A Synthetic Study of the Tropane and Homotropane Ring Systems

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A thesis submitted for the Degree of Doctor of Philosophy in the Faculty of Science at the University of Leicester.

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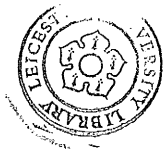
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STATEMENT

The accompanying thesis submitted for the degree of Ph.D entitled "A Synthetic Study of the Tropane and Homotropane Ring Systems" is based on work conducted by the author in the Department of Chemistry at the University of Leicester mainly during the period between September 1991 and October 1994.

All the work recorded in this thesis is original unless otherwise acknowledged in the text or by references.

None of the work has been submitted for another degree in this or any other University.

Signed: ..... Date: 21st May 1995.

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ABSTRACT

A SYNTHETIC STUDY OF THE TROPANE AND HOMOTROPANE RING SYSTEMS, BY DAVID JUSTICE

1,4-Functionalisation of cyclohepta-1,3-diene using a nitroso-cycloaddition strategy provided precursors which were converted into the N-methyl-8-azabicyclo-[3.2.1]octane (tropane) ring system. Cycloocta-1,3-diene was used as the starting material to prepare precursors to the N-methyl-9-azabicyclo[4.2.1]nonane (homotropane) ring system.

Homotropane has been constructed, either with or without a bridgehead substituent, using mercury-mediated cyclisation of nitrogen onto an sp^2 carbon centre. The versatile N-alkoxycarbonyl protecting group was employed to synthesise the corresponding norhomotropanes. This strategy was also used to prepare the 1-methyl-homotrop-7-ene analogue which could be epoxidised stereoselectively to yield the *exo*-epoxy derivative.

An efficient synthesis of homotropan-1-ol and norhomotropan-1-ol is described. Using variable-temperature ^1H and ^{13}C NMR spectroscopy these bicyclic hemi-aminals were shown to exist in tautomeric equilibria with monocyclic amino-ketones. A range of derivatives were made; it was found that the incorporation of a double bond or an epoxide group into the 2-carbon bridge of the homotropan-1-ol structure altered the position of equilibrium. Difficulties were encountered in making quantitative measurements for some tautomer ratios and in these cases qualitative estimates were made. An identical synthetic strategy was used to make the homologous tropan-1-ols. This work includes a five-step synthesis of the tropane alkaloid physoperuvine (N-methyl-8-azabicyclo[3.2.1]octan-1-ol) in racemic form and in an overall yield of 79%. Norphysoperuvine (8-azabicyclo[3.2.1]octan-1-ol), unsaturated, and epoxide derivatives were also prepared and a study of their tautomerism with amino-ketones was investigated.

A steroselective method of introducing an epoxide group into the 2-carbon bridge of homotropane was devised. Homotrop-7-ene, protected with an N-alkoxycarbonyl group, was prepared by intramolecular displacement at an sp^3 carbon centre by nitrogen. Epoxidation then gave the *exo*-epoxide but the overall yield was low because of difficulties associated with the cyclisation step. A more attractive procedure was developed which involved epoxidation of an allylic alcohol prior to cyclisation and provided access to both *exo*- and *endo*-epoxides in improved yields. Final removal of the N-alkoxycarbonyl protecting group at the end of the synthesis showed a substantial difference in epoxide stablity. The epoxide group of the *endo*-isomer was ring-opened by both hydride and hydrogenolysis reduction, whereas the *exo*-epoxide was suprisingly more resistant to attack. The homologous epoxides of the tropane series were prepared using a similar methodology. Again, the *exo*-epoxide was substantially more stable to reduction than the *endo*-epoxide.

Introduction of oxygen functionality at the C_3 position of the tropane ring system was developed using cyclohepta-3,5-dienol in the initial nitroso-cycloaddition reaction. Combining this with the established approach to epoxy-tropanes led to the synthesis of the alkaloid scopine. The versatility of this procedure is demonstrated with the preparation of pseudoscopine and novel nor-derivatives.

CONTENTS

ABBREVIATIONS

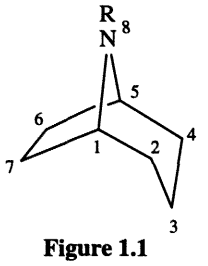
b.p.	boiling point
°C	centigrade
cm^{-1}	wavenumber
Decomp.	decomposition
DEPT	distortionless enhancement by polarisation transfer
DIBAH	diisobutylaluminium hydride
DMF	dimethylformamide
DMSO	dimethylsulphoxide
hr	hour
Hz	hertz
IR	infra-red
LAH	lithium aluminium hydride
lit.	literature
M^+	molecular ion
MHz	megahertz
min	minute
m.p.	melting point
mbar	millibar
mmol	millimole
MCPBA	*m*-chloroperoxybenzoic acid
MEM	β-methoxyethoxymethoxy
NMR	nuclear magnetic resonance
ppm	parts per million
TLC	thin layer chromatography
TBAF	tetrabutylammonium fluoride
TBDMSCl	*t*-butyldimethylsilyl chloride
THF	tetrahydrofuran

CHAPTER 1

Introduction

1.1 TROPANE ALKALOIDS

The tropane alkaloids are found in the plant families *solonaceae*, *convolvulaceae*, *erythroxylaceae*, *euphorbiaceae*, *proteaceae* and *rhizophoraceae*. They are hydroxylated derivatives of tropane (8-methyl-8-azabicyclo[3.2.1]octane) **(1)** or nortropane **(2)** (figure 1.1).

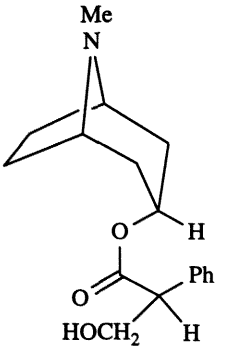


R=Me Tropane **(1)**
R=H Nortropane **(2)**

Figure 1.1

These alkaloids form a large class of natural products (approximately 200) with new structures continually being discovered.[1] Their interesting pharmacological properties and varied uses in medicine have prompted significant research into discovery, biogenesis, stereochemistry and synthesis.[2] This thesis describes the synthesis of both natural and novel non-natural tropanes and also of higher homologues, homotropanes.

Tropanes can be sub-classed according to the degree of hydroxylation, namely mono, di, and trihydroxytropanes. Atropine **(3)** and (-)-hyoscyamine are both tropic acid esters of monohydroxylated tropane, isolated in 1833[3] (figure 1.2). Atropine is

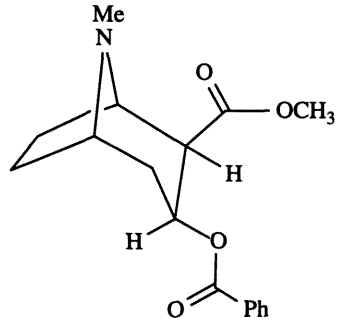


(±)-Hyoscyamine (atropine)
(3)

Figure 1.2

the racemic form of (-)-hyoscyamine and derives its name from the plant source from which it originates (*atropa belladonna*, more commonly known as deadly nightshade, a *solonaceous* plant). Other plants in this family include henbane (*hyoscyamus niger*), the source of hyoscyamine and the thorn apple (*datura stramonium*). Both these alkaloids are of historical interest in medicine; hyoscyamine was refered to in Eber's papyrus (*ca.* 1550 B.C.) as a treatment for 'magic of the belly' and was used to remedy abdominal distress. The name *belladonna* (beautiful lady) arose from the use of the plant's juices as a cosmetic drug to dilate the pupil of the eye. Extracts of *atropa belladonna* are still used as an antispasmodic and sedative in the treatment of gastrointestinal disorders.

Cocaine (**4**) was first isolated in 1862 from *erythroxylon coca lam*[4] which is indigenous to Peru and is a diester of tropan-3β-ol-2β-carboxylic acid (figure 1.3). The leaves of the coca plant have long been known as a central nervous system stimulant and were chewed by South Americans to alleviate the sub-zero temperatures of the regional climate. The isolation of cocaine led to its use as a local anaesthetic but because of its addictive and unpredictable nature the uses today are limited to eye, nose and throat anaesthesia. The recognition of the properties of cocaine has resulted in considerable research towards the synthesis of non-addictive analogues such as novocaine,[5] which still retain anaesthetic properties.

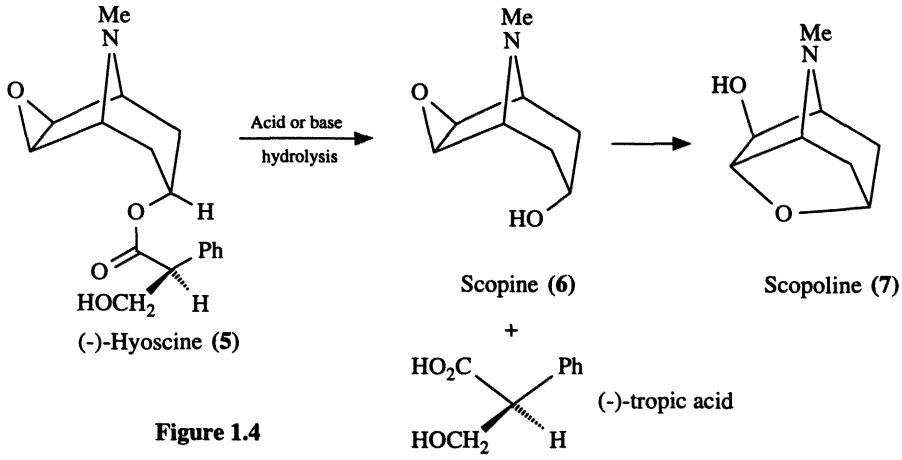


Cocaine (**4**)

Figure 1.3

Scopolamine can be formally considered as being derived from the trihydroxytropane skeleton. It is the tropic acid ester of scopine (**6**) and occurs as the

racemic form in *datura meteloides* and as the (-)-form, named (-)-hyoscine (**5**), from *hyoscyamus muticus*. On acid or base hydrolysis,[6] (-)-hyoscine is saponified to (-)-tropic acid and scopine (figure 1.4). Scopine reacts further under basic conditions to afford scopoline (**7**).

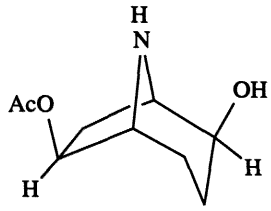


(-)-Hyoscine (**5**)

Figure 1.4

Scopolamine possesses sedative properties and is found in various sleep aids, more recently being used as a medicine for nausea. Scopolamine is also effective as an antidote for organophosphate nerve gases and was carried by troops in the recent Gulf war. Scopine, including a synthesis, is discussed in more detail later (chapter 7).

Bao gong teng (**8**) is an example of a recently discovered tropane alkaloid (figure 1.5) and was isolated from the Chinese herb *ericibe obtusifolia*, having the trivial name 'benth'. Traditionally the herb was used as a medicine for the treatment



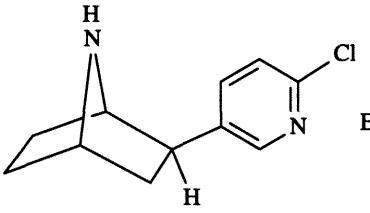
Bao gong teng (**8**)

Figure 1.5

of fevers but unfortunately had associated side-effects.[7] It has since been discovered that bao gong teng is an effective medicine in the treatment of glaucoma.[8] The

structure of (**8**) was assigned by a group of Chinese researchers[8] in 1981 and the absolute configuration determined[9] in 1989. As a result of its pharmacological properties, (**8**) has been the subject of two recent syntheses.[10]

Although it is not a tropane derivative, the alkaloid epibatidine (**9**) is based on the closely related 7-azabicyclo[2.2.1]heptane skeleton (figure 1.6) and is the first member of a new class of alkaloids. It was first isolated in 1992;[11] it was extracted from the poison frog *epipedobates tricolor*, used by Ecuadorian indians to poison arrow tips.



Epibatidine (**9**)

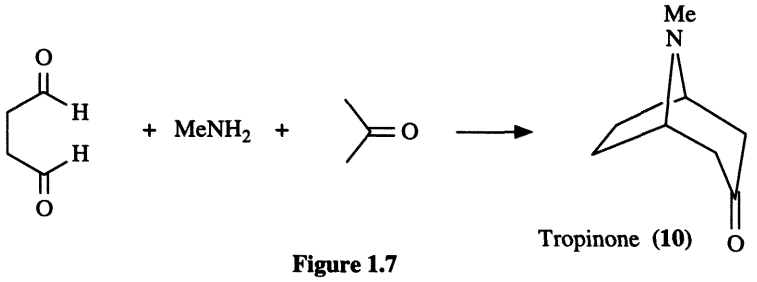
Figure 1.6

Daly[11] discovered that the analgesic potency of (**9**) was 200 to 500 times greater than that of morphine, and interestingly did not appear to bind to opiate receptors. The unusual pharmacological and novel structure of (**9**), coupled with the scarcity of obtainable material from natural sources, started a race to produce epibatidine synthetically. Broka[12] reported the first synthesis of (±)-(**9**) in 1993. This utilised an intramolecular displacement strategy as the key step, based on the pioneering synthesis of 7-azabicyclo[2.2.1]heptane by Fraser and Swingle.[13] Fletcher[14] independently published a synthesis of (±)-(**9**) and resolved an intermediate racemate to afford (+)- and (-)-epibatidine. A second enantiomeric synthesis was reported by Corey.[15] The rapid accumulation of syntheses[16] of epibatidine exemplifies the interest generated by azabicyclic compounds in natural product chemistry.

1.2 ESTABLISHED ROUTES TO TROPANES

The diverse range of tropane alkaloids has inspired numerous syntheses of the 8-azabicyclo[3.2.1]octane ring system. Efforts have focused in two main areas; firstly, the search for novel methods for preparing the basic tropane system and secondly, the application of these approaches to introduce functionality. The accumulation of this research ultimately leads to the syntheses of alkaloids. Some general synthetic strategies are described here with recent examples of specific natural product preparations.

Robinson[17] developed what has become a classical synthesis of tropinone **(10)** in 1917. This involved a Mannich base reaction between succindialdehyde, methylamine and acetone (figure 1.7) and forms the basis of the industrial preparation today.



Tropinone **(10)**

Figure 1.7

The yield was subsequently improved[18] by replacing acetone with the calcium salt of acetone dicarboxylic acid and altering the reaction conditions (pH 11, 20°C). Further derivation of the Robinson synthesis was made by Stoll[19] who introduced a hydroxyl group at the C_6 position (figure 1.8). Replacing succindialdehyde with a furan derivative led to the preparation of 6β-hydroxytropan-3-one **(14)**. Reaction of the dihydrofuran **(11)** with hypobromous acid, elimination and subsequent hydrogenation gave the 3-hydroxy-2,5-diethoxy-tetrahydrofuran **(12)**. Hydrolysis to the dialdehyde **(13)** followed by reaction with methylamine hydrochloride and acetone dicarboxylic acid gave **(14)** in good yield.

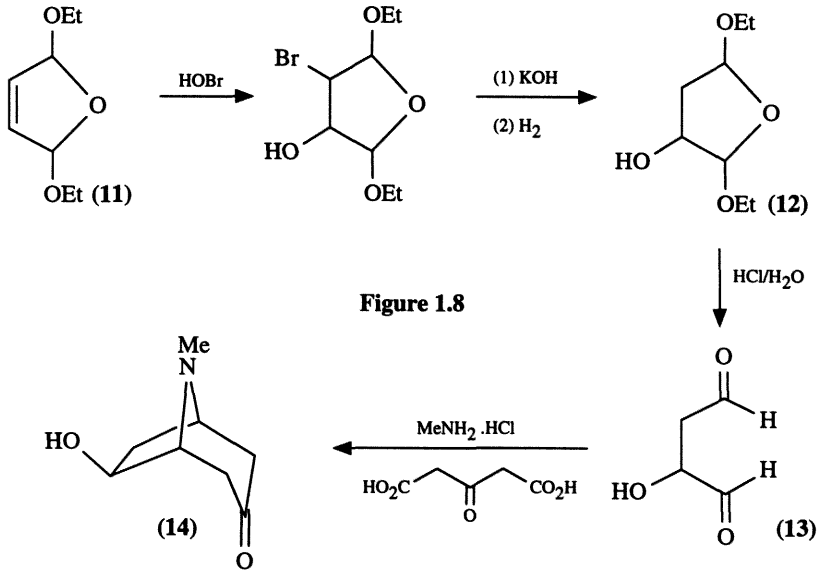
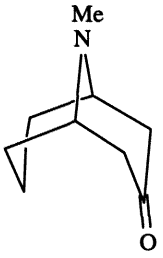


Figure 1.8

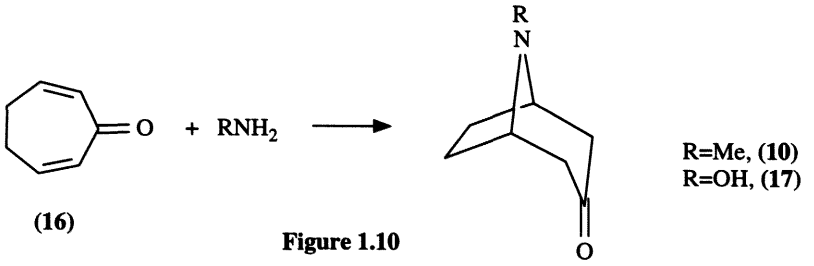
The Robinson strategy has been used to synthesise other azabicycles: for example, the homologue of tropane ψ-pelletierine[20] **(15)** was prepared by replacing succindialdehyde with glutaraldehyde (figure 1.9). Unfortunately, the Robinson methodology could not be used to prepare epoxide derivatives and failed when epoxysuccindialdehyde was used.[21] This method is therefore not applicable to the preparation of scopine.

Figure 1.9



ψ-pelletierine **(15)**

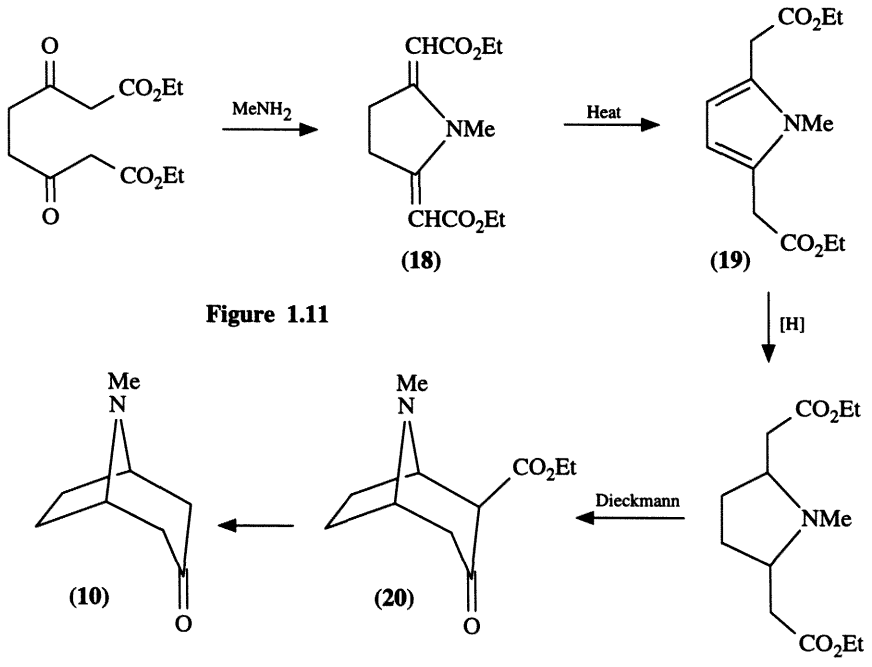
Bottini[22] produced tropinone **(10)** by condensing 2,6-cycloheptadienone **(16)** with methanolic methylamine to give a 95% yield of **(10)**. Other N-substituted tropinones could also be prepared using this approach[23] (figure 1.10). Replacing methylamine with hydroxylamine afforded N-hydroxytropinone **(17)**.



(16)

Figure 1.10

An earlier synthesis of tropinone by Willstätter and Pfannenstiel[24] used a Dieckmann ester condensation in the key step (figure 1.11). Heating the pyrrolidine **(18)** gave the pyrrole **(19)** which was subsequently hydrogenated and cyclised. Saponification and decarboxylation of 2-carbethoxytropinone **(20)** afforded **(10)**.



(18) (19)

(10) (20)

Figure 1.11

A variation of this method allows for the synthesis of non-natural analogues of tropane[25] (figure 1.12). N-Tosylation of *cis*-2,5-dicarbethoxypyrrolidine **(21)** followed by hydride reduction and chlorination gave *cis*-N-tosyl-2,5-bis-(chloromethyl)pyrrolidine **(22)**. Condensation of **(22)** with phenylacetonitrile and

sodium amide afforded (**23**) as the only stereoisomer. This was ultimately converted to 3-phenyltropane-3-carboxylic acid (**24**).

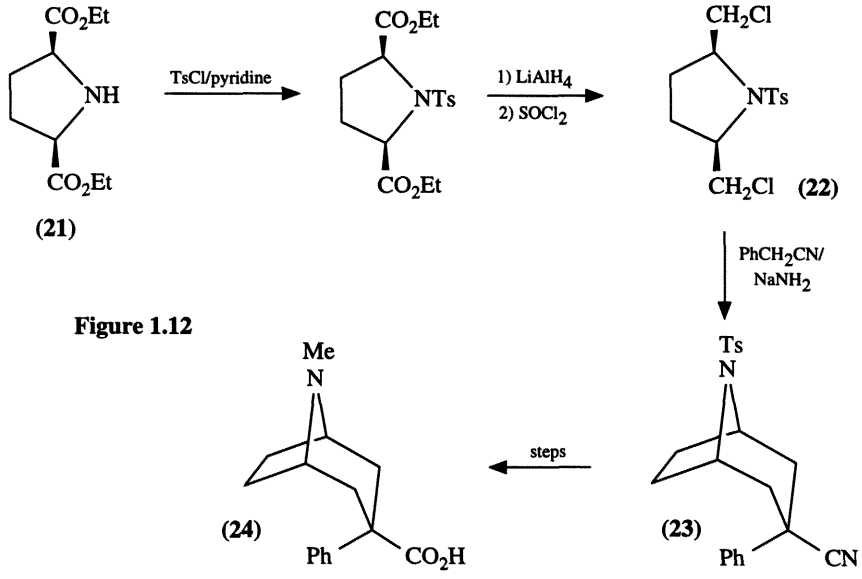


Figure 1.12

Based on an earlier observation by Bapat,[26] Tufariello[27] designed a synthesis of tropan-3β-ol (**28**) using a nitrone-induced cycloaddition reaction (figure 1.13). 4-Nitrobut-1-ene was treated with acrolein and sodium methoxide and acidification

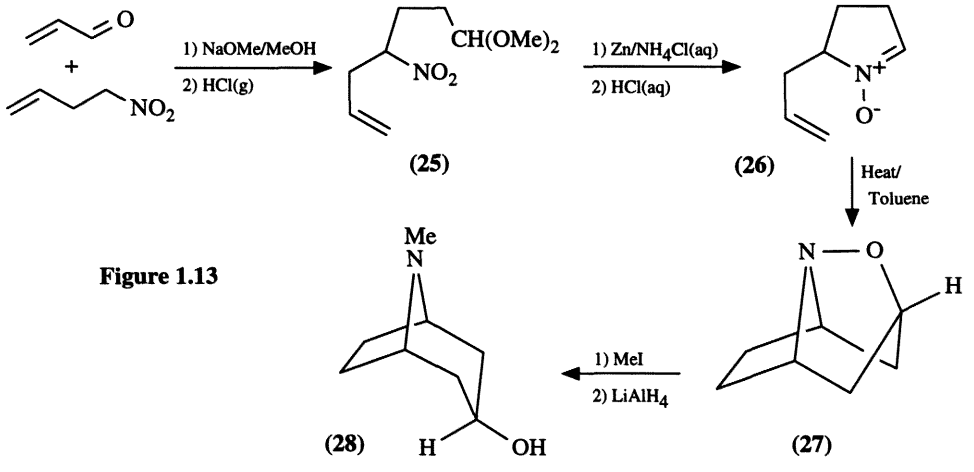
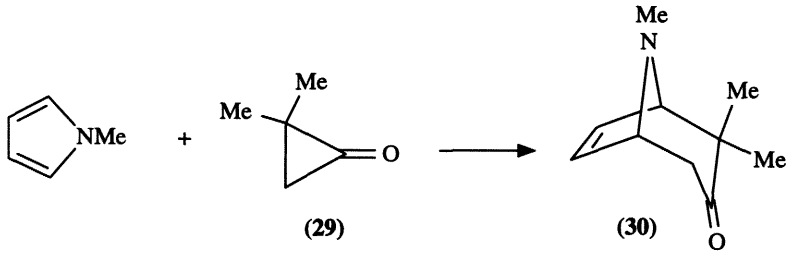


Figure 1.13

with hydrogen chloride gave the nitroacetal (**25**). Reaction of (**25**) with zinc in aqueous ammonium chloride and subsequent acidification yielded the intermediate nitrone (**26**) which cyclised to the isoxazolidine (**27**) on heating. Quaternisation with methyl iodide and reduction with lithium aluminium hydride afforded tropan-3β-ol (**28**) in 4 steps.

The methods described so far have involved a limited range of functionality. In order to synthesise tropane alkaloids such as scopolamine a means of elaborating the 2-carbon bridge is needed. Some methods are known: for instance, oxyallyl intermediates have been used to prepare trop-6-enes. Turro and Edelson[28] synthesised 2,2-dimethyltrop-6-en-3-one (**30**) by reacting 2,2-dimethylcyclopropanone (**29**) with N-methylpyrrole (figure 1.14).



(**29**) (**30**)

Figure 1.14

A similar approach was applied by Hoffmann:[29] dehalogenation of α,α'-dibromoketones in the presence of N-substituted pyrroles afforded functionalised trop-6-enes (**31**), again *via* an oxyallyl intermediate. A disadvantage of this method is that the reaction only proceeds in acceptable yield when the α,α'-dibromoketone is highly substituted (figure 1.15).

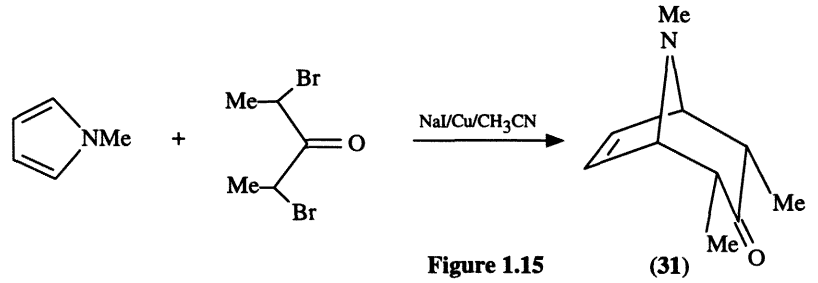


Figure 1.15 (**31**)

Noyori[30] used oxyallyls generated from 1,1,3,3-tetrabromoacetones and nonacarbonyldiiron. This allowed a reduction in the degree of substitution, but involved the use of hazardous and expensive reagents. More recently, Mann[31] has reported a highly efficient and versatile method of preparing tropanes using oxyallyls. This is discussed in chapter 7.

Modern preparative methods often target specific alkaloids, rather than general approaches to the ring system. Davies[32] designed an elegant synthesis of anhydroecognine (**36**) and ferruginine using vinyl carbenoids. Reaction of the N-protected pyrrole (**32**) with a vinyldiazomethane (**33**) in the presence of rhodium(II) hexanoate catalyst gave (**34**) in 75% yield. Selective hydrogenation and deprotection with tetrabutylammonium fluoride afforded anhydroecognine methyl ester (**35**). Reductive methylation with formaldehyde and sodium cyanoborohydride gave anhydroecognine (**36**) in excellent overall yield (figure 1.16).

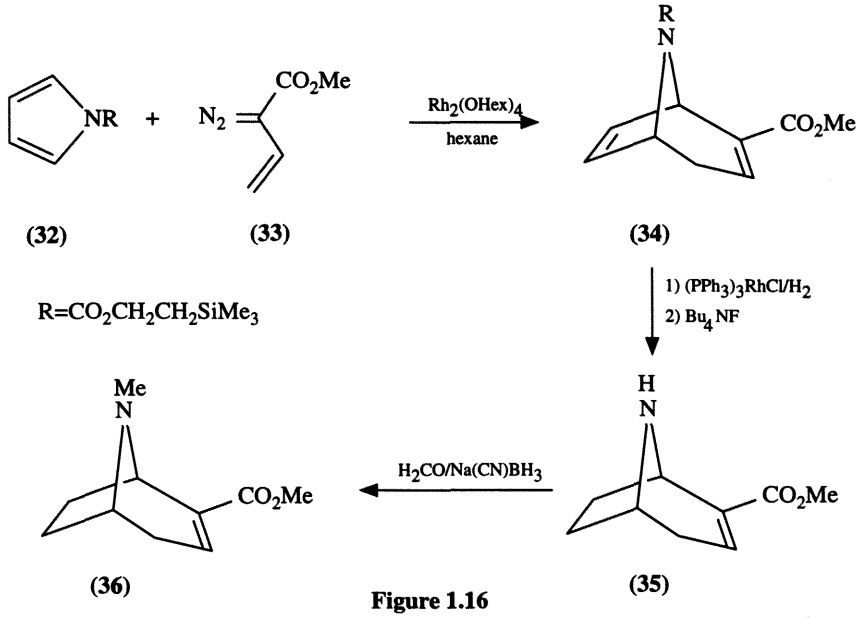
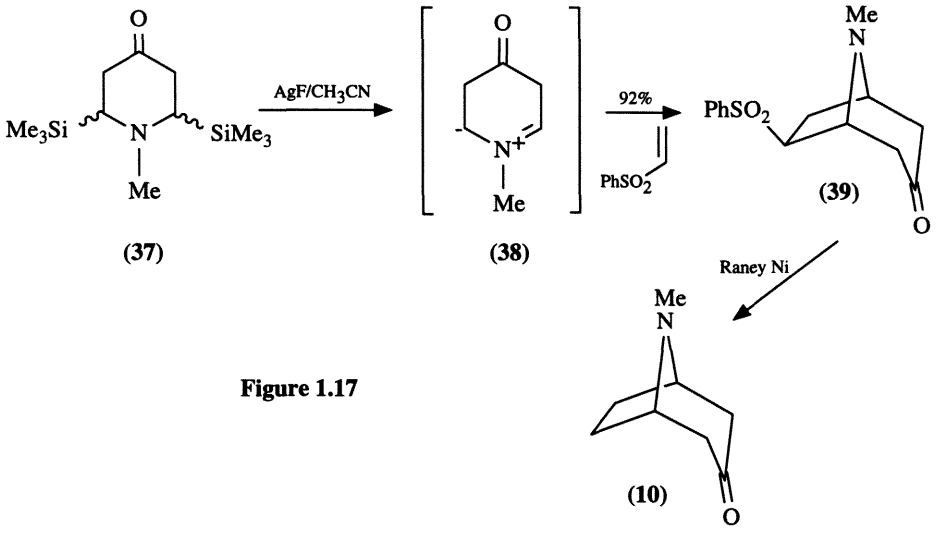


Figure 1.16

Pandey[33] used cyclic azomethine ylides in [3+2] cycloaddition reactions, the ylide being generated by a sequential double desilylation method (figure 1.17).

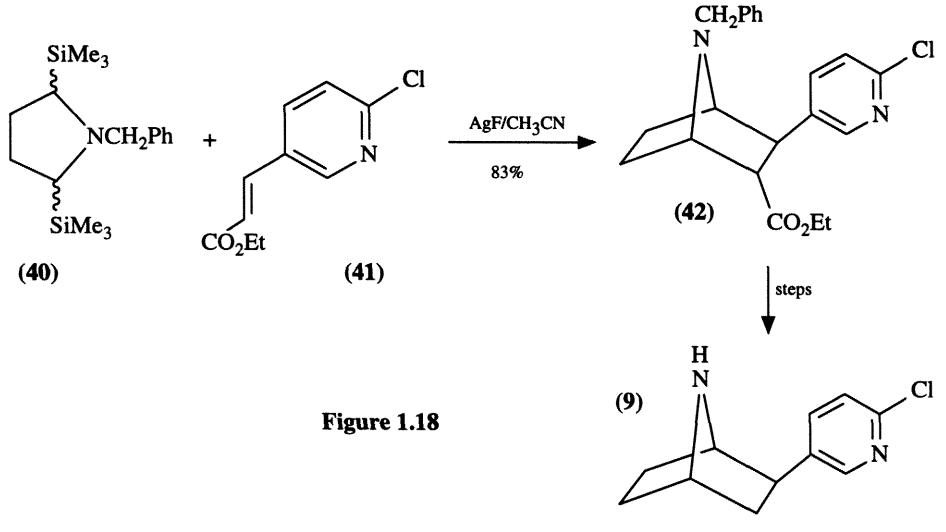
Reaction of the precursor (**37**) with silver fluoride and phenylvinylsulphone *in situ* gave the tropinone derivative (**39**) *via* the ylide (**38**). Desulphonlyation was achieved with Raney nickel to afford tropinone (**10**) in good yield.



(37) (38) (39) (10)

Figure 1.17

The versatility of this azomethine ylide approach was demonstrated by Pandey[16d] with a synthesis of epibatidine (figure 1.18). Using analogous precursors to the tropinone synthesis, a [3+2] cycloaddition reaction between the disilyl-



(40) (41) (42) (9)

Figure 1.18

pyrrolidine (**40**) and the cinnamate ester (**41**) gave the cycloadduct (**42**) in 83% yield. Radical decarboxylation and debenzylation resulted in an efficient synthesis of epibatidine (**9**).

1.3 THE NITROSO CYCLOADDITION / INTRAMOLECULAR DISPLACEMENT APPROACH TO TROPANES

In 1984 Kibayashi[34] reported a new approach to tropanes, the key step involving a Diels-Alder cycloaddition of a cyclic diene with a nitroso compound. This original work has since been considerably developed and has led to the synthesis of various natural products and homotropanes. The first target Kibayashi prepared was N-benzoylnortropane (figure 1.19). Reaction of cyclohepta-1,3-diene (**43**) with an acyl nitroso reagent, generated *in situ* by oxidation of benzohydroxamic acid, afforded the cycloadduct (**44**) in high yield. Reduction of the N-O bond with sodium amalgam gave (**45**) which was hydrogenated to the 1,4-functionalised cycloheptane (**46**). A portion of (**46**) was mesylated, and the remainder was treated with thionyl chloride and triethylamine to yield the *trans*-1,4-amido chloride (**47**). Attempts to cyclise the *cis*-1,4-amido mesylate (**48**) using a range of strong bases failed. However, the *trans*-chloride (**47**) was cyclised to N-benzoylnortropane (**49**) in 87% yield using potassium *t*-butoxide in hexamethylphosphoramide (HMPA) and benzene solvent. This strongly suggests that an S_N2 process is operating, with a *trans*-1,4 stereoelectronic arrangement of nucleophile and leaving group required for cyclisation.

Attempts to hydrolyse (**49**) to nortropane failed, hence tropane (**2**) could not be prepared *via* a benzoyl substituted nitrogen. Kibayashi tried to introduce different protecting groups at nitrogen, namely carbamate groups. This created difficulties in the chlorination step, as an elimination mechanism competed, resulting in the formation of olefinic products. The cyclisation of such olefins is discussed in detail later (chapter 2).

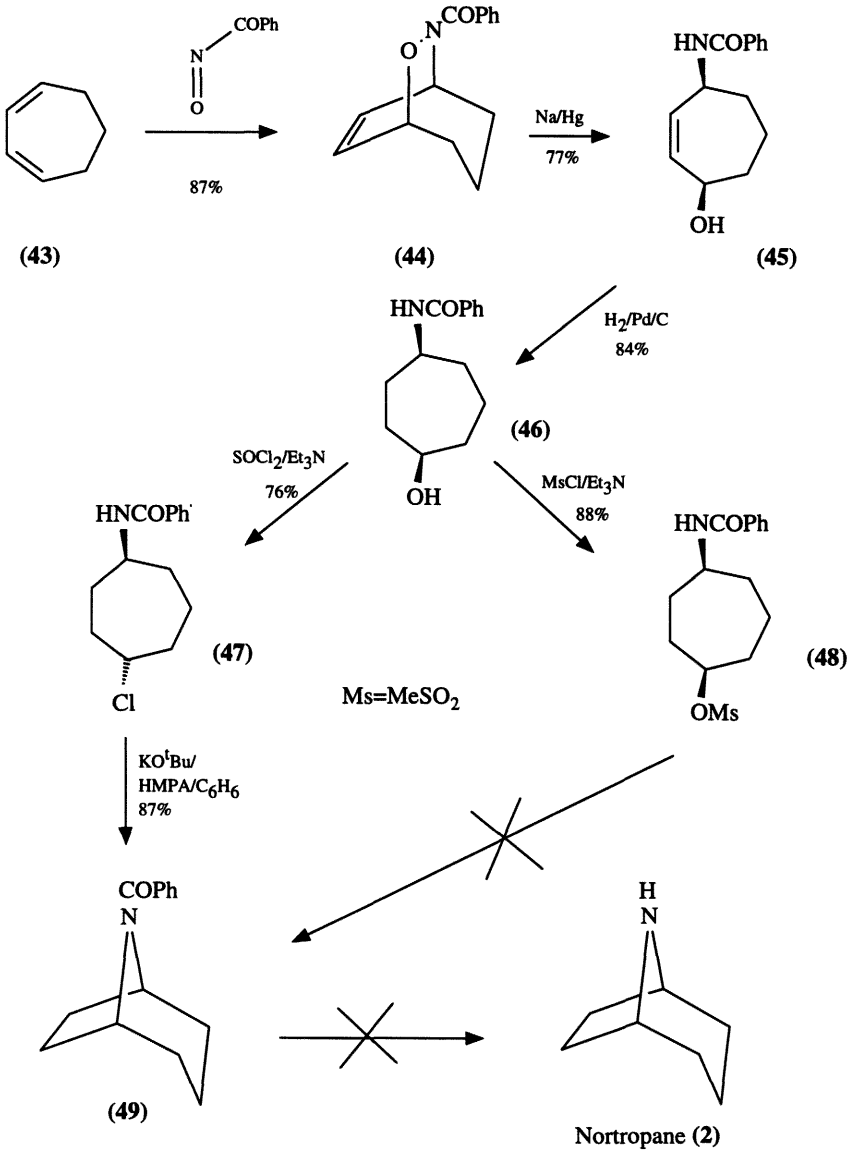
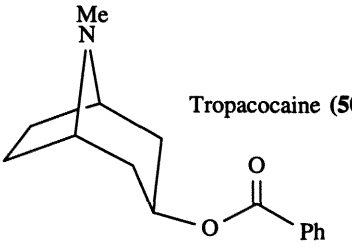


Figure 1.19

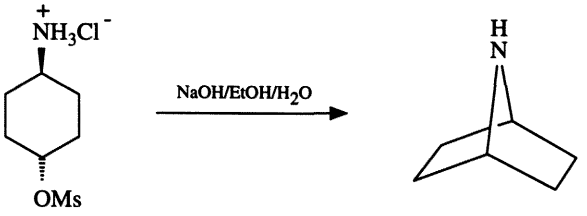
Kibayashi[34] demonstrated the practical uses of this approach, despite the difficulties encountered, by synthesising tropane, tropan-3β-ol (**28**) and tropacocaine (**50**) (figure 1.20). The latter two were prepared by elaborating the diene used in the

cycloaddition reaction.

Figure 1.20 Tropacocaine (**50**)



Fraser and Swingle[13] had previously reported an intramolecular displacement strategy for preparing 7-azabicyclo[2.2.1]heptane (**52**). The cyclisation step involved treating the primary amine (**51**) with sodium hydroxide in aqueous ethanol (figure 1.21). This is in contrast to the Kibayashi procedure of cyclising an amide-nitrogen



(**51**) (**52**)

Figure 1.21

with a strong organic base. The increased nucleophilicity of the amine nitrogen offers a more attractive means of synthesising azabicycles as milder conditions can be employed. Indeed Broka[12] has recently synthesised epibatidine, using the Fraser and Swingle procedure,[13] with the cyclisation step requiring no external base and proceeding in high yield. A second epibatidine synthesis used a very similar method.[16c]

Bathgate[35] developed the Kibayashi method by modifying the nitrogen substituent prior to nucleophilic displacement (figure 1.22). A benzoyl group offered a high yielding cycloaddition reaction and facile reduction to a benzyl group thus generating a nucleophilic nitrogen for cyclisation. Such a substituent is also potentially removable at the end of the synthesis. The cycloadduct (**44**) was prepared from cyclohepta-1,3-diene (**43**) using a very similar procedure to Kibayashi.[34] The

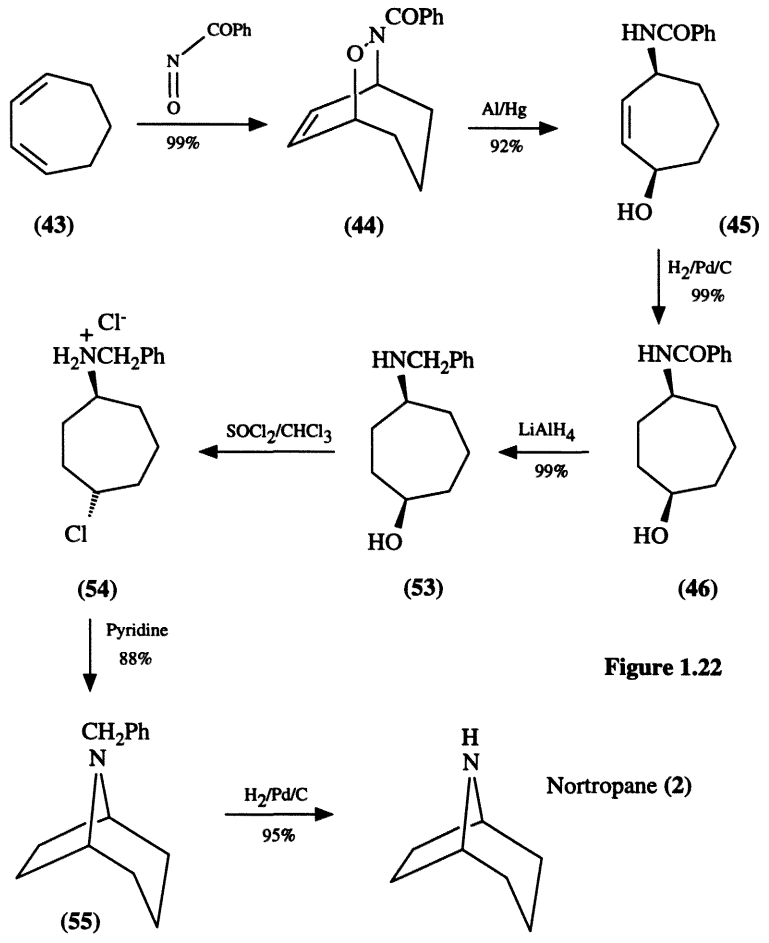


Figure 1.22

N-O bond was reductively cleaved and then hydrogenation of the olefin (**45**) afforded the *cis*-amido alcohol (**46**) which was reduced to the amine (**53**) using lithium aluminium hydride. Chlorination of (**53**) with thionyl chloride proceeded smoothly to give the *trans*-1,4-chloro-amine (**54**) as the hydrochloride salt. No external base was required for this step as the amine nitrogen acted as an internal base, reacting with the hydrogen chloride formed and generating the required inversion of stereochemistry. Direct basification of the crude hydrochloride (**54**) with pyridine gave the free amine which readily cyclised to N-benzylnortropane (**55**). Hydrogenolysis reduced the

benzyl group giving nortropane (**2**).

Bathgate[35] then applied this approach to preparation of the unsaturated analogues (figure 1.23). Reduction of (**45**) gave the amine (**56**) which reacted with thionyl chloride and lithium chloride to give the *trans*-1,4-chloro-amine salt (**57**).

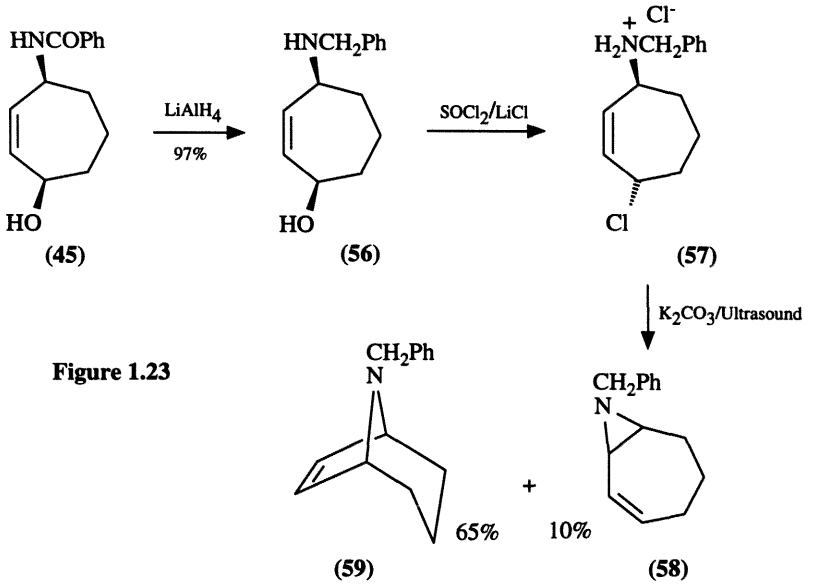


Figure 1.23

Addition of the heterogeneous base potassium carbonate to the crude hydrochloride (**57**) in an ultrasound bath resulted in cyclisation to benzylnortrop-6-ene (**59**) in 65% yield. This was accompanied by an aziridine by-product (**58**), formed by 1,2 rather than 1,4-cyclisation. Attempts to debenzylate (**59**) were unsuccessful. This method is nonetheless a significant entry into tropane synthesis, being a high yielding preparation of the uncommon trop-6-ene system.

At the same time an elegant method of preparing tropanes was published by Bäckvall,[36] using a similar approach to Bathgate. Palladium-catalysed single step 1,4-chloroacetoxylation of cyclohepta-1,3-diene (**43**) generated a 1,4-functionalised cycloheptane and is illustrated here by the synthesis of a simple tropane derivative. Stereoselective *cis*-chloroacetoxylation of (**43**) and substitution of the chloroacetate (**60**) with sodium *p*-toluenesulphonamide afforded the protected amide (**61**). Hydrogenation, saponification of the acetate and mesylation gave the *trans*-

1,4-mesylate (**62**). Cyclisation was achieved using potassium carbonate as base in methanol solvent (figure 1.24). Deprotection of (**63**) was not reported, but Bäckvall used this approach to synthesise 3-oxygenated stuctures, such as pseudotropine. Attempts to cyclise unsaturated substrates failed. Nonetheless, this is a versatile procedure that has been elaborated to prepare more complex tropanes such as scopine and derivatives[37] (Chapter 7).

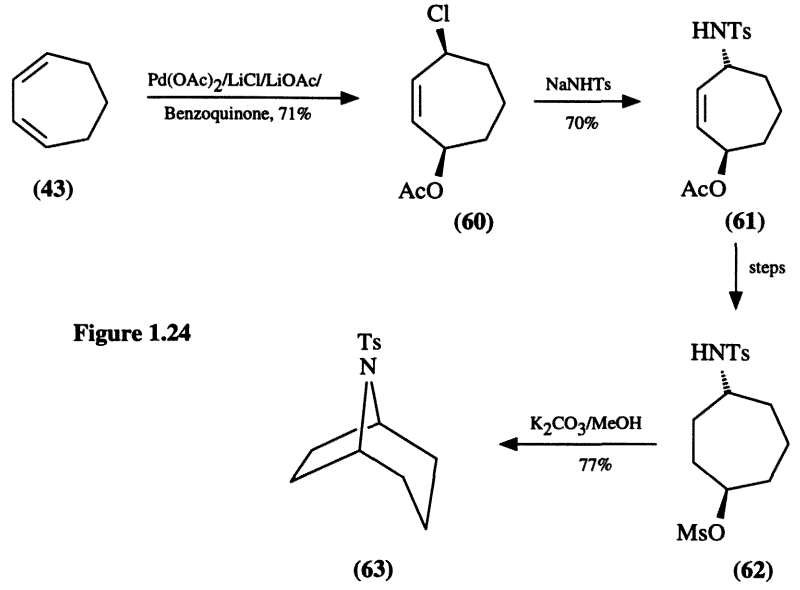
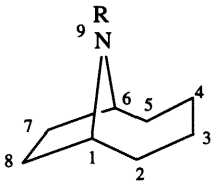


Figure 1.24

1.4 HOMOTROPANE ALKALOIDS

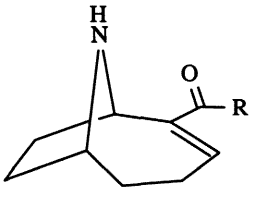
The second ring system discussed in this thesis is the higher homologue of tropane, the 9-azabicyclo[4.2.1]nonane system. The N-methyl and secondary amino-derivatives are called homotropane **(64)** and norhomotropane **(65)** respectively (figure 1.25).



R=Me Homotropane **(64)**
R=H Norhomotropane **(65)**

Figure 1.25

In contrast to the large array of alkaloids based on tropane, homotropanes are much less common in nature. Only two homotropane alkaloids have been discovered to date, both based on norhomotropane, namely anatoxin-a[38] **(66)** and homoanatoxin[39] **(67)**. The former was isolated from blooms of toxic freshwater algae, *anabaena flos-aquae*. Ingestion by wildlife of water containing high concentrations of this algae has resulted in fatal poisoning. Appropriately, it was named 'very fast death factor' (VFDF) and, after structural elucidation by X-ray crystallography[40] and spectroscopy,[41] was renamed anatoxin-a (figure 1.26).



R = Me Anatoxin-a (VFDF) **(66)**
R = Et Homoanatoxin **(67)**

Figure 1.26

Biological studies have shown anatoxin-a to be a potent muscarinic and nicotinic agonist,[42] and this has engendered considerable interest by organic chemists in designing syntheses. Campbell[43] reported the first synthesis of optically active **(66)** *via* a ring expansion of a cocaine derivative. Rapaport[44] used iminium salts to construct **(66)** and this method was later developed into a chirospecific synthesis[45]

using D- and L-glutamic acids. Tufariello[46] modified the previously described nitrone approach to tropanes[27] and reported a preparation of racemic material. Another synthesis was reported by Danheiser,[47] the key step involving a transannular substitution procedure. Although other approaches are known,[48] a recent example is discussed here: Somfai[49] reported a short, enantioselective method based on the cyclisation of an N-tosyl iminium ion (figure 1.27). Starting with a DIBAH reduction

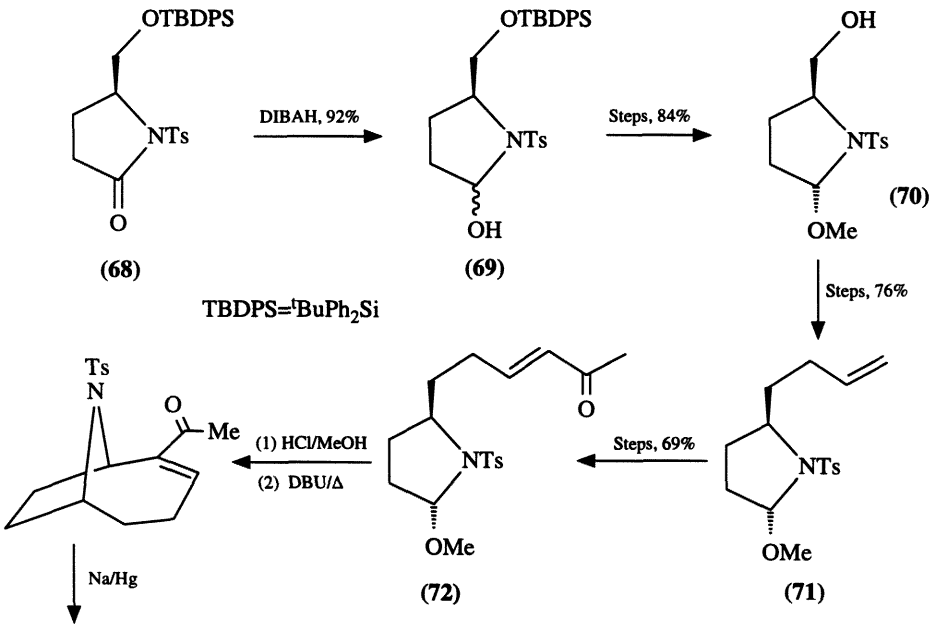


Figure 1.27

of the N-tosyl lactam **(68)** (derived from L-pyroglutamic acid[50]), the α-hydroxy sulphonamide **(69)** was prepared as an inseparable mixture of isomers. This was converted to the α-methoxy sulphonamide which, after removal of the silyl protecting group could be recrystallised as a single 2,5-substituted pyrrolidine derivative **(70)** (stereochemistry arbitrarily assigned). Deprotonation of **(70)** with *n*-butyllithium, followed by addition of phenyl chlorothionoformate yielded the thionocarbonate ester which was immediately reacted with allyltributyltin giving the alkene **(71)**. Ozonolysis and subsequent Wadsworth-Emmons reaction with dimethyl acetyl-

methylphosphonate afforded the (**72**). Acidification of (**72**) and elimination of the intermediate chloride with base, effected the desired elimination giving the N-tosyl derivative (**73**) which was deprotected to give anatoxin-a using sodium amalgam.

1.5 ESTABLISHED ROUTES TO HOMOTROPANES

Interest in the homotropane skeleton has largely been confined to anatoxin-a with over ten syntheses reported to date.[43-49] General methods of preparing other derivatives has for the most part, been relatively neglected. Early work by Cope[51] led to the first synthesis of homotropane based on a Tiffeneau expansion of tropinone (figure 1.28). The cyanohydrin (**74**) of tropinone (**10**) was hydrogenated to give the primary amine (**75**) which was treated with nitrous acid and gave the ring-expanded homotropinone (**76**) in 45% yield. Raney nickel reduction, elimination of water from the alcohol (**77**) and a second hydrogenation yielded homotropane (**64**). Although this

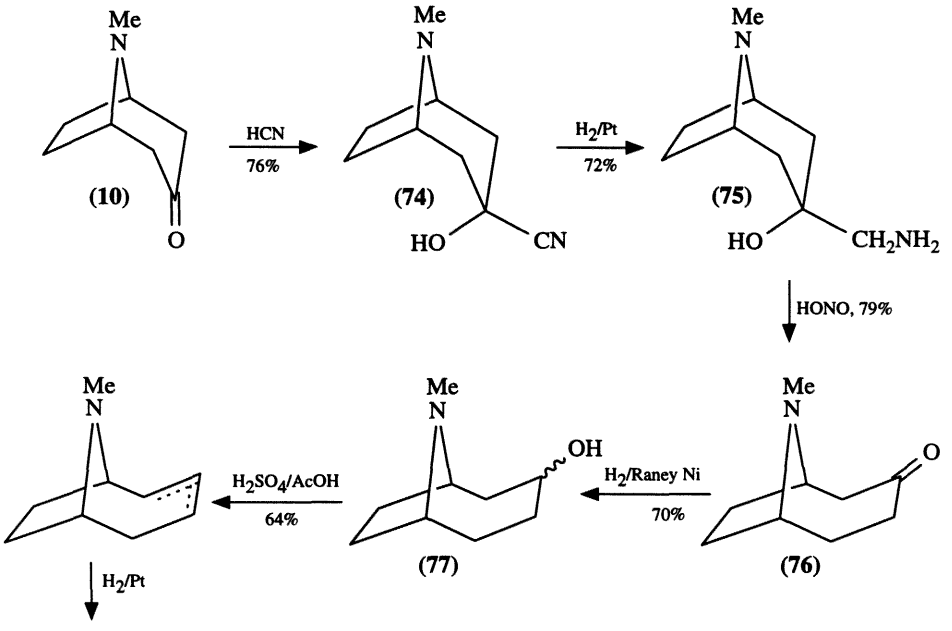
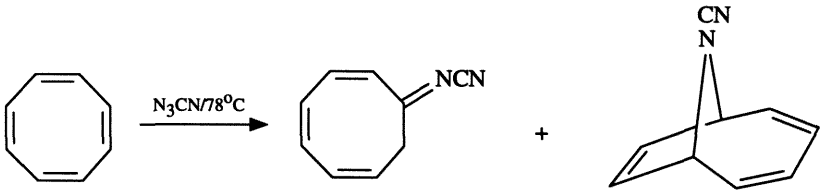


Figure 1.28

is an antecedent synthesis, the potential to prepare derivatives is somewhat limited.

Later work by Anastassiou[52] involved reaction of cyclooctatetrene (**78**) with cyanonitrene, generated by thermal fragmentation of cyanogen azide. A dilute solution of (**78**) in ethyl acetate was heated with cyanogen azide to 78°C and resulted in the evolution of nitrogen and the formation of two products in 31% yield (figure 1.29).



(**78**) (**79**), 21% (**80**), 10%

Figure 1.29

N-Cyano-9-azabicyclo[4.2.1]nona-2,4,7-triene (**80**) was formed by 1,4-addition of cyanonitrene (figure 1.30). Repeat reactions at lower temperatures afforded (**79**) exclusively, and under the optimum conditions for the formation of (**80**) the yield did not exceed 10%. Hydrogenation of (**80**) using a rhodium catalyst reduced all three double bonds, giving N-cyanonorhomotropane (**81**). More gentle hydrogenation[53]

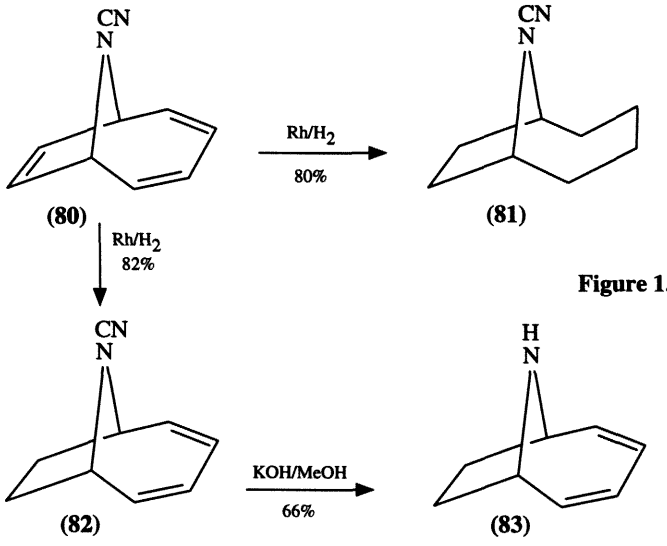


Figure 1.30

resulted in partial reduction giving the single dihydro-derivative (**82**). Hydrolysis furnished norhomotrop-2,4-diene (**83**).

Hobson[54] cyclised N-chloroamines as a means of preparing the homotropane skeleton (figure 1.31). Thermolysis of ethyl azidoformate in an excess of cycloocta-1,5-diene (**84**) gave (**85**) in high yield. Reduction of (**85**) with lithium aluminium hydride afforded N-methylcyclooct-4-eneamine (**86**) and chlorination at nitrogen was achieved with N-chlorosuccinimide (NCS). Addition of the radical initiator azobisisobutyronitrile (AIBN) to a solution of (**87**) gave a mixture of azabicycles (**88**) and (**89**), the 2-chlorohomotropane (**88**) being formed in 25% yield.

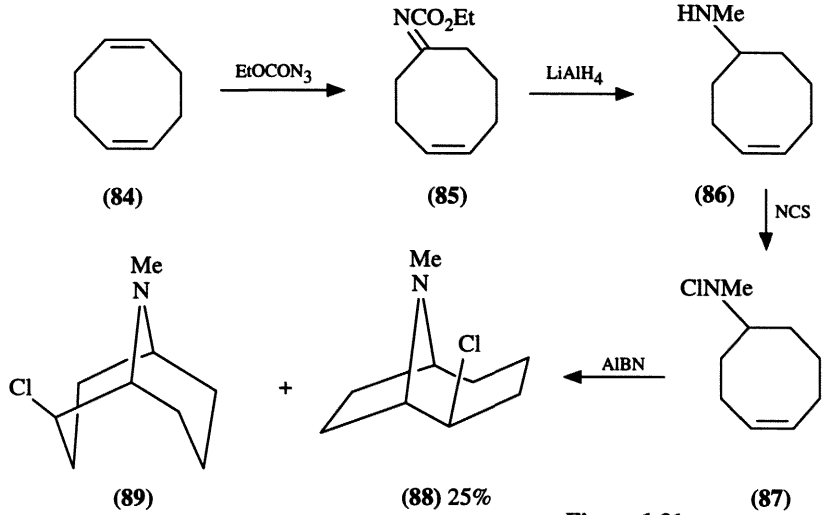


Figure 1.31

Haufe[55] also used cycloocta-1,5-diene (**84**) as a starting material in electrophilic haloamidation reactions to prepare homotropanes. This approach suffered the same drawback as that of Hobson, with two isomeric azabicyclic systems being formed in the cyclisation step. In 1979 Tardella[56] synthesised the N-ethoxycarbonyl derivative of norhomotropane, the pivotal step being cyclopropyl ring fission of bicyclo[5.1.0]octan-2-one (**90**) with pyridinium hydrochloride. The mixture of χ-chloroketones (**91**) and (**92**) was converted into oximes and reduced with lithium aluminium hydride. The amines were converted to N-ethoxycarbonyl derivatives and

separated by preparative gas chromatography. The homotropane (**94**) was isolated in 19% yield (figure 1.32). Again the formation of a second isomer, N-ethoxycarbonyl-7-azabicyclo[4.2.1]nonane (**93**), reduced the efficiency of this strategy as a means of preparing homotropanes.

