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Total Synthesis of Scopine, Pseudoscopine, and Nor- Derivatives

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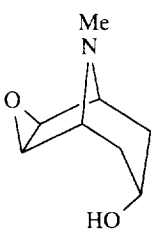
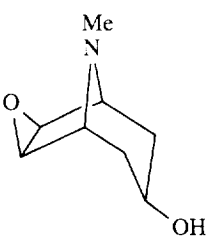
Abstract: Scopine and pseudoscopine have been synthesised from cyclohepta-3,5-dienol; the initial 1,4-fuctionalisation of the diene is based on a nitroso- cycloaddition. The use of the N-benzyloxycarbonyl group throughout the scheme allows ultimate reductive deprotection to yield N-methyl or novel NH (nor-) derivatives without damage to the *exo*-epoxide of the title compounds. Preliminary investigation of nitroso- cycloaddition to 5,6-epoxycyclohepta-1,3-diene is described. Copyright © 1996 Elsevier Science Ltd

Introduction

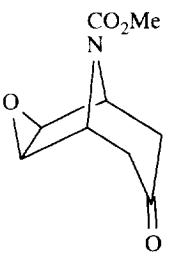
Scopine (**1**) is an important and interesting tropane derivative being the precursor to scopolamine and (-)-hyoscine.[1] It is unusual in having an *exo*- (β-) epoxide in the 2-carbon bridge of the tropane system in addition to the 3α-hydroxy substituent. There are very few established methods for introducing the 6,7-epoxide; unfortunately, the classic Robinson synthesis[2] cannot be adapted successfully. The simple approach, based on epoxidation of a 6,7- double bond in intact tropanes is limited by the availability of the necessary alkenes and by the inevitable attack by the oxidising agent at a bridging amino-nitrogen. The first partial synthesis of scopine[3] involved epoxidation of protonated 6,7-dehydrotropine but was slow and of low efficiency. There appears to have been no successful synthesis of scopine until an elegant procedure was reported by Bäckvall[4] in 1991. This approach to both scopine and the non-natural diastereoisomer pseudoscopine (**2**) was based on an earlier synthesis of simpler tropane alkaloids[5] using palladium-catalysed 1,4-chloroacetoxylation of a functionalised cycloheptadiene as the key step. A toluenesulphonamido- group was introduced stereoselectively and the *syn*- directive effect of this group was used to control the epoxidation. The N-tosyl group was retained during the subsequent bicyclisation and the synthesis was completed by deprotection of the bridging nitrogen followed by N-methylation.



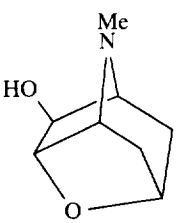
(**1**) Scopine



(**2**) Pseudoscopine



(**3**)



(**4**) Scopoline

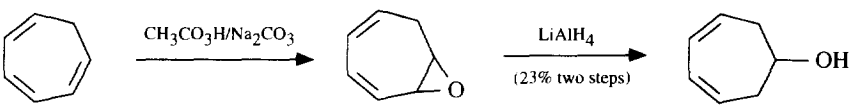
A recent paper by Mann[6] described a notable improvement to the original routes[7,8] to trop-6-enes from cycloaddition of oxyallyls (from polybromoketones) to pyrroles. Using this method, a range of both nitrogen- and oxygen-bridged bicycles was synthesised in good yield. Epoxidation of the N-protected nortrop-6-en-3-one derived from oxyallyl addition to 1-methoxycarbonylpyrrole gave the *exo*-epoxy-ketone (**3**) but reduction with an excess of DIBAH also initiated opening of the epoxide to give scopoline (**4**).[6]

In view of the limited approaches to scopine we chose to adapt our successful approach to epoxytropanes[9] and epoxyhomotropanes[10] (based on the addition of nitroso-compounds to cyclic dienes) to the synthesis of scopine, pseudoscopine and novel nor-derivatives. This second total synthesis complements the Bäckvall method.

A strategy to scopine and pseudoscopine precursors

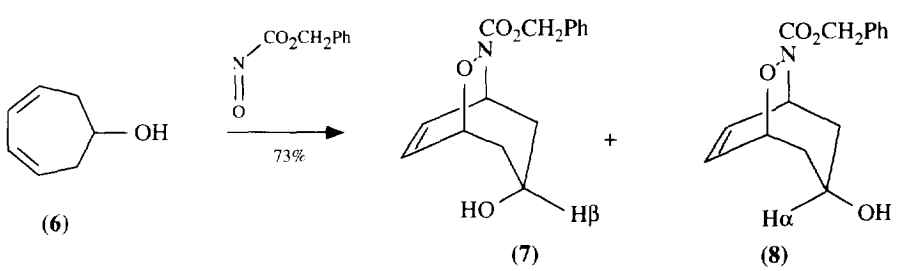
The 3-hydroxy substituent could be introduced by performing the initial nitroso cycloaddition reaction using cyclohepta-3,5-dienol (**6**). This diene can be prepared from tropone[11] but this approach did not give high yields[3b] in our hands. Instead, the procedure of Schiess and Wisson[12] was used (scheme 1). For large scale preparation of (**6**), the epoxide was not purified prior to reduction with lithium aluminium hydride. The overall yield was low but all the reagents were commercially available and of low cost. The reaction could also be scaled up to produce gramme quantities of the dienol.

Scheme 1



(**5**) (**6**)

The stereoselective introduction of the 3-hydroxy group was of prime importance for a successful synthesis of scopine (3α-hydroxy) and pseudoscopine (3β-hydroxy). When (**6**) was subjected to the standard conditions used for generation and cycloaddition of nitroso compounds, an acceptable yield of cycloadducts was produced but the reaction showed little selectivity giving a 35:65 mixture of (**7**) and (**8**) which could not be separated by chromatography (scheme 2).



(**6**) (**7**) (**8**)

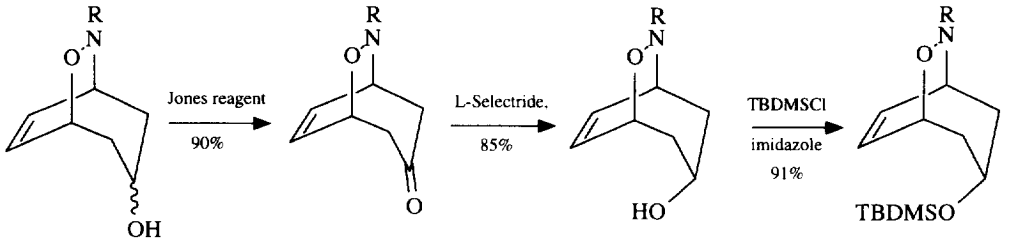
Scheme 2

35 : 65

The stereostructures of (**7**) and (**8**) were assigned on the basis of the relative chemical shifts of the α-hydroxy protons. The signal attributed to the 3α-proton of the major cycloadduct (**8**) was up-field (δ 3.67) as this lay within the shielding cone of the double bond. The 3β-proton of the minor adduct (**7**) was observed much further down-field at δ 4.24. These shifts are comparable to values for similar adducts (bearing different substituents at nitrogen) prepared by Howarth.[3b]

Rather than continue with a mixture of adducts in the hope of separation at a later stage, attempts were made to prepare purer samples of (**7**) and (**8**).

The stereoselective reduction of tropinone has been extensively studied by Beckett[13] who reported control involving kinetic and thermodynamic factors in the course of the reduction. Noyori[7] reported similar effects in the reduction of 6,7-dehydrotropinone. On the basis of the similarity of structure between tropinone and the ketone (**9**) [formed by oxidation of the adducts (**7**) and (**8**) with Jones reagent], reduction



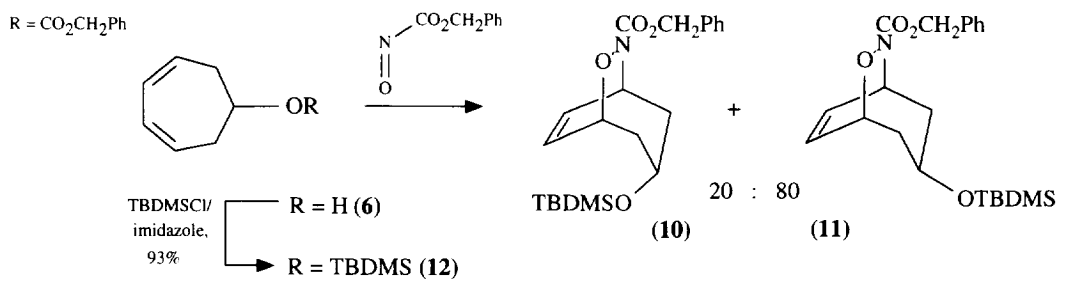
Scheme 3 $R = CO_2CH_2Ph$

of **(9)** was expected to favour the 3α-hydroxy stereoisomer **(7)** (kinetic control). Stereoselective reduction was achieved by treatment of **(9)** at -78°C with L-Selectride[14] to afford an 85% yield of a mixture of alcohols, substantially enriched (85%) in the 3α-isomer **(7)** (scheme 3) as shown by ^{1}H NMR spectroscopy. This was deemed to be of high enough purity for subsequent reactions.

The alcohol **(7)** was protected as the TBDMS ether **(10)**; the ^{1}H NMR spectrum of **(10)** confirmed the structure and also showed the presence of a small amount of the 3β-silyl ether, formed from the epimeric alcohol **(8)**. These stereoisomers could not be separated at this stage but, separation was achieved subsequently.

Inversion of the stereochemistry of the 3α-hydroxy group of **(7)** was not attempted in view of difficulties encountered previously with such reactions.[9b] Instead, the cyclohepta-3,5-dienol **(6)** was silylated with the TBDMS group prior to the cycloaddition reaction in the hope that a bulky group would alter the stereoselectivity. The silyl ether **(12)** was prepared in 93% yield and then reacted with benzyl nitrosoformate (scheme 4)

Scheme 4

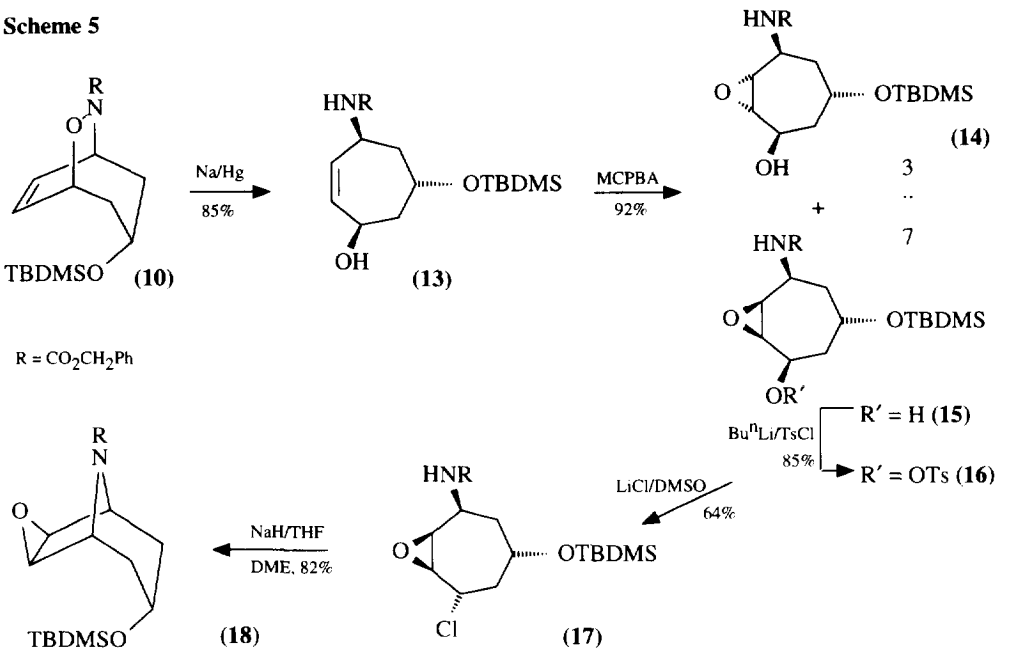


This approach was successful giving a 20:80 ratio of the adducts **(10)**:**(11)**. The 3α- proton of **(11)** was observed in the ^{1}H NMR spectrum as an approximate triplet of triplets (J = 10.3, 6.3 Hz) at δ 3.68. The chemical shift of this proton was notably up-field as a result of shielding by the double bond. This observation is in good agreement with the corresponding value (δ 3.67) for the 3α- proton of **(8)**.

