Synthesis and Functionalization of New Tropanes Designed for Use as Scaffolds in Combinatorial Chemistry

Jean-Laurent Paparin,[a] Christophe Crévisy,*[a] Loïc Toupet,[b] and René Grée*[a]

Keywords: Cycloadditions / Alkaloids / Combinatorial chemistry / Scaffolds / Tropanes

The [4+3] cycloaddition reaction between alkyloxycarbonyl-substituted pyrroles and α,α′-dibromo ketones in the presence of diethylzinc has been extended to a wide range of substrates. The functionalization of the resulting tropanes has been studied. It is demonstrated that such tropanes represent potentially useful scaffolds.

Introduction

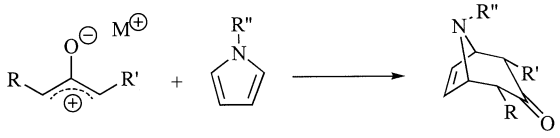
The development of novel scaffolds is a key step in generating molecular diversity and is important in combinatorial chemistry, especially with regard to the discovery of new leads for medicinal chemistry.[1] Scaffolds are molecules having a rigid skeleton that can be easily functionalized in all spatial directions. Consequently, tropanes have attracted our attention as potential candidates. Moreover, tropane-type alkaloids are biologically active[2,3] and, as far as we are aware, only two "tropane-like" scaffolds have hitherto been synthesized and used.[4,5]

In view of the potential of this framework as a scaffold, we initiated a research program in this area. We report here our preliminary results dealing specifically with two complementary aspects, the first being the development of a general strategy for the synthesis of tropanes, for which we chose to extend the [4+3] cycloaddition reaction between zinc oxyallyl cations and pyrroles; the second aspect concerns the scope and limitations of the functionalization of tropane derivatives. The combination of these studies should allow the design and preparation of tropanes that can be substituted at will at each part of the skeleton, as required for the preparation of libraries in combinatorial chemistry.

Results

Methodological Study on the Reaction of Oxyallyl Zinc Cations with Pyrroles

Among the various strategies available for the construction of the tropane skeleton,[2,6] the most efficient and widely used is the [4+3] cycloaddition reaction between an oxyallyl cation and a pyrrole (Scheme 1).



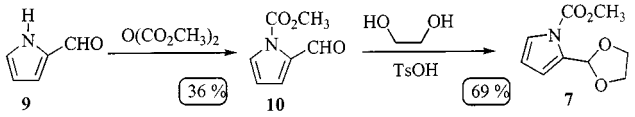
Scheme 1

Of the various methods that are known to generate oxyallyl cations, the reaction of diethylzinc with α,α′-dibromo ketones appeared to be most promising. Indeed, reaction of the resulting oxyallyl zinc cation with alkyloxycarbonylpyrroles yields the cycloadduct with high stereoselectivity and in good yield.[7] Nevertheless, the latter reaction, involving diethylzinc as an activator for the generation of the cation, has not been widely studied and only a few examples have been reported in the literature. We have therefore conducted a systematic study of this reaction using five different α,α′-dibromo ketones **1**−**5** and three different pyrroles **6**−**8** (Figure 1).

1 : R = R′ = CH_3 **4** : R = R′ = Ph **6** : R″ = CH_3, R‴ = H
2 : R = Ph, R′ = CH_3 **5** : R = R′ = CH_2Ph **7** : R″ = CH_3, R‴ = $CH(CH_2O)_2$
3 : R = Ph, R′ = H **8** : R″ = tBu, R‴ = H

Figure 1. Structures of dibromo ketones **1**−**5** and pyrroles **6**−**8**

Dibromo ketones **1**,[8] **2**,[9] **3**,[10] **4**,[11] and **5**[12] were prepared from the corresponding ketones according to known procedures. Pyrroles **6** and **8** are commercially available, while pyrrole **7** was obtained from carboxypyrrole **9** (Scheme 2).



Scheme 2

[a] Laboratoire de Synthèses et Activations de Biomolécules, UMR CNRS 6052, ENSCR,
Avenue du Général Leclerc, 35042 Rennes Cedex, France
Fax: (internat.) + 33-2/99871384
E-mail: rene.gree@ensc-rennes.fr
E-mail: christophe.crevisy@ensc-rennes.fr
[b] Groupe Matière Condensée et Matériaux, Université de Rennes I,
Avenue du Général Leclerc, 35042 Rennes Cedex, France
Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/eurjoc or from the author.

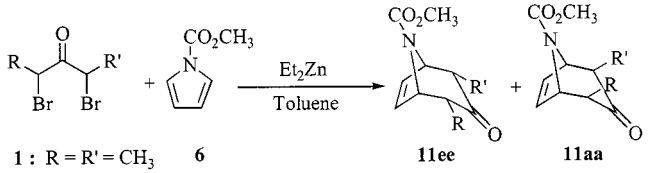
  1434−193X/00/1223−3909 $ 17.50+.50/0

Table 1. Cycloaddition of pyrrole **6** with dibromo ketones **1**−**3**

Entry	R, R′	DBK (*n* equiv.)	Et_2Zn (*n* equiv.)	Conditions	Total yield (%)	*de*[a] (%)	Yield of major isom. (%)	DBK recov. (%)
a	CH_3, CH_3	**1** (1.0)	1.0	3 h, 0 °C 17 h, room temp.	12	85	**11ee** (10)	n.a.
a′	CH_3, CH_3	**1** (3.5)	1.0	3 h, 0 °C 17 h, room temp.	66	85	**11ee** (57)	n.a.
a′′	CH_3, CH_3	**1** (3.0)	2.0	3 h, 0 °C 17 h, room temp.	69	90	**11ee** (n.c.)	n.a.
a′′′	CH_3, CH_3	**1** (5.0)	1.0	3 h, 0 °C 17 h, room temp.	88	85	**11ee** (81)	50
b	Ph, CH_3	**2** (1.5)	1.5	0.5 h add. 3 h, 0 °C 17 h, room temp.	74	90	**12ee** (69)	0
c	Ph, H	**3** (2.0)	2.0	3 h, 0 °C 17 h, room temp.	77	57	**13e** (59)	0
c′	Ph, H	**3** (2.2)	2.0	3 h, −15 °C 17 h, room temp.	70	78	**13e** (n.c.)	n.a.
c′′	Ph, H	**3** (1.5)	1.5	3 h, −15 °C 17 h, room temp.	50	87	**13e** (42)	n.a.

[a] Determined by GC analysis of the crude mixture.

Pyrrole **6** was first treated with dibromo ketones **1**−**3** (Scheme 3). The results are summarized in Table 1.



Scheme 3

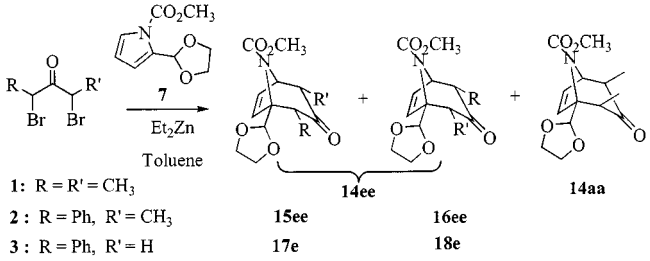
Initially, we subjected compound **1** to the conditions described by Mann.[7] A mixture of two diastereoisomers (**11ee** and **11aa**) was isolated with fairly high diastereoselectivity, but in low yield (12%; entry a). Consequently, the reaction conditions were varied (entries a′, a′′, a′′′) and it was found that a large excess of the α,α′-dibromo ketone is required to obtain an improved yield. The products have been described previously in the literature;[13] **11ee** bears two equatorial substituents at C2 and C4, while **11aa** bears two axial substituents at these positions.

The reaction of **6** with dibromo ketone **3** also gave a mixture of two diastereoisomers, **13e** and **13a**. However, in this case, only a twofold excess of **3** was required to obtain a good yield (entry c). From further results (entries c′ and c′′), it is clear that the reaction temperature has an influence on the diastereoselectivity. The configurations of the phenyltropanes **13a** and **13e** have been assigned on the basis of an X-ray crystal structure analysis of isomer **13e**.