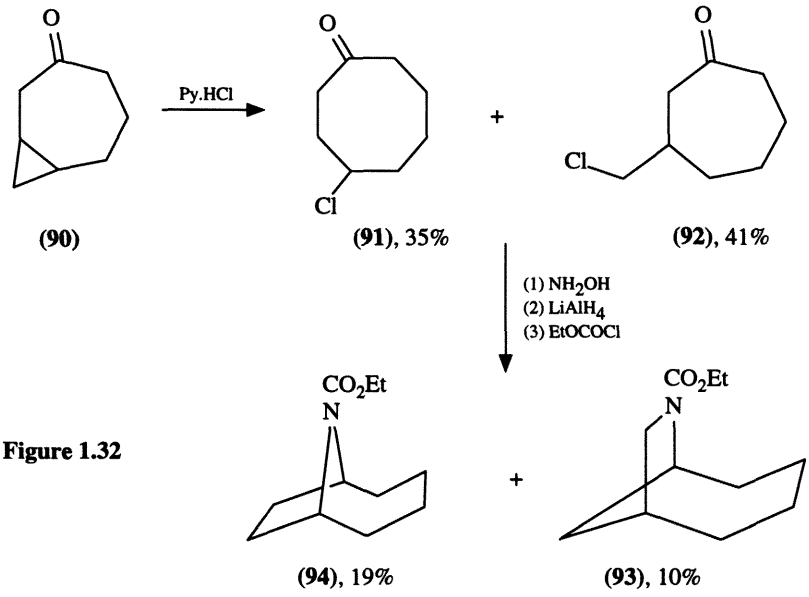
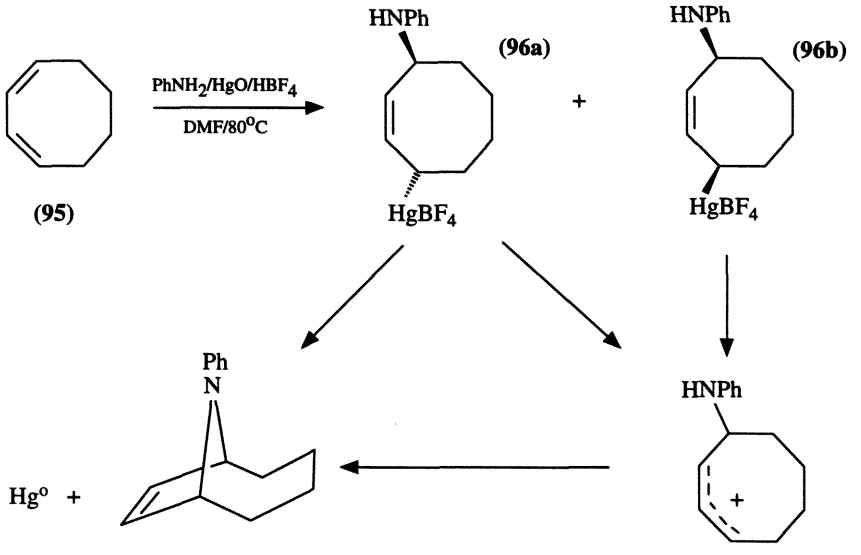


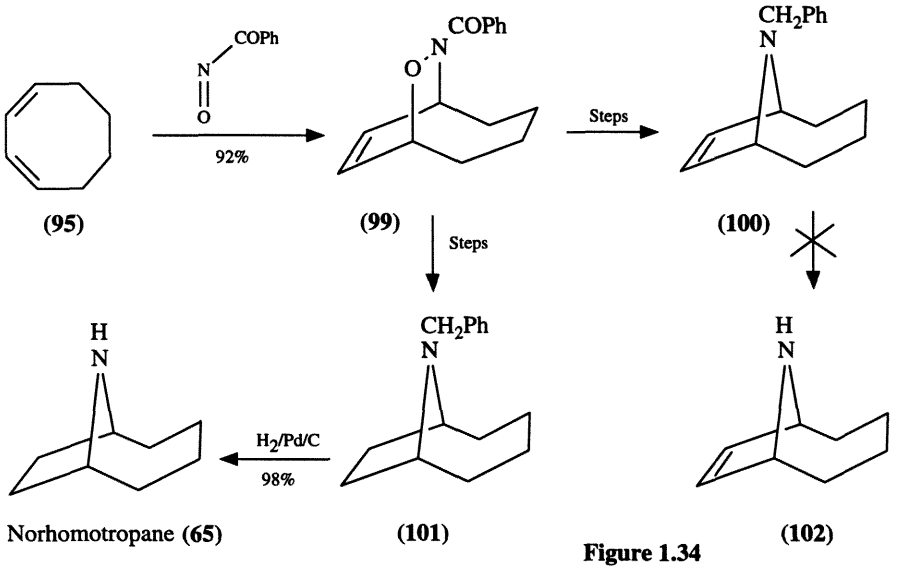
Figure 1.32

A synthesis developed by Barluenga[57] used the conjugated cycloocta-1,3-diene (**95**) as starting material. It has advantages over some of the previous methods described, giving the 9-azabicyclo[4.2.1]non-7-ene structure (**98**) as the sole product although it is only applicable to N-aryl derivatives. Heating (**95**) with aniline, mercury(II) oxide and tetrafluoroboric acid yielded (**98**) in a one-step process. The mechanism was envisaged as proceeding through the intermediate 1,4 adducts (**96a,b**), with cyclisation occurring either directly by displacement of mercury by nitrogen or *via* initial elimination of mercury to the allylic intermediate (**97**) with subsequent cyclisation (figure 1.33).



(98), 45% **Figure 1.33** (97)

The shortage of versatile routes to homotropanes led Smith[58] to investigate the potential derivation of the Kibayashi[34] and Bathgate[35] nitroso cycloaddition strategy, from tropanes to the higher homologues (figure 1.34). By increasing the ring size



Norhomotropane (65) (101) **Figure 1.34** (102)

from cyclohepta-1,3-diene (**43**) to cycloocta-1,3-diene (**95**) a simple approach to homotropanes and homotrop-7-enes was developed. Thus, reaction of (**95**) with the acyl nitroso compound generated in an identical manner to Bathgate[35] gave the homologous cycloadduct (**99**). Cleavage of the N-O bond with aluminium amalgam and further steps including cyclisation using tetramethylpiperidine resulted in the preparation of both unsaturated (**100**) and saturated (**101**) N-benzylnorhomotropanes.

N-Benzyl norhomotropane (**101**) could be hydrogenolysed to norhomotropane but this method was clearly not applicable to debenzylation of (**100**) as simultaneous reduction of the double bond would occur. Attempts by Smith to debenzylate (**100**) to (**102**) using alkali metals in ammonia or alkyl chloroformates failed. Bathgate[35] experienced similar difficulties in attempts to debenzylate other azabicycles. Smith[58] therefore approached the synthesis of the N-methyl systems by protecting the nitrogen with a benzyloxycarbonyl group which could be reduced to methyl at a later stage of the preparation (figure 1.35). Cycloocta-1,3-diene (**95**) was reacted with benzyl nitrosoformate, again generated *in situ*. Reduction of the cycloadduct (**103**) yielded

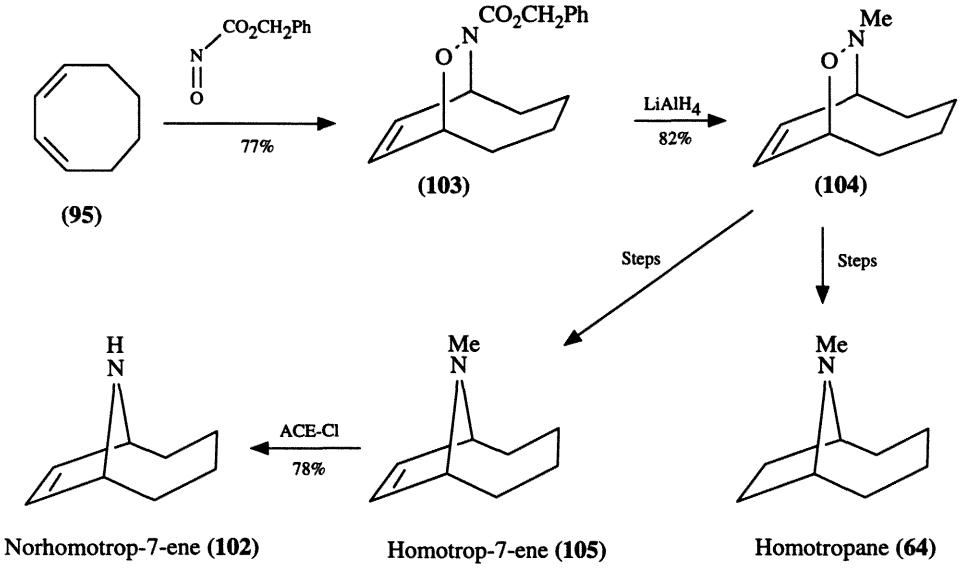


Figure 1.35

the oxazine **(104)**, which was transformed using essentially identical chemistry to that described in the previous syntheses of N-benzylnorhomotropane. Both homotropane **(64)** and homotrop-7-ene **(105)** were prepared; demethylation of the latter using α-chloroethyl chloroformate (ACE-Cl) proceeded cleanly to give norhomotrop-7-ene **(102)**.

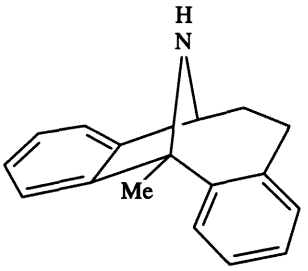
This thesis describes firstly the synthesis of functionalised homotropanes using intramolecular and amidomercuration strategies. The introduction of epoxide groups into the homotropane system is examined in detail and this work is extended to include epoxytropanes, leading ultimately to the synthesis of scopine and its derivatives. In addition a high yielding method of preparing homotropane and tropane azabicycles with hydroxy groups at the C_1-position is discussed.

CHAPTER 2

The Transannular Amidomercuration Strategy to Homotropanes and 1-Methylhomotropanes

2.1 INTRODUCTION

The dibenzo[*a,d*]cycloheptenimine MK-801[59] **(106)** has attracted considerable interest as an anticonvulsant and neuroprotective agent (figure 2.1). The structure is based on the 1-methylnortropane skeleton which is unknown in nature to date.



MK-801
(106)

Figure 2.1

In addition to MK-801, derivatives have also been prepared[60] (figure 2.2). Base-induced cyclisation of the intermediate **(107)** with potassium *t*-butoxide followed by reductive cleavage of the N-methoxy group gave the homologous dibenzonorhomotropane system **(108)**.

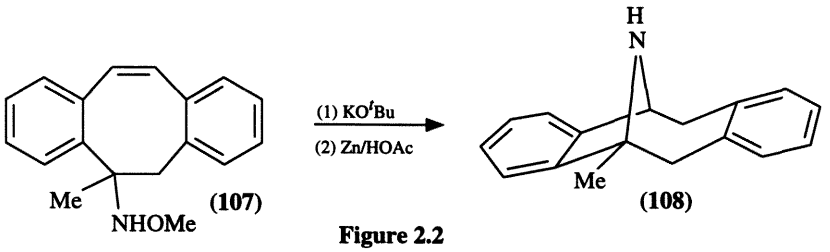
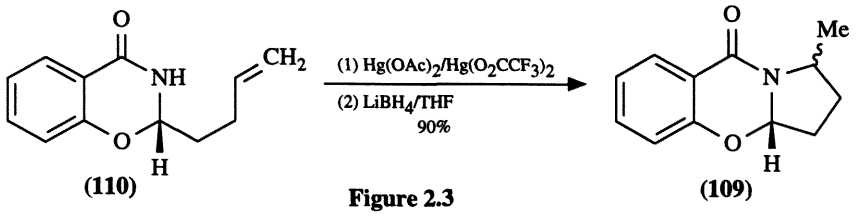


Figure 2.2

The cyclisation of alkenyl amine systems *via* electrophilic initiation with mercury(II) salts has been used to synthesise a variety of heterocycles[61] and natural products.[62] Takacs[63] employed this method to prepare N-acyl pyrrolidine and piperidines from alkenyl amidals (figure 2.3). The amidal **(109)** underwent rapid cyclisation mediated by mercury(II) acetate and mercury(II) trifluroacetate (1.5 equivalents of a 1:1 mixture) in acetonitrile. The intermediate organomercurial

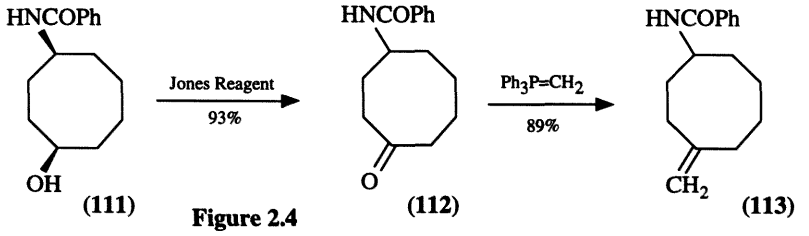
chloride was reductively cleaved to afford a 1:12.1 *cis:trans* mixture of diastereoisomers **(110)** in 90% yield.



(110) **(109)**

Figure 2.3

Smith[58] applied this procedure to synthesise the 1-methylhomotropane ring system **(116)** *via* cyclisation of an amide on to an sp^2 carbon of an *exo*-methylene group. Jones oxidation of the 1,4-amido-alcohol **(111)** gave the amido-ketone **(112)**; subsequent Wittig methylenation of the ketone gave **(113)**, the precursor to cyclisation (figure 2.4).



(111) **(112)** **(113)**

Figure 2.4

Stereoselective amidomercuration studies using δ- and ϵ-alkenyl-carbamates led Harding[64] to conclude that mercury(II) acetate induces cyclisation under non-equilibrating (kinetic) control, while mercury(II) trifluroacetate induces cyclisation under equilibrating (thermodynamic) control. Harding also demonstrated that the addition of either acetate or trifluroacetate salts is non-stereoselective and the results of Smith[58] reflect this theory of kinetic and thermodynamic control. Reaction of **(113)** with mercury(II) acetate resulted in two discrete non-interconvertible *trans*-**(114a)** and *cis*-**(114b)** acetoxymercurinium ions. Only the former has the correct stereoelectronic requirements for cyclisation to the organomercurial **(115)**. Assuming equal formation of **(114a)** and **(114b)** the optimum yield for the reaction would be 50%. However, if mercury(II) trifluroacetate were to be used instead and if

thermodynamic replaced kinetic control, then the two mercurinium ions would be interconvertible and the yield should be significantly improved (Figure 2.5).

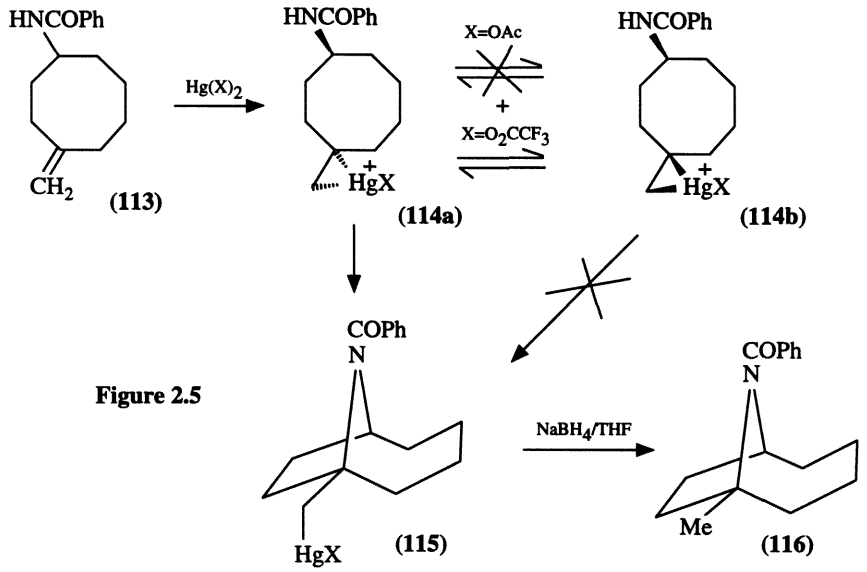


Figure 2.5

Treatment of **(113)** under the conditions used by Takacs[63] led to the isolation of **(116)** in 42% yield along with a hydroxylated by-product **(117)** in 22% yield (formed by acylation and subsequent reduction of the acetate). The yield was raised to 93% by omission of mercury(II) acetate, using 1.1 equivalents of mercury(II) trifluroacetate only. The N-benzyl derivative **(118)** was prepared by lithium aluminium hydride reduction of the amide **(117)** in high yield (figure 2.6).

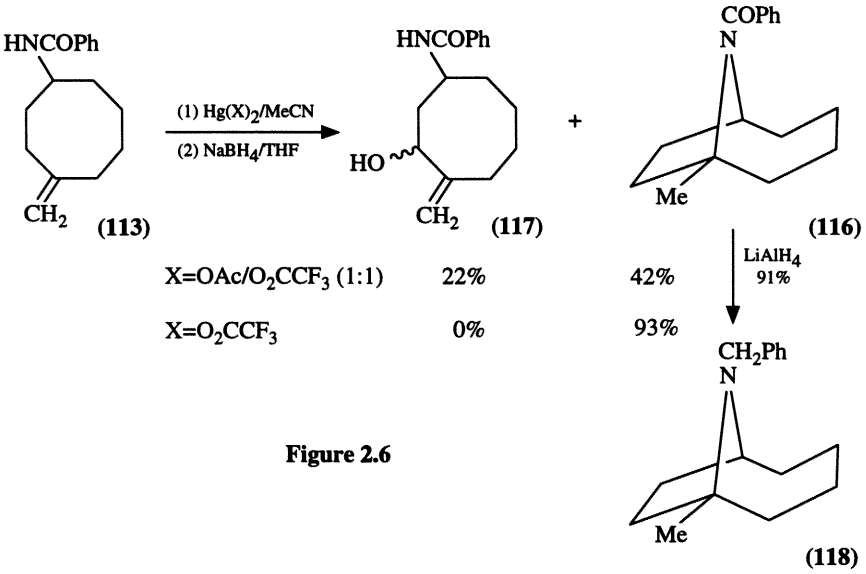


Figure 2.6

The amidomercuration procedure was then applied to the synthesis of the corresponding unsaturated system (figure 2.7). Barium manganate, a milder oxidant than Jones reagent, was used to convert the allylic alcohol (**119**) to an α,β-unsaturated ketone which was converted into the *exo*-methylene precursor (**120**). Cyclisation with mercury(II) trifluroacetate and subsequent reduction with borohydride afforded (**121**).

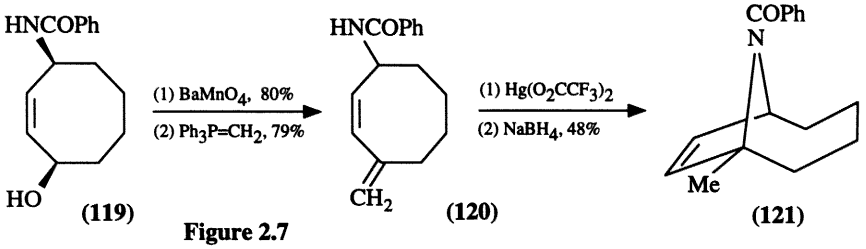


Figure 2.7

This chapter extends the procedure developed by Smith. Variation of the nitrogen protecting group extends the synthesis to the N-methyl system, in addition to the nor-systems. The amidomercuration method is also used to prepare the parent azabicyclo[4.2.1]nonane system without a bridgehead methyl group, *i.e* homotropane (**64**) and norhomotropane (**65**).

2.2 SYNTHESIS OF 1-METHYLHOMOTROPANE AND 1-METHYLNORHOMOTROPANE

Smith used hydrogenolysis with palladium on charcoal in methanol to debenzylate 1-methyl-N-benzylnorhomotropane **(118)** to 1-methylnorhomotropane **(122)** (figure 2.8).

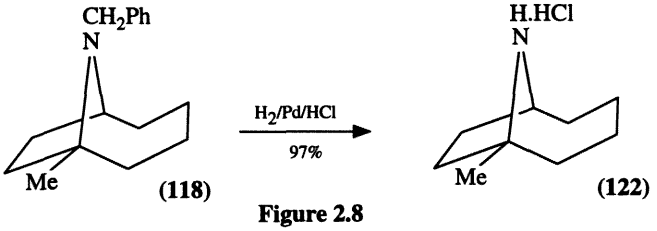


Figure 2.8

This procedure could not be applied to unsaturated benzyl-amines such as **(59)** because of competitive hydrogenation of the double bond. Attempts by Bathgate[35] to debenzylate **(59)** to the nor-derivative **(123)** using alkali metals in liquid ammonia or alkyl chloroformates failed (figure 2.9). This problem was overcome in the synthesis of homotropane **(64)** and homotrop-7-ene **(105)**, described in chapter 1.5. An N-benzyloxycarbonyl (R_2N-CO_2CH_2Ph) protected nitrogen (a carbamate) was used instead of an N-benzoyl group (R_2N-COPh) in the initial nitroso-cycloaddition and through the synthesis; lithium aluminium hydride reduction ultimately afforded N-methyl azabicycles.[58]

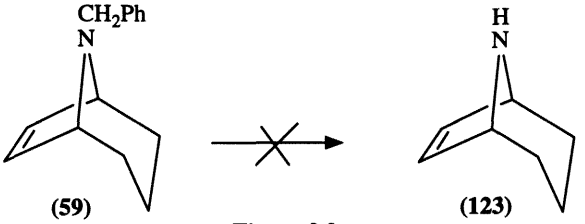
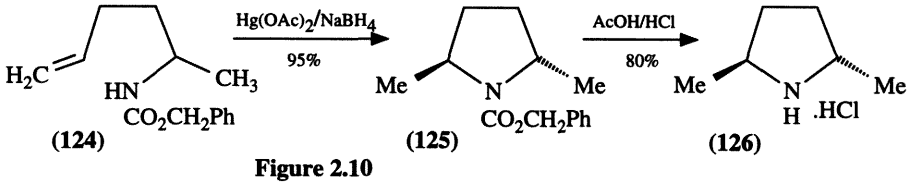


Figure 2.9

It was decided to apply the amidomercuration method using the more versatile carbamate group. Literature precedents existed for such cyclisations. Harding[61a]

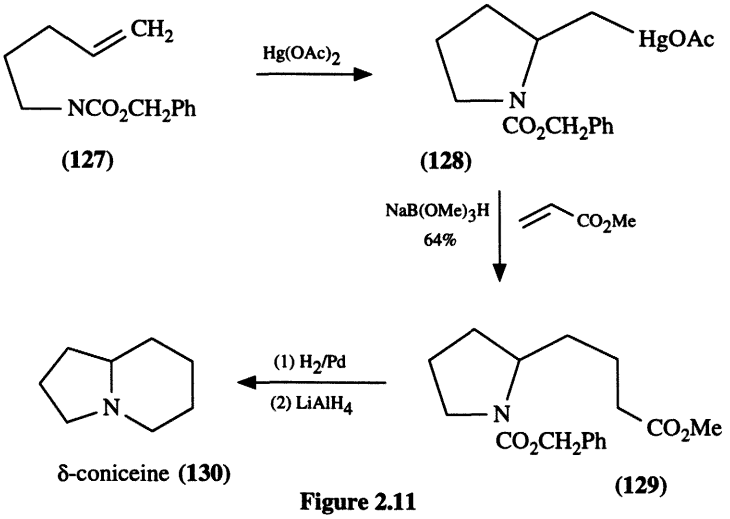
converted 3-[(benzyloxycarbonyl)amino]-5-hexene (**124**) into a *trans*-2,5-dimethyl-pyrrolidine (**125**) in excellent yield. Subsequent removal of the carbamate group afforded the amine (**126**) as outlined in figure 2.10.



(**124**) (**125**) (**126**)

Figure 2.10

Danishefsky[62b] prepared δ-coniceine in four steps (figure 2.11). Reaction of the carbamate (**127**) with mercury(II) acetate afforded an organomercury intermediate (**128**). Treatment of (**128**) with sodium trimethoxyborohydride and two mole equivalents of methyl acrylate gave the methyl ester (**129**) in an overall yield of 64%. Hydrogenolysis, cyclisation and then lithium aluminium hydride reduction of the lactam resulted in a straightforward synthesis of δ-coniceine (**130**).



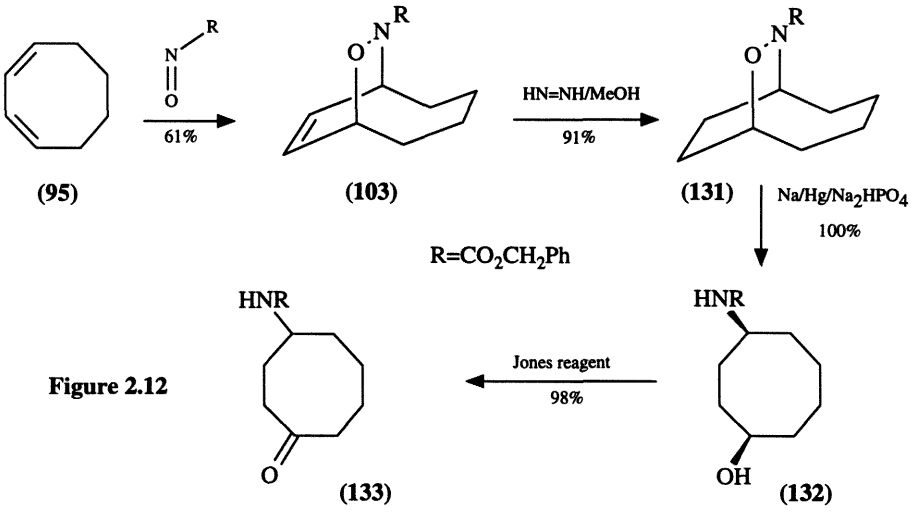
(**127**) (**128**)

δ-coniceine (**130**) (**129**)

Figure 2.11

The saturated 1-methylhomotropane system was the first synthetic target and an attempt was made to prepare (**136**) having the benzyloxycarbonyl-protected nitrogen. The previously described Diels-Alder[58] reaction between cycloocta-1,3-diene and

benzylnitrosoformate generated *in situ* from benzyl-N-hydroxycarbamate and tetramethylammonium periodate afforded cycloadduct **(103)** in 61% yield and the double bond was reduced to **(131)** using a diimide reduction.[65] Disappointingly, the yields did not exceed 40% in initial experiments using dichloromethane as solvent. Hamersma[66] reported that solvent had an important influence on reaction and indeed, by using methanol, the yield of **(131)** was raised to 91%. The formation of **(131)** was evident from the disappearance of the olefinic signals in the ^{1}H and ^{13}C NMR spectra, some ^{13}C signals were broadened however because of restricted rotation about the N-CO bond. The N-O bond of **(131)** was reductively cleaved in quantitative yield using freshly prepared and powdered sodium amalgam,[67] buffered with sodium phosphate (figure 2.12). Oxidation of **(132)** using the Jones procedure[68] gave a high

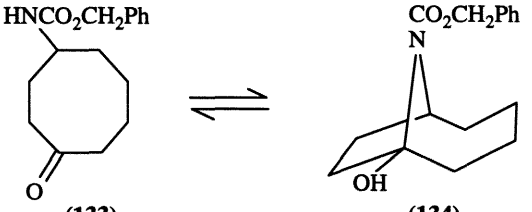


(95) (103) (131) (133) (132)

Figure 2.12

yield of the ketone **(133)** isolated as a crystalline white solid. This showed a carbonyl absorption at 1720 cm^{-1} in the IR spectrum and a carbonyl signal at δ 217.0 in the ^{13}C NMR spectrum. On leaving a solution of **(133)** to stand in $CDCl_3$ for several hours a second set of signals was detected. The ^{1}H NMR spectrum showed an AB quartet at δ 5.11 and δ 5.17 with a geminal coupling of 12.4 Hz. This corresponded to a diastereotopic pair of protons of the benzyloxy CH_2 group. A characteristic

quaternary signal at δ 92.9 in the ^{13}C NMR spectrum was also present. These signals were assigned to the tautomer of **(133)**, the bicyclic hemiaminal **(134)**, as depicted in figure 2.13. The phenomenon of tautomerism in 1,4-amino-ketone systems is discussed in more detail in chapters 3 and 4.



(133) **Figure 2.13** **(134)**

The alkene **(135)** was prepared using standard Wittig chemistry, following the Corey procedure[69] in which the methylene ylide is generated from methyl-triphenylphosphonium bromide and dimsyl anion as the base (figure 2.14). This was reported to be higher yielding than the classical Wittig method[70] which used *n*-butyllithium in diethyl ether to generate the ylide. The ketone was methylenated accordingly in 48% yield. The formation of **(135)** was apparent on inspection of the ^{13}C NMR spectrum; the carbonyl was replaced by a quaternary signal at δ 150.9 and a new methylene signal was present at δ 111.6. This spectroscopic data was similar to

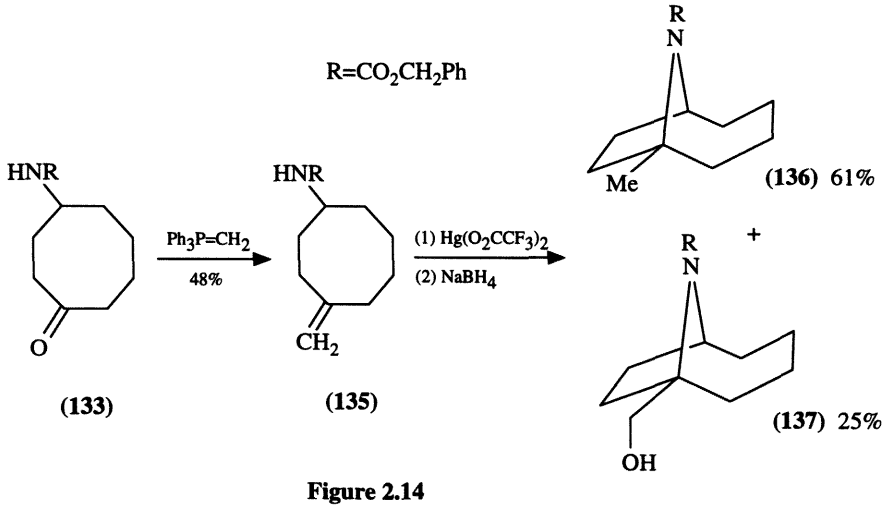


Figure 2.14

that of the closely related N-benzoyl derivative (**113**). Attempts to vary reaction conditions or prepare the ylide from other bases and solvents made no improvement to the yield. The intrinsic tautomerism process associated with (**133**) is the probable cause of the modest yield. The *exo*-methylene compound (**135**) was then reacted with 1.1 equivalents of mercury(II) trifluoroacetate and reduced with sodium borohydride, resulting in the isolation of (**136**) in 61% yield.

The ^{1}H and ^{13}C NMR analysis confirmed the structure of (**136**); although complicated by the presence of a pair of rotamers, the ^{1}H NMR spectrum showed a singlet corresponding to the methyl group at δ 1.60 (common to both rotamers). The ^{13}C NMR spectrum included methyl signals at δ 28.6 (major rotamer) and δ 29.7 (minor rotamer). The desired product was accompanied by a by-product (**137**) in 25% yield. The ^{1}H and ^{13}C NMR spectra of (**137**) differed to those of (**136**) with the methyl signals being replaced with an AB quartet at δ 3.60 and δ 3.70 (J = 11.7 Hz) in the ^{1}H NMR spectrum and a new methylene signal at δ 68.9 in the ^{13}C NMR spectrum. The mass spectrum exhibited an increase in relative molecular mass of 16 from (**136**), indicating the incorporation of oxygen, and the 1-hydroxymethyl structure was therefore assigned to (**137**).

The explanation for the formation of (**137**) is outlined in figure 2.15; reduction of an organomercurial acetate (**138**) to (**140**) using sodium borohydride generates a new C-H bond. This occurs via a free radical chain process,[71] initiated by collapse of the organomercurial hydride (**139**). Loss of elemental mercury then creates an alkyl

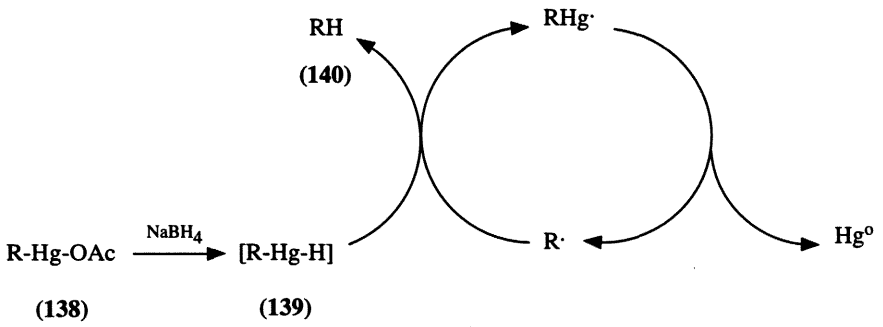


Figure 2.15

radical which abstracts hydrogen from **(139)**.

Evidence for such a process is supported by deuterium aluminium hydride studies.[72] Intermediates have also been trapped: Quirk[73] investigated the sodium borohydride reduction of 2,2,2-triphenylethylmercury(II) chloride in both anaerobic (equation **1**) and aerobic (equation **2**) conditions using basic aqueous THF as solvent (figure 2.16).

			Ph_3CMe	Ph_2CHCH_2Ph	$Ph_2C(OH)CH_2Ph$	Ph_3CCH_2OH
1.	$Ph_3CCH_2HgCl + NaBH_4 \xrightarrow{THF/H_2O}$		8%	92%	0%	0%
2.	$Ph_3CCH_2HgCl + NaBH_4 + O_2 \xrightarrow{THF/H_2O}$		13%	3%	58%	19%

Figure 2.16

The results indicate the formation of a radical proceeded by a 1,2-free radical rearrangement. Such rearrangements are less common than 1,2-nucleophilic shifts but are known for neophyl systems.[74] The oxygen acts as a radical scavenger in equation **2** and the oxygenated substrates are the predominant products. Further studies by Whitesides[75] have added credence to this mechanism. This explains the formation of the 1-hydroxymethyl azabicycle **(137)** as no inert atmosphere or degassing methods were used. When the formation of **(137)** was suppressed using an inert atmosphere, the yield of **(136)** increased to 73%.

Reduction of the carbamate **(136)** with lithium aluminium hydride afforded N-methyl-1-methyl-9-azabicyclo[4.2.1]nonane **(141)** in 78% yield (figure 2.17). The amine was volatile and was therefore handled and characterised as the hydrochloride salt. The ^1H NMR spectrum indicated a pair of diastereoisomeric quaternary ammonium salts in an integrated ratio of 8:1. The major N-methyl signal was observed at δ 2.73 as a doublet with a coupling of J = 4.4 Hz and was attributed to the equatorial diastereoisomer by analogy with the work of Bottini.[76] Hydrogenolysis gave the secondary amine **(122)** which had identical spectroscopic properties to the hydrochloride prepared by Smith.[58]

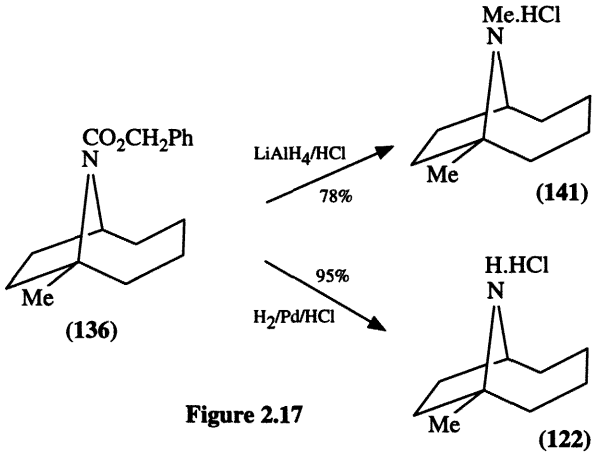


Figure 2.17

2.3 SYNTHESIS OF HOMOTROPANE AND NORHOMOTROPANE

Kibayashi[34] reported a new method of preparing tropanes using base-induced cyclisations of 1,4-amido-chlorides (chapter 1.3). However, when N-benzyloxy-carbonyl protected amino-alcohols were treated with thionyl chloride the formation of dehydration products competed (figure 2.18). Thus, the benzyl carbamate **(142)**, when treated with 2.5 equivalents of thionyl chloride, afforded **(143)** in 12% yield together with a 1:1 mixture of symmetrical and unsymmetrical cycloheptenes **(144a,b)**. In addition to base induced cyclisation of **(143)** using potassium *t*-butoxide in benzene and HMPA, the cycloheptenes were also cyclised to **(145)** using the amidomercuration method. The separation of **(144a)** and **(144b)** was not necessary as both olefins afforded the required 8-azabicyclo[3.2.1]octane product **(145)**. The 45% yield was low, which can be assumed to be because the use of mercury(II) acetate results in non-equilibrating conditions, the *cis*-mercurinium ion being unable to cyclise.

A decision was reached to examine amidomercuration as a means of preparing homotropane and norhomotropane. Using mercury(II) trifluroacetate instead of

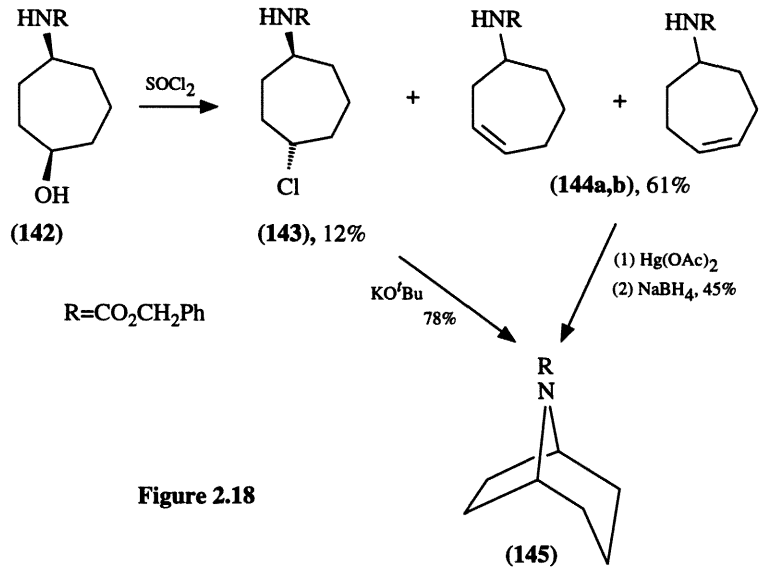


Figure 2.18

mercury(II) acetate was expected to result in a more efficient cyclisation than the 45% yield recorded by Kibayashi in the tropane series. The cyclooctenes **(147a,b)** were prepared from the ketone **(133)** using the Shapiro reaction[77] (figure 2.19). The tosylhydrazone was first synthesised using standard conditions,[78] by refluxing **(133)** with *p*-toluenesulphonyl hydrazide in ethanol with an acid catalyst. The ^{1}H NMR spectrum was entirely consistent with the hydrazone **(146)** and confirmed the incorporation of a tosyl group. The ^{13}C NMR spectrum was complex because of the mixture of isomers present. Reaction of **(146)** with four equivalents of *n*-butyllithium resulted in a pair of inseparable regioisomers **(147a,b)** in 42% yield, with olefinic

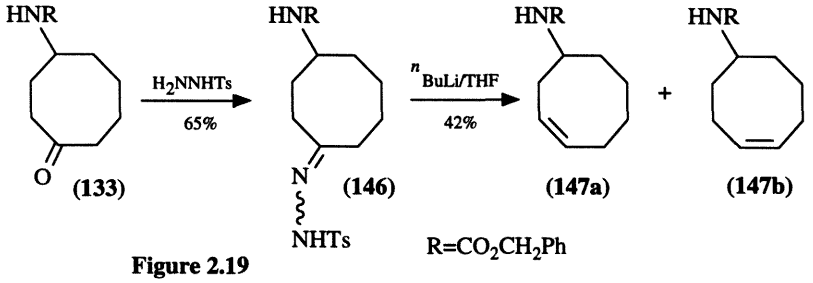


Figure 2.19

signals visible in the ^1H NMR spectrum between δ 5.57 and δ 5.80. Measurement of the ratio **(147a):(147b)** from the ^1H NMR spectrum was difficult as all the signals were superimposed but the ratio was estimated to be approximately 1:1 from ^{13}C NMR integrations. The ^{13}C NMR spectrum showed two (CH) methine signals at δ 51.2 and δ 51.6 corresponding to the α-nitrogen carbon, and a total of nine (CH_2) methylene ring carbons (two overlapping).

The mixture of cyclooctenes **(147a,b)** was then treated with mercuric(II) trifluroacetate and sodium borohydride, using identical conditions to the previous cyclisation of **(135)**. It was anticipated that cyclisation of the cyclooct-4-ene **(147b)** to give the azabicyclo[3.3.1]nonane system **(149)** might compete. Fortunately this was not the case and only the desired N-(benzyloxycarbonyl)-9-azabicyclo[4.2.1]-nonane **(148)** was isolated in 73% yield (figure 2.20). Recognition of **(148)** was

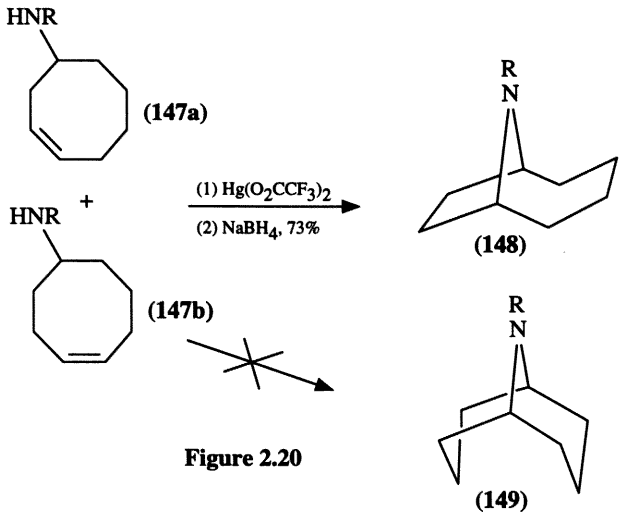


Figure 2.20

straightforward because of the simplicity of the ^{13}C NMR spectrum. Restricted rotation about the N-CO bond resulted in a pair of rotamers; three pairs of (CH_2) methylene signals were displayed at δ 24.1, δ 24.2, δ 29.3, δ 29.7 and δ 30.2, δ 31.3. The [3.3.1] system **(149)** would have shown only two such pairs because of the higher affiliated symmetry. The isolation of only **(148)** is in agreement with studies by

Barluenga[79] on the amidomercuration of cycloocta-1,5-diene **(84)**. Using mercury(II) acetate the [4.2.1] regioisomer was formed initially (under conditions of kinetic control) but subsequent pyrolysis produced the [3.3.1] isomer as thermodynamic replaced kinetic control.

The versatility of the carbamate group was then utilised. Lithium aluminium hydride reduction of **(148)** afforded homotropane **(64)** in 99% yield. Hydrogenolysis with palladium on charcoal gave norhomotropane **(65)** in 89% yield (figure 2.21). Both amines were stored as hydrochloride salts and had identical spectral properties to previously reported data.[58]

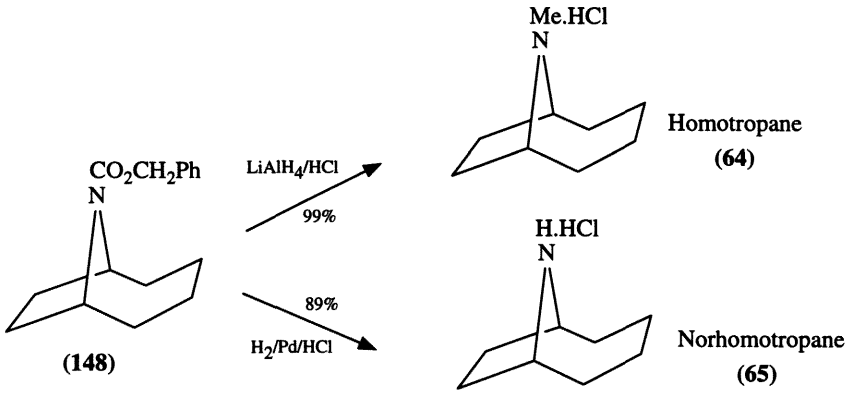


Figure 2.21

A concise synthesis of homotropane and norhomotropane has been demonstrated, the overall efficiency being reduced, however, by the disappointing yield of the Shapiro reaction. Preparation of the cyclooctenes **(147a,b)** by other means, such as dehydration of the alcohol **(132)** was not attempted although such an approach would be expected to improve the yield significantly.

2.4 SYNTHESIS OF 1-METHYLHOMOTROP-7-ENE

Attention was next turned to the synthesis of the 1-methylhomotrop-7-ene system (**155**), starting from the cycloadduct (**103**) but excluding the diimide step, as outlined if figure 2.22. Reduction of (**103**) using sodium amalgam gave the allylic alcohol (**150**) in 98% yield; the structure of (**150**) was confirmed by an exchangeable proton at δ 2.62 in the ^{1}H NMR spectrum. The presence of the double bond in (**150**) required a milder method of oxidation than Jones reagent and manganese dioxide[80] was used initially affording (**151**) and (**152**) in 62% yield. Firouzabadi[81] reported that barium manganate was a preferable reagent for the oxidation of allylic alcohols and an improvement to 85% yield resulted from its use.

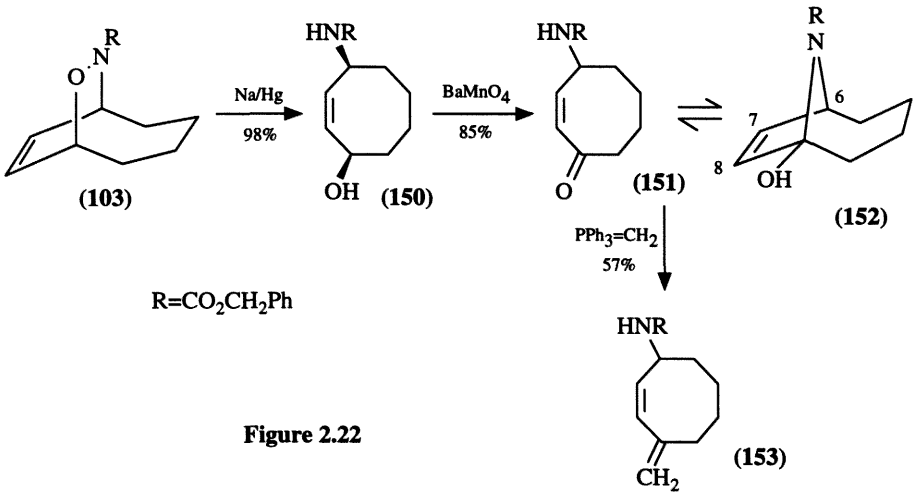


Figure 2.22

In accordance with the earlier observations concerning the unsaturated analogue (**133**), an equilibrium between the monocyclic α,β-unsaturated ketone (**151**) and the bicyclic hemiaminal (**152**) was shown to exist. Interestingly the interconversion between the two was slow and separation was possible using chromotography. The α,β-unsaturated ketone (**151**) was identified by a characteristic carbonyl signal at δ 203.4 in the ^{13}C NMR spectrum and an IR absorbance of 1715 cm^{-1}. The spectra of

the bicyclic tautomer **(152)** were more complex because of the presence of a pair of rotamers. The ^1H NMR of the major rotamer showed two olefinic signals, as part of an ABX system, with the H_8 proton at δ 5.74 having a vicinal coupling of 6.2 Hz to H_7 and a further w-coupling of 1.0 Hz. The olefinic proton H_7 at δ 5.86, displayed a further vicinal coupling to the H_6-bridgehead proton of 2.6 Hz. The ^{13}C NMR showed a quaternary (COH) signal at δ 95.7. The IR absorption of 1715 cm^{-1} was absent for **(151)**, but a broad O-H stretch was visible at 3470 cm^{-1}. If a solution of either **(151)** or **(152)** in $CDCl_3$ was left to stand, equilibration to a weighted ratio of 37:63 for **(151)** to **(152)** occurred over a period of days. Although such tautomerism processes are discussed later, it is worth comparing **(133)** and **(151)** and noting that the inclusion of a double bond shifts the equilibrium in favour of the bicyclic tautomer.

Wittig methylenation of the α,β-unsaturated ketone proved troublesome. The optimum conditions used a 5 molar excess of methylene ylide generated from dimsyl anion and resulted in a 57% yield of **(153)**. The ^{13}C NMR spectrum indicated the absence of a low field carbonyl signal, which was replaced by a quaternary ($C=CH_2$) signal at δ 146.0 and a new methylene signal at δ 118.9. The ^1H NMR spectrum showed the *exo*-methylene protons at δ 4.87 as a broad singlet and at δ 4.96 as a doublet with a geminal coupling of 1.0 Hz. In repeat reactions the formation of **(153)** was unpredictable, the yield varying between 40% and 0%. It was assumed that the tautomerism process was responsible, although attempts to methylenate freshly chromatographed α,β-unsatutated ketone **(151)** made no improvement.

As mercury(II) trifluroacetate had proved superior to mercury(II) acetate in previous reactions, it was used in the attempted cyclisation of **(153)**. This resulted in unexpected failure; the only isolated product was an interesting hydroxylated derivative **(154)** in 55% yield (figure 2.23). Resorting to mercury(II) acetate did produce the required homotrop-7-ene **(155)** but, as anticipated, only in the modest yield of 45%, for reasons discussed previously. In partial recompense for the mediocre yield, some starting material was recovered. The major rotamer of **(155)**

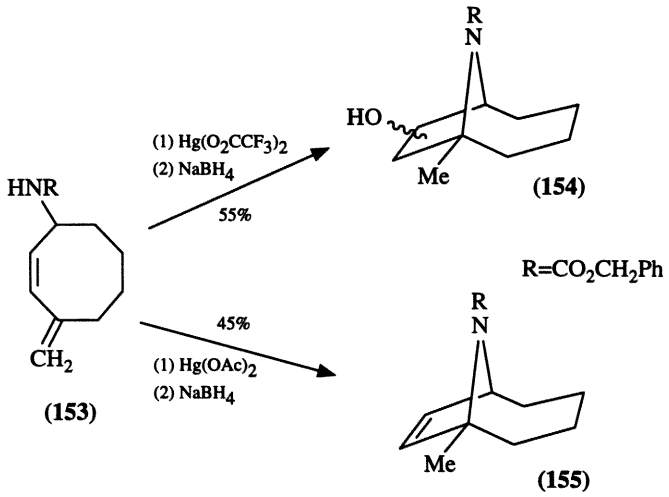


Figure 2.23

displayed a methyl carbon signal at δ 24.3 and two alkene carbon signals at δ 127.8 and δ 136.4 in the ^{13}C NMR spectrum. The ^{1}H NMR spectrum displayed an ABX system for the two olefinic protons H_A, H_B and the bridgehead proton H_X. Protons H_A (δ 5.49) and H_B (δ 5.64) showed a mutual vicinal coupling of 6.2 Hz. In addition H_B coupled vicinally (J = 2.6 Hz) to H_X, whereas H_A showed only had a small w-coupling of 0.8 Hz. A corresponding set of signals in both the ^{1}H and ^{13}C NMR were assigned to the minor rotamer of **(155)**.

Extensive studies were made to elucidate the exact stereochemistry of **(154)**. The ^{1}H and ^{13}C NMR spectra were complex at room temperature since they were recorded below the coalescence temperature of the rotamers, caused by restricted rotation about the N-CO bond. Attempts to assign signals to the two rotamers was not possible with confidence, but notable features in the ^{1}H NMR spectrum were an exchangeable proton at δ 2.58 and a series of broad multiplets between δ 3.86 and δ 4.40 assigned to the H_6 and α-hydroxy protons. Using variable temperature NMR and heating **(154)** in D_8-toluene resulted in initial broadening followed by signal coalescence at 363K. It became apparent that **(154)** was actually a pair of isomers, as

two individual bridgehead and two H_7 or H_8 α-hydroxy protons were identified. Up to four isomeric structures **(154a-d)** were therefore possible (figure 2.24).

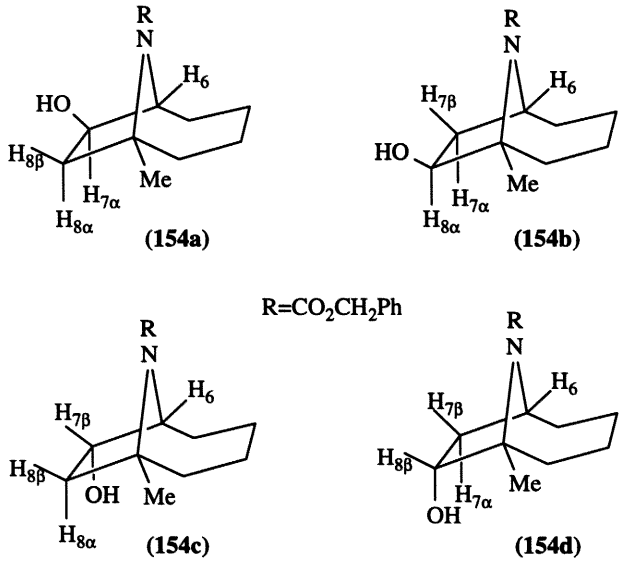


Figure 2.24

Integration of the NMR signals indicated that the broad multiplet at δ 4.32 due to the H_6-bridgehead was connected to the α-hydroxy doublet of doublets (J = 6.8, 4.8 Hz) at δ 3.74. The signals at δ 4.14 and δ 3.64 were likewise related. This was also confirmed by consecutive double irradiation experiments at 363K as illustrated in figure 2.25. Irradiation of the H_6 signal at δ 4.14 caused the broad (apparent) doublet at δ 3.64 (J = 6.8 Hz) to simplify to a doublet of doublets with vicinal couplings of 1.9 Hz and 6.7 Hz. Irradiation of the H_6 multiplet at δ 4.32 caused the doublet of doublets at δ 3.74 to remain unchanged. Two points can be deduced from these irradiations; firstly the doublet at δ 3.64 is vicinally coupled to the H_6 proton (J < 1 Hz), and therefore this proton must be either $H_{7\alpha}$ or $H_{7\beta}$. Secondly as no perturbation was observed when the H_6 multiplet at δ 4.32 was irradiated, it can be reasoned that the signal at δ 3.74 is either a $H_{8\alpha}$ or a $H_{8\beta}$ proton, unless the vicinal coupling between the two is effectively 0 Hz.

Some evidence is thus provided that **(154)** is a regioisomeric mixture. It was

300 MHz ^{1}H NMR Double irradiation experiments

of the hydroxylated homotropane (**154**)

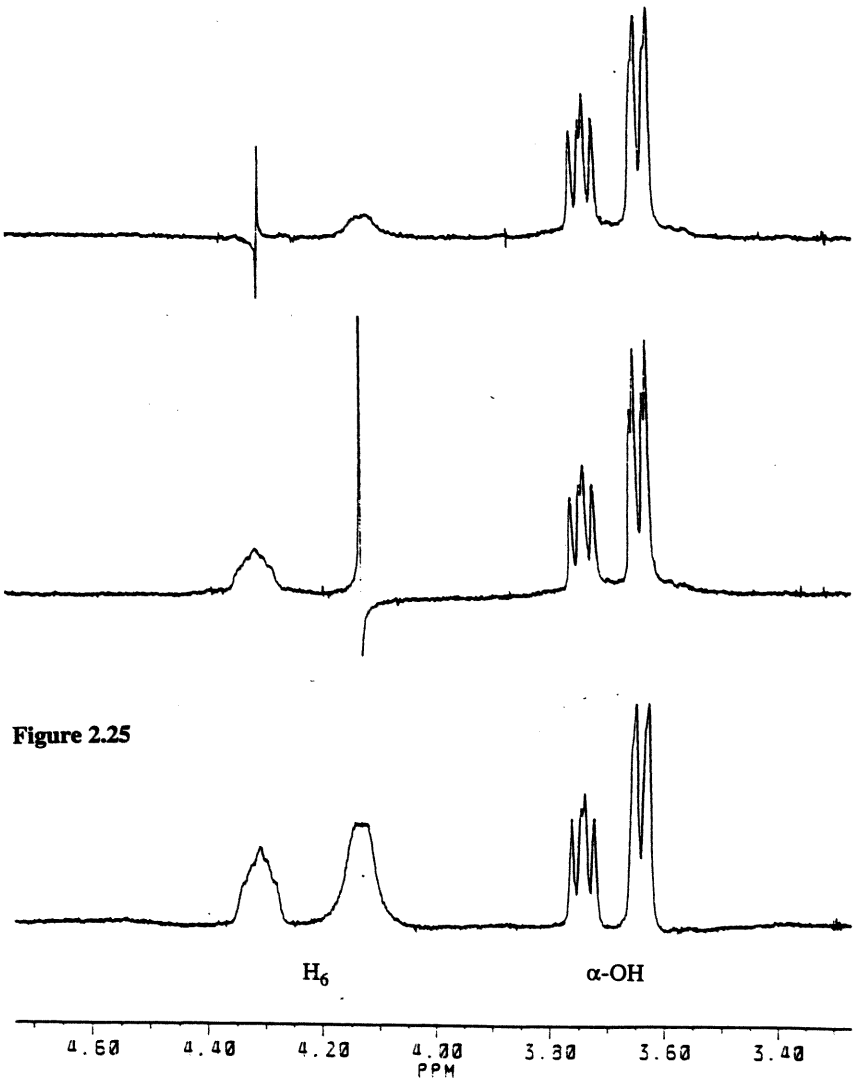
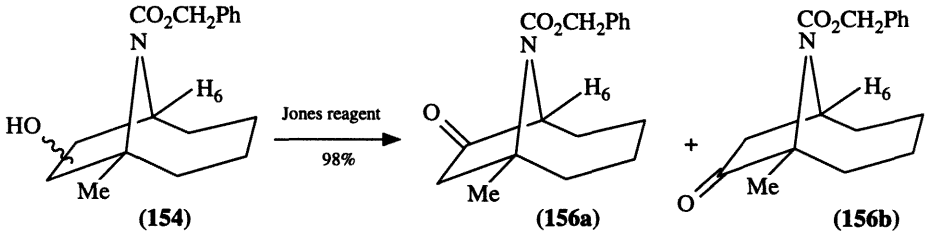


Figure 2.25

decided to oxidise a small portion of in an attempt to strengthen this proposal. If regioisomers existed then two ketones would result, whereas stereoisomers would afford only one such ketone. Oxidation of **(154)** using Jones reagent (figure 2.26) resulted in a ^1H NMR spectrum which was complex at room temperature. The oxidation was confirmed by a decrease in relative molecular mass of 2 with respect to



(154) **(156a)** **(156b)**

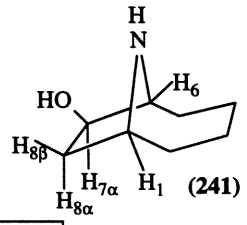
Figure 2.26

starting material. Variable temperature ^1H NMR spectroscopy was again used and coalescence occurred at 363K. Inspection of the signals at elevated temperature did indeed identify a mixture of 7-keto and 8-keto-1-methylhomotropanes **(156a,b)**. These were recognised by the presence of two H_6-bridgehead protons. A broad doublet at δ 4.02 (J = 8.4 Hz) was attributed to the 7-keto system **(156a)**, vicinally coupling to C_5 protons. This was simpler than the corresponding H_6 signal of **(156b)**, which showed additional coupling to the C_7 protons, appearing as a broad multiplet at δ 4.32. These assignments were confirmed from double irradiation experiments (see experimental).

It had now been demonstrated that **(154)** was indeed a mixture of regioisomers, but the α- or β-stereochemistry was still uncertain. This was rationalised after norhomotropan-7β-ol **(241)** and norhomotropan-7α-ol **(263)** had been synthesised (chapter 5). Full spectral data for both were recorded and are tabulated below.

The vicinal couplings for the stereoisomer of **(154)** with the α-hydroxy proton in either the $H_{7\alpha}$ or $H_{7\beta}$ position had values of $J_{7,8}$ = 6.7, 1.9 Hz and $J_{6,7}$ < 1Hz. The other stereoisomer of **(154)** with the α-hydroxy proton in either the $H_{8\alpha}$ or $H_{8\beta}$ position had values of $J_{7,8}$ = 6.8, 4.8 Hz and $J_{6,7}$ = 0 Hz. Comparison of these

δ / Hz	H_1				
H_1	3.30	H_6			
H_6	–	3.77	$H_{7\alpha}$		
$H_{7\alpha}$	–	–	4.12	$H_{8\alpha}$	
$H_{8\alpha}$	8.7*	–	6.2	1.97	$H_{8\beta}$
$H_{8\beta}$	3.3*	–	2.8	14.5	1.88

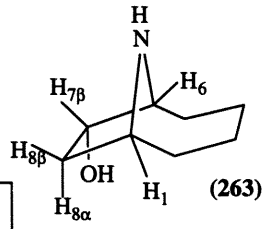


(241)

Figure 2.27

*Mutually assigned

δ / Hz	H_1				
H_1	3.46	H_6			
H_6	–	3.62	$H_{7\beta}$		
$H_{7\beta}$	–	≈7.0	4.40	$H_{8\alpha}$	
$H_{8\alpha}$	4.2*	–	7.7	1.37	$H_{8\beta}$
$H_{8\beta}$	≈10*	–	10.0	13.4	2.43



(263)

Figure 2.28

*Mutually assigned

coupling constants with the corresponding values of norhomotropan-7β-ol (figure 2.27) and norhomotropan-7α-ol (figure 2.28) with **(154a)** and **(154b)** indicated a close fit with norhomotropan-7β-ol **(241)** which displayed couplings of $J_{7,8}$ = 6.2, 2.8 Hz and $J_{6,7}$ = 0 Hz. The respective values of norhomotropan-7α-ol **(263)** bore no similarity to either **(154a)** or **(154b)**, as all vicinal couplings were much larger. It was therefore concluded with certainty that the mixture of alcohols was **(154a,b)** in which both hydroxy groups were β. The isomer which displayed a small coupling of $J_{6,7} < 1$ Hz was assigned to **(154a)** and the isomer which displayed no such coupling was

assigned to the β-hydroxy isomer (**154b**).

