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Nicotinic Acetylcholine Receptor Ligands from 2,4-Methanoproline Derivatives

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Statement

The accompanying thesis submitted for the degree entitled 'Nicotinic Acetylcholine Receptor Ligands from 2,4-Methanoproline Derivatives' is based on work conducted by the author in the Department of Chemistry at the University of Leicester during the period between September 2001 and December 2004.

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:..11...JULY...2006.

Part of this research has been published

November 2003

Modifications of 1-Substituents in the 2-Azabicyclo[2.1.1]hexane Ring System; Approaches to Potential Nicotinic Acetylcholine Receptor Ligands from 2,4-Methanoproline Derivatives

John R. Malpass, Anup B. Patel, John, W. Davies and Sarah Y. Fulford

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ॐ भूर्भुवः स्वः

तत्सवितुर्वरेण्यं

भर्गो देवस्य धीमहि

धियो योनः प्रचोदयात्।

Om Bhur Bhuva Suvah

Tat Savithur Varenyam

Bhargo Devasya Dheemahi

Dhiyo Yonah Prachodayat

We meditate on that most adorable, most desirable and most enchanting lustre of our supreme God, who is our creator, inspirer and source of eternal joy. May this light inspire and illuminate our intellect and dispel the darkness.

To,

Harsha,
Ranjana
&
Bhagwandas

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NICOTINIC ACETYLCHOLINE RECEPTOR LIGANDS FROM 2,4-METHANOPROLINE DERIVATIVES

Anup B. Patel

Abstract

Since the discovery of the powerful analgesic epibatidine in 1974 from the Ecuadorian poison frog *Epipedobates tricolor*, there has been global interest in the synthesis of analogue molecules. Epibatidine has the unique 7-azabicyclo[2.2.1]heptane structure with a chloropyridyl ring at the *exo* 2-position. Epibatidine acts at the nicotinic acetylcholine receptor (nAChR) and the aim of this work is to produce target compounds retaining therapeutic potential but with higher nAChR sub-type selectivity and lower toxicity. The only naturally occurring compound to have the 2-azabicyclo[2.1.1]hexane system is the nonproteinogenic amino acid 2,4-methanoproline. This alternative bicyclic framework opens the route to the construction of pioneering epibatidine analogues.

An intramolecular [2+2] photocycloaddition method was employed to construct the rigid 2-azabicyclo[2.1.1]hexane skeleton. Successful nucleophilic substitution at a methylene attached to the bridgehead position of the 2-azabicyclo[2.1.1]hexane ring system opened the way to construction of innovative derivatives. These have a wider range of functional groups attached at the 1-position *via* a methylene 'spacer' and provide access to epibatidine analogues containing heterocyclic substituents and to further homologation. Mechanistic studies indicate that displacements with loss of a nucleofuge require thermal activation but proceed without the rearrangement initially anticipated in such a strained bicyclic structure. A unique tricyclic carbamate has been isolated; nucleophilic attack on this carbamate leads directly to the isolation of *N*-deprotected substitution products with concomitant decarboxylation.

Target compounds with potential nicotinic activity having a *bis*-methylene 'spacer' have been synthesised. Mitsunobu chemistry has been utilised to synthesise a range of pyridyl ether compounds. The methylisoxazole heterocycle has also been incorporated to open the way to a wider range of analogues. Recent interest in 2,4-methanoproline has led us to synthesise the novel β-amino acid homologue. The analogues produced in this study are currently being pharmacologically tested and the results will determine the course of future synthetic approaches towards original targets.

Abbreviations

Å	Ångstrom unit, 10^{-8} cm
AIBN	α, α′-azo-*iso*-butyronitrile
Bn	benzyl
b.p.	boiling point
Boc	*t*-butoxycarbonyl
Cbz	benzyloxycarbonyl
cm^{-1}	per centimetre
CNS	central nervous system
conc.	concentrated
COSY	correlation spectroscopy
°C	degrees centigrade
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DEPT	distortionless enhancement by polarisation transfer
EI	electron impact
FAB	fast atom bombardment
g	grams
HOMO	highest occupied molecular orbital
h	hours
Hz	hertz
IR	infra-red
TMSI	iodotrimethylsilane
hv	irradiation with light
K	Kelvin
lit.	literature
LAH	lithium aluminium hydride
LUMO	lowest unoccupied molecular orbital
MsCl	methanesulfonyl chloride
MHz	megahertz
m.p.	melting point
μg	micrograms

µl	microlitres
mg	milligrams
ml	millilitres
mm	millimetres
mmol	millimole
min	minutes
M	molar
mol^{-1}	per mole
M^+	molecular ion
mol	moles
mAChR	muscarinic acetylcholine receptor
nm	nanometre
nM	nanomolar
NGP	neighbouring group participation
nAChR	nicotinic acetylcholine receptor
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
PMP	*para*-methoxyphenyl
PNS	peripheral nervous system
ppm	parts per million
pM	picomolar
QSAR	quantitative structure activity relationship
RT	room temperature
THF	tetrahydrofuran
TLC	thin-layer chromatography
TEA	triethylamine
TFA	trifluoroacetic acid
TMS	trimethylsilane
TTP	triphenylphosphine
VT	variable temperature
ν	wavenumber

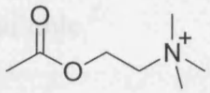
Contents

Chapter 1

Introduction

1.1 The Nicotinic Receptor

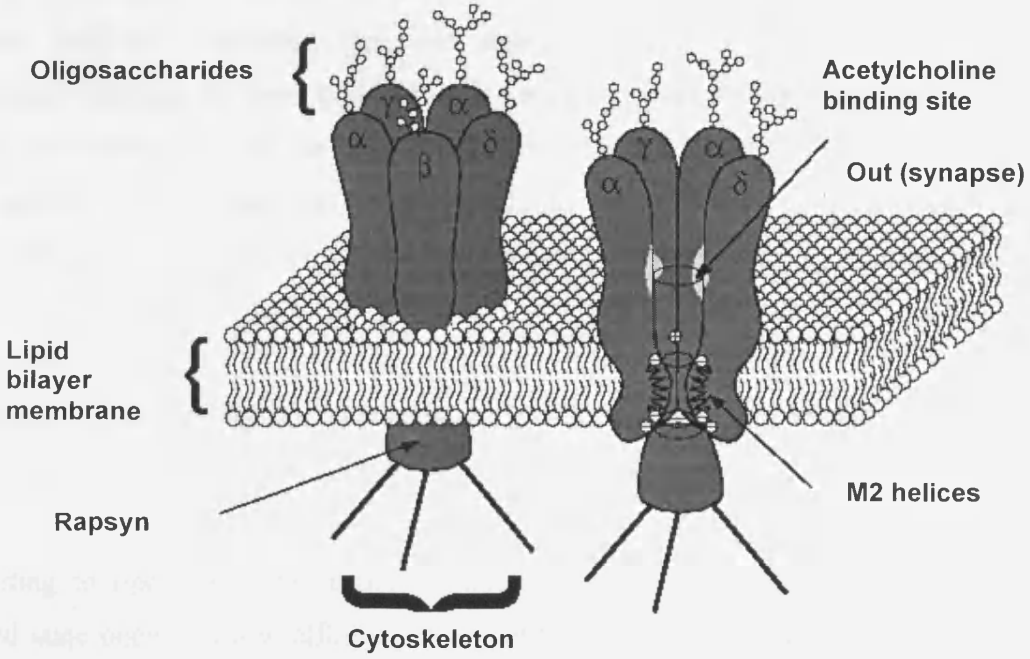
Acetylcholine is a neurotransmitter and a potent agonist of the acetylcholine division of receptors; here its principal role is as a messenger agonist for vasodilation. In the body, there are two main categories of acetylcholine receptors. The muscarinic acetylcholine receptor types (mAChR), more commonly known as G-protein coupled receptors, are located within the central nervous system, heart, smooth muscle and glands. The nicotinic acetylcholine receptor types (nAChR) are situated in the central and peripheral nervous system. It is considered that the nicotinic receptors have various functions such as neurotransmitter release and cognition. Nicotinic receptors can be divided further into two groups, muscle and neuronal types. Although the molecular structures of these are similar, they have different pharmacological properties when activated.[1]



Acetylcholine

The nicotinic acetylcholine receptor (nAChR) (**Figure 1.1**) is a channel-linked receptor; the receptor spans the cell membrane and is attached directly to an ion channel. The nAChRs are members of a superfamily of ligand-gated ion channels that include $5HT_3$, $GABA_A$, and glycine receptors. The single central nAChR ion-channel complex is composed of five protein sub-units constructed like the staves of a barrel around a central water-filled pore.[2,3]

Figure 1.1 The nicotinic acetylcholine receptor



Each nAChR subunit consists of about 500 amino acids, in one continuous polypeptide chain, where both the amino and carboxyl termini are extracellular. The subunits have four hydrophobic segments referred to as M1-M4, that transverse the plasma membrane. The M1, M3 and M4 domains separate the pore-lining region from the hydrophobic membrane. The large M3 and M4 segments are separated by an intracellular loop. The M2 domain is α-helical and provides the main lining of the cationic pore.[4,5]

Muscle type nAChRs are located in mammalian neuromuscular junctions and have been studied thoroughly, they are more accessible than neuronal types and the fast synaptic transmission can be measured. The muscle nAChR is composed of two α1 subunits and one each of β1, δ and either γ or ε.[2,6] However, neuronal nAChRs are more diverse than muscle nAChRs as more subunit variations are available.[2]

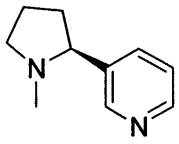
The current total of known mammalian neuronal nAChR subunits is eleven. The neuronal channels are assembled from a combination of eight α-alpha units (α2-α7, α9-α10) and three β-beta units (β2 to β4). Five α7 units form functional homomeric ion channels as do α8, α9 and α10. The additional α8 subunit has only been identified in bird species. Invertebrates are found to have seventeen nAChR subtypes. The exact combination and function of all the channels have yet to be determined.[4,5]

The receptor has three main functional states; closed, open and desensitised. In the resting state the ion-channel is closed, so the receptor is non-conducting. When two agonist molecules bind to a receptor, the open state of the receptor is stabilised for a few milliseconds, making the pore permeable to cations to pass through the membrane.[2] The increase in permeability of the membrane causes a net inward flow of cations, which depolarises the cell causing neuronal excitation and hence leading to physiological effects.[7] In the subsequent desensitised state, the ion-channel is closed and the receptor is refractory to the agonists.[2]

The nAChR ligand-binding site represents an interface between the N termini of two adjacent subunits, one of which is an α-subunit. Separate binding sites also exist for non-competitive antagonists and positive allosteric modulators. Nicotinic agonists act at the nAChR-binding site leading to opening of the cation-conducting pore. The agonist interaction with the activated state occurs at low affinity. Competitive antagonists interact reversibly with the nAChR-binding site, it stabilises the receptor in a closed channel conformation hence

preventing access for agonists. Inhibition by competitive antagonists can be overcome by increasing the concentration of agonist.[4]

A potential analogue compound may have multiple pharmacological properties at the nicotinic receptor. It may act at different receptor subtypes as a full agonist, a partial agonist or even as an antagonist. The affinity and efficacy can determine the potency of an analogue molecule. The affinity is the ability of the compound to bind at the receptor site. The efficacy indicates the relative intensity, which is how well the analogue activates a particular subtype; it is the tendency to stabilise the open state of the channel once bound to the receptor. Affinity is usually determined by experiments conducted on animal brain tissue as they contain nicotinic receptors. The tissue is saturated with a radioligand like tritium-labelled nicotine ([^{3}H]-nicotine) and a known concentration of the analogue compound is inserted. The equilibrium constant K_i measures the amount of radioligand displaced by the analogue compound. Efficacy is determined by electrophysiology experiments, again using animal brain tissue. The amplitude of the current of the analogue compound is compared to that of a natural full agonist. If the magnitude of the current is similar then the ligand is a full agonist. A decrease in magnitude indicates a partial agonist or antagonist. The measured EC_{50} value is the concentration of agonist needed to draw a current half of its maximum amplitude.[8]



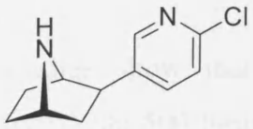
(*S*)-Nicotine

The endogenous nicotinic agonist acetylcholine binds with high affinity (K_i = 10 nM) at α4β2 nAChRs. The tobacco alkaloid nicotine can also bind to nAChRs, which is how the receptor was named. Nicotine (K_i = 1-11 nM) binds to the α4β2 nAChR with a similar affinity to acetylcholine. It is found that nicotine has many liabilities so cannot be used therapeutically; it has adverse side-effects on autonomic function and is the highly addictive component of tobacco. Clinical studies show that the antinociceptive effects of nicotine reinforce smoking by providing pain relief.[4,5] Research on nicotine and nicotinic analogues is described further in Chapter 5, Section 5.2.

1.2 Discovery of Epibatidine

In 1974, Daly and co-workers[9,10] from the National Institute of Health collected samples from the skins of poison frogs from the Pacific highlands in Ecuador. Whilst extracting skin samples from the frog *Epipedobates tricolor* (**Figure 1.2**) they isolated a compound initially called alkaloid 208/210 (its molecular weight from mass spectrometry). Daly demonstrated that this new alkaloid was a potent analgesic (as measured by the Straub-tail response when injected into mice). After subsequent trips to South America, there was still insufficient compound to make an accurate structural determination so the available sample was kept in storage for several years. During the early 1990s, as NMR instruments and methods became more sensitive and advanced, Daly's group was able to determine the structure of alkaloid 208/210, which was renamed epibatidine (1*R*, 2*R*, 4*S* *exo*-2-(6-chloro-3-pyridyl)-7-aza-bicyclo[2.2.1]heptane) after the species of frog. Epibatidine has a unique structure for a natural alkaloid having the 7-azabicyclo[2.2.1]heptane structure with a 2-chloro-5-pyridyl substituent attached at the 2-position of the bridge ring in an *exo*-orientation.

Figure 1.2 Epibatidine and *Epipedobates tricolor*



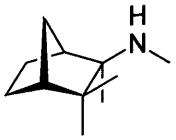
(-)-Epibatidine

It is found that frogs raised in captivity do not produce the analgesic material on their skin. As a result, it is assumed that the alkaloid is derived by *Epipedobates tricolor* through an indigenous dietary source.[10] Recent research indicates that the frog's diet of toxic-laden beetles is the source of a precursor to the powerful alkaloid. Exactly how the frogs can consume the beetle and accumulate toxins while remaining insensitive to them is unclear.[11]

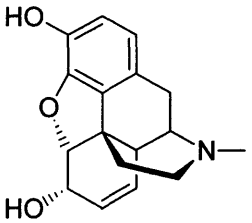
The discovery of epibatidine generated global interest in its synthesis. This was largely due to the scarcity of epibatidine, as it requires the skins of 750 frogs to yield less than 0.5 mg of material, and its potential pharmacological benefits. To date there are well over fifty different published syntheses, with two main approaches to the synthesis of epibatidine,[12,13]

although other methods have also been employed. After structural elucidation, preparation of large amounts of material allowed detailed pharmacological characterisation.[14,15]

Pharmacological testing of epibatidine shows that it binds with remarkably high affinity (K_i = 19 pM) at α4β2 nAChRs, (K_i = 230 pM) at α3β2 and (K_i = 380 pM) at α3β4.[4] Binding affinity at α7 is about 10,000-fold lower than α4β2 nAChRs (K_i ~ 200 nM).[4] The functional potency of epibatidine is also very high with sub-micromolar EC_{50} values for the receptor sub-types mentioned. The (+)- and the natural (-)-enantiomers of epibatidine were nearly equipotent in these tests of analgesic activity.[5] This lack of enantioselectivity contrasts with nicotine, where the naturally-occurring enantiomer, (-)-nicotine is more potent than (+)-nicotine. The blockade by the nAChR antagonist mecamylamine confirms that the antinociceptive actions of epibatidine require activation of nAChRs.[4]



Mecamylamine



Morphine

Pharmacological studies show that epibatidine possesses analgesic properties, having antinociceptive activity 200-500 times greater than that of morphine.[10] The mechanism of action of epibatidine was found to be non-opioid and it is a selective agonist at nicotinic acetylcholine receptors. Many potent pain-relieving drugs are opiates, morphine being a very familiar example. Morphine is an effective and potent analgesic although the potential for addiction and the development of morphine tolerance are major drawbacks to its use. In spite of the analgesic properties of epibatidine it could not be used therapeutically as it did not discriminate between nicotinic receptor sub-types and was found to cause hypertension, convulsions and respiratory distress.[10]

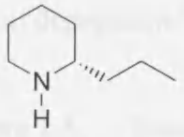
Epibatidine has generated a great interest in the synthesis of analogue molecules, which might be more selective to nicotinic receptor sub-types, have reduced toxicity and side-effects but would retain the analgesic properties for increased pharmacological value. Nicotinic therapy can be beneficial for a variety of diseases such as ulcerative colitis, Parkinson's disease, Alzheimer's disease and Tourette's syndrome. The drug binding

interaction of possible target compounds needs to be studied to investigate the structure-activity relationships (SAR).[1]

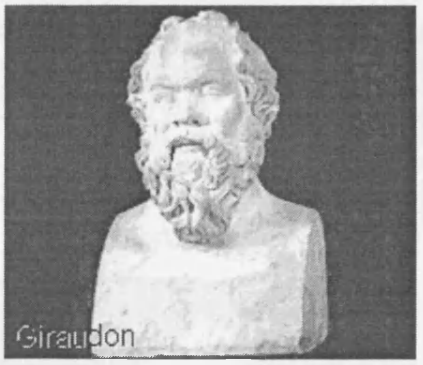
1.3 Alkaloids

Alkaloids are nitrogen containing alkaline compounds, mainly of plant, insect or amphibian origin. They have pharmacological activity therefore can produce strong physiological effects on the body, ranging from toxicity to pharmaceutical potential. Nearly 3000 natural alkaloids have been identified; coniine was the first to be prepared synthetically in 1886. It is highly poisonous as less than 200 mg is fatal. Coniine is obtained from seeds of the hemlock (*Conium maculatum*) and was the poison used by the ancient Greeks in the execution of the philosopher Socrates (**Figure 1.3**). This poisonous component in hemlock affects the nervous system and induces trembling, loss of coordination, and paralysis of respiration.[16]

Figure 1.3 Coniine, hemlock and Socrates



(*S*)-coniine

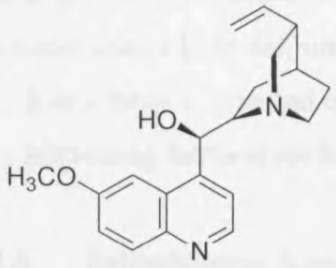


1.3.1 Alkaloids Obtained from Plants

Alkaloids of plant origin have properties that can be used for medicinal purposes. Two prime examples include quinine and reserpine. The first total syntheses of quinine and reserpine were accomplished in 1944 and 1956 respectively, by Robert Burns Woodward and co-workers.[17,18]

Quinine is based on the 1-azabicyclo[2.2.2]octane skeleton and is derived principally from the bark of the South American cinchona tree (*Cinchona pubescens*) (**Figure 1.4**). It is an efficient antipyretic and is used to reduce fever in many diseases. It was the only known remedy for malaria until the development in recent years of synthetic drugs.[16]

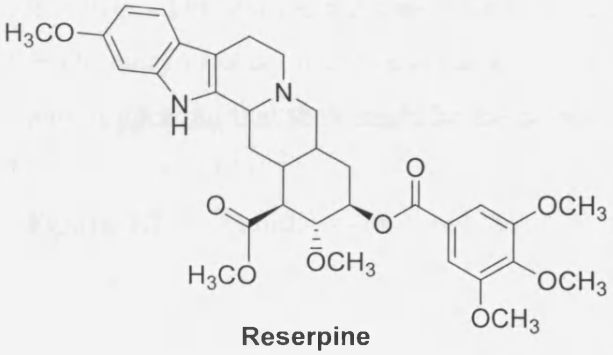
Figure 1.4 Quinine and the cinchona tree



Quinine

Reserpine is constructed of a series of adjoining ring systems; although not bicyclic it is composed of heterocyclic rings and includes a tertiary amino-nitrogen. It is found in the root of the Indian plant *Rauwolfia serpentine* (**Figure 1.5**). It was one of the first drugs to be applied in the treatment of hypertension and of psychiatric illness. Now it has been supplanted in the treatment of psychosis. Reserpine therapy is found to induce extreme mental depression.[16]

Figure 1.5 Reserpine and *Rauwolfia serpentine*



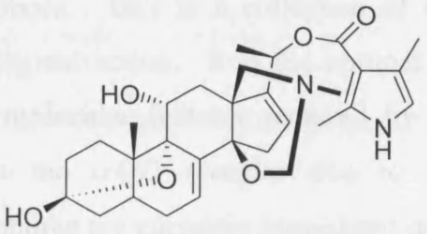
Reserpine

1.3.2 Alkaloids of Amphibian Origin

Other than epibatidine there are reports of various alkaloids isolated from South and Central American poison arrow frogs. Native Indians extracted the poison from the small brightly coloured frogs and used them for poison arrows and blowgun darts for hunting. Important examples include batrachotoxin A[19] and pumiliotoxin A.[20]

Batrachotoxin A is a toxic steroidal alkaloid secreted by the skin of the poison frog *Phyllobates aurotaenia* (**Figure 1.6**). The poison is harmless on skin contact but is lethal in the blood in low concentrations of two parts per billion. The compound prevents the closing of sodium-ion channels in the surface membrane of muscle and nerve cells inhibiting their function. It is a large compound composed of a series of ring systems; the complex structure has many interesting features including the pyrrole ester group.[19,21]

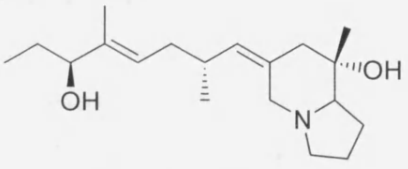
Figure 1.6 Batrachotoxin A and *Phyllobates aurotaenia*



Batrachotoxin A

Pumiliotoxin A is found on the poison frog *Dendrobates pumilio* (**Figure 1.7**). It is another toxic alkaloid having the indolizidine framework; a dose of 20 μg was found to cause death in mice. The compound was found to be a potent myotonic and cardiotonic agent with modulatory effects on sodium channels. Similar pumiliotoxins have also been discovered in ants suggesting that they might be the primary source of the poison.[20,22]

Figure 1.7 Pumiliotoxin A and *Dendrobates pumilio*



Pumiliotoxin A

Epibatidine is unique in the sense that it is the only naturally occurring alkaloid to have the 7-azabicyclo[2.2.1]heptane structure a chloropyridyl ring. It is also remarkable that epibatidine achieves most of the criteria for the 'rule of five'[23] for a potential drug, where the other naturally occurring alkaloids mentioned earlier do not. Epibatidine has a lower molecular weight, fewer hydrogen bond donors and acceptors than the above natural alkaloids, making the area for the synthesis of epibatidine analogues highly competitive and fascinating.

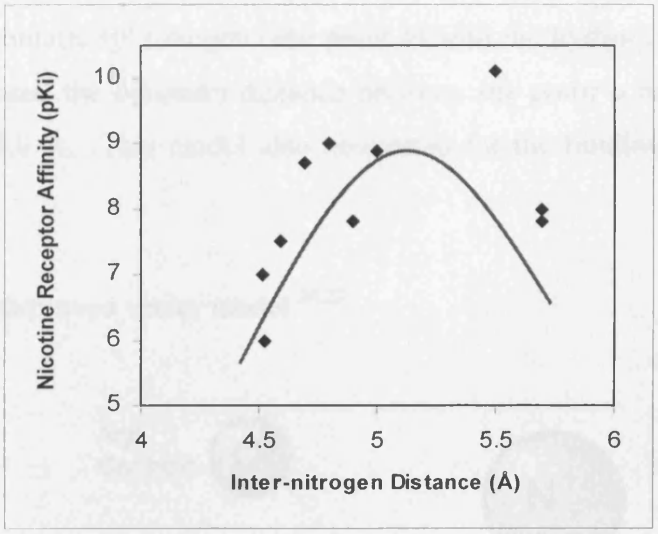
1.4 The Nicotinic Pharmacophore

The study of biologically active compounds usually involves development of a pharmacophore. This is a collection of the minimal structural features required to give pharmacological action. It is the optimal three-dimensional arrangement of chemical and structural molecular features required by a certain receptor. The most studied neuronal nAChR is the $\alpha4\beta2$ receptor due to its abundance in mammalian brain, therefore pharmacophores are currently formulated on this receptor type.[24] In 1970, Beers and Reich[25] suggested the first nicotinic pharmacophore. They stated that the nicotinic agonist should contain two important structural features; a hydrogen bond acceptor atom (e.g. pyridine N or carbonyl O) and a centre of positive charge (e.g. protonated basic nitrogen). The hydrogen bond formed as a result from the interaction with the receptor is 5.9 Å from the cationic centre. This distance is known as the 'inter-nitrogen distance' because most, analogues contain a pyridine nitrogen and a more basic nitrogen.

This model was refined by Sheridan *et al.*[26] who expanded the pharmacophore into a triangular model. In addition to the hydrogen bond acceptor atom and a centre of positive charge their model included a dummy atom that indicates where the hydrogen bond may form. In nicotine the dummy point is the centre of the pyridine ring. The pharmacophore model was only based on four ligands and did not include functional or binding data. When this model was proposed there were few nicotinic ligands available and understanding of the nAChR was poor. A better model was developed subsequently (**Figure 1.10**).

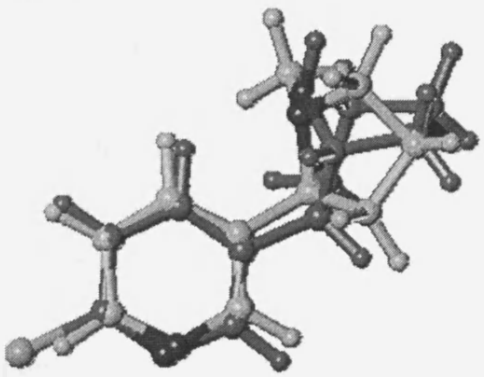
Dukat and co-workers[27] collected data on the inter-nitrogen distances of ten pyridine-containing molecules at the receptor site and concluded that the optimum inter-nitrogen distance is between 5.0-5.7 Å. This was confirmed by a parabolic relationship between the inter-nitrogen distance and affinity (**Figure 1.8**). Protonated epibatidine was found to have an inter-nitrogen distance of 5.51 Å for one of its two lowest-energy conformations.

Figure 1.8 The relationship between the inter-nitrogen distance and affinity



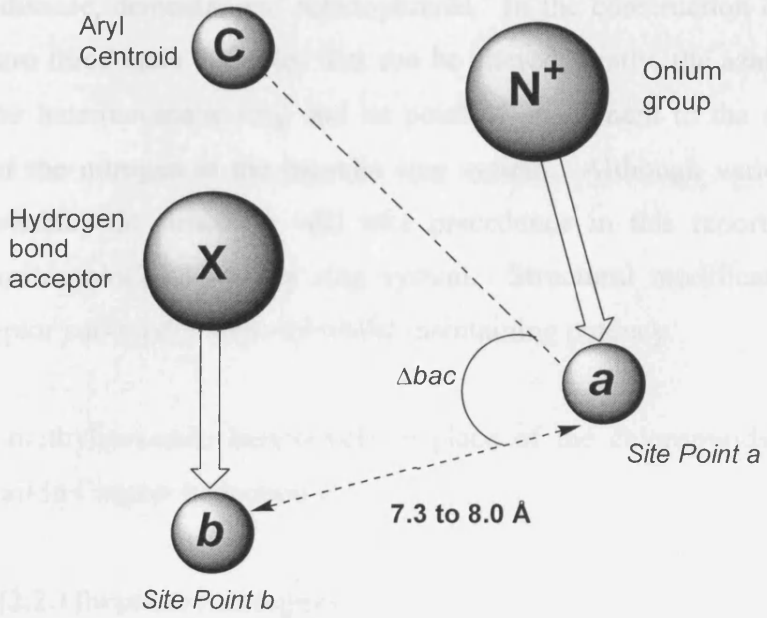
The binding of epibatidine to the receptor was investigated further from a comparison of the structures of nicotine and epibatidine. Both molecules contain a six-membered pyridine ring and a basic nitrogen linked to the pyridine ring by one or two carbons. In both cases these basic nitrogen atoms are part of a five-membered ring (in epibatidine the five-membered ring is part of the azabicycloheptane structure). The energy-minimised molecular models of the compounds could be overlaid such that major structural features are in similar positions in space (**Figure 1.9**).[28] This modelling experiment illustrates in a three-dimensional fashion that epibatidine and nicotine may interact with similar receptor features. However it should be remembered that epibatidine is much more potent than nicotine, so a slight variation in structure can have a huge influence on binding.

Figure 1.9 Superposition of nicotine (cyan) and epibatidine (red).
(Nitrogens are blue; chlorine is green).[28]



Recent research by Olesen and co-workers[29] suggests that the pharmacophore should include the sites of interaction of the sp^3 nitrogen (site point a) with the receptor protein and interaction of the aromatic sp^2 nitrogen (site point b) with the hydrogen bond donor (**Figure 1.10**). They calculated the optimum distance between *site point a* and *site point b* on the receptor to be 7.0-8.0 Å. This model also accounted for the binding of a range of ligand sizes.

Figure 1.10 The improved vector model [24,29]



Further research on the structure of nicotinic receptor would enable studies into the pharmacophore architecture. Recently, the use of scanning electron microscopy has enabled the study of muscle nAChR to the resolution of 4.6 Å.[30] Recent investigations of the structure, function and mutations of nAChRs may show the direction forward in designing a pharmacophore model leading to the synthesis of novel ligands.[31,32] There has been extensive work done on G-protein coupled receptors and CNS drug targets, but similar studies on nAChRs are less advanced.[6] Current work now uses computational studies and molecular modelling to calculate inter-nitrogen distances and determine superpositionings of novel ligands.[29] More recently, three-dimensional quantitative structure-activity relationship studies (3D QSAR) have been conducted on a range of 45 ligands on the $\alpha4\beta2$ nAChR.[33] These methods give a better idea to the design of ligands as they can make a more accurate prediction of nicotinic receptor interactions. However, there is still much research to be

conducted before the medicinal chemists can agree upon an accurate nicotinic pharmacophore model.

1.5 Selected Analogues of Epibatidine

The principal aim when synthesising epibatidine analogues is to make compounds that show greater receptor sub-type selectivity, producing drugs with therapeutic potential and minimal side-effects having a decreased toxicity. There needs to be a greater discrimination by nicotinic agonists between nAChR sub-types. Potential compounds may mediate neurotransmitter activity in the treatment of many neurological disorders such as Alzheimer's disease, Parkinson's disease, dementia and schizophrenia. In the construction of analogues of epibatidine, there are three main variables that can be altered; firstly, the azabicyclic ring structure, secondly the heteroaromatic ring and its point of attachment to the skeleton and finally the position of the nitrogen in the bicyclic ring system. Although various types of analogue exist, the azabicyclic structures will take precedence in this report, with most emphasis on the 2-azabicyclo[2.1.1]hexane ring system. Structural modifications should induce improved receptor sub-type selectivity whilst maintaining potency.

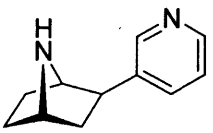
Analogues having a methylisoxazole heterocycle in place of the chloropyridyl group are described in more detail in Chapter 6, Section 6.1.

1.5.1 7-Azabicyclo[2.2.1]heptane Analogues

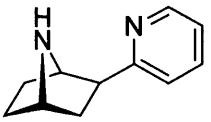
As stated earlier, epibatidine is much more effectual in binding at the nicotinic receptor than either nicotine or acetylcholine. Due to its failure to discriminate between receptor sub-types it cannot be used therapeutically. As a result of this epibatidine analogues have been synthesised maintaining the 7-azabicyclo[2.2.1]heptane structure, but having modifications to heterocycle.

The synthesis of deschloroepibatidine (DClEPB) indicated the importance of chlorine in the pyridyl heterocycle of epibatidine. The research demonstrated a decrease in efficacy at $\alpha4\beta2$ and $\alpha3\beta4$ subtypes with a small variation in the $\alpha7$ subtype for both enantiomers.

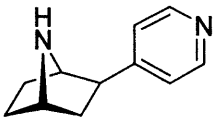
The (-)-DClEPB showed a 120-fold reduction in efficacy while (+)-DClEPB only showed a 40-fold reduction compared to the respective enantiomers of epibatidine. It was concluded that the chlorine is important for the activation of heteromeric nAChRs.[34]



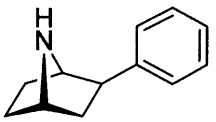
DCIEPB



2-PABH



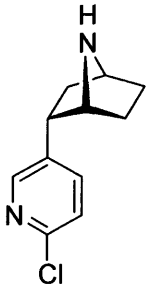
4-PABH



PABH

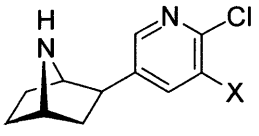
In the synthesis of 2-PABH the pyridine nitrogen was altered from the *meta* to the *ortho* position respective to the point of attachment to the azabicycle. As a result, this decreased the inter-nitrogen distance and spatial orientation of the pyridine nitrogen, leading to a huge decrease in efficacy of both enantiomers for the α4β2 and α3β4 subtypes. Only (-)-2-PABH showed binding at the α7 subtype. Having the pyridine nitrogen in the *para* position, forming 4-PABH or removing the nitrogen to give PABH, also led to a decrease in activity at the α4β2 and α7 subtypes, but showed efficacy at the α3β4 nAChR subtype.[34]

The orientation of the chloro-pyridyl ring was changed from *exo* to *endo* in (±)-*endo*-epibatidine, resulting in a 150-fold decrease in binding affinity (K_i = 7.6 nM) compared to epibatidine due to the increased inter-nitrogen distance.[35]



(±)-*endo*-epibatidine

There have been reports of the synthesis of a range of 3′-substituted epibatidine analogues **1a-f** and binding affinity data at α4β2 and α7 nAChR subtypes. Overall, the K_i values were found to be similar to that of (-)-epibatidine (K_i = 0.026 nM). The highest binding affinity was for the 3′-iodo **1d** (K_i = 0.008 nM) and 3′-amino **1e** (K_i = 0.01 nM). While compounds **1a-c** and **1f** all showed a higher affinity for the α7 subtype than epibatidine.[36,37]



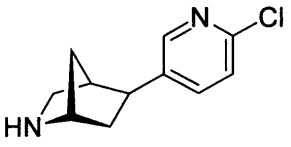
1

1a X = Cl **d** X = I
b X = F **e** X = NH_2
c X = Br **f** X = N_3

1.5.2 2- Azabicyclo[2.2.1]heptane Analogues

The orientation of the nitrogen in the azabicycle has been changed to the 2-position, to create a range of epibatidine analogues. Recently, the 2-azabicyclo[2.2.1]heptane system has been the focus of extensive work at Leicester.[38,39]

Both the *exo*-5- **2** and *exo*-6-(6′-chloro-3′-pyridyl)-2-azabicyclo[2.2.1]heptane isomers **3** of epibatidine have been constructed, using the reductive Heck reaction on 2-azabicyclo[2.2.1]-hept-5-ene derivatives. Both **2** and **3** showed a low affinity (K_i > 38 nM) for both α4β2 and α7 nAChRs. This was expected due to the large inter-nitrogen distances.



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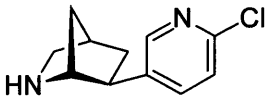

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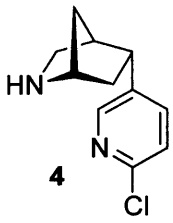

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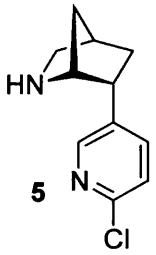
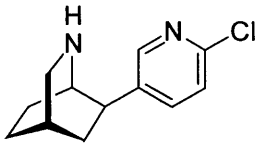


5

Further work, involved the synthesis of *endo*-5- **4** and *endo*-6-(6-chloro-3′-pyridyl) **5** derivatives which showed a high selectivity for α4β2 *versus* α7 nAChR subtypes and high affinity (K_i = 0.056 nM) and (K_i = 0.045 nM) respectively. The inter-nitrogen distances of both the *endo*-5- **4** and *endo*-6- **5** compounds were calculated and found to be similar to that of epibatidine. As the nitrogen has changed from the 7- to the 2-position, it is suggested that the nitrogen is asymmetric in the bicyclic structure leading to potential enantioselectivity at the receptor site. This demonstrates that epibatidine analogues can be synthesised with improved selectivity while maintaining the potency of epibatidine.[38] Research by another group[40,41] also show the synthesis of *endo*-6-(6-chloro-3′-pyridyl)-2-azabicyclo[2.2.1]-heptane **5**, using an alternative radical methodology.

1.5.3 2-Azabicyclo[2.2.2]octane Analogues

Subsequent research on higher homologues led to the synthesis of the 2′-(chloro-5′-pyridinyl)-2-azabicyclo[2.2.2]octanes **6** and **7**.[36,42] In these structures a methylene group has been added between the 7-aza group and bridgehead positions. Both the vicinal **6** (K_i = 0.47 nM) and distal **7** (K_i = 0.34 nM) analogues were less potent than epibatidine.[36,42]



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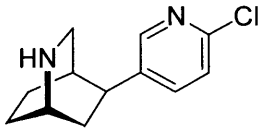
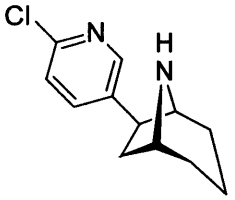


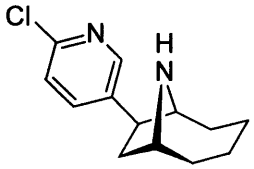
7

1.5.4 8-Azabicyclo[3.2.1]octane & 9-Azabicyclo[4.2.1]nonane Analogues

In recent years, much research emphasis has concentrated on larger ring systems. Work at Leicester led to the synthesis of (±)-homoepibatidine and (±)-*bis*-homoepibatidine, which have the 8-azabicyclo[3.2.1]octane and 9-azabicyclo[4.2.1]nonane frameworks respectively. (±)-Homoepibatidine was found to be as active as epibatidine; both (+)-homoepibatidine (K_i = 0.35 nM) and (-)-homoepibatidine (K_i = 0.13 nM) have a high affinity. (±)-*Bis*-Homoepibatidine (K_i = 1.25 nM) was found to have a low affinity due to an increase in the size of the larger bridge of the bicyclic system to four-carbon atoms.[43,44]

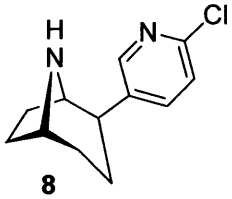


(±)-Homoepibatidine



(±)-*Bis*-Homoepibatidine

Due to the considerable potential offered by homoepibatidine, other compounds have been synthesised that also feature the 8-azabicyclo[3.2.1]octane ring system. However, moving the chloropyridyl ring to the 2β- **8** and 2α- **9** positions was found to reduce the binding affinities in comparison to homoepibatidine.[45,46]



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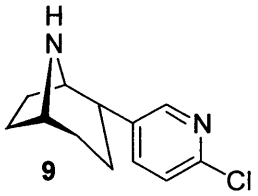
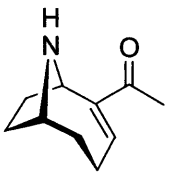
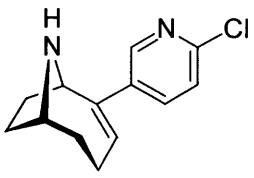


9

The alkaloid (+)-anatoxin-A is a 9-azabicyclo[4.2.1]nonene derivative originally isolated from freshwater blue-green algae, *Anabaena flos aqua*. It is a potent and stereoselective agonist at α4β2 nAChR subtypes, but has a low selectivity. Anantoxin-A (K_i = 1.25 nM) binds to this nAChR subtype with a higher affinity than nicotine. It has been employed to characterise nicotinic currents in brain neurones and nAChR-mediated dopamine release.[5]



(+)-Anatoxin-A

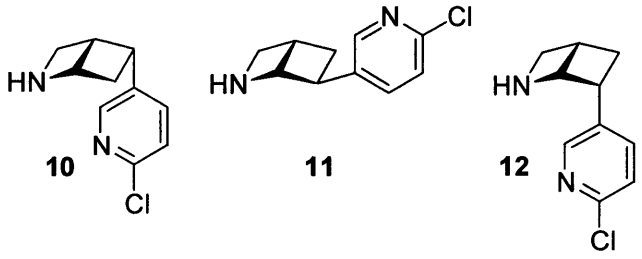


UB-165

UB-165 is a hybrid of anatoxin-A and epibatidine in which the acetyl group of anatoxin-A is replaced by the chloropyridyl ring of epibatidine.[47] It was found to have a high binding affinity and stimulant activity at α4β2 subtype receptors (K_i = 0.27 nM), but like its parent compounds lacked selectivity between α4β2, α3β4 and α7 nAChR subtypes.[48] A wide range of UB-165 analogues have been synthesised and pharmacologically tested, these compounds have the chloropyridyl ring replaced by other heterocycles.[49]

1.5.5 2-Azabicyclo[2.2.0]hexane Analogues

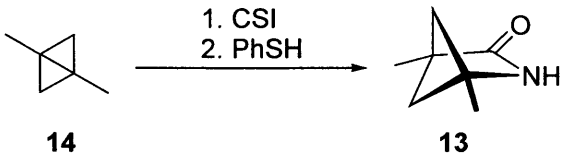
Smaller epibatidine analogues have also been synthesised that are more strained having a rigid framework. Krow and co-workers[50] have synthesised the rigid *endo*-5- **10**, *exo*-6- **11** and *endo*-6-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.0]hexane **12**, constructed by reductive Heck coupling of 2-azabicyclo[2.2.0]hex-5-ene compounds. These compounds **10** (K_i = 5.0 nM), **11** (K_i = 39.0 nM) and **12** (K_i = 3.9 nM) were found to have a weak binding affinity at α4β2 nAChR subtypes.



