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Exo- and Endo- 6-Hydroxy- and 6,7-Epoxytropanes; Total Synthesis of Scopine, Pseudoscopine, and Nor- Derivatives

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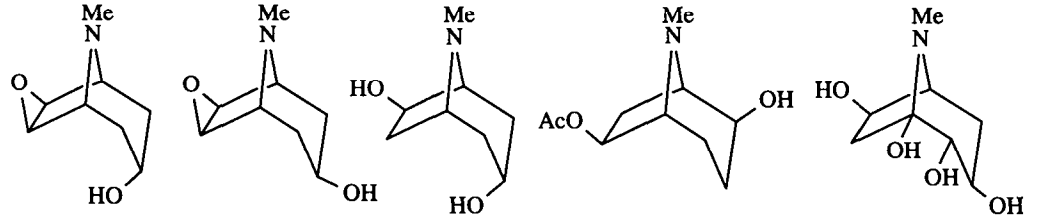
Abstract Novel *endo*- 6,7-epoxy-8-azabicyclo[3.2.1]octane derivatives and the corresponding *exo*-analogues have been synthesised and show substantially different reactivity; the resistance of the *exo*-epoxides to ring opening during hydride reduction and catalytic hydrogenolysis is exploited in a total synthesis of scopine, pseudoscopine, and nor- derivatives.

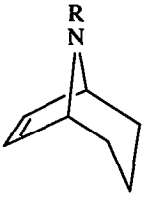
Tropane derivatives having epoxy and hydroxy groups in the 2-carbon bridge are of considerable importance.[1] Natural products such as scopolamine are based on the *exo*-6,7-epoxytropane derivative scopine (**1**); recent interest in 6-hydroxy- substituted tropanes has included valuable natural targets such as schizanthines[1d] based on the 3,6-dihydroxytropane skeleton (**3**), baogongteng derivatives[2] (e.g. baogongteng A (**4**)), and calystegines[3] (e.g. calystegine B_1 (**5**)) which are based on the 1-hydroxynortropane skeleton. We wished to obtain *exo*- epoxytropanes and were also intrigued by the lack of compounds bearing an *endo*-6,7-epoxy ring in the tropane skeleton (*endo*-(**7**)).



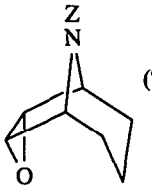
scopine (**1**) pseudoscopine (**2**) (**3**) (**4**) (**5**)

Classical methods such as the Robinson tropane synthesis fail to allow incorporation of an epoxy linkage into the 6,7 bridge.[4] Interest has been generated recently by the first practical synthesis of scopine and pseudoscopine (**2**)[5] (both of which contain an *exo*-6,7-epoxide) and by a significant improvement to the synthesis of trop-6-ene derivatives by addition of oxoallyls to pyrroles.[6] Whilst the *exo*- face of N-protected 6,7-dehydronortropanes is susceptible to epoxidation,[6] it is not easy to achieve efficiently in the case of 6,7-dehydrotropine (**6a**) itself[7] and we have avoided the use of N-protecting groups such as alkoxycarbonyl groups to date in the expectation that the epoxide would be opened in the deprotection step. We are currently developing methods for regio- and stereoselective incorporation of oxygen into azabicycles[8a] and have

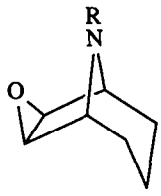
reported the incorporation of *exo*- and *endo*- epoxy groups into the 2-carbon bridge of homotropanes (9-azabicyclo[4.2.1]nonanes).[8b] Surprisingly, this work demonstrated that an *exo*-7,8-epoxide group in the homotropane skeleton was able to survive treatment with LAH or hydrogenolysis; it encouraged us to explore similar pathways in the tropane system and raised the expectation that a benzyloxycarbonyl group might be used to protect the nitrogen and yet be converted at a late stage into an NMe or NH group without affecting the epoxide. We now report the efficient incorporation of oxygen into both the 'non-natural' (*endo*-) face (**7**) and the 'natural' (*exo*-) face (**8**) of the 2-carbon bridge of tropanes and nortropanes together with an extension of the basic methodology in a total synthesis of scopine and pseudoscopine.