In the case of ketone **2**, only a slight excess of the reagent was necessary to obtain a mixture of two diastereoisomers, **12ee** and **12aa**, in good yield and with high diastereoselectivity (entry b). The configurations of phenyltropanes **12aa** and **12ee** were assigned through comparison of the ^1H and ^{13}C NMR spectra of **12aa**, **12ee**, **13a**, and **13e**. The ^1H signals of the equatorial C*H*Ph protons were observed upfield (δ = 3.28 for **12aa**, δ = 3.33 for **13a**) from those of the axial C*H*Ph protons (δ = 3.79 for **12ee**, δ = 3.77 for **13e**).

It is worth noting that the reaction of **6** with dibromo ketone **3** offers the possibility of directly synthesizing a tropane unsubstituted at C2 or C4. Such compounds have been prepared previously, but only in two steps starting from tetrabromo ketones.[7]

The influence of a substituent on the pyrrole ring was also examined. To this end, the protected aldehyde **7** was selected. While its reaction with ketone **1** led to a mixture of two diastereoisomers (**14ee** and **14aa**), the dissymmetric dibromo ketones **2** and **3** yielded two major regioisomers (**15ee**, **16ee** and **17e**, **18e**, respectively) along with many other compounds (Scheme 4).



Scheme 4

The configurations of the major isomers were established on the basis of ^1H NMR spectra (for Supporting Information see footnote on the first page of this article) and an X-ray crystallographic analysis of compound **15ee**.

The configuration of **17e** was deduced by comparing the chemical shift of its C*H*Ph proton signal with that of the corresponding signal of **15ee** (δ = 4.39 for **15ee**, δ = 4.37 for **17e**). Similarly, the configurations of **16ee** and **18e** were established through comparison of the chemical shifts of the C*H*Ph proton signals for **16ee**, **18e**, **12ee**, and **13e** (δ = 3.89 for **16ee**, δ = 3.91 for **18e**; δ = 3.79 for **12ee**; δ = 3.77 for **13e**).

It was not possible to isolate the minor isomers in pure form. Nevertheless, the NMR spectra of the crude mixture showed signals consistent with the structures of diastereoisomers of previously characterized diequatorial compounds.

Table 2. Cycloaddition of pyrrole **7** with dibromo ketones **1**−**3**

Entry	R, R′	DBK (*n* equiv.)	Et_2Zn (*n* equiv.)	Conditions	Total yield (%)	Isomeric ratio[a]	Yield of major isom. (%)
a	CH_3, CH_3	**1** (5.0)	1.0	3 h, 0 °C 17 h, room temp.	81	93:7	−
a′	CH_3, CH_3	**1** (3.5)	1.0	3 h, 0 °C 17 h, room temp.	68	93:7	**14ee** (61)
b	Ph, CH_3	**2** (2.0)	2.0	3 h, 0 °C 17 h, room temp.	50	10.5:2.5:1.7:1.7:1.2:1:1	**15ee/16ee** (20:5)
c	Ph, H	**3** (2.0)	2.0	3 h, 0 °C 17 h, room temp.	50	20:12.5:1:1	**17e/18e** (20:12)

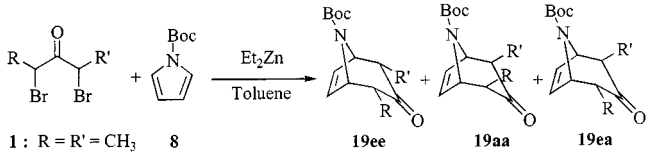
[a] Established from GC analysis or high-temperature ^1H NMR spectroscopy of the crude mixture.

The results are summarized in Table 2.

From these results, we conclude that the presence of the acetal function is compatible with the reaction conditions and does not change the reactivity.

Finally, the use of scaffolds in combinatorial chemistry requires the presence of protecting groups that can be easily and selectively removed. The methoxycarbonyl group is usually cleaved under rather drastic conditions,[5,14] while the *tert*-butyloxycarbonyl group (Boc) is eliminated under milder conditions and is therefore, a priori, more suitable for use in combinatorial chemistry. In order to demonstrate the compatibility of this group with the [4+3] cycloaddition reaction, we reacted pyrrole **8** with dibromo ketones **1**−**5**.

The reactions gave mixtures of three diastereoisomers, with the **ee** isomer being the major product (Scheme 5). The results are summarized in Table 3.

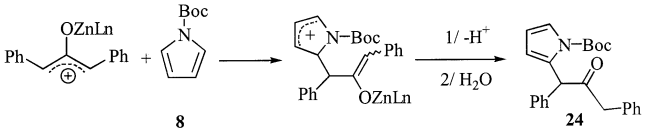


1 : R = R' = CH_3 **8**	**19ee**	**19aa**	**19ea**
2 : R = Ph, R' = CH_3	**20ee**	**20aa**	**20ea**
3 : R = Ph, R' = H	**21e**	**21a**	
4 : R = R' =Ph	**22ee**	**22aa**	**22ea**
5 : R = R' = CH_2Ph	**23ee**	**23aa**	**23ea**

Scheme 5

Comparison of these results (Table 3) with those obtained using methoxycarbonylpyrroles (Table 1) shows that the two pyrroles **6** and **8** exhibit similar reactivities. The reaction remains diastereoselective, although the formation of a very small amount of a third diastereoisomer is observed.

In the case of dibromo ketone **5**, the reaction is highly diastereoselective as only traces of another isomer were detected (entries e, e′). The results presented in entries d and d′ clearly show that dibromo ketone **4** exhibits a completely different reactivity to that of dibromo ketones **1**, **2**, **3**, and **5**. The reaction of **4** with **8** proceeded readily, affording a mixture of products, of which only two were amenable to separation and characterization. The expected tropane **22ee** was isolated in low yield (10−12%), along with pyrrole **24** (18%), which arises from an electrophilic substitution reaction[15] (Scheme 6).



Scheme 6

Interestingly, we found that the more electrophilic oxyallyliron cation[15] (entry d′′) gave a mixture of cycloadducts **22ee** and **22ea** in an acceptable yield (58%) accompanied by just 6% of **24**.

Table 3. Cycloaddition of pyrrole **8** with dibromo ketones **1**−**5**

Entry	R, R′	DBK (*n* equiv.)	Activator (*n* equiv.)	Conditions	Total yield (%)	Isomeric ratio[a] **ee/aa/ea**	Yield **ee** isom. (%)
a	CH_3, CH_3	**1** (3.8)	Et_2Zn (1.0)	3 h, 0 °C 17 h, room temp.	69	92:5:3	63
b	Ph, CH_3	**2** (1.5)	Et_2Zn (1.5)	6 h, −10 °C to +10 °C	76	90:8:2	65
c	Ph, H	**3** (2.0)	Et_2Zn (2.0)	6 h, −15 °C to +10 °C	61	90:10	51
d	Ph, Ph	**4** (1.5)	Et_2Zn (1.5)	1 h, 0 °C	<10	−	<10
d′	Ph, Ph	**4** (0.2)	Et_2Zn (0.2)	1 h, 0 °C	12	−	12
d′′	Ph, Ph	**4** (0.33)	$Fe_2(CO)_9$ (0.5)	room temp.	58	4:0:3	n.a.
e	Bn, Bn	**5** (1.5)	Et_2Zn (1.5)	6 h, 0 °C	33	>97/<3/−	−
e′	Bn, Bn	**5** (3.0)	Et_2Zn (2.0)	6 h, 0 °C	84	>97/<3/−	−

[a] Established from GC analysis or high-temperature ^1H NMR spectroscopy of the crude mixture.

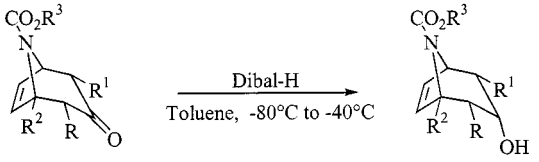
Functionalization of the Tropane Framework

To extend the utility of tropanes as scaffolds, it was necessary to study the functionalization of these molecules. Many reactions have already been reported in the literature, but essentially only on non-substituted tropanes.[4,5,6d,7,14,16]

We have focused our efforts on reactions that have been less well studied yet can be expected to offer a great potential for diversity, specifically the addition of electrophiles at the carbon α to the carbonyl group, the addition of nucleophiles to the carbonyl group, and selective deprotection of the nitrogen atom and the acetal group. It is interesting to note that these reactions have been performed on C-2 and/or C-4 substituted tropanes.

