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Synthesis of Exo- and Endo-6,7-Epoxytropanes

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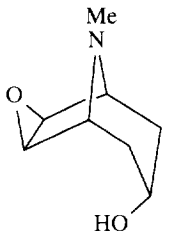
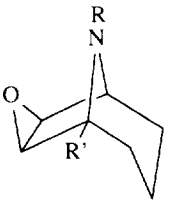
Abstract: Diastereoisomeric N-protected 2,3-epoxy-4-amino-cycloheptanols are synthesised: cyclisation of derivatives provides a practical route to N-protected *exo*-(β-)-6,7-epoxynortropanes and the first *endo*-(α-)-6,7-epoxy-nortropane. Hydride reduction gives the corresponding *exo*- and *endo*- 6-hydroxytropanes respectively. However, the *exo*-epoxide survives both hydride treatment at low temperature and hydrogenolysis, allowing retention of the epoxide during conversion of the benzyloxycarbonyl group respectively into N-methyl or NH derivatives thus opening an effective route to *exo*-6,7-epoxytropanes and -nortropanes. The N-protected 1-hydroxy-6,7-epoxytropane analogues actually exist as the monocyclic 2,3-epoxy-4-aminocycloheptanone tautomers.

Introduction

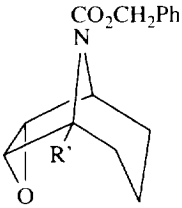
Tropane derivatives having epoxy and hydroxy groups in the 2-carbon bridge are of considerable importance.[1] Natural products such as scopolamine are based on the *exo*-6,7-epoxytropane derivative scopine (**1**); recent interest in *exo*-6-hydroxy- substituted tropanes has included valuable natural targets such as schizanthines,[1d] baogongteng derivatives,[2] and calystegins[3] (the latter family is based on the 1-hydroxynortropane skeleton). We wished to obtain *exo*- (β-) epoxytropanes (and hence hydroxy derivatives). We were also intrigued by the lack of compounds, natural or non-natural, bearing an *endo*-(α-) 6,7-epoxide in the tropane skeleton.



scopine (**1**)



(**2a**) R' = H, R = Me
(**2b**) R' = H, R = H
(**2c**) R' = H, R = CO_2CH_2Ph
(**4**) R' = OH, R = CO_2CH_2Ph



(**3a**) R' = H
(**5**) R' = OH

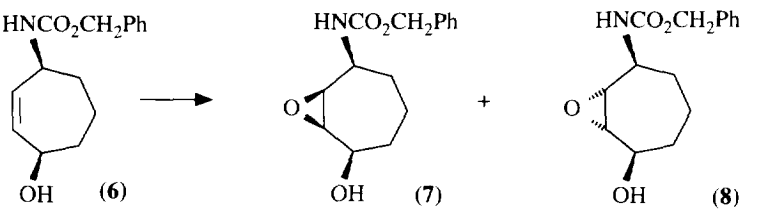
Classical methods such as the Robinson tropane synthesis[4a] fail to allow incorporation of an epoxy linkage into the 6,7 bridge.[4b] Interest has been generated recently by the first practical synthesis of scopine and pseudoscopine[5] (both of which contain an *exo*-6,7-epoxide) and by a significant improvement to the synthesis of trop-6-ene derivatives by addition of oxyallyls to pyrroles.[6] Whilst the *exo*- face of the π-bond in N-protected 6,7-dehydronortropanes is susceptible to epoxidation,[6] it is not easy to achieve efficiently in the case of 6,7-dehydrotropine itself[7] due to reaction at the amino- nitrogen. We avoided the use of N-protecting groups such as alkoxycarbonyl groups in our early work in the expectation that the epoxide would be opened in the deprotection step. However, during studies directed towards the regio- and stereoselective incorporation of *exo*- and *endo*- epoxy groups into the 2-carbon bridge of homotropanes (9-azabicyclo[4.2.1]nonanes)[8] we found that an *exo*-7,8-epoxide group in the homotropane skeleton was

able to survive treatment with LAH or hydrogenolysis. This encouraged us to explore similar pathways in the tropane system and raised the expectation that a benzyloxycarbonyl (or similar) 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-* (α-) face (**7**) and the 'natural' *exo-* (β-) face (**8**) of the 2-carbon bridge of tropanes and nortropanes.[9]

Exo- (β-) 6,7-epoxytropanes

Neither 6,7-dehydrotropanes nor N-protected 6,7-dehydronortropanes are readily available[10] so that the route to the *exo*-epoxides by direct epoxidation was closed to us. We therefore chose to prepare *exo-* and *endo-* epoxyhomotropanes by epoxidation of the readily-available key precursor (**6**)[11] prior to bicyclisation of the to form the tropane ring system. Existing work has shown that epoxidation of cyclooct-2-enol with peroxyacid proceeds with high anti-stereoselectivity,[12] whereas treatment of cyclohept-2-enol under similar conditions affords a mixture of *cis-* and *trans-* epoxides.[13] Treatment of (**6**) with 1.2 equivalents of MCPBA gave (**7**) and (**8**) in a ratio of 62:38. These two epoxides provided the entry, respectively, to the *exo-* and *endo-* 6,7-epoxytropane series and other reagents were explored with a view to manipulating the ratio of epoxides. The results are summarised in scheme 1. All yields are isolated pure yields and the ratios are calculated from ^{1}H NMR integrations of crude reaction mixtures.

Scheme 1



Reagent	Ratio			Yield
MCPBA/CH_2Cl_2	62	:	38	93%
MMPP/EtOH/H_2O	42	:	58	72%
$VO(acac)_2$/^{t}BuOOH	>95	:	<5	<40%

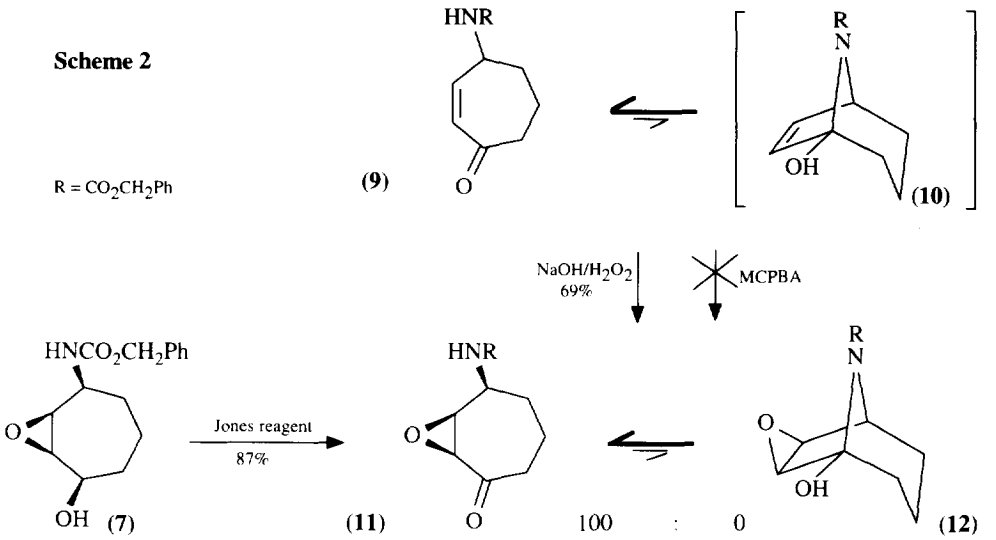
A slight shift towards the *endo-* epoxide was observed using magnesium monoperphthalate (MMPP).[14,15] A vanadium-catalysed peroxyacid procedure[16] was also used to epoxidise (**6**); in good agreement with literature precedent,[16] a high *syn-* stereoselectivity was observed but the yield was disappointing. The high-yielding MCPBA epoxidation, along with the easy separation of the two epoxides by chromatography provided the most efficient means of obtaining (**7**) and (**8**).

The stereostructures of the two epoxides were elucidated after comparison of the ^{1}H NMR spectra with those of the higher (cyclooctane-based) homologues. The *anti-* epoxide protons in (**8**) showed mutual vicinal coupling ($J_{2,3}$ = 5.0 Hz) together with additional vicinal coupling ($J_{1,2}$ = 6.6 and $J_{3,4}$ = 5.8 Hz) to the α-hydroxy and α-nitrogen protons (the homologous *anti-* epoxide showed similar, slightly larger couplings of 9.3 and 8.2 Hz to the α-hydroxy and α-nitrogen protons[8]). The *syn-* epoxide (**7**) displayed no coupling between H_1 and H_2 nor between H_3 and H_4. These assignments were supported by the chemical evidence of high *syn*-stereoselectivity for the vanadium-catalysed epoxidation and, ultimately, by comparison of spectra of *exo-* and *endo-* epoxytropanes with the epoxyhomotropane homologues.

