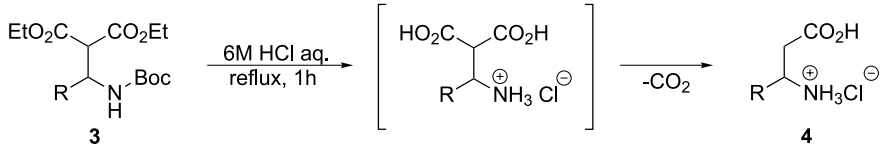


3	R	Yield (%)	3	R	Yield (%)
a	H	88	e	*i*-Bu	96
b	Me	94	f	*c*-C_6H_{11}	99
c	Et	98	g	Ph	81
d	*i*-Pr	98	h	*p*-MeO-C_6H_4	99

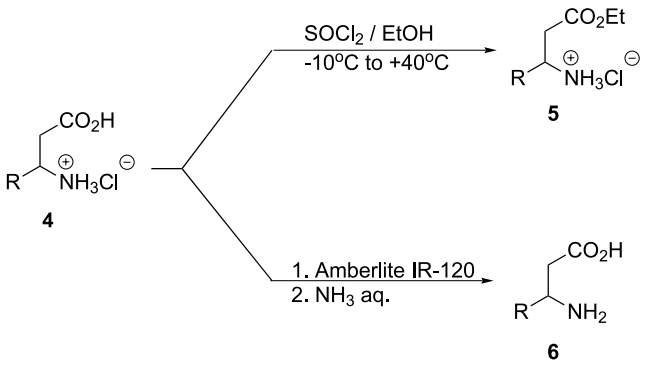
Scheme 1.



Scheme 2.

Ethyl ester hydrochlorides **5a–h** could be easily obtained from **4a–h** by the modified method described earlier.[10] This esterification procedure involved the treatment of **4a–h** with ethanol–thionyl chloride mixture at −10 °C followed by heating at 40 °C for ca. 3 h. The reaction progress was monitoring by thin-layer chromatography, (disappearance of starting material) (Scheme 3).

β^3-Amino acid hydrochlorides **4a–h** could be also almost quantitatively transformed into free β^3-amino acids **6a–h** using a column packed with Amberlite IR-120 ion-exchange resin. Compounds **6a–h** were spectroscopically pure (^{1}H NMR) and had melting points fully consistent with the literature data (see Section 4). The yields of compounds **5a–h** and **6a–h** are collected in Table 1.



Scheme 3.

Table 1. β^3-Amino acid hydrochlorides (**4a–h**), β^3-amino acid ethyl ester hydrochlorides (**5a–h**) and β^3-amino acids (**6a–h**)

Entry	R	(**4**) Yield (%)[a]	(**5**) Yield (%)[a]	(**6**) Yield (%)[a]
a	H	84	99	96
b	Me	96	99	93
c	Et	83	94	99
d	*i*-Pr	92	95	92
e	*i*-Bu	89	94	92
f	*c*-C_6H_{11}	92	90	99
g	Ph	92	84	91
h	*p*-MeO–C_6H_4	85	91	89

[a] Yields of crude, analytically pure products.

3. Conclusion

The outlined procedure for the synthesis of racemic β^3-amino acids represents a versatile and cost-effective approach to these compounds from easily available starting materials. It is operationally simple and can be conveniently applied for multigram scale preparation.

4. Experimental

4.1. General

Melting points (determined in open capillary tubes) are uncorrected. IR spectra (liquid films or KBr discs) were measured using a Specord M 80 (C. Zeiss) instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE DPX-250 spectrometer operating at 250 or 63 MHz, using $CDCl_3$ solutions unless otherwise stated. MS/CI were measured on Finnigan Mat mass spectrometer. FAB/MS were measured on an APO Electron (Ukraine) Model MI 12001 mass spectrometer. All commercially available starting materials were purchased from Fluka and used without additional purification. *N*-Boc-α-amidoalkyl-*p*-tolyl sulfones **1** were prepared as described before.[11]

4.2. Addition of sodium diethyl malonate to *N*-Boc imines (2)

General procedure. A solution of diethyl malonate (6.4 g,

0.04 mol) in THF (50 mL) was added dropwise with stirring and occasional cooling for ca. 30 min to a suspension of sodium hydride (1.92 g, 0.08 mol) and the corresponding sulfone **1** (0.04 mol) in anhydrous THF (100 mL). Stirring was continued for 2 h at room temperature. The mixture was then cooled to 10 °C and quenched with saturated NH_4Cl aq (30 mL). Water (20 mL) was then added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). Combined extracts were dried ($MgSO_4$) and the solvent evaporated in vacuo to give spectroscopically pure adducts **3a–h**.

