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Oxidative Nucleophilic Substitution (S_NOx) of the Benzylic Position as a Tunable Synthesis of Tetrahydroisoquinoline Natural Alkaloid Analogues

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Synthetic investigations of 1,3-dichloro-5,6-dicyanobenzoquinone-mediated benzylic oxidation is reported for the synthesis of natural alkaloid analogues. Extensive explorations of the oxidative nucleophilic substitution of the benzylic position of β-phenylethylamine derivatives and the synthesis of functionalized tetrahydroisoquinolines of ecteinascidin 743 precursors have been carried out. Starting from L-DOPA, a tunable oxazolidinone group was installed under oxidative benzylic conditions. This derivative **13** was submitted to benzylic oxidation reactions using a wide range of carboxylic acids and subsequent chemical transformations of these compounds were attempted. Moreover, an efficient synthesis of an aromatic ketone derivative **20** was achieved and gave rise to tetrahydroisoquinoline **24** through a direct Pictet–Spengler cyclisation reaction. Subsequently, **24** was transformed into functionalized α-amino alcohols **31a** and **31b**, precursors of ecteinascidin 743 analogues. In addition, in order to assess the viability of our synthetic strategy, the reaction of **24** with methyl thioglycolate was performed and the stereoselectivity confirmed by X-ray analysis of **33a**.

Introduction

Many tetrahydroisoquinoline alkaloids and β-phenylethylamine derivatives that possess functions at the benzylic position are of great biological interest.[1] Recently, one of them, a new (+)-norepinephrine derivative, syncarpamide (**1**), was isolated from the stem of *Zanthoxylum syncarpum* and differs from most of the natural β-phenylethylamines by the substitution of the benzylic position.[2] Moreover, syncarpamide displays interesting potential antiplasmodial activity.[2d,2e] Ecteinascidin 743 (**2**, Et 743), the most bioactive member of the tetrahydroisoquinoline family,[3] isolated from Caribbean tunicate *Ecteinascidia turbinate*[4] (Figure 1), revealed potent cytotoxic activity under phase II/III clinical trials for various human cancer cell lines.[5] This impressive architecture also exhibits a higher degree of oxidation at the C-4 benzylic position. Moreover, azapodophyllotoxin (**3**), structurally related to podophyllotoxin[6] and tetrahydroisoquinoline derivatives, possesses a higher degree of substitution at the benzylic position and has been the subject of a methodological study to introduce requisite functionalities at this position.[7]

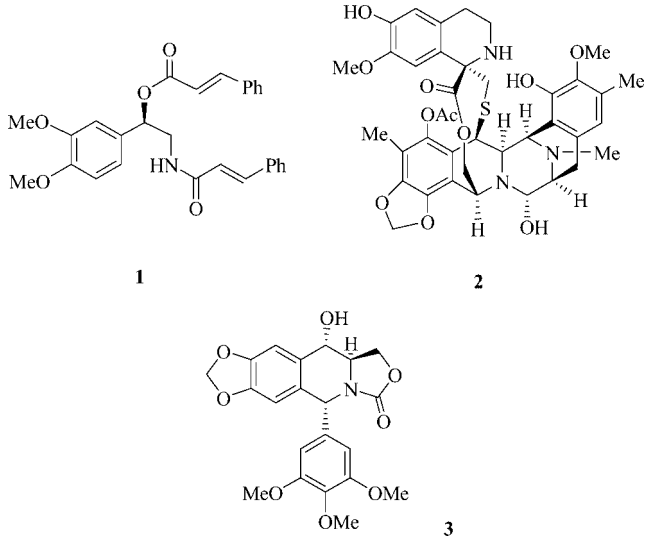

Figure 1. Alkaloids oxidized at the benzylic position.

Since 2004, our laboratory has developed a new methodology directed towards the synthesis of Et 743 analogues. We have reported the construction and the biological evaluation of pentacyclic analogues of piperazine-core alkaloids directed towards a general strategy for the construction of Et 743 analogues[8] which could give rise to the synthesis of many derivatives related to this family.[3] As a consequence of these results, we became interested in the direct introduction of different functions at the benzylic position of a L-DOPA derivative in order to use these precursors for the synthesis of natural tetrahydroisoquinoline analogues. In this work we considered a new approach to the synthesis of ecteinascidin precursors of the type **4** (Scheme 1). This pa-

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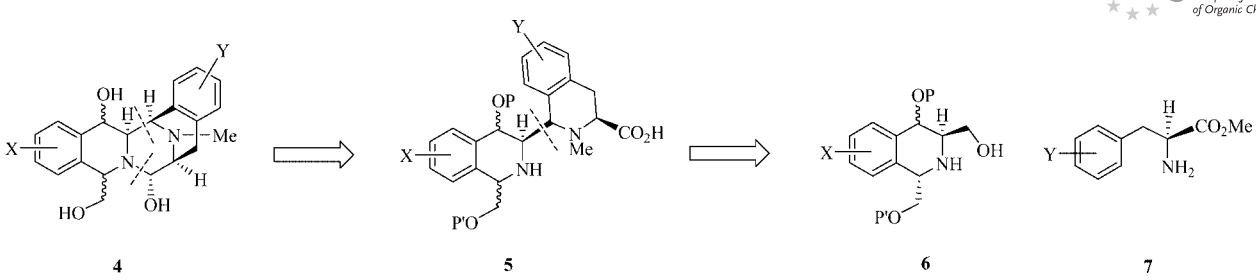


Scheme 1. Retrosynthetic analysis of the piperazine pentacylic structure.

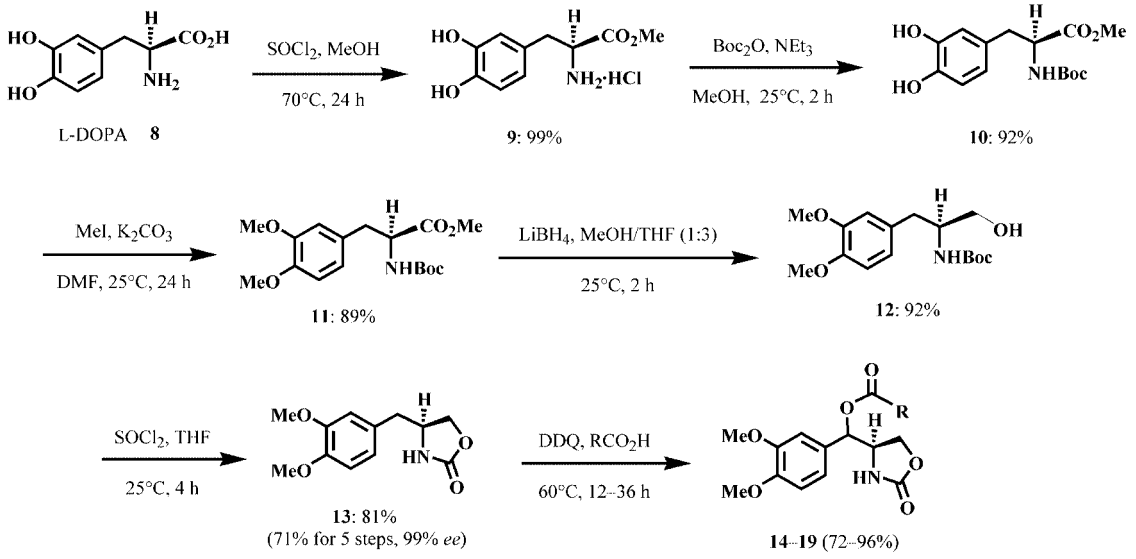
per deals with the preparation of compounds of type **6** and an investigation of the use of 1,3-dichloro-5,6-dicyanobenzoquinone (DDQ) for the oxidative nucleophilic substitution (S_NOx) of the benzylic position of a L-DOPA derivative in the synthesis of syncarpamide (**1**) and azapodophilotoxin (**3**) analogues.

DDQ is known to be a powerful reagent which has been used extensively as an oxidant in organic synthesis and is known to form charge-transfer complexes with aromatic substrates.[9] To date, several studies involving the mono-oxidation of the benzylic position of aromatic compounds mediated by DDQ have been realized. In 1965 Becker showed that DDQ is a specific reagent for the preparation of aromatic aldehydes and ketones.[10] The mechanism of 6-hydroxy- and 6-methoxytetrahydronaphthalene oxidation by DDQ to the corresponding ketone at the benzylic position was also studied by Turner[11] and Lalonde[12] and their co-workers. The formation of carbonyl derivatives was also attempted with success for the selective oxidation of the side-chain at the C-3 position of indoles by Yonemitsu[13] and Cook[14] and their co-workers. The benzylic oxidation of polyaromatic compounds through the action of DDQ in methanolic and acidic media has also been studied.[15] In the pavinan and isopavinan alkaloid series, DDQ also proved its efficiency in forming quinone methides as intermediates in the synthesis of precursors of these polycyclic alkaloids.[16] More generally, Guy and Lemaire and co-workers established the preparation of alkyl aryl ethers[17] and alkylarylcarbinols[18] by mono-oxidation at the benzylic position using DDQ. An asymmetric version of this reaction was also performed with a chiral substrate which induced a difference in the rate of reaction between the diastereotopic benzylic protons.[19] This method was also developed for the direct formation of C–N bonds by azidation[20] and C–CN bonds by cyanation[21] of enriched benzylic derivatives and aromatic steroids. More recently, additional studies concerning azapodophyllotoxin focused on the acylation of the benzylic position with DDQ.[7] In accord with these studies, we report here an extensive exploration of the functionalization of the benzylic position of β-phenylethylamine derivatives and the synthesis of Et 743 analogue precursors under the efficient conditions required for the Pictet–Spengler cyclization starting from L-DOPA.[22]

Results and Discussion

To establish a template for the oxidative benzylic functionalization of β-phenylethylamine derivatives, preliminary studies with the commercially available L-DOPA (**8**) were performed. First, protection of the sensitive amino acid and incorporation of appropriate functional groups were carried out in five steps by standard chemical reactions. Thus, oxazolidinone **13** was prepared by esterification of L-DOPA in MeOH, followed by protection of the resulting amino group giving access to **10**. Methylation of the aromatic hydroxy groups[22b] and reduction of the ester function with $LiBH_4$ in a mixture of MeOH/THF (1:3) afforded the corresponding *N*-protected α-amino alcohol **12**. Finally, intramolecular cyclization between the alcohol and the carbamate function of **12** with $SOCl_2$ in THF[7e] gave rise to **13** in an overall yield of 71% and up to 99% *ee*, as determined by HPLC analysis (Chiracel OJ-H) of the racemic mixture prepared by the same synthetic pathway (Scheme 2).

From compound **13**, available on a multigram scale, oxidative benzylic substitution with DDQ and several carboxylic acid derivatives was attempted. Several ester derivatives were incorporated at the benzylic position of **13** in the presence of 2 equivalents of DDQ at 60 °C in pure liquid carboxylic acid or with an excess of solid carboxylic acid in CH_2Cl_2 or $CHCl_3$ which are reported to be efficient solvents for DDQ dehydrogenation (Scheme 2, Table 1).[23] Whatever the nature of the carboxylic acid, a mixture of two diastereoisomers was obtained. Indeed, DDQ can remove either of the two diastereotopic benzylic protons and the proximity of an asymmetric stereocentre induces a difference in the rate of reaction between these two protons.[19] The deep-blue coloration which appeared when the reagents were first mixed and which disappeared as the reaction progressed is indicative of a charge-transfer interaction.[9a] In fact, substrate **13** acts as a donor and DDQ as an acceptor. The carboxylic acids act both as catalyst and as nucleophile during oxidation mediated by DDQ. At the end of the reaction, precipitation of the by-product 2,3-dichloro-5,6-dicyanohydroquinone (DDHQ) occurred. However, when the reaction was carried out at room temperature, the deep-blue coloration persisted even after 96 h and the starting material was recovered. Finally, when the reaction was carried out in pure carboxylic acid such as acetic acid or acrylic



Scheme 2. Preparation and oxidation of oxazolidinone **13**.

acid, complete disappearance of the donor–acceptor interaction and the precipitation of DDHQ were observed after 24 h at 60 °C. The corresponding diastereomeric mixtures of ester **14** and **15** were obtained in good yields. However, poor diastereomeric excesses were obtained (Table 1, entries 1 and 2). With solid carboxylic acids, reaction times and yields depended on the solubility of the acids in CH_2Cl_2 or $CHCl_3$ as well as their reactivity. In the case of compounds **16**, **17** and **18**, the yields slightly decreased and the diastereomeric excess remained stable in favour of the *anti* diastereoisomer (Table 1, entries 3–5). With phenylglyoxylic acid, better results were obtained in terms of reaction time and **19** was obtained in 96% yield (Table 1, entry 6). Thus, the rate of the reaction was enhanced and the reaction took 12 hours. The attempt to introduce a glyoxalate function directly at the benzylic position of **13** with glyoxylic acid monohydrate was unsuccessful and gave rise to the formation of ketone **20** (Table 1, entry 7). In this case, the benzylic oxidation seems to be sensitive to several factors. First, high concentrations of the nucleophile are necessary to obtain a high yield and shorter reaction time. Secondly, the degree of substitution also depends on the carboxylic acid structure. Finally, acid activation of the donor–acceptor complex seems important for the nucleophilic substitution of **13** by carboxylic acids. Despite good yields, the stereoselectivity remained poor in many cases. Moreover, in the case of sterically hindered carboxylic acids such as *trans*-cinnamic or phenylglyoxylic acid poor diastereoselectivities were also obtained.[19] Nevertheless, dioxidation was not observed, certainly due to the electron-withdrawing effect of the first ester group introduced.[18]

In order to determine the configuration of the new stereocentre at the benzylic position, we studied the chemical shift of the newly created stereocentre. The resonance signal of this carbon atom in the *anti* isomers was upfield relative to the assignments of the *syn* diastereoisomers (Table 2). Moreover, the carbon chemical shift of the stereocentre of the acetoxy derivative *anti*-**14** (δ =75.8 ppm, from a 2:8 mixture of *syn*/*anti* diastereoisomers)[24] correlated with those described by Petrini and co-workers (δ = 75.4 ppm).[7e] In fact, the chemical shift of the C–O bond for the carbon atom in *syn*-**14** (δ = 77.6 ppm) appeared at a lower field in the NMR spectra than those of the corresponding *anti* isomers (Table 2, entry 1).

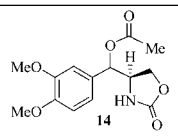
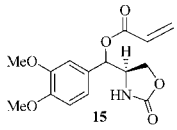
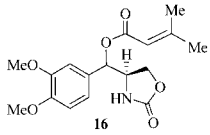
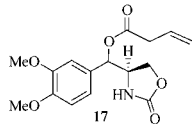
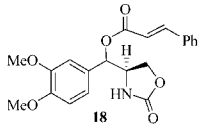
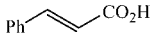
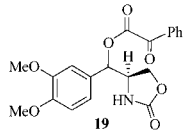
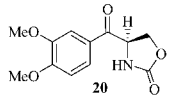
In addition, **19** displayed the same distinctive feature in terms of chemical displacement [δ(*syn*) = 80.2 ppm and δ(*anti*) = 77.9 ppm] and the structural elucidation hypothesis was corroborated by single-crystal X-ray analysis of *syn*-**19**[25] (Figure 2). Indeed, we observed the *syn* orientation of both 7-H and 8-H in the X-ray structure of *syn*-**19**. The *syn* and *anti* isomers also displayed distinctive features in terms of polarity. In the present series of compounds, **14** and **16**–**19**, the *syn* isomer is less polar than the *anti* isomer and consequently more easily isolated from the diastereoisomeric mixture.

We then focused our efforts on the direct introduction of a carbonyl function at the benzylic position of **13** for a suitable synthesis of α-amino alcohol compounds of type **6** (Scheme 3).