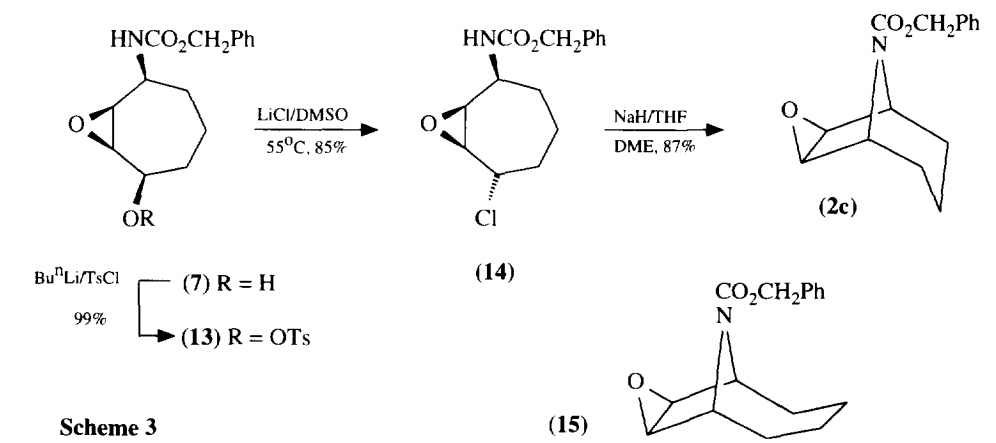
We had expected to be able to introduce an *exo*-epoxide into the 1-hydroxytropane skeleton by treatment of (**9**)[11] with MCPBA (which had proceeded smoothly in the case of the 8-ring homologue of (**9**) *via* the bicyclic hemiaminal[8]). However, there was no spectroscopic evidence for the existence of the corresponding bicyclic tautomer (**10**) in the tropane series and the reaction failed (scheme 2). Nevertheless,

treatment of **(9)** with alkaline hydrogen peroxide gave the cis-epoxy ketone **(11)** as the only product in 69% yield; **(11)** also existed only in the monocyclic form with no spectroscopic evidence for the hemiaminal **(12)**. These tautomeric preferences are in agreement with previous results in 4-aminocycloheptanones and -hept-2-enones bearing an alkoxycarbonyl group at nitrogen.[11]

Scheme 2



The epoxy-ketone **(11)** was also synthesised by Jones oxidation of the epoxy-alcohol **(7)** (scheme 2) in 87% yield; NMR spectra were identical to those of a sample prepared from **(9)**. The ^{13}C NMR spectrum displayed a characteristic ketone carbonyl signal at δ 208.5. The ^1H NMR spectrum showed two epoxide signals at δ 3.37 and δ 3.47 with very small vicinal coupling ($J_{3,4}$ = 0.9 Hz) between the α-nitrogen proton and the adjacent epoxide proton. The *trans*-1,4 stereochemistry necessary for cyclisation was introduced as shown in scheme 3.



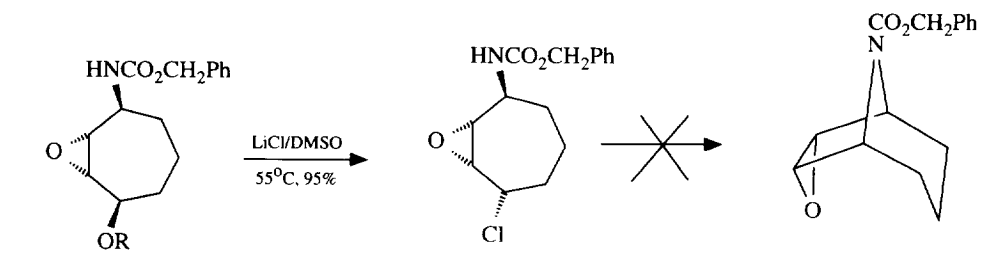
Scheme 3

The epoxy-alcohol **(7)** was converted into the tosylate **(13)** and the tosylate displaced by chloride ion with inversion to give **(14)**. Cyclisation was then achieved by treatment of **(14)** with sodium hydride and the ^1H NMR spectrum of the product **(2c)** was similar to that of the *exo*-epoxyhomotropane **(15)**.[8] As a result of slow N-CO rotation, two doublets at δ 3.42 (J = 3.2 Hz) and δ 3.45 (J = 3.2 Hz) were observed for the

epoxide protons together with two broad singlets at δ 4.33 and δ 4.41 for the bridgehead protons. The absence of measurable coupling between these two sets of signals confirmed the *exo*-stereochemistry of the epoxide group. Reductive deprotection of (**2c**) is described below.

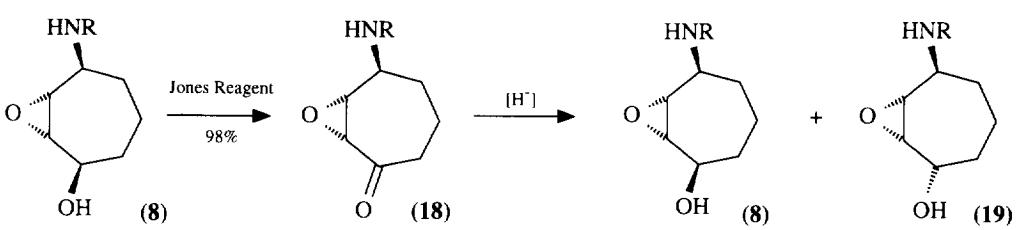
Endo- (α-) 6,7-epoxytropanes

The *trans*- epoxy-alcohol (**8**) was converted smoothly into the tosylate (**16**) and thence into the chloride (**17**) as a single stereoisomer (scheme 4). However, attempts to cyclise (**17**) failed despite the use of a variety of bases ranging from potassium carbonate to sodium hydride.



Scheme 4

A better leaving group was required to induce cyclisation. The alcohol (**8**) was oxidised with Jones reagent followed by reduction of the ketone (**18**) with hydride (scheme 5). The epoxy-ketone (**18**) existed only as the monocyclic tautomer; the NMR spectra were well resolved at room temperature and no evidence of the broadening associated with tautomerism was observed. The ^{13}C NMR spectrum displayed a carbonyl signal at δ 209.3 assigned to C_1.



R = CO_2CH_2Ph

Reagent	Ratio		Yield
$NaBH_4$/THF/Δ:	62	: 38	(95%)
L-Selectride/THF/-78°C:	45	: 55	(89%)

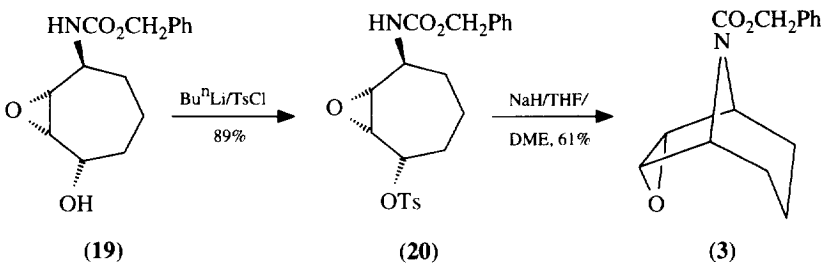
Scheme 5

Unfortunately, reduction of (**18**) with borohydride gave a mixture of both *cis*-1,4- (**8**) and *trans*-1,4- (**19**) isomers in a ratio of 62:38 (calculated from ^1H NMR integrations) although they were separable by chromatography. L-Selectride[17] was also used to reduce (**18**) and this proved to be preferable, giving a mixture richer in the *trans*-1,4 compound (**19**) in good overall yield. The redundant *cis*-1,4- alcohol (**8**) was recycled. The stereostructure of (**19**) was confirmed by the small vicinal coupling of 1.6 Hz between the α-hydroxy proton and the adjacent epoxide proton.

