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Stereoselective Oxygenation of the Homotropane Ring System; Synthesis of Exo- and Endo- 7-Hydroxy- and 7,8-Epoxyhomotropanes

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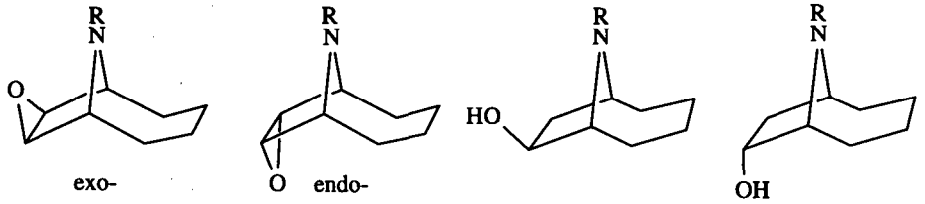
Abstract Stereoselective introduction of an *endo*- epoxide into the 2-carbon bridge of the homotropane (9-azabicyclo[4.2.1]nonane) ring system has been achieved via a 4-aminocyclooct-2-enol derivative; the direct route to the *exo*- analogue from 7,8-dehydrohomotropanes is less efficient but the novel *exo*- and *endo*- epoxides show substantially different reactivity. Completely different tautomeric preferences are observed for the two diastereoisomeric 1-hydroxy-7,8-epoxyhomotropanes, unexpectedly providing the method of choice for a clean and effective synthesis of the *exo*-epoxyhomotropane derivatives.

We have recently described the synthesis of homotropanes (9-azabicyclo[4.2.1]nonanes), homotrop-7-enes, and some simple 1-substituted derivatives[1] and we are currently investigating more general routes to analogues bearing substituents in the 2- and 4- carbon bridges. Other recent interest in the 9-azabicyclo-[4.2.1]nonane ring system has been confined almost entirely to the algal metabolite anatoxin-*a*;[2] oxygenated derivatives are rare[3] despite the well-known and important physiological activity of oxygenated derivatives of lower homologues (tropanes).[4] With this in mind, we now describe practical synthetic approaches to homotropanes and nor- derivatives **(1)** - **(4)**, bearing epoxy- and hydroxy- substituents in the 2-carbon bridge, which allow total control over *exo*- or *endo*- stereochemistry and open the way to higher homologues of biologically active tropane derivatives as well as novel anatoxin analogues.



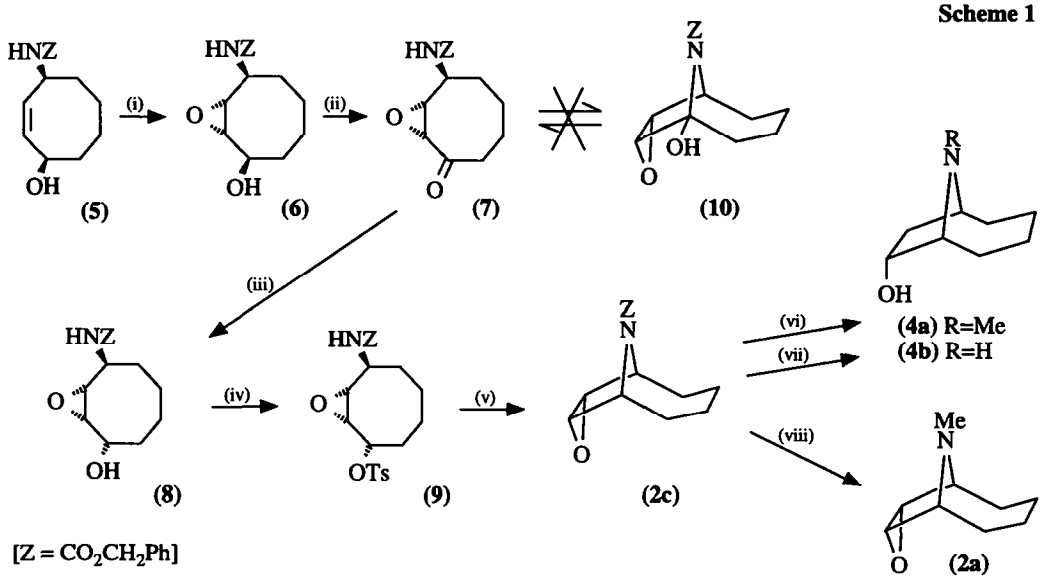
exo- O endo-

$R=CH_3$	**(1a)**	**(2a)**	**(3a)**	**(4a)**
R=H	**(1b)**		**(3b)**	**(4b)**
$R=CO_2CH_2Ph(Z)$	**(1c)**	**(2c)**	**(3c)**	