As already described for *para*-phenolic derivatives, the oxidation of the benzylic position of **13** into ketone derivative **20** with DDQ was attempted in methanol solution.[10,11,17] After 24 h at 60 °C with 2.2 equivalents of DDQ at a concentration of 0.4 mol/L, the formation of the corresponding methyl ether **21** was observed in 26% yield as an inseparable 4:6 mixture of *syn*/*anti* diastereoisomers and **13** recovered in 45% yield (Table 3, entry 1). However, when the oxidation was carried out in a mixture of MeOH/H_2O or THF/H_2O (9:1), the starting material **13** was recovered. After carrying out the reaction under a range of reac-

tion conditions, varying the solvents (CH_2Cl_2, $CHCl_3$, H_2O, AcOH, HCO_2H) and experimental procedures (Table 3), the best conditions for ketone formation were found to be an 8:2 mixture of HCO_2H/H_2O and 2.5 equivalents of DDQ at a concentration of 0.4 mol/L after only 3 hours of heating at 60 °C (Table 3, entry 9). This also corroborated

Table 1. Benzylic oxidation of **13** by nucleophilic substitution of carboxylic acids.

Entry	Product	Equiv. of carboxylic acid	Solvent	Time /h[a]	% Yield, isolated product (*syn*:*anti*)[b]	% Yield, isolated *syn*	% Yield, isolated *anti*
1	 **14**	CH_3CO_2H (37)	–	24	82 (45:55)	26	–
2	 **15**	$H_2C{=}CHCO_2H$ (37)	–	24	94 (45:55)	–	–
3	 **16**	$(CH_3)_2C{=}CHCO_2H$ (20)	$CHCl_3$	36	75 (40:60)	23	10
4	 **17**	$H_2C{=}CHCH_2CO_2H$ (20)	$CHCl_3$	36	73 (45:55)	22	13
5	 **18**	 (20)	$CHCl_3$	36	72 (40:60)	26	15
6	 **19**	$Ph(C{=}O)CO_2H$ (10)	CH_2Cl_2	12	96 (45:55)	29	22
7	 **20**	$OHCCO_2H{\cdot}H_2O$ (10)	$CHCl_3$	12	58	–	–

[a] Time required for complete discoloration of the deep-blue charge-transfer complexes. [b] Determined by ^1H NMR measurement of the crude product.

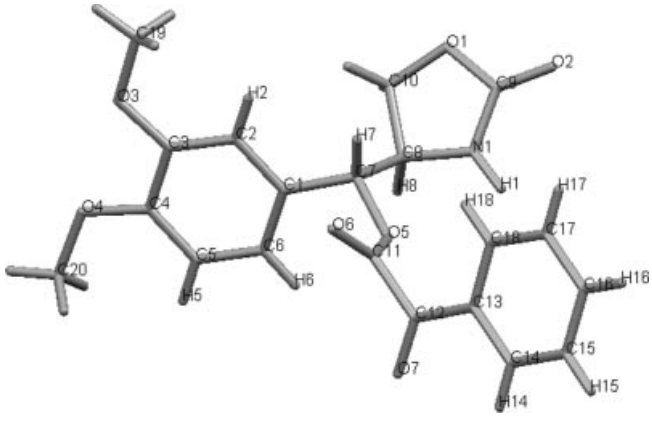


Figure 2. X-ray crystal structure of *syn*-**19**.

Table 2. Chemical shifts (δ, ppm) of the C–O carbon atom in the *syn* and *anti* diastereoisomers.

Entry	Compound	δ_{C-O}(*syn*)	δ_{C-O}(*anti*)
1	**14**	77.6	75.8[a]
2	**16**	76.3	74.9
3	**17**	77.8	75.9
4	**18**	77.5	76.0
5	**19**	80.2	77.9

[a] Determined from a 2:8 mixture of *syn*/*anti* diastereoisomers.

the need for acid activation to increase the rate of the oxidative nucleophilic substitution of this type of compound.

With this efficient method in hand for the preparation of ketone **20**, the Pictet–Spengler cyclization was then achieved with methyl dimethoxyacetate in refluxing CH_2Cl_2

Table 3. Benzylic oxidation of **13** to ketone **20**.

Entry	Solvent[a]	Solvent ratio	Equiv. DDQ	Time /h	Isolated product: % yield
1	MeOH	100:0	2.2	24[b]	**21**: 26[c]
2	MeOH/H_2O	90:10	2.2	24[b]	**20**: –[d]
3	THF/H_2O	90:10	2.2	24[b]	**20**: –[d]
4	CH_2Cl_2/H_2O	90:10	2.2	24[e]	**20**: 59
5	$CHCl_3$/H_2O	90:10	2.2	16[e]	**20**: 65
6	AcOH/H_2O	90:10	2.5	10[e]	**20/14**: 51:17
7	AcOH/H_2O	80:20	2.5	10[f]	**20/14**: 69:5
8	HCO_2H	100:0	2.5	10[f]	**20**: 49
9	HCO_2H/H_2O	80:20	2.5	3[f]	**20**: 84

[a] The reactions were performed at a substrate concentration of 0.4 mol/L. [b] The deep-blue coloration changed to dark red. [c] The corresponding methyl ether **21** was obtained in 26% yield as an inseparable 4:6 mixture of diastereoisomers and **13** recovered in 45% yield. [d] The starting material was recovered. [e] The deep-blue coloration changed to dark brown and DDHQ precipitated. [f] The deep-blue coloration turned to pale red and DDHQ precipitated.

in the presence of $BF_3{\cdot}Et_2O$, affording exclusively the 1,3-*trans*-tetrahydroisoquinoline derivative **22** in 90% yield (Scheme 4). No detectable traces of the corresponding *cis* isomer were observed. The stereochemical outcome of this reaction could be rationalized by the reaction proceeding through the less hindered (*E*)-iminium isomer **23** (Figure 3).[26]

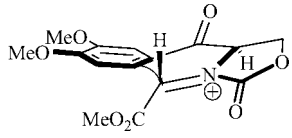
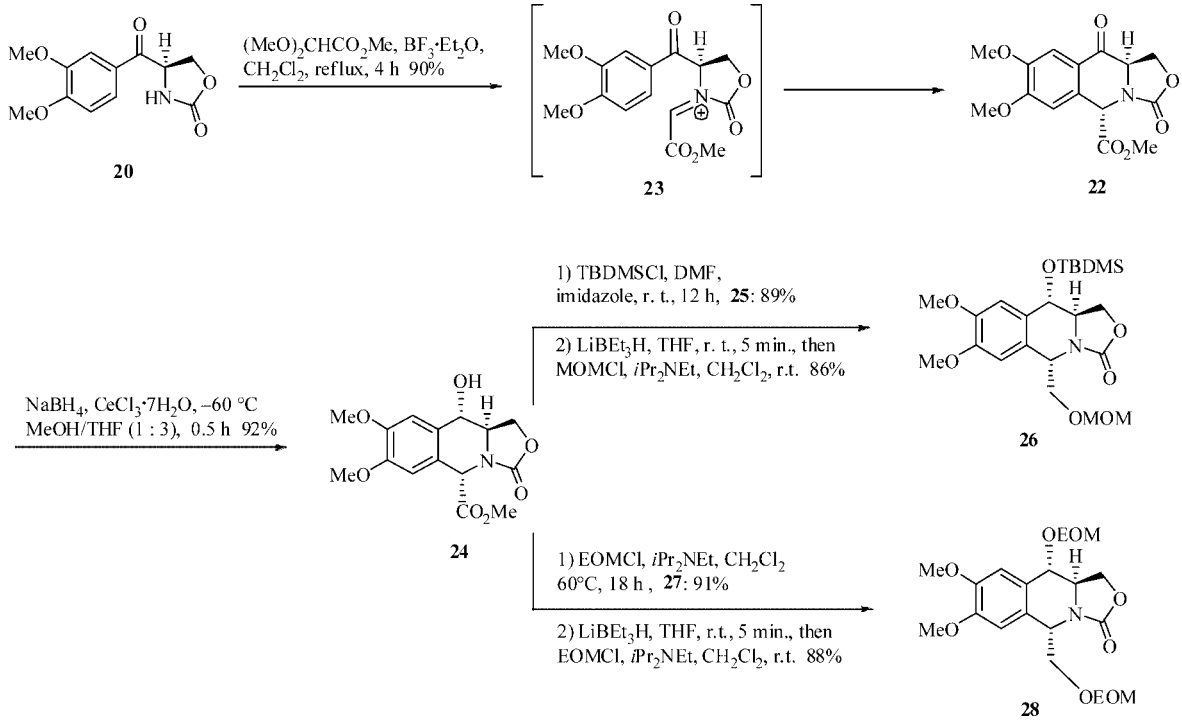


Figure 3. Postulated transition state of the (*E*)-iminium isomer **23** leading to **22**.

Upon exposure to Luche reduction conditions, the ketone function of **22** was reduced by $NaBH_4$ and $CeCl_3{\cdot}7H_2O$ in a mixture of MeOH/THF (1:3) at –60 °C, giving **24** in 92% yield.[27] This reaction proceeded with complete stereoselectivity by hydride attack on the β face and the stereochemistry of **24** was determined by single-crystal X-ray analysis (Figure 4).[28] The hydride attack occurred from the less hindered face, apparently due to the steric hindrance imposed by the ester functionality, through the activation of $CeCl_3$. Indeed, in the absence of $CeCl_3$, the reduction was not complete, but the stereoselectivity remained the same.

Alcohol **24** was then protected as the TBDMS ether in DMF in the presence of imidazole, giving **25** in 89% yield (Scheme 4).[29] The selective reduction of ester **25** was achieved with $LiBEt_3H$ in THF (super hydride®)[30] at room temperature giving the corresponding primary alcohol with the best results. The latter was immediately protected with



Scheme 4. Synthesis of the fully protected diols **26** and **28**.

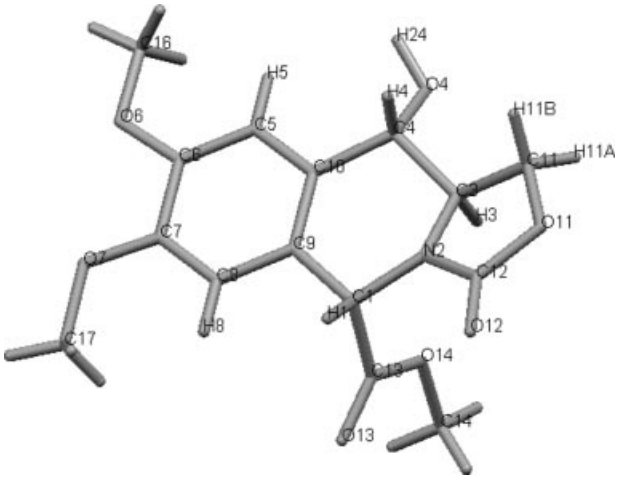
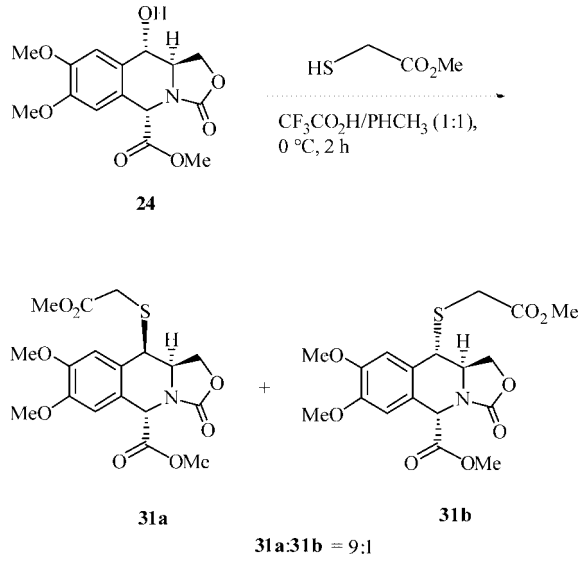


Figure 4. X-ray crystal structure of **24**.

methoxymethyl chloride (MOMCl) in the presence of *i*Pr_2NEt in CH_2Cl_2, affording **26** in 86% yield over two steps without observation of oxazolidinone ring-opening, which was confirmed by 2D NMR experiments (HMBC and NOESY). The alcohol **24** was also protected with ethoxymethyl chloride (EOMCl), affording **27** in 91% yield. The ester function was then reduced with $LiBEt_3H$ to the primary alcohol and protected with EOMCl, affording **28** in 88% yield over two steps.

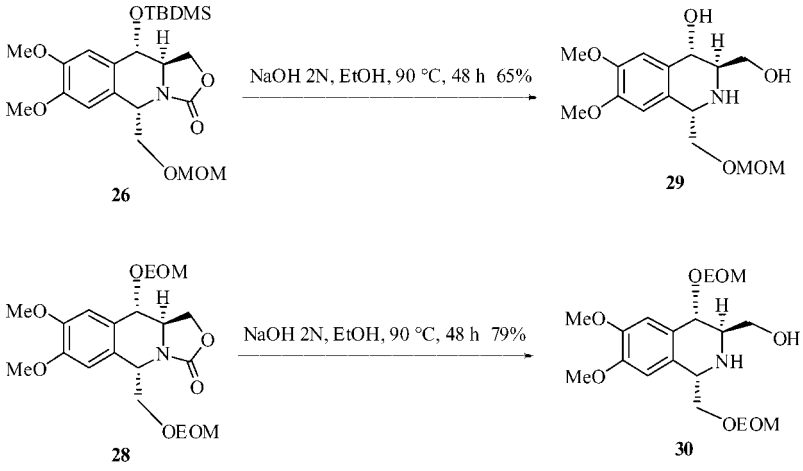
The oxazolidinone rings of **26** and **28** were then removed (Scheme 5) following a method described previously (2 N NaOH, EtOH, 48 h).[31] After removal of the oxazolidinone ring of **26**, hydrolysis of the TBDMS ether function was also observed. The resulting α-amino alcohols **29** and **30** were isolated in 65 and 79% yields respectively.

This method allowed the formation of differently protected α-amino alcohols substituted at the benzylic position and suitable for the synthesis of the piperazine systems found in the ecteinascidin family. In addition, in order to assess the viability of our synthetic strategy, the reaction of **24** with methyl thioglycolate was realized under the conditions established by Zhu and co-workers[32] (CF_3CO_2H/toluene, 0.03 M), which gave rise to **31a** and **31b** in 92% yield with a 9:1 diastereoselectivity (Scheme 6).



Scheme 6. Synthesis of methyl thioglycolate derivatives **31a** and **31b**.

The stereoselectivity could be explained by nucleophilic substitution process S_N1 or S_N2.[33] Competition between both these two mechanisms could also account for the stereoselective outcome of this substitution. In the case of an S_N1-type mechanism, the substitution would proceed through a carbocation or the equivalent *p*-quinone methide intermediate. The stereochemistry of **31a** was corroborated by X-ray single-crystal analysis (Figure 5).[34] The stereoselectivity seems to be influenced by the steric hindrance imposed by the ester function at the C-1 position and consequently the nucleophilic substitution of methyl thioglycolate occurred from the β face.



Scheme 5. Synthesis of α-amino alcohols **29** and **30**.

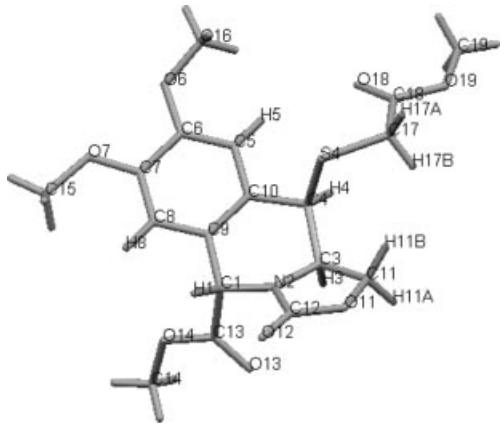


Figure 5. X-ray crystal structure of **33a**.

Conclusions

To conclude, this report describes how a readily available molecular template for the functionalization of β-phenylethylamine at the benzylic position by oxidative nucleophilic substitution (S_NOx) with DDQ can be achieved. New analogues of syncarpamide (**1**) were prepared in six steps starting from L-DOPA with a wide range of functions directly incorporated at the benzylic position (**14**–**19**). An improvement in the oxidation conditions of the benzylic position was also achieved with the necessary acid activation to yield the corresponding ketone derivative **20**. To assess the Pictet–Spengler cyclization reaction we used **20**, which served as the probe. After several chemical modifications, the synthesis of α-amino alcohol precursors for the construction of ecteinascidin analogues was accomplished. Our synthetic approach differs from most of those previously reported with respect to the introduction of a hydroxy group at the C-4 benzylic position in the course of ecteinascidin 743 total synthesis.[35] We will apply this approach to the synthesis of the fully functionalized core of the ecteinascidin family.