Successful conversion into (**3**) was then achieved by tosylation followed by treatment of the tosylate

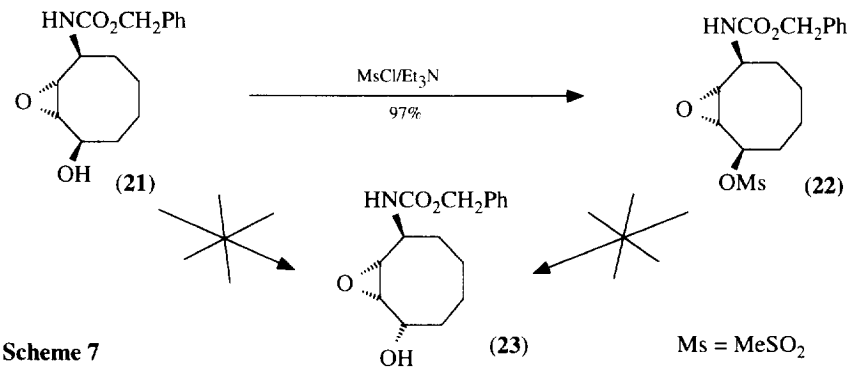
(**20**) with sodium hydride in THF:DME solvent (scheme 6); the *endo*- assignment followed from measurement of $J_{1,7}$ = 2.8 Hz.

Scheme 6



(**19**) (**20**) (**3**)

A more elegant method of preparing the *trans*-1,4 alcohol (**19**) would involve direct inversion of the alcohol group (rather than oxidation followed by reduction from the opposite face) and several literature methods were available.[18] The epoxy-alcohol (**21**), based on the 8-membered ring, was readily available and this was used for preliminary investigations.



Scheme 7 Ms = $MeSO_2$

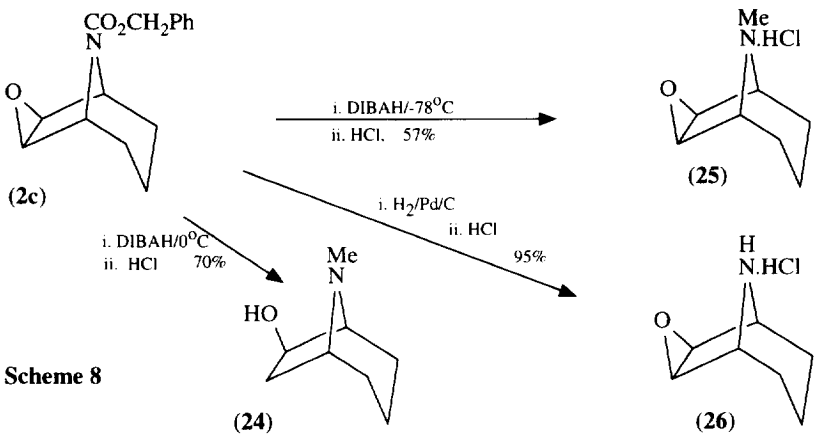
Kellogg[19] has described clean inversion of the stereochemistry of secondary alcohols by mesylation, inversion of configuration with caesium propionoate in DMF solvent, and then hydrolysis of the resulting ester. However, the mesylate (**22**) failed to give the desired inversion product when subjected to these conditions; only starting material was isolated (scheme 7). Ikegami[20] reported a modification of this procedure, inverting the stereochemistry of a mesylate with caesium acetate using benzene as solvent in the presence of 18-crown-6 but these conditions led to no detectable inversion of the mesylate of (**22**). When the reaction was repeated at higher temperature only a complex mixture of products was isolated.

Corey[21] inverted the mesylates of secondary alcohols using potassium superoxide in DMSO solvent, but this also failed when applied to (**22**). Finally, direct inversion of the alcohol (**21**) using the Mitsunobu[22] procedure was attempted, but without success. The failure of these reactions was disappointing but nonetheless, the overall efficiency of the oxidation and reduction procedure (scheme 5) was acceptable.

Reduction of N-protected epoxytropanes

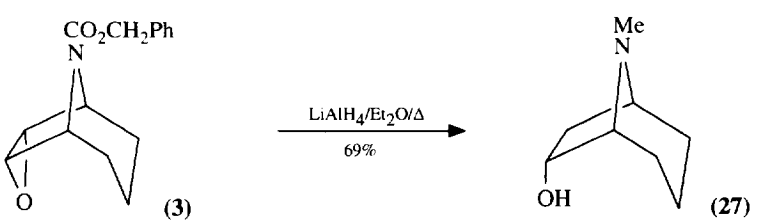
The epoxide moiety of N-alkoxycarbonyl-protected epoxyhomotropanes has been shown to withstand both hydride reduction and hydrogenolysis and, as a result, both *exo*-7,8-epoxyhomotropane and

endo-7,8-epoxyhomotropane are accessible.[8] A similar reductive procedure was applied to the N-protected *exo*-epoxytropane (**2c**) and whilst the epoxide was opened by DIBAH at 0°C to give tropan-6β-ol (**24**) (scheme 8), reduction at -78°C was selective, affording 6β,7β-epoxytropane (**25**). The epoxide group in (**2c**) was also stable to hydrogenolysis with hydrogen over a palladium catalyst at atmospheric pressure, giving 6β,7β-epoxynortropane (**26**). Both (**25**) and (**26**) were volatile and were handled as the hydrochloride salts.



Scheme 8

Reduction of the *endo*-epoxide (**3**) with lithium aluminium hydride in refluxing diethyl ether reduced both the epoxide and carbamate moities to give tropan-6α-ol (**27**) (scheme 8). An attempt to reduce the carbamate group selectively at -78°C led only to the isolation of (**27**). The hydrogenolysis of (**3**) was not attempted but ring-opening of the epoxide to the alcohol would have been expected in accord with behaviour of the homologous *endo*-epoxyhomotropane.



Endo-7,8-epoxyhomotropanes were observed to be more reactive than the *exo*-epimers in earlier studies.[8] The effect seems to be even more pronounced in the tropane series. The preferred conformation of the seven-membered ring of homotropane is known to be the boat form[22] whilst the 6-membered ring of tropane is a chair[23] and the observation of reduced *relative* reactivity of *exo*-epoxytropanes when compared to the *endo*- epimers is consistent, at first sight, with increased steric shielding of the *endo*-face. However, the *absolute* reactivity of the epoxytropanes appears to be greater. Whether this is a function of greater strain in the tighter ring system or whether the reactivity of the *endo*- epoxides is increased as a result of the involvement of bridging nitrogen in facilitating attack from the *exo*-face is still open to debate. Certainly, the anomalous hydride reduction of a C=C bridge in 7-azanorbornenes[24] has been attributed to coordination between the bridging nitrogen and the metal hydride and seems entirely plausible here.

Conclusion

The formation and cyclisation of N-protected 2,3-epoxy-4-amino-cycloheptanol derivatives provides a practical route to N-protected *exo*-6,7-epoxynortropanes and the first *endo*-6,7-epoxynortropane. These give the corresponding *exo*- and *endo*-6-hydroxytropanes respectively, on treatment with hydride reducing agents. More importantly, the stability of the *exo*-epoxide under reductive conditions at low temperature allows conversion of the benzyloxycarbonyl group into N-methyl or NH derivatives, making it a viable N-protecting group during the synthesis of *exo*-6,7-epoxytropanes and nortropanes as well as hydroxy-derivatives. The application of this approach to the synthesis of scopine and pseudoscopine is described in the following paper. Finally, the epoxide oxygen can be removed using a zinc/copper couple[25] so that 6,7-epoxytropanes can effectively be considered as masked 6,7-dehydrotropanes (which are otherwise difficult to obtain);[10] this approach has been of practical value in a synthesis of homoepibatidine.[26]

We are grateful to EPSRC for a studentship awarded to D.E.J.

Experimental

Routine ^1H NMR spectra were recorded on a Varian EM 390 (90 MHz) spectrometer. Higher field ^1H NMR (300, 250 MHz) and ^{13}C NMR (75, 63 MHz) spectra were recorded on Bruker AM 300 or ARX 250 spectrometers. Spectra were measured in $CDCl_3$ with tetramethylsilane (TMS) as internal reference unless indicated otherwise. Signal characteristics are described using standard abbreviations: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), quin (quintet), m (multiplet), br (broad) and v (very); protons identified as NH or OH were shown to be exchangeable with D_2O. In some circumstances, signals that appear in a more simplified form than the molecule allows are give the prefix ~. For example, a dddd which appears as a quintet is quoted as ~quin. Where data are quoted for two tautomers or rotamers, overlapping signals are shown in italics but may be quoted separately for reasons of clarity even though they are not fully resolved or assigned. In the ^{13}C spectra, C, CH, CH_2, CH_3 are used to indicate quaternary, methine, methylene and methyl carbons respectively, as shown by off-resonance decoupling or DEPT experiments.