Oxymercuration-demercuration[82] is a standard procedure for the Markovnikov addition of water to an olefin. The mechanism proceeds by electrophilic addition of a mercury(II) salt to a double bond and then sequential nucleophilic ring opening of the mercurinium ion by water. Demercuration of the resultant organomercurial is then effected by sodium borohydride reduction. It is postulated that the 7- and 8-hydroxy-1-methylhomotropanes (**154a,b**) were formed in such a manner, as a result of a trace quantity of water in either the acetonitrile or THF solvent, prior to reduction. The organomercurial (**157**) was presumed to have been formed and to have undergone a second electrophilic addition with mercury(II) trifluroacetate, to give the diorganomercurial species (**158**), which was subsequently ring opened by water to furnish (**159**). The formation of (**154a**) is shown in figure 2.29.

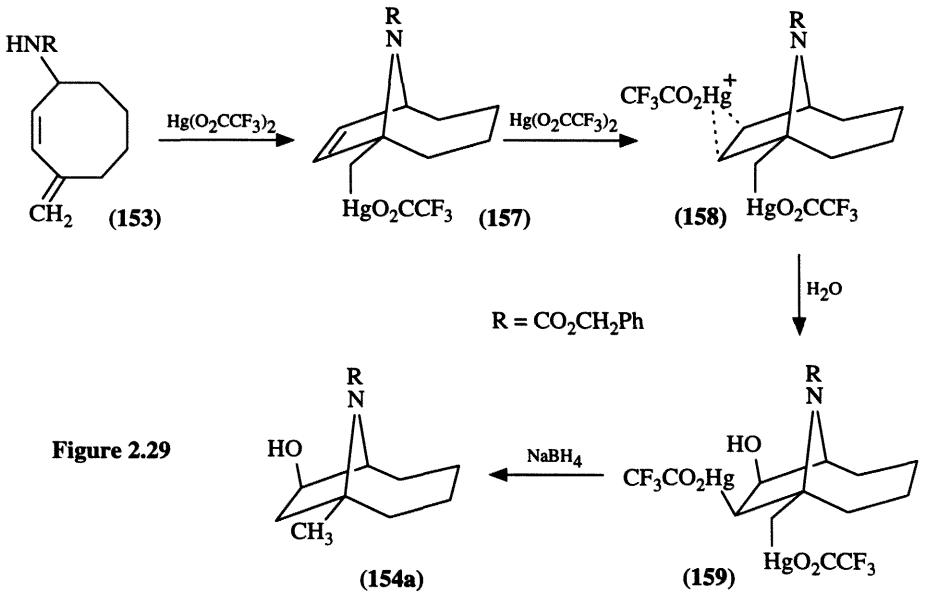


Figure 2.29

Traylor[83] demonstrated that for the strained carbobicycle norbornene, oxymercuration-demercuration results in stereoselective *exo*-hydroxylation *via* the formation of a *cis*-organomercurial intermediate such as (**159**) and this mechanism is illustrated in figure 2.29. Although a more detailed mechanistic study would be

required to demonstrate the applicability of this to less strained systems such as the homotrop-7-ene **(157)**, the results of Traylor may well explain the observed *exo*-stereochemistry for the conversion of **(153)** into **(154a,b)**.

A two molar stoichiometric quantity of mercury(II) trifluroacetate would be required for the complete conversion of **(153)** into **(154a,b)**. Only 1.1 equivalents were used resulting in a 55% yield. Repetition of the experiment with a larger excess of mercury salt, using standard aqueous oxymercuration conditions, was not investigated because of the shortage of starting material. Nevertheless, amidomercuration of **(153)** with mercury(II) acetate using rigorously dried solvents afforded the desired product **(155)** without competitive oxymercuration products. Lithium aluminium hydride reduction of **(155)** was not attempted as material was required for epoxidation studies. In accordance with the reduction of the saturated analogue **(136)**, high yielding reductions would have been expected.

2.5 EPOXIDATION OF 1-METHYLHOMOTROP-7-ENE

The 8-azabicyclo[3.2.1]octane system containing oxygen functionality in the C_6 and C_7 locations (either as ester or hydroxyl groups) is frequently encountered in nature.[1,2] Scopolamine is a unique example of a tropane alkaloid containing a 6,7-epoxy group and the epoxide is a potential precursor of hydroxy- and dihydroxy-compounds. The stereoselective introduction of such functionality is therefore of key importance in synthesising natural products and their analogues. Epoxidation of trop-6-ene derivatives offers a way of preparing epoxide functionalised tropanes, and hence a diverse range of oxygenated derivatives.

Fodor[84] has reported a total synthesis of scopolamine, *via* the synthesis of scopine **(6)**, with the key step involving the epoxidation of 3α-acetoxytrop-6-ene **(160)**. Difficulties were associated with this reaction since competitive oxidation of the amine resulted in N-oxide formation. Reaction of **(160)** with monoperoxyphthalic acid afforded the N-oxide **(161)** as the major product. An excess of peroxyacid gave a

poor yield of O-acetyl-scopine N-oxide (**162**), which could not be reduced back to the tertiary amine without simultaneous ring opening of the epoxide, affording the alcohol (**163**) (figure 2.30).

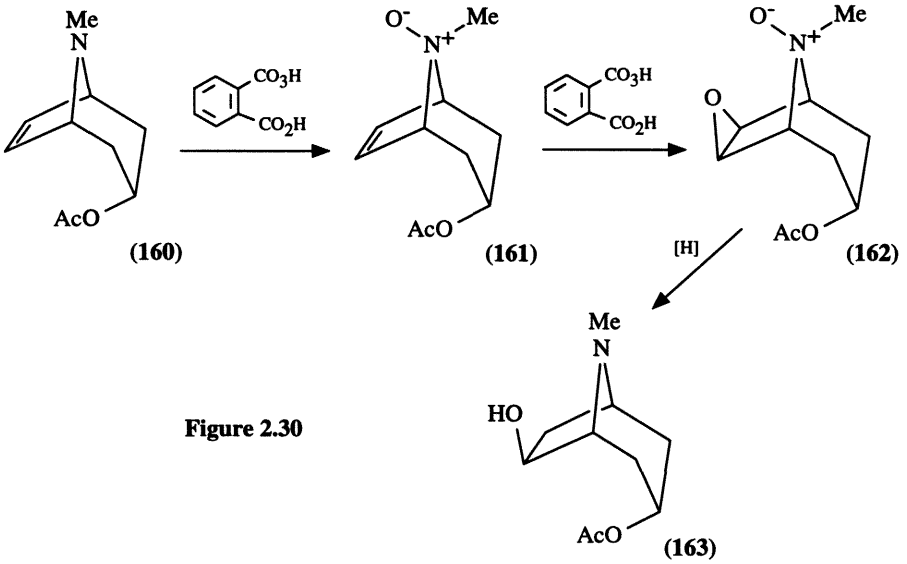


Figure 2.30

Epoxidation of (**160**) was achieved by first preparing the trifluroacetate salt of (**160**) and then treating with trifluroperoxyacetic acid in dichloromethane giving O-acetyl-scopine (**164**). This was subsequently saponified to scopine (**6**). No yield was quoted for the epoxidation step and the reaction was slow, taking eight days for completion (figure 2.31). Other syntheses of scopine are discussed in more detail in chapter 7.

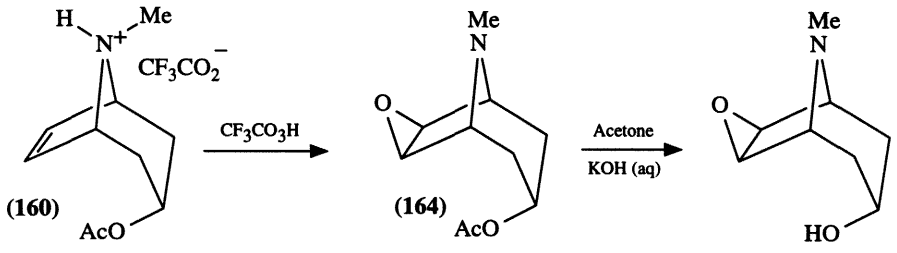
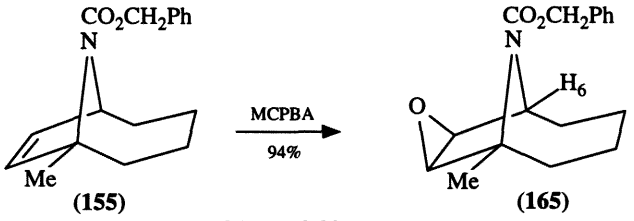


Figure 2.31

Scopine (**6**)

To assure efficient epoxidation a suitably protected nitrogen is therefore required. Extensive studies by Kočovsky[85] reported high yielding epoxidations of allylic and homoallylic carbamates. It was decided to attempt an epoxidation of the N-alkoxycarbonyl-protected 1-methylhomotrop-7-ene (**155**) to investigate the yield and also test the belief that a pronounced *exo*-stereoselectivity would predominate, in view of Fodor's results. MCPBA (50 - 60% purity) was the chosen peroxyacid; when (**155**) was stirred with 1.3 equivalents of MCPBA, (**165**) was isolated in excellent yield as the only stereoisomer (figure 2.32).



(**155**) (**165**)

Figure 2.32

The epoxide (**165**) was identified as a pair of rotamers; the major rotamer displayed characteristic epoxide proton signals in the ^{1}H NMR spectrum at δ 3.23 and δ 3.32 with a mutual vicinal coupling of 3.1 Hz, being part of an ABX system, including a small vicinal coupling (0.4 Hz) to the H_6-bridgehead proton at δ 4.36. The ^{13}C NMR spectrum displayed two new methine signals at δ 56.5 and δ 57.6 replacing the olefinic signals of (**155**). The assignment of *exo*-stereochemistry was based on three observations. Firstly epoxidation of norbornene[86] (**166**) resulted in the *exo*-epoxide (**167**) as the sole product, with the approach of the peracid from the less hindered face (figure 2.33). Model epoxidation studies by Howarth[87] of N-protected 7-azabicyclo[2.2.1]heptene systems such as (**168**) manifested the same stereoselectivity, giving only the *exo*-epoxide (**169**). Secondly, on moving to larger azabicycles, the *exo*-approach of peracids is preserved. Fodor only obtained the exo-epoxide (**164**) on epoxidation of the trop-6-ene derivative (**160**). Thirdly in later syntheses (chapter 5) both the *exo*- and *endo*-7,8-epoxyhomotropanes are prepared *via* the epoxidation of allylic alcohols. The coupling constants and chemical shifts of

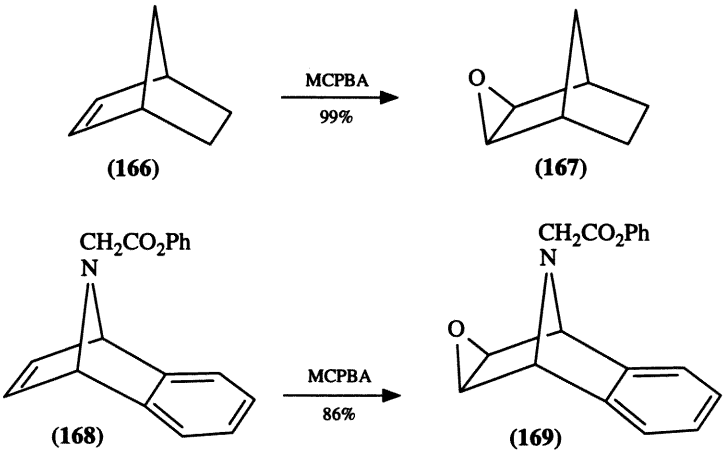


Figure 2.33

(165) in the ^1H NMR spectrum form a conclusive match with corresponding signals of the N-protected *exo*-7,8-epoxyhomotropane **(235)**, prepared later.

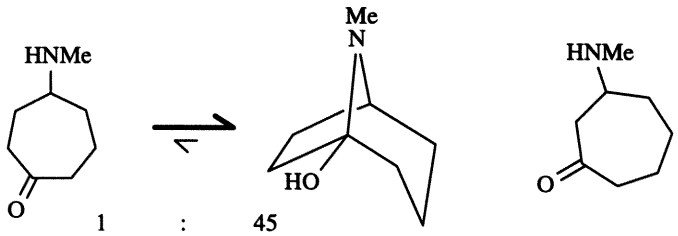
Attempts to remove the carbamate group of **(165)** were not made because of the shortage of material caused by the low yielding Wittig methylenation. Nonetheless, subsequent deprotection of the *exo*-7,8-epoxyhomotropane **(235)** was a straightforward process (chapter 5).

CHAPTER 3

Synthesis & Tautomerism of 9-Azabicyclo[4.2.1]nonan-1-ols

3.1 INTRODUCTION

The tropane alkaloid physoperuvine (**170** ⇌ **171**) was isolated from the roots of *physalis peruviana* in 1976 (figure 3.1).[88] Early studies showed physoperuvine to be isomeric with tropine (**28**) but the structure originally proposed, 3-(methylamino)-cycloheptanone (**172**), was incorrect. The structure was revised in 1982 and was assigned as 4-(methylamino)cycloheptanone (**170** ⇌ **171**) from spectroscopic studies.[89] This was later confirmed by X-ray crystallography of the hydrochloride salt.[90]



(170) **(171)** **(172)**

Figure 3.1

The hydrochloride salt of physoperuvine existed in the bicyclic form (**171.HCl**) only. Interestingly, from circular dichromism and IR spectroscopy, it was discovered that an equilibrium existed in solution between the amino-ketone (**170**) and the bicyclic hemiaminal (**171**) with an estimated ratio of 45:1. Interest in the 1-hydroxytropane skeleton has increased recently following the discovery of a new class of 1-hydroxytropane derivatives in 1988.[91] They were isolated from the roots of *calystegia sepium* (*convolvulaceae*) and were recognised as growth enhancers of nitrogen fixing bacteria. The structures were elucidated by Ducrot and Lallemand[92] two years later. The calystegines stimulated synthetic investigations which in turn have led to a revival of interest in preparing physoperuvine itself. The synthesis of these alkaloids and their derivatives is discussed fully in chapter 4. This chapter is

concerned with the higher homologues of physoperuvine, namely homotropan-1-ols (9-methyl-9-azabicyclo[4.2.1]nonan-1-ols), norhomotropan-1-ols (9-azabicyclo-[4.2.1]nonan-1-ols) and derivatives thereof.

Smith[58c,93] made preliminary investigations into the previously unstudied higher homologues. The first target chosen was 4-aminocyclooctanone (**176**) (figure 3.2) which, if a tautomeric equilibrium existed, would in effect be the parent norhomotropan-1-ol skeleton (**177**). The key intermediate for this synthesis, 4-hydroxycyclooctanone (**173**), was prepared *via* a singlet oxygen cycloaddition reaction with cycloocta-1,3-diene (**95**). Successive tosylation to give (**174**), substitution with azide ion, and hydrogenolysis of the azido-ketone (**175**) furnished 4-aminocyclooctanone (**176**).

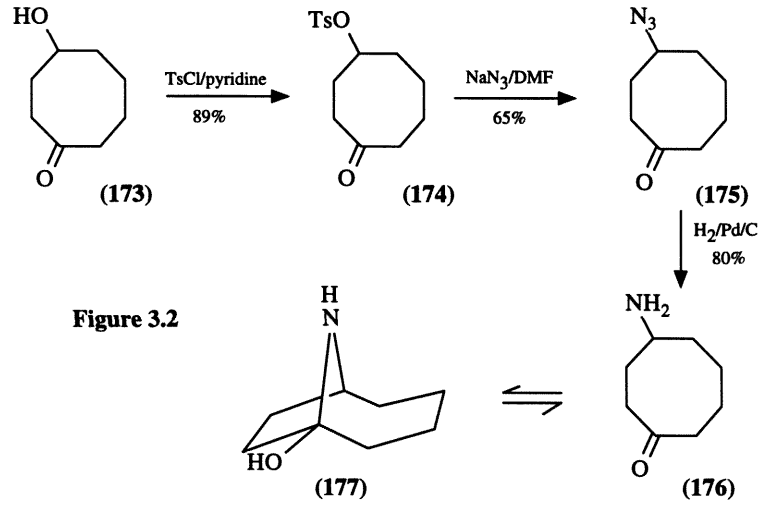


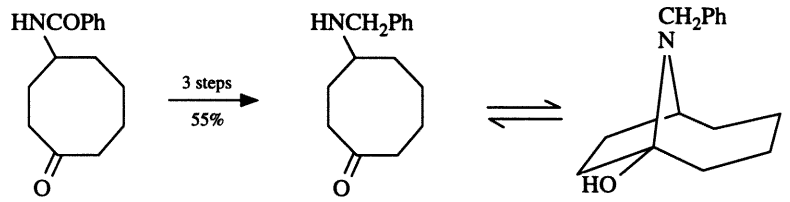
Figure 3.2

Temperature	Ratio
-20°C	82 : 18
-30°C	89 : 11
-50°C	>95 : <5

At room temperature the ^{1}H and ^{13}C NMR spectra of (**176**) were broad, suggesting that tautomeric interconversion was operating. At lower temperature the tautomerism was slowed sufficiently on the NMR time scale to allow identification of

both the amino-ketone (**176**) and the bicyclic hemiaminal (**177**). Integration of individual signals gave a quantitative measurement of the equilibrium ratio; this was found to be temperature-dependent showing an increasing preference for the bicyclic tautomer (**177**) with a decrease in temperature.

The N-benzyl derivative was produced from the previously described amido-ketone (**112**). Protection of the ketone moiety using an acetal group, hydride reduction and deprotection afforded 4-(benzylamino)cyclooctanone (**178**) in an overall yield of 55% (figure 3.3). At -50°C, the ^{1}H NMR spectrum indicated that the amino-ketone (**178**) was the major tautomer in equilibrium with 34% of the bicyclic hemiaminal (**179**).



(**112**) (**178**) (**179**)

Figure 3.3

Temperature	Ratio
-50°C	66 : 34

Attempts to prepare 7,8-dehydro derivatives of such hemiaminals starting from unsaturated analogues of (**173**), *via* tosylation and substitution with azide, were precluded because of the unexpected formation of a triazoline by an intramolecular cycloaddition between azide and the double bond. Smith[58c,93] therefore used an alternative approach to prepare unsaturated analogues starting from the amido-ketone (**180**). Deprotonation with *n*-butyllithium generated an anion which was trapped with 2-methoxyethoxymethyl-chloride (MEM-Cl) giving the protected bicyclic ether (**181**). This permitted hydride reduction of the benzoyl group (without simultaneous reduction of the carbonyl group) to afford (**182**). Deprotection of (**182**) was achieved using an excess of TFA yielding (**184**), which again existed in equilibrium with the amino-ketone (**183**) as the marginally favoured component (figure 3.4).

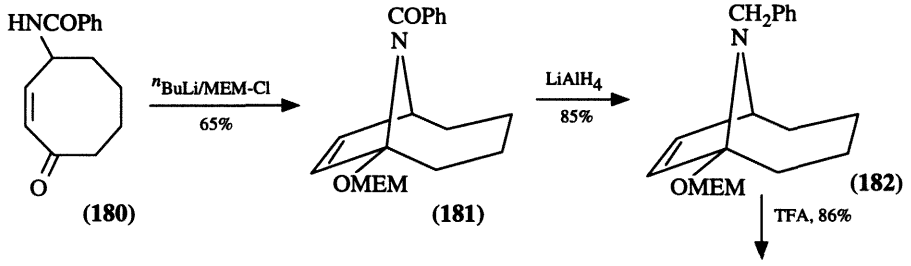
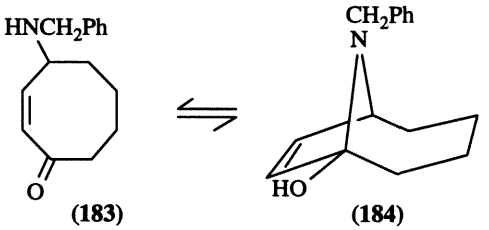


Figure 3.4



Temperature	Ratio
-55°C	58 : 42

The difficulties encountered in removing N-benzyl groups from azabicyclic systems,[58c,87] restricted the range of N-substituents that could be prepared using this approach. In particular, methyl derivatives were unobtainable using an N-benzoyl protecting group as an intermediate.

3.2 SYNTHESIS OF HOMOPHYSOPERUVINE, NORHOMOPHYSOPERUVINE AND DEHYDRO-DERIVATIVES

A universal method of preparing N-methyl derivatives was sought which would allow for the preparation of homologues of physoperuvine. The alkoxycarbonyl group was chosen (rather than the amide) for the reasons discussed previously. The α,β-unsaturated ketone **(151)** appeared to be an ideal substrate with which to employ the MEM-Cl protection strategy (figure 3.5), as it was found to be in tautomeric equilibrium with the bicyclic form **(152)**. Treating **(151 ⇌ 152)** with base and quenching the anion with MEM-Cl afforded the protected MEM-ether **(185)** in 73%

yield (figure 3.5). The ^{1}H and ^{13}C NMR spectra were complex because of the presence of a pair of rotamers; the ^{1}H NMR spectrum showed the incorporation of a MEM-ether with two signals at δ 3.35 and δ 3.38 corresponding to methoxy protons, other signals were also consistent with the incorporation of the protecting group. The NH signal was absent which suggested a bicyclic structure. The ^{13}C NMR spectrum exhibited two diagnostic quaternary signals for the newly created bridgehead carbon at δ 98.1 and δ 99.0 (two rotamers). Reduction of the carbamate **(185)** with lithium aluminium hydride and deprotection of the crude amine with excess TFA afforded N-methyl-9-azabicyclo[4.2.1]non-7-en-1-ol **(187)** in somewhat disappointing yield (45%, two steps).

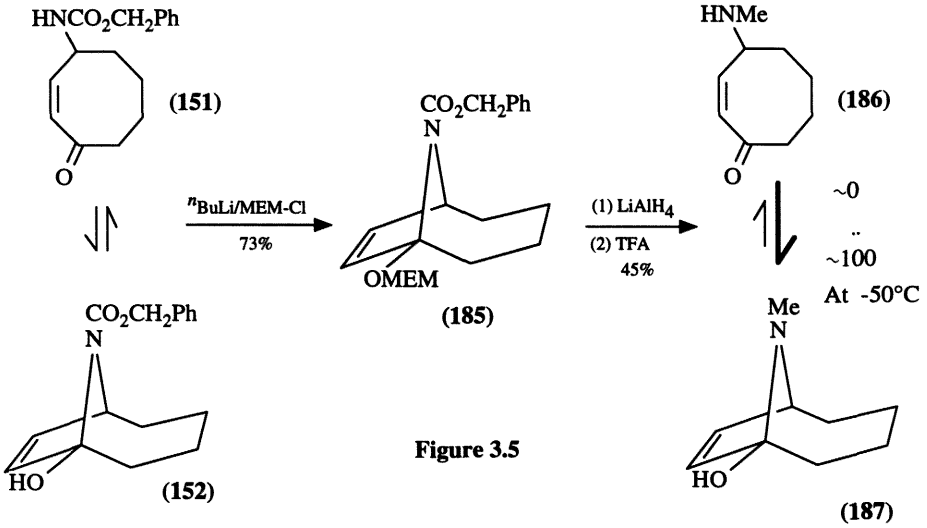


Figure 3.5

At room temperature both ^{1}H and ^{13}C NMR spectra were broadened indicating the existence of a monocyclic / bicyclic equilibrium. The IR spectrum of **(186 ⇌ 187)** included an absorption at 1705 cm^{-1} characteristic of the α,β-unsaturated carbonyl moiety of the monocyclic tautomer **(186)**. The ^{13}C NMR spectrum showed no evidence of either the α,β-unsaturated carbonyl carbon or bridgehead (COH) quaternary carbon signals because of the coalescence of these widely separated signals. However, measurement of the NMR spectrum at -50°C resulted in

sharpening of the ^{13}C spectrum and a quaternary bridgehead (COH) signal was now visible at δ 94.8. Other ^{13}C signals were present which were consistent with the bicyclic tautomer **(187)** as judged by comparison with the N-benzyl analogue **(184)**. No other signals were visible in the regions expected for signals unique to the monocyclic tautomer **(186)** and the ratio was therefore estimated to be ~0 : ~100 for **(186 ⇌ 187)** respectively at -50°C. Unfortunately, the ^{1}H NMR spectrum at this temperature was still broadened slightly and the signals due to the fractional concentration of the monocyclic tautomer **(186)** were not resolved; a quantitative estimate could not therefore be made. The observation of a carbonyl signal in the IR spectrum at ambient temperature, coupled with the observation of only the bicyclic tautomer **(187)** at reduced temperature, confirms a temperature-dependent equilibrium.

Synthesis of the saturated form of **(186 ⇌ 187)** was of interest for two reasons. Firstly this would be a first synthesis of the higher homologue of physoperuvine (homophysoperuvine). Secondly, the establishment of a tautomeric equilibrium in physoperuvine raised the question as to whether such a process would operate in homophysoperuvine **(190)**. It was decided to use the MEM-Cl protection method to prepare this compound (figure 3.6). Thus, reaction of the previously prepared

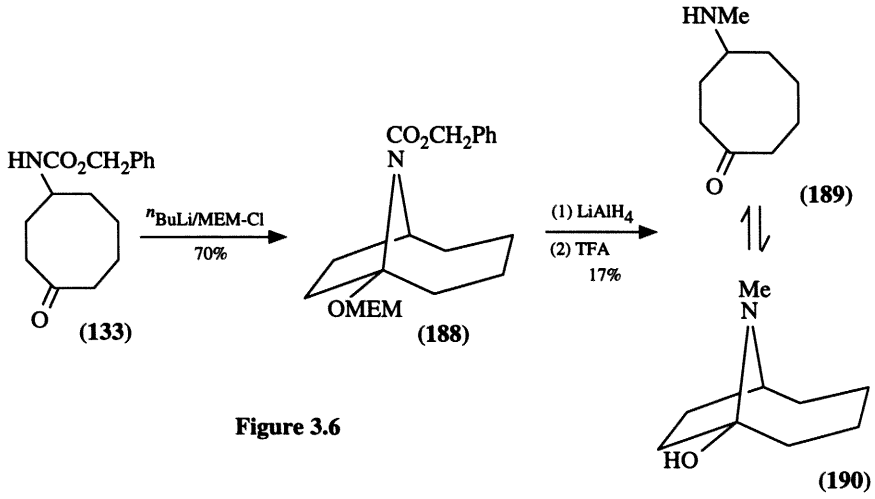
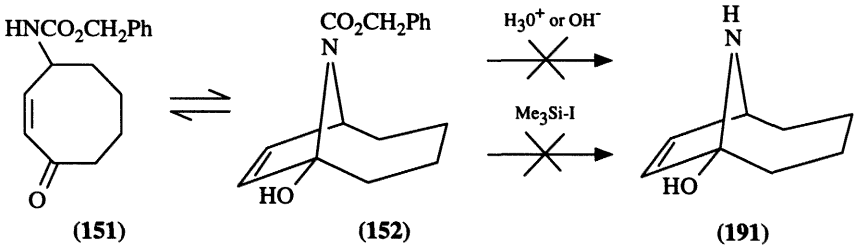


Figure 3.6

α,β-unsaturated ketone **(133)** with base and MEM-Cl gave the bicyclic ether **(188)** in 70% yield. Both the ^{1}H and ^{13}C NMR spectra were very similar to those of the unsaturated analogue **(185)**, showing characteristic (COMEM) signals at δ 95.6 and δ 96.3 (two rotamers). Reduction of **(188)** with lithium aluminium hydride and acidification of the unpurified MEM-ether with an excess of TFA gave crude homophysoperuvine **(190)**, but in a yield of only 17%.

Only 21 mg of crude product was isolated using this method and it could not be purified satisfactorily. Full spectroscopic characterisation and an investigation into tautomerism involving the amino-ketone form **(189)** was not possible at this stage. The major cause of the low yield was believed to be the high solubility of the amine in the aqueous layer during extraction. Despite meticulous care, using the minimum quantity of aqueous solution (saturated with sodium chloride) and repeated extraction with ethyl acetate, the yield could not be improved.

The preparation of norhomotrop-7-en-1-ol **(191)** was thwarted because of the same practical difficulties. Attempted acid or base hydrolysis of the carbamate **(151 ⇌ 152)** resulted in highly polar products which could not be fully isolated or identified. Application of the more modern deprotection reagent, iodotrimethyl-silane,[94] also failed giving only polymeric products (figure 3.7).

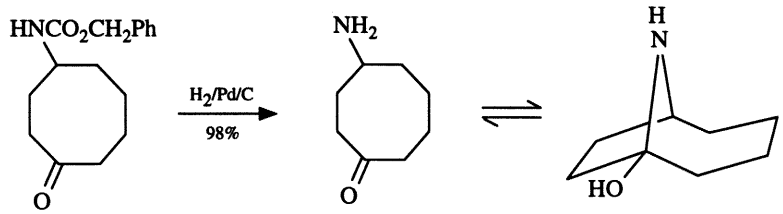


(151) **(152)** **(191)**

Figure 3.7

Norhomotropan-1-ol (norhomophysoperuvine) **(177)** could be prepared efficiently and simply from the saturated carbamate **(133)**. Hydrogenolysis with palladium on charcoal catalyst afforded **(176 ⇌ 177)** in near quantitative yield (figure 3.8). The ^{1}H and ^{13}C NMR spectra were found to be identical to a sample

previously prepared by Smith.[93]



(133) (176) (177)

Figure 3.8

3.3 AN EFFICIENT SYNTHESIS OF HOMOTROPAN-1-OLS

The use of a MEM-ether protecting group during the preparation of homophysoperuvine **(190)** and homophysoperuv-7-ene **(187)** was only partially successful as the yields were disappointing (17% and 45% respectively) and the former was not characterised. A more efficient procedure was developed which entailed direct oxidation of amino-alcohols, avoiding the necessity for a carbonyl protecting group. It was hoped that oxidation of saturated **(192)** and unsaturated **(193)** amino-alcohols, prepared from the respective carbamates **(132)** and **(150)** by hydride reduction, would provide a more direct approach (figure 3.9). Both amino-alcohols displayed identical spectroscopic properties to samples prepared by a different route.[93] Corey's[95] pyridinium dichromate (PDC) reagent was tried first as it was reportedly a mild reagent which could be used in aprotic media. However, attempted oxidation in both dichloromethane and DMF failed, resulting only in the isolation of starting material. A similar outcome resulted when the closely related pyridinium chlorochromate[96] (PCC) was employed. Barium manganate,[81] manganese dioxide[80] and tetrapropylammonium perruthenate[97] (TPAP) all failed similarly. Despite these early failures, the use of Jones reagent in a procedure which did not involve an aqueous work up gave good yields of both homophysoperuvine **(189 ⇌ 190)** and homophysoperuv-7-ene **(186 ⇌ 187)**.

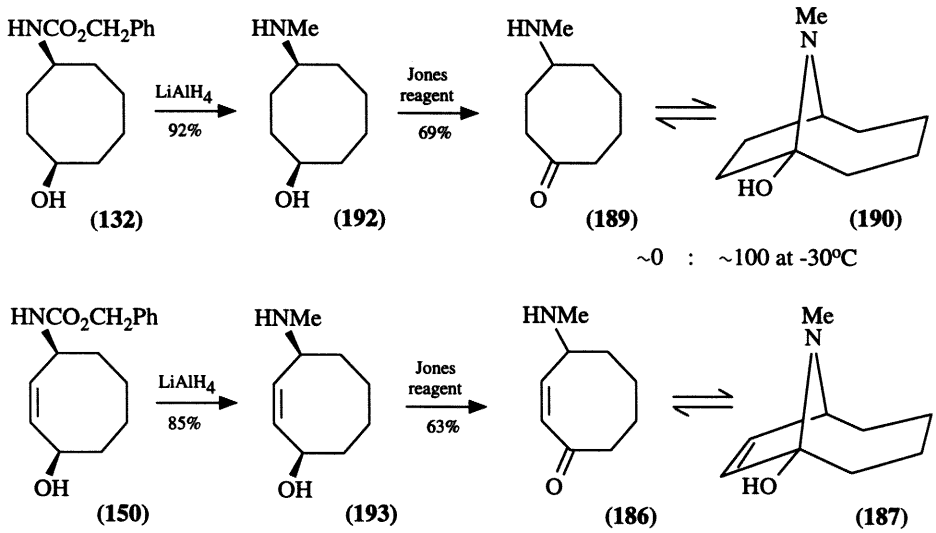


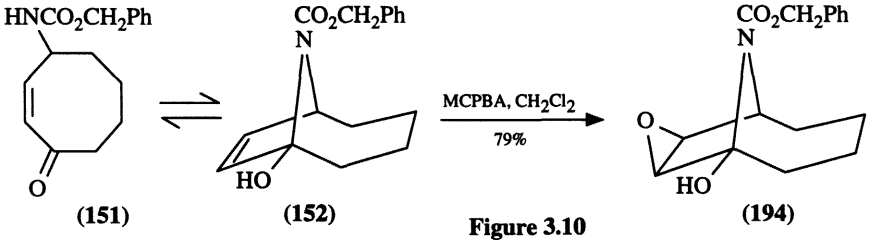
Figure 3.9

The successful oxidation of **(192)** was confirmed by the isolation of a product having identical spectroscopic properties to a sample prepared using the MEM-Cl protection method. The ^{1}H and ^{13}C NMR spectra of **(189 ⇌ 190)** bore a close resemblance to **(186 ⇌ 187)**, being broad at room temperature with no quaternary carbon signals visible in the ^{13}C NMR spectrum. The IR spectrum displayed an absorption at 1695 cm^{-1}, indicative of a non-conjugated carbonyl group, hence the monocyclic tautomer **(189)** was present at room temperature. Cooling the sample to -30°C made little difference to the ^{1}H NMR spectrum, but the ^{13}C NMR spectrum was now much sharper with the appearance of a new quaternary carbon signal at δ 92.0 together with other signals characteristic of the bicyclic hemiaminal **(190)**. The carbon shifts of both the quaternary bridgehead (δ 92.0) and the tertiary bridgehead (δ 58.1) in the ^{13}C NMR spectrum were in close accord with published data for calystegine A_3[92] which had values of δ 93.0 and δ 54.0. Analysis of the NMR spectra led to a similar conclusion to that reached for the unsaturated derivative **(186 ⇌ 187)**, namely that a temperature-dependent process was operating and that the equilibrium was weighted very heavily towards the bicyclic tautomer (effectively ~0 : ~100 for

(**189** ⇌ **190**) respectively) at -30°C. No other signals that might correspond to the monocyclic tautomer were observed. Discussion of the relative tautomer preferences will follow a description of similar studies of closely related epoxy-derivatives.

3.4 SYNTHESIS OF *EXO*-7,8-EPOXYHOMOTROPAN-1-OLS

In order to prepare novel higher homologues of calystegines and extend the study of tautomerism processes in derivatives of homophysoperuvine, the introduction of oxygen functionality in the 7,8-bridge was deemed to be important. One possible approach would be elaboration of the etheno-group of 7,8-dehydrohomophysoperuvine (**187**), but because practical difficulties were encountered in the handling of such amines, this was not considered to be a feasible approach. A more suitable substrate was sought; with the high-yielding and stereoselective epoxidation reaction of the previous chapter in mind, it was decided to attempt an epoxidation of the N-protected 4-aminocyclooct-2-enone (**151**) which had been found previously to be in equilibrium with the bicyclic tautomer (**152**). It was anticipated that epoxidation would occur *via* the more labile double bond of (**152**) rather than that of the less reactive α,β-unsaturated ketone. This was indeed the case as epoxidation of (**151** ⇌ **152**) with MCPBA furnished the *exo*-epoxide (**194**) as the only product in good yield (figure 3.10). If epoxidation of (**151**) had occurred then a mixture of stereoisomers may have resulted.



(**151**) (**152**) (**194**)

Figure 3.10

The ^{1}H and ^{13}C NMR spectra were consistent with the bicyclic tautomer (**194**) only and, as a consequence of slow rotation about the N-CO bond, two sets of signals

were observed. Signals due to both rotamers were well resolved at room temperature and there was no evidence of any monocyclic epoxy-ketone tautomer. In the ^1H NMR spectrum, the epoxide protons of the major rotamer appeared as two doublets at δ 3.33 and δ 3.48 which had a mutual vicinal coupling of 3.2 Hz. Similar signals for the minor rotamer were also present. No vicinal coupling between the H_6-bridgehead and the H_7-epoxide protons was seen. This is in close agreement with the analogous 1-methyl epoxide (**165**), which displayed only a small coupling of 0.4 Hz for $J_{6,7}$. The ^{13}C NMR spectrum of (**195**) included a characteristic quaternary (COH) signal at δ 91.4.

Having prepared the epoxide (**194**), it was expected that reaction with hydride would simultaneously reduce the carbamate to an N-methyl group and open the epoxide to yield a mixture of regioisomeric alcohols (**195a,b**). This was not the case: treatment of (**194**) with lithium aluminium hydride in THF at reflux resulted in reduction of the carbamate only, giving the novel epoxy-amine (**196**) in good yield (figure 3.11).

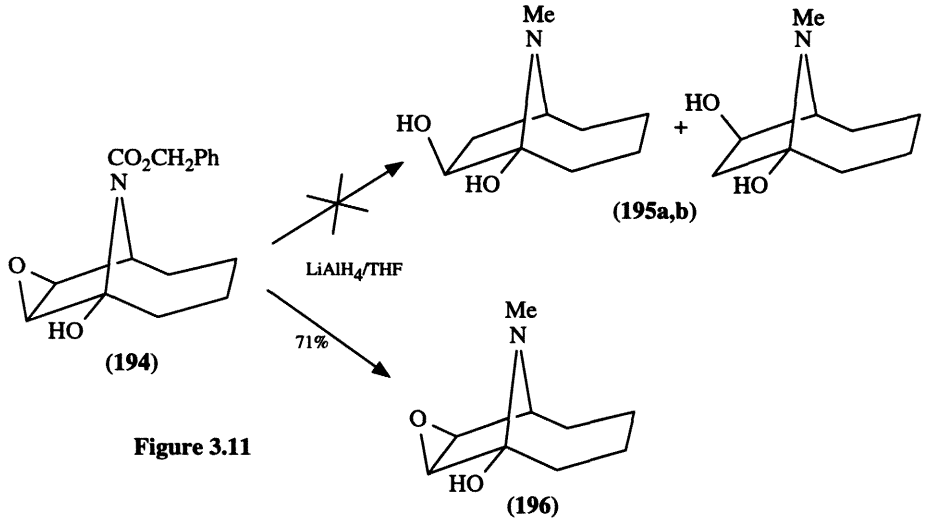
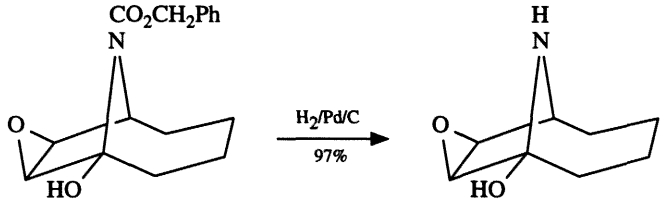


Figure 3.11

This was confirmed by the ^1H NMR spectrum which displayed very similar epoxide signals to (**194**), with two doublets at δ 3.34 and δ 3.38 exhibiting the characteristic vicinal coupling of 3.3 Hz. The formation of an N-methyl group was

shown by a singlet at δ 2.52 integrating to three protons in the ^1H NMR spectrum and a quartet at δ 28.9 in the ^{13}C NMR spectrum.

Similar chemoselectivity was observed when **(194)** was hydrogenolysed to **(197)** using a palladium on charcoal catalyst (figure 3.12). The epoxide protons ($H_{7,8}$)



(194) **(197)**

Figure 3.12

were magnetically equivalent in $CDCl_3$ solvent, but in D_6-acetone these were resolved and the ^1H NMR spectrum displayed two doublets at δ 3.27 and δ 3.31 ($J_{7,8}$ = 2.7 Hz). The ^{13}C NMR spectrum showed a bridgehead (COH) signal at δ 91.2 in close analogy to **(196)**.

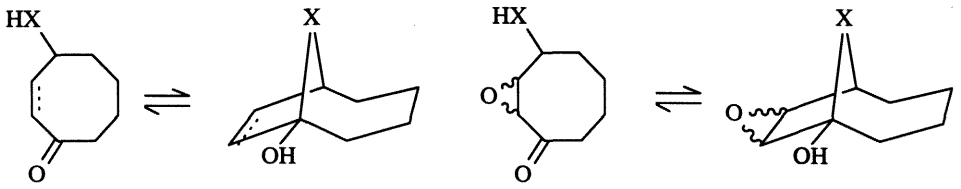
There was no spectroscopic evidence that either **(196)** or **(197)** existed in tautomeric equilibria at room temperature, in agreement with observations on **(194)**. The crude ^1H and ^{13}C NMR spectra of neither **(196)** nor **(197)** showed any indication at all of epoxide ring opening. This stability is suprising in view of the general lability of epoxides, and is not fully understood. An investigation into the relative reactivities of *exo*- and *endo*- epoxides is made later (chapter 6).

3.5 CONCLUSION

The ratios of monocyclic:bicyclic tautomers in the saturated, unsaturated and epoxyhomotropan-1-ol derivatives are summarised in table 1. The N-protected epoxide **(256)** having a *trans*-stereochemistry between the nitrogen and the epoxide, prepared later (chapter 5.3), is included for comparison.

The tautomeric ratios of primary and secondary amino-ketones in the saturated

Table 1. Ratios of monocyclic (M/C) : bicyclic (B/C) tautomers



X	Compound	Temp (°C)	M/C : B/C	^{13}C NMR(δ) M/C C_4	M/C CO	B/C C_1	B/C C_6
Saturated series							
NCO_2CH_2Ph	**(133 ⇌ 134)**	25	71 : 29	50.8	217.0	92.9	55.4
NMe	**(189 ⇌ 190)**	-30	~0 : ~100	-	-	92.0	58.1
NCH_2Ph	**(178 ⇌ 179)**	-30	70 : 30				
		-40	68 : 32				
		-50	66 : 34	56.1	218.6	92.2	54.2
NH	**(176 ⇌ 177)**	-20	18 : 82				
		-30	11 : 89	50.7	218.8	93.1	52.4
		-50	5 : 95				
Unsaturated series							
NCO_2CH_2Ph	**(151 ⇌ 152)**	25	37 : 63	50.6	203.4	95.7	60.8
NCH_2Ph	**(183 ⇌ 184)**	-55	58 : 42	55.3	203.3	94.7	60.1
NMe	**(186 ⇌ 187)**	-50	~0 : ~100	-	-	94.8	62.9
Epoxide series							
cis-NCO_2CH_2Ph	**(194)**	25	0 : 100	-	-	91.4	58.0
trans-NCO_2CH_2Ph	**(256)**	25	100 : 0	52.3	206.2	-	-
NMe	**(196)**	25	0 : 100	-	-	89.6	55.3
NH	**(197)**	25	0 : 100	-	-	91.2	54.6

and unsaturated series could not be measured at ambient temperature (with the exception of the epoxides) because of rapid interconversion between tautomers and the values in all these cases refer to temperatures of -20°C or below. The observation of carbonyl absorptions in the IR spectrum at room temperature, particularly for **(189 ⇌ 190)** and **(186 ⇌ 187)** (which appear to be totally bicyclic at low temperature) indicates that a temperature-dependent process is operating. The observation of variations of ratios with temperature means that comparisons between values

measured at different temperatures should be treated with caution. Interconversion of carbamate-protected amines was considerably slower (possibly because of the reduced nucleophilicity of the nitrogen) and as a result these ratios could be measured at room temperature.

The heavy preference for the bicycle **(190)** at -30°C corresponds closely with the 98:2 ratio measured for physoperuvine itself, both at ambient temperature[90a] and at reduced temperature[98] (chapter 4). The similar preference for the bicyclic tautomer measured for the nor-system **(176 ⇌ 177)** is also in agreement with the ratios measured in the lower homologues *i.e* norphysoperuvine[98] and calystegines.[92] The N-benzyl derivative differed somewhat showing a preference for the monocyclic tautomer **(178)** but, in accord with **(176 ⇌ 177)**, a decrease in temperature increased the proportion of bicycle **(179)**.

The introduction of a $C_{7,8}$-double bond into the N-benzyl derivative to give the dehydro-analogue **(183 ⇌ 184)** resulted in a minor perturbation towards the bicyclic tautomer **(185)**. This effect was exaggerated in the analogous carbamates with saturation favouring the monocyclic tautomer **(133)** and unsaturation favouring the bicyclic tautomer **(152)** at room temperature. In contrast, N-methyl derivatives were both effectively bicyclic, with or without a π-bond. The inclusion of an *exo*-epoxide group into the C_7,C_8 bridge has a marked effect on the position of equilibrium with the carbamate, N-methyl and nor- derivatives existing as the bicyclic tautomer only. The stereochemistry of this epoxide has a marked effect on tautomer preferences, with the *trans*-epoxide **(256)** existing in the anomolous monocyclic form only.

It is evident from these ratios that the position of equilibrium is dependent on both the nitrogen substituent and the substituents in the 2-carbon bridge. The incorporation of a double bond would be expected to stabilise the monocyclic tautomer considerably because of resonance in the α,β-unsaturated ketone group. As a consequence it might be anticipated that an equilibrium shift towards the α,β-unsaturated monocyclic tautomers would be observed. In fact there is only a marginal shift for the N-benzyl derivative **(183 ⇌ 184)** and the shift is actually

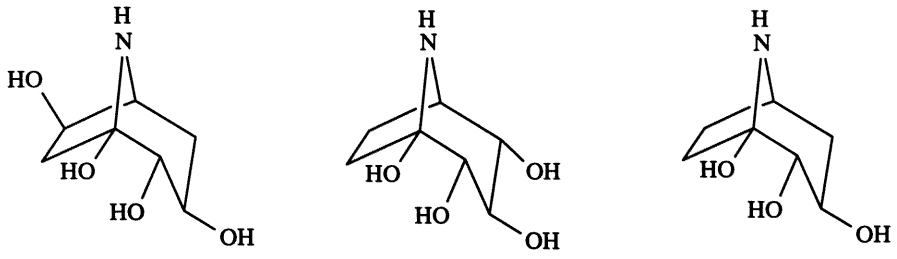
reversed for the carbamate (**133** ⇌ **134**) with the saturation of the double bond decreasing the proportion of monocycle (**151**). A double bond therefore appears to induce some stabilisation into the bicyclic tautomer. There is strong evidence[99] that rigid bicyclic systems such as 7-azabicyclo[2.2.1]hept-2-ene and hepta-2,5-diene derivatives experience a stabilising σ-π^* interaction between the bridging C-N bonds and the π-system, and such an effect would conveniently rationalise the observed change in ratio. However, this effect seems to be absent in larger, more flexible ring systems; ^{15}N NMR studies[99] have shown that the interaction is heavily attenuated in trop-6-enes and plays no detectable part in the homotrop-7-ene ring system. The influence of temperature on the position of equilibrium is a further factor. The increase in the proportion of monocyclic tautomer with an increase in temperature is to be expected in view of the increased entropy which results from the formation of the monocyclic over the bicyclic tautomer. The overall balance of factors influencing the relative stability of the two tautomers is clearly complex and cannot easily be discerned. A similar somewhat irrational pattern is also observed in the lower homologues, tropan-1-ols, discussed in the next chapter.

CHAPTER 4

8-Azabicyclo[3.2.1]octan-1-ols; Synthesis of Physoperuvine, Norphysoperuvine & Dehydro-derivatives

4.1 INTRODUCTION

Of the numerous alkaloids based on the tropane and nortropane skeleta, only physoperuvine (**171**) and the calystegines (**198 - 200**) have a hydroxy group at the C_1 position, thereby having the potential to exist in an equilibrium between monocyclic amino-ketone and bicyclic hemiaminal forms. The three calystegines[92] B_1, B_2 and A_3 (figure 4.1) which have been isolated recently are dissimilar to physoperuvine as they exist as the bicyclic tautomers only.[92] No explanation for this observation was offered by Lallemand,[92] other than the presence of substituents favouring a shift towards the bicyclic tautomer.



B_1 (**198**) B_2 (**199**) A_3 (**200**)

Figure 4.1

Physoperuvine has been prepared only twice, with the pivotal step in both cases based on diazomethane ring expansion of 4-amino cyclohexanone derivatives. As part of a study concerned with the structural assignment of physoperuvine, Pinder[89] reported the first synthesis in 1982 (figure 4.2). 4-(Methylamino)phenol sulphate (**201**) was catalytically reduced, using the procedure of Heckel and Adams,[100] to the cyclohexanol (**202**) as a mixture of *cis* and *trans* isomers. Oxidation to the amino-ketone (**203**) and subsequent homologation with diazomethane afforded physoperuvine (**170** $\rightleftharpoons$ **171**). Although the final step was high yielding, earlier steps were much less efficient, resulting in an overall yield of less than 10%.

The second synthesis was published by Lallemand[101] in 1992 and was based on

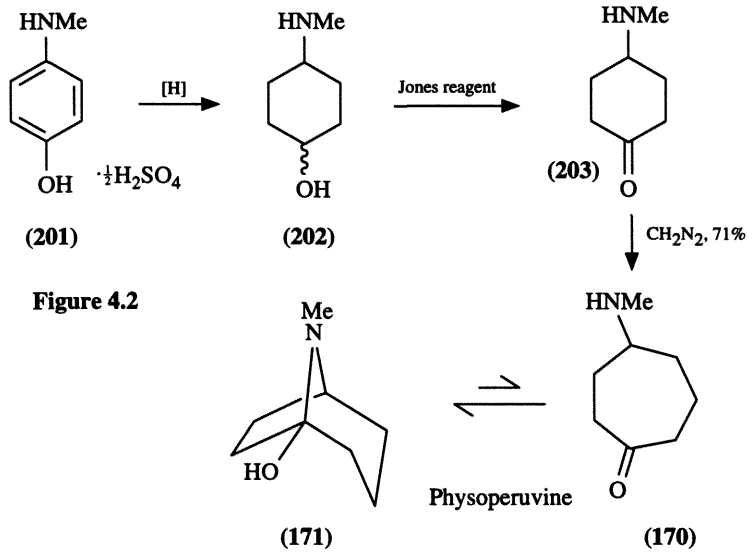


Figure 4.2

a similar ring expansion of a cyclohexanone derivative as outlined in figure 4.3. 4-Aminocyclohexanol hydrochloride (**204**) was sequentially benzylated to (**205**) and then oxidised to the amino-ketone (**206**). Treatment with diazomethane afforded

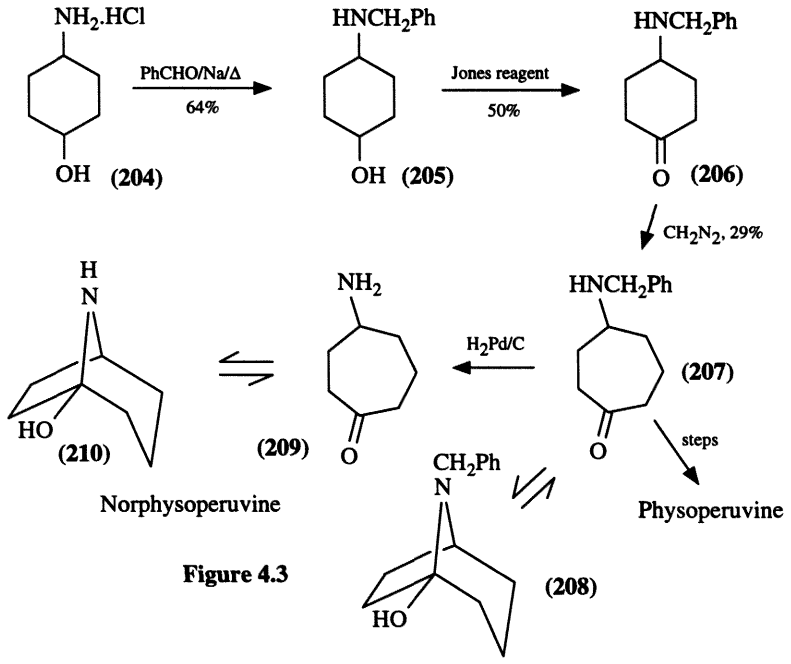


Figure 4.3

4-(benzylamino)cycloheptanone (**207**). Studies were not reported concerning the possible tautomerism of (**207**) with the hemiaminal (**208**). No procedure was detailed for the conversion of (**207**) to physoperuvine, but the overall efficiency could not exceed 10% because of the low yielding oxidation and homologation steps. Alternatively, hydrogenolysis of (**207**) afforded norphysoperuvine (**209** $\rightleftharpoons$ **210**) which was reported to exist as a reversible polymeric structure.

Other investigations into tropan-1-ol and nortropan-1-ol systems have concentrated on the preparation of calystegines. Preliminary investigations were made by Lallemand,[92] who devised an approach to the nortropan-1-ol system, but considerable advancements have been made since. The synthesis[101] of racemic calystegine A_3 is discussed in detail here (figure 4.4). The benzyloxycarbonyl-protected amino-ketone (**211**), prepared using a similar procedure to that outlined in figure 4.3, was the key starting material but an alternative ring enlargement strategy was employed which made accessible α- and β-hydroxylated compounds later in the synthesis. Cyclopropanation of the derived silylenol ether (**212**) and ring opening of the cyclopropane (**213**) furnished the α,β-unsaturated ketone (**214**) in an overall yield of 63% from (**211**). Epoxidation using alkaline hydrogen peroxide gave a 1:1 mixture of epoxides, (**215**) and (**216**), which were separated by HPLC. Two *trans*-diols, (**217**) and (**218**), were then obtained by acid-induced epoxide ring cleavage and the former was hydrogenolysed to give natural calystegine A_3 (**200**) Although this is only a moderate yielding synthesis (because of the formation of two pairs of isomers) it provides a means of preparing the non-natural *trans*-diaxial analogue (**220**). Interestingly, whereas calystegine A_3 existed as the hemiaminal tautomer only, NMR investigations showed the non-natural analogue (**219**) was in equilibrium with the monocyclic tautomer (**220**). The position of this equilibrium was not reported, but the observation points to the fine balance that exists between tautomers.

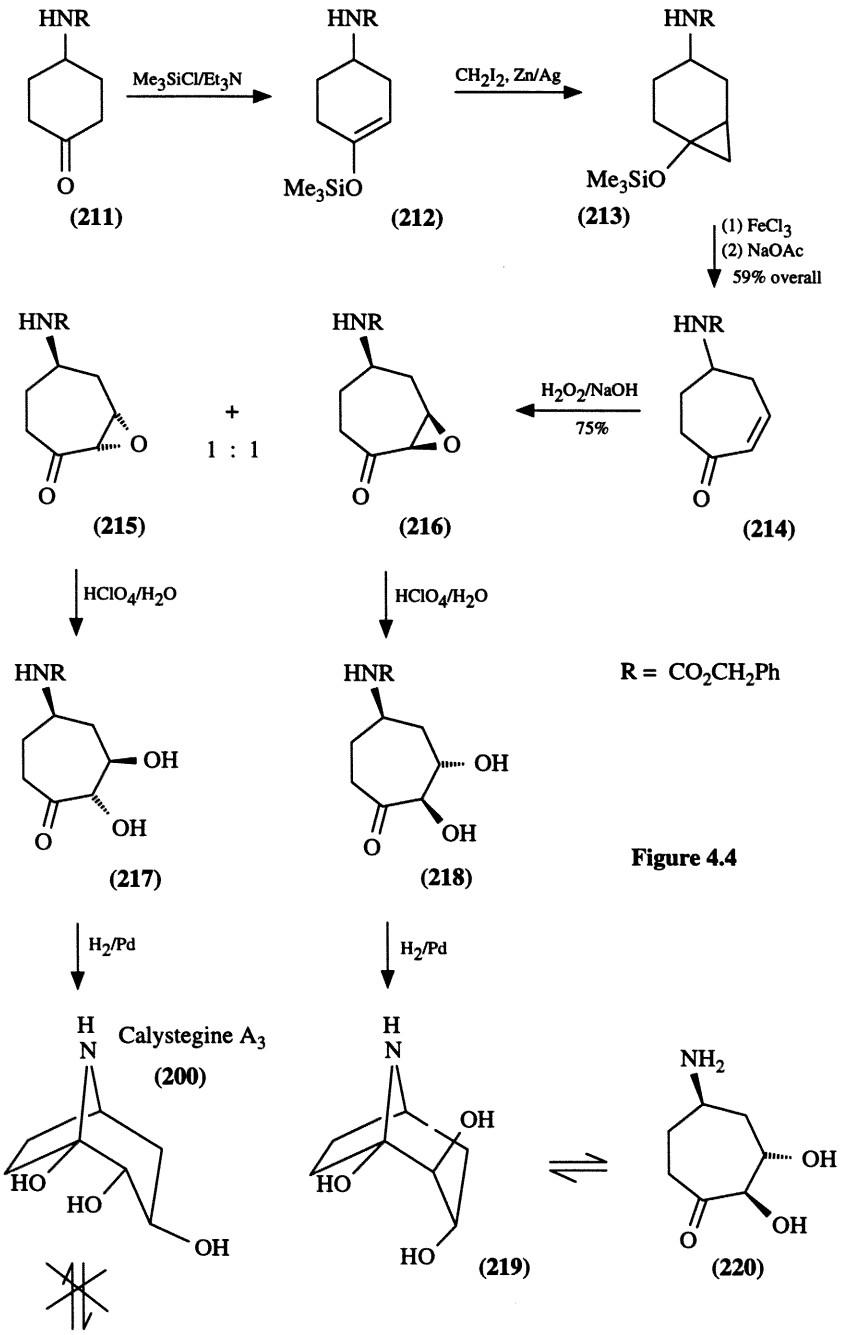

HNR
Me3SiCl/Et3N
CH2I2, Zn/Ag
Me3SiO
(211)
(212)
(213)
(1) FeCl3
(2) NaOAc
59% overall
H2O2/NaOH
75%
+
1 : 1
(215)
(216)
(214)
HClO4/H2O
HClO4/H2O
OH
(217)
(218)
R = CO2CH2Ph
H2/Pd
H2/Pd
Calystegine A3
(200)
NH2
(219)
(220)

Figure 4.4

Further syntheses of calystegines include an elegant method by Lallemand[102] of converting D-glucose into (-)-calystegine B_2 based on the previously described cyclopropanation to homologate a cyclohexanone derivative. Other homochiral syntheses[103] of both natural and non-natural calystegine B_2 have been undertaken, using isoxazoline chemistry, again starting from D-glucose. To date, however, a high yielding preparation of 8-azabicyclooctan-1-ols has not been reported, neither have detailed variable-temperature NMR studies been made of tautomeric equilibria of these systems. This chapter describes an effective synthesis of physoperuvine and simple derivatives thereof. An investigation into the tautomeric preferences is also made.

4.2 SYNTHESIS OF PHYSOPERUVINE AND NORPHYSOPERUVINE

The successful synthesis of homophysoperuvine **(191)** from cycloocta-1,3-diene **(95)** provided the impetus for a parallel synthesis of physoperuvine from cycloheptadiene as outlined in figure 4.5. The key cycloadduct **(221)** was thus made from **(43)** and benzylnitroso formate, with the use of a rigorously purified sample of the nitroso precursor, benzyl-N-hydroxycarbamate, resulting in a near quantitative yield. The spectroscopic properties of **(221)** were identical to those of a sample prepared by a previous route.[35] Reduction with diimide to **(222)**, followed by reductive cleavage of the N-O bond afforded **(223)** in 98% yield; subsequent reduction with lithium aluminium hydride gave the amino-alcohol **(224)**. The ^1H and ^{13}C NMR spectra of these compounds bore a close resemblance to those of the higher homologues. The final step used the Jones procedure (as described previously for homophysoperuvine) which did not use an aqueous work-up and provided physoperuvine **(170 ⇌ 171)** in an overall yield yield of 79% from cyclohepta-1,3-diene.