Experimental Section

General Methods: Reagents, starting material and solvents were supplied by Aldrich, Acros, Lancaster, Alfa Aeser and Fluka, purchased at the highest commercial quality and used without further purification. All reactions were carried out under argon with dry solvents under anhydrous conditions unless otherwise noted. NMR spectra were recorded either on a Bruker AMX-300 (^{1}H: 300 MHz; ^{13}C: 75 MHz) or a Bruker DPX-500 (^{1}H: 500 MHz; ^{13}C: 125 MHz) instrument using $CDCl_3$ or $(CD_3)_2SO$ as solvent. The chemical shifts (δ, ppm) and coupling constants (Hz) are reported in the standard fashion. In the NMR spectra, the nature of the carbon atoms (C, CH, CH_2, CH_3) was determined by recording DEPT 135 spectra. The following abbreviations have been used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed with a thermo Finnigan LCQ Advantage mass spectrometer. Analytical thin-layer chromatography was effected on silica gel Merck 60 F254 (0.25 mm). Flash chromatography was performed on Merck Si 60 silica gel (40–63 μm). Elemental analyses were performed by the Service Central d'Analyses du CNRS (Solaize, France). Optical rotations were measured at 23 °C using a Perkin–Elmer 241 polarimeter. Melting points were measured on a Kofler apparatus.

Methyl (*S*)-2-Amino-3-(3,4-dihydroxyphenyl)propanoate Hydrochloride (9):[36–38] Thionyl chloride (12 g, 0.101 mol) was slowly added during 1 h to L-DOPA (**8**) (10 g, 0.0507 mol) in dry methanol (500 mL) stirred at 0 °C. The solution was then refluxed over a period of 24 h before being cooled and co-evaporated with toluene (100 mL) giving amine chlorohydrate **9** in 99% yield (12.55 g) as a white solid, m.p. 174–175 °C (methanol/dichloromethane) (lit.: 172–174 °C,[36] 170–171 °C,[37] 170.5–171.5 °C[38]), $[\alpha]_D^{23}$ = +7.9 (methanol, c = 1) {lit.: $[\alpha]_D^{22}$ = +14.7 (methanol, c = 12.5)[38]}. ^{1}H NMR (300 MHz, D_2O, 23 °C): δ = 6.78 (d, J = 8.2 Hz, 1 H, 5-H), 6.78 (d, J = 1.8 Hz, 1 H, 2-H), 6.68 (dd, J = 1.8, 8.1 Hz, 1 H, 6-H), 4.35 (t, J = 6.6 Hz, 1 H, CH_2CHN), 3.82 (s, 3 H, OCH_3), 3.18 (dd, J = 5.9, 14.6 Hz, 1 H, CH_AH_BCHN), 3.06 (dd, J = 7.7, 14.6 Hz, 1 H, CH_AH_BCHN) ppm. ^{13}C NMR (75 MHz, D_2O, 23 °C): δ = 170.6 (C=O), 144.8 (Ar*C*), 144.2 (Ar*C*), 126.6 (Ar*C*), 122.3 (Ar*C*H), 117.4 (Ar*C*H), 117.1 (Ar*C*H), 54.8 (CH), 54.0 (OCH_3), 35.4 (CH_2) ppm. ESI-MS: m/z (%) = 212 (100) $[M + H]^+$. $C_{10}H_{14}ClNO_4$ (247.68): calcd. C 48.49, H 5.70, N 5.66; found C 48.24, H 5.42, N 5.36.

Methyl (*R*)-2-(*tert*-Butoxycarbonylamino)-3-(3,4-dihydroxyphenyl)-propanoate (10):[36,39,40] Triethylamine (0.0510 mol, 7.15 mL) and di-*tert*-butyl dicarbonate (11.1 g, 0.0510 mol) were added to ester **9** (12.5 g, 0.0505 mol) in methanol (275 mL) at room temperature. The solution was then stirred for 2 h. After completion (monitored by TLC, *n*-heptane/ethyl acetate, 5:5), the solvent was evaporated and the residue was acidified with 1 N hydrochloric acid (50 mL) at 0 °C. The solution was then extracted with ethyl acetate (3 × 50 mL), the organic layer was dried with magnesium sulfate and the solvents evaporated. The crude product was purified by flash chromatography (silica gel, *n*-heptane/ethyl acetate, 5:5) giving **10** in 92% yield (14.1 g) as a white solid, m.p. 134–135 °C (methanol) {lit.: 133–135 °C,[36] 140–141 °C (methanol/water),[39] 135 °C[40]}, R_f = 0.3 (*n*-heptane/ethyl acetate, 5:5), $[\alpha]_D^{23}$ = +6.9 (methanol, c = 1) {lit.: $[\alpha]_D^{26}$ = +7.6 (methanol, c = 1.2),[36] $[\alpha]_D^{25}$ = +7 (methanol, c = 1)[40]}. ^{1}H NMR (300 MHz, $CDCl_3$, 23 °C): δ = 6.75 (d, J = 8.1 Hz, 1 H, 5-H), 6.66 (br. s, 1 H, 2-H), 6.50 (dd, J = 1.8, 8.1 Hz, 1 H, 6-H), 5.08 (d, J = 8.2 Hz, 1 H, NH), 4.53 (m, 1 H, CH_2CHN), 3.72 (s, 3 H, CO_2CH_3), 2.99 (dd, J = 5.6, 13.9 Hz, 1 H, CH_AH_BCHN), 2.90 (dd, J = 6.5, 13.9 Hz, 1 H, CH_AH_BCHN), 1.41 [s, 9 H, $O(CH_3)_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 23 °C): δ = 172.9 (C=O), 155.6 (NC=O), 144.0 (Ar*C*), 143.1 (Ar*C*), 128.1 (Ar*C*), 121.4 (Ar*C*H), 116.1 (Ar*C*H), 115.4 (Ar*C*H), 80.6 (C), 54.7 (CH), 52.4 (OCH_3), 37.6 (CH_2), 28.2 ($3CH_3$) ppm. ESI-MS: m/z (%) = 334 (100) $[M + Na]^+$, 312 (28) $[M + H]^+$, 256 (40) $[M + H - C_4H_8]^+$, 212 (36) $[M + H - CO_2C_4H_8]^+$. $C_{15}H_{21}NO_6 \cdot 0.2H_2O$ (314.93): calcd. C 57.21, H 6.74, N 4.45; found C 57.18, H 6.96, N 4.12.

Methyl (*S*)-2-(*tert*-Butoxycarbonylamino)-3-(3,4-dimethoxyphenyl)-propanoate (11):[41] Compound **10** (14 g, 0.045 mol) and methyl iodide (27.5 g, 0.202 mol) were added to a stirred solution of dimethylformamide (100 mL) and potassium carbonate (55.9 g, 0.405 mol). The mixture was then stirred for 24 h. Monitoring by TLC (*n*-heptane/ethyl acetate, 7:3) indicated the disappearance of the starting material. The mixture was then filtered, extracted with diethyl oxide (3 × 60 mL) and washed twice with 1 N hydrochloric acid (20 mL). The organic layer was then dried with $MgSO_4$, filtered, evaporated and purified by flash chromatography (silica gel, *n*-heptane/ethyl acetate, 9:1 → 7:3) giving **11** in 89% yield (13.6 g) as a white solid, m.p. 77–78 °C (*n*-heptane/ethyl acetate) [lit.: 58–

60 °C (*n*-pentane)[41]], R_f = 0.4 (*n*-heptane/ethyl acetate, 1:1), $[\alpha]_D^{23}$ = +6.0 (methanol, *c* = 1) {lit.: $[\alpha]_D^{26}$ = +66 (dichloromethane, *c* = 1)[41]}. ^{1}H NMR (300 MHz, $CDCl_3$, 23 °C): δ = 6.72 (d, *J* = 7.9 Hz, 1 H, 5-H), 6.56 (m, 2 H, 6-H, 2-H), 4.98 (br. d, *J* = 8.1 Hz, 1 H, NH), 4.47 (dd, *J* = 6, 13.7 Hz, 1 H, CH_2CHN), 3.78 (s, 6 H, 3-OCH_3, CO_2CH_3), 3.64 (s, 3 H, 4-OCH_3), 2.94 (m, 1 H, CH_AH_BCHN), 2.93 (t, *J* = 6 Hz, 1 H, CH_AH_BCHN), 1.34 [s, 9 H, $O(CH_3)_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 23 °C): δ = 172.8 (C=O), 155.4 (NC=O), 149.2 (Ar*C*), 148.4 (Ar*C*), 128.8 (Ar*C*), 121.7 (Ar*C*H), 112.7 (Ar*C*H), 111.6 (Ar*C*H), 80.2 (C), 56.2 (OCH_3), 56.1 (OCH_3), 54.8 (CH), 52.6 (OCH_3), 38.2 (CH_2), 28.7 ($3CH_3$) ppm. ESI-MS: *m*/*z* (%) = 362 (100) $[M + Na]^+$, 284 (22) $[M + H - C_4H_8]^+$, 240 (29) $[M + H - CO_2C_4H_8]^+$. $C_{17}H_{25}NO_6$ (339.38): calcd. C 60.16, H 7.42, N 4.13; found C 59.84, H 7.32, N 4.11.

***tert*-Butyl [(*S*)-2-(3,4-Dimethoxyphenyl)-1-(hydroxymethyl)ethyl]-carbamate (12):**[41,42] Lithium borohydride (1.67 g, 0.0767 mol) was added to a stirred solution of ester **11** (13 g, 0.0383 mol) in a 1:2 solution of methanol/tetrahydrofuran (200 mL) at 0 °C. The reaction progress was then controlled by TLC (*n*-heptane/ethyl acetate, 5:5) until disappearance of the starting material. After 2 h of stirring, the solution was diluted with dichloromethane and acidified with 1 N hydrochloric acid (50 mL) and water (50 mL) at 0 °C. The organic layer was separated and the aqueous phase extracted with dichloromethane (2 × 50 mL). The organic layer was then dried with magnesium sulfate, filtered, evaporated and purified by flash chromatography (silica gel, *n*-heptane/ethyl acetate, 8:2 → 5:5) giving **12** in 92% yield (10.9 g) as a white solid, m.p. 91–92 °C (*n*-heptane/ethyl acetate) [lit.: 65–67 °C (*n*-pentane),[41] 92–93 °C[42]], R_f = 0.2 (*n*-heptane/ethyl acetate, 1:1), $[\alpha]_D^{23}$ = –19.6 (methanol, *c* = 0.3) {lit.: $[\alpha]_D^{26}$ = –26.7 (dichloromethane, *c* = 1),[41] $[\alpha]_D^{25}$ = –19.6 (*c* = 0.3, methanol)[42]}. ^{1}H NMR (300 MHz, $CDCl_3$, 23 °C): δ = 6.56 (m, 3 H, 2-H, 5-H, 6-H, ArH), 4.87 (br. s, 1 H, NH), 4.47 (dd, *J* = 6, 13.7 Hz, 1 H, CH_2CHN), 3.86 (s, 3 H, 3-OCH_3), 3.85 (s, 3 H, 4-OCH_3), 3.83 (m, 1 H, CH_2CHN), 2.94 (dd, *J* = 2.9, 11 Hz, 1 H, CH_AH_BOH), 3.56 (dd, *J* = 5.8, 10.9 Hz, 1 H, CH_AH_BOH), 2.78 (d, *J* = 7.1 Hz, 1 H, CH_AH_BCHN, CH_AH_BCHN), 2.63 (br. s, 1 H, OH), 1.41 [s, 9 H, $O(CH_3)_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 23 °C): δ = 156.6 (NC=O), 149.3 (Ar*C*), 148.1 (Ar*C*), 130.7 (Ar*C*), 121.7 (Ar*C*H), 112.8 (Ar*C*H), 111.7 (Ar*C*H), 80.1 (C), 64.6 (CH), 56.3 (OCH_3), 56.2 (OCH_3), 54.0 (CH), 37.6 (CH_2), 28.8 ($3CH_3$) ppm. ESI-MS: *m*/*z* (%) = 334 (100) $[M + Na]^+$, 212 (6) $[M + H]^+$, 256 (17) $[M + H - C_4H_8]^+$, 212 (38) $[M + H - CO_2C_4H_8]^+$. $C_{16}H_{25}NO_5$ (311.37): calcd. C 61.72, H 8.09, N 4.50; found C 61.54, H 8.21, N 4.29.

(*S*)-4-(3,4-Dimethoxybenzyl)oxazolidin-2-one (13):[43] Thionyl chloride (16.05 g, 0.135 mol) was slowly added to alcohol **12** (10.5 g, 0.0337 mol) in dry tetrahydrofuran (230 mL) stirred at 0 °C. The resulting solution was stirred at room temperature for 4 h. Then the solution was diluted with dichloromethane (200 mL), washed with a saturated sodium carbonate aqueous solution (3 × 150 mL) and brine (100 mL), dried with magnesium sulfate and filtered. The crude product was purified by flash chromatography (silica gel, *n*-heptane/ethyl acetate, 6:4 → 5:5) giving **13** in 81% yield (6.47 g) as a white solid, m.p. 92–93 °C (ethyl acetate), R_f = 0.4 (ethyl acetate), $[\alpha]_D^{23}$ = –51.6 (*c* = 1, dichloromethane). HPLC: Chiralcel OJ-H, 25 × 0.4 i.d., Daicel; retention time = 40.19 min, eluent: *n*-heptane/ethanol (60:40) isocratic conditions, flow 0.5 mL/min, UV 280 nm. ^{1}H NMR (300 MHz, $CDCl_3$, 23 °C): δ = 6.78 (d, *J* = 8.1 Hz, 1 H, 5-H), 6.78 (d, *J* = 1.9 Hz, 1 H, 2-H), 6.68 (dd, *J* = 1.9, 7.9 Hz, 1 H, 6-H), 5.65 (br. s, 1 H, NH), 4.44 (t, *J* = 8.2 Hz, 1 H, CH_2CHN), 4.13 (m, 1 H, $CHCH_AH_BO$), 4.05 (m, 1 H, $CHCH_AH_BO$), 3.87 (s, 3 H, 3-OCH_3), 3.86 (s, 3 H, 4-OCH_3), 3.06 (d, *J* = 6.8 Hz, 2 H, CH_AH_BCHN, CH_AH_BCHN) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 23 °C): δ = 160.3 (NC=O), 149.5 (Ar*C*), 148.5 (Ar*C*), 128.9 (Ar*C*), 121.5 (Ar*C*H), 112.6 (Ar*C*H), 111.9 (Ar*C*H), 69.9 (CH_2), 56.3 ($2OCH_3$), 54.2 (CH), 41.2 (CH_2) ppm. ESI-MS: *m*/*z* (%) = 238 (100) $[M + H]^+$. $C_{12}H_{15}NO_4$ (237.25): calcd. C 60.75, H 6.37, N 5.90; found C 60.41, H 6.380, N 5.85.