Our initial investigations concerned the *endo*-7,8-epoxy derivatives. There is no precedent for direct *endo*- epoxidation of 7,8-dehydro-homotropanes or homologues. However, in pursuing our initial interest in monocyclic/bicyclic tautomerism in cyclic amino-ketones,[1b,5] we have synthesised the epoxy-aminoketone derivative **(7)** which has opened the way to the novel *endo*-epoxides **(2)** and alcohols **(4)**. Thus, treatment of

the key *cis*-disubstituted cyclooctene (**5**) (available from cycloocta-1,3-diene in 75% yield[1]) with MCPBA provided the epoxide (**6**) in good yield as a single stereoisomer (scheme 1). Jones oxidation gave (**7**); subsequent reduction of (**7**) with borohydride gave only the *trans*- 1,4-amino-alcohol derivative (**8**)[6] and thence the tosylate (**9**) (scheme 1). Base-induced intramolecular displacement proceeded efficiently to yield (**2c**). Treatment of (**2c**) with LAH converted the N-benzyloxycarbonyl group to N-methyl but led concurrently to opening of the epoxide and formation of the *endo*- homotropan-7-ol (**4a**) in 70% yield; catalytic hydrogenolysis of (**2c**) provided the corresponding norhomotropanol (**4b**). The *endo*- epoxide (**2c**) was clearly reactive but further investigation demonstrated that partial conversion into the N-methyl derivative (**2a**) was possible on careful treatment with LAH at -78°C.

Scheme 1



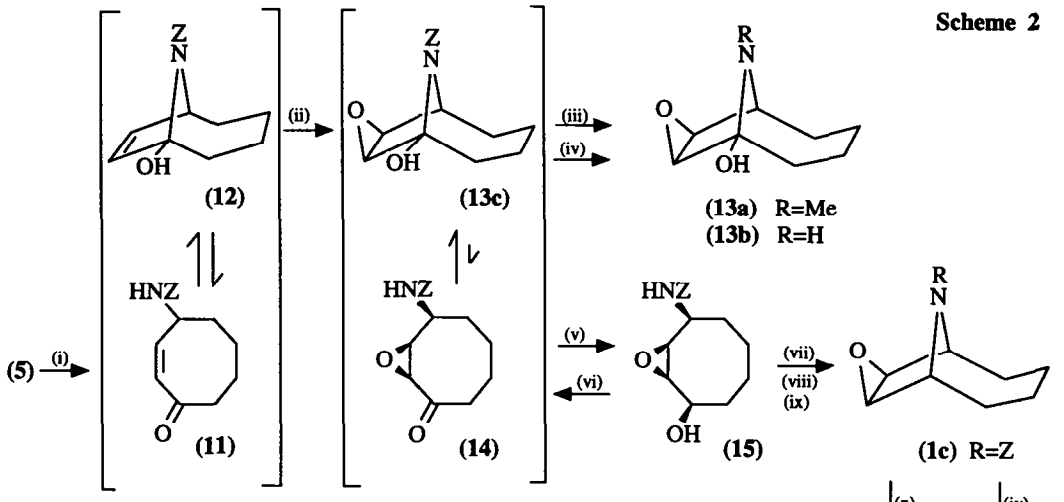
(i) MCPBA 95%; (ii) Jones 96%; (iii) $NaBH_4$/THF/heat 88%; (iv) BuLi/TosCl 96%; (v) NaH/THF 93%; (vi) LAH 70%; (vii) H_2/Pd 76%; (viii) LAH/-78°C 54% [+ unchanged (2c)]

Surprisingly, NMR spectra of (**7**) showed no evidence for the presence of any of the bicyclic tautomer (**10**) (scheme 2) in contrast to observations in simpler systems.[1b] We were intrigued by the control apparently being exerted by the epoxide over the position of the tautomeric equilibrium and therefore prepared the diastereoisomeric epoxide from the 4-aminocyclooct-2-enone derivative (**11**) which had previously been shown[1a] to exist in equilibrium with the bicyclic tautomer (**12**) (scheme 2). The anticipated lower reactivity of the α,β-unsaturated ketone (**11**) with MCPBA was confirmed by the isolation of the bicyclic *exo*-epoxide (**13c**) as a single stereoisomer. Furthermore, the NMR spectra of (**13c**) showed no evidence of the monocyclic tautomer (**14**), in total contrast to the behaviour of (**7**).

