HOMOTROPANES - SYNTHETIC APPROACHES TO THE 9-AZABICYCLO [4.2.1]NONANE/ENE RING SYSTEM

by

Craig Smith

A Thesis submitted for the Degree of
Dr. of Philosophy in the Faculty
of Science at the University
of Leicester

The Department of Chemistry,
The University,
Leicester, LE1 7RH

MARCH 1992

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

STATEMENT

The accompanying thesis submitted for the degree of Ph.D. entitled "Homotropanes - Synthetic Approaches To The 9-Azabicyclo[4.2.1]nonane/ene Ring System" is based on work conducted by the author in the Department of Chemistry at the University of Leicester mainly during the period between October 1988 and September 1991.

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:.....Craig Smith..... Date:19th March 1992

ACKNOWLEDGEMENTS

Firstly, I would like to thank Dr John Malpass for his guidance and encouragement over the three years. Next, I suppose, would be Mick Lee who was always happy to lend a hand when anything technical was required. Well, nearly always happy. I would also like to thank the many people who have worked in the lab in my time including Djaballah Belkacemi, Raj Misra, Andy Shimmin, Alison Thomas, Josh and Nicola Howarth, Steve Mills, Debbie Sawyer, John Williams, Sue Booth, Mark Buttrum, Dave Weiner, Dave Dawkins, Paul Edwards, Ramesh Menon, Keri Paul, Dave Baker, Mike Coogan, Paul Evans, Sab Jhooti and Dave Justice.

Carl Blackburn and Dr Graham Eaton deserve a mention for their technical assistance during the variable-temperature infra-red spectroscopy, as does Dr Bob Atkinson whose expert advice during John Malpass's vacation helped towards the elucidation of the structure of tetracyclic triazoline (198) before X-ray analysis.

As far as the production of this thesis is concerned, I would like to thank Mrs Ann Crane for the diagrams, but most of all my sister, Helen, for the many hours of typing. And for being so reasonable!

Finally, thanks to the Inorganics Lee, Gristy and Mat and to the Physical lot downstairs especially Podders, Nige, Steve and Carl.

HOMOTROPANES - SYNTHETIC APPROACHES TO THE 9-AZABICYCLO [4.2.1]NONANE/ENE RING SYSTEM, BY CRAIG SMITH

Homotropanes and homotrop-7-enes have been synthesised in reasonable yields by the method of intramolecular cyclisation of *cis*-1,4-aminocyclooctanols. The strategy of nitroso-cycloaddition to 1,3-cyclooctadiene provided the required *cis*-stereochemistry, and the choice of nitroso-compound determined the nitrogen protecting group of the resulting homotropane or homotrop-7-ene.

A modification of the scheme led to the construction of the 1-methylhomotropane skeleton *via* intramolecular cyclisation of nitrogen onto an sp^2 carbon of an exocyclic methylene group. A similar method was utilised to create the unsaturated 1-methylhomotrop-7-ene skeleton.

4-Hydroxycyclooctanone and 4-hydroxycyclooct-2-enone have been shown to exist in equilibrium with their respective bicyclic tautomers, as indicated by ^{1}H and ^{13}C NMR spectroscopy. The incorporation of a double bond into the hydroxy-ketone system results in a greater preference for the bicyclic form. The corresponding 4-aminocyclooctanones and 4-amino-cyclooct-2-enones have been synthesised and these amino-ketones show similar behaviour, but the equilibrium in these cases is much more evenly balanced. The position of equilibrium has also been found to vary with temperature and substitution.

The unsaturated bicyclic amines synthesised in this project were successfully N-demethylated and N-debenzylated using α-chloroethylchloroformate. This N-dealkylation to nor-homotrop-7-ene should allow future work to investigate epoxidation of the double bond by protection of the nitrogen of the free amine as a urethane.

Attempts to measure nitrogen inversion barriers of the N-chloroamines derived from the bicyclic secondary amines using variable temperature ^{1}H and ^{13}C NMR spectroscopy were unsuccessful. However, ^{15}N NMR spectra of various homotropanes synthesised were obtained, and these exhibit ^{15}N chemical shifts typical of normal secondary and tertiary amines. The nitrogen atoms in these homotropanes do not experience the deshielding associated with 7-azabicyclo[2.2.1]heptyl systems in which the "bicyclic effect" is thought to operate.

CONTENTS

ABBREVIATIONS

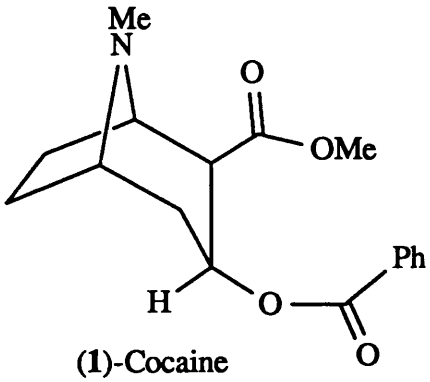
atm	atmosphere
b.p.	boiling point
^{o}C	centigrade
cm^{-1}	wavenumber
D.E.P.T	distortionless enhancement by polarisation transfer
DMF	dimethylformamide
DMSO	dimethylsulphoxide
h	hour
Hz	hertz
IR	infra-red
$kJmol^{-1}$	kilojoules per mole
lit.	literature
M^{+}	molecular ion
MHz	megahertz
min	minute
m.p.	melting point
mm Hg	millimetres of mercury
mmol	millimole
MCPBA	*m*-chloroperbenzoic acid
MEM	β-methoxyethoxymethoxy
NMR	nuclear magnetic resonance
ppm	parts per million
THF	tetrahydrofuran
TMP	2,2',6,6'-tetramethylpiperidine

Chapter One

INTRODUCTION

1.1 NATURALLY OCCURRING NITROGEN-BRIDGED RING SYSTEMS

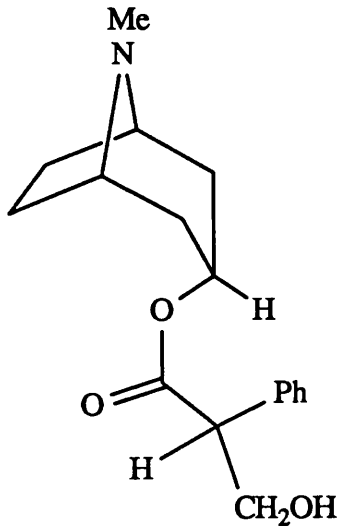
Bicyclic ring systems containing a nitrogen bridge are frequently encountered in nature. They are exemplified by compounds such as cocaine (1), atropine (2), and scopolamine (3).



(1)-Cocaine

Figure 1.1

Cocaine is a diester of tropan-3β-ol-2β-carboxylic acid (Figure 1.1). It was first isolated in 1862 from the leaves of *Erythroxylon coca* Lam.[1] which grows wild in Peru. The leaves have long been recognised as containing a central nervous system stimulant, and the isolation of cocaine led to its use as a local anaesthetic; it possesses vasoconstrictor properties that retain the drug at the site of action. However, in addition to stimulating the central nervous system, cocaine has high psychic dependence liabilities. Owing to its toxicity and addictive nature, its medicinal use today is limited to producing surface anaesthesia of the eye, nose and throat.

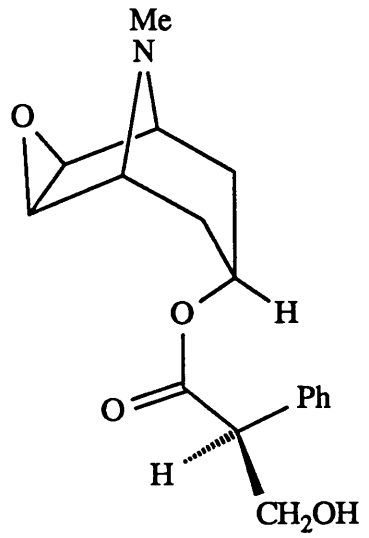


(2)(±)-Hyoscyamine (Atropine)

Figure 1.2

Atropine is the racemic form of hyoscyamine which is a tropic acid ester of tropan-3α-ol (Figure 1.2). Heating (-)-hyoscyamine under vacuum or boiling it in chloroform is sufficient to cause racemisation. (-)-Hyoscyamine, which has been known since 1833,[2] is the most ubiquitous alkaloid in plants of the Solanaceae family. Members of this family, which includes henbane (*Hyoscyamus niger* L.), deadly nightshade (*Atropa belladonna* L.), and the thorn apple (*Datura stramonium* L.), have a history of inducing hallucinations, severe illness, or even death. The alternative name for deadly nightshade, belladonna (beautiful lady), arose through the use of the plant's juice by women in ancient times as a cosmetic to dilate the pupil of the eye. However, the prolonged action of atropine makes it impractical for use in opthalmology. It is used for the relief of intestinal spasm and is an antidote for poisoning by organophosphate compounds. Atropine is an example of an

antimuscarinic agent, an antispasmodic that blocks the effects of acetylcholine.



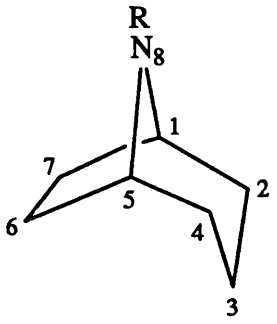
(3)(-)-Hyoscine (Scopolamine)

Figure 1.3

Scopolamine is the tropic acid ester of 6,7β-epoxytropan-3α-ol (Figure 1.3). It was initially obtained in 1881 from *Hyoscamus muticus* L.,[3] and later (1892) from *Scopolia atropoides* Bercht and Presl.[4] In addition to its antimuscarinic effects, scopolamine possesses sedative properties and is found in numerous sleep aids. It is also used in obstetrical and gynaecological procedures to produce "twilight sleep" in which there is a loss of memory concerning the events during labour.

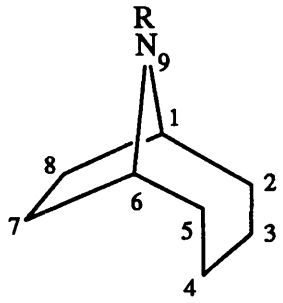
These compounds are 8-azabicyclo[3.2.1]octane derivatives and belong to a class of natural products known as the tropane alkaloids (Figure 1.4). Their pharmaceutical significance and unusual ring system has made this class of alkaloids the subject of intensive stereochemical and

8-Azabicyclo[3.2.1]octane



(4) R=Me (Tropane)
(5) R=H (Nortropane)

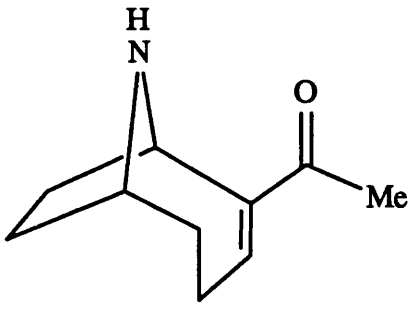
9-Azabicyclo[4.2.1]nonane



(6) R=Me (Homotropane)

Figure 1.4

synthetic work.[5] In contrast, only one naturally occurring 9-azabicyclo[4.2.1]nonane derivative has been identified to date. Toxic strains of the filamentous blue-green alga, *Anabaena flos-aquae*, have been responsible for numerous incidents of livestock and waterfowl poisoning in the midwestern United States and Canada. They produce a toxin that killed mice in 2 to 5 minutes, preceded by gasps and tremors. It was called, therefore, Very Fast Death Factor (VFDF) and subsequently renamed anatoxin *a* (Figure 1.5).[6]



(7) Anatoxin *a*

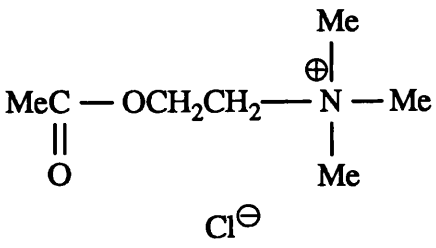
Figure 1.5

Its structure, determined by X-ray crystallography[7] and spectroscopy,[8] was identified as 2-acetyl-9-azabicyclo[4.2.1]non-2-ene, a homotropane derivative.

Anatoxin *a* has been identified as a powerful depolarising neuromuscular blocking agent possessing both muscarinic and nicotinic activity.[9] It is one of the most potent agonists at the nicotinic acetylcholine receptor discovered to date, and has proved to be a valuable research tool in elucidating the mechanism of intramuscular neurotransmission.[10]

1.2 MODE OF ACTION OF ANATOXIN *A* ON THE CHOLINERGIC NERVOUS SYSTEM

The cholinergic nervous system uses acetylcholine (8) as its neurotransmitter.[11]



(8)

Figure 1.6

Acetylcholine has been described as having muscarinic and nicotinic activity.[12] It combines with muscarinic and nicotinic receptors to produce depolarisation which is propagated along nerve cells. It is then hydrolysed by acetylcholinesterase and polarisation is restored

(Figure 1.7).

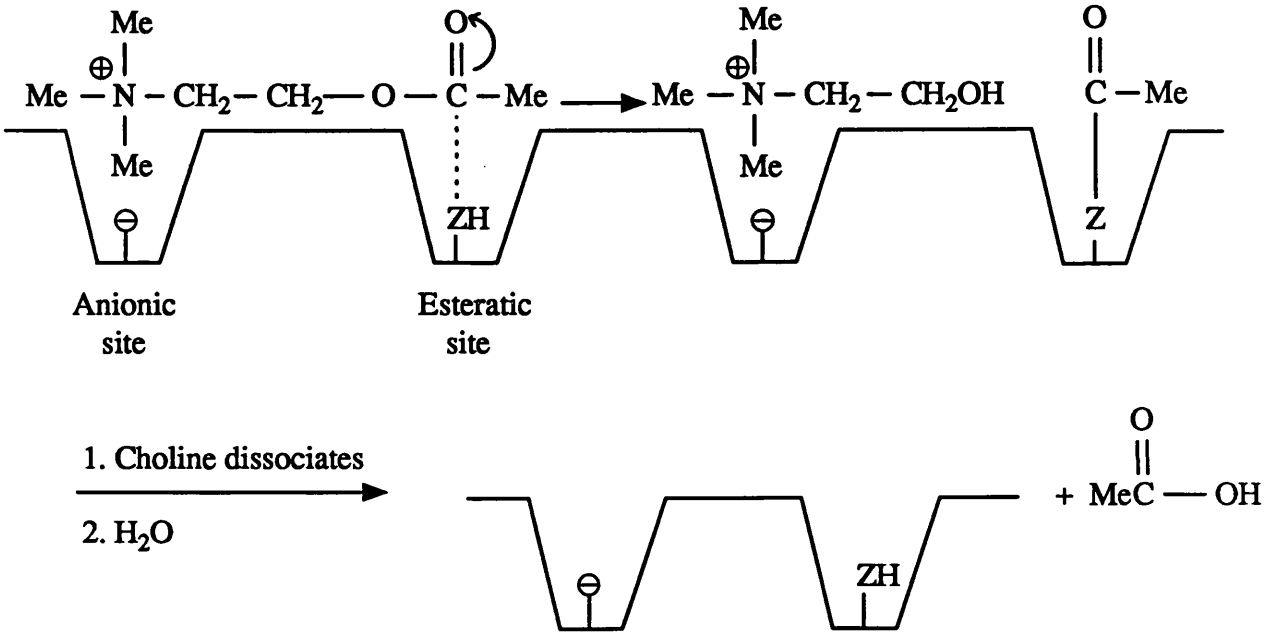
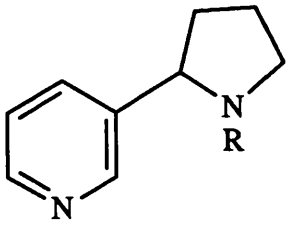
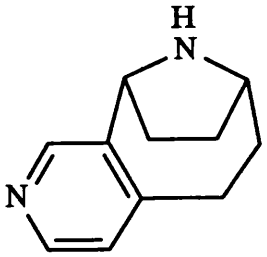


Figure 1.7 Cleavage of acetylcholine by acetylcholinesterase.
Z= Imidazole nitrogen of histidine present in the enzyme.

The primary point of attachment to muscarinic receptors is through a cationic head (a positively charged nitrogen). In the case of anatoxin *a*, where a secondary amine is present, it is implied that a cationic head is formed through protonation at the physiological pH. Another point of attachment is an electron-deficient site which accommodates the oxygen of the carbonyl of acetylcholine and anatoxin *a*. Atropine and scopolamine are antimuscarinics; they successfully compete for the anionic site of the muscarinic receptor and prevent acetylcholine from binding.

Anatoxin *a* is known to possess high activity at the nicotinic acetylcholine receptor.[13] Nornicotine (9), a potent agonist in its own right, has an activity significantly less than that of anatoxin *a*.[13] Kanne[14]



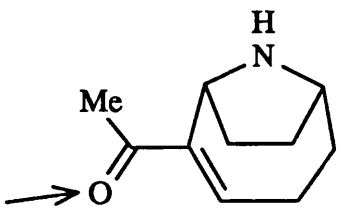


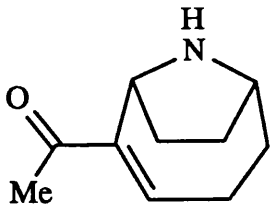
(9) R=H (nornicotine)
(10) R=CH_3 (nicotine)

(11)

Figure 1.8

recognised that one of the conformers of nornicotine would position the pyrrolidine nitrogen and a hydrogen-bond acceptor in the same spatial orientation as that found in the s-cis conformation (7a) of anatoxin *a*. The H-bond





(7a) (s-cis)

(7b) (s-trans)

Figure 1.9

acceptor of (11) (pyridine nitrogen lone pair) corresponds specifically to the distal lone pair on the carbonyl of s-cis-anatoxin *a* (see arrow). Insertion of a two-carbon bridge in nornicotine between the C_5, of the pyrrolidine and C_4 of the pyridine would "freeze" the structure in the desired conformation to yield the novel pyrido [3,4-

b]homotropane (11). The target compound (11) was formed, albeit in only 4% overall yield, and tested both *in vivo* and *in vitro* in order to determine its activity relative to nornicotine. It was found that the new derivative possessed 3 times the toxicological activity and 16 times the receptor binding of nornicotine. Pyridohomotropane was thus the first nicotinoid to combine high activity with conformational rigidity and helped to provide further understanding of the chemical and spatial requirements of the nicotinic acetylcholine receptor.

1.3 ESTABLISHED ROUTES TO ANATOXIN *A*

Most syntheses of the 9-azabicyclo[4.2.1]nonane ring system have been concerned with anatoxin *a*. The first reported synthesis was by Campbell[15] who made optically active anatoxin *a via* ring expansion from cocaine (Figure 1.10). Cocaine (1) was converted into the α,β-unsaturated acid (12), the lithium salt of which was reacted with methyllithium to produce the methyl ketone (13) in 76% yield. When this ketone was treated with sodium dimethyloxosulphonium methylide in DMSO, it gave a 65% yield of the endo cyclopropane derivative (14). Reductive fission of the cyclopropane ring of (14) using lithium in liquid ammonia followed by treatment with acetic anhydride gave a mixture of the two enol acetates (15) and (16). Addition of bromine to the enol acetates, followed by aqueous work-up gave the bromoketone (17). Elimination of hydrogen bromide from (17) using lithium bromide and lithium carbonate in DMF

gave N-methyl-anatoxin *a* (18). The N-methyl derivative of anatoxin *a* (18) was treated with diethyl azodicarboxylate to obtain the hydrochloride of anatoxin *a* in 30% yield.

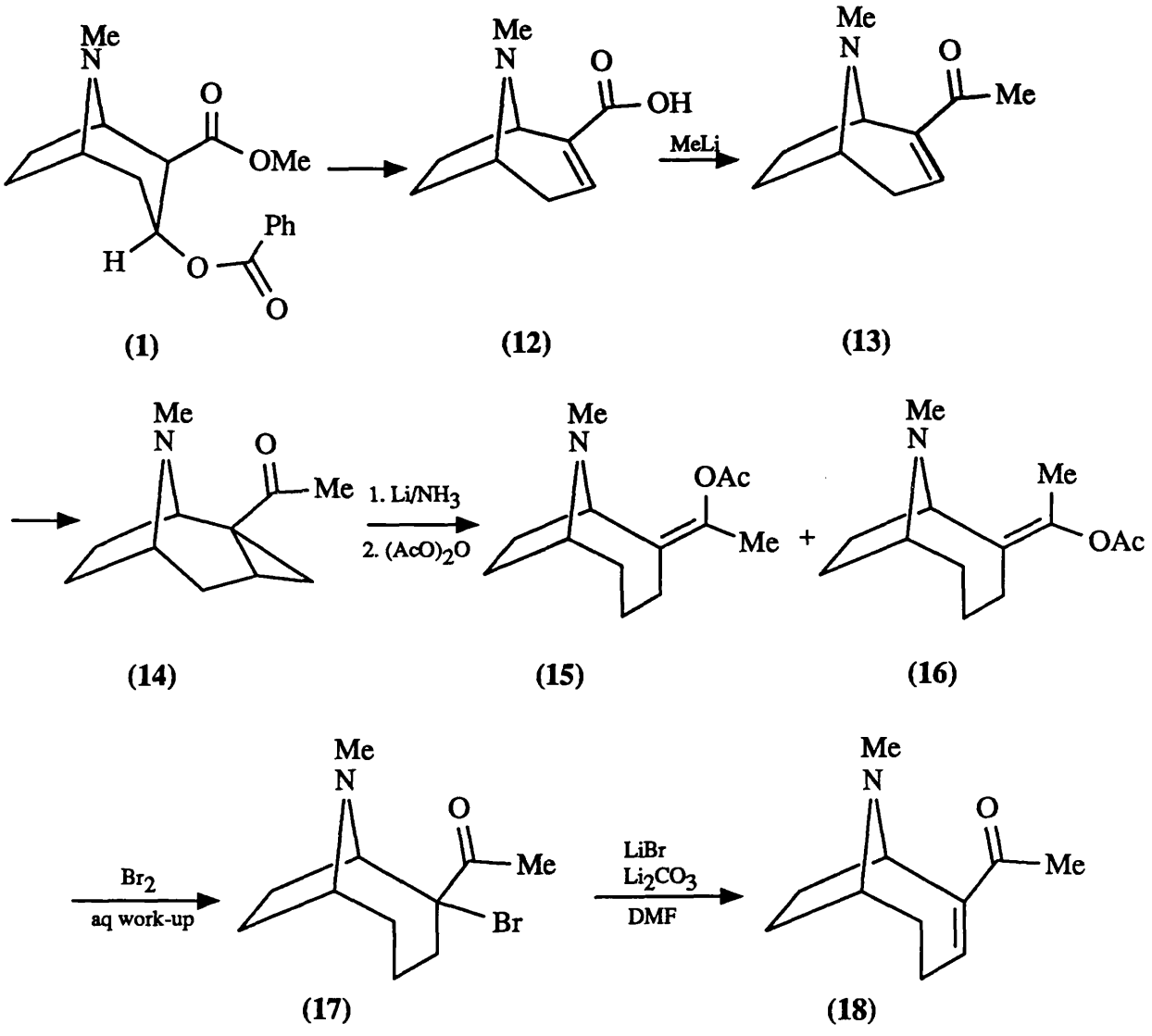


Figure 1.10

Rapoport[16] synthesised anatoxin *a* by exploiting intramolecular cyclisation between an iminium salt and a nucleophilic carbon to construct the 9-azabicyclo [4.2.1]nonane ring system (Figure 1.11). Friedel-Crafts acylation of 1-methylpyrrole (19) with the acid chloride of

hydrogen methyl glutarate (20) afforded ketone (21) in 51% yield. Wolff-Kishner reduction of ketone (21) gave 5-(1-methyl-2-pyrrolyl) pentanoic acid (22) in quantitative yield. After several steps, which included acylation of the pyrrole ring with trichloroacetyl chloride and catalytic reduction of the pyrrole to a pyrrolidine using rhodium/ alumina in acidic methanol, the keto amino acid (23) was formed which was decarbonylated with $POCl_3$ to afford iminium salt (24). A 47% yield of the bicyclic ketone (25) was attained by refluxing (24) in acidic methanol. The successful synthesis of bicyclic ketone (25) completed the synthesis of anatoxin *a*, since (25), prepared by Campbell,[15] had been converted in to anatoxin *a*. Intramolecular

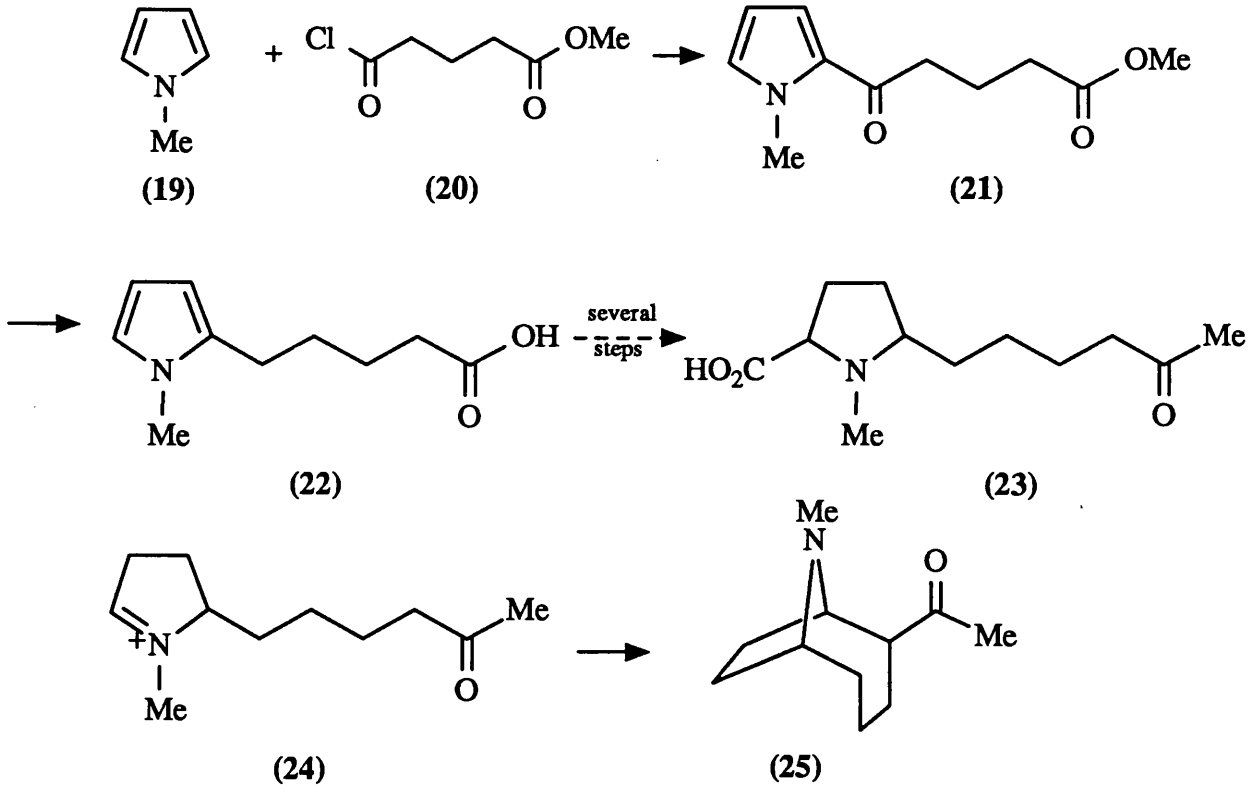


Figure 1.11

cyclisation of an iminium salt had thus been successfully utilised as the key step in the synthesis of anatoxin *a*.

Later, Rapoport[17] synthesised (+)- and (-)-anatoxin *a* of high optical purity directly from D- and L-glutamic acid, respectively (Figure 1.12). Pyroglutamic acid (27) made from D-glutamic acid (26) was converted, after several

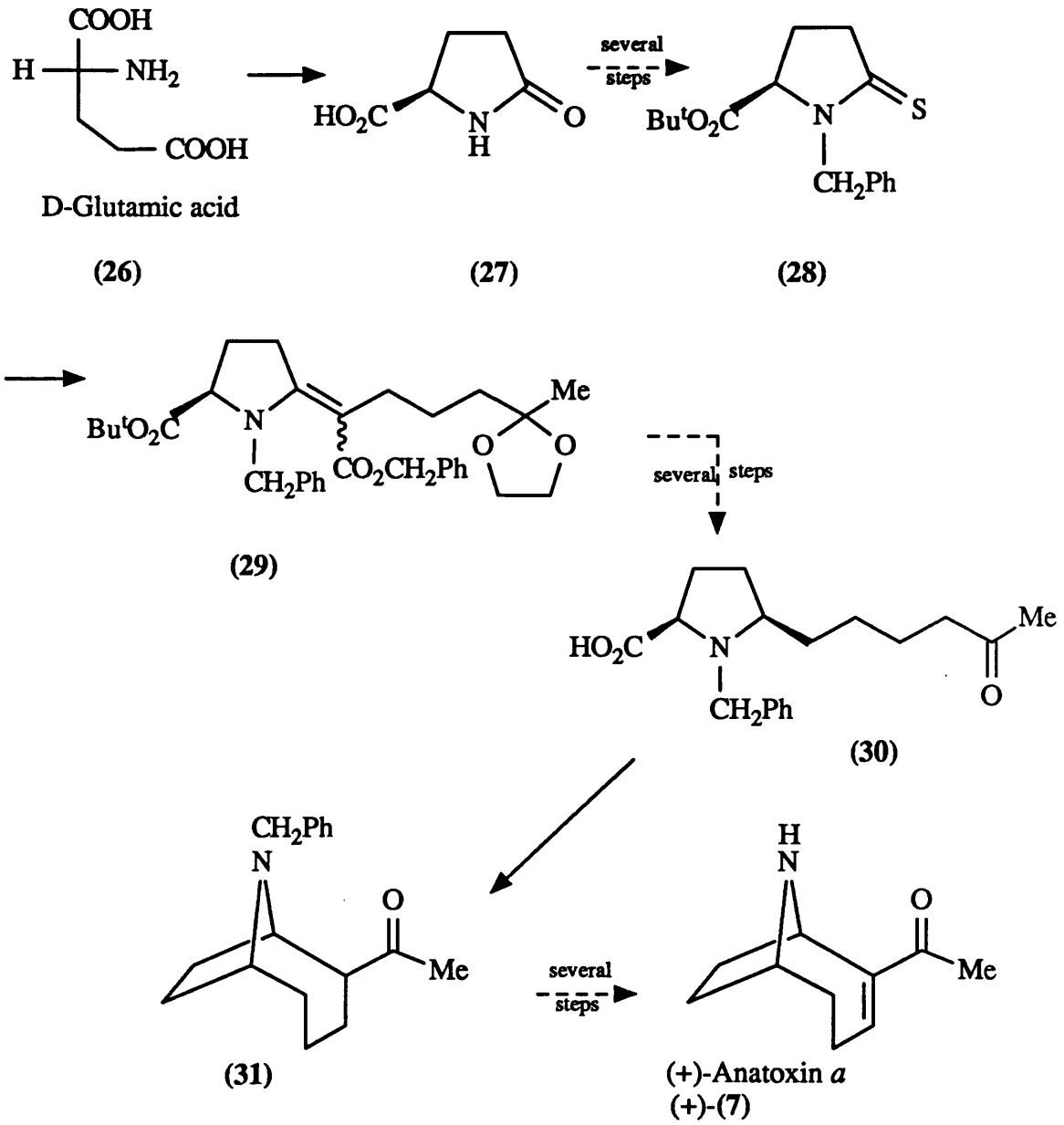


Figure 1.12

steps, to the thiolactam (28) required for a sulphide-contraction reaction which would introduce the C-5 carbon-carbon bond. Reaction with a benzyl triflate ester to form a thioiminium ion, followed by sulphide contraction gave the vinylogous carbamate (29) which was transfer-hydrogenated and then reduced over platinum to give pyrrolidines. These were rebenzylated and the protecting group removed from the ketone to give (30). By analogy with the previous cyclisation of the corresponding racemic N-methyl amino acid (23), N-benzyldihydroanatoxin (31) was isolated from acetal ester (29). (+)-Anatoxin *a* was synthesised from the bicyclic ketone after several steps in an overall yield of 5%. A similar "chirospecific" synthesis was used to synthesise (-)-anatoxin *a* in 4% overall yield after 17 steps starting with L-glutamic acid.

A nitrone-based entry to anatoxin *a* was reported by Tufariello.[18] Earlier, he had reported a nitrone-induced cycloaddition towards tropane alkaloids.[19] He anticipated that the addition of 1-pyrroline 1-oxide (32) to *trans*-3,5-hexadien-2-ol (33) would exhibit the desired site-selectivity and regioselectivity (Figure 1.13) to afford the isoxazolidine (34). Upon oxidation with manganese dioxide, (34) produced the ketone (35). Oxidative cleavage of the isoxazolidine ring with *m*-chloroperbenzoic acid gave the nitrone (36) in 79% yield. Warming of a solution containing the nitrone to 45°C led to the formation of a single cycloadduct, (37), in 71% overall yield from (35).

Subsequent acetalisation and mesylation resulted in the formation of acetal mesylate (38) which, when treated with a 1:1(molar)mixture of $LiAlH_4/NiCl_2$ in THF at -40°C led to (39). The hydroxy acetal (39) was treated with a stoichiometric amount of *p*-toluenesulphonic acid in acetone to induce both *trans*- acetalisation and dehydration, affording the *p*-toluenesulphonic acid salt (40) of anatoxin *a*.

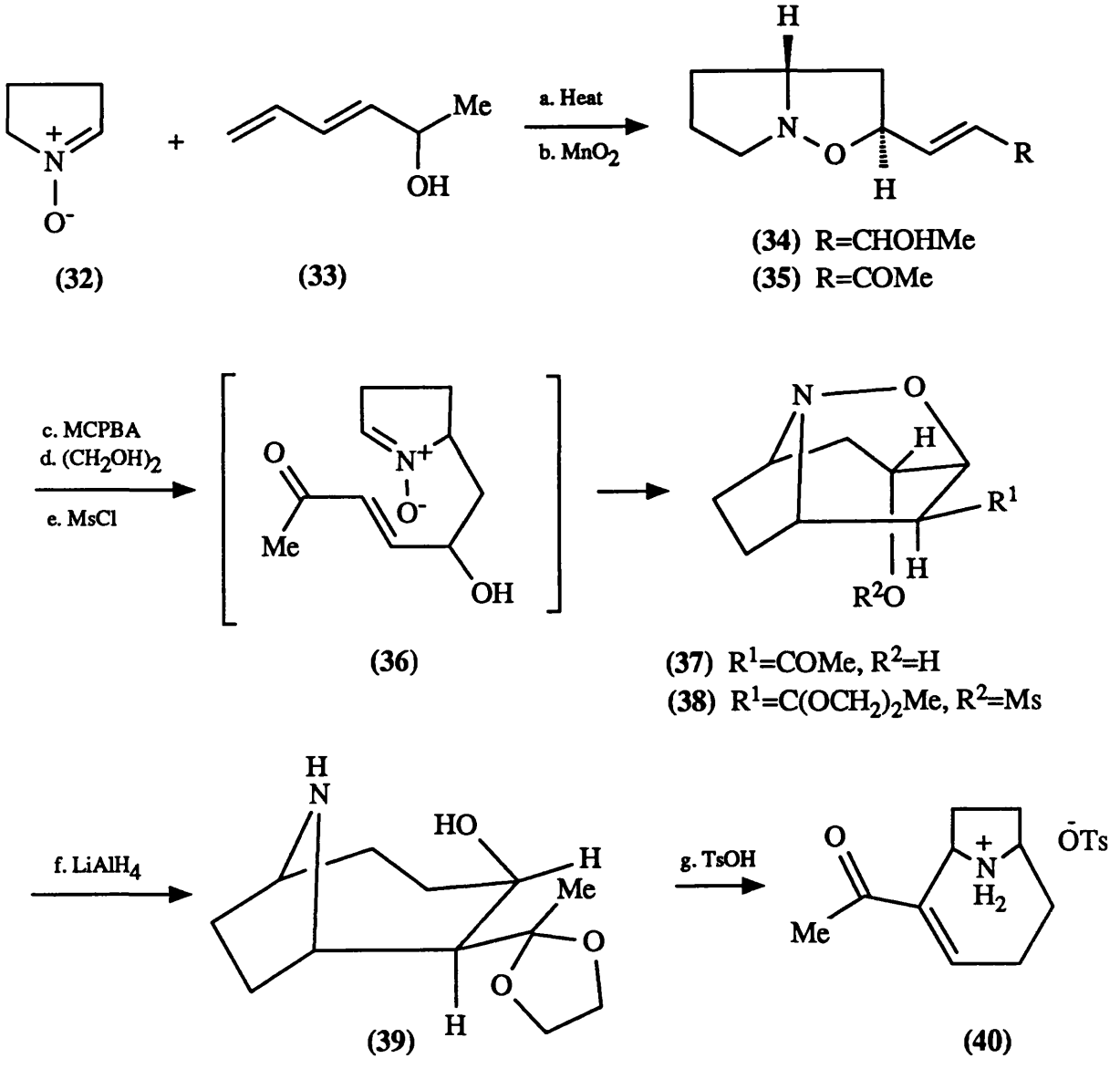


Figure 1.13

The pivotal step in the synthetic strategy developed by Danheiser[20] involved electrocyclic cleavage and transannular cyclisation (Figure 1.14). The starting material for the synthesis was the known tetrabromide

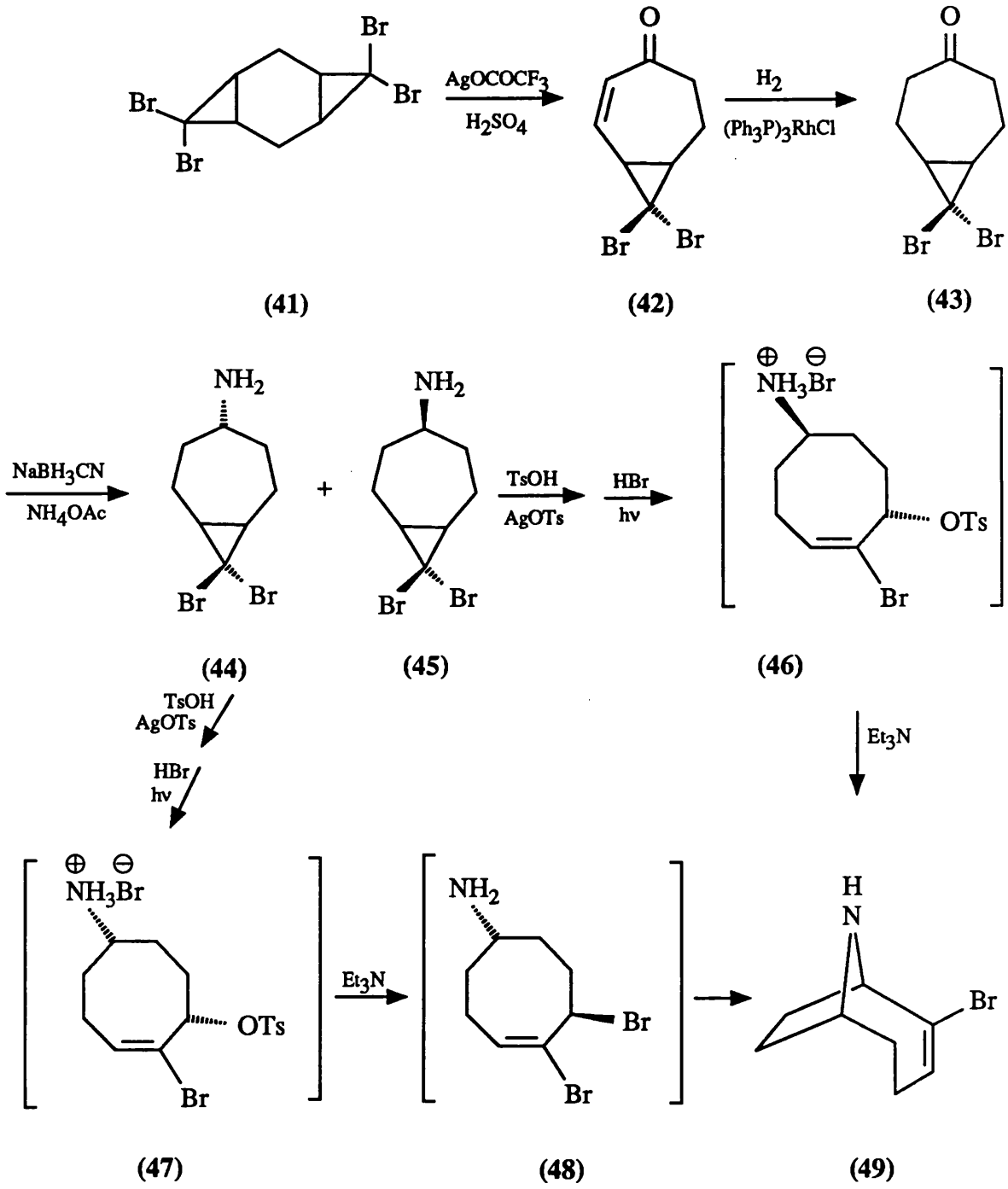


Figure 1.14

(41). Controlled electrocyclic opening of one cyclopropane ring in (41) was achieved by stirring a suspension of the tetrabromide and silver trifluoroacetate in a two-phase mixture of concentrated sulphuric acid and dichloromethane. The bicyclooctenone (42) was obtained in 29 - 35% yield by employing this procedure. The bicyclooctanone (43) was formed in 99% yield by catalytic hydrogenation of (42) over Wilkinson's catalyst in benzene. The reductive amination of (43) proceeded in high yield when a solution of the ketone in propan-2-ol was treated with sodium cyanoborohydride and ammonium acetate in the presence of 3Å molecular sieves. The aminobicyclooctane was produced in 94% yield as a 71:29 mixture of stereoisomers (44) and (45). Heating a solution of the isomeric tosylate salts (generated *in situ* from (44) and (45)) with an excess of silver tosylate in acetonitrile at 80°C for 2 days, followed by irradiation in a mixture of benzene and acetonitrile, and cyclisation with the addition of triethylamine gave the desired azabicyclononene (49). Anatoxin *a* was eventually synthesised in an overall yield of 8.3% by this method.

There have since been many other syntheses of anatoxin *a*[21] including that by Gallagher[22] which began with the synthesis and stereoselective cyclisation of the allenic amino ester (50) to give the cis-2,5-disubstituted pyrrolidine (51). Selective manipulation of both the ethoxycarbonyl and vinyl substituents of (51) led, in three steps, to bromide (52) in 47% overall yield from (51). Intramolecular alkylation of (52) gave the bicyclic ketosulphone (53). After several

steps, racemic anatoxin *a* was isolated, although in less than 3% overall yield from (50).

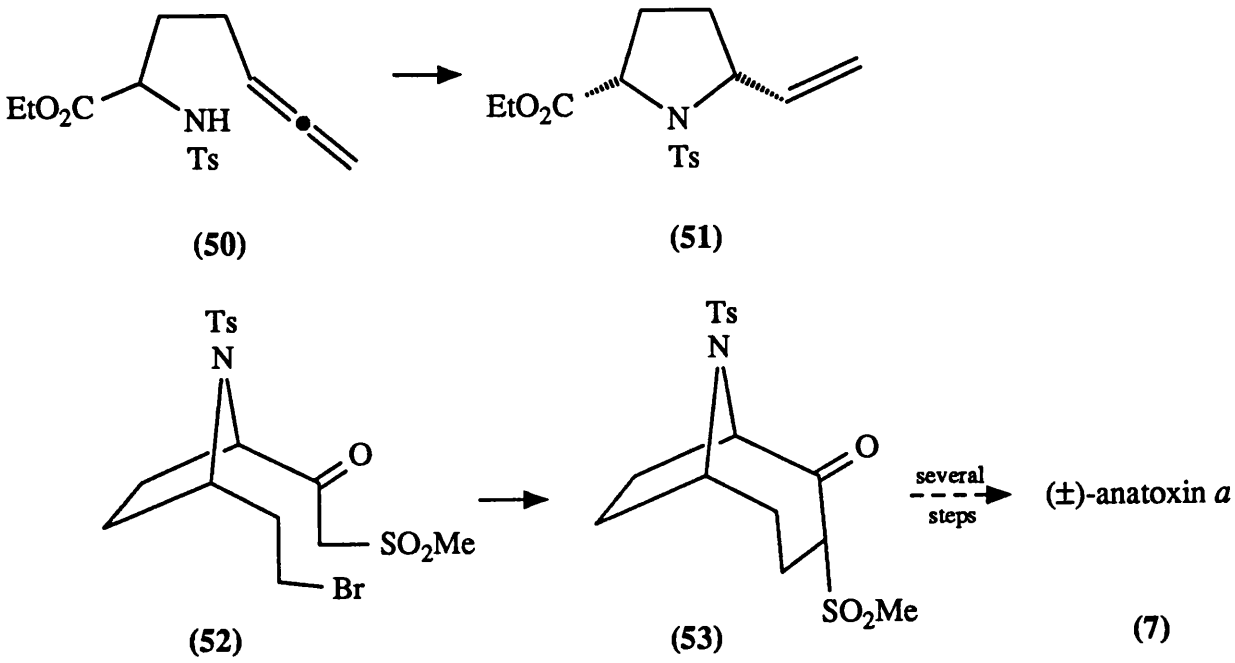
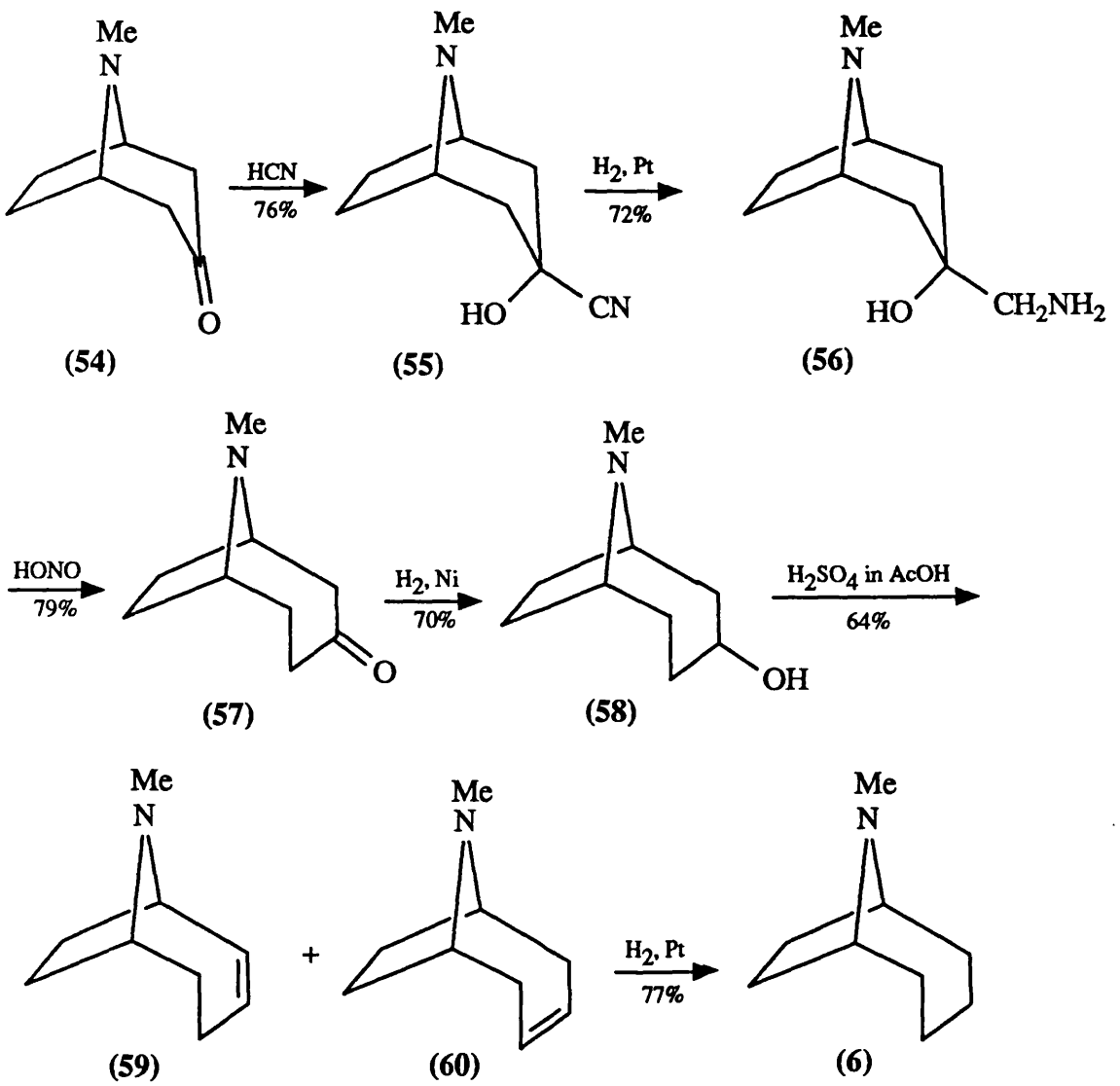


Figure 1.15

The application of naturally occurring toxins to the identification and classification of different neuronal receptors is a process that offers considerable potential in the study of neurotransmission pathways. The synthetic interest shown in anatoxin *a* could lead to the production of analogues which may help to establish the structural features of these receptor sites.

1.4 SYNTHESES OF THE HOMOTROPANE SKELETON

In contrast to the number of syntheses of anatoxin *a*, routes to other derivatives of the homotropane ring system are rare. The first synthesis of the homotropane skeleton was reported by Cope[23] as a ring expansion of tropinone (54) to homotropinone (57). The hydrogenation of tropinone cyanohydrin (55) to 3-aminomethyl-3-tropanol (56) was followed by treatment with sodium nitrite in aqueous acetic acid to give homotropinone (57) in 43% overall yield from



(54) (55) (56) (57) (58) (59) (60) (6)

Figure 1.16

tropinone. Catalytic hydrogenation of (57) in the presence of Raney nickel gave homotropanol (58) in 70% yield. Dehydration of (58) by treatment with sulphuric acid in glacial acetic acid yielded 64% of homo-2(or 3)-tropidine (59 or 60). Dehydration was expected to yield a mixture of the two isomers, but the narrow melting point of the product (17.2 - 18°C) suggested a single isomer. No evidence was obtained concerning the location of the double bond, a problem which nowadays would be solved in minutes by using ^{13}C NMR techniques which would show 9 carbon peaks for (59) but only 5 carbon peaks for the symmetrical (60). A sample of (59 or 60) was hydrogenated quantitatively to homotropane (6) and characterised as the picrate.

Following Cope's synthesis of homotropane, the majority of the work on this system was carried out by Anastassiou[24] who was particularly concerned with highly unsaturated systems.

Treatment of a dilute solution of cyclooctatetraene (61) in ethyl acetate with cyanogen azide at 78°C resulted in the formation of the 1,4-adduct, 9-cyano-9-azabicyclo[4.2.1]nona-2,4,7-triene (62) in ~ 10% yield. Anastassiou investigated the photochemical isomerisation of bicyclic π-systems such as (62).[25] On heating the nitrile (62) with 10% sodium hydroxide in aqueous acetone, the parent amine (63) was obtained in 71% yield. Careful hydrogenation of (62) over 5% rhodium on charcoal gave the diene (64) in 82% yield which was heated with 10% sodium

hydroxide in aqueous acetone to afford the parent amine (65) in 66% yield. The parent amines (63) and (65) were thought to be well suited structurally for a study of the general stereoelectronic factors controlling heteroatom extrusion.[26] They were expected to be ideal models for assessing the relative merits of linear versus nonlinear cheletropy within the same molecule. Subsequent studies revealed a distinct preference for linear over non-linear cheletropy in these model systems.[27]

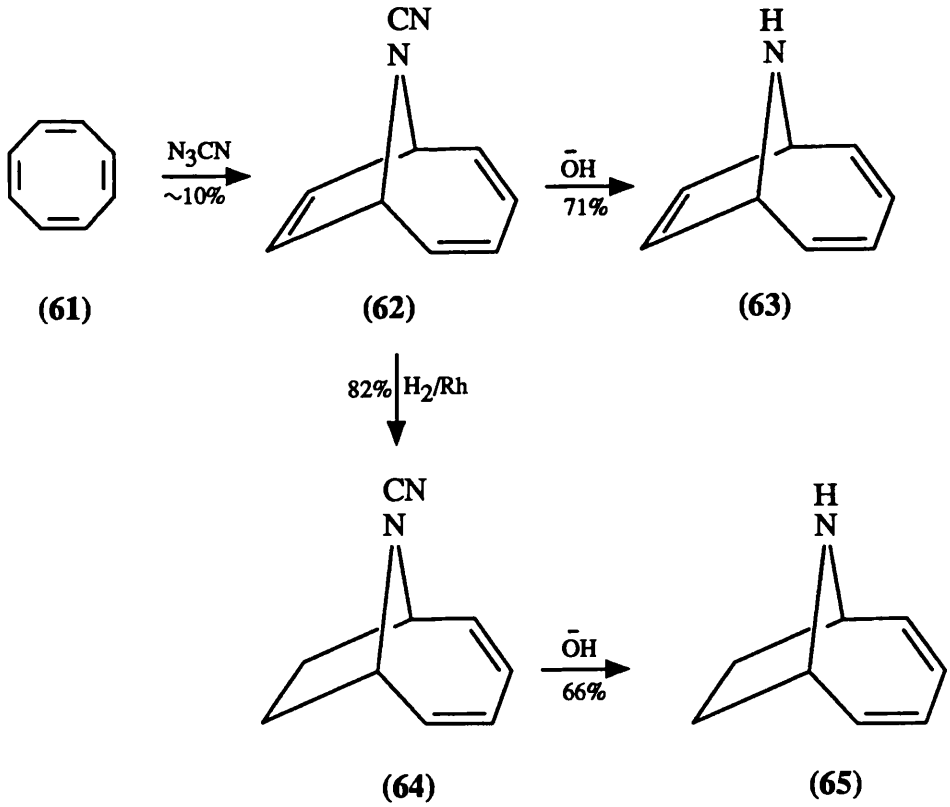


Figure 1.17

Tardella synthesised the parent 9-azabicyclo[4.2.1]nonane as the ethyloxycarbonyl derivative (69).[28] The key step in the synthesis was the cyclopropyl ring fission by pyridinium

chloride (Figure 1.18). A mixture of two chloroketones, (67) and (68), resulted from the pyridinium chloride treatment of bicyclo[5.1.0]octan-2-one (66). These were converted in to a mixture of oximes, reduced by lithium aluminium hydride and treated with ethyl chlorocarbonate to give N-ethoxycarbonyl-9-azabicyclo[4.2.1]nonane (69) in 19% yield.

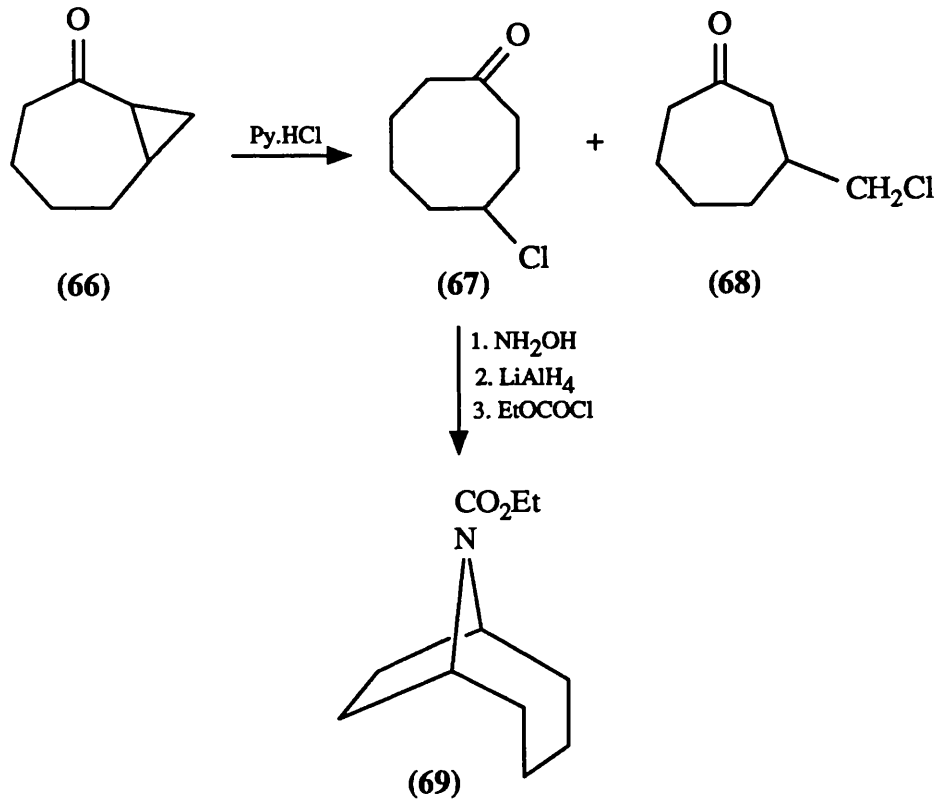


Figure 1.18

Other syntheses of the homotropane skeleton have begun with the cyclooctadienes. A transannular cyclisation of cyclic N-chloroamines was reported by Hobson[29] (Figure 1.19). He observed that thermolysis of ethyl azidoformate in an excess of 1,5-cyclooctadiene at 100°C gave high yields of

the carbamate (71). Reduction with lithium aluminium hydride gave N-methylcyclooct-4-enamine (72). The chloroamine (73) was obtained in virtually quantitative yield by reaction of (72) with N-chlorosuccinimide in dichloromethane. Addition of a small amount of radical initiator, azobisisobutyronitrile (AIBN) to a solution of (73) in cyclohexane at 60°C resulted in the formation of the bicyclic chlorides (74) and (75). The 2-chlorohomotropane (74) was formed in 25 - 30% yield from the chloroamine (73).