1.6 Synthesis of 2-Azabicyclo[2.1.1]hexane Systems

In 1971, Paquette and co-workers[51] reported the synthesis of the lactam **13** from the reaction of 1,3-dimethylbicyclo[1.1.0]butane **14** with chlorosulfonyl isocyanide (CSI) (**Scheme 1.1**). This synthesis of the 2-azabicyclo[2.1.1]hexane ring system was limited to compound **13**. Methods that are more contemporary include photochemical ring closure, synthesis from cyclobutanes, thermal reactions and construction from 2-azabicyclo[2.2.0]hex-5-enes. The recent interests, and the potential of the synthesis of nicotinic acetylcholine receptor ligands, make the synthesis of the 2-azabicyclo[2.1.1]hexane system a highly topical and competitive subject. The major synthetic methods for the construction of the 2-azabicyclo[2.1.1]hexane system will be discussed.[52]

Scheme 1.1

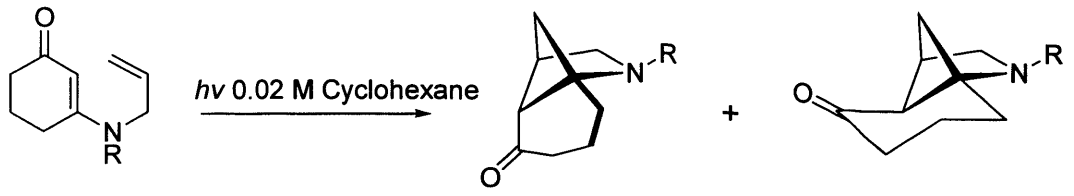


1.6.1 Synthesis of 2-Azabicyclo[2.1.1]hexanes from Photochemical Ring Closure

Photochemical ring closure to form the 2-azabicyclo[2.1.1]hexane system can be accomplished in two ways; using linearly-conjugated *N*-allyl-*N*-vinylamides (**Scheme 1.2**) or by cross-conjugated 1-acyl-*N*-vinyl-*N*-allylamines (**Scheme 1.3**).

The intramolecular photocycloaddition of linearly-conjugated *N*-allyl-*N*-vinylamides **15a-d** forms the 2-azabicyclo[2.1.1]hexane system with the *cis*-fused six-membered ketones **16a-d** (**Scheme 1.2**). The amide **15d** formed a mixture of the *cis*-fused **16d** and *trans*-fused **17d** ketones.[52,53] There have been no reports of this method being used to construct epibatidine analogues.

Scheme 1.2



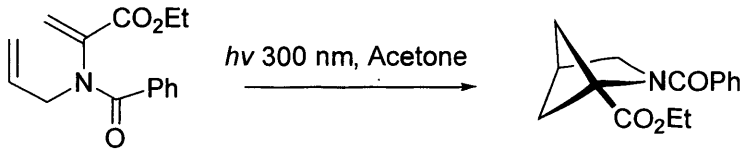
15a R = Me
b R = $CH_2CH{=}CH_2$
c R = Ph
d R = COMe

16a **b** **c** **d**

17d

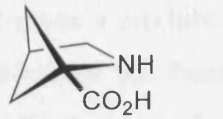
The irradiation of cross-conjugated 1-acyl-*N*-vinyl-*N*-allylamines gives the 2-azabicyclo-[2.1.1]hexane ring system (**Scheme 1.3**).[54,55]

Scheme 1.3



This was first constructed as part of the total synthesis of 2,4-methanoproline, isolated from the seeds of *Ateleia herbert smithii* (**Figure 1.11**).[54,55] The syntheses of compounds using this method are described in more detail in Chapter 2, Section 2.1.

Figure 1.11 2,4-Methanoproline and *Ateleia herbert smithii*

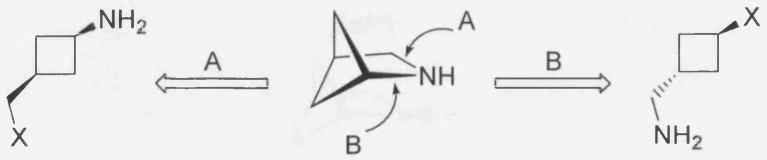


2,4-Methanoproline

1.6.2 Synthesis of 2-Azabicyclo[2.1.1]hexanes from Cyclobutanes

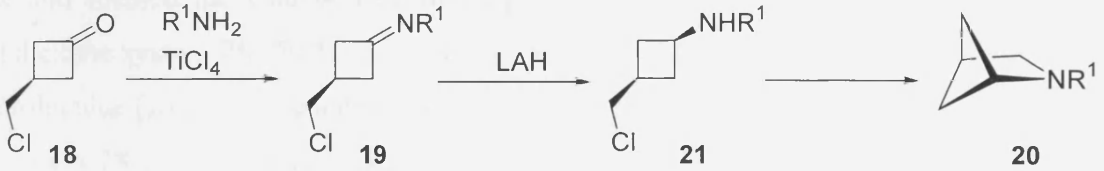
The synthesis of 2-azabicyclo[2.1.1]hexane systems from cyclobutanes can be achieved by two main routes; the aminocyclobutane route (bond A disconnection) or the aminomethyl cyclobutane route (bond B disconnection) (**Scheme1.4**).[52]

Scheme 1.4



Recently, the aminocyclobutane route has been used by Kimpe and co-workers[56] (**Scheme 1.5**). The 2-azabicyclo[2.1.1]hexane system can be constructed from 3-(chloromethyl)-cyclobutanone **18**, which is synthesised in two steps (31 % yield) from readily available starting materials.

Scheme 1.5

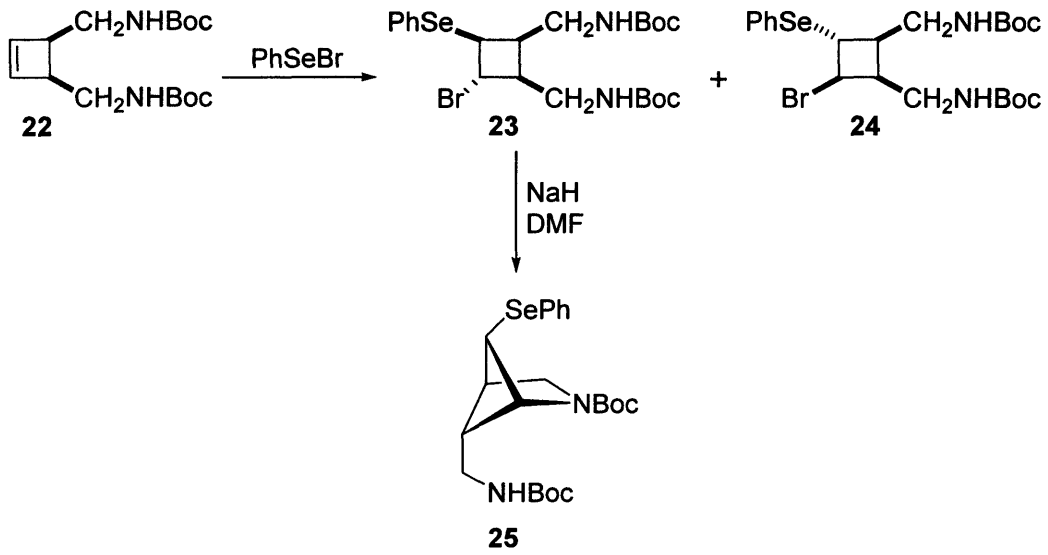


R^1 = *i*-Pr, Et, *c*-Hex, *s*-Bu, *t*-Bu

The 3-(chloromethyl)-cyclobutanone **18** can be converted into the imine **19** and then reduced *anti* to the chloromethyl substituent, to give the 2-azabicyclo[2.1.1]hexane product **20**, *via* intramolecular ring closure of **21**. Using this method it is possible to attach nucleophiles at the bridgehead C_1 position, although at present the synthesis of nicotinic acetylcholine ligands have not been reported.[52,57]

Contemporary research, using the aminomethyl cyclobutane method has been achieved by Huet and co-workers[58] to synthesise 5-*syn*-substituted 2-azabicyclo[2.1.1]hexanes (**Scheme 1.6**). Compound **22** can be prepared in seven steps from starting materials. The reaction of **22** with PhSeBr gives a mixture of two isomers **23** (73 % yield) and **24** (13 % yield). Ring closure of **23** produces the functionalised 2-azabicyclo[2.1.1]hexane ring system **25**. This synthesis allows the presence functional groups at the C_5 and C_6 positions, again there is no information on the synthesis of epibatidine analogues.

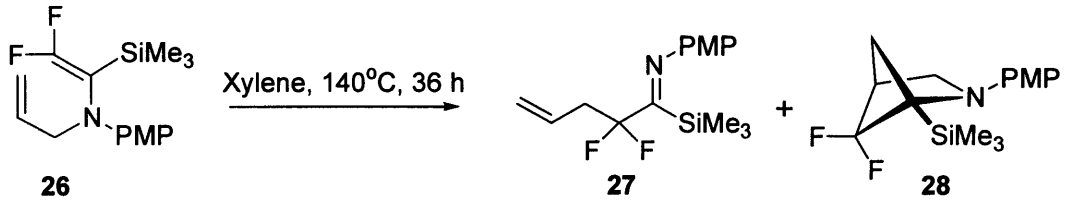
Scheme 1.6



1.6.3 Synthesis of 2-Azabicyclo[2.1.1]hexanes using Thermal Conditions

The unusual behaviour of *N*-allylic difluoroenamines was observed under thermal conditions by Uneyama and co-workers.[59] A solution of *N*-allyl difluoroenamine **26** was heated to reflux and formed the Claisen rearranged product **27** (41 % yield) and the 2-azabicyclo-[2.1.1]hexane system **28** (59 % yield) (**Scheme 1.7**). The formation of **28** was explained by intramolecular [2+2] cycloaddition of the allyl enamine. Their 2-azabicyclo[2.1.1]hexane ring system **28** is novel in having fluorine atoms on the C_5 position. In order to synthesise epibatidine analogues from **28**, the $SiMe_3$ group at the C_1 position would need to be replaced to allow the attachment of heterocycles and a valid method for the removal of the PMP group would need to be developed.

Scheme 1.7

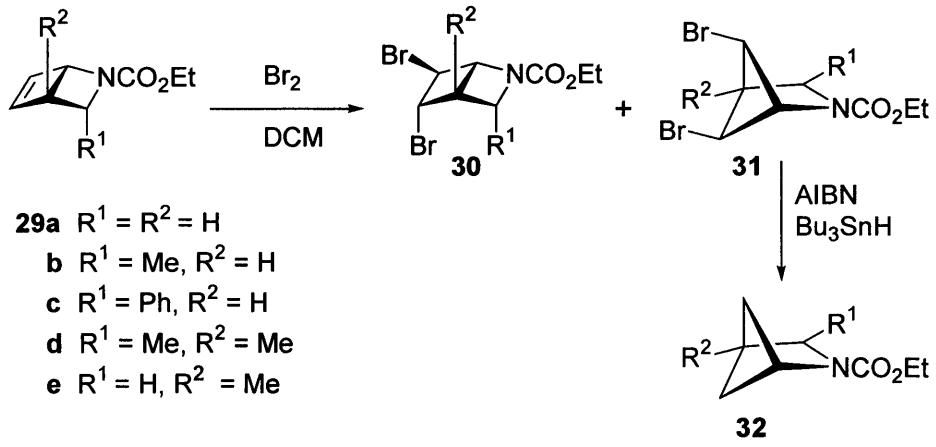


26 **27** **28**

1.6.4 Synthesis of 2-Azabicyclo[2.1.1]hexanes from 2-Azabicyclo[2.2.0]hex-5-enes

Recently, the construction of 2-azabicyclo[2.1.1]hexanes from 2-azabicyclo[2.2.0]hex-5-enes has been almost dominated by Krow and co-workers.[52] Pyridine or substituted pyridines have been the source of 1,2-dihydropyridines that can be irradiated to form *N*-(ethoxy-carbonyl)-2-azabicyclo[2.2.0]hexanes **29a-e**. Subsequent addition of bromine to **29d** forms a 55:45 mixture of the *trans*-dibromide **30d** and the substituted 2-azabicyclo[2.1.1]hexane ring system **31d** (**Scheme 1.8**). Reductive debromination of **31d** forms **32d** resulting in functionality at the C_3 and C_4 positions.[60,61]

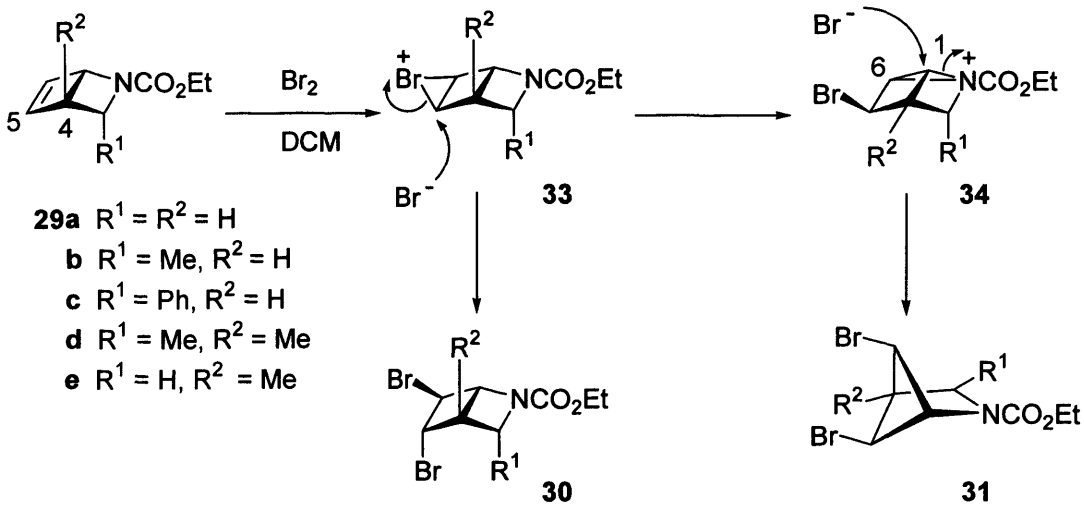
Scheme 1.8



29a $R^1 = R^2 = H$
b $R^1 = Me$, $R^2 = H$
c $R^1 = Ph$, $R^2 = H$
d $R^1 = Me$, $R^2 = Me$
e $R^1 = H$, $R^2 = Me$

The synthesis of the **30** and **31** are shown in **Scheme 1.9**. Bromide ion attack at C_5 of the bromonium ion **33** gives the dibromide **30**. A bulky R^1 substituent can block attack at the C_5 position, which results in the rearrangement of **33** to form the aziridinium ion **34**.[52,60,61]

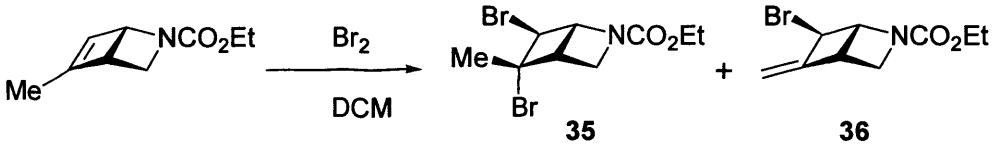
Scheme 1.9



29a $R^1 = R^2 = H$
b R^1 = Me, $R^2 = H$
c R^1 = Ph, $R^2 = H$
d R^1 = Me, R^2 = Me
e $R^1 = H$, R^2 = Me

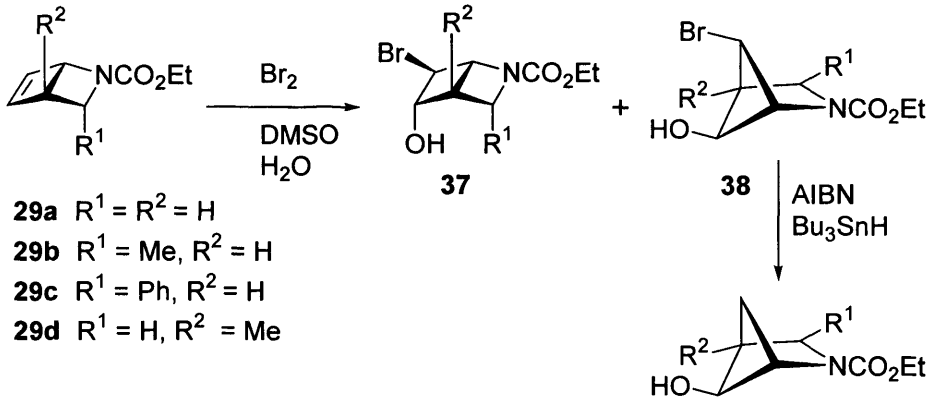
The rearrangement does not occur if a methyl group is on the alkene C_5 position. This results in the formation of a mixture of dibromide **35** and allylic bromide **36** (**Scheme 1.10**).[52,60,61]

Scheme 1.10



Similar observations have been noted for the reactions of alkenes **29a-c** with hypobromous acid in DMSO/water, where a 7:3 mixture of the unrearranged bromohydrin **37** and the substituted 2-azabicyclo[2.1.1]hexane ring system **38** was obtained (**Scheme 1.11**). As before, an unreactive R^1 substituent in alkenes **29b-c** hinders formation of the unrearranged bromohydrin **37b-c** and yields only the 2-azabicyclo[2.1.1]hexane system **38b-c**.[52,61,62]

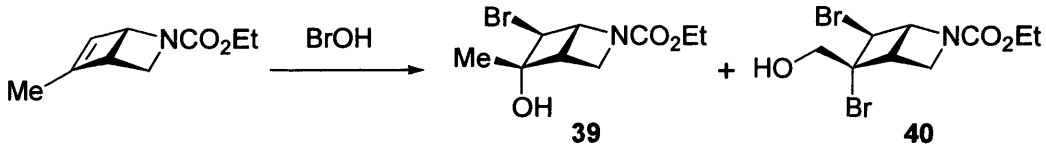
Scheme 1.11



29a $R^1 = R^2 = H$
29b R^1 = Me, $R^2 = H$
29c R^1 = Ph, $R^2 = H$
29d $R^1 = H$, R^2 = Me

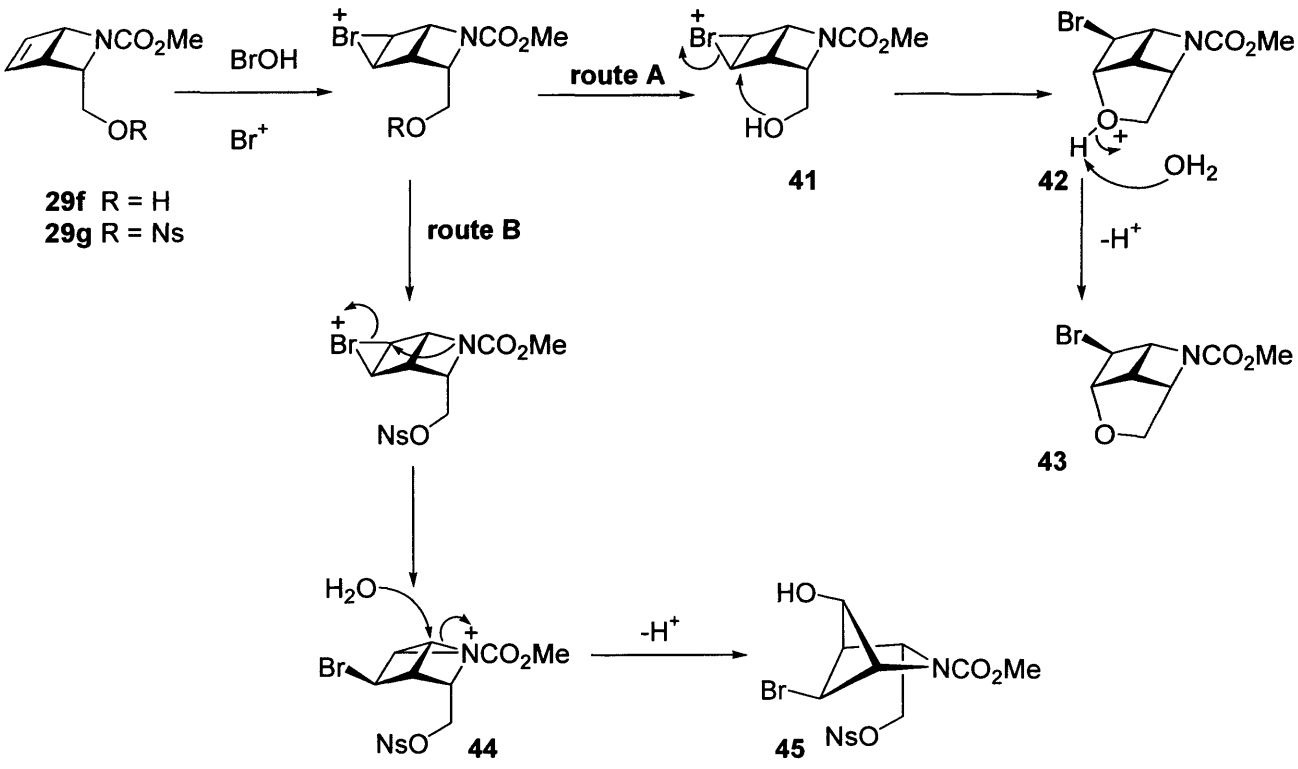
On this occasion, the presence of a cation-stabilising substituent on the alkene C_5 position blocks rearrangement to afford a mixture of bromohydrin **39** and dibromo-alcohol **40** (**Scheme 1.12**).[52,61,62]

Scheme 1.12



Krow and co-workers[52,63] have also used a rearrangement route to construct 2-azabicyclo[2.1.1]hexanes (**Scheme 1.13**). The nucleophilic oxygen of the 3-*endo*-hydroxy-methyl **29f** can attack the bromonium ion **41** to afford the oxonium ion **42**, deprotonation of this gives the tricycle **43** *via* route A. Neighbouring group participation by oxygen can be avoided by having a nosylate instead of an alcohol present (**29g**); this gives the aziridinium ion **44** (*via* route B) and hence the 2-azabicyclo[2.1.1]hexane **45**.[63]

Scheme 1.13

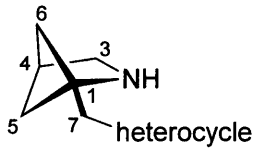


Further research elaborates the notion of rearrangement as a means of constructing 2-azabicyclo[2.1.1]hexanes[64,65,66] and has led to the synthesis of 2-azabicyclo[2.1.1]hexane systems with fluorine incorporated in the C_5 or C_6 positions.[67]

The research of Krow and co-workers[52] concentrates on the unusual mechanistic chemistry involved in the synthesis of the 2-azabicyclo[2.1.1]hexane system. Although there is no mention of the construction of heterocycles as nAChR ligands it is anticipated that these will be developed in the future, as these workers have employed various methods to incorporate functional groups at all positions of the 2-azabicyclo[2.1.1]hexane skeleton. At present, there is more emphasis on the synthesis of 2,4-methanoproline analogues, described in more detail in Chapter 7, Section 7.1.1.

1.7 Aims of the Research; Strategy for Target Compounds

Our methodology uses the 2-azabicyclo[2.1.1]hexane ring system in the synthesis of epibatidine analogues. It involves exploration of this relatively uncharted azabicyclic system that has not previously been used in the formation of epibatidine analogues. In the construction of such analogues, the rigid 2-azabicyclo[2.1.1]hexane ring system provides a framework for holding the structural requirements for activity at the nicotinic acetylcholine receptor in an appropriate orientation. With the heterocycle strategically at the C_1 position linked by a methylene carbon C_7, the ideal inter-nitrogen distance could be attained within the nicotinic acetylcholine pharmacophore. It also offers the chance to adjust this inter-nitrogen distance by extension of the chain and by incorporation of other atoms.



There have been no recent reports of functional group interconversion at C_7 position before our own research began.[68] The overall aim of the project is to synthesise nicotinic acetylcholine receptor active ligands from 2,4-methanoproline derivatives. This can be achieved by incorporating key functional groups at the C_7 position, in order to attach different heterocycles, this can be accomplished by manipulating protecting groups and extending the side-chain length will increase the range of compounds.

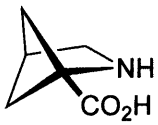
The inter-nitrogen distances of target compounds were estimated in their lowest energy conformation using molecular modelling studies. Inter-nitrogen distances were therefore calculated on the protonated analogues using Spartan Pro 1.05, which gave two minimum-energy conformations per molecule. The first in which the aromatic nitrogen was oriented close to the bridging nitrogen and the next where the carbon-aromatic bond was rotated by 180°.

Chapter 2

Synthesis of *N*-Benzyl Protected 2-Azabicyclo[2.1.1]hexane Systems

2.1 2,4-Methanoproline

At present in nature there is only one example of the 2-azabicyclo[2.1.1]hexane ring system, which is 2,4-methanoproline. It was isolated from the seeds of the Costa Rican tree *Ateleia herbert smithii* Pittier (Leguminosae) and provided much interest in synthetic approaches to 2-azabicyclo[2.1.1]hexanes.[54,55]



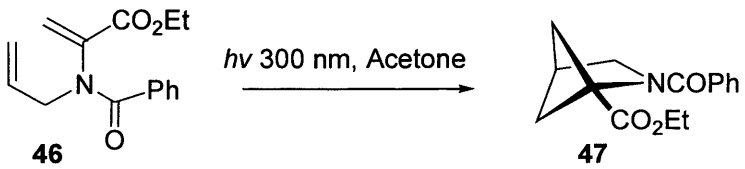
2,4-Methanoproline

2.1.1 Intramolecular [2+2] Cycloaddition

In 1980, the two independent groups of Pirrung[54] and Clardy[55] each published a total synthesis of 2,4-methanoproline. They used irradiation of cross-conjugated *N*-vinyl-*N*-allyl substrates to construct the bicyclic framework, which was then used to synthesise the amino acid.[54,55,69]

The route devised by Pirrung utilised an intramolecular [2+2] cycloaddition as the key step. This involves irradiation of **46** at 300 nm in acetone to form the azabicyclic structure **47** (**Scheme 2.1**). Hydrolysis in base gave 2,4-methanoproline in 72 % yield.[54]

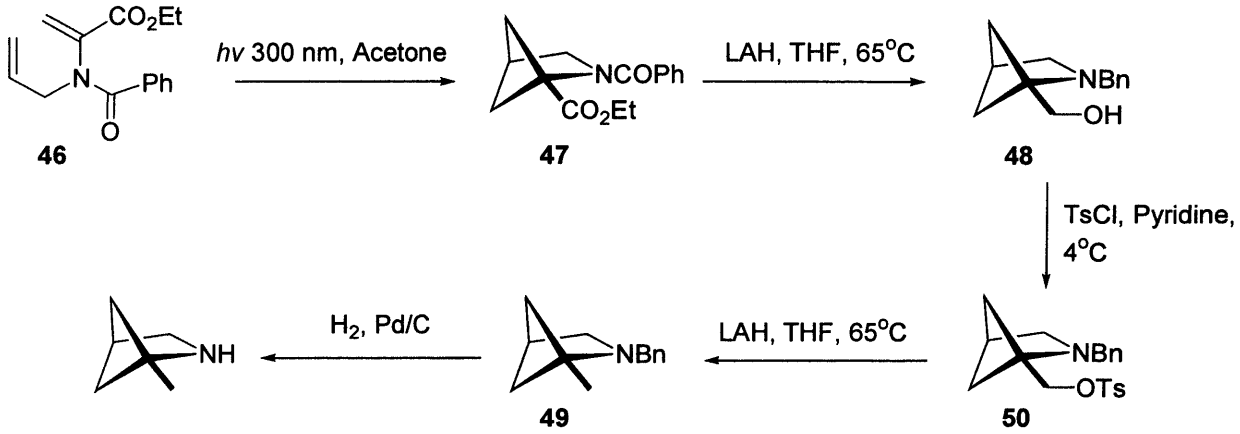
Scheme 2.1



46 **47**

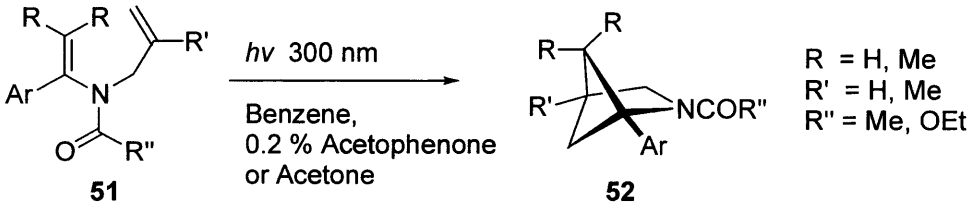
The photoadduct **47** has been modified to prepare other 1-substituted 2-azabicyclo[2.1.1]-hexanes. Malpass *et al.*[68,70] applied the route used by Pirrung to assemble the 2-azabicyclo-[2.1.1]hexane derivative **47**. Irradiation of **46** at 254 nm in benzene with 0.2 % acetophenone as a sensitizer, gave the product **47** in 54 % yield. A reductive route was used to convert **47** into the alcohol **48** and then to the 1-methyl structure **49** *via* tosylate **50** (X-ray crystal structure **Figure 2.1**) which was synthesised as part of studies of inversion at nitrogen (**Scheme 2.2**).[71]

Scheme 2.2



More recently, Piotrowski[72] has used the photochemical route from *N*-vinyl-*N*-allylamides **51** to synthesise a range of novel 1-aryl and 1-pyridyl-2-azabicyclo[2.1.1]hexanes **52** (**Scheme 2.3**). Cycloadditions were conducted in benzene using acetophenone as the initiator. By varying the ketone and allylamine starting materials, the substituent on the azabicyclic ring could be altered; so the heterocycle was directly attached to the C_1 position of the 2-aza-bicyclo[2.1.1]hexane system in all the examples studied.

Scheme 2.3



2.2 Target 2-Azabicyclo[2.1.1]hexane Compounds

Our two key synthetic target are **53** and **54**. Both structures have the 2-azabicyclo[2.1.1]-hexane skeleton with a heterocycle attached at the C_1 position by a methylene carbon C_7.

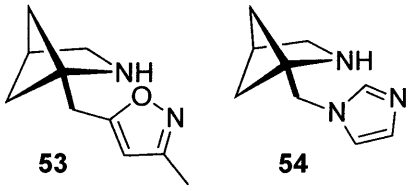
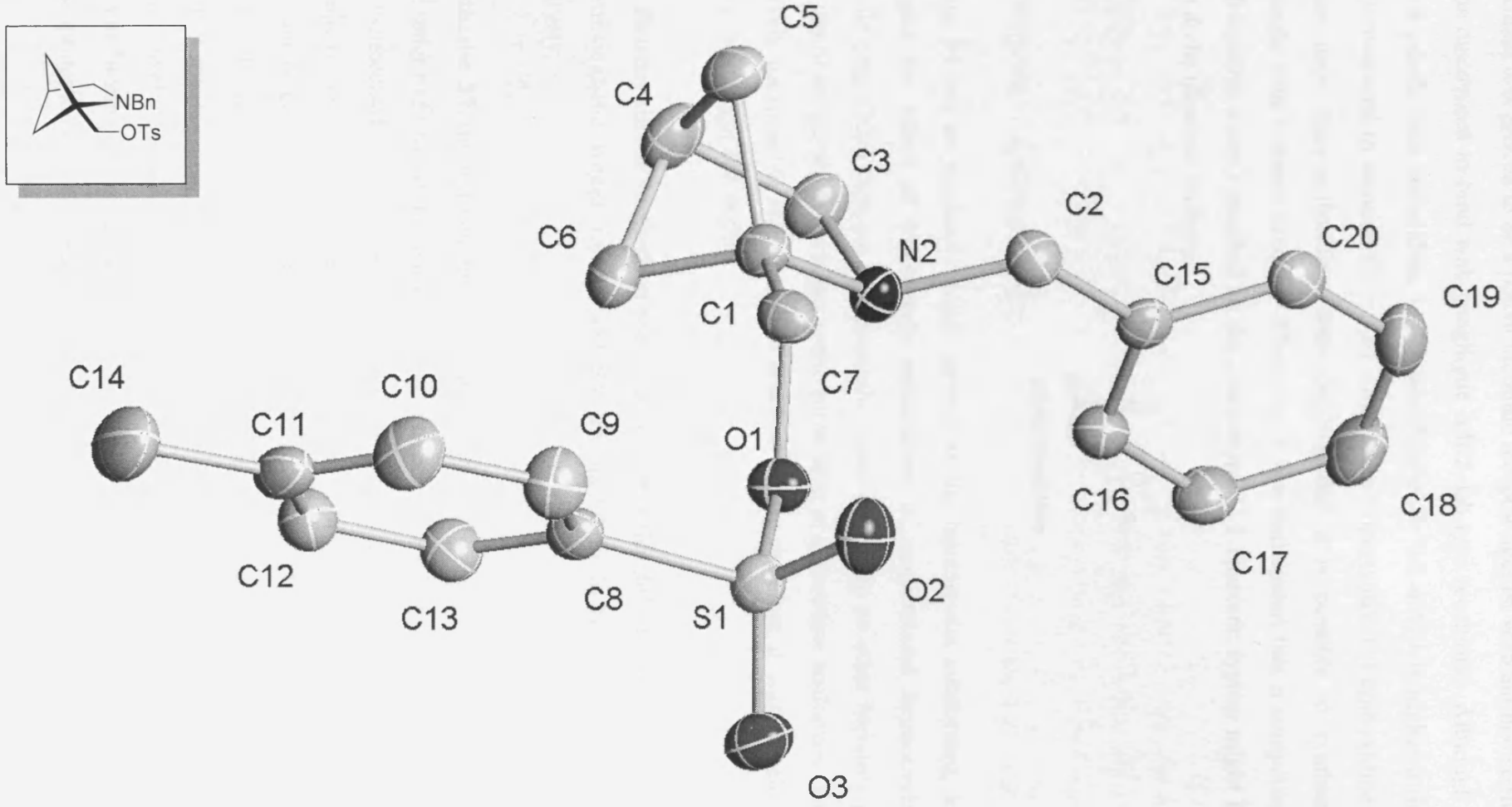
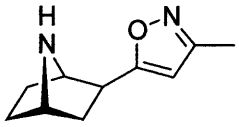


Figure 2.1 X-ray crystal structure of **50**



Structure **53** is an analogue of epiboxidine[73] having the methylisoxazole heterocycle. Epiboxidine was proved to be a potent nicotinic receptor agonist with antinociceptive activity and was discovered to bind with ganglionic α4β2 sub-type receptors. Although being ten-fold less potent than epibatidine, (±)-epiboxidine (K_i = 0.6 nM) has higher affinity to the nAChR compared to nicotine (K_i = 1.01 nM). More importantly, (±)-epiboxidine is twenty-fold less toxic than epibatidine, demonstrating that it is possible to synthesise potent compounds with lowered toxicity. Therefore it was anticipated that a compound with the methylisoxazole moiety attached on the 2-azabicyclo[2.1.1]hexane system might be a potent agonist at the nicotinic receptor.



(±)-Epiboxidine

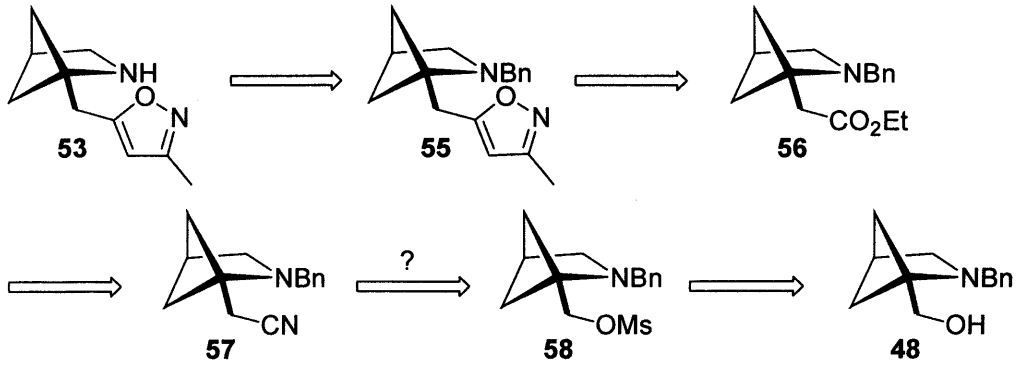
Structure **54** has an imidazole group present as the heterocyclic substituent, in order to investigate the effect of bioisosteric replacement of conventional heterocycles by the imidazole ring. Other than our own research,[68] there have been no other literature precedents for the use of imidazole as the heterocyclic substituent in epibatidine analogues. Imidazole is a relatively inexpensive reagent and is practical to use therefore it was the chosen model heterocycle to begin our studies.

2.2.1 Retrosynthetic Analysis of the Route to 2-Azabicyclo[2.1.1]hexane Compounds

The retrosynthetic routes for **53** and **54** are shown in **Scheme 2.4** and **Scheme 2.5** respectively.

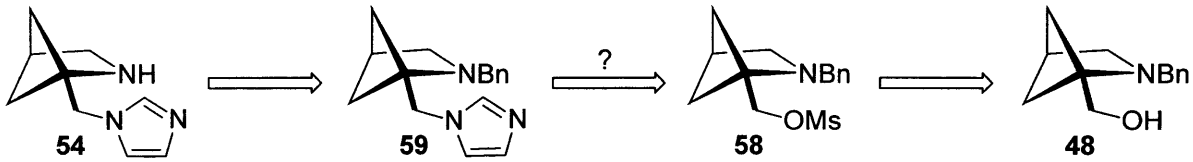
To synthesise **53**, the nitrogen must be protected (an *N*-benzyl protecting group is shown in **55**). In order to form the methylisoxazole ring in **55** an ester **56** is needed. The ethyl ester **56** can be synthesised from the nitrile **57** *via* the carboxylic acid and acid chloride. Compound **57** should be available by a nucleophilic substitution at C_7 from the mesylate **58**, which is synthesised from the alcohol **48** (**Scheme 2.4**).[71] Nucleophilic substitution at the carbon attached to C_1 has been demonstrated using hydride as nucleophile,[68,71] but investigations using other nucleophiles have not been reported. We did not expect to be able to achieve ready S_N2 displacement of a leaving group at the hindered ('pseudo-neopentyl') 1-methylene position in **58** using more sterically demanding nucleophiles, but felt that studies with a range of nucleophiles should be of interest.

Scheme 2.4



In the case of **54** the *N*-benzyl protecting group is the straightforward choice for exploratory work (**Scheme 2.5**). It was hoped that compound **59** could be formed from the mesylate **58** *via* a nucleophilic substitution at C_7 using the imidazolyl anion as a nucleophile. The compounds for subsequent steps are synthesised as stated before. In principle, the use of an *N*-benzyl protecting group is acceptable but the reductive removal of this group can be problematic, as selective debenzylation in the presence of a heterocycle is difficult. The use of alternative protecting groups will be discussed later (Section 2.9), but the *N*-benzyl system was used in initial investigations to establish whether the scheme was viable, in particular the key nucleophilic substitution at C_7.

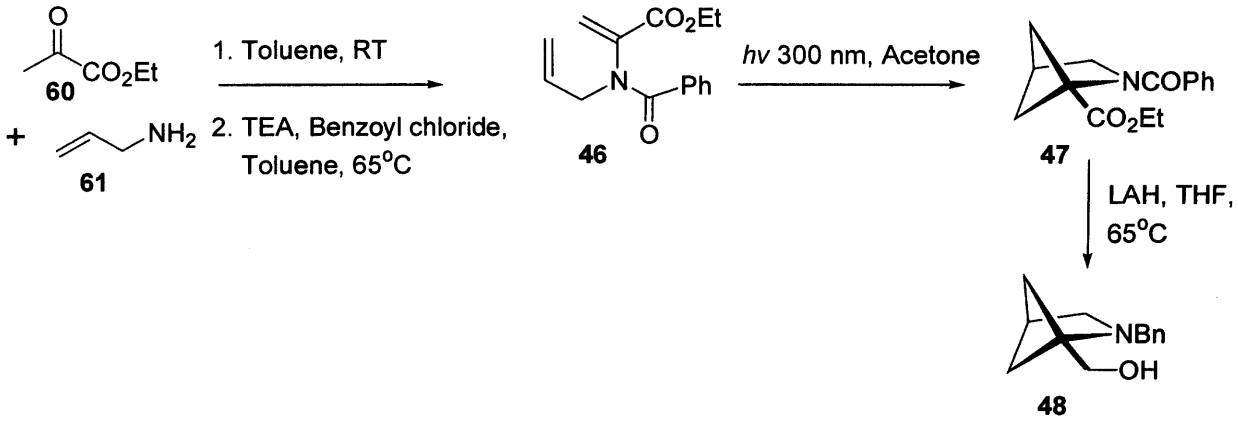
Scheme 2.5



2.3 Early Studies on 2-Azabicyclo[2.1.1]hexane Compounds

The condensation of ethyl pyruvate **60** and allylamine **61** formed the *N*-allyldehydroalanine ethyl ester, which was subsequently protected using benzoyl chloride to form *N*-benzoyl-*N*-allyldehydroalanine ethyl ester **46** in 37 % yield (**Scheme 2.6**). Irradiation of **46** at 254 nm in acetone gave the 2-azabicyclo[2.1.1]hexane product **47** in 38 % yield. An X-ray crystal structure of **47** confirmed the formation of the bicyclic system (**Figure 2.2**). The ester **47** was treated with lithium aluminium hydride to simultaneously reduce the *N*-protecting group to the benzyl and the bridgehead ester group to the primary alcohol and gave **48** in 96 % yield.