The epoxide in (**13c**) was remarkably stable; unlike the *endo*-epoxide (**2c**), it survived treatment with LAH at ambient temperature (which yielded the N-methyl derivative (**13a**)) and hydrogenolysis (which gave the nor- analogue (**13b**)). Despite the lack of NMR evidence for (**14**), the presence of at least a trace of this monocyclic tautomer in equilibrium with (**13c**) was indicated when treatment with $NaBH_4$ led to formation of the amino-alcohol (**15**) as a single stereoisomer in surprisingly good yield (98%). The contrast in the behaviour of (**13c**) under the different reducing conditions was unexpected. The interception of the bicyclic

tautomer (**13c**) with LAH must occur rapidly and the product (**13a**) is then unreactive, being totally bicyclic. In contrast, (**13c**) is unreactive to $NaBH_4$ and a slower reaction presumably syphons off the very small stationary concentration of the monocyclic ketone (**14**). The latter conversion was reversible, thus (**15**) reverted to (**13c**) in 95% yield on Jones oxidation.

Scheme 2

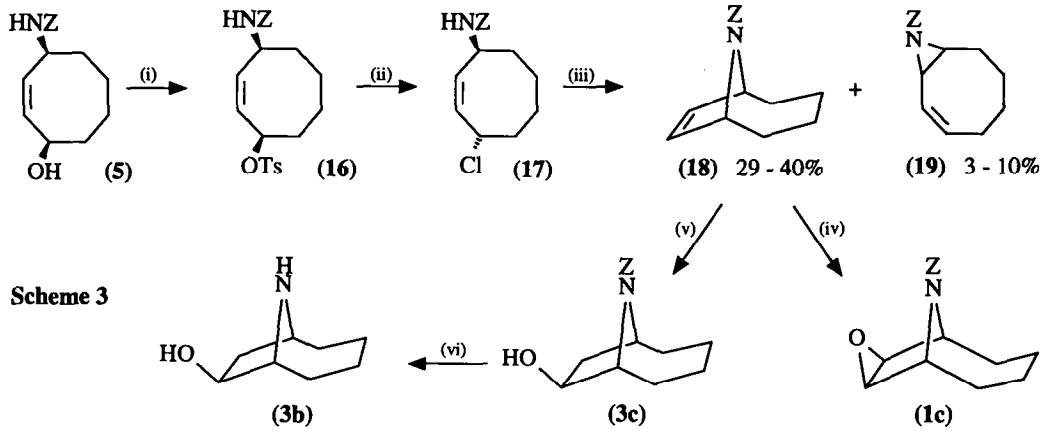


(i) $BaMnO_4$ 85%; (ii) MCPBA 79%; (iii) LAH 71%; (iv) H_2/Pd 86-97%; (v) $NaBH_4$ 98%; (vi) Jones 95%%; (vii) BuLi/TosCl 92%; (viii) LiCl/DMSO/60°C 87%; (ix) 98%; (x) DIBAH/25°C 81%

The isolation of (**15**) was very significant since, following conversion into the tosylate and thence the *trans*- chloro-compound,[7] cyclisation with sodium hydride yielded (**1c**) in 98% yield. The relative reactivity of the *exo*- (**1c**) and *endo*- (**2c**) epoxides was markedly different; the epoxide in (**1c**) survived modification of the nitrogen substituent by treatment with LAH at ambient temperature or catalytic hydrogenolysis, allowing isolation of the N-methyl and nor- derivatives (**1a**) and (**1b**) respectively (scheme 2). Whilst the isolation of *endo*-7,8-epoxyhomotropane (**2a**) had been possible only after careful hydride reduction of (**2c**) at -78°C, the *exo*- isomer (**1a**) was significantly more robust, surviving similar treatment at 25°.

This route to the *exo*-epoxides was welcome. Based on earlier studies in lower homologues,[8] our initial approach to the *exo*- epoxide (**1c**) involved direct epoxidation[9] of the N-protected alkene (**18**) but the overall conversion of (**5**) into (**18**) was less efficient than had been expected as shown in scheme 3. The intermediate tosylate (**16**) was unstable and, without very careful control of temperature, the chloro-compound (**17**) was always obtained as an inseparable mixture of stereoisomers. Yields were modest to poor, elimination led to by-products, and the sample of (**18**) formed in the base-induced cyclisation of (**17**), though separable chromatographically, was also accompanied by the aziridine (**19**) formed by competitive 1,2-addition.