4.2.1. Diethyl 2-(*N*-Boc-aminomethyl)malonate (3a). Yield 88%, colorless oil; [Found: C, 53.7; H, 7.9; N, 5.0. $C_{13}H_{23}NO_6$ requires C, 53.97; H, 8.01; N, 4.84%]; ν_{max} (liquid film) 3400, 3000, 2960, 1730, 1528, 1508, 1488, 1460, 1400, 1374, 1300, 1256, 1170, 1100, 1036, 960, 900, 870, 784, 650 cm^{-1}; δ_H 1.28 (6H, t, J=7.1 Hz, CH_3CH$_2$O), 1.43 (9H, s, *Me*$_3$C), 3.60–3.65 (3H, m, C*H*CH_2NH), 4.21 (4H, q, J=7.1 Hz, CH$_3$CH_2O), 5.15 (1H, br s, N*H*); δ_C 13.6, 27.9, 38.9, 51.6, 61.2, 79.1, 155.3, 167.8; FAB/MS: 290 (26, M+1), 234 (100), 190 (78%).

4.2.2. Diethyl 2-(1-*N*-Boc-aminoethyl)malonate (3b). Yield 94%, colorless solid; [Found: C, 55.6; H, 8.1; N, 4.8. $C_{14}H_{25}NO_6$ requires C, 55.43; H, 8.31; N, 4.62%]; ν_{max} (liquid film) 3370, 2980, 2930, 1750, 1708, 1528, 1460, 1380, 1368, 1308, 1250, 1176, 1156, 1100, 1080, 1050, 1020, 856, 834, 750, 660, 630 cm^{-1}; δ_H 1.24–1.32 (6H, m, CH_3CH$_2$O), 1.24–1.32 (3H, m, CH_3CH), 1.42 (9H, s, *Me*$_3$C), 3.56 (1H, d, J=4.5 Hz, C*H*(CO$_2$Et)), 4.13–4.30 (4H, m, CH$_3$CH_2O), 4.30–4.45 (1H, m, NHC*H*), 5.27–5.43 (1H, m, N*H*); δ_C 13.8, 18.9, 28.1, 45.75, 55.9, 61.2, 61.35, 79.1, 154.8, 167.55, 168; FAB/MS: 304 (46, M+1), 248 (100), 204 (28%).

4.2.3. Diethyl 2-(1-*N*-Boc-aminopropyl)malonate (3c). Yield 98%, colorless solid mp 53–55 °C; [Found: C, 56.9; H, 8.5; N, 4.2. $C_{15}H_{27}NO_6$ requires C, 56.77; H, 8.57; N, 4.41%]; ν_{max} (KBr) 3360, 2976, 2936, 1736, 1688, 1532, 1460, 1390, 1368, 1320, 1290, 1244, 1230, 1176, 1150, 1120, 1100, 1070, 1010, 650, 620 cm^{-1}; δ_H 0.95 (3H, t, J=7.4 Hz, CH_3CH$_2$CH), 1.27 (3H, t, J=7.1 Hz, CH_3CH$_2$O), 1.29 (3H, t, J=7.1 Hz, CH_3CH$_2$O), 1.42 (9H, s, *Me*$_3$C), 1.50–1.68 (2H, m, CH$_3$CH_2CH), 3.60 (1H, d, J=4.3 Hz, C*H*(CO$_2$Et)), 4.10–4.30 (2H, m, CH$_3$CH_2O), 4.10–4.30 (1H, m, NHC*H*), 5.40 (1H, d, J=10.1 Hz, N*H*); δ_C 10.5, 13.7, 13.8, 28.0, 51.5, 54.6, 61.1, 61.3, 78.7, 155.2, 167.7, 168.15; FAB/MS: 318 (1, M+1), 262 (7), 219 (23%).

4.2.4. Diethyl 2-(1-*N*-Boc-amino-2-methylpropyl)malonate (3d). Yield 98%, colorless oil; [Found: C, 58.2; H, 8.7; N, 4.4. $C_{16}H_{29}NO_6$ requires C, 57.99; H, 8.82; N, 4.23%]; ν_{max} (liquid film) 3440, 3390, 2980, 2930, 2910, 1724, 1500, 1470, 1392, 1368, 1348, 1280, 1264, 1232, 1172, 1100, 1090, 1034, 1010, 870, 660, 630 cm^{-1}; δ_H 0.93 (3H, d, J=6.4 Hz, *Me*$_2$CH), 0.96 (3H, d, J=6.4 Hz, *Me*$_2$CH), 1.27 (3H, t, J=7.1 Hz CH_3CH$_2$O), 1.29 (3H, t, J=7.1 Hz, CH_3CH$_2$O), 1.41 (9H, s, *Me*$_3$C), 1.64–1.82 (1H, m, Me$_2$C*H*), 3.69 (1H, d, J=4.3 Hz, C*H*(CO$_2$Et)), 3.94–4.05 (1H, m, C*H*–NH), 4.10–4.30 (4H, m, CH$_3$CH_2O), 5.55 (1H, d, J=10.5 Hz, N*H*); δ_C 13.7, 13.8, 19.0, 19.6, 28.0, 31.8, 53.1, 55.8, 61.1, 61.5, 78.6, 155.3, 168.0, 168.45; FAB/MS: 332 (42, M+1), 276 (100), 232 (54%).