Scheme 2.6



2.4 Nucleophilic Substitution at the Bridgehead Methylene

The hydroxyl group was converted into a mesylate so that displacement by nucleophiles might be investigated. Initial studies showed that conversion to the mesylate **58** (88 % yield) was as practical as the formation of the tosylate **50** (86 % yield). The mesylate **58** was treated with potassium cyanide using 18-crown-6 in acetonitrile, a polar aprotic solvent. The nucleophilic substitution reaction gave the nitrile **57** successfully and in good yield (65 %) (**Scheme 2.7**). This shows us that substitution at the 1-methylene position is possible with a more sterically demanding nucleophile than hydride. All spectroscopic data obtained were in agreement suggesting the synthesis of **57**. This result gave us verve as it indicated that functional group interconversion was possible, opening up new avenues for our research. The mechanistic aspects of nucleophilic substitution at the C_7 position are of particular interest and are discussed in more detail in Chapter 4, Section 4.1.

Scheme 2.7

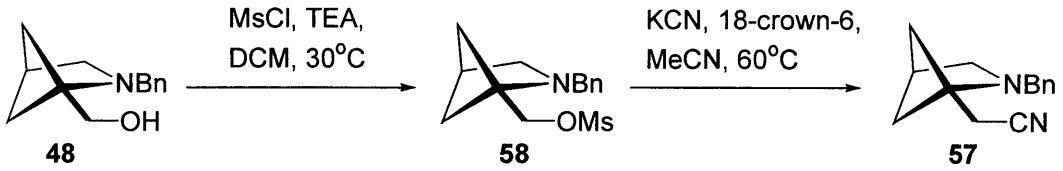
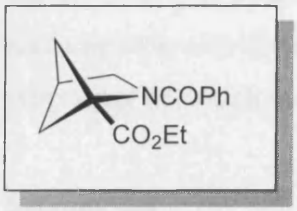
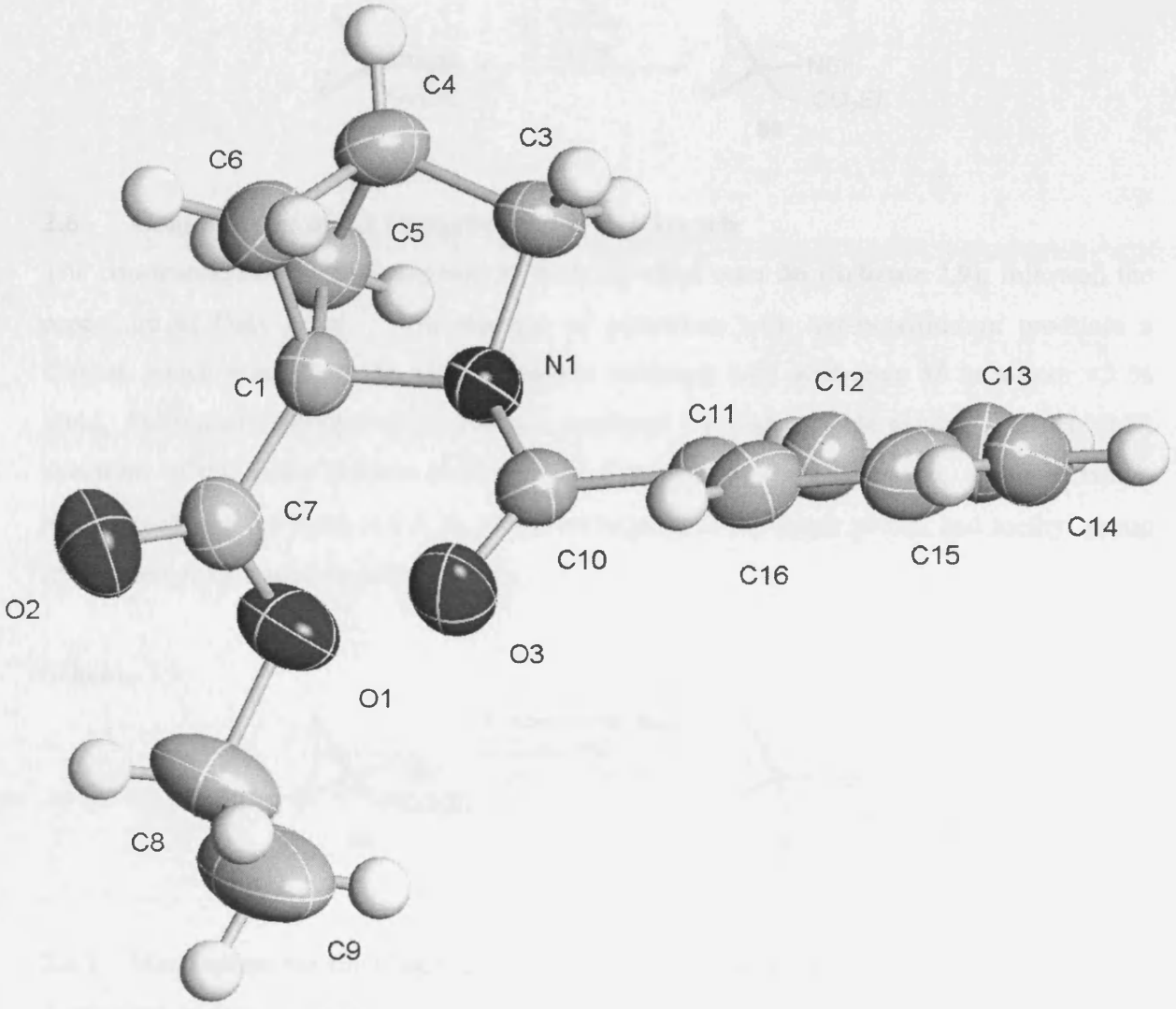


Figure 2.2 X-ray crystal structure of **47**

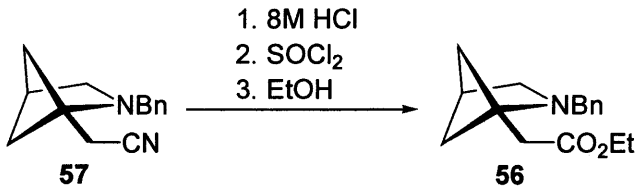




2.5 Synthesis of the Ethyl Ester 56

The ethyl ester **56** was constructed from the nitrile **57** (**Scheme 2.8**).[74] Hydrolysis of the nitrile **57** in 8M hydrochloric acid gave the carboxylic acid, which was converted into the acid chloride with thionyl chloride. Treatment of the acid chloride with ethanol produced the ethyl ester **56** which was obtained in an overall 35 % yield from **57**.

Scheme 2.8

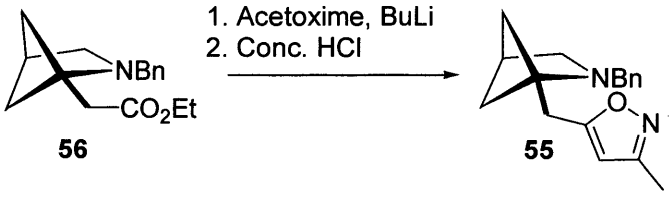


57 **56**

2.6 Construction of the Methylisoxazole Heterocycle

The construction of methylisoxazole **55** from the ethyl ester **56** (**Scheme 2.9**), followed the procedure of Daly *et al.*[73] The reaction of acetoxime with *tert*-butyllithium produces a dianion which reacts with **56** and subsequent treatment with acid gave **55** in a poor <5 % yield. Subsequent attempts at this reaction produced low and variable results. The ^{1}H NMR spectrum of the crude product indicated the formation of the heterocycle, as there was a singlet peak at δ 5.95 and at δ 2.26, which correspond to the single proton and methyl group of the methylisoxazole ring respectively.

Scheme 2.9



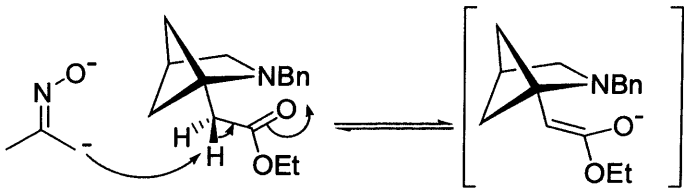
56 **55**

2.6.1 Mechanism for the Construction of the Methylisoxazole Heterocycle

Acetoxime is deprotonated using *tert*-butyllithium to form the reactive dianion intermediate, which attacks the carbonyl carbon of the ethyl ester **56**. Subsequent addition of concentrated hydrochloric acid and loss of water allows cyclisation to produce the methylisoxazole heterocycle **55**. The mechanism of methylisoxazole formation is shown and discussed in more detail in Chapter 6, Section 6.4.2.

An explanation for the low yield was sought. It may be that the protons α-to the carbonyl on the C_7 carbon are being removed to form the enolate **62**, which prevents and competes with ring formation (**Scheme 2.10**). This would explain the low conversion into **55**.

Scheme 2.10

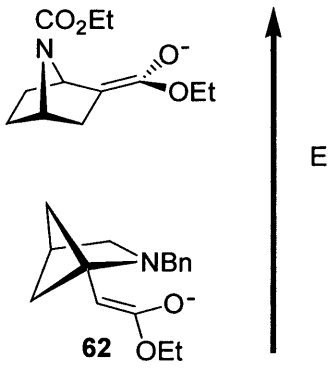


56 **62**

During the course of our work, Avenoza and co-workers[75] constructed the isoxazole ring directly at the C_1 position on the 7-azabicyclo[2.2.1]heptane skeleton but they did not have the problem of protons α-to the carbonyl being removed. They have used three different experimental procedures, varying the ratios of reagents, but reported low yields in all cases.

Daly *et al.*[73] have produced the isoxazole ring at the C_2 position of the 7-azabicyclo[2.2.1]-heptane system, where there is a single proton α-to the carbonyl present. There may be a competition between the two pathways in this case. The formation of the heterocycle is preferred in the Daly work giving epiboxidine in 47 % yield (conducted on a milligram scale). If an enolate formed in this case it would be a high energy intermediate due to angle strain on the C_2 position, so is less likely to exist (**Figure 2.3**). Presumably, this tips the balance in favour of the desired product and perhaps suggests that Daly was fortunate to obtain a 47 % yield. Methylisoxazole formation rarely gives yields greater than 50 %.[73]

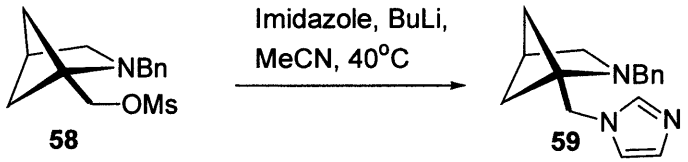
Figure 2.3 Enolate intermediates



2.7 Nucleophilic Substitution using Imidazole

Imidazole can be deprotonated using *tert*-butyllithium to form the reactive imidazolyl anion. Nucleophilic substitution of the mesylate **58** at C_7 produced the heterocyclic product **59** in 35 % yield (**Scheme 2.11**). A similar reaction using dry triethylamine instead of *tert*-butyllithium (as base) gave **59** in 29 % yield. The successful substitution reactions at the C_7 position was gratifying in view of our initial doubts concerning the level of reactivity at this position and demonstrated that the direct displacement approach was also productive using a nitrogen nucleophile. This result indicated that nucleophilic substitution is possible with different nucleophiles at this sterically hindered position. This unusual nature of the 2-aza-bicyclo[2.1.1]hexane system can allow us to construct analogue compounds.

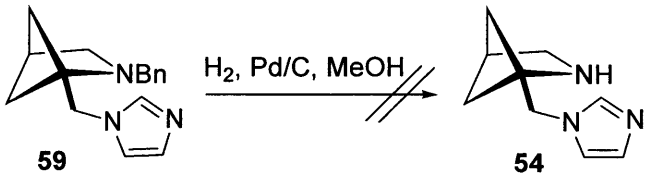
Scheme 2.11



2.8 Attempted Deprotection of the *N*-Benzyl Protecting Group

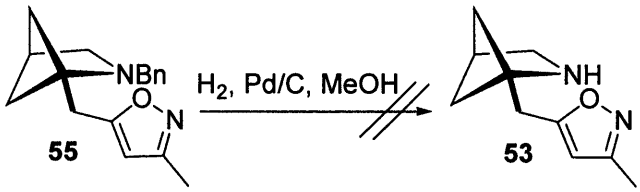
The removal of the *N*-benzyl group from the heterocyclic product **59** to form **54** was attempted by hydrogenolysis using hydrogen in the presence of a palladium on carbon catalyst (**Scheme 2.12**). This proved to be unsuccessful and a mixture of uncharacterised products was obtained. Selective removal of the benzyl group is difficult, presumably the heterocycle is also reduced under these conditions.

Scheme 2.12



Catalytic hydrogenation of the methylisoxazole derivative **55** to produce the target **53** was also unsuccessful (**Scheme 2.13**). Daly and co-workers[76] mention cleavage of the methylisoxazole heterocycle, whilst performing similar debenzylation reactions.

Scheme 2.13



As the final debenzylation proved to be problematic, a solution was to introduce an alternative protecting group earlier in the synthesis allowing the use of more gentle conditions for its final removal. The successful demonstration of heterocycle formation in the model systems **55** and **59** justified the widening of the scope of this investigation.

2.9 Variation of the *N*-Protecting Group

It was anticipated at an early stage that alternative *N*-protecting groups might be required so this was investigated simultaneously with the exploratory work based on the *N*-benzyl protecting group. Groups such as *N*-benzyloxycarbonyl (or other alkoxycarbonyl groups) are more appropriate and have been successfully used in other azabicyclic frameworks. Removal of *N*-benzyloxycarbonyl can be done using TMSI and hydrofluoroboric acid-diethyl ether complex under nitrogen.[77] Such groups could, in principle, be introduced before the photolysis (at an initial stage) or by an exchange process of deprotection and reprotection, after construction of the azabicyclic skeleton.

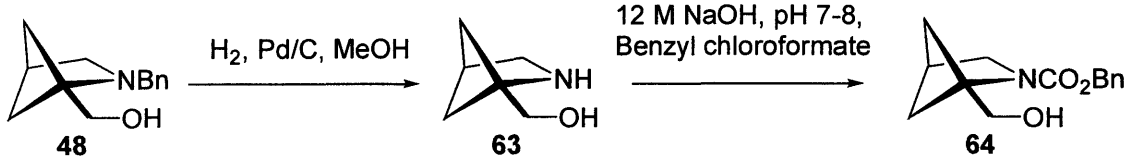
If an alternative protecting group could be introduced at the start of the synthesis then this would eliminate the need to deprotect the benzyl group and then reprotect later on. Piotrowski[72] illustrates the use of other protecting groups on nitrogen and by changing the ketone and allylamine starting materials, the substituent on the azabicyclic ring was varied. A method similar to that of Piotrowski was investigated as part of an undergraduate project at Leicester, but this was found to be unsuccessful.[78] Whilst the work of Piotrowski looked promising, it was decided to introduce the alternative protecting group after the successful intramolecular [2+2] photocycloaddition.

2.9.1 Alteration of *N*-Protection Group

N-Deprotection of the key alcohol **48** was attempted. The results from early work in deprotecting the benzyl group using ammonium formate[79] and the direct conversion using palladium hydroxide with *N-tert*-butoxycarbonylanhydride[80] were disappointing, giving a mixture of uncharacterised products.

Removal of the *N*-benzyl group using hydrogen and palladium on carbon produced the secondary amino-alcohol **63** in 100 % yield. The absence of aromatic protons in the ^{1}H NMR spectrum of the product confirmed the formation of **63**. A subsequent attempt to re-protect the nitrogen using sodium hydrogen carbonate and benzyl chloroformate did not succeed. Another method for re-protection of the amine **63** used 12M sodium hydroxide and benzyl chloroformate.[77,81] This gave the required benzyloxycarbonyl-protected nitrogen product **64** in a 45 % overall yield from **48** (**Scheme 2.14**).

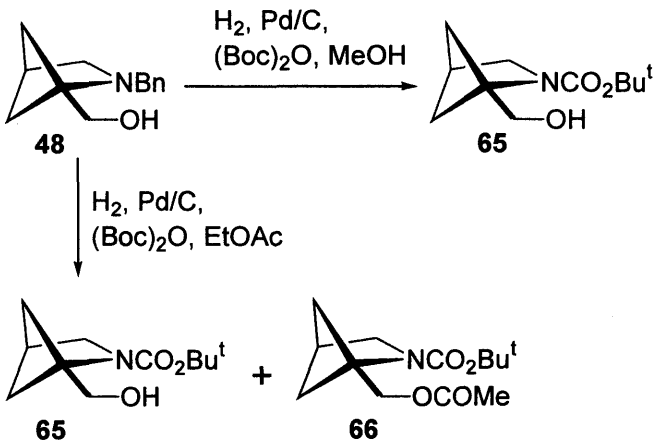
Scheme 2.14



The ^{1}H NMR spectrum of the alcohol product **64** includes a doublet at δ 3.95 with a coupling of 7 Hz; this signal corresponds to the two equivalent H_7 protons coupling with the proton from the hydroxyl group. This doublet signal collapsed to a singlet when the ^{1}H NMR spectrum was measured in D_2O. This is evidence that the protecting group is on the nitrogen and not on the oxygen of the hydroxyl group.

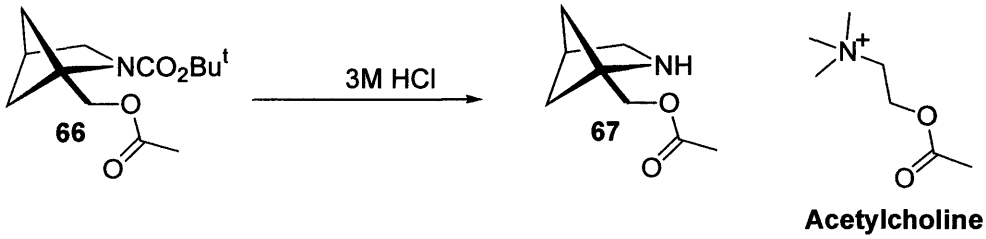
The overall conversion of **48** into the *N*-Boc protected compound **65** (in a 60 % overall yield) was also achieved, by means of a one-pot reaction using hydrogen and palladium on carbon with *N-tert*-butoxycarbonylanhydride in dry methanol.[82] The ^{1}H NMR spectrum for **65** also showed a doublet for the H_7 protons coupling with the proton from the hydroxyl group with a *J*-value of 7 Hz, at δ 3.86. Again the doublet collapsed to a singlet in D_2O. Incidentally when the reaction was conducted in dry ethyl acetate a mixture of **65** (30 % yield) and **66** (23 % yield) was obtained, as a result of transesterification involving the solvent (**Scheme 2.15**).

Scheme 2.15



The synthesis of the by-product **66** could be advantageous as it could be used to synthesise an acetylcholine analogue **67**, which could potentially mimic its activity (**Scheme 2.16**).

Scheme 2.16



In conclusion, the basic methodology of our approach has been established on the 2-aza-bicyclo[2.1.1]hexane ring system. We have demonstrated that nucleophilic substitution is possible on such a sterically hindered neopentyl position. The successful protection of the azabicyclic nitrogen with alkoxycarbonyl groups was expected to allow easier *N*-deprotection after incorporation of the heterocyclic substituent. This has enabled us to perform functional group interconversion reactions in order to construct heterocycles. It remained to demonstrate that nucleophilic substitution could be achieved efficiently in the *N*-alkoxy carbonyl series.

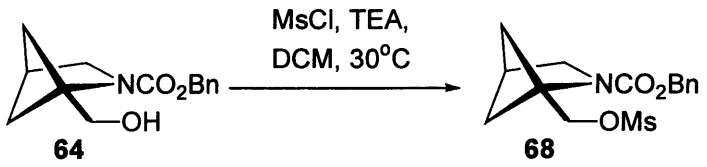
Chapter 3

Synthesis of *N*-Benzyloxycarbonyl Protected 2-Azabicyclo[2.1.1]hexane Systems

3.1 Nucleophilic Substitution at the 1-Methylene Position

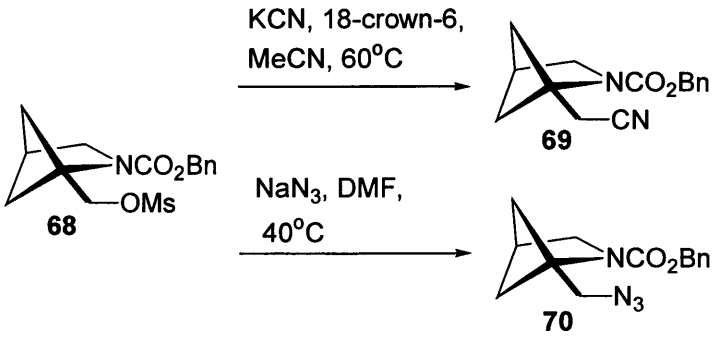
The key substitution reactions in the *N*-benzyl series were repeated for the *N*-benzyloxycarbonyl series. The primary alcohol **64** was converted into the mesylate **68** in 81 % yield shown in **Scheme 3.1**.

Scheme 3.1



The mesylate **68** was also reacted with potassium cyanide yielding the nitrile **69** in 78 % yield. Treatment of **68** with sodium azide produced the azide **70** in 85 % yield (**Scheme 3.2**). These reactions show that nucleophilic substitution is possible on the *N*-benzyloxycarbonyl series as well as the *N*-benzyl series.

Scheme 3.2

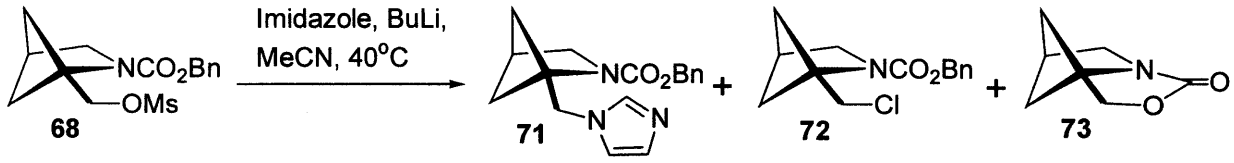


The substitution with cyanide ion to give the *N*-benzyloxycarbonyl nitrile **69** (78 % yield) was improved compared with the formation of the *N*-benzyl nitrile **57** (65 % yield). The general trend of yields for the nucleophilic substitution reactions in the *N*-benzyloxycarbonyl series is higher than for *N*-benzyl, which was a rewarding result.

3.2 Nucleophilic Substitution using Imidazole

Nucleophilic substitution of the mesylate **68** was conducted as before. The heterocyclic product **71** was obtained in 43 % yield (compared with 35 % yield for the same reaction in the *N*-benzyl series). This reaction also produced two side-products **72** and **73**. The chloro-compound **72** was formed because of methanesulfonyl chloride being present in the starting material (**Scheme 3.3**). A similar reaction using dry triethylamine instead of *tert*-butyllithium gave **71** in 36 % yield, but without any formation of **72**.

Scheme 3.3



3.2.1 Synthesis of the Cyclic Carbamate By-product 73

More intriguingly, the nucleophilic substitution using imidazole (**Scheme 3.3**) produced a compound, which was shown by ^{1}H NMR spectroscopy to have lost the *N*-protecting group and mass spectroscopy indicated a molecular weight of 140 g/mol [MH^{+}]. However a carbonyl group was observed in the ^{13}C NMR spectrum. This compound was deduced to be the unusual highly strained, but stable cyclic carbamate **73**. The structure was confirmed by X-ray crystallography (**Figure 3.1**). The cyclic carbamate **73** is formed by neighbouring group participation of the benzyloxycarbonyl oxygen with loss of the benzyl group. The synthesis and reactivity of the cyclic carbamate **73** are discussed in more detail in Chapter 4, Section 4.3.

3.2.2 Final Removal of the *N*-Benzyloxycarbonyl Protecting Group

The *N*-benzyloxycarbonyl protecting group was removed from **71** using TMSI to produce the target **54** in 87 % yield (**Scheme 3.4**). The ^{1}H NMR spectrum shows evidence for all the characteristic signals of the 2-azabicyclo[2.1.1]hexane system; doublet of doublets for H_{5s}, H_{6s}, multiplet for H_{5a}, H_{6a}, multiplet for H_4, singlet for H_{3x}, H_{3n} and singlet for H_7 all at distinctive chemical shifts. It also shows a singlet for each of the imidazole proton signals.

Scheme 3.4

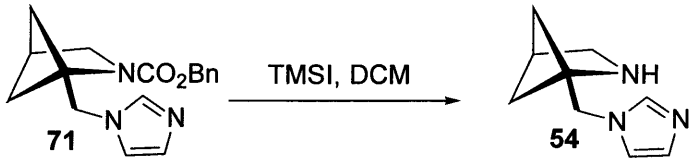
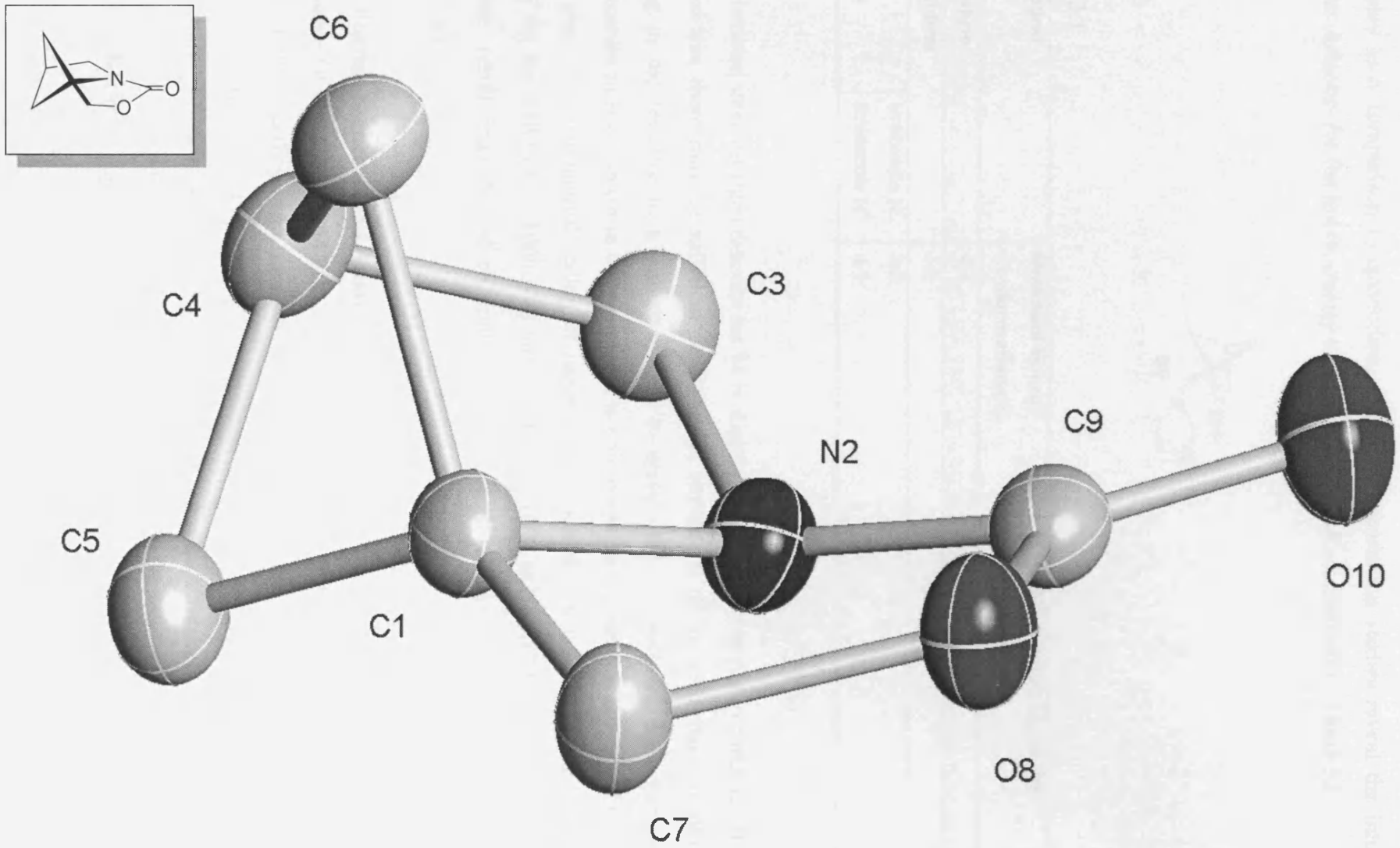
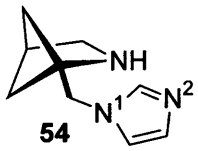


Figure 3.1 X-ray crystal structure of **73**



3.3 Calculation of Inter-nitrogen Distances

As described in Chapter 1, Section 7.1 the inter-nitrogen distances of target compounds are calculated as a comparison to epibatidine. Molecular modelling studies reveal the inter-nitrogen distances for the lowest-energy conformations of **54** summarised in **Table 3.1**.



54

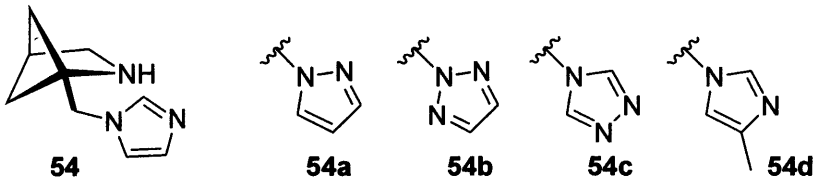
Table 3.1

Compound		Minimum Energy Conformation (Å)	180° rotation (Å) of the heterocycle
Epibatidine		4.3	5.5
Epiboxidine		4.2	5.2
54	Imidazole N^1	3.0	3.0
	Imidazole N^2	4.1	4.3

The calculated inter-nitrogen distance for **54** is slightly smaller than that for epibatidine. It is assumed that there may be sufficient flexibility of movement of the side-chain to allow docking in the receptor in a similar manner to epibatidine. Clearly the lowest-energy conformation in solution (or in the gas phase) is unlikely to be the same as that when in the active site. Pharmacological testing of racemic **54** indicated that it had a weak binding affinity for the $\alpha4\beta2$ (K_i = 1000 nM) and $\alpha3\beta4$ (K_i = 1000 nM) nAChR sub-types. This important result indicates which route to pursue next to synthesise more analogue compounds.

3.3.1 Further Structural Variations; Future Work

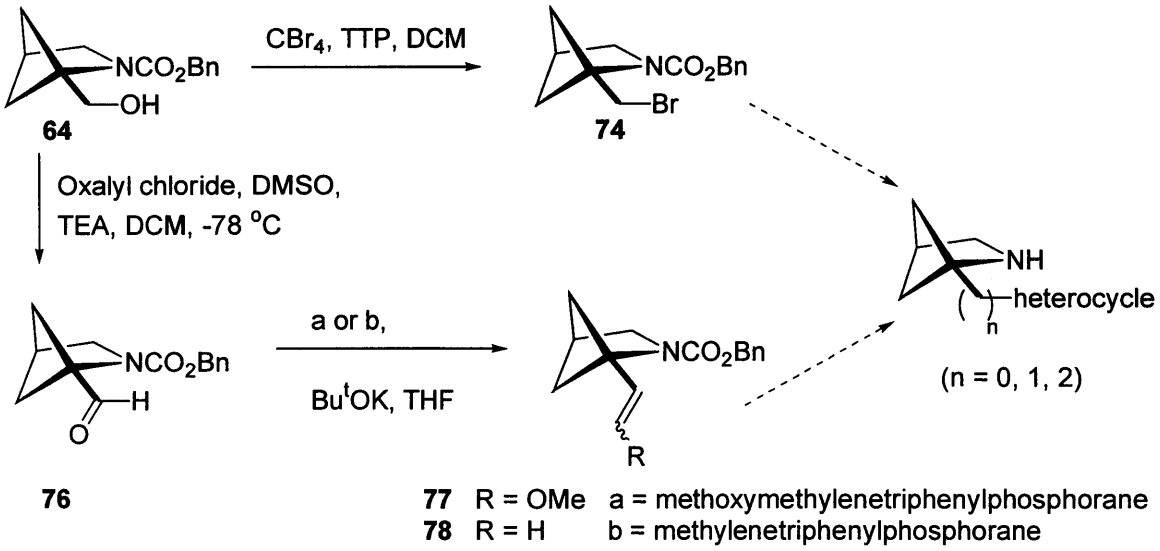
The successful synthesis of **54** demonstrates that nucleophilic displacement of a mesylate attached to the C_7 carbon in **68** is possible using an intact heterocycle. A range of imidazole-based compounds **54a-d** could be synthesised, in principle, by the same general methodology. All the new imidazole variants are attached at the C_7 carbon by the nitrogen of the heterocycle. Substitution using different nucleophiles could generate a library of novel compounds **54a-d** analogous to the original imidazole **54**.



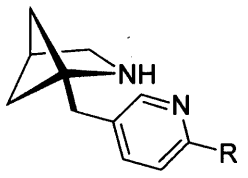
3.4 Attachment of a Wider Range of Functional Groups

There is potential for synthesis of a wider range of derivatives on the 2-azabicyclo-[2.1.1]hexane ring system as shown in **Scheme 3.5**.

Scheme 3.5

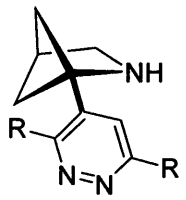


The bromo derivative **74** was obtained in 80 % yield using carbon tetrabromide and TPP, starting from the alcohol **64**. Thionyl bromide was also used to convert the alcohol **64** into the bromo derivative **74** but this gave less pure material. Coupling reactions of the bromo **74** may be possible to form novel pyridyl derivatives, which, also have one carbon atom in the bridge between the heterocycle and bicyclic system.



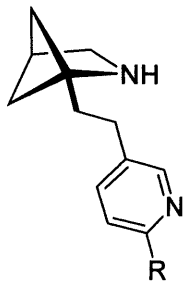
75a R = H
75b R = Cl

n = 1



79a R = H
79b R = Me

n = 0

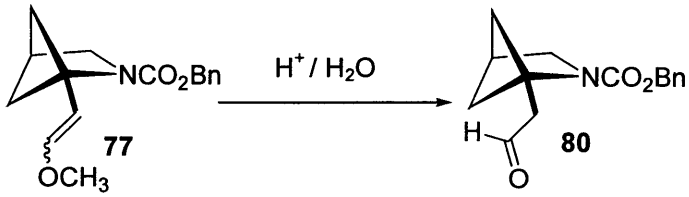


81a R = H
81b R = Cl

n = 2

Suzuki cross-coupling[83] could be used to construct potential targets **75a** and **75b** from the bromide **74**. Swern oxidation of **64** provided the aldehyde **76** which was converted into the mixture of vinyl ethers **77** or the alkene **78** using established Wittig methodology.[84] The vinyl ethers **77** are precursors of systems containing pendant heterocycles including diazines[84] and would allow formation of products having a heterocycle attached directly to the bridgehead position **79a** and **79b**. The crude vinyl ethers **77** needed no further purification. Evidence for the isolation of **77** was shown in the ^{1}H NMR by the presence of olefinic peaks of both *cis* and *trans* isomers (duplicated because of slow N-CO rotation). Flash chromatographic methods introduced acid and water, hence converted the vinyl ethers **77** to the aldehyde **80** (**Scheme 3.6**).

Scheme 3.6



Reductive Heck chemistry[38] could be used to convert the alkene **78** into longer-chain pyridyl derivatives, where there are two carbon atoms in the bridge between the heterocycle and bicyclic system. Potential target compounds are **81a** and **81b**.

3.4.1 Calculation of Inter-nitrogen Distances of Potential Compounds

The calculated inter-nitrogen distances for the lowest-energy conformations of the potential target compounds are shown in **Table 3.2**.

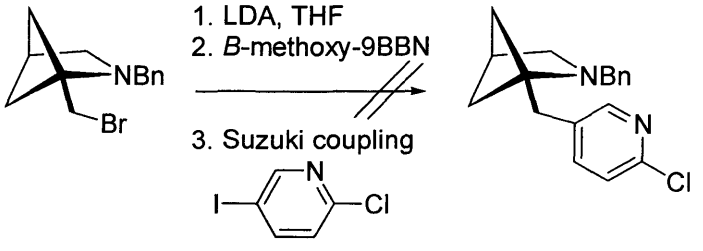
Table 3.2

Compound		Minimum Energy Conformation (Å)	180° rotation (Å) of the heterocycle
Epibatidine		4.3	5.5
75a n = 1		4.3	4.6
75b n = 1		4.3	4.7
81a n = 2		6.3	6.8
81b n = 2		6.4	6.8
79a n = 0	N^1	4.6	4.6
	N^2	5.1	5.1
79b n = 0	N^1	4.6	4.6
	N^2	5.1	5.0

3.4.2 Attempt at Suzuki Cross-coupling Reactions

The Suzuki cross-coupling reaction[85] was published in the late 1970s and has been used since in a variety of applications. It involves the palladium-catalysed coupling of a halide with an organoboron compound. This method was used in attempts to incorporate pyridyl heterocycles at the C_7 position of the 2-azabicyclo[2.1.1]hexane system (**Scheme 3.7**).

Scheme 3.7



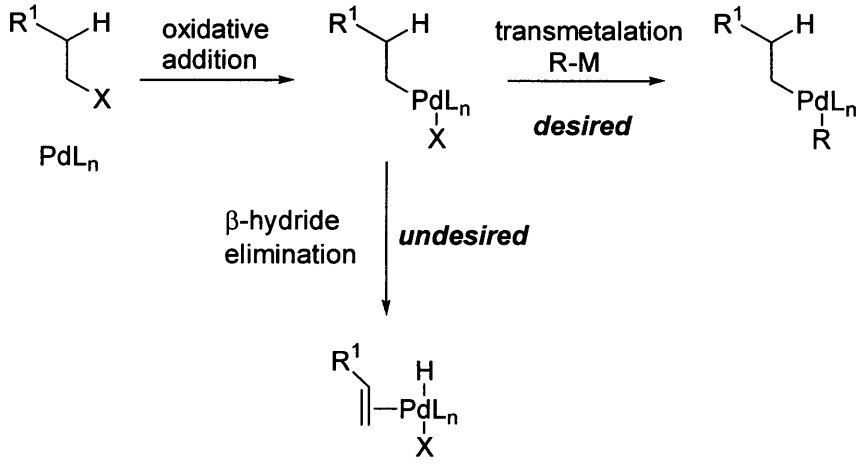
The Suzuki coupling approach has been attempted before on the 2-azabicyclo[2.1.1]hexane ring system but with the *N*-benzyl protecting group present.[77] The Suzuki coupling was attempted using the *B*-methoxy-9BBN boron reagent but proved to be unsuccessful. It was thought that the reaction failed due to the steric bulk of the two fragments. The bicyclic component may be loaded onto the catalyst but the correct alignment for bond formation may not have occurred. This method could be improved if a less bulky boron reagent can be used for the coupling.

The majority of studies of metal-catalysed cross-coupling reactions have employed a halide as the electrophile and an organometallic reagent as the nucleophile in which the carbon atoms to be coupled are all sp^2 hybridised.[86,87]

Using recently developed methods, palladium-catalysed coupling of sp^3 alkyl halides is possible overcoming the problems of slow oxidative addition of the alkyl halide to palladium and β-hydride elimination of the resulting alkyl-palladium complex (**Scheme 3.8**).[88,89]

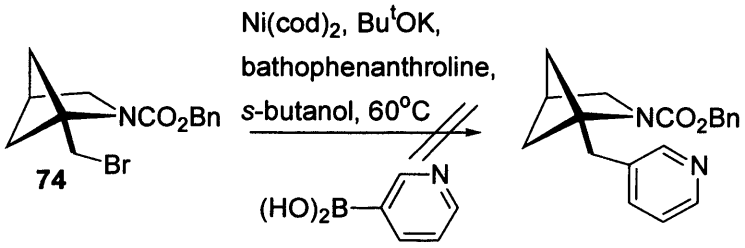
Contemporary work has demonstrated successful cross-coupling reactions of unactivated secondary alkyl bromides, using modified Suzuki methodology.[83,90,91] For optimum conditions a nickel catalyst[92] is employed for these couplings, where yields of up to 90 % have been reported. Although this method of Suzuki coupling is for secondary bromides, this approach was applied to the primary bromide **74** due to the success of coupling reactions of another azabicyclic system in the Malpass group.[93]

Scheme 3.8



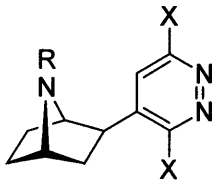
Unfortunately, the Suzuki cross-coupling[83] on the bromide **74** (in order to synthesise the targets **75a** and **75b**) was unsuccessful (**Scheme 3.9**). There was no evidence by ^1H NMR spectroscopy of the expected product. Again, it is assumed that steric factors restrict the coupling at this hindered position. The Suzuki method employed was designed for secondary alkyl bromides and not for primary. Suzuki couplings involving primary alkylborons[94] at a hindered position have not been studied to a great extent, therefore it is difficult to adopt a procedure for our unique azabicyclic system. For future work, a methodology for bromide coupling at the hindered primary position is required to attach a heterocycle. This would involve a more thorough review of the literature.