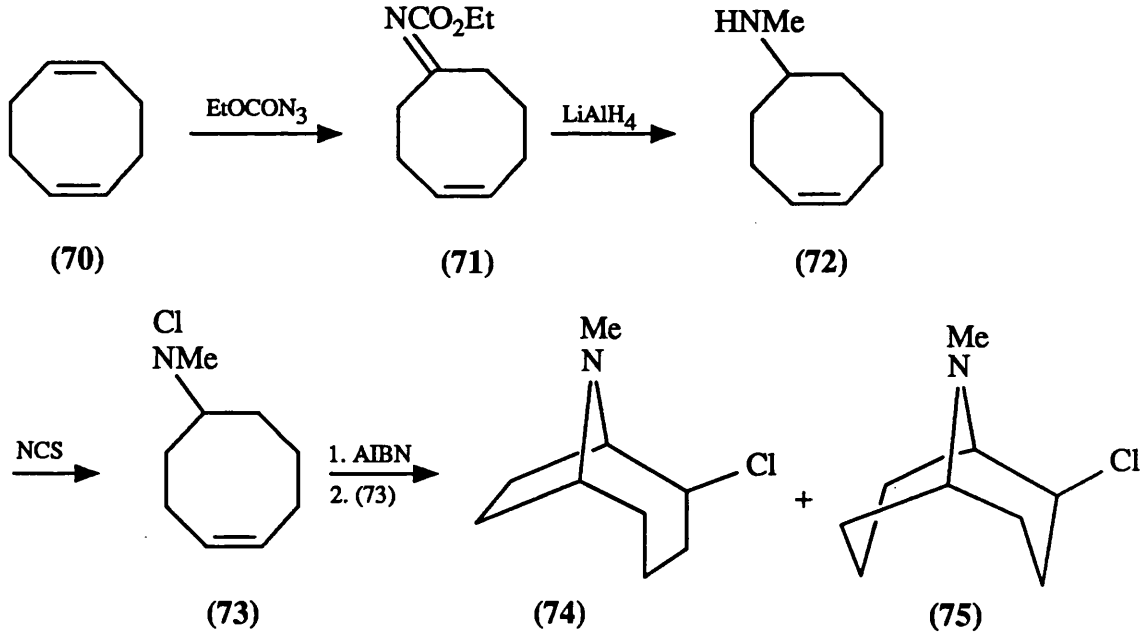
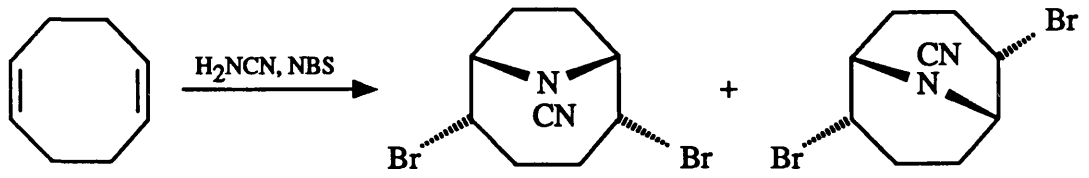


Figure 1.19

Haufe[30] found that the reaction of 1,5-cyclooctadiene (70) with cyanamide and N-bromosuccinimide (NBS), in ether at room temperature, occurred with transannular participation of the initially added cyanamido group yielding a 50:50

mixture of 2,5-dibromo-N-cyano-9-azabicyclo[4.2.1]nonane (76) and 2,6-dibromo-N-cyano-9-azabicyclo[3.3.1]nonane (77).



(70) (76) (77)

Figure 1.20

Finally, Barluenga[31] found that cyclic 1,3-dienes reacted with primary amines in the presence of mercury (II) oxide-tetrafluoroboric acid to afford 1,4-cycloamination products in a "one pot, one step" process (Figure 1.21). The 1,4-cycloamination of 1,3-cyclooctadiene (78) was envisaged as proceeding through the formation of an intermediate 1,4-adduct (80 or 81) in which mercury was displaced by amine with direct participation of the nucleophile in an assisted breakage of the *anti*-C-Hg bond, or by spontaneous reduction of mercury in the intermediate allylic organomercurial.

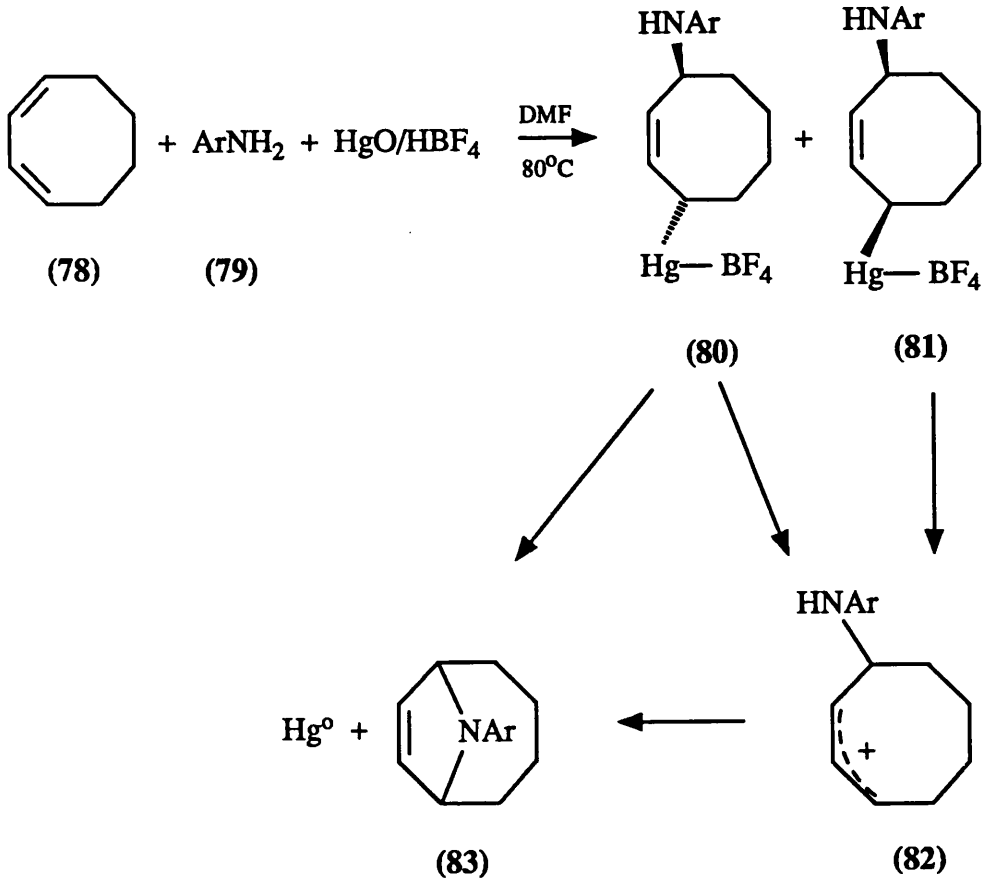


Figure 1.21

1.5 NITROSO CYCLOADDITION TO 1,3-CYCLIC DIENES

In 1984, a new synthetic route to tropane alkaloids was reported by Kibayashi.[32] This synthesis was based on [4+2] nitroso cycloaddition to 1,3-cycloheptadienes (Figure 1.22). N-Benzoylnortropane (91) was chosen as the first model to investigate the feasibility of the proposed scheme. The route involved a Diels-Alder reaction between 1,3-cycloheptadiene (84) and the acyl nitroso compound (85), generated *in situ*, to afford the [4+2] cycloadduct (86).

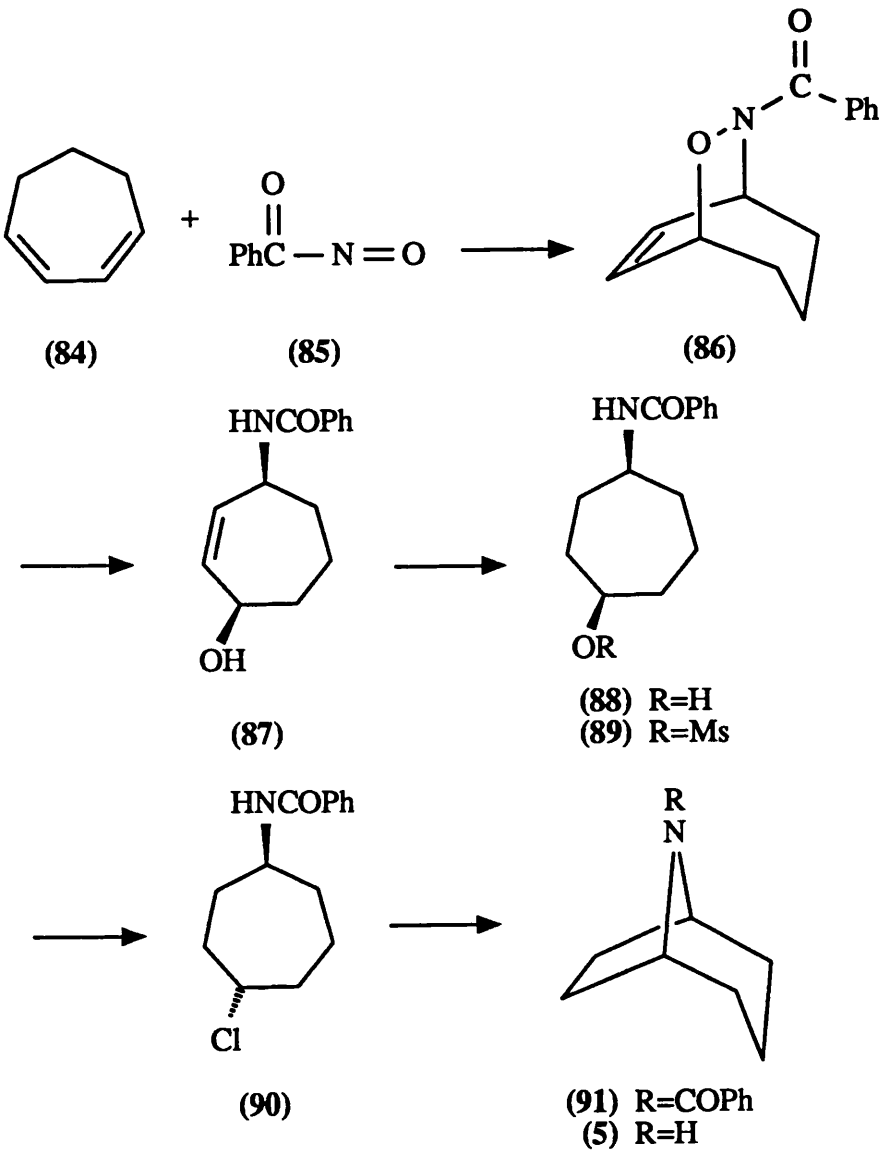


Figure 1.22

Reductive N-O bond cleavage of (86) with sodium amalgam in ethanol gave (87) which was then hydrogenated over palladium on charcoal to give the saturated alcohol (88). Treatment of (88) with thionyl chloride and triethylamine in chloroform at room temperature yielded the chloride (90) in 88% yield, which gave the desired N-benzoylnortropane (91) in 87% yield when treated with potassium *tert*-butoxide in a 1:1 hexamethylphosphoric triamide (HMPA)-benzene solution.

However, attempts at cyclisation of the mesylate (89), made by treatment of the alcohol (88) with mesyl chloride, were unsuccessful using various strong bases. This strongly suggested that the cyclisation step involved an internal S_N2 process, and so cyclisation would occur in (90) rather than in (89), since only in (90) was the benzoylamino group correctly placed for backside displacement of the anionic leaving group. Attempts to form nortropane (5) and tropane (4), using hydrolysis to remove the benzoyl group from (91), were unsuccessful.

Earlier, Fraser and Swingle had succeeded in synthesising 7-azabicyclo[2.2.1]heptane (97) by cyclisation of a *trans*-amino mesylate (96).[33] The *trans*-amido alcohol (93) was synthesised from 4-acetamidophenol (92) in 40% yield. Treatment of (93) with mesyl chloride gave the *trans*-amido mesylate (94) in 85% yield. It is possible that this compound could have been made to cyclise by treatment with strong base in an analogous way to the cyclisation of the *trans*-amido chloride (90) accomplished by Kibayashi. However, Fraser and Swingle chose to react (94) with triethyloxonium fluoroborate forming the imido ester (95) in 75% yield. Hydrolysis of (95) at pH 1.5 to 2.0 gave the amino mesylate salt (96) which was encouraged to cyclise by treatment with sodium hydroxide in aqueous ethanol to give (97) in 83% yield.

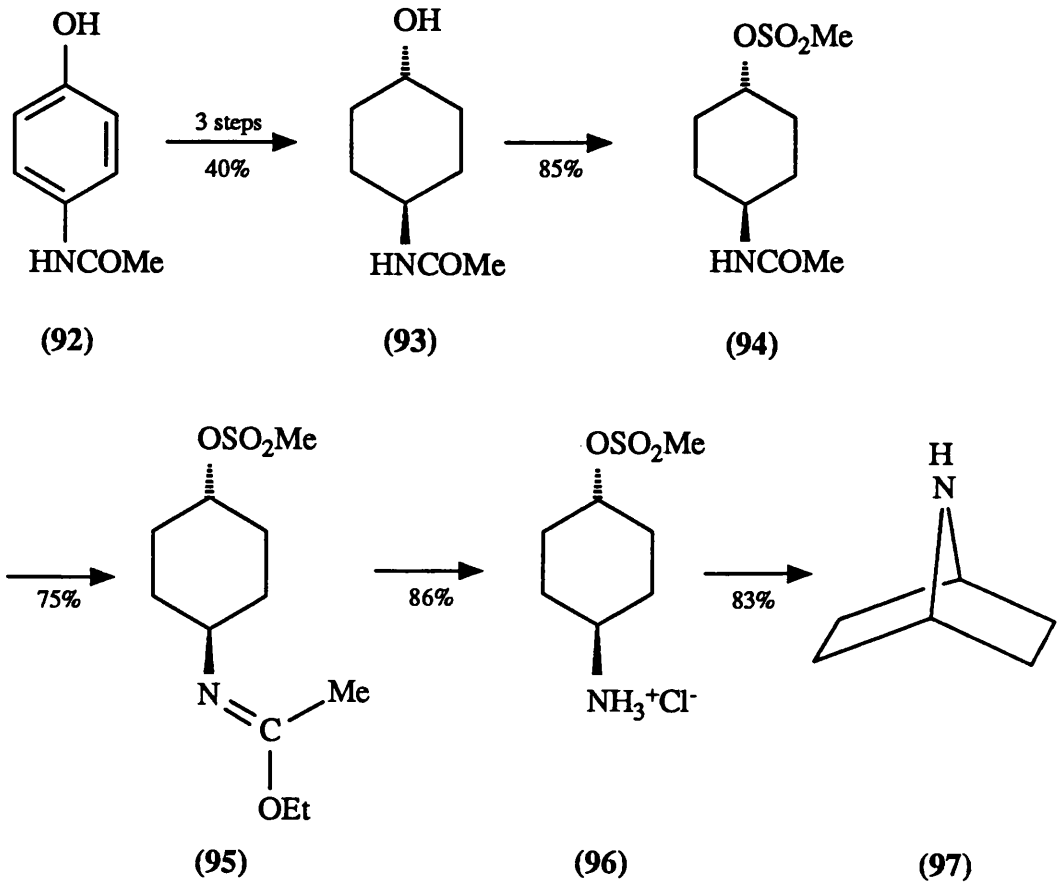


Figure 1.23

The cyclisation step of Fraser and Swingle involved a nucleophilic amine nitrogen compared with that of Kibayashi which involved a less nucleophilic amide nitrogen. Consequently, Kibayashi's cyclisation required a very strong base in the presence of hazardous co-solvents benzene and HMPA. It was apparent that a modification of Kibayashi's nitroso cycloaddition scheme might dispose of the need for such harsh conditions and introduce more flexibility. The next chapter describes such a modification and its subsequent development to yield 9-azabicyclo[4.2.1]nonanes (homotropanes) and -7-enes (homotrop-7-enes).

Chapter Two

INTRAMOLECULAR CYCLISATION STRATEGIES TO HOMOTROPANES AND HOMOTROP-7-ENES

2.1 INTRODUCTION

The content of this chapter is based on earlier work by Bathgate[34] and Howarth.[35] It is concerned with the development of the intramolecular cyclisation of eight-membered rings to yield 9-azabicyclo[4.2.1]nonanes (homotropanes) and -7-enes (homotrop-7-enes).

In 1987, Bathgate[34] reported a modification of Kibayashi's route[32] to tropane derivatives (Figures 2.1 and 2.2). This synthesis retained the nitroso-cycloaddition methodology to provide the required *cis*-stereochemistry of the 1,4-difunctionalised precursors but the nitrogen substituent was subsequently modified. Reduction of the amido benzoyl groups (88 and 87) to the respective benzylamino-nitrogens (98 and 101) led to an increase in the nucleophilic character of the nitrogen to improve the subsequent intramolecular nucleophilic displacement. The benzyl group was also a potentially removable substituent for completion of the synthesis of the parent nortropane (5) and nortrop-6-ene (108).

The Diels-Alder reaction involving 1,3-cycloheptadiene (84) and the acyl nitroso compound, generated *in situ* from benzohydroxamic acid[36] and tetramethylammonium periodate,[37] gave the cycloadduct (86) in 70% yield (Figure 2.1). The N-O bond was cleaved by treatment with aluminium amalgam in 92% yield and the resulting *cis*-amido-alcohol (87) was catalytically hydrogenated to (88). The saturated amido-

alcohol (88) was reduced with lithium aluminium hydride to give an almost quantitative yield of the *cis*-1,4-amino-alcohol (98) which was treated with a molar equivalent of thionyl chloride yielding the hydrochloride salt of the *trans*-1,4-amino-chloride (99). In Kibayashi's synthesis,[32] an organic base (*tert*-butoxide) had been added along with the thionyl chloride. This was unnecessary here since the amino-alcohol (98) contained a reactive secondary amine

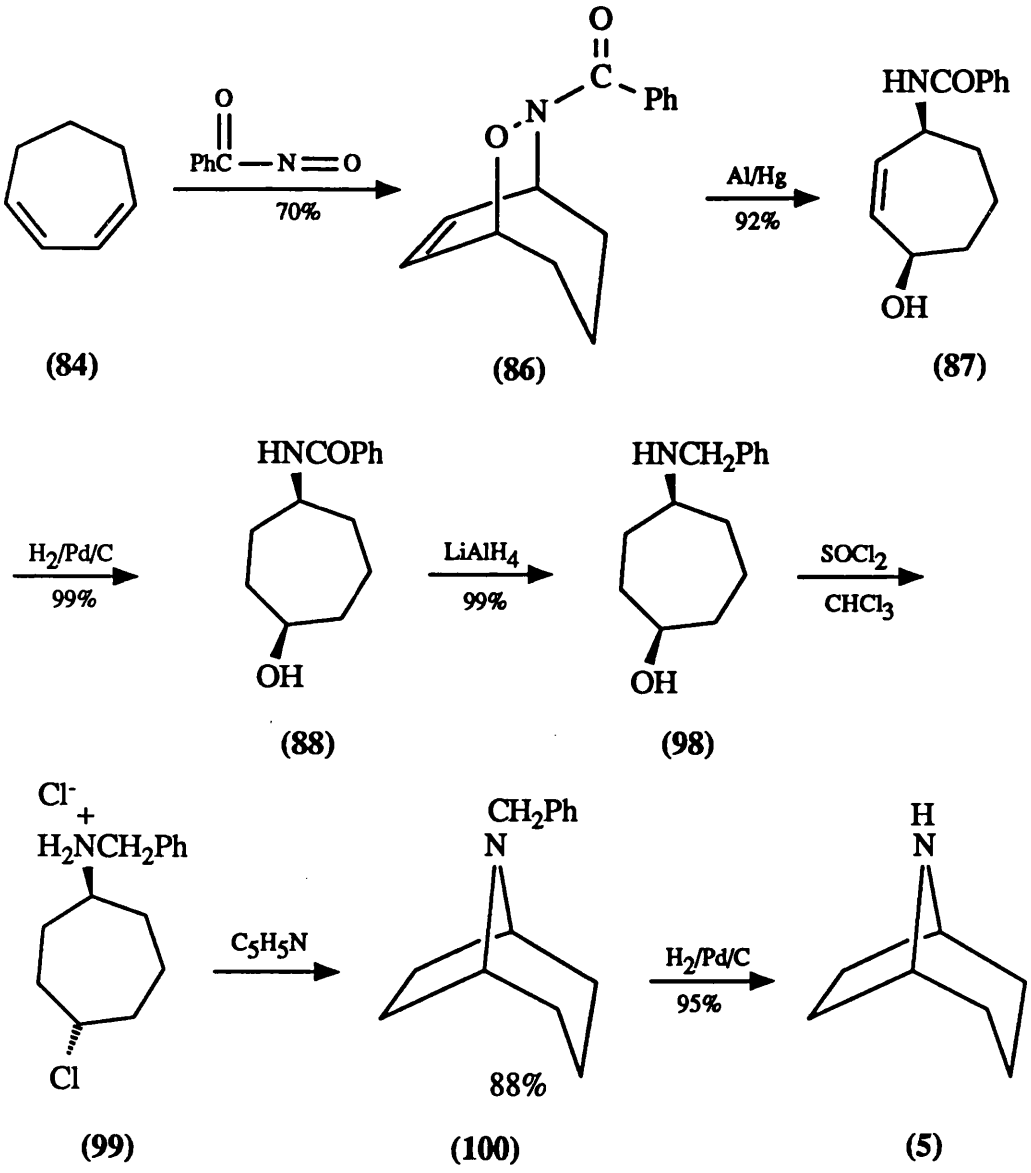


Figure 2.1

which acted as an effective intramolecular base and mopped up the hydrogen chloride formed in the reaction. This also ensured that the chloride ion attacked with inversion of configuration. Basification of the salt (99) with dry pyridine gave rise to the free amine which cyclised at room temperature to N-benzylnortropane (100) in 88% yield. Catalytic hydrogenation afforded the parent nortropane (5) in 95% yield. The benzylamino group had negated the need for such harsh conditions in the cyclisation step and constituted a removable nitrogen protecting group.

Exclusion of the catalytic hydrogenation step resulted in the formation of the unsaturated *cis*-1,4-amino-alcohol (101) in 97% yield from the amido-alcohol (87). Treatment with thionyl chloride in the presence of lithium chloride in chloroform, followed by the addition of the heterogeneous base, potassium carbonate, under the influence of ultrasound, led to the formation of N-benzylnortrop-6-ene (103) in 65% yield, together with the aziridine (104) which was isolated in 10% yield. However, attempts to remove the benzyl group from N-benzyltrop-6-ene were unsuccessful.[38] Catalytic hydrogenation could not be used here due to the presence of the double bond. In spite of this complication, this was the first synthesis of a simple derivative of nortrop-6-ene which had been achieved in significant yield and it demonstrated the practicability of the intramolecular displacement approach given an appropriately nucleophilic nitrogen.

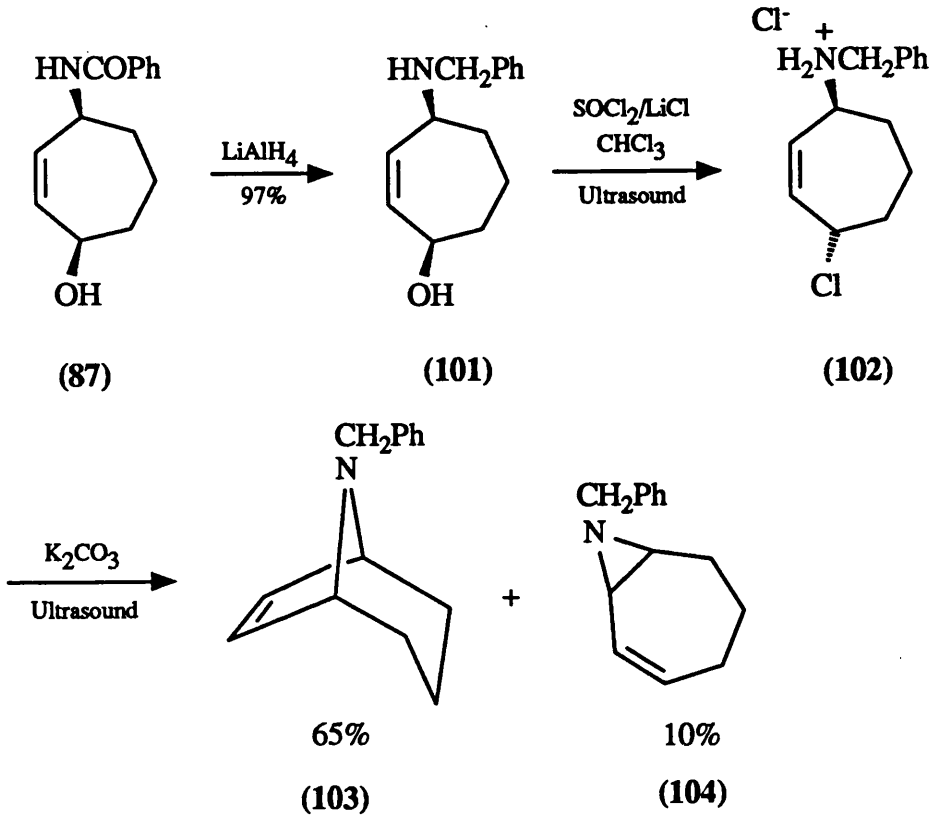
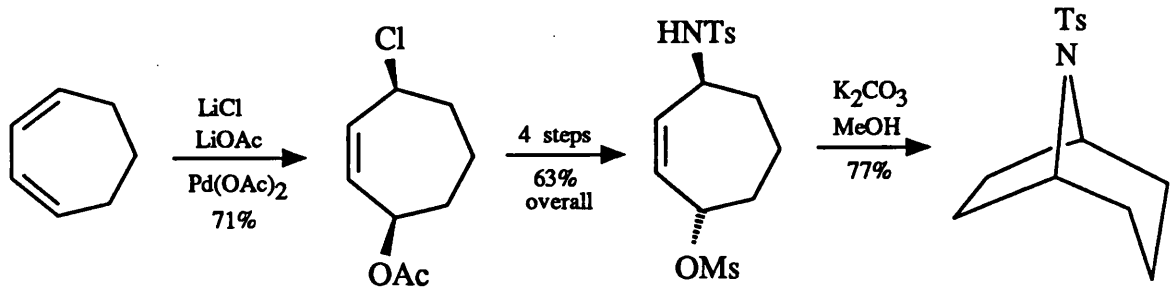


Figure 2.2

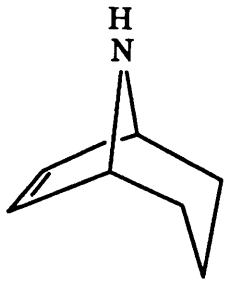
At the same time as Bathgate's report, Bäckvall[39] reported the application of intramolecular cyclisation of a *trans*-amido-mesylate (106) to yield the N-tosylnortropane (107). The approach was based on a dual stereocontrol in the 1,4-functionalisation of conjugated dienes (Figure 2.3). Palladium-catalysed 1,4-chloroacetoxylation gave the chloroacetate (105) which, when treated with sodium *p*-toluenesulphonamide (NaHTs) in acetonitrile-DMSO at 80°C, gave a *trans*-amido-acetate which was converted to the *trans*-amido-mesylate (106) after a further three steps. The trans-amido-mesylate (106) was cyclised to (107) by treatment with potassium carbonate in methanol.



(84) (105) (106) (107)

Figure 2.3

The necessary final detosylation of (107) was not reported, but would be expected to occur in ~80% yield. Bäckvall also reported an unsuccessful attempt to prepare the nortrop-6-ene skeleton (108). Thus, despite being unable to remove the benzyl protecting group from N-benzyl-nortrop-6-ene (103), the Bathgate synthesis was the first of a simple derivative of the parent nortrop-6-ene skeleton which had been achieved in high yield.



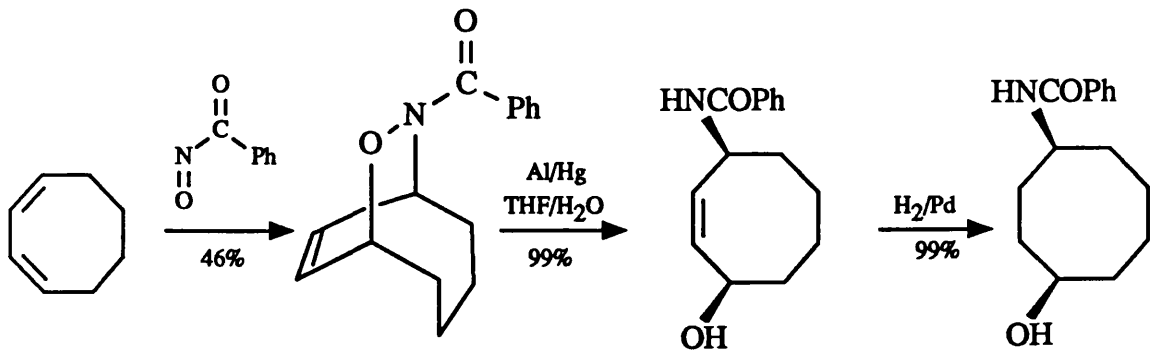
(108) Nortrop-6-ene

Figure 2.4

Following the success of Bathgate's approach, it was considered appropriate to investigate the application of this methodology towards the synthesis of a higher homologue of tropane; the homotropane ring system.

2.2 PRODUCTION OF HOMOTROPANES AND HOMOTROP-7-ENES HAVING A POTENTIALLY REMOVABLE N-BENZYL PROTECTING GROUP.

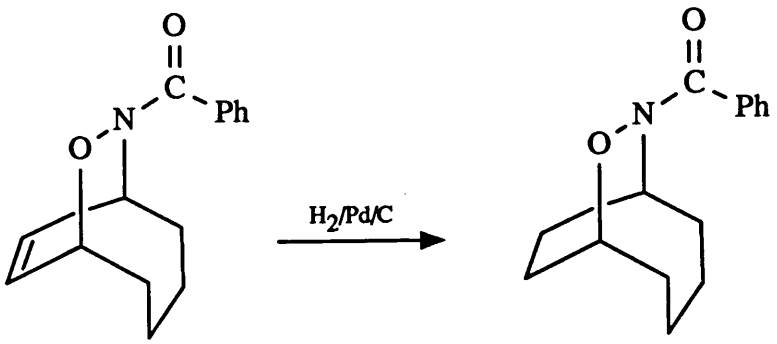
The investigation began with the attempt at synthesising N-benzyl-9-azabicyclo[4.2.1]nonane (116). Thus, the Diels-Alder reaction involving 1,3-cyclooctadiene (78) and the acyl nitroso compound, generated *in situ* from benzohydroxamic acid[36] and tetramethylammonium periodate,[37] gave the cycloadduct (109) in a reasonable 46% yield. The yield of cycloadduct was lower than in the case of the smaller 1,3-cycloheptadiene, presumably as a result of conformational restrictions on planarity of the diene. The N-O bond of the cycloadduct (109) was reductively cleaved affording the unsaturated *cis*-amido-alcohol (110). Catalytic hydrogenation of (110) gave an almost quantitative yield of the saturated *cis*-amido-alcohol (111).



(78) (109) (110) (111)

Figure 2.5

Catalytic hydrogenation of the cycloadduct (109) resulted in reduction of the C=C double bond forming (112) in 96% yield. However, subsequent reductive cleavage of the N-O bond in this saturated compound was not as clean and effective as the cleavage of the N-O bond in the unsaturated compound (109). Hence, when the saturated amido-alcohol (111) was required, first the N-O bond of (109) was cleaved, followed by reduction of the C=C double bond in (110).

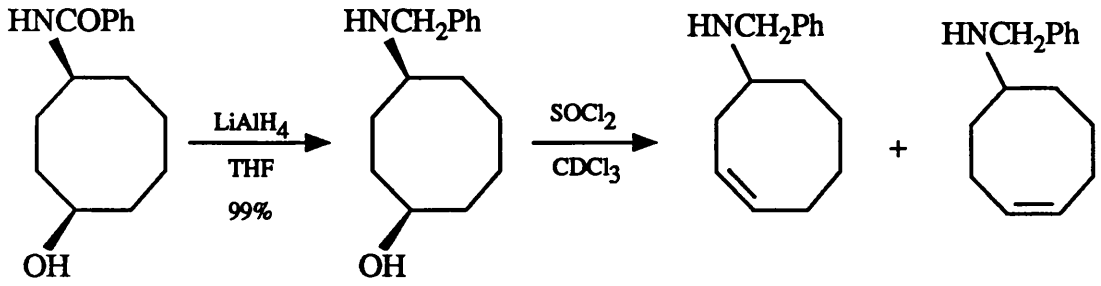


(109) (112)

Figure 2.6

The saturated amido-alcohol (111) was reduced in excellent yield to the *cis*-1,4-amino-alcohol (113) required for the intramolecular cyclisation step. Initial attempts to cyclise (113) were monitored by proton (90MHz) NMR. Addition of thionyl chloride to a solution of (113) in dry deuterochloroform brought about the development of the peaks assigned to the alkylchlorosulphite analogous to those observed by Bathgate[38] and Howarth.[35] However, decomposition of the alkylchlorosulphite to the desired *trans*-1,4-amino-chloride was not observed. The appearance of peaks in the olefinic region (5.5 - 6.0ppm) implied that the predominant process occurring was elimination producing

amino-alkenes (114) and (115).



(111) (113) (114) (115)

Figure 2.7

Owing to the lack of success with thionyl chloride, it was decided to examine the application of thionyl bromide in the cyclisation step. Howarth had experienced problems with the unsaturated compound (101) using the heterogeneous base, potassium carbonate, so 2,2,6,6-tetramethylpiperidine (TMP) was chosen since it is a stronger, non-nucleophilic base than pyridine which had been used to cyclise the saturated compound (98).

Initial experiments using thionyl bromide were carried out in dry deuterochloroform and monitored by proton (90MHz) NMR. In contrast to the result obtained using thionyl chloride, the use of thionyl bromide did not result in the development of olefinic peaks, rather its use led to the appearance of peaks which correlated well with those of the *trans*-bromide observed by Howarth.[35]

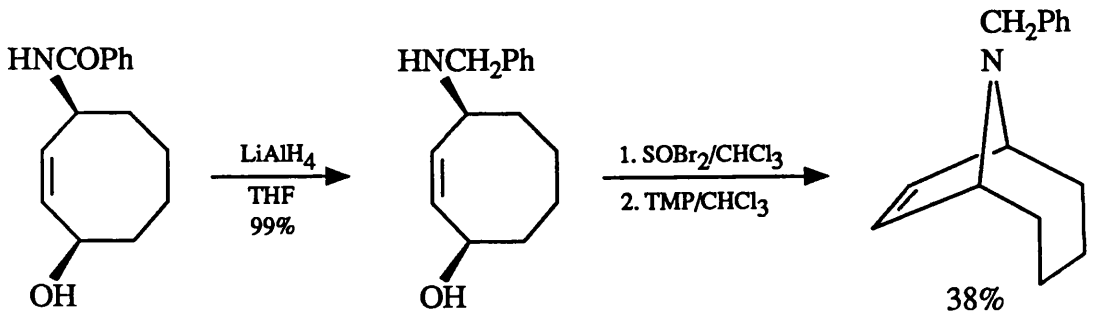
The experiment was carried out on a larger scale in dry chloroform, and when it appeared, from NMR experiments, that the *trans*-amino-bromide had been formed, the mixture was treated with TMP to induce cyclisation. On purification, N-benzyl-9-azabicyclo[4.2.1]nonane (116) was isolated in 41% yield. This N-benzylnorhomotropane was easily recognisable due to the simplicity of the ^{1}H NMR spectrum, in which the two bridgehead protons had the same chemical shift (δ3.29) and of the ^{13}C NMR spectrum which exhibited only nine

(113) **(116)**

Figure 2.8

signals on account of the symmetry of the system. The same method was applied to the synthesis of N-benzyl-9-azabicyclo[4.2.1] non-7-ene (118) from *cis*-4-(benzylamino)-2-cyclooctenol (117). The unsaturated amido-alcohol (110) was reduced almost quantitatively to the *cis*-1,4-amino-alcohol (117) required for the intramolecular cyclisation step. Treatment of a solution of (117) in dry chloroform with thionyl bromide, followed by the addition of TMP, afforded N-benzyl-9-azabicyclo[4.2.1]non-7-ene (118)

in 38% yield after purification. This N-benzylnorhomotrop-7-ene was also easily identified due to the simplicity of the ^1H NMR spectrum; the two bridgehead protons appeared together (δ3.63) as a doublet of doublet of doublets (J=6.4Hz, 1.7Hz, 1.0Hz). The J values 6.4Hz and 1.7Hz arose from coupling between the bridgehead proton and the neighbouring CH_2 group, and the value of 1.0Hz emanated from vicinal coupling with the olefinic proton which in turn, appeared as a doublet, J=1.0Hz at δ5.69. The ^{13}C NMR spectrum exhibited only nine signals as a result of the symmetry of the system. The bicyclic amine (118) was uncontaminated by the aziridine isomer which might have been expected to have resulted from competitive 1,2-cyclisation (cf. Figure 2.2).



(110) **(117)** **(118)**

Figure 2.9

Having demonstrated the practicability of the syntheses of N-benzyl-9-azabicyclo[4.2.1]nonane (116) and -non-7-ene (118), the next step was to attempt to optimise the yields as they were still fairly modest at ~40%.

Howarth looked at the effect of changing the solvent used in the cyclisation step from chloroform to a more polar solvent, acetone, since the cyclisation to form the bicyclic system was thought to occur by an internal S_N2 mechanism (Figure 2.10). The transition state involves a build-up of charge in this type of reaction, and so is aided by more polar

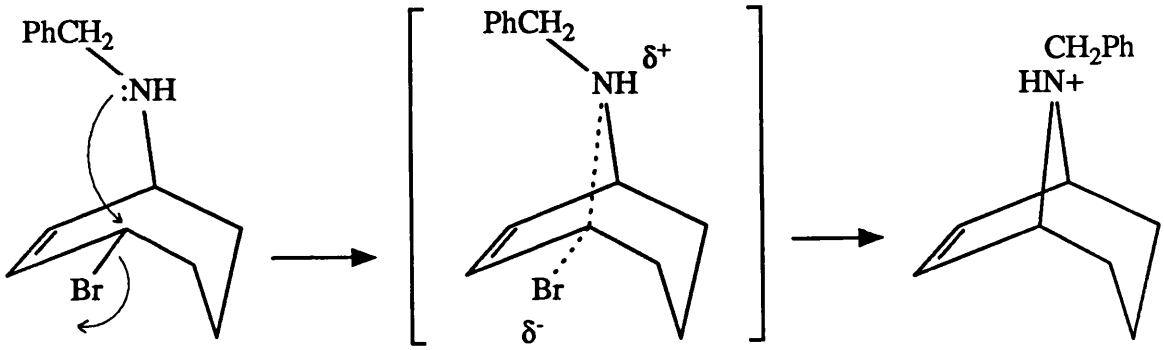
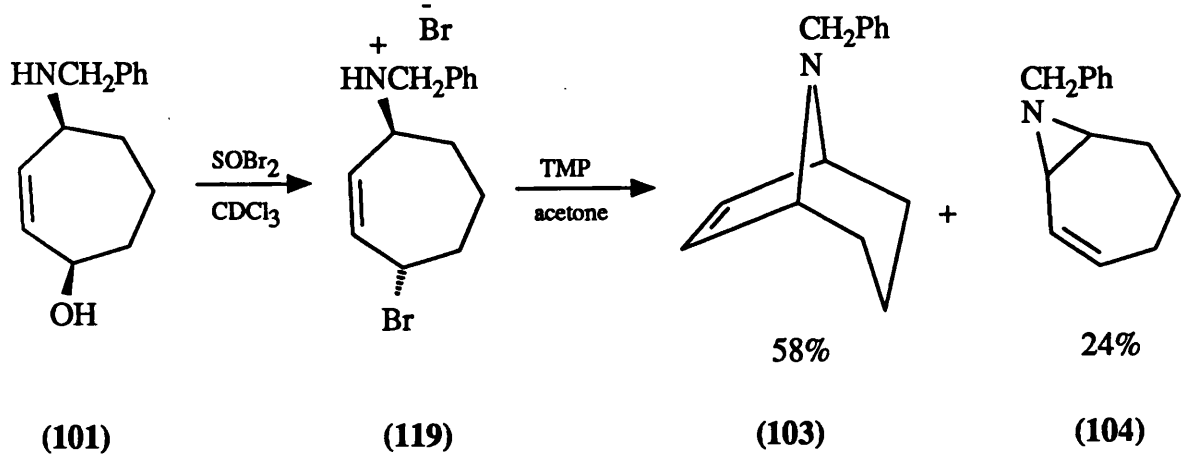


Figure 2.10

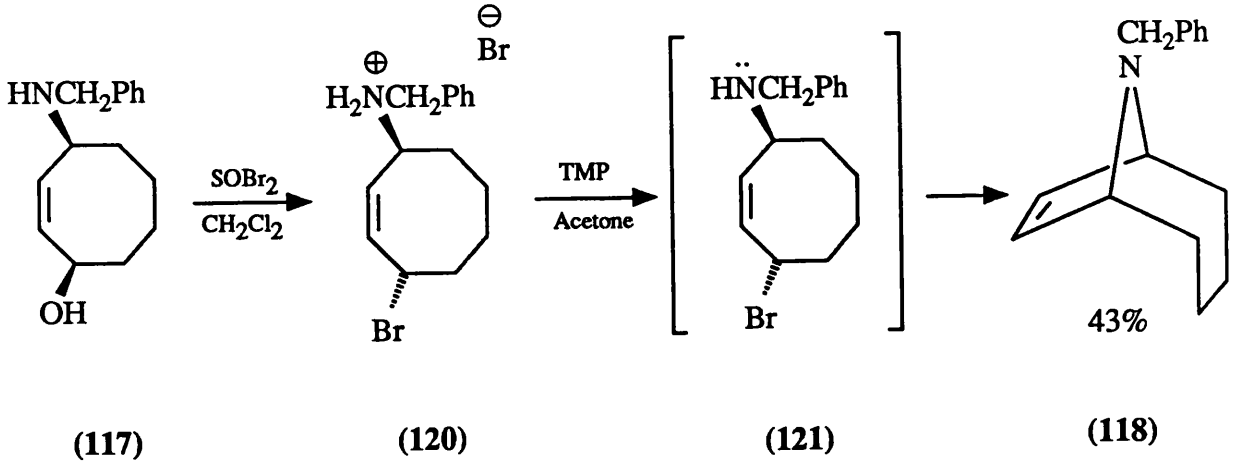
solvents which are able to stabilise the transition state to a greater degree and hence promote the reaction. Thionyl bromide was added to a solution of *cis*-4-(benzylamino)-2-cycloheptenol (101) in dry deuterochloroform to form the *trans*-1,4-amino-bromide (119). At this point, the deuterochloroform was removed and replaced with dry acetone. The solution of (119) in acetone was treated with TMP resulting in the formation of N-benzylnortrop-6-ene (103) in 58% yield together with the aziridine (104) which was isolated in 24% yield.



(101) (119) (103) (104)

Figure 2.11

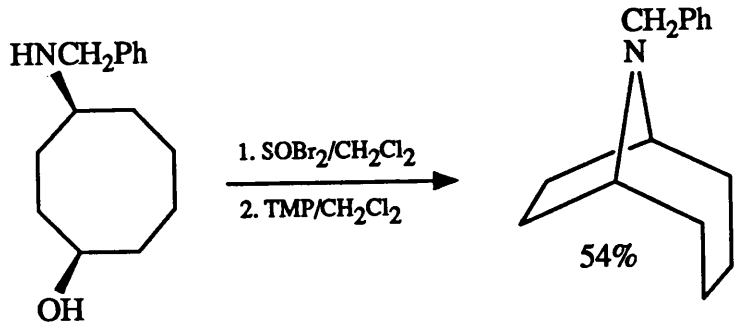
Thus, Howarth's change to a more polar solvent in the cyclisation step had increased the yield of N-benzylnortrop-6-ene (103) from 33% to a more acceptable 58%. Thionyl bromide was therefore added to a solution of *cis*-4-(benzylamino)-2-cyclooctenol (117) in dry chloroform to form the *trans*-amino-bromide (120). After removal of chloroform and replacement with dry acetone, the solution was treated with TMP resulting in the formation of N-benzyl-9-azabicyclo[4.2.1]non-7-ene (118) in 43% yield. Thus, the change in solvent from chloroform to the more polar acetone had caused a slight increase in yield from 38%, but this was modest by comparison with Howarth's increase.



(117) (120) (121) (118)

Figure 2.12

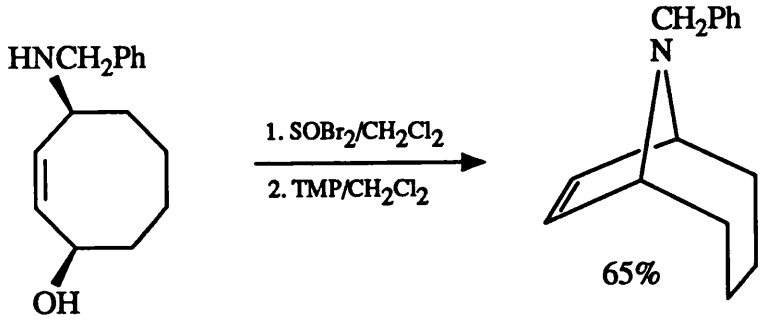
The best results for the cyclisation steps were obtained using freshly distilled, dry dichloromethane as the solvent. Treatment of a solution of (113) in dry dichloromethane with thionyl bromide, followed by the addition of TMP, afforded N-benzyl-9-azabicyclo[4.2.1] nonane (116) in an acceptable 54% yield.



(113) (116)

Figure 2.13

Surprisingly, a yield of 65% was obtained by the same approach for the cyclisation of (117) to N-benzyl-9-azabicyclo [4.2.1]non-7-ene (118).



(117) (118)

Figure 2.14

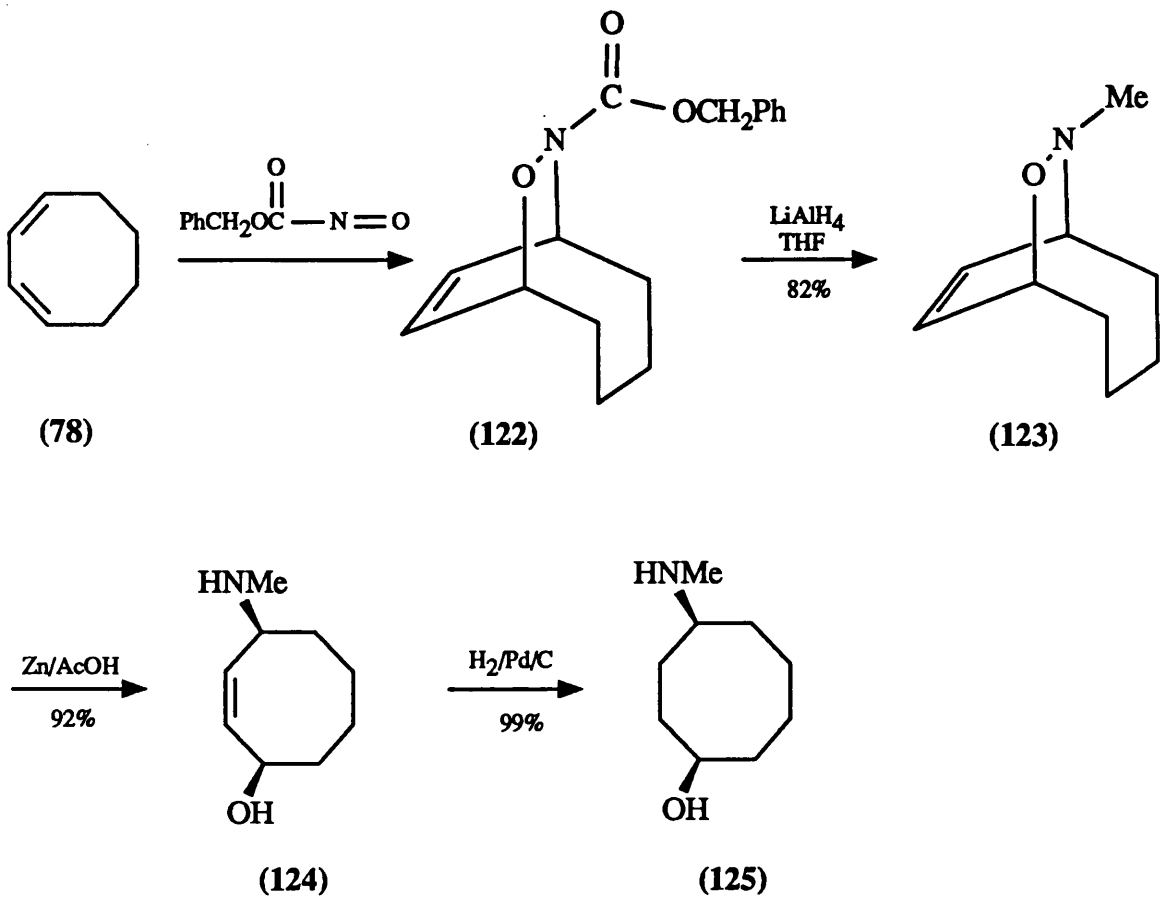
It was suspected that the reason for the lower yields of bicyclic amines obtained when chloroform was used might have

been due to traces of water and/or alcohol in the solvent. Chloroform for use in these experiments had been passed through a column of basic alumina,[40] a procedure which should remove both traces of water and ethanol present in the chloroform as a stabiliser. In contrast, there was no doubt as to the dryness of the dichloromethane solvent which was freshly distilled from calcium hydride.

2.3 PRODUCTION OF HOMOTROPANES AND HOMOTROP-7-ENES HAVING A POTENTIALLY REMOVABLE N-METHYL PROTECTING GROUP

As already mentioned in 2.1, Bathgate had experienced difficulties removing the benzyl group from N-benzyltrop-6-ene.[38] Since there was already literature precedent for the N-demethylation of nitrogen-bridged compounds (See Chapter 5), it was decided to attempt to synthesise homotropane (6) and homotrop-7-ene (126) to discover whether or not it was possible for them to be demethylated, and if so, to investigate the reason why N-debenzylation was so problematic.

The method of nitroso-cycloaddition was again utilised in the synthesis of homotropane (6) and homotrop-7-ene (126). Hence, the reaction of benzylnitrosoformate, generated *in situ* from benzyl N-hydroxycarbamate[36] and tetramethylammonium periodate,[38] with 1,3-cyclooctadiene (78) produced the Diels-Alder adduct (122) in 77% yield (Figure 2.15). On treatment with lithium aluminium hydride,



(78) (122) (123)

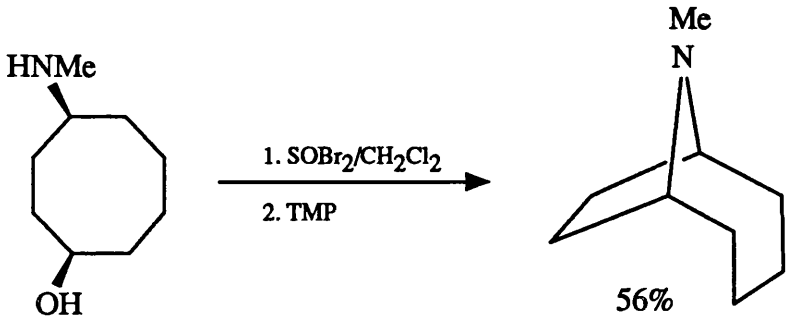
(124) (125)

Figure 2.15

(122) was converted into N-methyl-9-oxa-10-azabicyclo [4.2.1]deca-7-ene (123) in 82% yield. The O-N bond in this compound was cleaved efficiently using zinc in glacial acetic acid[41] forming *cis*-4-(methylamino)-2-cyclooctenol (124) in 92% yield. The unsaturated amino-alcohol was then catalytically hydrogenated almost quantitatively to *cis*-4-(methylamino)cyclooctanol (125).

Cyclisation of (125) was achieved using the same procedure as for the *cis*-benzylamino-alcohol (113) (Figure 2.13). Treatment of a solution of (125) in dry dichloromethane with thionyl bromide, followed by the addition of TMP, afforded N-methyl-9-azabicyclo[4.2.1]nonane, or homotropane,[23] (6)

in 56% yield. Homotropane was easily recognisable from the simple ^{1}H NMR spectrum and the ^{13}C NMR spectrum which exhibited the expected five signals. The picrate derivative of (6) had the same melting point as homotropane picrate synthesised by Cope.[23] The ^{13}C NMR spectrum was consistent with that recorded for homotropane by Barrelle[42] and Nádor[43] who both synthesised the compound by Cope's method.

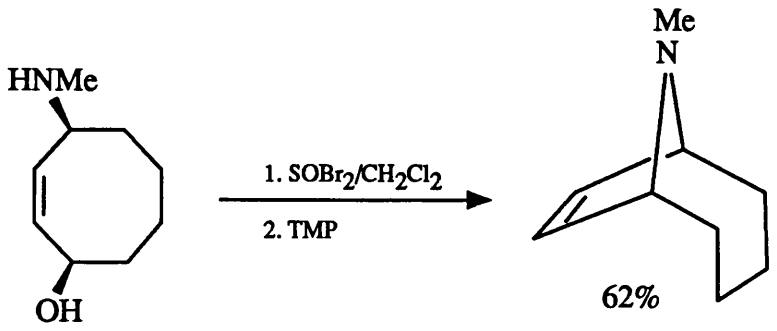


(125) (6)

Figure 2.16

Treatment of a solution of the unsaturated amino-alcohol (124) in dry dichloromethane with thionyl bromide followed by the addition of TMP produced N-methyl-9-azabicyclo [4.2.1]non-7-ene (126) in 62% yield. The two bridgehead protons appeared as a doublet of doublet of doublets (J=6.3Hz, 1.6Hz, 1.0Hz) at δ3.53, whilst the olefinic protons appeared as a doublet (J=1.0Hz) at δ5.66. These chemical shifts and coupling constants correlated well with those of the N-benzyl derivative (118). In addition, the ^{13}C NMR spectrum exhibited the expected five signals. The cyclisation of (124) to (126) paralleled that of the benzylamino-alcohol (117) to the bicyclic amine (118) in that the aziridine isomer which might have been expected to

have resulted from competitive 1,2-cyclisation was fortunately not detected.



(124) (126)

Figure 2.17

300MHz ^{1}H NMR spectrum of N-methyl-9-azabicyclo[4.2.1]non-7-ene (126) in $CDCl_3$.

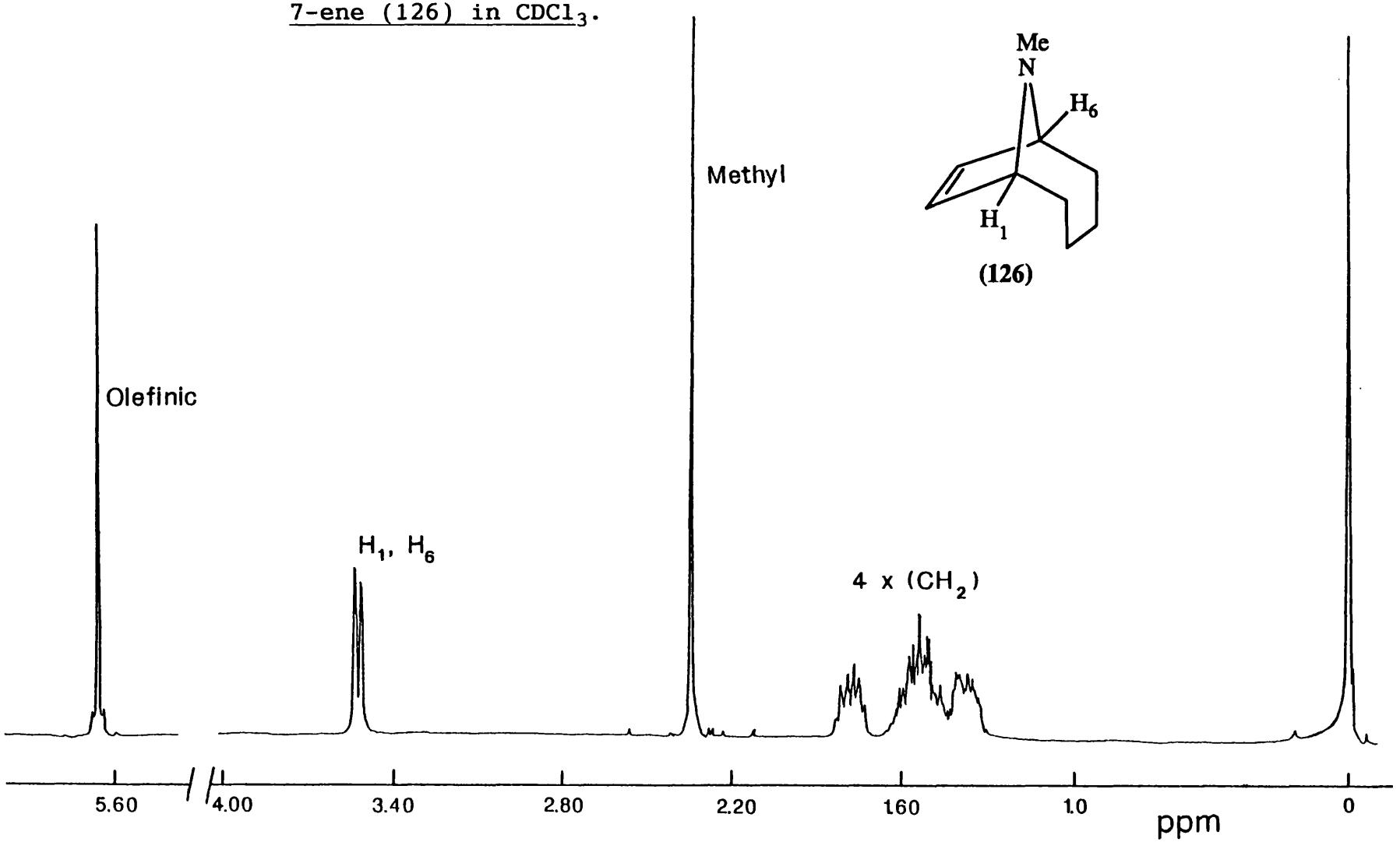
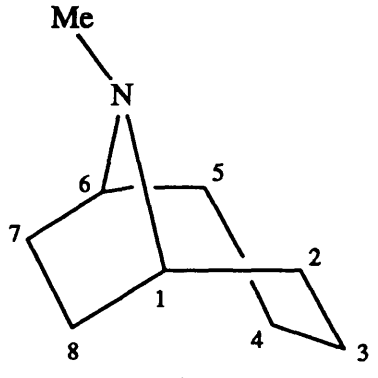


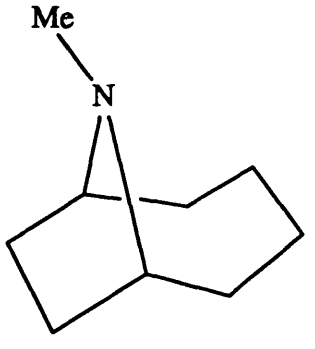
Figure 2.18

2.4 CONFORMATION OF THE HOMOTROPANES

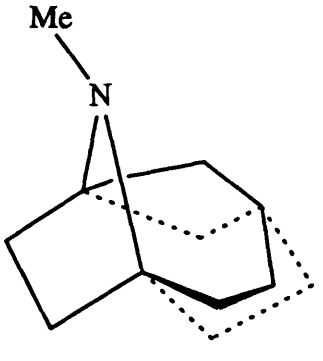
Barrelle[42] recorded and compared ^{13}C NMR spectra for a series of 9-oxa and 9-azabicyclo[3.3.1] and -[4.2.1] nonanes. The study yielded interesting results on the conformational equilibrium in each of these compounds which is a result of the flexibility of the seven-membered ring. It was concluded that the conformational equilibrium was displaced toward the boat form (6b) of the seven-membered ring for homotropane. This notion was later reinforced by Nádor.[43] Barrelle also proposed *gauche* conformations (6c) and (6d) for the homotropane substituted in position 2 by a



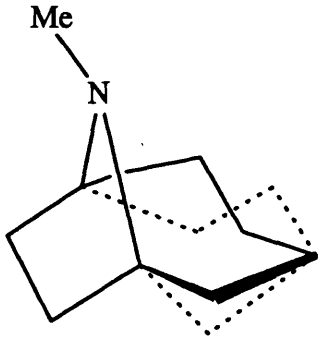
(6a) chair



(6b) boat



(6c) *gauche*



(6d) *gauche*

Figure 2.19

hydroxyl group in order to account for his experimental observations, and concluded that the methyl group was preferentially above the five-membered pyrrolidine ring. This parallels experimental observations which indicate that the N-alkyl group in the tropanes is also preferentially above the five-membered pyrrolidine ring, equatorial with respect to the six-membered piperidine ring which exists almost exclusively in the chair form.[44] Evidence for nitrogen inversion has, in fact, been observed in the study of low temperature ^{13}C NMR spectra of a few tropane derivatives.[45]

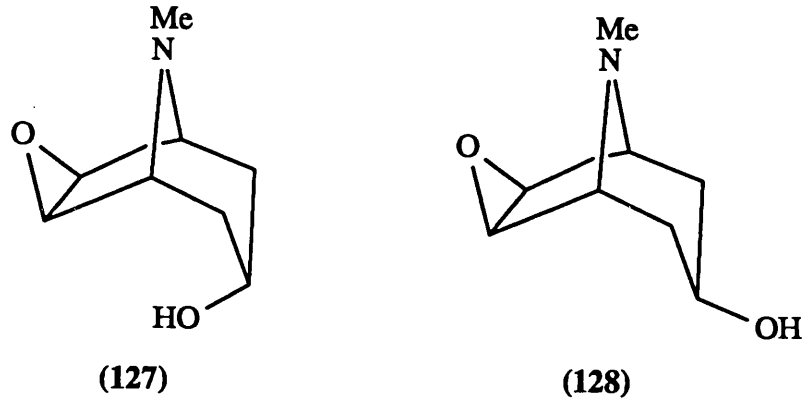
Although it is not the most energetically stable conformation, the homotropane structure is illustrated throughout this thesis as the chair form (6a) for the sake of clarity and as a comparison with the tropane structure (4) which exists almost exclusively in the chair form.