IR spectra were recorded on PE 1604 FT or PE 298 IR spectrometers as solutions in CH_2Cl_2 unless indicated otherwise. Band intensities are described using standard abbreviations: s (strong), m (medium), w (weak), br (broad), v (very). Mass spectra were measured routinely on VG Micromass 14 or Kratos Concept spectrometers and were obtained using ionisation by electron impact except where chemical ionisation was used (shown CI) or fast atom bombardment (shown FAB); intensities are given as percentages of the base peak. Accurate mass measurements were obtained using the Kratos Concept mass spectrometer at Leicester University or through the SERC service at the University College of Swansea.

Melting point measurements were made using a Kofler hot stage apparatus and are uncorrected. Combustion Analyses were performed by Butterworth Laboratories Ltd., Teddington, Middlesex.

Reactions were performed under dry nitrogen using solvents dried by standard methods. Diethyl ether was dried over sodium wire and distilled from $LiAlH_4$. Dichloromethane, toluene and benzene were distilled from calcium hydride. Petroleum ether and ethyl acetate were distilled prior to use. Methanol and ethanol were purified with magnesium and iodine.[27] Tetrahydrofuran was distilled from sodium-benzophenone. Triethylamine and pyridine were distilled from potassium hydroxide. All other solvents were dried and purified as described by Perrin.[28] Flash chromatography was carried out according to the method of Still[29] using Merck Kieselgel 60 (230 - 400 mesh). Thin-layer chromatography was conducted on standard commercial aluminium sheets pre-coated with a 0.2 mm layer of silica gel (Merck 60 - 254).

Compounds **(6)**,[11] **(9)**[11] and **(21)**[8b] were prepared as described earlier.

1β-Hydroxy-2β,3β-epoxy-4β-[(benzyloxycarbonyl)amino]cycloheptane (7) and 1β-Hydroxy-2α,3α-epoxy-4β-[(benzyloxycarbonyl)amino]cycloheptane (8)

MCPBA (50 - 60% purity, 3.38 g, 10.7 mmol) was added to stirred solution of **(6)** (2.340 g, 8.97 mmol) in dichloromethane (160 ml) and stirring was continued at room temperature for 3 hr. The solution was transferred to a separating funnel and washed with saturated sodium bicarbonate solution (2 x 20 ml), dried over anhydrous magnesium sulphate, filtered and the solvent distilled under vacuum. The crude solid obtained after removal of solvent was purified by flash chromatography, eluting with diethyl ether, to afford firstly **(8)** (741 mg, 30%) as a white solid, m.p. 135 - 136°C after recrystallisation from ethanol. δ_H (300 MHz, CD_3COCD_3): 1.42 (m, 2H), 1.57 - 1.81 (series of m, 6H), 3.01 (dd, J = 5.8, 5.0 Hz, 1H, HCO), 3.08 (dd, J = 6.6, 5.0 Hz, HCO, 1H), 3.64 (m, 1H), 3.79 (m, 1H), 4.47 (brs, 1H, exch), 5.07 (s, 2H, CH_2Ph), 6.54 (brm, 1H, NH), 7.37 (m, 5H). δ_C (75 MHz, $CDCl_3$): 18.9, 30.0 & 32.0 (3 x CH_2), 51.0 (CHN), 56.7 & 57.7 (2 x CHO), 66.8 (CH_2Ph), 70.6 (CHOH), 128.1 (2 x aryl CH), 128.5 (aryl CH), 136.4 (aryl C), 155.8 (C=O). υ_{max} (CH_2Cl_2): 3600w, 3430w, 3390brw, 2930m, 1715s, 1510m, 1440w, 1420brw, 1315w, 1220m, 1130w, 1070m, 1025m, 965w, 935w, 865w, 850w, 815 cm^{-1}. m/z (%): 277 (M^+, 3), 124 (3), 122 (3), 108 (67), 107 (44), 106 (24), 105 (25), 92 (11), 91 (100), 79 (50). Found: C, 65.16; H, 6.78; N, 4.89%. $C_{15}H_{19}NO_4$ requires: C, 64.96; H, 6.91; N, 5.05%.

Further elution with diethyl ether furnished **(7)** (1.572 g, 63%) as a white solid which had m.p. 151 - 152°C after recrystallisation from ethanol. δ_H (300 MHz, $CDCl_3$): 1.01 (m, 1H), 1.36 - 1.86 (series of m, 5H), 2.61 (brs, 1H, exch), 3.22 (d, J = 5.0 Hz, 1H, HCO), 3.29 (d, J = 5.0 Hz, 1H, HCO), 3.96 (dd, J = 11.4, 4.0 Hz, 1H), 4.03 (m, 1H), 5.10 (s, 2H, CH_2Ph), 5.39 (d, J = 8.8 Hz, NH), 7.34 (m, 5H). δ_C (75 MHz, $CDCl_3$): 22.0, 31.4 & 33.5 (3 x CH_2), 51.8 (CHN), 58.3 & 60.2 (2 x CHO), 66.9 (CH_2Ph), 71.5 (CHOH), 128.1, 128.2 & 128.5 (3 x aryl CH), 136.3 (aryl C), 155.7 (C=O). υ_{max} (CH_2Cl_2): 3600w, 3430w, 2940w, 2860w, 1720s, 1505m, 1445w, 1345w, 1305w, 1220m, 1110w, 1015m, 905w, 855w, 795w cm^{-1}. m/z (%): 277 (M^+, 5), 183 (5), 108 (24), 107 (10), 92 (10), 91 (100). Found: C, 65.29; H, 6.84; N, 4.97%. $C_{15}H_{19}NO_4$ requires: C, 64.96; H, 6.91; N, 5.05%.

Integration of signals in the ^1H NMR spectrum of a crude sample prior to chromatographic separation, indicated that **(7)**:**(8)** were formed in a ratio of 62:38, in close agreement with the isolated yields.

Epoxidation of (6) with magnesium monoperperphthalate (MMPP)

Using the procedure of Gillard[15] a solution of **(6)** (45 mg, 0.17 mmol) in ethanol:water (19:1, 5 ml) and MMPP (128 mg, 0.26 mmol) was stirred for 3 hr at room temperature. The bulk of the solvent was then removed under reduced pressure and the residual oil dissolved in dichloromethane (10 ml) and washed with water (5 ml). The organic layer was separated, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The crude oil was flash chromatographed to remove polar impurities; elution with diethyl ether affording **(7)** and **(8)** (34 mg, 72 %) in a 42:58 ratio (calculated from integration of the ^1H NMR spectrum of the crude sample).

Vanadium-catalysed epoxidation of (6)

The procedure of Teranishi[16] was followed: a catalytic quantity of vanadium(III) acetylacetonate was added to a solution of **(6)** (65 mg, 0.25 mmol) in benzene (4 ml) and stirred for 5 min. An anhydrous solution of *t*-butyl hydroperoxide (3M in 2,2,4-trimethylpentane, 140 µl, 0.42 mmol) was injected and the pale green solution immediately turned red. Stirring was continued for 1 hr and TLC analysis indicated the majority of the mixture was still starting material. A further portion of peroxide (50 µl, 0.15 mmol) was added and stirred for a further 5 hr. The bulk of the solvent was removed under reduced pressure and the residue was chromatographed using diethyl ether to remove polar impurities to give the epoxides **(7)**:**(8)** (28 mg, 40%) in a ratio of >95:<5, as calculated from ^1H NMR integrations.

2β,3β-Epoxy-4β-[(benzyloxycarbonyl)amino]cycloheptanone (11)

A solution of **(9)** (61 mg, 0.24 mmol) in THF:H_2O (4:1, 3 ml) was basified with sodium hydroxide solution (6M, 85 µl) at 0°C. An aqueous solution of hydrogen peroxide (30 weight %, 100 µl) was added, the solution warmed to room temperature and stirred for 4 hr. The bulk of the solvent was evaporated and the residual oil was partitioned between diethyl ether (7 ml) and water (2 ml). The organic layer was

washed with further water (2 ml), separated, dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure. The solid product was recrystallised from ethanol to afford **(11)** (45 mg, 69%) as a crystalline white solid, m.p. 147 - 148°C. δ_H (300 MHz, CD_3COCD_3): 1.27 (m, 1H), 1.83 (m, 3H), 2.21 (dd, J = 14.4, 4.3 Hz, 1H), 2.62 (ddd, J = 14.4, 11.4, 2.9 Hz, 1H), 3.37 (dd, J = 5.2, 0.9 Hz, 1H, HCO, β-N), 3.47 (d, J = 5.2 Hz, 1H, HCO), 3.97 (dd, J = 9.6, 4.3 Hz, 1H), 5.10 (s, 2H, CH_2Ph), 7.38 (m, 5H). δ_C (75 MHz, $CDCl_3$): 22.7, 30.6 & 40.7 (3 x CH_2), 51.2 (CHN), 57.9 & 59.0 (2 x CHO), 67.0 (CH_2Ph), 128.1, 128.2 & 128.5 (3 x aryl CH), 136.1 (aryl C), 155.5 (NC=O), 208.5 (C=O). υ_{max} (CH_2Cl_2): 3430m, 2940w, 2860w, 1715s, 1505s, 1450w, 1350w, 1305m, 1220s, 1115w, 1070w, 1015m, 925w, 960m cm^{-1}. m/z (%): 275 (M^+, 4), 108 (42), 107 (8), 92 (9), 91 (100). Found: C, 65.68; H, 6.08; N, 5.26%. $C_{15}H_{17}NO_4$ requires: C, 65.44; H, 6.23; N, 5.09%.

