Synthesis of Analogues of Epibatidine

Caroline D. Cox

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

October 2000

University *of* Leicester

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Statement

The accompanying thesis submitted for the degree entitled "Synthesis of Analogues of Epibatidine" is base on work conducted by the author in the Department of Chemistry at the University of Leicester mainly during the period between October 1997 and August 2000.

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

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

Signed:........................ Date: 21.12.00

To Paul

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Finally, I would like to thank my partner Paul, for his wholehearted support and encouragement in my studies. I would like to dedicate this thesis to him.

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Abstract

Synthesis of Analogues of Epibatidine

By Caroline Cox

The molecule epibatidine was isolated from the skin of the Ecuadorian poison frog, *Epipedobates tricolor*, in 1992. Pharmacological testing of this molecule on rodents revealed that epibatidine had analgesic qualities and that it was a potent stimulator of the nicotinic acetylcholine receptor. Epibatidine was, however, found to be toxic in analgetic doses and so interest developed into the synthesis of analogue molecules which would have useful pharmacological properties but reduced toxicity. Epibatidine has a unique, natural molecular structure, with a chloropyridyl substituent attached to a 7-azabicyclo[2.2.1]heptane skeleton. Our intentions were to design epibatidine analogues containing a distance between the two active nitrogen centres close to that shown by epibatidine itself, in concordance with the current pharmacophore.

A range of four different 5- and 6-chloropyridyl-substituted-2-azabicyclo[2.2.1]-heptane derivatives was constructed. The azabicyclic skeleton was made *via* a Diels-Alder reaction between cyclopentadiene and an iminium ion. The 5- and 6-*exo*-chloropyridyl derivatives were synthesised using a reductive Heck reaction to couple the chloropyridyl ring onto the *exo*- face of the azabicycle. 5- and 6-*endo*-chloropyridyl derivatives were synthesised *via* nucleophilic attack of a lithiated-chloropyridine onto the appropriate azabicyclic ketone. Dehydration of the adduct followed by reduction from the *exo*-face of the azabicycle ensured that the chloropyridine ring was in the *endo*- orientation. ^{1}H NMR spectroscopy was used to characterise these compounds. Preliminary pharmacological testing of the four molecules on rat tissue revealed that both *endo*- analogues were as active as epibatidine at the nicotinic receptor and that both the *exo*- and *endo*- isomers showed improved selectivity for the $\alpha4$ sub-type of this receptor as compared to the $\alpha7$.

As an extension of the design of analogues having a controlled N-N orientation and distance, two tropane-based spirocyclic epibatidine analogues have been synthesised. Both molecules were made from tropinone by functionalisation of the 3-keto-carbon. Characterisation of both molecules was carried out using ^{1}H NMR spectroscopy. The absolute configuration of one of the analogue molecules was confirmed by X-ray crystallography.

Work towards the synthesis of novel chloropyridine-substituted 2-azabicyclo[2.1.1]hexane analogue molecules was undertaken and future synthetic approaches suggested.

Abbreviations

b.p.	boiling point
CNS	central nervous system
COSY	correlation spectroscopy
°C	degrees centigrade
DEPT	distortionless enhancement by polarisation transfer
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EI	electron impact
FAB	fast atom bombardment
g	grams
Hz	hertz
hr	hour
IR	infra-red
TMSI	iodotrimethylsilane
lit.	literature
LDA	lithium diisopropylamine
L-Selectride	$Li[(C_2H_5(CH_3)CH)_3B]H$
MHz	megahertz
m.p.	melting point
MCPBA	*meta*-chloroperoxybenzoic acid
mmol	millimole
min	minute
M	molar
M^+	molecular ion
MHz	megahertz
min	minutes
ml	millilitres
mol	moles
mmol	millimoles
nAChR	nicotinic acetylcholine receptor
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance

PNS	peripheral nervous system
ppm	parts per million
BOC	*t*-butoxycarbonyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	tetramethylsilane
TMSI	iodotrimethylsilane
TPAP	tetrapropylammonium perruthenate
ν	wave number

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CHAPTER 1

Introduction

1.1 The Nicotinic Receptor

The functions of all the different cells in the body are controlled by a chemical communications system. The chemical messengers, which include hormones and neurotransmitters, interact with receptor sites attached to cells, initiating a response. Many therapeutically useful synthetic drugs act as either agonists, which stimulate the receptor, or antagonists, which block the receptor site against the action of chemical messengers.

No drug acts with complete specificity at an individual type of receptor and indiscriminate drug binding can lead to unwanted side effects; for example a drug aimed at treating a patient with asthma by stimulation of the receptor responsible for relaxation of the bronchial smooth muscle (β_2 adrenergic receptor) may also increase the rate of contraction of the heart (at the β_1 receptor) if it does not discriminate fully between them. The potency of a drug is also important in this regard because as the potency decreases, so the dose required to treat the patient increases together with the likelihood of the drug binding to sites other than the targeted one.

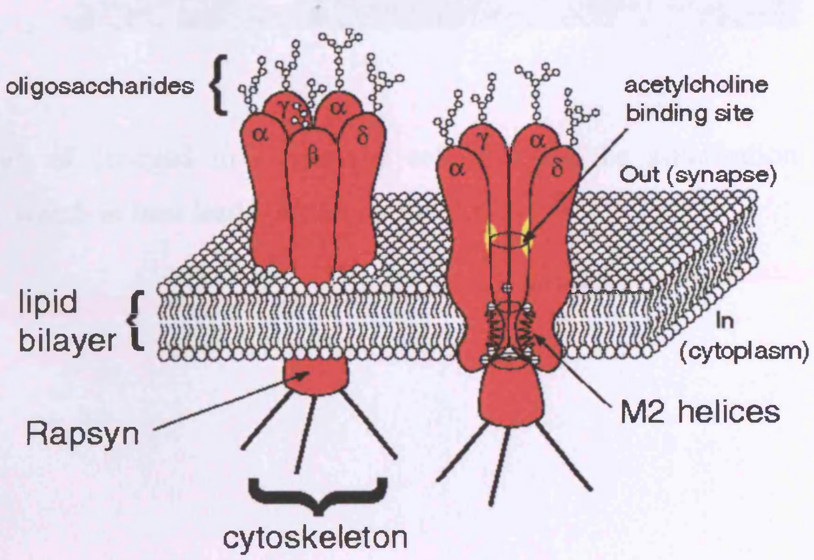
The acetylcholine class of receptors is named after the neurotransmitter, acetylcholine **(1)**, with which they all interact. Acetylcholine's primary function is as the messenger agonist for vasodilation. There are two main types of acetylcholine receptor in the body; firstly the muscarinic type (mAChR) which are found in the heart, smooth muscle, glands and the CNS and secondly the nicotinic type (nAChR) which are located in the central and peripheral nervous system. Table 1.1 illustrates the sub-types of nicotinic receptor and their functions according to Holladay and co-workers.[1]

Table 1.1 Nicotinic receptor overview

Receptor Location	***Number of Subtypes***	***Possible Functions***
Neuronal Central	At least four	• Cognition • Addiction • Neurotransmitter release • Sensory gating • Neuroprotection • Dopamine release
Ganglion	At least four	• Synaptic transmission • Neurotransmitter release • Cellular function • Neurite retraction • Adrenal catecholamine release
Muscle	One	• Contraction of skeletal muscle

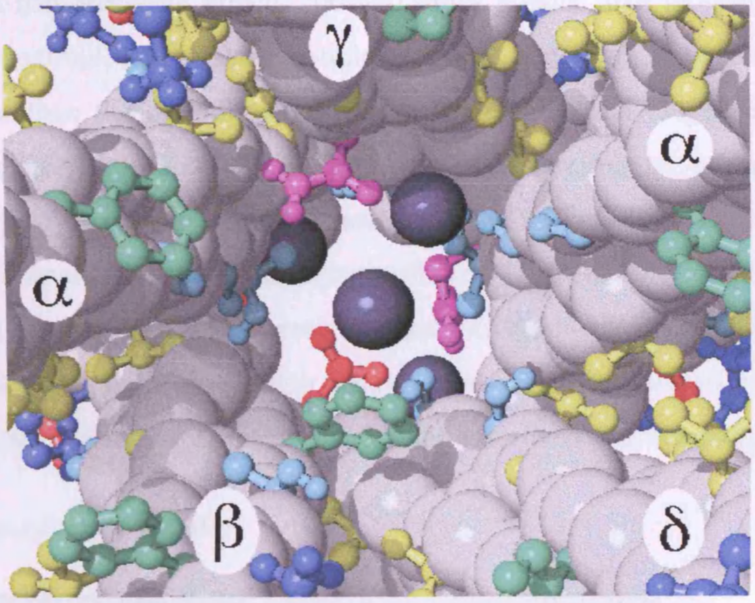
The nicotinic receptor is a channel-linked receptor; it is a receptor site set into a membrane and coupled directly to an ion channel. Channel-linked receptors are involved in very fast synaptic transmission in which ligand binding and channel opening occur within a millisecond.

Figure 1.2 Structure of the nicotinic receptor


oligosaccharides
α
γ
α
β
δ
γ
α
α
δ
acetylcholine binding site
Out (synapse)
lipid bilayer
In (cytoplasm)
Rapsyn
M2 helices
cytoskeleton

The receptor itself is made up of mixtures of four different types of protein sub-unit, named α, β, γ, and δ. The nicotinic receptor shown in Figure 1.2 has an oligomeric structure of five proteins (α_2,β, γ,δ) and has two acetylcholine binding sites, shown in yellow. Receptor agonists must occupy both binding sites in order for the receptor to be activated. Each protein sub-unit contains an M_2 helical segment which is positioned to form the lining of an ion channel. The helical segments are kinked in such a manner as to form a constriction half way through the cell membrane. Once the agonist molecules have bound to the receptor, the M_2 helices straighten out, thus opening the ion channel to a diameter of ~0.7nm and allowing the passage of sodium or potassium ions from outside into the cell (Figure 1.3).

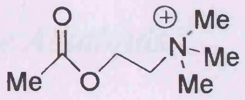
Figure 1.3 Ions flowing through the channel



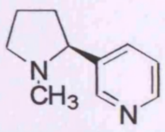
The passage of charged ions into the cell changes the polarisation of the cell membrane, which in turn leads to cellular effects.

Discovery of epibatidine

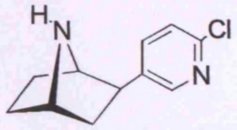
Figure 1.4 Nicotinic receptor agonists



Acetylcholine **(1)**



(S)-(-)- Nicotine **(2)**



(-)-Epibatidine **(3)**

Before 1992, it was thought that nicotine **(2)** (Figure 1.4) was the most effective agonist at the nicotinic receptor. However, in 1992, Daly and co-workers[2] extracted the molecule, epibatidine **(3)** from the skin of the Ecuadorian poison frog, *Epipedobates tricolor* (Figure 1.5). Pharmacological testing of epibatidine on rodents revealed that it had analgesic effects 200-500 times greater than morphine and that, uniquely, it was stimulation of the nicotinic receptors which was responsible for this analgesia rather than the opioid receptors which are the usual target of painkilling drugs. Unfortunately, epibatidine was found to be indiscriminate in its binding to different sub-types of nicotinic receptor and analgesic effects were accompanied by hypertension, convulsions and respiratory distress. In the world of chemistry, epibatidine has resulted in great interest, not just into the synthesis of this key target, but also of analogue molecules which would potentially be more selective in their binding properties, leading to reduced toxicity and increased pharmacological value.

Figure 1.5 *Epipedobates tricolor*

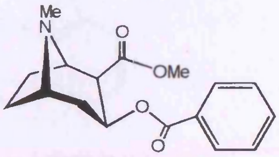
There are a variety of disease states in which nicotinic therapy could be beneficial. These include Alzheimer's disease, Parkinson's disease, Tourette's syndrome, anxiety, pain and depression.

1.2 The Alkaloids

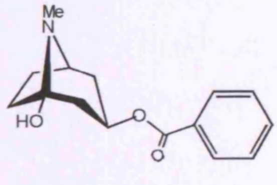
The alkaloids are, by definition, non-peptidic, non-nucleophilic compounds containing nitrogen. They are abundant in higher plants, insects, amphibians and fungi. Most alkaloids possess pharmacological activity, ranging from extreme toxicity to molecules of pharmaceutical value. The molecules found in plants take the form of salts having common carboxylic acids as counter-ions and are thus easily extracted into aqueous solution. After basification, the free amines can be extracted using organic solvents. There is a wide variety of alkaloid structures including monocyclic, bicyclic, tricyclic and tetracyclic molecules. Epibatidine is the only natural bicyclic alkaloid known to contain the 7-azabicyclo[2.2.1]heptane skeleton and is unique in possessing a chloropyridyl substituent.

Cocaine **(4)** and 1-hydroxytropacocaine **(5)** are examples of alkaloids having a tropane (8-azabicyclo[3.2.1]octane) skeleton and both are found in the leaves of the plants *Erythroxylum coca* (Figure 1.6) and *Erythroxylum novogranatense*. Cocaine was used over 2000 years ago by the Incas for its stimulant and psychoactive properties; these phenomena result from heightened concentrations of the neurotransmitter dopamine in the body, as cocaine blocks its metabolism. 1-Hydroxytropacocaine is a member of the calystegine family of alkaloids, known to be involved in rhizosphere ecology and also being potent glycosidase inhibitors. The first synthesis of this molecule was completed at Leicester only recently.[3]

Figure 1.6 Coca plant



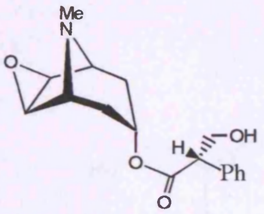
(4) Cocaine



(5) 1-Hydroxytropacocaine

Another physiologically active tropane derivative is hyoscine (scopolamine) **(6)** which is obtained from the plant *Atropa belladonna* (deadly nightshade) (Figure 1.7) and has euphoriant and anaesthetic qualities caused by antagonism of the nicotinic acetylcholine receptors. Current medical uses include prevention of travel sickness and premedication prior to surgery.

Figure 1.7 ***Atropa belladonna***

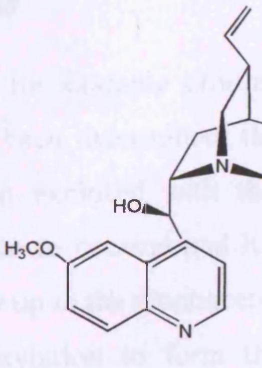


(6) (-)-Hyoscine

Quinine **(10)**, is based on the 1-azabicyco[2.2.2]octane skeleton and is isolated from the bark of the cinchona tree (Figure 1.9). It is used as an anti-malarial drug in doses of 0.6g, as a muscle relaxant in lower doses of 0.2g, and as a bitter flavouring in tonic water in trace amounts.

Figure 1.9 ***Cinchona pubescens***

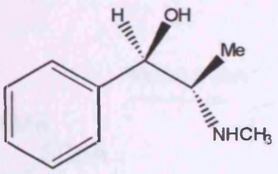
Cinchona pubescens
Rubiaceae
Charles H. Lamoureux



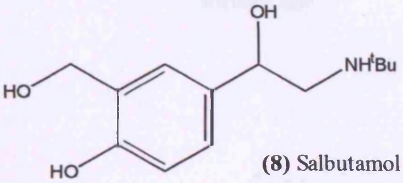
(10) Quinine

Simpler alkaloids are typified by ephedrine **(7)** which is produced by the *Ephedra* shrub (Figure 1.8) and has been used since 100 AD by the Chinese to treat respiratory illnesses such as bronchitis and asthma. Its structure was elucidated in 1923. Ephedrine acts as a bronchodilator by stimulation of the adrenergic receptors. However, it is not selective for the β_2 receptors and simultaneously stimulates the heart in the same manner as adrenaline. The pharmaceutical industry thus used ephedrine as a template in their design of a more discriminatory drug and came up with the highly successful anti-asthma treatment salbutamol (Ventolin) **(8)** and more recently the longer-acting salmeterol **(9)**

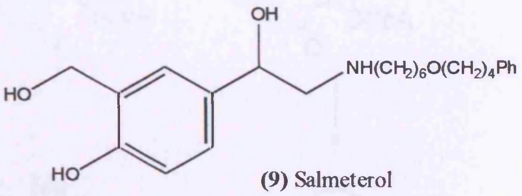
Figure 1.8 *Ephedra.*



(7) Ephedrine



(8) Salbutamol (Ventolin)



(9) Salmeterol

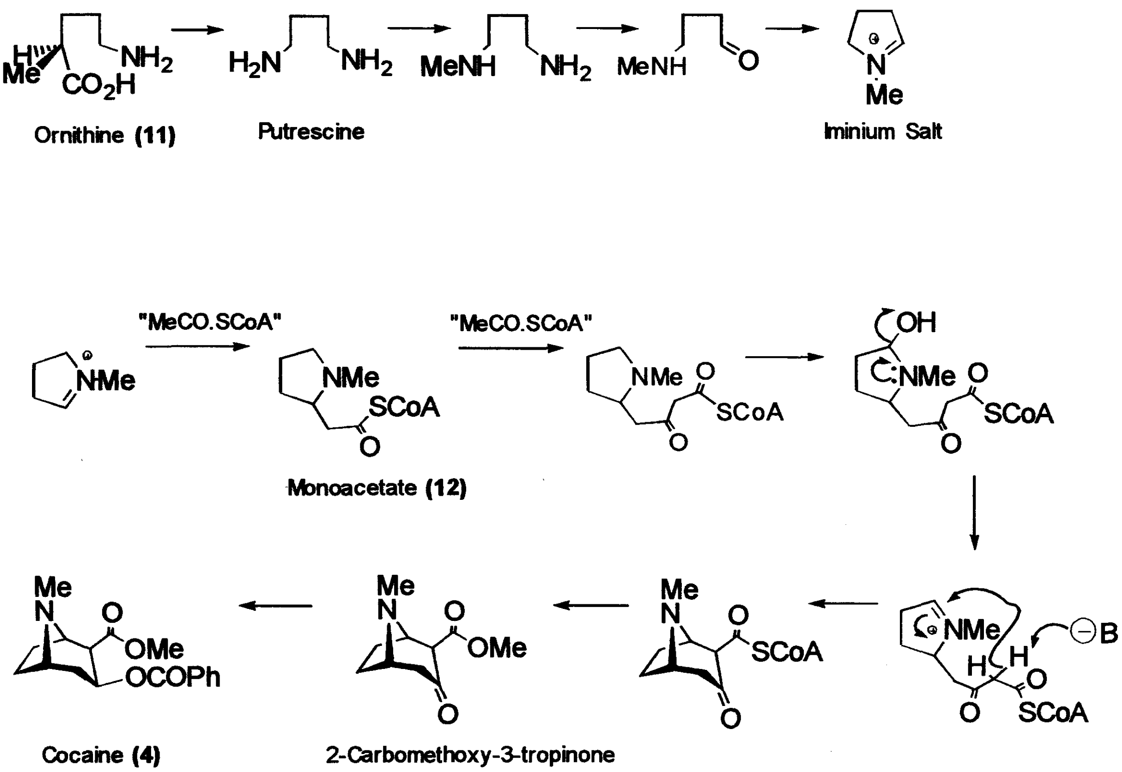
1.3 Biosynthetic Routes To Alkaloids

Most alkaloids derive from amino acids, for example ornithine **(11)**. Although the biosynthetic route to epibatidine has not been determined, the pathways to tropane alkaloids such as cocaine **(4)** have been explored with the aid of radiolabelled precursors. Scheme 1.10 outlines the route to cocaine and it is anticipated that the route to epibatidine would follow similarly up to the monoacetate **(12)**.

Ornithine undergoes enzymatic decarboxylation to form the diamine putrescine, which is then methylated. Transamination of the primary amine to an aldehyde followed by intramolecular condensation yields an iminium salt. Two molecules of acetate, in the form of acetyl-SCoA, are added to the iminium salt to form 2-carbomethoxy-3-tropinone which undergoes transformation into cocaine. The azabicyclic[3.2.1] framework is formed by nucleophilic attack of the di-keto α-carbon at the iminium carbon.

To form the azabicyclic[2.2.1] skeleton of epibatidine, ring-closure may occur by manipulation of the monoacetate **(12)**.

Scheme 1.10


Ornithine (11)
Putrescine
Iminium Salt
"MeCO.SCoA"
"MeCO.SCoA"
Monoacetate (12)
Cocaine (4)
2-Carbomethoxy-3-tropinone

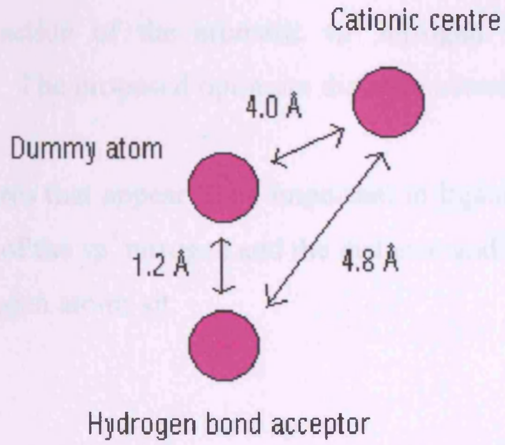
1.4 The Nicotinic Pharmacophore

A pharmacophore is a three-dimensional model of structural features that a molecule would require in order to bind to a receptor. A pharmacophore is developed with the aid of structure-affinity studies of a range of molecules at the receptor site.

The first nicotinic pharmacophore was proposed by Beers and Reich[4] in 1970. They proposed that there were two crucial structural features for a nicotinic agonist; a cationic centre (e.g. a protonated nitrogen) and a hydrogen bond acceptor site (e.g. a pyridine nitrogen). The hydrogen bond resulting from interaction with the receptor is situated 5.9 A^0 from the cationic centre.

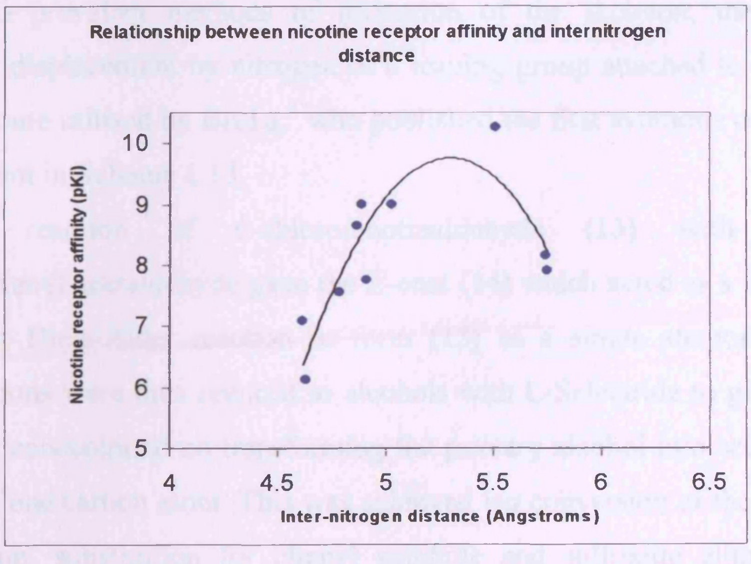
Sheridan and co-workers[5] developed this pharmacophore into a triangular model (see Figure 1.11), which in addition to a cationic centre and hydrogen bond acceptor, includes a dummy point which defines a line along which the hydrogen bond may form. In (S)-nicotine, this dummy point can be considered as orientated towards the centroid of the pyridine ring.

Figure 1.11 The Sheridan Pharmacophore



Dukat and co-workers[6] focussed their attentions on inter-nitrogen distances of ligands at the receptor site. Ten pyridine-containing molecules were selected, including epibatidine, and their affinities to nicotinic sites determined by biological assay. The distance between nitrogens was calculated via molecular modelling and a plot drawn of affinity versus inter-nitrogen distance (Figure 1.12).

Figure 1.12



The plot gives evidence of an optimum inter-nitrogen distance of between 5.0-5.7 A^0, epibatidine itself showing a distance of 5.51 A^0 for one of its two lowest-energy conformations (in which the aromatic nitrogen is oriented away from the bridging nitrogen). However, there is still a great deal of debate over which lowest-energy conformation of epibatidine is responsible for binding as detailed in one recent report[7] by Oleson and co-workers. This report also suggests that the pharmacophore should feature the superpositioned sites of a) interaction of the sp^3 nitrogen with the receptor protein and b) interaction of the aromatic sp^2 nitrogen with its complementary hydrogen-bond donor. The proposed optimum distance between these two sites on the receptor is 7.0-8.0 A^0.

Other structural features that appear to be important in ligand-binding to the receptor include the 'basicity' of the sp^3 nitrogen and the distance and angle between the planes in which the two nitrogen atoms sit.

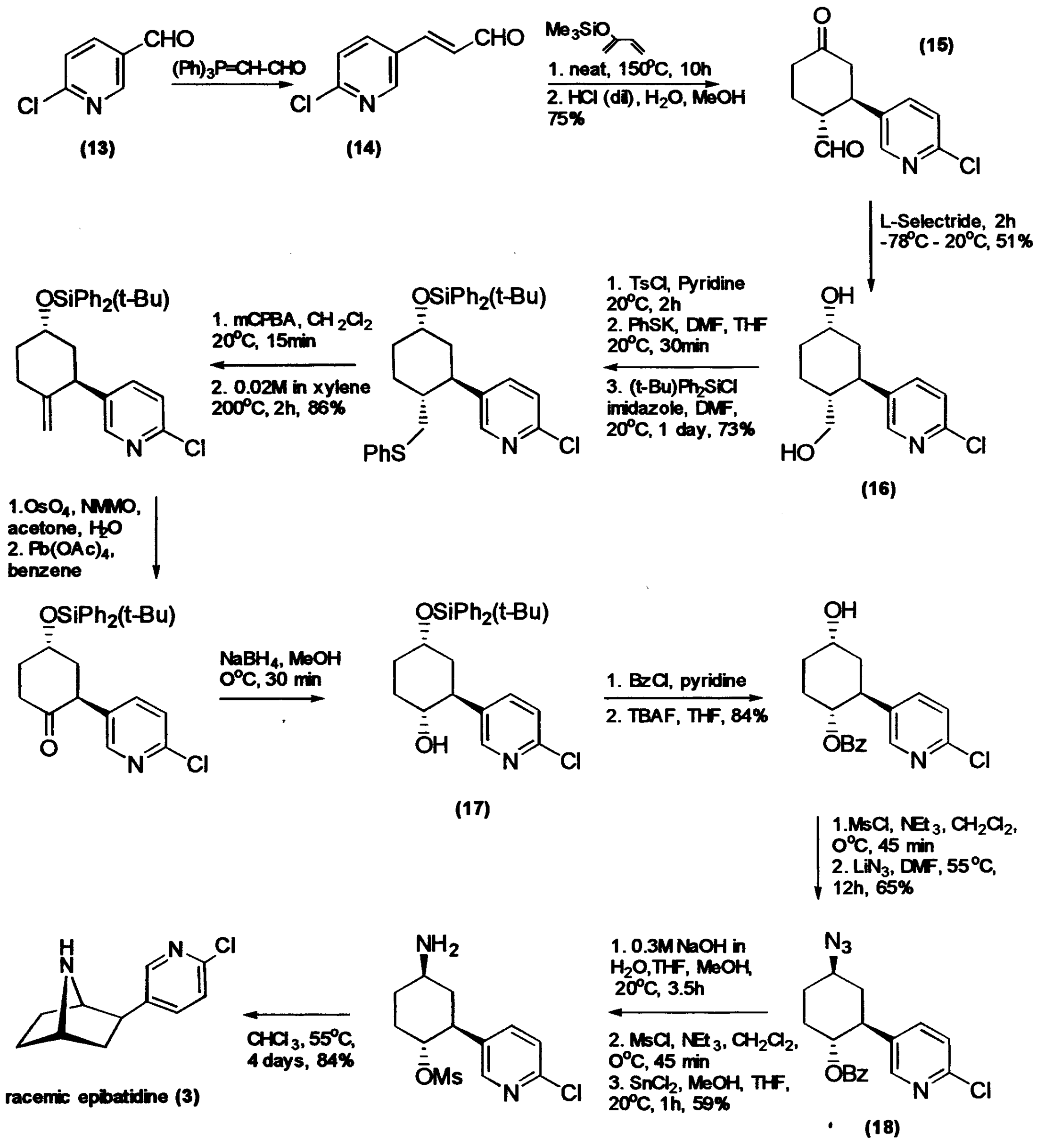
1.5 Approaches to the Synthesis of Epibatidine

The discovery of epibatidine with its unique, natural 7-azabicyclo[2.2.1]heptane structure, potent pharmacological properties and dearth of material (750 frogs yielded less than 0.5mg of epibatidine), sparked intense world-wide interest into its synthesis. There are over 50 published syntheses to date including many asymmetric approaches.[8] Illustrated below are some of the key methods employed to both form the 7-azabicyclic skeleton and attach the pyridine ring moiety.

There are two prevalent methods of formation of the skeleton; the first is an intramolecular displacement by nitrogen of a leaving group attached to an azacycle. This was the route utilised by Broka,[9] who published the first synthesis of epibatidine in 1993 as shown in Scheme 1.13.

The Wittig reaction of 6-chloronicotinaldehyde **(13)** with (triphenyl-phosphoranylidene) acetaldehyde gave the *E*-enal **(14)** which acted as a dienophile in the subsequent Diels-Alder reaction to form **(15)** as a single stereoisomer. Both carbonyl functions were then reduced to alcohols with L-Selectride to give **(16)**. The next few steps concentrated on transforming the primary alcohol into secondary with the removal of one carbon atom. This was achieved *via* conversion of the alcohol into a leaving group, substitution for phenyl sulphide and sulfoxide elimination. Dihydroxy-addition and oxidative cleavage of the alkene afforded a ketone which was reduced with hydride to a 5:1 (equatorial:axial) mixture of cyclohexanol epimers. The minor epimer was removed by column chromatography leaving **(17)**. It remained to substitute one of the alcohol positions for an amine which could displace the other alcohol derivative in an intramolecular substitution reaction, thus forming an azabicycle. In practice, this could only be achieved by conversion of the silane-protected alcohol furthest from the pyridine ring into an azide; reduction of the azide to an amine with tin(II) choride and heating in chloroform over 4 days gave epibatidine **(3)**.

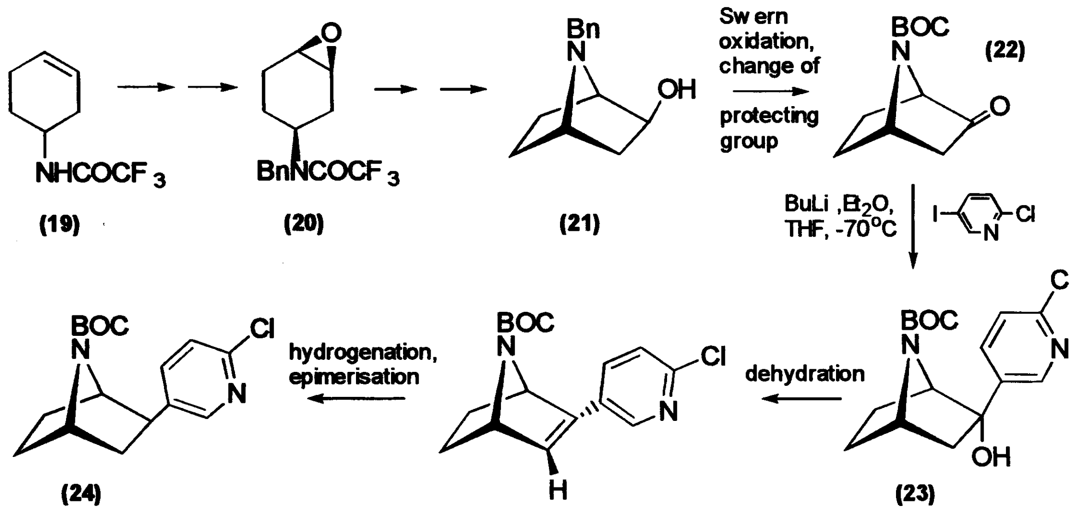
Scheme 1.13



CHO
Cl
N
(13)
(Ph)3P=CH-CHO
CHO
(14)
Me3SiO
1. neat, 150°C, 10h
2. HCl (dil), H2O, MeOH
75%
O
CHO
(15)
L-Selectride, 2h
-78°C - 20°C, 51%
OH
HO
(16)
1. TsCl, Pyridine
20°C, 2h
2. PhSK, DMF, THF
20°C, 30min
3. (t-Bu)Ph2SiCl
imidazole, DMF,
20°C, 1 day, 73%
OSiPh2(t-Bu)
PhS
1. mCPBA, CH2Cl2
20°C, 15min
2. 0.02M in xylene
200°C, 2h, 86%
OSiPh2(t-Bu)
1.OsO4, NMMO,
acetone, H2O
2. Pb(OAc)4,
benzene
OSiPh2(t-Bu)
O
NaBH4, MeOH
0°C, 30 min
OSiPh2(t-Bu)
OH
(17)
1. BzCl, pyridine
2. TBAF, THF, 84%
OH
OBz
1.MsCl, NEt3, CH2Cl2,
0°C, 45 min
2. LiN3, DMF, 55°C,
12h, 65%
N3
OBz
(18)
1. 0.3M NaOH in
H2O,THF, MeOH,
20°C, 3.5h
2. MsCl, NEt3, CH2Cl2,
0°C, 45 min
3. SnCl2, MeOH, THF,
20°C, 1h, 59%
NH2
OMs
CHCl3, 55°C,
4 days, 84%
H
N
Cl
racemic epibatidine (3)

Intramolecular substitution was also favoured by Fletcher[10] as shown in Scheme 1.14.

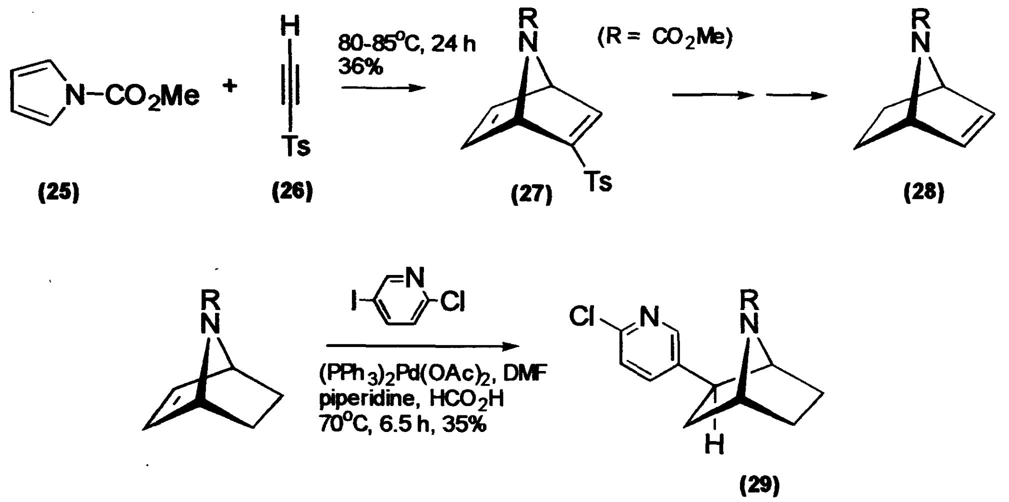
Scheme 1.14


NHCOCF3
(19)
O
BnNCOCF3
(20)
Bn
N
OH
(21)
Swern oxidation, change of protecting group
BOC
N
O
(22)
BuLi, Et2O, THF, -70°C
I
Cl
N
BOC
N
Cl
N
OH
(23)
dehydration
BOC
N
Cl
N
H
hydrogenation, epimerisation
BOC
N
Cl
N
(24)

N-[(Trifluoroacetyl)amino]cyclohex-3-ene **(19)** was alkylated with benzyl bromide followed by the introduction of an epoxide functionality with *m*CPBA (2.4:1 mixture of *cis*: *trans* epoxides which were separated by chromatography). In the case of the *cis*- epoxide **(20)**, mild base hydrolysis of the trifluoroacyl group followed by heating in *N*-methyl-2-pyrrolidinone resulted in unexpected *syn* attack of the nitrogen at the epoxide and formation of the bicycle **(21)** (it was discovered that the *trans*-epoxide decomposed under these conditions). The chloropyridyl moiety was introduced *via* nucleophilic attack on ketone **(22)** with a lithiated chloropyridine. The tertiary alcohol was converted to a xanthate and elimination formed an alkene. The alkene was hydrogenated with Adams catalyst to give a 4:1 mixture of *endo*- and *exo*-isomers. The overall yield of *exo*-isomer **(24)** was increased by base-catalysed epimerisation.

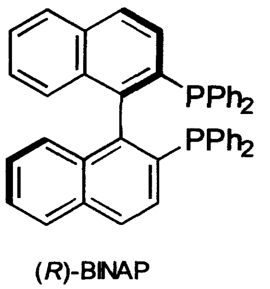
The second main method of forming the bicycle is *via* a Diels-Alder cycloaddition and this was the approach of Clayton and Regan[11] (Scheme 1.15). Diels-Alder cycloaddition between *N*-methoxycarbonylpyrrole **(25)** and *para*-toluenesulphonylacetylene **(26)** yielded the bicycle **(27)**. The non-conjugated double bond was reduced selectively using hydrogen with a palladium on carbon catalyst and the *para*-toluenesulphonyl group cleaved with sodium amalgam, to give molecule **(28)**. The chloropyridine moiety was introduced by a reductive Heck reaction using 2-chloro-5-iodopyridine; attack on the double bond produced the *exo*-isomer stereoselectively .

Scheme 1.15


N-CO2Me
+
H
Ts
80-85°C, 24 h
36%
R
N
(R = CO2Me)
Ts
(25)
(26)
(27)
(28)
I
N
Cl
(PPh3)2Pd(OAc)2, DMF
piperidine, HCO2H
70°C, 6.5 h, 35%
H
(29)

This reductive Heck reaction on **(28)** was developed by Kaufmann[12] into an asymmetric synthesis of both enantiomers of *N*-protected epibatidine. Reductive Heck reactions were carried out at 65°C in the presence of triethylamine as a base, formic acid as the hydride source and palladium acetate catalyst. However, the solvent was varied and chiral ligands introduced for co-ordination to palladium. Best results were achieved using BINAP ligands (Figure 1.16) and a summary of the reactions showing the best enantiomeric excesses are illustrated in Table 1.17.

Figure 1.16



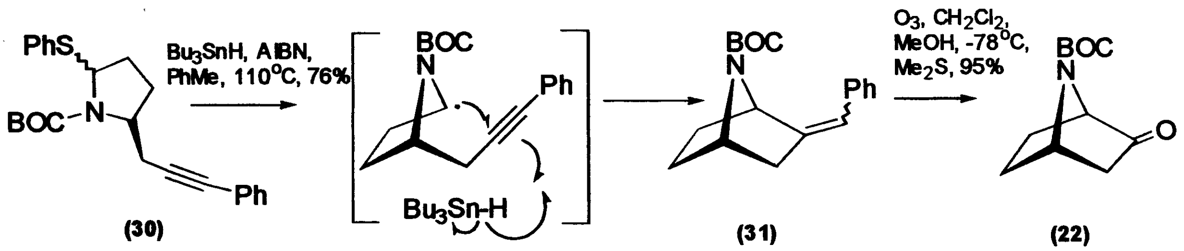
(*R*)-BINAP

Table 1.17 Diels-Alder cycloaddition reactions with chiral BINAP ligands[12]

Ligand	**Solvent**	**Time (d)**	**Conversion rate (%)**	**Isolated yield product (%)**	**Enantiomeric excess (%)**
(*R*)-BINAP	DMSO	3	55	49	73
(S)-BINAP	DMSO	3	55	44	72
(*R*)-BINAP	DMF	5	55	47	81
(*R*)-BINAP	THF	5	70	53	81

A more unusual method of constructing the azabicyclic skeleton is by radical cyclisation and this was the approach favoured by two research groups.[13] A brief outline of this cyclisation contained in the asymmetric synthesis of Clive and Yeh is detailed below in Scheme 1.18.

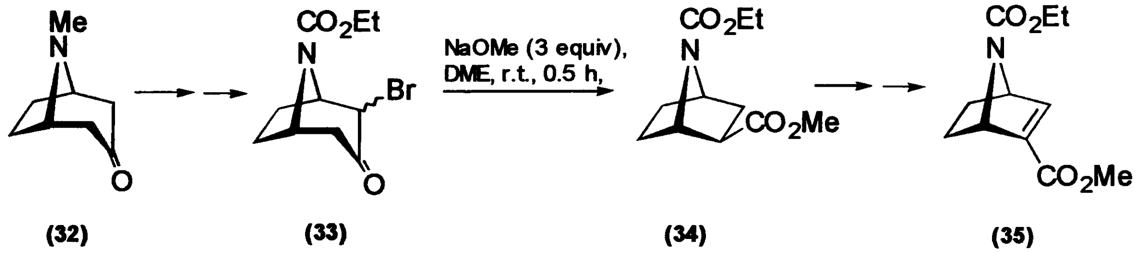
Scheme 1.18


PhS
BOC-N
Ph
(30)
Bu3SnH, AIBN, PhMe, 110°C, 76%
BOC
N
Ph
Bu3Sn-H
BOC
N
Ph
(31)
O3, CH2Cl2, MeOH, -78°C, Me2S, 95%
BOC
N
O
(22)

The alkyne **(30)** was synthesised in 9 steps from (*S*)-pyroglutamic acid. A carbon radical was generated by reaction of the thiophenyl group with the tributyltin radical; subsequent cyclisation can be described as 5-*exo*-digonal to give the azabicycle **(31)**. Ozonolysis of the double bond produced the enantiopure ketone **(22)** which could be converted into (-)-epibatidine in the manner of Fletcher described previously.

Ring-contraction of readily available tropinone **(32)** *via* Favorskii rearrangement was the novel approach of Bai[14] towards epibatidine (Scheme 1.19).

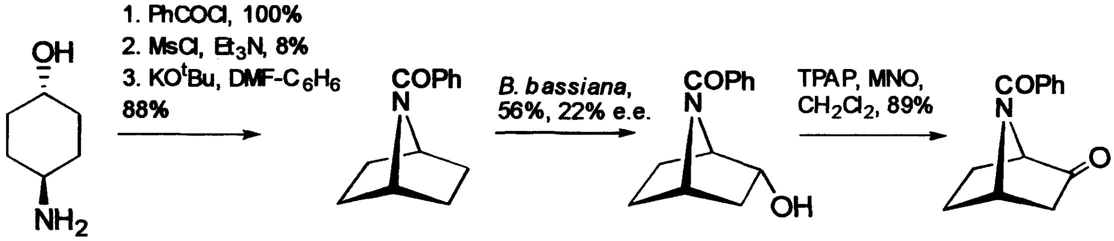
Scheme 1.19


Me
N
O
(32)
CO2Et
N
Br
O
(33)
NaOMe (3 equiv), DME, r.t., 0.5 h,
CO2Et
N
CO2Me
(34)
CO2Et
N
CO2Me
(35)

The *N*-methyl group was converted to *N*-ethyloxycarbonyl with ethyl chloroformate and the monobromide **(33)** generated by treatment with copper(II) bromide. Favorskii rearrangement of the 8-azabicyclo[3.2.1]octane ring to the 7-azabicyclo[2.2.1]heptane ring of **(34)** was achieved by treatment with base, in a yield of 48% yield from tropinone. Alkene **(35)** was synthesised by α-selenation of **(34)** followed by selenoxide elimination (the chloropyridyl ring could thence be introduced *via* a reductive Heck reaction).

Finally, a very interesting method of creating the ketone functionality on a basic 7-azabicylic skeleton *via* a biocatalytic route was published by Olivo[15] in 1999 (Scheme 1.20).

Scheme 1.20



(36) **(37)** **(38)** **(39)**

Commercially available *trans*-4-aminocyclohexanol hydrochloride **(36)** was transformed into *N*-benzoyl-7-azanorbornane **(37)** in 3 steps, incorporating an intramolecular displacement of the mesylated alcohol by nitrogen. Microbial oxidation of **(37)** with the fungus *Beauveria bassiana* gave the *endo*-alcohol stereoselectively, the (-)-(1*R*) enantiomer being slightly favoured. Oxidation of the alcohol gave ketone **(39)** which could be converted to epibatidine.

1.6 Background of Epibatidine Analogues

Since the discovery of epibatidine, many analogue molecules have been synthesised around the world in attempts to find molecules of high activity, but of lower toxicity than epibatidine at the nicotinic receptor site and therefore of increased potential pharmacological value.

A single analogue molecule may have multiple pharmacologies at the nicotinic receptor; it could act as a full agonist, a partial/weak agonist or as an antagonist at different receptor sub-types. In order to determine whether an analogue molecule has any potential pharmacological value, it is firstly important to determine how well it binds at the receptor site, this being called its affinity.

Affinity is determined by physiological experiments on animal tissue, for example rat brain; the tissue, containing nicotinic receptors, is saturated with a radio-ligand, for example tritium-labelled nicotine, and then a known concentration of the analogue molecule introduced. The amount of radio-ligand displaced by the analogue molecule can be measured and an equilibrium constant, K_i, calculated.

K_i values are:

- characteristic of the drug and the receptor
- equal to the concentration of the drug required to occupy 50% of the receptor sites at equilibrium
- the higher the affinity of the drug for the receptor, the lower K_i.

Once it has been determined that the analogue binds at the receptor site, it is then important to know how well it actually activates the receptor- its efficacy, and how discriminatory it is in activating a particular sub-type of receptor - its selectivity.

A receptor is in equilibrium between conformational states:[16]

- inactive (basal) (B)
- active (open) (A)
- intermediate (I)
- inactive desensitised (D)

A ligand preferentially stabilises one or more of these states; an agonist stabilises the A state, a partial agonist stabilises both open and closed states and an antagonist the B or D closed states. The efficacy of a compound reflects its ability to stabilise the A state whereas affinity reflects binding ability at the receptor at equilibrium.

Ligand efficacy is determined by voltage clamp electrophysiology experiments on animal tissue; the amplitude of the current evoked at saturation for a given ligand is compared to that of a natural, full agonist, for example acetylcholine. If the amplitudes are of a similar magnitude, then the given ligand is also a full agonist. Significant decreases in amplitude indicate the presence of a partial agonist or antagonist. The concentration of agonist required to elicit a current of half of its maximal amplitude corresponds to the agonists efficiency, measured as EC_{50} values.

Most analogue molecules contain characteristic structural features of epibatidine and/or nicotine. Illustrated in Table 1.21 are comparative efficiency values for nicotine, acetylcholine and epibatidine at different receptor sub-types, in tests on human tissue as compiled by Holladay.[1]

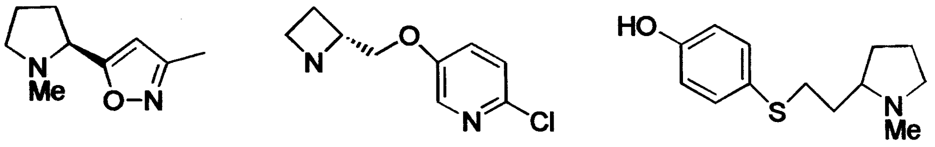
Table 1.21 Comparative efficiency values

	Nicotinic receptor sub-types (EC_{50} values in μM)			
Agonist	**Recombinant $\alpha 4\beta 2$**	**Recombinant $\alpha 7$**	**IMR-32 (ganglionic)**	**TE671 (muscle)**
(s)-(-)-Nicotine **(2)**	2-4	40-83	21	60-160
Acetylcholine **(1)**		79-155	30	5
(+/-)-Epibatidine **((+/-)-3)**	0.017	1.3-3.5	0.007	0.2

The table shows that (+/-)-epibatidine is much more efficient than nicotine and acetylcholine at the nicotinic receptor, however it is not selective for one sub-type and its potency at the different sub-types accounts for its toxicity. Nicotine also discriminates poorly between sub-types, but because it is not very potent it can have a wide spectrum of biological activity. Although smoking tobacco has the overwhelmingly undesirable, negative health effects of addiction, heart disease, cancer and respiratory disorders, nicotine ingestion can be beneficial in the form of improved cognitive and motor function, analgesic, neurorestorative, anti-anxiety, anti-depressant and anti-psychotic effects.[17]

There are several analogue molecules of nicotine that show potent activity at the nicotinic receptor. Figure 1.22 illustrates three examples that have undergone clinical trials for their potential medicinal properties as compiled by Lloyd and Williams.[17]

Figure 1.22



ABT-418 ABT-594 SIB 1553A

ABT-418 is an isoxazole analogue of nicotine and is a full and selective agonist at the α4β2 sub-type. It has shown short-term benefits in clinical trials on Alzheimer's sufferers and schizophrenia patients. Adults with attention-deficit hyperactivity disorder have shown considerable improvement on administration of ABT-418 and anxiolytic effects have also been demonstrated.

ABT-594, a 3-pyridyl ether, is a full agonist at the nicotinic receptor, showing enhanced selectivity for the α4β2 sub-type. It has shown potent pain-relieving properties.

SIB-1553A is an arylalkyl pyrrolidine that is selective for β4-containing sub-types compared to those with β2. It is an effective stimulant of acetylcholine in the CNS and has demonstrated attention and memory-enhancing effects in animal models.

The design of epibatidine analogues can involve changes in the azabicyclic ring structure and in the nature of the attached aromatic heterocycle. This thesis will concentrate on the design of azabicyclic analogue molecules, literature examples of which are described over the next few pages.

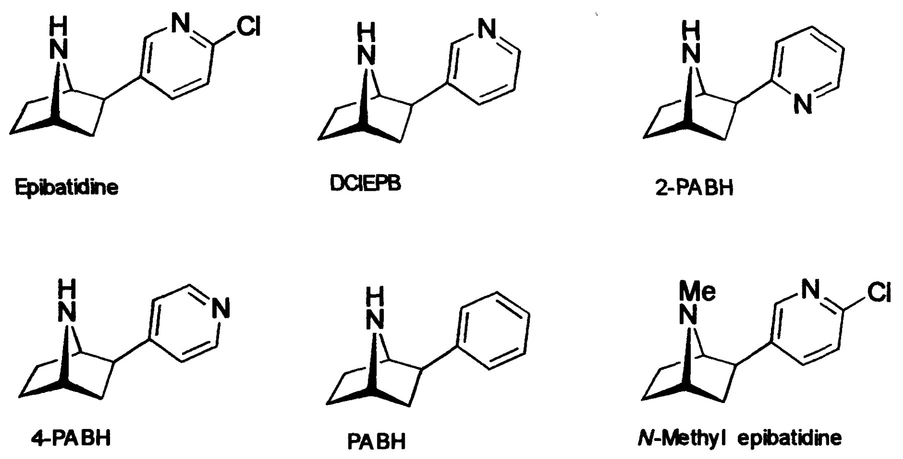
7-Azabicyclo[2.2.1]heptane Analogues

Westera and co-workers[16,18] have recently published efficacy studies on analogues shown in Figure 1.23. All of the analogue molecules were prepared *via* reductive Heck reactions with appropriate aromatic heterocycles in the manner of Clayton and Regan described previously (Scheme 1.15). The role of chlorine on the aromatic heterocycle was investigated by comparing the efficiency and efficacy of epibatidine and dechloroepibatidine (DClEPB) (Table 1.22). The study reveals a decrease in efficiency at α4β2 and α3β4 sub-types and little change at α7 for both enantiomers indicating that the chlorine is only important for binding at two of the sub-types.

Table 1.22 Comparative efficiency values

	EC_{50} (μM). (Efficacy in % ACh efficacy). Assay uses rat cDNA injected into *Xenopus* oocytes.		
Ligands	α4β2	α3β4	α7
(+)-epibatidine	0.021 (100)	0.036 (100)	2.5 (60)
(-)-epibatidine	0.023 (100)	0.019 (100)	2.03 (90)
(+)-DClEPB	0.93 (120)	0.51 (100)	5.25 (110)
(-)-DClEPB	2.8 (80)	0.25 (100)	4.6 (110)

Figure 1.23



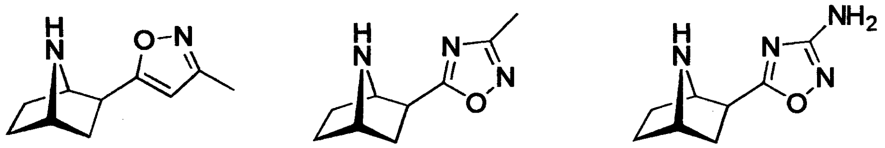
Changing the position of the pyridine nitrogen from the *meta* to the *ortho* position, in molecule 2-PABH, shortens the inter-nitrogen distance and alters the angle of orientation of the aromatic nitrogen. This modification drastically decreased the ability of the analogue to bind to and activate any of the receptor sub-types, with the exception of the (-)-analogue which acted as a full agonist at α7.

Locating the pyridine nitrogen in the *para* position, (4-PABH), or elimination of the aromatic nitrogen altogether, (PABH) had the result of effectively removing any activity at the α4β2 and α7 sub-types. However, these molecules behaved as full agonists at the α3β4 site. These results suggest that an aromatic nitrogen is not important for activation of the α3β4 sub-type but it appears that the α4β2 sub-type does require a *meta* nitrogen.

Pharmacological tests on *N*-methyl epibatidine revealed some enantioselectivity in the sensitivity of the receptor; the (+)-enantiomer was much less efficient than the corresponding epibatidine enantiomer, whilst both (-)-enantiomers had similar efficacies.

The chloropyridine ring has been exchanged for different types of heterocycle in the analogue molecules illustrated in Figure 1.24.

Figure 1.24



Epiboxidine CMI-936 CMI-1145

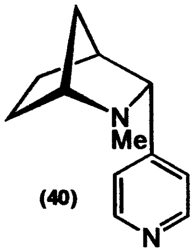
(+/-)-Epiboxidine synthesised by Daly [19] was tested for its antinociceptive properties and binding at ganglionic and central neuronal α4β2 sub-types in rats. Binding at ganglionic receptors was of a similar magnitude to epibatidine. Binding at α4β2 receptors and antinociceptive ability showed a 10-fold decrease in magnitude compared to epibatidine suggesting that the α4β2 sub-type may be involved in pain relief.

Compounds CMI-936 and CMI-1145 were synthesised by Ellis and co-workers[20] and were shown to exhibit antinociception *via* acetylcholine muscarinic receptors.

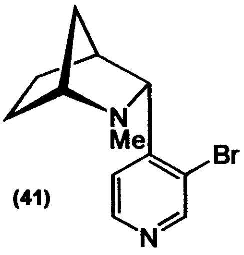
2-Azabicyclo[2.2.1]heptane Analogues

Few analogue molecules of this structure have been reported in the literature; the examples described in Figure 1.25 are taken from the review by Holladay[1] having been collated from patent literature.[21]

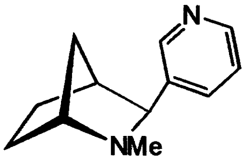
Figure 1.25



(40)



(41)



(42)

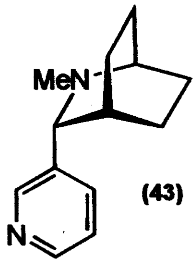
All three analogues have a pyridine ring attached to carbon 3 on the azabicyclic skeleton. Molecules **(40)** and **(42)** showed only weak affinity and efficacy at the nicotinic receptor and **(41)** (with a bromine at position 5 on the pyridine ring) showed even weaker activity. The weak activity could be due in part to the proximity of the two nitrogens. Synthesis of other 2-azabicyclo[2.2.1]heptane derivatives will be discussed in Chapter 2.