(*R*)-(3,4-Dimethoxyphenyl)[(*R*)-2-oxooxazolidin-4-yl]methyl Acetate (*syn*-14) and (*S*)-(3,4-Dimethoxyphenyl)[(*R*)-2-oxooxazolidin-4-yl]-methyl Acetate (*anti*-14): DDQ (0.479 g, 2.11 mmol) was added to a suspension of **13** (0.25 g, 1.05 mmol) in acetic acid (2.6 mL) and stirred at 60 °C for 24 h. After filtration of the precipitate the solution was diluted with dichloromethane (20 mL), washed with a saturated sodium hydrogen carbonate aqueous solution (2 × 15 mL) and brine (10 mL), dried with magnesium sulfate and filtered. The crude product was concentrated and purified by flash chromatography (silica gel, cyclohexane/ethyl acetate, 7:3 → 5:5) giving *syn*-**14** and *anti*-**14** in 82% yield (0.255 g) and as a 45:55 mixture of *syn*/*anti* diastereoisomers. The less polar diastereoisomer *syn*-**14** was separated in 26% yield (0.076 g) as a white solid, m.p. 160–161 °C (*n*-heptane/ethyl acetate), R_f = 0.6 (ethyl acetate), $[\alpha]_D^{23}$ = –54.4 (dichloromethane, *c* = 0.8). ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ = 6.97 (br. s, 1 H, NH), 6.91 (d, *J* = 8.2 Hz, 1 H, 6-H), 6.83 (m, 2 H, 2-H, 5-H), 5.62 (d, *J* = 7.1 Hz, 1 H, $CHOCOCH_3$), 4.20 (m, 2 H, $CHCH_AH_BO$, OCH_2CHN), 4.03 (m, 1 H, $CHCH_AH_BO$), 3.87 (s, 3 H, 3-OCH_3), 3.84 (s, 3 H, 4-OCH_3), 2.10 (s, 3 H, CH_3CO) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C): δ = 170.5 (OC=O), 160.2 (NC=O), 150.1 (Ar*C*), 149.7 (Ar*C*), 128.3 (Ar*C*), 120.3 (Ar*C*H), 111.7 (Ar*C*H), 110.6 (Ar*C*H), 77.6 (CH), 66.7 (CH_2), 56.5 (CH), 56.4 (OCH_3), 56.3 (OCH_3), 21.4 (CH_3CO) ppm. ESI-MS: *m*/*z* (%) = 318 (92) $[M + Na]^+$, 296 (35) $[M + H]^+$, 236 (100) $[M + H - CH_3CO_2H]^+$. $C_{14}H_{17}NO_6$ (295.29): calcd. C 56.94, H 5.80, N 4.74; found C 56.55, H 6.09, N 4.37.

(*R*)-(3,4-Dimethoxyphenyl)[(*R*)-2-oxooxazolidin-4-yl]methyl Acrylate (*cis*-15) and (*S*)-(3,4-Dimethoxyphenyl)[(*R*)-2-oxooxazolidin-4-yl]methyl Acrylate (*anti*-15): A suspension of **13** (0.25 g, 1.05 mmol) in acrylic acid (2.6 mL) and DDQ (0.479 g, 2.11 mmol) was stirred at 60 °C for 24 h. After filtration of the precipitate, the solution was diluted with dichloromethane (20 mL), washed with a saturated sodium hydrogen carbonate aqueous solution (2 × 15 mL) and brine (10 mL), dried with $MgSO_4$ and filtered. The crude product was concentrated and purified by flash chromatography (silica gel, *n*-heptane/ethyl acetate, 7:3 → 5:5) giving *syn*-**15** and *anti*-**15** in 94% yield (0.304 g) as a colourless oil and as an inseparable 45:55 mixture of *syn*/*anti* diastereoisomers. ESI-MS: *m*/*z* (%) = 330 (22) $[M + Na]^+$, 308 (19) $[M + H]^+$, 236 (100) $[M + H - CH_2CHCO_2H]^+$. $C_{15}H_{17}NO_6$ (307.29): calcd. C 58.63, H 5.58, N 4.56; found C 58.22, H 5.74, N 4.18.

(*R*)-(3,4-Dimethoxyphenyl)[(*R*)-2-oxooxazolidin-4-yl]methyl 3-Methylbut-2-enoate (*syn*-16) and (*S*)-(3,4-Dimethoxyphenyl)[(*R*)-2-oxooxazolidin-4-yl]methyl 3-Methylbut-2-enoate (*anti*-16): DDQ (0.479 g, 2.11 mmol) was added to a solution of **13** (0.25 g, 1.05 mmol) and 3,3-dimethylacrylic acid (2.11 g, 21.10 mmol) suspended in chloroform (2.6 mL). The resulting deep-blue mixture was stirred at 60 °C for 36 h. After filtration of the precipitate, the solution was diluted with dichloromethane (20 mL), washed with a saturated sodium bicarbonate aqueous solution (2 × 15 mL) and brine (10 mL), dried with magnesium sulfate and filtered. The crude product was concentrated and purified by flash chromatography (silica gel, *n*-heptane/ethyl acetate, 8:2 → 6:4) giving *syn*-**16** (23%, 0.081 g) and *anti* –**16** (10%, 0.035 g) as white solids in 75% overall yield (0.265 g) as a 40:60 mixture of *syn*/*anti* diastereoisomers. Data for compound *syn*-**16**: m.p. 70–71 °C (ethyl acetate), R_f = 0.7 (ethyl

acetate), $[\alpha]_D^{23}$ = –56.3 (dichloromethane, *c* = 0.65). ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ = 6.90 (dd, *J* = 1.9, 8.2 Hz, 1 H, 6-H), 6.84 (m, 2 H, 2-H, 5-H), 6.23 (br. s, 1 H, NH), 5.74 [m, 1 H, $(CH_3)_2CCHCO_2$], 5.61 [d, *J* = 7.3 Hz, 1 H, $CHOCOCHC(CH_3)_2$], 4.22 (dd, *J* = 8.5, 17 Hz, 1 H, $CHCH_AH_BO$), 4.18 (m, 1 H, OCH_2CHN), 4.08 (dd, *J* = 4.7, 16.8 Hz, 1 H, $CHCH_AH_BO$), 3.84 (s, 3 H, 3-OCH_3), 3.82 (s, 3 H, 4-OCH_3), 2.07 (d, *J* = 1.0 Hz, 3 H, CH_3), 1.85 (d, *J* = 1.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C): δ = 165.6 (OC=O), 159.7 (NC=O), 159.7 [$C(CH_3)_2$], 149.9 (Ar*C*), 149.7 (Ar*C*), 128.8 (Ar*C*), 119.9 (Ar*C*H), 115.5 [$(CH_3)_2CCHCO_2$], 111.8 (Ar*C*H), 110.3 (Ar*C*H), 76.3 (CH), 66.7 (CH_2), 56.6 (CH), 56.4 (OCH_3), 56.3 (OCH_3), 27.9 (CH_3), 20.8 (CH_3) ppm. ESI-MS: *m*/*z* (%) = 358 (100) $[M + Na]^+$, 236 (28) $[M + H – (CH_3)_2CCHCO_2H]^+$. $C_{17}H_{21}NO_6$ (335.35): calcd. C 60.89, H 6.31, N 4.18; found C 60.81, H 6.61, N 3.90. Data for compound *anti*-**16**: m.p. 64–65 °C (ethyl acetate), R_f = 0.6 (ethyl acetate), $[\alpha]_D^{23}$ = +16.2 (dichloromethane, *c* = 0.4). ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ = 6.93 (dd, *J* = 1.9, 8.2 Hz, 1 H, 6-H), 6.87 (m, 2 H, 2-H, 5-H), 5.77 [br. s, 1 H, $(CH_3)_2CCHCO_2$], 5.73 [d, *J* = 6.9 Hz, 1 H, $CHOCOCHC(CH_3)_2$], 5.02 (br. s, 1 H, NH), 4.46 (t, *J* = 8.8 Hz, 1 H, $CHCH_AH_BO$), 4.35 (dd, *J* = 5, 9.1 Hz, 1 H, $CHCH_AH_BO$), 4.19 (m, 1 H, OCH_2CHN), 3.91 (s, 3 H, 3-OCH_3), 3.89 (s, 3 H, 4-OCH_3), 2.17 (d, *J* = 0.9 Hz, 3 H, CH_3), 1.94 (d, *J* = 0.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C): δ = 165.5 (OC=O), 160.2 (NC=O), 159.0 [$C(CH_3)_2$], 149.9 (Ar*C*), 149.8 (Ar*C*), 128.9 (Ar*C*), 119.8 (Ar*C*H), 115.3 [$(CH_3)_2CCHCO_2$], 111.8 (Ar*C*H), 110.1 (Ar*C*H), 74.9 (CH), 67.4 (CH_2), 56.5 (CH), 56.4 (OCH_3), 56.4 (OCH_3), 28.0 (CH_3), 20.9 (CH_3) ppm. ESI-MS: *m*/*z* (%) = 358 (100) $[M + Na]^+$, 236 (25) $[M + H – (CH_3)_2CCHCO_2H]^+$. $C_{17}H_{21}NO_6$ (335.35): calcd. C 60.89, H 6.31, N 4.18; found C 60.78, H 6.60, N 3.90.

(*R*)-(3,4-Dimethoxyphenyl)[(*R*)-2-oxooxazolidin-4-yl]methyl But-3-enoate (*syn*-17) and (*S*)-(3,4-Dimethoxyphenyl)[(*R*)-2-oxooxazolidin-4-yl]methyl But-3-enoate (*anti*-17): A suspension of **13** (0.25 g, 1.05 mmol), but-3-enoic acid (1.82 g, 1.80 mL, 21.1 mmol) and DDQ (0.479 g, 2.11 mmol) in chloroform (0.86 mL) was stirred at 60 °C for 36 h. After filtration of the precipitate, the solution was diluted with dichloromethane (20 mL), washed with a saturated sodium bicarbonate aqueous solution (2 × 15 mL) and brine (10 mL), dried with magnesium sulfate and filtered. The crude product was concentrated and purified by flash chromatography (silica gel, *n*-heptane/ethyl acetate, 8:2 → 6:4) giving *syn*-**17** (22%, 0.075 g) and *anti*-**17** (13%, 0.044 g) as white solids in 73% overall yield (0.247 g) and as a 45:55 mixture of *syn*/*anti* diastereoisomers. Data for compound *syn*-**17**: m.p. 50–51 °C (dichloromethane), R_f = 0.7 (ethyl acetate), $[\alpha]_D^{23}$ = –63.4 (dichloromethane, *c* = 0.5). ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ = 6.90 (dd, *J* = 1.9, 8.2 Hz, 1 H, 6-H), 6.84 (m, 3 H, 2-H, 5-H, NH), 5.89 (m, 1 H, $COCH_2CHCH_2$), 5.64 (d, *J* = 7.6 Hz, 1 H, $CHOCOCH_3$), 5.16 (br. s, 1 H, $COCH_2CHCH_AH_B$), 5.13 (dd, *J* = 1.2, 5.3 Hz, 1 H, $COCH_2CHCH_AH_B$), 4.21 (m, 2 H, $CHCH_AH_BO$, OCH_2CHN), 4.05 (m, 1 H, $CHCH_AH_BO$), 3.87 (s, 3 H, 3-OCH_3), 3.86 (s, 3 H, 4-OCH_3), 3.14 (dd, *J* = 6.9, 16.7 Hz, 1 H, $COCH_AH_BCHCH_2$), 3.14 (dd, *J* = 7.0, 16.7 Hz, 1 H, $COCH_AH_BCHCH_2$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C): δ = 171.0 (OC=O), 160.2 (NC=O), 150.1 (Ar*C*), 149.8 (Ar*C*), 130.2 (CH), 128.2 (Ar*C*), 120.2 (Ar*C*H), 119.4 (CH_2), 111.8 (Ar*C*H), 110.5 (Ar*C*H), 77.8 (CH), 66.7 (CH_2), 56.6 (CH), 56.4 (OCH_3), 56.3 (OCH_3), 39.3 (CH_2) ppm. ESI-MS: *m*/*z* (%) = 344 (100) $[M + Na]^+$, 236 (258) $[M + H – H_2CCHCH_2CO_2H]^+$. $C_{16}H_{19}NO_6·H_2O$ (339.34): calcd. C 56.63, H 6.24, N 4.13; found C 56.60, H 6.16, N 4.18. Data for compound *anti*-**17**: m.p. 45–46 °C (dichloromethane), R_f = 0.6 (ethyl acetate), $[\alpha]_D^{23}$ = +56.9 (dichloromethane, *c* = 2). ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ = 6.87 (d, *J* = 8.6 Hz, 1 H, 6-H), 6.87 (d, *J* = 8.2 Hz, 1 H, 5-H), 6.84 (d, *J* = 1.2 Hz, 1 H, 2-H), 5.88 (m, 1 H, $COCH_2CHCH_2$), 5.77 (br. s, 1 H, NH), 5.73 (d, *J* = 6 Hz, 1 H, $CHOCOCH_3$), 5.19 (br. s, 1 H, $COCH_2CHCH_AH_B$), 5.17 (d, *J* = 5.4 Hz, 1 H, $COCH_2CHCH_AH_B$), 4.38 (t, *J* = 8.8 Hz, 1 H, $CHCH_AH_BO$), 4.29 (m, 1 H, $CHCH_AH_BO$), 4.29 (m, 1 H, OCH_2CHN), 3.86 (s, 3 H, 3-OCH_3), 3.85 (s, 3 H, 4-OCH_3), 3.15 (d, *J* = 6.6 Hz, 2 H, $COCH_AH_BCHCH_2$, $COCH_AH_BCHCH_2$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C): δ = 170.8 (OC=O), 159.5 (NC=O), 150.0 (Ar*C*), 149.7 (Ar*C*), 129.9 (CH), 128.1 (Ar*C*), 119.7 (CH_2), 119.6 (Ar*C*H), 111.8 (Ar*C*H), 110.2 (Ar*C*H), 75.9 (CH), 66.9 (CH_2), 56.4 (CH), 56.4 (OCH_3), 56.3 (OCH_3), 39.5 (CH_2) ppm. ESI-MS: *m*/*z* (%) = 344 (100) $[M + Na]^+$, 236 (258) $[M + H – H_2CCHCH_2CO_2H]^+$. $C_{16}H_{19}NO_6$ (321.33): calcd. C 59.81, H 5.96, N 4.36; found C 59.39, H 6.06, N 4.10.