Nevertheless, conversion of (**18**) into the epoxide (**1c**) did proceed as expected and preparation of the *exo*-7-hydroxy compound (**3c**) using diborane was straightforward; subsequent deprotection of (**3c**) by hydrogenolysis gave the secondary amino-alcohol (**3b**).



Scheme 3

(i) BuLi/TosCl 66%; (ii) LiCl/DMSO 38%; (iii) NaH/THF/DME; (iv) MCPBA 84%; (v) BH_3:THF/H_2O_2 71%; (vi) H_2/Pd 96%

We are presently extending our study of homotropanes to explore the factors which influence the relative stabilities of the stereoisomeric *exo-* and *endo-* epoxides and are extending the range of substituents in the 2-carbon bridge in the search for biological activity. The unexpected stability of the *exo-* epoxide linkage in these systems has led us to extend our investigations to lower homologues including *exo*-6,7-epoxytropanes and the first *endo*-6,7-epoxytropane derivatives.[11]

References and Notes

1. **a.** Homotropanes, 7,8-dehydrohomotropanes, and 1-alkyl derivatives: Smith, C.R.; Justice, D.E.; Malpass, J.R.; *Tetrahedron*, **1993**, *49*, 11037; **b.** 1-Hydroxyhomotropanes, nor-, and 7,8-dehydro-derivatives: Smith, C.R.; Justice, D.E.; Malpass, J.R.; *Tetrahedron*, **1994**, *50*, 11039.
2. e.g. P. Somfai and J. Åhman, *Tetrahedron Lett.*, **1992**, *33*, 3791 for a recent synthetic route and references to earlier work. See A. Hernandez and H. Rapoport, *J.Org.Chem.*, **1994**, *59*, 1058 for recent analogue work and additional references to earlier studies.
3. The 3-hydroxy- derivative has been prepared via ring expansion of tropinone: Cope, A,C.; Nace, H.R.; Estes, L.L. Jr., *J.Amer.Chem.Soc.*, **1950**, *72*, 1123. See also Bastable, J.W.; Hobson, J.D. Riddell, W.D. *J.Chem.Soc.Perkin Trans.1.*, **1972**, 2205.
4. **a.** See G. Fodor and R. Dharanipragada, *Natural Product Reports*, **1994**, *10*, 443; **1993**, *9*, 199 and earlier reports for recent reviews of tropanes and related compounds. **b.** *ibid.*, **1991**, *8*, 603. **c.** *ibid.*, **1990**, 7, 539.
5. Justice, D.E.; Malpass, J.R. *J.Chem.Soc.Perkin Trans.1.*, **1994**, 2559.
6. Application of standard Mitsunobu epimerisation conditions to (**6**) was not successful; neither was the use of KO_2 (Corey, E.J. Nicolaou, K.C.; Shibasaki, M.; Machida, Y; Shiner, L.S. *Tetrahedron Lett.*, **1975**, *16*, 3183) or caesium salts (Torisawa, Y.; Okabe, H.; Ikegami, S. *Chem. Lett.*, **1984**, 1555; Krnizinga, W.H.; Strijtveen, B.; Kellogg, R.M. *J.Org.Chem.*, **1981**, *46*,4323) on the mesylate.
7. It is important that the temperature of the reaction mixture be carefully controlled (maximum 50 - 60°C) during treatment of the tosylate with LiCl in order to prevent formation of the epimer.
8. **a.** Epoxidation of N-carboalkoxy-7-azabicyclo[2.2.1]hept-2-ene derivatives has been shown to give the *exo-* epoxide: Howarth, N.; Ph.D. thesis, University of Leicester, **1991**. **b.** e.g. epoxidation of N-methoxycarbonylnortrop-6-ene-3-one (methyl-3-oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate): Mann, J.; Barbosa, L-Z. de A. *J.Chem.Soc.Perkin Trans.1.*, **1992**, 787.
9. The presence of the N-alkoxycarbonyl group obviously avoids oxidation of the amino- nitrogen but it also appears to play an important role in directing the facial approach. An earlier report of epoxidation of 6,7-dehydrotropine (Dobó, P.; Fodor, G.; Janzsó, G.; Koczor, I.; Tóth, J.; Vincze, I. *J.Chem.Soc.*, **1959**, 3461) has been found by us and by others[10] to give low conversions.
10. Schink, H.E.; Petterson, H.; Bäckvall, J.E.; *J.Org.Chem.*, **1991**, *56*, 2769.
11. Justice, D.E.; Malpass, J.R.: following paper.

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