(6a) R=Me
(6b) R=H
(6c) R=CO_2CH_2Ph(Z)

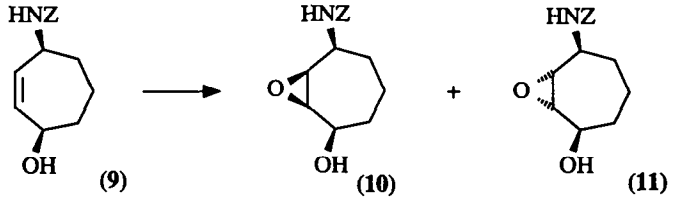


(7c)



(8a) R=Me
(8b) R=H
(8c) R=Z

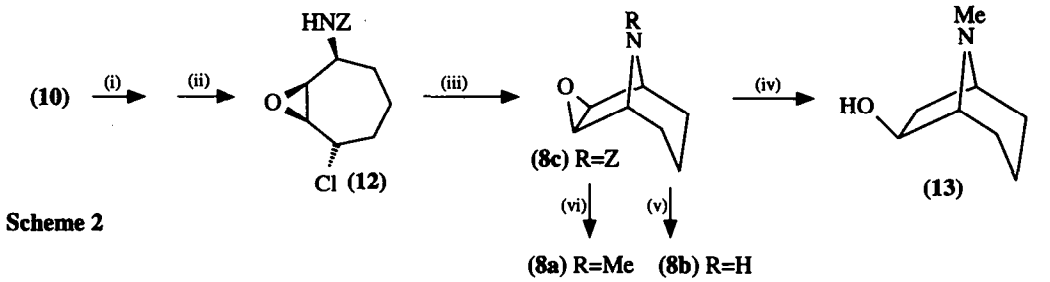
N-Benzyloxycarbonylnortrop-6-ene (**6c**) is not readily available[9] so that the obvious direct route to the *exo*-epoxide by treatment with MCPBA was closed to us. Even if the epoxidation of N-alkylnortrop-6-enes had been easy, the synthesis of nortrop-6-enes (**6b**) or N-alkyl derivatives such as (**6a**) is not possible in acceptable yields.[9] Attention was therefore turned to epoxidation of the precursor (**9**).[10] The difficulty in predicting stereoselectivity in the epoxidation of similar cycloheptene derivatives has already been noted.[5] MCPBA gave a mixture of the *syn*-epoxide (**10**) and the *anti*-isomer (**11**) in a ratio of approximately 3:2 and the ratio of epoxides varies according to the reagent used as shown in scheme 1. Complete *syn*-selectivity was shown by $Vo(acac)_2$[11] and other reagents are currently under study. The stereoisomers (**10**) and (**11**) were readily separable by chromatography and provided access to both (**8c**) and (**7c**) respectively.



(9) **(10)** **(11)** [Z = CO_2CH_2Ph]

Scheme 1				
	MCPBA	56%	37%	(All yields are
	$Vo(acac)_2/Bu^tO_2H$	43%	-	isolated yields)

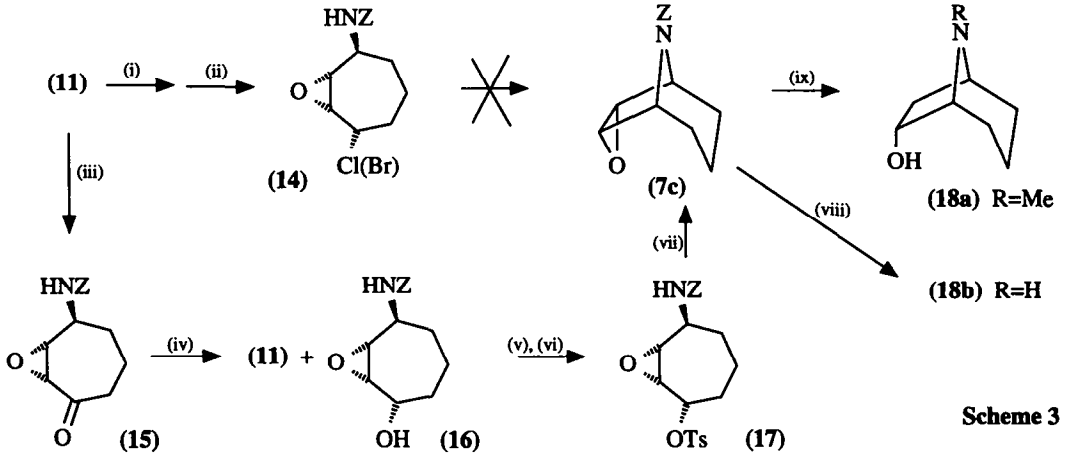
Tosylation of (**10**) was followed by inversion of configuration at C-4 with chloride ion (scheme 2); base-induced cyclisation of (**12**) then yielded (**8c**) in 73% overall yield from (**10**). The deprotection of nitrogen by catalytic hydrogenolysis proceeded efficiently to give exo-6,7-epoxynortropane (**8b**)[12] in 95% yield. Hydride reduction at 25°C reduced the benzyloxycarbonyl group to methyl but also opened the epoxide to afford *exo*-6-hydroxytropane (**13**) in 70% yield. However, *exo*-6,7-epoxytropane itself (**8a**)[12] was isolated from treatment of (**8c**) with DIBAH at -78°C.