(*R*)-(3,4-Dimethoxyphenyl)[(*R*)-2-oxooxazolidin-4-yl]methyl Cinnamate (*syn*-18) and (*S*)-(3,4-Dimethoxyphenyl)[(*R*)-2-oxooxazolidin-4-yl]methyl Cinnamate (*anti*-18): DDQ (0.479 g, 2.11 mmol) was added to a solution of **13** (0.25 g, 1.05 mmol) and *anti*-cinnamic acid (3.13 g, 21.10 mmol) suspended in chloroform (2.6 mL). The resulting deep-blue mixture was stirred at 60 °C for 36 h. After filtration of the precipitate, the solution was diluted with dichloromethane (20 mL) and washed with a saturated sodium hydrogen carbonate aqueous solution (2 × 15 mL) and brine (10 mL), dried with magnesium sulfate and filtered. The crude product was concentrated and purified by flash chromatography (silica gel, *n*-heptane/ethyl acetate, 8:2 → 5:5) giving *syn*-**18** (26%, 0.105 g) and *anti*-**18** (15%, 0.060 g) as white solids in 72% overall yield (0.290 g) and as a 40:60 mixture of *syn*/*anti* diastereoisomers. Data for compound *syn*-**18**: m.p. 88 °C (chloroform), R_f = 0.8 (ethyl acetate), $[\alpha]_D^{23}$ = +17.5 (dichloromethane, *c* = 1.1). ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ = 7.72 (d, *J* = 16.1, Hz 1 H, $C_6H_5CHCHCOO$), 7.90 (m, 2 H, 2′-H, 6′-H), 7.38 (m, 3 H, 3′-H, 4′-H, 5′-H), 6.94 (dd, *J* = 1.4, 8.5 Hz, 1 H, 6-H), 6.86 (m, 2 H, 2-H, 5-H), 6.48 (d, *J* = 16.1 Hz, 1 H, $C_6H_5CHCHCO_2$), 6.14 (br. s, 1 H, NH), 5.72 [d, *J* = 6.9 Hz, 1 H, $CHO(CO)C_2H_2C_6H_5$], 4.29 (m, 1 H, OCH_2CHN), 4.28 (m, 1 H, $CHCH_AH_BO$), 4.11 (m, 1 H, $CHCH_AH_BO$), 3.89 (s, 3 H, 3-OCH_3), 3.86 (s, 3 H, 4-OCH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C): δ = 166.3 (OC=O), 159.6 (NC=O), 150.1 (Ar*C*), 149.8 (Ar*C*), 146.8 (CH_{alkene}), 134.5 (Ar*C*), 131.1 (Ar*C*H), 129.3 (2Ar*C*H), 128.7 (2Ar*C*H), 128.4 (Ar*C*), 119.9 (Ar*C*H), 117.4 (CH_{alkene}), 111.9 (Ar*C*H), 110.3 (Ar*C*H), 77.5 (CH), 66.8 (CH_2), 56.6 (CH), 56.5 (OCH_3), 56.3 (OCH_3) ppm. ESI-MS: *m*/*z* (%) = 406 (100) $[M + Na]^+$, 236 (12) $[M + H – C_6H_5C_2H_2CO_2H]^+$. $C_{21}H_{21}NO_6$ (383.39): calcd. C 65.79, H 5.52, N 3.65; found C 65.78, H 5.62, N 3.55. Data for compound *anti*-**18**: m.p. 77–78 °C (dichloromethane), R_f = 0.7 (ethyl acetate), $[\alpha]_D^{23}$ = –75.0 (dichloromethane, *c* = 0.6). ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ = 7.73 (d, *J* = 16.1 Hz, 1 H, $C_6H_5CHCHCO_2$), 7.90 (m, 2 H, 2′-H, 6′-H), 7.38 (m, 3 H, 3′-H, 4′-H, 5′-H), 6.95 (dd, *J* = 1.7, 8.4 Hz, 1 H, 6-H), 6.87 (m, 2 H, 2-H, 5-H), 6.47 (d, *J* = 16.1 Hz, 1 H, $C_6H_5CHCHCOO$), 5.82 [d, *J* = 6.6 Hz, 1 H, $CHO(CO)C_2H_2C_6H_5$], 5.30 (br. s, 1 H, NH), 4.48 (m, *J* = 8.8 Hz, 1 H, $CHCH_AH_BO$), 4.38 (dd, *J* = 4.7, 9.1 Hz, 1 H, $CHCH_AH_BO$), 4.26 (m, 1 H, OCH_2CHN), 3.89 (s, 3 H, 3-OCH_3), 3.87 (s, 3 H, 4-OCH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C): δ = 166.2 (OC=O), 159.2 (NC=O), 150.1 (Ar*C*), 149.8 (Ar*C*), 147.0 (CH_{alkene}), 134.4 (Ar*C*), 131.2 (Ar*C*H), 129.4 (2Ar*C*H), 128.7 (2Ar*C*H), 128.4 (Ar*C*), 119.8 (Ar*C*H), 117.2 (CH_{alkene}), 111.8 (Ar*C*H), 110.3 (Ar*C*H), 76.0 (CH), 67.3 (CH_2), 56.5 (CH), 56.4 (OCH_3), 56.4 (OCH_3) ppm. ESI-MS: *m*/*z* (%) = 406 (100) $[M + Na]^+$, 236 (6) $[M + H – C_6H_5C_2H_2CO_2H]^+$. $C_{21}H_{21}NO_6·0.25CH_2Cl_2$ (404.62): calcd. C 63.02, H 5.31, N 3.46; found C 62.78, H 5.62, N 3.78.

(*R*)-(3,4-Dimethoxyphenyl)[(*R*)-2-oxooxazolidin-4-yl]methyl 2-Oxo-2-phenylacetate (*syn*-19) and (*S*)-(3,4-Dimethoxyphenyl)[(*R*)-2-oxooxazolidin-4-yl]methyl 2-Oxo-2-phenylacetate (*anti*-19): A suspension of oxazolidin-2-one **13** (0.25 g, 1.05 mmol), DDQ (0. 479 g, 2.11 mmol) in dichloromethane (2.6 mL) and phenylglyoxylic acid (2.53 g, 8.43 mmol) was stirred at 60 °C for 12 h. After filtration of the pale brown precipitate, the solution was diluted with dichloromethane (20 mL) and washed with a saturated sodium hydrogen carbonate aqueous solution (2 × 15 mL) and brine (10 mL), dried with magnesium sulfate and filtered. The crude product was concentrated and purified by flash chromatography (silica gel, *n*-heptane/ethyl acetate, 8:2 → 5:5) giving *syn*-**19** (29%, 0.117 g) and *anti*-**19** (22%, 0.089 g) as white solids in 96% overall yield (0.390 g) and as a 45:55 mixture of *syn*/*anti* diastereoisomers. Data for compound *syn*-**19**: m.p. 178–179 °C (dichloromethane), R_f = 0.8 (ethyl acetate), $[\alpha]_D^{23}$ = –72 (dichloromethane, *c* = 1). ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ = 7.90 (d, *J* = 7.2 Hz, 2 H, 2′-H, 6′-H), 7.64 (t, *J* = 7.9 Hz, 1 H, 4′-H), 7.47 (t, *J* = 7.9 Hz, 2 H, 3′-H, 5′-H), 7.01 (d, *J* = 1.5, 8.2 Hz, 1 H, 6-H), 6.92 (d, *J* = 1.3 Hz, 1 H, 2-H), 6.90 (d, *J* = 8.2 Hz, 1 H, 5-H), 6.26 (br. s, 1 H, NH), 5.82 [d, *J* = 8.2 Hz, 1 H, C*H*O(CO)$_2$C$_6$H$_5$], 4.35 (m, 1 H, OCH$_2$C*H*N), 4.25 (t, *J* = 9.0 Hz, 1 H, CHCH_AH$_B$O), 4.09 (dd, *J* = 5.3, 9.1 Hz, 1 H, CHCH$_A$$H_B$O), 3.91 (s, 3 H, 3-OCH$_3$), 3.90 (s, 3 H, 4-OCH$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C): δ = 185.6 (Ar*C*=O), 162.8 (OC=O), 159.3 (NC=O), 150.6 (Ar*C*), 150.0 (Ar*C*), 135.6 (Ar*C*H), 132.6 (Ar*C*), 130.5 (2Ar*C*H), 129.4 (2Ar*C*H), 126.8 (Ar*C*), 120.7 (Ar*C*H), 111.8 (Ar*C*H), 110.4 (Ar*C*H), 80.2 (CH), 66.3 (CH$_2$), 56.5 (OCH$_3$), 56.4 (OCH$_3$), 56.1 (CH) ppm. MS-ESI: *m*/*z* (%) = 408 (100) [M + Na]$^+$, 386 (57) [M + H]$^+$, 236 (83) [M + H – C$_6$H$_5$CO-CO$_2$H]$^+$. $C_{20}H_{19}NO_7$ (385.37): calcd. C 62.33, H 4.97, N 3.63; found C 61.96, H 5.03, N 3.57. Data for compound *anti*-**19**: m.p. 169–170 °C (dichloromethane), R_f = 0.7 (ethyl acetate), $[\alpha]_D^{23}$ = +23.2 (dichloromethane, *c* = 0.6). ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ = 7.89 (d, *J* = 7.3 Hz, 2 H, 2′-H, 6′-H), 7.52 (t, *J* = 7.5 Hz, 1 H, 4′-H), 7.48 (t, *J* = 7.8 Hz, 2 H, 3′-H, 5′-H), 6.97 (d, *J* = 8.2 Hz, 1 H, 6-H), 6.90 (d, *J* = 1.9 Hz, 1 H, 2-H), 6.88 (d, *J* = 8.2 Hz, 1 H, 5-H), 5.91 [d, *J* = 4.2 Hz, 1 H, C*H*O(CO)$_2$C$_6$H$_5$], 5.63 (br. s, 1 H, NH), 4.47 (t, *J* = 8.6 Hz, 1 H, CHCH_AH$_B$O), 4.35 (m, 1 H, CHCH$_A$$H_B$O), 4.31 (m, 1 H, OCH$_2$C*H*N), 3.88 (s, 3 H, 3-OCH$_3$), 3.86 (s, 3 H, 4-OCH$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C): δ = 185.7 (Ar*C*=O), 163.0 (OC=O), 159.1 (NC=O), 150.4 (Ar*C*), 150.0 (Ar*C*), 135.7 (Ar*C*H), 132.4 (Ar*C*), 130.4 (2Ar*C*H), 129.5 (2Ar*C*H), 127.1 (Ar*C*), 120.2 (Ar*C*H), 111.8 (Ar*C*H), 110.0 (Ar*C*H), 77.9 (CH), 67.1 (CH$_2$), 56.5 (OCH$_3$), 56.4 (OCH$_3$), 56.2 (CH) ppm. ESI-MS: *m*/*z* (%) = 408 (77) [M + Na]$^+$, 236 (100) [M + H – C$_6$H$_5$COCO$_2$H]$^+$. $C_{20}H_{19}NO_7$·0.2H$_2$O (388.97): calcd. C 61.76, H 4.99, N 3.60; found C 61.56, H 5.10, N 3.56.

(*R*)-4-(3,4-Dimethoxybenzoyl)oxazolidin-2-one (20): DDQ (2.40 g, 10.6 mmol) was added to oxazolidinone **13** (1 g, 4.22 mmol) in formic acid/water (8.48:2.12 mL). The resulting solution was stirred at 60 °C for 3 h. After filtration of the precipitate, the solution was diluted with dichloromethane (50 mL), washed with a saturated $NaHCO_3$ aqueous solution (4 × 50 mL) and brine (40 mL), dried with magnesium sulfate and filtered. The crude product was concentrated and purified by flash chromatography (silica gel, *n*-heptane/ethyl acetate, 6:4 → 5:5) giving **20** as a white solid in 84% yield (0.900 g), m.p. 168–169 °C (dichloromethane), R_f = 0.5 (ethyl acetate), $[\alpha]_D^{23}$ = +44.4 (dichloromethane, *c* = 0.5). ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ = 7.49 (d, *J* = 1.9 Hz, 1 H, 2-H), 7.34 (dd, *J* = 1.9, 8.5 Hz, 1 H, 6-H), 6.92 (d, *J* = 8.2 Hz, 1 H, 5-H), 5.89 (br. s, 1 H, NH), 5.22 (dd, *J* = 6.6, 10 Hz, 1 H, OCH$_2$C*H*N), 4.80 (t, *J* = 9.8 Hz, 1 H, CHCH_AH$_B$O), 4.43 (dd, *J* = 5.7, 9.8 Hz, 1 H, CHCH$_A$$H_B$O), 3.97 (s, 3 H, 3-OCH$_3$), 3.94 (s, 3 H, 3-OCH$_3$), 3.86 (s, 3 H, 4-OCH$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C): δ = 193.4 (C=O), 159.4 (NC=O), 155.0 (Ar*C*), 150.3 (Ar*C*), 126.7 (Ar*C*), 123.1 (Ar*C*H), 110.9 (Ar*C*H), 110.8 (Ar*C*H), 67.2 (CH$_2$), 56.8 (OCH$_3$), 56.7 (OCH$_3$), 56.5 (CH) ppm. ESI-MS: *m*/*z* (%) = 252 (100) [M + H]$^+$. $C_{12}H_{13}NO_5$ (251.24): calcd. C 57.37, H 5.22, N 5.58; found C 57.67, H 5.48, N 5.28.

(4*R*)-4-[(3,4-Dimethoxyphenyl)(methoxy)methyl]oxazolidin-2-one (21): DDQ (0.422 g, 1.86 mmol) was added to oxazolidinone **13** (0.2 g, 0.844 mmol) in MeOH (2.1 mL) and the solution stirred at 60 °C for 24 h. The dark-red solution was then diluted with dichloromethane (10 mL), washed with a saturated sodium hydrogen carbonate aqueous solution (3 × 10 mL) and brine (15 mL), dried with magnesium sulfate and filtered. The crude product was concentrated and purified by flash chromatography (silica gel, *n*-heptane/ethyl acetate, 7:3) giving **21** in 26% yield (0.059 g) as a pale-yellow oil and as an inseparable 4:6 mixture of *syn*/*anti* diastereoisomers. ESI-MS: *m*/*z* (%) = 290 (100) [M + Na]$^+$. $C_{13}H_{17}NO_5$·0.1H$_2$O (269.08): calcd. C 57.97, H 6.32, N 5.20; found C 57.55, H 6.53, N 4.93.

Methyl (5*S*,10a*R*)-7,8-Dimethoxy-3,10-dioxo-1,5,10,10a-tetrahydro-3*H*-oxazolo[3,4-*b*]isoquinoline-5-carboxylate (22): BF_3·Et$_2$O (11.3 g, 79.6 mmol) was added to a stirred solution of ketone **20** (1.0 g, 3.98 mmol) and methyl dimethoxyacetate (1.07 g, 79.7 mmol) in dichloromethane (42 mL), and the mixture was stirred at reflux for 4 h. After cooling, the solution was diluted with dichloromethane (50 mL), washed with a saturated sodium hydrogen carbonate aqueous solution (100 mL) and brine (20 mL), dried with magnesium sulfate and filtered. The crude product was concentrated and purified by flash chromatography (silica gel, cyclohexane/ethyl acetate, 6:4) giving **22** in 90% yield (1.15 g) as a pale-yellow solid, m.p. 79–80 °C (ethyl acetate), R_f = 0.6 (AcOEt), $[\alpha]_D^{23}$ = –78.0 (dichloromethane, *c* = 0.5). ^{1}H NMR (300 MHz, $CDCl_3$, 23 °C): δ = 7.34 (s, 1 H, 5-H), 6.79 (s, 1 H, 8-H), 5.44 (s, 1 H, C*H*CO$_2$Me), 4.71 (dd, *J* = 5.9, 8.9 Hz, 1 H, OCH$_2$C*H*N), 4.49 (m, 2 H, CHCH_AH$_B$O, CHCH$_A$$H_B$O), 3.74 (s, 3 H, 7-OCH$_3$), 3.50 (s, 3 H, OCH$_3$), 3.68 (s, 3 H, 6-OCH$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 23 °C): δ = 190.8 (C=O), 169.4 (CO$_2$Me), 157.1 (NC=O), 155.2 (Ar*C*), 150.2 (Ar*C*), 131.6 (Ar*C*), 122.9 (Ar*C*), 109.8 (Ar*C*H), 108.8 (Ar*C*H), 65.6 (CH$_2$), 56.9 (CH), 56.6 (OCH$_3$), 56.5 (OCH$_3$), 55.4 (CH), 53.6 (OCH$_3$) ppm. ESI-MS: *m*/*z* (%) = 344 (100) [M + Na]$^+$, 322 (26) [M + H]$^+$. $C_{15}H_{15}NO_7$ (321.28): calcd. C 56.08, H 4.71, N 4.36; found C 55.98, H 4.79, N 4.18.

Methyl (5*S*,10*S*,10a*R*)-10-Hydroxy-7,8-dimethoxy-3-oxo-1,5,10,10a-tetrahydro-3*H*-oxazolo[3,4-*b*]isoquinoline-5-carboxylate (24): A solution of ketone **22** (0.120 g, 0.374 mmol) and $CeCl_3$·7H$_2$O (0.417 g, 1.12 mmol) in tetrahydrofuran/methanol (2.7+0.9 mL) was cooled to –65 °C and treated with solid $NaBH_4$ (0.018 g, 0.411 mmol). After 0.5 h at –60 °C, the reaction mixture was diluted with dichloromethane (10 mL) and quenched with 1 N hydrochloric acid (2 mL). The aqueous layer was extracted twice with dichloromethane (2 × 5 mL). Combined extracts were washed with brine (5 mL), dried with magnesium sulfate and filtered. The crude product was concentrated and purified by flash chromatography (silica gel, *n*-heptane/ethyl acetate, 6:4) giving **24** in 92% yield (0.111 g) as a white solid, m.p. 219–220 °C (dichloromethane), R_f = 0.6 (ethyl acetate), $[\alpha]_D^{23}$ = –75.2 (methanol, *c* = 0.5). ^{1}H NMR [500 MHz, $(CD_3)_2SO$, 23 °C]: δ = 7.15 (s, 1 H, 5-H), 7.00 (s, 1 H, 8-H), 6.10 (d, *J* = 6.9 Hz, 1 H, OH), 5.27 (s, 1 H, C*H*CO$_2$Me), 4.73 (t, *J* = 8.5 Hz, 1 H, CHCH_AH$_B$O), 4.47 (t, *J* = 7.9 Hz, 1 H, C*H*OH), 4.38 (dd, *J* = 6.6, 9.8 Hz, 1 H, CHCH$_A$$H_B$O), 3.93 [dd, *J* = 8.2, 15.4 Hz, 1 H, CH(OH)C*H*N], 3.76 (s, 3 H, 6-OCH$_3$), 3.75 (s, 3 H, OCH$_3$), 3.74 (s, 3 H, 7-OCH$_3$) ppm. ^{13}C NMR [125 MHz,

$(CD_3)_2SO$, 23 °C]: δ = 171.1 (CO_2Me), 157.2 (NC=O), 149.7 (Ar*C*), 148.8 (Ar*C*), 131.6 (Ar*C*), 120.8 (Ar*C*), 110.4 (Ar*C*H), 109.9 (Ar*C*H), 68.9 (CH), 68.9 (CH_2), 56.6 (CH), 56.5 (OCH_3), 56.3 (OCH_3), 55.1 (CH), 53.7 (OCH_3) ppm. ESI-MS: *m*/*z* (%) = 346 (100) $[M + Na]^+$, 306 (12) $[M + H - H_2O]^+$, 246 (9) $[M + H - H_2O - HCO_2Me]^+$, 202 (6) $[M + H - H_2O - HCO_2Me - CO_2]^+$. $C_{15}H_{17}NO_7$ (323.30): calcd. C 55.73, H 5.30, N 4.33; found C 55.58, H 5.31, N 4.18.