Synthesis of scopine and norscopine

The silyl ether **(10)** was converted into the protected *exo*-6,7-epoxytropane system **(18)** using a similar sequence of reactions to that described for the preparation of simpler systems (scheme 5).[9] Reduction of **(10)** with sodium amalgam afforded **(13)** in good yield. Epoxidation of **(13)** produced a pair of stereoisomers **(14)** and **(15)** in a 3:7 ratio based upon isolated yields of the epoxides after chromatographic

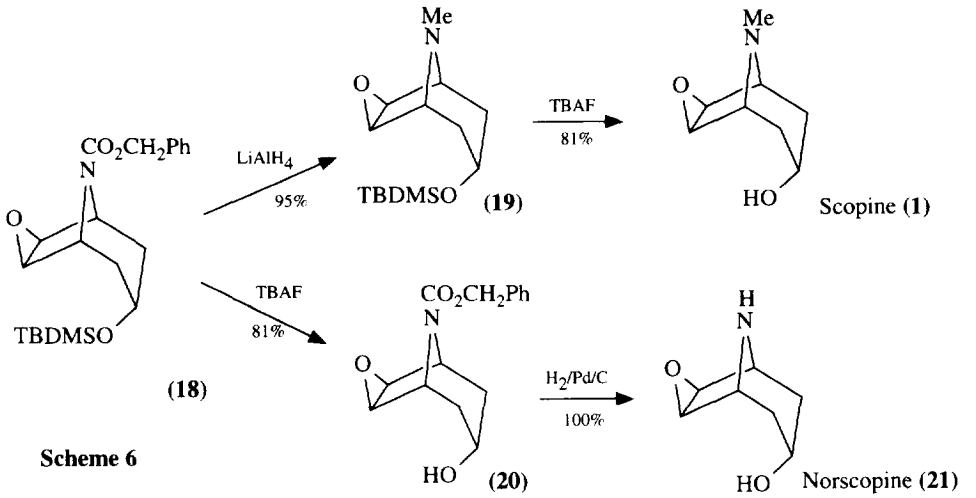
Scheme 5



separation. The ^{1}H NMR spectra of (**14**) and (**15**) were broad at ambient temperature but the product of *syn*- epoxidation (**15**) showed no measurable vicinal coupling between the epoxide protons and the adjacent protons α- to O and N. The minor product (**14**) did show vicinal coupling to the α-O and α-N protons in agreement with observations in the parent compounds which differed only in the lack of the OTBDMS group.[9] The necessary *trans*-1,4 stereochemistry between nitrogen and leaving group was achieved by tosylation and treatment of the tosylate (**16**) with lithium chloride to give (**17**). Chromatographic purification of (**16**) removed minor by-products that had arisen from contamination of (**10**) with the 6β-silyl ether. The inversion of configuration in the chlorination step was confirmed from a vicinal coupling of 4.6 Hz between epoxide and α-chlorine protons in the ^{1}H NMR spectrum of (**17**). Nucleophilic displacement initiated by sodium hydride then gave the doubly-protected epoxytropane structure (**18**). The epoxide and bridgehead signals were duplicated in the ^{1}H and ^{13}C NMR of (**18**) as a consequence of slow rotation about the N-CO bond which is typical of these bicyclic systems.[15] The epoxide protons in (**18**) appeared as doublets in the ^{1}H NMR spectrum with a mutual coupling of 3.5 Hz. The absence of any observable coupling between epoxide and bridgehead protons confirmed the *exo*- (β-) epoxide stereochemistry.

The final deprotection steps are shown in scheme 6. Reduction of (**18**) with lithium aluminium hydride in diethyl ether produced a high yield of (**19**) which showed an N-methyl singlet at δ 2.51 in the ^{1}H NMR spectrum and a methyl signal at δ 42.5 in the ^{13}C NMR spectrum. As anticipated from the behaviour of simpler systems,[9,10] the epoxide was stable to the reducing conditions. Removal of the O-protecting group of (**19**) was accomplished using TBAF[16] in THF to furnish scopine (**1**), the spectroscopic properties of which were in good agreement with literature data. Comments on the ^{1}H NMR spectrum of scopine will follow a description of the synthesis of pseudoscopine.

Hydrogenolysis of (**18**) with subsequent removal of the O-protecting group from (**20**), allowed for the preparation of the non-natural derivative norscopine (**21**). A partial synthesis of norscopolamine (from scopolamine) has been reported,[17] but no other total synthesis of norscopine has been undertaken to date.

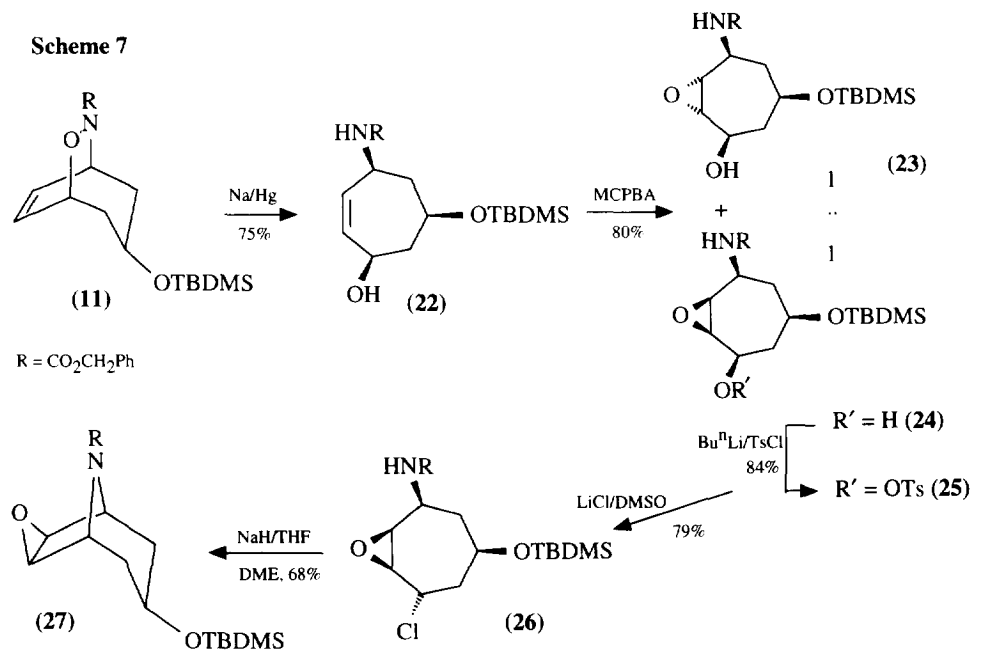


Scheme 6

Synthesis of pseudoscopine and norpseudoscopine

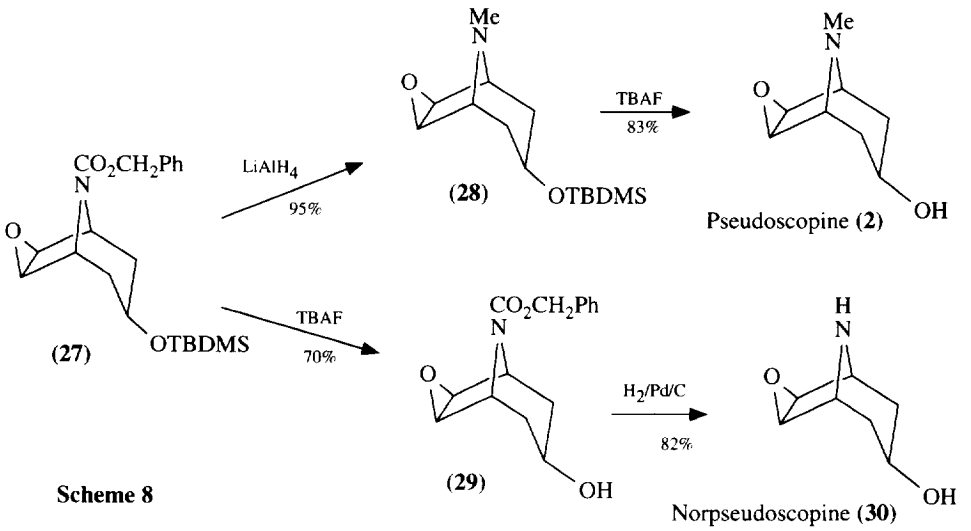
A partial synthesis of pseudoscopine was reported by Heusner and Zeile[18] in 1958 based on oxidation of scopine and subsequent reduction with potassium borohydride but the yield for the latter step was low. The Bäckvall method therefore represents the only practical synthesis of pseudoscopine to date. Our approach followed a parallel procedure to that described above for scopine beginning with the 3β-silyl ether (**11**) (scheme 7).

Scheme 7



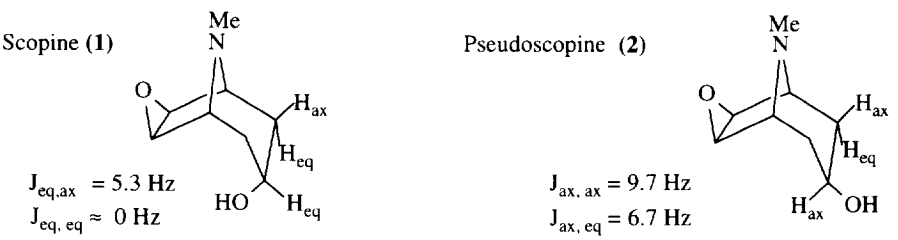
Reduction of (**11**) with sodium amalgam produced the allylic alcohol (**22**) which was epoxidised with MCPBA to furnish a 1:1 mixture of (**23**):(**24**). The epoxides were separable by chromatography; the isomer (**24**) with the epoxide *syn*- to the α-N and α-O was isolated in pure form but (**23**) contained minor impurities resulting from contamination by the 6α-silyl ether. Alternative epoxidising agents could have been used to vary the ratio, but (**23**) was retained as a synthetically useful by-product since it is a potential precursor to analogues of scopine. The *syn*-epoxide **24**) was converted into (**25**) and thence, via the chloro- compound (**26**), into the protected form (**27**) of pseudoscopine.

The deprotection procedures used to prepare pseudoscopine (**2**) and norpseudoscopine (**30**) were straightforward (scheme 8). Hydride reduction of (**27**) gave the N-methyl derivative (**28**) and hence pseudoscopine (**2**) on treatment with fluoride ion. Alternatively, initial desilylation of (**29**) followed by hydrogenolysis of (**29**) furnished norpseudoscopine (**30**), a novel compound.



Scheme 8

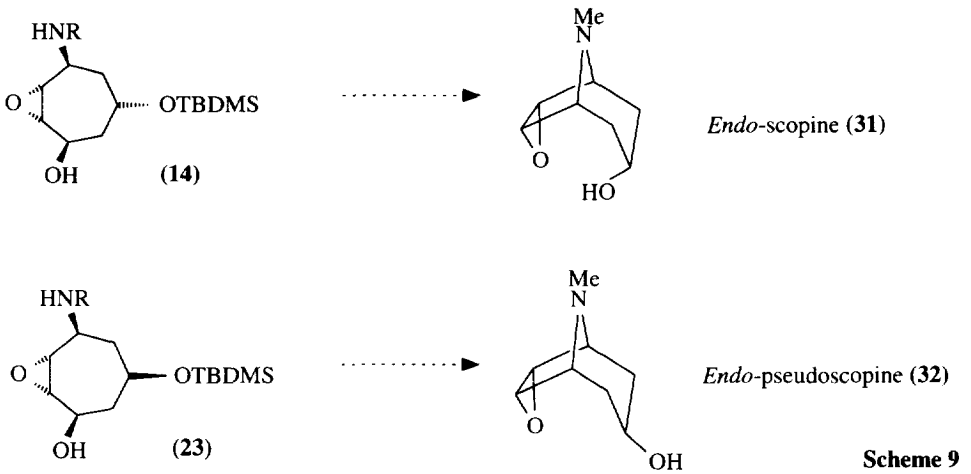
The successful synthesis of scopine and pseudoscopine was confirmed by comparison of ^{1}H, ^{13}C and mass spectra with published data.[19] Vicinal coupling to the proton on C-3 differed predictably.