CONCLUSION

Homotropanes and homotrop-7-enes can be obtained in reasonable yields by the method of intramolecular cyclisation of *cis*-1,4-amino-alcohols. A nitroso-cycloaddition strategy is used to provide the required *cis*-stereochemistry, and the choice of nitroso-compound determines the nitrogen protecting group of the resulting homotropane or homotrop-7-ene. Removal of these nitrogen protecting groups (benzyl or methyl) will be discussed in Chapter 5.

Surprisingly, better yields are attained when the unsaturated *cis*-amino-alcohols are cyclised to construct the homotrop-7-ene ring system than when the saturated *cis*-amino-alcohols are cyclised to the supposedly less-strained homotropane ring system.

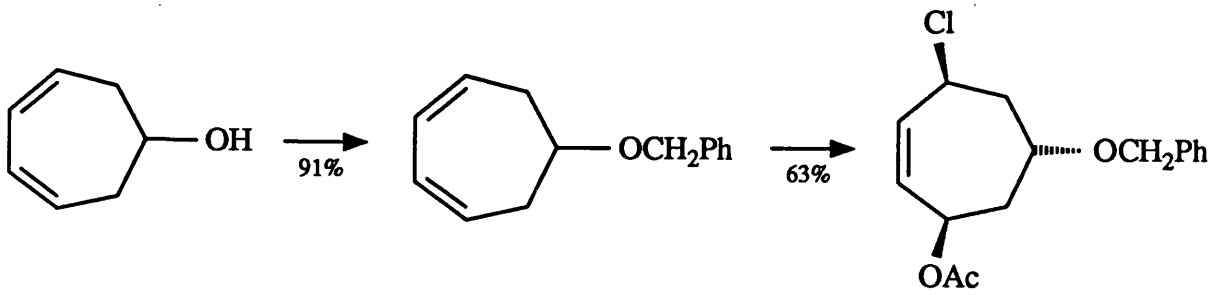
Very recently, Bäckvall[46] has reported the synthesis of scopine (127) and pseudoscopine (128) (Figure 2.20).



(127) (128)

Figure 2.20

The readily accessible 3,5-cycloheptadienol (129) was protected as its benzyl ether (130), and the palladium-catalysed 1,4-chloroacetoxylation, mentioned in 2.1, afforded chloro-acetate (131) in 63% yield. This compound was epoxidised prior to cyclisation to either scopine (127) or pseudoscopine (128).



(129) (130) (131)

Figure 2.21

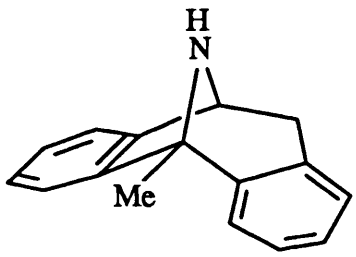
In the same way, the nitroso-cycloaddition strategy followed by intramolecular cyclisation is clearly adaptable to the production of a wider range of substituted homotropanes/enes by use of substituted 1,3-cyclooctadienes. Although not readily available, one example of a preparation of substituted 1,3-cyclooctadienes was reported by Cope[47] who prepared mono-and dibromo-1,3-cyclooctadienes which could be utilised as precursors to the desired substituted 1,3-cyclooctadienes.

Chapter Three

INTRAMOLECULAR CYCLISATION STRATEGIES TO 1-METHYL-HOMOTROPANES AND 1-METHYL-HOMOTROP-7-ENES

3.1 INTRODUCTION

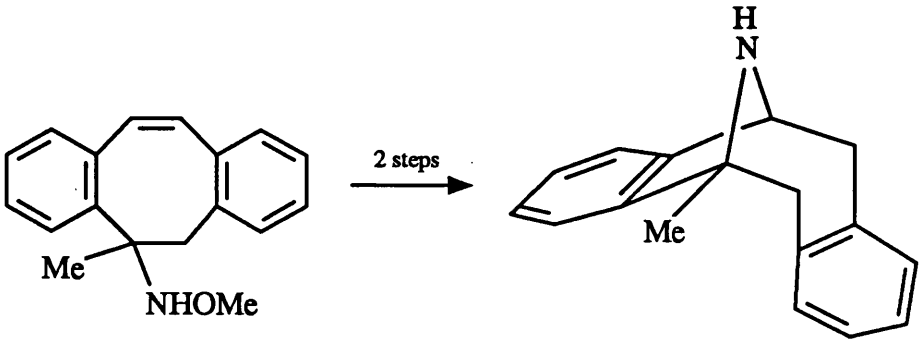
MK-801 (Figure 3.1) is a selective ligand for brain cyclidine (PCP) receptors which has attracted considerable recent attention as a potent anticonvulsive and neuroprotective agent.[48] It acts in the central nervous system by blocking specific calcium channels linked to the N-methyl-D-aspartate subtype of glutamic acid receptor.[49] Its construction is based on the 1-methylnortropane skeleton which remains unrecognised in nature to date.



(132) MK-801

Figure 3.1

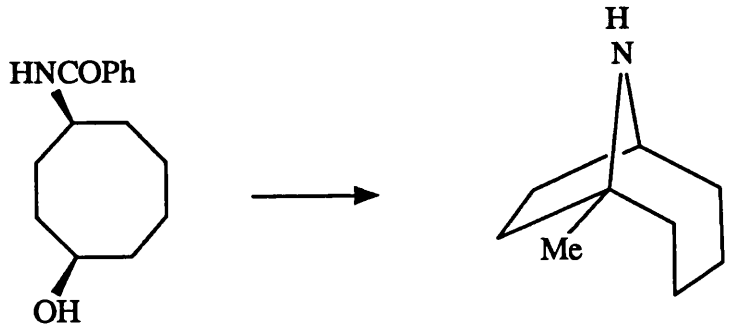
A ring homologue of MK-801 has recently been synthesised *via* base-catalysed ring-closure of (133).[50] Treatment of 5-hydroxylamino-dibenzo[*a*,*e*]cyclooctatriene (133) with potassium t-butoxide induced regiospecific ring closure, and reductive cleavage with zinc dust in glacial acetic acid removed the N-methoxy group to form the dibenzohomotropane (134) incorporating the 1-methylnor-homotropane skeleton.



(133) (134)

Figure 3.2

It became apparent that a modification of the *cis*-amido-alcohol (111) in Chapter 2 would give rise to compounds which could lead to 1-methylnorhomotropane (135) (Figure 3.3) conceivably by intramolecular cyclisation of nitrogen onto an sp^2 carbon of an exocyclic methylene group; this chapter describes the development of such an approach.

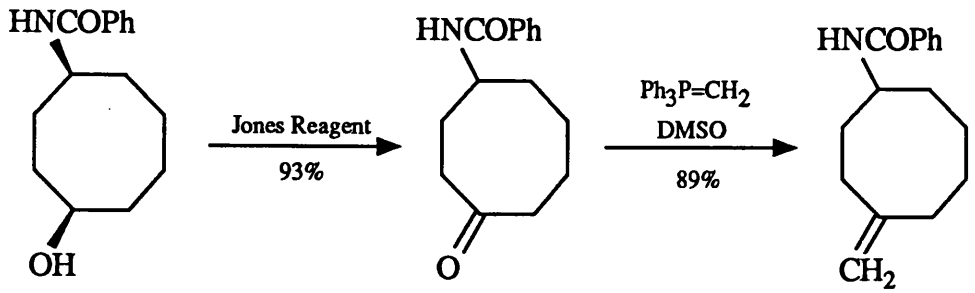


(111) (135) 1-Methyl-9-azabicyclo[4.2.1]nonane or 1-Methylnorhomotropane

Figure 3.3

3.2 SYNTHETIC APPROACH TO THE 1-METHYL-HOMOTROPANE SYSTEM

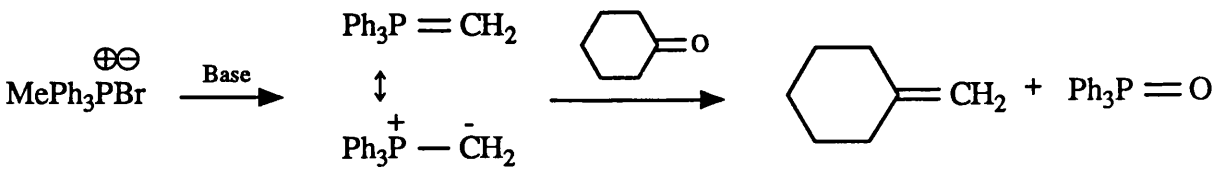
The strategy for production of an appropriate substrate (137) for intramolecular cyclisation to a 1-methylhomotropane involved Jones' oxidation of the amido-alcohol (111) to the amido-ketone (136) followed by a Wittig reaction (Figure 3.4).



(111) (136) (137)

Figure 3.4

Titration of a solution of the amido-alcohol (111) with Jones' reagent[51] gave the amido-ketone (136) in 93% yield. The IR data along with the ^1H and ^{13}C NMR data were entirely consistent with (136). The presence of the carbonyl group was confirmed by its ^{13}C NMR spectrum which exhibited a signal at δ217 and by its IR spectrum which absorbed strongly at 1695cm^{-1} within the range expected for a cyclooctanone. It was decided to generate the methylenetriphenylphosphorane Wittig reagent (139) required for the next step by treatment of methyltriphenylphosphonium bromide (138), in dimethyl sulphoxide, with the methylsulphinyl carbanion formed from dimethyl sulphoxide/ sodium hydride at 75 - 80°C.[52] This procedure, described



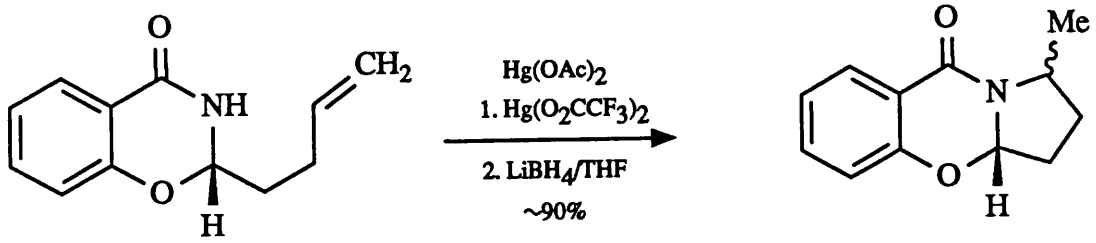
(138) (139) (140) (141)

Base	Yield of (140)
Bu^nLi/Et_2O	35-40%
NaH/DMSO	86%

Figure 3.5

by Corey, was utilised in preference to the classical method of Wittig,[53] since Corey obtained an 86% yield of methylenecyclohexane by this procedure which was more than twice the 35 - 40% yield obtained by Wittig (Figure 3.5). The subsequent Wittig methylenation of the amido-ketone (136) afforded N-benzoyl-4-methylenecyclo-octanamine (137) in 89% yield. The ^{13}C NMR spectrum revealed the *exo*-methylene (CH_2) signal downfield at δ111.8 and a quaternary (C) signal at δ150.9 which corresponded to the quaternary carbon adjacent to the *exo*-methylene group. The rest of the spectroscopic data was in accordance with (137).

Takacs[54] has reported the synthesis of substituted N-acyl pyrrolidines and piperidines *via* intramolecular amido-mercuration. It was found that amidal (142) underwent rapid amidocyclisation under the influence of a 1:1 mixture of mercuric acetate and mercuric trifluoroacetate to give a diastereomeric mixture of *cis* and *trans* amidals (143) in 90% yield (Figure 3.6). The high yield obtained in this mercury (II)-mediated amidocyclisation prompted the utilisation of the same mixture of mercury salts for the cyclisation of (137).



(142) (143)

Figure 3.6

Treatment of a solution of (137) in dry acetonitrile with a 1:1 mixture of mercuric acetate and mercuric trifluoroacetate followed by reduction with sodium borohydride in tetrahydrofuran led to the isolation of 1-methyl-N-benzoyl-9-azabicyclo[4.2.1]nonane (144) in 42% yield. The formation of (144) was apparent on inspection of the ^{13}C NMR spectrum which confirmed the loss of the olefinic carbons and the presence of a methyl carbon signal (δ28.1). The IR spectrum showed the absence of a secondary amide (no N-H stretch) and the ^{1}H NMR spectrum contained a broad singlet (at δ1.70) integrating to three protons. The broadening of the methyl signal was thought to be due to

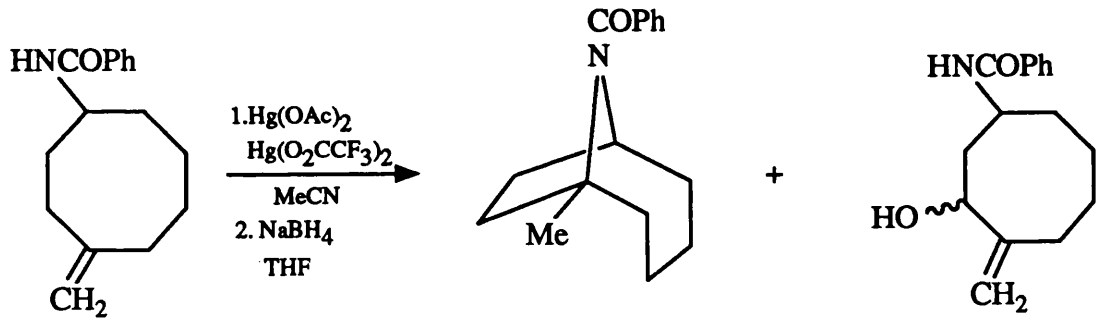
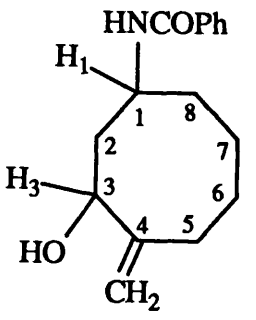


Figure 3.7

the slow rotation of the amide C-N bond. However, the cyclised product (144) was accompanied by a by-product, which appeared to be the hydroxylated derivative, 3-hydroxy-N-benzoyl-4-methylenecyclooctanamine (145) from ^{1}H and ^{13}C NMR spectral evidence.

The ^{13}C NMR spectrum of this compound displayed one less methylene (CH_2) signal but one more tertiary (CH) signal than the starting material (137). This tertiary carbon had a chemical shift of δ72.5 which suggested that an oxygen atom might be attached to it. The ^{1}H NMR spectrum supported this proposal because it contained an exchangable peak at δ4.50, most probably due to a hydroxyl proton, and a peak at δ4.30 thought to be an α-hydroxyl proton. Double-irradiation of the signal at δ4.30 revealed allylic coupling to the *exo*-methylene protons, so the hydroxyl group was located at either the C-3 or C-5 position (Figure 3.8). The double irradiation experiment also showed that the α-hydroxyl proton was coupled to a pair of geminal protons which would therefore be situated at either the C-2 or C-6 position. However, a 5-hydroxy compound would require each of the geminal protons at C-6 to appear as a doublet of doublet of doublet of doublets (dddd), whereas in reality each appeared (at δ2.00 - 2.09 and δ2.19 - 2.27) as a doublet of doublet of doublets (ddd). This is the multiplicity which would be expected for each of the geminal protons (H_a and H_b) at C-2 in the 3-hydroxy compound (145), and so this is the structure proposed on the basis of ^{1}H and ^{13}C NMR data. Unfortunately, only ^{1}H and ^{13}C NMR spectra were obtained and numerous attempts to repeat the experiment in order to obtain more material for complete characterisation of (145) have been unsuccessful.

Partial 300MHz ^1H NMR spectrum of 3-hydroxy-N-benzoyl-4-methylenecyclooctanamine (145) in $CDCl_3$, showing effects of double irradiaton of H_3.



(145)

Figure 3.8

Acyloxylation is known to occur with metallic acetates such as lead tetraacetate and mercuric acetate;[55] cyclooctene (146) and β-pinene (148) both form corresponding allylic acetates under these conditions (Figure 3.9). This was explained in terms of addition of the mercuric acetate to the double bond forming a cyclic mercurinium ion, capable of rearrangement to an allylic organomercurial, which is in turn solvolysed to allylic acetate.

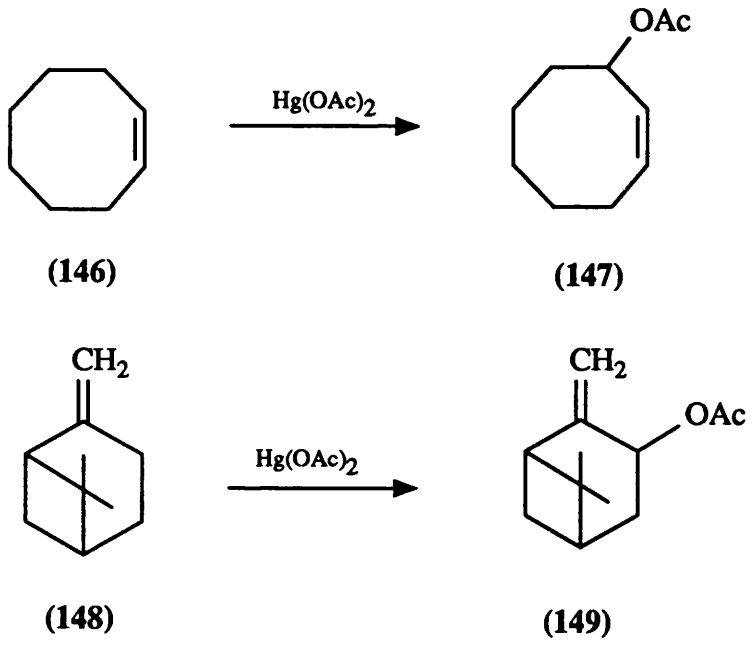


Figure 3.9

In the mercury (II)-mediated amidocyclisation of (137), the mercurinium ion can form *trans*- to the amide (150) or *cis*- to the amide (151). Only (150) has the required *trans*-stereochemistry for cyclisation to occur. The intermediate organomercurial acetate (152) formed can then be cleaved with sodium borohydride to yield the bridgehead methylated (144).

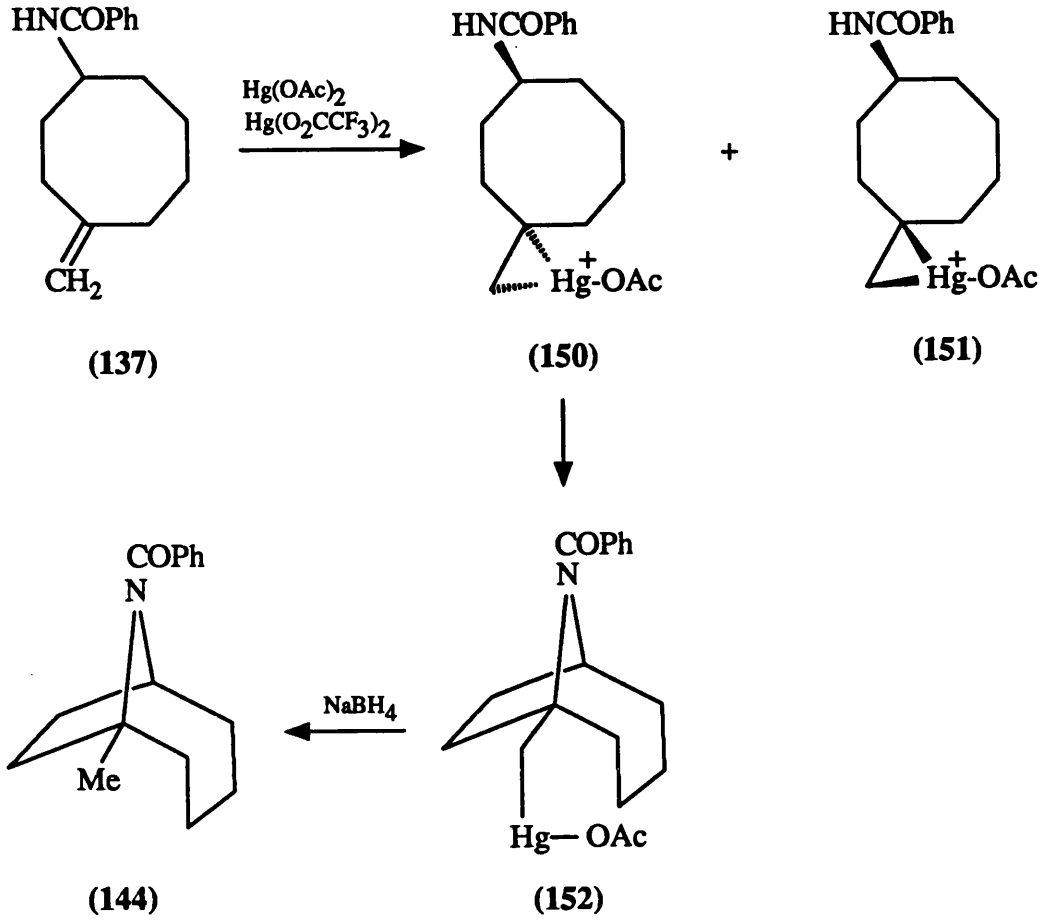
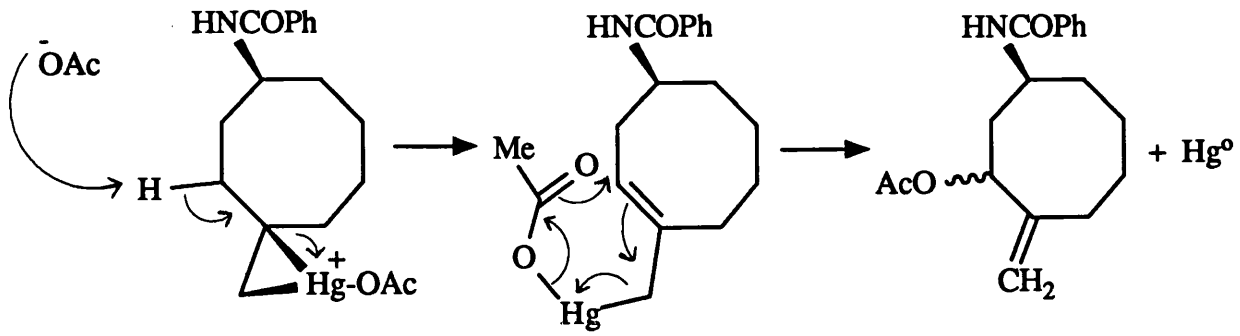


Figure 3.10

However, (151) possesses a *cis*-stereochemistry and cannot undergo intramolecular cyclisation. It is possible that this *cis*-amido-mercurial (151) gives rise to the hydroxylated product (145). Acetate ion acting as a base could abstract a proton from (151) resulting in the formation of (153) (Figure 3.11). The acetoxy group could be transferred intramolecularly to the 8-membered ring in a cyclic process involving a 7-membered transition state. This would lead to the production of the allylic acetate (154) and elemental mercury. The acetate transfer in such a



(151) (153) (154)

Figure 3.11

cyclic process might well be influenced by the amide group, giving rise to one major stereoisomer. Sodium borohydride is supposed to be unreactive towards esters. However, exceptions are known[56] and sodium borohydride can reduce esters in the presence of certain compounds,[57] for example lithium chloride or aluminium chloride. It is possible, then, that a reduction of the allylic acetate (154) with sodium borohydride resulted in the formation of the hydroxylated product (145).

Barluenga[53] has reported that the aminomercuration of *cis*-*cis*-1,5-cyclooctadiene (70) in the synthesis of N-aryl-9-azabicyclo[4.2.1]nonanes (Chapter 1) was found to be a reversible or irreversible process depending on the nature of the mercury (II) salt employed. Harding,[59] in his work on intramolecular amidomercuration, discovered that the use of mercuric acetate did not lead to equilibration, whereas mercuric trifluoroacetate did.

With this in mind, (137) was treated with mercuric (II) trifluoroacetate in the hope that the unwanted *cis*-amido-mercurial (155) formed might equilibrate to the required *trans*-amido-mercurial (157) resulting in an increased production of (158) which, after reduction with sodium borohydride, would give (144) in better yield. The result of this was a 93% yield of (144) which was subsequently reduced with lithium aluminium hydride to give (159) in 91% yield. 1-Methyl-N-benzyl-9-azabicyclo[4.2.1]nonane (159) was identified by inspection of its ^{1}H NMR spectrum which showed the bridgehead methyl group at δ1.21, the C-6 proton at δ3.33, and the benzyl-CH_2 protons as an AB quartet at δ3.84 (Figure 3.13). These chemical shifts compared favourably with those of N-benzyl-9-azabicyclo[4.2.1] nonane (116), the main difference being that the introduction of the bridgehead methyl group in (159) had broken the symmetry of the molecule causing the benzyl-CH_2 group to appear as an AB quartet rather than as a singlet in (116). The ^{13}C NMR spectrum of (159) exhibited a methyl carbon signal at δ29.3, and bridgehead carbon signals at δ57.1 (CH) and δ62.9 (C) which correlated well with the value of δ59.4 observed for the bridgehead carbon signals of the symmetrical (116).

Following the successful synthesis of 1-methyl-N-benzyl-9-azabicyclo[4.2.1]nonane (159), an attempt was made to synthesise the corresponding compound possessing an unsaturated two-carbon bridge.

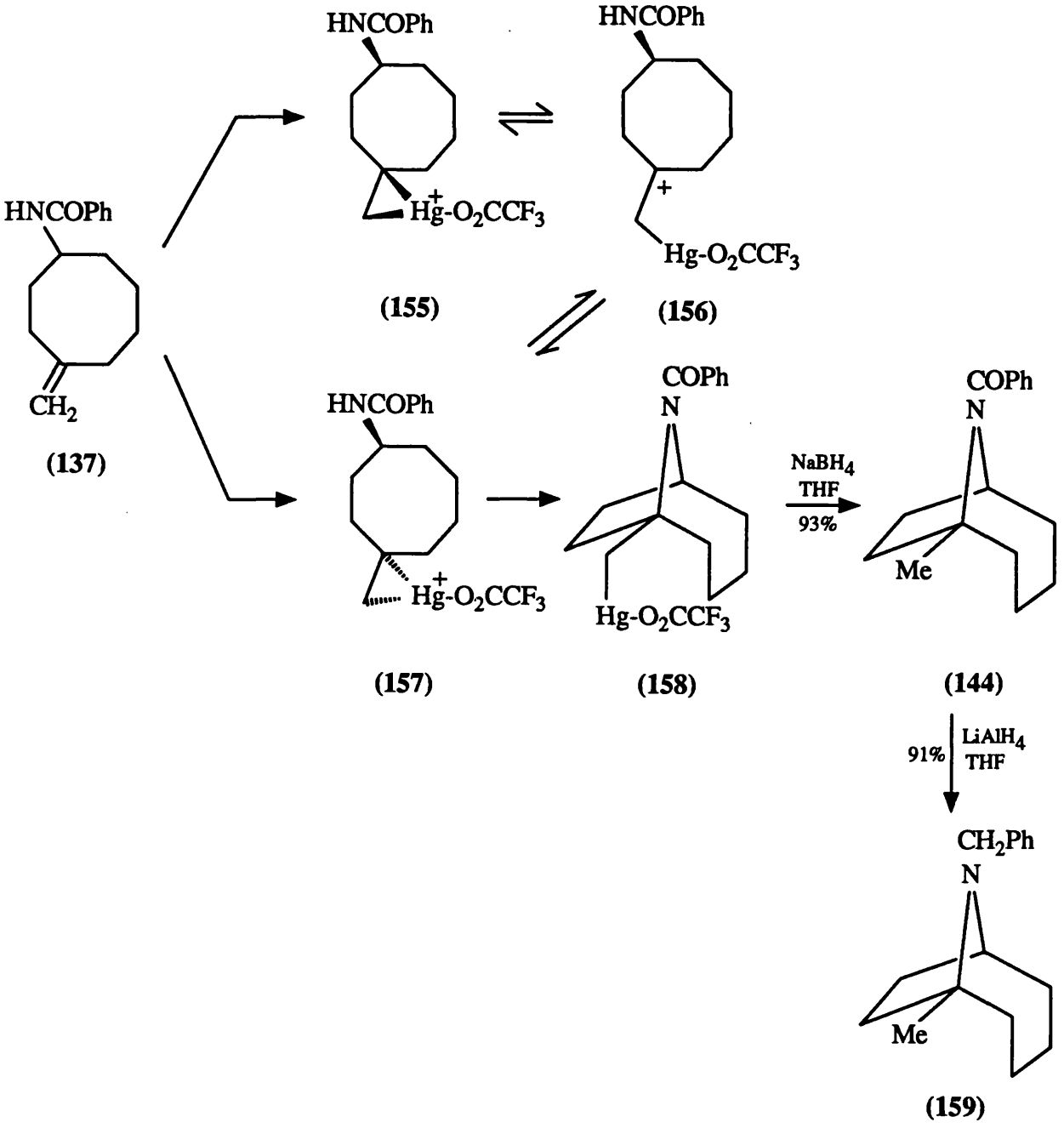

HNCOPh
CH2
(137)
HNCOPh
Hg+-O2CCF3
(155)
HNCOPh
+
Hg-O2CCF3
(156)
HNCOPh
Hg+-O2CCF3
(157)
COPh
N
Hg-O2CCF3
(158)
NaBH4
THF
93%
COPh
N
Me
(144)
91%
LiAlH4
THF
CH2Ph
N
Me
(159)

Figure 3.12

300MHz ^{1}H NMR spectrum of 1-methyl-N-benzyl-9-azabicyclo [4.2.1]nonane (159) in $CDCl_3$.

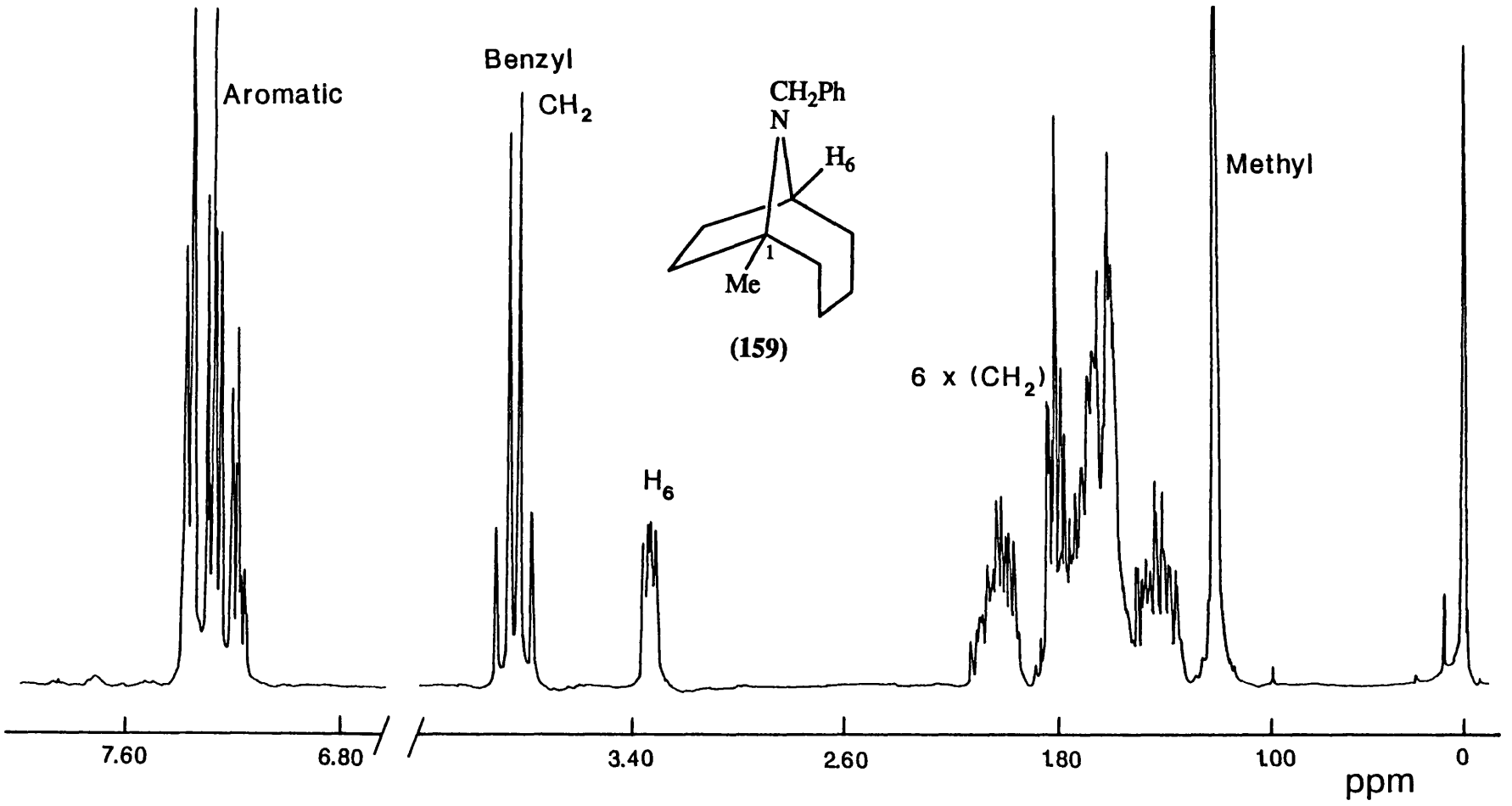


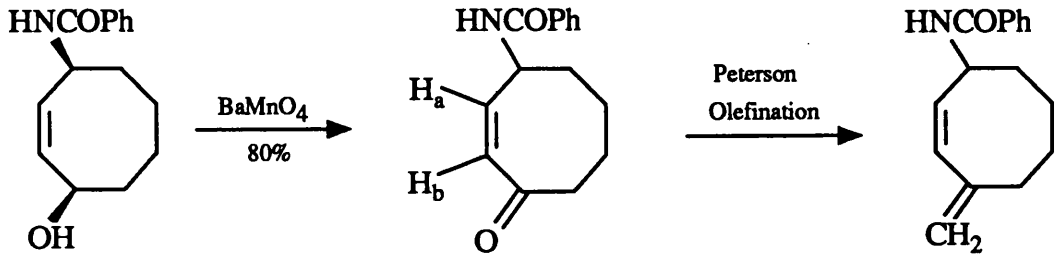
Figure 3.13

3.3 SYNTHETIC APPROACHES TO THE 1-METHYL-HOMOTROP-7-ENE SYSTEM

A similar methodology was applied to the synthesis of the 1-methyl-homotrop-7-ene system (Figure 3.14). A milder oxidising agent than Jones' reagent was sought for the oxidation of the allylic alcohol (110). Parish[60] used pyridinium chlorochromate in conjunction with 3,5-dimethylpyrazole for selective oxidation of steroidal allylic alcohols, whilst Attenburrow[61] used activated manganese dioxide for an oxidation of an allylic alcohol in his vitamin A synthesis. Although activated manganese dioxide is usually the preferred reagent for the oxidation of allylic alcohols, oxidation using barium manganate[62] has been reported to be superior to the use of activated manganese dioxide.[63] On the basis of this information, it was decided to compare manganese dioxide and barium manganate for the oxidation of (110).

It was found that manganese dioxide oxidised (110) to the α,β-unsaturated ketone (160) in 40% yield, whereas barium manganate achieved the same oxidation in 80% yield. The α,β-unsaturated ketone (160) was identified by its ^1H NMR spectrum in which the double bond proton H_a at δ6.19 coupled vicinally with both the α-amide proton at δ5.43 (J=5.7Hz) and the double bond proton H_b at δ6.03 (J=12.6Hz) to appear as a doublet of doublets (dd), whilst the double bond proton H_b coupled vicinally with the double bond proton H_a (J=12.6Hz), allylically with the α-amide proton at δ5.43

(J=1.8Hz), and exhibited a ω-coupling of 0.9Hz with one of the protons α- to the ketone, to appear as a doublet of doublet of doublets (ddd). Its ^{13}C NMR spectrum confirmed the presence of a carbonyl signal at δ203.7. The carbonyl IR absorption of the α,β-unsaturated ketone was coincident with that of the amide carbonyl (1660cm^{-1}) which was already present.



(110) **(160)** **(161)**

Figure 3.14

The Peterson olefination[64] was selected as an alternative to the Wittig reaction in order to produce the *exo*-methylene compound (161). It was decided to carry out the reaction of (160) with the trimethylsilylmethylmagnesium chloride Grignard reagent in the presence of cerium (III) chloride[65] to encourage 1,2-attack at the carbonyl group rather than the possible 1,4-attack at the double bond (Michael-type addition) which might occur in its absence. (Figure 3.15). It was hoped that 1,2-attack of the Grignard reagent to give (164) would result in the production of the β-hydroxysilane (165) on treatment with acid and that this would spontaneously eliminate water to produce the diene (161).

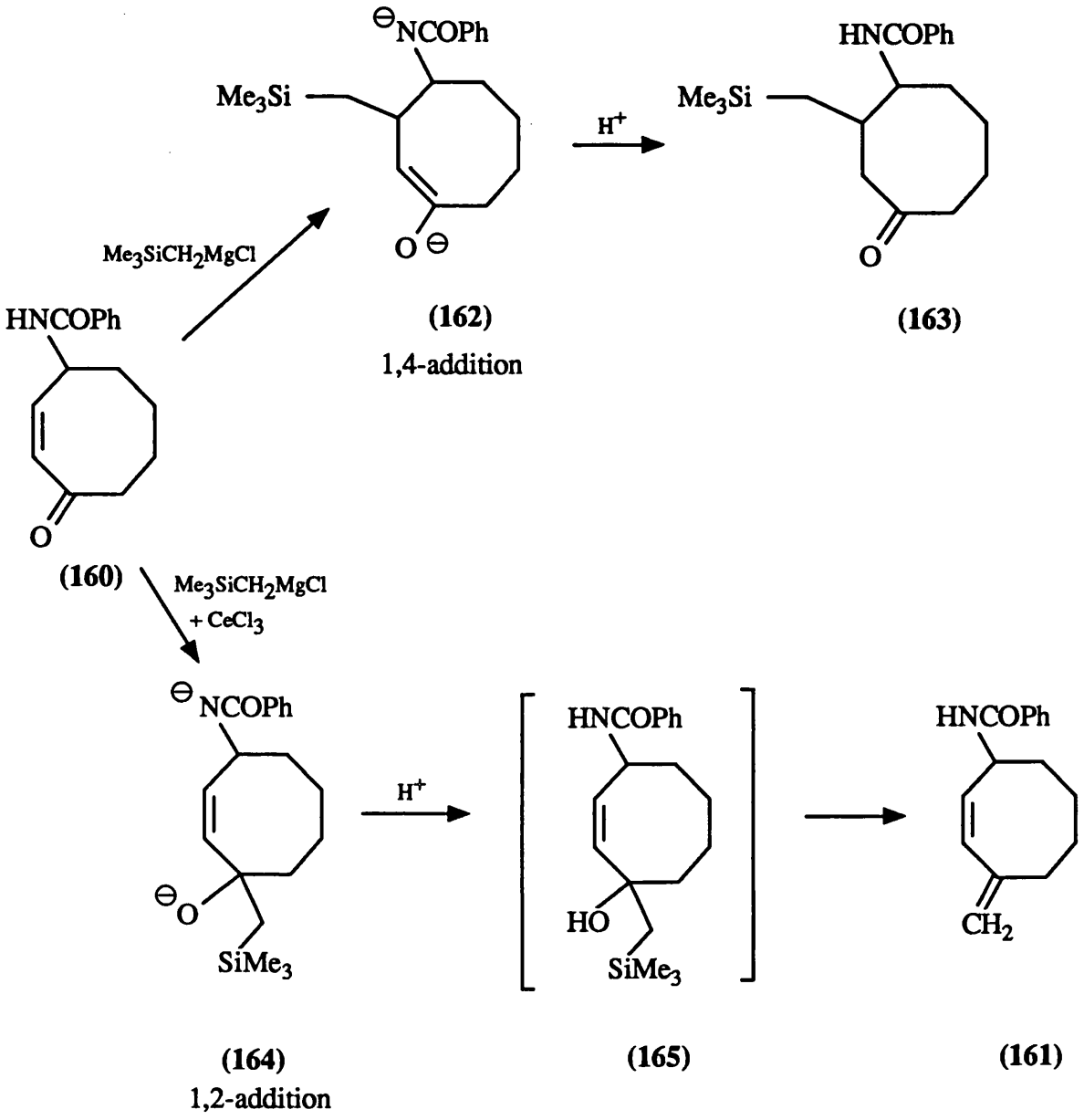
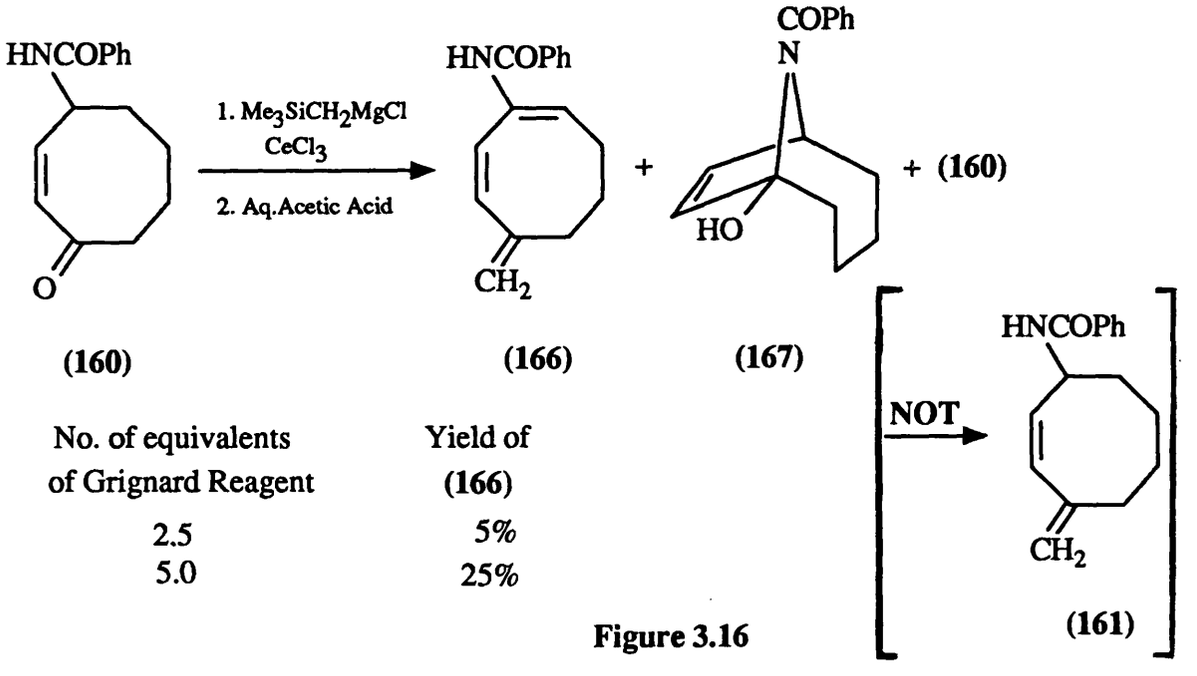


Figure 3.15

However, when this reaction was carried out using 2.5 equivalents of Grignard reagent and cerium (III) chloride, the triene (166) was isolated in only 5% yield together with 1-hydroxy-N-benzoyl-9-azabicyclo[4.2.1]non-7-ene (167) and the monocyclic starting material (160). Assuming that removal of the amide proton and subsequent cyclisation to the bicyclic coumpound (167) were rapid processes, the increase in formation of (161), *via* a bimolecular reaction, would require an increase in the concentration of Grignard

reagent to be added.

When the experiment was repeated using 5 equivalents of Grignard reagent and cerium (III) chloride (and under oxygen-free conditions in case O_2 was responsible for autoxidation) the triene was again isolated but in 25% yield together with (167) and (160). The yield of *exo*-methylene compound had increased, but the compound formed was



No. of equivalents of Grignard Reagent	Yield of (166)
2.5	5%
5.0	25%

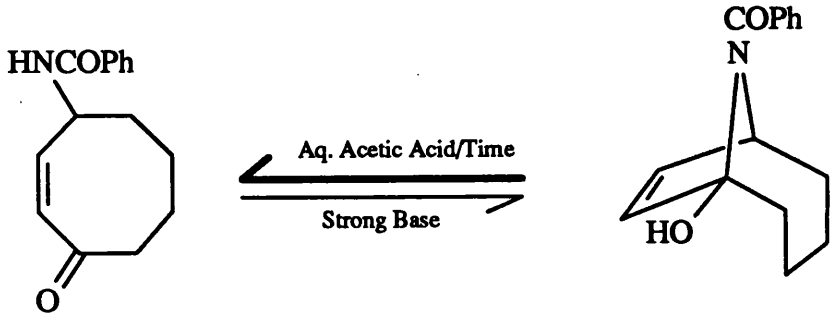
Figure 3.16

actually the triene (166) rather than the diene (161) which was needed (Figure 3.16). The triene (166) was identified by its ^1H NMR spectrum which showed that the endocyclic double bond protons at δ5.49 and δ6.15 coupled vicinally with each other (J=12.2Hz) to appear as a pair of doublets. The other endocyclic double bond proton at δ6.03 coupled vicinally (J=8.6Hz, 8.7Hz) with the geminal protons adjacent to it to

appear as a triplet. The *exo*-methylene protons appeared as broad peaks at δ4.95 and δ5.02, the broadness due to unresolved allylic coupling (<1Hz). The ^{13}C NMR spectrum of the triene (166) revealed the *exo*-methylene (CH_2) carbon signal downfield at δ120.3 and a quaternary (C) signal at δ147.3 which corresponded to the quaternary carbon adjacent to the *exo*-methylene group. The quaternary (C) signal at δ134.7 corresponded to the endocyclic carbon adjacent to the amide nitrogen. The remaining three endocyclic alkene carbons were seen as tertiary (CH) signals at δ120.1, δ122.1 and δ134.9.

In order to give some indication as to whether or not the cerium (III) chloride was responsible for the oxidation of any diene (161) which was formed in the reaction, the experiment was repeated in the absence of cerium (III) chloride. However, this resulted in the isolation of only starting material (160) and the bicyclic bridgehead-hydroxylated compound (167); neither 1,2- nor 1,4-addition was observed.

The bicyclic bridgehead-hydroxylated compound (167) was stable enough to be purified by column chromatography and characterised. Its ^{1}H NMR spectrum showed the double bond protons as a singlet integrating to 2 protons at δ5.84; there was no obvious allylic or vicinal coupling to the bridgehead proton H-6 at δ4.72 which itself appeared as a broad doublet (J=5.6Hz). The bridgehead-hydroxyl proton was observed as a broad, exchangeable singlet at δ5.71. The ^{13}C NMR spectrum



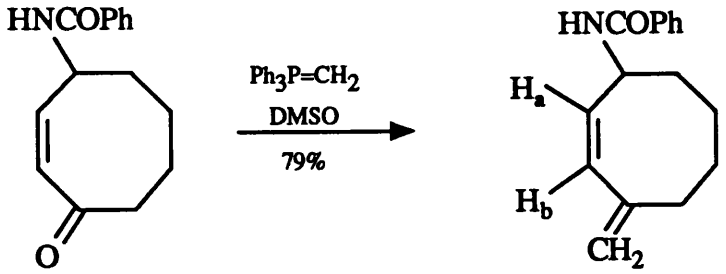
(160) (167)

Figure 3.17

showed the tertiary (CH) bridgehead carbon signal at δ63.2, the quaternary (C) bridgehead carbon signal at δ97.5, and the double bond carbons at δ129.9 and δ132.9. The bridgehead-hydroxylated compound (167) was found to be the less stable tautomer when equilibrated with the α,β-unsaturated ketone (160). A solution of (167) in $CDCl_3$ reverted completely to the α,β-unsaturated ketone (160) after three weeks when monitored by ^1H NMR. A sample of (167) was also found to revert to (160) in the presence of aqueous acetic acid (Figure 3.17).

The failure of the Peterson olefination to synthesise the required *exo*-methylene compound made it necessary to reconsider utilising the Wittig reaction. Mindful of the fact that the increase in the number of equivalents of Grignard reagent from 2.5 to 5 had increased the yield of the *exo*-methylene compound (166), it was decided to use a similar excess of Wittig reagent in the methylenation of (160) in order to minimise the competing intramolecular cyclisation reaction of (160) to (167). Surprisingly, the subsequent Wittig methylenation of the α,β-unsaturated

ketone (160) was successful and afforded the diene (161) in 79% yield.



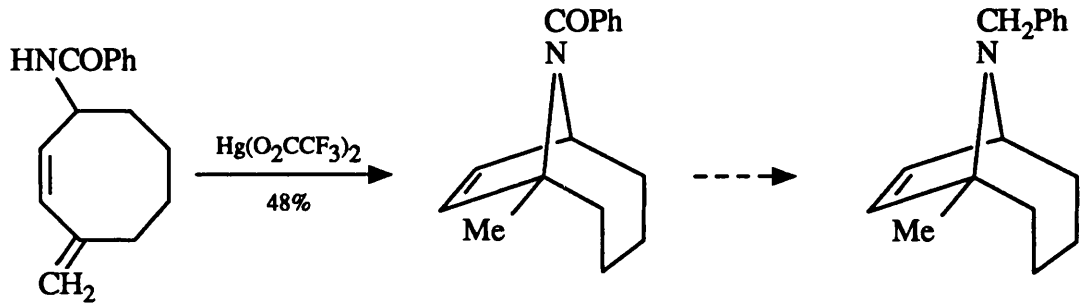
(160) (161)

Figure 3.18

The diene (161) was identified due to its similarity with the *exo*-methylene triene (166); the endocyclic double bond protons H_a and H_b at δ5.19 and δ6.22 respectively on the ^1H NMR spectrum showed mutual vicinal coupling (J=12.1Hz, cf.12.2Hz in (166)). However, H_a also coupled vicinally (J=6.7Hz) with the α-amide proton at δ5.62 to appear as a doublet of doublets (dd), and the doublet at δ6.22 assigned to H_b was broadened due to unresolved (<1Hz) allylic coupling. The *exo*-methylene protons appeared as broad peaks at δ4.90 and δ4.98 (cf. δ4.95 and δ5.02 in (166)), the broadness due to allylic coupling. The ^{13}C NMR spectrum of (161) showed the *exo*-methylene (CH_2) carbon signal downfield at δ118.9 (cf. δ120.3 in the triene (166)) and a quaternary (C) signal at δ147.3 (cf. δ146.1 in the triene (166)) which corresponded to the quaternary carbon of the exocyclic double bond. The two endocyclic alkene (CH) carbons appeared at δ129.7 and δ134.4.

Since the treatment of (137) with mercuric trifluoroacetate

and the subsequent reduction with sodium borohydride had resulted in such a high yield of the 1-methyl derivative (144), it was decided to use the same conditions for the amidocyclisation of (161). The result of treating a solution of (161) in acetonitrile with mercuric trifluoroacetate, and subsequent reduction with sodium borohydride, was a 48% yield of the unsaturated analogue (168). The reaction had obviously been complicated by the presence of two double bonds in the molecule.



(161) (168) (169)

Figure 3.19

The 1-methyl homotrop-7-ene derivative (168) was identified by its similarity to the saturated analogue (144); the ^{1}H NMR spectrum showed the bridgehead methyl protons at δ1.76 (cf. δ1.70 in (144)). The bridgehead proton H-6 and double bond protons of (168) were part of an ABX system and were studied by double resonance. Irradiation of the double bond (at δ5.58 - 5.62) led to collapse of the signal at δ4.70 (brddd, J=5.4Hz, J≈2.2Hz, J=1.6Hz) to (brdd, J=5.4Hz, J=1.6Hz). Irradiation of the bridgehead proton H-6 at δ4.70 collapsed the signals due to the double bond protons to a simple AB system (J≈6.1Hz). The ^{13}C NMR spectrum displayed the methyl

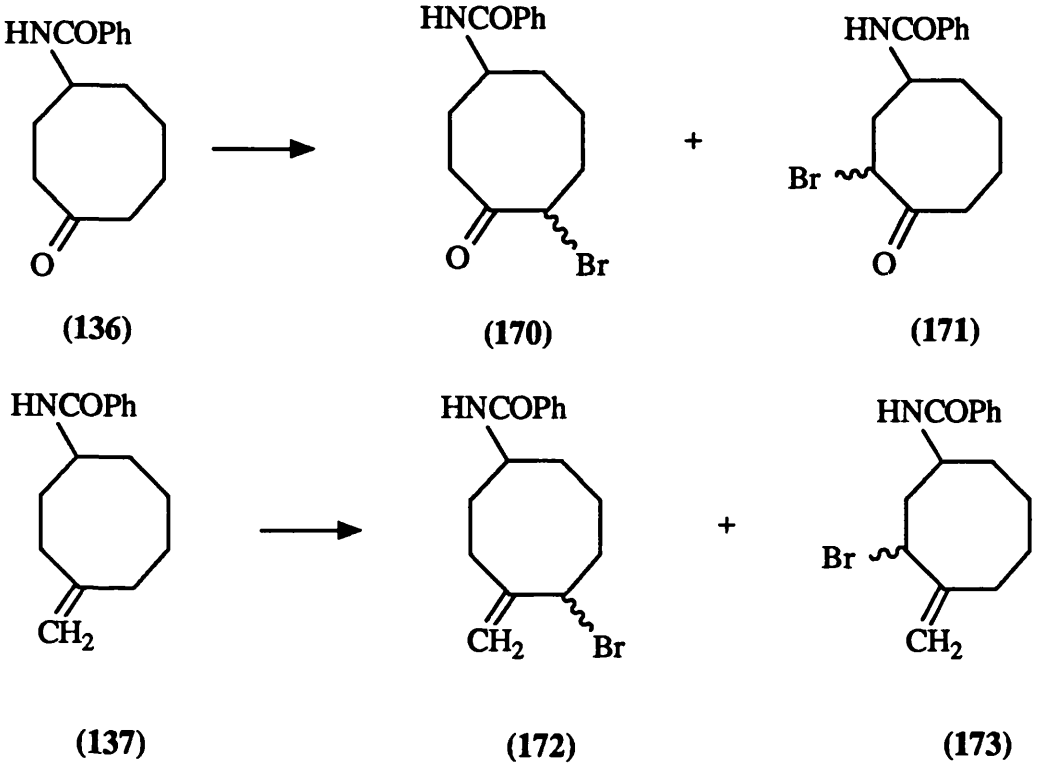
carbon signal at δ24.1 (cf. δ28.1 in (144)), the tertiary (CH) bridgehead carbon at δ65.4 (cf.δ60.7 in (144)) and the quaternary (C) bridgehead carbon at δ69.9 (cf. δ65.0 in (144)). The lithium aluminium hydride reduction of the amide (168) to the amine (169) was not attempted, but would be expected to result in formation of the amine (169) in good yield.

3.4 CONCLUSION

This chapter has described a practical method for the synthesis of 1-methyl homotropanes in high yield. Introduction of unsaturation to the two-carbon bridge resulted in a lower, but acceptable yield of the 1-methyl homotrop-7-ene skeleton. The factor responsible for the lower yield was most likely the presence of two double bonds in the substrate, resulting in the potential formation of two discrete cyclic mercurinium ions on treatment with mercury (II).

The methods described are clearly adaptable to the production of a wider range of substituted homotropanes/ enes both by use of substituted cyclooctadienes (as mentioned in Chapter 2) or more readily by further functionalisation of intermediates in the schemes. For example, amido-ketone (136) could be further functionalised by halogenation in the positions α- to the carbonyl[66] *via* enolate formation. Alternatively, the *exo*-methylene compound (137) could be further functionalised by allylic

halogenation.[67] (Figure 3.20).