Scheme 2

(i)BuLi/TosCl 99%; (ii) LiCl/DMSO/55°C 85%; (iii) NaH/THF/DME 87%; (iv) DIBAH/25°C 70%; (v) H_2/Pd 95%; (vi) DIBAH -78°C 57%

Application of the same approach starting from (**11**) proceeded smoothly up to the chloro- compound (**14**) but attempts to cyclise this (or the corresponding bromo- compound) using a variety of bases failed to give (**7c**). A better leaving group was clearly required in this case and a route to the tosylate (**17**) from (**11**) via oxidation and borohydride reduction is summarised in scheme 3.



Scheme 3

(i) BuLi/TosCl 92%; (ii) LiCl/DMSO 95%; (iii) Jones 95%; (iv) L-Selectride 89% (45% of (**11**) recycled); (v) separate (**16**); (vi) as (i) 89% (vii) NaH/THF/DME 61%; (viii) H_2/Pd 76%; (ix) LAH 70%.

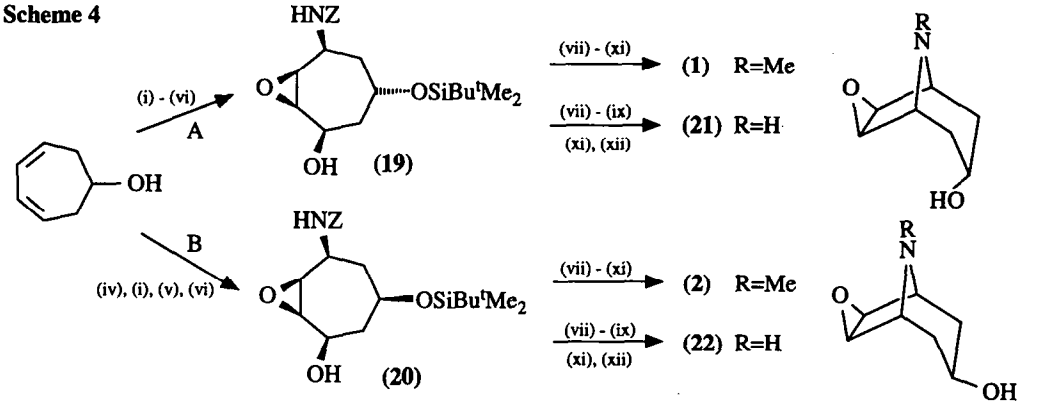
The *endo*-epoxide (**7c**) was formed on treatment of (**17**) with base and is, to the best of our knowledge, the first *endo*-6,7-epoxytropane derivative to have been reported. Further improvements to the efficiency of conversion of (**15**) into (**16**) are being sought. Hydride reduction and hydrogenolysis of (**7c**) confirmed the higher reactivity of the *endo*- epoxides which had been foreshadowed by results in the homotropane analogues;[8b] the products were the *endo*- hydroxy derivatives (**18a**) and (**18b**).

The formation and survival of the *exo*-epoxytropanes described here is entirely in line with the isolation of natural products containing an *exo*- (but not an *endo*-) three-membered ring. The availability of both stereoisomers will allow investigation of the factors influencing the relative reactivity of these ring systems and the possible influence of the bridging nitrogen in directing epoxide ring opening from the *exo*- face. Significantly, earlier work[13] has established that coordination to the bridging nitrogen of 7-azabicyclo[2.2.1]-heptene derivatives is important in increasing reactivity and controlling facial selectivity. The role of

nitrogen in the tropanes appears to be significant both in synthesis and possibly in biosynthesis (where hydroxylases operate on the *exo*- face).

The value of this general approach to epoxytropanes is illustrated (scheme 4) by syntheses of both scopine (**1**) and pseudoscopine (**2**) from readily-available cyclohepta-3,5-dienol *via* the key intermediates (**19**) and (**20**) respectively. The route is based on the approach in schemes 2 and 3 but with the addition of simple protection/deprotection steps. Here also, conversion of the N-benzyloxycarbonyl group into NMe or NH [yielding the novel norscopine (**21**) and norpseudoscopine (**22**)] was achieved with retention of the epoxide; details will be recorded in the full paper.

Scheme 4



(i) $PhCH_2OCONHOH/Me_4N^+IO_4^-$ 85% (includes 20% of the epimeric silyloxy compound in path B); (ii) Jones 90%; (iii) L-Selectride 74% (includes 15% of the epimeric alcohol); (iv) Bu^{t}Me$_2$SiCl/imidazole 91-93%; (v) Na/Hg 75-85%; (vi) MCPBA 81-92% [(**19**) is the major epoxide in path A, (**20**) is the minor epoxide in path B]; (vii) BuLi/TosCl 85%; (viii) LiCl/DMSO 68-79%; (ix) NaH 68-82%; (x) LAH 95%; (xi) Bu^{t}NH$_3^+F^-$ 81-83%; (xii) H_2/Pd 82-100%

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