Scheme 3.9



3.4.3 Attempted Formation of Diazine Derivatives

Epibatidine analogues have been constructed that have pyridazine ring present **82a-c**.[84] The most active compound was found to be **82a**, which had an inter-nitrogen distance similar to that of epibatidine.



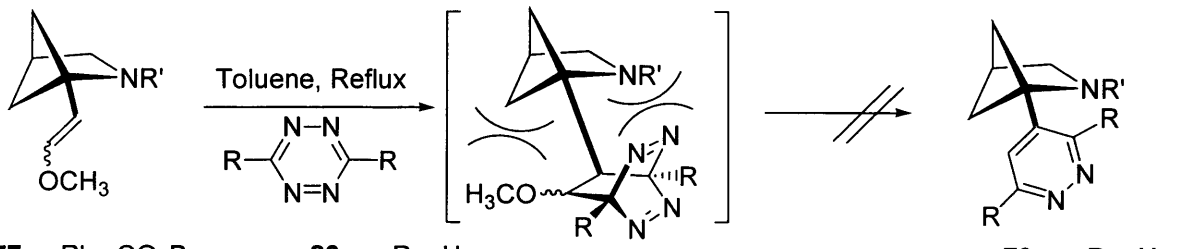
82

82a	R = H	X = H
82b	R = H	X = CF_3
82c	R = Me	X = H

This compound was found to be less potent than epibatidine but a highly effective agonist on neuronal and muscle nAChRs, particularly on the α4β2 sub-type. Both **82a** and its *N*-methyl derivative **82c** could differentiate between the α4β2 and α3β4 nAChR sub-types. As a result, this made the 2-azabicyclo[2.1.1]hexane diazine compounds **79a-b** attractive targets.

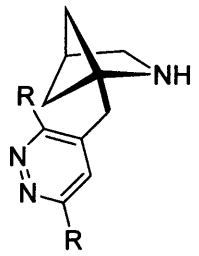
We investigated the Diels-Alder cycloaddition of the electron-rich dienophilic vinyl ether **77** with the electron-deficient diazadiene systems of the 1,2,4,5-tetrazines **83a** and **83b**.[95,96,97] The mechanism is an inverse [4+2] cycloaddition involving the LUMO of the diene and the HOMO of the dienophile followed by elimination of nitrogen and methanol (**Scheme 3.10**).[84,98,99]

Scheme 3.10



77	R' = CO_2Bn	**83a**	R = H	**79a**	R = H
84	R' = CO_2Bu^t	**83b**	R = Me	**79b**	R = Me

Unfortunately, the desired compound was not attained. It is believed that the required compounds **79a-b** could not be synthesised due to the large steric bulk of the bicyclic intermediate at the bridgehead position, making the cycloadduct too hindered for a Diels-Alder reaction to occur. This reaction was also repeated for the *N*-Boc protected vinyl ether **84** but again without success.



85a R = H
85b R = Me

A possible solution to this problem was to extend the chain length by an extra carbon atom. It was envisaged that this would avoid the steric congestion at the bridgehead position in the Diels-Alder step and that it would be possible to synthesise the new targets **85a** and **85b**.

Molecular modelling studies revealing the inter-nitrogen distances for the lowest-energy conformations of **85a** and **85b** are shown in **Table 3.3**.

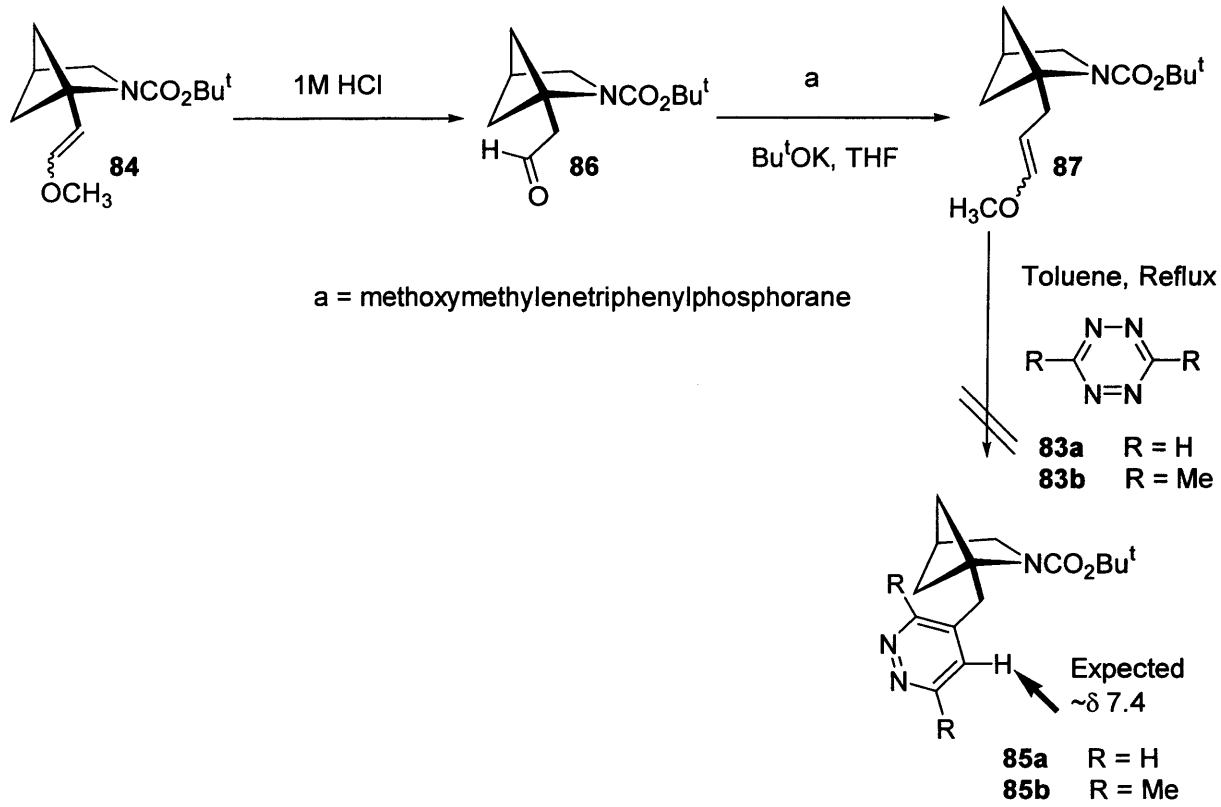
Table 3.3

Compound		**Minimum Energy Conformation (Å)**	**180° rotation (Å) of the heterocycle**
85a	N^1	4.3	4.6
(n = 1)	N^2	4.9	4.9
85b	N^1	4.4	4.7
(n = 1)	N^2	4.9	4.9

Like their parent compounds **79a** and **79b**, both **85a** and **85b** have similar values for both rotamers.

The vinyl ether **84** was converted into the extended aldehyde **86** and the extended vinyl ether **87** was synthesised using the Wittig methodology stated before. Evidence for the successful conversion was provided in the ^{1}H NMR spectrum of **87** by the presence of olefinic peaks of both *cis* and *trans* isomers (duplicated because of slow N-CO rotation). Reaction of **87** with the 1,2,4,5-tetrazines **83a** and **83b** again proved unsuccessful and the desired compounds were not obtained (**Scheme 3.11**). There was no evidence in the ^{1}H NMR spectra for starting material and the absence of an aromatic proton signal (at δ 7.4),[84] showing the product had not formed.

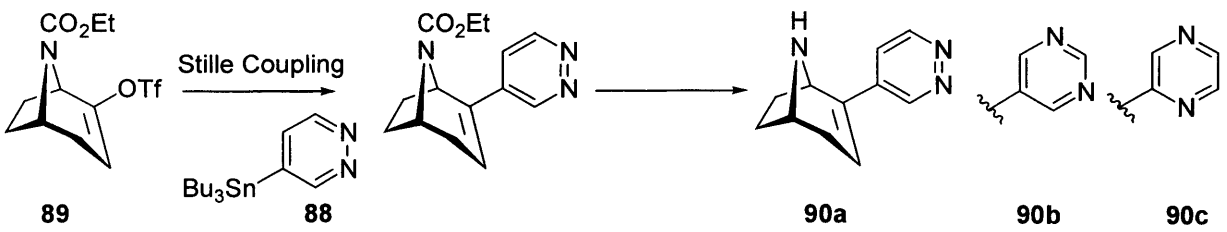
Scheme 3.11



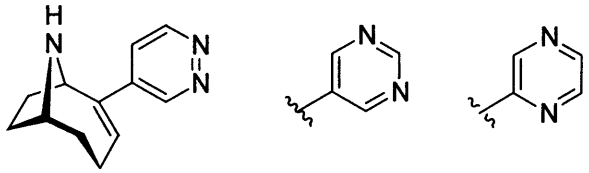
Recent research has explored the use of microwave chemistry on Diels-Alder reactions.[100] The methodology of microwave chemistry could be used to synthesise the diazine heterocycle on 2-azabicyclo[2.1.1]hexane systems. Reactions are normally performed in high-boiling solvents and have the advantage of a shorter reaction time.

Alternative methods for the attachment of diazines have been attempted successfully.[101,102,103] Seitz and co-workers employ a Stille cross-coupling of the corresponding tributylstannyl diazine **88** with the vinyl triflate **89**. Using this method a range of diazine analogues **90a-c** have been synthesised, where **90b** was found to be the most active compound (K_i = 3.7 nM) at α4β2 sub-types (**Scheme 3.12**).

Scheme 3.12



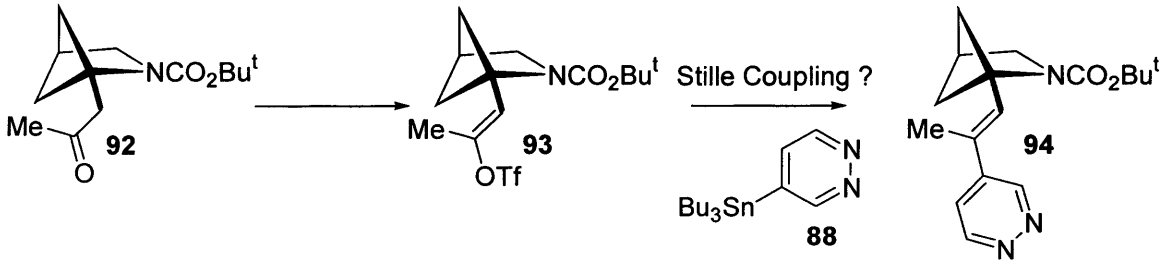
The Stille cross-coupling method has also been used for the synthesis of UB-165 analogues **91a-c**.[104] In this range of compounds **91b** was found to be the most active diazine analogue (K_i = 0.14 nM) at the α4β2 sub-type. Molecular modelling studies have been attempted on the entire library of analogues reported by Seitz and co-workers[33,105,106,107] in attempts to design novel ligands.



91a **91b** **91c**

It may be possible to replicate this type of chemistry on the 2-azabicyclo[2.1.1]hexane system but, we would need to synthesise a methyl ketone **92** to form a vinyl triflate **93** and hence allow potential Stille-cross coupling (**Scheme 3.13**). On the other hand, it presents us with the same steric problems experienced before at this hindered position. The product **94** also has an undesired methyl branch which would cause further rotation restrictions.

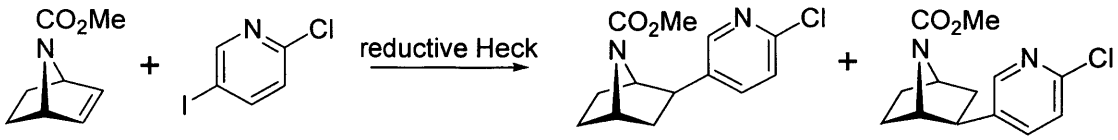
Scheme 3.13



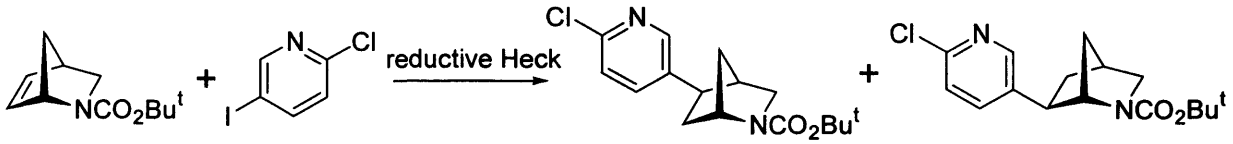
3.4.4 Attempt at Reductive Heck Coupling

The reductive Heck coupling[108] involves the palladium-catalysed reactions of organic halides with an olefinic compound, in order to produce a carbon-carbon bond. In the literature, there are several examples of the reductive Heck reaction, for example, in the total synthesis of epibatidine by Claydon and Regan[12] (**Scheme 3.14**) and the synthesis of epibatidine analogues by Malpass and Cox[109] (**Scheme 3.15**).

Scheme 3.14



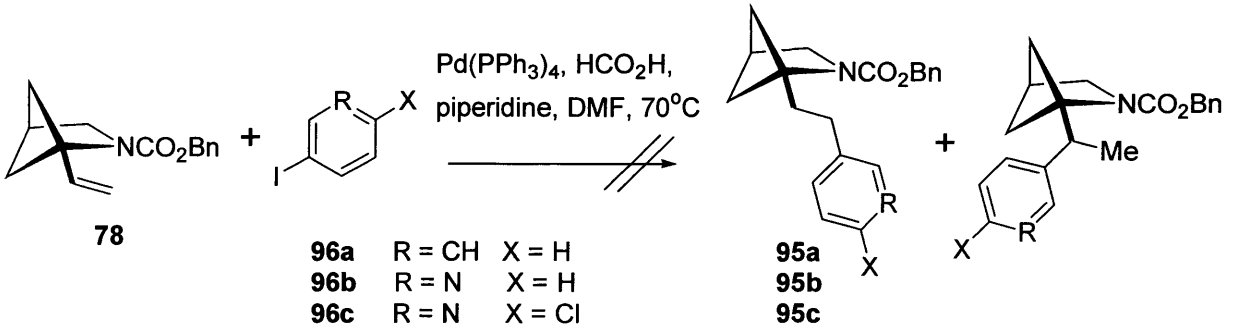
Scheme 3.15



Our attempt at reductive Heck coupling on the 2-azabicyclo[2.1.1]hexane system involved a terminal alkene **78**. Although there is no mention in the literature of the reductive Heck reaction in synthesis of epibatidine analogues *via* a terminal alkene, in theory the basic principle should remain the same. It was anticipated that the heterocycle would attach to the terminal carbon due to lower steric hinderance to give **95**, although a mixture of regioisomers (**Scheme 3.16**) may be possible, in principle.

The reductive Heck coupling was attempted on the alkene **78** using a variety of heterocycles including iodobenzene **96a**, 3-iodo-pyridine **96b** and 2-chloro-5-iodo-pyridine **96c** (**Scheme 3.16**). The reaction was performed using a range of palladium catalysts; $Pd(PPh_3)_4$, $Pd_2(dba)_3$ and $Pd(OAc)_2(PPh_3)_2$. Of these $Pd(PPh_3)_4$ was thought to be the most productive as result of its reduced steric bulk when compared to $Pd_2(dba)_3$ and $Pd(OAc)_2(PPh_3)_2$. Unfortunately, none of these conditions used gave the expected products **95a**, **95b** or **95c**. In all cases, the ^1H NMR spectrum displayed uncharacterisable material, which was not starting material or product.

Scheme 3.16



Palladium-catalysed couplings on terminal alkenes have been mentioned in the literature but these employ alternative methods to the reductive Heck coupling.[110,111] Therefore this could not be employed in our chemistry. It is thought that reductive Heck coupling is not possible on the 2-azabicyclo[2.1.1]hexane ring system. This is because the alkene is at such a hindered position that the bulky palladium catalyst cannot coordinate successfully.

To conclude, we have demonstrated that nucleophilic substitution can also be achieved in the *N*-alkoxycarbonyl series. This has enabled us to synthesise compounds with a range of functional groups. We have been successful in synthesising the imidazole target compound **54**, which is currently being tested for affinity and sub-type selectivity at nAChRs. We have also reported the synthesis of the novel cyclic carbamate **73** formed because of neighbouring group participation. Various other attempts have been made to construct heterocycles from a range of functional groups available, but due to restricting steric factors these have not been possible.

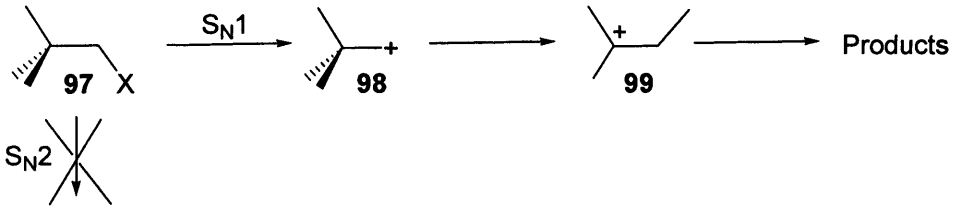
Chapter 4

Mechanistic & Rearrangement Studies on 2-Azabicyclo[2.1.1]hexane Systems

4.1 The Question of Rearrangement in 2-Azabicyclo[2.1.1]hexane Systems

We already know from the fundamental rules of organic mechanistic chemistry that S_N2 is not possible in a neopentyl system **97** (**Scheme 4.1**). Any reaction must go *via* the S_N1 pathway, in which the primary carbocation **98** rearranges to the more stable tertiary carbocation intermediate **99**.

Scheme 4.1

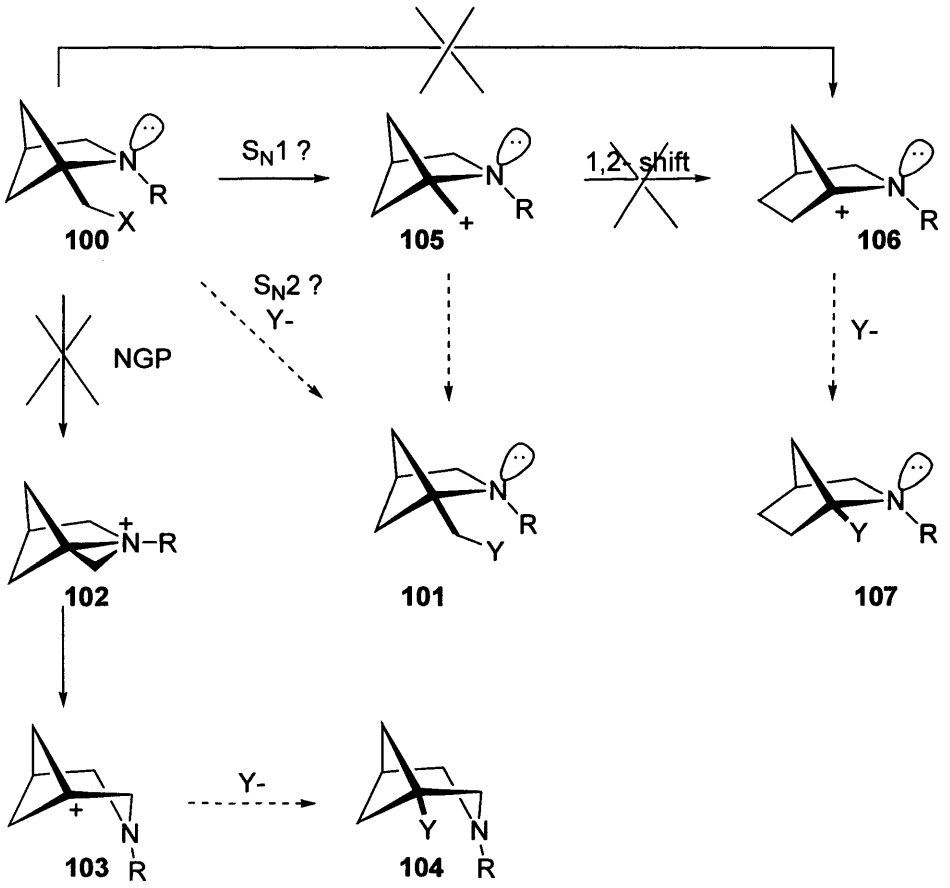


This leads us to the important question of how substitution is possible without rearrangement in the 2-azabicyclo[2.1.1]hexane system, which has a 'pseudo-neopentyl' structure. The only previous example of ready S_N2 displacement of a leaving group at the hindered 1-methylene position was achieved using hydride (Chapter 2, Section 2.1.1);[68,70] more sterically demanding nucleophiles had not been used prior to this work. How was the conversion of **100** into product **101** possible?

Conceivable substitution pathways from **100** are shown in **Scheme 4.2**. Any anticipation of 'double displacement' leading to substitution *via* neighbouring group participation (NGP) of the amino-nitrogen lone pair was unlikely on the basis of the orientation of the lone pair and the strain in intermediate **102**. In theory, relief of strain in **102** would be possible by C-N bond cleavage to produce **103** which has a 3-azabicyclo[3.1.1]heptane skeleton. Reaction of **103** with a nucleophile would provide **104**.

The notion of advantageous S_N1 substitution seemed unlikely in view of the inclination of the strained azabicyclo[2.1.1]hexane system to undergo skeletal rearrangement or fragmentation. However, further consideration was justified when the limited options for rearrangement of the primary carbocation **105** are contemplated. The strained rearranged bridgehead cation **106** should be intrinsically inaccessible; resonance stabilisation by the almost orthogonal nitrogen lone pair was clearly impossible, and the electronegative nitrogen would further destabilise the hypothetical cation.[68] In the presence of a nucleophile **106** would form **107**. Another pathway to the carbocation **106** could be directly from **100** (*via* NGP involving a σ-bond), without forming the intermediate **105**.

Scheme 4.2



4.1.1 Evidence for Retention of the Bicyclic Framework

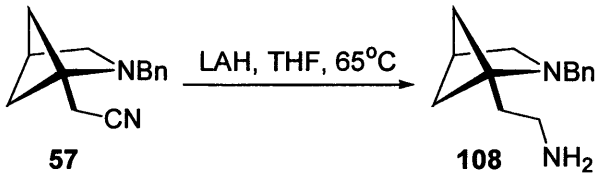
Spectroscopic data confirmed that the 2-azabicyclo[2.1.1]hexane framework was retained in the isolated product and that neither **104** or **107** are obtained as products. Further proof came from the products of other nucleophilic substitution reactions. If **104** had formed then in the ^{1}H NMR spectrum we would observe the downfield shifts of the four protons on C_2 and C_4 adjacent to the nitrogen. The α–N signals in the ^{1}H NMR spectrum of **107** would be similar to those of **101**, but these have been distinguished by the subsequent experiments thus proving that compound **57** was formed.

In the *N*-benzyl series the ^{1}H NMR spectrum of the nitrile **57** was examined in detail. It includes a singlet at δ 2.70 with an integration of five protons that are a result of coincidental equivalence of the H_{3x}, H_{3n}, H_4 and H_7 protons. The H_{5s} and H_{6s} appear as a doublet of doublets at δ 1.68 and the H_{5a} and H_{6a} as a multiplet at δ 1.79. Both benzyl protons appear as a singlet at δ 3.64. Finally, the aromatic protons show at δ 7.22-7.47 as a multiplet. By changing the NMR solvent to benzene-d_6, acetone-d_6 or toluene-d_6 it is possible to separate the protons H_{3x}, H_{3n}, H_4 and H_7. The treatment of a sample of **57** with 5μl of TFA in $CDCl_3$

leads to protonation of the bicyclic nitrogen hence the adjacent protons of H_{3x}, H_{3n} and the benzyl protons appear more downfield than usual. This shows that the 2-azabicyclo[2.1.1]-hexane skeleton is retained.

In a further experiment, **57** was reduced to the amine **108**. In the ^1H NMR spectrum of the amine product the presence of two adjacent -CH_2- groups was confirmed by the observation of two triplets having a *J*-value of 9 Hz, showing that they are connected (**Scheme 4.3**). This was confirmed by the ^1H-^1H COSY spectrum. This could only fit with structure **108** which therefore cannot be derived from either of the rearranged systems, based on **104** or **107**.

Scheme 4.3



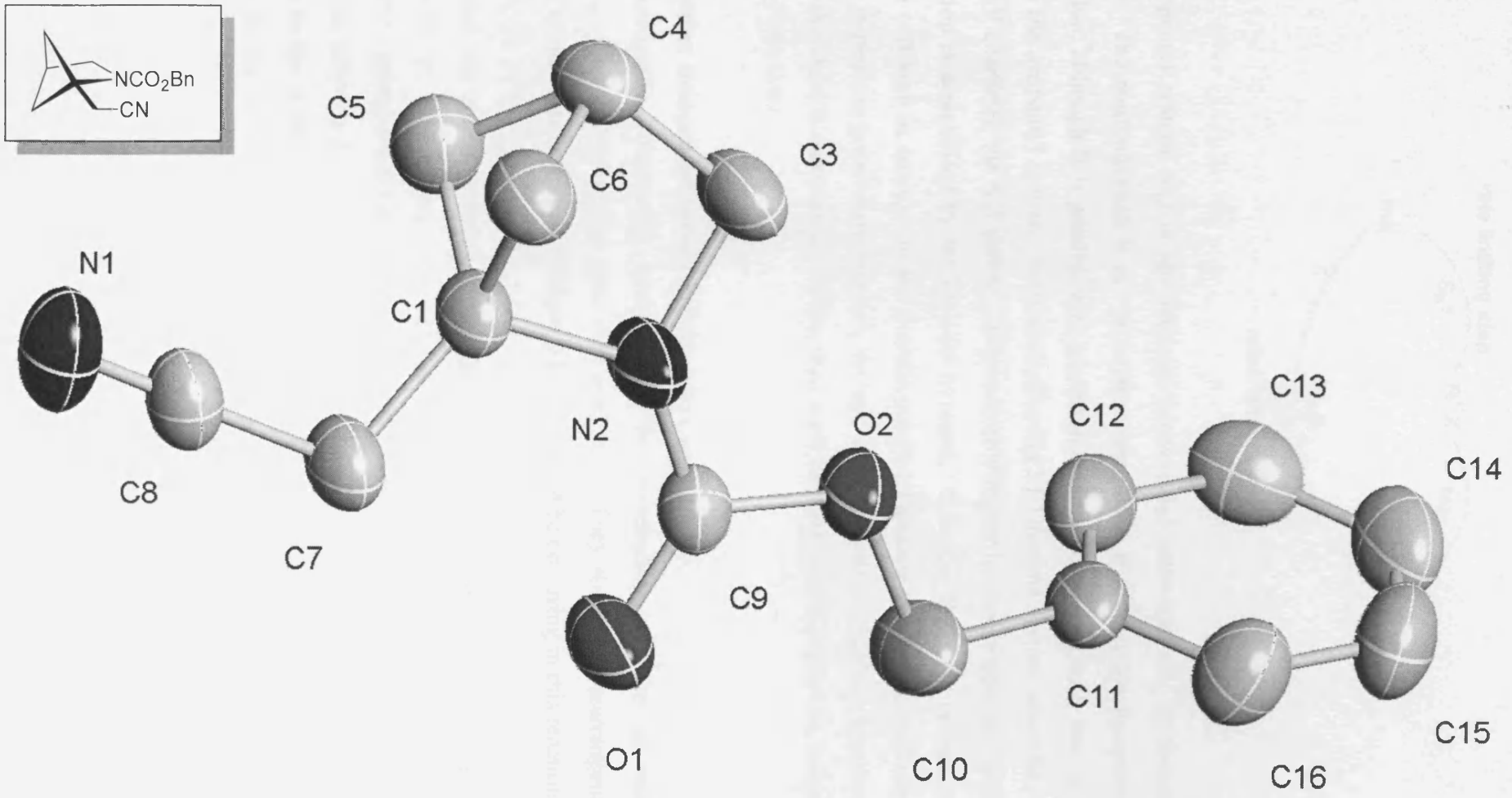
57 **108**

For the *N*-benzyloxycarbonyl series the structure of the nitrile **69** was confirmed by X-ray crystallography (**Figure 4.1**) and this provides evidence that the bicyclic skeleton was maintained. Nitrile **69** also has the characteristic ^1H NMR spectrum of *N*-benzyloxycarbonyl 2-azabicyclo[2.1.1]hexanes. Therefore, nucleophilic substitution is possible on the 2-aza-bicyclo[2.1.1]hexane system and the skeleton in retained, when the nitrogen was protected by both *N*-benzyl and *N*-benzyloxycarbonyl groups.

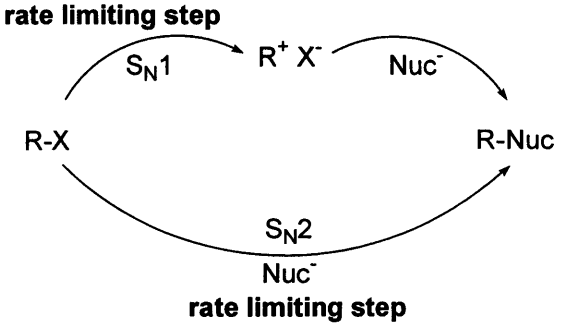
4.2 S_N1 Versus S_N2

As yet, there is no evidence concerning the balance between S_N1 and S_N2 mechanisms. The conditions for the nucleophilic substitution reactions (**Scheme 4.2**) are suggestive of S_N2 reactivity. The synthesis of **57** required: acetonitrile (a polar aprotic solvent), long reaction time, high temperatures and the use of 18-crown-6, all characteristic indications of S_N2 reaction. The methylene bridges of the azabicyclic system offer less steric hinderance than an actual neopentyl system. The effect of 18-crown-6 provides evidence favouring S_N2 because, in S_N1, the rate limiting step gives the ion pair R^+X^-, therefore being independent of the nucleophile concentration. On the other hand, S_N2 is dependent on the nucleophile concentration and 18-crown-6 to hold the K^+ cation in order for the reaction to occur, which is the rate limiting step. In the S_N1 pathway, addition of 18-crown-6 does not make a difference as the ion pair R^+X^- would already exist (**Scheme 4.4**).

Figure 4.1 X-ray crystal structure of **69**



Scheme 4.4



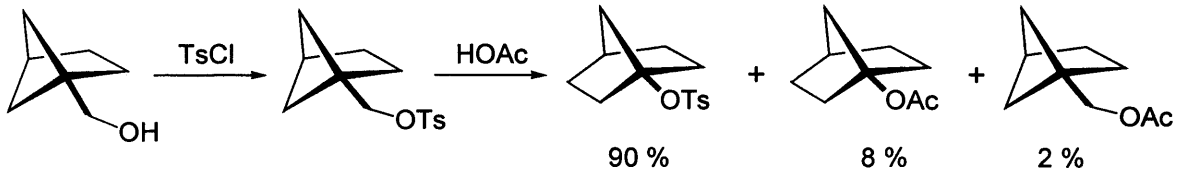
In a neopentyl system, S_N2 is not observed because S_N1 intervenes *via* the lower energy pathway. The rearrangement is not rate-determining since it follows the formation of the carbocation, although it is possible that migration could be concerted with loss of leaving-group in the neopentyl system. In the 2-azabicyclo[2.1.1]hexane system which has 'pseudo neopentyl' character, the S_N1 pathway is presumably higher in energy than S_N2 because the carbocation is destabilised by the adjacent nitrogen. Therefore S_N2 may become possible, although still high in energy. In the 2-azabicyclo[2.1.1]hexane system the pathway for the reaction is perhaps somewhere between the two extreme ends of S_N1/S_N2 spectrum. It is possible that there is more bond breaking than bond forming in an S_N2 process, hence having some S_N1 character.

4.2.1 Other Bridgehead-substituted Bicyclic Compounds

The nucleophilic substitution reactions at the 1-methylene position of substituted bicyclo[2.1.1]hexane derivatives have been studied.[112] They show both rearrangement and retention of the bicyclic system (**Scheme 4.5**); NGP must be occurring in this reaction.

The alcohol **109** is first converted to the tosylate **110,** the solvolysis reaction of the tosylate **110** occurs at an enhanced rate giving 90 % internal return of the rearranged bicyclo[2.2.1]heptyl-1-tosylate. The acetate **111** retaining the bicyclo[2.1.1]hexane ring system was only obtained in 2 % yield (by internal return). This suggests the pathway is *via* S_N1 due to the significant amount of rearranged product obtained by the 1,2 shift. This research distinguishes S_N1 without rearrangement from a unimolecular process involving NGP.[112]

Scheme 4.5

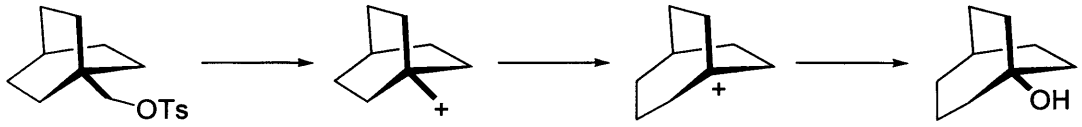


109 **110** **111**

Other research[113,114] has explored the chemistry of bridgehead-substituted bicyclo[2.2.1]-heptane systems using radical chemistry to allow change of the functional group. Starting with a halogen at the bridgehead position a variety of functional groups have been incorporated.

Nucleophilic substitution reactions at the 1-methylene position of bicyclo[2.2.2]octanes shows that rearrangement occurs to form the more stable tertiary carbocation, increasing the ring size, so forming the bicyclo[3.2.2]nonane (**Scheme 4.6**).[115]

Scheme 4.6

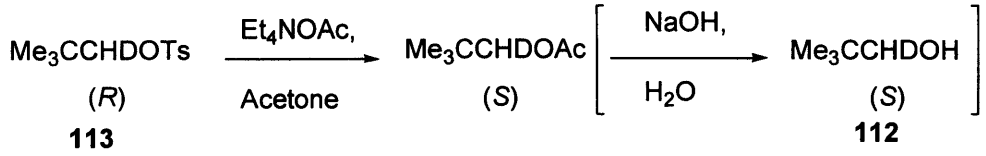


Therefore the 2-azabicyclo[2.1.1]hexane system differs from other all-carbon bicyclic systems in that rearrangement does not occur.

In the study of neopentyl systems, deuterium labelling has been used to determine the nucleophilic displacement pathway.[116] Deuterium labelling maintains the primary alcohol system so the S_N2 and S_N1 experiments could be conducted (**Scheme 4.7**). The stereochemistry of a typical S_N2 reaction was determined by acetate displacement on tosylate.

Wiess and co-workers[116] found that the (*S*)-alcohol **112** is formed from (*R*)-tosylate **113** meaning the acetate displacement-hydrolysis sequence occurs with overall inversion (**Scheme 4.7**). They argued that the reaction in the neopentyl system is predominantly S_N2, as S_N1 would give ~50 % inversion and ~50 % retention of configuration. The results were claimed to be clear and unambiguous. This experiment could be replicated for the 2-aza-bicyclo[2.1.1]hexane system.

Scheme 4.7

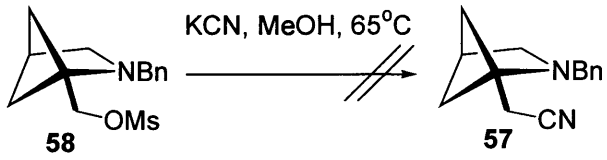


4.2.2 Solvent Effects

In many organic reactions, a change of solvent can have a dramatic effect on the rate of reaction and can often determine the reaction pathway. In order to further explore the S_N1/S_N2 question in the 2-azabicyclo[2.1.1]hexane system, the solvent was changed.

The established reaction for converting **58** into **57** used acetonitrile, a polar aprotic solvent which favours S_N2 reactivity. This was changed to methanol, a solvent more suitable for S_N1 (**Scheme 4.8**). The reaction was attempted keeping all other variables the same: temperature; reaction time and mesylate substrate **58**, but without 18-crown-6, for reasons mentioned earlier. This reaction was significantly slower using methanol as it did not produce the nitrile **57** in the same length of time as it did with acetonitrile. There was no evidence from the ^1H NMR spectrum of the product **57** being formed. Hence, from this we can deduce that the S_N1 pathway is much slower than S_N2 and therefore nucleophilic substitution in this system is likely to be S_N2 with S_N1 character.

Scheme 4.8

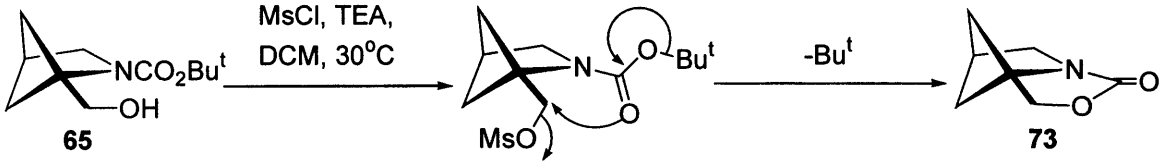


To summarise, the likely pathway for nucleophilic substitution reaction has been discussed. Various examples from the literature on all-carbon systems have been used as a means of comparison with the 2-azabicyclo[2.1.1]hexane system.

4.3 The Novel Cyclic Carbamate 73

The formation of the novel cyclic carbamate **73** as a by-product has been discussed in Chapter 3, Section 3.2. Predictably, **73** was produced more efficiently (88 % yield), *via* loss of *tert*-butyl from the *N*-Boc protected alcohol **65** (**Scheme 4.9**)[68] (using similar conditions to those described earlier for the *N*-benzyloxycarbonyl derivative).

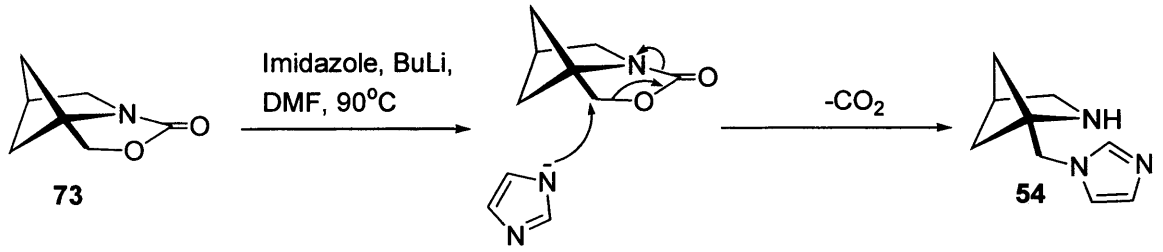
Scheme 4.9



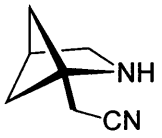
4.3.1 Nucleophilic Ring Opening

Nucleophilic attack at the 1-methylene position of **73** by the imidazolyl anion required more vigorous conditions than for mesylate **68**. However, this provided the *N*-deprotected compound **54** directly with concomitant decarboxylation in a good yield (69 % based on recovered starting material) (**Scheme 4.10**).

Scheme 4.10



Similar treatment of **73** with cyanide ion again required vigorous conditions and gave **114** in 70 % yield. To conclude, **73** is a convenient precursor for the direct synthesis of *N*-deprotected 1-functionalised derivatives of the 2-azabicyclo[2.1.1]hexane ring system.[68]

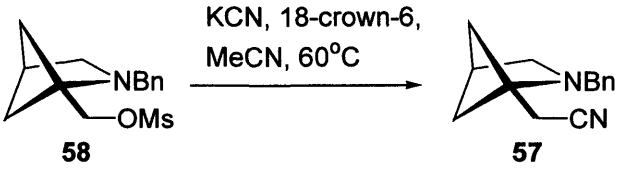


114

4.3.2 Effect of the *N*-protecting Group

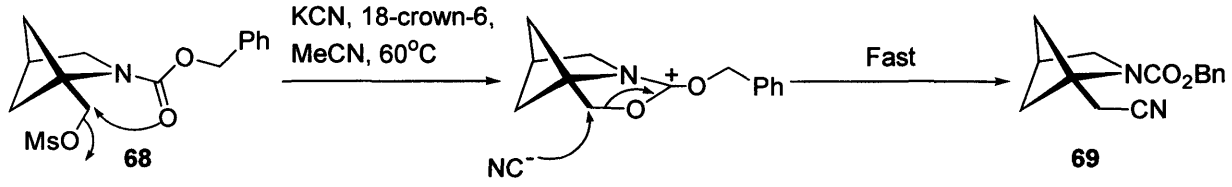
Nucleophilic substitution reactions have been successful in both the *N*-benzyl (*N*-Bn) and *N*-benzyloxycarbonyl (*N*-Cbz) series. In the reaction of *N*-benzyl mesylate **58**, nucleophilic substitution occurs to give nitrile **57** without any neighbouring group participation (NGP) by the amino nitrogen (**Scheme 4.11**).