(5*S*,10*S*,10a*R*)-10-(*tert*-Butyldimethylsilyloxy)-5-(hydroxymethyl)-7,8-dimethoxy-1,5,10,10a-tetrahydro-3*H*-oxazolo[3,4-*b*]isoquinolin-3-one (25): A solution of alcohol **24** (0.200 g, 0.619 mmol), *tert*-butyldimethylsilyl chloride (0.559 g, 3.72 mmol) and imidazole (0.506 g, 7.43 mmol) in dry dimethylformamide (2 mL) was stirred at room temperature for 12 h. The reaction was quenched by adding a saturated ammonium chloride aqueous solution (10 mL). The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined extracts were dried with magnesium sulfate and filtered. The crude product was concentrated and purified by flash chromatography (silica gel, *n*-heptane/ethyl acetate, 8:2) giving **25** in 89% yield (0.241 g) as a white solid, m.p. 145 °C (*n*-heptane), R_f = 0.8 (ethyl acetate), $[\alpha]_D^{23}$ = –46.4 (dichloromethane, *c* = 0.5). ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ = 7.01 (s, 1 H, 8-H), 6.97 (s, 1 H, 5-H), 5.31 (s, 1 H, C*H*CO_2Me), 4.68 (t, *J* = 8.5 Hz, 1 H, CHC$H_A$$H_B$O), 4.64 (d, *J* = 8.8 Hz, 1 H, C*H*OSi), 4.33 (dd, *J* = 6.6, 8.5 Hz, 1 H, CHC$H_A$$H_B$O), 4.17 (dd, *J* = 8.2, 15.1 Hz, 1 H, CH_2C*H*N), 3.87 (s, 3 H, 6-OCH_3), 3.85 (s, 3 H, 7-OCH_3), 3.77 (s, 3 H, OCH_3), 0.97 [9 H, (CH_3)$_3$CSi], 0.27 (3 H, CH_3Si), 0.18 (3 H, CH_3Si) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C): δ = 170.2 (CO_2Me), 156.9 (NC=O), 149.3 (Ar*C*), 148.7 (Ar*C*), 129.8 (Ar*C*), 120.4 (Ar*C*), 109.4 (Ar*C*H), 108.9 (Ar*C*H), 70.7 (CH), 68.3 (CH_2), 56.2 (OCH_3), 56.0 (OCH_3), 55.6 (CH), 54.8 (CH), 53.0 (OCH_3), 25.8 [(*C*H_3)$_3$CSi], 18.2 (CSi), –3.6 (CH_3Si), –3.8 (CH_3Si) ppm. ESI-MS: *m*/*z* (%) = 460 (100) $[M + Na]^+$, 306 (33) $[M + H - (CH_3)_3C(CH_3)_2SiOH]^+$. $C_{21}H_{31}NO_7Si$ (437.19): calcd. C 57.64, H 7.14, N 3.20; found C 57.46, H 7.07, N 2.92.

(5*S*,10*S*,10a*R*)-10-(*tert*-Butyldimethylsilyloxy)-7,8-dimethoxy-5-[(methoxymethoxy)methyl]-1,5,10,10a-tetrahydro-3*H*-oxazolo[3,4-*b*]-isoquinolin-3-one (26): A 1 M solution of lithium triethylborohydride in tetrahydrofuran (1.83 mL, 1.83 mmol) was added to a solution of ester **25** (0.200 g, 0.457 mmol) in tetrahydrofuran (12 mL). The reaction mixture was allowed to stir for 5 min and then quenched with a saturated ammonium chloride aqueous solution (10 mL) and stirred for an additional 10 min. The aqueous layer was extracted with dichloromethane (4 × 10 mL). The combined organic layers were dried with magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was then engaged in the next step without further purification. At 0 °C, diisopropylethylamine (0.177 g, 1.371 mmol) was added to a solution of the primary alcohol in dichloromethane (2 mL). The reaction mixture was stirred for 5 min and methoxymethyl chloride (0.055 g, 0.686 mmol) was added dropwise. The solution was then stirred for 12 h at room temperature. The reaction was quenched with H_2O (10 mL) and the aqueous layer extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried with magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (silica gel, *n*-heptane/ethyl acetate, 8:2) to give **26** in 86% yield (0.178 g) as a colourless oil, R_f = 0.8 (ethyl acetate), $[\alpha]_D^{23}$ = –51.7 (dichloromethane, *c* = 0.65). ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ = 6.97 (s, 1 H, 5-H), 6.70 (s, 1 H, 8-H), 4.91 (t, *J* = 4.4 Hz, 1 H, C*H*CH_2OCH_2-OCH_3), 4.62 (m, 2 H, C*H*OSi, $CH_2OCH_AH_BOCH_3$), 4.55–4.51 (m, 1 H, $CH_2OCH_AH_BOCH_3$, CHC$H_A$$H_B$O), 4.38 (dd, *J* = 3.8, 8.8 Hz, 1 H, CHC$H_A$$H_B$O), 3.96 (m, 1 H, CH_2C*H*N), 3.90 (m, 1 H, C$H_A$$H_B$$OCH_2OCH_3$, $CH_AH_BOCH_2OCH_3$), 3.87 (s, 3 H, 7-OCH_3), 3.85 (s, 3 H, 6-OCH_3), 3.22 (s, 3 H, CH_2OCH_3), 0.98 [9 H, (CH_3)$_3$CSi], 0.26 (3 H, CH_3Si), 0.18 (3 H, CH_3Si) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C): δ = 157.0 (NC=O), 148.6 (Ar*C*), 148.5 (Ar*C*), 130.2 (Ar*C*), 124.4 (Ar*C*), 109.0 (Ar*C*H), 108.7 (Ar*C*H), 96.3 (CH_2), 70.5 (CH), 70.1 (CH_2), 67.0 (CH_2), 56.5 (OCH_3), 56.3 (OCH_3), 56.0 (CH), 55.8 (OCH_3), 52.6 (CH), 26.0 [(*C*H_3)$_3$CSi], 18.3 (CSi), –3.5 (CH_3Si), –3.5 (CH_3Si) ppm. ESI-MS: *m*/*z* (%) = 476 (38) $[M + Na]^+$, 454 (100) $[M + H]^+$, 422 (41) $[M + H - CH_3OH]^+$. $C_{22}H_{35}NO_7Si$ (453.60): calcd. C 58.25, H 7.78, N 3.09; found C 58.10, H 7.80, N 2.99.

Methyl (5*S*,10*S*,10a*R*)-10-(Ethoxymethoxy)-7,8-dimethoxy-3-oxo-1,5,10,10a-tetrahydro-3*H*-oxazolo[3,4-*b*]isoquinoline-5-carboxylate (27): Ethoxymethyl chloride (0.117 g, 1.24 mmol) was added to a solution of **24** (0.200 g, 0.619 mmol) and diisopropylethylamine (0.798 g, 6.19 mmol) in dichloromethane (4 mL) and the reaction mixture was heated at 60 °C for 18 h. After cooling to room temperature, the solution was diluted with dichloromethane (10 mL), washed with water (10 mL) and brine (10 mL), dried with magnesium sulfate and filtered. After evaporation, the crude residue was purified by flash chromatography (silica gel, *n*-heptane/ethyl acetate, 8:2) to give **27** in 91% yield (0.215 g) as a colourless oil, R_f = 0.8 (ethyl acetate), $[\alpha]_D^{23}$ = –10.4 (dichloromethane, *c* = 1). ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ = 7.00 (s, 1 H, 8-H), 6.97 (s, 1 H, 5-H), 5.31 (s, 1 H, C*H*CO_2Me), 4.95 (d, *J* = 7.3 Hz, 1 H, OC$H_A$$H_B$O), 4.90 (d, *J* = 7.2 Hz, 1 H, OC$H_A$$H_B$O), 4.76 (dd, *J* = 7.2, 9.1 Hz, 1 H, CHC$H_A$$H_B$O), 4.47 (m, 2 H, C*H*$OCH_2OC_2H_5$, CHC$H_A$$H_B$O), 4.17 (m, 1 H, CH_2C*H*N), 3.87 (s, 3 H, 7-OCH_3), 3.86 (s, 3 H, 6-OCH_3), 3.76 (s, 3 H, OCH_3), 3.72 (m, 1 H, OCH_2O-C$H_A$$H_B$$CH_3$), 3.60 (m, 1 H, $OCH_2OCH_AH_BCH_3$), 1.25 (t, *J* = 7.1 Hz, 3 H, $OCH_2OCH_2CH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C): δ = 170.4 (CO_2Me), 157.3 (NC=O), 149.8 (Ar*C*), 149.4 (Ar*C*), 127.3 (Ar*C*), 121.5 (Ar*C*), 109.8 (Ar*C*H), 109.7 (Ar*C*H), 96.7 (CH_2), 78.2 (CH), 69.3 (CH_2), 64.8 (CH_2), 56.5 (OCH_3), 56.3 (OCH_3), 54.9 (CH), 54.8 (CH), 53.3 (OCH_3), 15.4 (CH_3) ppm. ESI-MS: *m*/*z* (%) = 404 (100) $[M + Na]^+$, 306 (31) $[M + H - C_2H_5O$-$CH_2OH]^+$, 246 (30) $[M + H - C_2H_5OCH_2OH - HCO_2Me]^+$, 202 (22) $[M + H - C_2H_5OCH_2OH - HCO_2Me - CO_2]^+$. $C_{18}H_{23}NO_8$ (381.38): calcd. C 56.69, H 6.08, N 3.67; found C 56.38, H 6.15, N 3.48.

10-(Ethoxymethoxy)-5-[(ethoxymethoxy)methyl]-7,8-dimethoxy-1,5,10,10a-tetrahydro-3*H*-oxazolo[3,4-*b*]isoquinolin-3-one (28): A 1 M solution of lithium triethylborohydride in tetrahydrofuran (1.05 mL, 1.05 mmol) was added to a solution of ester **27** (0.100 g, 0.262 mmol) in tetrahydrofuran (7.5 mL). The reaction mixture was allowed to stir for 5 min and then quenched with a saturated ammonium chloride aqueous solution (5 mL) and stirred for an additional 10 min. The aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried with magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was then engaged in a protection step without further purification. At 0 °C, diisopropylethylamine (0.110 g, 0.850 mmol) was added to a solution of the primary alcohol in dichloromethane (2 mL). The reaction mixture was stirred for 5 min and ethoxymethyl chloride (0.040 g, 0.425 mmol) was added dropwise. The solution was then stirred for 12 h at room temperature. The reaction was quenched with H_2O (10 mL) and the aqueous layer extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried with magnesium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (silica gel, *n*-heptane/ethyl acetate, 8:2) to give **28** in 88% yield (0.095 g) as a colourless oil, R_f = 0.8 (ethyl acetate), $[\alpha]_D^{23}$ = –27.1 (dichloromethane, *c* = 0.19). ^{1}H

NMR (500 MHz, $CDCl_3$, 23 °C): δ = 6.95 (s, 1 H, 5-H), 6.67 (s, 1 H, 8-H), 4.95 (d, J = 7.3 Hz, 1 H, OCH_AH$_B$O), 4.90 (d, J = 7.2 Hz, 1 H, OCH$_A H_B$O), 4.89 (m, 1 H, CHCH$_2$OCH$_2$OC$_2$H$_5$), 4.65 (d, J = 6.6 Hz, 1 H, OC$H_{A'}$H$_{B'}$O), 4.60 (m, 1 H, CHCH_AH$_B$O), 4.56 (d, J = 6.6 Hz, 1 H, OCH$_{A'} H_{B'}$O), 4.52 (m, 1 H, CHCH$_A H_B$O), 4.49 (m, 1 H, CHOCH$_2$OC$_2$H$_5$), 4.15 (m, 1 H, CH$_2$CHN), 3.93–3.87 (m, 2 H, CH_AH$_B$OCH$_2$OC$_2$H$_5$, CH$_A H_B$OCH$_2$OC$_2$H$_5$), 3.86 (s, 6 H, 6-OCH$_3$, 7-OCH$_3$), 3.74–3.68 (m, 1 H, OCH$_2$OCH_AH$_B$CH$_3$), 3.64–3.58 (m, 1 H, OCH$_2$OCH$_A H_B$CH$_3$), 3.46–3.36 (m, 1 H, OCH$_2$OC$H_{A'}$H$_{B'}$CH$_3$, OCH$_2$OCH$_{A'} H_{B'}$CH$_3$), 1.24 (t, J = 7.0 Hz, 3 H, OCH$_2$OCH$_2$CH_3), 1.12 (t, J = 6.9 Hz, 3 H, OCH$_2$OCH$_2$CH'_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C): δ = 156.9 (NC=O), 148.9 (ArC), 148.7 (ArC), 127.2 (ArC), 125.4 (ArC), 109.4 (ArCH), 108.7 (ArCH), 96.3 (CH$_2$), 94.9 (CH$_2$), 77.9 (CH), 69.9 (CH$_2$), 67.9 (CH$_2$), 64.3 (CH$_2$), 63.5 (CH$_2$), 56.1 (OCH$_3$), 56.0 (OCH$_3$), 54.3 (CH), 52.0 (CH), 15.1 (2CH$_3$) ppm. ESI-MS: m/z (%) = 434 (100) [M + Na]$^+$, 412 [M + H]$^+$, 366 (11) [M + H – C_2H_5OH]$^+$. $C_{20}H_{29}NO_8$ (411.45): calcd. C 58.38, H 7.10, N 3.40; found C 58.19, H 7.16, N 3.23.