4.2.5. Diethyl 2-(1-*N*-Boc-amino-3-methylbutyl)malonate (3e). Yield 96%, colorless solid, mp 58–60 °C; [Found: C, 59.0; H, 9.2; N, 4.2. $C_{17}H_{31}NO_6$ requires C, 59.11; H, 9.05; N, 4.05%]; ν_{max} (KBr) 3370, 3000, 2970, 1752, 1720, 1528, 1476, 1450, 1400, 1372, 1320, 1300, 1268, 1236, 1188, 1160, 1070, 1036, 1016, 630, 620 cm^{-1}; δ_H 0.92 (3H, d, J=6.25 Hz, *Me*$_2$CH), 0.95 (3H, d, J=6.25 Hz, *Me*$_2$CH), 1.27 (3H, t, J=7.1 Hz, CH_3CH$_2$O), 1.29 (3H, t, J=7.1 Hz, CH_3CH$_2$O), 1.41 (9H, s, *Me*$_3$C), 1.46–1.67 (1H, m, Me$_2$C*H*), 3.56 (1H, d, J=4.25 Hz, C*H*(CO$_2$Et)), 4.15–4.26 (4H, m, CH$_3$CH_2O), 4.27–4.35 (1H, m, C*H*–NH), 5.33 (1H, d, J=10.0 Hz, N*H*); δ_C 13.6, 21.5, 22.6, 24.6, 27.9, 42.2, 48.0, 55.1, 60.9, 61.1, 78.5, 154.8, 167.5, 167.9; FAB/MS; 346 (42, M+1), 290 (100), 246 (38%).

4.2.6. Diethyl 2-(*N*-Boc-aminocyclohexylmethyl)malonate (3f). Yield 99%, colorless oil; [Found: C, 61.6; H, 9.1; N, 3.6. $C_{19}H_{33}NO_6$ requires C, 61.43; H, 8.95; N, 3.77%]; ν_{max} (liquid film) 3450, 2990, 2950, 2870, 1736, 1500, 1450, 1400, 1374, 1350, 1316, 1284, 1256, 1174, 1150, 1100, 1046, 1020, 972, 870, 780, 650 cm^{-1}; δ_H 0.94–1.20 (5H, m, ring CH_2), 1.26 (3H, t, J=7.0 Hz, CH_3CH$_2$O), 1.29 (3H, t, J=7.0 Hz, CH_3CH$_2$O), 1.40 (9H, s, *Me*$_3$C), 1.40–1.55 (6H, m, ring CH_2), 3.71 (1H, d, J=4.0 Hz, C*H*(CO$_2$Et)), 4.02 (1H, dt, J=10.0, 4.0 Hz, C*H*NH), 4.10–4.32 (4H, m, CH$_3$CH_2O), 5.54 (1H, d, J=10.0 Hz, N*H*); δ_C 13.6, 13.7, 25.5, 25.6, 25.8, 29.2, 29.9, 28.0, 41.0, 52.45, 54.7, 61.0, 61.4, 78.5, 155.2, 168.1, 168.45; FAB/MS: 372 (20, M+1), 316 (47), 272 (28%).

4.2.7. Diethyl 2-(*N*-Boc-aminophenylmethyl)malonate (3g). Yield 81%, colorless solid, mp 69–70 °C; [Found: C, 62.3; H, 7.6; N, 4.0. $C_{19}H_{27}NO_6$ requires C, 62.45; H, 7.45; N, 3.83%]; ν_{max} (KBr) 3400, 2990, 2950, 1728, 1688, 1520, 1390, 1368, 1316, 1296, 1256, 1236, 1172, 1012, 754, 700 cm^{-1}; δ_H 1.13 (3H, t, J=7.1 Hz, CH_3CH$_2$O), 1.26 (3H, t, J=7.1 Hz, CH_3CH$_2$O), 1.41 (9H, s, *Me*$_3$C), 3.88 (1H, d, J=4.7 Hz, CH(CO$_2$Et)), 4.01–4.29 (4H, m, CH$_3$CH_2O), 5.49 (1H, br s, C*H*NH), 6.18 (1H, br s, N*H*), 7.20–7.36 (5H, m, H_{arom}); δ_C 13.5, 13.6, 27.95, 53.15, 56.6, 61.2, 61.5, 79.2, 126.0, 127.2, 128.2, 139.4, 154.7, 166.8, 167.7; FAB/MS: 366 (1, M+1), 266 (40%).