Scheme 4.11



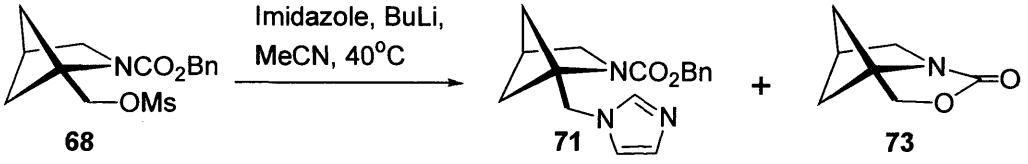
The observation of NGP in **Scheme 4.9** raises the possibility of wider involvement of the carbonyl of the Cbz protecting group in the displacement reaction (**Scheme 4.12**). However, the fact that corresponding reactions in the *N*-Bn and *N*-Cbz series require similar temperatures and reaction times weakens the case for NGP by the carbonyl group.

Scheme 4.12



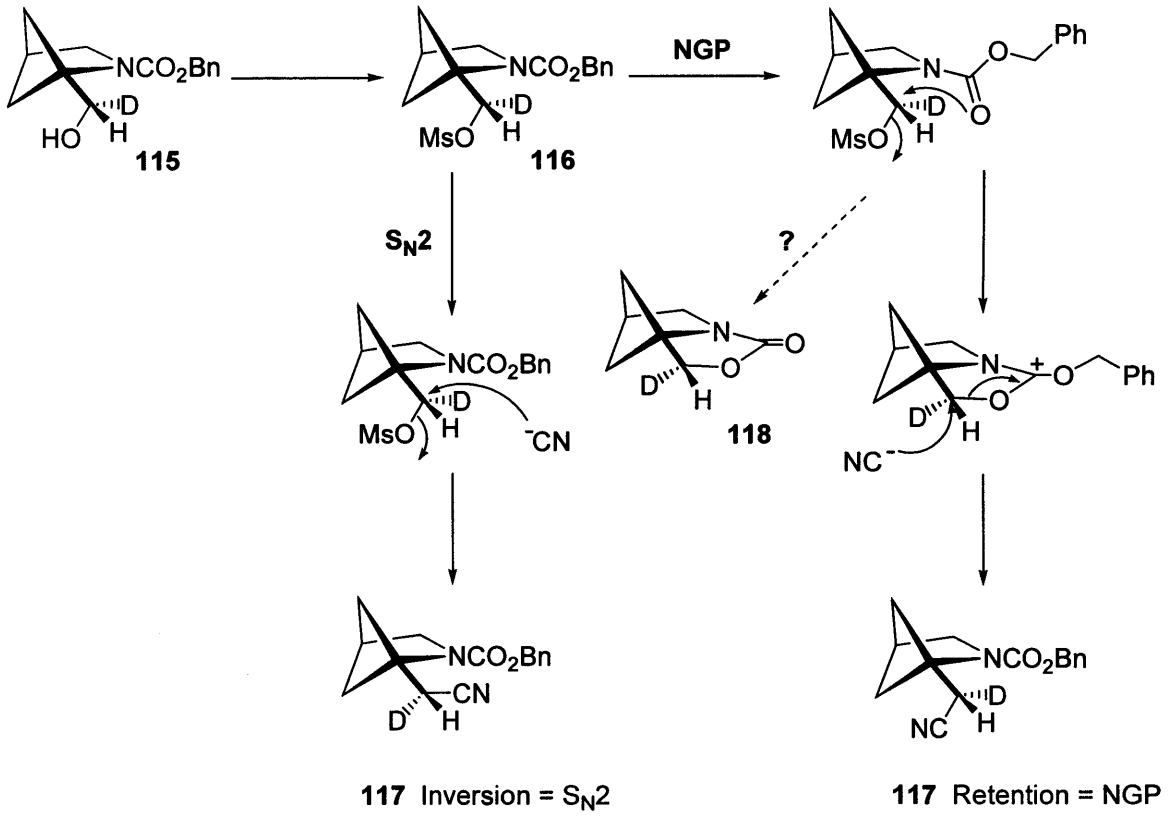
We know that NGP could occur because of formation of the cyclic carbamate **73** in the reaction to synthesise the imidazole compound **71** (**Scheme 4.13**), but there is no evidence to suggest that NGP does occur in the *N*-CBz series because the rate of reaction is similar to that of the *N*-Bn series.

Scheme 4.13

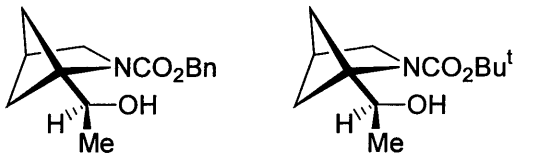


To investigate the phenomenon of NGP, deuterium labelling could be used (**Scheme 4.14**). One enantiomer of the alcohol **115** could be synthesised using a chiral deuterated reducing agent. Using one enantiomer of the alcohol **115** we could synthesise the mesylate **116** using previous methodology. Nucleophilic substitution could then used to form the nitrile **117**, which might occur either by NGP giving **117** with retention of configuration or by the S_N2 pathway resulting in the inversion of configuration. If the deuterated cyclic carbamate **118** were to be also produced this would be evidence of NGP, by the carbonyl oxygen. Such an experiment could help to determine the pathway of the reactions.

Scheme 4.14



We could synthesise the racemic alcohols **119** (*N*-Cbz) and **120** (*N*-Boc). However, it is possible that performing the reaction with these compounds would not give us an indication whether NGP is occurring because they are secondary alcohols and hence would produce a secondary carbocation which may favour S_N1.



119 (*R*) and (*S*) **120 (*R*) and (*S*)**

In summary, the synthesis of the novel cyclic carbamate **73** has been investigated. Its potential uses and formation has been examined, along with mechanistic information. Suggestions have also been made for possible further mechanistic investigations using deuterium labelling.

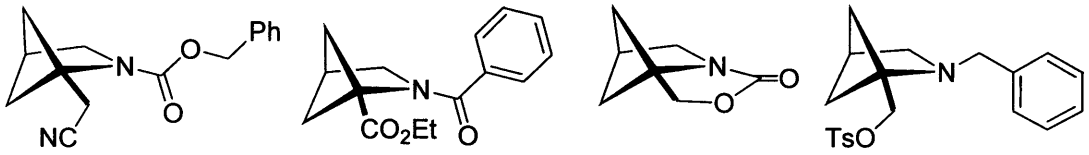
4.4 Shape at Nitrogen

The amide bond is an important structural linkage in peptides and proteins. The nitrogen atoms in amides are anticipated to be trigonal-planar due to the conjugation with the carbonyl group. Few peptides are thought to have non-planar amides. The rigid and planar amide linkage is essential in encoding protein folding and various other chemical and biological processes.[117]

The planarity of the amide group in a range of 7-azabicyclo[2.2.1]heptane amides has been studied in the solid state, in solution, and calculated for gas phase structures. Ohwada and co-workers[118] found that various degrees of pyramidalisation of the amide nitrogen occurs due to the CNC angle strain and twisting of the amide bond due to allylic strain. Non-planarity of the amide has also been studied in peptide analogue compounds.[119]

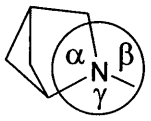
In this research on the 2-azabicyclo[2.1.1]hexane ring system we have X-ray crystal structures on four compounds (**Figure 4.2**) in which the shape at the bicyclic nitrogen ranges from trigonal-planar to pyramidal summarised in **Table 4.1**.

Figure 4.2 Compounds studied for shape at nitrogen research



69 **47** **73** **50**

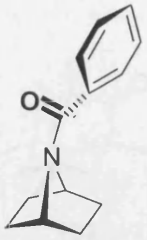
Table 4.1



$\theta = \alpha + \beta + \gamma$

Compound	θ	α	β	γ
69	358.4	103.2	126.3	128.9
47	349.6	102.7	124.9	122
73	341.7	104	129	108.7
50	328.7	100	113.1	115.6

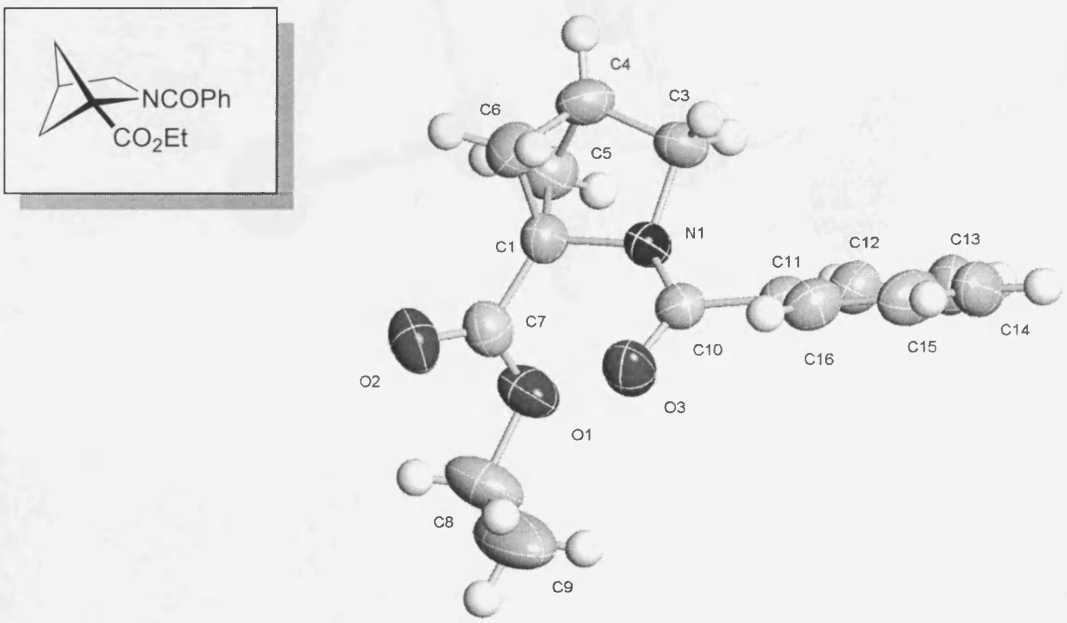
The existence of a partly-pyramidal amide nitrogen is shown in the X-ray crystal structure of *N*-benzoyl-7-azabicyclo[2.2.1]heptane **121**. The total angle θ was 349.5° and the CNC angle α was 97.2°. The angle θ suggests that the nitrogen adopts a shape between pyramidal sp^3 (θ = 328.4, α = 109.5) and trigonal-planar sp^2 (θ = 360, α = 120).[120]



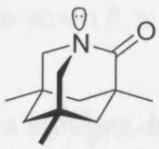
121

The X-ray crystal structure of **47** (**Figure 4.3**) was used to compare the 2-azabicyclo[2.1.1]-hexane system with the work of Ohwada[117] in the 7-azabicyclo[2.2.1]heptane ring system. Both **121** and **47** have the *N*-benzoyl protecting group. For **47** the total angle θ is 349.6° and the CNC angle α is 102.7°, meaning that a pyramidal amide nitrogen is also present in this ring system. The CNC angle is again reduced partly by bicyclic strain, leading to pyramidalisation despite the large outer angles β = 124.9° and γ = 122°. The angle of the aryl ring appears to be slightly tilted which implies reduced overlap with the amide carbonyl, as the aryl ring and amide carbonyl are not in the same plane. In comparison with **121**, **47** has a very similar total angle θ, but a slightly larger CNC angle α. Clearly the 7-azabicyclo[2.2.1]-heptane system is not unique as the bond-angles of the 2-azabicyclo[2.1.1]hexane system are similar.

Figure 4.3 X-ray crystal structure of **47**



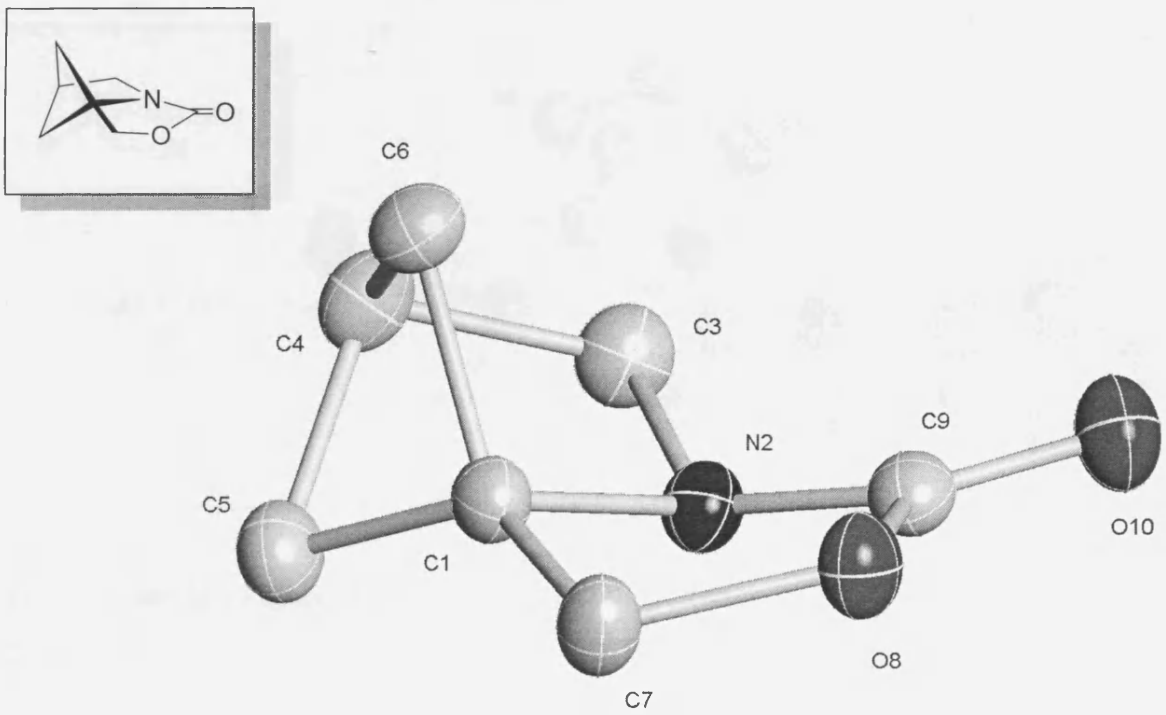
However, the 'most twisted amide' was reported by Kirby *et al.*[121,122] to be found in 1-aza-2-adamantanone **122**. This extreme case involves no overlap of the lone pair on the nitrogen atom with the π-system of the carbonyl group, due to the rigid geometry of the tricyclic skeleton. The X-ray crystal structure shows the total angle θ to be 325.7° making the nitrogen closer to pyramidal than trigonal-planar.



122

Of the crystal structures obtained in our work, the most pyramidal nitrogen is found in the cyclic carbamate **73**. The X-ray crystal structure (**Figure 4.4**) shows clear strain in the cyclic urethane and within the 2-azabicyclo[2.1.1]hexane ring system. The total angle θ is 341.7° and the tight CNC angle α is 104°. Structure **73** is clearly a very strained compound but is also very stable, as vigorous conditions were required to open the ring by nucleophilic substitution

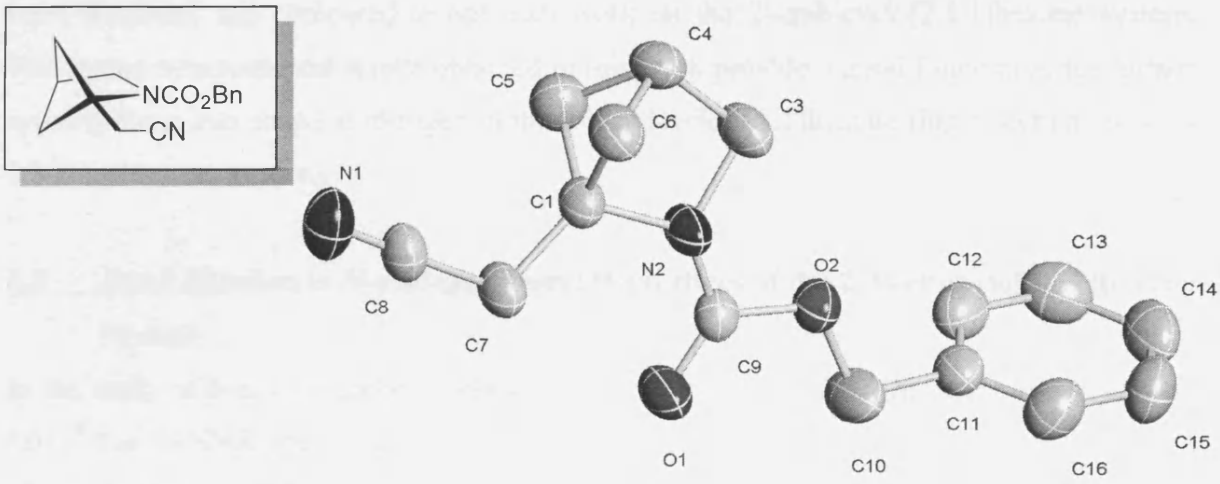
Figure 4.4 X-ray crystal structure of **73**



For structure **69** the nitrogen is trigonal-planar; the total angle θ is 358.4° and the CNC angle α is 103.2° (**Figure 4.5**). This structure has a benzyloxycarbonyl protecting group on the nitrogen, which is clearly having an effect on the geometry. This protecting group is more bulky, but more importantly there is orbital overlap in the urethane adding stability to the structure, so there is a preference for a trigonal shape. Although the CNC angle is quite tight the outer angles compensate for this slight strain β = 126.3° and γ = 128.9°.

Compound **47** has an aryl amide group on nitrogen, having a near-planar amide nitrogen. On the other hand, compound **69** has a urethane group, so having a trigonal planar geometry on nitrogen. Both of these compounds have a similar strained CNC angle. The β-angle is also similar for both **47** and **69**. The difference occurs in the γ-angle, where it is much larger in **69** to allow the trigonal planar geometry. As **69** is trigonal planar there seems to be better N-CO overlap than in the amide **47**. Resonance in **47** between the carbonyl and the aryl ring may reduce N-CO overlap, which may lead to the slightly pyramidalised geometry. This is observed in **Figure 4.3** as the carbonyl and aryl group are not in the same plane.

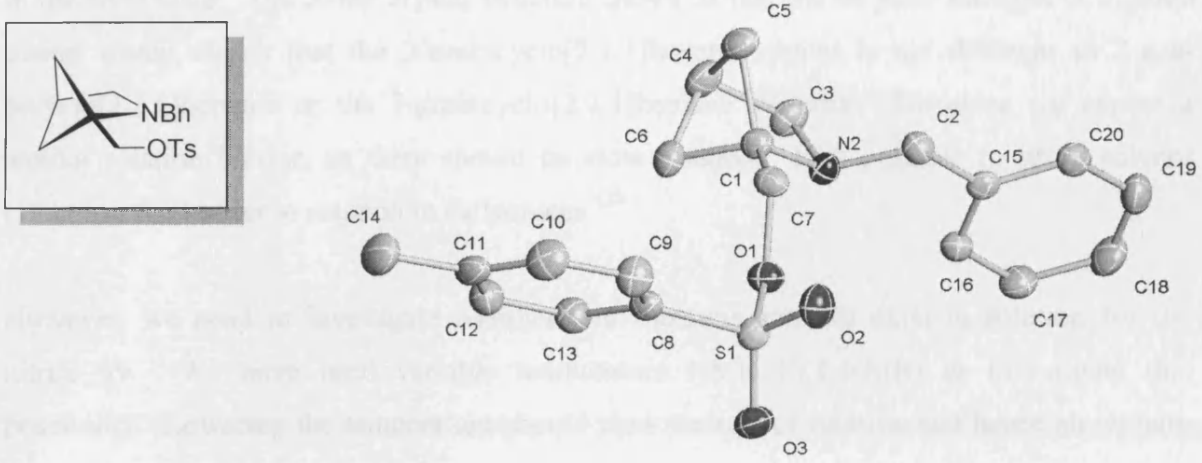
Figure 4.5 X-ray crystal structure of **69**



The tosylate **50** (**Figure 4.6**) has an *N*-benzyl protecting group therefore the nitrogen is pyramidal as expected for an amine (total angle θ is 328.7°). The tight CNC angle (100°) is again compensated by the large outer angles β = 113.1° and γ = 115.6°. The position of the carbon on the *N*-benzyl group is now *cis* compared to the *trans* preference of the amide protecting groups. The definition of *cis* is when the carbon atom adjacent to the bicyclic nitrogen is facing away from the functional group at C_7. While, *trans* is defined as when the

carbon atom adjacent to the bicyclic nitrogen is facing towards the functional group at C_7.[52] This structure is more pyramidal as there is no overlap of orbitals with a carbonyl group.

Figure 4.6 X-ray crystal structure of **50**



In conclusion, we have used X-ray crystallography to study the shape at nitrogen of the 2-azabicyclo[2.1.1]hexane ring system and discover that the shape at nitrogen changes as we alter the nitrogen protecting group. The research from the groups of Ohwada and Kirby has been discussed and compared to our own work on the 2-azabicyclo[2.1.1]hexane system. The crystal structures and results obtained in this work provide a good foundation for further investigations into shape at nitrogen in the 2-azabicyclo[2.1.1]hexane ring system as well as other azabicyclic systems.

4.5 Bond Rotation in *N*-alkoxycarbonyl Derivatives of the 2-Azabicyclo[2.1.1]hexane System

In the study of benzyloxycarbonyl derivatives of 2-azabicyclo[2.2.1]heptane ring system by Cox,[38] the ^{1}H NMR spectra always show the existence of two rotamers at room temperature. This is due to slow C-N bond rotation in the carbamate protecting group on nitrogen.

Despite the expectation of a similar rotation barrier, only one set of signals is seen in the ^{1}H NMR spectra of derivatives of the 2-azabicyclo[2.1.1]hexane ring system in the present work, making this system an unusual case. Therefore, either the C-N bond rotation must be very fast on the NMR time scale so one time-averaged set of signals is seen, or the energy barrier for interconversion is high and only one rotamer exists. If one rotamer is preferred, there must be a very significant energy difference between the *cis*- and *trans*- isomers. The

cis and *trans* geometry of the rotamers are defined according to the methodology used by Krow.[52]

The X-ray crystal structure of the nitrile **69** (**Figure 4.5**) shows only the major *trans* rotamer in the solid state. The X-ray crystal structure shows us that the bicyclic nitrogen is trigonal planar which means that the 2-azabicyclo[2.1.1]hexane system is not different to 2-aza-bicyclo[2.2.1]heptane or the 7-azabicyclo[2.2.1]heptane systems. Therefore we expect a similar rotation barrier, so there should be slow rotation. It is possible to study solvent effects on the barrier to rotation in carbamates.[123]

However, we need to investigate whether two rotamers actually exist in solution for the nitrile **69**. We have used variable temperature NMR (VT-NMR) to investigate this possibility. Lowering the temperature should slow the rate of rotation and hence show both rotamers of **69**.

An ^{1}H NMR spectrum of **69** was measured at 300 K and then the temperature was reduced to 233 K and 213 K. In comparing, the ^{1}H NMR spectrum taken at 300 K and at 213 K (**Figure 4.7**) we can observe new signals appearing corresponding to separation of the *cis* and *trans* rotamers. At 233 K and 213 K the ratio of the major *trans* rotamer to the minor *cis* rotamer was 4.5:1, at lower temperatures the equilibrium is weighted to the *trans* rotamer. The main changes in chemical shift of the VT-NMR spectra are summarised in **Table 4.2**. At 213 K for the *cis* rotamer the H_7 protons appear at δ 3.13, as the carbonyl group is pointing away the H_7 protons are shielded so appear at higher field. The H_3 and H_4 protons appear more downfield at δ 3.34 and at δ 2.91 respectively, as these are being deshielded. In contrast at 213 K for the *trans* rotamer the H_7 protons are slightly downfield at δ 3.42 than at 300 K, as the carbonyl group is pointing towards the H_7 protons causing deshielding. The H_3 and H_4 protons appear more upfield at δ 2.50 and at δ 2.82 respectively, as these are being shielded.

Figure 4.7 ^{1}H NMR Spectra of Nitrile **69** at 300K and 213 K.

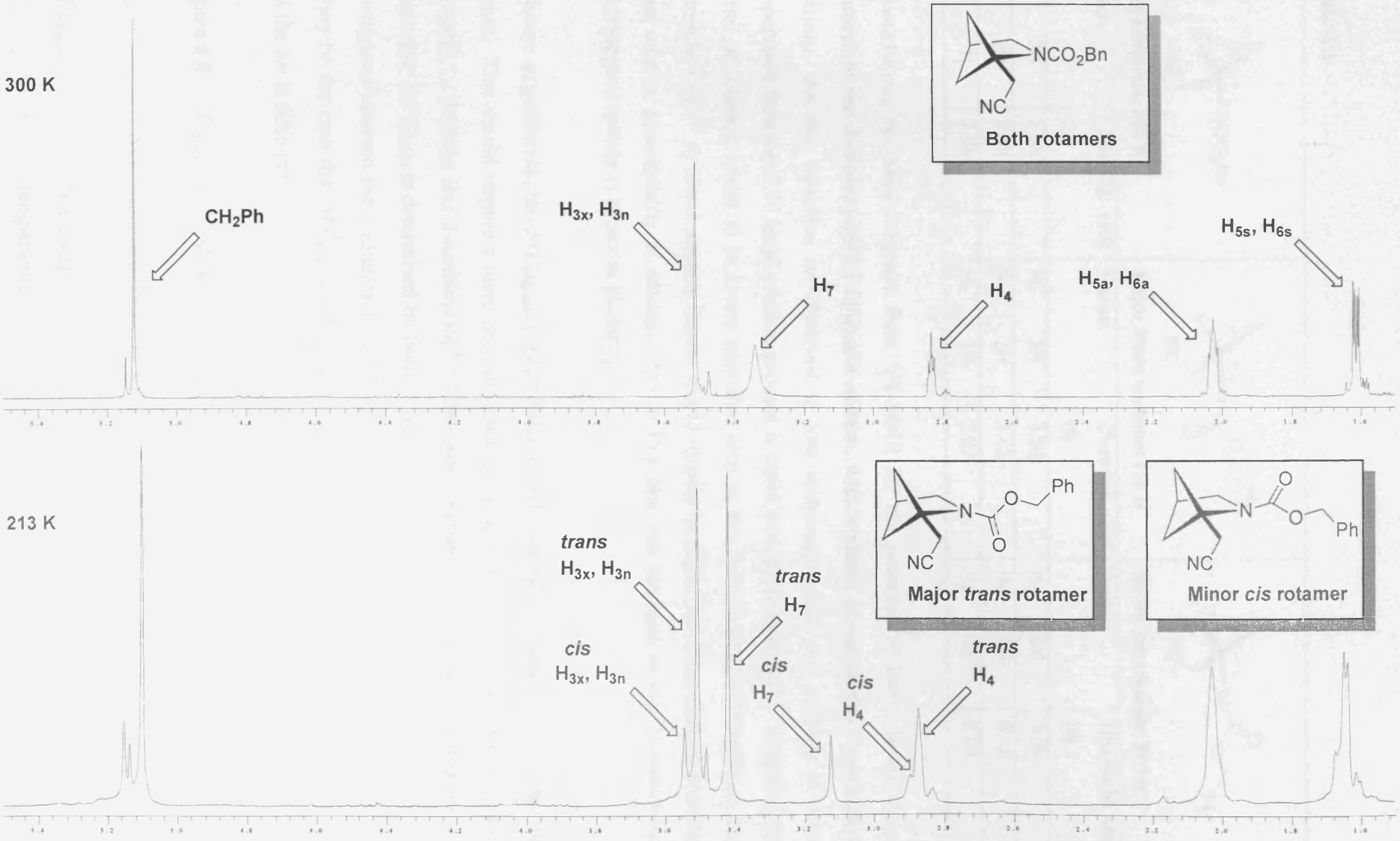
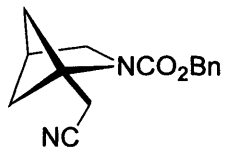
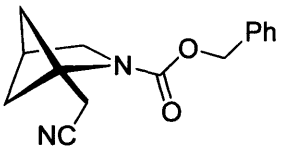
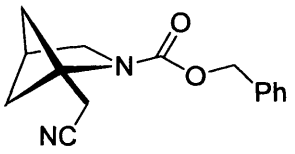


Table 4.2

 **Both rotamers 300 K**		 **Major *trans* rotamer 213 K**		 **Minor *cis* rotamer 213 K**	
Proton	Chemical shift (δ)	Proton	Chemical shift (δ)	Proton	Chemical shift (δ)
H_3 2H	3.51	H_3 2H	3.50	H_3 2H	3.54
H_7 2H	3.34	H_7 2H	3.42	H_7 2H	3.13
H_4 1H	2.83	H_4 1H	2.82	H_4 1H	2.91

In conclusion, we have evidence from VT-NMR for the presence of both *cis* and *trans* rotamers in the 2-azabicyclo[2.1.1]hexane system, with a nitrile group on the 1-methylene position. As two rotamers are observed at low temperature and one rotamer at room temperature then the C-N bond rotation process is rapid at room temperature. Therefore the barrier of rotation seems to be lower than that seen in the 2-azabicyclo[2.2.1]heptane ring system by Cox.[38] A lower rotation barrier would usually be associated with systems showing more relative pyramidality at nitrogen, but in this case the nitrogen in the 2-azabicyclo-[2.1.1]hexane system is nearer to planarity.

In future experiments, the $\Delta G^{\neq}_{rotation}$ could be determined for the 2-azabicyclo[2.1.1]hexane system. This would require a more accurate measurement of T_c and $\Delta\nu$ for both the 2-aza-bicyclo[2.1.1]hexane and 2-azabicyclo[2.2.1]heptane systems. The equation in **Figure 4.8** shows that $\Delta G^{\neq}_{rotation}$ is determined by both T_c and $\Delta\nu$. The variation in $\Delta\nu$ would need to be investigated between the 2-azabicyclo[2.1.1]hexane and 2-azabicyclo[2.2.1]heptane systems. It may be the case that $\Delta G^{\neq}_{rotation}$ is not very different in these azabicyclic ring systems but that the $\Delta\nu$ is different.

Figure 4.8 Equation to calculate $\Delta G^{\neq}_{rotation}$

$$\Delta G^{\neq}_{rotation} = 8.31\times10^{-3} \times T_c\,[23 + 2.3\log_{10}(T_c / \Delta\nu)]$$

$\Delta G^{\neq}_{rotation}$ = free energy of rotation (KJ mol^{-1})

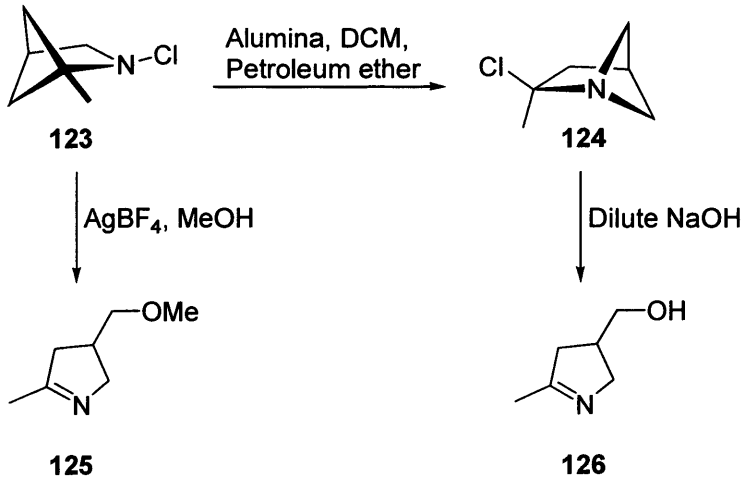
T_c = temperature of coalescence (K)

$\Delta\nu$ = change in frequency (Hz)

4.6 Synthesis of 1-Azabicyclo[2.1.1]hexane Systems; Future Research

The synthesis of 1-azabicyclo[2.1.1]hexanes from a 2-azabicyclo[2.1.1]hexane system has been reported in the Malpass group.[70] It was found that 1-methyl-*N*-chloro-2-azabicyclo-[2.1.1]hexane **123** rearranges to 2-chloro-2-methyl-1-azabicyclo[2.1.1]hexane **124** (**Scheme 4.15**), in the presence of alumina.[52] The most surprising result was the demonstration of retention of chlorine after elution of the product **124** from alumina with methanol. Alumina was thought to act as a mild Lewis acid.

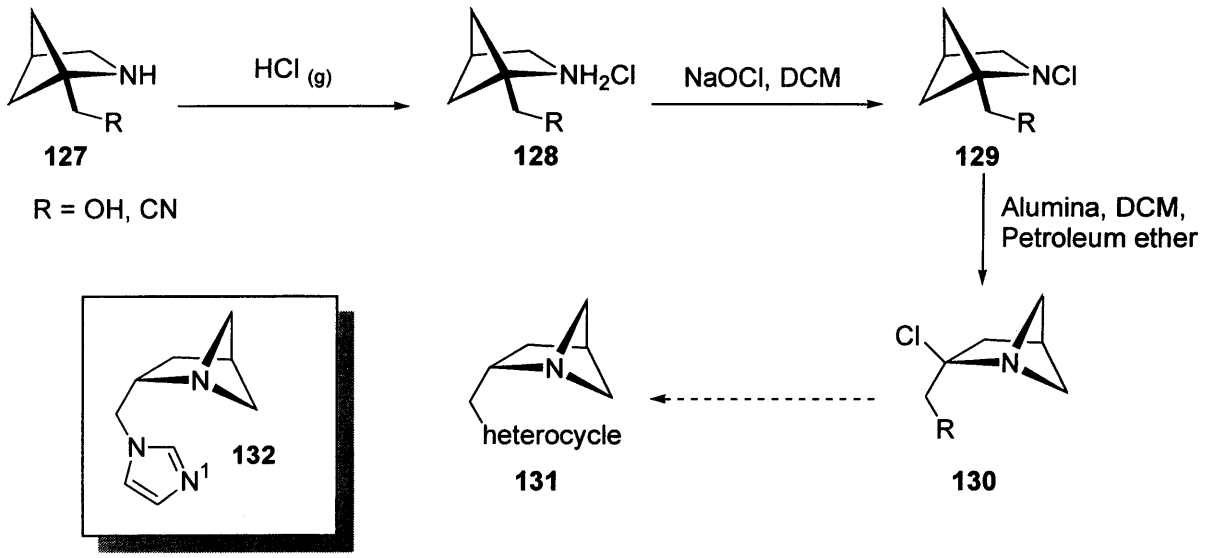
Scheme 4.15



It was deduced that rearrangement of the chloroamine **124** was achieved before methanol elution, as methanol does not incorporate into the product. It was proposed that there was a 'dyotropic shift' during which the chlorine was not separated into the medium so that methanol cannot intrude. Methanol would only react with a discrete carbocation (or a nearly-formed carbocation). As the chlorine 'slides' from the nitrogen to the carbon, a full carbocation doesn't form. In contrast, when **123** was treated with $AgBF_4$ in methanol the ring opened pyroline **125** was obtained as the major product. This was thought to arise *via* removal of the chloride ion and attack by methanol at C_5 or C_6 of a tertiary carbenium ion with relief of strain. The chloroamine **124** was stable in $AgBF_4$ in methanol so therefore cannot be the precursor of **125**, but in dilute base, the ring-opened alcohol product **126** was formed.[70,124]

This methodology could be adapted to synthesise a library of 1-azabicyclo[2.1.1]hexane analogues of epibatidine, using the same functional group interconversion techniques in the 2-azabicyclo[2.1.1]hexane system (**Scheme 4.16**).

Scheme 4.16

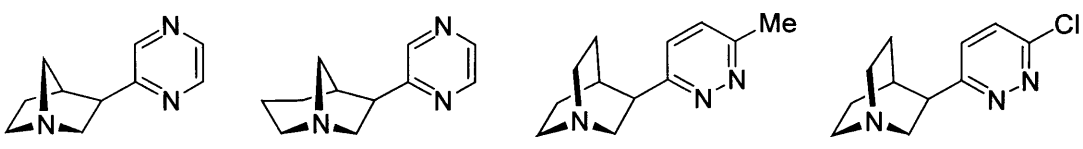


The secondary amine **127** could be treated with gaseous HCl to form the hydrochloride salt **128**. The chloroamine **129** could be synthesised by direct treatment of **128** with sodium hypochlorite solution. Subsequently, using the established rearrangement procedure we could form compound **130** using alumina in DCM and petroleum ether. Established functional group interconversion methods could be used to construct compounds with heterocycles present **131**. The inter-nitrogen distances for **132** are shown in **Table 4.3**. Compounds akin to **132** could be synthesised which have inter-nitrogen distances similar to that of epibatidine.

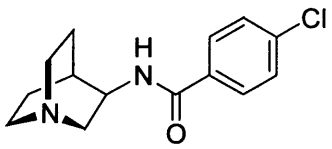
Table 4.3

Compound	Minimum Energy Conformation (Å)	180° rotation (Å) of the heterocycle
Epibatidine	4.3	5.5
132 **N^1**	4.4	4.7

A range of quinuclidine and azanorbornane derivatives **133a-d** has been synthesised by other groups. These compounds show high affinity and efficacy for the muscarinic acetylcholine receptor. The *exo*-1-azanorbornane **133a** was found to be one of the most efficacious and potent active muscarinic agonists known.[125]



Recent research by Myers and co-workers[126] has led to the synthesis of a library of quinuclidine benzamides and these were found to have α7 nAChR agonist activity. The most potent compound in the series was PNU-282987 (K_i = 27 nM). These compounds such as PNU-282987 will be used as templates for finding α7 nAChR agonists that may be useful for treating the cognitive and attentional deficits of schizophrenia.



PNU-282987

Overall, the 1-azabicyclo[2.1.1]hexane system could be used to synthesise a range of compounds having potential activity for the muscarinic receptor. This could be the key leading to a completely new system of potential analogue compounds.

In conclusion to this chapter, various mechanistics and rearrangement aspects of the 2-azabicyclo[2.1.1]hexane ring system have been investigated. Evidence for retention of the 2-azabicyclo[2.1.1]hexane framework during nucleophilic substitution has been discussed in detail. Attempts have been made to rationalise the mechanistic pathway for nucleophilic substitution in this unusual bicyclic ring system. The synthesis and reactivity of the novel cyclic carbamate **73** has been described, with suggestions for further research. Using X-ray crystal data, the shape at nitrogen of the 2-azabicyclo[2.1.1]hexane system has been compared and contrasted with existing literature on other azabicyclic systems. Evidence from VT-NMR spectroscopy studies shows the existence of rotamers in the 2-azabicyclo[2.1.1]hexane system, but suggests that the barrier to rotation may be lower in the 2-azabicyclo[2.1.1]hexane system than in the 2-azabicyclo[2.2.1]heptane system. Finally, suggestions have been made for future research on the synthesis of 1-azabicyclo[2.1.1]-hexane systems and how these could be manipulated in the construction of epibatidine analogue compounds.

Chapter 5

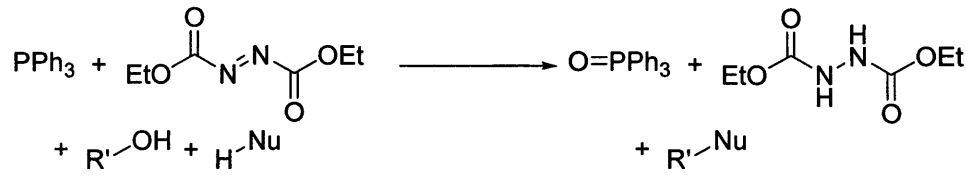
Mitsunobu Coupling Reactions on 2-Azabicyclo[2.1.1]hexane Systems

5.1 The Mitsunobu Reaction

The Mitsunobu reaction,[127,128] developed from pioneering work in the late 1960s, involves the condensation reaction of alcohols using the redox couple of trialkylphosphine and a dialkyl azodicarboxylate.

The reaction is summarised in **Scheme 5.1**, in which the alcohol (R'-OH) and acidic compound (H-Nu) are condensed to form the product (R'-Nu), while triphenylphosphine is oxidised to triphenylphosphineoxide and the azodicarboxylate is reduced to the hydrazine. The most widely used redox reagents are triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD), although many other combinations have been developed.