The oxidation of **(224)** was confirmed by a reduction in relative molecular mass of 2 as shown by mass spectroscopy and the presence of a weak absorption at 1695

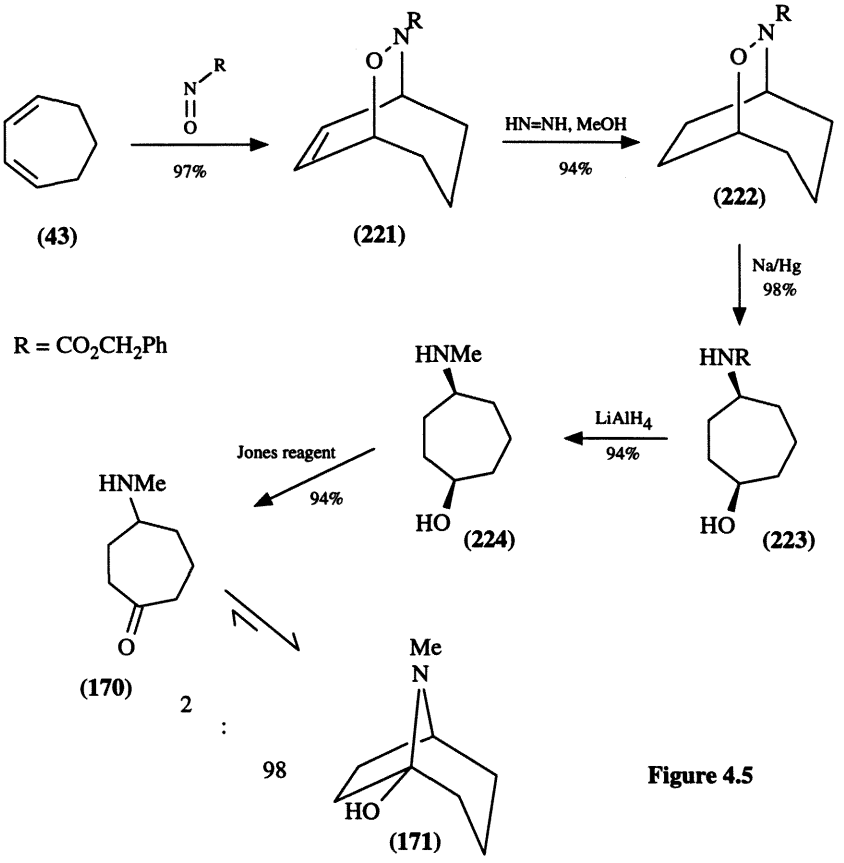


Figure 4.5

cm^{-1} in the IR spectrum, characteristic of a non-conjugated carbonyl stretching frequency. As with previous Jones oxidations the amine moiety was undamaged in this reaction. The specific observation of individual tautomers was not possible using NMR spectroscopy at ambient temperature because of relatively rapid interconversion; neither the ^{1}H nor the ^{13}C NMR spectra were fully analysable being broad and complex. However, the preference for the bicyclic tautomer **(171)** became apparent when the ^{13}C NMR spectrum was recorded at low temperature (figure 4.6). At -50°C, a characteristic quaternary signal appeared at δ 88.8 and was assigned to the (COH) bridgehead. After extended spectral accumulation (6000 scans) minor signals confirmed the presence of a small proportion of the monocyclic tautomer **(170)** but

the carbonyl signal was too weak (or broad) to be observed. A ratio of 2:98 was estimated from integration of the ^{13}C signals, in good agreement with the earlier estimate.[90a]

Norphysoperuvine (**209** ⇌ **210**) was prepared by hydrogenolysis of (**225**) which was prepared, in turn, by Jones oxidation of (**223**) as outlined in figure 4.6. The N-protected derivative (**225**) appeared to be totally monocyclic at ambient temperature as shown by a carbonyl signal at δ 213.7 assigned to the C_1 carbonyl of the monocyclic tautomer and the absence of a charateristic (COH) quaternary carbon signal in the δ 85 - 90 region of the ^{13}C NMR spectrum. The ^1H NMR spectrum was also consistent with only (**225**) showing no evidence of the slow N-CO rotation typical of the bicyclic carbamates. Hydrogenolysis of (**225**) gave norphysoperuvine (**209** ⇌ **210**) in 92% yield (overall yield 79% from cycloheptadiene). The ^1H and

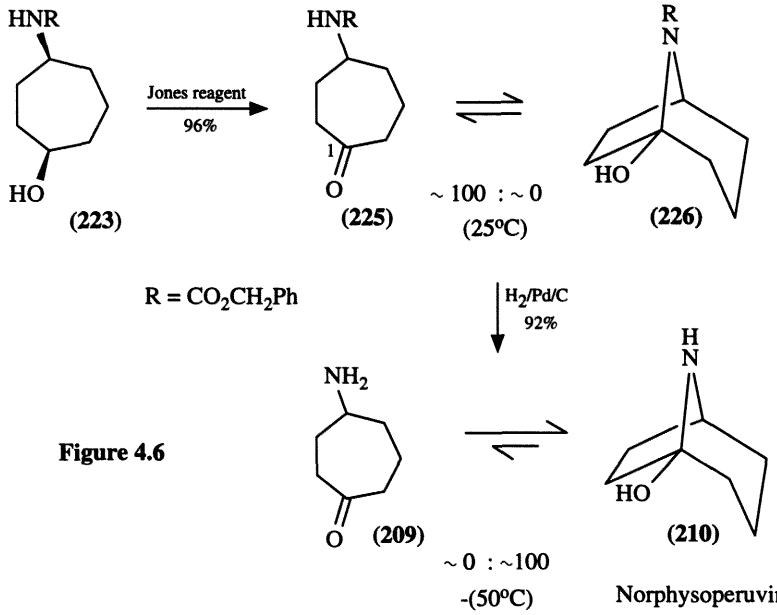


Figure 4.6

^{13}C NMR spectra of (**210**) were very similar to those observed for homophysoperuvine and physoperuvine being broad and unresolved at 25°C. On cooling to -50°C only one tautomer was observed, with a new signal appearing in the

^{13}C NMR spectrum at δ 89.5 assigned to the bicyclic tautomer (**210**). Some precipitation occurred from solution at this temperature so extended scanning to increase the signal to noise ratio was not an option. However, all spectroscopic data pointed to the presence of only one tautomer and the ratio of (**209** ⇌ **210**) was therefore estimated to be ~0 : ~100 respectively. Neither ^{1}H nor ^{13}C NMR spectra suggested any evidence of the polymerisation reported previously.[101]

4.3 DEHYDRO-DERIVATIVES OF PHYSOPERUVINE

A decision was reached to apply the oxidation of allylic alcohols to prepare dehydro-derivatives of physoperuvine. This would provide a comprehensive range of tropan-1-ol derivatives which could be compared with the homologous homotropan-1-ols and may offer some indication of the effect of cycloheptane compared with cyclooctane ring size on tautomer preferences. The benzyloxy-carbonyl-substituted compound (**229** ⇌ **230**) was synthesised by cleaving the N-O bond of the cycloadduct (**221**), with subsequent mild oxidation of the allylic alcohol (**227**) using barium manganate (figure 4.7). The N-methyl analogue (**231** ⇌ **232**) *i.e* 6,7-dehydrophysoperuvine was prepared from the corresponding allylic alcohol (**228**), a product of hydride reduction of (**227**). Oxidation of (**228**) proved more difficult than anticipated; the use of an identical Jones procedure to that described for the higher homologue resulted in the isolation of starting material with a minor quantity of polymeric material, which was probably formed during a final extended Soxhlet extraction. Various other oxidants[81,96,97] were tried but all failed to achieve the desired oxidation. It was postulated that a possible failure of the Jones oxidation was due to the protonation of the amine moiety of (**228**), generating an insoluble salt which precipitated from solution and was thus unreactive. Successful oxidation was finally achieved by modifying the reaction conditions slightly; the use of a more dilute solution acidified with TFA (to produce a soluble salt) prior to the addition of chromic acid afforded (**231** ⇌ **232**) in 40% yield after aqueous work-up.

Unfortunately the product was unstable, decomposing during chromatography, and as a result a pure sample was not obtained.

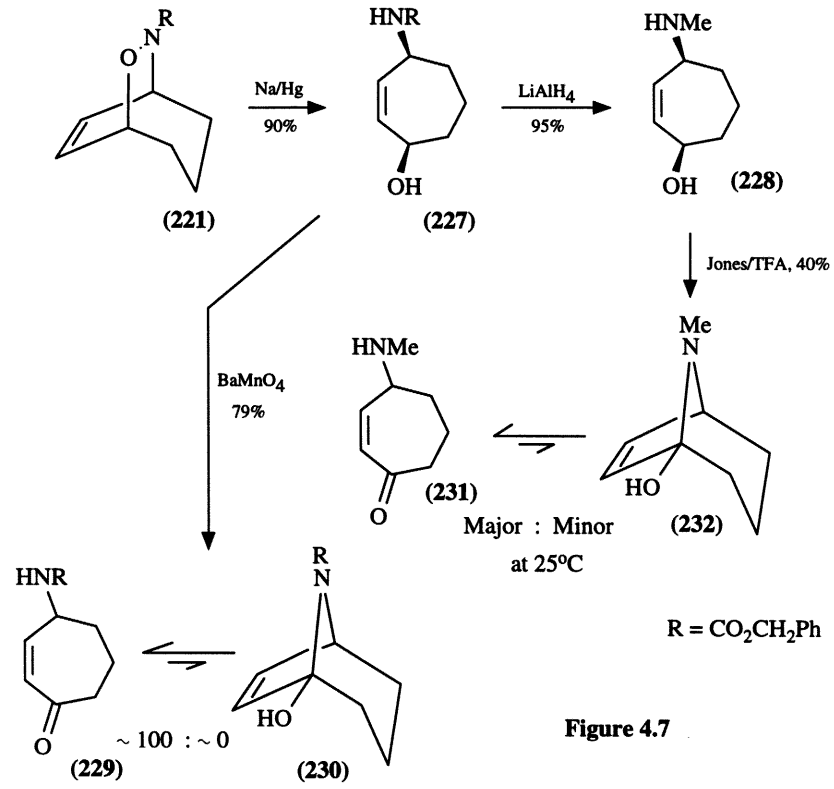


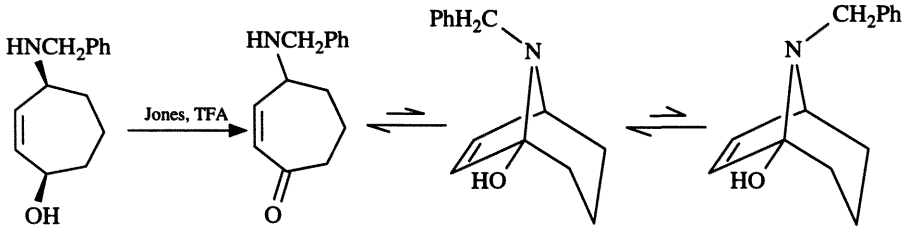
Figure 4.7

The NMR spectra of the carbamate derivative (**229** ⇌ **230**) were consistent with its existence solely as the the monocyclic tautomer (**229**) at 25°C, and the ^{13}C NMR spectrum showed a characteristic carbonyl signal at δ 202.9. The olefinic signals in the ^{1}H NMR spectrum at δ 5.92 and δ 6.34 displayed a mutual vicinal coupling of 12.4 Hz which, after comparison with the ^{1}H NMR spectrum of the homologue (**151**), also confirmed that the monocyclic tautomer was present. Attempts to deprotect (**229**) to give the nor-derivative using acid hydrolysis were unsuccessful.

Detailed NMR studies on 6,7-dehydrophysoperuvine (**231** ⇌ **232**) could not be performed because of its instability and limited availability. However, despite the

presence of minor impurities, the ^{1}H NMR spectrum was very similar to that of the analogous carbamate (**229**) showing a vicinal coupling between olefinic protons of 10.2 Hz. The IR spectrum showed a diagnostic absorption at 1665 cm^{-1} due to the α,β-unsaturated carbonyl and it was thus concluded that the major component at 25°C was the monocyclic tautomer (**231**). Insufficient sample was available for a satisfactory ^{13}C NMR spectrum to be obtained, so a more quantitative estimate could not be made.

The instability of the N-methyl amine restricted the spectroscopic investigations into tautomer preferences considerably. It was decided to synthesise a different N-substituted analogue in the hope of increased stability which might permit a more detailed NMR study. Howarth[87] had previously prepared *cis*-4-(benzylamino)cyclo-hept-2-enol (**56**) and a sample of this was oxidised to (**233** ⇌ **234**), again utilising an initial protonation of the amine moiety with TFA (figure 4.8). Solutions of (**233** ⇌ **234**) did decompose slowly on standing, but the yield of the reaction was better than that obtained for the N-methyl analogue (presumably because of increased solubility in the organic phase during work-up) and as a consequence the amine could be studied by ^{13}C NMR spectroscopy.



(**56**) (**233**) Equatorial (**234a**) Axial (**234b**)

Figure 4.8

The ^{1}H NMR spectrum of the benzyl analogue was similar to (**231**) at 25°C and the signals were consistent with the presence of the monocyclic tautomer (**233**). The olefinic protons were observed at δ 5.97 and δ 6.56 with a mutual vicinal coupling of 12.3 Hz. Double irradiation experiments confirmed the relationship between the

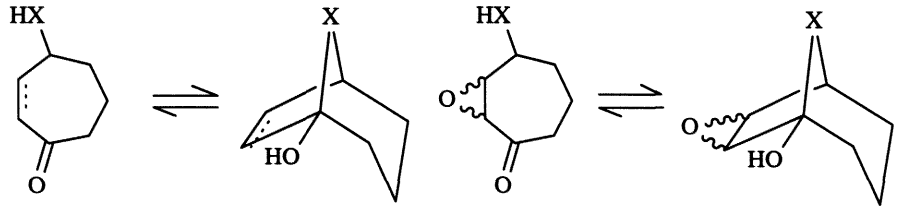
protons on C_2, C_3 and C_4 and a four-bond coupling was observed through the carbonyl group between protons on C_2 and C_7 (J = 1.0 Hz). At ambient temperature, the spectrum indicated that the monocyclic tautomer was the major component, but on closer inspection additional signals could also be discerned; as the sample was known to contain minor impurities it was not possible to assign these to the bicyclic tautomer. However, further signals appeared as the temperature was decreased to -50°C, including a broad carbonyl signal at δ 204.8 assigned to the monocycle (**233**). This behaviour indicated the existence of a tautomeric equilibrium and, although the spectra could not be fully interpreted, strongly suggested a heavy preference for the monocyclic tautomer. The difficulties associated with interpreting the low-temperature NMR spectra of the benzyl derivative may well be due to a second temperature-dependent process, namely inversion at nitrogen. This has already been shown[35] to cause spectral broadening for N-benzyl nortropane and N-benzyl nortrop-6-ene over a similar temperature range, even though both of these compounds show a heavy preference for the equatorial invertomer (**234a**) rather than the axial invertomer (**234b**).

4.4 CONCLUSION

The ratios of monocyclic:bicyclic tautomers observed for both the saturated and unsaturated derivatives are summarised in table 1. Two epoxy-ketones prepared later (chapter 6) in connection with other work, along with 4-benzylaminocycloheptanone (**207** ⇌ **208**) synthesised by Howarth[87] are included for comparison.

Both the saturated (**225** ⇌ **226**) and unsaturated (**229** ⇌ **230**) carbamates existed as the monocyclic tautomers only. This was in contrast to the situation for the homologous homotropan-1-ols, where a mixture of tautomers was present. Also, both *cis*- and *trans*-epoxy-carbamates (**269**) and (**276**) were monocyclic only, whereas the higher homologous showed a variation from being completely bicyclic to completely monocyclic depending on the stereochemistry of the epoxide. It can be concluded

Table 1. Ratios of Monocyclic (M/C) : Bicyclic (B/C) Tautomers



X	Compound	Temp (°C)	M/C : B/C	^{13}C NMR(δ) M/C		B/C	
				C_4	CO	C_1	C_6
Saturated series							
NCO_2CH_2Ph	**(225⇌226)**	25	~100 : ~0	52.7	213.7	-	-
NMe	**(170⇌171)**	-50	2 : 98	-	-	88.8	58.1
NCH_2Ph	**(207⇌208)**	-50	minor : major	-	-	88.9	56.2
NH	**(209⇌210)**	-50	~0 : ~100	-	-	89.5	53.3
Unsaturated series							
NCO_2CH_2Ph	**(229⇌230)**	25	~100 : ~0	51.6	202.9	-	-
NMe	**(231⇌232)**	25	major : minor	-	-	-	-
NCH_2Ph	**(233⇌234)**	-50	major : minor	56.7	204.8	-	-
Epoxide series							
cis-NCO_2CH_2Ph	**(269)**	25	100 : 0	51.2	208.5	-	-
trans-NCO_2CH_2Ph	**(276)**	25	100 : 0	48.8	209.3	-	-

that, for the saturated and unsaturated derivatives at least, an important factor governing tautomeric preferences is ring size *i.e.* the instability of the tropan-1-ol structure relative to homotropan-1-ol.

Both physoperuvine (**170** ⇌ **171**) and norphysoperuvine (**209** ⇌ **210**) bore a close resemblance to their respective higher homologues, showing a marked preference for the bicyclic forms. However, the incorporation of a double bond into physoperuvine to give 6,7-dehydrophysoperuvine (**231** ⇌ **232**) resulted in a shift towards the monocyclic tautomer. This is surprising as the reverse shift was previously seen for the respective higher homologues; it would appear that the apparent decreased stability upon incorporation of a shorter double bond into the already strained tropan-1-ol structure is the overriding effect here. A similar pattern

was observed for the N-benzyl derivatives (**207** ⇌ **208**) and (**233** ⇌ **234**).

Despite the difficulties encountered in measuring the tautomeric ratios of these compounds, some patterns can be discerned between derivatives. The factors controlling preferences are complex and not fully understood. Nonetheless, the syntheses of physoperuvine and norphysoperuvine were efficient. Further work on dehydro-derivatives was of limited value because of their instability.

CHAPTER 5

Stereoselective Oxygenation of Homotropane

5.1 INTRODUCTION

The synthesis of homotropane, norhomotropane and some C_1-substituted derivatives has been described, with the previous difficulties of removing N-protecting groups having been overcome by the use of N-alkoxycarbonyl groups. Oxygenation at the C_2-position of homotropane was achieved by Cope,[51] who described the ring expansion of tropinone, and by Hobson[54] who solvolysed 2-chlorohomotropanes. Other derivatives are rare and C_7,C_8 oxygenation is unknown. Methods of preparing unsaturated derivatives are known,[58] but these have not been extended to the synthesis of oxygenated derivatives. The scarcity of these compounds is suprising in view of the potent activity of anatoxin-a and the well established physiological properties of oxygenated tropanes.[1,2] With this in mind an investigation of the functionalisation of the 2-carbon bridge was considered a priority. The stereoselective introduction of both hydroxy and epoxide groups is of key importance in approaches to a range of novel homologues that may possess similar physiological properties to tropane alkaloids.

5.2 SYNTHESIS OF *EXO*-7,8-EPOXYHOMOTROPANE

So far, a strategy to systems bearing bridgehead substituents has been developed; both 1-methyl (**165**) and 1-hydroxy (**194**) derivatives of the N-protected 7,8-epoxyhomotropane ring system have been synthesised from the respective 1-substituted alkenes, with exclusive *exo*-stereoselectivity in each case (figure 5.1).

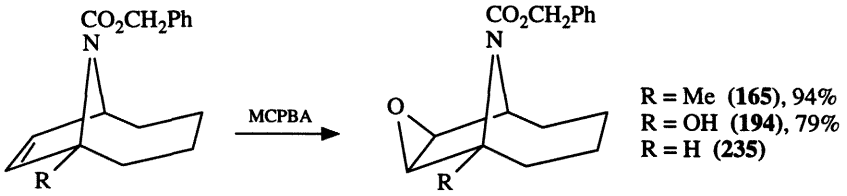


Figure 5.1

An obvious approach to the *exo*-epoxyhomotropane (**235**) was therefore epoxidation of the homotrop-7-ene without a bridgehead substituent. This strategy was also attractive since it allowed the straightforward deprotection of (**194**) at the conclusion of the synthesis without reduction of the epoxide group.

A modification of the previously described intramolecular displacement approach to homotropane[58] was employed to prepare the alkene (**238**). Although secondary amines have proved superior to carbamate groups in such cyclisations, an N-protected derivative was necessary to facilitate a successful epoxidation reaction, in view of the difficulties encountered by Fodor[84] whose reported epoxidation of an unsaturated amine does not proceed efficiently. Figure 5.2 outlines the approach to (**238**) starting from the known intermediate (**150**).

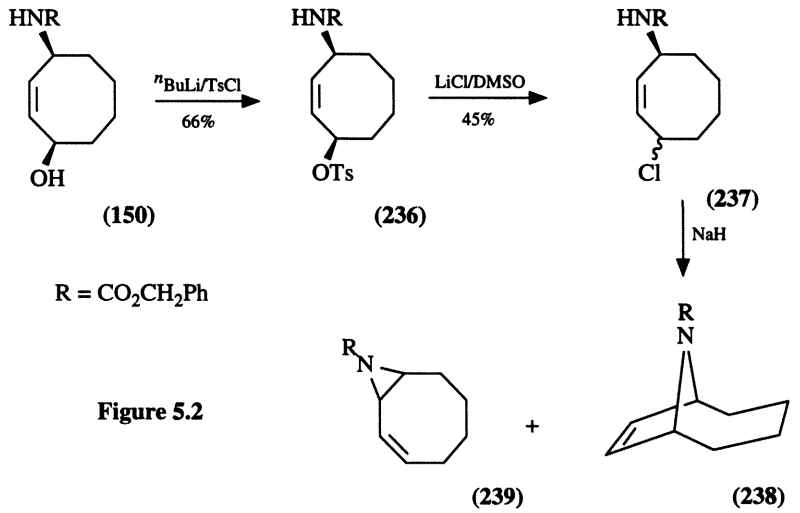


Figure 5.2

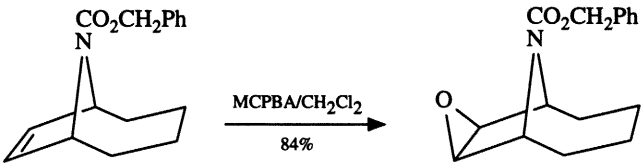
THF/Reflux :	10%	:	28%
THF/DME/60°C :	3%	:	40%

It was hoped that tosylation of the 4-hydroxy group and subsequent displacement with chloride ion would provide the required *trans*-1,4 stereoelectronic arrangement for cyclisation. Difficulties were encountered with these transformations, firstly because the tosylate (**236**) was unstable and could only be prepared in modest yield. Secondly, chlorination of (**236**) using lithium chloride in

DMSO solvent[104] resulted in epimerisation at the 4-position with the chloride **(237)** being isolated as an inseparable mixture of stereoisomers in a 7:3 *trans*:*cis* ratio (calculated from ^{1}H NMR signal integrations), again in a somewhat disappointing yield. Attempts to invert the hydroxy group of **(150)** to a chloride by other methods (such as Smith's[58] use of thionyl chloride or triphenylphosphine in carbon tetrachloride[105]) failed giving complex reaction mixtures. Nevertheless, base-induced cyclisation of **(237)** was achieved by refluxing with sodium hydride in THF solvent giving the homotrop-7-ene **(238)** in 28% yield together with a smaller quantity of aziridine by-product **(239)**, formed by a competitive 1,2-cyclisation. Examination of the ^{1}H NMR spectrum of the crude reaction product showed that benzyl alcohol was also formed as a result of deprotection of the benzyloxycarbonyl moiety. Milder conditions were therefore used: heating **(237)** at 60°C (rather than refluxing) in THF/DME solvent increased the yield of **(238)** to 40% and also suppressed the formation of aziridine. The NMR spectra of **(238)** were simplified somewhat because of the associated symmetry but, typical of bridged bicyclic carbamates, displayed duplication of signals as a result of slow N-CO rotation. The ^{1}H NMR spectrum showed two signals at δ 5.72 and δ 5.75 for the olefinic protons with mutual coupling of 6.8 Hz. Each proton showed further coupling (J = 2.3 Hz) to the bridgehead protons. These values were similar to those observed for the C_1-methyl analogue **(165)** prepared previously (chapter 2.5). The ^{1}H NMR spectrum of **(239)** displayed characteristic aziridine protons at δ 2.63 and δ 3.07 with a mutual coupling of 6.3 Hz. The ^{13}C NMR spectrum showed two (CH) aziridine signals at δ 40.0 and δ 44.4 which fits well with values of δ 42.4 and δ 47.6 for the analogous aziridine **(58)**, a by-product of a similar cyclisation in the tropane series.[35]

Epoxidation of **(238)** using MCPBA afforded the anticipated *exo*-epoxide **(235)** in high yield (figure 5.3). As a result of slow N-CO rotation, the ^{1}H NMR spectrum of **(235)** included two doublets at δ 3.36 (J = 3.0 Hz) and δ 3.37 (J = 3.0 Hz) for the epoxide protons and two further doublets at δ 4.35 (J = 6.2 Hz) and δ 4.41 (J = 6.2 Hz) for the bridgehead protons. The observation that the epoxide and the bridgehead

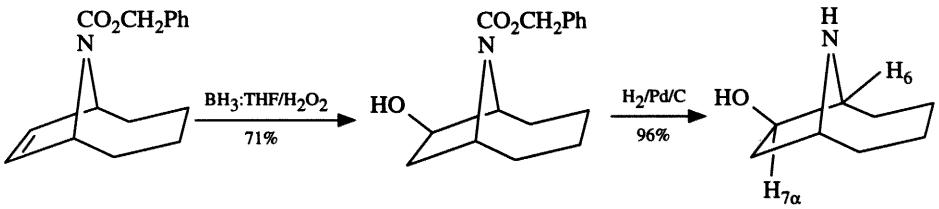
protons were not vicinally coupled fits well with observations for the C_1-methyl **(165)** and C_1-hydroxy **(194)** analogues and confirms the stereochemistry of the epoxide.



(238) **(235)**

Figure 5.3

The investigation of facial selectivity using reagents other than MCPBA was of interest. Earlier studies have shown that hydroboration-oxidation of norbornene afforded the *exo*-alcohol as the sole product[106] and, with this in mind, it was decided to use borane chemistry as a means of introducing an *exo*-hydroxy group into the homotropane skeleton. Using the procedure of Wilt and Narutis,[107] **(238)** was treated with 0.6 equivalents of a borane:THF complex which resulted in a good yield of the *exo*-alcohol **(239)** as the only product. Hydrogenolysis with palladium on charcoal catalyst afforded norhomotropan-7β-ol **(240)** in near quantitative yield (figure 5.4).



(238) **(240)** **(241)**

Figure 5.4

The incorporation of H_2O during the hydroboration-oxidation step was confirmed by an increment in relative molecular mass of 18. The ^1H NMR spectrum of **(240)** displayed the absence of olefinic signals and the appearance of a broad exchangeable signal at δ 2.89. Both the ^1H and ^{13}C NMR spectra were complex because of restricted rotation about the N-CO bond. However, these spectra were greatly simplified after hydrogenolysis; the ^1H NMR spectrum of **(241)** now showed a

doublet of doublets at δ 4.12 (J = 6.2, 2.8 Hz) corresponding to the α-hydroxy proton H_7. These two couplings were to protons on C_8 and no vicinal coupling between the H_7 proton and the H_6-bridgehead proton was observed. The absence of measurable coupling between H_7 and H_6 was also noted for the H_7 and H_6 protons of the *exo*-epoxide **(235)** which strengthens the assignment of β-hydroxy stereochemistry. The structure of **(241)** was further endorsed after comparison of ^1H NMR coupling constants with those measured for ring-opened *exo*- and *endo*-epoxyhomotropanes described later (section 4).

Although a strategy for the synthesis of N-protected *exo*-epoxyhomotropane **(235)** and norhomotropan-7β-ol **(241)** has been described, the efficiency was low owing principally to the presence of a double bond during the inversion of **(236)** and cyclisation of **(237)**. A more attractive approach would therefore be to introduce the epoxide group at an earlier stage of the synthesis which would prevent the formation of rearrangement and decomposition products, and should significantly improve the overall yield. Such a method was discovered fortuitously in an attempt to open the epoxide **(194)** to the alcohol **(242)**, as outlined in figure 5.5. It has been shown

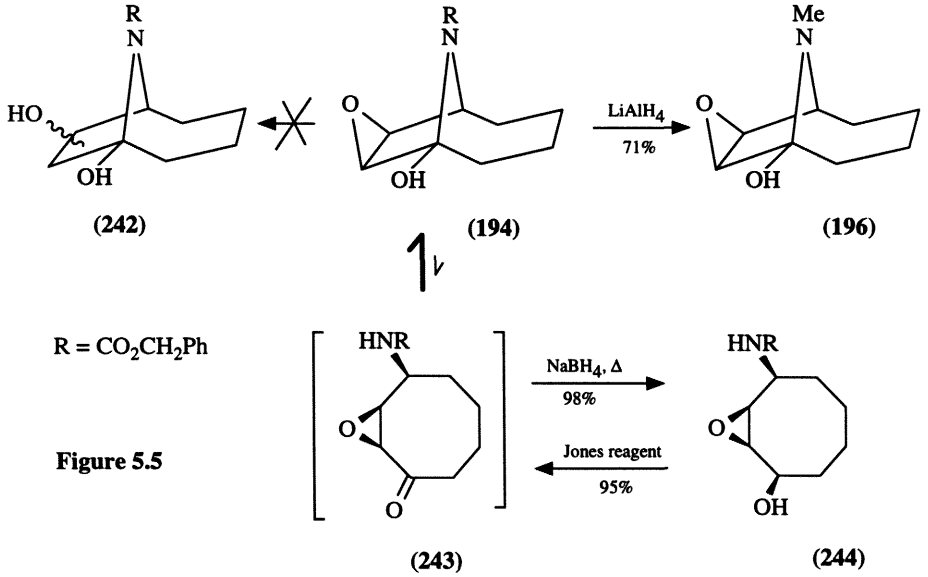


Figure 5.5

previously that the epoxide **(194)** was remarkably stable and could be reduced with lithium aluminium hydride to **(196)**, with neither **(194)** nor **(196)** showing any evidence of the presence of their respective monocyclic epoxy-ketones at room temperature. Various methods were employed in attempts to ring open the epoxide **(194)**; simple acid or base hydrolysis failed, giving mixtures of starting materials and deprotected products only. Numerous reductive ring opening methods have been reported in the literature.[108] Brown[109] used lithium metal in ethylenediamine to reduce norbornene oxide to norbornanols whilst Vankar[110] reduced epoxides with a combination of zinc and trimethlysilylchloride, but the application of both of these methods to **(194)** resulted in the isolation of starting material only. Soai[111] used sodium borohydride in mixed alcohol solvents and this method was also applied to **(194)**; the product was not the expected alcohol **(242)** but, suprisingly, the epoxy-alcohol **(244)** isolated as a single stereoisomer.

It would appear that at reflux a small stationary concentration of the monocyclic tautomer **(242)** was present which provided a means for the total reduction of **(194)**, with hydride attacking from the least sterically hindered face of the ketone. At first sight this reaction is unusual but becomes less so when it is realised that the ketone carbonyl is reactive towards borohydride but the carbamate carbonyl is not and that for all measurable tautomeric equilibria of homotropan-1-ols, the proportion of monocyclic tautomer increases with an increase in temperature. Although there was no spectral evidence for the presence of **(243)** at room temperature, it is not unreasonable to expect a small proportion of epoxy-ketone at elevated temperature and hence a conversion into **(244)**. This raises the question as to why the N-methyl epoxide **(196)** was not similarly reduced, as this had withstood hydride in refluxing THF. In this case lithium aluminium hydride had been used which reacted more rapidly with the carbamate moiety of **(194)** than with the small amount of **(243)**. The resulting amine **(196)** presumably existed completely in the bicyclic form even at 67°C, and was therefore resistant to attack by hydride.

The reduction of **(243)** to **(244)** was reversible: the alcohol could be oxidised

back to **(243)** using Jones reagent, which confirmed the structure as an epoxy-ketone. The *cis*-1,4 stereochemistry of **(244)** was elucidated from the ^1H NMR spectrum which showed a doublet of doublets at δ 2.91 (J = 4.5, 3.6 Hz) and a triplet at δ 3.11 (J = approximately 4.8 Hz) for the epoxide protons. The larger coupling of 4.5 Hz corresponds to a vicinal coupling between these protons, leaving two similar couplings of 3.6 Hz and approximately 4.8 Hz to the α-nitrogen and α-hydroxy protons. Had a *trans*-1,4 relationship existed, two significantly different values would have been observed and such an effect will be seen later for *trans*-1,4 systems. The conversion of **(244)** into the *exo*-epoxide **(235)** is outlined in figure 5.6.

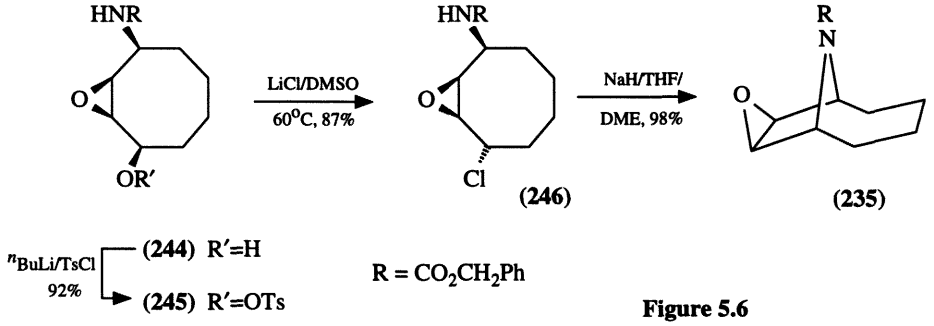
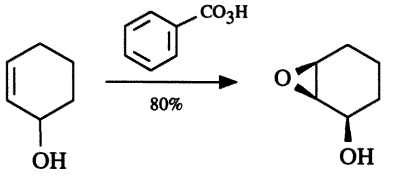


Figure 5.6

The alcohol **(244)** was tosylated to **(245)** in 92% yield and then converted into the chloride **(246)**, as a single stereoisomer as shown by NMR spectroscopy. The ^1H NMR spectrum of **(246)** showed the epoxide protons as a doublet of doublets at δ 3.14 and a triplet at δ 3.37, with a mutual vicinal coupling of 4.3 Hz. A coupling of approximately 4.8 Hz was seen between the epoxide and α-nitrogen protons, but the corresponding coupling to the α-chloride proton was much larger (J = 8.9 Hz), confirming the 1,4-*trans* stereochemistry. Cyclisation of **(246)** into **(235)** was achieved in near quantitative yield using sodium hydride as base and the product had identical spectroscopic properties to a sample prepared by oxidation of the alkene **(238)**.

5.3 SYNTHESIS OF *ENDO*-6,7-EPOXYHOMOTROPANE

In 1957 Henbest[112] reported that epoxidation of cyclohex-2-enol (**247**) with peroxybenzoic acid afforded the *cis*-epoxide (**248**) selectively (figure 5.7). The directing effect of the hydroxy group has been developed into a highly efficient method of constructing versatile intermediates in organic synthesis.



(247) (248)

Figure 5.7

Henbest attributed this steering effect to hydrogen-bonding between the hydroxy group and O(2) of the peroxyacid (figure 5.8.A). Whitham[113] investigated the syn-stereodirecting effect in more detail, studying the preferred transition state geometry of the process. Finally, Sharpless[114] proposed that the hydroxy group is co-ordinated to O(1) of the peroxyacid whose remaining lone pair then became favourably aligned with the π-system of the double bond (figure 5.8.B). Kočovsky[85] reported a similar pronounced syn-stereodirecting effect for allylic carbamate groups.

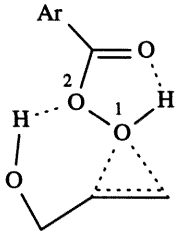


Figure 5.8A

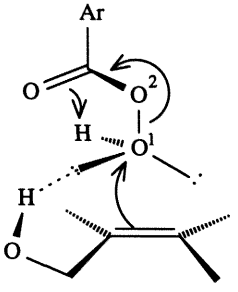
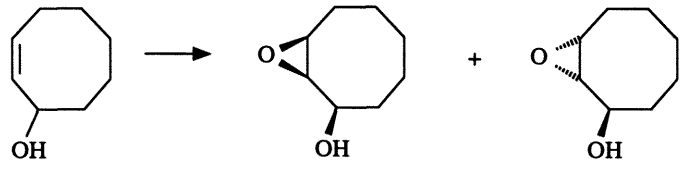


Figure 5.8B

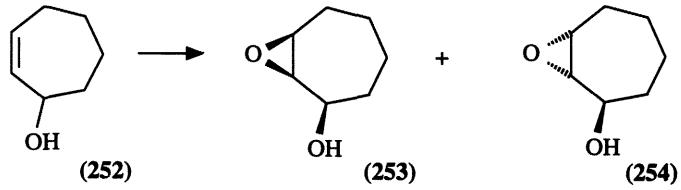
An anomolous result was obtained by Cope in medium ring allylic alcohols. The stereoselectivity of peroxyacid epoxidation of cyclooct-2-enol (**249**) was reversed

giving the *trans*-epoxide **(251)** only,[115] and cyclohept-2-enol **(252)** gave a mixture of *cis*- and *trans*-epoxides[116] **(253)** and **(254)** respectively. These observations were rationalised by Teranishi[117] after extensive epoxidation studies of five- to nine-membered ring allylic alcohols with both MCPBA and transition metal-catalysed peroxyacids. Interestingly, the use of vanadium-catalysed epoxidation afforded the *cis*-epoxides **(250)** and **(253)** with very high syn-stereoselectivity (figure 5.9).



(249) **(250)** **(251)**

Monoperoxyphthalic acid :	<1	:	>99	(81%)
$VO(acac)_2$/^{t}BuOOH:	97	:	3	(83%)



(252) **(253)** **(254)**

Monoperoxyphthalic acid :	66	:	34	(95%)
$VO(acac)_2$/^{t}BuOOH:	>99	:	<1	(87%)

Figure 5.9

It was therefore anticipated that the known allylic alcohol **(150)** would undergo peroxyacid epoxidation with high anti-stereoselectivity, thus providing an intermediate which could be converted to the *endo*-epoxyhomotropane **(259)**. Reaction of **(150)** with 1.2 equivalents of MCPBA did indeed furnish the *trans*-epoxide **(255)** in 95% yield as a single stereoisomer (figure 5.10). The ^{1}H NMR spectrum of **(255)** was similar to that of the *cis*-epoxide **(244)** prepared previously and showed a similar mutual vicinal coupling of 4.7 Hz between epoxide protons. However, two larger couplings of 8.2 Hz and 9.3 Hz to α-nitrogen and α-hydroxy protons were observed, compared to respective values of 3.6 Hz and approximately

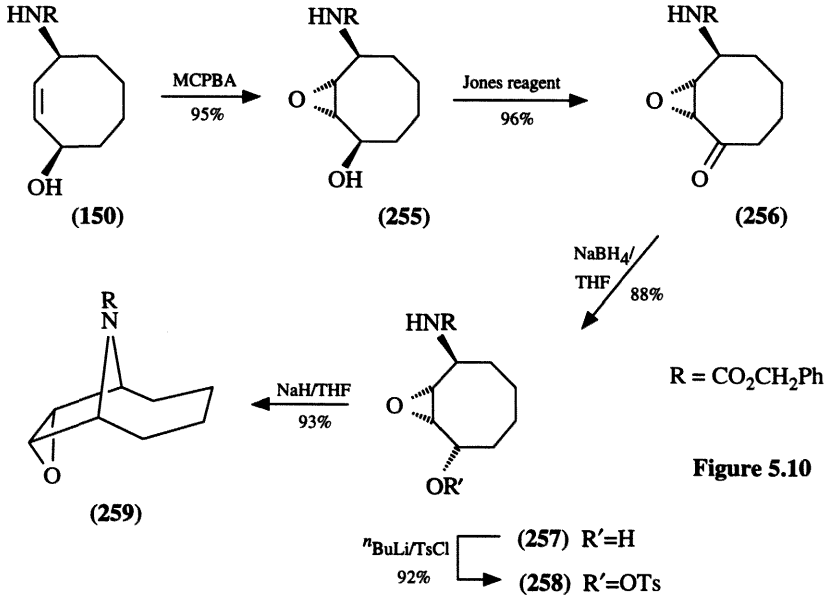


Figure 5.10

4.8 Hz for (**244**), confirming the *trans*-relationship of the epoxide and α-substituents. The crude ^{1}H NMR spectrum showed no signals that might correspond to the *cis*-epoxide.

The hydroxy substituent of (**255**) was inverted to give the *trans*-1,4 isomer firstly by oxidation with Jones reagent to (**256**). All spectroscopic data pointed to the epoxy-ketone existing as the monocyclic tautomer only at room temperature with, for example, a characteristic carbonyl signal at δ 206.2 in the ^{13}C NMR spectrum. This is in sharp contrast to the epoxy-ketone (**194**) with the opposite epoxide stereochemistry, which was discovered previously to exist as the bicyclic tautomer only. Reduction of (**256**) with sodium borohydride then afforded the epimeric alcohol (**257**) as a single stereoisomer. The remaining two steps were straightforward; tosylation of (**257**) gave (**258**) which cyclised with base to give the *endo*-epoxyhomotropane (**259**) in excellent yield. The ^{1}H NMR spectrum of (**259**) differed from that of the *exo*-epoxide (**235**) with the chemical shift of the epoxide protons appearing 0.53 ppm further downfield and a coupling of 3.6 Hz between epoxide and bridgehead protons.

5.4 REDUCTION OF N-PROTECTED EPOXYHOMOTROPANES

The final steps necessary to prepare the parent 6,7-epoxy-homotropane and norhomotropane skeleta were hydride reduction and hydrogenolysis respectively. The epoxide group of the 1-hydroxy derivative (**194**) withstood these reaction conditions and it was hoped that similar chemoselectivity could be achieved for the *exo*-epoxide (**235**). Reduction of (**235**) with lithium aluminium hydride in THF afforded the N-methyl epoxide (**260**) and hydrogenolysis using a palladium catalyst gave the corresponding norhomotropane (**261**), with the epoxide surviving both reductions as anticipated (figure 5.11). The N-methyl amine was stored as the hydrochloride salt although the NMR spectra were recorded on the free amine.

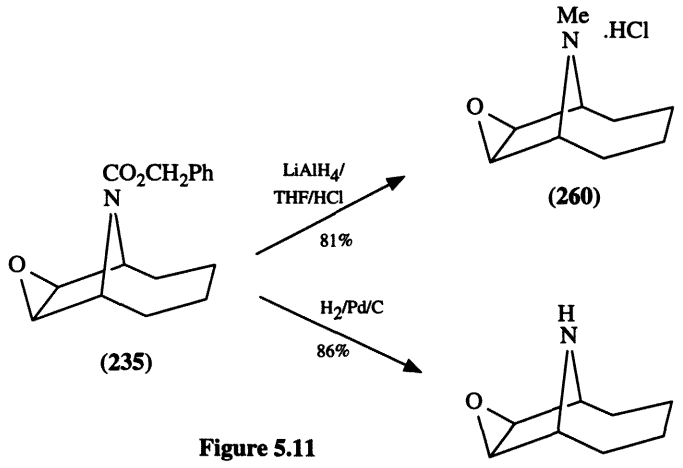


Figure 5.11

(261)

Reduction of the N-alkoxycarbonyl group simplified the NMR spectra and the two amines were easily identifiable. The ^{1}H spectrum of (**260**) showed a singlet at δ 2.55 for the newly formed methyl group and a second singlet at δ 3.43 for the two equivalent epoxide protons. Five signals were observed in the ^{13}C spectrum including a methyl carbon signal at δ 46.5. The spectra of (**261**) were similar, again showing no coupling between the epoxide and the bridgehead protons in the ^{1}H NMR spectrum.

The *endo*-epoxide (**259**) was also subjected to hydride and hydrogenolysis reductions, but in contrast to (**235**) the epoxide moiety was considerably more reactive being reduced to give homotropan-7α-ol (**262**) and norhomotropan-7α-ol (**263**) under normal conditions. However, the N-methyl epoxide (**264**) could be isolated if milder reducing conditions were employed (figure 5.12), although the product was contaminated with 10% of the alcohol (**262**).

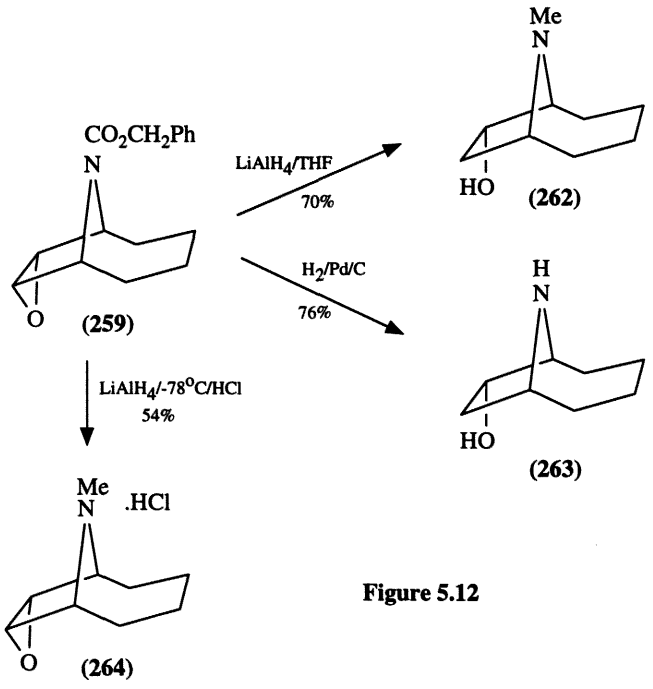


Figure 5.12

The ^{1}H NMR spectrum of (**262**) displayed a doublet of triplets at δ 4.55 for the α-hydroxy proton, due to vicinal coupling to both C_8 protons (J = 10.5, 6.4 Hz) and the C_6-bridgehead proton (J = 6.4 Hz). The ^{13}C NMR spectrum showed methyl and methine (CHOH) carbon signals at δ 39.2 and δ 71.7 respectively. The epoxide protons of (**264**) were coupled to the bridgehead protons (J = 3.2 Hz) in the ^{1}H NMR spectrum confirming the *endo*- (rather than *exo*-) stereochemistry of the epoxide. A parallel reactivity difference between homologous *exo*- and *endo*-epoxytropanes is noted in the next chapter and a discussion of their relative reactivities will follow

later.

5.5 CONCLUSION

In section 5.2 it was demonstrated that *exo*-epoxidation of a protected homotrop-7-ene (**238**) proceeded in good yield with high stereoselectivity, in accord with the behaviour of bridgehead functionalised analogues. However, the difficulties encountered in the synthesis of precursors limited the practical application of this approach, although preliminary investigation into the facial selectivity of the double bond was very promising. The potential to prepare dihydroxylated derivatives of homotropane using osmium chemistry[118] is a possibility here.

A more efficient approach was then developed which allowed the introduction of the epoxide function at an earlier stage of the synthesis, providing the *exo*-homotropane (**235**) *via* a serendipitous hydride reduction. The reversal of stereoselectivity for cyclooct-2-enols from syn- to anti- was used to full advantage to prepare the *endo*-epoxyhomotropane (**259**). After simple reductions, a full range of novel oxygenated homotropane derivatives was then isolated which are believed to be the first such derivatives to be reported.

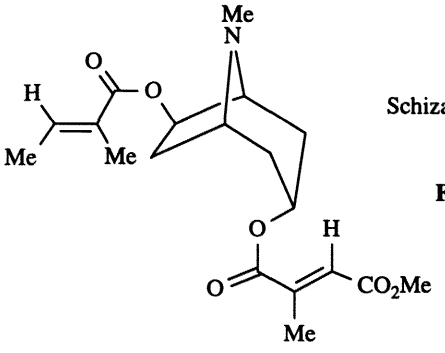
It was concluded that the success of this strategy, which uses cheap and commercially available reagents for all transformations, could easily be adapted to the tropane series and may ultimately lead to successful synthesis of tropane natural products.

CHAPTER 6

Stereoselective Oxygenation of Tropane

6.1 INTRODUCTION

Tropane derivatives having epoxy and hydroxy groups in the 2-carbon bridge are of considerable natural importance.[1,2] Alkaloids such as scopolamine (based on the *exo*-6,7-epoxytropane structure), bao gong teng **(8)** and the calystegines **(198 - 200)** all possess C_6-oxygenation and have been discussed previously. A further example is provided by the schizanthine class of tropane alkaloid which are all diester derivatives of 3α,6β-dihydroxytropane. These compounds were isolated in 1987 from *Schizanthus grahmii*[119] *and Schizanthus pinnatus.*[120] There are ten such alkaloids in total and Schizanthine F **(265)** is illustrated here (figure 6.1).



Schizanthine F **(265)**

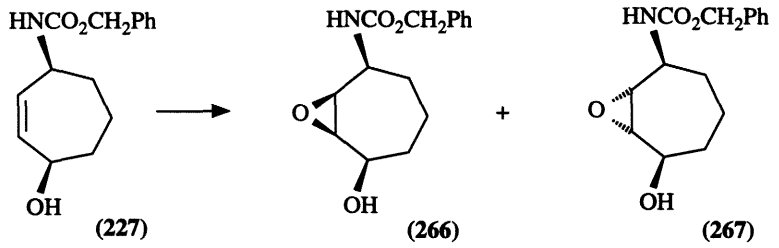
Figure 6.1

In view of the wealth of natural products containing C_6,C_7 functionality the application to tropanes of the epoxidation strategy already developed for homotropanes (chapter 5) was considered to be a worthwhile investigation.

6.2 SYNTHESIS OF *EXO*-6,7-EPOXYTROPANE

The method of choice for preparing *exo*- and *endo*-epoxyhomotropanes involved epoxidation of a monocyclic alkene prior to cyclisation to the homotropane, rather than epoxidation of an N-protected homotrop-7-ene. The key precursor for this synthesis is therefore the previously prepared allylic alcohol **(227)**. Cope had

reported that epoxidation of cyclooct-2-enol with peroxyacid proceeded with high anti-stereoselectivity,[115] whereas treatment of cyclohept-2-enol under similar conditions afforded a mixture of *cis*- and *trans*- epoxides.[116] A similar outcome was expected for the cyclohept-2-enol derivative (**227**) and this was indeed the case; treatment with 1.2 equivalents of MCPBA gave (**266**) and (**267**) in a respective ratio of 62:38. At this stage it was realised that if an approach to *exo*- and *endo*-epoxytropanes was to be developed, the overall efficiency of the two syntheses could be increased by varying the ratio of isomers isolated from the epoxidation reaction. Reagents other than MCPBA were therefore explored and the results are summarised in figure 6.2. All yields quoted are isolated pure yields and the ratios are calculated from ^{1}H NMR integrations of crude reaction mixtures.



(**227**) (**266**) (**267**)

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%

Figure 6.2

Magnesium monoperphthalate[121] (MMPP), a recently developed peroxygen product, was the first alternative reagent to MCPBA chosen. Using a literature protocol[122] (**225**) was epoxidised in a hydroxylic solvent (necessary to dissolve the reagent) and a slight shift towards the *trans*-epoxide (**267**), compared to MCPBA, resulted. A vanadium-catalysed peroxyacid procedure[117] was also used to epoxidise (**227**) and, in good agreement with literature precedent,[117] a high syn-stereoselectivity

was observed but unfortunately the yield was disappointing. The high yielding MCPBA epoxidation, along with the easy separation of the two epoxides by chromatography meant that this was the most efficient means of obtaining **(266)** and **(267)**.

The stereochemistry of each of the two epoxides was elucidated after comparison of the ^{1}H NMR spectra with those of the higher homologues **(244)** and **(255)**. The *trans*-epoxide **(267)** had a mutual vicinal coupling of 5.0 Hz between epoxide protons and further couplings of 5.8 and 6.6 Hz to the α-nitrogen and α-hydroxy protons. The homologous *trans*-epoxide **(255)** showed similar, slightly larger couplings of 8.2 and 9.3 Hz to α-nitrogen and α-hydroxy protons. A similar pattern was observed for the *cis*-epoxide **(266)** which displayed no coupling between the epoxide, α-nitrogen and α-hydroxy protons in contrast to respective small couplings of 3.6 and 4.8 Hz for the homologous *cis*-epoxide **(244)**. These assignments were supported by the chemical evidence of high syn-stereoselectivity for the vanadium-catalysed epoxidation and, ultimately, further spectral evidence from comparison of *exo*- and *endo*-epoxytropanes with homotropane homologues.

The *exo*-epoxide in the homotropane series was introduced by epoxidation of the tautomeric mixture of α,β-unsaturated ketone **(151)** and hemiaminal **(152)** as described in chapter 5.2. No such tautomerism existed for the α,β-unsaturated ketone **(229)** and as a result this was unreactive to MCPBA (figure 6.3). However, treatment of **(229)** with alkaline hydrogen peroxide afforded the *cis*-epoxy ketone **(269)** as the only product in 69% yield. This suggests that tautomerism of **(229)** is pH dependent and, in the presence of base, a small concentration of the electrophilic hemiaminal **(230)** was present which was readily epoxidised by MCPBA. The epoxy-ketone **(269)** isolated from this reaction existed only in the monocyclic form with no spectral evidence for the hemiaminal **(268)**.

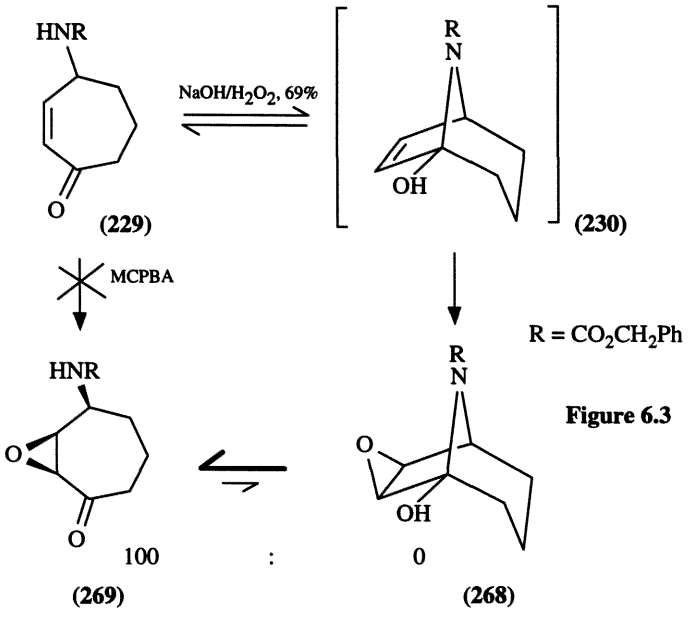


Figure 6.3

The epoxy-ketone **(269)** was also synthesised by Jones oxidation of the epoxy-alcohol **(266)** in 87% yield (figure 6.4). The NMR spectra of **(269)** prepared by each of these methods were identical. The ^{13}C NMR spectrum displayed a characteristic carbonyl carbon signal at δ 208.5. The ^{1}H NMR spectrum showed two epoxide signals at δ 3.37 and δ 3.47 with only a small vicinal coupling of 0.9 Hz observed between the epoxide proton and the α-nitrogen proton.

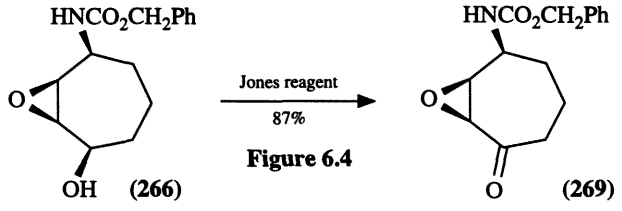


Figure 6.4

Two methods for introducing the *trans*-1,4 stereochemistry necessary for cyclisation were now possible. The epoxy-alcohol **(266)** could be tosylated and the tosylate replaced by chloride with inversion, or the epoxy-ketone **(269)** could be reduced with sodium borohydride and tosylated. The former route was chosen and

the synthesis of the *exo*-epoxy tropane (**272**) is outlined in figure 6.5. Both the formation of the tosylate (**270**) and subsequent transformation into the chloride (**271**) proceeded in excellent yield. Cyclisation was then achieved by treatment of (**271**) with sodium hydride and the ^{1}H NMR spectrum of (**272**) was similar to that of the *exo*-epoxyhomotropane (**235**). 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 (**272**) is reported in section 6.4.

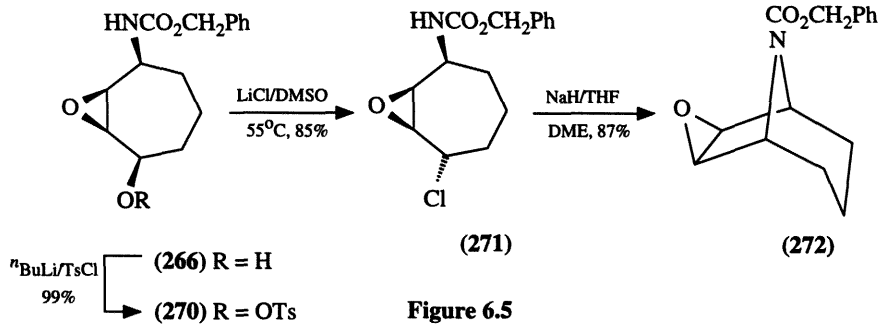


Figure 6.5

6.3 SYNTHESIS OF *ENDO*-6,7-EPOXYTROPANE

Starting from the *trans*-epoxide (**267**), the identical approach to that described above was applied to the formation of the *endo*-epoxide (**275**). The alcohol (**267**) was tosylated to (**273**) and then converted into the chloride (**274**) as a single stereoisomer (figure 6.6). Both of these transformations proceeded smoothly but attempts to cyclise (**274**) using a variety of bases including sodium hydride and potassium carbonate failed.

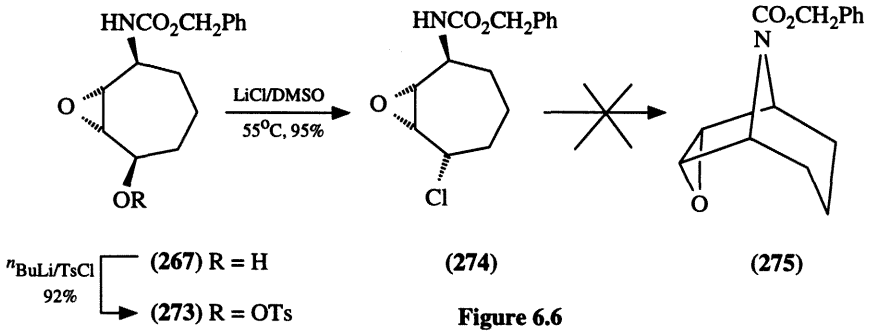


Figure 6.6

A better leaving group, namely a tosylate, was required to induce cyclisation and this was prepared by firstly oxidising the alcohol **(267)** with Jones reagent and then reducing the ketone **(276)** with hydride (figure 6.7). The epoxy-ketone **(276)** 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

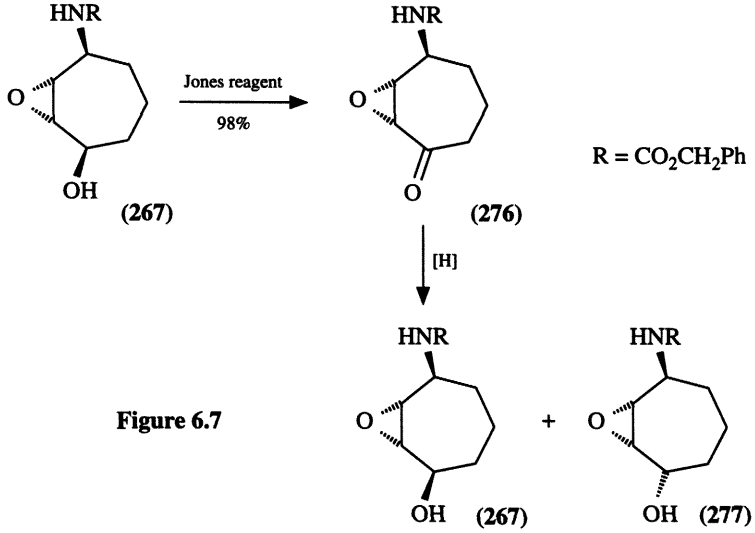
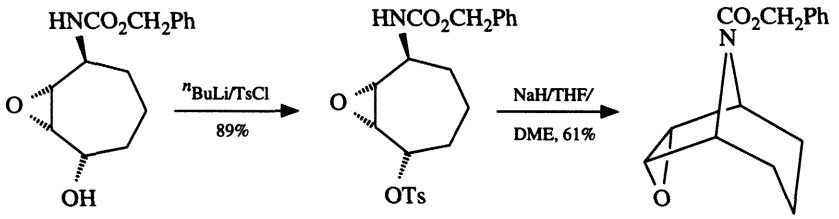


Figure 6.7

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

assigned to the ring-carbon C_1. The homologous 8-membered ring epoxy-ketone **(256)** gave only the *trans*-1,4 isomer **(257)** on reduction with sodium borohydride, but unfortunately reduction of **(276)** with borohydride gave a mixture of both *cis*-1,4 **(267)** and *trans*-1,4 **(277)** isomers in a ratio of 62:38 (calculated from ^{1}H NMR integrations) which were separable by chromatography. L-Selectride[123] was also used to reduce **(276)** and this proved to be a superior reagent, giving a richer mixture of the *trans*-1,4 **(277)** in good overall yield. The redundant *cis*-1,4 alcohol **(267)** could be recycled by oxidation to the ketone **(276)** followed by reduction. The stereochemistry of **(277)** was confirmed by the small vicinal coupling of 1.6 Hz between the epoxide and α-hydroxy protons in the ^{1}H NMR spectrum.

Successful formation of **(275)** was then achieved by tosylation and treatment of the tosylate **(278)** with sodium hydride in THF:DME solvent (figure 6.8).