Azabicyclo[2.2.2]octane Analogues

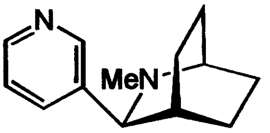
Three 2-azabicyclo[2.2.2]octane analogues **(43)**, **(44)** and **(45)**[21] and the 1-azabicyclo-[2.2.2]octane analogue **(46)**[22] are described in the Holladay review and are shown in Figure 1.26.

In the case of the *N*-methyl compounds **(43)** and **(44)**, extension of the azabicyclic skeleton from the 2-azabicyclo[2.2.1]heptane of **(40)** and **(42)** had a detrimental effect on binding. However, the desmethylated compound **(45)** showed efficacy at the α4β2 and muscle nAChRs comparable with that of nicotine. Racemic **(46)**, was found to have potent efficacy at the human muscle sub-type (EC_{50} 55nM, 130% efficacy of nicotine).

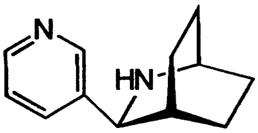
Figure 1.26



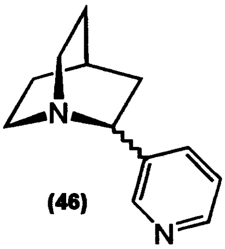
(43)



(44)



(45)

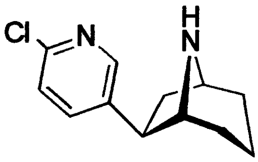


(46)

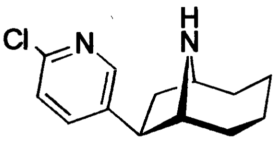
Azabicyclo[3.2.1]octane and Azabicyclo[4.2.1]nonane Analogues

Two analogue molecules in this category have been synthesised at Leicester;[23] homoepibatidine **(47)** by Malpass and Wallis and *bis*-homoepibatidine **(48)** by Malpass and Hemmings (Figure 1.27). The synthesis of homoepibatidine will be discussed fully in Chapter 4.

Figure 1.27



(47) Homoepibatidine



(48) *Bis*-Homoepibatidine

Initial pharmacological affinity tests were carried out on these molecules by S. Fletcher at Merck Sharpe and Dohme and the results are shown in column 2 of Table 1.28. Efficacy tests on homoepibatidine by Westera[16] have been recently reported in the literature and the results detailed in columns 3,4 and 5.

Table 1.28 Comparative affinity and efficacy of epibatidine analogues at nAChRs.

	Inhibition binding [^{3}H]-(-)-nicotine (rat) IC$_{50}$ (nM) (ref. a)	**EC$_{50}$ (μM). (Efficacy in % ACh efficacy). Assay uses rat cDNA injected into *Xenopus* oocytes.** (ref. b)		
		α4β2	α3β4	α7
(-)-Epibatidine	0.1	0.023 (100)	0.019 (100)	2.03 (90)
(+)-Epibatidine	0.24	0.021 (100)	0.036 (100)	2.5 (60)
(-)-Homoepibatidine	0.3	>1	0.6/1.6	(<1)
(+)-Homoepibatidine	0.8	0.02 (100)	0.02 (100)	
(+/-)-*Bis*-homoepibatidine	2.85			
(-)-Nicotine	7.8			

a : S. Fletcher, Merck Sharpe and Dohme.

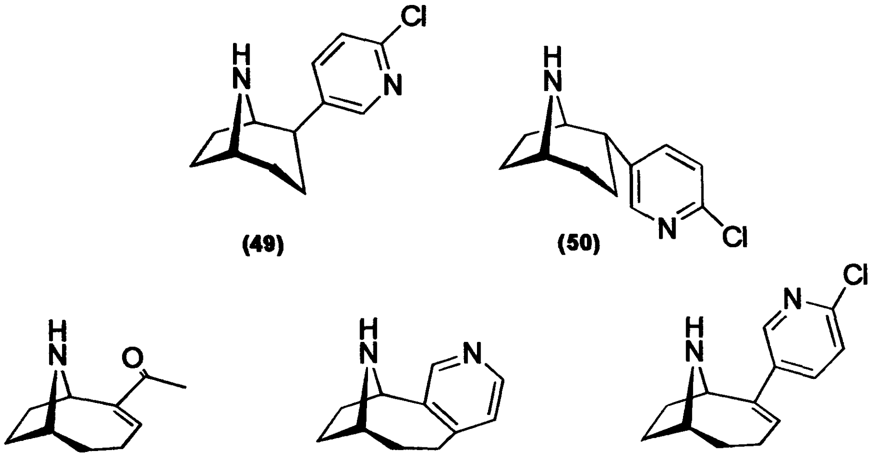
b : Westera et al.[16]

The affinity studies showed that homoepibatidine was as active as epibatidine at the nicotinic receptors but did not show a difference in binding of the two enantiomers. Binding affinity of *bis*-homoepibatidine was tenfold less than epibatidine, revealing that an increase in the size of the largest ring to 4 carbon atoms is not tolerated well by the receptor. *Bis*-homoepibatidine was not resolved into enantiomers.

The studies by Westera revealed a significant difference in activity between the two enantiomers of homoepibatidine. The (+)-enantiomer was as efficacious as epibatidine at the α4β2 and α3β4 sub-types. In contrast the (-)-enantiomer showed very low efficacy at α4β2 and α7 and reduced efficacy at α3β4. It therefore appears that extension of the azabicyclic ring induces enantioselectivity in receptor activation.

Trudell and co-workers[24] synthesised analogues **(49)** and **(50)** in which the chloropyridyl ring is oriented on the more flexible 3-carbon bridge of the azabicycle (Figure 1.29). [^{3}H]-Epibatidine displacement studies on *Torpedo californica* tissue found a 27-fold reduction in affinity of **(49)** compared to epibatidine and a 2500-fold reduction in affinity for **(50)** where the pyridine moiety is oriented on the opposite face of the molecule to the bridging nitrogen.

Figure 1.29



(49) **(50)**

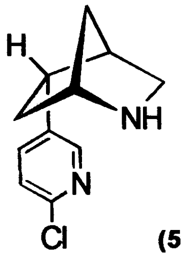
(+)-Anatoxin-a PHT UB-165

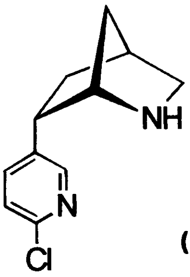
(+)-Anatoxin-a is a natural alkaloid isolated from freshwater bacteria and has a high affinity, but low selectivity for the nAChR (K_i<1-10nM).[1] Two highly potent hybrids of anatoxin-a and epibatidine have been synthesised, PHT[6] and UB-165[25], both of which have affinities intermediate between anatoxin-a and epibatidine. The individual enantiomers of UB-165 showed very different activity, the enantiomer illustrated being 20x more active.

1.7 Our Approach to Epibatidine Analogues

Existing nicotinic pharmacophores were not sufficiently detailed for accurate molecular design and so our approach to design was to take the general framework of the nicotinic pharmacophore as a guide, including one heteroaromatic and one basic nitrogen, with inter-nitrogen distances similar to epibatidine. However, we have varied the flexibility of the azabicyclic skeleton and the orientation of the two nitrogens in anticipation that this would lead to different binding properties at the receptor.

2-Azabicyclo[2.2.1]heptane Analogues


(51)


(52)

To the best of our knowledge, only (C-3-substituted)-2-azabicyclo[2.2.1]heptane analogues of epibatidine had been made. Therefore as novel epibatidine analogues, *endo*-5-(2'-chloro-5'-pyridyl)-2-azabicyclo[2.2.1]heptane **(51)** and *endo*-6-(2'-chloro-5'-pyridyl)-2-azabicyclo[2.2.1]heptane **(52)** were the first targets chosen for synthesis. It was noted that there was very little difference in the binding and activity of the two enantiomers of epibatidine at the nicotinic receptor and that epibatidine had a symmetrical 7-azabicyclic skeleton. Molecules **(51)** and **(52)** feature a secondary nitrogen placed asymmetrically in the bicyclic skeleton and it was anticipated that this would lead to greater enantioselectivity in the activity of the two pairs of enantiomers at the receptor site.

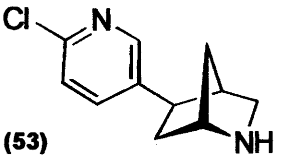
Inter-nitrogen distances were calculated on the protonated analogues using DTMM3 which gave two minimum-energy conformations per molecule, the first in which the aromatic nitrogen was oriented close to the bridging nitrogen and the second where the carbon-aromatic bond was rotated by 180^0. The results are summarised in Table 1.30.

Table 1.30 Inter-nitrogen distances of **(51)** and **(52)**

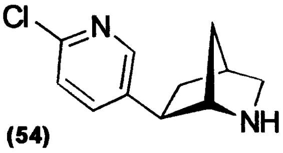
Compound	**Minimum energy conformation (A^0)**	**After 180^0 rotation (A^0)**
Epibatidine	4.3	5.5
(51)	4.7	5.7
(52)	4.1	4.9

Both target molecules have inter-nitrogen distances similar to epibatidine.

The stereo- and regioisomers **(53)** and **(54)** were also to be synthesised for comparison of structure and activity.



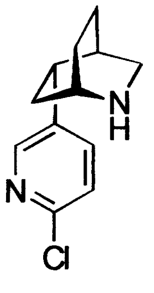
(53)



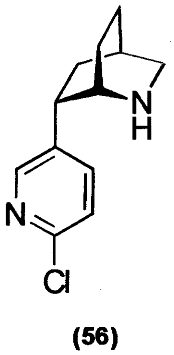
(54)

2-Azabicyclo[2.2.2]octane Analogues

It was decided that *endo*-5-(2'-chloro-5'-pyridyl)-2-azabicyclo[2.2.2]octane **(55)** and *endo*-6-(2'-chloro-5'-pyridyl)-2-azabicyclo[2.2.2]octane **(56)**, would also make good targets, these molecules featuring an increase in flexibility and bulk of the bicyclic skeleton as compared to the azabicyclo[2.2.1]heptane analogues. Comparison of the activity of the different sized azacycles in pharmacological assays would give an indication of how well the receptor site tolerates bulk on the opposite face of the molecule to the nitrogen interaction points.



(55)



(56)

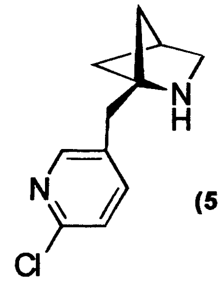
Table 1.31 shows molecular modelling calculations of inter-nitrogen distances; both molecules give similar values to epibatidine.

Table 1.31 Inter-nitrogen distances of **(55)** and **(56)**

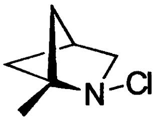
Compound	**Minimum energy conformation (A^0)**	**After 180^0 rotation (A^0)**
Epibatidine	4.3	5.5
(55)	4.6	5.6
(56)	4.3	5.0

2-Azabicyclo[2.1.1]hexane Analogue

1-[Methyl-(2'-chloro-5'-pyridyl)]-2-azabicyclo[2.1.1]hexane **(57)** was considered as a natural progression from the 2-azabicyclo[2.2.1]heptane structure. The molecule features a more compact and rigid azabicyclic skeleton although the chloropyridine ring is not directly attached to it. Molecular modelling studies elicited a variety of inter-nitrogen distances as the methyl carbon-pyridine bond and the bridgehead carbon-methyl bond can undergo rotation, but at least one lowest energy conformation had an inter-nitrogen distance similar to epibatidine.



(57)

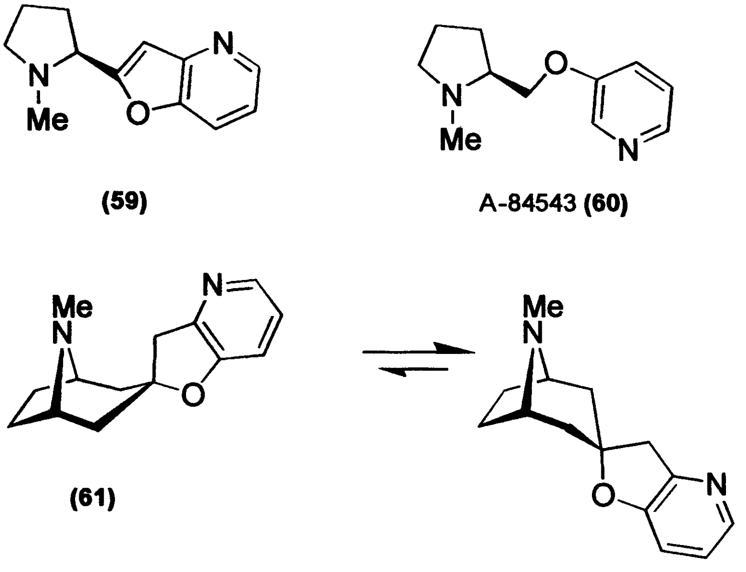


(58)

We have experience at Leicester in the synthesis of 2-azabicyclo[2.1.1]hexane systems; molecule **(58)** was synthesised by Malpass and Davies in their studies of inversion of substituents at nitrogen (see Chapter 5).

8-Azabicyclo[3.2.1]octyl Analogues

Figure 1.32



(59)

A-84543 (60)

(61)

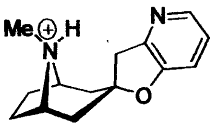
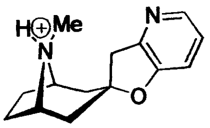
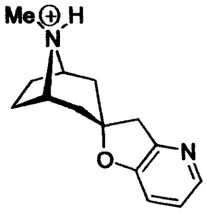
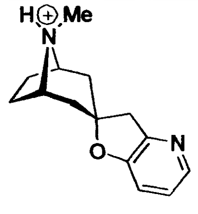
Spirocyclic molecule **(61)** (Figure 1.32) was designed as a selective α4β2 agonist inspired by molecules **(59)** and **(60)** synthesised by Holladay and co-workers.[1] Molecule **(59)** is a furo[3,2-b]pyridine, **(60)** a 3-pyridyl ether and both structures, based on nicotine, show high activity and good selectivity for the α4β2 nicotinic sub-type.

It was anticipated that **(61)** would have the two accessible conformations illustrated with a small energy barrier between them and this was confirmed by molecular modelling studies. The 'boat' conformation would be expected to be the one active at the receptor site. Inter-nitrogen distances are shown in Table 1.33.

It can be seen that, in addition to the two piperidine ring conformations, there are also two different orientations of the *N*-methyl group, the invertomer in which the methyl group is anti- to the heterocycle being favoured.[26]

This molecule incorporates a tertiary azabicyclic nitrogen in parallel with **(59)** and **(60)** (also note that *N*-methyl epibatidine showed high activity (Figure 1.23)). If desired, however, the nor-spirocyclic compound could potentially be obtained by demethylation.[27]

Table 1.33 Molecular modelling data for **(61)**

Conformation	**Energy (kcal/mol)**	**Inter-nitrogen distance (A^0)**	**Conformation**	**Energy (kcal/mol)**	**Inter-nitrogen distance (A^0)**
	-27.7	5.4		-25.7	5.8
	-32.7	6.2		-30.6	6.2

CHAPTER 2

Synthesis of Exo-5-(and 6-)aryl-2-azabicyclo[2.2.1]heptane Systems

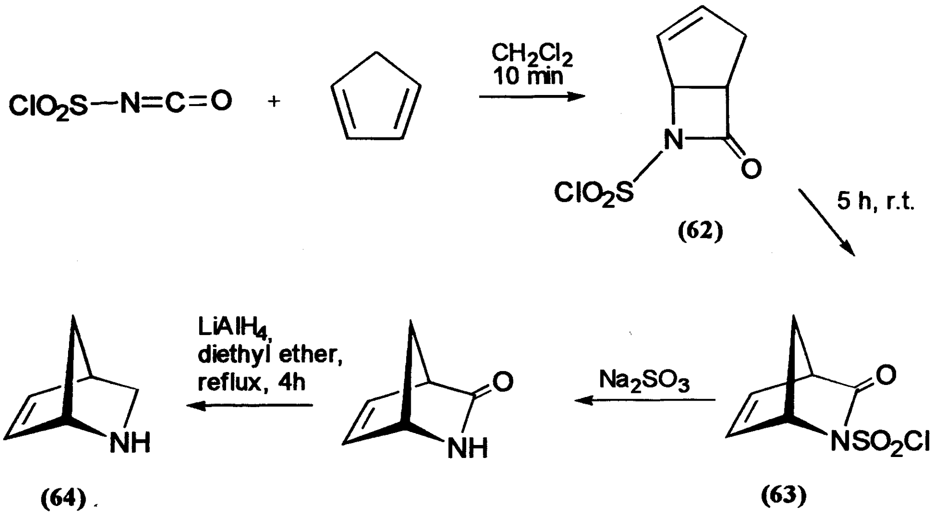
2.1 Synthetic Routes to 2-Azabicyclo[2.2.1]heptyl Ring Systems

The first 2-azabicyclo[2.2.1]heptane derivatives were made over 100 years ago and since then hundreds of syntheses of these compounds have been reported. The strategies employed in the construction of the bicyclic skeleton fall into three main categories: rearrangement; intramolecular ring closure; and Diels-Alder cycloaddition. The next few pages give selective illustrations of these strategies.

Rearrangement

A cycloaddition/rearrangement reaction was utilised by Malpass and Tweddle[28] in their synthesis of the empirical 2-azabicylo[2.2.1]hept-5-ene structure **(64)** (Scheme 2.1).

Scheme 2.1

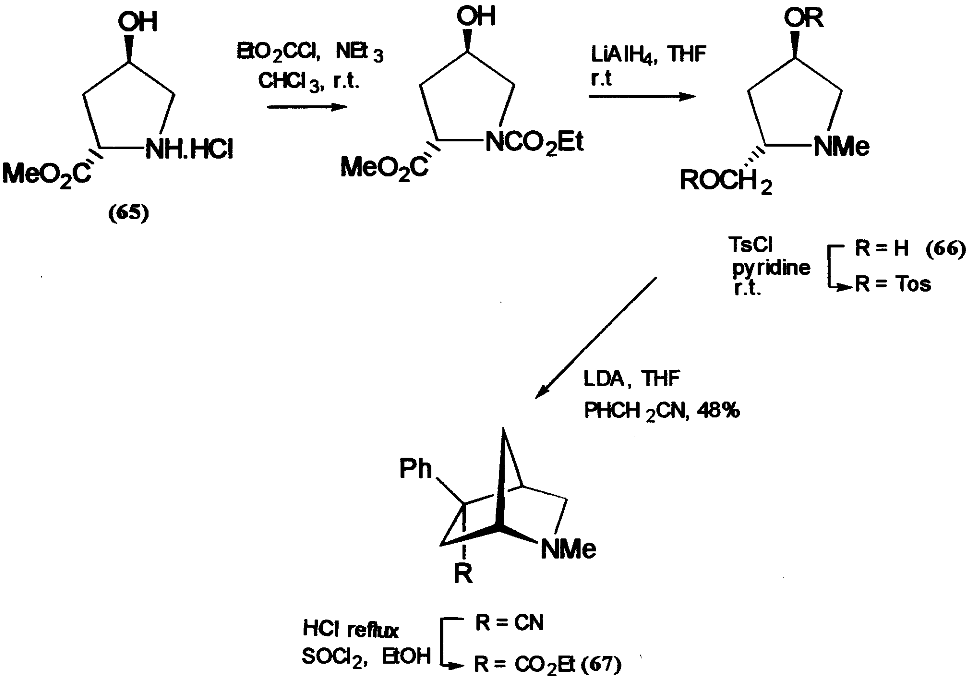


Reaction of chlorosulfonyl isocyanate with cyclopentadiene gave the *N*-chlorosulfonyl β-lactam **(62)** by formal 2πa + 2πs cycloaddition. Monitoring of the freshly generated lactam in solution revealed a gradual rearrangement of this molecule to **(63)** over 5 hours. Immediate treatment with aqueous sodium sulphite removed the *N*-chlorosulphonyl group and reduction with lithium aluminium hydride afforded 2-azabicyclo[2.2.1]hept-5-ene, **(64)**, in an overall yield of 22%.

Ring Closure

Bicyclic ring-closure can be achieved *via* displacement of one leaving group on a monocyclic precursor by an intramolecular nucleophile or by sequential displacement of two leaving groups by an intermolecular nucleophile. Newman and co-workers[29] took the latter approach in their synthesis of an analogue of meperidine (Scheme 2.2). Meperidine is a μ-opioid agonist that has been shown to fully substitute for cocaine in squirrel monkeys, in a drug discrimination model of drug abuse.[30]

Scheme 2.2



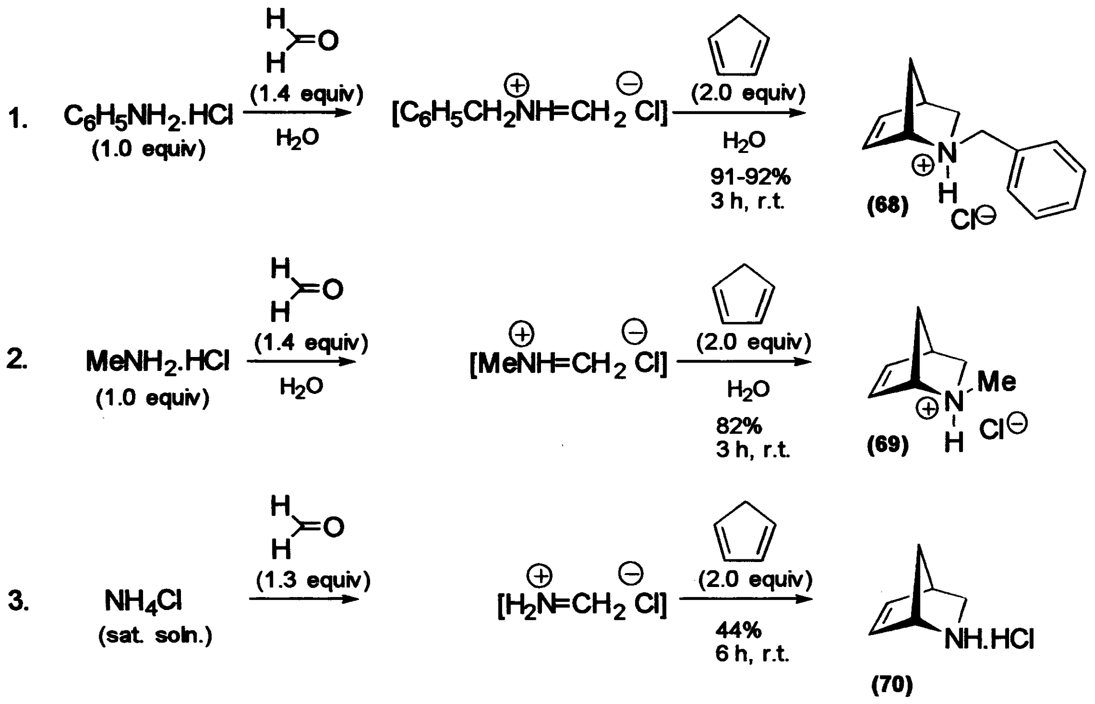
OH
NH.HCl
MeO2C
(65)
EtO2CCl, NEt3
CHCl3, r.t.
OH
NCO2Et
MeO2C
LiAlH4, THF
r.t
OR
NMe
ROCH2
TsCl
pyridine
r.t.
R = H (66)
R = Tos
LDA, THF
PhCH2CN, 48%
Ph
NMe
R
HCl reflux
SOCl2, EtOH
R = CN
R = CO2Et (67)

Compound (65) was made from commercially available *trans*-L-hydroxyproline. The protonated nitrogen was converted into the *N*-ethoxycarbonyl derivative using ethyl chloroformate and a base. The carbamate and ester groups were reduced with lithium aluminium hydride to yield the diol (66). The two alcohol groups were converted into tosyl leaving groups (yield 18% overall after this step) which were then substituted by a carbanion (generated via the action of LDA on the α-carbon protons of phenylacetonitrile) in 48% yield. Hydrolysis of the nitrile group followed by esterification yielded the meperidine analogue (67) as a single diastereoisomer.

Diels-Alder Cycloaddition

An efficient method based on the reaction of simple unactivated iminium salts, generated *in situ*, with dienes was methodology developed by Grieco.[31] Examples of the reactions of various iminium ions with cyclopentadiene are shown in Scheme 2.3.

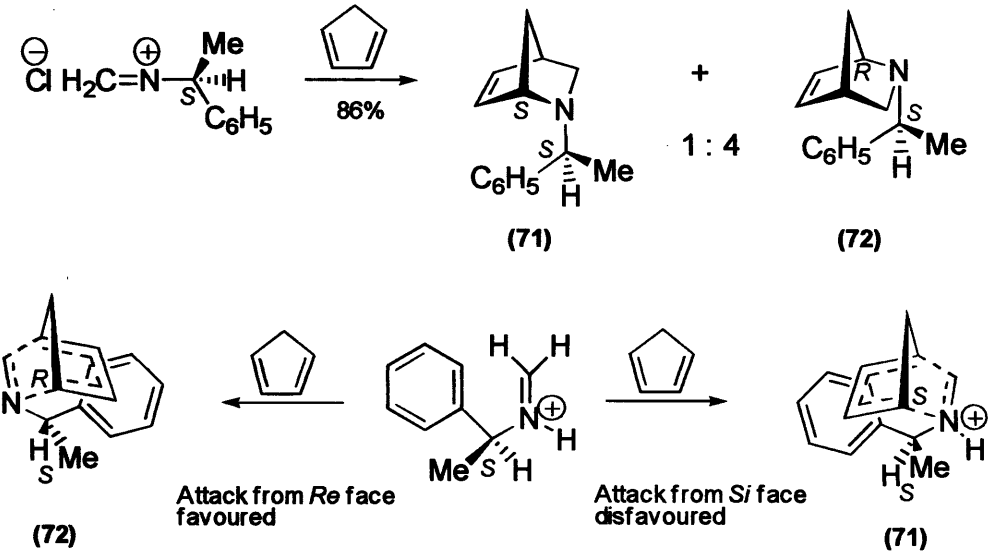
Scheme 2.3


1. $C_6H_5NH_2.HCl$ (1.0 equiv)
(1.4 equiv)
H_2O
$[C_6H_5CH_2\overset{\oplus}{N}H{=}CH_2\ \overset{\ominus}{Cl}]$
(2.0 equiv)
H_2O
91-92%
3 h, r.t.
(68)
2. $MeNH_2.HCl$ (1.0 equiv)
(1.4 equiv)
H_2O
$[Me\overset{\oplus}{N}H{=}CH_2\ \overset{\ominus}{Cl}]$
(2.0 equiv)
H_2O
82%
3 h, r.t.
Me
(69)
3. NH_4Cl (sat. soln.)
(1.3 equiv)
$[H_2\overset{\oplus}{N}{=}CH_2\ \overset{\ominus}{Cl}]$
(2.0 equiv)
44%
6 h, r.t.
NH.HCl
(70)

An aqueous solution of benzyliminium hydrochloride (entry 1) was generated from the reaction of benzylamine hydrochloride with formaldehyde. Freshly cracked cyclopentadiene was added to form a heterogeneous reaction mixture which was stirred vigorously for 3 hours at room temperature. *N*-Benzyl-2-azabicyclo[2.2.1]hept-5-ene **(68)** was formed in a 91-92% yield after neutralisation. In an analogous fashion, the *N*-methylated bicycle **(69)** was generated from methylamine hydrochloride (entry 2), the yield being lower due to increased volatility of the product. The secondary amine **(70)** was made from ammonium chloride, although the yield decreased significantly.

Grieco also carried out a reaction involving an optically active iminium ion to assess the potential for chiral induction in this type of Diels-Alder reaction (Scheme 2.4).

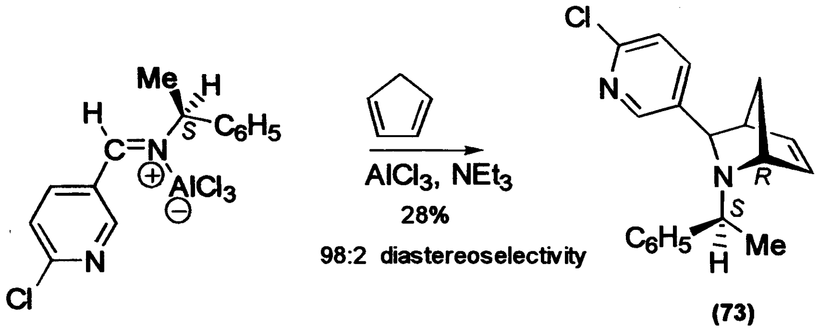
Scheme 2.4



The chiral iminium ion was generated from the action of formaldehyde on (-)-α-methylbenzylamine hydrochloride; cyclopentadiene was then added and the reaction left to stir for 20 hours at 0°C. The products of the reaction were found to be two diastereoisomers (the absolute configurations were not determined by Grieco) in a ratio of 4:1 and an 86% yield. The absolute configurations of the two diastereoisomers were however determined by Pombo-Villar and co-workers,[32] who repeated the reaction and carried out spectroscopic and crystallographic characterisation. The main diastereoisomer was found to be (1*R*, 1'*S*) **(72)**; formation of **(71)** being disfavoured owing to steric interactions of the methyl group with the diene at the transition state.

The asymmetric induction achieved by the use of chiral methylbenzylamine hydrochloride salts has recently been exploited in the preparation of enantiopure potential nicotinic agonists; Scheme 2.5 illustrates one example prepared by Loh.[33] The iminium ion was generated from the action of (-)-α-methylbenzylamine on 6-chloro-3-pyridinecarboxyaldehyde and was activated by co-ordination of aluminium chloride acting as a Lewis acid. The ion was allowed to react with cyclopentadiene in dry dichloromethane, at 0-5°C, with sonication and shaking over 2-3 days. Compound **(73)** was isolated in poor yield but with excellent diastereoselectivity. There is significant interest in the asymmetric Diels-Alder approach to other 2-azabicyclo[2.2.1]heptane molecules functionalised at carbon 3 with, for example, ester groups.[34]

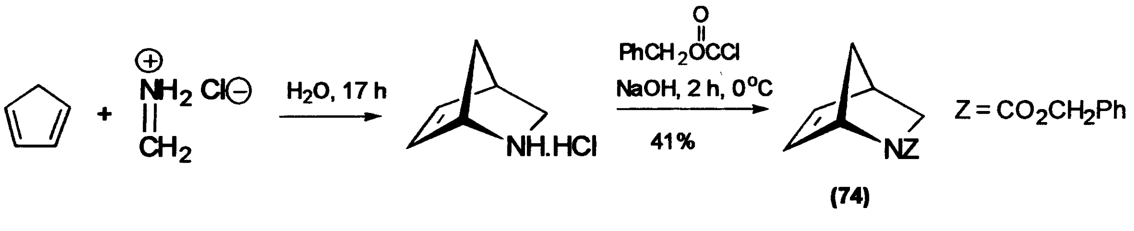
Scheme 2.5


Me
H
H
S
C₆H₅
C=N
AlCl₃
N
Cl
AlCl₃, NEt₃
28%
98:2 diastereoselectivity
Cl
N
N
R
S
C₆H₅
H
Me
(73)

2.2 Our Synthetic Routes to Epibatidine Analogues

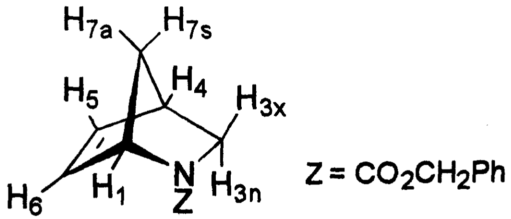
N-(Benzyloxycarbonyl)-2-azabicyclo[2.2.1]hept-5-ene **(74)** was synthesised as reported by Carroll,[35] the experimental route to this molecule having been adapted from the Grieco methodology shown in Scheme 2.3. The bicyclic amine was generated over 17 hours at room temperature as the HCl salt (Scheme 2.6), the free amine being obtained by neutralisation of the hydrochloride salt. Acylation of the free amine with benzyl chloroformate was carried out under basic conditions at 0°C and the crude product purified by flash chromatography in a yield of 41%.

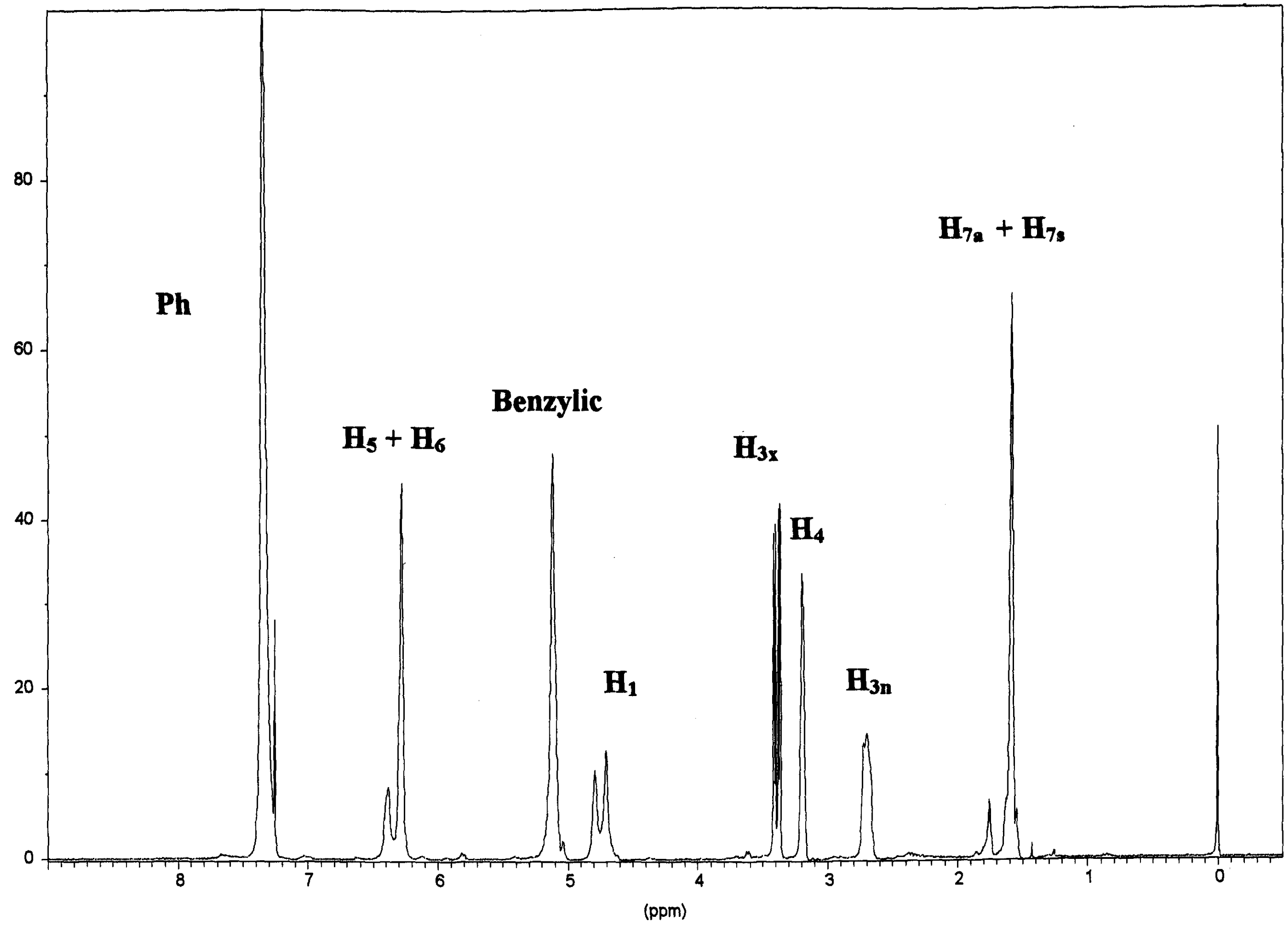
Scheme 2.6


NH₂ Cl
CH₂
+
H₂O, 17 h
NH.HCl
O
PhCH₂OCCl
NaOH, 2 h, 0°C
41%
NZ
(74)
Z = CO₂CH₂Ph

The ^{1}H NMR spectrum of **(74)** (Figure 2.7) revealed the presence of two rotamers in a ratio of 53:47, as measured by integration of the signals for H_1. Signals for two rotamers arise because of restricted rotation around the urethane N-CO bond, which is slow on the NMR timescale. Not all protons show two sets of signals on the spectrum however, as most signals overlap. H_4 was identified as a broad singlet upfield from H_1 which showed vicinal interactions with H_{3x} in HH COSY experiments. Geminal coupling was measured (9.5 Hz) between H_{3n} and H_{3x} and 'W' coupling was seen between H_{3n} and H_{7a}.

Figure 2.7 ^{1}H NMR Spectrum **(74)**

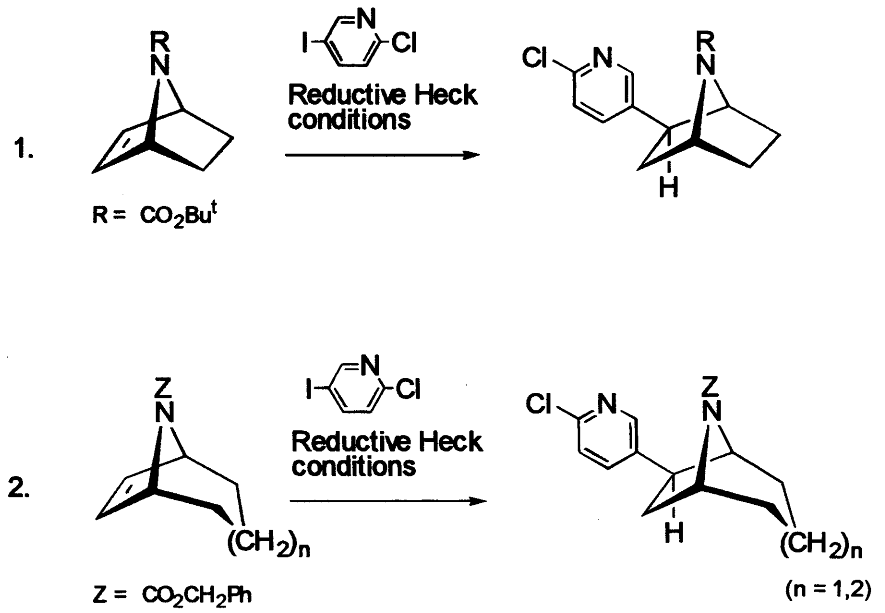

H7a
H7s
H5
H4
H3x
H6
H1
N
Z
H3n
Z = CO2CH2Ph



2.3 Synthesis of Epibatidine Analogues via a Reductive Heck Reaction

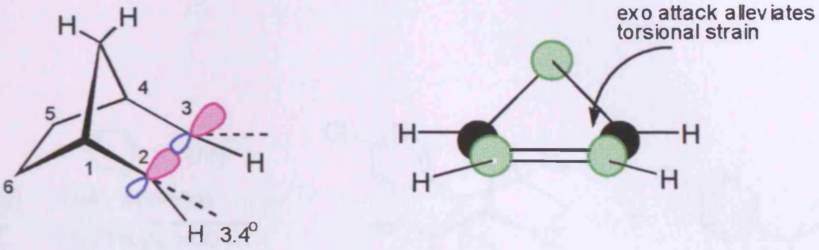
There are many examples of the use of the reductive Heck reaction in the synthesis of epibatidine and epibatidine analogues; two examples are shown in Scheme 2.8. Entry 1 is taken from Clayton and Regan's synthesis of epibatidine[11] discussed in Chapter 1 and entry 2 is taken from Malpass, Wallis and Hemming's syntheses of homoepibatidine and *bis*-homoepibatidine.[23]

Scheme 2.8



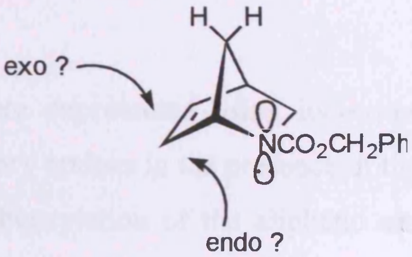
In both examples, addition occurs stereoselectively to the *exo-* face of the bicycle. Preferential addition to the *exo-* face in norbornene and norbornyl systems is well precedented.[36] Electron diffraction studies on norbornene have shown that the vinyl protons are oriented 3.4^0 below the plane of the molecule as defined by carbons 1, 2, 3 and 4 (Figure 2.9). It is thought that this pyramidal distortion occurs to minimise the interaction of the π-bond with the σ^*-bonds associated with C_1-C_6 and C_4-C_5. A consequence of this pyramidalization is that the alkene p-orbitals take on more s-character and the *exo-* lobes of the p-orbitals become larger than the *endo-* lobes. The Newman projection of norbonene seen from the perspective of the π-bond shows the orientation of the vinyl protons with respect to those at the bridgehead. It could be envisioned that attack on the π-bond from the *exo-* face by an electrophile would decrease torsional strain between the two different sets of protons early on in the reaction co-ordinate. These three factors help to explain the stereoselectivity of the reductive Heck reaction.

Figure 2.9



In the case of reaction on the 2-azabicyclo[2.2.1]heptene system, we were interested to see whether the lone electron pair on the nitrogen would co-ordinate to the palladium catalyst, bringing the chloropyridine ring in at the *endo-* face and thus compete with *exo-* attack (Figure 2.10).

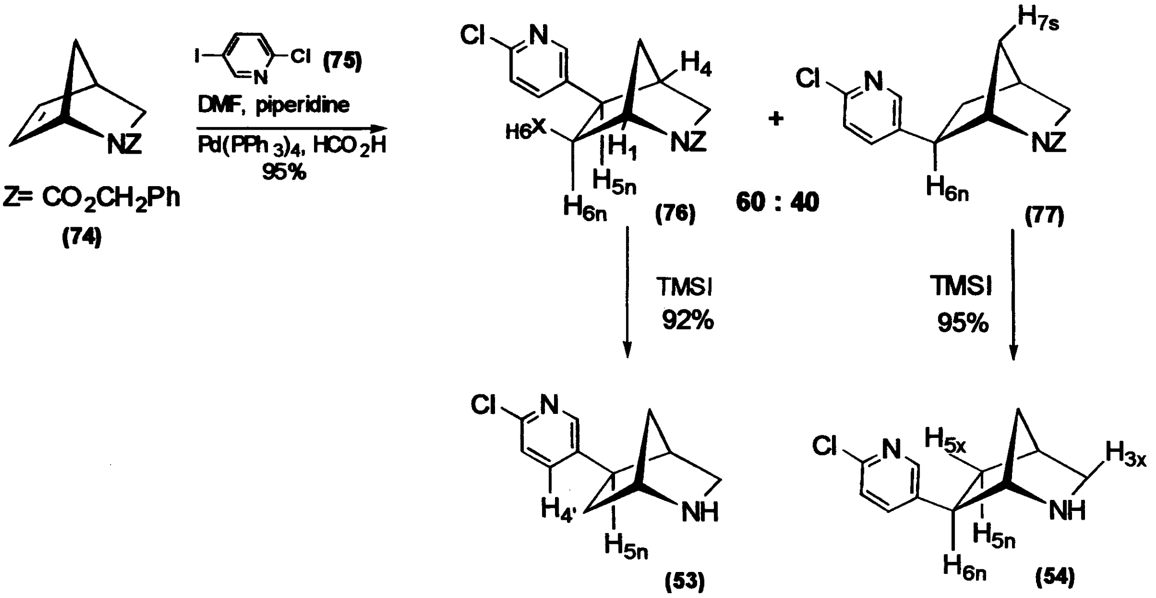
Figure 2.10



The reductive Heck reaction was carried out in a reactivial using an excess of 2-chloro-5-iodopyridine **(75)** and a catalytic amount of Pd(PPh$_3$)$_4$[37] at 75°C over 24 hours (Scheme 2.11). The crude product was examined by ^{1}H NMR spectroscopy (Figure 2.18) and found to contain the *exo-* adducts **(76)** and **(77)** in a ratio of 60:40; the regioisomers were separated using a chromatotron. The ratio of regioisomers was calculated by integration of the signals for H$_1$, present in the region δ 4.0-4.4, corresponding to the two pairs of rotamers.[38]

The 5-*exo-* orientation of the pyridine ring in **(76)** was assigned using ^{1}H NMR and HH COSY spectra; H$_{5n}$ appeared as a doublet of doublets at δ 3.01 and showed vicinal coupling to H$_{6n}$ and H$_{6x}$. Coupling of H$_{5n}$ to H$_4$ was very small (<1 Hz) and characteristic of two protons virtually orthogonal to each other. The presence of H_{6n} in **(77)** was confirmed by 'W'-coupling to H_{7s} and the absence of any significant coupling to H_1 indicated that there was no *exo-* proton on C_6.

Scheme 2.11



Both regioisomers were deprotected using iodotrimethylsilane taking care not to concentrate the secondary amines in the presence of the benzyl iodide by-product; this would result in some benzylation of the aliphatic nitrogen.[39] Excellent yields were achieved however, when the reaction mixtures were acidified prior to work-up.

Both **(53)** and **(54)** were characterised using ^1H NMR and HH COSY spectra. The 5-*exo-* orientation of the pyridine ring for **(53)** was confirmed by a coupling interaction between H_{5n} and $H_{4'}$ located on the pyridine ring; double irradiation of the signal for H_{5n} resulted in a simplification of the signal for $H_{4'}$; $J_{4',5n}$ was measured at 0.5 Hz. In the case of **(54)**, the lack of any coupling interactions between the protons on C_1 and C_6 and a cross-peak for a 'W'-coupling from H_{6n} to H_{7s} confirmed the *exo-* position of the chloropyridine ring on C_6. In addition, the signals for both protons on C_5 were identified *via* their coupling interactions: vicinal coupling to H_4 ($J_{4,5x} = 3.5$ Hz), 'W'-coupling to H_{3x} ($J_{3x,5x} = 3.0$ Hz) and geminal coupling ($J_{5x,5n} = 12.5$ Hz). Comparison of spectra for both *exo-* isomers with their corresponding *endo-* isomers (Chapter 3) adds further support to our assignments.

Table 2.12 illustrates comparative ^{1}H NMR data for the *N*-protected and deprotected *exo-* isomers.

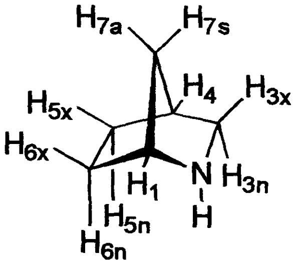
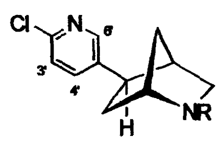
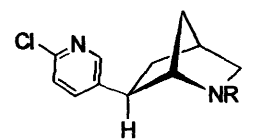
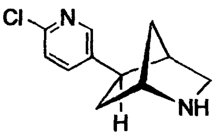
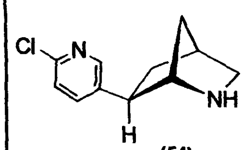


Table 2.12. Selected ^{1}H NMR data

(R = CO_2CH_2Ph)	 δ (ppm) (76)		 δ (ppm) (77)		 δ (ppm) (53)		 δ (ppm) (54)	
H_1	**4.41**, 4.48	bs	**4.22**, 4.35	bs	3.63	bs	3.46	bs
H_{3x}	**3.43**, 3.45	dd	*ca. 3.4*	m	3.03	dd	2.99	bddd
H_{3n}	**3.28**, 3.24	d	**3.19**, 3.16	d	2.81	d	2.71	d
H_4	*2.68*	bs	*2.72*	bs	2.55	m	2.58	bs
H_{5x}	--		*ca. 1.9*	m	--		1.73	dddd
H_{5n}	*3.01*	dd	*ca. 2.0*	m	2.97	dd	1.96	ddd
H_{6x}	*ca. 1.6-1.8*	m	--		1.74	ddd	--	
H_{6n}	**2.28**, 2.37	dddd	*ca. 3.3*	m	2.09	ddd	2.96	bdd
H_{7a}	*ca. 1.6-1.8*	m	*1.57*	AB(b)	1.62		1.59 *	AB(b)
H_{7s}	*ca. 1.6-1.8*	m	*1.66*	AB(b)	1.55		1.52 *	AB(b)
H_5'	8.25	d	**8.26**, 8.18	d	8.27	d	8.24	d
H_3'	*7.27*	d	*ca. 7.2 - 7.4*	m	7.25	dd	7.25	d
H_4'	*7.48*	dd	*ca. 7.4 - 7.5*	dd	7.49	ddd #	7.46	dd
Benzylic CH_2	*5.15*	AB	*5.08-5.27*	AB				
Phenyl	*7.30-7.40*	m	*7.21-7.41*	m				

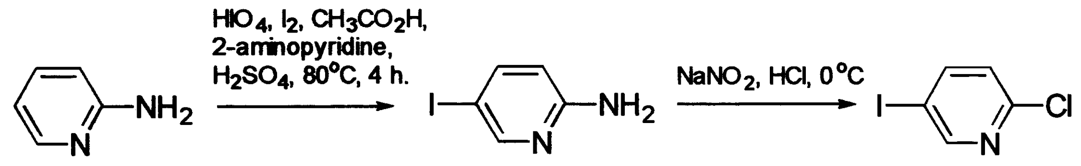
Figures in bold refer to the major rotamer, though ratios were close to 1:1 in most cases (see experimental section).

Figures in italics refer to overlapping peaks including signals due to two rotamers.

* H_{7s} and H_{7a} are too close to assign with confidence. # Coupling between H_{5n} and H_4' was resolved in this case ($J_{4',5n}$ = 0.5 Hz) and was confirmed by selective spin-decoupling.

2-Chloro-5-iodopyridine **(75)** used in these reactions was synthesised from 2-aminopyridine using a procedure developed by Magison and Menschikoff[40] (Scheme 2.13) in an overall yield of 26%.

Scheme 2.13

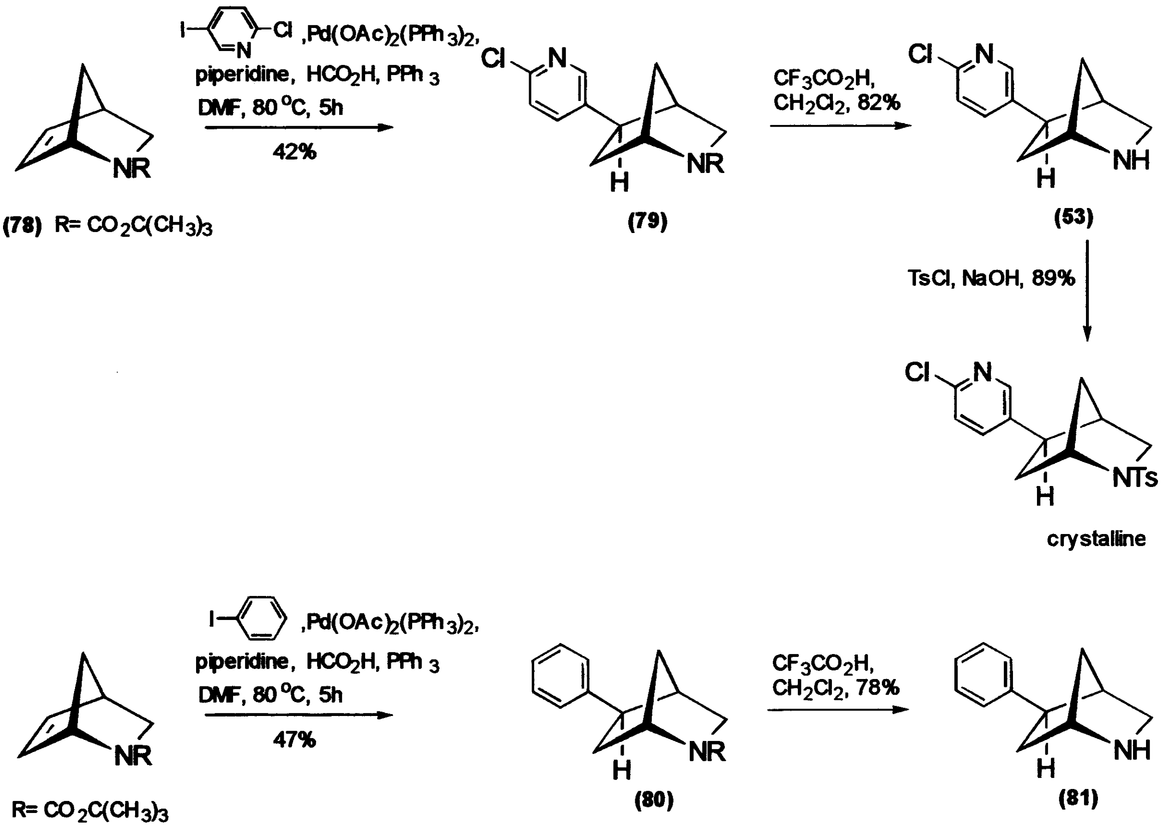

HIO4, I2, CH3CO2H,
2-aminopyridine,
H2SO4, 80°C, 4 h.
NH2
N
I
NaNO2, HCl, 0 °C
Cl

(75)

2.3 Reductive Heck Reactions Completed by the Maier Group

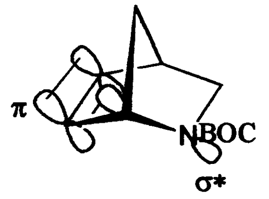
On completion of our synthesis of the *exo-* regioisomers, we were surprised to find a publication by the Maier group claiming that reductive Heck reactions in the 2-azanorborn-5-ene system give only the 5-*exo-* isomer.[41] Their reactions were carried out on the *N*-BOC protected azabicycles under reductive Heck conditions, firstly with 2-chloro-5-iodopyridine and secondly with iodobenzene (Figure 2.13). The *N*-BOC protected products were deprotected using trifluoroacetic acid and, in the case of **(53)**, the crystalline *N*-tosyl derivative was prepared and characterised using X-ray crystallography.

Figure 2.13 Claimed Formation of Single Regioisomer.[41]


I
Cl
N
,Pd(OAc)2(PPh3)2,
piperidine, HCO2H, PPh3
DMF, 80 °C, 5h
42%
NR
(78) R= CO2C(CH3)3
Cl
N
H
NR
(79)
CF3CO2H,
CH2Cl2, 82%
NH
(53)
TsCl, NaOH, 89%
NTs
crystalline
,Pd(OAc)2(PPh3)2,
piperidine, HCO2H, PPh3
DMF, 80 °C, 5h
47%
R= CO2C(CH3)3
(80)
CF3CO2H,
CH2Cl2, 78%
(81)

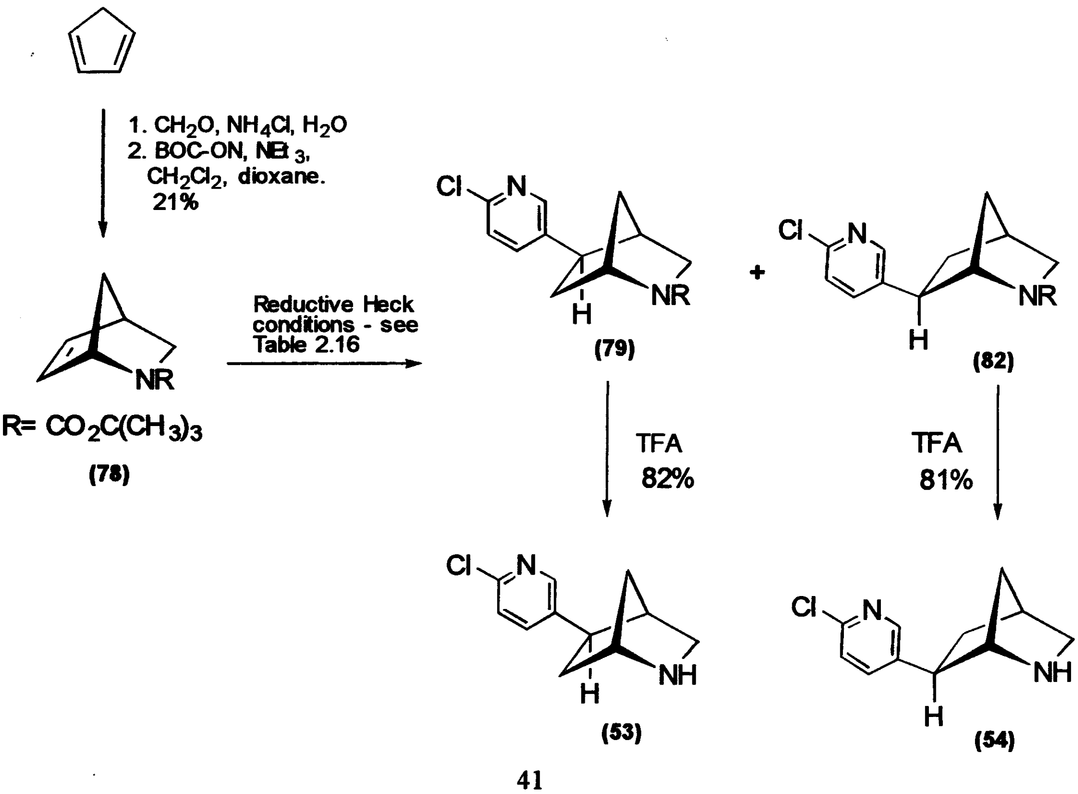
The claimed regiospecificity was rationalised on the basis of overlap of the σ^* orbital associated with C_1-N bond and the alkene π-bond (Figure 2.14).