The 3β- proton of scopine (**1**) at δ 4.20 is equatorial and coupling to each of the proximate axial protons resulted in a triplet (J = 5.3 Hz). Vicinal coupling to the equatorial protons was, predictably, too small to be measured. The 3α-proton of pseudoscopine (**2**) at δ 4.16 is axial and, as a consequence, the vicinal axial-axial couplings are much larger giving a triplet of triplets (J = 9.7, 6.7 Hz). The nor-derivatives (**21**) and (**30**) showed similar values as did the 3α- and 3β-oxygenated adducts (**7**) and (**8**), where the C_3-proton coupled to pseudo-axial and pseudo-equatorial protons and confirmed the earlier assignments based on chemical shift.

Further functionalisation of tropane

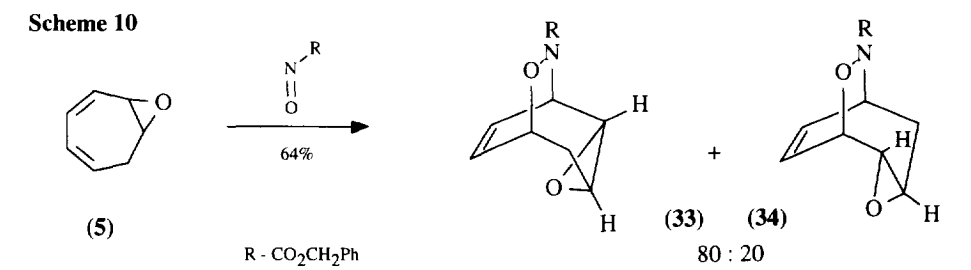
This paper has described a successful synthetic strategy to scopine, pseudoscopine and novel nor-derivatives and the stability of the *exo*-epoxide group has been used to full advantage. During the course of this work, two by-products (**14**) and (**23**) were isolated which had the epoxide group *anti-* to the N-substituent. These epoxides are potential precursors to '*endo*-scopine' (**31**) and '*endo*-pseudoscopine' (**32**) (scheme 9). There is no reference to such compounds in the literature to date. However, since the *endo*-6,7-epoxide of the tropane system has been shown[9] to be significantly more sensitive to ring-opening by hydride and hydrogenolysis than the *exo*-epoxide, a different protecting group at nitrogen will be required at the conclusion of the synthesis and this work has not yet been pursued.



Scheme 9

A preliminary investigation into the introduction of additional oxygen functionality into the C_2 and C_4 locations of tropane was made. This could provide further analogues of scopine and would also be of use in preparing other oxygenated tropane alkaloids including calystegins. The epoxide (**5**) was an intermediate in the synthesis of cyclohepta-3,5-dienol (**6**) and it was expected that the diene in (**5**) would undergo cycloaddition with nitroso compounds. A small portion of (**5**) was purified and subjected to the standard cycloaddition conditions employed previously. The reaction was successful and two epoxides (**33**) and an isomer (**34**) were isolated in an 80:20 ratio.

Scheme 10



The ^1H NMR spectrum displayed characteristic bridgehead protons of similar chemical shift to those of cycloadducts prepared previously. The two isomers could not be separated by chromatography and the assignment of relative stereo- and regiochemistries from ^1H NMR signals in the spectrum of the mixture could not be made with confidence. However, recrystallisation of the product mixture afforded the major cycloadduct (**33**) in pure form and a crystal was grown for X-ray analysis (figure).

This revealed that **(33)** had the stucture depicted in scheme 10 with an *endo*- epoxide. Although the tentative structure **(34)** could not be confirmed with certainty on the basis of the available data, this reaction does provide a highly functionalised cycloadduct **(33)** in pure form and in an acceptable yield. Using this as a starting material, there is scope to produce further natural and non-natural derivatives of tropane. The epoxides are precursors to hydroxy- and dihydroxy-tropanes[9] and the general approach described here is being adapted to a wider range of oxygenated tropanes.

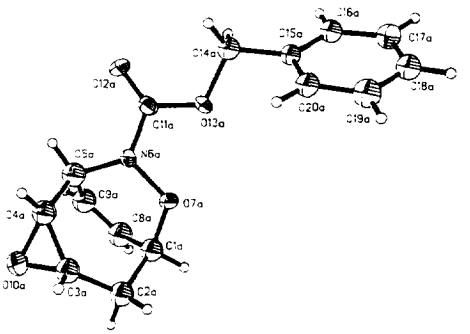


Figure: ORTEP diagram of **(33)**

We thank Dr. J. Fawcett and Dr. D.R. Russell for the X-ray crystal structure determination. 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.[20] 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.[21] Flash chromatography was carried out according to the method of Still[22] 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).

Cyclohepta-3,5-dienol (6)

Using a modified version of the procedure of Schiess and Wisson,[12] peroxyacetic acid (32 weight %, 117.0 g, 0.49 mol) was dripped into a stirred solution of cycloheptatriene (32.4 g, 0.35 mol) in dichloromethane (300 ml) containing anhydrous sodium carbonate (85.0 g, 0.80 mol) over 30 min at 0°C. Stirring was continued for a further 3 hr at 0°C and the solution was then filtered through celite and the filter cake washed thoroughly with dichloromethane. The solution was transferred to a separating funnel and washed with saturated sodium bicarbonate solution (2 x 60 ml) and brine (50 ml). The organic layer was separated, dried over anhydrous sodium sulphate, filtered, and the solvent evaporated at atmospheric pressure. The crude epoxide **(5)** was then dissolved in diethyl ether (100 ml) and dripped into a slurry of lithium aluminium hydride (5.70 g, 0.15 mol) in diethyl ether (240 ml) at 0°C. After complete addition (30 min) the mixture was stirred for a further 1 hr and an aliquot was removed for NMR analysis which indicated complete reaction. Excess hydride was destroyed by the careful addition of sodium hydroxide solution (2 M) and the mixture was dried over anhydrous sodium sulphate. Filtration through celite and evaporation of solvent under reduced pressure gave a yellow oil. Vacuum distillation of the oil at 20 mbar, 110°C removed volatile impurities. Further distillation at 5 mbar, 110°C furnished **(6)** (9.10 g, 23%) as a colourless oil. δ_H (90 MHz, $CDCl_3$): 2.50 (~t, J ≈ 4.5 Hz, 4H), 4.10 (m, 1H, α-OH), 5.40 - 5.60 (series of m, 4H).

N-(Benzyloxycarbonyl)-3α-hydroxy-6-oxa-7-azabicyclo[3.2.2]non-8-ene (7) and N-(benzyloxycarbonyl)-3β-hydroxy-6-oxa-7-azabicyclo[3.2.2]non-8-ene (8)

A solution of benzyl-N-hydroxycarbamate (5.91 g, 0.031 mol) in dichloromethane (12 ml) was added to a solution of cycloocta-3,5-dieneol **(6)** (3.42 g, 0.031 mol) and tetramethylammonium periodate (8.24 g, 0.031 mol) in dichloromethane (45 ml). The reaction and work-up followed the procedure used for the cycloaddition to cycloheptadiene itself.[23] An inseparable mixture of stereoisomers **(7)**:**(8)** (6.21 g, 73%) was obtained in a 35:65 ratio (calculated from ^{1}H NMR signal integrations) as a pale yellow oil after flash chromatography using 9:1 diethyl ether:petroleum ether (b.p. 40 - 60°C). The full assignment of NMR signals was possible after the preparation of an enriched sample of the 3α-hydroxy isomer **(7)**, described later. Signals common to both isomers are quoted in italics. δ_H (300 MHz, $CDCl_3$), 3α-Hydroxy isomer **(7)**: 1.99 (m, 1H), 2.04 (m, 1H), 2.44 (ddd, J ≈ 14 Hz, J = 5.5, 4.1 Hz, 1H). 2.47 (ddd, J ≈ 14 Hz, J = 5.5, 4.5 Hz, 1H), *2.55* (brs, exch, OH), 4.24 (~quin, J = 5.5 Hz, 1H, α-OSi), *4.74* (m, 1H, α-N), *4.90* (m, 1H, α-O), 5.17 (s, 2H, CH_2Ph), 6.39 (ddd, J = 9.1, 6.4, 1.3 Hz, 1H, HC=), 6.50 (ddd, J = 9.1, 6.4, 1.1 Hz, 1H, HC=), *7.33* (m, 5H). δ_C (75 MHz, $CDCl_3$): 38.4 & 40.8 (2 x CH_2), 51.6 (CHN), 66.9 (CHOH), 67.85 (CH_2Ph), 72.0 (CHO), *128.0, 128.2, & 128.4* (3 x aryl CH), *129.7* & 132.3 (2 x CH=), *135.9* (aryl C), 156.1 (C=O). δ_H (300 MHz, $CDCl_3$), 3β-Hydroxy isomer **(8)**: 1.79 - 1.98 (m, 2H), 2.24 (m, 2H), *2.55* (brs, exch, OH), 3.67 (~tt, J = 6.2, 4.4 Hz, 1H, α-OSi), *4.74* (m, 1H, α-N), *4.90* (m, 1H, α-O), 5.15 (s, 2H, CH_2Ph), 6.17 (ddd, J = 9.1, 6.2, 1.2 Hz, 1H, HC=), 6.32 (ddd, J = 9.1, 6.8, 0.6 Hz, 1H, HC=), *7.33* (m, 5H). δ_C (75 MHz, $CDCl_3$): 36.8 & 39.6 (2 x CH_2), 51.2 (CHN), 65.6 (CHOH), 67.77 (CH_2Ph), 72.4 (CHO), *128.0, 128.2, & 128.4* (3 x aryl CH), *129.7* & 132.0 (2 x CH=), *135.9* (aryl C), 156.4 (C=O). ν_{max} (CH_2Cl_2), Mixture of **(7)** and **(8)**: 3610w, 3490brw, 3040w, 2960s, 2930s, 2880w, 1705s, 1500w, 1455m, 1395m, 1355m, 1270brs, 1215w, 1175w, 1075s, 1045s, 1030w, 925w, 860w, 820w cm^{-1}. $^m/_z$ (%), mixture of **(7)** and **(8)**: 275 (M^+, 2), (231 (2), 92 (7), 91 (100). $C_{15}H_{17}NO_4$ [M^+] requires $^m/_z$ 275.1158; observed $^m/_z$ 275.1158.

N-(Benzyloxycarbonyl)-6-oxa-7-azabicyclo[3.2.2]non-8-en-3-one (9)

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 **(7)** and **(8)** (6.26 g, 0.023 mol) in dry acetone (110 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 **(9)** (5.68 g, 90%) as a pale yellow solid which was pure enough for the subsequent reaction. An analytical sample was prepared by recrystallising from toluene and petroleum ether (b.p. 60 - 80°C) to give a crystalline white solid (m.p. 82 - 83°C). δ_H (300 MHz, $CDCl_3$): 2.69 (m, 2H), 3.05 (dd, J ≈ 13 Hz, J = 2.8 Hz, 1H), 3.12 (dd, J ≈ 13 Hz, J = 3.9 Hz, 1H), 4.90 (m, 1H, α-N), 4.97 (m, 1H, α-O), 5.16 & 5.21 (ABq, J =

12.4 Hz, 2H, CH_2Ph), 6.40 (ddd, J = 9.2, 6.2, 1.3 Hz, 1H, HC=), 6.57 (ddd, J = 9.2, 6.8, 0.9 Hz, 1H, HC=), 7.34 (m, 5H). δ_C (75 MHz, $CDCl_3$): 47.1 & 49.8 (2 x CH_2), 50.6 (CHN), 66.1 (CH_2Ph), 70.6 (CHO), 128.1, 128.3, & 128.5 (3 x aryl CH), 131.4 & 132.7 (2 x CH=), 135.6 (aryl C), 156.6 (NC=O), 206.0 (C=O). ν_{max} (CH_2Cl_2): 3040w, 2950w, 1710s, 1500w, 1450w, 1395m, 1375m, 1355m, 1330m, 1270brs, 1215m, 1150w, 1095m, 1070s, 1040m, 1000w, 980w, 910m, 815w cm^{-1}. m/z (%): 273 (M^+, 2), 229 (9), 92 (11), 91 (100). $C_{15}H_{15}NO_4$ [M^+] requires m/z 273.1001; observed 273.1002. Found: C, 66.00; H, 5.61; N, 5.15%. $C_{15}H_{15}NO_4$ requires: C, 65.92; H, 5.53; N, 5.13%.