(277) **(278)** **(275)**

Figure 6.8

A more elegant method of preparing the *trans*-1,4 alcohol **(277)** would involve direct inversion of the alcohol group (rather than oxidising and reducing from the opposite face) and several literature methods for achieving this are known.[124] The epoxy-alcohol **(255)**, based on the 8-membered ring, was more readily available than **(267)** and this was used for preliminary investigations. Kellogg[125] inverted the stereochemistry of secondary alcohols by first mesylating the alcohol, inverting the mesylate with cesium propionoate in DMF solvent and then hydrolysing the resulting ester to the alcohol. This method was reported to be remarkably clean, proceeding without detectable amounts of elimination or racemisation products. The mesylate of **(255)** was duly prepared but when **(279)** was subjected to the conditions of Kellogg, it

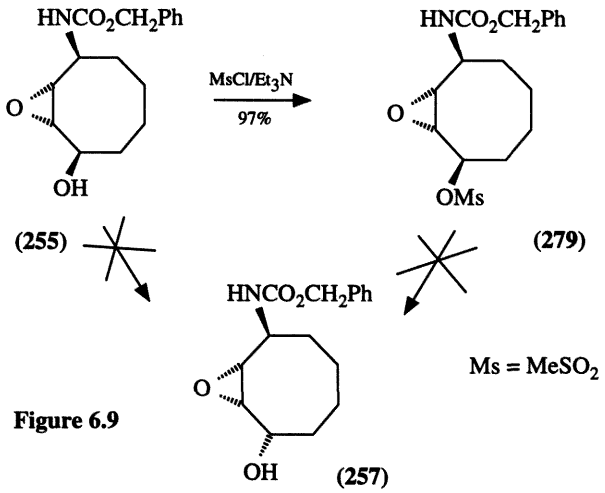


Figure 6.9

failed to give the desired inversion product; only starting material was isolated (figure 6.9). Ikegami[126] reported a modification of this procedure, inverting the stereochemistry of a mesylate with cesium acetate using benzene as solvent in the presence of 18-crown-6. Applying this method to **(279)** resulted in no observable inversion of the mesylate. When the reaction was repeated at higher temperature only a complex mixture of products was isolated.

Corey[127] inverted the mesylates of secondary alcohols using potassium superoxide in DMSO solvent, but this also failed when applied to **(279)**. Finally, direct inversion of the alcohol **(255)** was tried using the Mitsunobu[128] procedure but without success. The failure of these reactions was disappointing but nonetheless, the overall efficiency of the oxidation and reduction method was acceptable.

6.4 REDUCTION OF N-PROTECTED EPOXYTROPANES

The epoxide moiety of N-alkoxycarbonyl-protected epoxyhomotropanes was able to withstand both hydride and hydrogenolysis reduction and as a result, both *exo*-epoxyhomotropane (**260**) and *endo*-epoxyhomotropane (**264**) were accessible. A similar reductive procedure was applied to the N-protected *exo*-epoxytropane (**272**), but the epoxide was reactive and was ring-opened by DIBAH at 0°C to give tropan-6β-ol (**282**) (figure 6.10). However, when the reduction was repeated at -78°C,

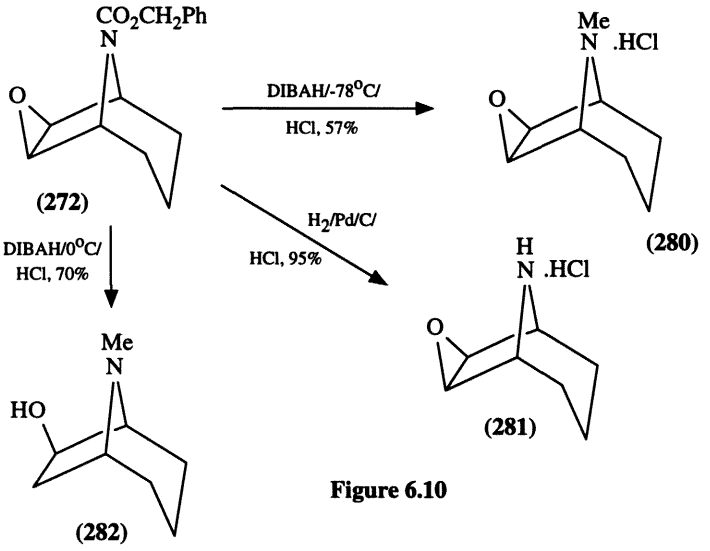
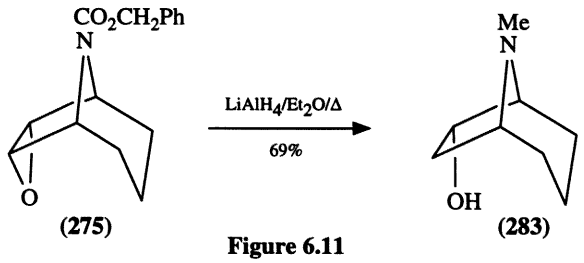


Figure 6.10

the carbamate was reduced chemoselectively to afford 6β,7β-epoxytropane (**280**). The epoxide of (**272**) was also stable to hydrogenolysis; reduction at 1 atmosphere with a palladium catalyst gave 6β,7β-epoxynortropane (**281**). Both (**280**) and (**281**) were volatile and were handled as the hydrochloride salts.

The *endo*-epoxide (**275**) was subjected to reduction with lithium aluminium hydride in refluxing diethyl ether and both epoxide and carbamate moities were reduced to give tropan-6α-ol (**283**) (figure 6.11). An attempt to reduce the carbamate group selectively by repeating the reaction at -78°C led only to the isolation of (**283**).

The hydrogenolysis of (**275**) 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 (**259**).



(**275**) (**283**)

Figure 6.11

The substantially greater reactivity of *endo*-epoxides compared to *exo*-epoxides in both the homotropane and tropane ring systems is surprising. The preferred conformation of the seven-membered ring of homotropane is known to be the boat form[129] and this gives no reason to expect significant steric shielding of the *endo*-face. However, the established role of bridging nitrogen in the hydride reduction of a C=C bridge in 7-azanorbornenes[130] suggests that the nitrogen may assist the attack of hydride reducing agents on the epoxide from the *exo*-face, explaining the increased lability of the *endo*-epoxide to hydride reducing agents.

CHAPTER 7

Total Synthesis of Scopine, Pseudoscopine & Nor-derivatives

7.1 INTRODUCTION

The first synthesis of scopine (**6**), the precursor to scopolamine and (-)-hyoscine, was reported by Fodor[84] in 1959. This synthesis was discussed in chapter 2.5 in connection with epoxidation studies of the homotrop-7-ene system. The efficiency of the epoxidation step was low because of the difficulties associated with epoxidation of an alkene in the presence of an amine group. Despite the extensive interest in the synthesis of other natural products based on azabicyclic systems (for example, the numerous syntheses of anatoxin-a[43-48]), endeavours to design an effective synthesis of scopine were neglected until an elegant procedure was reported by Bäckvall[37] in 1991. Based on earlier work involving the preparation of simpler tropane alkaloids[36] (chapter 1.3), Bäckvall prepared both scopine and pseudoscopine using palladium-catalysed 1,4-chloroacetoxylation of a functionalised cycloheptadiene in the key step of the synthesis. The synthesis of scopine (**6**) is summarised in figure 7.1. Treatment of (**284**) with palladium(II) acetate, lithium chloride, lithium acetate and benzoquinone afforded the 1,4,6-trisubstituted cycloheptane (**285**) which was then reduced to the alcohol (**286**). A requirement for preparing 3α-hydroxy isomers of tropane alkaloids (*i.e* scopine) is a *trans*-relationship between the nitrogen and benzyloxy groups. This was achieved by treating (**286**) with sodium *p*-toluenesulphonamide in the presence of a palladium(0) catalyst, the reaction proceeding with retention of configuration. The hydroxy group of (**287**) was inverted into the chloride (**288**) and then epoxidised to (**289**) with MCPBA. The epoxidation step gave high syn-stereoselectivity (>98%). Subsequent cyclisation of (**289**), induced with potassium carbonate, produced the 8-azabicyclo[3.2.1]octane structure. The N-methyl group was introduced by removing the N-tosyl group of (**290**) using a dissolving metal reduction followed by quenching with methyl iodide to give scopine benzyl ether (**291**). Hydrogenolysis then gave scopine (**6**) in 8 overall steps. Scopoline (**7**) was obtained as a by-product in the final deprotection step. The overall

yield for these transformations from the diene (**284**) to scopine was 16%.

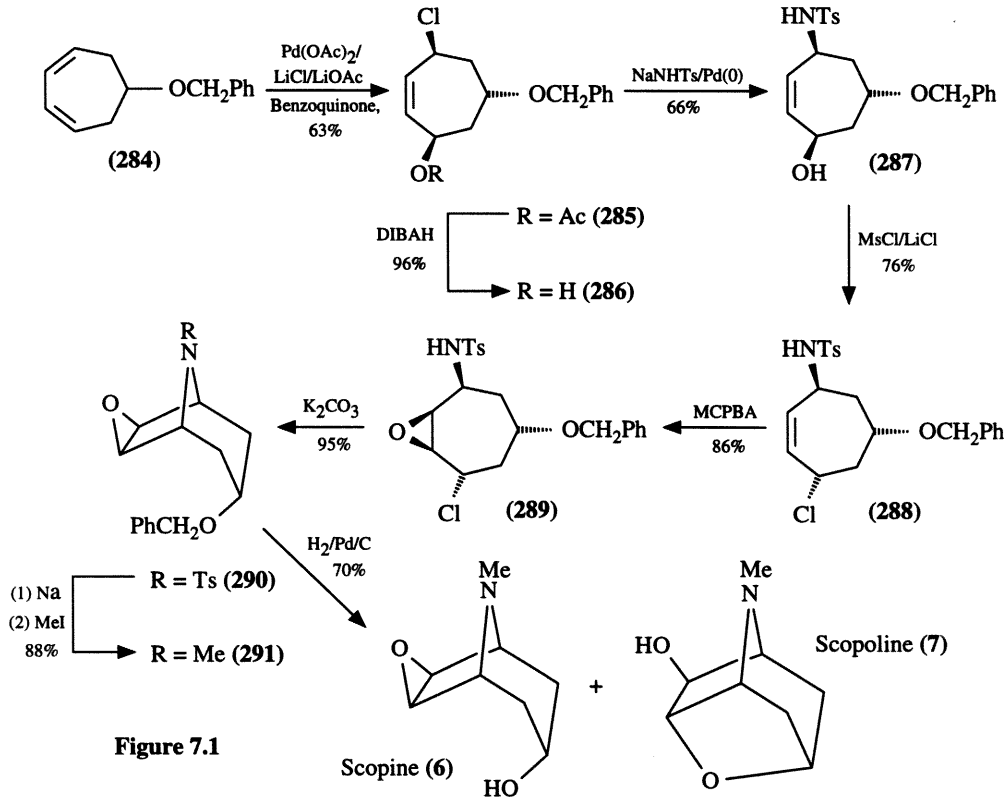
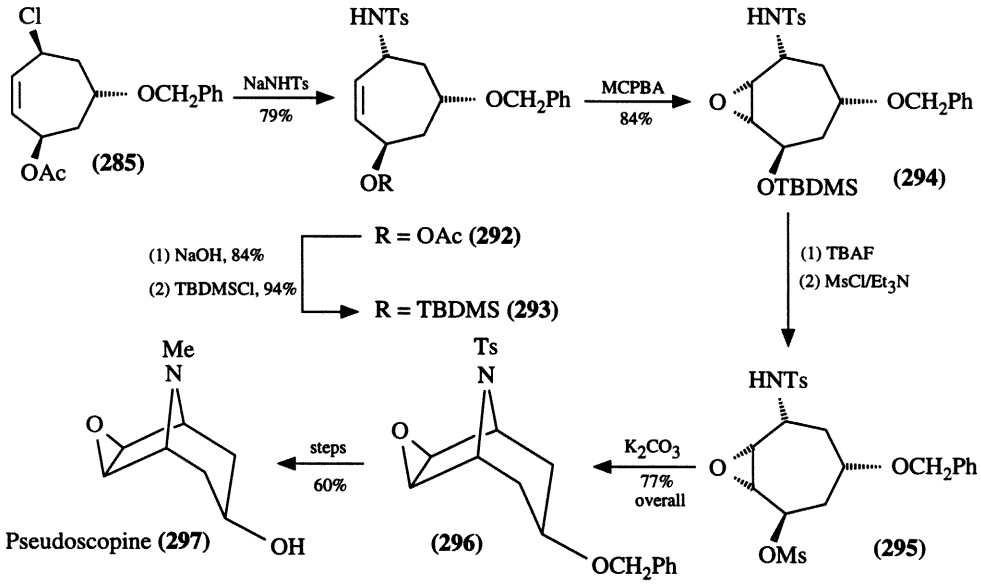


Figure 7.1

Bäckvall then applied this strategy to prepare the 6β-analogue of scopine, namely pseudoscopine (**297**), as outlined in figure 7.2. A stereochemical requirement for the synthesis of (**297**) is a *cis*-relationship between the nitrogen and the benzyloxy group in the monocyclic precursors. The conversion of (**285**) into (**292**) therefore required retention of configuration of the OR group which was achieved by treatment with sodium *p*-toluenesulphonamide in the absence of a palladium catalyst. The acetate group of (**292**) was saponified and the resultant alcohol was protected as the silyl ether (**293**). The bulky silyl ether group facilitated selective syn-epoxidation giving (**294**) as the major epoxide in a ratio of 87:13. Deprotection of the silyl ether and mesylation of the alcohol afforded (**295**) which was cyclised to (**296**) using potassium carbonate as base. The final deprotection and methylation steps were

identical to those described for the synthesis of scopine. The overall yield for the conversion of the diene (**284**) into pseudoscopine (**297**) was 25% and the relatively high efficiency of these two syntheses makes them the first effective preparations of scopine and pseudoscopine.



TBDMSCl = $^{t}BuMe_2SiCl$
TBAF = Bu_4NF

Figure 7.2

The reaction between pyrroles and oxyallyls is an established method of producing the tropane system and is significant as it allows access to uncommon trop-6-ene analogues. There are drawbacks to this approach; firstly both the pyrrole and the oxyallyl precursors often have to be highly substituted for the cycloaddition to proceed in a satisfactory yield. Secondly, the known methods of generating oxyallyls involve hazardous chemicals. In 1992, Mann[31] reported a notable improvement to this approach by generating oxyallyls from polybromoketones and diethylzinc. Using this method, a range of both nitrogen- and oxygen-bridged bicycles could be synthesised safely and in high yield. In addition, N-alkoxycarbonyl-protected pyrroles readily intercepted the oxyallyl intermediates and this has a specific bearing on the synthesis of epoxytropane derivatives as the nitrogen is suitably protected for

subsequent epoxidation. Mann demonstrated this with a synthesis of scopoline (**7**) which could be produced in gramme quantities (figure 7.3)

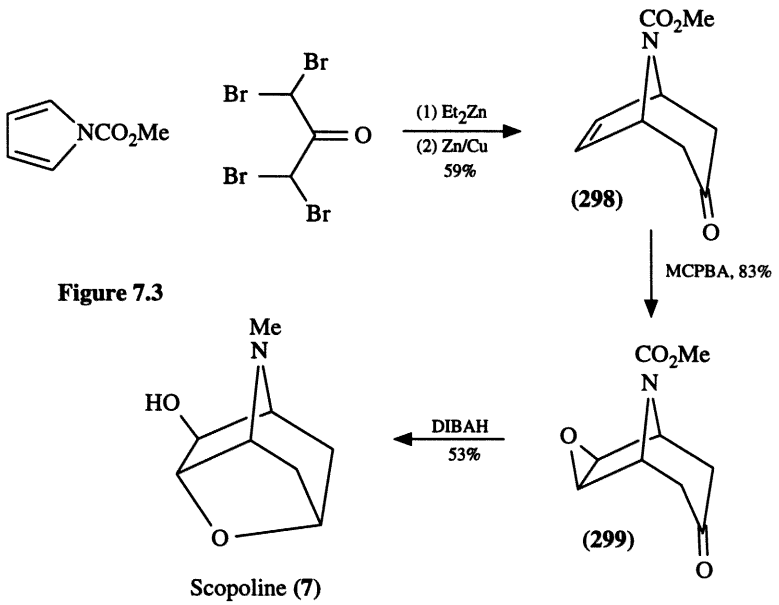


Figure 7.3

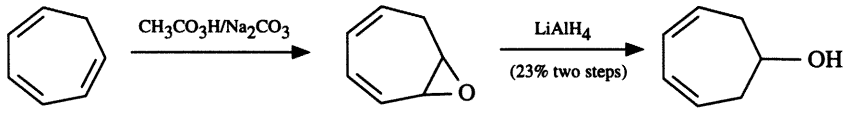
Scopoline (**7**)

Reaction of tetrabromoacetone and methyl pyrrole-N-carboxylate in the presence of diethylzinc followed by debromination of the cycloadduct produced (**298**) in good yield. Epoxidation of (**298**) with MCPBA then gave the *exo*-epoxide (**299**) which was reduced with an excess of DIBAH to afford scopoline (**7**). The attack of hydride presumably occurs exclusively from the β-face of the ketone as no by-products were reported for the reaction. In view of the high stability observed for *exo*-epoxytropanes (chapter 6) the use of milder reducing agents, or indeed a reversal in the order of epoxidation and reduction steps, may well diversify the range of products available from (**298**). This intermediate offers the potential to prepare scopine and pseudoscopine and this may result in future elaboration of the procedure.

The shortage of approaches to scopine warranted an investigation into a further synthesis. To this end, a new route to scopine, pseudoscopine and novel nor-derivatives is described here and is complimentary to the method reported by Bäckvall.

7.2 A STRATEGY TO SCOPINE AND PSEUDOSCOPINE PRECURSORS

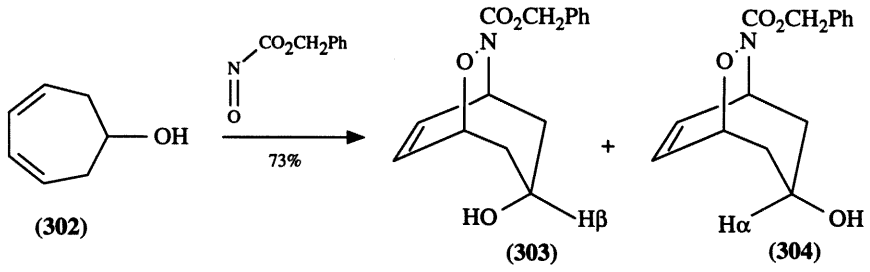
An efficient method of preparing *exo*-epoxytropanes was discussed in the previous chapter and this forms the basis for the synthesis of 3-oxygenated derivatives. The additional 3-hydroxy substituent could be introduced by performing the initial nitroso cycloaddition reaction using cyclohepta-1,3-dienol (**302**). This diene could could be prepared from tropone[131] but this approach was rejected in view of the difficulties encountered by Howarth[87] in producing (**302**) in high yield, and also because tropone is not a readily-available starting material. Instead, the procedure of Schiess and Wisson[132] was used which involved the peroxyacetic epoxidation of cycloheptatriene (**300**) and reduction of the resulting epoxide (**301**) with lithium aluminium hydride (figure 7.4). For large scale preparation of (**302**), the epoxide was not purified prior to reduction. 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.



(**300**) (**301**) (**302**)

Figure 7.4

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 (**302**) was subjected to the standard nitroso cycloaddition conditions an acceptable yield of cycloadducts was produced but the reaction showed little selectivity giving a 35:65 mixture of (**303**) and (**304**) which could not be separated by chromatography (figure 7.5). The stereostructures of (**303**) and (**304**) were assigned on the basis of the relative chemical shifts of the α-hydroxy protons. Two such signals were observed in the ^{1}H NMR spectrum with a difference in chemical shift of greater than δ 0.5. The signal attributed to the 3α-proton of the



(302) **(303)** **(304)**

Figure 7.5

35 : 65

major cycloadduct **(304)** was notably up-field (δ 3.67) as this lay within the shielding cone of the double bond. The 3β-proton of the minor adduct **(303)** 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.[87]

At this stage of the synthesis two options were available: either the mixture of adducts could be used in subsequent steps, with the hope of separation at a later stage, or attempts could be made to prepare purer samples of **(303)** and **(304)**. The latter approach was chosen as it was anticipated that difficulties might arise during attempts to identify and characterise compounds from reaction mixtures.

The stereoselective reduction of tropinone **(10)** has been extensively studied by Beckett[133] who reported the participation of kinetic and thermodynamic factors in the course of the reduction. Noyori[134] reported similar effects in the reduction of 6,7-dehydrotropinone. The structure of tropinone is similar to that of the adducts **(303)** and **(304)** and by analogy the reduction of the ketone, formed by oxidation of these alcohols, would be expected to furnish the 3α-hydroxy stereoisomer **(303)** as the major component (kinetic control). It was therefore decided to oxidise the alcohols first and then reduce (figure 7.6). Oxidation of the cycloadducts with Jones reagent produced the ketone **(305)** in high yield. The product was identified from an additional carbonyl signal at δ 206.0 in the ^{13}C NMR spectrum and by the absence of α-hydroxy protons in the δ 3.0 - 5.0 region of the ^{1}H NMR spectrum. Stereoselective reduction of the ketone under conditions of kinetic control was achieved by treatment

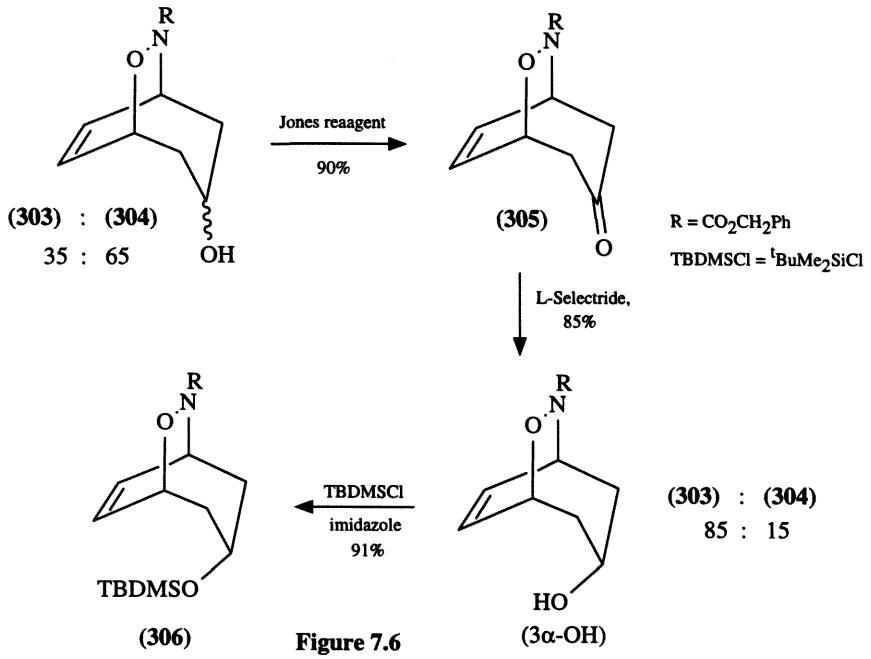


Figure 7.6

of (**305**) at -78°C with L-Selectride[123] to afford an 85% yield of alcohols. Inspection of the ^1H NMR spectrum of the crude reaction product indicated a substantial enrichment (compared to the cycloaddition reaction) of the 3α-hydroxy isomer (**303**) which comprised 85% of the mixture. This was deemed to be of high enough purity for subsequent reactions.

The hydroxy group of (**303**) was protected in order to allow manipulation of other groups at a later stage of the synthesis. The versatile *t*-butyldimethlysilyl protecting group was chosen since this was reported[135] to be sufficiently stable to withstand a wide range of reaction conditions and yet is easily introduced and removed. The alcohol (**303**) was protected as the silyl ether (**306**) using standard conditions. The ^1H NMR spectrum of (**306**) confirmed a successful reaction showing diagnostic up-field methyl signals; this compound was a suitably protected and functionalised precursor to scopine. The 3α-silyl ether (**306**) did however contain a minor impurity, namely the 3β-silyl ether, formed from the epimeric alcohol (**304**).

These stereoisomers could not be separated at this stage of the synthesis but, in subsequent transformations, products derived from this mixture could be isolated in pure form.

It was considered initially that a possible method of generating an enriched sample of the 3β-silyl ether **(308)** would be to invert the stereochemistry of the 3α-hydroxy group of **(303)** and then protect as the silyl ether. However, because of the difficulties encountered previously with such reactions (chapter 6.3) this approach was rejected. Instead, it was decided to investigate the effect of silylating cyclohepta-3,5-dienol **(302)** with TBDMS-Cl prior to the cycloaddition reaction, in the hope that a bulky group would alter the stereoselectivity. The silyl ether **(307)** was prepared in 93% yield and then reacted with benzyl nitrosoformate (figure 7.7).

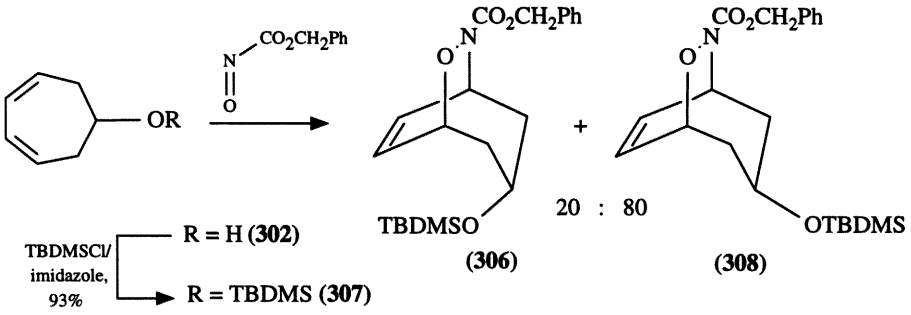


Figure 7.7

This approach was successful; from the integrations in the ^{1}H NMR spectrum of the reaction mixture a 20:80 ratio of the adducts **(306)**:**(308)** had been formed in favour of the 3β-silyl ether **(308)**. The α-silyl ether proton of **(308)** 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 for the α-hydroxy proton of **(304)** which had a very similar shift (δ 3.67). The minor signals in the NMR spectra of **(308)** corresponded to the other epimer **(306)**.

7.3 SYNTHESIS OF SCOPINE AND NORSCOPINE

The silyl ether (**306**) was converted into the protected *exo*-6,7-epoxytropane system (**314**) using an identical sequence of reactions to those described for the preparation of (**272**). These transformations are outlined in figure 7.8.

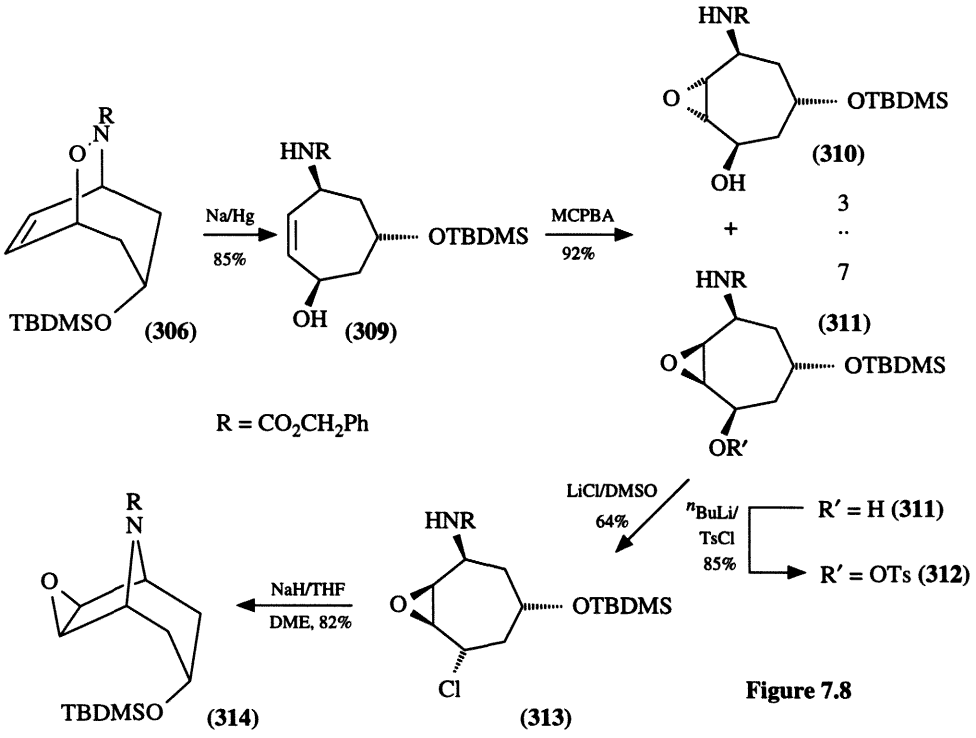


Figure 7.8

Reduction of (**306**) with sodium amalgam afforded the alcohol (**309**) in good yield which displayed an exchangeable hydroxy proton at δ 2.47 in the ^{1}H NMR spectrum. Epoxidation of (**309**) produced a pair of stereoisomers (**310**) and (**311**) in a 3:7 ratio based upon isolated yields of the epoxides after chromatographic separation. The epoxidation reaction had a moderate stereoselectivity in favour of the product (**311**) having the epoxide *trans* to the silyl ether and thus the correct stereochemistry for subsequent conversion into the *exo*-epoxytropane (**314**). The ^{1}H NMR spectra of (**310**) and (**311**) were broad at ambient temperature but the vicinal couplings of the

epoxide protons were discernible; assignment of stereochemistry was made on the basis of the magnitude of these values, in conjunction with the coupling constants of **(266)** and **(267)**. The stereoisomer **(311)** having the epoxide *cis* to the α-N and α-O displayed two doublets at δ 3.23 and δ 3.32 due to the epoxide protons with a mutual vicinal coupling of 5.0 Hz. The corresponding signals of **(310)**, a triplet at δ 3.13 ($J \approx$ 7.5 Hz) and a multiplet at δ 3.18, had additional vicinal couplings to the α-O and α-N protons. The *trans*-1,4 stereochemistry between nitrogen and a leaving group (necessary for cyclisation) was achieved by tosylating **(311)** and treating the tosylate **(312)** with lithium chloride to give **(313)**. Chromatographic purification of the tosylate intermediate **(312)** removed minor by-products that had arisen from 6β-silylether contamination of **(306)**. 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 **(313)**. Nucleophilic displacement initiated by sodium hydride as base then gave the doubly-protected tropane structure **(314)**. As a result of slow rotation about the N-CO bond, the epoxide and bridgehead signals were duplicated in the ^{1}H and ^{13}C NMR of **(314)**. The epoxide protons appeared as doublets in the ^{1}H NMR spectrum at δ 3.53 and δ 3.56, with a mutual coupling of 3.5 Hz. The absence of any observable coupling between epoxide and bridgehead protons confirmed the *exo*-epoxy stereochemistry of **(314)**.

The final deprotection steps are shown in figure 7.9. Reduction of **(314)** with lithium aluminium hydride in diethyl ether produced **(315)** in high yield which showed a 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, assigned to the N-methyl group. As anticipated from the behaviour of **(272)** (the analogue of **(314)** without a 3-oxy substituent) the epoxide was stable to the reducing conditions. Removal of the O-protecting group of **(315)** was achieved using TBAF[135] in THF solvent to furnish scopine **(6)**, the spectroscopic properties of which were in good agreement with literature data. A discussion of the ^{1}H NMR spectrum of scopine will follow a description of the synthesis of pseudoscopine.

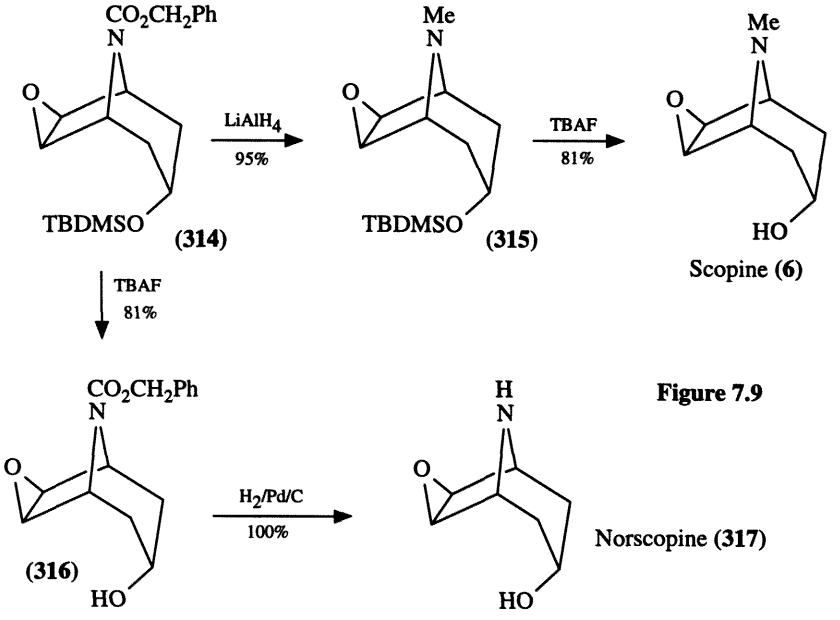


Figure 7.9

Hydrogenolysis of **(314)** instead of hydride reduction, with subsequent removal of the O-protecting group from **(316)**, allowed for the preparation of norscopine **(317)** a non-natural derivative of scopine. A partial synthesis of norscopolamine (from scopolamine) has been reported,[136] but no other total synthesis of norscopine has been undertaken to date.

7.4 SYNTHESIS OF PSEUDOSCOPINE AND NORPSEUDOSCOPINE

A partial synthesis of pseudoscopine was reported by Heusner and Ziele[137] in 1958 and involved oxidation of scopine and subsequent reduction with potassium borohydride. The yield for the latter step was low and this was not an effective synthesis. The method of preparing **(297)**, reported by Bäckvall, therefore represents the only practical synthesis of pseudoscopine to date. A second synthesis is described here which involves an identical procedure to that described for scopine but using the 3β-silyl ether **(308)** as starting material in the initial step (figure 7.10).

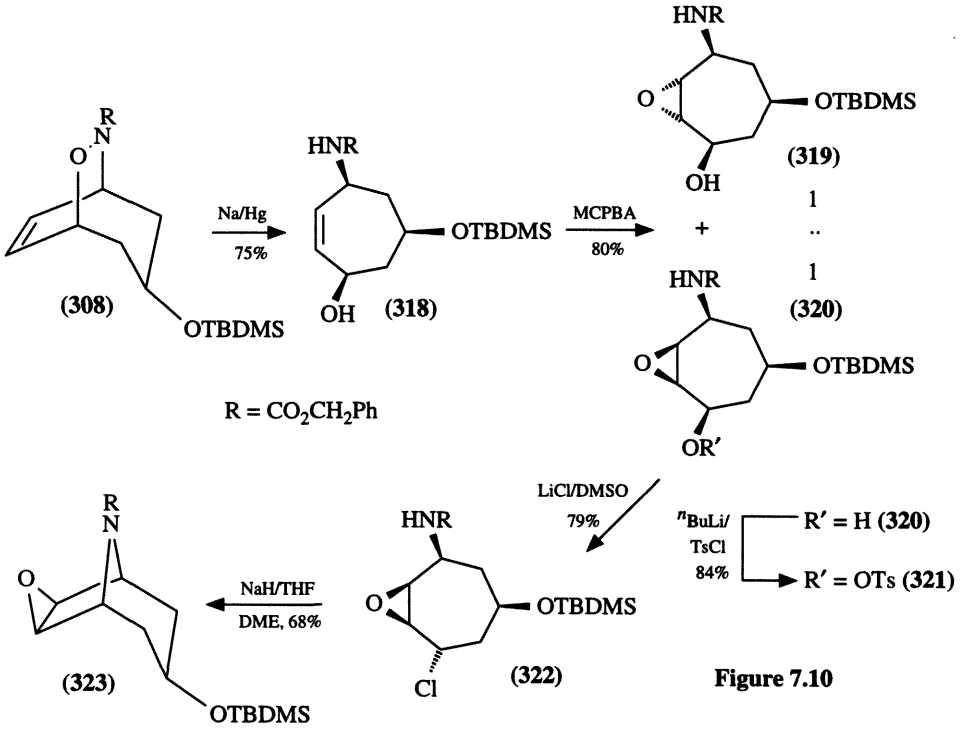


Figure 7.10

Reduction of **(308)** with sodium amalgam produced the allylic alcohol **(318)** which was epoxidised with MCPBA to furnish a 1:1 mixture of **(319)**:**(320)**. The epoxides were separable by chromatography; the isomer **(320)** with the epoxide *cis* to the α-N and α-O was isolated in pure form but **(319)** contained minor impurities resulting from contamination by the 6α-silyl ether. The epoxidation reaction was unselective and although alternative epoxidising agents could have been used to vary the ratio, **(319)** is a potential precursor to analogues of scopine (chapter 7.6) and is therefore a synthetically useful by-product which was retained. The *cis*-epoxide **(320)** was tosylated to **(321)** and then substituted with chloride ion to give **(322)**. Cyclisation of **(322)** using sodium hydride gave the protected form of pseudoscopine **(323)**.

The deprotection procedures used to prepare pseudoscopine **(297)** and norpseudoscopine **(326)** were the same as those applied to **(314)** and are outlined in

figure 7.11. Hydride reduction of (**323**) gave the N-methyl derivative (**324**) which was treated with fluoride ion to give pseudoscopine (**297**). Alternatively, initial desilylation of (**323**) followed by hydrogenolysis reduction of (**325**) furnished norpseudoscopine (**326**), a novel analogue.

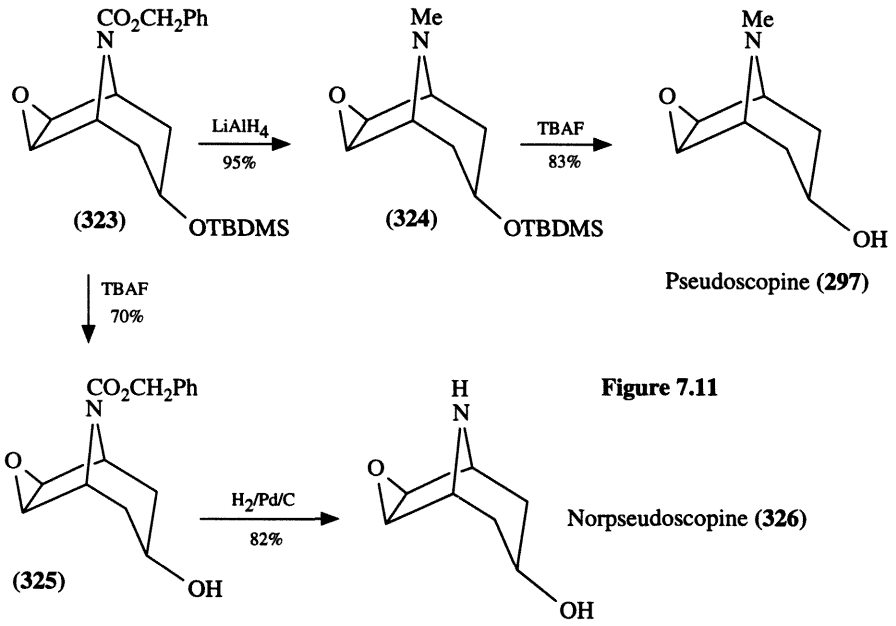


Figure 7.11

The successful synthesis of scopine and pseudoscopine was confirmed after comparison of ^{1}H, ^{13}C and mass spectra with published literature data[37] which showed a good match. The vicinal couplings between the α-hydroxy and neighbouring protons differed substantially for the two isomers in the ^{1}H NMR spectra (figure 7.12). The 3β-hydroxy proton of scopine (**6**) at δ 4.20 is in an equatorial position and only coupling to each of the proximate axial protons was observed resulting in a triplet. Vicinal coupling to equatorial protons was too small to be measured which is typical of equatorial-equatorial coupling. The 3α-proton of pseudoscopine (**297**) at δ 4.16 is in an axial position and as a consequence the vicinal axial-axial couplings are much larger and the signal appeared as a triplet of triplets (J = 9.7, 6.7 Hz). The nor derivatives (**317**) and (**326**) showed similar values. This

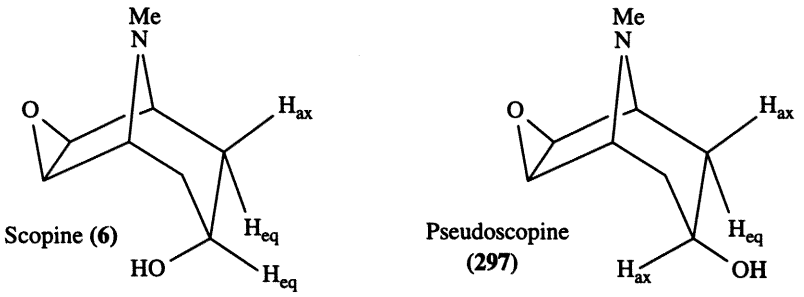
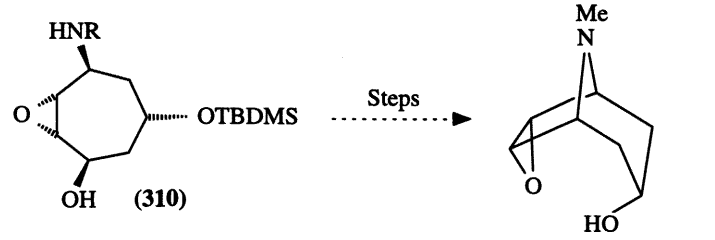


Figure 7.12

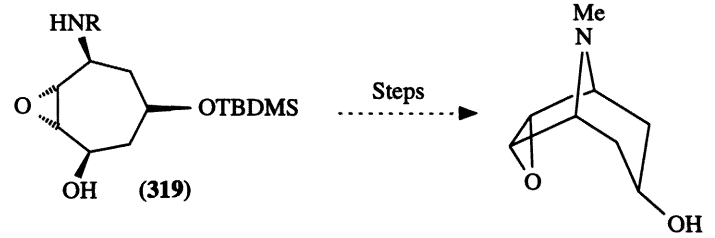
effect was also observed for the 3α- and 3β-oxygenated adducts, such as **(303)** and **(304)**, where the C_3-proton coupled to pseudo-axial and pseudo-equatorial protons and confirmed the earlier assignments based on chemical shift.

7.5 FURTHER FUNCTIONALISATION OF TROPANE

This chapter has described a successful synthetic strategy to scopine, pseudoscopine and novel nor-derivatives. The anticipated stability of the *exo*-epoxide group has been used to full advantage in this synthesis. During the course of this work, two by-products **(310)** and **(319)** were isolated which had the epoxide group *trans* to the α-O and α-N. These epoxides are potential precursors to '*endo*-scopine' **(327)** and '*endo*-pseudoscopine' **(328)** as depicted in figure 7.13. There is no reference to such compounds in the literature to date. As the *endo*-6,7-epoxide of the tropane system has been shown to be significantly more labile to hydride reduction than the *exo*-epoxide, a different protecting group at nitrogen would be required at the conclusion of the synthesis.



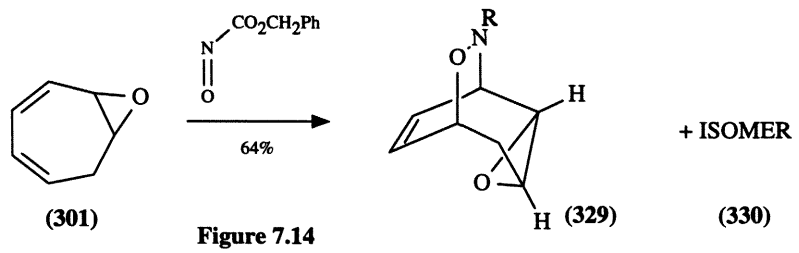
Endo-scopine (**327**)



Endo-pseudoscopine (**328**)

Figure 7.13

A preliminary investigation into introducing oxygen functionality in the C_2 and C_4 locations of tropane was studied. This could provide further analogues of scopine and would also be of use in preparing other oxygenated tropane alkaloids. The epoxide (**301**) was an intermediate in the synthesis of cyclohepta-3,5-dienol (**302**) and it was reasoned that the diene in (**301**) might undergo a cycloaddition reaction with nitroso compounds. A small portion of (**301**) was purified and subjected to the standard cycloaddition conditions employed previously. The reaction was successful and two isomeric epoxides (**329**) and (**330**) were isolated in an 80:20 ratio (Figure 7.14). The ^{1}H NMR spectrum displayed characteristic bridgehead protons of similar



(**301**) (**329**) (**330**)

Figure 7.14

80 : 20

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 ^{1}H NMR signals in the spectrum of the mixture could not be made with confidence. However, recrystallisation of the product mixture afforded the major cycloadduct **(329)** in pure form and a crystal was grown for X-ray analysis (appendix 1). This revealed that **(329)** had the stucture depicted in figure 7.14 with an *endo*-epoxide group.

Although the structure of **(330)** could not be elucidated without more extensive spectroscopic study, this reaction does provide a highly functionalised cycloadduct **(329)** in pure form and in an acceptable yield. Using this as a starting material, there is a clear scope to produce further natural and non-natural derivatives of tropane.

APPENDIX 1

X-Ray Crystal Data for the Epoxide Cycloadduct (329)

X-RAY CRYSTAL DATA FOR THE EPOXIDE CYCLOADDUCT (329)

Crystals suitable for X-ray single crystal determination were obtained from a 1 ml solution containing 20 mg of the recrystallised cycloadduct (**329**) in diethyl ether which was slowly evaporated at 0°C. The crystal used for data collection was a colourless block (0.48 x 0.45 x 0.39 mm) mounted on a glass fibre.

Crystal data for $C_{15}H_{15}NO_4$: M = 273.3, orthorhombic space group $Pna2_1$, $\underline{a}$ = 16,711 (4), $\underline{b}$ = 9.688 (2), $\underline{c}$ = 16.316 (2) Å, $\underline{V}$ = 2641.5 (9) $Å^3$, $\underline{Z}$ = 8, $\underline{\mu}$ = 0.10 mm^{-1}, $\underline{\lambda}(m_0\text{-}k_\alpha)$ = 0.7107 Å, $\underline{F}(000)$ = 1152, $\underline{D_c}$ = 1.374 mg/M^3.

The unit cell parameters were determined from the optimised setting angles of 22 automatically centered reflections, $9.9 < 2\theta < 23.0°$. The intensities of 2452 reflections were measured on a Siemens P4 diffractometer ($5 < 2\theta < 46°$) using a w scan technique. 3 Check reflections monitored every 100 reflections indicated no crystal decomposition. The data were corrected for Lorentz and polarisation effects and merged to give 2011 unique reflections (R_{int} = .032) and 1547 reflections with $F > 4\sigma(F)$.

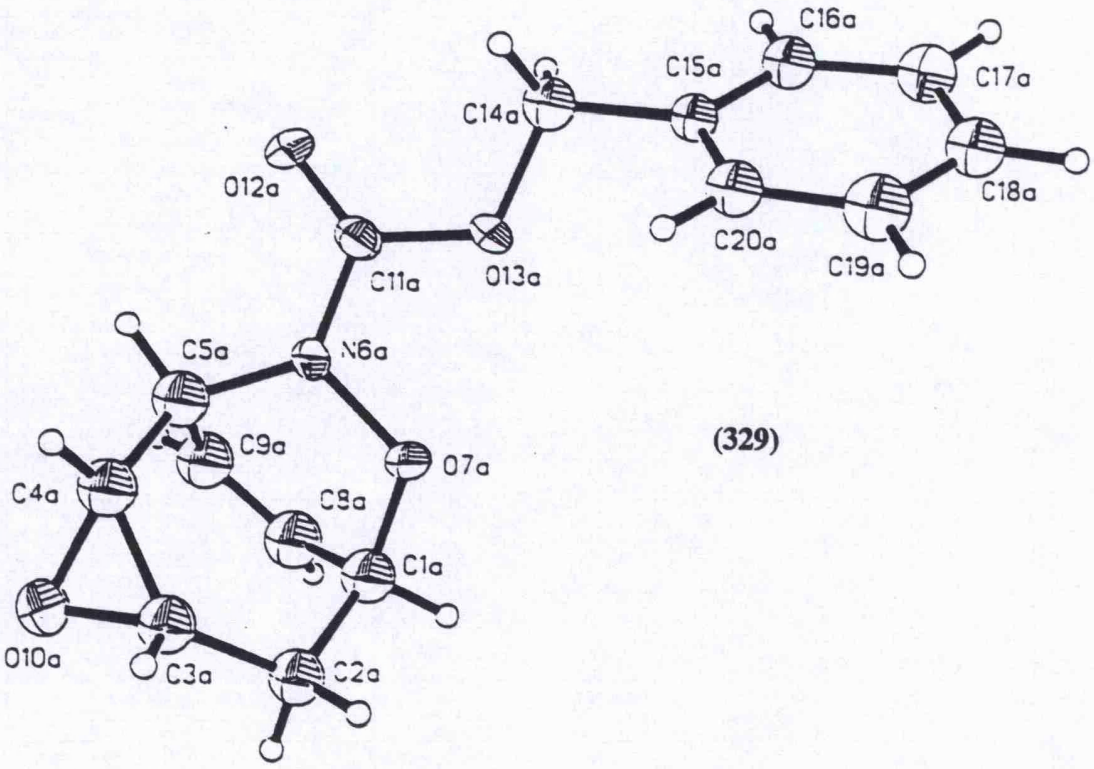
The structure was solved by direct methods and refined by full matrix least squares using the programme SHELXTL - pc.[138] Two unique but approximately superimposable molecules were found in the asymmetric unit.

Hydrogen atoms were included in calculated positions (C-H = 0.96 Å). The number of atoms refined with anisotropic displacement parameters was limited by the data to parameter ratio.

Final cycles of least-squares refinement used a weighting scheme $w = 1/(\sigma^2F + 0.0007\ F^2)$ and wR 0.0078. The final diffence Fourier map was featureless (+0.007 and -0.002e $Å^{-3}$).

The geometry of the molecule (**329**) is shown in figure A.1

X-ray Crystal Structure of the Epoxide Cycloadduct (329)



(329)

Figure A.1

Table 1. Atomic coordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2 x10^3$)

	x	y	z	U(eq)
C(1)	1075(6)	1368(10)	4459(8)	64(3)
C(2)	559(5)	1340(10)	5215(8)	68(4)
C(3)	840(6)	2133(9)	5930(9)	56(3)
C(4)	1549(5)	3024(9)	5915(8)	56(3)
C(5)	2047(5)	3199(9)	5163(8)	47(2)
N(6)	2392(4)	1842(6)	4971(7)	57(3)
O(7)	1857(3)	838(5)	4664	53(2)
C(8)	1126(8)	2833(13)	4092(9)	80(5)
C(9)	1623(7)	3724(10)	4474(9)	72(5)
O(10)	756(4)	3652(6)	5901(7)	71(3)
C(11)	3154(5)	1668(8)	4768(7)	41(3)
O(12)	3661(3)	2548(6)	4867(6)	57(2)
O(13)	3311(3)	408(5)	4493(6)	50(2)
C(14)	4162(5)	47(9)	4416(9)	62(4)
C(15)	4202(4)	-1451(4)	4238(6)	47(2)
C(16)	3862	-2381	4790	58(2)
C(17)	3892	-3794	4631	75(3)
C(18)	4261	-4278	3920	70(3)
C(19)	4601	-3349	3368	73(3)
C(20)	4571	-1935	3527	62(3)
C(1A)	3445(5)	3703(9)	2077(8)	52(2)
C(2A)	2918(5)	3730(8)	1341(8)	56(4)
C(3A)	3162(5)	2800(9)	644(8)	51(3)
C(4A)	3834(5)	1829(9)	675(8)	57(4)
C(5A)	4321(5)	1684(9)	1444(8)	56(3)
N(6A)	4742(4)	2967(6)	1601(8)	52(3)
O(7A)	4253(3)	4094(5)	1835(6)	65(3)
C(8A)	3426(7)	2358(14)	2506(9)	80(5)
C(9A)	3852(7)	1343(10)	2181(9)	70(4)
O(10A)	3014(3)	1325(6)	702(6)	63(2)
C(11A)	5511(5)	3003(8)	1874(7)	38(3)
O(12A)	5958(3)	2045(5)	1827(6)	53(2)
O(13A)	5697(3)	4257(5)	2127(6)	53(2)
C(14A)	6548(4)	4518(8)	2249(8)	53(3)
C(15A)	6644(3)	6036(4)	2377(5)	40(2)
C(16A)	7077	6518	3050	50(2)
C(17A)	7151	7934	3186	62(3)
C(18A)	6793	8868	2648	57(2)
C(19A)	6360	8386	1976	62(3)
C(20A)	6285	6970	1840	53(2)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 2. Bond lengths (Å)

C(1)-C(2)	1.507 (17)	C(1)-O(7)	1.444 (11)
C(1)-C(8)	1.542 (16)	C(2)-C(3)	1.473 (18)
C(3)-C(4)	1.466 (12)	C(3)-O(10)	1.479 (10)
C(4)-C(5)	1.492 (17)	C(4)-O(10)	1.459 (10)
C(5)-N(6)	1.469 (11)	C(5)-C(9)	1.422 (18)
N(6)-O(7)	1.413 (8)	N(6)-C(11)	1.327 (11)
C(8)-C(9)	1.350 (17)	C(11)-O(12)	1.212 (10)
C(11)-O(13)	1.327 (10)	O(13)-C(14)	1.469 (9)
C(14)-C(15)	1.481 (10)	C(1A)-C(2A)	1.488 (16)
C(1A)-O(7A)	1.458 (10)	C(1A)-C(8A)	1.480 (17)
C(2A)-C(3A)	1.508 (16)	C(3A)-C(4A)	1.466 (12)
C(3A)-O(10A)	1.453 (10)	C(4A)-C(5A)	1.502 (17)
C(4A)-O(10A)	1.456 (10)	C(5A)-N(6A)	1.450 (11)
C(5A)-C(9A)	1.473 (18)	N(6A)-O(7A)	1.416 (9)
N(6A)-C(11A)	1.360 (11)	C(8A)-C(9A)	1.326 (17)
C(11A)-O(12A)	1.195 (10)	C(11A)-O(13A)	1.320 (10)
O(13A)-C(14A)	1.459 (9)	C(14A)-C(15A)	1.495 (9)

Table 3. Bond angles (°)

C(2)-C(1)-O(7)	108.8(9)	C(2)-C(1)-C(8)	111.5(9)
O(7)-C(1)-C(8)	111.6(8)	C(1)-C(2)-C(3)	117.2(8)
C(2)-C(3)-C(4)	123.4(11)	C(2)-C(3)-O(10)	117.7(10)
C(4)-C(3)-O(10)	59.4(5)	C(3)-C(4)-C(5)	122.2(11)
C(3)-C(4)-O(10)	60.7(5)	C(5)-C(4)-O(10)	116.6(10)
C(4)-C(5)-N(6)	107.0(8)	C(4)-C(5)-C(9)	114.3(9)
N(6)-C(5)-C(9)	110.3(10)	C(5)-N(6)-O(7)	116.3(6)
C(5)-N(6)-C(11)	122.9(7)	O(7)-N(6)-C(11)	115.5(7)
C(1)-O(7)-N(6)	114.2(6)	C(1)-C(8)-C(9)	116.3(11)
C(5)-C(9)-C(8)	116.3(10)	C(3)-O(10)-C(4)	59.9(5)
N(6)-C(11)-O(12)	123.2(8)	N(6)-C(11)-O(13)	113.0(7)
O(12)-C(11)-O(13)	123.6(7)	C(11)-O(13)-C(14)	116.0(6)
O(13)-C(14)-C(15)	107.1(6)	C(14)-C(15)-C(16)	119.2(6)
C(14)-C(15)-C(20)	120.8(6)	C(2A)-C(1A)-O(7A)	109.0(9)
C(2A)-C(1A)-C(8A)	112.6(8)	O(7A)-C(1A)-C(8A)	112.1(7)
C(1A)-C(2A)-C(3A)	116.0(7)	C(2A)-C(3A)-C(4A)	124.4(11)
C(2A)-C(3A)-O(10A)	119.5(10)	C(4A)-C(3A)-O(10A)	59.8(5)
C(3A)-C(4A)-C(5A)	120.2(10)	C(3A)-C(4A)-O(10A)	59.7(5)
C(5A)-C(4A)-O(10A)	117.0(10)	C(4A)-C(5A)-N(6A)	109.2(9)
C(4A)-C(5A)-C(9A)	114.5(9)	N(6A)-C(5A)-C(9A)	107.9(10)
C(5A)-N(6A)-O(7A)	115.4(6)	C(5A)-N(6A)-C(11A)	122.5(7)
O(7A)-N(6A)-C(11A)	115.9(7)	C(1A)-O(7A)-N(6A)	114.1(5)
C(1A)-C(8A)-C(9A)	116.9(12)	C(5A)-C(9A)-C(8A)	116.5(10)
C(3A)-O(10A)-C(4A)	60.5(5)	N(6A)-C(11A)-O(12A)	123.4(8)
N(6A)-C(11A)-O(13A)	110.4(7)	O(12A)-C(11A)-O(13A)	125.9(8)
C(11A)-O(13A)-C(14A)	115.6(6)	O(13A)-C(14A)-C(15A)	107.1(6)
C(14A)-C(15A)-C(16A)	119.7(5)	C(14A)-C(15A)-C(20A)	120.3(5)

Table 4. Anisotropic displacement coefficients ($Å^2 x 10^3$)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(2)	37(5)	56(6)	111(10)	-2(5)	-4(6)	-2(6)
C(3)	68(6)	37(5)	64(7)	0(5)	4(6)	0(5)
C(4)	53(5)	50(5)	64(7)	9(5)	-12(6)	-17(5)
N(6)	35(4)	31(4)	104(7)	-4(3)	0(5)	-26(4)
O(7)	29(3)	39(3)	92(5)	4(3)	-6(4)	-14(4)
C(8)	92(9)	114(9)	35(7)	41(8)	-3(6)	7(6)
C(9)	89(8)	50(6)	78(9)	-6(6)	30(7)	-11(6)
O(10)	67(4)	61(4)	86(5)	13(3)	16(4)	-14(4)
C(11)	34(5)	40(5)	48(6)	-6(4)	-1(5)	-12(5)
O(12)	43(3)	57(3)	71(5)	-12(3)	7(4)	-17(4)
O(13)	29(3)	45(3)	75(5)	2(3)	-2(3)	-16(3)
C(14)	35(4)	59(6)	93(8)	6(5)	-7(5)	-13(6)
C(2A)	58(6)	36(5)	75(7)	-4(4)	8(6)	-8(5)
C(3A)	53(5)	43(5)	56(6)	-9(5)	-4(6)	1(5)
C(4A)	54(6)	50(5)	68(7)	-3(5)	7(6)	-7(5)
N(6A)	35(4)	25(4)	97(7)	2(3)	-12(4)	-25(4)
O(7A)	26(3)	34(3)	133(7)	2(2)	-6(4)	-23(4)
C(8A)	76(7)	110(9)	53(8)	-19(7)	-13(7)	2(7)
C(9A)	88(8)	45(5)	78(9)	-9(5)	-36(7)	12(6)
O(10A)	48(3)	52(4)	90(5)	-4(3)	-9(4)	-17(4)
C(11A)	33(4)	44(5)	38(5)	-2(4)	-1(5)	-3(5)
O(12A)	35(3)	43(3)	82(6)	12(3)	1(4)	-7(4)
O(13A)	25(3)	39(3)	96(5)	-5(2)	-7(3)	-22(3)
C(14A)	33(5)	55(5)	71(7)	-5(4)	-5(5)	-8(5)

The anisotropic displacement exponent takes the form:

$-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2hka^*b^*U_{12})$

Table 5. H-Atom coordinates ($x10^4$) and isotropic displacement coefficients ($Å^2 x10^3$)

	x	y	z	U
H(1A)	837	774	4056	80
H(2A)	509	390	5376	80
H(2B)	35	1663	5070	80
H(3A)	715	1727	6452	80
H(4A)	1830	3136	6424	80
H(5A)	2482	3813	5285	80
H(8A)	802	3096	3632	80
H(9A)	1705	4631	4253	80
H(14A)	4445	261	4912	80
H(14B)	4390	567	3973	80
H(16A)	3608	-2047	5279	80
H(17A)	3658	-4435	5012	80
H(18A)	4281	-5252	3811	80
H(19A)	4855	-3682	2879	80
H(20A)	4805	-1294	3147	80
H(1AA)	3255	4400	2447	80
H(2AA)	2882	4663	1147	80
H(2AB)	2392	3450	1510	80
H(3AA)	3051	3170	110	80
H(4AA)	4119	1660	174	80
H(5AA)	4710	966	1366	80
H(8AA)	3123	2244	3002	80
H(9AA)	3858	447	2432	80
H(14C)	6851	4214	1783	80
H(14D)	6736	4032	2725	80
H(16B)	7324	5875	3420	80
H(17B)	7449	8266	3649	80
H(18B)	6844	9842	2742	80
H(19B)	6113	9029	1606	80
H(20B)	5988	6638	1377	80

CHAPTER 8

Experimental

INSTRUMENTATION

Routine ^{1}H NMR spectra were recorded on Varian EM 390 (90 MHz) or Jeol JNM-PS100 (100 MHz) spectrometers. Higher field ^{1}H NMR (300 MHz, 250 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker AM 300 or an ARX 250 spectrometer. Chemical shifts were recorded in ppm (δ) downfield from the internal reference (TMS). 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 a VG Micromass 14 spectrometer 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 a Kratos Concept mass spectrometer either 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.