The ketone **(11)** could also be prepared in 87% yield by Jones oxidation[11] of the epoxy-alcohol **(7)** using an identical procedure to that described below for the conversion of **(8)** into **(18)**.

1β-[(*p*-Toluenesulphonyl)oxy]-2β,3β-epoxy-4β-[(benzyloxycarbonyl)amino]cycloheptane (13)

A solution of **(7)** (300 mg, 1.08 mmol) in dry THF (12 ml) was cooled to 0°C under a nitrogen atmosphere. *n*-Butyllithium (2.5M in hexane, 0.52 ml, 1.30 mmol) was introduced using a syringe and the mixture was stirred for a further 10 mins. A solution of *p*-toluenesulphonyl chloride (269 mg, 1.41 mmol) in THF (4 ml) was then injected, the solution was warmed to ambient temperature and stirred for a further 1.5h. Following TLC analysis to confirm the disappearance of **(7)**, water (0.5 ml) was added and the bulk of the solvent evaporated under reduced pressure. The residue was dissolved in diethyl ether and washed with water (3 x 5ml). The organic layer was dried over anhydrous magnesium sulphate and the solvent removed. The resulting oil was chromatographed on silica with 6:4 diethyl ether:petroleum ether (b.p. 40 - 60°C) to afford the tosylate **(13)** (460 mg, 99%) as a white solid. An analytical sample was prepared by recrystallisation from toluene and petroleum ether (b.p. 60 - 80°C), m.p. 106 - 107°C. δ_H (300 MHz, $CDCl_3$): 1.38 (m, 2H), 1.70 (m, 4H), 2.43 (s, 3H), 4.14 (d, J = 5.2 Hz, 1H, HCO), 3.17 (d, J = 5.2 Hz, 1H, HCO), 3.96 (m, 1H), 4.74 (dd, J = 11.2, 4.4 Hz, 1H), 5.07 (s, 2H, CH_2Ph), 5.36 (d, J = 8.7 Hz, 1H, NH), 7.31 - 7.39 (m, including d, 7H), 7.90 (d, J = 8.5 Hz, 2H). δ_C (75 MHz, $CDCl_3$): 21.6 (CH_2 & CH_3), 30.7 (CH_2), 51.3 (CHN), 57.3 & 57.6 (2 x CHO), 66.8 (CH_2Ph), 81.7 ($CHOSO_2$), 127.7, 127.8, 128.0, 128.1 & 129.8 (5 x aryl CH), 133.7 (aryl CMe), 136.2 (aryl CCH_2), 145.0 (aryl CSO_2), 155.5 (C=O). υ_{max} (CH_2Cl_2): 3430w, 3030w, 2930w, 2860w, 1715s, 1595w, 1500s, 1445w, 1360s, 1305m, 1215m, 1185s, 1170s, 1105w, 1095w, 1020w, 900m, 865m, 840m, 810m cm^{-1}. m/z (%): 431 (M^+, 2), 411 (2), 327 (2), 172 (3), 165 (3), 155 (4), 110 (9), 108 (13), 107 (16), 92 (13), 91 (100). $C_{22}H_{25}NO_6S$ [M^+] requires m/z 431.1403; observed 431.1406. Found: C, 61.10; H, 5.73; N, 3.14%. $C_{22}H_{25}NO_6S$ requires: C, 61.23; H, 5.84; N, 3.24%.

1α-Chloro-2β,3β-epoxy-4β-[(benzyloxycarbonyl)amino]cycloheptane (14)

Lithium chloride (410 mg, 9.76 mmol) and **(13)** (670 mg, 1.55 mmol) were added to dry DMSO (12 ml) and heated to 55°C with stirring for 1.5 hr. The solution was poured into an equal volume of water and extracted repeatedly with diethyl ether (3 x 25 ml). The organic layers were combined and washed with water (2 x 7 ml) and brine (5 ml), before drying over anhydrous magnesium sulphate. Filtration and distillation of solvent under reduced pressure gave a crude oil which was purified by flash chromatography using 3:7 diethyl ether:petroleum ether (b.p. 40 - 60°C) to afford the product **(14)** (407 mg, 85%) as a white solid after flash chromatography using 3:7 diethyl ether:petroleum ether (b.p. 40 - 60°C). A sample had m.p. 92 - 93 °C after recrystallisation twice from ethanol. δ_H (300 MHz, $CDCl_3$): 1.55 (m, 3H), 1.74 (m, 1H), 1.91 (m, 2H), 3.30 (m, 2H, CHO), 4.21 (m, 1H), 4.74 (m, 1H), 5.11 (s, 2H, CH_2Ph), 5.17 (brd, J ≈ 8.9 Hz, 1H, NH), 7.34 (m, 5H). δ_C (75 MHz, $CDCl_3$): 19.3, 30.9 & 32.2 (3 x CH_2), 51.2 (CHN), 56.8 (CHCl), 59.4 & 61.1 (2 x CHO), 66.7 (CH_2Ph), 128.1, 128.2 & 128.5 (3 x aryl CH), 136.3 (aryl C), 155.5 (C=O). υ_{max} (CH_2Cl_2): 3430m, 3300brw, 3030w, 2940m, 1715s, 1495s, 1445w, 1395w, 1325w, 1305m, 1210s, 1175w, 1120w, 1105w, 1015m, 975w, 930w, 910w, 840w, 800w cm^{-1}. m/z (%): 297 (M^+, 1), 295 (M^+, 3), 108 (42), 107 (17), 92 (9), 91 (100). $C_{15}H_{18}NO_3Cl$ [M^+] requires m/z 295.0975; observed 295.0975. Found: C, 60.61; H, 6.32; N, 4.60%. $C_{15}H_{18}NO_3Cl$ requires: C, 60.91; H, 6.13; N, 4.74%.

N-(Benzyloxycarbonyl)-6β,7β-epoxy-8-azabicyclo[3.2.1]octane (2c)

To a stirred slurry of sodium hydride (60% dispersion in mineral oil, 78 mg, 1.95 mmol) in dry

THF:DME (8:1, 2 ml) was injected a solution of **(14)** (338 mg, 1.14 mmol) in THF:DME (8:1, 11 ml) at 0°C. The solution was stirred at room temperature for 1 hr and then at 50°C for a further 1.5 hr. Excess hydride was destroyed by the addition of water at -78°C and diethyl ether (25 ml) was added. The ethereal layer was washed with water (2 x 5 ml) and brine (5 ml), separated, and dried over anhydrous magnesium sulphate. After filtration and removal of solvent under reduced pressure, the residual oil was purified by flash chromatography using 1:1 diethyl ether:petroleum ether (b.p. 40 - 60°C) to afford **(2c)** (256 mg, 87%) as an oil. The oily product solidified on cooling and was recrystallised from toluene and petroleum ether (b.p. 60 - 80°C) to give a white solid, m.p. 67 - 68°C. The signals quoted in italics are common to both rotamers (in a 1:1 ratio). δ_H (300 MHz, $CDCl_3$): *1.46 - 1.89* (series of m, 6H), 3.42 (d, J = 3.2 Hz, 1H, HCO), 3.45 (d, J = 3.2 Hz, 1H, HCO), 4.33 (brs, 1H, α-N), 4.41 (brs, 1H, α-N), *5.12* (s, 2H, CH_2Ph), *7.34* (m, 5H). δ_C (75 MHz, $CDCl_3$): *16.8*, 24.7 & 25.0 (3 x CH_2), 51.5 & 51.9 (2 x CHO), 53.3 & 53.8 (2 x CHN), *66.7* (CH_2Ph), *127.6, 127.7 & 128.3* (3 x aryl CH), *136.6* (aryl C), *156.3* (C=O). υ_{max} (CH_2Cl_2): 3040m, 2950s, 2930s, 2880m, 2860m, 1700s, 1495m, 1425s, 1360s, 1330w, 1295s, 1235s, 1215m, 1100s, 1040s, 1030w, 1000w, 980w, 940w, 910s, 900s cm^{-1}. m/z (%): 259 (M^+, 32), 172 (6), 152 (11), 125 (6), 92 (8), 91 (100), 65 (8). Found: C, 69.40; H, 6.70; N, 5.32%. $C_{15}H_{17}NO_3$ requires: C, 69.48; H, 6.61; N, 5.40%.