N-(Benzyloxycarbonyl)-3α-hydroxy-6-oxa-7-azabicyclo[3.2.2]non-8-ene (7) (enriched)

A solution of **(9)** (5.58 g, 0.020 mol) in THF (110 ml) was cooled with stirring to -78°C under a nitrogen atmosphere. A solution of L-Selectride (1M in THF, 21.5 ml, 0.022 mol), was slowly dripped in (down the side of the flask) over 30 min. The solution was stirred at -78°C for 2 hr, quenched with water (1 ml) and warmed to 0°C. Sodium hydroxide solution (1M, 20 ml) and aqueous hydrogen peroxide (30 weight %, 5 ml) were added and stirred for 10 min. The mixture was transferred to a separating funnel and diethyl ether (100 ml) was added. The aqueous layer was separated off and the ethereal layer was washed with water (20 ml) and brine (10 ml). After drying over anhydrous magnesium sulphate and filtration, the bulk of the solvent was evaporated under reduced pressure. The residual oil was purified by flash chromatography, eluting with diethyl ether, to give **(7)**:**(8)** (4.78 g, 85%) in a ratio of 85:15 as determined from ^1H NMR integrations. The two isomers were inseparable at this stage of the synthesis.

N-Benzyloxycarbonyl-3α-[(*t*-butyldimethylsilyl)oxy]-6-oxa-7-azabicyclo[3.2.2]non-8-ene (10) (enriched)

The 85:15 mixture of **(7)**:**(8)** (4.18 g, 0.015 mol) was dissolved in DMF (15 ml) and cooled to 0°C. Imidazole (1.67 g, 0.024 mol) and TBDMSCl (3.02 g, 0.020 mol) were added and the mixture stirred for 1.5 hr. Water (50 ml) was added, the mixture was transferred to a separating funnel and extracted with diethyl ether (3 x 70 ml). The combined ethereal layers were washed with water (15 ml) and brine (10 ml). After drying over anhydrous magnesium sulphate and filtration, the bulk of the solvent was evaporated under reduced pressure. The residual oil was purified by flash chromatography using 1:9 diethyl ether:petroleum ether (b.p. 40 - 60°C) to afford **(10)** (5.44 g, 91%) as a mobile yellow oil. Partial separation of **(10)** from the 3β-silylether **(11)** was possible by chromatography to give an improved ratio of 90:10 (from ^1H NMR integrations) but minor traces of **(11)** were still visible in the NMR spectra; these data are quoted in full below. δ_H (300 MHz, $CDCl_3$): 0.05 [s, 6H, $(CH_3)_2Si$], 0.88 [s, 9H, $(CH_3)_3CSi$], 1.76 (m, 2H), 2.42 (m, 2H), 4.40 (~tt, J = 7.7, 5.9 Hz, 1H, α-OSi), 4.77 (brt, J ≈ 4 Hz, 1H, α-N), 4.92 (brt, J ≈ 5 Hz, 1H, α-O), 5.19 & 5.24 (ABq, J = 12.3 Hz, 2H, CH_2Ph), 6.35 (ddd, J = 9.1, 6.4, 1.3 Hz, 1H), 6.45 (ddd, J = 9.1, 7.1, 1.0 Hz, 1H), 7.31 - 7.40 (m, 5H). δ_C (75 MHz, $CDCl_3$): -4.9 [$(CH_3)_2Si$], 17.7 [$(CH_3)_3CSi$], 25.6 [$(\mathbf{CH_3})_3CSi$], 36.5 & 40.7 (2 x CH_2), 51.0 (CHN), 67.6 (CHOSi), 67.8 (CH_2Ph), 72.4 (CHO), 127.9, 128.0 & 128.3 (3 x aryl CH), 131.5 & 131.6 (2 x CH=), 135.9 (aryl C), 156.2 (C=O). ν_{max} (CH_2Cl_2): 2930m, 2850m, 1690s, 1555w, 1380w, 1350m, 1290w, 1260w, 1135w, 1080s, 1030w, 1005w, 925w, 905m, 835m, 740vbrm. m/z (%): 389 (M^+, 3), 332 (5), 288 (8), 273 (16), 167 (13), 147 (8), 91 (100). $C_{21}H_{31}NO_4Si$ [M^+] requires m/z 389.2022; observed 389.2022.

6-[(*t*-Butyldimethylsilyl)oxy]cyclohepta-1,3-diene (12)

A solution of **(6)** (1.506 g) in dry DMF (24 ml) was stirred at 0°C under a nitrogen atmosphere. Imidazole (1.489 g, 21.9 mmol) and TBDMSCl (2.687 g, 17.8 mmol) were added and the mixture stirred for 2.5 hr. The reaction mixture was poured into water (30 ml) and repeatedly extracted with diethyl ether (2 x 75 ml, 1 x 50 ml). The combined ethereal layers were washed with water (20 ml), brine (10 ml) and then dried over anhydrous magnesium sulphate. Filtration and evaporation of solvent under reduced pressure gave a crude oil which was purified by flash chromatography, eluting with petroleum ether (b.p. 40 - 60 °C) to afford **(12)** (2.847 g, 93%) as a colourless oil. δ_H (300 MHz, $CDCl_3$): 0.12 [s, 6H, $(CH_3)_2Si$], 0.95 [s, 9H, $(CH_3)_3CSi$], 2.51 (m, 4H), 4.11 (tt, J = 8.0, 4.8 Hz, 1H, α-OSi), 5.71 (m, 2H), 5.82 (m, 2H). δ_C (75 MHz, $CDCl_3$): -4.8 [$(CH_3)_2Si$], 18.1 [$(CH_3)_3CSi$], 25.9 [$(\mathbf{CH_3})_3CSi$], 40.9 (2 x CH_2), 71.4 (CHOSi), 126.0 (2 x CH), 127.9 (2 x CH). ν_{max} (CH_2Cl_2): 3010w, 2930s, 2895s, 2850s, 1465m, 1380m, 1360m, 1240w, 1075brs, 1030s, 1005m, 965w, 940w, 910s, 875w, 835s, 720vbrm cm^{-1}.

N-Benzyloxycarbonyl-3β-([*t*-butyldimethylsilyl)oxy]-6-oxa-7-azabicyclo[3.2.2]non-8-ene (11) (enriched)

Tetramethylammonium periodate (4.04 g, 0.015 mol) and **(12)** (2.85 g, 0.013 mol) in dichloromethane (65 ml) were stirred at -78°C. A solution of benzyl-N-hydroxycarbamate (2.55 g, 0.015 mol) in dichloromethane (20 ml) was dripped in over 10 min and the solution was then warmed to ambient temperature and stirred for 1.5 hr. The reaction and work-up followed the procedure used for the cycloaddition to cycloheptadiene itself.[23] Purification of the crude oil by flash chromatography, eluting with 1:4 diethyl ether:petroleum ether (b.p. 40 - 60°C), afforded **(11)**:**(10)** (4.18 g, 85%) in an 80:20 ratio as a colourless oil. The two isomers were inseparable at this stage of the synthesis. δ_H (300 MHz, $CDCl_3$): 0.01 [s, 6H, $(CH_3)_2Si$], 0.85 [s, 9H, $(CH_3)_3CSi$], 1.88 (ddd, J = 14.6, 10.3, 1.2 Hz, 1H), 1.95 (ddd, J = 14.6, 10.3, 1.7 Hz, 1H), 2.14 (m, 2H), 3.68 (~tt, J = 10.3, 6.3 Hz, 1H, α-OSi), 4.70 (brt, J ≈ 5 Hz, 1H, α-N), 4.84 (brt, J ≈ 7 Hz, 1H, α-O), 5.15 (s, 2H, CH_2Ph), 6.18 (ddd, J = 9.1, 6.2, 1.3 Hz, 1H), 6.31 (ddd, J = 9.1, 6.8, 0.8 Hz, 1H), 7.32 (m, 5H). δ_C (75 MHz, $CDCl_3$): -4.8 [$(CH_3)_2Si$], 17.9 [$(CH_3)_3CSi$], 25.6 [$(\mathbf{CH_3})_3CSi$], 37.2 & 39.8 (2 x CH_2), 51.0 (CHN), 66.3 (CHOSi), 67.5 (CH_2Ph), 72.3 (CHO), 127.86, 127.92 & 128.0 (3 x aryl CH), 128.5 & 129.4 (2 x CH=), 136.0 (aryl C), 156.0 (C=O). Minor signals corresponding to the 3α-isomer **(10)** were observed in the NMR spectra of **(11)**. ν_{max} (CH_2Cl_2): 2930m, 2860m, 1690s, 1450brm, 1380m, 1350m, 1270brm, 1230w, 1220w, 1080s, 1005w, 940w, 925w, 905s, 875m, 860w, 835s, 740vbrm cm^{-1}. m/z (%): 389 (M^+, 2), 288 (4), 167 (14), 91 (100). $C_{21}H_{31}NO_4Si$ [M^+] requires m/z 389.2022; observed 389.2022.

1β-Hydroxy-4β-[(benzyloxycarbonyl)amino]-6α-[(*t*-butyldimethylsilyl)oxy]cyclohept-2-ene (13)

A 90:10 mixture of **(10)**:**(11)** (5.24 g, 0.013 mol) was reduced with freshly prepared and powdered sodium amalgam (70 g) and sodium phosphate (11.20 g, 0.079 mol) using the procedure described previously for the unsubstituted analogue.[23] The oily solid obtained was purified by flash chromatography, using 1:1 diethyl ether:petroleum ether (b.p. 40 - 60°C), to afford **(13)** (4.49 g, 85%) as a white solid which had m.p. 93 - 100°C after recrystallisation from toluene and petroleum ether (b.p. 60 - 80°C). δ_H (300 MHz, $CDCl_3$): 0.11 [s, 6H, $(CH_3)_2Si$], 0.95 [s, 9H, $(CH_3)_3CSi$], 1.67 - 1.88 (brm, 3H), 1.93 (brm, 1H), 2.47 (brs, 1H, exch), 4.24 (brm, 1H, α-OSi), 4.67 (brm, 1H, α-N), 4.79 (brd, J ≈ 9.2 Hz, 1H, α-OH), 5.11 (brs, 2H, CH_2Ph), 5.16 (brm, 1H, HN), 5.59 (brd, J ≈ 12Hz, 1H), 5.80 (brd, J ≈ 12 Hz, 1H), 7.35 (m, 5H). δ_C (75 MHz, $CDCl_3$): -4.9 [$(CH_3)_2Si$], 18.0 [$(CH_3)_3CSi$], 25.8 [$(\mathbf{CH_3})_3CSi$], 41.5 & 43.5 (2 x CH_2), 45.9 (CHN), 65.5 (CHOSi or CHOH), 66.5 (CH_2Ph), 66.7 (CHOSi or CHOH), 127.9 (2 x aryl CH), 128.4 (aryl CH), 131.7 (CH=), 136.4 (aryl C), 137.5 (CH=), 155.3 (C=O). Minor signals corresponding to the 6β-isomer **(22)** were observed. These values are quoted in full later. ν_{max} (CH_2Cl_2): 3600w, 3440w, 3040w, 2950m, 2930m, 2880w, 2850w, 1720s, 1505m, 1420brm, 1265brm, 1230m, 1085m, 1040m, 1005w, 940w, 895w, 870w, 835m cm^{-1}. m/z (%): 373 (M^+ - H_2O, 1), 335 (14), 334 (36), 290 (20), 272 (10), 208 (11), 183 (17), 91 (100). Found: C, 64.22; H, 8.39; N, 3.63%. $C_{21}H_{33}NO_4Si$ requires: C, 64.41; H, 8.49; N, 3.58%.