4.2.8. Diethyl 2-(*N*-Boc-amino-(4-methoxyphenyl) methyl)malonate (3h). Yield 99%, colorless solid, mp 64–66 °C; [Found: C, 60.5; H, 7.6; N, 3.4. $C_{20}H_{29}NO_7$ requires C, 60.74; H, 7.39; N, 3.54%]; ν_{max} (KBr) 3390, 2990, 1744, 1728, 1684, 1520, 1368, 1300, 1250, 1172, 1104, 1024, 832, 630, 620 cm^{-1}; δ_H 1.16 (3H, t, J=7.1 Hz, CH_3CH$_2$O), 1.26 (3H, t, J=7.1 Hz, CH_3CH$_2$O), 1.41 (9H, s, *Me*$_3$C), 3.78 (3H, s, CH_3O), 3.84 (1H, d, J=5.0 Hz), C*H*(CO_2Et)), 4.00–4.30 (4H, m, CH$_3$CH_2O), 5.42 (1H, br s, C*H*NH), 6.12 (1H, br s, N*H*), 6.84 (2H, d, J=8.7 Hz, H_{arom}), 7.22 (2H, d, J=8.7 Hz, H_{arom}); δ_C 13.8, 13.9, 28.2, 52.9, 55.2, 57.0, 61.5, 61.8, 79.5, 113.8, 127.4, 131.7, 158.85, 154.9, 167.0, 168.0; FAB/MS: 396 (1, M+1), 294 (11), 279 (38), 180 (100%).

4.3. Preparation of β[3]-amino acid hydrochlorides (4a–h)

General procedure. A mixture of the adduct **3** (0.02 mol) and ca. 20% HCl aq (40 mL) was refluxed for 1 h. Active charcoal (ca. 1 g) was added to the resultant solution, heating was continued for 10 min, and the hot solution was filtered and evaporated to dryness in vacuo. The residue was treated with ether (30 mL) and refrigerated overnight. Crystalline β[3]-amino acid hydrochlorides (**4a–h**) were filtered off, washed with ether and dried over P_2O_5. All crude products were analytically pure.

4.3.1. 3-Aminopropanoic acid hydrochloride (4a). Yield 84%, colorless solid, mp 104–106 °C, mp after recrystallization from isopropyl alcohol—122–124 °C (lit.[12] mp 123–125 °C); [Found: C, 28.6; H, 6.5; N, 11.1. $C_3H_8ClNO_2$ requires C, 28.70; H, 6.42; N, 11.16%]; ν_{max} (CCl_4) 3030, 2920, 1730, 1716, 1700, 1590, 1504, 1480, 1410, 1330, 1304, 1260, 1200, 1130, 1096, 1056, 950, 916, 650 cm^{-1}; δ_H (D_2O) 2.82 (2H, t, J=6.5 Hz, CH_2CO_2H), 3.28 (2H, t, J=6.5 Hz, CH_2NH_3).

4.3.2. 3-Aminobutanoic acid hydrochloride (4b). Yield 96%, colorless solid, mp 94–98 °C (lit.[13] mp 109.5–110.5 °C); [Found: C, 34.5; H, 7.4; N, 10.1. $C_4H_{10}ClNO_2$ requires C, 34.42; H, 7.22; N, 10.03%]; ν_{max} (KBr) 3120, 2940, 2840, 1696, 1616, 1596, 1500, 1436, 1392, 1376, 1306, 1244, 1192, 928, 896, 696 cm^{-1}; δ_H (D_2O) 1.36 (3H, d, J=6.7 Hz, CH_3CH), 2.72 (1H, dd, J=17.5, 7.2 Hz, CH_2CO_2H), 2.80 (1H, dd, J=17.5, 5.8 Hz, CH_2CO_2H), 3.67–3.88 (1H, m, CH_3CH).

4.3.3. 3-Aminopentanoic acid hydrochloride (4c). Yield 83%, colorless solid, mp 118–123 °C; [Found: C, 39.3; H, 8.0; N, 9.0. $C_5H_{12}ClNO_2$ requires C, 39.10; H, 7.87; N, 9.12%]; ν_{max} (KBr) 3400, 2980, 1720, 1600, 1500, 1460, 1408, 1204, 1176, 654, 630 cm^{-1}; δ_H (D_2O) 0.99 (3H, t, J=7.4 Hz, CH_3CH_2), 1.73 (2H, qt, J=7.4 Hz, CH_3CH_2), 2.69 (1H, dd, J=17.6, 8.2 Hz, CH_2CO_2H), 2.85 (1H, dd, J=17.6, 4.6 Hz, CH_2CO_2H), 3.51–3.65 (1H, m, C$H$$NH_3$).

4.3.4. 3-Amino-4-methylpentanoic acid hydrochloride (4d). Yield 92%, colorless solid, mp 162–167 °C; [Found: C, 43.1; H, 8.6; N, 8.4. $C_6H_{14}ClNO_2$ requires C, 42.99; H, 8.42; N, 8.36%]; ν_{max} (KBr) 3270, 2980, 2920, 1720, 1604, 1500, 1472, 1420, 1396, 1220, 1176, 1124, 812, 654 cm^{-1}; δ_H (D_2O) 0.99 (3H, d, J=6.8 Hz, Me_2CH), 1.00 (3H, d, J=6.8 Hz, Me_2CH), 2.02 (1H, 8 lines, J=6.8 Hz, Me_2CH), 2.67 (1H, dd, J=17.8, 9.0 Hz, CH_2CO_2H), 2.86 (1H, dd, J=17.8, 3.9 Hz, CH_2CO_2H), 3.45–3.55 (1H, m, C$H$$NH_3$).