Nucleophilic Additions to the Carbonyl Group

First, we studied the reduction of the C=O bond. Addition of DIBAL-H to compounds **13e**, **14ee**, and **20ee** at low temperature provided alcohols **25**, **26**, and **27** in very high yields. In these examples, only one diastereoisomer could be detected (Scheme 7). However, the reduction proved to be less stereoselective when performed with $NaBH_4$ (*dr* ≈ 2:1). In contrast, the carbamate group was not affected under these conditions.



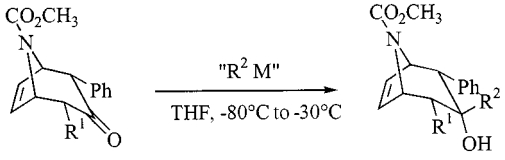
13e : R = Ph, $R^1 = R^2 = H$, $R^3 = CH_3$ **25** 75 %

14ee : R = $R^1 = CH_3$, $R^2 = CH(CH_2O)_2$, $R^3 = CH_3$ **26** 99 %

20ee : R = Ph, $R^1 = CH_3$, $R^2 = H$, $R^3 = t$Bu **27** 86 %

Scheme 7

The addition of organometallic species to the carbonyl group was also studied (Scheme 8).



Scheme 8

The reaction gave the corresponding α-alcohols in a highly stereoselective manner, albeit in only moderate yields (20−54%). The reactions did not reach completion and large amounts of the starting ketone were recovered (30−50%). The results are summarized in Table 4.

Attempts to drive the reaction to completion by adding LiBr (entry c), changing the nature of the metal (entry f), using a less bulky nucleophile or a less bulky ketone (entries d and g, respectively), or by using a less basic nucleophile (entry e) were unsuccessful. These results give an indication as to the limitations of addition to the carbonyl group and are in good agreement with recent literature data.[14]

Addition of Electrophiles at the Carbon α to the Carbonyl Group: Aldol Reaction and Alkylation

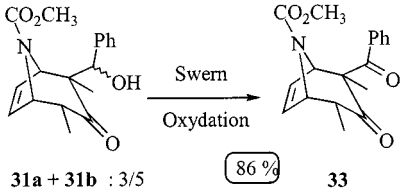
The aldol reaction was performed on ketones **11ee**, **12ee**, and **13e** (Scheme 9).

The results are summarized in Table 5.

Reaction of ketones **11ee** and **13e** gave the aldol products as mixtures of two diastereoisomers (**31a**, **31b** and **32a**, **32b**, respectively) in good overall yields. The stereochemical assignment was confirmed by converting the diastereoisomeric mixture of **31a** and **31b** into a single ketone **33** (Scheme 10).

Unexpectedly, the aldol reaction was not successful in the case of ketone **12ee**, possibly due to steric hindrance.

Methylation at the carbon α to the carbonyl group was also performed on ketones **11ee**, **12ee**, and **13e**. While the alkylation of **11ee** cleanly afforded compound **34** (Scheme 11), the corresponding reactions of compounds **12ee** and **13e** provided mixtures of products. From the NMR spectra, it became apparent that the expected compounds were formed along with products of dialkylation, thus making these reactions less useful from a synthetic point of view.



31a + 31b : 3/5 86 % **33**

Scheme 10

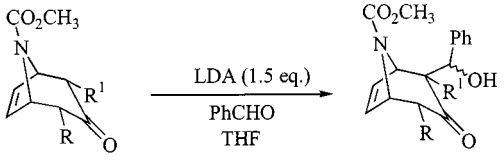
Table 4. Addition of organometallic species on tropanes **12ee** and **13e**

Entry	R^1	Tropane	R^2M (*n* equiv.)	Alcohol	Isol. yield (%)	Start. mater. recov. (%)
a	CH_3	**12ee**	MeLi (1.5)	**28**	52	37
b	CH_3	**12ee**	MeLi (2.5)	**28**	50	37
c	CH_3	**12ee**	MeLi/LiBr (1.5)	**28**	50	29
d	CH_3	**12ee**	$Me_3Si-C\equiv C-Li$ (2.0)	**29**	20	34
e	CH_3	**12ee**	$Me_3Si-C\equiv C-CeCl_2$ (2.0)	**29**	21	38
f	CH_3	**12ee**	CH_3MgI (1.5)	**28**	54	30
g	H	**13e**	MeLi/LiBr (1.5)	**30**	27	49

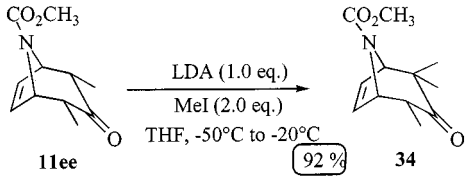
Table 5. Aldol reactions on tropanes **11ee**, **12ee** and **13e**

Entry	R, R^1	Ketone	Conditions	Total yield (%)	*dr*[a]	Maj. diast. (yield %)	Start. mater. recov. (%)
a	CH_3, CH_3	**11ee**	PhCHO (1.5 equiv.), −50 to −20 °C (2 h)	89	3:1	**31a** (67)	6
b	Ph, CH_3	**12ee**	PhCHO (7.0 equiv.), −50 °C to room temp.	0	–	–	88
c	Ph, H	**13e**	PhCHO (1.5 equiv.), −80 to −20 °C (2 h)	71	4:1	**32a** (57)	16

[a] Diastereoisomeric ratio established from ^{1}H NMR spectra of the crude mixture.



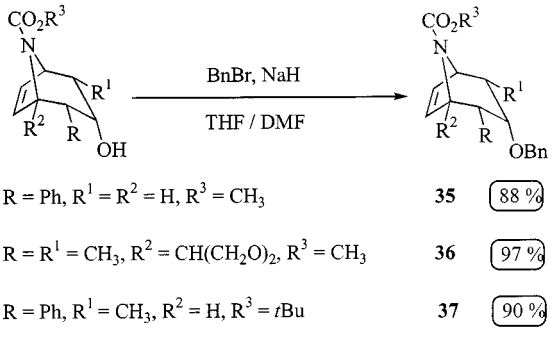
Scheme 9



Scheme 11

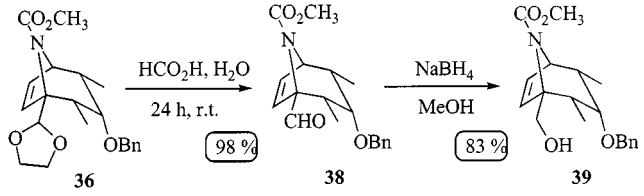
Selective Deprotection of the Acetal Group and Nitrogen Atom − Functionalization of the Latter

As the cycloadducts are unstable under various conditions,[17] further studies were conducted on the benzyl ether derivatives **35**, **36**, and **37** (Scheme 12).



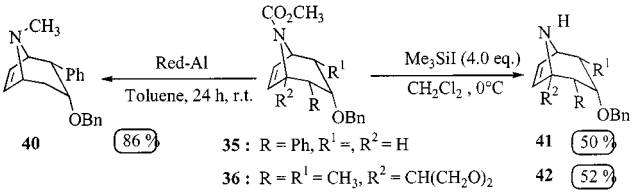
Scheme 12

Thus, the lateral C-3 acetal chain of compound **36** was efficiently deprotected using formic acid, without affecting the other protecting groups. The aldehyde **38** was isolated in 98% yield and could be transformed to the primary alcohol **39** in the presence of sodium borohydride (Scheme 13).



Scheme 13

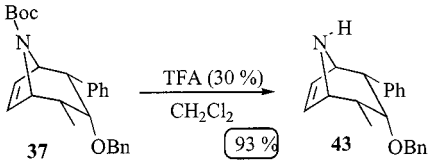
Deprotection of the methylcarbamate was subsequently undertaken. Reaction of compound **35** with Red-Al® was expected to give the deprotected amine, but afforded instead the methylamine **40** in high yield (Scheme 14).



Scheme 14

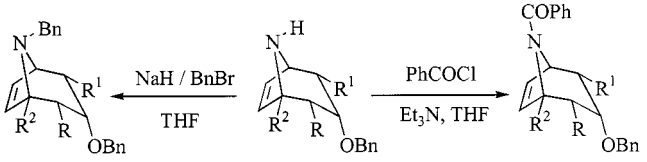
Alternatively, treatment of compounds **35** and **36** with Me_3SiI [5] produced amines **41** and **42** in fairly good yields. It is noteworthy that the acetal group of **36** was not affected under these conditions (Scheme 14) and thus this compound possesses three orthogonal protecting groups.