(1*S*,3*R*,4*S*)-3-(Hydroxymethyl)-6,7-dimethoxy-1-[(methoxymethoxy)methyl]-1,2,3,4-tetrahydroisoquinolin-4-ol (29): A 2 N solution of sodium hydroxide (0.9 mL) was added to a solution of **26** (0.100 g, 0.221 mmol) in ethanol (1.8 mL). This solution was degassed by bubbling through a stream of $N_{2(g)}$ and then heated for 48 h at 90 °C. After cooling to room temperature, the solution was diluted with dichloromethane (6 mL) and brine (3 mL) was added. After separation of the organic layer, the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined extracts were dried with sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was recrystallized from dichloromethane giving **29** in 65% yield (0.045 g) as a white solid, m.p. 209–210 °C (dichloromethane), R_f = 0.1 (dichloromethane/methanol, 10:1), $[\alpha]_D^{23}$ = –17.8 (dichloromethane/methanol, 8:2, c = 0.5). ^{1}H NMR [500 MHz, $CDCl_3$/MeOD (10:1), 23 °C]: δ = 6.97 (s, 1 H, 5-H), 6.47 (s, 1 H, 8-H), 4.61 (d, J = 6.6 Hz, 2 H, OCH_AH$_B$O), 4.58 (d, J = 6.6 Hz, 2 H, OCH$_A H_B$O), 4.28 (d, J = 9.5 Hz, 1 H, CHOH), 4.01 (dd, J = 3.8, 9.4 Hz, 1 H, CHCH$_2$OCH$_2$OCH$_3$), 3.83 (dd, J = 4.1, 11.0 Hz, 1 H, CHCH_AH$_B$O), 3.76 (s, 3 H, 6-OCH$_3$) 3.74 (s, 3 H, 7-OCH$_3$), 3.71 (br. s, 3 H, NH, 2OH), 3.69 (m, 1 H, CH_AH$_B$OCH$_2$OCH$_3$), 3.58 (dd, J = 3.7, 11.1 Hz, 1 H, CH$_A H_B$OCH$_2$OC$_2$H$_5$), 3.49 (dd, J = 7.6, 11 Hz, 1 H, CHCH$_A H_B$O), 3.29 (s, 3 H, CHCH$_2$OCH$_2$OCH_3), 2.96 (m, 1 H, CH$_2$CHN) ppm. ^{13}C NMR [125 MHz, $CDCl_3$/MeOD (10:1), 23 °C]: δ = 148.4 (ArC), 148.1 (ArC), 130.5 (ArC), 125.9 (ArC), 110.0 (ArCH), 108.9 (ArCH), 96.6 (CH$_2$), 69.4 (CH$_2$), 67.4 (CH), 63.1 (CH$_2$), 55.8 (OCH$_3$), 55.7 (OCH$_3$), 55.4 (OCH$_3$), 55.3 (CH), 54.2 (CH) ppm. ESI-MS: m/z (%) = 314 (100) [M + H]$^+$, 296 (85) [M + H – H_2O]$^+$, 264 (35) [M + H – H_2O – CH_3OH]$^+$. $C_{15}H_{23}NO_6$·CH_2Cl_2 (397.28): calcd. C 48.25, H 6.33, N 3.52; found C 47.86, H 6.25, N 3.69.

{(1*S*,3*R*,4*S*)-4-(Ethoxymethoxy)-1-[(ethoxymethoxy)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-3-yl}methanol (30): A 2 N solution of sodium hydroxide (1 mL) was added to a solution of **28** (0.200 g, 0.486 mmol) in ethanol (4 mL). This solution was degassed by bubbling through a stream of $N_{2(g)}$ and then heated for 48 h at 90 °C. After cooling to room temperature, the solution was diluted with dichloromethane (10 mL) and brine (5 mL) was added. After separation of the organic layer, the aqueous layer was extracted with dichloromethane (3 × 5 mL). Combined extracts were dried with sodium sulfate, filtered, concentrated under reduced pressure and purified by flash chromatography (silica gel, dichloromethane/methanol, 10:1) giving **30** in 79% yield (0.142 g) as a pale-yellow solid, m.p. 68 °C (*n*-heptane/dichloromethane), R_f = 0.6 (dichloromethane/methanol, 10:1), $[\alpha]_D^{23}$ = +35.4 (dichloromethane, c = 1). ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ = 6.86 (s, 1 H, 5-H), 6.62 (s, 1 H, 8-H), 4.81 (s, 2 H, OCH_AH$_B$O), 4.72 (d, J = 6.6 Hz, 1 H, OC$H_{A'}$H$_{B'}$O), 4.68 (d, J = 6.6 Hz, 1 H, OCH$_{A'} H_{B'}$O), 4.44 (d, J = 5.4 Hz, 1 H, CHOCH$_2$OC$_2$H$_5$), 4.09 (dd, J = 3.8, 7.6 Hz, 1 H, CHCH$_2$OCH$_2$OC$_2$H$_5$), 3.85 (s, 3 H, 7-OCH$_3$) 3.84 (s, 3 H, 6-OCH$_3$), 3.81 (m, 1 H, CH_AH$_B$OCH$_2$OC$_2$H$_5$), 3.76 (dd, J = 4.0, 10.2 Hz, 1 H, CH$_A H_B$OCH$_2$OC$_2$H$_5$), 3.72–3.67 (m, 2 H, OCH$_2$OCH_AH$_B$CH$_3$, OCH$_2$OCH$_A H_B$CH$_3$), 3.65 (m, 1 H, CHCH_AH$_B$O), 3.60–3.55 (m, 2 H, OCH$_2$OC$H_{A'}$H$_{B'}$CH$_3$, OCH$_2$OCH$_{A'} H_{B'}$CH$_3$), 3.52 (m, 1 H, CHCH$_A H_B$O), 3.31 (m, 1 H, CH$_2$CHN), 2.68 (br. s, 2 H, NH, OH), 1.24 (t, J = 6.9 Hz, 3 H, OCH$_2$OCH$_2$CH_3), 1.19 (t, J = 7.1 Hz, 3 H, OCH$_2$OCH$_2$CH'_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C): δ = 148.8 (ArC), 148.1 (ArC), 128.2 (ArC), 127.1 (ArC), 112.0 (ArCH), 108.9 (ArCH), 95.4 (CH$_2$), 94.7 (CH$_2$), 73.2 (CH), 70.9 (CH$_2$), 64.0 (CH$_2$), 63.6 (CH$_2$), 62.0 (CH$_2$), 56.0 (OCH$_3$), 55.9 (OCH$_3$), 55.8 (CH), 53.0 (CH), 15.2 (2CH$_3$) ppm. ESI-MS: m/z (%) = 408 (4) [M + Na]$^+$, 386 (100) [M + H]$^+$, 310 (70) [M + H – $C_2H_5OCH_2OH$]$^+$, 264 (27) [M + H – C_2H_5O-CH_2OH – C_2H_5OH]$^+$, 202 (14) [M + H – $C_2H_5OCH_2OH$ – C_2H_5O-CH_2OH]$^+$. $C_{19}H_{31}NO_7$·0.3H_2O (390.86): calcd. C 58.33, H 8.08, N 3.58; found C 58.34, H 8.05, N 3.44.

Methyl (5*S*,10*R*,10a*R*)-7,8-Dimethoxy-10-(2-methoxy-2-oxoethylthio)-3-oxo-1,5,10,10a-tetrahydro-3*H*-oxazolo[3,4-*b*]isoquinoline-5-carboxylate (31a) and Methyl (5*S*,10*S*,10a*R*)-7,8-Dimethoxy-10-(2-methoxy-2-oxoethylthio)-3-oxo-1,5,10,10a-tetrahydro-3*H*-oxazolo-[3,4-*b*]isoquinoline-5-carboxylate (31b): A solution of methyl thioglycolate (0.036 g, 0.341 mmol) in dry toluene (5.16 mL) was added to a solution of trifluoroacetic acid (5.16 mL) containing the benzylic alcohol **24** (0.100 g, 0.310 mmol) at 0 °C and stirred for 1 h. The reaction mixture was diluted with dichloromethane (10 mL) and washed with a saturated sodium carbonate aqueous solution (5 mL) and brine (4 mL). The organic layer was dried with magnesium sulfate and filtered. The crude product was concentrated and purified by flash chromatography (silica gel, *n*-heptane/ethyl acetate, 8:2) giving **31a** (0.090 g, 71%) and **31b** (0.010 g, 8%) as white solids in 92% overall yield (0.117 g) and as a 9:1 mixture of diastereoisomers **31a/31b**. Data for compound **31a**: m.p. 157–158 °C (dichloromethane), R_f = 0.6 (ethyl acetate), $[\alpha]_D^{23}$ = –147.0 (dichloromethane, c = 0.6). ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ = 7.03 (s, 1 H, 8-H), 6.84 (s, 1 H, 5-H), 5.29 (s, 1 H, CHCO$_2$Me), 4.83 (m, 1 H, CHCH_AH$_B$O), 4.67–4.59 (m, 2 H, CHCH$_A H_B$O, CH$_2$CHN), 4.17 (br. s, 1 H, CHSCH$_2$CO$_2$Me), 3.87 (s, 6 H, 7-OCH$_3$, 6-OCH$_3$), 3.77 (s, 3 H, OCH$_3$), 3.67 (s, 3 H, OCH$_3$), 2.98 (s, 2 H, SCH$_2$CO$_2$Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 23 °C): δ = 170.6 (CO$_2$Me), 170.2 (CO$_2$Me), 157.1 (NC=O), 149.3 (2ArC), 125.2 (ArC), 120.9 (ArC), 112.6 (ArCH), 109.3 (ArCH), 66.8 (CH$_2$), 56.1 (OCH$_3$), 56.0 (OCH$_3$), 54.7 (CH), 53.6 (CH), 53.0 (OCH$_3$), 52.7 (OCH$_3$), 45.8 (CH), 31.8 (CH$_2$) ppm. ESI-MS: m/z (%) = 434 (100) [M + Na]$^+$, 306 (59) [M + H – HSCH$_2$CO$_2$Me]$^+$, 246 (79) [M + H – HSCH$_2$CO$_2$Me – HCO$_2$Me]$^+$, 202 (66) [M + H – HSCH$_2$CO$_2$Me – HCO$_2$Me – CO$_2$]$^+$. $C_{18}H_{21}NO_8S$ (411.43): calcd. C 52.55, H 5.14, N 3.40; found C 52.46, H 5.23, N 3.39. Data for compound **31b**: m.p. 64–65 °C (tetrahydrofuran), R_f = 0.7 (ethyl acetate), $[\alpha]_D^{23}$ = –105.7 (dichloromethane, c = 0.4). ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ = 7.37 (s, 1 H, 5-H), 6.99 (s, 1 H, 8-H), 5.38 (s, 1 H, CHCO$_2$Me), 4.77 (t, J = 8.3 Hz, 1 H, CHCH_AH$_B$O), 4.47 (m, 1 H, CH$_2$CHN), 4.47 (dd, J = 5.3, 8.8 Hz, 1 H, CHCH$_A H_B$O), 3.90 (s, 6 H, 7-OCH$_3$, 6-OCH$_3$), 3.87 (s, 1 H, CHSCH$_2$CO$_2$Me), 3.80 (s, 3 H, OCH$_3$), 3.65 (s, 3 H, OCH$_3$), 3.17 (d, J = 15.1 Hz, 1 H, SCH$_2$CO$_2$Me), 3.13 (d, J = 15.3 Hz, 1 H, SCH$_2$CO$_2$Me) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C): δ = 170.5 (CO$_2$Me), 170.3 (CO$_2$Me), 156.6 (NC=O), 149.6 (ArC), 149.0

(Ar*C*), 124.2 (Ar*C*), 123.2 (Ar*C*), 111.1 (Ar*C*H), 110.1 (Ar*C*H), 66.8 (CH_2), 56.3 (OCH_3), 56.2 (OCH_3), 54.8 (CH), 53.5 (CH), 53.1 (OCH_3), 52.8 (OCH_3), 46.9 (CH), 30.6 (CH_2) ppm. ESI-MS: *m/z* (%) = 434 (100) $[M + Na]^+$, 306 (30) $[M + H - HSCH_2CO_2Me]^+$, 246 (35) $[M + H - HSCH_2CO_2Me - HCO_2Me]^+$, 202 (26) $[M + H - HSCH_2CO_2Me - HCO_2Me - CO_2]^+$. $C_{18}H_{21}NO_8S$ (411.43): calcd. C 52.55, H 5.14, N 3.40; found C 52.42, H 5.13, N 3.07.

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[1] a) K. W. Bentley, *The isoquinoline Alkaloids*, Harvard Academic Publisher, Amsterdam, **1998**; b) K. W. Bentley, *Nat. Prod. Rep.* **2003**, *20*, 342–365; c) K. W. Bentley, *Nat. Prod. Rep.* **2004**, *21*, 395–424; d) K. W. Bentley, *Nat. Prod. Rep.* **2005**, *22*, 249–268; e) K. W. Bentley, *Nat. Prod. Rep.* **2006**, *23*, 444–463.

[2] a) V. A. Facundo, S. M. De Morais, R. Braz Filho, I. J. de A. Matos, R. T. Souza, *Rev. Bras. Farm.* **1997**, *78*, 57–59; b) V. A. Facundo, S. M. De Morais, M. I. L. Machado, F. J. de A. Matos, L. C. M. Da frota, *J. Essent. Oil Res.* **1999**, *11*, 426–428; c) S. M. De Morais, V. A. Facundo, R. Braz Filho, *J. Essent. Oil Res.* **2002**, *14*, 274–275; d) S. A. Ross, G. N. N. Sultana, C. L. Burandt, M. A. ElSohly, J. P. J. Marais, D. Ferreira, *J. Nat. Prod.* **2004**, *67*, 88–90; e) S. A. Ross, M. A. Al-Azeib, K. S. Krishnaveni, F. R. Fronczek, C. L. Burandt, *J. Nat. Prod.* **2005**, *68*, 1297–1299.

[3] For a review, see: J. Scott, R. M. Williams, *Chem. Rev.* **2002**, *102*, 1669–1730.

[4] a) K. L. Rinehart, T. G. Holt, N. L. Fregeau, T. J. Perun Jr, D. S. Seigler, G. R. Wilson, L. S. Shield, *Pure Appl. Chem.* **1990**, *62*, 1277–1280; b) K. L. Rinehart, T. G. Holt, N. L. Fregeau, P. A. Keifer, F. Sun, H. Li, D. G. Martin, *J. Org. Chem.* **1990**, *55*, 4512–4515; c) A. E. Wright, D. A. Forleo, G. P. Gunawardana, S. P. Gunasekera, F. E. Koehn, O. J. McConnel, *J. Org. Chem.* **1990**, *55*, 4508–4512; d) R. Sakai, K. L. Rinehart, Y. Guan, A. H.-J. Wang, *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 11456–11460; e) R. Sakai, E. Jares-Erijaman, I. Manzanares, M. V. Elipe, K. L. Rinehart, *J. Am. Chem. Soc.* **1996**, *118*, 9017–9023; f) K. Suwanboriux, K. Chapurant, S. Amnuoypol, S. Pummangura, A. Kubo, N. Saito, *J. Nat. Prod.* **2002**, *65*, 935–937.

[5] a) L. Zelek, A. Yovine, B. Etienne, J. Jimeno, A. Taama, C. Martin, M. Spielmann, E. Cvitkovic, J. L. Misset, *Ecteinascidin-743 in taxane/Antracycline pretreated advanced/metastatic breast cancer patients: preliminary results with the 24 h continuous infusion Q3 week schedule*, presented at the American Society of Clinical Oncology, 36th Annual Meeting, New Orleans, 20–23 May, **2000**, Abstract number 592; b) S. Delaloge, A. Yovine, A. Taama, P. Cottu, M. Riofrio, E. Raymond, E. Brain, M. Marty, J. Jimeno, E. Cvitkovic, J. L. Misset, *Preliminary evidence of activity of Ecteinascidin-743 (ET-743) in heavily pretreated patients with bone and soft tissue sarcomas*, presented at the American Society of Clinical Oncology, 36th Annual Meeting, New Orleans, 20–23 May, **2000**, Abstract number 2181; c) A. Le Cesne, I. Judson, J. Y. Blay, J. Radford, A. van Oosterom, P. Lorigan, E. Rodenhuis, E. Donato Di Paoula, M. Van Glabbeke, J. Jimeno, J. Verweij, *Phase II of ET-743 in advance soft tissue sarcoma in adult: a STBSG-EORTC trial*, presented at the American Society of Clinical Oncology, 36th Annual Meeting, New Orleans, 20–23 May, **2000**, Abstract number 2182; d) E. Izbicka, R. Lawrence, E. Raymond, G. Eckhardt, G. Faircloth, J. Jimeno, G. Clark, D. D. Von Hoff, *Annals Oncol.* **1998**, *9*, 981–987; e) G. Valoti, M. I. Nicoletti, A. Pellegrino, J. Jimeno, H. Hendriks, M. D'Incalci, G. Faircloth, R. Giavazzi, *Clin. Cancer Res.* **1998**, *4*, 1977–1983; f) D. P. Ryan, J. G. Supko, J. P. Eder, M. V. Seiden, G. Demetri, T. J. Lynch, A. J. Fischman, J. Davis, J. Jimeno, J. W. Clark, *Clin. Cancer Res.* **2001**, *7*, 231–242; g) N. Takashi, W. Li, D. Banerjee, Y. Guan, Y. Wada-Takahashi, M. F. Brennan, T. C. Chou, K. W. Scotto, J. R. Bertino, *Cancer Res.* **2002**, *62*, 6909–6915; h) G. J. Aune, T. Furuta, Y. Pommier, *Anti-Cancer Drugs* **2002**, *13*, 545–555; i) J. Y. Blay, A. Le Cesne, J. Verweij, M. Scurr, C. Seynaeve, S. Bonvalot, P. Hogendoorn, J. Jimeno, V. Evrard, M. van Glabbeke, I. Judson, *Eur. J. Cancer* **2004**, *40*, 1327–1331; j) L. Zelek, A. Yovine, E. Brain, F. Turpin, A. Taamma, M. Riofrio, M. Spielman, J. Jimeno, J. L. Misset, *Br. J. Cancer* **2006**, *94*, 1610.