TECHNICAL

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.[139] 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.[140]

Flash chromatography was carried out according to the method of Still[141] 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).

Tetramethylammonium periodate[142]

Paraperiodic acid (18.75 g, 0.082 mol) was dissolved in water (45 ml) and added in portions to a stirred 25% solution of tetramethylammonium hydroxide (30.04 g, 0.082 mol) at 0°C. The precipitated white solid was filtered, washed with cold methanol (40 ml) and dried to afford tetramethylammonium periodate (18.02 g, 83%) as a crystalline white solid. M.p. 252 - 254°C.

Benzyl-N-hydroxycarbamate[143]

Benzyl chloroformate (25.1 ml, 0.176 mol) was dripped into a stirred solution of hydroxylamine hydrochloride (13.41 g, 0.19 mol) and sodium hydroxide (15.80 g, 0.40 mol) in water (180 ml) at 0°C. On complete addition the mixture was warmed to room temperature and stirred for 4.5 hr. The pH was adjusted to 2 by adding HCl solution (6M) and the liberated oil was then repeatedly extracted with diethyl ether (3 x 90 ml). The combined organic layers were washed with water (50 ml) and the ethereal layer dried over anhydrous sodium sulphate. After filtration and evaporation of solvent at reduced pressure, the yellow solid was recrystallised twice from toluene and petroleum ether (b.p. 60 - 80°C) to yield benzyl-N-hydroxycarbamate (20.89 g, 71%) as a crystalline white solid. M.p. 67 - 69°C (Lit.[143] m.p 71°C).

N-(Benzyloxycarbonyl)-7-aza-8-oxabicyclo[4.2.2]dec-9-ene (**103**)

Tetramethylammonium periodate (37.90 g, 0.143 mol) and cycloocta-1,3-diene (**95**)

(14.32 g, 0.132 mol) in dichloromethane (180 ml) was stirred at 0°C. A solution of benzyl-N-hydroxycarbamate (23.90 g, 0.143 mol) in dichloromethane (85 ml) was dripped in over 20 min. The mixture was warmed to room temperature on complete addition and stirred for a further 5 hr. The solution was filtered, washed with saturated sodium thiosulphate solution (3 x 70 ml) and water (50 ml). The organic layer was separated, dried over anhydrous magnesium sulphate, filtered and the solvent distilled under reduced pressure. The residual yellow oil was purified by flash chromatography using 1:9 diethyl ether:petroleum ether (b.p. 40 - 60°C) to afford **(103)** (22.07 g, 61%) as a white solid. M.p. 60 - 61 °C (Lit[58] m.p. 61.0 - 61.5°C).

δ_H (90 MHz, $CDCl_3$): 1.45 - 2.30 (series of m, 8H), 4.65 (m, 1H, α-N), 4.90 (m, 1H, α-O) 5.15 (s, 2H, CH_2Ph), 5.75 (dd, J =10, 7 Hz, 1H), 6.30 (dd, J = 10, 7 Hz, 1H), 7.30 (s, 5H).

Potassium azodicarboxylate[144]

Azodicarbonamide (30.0 g, 0.26 mol) was stirred with a 1:1 solution of potassium hydroxide (75 ml) at 0°C. After the complete evolution of ammonia, the solution was filtered leaving a yellow solid. This was dissolved in the minimum quantity of cold water (80 ml) and poured into 4 volumes of ethanol, resulting in the precipitation of a bright yellow solid, which was filtered and washed with methanol (3 x 25 ml). The process was repeated to afford potassium azodicarboxylate (24.1 g, 48%), which was dried over P_2O_5.

N-(Benzyloxycarbonyl)-7-aza-8-oxabicyclo[4.2.2]decane **(131)**

Into a stirred slurry of potassium azodicarboxylate (17.68 g, 0.09 mol) and **(103)** (5.03 g, 0.018 mol) in methanol (155 ml) at 0°C was added dropwise glacial acetic acid (10.5 ml, 0.18 mol) over 40 min. The mixture was allowed to warm to room temperature and stirred for 3 hr when a further portion of potassium azodicarboxylate (7.28 g, 0.038 mol) was added and stirred for a further 2 hr. Water (12 ml) was added and the bulk of the solvent removed under vacuum. The oily residue was partitioned between dichloromethane (105 ml) and 5% sodium bicarbonate solution (40 ml). After washing with further bicarbonate solution (2 x 40 ml) the organic layer was dried over magnesium sulphate. Filtration and removal of solvent under vacuum gave a crude oil which was purified by flash chromatography using 2:8 diethyl ether:petroleum ether (b.p. 40-60°C) to yield **(131)** (4.59 g, 91%) as a colourless oil.

δ_H (300 MHz, $CDCl_3$): 1.51 - 1.79 (series of m, 10H), 1.99 (brm, 1H), 2.13 - 2.28 (brm, 1H), 4.48 (brm, 1H, α-N), 4.59 (brm, 1H, α-O), 5.21 (s, 2H, CH_2Ph), 7.28 - 7.37 (m, 5H).

δ_C (75 MHz, $CDCl_3$), Signals in italics were broadened due to rotation about the N-CO bond and values are approximate; the signal due to C_1 of the benzyl group was not visible: *20.5*, *22.3*, 23.7, 24.6, *33.0*, 34.4 (6 x CH_2), *51.2* (CHN), 67.1 (CH_2Ph), *76.5* (CHO), 127.8 (2 x aryl CH), 128.3 (aryl CH).

ν_{max} (CH_2Cl_2): 3090w, 3060w, 3040w, 2930s, 2860m, 1725s, 1690s, 1590w, 1495w, 1400m, 1355m, 1330m, 1315m, 1290m, 1260m, 1210w, 1195m, 1150w, 1095s, 1070s, 1020m, 990w, 930w cm^{-1}.

$^m/z$ (%): 275 (M^+, 13), 231 (7), 146 (5), 140 (7), 132 (10), 92 (14), 91 (100), 81 (4).

$C_{16}H_{21}NO_3$ [M^+] requires $^m/z$ 275.1521; observed 275.1525.

Cis-4-[(Benzyloxycarbonyl)amino]cyclooctanol (**132**)

To a solution of **(131)** (1.26 g, 4.56 mmol) in dry ethanol (18 ml) was added sodium phosphate (3.12 g, 22 mmol). The suspension was stirred for 5 min and freshly prepared[67] and powdered 6% sodium amalgam (14 g) was added at 0°C under a nitrogen atmosphere. After stirring for 3 hr the solution was filtered and the solvent removed under vacuum. The oil was dissolved in water (40 ml) and extracted into dichloromethane (3 x 20 ml). The combined organic layers were dried over anhydrous magnesium sulphate, filtered, and the solvent removed under vacuum to afford **(132)** (1.26 g, 100%) as a colourless oil.

δ_H (300 MHz, $CDCl_3$): 1.48 - 1.74 (brm, 12H), 2.15 (brs, OH), 3.65 (brm, 1H, α-N), 3.81 (brm, 1H, α-O), 4.94 (d, J = 7.3 Hz, 1H, NH), 5.06 (s, 2H, CH_2Ph), 7.26 - 7.37 (m, 5H).

δ_C (75 MHz, $CDCl_3$): 22.0, 23.4, 28.0, 30.9, 31.2 & 33.2 (6 x CH_2), 51.2 (CHN), 66.5 (CH_2Ph), 71.2 (CHO), 128.0 (2 x aryl CH), 128.4, (aryl CH), 136.6 (aryl C), 155.4 (C=O).

ν_{max} (CH_2Cl_2): 3600m, 3420m, 3015w, 2930s, 2860m, 1710s, 1500s, 1450w,

1315brw, 1215s, 1080w, 1055s, 1010m, 975m, 910m cm^{-1}.

m/z (%): 277 (M^+, 6), 168 (19), 146 (34), 142 (31), 126 (16), 125 (21), 124 (17), 123 (19), 114 (10), 112 (23), 110 (13), 109 (18), 108 (100), 107 (100), 105 (14).

$C_{16}H_{23}NO_3$ [M^+] requires m/z 277.1680; observed 277.168.

4-[(Benzyloxycarbonyl)amino]cyclooctanone **(133)**

Jones reagent,[68] prepared form chromium trioxide (12.35 g), concentrated sulphuric acid (11.5 ml) and water (20 ml), was dripped into a solution of **(132)** (1.234 g, 4.45 mmol) in dry acetone (36 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 distilled under reduced pressure. The oil was dissolved in dichloromethane (30 ml) and washed with water (2 x 7 ml) and brine (5 ml). The organic layer was separated, dried over magnesium sulphate, filtered, and the solvent removed under vacuum to yield **(133)** (1.206 g, 98%) which, after recrystallisation from petroleum ether (b.p. 80 - 100°C), had m.p. 117 - 118°C. On leaving a solution of **(133)** to stand in $CDCl_3$ for several hours a second set of minor signals were observed which corresponded to the bicyclic tautomer **(134)** in a ratio of 71:29. Data for the bicyclic tautomer **(134)** are given separately below; the figures quoted in italics are common to both tautomers.

δ_H (300 MHz, $CDCl_3$), Monocyclic tautomer: *1.33 - 1.65* (series of m, 4H), *1.82 - 2.04* (series of m, 2H), *2.07 - 2.31* (brm, 2H), *2.34 - 2.50* (brm, 3H), 3.75 (m, 1H), 4.96 (brd, J = 6.9 Hz, NH), 5.07 (s, 2H), *7.34* (s, 5H).

δ_C (75 MHz, $CDCl_3$): 23.4, 28.2, 28.4, 31.2, 39.8 & 40.4 (6 x CH_2), 50.8 (CHN), 66.5 (CH_2Ph), 128.0 (2 x aryl CH), 128.4, (aryl CH), 136.5 (aryl C), 155.4 (NC=O), 217.0 (CC=O).

The bicyclic tautomer **(134)** showed signals as shown in italics above together with signals at δ 4.32 (m, 1H), 5.11 & 5.17 (ABq, J = 12.4 Hz, 2H, CH_2Ph) in the ^1H NMR spectrum and at δ 23.0, 23.7, 27.8, 34.7, 37.7 & 40.0 (6 x CH_2), 55.4 (CHN), 66.6 (CH_2Ph), 92.9 (COH), 127.7, 128.0 & 128.5 (3 x aryl CH), 136.4 (aryl C), 155.1 (C=O) in the ^{13}C NMR spectrum.

ν_{max} (CH_2Cl_2): 3440m, 3340brw, 3060w, 3015w, 2940s, 2860m, 1720vs, 1505s, 1465m, 1450m, 1405w, 1340m, 1310m, 1215w, 1150w, 1125w, 1085m, 1060w, 1035m, 1025w, 1005w, 980w, 845w cm^{-1}.

m/z (%): 275 (M^+, 10), 184 (6), 146 (7), 140 (15), 108 (9), 92 (9), 91 (100), 84 (14).

Found: C, 69.93; H, 7.46; N, 5.09%.
$C_{16}H_{21}NO_3$ requires: C, 69.79; H, 7.69; N, 5.10%.

4-Methylene-[(benzyloxycarbonyl)amino]cyclooctane **(135)**

A 50 ml two-necked round bottom flask was charged with sodium hydride (80% dispersion in mineral oil, 183 mg, 3.82 mmol). The flask was equipped with a rubber septum cap and condenser. The system was alternately purged and evacuated with nitrogen; dry DMSO (4 ml) was injected *via* syringe and the system was warmed to 80°C with stirring for 45 min. On cooling to room temperature methyltripheny-phosphonium bromide (1.363 g, 3.82 mmol) in DMSO (5 ml) was introduced and stirred at room temperature for 10 min. A solution of **(133)** (300 mg, 1.09 mmol) in DMSO (4 ml) was injected and stirred at room temperature for 18 hr. The bulk of the solvent was distilled under reduced pressure, the residue dissolved in water (15 ml) and extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried over anhydrous magnesium sulphate, filtered, and the solvent distilled under reduced pressure. After flash chromatography using 1:10 diethyl ether:petroleum ether (b.p. 40 - 60°C), **(135)** (142 mg, 48%) was isolated as a colourless oil.

δ_H (300 MHz, $CDCl_3$): 1.49 - 1.81 (brm, 7H), 1.95 (m, 1H), 2.14 - 2.23 (m, 3H), 2.34 (m, 1H), 3.73 (m, 1H, α-N), 4.78 and 4.80 (each s, 1H, $=CH_2$), 4.88 (d, J = 6.8 Hz, NH), 5.06 (s, 2H), 7.25 - 7.34 (m, 5H).

δ_C (75 MHz, $CDCl_3$): 23.4, 30.2, 30.4, 32.0, 32.5 & 33.6 (6 x CH_2), 51.1 (CHN), 66.4 (CH_2Ph), 111.6 ($=CH_2$), 128.0, 128.1 & 128.4 (3 x aryl CH), 136.6 (aryl C), 150.9 ($\mathbf{C}=CH_2$), 155.4 (C=O).

ν_{max} (CH_2Cl_2): 3330m, 3065w, 3030w, 2925s, 2850m, 1695s, 1640w, 1530s, 14850m, 1405w, 1315m, 1235s, 1145w, 1100w, 1075w, 1035w, 970w, 885m, 740m, 695m cm^{-1}.

$^{m}/z$ (%, CI): 274 (MH^+, 100), 230 (52), 140 (20), 138 (24), 123 (22), 108 (32), 91 (73).

$C_{17}H_{24}NO_2$ [MH^+] requires $^{m}/z$ 274.1807; observed 274.181.

N-(Benzyloxycarbonyl)-1-methyl-9-azabicyclo[4.2.1]nonane **(136)**

Mercury(II) trifluoroacetate (152 mg, 0.36 mmol) was added to a stirred solution of **(135)** (92 mg, 0.34 mmol) in dry acetonitrile (12 ml) at room temperature. Stirring was continued for 2.5 hr and the bulk of the solvent was distilled under reduced pressure to afford an oil which was dissolved in THF (10 ml). The solution was cooled to -78°C and sodium borohydride (26 mg, 0.66 mmol) was added with stirring under an nitrogen atmosphere, resulting in the precipitation of mercury. The solution was warmed to room temperature and stirred for a further 30 min. Excess hydride was destroyed by the dropwise addition of water and the solution was dried with anhydrous sodium sulphate and filtered through celite. The solvent was distilled under reduced pressure and the crude oil was purified by flash chromatography using 1:4 diethyl ether:petroleum ether (b.p. 40 - 60°C) to give **(136)** (57 mg, 61%) as an oil. When the reaction was repeated under a nitrogen atmosphere, the yield of **(136)** was increased to 73%. Figures quoted in italics are common to both rotamers.

δ_H (300 MHz, $CDCl_3$), Major rotamer: *1.33 - 1.56* (series of m, 6H), *1.60* (s, 3H), *1.80 - 2.15* (series of m, 6H), 4.34 (brt, J ≈ 7.2 Hz, 1H), *5.03 & 5.14* (ABq, J = 12.5 Hz, 2H, CH_2Ph), *7.25 - 7.37* (m, 5H).

Minor rotamer: *1.33 - 1.56* (series of m, 6H), *1.60* (s, 3H), *1.80 - 2.15* (series of m, 6H), 4.41 (m, 1H), *5.03 & 5.14* (ABq, J = 12.5 Hz, 2H, CH_2Ph), *7.25 - 7.37* (m, 5H).

δ_C (75 MHz, $CDCl_3$), Major rotamer: 23.6 & *25.0* (2 x CH_2), 28.6 (CH_3), *29.4*, 34.8, 38.8 & 39.6 (4 x CH_2), 57.7 (CHN), 63.9 (C), 66.0 (CH_2), *127.7*, *127.8 & 128.4* (3 x aryl CH), *137.2* (aryl C), *154.3* (C=O).

Minor rotamer: 23.5 & *25.0* (2 x CH_2), 29.7 (CH_3), *29.4*, 33.1, 40.4 & 41.2 (4 x CH_2), 58.7 (CHN), 63.1 (C), 66.6 (CH_2), *127.7*, *127.8 & 128.4* (3 x aryl CH), *137.2* (aryl C), *154.3* (C=O) .

ν_{max} (CH_2Cl_2): 2930s, 2850m, 2690w, 1700s, 1450m, 1440m, 1340m, 1320m, 1120m,

1060m cm^{-1}.

$^m/z$ (%, CI): 274 (MH^+, 22), 173 (10), 172 (14), 138 (29), 91 (100).

$C_{17}H_{24}NO_2$ [MH^+] requires $^m/z$ 274.1807; observed 274.181.

N-(Benzyloxycarbonyl)-1-hydroxymethyl-9-azabicyclo[4.2.1]nonane **(137)**

The hydroxymethyl compound **(137)** (25 mg, 25%) was isolated as a by-product during chromatographic separation of a crude sample of **(136)** prepared as described above.

δ_H (300 MHz, $CDCl_3$): 1.26 - 1.66 (series of m, 7H), 1.81 (m, 2H), 2.08 (m, 2H), 2.31 (m, 1H), 3.60 & 3.70 (ABq, J = 11.7 Hz, 2H), 4.38 (m, 1H), 5.08 & 5.16 (ABq, J = 12.4 Hz, 2H), 7.28 - 7.36 (m, 5H).

δ_C (75 MHz, $CDCl_3$): 24.0, 24.1, 29.1, 33.9, 34.2 & 35.8 (6 x CH_2), 58.6 (CHN), 67.0 (CH_2Ph), 68.7 (C), 68.9 (CH_2OH), 127.8, 128.0 & 128.5 (3 x aryl CH), 136.6 (aryl C), 156.0 (C=O).

ν_{max} (CH_2Cl_2): 3385brs, 3075w, 3060w, 3030w, 2930s, 2850m, 1675s, 1545w, 1455m, 1410m, 1345m, 1325m, 1280m, 1233m, 1205m, 1165m, 1120m, 1080m, 1060m, 1020m, 980w, 965w, 910w, 770m cm^{-1}.

$^m/z$ (%): 289 (M^+, 5), 181 (49), 154 (19), 153 (65), 152 (52), 138 (11), 137 (11), 136 (11), 125 (15), 124 (24), 122 (12), 110 (10), 109 (61), 108 (100), 107 (87), 106 (12), 105 (14), 95 (100) 91 (100).

$C_{17}H_{23}NO_2$ [M^+] requires $^m/z$ 289.1678; observed 289.168.

N-Methyl-1-methyl-9-azabicyclo[4.2.1]nonane **(141)**

A solution of **(136)** (102 mg, 0.37 mmol) in dry THF (4 ml) was added dropwise to a stirred slurry of LAH (28 mg, 0.73 mmol) in dry THF (1 ml) under nitrogen at 0°C. The system was allowed to warm to ambient temperature, stirred for 3 hr, then heated at reflux for 1 hr. The excess hydride was destroyed by addition of water-saturated diethyl ether and the solution was dried with sodium sulphate and filtered through celite. The solution was cooled to 0°C, acidified with gaseous HCl, and the solvent

was evaporated under reduced pressure. The resulting oil was repeatedly triturated with diethyl ether to remove benzyl alcohol and to induce crystallisation of **(141.HCl)** as a hygroscopic pale yellow solid (54 mg, 78%) which was recrystallised from toluene.

δ_H (300 MHz, $CDCl_3$): 1.61 (s, 3H), 1.76 (m, 6H), 1.95 - 2.29 (m, 3H), 2.30 (m, 1H), 2.60 (m, 2H), 2.73 (d, $J_{Me, NH}$ = 4.4 Hz, 3H), 4.08 (bm, 1H), 11.62 (NH); in addition, small signals at δ 3.85 and δ 11.06 corresponded to H6 and the NH protons of the minor stereoisomeric quaternary salt. An 8:1 ratio of equitorial:axial stereoisomers was calculated from the signal integrations.

δ_C (75 MHz, $CDCl_3$), Major stereoisomer: 22.7 & 23.6 (2 x CH_2), 24.8 (CH_3), 28.1 & 28.2, (2 x CH_2), 29.3 (CH_3), 34.6 (CH_2), 37.1 (CH_2), 62.7 (CHN), 70.0 (C).

ν_{max} (CH_2Cl_2): 3680w, 3380br, 3025m, 2940s, 2870m, 2390vbr, 1465m, 1445m, 1380m, 1265w, 1215w, 1205w, 1100m, 1085w, 1065w, 1045w, 1010w, 995w, 970w, 905s, 845w cm^{-1}.

$^m/_z$ (%): 153 (M^+- HCl, 28), 152 (5), 126 (6), 124 (20), 111 (12), 110 (95), 98 (6), 97 (69), 96 (100), 82 (6), 81 (6), 71 (5), 56 (26), 55 (10).

$C_{10}H_{19}N$ [M^+ - HCl] requires $^m/_z$ 153.1517; observed: 153.1516.

1-Methyl-9-azabicyclo[4.2.1]nonane **(122)**

A solution of **(136)** (69 mg, 0.25 mmol) in dry methanol (6 ml) was hydrogenolysed with a catalytic amount of 5% palladium on charcoal at 1 atmosphere. After 4 hr the solution was filtered through a Millipore 0.2μ Millex-FG disposable filter unit giving a colourless solution. This was acidified with gaseous hydrogen chloride before evaporation of solvent under reduced pressure yielding **(122.HCl)** (42 mg, 95%) as a hygroscopic pale yellow solid. The 300 MHz ^1H NMR spectrum was identical to that of a sample prepared by Smith.[58]

δ_H (300 MHz, $CDCl_3$): 1.46 - 2.35 (series of m, 11H [plus δ 1.71 (s, 3H)]), 2.51 (m, 1H), 4.21 (m, 1H, α-N), 9.23 (brm, 1H, NH_2), 9.66 (brm, 1H, NH_2).

4-([Benzyloxycarbonyl]amino)cyclooctanone-*p*-toluenesulphonylhydrazone (**146**)

The ketone (**133**) (1.600 g, 5.82 mmol) was added to absolute ethanol (45 ml) and warmed until fully dissolved. *p*-Toluenesulphonylhydrazide (1.082 g, 5.82 mmol) was added with a catalytic quantity of *p*-toluenesulphonic acid. The solution was refluxed for 3 hr and the volume of solvent was then concentrated to two thirds of the original volume by distillation under reduced pressure. After refrigeration overnight, the crystals that formed were filtered and washed with cold ethanol and dried to afford (**146**) (1.688 g, 65%) as a crystalline white solid. M.p. 156 - 159°C.

δ_H (300 MHz, CD_3SOCD_3): 1.25 - 1.83 (series of m, 8H), 2.08 (m, 1H), 2.03 - 2.42 (series of m, 3H [plus 2.73 (s, 3H)]), 3.46 (m, 1H, α-N), 5.01 (s, 2H, CH_2Ph), 7.29 - 7.42 (m, 5H plus part of AA'BB', 2H), 7.75 (part of AA'BB', 2H). The NH signals were not observed.

ν_{max} (Nujol): 3360w, 3240w, 1690s, 1535w, 1335w, 1325w, 1310w, 1245w, 1160m, 1040w, 810w cm^{-1}.

$^m/z$ (%): 443 (M^+, 1), 387 (9), 316 (13), 315 (17), 288 (43), 260 (26), 259 (100), 258 (100).

Found: C, 62.26; H, 6.74; N, 9.41%.
$C_{23}H_{29}N_3O_4S$ requires: C, 62.28; H, 6.59; N, 9.47%.

[(Benzyloxycarbonyl)amino]cyclooct-3-ene and -4-ene (**147a,b**)

A solution of (**146**) (261 mg, 0.59 mmol) in THF (12ml) was cooled to -78°C and stirred under a nitrogen atmosphere. A solution of *n*-butyllithium (2.5M in hexane, 0.94 ml, 2.36 mmol) was injected and warmed to -10°C after 10 min. After a further 15 min the brick red solution was warmed to room temperature and quenched with water (200 μl). The solvent was concentrated under reduced pressure, the residual oil taken up in diethyl ether (15 ml) and washed with water (2 x 4 ml). The ethereal layer was separated, dried over anhydrous magnesium sulphate, filtered, and the solvent distilled under reduced pressure. The crude oil was purified by flash column chromatography using 1:5 diethyl ether:petroleum ether (b.p. 40 - 60°C) to afford a mixture of alkenes (**147a,b**) (64 mg, 42 %) as a crystalline white solid, which after recrystallisation from toluene and petroleum ether (b.p. 40 - 60°C), gave m.p. 59 - 61 °C (mixture of **147a,b**). The signals given in italics are common to both

regioisomers.

δ_H (300 MHz, $CDCl_3$): *1.26 - 1.96* (series of m, 7H), *2.04 - 2.47* (series of m, 3H), *3.71* (brm, 1H, α-N), *4.76* (brm, 1H, HN), *5.07* (s, 2H, CH_2Ph), *5.57 - 5.80* (series of m, 2H), *7.27 - 7.40* (m, 5H).

δ_C (75 MHz, $CDCl_3$): 22.5, 23.3, 25.85, 25.9, 28.7, 31.0, 32.1, 34.7 & 35.5 (9 x CH_2), 51.2 (CHN), 51.6 (CHN), *66.5* (CH_2Ph), 126.0 (=CH_2), *128.0, 128.1 & 128.5* (3 x aryl CH), 129.6, 130.1 & 133.0 (3 x =CH_2), *136.6* (aryl CH_2), *155.3* (C=O).

ν_{max} (CH_2Cl_2): 3420m, 3030m, 2940m, 2860w, 1720s, 1510s, 1450w, 1395w, 1355s, 1300w, 1225s, 1170s, 1125w, 1090w, 1025m, 970m, 935s, 900w, 880w, 855m, 820w cm^{-1}.

$^m/z$ (%): 259 (M^+, 3), 231 (8), 168 (9), 146 (4), 124 (8), 92 (9), 91 (100).

$C_{16}H_{21}NO_2$ [M^+] requires $^m/z$ 259.1572; observed 259.1572.

Found: C, 74.15; H, 8.20; N, 5.39%.
$C_{16}H_{21}NO_2$ requires: C, 74.10; H, 8.16; N, 5.40%.

N-(Benzyloxycarbonyl)-9-azabicyclo[4.2.1]nonane **(148)**

Mercury(II) trifluroacetate (98 mg, 0.23 mmol) was added to a solution of **(147a,b)** (55 mg, 0.21 mmol) in acetonitrile (5 ml) and stirred for 18 hr, under a nitrogen atmosphere, as described for the preparation of **(136)**. Following treatment with sodium borohydride (19 mg, 0.50 mmol) and purification by flash chromatography using 1:11 diethyl ether:petroleum ether (b.p. 40 - 60 °C) **(148)** was isolated (40 mg, 73 %) as a colourless oil. The figures in italics refer to signals common to both rotamers.

δ_H (300 MHz, $CDCl_3$): *1.34 - 1.71* (series of multiplets, 8H), *1.94 - 2.22* (series of m, 4H), *4.33* (m, 2H, α-N), *5.09 & 5.16* (ABq, J = 12.6 Hz, 2H, CH_2Ph), *7.33* (m, 5H).

δ_C (75 MHz, $CDCl_3$): 24.1 & 24.2 (2 x CH_2), 29.3 & 29.7 (2 x CH_2), 30.2 & 31.3 (2 x CH_2), 55.3 & 55.7 (2 x CHN), *127.65, 127.7 & 128.4* (3 x aryl CH), *137.2* (aryl C), *153.7* (C=O).

ν_{max} (CH_2Cl_2): 3030w, 2920s, 2860w, 1680s, 1415s, 1360m, 1330s, 1210w, 1080w, 1100s, 1030w, 990m, 945m, 905m, 870w cm^{-1}.

$^m/z$ (%): 259 (M^+ 30), 172 (5), 168 (9), 159 (6), 158 (20), 124 (17), 92 (9), 91 (100).

$C_{16}H_{21}NO_2$ [M^+] requires $^m/z$ 259.1572; observed 259.1573.

N-Methyl-9-azabicyclo[4.2.1]nonane (homotropane) **(64)**

A solution of **(148)** (35 mg, 0.14 mmol) in dry diethyl ether (7 ml) and LAH (16 mg, 0.42 mmol) was refluxed under an nitrogen atmosphere for 45 min. The solution was cooled in an ice bath and excess hydride was destroyed by the dropwise addition of water-saturated diethyl ether. After complete decomposition the solution was dried over anhydrous sodium sulphate and filtered through celite to afford a colourless solution. This was cooled to 0°C, acidified with gaseous hydrogen chloride and the solvent was evaporated under reduced pressure. The resultant oil was repeatedly triturated with a 1:1 mixture of diethyl ether:petroleum ether (b.p. 40 - 60°C) to remove benzyl alcohol and to induce solidification of **(64.HCl)** (23 mg, 97%) as a hygroscopic white solid. The hydrochloride salt **(64.HCl)** was dissolved in $CDCl_3$, basified with gaseous ammonia and filtered to afford the free amine **(64)**. The 300 MHz ^1H NMR spectrum was identical to that of a sample prepared by Smith.[58]

δ_H (300 MHz, $CDCl_3$): 1.37 - 1.63 (series of m, 8H), 1.79 - 1.86 (m, 2H), 2.12 - 2.24 (m, 2H), 2.42 (s, 3H), 3.25 (m, 2H, α-N).

$^m/z$ (%): 139 (M^+ - HCl, 47), 110 (22), 97 (12), 96 (100), 83 (32), 82 (61).

9-Azabicyclo[4.2.1]nonane (norhomotropane) **(65)**

A solution of **(148)** (36 mg, 0.14 mmol) in absolute ethanol (5 ml) was hydrogenolysed in the presence of a catalytic quantity of 5% palladium on charcoal at 1 atmosphere. After 4 hr the solution was filtered through a Millipore 0.2μ Millex-FG disposable filter unit giving a clear solution which was acidified with gaseous hydrogen chloride at 0°C. Distillation of the solvent under reduced pressure furnished **(65.HCl)** (20 mg, 89%) as a hygroscopic white solid, with an identical 300 MHz spectrum to that of a sample prepared by Smith.[58]

δ_H (300 MHz, $CDCl_3$): 1.63 - 1.83 (series of m, 6H), 1.96 (m, 2H). 2.23 (m, 2H), 2.39 (m, 2H), 4.19 (m, 2H, α-N), 9.08 (brm, 1H, NH), 9.95 (brm, 1H, NH).

Cis-4-[(Benzyloxycarbonyl)amino]cyclooct-2-enol **(150)**

To a solution of **(103)** (4.80 g, 18 mmol) in dry ethanol (41 ml) was added sodium phosphate (11.40 g, 80 mmol). The suspension was stirred under a nitrogen atmosphere for 5 min. Freshly prepared[67] and powdered 6% sodium amalgam (47 g) was added and the mixture was stirred for 1 hr. The solution was filtered through celite and the solvent removed under vacuum. The residual oil was partitioned between water (30 ml) and dichloromethane (40 ml). The organic layer was separated and the aqueous layer was extracted further with dichloromethane (2 x 40 ml). The combined organic layers were dried over magnesium sulphate, filtered, and the solvent removed under vacuum. The resulting oil was triturated with petroleum ether (b.p. 40 - 60°C) to yield **(150)** (4.74 g, 98%) as a white solid (4.74 g, 98%) which was recrystallised from toluene and petroleum ether (b.p. 40 - 60°C) to afford a crystalline white solid, m.p. 127 - 128°C.

δ_H (300 MHz, $CDCl_3$): 1.25 - 1.62 (m, 6H), 1.88 (m, 2H), 2.62 (brs, OH), 4.41 (brs, 1H, α-N), 4.62 (brm, 1H, α-OH), 5.01 (d, J = 5.7 Hz, NH), 5.06 (s, 2H), 5.25 (ddd, J = 10.4, 8.3, 1.5 Hz, 1H), 5.60 (dd, J = 10.4, 7.0 Hz, 1H), 7.33 (m, 5H).

δ_C (75 MHz, $CDCl_3$): 23.4, 24.0, 36.5 & 38.3 (4 x CH_2), 49.4 (CHN), 66.6 (CH_2Ph), 69.3 (CHO), 128.0 (2 x aryl CH), 128.4, (aryl CH), 129.4 & 139.4 (2 x =CH), 136.4 (aryl C), 155.7 (C=O).

ν_{max} (CH_2Cl_2): 3600m, 3430m, 3420m, 2930s, 2860w, 1715s, 1505s, 1450w, 1395w, 1315brw, 1235m, 1210m, 1130w, 1085w, 1045m, 1015m, 950w, 860w cm^{-1}.

$^m/z$ (%): 275 (M^+, 1), 184 (19), 172 (6), 140 (13), 123 (5), 108 (9), 107 (5), 95 (4), 92 (9), 91 (100), 80 (4), 79 (7).

Found: C, 69.87; H, 7.74; N, 5.08%.
$C_{16}H_{21}NO_3$ requires: C, 69.79; H, 7.69; N, 5.09%.

4-[(Benzyloxycarbonyl)amino]cyclooct-2-enone (**151**) and
N-benzyloxycarbonyl-1-hydroxy-9-azabicyclo[4.2.1]non-7-ene (**152**)

Barium manganate[81] (48.0 g, 180 mmol) was added to a stirred solution of (**150**) (4.56 g, 16.6 mmol) in dry dichloromethane (215 ml) under nitrogen. The suspension was stirred at room temperature for 48 hr. Dichloromethane (100 ml) was added with stirring and the mixture was filtered through celite. The solvent was removed under vacuum and the resulting oil purified by flash chromatography using 1:4 diethyl ether:petrol (b.p. 40 - 60°C) to yield firstly (**152**) as a yellow oil. Further elution afforded (**151**) also as a yellow oil, the two tautomers having a combined weight of 3.83 g, 85%. Leaving a solution of either tautomer to stand over a period of days resulted in equilibration to a 37:63 ratio of (**151**):(**152**) respectively (calculated from signal integrations). Data for the monocyclic (**151**) and bicyclic (**152**) tautomers are given separately below; where signals due to two rotamers were visible, figures given italics are common to both rotamers.

δ_H (300 MHz, $CDCl_3$), Monocyclic tautomer: 1.44 - 2.01 (series of m, 6H), 2.54 (m, 1H), 2.84 (m, 1H), 4.95 (m, NH), 5.01 (m, 1H, α-N), 5.12 (s, 2H), 6.09 (m, 2H, =CH).

Bicyclic tautomer: *1.27 - 1.66* (series of m, 5H), *1.89* (m, 1H), *2.02* (m, 1H), *2.29* (m, 1H), 4.71 (m, 1H, α-N, major rotamer), 4.75 (m, 1H, α-N, minor rotamer), *5.13, 5.20* (ABq, J = 12.2 Hz, 2H, CH_2Ph), 5.71 (d, J = 6.2 Hz, 1H, =CH, minor rotamer), 5.74 (dd, J = 6.2, 1.0 Hz, 1H, =CH, major rotamer), 5.86 (dd, J = 6.2, 2.6 Hz, 1H, =CH, major rotamer), 5.89 (dd, J = 6.2, 2.6 Hz, 1H, =CH, minor rotamer), 7.30 - 7.37 (m, 5H).

δ_C (75 MHz, $CDCl_3$), Monocyclic tautomer: 22.4, 22.6, 31.0 & 42.0 (4 x CH_2), 50.6 (CHN), 67.0 (CH_2Ph), 128.16, 128.22 & 128.5 (3 x aryl CH), 132.7 (=CH), 136.1 (aryl C), 144.1 (=CH), 155.6 (NC=O), 203.4 (α,β-unsaturated CO).

Bicyclic tautomer: 23.2, 23.6, 30.8 & 38.7 (4 x CH_2), 60.8 (CHN), 66.4 (CH_2Ph), 95.7 (COH), 127.8, 128.0 & 128.4 (3 x aryl CH), 131.6 & 132.3 (2 x =CH), 136.4 (aryl C), 154.0 (C=O).

ν_{max} (CH_2Cl_2), Monocyclic tautomer: 3430m, 2950m, 2860m, 1715s, 1660m, 1500m, 1350w, 1320brm, 1215m, 1170w cm^{-1}.

ν_{max} (CH_2Cl_2), Bicyclic tautomer: 3470brw, 2930m, 2850w, 1670s, 1415m, 1350m, 1320m, 1190m, 1125m, 1095m, 1040w, 1020w, 995m, 945w, 835w cm^{-1}.

m/z (%): 273 (M^+, 13), 229 (10), 186 (34), 165 (12), 138 (23), 137 (11), 124 (16), 122 (22), 121 (21), 120 (17), 109 (26), 108 (87), 107 (61), 106 (10), 105 (30), 91 (100).

$C_{16}H_{19}NO_3$ [M^+] requires m/z 273.1365; observed 273.136.

4-Methylene-[(benzyloxycarbonyl)amino]cyclooct-2-ene **(153)**

The *exo*-methylene derivative **(153)** was prepared using the method described for **(135)** using sodium hydride (80% dispersion, 384 mg, 12.8 mmol) in dry DMSO (8 ml), methyltriphenylphosphonium bromide (4.75 g, 13 mmol) in DMSO (13 ml), and **(151 ⇌ 152)** (698 mg, 2.56 mmol) in DMSO (8 ml). After flash chromatography using 1:9 diethyl ether:petrol ether (b.p. 40 - 60°C) **(153)** was obtained as a white solid (397 mg, 57%) which had m.p. 94 - 95°C after recrystallisation from petroleum ether (b.p. 80 - 100°C).

δ_H (300 MHz, $CDCl_3$): 1.31 (m, 1H), 1.60 (m, 4H), 1.90 (m, 1H), 2.36 (m, 1H), 2.68 (m, 1H), 4.87 (brs, 1H, $=CH_2$), 4.90 (s, NH), 4.96 (d, J = 1.0 Hz, 1H, $=CH_2$), 5.08, (s, 2H, CH_2Ph), 5.09 (m, 1H, =CH), 5.15 (m, 1H, α-N), 6.18 (d, J = 11.5 Hz, 1H, =CH), 7.32 (m, 5H).

δ_C (75 MHz, $CDCl_3$): 21.6, 28.1, 33.6 & 34.4 (4 x CH_2), 49.6 (CHN), 66.6 (CH_2Ph), 118.9 ($C=CH_2$), 128.0, 128.1 & 128.4 (3 x aryl CH), 130.1 (=CH), 134.1 (=CH), 136.5 (aryl C), 146.0 ($C=CH_2$), 155.7 (C=O).

ν_{max} (CH_2Cl_2): 3430m, 3010, 2940m, 2850w, 1715s, 1590w, 1505s, 1470w, 1460w, 1320w, 1220m, 1040m, 1030m, 975w, 895w cm^{-1}.

m/z (%, CI): 272 (MH^+, 100), 228 (91), 211 (20), 136 (22), 121 (36), 108 (25), 91 (17).

$C_{17}H_{22}NO_2$ [MH^+] requires m/z 272.1651; observed 272.165.

Found: C, 75.19; H, 7.97; N, 5.17%.
$C_{17}H_{21}NO_2$ requires C, 75.24; H, 7.80; N, 5.16%.

N-(Benzyloxycarbonyl)-1-methyl-7β-hydroxy-9-azabicyclo[4.2.1]nonan-7-ol (**154a**) and N-(benzyloxycarbonyl)-1-methyl-8β-hydroxy-9-azabicyclo[4.2.1]nonan-7-ol (**154b**)

The cyclisation of (**153**) was carried out according to the method described for preparing (**136**) using mercury(II) trifluoroacetate (216 mg, 0.51 mmol) and (**153**) (131 mg, 0.48 mmol) in dry acetonitrile (8 ml). The reduction was carried out using sodium borohydride (37 mg, 0.98 mmol) in dry THF (14 ml) to give (**154a,b**) (76 mg, 54%) after flash chromatography using 2:3 diethyl ether:petrol ether (b.p. 40 - 60°C).

δ_H (300 MHz, $CDCl_3$): 1.21 - 1.66 (series of m, including CH_3, 8H), 1.79 - 2.41 (series of m, 5H), 2.58 (s, 1H, exch), 3.86 - 4.40 (series of m, α-N & α-OH, 2H), 5.08 (m, 2H, CH_2Ph), 7.33 (m, 5H). The high-resolution ^1H and ^{13}C NMR spectra of the mixture were complicated at ambient temperature due to slow rotation around the N-CO bond.

δ_H (300 MHz, 363K, D_8-toluene): *1.10 - 1.81* (series of m, including CH_3, 13H), *5.02 & 5.12* (ABq, J = 12.3 Hz, 2H), *6.98 - 7.27* (m, 5H).
7-Hydroxy (**154a**): 2.06 (dd, J = 14.4, 6.7 Hz, 1H, β-OH), 3.64 (brd, J = 6.7 Hz, 1H, α-OH), 4.14 (m, 1H, α-N).
Double irradiation at δ 4.14 caused the brd at δ 3.64 to simplify to a dd (J = 6.7, 1.9 Hz) indicating a small vicinal coupling between α-OH and α-N protons (J < 1 Hz). This confirmed the C_7 placing of the hydroxyl group. Double irradiation at δ 3.63 removed the vicinal coupling of 6.7 Hz at δ 2.06 leaving a doublet (J = 14.4 Hz).
8-Hydroxy (**154b**): 3.74 (dd, J = 6.8, 4.8 Hz, 1H, α-OH), 4.32 (m, 1H, α-N).
Double irradiation at δ 4.32 resulted in no pertubation at δ 3.74 confirming the C_8 placing of the hydroxy group.

ν_{max} (CH_2Cl_2): 3440br, 2930s, 2960m, 1680s, 1575w, 1530w, 1500w, 1450m, 1335m, 1235m, 1200m, 1160m, 1135m, 1050m cm^{-1}.

$^m/z$ (%): 289 (M^+, 17), 271 (6), 228 (6), 184 (8), 154 (24), 110 (11), 108 (13), 107 (12), 106 (13), 105 (12), 91 (100).

$C_{17}H_{23}NO_3$ [M^+] requires $^m/z$ 289.1680; observed 289.168.

N-(Benzyloxycarbonyl)-1-methyl-9-azabicyclo[4.2.1]non-7-ene **(155)**

The cyclisation of **(153)** was carried out according to the method described for preparing **(136)** using mercury(II) acetate (190 mg, 0.60 mmol) and **(153)** (80 mg, 0.30 mmol) in dry acetonitrile (19 ml). Reduction with sodium borohydride (23 mg, 0.61 mmol) in dry THF (12 ml) gave **(155)** (36 mg, 45%) as an oil after flash chromatography using 1:9 diethyl ether:petroleum ether (b.p. 40 - 60°C) together with unchanged **(153)** (26 mg). Chemical shifts in italics refer to overlapping signals due to major and minor rotamers.

δ_H (300 MHz, $CDCl_3$): *1.26 - 1.61* (m, 6H), 1.52 (s, 3H, minor rotamer), 1.65 (s, 3H, major rotamer), *1.97* (m, 1H), *2.16* (m, 1H), 4.72 (ddd, J ≈ 6.0, 2.6, 1 Hz, 1H, major rotamer), 4.79 (brd, J ≈ 5.5 Hz, 1H, minor rotamer), 5.07, 5.18 (ABq, J = 12.5 Hz, 2H, CH_2Ph, major rotamer), 5.18 (s, 2H, CH_2Ph, minor rotamer), 5.47 (d, J ≈ 6.2 Hz, 1H, minor rotamer), 5.49 (dd J = 6.2, 0.8 Hz, 1H, major rotamer), 5.64 (dd, J = 6.2, 2.6 Hz, major rotamer), 5.67 (dd, J ≈ 6.2, 2.6 Hz, 1H, minor rotamer), *7.27 - 7.37* (m, 5H).

δ_C (75 MHz, $CDCl_3$), Major rotamer: 23.7 (CH_2), 24.3 (CH_3), 24.8, 31.7 & 37.0 (3 x CH_2), 62.8 (CHN), 66.1 (CH_2Ph), 68.8 (CCH_3), 127.75 (=CH), 127.8, 128.0 & 128.4 (3 x aryl CH), 136.4 (=CH), 137.0 (aryl C).

Minor rotamer: 23.4 & 25.0 (2 x CH_2), 25.6 (CH_3), 30.3 & 38.1 (2 x CH_2), 63.8 (CH), 66.6 (CH_2Ph), 68.0 (CCH_3), 127.7 (aryl CH), 127.8 (=CH), 128.1 & 128.5 (2 x aryl CH), 137.1 (=CH), 137.1 (aryl C); the CO signals were too weak to be resolved.

ν_{max} (CH_2Cl_2): 3025m, 2865w, 1695s, 1630w, 1570w, 1560w, 1550w, 1520w, 1510w, 1505w, 1445w, 1405s, 1235m, 1155w, 1100m, 1040m, 935 cm^{-1}.

$^m/z$ (%): 271 (M^+, 5), 185 (7), 92 (8), 91 (42), 44 (39), 32 (100).

$C_{17}H_{21}NO_2$ [M^+] requires $^m/z$ 271.1572; observed 271.157.

N-(Benzyloxycarbonyl)-1-methyl-9-azabicyclo[4.2.1]nonan-7-one **(156a)**
and -8-one **(156b)**

A solution of **(154)** (33 mg, 0.11 mmol) was oxidised with Jones reagent[68] using the

procedure described for the conversion of **(132)** into **(133)**. The regioisomeric mixture of ketones **(156a,b)** (32 mg, 98%) was obtained as a pale yellow oil which was pure enough for spectroscopic analysis without chromatography. Signals common to both isomers are quoted in italics.

δ_H (90 MHz, $CDCl_3$): *0.70 - 2.80* (series of m including CH_3 signals, 13H), *4.10 - 4.70* (1H, α-N), *5.00 - 5.25* (m, 2H, CH_2Ph), *7.30* (brs, 2H).

δ_H (300 MHz, 363K, D_8-toluene): *0.75 - 2.23* (series of m, 10H, [including δ *1.56* (s, 3H)]), *4.86 & 5.17* (ABq, J = 12.0 Hz, 2H, CH_2Ph), *6.98 - 7.24* (m, 5H).
7-Keto **(156a)**: 1.83 & 2.02 (ABq, J = 18.0 Hz, 2H, α-C=O), 4.02 (d, J = 8.4 Hz, 1H, α-N).
Double irradiation at δ 4.02 sharpened one half of the ABq (w-coupling) but the lack of vicinal coupling confirmed the position of the C=O at C_7.
8-Keto **(156b)**: 2.18 (dd, J = 17.4, 8.7 Hz, 1H, α-C=O), 4.32 (vbrm, 1H, α-N).
Double irradiation at δ 4.32 removed the vicinal coupling of 8.7 Hz at δ 2.18, leaving a d (J = 17.4 Hz), confirming the placing of the CH_2 at C_7 and the C=O at C_8.

ν_{max} (CH_2Cl_2): 2930m, 2860w, 1755s, 1695s, 1445w, 1395m, 1355w, 1335m, 1325w, 1260brw, 1205w, 1170w, 1110m, 1050m, 1025w, 965w, 950w, 930w, 905w cm^{-1}.

$^m/z$ (%): 287 (M^+, 4), 259 (7), 151 (6), 149 (4), 124 (11), 92 (9), 91 (100), 65 (6).

$C_{17}H_{21}NO_3$ [M^+] requires $^m/z$ 287.1521; observed 287.1521.

N-(Benzyloxycarbonyl)-1-methyl-7β,8β-epoxy-9-azabicyclo[4.2.1]nonane **(165)**
MCPBA (50 - 60 % purity, 49 mg, 0.16 mmol) was added to a stirred solution of **(155)** (41 mg, 0.14 mmol) in dichloromethane (6 ml). After stirring for 16 hr a further portion of MCPBA (10 mg, 0.03 mmol) was added and stirred for a further 24 hr. The solution was evaporated under reduced pressure and the residual oil was taken up in diethyl ether (14 ml), washed with saturated sodium bicarbonate solution (4 x 3 ml) and water (3 ml). The ethereal layer was dried over anhydrous magnesium sulphate, filtered, and the solvent distilled under reduced pressure. The resultant oil was purified by flash chromatography using 1:9 diethyl ether:petroleum ether (b.p. 40 - 60°C) to yield **(165)** (41 mg, 94 %) as a colourless oil. Chemical shifts in italics refer to overlapping signals due to major and minor rotamers.

δ_H (300 MHz, $CDCl_3$): *1.26 - 1.65* (series of m, 6H), 1.54 (s, 3H, minor rotamer), 1.67 (s, 3H, major rotamer), *1.86 - 2.27* (series of m, 2H), 3.22 (d, J = 3.1 Hz, 1H, HCO, minor rotamer), 3.23 (dd, J = 3.1, 0.4 Hz, 1H, HCO, major rotamer), 3.32 (d, J = 3.1 Hz, 1H, HCO, major rotamer), 3.33 (d, J = 3.1 Hz, 1H, HCO, minor rotamer), 4.36 (d, J = 6.8 Hz, α-N, major rotamer), 4.42 (d, J = 6.5 Hz, α-N, minor rotamer), *5.00 & 5.16* (ABq, J = 12.3 Hz, 2H, CH_2Ph), *7.27 - 7.40* (m, 5H).

δ_C (75 MHz, $CDCl_3$), Major rotamer: 21.2 (CH_3), 23.66, 24.5, 29.6 & 35.2 (4 x CH_2), 56.5 (CHO), 57.6 (CHO), *62.3* (CHN), 63.2 (CN), 66.4 (CH_2Ph), *127.9* (2 x aryl CH), *128.3* (aryl CH), *136.7* (aryl C), *155.0* (C=O).

Minor rotamer: 22.5 (CH_3), 23.75, 24.6, 28.3 & 36.5 (4 x CH_2), 56.1 & 58.3 (2 x CHO), *62.3* (CHN), 63.3 (CN), 66.9 (CH_2Ph), *127.9* (2 x aryl CH), *128.3* (aryl CH), *136.7* (aryl C), *155.0* (C=O).

ν_{max} (CH_2Cl_2): 3070w, 3045w, 3015w, 2920s, 2850m, 1710brs, 1580w, 1570w, 1535w, 1495w, 1450m, 1425m, 1395m, 1360m, 1350m, 1275w, 1260w, 1230w, 1210m, 1180m, 1145m, 1125m, 1070m, 1030w, 1000w, 960w, 945w, 925w cm^{-1}.

$^m/z$ (%): 287 (M^+, 30), 180 (37), 153 (13), 152 (41), 124 (15), 110 (21), 108 (12), 107 (11), 106 (13), 105 (10), 91 (100).

$C_{17}H_{21}NO_3$ [M^+] requires $^m/z$ 287.1521; observed 287.1521.

N-Benzyloxycarbonyl-1-methoxyethyoxymethoxy-9-azabicyclo[4.2.1]non-7-ene **(185)**

A solution of *n*-butyllithium (2.5 M in hexane, 1.44 ml, 3.60 mmol) was injected into a stirred solution of **(151 ⇌ 152)** (893 mg, 3.27 mmol) in THF (25 ml) at 0°C under a nitrogen atmosphere. After 15 min, MEM-Cl (0.52 ml, 4.58 mmol) was injected. The solution was allowed to warm to room temperature, then heated at reflux for 5 hr. The solvent was removed under reduced pressure and the residue dissolved in dichloromethane (55 ml), washed with water (3 x 20 ml), separated and dried over anhydrous magnesium sulphate. Filtration and evaporation of solvent afforded a yellow oil which was purified by flash chromatography using 1:1 diethyl ether:petroleum ether (b.p. 40 - 60°C) yielding **(185)** (863 mg, 73%) as an oil.

δ_H (300 MHz, $CDCl_3$), Slow rotation about the N-CO bond was observed and signals due to the two rotamers are shown separately where they were resolved; where signals overlapped, δ values are shown in italics: *1.29 - 1.60* (series of m, 5H), *1.81* (m, 1H), 2.03 (m, 1H), *2.29* (m, 1H), 2.50 (m, 1H), 3.35 (s, 3H, MeO), 3.38 (s, 3H, MeO), *3.53* (m, 2H), *3.63 - 3.87* (series of m, 2H), 4.58 and 4.88 (ABq, J = 6.9 Hz, 2H, O-CH_2-O), *4.70* (m, 1H, α-N), 4.72 and 4.91 (ABq, J = 7.2 Hz, 2H, O-CH_2-O), 5.15 (ABq, J = 12.4 Hz, 2H, benzyl CH_2), 5.21 (ABq, J = 12.8 Hz, 2H, CH_2Ph), *5.77* (dd, J = 6.2, 0.6 Hz, 1H), 5.85 (dd, J = 6.2, 2.6 Hz, 1H), 5.88 (dd, J = 6.2, 2.6 Hz, 1H), *7.34* (m, 5H).

δ_C (75 MHz, $CDCl_3$): 22.7 & 23.0 (2 x CH_2), 23.1 & 23.4 (2 x CH_2), 30.1 & 31.5 (2 x CH_2), 35.7 & 36.9 (2 x CH_2) 58.8 & 58.9 (2 x CH_2), 61.0 & 61.6 (2 x CH_2), 66.2 & 66.6 (2 x CH_2), 67.4 & 67.5 (2 x CH_2), *71.7* (CH_2), 89.9 & 90.0 (2 x CH_2), 98.1 & 99.0 (2 x COH), *127.8* (aryl CH), 127.9 & 128.1 (2 x aryl CH), *128.4* (aryl CH), 131.0 & 131.4 (2 x =CH), 133.1, 133.8 (2 x =CH), *136.7* (C), 152.9 & 154.3 (2 x C=O).

ν_{max} (thin film): 3080w, 3060w, 3020w, 2920s, 2870s, 2800w, 1695brs, 1620w, 1580w, 1490w, 1440m, 1395s, 1345s, 1300s, 1250m, 1195m, 1170m, 1090brs, 1020s, 980s, 935m, 845w, 830w, 805w, 790m, 770m, 730m, 695m cm^{-1}.

$^m/z$ (%): 361 (M^+, 32), 285 (26), 274 (35), 273 (39), 256 (67), 241 (50), 228 (29), 212 (34), 199 (42), 186 (34), 165 (24), 150 (100), 138 (42).

$C_{20}H_{27}NO_5$ [M^+] requires $^m/z$: 361.1889; observed 361.189.

N-Methyl-9-azabicyclo[4.2.1]non-7-en-1-ol (**186** ⇌ **187**)

In flame-dried apparatus, a solution of **(185)** in THF (12 ml) was injected into a slurry of LAH (123 mg, 3.24 mmol) under nitrogen at 0°C. The mixture was subsequently heated at reflux for 4 hr. Quenching of excess hydride with water-saturated ether, drying over sodium sulphate, filtration through celite and distillation of solvent afforded an oil **(186 ⇌ 187)** (292 mg) which was deprotected without further purification. The oil was dissolved in dichloromethane (11 ml) and trifluroacetic acid (0.52 ml, 6.77 mmol) was added. After stirring for 2 hr, water (15 μl) was added, the mixture was stirred for a futher 10 min, and the solvent was removed under vacuum ensuring complete removal of methanal. The residue was dissolved in water (3 ml)

and extracted with diethyl ether (2 x 4 ml) to remove benzyl alcohol. The pH of the aqueous layer was adjusted to pH 9 by addition of sodium hydroxide solution (2 M) and the product was extracted into dichloromethane (5 x 4 ml). Futher basification (pH 11) and extraction afforded a yellow solid (total 95 mg) after drying with $MgSO_4$ and evaporation of solvent. The crude product was recrystallised from petrol (b.p. 80 - 100°C) to afford (**186** ⇌ **187**) (74 mg, 45% overall) as an off-white solid, m.p. 94 - 110°C.

δ_H (300 MHz, 298 K, $CDCl_3$): 1.59 (m, 6H), 1.86 (m, 1H), 2.17 (m, 1H), 2.55 (s, 3H, CH_3), 3.87 (m, 1H, α-N), 5.90 (d, J = 7.8 Hz, 1H), 6.01 (dd, J = 7.8, 3.4 Hz, 1H).

δ_C (75 MHz, 298 K, $CDCl_3$), The italicised signals were broadened at this temperature): 22.8 (CH_2), 23.3 (CH_2), *29.7* (CH_2), *31.0* (CH_2), *37.9* (CH_2), *62.4* (CH), *136.3* (CH).

δ_H (300 MHz, 223 K $CDCl_3$): 1.45 - 2.18 (series of m, 8 H), 2.55 (s, 3 H), 3.78 (m, 1 H), 5.86 (br d, J ≈ 5.8 Hz), 5.98 (vbr d, J ≈ 5.8 Hz).

δ_C (75 MHz, 223 K $CDCl_3$): 22.5, 23.6, 28.3, 28.7 & 35.6 (5 x CH_2), 62.9 (CH), 94.8 (COH), 132.8, 137.4 (2 x =CH).

ν_{max} (CH_2Cl_2): 3570w, 3055vbrs, 2940s, 1705m, 1645s, 1610s, 1400m, 1360w, 1305m, 1215w, 1135m, 1090m, 1055m, 1020m, 910m cm^{-1}.

$^m/z$ (%): 153 (M^+, 18), 125 (11), 110 (100), 97 (38), 96 (39), 70 (17), 68 (14).

$C_9H_{15}NO$ [M^+] requires $^m/z$ 153.1154; observed 153.1156.

N-Benzyloxycarbonyl-1-methoxyethoxymethoxy-9-azabicyclo[4.2.1]nonane (**188**)

n-Butyllithium (2.5 M in hexane, 0.58 ml, 1.45 mmol) was injected into a stirred solution of (**133**) (364 mg, 1.32 mmol) in THF (13 ml) at 0°C. After 15 min, MEM-Cl (0.21 ml, 1.83 mmol) was added and the solution was heated under reflux for 3 hr. The bulk of the solvent was distilled in vacuo and the residual oil dissolved in dichloromethane (22 ml) and washed with water (2 x 10 ml). The organic layer was separated, dried with anhydrous magnesium sulphate, filtered and the solvent distilled. The crude product was purified by flash chromatography using 2:3 diethyl

ether:petroleum ether (b.p. 40 - 60°C) to afford **(188)** (336 mg, 70%) as a pale yellow oil.

δ_H (300 MHz, $CDCl_3$), Broadening and/or signal overlap due to slow N-CO rotation is indicated using italics: *1.24 - 2.63* (series of m, 12H), 3.33 (s, 3H), 3.36 (s, 3H), *3.51* (m, 2H), 3.68 (m, 2H), 3.81 (m, 2H), 4.33 (m, 1H, α-N), *4.58, 4.77 & 4.91* (series of m, 2H, O-CH_2-O & α-N, 1H), *5.15* (m, 2H, CH_2Ph), *7.32* (m, 5H).

δ_C (75 MHz, $CDCl_3$): *22.9* (CH_2), *23.6* (CH_2), 27.1 & 27.7 (2 x CH_2), 33.3 & 35.0 (2 x CH_2), 36.0 & 36.6 (CH_2) 37.4 & 38.4 (2 x CH_2), 56.2 & 57.0 (2 x CH), *58.8* (*CH_3*), 66.2 & 66.6 (2 x CH_2Ph), 66.7 & 67.4 (CH_2), *71.7* (*CH_2*), 90.0 (CH), 95.6 & 96.3 (C), *127.8, 127.9 & 128.3* (3 x aryl CH), *136.8* (aryl C), 153.6 & 154.9 (2 x C=O).

ν_{max} (CH_2Cl_2): 2930m, 2895w, 1695s, 1500w, 1450w, 1395m, 1355w, 1335w, 1315w, 1275brw, 1215w, 1160w, 1115m, 1095m, 1030s, 995w, 955w, 935w, 910w, 850w cm^{-1}.

$^m/_z$ (%): 363 (M^+, 2), 274 (14), 258 (25), 214 (10), 168 (18), 152 (39), 140 (11), 124 (10), 91 (100).

$C_{20}H_{29}NO_5$ [M^+] requires $^m/_z$ 363.2050; observed 363.2049.

N-Methyl-9-azabicyclo[4.2.1]nonan-1-ol **(189 ⇌ 190)**

The protected carbamate **(188)** (290 mg, 1.20 mmol) was reduced with hydride and deprotected with trifluoroacetic acid using identical procedures to those described for the preparation of **(186 ⇌ 187)**. The product **(189 ⇌ 190)** was isolated as an impure oil (21 mg, 17%). An improved route to **(189 ⇌ 190)** from **(192)** is described below.

9-Azabicyclo[4.2.1]nonan-1-ol **(176 ⇌ 177)**

A solution of **(133)** (330 mg, 1.20 mmol) in ethanol (18 ml) was hydrogenolysed with a catalytic amount of 5% palladium on charcoal at 1 atmosphere. After 2 hr the solution was filtered through a Millipore 0.2μ Millex-FG disposable filter unit and the solvent distilled under reduced pressure to afford **(176 ⇌ 177)** (165 mg, 98%) as an off white solid. A sample prepared using this method had identical spectroscopic properties to data recorded by Smith.[93]

δ_H (90 MHz, $CDCl_3$): 1.55 (m, 6H), 2.10 (m, 6H), 2.80 (brs, 2H, exch, OH & NH), 3.25 (brm, 1H, α-N).

Cis-4-(Methylamino)cyclooctanol **(192)**

A 100 ml 2-necked flame dried flask was charged with LAH and stirred with dry THF (2 ml). The system was alternately charged and evacuated with nitrogen and cooled to 0°C. A solution of **(132)** (1.353 g, 4.88 mmol) in THF (24 ml) was injected. After complete addition, the mixture was refluxed for 1 hr. Excess hydride was destroyed by dropwise addition of water-saturated diethyl ether, the solution dried with sodium sulphate and filtered through celite. The solvent was distilled under reduced pressure and the residual oil purified by flash chromatograpy using 4:1 dichloromethane: methanol (saturated with ammonia) to afford product **(192)** (709 mg, 92%) as a colourless oil which was identical to a sample prepared previously by a different route.[58]

δ_H (90MHz, $CDCl_3$): 1.20 - 1.85 (m, 12H), 2.25 (s, 3H), 2.40 (m, 1H, α-N), 3.30 (brs, exch, 2H), 3.70 (m, 1H, α-O).