It was expected that the Boc group could be cleaved more easily under less drastic conditions. Indeed, deprotection of the nitrogen in **37** with TFA gave amine **43** in very high yield (Scheme 15).



Scheme 15

Finally, amines **41** and **42** were converted into ethers **44**, **45** and amides **46**, **47** in order to verify that the nitrogen is indeed a potential site for the introduction of diversity (Scheme 16).



Scheme 16

Conclusion

We have extended the [4+3] cycloaddition reaction of α,α′-dibromo ketones with pyrroles in the presence of di-

ethylzinc to a wide range of substrates. In particular, we have shown that the presence of an acetal substituent at the C-2 position of pyrroles has no influence on the reactivity and that the formerly used methoxycarbonyl-urethane protecting group can be replaced by the more easily removed Boc group. Even though some limitations remain, it is clear that the skeleton of such cycloadducts can readily be functionalized in various positions.

Thus, tropanes represent good candidates as scaffolds. The preparation of tropane libraries is currently in progress and the relevant results will be reported in due course.

Experimental Section

General: All reactions were carried out under dry nitrogen, unless mentioned otherwise. Standard syringe techniques were employed for the transfer of dry solvents and air- or moisture-sensitive reagents. − Melting points are uncorrected. − IR spectra were determined on a Nicolet 205 FT-IR spectrophotometer; absorption bands are given in cm^{-1}. − NMR spectra were obtained at 400 MHz on a Bruker ARX 400 instrument using deuteriochloroform as solvent (unless specified otherwise). Chemical shifts (δ) are given in ppm relative to tetramethylsilane (δ = 0) for spectra run in deuteriochloroform or to an internal standard of (residual protons in) the solvent for those run in deuteriobenzene (δ = 7.20 and 128.7) and deuteriotoluene (δ = 2.09 and 20.4). − C and H microanalyses were provided by the "Service de Microanalyse" I.C.S.N. − C.N.R.S., Gif-sur-Yvette, France. − High-resolution mass spectra (HRMS) were measured at the "Centre Régional de Mesures Physiques de l'Ouest" on a Varian MAT 311 spectrometer operating at 70 eV. − Crystallographic data were obtained using an Enraf−Nonius CAD 4 diffractometer. Crystal data are given in Table 1 (for **13e**) and Table 2 (for **15ee**). − Merck silica gel 60H was used for column chromatography. TLC was performed on Merck 0.25 mm silica gel 60 F_{254} plates (analytical). Compounds on chromatography plates were visualized by spraying with a solution of 5% *p*-anisaldehyde, 5% sulfuric acid, and 0.1% acetic acid in ethanol followed by heating. − GC analyses were carried out on an HP 5890A system equipped with an HP1 column (cross-linked methyl siloxane), 30 m × 0.32 mm × 0.25 μm film thickness (retention times are reported in minutes). − Ethyl acetate and petroleum ether (40−60 °C) were distilled before use. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from sodium benzophenone ketyl prior to use. Toluene and methanol were freshly distilled from sodium; dichloromethane and acetonitrile were dried and distilled from CaH_2 before use.

Crystallographic Data for 13e and 15ee: Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-149189 (**13e**) and CCDC-149190 (**15ee**). Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [Fax: (internat.) +44 (0)1223/336033; E-mail: deposit@ccdc.cam.ac.uk].

Spectroscopic characterization data for all new compounds are given in the Supporting Information.

Methyl 2-Formyl-1*H*-pyrrole-1-carboxylate (10): To an ice-cooled solution of 4-(dimethylamino)pyridine (256 mg, 2.00 mmol) and pyrrole-2-carboxaldehyde (2.00 g, 21 mmol) in dry acetonitrile (10 mL), dimethyl pyrocarbonate (4.52 mL, 42 mmol) was added dropwise. The solvent was then removed under reduced pressure and the residue was purified by flash chromatography on silica gel (toluene/diethyl ether/triethylamine, 4:1:0.2) to give the required product **10** (1.16 g, 36%) as a yellow oil.

Methyl 2-(1′,3′-Dioxolan-2-yl)pyrrole-1-carboxylate (7). − Preparation of the *p*-Toluenesulfonic Acid Catalyst: *p*-Toluenesulfonic acid hydrate (100 mg) was refluxed with benzene (200 mL) in an apparatus fitted with a Dean−Stark head for 2 h until a clear solution was obtained and no further water was azeotropically distilled. The catalyst solution thus obtained proved to be very hygroscopic and had to be protected from moisture.

Preparation of the Pyrrole Acetal: Pyrrole **10** (500 mg, 3.26 mmol) and an excess of ethylene glycol (430 μL, 7.84 mmol, 2.4 equiv.) were dissolved in benzene (30 mL) and the resulting solution was refluxed in an apparatus fitted with a Dean−Stark head for 30 min. Reflux conditions were maintained as the aforementioned *p*-toluenesulfonic acid catalyst solution (10 mL, 0.03 mmol, $8\cdot10^{-3}$ equiv.) was added dropwise over a period of 30 min. The progress of the reaction was followed by gas chromatography (50 °C/5 min → 200 °C, 10 °C/min). After 2 h, the reaction mixture was allowed to cool to room temperature, quickly washed with several portions of 5% aqueous sodium hydrogen carbonate solution, and then dried ($MgSO_4$). Removal of the solvent gave the crude acetal, which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 2:1) to give compound **7** (t_R = 17.0 min, 440 mg, 69%) as an orange oil.

[4+3] Cycloaddition with Diethylzinc. − General Procedure: To an ice-cooled solution of the α,α′-dibromo ketone and the alkyl pyrrole-1-carboxylate in dry toluene, a 1 M solution of diethylzinc in hexane was added dropwise. The mixture was stirred at 0 °C for 3 h and at room temperature for 17 h, and then poured into an ice-cooled saturated solution of Na_2EDTA. The resulting mixture was extracted three times with ethyl acetate, and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to leave the crude cycloadduct mixture. The diastereoselectivity of the reaction was determined by ^1H NMR (high temperature) or GC analysis of the crude mixture. The products were isolated by column chromatography on silica gel.

Methyl 2α,4α-Dimethyl-3-oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (11ee) and Methyl 2β,4β-Dimethyl-3-oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (11aa): These products were obtained from the reaction of 2,4-dibromopentan-3-one **1** (689 μL, 5.00 mmol, 5.0 equiv.) and methyl pyrrole-1-carboxylate **6** (112 μL, 1.00 mmol) with 1 M diethylzinc (1.00 mL, 1.00 mmol, 1.0 equiv.) in toluene (80 mL). The diastereoisomeric excess (*de* = 85%) was established by GC analysis (50 °C/5 min → 200 °C, 10 °C/min). The crude mixture was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 4:1) to give compound **11ee** (t_R = 17.2 min, 171 mg, 81%) followed by compound **11aa** (t_R = 16.6 min, 14 mg, 6%), both as white solids.

Methyl 2α-Methyl-3-oxo-4α-phenyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (12ee) and Methyl 2β-Methyl-3-oxo-4β-phenyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (12aa): These products were obtained from the reaction of 1,3-dibromo-1-phenylbutan-2-one **2** (2.75 g, 9.00 mmol, 1.5 equiv.) and methyl pyrrole-1-carboxylate **6** (675 μL, 6.00 mmol) with 1 M diethylzinc (9.00 mL, 9.00 mmol, 1.5 equiv.) in toluene (120 mL). The diastereoisomeric excess (*de* = 90%) was established by GC analysis (50 °C/5 min → 200 °C, 10 °C/min). The crude mixture was purified by column chromatography on silica gel (toluene/diethyl ether, 100:12) to give com-

pound **12aa** (t_R = 16.9 min, 84 mg, 5%) followed by compound **12ee** (t_R = 18.5 min, 1.01 g, 69%), both as pale-yellow syrups.