4.3.5. 3-Amino-5-methylhexanoic acid hydrochloride (4e). Yield 89%, colorless solid, mp 154–156 °C; [Found: C, 46.2; H, 9.0; N, 7.8. $C_7H_{16}ClNO_2$ requires C, 46.28; H, 8.88; N, 7.71%]; ν_{max} (KBr) 3100, 2940, 1720, 1608, 1580, 1500, 1428, 1400, 1372, 1278, 1222, 1190, 1134, 1120, 1060, 860, 700 cm^{-1}; δ_H (D_2O) 0.92 (3H, d, J=6.6 Hz, Me_2CH), 0.94 (3H, d, J=6.6 Hz, Me_2CH), 1.56 (2H, t, J=6.6 Hz, CH_2CHNH), 1.69 (1H, 9 lines, J=6.6 Hz, Me_2CH), 2.68 (1H, dd, J=17.5, 8.1 Hz, CH_2CO_2H), 2.85 (1H, dd, J=17.5, 4.5 Hz, CH_2CO_2H), 3.64–3.75 (1H, m, C$H$$NH_3$).

4.3.6. 3-Amino-3-cyclohexylpropanoic acid hydrochloride (4f). Yield 92%, colorless solid, mp 230–232 °C; [Found: C, 52.1; H, 8.8; N, 6.5. $C_9H_{18}ClNO_2$ requires C, 52.5; H, 8.74; N, 6.74%]; ν_{max} (KBr) 3260, 2950, 2870, 1720, 1608, 1590, 1500, 1444, 1420, 1388, 1350, 1230, 1200, 1164, 806, 796, 630, 620 cm^{-1}; δ_H (D_2O) 0.92–1.27 (5H, m, ring CH_2), 1.47–1.73 (6H, m, ring CH_2), 2.62 (1H, dd, J=17.8, 8.75 Hz, CH_2CO_2H), 2.80 (1H, dd, J=17.8, 4.0 Hz, CH_2CO_2H), 3.38–3.43 (1H, m, C$H$$NH_3$).

4.3.7. 3-Amino-3-phenylpropanoic acid hydrochloride (4g). Yield 92%, colorless solid, mp 215–219 °C (lit.[14] mp 217–218 °C); [Found: C, 53.5; H, 6.2; N, 7.1 $C_9H_{12}ClNO_2$ requires C, 53.61; H, 6.00; N, 6.95%]; ν_{max} (KBr) 3060, 3000, 2920, 1730, 1600, 1490, 1416, 1384, 1370, 1224, 1022, 830, 760, 696, 630, 620 cm^{-1}; δ_H (D_2O) 3.12 (1H, dd, J=17.1, 6.8 Hz, CH_2CO_2H), 3.23 (1H, dd, J=17.1, 7.6 Hz, CH_2CO_2H), 7.45–7.55 (5H, m, H_{arom}).

4.3.8. 3-Amino-3-(4-methoxyphenyl)propanoic acid hydrochloride (4h). Yield 85%, colorless solid, mp 198–203 °C (lit.[15] mp 205 °C); [Found: C, 51.9; H, 6.0; N, 6.2. $C_{10}H_{14}ClNO_3$ requires C, 51.84; H, 6.09; N, 6.05%]; ν_{max} (KBr) 2980, 2910, 1710, 1600, 1574, 1522, 1474, 1400, 1304, 1280, 1260, 1176, 1116, 1020, 840, 820, 790, 540 cm^{-1}; δ_H (D_2O) 3.07 (1H, dd, J=17.0, 6.9 Hz, CH_2CO_2H), 3.20 (1H, dd, J=17.0, 7.7 Hz, CH_2CO_2H), 3.85 (3H, s, CH_3), 7.07 (2H, d, J=8.7 Hz, H_{arom}), 7.44 (2H, d, J=8.7 Hz, H_{arom}).

4.4. Preparation of β[3]-amino acid ethyl ester hydrochlorides (5a–h)

General procedure. Thionyl chloride (0.8 mL, 0.011 mol) was added dropwise with efficient stirring to ethanol (12 mL) cooled to −10 °C. Stirring was continued for 30 min at −10 °C, β[3]-amino acid hydrochloride (**4a–h**, 0.01 mol) was then added and the temperature was raised to 20–25 °C. After 1 h at this temperature stirring was continued at 40 °C for approximately 3 h (until disappearance of the substrate spot on TLC plate, $CHCl_3$/MeOH, 3:1 being used as eluent). Ethanol was then evaporated in vacuo and ether or hexane was added to the residual oil. Crystals of **5a–h** obtained on refrigeration were analytically pure.