Figure 2.14



We decided to investigate these findings by synthesising the *N*-BOC protected azanorbornene and carrying out a range of reductive Heck reactions with variation of the reaction conditions and catalyst employed. The *N*-BOC protected bicycle **(78)** was prepared by protection of the nor-compound using BOC-ON and triethylamine in an overall yield of 21% (Scheme 2.15). Reaction of **(78)** with 2-chloro-5-iodopyridine using $Pd(PPh_3)_4$ as a catalyst gave a mixture of the 5- and 6-*exo*-chloropyridyl compounds **(79)** and **(82)** in good yield. The ratio of regioisomers was again obtained by integration of the signals for H_1 shown clearly on the crude spectrum (Figure 2.18) and found to be 55:45. Both compounds showed similar NMR spectra to their corresponding benzyloxycarbonyl-protected analogues, however, there were some differences between the ^1H NMR signals observed by ourselves and those reported by Maier (see experimental section for details).

Scheme 2.15


1. CH2O, NH4Cl, H2O
2. BOC-ON, NEt3, CH2Cl2, dioxane.
21%
NR
R= CO2C(CH3)3
(78)
Reductive Heck conditions - see Table 2.16
Cl
N
H
NR
(79)
+
(82)
TFA
82%
TFA
81%
NH
(53)
(54)

Both **(79)** and **(82)** were deprotected with trifluoroacetic acid in good yield to give the nor-compounds which were identical with the samples prepared earlier. Comparison of ^1H NMR values for **(53)** as quoted by Maier again revealed differences from those observed by ourselves, indeed some of their values were characteristic of the 6-*exo*-isomer rather than the 5-isomer (see experimental).

Variation in the reaction conditions and choice of catalyst resulted in small differences in both yields and ratios of regioisomers; these results are summarised in Table 2.16.

Table 2.16 Reductive Heck reactions on 2-azabicyclo[2.2.1]hept-5-ene derivatives (74) (*N*-benzyloxycarbonyl-protected) and (78) (*N*-BOC-protected).

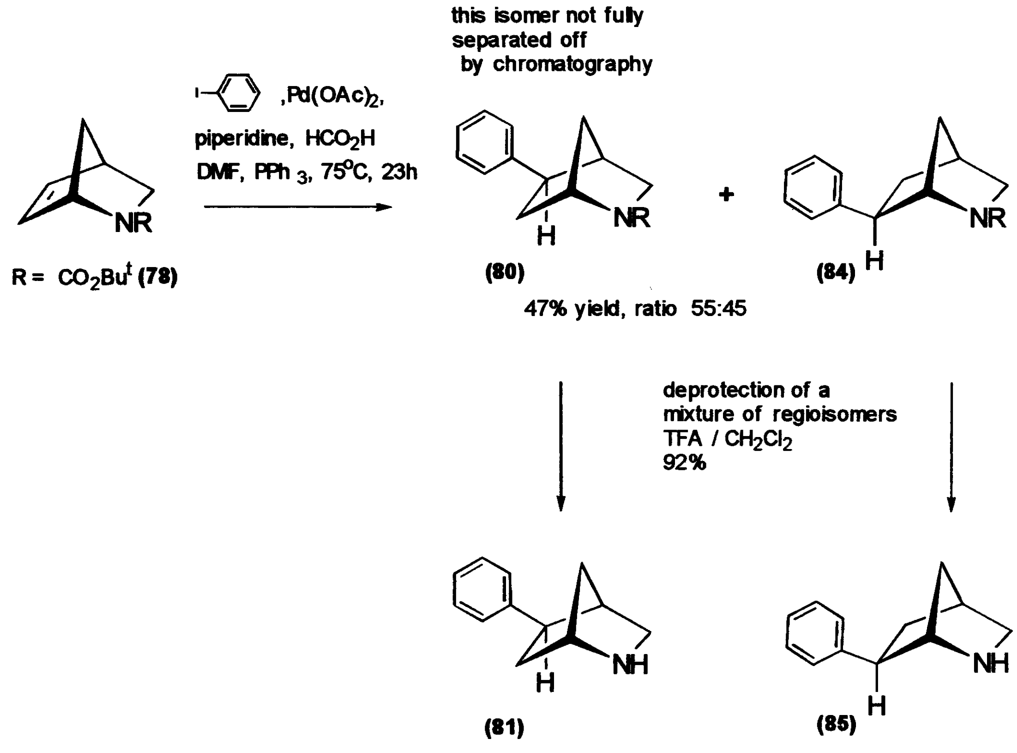
Compound	**Reaction conditions**	**Products and ratio**[a]	**yield**[b]
74	**75** (3 eq.), $Pd(PPh_3)_4$, piperidine, HCO_2H, DMF, 75 C, 21h	**76 : 77** 60 : 40	95%
78	**75** (3 eq.), $Pd(PPh_3)_4$, piperidine, HCO_2H, DMF, 75 C, 24h	**79 : 82** 55 : 45	85%
78	**75** (3 eq.), $Pd_2(dba)_3$, piperidine, HCO_2H, ethyl ethanoate, 75 C, 22h	**79 : 82** 45 : 55	68%
78	**75** (1 eq.), $Pd(OAc)_2$ $(PPh_3)_2$, piperidine, HCO_2H, DMF, 80 C, 24h	**79 : 82** *ca.* 65 : 35	40%
78	**75** (1 eq.), $Pd(OAc)_2$ $(PPh_3)_2$, piperidine, HCO_2H, DMF, 80 C, 5h[c]	**79 : 82** complex[d]	46%[d]
78	**83** (3 eq.), $Pd(OAc)_2$ $(PPh_3)_2$, piperidine, HCO_2H, DMF, 80 C, 23h	**80 : 84** 55 : 45	47%

a. Ratios are measured from ^1H NMR spectra of crude reaction products and are approximate owing to peak overlap with minor by-products of the reaction work-up; they are considered accurate to *ca.* ± 5%.
b. Overall yields are of isolated material after chromatography, except for the fifth entry in the table.
c. Conditions as used in ref. 41. Conditions were not optimised in our work.
d. The ^1H NMR spectrum of the crude product was complex but showed clear evidence of both **(79)** and **(82)** (overall yield estimated by integration relative to an internal standard); **(79)** and **(82)** were also identified after chromatography.

The use of $Pd_2(dba)_3$ led to a decrease in yield; this may have been due to the increased steric bulk of the catalyst not being well tolerated by the substrate. Entry 5 in the table (using $Pd(OAc)_2(PPh_3)_2$ as catalyst and 1 equivalent of **(75)** in reaction for 5 hours at 80°C) was an exact duplication of the conditions used by the Maier group. The crude ^1H NMR spectrum, although complex, clearly showed the presence of both regioisomers which were then both isolated by column chromatography. The yield was estimated at 40 ± 10% using an internal standard (CH_2Cl_2), but this decreased to 25% after chromatography. An improved overall yield of 40% was achieved by allowing the reaction to continue for 24 hours. The crude reaction spectrum was clear enough to assign a ratio of *ca* 65:35 for **(79)**:**(82)**. In our hands, $Pd(PPh_3)_4$ was the most effective catalyst for this reaction and an excess of **(75)** improved the yield.

We also carried out a reductive Heck reaction on **(78)** with iodobenzene **(83)**, this being an additional check on the claimed formation of a single regioisomer in the Maier work (Scheme 2.17). The reaction again gave both regioisomers in a ratio of 55:45 for **(80)**:**(84)** (Table 2.16) as calculated from the crude NMR spectrum (Figure 2.18). The regioisomers were very difficult to separate by flash chromatography; a pure sample of **(84)** was obtained, but **(80)** was eluted mixed with **(84)**. It was, however, possible to separate the two compounds once they had undergone deprotection.

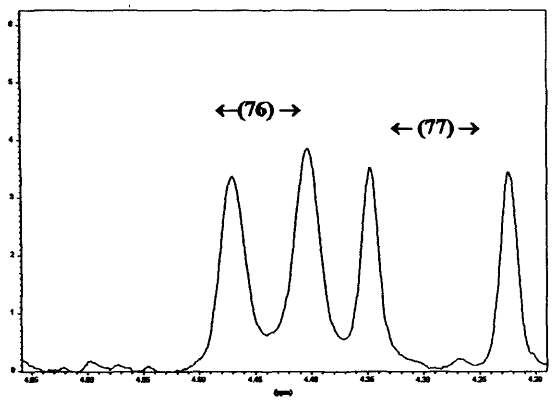
Scheme 2.17

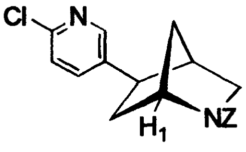

this isomer not fully separated off by chromatography
,Pd(OAc)2,
piperidine, HCO2H
DMF, PPh 3, 75°C, 23h
NR
R = CO2Bu^t (78)
H
NR
(80)
+
NR
(84)
H
47% yield, ratio 55:45
deprotection of a mixture of regioisomers
TFA / CH2Cl2
92%
H
NH
(81)
NH
(85)
H

A full investigation of comparative ^{13}C NMR data recorded by ourselves and the Maier group was undertaken and the results are summarised in Table 2.19. Spectra for *N*-protected amines were complicated by the presence of two rotamers both in ^1H and

Figure 2.18 ^{1}H NMR spectra of crude reductive Heck reaction products showing peaks corresponding to the two rotamers of H_1

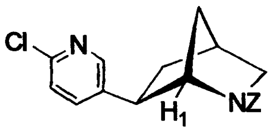
From Scheme 2.11





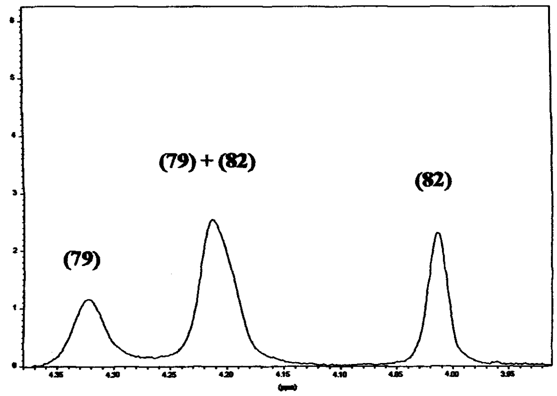
(76)

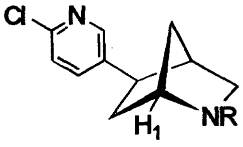
ratio 60 : 40



(77) Z= CO_2CH_2Ph

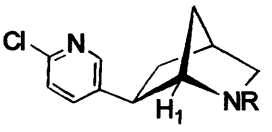
From Scheme 2.15





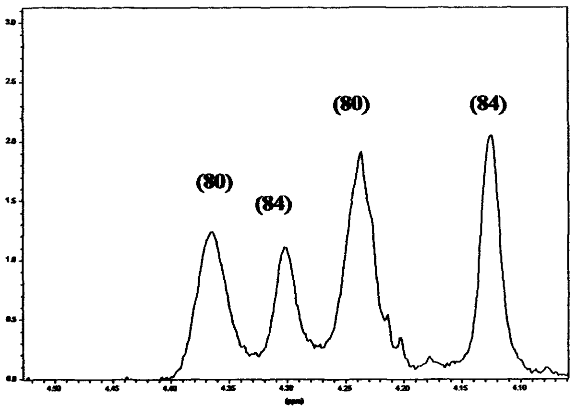
(79)

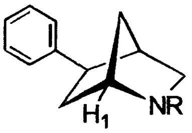
ratio 55 : 45



(82) R= $CO_2C(CH_3)_3$

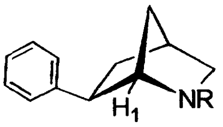
From Scheme 2.17





(80)

ratio 55 : 45



(84) R= $CO_2C(CH_3)_3$

^{13}C NMR. ^{13}C and ^{1}H NMR signals were matched for each molecule using CH COSY spectra. In the case of secondary amines, careful basification of NMR samples was necessary to ensure accurate chemical shifts; traces of acid shifted δ-values downfield. Chemical shifts for each common carbon atom in the 5-*exo*-series of molecules showed similar values; this was reflected in the 6-series.

Table 2.19 Comparative ^{13}C NMR data

	5-Clpyr *N*-CO$_2$Bn (**76**)*	5-Clpyr *N*-BOC (**79**)*	5-Clpyr *N*-H (**53**)*	5-phenyl *N*-BOC (**80**)*	5-phenyl *N*-H (**81**)*	6-Clpyr *N*-CO$_2$Bn (**77**)*	6-Clpyr *N*-BOC (**82**)*	6-Clpyr *N*-H (**54**)*	6-phenyl *N*-BOC (**84**)*	6-phenyl *N*-H (**85**)*	Clpyr *N*-BOC ‡	Clpyr *N*-H ‡	phenyl *N*-BOC ‡	phenyl *N*-H ‡
C$_1$	56.9 57.1	56.2 57.2	56.4	56.3 57.3	56.1	61.2 61.8	60.6 62.3	61.3	61.2 62.6	61.7	60.5 62.2	61.2	62.2 63.6	62.6
C$_3$	53.4 53.5	53.1 53.6	51.4	53.3 53.8	52.1	52.4 52.5	52.0 52.6	50.2	52.2 52.7	53.4	52.0 52.5	50.3	53.1 53.7	52.5
C$_4$	43.3	43.4	42.3$^{\#}$	43.0 43.6	42.9	37.0 37.6	37.1 37.6	36.8	37.0 37.5	37.0	37.0 37.6	36.8	39.7$^{\#}$ 39.9$^{\#}$	37.7$^{\#}$
C$_5$	42.6	42.6 42.7	42.9$^{\#}$	45.4 45.6	46.1	34.6$^{\#}$ 35.0$^{\#}$	34.6$^{\#}$ 34.8$^{\#}$	36.3	34.5$^{\#}$ 34.7$^{\#}$	36.6$^{\#}$	34.4† 34.7†	36.4	38.0$^{\#}$ 38.5$^{\#}$	37.3$^{\#}$
C$_6$	39.4 39.9	39.5 39.9	39.7	39.5 39.9	41.4	45.2 45.9	45.2 45.8	46.3	48.3 49.0	50.8	45.1 45.7	46.7	46.4 46.6	46.6
C$_7$	35.3 35.8	35.2 35.7	35.6	35.2 35.7	35.6	34.4$^{\#}$	33.9$^{\#}$ 34.5$^{\#}$	35.5	34.0$^{\#}$ 34.4$^{\#}$	35.4$^{\#}$	34.4† 34.7†	35.4	35.0$^{\#}$ 35.3$^{\#}$	36.3$^{\#}$
C$_{6'}$	148.4 148.5	148.4 148.5	148.5	-	-	148.6 148.8	148.5 149.0	148.7	-	-	148.6	148.7	-	-
C$_{5'}$	139.3	139.5	139.4	-	-	137.0 137.2	137.2	138.0	-	-	138.0	138.4	-	-
C$_{4'}$	136.9	137.2	137.2	-	-	137.5 137.9	137.3 138.0	137.5	-	-	137.3 137.4	137.4	-	-
C$_{3'}$	124.0	124.0	124.0	-	-	124.0	123.9 124.0	123.9	-	-	124.0	123.9	-	-
C$_{2'}$	149.3	149.2	149.2	-	-	149.4	149.3	149.2	-	-	149.1	149.0	-	-
PhCH$_2$	66.6 66.8	-	-	-	-	66.7 66.9	-	-	-	-	-	-		
aryl	127.9 128.0 128.5 137.2	-	-	126.0 126.8 128.5 145.4	125.8 126.9 128.4 146.0	127.8§ 128.0 128.1 128.5 128.6 136.8	-	-	126.0 126.1 127.2 127.3 128.3 128.4 143.0 143.1	125.9 127.2 128.4 144.6	-	-	127.1 127.9 128.3 129.55 129.61 144.2 146.5	127.1 127.9 129.6 146.4
C-Me$_3$	-	79.4	-	79.0 79.2	-	-	79.4 79.7	-	79.1 79.3	-	79.4	-	79.9 80.2	
CH$_3$	-	28.5	-	28.6 28.7	-	-	28.55 28.62	-	29.0 29.1	-	28.46 28.53	-	29.6 29.9	
C=O	154.5 154.8	154.2 154.5	-	154.7	-	154.4 154.5	154.2 154.3	-	154.2 154.5	-	no data	-	no data	

* data from this work $^{\#}$ values may be interchanged ‡ data and compound numbers from reference 41 - plausible assignments are given here but these are conjectural (^{13}C shifts are rounded to 1 decimal place except where 2 signals would otherwise appear to be identical) † signals for C$_5$ and C$_7$ cannot be assigned with confidence § The duplicate aryl carbon signals are not all resolved

For the *N*-BOC-protected chloropyridyl compounds, comparison of our NMR values with those of the claimed 5-*exo*-isomer[41] reveal that the Maier compound actually correlates more closely to our 6-*exo*-isomer **(82)**. This correlation also holds for the secondary amine.

We must conclude that both isomers were formed by the other group, but that this was not realised. This omission may been due to the complicated nature of the ^{1}H NMR spectrum of the crude product and difficulty in the visualisation of the 6-*exo*-isomer **(82)** after separation by TLC; this isomer did not stain in PMA, however both isomers were visualised by U.V. light. The isolation of a single *N*-tosyl-5-*exo*-derivative in crystalline form must have been the result of either adventitious separation at some stage in the reaction sequence or the preferential crystallisation of one isomer over the other. It would be difficult to reproduce and interpret the Maier results without access to their full experimental records and NMR spectra.

Turning to the *N*-BOC-protected phenyl compounds, the Maier group claimed 5-*exo*-compound shows signals largely similar to our 6-*exo*-isomer **(84)** although there may be some signals relating to **(80)** present. Duplication of the aryl signals in their case especially is more characteristic of the 6-*exo*-isomer **(84)** in which the proximity of the phenyl ring to the slowly-rotating urethane N-CO bond strongly influences the aryl group (duplication is not seen in the 5-*exo*-isomers). The signals for the secondary amine[41] also show more in common with our 6-*exo*-isomer.

In conclusion, the results of the Maier group must have resulted from adventitious or incomplete separation of regioisomers. The presence of two compounds in the crude reaction mixture may have been missed due to the complexity of the NMR spectra and the difficulty in separation of the compounds by chromatography hindered by the lack of response by both **(82)** and **(84)** to PMA stain. All of the compounds made by us were shown to be stable to column chromatography.

Our work shows that the choice of catalyst and reaction conditions does not significantly influence regioselectivity and that there is no evidence for any ground-state orbital interactions of the substrate with the catalyst. Finally, we saw no evidence for the presence of *endo*-isomers in our experiments.

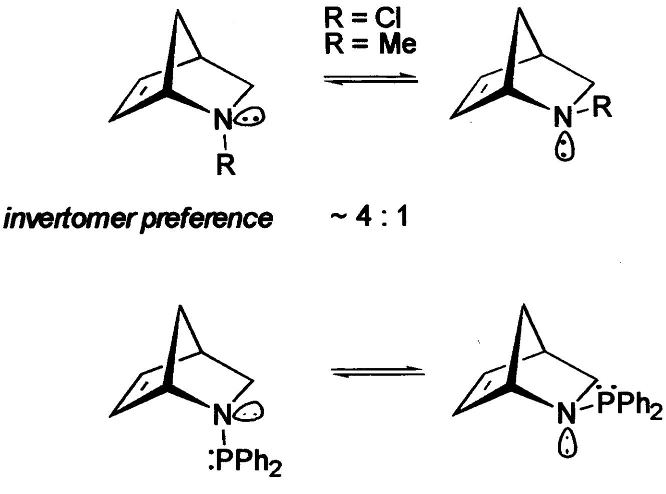
CHAPTER 3

Synthesis of Endo-5-(and 6-)
(2'-chloro-5'-pyridyl)-2-azabicylo-[2.2.1]heptanes

3.1 Attempt to Influence Facial Selectivity in the Reductive Heck Reaction on 2-Azabicyclo[2.2.1]hept-5-ene Derivatives

On completion of the synthesis of *exo*-chloropyridyl-substituted azanorbornyl compounds **(53)** and **(54)** *via* the reductive Heck reaction, it was then necessary to devise a means of connecting the chloropyridyl ring to the *endo*- face of the azabicycle. One initial strategy was to attach a group to the azabicycle which might co-ordinate to the palladium catalyst during a reductive Heck reaction and bring the aryl group into the *endo*- face (the lone pair on the nitrogen was ineffective in this role as described in Chapter 2). Malpass and Tweddle[42] synthesised 2-azabicyclo[2.2.1]hept-5-ene analogues with different substituents on nitrogen in order to measure invertomer preferences (Figure 3.1). In the case of *N*-chloro- and *N*-methyl substituents, an approximate 4:1 preference for the *endo*- orientation was observed by low temperature ^{1}H NMR spectroscopy.

Figure 3.1

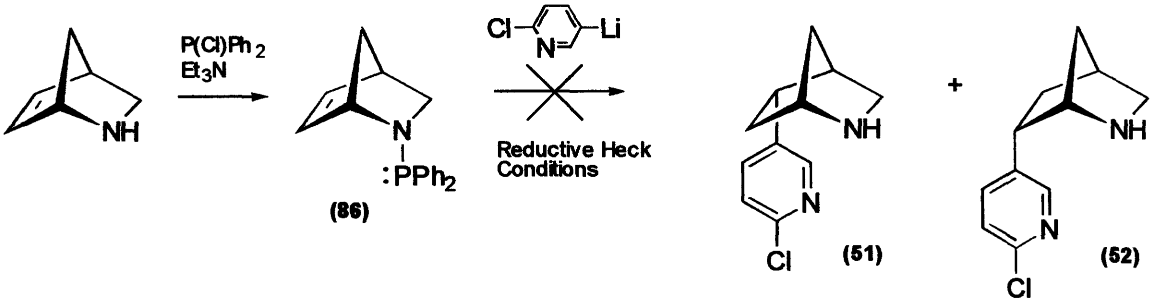


endo-**(86)** exo-**(86)**

It was envisaged that a diphenylphosphine moiety attached to the nitrogen would prefer the *endo*- orientation and the lone-pair of electrons associated with the phosphorus would then be available for co-ordination to the palladium catalyst.

Synthesis of **(86)** was attempted as shown in Scheme 3.2. The secondary amine, 2-azabicyclo[2.2.1]heptane, was generated from cyclopentadiene and methyliminium hydrochloride, as discussed in Chapter 2, extracted into dichloromethane and dried over molecular sieves. A known quantity of the amine was placed in an NMR tube, diphenylphosphine chloride added together with deuterated chloroform and the sample monitored by NMR spectroscopy. Formation of a product was suggested by a new peak at 45ppm in the ^{31}P NMR spectrum, but it proved impossible to isolate this compound. A 'one-pot' reaction was then attempted where any **(86)** generated was subjected to reductive Heck conditions with 2-chloro-5-iodopyridine. None of the expected Heck adducts having either the *endo-* or *exo-* configuration were obtained.

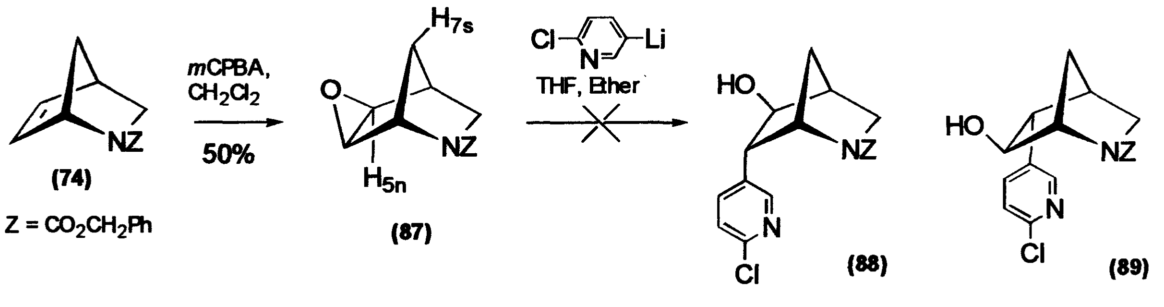
Scheme 3.2


P(Cl)Ph2
Et3N
NH
N
:PPh2
(86)
Cl
N
Li
Reductive Heck
Conditions
NH
N
Cl
(51)
+
NH
N
Cl
(52)

3.2 Attempted Synthesis via an Exo-5,6- epoxide

A second strategy directed towards the synthesis of the *endo*-chloropyridyl analogues involved the formation of the *exo-* epoxide **(87)** (Scheme 3.3) which would be ring-opened using a chloropyridyl lithium reagent. The regioselectivity of ring-opening would be unpredictable, but both regioisomers were required. The adducts **(88)** and **(89)** would then be dehydrated, hydrogenation from the *exo-* face giving the *N*-protected derivatives of the *endo-* substituted targets **(51)** and **(52)**.

Scheme 3.3

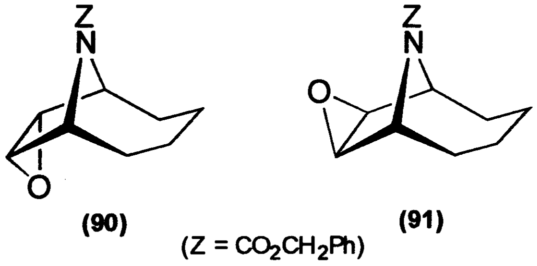

NZ
(74)
Z = CO2CH2Ph
mCPBA,
CH2Cl2
50%
H7s
O
NZ
H5n
(87)
Cl
N
Li
THF, Ether
HO
NZ
N
Cl
(88)
HO
NZ
N
Cl
(89)

The epoxide **(87)**, originally made by Carroll,[35] was generated using *m*CPBA in dichloromethane in 50% yield. Limited spectroscopic analysis was provided[35] so a thorough spectroscopic evaluation of this compound was carried out using HH COSY spectra and selective double-irradiation experiments, enabling all of the peaks seen in the ^{1}H NMR spectrum to be assigned (see Chapter 7). The proton at H_5 was identified as a broad doublet at δ3.26; double irradiation of H_{7s} resulted in a sharpening of this signal into a doublet of doublets ($J_{5,6}$ = 3.5 Hz, $J_{4,5}$ = <1 Hz). This observation of 'W'-coupling to H_{7s} confirmed the $H_{5\text{-endo}}$ assignment and therefore placed the epoxide in the *exo-* configuration.

Butyl lithium was added dropwise to a solution of 2-chloro-5-iodopyridine in diethyl ether/THF at –78°C to form the aryl lithium reagent with which to attack the epoxide. A solution of the epoxide **(87)** in diethyl ether was then added dropwise to the reaction flask and stirred, initially at -78 °C. No reaction occurred despite using higher reaction temperatures over two separate experiments. It was concluded that the aryl anion was not a good enough nucleophile to overcome the steric constraints associated with *endo-* attack of the epoxide.

This approach could be explored further by attempting to synthesise the *endo-* epoxide for example, by using different epoxide-generating reagents; the *endo-* epoxide **(90)** was shown to be more reactive towards nucleophilic attack than its *exo-* analogue **(91)** in reactions carried out by Malpass and Justice[43] (Figure 3.4).

Figure 3.4

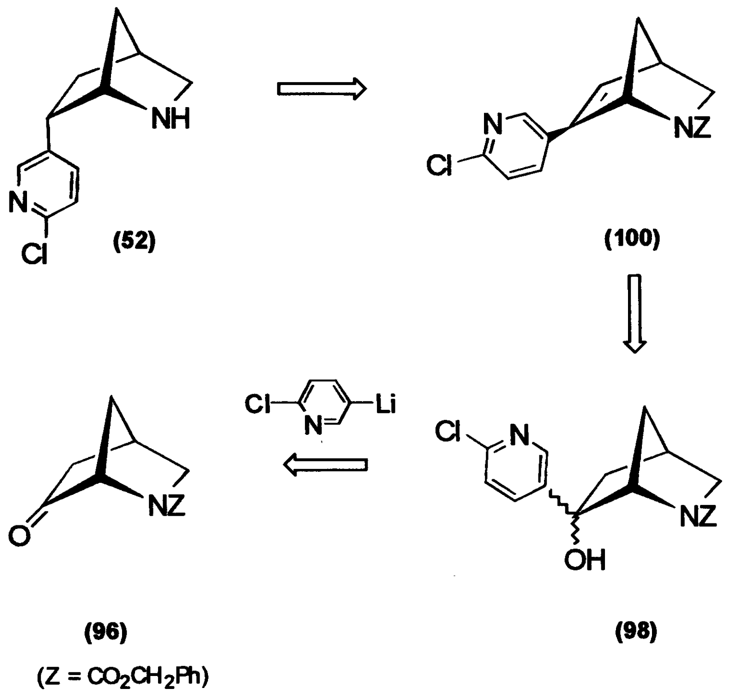


We chose not to explore this avenue, however, in favour of another route detailed on the next page.

3.3 Synthesis of Endo-5- and Endo-6- Substituted Azanorbornanes From 5-Keto- and 6-Keto- Precursors

Our third and successful route to the *endo*- chloropyridyl regioisomers was *via* nucleophilic attack on the appropriate ketones.[38] Retrosynthetic analysis of the route to the 6-*endo*-chloropyridyl-substituted azabicycle **(52)** is shown in Scheme 3.5.

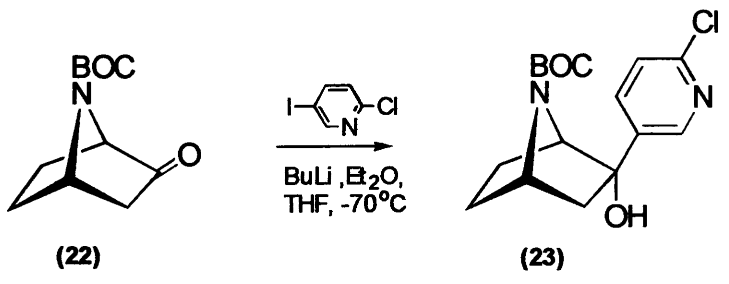
Scheme 3.5


NH
(52)
Cl
N
NZ
(100)
Cl
N
Cl
N
Li
O
NZ
(96)
(Z = CO2CH2Ph)
Cl
N
OH
NZ
(98)

The ketone is attacked with lithiated chloropyridine and the resultant tertiary alcohol dehydrated to give an olefin. Hydrogenation of the olefin should occur from the *exo*-face of the bicycle to yield the *endo*- regioisomer **(52)**.

Nucleophilic attack of a ketone with a lithiated chloropyridine was successfully utilised by Fletcher[10] in his synthesis of epibatidine as discussed in Chapter 1 (Scheme 3.6).

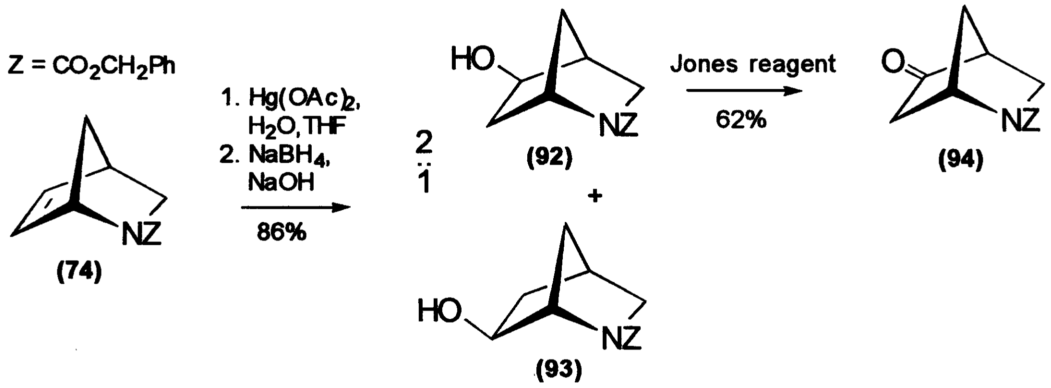
Scheme 3.6


BOC
N
O
(22)
I
Cl
N
BuLi ,Et2O,
THF, -70°C
BOC
N
Cl
N
OH
(23)

Synthesis of Ketones (94) and (96)

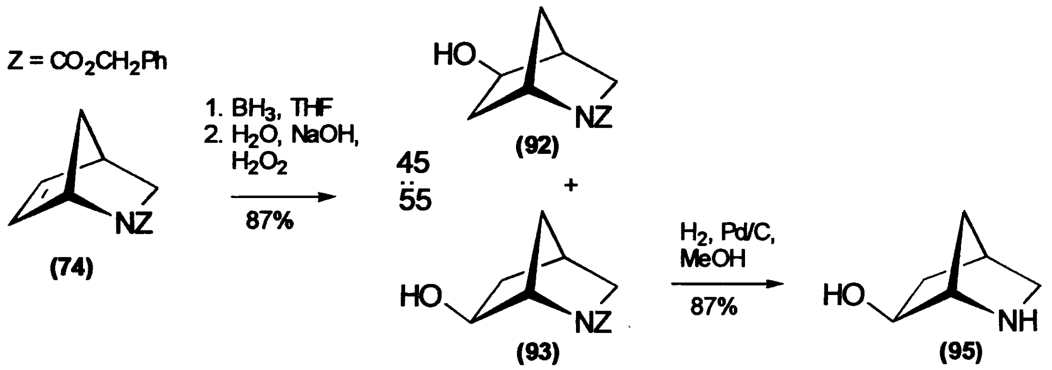
The ketone **(94)** was originally made by Carroll,[35] as illustrated in Scheme 3.7. The alkene **(74)** was hydrated *via* oxymercuration to yield the alcohols **(92)** and **(93)**, in a 2:1 ratio. It was noted, however, that only the C_5-alcohol was examined by ^1H NMR spectroscopy, and was not characterised fully. Alcohol **(92)** was oxidised to the ketone **(94)** using Jones' reagent.

Scheme 3.7


Z = CO2CH2Ph
(74)
1. Hg(OAc)2, H2O,THF
2. NaBH4, NaOH
86%
2 : 1
HO
NZ
(92)
+
HO
NZ
(93)
Jones reagent
62%
O
NZ
(94)

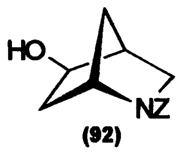
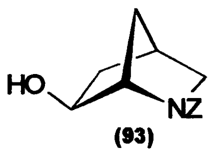
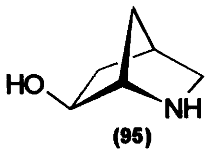
We chose to use diborane, this reagent being less toxic than mercuric acetate (Scheme 3.8). The alcohols **(92)** and **(93)** were produced in a 45:55 ratio in 87% yield after column chromatography. It was not possible to accurately determine the ratio of alcohols from the ^1H NMR spectrum of the crude product owing to peak overlap, however the alcohols were almost completely separated on the column. The ^1H NMR spectra of the two alcohols were complicated by the presence of two rotamers and, in order to be certain of signal assignments, **(93)** was deprotected using hydrogen over a palladium catalyst.

Scheme 3.8


Z = CO2CH2Ph
(74)
1. BH3, THF
2. H2O, NaOH, H2O2
87%
45 : 55
HO
NZ
(92)
+
HO
NZ
(93)
H2, Pd/C, MeOH
87%
HO
NH
(95)

The secondary amine (95) was fully characterised by ^{1}H NMR and HH COSY spectra. The signal for H_{5x} was identified at δ 1.36; vicinal coupling to H_4 was measured at J = 5.5 Hz, geminal coupling $J_{5x,5n}$ was 13.0 Hz. H_{6n} was identified by 'W' coupling to H_{7s} and no significant coupling interaction was seen between H_6 and H_1 confirming that H_6 was *endo-* and the 6-hydroxy group was *exo-*.

Table 3.9 ^{1}H NMR signal and coupling constant data

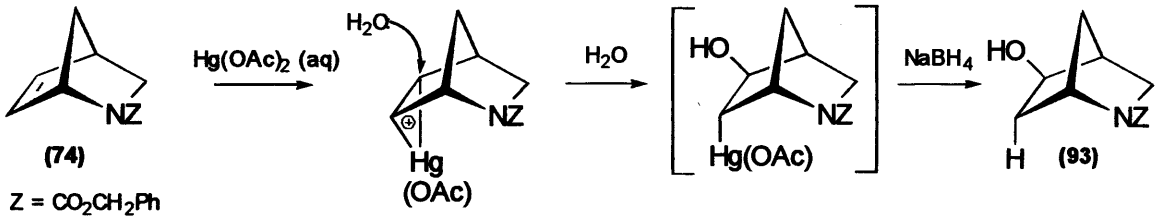
	 **(92)** (Z = CO_2CH_2Ph)			 **(93)**		 **(95)**	
Signal	**δ (ppm)**		**Signal**	**δ (ppm)**		**δ (ppm)**	
H_1	**4.27**, 4.32	bs	H_1	**4.14**, 4.08	bs	3.27	bs
H_{3x}	**3.27**, 3.28	d	H_{3x}	**3.22**, 3.23	ddd	2.78	ddd
H_{3n}	**2.93**, 2.91	dd	H_{3n}	**2.89**, 2.91	dd	2.34-2.44	m
H_4	*2.49*	bs	H_4	*2.56*	bs	2.34-2.44	m
H_{5n}	*4.02*	d	H_{5x}	**1.48**, 1.45	dddd	1.36	dddd
H_{6x}	**1.47**, 1.49	dddd	H_{5n}	**1.83**, 1.84	ddd	1.81	ddd
H_{6n}	**2.07**, 2.15	ddd	H_{6n}	**4.04**, 3.98	d	3.83	ddd
H_{7a}	*1.85*	d	H_{7a}	**1.82**, 1.78	m	1.70	dddd
H_{7s}	**1.59**, 1.57	ddddd	H_{7s}	**1.54**, 1.57	d	1.44	ddddd
Benzylic	*5.05-5.20*	m	Benzylic	*5.05-5.20*	m		
Phenyl	*7.25-7.50*	m	Phenyl	*7.25-7.50*	m		
		J values (Hz)			**J values (Hz)**		**J values (Hz)**
	${}^{4}J_{1,4}$	<1		${}^{4}J_{1,4}$	<1	${}^{3}J_{1,6n}$	~1.0
	${}^{3}J_{1,6x}$	2.5		${}^{3}J_{1,7a}$	~1	${}^{3}J_{1,7a}$	~1.5
	${}^{3}J_{1,6n}$	<1		${}^{3}J_{1,7s}$	~1	${}^{3}J_{1,7s}$	~1.5
	${}^{3}J_{1,7a}$	~1.5		${}^{2}J_{3,3}$	9.0	${}^{2}J_{3,3}$	9.5
	${}^{3}J_{1,7s}$	~1.5		${}^{3}J_{3x,4}$	3.0	${}^{3}J_{3x,4}$	~3.0
	${}^{2}J_{3,3}$	10.0		${}^{4}J_{3x,5x}$	3.0	${}^{4}J_{3x,5x}$	~3.0
	${}^{3}J_{3x,4}$	3.0		${}^{4}J_{3n,7s}$	<1	${}^{4}J_{3n,7a}$	1.5
	${}^{4}J_{3n,7a}$	~1		${}^{4}J_{3n,7a}$	1.5	${}^{3}J_{4,5x}$	5.5
	${}^{3}J_{4,7a}$	1.5		${}^{3}J_{4,5x}$	5.0	${}^{3}J_{4,7s}$	~1.5
	${}^{3}J_{4,7s}$	~1.5		${}^{3}J_{4,7s}$	~1	${}^{3}J_{4,7a}$	~3.0
	${}^{3}J_{4,5n}$	<1		${}^{3}J_{4,7a}$	~1	${}^{2}J_{5,5}$	13.0
	${}^{3}J_{5n,6n}$	6.5		${}^{2}J_{5,5}$	13.5	${}^{3}J_{5x,6n}$	3.0
	${}^{3}J_{5n,6x}$	2.5		${}^{3}J_{5x,6n}$	2.5	${}^{3}J_{5n,6n}$	7.0
	${}^{4}J_{5n,7s}$	2.5		${}^{3}J_{5n,6n}$	7.0	${}^{4}J_{5n,7s}$	2.5
	${}^{2}J_{6,6}$	13.5		${}^{4}J_{5n,7s}$	4.0	${}^{4}J_{6n,7s}$	1.5
	${}^{4}J_{6n,7s}$	2.5		${}^{2}J_{7,7}$	~11	${}^{2}J_{7,7}$	10.0
	${}^{2}J_{7,7}$	~10.0					
	${}^{4}J_{6x,7a}$	~1					

Both (92) and (93) were observed as two rotamers by ^{1}H NMR spectroscopy. Where the two rotamer signals are distinguishable, the major rotamer is shown in bold type, the minor in standard type. Signals common to both rotamers are listed in italics.

Alcohols **(92)** and **(93)** were also fully characterised by ^1H NMR spectroscopy and coupling interactions were confirmed by HH COSY and selective double-irradiation experiments. The *exo-* orientation of the alcohol group in **(92)** was confirmed by observation of 'W'-coupling between H_{5n} and H_{7s} and no significant vicinal interaction between H_4 and H_5. Furthermore, double irradiation of H_{5n} led to a sharpening of the signals for the -OH proton and H_{7s}. A full evaluation of the ^1H NMR data from Scheme 3.8 is illustrated in Table 3.9.

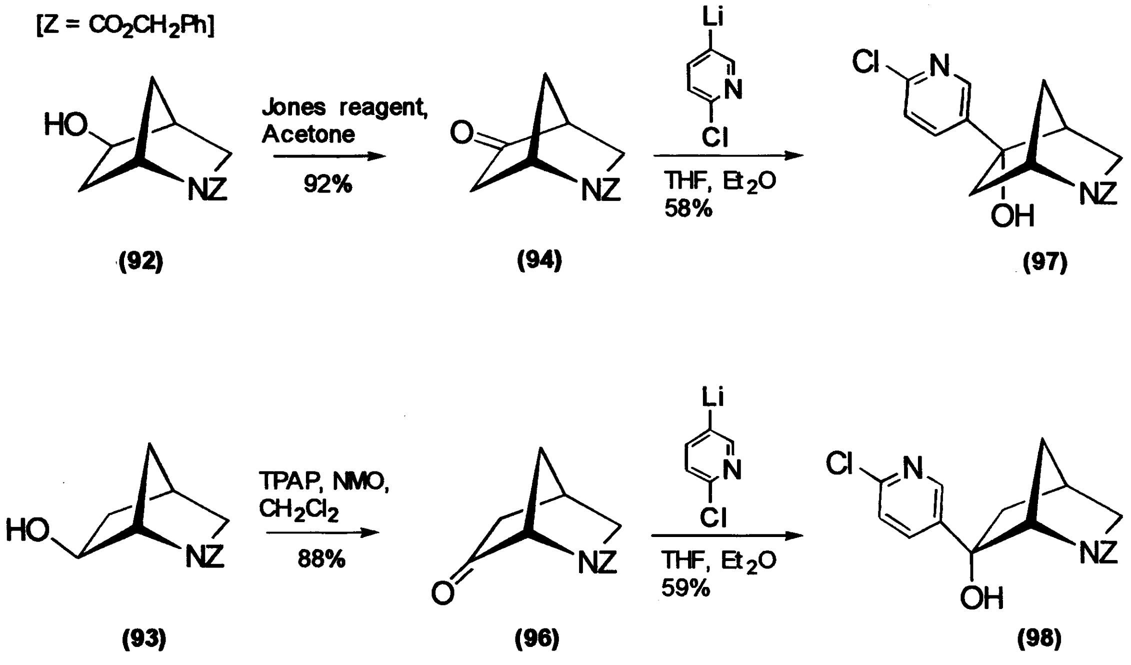
It is interesting to note the differing ratios of regioisomers formed on hydration of the alkene **(74)** depending on which reagent is used. In the case of the mercuric acetate, a 2:1 excess of the C_5 alcohol was formed[35] compared with an almost equal distribution of regioisomers with borane. The regioselectivity shown by mercuric acetate can be rationalised by considering the mechanism of the reaction. Mercuric acetate adds across the double bond forming a bridged cation (Scheme 3.10). Water then attacks the carbon atom best able to support the positive charge, which in this case appears to be C_5 (C_6 may be more electron-deficient owing to the electron-withdrawing effect of the urethane group).

Scheme 3.10



Steric factors predominate in the addition of borane to a double bond and in the case of **(74)**, there is little steric difference between C_5 and C_6; this explains the near equal distribution of regioisomers.

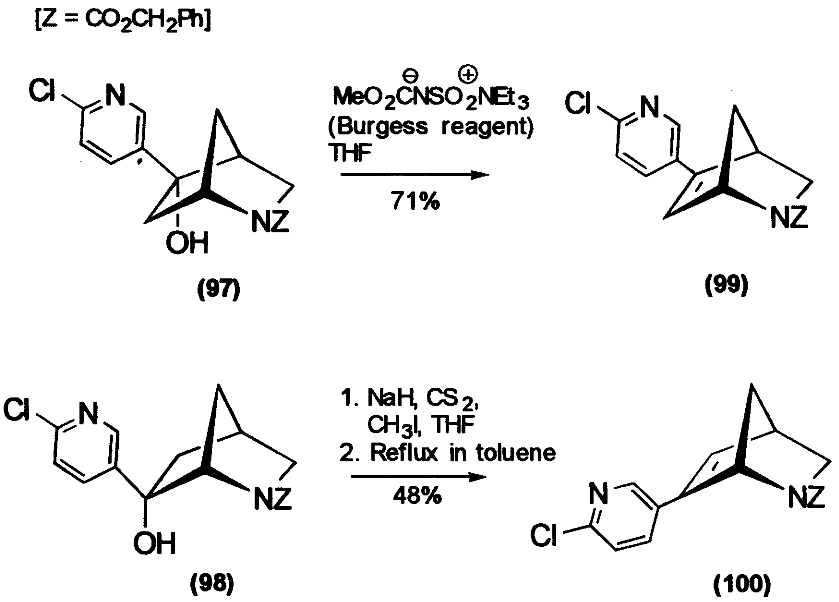
Scheme 3.11



Oxidation of **(92)** was accomplished in the best yield using Jones' reagent (Scheme 3.11) and, in the case of **(93)**, N-methylmorpholine-N-oxide catalysed by tetrapropylammonium perruthenate was most effective. Both reactions were complete in 30 minutes and good yields were recorded after column chromatograpy. Infra-red spectroscopy confirmed the presence of new carbonyl groups at 1755-1760cm^{-1}. Nucleophilic attack on the ketone groups was carried out with a 5-lithiated-2-chloropyridine reagent generated *in situ* from 2-chloro-5-iodopyridine and *n*-butyllithium at –78°C. Each of the adducts **(97)** and **(98)** appeared to be predominately one stereoisomer. Determination of whether the chloropyridine groups were oriented *exo-* or *endo-* proved to be difficult. As the next step in the syntheses was to be removal of the hydroxyl groups by dehydration, and loss of configuration at these sites, determination of the latter was not pursued. However, *exo-* orientations of the aromatic rings were considered to be most likely.

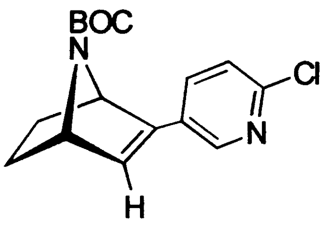
The dehydration steps to form alkenes **(99)** and **(100)** (Scheme 3.12) were not straightforward; several dehydrating agents had to be tried before successful reactions in reasonable yields were achieved. Attempted dehydration involving the conversion of the hydroxyl group into a methyl oxalyl ester followed by radical deoxygenation[44] was unsuccessful in both cases. Dehydration with phosphorus oxychloride produced some alkene product, but in very low yield which could not be improved by variation of the reaction conditions.

Scheme 3.12

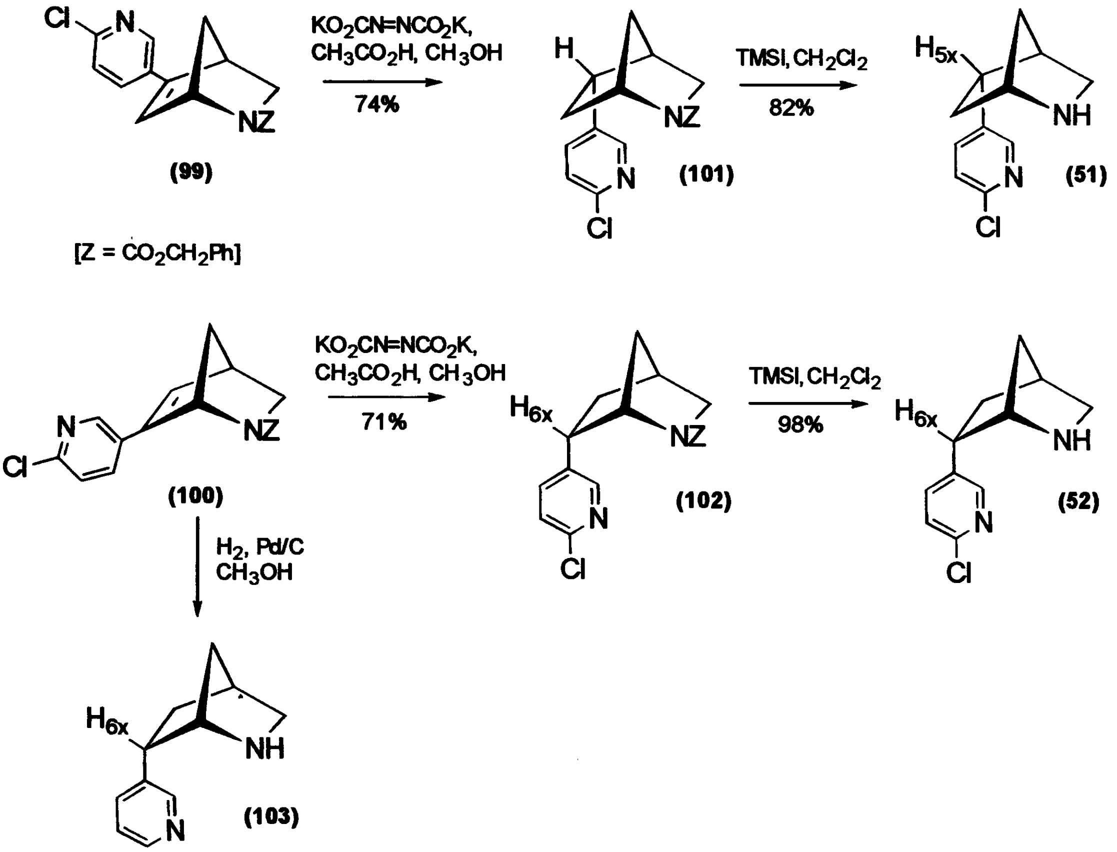

[Z = CO2CH2Ph]
Cl
N
OH
NZ
(97)
MeO2CNSO2NEt3
(Burgess reagent)
THF
71%
Cl
N
NZ
(99)
Cl
N
OH
NZ
(98)
1. NaH, CS2, CH3I, THF
2. Reflux in toluene
48%
N
Cl
NZ
(100)

Successful dehydrations were accomplished by conversion of the hydroxyl group into N-carboxysulfamate esters using (carboxysulfamoyl) triethylammonium hydroxide, inner salt, methyl ester (also known as Burgess's reagent), followed by thermolysis. The yield of **(99)** was good at 71%, but only 10% yield could be achieved for **(100)** by this method. An improved yield of 48% was obtained for **(100)** by conversion of the hydroxyl group into a xanthate using carbon disulfide and methyl iodide in the presence of a base, followed by thermolysis. Dehydration was confirmed by observation of characteristic vinylic proton signals for both regioisomers and their respective rotamers in the range of 6.59-6.69 ppm (c.f. the alkene shown in Figure 3.13 made by Fletcher,[10] where the vinylic proton signal was recorded at 6.55 ppm).

Figure 3.13



Scheme 3.14

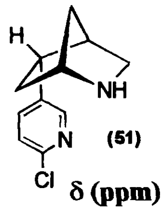
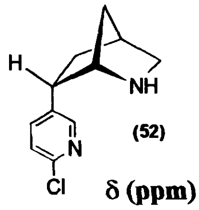
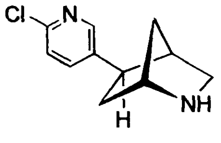
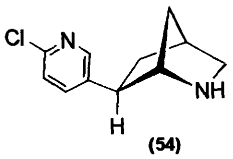

(99)
[Z = CO$_2$CH$_2$Ph]
KO$_2$CN=NCO$_2$K, CH$_3$CO$_2$H, CH$_3$OH
74%
H
NZ
N
Cl
(101)
TMSI, CH$_2$Cl$_2$
82%
H$_{5x}$
NH
(51)
(100)
KO$_2$CN=NCO$_2$K, CH$_3$CO$_2$H, CH$_3$OH
71%
H$_{6x}$
(102)
TMSI, CH$_2$Cl$_2$
98%
(52)
H$_2$, Pd/C CH$_3$OH
(103)

Addition of hydrogen across the double bond of **(100)** was attempted initially using hydrogen gas and a palladium-on-charcoal catalyst (Scheme 3.14). Hydrogenation proceeded from the *exo-* face as anticipated, however this approach resulted in complete, concomitant, removal of the pyridyl chlorine atom. A slower reaction time did not solve this problem. The double bond was therefore saturated using diimide, generated *in situ* from the reaction of potassium azodicarboxylate with glacial acetic acid in methanol; **(101)** and **(102)** were obtained in good yield by this method. ^{1}H NMR spectroscopy confirmed the absence of the vinyl protons and the addition of two new signals for each regioisomer.

Iodotrimethylsilane was used to deprotect the regioisomers giving the target molecules **(51)** and **(52)** as pale yellow oils. Both molecules were fully characterised by ^{1}H NMR and HH COSY spectroscopy. In the case of **(51)**, H_{6x} was identified as a doublet of doublet of doublets at δ2.07 showing geminal coupling to H_{6n} of J = 13.5 Hz and vicinal coupling to H_1 of 3.0 Hz. The proton at C_5 showed a vicinal coupling of J = 4.0 Hz to H_4 and a 'W'-coupling to H_{3x} of J = 2.5 Hz; double irradiation of H_{3x}

resulted in loss of this coupling confirming the proton at C_5 to be in the *exo*-orientation and the chloropyridyl ring *endo*-. The *exo*- orientation of the proton at C_6 for **(52)** was confirmed by a coupling constant of 2.5 Hz to H_1. Signals for H_{5n} and H_{5x} were identified at δ1.46 and δ2.12 respectively with a geminal coupling of J = 12.5 Hz. Finally the proton signals for **(51)** and **(52)** were compared with their *exo*-chloropyridyl epimers to confirm that all four compounds were different (Table 3.15).