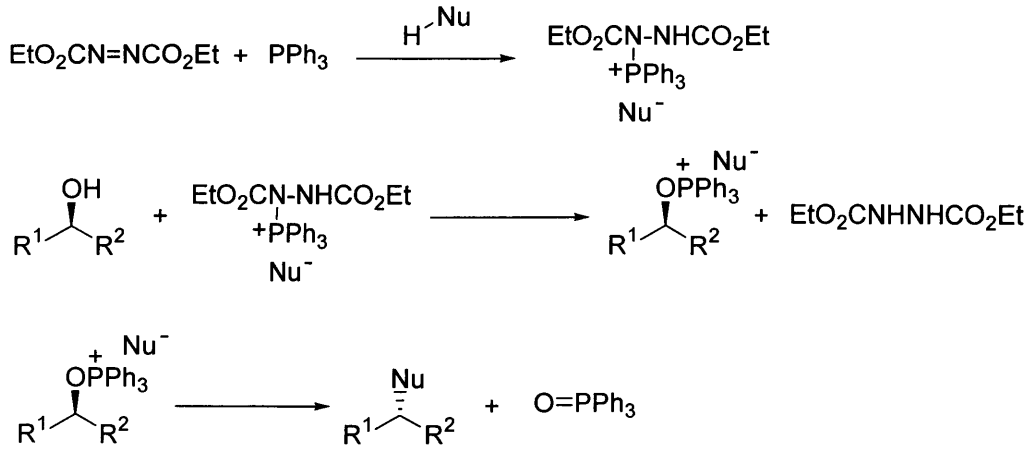
Scheme 5.1



5.1.1 General Mitsunobu Mechanism

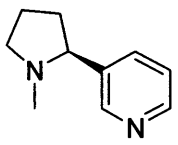
In the Mitsunobu mechanism the dehydration reaction of alcohols using TPP and DEAD occurs in three main steps **Scheme 5.2**. The first is adduct formation, in which the reaction of TPP and DEAD in the presence of the acidic component forms a salt and a phosphorus-nitrogen bond is formed. The next step is alcohol activation where reaction of the salt adduct with the alcohol forms an activated oxyphosphonium ion intermediate. The final step involves an S_N2 displacement to form the inverted product.[127,128]

Scheme 5.2

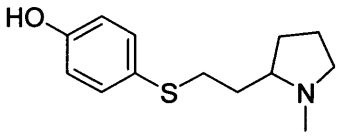


5.2 Analogues of Nicotine

(*S*)-Nicotine has a high binding affinity (K_i = 1-11 nM) for the nicotinic acetylcholine receptor (nAChR), but is poor in identifying different sub-types . Clinical studies illustrate that the administration of nicotine to humans has had beneficial effects for cognitive and attention deficits, Parkinson's disease, anxiety, Tourette's syndrome, ulcerative colitis and smoking cessation. Nicotine also has the potential to delay the advance of neurodegenerative diseases. Despite these beneficial properties of nicotine it has many negative effects such as addiction, cardiovascular and gastrointestinal problems, sleep disturbance and respiratory ailments.[1]



(*S*)-Nicotine

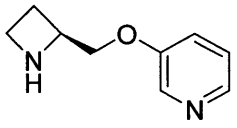


SIB-1553A

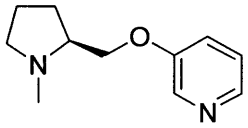
The synthesis of nicotinic analogues is aimed at compounds having binding affinities at least as high as nicotine but having fewer negative effects. The aryl-alkyl pyrrolidine SIB-1553A was found to be a stimulant of acetylcholine production in the CNS and has potential attention and memory-enhancing effects.[1]

5.2.1 Research on 3-Pyridyl-ether Compounds

Recent research at Abbott Laboratories[129] has led to the synthesis of a range of nicotine analogues containing the 3-pyridyl-ether motif. The key ether-forming step for all analogues was carried out using Mitsunobu methodology,[127] using the appropriate primary alcohol and 3-pyridinol. The compounds A-85380 and A-84543 were found to have a high affinity for nAChRs (K_i = 0.052 ± 0.001 nM and K_i = 0.15 ± 0.01 nM respectively) and a high selectivity for the α4β2 sub-type.



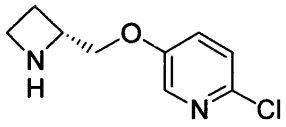
A-85380



A-84543

5.2.2 Research on Tebanicline (ABT-594)

Tebanicline (ABT-594)[130] is a first-generation nAChR agonist that was under development in Abbott Laboratories. In the latter part of the 1990s it entered clinical trials as an analgesic due to its improved separation of antinociceptive effects and nicotinic side-effects.

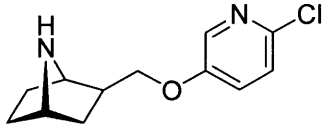


Tebanicline (ABT-594)

The chloro substituent and the azetidine ring were found to be important structural elements for potent analgesic activity.[131] Tebanicline was found to have a high affinity for nAChRs (K_i = 0.04 ± 0.03 nM). It was 180 fold less potent than (±)-epibatidine in activating peripheral skeletal muscle-type nAChRs.[132]

Tebanicline[130] is confirmed to be selective for neuronal nAChRs and, in comparison with (±)-epibatidine, the *in vivo* side-effect profile is improved. In comparing the antinociceptive and toxic effects with those of (-)-nicotine and (+)-epibatidine, tebanicline was found to have a nicotine type dependence liability. This suggests that tebanicline is not significantly improved over other nicotinic analgesics. It was found to bind with greater affinity to α3β4 than to α4β2 receptors and this is thought to be the cause of the observed unfavourable gastrointestinal effects. As a result, clinical trials of tebanicline have been discontinued due to the adverse effects reported in clinical trials.[133]

Compound **134** represents a hybrid structure of epibatidine and tebanicline in which the bicyclic structure of epibatidine is combined with the 2-chloro-5-pyridyl-ether heterocycle of tebanicline. Compound **134** was found to be much lower in potency than epibatidine, nicotine or tebanicline. From this it was deduced that the main structural features for the potency in epibatidine and tebanicline cannot be combined.[134]

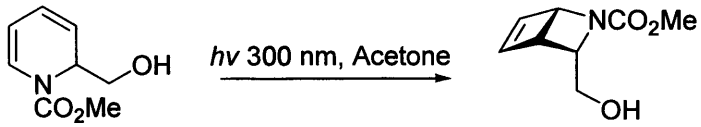


134

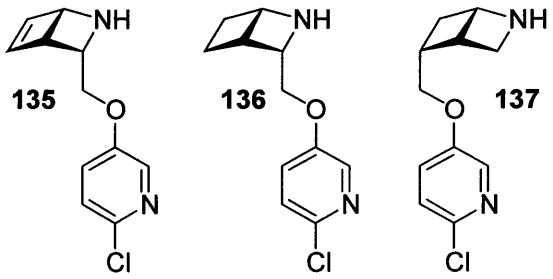
5.2.3 Research on 2-Azabicyclo[2.2.0]hexane Analogues

Tebanicline analogues which have the 2-azabicyclo[2.2.0]hexane framework have also been synthesised by Krow and co-workers.[135] The ABT-594 analogue systems of 3-*endo*-(6-chloro-3-pyridoxy)-methyl-2-azabicyclo[2.2.0]hex-5-ene **135** and 3-*endo*- **136** and 5-*endo*-(6-chloro-3-pyridoxy)-methyl-2-azabicyclo[2.2.0]hexane **137** were synthesised using stereoselective photochemical ring closure of the appropriate dihydropyridine (**Scheme 5.3**).

Scheme 5.3

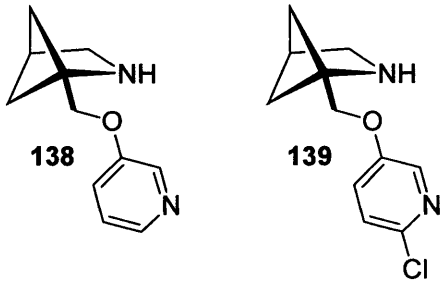


The targets were obtained using the Mitsunobu coupling reaction of the respective 2-azabicyclo[2.2.0]hexane alcohol with 2-chloro-5-hydroxypyridine. These compounds **135** (K_i = 14 nM), **136** (K_i = 2.3 nM), **137** (K_i = 12 nM) were found to be less effective as nicotinic agonists than epibatidine or tebanicline.[135]



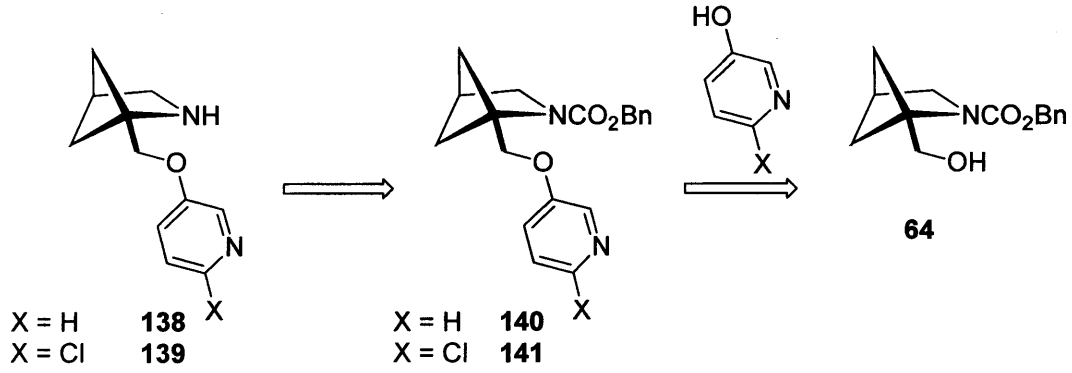
5.3 Synthesis of 2-Azabicyclo[2.1.1]hexane Pyridyl Ethers

The target compounds in our synthesis of 2-azabicyclo[2.1.1]hexane pyridyl ethers are **138** and **139**. These have the 3-pyridyl-ether and 2-chloro-5-pyridyl-ether heterocycles attached, therefore being analogues of A-85380 and tebanicline respectively. In the synthesis of these compounds we are also meeting one of our prime objectives, which is to increase the chain length in order to increase flexibility. In this range of compounds we have two atoms (C and O) in the bridge between the azabicyclic system and the heterocycle.



Retrosynthetic analysis of the route to the pyridyl ethers **138** and **139** is shown in **Scheme 5.4**. The secondary amino nitrogen of **138** and **139** was protected using a *N*-benzyloxy-carbonyl group to give **140** and **141** respectively. Compounds **140** and **141** were constructed by coupling the appropriate hydroxypyridine with the alcohol **64**.

Scheme 5.4



5.3.1 Calculation of Inter-nitrogen Distances

Molecular modelling studies revealing the inter-nitrogen distances for the lowest-energy conformations of **138** and **139** are summarised in **Table 5.1**.

Table 5.1

Compound	Minimum Energy Conformation (Å)	180° rotation (Å) of the heterocycle
Epibatidine	4.3	5.5
A-85380	5.9	6.2
Tebanicline (ABT-594)	5.9	6.2
138	6.2	6.3
139	6.2	6.3

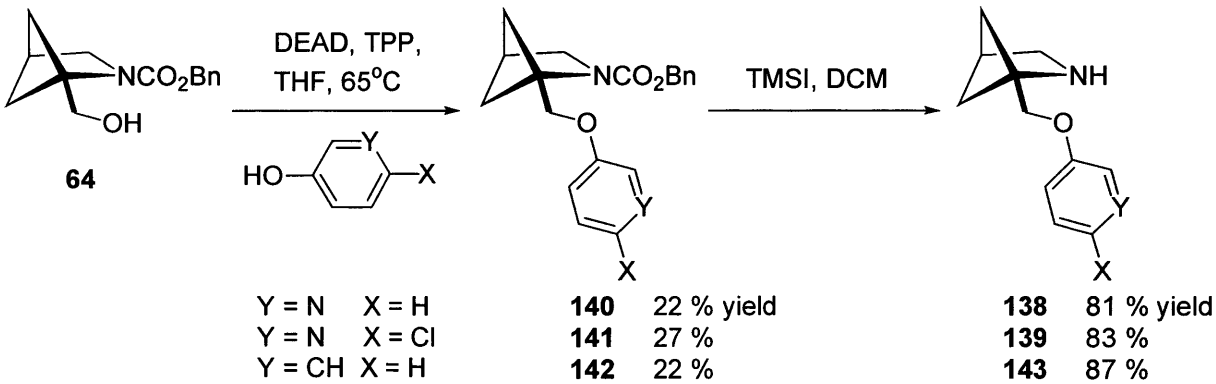
Although the calculated inter-nitrogen distances are larger than those of epibatidine, they resemble the distances for A-85380 and tebanicline very closely. It is therefore likely that **138** and **139** may show activity similar to the parent structures. It must also be taken into account that there is free rotation in these compounds, the C_7 arm on the 2-azabicyclo[2.1.1]-hexane system would enable a higher degree of flexibility when docking in the nicotinic acetylcholine receptor. Having the two atoms in the bridge between the bicyclic system and the heterocycle would also give extra flexibility once in the receptor, as opposed to traditional compounds that have heterocycles attached directly to the bicycle.

5.3.2 Mitsunobu Coupling on 2-Azabicyclo[2.1.1]hexane Alcohols

In order to establish the methodology in 2-azabicyclo[2.1.1]hexane systems, the Mitsunobu coupling reaction was first attempted with the primary alcohol **64** and phenol to form **142**. The protecting group was then easily removed on treatment with TMSI to give **143** (**Scheme 5.5**).

As this was successful the Mitsunobu coupling reactions and subsequent deprotections were repeated to produce **138** and **139**. The alcohol **64** was coupled with 3-hydroxypyridine and 2-chloro-5-hydroxypyridine giving **140** or **141** respectively.

Scheme 5.5



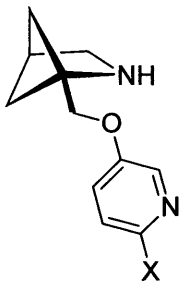
Although the yields for all the couplings reactions are modest, removal of the protecting group can be done without the need for purification and in high yield. This research on 2-azabicyclo[2.1.1]hexane shows that Mitsunobu coupling is possible despite the potential steric hinderance at this position.

Diisopropyl azodicarboxylate (DIAD) can be used instead of DEAD as an alternative Mitsunobu reagent.[127,128] It has the advantages of not being carcinogenic or explosive like DEAD. Alternative phosphine reagents include tributylphosphine which has the advantage of being less bulky than triphenylphosphine and hence may increase the yield as the primary alcohol in the 2-azabicyclo[2.1.1]hexane system is hindered. The disadvantage of tributylphosphine is that it will easily decompose when exposed to air, shortening the lifetime and capability of the reagent.[127,128] Overall we have successfully synthesised a range of compounds **138**, **139** and **143** which are to be tested in the near future for biological activity at nAChRs by our industrial collaborators. If any of these compounds show a high affinity or selectivity for nicotinic sub-types, this will form the basis for design of improved structural variants in this series.

5.4 Variation of Substituents in the Heterocycle; Future Research

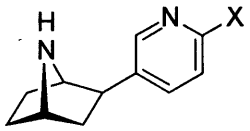
5.4.1 Bioisosteric Replacements

It is possible to replace the 2-chloro substituent of tebanicline with larger iodo or bromo substituents or with a smaller fluorine atom. Targets based on the 2-azabicyclo[2.1.1]hexane system include the iodo **144a**, bromo **144b** and fluoro **144c** substituents. Mitsunobu coupling can be used as before to form the targets from the appropriate hydroxypyridine.



144a X = I
144b X = Br
144c X = F

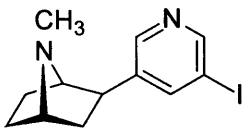
Substitution has already been performed on epibatidine where the 2-chloro moiety has been replaced by other groups and their pharmacological properties determined.[36,136,137,138] The chlorine atom has been replaced by fluorine, bromine and iodine **145a-c**, these modifications were found to have very little effect on the binding affinity for neuronal nAChRs in comparison with epibatidine, despite their different sizes. On the other hand, compounds that had amino or electron-donating groups **145d-f** on the 2-position were found to have a lower binding affinity and potency than epibatidine.



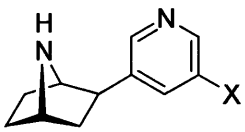
145

145a	X = F	**145d**	X = OH
145b	X = Br	**145e**	X = NH_2
145c	X = I	**145f**	X = $N(CH_3)_2$

Recent research by Carroll and co-workers[139] shows the synthesis of a series of 3′-substituted deschloroepibatidine analogues **146** and **147a-g**, these were found to have a high affinity for α4β2 nAChRs. The most potent compounds were the 3′-ethynyl **147g** (K_i = 0.02 nM) and 3′-fluoro **147a** (K_i = 0.037 nM) analogues. Overall, substitution with either an electron-donating or electron-withdrawing group at position-3 reduced the agonist potency.



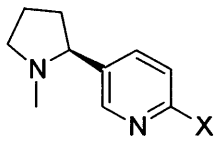
146



147

147a	X = F	**147e**	X = NH_2
147b	X = Cl	**147f**	X = -HC=CH_2
147c	X = Br	**147g**	X = -C≡CH
147d	X = I		

Similar modifications have yet to be reported on the azetidine or the 2-azabicyclo-[2.1.1]hexane ring systems but they may lead to an improvement in the binding affinity. The binding affinity and activity of racemic 6-substituted nicotine analogues have been reported.[1,140] Introduction of a chloro **148a**, bromo **148b** or methyl **148c** substituent at the 6-position of nicotine affords analogues showing similar affinity to that of nicotine at α4β2 nAChR sub-types. Compounds **148a** and **148b** were fifteen-fold more potent than nicotine.



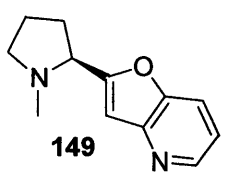
148

148a	X = Cl
148b	X = Br
148c	X = Me

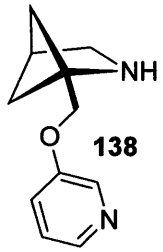
5.4.2 Constrained Analogues

A recent report describes the synthesis and pharmacology of furo[3,2-*b*]pyridinyl pyrrolidine analogues.[35,141,142] This type of ligand was designed from conformationally constrained 3-pyridyl ethers. Generally these were not as potent as the parent analogues of the 3-pyridyl ether series. The furo[3,2-*b*]pyridine **149** displayed a low binding affinity (K_i = 2.7 nM) for the α4β2 nAChR sub-types.

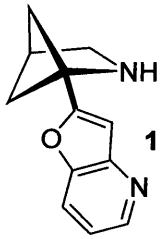
Conformationally constrained analogues could be synthesised in the 2-azabicyclo-[2.1.1]hexane ring system **150**. This could be accomplished by adopting the same methodology and may lead to an improved binding affinity.



149

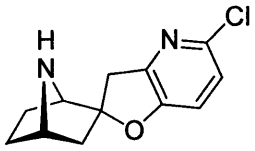


138

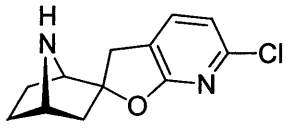


150

There have been further recent reports of the synthesis of constrained analogues of epibatidine.[143,144] The spirofuropyridine analogues of epibatidine *syn*-**151** and *anti*-**151** have a shorter and longer inter-nitrogen distances respectively. The binding studies show that *syn*-**151** (K_i = 136 nM) had a stronger binding affinity than *anti*-**151** (K_i = >1000 nM) for nAChRs.



syn- **151**



anti- **151**

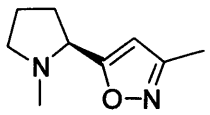
In conclusion, the Mitsunobu reaction has been effectively performed in order to synthesise a range of tebanicline analogue compounds; **138**, **139** and **143**. These compounds have a longer side-chain length, having two atoms. These promising ligands will be pharmacologically tested for activity at the nicotinic acetylcholine receptor. If these compounds show potential suggestions have also been made for further chemistry, these modifications may enhance the nicotinic activity.

Chapter 6

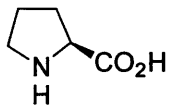
Methylisoxazole Formation in 2-Azabicyclo[2.1.1]hexane Systems

6.1 Research on ABT-418

The compound ABT-418[145,146] an isosteric analogue of nicotine, was synthesised at Abbott Laboratories. It possesses the characteristic 5-membered ring of nicotine with a methylisoxazole group replacing the pyridine heterocycle, the compound was synthesised from (*L*)-proline. ABT-418 was found to be a full agonist at α4β2 receptors (K_i = 10 nM), with improved selectivity compared to nicotine. Animal models show that administration of ABT-418 is capable in enhancing cognition and a reduction in side-effects compared to nicotine was observed.



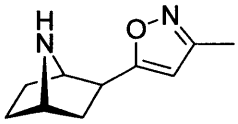
ABT-418



(*L*)-Proline

6.1.1 Synthesis of Epiboxidine

Epibatidine analogues have been synthesised which maintain the 7-azabicyclo[2.2.1]heptane structure, but have different heterocycles in place of the chloropyridyl ring. The aim of bioisosteric replacement of the chloropyridyl ring is to improve the subtype selectivity. One interesting analogue is (±)-epiboxidine, a hybrid of epibatidine and ABT-418, synthesised by Daly and co-workers[73] (See Chapter 2, Section 2.2).

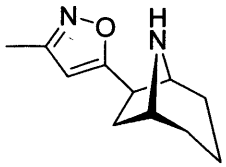


(±)-Epiboxidine

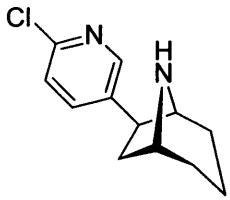
6.1.2 Synthesis of Homoepiboxidine

More recent research by Daly and co-workers[76] has replaced the chloropyridyl ring of (±)-homoepibatidine,[44] combining the interesting features of the azabicyclic system of homoepibatidine and the methylisoxazole heterocycle of epiboxidine. (±)-Homoepiboxidine (K_i = 0.74 nM) was found to have a slightly lower affinity compared with epiboxidine (K_i = 0.46 nM) and both of these were much lower than epibatidine (K_i = 0.093 nM). Homoepiboxidine variants having a *N*-methyl or *N*-benzyl group showed greatly reduced binding affinity (six-fold and forty-fold respectively). (±)-Homoepiboxidine was found to have a similar potency to (±)-epiboxidine and was less toxic than epibatidine.[76] (±)-Homoepibatidine synthesised at Leicester,[44] was also found to be slightly less active than epibatidine. Both (+)-homoepibatidine (K_i = 0.35 nM) and (-)-homoepibatidine (K_i = 0.13 nM) have a higher affinity than epiboxidine. (±)-*Bis*-Homoepibatidine (K_i = 1.25 nM) was

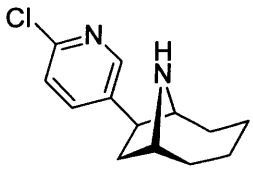
found to have a low affinity due to an increase in the size of the larger bridge of the bicyclic system to four carbon atoms.[34,44] Overall, the relationship between (±)-homoepiboxidine and (±)-epiboxidine is similar to that of (±)-homoepibatidine with epibatidine. In both cases, as the ring size increases the affinity is reduced.



(±)-Homoepiboxidine

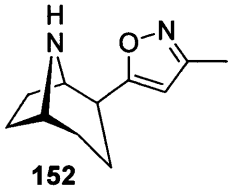


(±)-Homoepibatidine

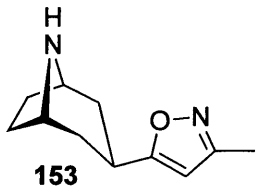


(±)-*Bis*-Homoepibatidine

Further epiboxidine homologues have also been synthesised on the 8-azabicyclo[3.2.1]octane system with the methylisoxazole substituted at the 2β- **152** and 3β- **153** positions. Both **152** (K_i = 3.0 nM) and **153** (K_i = 148 nM) were found to have a lower binding affinity than homoepiboxidine.[147]



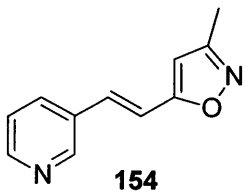
152



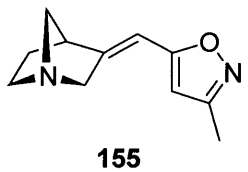
153

6.2 Research on Epiboxidine Analogues

Recently, methylisoxazole analogues have been constructed from pyridyl-substituted α,β-unsaturated esters.[148] Biological testing has established the antinociceptive properties of a range of these compounds, where **154** was found to be the best in the series. Using α,β-unsaturated esters as a precursor to methylisoxazole synthesis offers a solution to the problem of removal of the α-carbonyl proton during base treatment (See Chapter 2, Section 2.6.1).



154

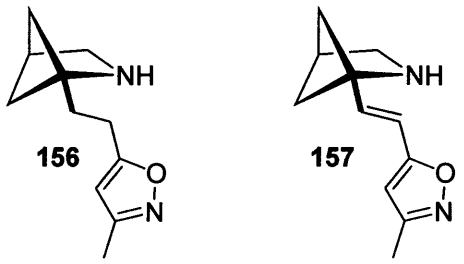


155

The synthesis of quinuclidine systems[29] (in which the bicyclic nitrogen is at the bridgehead position), having a methylisoxazole heterocycle attached by an alkene to the bicyclic ring has been reported; an example is provided by **155**.

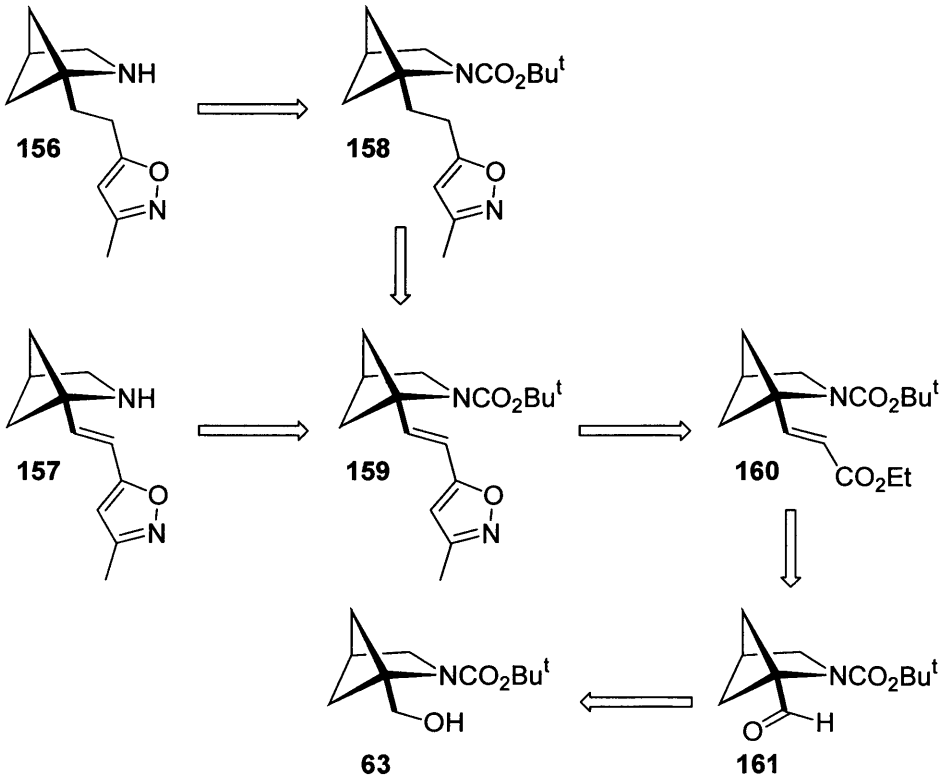
6.3 Synthesis of Target Compounds 156 & 157

The targets in our synthesis of 2-azabicyclo[2.1.1]hexane epiboxidine analogues are **156** and **157**. These have the methylisoxazole heterocycle attached, by a *bis*-methylene chain in the case of **156** and by an ethene-group in the case of **157**. In the synthesis of these compounds we are also meeting two of our objectives, which is to increase the chain length and to demonstrate the use of a Boc protecting group at nitrogen. These compounds offer potential flexibility when docking in the receptor, although there is greater conformational restriction in the case of **157**.



Retrosynthetic analysis for **156** and **157** is shown in **Scheme 6.1**. The target **156** is protected using a Boc group to give **158**. The bridge between the bicyclic system and methylisoxazole is converted to the alkene methylisoxazole **159**.

Scheme 6.1

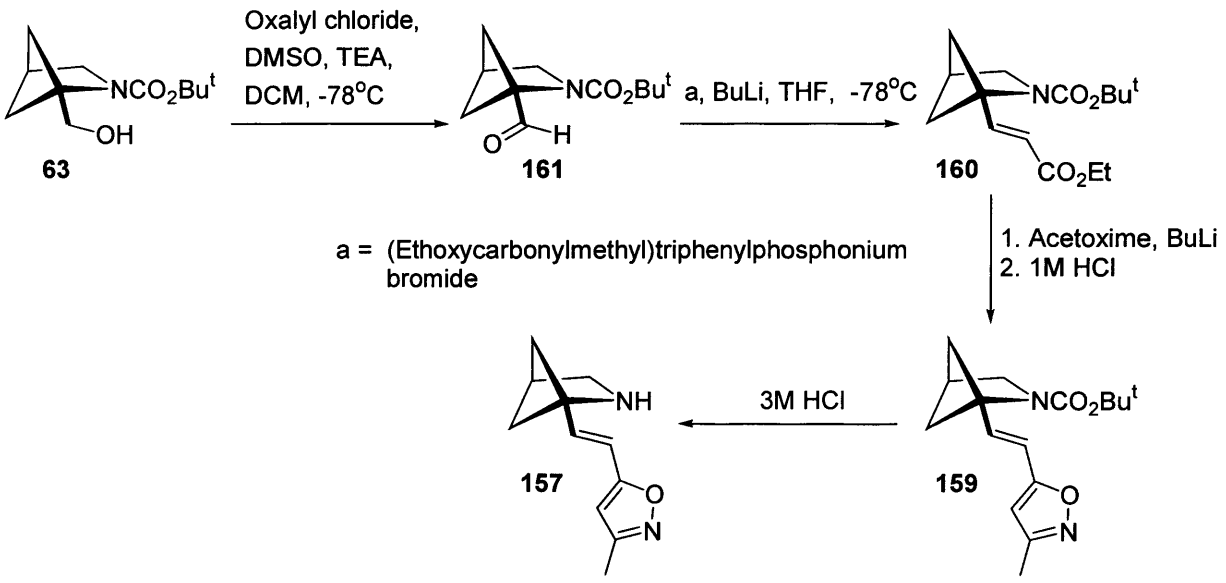


The target **157** can be protected as before using a Boc protecting group to give **159**. The methylisoxazole ring is constructed from the α,β-unsaturated ethyl ester **160**, which is synthesised from the aldehyde **161**. The synthesis starts from the Boc protected alcohol **65**, described in Chapter 2, Section 2.9.1.

6.3.1 Synthesis of Target Compound 157

The Boc-protected alcohol **65** was oxidised to form the aldehyde **161** at the bridgehead position using a Swern oxidation in 97 % yield. Wittig methodology[149,150,151] was then employed to form the α,β-unsaturated ester **160** in 24 % yield. The α,β-unsaturated methylisoxazole **159** was then constructed using the method of Daly and co-workers[76] in 30 % yield. Deprotection of the Boc group with 3M hydrochloric acid gave the desired product **157** in 97 % yield (**Scheme 6.2**). Evidence from ^{1}H NMR shows the construction of the methylisoxazole heterocycle in **159**. The singlet at δ 2.21 corresponds to the methyl group and the singlet at δ 5.95 is the olefinic proton in the ring system. The *J*-coupling of 16 Hz confirms that the structure is *trans*.

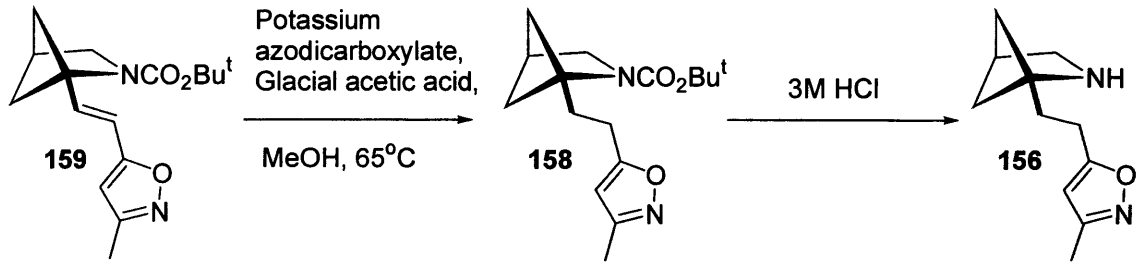
Scheme 6.2



6.3.2 Synthesis of Target Compound 156

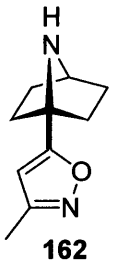
The double bond of **157** was selectively reduced using potassium azodicarboxylate to give the saturated methylisoxazole **158** in 34 % yield. Removal of the Boc group as before gave **156** in a yield of 99 % (**Scheme 6.3**). To summarise, synthesis of the methylisoxazole compounds **156** and **157**, has been achieved successfully.

Scheme 6.3



6.4 Attachment of a Methylisoxazole at the Bridgehead Position

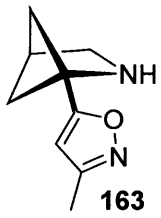
Another method to avoid enolisation during construction of the methylisoxazole is to incorporate this heterocycle directly at the bridgehead position. The methylisoxazole has been incorporated at the bridgehead position of the 7-azabicyclo[2.2.1]heptane system **162**,[75] but this ABT-418 analogue was found to have a low affinity at the nAChR compared to ABT-418 itself due to lack of flexibility and rigidity. Work by Piotrowski[72] has described compounds containing a range of pyridyl heterocycles at the bridgehead position of 2-aza-bicyclo[2.1.1]hexanes.



162

6.4.1 The Target Bridgehead Methylisoxazole Compound

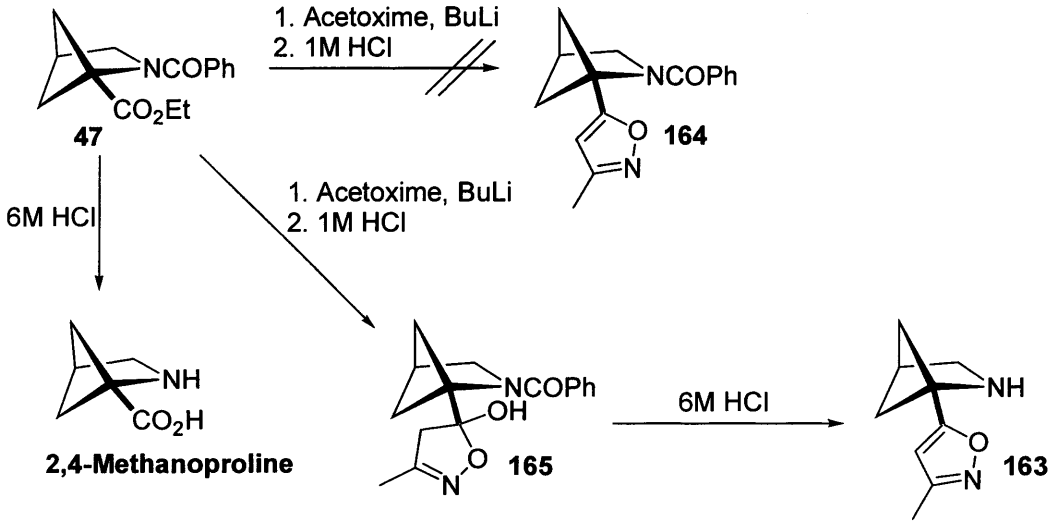
The target bridgehead methylisoxazole compound of the 2-azabicyclo[2.1.1]hexane system is **163**. This has the heterocycle directly attached at the C_1 carbon, similar to the research of Avenoza[75,152] and Piotrowski.[72]



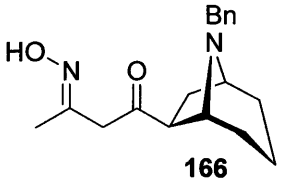
163

The bridgehead ethyl ester compound **47** was formed as described before (Chapter 2, Section 2.3) and the methylisoxazole synthesis was attempted in the hope of making **164** (**Scheme 6.4**). Bizarrely, we isolated the novel intermediate **165** (61 % yield, based on recovered material) instead; such a non-aromatised intermediate has not been reported before during methylisoxazole synthesis. The synthesis of **165** was confirmed by X-ray crystallography, which showed hydrogen bonding between the carbonyl-oxygen and hydrogen from the alcohol, hence forming a seven-membered ring (**Figure 6.1**). The stabilisation provided by hydrogen bonding is thought to be the reason for the fascinating observation that **165** can be isolated. The treatment of **47** with 6M hydrochloric acid would produce 2,4-methanoproline as publicised in its total synthesis.[54,55] Therefore, using this principle, **165** was converted into the target **163**, allowing both elimination and deprotection of the nitrogen in the same step.

Scheme 6.4



Daly and co-workers[76] have reported the isolation of other minor by-products including; β-ketooxime **166** and dimethylpyridyl *N*-oxide **167**, in the synthesis of homoepiboxidine but there are no reports of compounds akin to **165**.



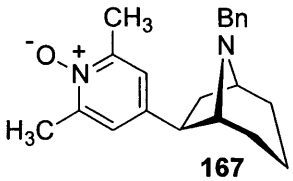
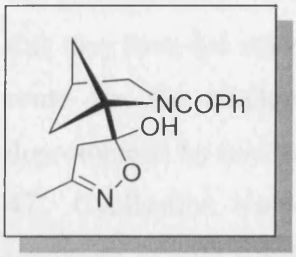
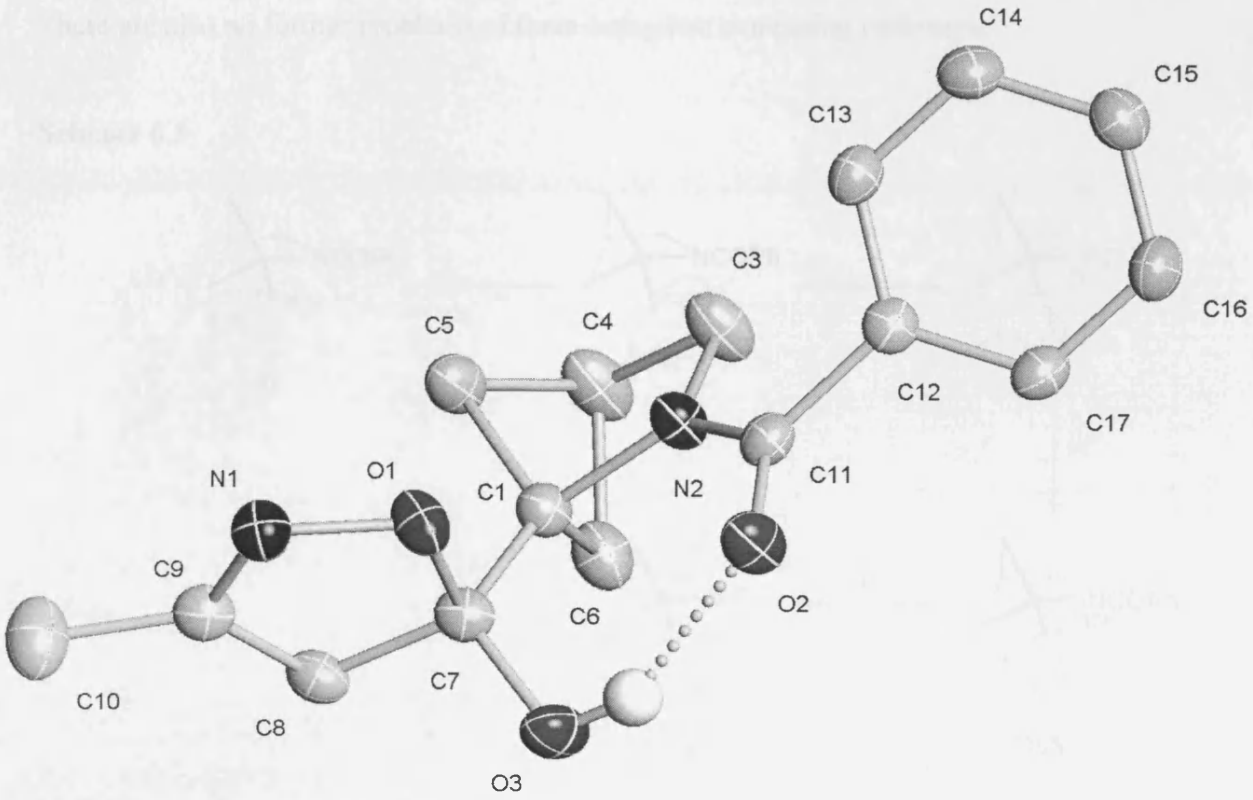


Figure 6.1 X-ray crystal structure of **165**

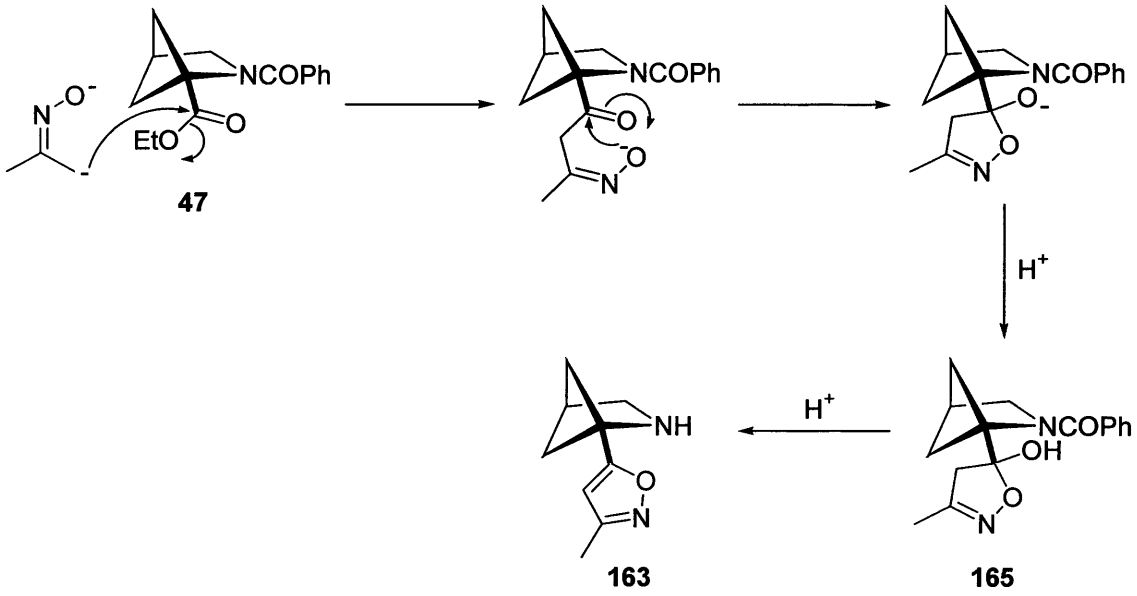




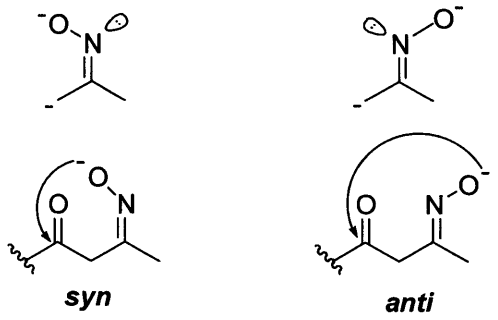
6.4.2 Mechanism of Methylisoxazole Synthesis

In the synthesis of **165**, 1M hydrochloric acid was used which was not sufficient to induce the elimination of water. It may well be that if 10M hydrochloric acid had been used instead; this may have led straight to **163**. However, the synthesis of **165** allows us to understand the route for the mechanism of methylisoxazole synthesis (**Scheme 6.5**). Acetoxime is deprotonated by *tert*-butyllithium to form the dianion to attack the carbonyl of the ethyl ester **47**. Cyclisation would occur from the deprotonated oxygen of the acetoxime and hence treatment of acid would eventually produce **163** *via* intermediate **165**. As the ester **47** is at the bridgehead position there are no problems of protons α-to the carbonyl being removed. There are also no further problems of there being two competing pathways.