1β-Hydroxy-2α,3α-epoxy-4β-[(benzyloxycarbonyl)amino]-6α-[(*t*-butyldimethylsilyl)oxy]cycloheptane (14) and 1β-hydroxy-2β,3β-epoxy-4β-[(benzyloxycarbonyl)amino]-6α-[(*t*-butyldimethylsilyl)oxy]-cycloheptane (15)

MCPBA (50 - 60% purity, 2.581 g, 1.2 equivalents) was added to stirred solution of **(13)** (2.674 g, 6.84 mmol) in dry dichloromethane 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, dried over anhydrous magnesium sulphate, filtered and the solvent distilled under vacuum. The residual oil was purified by flash chromatography, eluting with 1:1 diethyl ether:petroleum ether (b.p. 40 - 60°C), to afford firstly the 2β,3β-epoxide **(15)** (1.881 g, 68%). An analytical sample was prepared by recrystallising from from toluene and petroleum ether (b.p. 60 - 80°C) to give a white solid (m.p. 114 - 120°C). δ_H (300 MHz, $CDCl_3$): 0.07 [s, 3H, $(CH_3)_2Si$], 0.09 [s, 3H, $(CH_3)_2Si$], 0.92 [s, 9H, $(CH_3)_3CSi$], 1.59 (brd, J ≈ 12 Hz, 1H), 1.67 (brd, J ≈ 12 Hz, 1H), 1.78 (m, 1H), 1.96 (m, 1H), 3.18 (brs, 1H, exch), 3.23 (d, J = 5.0 Hz, 1H, HCO), 3.32 (d, J = 5.0 Hz, 1H, HCO), 3.96 (m, 1H, α-OSi), 4.37 (brd, J ≈ 8Hz, 1H, α-N), 4.47 (brt, J ≈ 9 Hz, 1H, α-OH), 5.08 & 5.14 (ABq, J = 12.0 Hz, 2H, CH_2Ph), 5.64 (brd, J ≈ 9.2 Hz, 1H, HN), 7.34 (m, 5H). δ_C (75 MHz, $CDCl_3$): -5.2 [$(CH_3)_2Si$], 17.9 [$(CH_3)_3CSi$], 25.7 [$(\mathbf{CH_3})_3CSi$], 38.1 & 40.0 (2 x CH_2), 45.5 (CHN),

58.5 & 60.1 (2 x CHO), 64.8 (CHOSi or CHOH), 65.5 (CHOSi or CHOH), 66.5 (CH_2Ph), 127.9 (2 x aryl CH), 128.3 (aryl CH), 136.3 (aryl C), 155.0 (C=O). ν_{max} (CH_2Cl_2): 3600w, 3440w, 3040m, 2950m, 2930m, 2890w, 2860w, 1720s, 1510m, 1420m, 1245m, 1150w, 1095m, 1070m, 1030m, 1000w, 890m, 835m, 730vbrm cm^{-1}. m/z (%): 407 (M^+, 0.5), 350 (31), 306 (19), 91 (100). Found: C, 61.78; H, 8.25; N, 3.55%. $C_{21}H_{33}NO_5Si$ requires: C, 61.88; H, 8.16; N, 3.44%.

Further elution with 1:1 diethyl ether:petroleum ether (b.p. 40 - 60°C) afforded the 2α,3α-epoxide **(14)** (665 mg, 24%) as a white solid which had m.p. 118 - 123°C after recrystallisation from toluene and petroleum ether (b.p. 60 - 80°C). δ_H (300 MHz, $CDCl_3$): 0.07 [s, 6H, $(CH_3)_2Si$], 0.89 [s, 9H, $(CH_3)_3CSi$], 1.66 - 2.12 (series of brm, 4H), 2.96 (brs, 1H, exch), 3.13 (t, J ≈ 7.5 Hz, 1H, HCO), 3.18 (brm, 1H, HCO), 3.93 (brm, 1H, α-OSi), 4.14 (brm, 2H, α-OH & α-N), 5.13 (brs, 2H, CH_2Ph), 5.41 (brd, J ≈ 8 Hz, 1H, HN), 7.36 (m, 5H). δ_C (75 MHz, $CDCl_3$), The signals quoted in italics were broadened: -5.1 [$(CH_3)_2Si$], 17.7 [$(CH_3)_3CSi$], 25.8 [$(\mathbf{CH_3})_3CSi$], 39.3 & 40.7 (2 x CH_2), *47.8* (CHN), *56.6* & 58.7 (2 x CHO), 64.6 (CHOSi), *66.6* (CH_2Ph), 67.0 (CHOSi), 127.9 (2 x aryl CH), 128.3 (aryl CH), 136.2 (aryl C), 155.5 (C=O). ν_{max} (CH_2Cl_2): 3600w, 3430w, 3040m, 2950m, 2930m, 2850m, 1720m, 1510m, 1440m, 1240m, 1145w, 1085w, 1060w, 1040w, 1025w, 1015w, 920w, 890m, 875w, 835m, 730brm cm^{-1}. m/z (%): 407 (M^+, 1), 351 (9), 350 (37), 306 (18), 91 (100). $C_{21}H_{33}NO_5Si$ [M^+] requires m/z 407.2128; observed 407.2125. Found: C, 62.23; H, 8.14; N, 3.28%. $C_{21}H_{33}NO_5Si$ requires: C, 61.88; H, 8.16; N, 3.44%.

The NMR spectra of both **(14)** and **(15)** showed evidence of contamination by minor quantities of the 6β-isomers **(23)** and **(24)**. A ratio of 3:7 was determined for **(14)**:**(15)** from the isolated yields as the ^1H NMR spectra were broad.

1β-[*p*-Toluenesulphonyl)oxy]-2β,3β-epoxy-4β-[(benzyloxycarbonyl)amino]-6α-[(*t*-butyldimethylsilyl)-oxy]cycloheptane (16)

A solution of **(15)** (1.280 g, 3.14 mmol) in dry THF (35 ml) was cooled to 0°C under a nitrogen atmosphere. *n*-Butyllithium (2.5M in hexane, 1.51 ml, 3.78 mmol) was introduced using a syringe and the mixture was stirred for a further 10 mins. A solution of *p*-toluenesulphonyl chloride (781 mg, 4.09 mmol) in THF (5 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 (2 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 20 ml). The organic layer was dried over anhydrous magnesium sulphate and the solvent removed. The tosylate **(16)** (1.408 g), 85%) was isolated as a foam after flash chromatography, using 3:7 diethyl ether:petroleum ether (b.p. 40 - 60°C). NMR analysis indicated that **(16)** was not contaminated with minor isomers. δ_H (300 MHz, $CDCl_3$): -0.01 [s, 3H, $(CH_3)_2Si$], 0.04 [s, 3H, $(CH_3)_2Si$], 0.90 [s, 9H, $(CH_3)_3CSi$], 1.62 (brm, 1H), 1.71 - 2.01 (series of brm, 3H), 2.47 (s, 3H), 3.18 (d, J = 5.0 Hz, 1H, HCO), 3.25 (d, J = 5.0 Hz, 1H, HCO), 3.94 (m, 1H, α-OSi), 4.42 (m, 1H, α-N), 5.02 - 5.23 (m, 4H, NH, CH_2Ph & α-OSO_2Ar), 7.35 (m, 7H, aryl & part of AA'BB'), 7.82 (2H, part of AA'BB' system). δ_C (75 MHz, $CDCl_3$): -5.5 & -5.2 [2 x $(CH_3)_2Si$], 17.9 [$(CH_3)_3CSi$], 21.6 (CH_3Ar), 25.7 [$(\mathbf{CH_3})_3CSi$], 37.5 & 37.2 (2 x CH_2), 45.1 (CHN), 56.9 & 57.4 (2 x CHO), 64.1 (CHOSi), 66.7 (CH_2Ph), 77.5 ($CHOSO_2$), 127.7, 127.95, 128.04, 128.4 & 130.0 (5 x aryl CH), 133.5 (aryl CMe), 136.1 (aryl CCH_2), 144.8 (aryl CSO_2), 155.3 (C=O). ν_{max} (CH_2Cl_2): 3430w, 3040w, 2950s, 2930s, 2830s, 1725s, 1600w, 1505s, 1440brm, 1360s, 1235s, 1185s, 1175s, 1100s, 1065s, 1040s, 1025w, 1015w, 1005w, 935s, 900s, 870m, 835s, 810m, 725brm cm^{-1}. m/z (%): 504 [M^+ - $(CH_3)_3C$, 6], 350 (6), 306 (4), 229 (18), 91 (100).

1α-Chloro-2β,3β-epoxy-4β-[(benzyloxycarbonyl)amino]-6α-[(*t*-butyldimethylsilyl)oxy]cycloheptane (17)

Lithium chloride (690 mg, 16.42 mmol) and **(16)** (1.402 g, 2.50 mmol) in dry DMSO (27 ml) were 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 30 ml). The organic layers were combined and washed with water (2 x 10 ml) and brine (10 ml), before drying over anhydrous magnesium sulphate. Filtration and evaporation of solvent under reduced pressure gave a crude oil which was purified by flash chromatography, eluting with 1:9 diethyl ether:petroleum ether (b.p. 40 - 60°C). The chloride **(17)** was isolated as an oil. δ_H (300 MHz, $CDCl_3$): 0.08 [s, 6H, $(CH_3)_2Si$], 0.92 [s, 9H, $(CH_3)_3CSi$], 1.66 (m, 1H), 2.00 (m, 1H), 2.17 (m, 2H), 3.33 (m, 1H, HCO, β-N), 3.45 (t, J = 4.6 Hz, 1H, HCO, β-Cl), 4.02 (m, 1H, α-N), 4.19 (m, 1H, α-OSi), 4.56 (m, 1H,

α-Cl), 5.06 (brm, 1H, HN), 5.15 (s, 2H, CH_2Ph), 7.38 (m, 5H). δ_C (75 MHz, $CDCl_3$): -5.0 & -4.9 [2 x $(CH_3)_2Si$], 17.9 [$(CH_3)_3CSi$], 25.7 [$(\mathbf{CH_3})_3CSi$], 36.7 & 42.2 (2 x CH_2), 45.0 (CHN), 54.2 (CHCl), 58.4 & 60.5 (2 x CHO), 66.0 (CHOSi), 66.8 (CH_2Ph), 128.07, 128.12 & 128.5 (3 x aryl CH), 136.3 (aryl C), 155.3 (C=O). ν_{max} (CH_2Cl_2): 3430w, 3040w, 2950m, 2930m, 2880w, 2850m, 1720s, 1505m, 1465w, 1455w, 1435w, 1420w, 1390w, 1360w, 1335w, 1275m, 1240m, 1220m, 1090m, 1065m, 1025w, 1005w, 940w, 905s, 865w, 835m, 725vbrm cm^{-1}. m/z (%): 425 (M^+, 1), 370 (26), 369 (20), 368 (45), 326 (8), 324 (18), 308 (2), 306 (5), 193 (4), 191 (12), 107 (14), 91 (100). $C_{21}H_{32}NO_4ClSi$ [M^+] requires m/z 425.1789; observed 425.1789.

N-Benzyloxycarbonyl-3α-[(*t*-butyldimethylsilyl)oxy]-6β,7β-epoxy-8-azabicyclo[3.2.1]octane (18)

Sodium hydride (60% dispersion in mineral oil, 146 mg, 3.65 mmol) was slurried with THF:DME (5:1, 2 ml) under a nitrogen atmosphere. A solution of **(17)** (310 mg, 0.73 mmol) in THF:DME (5:1, 14 ml) was injected and the mixture was stirred at room temperature for 2 hr. A further portion of sodium hydride (41 mg, 1.03 mmol) was added and stirring was continued at 50°C for 1 hr. The reaction was cooled to -78°C and quenched with the minimum quantity of water. Diethyl ether (30 ml) was added and the organic solution was then washed with water (2 x 7 ml) and brine (7 ml). After drying over anhydrous magnesium sulphate and filtration, the solvent was evaporated under reduced pressure. The crude oil was purified by flash chromatography, eluting with 1:4 diethyl ether:petroleum ether (b.p. 40 - 60°C), to afford **(18)** (233 mg, 82%) as a white solid which had m.p. 53 - 54°C after recrystallisation from petroleum ether (b.p. 40 - 60°C). The chemical shifts quoted in italics were common to both rotamers. δ_H (300 MHz, $CDCl_3$): 0.05 [s, 3H, $(CH_3)_2Si$], 0.06 [s, 3H, $(CH_3)_2Si$], *0.90* [s, 9H, $(CH_3)_3CSi$], 1.64 (brdd, J ≈ 15, 2 Hz, 1H), 1.69 (brdd, J ≈ 15, 2 Hz, 1H), 2.04 (dt, J ≈ 15, 4, 4 Hz, 1H), 2.10 (dt, J ≈ 15, 4, 4 Hz, 1H), 3.53 (d, J = 3.5 Hz, 1H, HCO), 3.56 (d, J = 3.5 Hz, 1H, HCO), *4.00* (~t, J ≈ 4.5 Hz, 1H), 4.42 (brdd, J ≈ 3.5, 2.0 Hz, 1H, HCN), 4.50 (brdd, J ≈ 3.5, 2.0 Hz, 1H, HCN), *5.15 & 5.18* (ABq, J = 12.6 Hz, 2H, CH_2Ph), *7.37* (m, 5H). δ_C (75 MHz, $CDCl_3$): *-5.0* [$(CH_3)_2Si$], *17.7* [$(CH_3)_3CSi$], *25.7* [$(\mathbf{CH_3})_3CSi$], 34.6 & 34.9 (2 x CH_2), 53.2 & 53.4 (2 x CHO), *53.7* (2 x CHN), *63.4* (CHOSi), *66.7* (CH_2Ph). *127.7, 127.8 & 128.4* (3 x aryl CH), *136.6* (aryl C), *156.6* (C=O). ν_{max} (CH_2Cl_2): 3040w, 2950m, 2930m, 2890w, 2860w, 1700s, 1430m, 1360m, 1270brm, 1100w, 1080s, 1040m, 1025w, 1005w, 970w, 940w, 910m, 890m, 840s, 740brm cm^{-1}. m/z (%): 389 (M^+, 8), 288 (19), 283 (11), 260 (10), 254 (10), 226 (29), 198 (11), 143 (11), 92 (26), 91 (100). $C_{21}H_{31}NO_4Si$ [M^+] requires m/z 389.2022; observed m/z 389.2022. Found: C, 64.53; H, 7.93; N, 3.51%. $C_{21}H_{31}NO_4Si$ requires: C, 64.74; H, 8.02; N, 3.60%.