4.4.1. Ethyl 3-aminopropanoate hydrochloride (5a). Yield 99%, colorless solid, mp 48–50 °C (lit.[12] mp 69–70 °C); [Found: C, 39.2; H, 7.8; N, 9.1. $C_5H_{12}ClNO_2$ requires C, 39.10; H, 7.87; N, 9.12%]; ν_{max} (KBr) 3450, 3000, 1724, 1670, 1600, 1480, 1464, 1404, 1380, 1230, 1100, 1024, 630, 620 cm^{-1}; δ_H (D_2O) 1.26 (3H, t, J=7.2 Hz, CH_3CH_2O), 2.81 (2H, t, J=6.5 Hz, CH_2CO), 3.29 (2H, t, J=6.5 Hz, CH_2NH_3), 4.21 (2H, q, J=7.2 Hz, CH_3CH_2O; δ_C (D_2O) 13.3, 31.2, 35.0, 62.1, 172.5; MS/CI 118 (M_K, 100%).

4.4.2. Ethyl 3-aminobutanoate hydrochloride (5b). Yield 99%, colorless oil; [Found: C, 42.9; H, 8.5; N, 8.3. $C_6H_{12}ClNO_2$ requires C, 42.99; H, 8.42; N, 8.36%]; ν_{max} (liquid film) 2980, 2912, 1728, 1600, 1496, 1450, 1396, 1324, 1208, 1186, 1130, 1090, 1024, 650, 624 cm^{-1}; δ_H (D_2O) 1.26 (3H, t, J=7.2 Hz, CH_3CH_2O), 1.35 (3H, d, J=6.6 Hz, CH_3CH), 2.76 (2H, d, J=6.6 Hz, CH_2CO_2Et), 3.77

(1H, 6 lines, J=6.6 Hz, CH_3CH), 4.20 (2H, q, J=7.2 Hz, CH_3CH_2O); δ_C (D_2O) 12.6, 16.85, 37.0, 45.0, 61.0, 170.75; MS/CI 132 (M_K, 100%).

4.4.3. Ethyl 3-aminopentanoate hydrochloride (5c). Yield 94%, colorless solid, mp 40–43 °C; [Found: C, 46.1; H, 9.1; N, 7.9. $C_7H_{16}ClNO_2$ requires C, 46.28; H, 8.88; N, 7.71%]; ν_{max} (KBr) 3420, 2920, 1736, 1600, 1512, 1460, 1388, 1374, 1276, 1240, 1200, 1170, 1130, 1100, 1024, 620, 610 cm^{-1}; δ_H (D_2O) 1.01 (3H, t, J=7.4 Hz, CH_3CH_2CH), 1.29 (3H, t, J=7.2 Hz, CH_3CH_2O), 1.75 (2H, qt, J=7.4 Hz, CH_3CH_2CH), 2.73 (1H, dd, J=17.4, 8.0 Hz, CH_2CO_2Et) 2.88 (1H, dd, J=17.4, 4.8 Hz, CH_2CO_2Et), 3.55–3.72 (1H, m, CH_3CH_2CH), 4.23 (2H, q, J=7.2 Hz, CH_3CH_2O); δ_C (D_2O) 8.0, 12.4, 24.0, 34.7, 48.4, 61.0, 170.9; MS/CI 146 (M_K, 100%).

4.4.4. Ethyl 3-amino-4-methylpentanoate hydrochloride (5d). Yield 95%, colorless solid, mp 69–71 °C; [Found: C, 49.3; H, 9.1; N, 7.2. $C_8H_{18}ClNO_2$ requires C, 49.10; H, 9.27; N, 7.16%]; ν_{max} (KBr) 3450, 2976, 2920, 1728, 1600, 1500, 1470, 1394, 1380, 1344, 1300, 1240, 1204, 1194, 1170, 1150, 1130, 1024 cm^{-1}; δ_H (D_2O) 1.08 (3H, d, J=6.8 Hz, Me_2CH), 1.10 (3H, d, J=6.8 Hz, Me_2CH), 1.28 (3H, t, J=7.1 Hz,CH_3CH_2O), 2.16 (1H, 8 lines, J=6.8 Hz, Me_2CH), 2.74 (1H, dd, J=16.9, 5.8 Hz, CH_2CO_2Et), 2.88 (1H, dd, J=16.9, 6.8 Hz, CH_2CO_2Et), 3.54 (1H, m, Me_2CHCH), 4.20 (2H, q, J=7.1 Hz, CH_3CH_2O); δ_C (D_2O) 12.2, 15.8, 16.3, 28.75, 32.6, 52.3, 61.2, 171.5; MS/CI 160 (M_K, 100%).