Scheme 6.5



Methylisoxazole formation also depends upon how acetoxime is deprotonated. It may deprotonate either the *syn-* or *anti-* oxime -OH. If *syn* deprotonation occurs, then in the cyclisation step the deprotonated oxygen of acetoxime has a shorter distance to cyclise with no steric hinderance. On the other hand, *anti* deprotonation would mean a longer distance to cyclise, and methylisoxazole formation is unlikely to occur. The energy barrier between *syn-* and *anti-* is too great for any inversion to occur. This may well be a fundamental factor to explain why the yields observed for methylisoxazole synthesis are always less than 50 %. It would also explain the fact why Daly[76] in the synthesis of homoepiboxidine retrieved some β-ketooxime **166** which had failed to cyclise to form the methylisoxazole heterocycle.



6.5 Calculation of Inter-nitrogen Distances

Molecular modelling studies reveal the inter-nitrogen distances for the lowest-energy conformations of **156**, **157** and **163** summarised in **Table 6.1**.

Table 6.1

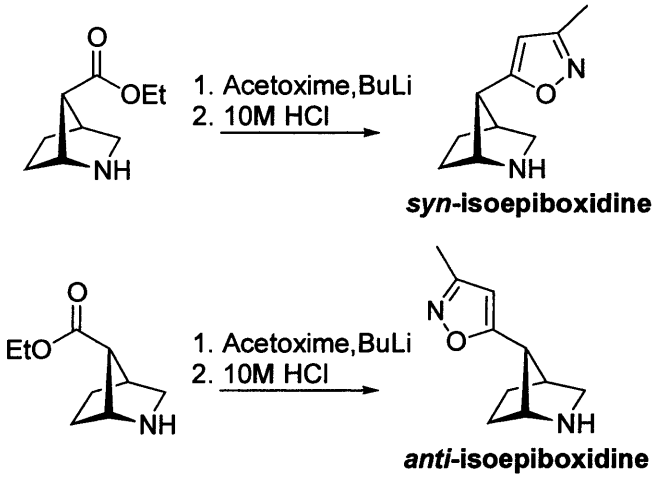
Compound	Minimum Energy Conformation (Å)	180° rotation (Å) of the heterocycle
Epiboxidine	4.2	5.2
ABT-418	4.3	4.7
156 (n = 2)	5.8	6.6
157 (n = 2)	6.4	6.6
163 (n = 0)	4.2	4.4

The calculated inter-nitrogen distances for both **156** and **157** are much larger than for epiboxidine and ABT-418. Due to rotation and flexibility in **156** a more favourable inter-nitrogen distance should be obtained. The values for both rotamers of **157** are similar due to limitations of rotation. As expected the inter-nitrogen distance for both rotamers of target **163** was calculated to be similar to ABT-418.

6.6 Methylisoxazole Synthesis with a Secondary Amino-nitrogen

Recently published work from the Malpass group[153] on the 2-azabicyclo[2.2.1]heptane system shows that methylisoxazole formation can be achieved at the C_7 position without the need to protect the bicyclic nitrogen first (**Scheme 6.6**).

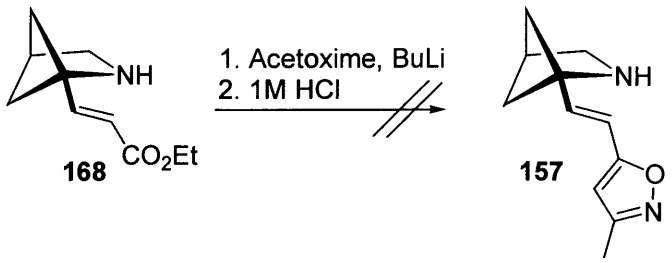
Scheme 6.6



Protection of the secondary amino-nitrogen was thought to be an essential feature prior to this observation. Both *syn-* (26 % yield) and *anti-* isoepiboxidine (24 % yield) have been synthesised using this methodology, which clearly reduces the number of steps involved by avoiding protection and deprotection of the nitrogen. Pharmacological testing of *syn-* and *anti-* isoepiboxidine showed that as anticipated, *syn*-isoepiboxidine had a high affinity for the α4β2 (K_i = 0.76 nM) and α3β4 (K_i = 9.51 nM) sub-types, while *anti*-isoepiboxidine had a weak binding affinity for the α4β2 (K_i = 1000 nM) and α3β4 (K_i = 1000 nM) subtypes due to the increased inter-nitrogen distance.

This novel approach was attempted on the 2-azabicyclo[2.1.1]hexane system. The α,β-unsaturated ethyl ester **160** was converted into the secondary amine **168**, but methylisoxazole formation on this was unsuccessful (**Scheme 6.7**). Neither the expected product **157** or starting material was obtained. This observation shows that methylisoxazole formation on a secondary amino-nitrogen may not possible in all azabicyclic systems.

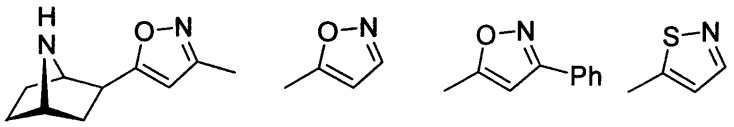
Scheme 6.7



6.7 Variation of Substituents in the Heterocycle; Future Research

6.7.1 Bioisosteric Replacements

Current publications,[36,154] show attempts in the modification of the methylisoxazole heterocycle, in epiboxidine. Both the unsubstituted isoxazole containing isostere **169a** (K_i = 3.17 nM) and the 3-phenylisoxazole **169b** (K_i = 147 nM) showed a lower binding potency compared to epiboxidine showing that the removal of the methyl group or addition of a larger substituent greatly decreases binding affinity at the nAChR. Further work[155] shows that the replacement of the oxygen with a sulphur to form a 2-thiazolyl group **169c** (K_i = 5800 nM) reduces binding even more leading to very low affinity for nAChRs.



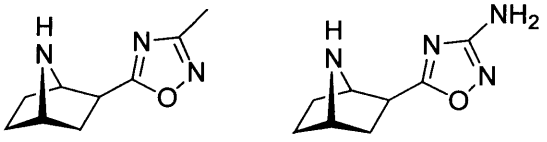
(±)-Epiboxidine **169a** **169b** **169c**

6.7.2 Further Structural Variations

A series of quinuclidine-based ligands **170** and **171** for the muscarinic cholinergic receptor has been synthesised containing the 1,2,4-oxadiazole heterocycle.[156] It was correctly anticipated that increasing the hydrogen-bonding of the 1,2,4-oxadiazole in going from **170** to **171** would improve the efficacy of the ligand by increasing binding. The *in vitro* binding data found **171** to be one of the most efficacious and potent muscarinic agonists known.

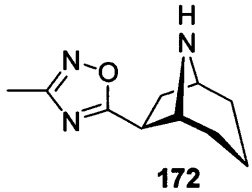
170 **171**

Ellis and co-workers[157] synthesised CMI-936 and CMI-1145 which are potent antinociceptive agents at the acetylcholine muscarinic receptors. Both these structures have a 1,2,4-oxadiazole ring attached to the bicycle in an *exo* configuration.



CMI-936 **CMI-1145**

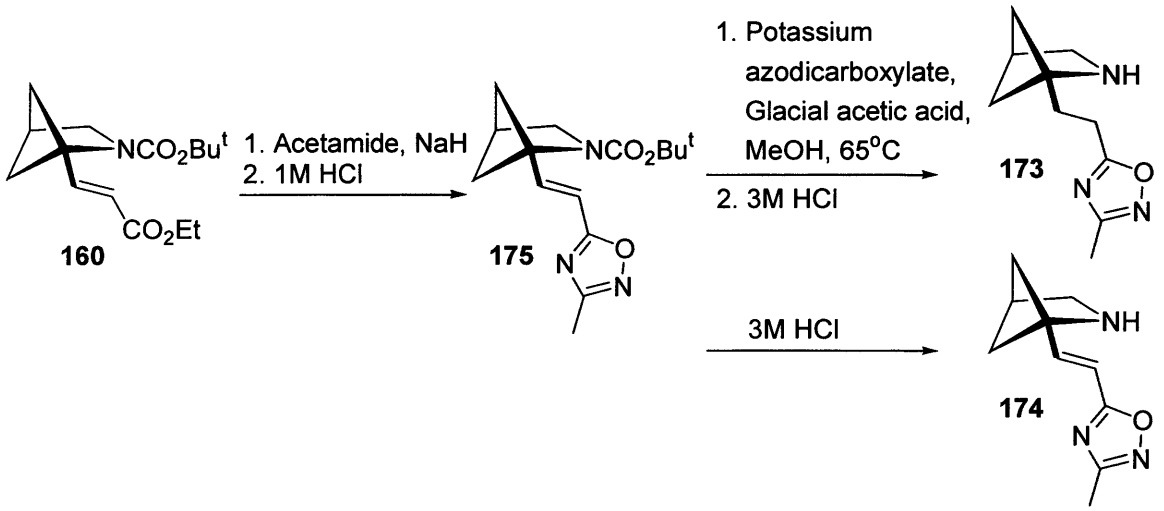
The Daly group[76] have synthesised the methyloxadiazole **172** (K_i = 11 nM) which had a low affinity for the neuronal receptors and very low affinity for ganglionic-type receptors.



172

The same procedure[76] to construct the 1,2,4-oxadiazole heterocycle could be used to synthesise the compounds **173** and **174** on the 2-azabicyclo[2.1.1]hexane system. The α,β-unsaturated ethyl ester **160** could be used to construct the methyloxadiazole ring using acetamide oxime and sodium hydride, forming **175**. Compound **175** could then be taken on to form the targets **173** and **174** using established methodology (**Scheme 6.8**).

Scheme 6.8



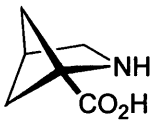
Overall, a range of methylisoxazole compounds have been synthesised on the 2-azabicyclo-[2.1.1]hexane system, with differing number of carbon atoms in the chain; **163** (n = 0), **55** (n = 1), **156** (n = 2 alkane) and **157** (n = 2 alkene). The contrast between **156** and **157** may be interesting once pharmacological testing has been conducted, as this gives a direct comparison of restricted rotation and free-rotation. These will be tested in the future for biological activity at nAChRs by our industrial collaborators. The X-ray crystal structure of the intermediate **165** was found to be a useful key compound used to investigate the mechanism of methylisoxazole formation. Further suggestions have been made on modifications and variations in the methylisoxazole heterocycle. These experiments can easily be conducted to generate more compounds in the library of 2-azabicyclo[2.1.1]hexane system nAChR ligands.

Chapter 7

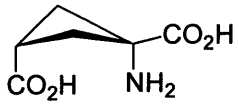
Synthesis of a 2,4-Methanoproline Homologue

7.1 Further Research on 2,4-Methanoproline Derivatives

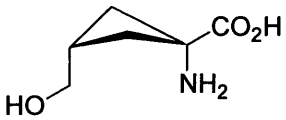
Bell and co-workers[158] working in the Santa Rosa National Park in Costa Rica, isolated two new amino acids found in the seeds of the legume *Ateleia herbert smithii*. Analysis by X-ray crystallography showed the structures to be 2,4-methanoproline and 2,4-methanoglutamic acid. Also isolated were the hydroxyl amino acid **176** and 2,4-methanopyroglutamic acid, which is believed to be an intermediate in the biosynthesis of the three amino acids. The nonproteinogenic amino-acid 2,4-methanoproline has strong antifeedant activity and protects the seeds of this plant against over 100 predators in its natural habitat.[158]



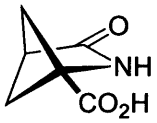
2,4-Methanoproline



2,4-Methanoglutamic acid



176



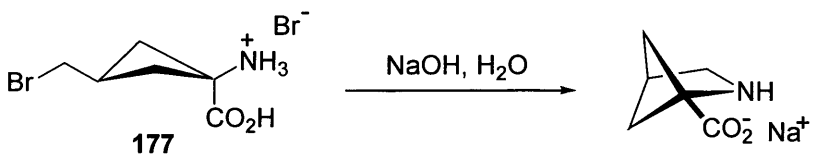
2,4-Methanopyroglutamic acid

The syntheses of all four compounds has been achieved in the laboratory.[69] As described earlier (Chapter 2, Section 2.1.1) for the total synthesis of 2,4-methanoproline both the Pirrung[54] and the Clardy[55] methods use the intramolecular [2+2] photocycloaddition as the key step.

7.1.1 2,4-Methanoproline Analogues

Another method for the synthesis of 2,4-methanoproline uses an intramolecular nucleophilic substitution as the key step for the formation of the bicyclic skeleton.[159] The 3-bromomethyl-cyclobutanyl amino acid **177** was refluxed in sodium hydroxide which converted it into 2,4-methanoproline in 91 % yield after recrystallisation (**Scheme 7.1**).

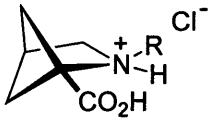
Scheme 7.1



177

The total synthesis was achieved in 5 steps in an overall 10 % yield. Stevens *et al.*[159] mention that this method could be used for large-scale synthesis, where previous methods have been problematic.

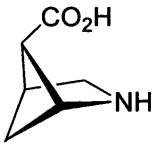
This procedure has been replicated to synthesise a series of 2,4-methanoproline analogues.[56] Recent research by Stevens and co-workers[160] depicts 2,4-methanoproline derivatives **178** being utilised as insect repellents and antifeedants against leaf- and seed-feeding pest insects. As a result, the 2-azabicyclo[2.1.1]hexane system can be used to synthesise compounds in this area of chemistry as well as construct epibatidine analogues in the search for high affinity and high subtype selectivity at the nAChR.



R = isopropyl, *sec*-butyl, allyl, *tert*-butyl, *n*-propyl or benzyl

178

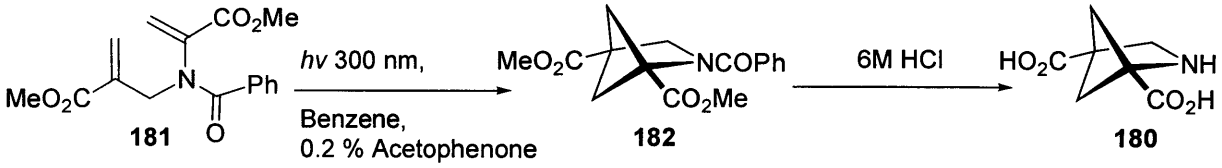
The synthesis of constrained amino acids and modified peptides with biological activity is becoming an increasingly well-investigated and competitive area of organic chemistry. Research by Huet and co-workers[58] recorded the synthesis of the first β-isomer of 2,4-methanoproline **179** in a laborious 18 step sequence. Their strategy involved the ring closure of a cyclobutane intermediate to form the 2-azabicyclo[2.1.1]hexane system.



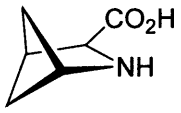
179

Subsequently, the Esslinger group[161] used the Pirrung[54] method to synthesise 2,4-methano-pyrrolidine-2,4-dicarboxylic acid **180** (82 % yield) by irradiation of the amide **181** and then hydrolysis of the photoadduct **182** (**Scheme 7.2**). The dicarboxylic acid **180** was found to act as a substrate for glutamate uptake.[52]

Scheme 7.2



Recently, Krow and co-workers[162] have synthesised 3,5-methanoproline **183** which has its potential uses in the study of conformational effects on collagen stability. Further work[163] shows the synthesis of the 5-*syn*- **184** and 5-*anti*-carboxy-2,4-methanopyrrolidines **185** using the photocycloaddition method to synthesise the 2-azabicyclo[2.1.1]hexane ring system. These compounds are thought to be precursors for a wide array of novel 2,4-methano-pyrrolidines.



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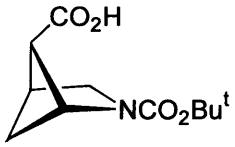

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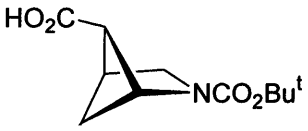
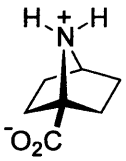


185

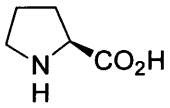
A 2,4-methanoproline analogue **186** has been synthesised on the 7-azabicyclo[2.2.1]heptane system at the bridgehead position, this restricted analogue was synthesised in five steps. In future work the authors hope to introduce the restricted analogue into small peptides.[164]



186

7.1.2 2,4-Methanoproline in Conformationally Restricted Peptides

The naturally occurring 2,4-methanoproline has been used in the area of peptidomimetics as a constrained counterpart of (*L*)-proline to study its conformational properties in peptides.[165,166,167] The effect of replacing (*L*)-proline with 2,4-methanoproline on the tertiary peptide bond *cis*/*trans* equilibrium has been investigated in small peptides using NMR spectroscopy (**Scheme 7.3**).

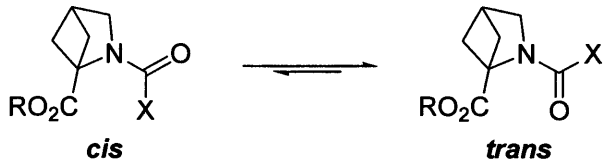


(*L*)-Proline

The peptide residues studied were *N*-acetyl-2,4-methanoproline-*N'*-methylamide (Ac-2,4-MePro-NHMe) and *N*-acetyl-$_L$-Tyrosine-2,4-methanoproline-*N'*-methylamide (Ac-$_L$-Tyr-2,4-MePro-NHMe). In aqueous solution the (*L*)-proline peptides exists as an equilibrium mixture of isoenergetic *cis* and *trans* conformers. The replacement by 2,4-methanoproline resulted in less flexibility in selective stabilisation of the *trans* tertiary peptide bond conformation. This

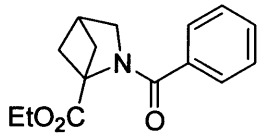
was confirmed by NOESY experiments. The results suggest that the more rigid 2,4-methanoproline may be a useful (*L*)-proline analogue for polypeptide molecular design.[165]

Scheme 7.3



Research by the same group[166,167] using solid state X-ray crystallography and theoretical conformational energy analysis of the peptides show evidence in support of their assumptions.

Our own research[68] indicates preference for the *trans* rotamer of **47** (**Figure 2.5**). Compound **47** is a precursor of 2,4-methanoproline.

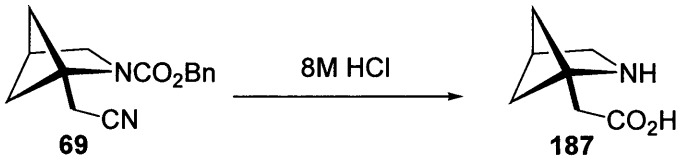


47

7.1.3 Synthesis of a 2,4-Methanoproline Homologue

The recent interest in 2,4-methanoproline has led us to synthesise the novel homologue, the β-amino acid **187**, by hydrolysis of the 1-cyanomethyl derivative **69** (**Scheme 7.4**).[68] The synthesis of **187** can be achieved in a total of 9 steps.

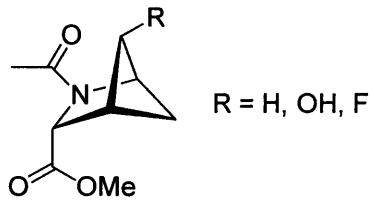
Scheme 7.4



69 **187**

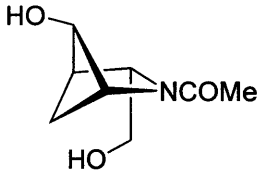
The crude hydrochloride salt was isolated directly in good yield after hydrolysis. Ion-exchange chromatography provided the crystalline amino acid **187**. On the basis, of work by Kite *el al.*[168] this β-amino acid could be tested biologically for its properties towards crop protection. In the area of peptidomimetics it would be fascinating to incorporate the 2,4-methanoproline homologue **187** into peptides as a proline constrained analogue and to study the resulting conformational effects.[165,166,167]

Consequently, Krow and co-workers[169] have synthesised a range of substituted 2-azabicyclo-[2.1.1]hexanes **188** as constrained proline analogues and studied the implications of the enforced conformational restrictions for collagen stability. These sets of compounds have been used to construct small peptides and their conformations studied.

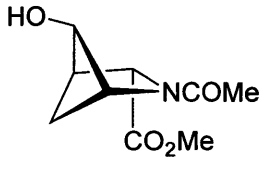


188

The latest published research by the Krow group[170] shows the synthesis of further derivatives of **184**. An alternative rearrangement route was employed to construct the 3-carboxy- **189** and 3-hydroxymethyl-2-azabicyclo[2.1.1]hexanes **190**, increasing the range of potential bioactive compounds.



189



190

In conclusion, we have synthesised the novel β-amino acid homologue **187**. Recent innovations in peptide chemistry and the development in proline analogues may prove **187** valuable. Collagen is the most abundant protein in animals.[171] For instance, collagen constitutes of one-third of all the protein in humans and three-quarters of the weight of human skin. Raines and co-workers[171] found that alternations in the *trans/cis* ratio arise from changes in ring pucker, it was deduced that pyrrolidine ring pucker is a key feature of the stability present in proline residues on collagen. As part of future studies in this interesting area, it may be possible to develop similar studies based on **187** or its many derivatives.

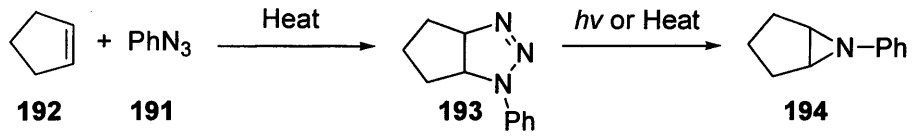
Chapter 8

Synthesis of Phenyl Aziridine Heterocycles

8.1 Synthesis of Phenyl Aziridine Heterocycles

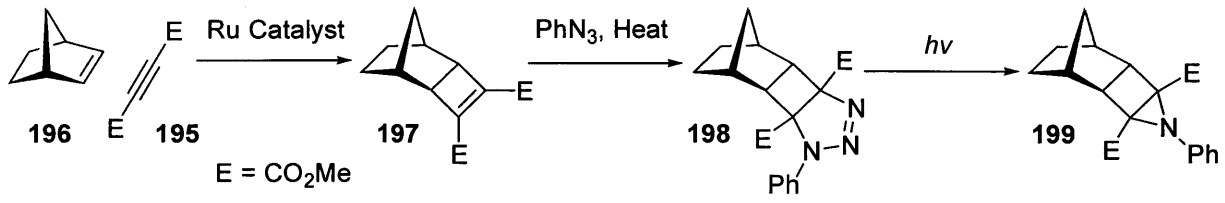
There are many examples in the literature[172,173,174] involving the 1,3-dipolar cycloaddition reaction of azides such as phenyl azide **191** with olefins **192** (**Scheme 8.1**). The cycloaddition forms the 1,2,3-triazoline **193**, reactions often require elevated temperatures. Triazolines are used to synthesise aziridines (e.g. **194**) by either photolytic or thermal elimination of nitrogen.[172]

Scheme 8.1



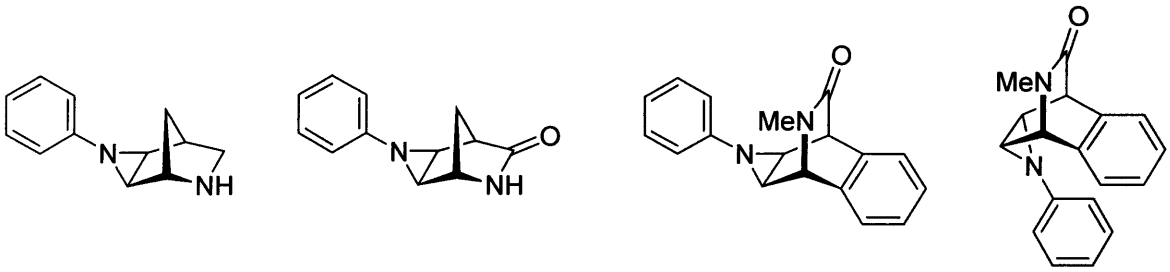
Work by Mitsudo and co-workers[175] shows the ruthenium-catalysed addition of dimethyl-acetylenedicarboxylate **195** to an olefin **196** forms cyclobutene 1,2-diesters **197**. A subsequent high-pressure 1,3-dipolar reaction with phenyl azide resulted in the formation of 1,2,3-triazoline cycloadducts **198**. Photochemical loss of nitrogen gave aziridines **199** in high yield (**Scheme 8.2**). These compounds have been reacted further in order to synthesise 7-azanorbornane systems to study the effect of *N*-hybridisation[176,177] and to study nitrogen inversion barriers using ^{15}N chemical shifts.[178]

Scheme 8.2



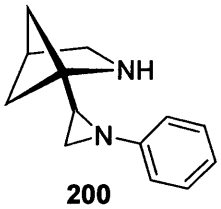
More recently work at Leicester[179] has demonstrated the synthesis of a range or aziridine compounds based on the 2-azabicyclo[2.2.1]hept-5-ene, 2-azabicyclo[2.2.1]hept-5-ene-3-one and 2-azabicyclo[2.2.2]oct-5-ene-3-one ring systems. These were formed by reaction of the appropriate bicyclic alkene compound with phenyl azide followed by photolysis of the respective 1,2,3-triazolines (**Figure 8.1**).

Figure 8.1 Phenyl aziridine compounds synthesised at Leicester



8.2 Phenyl Aziridine; A Novel Heterocycle

It was envisaged that the target compound **200** could be synthesised as a potential nAChR ligand. Although the nitrogen is not part of an aromatic heterocycle like other epibatidine analogues, it has the potential for some overlap between the nitrogen lone-pair and the phenyl ring (as in aniline). Synthesis of this type of compound as a potential epibatidine analogue is a novel idea; there are no previous reports of its use as a nAChR ligand in the literature.

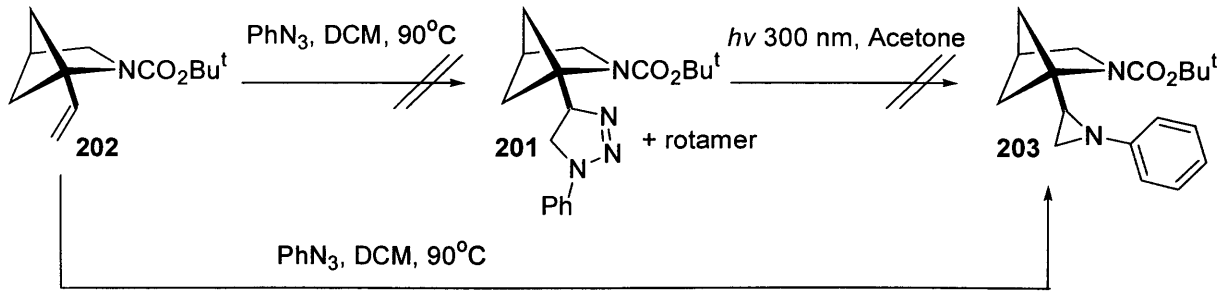


200

8.2.1 Construction of Phenyl Aziridine at the Bridgehead Position

Using previous methodology,[179,180] we attempted to form the 1,2,3-triazoline **201** from the reaction of alkene **202** and phenyl azide in DCM using a reactivial system. The subsequent product (thought to be **201**) was isolated and irradiated under ultraviolet light, but strangely only unchanged material was obtained. The loss of nitrogen is known to be a straightforward step both thermally and photolytically and it was deduced that **203** had formed directly from **202** in a thermal reaction, without isolating the 1,2,3-triazoline intermediate **201** (**Scheme 8.3**).[181,182]

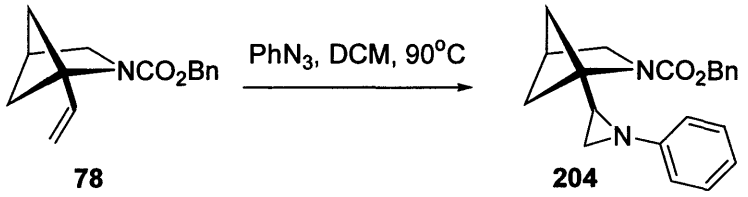
Scheme 8.3



An X-ray crystal structure (**Figure 8.2**) proved our assumptions to be correct. The thermal reaction provides **203** directly as the sole product. The synthesis of phenyl aziridines thermally from 1,2,3-triazolines, as well as the synthesis of a mixture phenyl aziridine and 1,2,3-triazoline compounds from the initial reaction of the olefin and phenyl azide has been reported.[173]

The phenyl aziridine synthesis was repeated for the *N*-benzyloxycarbonyl protected system. Once more the reaction of the alkene **78** with phenyl azide formed the phenyl aziridine **204**, without isolation of the intermediate triazoline (**Scheme 8.4**). The ^{1}H NMR spectra for both the aziridine compounds **203** and **204** have a distinctive pattern.

Scheme 8.4

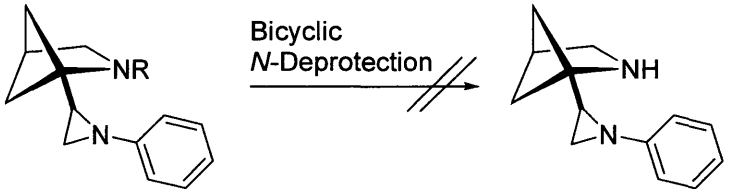


78 **204**

8.2.2 Attempts at Nitrogen-deprotection

Attempts at nitrogen deprotection for both **203** and **204** were unsuccessful and the target **200** was not obtained (**Scheme 8.5**). A range of standard nitrogen-deprotection methods was employed.[183,184]

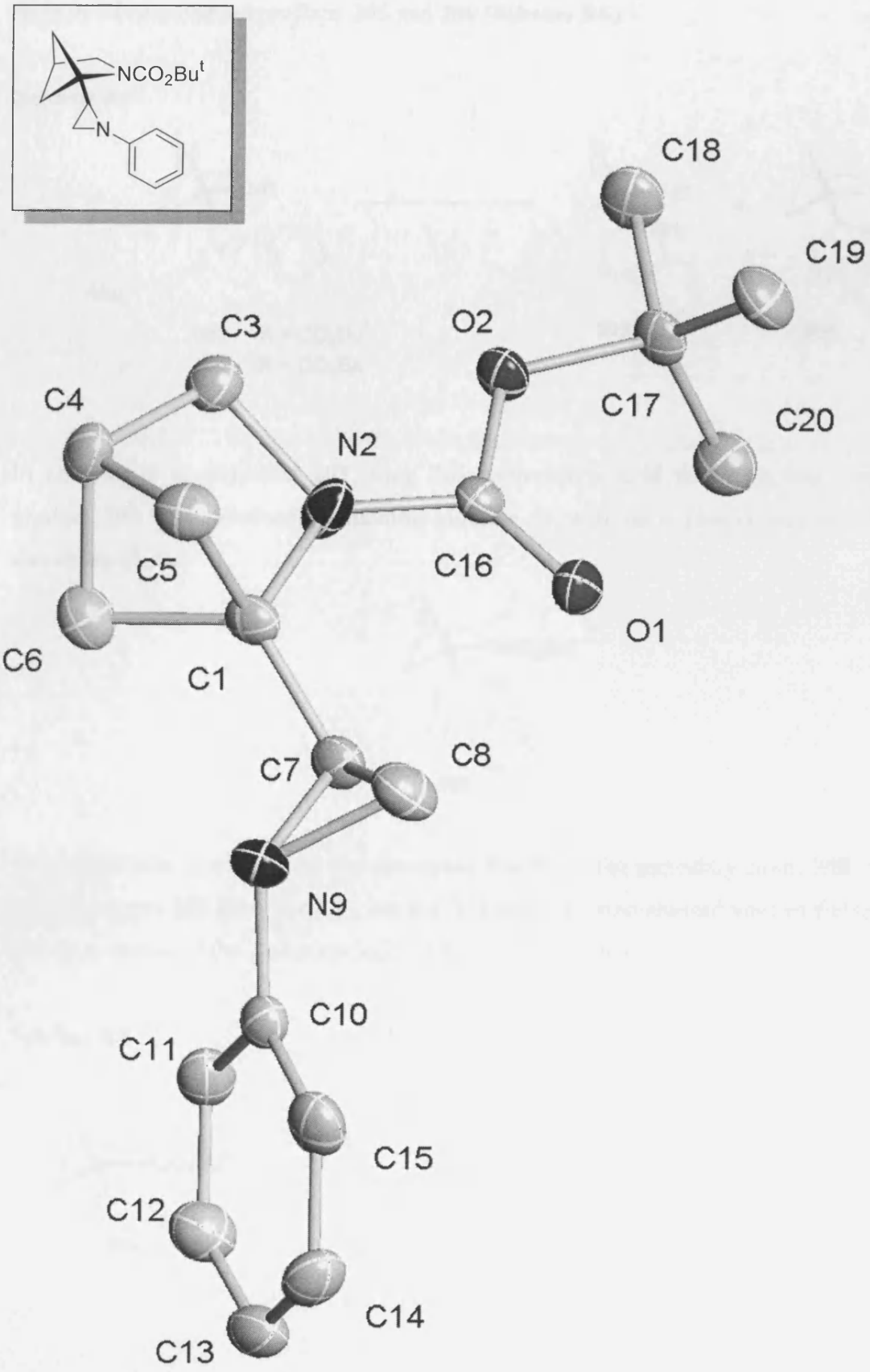
Scheme 8.5



203 R = CO_2Bu^t
204 R = CO_2Bn

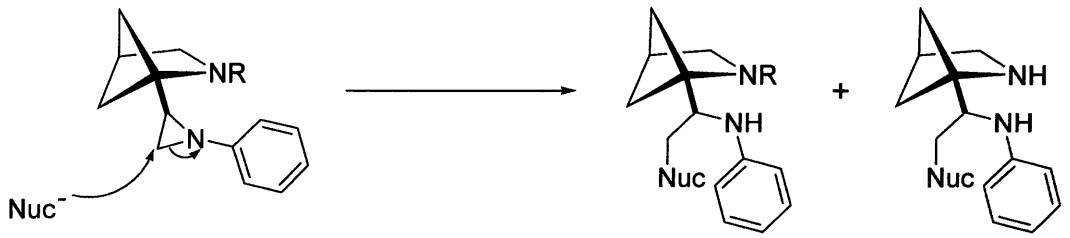
200

Figure 8.2 X-ray crystal structure of **203**



Many laborious attempts were made to try to form the target **200**. In all attempts, the reagent acted as a nucleophile opening the highly strained phenyl aziridine ring system, resulting in a mixture of ring-opened products **205** and **206** (**Scheme 8.6**).

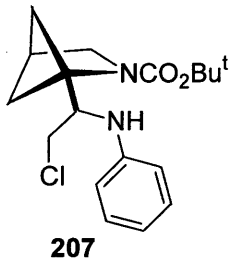
Scheme 8.6



203 R = CO_2Bu^t
204 R = CO_2Bn

205 **206**

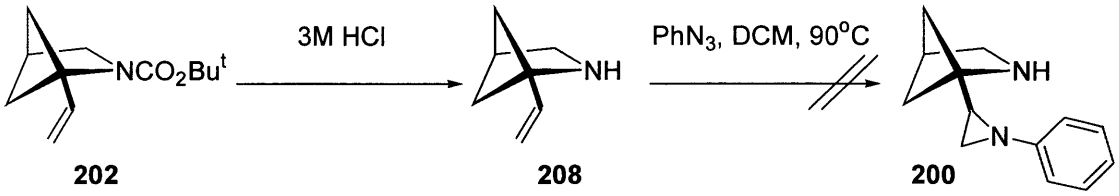
In an attempt to deprotect **203** using 3M hydrochloric acid the interesting ring opened product **207** was obtained, containing chlorine as well as a phenyl ring attached to a secondary amine.



207

Phenyl aziridine synthesis was also attempted directly on the secondary amine **208** in order to form the target **200** (**Scheme 8.7**), but the ^1H NMR spectrum showed unidentifiable material and no evidence of the 2-azabicyclo[2.1.1]hexane ring system.

Scheme 8.7

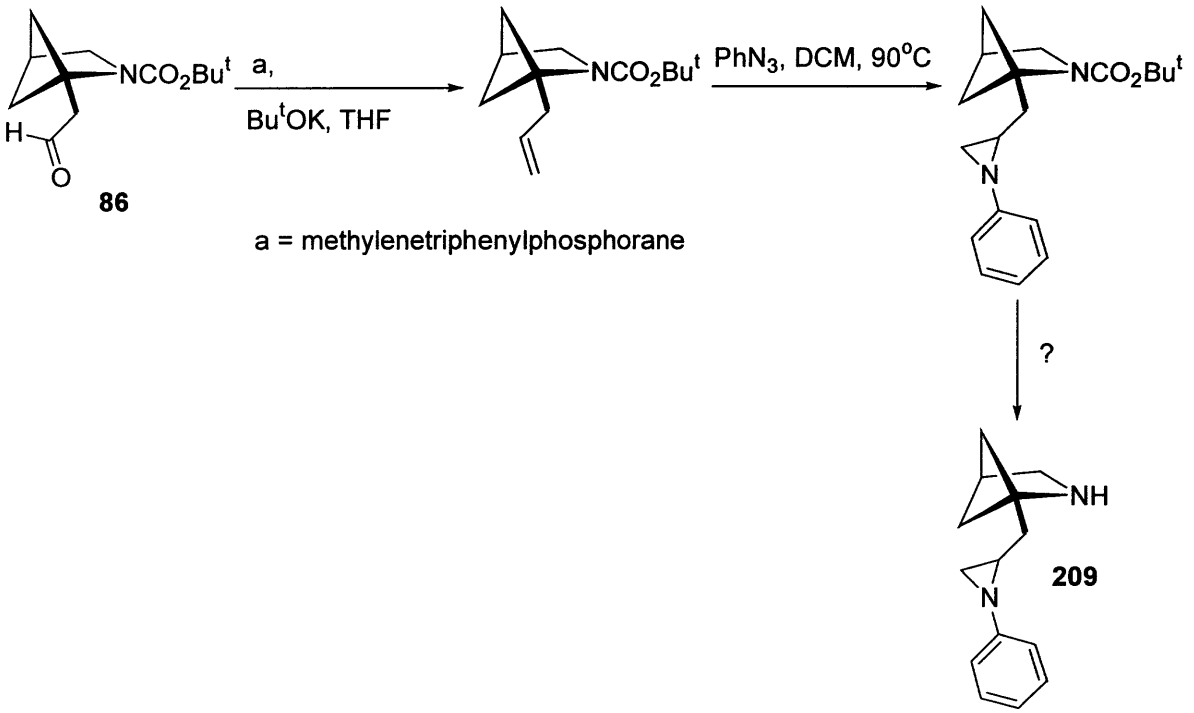


202 **208** **200**

8.3 Chain Extension; Future Research

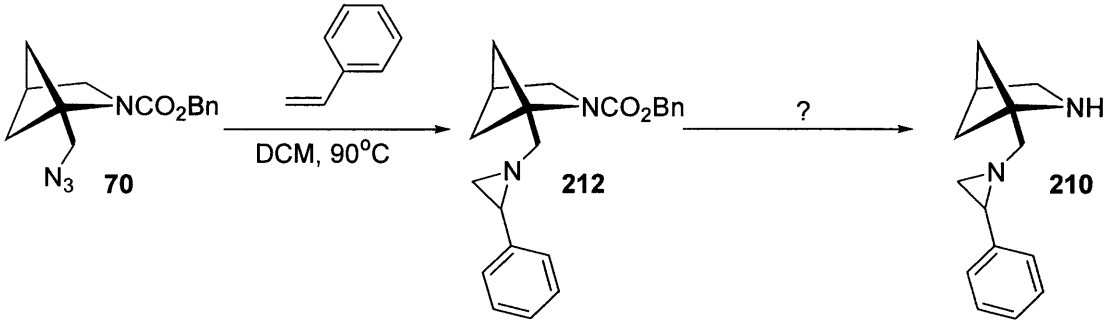
For a longer-term project, a more selective method needs to be developed to remove a suitable *N*-protecting group in order to form the target **200** (**Scheme 8.8**). Once deprotection is possible the target **209** having a longer chain, could be synthesised using established methodology.