N-Methyl-9-azabicyclo[4.2.1]nonan-1-ol **(189 ⇌ 190)**

To a stirred solution of **(192)** (279 mg, 1.80 mmol) in propanone (12 ml) was oxidised by the dropwise addition of Jones reagent.[68] After 25 min, isopropanol was added until a permanent green colouration remained and the solution was then filtered through celite. The inorganic residues were washed further with methanol (2 x 10 ml). The solvent was distilled in vacuo and the residue dissolved in water (7 ml) and basified to pH 12 using sodium hydroxide solution (2 M). The water was removed in vacuo and the inorganic solids extracted with chloroform (80 ml), using a Soxhlet apparatus, for 18 hr. Distillation of solvent afforded **(189 ⇌ 190)** as a waxy yellow solid (189 mg, 69%).

δ_H (300 MHz, 298 K, $CDCl_3$,): 1.46 (m, 1H), 1.61 (m, 6H), 1.86 (m, 1H), 2.11 (m, 5H), 2.45 (s, 3H), 3.17 (m, 1H), 4.30 (brs, 1H exch).

δ_C (75 MHz, 298 K, $CDCl_3$), Broad signals are italicised: 23.6 (CH_2), *24.0* (CH_2), 26.8 (CH_2), *30.1* (CH_3), 32.0 (CH_2), *38.4* (CH_2), 39.8 (CH_2), 58.7 (CH).

δ_H (300 MHz, 243 K, $CDCl_3$): 1.49 (m, 2H), 1.63 (m, 5H), 1.94 (m, 4H), 2.20 (m,

2H), 2.49 (s, 3H), 3.34 (m, 1H), 6.18 (vbrs, 1H).

δ_C (75 MHz, 243 K, $CDCl_3$): 22.4, 23.4 & 25.9 (3 x CH_2), 28.8 (CH_3), 31.9, 37.4 & 39.4 (3 x CH_2), 58.1 (CHN), 92.0 (COH).

ν_{max} (CH_2Cl_2): 3180vbr, 2940s, 2870m, 2800w, 1695m, 1470w, 1450w, 1365w, 1340w, 1230w, 1210w, 1180w, 1155w, 1130w, 1080w, 1055w, 1045w, 1005w, 975w, 940w, 915w, 865w, 835w, 815w cm^{-1}.

$^m/_z$ (%): 155 (M^+, 8), 149 (13), 141 (6), 137 (3), 126 (17), 112 (20), 108 (13), 98 (32), 94 (18), 70 (100).

$C_9H_{17}NO$ [M^+] requires $^m/_z$ 155.1310; observed 155.1311.

Cis-4-(Methylamino)cyclooct-2-enol (**193**)

The protected amino-alcohol (**150**) (308 mg, 1.12 mmol) in dry THF (6 ml) was added to a slurry of LAH (83 mg, 2.18 mmol) in dry THF at 0°C following thorough evacuation/purging of the reaction flask with nitrogen. The mixture was heated at reflux for 2.5 hr and excess hydride was then destroyed using water-saturated diethyl ether. Filtration through celite and distillation of solvent afforded a white solid which was repeatedly triturated with a 1:1 mixture of diethyl ether:petrol (b.p. 40 - 60°C) to remove benzyl alcohol. The product (**193**) was obtained as a white solid, (145 mg, 84%), m.p. 123 - 125°C showing identical spectroscopic properties to a sample prepared previously by a different route[93] (lit. m.p. 125 - 126°C).

δ_H (90 MHz, $CDCl_3$): 1.20 - 1.95 (series of m, 8H), 2.20 (brs, exch, 2H), 3.40 (m, 1H, α-N), 4.55 (m, 1H, α-O), 5.40 (t, J = 11 Hz, 1H), 5.70 (dd, J = 11, 7 Hz, 1H).

N-Methyl-9-azabicyclo[4.2.1]non-7-en-1-ol (**186** ⇌ **187**)

The allylic alcohol (**193**) (297 mg, 1.92 mmol) was treated with Jones reagent[68] using an identical procedure to that described below for conversion of (**192**) into (**189** ⇌ **190**). Extraction into chloroform using a Soxhlet apparatus gave a yellow solid which was recrystallised from toluene and petroleum ether (b.p. 60 - 80°C) to afford (**186** ⇌ **187**) (176 mg, 63%) as a slightly yellow solid which was identified by comparison of spectra with those of the sample obtained earlier from (**185**).

N-Benzyloxycarbonyl-7β,8β-epoxy-9-azabicyclo[4.2.1]nonan-1-ol (**194**)

MCPBA (50-60% purity, 2.680g, 8.57 mmol) was added in portions to a stirred solution of (**151** ⇌ **152**) (1.942 g, 7.11 mmol) in dichloromethane (67 ml). After stirring for 24 hr a further portion of MCPBA (0.80 g, 2.54 mmol) was added and stirred for a further 48 hr. The solvent was concentrated under reduced pressure and the residual oil was dissolved in diethyl ether (65 ml) and repeatedly washed with saturated sodium bicarbonate solution (5 x 20 ml) and brine (20 ml). The ethereal layer was separated, dried over anhydrous magnesium sulphate, filtered and the solvent distilled under reduced pressure. After flash column chromatography using 3:2 diethyl ether:petroleum ether (b.p. 40 - 60°C) (**194**) was isolated as a white solid (1.626 g, 79%) which had m.p. 66 - 68°C after recrystallisation from toluene and petroleum ether (b.p. 40 - 60°C).

δ_H (300 MHz, $CDCl_3$), Signals common to both rotamers are quoted in italics: *1.19 - 1.62* (series of m, 5H), *2.04* (m, 2H), *2.22* (m, 1H), 3.33 (d, J = 3.2 Hz, 1H, HCO, major rotamer), 3.37 (d, J = 3.2 Hz, 1H, HCO, minor rotamer), 3.46 (d, J = 3.2 Hz, 1H, HCO, minor rotamer), 3.48 (d, J = 3.2 Hz, 1H, HCO, major rotamer) 4.35 (d, J = 6.9 Hz, 1H, α-N major rotamer), 4.41 (d, J = 6.2 Hz, 1H, α-N minor rotamer), 5.05 & 5.18 (ABq, J = 12.3 Hz, 2H, CH_2Ph, major rotamer), 5.13 & 5.23 (ABq, J = 12.3 Hz, 2H, CH_2Ph, minor rotamer), *7.33* (m, 5H).

δ_C (75MHz, $CDCl_3$), The heavy weighting towards the major rotamer resulted in the minor rotamer signals being too weak to be observed): 23.2 (2 x CH_2), 29.1 & 37.6 (2 x CH_2), 54.1 & 55.7 (2 x CHO), 58.0 (CHN), 66.8 (CH_2Ph), 91.4 (COH), 127.9, 128.1 & 128.5 (3 x aryl CH), 136.0 (aryl C), 155.9 (CO).

ν_{max} $(CH_2Cl)_2$: 3450brm, 3090w, 3050w, 3020w, 2920s, 2850m, 1670s, 1490w, 1420s, 1390s, 1345s, 1255w, 1235w, 1220w, 1190m, 1145m, 1110m, 1085m, 1050m, 1020m, 990m, 970m cm^{-1}.

$^m/_z$ (%): 289 (M^+, 27), 271 (19), 245 (17), 227 (27), 155 (25), 154 (76), 126 (49), 113 (19), 112 (59), 108 (61), 91 (100).

$C_{16}H_{19}NO_4$ [M^+] requires $^m/_z$ 289.1314; observed 289.131.

Found: C, 66.46; H, 6.58; N, 4.66%.
$C_{16}H_{19}NO_4$ requires: C, 66.42; H, 6.62; N, 4.84%.

N-Methyl-7β,8β-epoxy-9-azabicyclo[4.2.1]nonan-1-ol **(196)**

A solution of **(194)** (213 mg, 0.74 mmol) in dry THF (4 ml) was injected into a stirred slurry of LAH in dry THF (2 ml). The solution was refluxed for 30 min under a nitrogen atmosphere and excess hydride was quenched by the addition of water-saturated diethyl ether and then dried with anhydrous sodium sulphate. The colourless solution was filtered through celite and the solvent was evaporated under reduced pressure to afford an oil. Repeated trituration with petroleum ether (b.p. 40 - 60°C) to remove benzyl alcohol gave **(196)** (89 mg, 71%) as a crystalline white solid having m.p. 119 - 120 °C (decomp.) after recrystallisation from ethanol.

δ_H (300 MHz, $CDCl_3$): 1.55 (m, 5H), 1.97 (m, 3H), 2.52 (s, 3H), 2.99 (brs, exc, 1H), 3.34 (d, J = 3.3 Hz, 1H, HCO), 3.38 (d, J = 3.3 Hz, 1H, HCO), 3.41 (d, J = 4.9 Hz, 1H, α-N).

δ_C (75MHz, $CDCl_3$): 22.7 & 24.0 (2 x CH_2), 28.9 (CH_3), 29.1 & 35.0 (2 x CH_2), 55.3 (CHN), 57.5 & 59.9 (2 x CHO), 89.6 (COH).

ν_{max} ($CH_2Cl)_2$: 3560w, 2930s, 2870m, 1465w, 1440w, 1370w, 1340w, 1240w, 1210w, 1190w, 1105w, 1080m, 1020m, 945w, 880m, 860w, 850w, 830w cm^{-1}.

$^m/z$ (%): 169 (M^+, 72), 149 (17), 140 (46), 127 (26), 126 (78), 113 (36), 112 (100), 98 (21), 84 (42), 70 (40).

Found: C, 63.82; H, 9.14; N, 8.31%.
$C_9H_{15}NO_2$ requires: C, 63.88; H, 8.93; N, 8.23%.

7β,8β-Epoxy-azabicyclo[4.2.1]nonan-1-ol **(197)**

A solution of **(194)** (981 mg, 3.39 mmol) in absolute ethanol (54 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 **(197)** (510 mg, 97%) as a gum.

δ_H (300 MHz, $CDCl_3$): 1.35 (m, 1H), 1.47 - 1.73 (series of m, 4H), 1.82 (m, 2H), 2.00 (ddd, J = 13.9, 6.9, 4.4 Hz, 1H), 3.36 (m, 2H, HCO), 3.53 (d, J = 6.9 Hz, 1H, α-N).

δ_H (300 MHz, CD_3COCD_3): 1.29 (m, 1H), 1.46 (m, 2H), 1.58 - 1.79 (series of m, 4H), 1.89 (m, 1H), 3.27 (d, J = 2.7 Hz, 1H, HCO), 3.31 (d, J = 2.7 Hz, 1H, HCO), 3.37 (d, J = 7.1 Hz, 1H, α-N), 3.72 (brs, 2H, exc, OH & NH).

δ_C (75 MHz, $CDCl_3$): 23.2, 23.7, 30.7 & 38.9 (4 x CH_2), 54.6 (CHN), 58.4 & 59.4 (2 x CHO), 91.2 (COH).

ν_{max} ($CH_2Cl)_2$: 3560w, 3300brs, 2930s, 2860s, 1425brm, 1340m, 1300m, 1265m, 1185m, 1105s, 1025m, 990m, 980m, 945m, 930m cm^{-1}.

$^m/z$ (%): 155 (M^+, 47), 126 (100), 112 (74), 98 (72), 85 (28), 72 (58).

$C_8H_{13}NO_2$ [M^+] requires $^m/z$ 155.0946; observed 155.0946.

N-(Benzyloxycarbonyl)-6-aza-7-oxabicyclo[3.2.2]non-8-ene **(221)**

Tetramethylammonium periodate (14.56 g, 0.055 mol) and cyclohepta-1,3-diene **(43)** (4.31 g, 0.046 mol) in dichloromethane (70 ml) was stirred at 0°C. A solution of benzyl-N-hydroxycarbamate (9.18 g, 0.055 mol) in dichloromethane (18 ml) was dripped in over 15 min. The mixture was warmed to room temperature on complete addition and stirred for a further 4 hr. The solution was filtered, washed with saturated sodium thiosulphate solution (2 x 30 ml) and water (30 ml). The organic layer was separated, dried over anhydrous magnesium sulphate, filtered and the solvent distilled under reduced pressure. The residual yellow oil was purified by flash chromatography using 2:8 diethyl ether:petroleum ether (b.p 40 - 60°C) to afford **(221)** (11.51 g, 97%) as an oily yellow solid. This compound was prepared earlier by Bathgate[35] in 90% yield.

δ_H (90 MHz, $CDCl_3$): 1.45 (m, 2H), 1.80 (m, 4H), 4.75 (brm, 2H, α-O & α-N), 5.20 (s, 2H, CH_2Ph), 6.20 (m, 2H), 7.30 (s, 5H).

N-(Benzyloxycarbonyl)-6-aza-7-oxabicyclo[3.2.2]nonane **(222)**

To a stirred solution of potassium azodicarboxylate (12.74 g, 65.7 mmol) and **(221)** (3.40 g, 13.12 mmol) in methanol (90 ml) at 0°C was added glacial acetic acid (7.60

ml, 139.2 mmol) over 10 min. The mixture was warmed to room temperature and stirred for a further 2 hr. The reaction was quenched with water (3 ml), filtered and the bulk of the solvent distilled under reduced pressure. The residue was partitioned between dichloromethane (70 ml) and saturated sodium bicarbonate solution (20 ml), washed with further bicarbonate solution (10 ml) and water (20 ml). The organic layer was separated, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The oil was purified by flash chromatography using 3:7 diethyl ether:petroleum ether (b.p. 40 - 60°C) to afford **(222)** as a colourless oil (3.20 g, 94%) which solidified on standing and had m.p. 52 - 53°C after recrystallisation from petroleum ether (b.p. 40 - 60°C).

δ_H (300 MHz, $CDCl_3$): 1.59 - 2.10 (series of m, 10H), 4.40 (m, 1H, α-N), 4.51 (m, 1H, α-N), 5.19 (s, 2H), 7.30 (m, 5H).

δ_C (75 MHz, $CDCl_3$), Signals shown in italics were broadened due to slow N-CO rotation: 19.2, 21.2, 21.6, *32.3* & 32.7 (5 x CH_2) *51.3* (CHN), 67.0 (CH_2Ph), 76.2 (CH0), 127.9 (2 x aryl CH), 128.3 (aryl CH), 136.5 (aryl C), 154.1 (C=O).

ν_{max} (CH_2Cl_2): 3035w, 2945s, 2875w, 1715s, 1685s, 1495w, 1435br, 1345m, 1325w, 1300m, 1255w, 1210w, 1150w, 1105s, 1085s, 1035 w, 1030w, 1000w, 925w, 870w cm^{-1}.

$^m/z$ (%): 261 (M^+, 5), 218 (5), 217 (28), 149 (7), 132 (4), 126 (6), 92 (21), 91 (100), 81 (4), 77 (5).

$C_{15}H_{19}NO_3$ [M^+] requires $^m/z$ 261.1365; observed 261.136.

Found: C, 68.79; H, 7.30; N, 5.33%.
$C_{15}H_{19}NO_3$ requires: C, 68.94; H, 7.33; N, 5.36%.

Cis-4-[(Benzyloxycarbonyl)amino]cycloheptanol **(223)**

A solution of **(222)** (2.21 g, 8.47 mmol) in dry ethanol (35 ml) was buffered with sodium phosphate (5.24 g, 36.9 mmol) and stirred for 5 min at 0°C. Freshly prepared[67] and powdered 6% sodium amalgam (33 g) was added and stirring was continued for 1 hr. The mixture was then filtered through celite, and the solvent removed under reduced pressure. The residual solution was partitioned between

dichloromethane (30 ml) and water (20 ml). The aqueous layer was extracted with further dichloromethane (2 x 25 ml), the organic layers combined and dried over anhydrous magnesium sulphate. After filtration the solvent was removed under vacuum to afford a white solid which was triturated with 1:1 diethyl ether:petroleum ether to afford **(223)** (2.18 g, 98 %) which had m.p. 70 - 72°C and was used without further purification. This compound was prepared earlier by Kibayashi[34] in 84% yield (m.p. 72 - 74°C) by reaction of *cis*-4-aminocycloheptanol with benzyl chloroformate and base.

δ_H (90 MHz, $CDCl_3$): 1.05 - 2.45 (series of m, 10H), 2.50 (brs, 1H, exch), 3.75 (brm, 2H, α-O & α-N), 5.10 (s including m, 3H, CH_2Ph and NH), 7.30 (m, 5H).

Cis-4-(Methylamino)cycloheptanol **(224)**

A 100 ml flame-dried 2-necked flask fitted with a septum cap and reflux condenser was charged with LAH (220 mg, 5.79 mmol). Dry THF (5 ml) was injected and the system was alternately evacuated and purged with nitrogen gas. The slurry was cooled with stirring to 0°C and a solution of **(223)** (970 mg, 3.69 mmol) in dry THF (19 ml) was introduced. The mixture was heated at reflux for 2 hr, cooled to 0°C and the minimum of water-saturated diethyl ether was added carefully to destroy excess hydride. The suspension was dried with anhydrous sodium sulphate, filtered through celite and the inorganic residues washed with ethyl acetate (2 x 7 ml). The solvent was removed under reduced pressure from the combined organic extracts to give an oil. This was flash chromatographed (to remove benzyl alcohol) using 1:4 methanol:dichloromethane saturated with ammonia, affording **(224)** (495 mg, 94%) as a colourless oil which was identical to a sample prepared[87] by hydrogenation of **(226)**. Partition between organic solvents and aqueous solution was avoided since it led to loss of material into the aqueous layer.

δ_H (90 MHz, $CDCl_3$): 1.80 (m, 10H), 2.45 (s, 3H), 2.70 (m, 1H, α-N), 3.25 (s, 2H, exch), 3.90 (m, 1H, α-O).

N-Methyl-8-azabicyclo[3.2.1]octan-1-ol (physoperuvine) **(170 ⇌ 171)**

A solution of **(224)** (97 mg, 0.68 mmol) was oxidised using an identical procedure to that described for the preparation of **(189 ⇌ 190)** from **(192)**. After removal of acetone under vacuum the residual green solution was dissolved in water (6 ml) and basified to pH 12 using 1M sodium hydroxide solution. The water was evaporated

under reduced pressure and the residue was extracted continuously with chloroform (25 ml) for 18 hr using a Soxhlet apparatus. After removal of the chloroform under vacuum, **(170 ⇌ 171)** (90 mg, 94%) was obtained as a white solid which had m.p. 73 - 74°C after recrystallisation from petrol (b.p. 60 - 80°C) (lit.[89] m.p. 75°C).

δ_H (300 MHz, 289 K, $CDCl_3$): 1.09 (m, 1H), 1.47 (m, 2H), 1.68 (m, 2H), 1.85 (m, 3H), 2.01 (m, 2H), 2.36 (s, 3H), 3.20 (m, 1H, α-N), 5.28 (brs, 1H, exch).

δ_C (75 MHz, 298 K, CD_2Cl_2), Signals shown in italics were broadened: 18.3, *23.0* & 25.4 (3 x CH_2), *29.9* (CH_3), *30.3* (CH_2), 35.9 (CH_2), 58.8 (CHN); the COH signal was not visible at this temperature due to coalescence.

δ_H (300 MHz, 223 K, CD_2Cl_2): 0.86 (brd, J ≈ 12.5 Hz, 1H), 1.12 (brd, J ≈ 12 Hz, 1H), 1.37 (brm, 1H), 1.47 - 2.03 (series of m, 7H), 2.24 (s, 3H), 3.14 (brd, J ≈ 6 Hz, α-N), 6.65 (brs, 1H, exch).

δ_C (75 MHz, 223 K, CD_2Cl_2), Bicyclic tautomer: 18.3, 21.1, 25.4 & 27.8 (4 x CH_2), 29.2 (CH_3), 36.1 (CH_2), 58.1 (CHN), 88.8 (COH).

Monocyclic tautomer (low intensity signals; some were broadened and not all signals were visible): 19.6, 30.9, 35.2, 39.0, 63.3. The ratio of major:minor tautomers was estimated to be approximately 98:2 from integration of the ^{13}C NMR signals.

ν_{max} (CH_2Cl_2): 3570w, 3100br, 2940s, 2850m, 2790w, 1695w, 1475m, 1445w, 1325m, 1195m, 1180w, 1145w, 1115m, 1100w, 1040w, 1010m, 975w, 955w, 925w, 910w, 870m, 805w cm^{-1}.

$^m/z$ (%): 141 (M^+, 65), 140 (7), 113 (60), 112 (70), 99 (57), 98 (85), 84 (36), 71 (21), 70 (100).

$C_8H_{15}NO$ [M^+] requires: $^m/z$ 141.1154; observed 141.1153.

4-([Benzyloxycarbonyl]amino)cycloheptanone **(225 ⇌ 226)**

A solution of **(223)** (1.02 g, 3.88 mmol) in acetone (18 ml) was oxidised with Jones reagent[68] using the procedure described for the oxidation of **(132)** into **(133)**. After work-up, the oil was purified by flash chromatography using 4:1 diethyl

ether:petroleum ether (b.p. 40 - 60°C) to give **(225 ⇌ 226)** (975 mg, 96%) as a waxy solid.

δ_H (300 MHz, $CDCl_3$): 1.41 (m, 1H), 1.60 (m, 2H), 1.81 (m, 1H), 2.03 (m, 2H), 2.46 (m, 4H), 3.70 (m, 1H, α-N), 5.06 (s, 2H, CH_2Ph), 5.35 (brd J = 7.1 Hz, 1H, NH), 7.31 (s, 5H).

δ_C (75 MHz, $CDCl_3$): 20.5, 30.4, 36.2, 39.4 & 43.4 (5 x CH_2), 52.7 (CHN), 66.5 (CH_2Ph), 128.0 (2 x aryl CH), 128.4 (aryl CH), 136.5 (aryl C), 155.4 (NC=O), 213.7 (C=O).

ν_{max} (CH_2Cl_2): 3440m, 3340br, 3030w, 2930m, 2860w, 1705s, 1500s, 1450m, 1405w, 1365w, 1340w, 1310m, 1215s, 1115m, 1065w, 1035w, 1005m, 910w, 875w cm^{-1}.

$^m/z$ (CI, %): 262 (MH^+, 46), 218 (34), 200 (21), 171 (100), 170 (23), 154 (82), 127 (24), 108 (40), 98 (21), 91 (22), 84 (25).

$C_{15}H_{20}NO_3$ [MH^+] requires $^m/z$ 262.1443; observed 262.1443.

<u>1-Hydroxy-8-azabicyclo[3.2.1]octan-1-ol (norphysoperuvine) **(209 ⇌ 210)**</u>

A solution of **(225 ⇌ 226)** (593 mg, 2.27 mmol) in absolute ethanol (24 ml) was hydrogenolysed using the procedure described for the reduction of **(133)** into **(176 ⇌ 177)**. The solvent was removed under reduced pressure to give a sample of good purity as shown by ^1H NMR (265 mg, 92%). Recrystallisation from toluene and petroleum ether (40 - 60 °C) afforded **(209 ⇌ 210)** (225 mg, 78%) as a pale yellow solid, m.p. 97 - 101°C.

δ_H (300 MHz, 298 K, $CDCl_3$): 1.41 (m, 1H), 1.56 (m, 2H), 1.75 (m, 2H), 1.97 (m, 5H), 3.39 (m, 1H, α-N), 3.86 (brm, 2H, exch, NH & OH).

δ_C (75 MHz, 298 K, $CDCl_3$), Signals shown in italics were broadened): 19.3, *28.6*, *33.7*, *36.0* & *39.8* (5 x CH_2), 53.8 (CHN), the COH signal was not resolved at this temperature.

δ_H (300 MHz, 223 K, $CDCl_3$): 1.35 - 1.97 (series of m, 9H), 2.12 (m, 1H), 3.52 (brd, J = 5.4 Hz, 1H, α-N).

δ_C (75 MHz, 223 K, $CDCl_3$): 18.7, 26.9, 31.5, 35.0 & 38.7 (5 x CH_2), 53.3 (CHN), 89.5 (COH).

ν_{max} (CH_2Cl_2): 3660w, 3570w, 3080br, 2930s, 2860m, 1695m, 1590brw, 1445w, 1375w, 1350w, 1325w, 1315w, 1225w, 1185m, 1120m, 1085w, 1025m, 985w, 950w, 880w cm^{-1}.

$^m/z$ (%): 127 (M^+, 81), 99 (80), 98 (76), 85 (30), 84 (67), 82 (7), 71 (16), 70 (100).

$C_7H_{13}NO$ [M^+] requires $^m/z$ 127.0997; observed 127.0996.

Cis-4-([Benzyloxycarbonyl]amino)cyclohept-2-enol (**225**)

A solution of (**221**) (3.12 g, 12.0 mmol) in absolute ethanol (75 ml) was stirred at 0°C with sodium phosphate (7.70 g, 54.2 mmol) for 5 min. Freshly prepared[67] and powdered 6% sodium amalgam (44 g) was added and stirring was continued at 0°C for 30 min. The mixture was filtered through celite and the bulk of the solvent distilled under reduced pressure. The residual solution was partitioned between water (40 ml) and dichloromethane (70 ml). The aqueous layer was extracted with further CH_2Cl_2 (2 x 40 ml) and the organic layers combined and dried over anhydrous magnesium sulphate. Filtration and evaporation of solvent left a solid which was recrystallised from ethanol to afford (**225**) (2.82 g, 90%) as a white solid, m.p. 143 - 144°C. The spectroscopic properties were identical to those of a sample prepared earlier by a different route[35] where it was obtained in 95% yield from *cis*-4-amino-cyclohept-2-enol by reaction with base followed by benzyl chloroformate, and isolated as an oil.

δ_H (90 MHz, $CDCl_3$): 1.10 - 2.20 (brm, 6H), 4.30 (brm, 2H, α-N & α-O), 5.10 (s including m, 3H, CH_2Ph & NH), 5.50 (brd, J = 12 Hz, 1H), 5.80 (brd, J = 12 Hz, 1H), 7.30 (m, 5H).

Found C, 69.11; H, 7.14; N, 5.28%.
$C_{15}H_{19}NO_3$ requires: C, 68.94; H, 7.33; N, 5.36%.

Cis-4-(Methylamino)cyclohept-2-enol (**228**)

This compound[35] was prepared by reduction of (**227**) with LAH using the method

described above for **(224)**. The yield was improved to 95% by working up the reaction mixture using water-saturated diethyl ether to destroy the excess hydride. The ethereal solution was then dried with magnesium sulphate, filtered, evaporated, and the product was flash chromatographed using methanol:dichloromethane (1:19) saturated with ammonia gas. The oily product solidified on standing. As in the preparation of **(224)**, partition between organic solvents and aqueous solution was avoided since it led to losses.

δ_H (90 MHz, $CDCl_3$): 2.60 (m, 6H), 2.30 (s, 3H), 3.05 (m, 1H, α-N), 3.80 (brs, 2H, exch), 4.15 (m, 1H, α-O), 5.60 (dd, J = 11, 6 Hz, 1H), 5.90 (dd, J = 11, 6 Hz, 1H).

4-[(Benzyloxycarbonyl)amino]cyclohept-2-enone **(229 ⇌ 230)**

A solution of **(225)** (792 mg, 3.03 mmol) in dichloromethane (55 ml) was stirred at room temperature. Barium manganate[81] (8.50 g, 33.2 mmol) was added and stirring was continued for a further 36 hr. The slurry was filtered through celite and the inorganic residues were washed firstly with dichloromethane (2 x 15 ml) and then with warm ethyl acetate (2 x 15 ml). The solutions were combined and the solvent was removed 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 **(229 ⇌ 230)** as a pale yellow solid (657 mg, 84%), which had m.p. 56 - 58°C after recrystallisation from toluene and petroleum ether (b.p. 40 - 60°C).

δ_H (300 MHz, $CDCl_3$): 1.77 (m, 3H), 2.11 (m, 1H), 2.54 (m, 2H), 4.53 (m, 1H), 5.08 (s, 2H, CH_2Ph), 5.69 (brd, J ≈ 8.0 Hz, 1H, NH), 5.92 (dd, J = 12.4, 2.2 Hz, 1H), 6.34 (dd, J = 12.4, 2.9 Hz, 1H), 7.31 (s, 5 H).

δ_C (75 MHz, $CDCl_3$): 18.9, 32.9 & 42.9 (3 x CH_2), 51.6 (CHN), 66.8 (CH_2Ph), 128.0, 128.1 & 128.5 (3 x aryl CH), 130.9 (=CH), 136.2 (aryl C), 146.7 (=CH), 155.6 (NC=O), 202.9 (C=O).

ν_{max} (CH_2Cl_2): 3440m, 3325br, 3030w, 2960m, 2870w, 1715s, 1665s, 1585w, 1500s, 1450m, 1215s, 1155w, 1125w, 1050w, 1020m, 980w, 900w, 795w cm^{-1}.

m/z (%): 259 (M^+, 4), 241 (3), 215 (18), 198 (6), 172 (12), 168 (16), 159 (21), 140 (6), 124 (17), 110 (66), 91 (100).

Found: C, 69.49; H, 6.52; N, 5.19%;
$C_{15}H_{17}O_3N$ requires: C, 69.48; H, 6.61; N, 5.40%.

4-(Methylamino)cyclohept-2-enone (**231** ⇌ **232**)

A solution of the amino-alcohol (**226**) (48 mg, 0.34 mmol) in acetone (7 ml) was acidified with trifluoroacetic acid (30 µl, 0.39 mmol) at ambient temperature. The solution was titrated with Jones reagent[68] and stirred for a further 5 min before the addition of excess isopropanol. The solution was filtered and the solid washed with methanol (2 x 5 ml). The organic solvent was distilled off under reduced pressure and the residual oil was dissolved in water (5 ml), and the solution was basified to pH 12 using aqueous sodium hydroxide solution (2M). The solution was extracted with ethyl acetate (3 x 7 ml), the organic layers were combined, dried over anhydrous magnesium sulphate, filtered, and the solvent distilled under vacuum to afford the amino-ketone (**231** ⇌ **232**) as an oil (19 mg, 40%). The compound decomposed during chromatography. Salts of the amine were not easy to handle, for example the HBF_4 salt separated from dry diethyl solution as an oil and a pure sample was not obtained. The free amine decomposed over a period of hours.

δ_H (300 MHz, $CDCl_3$): 1.75 - 2.76 (series of m, 6H), 2.59 (s, 3H), 3.74 (s, 1H, α-N), 6.01 (dd, J = 10.2, 0.9 Hz, 1H), 6.35 (dd, J = 10.2, 3.2 Hz, 1H).

ν_{max} (CH_2Cl_2): 3040w, 2920m, 2840w, 2790w, 1665m) with shoulders at 1755w and 1700m, 1425w, 1200s, 1180m, 1140m, 905s cm^{-1}.

m/z (%) [measured using (**3:HCl**)]: 140 (MH^+, 32), 139 (M^+, 100), 124 (22), 113 (43), 112 (43), 111 (54) 110 (40), 98 (43), 96 (28), 83 (98), 82 (58), 70 (62), 69 (27), 68 (97), 57 (63), 55 (91).

4-(Benzylamino)cyclohept-2-enone (**233** ⇌ **234**)

A solution of (**56**)[35] (84 mg, 0.39 mmol) in acetone (12 ml) was cooled to 0°C and acidified with trifluoroethanoic acid (60 µl, 0.62 mmol). The solution was titrated with Jones reagent[68] until an orange/brown colour persisted and excess oxidant destroyed immediately by addition of excess isopropanol. The solution was filtered through celite and the remaining solid washed with acetonee (3 x 4 ml). The bulk of the solvent was distilled under reduced pressure and the resulting green oil was dissolved in water (3 ml) and basified to pH 12 with sodium hydroxide solution (2M).

The solution was extracted with ethyl acetate (3 x 10 ml), the organic layers were combined, washed with brine (5 ml) and dried over anhydrous magnesium sulphate. Separation, filtration and distillation of solvent under reduced pressure afforded (**233** ⇌ **234**) as a pale yellow oil (71 mg, 85%) which was approximately 90% pure (from ^{1}H NMR integration) but decomposed on standing in solution.

δ_H (300 MHz, $CDCl_3$): 1.75 (m, 3H), 2.11 (m, 1H), 2.52 (m, 2H), 3.55 (m, α-N, 1H), 3.84 (ABq, J = 13.1 Hz, 2H, CH_2Ph), 5.97 (ddd, J = 12.3, 2.3, 1.0 Hz, 1H), 6.56 (ddd, J = 12.3, 3.7, 1.0 Hz, 1H), 7.32 (m, 5 H).
Double irradiation at δ 2.52 caused the ddd at δ 5.97 to simplify to a dd (J = 12.3, 2.3 Hz). Double irradiation at δ 3.55 caused the ddd at δ 5.97 to simplify to a doublet (J = 12.3 Hz) and the ddd at δ 6.56 to simplify to a dd (J = 12.3, 1.0 Hz).

δ_C (75 MHz) 19.1, 32.2 & 42.7 (3 x CH_2), 51.5 (CH_2Ph), 56.7 (CHN), 127.1, 128.1 & 128.5 (3 x aryl CH), 130.7 (=CH), 139.5 (aryl C), 149.5 (=CH); the cycloheptenone carbonyl signal was observed only at 233 K (δ_C 204.8). The ^{13}C NMR spectrum at 233K showed additional signals but the peaks could not be fully assigned; pronounced broadening of the minor signals was probably associated with slow inversion at nitrogen in the bicyclic tautomer.

ν_{max} (CH_2Cl_2): 3380brw, 3030w, 2940s, 2870m, 1665s (with shoulders at 1755m and 1705m), 1610w, 1495 w, 1455m, 1395w, 1340w, 1200m, 1140w, 1105w, 1070w, 1030w, 980w, 910s cm^{-1}.

$^m/_z$ (%) [measured using (**233** ⇌ **234.HCl**)]: 216 (MH^+, 14), 215 (M^+, 16), 133 (11), 126 (19), (121 (14), 106 (16), 105 (45), 104 (11), 98 (45), 92 (16), 91 (100), 77 (25).

$C_{14}H_{17}NO$ requires $^m/_z$ 215.1310; observed 215.1309.

Attempts to obtain a salt with anhydrous HBF_4 in diethyl ether gave only a gum. Passage of anhydrous HCl through a diethyl ether solution of the amino-ketone gave a salt which could not be recrystallised but was partially purified by trituration with anhydrous diethyl ether; it was hygroscopic and deteriorated on standing in air.

Cis-4-[(Benzyloxycarbonyl)amino]-1-[(*p*-toluenesulphonyl)oxycyclooct-2-ene (**236**)
A solution of *n*-butyllithium (2.5M in hexane, 2.69 ml, 6.72 mmol) was injected into a

stirred solution of **(150)** (1.683 g, 6.23 mmol) in THF (28 ml) at -78°C under a nitrogen atmosphere. After 10 min a solution of *p*-toluenesulphonyl chloride (1.510 g, 7.91 mmol) in THF (8 ml) was added and warmed to room temperature. After stirring for 1 hr the reaction was quenched with water (1 ml) and the bulk of the solvent was distilled under reduced pressure. The residual oil was dissolved in diethyl ether (45 ml), dried over anhydrous magnesium sulphate, filtered and the solvent evaporated under reduced pressure. The crude oil was purified by flash chromatography using 1:1 diethyl ether:petroleum ether (b.p. 40 - 60°C) to yield **(236)** (1.740 g, 66%) as a yellow oil. Some decomposition occured during chromatography and also on standing. Full characterisation was not attempted and the tosylate was used immediately in the next reaction.

δ_H (300 MHz, $CDCl_3$): 1.27 - 2.08 (series of m, 8H), 2.39 (s, 3H), 3.95 (m, 1H), 4.29 (m, 1H), 4.86 (brd, J = 5.4 Hz, NH), 5.11 (s, 2H, CH_2Ph), 5.28 (m, 1H), 5.40 (dd, J = 10.4, 6.9 Hz, 1H), 7.27 (part of AA'BB', 2H), 7.36 (m, 5H), 7.81 (part of AA'BB', 2H).

Trans/cis-4-[(Benzyloxycarbonyl)amino]-1-chlorocyclooct-2-ene **(237)**

Lithium chloride (1.102 g, 26 mmol) was dissolved in DMSO (16 ml) and warmed with stirring to 60°C. A solution of **(236)** (1.610 g, 3.75 mmol) was added and stirred for 45 min. The solution was poured into water (15 ml) and extracted with diethyl ether (4 x 20 ml). The combined organic layers were washed with water (7 ml) and brine (5 ml). After drying with anhydrous magnesium sulphate and filtration, the solvent was distilled under reduced pressure. The crude oil was purified by flash chromatography eluting with 3:7 diethyl ether:petroleum ether (b.p. 40 - 60°C). The first fraction to be eluted (87 mg) was unidentifiable, but further elution afforded **(237)** (489 mg, 45%) as a white solid which had m.p. 87 - 88°C after recrystallisation from ethanol. The ^1H NMR indicated a 7:3 *trans*:*cis* mixture of isomers from signal integration; figures quoted in italics are common to both isomers.

δ_H (300 MHz, $CDCl_3$): *1.34* (m, 1H), *1.45 - 1.74* (series of m, 3H), *1.86* (m, 2H), *2.13* (m, 2H), *4.44* (brm, 1H), *4.78* (brm, 1H), *4.91* (brm, 1H), *5.08* (s, 2H, CH_2Ph), 5.31 (ddd, J = 10.7, 8.1, 1.3 Hz, 1H, *trans*-isomer), 5.38 (dd, J = 12.4, 6.1, 1H, *cis*-isomer), 5.67 (ddd, J = 10.7, 8.0, 1.4 Hz, 1H, *trans*-isomer), 5.76 (dd, J = 12.1, 6.1 Hz, 1H, *cis*-isomer), *7.33* (m, 5H).

δ_C (75 MHz, $CDCl_3$), *Trans*-isomer: 23.5, 24.9, 36.7 & 40.1 (4 x CH_2), 49.3 (CHN), 56.7 (CHCl), *66.6* (CH_2Ph), *128.0* (aryl CH), *128.4* (2 x CH), *130.9* (=CH_2), *132.1* (=CH_2), *136.2* (aryl C), *155.4* (C=O).

Cis-isomer: 22.7, 23.9, 33.6 & 36.5 (4 x CH_2), 49.2 (CHN), 57.9 (CHCl), *66.6* (CH_2Ph), *128.0* (aryl CH), *128.4* (2 x CH), *130.9* (=CH_2), *132.1* (=CH_2), *136.2* (aryl C), *155.4* (C=O).

υ_{max} (CH_2Cl_2): 3440m, 3340w, 3030w, 2940m, 2860w, 1715s, 1505s, 1465w, 1450m, 1395w, 1370w, 1325m, 1215s, 1130w, 1085w, 1025m, 980w, 910w, 800w, 790w cm^{-1}.

$^m/_z$ (%): 295 (M^+, 0.5), 293 (M^+, 2), 259 (18), 258 (100), 249 (8), 214 (37), 204 (4), 202 (11), 197 (9), 172 (41), 166 (9), 108 (10).

Found: C, 65.12; H, 6.67; N, 4.76%.
$C_{16}H_{20}NO_2Cl$ requires: C, 65.40; H, 6.86; N, 4.77%.

N-(Benzyloxycarbonyl)-9-azabicyclo[4.2.1]non-7-ene (**238**)

Sodium hydride (60% dispersion in mineral oil, 97 mg, 2.43 mmol) was slurried with THF (2 ml) under a nitrogen atmosphere. A solution of **(237)** (341 mg, 1.16 mmol) in THF (8 ml) was injected *via* syringe and stirred at ambient temperature for 1.5 hr and then refluxed for a further 2.5 hr. Excess hydride was destroyed by quenching with the minimum quantity of water at -78°C. The bulk of the solvent was distilled under reduced pressure and the oily residue was partitioned between diethyl ether (18 ml) and water (7 ml). After washing with further water (5 ml), the organic layer was separated, dried with anhydrous magnesium sulphate, filtered and the solvent distilled under vacuum. Purification by flash chromatography using 1:4 diethyl ether: petroleum ether (b.p. 40 - 60°C) afforded firstly the aziridine **(239)** (31 mg, 10%) as a pale yellow oil.

δ_H (300 MHz, $CDCl_3$), Double irradiation of the two aziridine protons allowed for full measurement of the coupling constants: 1.22 - 1.44 (m, 2H), 1.51 - 1.84 (series of m, 3H), 1.99 (m, 1H), 2.15 (dddd, J = 13.8, 5.8, 3.4, J ≈ 3 Hz, 1H), 2.28 (m, 1H), 2.63 (ddd, J = 10.1, 6.3, 3.4 Hz, 1H, α-N), 3.07 (ddd, J = 6.3, 1.7, 1.1 Hz, 1H, α-N), 5.13 (s, 2H, CH_2Ph), 5.57 (dd, J = 11.1, 1.1 Hz, 1H, HC=), 5.75 (dddd, J = 11.1, 7.6, 5.8,

1.7 Hz, 1H, HC=), 7.35 (m, 5H).

δ_C (75 MHz, $CDCl_3$): 25.7, 26.7, 27.1 & 28.8 (4 x CH_2), 40.0 & 44.4 (2 x CHN), 68.0 (CH_2Ph), 122.3 (=CH_2), 128.1, 128.2 & 128.5 (3 x aryl CH), 134.9 (=CH), 136.0 (aryl C), 163.8 (C=O).

υ_{max} (CH_2Cl_2): 3030w, 2940m, 2860w, 1715s, 1495w, 1450w, 1425w, 1380w, 1270brs, 1215s, 1170w, 1110w, 1090w, 1045w, 1025w, 910w cm^{-1}.

$^m/_z$ (%): 257 (M^+, 1), 171 (10), 170 (16), 122 (14), 92 (9), 91 (100).

$C_{16}H_{19}NO_2$ [M^+] requires $^m/_z$ 257.1416; observed 257.1416.

Further elution with 3:7 diethyl ether:petroleum ether (b.p. 40 - 60°C) yielded **(238)** (86 mg, 28%) as a colourless oil; the signals quoted below in italics are common to both rotamers (in a 1:1 ratio).

δ_H (300 MHz, $CDCl_3$): *1.27 - 1.66* (series of m, 6H), *1.94* (m, 1H), *2.07* (m, 1H), 4.72 (brd, J = 6.1 Hz, 1H, α-N), 4.78 (brd, J = 6.0 Hz, 1H, α-N), *5.13 & 5.18* (ABq, J = 12.5 Hz, 2H, CH_2Ph), 5.72 (dd, J = 6.8, 2.3 Hz, 1H), 5.75 (dd, J = 6.8, 2.3 Hz, 1H), *7.35* (m, 5H).

δ_C (75 MHz, $CDCl_3$): 24.0 & 24.2 (2 x CH_2), 30.8 & 31.7 (2 x CH_2), 60.9 & 61.3 (2 x CHN), *127.7, 127.8 & 128.4* (3 x aryl CH), 130.9 & 131.0 (2 x =CH), *137.1* (aryl C), *153.2* (C=O).

υ_{max} (CH_2Cl_2): 3030w, 2930s, 2860m, 1695s, 1615w, 1585w, 1495m, 1430s, 1365m, 1350m, 1315s, 1265brw, 1230w, 1210w, 1195w, 1180w, 1140m, 1115s, 1100s, 1095s, 1070s, 1025w, 975m, 960w cm^{-1}.

$^m/_z$ (%): 257 (M^+, 11), 171 (12), 170 (21), 92 (9), 91 (100).

$C_{16}H_{19}NO_2$ [M^+] requires $^m/_z$ 257.1416; observed 257.1418.

In a repeat experiment, the yield of **(238)** was increased to 40% by using a 6:1 mixture of THF:DME as solvent and stirring at 60°C for 2.5 hr, rather than refluxing.

The yield of aziridine **(239)** was suppressed to 3% using these conditions.

N-(Benzyloxycarbonyl)-7β,8β-epoxy-9-azabicyclo[4.2.1]nonane **(235)**

A solution of **(238)** (39 mg, 0.15 mmol) in dichloromethane (4 ml) was epoxidised with MCPBA (50 - 60% purity, 57 mg, 0.18 mmol) using an identical procedure to that described for the conversion of **(151 ⇌ 152)** into **(194)**. Purification of the crude product by flash chromatography using 1:1 diethyl ether:petroleum ether (b.p. 40 - 60°C) afforded **(235)** (34 mg, 84%) as a colourless oil. The chemical shifts quoted in italics refer to signals common to both rotamers (in a 1:1 ratio).

δ_H (300 MHz, $CDCl_3$): *1.48* (m, 6H), *1.90* (m, 1H), *2.03* (m, 1H), 3.36 (d, J = 3.0 Hz, 1H, HCO), 3.37 (d, J = 3.0 Hz, 1H, HCO), 4.35 (d, J = 6.2 Hz, 1H, α-N), 4.41 (d, J = 6.2 Hz, 1H, α-N), *7.33* (m, 5H).

δ_C (75 MHz, $CDCl_3$): *24.3* (2 x CH_2), 28.8 & 29.6 (2 x CH_2), 55.9 & 56.0 (2 x CHO), 56.8 & 57.3 (2 x CHN), *66.7* (CH_2Ph), *127.7, 127.9 & 128.4* (3 x aryl CH), *136.8* (aryl C), *155.1* (C=O).

υ_{max} (CH_2Cl_2): 3040w, 2930m, 2860w, 1695s, 1495w, 1425s, 1350w, 1320m, 1295w, 1195w, 1155w, 1115m, 1095m, 1035w, 1025w, 980w, 900w, 850m cm^{-1}.

$^m/_z$ (%): 273 (M^+, 22), 166 (13), 138 (8), 110 (5), 92 (8), 91 (100).

$C_{16}H_{19}NO_3$ [M^+] requires $^m/_z$ 273.1365; observed 273.1363.

N-(Benzyloxycarbonyl)-7β-hydroxy-9-azabicyclo[4.2.1]nonane **(240)**

A solution of **(238)** (78 mg, 0.30 mmol) in THF (4 ml) was cooled with stirring to -78°C under a nitrogen atmosphere. Borane:THF complex (1M in THF, 0.18 ml, 0.18 mmol) was injected and the solution was slowly warmed to room temperature. After 2.5 hr the reaction was quenched by the sequential addition of water (200 μl), sodium hydroxide solution (6M, 200 μl) and hydrogen peroxide solution (30 weight %, 200 μl). The reaction mixture was stirred for a further 10 min, the bulk of the solvent distilled under reduced pressure and the residue partitioned between diethyl ether (20 ml) and water (5 ml) and then washed with further water (5 ml) and brine (5 ml). The diethyl ether layer was dried over anhydrous magnesium sulphate, filtered and the solvent distilled in vacuum. The resultant crude oil was purified by flash

chromatography using 1:1 diethyl ether:petroleum ether (b.p. 40 - 60°C) to afford **(240)** (59 mg, 71%) as a colourless oil. The chemical shifts quoted in italics refer to signals common to both rotamers.

δ_H (300 MHz, $CDCl_3$): *1.24 - 1.64* (m, 4H), *1.81 - 2.16* (series of m, 6H), *2.89* (brs, 1H, exch), *4.17* (m, 1H), *4.49* (m, 1H), *5.05 & 5.18* (ABq, J = 12.4 Hz, 2H, CH_2Ph), *7.33* (s, 5H).

δ_C (75 MHz, $CDCl_3$): 23.8, 23.9, 24.0 & 24.1 (4 x CH_2), 30.5, 31.5, 32.0 & 33.1 (4 x CH_2), 40.1 & 40.7 (2 x CH_2), 55.2 & 55.8 (2 x CHN), 65.2 & 65.4 (2 x CHN), 66.5 & 66.6 (2 x CH_2Ph), 77.4 & 78.4 (2 x CHOH), *127.4 & 127.5* (2 x aryl CH), 127.8 (aryl CH), 128.3 (aryl CH), 136.7 & 136.8 (2 x aryl C), 154.3 & 154.5 (2 x C=O).

υ_{max} (CH_2Cl_2): 3600w, 3460brw, 3040w, 2940w, 2860w, 1690s, 1500w, 1445w, 1420m, 1360w, 1335m, 1215w, 1190w, 1115m, 1095m, 1020w, 1000w, 965w, 940w, 910 cm^{-1}.

$^m/_z$ (%): 275 (M^+, 17), 184 (11), 168 (5), 141 (4), 140 (40), 96 (20), 91 (100).

$C_{16}H_{21}NO_3$ [M^+] requires $^m/_z$ 275.1521; observed 275.1524.

Norhomotropan-7β-ol **(241)**

The carbamate **(240)** (49 mg, 0.18 mmol) was hydrogenolysed in absolute ethanol (5 ml) using the procedure described for the conversion of **(194)** into **(197)**. The amine **(241)** (24 mg, 96%) was isolated as a thick oil after distillation of solvent under vacuum.

δ_H (300 MHz, CD_3OD): 1.38 - 1.81 (series of m, 8H), 1.88 (ddd, J = 14.5, 8.7, 2.8 Hz), 1.97 (ddd, J = 14.5, 6.2, 3.3 Hz), 3.30 (brd overlapping with solvent signal, 1H, α-N), 3.77 (m, 1H, α-N), 4.12 (dd, J = 6.2, 2.8 Hz, 1H, α-OH).

δ_C (75 MHz, $CDCl_3$): 24.3, 24.7, 33.4, 35.4 & 42.2 (5 x CH_2), 57.3 & 66.5 (2 x CHN), 79.8 (CHOH).

υ_{max} (CH_2Cl_2): 3600w, 3300brw, 2930s, 2860w, 1460w, 1440w, 1255w, 1180w, 1120w, 1050w, 995w, 950w, 905m cm^{-1}.

$^{m}/_{z}$ (%): 141 (M^+, 31), 124 (31), 98 (33), 97 (100), 96 (17), 84 (17), 82 (51), 70 (11), 69 (30), 68 (36).

$C_8H_{15}NO$ [M^+] requires $^{m}/_{z}$ 141.1154; observed 141.1153.

1β-Hydroxy-2β,3β-epoxy-4β-[(benzyloxycarbonyl)amino]cyclooctane (**244**)

Using the procedure of Soai;[111] methanol (300 μl) was added over 45 min *via* a syringe pump to a refluxing solution of (**194**) (126 mg, 0.44 mmol) and sodium borohydride (42 mg, 1.11 mmol) and the solution was then refluxed for 2 hr. After cooling to room temperature, saturated ammonium chloride solution (1 ml) was added to destroy excess hydride. Diethyl ether (20 ml) was added and washed with saturated ammonium chloride solution (12 ml). The ethereal layer was separated, dried with anhydrous magnesium sulphate, filtered and the solvent distilled under reduced pressure. The residual oil was purified by flash chromatography using 3:2 diethyl ether:petroleum ether (b.p. 40 - 60°C) to afford (**244**) (92 mg, 73%) as a colourless oil. In subsequent preparations the yield of (**244**) could be improved to 98% by refluxing in THF for 3 hr with 2 M equivalents of sodium borohydride (without the addition of methanol). The product isolated using this procedure was pure enough for further reactions without chromatography.

δ_H (300 MHz, $CDCl_3$): 1.38 (m, 2H), 1.66 (m, 4H),1.86 (m, 2H), 2.91 (dd, J = 4.5, 3.6 Hz, 1H, HCO), 3.11 (t, J = 4.5, J ≈ 4.8 Hz, 1H, HCO), 3.62 (brs, 1H, exch), 4.42 (brd, J ≈ 3.4 Hz, 1H), 4.47 (m, 1H), 5.06 (s, 2H, CH_2Ph), 7.15 (d, J = 9.3 Hz, 1H, NH), 7.31 (m, 5H).

δ_C (75 MHz, $CDCl_3$): 22.0, 22.9, 31.3 & 32.0 (4 x CH_2), 46.5 (CHN), 57.1 & 58.6 (2 x CHO), 65.5 (CHOH), 66.4 (CH_2Ph), 127.8, 127.9 & 128.3 (3 x aryl CH), 136.8 (aryl C), 156.2 (C=O).

υ_{max} (CH_2Cl_2): 3570brw, 3330brw, 3030w, 2940m, 2870w, 1710s, 1525m, 1450w, 1380w, 1340w, 1305w, 1235m, 1165w, 1130w, 1085w, 1070w, 1040m, 1025w, 1005w, 925w, 905m cm^{-1}.

$^{m}/_{z}$ (%): 291 (M^+, 3), 156 (6), 146 (5), 108 (13), 91 (100).

$C_{16}H_{21}NO_4$ [M^+] requires $^m/_z$ 291.1471; observed 291.1474.

The above reaction was reversible using the previously described Jones procedure used to oxidise **(132)**; a solution of **(244)** (34 mg, 0.12 mmol) was oxidised to **(243)** (32 mg, 95%) which appeared pure from the 90 MHz ^{1}H NMR spectrum.

1β-[(*p*-Toluenesulphonyl)oxy]-2β,3β-epoxy-4β-[(benzyloxycarbonyl)amino]-cyclooctane **(245)**

A solution of **(244)** (520 mg, 1.78 mmol) in dry THF (11 ml) was stirred at 0°C under a nitrogen atmosphere. A solution of *n*-butyllithium (2.5M in hexane, 0.86 ml, 2.15 mmol) was injected and stirred for 5 min, before the addition of *p*-toluenesulphonyl chloride (443 mg, 2.32 mmol) in THF (4 ml). The solution was warmed to room temperature and stirred a further 1.5 hr and then quenched with water (0.5 ml). Diethyl ether (30 ml) was added, the solution transferred to a separating funnel, and washed with water (2 x 7 ml) and brine (7 ml). After separation the ethereal layer was dried over anhydrous magnesium sulphate, filtered, and the solvent distilled under reduced pressure. The tosylate **(245)** (728 mg, 92%) was isolated as a foam by purification of the crude oil using flash chromatography, eluting with 1:1 diethyl ether:petroleum ether (b.p. 40 - 60°C).

δ_H (300 MHz, $CDCl_3$): 1.08 - 1.36 (brm, 2H), 1.44 - 1.73 (series of m, 5H), 2.02 (m, 1H), 2.42 (s, 3H, Me), 3.11 (m, 2H, CHO), 4.11 (m, 1H, α-N), 4.91 (brd, J = 9.1 Hz, 1H, α-OSO_2Ar), 5.09 (s, 2H, CH_2Ph), 5.41 (brd, J = 8.8 Hz, 1H, NH), 7.29 - 7.33 (s, 5H plus, part of AA'BB', 2H), 7.80 (part of AA'BB', 2H).

δ_C (75 MHz, $CDCl_3$): 21.7 (CH_3), 22.3, 23.3, 27.3 & 27.4 (4 x CH_2), 49.3 (CHN), 59.1 & 59.5 (2 x CHO), 66.8 (CH_2Ph), 79.4 ($CHOSO_2$), 127.8, 128.0, 128.1, 128.5 & 130.0 (5 x aryl CH), 133.7 (aryl C), 136.4 (aryl CCH_2), 145.0 (aryl CSO_3), 155.6 (C=O).

υ_{max} (CH_2Cl_2): 3440w, 3030w, 2940w, 2870w, 1720s, 1600w, 1505m, 1455w, 1365m, 1220w, 1190m, 1185s, 1095w, 1045w, 1025w, 900m, 855m, 810w cm^{-1}.

$^m/_z$ (%): 445 (M^+,9), 395 (23), 377 (21), 363 (74), 352 (21), 345 (58), 335 (61), 329 (59), 320 (100).

$C_{23}H_{27}NO_6$ [M^+] requires $^m/_z$ 445.1559; observed 445.1558.

1α-Chloro-2β,3β-epoxy-4β-[(benzyloxycarbonyl)amino]cyclooctane (**246**)

Lithium chloride (870 mg, 21 mmol) and (**245**) (1.538 g, 3.46 mmol) were added to DMSO (17 ml) and heated to 60°C with stirring for 1.5 hr. The solution was poured into an equal volume of water and repeatedly extracted 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 (**246**) (928 mg, 87%) as a white solid. An analytical sample was prepared by recrystallisation from ethanol (m.p. 94 - 95°C).

δ_H (300 MHz, $CDCl_3$): 1.43 (m, 2H), 1.58 (m, 1H), 1.66 - 1.92 (series of m, 3H), 2.04 (m, 2H), 3.14 (dd, J = 8.9, 4.3 Hz, HCO, β-Cl), 3.37 (t, J ≈ 4.3 Hz, HCO, β-N), 4.24 (m, 2H, α-N & α-Cl), 5.08 & 5.12 (ABq, J = 12.2 Hz, 3H, CH_2Ph & NH), 7.35 (m, 5H).

δ_C (75 MHz, $CDCl_3$): 22.6, 24.0, 29.8 & 36.2 (4 x CH_2), 49.3 (CHN), 58.6 & 59.1 (2 x CHO), 61.7 (CHCl), 66.9 (CH_2Ph), 128.1, 128.2 & 128.5 (3 x aryl CH), 136.2 (aryl C), 155.6 (C=O).

υ_{max} (CH_2Cl_2): 3680w, 3430w, 2940w, 2860w, 1720s, 1605w, 1500m, 1450w, 1335w, 1310w, 1220m, 1165w, 1130w, 1105w, 1055w, 1035w, 895 cm^{-1}.

$^m/_z$ (%): 311(M^+, 12), 309 (M^+, 32), 273 (18), 230 (11), 122(6), 108 (21), 107 (7), 92 (7), 91 (100).

Found: C, 62.17; H, 6.41; N, 4.64%.
$C_{16}H_{20}NO_3Cl$ requires: C, 62.02; H, 6.51; N, 4.52%.

N-(Benzyloxycarbonyl)-7β,8β-epoxy-9-azabicyclo[4.2.1]nonane (**235**)

To a solution of (**246**) (414 mg, 1.34 mmol) in THF:DME (5:1, 8 ml) was added sodium hydride (60% dispersion in mineral oil, 107 mg, 2.68 mmol) and stirred for 2 hr. The solution was cooled to -78°C and excess hydride was destroyed by the addition of the minimum quantity of water. Diethyl ether (15 ml) was added and

washed with water (2 x 5 ml) and brine (5 ml). The organic layer was dried with anhydrous magnesium sulphate, filtered, and the solvent distilled under reduced pressure. The crude oil was purified by flash chromatography, eluting with 2:3 diethyl ether:petroleum ether (b.p. 40 - 60°C), to afford **(235)** (358 mg, 98%) as a colourless oil. The epoxide prepared using this method was identical to a sample prepared by epoxidation of the alkene **(238)**.

1β-Hydroxy-2α,3α-epoxy-4β-[(benzyloxycarbonyl)amino]cyclooctanone **(255)**

MCPBA (50 - 60% purity, 4.21 g, 13.4 mmol) was added to stirred solution of **(150)** (3.07 g, 11.2 mmol) 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 residual oil was purified by flash chromatography, eluting with diethyl ether, to afford **(255)** (3.10 g, 95%) as a white solid which had m.p. 125 - 126°C after recrystallisation from ethanol.

δ_H (300 MHz, $CDCl_3$): 1.39 - 1.70 (series of m, 6H), 1.86 (brm, 2H), 2.95 (dd, J = 4.7, 9.3 Hz, 1H, HCO), 3.03 (dd, J = 4.7, 8.2 Hz, HCO), 3.56 (m, 1H), 3.70 (m, 1H), 4.16 (brs, 1H, exch), 5.01 (m, 1H, NH), 5.29 (s, 2H, CH_2Ph), 7.34 (m, 5H).

δ_C (75 MHz, $CDCl_3$): 23.2, 24.4, 33.6 & 34.8 (4 x CH_2), 51.3 (CHN), 57.9 & 60.3 (2 x CHO), 66.7 (CH_2Ph), 71.2 (CHOH), 128.0 (2 x aryl CH), 128.4 (aryl CH), 136.4 (aryl C), 155.7 (C=O).

υ_{max} (CH_2Cl_2): 3600w, 3430w, 2930m, 2860w, 1720s, 1510m, 1450w, 1315brw, 1225m, 1145w, 1090w, 1045m, 1025w, 965w, 900w cm^{-1}.

$^m/_z$ (%): 291 (M^+, 45), 256 (22), 237 (58), 213 (29), 200 (22), 184 (46), 167 (77), 108 (49), 91 (100).

$C_{16}H_{21}NO_4$ [M^+] requires $^m/_z$ 291.1471; observed 291.1474.

Found: C, 66.28; H, 7.46; N, 5.00%.
$C_{16}H_{21}NO_4$ requires: C, 65.96; H, 7.27; N, 4.81%.

2α,3α-Epoxy-4β-[(benzyloxycarbonyl)amino]cyclooctanone (**256**)

A solution of (**255**) (551 mg, 1.90 mmol) in acetone (25 ml) was oxidised with Jones reagent using the procedure described previously for the conversion of (**132**) into (**133**). Recrystallisation of the crude product with ethanol afforded (**256**) (523 mg, 96%) as a crystalline white solid (m.p. 145 - 146°C).

δ_H (300 MHz, $CDCl_3$): 1.48 (m, 1H), 1.62 - 1.94 (series of m, 5H), 2.35 (ddd, J = 13.4, 10.2, 3.7 Hz, 1H), 2.63 (m, 1H), 3.04 (m, 1H, α-N), 3.36 (m, 1H, HCO), 3.82 (d, J = 5.2 Hz, 1H, HCO), 5.03 (s, 2H, CH_2Ph), 5.61 (brd, J = 6.1 Hz, 1H, NH), 7.30 (s, 5H).