(136) (170) (171)

(137) (172) (173)

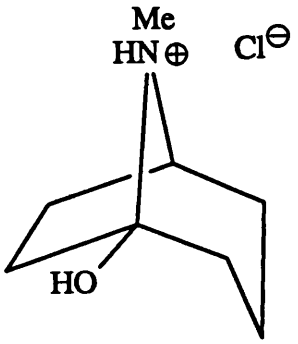
Figure 3.20

Chapter Four

MONO-/BICYCLIC TAUTOMERISM IN 4-AMINOCYCLOOCTANONES AND 4-AMINOCYCLOOCTENONES

4.1 INTRODUCTION

Physoperuvine is a tropane alkaloid isolated from the roots of *Physalis peruviana*, a member of the *Solanaceae* plant family. It has been shown to exist exclusively in the

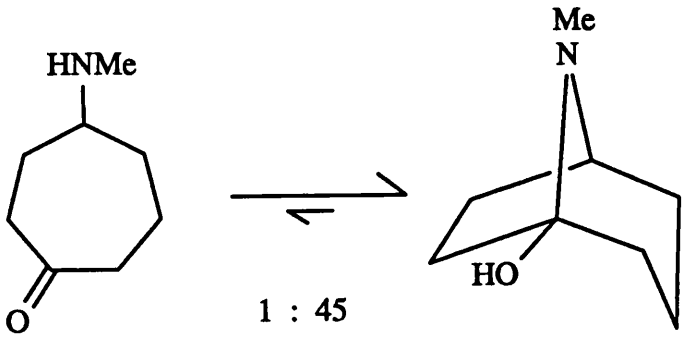


Physoperuvine Hydrochloride

(174)

Figure 4.1

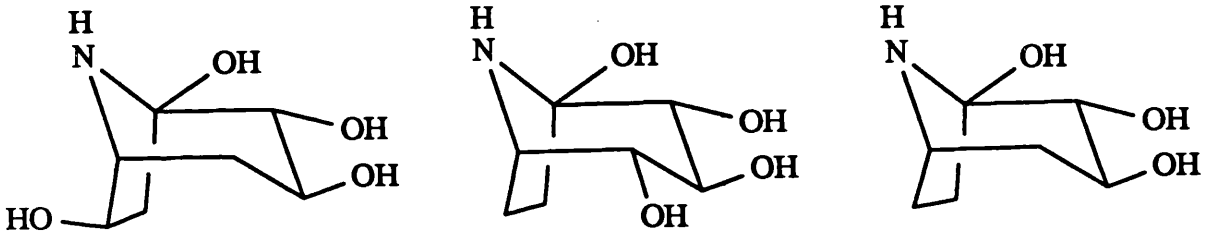
bicyclic amino-alcohol form (174) as the hydrochloride salt, but circular dichroism measurements and IR data suggested the existence of a tautomeric equilibrium (175)=(176) for the free base.[68] The ratio of the amino-ketone (175) to the amino-alcohol (176) was estimated to be 1:45 (Figure 4.2).



(175) **(176)**

Figure 4.2

More recently, three new alkaloids of the nortropane family, called *calystegines* B_1 (177), B_2 (178), and A_3 (179), have been isolated from the roots of *Calystegia sepium*; they are supposed to enhance the growth of the *Rhizobium* species of bacteria.[69] These *Calystegines* are hydroxylated derivatives of the 1-hydroxy-8-azabicyclo[3.2.1]octane (1-hydroxynortropane) skeleton, and exist entirely in the bicyclic form.[70] No reason was given for the absence of tautomerism except for a suggestion that the presence of substituents on the seven-membered ring might favour the shift towards the cyclised form.



(177) B_1 (178) B_2 (179) A_3

Figure 4.3

The existence of a tautomeric equilibrium in physoperuvine prompted an investigation of possible tautomerism in homotropanes. To this end, synthetic routes towards higher homologues possessing the 1-hydroxy-9-azabicyclo[4.2.1] nonane (1-hydroxynorhomotropane) skeleton were sought; the approach was based on intramolecular cyclisation of 4-aminocyclooctanones.

4.2 A POTENTIAL ROUTE TO HIGHER HOMOLOGUES OF PHYSOPERUVINE

A decision was reached to utilise the Diels-Alder cycloaddition of singlet oxygen[71] as a means of synthesising 4-hydroxycyclooctanone (183) and convert this precursor into a series of N-substituted aminocyclooctanones which could undergo intramolecular cyclisation to their respective bicyclic tautomers. Thus, addition of singlet oxygen to 1,3-cyclooctadiene (78)[72] afforded 9,10-dioxabicyclo[4.2.2]deca-7-ene (180) in 26% yield. Treatment of (180) with triethylamine gave 1-hydroxy-9-oxabicyclo[4.2.1]non-7-ene (181) in 80% yield, whereas reduction of (180) with diimide [71] followed by treatment with

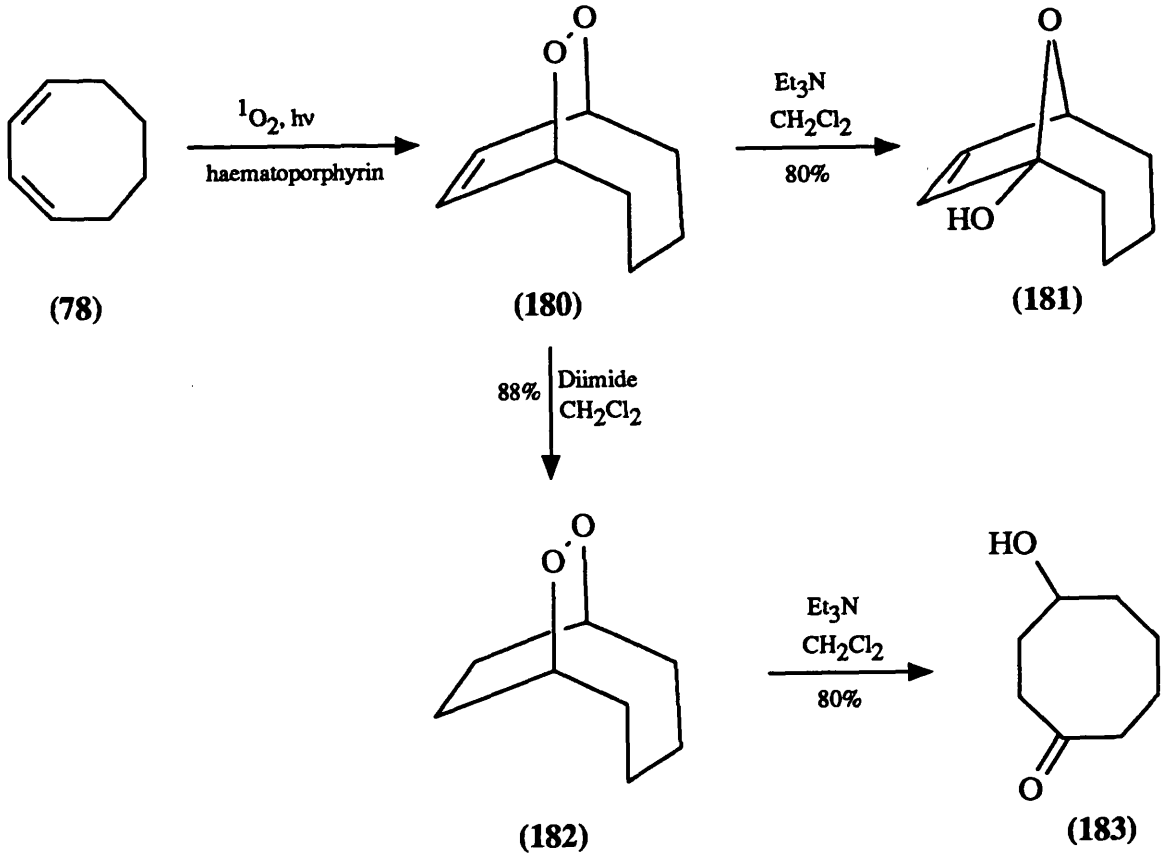
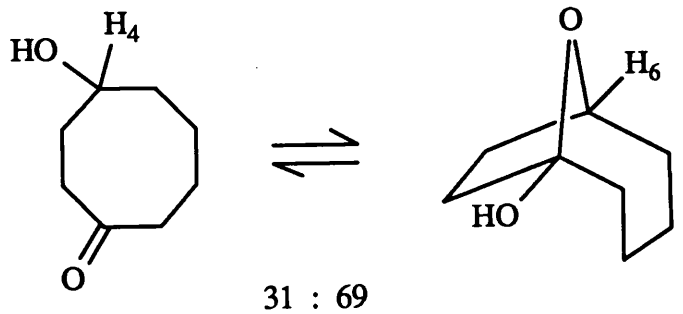


Figure 4.4

triethylamine gave 4-hydroxycyclooctanone (183) in 70% overall yield from (180) (Figure 4.4).

The hydroxy-ketone (183) was formerly considered to be the monocycle; [73] Barrelle and Apparu assigned a signal at δ4.4 on the ^{1}H NMR spectrum to H-4, and that at δ3.8 to the hydroxyl proton. However, it has been shown that the signal at δ3.83 is not due to an exchangeable proton but is, in fact, assigned to H-4. A signal at δ4.52 is assigned to the bridgehead proton, H-6, of the bicyclic form (184). Sixteen individual signals were exhibited on the ^{13}C NMR spectrum including the carbonyl signal (δ217.0) and the C-O carbon signal (δ70.7) of (183) together with the quaternary (C) bridgehead signal (δ108.3) and the tertiary (CH) bridgehead signal (δ76.0) of its bicyclic tautomer. Subsequent analysis of the ^{1}H and ^{13}C NMR spectroscopic data indicated that (183) was the minor tautomer in equilibrium with 69% of the bicyclic form (184) (Figure 4.5).

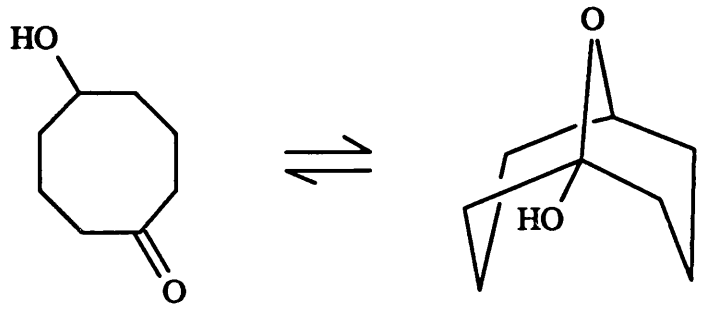


(183) (184)

Figure 4.5

This kind of hydroxy-ketone/hemiacetal tautomerism has also been observed in 5-hydroxycyclooctanone (185) which exists

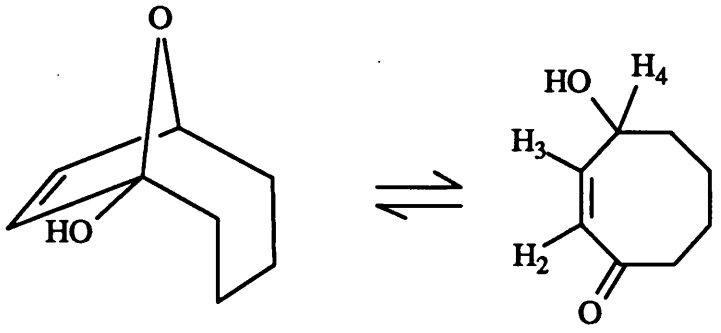
almost completely (96%) in the transannular hemiacetal form (186).[74]



(185) (186)

Figure 4.6

The unsaturated hemiacetal (181) had formerly been thought to be formed irreversibly from (187),[72] but, on closer inspection of the ^{1}H and ^{13}C NMR spectra, signals were observed which corresponded to the presence of about 5% of the monocyclic tautomer (187) at equilibrium. The monocyclic form (187) showed signals on the ^{1}H NMR spectrum consistent with those of an α,β-unsaturated ketone system; H-3 at δ6.38 showed vicinal coupling with both the α-hydroxyl proton, H-4, at δ5.20 (J=5.5Hz) and H-2 at δ6.03 (J=12.7Hz) to appear as a doublet of doublets (dd), while H-2 coupled vicinally with H-3 (J=12.7Hz), allylically with the α-hydroxyl proton, H-4, (1.9Hz), and exhibited a ω-coupling of 0.8Hz with one of the protons α-to the ketone, to appear as a doublet of doublet of doublets (ddd). The ^{13}C NMR spectrum confirmed the presence of the ketone by showing a carbonyl signal at δ202.0.



(181) (187)

95 : 5

Figure 4.7

The hydroxy-ketone/hemiacetal tautomeric equilibrium was finely balanced, but the greater preference for the bicyclic form (181) on incorporation of the shorter C=C double bond into the ring system (cf. 184) was unexpected. It was speculated that the incorporation of a double bond into a 4-aminocyclooctanone ring system might also shift the equilibrium towards its bicyclic form. Consequently, a scheme was sought which would provide a route to both 4-aminocyclooctanones and 4-aminocyclooct-2-enones so that a comparison of their tautomeric equilibria could be made.

The proposed scheme for the synthesis of higher homologues of physoperuvine (Figure 4.8) involved reacting the tautomeric mixture of hemiacetal (181) and hydroxy-ketone (187) with ethane-1,2-diol and acid catalyst to form the hydroxy-acetal (188). Treatment with *p*-toluenesulphonyl chloride would form the tosylate (189) which, when treated with a nucleophile such as azide ion, would give the azide (190). Reduction of the azide and subsequent removal of the acetal protecting group would produce 4-aminocyclooct-2-

enone (191) which would be expected to exist in equilibrium with its bicyclic tautomer (192). Similarly, treatment of the tosylate (189) with a primary amine followed by

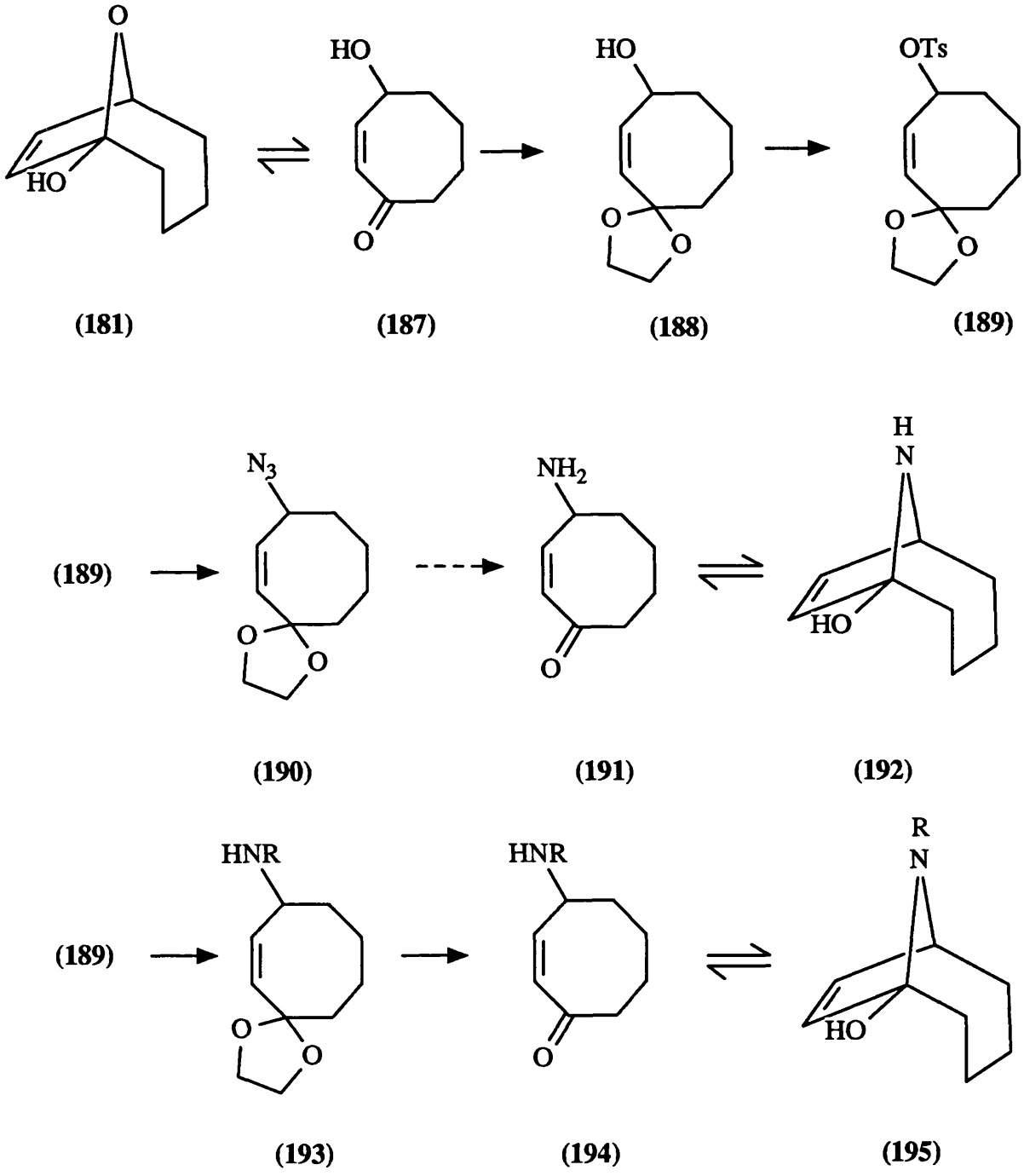


Figure 4.8 Proposed scheme for synthesis of "Homophysoperuvines."

removal of the acetal protecting group would give rise to an N-substituted 4-aminocyclooct-2-enone (194) together with its N-substituted bicyclic tautomer. By using the same scheme starting with the tautomeric mixture of saturated hydroxy-ketone (183) and hemiacetal (184), it was anticipated that the synthesis of the corresponding saturated 4-aminocyclooctanones could be achieved.

However, reaction of the tautomeric mixture of hemiacetal (181) and hydroxy-ketone (187) with ethane-1,2-diol and acid catalyst, followed by tosylation[75] and subsequent treatment with sodium azide, yielded not the required azide (190) but a crystalline compound whose IR spectrum showed the absence of an azide absorption (2000 - 2200cm^{-1}). Its ^{13}C NMR spectrum exhibited 10 signals, but the furthest downfield was that of a quaternary (C) carbon at only δ108.0. The absence of both double bond carbon signals in the ^{13}C NMR and azide absorption in the IR spectrum suggested that the azide had undergone intra- or intermolecular cycloaddition with the double bond. Full characterisation was thwarted by the complexity of the ^{1}H NMR spectrum, but eventually the structure of this crystalline compound was elucidated by employing the technique of X-ray crystallography. This showed the compound to be a tetracyclic triazoline (198) (Figure 4.9 and 4.10). Hence, there had been an intramolecular cycloaddition of the azide to the double bond, but the azide responsible had to have been derived from the primary tosylate (197) which, in turn, had to have arisen from the primary alcohol (196). Thus, reaction of

ethane-1,2-diol with the tautomeric mixture (181)/(187) had probably given rise to the hydroxy-acetal (188) which, in the presence of acid catalyst, underwent transannular cyclisation to yield (196). This is presumably more stable than (188) since it seems to be the sole product.

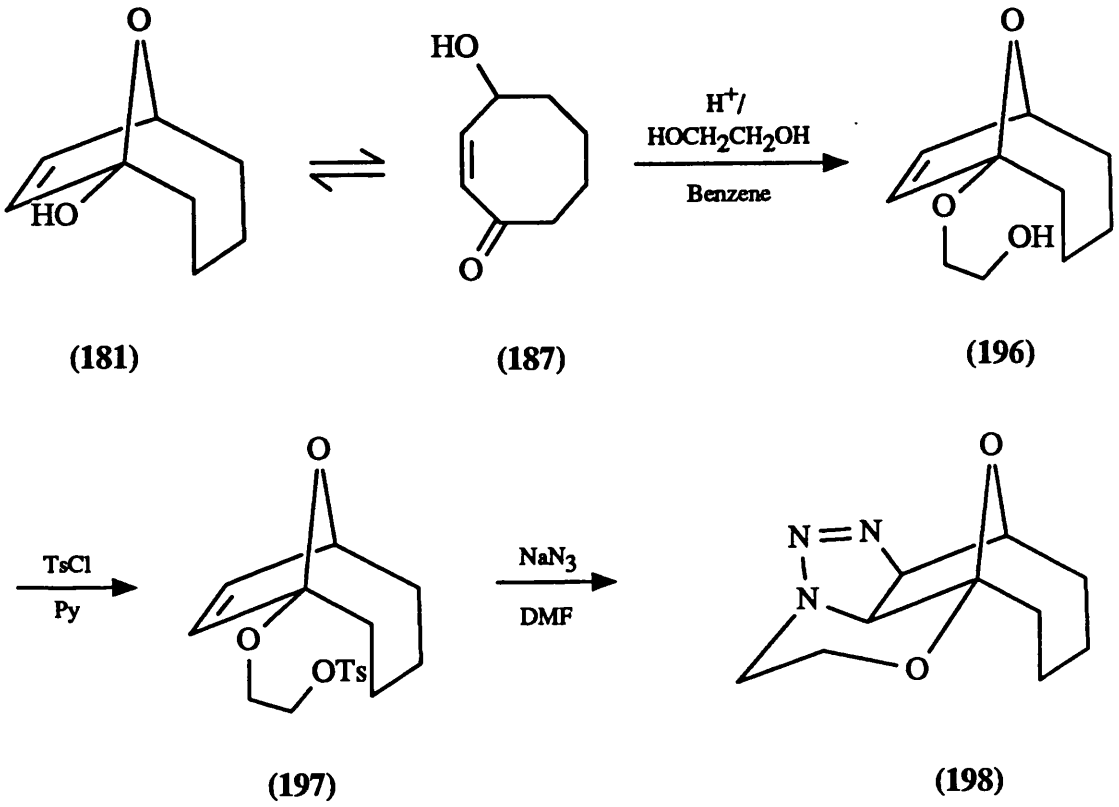
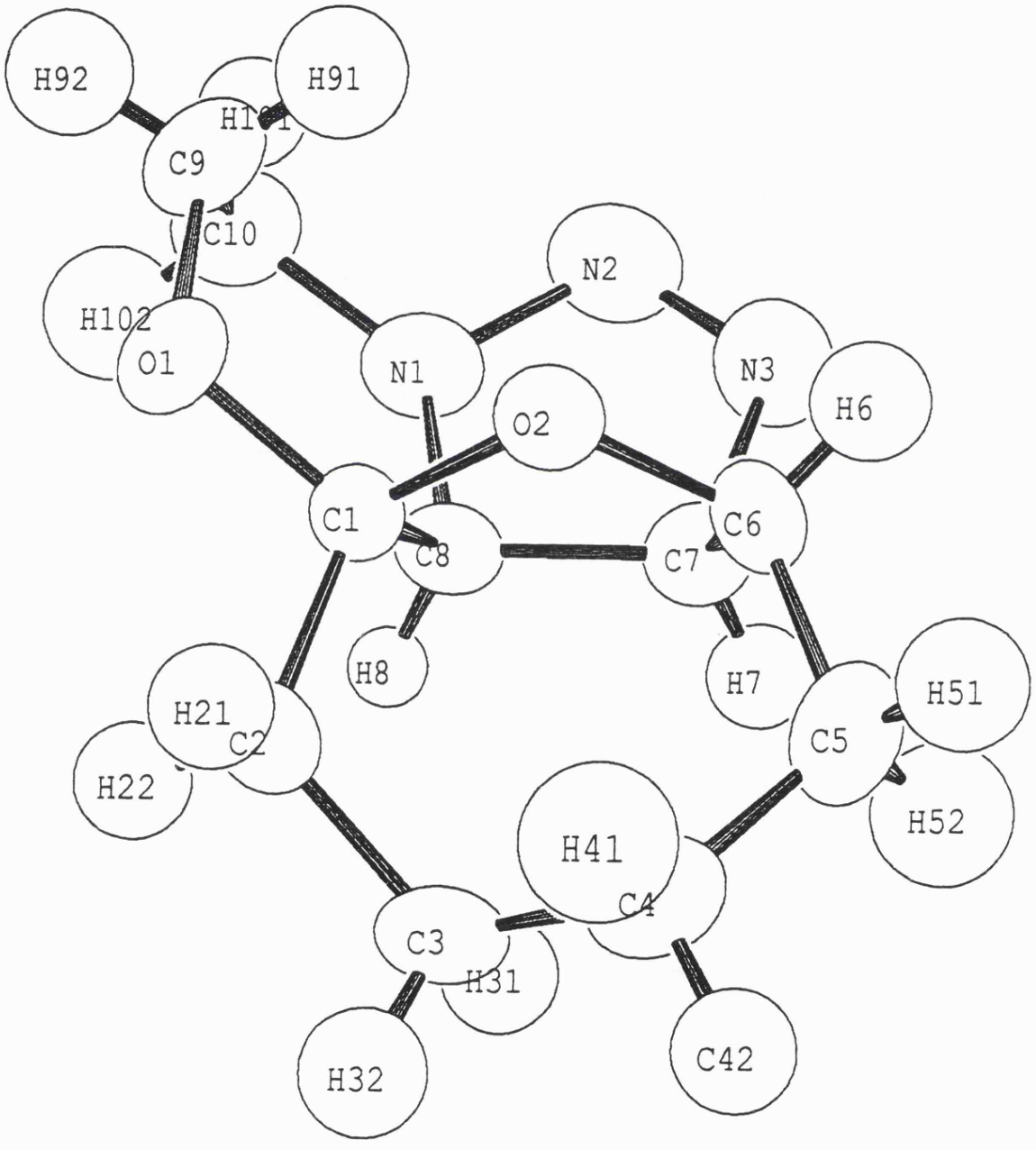


Figure 4.9

Tosylation of a secondary hydroxyl group as in (188) was expected to have taken a few days (cf. formation of 4-oxocyclooctanyl tosylate (199) from 4-hydroxycyclooctanone (183), later). However, the presence of a primary hydroxyl group in (196) explained the rapid tosylation which was observed; the reaction went to completion in less than 2 hours. The tosylate so formed was converted to the azide which subsequently underwent 1,3-dipolar addition to the double bond yielding the tetracyclic triazoline (198).

X-Ray Crystal Structure of Tetracyclic Triazoline (198).



(198)

Figure 4.10

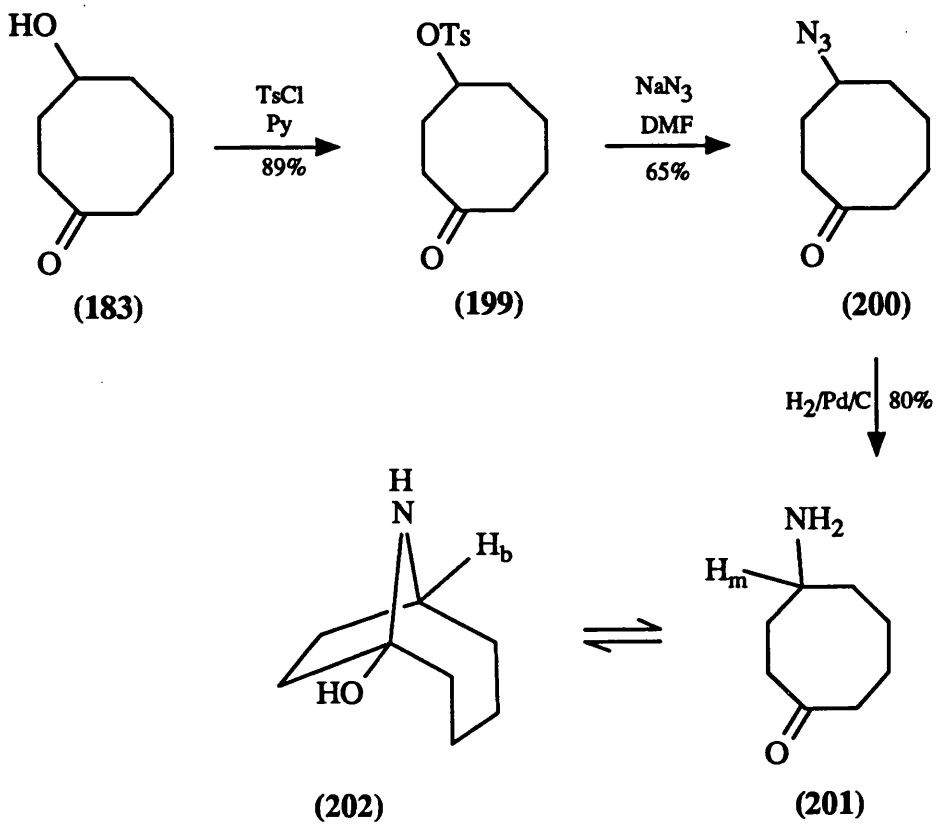
$C_{10}H_{15}N_3O_2$

4.3 SYNTHESIS AND TAUTOMERISM OF 4-AMINOCYCLOOCTANONE

The scheme (Figure 4.8) had required the hydroxy-ketone (187) to be protected as its acetal (188) to avoid imine formation on treatment of the derived tosylate (189) with a primary amine. Nevertheless, it was believed that the treatment of a tosylate with sodium azide in the presence of a ketone group would not cause any problems, so it was decided to carry out the scheme with the omission of the acetal formation step. However, this would limit the scheme to the production of the unsaturated 4-aminocyclooct-2-enone (191) and the saturated derivative, 4-amino-cyclooctanone (201), i.e. the primary amino-ketones/ bicyclic secondary amino-alcohols.

Treatment of a solution of 4-hydroxycyclooctanone (183) in pyridine with *p*-toluenesulphonyl chloride [75] for 3½ days gave the tosylate (199) in 89% yield. Displacement of the *p*-toluenesulphonate group by sodium azide in DMF [76] afforded a 65% yield of the azido-ketone (200) which was easily identified due to its IR spectrum which showed two very strong absorptions at 2090cm^{-1} (azide stretch) and 1695cm^{-1} (carbonyl stretch). The presence of the carbonyl group was confirmed by its ^{13}C NMR spectrum which exhibited a carbonyl signal at δ215.8. Lithium aluminium hydride [77] is a reagent commonly employed for the reduction of azides to amines, but this could not be used here due to the presence of a carbonyl group. Instead, the azide was reduced using catalytic hydrogenation to the 4-aminocyclooctanone (201)

in 80% yield.



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

Figure 4.11

Spectroscopic studies confirmed the successful synthesis of 4-aminocyclooctanone (201). Its IR spectrum retained the strong carbonyl absorption at 1695cm^{-1} and its high resolution mass spectrum possessed the required ion peak at $^{m}/_{z}$ 114.115, identical to that of its isomer, physoperuvine. However, broad ^{1}H and ^{13}C NMR signals at ambient temperature suggested the existence of a tautomeric equilibrium (201)=(202). At lower temperatures, the tautomerism was slowed sufficiently on the NMR time scale to identify the presence of both the amino-alcohol form and the monocyclic

amino-ketone (202). Using ^{1}H NMR spectroscopy to compare the integration of the monocyclic α-NH_2 proton H_m at δ3.04 with that of the bicyclic bridgehead proton H_b at δ3.59 at different temperatures, a temperature-dependent ratio was observed (Figure 4.11). This was confirmed by variable temperature IR measurements which showed a gradual reduction in the intensity of the carbonyl absorption at 1695cm^{-1} as the temperature of a solution in dichloromethane was lowered. At -30°C, the ^{13}C NMR showed the carbonyl signal (δ218.0) and the C-NH_2 carbon signal (δ50.7) of the monocyclic form (201) together with the quaternary (C) bridgehead signal (δ93.1) and the tertiary (CH) bridgehead signal (δ52.4) of its bicyclic tautomer (202). At -50°C, the signals observed were almost exclusively due to the bicyclic tautomer (202). Incidentally, the chemical shifts of the bridgehead carbons of (202) (δ93.1, δ52.4) correlated well with those of *calystegine* A_3 (δ93.0, δ54.0). [70]

The ring opening reaction is expected to be accompanied by an increase in entropy due to the monocyclic system being more disordered than its corresponding bicyclic tautomer. The gradual shift of the equilibrium (202) ⇌ (201) towards the monocyclic tautomer (201) with increase in temperature is not surprising; the temperature-dependence follows from the equation $\Delta G = \Delta H - T\Delta S$.

An attempt was made to follow a similar approach to prepare the unsaturated analogues. Treatment of a solution of (181)=(187) in pyridine with *p*-toluenesulphonyl chloride[75]

gave, after 16 days, a mixture of allylic tosylate (203), allylic chloride (204), and polymeric material. Displacement of the *p*-toluenesulphonate group by sodium azide in DMF afforded an 81% yield of the unsaturated azido-ketone (205) whose IR spectrum showed the expected strong absorptions at 2100^{-1} (azide stretch) and $1670cm^{-1}$ (α, β-unsaturated carbonyl stretch). Sodium azide also effected the displacement of the chloride group in (204) but this reaction was slower than that of the tosylate (203) and required a higher temperature to go to completion. Catalytic hydrogenation could not be used here for the reduction of the azide to the amine because of the presence of the double bond, so it was decided to employ the Staudinger reaction [78] which is known to occur under very

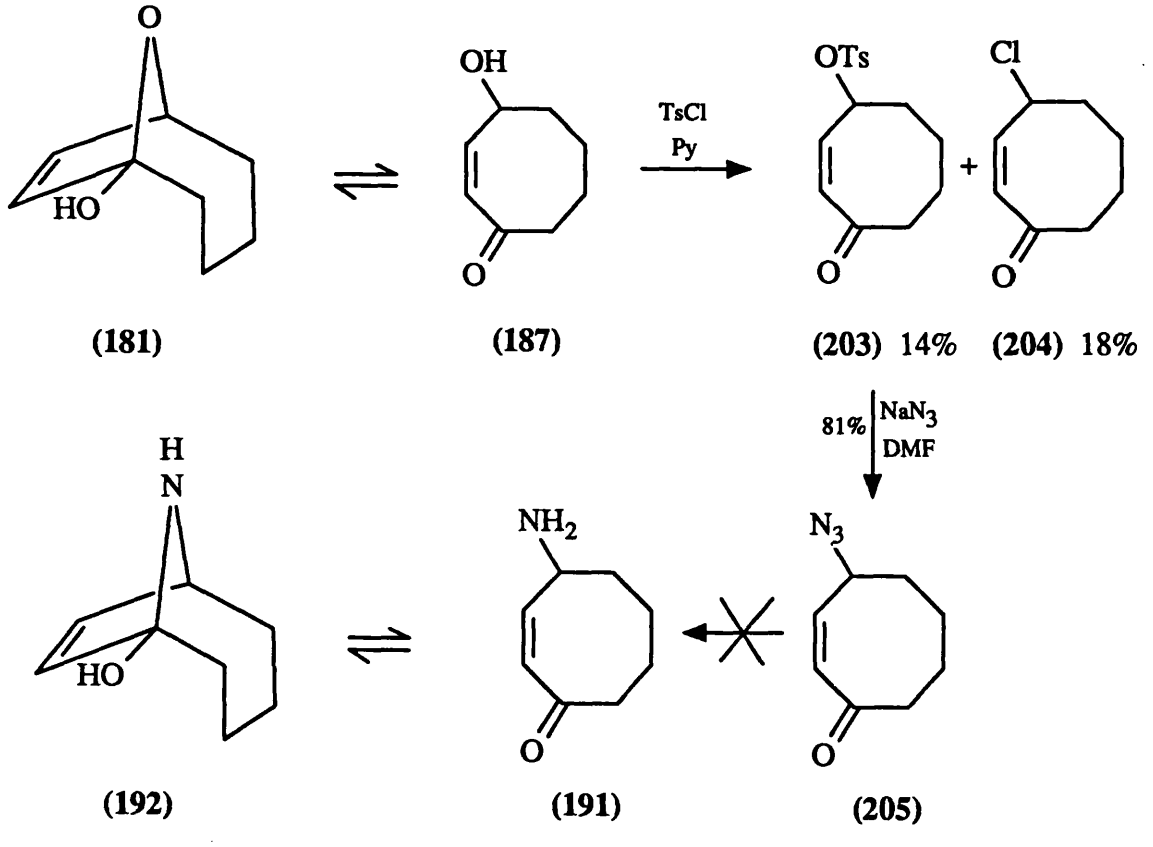
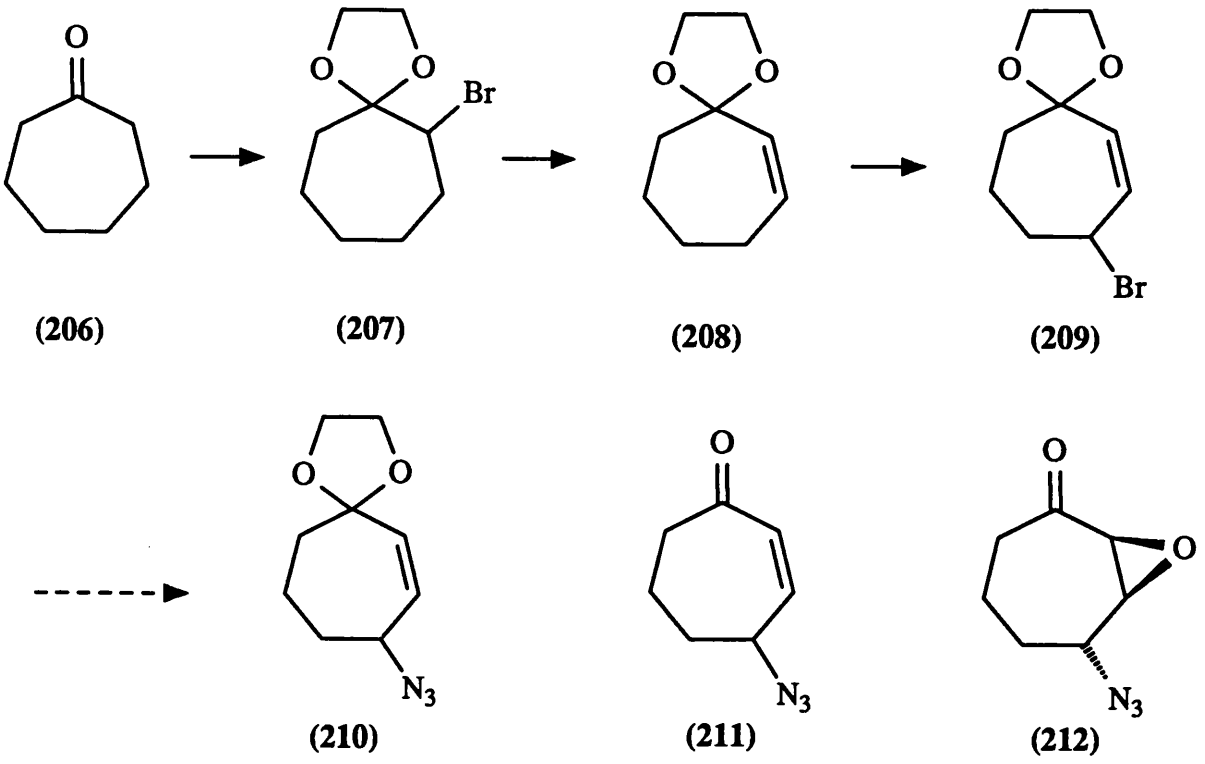


Figure 4.12

mild conditions. Treatment of the azide (205) with one equivalent of triphenylphosphine in anhydrous tetrahydrofuran was expected to form the corresponding iminophosphorane which could then be hydrolysed with 1.5 equivalents of water to the primary amine (191). Unfortunately, the reaction was unsuccessful and gave a mixture of products showing no signals in the olefinic region on the ^{1}H NMR spectrum.

At the same time as this work was being carried out, a synthetic approach to the 1-hydroxynortropane system was reported. [70] Cycloheptanone (206) was treated with bromine in anhydrous ethane-1,2-diol to afford the 2-bromo ethylene acetal (207) in 94% yield; this was heated with sodium methoxide in methanol to give an 84% yield of the



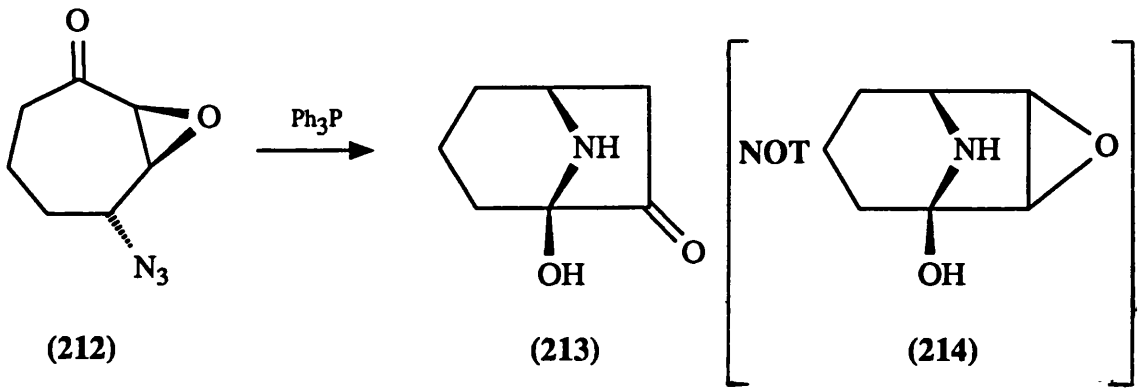
(206) (207) (208) (209)

(210) (211) (212)

Figure 4.13

protected cycloheptenone (208). Allylic bromination of (208) with N-bromosuccinimide, followed by heating the resulting mixture with sodium azide in anhydrous tetrahydrofuran gave the azide (210) in 52% yield after purification. Deprotection of the keto group followed by epoxidation of the double bond of the resulting enone (211) afforded (212) in 35% yield from the azide (210). Epoxidation of the double bond was found to be necessary to suppress "side reactions".

Several standard methods for reduction of azides, including catalytic hydrogenation, failed to give the expected product (214). The Staudinger reaction was employed, but this afforded a compound for which structure (213) was assigned on the basis of ^{1}H and ^{13}C spectroscopic data.



(212) (213) (214)

Figure 4.14

There was no observation of any equilibrium between the open and closed forms of the aminoketal system. The complete shift towards the bicyclic form was thought to be due to the lower stability of the α-diketone system present in the monocyclic form, or to a stabilising hydrogen bond between the hydroxy group and the vicinal carbonyl.

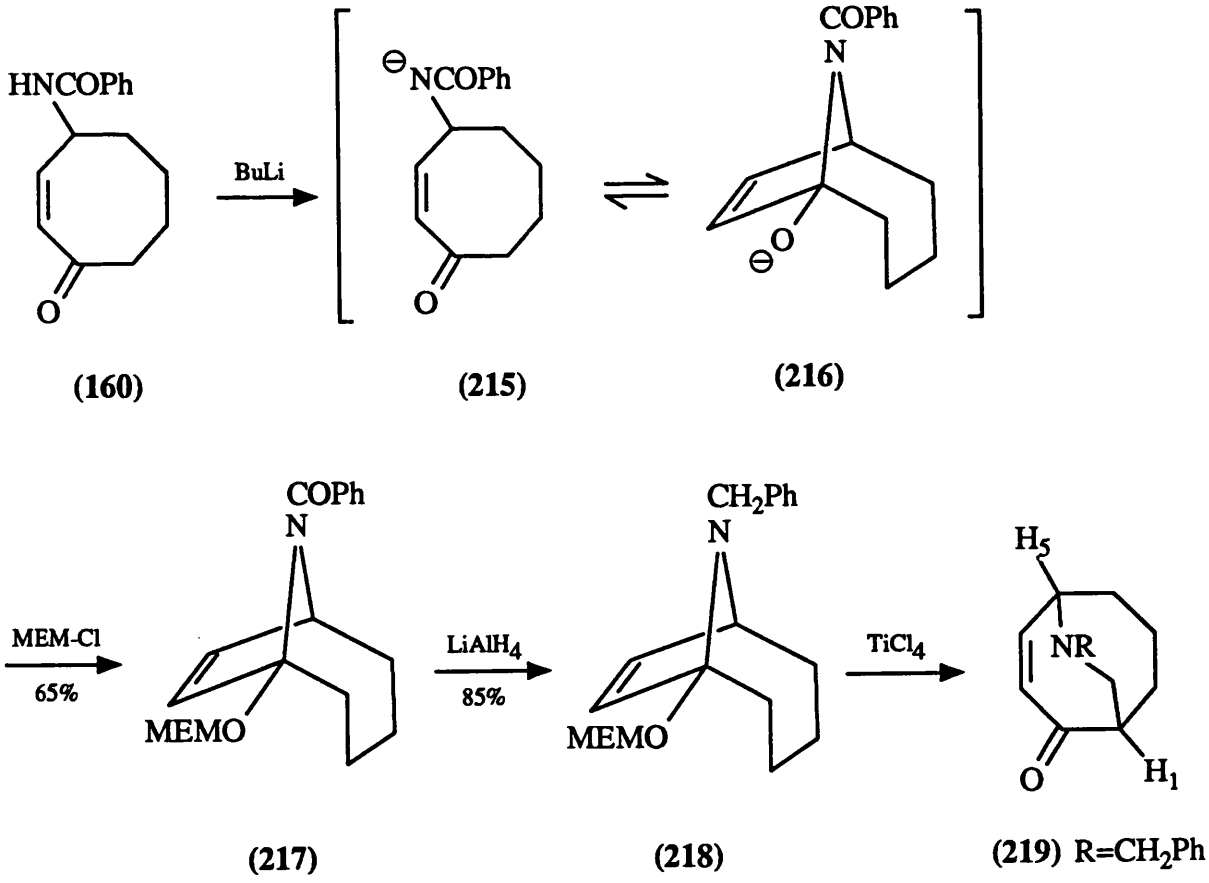
The failure to synthesise the unsaturated 4-amino-cyclooct-2-enone (191) to provide a comparison with 4-aminocyclooctanone (201) necessitated a new synthesis which would produce both unsaturated and saturated derivatives. This would help to explore the effect of incorporation of a double bond into the ring system on the tautomeric equilibrium.

4.4 SYNTHESIS OF 1-HYDROXY-N-BENZYL-9-AZABICYCLO[4.2.1] NONANE

It was noted in chapter 3 that the unsaturated amido-ketone (160) cyclised to the amido-alcohol (167) on treatment with base. If the anion of this amido-alcohol could be "trapped" in the bicyclic form as an ether, then this would allow reduction of the bridging amide benzoyl group to a benzyl group without fear of reducing the carbonyl group of the monocyclic form. Subsequent deprotection of the alcohol would yield 1-hydroxy-N-benzyl-9-azabicyclo[4.2.1]non-7-ene (220). Consequently, MEM-chloride [79] was chosen to protect the hydroxyl group and trap the bicyclic form since it was a suitable reagent for tertiary alcohols, and subsequent removal of the MEM group could be accomplished under aprotic conditions under the influence of a mild Lewis acid such as zinc bromide or titanium tetrachloride. Treatment of the unsaturated amido-ketone (160) with butyllithium gave the anion(s) which reacted with MEM-chloride to give the protected bicyclic amido-alcohol (217) in 65% yield. Reduction of the benzoyl group (217) with

lithium aluminium hydride gave an 85% yield of the protected bicyclic amino-alcohol (218) which was then deprotected with titanium tetrachloride. However, the compound isolated from this deprotection was found to be the rearranged bicyclic amine (219).

The ^{13}C NMR spectrum of (219) exhibited 14 carbon signals, so an extra carbon atom had been incorporated into the molecule. These included signals due to two double bond carbons and a carbonyl signal at δ206.9 which indicated the presence of an α, β- unsaturated ketone. Two tertiary (CH) carbon signals at δ49.1 and δ58.8 suggested bridgehead carbons of a bicyclic system. The IR spectrum confirmed the presence of an α, β-unsaturated carbonyl with a strong



(160) (215) (216)

(217) (218) (219) R=CH_2Ph

Figure 4.15

absorption at 1665cm^{-1} and showed no NH or OH absorption. The ^{1}H NMR spectrum showed the two protons of the bridging N-CH_2 at δ2.63 (dd, J=12.4Hz, J=1.3Hz) and δ3.01 (ddd, J=12.4Hz, J=5.6Hz, J=0.6Hz). The 12.4Hz coupling was consistent with geminal coupling and the values 1.3Hz and 5.6Hz were due to vicinal coupling with the bridgehead proton, H-1, at δ2.80. The J value of 0.6Hz was shown by 2D NMR to emanate from ω-coupling with the α-N bridgehead proton, H-5, at δ3.68 - 3.78. On addition of one equivalent of trifluoroacetic acid to (219), the expected downfield chemical shifts of the protons α- to nitrogen caused by protonation of the amine moiety were observed (See Experimental).

The formation of (219) was totally unexpected and called for an analysis of the mechanism of cleavage of MEM esters. The two accepted mechanisms of cleavage of MEM ethers[79] were 1) that bidentate coordination of the MEM group to a Lewis acid would facilitate the cleavage of MEM ethers as indicated (for $ZnBr_2$) in equation A, or 2) that ready cleavage might occur by the mechanism shown in equation B (Figure 4.16). In either of these mechanisms, hydrated methanal is formed by breakdown of the MEM group.

The extra carbon atom which had been incorporated into (219) was thought to have originated from this methanal formed in the cleavage of the MEM ether. It was thought that titanium tetrachloride did, in fact, cleave the MEM-ether (218) to give the bicyclic amino-alcohol (220) which was expected

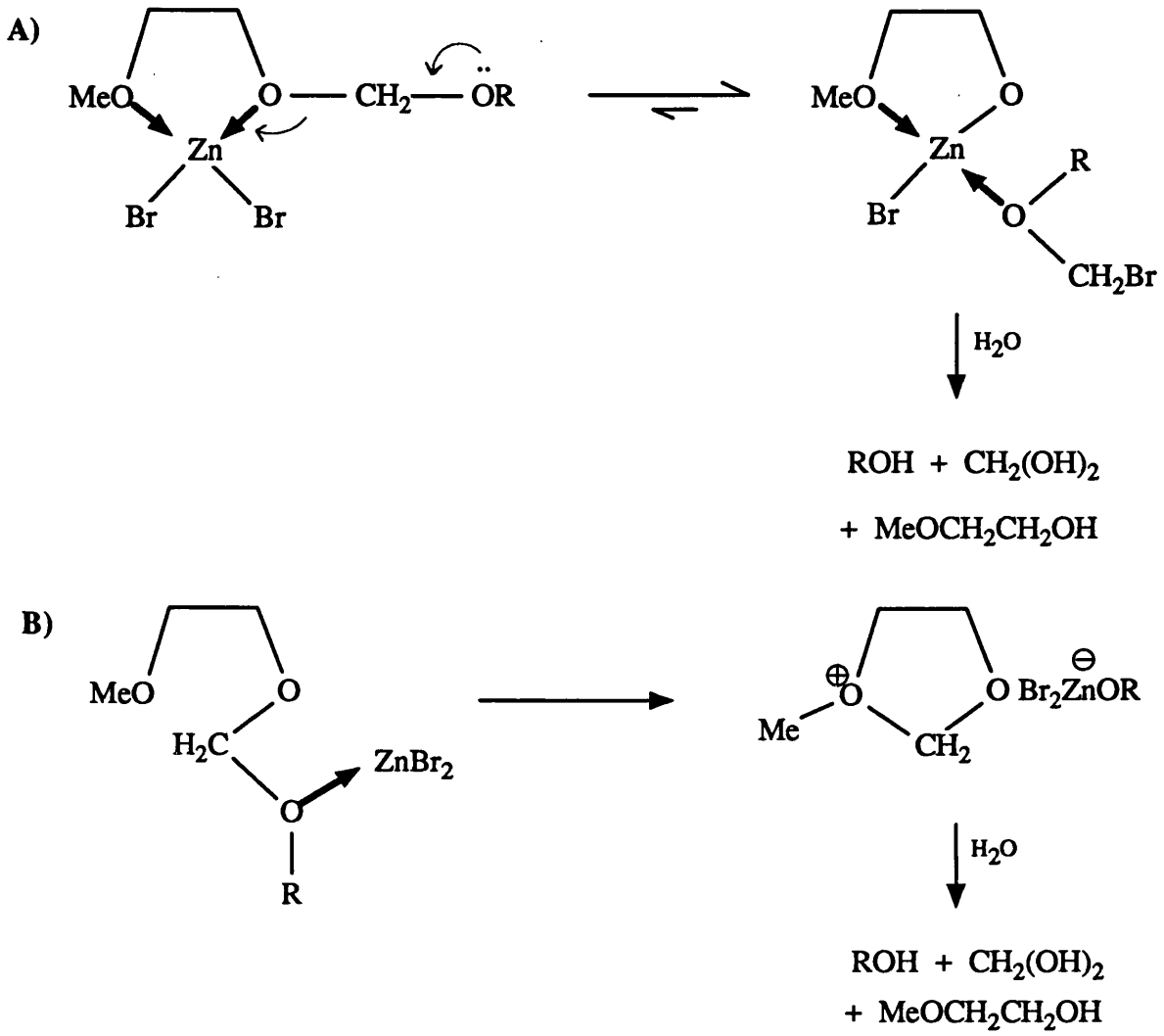


Figure 4.16 Mechanisms of cleavage of MEM ethers by Lewis acids.

to exist in equilibrium with the monocyclic amino-ketone (221). The secondary amino-group in (221) could react with the methanal to form the hemiaminal (222), which, under the conditions of the reaction (titanium tetrachloride acting as a drying agent[80]) could lose water to form the iminium ion (223). The titanium tetrachloride might also facilitate enolate formation, as in (224), and this enolate could react with the iminium ion by the mechanism shown in (224). The scheme for this "intramolecular Mannich reaction" is depicted in Figure 4.17.

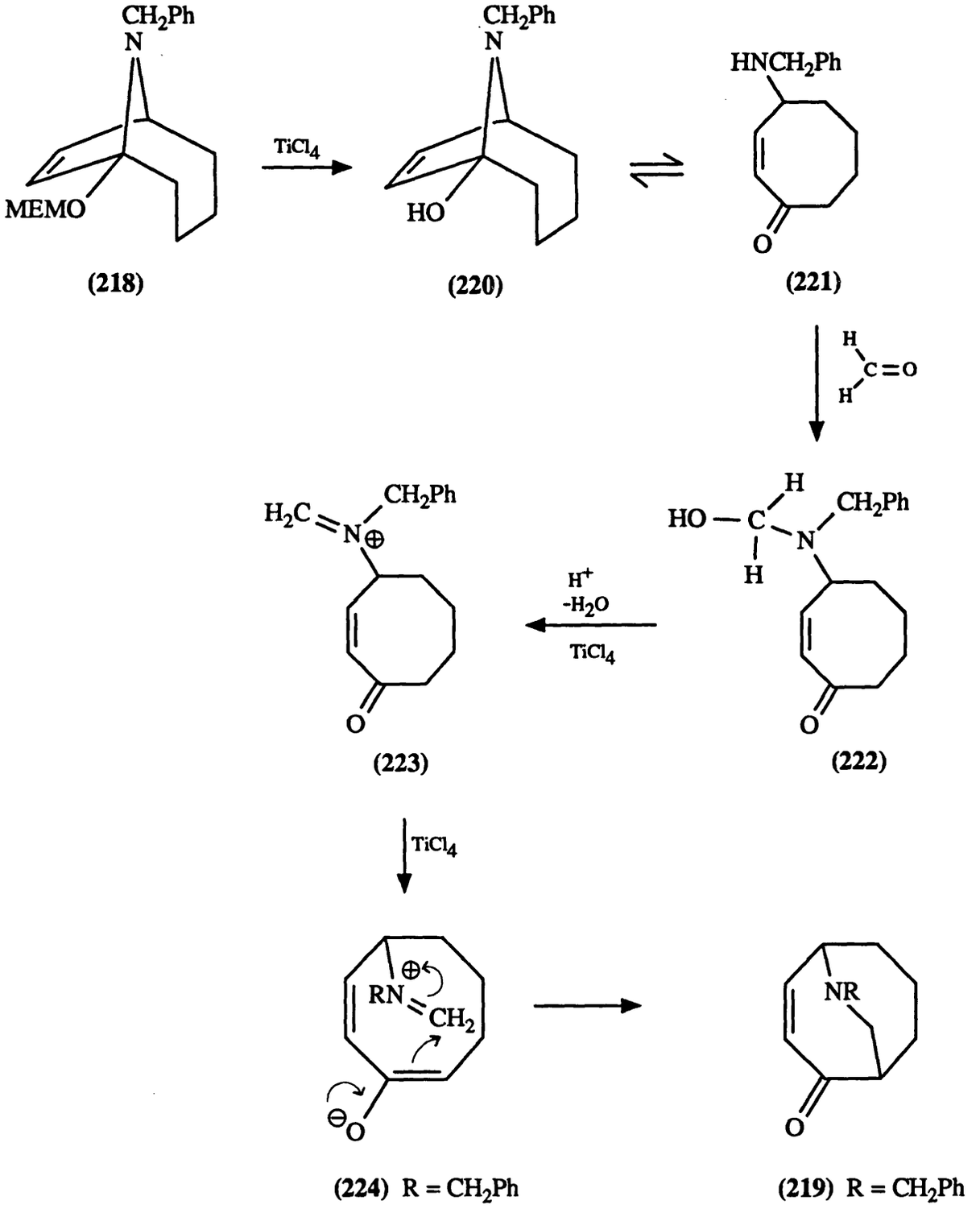
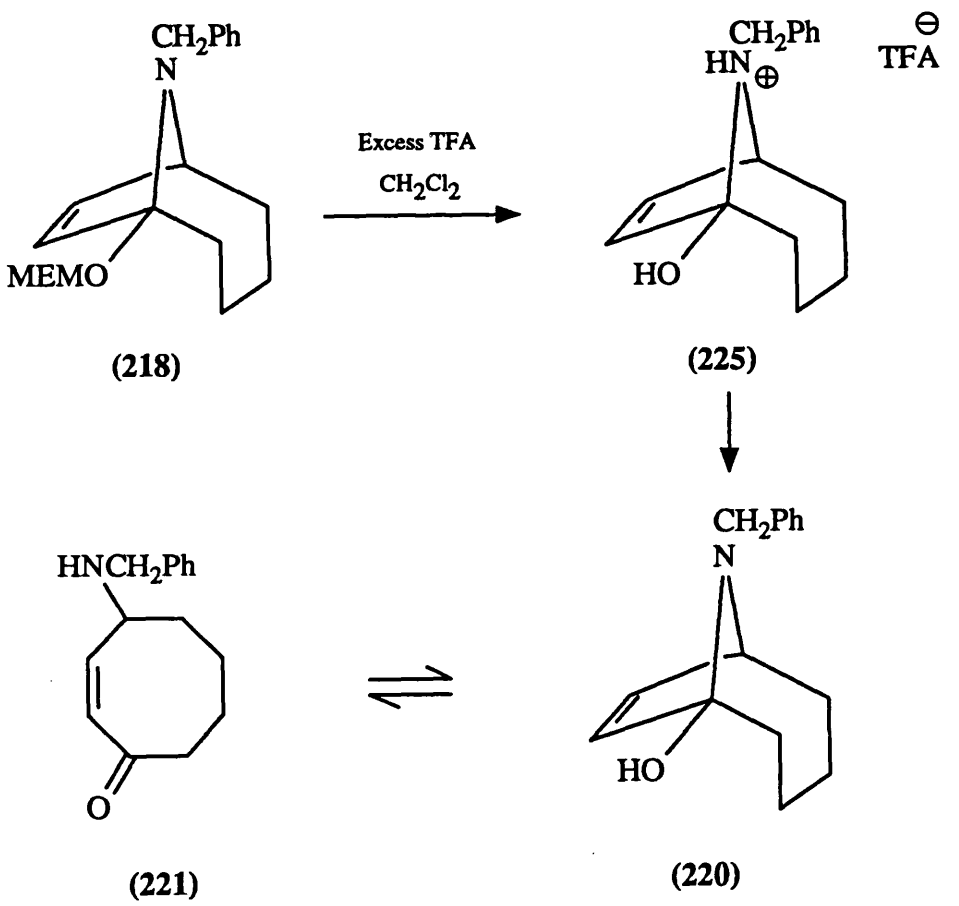


Figure 4.17

The root of the problem during deprotection of the MEM ether in (218) lay in the production of the monocyclic amino-ketone (221) which was prone to react with the methanal.