Table 3.15 Comparative ^1H NMR data

	 **(51)** **δ (ppm)**		 **(52)** **δ (ppm)**		 **(53)** **δ (ppm)**		 **(54)** **δ (ppm)**	
H_1	3.56	bs	3.44	bs	3.63	bs	3.46	bs
H_{3x}	2.70	d	3.00	ddd	3.03	dd	2.99	bddd
H_{3n}	2.50-2.60	m	2.68	d	2.81	d	2.71	d
H_4	2.50-2.60	m	2.54	bs	2.55	m	2.58	bs
H_{5x}	3.24	dddd	2.12	dddd	--		1.73	dddd
H_{5n}			1.46	ddd	2.97	dd	1.96	ddd
H_{6x}	2.07	ddd	3.25	ddd	1.74	ddd	--	
H_{6n}	1.65	dd			2.09	ddd	2.96	bdd
H_{7a}	1.70-1.74	m	1.75-1.80	m	1.62	AB(b)	1.59 *	AB(b)
H_{7s}	1.70-1.74	m	1.75-1.80	m	1.55	AB(b)	1.52 *	AB(b)
H_6'	8.22	d	8.25	d	8.27	d	8.24	d
H_3'	7.22	d	7.29	d	7.25	dd	7.25	d
H_4'	7.54	ddd	7.53	ddd	7.49	ddd $^{\#}$	7.46	dd

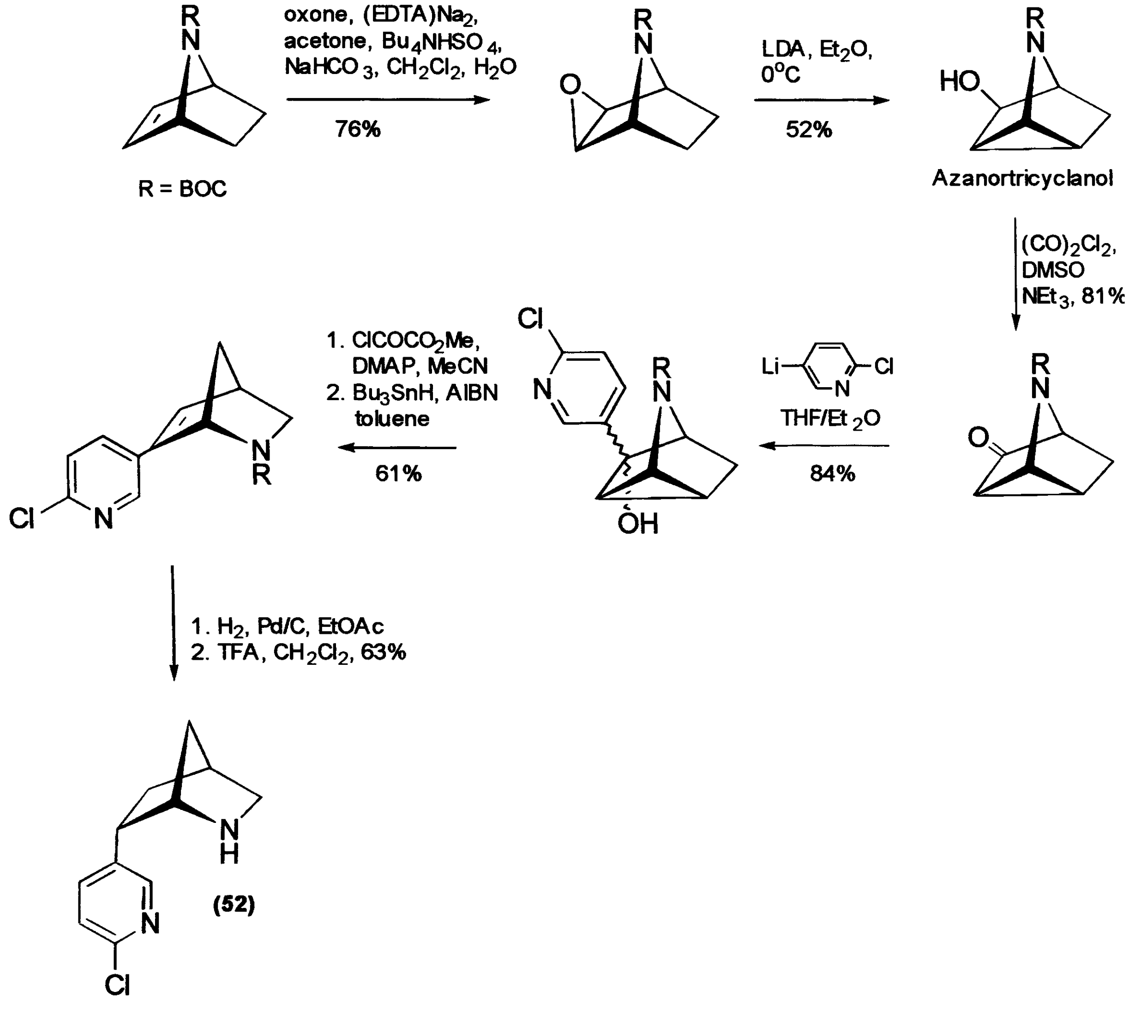
* Interchangeable

$^{\#}$ Coupling observed to H_{5n}

Synthesis of *endo*-6-(2'-Chloro-5'-pyridyl)-2-azabicyclo[2.2.1]heptane (52) by Hodgson

On completion of our synthesis of **(51)** and **(52)**, an alternative synthesis of **(52)** was published by Hodgson and co-workers.[45] This synthesis involved a free-radical induced rearrangement of a 7-azanorbornyl system to a 2-azabicyclonorbornyl derivative (Scheme 3.16). The *N*-BOC protected alkene was made in three steps from *N*-BOC pyrrole and tosyl ethyne. Oxone was used to generate the epoxide which rearranged to an azanortricyclanol on treatment with base. The alcohol functionality was oxidised to a ketone which subsequently suffered nucleophilic attack by 5-lithio-2-chloropyridine to give the tertiary alcohol. This molecule was subjected to radical deoxygenation, upon which, it rearranged to a 2-azanorbornene system. Finally, hydrogenation from the *exo*- face of the bicycle and removal of the *N*-BOC protecting group furnished **(52)**.

Scheme 3.16



R = BOC
oxone, (EDTA)Na2, acetone, Bu4NHSO4, NaHCO3, CH2Cl2, H2O
76%
LDA, Et2O, 0°C
52%
Azanortricyclanol
(CO)2Cl2, DMSO NEt3, 81%
Li–(2-chloropyridin-5-yl) THF/Et2O
84%
1. ClCOCO2Me, DMAP, MeCN
2. Bu3SnH, AIBN toluene
61%
1. H2, Pd/C, EtOAc
2. TFA, CH2Cl2, 63%
(52)

3.4 Pharmacological Test Results

Samples of each of our racemic epibatidine analogues were sent to Astra Arcus for pharmacological testing on rat hippocampal membrane tissue.[46] The molecules were tested for their ability to displace ^{125}I-labelled α-bungarotoxin at the nicotinic receptor α7 sub-type and ^{3}H nicotine at the α4 sub-type; affinity values are shown in Table

3.17. The results show that both *endo-* analogues bind as strongly to the receptors as epibatidine. Both *endo-* and *exo*-analogues show good selectivity for α4 *versus* α7. At this point in time, we are awaiting the results of further pharmacological tests on the separate enantiomers of the 5-*endo-* and 6-*endo-* derivatives **(51)** and **(52)** following resolution on a chiral HPLC column.

Table 3.17 Pharmacological testing data - α7 (^{125}I α-bungarotoxin binding to rat hippocampal membranes), α4 (^{3}H nicotine binding to rat cortical membranes).

	α7 Ki (nM)	**α4 Ki (nM)**	**α4/α7**
(-) Epibatidine	3.9; 6.8; 12	0.020	0.0026
(+) Epibatidine	6.3; 3.9	0.020	0.0039
5-*exo* (racemic)	>480; 3300	>1.1; >38*	>0.012
6-*exo* "	>480; 1600	>1.1; >38*	>0.022
5-*endo* "	<4.8; 3.1	0.056	0.018
6-*endo* "	<4.8; 2.0	0.045	0.022

* Approx. 40-50nM.
Test data courtesy of Astra Arcus.

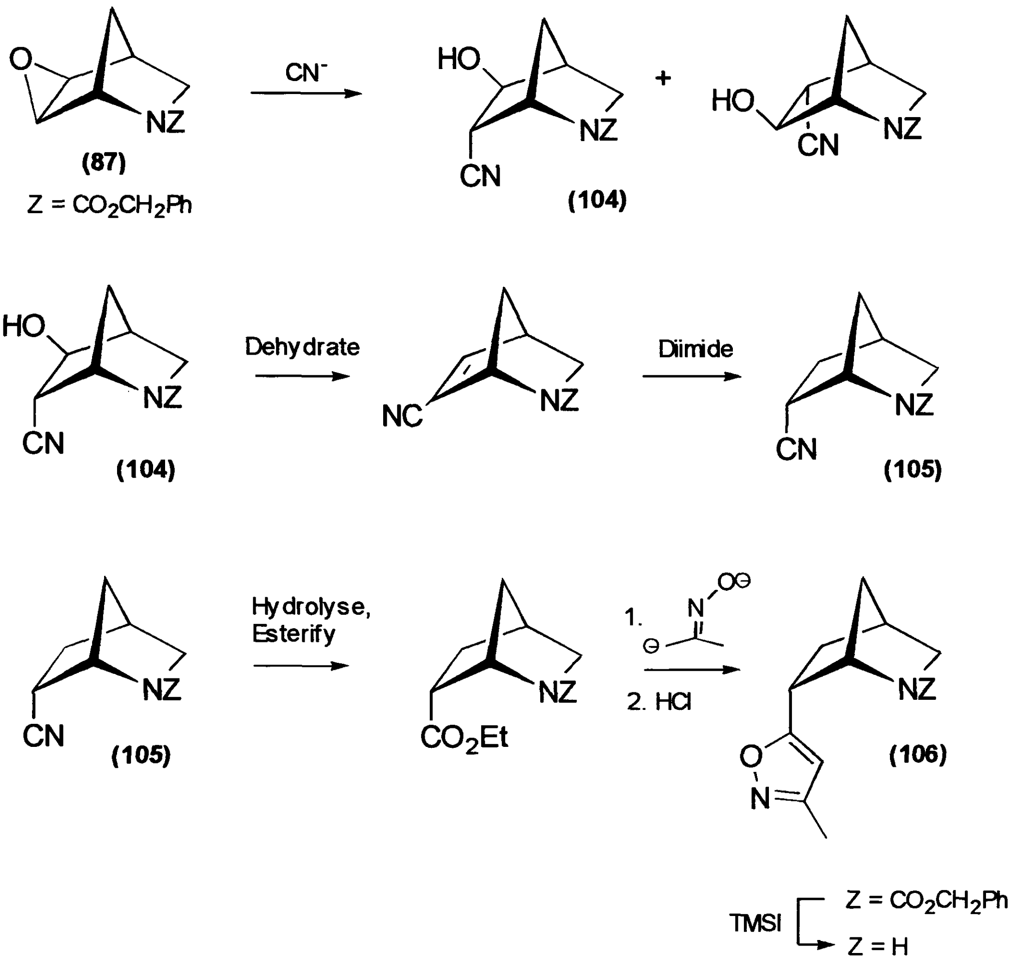
3.5 Future Work

Pharmacological tests have revealed that **(51)** and **(52)** bind strongly at the nicotinic receptor. It should be possible to synthesise molecules of this type with different heterocycles attached, for example with an isoxazole substituent in place of the chloropyridine as illustrated by analogue **(106)** (Scheme 3.18). Scheme 1.24 in Chapter 1 gave examples of three different heterocycles that have been attached to the 2-position of the 7-azanorbornyl system and their effects on binding affinity and selectivity.

Scheme 3.18 summarises the proposed route to **(106)** starting from the epoxide **(87)**. Although it proved impossible to ring-open this epoxide with a chloropyridyl lithium reagent (see Scheme 3.3), a more effective, less bulky nucleophile such as the cyanide anion may be more successful. Ring-opening should give both the C6-nitrile **(104)** and the corresponding C5-nitrile. The hydroxyl group could be removed in a dehydration step and the resulting double bond saturated with diimide.

Heterocycles may then be built up from **(105)**; functional group interconversion of the nitrile group into an ester, followed by reaction with the acetone oxime dianion,[19] then acid catalysed dehydration could lead to the *N*-protected methyl isoxazole derivative **(106)**. It is envisaged that the C_5 substituted analogue could be made in the same way. This synthesis is now underway at Leicester.[47]

Scheme 3.18

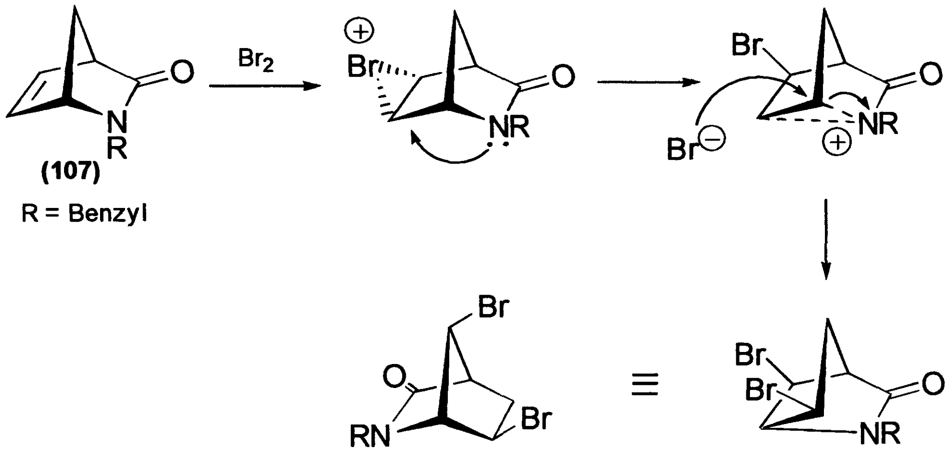

O
NZ
(87)
Z = CO2CH2Ph
CN⁻
HO
NZ
CN
(104)
+
HO
CN
NZ
HO
NZ
CN
(104)
Dehydrate
NC
NZ
Diimide
NZ
CN
(105)
NZ
CN
(105)
Hydrolyse,
Esterify
NZ
CO2Et
1.
N
O⊖
⊖
2. HCl
NZ
O
N
(106)
TMSI
Z = CO2CH2Ph
Z = H

In addition, asymmetric synthesis of both the chloropyridine and isoxazole derivatives should be possible by using a chiral protecting group at the azabicyclic nitrogen; chiral methylbenzylamine protecting groups were discussed in Chapter 2.

3.6 Participation of the Nitrogen Lone Pair in Addition to Π-Bonds.

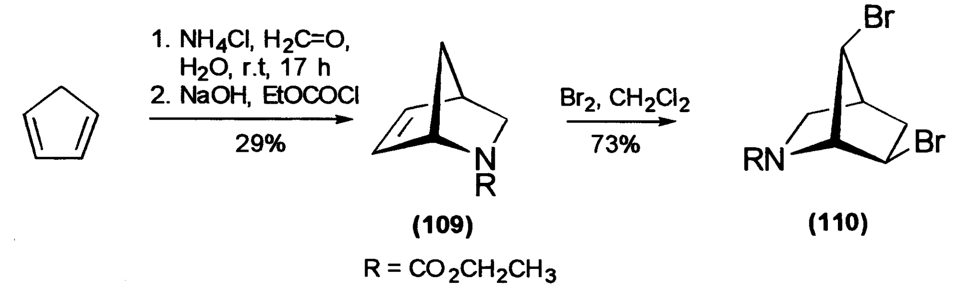
Snider and co-workers[48] have shown that the amido nitrogen of a 2-aza-bicyclo-[2.2.1]hept-5-en-2-one ring system **(107)** can stabilise a developing positive charge during electrophilic addition to a π-bond, leading to skeletal rearrangement. Scheme 3.19 illustrates the mechanism of addition of bromine to **(107)**. Initially, a bromonium ion is formed at the *exo-* face of the bicycle and this cation is stabilised by participation of the nitrogen lone pair. The bromonium ion is ring-opened and the positive charge becomes delocalised between the point of ring-opening, the nitrogen and the bridgehead carbon; the bromide ion attacks at this position to give **(108)**.

Scheme 3.19



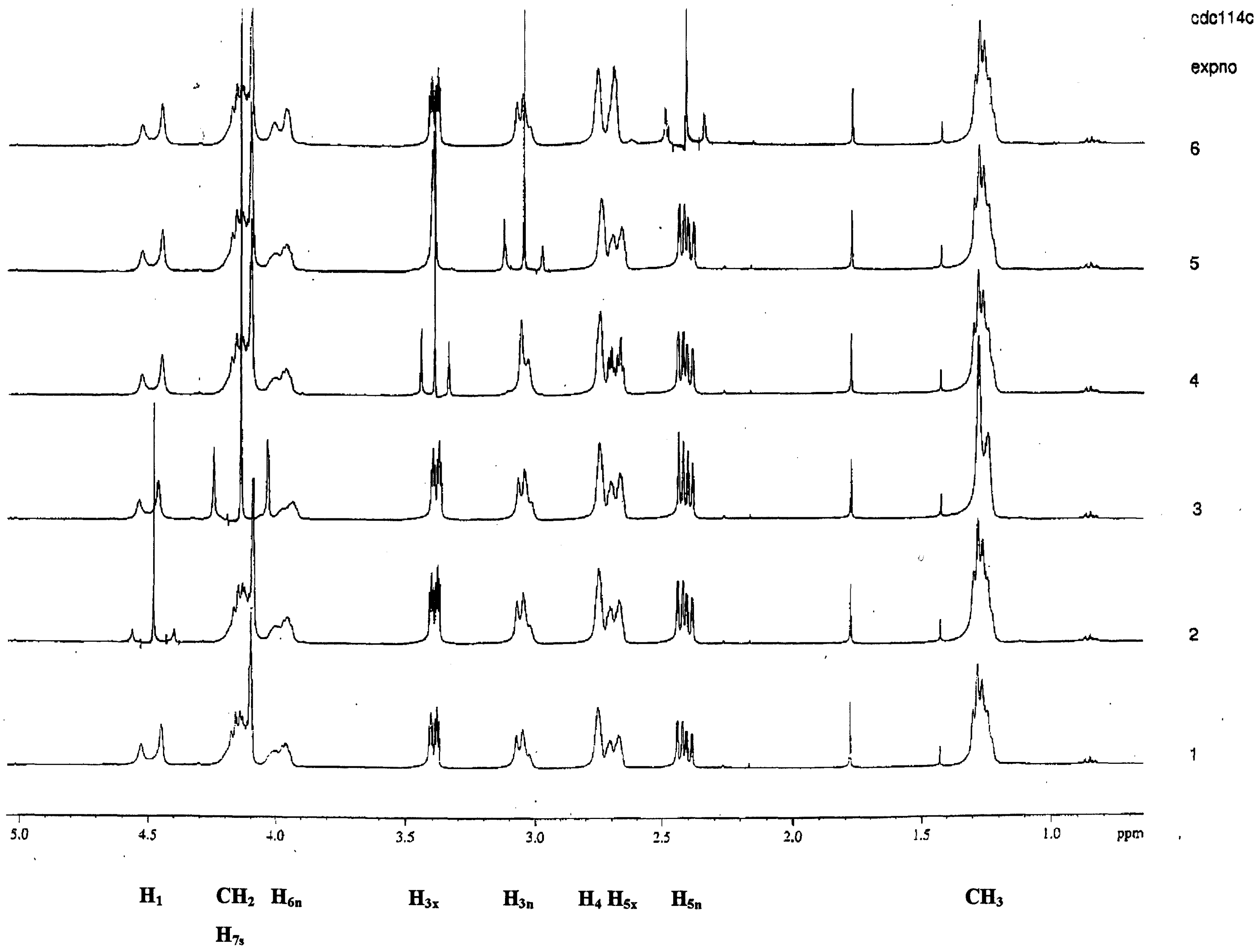
We considered that it would be interesting to see if this rearrangement was possible with a urethane-protected nitrogen and chose molecule **(109)**, containing the sterically less-bulky ethyloxycarbonyl group, as a substrate. The bicycle **(109)** was synthesised according to the procedure by Heesing and Keller[49] (Scheme 3.20) and reacted with bromine in the dark at room temperature overnight. The product **(110)** was isolated as a colourless oil in a yield of 73% after column chromatography and fully characterised by ^1H NMR spectroscopy using HH COSY and selective spin decoupling experiments (see Figure 3.21).

Scheme 3.20



The proton H_4 was identified as a broad singlet at δ 2.75 which showed vicinal coupling of J = 3.0 Hz to H_{5x}. H_{5x} showed $^2J_{5n,5x}$ = 14.5 Hz to H_{5n} and 'W'-coupling of J = 2.5 Hz to H_{3x}. H_{7s} was identified as a doublet of doublets at δ 4.10; double irradiation of H_{7s} showed a loss of 'W'-couplings to H_{5n} and H_{6n} (experiment number 3 in Figure 3.21) confirming the presence of both *endo*- protons. H_1 was identified as two broad signals at δ 4.45 and δ 4.53 as a result of slow N-CO rotation; no coupling was observed between this signal and H_6 confirming the absence of an *exo*-C_6-proton. These results confirmed that rearrangement did occur to give **(110)** and therefore the nitrogen lone pair can participate as a neighbouring group in a reaction, even though delocalised to an extent within the urethane group. It is also notable that the rearrangement was possible with the simple 2-azabicyclo[2.2.1]hept-5-ene derivative in parallel to the 2-aza-bicyclo-[2.2.1]hept-5-en-2-one ring system **(107)**.

Figure 3.21 Selective Spin Decoupling Experiments (110)



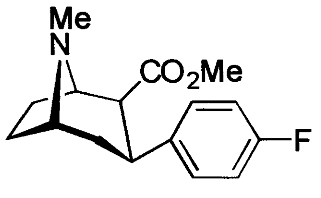
CHAPTER 4

Synthesis of Spirocyclic Tropane-based Molecules

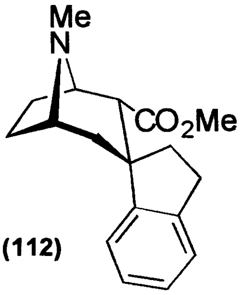
4.1 Pharmacological Applications of 8-Azabicyclo[3.2.1]octane Systems

8-Azabicyclo[3.2.1]octane (tropane) derivatives have a broad spectrum of pharmacological applications; Chapter 1 included mention of hyoscine, which has anaesthetic qualities, and the glycosidase inhibitory effects of the calystegine family of alkaloids. The development of 8-azabicyclo[3.2.1]octane derivatives, such as homoepibatidine, as nicotinic receptor agonists was also discussed in Chapter 1.
Another large area of interest concerns the synthesis of analogue molecules of cocaine for the treatment of cocaine abuse. Analogue molecules are used as probes to study the monamine transporters to which cocaine is thought to bind in the mammalian brain; especially important are those molecules which selectively bind to the dopamine transporter, which cocaine is thought to inhibit, and not to the serotonin transporter.

Figure 4.1



(111)



(112)

One of the first useful cocaine analogues developed was 3β-(4-fluorophenyl)tropane-2β-carboxylic acid methyl ester **(111)** (Figure 4.1) reported by Clarke,[50] which has moderately high affinity and selectivity for the dopamine transporter and is used, in radiolabelled form, in the study of cocaine binding sites. A very recent publication details the synthesis of the analogue molecule **(112)**, a spirocyclic system.[51]

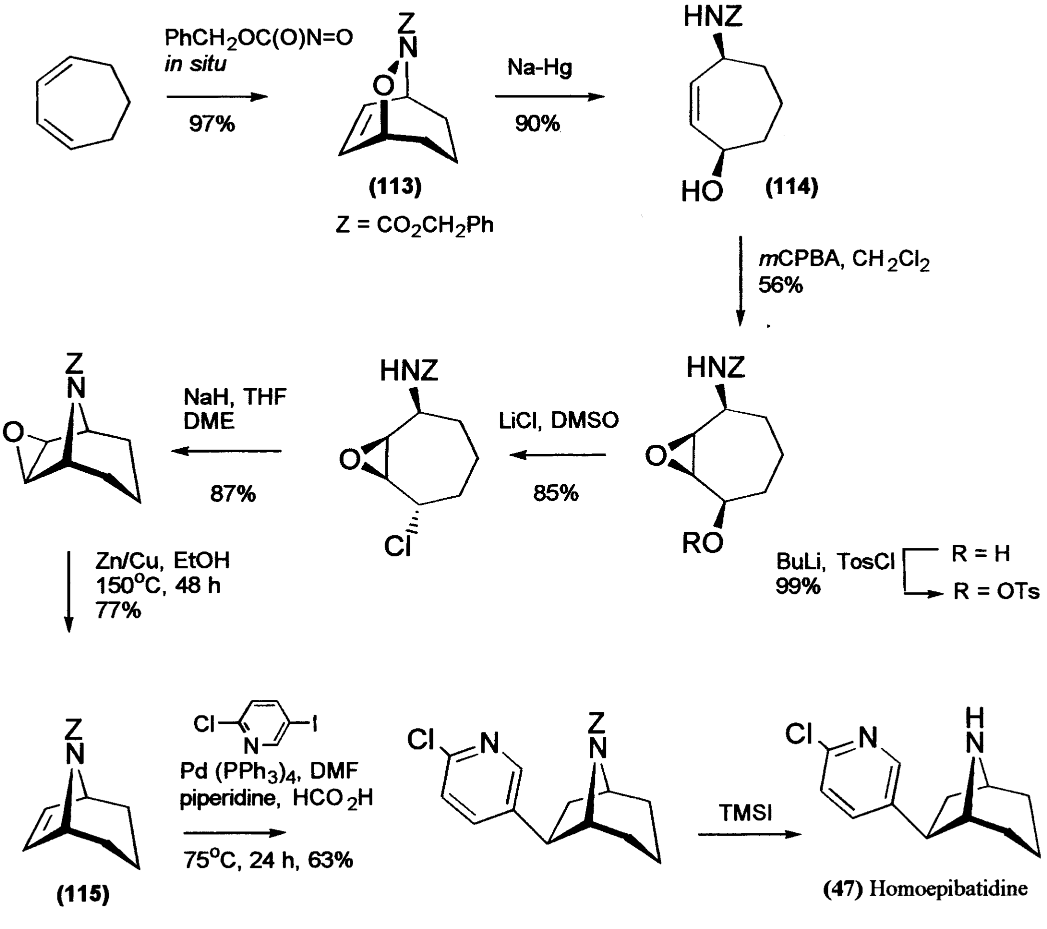
4.2 Synthesis of 8-Azabicyclo[3.2.1]octanes

There are many approaches to the synthesis of tropanes[52] but here we will illustrate two of the most widely used currently: the first is from acyclic precursors which are ring-closed *via* intramolecular nucleophilic displacement; the second is by modification of natural products such as tropinone or cocaine. Examples of these approaches are given below.

Synthesis *via* Nucleophilic Displacement

The epibatidine analogue homoepibatidine **(47)** was synthesised at Leicester by Malpass and Wallis[23] in eight steps as illustrated in Scheme 4.2. The bicyclic isoxazole **(113)** was made by a Diels Alder reaction between cyclohepta-1,3-diene and the benzyloxycarbonyl nitroso compound formed *in situ* from benzyl-*N*-hydroxy-carbamate and tetramethylammonium periodate. Reductive cleavage of the N-O bond furnished the monocycle **(114)** which was reacted with *m*CPBA to give a mixture of *cis-* and *anti*-epoxides in a ratio of 6:4.

Scheme 4.2


PhCH₂OC(O)N=O
in situ
97%
Z
N
O
(113)
Z = CO₂CH₂Ph
Na-Hg
90%
HNZ
HO
(114)
mCPBA, CH₂Cl₂
56%
HNZ
O
RO
BuLi, TosCl
99%
R = H
R = OTs
LiCl, DMSO
85%
HNZ
O
Cl
NaH, THF
DME
87%
Z
N
O
Zn/Cu, EtOH
150°C, 48 h
77%
Z
N
(115)
Cl
N
I
Pd (PPh₃)₄, DMF
piperidine, HCO₂H
75°C, 24 h, 63%
Cl
N
Z
N
TMSI
Cl
N
H
N
(47) Homoepibatidine

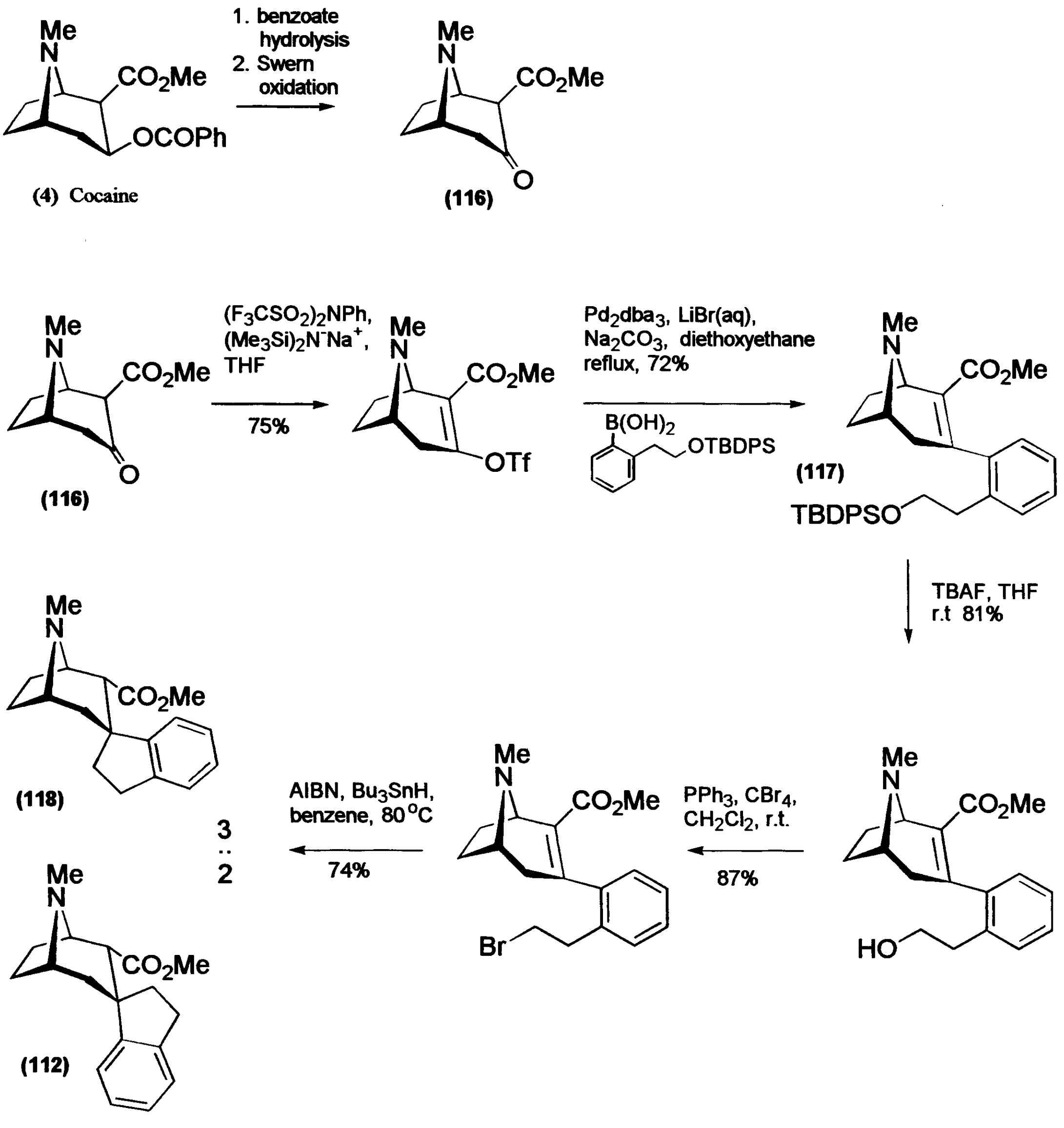
The *cis*-epoxide was used for the next stage in the synthesis. Tosylation of the alcohol was followed by S_N2 substitution by chloride. Intramolecular displacement of the chloride with a urethane nitrogen was facilitated by *N*-deprotonation with sodium hydride. Deoxygenation of the epoxide with a zinc/copper couple resulted in the alkene **(115)**. The chloropyridyl functionality was introduced *via* the reductive Heck reaction in a 63% yield, resulting in the *N*-protected bicycle which was deprotected with iodotrimethylsilane to give homoepibatidine.

Synthesis of Analogue Molecules From Cocaine

Natural cocaine can be obtained commercially under special licence and can prove a useful, chiral starting material. The spirocycle **(112)** was synthesised by Kozikowski and co-workers[51] from naturally occurring (*R*)-(-)-cocaine **(4)** (Scheme 4.3).

The first step in the synthesis involved hydrolysis of the benzoate group followed by Swern oxidation of the resulting alcohol. The ketone **(116)** was converted into an enol triflate with *N*-phenyltrifluoromethane-sulfonimide and sodium bis(trimethylsilyl)-amide. Suzuki coupling of the enol triflate with an arylboronic acid proceeded in good yield to give the adduct **(117)**. The silane group was removed with TBAF and the resultant hydroxide group converted to bromine. Radical cyclisation of the alkyl chain onto the double bond was achieved using tributyltin hydride initiated with AIBN, in a 5-*exo*-trigonal mechanism. Two stereoisomers, **(118)** and **(112)**, were formed in a ratio of 3:2 and were separated by column chromatography. Both structures were confirmed by X-ray crystallography and show the ester groups in equatorial orientations; radicals formed after the cyclisation step were trapped by tributyltin hydride from the sterically less hindered *exo*- faces. Both stereoisomers were formed as a single enantiomer.

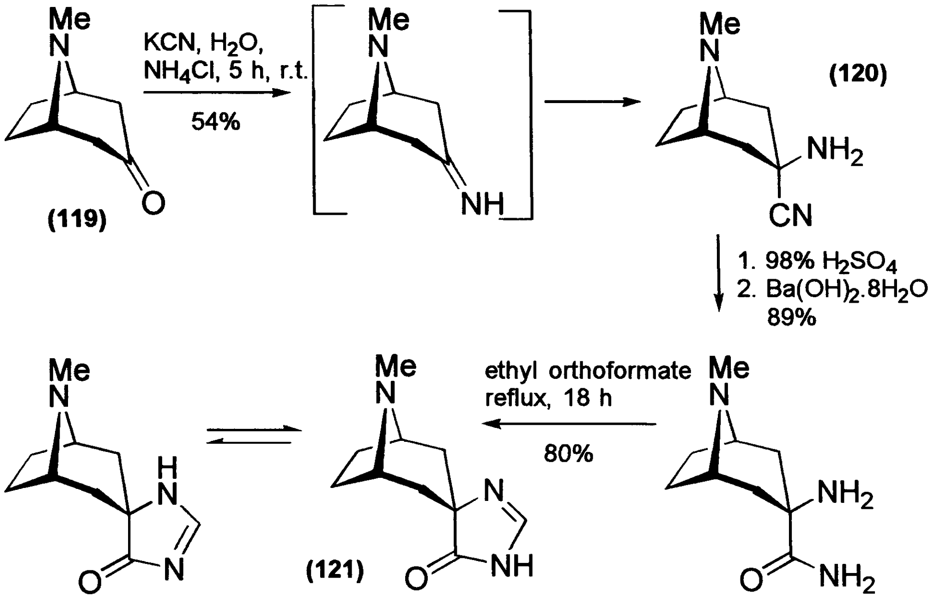
Scheme 4.3


Me
N
CO_2Me
OCOPh
(4) Cocaine
1. benzoate hydrolysis
2. Swern oxidation
O
(116)
$(F_3CSO_2)_2NPh$, $(Me_3Si)_2N^-Na^+$, THF
75%
OTf
Pd_2dba_3, LiBr(aq), Na_2CO_3, diethoxyethane reflux, 72%
$B(OH)_2$
OTBDPS
(117)
TBDPSO
TBAF, THF r.t 81%
HO
PPh_3, CBr_4, CH_2Cl_2, r.t.
87%
Br
AIBN, Bu_3SnH, benzene, 80 °C
74%
(118)
3 : 2
(112)

Synthesis of Analogue Molecules From Tropinone

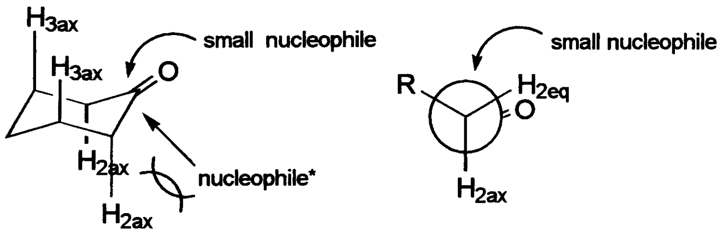
There are many published examples of molecules derived from tropinone **(119)**, a substance which is inexpensive and readily available commercially. Reactions on tropinone often involve nucleophilic attack at the C_3-ketone group, introducing new functional groups at this site. The construction of the hydantoins shown in Schemes 4.4 and 4.6 illustrate that placement of a cyano-group on the α-(axial) face or the β-(equatorial) face of the ketone can be controlled by the reaction conditions.

Scheme 4.4


KCN, H_2O, NH_4Cl, 5 h, r.t.
54%
(119)
(120)
NH
NH_2
CN
1. 98% H_2SO_4
2. $Ba(OH)_2.8H_2O$
89%
ethyl orthoformate
reflux, 18 h
80%
(121)
Me
N
H
O

Scheme 4.4[53] shows formation of the aminonitrile **(120)** from tropinone. The ketone is initially converted into a ketimine by the action of ammonium chloride and is then attacked from the axial face by the small cyanide ion. An explanation for this orientation of attack may lie in consideration of torsional factors. It is known that in nucleophilic attack on cyclohexanone, axial attack is favoured with small nucleophiles such as hydride ion (Figure 4.5). From the perspective of a Newman projection, the initial carbonyl group is nearly eclipsed by the adjacent equatorial protons H_{2eq} and attack from the axial face relieves this bond angle. Attack from the equatorial face forces these protons and the carbonyl through an eclipsed conformation.[54] There is also potential torsional strain involving the axial protons H_{2ax} as the nucleophile* approaches the carbonyl carbon at a tetrahedral angle. A large nucleophile is less likely to attack from the axial face, however, as 1,3 diaxial strain between the nucleophile and the axial protons H_{3ax} in the product becomes a major discouraging factor.[55]

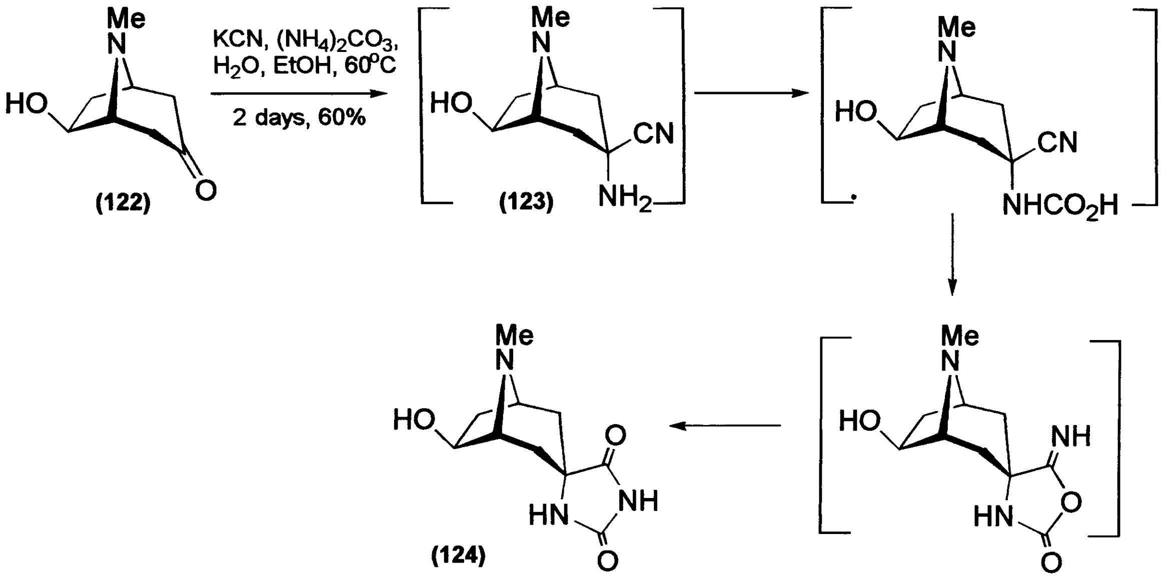
Figure 4.5


H_{3ax}
H_{3ax}
small nucleophile
O
H_{2ax}
nucleophile*
H_{2ax}
small nucleophile
R
H_{2eq}
O
H_{2ax}

Synthesis of the hydantoin **(121)** was completed *via* hydration of the nitrile group followed by condensation with ethyl orthoformate.

Scheme 4.6[56] shows how the cyanide anion can be made to join the carbonyl group from the equatorial face by increasing the reaction temperature and thereby favouring the thermodynamic product; the nitrile group, being slightly more bulky than the alcohol, assumes an equatorial orientation thereby minimising 1,3-diaxial interactions. The reaction of **(122)**, a 6β-hydroxylated derivative of tropinone, with potassium cyanide and ammonium carbonate proceeds at 60°C over 2 days to give the hydantoin **(124)** in one step and 60% yield. The structure of **(124)** was rationalised by NMR spectroscopic studies. From a pharmacological perspective, several hydantoins have shown anti-cholinergic, anti-convulsant and anti-inflammatory properties, making them a valuable area of study.

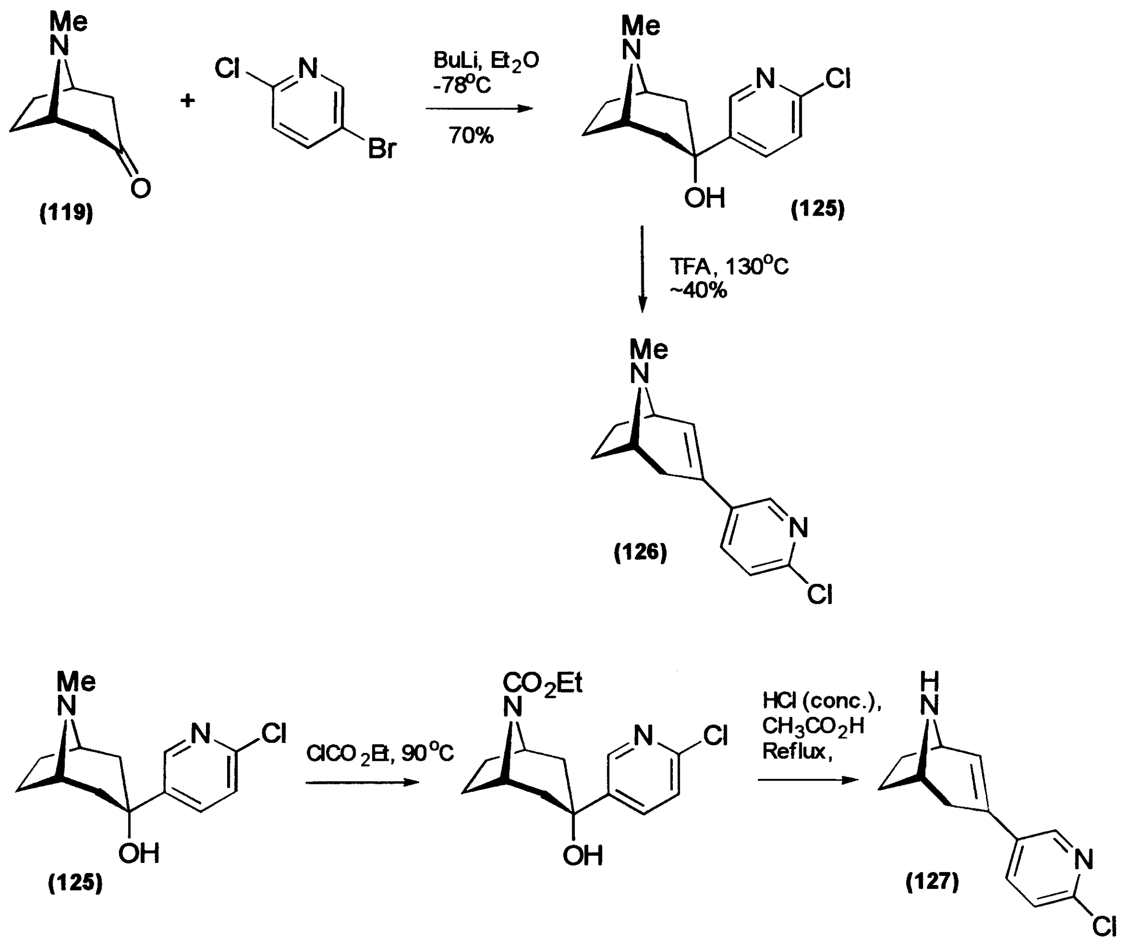
Scheme 4.6



A very recent publication by Radl[57] details the synthesis of an epibatidine analogue **(126)** *via* attack at the keto-carbon of tropinone using a bulky aryl nucleophile (Scheme 4.7). The keto-carbon was attacked exclusively from the β-face by 5-lithio-2-chloropyridine to produce the tertiary alcohol **(125)**. The configuration of the C_3 stereocentre in **(125)** was rationalised by NMR spectroscopic studies including 2D-

NOESY experiments. Dehydration of the alcohol with trifluoroacetic acid gave **(126)**. The *N*-unsubstituted version of **(126)** was also made; reaction of **(125)** with ethyl chloroformate in toluene produced the corresponding *N*-ethoxycarbonyl compound as a crystalline solid, in over 70% yield after chromatography. Dehydration and hydrolysis of the carbamate group was achieved with a mixture of hydrochloric and acetic acids resulting in **(127)**. Pharmacological assay revealed that both **(126)** and **(127)** showed nanomolar binding affinity to nicotinic receptors.

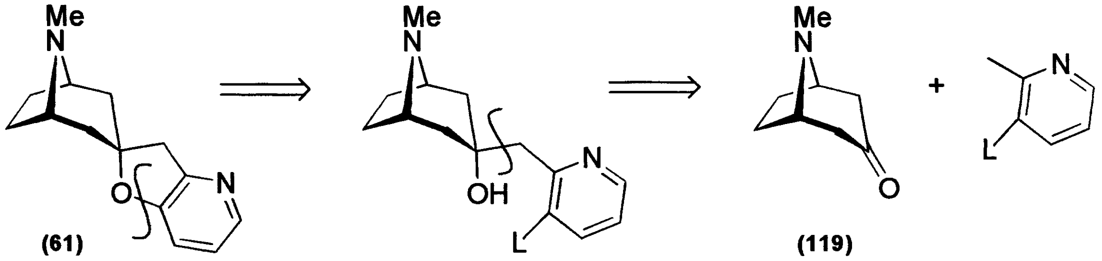
Scheme 4.7


Me
N
O
(119)
+
Cl
N
Br
BuLi, Et2O
-78°C
70%
Me
N
N
Cl
OH
(125)
TFA, 130°C
~40%
Me
N
(126)
N
Cl
Me
N
N
Cl
OH
(125)
ClCO2Et, 90°C
CO2Et
N
N
Cl
OH
HCl (conc.),
CH3CO2H
Reflux,
H
N
(127)
N
Cl

4.3 Our Synthesis of Spirocyclic Tropane-Based Molecules

The first target molecule in the present work was **(61)**; a potential nicotinic receptor agonist. Retrosynthetic analysis towards the construction of this molecule is shown in Scheme 4.8.

Scheme 4.8

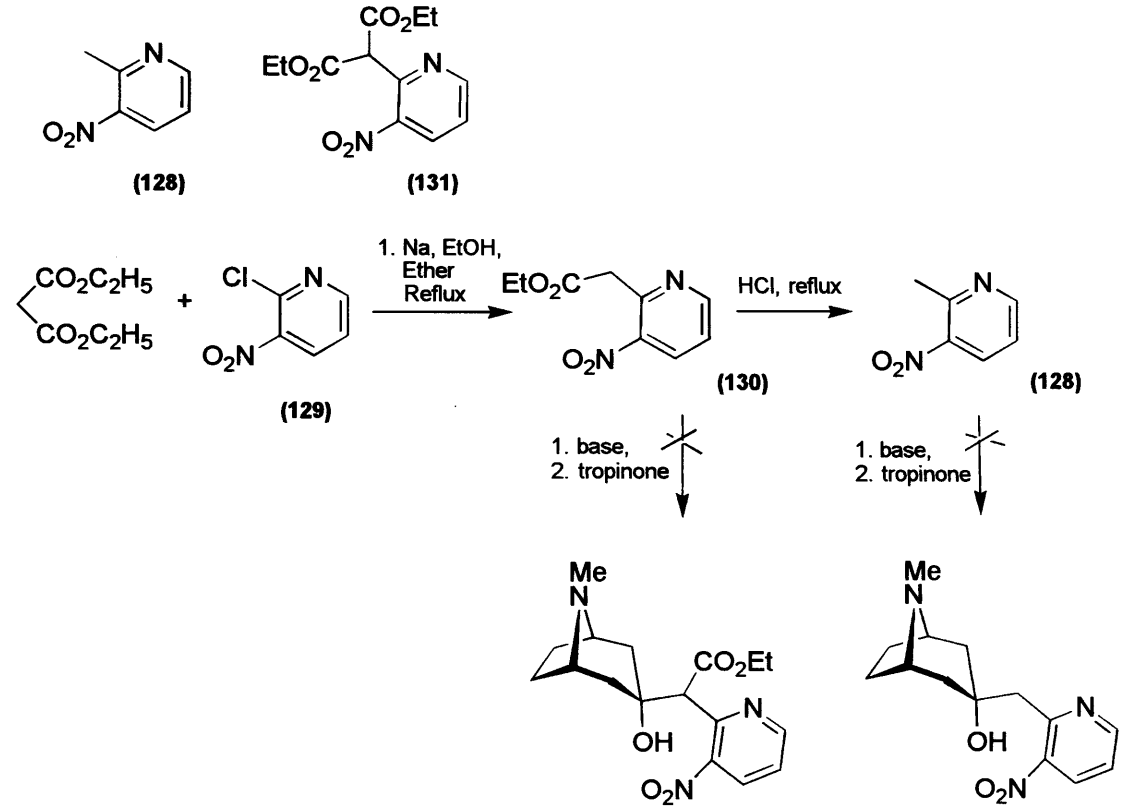


The first step involves generation of a lithiated picoline for nucleophilic attack on tropinone from the β-face. The resultant tertiary alcohol would then cyclise back onto the picoline, displacing the leaving group.

An S_N1 Approach to Spiro-cyclisation

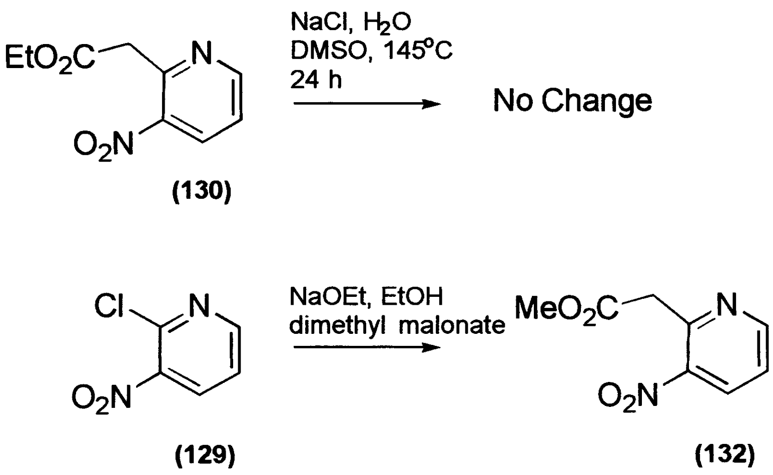
The initial choice of picoline for lithiation was 3-nitro-2-picoline **(128)** which was made by modification of the published procedure by Hurst and Wibberly[58] (Scheme 4.9). It was envisaged that the addition of one mole equivalent of base to the picoline would deprotonate at the acidic methyl site. It was hoped that the lithiated picoline would then attack tropinone at the keto-carbon giving a tertiary alcohol after work-up. Reduction and diazotisation of the nitro group would leave an electron-deficient site on the picoline for nucleophilic attack by the hydroxyl oxygen resulting in **(61)**.

Scheme 4.9



Reaction of commercially available 2-chloro-3-nitropicoline **(129)** with diethyl malonate anion proceeded by an S_NAr mechanism to give an intermediate ester which was hydrolysed and decarboxylated, by reflux in acid, to the picoline **(128)** in 65% yield. Deprotonation of **(128)** was attempted with one mole equivalent of butyl lithium at –78°C, followed by addition of tropinone. Unfortunately, addition did not occur; the crude ^{1}H NMR spectrum showed only unreacted tropinone. The picoline was believed to have been either destroyed or polymerised. Despite variation in the reaction conditions and the use of different bases, reaction could not be achieved. We considered that a more stable picoline anion would be generated if conjugated to an ester group and therefore isolated the intermediate ester formed during the reaction sequence to **(128)**. Integration of the ethyl protons shown by ^{1}H NMR spectroscopy and observation of a mass spectrum peak [MH]$^+$ at 211 indicated that the isolated intermediate was the monoester **(130)**, not the expected diester **(131)**. To confirm this observation, **(130)** was subjected to dealkoxycarbonylation conditions (Scheme 4.10); it has been shown that reflux of malonate esters in the presence of sodium chloride in dipolar aprotic media, such as dimethyl sulfoxide, results in the removal of just one of the two ester groups.[59] No change in the reaction intermediate was observed. As a further check, 2-chloro-3-nitropicoline was reacted with the dimethyl malonate anion. Mass spectra and ^1H NMR spectroscopy again revealed the presence of a monoester **(132)**.