[6] a) I. Jardine, *Anticancer Aganents Based on Natural Products Models*, Academic Press, New York, **1980**, vol. 3, pp. 319–351; b) H. F. Stähelin, A. Von Wartburg, *Cancer Res.* **1991**, *51*, 5–15; c) R. S. Ward, *Synthesis* **1992**, 719–730; d) C. Canel, R. M. Moraes, F. E. Dayan, D. Ferreira, *Phytochemistry* **2000**, *54*, 115–120.

[7] a) K. Tomioka, Y. Kubota, K. Koga, *J. Chem. Soc. Chem. Commun.* **1989**, 1622–1624; b) K. Tomioka, Y. Kubota, K. Koga, *Tetrahedron* **1993**, *49*, 1891–1900; c) J.-O. Bosmans, J. Van der Eycken, M. Vandewalle, *Tetrahedron Lett.* **1989**, *30*, 3877–3880; d) H. L. Pearce, N. J. Bach, T. L. Cramer, *Tetrahedron Lett.* **1989**, *30*, 907–910; e) E. Marcantoni, M. Petrini, R. Profeta, *Tetrahedron Lett.* **2004**, *45*, 2133–2136.

[8] a) S. Aubry, S. Pellet-Rostaing, B. Fenet, M. Lemaire, *Tetrahedron Lett.* **2006**, *47*, 1319–1323; b) S. Aubry, J. Fournier dit Chabert, S. Pellet-Rostaing, S. Ducki, M. Lemaire, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2598–2602.

[9] a) D. Walker, J. D. Hiebert, *Chem. Rev.* **1967**, *67*, 153–195; b) A. B. Turner, *Synthetic Reagents* (Ed.: J. S. Pizey), Wiley, New York, **1977**, vol. 3, pp. 193–225.

[10] a) H. D. Becker, *J. Org. Chem.* **1965**, *30*, 982–989; b) H. D. Becker, *J. Org. Chem.* **1969**, *34*, 1203–1210.

[11] J. W. A. Findlay, A. B. Turner, *J. Chem. Soc. C* **1971**, 23–29.

[12] F. D. Ramdayal, D. J. Kiemle, R. T. Lalonde, *J. Org. Chem.* **1999**, *64*, 4607–4609.

[13] a) Y. Oikawa, T. Yoshioka, K. Mohri, O. Yonemitsu, *Heterocycles* **1979**, *12*, 1457–1462; b) Y. Oikawa, O. Yonemitsu, *J. Org. Chem.* **1977**, *42*, 1213–1216.

[14] a) K. Narayanan, J. M. Cook, *Heterocycles* **1991**, *32*, 2005–2014; b) M. Cain, R. Mantei, J. M. Cook, *J. Org. Chem.* **1982**, *47*, 4933–4936; c) T. J. Hagen, K. Narayanan, J. Names, J. M. Cook, *J. Org. Chem.* **1989**, *54*, 2170–2178.

[15] a) P. P. Fu, R. G. Harvey, *Chem. Rev.* **1978**, *78*, 317–361; b) P. P. Fu, C. Cortez, K. B. Sukumaran, R. G. Harvey, *J. Org. Chem.* **1979**, *44*, 4265–4271; c) H. Lee, R. G. Harvey, *J. Org. Chem.* **1983**, *48*, 749–751; d) H. Lee, R. G. Harvey, *J. Org. Chem.* **1988**, *53*, 4587–4589; e) R. E. Lehr, P. L. Kole, K. D. Tschappat, *Tetrahedron Lett.* **1986**, *27*, 1649–1652.

[16] K. C. Rice, W. C. Ripka, J. Reden, A. Brossi, *J. Org. Chem.* **1980**, *45*, 601–607.

[17] M. Bouquet, A. Guy, M. Lemaire, J.-P. Guetté, *C. R. Acad. Sci., Ser. IIc: Chim.* **1984**, *299*, 1389–1390.

[18] M. Bouquet, A. Guy, M. Lemaire, J.-P. Guetté, *Synth. Commun.* **1985**, *15*, 1153–1157.

[19] a) M. Lemaire, A. Guy, D. Imbert, J.-P. Guetté, *J. Chem. Soc. Chem. Commun.* **1986**, 741–742; b) A. Guy, A. Lemor, D. Imbert, M. Lemaire, *Tetrahedron Lett.* **1989**, *30*, 327–330; c) M. Lemaire, A. Guy, D. Imbert, J.-P. Guetté, *New J. Chem.* **1991**, *15*, 379–384.

[20] a) A. Guy, A. Lemor, J. Doussot, M. Lemaire, *Synthesis* **1988**, 900–902; b) A. Guy, J. Doussot, M. Lemaire, *Synthesis* **1991**, 460–462.

[21] a) M. Lemaire, J. Doussot, A. Guy, *Chem. Lett.* **1988**, 1581–1584; b) A. Guy, J. Doussot, J.-P. Guetté, R. Garreau, M. Lemaire, *Synlett* **1992**, 821–822.

[22] a) For a review, see: E. D. Cox, J. M. Cook, *Chem. Rev.* **1995**, *95*, 1797; b) S. Aubry, S. Pellet-Rostaing, R. Faure, M. Lemaire, *J. Heterocycl. Chem.* **2006**, *43*, 139–148.
[23] A. Ohki, T. Nishiguchi, K. Fukuzumi, *Tetrahedron* **1979**, *35*, 1737–1743.
[24] The chemical shift of the benzylic carbon was determined from the ^{13}C NMR spectrum of a 80:20 mixture of *trans*-**14**/*cis*-**14** recorded on a Bruker DPX-500 spectrometer (^1H: 500 MHz; ^{13}C: 100 MHz).
[25] X-ray crystal structure analysis of *syn*-**19**: Colourless crystal from CH_2Cl_2; size [mm]: $0.80 \times 0.20 \times 0.05$; formula $C_{20}H_{19}NO_7$, M = 385.37; data set collected with a Nonius-KappaCCD diffractometer; orthorhombic; space group: $P2_12_12_1$; a = 7.2720(3), b = 16.0890(9), c = 16.341(1) Å; V = 1911.9(2) Å^3; Z = 4; ρ = 1.339 g cm^{-3}; $2\theta_{max}$ = 55.8°; λ(Mo-K_α) = 0.71073 Å; T = 291 K; 4340 measured reflections; 2736 [$I > 2\sigma(I)$]; μ(Mo-K_α) = 0.102 mm^{-1}; T_{min} = 0.923, T_{max} = 0.995; SHELXTL; 253 parameters; hydrogen atoms calculated and refined as riding atoms; R = 0.053, wR = 0.137; refinement of F^2 against all reflections; $\Delta\rho_{max}$ = 0.28, $\Delta\rho_{min}$ = –0.22 e Å^{-3}. CCDC-628764 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[26] a) A. R. Katritzky, J. Cobo-Domingo, B. Yang, P. J. Steel, *Tetrahedron: Asymmetry* **1999**, *10*, 255–263; b) O. Koepler, S. Laschat, A. Baro, P. Fischer, B. Miehlich, M. Hotfilder, C. le Viseur, *Eur. J. Org. Chem.* **2004**, 3611–3622.
[27] J.-L. Luche, *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.
[28] X-ray crystal structure analysis of **26**: Colourless crystal from CH_2Cl_2; size [mm]: $0.50 \times 0.40 \times 0.25$; formula $C_{15}H_{17}NO_7$, M = 323.30; data set collected with a Nonius-KappaCCD diffractometer; orthorhombic; space group: $P2_12_12_1$; a = 7.7550(2), b = 11.9840(5), c = 16.0200(7) Å; V = 1488.8(1) Å^3; Z = 4; ρ = 1.442 g cm^{-3}; $2\theta_{max}$ = 55.8°; λ(Mo-K_α) = 0.71073 Å; T = 291 K; 3432 measured reflections; 2970 [$I > 2\sigma(I)$]; μ(Mo-K_α) = 0.116 mm^{-1}; T_{min} = 0.945, T_{max} = 0.971; SHELXTL; 209 parameters; alcoholic hydrogen atom clearly evidenced on Fourier difference map; all other hydrogen atoms calculated and refined as riding atoms; R = 0.044, wR = 0.115; refinement of F^2 against all reflections; $\Delta\rho_{max}$ = 0.23, $\Delta\rho_{min}$ = –0.32 e Å^{-3}. CCDC-628658 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[29] X.-M. Zhou, K. J.-H. Lee, J. Cheng, S.-S. Wu, H.-X. Chen, X. Guo, Y.-C. Cheng, K.-H. Lee, *J. Med. Chem.* **1994**, *37*, 287–292.
[30] H. C. Brown, S. Krishnamurthy, *J. Am. Chem. Soc.* **1973**, *95*, 1669–1671.
[31] a) M. Katoh, H. Inoue, A. Suzuki, T. Honda, *Synlett* **2005**, 2820–2822; b) M. Katoh, H. Inoue, A. Suzuki, T. Honda, *Heterocycles* **2007**, *72*, 497.
[32] M. De Paolis, J. Blankenstein, M. Bois-Choussy, J. Zhu, *Org. Lett.* **2002**, *4*, 1235–1238.
[33] a) T. Hashiyama, H. Inoue, M. Takeda, K. Aoe, K. Kotera, *J. Chem. Soc. Perkin Trans. 1* **1985**, 421–427; b) H. D. H. Showalter, R. T. Winters, A. D. Sercel, A. Michel, *Tetrahedron Lett.* **1991**, *32*, 2849–2852; c) A. Elomri, S. Mitaku, S. Michel, A. L. Skaltsounis, F. Tillequin, M. Koch, A. Pierre, N. Guilbaud, S. Léonce, L. Kraus-Berthier, Y. Rolland, G. Atassi, *J. Med. Chem.* **1996**, *39*, 4762–4766.
[34] X-ray crystal structure analysis of **33a**: Colourless crystal from CH_2Cl_2; size [mm]: $0.60 \times 0.50 \times 0.40$; formula $C_{18}H_{21}NO_8S$, M = 411.42; data set collected with a Nonius-KappaCCD diffractometer; monoclinic; space group: $P2_1$; a = 4.8190(1), b = 16.8130(7), c = 11.8460(5) Å; β = 96.707(2)°; V = 953.22(6) Å^3; Z = 2; ρ = 1.433 g cm^{-3}; $2\theta_{max}$ = 55.6°; λ(Mo-K_α) = 0.71073 Å; T = 294 K; 3747 measured reflections; 3597 [$I > 2\sigma(I)$]; μ(Mo-K_α) = 0.216 mm^{-1}; T_{min} = 0.881, T_{max} = 0.918; SHELXTL; 252 parameters; hydrogen atoms calculated and refined as riding atoms; R = 0.030, wR = 0.085; refinement of F^2 against all reflections; $\Delta\rho_{max}$ = 0.19, $\Delta\rho_{min}$ = –0.21 e Å^{-3}. CCDC-641202 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[35] a) E. J. Corey, D. Y. Gin, R. S. Kania, *J. Am. Chem. Soc.* **1996**, *118*, 9202–9203; b) E. J. Martinez, E. J. Corey, *Org. Lett.* **2000**, *2*, 993–996; c) A. Endo, T. Kann, T. Fukuyama, *Synlett* **1999**, 1103–1105; d) A. Endo, A. Yanagisawa, M. Abe, S. Tohma, T. Kan, T. Fukuyama, *J. Am. Chem. Soc.* **2002**, *124*, 6552–6554; e) C. Cuevas, M. Pérez, M. J. Martín, J. L. Chicharro, C. Fernández-Rivas, M. Flores, A. Francesch, P. Gallego, M. Zarzuelo, F. de la Calle, J. García, C. Polanco, I. Rodríguez, I. Manzanares, *Org. Lett.* **2000**, *2*, 2545–2548; f) R. Menchaca, V. Martínez, A. Rodríguez, N. Rodríguez, M. Flores, P. Gallego, I. Manzanares, C. Cuevas, *J. Org. Chem.* **2003**, *68*, 8859–8866; g) N. Saito, K. Tashiro, Y. Maru, K. Yamaguchi, A. Kubo, *J. Chem. Soc. Perkin Trans. 1* **1997**, 53–69; h) N. Saito, H. Kamayachi, M. Tachi, A. Kubo, *Heterocycles* **1999**, *51*, 9–12; i) N. Saito, M. Tachi, R. Seki, H. Kamayachi, A. Kubo, *Chem. Pharm. Bull.* **2000**, *48*, 1549–1557; j) N. Saito, R. Seki, N. Kameyama, R. Sugimoto, A. Kubo, *Chem. Pharm. Bull.* **2003**, *51*, 821–831; k) B. Zhou, S. Edmonson, J. Padron, S. J. Danishefsky, *Tetrahedron Lett.* **2000**, *41*, 2039–2042; l) B. Zhou, J. Guo, S. J. Danishefsky, *Tetrahedron Lett.* **2000**, *41*, 2043–2046; m) S. Zheng, C. Chan, T. Furuuchi, B. J. D. Wright, B. Zhou, J. Guo, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2006**, *45*, 1754–1759; n) X. Chen, J. Chen, M. De Paolis, J. Zhu, *J. Org. Chem.* **2005**, *70*, 4397–4408; o) J. Chen, X. Chen, M. Bois-Choussy, J. Zhu, *J. Am. Chem. Soc.* **2006**, *128*, 87; p) X. Chen, J. Chen, M. Bois-Choussy, J. Zhu, *Synthesis* **2006**, 4081–4086; q) J. Chen, X. Chen, M. Willot, J. Zhu, *Angew. Chem. Int. Ed.* **2006**, *45*, 8028–8032; r) C. Rondot, P. Retailleau, J. Zhu, *Org. Lett.* **2007**, *9*, 247–250; s) W. Jin, S. Metebo, R. M. Williams, *Org. Lett.* **2003**, *5*, 2095–2098; t) D. Fishlock, R. M. Williams, *Org. Lett.* **2006**, *8*, 3299–3301; u) S. Chandrasekhar, N. R. Reddy, Y. S. Rao, *Tetrahedron* **2006**, *62*, 12098–12107.
[36] S. N. Banerjee, C. Ressler, *J. Org. Chem.* **1976**, *41*, 3056–3058.
[37] K. Vogler, H. Baumgartner, *Helv. Chim. Acta* **1952**, *35*, 1776–1780.
[38] N. Bodor, K. D. Sloan, T. Higuchi, K. Sasahara, *J. Med. Chem.* **1977**, *20*, 1435–1445.
[39] E. A. Rudd, W. C. Cunnigham, J. W. Thanassi, *J. Med. Chem.* **1979**, *22*, 233–237.
[40] A. Gaucher, L. Dutot, O. Barbeau, W. Hamchaoui, M. Wakselman, J.-P. Mazaleyrat, *Tetrahedron: Asymmetry* **2005**, *16*, 857–864.
[41] E. García, S. Arrasate, A. Ardeo, E. Lete, N. Sotomayor, *J. Org. Chem.* **2005**, *70*, 10368–10374.
[42] R. D. Clark, J. Berger, C.-H. Lee, J. M. Muchowski, *Heterocycles* **1987**, *26*, 1291–1302.
[43] D. C. Humber, N. C. Cammack, J. A. V. Coates, D. C. Orr, R. Storer, G. G. Weingarten, M. P. Weir, *J. Med. Chem.* **1992**, *35*, 3081–3084.

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