Scopine *t*-butyldimethylsilyl ether (19)

A solution of **(18)** (88 mg, 0.23 mmol) in diethyl ether (6 ml) and lithium aluminium hydride (45 mg, 1.18 mmol) were gently refluxed under a nitrogen atmosphere for 2 hr. Excess hydride was destroyed by the dropwise addition of water-saturated diethyl ether and the solution was dried over anhydrous sodium sulphate. Filtration and evaporation of solvent under reduced pressure leaving an oil which was purified by flash chromatography, eluting firstly with diethyl ether to remove benzyl alcohol, and secondly with 9:1 ethyl acetate:triethylamine to afford **(19)** (58 mg, 95%) as a colourless oil. δ_H (250 MHz, $CDCl_3$): 0.00 [s, 6H, $(CH_3)_2Si$], 0.86 [s, 9H, $(CH_3)_3CSi$], 1.47 (dd, J = 14.6, 1.1 Hz, 2H), 2.02 (dt, J = 14.6 Hz, J ≈ 4 Hz, 2H), 2.51 (s, 3H), 3.14 (brdd, J ≈ 4 Hz, J = 1.1 Hz, 2H, α-N), 3.62 (s, 2H, HCO), 3.89 (t, J = 4.9 Hz, 1H, α-OSi). δ_C (63 MHz, $CDCl_3$): -4.6 [$(CH_3)_2Si$], 18.1 [$(CH_3)_3CSi$], 26.6 [$(\mathbf{CH_3})_3CSi$], 35.1 (2 x CH_2), 42.5 (CH_3), 57.7 (2 x CHN), 59.0 (2 x CHO), 64.1 (CHOSi). ν_{max} (CH_2Cl_2): 3030w, 2930s, 2890s, 2850s, 2795w, 1460m, 1450m, 1390w, 1360w, 1330m, 1240m, 1200m, 1075s, 1040s, 1020s, 1005s, 960w, 935w, 875w, 860s, 840s, 830s, 795m, 720brm cm^{-1}. m/z (%): 269 (M^+, 28), 255 (35), 240 (11), 226 (12), 213 (11), 199 (18), 198 (20), 155 (13), 143 (22), 138 (55), 110 (16), 94 (47), 80 (26), 75 (100). $C_{14}H_{27}NO_2Si$ [M^+] requires m/z 269.1811; observed m/z 269.1811.

Scopine (1)

TBAF (1M in THF, 0.64 ml, 0.64 mmol) was injected into a solution of **(19)** (58 mg, 0.22 mmol) in THF (3 ml) under a nitrogen atmosphere. The solution was stirred for 18 hr and the bulk of the solvent was evaporated under reduced pressure. The residual oil was dissolved in chloroform (6 ml) and washed with potassium carbonate solution (10 weight %, 2 ml) and brine (2 ml). The organic layer was dried over

anhydrous magnesium sulphate, filtered, and the solvent evaporated under reduced pressure. The oil was purified by flash chromatography eluting firstly with 1:4 triethylamine:ethyl acetate and then with 1:1:8 methanol:triethylamine:ethyl acetate. The latter fraction afforded scopine **(1)** (27 mg, 81%) as a white solid which had m.p. 64 - 66°C (literature m.p. 72°C).[3a] δ_H (250 MHz, $CDCl_3$): 1.72 (brdd, J = 15.1 Hz, J ≈ 1.5 Hz, 2H), 2.30 (ddd, J = 15.1, 5.3, 4.1 Hz, 2H), 2.35 (brs, 1H, exch), 2.71 (s, 3H), 3.38 (brdd, J = 4.1 Hz, J ≈ 1.5 Hz, 2H, α-N), 3.86 (s, 2H, HCO), 4.20 (t, J = 5.3 Hz, 1H, α-OH). δ_C (63 MHz, $CDCl_3$): 34.1 (2 x CH_2), 41.9 (CH_3), 57.2 (2 x CHN), 58.6 (2 x CHO), 63.4 (CHOH). ν_{max} (CH_2Cl_2): 3600w, 3450brw, 3020w, 2930m, 1415w, 1390w, 1265brw, 1205w, 1070m, 1040w, 1020w, 975m, 930w, 905w, 865m, 835 cm^{-1}. m/z (%): 155 (M^+, 93), 138 (21), 126 (20), 112 (74), 110 (63), 108 (26), 94 (100), 82 (91), 70 (64), 68 (62). $C_8H_{13}NO_2$ [M^+] requires m/z 155.0946;observed m/z 155.0947.

N-Benzyloxycarbonyl-3α-hydroxy-6β,7β-epoxy-8-azabicylo[3.2.1]octane (20)

A solution of **(18)** (72 mg, 0.19 mmol) in THF (4 ml) was stirred with TBAF (1M in THF, 0.46 ml, 0.46 mmol) using the reaction and work-up procedure described for the preparation of scopine **(1)** from **(19)**. The alcohol **(20)** (41 mg, 81%) was isolated as a pale yellow oil after flash chromatography, eluting firstly with 1:1 diethyl ether:petroleum ether (b.p. 40 - 60°C) and then with ethyl acetate. Signals quoted in italics are common to both rotamers (in a 1:1 ratio). δ_H (250 MHz, $CDCl_3$): 1.61 (brdd, J = 15.1 Hz, J ≈ 2 Hz, 1H), 1.65 (brdd, J = 15.1 Hz, J ≈ 2 Hz, 1H), 2.01 (ddd, J = 15.1, J ≈ 4.5, 4.5 Hz, 1H), 2.07 (ddd, J = 15.1, J ≈ 4.5, 4.5 Hz, 1H), *2.20* (brs, 1H, exch), 3.47 (d, J = 3.3 Hz, 1H, HCO), 3.50 (d, J = 3.3 Hz, 1H, HCO), *4.01* (t, J ≈ 4.5 Hz, 1H,α-OSi), 4.32 (brdd, J ≈ 4.5, 2Hz, 1H, α-N), 4.40 (brdd, J ≈ 4.5,2 Hz, 1H, α-N), *5.06* (s, 2H, CH_2Ph), *7.28* (m, 5H). δ_C (63 MHz, $CDCl_3$): *34.3 & 34.4* (2 x CH_2), 53.4 & 53.5 (2 x CHO or CHN), 53.8 & 53.9 (2 x CHO or CHN), *63.4* (CHOH), *67.4* (CH_2Ph), *128.1, 128.4 & 128.9* (3 x aryl CH), *136.9* (aryl C), *157.3* (C=O). ν_{max} (CH_2Cl_2): 3600w, 2930w, 1705s, 1410w, 1385w, 1375w, 1350w, 1295m, 1260w, 1220w, 1100m, 1080m, 1040m, 985w, 910m, 870w, 845w, 835w cm^{-1}. m/z (%): 275 (M^+, 8), 169 (24), 140 (7), 91 (100). $C_{15}H_{17}NO_4$ [M^+] requires m/z 275.1158;observed m/z 275.1158.

Norscopine (21)

A solution of **(20)** (37mg, 0.31 mmol) in absolute ethanol (4 ml) was hydrogenolysed 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. Evaporation of ethanol under reduced pressure yielded norscopine **(21)** (19 mg, 100%) as a pale yellow waxy solid. δ_H (250 MHz, $CDCl_3$): 1.53 (dd, J = 14.9, J ≈ 1.3 Hz, 2H), 2.01 (~dt, J = 14.9, 4.9 Hz, J ≈ 4Hz, 2H), 2.25 (brs, exch, 2H, OH & NH), 3.20 (brdd, J ≈ 4, 1.3 Hz, 1H, α-N), 3.53 (s, 2H, HCO), 3.94 (t, J = 4.9 Hz, α-OH). δ_C (63 MHz, $CDCl_3$): 34.9 (2 x CH_2), 52.7 (2 x CHN), 54.9 (2 x CHO), 63.5 (CHOH). ν_{max} (CH_2Cl_2): 3610w, 3320vbrw, 3000w, 2950s, 1420w, 1395w, 1350w, 1340w, 1325w, 1225brm, 1080s, 1055m, 1045m, 1015w, 985m, 935w, 915w, 865s, 840s cm^{-1}. m/z (%): 141 (M^+, 36), 122 (33), 112 (36), 84 (24), 83 (35), 82 (44), 80 (61), 72 (28), 70 (77), 69 (79), 68 (100). $C_7H_{11}NO_2$ [M^+] requires m/z 141.0790; observed m/z 141.0790.

1β-Hydroxy-4β-[(benzyloxycarbonyl)amino]-6β-[(*t*-butyldimethylsilyl)oxy]cyclohept-2-ene (22)

An 80:20 mixture of **(11)**:**(10)** (4.05 g, 0.010 mol) was treated with freshly prepared[23] and powdered sodium amalgam (65 g) and sodium phosphate (11.30 g , 0.080 mol) using the procedure described previously for the reduction of **(10)** to **(13)**. The isolated solid was recrystallised from toluene and petroleum ether (b.p. 60 - 80°C) to afford **(22)** (3.57 g, 75%) as a crystalline white solid (m.p. 50 - 51°C). Despite repeeated recrystallisation the product remained contaminated with the 6α-isomer **(13)**. δ_H (300 MHz, $CDCl_3$): 0.12 [s, 3H, $(CH_3)_2Si$], 0.13 [s, 3H, $(CH_3)_2Si$], 0.92 [s, 9H, $(CH_3)_3CSi$], 1.69 - 1.91 (brm, 2H), 2.03 (brd, J ≈ 13 Hz, 1H), 2.15 (brd, J ≈ 13 Hz, 1H), 2.70 (brs, 1H, exch), 4.10 (brm, 1H, α-OSi), 4.28 (brm, 2H, α-N & α-OH), 5.13 (brs, 2H, CH_2Ph), 5.54 (brd, J ≈ 7 Hz, 1H, HN), 5.61 (brd, J ≈ 12 Hz, 1H, HC=), 5.80 (brd, J ≈ 12 Hz, 1H, HC=), 7.38 (m, 5H). δ_C (75 MHz, $CDCl_3$): -4.9 [$(CH_3)_2Si$], 17.8 [$(CH_3)_3CSi$], 25.8 [$(\mathbf{CH_3})_3CSi$], 41.8 & 44.8 (2 x CH_2), 47.7 (CHN), 66.6 (CH_2Ph), 66.7 (CHOSi), 69.3 (CHOH), 127.88, 127.92 & 128.3 (3 x aryl CH), 131.7 & 136.4 (2 x CH=), 136.6 (aryl C), 155.3 (C=O). ν_{max} (CH_2Cl_2): 3600w, 3440w, 3040w, 2930s, 2890w, 2850m, 1715s, 1505s, 1415m, 1360w, 1340w, 1305w, 1245m, 1220m, 1085s, 1025s, 940w, 885m, 835s, 730brs cm^{-1}. m/z (%): 373 (M^+ - H_2O, 2), 334 (5), 316 (5), 272 (7), 226 (9), 182 (20), 165 (9), 108 (10), 91 (100). Found: C, 64.34; H, 8.56; N, 3.62%.

$C_{21}H_{33}NO_4Si$ requires: C, 64.41; H, 8.49; N, 3.58%.