However, it was believed that the production of (221) might be avoided if the amino-alcohol (220) was locked in the bicyclic form by, for example, protonation. This would create an opportunity to remove the methanal before the required amino-alcohol (220) was regenerated. Hence, it was decided to add a large excess of trifluoroacetic acid to the MEM-protected amino-alcohol (218) both to protonate the bicyclic amine and cleave the MEM ether. After treatment with a large excess of trifluoroacetic acid, all solvent



(218) (225) (221) (220)

Temperature	Ratio
-55°C	58 : 42

Figure 4.18

was removed from the reaction mixture, ultimately at 0.4mm Hg thus ensuring that all methanal had been removed. Subsequent basification of the residue successfully afforded 1-hydroxy-N-benzyl-9-azabicyclo[4.2.1]non-7-ene (220) in 86% yield.

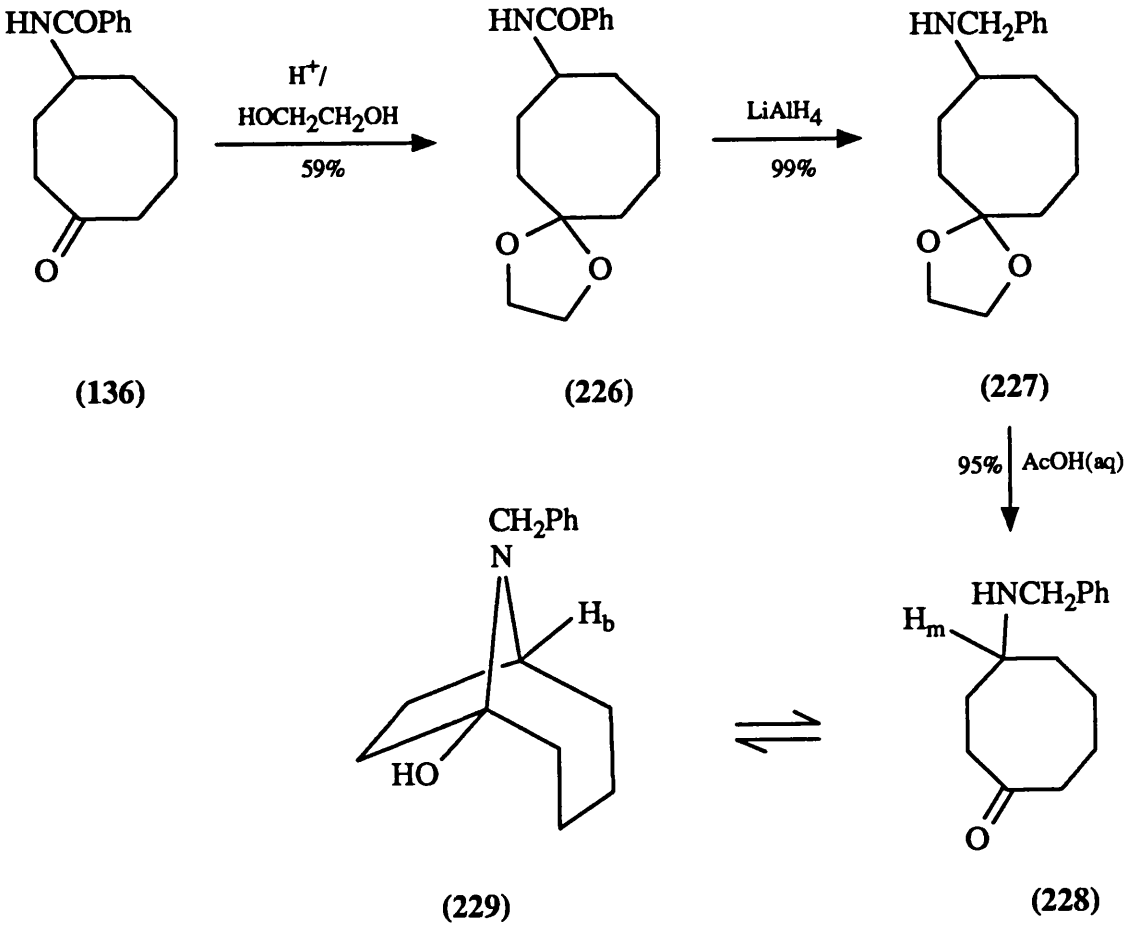
The IR spectrum of the product included a carbonyl absorption at 1655cm^{-1} which suggested the co-existence of its α, β- unsaturated ketone tautomer (221). As with 4-aminocyclooctanone, the interconversion was relatively slow on the NMR time scale at room temperature as shown by broad ^{1}H and ^{13}C NMR signals, but the two tautomers were discernible at lower temperatures. At -55°C, ^{1}H NMR spectra showed that the bicyclic tautomer (220) was the minor component and was accompanied by 58% of the monocyclic form, 4-benzylaminocyclooct-2-enone (221). The ^{1}H NMR spectrum also showed the double bond protons of the bicyclic form (220) as a singlet at δ5.93, almost identical with that of the MEM-protected amino-alcohol (218) at δ5.92. The olefinic protons of the monocyclic form (221) demonstrated the expected chemical shifts and coupling constants for this α, β- unsaturated ketone system. The ^{13}C NMR showed the carbonyl signal (δ203.3) and the C-N carbon signal (δ55.3) of the monocyclic form (221) together with the quaternary (C) bridgehead signal (δ94.7) and the tertiary (CH) bridgehead signal (δ60.1) of its bicyclic tautomer.

Having successfully synthesised an unsaturated 4-amino-cyclooct-2-enone and determined a ratio for the tautomeric

equilibrium, the corresponding saturated 4-amino-cyclooctanone was required before any conclusion could be drawn as to whether the incorporation of a double bond into the ring system affected the tautomeric equilibrium.

4.5 MONO-/BICYCLIC TAUTOMERISM IN 4-BENZYLAMINO CYCLOOCTANONE

The saturated amido-ketone (136) from chapter 3 was protected as its ethylene acetal (226) by reaction with ethane-1, 2-diol in the presence of an acid catalyst.



Temperature	Ratio
-50°C	34 : 66

Figure 4.19

Reduction of the amide benzoyl group with lithium aluminium hydride in 99% yield followed by the subsequent removal of the acetal protecting group [81] in aqueous acetic acid gave the saturated amino-alcohol (228) in 95% yield. Its IR spectrum showed the expected absorption for a saturated cyclooctanone at 1690cm^{-1} and at low temperature the bicyclic tautomer was detected by ^{1}H and ^{13}C NMR spectroscopy. At -50°C, the ^{1}H NMR spectrum (Figure 4.20) indicated that the amino-ketone (228) was the major tautomer in equilibrium with 34% of the bicyclic amino-alcohol (229). The ^{13}C NMR spectrum showed the carbonyl signal (δ218.6) and the C-N carbon signal (δ56.1) of the monocyclic form (228) together with the quaternary (C) bridgehead signal (δ92.2) and the tertiary (CH) bridgehead signal (δ54.2) of its bicyclic tautomer. These chemical shifts correlated very well with those of the saturated 4-aminocyclooctanone (201) (carbonyl signal at δ218.8 and the C-N carbon signal at δ50.7) and its bicyclic tautomer (202) (quaternary (C) bridgehead signal at δ93.1 and the tertiary (CH) bridgehead signal at δ52.4).

300 MHz ^{1}H NMR spectrum showing mono-/bicyclic tautomerism in 4-(benzylamino)cyclooctanone (228) in $CDCl_3$ at -50°C.

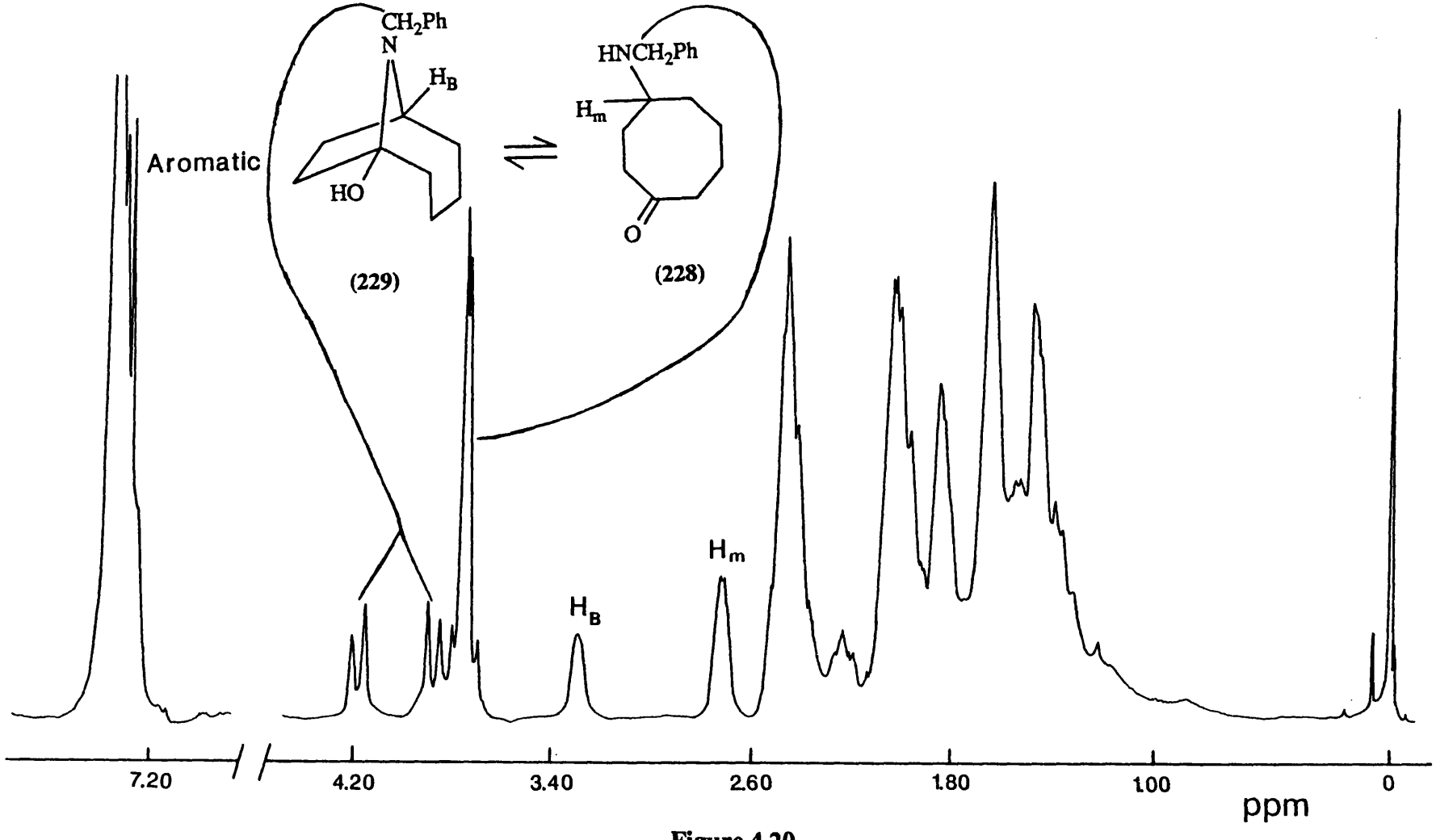


Figure 4.20

4.6 CONCLUSION

It has been shown that 4-hydroxycyclooctanone (183) and 4-hydroxycyclooct-2-enone (187) exist in equilibrium with their respective bicyclic tautomers. The incorporation of a double bond into the hydroxy-ketone system results in a greater preference for the bicyclic form.

The corresponding N-benzyl-4-aminocyclooctanone (228) and N-benzyl-4-aminocyclooct-2-enone (221) have been synthesised and these amino-ketones show similar behaviour, but the equilibrium in these cases is much more evenly balanced. Incorporation of a double bond into the amino-ketone system to construct (221) disturbs the balance marginally towards the bicyclic tautomer (220) (42% of the unsaturated bicyclic (220) at -55°C compared with 34% of the saturated bicyclic (229) at -50°C) but the effect here is less pronounced than for hydroxy-ketones. The position of equilibrium has also been found to vary with temperature and substitution. At -50°C, the unsubstituted 4-aminocyclooctanone (201) exists almost exclusively (95%) as its bicyclic tautomer (202), whereas at this temperature the bicyclic form of the N-benzyl derivative (229) is the minor tautomer at 34%.

These results may appear to be contrary to expectations. The incorporation of a double bond creates an α,β-unsaturated carbonyl system which is stabilised with respect to the corresponding saturated monocyclic system due to resonance. The subsequent stabilisation would be expected to influence

the tautomeric equilibrium in favour of the monocyclic tautomer in unsaturated systems. However, the observation that the position of equilibrium is disturbed marginally towards the bicyclic tautomer indicates that the unsaturated bicyclic tautomers are more stable than expected. The resonance stabilisation in the α,β-unsaturated carbonyl systems is somehow offset by their bicyclic tautomers. The presence of a double bond in the bicyclic framework apparently contributes in some way to the stability of the unsaturated hemi-acetal and hemi-aminal systems. Work in norbornene[82] and 7-azabicyclo[2.2.1] nonane/ene[83] systems has suggested the existence of σ-π* interactions (See Chapter 5). It is possible that similar σ-π* effects operate in the unsaturated bicyclic tautomers and, if so, they may explain the unexpected stabilisation in these systems.

The tautomeric ratio in physoperuvine was estimated using circular dichroism. Bearing in mind the results for the higher homologues, it would be reasonable for future work to investigate the equilibria in 4-aminocycloheptanones and hept-2-enones directly using ^{1}H and ^{13}C NMR spectroscopy. An investigation of tautomerism in 4-aminocyclohexanones and hex-2-enones could indicate how important ring strain is and may also show evidence of the "bicyclic effect" (See Chapter 5) in the 1-hydroxy-7-azabicyclo[2.2.1]heptane/ene tautomers. It would be interesting to discover just how important the presence of a double bond is in stabilising the bicyclic tautomers in these more strained systems.

Chapter Five

DEALKYLATION OF BICYCLIC TERTIARY AMINES AND SYNTHESIS OF N-CHLOROAMINES

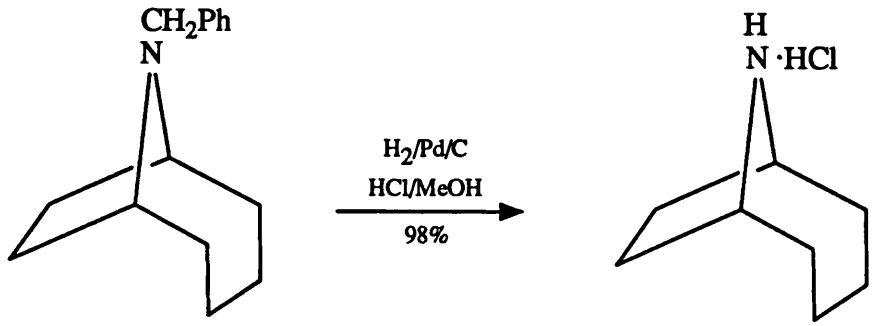
5.1 INTRODUCTION

Epoxidation of the etheno bridges in the unsaturated norhomotrop-7-ene derivatives synthesised in chapters 2 and 3 could lead to the production of non-natural analogues of the tropane alkaloid scopolamine (Figure 1.3). However, in the presence of an unprotected tertiary amine, formation of the corresponding N-oxide would compete with epoxidation of the double bond. If the unsaturated norhomotrop-7-ene derivatives were successfully dealkylated, suitable protection of the nitrogen of the free amines should allow epoxidation of the double bond to take place.

Amongst bicyclic amines, 7-azabicyclo[2.2.1]heptane derivatives are unique in having anomalously high inversion barriers. [84] Unusual deshielding of the bridging nitrogen in ^{15}N NMR studies has also been observed in these systems (see Appendix 1). [85] The unusual nature of the bridging nitrogen in the 7-azabicyclo[2.2.1]heptane system has generated interest in homologous systems. Dealkylation of the 9-azabicyclo[4.2.1]nonane and non-7-ene systems would provide their respective secondary amines which could undergo subsequent N-chlorination. The expected increase in the inversion barrier due to the introduction of chlorine at the nitrogen atom [86] should facilitate observation of the inversion phenomenon using variable-temperature ^{1}H or ^{13}C NMR spectroscopy.

5.2 DEBENZYLATION OF TERTIARY AMINES

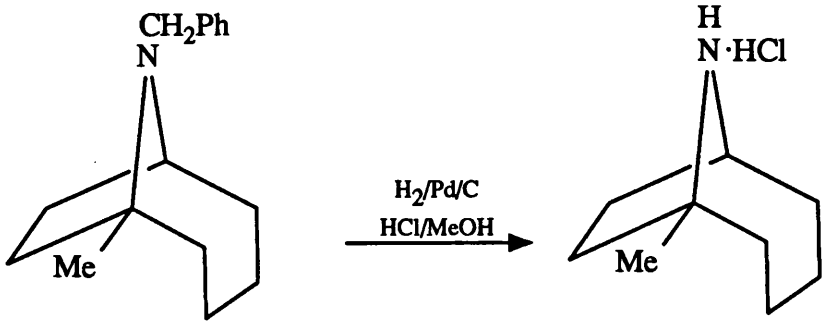
Debenzylation of N-benzylnorhomotropane (116) to afford the hydrochloride salt of norhomotropane (230) was achieved in high yield by hydrogenation of the hydrochloride salt of (116) over palladium on charcoal.



(116) (230)·HCl

Figure 5.1

Similarly, debenzylation of 1-methyl-N-benzylnorhomotropane (159) yielded 1-methyl-norhomotropane (135) which was isolated and stored as its hydrochloride salt.

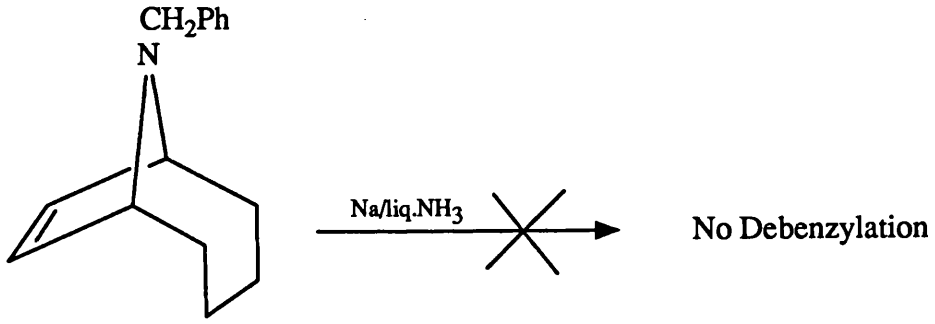


(159) (135) .HCl

Figure 5.2

The method of catalytic hydrogenation could not be applied to the unsaturated analogue, N-benzylnorhomotrop-7-ene (118), due to the presence of the double bond. Bathgate [38] investigated a variety of methods for the debenzylation of N-benzylnortrop-6-ene (103), including treatment with alkali metals (lithium, sodium and potassium) in liquid ammonia and with alkyl chloroformates. However, these attempts all resulted, unexpectedly, in failure.

Treatment of N-benzylnorhomotrop-7-ene (118) with sodium in liquid ammonia also failed to effect debenzylation, and only starting material was recovered from the reaction.



(118)

(Figure 5.3)

Reductions involving sodium metal in liquid ammonia are believed to proceed by formation of a radical anion followed by elimination of a stable anion or a good leaving group. Treatment of (118) with sodium in liquid ammonia would give rise to the radical anion (231). For debenzylation to take place, this radical anion would be expected to eliminate the nitrogen anion, $N^{\ominus}$, which is relatively unstable.

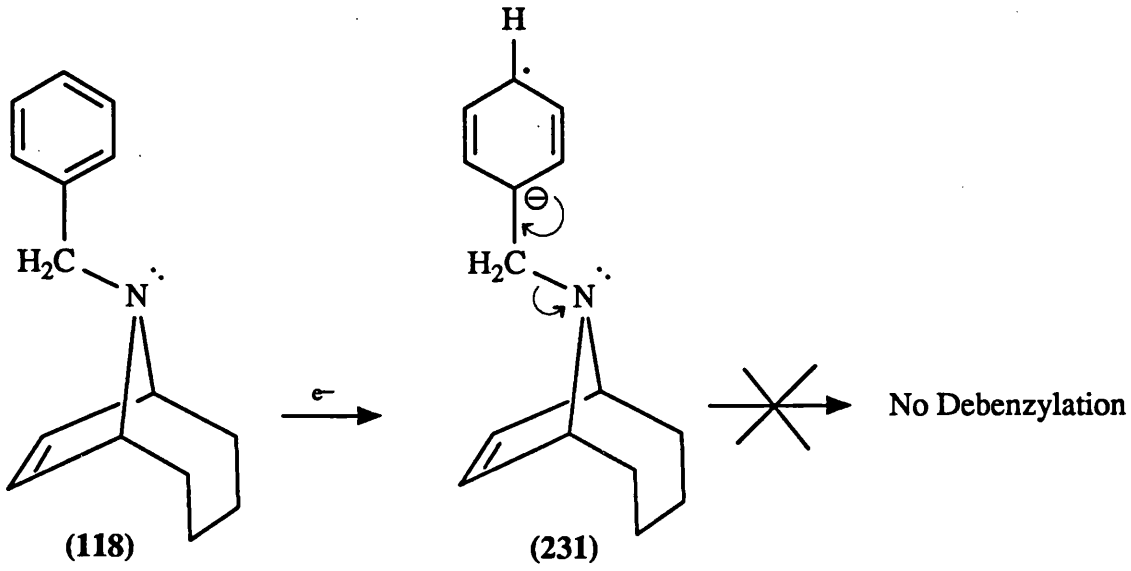


Figure 5.4

5.3 QUATERNISATION AND SELECTIVE DEBENZYLATION

It was decided to investigate debenzylation of the corresponding methiodide of N-benzylnorhomotrop-7-ene (118). The quaternary ammonium salt (232) was isolated in 57% yield by heating (118) with a large excess of methyl iodide in an equivalent volume of acetone. [87]

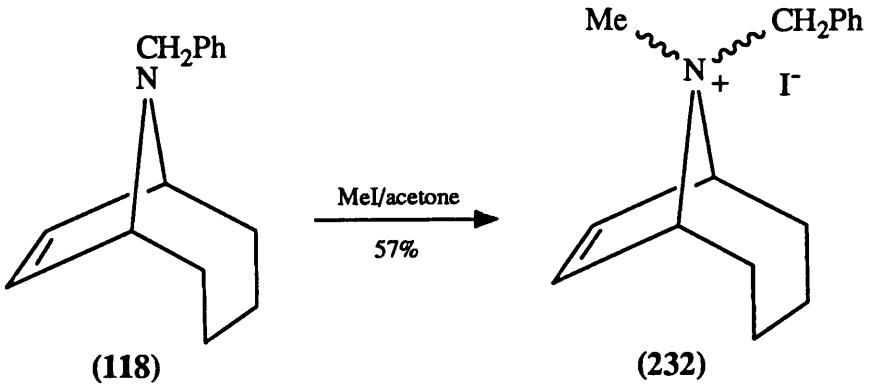
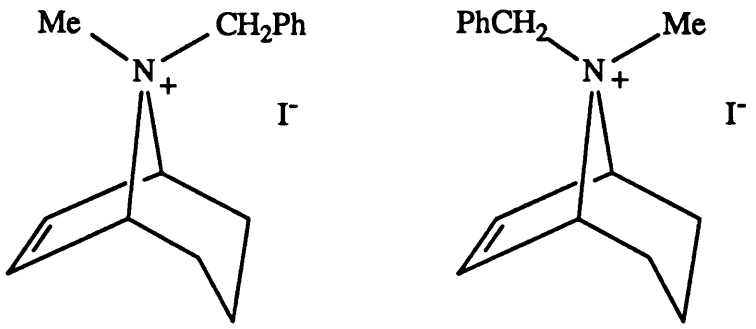


Figure 5.5

Howarth[35] found that the corresponding quaternisation of N-benzylnortrop-6-ene (103) resulted in the isolation of a mixture of diastereoisomers which were present in a ratio of

2:1 in favour of the diastereoisomer formed by equatorial attack of the nitrogen of the six-membered piperidine ring (Figure 5.6).



Equatorial Attack : Axial Attack

2 : 1

Figure 5.6

Treatment of N-benzylnorhomotrop-7-ene (118) with methyl iodide was expected to have resulted in the isolation of the quaternary salt (232) as a pair of diastereoisomers. However, only one set of signals were observed on inspection of the ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectrum exhibited a singlet at δ3.20 due to the methyl protons and a singlet at δ5.28 assigned to the benzylic methylene protons. These signals correlated well with those of the N-methyl-N-benzylnortrop-7-enium iodide in Figure 5.6 formed by equatorial attack (δ3.14 and δ5.29 respectively), indicating that the methyl group of (232) lay within the shielding cone of the double bond. A review by Bottini [88] has described many examples of preferred equatorial attack during quaternisation of tropanes, and so these results were not unexpected.

Treatment of (232) with sodium in liquid ammonia resulted in the formation of N-methyl-9-azabicyclo[4.2.1]non-7-ene (126) in 71% yield. The spectroscopic data obtained (NMR, IR) were identical with those obtained from (126) synthesised by intramolecular cyclisation of (124).

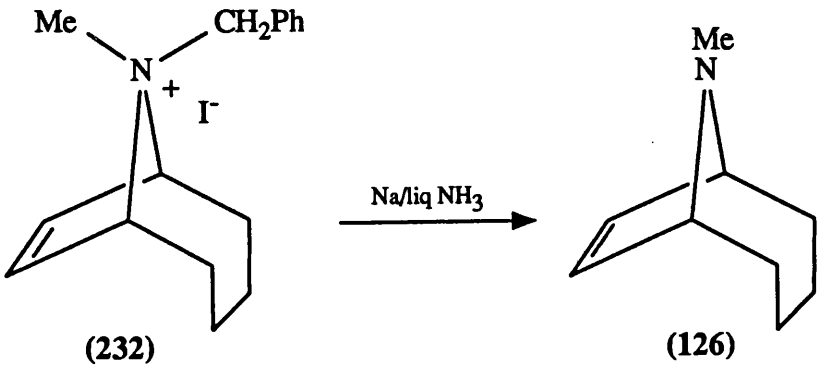


Figure 5.7

Selective debenzylation was also achieved using Emde's reduction. [89] Sodium amalgam was added in portions to a solution of (232) in water which was then heated to reflux. However, this reaction produced a 1:1 mixture of the debenzylated product (126) and unreacted starting material (232).

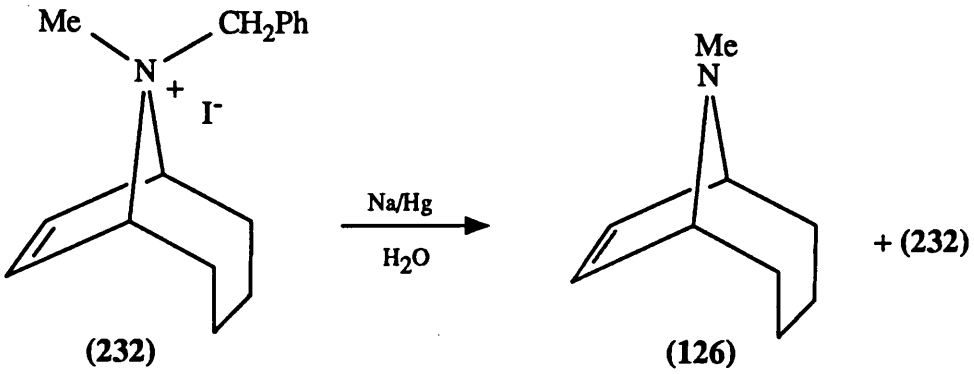


Figure 5.8

Selective debenzylation had been achieved under these reducing conditions using the quaternary ammonium salt. This was not an unexpected result since the positively charged nitrogen would create a good neutral leaving group (126) on elimination of the stable benzyl radical from the radical anion (233) (Figure 5.9).

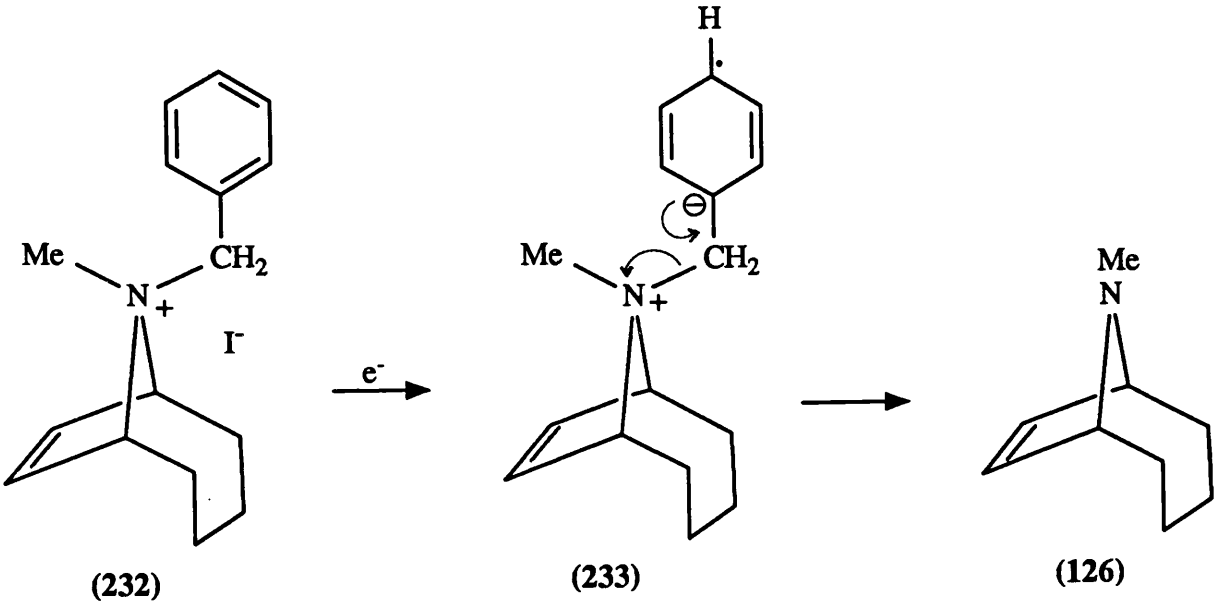


Figure 5.9

Nevertheless, the dealkylation of bicyclic tertiary amines to the parent secondary amines still remained a problem.

5.4 N-DEMETHYLATION AND N-DEBENZYLATION OF TERTIARY AMINES

The use of cyanogen bromide to dealkylate tertiary amines is known as the von Braun reaction. [90] It proceeds through a quaternary ammonium bromide intermediate which may react

further by either nucleophilic attack of the bromide ion on the alkyl group (S_N2) or loss of the alkyl group as a carbocation (S_N1) to form the products (Figure 5.10).

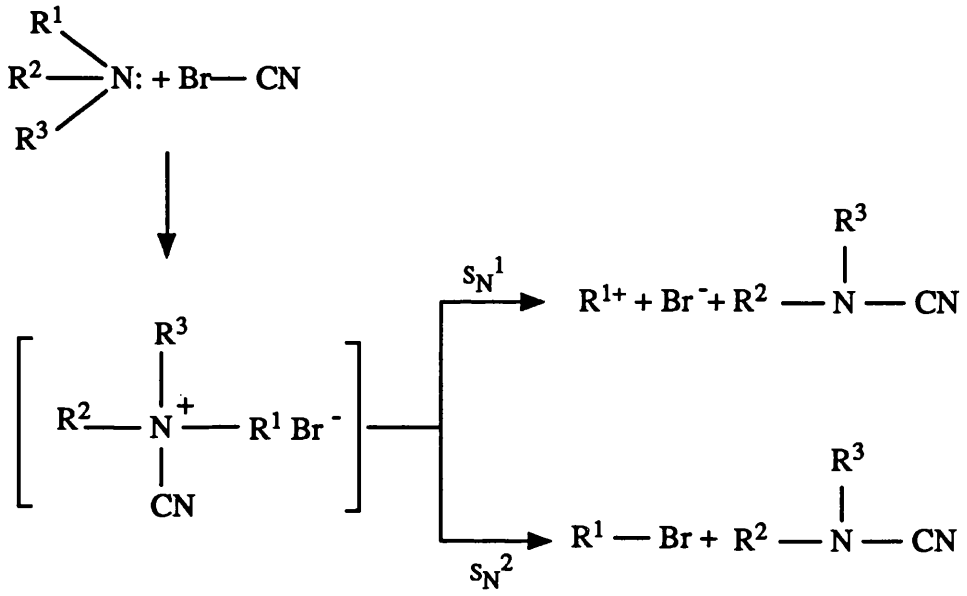


Figure 5.10

The tertiary amine can be either cyclic or acyclic and the operative mechanism for the second step is dependent on the nature of the substituents.

Nowadays, the use of cyanogen bromide in the dealkylation of tertiary amines has been replaced with chloroformate reagents, which have proven to be more selective and to produce cleaner reaction products. The generally accepted reaction sequence is shown in Figure 5.11. [91] The 1:1 complex formed has two fates:nucleophilic attack on the *O*-alkyl portion, which has no net effect on the amine (path b), or nucleophilic attack by chloride ion on one of the substituents on nitrogen (path a) leading to a carbamate

ester, which can then be hydrolysed to give a secondary amine.

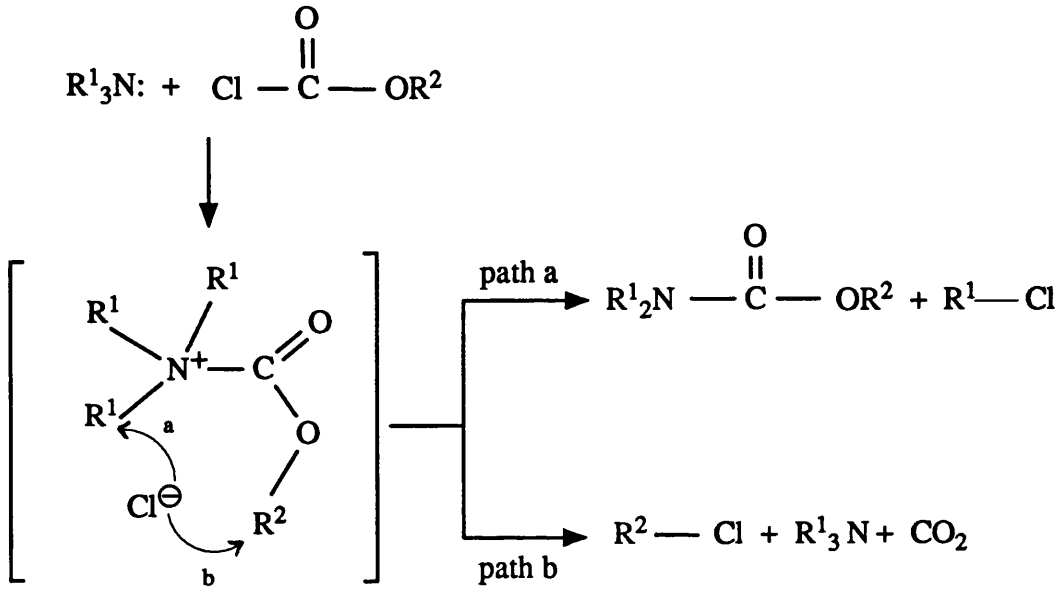
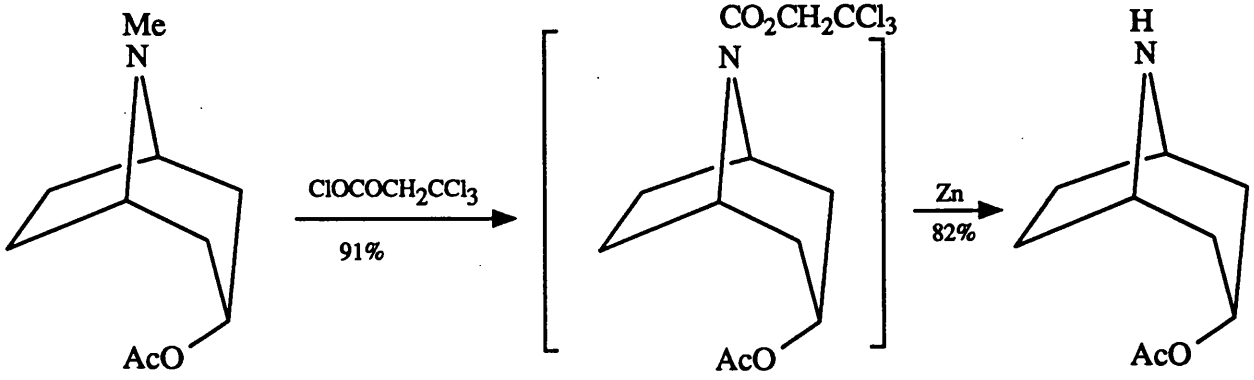


Figure 5.11

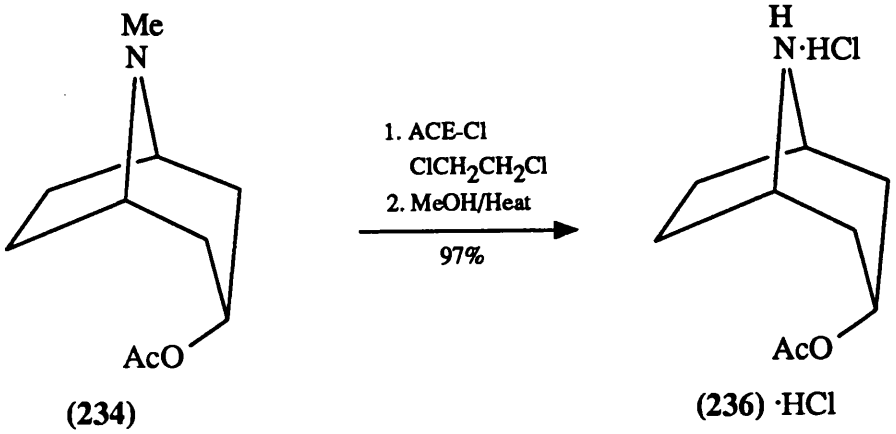
There have been several different chloroformates reported in the literature, each new one claimed to be an improvement over the last. Montzka *et al.* [92] used 2,2,2-trichloroethyl chloroformate which formed highly crystalline intermediate carbamate derivatives which were easily purified. The attractive advantage of this reagent was that these trichloroethyl carbamate derivatives were easily converted into secondary amines in high yields by treatment with zinc in either methanol or 90% acetic acid. Acetyltropine (234) was N-demethylated to noracetyltropine (236) in 75% overall yield using this reagent (Figure 5.12).



(234) (235) (236)

Figure 5.12

The best method found in the literature to date for the N-dealkylation of tertiary amines was published in 1984 by Olofson *et al.*, [93] when they presented the use of the inexpensive reagent α-chloroethyl chloroformate (ACE-Cl). Using the reagent, acetyltropine (234) was demethylated to noracetyltropine (236) which was isolated in 97% yield as its hydrochloride salt (Figure 5.13).



(234) (236) ·HCl

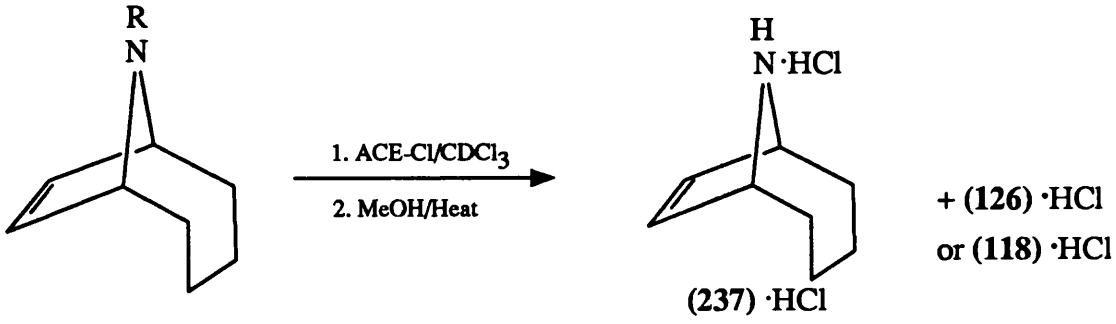
Figure 5.13

The cleavage of the α-chloroethyl carbamate ester was achieved by simply heating it in methanol. The explanation for the high yield was that the α-chloroethyl group was sterically hindered to S_N2 attack by chloride and also that the related cation was unstable.

Mindful of Bathgate's [38] failure to debenzylate N-benzyl-nortrop-6-ene (103) using alkyl chloroformates, it was decided to attempt demethylation of N-methyl-9-azabicyclo[4.2.1]non-7-ene (126) initially since such a high yield of noracetyltropine (236) had been obtained in the demethylation of acetyltropine (234) using ACE-Cl.

The initial reaction of ACE-Cl with (126) was monitored by 90 MHz ^1H NMR spectroscopy. Addition of ACE-Cl to a dry solution of (126) in $CDCl_3$ at O°C resulted in the almost instantaneous disappearance of the signals corresponding to (126) and simultaneous formation of a signal at δ4.7 attributed to the bridgehead protons of the α-chloroethyl carbamate ester and a less intense signal at δ4.25 which was found to be associated with the bridgehead protons of the hydrochloride salt of (126). Addition of methanol and subsequent heating gave rise to the hydrochloride salts of the demethylated product (237) and starting material (126) in a ratio of 79:21 respectively, as measured by 300MHz ^1H NMR spectroscopy. Following the successful demethylation, it was decided to attempt the debenzylation of (118) with ACE-Cl. This time, however, the addition of ACE-Cl to a dry solution of (118) in $CDCl_3$ at O°C produced no immediate

change in the ^1H NMR spectrum; heating at 60°C was required before any reaction was observed by ^1H NMR spectroscopy. After a total of 24 hours at 60°C, all signals corresponding to (118) had disappeared. As in the demethylation of (126), a signal at δ4.7 was attributed to the bridgehead protons of the carbamate ester and a weak signal at δ4.35 was found to be due to the bridgehead protons of the hydrochloride salt of (118). Hydrolysis of the carbamate ester with methanol produced the hydrochloride salts of the debenzylated product (237) and starting material in a ratio of 87:13 respectively, as indicated by ^1H NMR spectroscopy.



(126) R=Me	79	:	21
(118) R=CH_2Ph	87	:	13

Figure 5.14

The formation of the hydrochloride salts of the starting materials in these dealkylation reactions was thought to be due to the presence of a small amount of water. Consequently, the reaction was repeated on a large scale under totally anhydrous conditions using freshly distilled, dry dichloromethane and further drying of the amine solution

with anhydrous potassium carbonate. After treatment with ACE-Cl and subsequent hydrolysis with methanol, the hydrochloride salt of the demethylated product (237) was isolated in 99% yield.

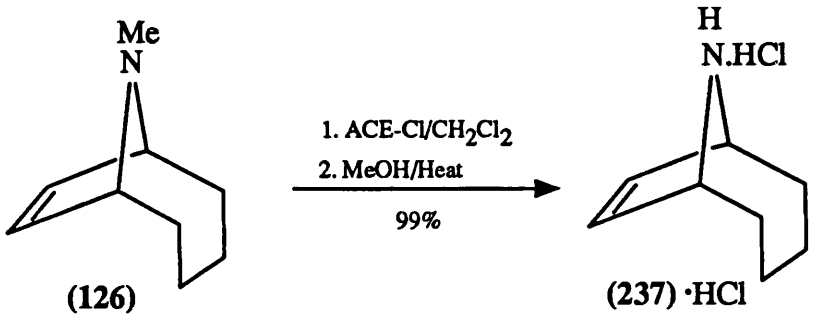
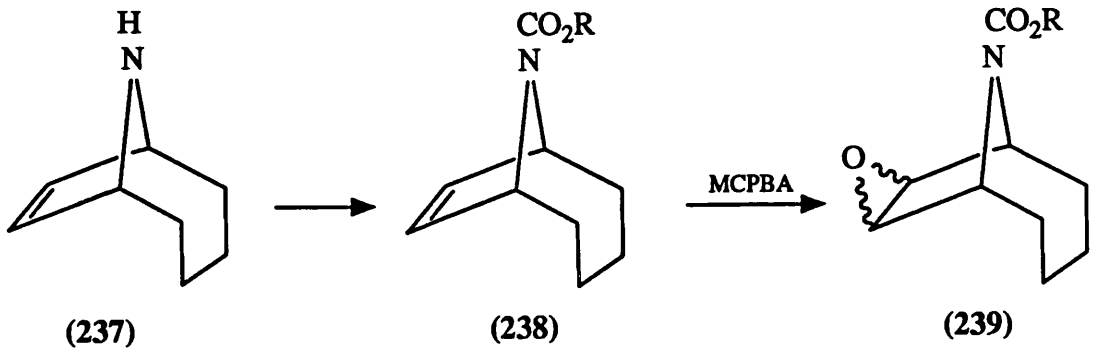


Figure 5.15

The ^{13}C NMR spectrum of 9-azabicyclo[4.2.1]non-7-ene (237) exhibited the expected four signals, and the rest of the spectroscopic data (^{1}H NMR, IR, M^{+}) and microanalysis of the picrate were all in accordance with the proposed structure.

Howarth [35] found that epoxidation of an alkene with MCPBA could proceed smoothly without any complications provided that the amino nitrogen was suitably protected, for example as a urethane. The N-demethylation and N-debenzylation of the unsaturated bicyclic tertiary amines (126) and (118) has successfully provided the parent secondary amine (237) which could be reprotected as a urethane (238) to enable epoxidation of the unsaturated etheno bridge with MCPBA to be achieved. It is therefore feasible that non-natural analogues of scopolamine could ultimately be synthesised

(Figure 5.16).



(237) (238) (239)

Figure 5.16

In this way, it may be possible, by increasing the size of the urethane substituent, to hinder approach from the exo-face and thus produce the non-natural endo-epoxides. It will be difficult to remove the urethane function at the end of the synthesis without affecting the epoxide group. However, having made the epoxide, a number of other reactions could be studied including reduction with lithium aluminium hydride to give 7-hydroxy derivatives, and treatment with base to afford 7, 8-dihydroxy derivatives.

5.5 FACTORS INFLUENCING INVERSION AT NITROGEN

In the ground state, amines exist in an approximately pyramidal sp^3 hybridised state which may undergo spontaneous inversion *via* an sp^2 coplanar transition state to form the other invertomer. [84] The energy required to effect the rapid interconversion of the two invertomers is called the inversion barrier, $\Delta G^{\ddagger}$. Several factors influence either the energy of the ground state or the transition state, and

hence the magnitude of the barrier to inversion at nitrogen. These electronic and steric effects are summarised in Figure 5.17.

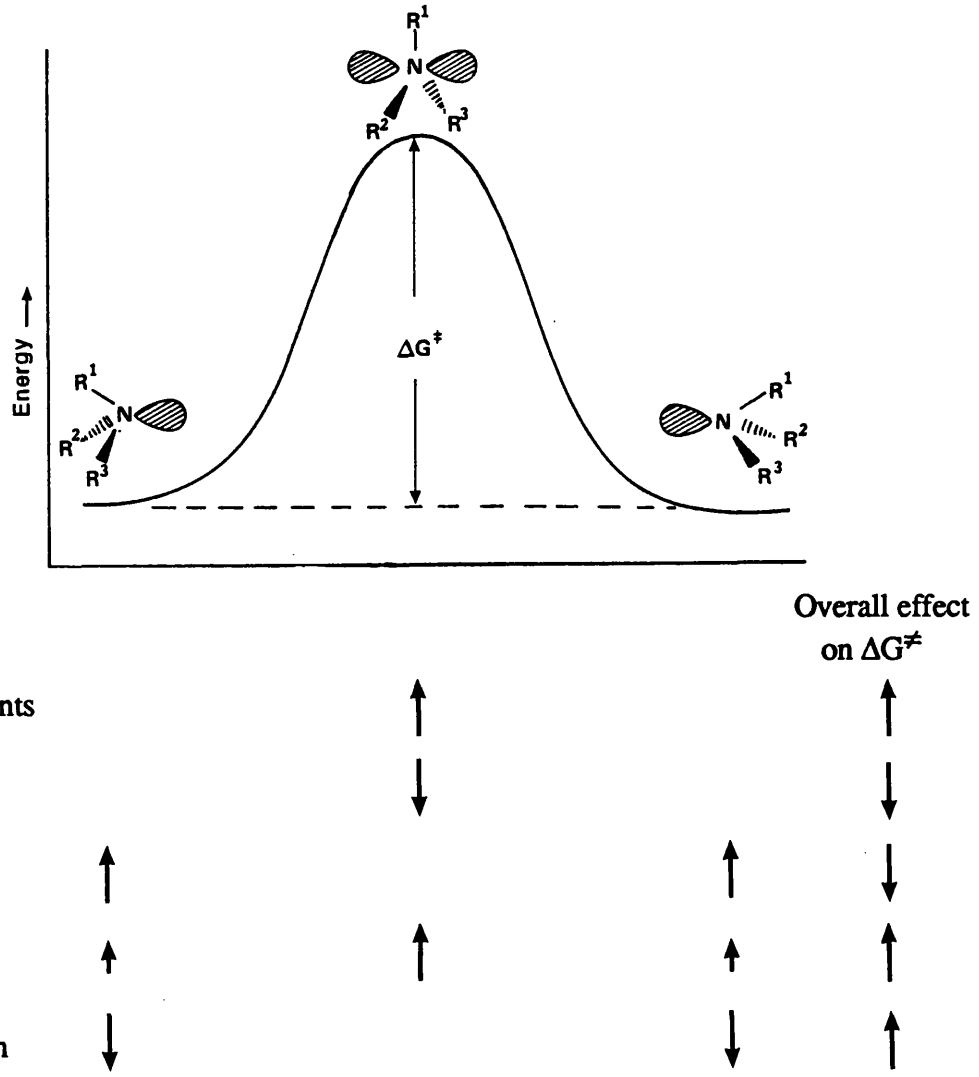


Figure 5.17

7-Azabicyclo[2.2.1]heptane derivatives have especially high nitrogen inversion barriers. Nelson has employed diethoxytriphenylphosphorane [94] to convert (240) to (97) in a single operation. Fraser and Swingle's earlier conversion[33] of (240) to (97) required four steps,

proceeding in 38% overall yield (See Chapter 1). When two mol of diethoxy-phosphorane was used per mol of (240), a 1:1 mixture of (97) and (241) was formed. Treatment of the mixture with ethyl chloroformate in ether efficiently precipitated (241) as its hydrochloride salt, leaving (242) in solution for subsequent reduction to the desired methyl derivative (243) with lithium aluminium hydride.

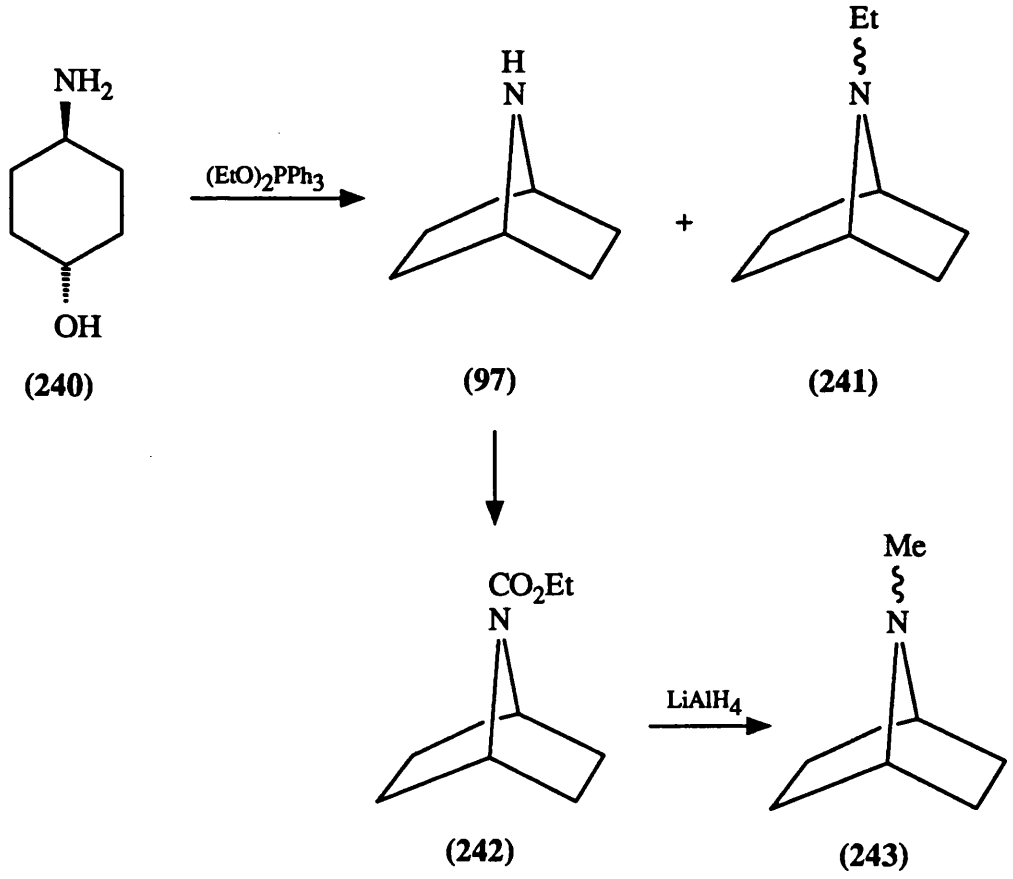


Figure 5.18

Both the methyl and ethyl derivatives were desired for NMR studies and were found to exhibit inversion barriers of $59.0 kJmol^{-1}$ and $55.1 kJmol^{-1}$, respectively. The restriction of the $C_1N_7H_4$ angle by the bicyclic ring system is a factor causing the high $\Delta G^{\neq}$ values observed, but Lehn [84] had

suggested much earlier that there is also a "bicyclic effect" which raises nitrogen inversion barriers in 7-azabicyclo[2.2.1]heptane derivatives, because their inversion barriers are substantially higher than might be expected from the C-N-C angle imposed by the bicyclic framework. The origins of this "bicyclic effect" were not explained satisfactorily by Lehn and remain controversial. The C-N-C bond angle in these azabicycles is ~96°, similar to that in azetidines but the inversion barriers are considerably higher, (Figure 5.19).[84, 95]

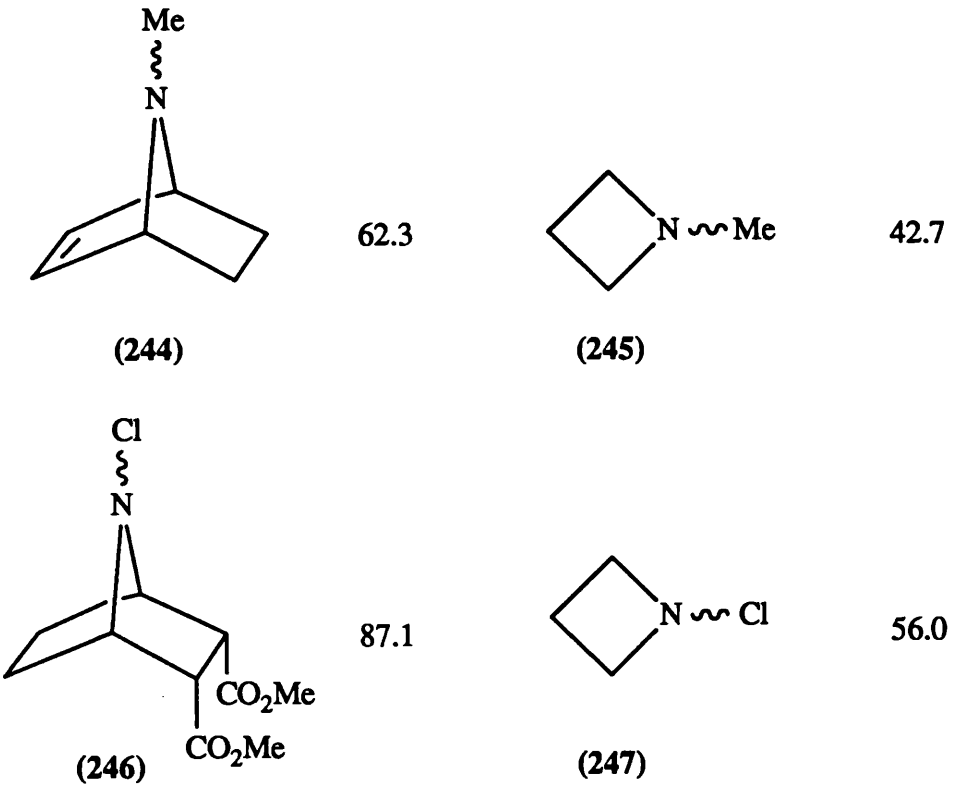
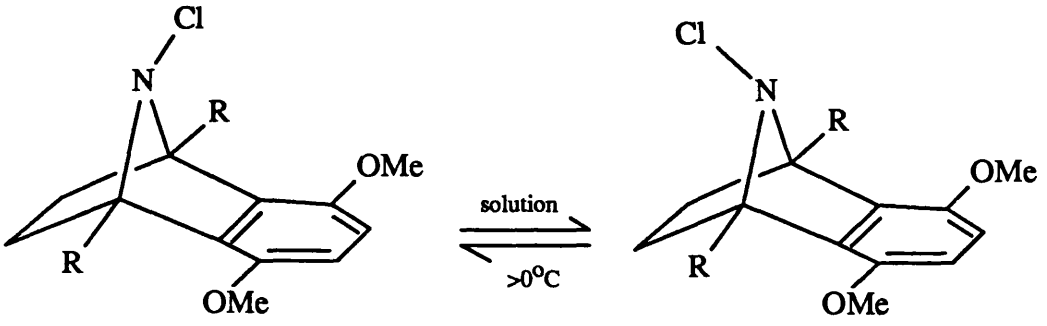


Figure 5.19 Inversion Barrier ($\Delta G^{\ddagger}$/kJ mol^{-1})

Two N-chloroamines incorporating the 7-azabicyclo[2.2.1] heptane skeleton, (248) and (249), have been isolated as stable, crystalline, single diastereoisomers, each of which

retains its stereochemistry indefinitely in the solid state at ambient temperature. [86] The bond angles at the bridgehead carbons in (248) and (249) are unusual. The C-N-C bridge is tilted significantly towards the aryl ring in *anti*-(248) and away from the aryl ring in *syn*-(248). Similar behaviour was observed in (249). The distortion in these molecules was thought to be due to stabilising interactions between the N-Cl bond and the antiperiplanar C-C bonds. Such ground-state stabilisation together with the angle strain at nitrogen in the transition state for inversion were given as explanations for the unusually high inversion barriers observed; 85.8kJmol^{-1} for (249) and >94.6kJmol^{-1} for (248).



syn-(**248**), R=H
syn-(**249**), R=Me

anti-(**248**), R=H
anti-(**249**), R=Me

Figure 5.20

Bathgate [38] treated the hydrochloride of nortropane (5) with sodium hypochlorite in water to yield N-chlorotropane (250). Two invertomers were observed by low temperature ^{13}C NMR spectroscopy in the ratio 95:5, the major invertomer being assigned the structure having the more stable

equatorial orientation of chlorine. [45] The presence of a small amount of the axial-conformer was thought to be due to a stabilising interaction between the N-Cl and the antiperiplanar C(1)-C(7) and C(5)-C(6) bonds, similar to that observed in the 7-azabicyclo[2.2.1]heptane derivatives (248) and (249).