Methyl 3-Oxo-2α-phenyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (13e) and Methyl 3-Oxo-2β-phenyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (13a): These products were obtained from the reaction of 1,3-dibromo-1-phenylpropan-2-one **3** (2.34 g, 8.00 mmol, 2.0 equiv.) and methyl pyrrole-1-carboxylate **6** (450 μL, 4.00 mmol) with 1 M diethylzinc (8.00 mL, 8.00 mmol, 2.0 equiv.) in toluene (80 mL). The diastereoisomeric excess (*de* = 57%) was established by GC analysis (50 °C/5 min → 200 °C, 10 °C/min). The crude mixture was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 3:1) to give compound **13a** (t_R = 16.8 min, 154 mg, 15%) followed by compound **13e** (t_R = 17.8 min, 606 mg, 59%), both as orange oils. Compound **13e** was crystallized (dichloromethane/hexane) to give orange crystals.

Methyl 1-(1′,3′-Dioxolan-2′-yl)-2α,4α-dimethyl-3-oxo-8-azabicyclo-[3.2.1]oct-6-ene-8-carboxylate (14ee) and Methyl 1-(1′,3′-Dioxolan-2′-yl)-2β,4β-dimethyl-3-oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (14aa): These products were obtained from the reaction of 2,4-dibromopentan-3-one **1** (1.3 mL, 9.40 mmol, 3.5 equiv.) and methyl 2-(1′,3′-dioxolan-2-yl)pyrrole-1-carboxylate **7** (530 mg, 2.70 mmol) with 1 M diethylzinc (2.70 mL, 2.70 mmol, 1.0 equiv.) in toluene (60 mL). The diastereoisomeric excess (*de* = 86%) was established by GC analysis (50 °C/5 min → 200 °C, 10 °C/min). The crude mixture was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 2:1) to give compound **14ee** (t_R = 23.8 min, 460 mg, 61%) followed by compound **14aa** (t_R = 23.4 min, 30 mg, 4%), both as white solids.

Methyl 1-(1′,3′-Dioxolan-2′-yl)-4α-methyl-3-oxo-2α-phenyl-8-azabicyclo-[3.2.1]oct-6-ene-8-carboxylate (15ee) and Methyl 1-(1′,3′-Dioxolan-2′-yl)-2α-methyl-3-oxo-4α-phenyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (16ee): These products were obtained from the reaction of 1,3-dibromo-1-phenylbutan-2-one **2** (1.4 g, 4.57 mmol, 2.0 equiv.) and methyl 2-(1′,3′-dioxolan-2-yl)pyrrole-1-carboxylate **7** (450 mg, 2.29 mmol) with 1 M diethylzinc (4.60 mL, 4.60 mmol, 2.0 equiv.) in toluene (50 mL). The diastereoisomeric ratio (*dr* = 1:1:1.2:1.2:1.7:1.7:2.5:10.5) was established by ^{1}H NMR analysis (C_6D_6, 333 K). The crude mixture was purified by column chromatography on silica gel (diethyl ether/petroleum ether, 2:1 → 3:1) to give compound **15ee** (204 mg) followed by compound **16ee** (40 mg, 5%), both as white solids. Compound **15ee** was crystallized (diethyl ether/hexane) to give white crystals (160 mg, 20%).

Methyl 1-(1′,3′-Dioxolan-2′-yl)-3-oxo-2α-phenyl-8-azabicyclo[3.2.1]-oct-6-en-8-carboxylate (17e) and Methyl 1-(1′,3′-Dioxolan-2′-yl)-3-oxo-4α-phenyl-8-azabicyclo[3.2.1]oct-6-en-8-carboxylate (18e): These products were obtained from the reaction of 1,3-dibromo-1-phenylpropan-2-one **3** (1.33 g, 4.57 mmol, 2.0 equiv.) and methyl 2-(1′,3′-dioxolan-2-yl)pyrrole-1-carboxylate **7** (450 mg, 2.29 mmol) with 1 M diethylzinc (4.60 mL, 4.60 mmol, 2.0 equiv.) in toluene (50 mL). The diastereoisomeric ratio (*dr* = 1:1:12.5:20) was established by ^{1}H NMR analysis (C_6D_6, 333 K). The crude mixture was purified by column chromatography on silica gel (toluene/ethyl acetate, 3:1) to give compound **17e** (168 mg, 22%) followed by a mixture of isomers, which was further purified by chromatography (diethyl ether/petroleum ether, 2:1→ 3:1) to give compound **18e** (90 mg, 12%) as a white solid. Compound **17e** was crystallized from diethyl ether to give white crystals (154 mg, 20%).

***tert*-Butyl 2α,4α-Dimethyl-3-oxo-8-(oxycarbonyl)-8-azabicyclo-[3.2.1]oct-6-ene-8-carboxylate (19ee), *tert*-Butyl 2β,4β-Dimethyl-3-oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (19aa), and *tert*-Butyl 2α,4β-Dimethyl-3-oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (19ea):** These products were obtained from the reaction of 2,4-dibromopentan-3-one **1** (1.05 mL, 7.60 mmol, 3.8 equiv.) and *N*-(*tert*-butyloxycarbonyl)pyrrole **8** (334 μL, 2.00 mmol) with 1 M diethylzinc (3.00 mL, 3.00 mmol, 1.5 equiv.) in toluene (50 mL). The diastereoisomeric ratio (*dr* = 92:5:3) was established by GC analysis (50 °C/5 min → 200 °C, 10 °C/min). The crude mixture was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 10:1) to give compound **19ee** (t_R = 18.8 min, 314 mg, 63%) as a white solid, followed by a 2:1 isomeric mixture (20 mg, 4%) of compound **19aa** (t_R = 18.4 min) and compound **19ea** (t_R = 18.6 min) as a colorless syrup.

***tert*-Butyl 2α-Methyl-3-oxo-4α-phenyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (20ee), *tert*-Butyl 2β-Methyl-3-oxo-4β-phenyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (20aa), and *tert*-Butyl 2β-Methyl-3-oxo-4α-phenyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (20ea):** These products were obtained from the reaction of 1,3-dibromo-1-phenylbutan-2-one **2** (918 mg, 3.00 mmol, 1.5 equiv.) and *tert*-butyl pyrrole-*N*-carboxylate **8** (335 μL, 2.00 mmol) with 1 M diethylzinc (3.00 mL, 3.00 mmol, 1.5 equiv.) in toluene (50 mL). The diethylzinc was added at −10 °C, the temperature was allowed to rise to +10 °C over 6 h. The diastereoisomeric ratio (*dr* = 90:8:2) was established by GC analysis (100 °C → 200 °C, 10 °C/min). The crude mixture was purified by column chromatography on silica gel (toluene/diethyl ether, 15:1) to give a mixture of isomers, which was further purified by chromatography (petroleum ether/diethyl ether, 3:1) to give compound **20ee** (t_R = 15.5 min, 402 mg, 65%) followed by a 4:1 isomeric mixture (35 mg, 6%) of compound **20aa** (t_R = 13.5 min) and compound **20ea** (t_R = 15.2 min), both as pale-yellow syrups.

***tert*-Butyl 3-Oxo-2α-Phenyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (21e) and *tert*-Butyl 3-Oxo-2β-Phenyl-8-(*tert*-butyloxycarbonyl)-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (21a):** These products were obtained from the reaction of 1,3-dibromo-1-phenylpropan-2-one **3** (1.17 g, 4.00 mmol, 2.0 equiv.) and *tert*-butyl pyrrole-*N*-carboxylate **8** (335 μL, 2.00 mmol) with 1 M diethylzinc (4.00 mL, 4.00 mmol, 2.0 equiv.) in toluene (50 mL). The diethylzinc was added at −15 °C, the temperature was allowed to rise to +10 °C over 6 h. The diastereoisomeric excess (*de* = 79%) was established by GC analysis (100 °C → 200 °C, 10 °C/min). The crude mixture was purified by column chromatography on silica gel (toluene/diethyl ether, 10:1) to give a mixture of isomers (364 mg, 61%), which was further purified by chromatography (petroleum ether/diethyl ether, 3:1 → 2:1) to give compound **21e** (t_R = 14.7 min, 308 mg, 51%) followed by compound **21a** (t_R = 13.4 min, 27 mg, 5%), both as white solids. Compound **21e** was crystallized (dichloromethane/hexane) to give white crystals.