δ_C (75 MHz, $CDCl_3$): 24.2, 24.7, 33.3 & 42.6 (4 x CH_2), 52.3 (CHN), 57.5 & 58.5 (2 x CHO), 66.6 (CH_2Ph), 128.0 (2 x aryl CH), 128.4 (aryl CH), 136.4 (aryl C), 155.5 (NC=O), 206.2 (C=O).

υ_{max} (CH_2Cl_2): 3430w, 3030w, 2940w, 1725s, 1505m, 1450w, 1375w, 1315w, 1220m, 1185w, 1135w, 1100w, 1070w, 1020m, 950w, 915w, 845w cm^{-1}.

$^m/_z$ (%): 289 (M^+,8), 183 (3), 112 (4), 108 (15), 107 (9), 92 (9), 91 (100).

Found: C, 66.46; H, 6.46; N, 5.02%.
$C_{16}H_{19}NO_4$ requires: C, 66.42; H, 6.62; N, 4.84%.

1α-Hydroxy-2α,3α-epoxy-4β-[(benzyloxycarbonyl)amino]cyclooctane (**257**)

A solution of (**256**) 1.105 g, 3.82 mmol) and sodium borohydride (350 mg, 9.46 mmol) in THF (45 ml) was refluxed for 1.5 hr. Saturated ammonium chloride solution (2 ml) was added to destroy excess hydride and the bulk of the solvent was distilled under reduced pressure. The residual oil was dissolved in diethyl ether (30 ml) and washed with saturated ammonium chloride solution (10 ml) and water (10 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 7:3 diethyl ether:petroleum ether (b.p. 40 - 60°C), to afford (**257**) (982 mg, 88%) as a foam. The foam was triturated to a white solid with petroleum ether (b.p. 40 - 60°C) and an analytical sample was prepared by recrystallisation with ethanol (m.p. 103 - 104 °C). The ^1H NMR spectrum was broad when recorded in $CDCl_3$, but signals were better resolved in CD_3COCD_3.

δ_H (300 MHz, $CDCl_3$): 1.20 (m, 1H), 1.39 - 1.66 (m, 4H), 1.82 (m, 2H), 2.09 (m, 1H), 2.75 (vbrs, 1H, exch), 3.04 (brm, 2H, HCO), 4.42 (brm, 2H, α-N & α-OH), 5.08 (m, 3H, CH_2Ph & NH), 7.33 (m, 5H).

δ_H (300 MHz, CD_3COCD_3): 1.34 (m, 1H), 1.52 - 1.89 (series of m, 6H), 2.01 (m, 1H), 2.93 (dd, J = 9.4, 4.2 Hz, 1H, HCO, β-N), 3.06 (t, J = 4.2 Hz, 1H, HCO, β-OH), 3.41 (brs, 1H, exch), 4.39 (m, 1H), 4.52 (brm, 1H), 5.05 (s, 2H, CH_2Ph), 6.44 (brd, J = 6.8 Hz, NH, 1H), 7.35 (m, 5H).

δ_C (75 MHz, $CDCl_3$): 19.3 & 25.0 (2 x CH_2), 32.6 (2 x CH_2), 48.8 (CHN), 57.2 & 59.3 (2 x CHO), 65.4 (CHOH), 66.7 (CH_2Ph), 128.1 (2 x aryl CH), 128.5 (aryl CH), 136.5 (aryl C), 156.0 (C=O).

υ_{max} (CH_2Cl_2): 3560m, 3430m, 3350w, 3040w, 2940s, 2865m, 1720s, 1505s, 1455m, 1405w, 1305w, 1235s, 1220s, 1180w, 1165w, 1140w, 1095s, 1025s, 985w, 930w, 910w, 890m cm^{-1}.

$^m/_z$ (CI, %): 292 (MH^+, 100), 248 (9), 201 (10), 156 (27), 140 (16), 108 (26).

$C_{16}H_{22}NO_4$ [MH^+] requires $^m/_z$ 292.1549; observed 292.1549.

Found: C, 65.95; H, 7.13; N, 4.72%.
$C_{16}H_{19}NO_4$ requires: C, 65.96; H, 7.27; N, 4.81%.

1α-[(*p*-toluenesulphonyl)oxy]-2α,3α-epoxy-4β-[(benzyloxycarbonyl)amino]cyclo-octane (**258**)

A solution of **(257)** (307 mg, 1.05 mmol) was tosylated using the procedure described previously for the tosylation of **(244)**. The residual oil was purified by flash chromatography, eluting with 4:1 diethyl ether:petroleum ether (b.p. 40 - 60°C), to afford **(258)** (451 mg, 96%) as a gum. The ^1H NMR spectrum was broad when recorded in $CDCl_3$, but signals were better resolved in CD_3COCD_3.

δ_H (300 MHz, CD_3COCD_3): 1.38 - 1.59 (m, 2H), 1.61 - 1.83 (series of m, 5H), 1.98 (m, 1H), 2.43 (s, 3H), 2.90 (dd, J = 9.3, 4.2 Hz, 1H, HCO, β-N), 3.12 (t, J = 4.2 Hz, 1H, HCO, β-OSO_2Ar), 4.13 (m, 1H, α-N), 5.08 (s, 2H, CH_2Ph), 5.20 (ddd, J = 6.2,

3.7, 2.2 Hz, 1H, α-OSO_2Ar), 6.48 (m, 1H, NH), 7.38 (m, 5H, plus part of AA'BB', 2H), 7.89 (part of AA'BB', 2H).

δ_C (75 MHz, $CDCl_3$): 20.7 (CH_2), 21.6 (CH_3), 23.8, 31.4 & 32.5 (3 x CH_2), 49.5 (CHN), 58.4 & 57.7 (2 x CHO), 66.5 (CH_2Ph), 75.7 ($CHOSO_2Ar$), 127.8 (2 x aryl CH), 128.1, 128.4 & 129.4 (3 x aryl CH), 133.7 (aryl CMe), 136.5 (aryl CCH_2), 144.5 (aryl CSO_2), 155.3 (C=O).

υ_{max} (CH_2Cl_2): 3440m, 3040w, 2940m, 2865w, 1725s, 1600w, 1510s, 1455m, 1395w, 1360s, 1325w, 1305w, 1220s, 1190s, 1175s, 1140w, 1120w, 1095m, 1080m, 1040m, 1025m, 1015m, 930s, 880w, 825m, 815m cm^{-1}.

$^m/_z$ (%): 445 (M^+, 1), 273 (7), 187 (45), 186 (18), 170 (10), 169 (100), 155 (40), 149 (15), 138 (54), 123 (14), 109 (21), 95 (29), 91 (56).

$C_{23}H_{27}NO_6S$ [M^+] requires $^m/_z$ 445.1559; observed 445.1557.

N-(Benzyloxycarbonyl)-7α,8α-epoxy-9-azabicyclo[4.2.1]nonane **(259)**

Sodium hydride (60% dispersion, 97 mg, 2.43 mmol) and THF (1 ml) were stirred in a 25ml two-necked flask under a nitrogen atmosphere at 0°C. A solution of **(258)** (451 mg, 1.01 mmol) in THF (4 ml) was injected, warmed to room temperature and stirred for 3 hr. The reaction was worked up using an identical procedure to that described for the *exo*-epoxide **(235)**. Purification of the resultant crude oil by flash chromatography, eluting with 1:1 diethyl ether:petroleum ether (b.p. 40 - 60°C), afforded **(259)** (258 mg, 93%) as an oil which solidified on standing. An analytical sample was prepared by recrystallisation from toluene and petroleum ether (b.p. 40 - 60°C) to give a white solid (m.p. 49 - 50°C). The NMR shifts given in italics refer to signals common to both rotamers (in a 1:1 ratio).

δ_H (300 MHz, $CDCl_3$): *1.43* (m, 2H), *1.71 - 2.11* (series of m, 6H), 3.87 (dd, J = 7.4, 3.6 Hz, 1H, HCO), 3.89 (dd, J = 7.4, 3.6 Hz, 1H, HCO), *4.23* (m, 2H, α-N), *5.10* (s, 2H, CH_2Ph), *7.33* (m, 5H).

δ_C (75 MHz, $CDCl_3$): 25.0 & 25.2 (2 x CH_2), 28.1 & 29.0 (2 x CH_2), 55.6 & 55.8 (2 x CHO), 62.6 & 62.7 (2 x CHN), *66.6* (CH_2Ph), *127.8, 127.9 & 128.4* (3 x aryl CH), *136.8* (aryl C), *152.7* (C=O).

υ_{max} (CH_2Cl_2): 3040w, 2925m, 2860w, 1695s, 1440s, 1385w, 1370w, 1350w, 1325m, 1315m, 1300w, 1230w, 1200w, 1190w, 1155w, 1120m, 1095m, 1080w, 1030w, 1015w, 970w, 940w, 910m, 865w, 840w cm^{-1}.

$^m/_z$ (%): 273 (M^+, 28), 138 (12), 92 (8), 91 (100).

$C_{16}H_{19}NO_3$ [M^+] requires $^m/_z$ 273.1365; observed 273.1370.

Found: C, 70.06; H, 7.02; N, 5.14%.
$C_{16}H_{19}NO_3$ requires: C, 70.31; H, 7.02; N, 5.12%.

N-Methyl-7β,8β-epoxy-9-azabicyclo[4.2.1]nonane **(260)**

A solution of **(235)** (107 mg, 0.39 mmol) in dry THF (5 ml) was cooled with stirring to 0°C under a nitrogen atmosphere. A solution of DIBAH (1M in hexane, 2.16 ml, 2.16 mmol) was injected, warmed to room temperature and stirred for 3 hr. Excess hydride was destroyed by addition of the minimum quantity of water-saturated diethyl ether, the solution was dried over anhydrous sodium sulphate and then filtered through celite. The colourless solution was acidified with hydrogen chloride gas at 0°C and the solvent was distilled under reduced pressure. The residual white solid was repeatedly triturated with diethyl ether to remove benzyl alcohol yielding **(260.HCl)** (60 mg, 81%) as a hygroscopic white solid. The amine was volatile and NMR spectra of the free amine **(260)** were recorded by dissolving the salt in the minimum quantity of $CDCl_3$, basifying with ammonia gas and filtering. The amine was stored as the hydochloride salt.

δ_H (300 MHz, $CDCl_3$): 1.33 - 1.52 (series of m, 4H), 1.58 (m, 2H), 1.74 (m, 2H), 2.55 (s, 3H, CH_3), 3.18 (dd, J = 7.0, 1.6 Hz, 2H, α-N), 3.43 (s, 2H, HCO).

δ_C (75 MHz, $CDCl_3$): 24.7 (2 x CH_2), 30.8 (2 x CH_2), 46.5 (CH_3), 61.1 (2 x CHN), 63.6 (2 x CHO).

υ_{max} ($CDCl_3$): 3030w, 2930m, 2850w, 1445w, 1340w, 1305w, 1220w, 1165w, 1125w, 1080w, 1035w, 950w, 845w cm^{-1}.

$^m/_z$ (%) [measured using **(260.HCl)**]: 153 (M^+ - HCl, 41), 139 (23), 124 (22), 110

(100), 96 (85), 82 (48), 68 (36).

$C_9H_{15}NO$ [M^+ - HCl] requires $^m/_z$ 153.1154; observed 153.1154.

7β,8β-Epoxy-9-azabicyclo[4.2.1]nonane (**261**)

A solution of (**235**) (50 mg, 0.18 mmol) in dry methanol (4 ml) was hydrogenolysed using the procedure described for the conversion of (**194**) into (**197**). Distillation of solvent under reduced pressure afforded (**261**) (22 mg, 86%) as a waxy solid.

δ_H (300 MHz, $CDCl_3$): 1.32 - 1.83 (series of m, 8H), 2.25 (s, 1H, NH), 3.34 (s, 2H, HCO), 3.42 (dd, J = 6.7, 1.7, 2H, α-N).

δ_C (75 MHz, $CDCl_3$): 24.7 (2 x CH_2), 31.0 (2 x CH_2), 56.4 (2 x CHO), 58.9 (2 x CHN).

υ_{max} (CH_2Cl_2): 3350w, 3030w, 2930s, 2860m, 1445w, 1425w, 1395w, 1340w, 1310w, 1265brw, 1215w, 1200w, 1160w, 1135w, 1110w, 1040w, 1010w, 950w, 930w, 860m, 840m, 825w, 815w, 795w cm^{-1}.

$^m/_z$ (%): 139 (M^+, 54), 110 (61), 97 (27), 96 (100), 83 (43), 82 (50), 80 (20), 68 (28), 55 (43).

$C_8H_{13}NO$ [M^+] requires $^m/_z$ 139.0997; observed 139.0998.

Homotropan-7α-ol (**262**)

To a slurry of LAH (21 mg, 0.55 mmol) in dry THF (1 ml) was injected a solution of (**259**) (95 mg, 0.35 mmol) in THF (5 ml) which was then refluxed under nitrogen for 3 hr. Excess hydride was destroyed by the dropwise addition of the minimum quantity of water-saturated diethyl ether and the solution was then dried over anhydrous sodium sulphate. Filtration through celite and distillation of solvent under reduced pressure gave an oil which was purified by flash chromatography, eluting with 1:9 methanol:dichloromethane saturated with ammonia gas, to afford (**262**) (38 mg, 70%) as a waxy solid.

δ_H (300 MHz, $CDCl_3$): 1.40 (ddd, J = 13.7, 6.4, 3.1 Hz, 1H), 1.46 (m, 1H), 1.66 (m, 5H), 1.90 (m, 2H), 2.50 (s, 3H, CH_3), 2.63 (ddd, J = 13.7, 10.4, 9.5 Hz, 1H), 3.18 (m,

1H, α-N), 3.24 (m, 1H, α-N), 4.55 (dt, J = 10.4, 6.4, 6.4 Hz, 1H, α-OH).

δ_C (75 MHz, $CDCl_3$): 24.8 (2 x CH_2), 26.7 & 33.6 (2 x CH_2), 39.2 (CH_3), 39.9 (CH_2), 61.1 & 65.3 (2 x CHN), 71.7 (CHOH).

υ_{max} (CH_2Cl_2): 3620m, 3370brm, 3040w, 2920s, 1465w, 1375w, 1260brw, 1180w, 1125w, 1090w, 1050m, 1010w, 985w, 970w, 920w cm^{-1}.

$^m/_z$ (%): 155 (M^+, 50), 149 (17), 138 (80), 112 (68), 111 (90), 110 (26), 100 (12), 97 (24), 96 (60), 91 (25), 83 (63), 82 (100).

$C_9H_{17}NO$ [M^+] requires $^m/_z$ 155.1310; observed 155.1312.

Norhomotropan-7α-ol **(263)**

A solution of the epoxide **(259)** (38 mg, 0.14 mmol) in dry methanol (4 ml) was hydrogenolysed using the procedure described previously for the conversion of **(194)** into **(197)**. Reduction of both carbamate and epoxide occured to afford **(263)** (15 mg, 76%) as a thick yellow oil.

δ_H (300 MHz, $CDCl_3$): 1.37 (ddd, J = 13.4, 7.7, 4.2 Hz, 1H), 1.68 (m, 7H), 1.98 (m, 1H), 2.43 (dt, J = 13.4, 10.0, J ≈ 10.0 Hz, 1H), 3.46 (m, 1H, α-N), 3.57 (s, 1H, HN), 3.62 (m, 1H, α-N), 4.40 (dt, J = 10.0, 7.7, J ≈ 7.7 Hz, 1H, α-N).

δ_C (75 MHz, $CDCl_3$): 24.4, 24.5, 27.5, 35.0 & 38.1 (5 x CH_2), 55.2 (CHN), 58.6 (CHN), 73.4 (CHOH).

υ_{max} (CH_2Cl_2): 3610w, 3320brm, 3040w, 2920s, 2860m, 1445brw, 1335brw, 1255w, 1130w, 1070w cm^{-1}.

$^m/_z$ (%): 141 (M^+,32), 138 (17), 124 (39), 112 (18), 111 (20), 98 (37), 97 (100), 96 (34), 91 (33), 82 (55), 69 (43), 68 (47).

$C_8H_{15}NO$ [M^+] requires $^m/_z$ 141.1154; observed 141.1154.

N-Methyl-7α,8α-epoxy-9-azabicyclo[4.2.1]nonane **(264)**

To a slurry of LAH (65 mg, 1.71 mmol) was injected a solution of **(259)** (140 mg,

0.51 mmol) in diethyl ether (7 ml) which was then stirred at -78°C for 3 hr. The reaction was then worked up as described previously for the *exo*-isomer **(260)**; the amine was volatile and the solution was acidified with hydrogen chloride gas prior to distillation of solvent under reduced pressure. Trituration with diethyl ether afforded **(264.HCl)** (52 mg, 54%) as a hygroscopic white solid. The free amine **(264)** was used to record NMR spectra which displayed a 10% impurity of the ring opened product **(262)**.

δ_H (300 MHz, $CDCl_3$): 1.45 - 2.01 (brm, 8H), 2.41 (s, 3H, CH_3), 2.95 (brd, J = 4.1 Hz, 2H, α-N), 3.97 (d, J = 3.2 Hz, 2H, HCO).

δ_C (75 MHz, $CDCl_3$): 25.7 (2 x CH_2), 29.8 (2 x CH_2), 46.7 (CH_3), 65.3 (2 x CHN), 65.8 (2 x HCO).

υ_{max} ($CDCl_3$): 3600w, 3020w, 2920s, 2860w, 1440brw, 1380w, 1125w, 1110w, 1070w, 1000w, 905w cm^{-1}.

$^m/_z$ (%)[measured using **(263.HCl)**]: 153 (M^+ - HCl, 45), 138 (16), 124 (31), 110 (100), 96 (69), 91 (55), 82 (42), 68 (29).

$C_9H_{15}NO$ [M^+ - HCl] requires $^m/_z$ 153.1154; observed 151.1154.

1β-Hydroxy-2β,3β-epoxy-4β-[(benzyloxycarbonyl)amino]cycloheptane **(266)** and 1β-Hydroxy-2α,3α-epoxy-4β-[(benzyloxycarbonyl)amino]cycloheptane **(267)**

A solution of **(227)** (2.340 g, 8.97 mmol) in dichloromethane (160 ml) was epoxidised with MCPBA (50 - 60% purity, 3.38 g, 10.7 mmol) using the procedure described for the homologous allylic alcohol **(255)**. The crude solid obtained after distillation of solvent was purified by flash chromatography, eluting with diethyl ether, to afford firstly **(267)** (741 mg, 30%) as a white solid which had 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 **(266)** (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%.

From ^1H NMR signal integration of a crude sample, The ratio of **(266)**:**(267)** was determined to be 62:38 in close agreement with the isolated yields.

Magnesium monoperperphthalate (MMPP) epoxidation of (227)

Using the procedure of Gillard[122] a solution of (227) (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 distilled 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 distilled under reduced pressure. The crude oil was flash chromatographed to remove polar impurities, eluting with diethyl ether, affording (266) and (267) (34 mg, 72 %) in a 42:58 ratio (calculated from crude ^{1}H NMR integrations).

Vanadium-catalysed epoxidation of (227)

The procedure of Teranishi[117] was followed: a catalytic quantity of vanadium(III) acetylacetonate was added to a solution of (227) (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 distilled under reduced pressure and the residue was chromatographed with diethyl ether to remove polar impurities to give epoxides (28 mg, 40%) in a ratio of >95:<5 (266):(267), as calculated from ^{1}H NMR integrations.

2β,3β-Epoxy-4β-[(benzyloxycarbonyl)amino]cycloheptanone (269)

A solution of (229) (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 distilled 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 distilled under reduced pressure. The resulting crude solid was recrystallised from ethanol to afford (269) (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 **(269)** could also be prepared in 87% yield by Jones oxidation[68] of the epoxy-alcohol **(266)** using an identical procedure to that described previously for the conversion of **(132)** into **(133)**

1β-[(*p*-Toluenesulphonyl)oxy]-2β,3β-epoxy-4β-[(benzyloxycarbonyl)amino]cyclo-heptane **(270)**

A solution of **(266)** (300 mg, 1.08 mmol) in THF (12 ml) was tosylated by sequential addition of *n*-butyllithium (2.5M in hexane, 0.52 ml, 1.30 mmol) and *p*-toluenesulphonyl chloride (269 mg, 1.41 mmol) in THF (4 ml), using the procedure described for tosylating the homologous epoxy-alcohol **(244)**. The tosylate **(270)** (460 mg, 99%) was obtained as a white solid after flash chromatography eluting with 3:2 diethyl ether:petroleum ether (b.p. 40 - 60°C). An analytical sample having m.p. 106 - 107°C was prepared by recrystallisation from toluene and petroleum ether (b.p. 60 - 80°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 **(271)**

A solution of **(270)** (670 mg, 1.55 mmol) in DMSO (12 ml) was chlorinated at 55°C with lithium chloride (410 mg, 9.76 mmol) using the procedure described for the preparation **(246)**. The product **(271)** (407 mg, 85%) was obtained as a white solid after flash chromatography using 3:7 diethyl ether:petroleum ether (b.p. 40 - 60°C) and had m.p. 92 - 93 °C after recrystallising 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 (**272**)

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 (**271**) (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), brine (5 ml), separated and dried over anhydrous magnesium sulphate. After filtration and distillation 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 (**272**) (256 mg, 87%) as an oil. On refrigeration the oil solidified 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 (**273**)

A solution of (**267**) (739 mg, 2.67 mmol) in THF (18 ml) was tosylated by sequential addition of *n*-butyllithium (2.5M in hexane, 1.17 ml, 2.94 mmol) and *p*-toluene-sulphonyl chloride (662 mg, 3.47 mmol) in THF (6 ml), using the procedure described for tosylating the homologous epoxy-alcohol (**244**). The tosylate (**273**) (1.053 g, 92%) was obtained as a foam after flash chromatography eluting 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 (**274**)

A solution of (**273**) (930 mg, 2.16 mmol) in DMSO was chlorinated with lithium chloride (552 mg, 13.1 mmol) at 55°C using the procedure described for the conversion of (**245**) into (**246**). The product (**274**) (604 mg, 95%) was obtained as a white solid after flash chromatography, eluting 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 **(276)**

A solution of **(267)** (114 mg, 0.41 mmol) was oxidised with Jones reagent[68] using the procedure described for the conversion of **(132)** into **(133)**. The ketone **(276)** (108 mg, 95%) was obtained as a colourless oil and 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 (**277**)

A solution of (**276**) (234 mg, 0.85 mmol) in THF (14 ml) was gently refluxed with sodium borohydride (79 mg, 2.14 mmol) for 1 hr before destroying 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 epimers (223 mg, 95%) as an oil. The ^{1}H NMR spectrum was free of impurities and the ratio of (**267**):(**277**) was calculated to be 62:38 respectively from signal integrations. The epimers were separated by flash chromatography, eluting with 4:1 diethyl ether:petroleum ether (b.p. 40 - 60°C), to afford firstly the *cis*-1,4 alcohol (**267**) which had identical NMR spectra to a sample prepared by epoxidation of (**227**). Further elution afforded the *trans*-1,4 alcohol (**277**) 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 (**276**)

A solution of (276) (640 mg, 2.33 mmol) in 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 (**267**) (262 mg, 41%). Further elution afforded the *trans*-1,4 alcohol (**277**) (313 mg, 48%).

1α-[(*p*-Toluenesulphonyl)oxy]-2α,3α-epoxy-4β-[(benzyloxycarbonyl)amino]-cycloheptane (**278**)

A solution of (**277**) (220 mg, 0.79 mmol) in 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 (244). The tosylate (**278**) (303 mg, 89%) was obtained as a white solid after flash chromatography eluting 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) which had 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 (**275**)

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 (**278**) (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 washed with water (2 x 3 ml) and brine (3 ml) and then dried over anhydrous magnesium sulphate. Distillation of solvent under reduced pressure gave an oil which was purified by flash chromatography, eluting with 1:4 diethyl ether:petroleum ether (b.p. 40 - 60°C), to furnish (**275**) (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 (**279**)

Triethylamine (293 µl, 2.11 mmol) and (**255**) (409 mg, 1.40 mmol) in 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 distilled under reduced pressure to afford (**279**) (505 mg, 97%) as a foam which was determined to be pure from 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) to give 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%.

N-Methyl-6β,7β-epoxy-8-azabicyclo[3.2.1]octane (**280**)

A solution of (**272**) (70 mg, 0.27 mmol) in 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. A further portion of DIBAH (0.40 ml, 0.40

mmol) was added and 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 distilled 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) to afford **(280.HCl)** (27 mg, 57%) as a hygroscopic white solid. All spectra below were recorded on the free amine by dissolving **(280.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 **(281.HCl)**

A solution of **(272)** (66 mg, 0.25 mmol) in absolute ethanol (8 ml) was hydrogenolysed for 3 hr at 1 atmosphere using the procedure described for the conversion of **(194)** into **(197)**. The solution was acidified with hydrogen chloride gas prior to distillation of solvent to afford **(281.HCl)** (39 mg, 95%) as a hygroscopic white solid. All spectral data quoted below was 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-6β-ol (**282**)

A solution of (**272**) (79 mg, 0.31 mmol) in 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 salts that precipitated were filtered off through celite. The colourless solution was acidified with gaseous hydrogen chloride gas and the solvent was distilled under reduced pressure. The residual oil was triturated with 1:1 diethyl ether:petroleum ether (b.p. 40 - 60°C) to afford (**282.HCl**) (38 mg, 70%) as a gum. Dissolving the salt in the minimum quantity of $CDCl_3$, basifying with ammonia gas and filtering gave a sample of the free amine (**282**) for NMR and IR spectroscopy.

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.

Tropan-6α-ol (**283**)

A solution of (**275**) (48 mg, 0.18 mmol) in diethyl ether (5 ml) was refluxed with LAH (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 distillation 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 (**283**) (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.

Cyclohepta-3,5-dienol (**302**)

Using a modified version of the procedure of Schiess and Wisson,[132] peroxyacetic acid (32 weight %, 117.0 g, 0.49 mol) was dripped into a stirred solution of cycloheptatriene (**300**) (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 with thorough washing of the filter cake 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 distilled at atmospheric pressure. The crude epoxide (**301**) was then dissolved in diethyl ether (100 ml) and dripped into a slurry of LAH (5.70g, 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 distillation of solvent under reduced pressure gave a crude yellow oil. Vacuum distillation of the oil at 20 mbar, 110°C removed volatile impurities. Further distillation at 5 mbar,

110°C furnished **(302)** (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-aza-7oxabicyclo-[3.2.2]non-8-ene **(303)** and N-(benzyloxycarbonyl)-3β-hydroxy-6-aza-7oxabicyclo-[3.2.2]non-8-ene **(304)**

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 **(302)** (3.42 g, 0.031 mol) and tetramethylammonium periodate (8.24 g, 0.031 mol) in dichloromethane (45 ml). An identical reaction and work-up procedure to that described for the preparation of the unsubstituted cycloadduct **(221)** was used. An inseparable mixture of stereoisomers **(303)**:**(304)** (6.21 g, 73%) was obtained in a 35:65 ratio (calculated from ^1H 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 **(303)**, described later. Signals common to both isomers are quoted in italics.

δ_H (300 MHz, $CDCl_3$), 3α-Hydroxy isomer **(303)**: 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 **(304)**: 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 **(303)** and **(304)**: 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 **(303)** and **(304)**: 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-aza-7oxabicyclo[3.2.2]non-8-en-3-one **(305)**

A solution of **(303)** and **(304)** (6.26 g, 0.023 mol) in acetone (110 ml) was oxidised with Jones reagent[68] using the procedure described for the conversion of **(132)** into **(133)**. The ketone **(305)** (5.68 g, 90%) was isolated as a pale yellow solid and was pure enough for the subsequent reaction without purification. 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-aza-7oxabicyclo[3.2.2]non-8-ene (**303**)

A solution of (**305**) (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 distilled under reduced pressure. The residual oil was purified by flash chromatography, eluting with diethyl ether, to give (**303**):(**304**) (4.78 g, 85%) in a ratio of 85:15 as determined from ^{1}H NMR integrations. The two isomers were inseperable at this stage of the synthesis.

N-Benzyloxycarbonyl-3α-[(*t*-butyldimethylsilyl)oxy]-6-aza-7oxabicyclo[3.2.2]-non-8-ene (**306**)

The 85:15 mixture of (**303**):(**304**) (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 stirred for 1.5 hr. Water (50 ml) was added, the mixture 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 distilled 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 (**306**) (5.44 g, 91%) as a thin yellow oil. Partial separation of (**306**) from the 3β-silylether (**308**) was possible by chromatography to give an improved ratio of 90:10 (from ^{1}H NMR integrations) but minor traces of (**308**) were still visible in the NMR spectra; this data is quoted in full later.

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 (**307**)

A solution of (**302**) (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 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 distillation 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 (**307**) (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-aza-7oxabicyclo[3.2.2]-non-8-ene (**308**)

Tetramethylammonium periodate (4.04 g, 0.015 mol) and (**307**) (2.85 g, 0.013 mol) in dichloromethane (65 ml) were stirred at -78°C. A solution of benzyl-N-hydroxy-carbamate (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 was worked up using an identical procedure to that described for the preparation of the unsubstituted cycloadduct (**221**). Purification of the crude oil by flash chromatography, eluting with 1:4 diethyl ether:petroleum ether (b.p. 40 - 60°C), afforded (**308**):(**306**) (4.18 g, 85%) in an 80:20 ratio as a colourless oil. The two isomers were inseperable 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 (**306**) were observed in the NMR spectra of (**308**).

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 (**309**)

A 9:1 mixture of (**306**):(**308**) (5.24 g, 0.013 mol) was reduced with freshly prepared[67] and powdered sodium amalgam (70 g) and sodium phosphate (11.20 g, 0.079 mol) using the procedure described previously for the conversion of (**222**) into (**223**). The residual oily solid obtained was purified by flash chromatography, using 1:1 diethyl ether:petroleum ether (b.p. 40 - 60°C), to afford (**309**) (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 (**318**) 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 (**310**) and
1β-hydroxy-2β,3β-epoxy-4β-[(benzyloxycarbonyl)amino]-6α-[(*t*-butyldimethylsilyl)oxy]cycloheptane (**311**)

A solution of (**309**) (2.674 g, 6.84 mmol) was epoxidised with 1.2 equivalents of MCPBA (50 - 60% purity) using the procedure described for the conversion of (**150**) into (**255**). 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 2β,3β-epoxide (**311**) (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 **(310)** (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 **(310)** and **(311)** were contaminated with minor quantities of the 6β-isomers **(319)** and **(320)**. As the ^1H NMR spectra were broad, a ratio of 3:7 was determined for **(310)**:**(311)** from the isolated yields.

1β-[*p*-Toluenesulphonyl)oxy]-2β,3β-epoxy-4β-[(benzyloxycarbonyl)amino]-6α-[(*t*-butyldimethylsilyl)oxy]cycloheptane **(312)**

A solution of **(311)** (1.280 g, 3.14 mmol) in THF (35 ml) was tosylated by the sequential addition of *n*-butyllithium (2.5M in hexane, 1.51 ml, 3.78 mmol) and *p*-toluenesulphonyl chloride (781 mg, 4.09 mmol) in THF (5 ml) using the procedure described for the tosylation of **(244)**. The tosylate **(312)** (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 **(312)** was uncontaminated 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').

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 **C**Me), 136.1 (aryl **C**CH_2), 144.8 (aryl **C**SO_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 (**313**)

A solution of (**312**) (1.402 g, 2.50 mmol) in DMSO (27 ml) was stirred at 60°C with lithium chloride (690 mg, 16.42 mmol) using the procedure described for the conversion of (**245**) into (**246**). The chloride (**313**) (681 mg, 64%) was isolated as an oil after flash chromatography, eluting with 1:9 diethyl ether:petroleum ether (b.p. 40 - 60°C).

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 [$(CH_3)_3CSi$], 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 (**314**)

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 (**313**) (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 distilled 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 **(314)** (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 **(315)**

A solution of **(314)** (88 mg, 0.23 mmol) in diethyl ether (6 ml) and LAH (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 distillation of solvent under reduced pressure gave a residual 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 (**315**) (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 (**6**)

TBAF (1M in THF, 0.64 ml, 0.64 mmol) was injected into a solution of (**315**) (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 distilled 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 distilled 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 (**9**) (27 mg, 81%) as a white solid which had m.p. 64 - 66°C (literature[84b] m.p. 72°C).

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 (**316**)

A solution of **(314)** (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 **(6)** from **(315)**. The alcohol **(316)** (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 (**317**)

A solution of (**316**) (37mg, 0.31 mmol) in absolute ethanol (4 ml) was hydrogenolysed at 1 atmosphere using the procedure described for reducing (**194**). Norscopine (**317**) (19 mg, 100%) was isolated 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 (**318**)

An 80:20 mixture of (**308**):(**306**) (4.05 g, 0.010 mol) was treated with freshly prepared[67] and powdered sodium amalgam (65 g) and sodium phosphate (11.30 g , 0.080 mol) using the procedure described previously for the reduction of (**222**) into (**223**). The solid isolated was recrystallised from toluene and petroleum ether (b.p. 60 - 80°C) to afford (**318**) (3.57 g, 75%) as a crystalline white solid (m.p. 50 - 51°C). Despite repetitive recrystallisation the product remained contaminated with the 6α-isomer (**309**).

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 (**319**) and
1β-Hydroxy-2β,3β-epoxy-4β-[(benzyloxycarbonyl)amino]-6β-[(*t*-butyldimethylsilyl)-oxy]cycloheptane (**320**)

A solution of (**318**) (2.129 g, 5.41 mmol) was epoxidised with 1.2 equivalents of MCPBA (50 - 60% purity) using the procedure described for the epoxidation of (**150**) into (**255**). 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 (**319**) (980 mg, 44%). NMR analysis indicated that (**319**) was contaminated with (**311**). An analytical sample was prepared by recrystallisation from toluene and petroleum ether (b.p. 60 - 80°) and had m.p. 126 - 129°C, although the 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 **(320)** (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). An estimated ratio of 1:1 was made from the isolated yields of the two epoxides.

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%.
$C_{21}H_{33}NO_5Si$ 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 **(321)**

A solution of **(320)** (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 **(244)**. The tosylate **(320)** (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 **C**Me), 136.5 (aryl **C**CH_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 **(322)**

A solution of **(321)** (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 **(245)** into **(246)**. The chloride **(322)** (534 mg, 79%) was isolated as an 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 [$(\mathbf{CH_3})_3CSi$], 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 (**323**)

A solution of **(322)** (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 **(313)** into **(314)**. After flash chromatography, eluting with 1:4 diethyl ether:petroleum ether (b.p. 40 - 60°C), **(323)** (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* [$(\mathbf{CH_3})_3CSi$], 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 (**324**)

This compound was prepared by reducing (**323**) (93 mg, 0.24 mmol) in diethyl ether (5 ml) with LAH (40 mg, 1.05 mmol) using the procedure described for the reduction of (**314**). The amine was purified by flash chromatography, eluting firstly with diethyl ether and then with ethyl acetate:triethylamine (9:1), to afford (**324**) (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 [$(\mathbf{CH_3})_3CSi$], 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 (**297**)

This compound was prepared by treating (**324**) (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 (**315**). 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 **(297)** (29 mg, 83%) as a white solid. M.p. 120 - 122°C (lit.[37] 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 **(325)**

A solution of **(323)** (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 **(6)** from **(315)**. The alcohol **(325)** (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 (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 (**326**)

A solution of (**325**) (31 mg, 0.11 mmol) in absolute ethanol (5 ml) was hydrogenolysed at 1 atmosphere, using the procedure described for reducing (**194**) into (**197**). Norpseudoscopine (**326**) (13 mg, 82%) was isolated as a white solid which had no specific m.p.

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 (**329**)

A small portion of the crude epoxide (**301**), used previously to prepare (**302**), was purified by vacuum distillation (18 mbar, 40°C). Tetramethylammonium periodate (283 mg, 0.89 mmol) was added to a solution of (**301**) (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 distilled 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 **(329)**:**(330)** in an 80:20 ratio (estimated from ^{1}H 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 **(329)** in pure form (m.p 86 - 87°C). The stereo- and regiochemistry of **(329)** was elucidated from a crystal structure (appendix 1).

δ_H (300 MHz, $CDCl_3$), Major cycloadduct **(329)**: 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=0).

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 **(330)**:
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).

References

1. (a) G. Fodor and R. Dharanipragada, *Nat. Prod. Rep.,* 1988, **5**, 67.
(b) G. Fodor and R. Dharanipragada, *ibid.,* 1990, **7**, 539.
(c) G. Fodor and R. Dharanipragada, *ibid.,* 1991, **8**, 603.
(d) G. Fodor and R. Dharanipragada, *ibid.,* 1992, **10**, 199.
(e) G. Fodor and R. Dharanipragada, *ibid.,* 1994 **10**, 443.

2. (a) H.C.S Wood and R. Wrigglesworth, in *Rodds Chemistry of Carbon Compounds*, ed. S. Coffey, Elsevier Scientific Publishing Co., 1977, Vol. 4 part B, p. 201.
(b) H.L. Holmes, in *The Alkaloids*, ed. R.H.F Manske, Academic Press, New York, 1950, Vol. 1, p.271.
(c) G. Fodor, *ibid,* 1960, Vol. 6, p. 145.
(d) G. Fodor, *ibid,* 1967, Vol. 9, p. 269.
(e) G. Fodor, *ibid,* 1971, Vol. 13, p. 351.
(f) R. L. Clarke, *ibid,* 1977, Vol. 16, p. 83.
(g) M. Lounasmaa, *ibid,* 1988, Vol. 33, p. 1.
(h) M. Lounasmaa and T. Tamminen, *ibid,* 1994, Vol. 44, p. 1.

3. L. Geiger and C. Hesse, *Ann.*, 1833, **5**, 43; 1833, **6**, 44; 1833, **7**, 269.

4. F. Wöhler, *Ann.*, 1862, **121**, 372.

5. (a) J. Berberich, *Deut. Med. Wochschr*, 1931, **57**, 1579.
(b) D.E. Adelson, L.G. MacDowell and C.B. Pollard, *J. Am. Chem. Soc.,* 1935, **57**, 1988.

6. R. Willstätter and E. Berner, *Chem. Ber.*, 1923, **56**, 1079.

7. Bao Gong Teng Cooperative Research Group, *Zhongcaoyao*, 1982, **13**, 20.

8. T. Yao, Z. Chen, D. Yi and G. Xu, *Yaoxue Xuebao*, 1981, **16**, 582; *Chem. Abstr.* 1982, **96**, 48972c.

9. P. Wang, T. Yao and Z. Chen, *Huaxue Xuebao*, 1989, **47**, 1002; *Chem. Abstr.* 1990, **113**, 78746u.

10. (a) Z. Xiang, J.E. Zhou, Z. N. Chen, L.P. Wang, H.N Wang, T.R. Yao, J.X. Xie, G.Y. Xu and D.N. Yi, *Yaoxue Xuebao*, 1989, **24**, 105; *Chem. Abstr.* 1990, **112**, 198846c.
(b) M.E. Jung, Z. Longmei, P. Tangsheng, Z. Huiyan, L. Yan and S. Jingyu, *J. Org. Chem.,* 1992, **57**, 3528.

11. T.F. Spande, H.M. Garraffo, M.W. Edwards, H.J.C Yeh, L. Pannell and J.W. Daly, *J. Am. Chem. Soc.,* 1992, **114**, 3475.

12. C.A. Broka, *Tetrahedron Lett.,* 1993, **34**, 3251.

13. R.R. Fraser and R.B. Swingle, *Can. J. Chem.,* 1970, **48**, 2065.

14. S.R. Fletcher, R. Baker, M.S. Chambers, S.C. Hobbs and P.J. Mitchell, *J. Chem. Soc., Chem. Commun.,* 1993, 1216.

15. E.J. Corey, T-P. Loh, S. Achyutharao, D.C. Daley and S. Sarshar, *J. Org. Chem.,* 1993, **58**, 5600.

16. (a) D.F. Huang and T.Y. Chen, *Tetrahedron Lett.*, 1993, **34**, 4477.
(b) S.C. Clayton and A.C. Regan, *Tetrahedron Lett.*, 1993, **34**, 7493.
(c) C. Szántay, Z. Kardos-Balogh, I. Moldvai, C. Szántay Jr., E. Temesvári-Major and G. Blaskó, *Tetrahedron Lett.*, 1994, **35**, 3171.
(d) G. Pandey, T.D. Bagul and G. Lakshmaiah, *Tetrahedron Lett.*, 1994, **35**, 7439.
(e) E. Albertini, A. Barco, S. Benetti, C. De Risi, G.P. Pollini, R. Romagnoli and V. Zanirato, *Tetrahedron Lett.*, 1994, **35**, 9297.
(f) S.Y. Ko, J. Lerpiniere, I.D. Linney, and R. Wrigglesworth, *J. Chem. Soc., Chem. Commun.,* 1994, 1775.

17. R. Robinson., *J. Chem. Soc.,* 1917, **111**, 762.

18. C. Schöpf and G. Lehmann, *Ann.,* 1935, **518**, 1.

19. A. Stoll, B. Becker and E. Jucker, *Helv. Chim. Acta.,* 1952, **35**, 1263.

20 R.C. Menzies and R. Robinson, *J. Chem. Soc.,* 1924, **125**, 2163.

21. C. Schöpf and A. Schmetterling, *Angew. Chem.,* 1952, **64**, 591.

22. A.T. Bottini and J. Gal, *J. Org. Chem.,* 1971, **36**, 1718.

23. Y. Kashman and S. Cherkez, *Synthesis*, 1974, 885.

24. R. Willstätter and A. Pfannenstiel, *Ann.,* 1922, **422**, 1.

25. G. Cignarella, G.G. Gallo and E. Testa, *J. Am. Chem. Soc.,* 1961, **43**, 4999.

26. J.B. Bapat, D.St.C. Black, R.F.C. Brown and C. Ichlov, *Aust. J. Chem.,* 1972, **25**, 2445.

27. (a) J.J. Tufariello and E.J. Trybulski, *J. Chem. Soc., Chem. Commun.,* 1973, 720.
(b) J.J. Tufariello, G.B. Mullen, J.J. Teegler and E.J. Trybulski, *J. Am. Chem. Soc.,* 1979, **101**, 2435.

28. (a) N.J. Turro and S.S. Edelson, *J. Am. Chem. Soc.,* 1968, **90**, 4499.
(b) N.J. Turro, S.S. Edelson, J.R. Williams, T.R. Darling and W.B. Hammond, *J. Am. Chem. Soc.,* 1969, **91**, 2283.

29. G. Fierz, R. Chidgey and H.M.R. Hoffmann, *Angew. Chem.*, 1974, **86**, 444

30. Y. Hayakawa, Y. Baba, S. Makino and R. Noyori, *J. Am. Chem. Soc.,* 1974, **100**, 1786.

31. J. Mann and L.C. de A. Barbosa, *J. Chem. Soc., Perkin Trans. 1*, 1992, 787.

32. (a) H.M.L. Davies, W.B. Young and H.D. Smith, *Tetrahedron Lett.*, 1989, **30**, 4653.
(b) H.M.L. Davies, E. Saikali and W.B. Young, *J. Org. Chem.*, 1991, **56**, 5696.

33. G. Pandey, G. Lakshmaiah and A. Ghatak, *Tetrahedron Lett.*, 1994, **34**, 7301.

34. (a) H. Iada, Y. Watanabe and C. Kibayashi, *Tetrahedron Lett.*, 1984, **25**, 5091.
(b) H. Iada, Y. Watanabe and C. Kibayashi, *J. Org. Chem.*, 1985, **50**, 1818.

35. (a) A. Bathgate and J.R. Malpass, *Tetrahedron Lett.*, 1987, **28**, 5937.
(b) A. Naylor (née Bathgate), N. Howarth and J.R.Malpass, *Tetrahedron*, 1993, **49**, 451.
(c) A. Bathgate, *Syntheses and Reactions of Azabicycles*, Ph.D. Thesis, University of Leicester, England, 1988.

36. J.E. Bäckvall, Z.D. Renko and S.E. Byström, *Tetrahedron Lett.*, 1987, **28**, 4199.

37. H.E. Schink, H. Petterson and J.E. Bäckvall, *J. Org. Chem.*, 1991, **56**, 2769.

38. W.W. Carmichael, D.F. Biggs and P.R. Gorham, *Science*, 1975, **187**, 542.

39. O.M. Skulberg, W.W. Carmicheal, R.A. Anderson, S.Matsunaga, R.E. Moore and R. Skulberg, *Environ. Toxicol. Chem.*, 1992, **11**, 321.

40. C.S. Huber, *Actacrystallogr. Sect. B.*, 1972, **78**, 2577.

41. J.P. Devlin, O.E. Edwards, P.R. Gorman, N.R. Hunter, R.K. Pike and B. Stavric, *Can. J. Chem.*, 1977, **55**, 1367.

42. (a) W.W. Carmicheal, D.F. Biggs and M.A. Peterson, *Toxicon*, 1979, **17**, 229.
(b) C.E. Spivak, B. Witcop and E.X. Albuquerque, *Mol. Pharmacol.*, 1980, **18**, 384.
(c) C.E. Spivak, J. Waters, B. Witkop and E.X. Albuquerque, *Mol. Pharmacol.*, 1983, **23**, 337.

43. H.F. Campbell, O.E. Edwards and R. Kolt, *Can. J. Chem.*, 1977, **55**, 1372.

44. H.A. Bates and H. Rapaport, *J. Am. Chem. Soc.*, 1979, **101**, 1259.

45. J.S. Peterson, G. Fels and H. Rapaport, *J. Am. Chem. Soc.*, 1984, **106**, 4539.

46. J.J Tufariello, H. Meckler, K. Pushpananda and A. Sanarante, *J. Am. Chem. Soc.*, 1984, **106**, 7979.

47. R.L. Danheiser, J.M. Morin Jr. and E.J. Salaski, *J. Am. Chem. Soc.*, 1985, **107**, 8066.

48. (a) K.H. Melching, H. Hiemstra, W.J. Klaver and W.N. Speckamp, *Tetrahedron Lett.*, 1986, **27**, 4799.
(b) J.R. Wiseman and S.Y. Lee, *J. Org. Chem.*, 1986, **51**, 2485.
(c) P.M. Esch, H. Hiemstra, W.J. Klaver and W.N. Speckamp, *Heterocycles*, 1987, **26**, 75.
(d) T. Shono, Y. Matsumura, K. Uchida and K. Tagami, *Chemistry Lett.*, 1987, 919.
(e) P. Vernon and T. Gallagher, *J. Chem. Soc., Chem. Commun.*, 1987, 245.

49. P. Somfai and J. Åhman, *Tetrahedron Lett.*, 1992, **33**, 3791.

50. P. Somfai, H.M.He and D. Tanner, *Tetrahedron Lett.*, 1991, **32**, 283.

51. A.C. Cope, H.R. Nace and L.L. Esters Jr., *J. Am. Chem. Soc.*, 1950, **72**, 1123.

52. (a) A.G. Anastassiou, *J. Am. Chem. Soc.*, 1965, **87**, 5512.
(b) A.G. Anastassiou, *J. Am. Chem. Soc.*, 1968, **90**, 1527.

53. A.G. Anastassiou and R.P. Cellura, *J. Org. Chem.*, 1972, **37**, 3126.

54. J.W. Bastable, J.D. Hobson and W.D Riddell, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2205.

55. (a) G. Haufe and E. Kleinpeter, *Tetrahedron Lett.*, 1982, **23**, 3555.
(b) G. Haufe, U. Rolle, E. Kleinpeter, J. Kivikoski and K. Rissanen, *J. Org. Chem.*, 1993, **58**, 7084.

56. M.A. Loreto, L. Pellacani and P.A. Tardella, *J. Heterocycl. Chem.*, 1979, **16**, 1233.

57. J. Barluenga, J. Pérez-Prieto and G. Asensio, *J. Chem. Soc., Chem. Commun.*, 1982, 1181.

58. (a) C.R. Smith and J.R. Malpass, *Tetrahedron Lett.*, 1992, **33**, 273
(b) C.R. Smith, D.E. Justice and J.R. Malpass, *Tetrahedron*, 1993, **49**, 11037.
(c) C.R. Smith, *Homotropanes - Synthetic Approaches to the 9-Azabicyclo[4.2.1]nonane/ene Ring System*, Ph.D. Thesis, University of Leicester, England, 1992.

59. (a) M.E. Christy, P.S. Anderson, S.F. Britcher, C.D. Colton, B.E. Evans, D.C. Remy and E. Engelhardt, *J. Org. Chem.*, 1979, **44**, 3117.

(b) T.R Lamanec, D.R. Bender, A.M. DeMarco, S. Karady, R.A. Reamer, and L.W. Weinstock, *J. Org. Chem.*, 1988, **53**, 1768.

60. P.D. Leeson, K. James and R. Baker, *J. Chem. Soc., Chem. Commun.*, 1989, 433.

61. (a) K.E.Harding and S.R. Burks, *J. Org. Chem.*, 1981, **46**, 3920.
(b) K.E. Harding and M.W. Jones, *Heterocycles*, 1989, **28**, 663.

62. (a) K.E.Harding and S.R. Burks, *J. Org. Chem.*, 1984, **49**, 40.
(b) S. Danishefsky, E. Taniyama and R.R. Webb II, *Tetrahedron Lett.*, 1983, **24**, 11.

63. J.M Takacs, M.A. Helle and F. Takusagawa, *Tetrahedron Lett.*, 1983, **24**, 11.

64. K.E Harding and T.H. Marman, *J. Org. Chem.*, 1984, **49**, 2838.

65. (a) C.E. Miller, *J. Chem. Educ.*, 1965, **42**, 1965.
(b) W. Adam, O. Cueto, O. De Lucci, K. Peters, E-M. Peters and H.G. Von Schnering, *J. Am. Chem. Soc.*, 1981, **103**, 5822.

66. J. W. Hamersma and E.I Snyder, *J. Org. Chem.*, 1965, **30**, 3985.

67. (a) S.F. Martin, M. Hartmann and J.A. Josey, *Tetrahedron Lett.*, 1992, **33**, 3583.
(b) Fieser and Fieser, *Reagents for Organic Synthesis*, J. Wiley and Sons, 1967, Vol. 1, p.1030.

68. (a) K. Bowden, I.M. Heibron, E.R.H Jones and B.C.L. Weedon, *J. Chem. Soc.*, 1946, 39.
(b) A. Bowers, T.G Halsall, E.R.H. Jones and A.J. Lemin, *J. Chem. Soc.*, 1953, 2548.

69. R. Greenwald, M. Chaykovsky and E.J. Corey, *J. Org. Chem.*, 1963, **28**, 1128.

70. G. Wittig and U. Schöllkopf, *Org. Syn.*, 1960, **40**, 66.

71. (a) G.A. Gray and W.R. Jackson, *J. Am. Chem. Soc.*, 1969, **91**, 6205.
(b) B. Giese and J. Meister, *Chem. Ber.*, 1977, **110**, 2588.
(c) J. Barluenga and M. Yus, *Chem. Rev.*, 1988, **88**, 487.

72. G.M. Whitesides and J. San Filippo, Jr., *J. Am. Chem. Soc.*, 1970, **92**, 6611.

73. R.P. Quirk, *J. Org. Chem.*, 1972, **37**, 3554.

74. (a) F.H. Senbold, *J. Am. Chem. Soc.*, 1953, **75**, 25332.
(b) E.J. Hamilton Jr., and H. Fischer, *Helv. Chim. Acta.*, 1973, **56**, 795.

75. C.L. Hill and G.M. Whitesides, *J. Am. Chem. Soc.*, 1974, **96**, 870.

76. A. Bottini, *Selective Organic Transformations*, ed. B.S. Thyagarajan,

Wiley Interscience, New York, 1970, p. 89.

77. (a) R.H. Shapiro and M.J. Heath, *J. Am. Chem. Soc.*, 1967, **89**, 5734.
(b) R.H. Shapiro, *Org. React. (N.Y.)*, 1975, **23**, 405.
(c) R.H. Shapiro, M.F. Lipton, K.J. Kolonko, R.L. Buswell and L.A. Capuan, *Tetrahedron Lett.*, 1975, 1811.

78. J. Casanova, B. Waegell, G. Kouokoua and V. Toure, *J. Org. Chem.*, 1979, **44**, 3976.

79. J. Barluenga, J. Perez-Prieto, G. Asensio, S. Garcia-Granda and M.A. Salvado, *Tetrahedron*, 1992, **48**, 3813.

80. J. Attenburrow, A.F.B. Cameron, J.H. Chapman, R.M. Evans, B.A. Hems, A.B.A. Jansen and T. Walker, *J. Chem. Soc.*, 1952, 1094.

81. H. Firouzabadi and E. Ghaderi, *Tetrahedron Lett.*, 1978, 839.

82. (a) H.C. Brown and P.J. Geoghegan Jr., *J. Org. Chem.*, 1970, **35**, 1844.
(b) H.C. Brown, P.J. Geoghegan Jr., G.J Lynch and J.T. Kurek, *J. Org. Chem.*, 1972, **37**, 1941.

83. (a) T.G Traylor and A.W. Baker, *Tetrahedron Lett.*, 1959, 14.
(b) T.G Traylor and A.W. Baker, *J. Am. Chem. Soc.*, 1963, **85**, 2746.

84. (a) G. Fodor, J. Tóth, I. Koczor, P. Dobó and I. Vincze, *Chem. Ind. (London)*, 1956, 764.
(b) P. Dobó, G. Fodor, G, Janzsó, I. Koczor, J. Tóth and I. Vincze, *J. Chem. Soc.*, 1959, 3461.

85. P. Kočovsky and I. Stary, *J. Org. Chem.*, 1990, **55**, 3236.

86. H.C. Brown, J.H. Kawakami and S. Ikegami, *J. Am. Chem. Soc.*, 1970, **92**, 6914.

87. N. Howarth, *Synthetic Approaches to Derivatives of Tropane*, Ph.D Thesis, University of Leicester, England, 1991.

88. (a) A.B. Ray, M. Sahai and P.D. Sethi, *Chem. Ind. (London)*, 1976, 454.
(b) A.B. Ray and M. Sahai, *J. Org. Chem.*, 1980, **45**, 3265.

89. A.R. Pinder, *J. Org. Chem.*, 1982, **47**, 3607.

90. (a) A.B. Ray, Y. Oshima, H.Hikino and C. Kabuto, *Heterocycles*, 1982, **19**,1233.
(b) A.T. McPhail and A.R. Pinder, *Tetrahedron*, 1984, **40**, 1661.

91. D. Tepfler, A. Goldmann, N. Pamboukdian, M. Maille, A. Lepingle, D.Chevalier, J. Denarié and C. Rosenbury, *J. of Bact.*, 1988, **170**, 1153.

92. (a) P-H. Ducrot and J.Y Lallemand, *Tetrahedron Lett.*, 1990, **31**, 3879.
(b) P-H. Ducrot and J.Y Lallemand, *ibid*, 1990, **31**, 3883.

93. (a) C.R. Smith and J.R. Malpass, *Tetrahedron Lett.*, 1992, **33**, 277.
(b) C.R. Smith, D.E. Justice and J.R. Malpass, *Tetrahedron*, 1994, 50, 11039.
94. R.S. Lott, V.S. Chauhan and C.H. Stammer, *J. Chem. Soc., Chem. Commun.*, 1979, 495.
95. E.J. Corey and G. Schmidt, *Tetrahedron Lett.*, 1979, 399.
96. (a) E.J. Corey and J.W. Suggs, *Tetrahedron Lett.*, 2647, 1975.
(b) E.J. Corey and D.L. Boger, *ibid.*, 2461, 1978.
97. W.P. Griffith, S.V. Ley, G.P. Whitcombe and A.D. White, *J. Chem. Soc., Chem. Commun.*, 1987, 1625.
98. D.E. Justice and J.R. Malpass, *J. Chem. Soc., Perkin Trans.*, 1994, 2559.
99. D. Belkacemi, J.W. Davies, J.R. Malpass, A. Naylor (née Bathgate) and C.R. Smith, *Tetrahedron*, 1992, **48**, 10161.
100. H. Heckel and R. Adams, *J. Am. Chem. Soc.*, 1925, **47**, 1712.
101. F-D. Boyer, P-H. Ducrot, V. Henryon, J.Soulié and J-Y. Lallemand, *Synlett*, 1992, 357.
102. F-D. Boyer and J-Y. Lallemand, *Synlett*, 1992, 969.
103. (a) O. Duclos, A. Duréault and J.C. Depezay, *Tetrahedron Lett.*, 1992, **33**, 1059.
(b) O. Duclos, M. Mondange, A. Duréault and J.C. Depezay, *ibid*, 8061.
104. R.G. Weiss and E.I. Snyder, *J. Org. Chem.*, 1971, **36**, 403.
105. (a) R.G. Weiss and E.I. Snyder, *Chem. Commun.*, 1968, 1358.
(b) J.D. Slagle, T.T-S. Huang and B. Franzus, *J. Org. Chem.*, 1981, **46**, 3526.
106. H.C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, 1961, **83**, 2544.
107. R.G. Wilt and V.P. Narutis, *J. Org. Chem.*, 1979, **44**, 4899.
108. S. Murai, T. Murai and S. Kato, in *Comprehensive Organic Synthesis*, ed. B.M. Trost, Pergamon Press, 1991, Vol. 8, part 4.4, p. 871.
109. H.C. Brown, S. Ikegami and J.H. Kawakami, *J. Org. Chem.*, 1970, **35**, 3243.
110. Y.D. Vankar, S. Padmashree, A. Trinada Rao and C. Trinada Rao, *Synth. Commun.*, 1983, **13**, 869.
111. A. Ookawa, H. Hiratsuka and K. Soai, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 1813.
112. (a) H.B. Henbest and R.A. Wilson, *Chem. Ind. (London)*, 1956, 659.
(b) H.B. Henbest and R.A. Wilson, *J. Chem. Soc.*, 1957, 1958.

113. P. Chamberlain, M.L. Roberts and G.H. Whitham, *J. Chem. Soc. (B)*, 1970, 1374.
114. K.B. Sharpless and T.R. Verhoeven, *Aldrichimica Acta*, 1979, **12**, 63.
115. A.C. Cope, A.H. Keough, P.E. Peterson, H.E. Simmons and G.W. Wood, *J. Am. Chem. Soc.*, 1957, **79**, 3900.
116. A.C. Cope, T.A. Liss and G.W. Wood, *J. Am. Chem. Soc.*, 1957, **79**, 6287.
117. T. Itoh, K. Jitsukawa, K. Kaneda and S. Teranishi, *J. Am. Chem. Soc.*, 1979, **101**, 159.
118. M. Schröder, *Chem. Rev.*, 1980, **80**, 187.
119. A. San-martin, C. Labbe, O. Monuz, M. Castillo, G. De la Fuente and A. Gonzalez, *Phytochemistry*, 1987, **26**, 819.
120. G. De la Fuente, M. Reina, A. San Martin and J-P. Girault, *Heterocycles*, 1988, 27, 887.
121. H. Heaney, *Aldrichimica Acta*, 1993, **26**, 35.
122. J.R. Gillard, M.J. Newlands, J.N. Bridson, and D.J. Burnell, *Can. J. Chem.*, 1991, **69**, 1337.
123. H.C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, 1972, **94**, 7159.
124. O. Mitsunobu, in *Comprehensive Organic Synthesis*, ed. B.M. Trost, Pergamon Press, 1991, Vol. 6, part 1.1, p. 1.
125. W.H. Kruizinga, B. Strijtveen and R.M. Kellogg, *J. Org. Chem.*, 1981, **46**, 4321.
126. Y. Torisawa, H. Okabe and S. Ikegami, *Chem. Lett.*, 1984, 1555.
127. E.J. Corey, K.C. Nicolaou, M. Shibasaki, Y. Machida and C.S. Shiner, *Tetrahedron Lett.*, 1975, 3183.
128. O. Mitsunobo. *Synthesis*, 1981, 1.
129. (a) M.Barrelle, M. Apparu and C. Gey, *Can. J. Chem.*, 1978, **56**, 85.
(b) P. Schieber and K. Nádor, *Liebigs Ann. Chem.*, 1985, 913.
130. A.P. Marchand and R.W. Allen, *Tetrahedron Lett.*, 1975, 67.
131. D.I. Schuster, J.M. Palmer and S. Carlton Dickermann, *J. Org. Chem.*, 1966, **31**, 4281.
132. P. Schiess and M. Wisson, *Helv. Chim. Acta.*, 1974, **54**, 980.
133. A.H. Beckett, N.J. Harper, A.D.J. Balon and T.H.E. Watts, *Tetrahedron*, 1959, **6**, 319.
134. R. Noyori, Y. Baba and H. Hayakawa, *J. Am. Chem. Soc.*, 1974, **96**, 3336.
135. E.J.Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 1972, **94**, 6190.
136. G. Werner and R. Schickfluß, *Liebigs Ann. Chem.*, **729**, 152, 1969.

137. A. Heusner and K. Ziele, *Chem. Ber.*, 1958, **91**, 2399.
138. G.M. Sheldrick, SHELXTL-pc, Release 4.2, Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, 1991.
139. *Vogels Textbook of Practical Organic Chemistry*, Longman press, London, 5th edn., 1989.
140. D.D. Perrin and W.L.F. Armarego, *Purification of Laboratory Chemicals*, Pergamon Press, Oxford, 3rd edn., 1988
141. W.C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
142. A.A. Qureshi and B. Sklarz, *J. Chem. Soc. (C)*, 1966, 412.
143. E. Boyland and R. Nery, *J. Chem. Soc. (C)*, 1966, 354.
144. J. Thiele. *Ann.*, 1892, **271**, 127.