1β-[(*p*-Toluenesulphonyl)oxy]-2α,3α-epoxy-4β-[(benzyloxycarbonyl)amino]cycloheptane (16)

A solution of **(8)** (739 mg, 2.67 mmol) in dry THF (18 ml) was tosylated by sequential addition of *n*-butyllithium (2.5M in hexane, 1.17 ml, 2.94 mmol) and *p*-toluenesulphonyl chloride (662 mg, 3.47 mmol) in THF (6 ml), using the procedure described for production of **(13)** from **(7)**. The tosylate **(16)** (1.053 g, 92%) was obtained as a foam after flash chromatography with 1:1 diethyl ether:petroleum ether (b.p. 40 - 60°C). δ_H (300 MHz, $CDCl_3$): 2.56 (m, 1H), 1.47 - 1.86 (series of m, 5H), 2.41 (m, 3H), 3.09 (m, 2H, HCO), 4.05 (m, 1H), 4.88 (m, 1H), 5.10 (s, 2H, CH_2Ph, including brs, 1H, NH), 7.28 (part of AA'BB' 2H), 7.36 (m, 5H), 7.80 (part of AA'BB' 2H). δ_C (75 MHz, $CDCl_3$): 19.0 (CH_2), 21.7 (CH_3), 29.9 & 30.4 (2 x CH_2), 51.0 (CHN), 55.3 & 56.6 (2 x CHO), 66.9 (CH_2Ph), 81.6 ($CHOSO_2$), 127.7, 128.2, 128.6 & 130.0 (4 x aryl CH), 133.5 (aryl CMe), 136.3 (aryl CCH_2), 145.1 (aryl CSO_2), 155.6 (C=O). υ_{max} (CH_2Cl_2): 3440w, 3060w, 2950w, 2870w, 1725s, 1600w, 1510s, 1465w, 1455w, 1365m, 1325w, 1230m, 1215m, 1190s, 1180s, 1090w, 1065w, 1030w, 1020w, 955m, 910m, 860w, 840w, 815w cm^{-1}. m/z (%): 431 (M^+, 9), 296 (5), 152 (8), 126 (6), 110 (19), 108 (30), 107 (34), 92 (16), 91 (100), 81 (10). $C_{22}H_{25}NO_6S$ [M^+] requires m/z 431.1403; observed 431.1403.

1α-Chloro-2α,3α-epoxy-4β-[(benzyloxycarbonyl)amino]cycloheptane (17)

A solution of **(16)** (930 mg, 2.16 mmol) in dry DMSO (14 ml) was treated with lithium chloride (552 mg, 13.1 mmol) at 55°C using the procedure described for the conversion of **(13)** into **(14)**. The product **(17)** (604 mg, 95%) was obtained as a white solid after flash chromatography, with 2:3 diethyl ether:petroleum ether (b.p. 40 - 60°C), and had m.p. 75 - 76°C after recrystallisation from toluene and petroleum ether (b.p. 60 - 80°C). δ_H (300 MHz, CD_3COCD_3): 1.36 (m, 1H), 1.53 (m, 2H), 1.76 (m, 2H), 2.03 (m, 1H), 3.19 (t, J = 4.6 Hz, HCO, β-N), 3.39 (d, J = 4.5 Hz, HCO, β-Cl), 4.55 (m, 1H), 4.73 (dd, J = 11.9, 4.0 Hz, 1H), 5.04 & 5.09 (ABq, J = 12.4 Hz, 2H, CH_2Ph), 6.58 (brd, J = 6.5 Hz, 1H, NH), 7.36 (m, 5H). δ_C (75 MHz, $CDCl_3$): 20.0, 29.3 & 34.6 (3 x CH_2), 49.6 (CHN), 57.0 (CHCl), 60.0 & 61.1 (2 x CHO), 67.1 (CH_2Ph), 128.3, 128.5 & 128.6 (3 x aryl CH), 136.0 (aryl C), 156.0 (C=O). υ_{max} (CH_2Cl_2): 3440m, 3030w, 2940m, 2860w, 1740s, 1500s, 1325m, 1220s, 1080w, 1145w, 1120w, 1070m, 1040w, 1025w, 1000w, 975w, 940w, 905w, 850w, 830m. m/z (%): 297 (M^+, 14), 295 (M^+, 31), 216 (10), 108 (51), 107 (55), 108 (51), 109 (6), 110 (8), 92 (13), 91 (100). $C_{15}H_{18}NO_3Cl$ [M^+] requires m/z 295.0975; observed 295.0973. Found: C, 61.05; H, 6.25; N, 4.73%. $C_{15}H_{18}NO_3Cl$ requires: C, 60.91; H, 6.13; N, 4.74%.

2α,3α-Epoxy-4β-[(benzyloxycarbonyl)amino]cycloheptanone (18)

Chromic acid, prepared from chromium trioxide (12.35 g), concentrated sulphuric acid (11.5 ml) and water (20 ml), was added dropwise to a solution of **(8)** (114 mg, 0.41 mmol) in dry acetone (12 ml). A persistent orange colouration indicated complete oxidation and excess oxidant was destroyed by dropwise addition of isopropanol. The mixture was filtered through celite and the bulk of the solvent was removed under vacuum. The residue was dissolved in dichloromethane and washed three times with brine. The

organic layer was dried over magnesium sulphate, filtered, and the solvent removed under vacuum to yield the ketone **(18)** (108 mg, 95%) as a colourless oil which was pure enough for the next reaction without purification. δ_H (300 MHz, $CDCl_3$): 1.24 (m, 1H), 1.63 (m, 1H), 1.76 - 2.03 (m, 2H), 2.28 (m, 1H), 2.61 (m, 1H), 3.38 (dd, J = 4.8, 1.2 Hz, 1H, HCO), 3.42 (t, J = 4.8 Hz, 1H, HCO, β-N), 4.79 (m, 1H), 5.05 & 5.10 (ABq, J = 12.1 Hz, 2H, CH_2Ph), 5.32 (d, J = 8.7 Hz, 1H, NH), 7.31 (m, 5H). δ_C (75 MHz, $CDCl_3$): 16.7, 28.2 & 40.2 (3 x CH_2), 48.8 (CHN), 55.6 & 58.4 (2 x CHO), 67.0 (CH_2Ph), 128.1, 128.2 & 128.5 (3 x aryl CH), 136.0 (aryl C), 155.7 (NC=O), 209.3 (C=O). υ_{max} (CH_2Cl_2): 3430m, 2950m, 2870w, 1715s, 1505s, 1450w, 1420w, 1400w, 1325m, 1215s, 1145w, 1120w, 1060m, 1025w, 985m, 935w, 905w, 880w, 860w, 825w cm^{-1}. $^m/_z$ (%): 275 (M^+, 3), 169 (3), 108 (26), 107 (12), 91 (100). $C_{15}H_{17}NO_4$ [M^+] requires $^m/_z$ 275.1158; observed 275.1157.

1α-Hydroxy-2α,3α-epoxy-4β-[(benzyloxycarbonyl)amino]cycloheptane (19)

A solution of **(18)** (234 mg, 0.85 mmol) in dry THF (14 ml) was heated under gentle reflux with sodium borohydride (79 mg, 2.14 mmol) for 1 hr before destruction of the excess hydride with saturated ammonium chloride solution (1 ml). Diethyl ether (25 ml) was added, the solution transfered to a separating funnel, and washed with water (2 x 5 ml) and brine (5 ml). The organic layer was dried over anhydrous magnesium sulphate, filtered, and the solvent distilled under reduced pressure to afford a mixture of **(8)**:**(19)** (223 mg, 95%) as an oil. The ^1H NMR spectrum was free of impurities and the ratio of **(8)**:**(19)** was calculated to be 62:38 from ^1H NMR signal integrations. The epimers were separated by flash chromatography using 4:1 diethyl ether:petroleum ether (b.p. 40 - 60°C), to afford firstly the *cis*-1,4 alcohol **(8)** which had identical NMR spectra to a sample prepared by epoxidation of **(6)**.