***tert*-Butyl 3-Oxo-2α,4α-Diphenyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (22ee) and *tert*-Butyl 2-(2′-Oxo-1′,3′-diphenylpropanyl)-pyrrole-*N*-carboxylate (24):** These products were obtained from the reaction of 1,3-dibromo-1,3-diphenylpropan-2-one **4** (300 mg, 0.81 mmol) and *tert*-butyl pyrrole-*N*-carboxylate **8** (680 μL, 4.00 mmol, 5.0 equiv.) with 1 M diethylzinc (810 μL, 0.81 mmol, 1.0 equiv.) in toluene (5 mL). The 1,3-dibromo-1,3-diphenylpropan-2-one **4** was completely consumed within 1 h at 0 °C. The crude mixture was purified by column chromatography on silica gel (petroleum ether/diethyl ether, 10:1) to afford impure compound **24** (70 mg) and compound **22ee** (60 mg). Compound **24** was further purified by column chromatography on silica gel (petroleum ether/diethyl ether, 5:1) to give (53 mg, 18%) as an orange oil. Compound **22ee** was further purified by column chromatography on silica gel (toluene/diethyl ether, 30:1) to give (37 mg, 12%) as a white solid.

***tert*-Butyl 2α,4α-Dibenzyl-3-oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (23ee):** This product was obtained from the reaction of

2,4-dibromo-1,5-diphenylpentan-3-one **5** (396 mg, 1.00 mmol, 3.0 equiv.) and *tert*-butyl pyrrole-*N*-carboxylate **8** (56 μL, 0.33 mmol) with 1 M diethylzinc (660 μL, 0.66 mmol, 2.0 equiv.) in toluene (10 mL). The reaction was allowed to proceed for 6 h at 0 °C. The diastereoisomeric excess (*de* = 96−97%) was established by ^{1}H NMR analysis (C_7D_8, 373 K) of the crude mixture. The crude mixture was purified by column chromatography on silica gel (petroleum ether/diethyl ether, 9:2) to give compound **23ee** (113 mg, 84%), which was crystallized (dichloromethane/hexane) to give white crystals.

[4+3] Cycloaddition with $Fe_2(CO)_9$: Preparation of *tert*-Butyl 2α,4β-Diphenyl-3-oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (22ea): A mixture of 1,3-dibromo-1,3-diphenylpropan-2-one **4** (200 mg, 0.54 mmol, 1.0 equiv.), *tert*-butyl pyrrole-*N*-carboxylate **8** (91 μL, 0.54 mmol), and $Fe_2(CO)_9$ (271 mg, 0.74 mmol, 1.4 equiv.) in dry toluene (5 mL) was stirred under irradiation by visible light at room temperature for 1 h. The reaction mixture was then diluted with ethyl acetate and a saturated aqueous solution of $NaHCO_3/KNO_3$ was added. The mixture was extracted three times with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The diastereomeric ratio (4:3) was determined by ^{1}H NMR analysis (C_7D_8, 373 K) of the crude mixture. The residue was purified by column chromatography on silica gel (petroleum ether/diethyl ether, 10:1 → 3:1) to give compound **24** (13 mg, 6%) as an orange oil, followed by an inseparable diastereoisomeric mixture of compounds **22ee** and **22ea**. This mixture was further purified by column chromatography on silica gel (toluene/diethyl ether, 30:1) to give the pure diastereoisomeric mixture (118 mg, 58%) as a white solid.

Representative Procedure for the Reduction with DIBAL-H: Preparation of Methyl 3α-Hydroxy-2α-phenyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (25): A solution of methyl 2α-phenyl-3-oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate **13e** (400 mg, 1.55 mmol) in toluene (50 mL) was cooled to −78 °C, whereupon a 1 M solution of DIBAL-H in toluene (2.3 mL, 2.30 mmol) was added dropwise. The reaction mixture was stirred and allowed to warm to −40 °C, diluted with diethyl ether, and washed with a saturated aqueous solution of sodium potassium tartrate. The aqueous layer was extracted three times with dichloromethane and the combined organic phases were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 1:1) to give compound **25** (300 mg, 75%) as a colorless syrup.

Methyl 1-(1′,3′-Dioxolan-2′-yl)-3α-hydroxy-2α,4α-dimethyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (26): This product was obtained from methyl 1-(1′,3′-dioxolan-2′-yl)-2α,4α-dimethyl-3-oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate **14ee** (190 mg, 0.67 mmol). The residue was purified by column chromatography on silica gel (toluene/ethyl acetate, 1:1) to give compound **26** (191 mg, 99%) as a colorless syrup.

***tert*-Butyl 3α-Hydroxy-2α-methyl-4α-phenyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (27):** This product was obtained from *tert*-butyl 2α-methyl-4α-phenyl-3-oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate **20ee** (190 mg, 0.67 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/diethyl ether, 1:1) to give compound **27** (295 mg, 86%), which was crystallized from hexane to give white crystals.

Procedures for Nucleophilic Addition to the Carbonyl Group

Preparation of Methyl 3α-Hydroxy-2α,3β-dimethyl-4α-phenyl-8-azabicyclo[3.2.1]oct-6-en-8-carboxylate (28). − Procedure with MeLi: To a solution of methyl 2α-methyl-3-oxo-4α-phenyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate **12ee** (97 mg, 0.35 mmol) in THF (4 mL) cooled to −78 °C, a 1.6 M solution of methyllithium in diethyl ether (335 μL, 0.54 mmol, 1.5 equiv.) was added dropwise. The reaction mixture was allowed to warm to −60 °C, quenched with saturated NH_4Cl solution (20 mL), then diluted with diethyl ether (20 mL) and allowed to warm to room temperature. The aqueous layer was extracted three times with dichloromethane and the combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/diethyl ether, 6:4) to give compound **12ee** (36 mg, 37%) followed by compound **28** (53 mg, 52%), both as colorless syrups.

Procedure with MeMgI: To a solution of methyl 2α-methyl-3-oxo-4α-phenyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate **12ee** (100 mg, 0.37 mmol) in THF (4 mL) cooled to −20 °C, a 1.5 M solution of methylmagnesium bromide in diethyl ether (369 μL, 0.55 mmol, 1.5 equiv.) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The reaction was then quenched with saturated NH_4Cl solution (20 mL) and diluted with diethyl ether (20 mL). The aqueous layer was extracted three times with dichloromethane and the combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (toluene/diethyl ether, 8:3) to give compound **12ee** (30 mg, 30%) followed by compound **28** (58 mg, 54%), both as colorless syrups.

Preparation of Methyl 3α-Hydroxy-2α-methyl-3β-trimethylsilylacetylene-4α-phenyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (29): To a solution of trimethylsilyl acetylene (161 μL, 1.14 mmol, 2.0 equiv.) in THF (1 mL) cooled to −80 °C, a 0.5 M solution of lithium diisopropylamide in THF/hexane (2.3 mL, 1.14 mmol) was added dropwise. After 15 min, a solution of methyl 2α-methyl-3-oxo-4α-phenyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate **12ee** (155 mg, 0.57 mmol) in THF (2 mL) was added dropwise. The reaction mixture was allowed to warm to −20 °C, quenched with saturated NH_4Cl solution (20 mL), then diluted with diethyl ether (20 mL) and allowed to warm to room temperature. The aqueous layer was extracted three times with dichloromethane and the combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/diethyl ether, 3:1) to give compound **29** (40 mg, 20%) as a colorless syrup followed by compound **12ee** (84 mg, 54%).

Preparation of Methyl 3α-Hydroxy-3β-methyl-4α-phenyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (30): The procedure used was similar to that reported above for compound **28**, starting from methyl 3-oxo-2α-phenyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate **13e** (266 mg, 1.30 mmol). The residue was purified by column chromatography on silica gel (toluene/diethyl ether, 8:3) to give compound **13e** (131 mg, 49%) followed by compound **30** (76 mg, 27%), both as colorless syrups.