Scheme 4.10



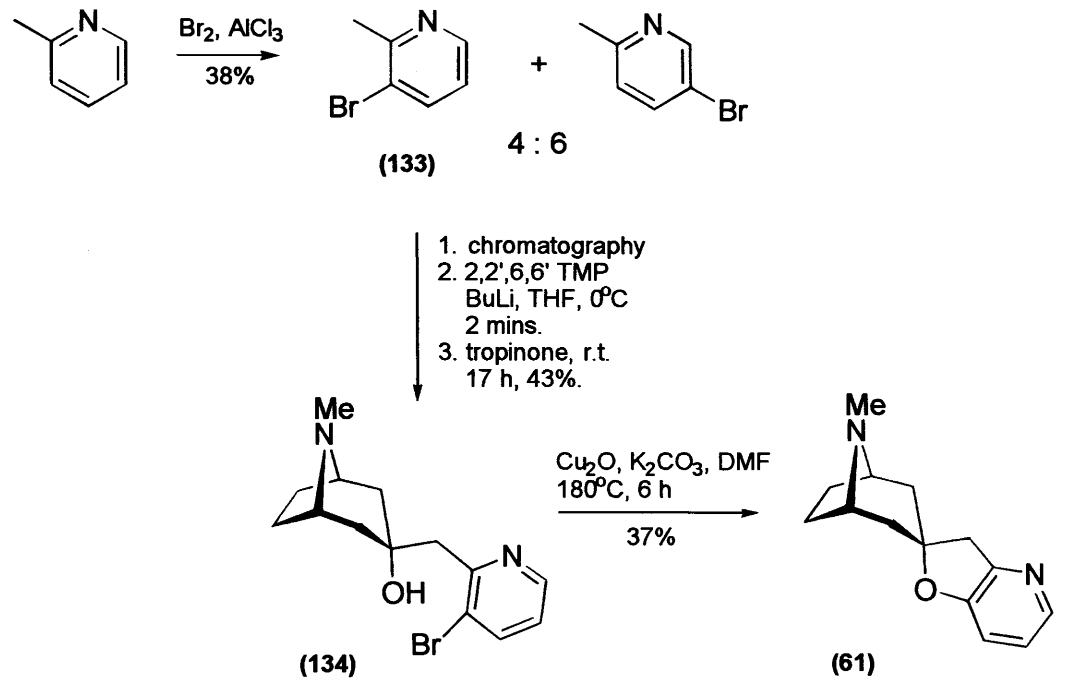
It is noted that sodium chloride is a by-product of the reaction of dimethyl malonate with **(129)** and it is therefore conceivable that reaction conditions favoured sequential dealkoxycarbonylation of an intermediate diester to give the monoester **(132)**, despite the difference in solvent polarity (ether/ethanol with traces of water vs. ideal conditions of DMSO/water).

The presence of the ester group in **(130)** did not improve the situation regarding nucleophilic attack on tropinone, however, and reaction with tropinone was unsuccessful.

A Benzyne Approach to Spiro-cyclisation

Our next strategy employed lithiated 3-bromo-2-picoline as nucleophile. 3-Bromo-2-picoline **(133)** was synthesised by Friedel-Crafts reaction between bromine and 2-picoline in the presence of aluminium chloride[60] (Scheme 4.11). Both the 3- and 5-brominated picolines were formed in a ratio of 4:6 and these were easily separated by column chromatography. Lithiation of **(133)** was carried out using lithium tetramethyl piperidide at 0°C, stirring for 2 minutes. Tropinone was added and the reaction stirred overnight at room temperature.

Scheme 4.11



The tertiary alcohol **(134)** was isolated as a pale yellow oil in 43% yield after chromatography; competing enolisation of tropinone meant that the reaction did not go to completion. Accurate mass measurement confirmed the expected relative molecular mass of **(134)** and the IR spectrum showed a broad hydroxyl peak at 3350 cm^{-1}. The compound was also fully characterised by ^{1}H NMR and HH COSY spectra; the hydroxyl proton was observed as a broad singlet at δ 5.78 and the pyridyl methylene protons as a singlet integrating for 2 protons at δ 2.96. Verification of the configuration at the C$_3$ centre could not be carried out by conventional X-ray analysis as **(134)** was not a solid. Literature precedent discussed above does, however, point to equatorial addition of the bulky pyridine derivative and thus the stereostructure of **(134)** has been assumed to be as illustrated.

Cyclisation of the alcoholic oxygen onto the pyridine ring proved to be very difficult; the addition of base did not result in the anticipated benzyne elimination of HBr followed by nucleophilic attack by the hydroxyl. Attempted coupling between the 3-OH group and the pyridine ring using palladium acetate also failed. Successful reaction was however achieved using copper(I) oxide and anhydrous potassium carbonate in DMF, heating the reagents in a reactivial at 180°C for 6 hours (methodology developed by Barker[61]). Unfortunately, the yield of **(61)**, a yellow oil, was only 37% and this could not be improved on by changing the reaction conditions. Cyclisation was confirmed by the absence of alcohol peaks both in ^{1}H NMR and I.R. spectra and by observation of the expected relative molecular mass. Verification of the configuration at the spiro centre was attempted with HH NOESY experiments, but they proved to be inconclusive. Full characterisation by ^{1}H NMR spectroscopy was carried out, using trifluoroacetic acid to protonate the aliphatic nitrogen and remove peak overlap where necessary; a summary of these data and a comparison with **(134)** and tropinone **(119)** is shown in Table 4.13. Figure 4.12 details the proton labels given to **(61)**.

Figure 4.12

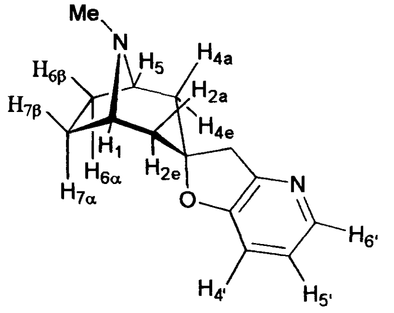
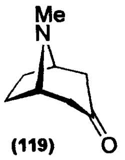
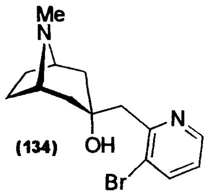
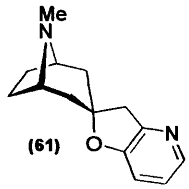


Table 4.13 Selective ^{1}H NMR Data.

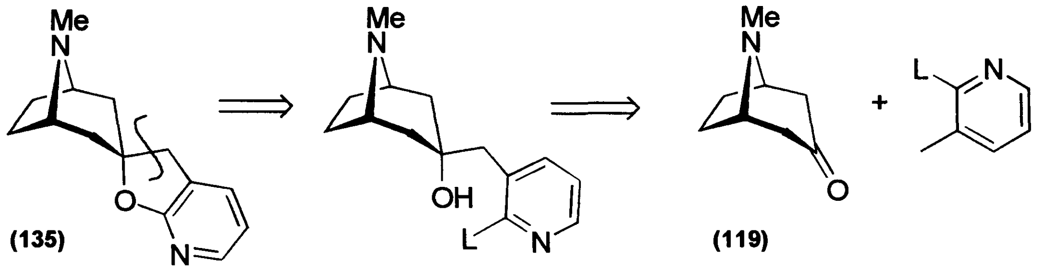
	 (119) δ (ppm)		 (134) δ (ppm)		 (61) δ (ppm)	
N-CH$_3$	2.49	s	2.23	s	2.36	s
H_1, H_5	3.45	bs	3.05	bs	3.22	bs
H_{2a}, H_{4a}	2.69	dd	1.86	dd	2.07	d
H_{2e}, H_{4e}	2.20	dd	1.75	bd	~2.11	bd
$H_{6\beta}$, $H_{7\beta}$	2.12	bm	1.75-1.90	m	2.01-2.07	m
$H_{6\alpha}$, $H_{7\alpha}$	1.61	(½AA'BB')	2.14	(½AA'BB')	2.22	(½AA'BB')
-CH$_2$-			2.96	s	3.08	s
$H_{4'}$			7.81	dd	6.93	dd
$H_{5'}$			7.00	dd	6.99	dd
$H_{6'}$			8.36	dd	7.99	dd
-OH			5.78	bs		

It should be noted that the streostructure of **(61)** is based on that assumed for **(134).**

4.4 Synthesis of Spirocyclic Cocaine Analogue

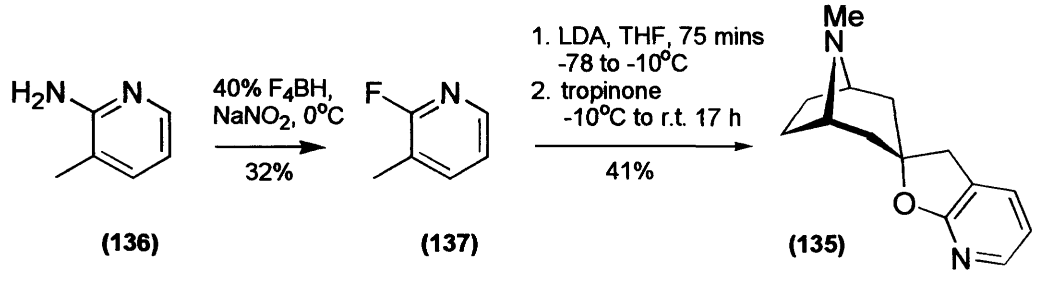
On completion of the synthesis of **(61)**, an approach to **(135)** was proposed as a potential cocaine analogue (Scheme 4.3 illustrated the synthesis of a complementary tropane-based spirocyclic molecule for this purpose). The retrosynthetic analysis in Scheme 4.14 shows that placement of the aromatic methyl group on C_3 of the picoline and a leaving group on C_2 should provide the target molecule.

Scheme 4.14



Fluorine was chosen as the leaving group in this case in an attempt at a successful S_NAr displacement by the hydroxyl group. Therefore, 2-fluoro-3-picoline **(137)** was synthesised from commercially available 2-amino-3-picoline **(136)** *via* diazotisation and reaction with fluoroboric acid[62] (Scheme 4.15). Deprotonation of **(137)** was achieved with lithium diisopropylamine; tropinone in THF was then added and the reaction stirred overnight. ^{1}H NMR spectra and a mass spectrum of the product revealed to our surprise that not only had nucleophilic attack on the keto-carbon occurred, but also subsequent cyclisation. Unreacted tropinone was also obtained and this was removed from the crude reaction mixture with a sodium bisulphate wash. The product **(135)** was obtained in 41% yield as a yellow waxy solid after column chromatography.

Scheme 4.15


(136)
40% F4BH, NaNO2, 0°C
32%
(137)
1. LDA, THF, 75 mins -78 to -10°C
2. tropinone -10°C to r.t. 17 h
41%
(135)

Recrystallisation of **(135)** in acetonitrile yielded some small white crystals which were analysed by X-ray crystallography (Figure 4.16). The X-ray structure revealed that two molecules of protonated **(135)** had crystallised out with one $S_2O_6^{2-}$ anion. It was thought that the anion had originated as a contaminant in the sodium bisulphate wash used to remove unreacted tropinone from the crude reaction mixture. The X-ray structure confirms the expected orientation of the spiro centre with the oxygen in an α-axial position. The five-membered ring is kinked at an angle of 20° with respect to the plane of symmetry through the tropane fragment as shown in Figure 4.16a.

Following the successful one-step generation of **(135)** from 2-fluoro-3-picoline **(137)** and tropinone, the synthesis of 3-fluoro-2-picoline **(139)**, following the published procedure by Talik,[63] was attempted to see if the spirocycle **(61)** could be generated in the same efficient manner. 3-Amino-2-picoline **(138)** was obtained by the reduction of **(128)** in quantitative yield (Scheme 4.17). Diazotisation of the amino group and replacement by fluorine was, however, largely unsuccessful. Despite variation in the reaction temperature and the type of fluoroboric acid complex employed (aqueous or organic solvent-based), only tiny amounts of **(139)** were ever obtained; ^{19}F NMR registered a peak at δ 124.9 (measured at 235.4 MHz in $CDCl_3$).

Scheme 4.17

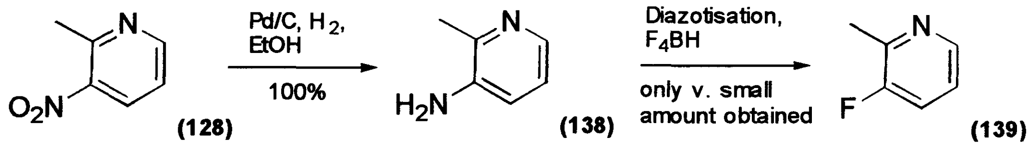
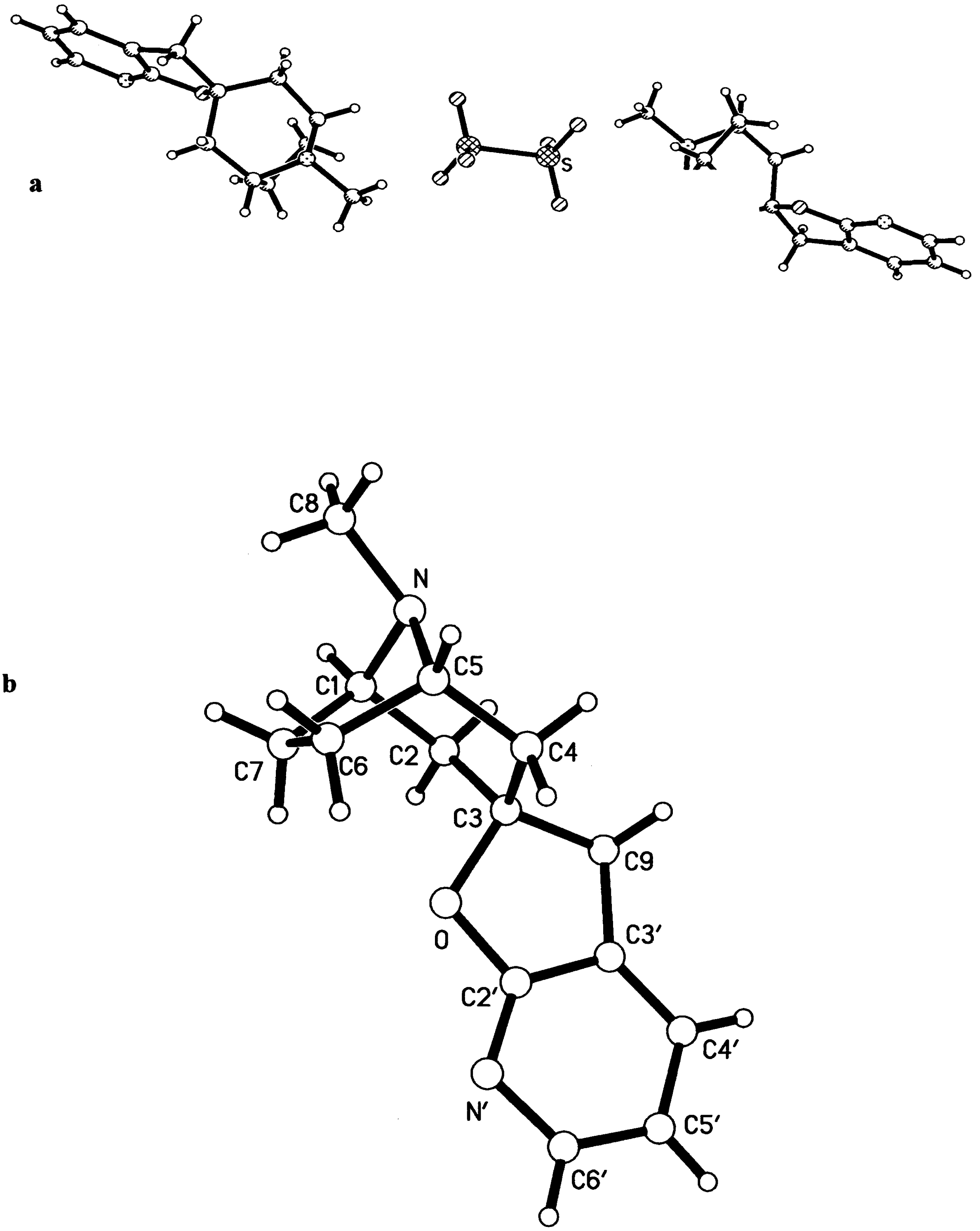

(128)
Pd/C, H2, EtOH
100%
(138)
Diazotisation, F4BH
only v. small amount obtained
(139)

Figure 4.16 X-Ray structures showing counterions and labelled enlargement of **(135)**

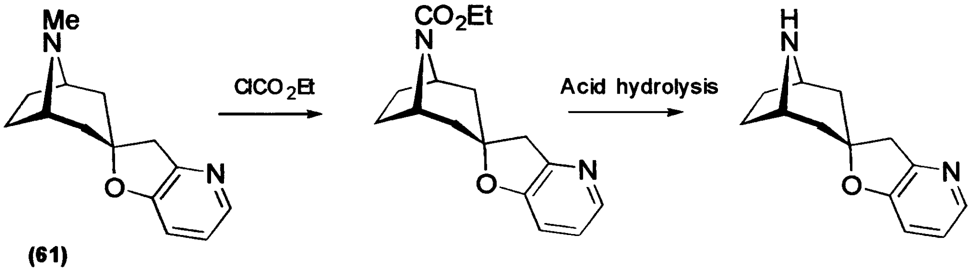

a
S
b
C8
N
C5
C1
C7
C6
C2
C4
C3
C9
O
C3′
C2′
C4′
N′
C5′
C6′

4.5 Future Work

We anticipate that pharmacological testing of the two spirocyclic molecules will be carried out in the near future. If results are encouraging, then both molecules could be adapted to provide further analogues.

In the case of **(61)**, production of the nor-compound could be facilitated by acylation of the *N*-methyl group followed by hydrolysis of the carbamate (Scheme 4.18). Removal of the methyl group may have an effect on binding at the nicotinic receptor.

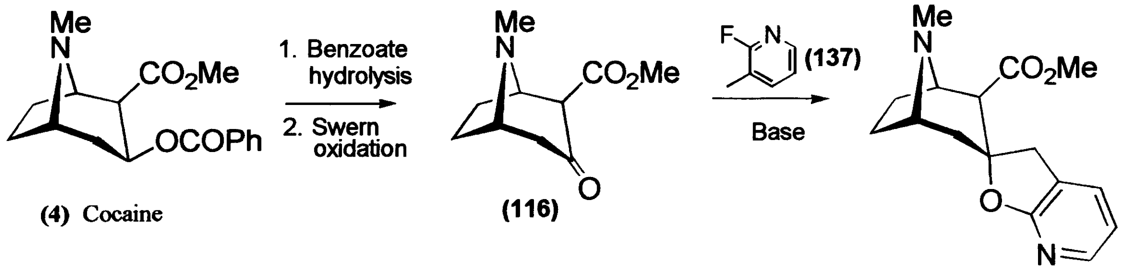
Scheme 4.18


Me
N
N
O
ClCO2Et
CO2Et
N
N
O
Acid hydrolysis
H
N
N
O

(61)

In the case of **(135)**, incorporation of an ester group at C_2 by analogy with cocaine could be achieved by using natural (*R*)-(-)-cocaine as a precursor (Scheme 4.19). The ketone **(116)** could be produced using the method of Kozikowski[51] shown above. Reaction with the picoline **(137)** should generate the desired spirocycle although yields may be low due to competing enolisation of the ketone (which would be encouraged by the β-ester group). Prior functional group interconversion of the methyl ester may be necessary in this eventuality.

Scheme 4.19


Me
N
CO2Me
OCOPh
1. Benzoate hydrolysis
2. Swern oxidation
Me
N
CO2Me
O
F
N
(137)
Base
Me
N
CO2Me
O
N

(4) Cocaine

(116)

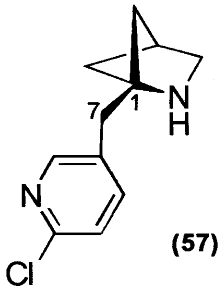
CHAPTER 5

Synthesis Towards 7-(6'-Chloro-3'-pyridyl)-1-methyl-2-azabicyclo[2.1.1]hexane

5.1 Synthesis of 2-Azabicyclo[2.1.1]hexanes

In the design of epibatidine analogues, the 2-azabicyclo[2.1.1]hexane ring system offers a very rigid and compact skeleton on which to place a heteroaromatic ring. From a synthetic point of view, we concluded that the most practical position on which to place the heteroaromatic ring would be on the bridgehead carbon adjacent to the aliphatic nitrogen (C1) (see retrosynthetic analysis, Scheme 5.4). Molecular modelling studies revealed that in order to generate an inter-nitrogen distance between the aliphatic and aromatic nitrogens of the same magnitude as epibatidine, the heteroaromatic ring would have to be linked by a methylene carbon (C7) to the azabicycle. In conclusion, we decided that **(57)** would make a good target. An inter-nitrogen distance of 5.4 A^0 was recorded for the particular lowest-energy conformation shown in Figure 5.1.

Figure 5.1

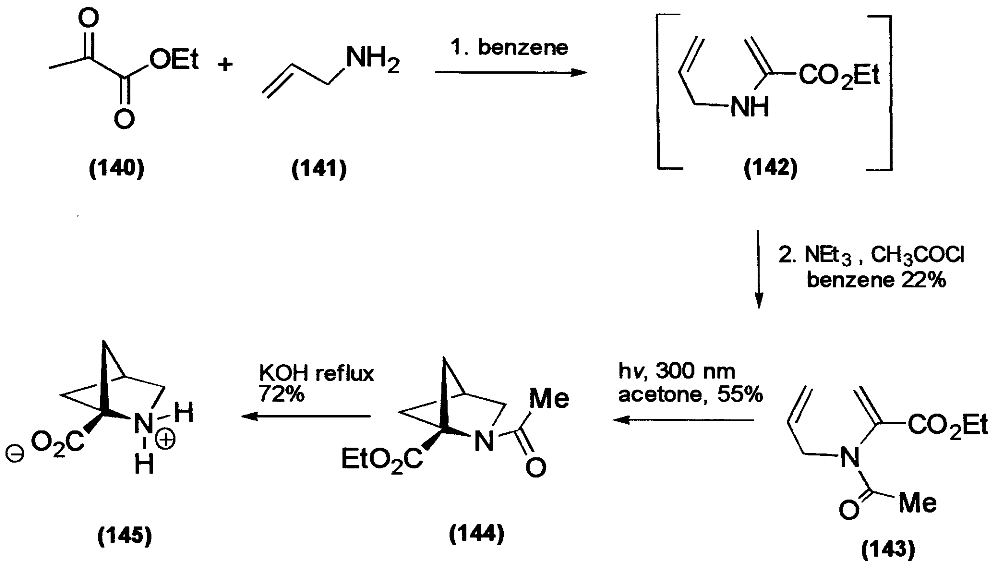


(57)

The only example of a 2-azabicyclo[2.1.1]hexane system found in nature is 2,4-methaneproline **(145)**, isolated from the seeds of the Costa Rican tree *Atelia herbert smithii.*[64] This amino acid is thought to act as a potential toxin in defence of the seeds against predatory insects. Two groups published very similar syntheses of **(145)** at the same time;[65] the route by Pirrung[65a] is detailed in Scheme 5.2.

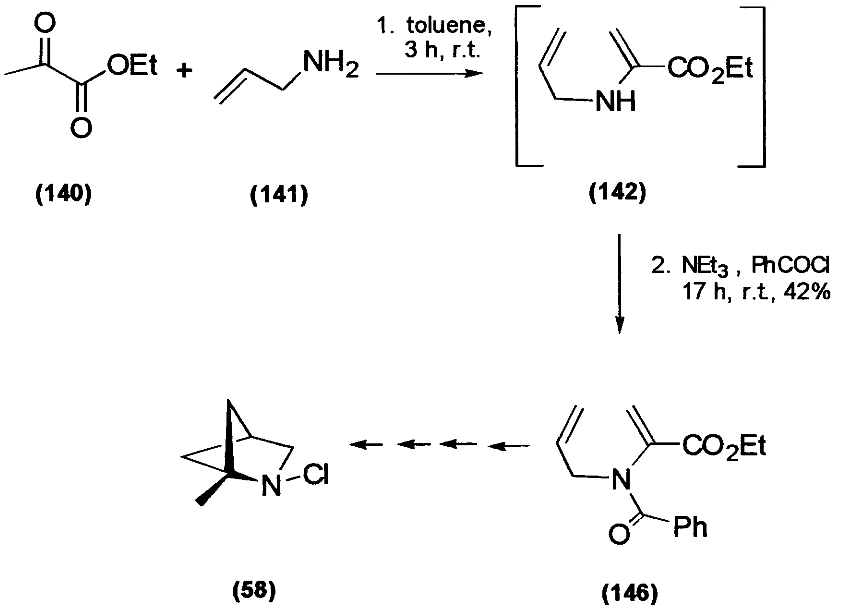
Condensation of ethyl pyruvate **(140)** with allylamine **(141)** formed *N*-allyl-dehydroalanine ethyl ester **(142)** (not isolated) which was immediately *N*-protected with acetyl chloride to produce the *N*-acetyl-*N*-allyl-dehydroalanine ethyl ester **(143)** in 22% yield. Irradiation at 300nm in acetone enabled formal 2πs + 2πs cycloaddition to yield the azabicycle **(144)**. Finally, base hydrolysis gave **(145)** in 72% yield.

Scheme 5.2


OEt
NH2
1. benzene
CO2Et
NH
(140)
(141)
(142)
2. NEt3 , CH3COCl
benzene 22%
N-H
⊖O2C
H
KOH reflux
72%
Me
EtO2C
N
O
hv, 300 nm
acetone, 55%
CO2Et
N
O
Me
(145)
(144)
(143)

Malpass, Davies and Walker[66] constructed their 2-azabicyclic[2.1.1]hexanes based on the above route, but protected **(142)** using benzoyl chloride (Scheme 5.3) to give **(146)**.

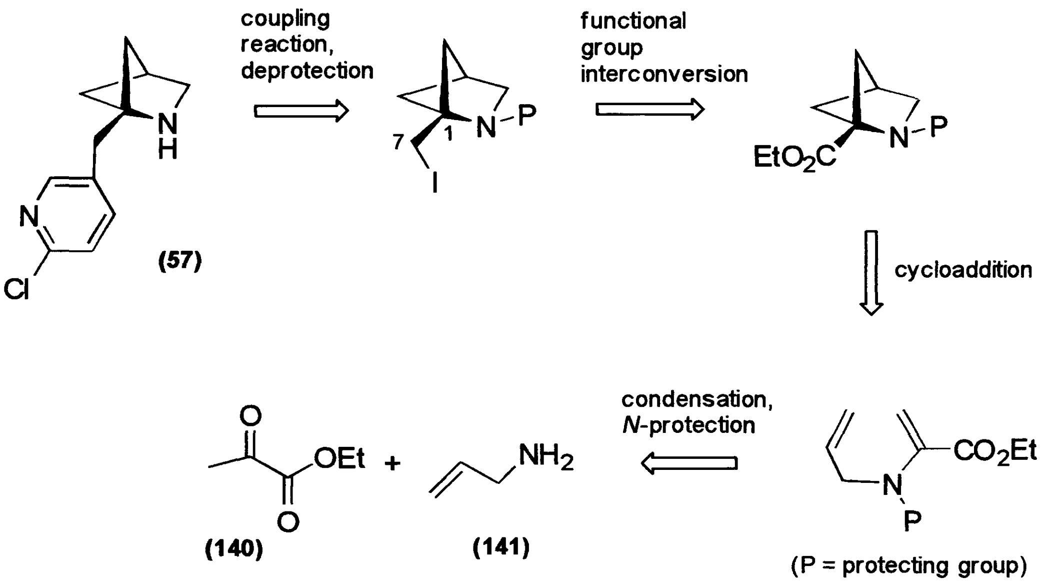
Scheme 5.3


OEt
NH2
1. toluene,
3 h, r.t.
CO2Et
NH
(140)
(141)
(142)
2. NEt3 , PhCOCl
17 h, r.t, 42%
N-Cl
CO2Et
N
O
Ph
(58)
(146)

5.2 Our Attempted Synthesis of 1-[Methyl-(2'-chloro-5'-pyridyl)]-2-azabicyclo[2.1.1]hexane (57)

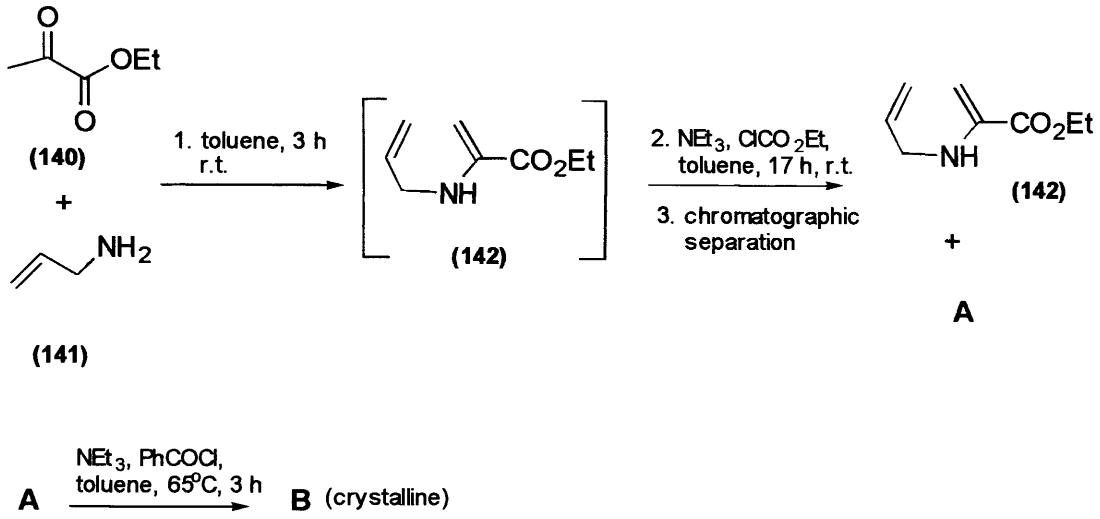
Our synthesis of **(57)** was also based on the route by Pirrung. A retrosynthetic analysis is shown in Scheme 5.4. It was anticipated that the chloropyridine ring would be introduced onto the exocyclic carbon at position 7 *via* an organometallic coupling reaction.

Scheme 5.4


coupling reaction, deprotection
functional group interconversion
N
H
N
Cl
(57)
7
1
N-P
I
EtO2C
N-P
cycloaddition
O
OEt +
O
(140)
NH2
(141)
condensation, N-protection
CO2Et
N
P
(P = protecting group)

Our original choice of protecting group for the *N*-allyl-dehydroalanine ethyl ester **(142)** was ethyloxycarbonyl as it can be easily removed by acid hydrolysis. However, attempted synthesis of this molecule, using a 10% excess of both ethyl chloroformate and triethylamine, did not proceed as expected and two main products were isolated from the reaction on chromatography of a sample of the crude mixture: the non-protected amine **(142)** (33% yield from allylamine), and an unidentified oil, **A** (Scheme 5.5). The ^{1}H NMR spectrum of **A** showed similarities to that of **(142)** but with duplication of the allyl signals, an unexpected methyl group and a single secondary amine. We decided to protect the secondary amine in the hope of obtaining a crystalline compound on which X-ray analysis could be undertaken. The unidentified oil **A** was heated with benzoyl chloride in base for 3 hours. The crude product was purified by column chromatography to give a white crystalline compound, **B**. Recrystallisation of **B** from ether provided crystals suitable for X-ray crystallography.

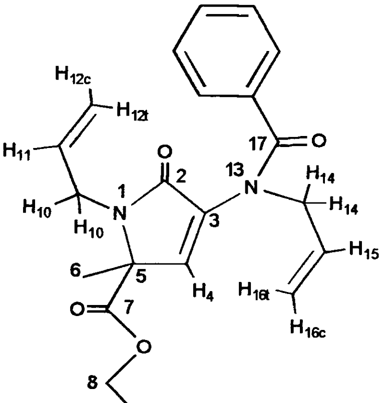
Scheme 5.5


O
OEt
O
(140)
+
NH2
(141)
1. toluene, 3 h
r.t.
CO2Et
NH
(142)
2. NEt3, ClCO2Et,
toluene, 17 h, r.t.
3. chromatographic
separation
CO2Et
NH
(142)
+
A
A
NEt3, PhCOCl,
toluene, 65°C, 3 h
B (crystalline)

Initially, only a partial crystal structure for **B** was resolved; however the structure clearly showed the presence of a 5-membered, cyclic α,β-unsaturated lactam core with exocyclic substituents. Based on this new evidence, we were able to suggest a structure for **B** in the form of **(148)** after a thorough analysis of the ^{1}H NMR spectrum (Figure 5.6a) using HH COSY and NOESY spectra to aid assignments (Table 5.7).

Table 5.7 ^{1}H NMR Data **(148)**

Signal	**δ value (ppm)**	
H_4	6.21	s
3 x H_6	1.37	s
2 x H_8 (2 rotamers)	4.03 (minor) 4.04 (major)	q q
3 x H_9	1.17	t
H_{10a}	3.82	dddd
H_{10b}	4.12	dddd
H_{11}	5.74	ddt
H_{12t}	5.05	ddt
H_{12c}	5.08	ddt
2 x H_{14}	4.51	bdd
H_{15}	5.90	ddt
H_{16c}	5.17	ddt
H_{16t}	5.21	ddt
Ph	7.25-7.51	m


H12c
H12t
H11
H10
H10
O
2
1
N
3
5
6
7
O
O
8
9
H4
17
O
13
N
H14
H14
H15
H16t
H16c

(148)

Figure 5.6a ^{1}H NMR Spectrum (148)

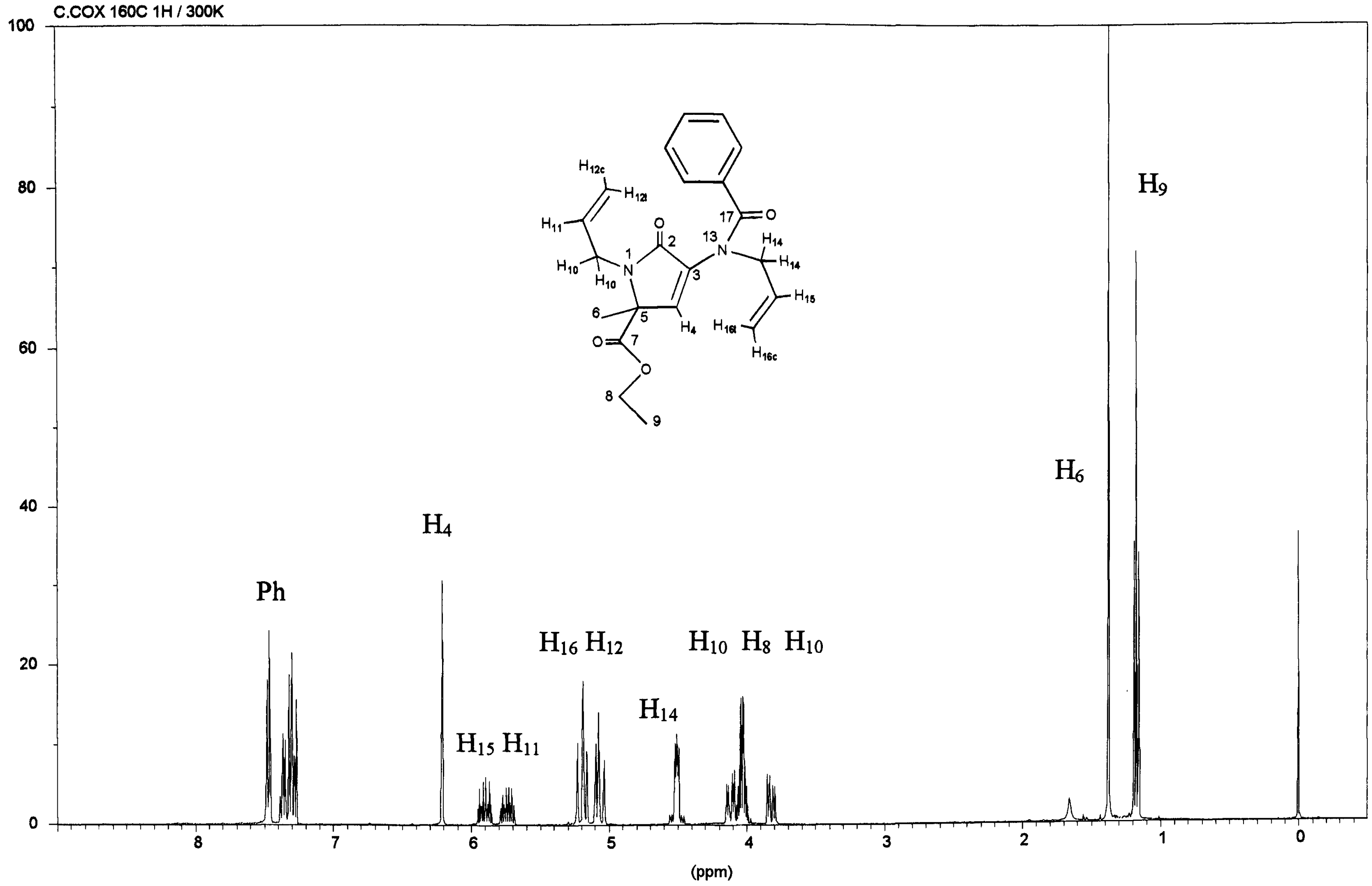
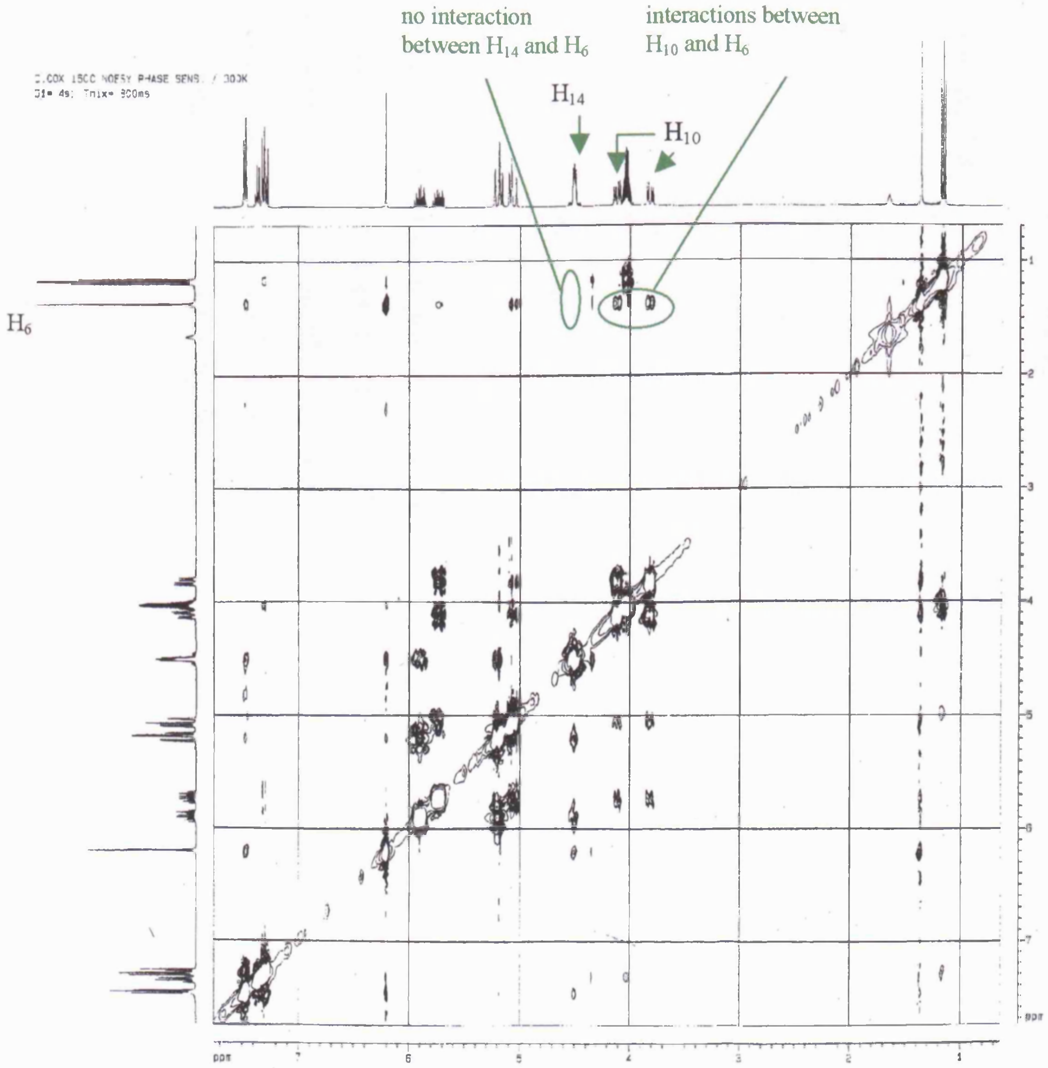


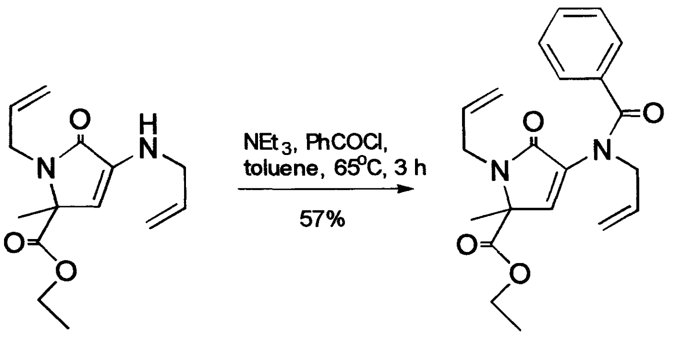
Figure 5.6b ^{1}H NOESY Spectrum **(148)**



The methyl group labelled 6 was observed as a singlet at δ 1.37. ^1H NOESY interactions between H_{10} and H_6 were observed which distinguished between the two *N*-allyl groups and allowed confirmation of the correct signal assignments; no interaction was observed between H_6 and H_{14} (Figure 5.6b). Protons H_{10a} and H_{10b} are diastereotopic and appeared at different chemical shifts (as opposed to the signals for H_{14} which overlap).

Our structure for **(148)** was subsequently confirmed by complete X-ray analysis and the final crystal structure is shown in Figure 5.9c. **A** was assigned the same structure minus the benzoyl protecting group (Scheme 5.8). The unoptimised yield of **A** from allylamine was calculated at 27%.

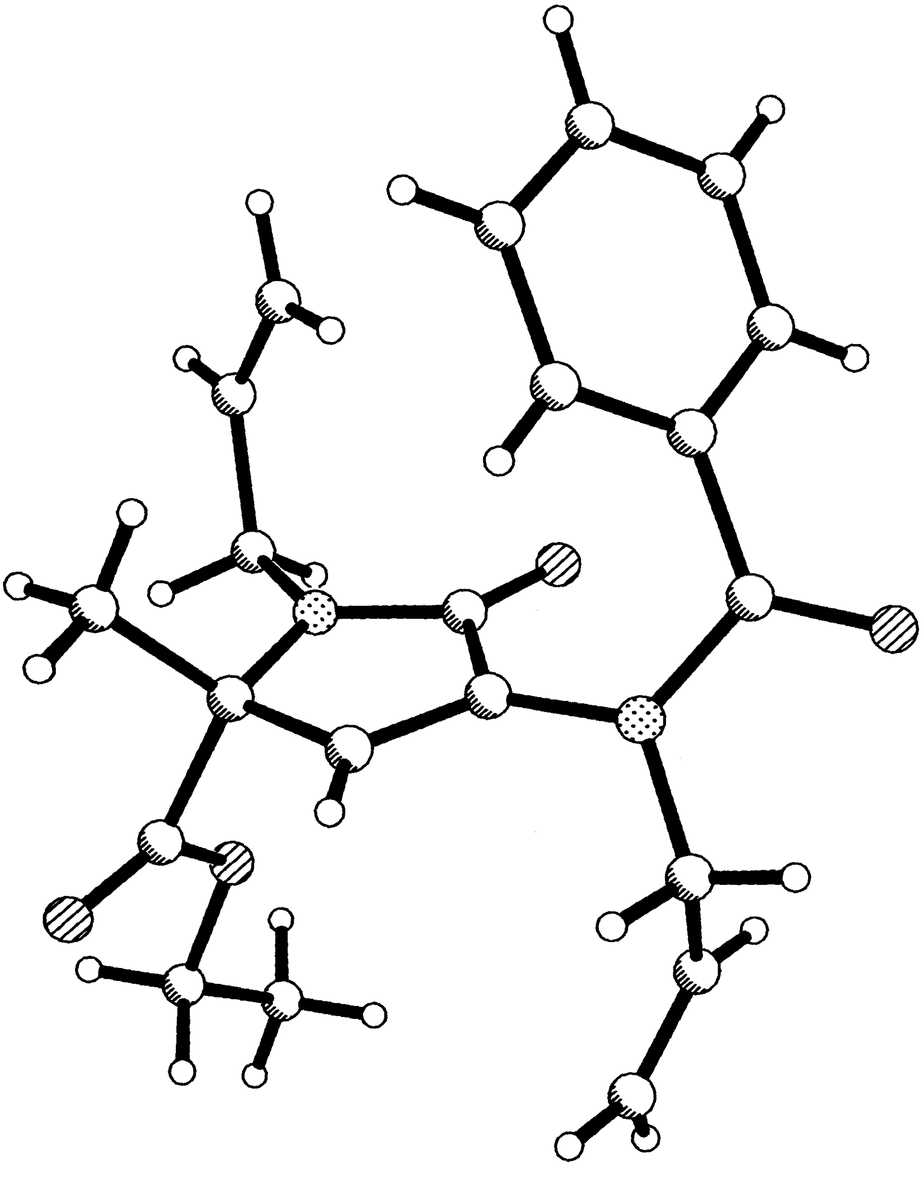
Scheme 5.8



A (147) **B (148)** crystalline

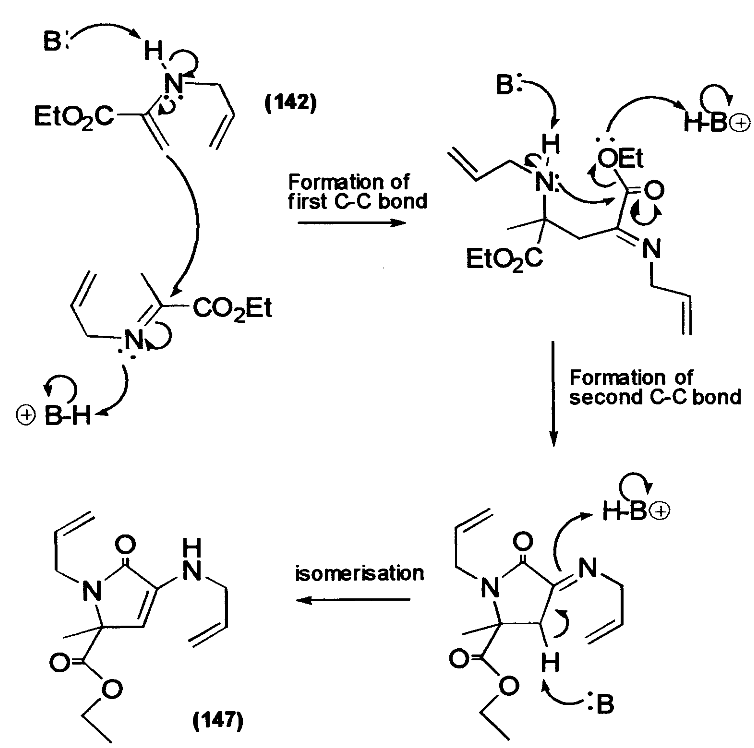
It has been mentioned previously that the *N*-allyl-dehydroalanine ethyl ester **(142)** was successfully *N*-protected with acetyl chloride (Scheme 5.2) and benzoyl chloride (Scheme 5.3). It seems likely however that with ethyl chloroformate, *N*-protection of **(142)** was not such facile a reaction and that a competing reaction to form **(147)** occurred, this reaction having been suppressed in the previous two cases.

Figure 5.9c X-Ray Structure of **(148)**



We have proposed a mechanism for the formation of **(147)** and this is illustrated in Scheme 5.10. The reaction must have occurred in neutral to basic conditions (equal measures of ethyl chloroformate and triethylamine). The sequence begins with a nucleophilic attack of one enamine with its tautomer, to form the first carbon-carbon bond needed to make the lactam. Nucleophilic attack by nitrogen at the most distant ester group with displacement of ethoxide provides the second carbon-carbon bond link and formation of the lactam. Finally, isomerisation of the imine group into an enamine moiety provides the product **(147)**.

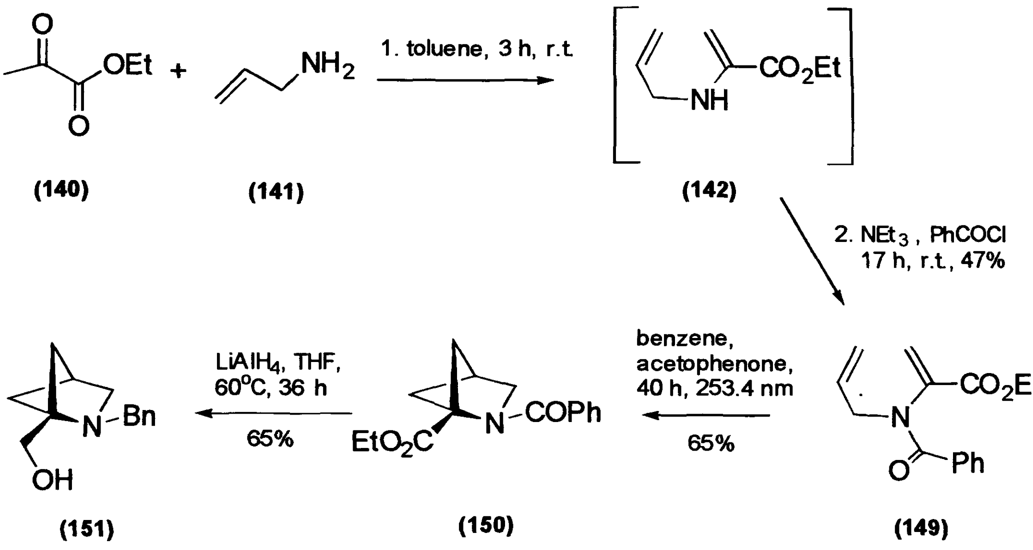
Scheme 5.10


B:
H
N
EtO2C
(142)
CO2Et
N
⊕ B-H
Formation of first C-C bond
B:
H
N:
OEt
O
H-B⊕
EtO2C
N
Formation of second C-C bond
H-B⊕
O
N
N
H
:B
isomerisation
O
H
N
N
O
O
(147)

Molecule **(147)** has an unusual structure featuring an α,β-unsaturated lactam ring and two exocyclic allyl groups. It should prove possible to build up many other interesting structures from **(147)** using a variety of experimental techniques, for example by metathesis of the double bonds, cycloadditions or reaction of the unsaturated nitrogen.

We now continued with our synthesis of the target bicyclic molecule **(57)**. Following failure to protect the *N*-allyl-dehydroalanine ethyl ester **(142)** using ethyl chloroformate, we had to choose another protecting group. Compound **(142)** was therefore protected using benzoyl chloride (Scheme 5.11) as used successfully by Malpass, Davies and Walker.[66]

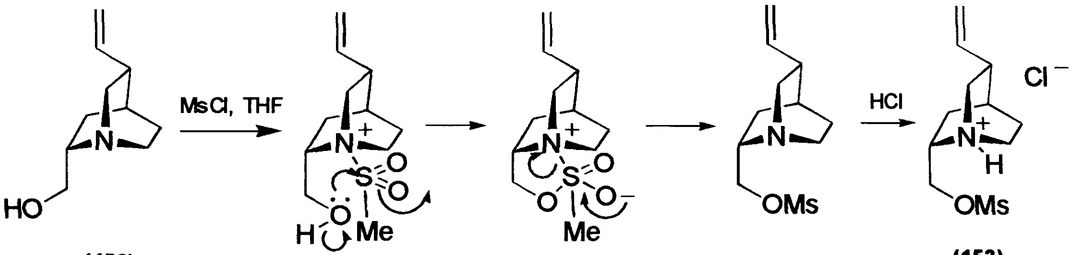
Scheme 5.11



N-Benzoyl-*N*-allyldehydroalanine ethyl ester **(149)** was made in 47% yield after column chromatography. The ester was dissolved in dry benzene, placed in a quartz tube with 0.2 mol% acetophenone and irradiated in Rayonet apparatus for 40 hours to provide 1-ethoxycarbony-2-benzoyl-2-azabicyclo[2.1.1]hexane **(150)** in 65% yield after chromatography. Treatment of **(150)** with lithium aluminium hydride reduced the *N*-protecting group down to benzyl with concomitant reduction of the ester group, affording the alcohol **(151)**. The NMR data of all three compounds **(149-151)** were in agreement with data provided by Davies[67] but high resolution ^1H and ^{13}C NMR spectroscopy allowed fuller characterisation of them (see experimental).

The next objective was functional group interconversion of the exocyclic hydroxymethyl with a view to attachment of a heterocyclic substituent. A recent publication by Schrake demonstrated how an azabicyclic nitrogen can participate as a neighbouring group, in a reaction to functionalise an exocyclic alcohol.[68] Scheme 5.12 illustrates how O-sulfonylation of the hydroxymethyl group in Quincorine **(152)** is aided by the bridgehead nitrogen. The nitrogen acts as an intramolecular catalyst in the reaction, behaving as a base; the lone pair of electrons co-ordinate to the mesyl group, holding it in place and enabling nucleophilic attack on the sulfur by the hydroxyl oxygen. The sulfur-nitrogen bond subsequently breaks affording the O-mesylated product **(153)**.

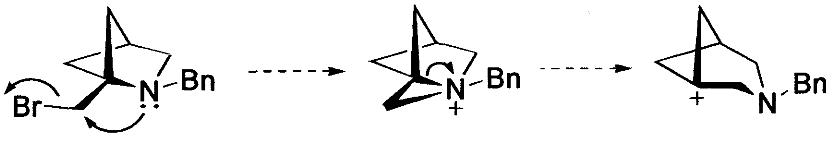
Scheme 5.12



(152) **(153)**

The above reaction prompted us to consider the possibility that conversion of the hydroxyl group in **(151)** into a halide might encourage the basic nitrogen to attack at the methylene carbon, displacing the halogen and effecting rearrangement of the azabicyclic skeleton. However, the potential cations resulting from such a scenario seem strained and unlikely, as demonstrated by **(155)** and **(156)** shown in Scheme 5.13.

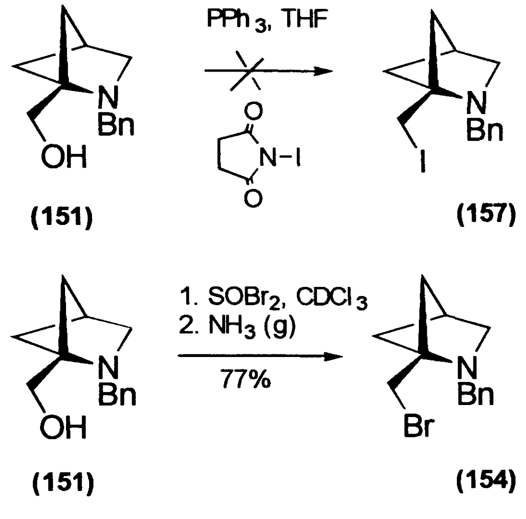
Scheme 5.13



(154) **(155)** **(156)**

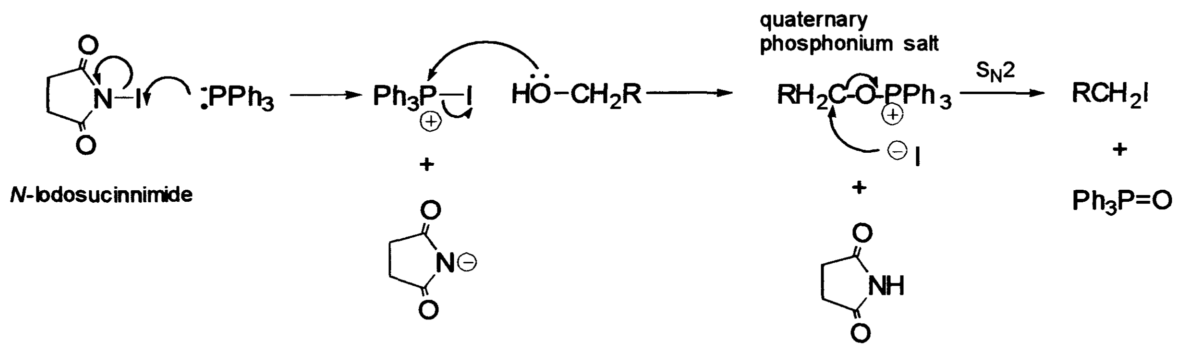
Attempted iodination of **(151)** using *N*-iodosuccinimide and triphenylphosphine failed to produce any product. Conversely, bromination of **(151)** with thionyl bromide did succeed in good yield (Scheme 5.14).