Further elution afforded the *trans*-1,4 alcohol **(19)** as a white solid which had m.p. 128 - 129°C after recrystallisation from toluene. δ_H (300 MHz, $CDCl_3$): 1.17 (m, 1H), 1.67 (m, 5H), 2.80 (brs, 1H, exch), 3.12 (m, 1H, HCO, β-N), 3.17 (dd, J = 4.7, 1.6, 1H, HCO, β-OH), 4.08 (m, 1H), 4.34 (m, 1H), 5.08 (brs, 3H, CH_2Ph and NH), 7.34 (m, 5H). δ_C (75 MHz, $CDCl_3$): 18.5, 30.5 & 32.0 (3 x CH_2), 50.5 (CHN), 56.3 & 59.3 (2 x CHO), 67.0 (CH_2Ph), 69.2 (CHOH), 128.1, 128.2 & 128.5 (3 x aryl CH), 136.2 (aryl C), 155.7 (C=O). υ_{max} (CH_2Cl_2): 3590w, 3440w, 2930w, 2860w, 1720s, 1505s, 1450w, 1395w, 1325w, 1225m, 1210m, 1070w, 1025w, 1000w, 935w, 905m, 835w, 805w cm^{-1}. $^m/_z$ (%): 277 (M^+, 53), 186 (32), 168 (11), 124 (15), 107 (16), 91 (100). $C_{15}H_{19}NO_4$ [M^+] requires $^m/_z$ 277.1314; observed 277.1315. Found: C, 64.66; H, 6.95; N, 4.91%. $C_{15}H_{19}NO_4$ requires: C, 64.96; H, 6.91; N, 5.05%.

L-Selectride Reduction of (18)

A solution of **(18)** (640 mg, 2.33 mmol) in dry THF (25 ml) was cooled with stirring to -78°C. L-Selectride (1M solution in THF, 2.79 ml, 0.28 mmol) was slowly injected and stirring was continued at reduced temperature for 1 hr. The solution was quenched with water (200 μl) and warmed to room temperature. The bulk of the solvent was distilled under reduced pressure and the residual oil was partitioned between diethyl ether (55 ml) and sodium hydroxide solution (1M, 10 ml) and then washed with water (7 ml) and brine (7 ml). The organic layer was dried over anhydrous magnesium sulphate, filtered and the solvent distilled under reduced pressure. The crude oil was purified by flash chromatography, eluting with 4:1 diethyl ether:petroleum ether (b.p. 40 - 60°C). The first fraction to be eluted was the *cis*-1,4 alcohol **(8)** (262 mg, 41%). Further elution afforded the *trans*-1,4 alcohol **(19)** (313 mg, 48%).

1α-[(*p*-Toluenesulphonyl)oxy]-2α,3α-epoxy-4β-[(benzyloxycarbonyl)amino]cycloheptane (20)

A solution of **(19)** (220 mg, 0.79 mmol) in dry THF (8 ml) was tosylated by sequential addition of *n*-butyllithium (2.5M in hexane, 0.41 ml, 1.03 mmol) and *p*-toluenesulphonyl chloride (197 mg, 1.03 mmol) in THF (2 ml), using the procedure described for tosylating the epoxy-alcohol **(7)**. The tosylate **(20)** (303 mg, 89%) was obtained as a white solid after flash chromatography with 3:2 diethyl ether:petroleum ether (b.p. 40 - 60°C). An analytical sample was prepared by recrystallising from toluene and petroleum ether (b.p. 60- 80°C), m.p. 139 - 140°C. δ_H (300 MHz, $CDCl_3$): 1.03 (m, 1H), 1.46 (m, 2H), 1.76 (m, 3H), 2.42 (s, 3H), 3.14 (brt, J = 4.5 Hz, HCO, β-N), 3.25 (d, J = 4.5 Hz, HCO, β-OSO_2Ar), 4.56 (brm, 1H), 4.98 (brm, 1H), 5.08 (brs, 2H, CH_2Ph), 5.15 (brd, J = 8.6 Hz, 1H, NH), 7.33 (m, 7H), 7.79 (part of AA'BB', 2H). δ_C (75 MHz, $CDCl_3$): 17.0 (CH_2), 21.7 (CH_3), 29.0 & 30.4 (2 x CH_2), 49.3 (CHN), 54.2 & 58.5 (2 x CHO), 67.1 (CH_2Ph), 81.4 ($CHOSO_2$), 127.6, 128.2, 128.5 & 129.9 (4 x aryl CH), 133.9 (aryl CMe), 136.1 (aryl

CCH_2), 144.9 (aryl CSO_2), 155.7 (C=O). υ_{max} (CH_2Cl_2): 3430w, 2930w, 2870w, 1720s, 1600w, 1500s, 1445m, 1400w, 1360s, 1330s, 1215s, 1190s, 1185s, 1220w, 1095m, 1085m, 1005w, 950s, 895s, 850m, 835m, 815m cm^{-1}. $^m/z$ (%): 431 (M^+, 21), 307 (8), 259 (6), 107 (54), 91 (100). $C_{22}H_{25}NO_6S$ [M^+] requires $^m/z$ 431.1403; observed 431.1406. Found: C, 61.27; H, 5.81; N, 3.13%. $C_{22}H_{25}NO_6S$ requires: C, 61.23; H, 5.84; N, 3.25%.

N-(Benzyloxycarbonyl)-6α,7α-epoxy-8-azabicyclo[3.2.1]octane (3)

A 25 ml oven-dried two-necked flask was charged with sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol) and slurried with dry THF:DME (5:1, 1 ml). The system was fitted with a condenser and septum cap and repeatedly purged and evacuated with nitrogen. A solution of **(20)** (55 mg, 0.13 mmol) in THF:DME (5:1, 4 ml) was injected and the solution was stirred at room temperature for 1 hr and then at 40°C for a further 1 hr. After cooling to -78°C the reaction was quenched by the addition of water (200 µl). Diethyl ether (10 ml) was added and the organic layer washed with water (2 x 3 ml), brine (3 ml), and then dried over anhydrous magnesium sulphate. Evaporation of solvent under reduced pressure gave an oil which was purified by flash chromatography with 1:4 diethyl ether:petroleum ether (b.p. 40 - 60°C), to furnish **(3)** (20 mg, 61%) as a pale yellow oil. Restricted rotation about the N-CO bond caused some NMR signals to be broadened (italics) as the spectra were recorded close to the coalescence temperature. δ_H (300 MHz, $CDCl_3$): 1.26 (m, 2H), 1.73 (m, 2H), 1.98 (m, 2H), 3.95 (brd, J = 2.8 Hz, 2H, HCO), 4.24 (brm, 2H, α-N), 5.12 (s, 2H, CH_2Ph), 7.34 (m, 5H). δ_C (75 MHz, $CDCl_3$): *16.7*, 22.7 & 23.4 (3 x CH_2), *53.3* (2 x CHN), *62.9* (2 x CHO), 66.8 (CH_2Ph), 127.8, 128.0 & 128.5 (3 x aryl CH), 136.7 (aryl C), 152,9 (C=O). υ_{max} (CH_2Cl_2): 2930w, 1690s, 1495w, 1410m, 1360w, 1310m, 1265brw, 1220w, 1100m, 1065w, 1040w, 955w, 900w, 855w cm^{-1}. $^m/z$ (%): 259 (M^+, 3), 172 (4), 124 (9), 92 (8), 91 (100). $C_{15}H_{17}NO_3$ [M^+] requires $^m/z$ 259.1208; observed 259.1206.