Representative Procedure for the Aldol Reaction of Substituted Tropanes: Preparation of Methyl 2β-(1-Hydroxybenzyl)-2α,4α-dimethyl-3-oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (31a and 31b): To a solution of methyl 2α,4α-dimethyl-3-oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate **11ee** (210 mg, 1.00 mmol) in THF (2 mL) cooled to −50 °C, a 0.5 M solution of lithium diisopropylamide in THF/hexane (3.0 mL, 1.5 mmol, 1.5 equiv.) was added dropwise, followed by benzaldehyde (168 μL, 1.50 mmol, 1.5 equiv.). The solution was allowed to warm to −20 °C and stirred for 2 h. The reaction was then quenched with saturated NH_4Cl solution (20 mL),

diluted with diethyl ether (20 mL), and allowed to warm to room temperature. The aqueous layer was extracted three times with ethyl acetate and the combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The diastereoisomeric ratio (**31a/31b**, 3:1) was determined by ^1H NMR analysis (C_7D_8, 363 K) of the crude mixture. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 3:1) to give compound **11ee** (13 mg, 6%) followed by compound **31a** (210 mg, 67%) and compound **31b** (70 mg, 22%), all as white solids. Compound **31a** was crystallized (ethyl acetate/hexane) to give white crystals.

Methyl 4β-(1-Hydroxybenzyl)-3-oxo-2α-phenyl-8-azabicyclo[3.2.1]-oct-6-ene-8-carboxylate (32a and 32b): These compounds were obtained from methyl 3-oxo-2α-phenyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate **13e** (257 mg, 1.00 mmol). The diastereoisomeric ratio (**32a/32b**, 4:1) was determined by ^1H NMR analysis (C_7D_8, 373 K) of the crude mixture. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 3:1) to give compound **13e** (43 mg, 16%) followed by impure compound **32b** (47 mg) and pure compound **32a** (197 mg, 57%), both as white solids. Compound **32a** was crystallized (diethyl ether/hexane) to give white crystals.

Methyl 2β-Benzoyl-2α,4α-dimethyl-3-oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (33): To a solution of oxalyl chloride (44.3 μL, 0.50 mmol) in dichloromethane (1.5 mL) cooled to −70 °C was added dimethyl sulfoxide (37.8 μL, 0.53 mmol). After 15 min, a solution of alcohols **31a** and **31b** (ratio 3:5) (101 mg, 0.32 mmol) in dichloromethane (1.5 mL) was added. The resulting mixture was stirred at −70 °C for 40 min. Triethylamine (141 μL, 1.00 mmol) was then added and the stirred mixture was allowed to warm to −5 °C over a period of 2 h. It was then diluted with dichloromethane (20 mL) and washed with brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 2:1) to give the expected product **33** (88 mg, 86.5%) as a colorless syrup.

Methyl 2α,2β,4α-Trimethyl-3-oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (34): To a solution of methyl 2α,4α-dimethyl-3-oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate **11ee** (100 mg, 0.47 mmol) in THF (1.5 mL) cooled to −50 °C, a 0.5 M solution of lithium diisopropylamide in THF/hexane (956 μL, 0.47 mmol, 1.0 equiv.) was added dropwise, followed by methyl iodide (60 μL, 0.94 mmol, 2.0 equiv.). The resulting mixture was allowed to warm to −20 °C and stirred for 3 h. It was then quenched with saturated NH_4Cl solution (20 mL), diluted with diethyl ether (20 mL), and allowed to warm to room temperature. The aqueous layer was extracted three times with ethyl acetate and the combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 5:1) to give compound **34** (98 mg, 92%) as a white solid, followed by compound **11ee** (6 mg, 6%). Compound **34** was crystallized from hexane to give white crystals.

Representative Procedure for Tropine Benzylation: Preparation of Methyl 3α-Benzyloxy-2α-phenyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (35): To a solution of methyl 3α-hydroxy-2α-phenyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate **25** (300 mg, 1.15 mmol) and sodium hydride (230 mg, 5.75 mmol, 5.0 equiv.) in THF/DMF (8:1; 17 mL) was added benzyl bromide (668 μL, 5.75 mmol, 5.0 equiv.). The mixture was stirred at room temperature for 24 h, then quenched with saturated NH_4Cl solution (20 mL) and diluted with diethyl ether (20 mL). The aqueous layer was extracted three times with dichloromethane and the combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 3:1) to give compound **35** (354 mg, 88%) as a colorless syrup.

Methyl 3α-Benzyloxy-1-(1′,3′-dioxolan-2′-yl)-2α,4α-dimethyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (36): This product was obtained from methyl 3α-hydroxy-1-(1′,3′-dioxolan-2′-yl)-2α,4α-dimethyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate **26** (340 mg, 1.2 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 3:1 → 2:1) to give compound **36** (431 mg, 97%) as a colorless syrup.

***tert*-Butyl 3α-Benzyloxy-2α-methyl-4α-phenyl-8-azabicyclo[3.2.1]-oct-6-ene-8-carboxylate (37):** This product was obtained from *tert*-butyl 3α-hydroxy-2α-methyl-4α-phenyl-8-azabicyclo[3.2.1]oct-6-en-8-carboxylate **27** (230 mg, 0.73 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 4:1) to give compound **37** (265 mg, 90%), which was crystallized from hexane to give white crystals.

Methyl 3α-Benzyloxy-1-carboxaldehyde-2α,4α-dimethyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (38): A mixture of methyl 3α-benzyloxy-1-(1′,3′-dioxolan-2′-yl)-2α,4α-dimethyl-8-azabicyclo-[3.2.1]oct-6-ene-8-carboxylate **36** (90 mg, 0.24 mmol), formic acid (4 mL), and water (50 μL) was stirred for 4 h at room temperature. The reaction was then quenched with water (15 mL) and diluted with dichloromethane (15 mL). The aqueous layer was extracted three times with dichloromethane and the combined organic layers were washed with saturated $NaHCO_3$ aqueous solution, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (toluene/ethyl acetate, 4:1) to give compound **38** (78 mg, 98%) as a colorless syrup.

Methyl 3α-Benzyloxy-1-hydroxymethyl-2α,4α-dimethyl-8-azabicyclo[3.2.1]oct-6-ene-v. (39): To a solution of methyl 3α-benzyloxy-1-formyl-2α,4α-dimethyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate **38** (47 mg, 0.14 mmol) in methanol (5 mL) was added sodium borohydride (12 mg, 0.32 mmol, 2.3 equiv.). The reaction mixture was stirred for 3 h at room temperature, quenched with water (15 mL), and diluted with diethyl ether. The aqueous layer was extracted three times with diethyl ether and the combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (toluene/ethyl acetate, 3:1) to give compound **39** (39 mg, 83%) as a colorless syrup.

3α-Benzyloxy-2α-phenyl-8-methyl-8-azabicyclo[3.2.1]oct-6-ene (40): To a solution of methyl 3α-benzyloxy-2α-phenyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate **35** (70 mg, 0.20 mmol) in toluene (5 mL) at room temperature was added a 0.85 M solution of Red-Al in toluene (4.0 mL, 3.4 mmol, 17 equiv.). The reaction mixture was stirred for 24 h, then hydrolyzed with a saturated aqueous solution of sodium potassium tartrate and diluted with diethyl ether. The aqueous layer was extracted three times with diethyl ether and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (toluene/methanol, 10:1) to give compound **40** (50 mg, 86%) as a white solid.

Representative Procedure for the Selective Deprotection of *N*-Methyl Carbamate with Trimethylsilyl Iodide. − Preparation of 3α-Benzyloxy-2α-phenyl-8-azabicyclo[3.2.1]oct-6-ene (41): To an ice-cooled solution of methyl 3α-benzyloxy-2α-phenyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate **35** (350 mg, 1.0 mmol) in dry

dichloromethane (6 mL) was added trimethylsilyl iodide (620 μL, 4.00 mmol, 4.0 equiv.). The cooling bath was removed and the solution was stirred for 2 h at room temperature. The reaction mixture was then poured into a mixture of methanol (6 mL), dichloromethane (60 mL), saturated $Na_2S_2O_5$ solution (18 mL), and saturated $NaHCO_3$ solution (60 mL). After separation of the layers, the aqueous layer was extracted three times with dichloromethane and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (toluene/ethyl acetate/methanol, 5:5:3) to give compound **41** (141 mg, 50%) as a colorless syrup.

3α-Benzyloxy-1-(1′,3′-dioxolan-2′-yl)-2α,4α-dimethyl-8-azabicyclo-[3.2.1]oct-6-ene (42): This product was obtained from methoxy 3α-benzyloxy-1-(1′,3′-dioxolan-2′-yl)-2α,4α-dimethyl-8-azabicyclo-[3.2.1]oct-6-ene-8-carboxylate **36** (200 mg, 0.53 mmol). The residue was purified by column chromatography on silica gel (ethyl acetate/methanol/triethylamine, 10:3:0.1) to give compound **42** (88 mg, 52%) as a colorless syrup.