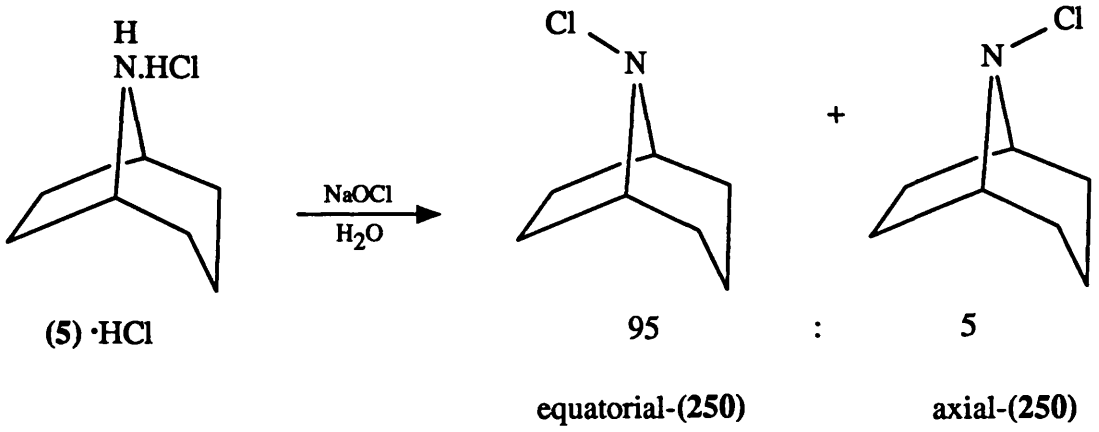


Figure 5.21

5.6 N-CHLOROAMINE SYNTHESIS AND CONCLUSION

The barriers to inversion at nitrogen in 7-azabicyclo [2.2.1]heptane derivatives are due to the "bicyclic effect" which creates an unusual ground-state stabilisation. This stabilisation is increased further by the addition of a π-system into the rigid framework.[83] Cristl[82] commented on the downfield shift of the carbon atom at the 7-position of norbornene and norbornadiene. The π* orbital in norbornene is of relatively low energy which causes a σ-π* interaction. This interaction leads to a downfield shift of C_7. In norbornadiene, the interaction of two double bonds leads to a low-lying π* orbital and hence a substantial

electron-withdrawal from C_7 (Figure 5.22).

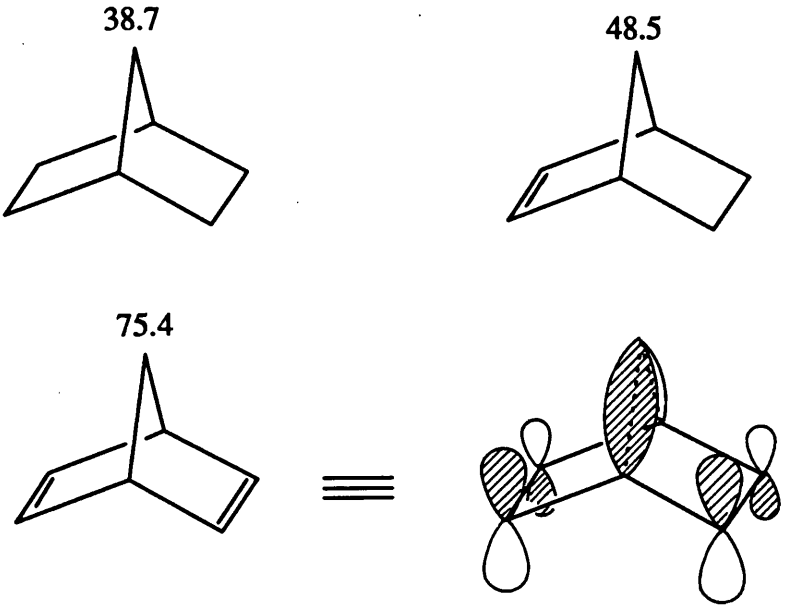
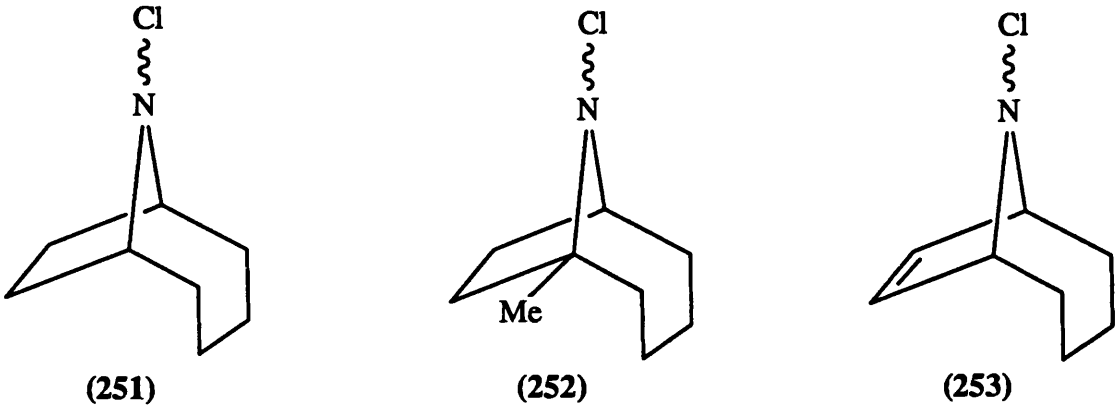


Figure 5.22

The N-chloroamines (251), (252) and (253) were synthesised in almost quantitative yields by treating the respective hydrochloride or picrate salts of the secondary amines with sodium hypochlorite in water. It was hoped that variable temperature NMR spectroscopy would help to determine the inversion barriers in these compounds. The introduction of chlorine at the nitrogen atom[86] was expected to increase the inversion barrier and facilitate observation of the inversion phenomenon.



(251) **(252)** **(253)**

Figure 5.23

The "bicyclic effect" was not expected to operate to a great extent in these rather flexible molecules. However, the incorporation of an etheno-bridge in (253) was expected to raise the inversion barrier with respect to (251) because of destabilising interactions between the bridging π-bond and the nitrogen p-orbital at the transition state for inversion and also because of possible σ-π* interactions stabilising the ground-state of (253). Additionally, the inversion barrier of (251) was expected to be lower than that of (253) because of destabilisation of the ground state due to steric interactions. It would be difficult to separate ground state and transition state effects, both of which would be expected to influence the inversion barrier at nitrogen. Unfortunately, the invertomers of these N-chloroamines were not observed in the temperature range investigated (down to -60°C) and measurements of the inversion barriers could not be made.

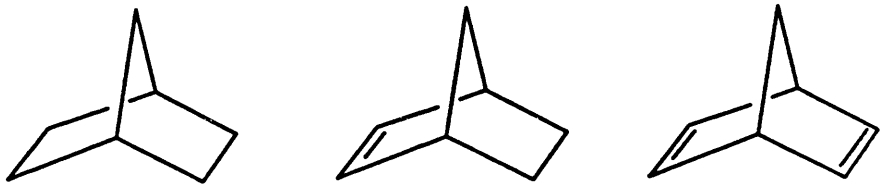
The explanation for this is that either the nitrogen inversion barriers were much lower than those observed in the tropanes or that the invertomer ratios were very heavily weighted to one side in which case coalescence would not be observed. Barrelle[42] concluded that the methyl group in homotropane was preferentially above the five-membered pyrrolidine ring. N-benzyl-9-azabicyclo[4.2.1]non-7-ene (118) would be expected to share this preference, especially as there is less steric hindrance due to the etheno-bridge. The subsequent quaternisation resulted in the formation of only one diastereoisomer *via* the less stable invertomer

which coincided with Bottini's[88] observations that quaternisation of tropanes occurred by preferential attack of the less stable invertomer (i.e. equatorial attack of the axial invertomer). Because of the observation of only one diastereoisomer, it seems likely that the invertomer ratio in (118) is very heavily weighted to one side. As the N-chloroamines (251), (252) and (253) are expected to share the same invertomer preference as in homotropane (6) and (118), it would seem likely that the invertomer ratios were very heavily weighted to one side with the result that coalescence was not observed.

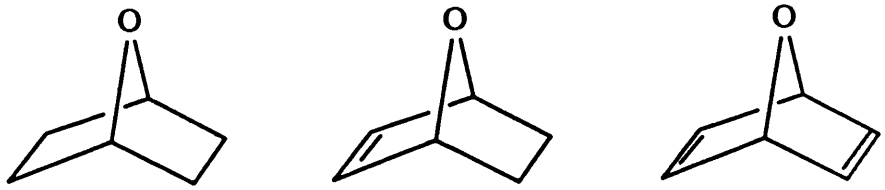
Appendix One

A1.1 INTRODUCTION

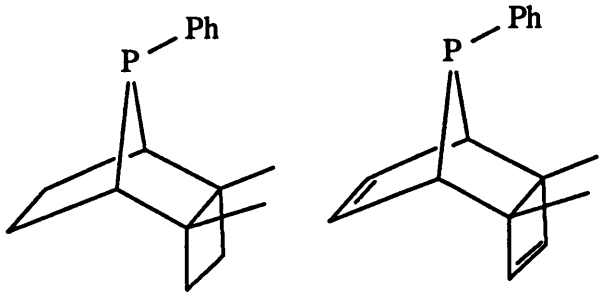
It has been observed that bridging atoms in unsaturated bicyclo [2.2.1] heptyl systems display unusually large deshielding in their NMR spectra. Figure A1.1 illustrates the dependence of deshielding on the degree of unsaturation of the two-carbon bonds. The greater the extent of unsaturation in the bicyclo[2.2.1]heptyl skeleton, the larger the downfield shift of the atom in the 7-position.



δ_c 38.4 48.5 75.1



δ_o 85.5 110.0 192.5



δ_p 22.0 147.0

Figure A1.1 Chemical Shifts of 7-Position Atom (ppm)

A possible explanation for this effect was that ground state polarisation arising from σ - π conjugation [96] might give rise to positive character at the 7-position, thus causing deshielding (Figure A1.2).

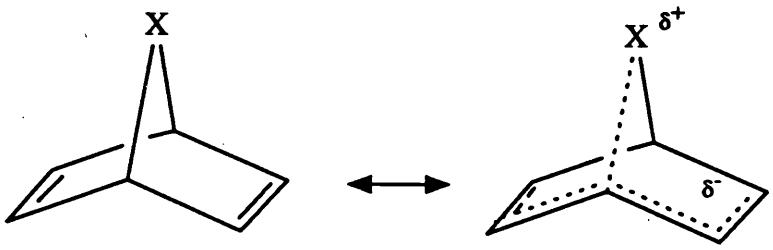
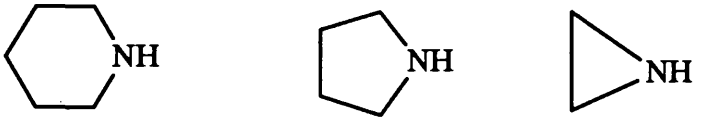


Figure A1.2

However, Cristl's[82] idea (Chapter 5) seems to be a more convincing and better explanation than this idea of enhanced polarisation at the ground state. The acquisition of ^{15}N NMR spectra from samples containing ^{15}N at natural abundance is not simple [97] due to the low natural abundance (0.36%) of ^{15}N and the insensitivity of its nucleus. Thus, it is necessary to use sensitive high field Fourier Transform (FT) NMR spectrometers together with highly concentrated samples. The slow relaxation time of the ^{15}N nucleus necessitates exceptionally long spectral acquisition times. Another drawback is that nuclear Overhauser enhancement factors are negative for ^{15}N, so that the signals became more negative with proton decoupling. Typical chemical shifts (relative to nitromethane) of various amines [98] are quoted in Figure A1.3.

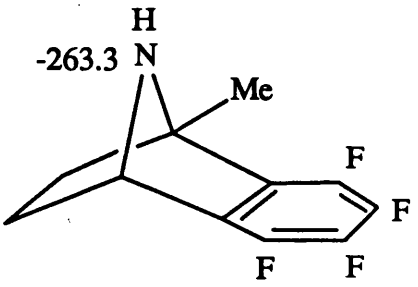
Amine	Chemical Shift (ppm)
RNH_2	-325 → -380
R_2NH	-300 → -370
R_3N	-325 → -330



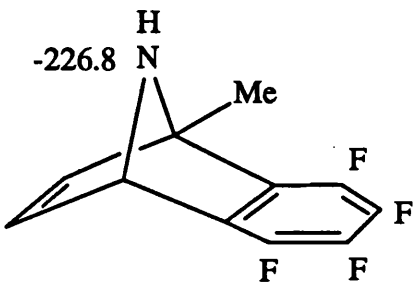
-320 -342 -393

Figure A1.3

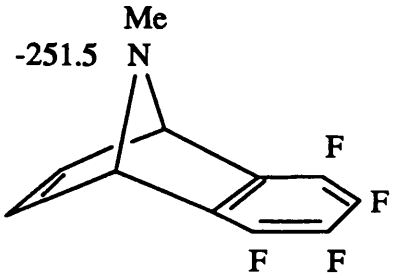
The bridging nitrogen in 7-azabicyclo[2.2.1]heptyl derivatives is unusual, exhibiting anomalously high barriers to inversion. ^{15}N NMR spectroscopy studies [85] have revealed that such systems exhibited extraordinary deshielding in the 7-position as with oxygen [99], phosphorus[96a] and silicon[96b]. Moreover, these amines displayed the lowest field ^{15}N signals yet recorded for secondary and tertiary amines (Figure A1.4).[85] It seems unlikely that angle strain at the 7-position is the major factor for this deshielding phenomenon as atoms in strained rings are normally highly shielded (cf. aziridine in Figure A1.3).



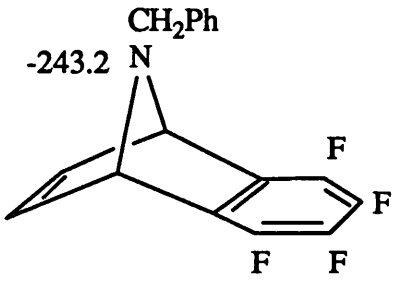
(254)



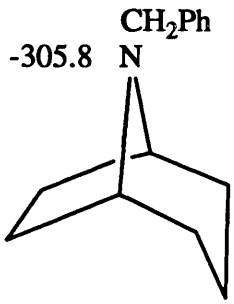
(255)



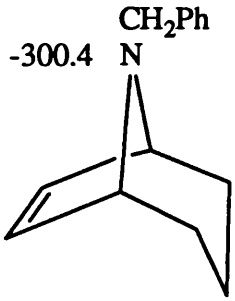
(256)



(257)



(100)



(103)

Figure A1.4 ^{15}N Chemical Shifts (ppm relative to CH_3NO_2)

The 7-azabicyclo[2.2.1]heptane derivatives in Figure A1.4 containing a bridging nitrogen at the 7-position all display low-field ^{15}N NMR signals. The downfield chemical shift of -226.8ppm in the etheno-bridged compound (255) compared with -263.3 ppm in the ethano-bridged analogue (254) parallels similar trends in carbon, [100] phosphorus [96a] and oxygen [99] systems.

Amines (100) and (103) both possess nitrogen inversion

barriers (36.05kJmol^{-1} and 39.0kJmol^{-1}, respectively) which are low; they also have ^{15}N chemical shifts typical of normal tertiary amines. Incorporation of an etheno-bridge in (103) has a slight deshielding effect with respect to (100). However, the extraordinary deshielding of nitrogen in the 7-azabicyclo[2.2.1]heptane derivatives and not in the 8-azabicyclo[3.2.1]octane derivatives suggests that there is a correlation between the ^{15}N chemical shifts and the inversion barriers at nitrogen.

A1.2 ^{15}N NMR CHEMICAL SHIFTS OF VARIOUS BICYCLIC AMINES

Figure A1.5 presents the ^{15}N NMR spectra accumulated during this study.

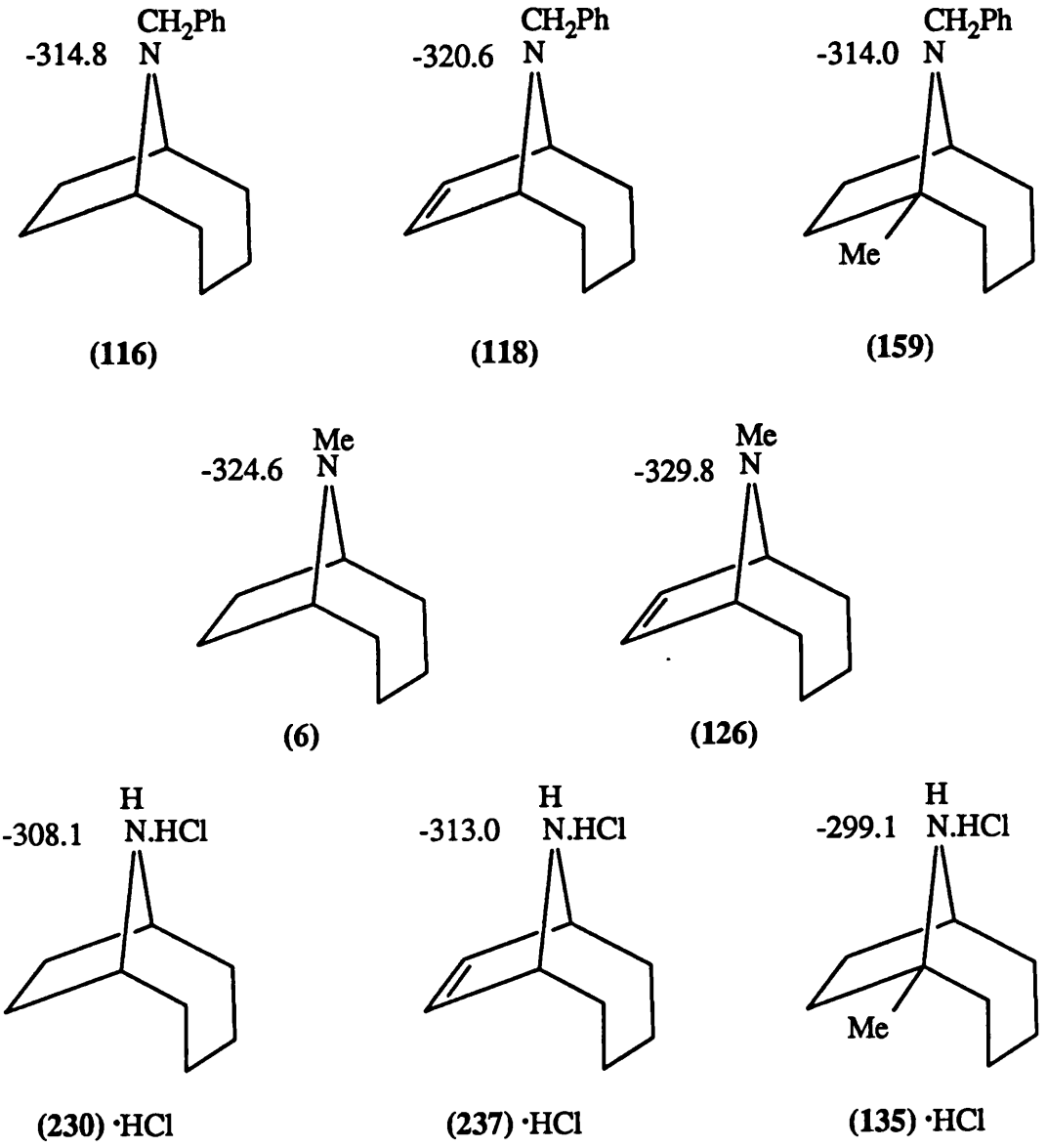


Figure A1.5 ^{15}N Chemical Shifts (ppm relative to CH_3NO_2).

All these amines have ^{15}N chemical shifts typical of normal secondary and tertiary amines. The bridging nitrogen atoms in the N-benzyl derivatives are slightly more deshielded than those in the N-methyl derivatives. This correlates with the observation that the bridging nitrogen in the N-

benzyl benzazanorbornadiene derivative (257) is more deshielded with respect to the N-methyl derivative (256). However, incorporation of an etheno-bridge in these compounds has a slight shielding effect with respect to the saturated derivatives in contrast to the N-benzylnortropanes (100) and (103) which show a slight deshielding effect on incorporation of an etheno-bridge. The presence of the methyl group in (159) has a negligible effect on the ^{15}N chemical shift, but the secondary amine (135) is ~8ppm more deshielded than would be expected.

^{15}N NMR spectroscopy has shown that all the amines containing a bridging nitrogen at the 7-position in the 7-azabicyclo [2.2.1] heptane derivatives display low field ^{15}N NMR signals. Incorporation of a π-system into the rigid framework results in further deshielding of the nitrogen atom. This observation is consistent with Cristl's [82] idea of a σ-π^* interaction resulting in electron withdrawal into the bicyclic framework. The subsequent ground-state stabilisation is thought to be responsible for the further increase in the nitrogen inversion barrier on addition of a π-system. The 8-azabicyclo [3.2.1]octane and 9-azabicyclo[4.2.1]nonane derivatives show ^{15}N NMR chemical shifts typical of normal tertiary amines. These more flexible systems do not seem to possess ground-state stabilisation due to the "bicyclic effect" and incorporation of a π-system has a neglible effect on the ^{15}N NMR chemical shifts.

Appendix Two

A.2 X-RAY CRYSTAL DATA FOR TRIAZOLINE (198)

Crystal Data $C_{10}H_{15}N_3O_2$, M= 209.25, orthorhombic, space group= $P2_12_12_1$, a= 10.271 (9), b= 10.581 (5), c= 9.327 (7) Å, U= 1013.6 $Å^3$, z= 4, μ= 0.59cm^{-1}, λ (Mo-kα) = 0.7107Å, F(000)= 448.0, D_C= 1.37g cm^{-3}

The unit cell parameters were determined by least squares refinement of omega measurements for different layers.[101] The intensities of 2056 unique reflections with $2\theta < 54^o$ and (+h,±k,±l) were measured on a Stoe STADI-2 Weissenberg diffractometer, with graphite monochromated Mo-k_α radiation using an omega-scan technique. The data were corrected for Lorentz and polarisation effects to yield 1389 reflections with $I>3\sigma(I)$.

The structure was solved using the TREF option of SHELXS86.[102] All subsequent calculations were carried out using the computer program SHELX-76.[103]

All hydrogen atoms were located from a difference Fourier map and were included in the final cycles of least squares with isotropic thermal parameters. All other atoms were refined with anisotropic thermal parameters.

Final cycles of refinement employed a weighting parameter g(.0007) $\{w=1/[\sigma^2(F)+g(F)^2]\}$ and gave the final residual indices $R\{=\Sigma|(|Fo|-Fc|)|/\Sigma|Fo|\}$ 0.039 and $Rw\{=[\Sigma w(|Fo|-|Fc|)^2/\Sigma w|Fo|^2]^{1/2}\}$ 0.039. The final difference Fourier was featureless and an analysis of the weighting scheme over |Fo| and $\sin\theta/\lambda$ was satisfactory.

The geometry of the molecule is shown in Figure 4.10. Final atomic positional and thermal parameters have been deposited as supplementary material with the editor from whom copies are available on request.

Table A.2.1 Fractional atomic co-ordinates for $C_{10}H_{15}N_3O_2$

Atom	x	y	z
O(1)	0.24902(25)	0.16993(17)	0.21620(20)
O(2)	0.24089(19)	0.28785(15)	0.01106(18)
N(1)	0.45109(25)	0.34748(22)	0.24807(25)
N(2)	0.4371(3)	0.47327(24)	0.2148(3)
N(3)	0.4465(3)	0.49493(23)	0.0838(3)
C(1)	0.31875(27)	0.20103(23)	0.09125(27)
C(2)	0.3387(3)	0.07740(25)	0.0122(3)
H(21)	0.254(4)	0.0411(26)	-0.0049(29)
H(22)	0.386(3)	0.0220(29)	0.074(3)
C(3)	0.4065(3)	0.0883(3)	-0.1318(3)
H(31)	0.499(3)	0.125(3)	-0.125(3)
H(32)	0.419(3)	0.006(3)	-0.167(3)
C(4)	0.3310(4)	0.1609(3)	-0.2437(3)
H(41)	0.242(5)	0.130(3)	-0.243(4)
C(42)	0.361(3)	0.1387(27)	-0.340(3)
C(5)	0.3361(5)	0.3040(3)	-0.2324(3)
H(51)	0.273(4)	0.3424(27)	-0.290(3)
H(52)	0.412(4)	0.337(3)	-0.274(4)
C(6)	0.3236(3)	0.36021(27)	-0.0816(3)
H(6)	0.287(3)	0.4407(29)	-0.0861(29)
C(7)	0.4506(3)	0.37348(25)	0.0023(3)
H(7)	0.524(3)	0.3715(27)	-0.053(3)
C(8)	0.44722(29)	0.27117(26)	0.11578(28)
H(8)	0.5171(25)	0.2174(24)	0.1173(25)
C(9)	0.2418(4)	0.2675(3)	0.3229(3)
H(91)	0.204(4)	0.345(3)	0.286(4)
H(92)	0.196(3)	0.2332(29)	0.400(4)
C(10)	0.3765(4)	0.3034(4)	0.3701(4)
H(101)	0.375(3)	0.364(3)	0.439(4)
H(102)	0.421(4)	0.228(4)	0.405(4)

Table A.2.2 Atomic Thermal Parameters (x10**4) for $C_{10}H_{15}N_3O_2$

Atom	U or U11	U22	U33	U23	U13	U12
O(1)	580(13)	490(11)	425(10)	10(8)	134(10)	-105(11)
O(2)	295(10)	425(9)	426(9)	3(8)	-29(9)	16(9)
N(1)	456(16)	523(15)	434(13)	-129(12)	-110(12)	10(12)
N(2)	603(18)	493(16)	667(19)	-193(14)	-64(15)	-97(13)
N(3)	760(21)	416(14)	634(18)	-71(12)	4(17)	-151(14)
C(1)	316(14)	332(13)	375(14)	23(11)	7(12)	8(12)
C(2)	467(19)	326(14)	512(18)	-25(14)	-24(16)	-38(14)
H(21)	508(78)					
H(22)	481(85)					
C(3)	576(22)	411(18)	598(21)	-161(16)	133(16)	-5(15)
H(31)	512(86)					
H(32)	568(89)					
C(4)	714(26)	610(20)	380(17)	-135(15)	5(17)	-67(19)
H(41)	785(115)					
C(42)	505(84)					
C(5)	703(24)	641(20)	366(16)	88(15)	-75(18)	-37(19)
H(51)	577(98)					
H(52)	712(117)					
C(6)	521(18)	333(14)	447(16)	61(12)	-30(15)	43(14)
H(6)	516(84)					
C(7)	392(18)	402(15)	490(15)	-40(13)	50(17)	-86(13)
H(7)	430(81)					
C(8)	291(14)	415(14)	404(14)	-51(12)	-43(13)	50(13)
H(8)	257(62)					
C(9)	656(23)	648(22)	404(16)	-14(15)	121(18)	-42(20)
H(91)	642(105)					
H(92)	578(91)					
C(10)	733(24)	668(23)	384(17)	-91(17)	-78(16)	68(20)
H(101)	503(87)					
H(102)	735(110)					

Table A.2.3 Bond lengths (Å) for $C_{10}H_{15}N_3O_2$

C(1)-O(1)	1.407(3)	C(9)-O(1)	1.436(4)
C(1)-O(2)	1.429(3)	C(6)-O(2)	1.434(4)
N(2)-N(1)	1.374(3)	C(8)-N(1)	1.475(3)
C(10)-N(1)	1.449(4)	N(3)-N(2)	1.247(4)
C(7)-N(3)	1.493(4)	C(2)-C(1)	1.515(3)
C(8)-C(1)	1.531(4)	H(21)-C(2)	0.96(4)
H(22)-C(2)	0.96(3)	C(3)-C(2)	1.517(5)
H(31)-C(3)	1.03(3)	H(32)-C(3)	0.94(3)
C(4)-C(3)	1.511(5)	H(41)-C(4)	0.97(5)
C(42)-C(4)	0.97(3)	C(5)-C(4)	1.518(5)
H(51)-C(5)	0.93(4)	H(52)-C(5)	0.94(4)
C(6)-C(5)	1.533(4)	H(6)-C(6)	0.93(3)
C(7)-C(6)	1.527(5)	H(7)-C(7)	0.91(3)
C(8)-C(7)	1.514(4)	H(8)-C(8)	0.916(27)
H(91)-C(9)	0.97(3)	H(92)-C(9)	0.93(4)
C(10)-C(9)	1.501(5)	H(101)-C(10)	0.91(3)
H(102)-C(10)	0.97(4)		

Table A.2.4 Bond Angles (°) for $C_{10}H_{15}N_3O_2$

C(9)-O(1)-C(1)	115.6(2)	C(6)-O(2)-C(1)	109.1(2)
C(8)-N(1)-N(2)	109.8(2)	C(10)-N(1)-N(2)	115.7(3)
C(10)-N(1)-C(8)	117.8(2)	N(3)-N(2)-N(1)	113.0(2)
C(7)-N(3)-N(2)	110.0(2)	O(2)-C(1)-O(1)	107.4(2)
C(2)-C(1)-O(1)	105.6(2)	C(2)-C(1)-O(2)	112.1(2)
C(8)-C(1)-O(1)	115.4(2)	C(8)-C(1)-O(2)	104.4(2)
C(8)-C(1)-C(2)	112.0(2)	H(21)-C(2)-C(1)	107.6(17)
H(22)-C(2)-C(1)	107.6(18)	H(22)-C(2)-H(21)	108.3(25)
C(3)-C(2)-C(1)	115.3(2)	C(3)-C(2)-H(21)	107.3(17)
C(3)-C(2)-H(22)	110.5(18)	H(31)-C(3)-C(2)	113.3(16)
H(32)-C(3)-C(2)	107.3(19)	H(32)-C(3)-H(31)	104.3(27)
C(4)-C(3)-C(2)	114.5(3)	C(4)-C(3)-H(31)	109.1(17)
C(4)-C(3)-H(32)	107.6(20)	H(41)-C(4)-C(3)	107.7(22)
C(42)-C(4)-C(3)	110.7(18)	C(42)-C(4)-H(41)	102.6(28)
C(5)-C(4)-C(3)	116.2(3)	C(5)-C(4)-H(41)	111.8(23)
C(5)-C(4)-C(42)	107.1(17)	H(51)-C(5)-C(4)	111.9(19)
H(52)-C(5)-C(4)	112.0(22)	H(52)-C(5)-H(51)	100(3)
C(6)-C(5)-C(4)	116.6(3)	C(6)-C(5)-H(51)	107.4(19)
C(6)-C(5)-H(52)	107.4(21)	C(5)-C(6)-O(2)	113.3(2)
H(6)-C(6)-O(2)	106.1(19)	H(6)-C(6)-C(5)	110.3(17)
C(7)-C(6)-O(2)	104.3(2)	C(7)-C(6)-C(5)	115.8(3)
C(7)-C(6)-H(6)	106.4(18)	C(6)-C(7)-N(3)	108.4(3)
H(7)-C(7)-N(3)	109.3(19)	H(7)-C(7)-C(6)	114.2(19)
C(8)-C(7)-N(3)	105.0(2)	C(8)-C(7)-C(6)	105.8(2)
C(8)-C(7)-H(7)	113.5(18)	C(1)-C(8)-N(1)	114.4(2)
C(7)-C(8)-N(1)	101.1(2)	C(7)-C(8)-C(1)	105.2(2)
H(8)-C(8)-N(1)	107.8(15)	H(8)-C(8)-C(1)	112.1(15)
H(8)-C(8)-C(7)	115.9(15)	H(91)-C(9)-O(1)	112.6(20)
H(92)-C(9)-O(1)	106.3(20)	H(92)-C(9)-H(91)	113.9(29)
C(10)-C(9)-O(1)	109.7(3)	C(10)-C(9)-H(91)	104.7(22)
C(10)-C(9)-H(92)	109.5(21)	C(9)-C(10)-N(1)	109.8(3)
H(101)-C(10)-N(1)	109.7(20)	H(101)-C(10)-C(9)	111.7(20)
H(102)-C(10)-N(1)	106.2(22)	H(102)-C(10)-C(9)	108.7(23)
H(102)-C(10)-H(101)	111(3)		

Table A.2.5 Non-bonded Contacts (Å) for $C_{10}H_{15}N_3O_2$

O(2)...O(1)	2.286	C(2)...O(1)	2.329
C(8)...O(1)	2.484	H(91)...O(1)	2.020
H(92)...O(1)	1.919	C(10)...O(1)	2.402
C(2)...O(2)	2.443	C(5)...O(2)	2.478
H(6)...O(2)	1.913	C(7)...O(2)	2.338
C(8)...O(2)	2.340	N(3)...N(1)	2.187
C(1)...N(1)	2.527	C(7)...N(1)	2.308
H(8)...N(1)	1.960	C(9)...N(1)	2.413
H(101)...N(1)	1.956	H(102)...N(1)	1.956
C(7)...N(2)	2.250	C(8)...N(2)	2.332
C(10)...N(2)	2.390	C(6)...N(3)	2.450
H(6)...N(3)	2.350	H(7)...N(3)	1.991
C(8)...N(3)	2.386	H(21)...C(1)	2.028
H(22)...C(1)	2.023	C(3)...C(1)	2.561
C(6)...C(1)	2.332	C(7)...C(1)	2.419
H(8)...C(1)	2.059	C(9)...C(1)	2.406
C(10)...C(1)	2.879	H(31)...C(2)	2.144
H(32)...C(2)	2.006	C(4)...C(2)	2.547
C(8)...C(2)	2.526	H(22)...H(21)	1.558
C(3)...H(21)	2.026	C(3)...H(22)	2.058
H(41)...C(3)	2.026	C(42)...C(3)	2.065
C(5)...C(3)	2.571	H(32)...H(31)	1.553
C(4)...H(31)	2.088	C(4)...H(32)	2.003
H(51)...C(4)	2.055	H(52)...C(4)	2.064
C(6)...C(4)	2.596	C(42)...H(41)	1.515
C(5)...H(41)	2.081	C(5)...C(42)	2.030
H(6)...C(5)	2.051	C(7)...C(5)	2.592
H(52)...H(51)	1.436	C(6)...H(51)	2.017
C(6)...H(52)	2.025	H(7)...C(6)	2.076
C(8)...C(6)	2.426	C(7)...H(6)	2.001
H(8)...C(7)	2.084	C(8)...H(7)	2.056
C(9)...C(8)	2.861	C(10)...C(8)	2.504
H(101)...C(9)	2.026	H(102)...C(9)	2.032
H(92)...H(91)	1.596	C(10)...H(91)	1.985
C(10)...H(92)	2.014	H(102)...H(101)	1.549

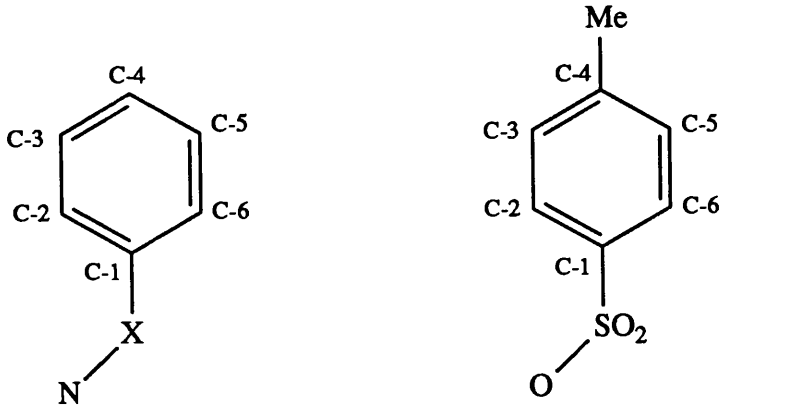
Chapter Six

EXPERIMENTAL

EXPERIMENTAL

INSTRUMENTATION

Low field ^{1}H NMR spectra were recorded on a Perkin-Elmer EM 390 spectrometer. High field ^{1}H NMR (300 MHz), ^{13}C (75.468 MHz) and ^{15}N (30.423 MHz) spectra were recorded on a Bruker M 300 spectrometer. ^{13}C NMR spectra were run with broad band decoupling and multiplicities were determined using the D.E.P.T pulse sequence. Chemical shifts were recorded in ppm (δ) downfield from the internal reference tetramethylsilane (TMS) for ^{1}H and ^{13}C, and upfield from the external reference nitromethane for ^{15}N. ^{13}C NMR signals of the aromatic ring in benzoyl, benzyl and *p*-toluenesulphonate (tosyl) groups gave been assigned using the following numbering system:



X=C=O (Benzoyl)

X=CH_2 (Benzyl)

Tosyl

Signal characteristics are described using the following standard abbreviations and combinations of these:

(s) - singlet, (d) - doublet, (t) - triplet,

(q) - quartet, (m) - multiplet, (exch) - exchangeable,

(br) - broad.

Infra-red spectra were recorded as solutions in CH_2Cl_2 on a Perkin-Elmer 298 spectrometer using 0.1mm sodium chloride solution cells. Band positions, given in wavenumbers (cm^{-1}) are described by the standard abbreviations:
(s) - strong, (m) - medium, (w) - weak, (br) - broad.
Variable-temperature infra-red spectra were recorded on a Perkin-Elmer 681 spectrometer with a low temperature Specac attachment.

Routine mass spectra were obtained using a VG Micromass 16B spectrometer in this department, and a VG:TRIO 3 spectrometer at Leicester Polytechnic. High resolution mass spectra were obtained by the S.E.R.C. Mass Spectrometry Centre at the University College of Swansea.

Elemental analyses were carried out by Butterworth Laboratories Ltd, Teddington, Middlesex.

Melting points were determined using a Kofler microheating stage and are uncorrected. Melting points of the amine picrate salts were determined using a Griffin melting point apparatus and are uncorrected.

TECHNICAL

Diethyl ether was dried over sodium wire and then distilled from lithium aluminium hydride.

Dichloromethane, toluene and benzene were distilled from calcium hydride.

Petroleum ether and ethyl acetate were distilled prior to use.

Methanol and ethanol were dried and purified with magnesium and iodine as described by Vogel.[40]

Tetrahydrofuran was distilled from sodium-benzophenone.

Triethylamine and pyridine were distilled from potassium hydroxide.

All other solvents and reagents were dried and purified as described by Perrin *et al.* (104). Flash chromatography was carried out according to the method of Still *et al.* (105) using silica gel manufactured by Merck and Co., Kieselgel 60, 230 - 400 mesh (ASTM). Thin layer chromatography was conducted on pre-coated aluminium sheets (60 - 254) with a 0.2mm layer thickness of silica gel, manufactured by Merck and Co.

TETRAMETHYLAMMONIUM PERIODATE[37]

A solution of paraperiodic acid (18.60g, 81.6mmol) in water (48ml) was added in portions to a 20% solution of tetramethylammonium hydroxide in methanol (37.19g, 81.6mmol), whilst stirring at 0°C. The precipitate was separated by filtration, washed with cold methanol and dried in a vacuum desiccator yielding tetramethylammonium periodate (17.25g, 80%) as a white crystalline solid, m.p. 253 - 254°C.

N-BENZOYL-9-OXA-10-AZABICYCLO[4.2.2]DECA-7-ENE (109)[38]

1,3-Cyclooctadiene (7.8ml, 62.97mmol) was added to a suspension of tetramethylammonium periodate (23.00g, 86.80mmol) in chloroform (700ml). A solution of benzohydroxamic acid (12.35g, 89.86mmol) in dimethylformamide (80ml) and chloroform (190ml) was added to this mixture dropwise, with stirring, over 30 minutes. After stirring at room temperature for a further 15h, the solution was filtered and the solvent distilled at reduced pressure yielding an oil which was dissolved in diethyl ether (1.3l) and washed with water (3 x 300ml). The organic layer was separated, dried over anhydrous magnesium sulphate, and the solvent was evaporated at reduced pressure producing a yellow-orange oil which was purified by flash chromatography (3:2 petroleum ether (40 - 60°C): diethyl ether) to yield (109) (6.82g, 45%) as colourless crystals, m.p. 72.5 - 73.5°C (from petroleum ether (40 - 60°C)).

δ_H (300MHz, $CDCl_3$, 40°C): 1.43 - 2.36 (series of m, 8H), 4.69 (very brm, 1H, *bridgehead α-N*) 5.26 (very brm, 1H, *bridgehead α-O*), 5.90 (dd, J=10.0Hz, J=5.1Hz, 1H, *double bond, β-N*) 6.32 (dd, J=10.0Hz, J=7.2Hz, 1H, *double bond, β-O*), 7.33 - 7.44 (m,3H, *aromatic*), 7.67 (brs,2H, *aromatic*).

δ_C (75MHz, $CDCl_3$, 40°C): 22.7 (CH_2), 24.8 (CH_2), 31.3 (CH_2), 34.5 (CH_2), 50.9 (CH, *bridgehead C-N*), 77.1 (CH, *bridgehead C-O*), 127.0 (CH, *double bond*), 127.6 (CH, *benzoyl C-2/C-6*), 128.4 (CH, *benzoyl C-3/C-5*), 130.2 (CH, *benzoyl C-4*), 130.6 (CH, *double bond*), 134.7 (C, *benzoyl C-1*), 167.3 (C, *benzoyl C=O*).

ν_{max} (CH_2Cl_2): 3050w, 2930s, 2860w, 1620vs, 1575m, 1445m, 1425m, 1385m, 1320w, 1270w, 1215w, 1185m cm^{-1}.

$^m/_z$ (%): 243 (M^+,7), 122 (3), 106 (9), 105 (100), 77 (26), 51 (6).

Found: C, 73.85; H, 7.06; N, 5.80%

$C_{15}H_{17}NO_2$ requires: C, 74.05; H, 7.04; N, 5.76%

CIS-4-(BENZOYLAMINO)-2-CYCLOOCTENOL(110)

A solution of (109) (15.85g, 65.2mmol) in aqueous tetrahydrofuran (420ml) (THF:H_2O, 10:1) was cooled to 0°C with stirring under N_2. Aluminium amalgam, prepared by sequential exposure (1 min) of small strips of aluminium foil (17.6g, 0.652mol, 10equivs) to 1M (aq) potassium

hydroxide solution, distilled water, 0.5% mercuric chloride, distilled water and tetrahydrofuran, was then added to the solution of Diels-Alder adduct. Stirring was continued at 0°C for 16h. The reaction mixture was diluted with tetrahydrofuran (1.3l), stirred vigorously for 1.5h, then filtered through a sintered glass funnel. The inorganic residue was washed with ethyl acetate and the organic solutions were combined and concentrated at reduced pressure yielding an oil which was diluted with toluene and evaporated at reduced pressure to give (110) (15.82g, 99%) as a white crystalline solid, m.p. 186 - 187°C (from ethyl acetate).

δ_H (300MHz, $CDCl_3$): 1.40 - 1.76 (m,6H), 1.87 - 2.05 (m, 2H), 2.17 (brs, exch *-OH*, 1H), 4.75 (brm, 1H, *α-NHCOPh*), 4.89 (brm, 1H, *α-OH*), 5.37 (ddd, J=10.8Hz, J=8.3Hz, J=1.7Hz, 1H, *double bond*), 5.67 (ddd, J=10.8Hz, J=6.9Hz, J=1.4Hz, 1H, *double bond*), 6.20 (brd, J=6.7Hz, exch *-NH*, 1H), 7.39 - 7.52 (m, 3H, *aromatic*), 7.71 - 7.80 (m, 2H, *aromatic*).

δ_C (75MHz, CD_3OD): 24.5 (CH_2), 25.4 (CH_2), 37.2 (CH_2), 39.7 (CH_2), 49.3 (CH, *C-NHCOPh*), 70.1 (CH, *C-OH*), 128.2 (CH, *benzoyl C-2/C-6*), 129.4 (CH, *benzoyl C-3/C-5*), 129.8 (CH, *double bond*), 132.5 (CH, *benzoyl C-4*), 135.8 (C, *benzoyl C-1*), 136.0 (CH, *double bond*), 169.3 (C, *benzoyl C=O*).

ν_{max} (CH_2Cl_2): 3600m, 3410m, 3050w, 2915m, 2860w, 1665s, 1580w, 1510s, 1485m, 1365m cm^{-1}.

$^{m}/_{z}$ (%): 245 (M^+, 3), 227 (13), 140 (7), 130 (6), 124 (15), 122 (22), 106 (17), 105 (100), 104 (21), 77 (49), 51 (11).

Found: C, 73.25; H, 7.92; N, 5.69%

$C_{15}H_{19}NO_2$ requires: C, 73.44; H, 7.81; N, 5.71%

CIS-4-(BENZOYLAMINO)CYCLOOCTANOL (111)

A solution of (110) (9.50g, 38.72mmol) in dry methanol (200ml) was hydrogenated at 1 atm in the presence of 10% palladium on charcoal. After 28h, the solution was filtered through celite and then through a Millipore 0.2μ Millex-FG disposable filter unit giving a clear solution which was evaporated at reduced pressure yielding (111) (9.53g, 100%) as a white solid, m.p. 110.5 - 112°C (from ethyl acetate).

δ_H (300MHz, $CDCl_3$): 1.51 - 2.03 (series of m, incl. exch *-OH*, 12H + 1H), 3.88 (brm, 1H, *α-NHCOPh*), 4.12 (brm, 1H, *α-OH*), 6.25 (brd, J=7.5Hz, exch *-NH*, 1H), 7.36 - 7.50 (m, 3H, *aromatic*), 7.70 - 7.77 (m,2H, *aromatic*).

δ_C (75MHz, $CDCl_3$): 22.0 (CH_2), 23.6 (CH_2), 27.9 (CH_2), 30.9 (CH_2), 31.4 (CH_2) 33.2 (CH_2), 49.9 (CH, *C-NHCOPh*), 71.0 (CH, *C-OH*), 126.8 (CH, *benzoyl C-2/C-6*), 128.4 (CH, *benzoyl C-3/C-5*), 131.2 (CH, *benzoyl C-4*), 134.9 (C, *benzoyl C-1*), 166.4 (C, *benzoyl C=O*).

ν_{max} (CH_2Cl_2): 3600m, 3460m, 3020w, 2935s, 2860m, 1655s, 1580w, 1515s, 1485m, 1445w, 1365m, 1315w, 1270w cm^{-1}.

$^m/_z$ (%): 247 (M^+, 2) 229 (18), 201 (8), 147 (10), 121 (73), 108 (23), 106 (19), 105 (100), 103 (27), 77 (98), 51 (20).

Found: C, 72.72; H, 8.30; N, 5.68%

$C_{15}H_{21}NO_2$ requires: C, 72.84; H, 8.56; N, 5.66%

N-BENZOYL-9-OXA-10-AZABICYCLO[4.2.2] DECANE(112)

A solution of (109) (5.90g, 24.27mmol) in dry methanol (100ml) was hydrogenated at 1 atm in the presence of 10% palladium on charcoal. After 6h, the solution was filtered through celite and then through a Millipore 0.2μ Millex-FG disposable filter unit giving a clear solution which was evaporated at reduced pressure yielding (112)(5.69g, 96%) as a white solid, m.p. 78 - 80°C (from petroleum ether (40 - 60°C)).

δ_H (300MHz, $CDCl_3$): 1.44 - 2.45 (series of m, 12H), 4.45 (m, 1H, *bridgehead α-N*), 4.90 (m, 1H, *bridgehead α-O*), 7.31 - 7.45 (m, 3H, *aromatic*), 7.63 - 7.73 (brdd, J=7.4Hz, J=2.0Hz, 2H, *aromatic*).

δ_C (75MHz, $CDCl_3$): 20.7 (CH_2), 22.5 (CH_2), 23.9 (CH_2), 24.6 (CH_2), 32.5 (CH_2) 34.5 (CH_2), 49.9 (CH, *bridgehead C-N*), 77.0 (CH, *bridgehead C-O*), 127.6 (CH, *benzoyl C-2/C-6*),

128.6 (CH, *benzoyl C-3/C-5*), 130.0 (CH, *benzoyl C-4*), 134.5 (C, *benzoyl C-1*), 167.3 (C, *benzoyl C=O*).

ν_{max} (CH_2Cl_2): 3020w, 2930s, 2860m, 1615vs, 1575m, 1445s, 1425m, 1365m, 1340w, 1320w, 1295w, 1230w, 1200m, 1085m cm^{-1}.

$m/_z$ (%): 245 (M^+, 6), 140 (3), 106 (20), 105 (100), 77 (50), 67 (6), 51 (17), 41 (11).

Found: C, 73.22; H, 7.90; N, 5.69%

$C_{15}H_{19}NO_2$ requires: C, 73.44; H, 7.81; N, 5.71%

CIS-4-(BENZYLAMINO)CYCLOOCTANOL (113)

A solution of (111) (2.33g, 9.42mmol) in dry tetrahydrofuran (100ml) was added dropwise to a stirred slurry of lithium aluminium hydride (1.43g, 37.68mmol) in dry tetrahydrofuran (50ml). After refluxing for 24h, decomposition of excess hydride was effected by addition of water. The inorganic solids were removed by filtration and washed with warm ethyl acetate. The combined organic solutions were evaporated at reduced pressure to yield (113) (2.17g, 99%) as a white solid, m.p. 85.5 - 87.0°C (from ethyl acetate).

δ_H (300MHz, $CDCl_3$): 1.40 - 1.88 (series of m, incl. 2H exch - *NH and -OH*, 12H + 2H) 2.68 (m, 1H, *α-NHCH$_2$Ph*), 3.76 (s, 2H, *benzyl CH$_2$*), 3.82 (m, 1H, *α-OH*), 7.21 - 7.35 (m, 5H, *aromatic*).

δ_C (75MHz, $CDCl_3$): 22.2 (CH_2), 24.1 (CH_2), 28.2 (CH_2), 31.0 (CH_2), 31.3 (CH_2), 33.8 (CH_2), 51.4 (CH_2, *benzyl* CH_2), 56.9 (CH, *C-NHCH$_2$Ph*), 71.5 (CH, *C-OH*), 126.8 (CH, *benzyl C-4*), 128.1 (CH, *benzyl C-2/C-6*), 128.4 (CH, *benzyl C-3/C-5*), 140.6 (C, *benzyl C-1*).

ν_{max} (CH_2Cl_2): 3605m, 3440brw, 3030m, 2930s, 2860m, 1600w, 1495w, 1450m, 1365w, 1275w, 1200w, 1100m, 1060m, 1030m, 1005w cm^{-1}.

$^m/_z$ (%): 233 (M^+, 7), 147 (11), 146 (61), 133 (41), 132 (12), 120 (8), 106 (14), 92 (9), 91 (100).

Found: C, 77.32; H, 10.02; N, 6.04%

$C_{15}H_{23}NO$ requires: C, 77.21; H, 9.93; N, 6.00%

N-BENZYL-9-AZABICYCLO[4.2.1]NONANE (116)

Thionyl bromide (1.029g, 383µl, 4.95mmol) was added dropwise to a solution of (113) (1.10g, 4.71mmol) in dry dichloromethane (50ml) with stirring at 0°C under dry N_2. The reaction mixture was allowed to warm to room temperature and stirred for a further 12h. After cooling to 0°C, dry TMP (700mg, 836µl, 4.95mmol) was added and the solution was stirred for 24h at room temperature. The mixture was filtered and the filtrate was concentrated at reduced pressure giving a yellow-orange oil which was purified by flash chromatography (1:1 petroleum ether (40 - 60°C): diethyl ether, saturated with gaseous ammonia) to yield

(116) (547mg, 54%) as a pale yellow oil, b.p. 140°C (0.4mm Hg).

δ_H (300MHz, $CDCl_3$): 1.22 - 2.17 (series of m, 12H), 3.29 (brm, 2H, *bridgeheads*), 3.74 (s, 2H, *benzyl CH_2*), 7.17 - 7.40 (m, 5H, *aromatic*).

δ_C (75MHz, $CDCl_3$): 24.9 (CH_2), 30.7 (CH_2), 35.9 (CH_2), 59.4 (CH, *bridgeheads*), 62.6 (CH_2, *benzyl CH_2*), 126.4 (CH, *benzyl C-4*), 128.0 (CH, *benzyl C-2/C-6*), 128.1 (CH, *benzyl C-3/C-5*), 141.5 (C, *benzyl C-1*).

ν_{max} (CH_2Cl_2): 3080w, 3020w, 2920s, 1600w, 1495m, 1470m, 1450m, 1385w, 1345m, 1300w, 1205w, 1150m, 1130m, 1100m, 1070m, 1030m, 945m cm^{-1}.

$^m/_z$ (%): 216 (10), 215 (M^+, 18), 167 (31), 149 (94), 91 (100), 71 (42), 57 (71).

$C_{15}H_{21}N$ [M^+] Requires: 215.1674
Found: 215.167

CIS-4-(BENZYLAMINO)-2-CYCLOOCTENOL (117)

A solution of (110) (3.30g, 14.26mmol) in dry tetrahydrofuran (140ml) was added dropwise to a stirred slurry of lithium aluminium hydride (2.16g, 57.0mmol) in dry tetrahydrofuran (80ml). After refluxing for 24h, decomposition of excess hydride was effected by addition of

water. The inorganic solids were removed by filtration and washed with warm ethyl acetate. The combined organic solutions were evaporated at reduced pressure to yield (117) (3.25g, 99%) as a white solid, m.p. 120.5 - 121.5°C (from ethyl acetate).

δ_H (300MHz, $CDCl_3$): 1.34 - 1.91 (series of m, incl. 2H exch - *NH and -OH*, 8H + 2H), 3.48 (m, 1H, *α-NHCH$_2$Ph*), 3.63, 3.79 (ABq, J=13.0Hz, 2H, *benzyl CH$_2$*), 4.47 (m, 1H, *α-OH*), 5.42 (ddd, J=11.0Hz, J=8.2Hz, J=1.7Hz, 1H, *double bond*), 5.65 (ddd, J=11.0Hz, J=6.9Hz, J=1.3Hz, 1H, *double bond*) 7.21 - 7.36 (m, 5H, *aromatic*).

δ_C (75MHz, CD_3OD): 24.8 (CH_2), 25.4 (CH_2), 37.0 (CH_2), 39.9 (CH_2), 52.3 (CH_2, *benzyl CH$_2$*), 55.0 (CH, *C-NHCH$_2$Ph*), 70.5 (CH, *C-OH*), 128.1 (CH, *benzyl C-4*), 129.4 (CH, *benzyl C-2/C-6*), 129.7 (CH, *benzyl C-3/C-5*), 132.1 (CH, *double bond*), 137.4 (CH, *double bond*), 140.5 (C, *benzyl C-1*).

ν_{max} (CH_2Cl_2): 3600m, 3020w, 2930s, 2850m, 1490w, 1450m, 1195w, 1100m, 1035m cm^{-1}.

$^m/_z$ (%): 232 (9), 231 (M^+, 6), 172 (13), 172 (15), 147 (8), 146 (9), 141 (9), 140 (6), 92 (11), 91 (100).

Found: C, 77.88; H, 9.31; N, 6.06%

$C_{15}H_{21}NO$ requires: C, 77.88; H, 9.15; N, 6.05%

N-BENZYL-9-AZABICYCLO[4.2.1]NON-7-ENE (118)

Thionyl bromide (2.328g, 868µl, 11.20mmol) was added dropwise to a solution of (117) (2.47g, 10.67mmol) in dry dichloromethane (100ml) with stirring at 0°C under dry N_2. The reaction mixture was allowed to warm to room temperature and stirred for a further 12h. After cooling to 0°C, dry TMP (1.582g, 1.896ml, 11.20mmol) was added and the solution was stirred for 24h at room temperature. The mixture was filtered and the filtrate was concentrated at reduced pressure giving an orange oil which was purified by flash chromatography (1:1 petroleum ether (40 - 60°C)): diethyl ether, saturated with gaseous ammonia) to yield (118) (1.47g, 65%) as a pale yellow oil, b.p. 150°C (0.4mmHg).

δ_H (300MHz, $CDCl_3$): 1.26 - 1.36 (m, 2H), 1.43 - 1.55 (m, 2H), 1.66 - 1.78 (m, 4H), 3.63 (ddd, J=7.6Hz, J=1.7Hz, J=1.0Hz, 2H, *bridgeheads*), 3.66 (s, 2H), 5.69 (d, J=1.0Hz, 2H, *double bond*), 7.17 - 7.43 (m, 5H, *aromatic*).

δ_C (75MHz, $CDCl_3$): 25.0 (CH_2), 33.1 (CH_2), 61.4 (CH_2, *benzyl* CH_2), 69.4 (CH, *bridgeheads*), 126.4 (CH, *benzyl C-4*), 128.0 (CH, *benzyl C-2/C-6*), 128.1 (CH, *benzyl C-3/C-5*), 131.2 (CH, *double bond*), 141.5 (C, *benzyl C-1*).

ν_{max} (CH_2Cl_2): 3080w, 3060m, 3020m, 2920s, 2850m, 2800m, 1720w, 1600w, 1490m, 1435m, 1370w, 1350m, 1335m, 1320m, 1195m, 1120m, 1100m, 1080m, 1070m, 1025m, 970m, 910s cm^{-1}.

$^{m}/_{z}$ (%) 214 (14), 213 (M^+, 72), 184 (7), 171 (67), 170 (100), 157 (9), 92 (23), 91 (100), 80 (13), 65 (29).

$C_{15}H_{19}N[M^+]$ Requires: 213.1518

Found: 213.152

N-(BENZYLOXYCARBONYL)-9-OXA-10-AZABICYCLO[4.2.2]DECA-7-ENE (122)

1,3-Cyclooctadiene (46.36g, 53.35ml, 428.5mmol) was added to a suspension of tetramethylammonium periodate (116.62g, 440mmol) in chloroform (2.8l). A solution of benzyl-N-hydroxycarbamate[36] (73.56g, 440mmol) in chloroform (1.1l) was added to this mixture dropwise, with stirring, over 15 min. After stirring at room temperature for a further 17h, the solution was filtered and the solvent distilled at reduced pressure yielding an oil which was dissolved in diethyl ether (3.5l) and washed with water (3 x 500ml). The organic layer was separated, dried over anhydrous magnesium sulphate, and the solvent was evaporated at reduced pressure producing a yellow-orange oil which crystallised on standing to yield (122) (90.03g, 77%) as colourless crystals, m.p. 61.0 - 61.5°C (from petroleum ether (40 - 60°C)).

δ_H (300MHz, $CDCl_3$): 1.49 - 1.82 (series of m, 5H), 1.91 - 2.18 (series of m, 3H), 4.66 (brm, 1H, *bridgehead α-N*), 4.91 (brm, 1H, *bridgehead α-O*), 5.14, 5.19 (ABq, J=12.4Hz, 2H, *benzyl CH_2*), 5.77 (dd, J=10.5Hz, J=7.5Hz, 1H, *double bond β-N*),

6.33 (dd, J=10.5Hz, J=9.0Hz, 1H, *double bond β-O*), 7.24 - 7.35 (m, 5H, *aromatic*).