4.4.5. Ethyl 3-amino-5-methylhexanoate hydrochloride (5e). Yield 94%, colorless, low melting solid; [Found: C, 51.5; H, 9.7; N, 6.8. $C_9H_{20}ClNO_2$ requires C, 51.54; H, 9.61; N, 6.68%]; ν_{max} (CCl_4) 3416, 2970, 1740, 1608, 1530, 1512, 1460, 1384, 1370, 1350, 1324, 1250, 1200, 1140, 1032, 650 cm^{-1}; δ_H (D_2O) 0.92 (3H, d, J=6.4 Hz, Me_2CH), 0.93 (3H, d, J=6.4 Hz, Me_2CH), 1.27 (3H, t, J=7.2 Hz, CH_3CH_2O), 1.45–1.58 (2H, m, CH_2CHNH_3), 1.68 (1H, 9 lines, J=6.4 Hz, Me_2CHCH_2), 2.70 (1H, dd, J=17.4, 7.6 Hz, CH_2CO_2Et), 2.85 (1H, dd, J=17.4, 4.6 Hz, CH_2CO_2Et), 3.65–3.77 (1H, m, $CHNH_3$), 4.21 (2H, q, J=7.2 Hz, CH_3CH_2O); δ_C (D_2O) 13.3, 21.3, 21.5, 23.7, 36.4, 40.8, 46.5, 62.2, 172.2; MS/CI 174 (M_K, 100%).

4.4.6. Ethyl 3-amino-3-cyclohexylpropanoate hydrochloride (5f). Yield 90%, colorless solid, mp 103–105 °C; [Found: C, 56.0; H, 9.3; N, 6.1. $C_{11}H_{22}ClNO_2$ requires C, 56.04; H, 9.41; N, 5.94%]; ν_{max} (KBr) 3440, 2930, 2870, 1730, 1600, 1504, 1450, 1408, 1380, 1370, 1330, 1300, 1268, 1210, 1184, 1160, 1114, 1040, 630, 620 cm^{-1}; δ_H (D_2O) 0.98 (5H, m, ring CH_2), 1.26 (3H, t, J=7.2 Hz, CH_3CH_2O), 1.64–1.81 (6H, m, ring CH_2), 2.70 (1H, dd, J=17.5, 8.5 Hz, CH_2CO_2Et), 2.87 (1H, dd, J=17.5, 4.25 Hz, CH_2CO_2Et), 3.47–3.54 (1H, m, $CHNH_3$), 4.21 (2H, q, J=7.2 Hz, CH_3CH_2O); δ_C 13.3, 25.2, 25.3, 27.6, 28.0, 33.95, 39.4, 52.6, 62.2, 172.4; MS/CI 200 (M_K, 100%).

4.4.7. Ethyl 3-amino-3-phenylpropanoate hydrochloride (5g). Yield 84%, colorless solid, mp 138–141 °C (lit.[16] mp 134–136 °C); [Found: C, 57.4; H, 7.1; N, 6.0. $C_{11}H_{16}ClNO_2$ requires C, 57.52; H, 7.02; N, 6.10%]; ν_{max} (KBr) 3450, 2880, 1740, 1590, 1500, 1450, 1376, 1364, 1306, 1246, 1176, 1104, 1084, 1026, 1008, 912, 750, 690, 624, 614, 540 cm^{-1}; δ_H (D_2O) 1.17 (3H, t, J=7.1 Hz, CH_3CH_2O), 3.13 (1H, dd, J=16.8, 7.3 Hz, CH_2CO_2Et), 3.22 (1H, dd, J=16.8, 7.3 Hz, CH_2CO_2Et), 4.13 (2H, q, J=7.3 Hz, CH_3CH_2O), 4.82 (1H, t, J=7.3 Hz, $CHNH_3$), 7.42–7.54 (5H, m, H_{arom}); δ_C (D_2O) 12.1, 37.0, 50.3, 61.0, 126.0, 128.2, 128.5, 133.8, 170.0; MS/CI 194 (M_K, 100%).

4.4.8. Ethyl 3-amino-3-(4-methoxyphenyl)-propanoate hydrochloride (5h). Yield 91%, colorless solid, mp 133–137 °C; [Found: C, 55.4; H, 6.9; N, 5.5. $C_{12}H_{18}ClNO_3$ requires C, 55.49; H, 6.99; N, 5.39%]; ν_{max} (KBr) 3470, 3210, 2904, 1736, 1616, 1600, 1520, 1500, 1460, 1380, 1364, 1300, 1264, 1250, 1184, 1110, 1024, 832, 620, 610, 552 cm^{-1}; δ_H ($CDCl_3$) 1.15 (3H, t, J=7.0 Hz, CH_3CH_2O), 3.78 (3H, s, CH_3O), 4.01–4.09 (2H, m, CH_2CO_2Et), 4.64 (1H, m, $CHNH_3$), 6.86 (d, J=8.2 Hz, H_{arom}), 7.44 (2H, d, J=8.2 Hz, H_{arom}), 8.69 (3H, br s, NH_3^+); δ_C (D_2O) 12.0, 36.9, 49.8, 54.2, 61.0, 113.4, 126.2, 127.6, 158.4, 170.1; MS/CI 224 (M_K, 14%).