Procedure for the Selective Deprotection of *N*-*tert*-Butyl Carbamate with Trifluoroacetic Acid. − Preparation of 3α-Benzyloxy-2α-methyl-4α-phenyl-8-azabicyclo[3.2.1]oct-6-ene (43): To an ice-cooled solution of *tert*-butyl 3α-benzyloxy-2α-methyl-4α-phenyl-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate **37** (105 mg, 0.26 mmol) in dry dichloromethane (1 mL) was added a solution of 50% trifluoroacetic acid in dichloromethane (2.6 mL). The reaction was subsequently quenched with saturated $NaHCO_3$ solution and the mixture was diluted with dichloromethane. The aqueous layer was extracted three times with dichloromethane and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate/methanol/triethylamine, 10:1:0.1) to give compound **43** (73 mg, 93%) as a colorless syrup.

Representative Procedure for Nortropane Benzylation. − Preparation of 8-Benzyl-3α-benzyloxy-2α-phenyl-8-azabicyclo[3.2.1]oct-6-ene (44): To an ice-cooled solution of 3α-benzyloxy-2α-phenyl-8-azabicyclo[3.2.1]oct-6-ene **41** (68 mg, 0.23 mmol) and triethylamine (97 μL, 0.69 mmol, 3.0 equiv.) in THF (4 mL), benzyl bromide (28 μL, 0.25 mmol, 1.1 equiv.) was added dropwise. The cooling bath was then removed and the solution was stirred for 24 h at room temperature. The reaction was subsequently quenched with saturated $NaHCO_3$ solution and the mixture was diluted with dichloromethane. The aqueous layer was extracted three times with dichloromethane and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 2:1) to give compound **44** (70 mg, 79%) as a white solid.

8-Benzyl-3α-benzyloxy-1-(1′,3′-dioxolan-2′-yl)-2α,4α-dimethyl-8-azabicyclo[3.2.1]oct-6-ene (45): This product was obtained from 3α-benzyloxy-1-(1′,3′-dioxolan-2′-yl)-2α,4α-dimethyl-8-azabicyclo-[3.2.1]oct-6-ene **42** (29 mg, 0.09 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 5:1) to give compound **45** (26 mg, 70%) as a white solid.

Representative Procedure for Nortropane Benzoylation. − Preparation of 8-Benzoyl-3α-benzyloxy-2α-phenyl-8-azabicyclo[3.2.1]oct-6-ene (46): To an ice-cooled solution of 3α-benzyloxy-2α-phenyl-8-azabicyclo[3.2.1]oct-6-ene **41** (50 mg, 0.17 mmol) and triethylamine (70 μL, 0.50 mmol, 3.0 equiv.) in THF (4 mL), benzoyl chloride (20 μL, 0.18 mmol, 1.1 equiv.) was added dropwise. The reaction mixture was stirred for 2 h and was then quenched with saturated aq. $NaHCO_3$ solution and diluted with diethyl ether. The aqueous layer was extracted three times with diethyl ether and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 2:1) to give compound **46** (64 mg, 94%) as a white solid.

8-Benzoyl-3α-benzyloxy-1-(1′,3′-dioxolan-2′-yl)-2α,4α-dimethyl-8-azabicyclo[3.2.1]oct-6-ene (47): This product was obtained from 3α-benzyloxy-1-(1′,3′-dioxolan-2′-yl)-2α,4α-dimethyl-8-azabicyclo-[3.2.1]oct-6-ene **42** (25 mg, 0.08 mmol). The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 2:1) to give compound **47** (33 mg, 98%) as a white solid.

Acknowledgments

We thank P. Guenot for performing the mass spectral experiments, Dr. F. Bellamy (Laboratories Fournier, Dijon) for fruitful discussions and financial support, and Drs. R. Uma and Maxwell Davies for help in correcting the English.

[1] *Molecular Diversity and Combinatorial Chemistry* (Proceedings of two conferences sponsored by the Cambridge Healthtech Institute, Coronado, California, January 28−February 2, 1996) (Eds.: I. M. Chaiken, K. D. Janda), American Chemical Society, Washington DC, **1996**.
[2] M. Lounasmaa, T. Tamminen, in: *The Alkaloids* (Ed.: G. A. Cordell), Academic Press, San Diego, **1993**, Vol. 44, Chapter 1.
[3] G. Fodor, R. Dharanipragada, *Nat. Prod. Rep.* **1993**, *10*, 199−206.
[4] J. S. Koh, J. A. Ellman, *J. Org. Chem.* **1996**, *61*, 4494−4495.
[5] P. E. Thompson, D. L. Steer, M. I. Aguilar, M. T. W. Hearn, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2699−2704.
[6] [6a] H. M. L. Davies, J. J. Matasi, L. M. Hodges, N. J. S. Huby, C. Thornley, N. Kong, J. H. Houser, *J. Org. Chem.* **1997**, *62*, 1095−1105. − [6b] I. Gauthier, J. Royer, H.-P. Husson, *J. Org. Chem.* **1997**, *62*, 6704−6705. − [6c] J. H. Rigby, F. C. Pigge, *Org. React.* (Ed.: L. A. Paquette), Wiley, New York, **1997**, Vol. 51, Chapter 3, 351−478. − [6d] A. S. Hernandez, A. Thaler, J. Castells, H. Rapoport, *J. Org. Chem.* **1996**, *61*, 314−323. − [6e] H. E. Schink, H. Petterson, J.-E. Bäckvall, *J. Org. Chem.* **1991**, *56*, 2769−2774 and references cited therein.
[7] J. Mann, L. C. de Almeida Barbosa, *J. Chem. Soc., Perkin Trans. 1* **1992**, 787−790.
[8] C. Rappe, *Acta Chem. Scand.* **1962**, *16*, 2467−2468.
[9] S. S. Dehmlow, E. V. Dehmlow, *Z. Naturforsch. B., Anorg. Chem. Org. Chem.* **1975**, *30*, 404−408.
[10] A. J. Fry, J. J. O'Dea, *J. Org. Chem.* **1975**, *40*, 3625−3631.
[11] G. G. Hoffman, H. Klein, *Chem. Ber.* **1986**, *119*, 514−523.
[12] R. E. Lutz, T. A. Martin, J. F. Codinton, T. M. Amaker, R. K. Allison, N. H. Leake, R. J. Rewlett, Jr., J. D. Smith, J. W. Wilson III, *J. Org. Chem.* **1949**, *14*, 982−1000.
[13] H. Takaya, S. Makino, Y. Hayakawa, R. Noyori, *J. Am. Chem. Soc.* **1978**, *100*, 1765−1777.
[14] H. F. Olivo, D. A. Colby, M. S. Hemenway, *J. Org. Chem.* **1999**, *64*, 4966−4968.
[15] [15a] H. M. R. Hoffman, *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 1−88. − [15b] J. Mann, *Tetrahedron* **1986**, *42*, 4611−4659.
[16] [16a] Y. Hayakawa, Y. Baba, S. Makino, R. Noyori, *J. Am. Chem. Soc.* **1978**, *100*, 1786−1790. − [16b] M. Majewski, R. Lazny, *J. Org. Chem.* **1995**, *60*, 5825−5830. − [16c] R. M. Moriarty, O. Prakash, P. R. Vavilikolanu, R. K. Vaid, W. A. Freeman, *J. Org. Chem.* **1989**, *54*, 4008−4010. − [16d] A. Armstrong, B. R. Hayter, *J. Chem. Soc., Chem. Commun.* **1998**, 621−622. − [16e] D. Simoni, M. Roberti, V. Andrisano, M. Manferdini, R. Rondanin, A. P. Kozikowski, *J. Org. Chem.* **1998**, *63*, 4834−4837. − [16f] M. Node, S. Nakamura, D. Nakamura, T. Katoh, K. Nishide, *Tetrahedron Lett.* **1999**, *40*, 3357−3360.
[17] J. L. Paparin, C. Crévisy, R. Grée, *Tetrahedron Lett.* **2000**, *41*, 2343−2346.

Received February 29, 2000
[O00102]