δ_C (75MHz, $CDCl_3$): 22.3 (CH_2), 25.5 (CH_2), 31.5 (CH_2), 34.3 (CH_2), 53.9 (CH, *bridgehead C-N*), 67.6 (CH_2, *benzyl* CH_2), 76.0 (CH, *bridgehead C-O*), 126.5 (CH, *double bond*), 127.8 (CH, *benzyl C-2/C-6*), 128.0 (CH, *benzyl C-4*), 128.4 (CH, *benzyl C-3/C-5*), 131.7 (CH, *double bond*), 136.2 (C, *benzyl C-1*), 157.9 (C, *carbamate C=O*).

ν_{max} (CH_2Cl_2): 3030w, 2920s, 2860m, 1705vs, 1495w, 1445m, 1380m, 1345m, 1330m, 1310m, 1300m, 1265s, 1205m, 1175m, 1070s cm^{-1}.

$^m/_z$ (%): 273 (M^+, 9), 229 (11), 186 (32), 149 (20), 138 (22), 108 (29), 92 (98), 91 (100), 80 (46), 79 (78), 77 (55), 65 (77).

Found: C, 70.29; H, 6.84; N, 5.16%

$C_{16}H_{19}NO_3$ requires: C, 70.31; H, 7.01; N, 5.12%

N-METHYL-9-OXA-10-AZABICYCLO[4.2.2]DECA-7-ENE (123)

A solution of (122) (30.00g, 109.76mmol) in dry tetrahydrofuran (300ml) was added to a slurry of lithium aluminium hydride (8.35g, 220mmol) in dry tetrahydrofuran (85ml). After refluxing for 3h and stirring at room temperature for a further 15h, decomposition of excess

hydride was effected by addition of water. The inorganic solids were removed by filtration and washed with warm ethyl acetate. The combined organic solutions were evaporated at reduced pressure and the residue dissolved in dichloromethane. The solution was dried over anhydrous magnesium sulphate and evaporated at reduced pressure producing an oil, contaminated with the benzyl alcohol by-product, which was purified by flash chromatography (diethyl ether) to yield (123) (13.78g, 82%) as a colourless oil, b.p. $75^{0}C$ (0.4mm Hg).

δ_H (300MHz, $CDCl_3$): 1.48 - 1.79 (series of m, 5H), 1.87 - 2.17 (series of m, 3H), 2.70 (s, 3H, *N-methyl*), 3.28 (m, 1H, *bridgehead α-N*), 4.56 (brm, 1H, *bridgehead α-O*), 5.93 (dd, J=10.15Hz, J=4.5Hz, 1H, *double bond*), 6.12 (dd, J=10.15Hz, J=6.8Hz, 1H, *double bond*).

δ_C (75MHz, $CDCl_3$): 22.6 (CH_2), 25.6 (CH_2), 32.6 (CH_2), 34.8 (CH_2), 44.6 (CH_3), 59.4 (CH, *bridgehead C-N*), 70.9 (CH, *bridgehead C-O*), 126.5 (CH), 127.7 (CH).

ν_{max} (CH_2Cl_2): 3040w, 2950m, 2920s, 2890m, 2860m, 1440w, 1175m, 1140m, 1115m, 1055w, 1010m, 990m, 930m, 910s, 805m cm^{-1}.

$^{m}/_{z}$ (%): 153 (M^+, 23), 124 (7), 110 (67), 108 (16), 94 (31), 84 (40), 79 (79), 68 (37), 67 (42), 57 (41), 55 (44), 43 (100), 42 (74), 39 (57), 29 (100).

$C_9H_{15}NO[M^+]$ Requires: 153.1154

Found: 153.115

CIS-4-(METHYLAMINO)-2-CYCLOOCTENOL (124)

Zinc powder (52.35g, 1.154mol) was added to a stirred solution of (123) in glacial acetic acid (450ml) at room temperature. The reaction mixture was heated at 60°C for 6h and then filtered. The residue was washed with glacial acetic acid (600ml) and the filtrate evaporated at reduced pressure producing a residue which was dissolved in water (100ml), washed with diethyl ether (3 x 50ml) and basified to pH 14 with concentrated sodium hydroxide solution. The product was extracted into dichloromethane (5 x 100ml) and the combined organic layers were dried over anhydrous magnesium sulphate and the solvent evaporated at reduced pressure to yield (124) (11.01g, 92%) as a white solid, m.p. 125 - 126°C (from ethyl acetate).

δ_H (300MHz, $CDCl_3$): 1.26 - 1.93 (series of m, incl. exch *-NH or -OH*, 8H + 1H), 2.38 (s, 3H, *N-methyl*), 2.65 (very brs, exch *-NH or -OH*, 1H), 3.35 (m, 1H, *α-NHMe*), 4.53 (m, 1H, *α-OH*), 5.30 (ddd, J=11.0Hz, J=8.1Hz, J=1.6Hz, 1H, *double bond*), 5.63 (ddd, J=11.0Hz, J=7.0Hz, J=1.3Hz, 1H, *double bond*).

δ_C (75MHz, $CDCl_3$): 23.9 (CH_2), 24.4 (CH_2), 34.5 (CH_3), 36.7 (CH_2), 38.9 (CH_2), 57.7 (CH, *C-NHMe*), 69.1 (CH, *C-OH*), 132.1 (CH), 136.0 (CH).

ν_{max} (CH_2Cl_2): 3600m, 3300brm, 3150brm, 3010m, 2930s, 2850m, 2790m, 1470m, 1445m, 1385w, 1140m, 1110m, 1030cm^{-1}.

$^m/_z$ (%): 155 (M^+, 4), 112 (12), 96 (45), 83 (12), 70 (100), 68 (19), 57 (23), 55 (14), 44 (22), 42 (26), 41 (26), 39 (18).

Found: C, 69.58; H, 10.89; N, 9.16%

$C_9H_{17}NO$ requires: C, 69.63; H, 11.04; N, 9.02%

CIS-4-(METHYLAMINO)CYCLOOCTANOL (125)

A solution of (124) (2.08g, 13.39mmol) in dry methanol (100ml) was hydrogenated at 1atm in the presence of 10% palladium on charcoal. After 10h, the solution was filtered through celite and then through a Millipore 0.2μ Millex-FG disposable filter unit giving a clear solution which was evaporated at reduced pressure yielding (125) (2.08g, 99%) as a colourless oil.

δ_H (300MHz, $CDCl_3$): 1.40 - 1.79 (series of m, 12H), 2.37 (s, 3H, *N-methyl*), 2.49 (m, 1H, *α-NHMe*), 2.66 (brs, exch *-NH and -OH*, 2H), 3.79 (m, 1H, *α-OH*).

δ_C (75MHz, $CDCl_3$): 22.4 (CH_2), 24.3 (CH_2), 27.9 (CH_2), 30.6 (CH_2), 31.4 (CH_2), 33.8 (CH_2) 33.9 (CH_3), 59.7 (CH, *C-NHMe*), 70.9 (CH, *C-OH*).

ν_{max} (CH_2Cl_2): 3600m, 3230brw, 2920s, 2850m, 2790m, 1470m, 1445m, 1365w, 1130m, 1095m, 1045m, 1005m cm^{-1}.

$^m/_z$ (%): 157 (M^+, 4) 100 (8), 98 (4), 96 (3), 84 (7), 71 (13), 70 (100), 67 (4), 58 (8), 57 (90), 55 (11), 44 (23), 42 (15), 41 (23).

$C_9H_{19}NO$ [M^+] Requires: 157.1467

Found: 157.147

N-METHYL-9-AZABICYCLO[4.2.1]NONANE (6) (HOMOTROPANE)[23]

Thionyl bromide (1.659g, 618µl, 7.98mmol) was added dropwise to a solution of (125) (1.20g, 7.60mmol) in dry dichloromethane (65ml) with stirring at 0°C under dry N_2. The reaction mixture was allowed to warm to room temperature and stirred for a further 12h. After cooling to 0°C, dry TMP (1.127g, 1.347ml, 7.98mmol) was added and the solution was stirred for 24h at room temperature. The mixture was filtered and the dichloromethane distilled off at atmospheric pressure giving an orange oil which was purified by flash chromatography (1:1 petroleum ether (40 - 60°C): diethyl ether, saturated with gaseous ammonia). The fractions containing product alone were acidified with dry hydrogen chloride gas, and the combined fractions were evaporated at reduced pressure yielding the HCl salt of (6) (813mg, 61%) as a white, hygroscopic solid. On basification with sodium hydroxide solution, extraction with dichloromethane, and drying over anhydrous magnesium

sulphate (6) (592mg, 56%) was obtained, by distillation at atmospheric pressure, as a pale yellow oil, b.p. 156°C.

δ_H (300MHz, $CDCl_3$): 1.34 - 1.63 (series of m, 8H), 1.79 - 1.86 (m, 2H), 2.08 - 2.28 (m, 2H), 2.42 (s, 3H, *N-methyl*), 3.24 (m, 2H, *bridgeheads*).

δ_C (75MHz, $CDCl_3$): 24.6 (CH_2), 30.2 (CH_2), 35.5 (CH_2), 42.9 (CH_3), 64.6 (CH).

ν_{max} (CH_2Cl_2): 3030w, 2920s, 2860m, 2810m, 1625brw, 1470m, 1445m, 1370m, 1350w, 1320w, 1210m, 1175m, 1130m, 1115m, 1090m, 1080m, 985m, 945m, cm^{-1}.

$^m/_z$ (%): 140 (MH^+, 100), 126 (4), 110 (2), 96 (7), 82 (8), 58 (4) 44 (8).

$C_9H_{17}N$ [M^+] Requires: 139.1361
Found: 139.136

The picrate of (6) was prepared in 95% ethanol, m.p. 272 - 273°C (decomp.) (lit.[23] m.p. 272 - 273°C) (from 1:1 ethanol: acetone):

Found: C, 49.18; H, 5.47; N, 14.96%
$C_9H_{17}N.C_6H_3N_3O_7$ Requires: C, 48.91; H, 5.47; N, 15.21%

N-METHYL-9-AZABICYCLO[4.2.1]NON-7-ENE (126).

Thionyl bromide (8.139g, 3.033ml, 39.15mmol) was added dropwise to a solution of (124) (5.79g, 37.29mmole) in dry dichloromethane (330ml) with stirring at 0°C under dry N_2. The reaction mixture was allowed to warm to room temperature and stirred for a further 12h. After cooling to 0°C, dry TMP (5.530g, 6.607ml, 39.15mmol) was added and the solution was stirred for 24h at room temperature. The mixture was filtered and the dichloromethane distilled off at atmospheric pressure giving an orange oil which was purified by flash chromatography (1:1 petroleum ether (40 - 60°C):diethyl ether, saturated with gaseous ammonia). The fractions containing product were acidified with dry hydrogen chloride gas, and the combined fractions were evaporated at reduced pressure yielding the HCl salt of (126) (4.20g, 65%) as a white, hygroscopic solid. On basification with sodium hydroxide solution, extraction with dichloromethane, and drying over anhydrous magnesium sulphate, (126) (3.17g, 62%) was obtained by distillation at atmospheric pressure, as a pale yellow oil, b.p. 170°C.

δ_H (300MHz, $CDCl_3$): 1.32 - 1.64 (series of m, 6H), 1.73 - 1.83 (m, 2H), 2.35 (s, 3H, *N-methyl*), 3.53 (ddd, J=6.3Hz, J=1.6Hz, J=1.0Hz, 2H, *bridgeheads*) 5.66 (d, J=1.0Hz, 2H, *double bond*).

δ_C (75MHz, $CDCl_3$): 24.7 (CH_2), 32.6 (CH_2), 45.7 (CH_3), 71.9 (CH, *bridgehead*), 130.4 (CH, *double bond*).

ν_{max} (CH_2Cl_2): 3030w, 2920s, 2850m, 2790m, 1660w, 1440m, 1360w, 1340m, 1320m, 1305w, 1200m, 1120m, 1100m, 1080m, 1005m, 970m, 865m, 795m cm^{-1}.

$^m/_z$ (%): 138 (MH^+, 100), 124 (2), 108 (3), 94 (16), 91 (3), 81 (4), 58 (3), 44 (2).

$C_9H_{15}N[M^+]$ Requires: 137.1204
Found: 137.120

The picrate of (126) was prepared in 95% ethanol, m.p. 265 - 266°C (decomp.) from 1:1 ethanol:acetone):

Found: C, 49.49; H, 4.97; N, 15.18%
$C_9H_{15}N.C_6H_3N_3O_7$ Requires: C, 49.18; H, 4.95; N, 15.29%

4-(BENZOYLAMINO)CYCLOOCTANONE (136)

A solution of (111) (9.00g, 36.38mmol) in acetone (400ml) was titrated at room temperature with a solution of chromic acid prepared from chromium trioxide (12.35g), concentrated sulphuric acid (11.5ml) and water (20ml). A persistent orange-brown colouration indicated the end-point. Ethanol was added to this solution which on filtering gave a green solution. The solvent was removed under reduced pressure, dichloromethane added to the green oil, and the green

solution was passed down a short column of silica to remove any chromium residues. The eluted solution was dried over anhydrous magnesium sulphate and the solvent evaporated at reduced pressure to yield (136) (8.33g, 93%) as a white solid, m.p. 138 - 139°C (from toluene).

δ_H (300MHz, $CDCl_3$): 1.37 - 1.50 (m, 1H), 1.55 - 2.16 (series of m, 6H), 2.28 - 2.62 (series of m, 5H), 4.22 (m, 1H, *α-NHCOPh*), 6.48 (brd, J=7.2Hz, exch *-NH*, 1H), 7.37 - 7.51 (m, 3H, *aromatic*), 7.70 - 7.79 (m, 2H, *aromatic*).

δ_C (75MHz, $CDCl_3$): 23.9 (CH_2), 28.0 (CH_2), 28.6 (CH_2), 31.3 (CH_2), 39.7 (CH_2), 40.7 (CH_2), 49.6 (CH, *α-NHCOPh*), 126.9 (CH, *benzoyl C-2/C-6*), 128.5 (CH, *benzoyl C-3/C-5*), 131.4 (CH, *benzoyl C-4*), 134.6 (C, *benzoyl C-1*), 166.7 (C, *benzoyl C=O*), 217.0 (C, *C=O*).

ν_{max} (CH_2Cl_2): 3440m, 3370brw, 3040w, 2940m, 2860m, 1695s, 1655vs, 1600m, 1580m, 1515vs, 1485s, 1465m, 1445m, 1350m, 1315m, 1225w, 1205w cm^{-1}.

$^m/_z$ (%) 245 (M^+, 1), 163 (8), 141 (5), 122 (26), 106 (10), 105 (100), 77 (53), 74 (18), 44 (24).

Found: C, 73.25; H, 7.81; N, 5.55%

$C_{15}H_{19}NO_2$ Requires: C, 73.44; H, 7.81; N, 5.71%

N-BENZOYL-4-METHYLENECYCLOOCTANAMINE (137)

A 250ml three-necked round bottomed flask was charged with sodium hydride (2.054g, 85.59mmol) which had been washed with several portions of dry petroleum ether (40 - 60°C) to remove the mineral oil. The flask was equipped with rubber septum caps, a reflux condenser fitted with a three-way tap, and a magnetic stirring bead. The system was alternately evacuated and filled with N_2; dry DMSO (50ml) was introduced *via* syringe, and the mixture was heated at 75 - 80°C for 45min. The resulting solution of methylsulphinyl carbanion[52] was cooled in an ice-water bath, and methyltriphenylphosphonium bromide (30.58g, 85.59mmol) in warm, dry DMSO (60ml) was added. The resulting orange-green solution of the ylide was stirred at room temperature for 10min before use. A solution of (136) (7.00g, 28.53mmol) in dry DMSO (75ml) was added to the ylide and the resulting solution was stirred for 15h at room temperature. The solvent was removed at reduced pressure, the residue extracted with dichloromethane, and the organic solution filtered. The filtrate was evaporated at reduced pressure giving a brown oil which was purified by flash chromatography (diethyl ether) to yield (137) 6.18g, 89%) as white crystals, m.p. 97°C (from petroleum ether (80 - 100°C)).

δ_H (300MHz, $CDCl_3$): 1.53 - 1.91 (series of m, 7H), 1.99 - 2.09 (m, 1H), 2.15 - 2.44 (series of m, 4H), 4.18 (m, 1H, *α-NHCOPh*), 4.82 (m, 1H, *exo-methylene*), 4.85 (m, 1H, *exo-*

methylene), 6.24 (brd, J=6.9Hz, exch -*NH*, 1H), 7.36 - 7.50 (m, 3H, *aromatic*), 7.70 - 7.78 (m, 2H, *aromatic*).

δ_C (75MHz, $CDCl_3$): 23.7 (CH_2), 29.9 (CH_2), 30.6 (CH_2), 32.1 (CH_2), 32.7 (CH_2), 33.9 (CH_2), 49.9 (CH), 111.8 (CH_2, *C=CH_2*), 126.8 (CH, *benzoyl C-2/C-6*), 128.4 (CH, *benzoyl C-3/C-5*), 131.2 (CH, *benzoyl C-4*), 135.1 (C, *benzoyl C-1*), 150.9 (C, *C=CH_2*), 166.3 (C, *benzoyl C=O*).

ν_{max} (CH_2Cl_2): 3440m, 3320brw, 3070w, 2930s, 2860m, 1655vs, 1600m, 1580m, 1515vs, 1485s, 1445m, 1315m, 1140m, 1095m, 1075w, 1030w, 910m, 890m cm^{-1}.

$^m/_z$ (%): 243 (M^+, 1), 215 (2), 174 (2), 122 (39), 106 (9), 105 (100), 93 (12), 77 (54), 51 (13), 41 (9).

Found: C, 78.84; H, 8.80; N, 5.73%.
$C_{16}H_{21}NO$ Requires: C, 78.98; H, 8.70; N, 5.76%.

1-METHYL-N-BENZOYL-9-AZABICYCLO[4.2.1]NONANE (144)

Mercuric trifluoroacetate (753mg, 1.75mmol) was added to a stirred solution of (137) (406mg, 1.67mmol) in dry acetonitrile (30ml) at room temperature. The mercury salt dissolved forming a colourless solution which was stirred for 2½h and then filtered. The filtrate was evaporated at reduced pressure to give an oil which was dissolved in dry tetrahydrofuran (40ml). Sodium borohydride (126mg, 3.34mmol) was added to this solution with stirring at -78°C,

and the solution was allowed to warm to room temperature. After stirring for 3½h at room temperature, decomposition of excess borohydride was effected by addition of water and the solution was filtered. The filtrate was evaporated at reduced pressure and the residue purified by flash chromatography (1:1 petroleum ether (40 - 60°C):diethyl ether) to yield (144) (377mg, 93%) as a white, waxy solid, m.p. 68 - 69°C (from petroleum ether (40 - 60°C)).

δ_H (300MHz, $CDCl_3$): 1.19 - 1.70 (incl. 1.70 (brs, 3H, *methyl*), series of m, 8H + 3H), 1.93 - 2.22 (series of m, 3H), 2.45 (brm, 1H), 4.21 (brm, 1H, *bridgehead*), 7.27 - 7.42 (m, 5H, *aromatic*).

δ_C (75MHz, $CDCl_3$): 23.5 (CH_2), 25.4 (CH_2), 28.1 (CH_3), 29.0 (CH_2), 36.0 (CH_2), 38.3 (CH_2), 40.8 (CH_2), 60.7 (CH, *bridgehead*), 65.0 (C, *bridgehead*), 126.6 (CH, *benzoyl C-2/C-6*), 128.1 (CH, *benzoyl C-3/C-5*), 129.1 (CH, *benzoyl C-4*), 138.7 (C, *benzoyl C-1*), 171.1 (C, *benzoyl C=O*).

ν_{max} (CH_2Cl_2): 2960m, 2930m, 2860w, 1625s, 1445m, 1440s, 1370w, 1355w, 1200m cm^{-1}.

$^m/_z$ (%): 244 (6), 243 (M^+, 36), 186 (7), 139 (6), 138 (65), 106 (8), 105 (100), 77 (46).

$C_{16}H_{21}NO[M^+]$ Requires: 243.1623

Found: 243.162

3-HYDROXY-N-BENZOYL-4-METHYLENECYCLOOCTANAMINE (145)

The first attempt to cyclise (137) using a 1:1 mixture of mercuric acetate:mercuric trifluoroacetate under the same conditions as for the preparation of (144), resulted in the isolation of what appeared to be (145) in 22% yield, together with the required product (144) in 42% yield and starting material (28%). Unfortunately, only ^{1}H and ^{13}C spectra were obtained and numerous attempts to repeat the experiment in order to obtain more material for complete characterisation have been unsuccessful.

δ_H (300MHz, $CDCl_3$): 1.47 - 1.84 (series of m, 6H), 2.00 - 2.09 (m, [incl. ddd, J=15.0Hz, J≈5.2Hz, J≈2.2Hz, 1H] 1H + 1H), 2.19 - 2.27 (ddd, J=15.0Hz, J=6.6Hz, J=3.4Hz, 1H), 2.36 - 2.46 (m, 1H), 4.14 (m, 1H, *α-NHCOPh*), 4.30 (dddd, J≈5.2Hz, J=3.4Hz, J≈1.5Hz, J≈1.0Hz, *α-OH*), 4.50 (very brs, exch *-OH*, 1H), 4.96 (brddd, J≈1.5Hz, J≈1.5Hz, J≈1.0Hz, 1H, *exo-methylene*), 5.32 (dd, J≈1.5Hz, J≈1.5Hz, 1H, *exo-methylene*), 6.55 (brd, J=6.7Hz, *exch -NH, 1H*), 7.30 - 7.52 (m, 3H, *aromatic*), 7.67 - 7.77 (m, 2H, *aromatic*).

Double irradiation of the signal at δ4.30 (assigned as the α-OH proton) caused the following noticeable changes:
2.00 - 2.09 (m, [incl. dd, J=15.0Hz, J≈2.2Hz, 1H] 1H + 1H), 2.19 - 2.27 (dd, J= 15.0Hz, J=6.6Hz, 1H), 4.96 (brdd, J≈1.5Hz, J≈1.5Hz, 1H), 5.32 (d, J≈1.5Hz).

δ_C (75MHz, $CDCl_3$): 22.7 (CH_2), 28.6 (CH_2), 30.6 (CH_2), 33.5 (CH_2), 40.0 (CH_2), 45.4 (CH, *C-NHCOPh*), 72.5 (CH, *C-OH*), 114.0 (CH_2, *C=CH_2*), 126.9 (CH, *benzoyl C-2/C-6*), 128.5 (CH, *benzoyl C-3/C-5*), 131.5 (CH, *benzoyl C-4*), 134.2 (C, *benzoyl C-1*), 151.1 (C, *C=CH_2*), 167.3 (C, *benzoyl C=O*).

1-METHYL-N-BENZYL-9-AZABICYCLO[4.2.1]NONANE (159)

A solution of (144) (445mg, 1.83mmol) in dry tetrahydrofuran (7ml) was added dropwise to a stirred slurry of lithium aluminium hydride (139mg, 3.66mmol) in dry tetrahydrofuran (7ml). After refluxing for 10h, decomposition of excess hydride was effected by addition of water. The inorganic solids were removed by filtration and washed with warm ethyl acetate. The combined organic solutions were evaporated at reduced pressure producing a residue which was dissolved in 1M HCl (10ml) and washed with diethyl ether (3 x 10ml). The aqueous layer was basified to pH 14 with concentrated sodium hydroxide solution, extracted with dichloromethane (5 x 10ml), and the combined organic solutions were dried ($MgSO_4$) and evaporated under reduced pressure to yield (159) (380mg, 91%) as a pale yellow oil.

δ_H (300MHz, $CDCl_3$): 1.21 (s, 3H, *methyl*), 1.33 - 1.88 (series of m, 10H), 1.94 - 2.13 (m, 2H), 3.33 (m, 1H, *bridgehead*), 3.81, 3.87 (ABq, J=14.6Hz, 2H, *benzyl CH_2*), 7.10 - 7.37 (m, 5H, *aromatic*).

δ_C (75MHz, $CDCl_3$): 24.8 (CH_2), 25.2 (CH_2), 29.3 (CH_3), 29.8 (CH_2), 32.8 (CH_2), 38.5 (CH_2), 41.2 (CH_2), 47.3 (CH_2, *benzyl* CH_2), 57.1 (CH, *bridgehead*), 62.9 (C, *bridgehead*), 126.3 (CH, *benzyl C-4*), 127.9 (CH, *benzyl C-2/C-6*), 128.0 (CH, *benzyl C-3/C-5*), 141.8 (C, *benzyl C-1*).

ν_{max} (CH_2Cl_2): 3020w, 2950m, 2920s, 2860m, 1620m, 1490w, 1445m, 1400m, 1355w, 1205m, 1155m, 1025w cm^{-1}.

$^m/_z$ (%): 230 (7), 229 (M^+, 32), 186 (46), 173 (35), 172 (50), 104 (20), 91 (100), 82 (39), 65 (14), 57 (19), 55 (27), 41 (32).

$C_{16}H_{23}N$ [M^+] Requires: 229.1830
Found: 229.183

4-(BENZOYLAMINO)-2-CYCLOOCTENONE (160)

Barium manganate[62] (81.0g, 0.344mol) was added to a stirred solution of (110) (9.70g, 39.54mmol) in dry dichloromethane (11). After 18h, the solution was filtered through a sinter and the inorganic residue was washed with ethyl acetate. The combined organic solutions were evaporated at reduced pressure giving an oil which was purified by flash chromatography (diethyl ether) to yield (160) (7.65g, 80%) as a colourless oil.

δ_H (300MHz, $CDCl_3$): 1.47 - 2.03 (series of m, 6H), 2.53 (brm, 1H), 2.89 (ddd, J=14.1Hz, J=10.2Hz, J=7.0Hz, 1H),

5.43 (m, 1H, *α-NHCOPh*), 6.03 (ddd, J=12.6Hz, J=1.8Hz, J=0.9Hz, 1H, *double bond*), 6.19 (dd, J=12.6Hz, J=5.7Hz, 1H, *double bond*), 6.84 (brd, J=7.4Hz, exch *-NH*, 1H), 7.38 - 7.80 (series of m, 5H, *aromatic*).

δ_C (75MHz, $CDCl_3$): 22.5 (CH_2), 22.6 (CH_2), 30.7 (CH_2), 42.0 (CH_2), 49.3 (CH, *C-NHCOPh*), 127.1 (CH, *benzoyl C-2/C-6*), 128.4 (CH, *benzoyl C-3/C-5*), 131.6 (CH, *benzoyl C-4*), 132.6 (CH, *double bond*), 134.0 (C, *benzoyl C-1*), 144.2 (CH, *double bond*), 167.1 (C, *benzoyl C=O*), 203.7 (C, *C=O*).

ν_{max} (CH_2Cl_2): 3440m, 3320brw, 2940m, 2860w, 1660vs, 1600m, 1580m, 1510s, 1485m, 1455m, 1390w, 1350m, 1320m cm^{-1}.

$^m/_z$ (%) 244 (MH^+, 100), 226 (6), 139 (24), 123 (8), 122 (89), 105 (14), 94 (3).

$C_{15}H_{17}NO_2$ [MH^+] Requires: 244.1338
Found: 244.134

N-BENZOYL-4-METHYLENECYCLOOCTA-2,8-DIENAMINE (166)

Anhydrous cerium (II) chloride[65] (2.93g, 12.3mmol) was placed in a two-necked flask and heated gradually to 135 - 140°C in an oil bath with evacuation. After maintenance of the cerium chloride at a constant temperature for 1h, a magnetic stirrer bar was placed in the flask and the cerium chloride was completely dried *in vacuo* by stirring at the same temperature for an additional 2h. While the flask was

still hot, dry N_2 was introduced and the flask was then cooled in an ice-bath. Freshly distilled tetrahydrofuran (10ml) was added all at once with vigorous stirring. The ice-bath was removed and the suspension was well stirred for 20h under N_2 at room temperature.

Magnesium turnings (299mg, 12.3mmol) were placed in a two-necked flask fitted with a reflux condenser and an N_2 bubbler, and a crystal of iodine was added. Chloromethyltrimethylsilane (252µl, 1.81mmol) was added together with dry tetrahydrofuran (0.5ml). When a reaction had started, the stirrer was set in motion and a solution of chloromethyltrimethylsilane (1.464ml, 10.49mmol) in dry tetrahydrofuran (3.5ml) was added over 20min.

The flask containing cerium chloride was again immersed in an ice-bath and the Grignard reagent (12.3mmol) was added. After stirring the Grignard reagent with the cerium chloride suspension for 1.5h at 0°C, a solution of (160) (598mg, 2.46mmol) in dry tetrahydrofuran (5ml) was added and the stirring was continued for 30min at 0°C. A solution of acetic acid (25ml of a 10% solution) was added and the product was extracted into diethyl ether, washed with sodium bicarbonate solution and water, and dried over anhydrous magnesium sulphate. The solvent was evaporated at reduced pressure to give an orange oil which was purified by flash chromatography yielding (166) (141mg, 25%) as a yellow oil, together with starting material (160) (299mg, 50%) and

1-hydroxy-N-benzoyl-9-azabicyclo[4.2.1]non-7-ene (167) (132mg, 22%) as a colourless oil.

N-BENZOYL-4-METHYLENECYCLOOCTA-2,8-DIENAMINE (166)

δ_H (300MHz, $CDCl_3$): 1.60 - 1.69 (brm, 2H), 2.27 - 2.35 (brm, 2H), 2.50 - 2.60 (brm, 2H), 4.95 (brd, J=0.8Hz, 1H, *exo-methylene*), 5.02 (brm, 1H, *exo-methylene*), 5.49 (d, J=12.2Hz, 1H, *double bond*), 6.03 (dd, J=8.7Hz, J=8.6Hz, 1H, *double bond*), 6.15 (d, J=12.2Hz, 1H, *double bond*), 7.20 - 7.87 (series of m, 5H, *aromatic*).

δ_C (75MHz, $CDCl_3$): 25.1 (CH_2), 29.1 (CH_2), 30.2 (CH_2), 120.1 (CH, *double bond*), 120.3 (CH_2, *C=CH$_2$*), 122.1 (CH, *double bond*), 126.9 (CH, *benzoyl C-2/C-6*), 128.3 (CH, *benzoyl C-3/C-5*), 131.2 (CH, *benzoyl C-4*), 134.2 (C, *benzoyl C-1*), 134.7 (C, *double bond*), 134.9 (CH, *double bond*), 147.3 (C, *C=CH$_2$*), 166.1 (C, *benzoyl C=O*).

ν_{max} (CH_2Cl_2): 3420m, 2930m, 2860m, 1670s, 1600m, 1580m, 1510s, 1480m, 1450m, 1345m, 1325m, 1295w, 1205w cm^{-1}.

$^m/_z$ (%): 240 (MH^+, 100), 207 (7), 194 (13), 167 (4), 139 (12), 122 (41), 105 (20), 90 (13), 71 (2).

$C_{16}H_{18}NO$ [MH^+] Requires: 240.1388

Found: 240.139

1-HYDROXY-N-BENZOYL-9-AZABICYCLO[4.2.1]NON-7-ENE (167)

δ_H (300MHz, $CDCl_3$): 1.22 - 1.70 (series of m, 6H), 1.96 (m, 1H), 2.55 (m, 1H), 4.72 (brd, J=5.6Hz, 1H, *bridgehead*), 5.71 (brs, exch *-OH*, 1H), 5.84 (s, 2H, *double bond*), 7.33 - 7.55 (m, 5H, *aromatic*)

δ_C (75MHz, $CDCl_3$): 23.1 (CH_2), 23.9 (CH_2), 31.8 (CH_2), 38.5 (CH_2), 63.2 (CH, *bridgehead*), 97.5 (C, *bridgehead*), 126.5 (CH, *benzoyl C-2/C-6*), 128.5 (CH, *benzoyl C-3/C-5*), 129.9 (CH, *double bond*), 131.0 (CH, *benzoyl C-4*), 132.9 (CH, *double bond*), 135.6 (C, *benzoyl C-1*), 170.7 (C, *benzoyl C=O*).

ν_{max} (CH_2Cl_2): 3440brw, 2930m, 2860w, 1635m, 1610s, 1600s, 1575m, 1490w, 1440s, 1400m, 1325w, 1230w, 1195m, 1150m, 1130m, 1115m cm^{-1}.

A solution of (167) in $CDCl_3$ reverted completely to (160) over a period of three weeks, as indicated by 90MHz ^1H NMR.

N-(BENZOYL)-4-METHYLENECYCLOOCT-2-ENAMINE (161)

A 50ml three-necked round bottomed flask was charged with sodium hydride (384mg, 16.00mmol) which had been washed with several portions of dry petroleum ether (40 - 60°C) to remove the mineral oil. The flask was equipped with rubber septum caps, a reflux condenser fitted with a three-way tap, and a

magnetic stirring bead. The system was alternatively evacuated and filled with N_2; dry DMSO (4ml) was introduced *via* a syringe, and the mixture was heated at 75 - 80°C for 45min. The resulting solution of methylsulphinyl-carbanion[52] was cooled in an ice-water bath, and methyltriphenyl-phosphonium bromide (5.72g, 16.00mmol) in warm, dry DMSO (11ml) was added. The resulting orange-green solution of the ylide was stirred at room temperature for 10min before use. A solution of (160) (710mg, 2.91mmol) in dry DMSO (5ml) was added to the ylide and the resulting solution was stirred for 15h at room temperature. The solvent was removed at reduced pressure, the residue dissolved in dichloromethane, and the solution washed with water. After drying over anhydrous magnesium sulphate, the solution was evaporated at reduced pressure giving an oil which was purified by flash chromatography (1:1 petroleum ether (40 - 60°C):diethyl ether) to yield (161) (555mg, 79%) as white crystals, m.p. 147.5 - 148.5°C (from toluene).

δ_H (300MHz, $CDCl_3$); 1.46 (m, 1H), 1.60 - 1.77 (m, 4H), 1.98 (m, 1H), 2.39 (brdd, J=14.4Hz, J=6.5Hz, 1H), 2.83 (m, 1H), 4.90 (brs, 1H, *exo-methylene*), 4.98 (brd, J=1.9Hz, 1H, *exo-methylene*), 5.19 (dd, J=12.1Hz, J=6.7Hz, 1H, *double bond*), 5.62 (m, 1H), *α-NHCOPh*), 6.22 (brd, J=12.1Hz, 1H, *double bond*), 6.39 (very brd, J=7.5Hz, exch *-NH*, 1H), 7.26 - 7.49 (m, 3H, *aromatic*), 7.72 - 7.80 (m, 2H, *aromatic*).

δ_C (75MHz, $CDCl_3$): 21.7 (CH_2), 28.2 (CH_2), 33.6 (CH_2), 34.3 (CH_2), 48.2 (CH, C-*NHCOPh*), 118.9 (CH_2, *C=CH_2*), 126.9 (CH,

benzoyl C-2/C-6), 128.4 (CH, *benzoyl C-3/C-5*), 129.7 (CH, *double bond*), 131.3 (CH, *benzoyl C-4*), 134.4 (CH, *double bond*), 134.6 (C, *benzoyl C-1*), 146.1 (C, *C=CH_2*), 166.7 (C, *benzoyl C=O*).

ν_{max} (CH_2Cl_2): 3440m, 2940m, 2850m, 1660s, 1600w, 1590m, 1580m, 1515s, 1485m, 1325m, 1180w, 1140w cm^{-1}.

$^m/_z$ (%): 241 (M^+, 8), 213 (3), 146 (3), 136 (6), 120 (11), 106 (10), 105 (100), 91 (17), 77 (87), 65 (6), 51 (25), 41 (6).

Found: C, 79.60; H, 7.95; N, 5.73%

$C_{16}H_{19}NO$ Requires: C, 79.63; H, 7.94; N, 5.80%

1-METHYL-N-BENZOYL-9-AZABICYCLO[4.2.1]NON-7-ENE (168)

Mercuric trifluoroacetate (374mg, 0.87mmol) was added to a stirred solution of (161) (200mg), 0.83mmol) in dry acetonitrile (15ml) at room temperature. The mercury salt dissolved giving a pale yellow solution which was stirred for 1h and then filtered. The filtrate was evaporated at reduced pressure to give an oil which was stirred for 1h and then filtered. The filtrate was evaporated at reduced pressure to give an oil which was dissolved in dry tetrahydrofuran (20ml). Sodium borohydride (62.7mg, 1.66mmol) was added to this solution with stirring at -78°C, and the solution was allowed to warm to room temperature. After stirring for 3½h at room temperature, decomposition of

excess borohydride was effected by addition of water and the solution was filtered. The filtrate was evaporated at reduced pressure and the residue purified by flash chromatography (3:2 petroleum ether (40 - 60°C):diethyl ether) to yield (168) (95mg, 48%) as a pale yellow oil.

δ_H (300MHz, $CDCl_3$): 1.20 - 1.36 (m, 2H), 1.43 - 1.76 (incl. 1.76 (s, 3H, *methyl*), series of m, 5H + 3H), 2.43 (m, 1H), 4.70 (brddd, J=5.4Hz, J≈2.2Hz, J=1.6Hz, 1H, *bridgehead*), 5.58 - 5.62 (AB of ABX system, J_{AB}≈6.1Hz, J_{BX}≈2.2Hz, J_{AX}≈0Hz, 2H, *double bond*), 7.33 - 7.49 (m, 5H, *aromatic*).

The bridgehead proton and double bond protons of (168) were part of an ABX system which were studied by double resonance: Irradiation of the double bond (5.58 - 5.62ppm) led to collapse of the signal δ4.70 (brddd, J=5.4Hz, J≈2.2Hz, J=1.6Hz) to (brdd, J=5.4Hz, J=1.6Hz).

Irradiation of the bridgehead proton (4.70ppm) collapsed the signals due to the double bond protons to a simple AB system (J≈6.1Hz).

δ_C (75MHz, $CDCl_3$): 23.2 (CH_2), 24.1 (CH_3), 25.3 (CH_2), 33.0 (CH_2), 36.2 (CH_2), 65.4 (CH, *bridgehead*), 69.9 (C, *bridgehead*), 126.9 (CH, *benzoyl C-2/C-6*), 127.3 (CH, *double bond*), 128.2 (CH, *benzoyl C-3/C-5*), 129.4 (CH, *benzoyl C-4*), 137.5 (CH, *double bond*), 137.6 (C, *benzoyl C-1*), 170.3 (C, *benzoyl C=0*).

ν_{max} (CH_2Cl_2): 2930s, 2860m, 1640s, 1615s, 1580m, 1510w, 1480w, 1445m, 1405s, 1360m, 1325m, 1205m, 1170m cm^{-1}.

$^m/_z$ (%): 242 (7), 241 (M^+, 13), 198 (4), 136 (2), 120 (6), 106 (10), 105 (100), 94 (4), 77 (41), 65 (2), 51 (7).

$C_{16}H_{19}NO$ [M^+] Requires: 241.1467
Found: 241.147

9,10-DIOXABICYCLO[4.2.2]DECA-7-ENE (180)[72]

Haematoporphyrin (1.0g) was added to a solution of 1, 3 - cyclooctadiene (50ml, 0.403mol) in acetone (1.75l) and oxygen bubbled vigorously through the stirred solution. The solution was exposed to light from a 125W sodium street lamp for 10 days during which time evaporation was minimised with the aid of a dry ice condenser attached to the apparatus. The solvent was removed at reduced pressure giving an oil which was purified by flash chromatography (4:1 petroleum ether (40 - 60°C):diethyl ether) to yield (180) (14.5g, 26%) as a pale yellow oil.

δ_H (90MHz, $CDCl_3$): 1.35 - 2.30 (series of m, 8H), 4.65 (brm, 2H, *bridgeheads*), 6.10 (dd, J=3.6Hz, J=2.0Hz, 2H, *double bond*).

9,10-DIOXABICYCLO[4.2.2]DECANE (182)[71]

A solution of (180) (2.35g, 16.76mmol) in dry dichloromethane (45ml) was added to a slurry of potassium azodicarboxylate[71] (16.26g, 83.78mmol) in dry dichloromethane (110ml) which had been cooled to 0°C. A solution of glacial acetic acid (12.48ml, 0.218mol) in dry chloromethane (45ml) was added to the stirred solution, dropwise, within 30min, and the mixture was stirred at room temperature for 24h. Water (60ml) was added to the mixture and the organic layer was washed with 5% sodium bicarbonate solution (3 x 50ml) and water (50ml). The organic layer was separated, dried over anhydrous magnesium sulphate, and the solvent evaporated at reduced pressure producing an oil which was purified by flash chromatography (4:1 petroleum ether (40 - 60°C):diethyl ether) to yield (182) (2.10g, 88%) as a pale yellow oil.

δ_H (90MHz, $CDCl_3$):1.40 - 2.35 (series of m, 12H), 4.50 (brm, 2H, *bridgeheads*).

4-HYDROXYCYCLOOCTANONE (183)[73]

A solution of triethylamine (1.37ml, 9.84mmol) in dichloromethane (24ml) was added slowly to a solution of (182) (700mg, 4.92mmol) in dichloromethane (24ml) which had been cooled to 0°C. After addition, the solution was refluxed for 24h. The solvent was evaporated at reduced pressure producing an oil which was purified by flash

chromatography (95:5 dichloromethane:methanol) to yield (183) (560mg, 80%) as a yellow oil.

δ_H (300MHz, $CDCl_3$): 1.29 - 2.57 (series of m, 12H), 3.20 (brs, exch *-OH*, 1H), 3.83 (dddd, J=8.4Hz, J≈4.8Hz, J≈4.8Hz, J≈4.5Hz, 1H, *α-OH*).

δ_C (75MHz, $CDCl_3$): 21.9 (CH_2), 28.7 (CH_2), 30.5 (CH_2), 33.6 (CH_2), 39.5 (CH_2), 40.2 (CH_2), 70.7 (CH, *C-OH*), 217.0 (C, *C=O*).

Using ^1H and ^{13}C NMR it was also found that (183) was the minor tautomer in equilibrium with 69% of the bicyclic form 1-hydroxy-9-oxabicyclo[4.2.1]nonane (184).

δ_H (300MHz, $CDCl_3$): 1.29 - 2.57 (series of m, 12H), 3.20 (brs, exch *-OH*, 1H), 4.52 (dddd, J=8.4Hz, J=6.9Hz, J≈2.0Hz, J≈2.0Hz, 1H, *bridgehead*).

δ_C (75MHz, $CDCl_3$): 23.3 (CH_2), 23.8 (CH_2), 31.2 (CH_2), 36.4 (CH_2), 37.1 (CH_2), 41.7 (CH_2), 76.0 (CH, *bridgehead*), 108.3 (C, *bridgehead*).

ν_{max} (CH_2Cl_2): 3580m, 3400brm, 3050w, 2940s, 2860m, 1695s, 1470m, 1450m, 1355m, 1330m, 1220m, 1130m, 1080m, 995m, 930m cm^{-1}.

$^m/_z$ (%): 142 (M^+, 2), 124 (7), 113 (25), 96 (18), 85 (47), 83 (68), 67 (41), 57 (57), 55 (100), 43 (77), 41 (93).

1-HYDROXY-9-OXABICYCLO[4.2.1]NON-7-ENE (181)[72]

A solution of triethylamine (29ml, 209mmol) in dichloromethane (200ml) was added slowly to a solution of (180) (14.5g, 104mmol) in dichloromethane (500ml) which had been cooled to 0°C. After addition, the solution was refluxed for 24h. The solvent was evaporated at reduced pressure producing an oil which was purified by flash chromatography (95:5 dichloromethane:methanol) to yield (181) (11.3g, 78%) as a white solid, m.p. 92 - 93°C (lit.[73] m.p. 92 - 93°C) (from petroleum ether (80 - 100°C)).

δ_H (300MHz, $CDCl_3$): 1.43 - 1.70 (m, 5H), 1.85 - 2.02 (m, 3H), 4.26 (brs, exch *-OH*, 1H), 4.96 (dddd, J=6.3Hz, J=1.9Hz, J=1.9Hz, J=1.2Hz, 1H, *bridgehead*), 5.78 (dd, J=5.8Hz, J=1.2Hz, 1H, *double bond*), 5.96 (dd, J=5.8Hz, J=1.9Hz, 1H, *double bond*).

δ_C (75MHz, $CDCl_3$): 23.1 (CH_2), 23.7 (CH_2), 33.4 (CH_2), 39.3 (CH_2), 81.3 (CH, *bridgehead*), 111.5 (C, *bridgehead*), 132.7 (CH, *double bond*), 133.8 (CH, *double bond*).

Using ^1H and ^{13}C NMR it was also found that (181) was the major tautomer in equilibrium with 5% of the monocyclic form 4-hydroxycyclooct-2-enone (187):

δ_H (300MHz, $CDCl_3$): 1.43 - 1.70 (m, 6H), 2.53 (very br dd, J=13.2Hz, J=6.3Hz, 1H), 2.72 (ddd, J=13.2Hz, J=11.8Hz, J=6.9Hz, 1H), 3.97 (brs, exch *-OH*, 1H), 5.20 (very brm, 1H,

α-OH), 6.03 (ddd, J=12.7Hz, J=1.9Hz, J=0.8Hz, 1H, *double bond*), 6.38 (dd, J=12.7Hz, J=5.5Hz, 1H, *double bond*).

δ_C (75MHz, $CDCl_3$): 22.2 (CH_2), 23.0 (CH_2), 33.6 (CH_2), 42.1 (CH_2), 69.2 (CH, *C-OH*), 131.5 (CH, *double bond*), 148.8 (CH, *double bond*), 202.0 (C, *C=O*).

ν_{max} (CH_2Cl_2): 3560m, 3360brw, 2930s, 2860m, 1655w, 1440w, 1365m, 1350m, 1300w, 1205m, 1130m, 110m, 1090m, 1070s, 1035m, 1000m cm^{-1}.

$^m/_z$ (%): 140 (M^+, 2), 111 (11), 97 (100), 95 (18), 84 (37), 80 (55), 67 (27), 55 (66), 53 (21), 43 (26), 41 (45), 39 (50).

1-(β-HYDROXYETHOXY)-9-OXABICYCLO[4.2.1]NON-7-ENE (196)

Ethane-1, 2-diol (388μl, 7.00mmol) was added to a solution of (181) (891mg, 6.36mmol) in benzene (20ml) contained in a 50ml round-bottomed flask fitted with a Dean and Stark water separator and a reflux condenser. A few crystals of *p*-toluenesulphonic acid and a stirring bead were added, and the solution was heated and stirred so that the benzene refluxed vigorously. After refluxing for 1h, the solution was allowed to cool to room temperature. The solvent was removed at reduced pressure producing an oil which was purified by flash chromatography (94:5:1 dichloromethane: methanol:triethylamine) to yield (196) (750mg, 64%) as a colourless oil.

δ_H (300MHz, $CDCl_3$): 1.44 - 1.71 (m, 5H), 1.81 - 2.04 (m, 3H), 3.32 (brs, exch *-OH*, 1H), 3.50 - 3.75 (m, 4H, *O-CH_2CH_2-O*), 5.01 (dddd, J=6.3Hz, J=1.9Hz, J=1.9Hz, J=1.5Hz, 1H, *bridgehead*), 5.74 (dd, J=5.9Hz, J=1.5Hz, 1H, *double bond*), 6.05 (dd, J=5.9Hz, J=1.9Hz, 1H, *double bond*).

δ_C (75MHz, $CDCl_3$): 23.2 (CH_2), 23.8 (CH_2), 33.6 (CH_2), 39.1 (CH_2), 62.1 (CH_2, *O-CH_2*), 64.7 (CH_2, *O-CH_2*), 81.5 (CH, *bridgehead*), 115.1 (C, *bridgehead*), 131.0 (CH, *double bond*), 135.0 (CH, *double bond*).

ν_{max} (CH_2Cl_2): 3600w, 3420brw, 2940s, 2860m, 1590w, 1440w, 1345m, 1210w, 1155m, 1130m, 1085m, 1060s, 1040m, 1010m, 940m, 910s cm^{-1}.

$^m/_z$ (%): 185 (MH^+, 26), 167 (14), 155 (3), 141 (18), 140 (100), 124 (32), 123 (100), 95 (9), 81 (5), 65 (1), 53 (3).

$C_{10}H_{16}O_3$ [M^+] Requires: 184.1099
Found: 184.110

1-(β-TOSYLOXYETHOXY)-9-OXABICYCLO[4.2.1]NON-7-ENE (197)

Pyridine (530µl, 6.54mmol) was added to a solution of (196) (602mg, 3.27mmol) in chloroform (6ml), which had been passed through an alumina column, and cooled in an ice-bath at 0°C. This was followed by the addition of *p*-toluenesulphonyl chloride (933mg, 4.91mmol) in small portions with constant

stirring. After 2h at room temperature, the solvent was removed at reduced pressure and the resulting oil was purified by flash chromatography (dichloromethane to remove excess *p*-toluenesulphonyl chloride, then 98:2 dichloromethane:methanol) to yield (197) (740mg, 67%) as a colourless oil.

δ_H (300MHz, $CDCl_3$): 1.41 - 2.04 (series of m, 8H), 2.44 (s, 3H, *tosyl methyl*), 3.53 - 3.73 (m, 2H, *O-CH*$_2$), 4.12 - 4.16 (m, 2H, *O-CH*$_2$), 4.94 (dddd, J=6.2Hz, 1.9Hz, 1.9Hz, 1.5Hz, 1H, *bridgehead*), 5.64 (dd, J=5.9Hz, J=1.5Hz, 1H, *double bond*), 6.01 (dd, J=5.9Hz, J=1.9Hz, 1H, *double bond*), 7.33 (d, J=8.2Hz, 2H, *aromatic*), 7.79 (d, J=8.2Hz, 2H, *aromatic*).

δ_C (75MHz, $CDCl_3$): 21.6 (CH_3, *tosyl methyl*), 23.1 (CH_2), 23.7 (CH_2), 33.7 (CH_2), 38.8 (CH_2), 60.1 (CH_2, *O-CH*$_2$), 69.7 (CH_2, *O-CH*$_2$), 81.7 (CH, *bridgehead*), 115.0 (C, *bridgehead*), 127.9 (CH, *tosyl C-2/C-6*), 129.7 (CH, *tosyl C-3/C-5*), 130.8 (CH, *double bond*), 133.1 (C, *tosyl C-4*), 135.3 (CH, *double bond*), 144.6 (C, *tosyl C-1*).

ν_{max} (CH_2Cl_2): 3060w, 2940m, 2860m, 1600m, 1500w, 1455m, 1360s, 1300w, 1215m, 1195vs, 1180vs, 1160m, 1130m, 1100m, 1080m, 1060m, 1025m, 1010m, 930s, 820s cm^{-1}.

$^m/_z$ (%): No observed M^+, 217 (3), 199 (74), 167 (20), 155 (29), 139 (6), 123 (89), 91 (100), 79 (55), 65 (49), 55 (61), 41 (35).

$C_{16}H_{26}NSO_5$ $[MNH_4^+]$ Requires: 356.1532

Found: 356.153

TETRACYCLIC TRIAZOLINE (198)

Sodium azide (119mg, 1.82mmol) was added in small portions at room temperature to a solution of (197) (440mg, 1.30mmol) in dimethyl sulphoxide (4ml). After stirring at room temperature for 1 day, the solution was evaporated at reduced pressure, the residue was dissolved in dichloromethane (20ml) and the solution was washed repeatedly with water. The solution was dried over anhydrous magnesium sulphate and evaporated at reduced pressure giving an oil which was purified by flash chromatography (diethyl ether) to yield (198) (238mg, 87%) as white crystals, m.p. 116 - 117°C.

δ_H (300MHz, $CDCl_3$): 1.26 - 1.41 (m, 1H), 1.51 - 2.00 (series of m, 6H), 2.07 - 2.19 (m, 1H), 3.49 - 3.77 (complex m, 4H), 4.13 (brdd, J=13.6Hz, J=2.4Hz, 1H), 4.46 (brd, J=7.2Hz, 1H), 4.85 (dd, J=9.7Hz, J=1.6Hz, 1H).

δ_C (75MHz, $CDCl_3$): 22.4 (CH_2), 23.6 (CH_2), 34.7 (CH_2), 41.5 (CH_2), 44.5 (CH_2), 57.8 (CH), 58.5 (CH_2), 80.3 (CH), 90.0 (CH), 108.0 (C).

ν_{max} (CH_2Cl_2): 3050w, 2940s, 2860m, 1590brm, 1490m, 1455m, 1350w, 1320m, 1245m, 1210m, 1165m, 1155m, 1120m, 1095s, 1060m, 1040m, 1000m, 965s, 955m cm^{-1}.

Found: C, 57.17; H, 7.41; N, 20.30%.

$C_{10}H_{15}N_3O_2$ Requires: C, 57.40; H, 7.22; N, 20.08%.

X-ray Crystal Data $C_{10}H_{15}N_3O_2$, M=209.25, orthorhombic, space group = P2,2,2,, a + 10.271 (9), b = 10.581 (5), c = 9.327 (7) Å, U = 1013.6Å^3, z = 4, μ = 0.59cm^{-1}, λ (Mo-Kα) = 0.7107 Å, F(000) = 448.0, D_c = 1.37g cm^{-1}. See appendix 2.

4-OXOCYCLOOCTANYL TOSYLATE(199)

Pyridine (1.068ml, 13.2mmol) was added to a solution of (183) (941mg, 6.6mmol) in chloroform (8ml), which had been passed through an alumina column, and cooled in an ice-bath at 0°C. This was followed by the addition of *p*-toluenesulphonyl chloride (1.881g, 9.90mmol) in small portions with constant stirring. After 3.5 days at room temperature, chloroform (30ml) and water (6ml) were added and the organic layer was washed successively with 2M HCl, 5% sodium bicarbonate solution and water, and then dried over anhydrous magnesium sulphate. The solvent was purified by flash chromatography (dichloromethane to remove excess *p*-toluenesulphonyl chloride, then 98:2 dichloromethane: methanol) to yield (199) (1.72g, 88%) as a white solid, m.p. 84.5 - 86°C.

δ_H (300MHz, $CDCl_3$): 1.41 - 1.54 (m, 2H), 1.61 - 1.92 (m, 4H), 2.14 - 2.31 (m, 3H), 2.34 - 2.57 (incl. 2.44 (s, 3H, *tosyl methyl*), m, 3H + 3H), 4.61 (m, 1H, *α-OTs*), 7.34 (d, J=8.3Hz, 2H, *tosyl*), 7.77 (d, J=8.3Hz, 2H, *tosyl*).

δ_C (75MHz, $CDCl_3$): 21.6 (CH_3, *tosyl methyl*), 21.7 (CH_2), 28.1 (CH_2), 28.6 (CH_2), 30.8 (CH_2), 38.8 (CH_2), 40.1 (CH_2), 81.9 (CH, *C-OTs*), 127.5 (CH, *tosyl C-2/C-6*), 129.8 (CH, *tosyl C-3/C-5*), 134.3 (C, *tosyl C-4*), 144.7 (C, *tosyl C-1*), 215.4 (C, *C=O*).

ν_{max} (CH_2Cl_2): 3060w, 2950s, 2870m, 1700vs, 1600m, 1495w, 1470m, 1450m, 1410m, 1355s, 1230m, 1190s, 1175s, 1120m, 1100s, 910s, 820s, 665s cm^{-1}.

$^m/_z$ (%): 296 (M^+,5), 172 (12), 155 (20), 141 (19), 124 (57), 105 (20), 96 (27), 95 (40), 91 (64), 75 (69), 67 (59), 54 (53), 32 (43), 28 (100).

$C_{15}H_{20}SO_4$ [M^+] Requires: 296.1082
Found: 296.108

4-AZIDOCYCLOOCTANONE (200)

Sodium azide (168mg, 2.54mmol) was added in small portions at room temperature to a stirred solution of (199) (630mg, 2.12mmol) in dimethylformamide (15ml), and the solution was heated for 10h at 40°C. The solution was evaporated at reduced pressure, the residue was dissolved in dichloromethane (50ml) and the solution was washed repeatedly with water. The solution was dried over anhydrous magnesium sulphate and evaporated at reduced pressure giving an oil which was purified by flash chromatography (3:2 petroleum ether (40 - 60°C): diethyl

ether) to yield (200) (233mg, 65%) as a yellow oil.

δ_H (300MHz, $CDCl_3$): 1.41 - 1.97 (series of m, 6H), 2.05 - 2.26 (m, 2H), 2.30 - 2.58 (m, 4H), 3.63 (m, 1H, *α-N_3*).

δ_C (75MHz, $CDCl_3$): 22.5 (CH_2), 27.7 (CH_2), 28.3 (CH_2), 29.8 (CH_2), 39.9 (CH_2), 40.2 (CH_2), 61.2 (CH, *C-N_3*), 215.8 (C, *C=O*).

ν_{max} (CH_2Cl_2): 2940s, 2860m, 2480w, 2090vs, 1695vs, 1465m, 1450m, 1410w, 1360m, 1340m, 1320m, 1240m, 1200m, 1150w, 1115w cm^{-1}.

$^m/_z$ (%): 185 (MH^+, 14), 168 (11), 157 (13), 141 (85), 140 (100), 122 (27), 110 (21), 97 (10), 84 (18), 69 (11), 55 (16).

$C_8H_{17}N_4O$ [MNH_4^+] Requires: 185.1402
Found: 185.140

4-AMINOCYCLOOCTANONE (201)

A solution of (200) (160mg, 0.94mmol) in dry methanol (10ml) was hydrogenated at 1atm in the presence of 10% palladium on charcoal. After 5h, the solution was filtered through celite and then through a Millipore 0.2μ Millex-FG disposable filter unit giving a clear solution which was evaporated at reduced pressure producing a residue which was dissolved in 1M HCl (4ml) and washed with diethyl ether (3 x

4ml). The aqueous layer was basified to pH 14 with concentrated sodium hydroxide solution, extracted with dichloromethane (5 x 5ml) and the combined organic solutions were dried (K_2CO_3) and evaporated under reduced pressure to yield (201) (106mg, 80%) as a colourless oil.

(300MHz, $CDCl_3$, -30°C): 1.48 - 2.47 (series of brm, 12H) 3.04 (br, 1H, *α-NH_2*).

(75MHz, $CDCl_3$, -30°): 21.9 (CH_2), 28.7 (CH_2), 30.7 (CH_2), 33.5 (CH_2), 40.1 (CH_2), 40.5 (CH_2), 50.7 (CH, C-NH_2), 218.8 (C, *C=O*).

Using variable temperature ^1H and ^{13}C NMR it was also found that (201) was the minor tautomer at -30°C in equilibrium with 89% of the bicyclic form 1-hydroxy-9-azabicyclo [4.2.1] nonane (202):

δ_H (300MHz, $CDCl_3$, -30°C): 1.48 - 2.47 (series of brm, 12H), 3.59 (brm, 1H, *bridgehead*).