1β-Hydroxy-2α,3α-epoxy-4β-[(benzyloxycarbonyl)amino]-6β-[(*t*-butyldimethylsilyl)oxy]cycloheptane (23) and 1β-Hydroxy-2β,3β-epoxy-4β-[(benzyloxycarbonyl)amino]-6β-[(*t*-butyldimethylsilyl)oxy]-cycloheptane (24)

A solution of **(22)** (2.129 g, 5.41 mmol) was epoxidised with 1.2 equivalents of MCPBA (50 - 60% purity) using the procedure described above for the epoxidation of **(13)**. The resultant crude oil was purified by flash chromatography, eluting with 1:1 diethyl ether:petroleum ether (b.p. 40 - 60°C) to afford firstly the 2α,3α-epoxide **(23)** (980 mg, 44%). NMR analysis indicated that **(23)** was contaminated with **(15)**. An analytical sample was prepared by recrystallisation from toluene and petroleum ether (b.p. 60 - 80°) and had m.p. 126 - 129°C, although some impurity was still present after recrystallisation. δ_H (300 MHz, $CDCl_3$): 0.09 [s, 6H, $(CH_3)_2Si$], 0.89 [s, 9H, $(CH_3)_3CSi$], 1.58 - 1.71 (series of brm, 4H), 3.23 (brs, 2H, CHO), 3.88 (vbrs, exch, 1H), 4.13 (brm, 2H, α-N & α-OH), 4.40 (m, 1H, α-OSi), 5.08 & 5.14 (brABq, J ≈ 13 Hz, 2H, CH_2Ph), 5.82 (brd, J ≈ 8 Hz, 1H, HN), 7.34 (s, 5H). δ_C (75 MHz, $CDCl_3$), Signals in italics were broadened: -5.1 [$(CH_3)_2Si$], 17.7 [$(CH_3)_3CSi$], 25.6 [$(\mathbf{CH_3})_3CSi$], *37.5 & 39.3* (2 x CH_2), 49.1 (CHN), 57.2 & 59.0 (2 x CHO), *66.7* (CH_2Ph), 69.2 (CHOSi or CHOH), 71.2 (CHOSi or CHOH), 127.9 (2 x aryl CH), 128.3 (aryl CH), 136.1 (aryl C), 155.6 (C=O). ν_{max} (CH_2Cl_2): 3600w, 3440m, 3040m, 2920s, 2860s, 1715s, 1500s, 1465m, 1415m, 1335m, 1230s, 1150m, 1065s, 1025s, 1005m, 950m, 930m, 885m, 830s, 730vbrs cm^{-1}. $^m/z$ (%): 407 (M^+, <1), 350 (21), 306 (15), 91 (100). Found: C, 61.84; H, 8.08; N, 3.29%. $C_{21}H_{33}NO_5Si$ requires: C, 61.88; H, 8.16; N, 3.44%.

Further elution with 1:1 diethyl ether:petroleum ether (b.p. 40 - 60°C) afforded the 2β,3β-epoxide **(24)** (796 mg, 36%) as a white solid which had m.p. 74 - 78°C after recrystallisation from toluene and petroleum ether (b.p. 60 - 80°C). The ratio the two epoxides was estimated to be 1:1. δ_H (300 MHz, $CDCl_3$): 0.068 [s, 3H, $(CH_3)_2Si$], 0.074 [s, 3H, $(CH_3)_2Si$], 0.88 [s, 9H, $(CH_3)_3CSi$], 1.71 - 1.86 (m, 2H), 1.92 (m, 2H), 3.22 (d, J = 5.1 Hz, 1H, CHO), 3.29 (d, J = 5.1 Hz, 1H, CHO), 3.49 (m, 1H, α-N), 4.04 (m, 1H, α-OH), 4.13 (m, 1H, α-OSi), 5.12 (s, 2H, CH_2Ph), 5.61 (brd, J ≈ 9 Hz, 1H, HN), 7.35 (s, 5H). δ_C (75 MHz, $CDCl_3$): -5.0 [$(CH_3)_2Si$], 17.9 [$(CH_3)_3CSi$], 25.7 [$(\mathbf{CH_3})_3CSi$], 40.3 & 42.7 (2 x CH_2), 47.3 (CHN), 58.4 & 60.2 (2 x CHO), 66.6 (CH_2Ph), 66.7 (CHOSi or CHOH), 67.5 (CHOSi or CHOH), 128.0, 128.1 & 128.3 (3 x aryl CH), 136.1 (aryl C), 155.5 (C=O). ν_{max} (CH_2Cl_2): 3600w, 3430w, 2950s, 2930s, 2890w, 2880m, 1720s, 1510s, 1470w, 1460w, 1360w, 1330w, 1220s, 1090brw, 1020s, 940w, 910w, 855m, 840s, 730brm cm^{-1}. $^m/z$ (%): 407 (M^+, <1), 350 (8), 306 (11), 91 (100). $C_{21}H_{33}NO_5Si$ [M^+] requires $^m/z$ 407.2128; observed $^m/z$ 407.2124. Found: C, 61.71; H, 7.85; N, 3.25%. requires: C, 61.88; H, 8.16; N, 3.44%.

1β-[*p*-Toluenesulphonyl)oxy]-2β,3β-epoxy-4β-[(benzyloxycarbonyl)amino]-6β-[(*t*-butyldimethylsilyl)-oxy]cycloheptane (25)

A solution of **(24)** (768 mg, 1.89 mmol) in THF (14 ml) was tosylated by the sequential addition of *n*-butyllithium (2.5M in hexane, 0.91 ml, 2.30 mmol) and *p*-toluenesulphonyl chloride (468 mg, 2.45 mmol) in THF (3 ml) using the procedure described for the tosylation of **(15)**. The tosylate **(25)** (891 mg, 84%) was isolated as a white foam after flash chromatography, eluting with 3:7 diethyl ether:petroleum ether (b.p. 40 - 60°C). δ_H (250 MHz, $CDCl_3$): 0.00 [s, 3H, $(CH_3)_2Si$], 0.03 [s, 3H, $(CH_3)_2Si$], 0.88 [s, 9H, $(CH_3)_3CSi$], 1.64 - 1.98 (m, 3H), 2.12 (m, 1H), 2.53 (s, 3H), 3.25 (d, J = 5.0 Hz, 1H, HCO), 3.33 (d, J = 5.0 Hz, 1H, HCO), 3.43 (m, 1H, α-OSi), 4.15 (m, 1H, α-N), 4.84 (dd, J = 12.0, 3.3 Hz, 1H, α-OSO_2Ar), 5.18 (s, 2H, CH_2Ph), 5.32 (brd, J ≈ 9 Hz, 1H), 7.42 (m, 7H, aryl & part of AA'BB'), 7.90 (2H, part of AA'BB'). δ_C (67 MHz, $CDCl_3$): -4.6 & -4.7 [2 x $(CH_3)_2Si$], 18.3 [$(CH_3)_3CSi$], 22.1 (CH_3Ar), 26.0 [$(\mathbf{CH_3})_3CSi$], 40.0 & 40.4 (2 x CH_2), 47.4 (CHN), 57.8 & 58.2 (2 x CHO), 67.4 (CHOSi & CH_2Ph), 77.4 ($CHOSO_2$), 128.2, 128.5, 128.7, 129.0 & 129.2 (5 x aryl CH), 134.0 (aryl CMe), 136.5 (aryl CCH_2), 145.6 (aryl CSO_2), 155.9 (C=O). ν_{max} (CH_2Cl_2): 3430w, 3030w, 2950s, 2930s, 2890w, 2860s, 1725s, 1600w, 1510s, 1465m, 1370s, 1360s, 1305w, 1220s, 1190s, 1175s, 1095s, 1045m, 1035m, 1005w, 980w, 945s, 920s, 860s, 835s, 810s, 740vbrs cm^{-1}. $^m/z$ (%, FAB): 562 (MH^+, 27), 504 (4), 454 (3), 428 (8), 390 (4), 213 (26).

1α-Chloro-2β,3β-epoxy-4β-[(benzyloxycarbonyl)amino]-6β-[(*t*-butyldimethylsilyl)oxy]cycloheptane (26)

A solution of **(25)** (891 mg, 1.59 mmol) in DMSO (12 ml) was stirred at 75°C with lithium chloride

(414 mg, 9.86 mmol) using the procedure described for the conversion of (**16**) into (**17**). The chloride (**26**) (534 mg, 79%) was isolated as a foam after flash chromatography, eluting with 1:4 diethyl ether:petroleum ether (b.p. 40 - 60°C). δ_H (250 MHz, $CDCl_3$): 0.00 [s, 6H, $(CH_3)_2Si$], 0.80 [s, 9H, $(CH_3)_3CSi$], 1.67 - 1.82 (m, 2H), 2.02 (m, 2H), 3.18 (brdd, J ≈ 8, 4.5 Hz, HCO, β-Cl), 3.22 (d, J = 4.7 Hz, 1H, HCO, β-N), 3.92 (m, 1H, α-OSi), 4.25 (m, 1H, α-N), 4.52 (brdd, J ≈ 8, 4.5 Hz, 1H, α-Cl), 5.02 (s, 2H, CH_2Ph), 5.45 (brd, J ≈ 9 Hz, 1H, HN), 7.27 (m, 5H). δ_C (63 MHz, $CDCl_3$): -4.4 [$(CH_3)_2Si$], 18.4 [$(CH_3)_3CSi$], 26.1 [$(\mathbf{CH_3})_3$CSi], 39.7 & 41.8 (2 x CH_2), 47.4 (CHN), 56.0 & 57.8 (2 x CHO), 60.5 (CHCl), 66.5 (CH_2Ph), 67.3 (CHOSi), 128.5, 128.6 & 128.9 (3 x aryl CH), 136.8 (aryl C), 156.0 (C=O). ν_{max} (CH_2Cl_2): 3430w, 2950m, 2930m, 2890w, 2860w, 1720s, 1505s, 1465w, 1455w, 1390w, 1375w, 1360w, 1330w, 1265brw, 1230m, 1220m, 1175w, 1115w, 1075m, 1020w, 1005w, 940w, 910m, 855m, 835m, 740brw cm^{-1}. m/z (%): 425 (M^+, <1), 370 (4), 368 (11), 326 (2), 324 (6), 149 (5), 91 (100). $C_{21}H_{32}NO_4SiCl$ [M^+] requires m/z 425.1789; observed m/z 425.1789.

N-Benzyloxycarbonyl-3β-[(*t*-butyldimethylsilyl)oxy]-6β,7β-epoxy-8-azabicylo[3.2.1]octane (27)

A solution of (**26**) (154 mg, 0.36 mmol) in THF:DME (5:1, 10 ml) was cyclised with sodium hydride (60% dispersion in mineral oil, 105 mg, 2.63 mmol) using the procedure described for the conversion of (**17**) into (**18**). After flash chromatography, eluting with 1:4 diethyl ether:petroleum ether (b.p. 40 - 60°C), (**27**) (96 mg, 68%) was isolated as a colourless oil. The signals quoted in italics are common to both rotamers (in a 1:1 ratio). δ_H (250 MHz, $CDCl_3$): *0.00* [s, 6H, $(CH_3)_2Si$], *0.83* [s, 9H, $(CH_3)_3CSi$], 1.65 (dt, J = 10.2, 10.2, J ≈ 3 Hz, 1H), 1.72 (dt, J = 10.2, 10.2, J ≈ 3 Hz, 1H), 1.90 (ddd, J = 10.2, 6.7, J ≈ 3 Hz, 1H), 1.94 (ddd, J = 10.2, 6.7, J ≈ 3 Hz, 1H), 3.34 (d, J = 3.1 Hz, 1H, HCO), 3.38 (d, J = 3.1 Hz, 1H, HCO), *4.08* (tt, J = 10.2, 6.7, 1H, α-OSi), 4.37 (t, J ≈ 3 Hz, 1H, α-N), 4.46 (t, J ≈ 3 Hz, 1H, α-N), *5.10* (s, 2H, CH_2Ph), *7.32* (m, 5H). δ_C (63 MHz, $CDCl_3$): *-4.3* [$(CH_3)_2Si$], *18.4* [$(CH_3)_3CSi$], *26.1* [$(\mathbf{CH_3})_3$CSi], 35.8 & 36.1 (2 x CH_2), 52.1 & 52.4 (2 x CHO), 53.8 & 54.2 (2 x CHN), *64.5* (CHOSi), *67.4* (CH_2Ph). *128.2, 128.4 & 128.9* (3 x aryl CH), *137.0* (aryl C), *156.7* (C=O). ν_{max} (CH_2Cl_2): 2950m, 2930m, 2895w, 2860m, 1705s, 1505w, 1410brm, 1365w, 1330w, 1295m, 1230m, 1100s, 1080m, 1030w, 1005w, 975w, 940w, 915w, 880m, 860m, 845m, 835m cm^{-1}. m/z (%): 389 (M^+, < 1), 332 (37), 288 (5), 256 (8), 182 (68), 91 (100). $C_{21}H_{31}NO_4Si$ [M^+] requires m/z 389.2022; observed m/z 389.2021.