1β-(Mesyloxy)-2α,3α-epoxy-4β-[(benzyloxycarbonyl)amino]cyclooctane (22)

Triethylamine (293 µl, 2.11 mmol) and **(21)** (409 mg, 1.40 mmol) in dry dichloromethane (25 ml) were stirred at 0°C under a nitrogen atmosphere. Methanesulphonyl chloride (120 µl, 1.78 mmol) was injected and the solution was stirred at room temperature for 1 hr. The solution was transferred to a separating funnel and washed with hydrochloric acid (1M, 5 ml), saturated sodium bicarbonate solution (5 ml) and water (5 ml). The organic layer was separated, dried over anhydrous magnesium sulphate, filtered and the solvent evaporated under reduced pressure to afford **(22)** (505 mg, 97%) as a foam which was shown to be pure by NMR spectroscopy. The foam solidified on refrigeration and an analytical sample was prepared by recrystallising from toluene and petroleum ether (b.p. 60 - 80°C) yielding a white solid, m.p. 138 - 140°C. δ_H (300 MHz, $CDCl_3$): 1.38 - 1.69 (brm, 5H), 1.83 (m, 2H), 2.04 (m, 1H), 3.07 (brs, 4H, $MeSO_2$ & HCO), 3.16 (dd, J = 8.3, 4.6 Hz, 1H, HCO), 3.49 (m, 1H, α-N), 4.48 (m, 1H, α-OSO_2Me), 5.05 & 5.11 (ABq, J = 11.3 Hz, 2H, CH_2Ph), 5.46 (d, J= 7.8 Hz, 1H, NH), 7.33 (m, 5H). δ_C (75 MHz, $CDCl_3$): 22.8, 23.9, 33.3 & 33.7 (4 x CH_2), 38.3 (CH_3), 51.4 (CHN), 56.7 & 57.7 (2 x CHO), 66.8 (CH_2Ph), 83.6 ($CHOSO_2$), 128.1 (2 x aryl CH), 128.5 (aryl CH), 136.3 (aryl C), 155.6 (C=O). υ_{max} (CH_2Cl_2): 3430m, 3030w, 2940m, 2870w, 1720s, 1510s, 1450m, 1355s, 1300w, 1225s, 1175s, 1125w, 1090w, 1025m, 980m, 940s, 900w, 880w, 860m cm^{-1}. $^m/z$ (%): 369 (M^+, 14), 149 (6), 124 (5), 108 (25), 107 (30), 91 (100), 79 (12). Found: C, 55.24; H, 6.32; N, 3.76%. $C_{17}H_{23}NO_6S$ requires: C, 55.28; H, 6.27; N, 3.79%.

Tropan-6β-ol (24)

A solution of **(2c)** (79 mg, 0.31 mmol) in dry diethyl ether (6 ml) was cooled with stirring to 0°C. A solution of DIBAH (1M in hexane, 1.68 ml, 1.68 mmol) was injected and stirred under a nitrogen atmosphere for 3 hr. The solution was quenched with the minimum quantity of water-saturated diethyl ether and the precipitated salts were filtered off through celite. The colourless solution was acidified with gaseous hydrogen chloride gas and the solvent was evaporated under reduced pressure. The residual oil was triturated with 1:1 diethyl ether:petroleum ether (b.p. 40 - 60°C) to afford **(24:HCl)** (38 mg, 70%) as a gum. Dissolution of the salt in the minimum quantity of $CDCl_3$, basification with ammonia gas, and filtration gave a sample of the free amine **(24)** for NMR and IR spectroscopic measurements. δ_H (300 MHz, $CDCl_3$): 1.12 (m, 1H), 1.24 - 1.54 (series of m, 3H), 1.66 - 1.87 (series of m, 2H), 1.98 (ddd, J = 13.6, 6.9, 3.1 Hz, 1H), 2.09 (dd, J = 13.6, 7.2 Hz, 1H), 2.54 (s, 3H), 2.96 (brs, 1H, α-N), 3.29 (m, 1H, α-N), 4.26 (dd, J = 7.2,

3.1 Hz, 1H, α-N). δ_C (75 MHz, $CDCl_3$): 17.7, 24.4 & 25.7 (3 x CH_2), 37.6 (CH_3), 40.0 (CH_2), 60.8 & 66.6 (2 x CHN), 75.7 (CHOH). υ_{max} ($CDCl_3$): 3300vbrm, 2930m, 1640w, 1440w, 1340w, 1255w, 1230w, 1220w, 1130w, 1030s, 910brm cm^{-1}. m/z (%): 141 (M^+ - HCl, 34), 117 (14), 97 (100), 96 (39), 91 (52), 82 (30). $C_8H_{15}NO$ [M^+ - HCl] requires m/z 141.1154; observed 141.1155.

N-Methyl-6β,7β-epoxy-8-azabicyclo[3.2.1]octane (25)

A solution of **(2c)** (70 mg, 0.27 mmol) in dry diethyl ether (5 ml) was cooled with stirring to -78°C. A solution of DIBAH (1M in hexane, 0.95 ml, 0.95 mmol) was injected and stirred at -78°C for 45 min. An additional portion of DIBAH (0.40 ml, 0.40 mmol) was added and the mixture stirred for a further 2 hr. The reaction was quenched with water (60 µl), warmed to room temperature and dried with anhydrous sodium sulphate. The solution was filtered through celite and acidified with gaseous hydrogen chloride at 0°C. The solvent was evaporated under reduced pressure and the residual oil was repeatedly triturated (to remove benzyl alcohol) with 1:1 diethyl ether:petroleum ether (b.p. 40 - 60°C) affording **(25:HCl)** (27 mg, 57%) as a hygroscopic white solid. All spectra below were recorded on solutions of the free amine obtained by dissolving **(25:HCl)** in the minimum quantity of $CDCl_3$, basifying with ammonia gas and filtering. δ_H (300 MHz, $CDCl_3$): 1.45 (m, 2H), 1.63 - 1.78 (m, 2H), 2.52 (s, 3H), 3.12 (m, 2H, α-N), 3.56 (s, 2H, HCO). δ_C (75 MHz, $CDCl_3$): 16.7 (CH_2), 24.3 (2 x CH_2), 41.5 (CH_3), 55.7 (2 x CHN), 58.8 (2 x CHO). υ_{max} ($CDCl_3$): 2930s, 1475w, 1440w, 1385w, 1330w, 1280w, 1080w, 1040w, 1015w, 905s, 850m cm^{-1}. m/z (%): 139 (M^+, 91), 110 (51), 96 (100), 94 (16), 91 (25), 82 (28), 70 (22). $C_8H_{13}NO$ [M^+] requires m/z 139.0997; observed 139.0999.

6β,7β-Epoxy-8-azabicyclo[3.2.1]octane hydrochloride (26:HCl)

A solution of **(2c)** (66 mg, 0.25 mmol) in absolute ethanol (8 ml) was hydrogenolysed for 3 hr at 1 atmosphere with a catalytic quantity of 5% palladium on charcoal. After 2.5 hr the solution was filtered through a Millipore 0.2µ Millex-FG disposable filter unit. The solution was acidified with hydrogen chloride gas prior to evaporation of solvent to afford **(26:HCl)** (39 mg, 95%) as a hygroscopic white solid. All spectroscopic data quoted below were recorded on the hydrochloride salt, rather than the free amine. δ_H (300 MHz, CD_3OD): 1.61 (m, 1H), 1.82 - 2.11 (series of m, 5H), 3.94 (s, 2H, CHO), 4.01 (brs, 2H, α-N). δ_C (75 MHz, $CDCl_3$): 16.6 (CH_2), 23.7 (2 x CH_2), 52.2 (2 x CHN), 55.1 (2 x CHO). m/z (%): 125 (M^+ - HCl, 46), 108 (16), 96 (100), 82 (56), 69 (33), 56 (14). $C_7H_{11}NO$ [M^+ - HCl] requires m/z 125.0841; observed 125.0840.

Tropan-6α-ol (27)

A solution of **(3)** (48 mg, 0.18 mmol) in dry diethyl ether (5 ml) was heated under reflux with lithium aluminium hydride (26 mg, 0.70 mmol) under a nitrogen atmosphere for 1 hr. Excess hydride was destroyed by the addition of water-saturated diethyl ether and the solution was dried with anhydrous magnesium sulphate. Filtration through celite and evaporation of solvent under reduced pressure gave a crude oil which was purified by flash chromatography, using 7:3 diethyl ether:petroleum ether (b.p. 40 - 60°C) to elute benzyl alcohol and 1:1:3 triethylamine:methanol:ethyl acetate to elute **(27)** (18 mg, 69%) as a yellow oil. δ_H (250 MHz, $CDCl_3$): 1.28 (m, 1H), 1.43 - 2.06 (series of m, 6H), 2.47 (s, 3H), 2.59 (ddd, J = 13.5, 10.6, 7.5 Hz, 1H), 3.06 (m, 1H, α-N), 3.13 (m, 1H, α-N), 3.87 (brs, 1H, exch), 4.66 (ddd, J = 10.6, 6.0, 4.1 Hz, 1H, α-OH). δ_C (63 MHz, $CDCl_3$): 17.1, 21.7, 26.7 & 37.1 (4 x CH_2), 37.7 (CH_3), 59.8 & 63.1 (2 x CHN), 71.9 (CHOH). υ_{max} (CH_2Cl_2): 3320brs, 3050s, 2990s, 2940s, 1440s, 1420s, 1375w, 1355w, 1265s, 1150brw, 1120w, 1105w, 1090w, 1070m, 1005m, 990w, 970w, 960w, 895s, 850 cm^{-1}. m/z (%): 141 (M^+, 13), 124 (3), 112 (4), 97 (100), 82 (57), 68 (10). $C_8H_{15}NO$ [M^+] requires m/z 141.1154; observed 141.1154.

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