δ_C (75MHz, $CDCl_3$, -30°C): 22.6 (CH_2), 23.9 (CH_2), 31.1 (CH_2), 36.4 (CH_2), 37.8 (CH_2), 43.1 (CH_2), 52.4 (CH, *bridgehead*), 93.1 (C, *bridgehead*).

ν_{max} (CH_2Cl_2): 3580m, 3160brm, 3040m, 2930s, 2860m, 1695s, 1465m, 1410m, 1330m, 1205m, 1165w, 1100m, 1085m, 985m cm^{-1}.

Using the technique of variable temperature IR it was found that the carbonyl signal at 1695cm^{-1} showed a gradual reduction in its intensity as the temperature of the solution in CH_2Cl_2 was lowered.

$^{m}/_{z}$ (%): 141 (M^+, 27), 113 (22), 112 (22), 99 (17), 98 (53), 85 (41), 84 (30), 57 (30), 56 (100).

$C_8H_{15}NO$ [M^+] Requires: 141.1154
Found: 141.115

4-OXOCYCLOOCT-2-ENYL TOSYLATE(203)

Pyridine (1.973ml, 24.39mmol) was added to a solution of (181) (1.14g, 8.13mmol) in chloroform (12ml), which had been passed through an alumina column, and cooled in an ice-bath at 0°C. This was followed by the addition of *p*-toluenesulphonyl chloride (2.317g, 12.20mmol) in small portions with constant stirring. After 16 days at room temperature, the solution was evaporated at reduced pressure giving a dark brown oil which was purified by flash chromatography to yield (203) (328mg, 14%) and 4-chlorocyclooct-2-enone (204) (228mg, 18%) as colourless oils.

4-OXOCYCLOOCT-2-ENYL TOSYLATE (203):

δ_H (300MHz, $CDCl_3$): 1.39 - 2.06 (series of m, 6H), 2.37 - 2.65 (incl 2.44 (s, 3H, *tosyl methyl*), m, 5H), 5.78 (m, 1H, *α*-

OTs), 5.95 (ddd, J=13.0Hz, J=1.9Hz, J=0.8Hz, 1H, *double bond*), 6.12 (dd, J=13.0Hz, J=5.3Hz, 1H, *double bond*), 7.38 (d, J=8.2Hz, 2H, *tosyl*), 7.81 (d, J=8.2Hz, 2H, *tosyl*).

δ_C (75MHz, $CDCl_3$): 21.6 (CH_3, *tosyl methyl*), 21.8 (CH_2), 22.4 (CH_2), 30.6 (CH_2), 42.0 (CH_2), 79.3 (CH, *C-OTs*), 127.7 (CH, *tosyl C-2/C-6*), 130.0 (CH, *double bond*), 132.6 (CH, *tosyl C-3/C-5*), 133.7 (C, *tosyl C-4*), 139.5 (CH, *double bond*), 145.2 (C, *tosyl C-1*), 202.0 (C, *C=O*).

ν_{max} (CH_2Cl_2): 3060w, 2940m, 2860w, 1665s, 1595m, 1490w, 1450m, 1390m, 1360s, 1305m, 1210m, 1190s, 1175vs, 1120m, 1095m, 950s, 850m, 815m cm^{-1}.

$^m/_z$ (%): No observed M^+, 212 (97), 155 (22), 139 (20), 122 (26), 108 (43), 107 (56), 94 (32), 91 (100), 79 (53), 75 (36), 65 (70), 39 (60).

$C_{15}H_{18}SO_4$ [M^+] Requires: 294.0926
Found: 294.093

<u>4-CHLOROCYCLOOCT-2-ENONE (204)</u>

δ_H (300MHz, $CDCl_3$): 1.65 - 2.03 (series of m, 5H), 2.16 (m, 1H), 2.48 - 2.70 (m, 2H), 5.08 (m, 1H, *α-Cl*), 5.92 (ddd, J=13.0Hz, J=1.9Hz, J=0.8Hz, 1H, *double bond*), 6.28 (dd, J=13.0Hz, J=5.4Hz, 1H, *double bond*).

δ_C (75MHz, $CDCl_3$): 21.7 (CH_2), 24.3 (CH_2), 33.2 (CH_2),

42.7 (CH_2), 57.6 (CH, *C-Cl*), 130.1 (CH, *double bond*), 140.3 (CH, *double bond*), 204.7 (C, *C=O*).

ν_{max} (CH_2Cl_2): 2940m, 2860w, 1665s, 1450m, 1385m, 1320w, 1205w, 1170w, 1130w cm^{-1}.

$^m/_z$ (%): 160 (^{37}Cl M^+, 3), 158 (^{35}Cl M^+, 10), 123 (25), 122 (18), 115 (42), 95 (48), 81 (100), 80 (86), 79 (70), 67 (46), 55 (48), 53 (58).

$C_8H_{11}OCl$ [M^+] Requires: 158.0498
Found: 158.050

4-AZIDOCYCLOOCT-2-ENONE (205)

Sodium azide (199mg, 3.00mmol) was added in small portions at room temperature to a stirred solution of (203) (175mg, 0.60mmol) in dimethylformamide (2ml). The solution was stirred at room temperature for 17h, filtered, and evaporated at reduced pressure giving a residue which was dissolved in dichloromethane (20ml), washed with water (2ml) and dried over anhydrous magnesium sulphate. The solution was evaporated at reduced pressure giving an oil which was purified by flash chromatography (3:2 petroleum ether:diethyl ether) to yield (205) (80mg, 81%) as a pale yellow oil.

δ_H (300MHz, $CDCl_3$): 1.50 - 2.09 (series of m, 6H), 2.55 (m, 1H), 2.71 (ddd, J=14.2Hz, J=11.0Hz, J=6.4Hz, 1H), 4.80 (m,

1H, *α-N_3*), 6.08 - 6.19 (m, 2H, *double bond*).

δ_C (75MHz, $CDCl_3$): 22.5 (CH_2), 22.7 (CH_2), 30.1 (CH_2), 42.3 (CH_2), 60.2 (CH, *C-N_3*), 133.2 (CH, *double bond*), 140.0 (CH, *double bond*), 202.9 (C, *C=O*).

ν_{max} (CH_2Cl_2): 2940m, 2860m, 2100vs, 1670vs, 1450m, 1385m, 1340m, 1240m, 1215m, 1170m, 1120m, 1090m cm^{-1}.

$^m/_z$ (%): No observed M^+, 149 (12), 139 (19), 123 (37), 122 (100), 105 (20), 95 (79), 94 (72), 93 (44), 91 (78), 79 (54), 77 (49), 67 (48), 65 (40), 55 (49), 41 (75).

$C_8H_{15}N_4O$ [MNH_4^+] Requires: 183.1246
Found: 183.125

<u>1-(β-METHOXYETHOXYMETHOXY)-N-BENZOYL-9-AZABICYCLO [4.2.1]NON-7-ENE (217)</u>

A solution of n-butyllithium (11.40ml of a 2.5M solution in hexanes, 28.49mmol) was added to a solution of (160) (6.60g, 27.13mmol) in dry tetrahydrofuran (300ml) at 0°C under dry N_2. The stirred solution was allowed to warm to room temperature, and after 15min MEM-chloride (4.31ml, 37.81mmol) was added and the solution was refluxed for 7h. The solution was evaporated at reduced pressure and the residue dissolved in dichloromethane (400ml) and washed with water (2 x 100ml). The organic solution was dried over anhydrous magnesium sulphate and then evaporated at reduced

pressure producing an oil which was purified by flash chromatography (diethyl ether) to yield (217) (5.37g, 65%) as a yellow oil.

δ_H (300MHz, $CDCl_3$): 1.26 - 1.65 (series of m, 6H), 1.87 (m, 1H), 2.79 (m, 1H), 3.30 (s, 3H, *MEM Methyl*), 3.37 - 3.48 (m, 2H, *MEM O-CH_2*), 3.66 -3.82 (m, 2H, *MEM O-CH_2*), 4.69 (brd, J=5.0Hz, *bridgehead*), 4.94, 4.98 (ABq, J=7.3Hz, 2H, *MEM O-CH_2-O*), 5.83 (s, 2H, *double bond*), 7.27 - 7.55 (series of m, 5H, *aromatic*).

δ_C (75MHz, $CDCl_3$): 22.6 (CH_2) 23.6 (CH_2), 33.1 (CH_2), 35.5 (CH_2), 58.8 (CH_3, *O-Me*), 63.6 (CH, *bridgehead*), 67.7 (CH_2, *MEM O-CH_2*), 71.7 (CH_2, *MEM O-CH_2*), 90.2 (CH_2, *MEM O-CH_2-O*), 99.7 (C, *bridgehead*), 127.1 (CH, *benzoyl C-2/C-6*), 128.3 (CH, *benzoyl C-3/C-5*), 129.8 (CH, *double bond*), 130.9 (CH, *benzoyl C-4*), 134.0 (CH, *double bond*), 137.2 (C, *benzoyl C-1*), 170.3 (C, *benzoyl C=O*).

ν_{max} (CH_2Cl_2): 2930m, 2890m, 2820w, 1765w, 1645m, 1630m, 1600m, 1575w, 1445m, 1390s, 1360m, 1345m, 1320w, 1200m, 1110brm, 1100m, 1070s, 1020s cm^{-1}.

$^m/_z$ (%): 332 (MH^+, 100), 256 (10), 243 (23), 226 (37), 122 (5), 105 (12), 94 (2), 59 (2), 44 (2).

$C_{19}H_{26}NO_4$ [MH^+] Requires: 332.1862

Found: 332.186

1-(β-METHOXYETHOXYMETHOXY)-N-BENZYL-9-AZABICYCLO [4.2.1]NON-7-ENE (218)

A solution of (217) (2.44g, 7.36mmol) in dry tetrahydrofuran (30ml) was added dropwise to a slurry of lithium aluminium hydride (421mg, 11.04mmol) in dry tetrahydrofuran (30ml). The stirred slurry was refluxed for 6h after which time decomposition of excess hydride was affected by addition of water. The inorganic solids were removed by filtration and washed with warm ethyl acetate. The combined organic solutions were evaporated at reduced pressure producing a residue which was dissolved in dichloromethane and dried over anhydrous magnesium sulphate. The solution was evaporated at reduced pressure producing an oil which was purified by flash chromatography (65:35 petroleum ether (40 - 60°C):diethyl ether, saturated with gaseous ammonia) to yield (218) (1.98g, 85%) as a colourless oil.

δ_H (300MHz, $CDCl_3$): 1.37 - 1.45 (m, 1H), 1.52 - 1.76 (series of m, 4H), 1.91 - 2.16 (series of m, 3H), 3.35 (s, 3H, *MEM methyl*), 3.48 - 3.62 (m, 3H, *bridgehead and MEM O-CH_2*), 3.78 - 3.88 (m, 2H, *MEM O-CH_2*), 4.06, 4.14 (ABq, J=14.5Hz, 2H, *benzyl CH_2*), 4.54 (d, J=6.8Hz, 1H, *MEM O-CH-O*), 5.18 (d, J=6.8Hz, 1H, *MEM O-CH-O*), 5.92 (s, 2H, *double bond*), 7.17 - 7.37 (series of m, 5H, *aromatic*).

δ_C (75MHz, $CDCl_3$): 23.0 (CH_2), 23.6 (CH_2), 29.5 (CH_2), 37.0 (CH_2), 45.8 (CH_2, *benzyl CH_2*), 58.9 (CH_3, *O-Me*), 59.8 (CH, *bridgehead*), 67.0 (CH_2, *MEM O-CH_2*), 71.9 (CH_2, *MEM O-*

CH_2), 89.1 (CH_2, *MEM O-CH_2-O*), 99.3 (C, *bridgehead*), 126.4 (CH, *benzyl C-4*), 128.0 (CH, *benzyl C-2/C-6*), 128.1 (CH, *benzyl C-3/C-5*), 133.7 (CH, *double bond*), 135.8 (CH, double bond), 140.4 (C, *benzyl C-1*).

ν_{max} (CH_2Cl_2): 2920m, 2880m, 1480w, 1445w, 1350brw, 1185brm, 1100m, 1050m, 1030m, 1015m, 985m cm^{-1}.

$^{m}/_{z}$ (%): 318 (MH^+, 100), 228 (8), 212 (77), 122 (4), 109 (4), 91 (7), 59 (4), 44 (3).

$C_{19}H_{28}NO_3$ [MH^+] Requires: 318.2069
Found: 318.207

N-BENZYL-9-AZABICYCLO[3.3.2]DECA-3-EN-2-ONE (219)

Titanium (IV) chloride (6.24ml of a 1.0M solution in dichloromethane, 6.24mmol) was added to a solution of (218) (660mg, 2.08mmol) in dry dichloromethane (10ml) at 0°C under N_2. After 2h at room temperature, the solution was quenched with concentrated ammonium hydroxide solution and extracted with dichloromethane. The organic solution was dried over anhydrous magnesium sulphate and evaporated at reduced pressure producing an oil which was purified by flash chromatography (1:1 petroleum ether (40 - 60°C):diethyl ether, saturated with gaseous ammonia) to yield (219) (255mg, 51%) as a yellow oil.

δ_H (300MHz, $CDCl_3$): 1.19 (m, 1H), 1.51 - 1.82 (series of m, 4H), 2.05 (m, 1H), 2.63 (dd, J=12.4Hz, J=1.3Hz, 1H, *bridging N-CH*), 2.80 (m, 1H, *bridgehead α-C=O*), 3.01 (ddd, J=12.4Hz, J=5.6Hz, J=0.6Hz, 1H, *bridging N-CH*), 3.68 - 3.78 (m (incl. ABq, 2H), 2H + 1H, *benzyl CH_2 and bridgehead α-N*), 6.26 (dd, J=11.7Hz, J=1.9Hz, 1H, *double bond*), 6.43 (dd, J=11.7Hz, J=8.6Hz, 1H, *double bond*), 7.20 - 7.35 (m, 5H, *aromatic*).

δ_C (75MHz, $CDCl_3$): 20.6 (CH_2), 27.4 (CH_2), 32.8 (CH_2), 49.1 (CH, *bridgehead C-C=O*), 52.7 (CH_2, *bridging N-CH_2*), 58.8 (CH, *bridgehead C-N*), 62.5 (CH_2, *benzyl CH_2*), 127.0 (CH, *benzyl C-4*), 128.2 (CH, benzyl C-2/C-6), 128.4 (CH, *benzyl C-3/C-5*), 135.4 (CH, *double bond*), 139.4 (C, *benzyl C-1*), 141.8 (CH, *double bond*), 206.9 (C, *C=O*).

ν_{max} (CH_2Cl_2): 3020w, 2940m, 2870m, 2820m, 1665s, 1490w, 1450w, 1390w, 1350m, 1235w, 1195m, 1160m, 1125m, 1105m cm^{-1}.

$^m/_z$ (%): 241 (M^+, 36), 214 (10), 213 (10), 171 (15), 170 (15), 158 (11), 150 (25), 122 (10), 91 (100), 85 (38), 83 (65), 76 (14), 65 (15), 51 (28), 49 (83).

$C_{16}H_{19}NO$ [M^+] Requires: 241.1467

Found: 241.147

TRIFLUOROACETIC ACID SALT OF (219)

Compound (219) was acidified with one equivalent of trifluoroacetic acid to observe the changes in chemical shift caused by protonation of the amine moiety:

δ_H (300MHz, $CDCl_3$): 1.30 (m, 1H), 1.75 - 1.85 (m, 2H), 1.99 (m, 1H), 2.19 (m, 1H), 2.42 (m, 1H), 3.03 (m, 1H, *bridgehead α-C=O*), 3.19 (brd, J=13.8Hz, 1H, *bridging N-CH*), 3.97 (brdd, J=13.8Hz, J=5.1Hz, 1H, *bridging N-CH*), 4.20, 4.48 (ABq, J=12.9Hz, 1H, *benzyl CH_2*), 4.51 (m, 1H, *bridgehead α-N*), 6.31 (dd, J=12.0Hz, J=8.4Hz, 1H, *double bond*), 6.43 (dd, J=12.0Hz, J=1.9Hz, 1H, *double bond*), 7.33 - 7.56 (m, 5H, *aromatic*).

δ_C (75MHz, $CDCl_3$): 19.5 (CH_2), 26.8 (CH_2), 28.1 (CH_2), 47.5 (CH, *bridgehead C-C=O*), 51.4 (CH_2, *bridging N-CH_2*), 59.6 (CH, *bridgehead C-N*), 62.0 (CH_2, *benzyl CH_2*), 129.0 (C, *benzyl C-1*), 129.5 (CH, *benzyl C-2/C-6 or C-3/C-5*), 130.4 (CH, *benzyl C-4*), 131.2 (CH, *benzyl C-3/C-5 or C-2/C-6*), 134.0 (CH, *double bond*), 138.9 (CH, *double bond*), 201.7 (C, *C=O*).

1-HYDROXY-N BENZYL-9-AZABICYCLO[4.2.1]NON-7-ENE (220)

Trifluoroacetic acid (2.23ml, 28.9mmol) was added all at once to a solution of (218) (920mg, 2.89mmol) in dichloromethane (20ml) at 0°C. After 6h at room temperature, water (550µl, 30.5mmol) was added and the

solution was left for a further 24h at room temperature. The solution was evaporated at reduced pressure to remove solvent and then rid of hydrated methanal by-product [79] using an oil pump (0.4mm Hg). The residue was dissolved in water (50ml) and diethyl ether (50ml) and the aquous layer was washed with more diethyl ether (2 x 10ml). The aqueous layer was basified to pH 14 with 2M sodium hydroxide solution and then extracted with dichloromethane. The combined dichloromethane extractions were dried over anhydrous magnesium sulphate and evaporated at reduced pressure producing an oil which was purified by flash chromatography (7:3 ethyl acetate:petroleum ether (40 - 60°C), saturated with gaseous ammonia) to yield (220) (569mg, 86%) as a colourless oil.

δ_H (300MHz, $CDCl_3$, -55°C): 1.24 - 2.09 (series of m, 8H), 3.80 (br, 1H, *bridgehead*), 4.12, 4.30 (ABq, J=14.6Hz, 2H, *benzyl* CH_2), 5.93 (s, 2H, *double bond*), 7.18 - 7.74 (m, 5H, *aromatic*).

δ_C (300MHz, $CDCl_3$, -55°C): 21.4 (CH_2), 23.0 (CH_2), 28.7 (CH_2), 36.3 (CH_2), 45.7 (CH_2, *benzyl* CH_2), 60.1 (CH, *bridgehead*), 94.7 (C, *bridgehead*), 126.4 (CH, *benzyl C-4*), 127.9 (CH, *benzyl C-2/C-6*), 128.1 (CH, *benzyl C-3/C-5*), 133.2 (CH, *double bond*), 137.4 (CH, *double bond*), 140.6 (C, *benzyl C-1*).

Using variable temperature ^1H and ^{13}C NMR it was also found that (220) was the minor tautomer at -55°C in equilibrium

with 58% of the monocyclic form 4-benzylaminocyclooct-2-enone (221):

δ_H (300MHz, $CDCl_3$, -55°C): 1.24 - 2.09 (series of m, 6H), 2.53 (m, 1H, *α-C=O*), 2.78 (m, 1H, *α-C=O*), 3.72, 3.90 (ABq, J=12.7Hz, 2H, *benzyl* CH_2), 4.23 (m, 1H, *α-*$NHCH_2Ph$), 6.25 (brd, J=12.4Hz, 1H, *double bond*), 6.40 (brdd, J=12.4Hz, J=6.2Hz, 1H, *double bond*), 7.18 - 7.74 (m, 5H, *aromatic*).

δ_C (75MHz, $CDCl_3$, -55°C): 22.7 (CH_2), 22.8 (CH_2), 31.1 (CH_2), 42.1 (CH_2), 52.1 (CH_2, *benzyl* CH_2), 55.3 (CH, *C-*$NHCH_2Ph$), 127.2 (CH, *benzyl C-4*), 128.3 (CH, *benzyl C-2/C-6*), 128.5 (CH, *benzyl C-3/C-5*), 134.8 (CH, *double bond*), 138.8 (C, *benzyl C-1*), 149.9 (CH, *double bond*), 203.3 (C, *C=O*).

ν_{max} (CH_2Cl_2): 3560w, 3020w, 2930m, 2850m, 2820brw, 1690w, 1655m, 1490w, 1450m, 1350brw, 1205w cm^{-1}.

$^m/_z$ (%): 229 (M^+, 5), 211 (40), 210 (10), 183 (29), 182 (10), 91 (100), 77 (6), 65 (17), 44 (16), 36 (18).

$C_{15}H_{19}NO$ [M^+] Requires: 229.1467
Found: 229.147

<u>4-(BENZOYLAMINO)CYCLOOCTANONE ETHYLENE ACETAL (226)</u>

Ethane-1,2-diol (149µl, 2.68mmol) was added to a solution of (136) (600mg, 2.44mmol) in benzene (20ml) contained in a 50ml round-bottomed flask fitted with a Dean and Stark water

separator and a reflux condenser. A few crystals of *p*-toluenesulphonic acid and a stirring bead were added, and the solution was heated and stirred so that that benzene refluxed vigorously. After refluxing for 3h, the solution was allowed to cool to room temperature. The solvent was removed at reduced pressure producing an oil which was dissolved in dichloromethane (20ml) and the resulting solution was washed with 5% sodium bicarbonate solution (5ml), water (2 x 5ml) and dried over anhydrous potassium carbonate. The solvent was evaporated at reduced pressure producing an oil which was purified by flash chromatography (diethyl ether) to yield (226) (416mg, 59%) as a white foam.

δ_H (300MHz, $CDCl_3$): 1.57 - 2.18 (series of m, 12H), 3.87 - 3.94 (m, 4H, *acetal O-CH_2CH_2-O*), 4.18 (m, 1H, *α-NHCOPh*), 6.20 (brd, J=7.4Hz, exch *-NH*, 1H), 7.37 - 7.51 (m, 3H, *aromatic*), 7.72 - 7.75 (m, 2H, *aromatic*).

δ_C (75MHz, $CDCl_3$): 21.8 (CH_2), 23.3 (CH_2), 28.2 (CH_2), 30.4 (CH_2), 32.3 (CH_2), 33.5 (CH_2), 50.0 (CH, *C-NHCOPh*), 64.2 (CH_2, *acetal O-CH_2*), 64.4 (CH_2, *acetal O-CH_2*), 111.6 (C, *acetal C*), 126.8 (CH, *benzoyl C-2/C-6*), 128.5 (CH, *benzoyl C-3/C-5*), 131.2 (CH, *benzoyl C-4*), 134.9 (C, *benzoyl C-1*), 166.4 (C, *benzoyl C=O*).

ν_{max} (CH_2Cl_2): 3430m, 3370brw, 2940m, 2880m, 1655s, 1600w, 1580m, 1510s, 1485m, 1315m, 1115m, 1090m cm^{-1}.

$^{m}/_{z}$ (%): 290 (MH^+, 100), 260 (5), 246 (42), 228 (7), 168 (5), 148 (2), 139 (2), 124 (9), 105 (23), 99 (7), 86 (6), 77 (2), 55 (2).

$C_{17}H_{24}NO_3$ [MH^+] Requires: 290.1756
Found: 290.176

4-(BENZYLAMINO)CYCLOOCTANONE ETHYLENE ACETAL (227)

A solution of (226) (340mg, 1.17mmol) in dry tetrahydrofuran (12ml) was added dropwise to a stirred slurry of lithium aluminium hydride (133mg, 3.51mmol) in dry tetrahydrofuran (6ml). After refluxing for 24h, decomposition of excess hydride was effected by addition of water. The inorganic solids were removed by filtration and washed with warm ethyl acetate. The combined organic solutions were evaporated at reduced pressure to yield (227) (320mg, 99%) as a colourless oil.

δ_H (300MHz, $CDCl_3$): 1.36 - 2.02 (series of m, incl. exch *-NH*, 12H + 1H), 2.74 (m, 1H, *α-NHCH$_2$Ph*), 3.75 (s, 2H, *benzyl CH$_2$*), 3.89 (s, 4H, *acetal O-CH$_2$CH$_2$-O*), 7.18 - 7.37 (m, 5H, *aromatic*).

δ_C (75MHz, $CDCl_3$): 22.2 (CH_2), 24.1 (CH_2), 28.3 (CH_2), 30.6 (CH_2), 31.6 (CH_2), 34.1 (CH_2), 51.5 (CH_2, *benzyl CH$_2$*), 57.0 (CH, *C-NHCH$_2$Ph*), 64.1 (CH_2, *acetal O-CH$_2$*), 64.3 (CH_2, *acetal O-CH$_2$*), 112.1 (C, *acetal C*), 126.7 (CH, *benzyl C-4*),

128.0 (CH, *benzyl C-2/C-6*), 128.3 (CH, *benzyl C-3/C-5*), 140.7 (C, *benzyl C-1*).

ν_{max} (CH_2Cl_2): 3020w, 2930s, 2880m, 2820brm, 1465m, 1450m, 1360m, 1215w, 1150m, 1110m, 1090m, 1040m, 945m cm^{-1}.

$^m/_z$ (%): 276 (MH^+, 100), 232 (3), 214 (6), 184 (2), 169 (2), 159 (2), 146 (6), 129 (26), 108 (3), 99 (3), 91 (14), 55 (2).

$C_{17}H_{26}NO_2$ [MH^+] Requires: 276.1964
Found: 276.196

4-(BENZYLAMINO)CYCLOOCTANONE (228)

A solution of (227) (175mg, 0.64mmol) in aqueous acetic acid (4ml of 2:1 glacial acetic acid: water) was heated at 90°C for 2h. The solution was allowed to cool and then washed with diethyl ether (2 x 1ml), carefully neutrallised and basified to pH 14 with 2M sodium hydroxide solution, and then extracted with dichloromethane (5 x 10ml). The combined organic solutions were washed with water (2 x 10ml) dried over anhydrous magnesium sulphate and evaporated at reduced pressure to yield (228) (140mg, 95%) as a pale yellow oil.

δ_H (300MHz, $CDCl_3$, -50°): 1.23 - 2.48 (series of m, 12H), 2.73 (brm, 1H, *α-NHCH$_2$Ph*), 3.74, 3.78 (ABq, J=13.4Hz, 2H, *benzyl CH$_2$*), 7.28 - 7.35 (m, 5H, *aromatic*).

δ_C (75MHz, $CDCl_3$, -50°C): 22.7 (CH_2), 28.1 (CH_2), 28.5 (CH_2), 30.1 (CH_2), 40.0 (CH_2), 40.7 (CH_2), 51.0 (CH_2, *benzyl CH$_2$*), 56.1 (CH, *C-NHCH$_2$Ph*), 126.9 (CH, *benzyl C-4*), 128.0 (CH, *benzyl C-2/C-6*), 128.4 (CH, *benzyl C-3/C-5*), 139.8 (C, *benzyl C-1*), 218.6 (C, *C=O*).

Using variable temperature ^1H and ^{13}C NMR it was also found that (228) was the major tautomer at -50°C in equilibrium with 34% of the bicyclic form 1-hydroxy-N-benzyl-9-azabicyclo[4.2.1]nonane (229):

δ_H (300MHz, $CDCl_3$, -50°C): 1.23 - 2.48 (series of m, 12H), 3.31 (brm, 1H, *bridgehead*), 3.89, 4.17 (ABq, J=14.2Hz, 2H, *benzyl CH$_2$*), 7.28 - 7.35 (m, 5H, *aromatic*).

δ_C (75MHz, $CDCl_3$, -50°C): 22.6 (CH_2), 23.5 (CH_2), 26.0 (CH_2), 32.0 (CH_2), 38.2 (CH_2), 40.7 (CH_2), 45.7 (CH_2, *benzyl CH$_2$*), 54.2 (CH, *bridgehead*), 92.2 (C, *bridgehead*), 126.4 (CH, *benzyl C-4*), 127.8 (CH, *benzyl C-2/C-6*), 128.0 (CH, *benzyl C-3/C-5*), 140.8 (C, *benzyl C-1*).

ν_{max} (CH_2Cl_2): 3570w, 3020w, 3030s, 2860m, 2820brm, 1690m, 1490w, 1465m, 1450m, 1350m, 1205w, 1110m, 1070m, 1025w cm^{-1}.

$^{m}/_{z}$ (%): 232 (7), 231 (M^+, 8), 202 (9), 188 (3), 174 (13), 159 (8), 146 (100), 132 (13), 118 (3), 106 (6), 91 (92), 84 (6), 77 (3), 65 (11), 55 (5).

$C_{15}H_{21}NO$ [M^+] Requires: 231.1623
Found: 231.162

9-AZABICYCLO[4.2.1]NONANE (230)

A solution of (116) (190mg, 0.88mmol) in dry methanol (9ml) was acidified with gaseous hydrogen chloride and hydrogenated at 1atm in the presence of 10% palladium on charcoal. After 16h, the solution was filtered through celite and then through a Millipore 0.2μ Millex-FG disposable filter unit giving a clear solution which was evaporated at reduced pressure to yield the hydrochloride salt of (230) (139mg, 0.86mmol, 98%) as a white, hygroscopic solid.

δ_H (300MHz, $CDCl_3$): 1.40 - 2.50 (brm, 12H), 4.19 (brs, 2H, *bridgeheads*), 9.01 (very brs, 1H, *of* NH_2^+), 9.88 (very brs, 1H, *of* NH_2^+).

δ_C (75MHz, $CDCl_3$): 23.2 (CH_2), 29.7 (CH_2), 31.6 (CH_2), 57.2 (CH).

ν_{max} (CH_2Cl_2): 2930brs, 2800brs, 2760brs, 2710m, 2650m, 2560m, 2500m, 1590s, 1470brm, 1265w cm^{-1}.

$^{m}/_{z}$ (%): 125 (M^{+} -HCl, 36), 96 (18), 82 (100), 69 (44), 68 (81), 56 (21), 43 (36), 42 (37), 41 (86), 39 (75).

On basification with sodium hydroxide solution, extraction with dichloromethane and the addition of one equivalent of picric acid (220mg, 0.86mmol), the picrate of (230) was formed, mp 229 - 230°C (decomp) (lit.[106] mp 228°C, decomp) (from ethanol):

Found: C, 47.95; H, 5.13; N, 15.76%

$C_8H_{15}N.C_6H_3N_3O_7$ Requires: C, 47.46; H, 5.12; N, 15.81%

1-METHYL-9-AZABICYCLO[4.2.1]NONANE (135)

A solution of (159) (1.05g, 4.58mmol) in dry methanol (30ml) was acified with gaseous hydrogen chloride and hydrogenated at 1atm in the presence of 10% palladium on charcoal. After 16h, the solution was filtered through celite and then through a Millipore 0.2μ Millex-FG disposable filter unit giving a clear solution which was evaporated at reduced pressure to yield the hydrochloride salt of (135) (778mg, 4.43mmol, 97%) as a white, hygroscopic solid.

δ_H (300MHz, $CDCl_3$): 1.55 - 2.27 (incl 1.70 (s, 3H, *methyl*), 11H + 3H), 2.50 (m, 1H), 4.19 (brm, 1H, *bridgehead*), 9.27 (very brd, J=10.2Hz, 1H, *of* NH_2^+), 9.63 (very brs, 1H, *of* NH_2^+).

δ_C (75MHz, $CDCl_3$): 22.2 (CH_2), 22.3 (CH_2), 26.1 (CH_3), 29.8 (CH_2), 30.0 (CH_2), 35.2 (CH_2), 38.9 (CH_2), 55.9 (CH, *bridgehead*), 66.1 (C, *bridgehead*).

ν_{max} (CH_2Cl_2): 2930brs, 2800brm, 2720brs, 2490brm, 1590s, 1475m, 1465m, 1420m, 1380m, 1210w cm^{-1}.

m/z (%): 139 (M^+ -HCl, 25), 110 (10), 96 (74), 84 (57), 82 (100), 79 (45), 67 (26), 55 (21), 41 (40).

On basification with sodium hydroxide solution, extraction with dichloromethane and the addition of one equivalent of picric acid (1.015g, 4.43mmol), the picrate of (135) was formed, mp 275 - 276°C (decomp.) (from ethanol):

Found: C, 49.05; H, 5,45; N, 15,00%

$C_9H_{17}N.C_3H_3N_3O_7$ Requires: C, 48.91; H, 5.47; N, 15.21%

N-METHYL-N-BENZYL-9-AZABICYCLO[4.2.1]NON-7-ENIUM IODIDE (232)

Methyl iodide (300µl, 4.82mmol) was added to a solution of (118) (105mg, 0.491mmol) in dry acetone (300µl) at 0°C. After heating the reaction at reflux for 6h, the solution was evaporated at reduced pressure producing an orange solid which was triturated with cold acetone to yield (232) (100mg, 57%) as a pale yellow solid.

δ_H(300MHz, $CDCl_3$): 1.86 - 1.90 (m, 2H), 2.08 - 2.17 (m, 4H), 2.61 - 2.69 (m, 2H), 3.20 (s, 3H, *N-methyl*) 4.98 (brm, 2H, *bridgeheads*), 5.28 (s, 2H, *benzyl* CH_2), 6.18 (s, 2H, *double bond*), 7.45 - 7.48 (m, 3H, *aromatic*), 7.75 - 7.80 (m, 2H, *aromatic*).

δ_C (75MHz, $CDCl_3$): 23.2 (CH_2), 27.1 (CH_2), 52.1 (CH_3), 56.8 (CH_2, *benzyl* CH_2), 78.6 (CH, *bridgeheads*), 129.0 (C, *benzyl C-1*), 129.6 (CH, *benzyl C-2/C-6 or C-3/C-5*), 130.1 (CH, *benzyl C-2/C-6 or C-3/C-5*), 130.3 (CH, *benzyl C-4*), 131.5 (CH, *double bond*).

DEBENZYLATION OF (232) WITH SODIUM IN LIQUID AMMONIA

A suspension of (232) (100mg, 0.282mmol) in dry tetrahydrofuran (3ml) was added to dry, distilled liquid ammonia containing the minimum amount of sodium required to make the solution turn blue. On addition of the suspension, the ammonia solution turned orange in colour. A small piece of sodium was added to maintain the blue colour. The solution was left to stir and reflux at -33°C for 2h after which time the solution was quenched with solid ammonium chloride until the blue colour disappeared. The ammonia was allowed to evaporate, the residue was extracted with dichloromethane, and the solution was filtered. This solution was saturated with hydrogen chloride gas, filtered and evaporated at reduced pressure to yield the hydrochloride salt of (126) (35mg, 71%) as a white solid.

δ_H (90MHz, $CDCl_3$): 1.4 - 2.7 (series of m, 8H), 3.0 (d, J≈5Hz, 3H, *methyl*), 4.3 (brd, J≈6Hz, 2H, *bridgeheads*), 5.9 (s, 2H, *double bond*), 7.2 (br, 1H, NH^+).

The deuterated chloroform solution was basified with ammonia gas and filtered to yield the free amine (126) from which was obtained spectroscopic data (NMR, IR) identical with those obtained from (126) synthesised by intramolecular cyclisation of (124).

DEBENZYLATION OF (232) WITH SODIUM AMALGAM (EMDES REDUCTION[89])

A solution of (232) (91mg, 0.257mmol) in water (4ml) was heated to reflux and sodium amalgam (2.06g of 5% amalgam) was added in 200 - 250mg portions over 15min. The solution was stirred at reflux for 5h and at room temperature for a further 16h. The solution was filtered and the filtrate acidified with 2M hydrochloric acid. The solution was evaporated at reduced pressure and the residue was extracted with dichloromethane. This dichloromethane solution was evaporated at reduced pressure producing an orange oil which was found by NMR to be a 1:1 mixture of starting material (232) and the hydrochloride salt of (126). The product was not purified further.

9-AZABICYCLO[4.2.1]NON-7-ENE (237)

α-Chloroethyl chloroformate (2.456ml, 22.74mmol) was added dropwise, under dry N_2, to a stirred solution of (126) (1.04g, 7.58mmol), in dry dichloromethane (10ml), which had been dried over anhydrous potassium carbonate, and the solution was heated at 35°C for 4h. The solvent was evaporated at reduced pressure and the residue was dissolved in methanol (20ml) and heated at 55°C for 3h. The solution was evaporated at reduced pressure to yield the hydrochloride salt of (237) (1.203g, 7.53mmol, 99%) as a white, hygroscopic solid.

δ_H (300MHz, $CDCl_3$): 1.40 - 2.50 (brm, 8H), 4.69 (brs, 2H, *bridgeheads*), 5.86 (s, 2H, *double bond*), 9.31 (very brs, 1H, *of* NH_2^+), 10.35 (very brs, 1H, *of* NH_2^+).

δ_C (75MHz, $CDCl_3$): 23.2 (CH_2), 29.1 (CH_2), 62.3 (CH), 129.7 (CH).

ν_{max} (CH_2Cl_2): 2930brs, 2810m, 2790m, 2740m, 2690m, 2650m, 2610m, 2540m, 1710m, 1580s, 1450brm, 1410m, 1360m, 1220w cm^{-1}.

$^m/_z$ (%): 123 (M^+ -HCl, 12), 94 (16), 80 (100), 67 (38), 53 (10), 41 (36), 40 (12), 39 (40).

On basification with sodium hydroxide solution, extraction with dichloromethane and the addition of one equivalent of

picric acid (1.725g, 7.53mmol), the picrate of (237)was formed, mp 226 - 227°C (decomp.) (from ethanol):

Found: C, 48.11; H, 4.58; N, 15.69%

$C_8H_{13}N.C_6H_3N_3O_7$ Requires: C, 47.73; H, 4.58; N, 15.90%

N-CHLORO-9-AZABICYCLO[4.2.1]NONANE (251)

A solution of the hydrochloride salt of (230) (130mg, 0.80mmol) in water (10ml) was treated with sodium hypochlorite (5% chlorine content, 18ml) and stirred at room temperature for 1h. The product was extracted into trichlorofluoromethane (3 x 10ml) and the combined organic layers dried over anhydrous magnesium sulphate. The solvent was evaporated by passing a gentle stream of N_2 over it to yield (251) (119mg, 93%) as a pale yellow oil.

δ_H (300MHz, $CFCl_3$): 1.28 - 1.72 (series of m, 8H), 1.90 - 2.01 (m, 2H), 2.42 - 2.58 (m, 2H), 3.89 (m, 2H, *bridgeheads*).

δ_C (75MHz, $CFCl_3$): 25.6 (CH_2), 32.0 (CH_2), 36.2 (CH_2), 76.0 (CH).

$^m/_z$ (%): 162 (^{37}Cl MH^+, 30), 160 (^{35}Cl MH^+, 97), 124 (100), 102 (9), 96 (11), 82 (38), 69 (39), 68 (73), 55 (11), 41 (19).

$C_8H_{14}NCl$ [MH^+] Requires: 160.0893

Found: 160.089

1-METHYL-N-CHLORO-9-AZABICYCLO[4.2.1]NONANE (252)

A solution of the hydrochloride salt of (135) (100mg, 0.60mmol) in water (10ml) was treated with sodium hypochlorite (5% chlorine content, 18ml) and stirred at room temperature for 1h. The product was extracted into trichlorofluoromethane (3 x 10ml) and the combined organic layers dried over anhydrous magnesium sulphate. The solvent was evaporated by passing a gentle stream of N_2 over it to yield (252) (99mg, 95%) as a pale yellow oil.

δ_H (300MHz, $CFCl_3$): 1.29 (s, 3H), 1.49 - 1.96 (m, 10H), 2.17 - 2.32 (m, 2H), 3.82 (m, 1H, *bridgehead*).

δ_C (75MHz, $CFCl_3$): 25.6 (CH_2), 25.7 (CH_2), 30.1 (CH_3), 30.2 (CH_2), 35.3 (CH_2), 36.4 (CH_2), 42.0 (CH_2), 68.3 (CH, *bridgehead*), 70.2 (C, *bridgehead*).

$^m/_z$ (%): 176 (^{37}Cl MH^+, 4), 174 (^{35}Cl MH^+, 13), 158 (2), 140 (100), 122 (3), 106 (8), 96 (13), 82 (12), 58 (5), 44 (10).

$C_9H_{16}NCl$ $[M^+]$ Requires: 173.0970

Found: 173.097

N-CHLORO-9-AZABICYCLO[4.2.1]NON-7-ENE (253)

A solution of the picrate of (237) (274mg, 0.78mmol) in water (10ml) was treated with sodium hypochlorite (5% chlorine

content, 18ml) and stirred at room temperature for 1½h. The product was extracted into trichlorofluoromethane (3 x 10ml) and the combined organic layers dried over anhydrous magnesium sulphate. The solvent was evaporated by passing a gentle stream of N_2 over it to yield (253) (120mg, 98%) as a pale yellow oil.

δ_H (300MHz, $CFCl_3$): 1.33 - 1.63 (series of m, 6H), 1.90 - 2.01 (m, 2H), 4.27 (ddd, J=6.6Hz, J=1.8Hz, J=1.0Hz, 2H, *bridgeheads*), 5.82 (d, J=1.0Hz, 2H, *double bond*).

δ_C (75MHz, $CFCl_3$): 24.5 (CH_2), 31.9 (CH_2), 80.6 (CH, *bridgeheads*), 130.8 (CH, *double bond*).

$^m/_z$ (%): 160 (^{37}Cl MH^+, 5), 158 (^{35}Cl MH^+, 17), 124 (13), 114 (18), 94 (10), 81 (23), 80 (100), 67 (26), 53 (8).

$C_8H_{12}NCl$ $[M^+]$ Requires: 157.0660

Found: 157.066

References

1. F. Wöhler, *Ann.*, **1886**, 121, 372.

2. L. Geiger, C. Hesse, *Ann.*, **1833**, 5, 43; **1833**, 6, 44; **1833**, 7, 269.

3. A. Ladenburg, *Ann.*, **1881**, 206, 274.

4. E. Schmidt, *Arch. Pharm.*, **1892**, 230, 207.

5. (a) H.L. Holmes, "The Alkaloids", Vol.1; R.H.F. Manske, Ed. Academic Press, New York, 1950, Chapter 6.
(b) G. Fodor, *ibid.*, Vol.6, 1960, Chapter 6.
(c) G. Fodor, *ibid.*, Vol.9, 1967, Chapter 7.
(d) G. Fodor, *ibid.*, Vol.13, 1971, Chapter 8.
(e) R.L. Clarke, *ibid.*, Vol.16, 1977, Chapter 2.
(f) M. Lounasmaa, *ibid.*, Vol 33, 1988, Chapter 1.
(g) G. Fodor, "Chemistry of The Alkaloids", S.W. Pelletier, Ed. 1970.
(h) G. Fodor, R.Dharanipragada, Nat.Prod.Rep., **1988**, 5, 67.

6. W.W. Carmichael, D.F. Biggs, P.R. Gorham, *Science*, **1975**, 187, 542.

7. C.S. Huber, *Acta Crystallogr., Sect.B*, **1972**, 78, 2577.

8. J.P. Devlin, O.E. Edwards, P.R. Gorham, N.R. Hunter, R.K. Pike, B. Stavric, *Can.J. Chem.*, **1977**, 55, 1367.

9. W.W. Carmichael, D.F. Biggs, M.A. Peterson, *Toxicon*, **1979**, 17, 229.

10. (a) C.E. Spivak, B. Witcop, E.X. Albuquerque, *Mol.Pharmacol.*, **1980**, 18, 384.
(b) C.E. Spivak, J. Waters, B. Witkop, E.X. Albuquerque, *Mol.Pharmacol.*, **1983**, 23, 337.

11. L. Stryer, Biochemistry, Freeman, **1981**.

12. O. Leroy Salerni, Natural and Synthetic Organic Medicinal Compounds, The C.V. Mosby Company, Chapter 9.

13. (a) R.S. Aronstam, B. Witkop, *Proc.Natl.Acad.Sci.USA*, **1981**, 78, 4639.
(b) A.M.P. Koskinen, H. Rapoport, *J.Med.Chem.*, **1985**, 28, 1301.

14. D.B. Kanne, D.J. Ashworth, M.T. Cheng, L.C. Mutter, *J.Am.Chem.Soc.*, **1986**, 108, 7864.

15. H.F. Campbell, O.E. Edwards, R. Kolt, *Can.J.Chem.*, **1977**, 55, 1372.

16. H.A. Bates, H. Rapoport, *J.Am.Chem.Soc.*, **1979**, 101, 1259.

17. J.S. Petersen, G. Fels, H. Rapoport, *J.Am.Chem.Soc.*, **1984**, 106, 4539.

18. J.J. Tufariello, H. Meckler, K. Pushpananda A. Senaratne, J.Am.Chem.Soc., **1984**, 106, 7974.

19. (a) J.J. Tufariello, E.J. Trybulski, *J.Chem.Soc., Chem.Commun.*, **1973**, 720.
(b) J.J. Tufariello, G.B. Mullen, J.J. Teegler, E.J. Trybulski, *J.Am.Chem.Soc.*, **1979**, 101, 2435.

20. R.L. Danheiser, J.M. Morin, Jr., E.J. Salaski, *J.Am.Chem.Soc.*, **1985**, 107, 8066.

21. (a) P.M. Esch, H. Hiemstra, W.J. Klaver, W.N. Speckamp, *Heterocyles*, **1987**, 26, 75.
(b) T. Shono, Y. Matsamura, K. Uchida, K. Tagami, *Chem.Lett.*, **1987**, 919.
(c) K.H. Melching, H. Hiemstra, W.J. Klaver, W.N. Speckamp, *Tetrahedron Lett.*, **1986**, 27,4799.

(d) B. Lindgren, P. Stjernlöf, L. Trogen, *Acta Chem.Scand., Ser B*, **1987**, 41, 180.

22. P. Vernon, T. Gallagher, *J.Chem.Soc., Chem. Commun.*, **1987**, 245.

23. A.C. Cope, H.R. Nace, L.L. Estes, *J.Am.Chem.Soc.*, **1950**, 72, 1123.

24. (a) A.G Anastassiou, *J.Am.Chem.Soc.*, **1965**, 87, 5512.
(b) A.G Anastassiou, *J.Am.Chem.Soc.*, **1968**, 90, 1527.

25. (a) A.G. Anastassiou, R.P. Cellura, *J.Chem.Soc., Chem.Commun.*, **1967**, 762.
(b) A.G. Anastasiou, R.P Cellura, *J.Org.Chem.*, **1972**, 37, 3126.

26. A.G. Anastassiou, R.P. Cellura, *J.Am.Chem.Soc.*, **1972**, 94, 5112.

27. A.G. Anastassiou, H. Yamamoto, *J.Chem.Soc., Chem.Commun.*, **1973**, 840.

28. M.A. Loreto, L. Pellacani, P.A. Tardella, *J.Heterocycl.Chem.*, **1979**, 16, 1233.

29. J.W Bastable, J.D Hobson, W.D. Riddel, *J.Chem.Soc., Perkin Trans.1*. **1972**, 2205.

30. G. Haufe, E. Kleinpeter, *Tetrahedron Lett.*, **1982**, 23, 3555.

31. J. Barluenga, J. Pérez-Prieto, G. Asensio, *J.Chem. Soc., Chem.Commun.*, **1982**, 1181.

32. H. Iida, Y. Watanabe, C. Kibayashi, *J.Org.Chem.*, **1985**, 50, 1818.

33. R.R. Fraser, R.B. Swingle, *Can.J.Chem.*, 1970, 48, 2065.

34. A. Bathgate, J.R. Malpass, *Tetrahedron Lett.*, 1987, 28, 5937.

35. N. Howarth, "Synthetic Approaches to Derivatives of Tropane", Ph.D Thesis, 1991, University of Leicester, England.

36. E. Boyland, R. Nery, *J.Chem.Soc (C)*, 1966, 354.

37. A.K. Qureshi, B. Sklarz, *J.Chem.Soc. (C)*, 1966, 412.

38. A. Bathgate, "Syntheses and Reactions of Azabicycles", Ph.D. Thesis, 1988, University of Leicester, England.

39. J-E. Bäckvall, Z.D. Renko, S.E. Byström, *Tetrahedron Lett.*, 1987, 28, 4199.

40. "Vogel's Textbook of Practical Organic Chemistry", 4th Edition, Longman Scientific and Technical, 1987.

41. J. Firl, G. Kresze, *Chem.Ber.* 1966, 99, 3695.

42. M. Barrelle, M. Apparu, C. Gey, *Can.J.Chem.*, 1978, 56, 85.

43. P. Scheiber, K. Nádor, *Liebigs Ann.Chem.*, 1985, 913.

44. (a) S. Archer, M.R. Bell, T.R. Lewis, J.W. Schulenberg, M.J. Unser, *J.Am.Chem.Soc.*, 1957, 79, 6337.
(b) A.T. Bottini, C.A. Grob, E. Schumacher, J. Zergenyi, *Helv.Chim.Acta.*, 1966, 49, 2516.
(c) E.J. Gabe, W.H. Barnes, *Acta.Cryst.*, 1963, 16, 796.

(d) E. Wenkert, J.S. Bindra, C-J. Chang, D.W Cochran, F.M Schell, *Acc.Chem.Res.*, **1974**, 7, 46.

45. H.J. Schneider, L. Sturm, *Angew.Chem., Int.Ed.Engl.*, 1976, 15, 545.

46. H.E. Schink, H. Pettersson, J-E. Bäckvall, *J.Org. Chem.*, **1991**, 56, 2769.

47. A.C. Cope, C.L. Stevens. F.A. Hochstein, *J.Am.Chem. Soc.*, **1950**, 72, 2510.

48. (a) M.E. Christy, P.S. Anderson, S.F. Britcher, C.D. Colton, B.E. Evans, D.E. Remy, E.L. Engelhardt, *J.Org.Chem.*, **1979**, 44, 3117.
(b) T.R. Lamanec, D.R. Bender, A.M. DeMarco, S. Karady, R.A. Reamer, L. Weinstock, *J.Org.Chem.*, **1988**, 53, 1768.

49. (a) E.H.F. Wong, J.A. Kemp, T. Priestley, A R. Knight, G.N. Woodruff, L.L. Iversen, *Proc.Natl.Acad. Sci., USA*, **1986**, 83, 7104.
(b) J.A. Kemp, A.C. Foster, E.H.F. Wong, *Trends Neurosci.* **1987**, 10, 294.

50. P.D. Leeson, K. James, R. Baker, *J.Chem.Soc., Chem. Commun.*, **1989**, 433.

51. (a) K. Bowden, I.M. Heilbron, E.R.H. Jones, B.C.L. Weedon, *J.Chem.Soc.*, **1946**, 39.
(b) A. Bowers, T.G. Halsall, E.R.H. Jones, A.J. Lemin, *J.Chem.Soc.*, **1953**, 2548.

52. R. Greenwald, M Chaykovsky, E.J. Corey, *J.Org.Chem.*, **1963**, 28, 1128.

53. G. Wittig, U. Schöllkopf, *Org.Syn.*, **1960**, 40, 66.

54. J.M. Takacs, M.A. Helle, F. Takusagawa, *Tetrahedron Lett.*, 1989, 30, 7321.

55. D.J. Rawlinson, G. Sosnovsky, *Synthesis*, 1973, 567.

56. M.S. Brown, H. Rapoport, *J.Org.Chem.*, 1963, 28, 3261.

57. (a) Y. Kikugawa, *Chem.Lett.*, 1975, 1029.
(b) E. Santaniello, P. Ferraboschi, P. Sozzani, *J.Org.Chem.*, 1981, 46, 4584.
(c) K. Soai, H. Oyamada, A. Ookawa, *Synth.Commun.*, 1982, 12, 463
(d) H.C. Brown, S. Narasimhan, Y.M. Choi, *J.Org.Chem.*, 1982, 47, 4702.

58. J. Barluenga, J. Pérez-Prieto, A.M. Bayón, G. Asensio, *Tetrahedron*, 1984, 40, 1199.

59. (a) K.E. Harding, T.H. Marman, *J.Org.Chem.*, 1984, 49, 2838.
(b) K.E. Harding, S.R. Burks, *J.Org.Chem.*, 1984, 49, 40.

60. E.J. Parish, A.D. Scott, *J.Org.Chem.*, 1983, 48, 4766.

61. J. Attenburrow, A.F.B Cameron, J.H. Chapman, R.M. Evans, B.A. Hems, A B A. Jansen, T. Walker, *J.Chem.Soc.*, 1952, 1094.

62. H. Firouzabadi, E. Ghaderi, *Tetrahedron Lett.*, 1978, 839.

63. P.J. De Clerq, L.A. Van Royen, *Synth.Commun.*, 1979, 9, 771.

64. D.J. Peterson, *J.Org.Chem.*, 1968, 33, 780.

65. T. Imamoto, N. Takiyami, K. Nakamura, T. Hatajima, Y. Kamiya, *J.Am.Chem.Soc.*, 1989, 111, 4392.

66. H.O. House, *Modern Synthetic Reactions*, 2nd Edition, pp. 459 - 478, W A. Benjamin, New York, 1972.

67. (a) A. Nechvatal, Adv. *Free-Radical Chem.* 1972, 4, 175.
(b) L. Horner, E.H. Winkelmann, *Newer Methods Prep. Org.Chem.*, 1964, 3, 151.

68. A.B. Ray, Y. Oshima, H. Hikino, C. Kabuto, *Heterocycles*, 1982, 19, 1233.

69. D. Tepfer, A. Goldmann, N. Pamboukdian, M. Maille, A. Lepingle, D. Chevalier, J. Denarié, C. Rosenburg, *J.of Bact.*, 1988, 170, 1153.

70. P-H. Ducrot, J.Y. Lallemand, *Tetrahedron Lett.*, 1990, 31, 3879; P-H. Ducrot, J. Beauhaire, J.Y. Lallemand, *ibid*, 3883.

71. (a) M. Balci, *Chem.Rev.*, 1981, 81, 91.
(b) W. Adam, O. Cueto, O. De Lucchi, K. Peters, E-M. Peters, H.G. von Schnering, *J.Am.Chem.Soc*, 1981, 103, 5822.
(c) W. Adam, G. Klug, *Tetrahedron Lett.*, 1982, 23, 3155.

72. Y. Kayama, M. Oda, Y. Kitahara, *Chem.Lett.*, 1974, 345.

73. M. Barrelle, M. Apparu, *Bull.Soc.Chim.France.*, 1972, 2016

74. G.I. Glover, R.B. Smith, H. Rapoport, *J.Am.Chem. Soc.*, 1965, 87, 2003.

75. G.W. Kabalka, M. Varma, R.S. Varma, *J.Org.Chem.*, 1986, 51, 2386.

76. E.J. Reist, R.R. Spencer, B.R. Baker, L. Goodman, *Chem.Ind.(London)*, 1962, 1794.

77. J.H. Boyer, *J.Am.Chem.Soc.*, 1951, 73, 5865.

78. (a) M. Vaultier, N. Knouzi, R. Carrié, *Tetrahedron Lett.*, 1983, 24, 763.
(b) Y.G. Gololobov, I.N. Zhmurova, L.F. Kasukhin, *Tetrahedron*, 1981, 37, 437.

79. E.J. Corey, J-L. Gras, P. Ulrich, *Tetrahedron Lett.*, 1976, 11, 809.

80. H. Weingarten, J.P. Chupp, W.A. White, *J.Org.Chem.*, 1967, 32, 3246.
W.A. White, H. Weingarten, *J.Org.Chem.*, 1967, 32, 213.

81. N.H. Andersen, H. Uh, *Synth.Commun.*, 1973, 3, 125.

82. M. Christl, R. Herbert, *Org.Mag.Res.*, 1979, 12, 150.

83. D. Belkacemi, "Synthesis, ^{15}N NMR Spectroscopy and Cycloaddition Reactions of some Azabicycles", Ph.D. Thesis, 1991, University of Leicester, England.

84. (a) J.M. Lehn, *Fortschr.Chem.Forsch.*, 1970, 15, 311.
(b) J.B. Lambert, *"Topics in Stereochemistry"*, ed.N.L. Allinger, L. Eliel, Wiley-Interscience, New York, 1971, 6, 19.
(c) W.B. Jennings, S.D. Worley, *J.Chem.Soc.Perkin Trans. 2*, 1980, 1512.

85. J.W. Davies, J.R. Malpass, *Tetrahedron Lett.*, 1985, 26, 4537.

86. J.W. Davies, J.R. Malpass, J. Fawcett, L.J.S. Prouse, R. Lindsay, D.R. Russell, *J.Chem.Soc.Chem.Commun.*, **1986**, 1135.

87. D.R. Brown, R. Lygo, J. McKenna, J.M. McKenna, B.G. Hutley, *J.Chem.Soc (B)*, **1967**, 1184.

88. A.T. Bottini, *"Selective Organic Transformations"*, B.S Thyagarajan, Ed., Willey-Interscience, New York, **1970**, 89.

89. W.R. Bransen, C.R. Hauser, *Org.Synth.Coll.Vol.4*, 508.

90. J.Von Braun, *Chem.Ber.*, **1900**, 33, 1438.

91. J.D. Hobson, J.G.McCluskey, *J.Chem.Soc.C*, **1967**, 2015.

92. T.A. Montzka, J.D Matiskella, R.A. Partyka, *Tetrahedron Lett.*, **1974**, 1325.

93. R.A. Olofson, J.T. Martz, J.-P. Senet, M. Piteau, T. Malfroot, *J.Org.Chem.*, **1984**, 49, 2081.

94. S.F. Nelson, J.T. Ippoliti, T.B. Frigo, P.A. Petillo, *J.Am.Chem.Soc.*, **1989**, 111, 1776.

95. A.P. Marchand, R.W. Allen, *Tetrahedron Lett.*, **1977**, 619.

96. (a) L.D. Quin, K.C. Caster, J.C. Kisalus, K.A. Mesch, *J.Am.Chem.Soc.*, **1984**, 106, 7021.
(b) H. Sakurai, Y. Nakadaira, T. Koyama, H. Sakaba, *Chem.Lett.*, **1983**, 213.

97. J. Mason, *Chem.Rev.*, **1981**, 81, 205.

98. G.J. Martin, M.L. Martin, J.P. Gouesnord, *^{15}N NMR Spectroscopy"*, Springer-Verlarg, Berlin (1981).

99. T.T.T Nguyên, C. Delseth, J.P. Kintzinger, P.A. Carrupt, P. Vogel, *Tetrahedron*, **1980**, 36, 2793.

100. J.B. Grutzner, M. Jautelat, J.B. Dence, R.A. Smith, J.D. Roberts, *J.Am.Chem.Soc.*, **1970**, 92, 7107.

101. W. Clegg, G.M. Sheldrick Z. Krist 1984, 167 (1-2), 23-7.

102. G.M. Sheldrick SHELXS86. Program for crystal structure solution. Univ. of Göttingen. Federal Republic of Germany.

103. G.M Sheldrick SHELX76. Program for crystal structure determination. Univ. of Camb. 1976.

104. D.D. Perrin, D.R. Perrin, W.L.F. Armarego, "Purification of Laboratory Chemicals", Second edition, Pergamon Press, Oxford.

105. W.C. Still, M. Kahn, A. Mitra, *J.Org.Chem.*, **1978**, 43, 2923.

106. J.M. Patterson, J. Brasch, P. Drenchko, *J.Org.Chem.*, **1962**, 27, 1652.