Scheme 5.14


PPh3, THF
N-I
OH
N
Bn
I
(151)
(157)
1. SOBr2, CDCl3
2. NH3 (g)
77%
Br
(151)
(154)

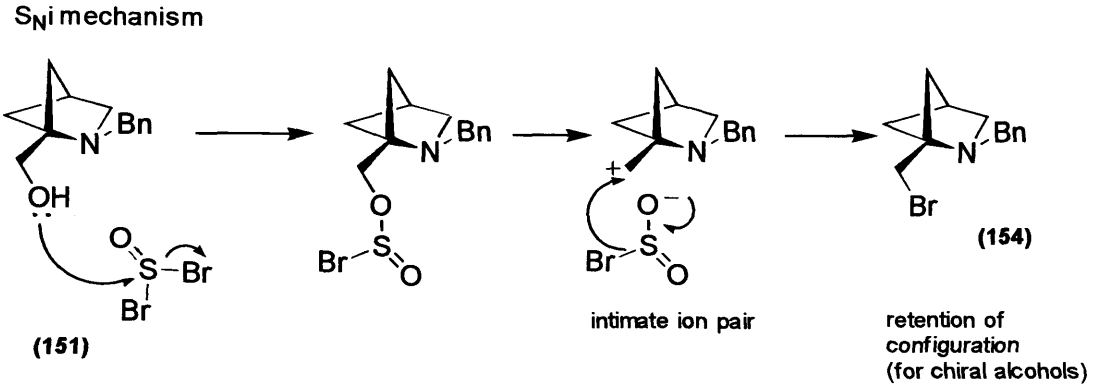
Iodination is thought to proceed *via* an S_N2 mechanism where the intermediate quaternary phosphonium salt is cleaved by iodine with inversion of stereochemistry[69] (Scheme 5.15). The steric restraints associated with such an S_N2 reaction at a neopentyl-like centre may have been the cause of the reaction's failure.

Scheme 5.15


N-Iodosucinnimide
:PPh3
Ph3P–I
HO-CH2R
quaternary phosphonium salt
RH2C-O-PPh3
I
NH
N
SN2
RCH2I
+
Ph3P=O

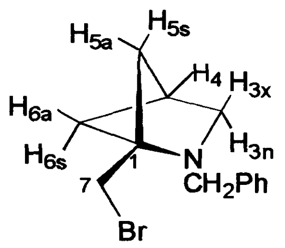
In contrast, thionyl bromide is thought to react *via* an internal nucleophilic substitution mechanism - S_Ni[70] (Scheme 5.16). Nucleophilic attack by the hydroxyl oxygen onto the thionyl sulfur is followed by fragmentation into an intimate ion pair. The nearby bromide ion is able to shift onto the methylene carbocation to give 1-bromomethyl-2-benzyl-2-azabicyclo[2.1.1.]hexane **(154)**.

Scheme 5.16


S_Ni mechanism
Bn
N
OH
O
S
Br
Br
(151)
Bn
N
O
S
Br
O
Bn
N
+
O
S
Br
O
intimate ion pair
Bn
N
Br
(154)
retention of
configuration
(for chiral alcohols)

The ^1H NMR spectrum of **(154)** shows only four singlets in addition to an aryl multiplet (Figure 5.17). The presence of many small couplings for each proton results in broadened aliphatic signals. The singlet at δ 1.68 is the result of accidental equivalence of the 'anti'-protons H_{5a}, H_{6a} and the 'syn'-protons H_{5s}, H_{6s} (see Figure 5.18 for proton labels).

Figure 5.18


H5a
H5s
H4
H3x
H6a
H6s
1
N
H3n
7
CH2Ph
Br

(154)

The bridgehead proton H_4 appears at δ 2.63, H_{3n} and H_{3x} at δ 2.68, the benzylic protons plus two for H_7 at δ 3.63 and finally the aryl signals at δ 7.20-7.48.

Many different methods were subsequently employed in an attempt to couple the chloropyridine ring onto the methylene carbon. An initial strategy involved generating a Grignard reagent from **(154)**, with activated magnesium, and coupling it with 2-chloro-5-iodopyridine **(75)** using a transition metal catalyst. Mass spectrometry revealed that the product formed was actually **(157)**, the iodinated version of **(154)** (Figure 5.19).

Figure 5.17 ^{1}H NMR Spectrum (154)

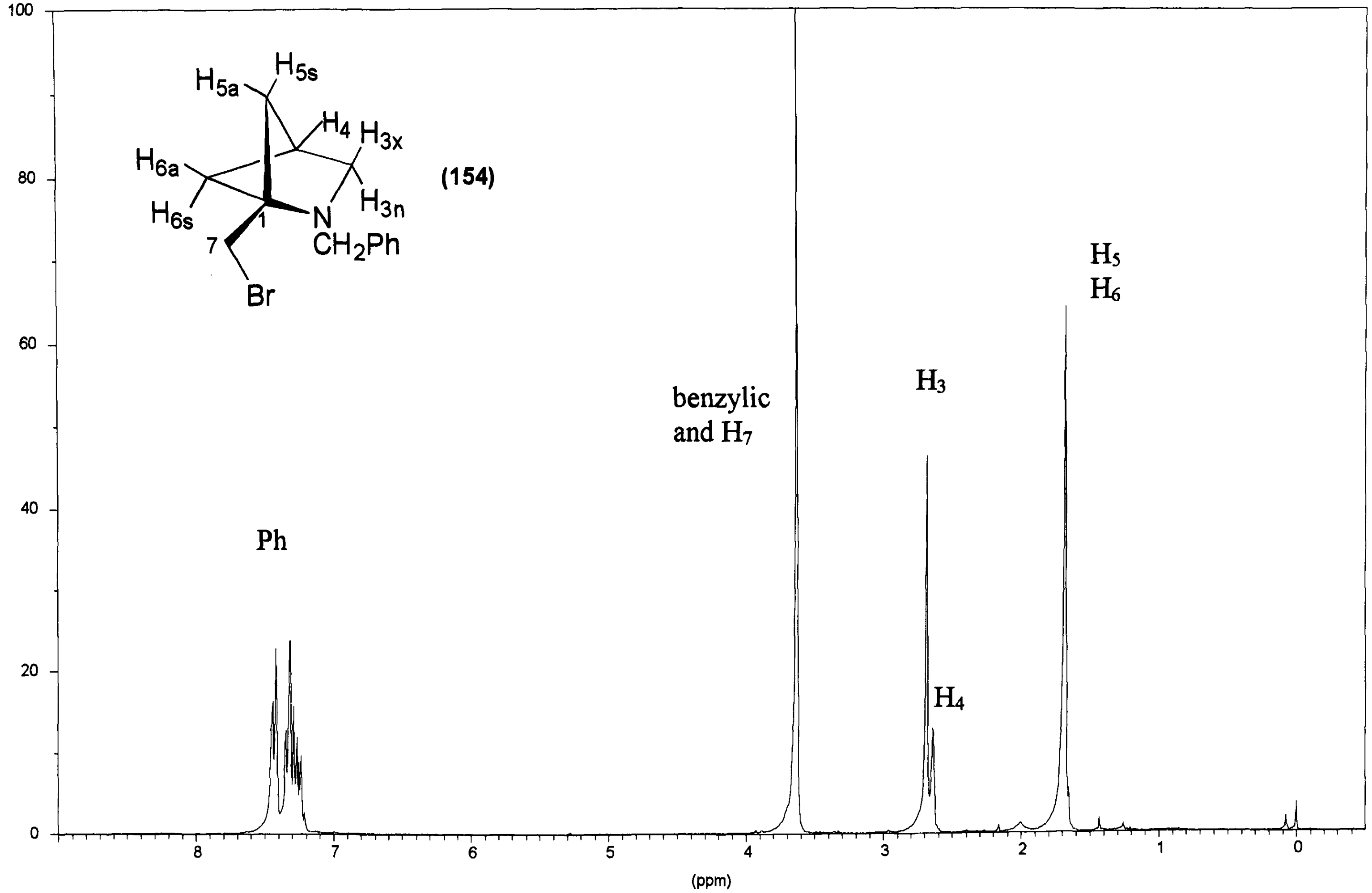
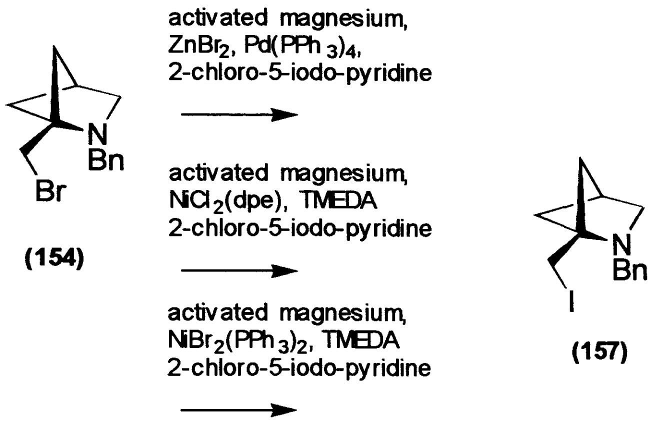
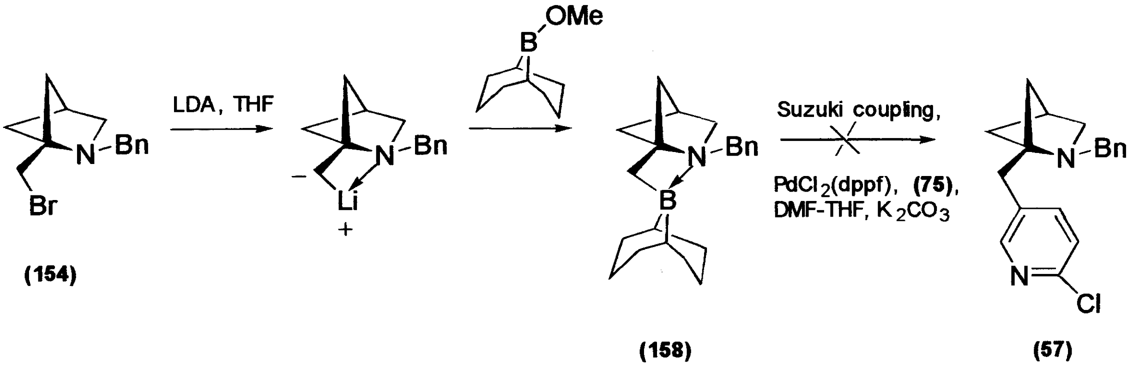


Figure 5.19


activated magnesium,
ZnBr2, Pd(PPh3)4,
2-chloro-5-iodo-pyridine
activated magnesium,
NiCl2(dpe), TMEDA
2-chloro-5-iodo-pyridine
activated magnesium,
NiBr2(PPh3)2, TMEDA
2-chloro-5-iodo-pyridine
N
Bn
Br
(154)
N
Bn
I
(157)

A Suzuki coupling approach was also attempted; exchange of the bromine for boron using *B*-methoxy-9BBN to form the intermediate **(158)**, was confirmed on observation of the molecular ion by mass spectrometry. Coupling of **(158)** with **(75)** using the transition metal catalyst was, however, unsuccessful (Figure 5.20).

Figure 5.20

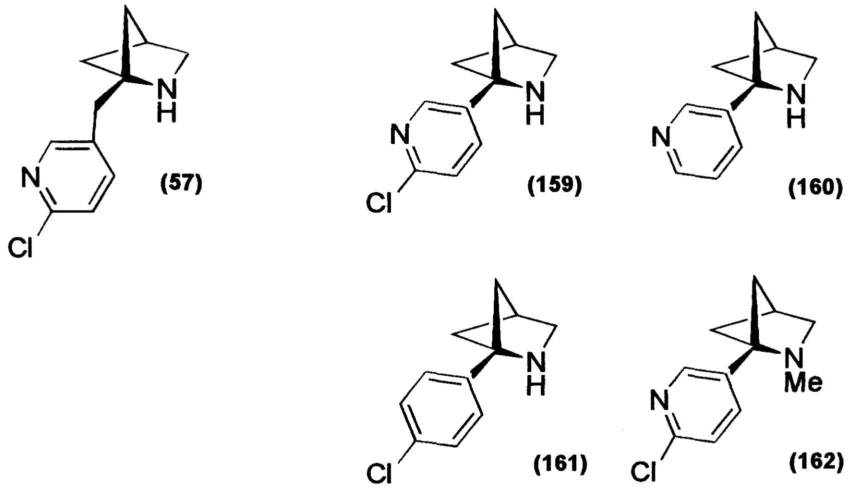

N-Bn
Br
(154)
LDA, THF
N-Bn
Li
+
-
OMe
B
N-Bn
B
(158)
Suzuki coupling,
PdCl2(dppf), (75),
DMF-THF, K2CO3
N-Bn
N
Cl
(57)

The coupling reactions may have failed due to the steric bulk of the two fragments that were to be connected. Although both the azabicyclic and aromatic components may well have loaded onto the catalyst, the correct alignment of the two fragments required for bond formation may not have occurred. This led to the fragments being released separately.

5.3 Epibatidine Analogues Synthesised by Piotrowski

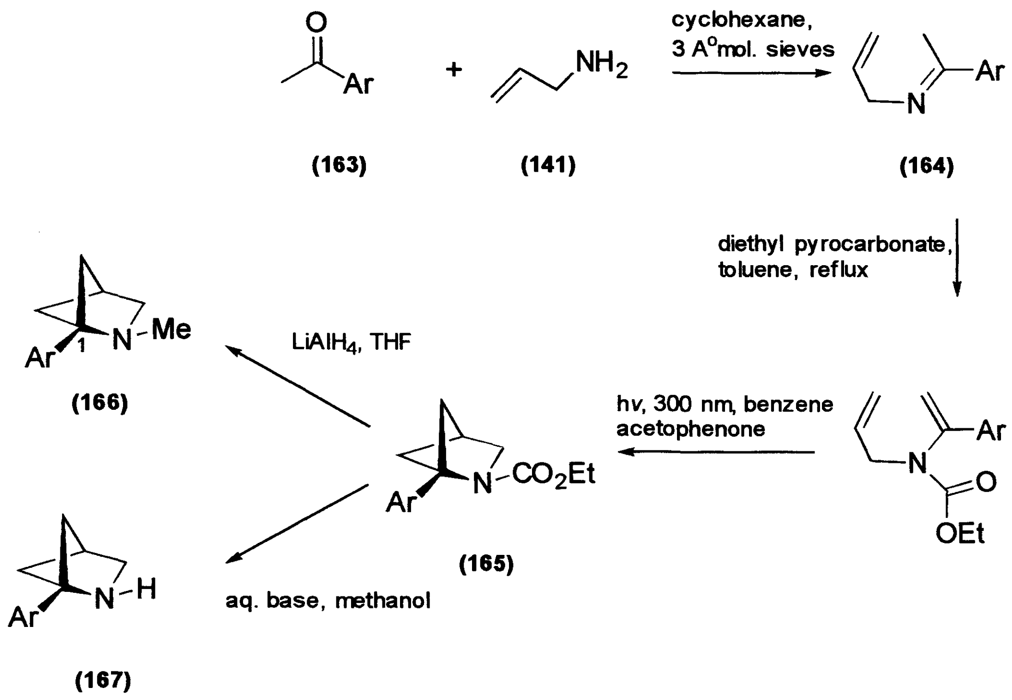
On commencement of our work on 2-azabicyclo[2.1.1]hexane systems as epibatidine analogues, we were unaware of any other activity in this specific area. A recent publication by Piotrowski,[71] however, illustrates the synthesis of several epibatidine analogues including **(159-162)**. All of these analogues contain a heteroaromatic ring attached directly to the bicycle (Figure 5.21) in contrast to our intended analogue **(57)** in which the aromatic heterocycle is attached *via* a methylene chain.

Figure 5.21



The general synthetic route to the molecules made by Piotrowski was based on that devised by Pirrung in Scheme 5.2. Scheme 5.22 shows that by having used an appropriately substituted ketone **(163)** in the condensation reaction with allylamine **(141)**, an arylated imine **(164)** was produced which, after *N*-protection, underwent cycloaddition to form a 1-arylated-2-azabicyclo[2.1.1]hexane derivative **(165)**. The *N*-ethoxycarbonyl group was either reduced to methyl **(166)** with lithium aluminium hydride or cleaved in base to give the nor-analogue **(167)**. Individual yields for every step were not quoted.

Scheme 5.22



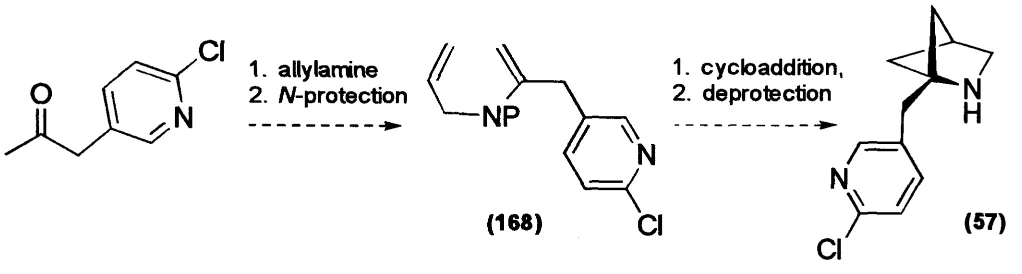
Ar
+
NH2
cyclohexane,
3 A°mol. sieves
Ar
N
(163)
(141)
(164)
diethyl pyrocarbonate,
toluene, reflux
Ar
1
N-Me
(166)
LiAlH4, THF
hv, 300 nm, benzene
acetophenone
Ar
N-CO2Et
N
Ar
O
OEt
(165)
Ar
N-H
aq. base, methanol
(167)

Pharmacological testing on the analogue molecules showed that **(162)** acted as a nicotinic agonist in embryonic cockroach neuronal cells, although the level of potency was not indicated. Molecular modelling studies performed by Piotrowski revealed inter-nitrogen distances for **(162)** ranging from 4.32-4.99 A^0, depending on rotation of the C_1-aryl bond.

5.4 Future Work

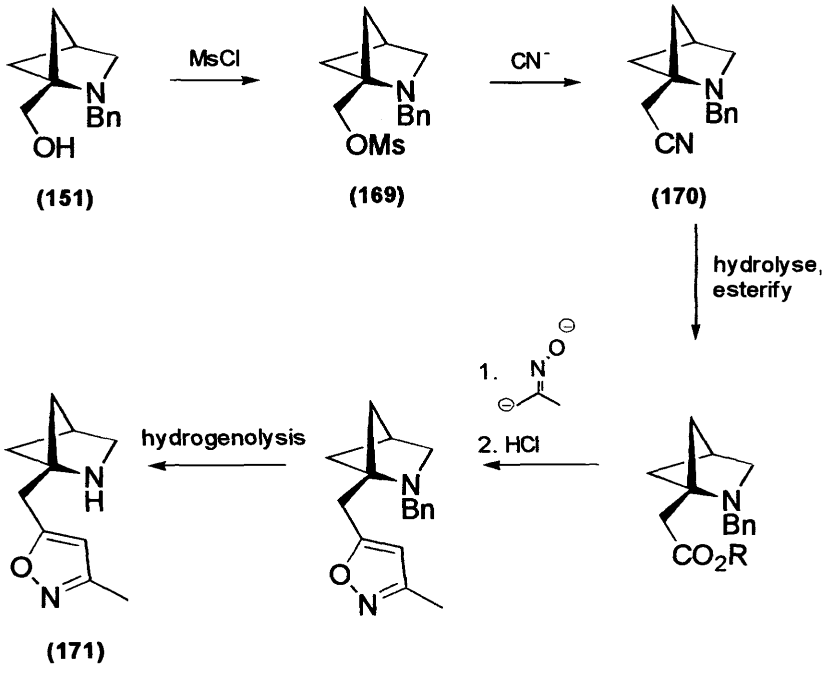
It may be possible to synthesise **(57)** *via* the route devised by Piotrowski,[71] whereby the chloropyridine ring is incorporated into the acyclic imine **(168)** before cycloaddition (Scheme 5.23). This imine is not however conjugated to a carbonyl or aryl group at the 2-position (c.f. **(146)**,**(164)**) and this may potentially affect the ease of cycloaddition.

Scheme 5.23


Cl
O
N
1. allylamine
2. N-protection
NP
N
(168)
Cl
1. cycloaddition,
2. deprotection
N
H
N
Cl
(57)

Although it proved impossible to synthesise **(57)** by the route followed by ourselves, this route might be utilised to make the isoxazole derivative **(171)** (Scheme 5.24).

Scheme 5.24


N
Bn
OH
(151)
MsCl
N
Bn
OMs
(169)
CN⁻
N
Bn
CN
(170)
hydrolyse,
esterify
N
Bn
CO2R
1.
2. HCl
N
Bn
O
N
hydrogenolysis
N
H
O
N
(171)

Conversion of the alcohol **(151)** into the mesylate **(169)** followed by nucleophilic substitution for cyanide should give **(170)**. These two reactions were performed on Quincorine **(152)** by Schrake and the conditions optimised.[68] Subsequent reaction to form the oxazole moiety should follow the path described previously (Chapter 3, Scheme 3.18).

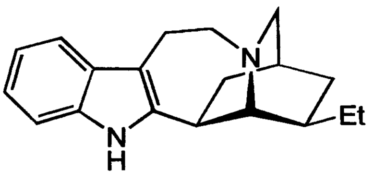
CHAPTER 6

Synthetic Approaches Towards Endo-5-(and 6-)(2'-chloro-5'-pyridyl)-2-azabicylo[2.2.2]octanes

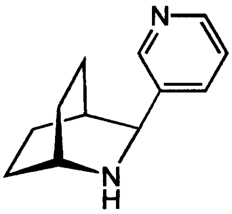
6.1 2-Azabicyclo[2.2.2]octane Analogues of Epibatidine

There are many azabicyclo[2.2.2]octane-based alkaloids found in nature. Amongst those that contain the nitrogen in position 2 are the *Iboga* alkaloids of which Ibogaine **(172)** (Figure 6.1) is a member. Ibogaine is extracted from the African shrub, *Tabernanthe iboga* and has been shown to act as an antagonist at the nicotinic receptor, blocking both ganglionic neurotransmission and central dopamine release. Chapter 1 gave examples of some 3-substituted-2-azabicyclo[2.2.2]octanes that have been synthesised as epibatidine analogues; analogue **(45)** was shown to be active at the nicotinic receptor.[1]

Figure 6.1



(172) Ibogaine

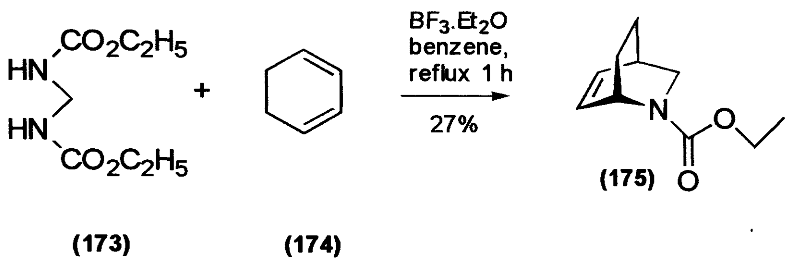


(45)

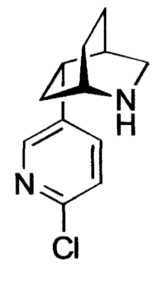
6.2 Synthesis of 2-Azabicyclo[2.2.2]octanes

A simple approach to the synthesis of the 2-azabicyclo-[2.2.2]oct-5-ene skeleton based on Diels-Alder cycloaddition, was devised by Cava.[72] The reaction involves the addition of 1,3-cyclohexadiene **(174)** to methyleneurethane; the latter having been generated *in situ* by the action of boron trifluoride on methylenebisurethane **(173)** (Scheme 6.2).

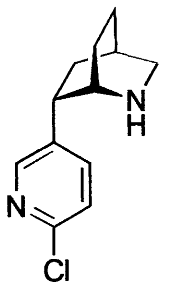
Scheme 6.2


$CO_2C_2H_5$
HN
HN
$CO_2C_2H_5$
+
$BF_3.Et_2O$
benzene,
reflux 1 h
27%
N
O
O
(175)
(173)
(174)

We considered that **(55)** and **(56)** would make interesting targets as they offer increased flexibility in the azabicyclic skeleton as compared to the azabicyclo[2.2.1]heptane skeleton of **(51)** and **(52)**. Pharmacological testing would highlight how this flexibility affects affinity and selectivity at the nAChR. Our initital strategy for the synthesis of **(55)** and **(56)** was *via* a reductive Heck reaction on **(175)** followed by *N*-deprotection.



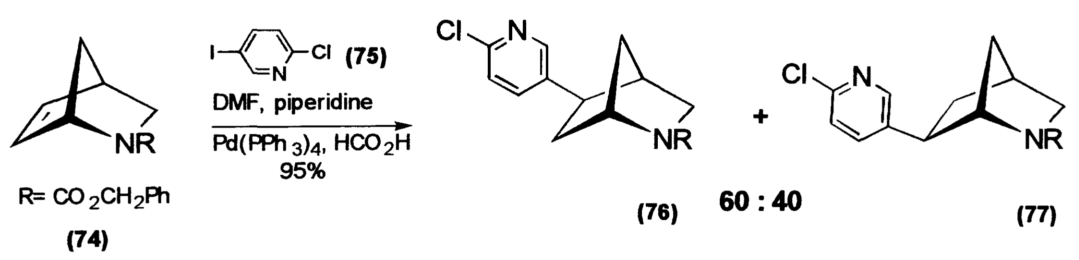
(55)



(56)

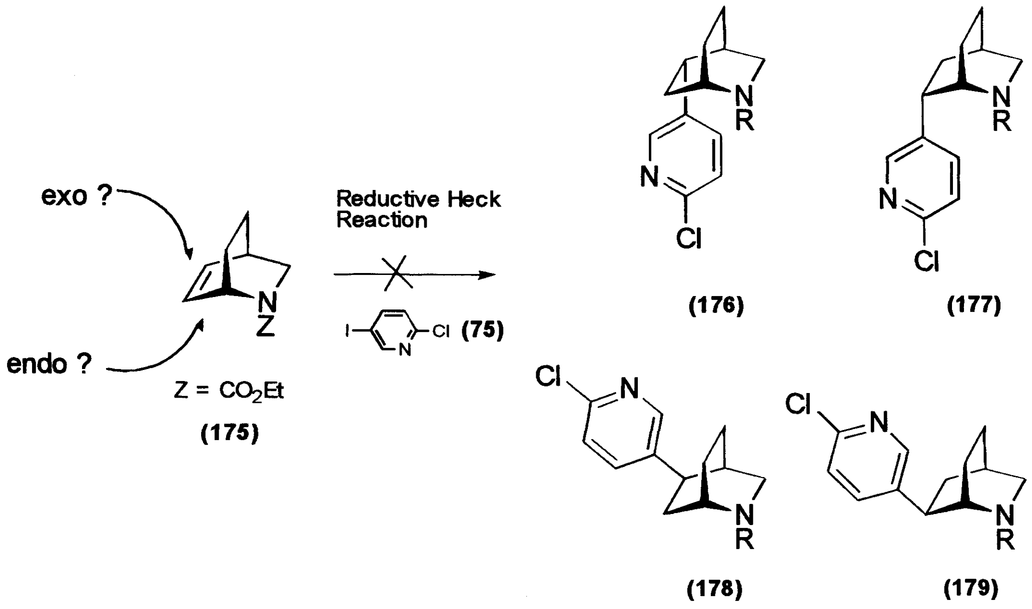
It will be recalled that a reductive Heck reaction on the 2-azanorbornene system **(74)** resulted solely in the production of *exo-* regioisomers **(76)** and **(77)** (Scheme 6.3).

Scheme 6.3


NR
R= CO_2CH_2Ph
(74)
I
Cl
N
(75)
DMF, piperidine
$Pd(PPh_3)_4$, HCO_2H
95%
Cl
N
NR
(76)
60 : 40
+
Cl
N
NR
(77)

The azabicycle **(175)** however, has increased steric bulk on the *exo*-face of the molecule, owing to the two-carbon bridge; we hoped that this may decrease the preference for approach of an electrophile from the *exo*-face. We considered that it would be interesting to discover which of the four possible regio- and stereoisomers **(176-9)** would be formed (Scheme 6.4).

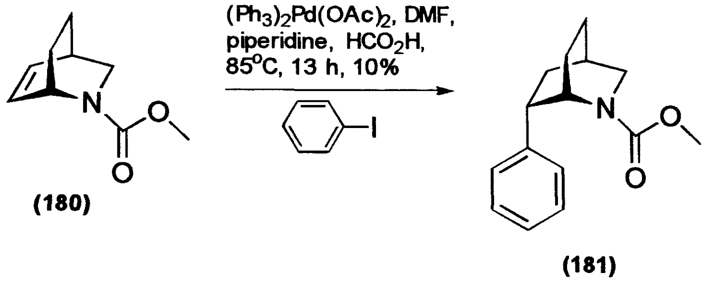
Scheme 6.4



We prepared the azabicycle **(175)** in 55% yield after column chromatography. Unfortunately, the reductive Heck reaction gave only a very small quantity of a mixture of crude products, possibly from coupling (less than 5%), which was impossible to separate by chromatography. No improvement in the reaction resulted from increasing the temperature from 80°C up to 150°C.

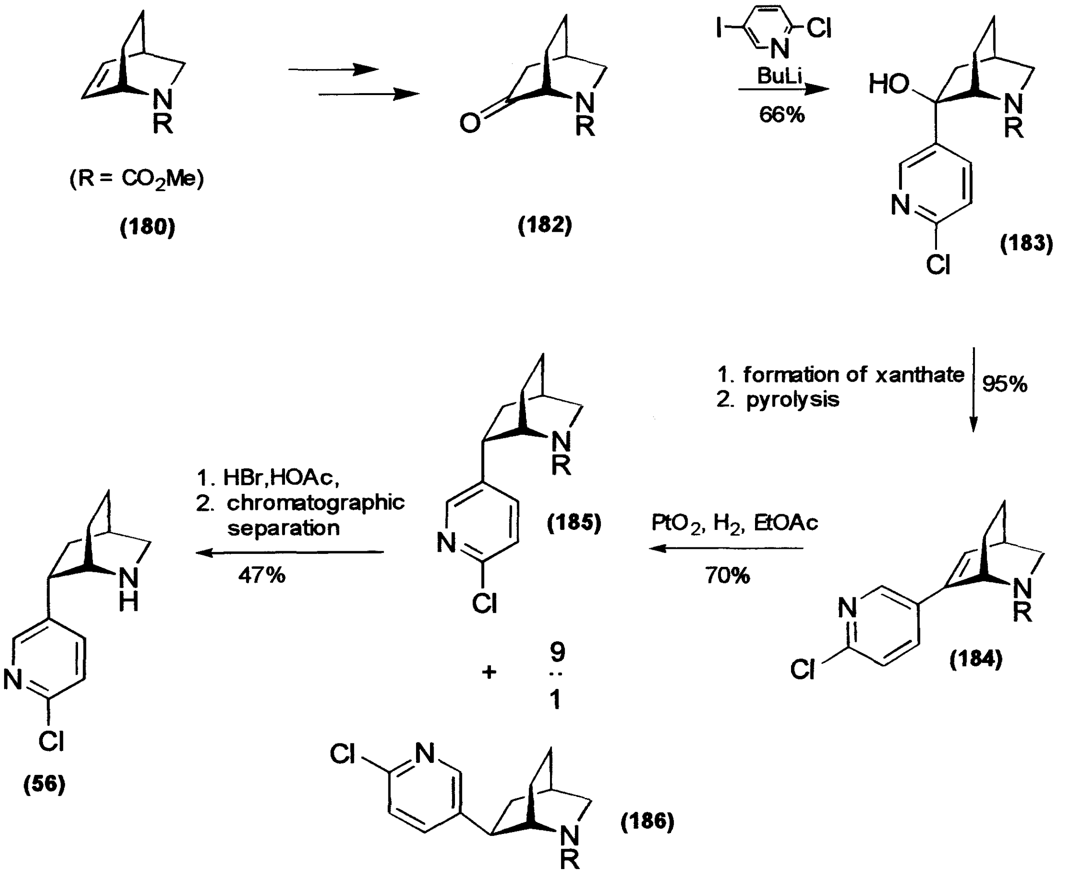
Before we could consider another synthetic approach, a complete synthesis of the target products **(55)** and **(56)** was published by Krow and co-workers.[73] One of their approaches had also been the reductive Heck reaction; in pilot studies, iodobenzene was coupled with the *N*-methoxycarbonyl protected azabicycle **(180)**. Surprisingly, only one isomer **(181)** was isolated from the crude product in a poor 10% yield (Scheme 6.5). In agreement with our own work, their attempts to couple 2-chloro-5-iodopyridine **(75)** with the azabicycle **(180)** failed.

Scheme 6.5


(Ph3)2Pd(OAc)2, DMF,
piperidine, HCO2H,
85°C, 13 h, 10%
I
N
O
O
(180)
(181)

The Krow group did successfully synthesise the *endo*-chloropyridyl-substituted azabicycles **(55)** and **(56)** from keto-precursors, in a route that mirrored our own synthesis of the 2-azanorbornyl analogues **(51)** and **(52)**. Synthesis of **(56)** is detailed in Scheme 6.6.

Scheme 6.6


N
R
(R = CO2Me)
(180)
O
(182)
I
N
Cl
BuLi
66%
HO
(183)
1. formation of xanthate
2. pyrolysis
95%
PtO2, H2, EtOAc
70%
(184)
(185)
1. HBr,HOAc,
2. chromatographic separation
47%
N
H
(56)
+
9 : 1
(186)

Nucleophilic attack on the ketone **(182)** resulted in the tertiary alcohol **(183)** which was confirmed as one stereoisomer by X-ray crystallography. Dehydration of the alcohol was achieved by conversion to, and pyrolysis of, the xanthate. Hydrogenation of **(184)** over a platinum oxide catalyst gave a mixture of *endo*- and *exo*-stereoisomers **(185)** and **(186)** in a ratio of 9:1. The stereoisomers were deprotected under acidic conditions before chromatographic separation and **(56)** isolated in 47% yield. The 5-*endo*-chloropyridyl-substituted azabicycle was made in the same way. This synthesis shows that increasing the upper carbon bridge to 2 carbon atoms makes the *exo*- face of the 2-azabicyclo[2.2.2]octane system more sterically hindered. This can be seen by the results of nucleophilic attack on the ketone **(183)**; where addition from the *endo*- face was preferred and in the hydrogenation of **(184)** where some of the *exo*-stereoisomer **(186)** was produced.

Both **(55)** and **(56)** underwent biological evaluation as their oxalate salts. Tests on rat tissue revealed that both molecules were active as nicotinic agonists but were less selective in binding than epibatidine. This was suggested by the severe side effects observed on administration of analgetic doses of the analogues to live rats.

It can be concluded that the extra flexibility associated with an 2-azabicyclo-[2.2.2]octane skeleton, as compared to the 7-azabicyclo[2.2.1]heptane skeleton of epibatidine, has had a detrimental effect on the selectivity of analogue molecules in binding to the nicotinic receptor. This is analogous with the decrease in binding affinity noted when the 8-azabicyclo[3.2.1]octane skeleton of homoepibatidine **(47)** was increased to the 9-azabicyclo[4.2.1]nonane system of *bis*-homoepibatidine **(48)** (see Chapter 1 for details).

CHAPTER 7

Experimental

Instrumentation

NMR spectra were recorded at 250 MHz using a Bruker ARX 250 spectrometer, at 300 MHz using a Bruker DPX 300 spectrometer and at 400 MHz using a Bruker DRX 400 spectrometer. Chemical shifts are expressed in p.p.m. (δ) relative to an internal standard (TMS). Signal characteristics are described using standard abbreviations : s (singlet), d (doublet), dd (doublet of doublets), t (triplet), m (multiplet), b (broad). Signals were assigned with the routine assistance of ^1H-^1H COSY and ^1H-^{13}C COSY spectra and selective proton spin decoupling experiments. Where data are quoted for two rotamers, overlapping signals are shown in italics but may be quoted separately for reasons of clarity even though they may not be fully resolved or assigned.

Nominal mass spectra were measured on a Micromass Quattro L.C. Triple Quadropole spectrometer and were obtained using ionisation by electrospray. Accurate mass measurements were measured on a Kratos Concept 1H Sector mass spectrometer and were obtained using ionisation by fast atom bombardment (unless electron ionisation (e.i.) is indicated). Mass spectra were determined in units of mass relative to charge ($^m/z$).

IR spectra were recorded on a PE 298 FT spectrometer. Band intensities are described using standard abbreviations: s (strong), m (medium), w (weak), br (broad).

Melting point measurements were made using a Kofler hot stage apparatus and are uncorrected.

Removal of solvent under reduced pressure was carried out using a rotary evaporator followed by a high vacuum pump.

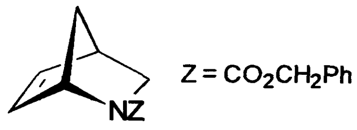
Technical

Reactions were performed under dry nitrogen where indicated using solvents dried by standard methods. Dry dichloromethane, toluene, benzene and triethylamine were distilled from calcium hydride. Diethyl ether was distilled from $LiAlH_4$. Petroleum ether was distilled prior to use. Tetrahydrofuran was distilled from benzophenone in the presence of sodium wire. Methanol and ethanol were purified with magnesium and iodine. All other solvents, formic acid and piperidine were purified as described by Perrin.[74]

Flash chromatography was carried out using silica gel (60) manufactured by Fischer. *The silica was basified before use by immersion in the eluting solvent saturated with ammonia gas. Thin layer chromatography was conducted on standard commercial aluminium sheets pre-coated with a 0.2mm layer of silica gel (Merck Kieselgel 60-254).

Samples of potassium azodicarboxylate and methylenebisurethane were kindly provided by Anna Wallis and Leah Walker respectively. All other reagents were supplied by The Aldrich Chemical Company and used as received with the exception of Burgess's reagent, supplied by Sigma, and iodotrimethylsilane, supplied by Lancaster.

N-(Benzyloxycarbonyl)-2-azabicyclo[2.2.1]hept-5-ene (74)



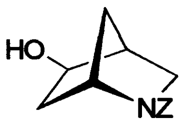
(74)

Based on the literature procedure of Carroll,[35] formaldehyde (37% soln., 9.20ml, 0.114mol) was added to a solution of ammonium chloride (12.1g, 0.227mol) in 42ml water and stirred for 30 min. Freshly distilled cyclopentadiene (5.00g, 0.0756mol) was added and stirring continued at room temperature for 17 hrs. The aqueous solution was washed with ether (2 x 15ml) and cooled to 0°C. Sodium hydroxide (12M soln.,15ml) was added dropwise to the solution and when addition was halfway through (at pH 12), benzyl chloroformate (10.5ml, 0.0733mol) was added dropwise simultaneously. Addition of the sodium hydroxide was finished just after that of the chloroformate and stirring continued for 2 hrs. Water (42ml) was added to the reaction mixture which was extracted with dichloromethane (4 x 42ml). The organic layers were combined, dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography* using 7:3 petroleum ether (b.p. 40-60°C): diethyl ether (r.f. 0.34) to yield **(74)** (7.10g, 41%) as a pale yellow oil.

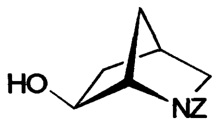
δ_H (250 MHz, $CDCl_3$) (rotamer ratio *ca.*53:47; signals common to both rotamers are listed in italics): *1.58* (bs, 2H, $H_{7s/7a}$), *2.71* (2 overlapping bd, J = 9.5 Hz, 1H, H_{3n}), *3.19* (bs, 1H, H_4), *3.39* (dd, J = 9.5, 3.0 Hz, 1H, H_{3x}), [4.70 (s, major rotamer) and 4.80 (s, minor rotamer), 1H, H_1], *5.12* (m, 2H benzylic CH_2), *6.28* (bs, 1H, H_5), [6.38 (bs, major rotamer) and 6.28 (bs, minor rotamer), 1H, H_6], *7.35* (bs, 5H, Ph). Many signals remained broad at this temperature/field but all the expected spin-spin interactions (including long-range 'W' interactions) were revealed by the HH COSY spectrum.

[Comparative literature data:[35] ^1H NMR δ_H (250MHz, $CDCl_3$) 1.53-1.58 (m,2H), 2.6-2.72 (m, 1H), 3.19-3.2 (m,1H), 3.36-3.41 (m,1H), 4.61-4.8 (m,1H), 5.11-5.25 (m,2H), 6.27-6.38 (m,2H), 7.25-7.39 (m,5H)].

exo-N-(Benzyloxycarbonyl)-2-azabicyclo[2.2.1]heptan-5-ol (92)
exo-N-(Benzyloxycarbonyl)-2-azabicyclo[2.2.1]heptan-6-ol (93)



(92)



(93)

Z = CO_2CH_2Ph

A solution of **(74)** (6.38g, 27.8mmol) in THF (340ml) was placed in a flame-dried, 3-necked flask equipped with a septum cap, under a nitrogen atmosphere and stirred at -78°C. BH_3.THF complex (1M, 720ml, 72.0mmol) was injected dropwise through the septum and after 10 mins the solution allowed to warm to room temperature. Stirring was continued for 2.5 hours when the reaction was quenched by sequential addition of water (16ml), sodium hydroxide (6M, 16ml, 96mmol) and hydrogen peroxide (30%w.v., 16ml, 141mmol). The reaction mixture was then stirred for a further 30 mins after which the solvent was removed under reduced pressure. The white residue was partitioned between diethyl ether (300ml) and water (50ml), the organic layer was washed with water (50ml) then brine (50ml), dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography*, eluting with diethyl ether to yield **(93)** (r.f. 0.38) (3.26g, 13.2mmol, 47.5%) and **(92)** (r.f. 0.18) (2.69g, 10.9mmol, 39.2%) as pale yellow oils, ratio 55:45 (**(93)**:**(92)**).

(92): δ_H (400 MHz, $CDCl_3$) (rotamer ratio 53:47; signals common to both rotamers are listed in italics):

major rotamer: 1.47 (dddd, J = 13.5, 2.5, 2.5, ~1 Hz, 1H, H_{6x}), 1.59 (ddddd, J = 10.0, 2.5, 2.5, 1.5, 1.5, 1H, H_{7s}), *1.85* (ddddd, J = 10.0, 1.5, 1.5, ~1.0, ~1.0 Hz, 1H, H_{7a}), 2.07 (dddd, J = 13.5, 7.0, 2.5, <1 Hz, 1H, H_{6n}), *2.49* (bs, 1H, H_4), 2.77 (bs, 1H, OH), 2.93 (dd, J = 10.0, ~1 Hz, 1H, H_{3n}), 3.28 (dd, 10.0, 3.0 Hz, 1H, H_{3x}), *4.02* (dddd, J = 6.5, 2.5, 2.5, <1 Hz, 1H, H_{5n}), 4.27 (bs, 1H, H_1), *5.05-5.20* (m, 2H, benzylic CH_2), *7.25-7.50* (m, 5H, Ph).

minor rotamer: 1.49 (dddd, J = 13.5, 2.5, 2.5, ~1 Hz, 1H, H_{6x}), 1.57 (ddddd, J = 10.0, 2.5, 2.5, 1.5, 1.5, 1H, H_{7s}), *1.85* (ddddd, J = 10.0, 1.5, 1.5, ~1.0, ~1.0 Hz, 1H, H_{7a}), 2.15 (dddd, J = 13.5, 7.0, 2.5, <1 Hz, 1H, H_{6n}), *2.49* (bs, 1H, H_4), 2.73 (bs, 1H, OH), 2.91 (dd, J = 10.0, ~1 Hz, 1H, H_{3n}), 3.27 (dd, 10.0, 3.0 Hz, 1H, H_{3x}), *4.02* (dddd, J =

6.5, 2.5, 2.5, <1 Hz, 1H, H_{5n}), 4.32 (bs, 1H, H_1), *5.05-5.20* (m, 2H, benzylic CH_2), *7.25-7.50* (m, 5H, Ph).

δ_C (100.61 MHz, $CDCl_3$) (signals common to both rotamers are listed in italics): 44.3, 44.3, 55.8, 56.0, 72.3, 72.2 (3 x CH), 33.5, 34.0, 42.7, 42.9, 47.9, 48.0 (3 x CH_2), 66.4, 66.6 ($\underline{C}H_2Ph$), *127.6, 127.8, 128.3* (5 x aryl CH), *136.6* (1 x aryl C), 154.3, 154.6 (C=O).

ν_{max} (CH_2Cl_2): 3600w, 2940w, 2240w, 1680brs, 1420s, 1360m, 1330w, 1260w, 1100m, 1075m cm^{-1}.

$^m/_z$: 248 (MH^+), 270 (MNa^+)

$C_{14}H_{18}NO_3$ [MH^+] requires $^m/_z$ 248.12860; observed 248.12867

(93): δ_H (400 MHz, $CDCl_3$) (rotamer ratio 55:45; signals common to both rotamers are listed in italics):

major rotamer: 1.48 (dddd, J = 13.5, 4.8, 2.5, 2.5 Hz, 1H, H_{5x}), 1.54 (ddddd, J = 10.0, 4.0, 2.5, ~1, ~1 Hz, 1H, H_{7s}), 1.82 (dddd, J = 10.0, 1.5, ~1, ~1 Hz, 1H, H_{7a}), 1.83 (ddd, J = 13.5, 7.0, 2.5 Hz, 1H, H_{5n}), 2.30 (s, 1H, OH), *2.56* (bs, 1H, H_4), 2.89 (ddd, J = 9.0, 1.5, <1 Hz, 1H, H_{3n}), 3.22 (ddd, J = 9.0, 3.0, 3.0 Hz, 1H, H_{3x}), 4.04 (ddd, J = 7.0, 2.5, 4.0 Hz, 1H, H_{6n}), 4.14 (bs, 1H, H_1), *5.05-5.20* (m, 2H, benzylic CH_2), *7.25-7.50* (m, 5H, Ph).

minor rotamer: 1.45 (dddd, J = 13.5, 4.8, 2.5, 2.5 Hz, 1H, H_{5x}), 1.57 (ddddd, J = 10.0, 4.0, 2.5, ~1, ~1 Hz, 1H, H_{7s}), 1.78 (dddd, J = 10.0, 1.5, ~1, ~1 Hz, 1H, H_{7a}), 1.84 (ddd, J = 13.5, 7.0, 2.5 Hz, 1H, H_{5n}), 2.00 (s, 1H, OH), *2.56* (bs, 1H, H_4), 2.91 (ddd, J = 9.0, 1.5, <1 Hz, 1H, H_{3n}), 3.23 (ddd, J = 9.0, 3.0, 3.0 Hz, 1H, H_{3x}), 3.98 (ddd, J = 7.0, 2.5, 4.0 Hz, 1H, H_{6n}), 4.08 (bs, 1H, H_1), *5.05-5.20* (m, 2H, benzylic CH_2), *7.25-7.50* (m, 5H, Ph).

δ_C (100.61 MHz, $CDCl_3$) (signals common to both rotamers are listed in italics): 35.8, 35.3, *60.9*, 72.2, 71.6 (3 x CH), 33.7, 33.1, 39.4, 38.9, *51.6* (3 x CH_2), *66.6* ($\underline{C}H_2Ph$), *127.7, 127.8, 128.4* (5 x aryl CH), 136.8, 136.7 (1 x aryl C), *154.7* (C=O).

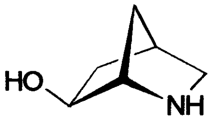
ν_{max} (CH_2Cl_2): 3620w, 2980w, 2890w, 2240w, 1695brs, 1430s, 1360m, 1160w, 1100m, 890m cm^{-1}.

$^m/_z$: 248 (MH^+), 270 (MNa^+)

$C_{14}H_{18}NO_3$ [MH^+] requires $^m/_z$ 248.12866; observed 248.12867

[For ^{1}H NMR comparative literature data see[35]]

exo-2-Azabicyclo[2.2.1]heptan-6-ol (95)



(95)

Compound **(93)** (0.033g, 0.13mmol) was dissolved in dry methanol (5ml) in a round-bottom flask equipped with a 3-way tap. Palladium on carbon catalyst (5%, 0.01mmol) was added and the reaction mixture stirred under hydrogen for 5 hours. The catalyst was filtered off through celite and the solvent removed under reduced pressure to yield **(95)** (13mg, 87%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$): 1.36 (ddd, J = 13.0, 5.5, 3.0 Hz, 1H, H_{5x}), 1.44 (ddddd, J = 10.0, 1.5, 1.5, 1.5, 1.5 Hz, 1H, H_{7s}), 1.70 (dddd, J = 10.0, 1.5, 1.5, 1.5 Hz, 1H, H_{7a}), 1.81 (ddd, J = 13.0, 7.0, 2.5 Hz, 1H, H_{5n}), 2.34-2.44 (m, 3H, H_{3n}, H_4, OH), 2.78 (ddd, J = 9.5, 3.0, 3.0 Hz, 1H, H_{3x}), 3.27 (bs, 1H, H_1), 3.83 (dddd, J = 7.0, 3.0, 1.5, 1.0 Hz, 1H, H_{6n}).

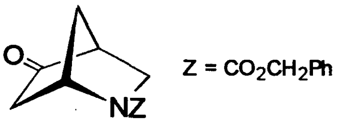
δ_C (100.61 MHz, $CDCl_3$): 33.5, 41.0, 50.0 (3 x CH_2), 36.0, 61.5 (2 x CH), 74.5 (CH(OH)).

ν_{max} ($CDCl_3$): 3640m, 2940m, 2250m, 1020s, 890s, 700m cm^{-1}.

$^m/_z$: 113 (M^+) (e.i.)

$C_6H_{11}NO$ [M^+] requires $^m/_z$ 113.08405; observed 113.08406

N-(Benzyloxycarbonyl)-2-azabicyclo[2.2.1]heptan-5-one (94)



(94)

Compound **(92)** (0.52g, 2.10mmol) was dissolved in acetone (200ml) with stirring and cooled to 0°C. Jones reagent was added dropwise until in excess and left stirring for 30 minutes. After ensuring that the solution remained orange, the excess chromic acid was destroyed by dropwise addition of propan-2-ol. The solution was basified with 6M sodium hydroxide and the solvent removed under reduced pressure. Water (150ml) was added and the solution extracted with dichloromethane (4 x 300ml). The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure. The crude product was purified by flash chromatography*, eluting with diethyl ether (r.f. 0.41) to yield **(94)**. (0.48g, 1.96mmol, 92%) as pale yellow oil.

Two rotamers were observed in a ratio of 54:46. For ^{1}H and ^{13}C NMR data, signals common to both rotamers are listed in italics.

δ_H (250 MHz, $CDCl_3$): *1.96* (d, J = 10.0 Hz, 1H, H_{7a}), *2.25* (d, J = 10.0 Hz, 1H, H_{7s}), *2.14-2.42* (m, 2H, H_{6x} and H_{6n}), *2.91* (bs, 1H, H_4), *3.40* (d, J = 11.0 Hz, 1H, H_{3n}), *3.54* (d, J = 11.0 Hz, 1H, H_{3x}), 4.66 (bs, 1H, H_1, minor rotamer), 4.71 (bs, 1H, H_1, major rotamer), *5.05-5.20* (m, 2H, benzylic), *7.20-7.50* (m, 5H, Ph).

δ_C (62.90 MHz, $CDCl_3$): 50.0, 50.7, 55.9, 56.1 (2 x CH), 37.2, 37.6, 45.5, 45.7, *47.3* (3 x CH_2), *66.9* ($\underline{C}H_2Ph$), *127.8*, *128.0*, *128.4* (5 x aryl CH), *136.4* (aryl C), *154.5* (urethane C=O), 212.5, 213.0 (C=O).

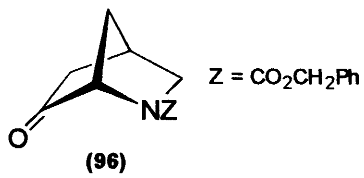
ν_{max} (CH_2Cl_2): 3050w, 2990w, 1755s, 1700s, 1420s, 1360w, 1260m, 1100m, 770-590w cm^{-1}.

$^{m}/_{z}$: 246 (MH^+), 268 (MNa^+)

$C_{14}H_{16}NO_3$ [MH^+] requires $^{m}/_{z}$ 246.11300; observed 246.11302

[For ^{1}H NMR comparative literature data see[35]]

N-(Benzyloxycarbonyl)-2-azabicyclo[2.2.1]heptan-6-one (96)



(96)

Compound **(93)** (3.26g, 13.2mmol) was dissolved in dichloromethane (27ml) in a 3-necked flask containing powdered molecular sieves (4A°, 6.7g) under an argon atmosphere, and stirred for 10 mins. To the stirred mixture was added NMO (2.31g, 19.7mmol) followed by TPAP (230mg, 0.65mmol) and the reaction was judged to be complete by TLC after 30 minutes. The crude reaction mixture was immediately subjected to flash chromatography*, eluting with dichloromethane (r.f. 0.10) to yield **(96)** (2.83g, 11.5mmol, 87.5%) as a colourless oil.

For both ^{1}H and ^{13}C NMR spectra, major and minor rotamer signals were assumed to be overlapping.

δ_H (250 MHz, $CDCl_3$): 1.72 (d, J = 11.0 Hz, 1H, H_{7a}), 1.91 (d, J = 11.0 Hz, 1H, H_{7s}), 2.00 (dd, J = 17.5, 4.0 Hz, 1H, H_{5n}), 2.23 (ddd, J = 17.5, 4.5, 1.5 Hz, 1H, H_{5x}), 2.85 (bs, 1H, H_4), 3.23 (d, J = 10.0 Hz, 1H, H_{3n}), 3.51 (ddd, J = 10.0, 2.5, 1.5 Hz, 1H, H_{3x}), 4.27 (bs, 1H, H_1), 5.05-5.25 (m, 2H, benzylic CH_2), 7.25-7.50 (m, 5H, Ph).

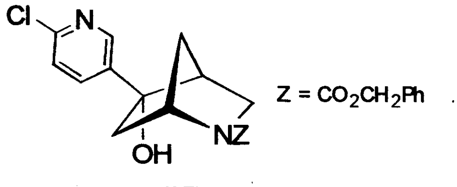
δ_C (62.90 MHz, $CDCl_3$): 34.0, 61.9 (2 x CH), 36.3, 41.4, 50.7 (3 x CH_2), 67.0 ($\underline{C}H_2Ph$), 127.6, 127.8, 128.3 (5 x aryl CH), 136.2 (aryl C), 154.6 (urethane C=O), 205.0 (C=O).

ν_{max} ($CDCl_3$): 2960w, 1760s, 1695s, 1420m, 1360m, 1100m, 910s, 750-700s cm^{-1}.