Pseudoscopine *t*-butyldimethylsilyl ether (28)

This compound was prepared by reducing (**27**) (93 mg, 0.24 mmol) in diethyl ether (5 ml) with lithium aluminium hydride (40 mg, 1.05 mmol) using the procedure described for the reduction of (**18**). The amine was purified by flash chromatography, eluting firstly with diethyl ether and then with ethyl acetate:triethylamine (9:1), to afford (**28**) (61 mg, 95%) as a colourless oil. δ_H (250 MHz, $CDCl_3$): 0.00 [s, 6H, $(CH_3)_2Si$], 0.84 [s, 9H, $(CH_3)_3CSi$], 1.70 (m, 4H), 2.49 (s, 3H), 3.22 (t, J = 2.9 Hz, 2H, α-N), 3.44 (s, 2H, HCO), 4.00 (tt, J = 9.1, 7.8 Hz, 1H, α-OSi). δ_C (63 MHz, $CDCl_3$): -4.2 [$(CH_3)_2Si$], 18.4 [$(CH_3)_3CSi$], 26.2 [$(\mathbf{CH_3})_3$CSi], 33.9 (2 x CH_2), 39.0 (CH_3), 55.6 (2 x CHN), 58.7 (2 x CHO), 64.4 (CHOSi). ν_{max} (CH_2Cl_2): 3030w, 2950s, 2930s, 2890s, 2870s, 1470w, 1475w, 1390w, 1360w, 1335w, 1245w, 1205w, 1165w, 1095s, 1080s, 1030w, 1005w, 980w, 965w, 940w, 875s, 865s, 845s, 835s, 740brm cm^{-1}. m/z (%): 269 (M^+, 9),,226 (12), 224 (12), 212 (29), 138 (28), 114 (13), 111 (18), 108 (25), 101 (12), 97 (23), 94 (28), 91 (100). $C_{14}H_{27}NO_2Si$ [M^+] requires m/z 269.1811; observed m/z 269.1811.

Pseudoscopine (2)

This compound was prepared by treating (**28**) (61mg, 0.23 mmol) in THF (4 ml) with TBAF (1M in THF, 0.66 ml, 0.66 mmol) using the procedure described to deprotect (**19**). Pseudoscopine was purified by flash chromatography, eluting firstly with 1:4 triethylamine:ethyl acetate and secondly with 1:3:1 methanol:ethyl acetate:triethylamine to afford (**2**) (29 mg, 83%) as a white solid. M.p. 120 - 122°C (lit.[5] 121 - 122°C). δ_H (250 MHz, $CDCl_3$): 1.83 (ddd, J = 13.5, 9.7 Hz, J ≈ 3.5 Hz, 2H), 2.00 (ddd, J = 13.5, 6.7, 2.4 Hz, 2H), 2.66 (s, 3H), 2.90 (brs, exch, 1H), 3.41 (dd, J ≈ 3.5 Hz, J = 2.4 Hz, 2H, α-N), 3.63 (s, 2H, HCO), 4.16 (tt, J = 9.7, 6.7 Hz, 1H, α-OH). δ_C (63 MHz, $CDCl_3$): 33.9 (2 x CH_2), 40.1 (CH_3), 55.8 (2 x CHN), 58.7 (2 x CHO), 63.8 (CHOH). ν_{max} (CH_2Cl_2): 3620w, 3400brw, 3030w, 2940s, 1520w, 1470w, 1440, 1390w, 1370w, 1335w, 1270brw, 1220w, 1160w, 1140w, 1075m, 1055s, 1030w, 980w, 970w, 960w, 910w, 870s, 845s, 815w cm^{-1}. m/z (%): 155 (M^+, 100), 138 (30), 126 (23), 112 (56), 110 (75), 108 (12), 97 (20),

94 (32), 86 (22), 84 (25), 82 (42), 70 (26), 68 (24), 57 (79). $C_8H_{13}NO_2$ [M^+] requires $^m/_z$ 155.0946; observed $^m/_z$ 155.0946.

N-Benzyloxycarbonyl-3β-hydroxy-6β,7β-epoxy-8-azabicylo[3.2.1]octane (29)

A solution of **(27)** (81 mg, 0.21 mmol) in THF (5 ml) was stirred with TBAF (1M in THF, 0.52 ml, 0.52 mmol) using the reaction and work-up procedure described for the preparation of scopine **(1)** from **(19)**. The alcohol **(29)** (40 mg, 70%) was isolated as a yellow oil after flash chromatography, eluting with ethyl acetate. Signals quoted in italics are common to both rotamers (present in a 1:1 ratio). δ_H (250 MHz, $CDCl_3$): 1.55 (ddd, J = 13.6, 10.6 Hz, J ≈ 3 Hz, 1H), 1.60 (ddd, J = 13.6, 10.6 Hz, J ≈ 3 Hz, 1H), *1.99* (m, 2H), 2.28 (brs, 1H, exch), 3.30 (d, J = 3.1 Hz, 1H, HCO), 3.33 (d, J = 3.1 Hz, 1H, HCO), *4.04* (tt, J = 10.6, 6.6 Hz, 1H, α-OH), 4.35 (brt, J ≈ 3 Hz, 1H, α-N), 4.42 (brt, J ≈ 3 Hz, 1H, α-N), *5.04* (s, 2H, CH_2Ph), *7.27* (m, 5H). δ_C (63 MHz, $CDCl_3$): 35.4 & 35.6 (2 x CH_2), 52.0 & 52.3 (2 x CHO or CHN), 53.8 & 54.1 (2 x CHO or CHN), *63.9* (CHOH), *67.5* (CH_2Ph), *128.2, 128.5 & 128.9* (3 x aryl CH), *136.8* (aryl C), *156.8* (C=O). ν_{max} (CH_2Cl_2): 3600w, 3490brw, 3050w, 3950w, 3930w, 2860w, 1710s, 1500w, 1410brm, 1365m, 1280brm, 1220w, 1100m, 1080m, 1060s, 1025w, 995w, 970w, 910w, 870w, 860w, 855m cm^{-1}. $^m/_z$ (%): 275 (M^+, 24), 141 (3), 124 (3), 108 (3), 168 (12), 91 (100). $C_{15}H_{17}NO_4$ [M^+] requires $^m/_z$ 275.1158; observed $^m/_z$ 275.1157.

Norpseudoscopine (30)

A solution of **(29)** (31 mg, 0.11 mmol) in absolute ethanol (5 ml) was hydrogenolysed at 1 atmosphere, using the procedure described for conversion of **(20)** into **(21)**. Norpseudoscopine **(30)** (13 mg, 82%) was isolated as a white solid. δ_H (250 MHz, $CDCl_3$): 1.60 (ddd, J = 13.4, 9.9 Hz, J ≈ 3.5 Hz, 2H), 1.92 (ddd, J = 13.4, 6.5 Hz, J ≈ 3.5 Hz, 2H), 2.42 (brs, exch, 2H, OH & NH), 3.28 (brt, J ≈ 3.5 Hz, 2H, α-N), 3.33 (s, 2H, HCO), 3.88 (tt, J = 9.9, 6.5 Hz, 1H, α-OH). δ_C (63 MHz, $CDCl_3$): 36.1 (2 x CH_2), 53.3 (2 x CHN or CHO), 53.5 (2 x CHN or CHO), 64.1 (CHOH). ν_{max} (CH_2Cl_2): 3600w, 3030w, 2950m, 2850w, 1270brw, 1075m, 1055m, 970w, 910m, 865w, 840w, 835w cm^{-1}. $^m/_z$ (%): 141 (M^+, 18), 124 (37), 122 (35), 112 (73), 98 (51), 97 (70), 96 (79), 94 (42), 82 (24), 80 (31), 70 (85), 68 (100). $C_7H_{11}NO_2$ [M^+] requires $^m/_z$ 141.0790; observed $^m/_z$ 141.0790.

N-(Benzyloxycarbonyl)-3α,4α-epoxy-6-aza-7-oxabicyclo[3.2.2]non-8-ene (33)

A small portion of the crude epoxide **(5)**, used previously to prepare **(6)**, was purified by vacuum distillation (18 mbar, 40°C). Tetramethylammonium periodate (283 mg, 0.89 mmol) was added to a solution of **(5)** (80 mg, 0.74 mmol) in dichloromethane (7 ml) and stirred at 0°C. A solution of benzyl-N-hydroxycarbamate (148 mg, 0.89 mmol) in dichloromethane (5 ml) was dripped in over 10 min. The mixture was warmed to ambient temperature and stirred for a further 3 hr. The solution was filtered, washed with saturated sodium thiosulphate solution (2 x 5 ml), saturated sodium bicarbonate solution (5 ml) and brine (5 ml). The organic layer was dried over anhydrous magnesium sulphate, filtered and the solvent evaporated under reduced pressure to afford a crude oil. The oil was purified by flash chromatography, eluting with 6:4 diethyl ether:petroleum ether (b.p. 40 - 60 °C) to afford a mixture of **(33)**:**(34)** in an 80:20 ratio (estimated from ^1H NMR integrations) as a white solid (130 mg, 64%). The two isomers were inseparable by chromatography but recrystallisation from diethyl ether and petroleum ether (b.p. 60 - 80 °C) furnished **(33)** in pure form (m.p. 86 - 87°C). The stereo- and regiochemistry of **(34)** was elucidated from a crystal structure (appendix 1). δ_H (300 MHz, $CDCl_3$), Major cycloadduct **(33)**: 2.32 (m, 2H), 2.14 (m, 1H, HCO), 3.37 (dd, J = 6.2, 4.4 Hz, 1H, HCO), 4.58 (m, 1H, bridgehead α-N), 5.18 & 5.23 (ABq, J = 12.3 Hz, 2H, CH_2Ph), 5.41 (dt, J = 6.2, 6.2, 1.7 Hz, 1H, bridgehead α-O), 5.40 (ddd, J = 9.2, 7.1, 1.1 Hz, 1H, HC=), 6.22 (ddd, J = 9.2, 6.2, 1.6 Hz, 1H, HC=), 7.36 (m, 5H). δ_C (75 MHz, $CDCl_3$): 31.4 (CH_2), 50.0 & 53.3 (2 x epoxide CHO), 54.6 (CHN), 68.1 (CH_2Ph), 72.7 (bridgehead CHO), 128.0 (aryl CH), 128.1 (HC=), 128.2 & 128.5 (2 x aryl CH), 129.6 (HC=), 135.6 (aryl CH), 157.3 (C=O). υ_{max} (CH_2Cl_2): 3060w, 3040w, 3000w, 2950w, 2920w, 1705s, 1500w, 1445m, 1395m, 1380m, 1350m, 1275brs, 1155w, 1095m, 1070m, 1050m, 1040m, 980w, 960w, 945w, 905w, 870m, 860m cm^{-1}. $^m/_z$ (%): 273 (M^+, 2), 229 (6), 108 (7), 107 (7), 92 (18), 91 (100), 79 (13), 97 (10). Found: C, 65.66; H, 5.36; N, 5.19%. $C_{15}H_{15}NO_4$ requires: C, 65.90; H, 5.53; N, 5.13%.

Additional signals in the NMR spectra (before recrystallisation) corresponded to the minor cycloadduct (**34**): δ_H (300 MHz, $CDCl_3$): 4.68 (m, 1H, bridgehead α-N), 5.14 (m, 1H, bridgehead α-O), 6.06 (dd, J = 9.1, 7.4 Hz, 1H, HC=), 6.33 (m, 1H, HC=). δ_C (75 MHz, $CDCl_3$): 29.7 (CH_2), 51.1, 51.6 & 54.0 (3 x CH), 67.7 (CH_2Ph), 74.7 (bridgehead CHO).

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