4.5. Preparation of β³-amino acids (6a–h)

General procedure. Conventional treatment of β³-amino acid hydrochlorides (**4a–h**) with Amberlite IR-120 ion-exchange resin followed by washing the column with 2 M NH_3 aq and evaporation of water in vacuo afforded analytically pure β³-amino acids (**6a–h**) in almost quantitative yields.

4.5.1. 3-Aminopropanoic acid (6a). Yield 96%, colorless solid, mp 197–199 °C (dec) (lit.[17] mp 197–198 °C (dec)); δ_H (D_2O) 2.54 (2H, t, J=6.7 Hz, CH_2NH_2), 3.17 (2H, t, J=6.7 Hz, CH_2CO_2H).

4.5.2. 3-Aminobutanoic acid (6b). Yield 93%, colorless solid, mp 187–191 °C (dec) (lit.[18] mp 187–189 °C (dec)); δ_H (D_2O) 1.31 (3H, d, J=6.8 Hz, CH_3CH), 2.48 (2H, d, J=6.8 Hz, CH_2CO_2H), 3.60 (1H, 6 lines, J=6.8 Hz, CH_3CH).

4.5.3. 3-Aminopentanoic acid (6c). Yield 99%, colorless solid, mp 184–187 °C (dec) (lit.[19] mp 189–191 °C (dec)); δ_H (D_2O) 0.98 (3H, t, J=7.4 Hz, CH_3CH_2CH), 1.67 (2H, qt, J=7.4 Hz, CH_3CH_2CH), 2.41 (1H, dd, J=16.6, 8.2 Hz, CH_2CO_2H), 2.55 (1H, dd, J=16.6, 5.0 Hz, CH_2CO_2H), 3.34–3.48 (1H, m, CH_3CH_2CH).

4.5.4. 3-Amino-4-methylpentanoic acid (6d). Yield 92%, colorless solid, mp 192–195 °C (dec) (lit.[20] mp 202–210 °C (dec)); δ_H (D_2O) 0.98 (3H, d, J=6.8 Hz, Me_2CH), 0.99 (3H, d, J=6.8 Hz, Me_2CH), 1.94 (1H, 8 lines, J=6.8 Hz, Me_2CH), 2.39 (1H, dd, J=16.8, 9.2 Hz, CH_2CO_2H), 2.57 (1H, dd, J=16.8, 4.3 Hz, CH_2CO_2H), 3.28–3.41 (1H, m, $CHNH_2$).

4.5.5. 3-Amino-5-methylhexanoic acid (6e). Yield 92%, colorless solid, mp 225–226 °C (dec) (lit.[21] mp 215–216 °C (dec)); δ_H (D_2O) 0.92 (3H, d, J=6.8 Hz, Me_2CH), 0.93 (3H, d, J=6.8 Hz, Me_2CH), 1.49 (2H, t, J=6.8 Hz, Me_2CHCH_2), 1.66 (1H, 9 lines, J=6.8 Hz, Me_2CHCH_2), 2.39 (1H, dd, J=16.5, 8.0 Hz, CH_2CO_2H), 2.60 (1H, dd, J=16.5, 4.7 Hz, CH_2CO_2), 3.52–3.60 (1H, m, $CHNH_2$).

4.5.6. 3-Amino-3-cyclohexylpropanoic acid (6f). Yield 99%, colorless solid, mp 224–225 °C (dec) (lit.[22] mp 229–230 °C

(dec)); δ_H (D_2O) 0.94–1.33 (5H, m, ring, CH_2), 1.55–1.74 (6H, m, ring CH_2), 2.39 (1H, dd, $J=16.8$, 9.0 Hz, CH_2CO_2H), 2.59 (1H, dd, $J=16.8$, 4.2 Hz, CH_2CO_2H), 3.28–3.36 (1H, m, CHNH_3).

4.5.7. 3-Amino-3-phenylpropanoic acid (6g). Yield 81%, colorless solid, mp 220–222 °C (dec) (lit.[23] mp 221–223 °C (dec)); δ_H (D_2O) 2.82 (1H, dd, $J=16.2$, 6.9 Hz, CH_2CO_2H), 2.93 (1H, dd, $J=16.2$, 6.9 Hz, CH_2CO_2H), 4.65 (1H, dd, $J=6.9$ Hz, CHNH_2), 7.40–7.52 (5H, m, H_{arom}).

4.5.8. 3-Amino-3-(4-methoxyphenyl)-propanoic acid (6h). Yield 89%, colorless solid, mp 226–228 °C (dec) (lit.[23] mp 228–229 °C (dec)); δ_H (D_2O) 2.79 (1H, dd, $J=$ 16.1, 6.8 Hz, CH_2CO_2H), 2.90 (1H, dd, $J=16.1$, 8.0 Hz, CH_2CO_2H), 3.84 (3H, s, CH_3O), 4.61 (1H, m, CHNH_2), 7.05 (2H, d, $J=8.7$ Hz, H_{arom}), 7.41 (2H, d, $J=8.7$ Hz, H_{arom}).

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