$^m/_z$: 246 (MH^+), 268 (MNa^+)

$C_{14}H_{16}NO_3$ [MH^+] requires $^m/_z$ 246.11308; observed 246.11302

5-(2'-Chloro-5'-pyridyl)-N-(benzyloxycarbonyl)-2-azabicyclo[2.2.1]heptan-5-ol (97)



(97)

2-Chloro-5-iodopyridine (0.25g, 1.00mmol) was dissolved in diethyl ether (7ml) and THF (4ml) in a flame-dried flask, under a nitrogen atmosphere and cooled to -78°C. Butyl lithium (1.6M, 625μL, 1.00mmol) was added dropwise and the solution stirred for 20 mins. A solution of **(94)** (0.202g, 0.83mmol) in THF (4ml) was added dropwise and stirring continued for 2 hours. The reaction was warmed to -50°C and maintained at this temperature for 30 mins, before it was quenched by the addition of ammonium chloride (0.5ml) and warmed to room temperature. Water (1.5ml) was added and the organic layer separated off. The aqueous layer was extracted with diethyl ether (4 x 5ml), the organic extracts were combined, dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography*, eluting with diethyl ether (r.f. 0.31) to yield **(97)** (0.17g, 0.48mmol, 58%) as a pale yellow foam.

δ_H (250 MHz, $CDCl_3$) (rotamer ratio 51:49; signals common to both rotamers are listed in italics):

major rotamer: *1.63* (d, J = 11.0 Hz, 1H, H_{7a}), *1.81* (m, 1H, H_{7s}), 2.05 (dd, J = 11.0, 3.5 Hz, 1H,H_{6n}), 2.21 (dd, J = 11.0, 2.5 Hz, 1H, H_{6x}), 2.78 (bs, 1H, H_4), 3.29 (dd, J = 9.5, 3.5 Hz, 1H, H_{3x}), 3.71 (s, 1H, OH), 4.05 (d, J = 9.5 Hz, 1H, H_{3n}), *4.32* (bs, 1H, H_1), *5.05-5.20* (m, 2H, benzylic CH_2), *7.20-7.50* (m, 6H, Ph and $H_{3'}$), *7.79* (dd, J = 8.0, 2.5 Hz, 1H, $H_{4'}$), *8.40* (m, 1H, $H_{6'}$).

minor rotamer: *1.63* (d, J = 11.0 Hz, 1H, H_{7a}), *1.81* (m, 1H, H_{7s}), 2.00 (dd, J = 11.0, 3.5 Hz, 1H, H_{6n}), 2.26 (dd, J = 11.0, 2.5 Hz, 1H, H_{6x}), 2.73 (bs, 1H, H_4), 3.26 (dd, J = 9.5, 3.5 Hz, 1H, H_{3x}), 3.54 (s, 1H, OH), 3.99 (d, J = 9.5 Hz, 1H, H_{3n}), *4.32* (bs, 1H, H_1), *5.05-5.20* (m, 2H, benzylic CH_2), *7.20-7.50* (m, 6H, Ph and $H_{3'}$), *7.79* (dd, J = 8.0, 2.5 Hz, 1H, $H_{4'}$), *8.40* (m, 1H, $H_{6'}$).

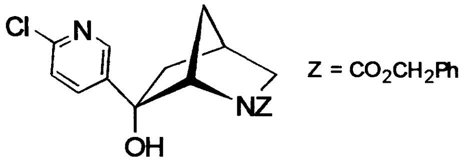
δ_C (62.90 MHz, $CDCl_3$) (signals common to both rotamers are listed in italics): 47.5, 48.3, 57.4, 57.6 (2 x CH), 37.4, 38.0, 46.0, 46.1, 46.6, 47.3 (3 x CH_2), *65.7* ($\underline{C}$-OH), 66.5, 66.7 (CH_2Ph), 127.5, 127.7, 127.8, 127.9, *128.4* (5 x aryl CH), 136.6, 136.8 (1 x aryl C), *124.0*, *137.0*, 146.8, 146.9 (3 x pyridyl CH), *142.0* (pyridyl C), *150.1* (pyridyl $\underline{C}$-Cl), *154.5* (urethane C=O).

ν_{max} (CH_2Cl_2): 3050s, 2995s, 2300m, 1700m, 1420s, 1275s, 1260s, 900m, 960m, 720m cm^{-1}.

$^{m}/_{z}$: 359 (MH^+), 381 (MNa^+)

$C_{19}H_{20}N_2O_3Cl$ [MH^+] requires $^{m}/_{z}$ 359.11618; observed 359.11625.

6-(2'-Chloro-5'-pyridyl)-N-(benzyloxycarbonyl)-2-azabicyclo[2.2.1]heptan-6-ol (98)



(98)

2-Chloro-5-iodopyridine (0.36g, 1.52mmol) was dissolved in diethyl ether (7.5ml) and THF (4ml) in a flame-dried flask under a nitrogen atmosphere and cooled to -78°C. Butyl lithium (1.6M, 152μL, 1.52mmol) was added dropwise and stirred for 20 mins. A solution of **(96)** (0.37g, 1.52mmol) in diethyl ether (4ml) was added dropwise and stirring continued for 2 hours. The reaction was warmed to -50°C and maintained at this temperature for 30 mins. The reaction was quenched by the addition of aqueous ammonium chloride (0.75ml) and warmed to room temperature. Water (2.5ml) was added and the organic layer separated off. The aqueous layer was extracted with diethyl ether (4 x 5ml), the organic extracts were combined, dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography* eluting with diethyl ether (r.f. 0.21) to yield **(98)** (0.32g, 0.89mmol, 59%) as a pale yellow foam.

For both ^1H and ^{13}C NMR spectra, major and minor rotamer signals were assumed to be overlapping.

δ_H (250 MHz, $CDCl_3$): 1.57-1.84 (m, 2H, H_{7a}, H_{7s}), 1.92-2.44 (m, 2H, H_{5x}, H_{5n}), 2.63 (bs, 1H, H_4), 3.28 (d, J = 9.5 Hz, 1H, H_{3n}), 3.47 (dd, J = 9.5, 1.5 Hz, 1H, H_{3x}), 4.20-

4.53 (m, 1H, H_1), 5.03-5.25 (m, 2H, benzylic CH_2), 7.23-7.42 (m, 5H, Ph), 7.25 (d, J = 8.5 Hz, 1H, $H_{3'}$), 7.74 (d, J = 8.5 Hz, 1H, $H_{4'}$), 8.43 (bs, 1H, $H_{6'}$).

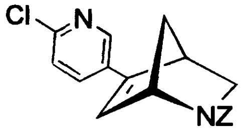
δ_C (62.90 MHz, $CDCl_3$):37.6, 64.3 (2 x CH), 36.8, 43.5, 52.0 (3 x CH_2), 66.7 ($\underline{C}H_2Ph$), 80.2 ($\underline{C}$-OH), 127.4, 127.7, 128.3 (5 x aryl CH), 136.5 (1 x aryl C), 123.7, 137.0, 147.2 (3 x pyridyl CH), 149.9 (pyridyl $\underline{C}$-Cl)
Signals for pyridyl C and urethane C=O were lost in the noise.

ν_{max} (CH_2Cl_2): 2960w, 1695s, 1420s, 1320m, 1050s, 685m cm^{-1}.

$^m/_z$: 359 (MH^+), 381 (MNa^+)

$C_{19}H_{20}N_2O_3Cl$ [MH^+] requires $^m/_z$ 359.11620; observed 359.11625.

5-(2'-Chloro-5'-pyridyl)-N-(benzyloxycarbonyl)-2-azabicyclo[2.2.1]hept-5-ene (99)



(99)

Z = CO_2CH_2Ph

Burgess's reagent (0.385g, 1.62mmol) was dissolved in THF (3ml) under a nitrogen atmosphere. A solution of vacuum oven-dried **(97)** (0.433g, 1.21mmol) in THF (3ml) was added dropwise and stirring continued for 17.5 hours at room temperature. The solution was heated for 30 mins at 50°C and then left to cool to room temperature. The reaction was quenched by the addition of water (0.2ml), neutralised with sodium hydroxide solution and the solvent removed under reduced pressure. The crude mixture was extracted with chloroform (4 x 3ml), the organic layers combined, dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography*, eluting with 7:3 diethyl ether : petroleum ether (b.p. 40-60°C) (r.f. 0.23) to yield **(99)** (0.290g, 0.852mmol, 70.7%), as a pale yellow oil.

δ_H (250 MHz, $CDCl_3$) (rotamer ratio 51:49; signals common to both rotamers are listed in italics):

major rotamer: *1.66-1.80* (m, 2H, H_{7a}, H_{7s}), *2.71-2.85* (m, 1H, H_{3n}), 3.49 (d, J = 9.5 Hz, 1H, H_{3x}), *3.57* (bs, 1H, H_4), 4.85 (bs, 1H, H_1), *4.96-5.12* (m, 2H, benzylic CH_2), 6.69 (bs, 1H, H_6), *7.18-7.33* (m, 6H, Ph, $H_{4'}$), *7.56* (d, J = 7.5 Hz, 1H, $H_{3'}$), *8.35* (d, J = 2.0 Hz, 1H, $H_{6'}$).

minor rotamer: *1.66-1.80* (m, 2H, H_{7a}, H_{7s}), *2.71-2.85* (m, 1H, H_{3n}), 3.47 (d, J = 9.5 Hz, 1H, H_{3x}), *3.57* (bs, 1H, H_4), 4.77 (bs, 1H, H_1), *4.96-5.12* (m, 2H, benzylic CH_2), 6.54 (bs, 1H, H_6), *7.18-7.33* (m, 6H, Ph, $H_{4'}$), *7.56* (d, J = 7.5 Hz, 1H, $H_{3'}$), *8.35* (d, J = 2.0 Hz, 1H, $H_{6'}$).

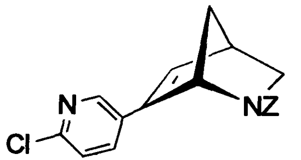
δ_C (100.61 MHz, $CDCl_3$) (signals common to both rotamers are listed in italics): 44.1, 44.6, 61.4, 61.8 (2 x CH), 46.1, 46.3, 47.4, 47.7 (2 x CH_2), *66.8* ($\underline{C}H_2Ph$), *128.8* (C_5), 129.7, 130.3 (C_6), *127.9*, *128.0*, *128.4* (5 x aryl CH), *136.7* (1 x aryl C), *124.2*, *135.2*, *146.4* (3 x pyridyl CH), *145.2* (pyridyl C), *150.5* (pyridyl C-Cl), *155.7* (C=O).

ν_{max} (CH_2Cl_2): 3060w, 2950w, 1695s, 1580w, 1450m, 1410s, 1355s, 1160m, 1105s, 830m, 800w.

$^m/_z$: 341 (MH^+), 363 (MNa^+)

$C_{19}H_{18}N_2O_2Cl$ [MH^+] requires $^m/_z$ 341.10567; observed 341.10568

6-(2'-Chloro-5'-pyridyl)-N-(benzyloxycarbonyl)-2-azabicyclo[2.2.1]hept-6-ene (100)



Z = CO_2CH_2Ph

(100)

Sodium hydride (95%, 120mg, 4.75mmol) was stirred in THF (4.5ml), in a flame-dried flask fitted with a septum, under a nitrogen atmosphere at 0°C. Compound **(98)** (283mg,.0789 mmol), dissolved in THF (2.7ml) was added dropwise and stirred for 50 mins at room temperature. The reaction flask was cooled to 0°C and carbon disulfide (60μL, 0.98mmol) added through the septum, after which the reaction was allowed to warm to room temperature and stirred for 15 mins. Methyl iodide (61μL, 0.99mmol) was added dropwise, stirring being continued for a further 25 minutes. Water (1.5ml) was added to quench and the solvent removed under reduced pressure. The residue was partitioned between water (4ml) and dichloromethane (4 x 4ml), the organic layers combined, dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The crude xanthate was dissolved in toluene (15ml) and heated at reflux for 5 hours. The toluene was removed under reduced pressure and the crude product purified by flash chromatography*, eluting with 7:3 diethyl ether : petroleum ether (b.p. 40-60°C) (r.f. 0.12) to yield **(100)** (120mg, 0.353mmol, 44.7%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) (rotamer ratio 56:44; signals common to both rotamers are listed in italics):

major rotamer: *1.76-1.85* (m, 2H, H_{7a}, H_{7s}), 2.85 (d, J = 9.0 Hz, 1H, H_{3n}), *3.39* (m, 1H, H_4), *3.58* (dd, J = 9.0, 3.0 Hz, 1H, H_{3x}), *5.00-5.20* (m, 3H, H_1, benzylic CH_2), 6.59 (d, J = 1.5 Hz, 1H, H_5), *7.20-7.40* (m, 5H, Ph), 7.03 (d, J = 8.5 Hz, 1H, $H_{3'}$), 8.00 (dd, J = 8.5, 2.0 Hz, 1H, $H_{4'}$), 8.60 (d, J = 2.0 Hz, 1H, $H_{6'}$).

minor rotamer: *1.76-1.85* (m, 2H, H_{7a}, H_{7s}), 2.91 (d, J = 9.0 Hz, 1H, H_{3n}), *3.39* (m, 1H, H_4), *3.58* (dd, J = 9.0, 3.0 Hz, 1H, H_{3x}), *5.00-5.20* (m, 3H, H_1, benzylic CH_2), 6.64 (d, J = 1.5 Hz, 1H, H_5), *7.20-7.40* (m, 5H, Ph), 7.31 (d, J = 8.5 Hz, 1H, $H_{3'}$), 7.59 (dd, J = 8.5, 2.0 Hz, 1H, $H_{4'}$), 8.49 (d, J = 2.0 Hz, 1H, $H_{6'}$).

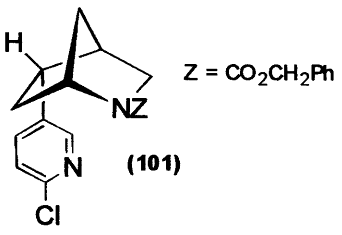
δ_C (100.61 MHz, $CDCl_3$) (signals common to both rotamers are listed in italics): 43.5, 44.2, 61.6, 61.9 (2 x CH), 46.7, 46.9, 47.9, 48.3 (2 x CH_2), 66.8, 67.2 ($\underline{C}H_2Ph$), 131.5, 131.7 (C_5), *129.2* (C_6), 127.8, 127.9, *128.3*, 128.4, 128.6 (5 x aryl CH), 136.2, 136.7 (1 x aryl C), 123.8, 124.1, 135.3, 135.9, 146.6, 146.8 (3 x pyridyl CH), 143.9, 145.1 (pyridyl C), *149.9* (pyridyl C-Cl), *155.1* (C=O).

ν_{max} ($CDCl_3$): 2960w, 1685s, 1450m, 1420s, 1355m, 1250w, 1160w, 1105m, 900w, 820w, 690w.

$^m/_z$: 341 (MH^+), 363 (MNa^+)

$C_{19}H_{18}N_2O_2Cl$ [MH^+] requires $^m/_z$ 341.10561; observed 341.10568

***endo*-5-(2'-Chloro-5'-pyridyl)-N-(benzyloxycarbonyl)-2-azabicyclo[2.2.1]heptane (101)**



(101)

Potassium azodicarboxylate (74mg, 0.38mmol) and **(99)** (21.0mg, 0.062mmol) were dissolved in dry methanol (0.65ml) under a nitrogen atmosphere. Dry glacial ethanoic acid (44μL, 0.76mmol) was added dropwise and the solution stirred for 20 hours at room temperature. Further potassium azodicarboxylate (20mg, 0.10mmol) was added and the reaction stirred for 3 more hours. The reaction was quenched with water (0.5ml) and the solvent removed under reduced pressure. The residue was partitioned between dichlomethane (4ml) and sodium hydrogen carbonate solution (1ml). The dichlomethane extract was washed with sodium hydrogen carbonate solution (0.5ml) and brine (1ml), dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography*, eluting with diethyl ether : petroleum ether (b.p. 40-60°C) (r.f. 0.46). Compound **(101)** (16mg, 0.045mmol, 74%) was isolated as a pale yellow oil.

δ_H (300 MHz, $CDCl_3$) (rotamer ratio 55:45; signals common to both rotamers are listed in italics):

major rotamer: *1.76-1.85* (m, 2H, H_{7a}, H_{7s}), *1.88-1.98* (m, 1H, H_{6n}), *2.15* (ddd, J = 12.5, 11.0, 2.5 Hz, 1H, H_{6x}), *2.71* (bs, 1H, H_4), 3.07 (dd, J = 10.5, 1.0 Hz, 1H, H_{3n}), 3.17 (ddd, J = 10.5, 3.5, 1.5 Hz, 1H, H_{3x}), 3.40 (ddd, J = 11.0, 5.5, 3.5 Hz, 1H, H_{5x}), 4.45 (bs, 1H, H_1); *5.05-5.21* (m, 2H, benzylic CH_2), 7.17 (d, J = 8.0 Hz, 1H, $H_{3'}$), *7.29-7.41* (m, 7H, Ph, $H_{3'}$, $H_{4'}$), 8.23 (d, J = 2.5 Hz, 1H, $H_{6'}$).

minor rotamer: *1.76-1.85* (m, 2H, H_{7a}, H_{7s}), *1.88-1.98* (m, 1H, H_{6n}), *2.15* (ddd, J = 12.5, 11.0, 2.5 Hz, 1H, H_{6x}), *2.71* (bs, 1H, H_4), 3.02 (dd, J = 10.5, 1.0 Hz, 1H, H_{3n}), 3.19 (ddd, J = 10.5, 3.5, 1.5 Hz, 1H, H_{3x}), 3.43 (ddd, J = 11.0, 5.5, 3.5 Hz, 1H, H_{5x}), 4.39 (bs, 1H, H_1), *5.05-5.21* (m, 2H, benzylic CH_2), 7.25 (d, J = 8.0 Hz, 1H, $H_{3'}$) *7.29-7.41* (m, 7H, Ph, $H_{3'}$, $H_{4'}$), 8.22 (d, J = 2.5 Hz, 1H, $H_{6'}$).

δ_C (75.81 MHz, $CDCl_3$) (signals common to both rotamers are listed in italics): *40.6*, 43.1, 43.6, 57.5, 57.7 (3 x CH), 35.4, 36.2, 39.5, 40.0, *46.9* (3 x CH_2), 66.5, 66.8

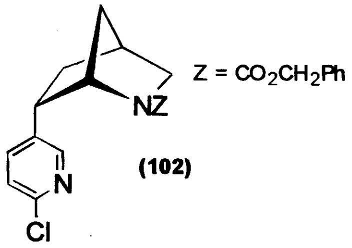
(CH_2Ph), *127.9*, *128.0*, *128.5* (5 x aryl CH), *136.9* (1 x aryl C), 123.9, 124.0, 137.8, 137.9, 149.8, 149.9 (3 x pyridyl CH), 135.7, 135.8 (pyridyl C), *149.4* (pyridyl C-Cl), 154.3, 154.5 (urethane C=O).

ν_{max} ($CDCl_3$): 2595w, 1690s, 1450m, 1425s, 1360m, 1330m, 1290w, 1160m, 1110s, 1250w, 900w, 835w, 700w.

$^m/_z$: 343 (MH^+), 365 (MNa^+)

$C_{19}H_{20}N_2O_2Cl$ [MH^+] requires $^m/_z$ 343.12130; observed 343.12133

endo-6-(2'-Chloro-5'-pyridyl)-N-(benzyloxycarbonyl)-2-azabicyclo[2.2.1]heptane (102)



(102)

Potassium azodicarboxylate (341mg, 1.76mmol) and **(100)** (115mg, 0.351mmol) were dissolved in dry methanol (3ml) under a nitrogen atmosphere. Dry glacial ethanoic acid (200μL, 3.51mmol) was added dropwise and the solution stirred for 22 hours at room temperature, after which further potassium azodicarboxylate (100mg,0.515mmol) was added. Stirring was continued for a further 7 hours at which point the reaction was quenched with water (0.5ml) and the solvent removed under reduced pressure. The residue was partitioned between dichlomethane (15ml) and sodium hydrogen carbonate solution (3ml). The dichlomethane extract was washed with sodium hydrogen carbonate solution (3ml) and brine (3ml), dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography*, eluting with 7:3 diethyl ether : petroleum ether (b.p. 40-60°C) (r.f. 0.22). Compound **(102)** (81.7mg, 0.238mmol, 71%) was isolated as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$) (rotamer ratio 62:38; signals common to both rotamers are listed in italics):

major rotamer : *1.51* (dddd, J = 13.0, 5.5, 2.5, 2.5 Hz, 1H, H_{5n}), *1.75-1.82* (m, 1H, H_{7s}), *1.86* (ddd, J = 10.0, 3.5, 2.0 Hz, 1H, H_{7a}), *2.19-2.33* (m, 1H, H_{5x}), *2.70-2.76* (m, 1H, H_4), 3.15 (dd, J = 10.0, 1.0 Hz, 1H, H_{3n}), *3.32* (ddd, J = 11.5, 5.5, 2.5 Hz,1H, H_{6x}), 3.53 (ddd, J = 10.0, 3.0, 3.0, 1H, H_{3x}), 4.29 (bs, 1H, H_1), 4.71, 4.78 (d, J = 12 Hz, 2H, benzylic CH_2), *6.98* (dd, J = 8.5, 2.5 Hz, 1H, $H_{4'}$), 7.13 (d, J = 8.5 Hz, 1H, $H_{3'}$), *7.27-7.40* (m, 5H, Ph), 8.22 (d, J = 2.5Hz, 1H, $H_{6'}$).

minor rotamer: *1.51* (dddd, J = 13.0, 5.5, 2.5, 2.5 Hz, 1H, H_{5n}), *1.75-1.82* (m, 1H, H_{7s}), *1.86* (ddd, J = 10.0, 3.5, 2.0 Hz, 1H, H_{7a}), *2.19-2.33* (m, 1H, H_{5x}), *2.70-2.76* (m, 1H, H_4), 3.24 (dd, J = 10.0, 1.0 Hz, 1H, H_{3n}), *3.32* (ddd, J = 11.5, 5.5, 2.5 Hz,1H, H_{6x}), 3.48 (ddd, J = 10.0, 3.0, 3.0, 1H, H_{3x}), 4.49 (bs, 1H, H_1), 4.95, 5.05 (d, J = 12 Hz, 2H, benzylic CH_2), *6.98* (dd, J = 8.5, 2.5 Hz, 1H, $H_{4'}$), 7.07 (d, J = 8.5 Hz, 1H, $H_{3'}$), *7.27-7.40* (m, 5H, Ph), 8.23 (d, J = 2.5Hz, 1H, $H_{6'}$).

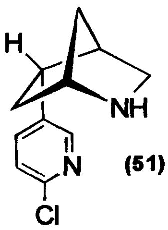
δ_C (100.61 MHz, $CDCl_3$) (signals common to both rotamers are listed in italics): 37.5, 38.0, 45.5, 45.8, 60.7, 61.8 (3 x CH), 33.9, 34.2, 39.2, 39.9, *53.4* (3 x CH_2), 65.9, 66.5, *66.7* ($\underline{C}H_2Ph$), 127.89, 127.93, *128.0*, 128.4, 128.5 (5 x aryl CH), 136.1, 136.9 (1 x aryl C), *123.6*, 137.4, 138.0, 149.4, 150.0 (3 x pyridyl CH), *135.8* (pyridyl C), *149.5* (pyridyl C-Cl), *154.7* (urethane C=O).

ν_{max} ($CDCl_3$): 2980w, 2880w, 1690vs, 1455s, 1425s, 1360m, 1340w, 1155m, 1110s, 1025w, 900m, 700m.

$^m/_z$: 343 (MH^+), 365 (MNa^+)

$C_{19}H_{20}N_2O_2Cl$ [MH^+] requires $^m/_z$ 343.12143; observed 343.12133

***endo*-5-(2'-Chloro-5'-pyridyl)-2-azabicyclo[2.2.1]heptane (51)**



(51)

Compound **(101)** (13.4mg, 0.0391mmol) was dissolved in chloroform (0.5ml) and stirred under a nitrogen atmosphere. TMSI (28μL, 0.20 mmol) was added and stirred for 7 mins followed by hydrofluoroboric acid - diethyl ether complex (11μL, 0.078mmol) stirring for a further 5 mins. The reaction mixture was quenched with water (100μl) and the solvent removed under reduced pressure. Water (0.5ml) was added and the solution washed with petroleum ether (b.p. 40-60°C) (2 x 0.1ml). The solution was neutralised with solid potassium carbonate and the product extracted with dichloromethane (4 x 2ml). The dichloromethane layer was dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The crude residue was passed through a pipette half-filled with silica gel, eluting with methanol saturated with ammonia gas. The product (6.7mg, 0.032mmol, 82%) was isolated as a pale yellow oil.

δ_H (250 MHz, $CDCl_3$): 1.65 (dd, J = 13.5, 5.5 Hz, 1H, H_{6n}), 1.70-1.74 (m, 2H, H_{7a}, H_{7s}), 2.07 (ddd, J = 13.5, 11.5, 3.0 Hz, 1H, H_{6x}), 2.50-2.60 (m, 2H, H_{3n}, H_4), 2.70 (d, J = 10.5 Hz, 1H, H_{3x}), 3.24 (dddd, J = 11.5, 5.5, 4.0, 2.5 Hz, 1H, H_{5x}), 3.56 (bs, 1H, H_1), 7.22 (d, J = 8.5 Hz, 1H, $H_{3'}$), 7.54 (ddd, J = 8.5, 2.5, <1 Hz, 1H, $H_{4'}$), 8.22 (d, J = 2.5 Hz, 1H, $H_{6'}$).

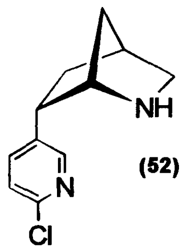
δ_C (100.61 MHz, $CDCl_3$): 41.5, 42.6, 57.0 (3 x CH), 34.7, 39.9, 44.2 (3 x CH_2), 123.9, 138.6, 149.9 (3 x pyridyl CH), 135.7 (pyridyl C), 149.5 (pyridyl C-Cl).

ν_{max} (CH_2Cl_2): 2970s, 1590m, 1565m, 1460s, 1400m, 1335w, 1270m, 1150w, 1110s, 1025m, 840w, 800w, 700w.

$^m/_z$: 209 (MH^+)

$C_{11}H_{14}N_2Cl$ [MH^+] requires $^m/_z$ 209.08451; observed 209.08455

***endo*-6-(2'-Chloro-5'-pyridyl)-2-azabicyclo[2.2.1]heptane (52)**



(52)

Compound **(102)** (51mg, 0.15mmol) was dissolved in dichloromethane (0.5ml) and stirred under a nitrogen atmosphere. TMSI (105μL, 0.74mmol) was added and stirred for 7 mins followed by hydrofluoroboric acid - diethyl ether complex (44μL, 0.30mmol), stirring for a further 5 mins. The reaction mixture was quenched with water (100μl) and the solvent removed under reduced pressure. Water (0.5ml) was added and the solution washed with petroleum ether (b.p. 40-60°C) (2 x 0.1ml). The solution was neutralised with solid potassium carbonate and the product extracted with dichloromethane (4 x 2ml), dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude residue was passed through a pipette half-filled with silica gel, eluting with methanol saturated with ammonia gas. The product was isolated as a pale yellow oil (31mg, 0.15mmol, 98%).

δ_H (250 MHz, $CDCl_3$): 1.46 (ddd, J = 12.5, 5.5, 2.0 Hz, 1H, H_{5n}), 1.77 (m, 2H, H_{7a}, H_{7s}), 2.12 (dddd, J = 12.5, 12.0, 4.5, 3.0 Hz, 1H, H_{5x}), 2.54 (bs, 1H, H_4), 2.68 (d, J = 9.5 Hz, 1H, H_{3n}), 3.00 (ddd, J = 9.5, 3.0, 3.0 Hz, 1H, H_{3x}), 3.25 (ddd, J = 12.0, 5.5, 2.5 Hz, 1H, H_{6x}), 3.44 (bs, 1H, H_1), 7.29 (d, J = 8.5 Hz, 1H, $H_{3'}$), 7.53 (ddd, J = 8.5, 2.5, <1Hz, 1H, $H_{4'}$), 8.25 (d, J = 2.5 Hz, 1H, $H_{6'}$).

δ_C (62.89 MHz, $CDCl_3$): 37.8, 45.5, 60.3 (3 x CH), 33.9, 39.8, 51.7 (3 x CH_2), 123.7, 138.6, 149.6 (3 x pyridyl CH), 136.3 (pyridyl C), 149.2 (pyridyl C-Cl).

ν_{max} (CH_2Cl_2): 3050m, 2960m, 2930m, 1730w, 1705w, 1590w, 1565w, 1460s, 1420m, 1260s, 1110s, 1025w, 895w, 750m.

$^m/_z$: 209 (MH^+)

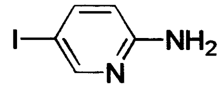
$C_{11}H_{14}N_2Cl$ [MH^+] requires $^m/_z$ 209.08458; observed 209.08455

Tetrakis (triphenylphosphine) palladium(0), $Pd(PPh_3)_4$

Following the literature procedure,[37] a mixture of $PdCl_2$ (5.00g, 28.2mmol), PPh_3 (36.98g, 141mmol) and DMSO (375ml) were placed in a dry flask under a nitrogen atmosphere and heated at 150°C until all of the solid was in solution. The flask was removed from the heat source and hydrazine hydrate (5.50ml, 113mmol) added. The product crystallised out on cooling in ice and was filtered off under nitrogen. The filtrate was washed with ethanol (4 x 150ml) and diethyl ether (4 x 200ml) and then dried under high vacuum. The product was collected as yellow crystals (30.1g, 92.3%). ^{31}P NMR confirmed that the product was sufficiently pure for use.

δ_P (250 MHz, CD_2Cl_2): 12.01
[Comparative literature data:[37] δ_P (250 MHz, CD_2Cl_2) 15.5 (br).]

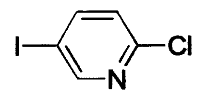
2-Amino-5-iodo-pyridine



Following the literature procedure,[40] 2-aminopyridine (50g, 0.53mol), periodic acid (25g, 0.11mol) and iodine (54g, 0.21mol) were dissolved in glacial acetic acid (300ml), water (60ml) and conc. H_2SO_4 (12M, 9.5ml) and stirred at 80°C for 4 hours. The reaction mixture was poured into a flask of saturated $Na_2S_2O_3$ solution (300ml) and water (240ml) to remove unreacted iodine. The solution was extracted with diethyl ether (3 x 300ml), the organic extracts were combined, washed with sodium hydroxide solution (1M, 3 x 100ml), and dried over anhydrous potassium carbonate. The product was filtered and the solvent removed under reduced pressure. The ^1H NMR spectrum confirmed the product to be 2-amino-5-iodo-pyridine, pure enough to move onto the next step.

δ_H (250 MHz, $CDCl_3$): 6.40 (d, J = 9.0 Hz, 1H), 7.64 (dd, J = 9.0, 2.5 Hz, 1H), 8.13 (d, J = 2.5Hz, 1H), 4.19 (bs, $\underline{N}H_2$).

2-Chloro-5-iodo-pyridine (75)



(75)

Based on the literature procedure,[40] 2-amino-5-iodo-pyridine was dissolved in conc. HCl (12M, 300ml) to form an orange suspension. The suspension was cooled to 0°C and sodium nitrite (33g, 0.48mol) added in portions over two hours. Initially sodium chloride, then a yellow sandy ppt. came out of the solution which was stirred overnight at room temperature. The reaction mixture was poured into water (100ml) and warmed over a steam bath. A yellow ppt. formed which was filtered off and dried over anhydrous phosphorus pentoxide in a vacuum desiccator. The product was recrystallised from 2:1 ethanol : water to yield 73g of crude product. 10g of the crude product was subjected to further purification by flash chromatography* eluting with 0.5:9.5 diethyl ether : petroleum ether (b.p. 40-60°C) (r.f. 0.32) to yield **(75)** (4.6g, 0.019mol, 26%) as pale yellow crystals (m.p. 97-98°C, lit.[40] 99°C).

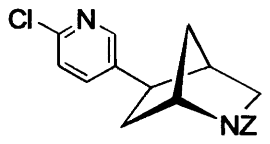
δ_H (250 MHz, $CDCl_3$): 7.13 (d, J = 8.0 Hz, H_3), 7.92 (dd, J = 8.0, 2.5 Hz, H_4), 8.61 (d, J = 2.5 Hz, H_6).

δ_C (62.90 MHz, $CDCl_3$): 126.1, 146.7, 155.6 (3 x CH), 90.7 (C-I), 150.9 (C-Cl).

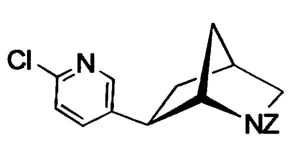
[Comparative literature data:[10] δ_H (250 MHz, $CDCl_3$) 7.13 (d, J = 8.4 Hz, 1H), 7.92 (dd, J = 8.4, 2.6 Hz, 1H), 8.61 (d, J = 2.6 Hz, 1H)].

N-(Benzyloxycarbonyl)-5-*exo*-(2′-chloro-5′-pyridyl)-2-azabicyclo[2.2.1]heptane (76)

N-(Benzyloxycarbonyl)-6-*exo*-(2′-chloro-5′-pyridyl)-2-azabicyclo[2.2.1]heptane (77)



(76)



(77)

Z= CO_2CH_2Ph

In a 2ml reactivial were placed **(74)** (50mg, 0.218mmol), $Pd(PPh_3)_4$ (23mg, 0.020mmol), 2-chloro-5-iodopyridine **(75)** (156mg, 0.654mmol), DMF (0.5 ml) and piperidine (75μl, 0.763mmol). To the stirred solution was added formic acid (25μl, 0.654mmol) and the solution was heated at 75°C for 21 hours. Dichloromethane (12ml) was added to the crude reaction mixture which was washed with water (2 x 1ml), dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The crude product was examined by ^1H NMR spectroscopy and shown to contain **(76)** and **(77)** in a ratio of 60:40 respectively. Purification by flash chromatography*, eluting with 1:1 petroleum ether : diethyl ether yielded **(77)** (R_f 0.17) and **(76)** (R_f 0.10) (combined yield 71mg, 0.207mmol, 95%) as pale yellow oils. The sample of **(76)** was contaminated with a small amount of **(77)**. Complete separation was performed using a chromatotron; a sample of 363 mg of the chromatographed mixture gave pure samples of **(76)** (255 mg) and **(77)** (108 mg) as colourless oils using 1:1 diethyl ether: petroleum ether as solvent. Two rotamers were observed for each of the bicyclic urethanes; ^1H and ^{13}C NMR signals common to both rotamers are listed in italics.

(76): δ_H (300 MHz, $CDCl_3$) (rotamer ratio: 52:48)

major rotamer: *1.62-1.82* (m, 3H. H_{7s}, H_{7a} & H_{6x}), 2.28 (dddd, 1H, $J_{6,6}$ = 13.5, $J_{5n,6n}$ = 9.0, $J_{6n,7s}$ = 1.5, $J_{1,6n}$ <1 Hz, H_{6n}), *2.68* (bs, 1H, H_4), *3.01* (dd, 1H, $J_{5n,6n}$ = 9.0, $J_{5n,6x}$ =

5.5 Hz, H_{5n}), 3.28 (bd, 1H, $J_{3,3}$ = 10.0 Hz, H_{3n}), 3.43 (dd, 1H, $J_{3,3}$ = 10.0, $J_{3x,4}$ = 3.5 Hz, H_{3x}), 4.41 (bs, 1H, H_1), *5.15* (AB, 2H, J = 13.0 Hz, benzylic), *7.30-7.40* (m, 5H, aryl), *7.27* (d, 1H, $J_{4',3'}$ = 8.0 Hz, $H_{3'}$), *7.48* (dd, 1H, $J_{4',3'}$ = 8.0, $J_{6',4'}$ = 3.0 Hz, $H_{4'}$), *8.25* (d, 1H, $J_{6',4'}$ = 3.0 Hz, $H_{6'}$).

minor rotamer: 1.62-1.82 (m, 3H. H_{7s}, H_{7a} & H_{6x}), 2.37 (dddd, $J_{6,6}$ = 13.5, $J_{5n,6}$ = 9.0, $J_{6n,7s}$ =1.5, $J_{1,6n}$ <1 Hz, 1H, H_{6n}), *2.68* (bs, 1H, H_4), *3.01* (dd, 1H, $J_{5n,6n}$ = 9.0, $J_{5n,6x}$ = 5.5 Hz, H_{5n}), 3.24 (bd, 1H, $J_{3,3}$ = 10.0 Hz, H_{3n}), 3.45 (dd, $J_{3,3}$ = 10.0, $J_{3x,4}$ = 3.5 Hz, 1H, H_{3x}), 4.48 (bs, 1H, H_1), *5.15* (AB, 2H, J = 13.0 Hz, benzylic), *7.30-7.40* (m, 5H, aryl), *7.27* (d, $J_{4',3'}$ = 8.0 Hz, 1H. $H_{3'}$), *7.48* (dd, $J_{4',3'}$ = 8.0, $J_{6',4'}$ = 3.0 Hz, 1H, $H_{4'}$), *8.25* (d, $J_{6',4'}$ = 3.0 Hz, 1H, $H_{6'}$).

δ_c (62.90 MHz, $CDCl_3$): see Table 2.20.

ν_{max} ($CDCl_3$): 2960w, 2240w, 1690s, 1430ss, 1560m, 1160w, 1105s, 925-890s, 760-695s cm^{-1}.

$^m/_z$: 343 (MH^+), 365 (MNa^+)

$C_{19}H_{20}N_2O_2Cl$ [MH^+] requires $^m/_z$ 343.12133; observed 343.12140.

(77): δ_H (250 MHz, $CDCl_3$) (rotamer ratio: 53:47):

major rotamer: 1.57 & 1.66 (broad AB, 2H, $J_{7,7}$ ≈ 11 Hz, H_{7a} & H_{7s}), *ca. 1.9 & 2.0* (m, 2H, H_{5n} & H_{5x}), *2.72* (bs, 1H, H_4), 3.19 (d, 1H, $J_{3,3}$ = 10.0 Hz, H_{3n}), *ca. 3.3* (m, 1H, H_{6n}), *ca. 3.4* (m, 1H, H_{3x}), 4.22 (bs, 1H, H_1), *5.08-5.27* (AB, 2H, J_{gem} ≈ 12 Hz, benzylic), *7.21-7.41* (m, 6H, aryl & $H_{3'}$), *ca.* 7.4 & 7.5 (dd, 1H, $J_{4',3'}$ = 8.5, $J_{6',4'}$ = 2.5 Hz, $H_{4'}$), 8.26 (d, $J_{6',4'}$ = 2.5 Hz, 1H, $H_{6'}$).

minor rotamer: 1.57 & 1.65 (broad AB, 2H, $J_{7,7}$ ≈ 11 Hz, H_{7a} & H_{7s}), ca. *1.9 & 2.0* (m, 2H, H_{5n} & H_{5x}), *2.72* (bs, 1H, H_4), 3.16 (d, 1H, $J_{3,3}$ = 10.0 Hz, H_{3n}), *ca. 3.3* (m, 1H, H_{6n}), *ca. 3.4* (m, 1H, H_{3x}), 4.35 (bs, 1H, H_1), *5.08-5.27* (AB, 2H, J_{gem} ≈ 12 Hz, benzylic), *7.21-7.41* (m, 6H. aryl & $H_{3'}$), *ca.* 7.4 & 7.5 (dd, 1H, $J_{4',3'}$ = 8.5, $J_{6',4'}$ = 2.5 Hz, $H_{4'}$), 8.18 (d, 1H, $J_{6',4'}$ = 2.5 Hz, $H_{6'}$).

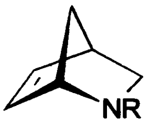
δ_c (62.90 MHz, $CDCl_3$): see Table 2.20.

ν_{max} ($CDCl_3$): 2950w, 2230w, 1685s, 1420s, 1360m, 1100s cm^{-1}.

$^{m}/_{z}$: 343 (MH^+), 365 (MNa^+)

$C_{19}H_{20}N_2O_2Cl$ [MH^+] requires $^{m}/_{z}$ 343.12133; observed 343.12142.

N-(t-Butyloxycarbonyl)-2-azabicyclo[2.2.1]hept-5-ene (78)



(78)

R= $CO_2C(CH_3)$

Formaldehyde (37% soln., 1.08ml, 0.013mol) was added to a solution of ammonium chloride (1.42g, 0.027mol) in 5ml water and stirred for 30 min. Freshly distilled cyclopentadiene (0.59g, 0.009mol) was added and stirring continued at room temperature for 17 hrs. The solution was extracted with ether (2 x 1ml), ice-cooled and taken to pH 12 with sodium hydroxide solution. The aqueous solution was extracted with dichloromethane (4 x 10ml), the organic layers combined, dried with anhydrous sodium sulfate and left to dry further in a freezer over activated molecular sieves. 14.5ml of the dichloromethane solution of the amine, was placed in a 2-necked flask with triethylamine (0.45ml, 0.0032mol) and water (6ml), and stirred. BOC-ON (0.79g, 0.0032mol) and dioxane (1.7ml) were then added and stirring continued for 23 hours at which point the reaction mixture was poured into water (4ml) and extracted with diethyl ether (4 x 8ml). The ethereal extract was washed with citric acid (4ml, 5% soln.), dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure to yield the crude product (1.10g). A fraction of the crude product (0.78g) was purified by flash chromatography using a chromatotron, eluting with 9:1 petroleum ether (b.p. 40-60°C) : diethyl ether (r.f. 0.10) to yield product (0.14g) contaminated with an impurity of the same polarity. Further purification by Kugelrohr distillation (50°C , 1 x 10^{-3} bar) afforded *N*-(t-butyloxycarbonyl)-2-azabicyclo-[2.2.1]hept-5-ene **(78)** (93mg, 0.48mmol, 21%) as a colourless oil.

δ_H (250 MHz, $CDCl_3$) (two rotamers were observed in a ratio of 56:44, signals common to both rotamers are listed in italics): *1.44* (s, 9H, 3 x CH_3), *1.49-1.62* (m, 2H, H_{7a} + H_{7s}), *2.61* (bs, 1H, H_4), *3.15* (bs, 1H, H_{3n}), *3.30* (dd, J = 6.0, 3.0 Hz, 1H,

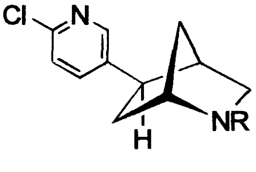
H_{3x}), 4.57 (bs, 1H, H_1, major rotamer), 4.70 (bs, 1H, H_1, minor rotamer), *6.26* (bs, 1H, H_5), [6.36 (bs, major rotamer) and 6.26 (bs, minor rotamer), 1H, H_6].

Comparative literature data,[41] δ_H (500 MHz, $CDCl_3$): 1.34 (s, 9H), 1.42-1.47 (m, 2H), 2.51-2.56 (m, 1H), 3.06 (s, 1H), 3.20 (dd, J=2.9, 6.1 Hz, 1H), 4.47, 4.61 (2s, 1H), 6.17, 6.27 (2s, 2H).

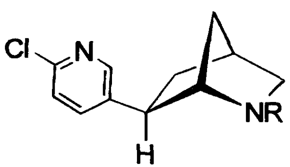
N-(*t*-Butyloxycarbonyl)-5-*exo*-(2′-chloro-5′-pyridyl)-2-azabicyclo[2.2.1]heptane (79)

N-(*t*-Butyloxycarbonyl)-6-*exo*-(2′-chloro-5′-pyridyl)-2-azabicyclo[2.2.1]heptane (82)

a. using $Pd(PPh_3)_4$ catalyst



(79)



(82)

R= $CO_2C(CH_3)_3$

In a 2ml reactivial were placed **(78)** (26mg, 0.13mmol), $Pd(PPh_3)_4$ (15mg, 0.013mmol), 2-chloro-5-iodopyridine **(75)** (95mg, 0.40mmol), DMF (0.5 ml) and piperidine (46μl, 0.46mmol). To the stirred solution was added formic acid (15μl, 0.39mmol) and the solution heated at 75°C for 24 hours. Dichloromethane (7ml) was added to the reaction mixture which was washed with water (3 x 2ml), dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The crude product was examined by NMR and shown to contain **(79)** and **(82)** in a ratio of 55:45. The sample was purified by flash chromatography*, eluting with 7:3 petroleum ether : diethyl ether to yield **(82)** (R_f 0.19, spot visualised by u.v., did not stain in PMA) and **(79)** (R_f 0.11, spot visualised by u.v. and PMA) (combined yield 35mg, 0.112mmol, 85%) as colourless oils. Rotamer ratios for **(79)** and **(82)** were similar; signals common to both rotamers are shown in italics below.

(79): δ_H (250 MHz, $CDCl_3$) (rotamer ratio 55:45):
major rotamer: *1.48* (s, 9H, Bu^t), *1.62* (half of broad AB, 1H, H_7) *1.64 - 1.80* (half of broad AB, 1H, H_7), *1.71* (ddd, 1H, $J_{6,6} \approx 12.5$ Hz, $J_{5n,6x} \approx 5.5$ Hz, $J_{1,6x} \approx 2.5$ Hz, H_{6x}), *2.2 - 2.4* (m, 1H, H_{6n}), *2.64* (bs, 1H, H_4), *3.00* (dd, 1H, $J_{5n,6n} = 9.0$ Hz, $J_{5n,6x} = 5.5$ Hz,

H_{5n}), 3.20 (bd, 1H, $J_{3,3}$ = 10.0 Hz, H_{3n}), *3.36* (bd, 1H, J = 10.0 Hz, H_{3x}), 4.28 (bs, 1H, H_1), *7.26* (d, 1H, $J_{4',3'}$ = 8.3 Hz, $H_{3'}$), *7.48* (dd, 1H, $J_{4',3'}$ = 8.3, $J_{6',4'}$ = 2.5 Hz, $H_{4'}$), *8.26* (d, 1H, $J_{6',4'}$ = 2.5 Hz, $H_{6'}$).
minor rotamer: *1.48* (s, 9H, Bu^t), *1.62* (half of broad AB, 1H, H_7) *1.64 - 1.80* (m, 1H, H_7), *1.71* (ddd, 1H, $J_{6,6}$ ≈ 12.5 Hz, $J_{5n,6x}$ ≈ 5.5 Hz, $J_{1,6x}$ ≈ 2.5 Hz, H_{6x}), *2.2 -2.4* (m, 1H, H_{6n}), *2.64* (bs, 1H, H_4), *3.00* (dd, 1H, $J_{5n,6n}$ = 9.0 Hz, $J_{5n,6x}$ = 5.5 Hz, H_{5n}), 3.15 (bd, 1H, $J_{3,3}$ = 10.0 Hz, H_{3n}), *3.36* (bd, 1H, J = 10.0 Hz, H_{3x}), 4.40 (bs, 1H, H_1), *7.26* (d, 1H, $J_{4',3'}$ = 8.3 Hz, $H_{3'}$), *7.48* (dd, 1H, $J_{4',3'}$ = 8.3, $J_{6',4'}$ = 2.5 Hz, $H_{4'}$), *8.26* (d, 1H, $J_{6',4'}$ = 2.5 Hz, $H_{6'}$).

δ_c (100.61 MHz, $CDCl_3$): see Table 2.20.

ν_{max} ($CDCl_3$): 2975w, 1675s, 1455m, 1410s, 1370m, 1255w, 1155m, 1105m, 900w, 830w.

$^m/_z$: 309 (MH^+), 331 (MNa^+).

$C_{16}H_{22}N_2O_2Cl$ [MH^+] requires $^m/_z$ 309.13698; observed 309.13694.

(82): δ_H (400 MHz, $CDCl_3$) (rotamer ratio 54:46):
major rotamer: 1.52 (s, 9H, Bu^t), 1.64 & *ca.*1.53 (broad AB, 2H, $J_{7,7}$ = 11 Hz, H_{7s}/H_{7a}), *1.86-2.04* (m, 2H, H_{5x} & H_{5n}), *2.69* (bs, 1H, H_4), 3.15 (d, 1H, $J_{3,3}$ = 9.5 Hz, H_{3n}), 3.18 (bdd, 1H, $J_{5n,6n}$ ≈ *ca.* 8.5, $J_{5x,6n}$ ≈ 5.5 Hz, H_{6n}), 3.33 (bddd, 1H, $J_{3,3}$ ≈ 9.5, $J_{3x,4x}$ ≈ 2.5, $J_{3x,5x}$ ≈ 2.5 Hz, H_{3x}), 4.10 (bs, 1H, H_1), 7.30 (d, 1H, $J_{4',3'}$ = 8.5 Hz, $H_{3'}$), 7.47 (dd, 1H, $J_{4',3'}$ = 8.5, $J_{6',4'}$ = 2.2 Hz, $H_{4'}$), *8.27* (d, 1H, $J_{6',4'}$ = 2.2 Hz, $H_{6'}$).
minor rotamer: 1.49 (s, 9H, Bu^t),), 1.61 & *ca.*1.53 (AB, 2H, H_{7s}/H_{7a}), *1.86-2.04* (m, 2H, H_{5x} & H_{5n}), *2.69* (bs, 1H, H_4), 3.06 (d, 1H, J = 9.5 Hz, H_{3n}), 3.25 (bdd, 1H, $J_{5n,6n}$ ≈ 8.5 Hz, $J_{5x,6n}$ ≈ 5.5 Hz, H_{6n}), 3.31 (bddd, 1H, $J_{3,3}$ ≈ 9.5 Hz, $J_{3x,4x}$ ≈ 2.5 Hz, $J_{3x,5x}$ ≈ 2.5 Hz, H_{3x}), 4.31 (bs, 1H, H_1), 7.26 (d, 1H, $J_{4',3'}$ = 8.5 Hz, $H_{3'}$), 7.54 (dd, 1H, $J_{4',3'}$ = 8.5, $J_{6',4'}$ = 2.2 Hz, $H_{4'}$), *8.27* (d, $J_{6',4'}$ = 2.2 Hz, 1H, $H_{6'}$).

δ_c (100.61 MHz, $CDCl_3$): see Table 2.20.

ν_{max} ($CDCl_3$): 2970m, 2880w, 1675s, 1455m, 1410s, 1370m, 1250w, 1150s, 1105s, 870w, 830w, 700w.

$^m/_z$: 309 (MH^+), 331 (MNa^+)

$C_{16}H_{22}N_2O_2Cl$ [MH^+] requires $^m/_z$ 309.13698; observed 309.13696.

Comparative literature data for **(79)**:[41] ^{1}H NMR δ_H (500 MHz, $CDCl_3$): 0.79-0.86 (m, 1H) [we assume that these signals correspond to petrol residues], 1.45, 1.47 (2s, 9H), 1.54-1.62 (m, 1H), 1.90-1.94 (m, 2H), 2.66 (s, br.,1H), 3.03-3.28 (m, 3H), 4.06, 4.26 (2s, 1H), 7.20-7.27 (m, 1H), 7.41-7.47 (m, 1H), 8.23 (d, J = 2.3 Hz, 1H). ^{13}C NMR δ_C (125 MHz, $CDCl_3$): 28.46, 28.53, 34.42, 34.67, 37.02, 37.58, 45.13, 45.72, 51.97, 52.52, 60.54, 62.21, 79.40, 124.01, 137.25, 137.35, 138.02, 148.63, 149.07. Some variations in chemical shift may be due to changes of concentration and/or pH; even traces of acid give rise to downfield shifts as a result of *N*-protonation. Nevertheless, some differences of interpretation remain and the quoted signals at δ 4.06 and 4.26[41] actually correspond quite closely to our shifts for H_1 in the two rotamers of **(82)**, rather than **(79)**.

b. Synthesis of (79) and (82) using $Pd_2(dba)_3$ as catalyst.

In a 2ml reactivial were placed **(78)** (21mg, 0.11mmol), $Pd_2(dba)_3$ (11mg, 0.011mmol), 2-chloro-5-iodopyridine **(75)** (79mg, 0.33mmol), ethyl ethanoate (0.5 ml) and piperidine (38μl, 0.39mmol). To the stirred solution was added formic acid (13μl, 0.33mmol) and the solution heated at 75°C for 21.5 hours. Work-up as described above gave a sample containing **(79)** and **(82)** in a ratio of 45:55 (NMR). Purification by flash chromatography*, eluting with 7:3 petroleum ether : diethyl ether yielded **(82)** (12.9 mg; R_f 0.19, visualised by u.v., did not stain in PMA; contaminated with **(79)** 1.7 mg) and **(79)** (8.6 mg; R_f 0.11, spot visualised both by u.v. and PMA) (combined yield 23mg, 0.075mmol, 68%) as colourless oils.

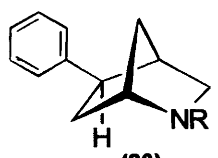
c. Synthesis of (79) and (82) using $Pd(OAc)_2(PPh_3)_2$ as catalyst

In a 2ml reactivial were placed **(78)** (40mg, 0.20mmol), $Pd(OAc)_2$ (2.4mg, 0.01mmol), triphenylphosphine (6.0mg, 0.021mmol), 2-chloro-5-iodopyridine (48mg, 0.20mmol), DMF (0.6 ml) and piperidine (64μL, 0.65mmol). To the slightly basic, stirred solution was added formic acid (21μL, 0.55mmol) and the solution was heated at 80°C for 5 hours. Work-up as above (using ethyl ethanoate as solvent) gave crude product (46% relative to an internal standard) showing a complex ^{1}H NMR spectrum. Chromatography (7:3 petroleum ether : diethyl ether) yielded a mixture of **(79)** and **(82)** (15.5mg, 0.05mmol, 25%).

A similar small-scale reaction (58 mg of **(75)** using identical ratios of reagents but a longer reaction time (24h) gave a mixture of **(79)** and **(82)** (ratio 65:35) in 40% yield after chromatography.

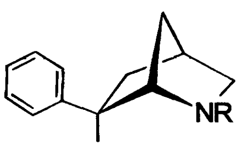
N-(*t*-Butyloxycarbonyl)-5-*exo*-phenyl-2-azabicyclo[2.2.1]heptane (80)

N-(*t*-Butyloxycarbonyl)-6-*exo*-phenyl-2-azabicyclo[2.2.1]heptane (84)



(80)

R = CO_2Bu^t



(84)

In a 2ml reactivial were placed **(78)** (31mg, 0.16mmol), $Pd(OAc)_2$ (5mg, 0.02mmol), triphenylphosphine (10mg, 0.04mmol), benzyl iodide (53μL, 0.48mmol), DMF (0.5 ml) and piperidine (55μL, 0.56mmol). To the slightly basic, stirred solution was added formic acid (18μL, 0.48mmol) and the solution was heated at 75°C for 23 hours. The usual work-up gave a sample which was purified by flash chromatography using a chromatotron, eluting with 9.5: 0.5 petroleum ether : diethyl ether to give **(84)** (R_f 0.1, spot visualised by u.v., did not stain in PMA) (7.0mg, 0.026mmol) and a mixture of the two regioisomers (compound **(80)** had R_f 0.05, spot visualised both by u.v. and PMA) (13.5mg, 0.075mmol) as pale yellow oils in a yield of 47% and a ratio of 55:45 ((**80**):(**84**)). ^{13}C NMR data for **(80)** and **(84)** are summarised in Table 2.20. Rotamer ratios differed for **(80)** and **(84)**; signals common to both rotamers are shown in italics below.

(80): δ_H (400 MHz, $CDCl_3$) (rotamer ratio 35:65):

*major rotamer:*1.52 (s, 9H, Bu^t), *1.60-1.73* (m, 2H, H_{7a}/H_{7s}), *1.78* (m, 1H H_{6x}), 2.21 (dd, 1H, $J_{6,6}$ = 12.5, $J_{5n,6n}$ = 9.0 Hz, H_{6n}), *2.64* (bs, 1H, H_4), *3.01* (dd, 1H, $J_{5n,6n}$ = 9.0, $J_{5n,6x}$ = 5.5 Hz, H_{5n}), 3.12, 3.19 (cannot determine which is major rotamer) (d, 1H, $J_{3,3}$

= 10.0 Hz, H_{3n}), *3.34* (dd, 1H, $J_{3,3}$ = 10.0, $J_{3x,4}$ = 3.0 Hz, H_{3x}), 4.24 (bs, 1H, H_1), *7.16-7.35* (m, 5H, aryl).
minor rotamer: 1.48 (s, 9H, Bu^t), *1.60-1.73* (m, 2H, H_{7a}/H_{7s}), *1.78* (m, 1H H_{6x}), 2.29 (dd, 1H, $J_{6,6}$ = 12.5, $J_{5n,6n}$ = 9.0 Hz, H_{6n}), *2.64* (bs, 1H, H_4), *3.01* (dd, 1H, $J_{5n,6n}$ = 9.0, $J_{5n,6x}$ = 5.5 Hz, H_{5n}), 3.12, 3.19 (cannot determine which is major rotamer) (d, 1H, $J_{3,3}$ = 10.0 Hz, H_{3n}), *3.34* (dd, 1H, $J_{3,3}$ = 10.0, $J_{3x,4}$ = 3.0 Hz, H_{3x}), 4.37 (bs, 1H, H_1), *7.16-7.35* (m, 5H, aryl).

δc (100.61 MHz, $CDCl_3$): see Table 2.20.

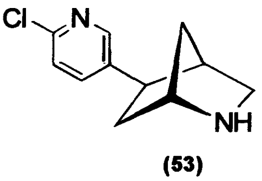
(84): δ_H (400 MHz, $CDCl_3$) (rotamer ratio 45:55,):
major rotamer: 1.52 (s, 9H, Bu^t), *1.55-1.63* (m, 2H, H_{7s}/H_{7a}), *1.90* (ddd, 1H, $J_{5,5}$ = 13.0, $J_{5n,6n}$ =8.5, $J_{5n,7s}$ = 2.0 Hz, H_{5n}), *1.99* (m, 1H, H_{5x}), *2.64* (bs, 1H, H_4), 3.12 (d, 1H, $J_{3,3}$ = 9.5 Hz, H_{3n}), 3.16 (dd, 1H, $J_{5n,6n}$ = 8.5, $J_{5x,6n}$ = 5.5 Hz, H_{6n}), 3.30 (ddd, 1H, $J_{3,3}$ = 9.5, $J_{3x,4}$ = 2.5, $J_{3x,5x}$ = 2.5 Hz, H_{3x}), 4.13 (bs, 1H, H_1), *7.15-7.35* (m, 5H, aryl).
minor rotamer: 1.48 (s, 9H, Bu^t), *1.55-1.63* (m, 2H, H_{7s}/H_{7a}), *1.90* (ddd, 1H, $J_{5,5}$ = 13.0, $J_{5n,6n}$ =8.5, $J_{5n,7s}$ = 2.0 Hz, H_{5n}), *1.99* (m, 1H, H_{5x}), *2.64* (bs, 1H, H_4), 3.03 (d, 1H, $J_{3,3}$ = 9.5 Hz, H_{3n}), 3.27 (dd, 1H, $J_{5n,6n}$ = 8.5, $J_{5x,6n}$ = 5.5 Hz, H_{6n}), 3.27 (ddd, 1H, $J_{3,3}$ = 9.5, $J_{3x,4}$ = 2.5, $J_{3x,5x}$ = 2.5 Hz, H_{3x}), 4.31 (bs, 1H, H_1), *7.15-7.35* (m, 5H, aryl).

δc (100.61 MHz, $CDCl_3$): see Table 2.20.

$^m/_z$: 274 (MH^+)

$C_{17}H_{24}NO_2$ [MH^+] requires $^m/_z$ 274.18070; observed 274.18068.

***exo*-5-(2′-Chloro-5′-pyridyl)-2-azabicyclo[2.2.1]heptane (53)**



(53)

A solution of **(76)** (20mg, 0.058mmol) in CH_2Cl_2 (2ml) was stirred in a round-bottom flask under a nitrogen atmosphere. TMSI (41μl, 0.29mmol) was added and the solution stirred for 7 mins at which point HBF_4.diethyl ether complex (43μl, 0.29mmol) was added. The reaction was quenched with water (0.5ml), and the solvent removed under reduced pressure. Petroleum ether (1ml) was added to the residue and the amine salt extracted with water (3 x 3ml). The aqueous layers were combined and basified with ammonia gas. The water was removed under reduced pressure and the residue extracted with chloroform (3 x 3ml), the extracts combined, dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography, eluting with 9:1 dichloromethane:methanol, saturated with ammonia gas (R_f 0.42) to yield the free amine **(53)** (11mg, 0.052mmol, 92%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$): 1.55 (half of broad AB, 1H, $J_{7,7} \approx$ 10.5 Hz, H_{7s}), 1.62 (half of broad AB, 1H, $J_{7,7} \approx$ 10.5 Hz, H_{7a}), 1.74 (ddd, 1H, $J_{6,6}$ = 13.5, $J_{5n,6x}$ = 5.5, $J_{1,6x}$ = 3.0 Hz, H_{6x}), 1.96 (bs, NH; variable shift), 2.09 (ddd, 1H, $J_{6,6}$ = 13.5, $J_{5n,6n}$ = 9.0, $J_{6n,7s}$ = 1.5 Hz, H_{6n}), 2.55 (m, 1H, H_4), 2.81 (d, 1H, $J_{3,3}$ = 10.0 Hz, H_{3n}), 2.97 (dd, 1H, $J_{5n,6n}$ = 9.0, $J_{5n,6x}$ = 5.5 Hz, H_{5n}), 3.03 (dd, 1H, $J_{3,3}$ = 10.0, $J_{3x,4}$ = 3.5 Hz, H_{3x}), 3.63 (bs, 1H, H_1), 7.25 (dd, 1H, $J_{4',3'}$ = 8.0, $J_{6',3'}$ = 0.3 Hz, $H_{3'}$), 7.49 (ddd, 1H, $J_{4',3'}$ = 8.0, $J_{6',4'}$ = 3.0, $J_{4',5n}$ = 0.5 Hz, $H_{4'}$), 8.27 (bd, 1H, $J_{6',4'}$ = 3.0 Hz, $H_{6'}$).

δ_C (100.61 MHz, $CDCl_3$): see Table 2.20.

ν_{max} ($CDCl_3$): 2980s, 2220w, 1560w, 1455m, 1260s, 1090s, 1010s, 800s cm^{-1}.

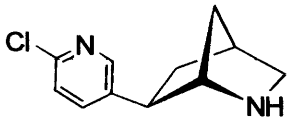
$^m/_z$: 209 (MH^+)

$C_{11}H_{14}N_2Cl$ [MH^+] requires $^m/_z$ 209.08455; observed 209.08459

Comparative literature data for **(53)**:[41] NMR δ_H (200 MHz, $CDCl_3$): 1.47-1.57 (m, 2H), 1.64-1.72 (m, 1H), 1.86-1.95 (m, 1H), 2.23 (s, br.,1H), 2.54 (s, 1H), 2.73 (d, J = 9.5 Hz, 1H), 2.95-2.99 (m, 1H), 3.02-3.06 (m, 1H), 3.52 (s, 1H), 7.23 (d, 1H, J = 8.2 Hz,), 7.45 (dd, 1H, J = 2.6, 5.7 Hz), 8.24 (d, 1H, J = 2.5 Hz). ^{13}C NMR δ_C (50 MHz, $CDCl_3$): 35.41, 36.35, 36.82, 46.71, 50.31, 61.17, 123.86, 137.37, 138.35, 148.70, 149.02.

Deprotection of the *N*-BOC analogue **(79)** with TFA (method below) also gave **(53)** in 82% yield.

exo-6-(2′-Chloro-5′-pyridyl)-2-azabicyclo[2.2.1]heptane (54)



(54)

A solution of the *N*-benzyloxycarbonyl-protected amine **(77)** (8.0mg, 0.023mmol) in CH_2Cl_2 (2ml) was treated with TMSI (16µl, 0.12mmol) as described for conversion of **(76)** into **(53)** above. The crude product was purified by flash chromatography, eluting with 19:1 dichloromethane:methanol saturated with ammonia gas (R_f 0.28), to yield the free amine **(54)** (4.6mg, 0.022mmol, 95%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$): 1.52 & 1.59 (broad AB, 2H, $J_{7,7}$ = 13 Hz, H_{7s}/H_{7a}), 1.73 (dddd, 1H, $J_{5,5}$ = 12.5, $J_{5x,6n}$ = 6.0, $J_{4,5x}$ = 3.5, $J_{3x,5x}$ = 3.0 Hz, H_{5x}), 1.82 (bs, NH), 1.96 (ddd, 1H, $J_{5,5}$ = 12.5, $J_{5n,6n}$ = 9.0, $J_{5n,7s}$ = 2.0 Hz, H_{5n}), 2.58 (bs, 1H, H_4), 2.71 (d, 1H, $J_{3,3}$ = 10 Hz, H_{3n}), 2.99 (bddd, 1H, $J_{3,3}$ = 10, $J_{3x,4}$ = 3.5, $J_{3x,5x}$ = 3.0 Hz, H_{3x}), 2.96 (bdd, 1H, $J_{5n,6n}$ = 9.0, $J_{5x,6n}$ = 6.0 Hz, H_{6n}), 3.46 (bs, 1H, H_1), 7.25 (d, 1H, $J_{4',3'}$ = 8.5 Hz, $H_{3'}$), 7.46 (dd, 1H, $J_{4',3'}$ = 8.5, $J_{6',4'}$ = 2.5 Hz, $H_{4'}$), 8.24 (d, 1H, $J_{6',4'}$ = 2.5 Hz, $H_{6'}$).

δ_C (100.61 MHz, $CDCl_3$): 35.9 (C_7), 36.7 (C_5), 37.2 (C_4), 46.7 (C_6), 50.6 (C_3), 61.7 (C_1), 124.4 ($C_{3'}$), 137.9 ($C_{4'}$), 138.4 ($C_{5'}$), 149.1 ($C_{6'}$), 149.6 ($C_{2'}$).

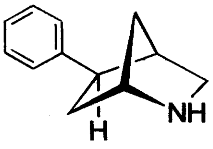
ν_{max} ($CDCl_3$): 2980s, 2220m, 1560m, 1460s, 1380m, 1100s, 900m cm^{-1}.

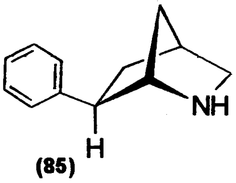
$^m/_z$: 209 (MH^+)

$C_{11}H_{14}N_2Cl$ [MH^+] requires $^m/_z$ 209.08455; observed 209.08450.

Deprotection of the *N*-BOC analogue **(82)** with TFA (method below) also gave **(54)** in 81% yield.

exo-5-Phenyl-2-azabicyclo[2.2.1]heptane (81) and *exo*-6-phenyl-2-azabicyclo-[2.2.1]heptane (85)


(81)


(85)

A mixture of **(80)** and **(84)** (13.5mg, 0.0494mmol) was stirred in dichloromethane (0.5ml) under a nitrogen atmosphere. TFA (50μL, 0.66mmol) was added and left for 4 hours. The mixture was quenched with sodium hydrogen carbonate soln. (0.5ml) and basified to pH 10. After extraction with dichloromethane (4 x 2ml), the organic layers were combined, dried with anhydrous magnesium sulphate and the solvent removed under reduced pressure. Separation by flash chromatography, eluting with dichloromethane : methanol (9.5:0.5) saturated with ammonia gave **(85)** (3.6mg, 0.021mmol) (r.f. 0.22) and **(81)** (4.2mg, 0.024mmol) (r.f. 0.13) as pale yellow oils (combined yield 92%). Separate conversion of pure **(84)** into **(85)** gave a similar yield.

(81): δ_H (250 MHz, CDCl$_3$): 1.51 (half of broad AB, 1H, $J_{7,7} \approx$ 10.5 Hz, H_{7s}), 1.70 (half of broad AB, 1H, $J_{7,7} \approx$ 10.5 Hz, H_{7a}), 1.82 (ddd, 1H, $J_{6,6}$ = 13.0, $J_{5n,6x}$ = 5.0, $J_{1,6x}$ = 3.0 Hz, H_{6x}), 2.05 (bs, NH; variable shift), 2.05 (m, 1H, H_{6n}), 2.58 (bs, 1H, H_4), 2.80 (d, 1H, $J_{3,3}$ = 10.0 Hz, H_{3n}), 2.98 (dd, 1H, $J_{5n,6n}$ = 9.0, $J_{5n,6x}$ = 5.0 Hz, H_{5n}), 3.00 (dd, 1H, $J_{3,3}$ = 10.0, $J_{3x,4}$ = 3.5 Hz, H_{3x}), 3.60 (bs, 1H, H_1), 7.14 - 7.34 (m, 5H, phenyl).

δ_C data in table 2.20.

$^m/_z$: 173 (M^+, E.I.)

$C_{12}H_{15}N$ [M^+] requires $^m/_z$ 173.12045; observed 173.12045.

(85): δ_H (250 MHz, CDCl$_3$): 1.46 (ddddd, 1H, $J_{7,7}$ = 10.5, $J_{1,7s} \approx$ 1.5, $J_{4,7s} \approx$ 1.5, $J_{5n,7s} \approx$ 2.5, $J_{6n,7s} \approx$ 1.5 Hz, H_{7s}), 1.67 (half of broad AB, 1H, $J_{7,7}$ = 10.5 Hz, H_{7a}), 1.82 (dddd, 1H, $J_{5,5}$ = 13.0, $J_{5x,6n}$ = 6.0, $J_{4,5x}$ = 3.5, $J_{3x,5x}$ = 3.0 Hz, H_{5x}), 1.69 (bs, NH), 1.91 (ddd, 1H, $J_{5,5}$ = 13.0, $J_{5n,6n}$ = 9.0, $J_{5n,7s} \approx$ 2.5 Hz, H_{5n}), 2.53 (bs, 1H, H_4), 2.70 (d, 1H,

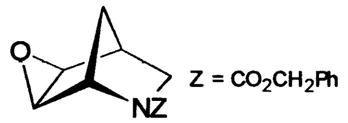
$J_{3,3}$ = 9.5 Hz, H_{3n}), 2.95 (ddd, 1H, $J_{3,3}$ = 9.5, $J_{3x,4}$ = 3.0, $J_{3x,5x}$ = 3.0 Hz, H_{3x}), 3.00 (dd, 1H, $J_{5n,6n}$ = 9.0, $J_{5x,6n}$ = 6.0 Hz, H_{6n}), 3.48 (bs, 1H, H_1), 7.13 - 7.34 (m, 5H, phenyl).

δ_C data in table 2.20.

$^m/_z$: 173 (M^+, E.I)

$C_{12}H_{15}N$ [M^+] requires $^m/_z$ 173.12045; observed 173.12044.

Exo-5,6-Epoxy-N-(benzyloxycarbonyl)-2-azabicyclo[2.2.1]heptane (87)



(87)

Following the literature procedure,[35] **(74)** (0.50g, 2.2mmol) was dissolved in dry dichloromethane (50ml) to which *m*CPBA (71.5%, 0.63g, 2.6mmol) was added, and the solution stirred at room temperature for 130 hours. The reaction solution was washed with sodium hydrogen carbonate solution (2 x 10ml) and water (2 x 10ml). The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography* eluting with 5:5 diethyl ether : petroleum ether (b.p. 40-60°C) (r.f. 0.17) to yield **(87)** (0.27g, 1.1mol, 51%).

δ_H (400 MHz, $CDCl_3$) (rotamer ratio 54:46; signals common to both rotamers are listed in italics):

major rotamer : 1.19 (d, J = 10, <1 Hz, 1H, H_{7s}), *1.64* (d, J = 10 Hz, 1H, H_{7a}), *2.82* (ddd, J = 3.0, 1.5, <1 Hz, 1H, H_4), 3.09 (d, J = 10.0 Hz, 1H, H_{3n}), *3.26* (dd, J = 3.5,<1 Hz, 1H, H_5), *3.31* (d, J = 10.0 Hz, 1H, H_{3x}), 3.38 (bs, 1H, H_6), 4.45 (bs, 1H, H_1), *5.10-5.20* (bs, 2H, benzylic CH_2), *7.20-7.40* (m, 5H, Ph).

minor rotamer: 1.15 (d, J = 10 Hz, 1H, H_{7s}), *1.64* (d, J = 10, <1 Hz, 1H, H_{7a}), *2.82* (ddd, J = 3.0, 1.5, <1 Hz, 1H, H_4), 3.05 (d, J = 10.0 Hz, 1H, H_{3n}), *3.26* (d, J = 3.5, <1 Hz, 1H, H_5), *3.31* (d, J = 10.0 Hz, 1H, H_{3x}), 3.49 (bs, 1H, H_6), 4.54 (bs, 1H, H_1), *5.10-5.20* (bs, 2H, benzylic CH_2), *7.20-7.40* (m, 5H, Ph).

[Comparative literature data:[35] ^{1}H NMR δ_H (250MHz, $CDCl_3$) 1.1-1.17 (m, 1), 1.6-1.7 (m, 1), 2.78-2.79 (m, 1), 3.0-3.1 (m, 1), 3.22-3.45 (m, 3), 4.07-4.17 (m, 1), 5.0-5.2 (m, 2), 7.32-7.35 (m, 5)].

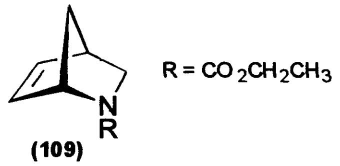
δ_C (62.90 MHz, $CDCl_3$) (signals common to both rotamers are listed in italics): 37.2, 37.8, 57.2, 57.5 (2 x CH), *49.0*, *49.3* (2 x epoxy CH), 25.5, 26.0, 46.9, 47.1 (2 x CH_2), *66.8* (CH_2Ph), *127.8*, *128.0*, *128.4* (5 x aryl CH), *136.6* (1 x aryl C), *155.1* (urethane C=O).

ν_{max} (CH_2Cl_2): 3020w, 2960w, 2900w, 1700s, 1400s, 1360s, 1305m, 1215m, 1165m, 1100s, 1005m, 860s, 695w cm^{-1}.

$^m/_z$: 246 (MH^+), 268 (MNa^+)

$C_{14}H_{16}NO_3$ [MH^+] requires $^m/_z$ 246.11301; observed 246.11302

_N_-(Ethyloxycarbonyl)-2-azabicyclo[2.2.1]hept-5-ene (109)



(109)

Formaldehyde (37% soln., 3.25ml, 0.040mol) was added to a solution of ammonium chloride (4.25g, 0.080mol) in 15ml water and stirred for 30 min. Freshly distilled cyclopentadiene (1.76g, 0.026mol) was added and stirring continued at room temperature for 17 hrs. The solution was washed with ether (2 x 3ml) and cooled to 0°C. Sodium hydroxide (12M soln.,5ml) was added dropwise to the reaction solution and, when addition was halfway through at pH 12, ethyl chloroformate (2.49ml, 0.026mol) was added dropwise simultaneously. Addition of the sodium hydroxide was finished just after the chloroformate and stirring continued for 2 hrs. Water (5ml) was added to the reaction mixture which was extracted with dichloromethane (4 x 20ml). The organic layers were combined, dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography* eluting with 5:5 petroleum ether (b.p. 40-60°C): diethyl ether (r.f. 0.43) to yield **(109)** (1.29g, 9.5mmol, 30%) as a pale yellow oil.

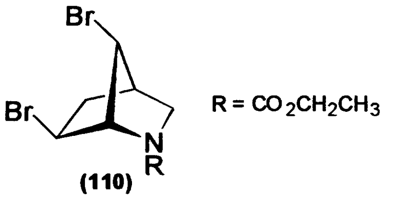
δ_H (250 MHz, $CDCl_3$) (rotamer ratio 55:45; signals common to both rotamers are listed in italics):

major rotamer: *1.25* (t, J = 7.0 Hz, 3H, CH_3), *1.52-1.64* (m, 2H, H_{7a}, H_{7s}), *2.58-2.73* (m, 1H, H_{3n}), *3.19* (bs, 1H, H_4), *3.35* (dd, J = 8.5, 3.0 Hz, 1H, H_{3x}), *4.11* (q, J = 7.0 Hz, 2H, $C\underline{H_2}CH_3$), 4.66 (bs, 1H, H_1), *6.24-6.43* (m, 2H, H_5, H_6).

minor rotamer: *1.25* (t, J = 7.0 Hz, 3H, CH_3), *1.52-1.64* (m, 2H, H_{7a}, H_{7s}), *2.58-2.73* (m, 1H, H_{3n}), *3.19* (bs, 1H, H_4), *3.35* (dd, J = 8.5, 3.0 Hz, 1H, H_{3x}), *4.11* (q, J = 7.0 Hz, 2H, $C\underline{H_2}CH_3$), 4.75 (bs, 1H, H_1), *6.24-6.43* (m, 2H, H_5, H_6).

[For comparative literature data see[49]]

***exo*-6-*anti*-7-*N*-(Ethyloxycarbonyl)-(dibromo)-2-azabicyclo[2.2.1]heptane (110)**



(110)

To a stirred solution of the alkene **(109)** (80mg, 0.48mmol) in dichloromethane (1ml), under a nitrogen atmosphere, was added dropwise a solution of molecular bromine (25µL, 0.48mmol) in dichloromethane (0.5ml). The flask was covered in foil and left to stir for 17 hours at which point TLC revealed full reaction. The reaction mixture was extracted with saturated sodium thiosulfate solution (0.5ml), dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography*, eluting with 7:3 diethyl ether : petroleum ether (b.p. 40-60°C) (r.f. 0.5) to yield **(110)** (114mg, 0.35mmol, 73%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) (rotamer ratio 58:42; signals common to both rotamers are listed in italics):

major rotamer: *1.20-1.32* (m, 3H, CH_3), *2.41* (ddd, J = 14.5, 7.5, 1.5 Hz, 1H, H_{5n}), *2.69* (dddd, J = 14.5, 3.0, 3.0, 2.5 Hz, 1H, H_{5x}), *2.75* (bs, 1H, H_4), 3.07 (d, J = 10.0 Hz, 1H, H_{3n}), *3.39* (ddd, J=10.0, 3.0, 2.5 Hz, 1H, H_{3x}), *3.92-4.04* (m, 1H, H_{6n}), *4.10* (dd, J = 1.5, 1.5 Hz, H_{7s}), *4.10-4.19* (m, 2H, $C\underline{H_2}CH_3$), 4.45 (bs, 1H, H_1).

minor rotamer: *1.20-1.32* (m, 3H, CH_3), *2.41* (ddd, J = 14.5, 7.5, 1.5 Hz, 1H, H_{5n}), *2.69* (dddd, J = 14.5, 3.0, 3.0, 2.5 Hz, 1H, H_{5x}), *2.75* (bs, 1H, H_4), 3.03 (d, J = 10.0

Hz, 1H, H_{3n}), *3.39* (ddd, J=10.0, 3.0, 2.5 Hz, 1H, H_{3x}), *3.92-4.04* (m, 1H, H_{6n}), *4.10* (dd, J = 1.5, 1.5 Hz, H_{7s}), *4.10-4.19* (m, 2H, $C\underline{H_2}CH_3$), 4.53 (bs, 1H, H_1).

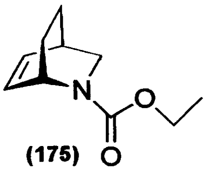
δ_C (62.9MHz, $CDCl_3$) (signals common to both rotamers are listed in italics): 42.7, 42.9, 44.4, 44.9,*47.6*, 63.2, 63.7, (4 x CH), 39.0, 39.4, *49.6*, *61.8* (3 x CH_2), *14.6* (CH_3), *153.7* (C=O).

ν_{max} ($CDCl_3$): 2980w, 1690s, 1425s, 1380m, 1350m, 1330m, 1300m, 1255w, 1230m, 1205w, 1175w, 1105m, 1020w, 890m, 815w, 700m.

$^m/_z$: 328 (MH^+)

$C_9H_{14}NO_2Br_2$ [MH^+] requires $^m/_z$ 327.93728; observed 327.93721.

N-(Ethyloxycarbonyl)-2-azabicyclo[2.2.2]oct-5-ene (175)



(175)

Based on the literature procedure,[72] boron trifluoride etherate (2.50g, 2.21ml, 17.6mmol) and methylenebisurethane (12.0g, 63.0mmol) were stirred in anhydrous benzene (100ml), in a 3-necked flask under a nitrogen atmosphere. The solution was heated to reflux and cyclohexadiene (6.25g, 7.43ml, 78.0mmol) added dropwise over a 30 min period. Reflux was continued for a further hour after which the solution was cooled to room temperature.

The crude solution was washed with sodium bicarbonate solution (sat., 2 x 50ml), ensuring a pH of 8, and then further washed with water (2 x 30ml). The organic phase was dried with anhydrous magnesium sulfate, filtered and the benzene was removed under reduced pressure. The crude product was purified by flash chromatography, eluting with dichloromethane to yield **(175)** (6.26g, 34.5mmol, 55%) as a colourless oil.

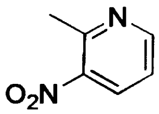
δ_H (250 MHz, $CDCl_3$) (rotamer ratio 59:41; signals common to both rotamers are listed in italics): *1.20* (q, J = 7.0 Hz, 3H, CH_3), *1.32* (m, 2H, H_{8a}, H_{8s}), *1.57, 1.91* (2 x m, 2H, H_{7a}, H_{7s}), *2.68* (bs, 1H, H_4), *2.94* (m, 1H, H_{3n}), *3.23* (dd, J = 10.5, 2.2 Hz, 1H,

H_{3x}), *4.06* (m, 2H, $C\underline{H_2}CH_3$), 4.58 (bs, 1H, H_1, minor rotamer), 4.71 (bs, 1H, H_1, major rotamer), *6.35* (m, 2H, H_5, H_6).

δ_C (62.90 MHz, $CDCl_3$) (signals common to both rotamers are listed in italics): 14.3, 14.5 (CH_3), 30.1, 31.3, 45.0, 45.5 (2 x CH), *20.21*, 26.5, 27.7, 47.7, 47.9, 60.5, 60.6 (4 x CH_2), 132.0, 132.6, 133.5, 133.9 (2 x vinyl CH), 154.9, 155.3 (C=O).

[For comparative literature data see[73]].

3-Nitro-2-picoline (128)



(128)

Dry diethyl malonate (15.0g, 27.0ml, 94.0mmol) was added to a solution of sodium (2.10g, 91.3mmol) in distilled ethanol (30ml) over a period of 25mins. Approx. 25ml of the ethanol was removed by distillation and dry ether (30ml) added to the residue. A solution of 2-chloro-3-nitropyridine **(129)** (5.00g, 31.5mmol) in a solvent mixture of dry diethyl ether (55ml) and distilled ethanol (11ml) was added *via* a cannula and heated at reflux for 17 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed using a rotary evaporator. Hydrochloric acid (10%, 70ml) was added to the flask and heated at reflux for 4 hours. The crude mixture was extracted with diethyl ether (150ml), basified with sodium hydroxide solution and the product extracted with ether (4 x 150ml) (note: it was impossible to detect the phase barrier between the organic and aqueous phases; separation was achieved by observation of the differences in manner in which the two phases flowed through the separating funnel). The organic fractions were combined, dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by Kugelrohr distillation (70°C, 2 x 10^{-1} bar) to yield **(128)** (2.83g, 20.4mol, 65%) as a colourless oil.

δ_H (250 MHz, $CDCl_3$): 2.87 (s, 3H, CH_3), 7.37 (dd, J = 8.0, 5.0 Hz, 1H, H_5), 8.28 (dd, J = 8.0, 1.0 Hz, 1H, H_4), 8.74 (dd, J = 5.0, 1.0 Hz, 1H, H_6).

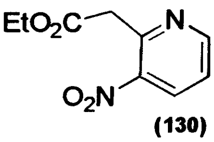
δ_C (62.9 MHz, $CDCl_3$): 23.5 (CH_3), 121.7, 132.2, 152.5 (3 x CH), 145.5 (C_2), 153.4 (C_3).

ν_{max} (CH_2Cl_2): 1610s, 1575w, 1530m, 1440w, 1355m, 1310m, 1090w, 1025w, 860w.

$^m/_z$: 138 (M^+) (e.i.)

$C_6H_6N_2O_2$ [M^+] requires $^m/_z$ 138.04296; observed 138.04293.

Ethyl-3-nitro-2-pyridylacetate (130)



(130)

Dry diethyl malonate (9.07g, 8.61ml, 56.7mmol) was added to a solution of sodium (1.30g, 56.7mmol) in distilled ethanol (30ml) over a period of 25mins. A solution of 2-chloro-3-nitropyridine **(129)** (3.00g, 18.9mmol) in a solvent mixture of THF (20ml) and distilled ethanol (40ml) was added *via* a cannula and heated at 50°C for 17 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed using a rotary evaporator. The residue was apportioned between diethyl ether (250ml) and water (250ml). The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography*, eluting with 7:3 petroleum ether (b.p. 40-60°C): diethyl ether (r.f. 0.63) to yield **(130)** (1.45g, 5.12mmol, 27.3%) as a colourless oil.

δ_H (250 MHz, $CDCl_3$): 1.46 (t, J = 7.5 Hz, 3H, CH_3), 4.57 (q, J = 7.5 Hz, 2H, $C\underline{H_2}CH_3$), 7.02 (dd, J = 8.0, 5.0 Hz, 1H, H_5), 8.24 (dd, J = 8.0, 2.0 Hz, 1H, H_4), 8.38 (dd, J = 5.0, 2.0 Hz, 1H, H_6).

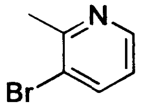
δ_C (100.6 MHz, $CDCl_3$): 14.3 (CH_3), 63.6 (CH_2CH_3), 116.2, 135.0, 151.7 (3 x CH), 133.8 (C_2), 156.2 (C_3), 173.0 (C=O).

ν_{max}: 2980m, 1750s, 1605s, 1570m, 1530m, 1440m, 1350w, 1310m, 1250m, 1150w, 1030m, 860m, 765m.

$^{m}/_{z}$: 211 (MH^+) (e.i.)

[We were unable to obtain an accurate mass of this compound.]

3-Bromo-2-picoline (133)



(133)

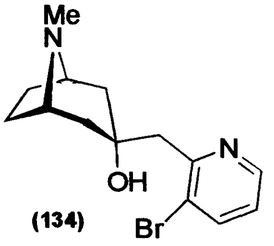
$AlCl_3$ (100g, 0.75mol) was weighed into a dry 3-necked flask under a nitrogen atmosphere, to which a mechanical stirrer and reflux condenser were attached. Distilled 2-picoline (23.3g, 22.7ml, 0.250mol) was added and the mixture stirred at 100°C. Bromine (20.0g, 6.41ml, 0.125mol) was added over a period of 2 hours and heating continued for a further 45 mins. The reaction mixture was poured into a beaker containing ice-water (300ml) and hydrochloric acid (conc.,40ml) ensuring a resultant pH of 1. Excess $NaHSO_3$ was added and the mixture left overnight. The black solid was filtered off and the aqueous solution washed with dichloromethane (2 x 50ml). The aqueous layer was basified to pH 12 with 12M sodium hydroxide solution and filtered. The residue was repeatedly washed with ether (5 x 100ml), the organic layers combined, dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography*, eluting with 9:1 petroleum ether (b.p. 40-60°C): diethyl ether to yield 5-bromo-2-picoline (4.90g, 28.5mmol, 23%, r.f. 0.5, white solid) and 3-bromo-2-picoline **(133)** (3.35g, 19.4mmol, 16%, r.f. 0.4, pale red oil) in a ratio of 60:40.

(133) δ_H (250 MHz, $CDCl_3$): 2.66 (s, 3H, CH_3), 6.99 (dd, J = 8.0, 4.5 Hz, 1H, H_5), 7.78 (dd, J = 8.0, 1.5 Hz, 1H, H_4), 8.38 (dd, J = 5.0, 1.5 Hz, 1H, H_6).

[Comparative literature data:[75] δ_H (60 MHz, CCl_4) 2.60 (s, 3H, CH_3), 6.90 (dd, J = 7.5, 4.5 Hz, 1H, H_5), 7.70 (dd, J = 7.5, 1.5 Hz, 1H, H_4), 8.31 (dd, J = 4.5, 1.5 Hz, 1H, H_6)]

δ_C (62.9 MHz, $CDCl_3$): 24.8 (CH_3), 122.2, 139.6, 149.9 (3 x CH), 121.4 (C_2), 157.2 (C_3).

N-Methyl-3-hydroxy-3-methylene-tropane-3'-bromo-2'-pyridine (134)



(134)

Distilled 2,2',6,6'-tetramethylpiperidine (850mg, 101μL, 0.599mmol) and butyl lithium (1.6M, 374μL, 0.599mmol) were stirred in THF (1ml) at room temperature under a nitrogen atmosphere for 30 mins. The solution was cooled to 0°C then 3-bromo-2-picoline (103mg, 0.599mmol) in THF (0.2ml) added dropwise and stirred for 2 mins. Dry tropinone (83mg, 0.599mmol) in THF (0.2ml) was syringed into the solution, the ice-bath was removed and the reaction left to stir overnight at room temperature. The reaction was quenched with water (100μL) and the solvent removed under reduced pressure. The residue was apportioned between chloroform (9ml) and water (1ml), the organic layer dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography using a chromatotron, eluting with 9:1 diethyl ether: methanol, sat. with NH_3(g) (r.f.0.11) to yield **(134)** (79.2mg, 0.255mmol, 42.6%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$): 1.75 (bd, 2H, J = 14.0 Hz, 2H, H_{2e}, H_{4e}), 1.75-1.90 (m, 2H, $H_{6\beta}$, $H_{7\beta}$), 1.86 (dd, J = 14.0, 3.5 Hz, 2H, H_{2a}, H_{4a}), 2.14 ($^1/_2$ AA'BB', 2H, $H_{6\alpha}$, $H_{7\alpha}$), 2.23 (s, 3H, CH_3), 2.96 (s, 2H, pyridyl CH_2), 3.05 (bs, 2H, H_1, H_5), 5.78 (bs, 1H, OH), 7.00 (dd, J = 8.0, 4.5 Hz, 1H, $H_{5'}$), 7.81 (dd, J = 8.0, 2.5 Hz, 1H, $H_{4'}$), 8.36 (dd, J = 4.5, 1.5 Hz, 1H, $H_{6'}$).

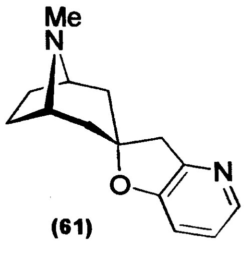
δ_C (62.9 MHz, $CDCl_3$): 60.6 (2 x CH), 25.1, 43.9, 48.4 (5 x CH_2), 40.2, 39.4 (CH_3, 2 invertomers), 70.6 (C-OH), 122.5, 140.7, 146.3 (3 x pyridyl CH), 122.4 ($C_{3'}$), 158.3 ($C_{2'}$).

ν_{max} ($CDCl_3$): 3350br, 2940s, 2240w, 2160w, 1580m, 1430s, 1350m, 1230m, 1130m, 1120m, 1060s, 1030m, 930br, 795m, 640w.

$^m/_z$: (MH^+) 311

$C_{14}H_{20}N_2OBr$ [MH^+] requires $^m/_z$ 311.07585; observed 311.07590.

N-Methyl-3-spiro-tropane-3'-oxy-2'methylene-pyridine (61)



(61)

(134) (20.0mg, 0.064mmol), copper(I) oxide (1mg,0.007mmol), anhydrous potassium carbonate (10.0mg, 0.072mmol) and DMF (100μL) were placed in a dry reactivial under a nitrogen atmosphere and heated at 180°C for 6 hours. Water (4ml) basified with sodium hydroxide solution was added to the reaction mixture, which was then extracted with ether (3 x 10ml). The organic layers were combined, dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield **(61)** (5.5mg, 0.024mmol, 37.4%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$): 2.01-2.07 (m, 2H, $H_{6\beta}$, $H_{7\beta}$), 2.07 (d, J = 15.5 Hz, 2H, H_{2a}, H_{4a}), *c*2.11 (bd, 2H, J = 15.5 Hz, 2H, H_{2e}, H_{4e}), 2.22 ($^1/_2$ AA'BB', 2H, $H_{6\alpha}$, $H_{7\alpha}$), 2.36 (s, 3H, CH_3), 3.08 (s, 2H, pyridyl CH_2), 3.22 (bs, 2H, H_1, H_5), 6.93 (dd, J = 8.5, 1.0 Hz, 1H, $H_{4'}$), 6.99 (dd, J = 8.5, 4.5 Hz, 1H, $H_{5'}$), 7.99 (dd, J = 4.5, 1.0 Hz, 1H, $H_{6'}$).

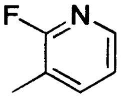
δ_C (100.6 MHz, $CDCl_3$): 60.7 (2 x CH), 25.3, 43.4, 45.8 (5 x CH_2), 40.0, 42.5 (CH_3, 2 invertomers), 86.4 (spiro C), 115.6, 122.4, 141.2 (3 x pyridyl CH) (signals for $C_{2'}$ and $C_{3'}$ were lost in the noise).

ν_{max} ($CDCl_3$): 2900m, 1730m, 1650m, 1450w, 1375m, 1270w, 1110m, 900w.

$^m/_z$: 231 (MH^+) (e.i.)

$C_{14}H_{19}N_2O$ [MH^+] requires $^m/_z$ 231.14969; observed 231.14974.

2-fluoro-3-picoline (137)



(137)

2-Amino-3-picoline **(136)** (20.0g, 18.6ml, 0.185mol) and F_4BH (40% in water, 77.5ml, 0.35mol) were placed in a 3-necked flask with a large stirring bead and cooled in ice. Sodium nitrite (12.75g, 0.185mol) was added in portions over 30 mins then stirred for a further 30 mins. The reaction was warmed to 45°C to ensure complete decomposition, cooled to room temperature and neutralised with solid sodium carbonate. The organic and aqueous layers were separated and the water layer extracted with ether (250ml). The organic layers were combined, the solvent removed under reduced pressure and the residue steam distilled to give approx. 7g crude product The organic layers were combined, dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was distilled under atmospheric pressure (b.p.150.5-151.0°C) to yield **(137)** (6.58g, 59.2mmol, 32.0%) as a colourless oil.

δ_H (250 MHz, $CDCl_3$): 2.29 (bs, 1H, CH_3), 7.08 (ddd, J = 7.0, 5.0, 2.0 Hz, 1H, H_5), 7.59 (ddq, J = 10.0, 7.0, 1.0 Hz, 1H, H_4), 8.03 (bd, J = 5.0 Hz, 1H. H_6).

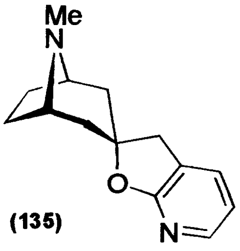
δ_C (62.9 MHz, $CDCl_3$): 14.2 (CH_3), 119.5 (d, J = 32 Hz, C_3), 121.1 (d, J = 4 Hz, C_5), 141.3 (d, J = 6 Hz, C_4), 144.6 (d, J = 14 Hz, C_6), 162.1 (d, J = 238 Hz, C_2).

δ_F (235.4 MHz, $CDCl_3$): 72.4.

ν_{max} ($CDCl_3$): 2940m, 1615s, 1590s, 1425m, 1250m, 1185m, 1120m, 995w, 865m, 800m.

[We were unable to obtain a mass spectrum of this compound].

N-Methyl-3-spiro-tropane-2'-oxy-3'-methylene-pyridine (135)



(135)

Distilled diisopropylamine (423μL, 2.50mmol) was stirred in THF (10ml) at –78°C under a nitrogen atmosphere. Butyl lithium (1.6M, 1.57ml, 2.50mmol) was added and stirring continued for 30mins. 2-Fluoro-3-picoline **(137)** (253mg, 2.28mmol) dissolved in THF (5ml) was added dropwise and allowed to warm to –10°C over 75mins. Tropinone (317mg, 2.28mmol), dissolved in THF (5ml), was added and the solution allowed to warm to room temperature overnight. The reaction was quenched with water (0.5ml) and the solvent removed under reduced pressure. The residue was added to chloroform (10ml) and washed with sodium bisulphate solution (sat., 3 x 1ml) to remove unreacted tropinone. The chloroform layer was dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography, eluting with 9:1 diethyl ether: methanol, sat. with NH_3(g) (r.f.0.15) to yield **(135)** (0.216mg, 0.939mmol, 41.2%) as a yellow waxy solid.

δ_H (400 MHz, $CDCl_3$): 1.96-2.14 (m, 2H, $H_{6\beta}$, $H_{7\beta}$), 1.96-2.14 (bd, 2H, J = 15.5 Hz, 2H, H_{2e}, H_{4e}), 2.24-2.33 (dd, J = 15.5, 2.5 Hz, 2H, H_{2a}, H_{4a}), 1.96-2.14 ($^1/_2$ AA'BB', 2H, $H_{6\alpha}$, $H_{7\alpha}$), 2.32 (s, 3H, CH_3), 2.96 (s, 2H, pyridyl CH_2), 3.18 (bs, 2H, H_1, H_5), 6.72 (dd, J =7.0, 5.5 Hz, 1H, $H_{5'}$), 7.38 (dd, J = 7.0, 1.0 Hz, 1H, $H_{4'}$), 7.95 (dd, J = 5.0, 1.0 Hz, 1H, $H_{6'}$).

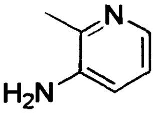
δ_C (62.9 MHz, $CDCl_3$): 62.6 (2 x CH), 24.2, 41.4, 41.8 (5 x CH_2), 39.1 (CH_3), 82.8 (spiro C), 117.0, 133.8, 146.7 (3 x pyridyl CH), 119.0 ($C_{3'}$), 166.5 ($C_{2'}$).

ν_{max} ($CDCl_3$): 3690w, 3640w, 1605m, 1425m, 1230w, 1020m, 895w.

$^m/_z$: 231 (MH^+) (e.i.)

$C_{14}H_{19}N_2O$ [MH^+] requires $^m/_z$ 231.14978; observed 231.14974.

3-Amino-2-picoline (138)


(138)

3-Nitro-2-picoline (0.633g, 4.58mmol) was dissolved in distilled ethanol (7ml) and palladium on carbon catalyst (5%, 100mg, 0.0458mmol) added. The mixture was stirred under a hydrogen atmosphere for 6 hours at which point the reaction was judged to be complete by TLC. The catalyst was filtered off through celite, the solution dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The product was obtained as a waxy yellow solid (0.495, 4.58mmol, 100%) pure enough to go on to the next step.

δ_H (250 MHz, $CDCl_3$): 2.41 (s, 3H, CH_3), 3.58 (bs, 2H, NH_2), 6.90 (dd, J = 8.0, 1.5 Hz, 1H, H_4), 6.96 (dd, J = 8.0, 4.5 Hz, 1H, H_5), 7.95 (dd, J = 4.5, 1.5 Hz, 1H, H_6).

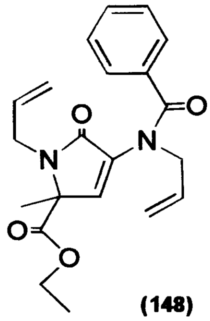
δ_C (62.9 MHz, $CDCl_3$): 20.2 (CH_3), 121.1, 122.0, 139.2 (3 x pyridyl CH), 140.4, 143.7 (2 x pyridyl C).

ν_{max} ($CDCl_3$): 3490w, 3400w, 1625m, 1595w, 1460s, 1305w, 1240w, 800m.

$^m/_z$: 108 (M^+) (e.i.)

$C_6H_8N_2$ [M^+] requires $^m/_z$ 108.06869; observed 108.06875.

Pyrrolone (148)



(148)

Ethyl pyruvate (13.7g, 125mmol) was stirred in toluene (150ml) and allylamine (9.38ml, 125mmol) added dropwise. Stirring was continued for 3 hours at room temperature, then the reaction mixture placed in a separating funnel and the layers allowed to separate. The organic layer was run off and the aqueous layer extracted with toluene (3 x 150ml). The organic layers were combined, dried with anhydrous magnesium sulfate, filtered and placed in a 1L 3-necked flask under a nitrogen atmosphere. Distilled triethylamine (19.5ml, 140mmol), then ethyl chloroformate (13.4ml, 140mmol) were added dropwise to the flask and the reaction left to stir overnight. The solution was filtered to remove triethylamine hydrochloride and the solvent removed under reduced pressure to give 24.3g of an orange oily residue. ^{1}H NMR spectroscopy revealed a mixture of products, 10g of which were subjected to flash chromatography*, eluting with 5:5 petroleum ether (b.p. 40-60°C): diethyl ether to give two main products: spot 1 **(142)** (r.f. 0.48, 2.61g); and spot 2 **(147)** (r.f. 0.32, 1.82g).

The second fraction was dissolved in toluene (50ml) in a 3-necked flask equipped with a nitrogen line and reflux condenser. Triethylamine (1.81ml, 13.0mmol) was added to the stirred solution followed by benzoyl chloride (1.51ml, 13.0mmol) which was added dropwise over 10 mins. The reaction was heated at 65°C for 3 hours, cooled, filtered and the solvent removed under reduced pressure. The crude reaction mixture was purified by flash chromatography*, eluting with 3:1 petroleum ether (b.p. 40-60°C): diethyl ether to give **(148)** (r.f.0.05) (1.43g, 3.89mmol) as a colourless oil which crystallised out when left in the fridge. The overall yield from allylamine was 15.1%. A small sample of the crystals was re-crystallised from diethyl ether to constant melting-point (m.p. 70-71^{0}C).

δ_H (250 MHz, $CDCl_3$) (2 rotamers were observed [ratio not measured], signals common to both rotamers are listed in italics): *1.17* (t, J = 7.0 Hz, 3H, H_9), *1.37* (s, 3H, H_6), *3.82* (dddd, J = 16.5, 6.0, 1.0, 1.0 Hz, 1H, H_{10a}), 4.03 (q, J = 7.0 Hz, 2H, H_8, *minor rotamer*), 4.04 (q, J = 7.0 Hz, 2H, H_8, *major rotamer*), *4.12* (dddd, J = 16.5, 5.5, 1.5, 1.5 Hz, 1H, H_{10b}), *4.51* (bdd, J = 6.0, 1.0 Hx, 2H, H_{14}), *5.05* (ddt, J = 17.0, 1.5, 1.5 Hz, 1H, H_{12t}), *5.08* (ddt, j = 10.5, 1.5, 1.0 Hz, 1H, H_{12c}), *5.17* (ddt, J = 10.0, 1.5, 1.0 Hz, 1H, H_{16c}), *5.21* (ddt, J = 17.0, 1.5, 1.5 Hz, 1H, H_{16t}), *5.74* (ddt, J = 17.0, 10.5, 6.0 Hz, 1H, H_{11}), *5.90* (ddt, J = 17.0, 10.0, 6.0 Hz, 1H, H_{15}), *6.21* (s 1H, H_4), 7.25-7.51 (m, 5H, Ph).

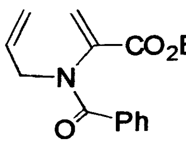
δ_C (62.9 MHz, $CDCl_3$): 13.9 (C_6), 20.0 (C_9), 43.4 (C_{10}), 49.5 (C_{14}), 62.1 (C_8), 117.0 (C_{12}), 118.1 (C_{16}), 66.9, 135.5, 138.3 (C_3, C_5, aryl C), 127.9, 128.1, 130.2, 132.76, 132.81 (5 x aryl CH, C_{11}, C_{15}), 137.6 (C_4), 166.0, 168.9, 170.6 (3 x C=O).

ν_{max} (CH_2Cl_2): 3000w, 1740s, 1710s, 1650s, 1430w, 1380s, 1300w, 1240m, 1195w, 1110m, 1020w, 995w, 930w, 860w.

$^m/_z$: 369 (MH^+)

$C_{21}H_{25}N_2O_4$ [MH^+] requires $^m/_z$ 369.18147; observed 369.18143.

N-Benzoyl-*N*-allyldehydroalanine ethyl ester (149)



(149)

Following the procedure of Davies,[67] ethyl pyruvate (13.7g, 125mmol) was stirred in toluene (150ml) and allylamine (9.38ml, 125mmol) added dropwise. Stirring was continued for

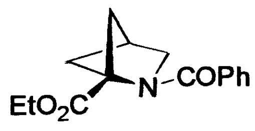
3 hours at room temperature, then the reaction mixture placed in a separating funnel and the layers allowed to separate. The organic layer was run off and the aqueous layer extracted with toluene (3 x 150ml). The organic layers were combined, dried with anhydrous magnesium sulfate, filtered and placed in a 1L 3-necked flask under a nitrogen atmosphere. Distilled triethylamine (19.5ml, 140mmol) then benzoyl chloride (16.3ml, 140mmol) were added dropwise to the flask, the latter added over 15 mins, and the reaction left to stir overnight. The solution was filtered to remove triethylamine hydrochloride and the solvent removed under reduced pressure to give 42.91g of crude product. 18.36g of the crude product was purified by flash chromatography*, eluting with 7:3 petroleum ether (b.p. 40-60°C): diethyl ether to give **(149)** (r.f. 0.19) (6.53g, 25.2mmol, 47.1%) as a pale yellow oil.

δ_H (250 MHz, $CDCl_3$): 1.17 (t, J = 7.0 Hz, 3H, CH_3), 4.07 (q, J = 7.0 Hz, 2H, $C\underline{H}_2CH_3$), 4.31 (bd, J = 6.0 Hz, 2H, H_{4a}, H_{4b}), 5.20 (ddt, J = 10.0, 1.5, 1.0 Hz, 1H, H_{6E}), 5.24 (ddt, J = 17.0, 1.5, 1.5 Hz, 1H, H_{6Z}), 5.51 (bs, 1H, H_{1E} or H_{1Z}), 5.92 (ddt, J = 17.0, 10.0, 6.0 Hz, 1H, H_5), 6.07 (bs, 1H, H_{1E} or H_{1Z}), 7.26-7.52 (m, 5H, Ph).

δ_C (62.9 MHz, $CDCl_3$): 13.8 (CH_3), 51.8 (C_4), 61.4 ($\underline{C}H_2CH_3$), 117.8 (C_6), 121.8 (C_1), 127.9, 130.0, 132.8 (5 x aryl CH and C_5), 135.6 (aryl C), 140.6 (C_2), 163.7, 170.6 (2 x C=O).

[For comparative NMR data see[67]]

1-Ethoxycarbony-2-benzoyl-2-azabicyclo[2.1.1]hexane (150)



(150)

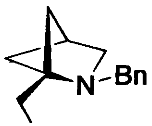
Based on the procedure of Davies,[67] **(149)** (1.00g, 3.86mmol) and acetophenone (146µL) in 73ml dry benzene were placed in a dry 100ml quartz tube, with internal cooler, and irradiated in a Rayonet apparatus for 40 hours at 253.7nm. The solvent was removed under reduced pressure and the residue purified by flash chromatography* eluting with 5:5 petroleum ether (b.p. 40-60°C) : diethyl ether to give **(150)** (r.f. 0.1), (650mg, 2.51mmol, 65.0%) as a white crystals (m.p. 105.5 - 106.5°C).

δ_H (250 MHz, CDCl$_3$): 1.31 (t, J = 7.0Hz, 3H, CH$_3$), 1.80 (dd, J = 5.0, 2.0 Hz, 2H, H$_{5a}$, H$_{5s}$), 2.20 (m, 2H, H$_{6n}$, H$_{6x}$), 2.80 (m, 1H, H$_4$), 3.56 (bs, 2H, H$_{3n}$, H$_{3x}$), 4.27 (q, J = 7.0 Hz, 2H, C$\underline{H}_2$CH$_3$), 7.36-7.52, 7.71-7.79 (m, 5H, Ph).

δ_C (62.9 MHz, CDCl$_3$): 14.0 (CH$_3$), 35.2 (C$_4$), 39.1 (C$_6$), 41.7 (C$_5$), 55.1 (C$_3$), 61.0 ($\underline{C}$H$_2$CH$_3$), 70.2 (C$_1$), 128.2, 128.4, 131.3 (5 x aryl CH), 134.5 (aryl C), 168.4, 173.8 (2 x C=O).

[For comparative NMR data see[67]]

1-Hydroxymethyl-2-benzyl-2-azabicyclo[2.1.1.]hexane (151)



(151)

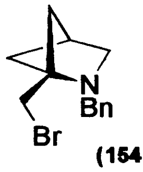
Following the procedure of Davies,[67] **(150)** (802mg, 3.09mmol) dissolved in THF (16ml) was added dropwise to a stirred suspension of lithium aluminium hydride (469mg, 12.36mmol) in THF (16ml), and heated at 60°C for 36 hours. The reaction was quenched with water-saturated ether, the slurry filtered through celite and the solvent removed under reduced pressure. The crude product was purified by flash chromatography, eluting with ether to run off the less polar impurities. The product was then flushed off the column with ether : methanol, 9:1 (sat. with NH$_3$(g)). **(151)** (410mg, 2.02mmol, 65.2%) was recovered as white crystals.

δ_H (250 MHz, CDCl$_3$): 1.62 (bs, 4H, H$_{5a}$, H$_{5s}$, H$_{6x}$, H$_{6n}$), 2.50 (bs, 1H, OH), 2.67 (bs, 1H, H$_4$), 2.68 (bs, 2H, H$_{3x}$, H$_{3n}$), 3.67 (bs, 2H, C$\underline{H}_2$Ph), 3.79 (bs, 2H, CH$_2$OH), 7.20-7.44 (m, 5H, Ph).

δ_C (62.9 MHz, CDCl$_3$): 36.8 (C$_4$), 37.7, 39.1 (C$_5$, C$_6$), 55.8 ($\underline{C}$H$_2$Ph), 57.6 (C$_3$), 61.6 ($\underline{C}$H$_2$OH), 73.7 (C$_1$), 126.8, 128.3, 128.5 (5 x aryl CH), 139.7 (aryl C).

[For comparative NMR data see[67]]

1-Bromomethyl-2-benzyl-2-azabicyclo[2.1.1.]hexane (154)



(154)

(151) (28.0mg, 138mmol) was dissolved in $CDCl_3$ (1ml) in an NMR tube. Thionyl bromide (34mg, 13µL, 164mmol) was added, the tube shaken and left for 17 hours. NH_3(g) was bubbled through the reaction mixture until an alkaline pH was observed, the ammonium bromide salt filtered off and the solvent removed under reduced pressure. The crude product was purified by flash chromatography*, eluting with 3:1 petroleum ether (b.p. 40-60°C): diethyl ether (r.f. 0.29) to give **(162)** (28.3mg, 106mmol, 77.0%) as a colourless oil.

δ_H (250 MHz, $CDCl_3$): 1.68 (bs, 4H, H_{5a}, H_{5s}, H_{6a}, H_{6s}), 2.63 (bs, 1H, H_4), 2.68 (bs, 2H, H_{3x}, H_{3n}), 3.63 (bs, 4H, $C\underline{H_2}Br$, $C\underline{H_2}Ph$), 7.20-7.48 (m, 5H, Ph).

δ_C (62.9 MHz, $CDCl_3$): 35.9 (C_4), 32.8 (CH_2Br), 39.2, 39.2, 57.7 (3 x CH_2), 55.6 ($\underline{C}H_2Ph$), 71.6 (C_1), 126.8, 128.2, 128.8 (5 x aryl CH), 139.5 (aryl C).

ν_{max} ($CDCl_3$): 3000s, 2882s, 1500w, 1440m, 1230s, 1180w, 1145m, 1070w, 645m.

$^m/_z$: 266 (MH^+)

$C_{13}H_{17}NBr$ [MH^+] requires $^m/_z$ 266.05452; observed 266.05444.

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