Scheme 8.8

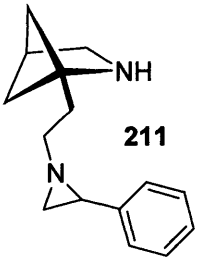


Other similar aziridine compounds **210** and **211** may be synthesised as part of this potential library of compounds. The azide **70** could be reacted with styrene to form **212**, where the azide and alkene components are reversed (**Scheme 8.9**). Subsequent deprotection would give the target **210**.

Scheme 8.9



This may be repeated to form the extended chain version **211**, having a more desirable inter-nitrogen distance. The disadvantage of these compounds is that the aziridine nitrogen is no longer conjugated with the phenyl ring in **200** and **209** hence this is likely to lead to a reduced binding affinity and sub-type selectivity.



211

8.3.1 Calculation of Inter-nitrogen Distances

Molecular modelling studies reveal the inter-nitrogen distances for the lowest-energy conformations summarised in **Table 8.1**.

Table 8.1

Compound	Minimum Energy Conformation (Å)	180° rotation (Å) of the heterocycle
Epibatidine	4.3	5.5
200 (n = 0)	2.7	3.1
209 (n = 1)	3.2	3.3
210 (n = 1)	3.0	3.0
211 (n = 2)	4.5	4.5

The inter-nitrogen distances are very small in comparison with all other compounds in the 2-azabicyclo[2.1.1]hexane series. For all the compounds of this type, the inter-nitrogen distances for both rotamers are very similar.

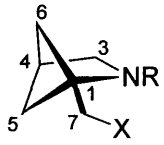
To conclude, we have synthesised the two phenyl aziridine compounds **203** and **204** on the 2-azabicyclo[2.1.1]hexane system. Numerous techniques have been employed to remove the nitrogen-protecting group, but a suitable methodology has yet to be developed to form **200**. Once a valid method could be used, it would be possible to synthesise a library of these compounds.

Chapter 9

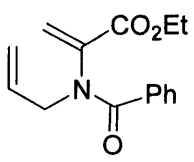
Experimental

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 tetramethylsilane (TMS). Signal characteristics are described using standard abbreviations: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), bs (broad singlet), AB (AB-system). Signals in ^{13}C NMR were determined by DEPT experiments. Signals were assigned with assistance of ^{1}H-^{1}H COSY and ^{1}H-^{13}C COSY spectra. Routine 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. Mass spectra were determined in units of mass relative to charge ($^{m}/_{z}$). IR spectra were recorded on a Perkin Elmer 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. All reactions were performed under nitrogen unless stated otherwise. Removal of solvent under reduced pressure was carried out using a Büchi rotary evaporator followed by a high vacuum pump. Solvents were distilled using standard methods.[185] Flash chromatography was carried out using silica gel (60) manufactured by Fisher. Thin layer chromatography was conducted on standard commercial aluminium sheets pre-coated with 0.2 mm layer of silica gel (Merck Kieselgel 60-254). Chromatography solvents were routinely saturated with ammonia gas for amine and *N*-protected amine) separations. The Aldrich Chemical Company, Sigma or Lancaster supplied the reagents used.



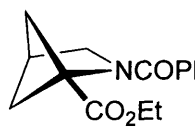
2-(Allyl-benzoyl-amino)-acrylic acid ethyl ester 46



Ethyl pyruvate (9.68 g, 83.35 mmol) was stirred in toluene (100 ml) and allylamine (4.77 g, 83.35 mmol) added dropwise. The resulting solution was stirred for 3 h at room temperature; the organic layer was then separated from water in the reaction and this aqueous layer extracted with toluene (3 × 100 ml). The organic layers were combined, dried with anhydrous magnesium sulfate, filtered and placed in a 3-neck flask under nitrogen. Dry triethylamine (13 ml, 93.30 mmol) was added to the filtrate, then benzoyl chloride (10.84 ml, 93.30 mmol) was added dropwise over 15 min. The reaction mixture was stirred for 3 h at 65°C. The solution was allowed to cool and before removal of triethylamine hydrochloride by filtration. The solvent was removed under reduced pressure to give the crude product (18.81 g) as a brown viscous oil. 8.55 g of the crude product was purified by flash chromatography, eluting with 7:3 petroleum ether (b.p. 40-60°C): diethyl ether to give **46** (R_f 0.21) (3.15 g, 12.20 mmol, 37 % yield) as a yellow oil. Spectroscopic data were in full agreement with literature data.[68,71]

δ_H (250 MHz, $CDCl_3$): 1.17 (t, J = 7.0 Hz, 3 H, CH_3), 4.07 (q, J = 5.0, 2.0 Hz, 2 H, $C\underline{H}_2CH_3$), 4.31 (bd, J = 6.0 Hz, 2 H, H_{4a}, H_{4b}), 5.20 (ddt, J = 10.0, 1.5, 1.0 Hz, 1 H, H_{6E}), 5.24 (ddt, J = 17.0, 1.5, 1.5 Hz, 1 H, H_{6Z}), 5.51 (bs, 1 H, H_{1E} or H_{1Z}), 5.92 (ddt, J = 17.0, 10.0, 6.0 Hz, 1 H, H_5), 6.07 (bs, 1 H, H_{1E} or H_{1Z}), 7.27-7.53, (m, 5 H, Ph). δ_C (62.9 MHz, $CDCl_3$): 14.33 (CH_3), 52.39 (C_4), 61.95 ($\underline{C}H_2CH_3$), 118.38 (C_6), 122.33 (C_1), 128.43, 130.64, 133.32 (5 × aryl CH, C_5), 136.18 (aryl C), 141.12 (C_2), 164.21, 171.17 (2 × C=O). ν_{max} ($CDCl_3$): 2977s (C-H), 2870s (C-H), 1702s (C=O), 1652m (C=C), 1625w (C=C), 1446m, 1383m, 1307w, 1252w, 1112s cm^{-1}. $^m/_z$ (%): 260 (MH^+, 100), 222 (8), 132 (5), 105 (15), 91 (2). $C_{15}H_{18}NO_3$ [MH^+] requires $^m/_z$ 260.1287; observed 260.1286.

2-Benzoyl-2-azabicyclo[2.1.1]hexane-1-carboxylic acid ethyl ester 47

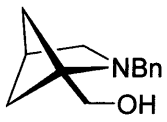


Compound **46** (3 g, 11.57 mmol) dissolved in reagent grade acetone (180 ml) was placed in a dry quartz tube, fitted with a condenser and calcium chloride tube, and irradiated in a Rayonet apparatus for 60 h at 254 nm. The solvent was removed under reduced pressure and the residue was purified by flash chromatography, eluting with 1:1 petroleum ether (b.p. 40-60°C): diethyl ether to give **47** (R_f 0.30) (1.15 g, 4.44 mmol, 38 % yield) as a white crystalline solid. A sample was recrystallised from petroleum ether (b.p. 40-60°C): diethyl ether to afford white crystals (m.p.

106-107°C). (Literature m.p. 106.5-107°C).[68,71] A small sample was recrystallised from diethyl ether for CHN analysis and X-ray crystal determinations.

δ_H (250 MHz, $CDCl_3$): 1.31 (t, J = 7.0 Hz, 3 H, CH_3), 1.81 (dd, J = 5.0, 2.0 Hz, 2 H, H_{5s}, H_{6s}), 2.17-2.21 (m, 2 H, H_{5a}, H_{6a}), 2.80-2.82 (m, 1 H, H_4), 3.56 (bs, 2 H, H_{3x}, H_{3n}), 4.28 (q, J = 7.0 Hz, 2 H, $C\underline{H}_2CH_3$), 7.36-7.52, 7.71-7.79 (m, 5 H, Ph). δ_C (62.9 MHz, $CDCl_3$): 14.48 (CH_3), 35.71 (C_4), 42.19 (C_5, C_6), 55.54 (C_3), 61.45 ($\underline{C}H_2CH_3$), 70.72 (C_1), 128.69, 128.86, 131.75 (5 × aryl CH), 135.00 (aryl C), 168.89, 174.27 (2 × C=O). ν_{max} ($CDCl_3$): 2977s (C-H), 2880m (C-H), 1733s (C=O), 1652s, 1374m, 1111s cm^{-1}. $^m/_z$ (%): 260 (MH^+, 100), 214 (62), 109 (14), 102 (11). $C_{15}H_{18}NO_3$ [MH^+] requires $^m/_z$ 260.1287; observed 260.1286. Analysis calculated for $C_{15}H_{17}NO_3$: C, 68.48; H, 6.61; N, 5.40. Found: C, 68.42; H, 6.65; N, 5.43. X-ray crystallographic data is in supporting information.

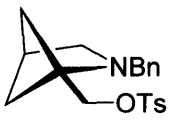
(2-Benzyl-2-azabicyclo[2.1.1]hex-1-yl)-methanol 48



Compound **47** (2.32 g, 8.95 mmol) dissolved in dry THF (20 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (1.36 g, 35.78 mmol) in dry THF (20 ml). The mixture was heated at 68°C for 36 h under an atmosphere of nitrogen. The reaction mixture was cooled and quenched with water-saturated ether. The slurry was filtered through celite and the solvent removed under reduced pressure to yield **48** (1.75 g, 8.56 mmol, 96 % yield) as a clear oil. (R_f 0.10 in 9:1 diethyl ether: methanol saturated with NH_3). A sample was recrystallised from petroleum ether (b.p. 40-60°C) to afford white crystals (m.p. 58-59°C). (Literature m.p. 58-58.5°C).[68,71]

δ_H (250 MHz, $CDCl_3$): 1.62 (bs, 4 H, H_{5s}, H_{6s}, H_{5a}, H_{6a}), 2.60 (bs 1 H, OH), 2.66 (bs, 1 H, H_4), 2.67 (bs, 2 H, H_{3x}, H_{3n}), 3.69 (bs, 2 H, $C\underline{H}_2Ph$), 3.79 (bs, 2 H, $C\underline{H}_2OH$), 7.20-7.44 (m, 5 H, Ph). δ_C (62.9 MHz, $CDCl_3$): 37.25 (C_4), 38.19 (C_5, C_6), 55.80 ($\underline{C}H_2Ph$), 57.56 (C_3), 61.56 ($\underline{C}H_2OH$), 74.32 (C_1), 127.37, 128.78, 129.04 (5 × aryl CH), 139.85 (aryl C). ν_{max} ($CDCl_3$): 3380br (O-H), 3062s (C-H), 2996s (C-H), 2875m (C-H), 1565w, 1558m, 1513w, 1488m, 1430w cm^{-1}. $^m/_z$ (%): 204 (MH^+, 100), 132 (14), 105 (39), 91 (27). $C_{13}H_{18}NO$ [MH^+] requires $^m/_z$ 204.1388; observed 204.1388. Analysis calculated for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 77.06; H, 8.41; N, 6.88.

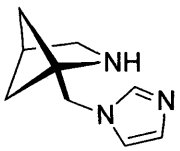
Toluene-4-sulfonic acid (2-benzyl-2-azabicyclo[2.1.1]hex-1-ylmethyl) ester 50



In the procedure of Davies,[68,71] the alcohol **48** (2.03 g; 10 mmol) was dissolved in dry pyridine (50 ml) and cooled in an ice bath. Tosyl chloride (3.81 g; 20 mmol) was added portionwise so that the temperature did not exceed 10°C. The mixture was left overnight at 4°C, poured into ice water and basified with aqueous ammonia. The resulting yellow slurry was filtered and washed with ice water (2 × 100 ml). The solid was dried under vacuum to afford the tosylate **50** (3.08 g, 8.60 mmol, 86 % yield). A sample was recrystallised from diethyl ether to afford yellow crystals (m.p. 97-98°C).

δ_H (250 MHz, $CDCl_3$): 1.50-1.54 (m, 2 H, H_{5s}, H_{6s}), 1.66-1.70 (m, 2 H, H_{5a}, H_{6a}), 2.43 (s, 3 H, $C\underline{H}_3$), 2.63-2.67 (m, 3 H, H_{3x}, H_{3n}, H_4), 3.58 (bs, 2 H, $C\underline{H}_2Ph$), 4.18 (s, 2 H, $C\underline{H}_2O$), 7.20-7.30 (m, 7H, Ph), 7.75 (d, J = 8.0 Hz, 2 H, Ph). δ_C (62.9 MHz, $CDCl_3$): 22.04 (CH_3), 37.19 (CH), 38.42, 56.89, 58.06, 69.82 (CH_2), 70.94 (C), 127.16, 128.32, 128.57, 128.93, 130.22 (CH), 133.28, 139.91, 145.24 (C). ν_{max} (CH_2Cl_2): 1598 cm^{-1}. $^m/_z$ (%): 358 (MH^+, 100), $C_{20}H_{24}NO_3S$ [MH^+] requires $^m/_z$ 358.1476; observed 358.1476. X-ray crystallographic data is in supporting information.

1-Imidazol-1-ylmethyl-2-azabicyclo[2.1.1]hexane 54 from 71



Compound **71** (57 mg, 0.19 mmol) was dissolved in dry dichloromethane (1.5 ml) and stirred under a nitrogen atmosphere. TMSI (136 µl, 0.96 mmol) was added and stirred for 7 min followed by hydrofluoroboric acid-diethyl ether complex (29 µl, 0.38 mmol) stirring for a further 6 min. The reaction mixture was quenched with water (200 µl) and the solvent removed under reduced pressure. Water (0.5 ml) was added and the solution washed with petroleum ether (b.p. 40-60°C) (2 × 2 ml). The aqueous solution was neutralised with solid potassium carbonate and the product extracted with dichloromethane (5 × 5 ml). The organic 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 dichloromethane: methanol saturated with NH_3 (R_f 0.14) to give **54** (27 mg, 0.17 mmol, 87 % yield) as a yellow oil.

1-Imidazol-1-ylmethyl-2-azabicyclo[2.1.1]hexane 54 from 73

Imidazole (34 mg, 0.24 mmol) (dried by azeotropic distillation with benzene) was dissolved in dry DMF (2 ml) under an atmosphere of nitrogen. *tert*-Butyllithium (0.2 ml, 1.57 M in hexanes, 0.24 mmol) was then added and the mixture stirred for 15 min, forming a white precipitate. The cyclic urethane **73** (34 mg, 0.24 mmol) was dissolved in dry DMF (3 ml) and added to the mixture. The reaction mixture was heated at 90°C for 144 h. The crude product was purified by flash chromatography, eluting with 9:1 dichloromethane: methanol saturated with NH_3 (R_f 0.14) to give **54** (22 mg, 0.13 mmol, 55 % yield, 69 % recovered yield as a yellow oil.

δ_H (300 MHz, $CDCl_3$): 1.25 (dd, J = 4.4, 1.8 Hz, 2 H, H_{5s}, H_{6s}), 1.57-1.61 (m, 2 H, H_{5a}, H_{6a}), 2.71-2.72 (m, 1 H, H_4), 2.93 (s, 2 H, H_{3x}, H_{3n}), 4.19 (s, 2 H, $C\underline{H}_2N$), 6.87 (s, 1 H, heterocycle), 6.98 (s, 1 H, heterocycle), 7.44 (s, 1 H, heterocycle). δ_C (75.5 MHz, $CDCl_3$): 37.65 (C_4), 41.37 (C_5, C_6), 49.38 ($\underline{C}H_2N$), 50.04 (C_3), 69.44 (C_1), 120.01, 129.82, 137.99 (3 × heterocycle). ν_{max} (CH_2Cl_2): 3330w (N-H), 2920s (C-H), 2860m (C-H), 1280br, 1130m, 1080m cm^{-1}. $^m/_z$ (%): 163 (MH^+, 20), 124 (5), 96 (5), 69 (100). $C_9H_{13}N_3$ [MH^+] requires $^m/_z$ 163.1109; observed 163.1109.

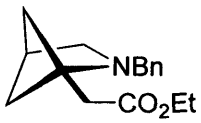
2-Benzyl-1-(3-methylisoxazolyl-5-ylmethyl)-2-azabicyclo[2.1.1]hexane 55

Using the procedure described by Daly *et al.*,[73] *tert*-butyllithium (0.8 ml, 1.57 M in hexanes, 0.36 mmol) was added to acetoxime (13 mg, 0.18 mmol) in dry THF (0.5 ml). The solution was heated at 60°C for 5 min in a sealed reactivial. A solution of the ethyl ester **56** (40 mg, 0.15 mmol) in dry THF (2 ml) was added and the mixture was stirred at 60°C for 45 min. Concentrated HCl (12M, 8 ml) was added, and the solution was heated in the sealed reactivial at 100°C for 3 h. The aqueous layer was basified with sodium hydrogen carbonate (8 ml) and extracted with ethyl acetate (5 × 10 ml). The organic layers were combined, dried with 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 saturated with NH_3 (R_f 0.35) to give an impure sample of **55** (10 mg, 0.01 mmol, <5 % yield) as a brown oil.

δ_H (250 MHz, $CDCl_3$): 1.44-1.63 (m, 4 H, H_{5s}, H_{6s}, H_{5a}, H_{6a}), 2.26 (s, 3 H, CH_3), 2.58-2.63 (m, 3 H, H_{3x}, H_{3n}, H_4), 3.10 (s, 2 H, H_7), 3.68 (s, 2 H, $C\underline{H}_2Ph$), 5.95 (s, 1 H, =CH), 7.21-7.41

(m, 5 H, Ph). $^{m}/_{z}$ (%): 269 (MH^+). Yields from later attempts to produce **55** were low and variable.

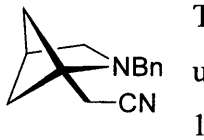
(2-Benzyl-2-azabicyclo[2.1.1]hex-1-yl)-acetic acid ethyl ester 56



The nitrile **57** (691 mg, 3.25 mmol) was added to 8M HCl (5 ml) and the solution was heated at 90°C for 96 h. The reaction mixture was evaporated to dryness and thionyl chloride (4 ml, 54.37 mmol) added. The solution was heated to 40°C for 6 h and then evaporated to dryness. Dry ethanol (5 ml) was added and the solution stirred overnight at room temperature before evaporating to dryness. The resulting solid was dissolved in 1M HCl (5 ml) and washed with ethyl acetate (2 × 5 ml). The aqueous layer was basified with ammonium hydroxide (3 ml) and extracted with dichloromethane (5 × 10 ml). The organic layers were combined, dried with 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 saturated with NH_3 (R_f 0.43) to give **56** (296 mg, 1.14 mmol, 35 % yield) as a colourless oil.

δ_H (250 MHz, $CDCl_3$): 1.25 (t, J = 7.0 Hz, 3 H, CH_3), 1.66 (dd, J = 4.6, 1.6 Hz, 2 H, H_{5s}, H_{6s}), 1.68-1.72 (m, 2 H, H_{5a}, H_{6a}), 2.68 (s, 2 H, H_{3x}, H_{3n}), 2.71 (s, 2 H, H_7) 3.66 (s, 2 H, $C\underline{H}_2Ph$), 3.72-3.74 (m, 1 H, H_4), 4.14 (q, J = 7.0 Hz, 2 H, $C\underline{H}_2CH_3$), 7.18-7.45 (m, 5 H, Ph).
δ_C (62.9 MHz, $CDCl_3$): 14.69 (CH_3), 36.90 (C_4), 37.68 (C_7), 40.09 (C_5, C_6), 57.87 (C_3), 60.2 ($\underline{C}H_2CH_3$), 70.22 (C_1), 128.67, 128.78, 129.15 (5 × aryl CH), 140.48 (aryl C), 171.64 (C=O).
ν_{max} ($CDCl_3$): 2980s (C-H), 2875m (C-H), 1732s (C=O), 1493m, 1453s, 1366s, 1256w, 1207s, 1028m cm^{-1}. $^{m}/_{z}$ (%): 260 (MH^+, 100), 222 (11), 132 (7), 91 (11), 79 (4). $C_{16}H_{22}NO_2$ [MH^+] requires $^{m}/_{z}$ 260.1650; observed 260.1650.

(2-Benzyl-2-azabicyclo[2.1.1]hex-1-yl)-acetonitrile 57

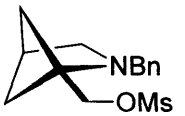


The mesylate **58** (1.58 g, 5.63 mmol) was dissolved in dry acetonitrile (8 ml) under a nitrogen atmosphere. Potassium cyanide (1.47 g, 22.51 mmol) and 18-crown-6 (0.24 g, 0.90 mmol) were added to the solution. The mixture was heated at 60°C for 72 h. The reaction mixture was triturated with ether. The solid filtered and the solvent removed under reduced pressure. The crude product was purified by flash

chromatography, eluting with 8:2 petroleum ether (b.p. 40-60°C): diethyl ether saturated with NH_3 (R_f 0.77) to give **57** (0.78 g, 3.66 mmol, 65 % yield) as a white oil.

δ_H (250 MHz, $CDCl_3$): 1.68 (dd, J = 4.6, 1.6 Hz, 2 H, H_{5s}, H_{6s}), 1.77-1.81 (m, 2 H, H_{5a}, H_{6a}), 2.70 (bs, 5 H, H_{3x}, H_{3n}, H_4, $C\underline{H}_2CN$), 3.64 (s, 2 H, $C\underline{H}_2Ph$), 7.22-7.47 (m, 5 H, Ph). δ_C (62.9 MHz, $CDCl_3$): 21.42 ($\underline{C}H_2CN$), 36.89 (C_4), 39.76 (C_5, C_6), 56.33 ($\underline{C}H_2Ph$), 58.33 (C_3), 68.75 (C_1), 117.83 ($\underline{C}N$), 127.43, 128.75, 128.96 (5 × aryl CH), 139.64 (aryl C). ν_{max} ($CDCl_3$): 3053s (C-H), 2987s (C-H), 2880m (C≡N), 1499w, 1468m, 1421s, 1314w, 1264s, 1188w, 1155w cm^{-1}. $^m/_z$ (%): 213 (MH^+, 100), 204 (61), 132 (22), 91 (68). $C_{14}H_{17}N_2$ [MH^+] requires $^m/_z$ 213.1392; observed 213.1392.

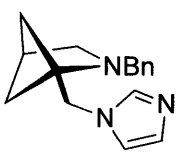
Methanesulfonic acid 2-benzyl-2-azabicyclo[2.1.1]hex-1-ylmethyl ester 58



The alcohol **48** (1.74 g, 8.53 mmol) was dissolved in dry dichloromethane (15 ml) under a nitrogen atmosphere. Methanesulfonyl chloride (0.73 ml, 9.39 mmol) was added dropwise followed by dry triethylamine (2.38 ml, 17.06 mmol). The reaction was then heated to 30°C for 20 h. The solution was filtered to remove triethylamine hydrochloride. The solution was then washed with water (2 × 20 ml) and then saturated sodium hydrogen carbonate (30 ml). The organic layer was dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield **58** (2.10 g, 7.47 mmol, 88 % yield) as a brown oil. (R_f 0.29 in diethyl ether saturated with NH_3).

δ_H (250 MHz, $CDCl_3$): 1.67 (dd, J = 4.6, 1.4 Hz, 2 H, H_{5s}, H_{6s}), 1.74-1.78 (m, 2 H, H_{5a}, H_{6a}), 2.73 (s, 3 H, H_{3x}, H_{3n}, H_4), 2.99 (s, 3 H, S-$C\underline{H}_3$), 3.73 (s, 2 H, $C\underline{H}_2Ph$), 4.42 (s, 2 H, $C\underline{H}_2O$), 7.21-7.44 (m, 5 H, Ph). δ_C (62.9 MHz, $CDCl_3$): 37.17 (C_4), 37.85 (S-$\underline{C}H_3$), 38.58 (C_5, C_6), 56.94 ($\underline{C}H_2Ph$), 58.14 (C_3), 68.88 ($\underline{C}H_2O$), 71.34 (C_1), 127.42, 128.67, 129.01 (5 × aryl CH), 139.78 (aryl C). ν_{max} ($CDCl_3$): 3430br, 3012m (C-H), 2990w (C-H), 1638m, 1628w, 1488w, 1435w, 1370m, 1265s, 1176m cm^{-1}. $^m/_z$ (%): 282 (MH^+, 100), 260 (5), 222 (52), 204 (73), 164 (5), 132 (6), 91 (28). $C_{14}H_{20}NO_3S$ [MH^+] requires $^m/_z$ 282.1164; observed 282.1164.

2-Benzyl-1-imidazol-1-ylmethyl-2-azabicyclo[2.1.1]hexane 59

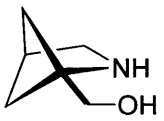


Imidazole (62 mg, 0.92 mmol) was dried by azeotropic distillation with benzene. *tert*-Butyllithium (0.58 ml, 1.57 M in hexanes, 0.92 mmol) in dry acetonitrile (4 ml) was then added and the mixture stirred for 15 min, forming

a white precipitate. The mesylate **58** (198 mg, 0.70 mmol) was dissolved in dry acetonitrile (3 ml) and was added dropwise and the mixture was heated at 40°C for 72 h. After basification with gaseous ammonia, the crude product was purified by flash chromatography, eluting with 8:2 petroleum ether (b.p. 40-60°C): diethyl ether saturated with NH_3 (R_f 0.45) to give **59** (63 mg, 0.25 mmol, 35 % yield) as a white oil. A similar reaction using dry triethylamine instead of *tert*-butyllithium gave **59** in 29 % yield.

δ_H (250 MHz, $CDCl_3$): 1.47-1.51 (m, 2 H, H_{5a}, H_{6a}), 1.60 (dd, J = 4.6, 1.5 Hz, 2 H, H_{5s}, H_{6s}), 2.61-2.63 (m, 1 H, H_4), 2.69 (s, 2 H, H_{3x}, H_{3n}), 3.74 (s, 2 H, $C\underline{H}_2Ph$), 4.19 (s, 2 H, $C\underline{H}_2N$), 6.95 (s, 1 H, heterocycle), 7.06 (s, 1 H, heterocycle), 7.26-7.40 (m, 5 H, Ph), 7.50 (s, 1 H, heterocycle). δ_C (62.9 MHz, $CDCl_3$): 36.45 (C_4), 38.55 (C_5, C_6), 48.14 ($\underline{C}H_2N$) 56.33 ($\underline{C}H_2Ph$), 58.35 (C_3), 72.95 (C_1), 120.32 (heterocycle), 127.45 (heterocycle), 128.82, 128.94, 129.55 (5 × aryl CH), 139.62 (aryl C), 138.19 (heterocycle). ν_{max} ($CDCl_3$): 3775w, 3480m, 3015s (C-H), 2990s (C-H), 1676w, 1513m, 1502m, 1490w, 1435m cm^{-1}. $^m/_z$ (%): 254 (MH^+, 100), 186 (42), 159 (10), 132 (3), 91 (4). $C_{16}H_{20}N_3$ [MH^+] requires $^m/_z$ 254.1657; observed 254.1657.

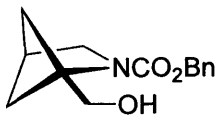
(2-Azabicyclo[2.1.1]hex-1-yl)-methanol 63



The alcohol **48** (768 mg, 3.78 mmol) was dissolved in dry methanol (20 ml) in a round-bottom flask equipped with a 3-way tap. Palladium activated on carbon (10 %) was added to the solution. The reaction vessel was evacuated three times and the heterogeneous mixture was stirred vigorously at room temperature for 24 h. The mixture was basified by bubbling ammonia through the solution. The mixture was filtered through celite, washed with methanol (100 ml) saturated with ammonia gas and the solvent removed under reduced pressure to yield **63** (427 mg, 3.78 mmol, 100 % yield) as a yellow oil. (R_f 0.10 in 6:4 diethyl ether: methanol saturated with NH_3).

δ_H (250 MHz, $CDCl_3$): 1.53 (dd, J = 4.4, 1.8 Hz, 2 H, H_{5s}, H_{6s}), 1.84-1.88 (m, 2 H, H_{5a}, H_{6a}), 2.78-2.80 (m, 1 H, H_4), 3.05 (s, 2 H, H_{3x}, H_{3n}), 3.74 (s, 2 H, $C\underline{H}_2OH$). δ_C (62.9 MHz, $CDCl_3$): 38.05 (C_4), 40.73 (C_5, C_6), 49.29 (C_3) 63.24 ($\underline{C}H_2OH$), 77.05 (C_1). ν_{max} ($CDCl_3$): 3375br (O-H) and (N-H), 2975m (C-H), 2925m (C-H), 2860m (C-H), 1650w, 1638m, 1425w, 1375w, 1238w cm^{-1}. $^m/_z$ (%): 114 (MH^+, 100), 97 (20). $C_6H_{12}NO$ [MH^+] requires $^m/_z$ 114.0919; observed 114.0918.

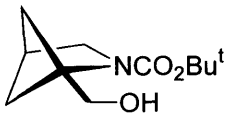
1-Hydroxymethyl-2-azabicyclo[2.1.1]hexane-2-carboxylic acid benzyl ester 64



The amine **63** (908 mg, 8.03 mol) was dissolved in water (10 ml) and cooled to 0°C. Sodium hydroxide (12 M, 2.5 ml) and benzyl chloroformate (3.44 ml, 24.10 mol) were added dropwise simultaneously, while maintaining a pH between 7 to 8. Addition of the sodium hydroxide was finished just after that of the benzyl chloroformate and stirring continued at 0°C for 15 min then at room temperature for 24 h. Water (10 ml) was added to the reaction mixture. The organic layer was run off and the aqueous layer extracted with dichloromethane (6 × 50 ml). 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 7:3 petroleum ether (b.p. 40-60°C): diethyl ether saturated with NH_3 (R_f 0.17) to give **64** (884 mg, 3.75 mol, 45 % yield) as a yellow oil.

δ_H (250 MHz, $CDCl_3$): 1.57 (dd, J = 4.8, 1.8 Hz, 2 H, H_{5s}, H_{6s}), 1.77-1.81 (m, 2 H, H_{5a}, H_{6a}), 2.77-2.79 (m, 1 H, H_4), 3.46 (s, 2 H, H_{3x}, H_{3n}), 3.95 (d, J = 7.0 Hz, 2 H, $C\underline{H_2}OH$), 4.60 (bs, 1 H, OH), 5.14 (s, 2 H, $C\underline{H_2}Ph$), 7.26-7.38 (m, 5 H, Ph). δ_C (62.9 MHz, $CDCl_3$): 34.75 (C_4), 42.08 (C_5, C_6), 52.45 (C_3) 61.96 ($\underline{C}H_2OH$), 67.15 ($\underline{C}H_2Ph$), 74.96 (C_1), 128.21, 128.45, 128.94 (5 × aryl CH), 137.06 (aryl C), 156.02 (C=O). ν_{max} ($CDCl_3$): 3420br (O-H), 2951s (C-H), 1684s (C=O), 1575w, 1520w, 1419m, 1357w, 1154w, 1116m, 1043m cm^{-1}. $^m/_z$ (%): 270 (MNa^+, 34), 248 (MH^+, 5), 204 (32), 149 (12), 91 (100). $C_{14}H_{18}NO_3$ [MH^+] requires $^m/_z$ 248.1287; observed 248.1287.

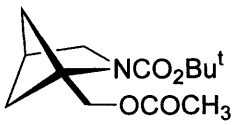
1-Hydroxymethyl-2-azabicyclo[2.1.1]hexane-2-carboxylic acid *tert*-butyl ester 65



The alcohol **48** (60 mg, 0.29 mmol) was dissolved in dry methanol (1 ml) in a round-bottom flask equipped with a 3-way tap. Palladium activated on carbon (10 %) and *N-tert*-butoxycarbonylanhydride (45 mg, 0.21 mmol) were added to the solution. The reaction vessel was evacuated three times and the heterogeneous mixture was stirred vigorously at room temperature for 24 h. The mixture was filtered through celite, washed with ethyl acetate (30 ml) saturated with ammonia gas and methanol (30 ml) saturated with ammonia gas 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 saturated with NH_3 (R_f 0.58) to give **65** (38 mg, 0.18 mmol, 60 % yield) as a white oil.

δ_H (250 MHz, $CDCl_3$): 1.41 (s, 9 H, 3 × CH_3), 1.49 (dd, J = 4.6, 1.8 Hz, 2 H, H_{5s}, H_{6s}), 1.67-1.71 (m, 2 H, H_{5a}, H_{6a}), 2.67-2.69 (m, 1 H, H_4), 3.30 (s, 2 H, H_{3x}, H_{3n}), 3.86 (d, J = 7.0 Hz, 2 H, $C\underline{H}_2OH$). δ_C (62.9 MHz, $CDCl_3$): 28.95 (3 × $\underline{C}H_3$), 34.60 (C_4), 42.11 (C_5, C_6), 52.81 (C_3), 62.14 ($\underline{C}H_2OH$), 74.54 (C_1), 80.24 ($\underline{C}(CH_3)_3$), 156.18 (C=O). ν_{max} (CH_2Cl_2): 3360br (O-H), 2920m (C-H), 1660s (C=O), 1405m, 1360m, 1160m, 1130s, 1050m cm^{-1}. $^m/_z$ (%): 236 (MNa^+, 100), 214 (MH^+, 4), 180 (32), 158 (76), 114 (52), 97 (21). $C_{11}H_{20}NO_3$ [MH^+] requires $^m/_z$ 214.1443; observed 214.1443.

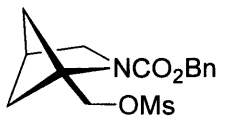
1-Acetoxymethyl-2-azabicyclo[2.1.1]hexane-2-carboxylic acid *tert*-butyl ester 66



The alcohol **48** (2.45 g, 12.05 mmol) was dissolved in ethyl acetate (10 ml) in a round-bottom flask equipped with a 3-way tap. Palladium activated on carbon (10 %) and *N-tert*-butoxycarbonylanhydride (2.76 g, 12.05 mmol) were added to the solution. The reaction vessel was evacuated three times and the heterogeneous mixture was stirred vigorously at room temperature for 24 h. The mixture was filtered through celite, washed with ethyl acetate (250 ml) saturated with ammonia gas and methanol (250 ml) saturated with ammonia gas 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 saturated with NH_3 (R_f 0.58) to give **65** (0.77 g, 3.61 mmol, 30 % yield) as a white oil and **66** (R_f 0.64) (0.70 g, 2.73 mmol, 23 % yield) as a yellow oil.

δ_H (300 MHz, $CDCl_3$): 1.22 (bs, 11 H, (3 × CH_3, H_{5s}, H_{6s}), 1.64-1.68 (m, 2 H, H_{5a}, H_{6a}), 1.88 (s, 3 H, $COC\underline{H}_3$), 2.50-2.52 (m, 1 H, H_4), 3.16 (s, 2 H, H_{3x}, H_{3n}), 4.42 (s, 2 H, $C\underline{H}_2O$). δ_C (75.5 MHz, $CDCl_3$): 21.26 ($COC\underline{H}_3$), 28.78 (3 × $C\underline{H}_3$), 34.50 (C_4), 41.93 (C_5, C_6), 52.73 (C_3), 63.58 ($\underline{C}H_2O$), 71.43 (C_1), 79.93 ($\underline{C}(CH_3)_3$), 155.86 (NC=O), 170.96 (OC=O). ν_{max} (CH_2Cl_2): 2940m (C-H), 1730br (C=O), 1700br (C=O), 1500m, 1370m, 1150m, 1115m, 1050m cm^{-1}. $^m/_z$ (%): 255 (MH^+, 100), 200 (21), 156 (18). $C_{13}H_{21}NO_4$ [MH^+] requires $^m/_z$ 255.1471; observed 255.1471.

1-Methanesulfonyloxymethyl-2-azabicyclo[2.1.1]hexane-2-carboxylic acid benzyl ester 68

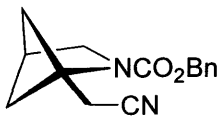


The alcohol **64** (606 mg, 2.45 mmol) was dissolved in dry dichloromethane (10 ml) under an atmosphere of nitrogen. Methanesulfonyl chloride (0.21 ml, 2.70 mmol) was added dropwise

followed by dry triethylamine (0.68 ml, 4.90 mmol). The reaction was then heated to 30°C for 24 h. The solution was filtered to remove triethylamine hydrochloride and washed with dry dichloromethane (10 ml). The solution was then washed with water (2 × 20 ml) and then saturated sodium hydrogen carbonate (30 ml). The organic layer was dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield **68** (670 mg, 2.15 mmol, 88 % yield) as a pale yellow oil. (R_f 0.76 in 8:2 petroleum ether (b.p. 40-60°C): diethyl ether saturated with NH_3).

δ_H (250 MHz, $CDCl_3$): 1.56 (dd, J = 4.0, 1.7 Hz, 2 H, H_{5s}, H_{6s}), 2.00-2.04 (m, 2 H, H_{5a}, H_{6a}), 2.81-2.83 (m, 1 H, H_4), 3.01 (s, 3 H, S-C$\underline{H}_3$), 3.50 (s, 2 H, H_{3x}, H_{3n}), 4.86 (s, 2 H, C$\underline{H}_2$O), 5.11 (s, 2 H, C$\underline{H}_2$Ph), 7.22-7.39 (m, 5 H, Ph). δ_C (62.9 MHz, $CDCl_3$): 35.05 (C_4), 37.69 (S-$\underline{C}H_3$), 41.99 (C_5, C_6), 52.63 (C_3) 67.04 ($\underline{C}H_2$Ph), 69.02 ($\underline{C}H_2$O), 70.98 (C_1), 128.26, 128.47, 128.94 (5 × aryl CH), 136.71 (aryl C), 156.02 (C=O). ν_{max} ($CDCl_3$): 3408br, 3011w (C-H), 3002w (C-H), 1750w, 1685m (C=O), 1636m, 1431w, 1358w, 1265s, 1185w cm^{-1}. $^m/_z$ (%): 326 (MH^+, 5), 282 (100), 230 (14), 140 (12), 102 (15), 91 (52). $C_{15}H_{20}NO_5S$ [MH^+] requires $^m/_z$ 326.1062; observed 326.1062.

1-Cyanomethyl-2-azabicyclo[2.1.1]hexane-2-carboxylic acid benzyl ester 69

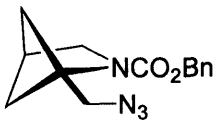


The mesylate **68** (350 mg, 1.08 mmol) was dissolved in dry acetonitrile (5 ml) under a nitrogen atmosphere. Potassium cyanide (280 mg, 4.30 mmol) and 18-crown-6 (4 mg, 0.16 mmol) were added to the solution. The mixture was heated at 60°C for 48 h. The reaction mixture was triturated with ether. The solid 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 saturated with NH_3 (R_f 0.23) to give **69** (215 mg, 0.84 mmol, 78 % yield) as a white crystalline solid. A small sample was recrystallised from diethyl ether for CHN analysis and X-ray crystal determinations, (m.p. 86.5-88.0°C).

δ_H (250 MHz, $CDCl_3$): 1.51 (dd, J = 4.7, 1.9 Hz, 2 H, H_{5s}, H_{6s}), 1.90-1.94 (m, 2 H, H_{5a}, H_{6a}), 2.72-2.75 (m, 1 H, H_4), 3.24 (s, 2 H, C$\underline{H}_2$CN), 3.42 (s, 2 H, H_{3x}, H_{3n}), 5.04 (s, 2 H, C$\underline{H}_2$Ph), 7.12-7.29 (m, 5 H, Ph). δ_C (62.9 MHz, $CDCl_3$): 22.12 ($\underline{C}H_2$CN), 34.65 (C_4), 43.44 (C_5, C_6), 52.92 (C_3), 67.09 ($\underline{C}H_2$Ph), 68.77 (C_1), 117.44 ($\underline{C}$N), 128.17, 128.36, 128.94 (5 × aryl CH), 136.95 (aryl C), 156.38 (C=O). ν_{max} (CH_2Cl_2): 2960s (C-H), 2260w (CN), 1700s (C=O), 1410s, 1360s, 1130s cm^{-1}. $^m/_z$ (%): 257 (MH^+, 69), 213 (82), 91 (100). $C_{15}H_{17}N_2O_2$ [MH^+] requires $^m/_z$ 257.1290; observed 257.1290. Analysis calculated for $C_{15}H_{17}N_2O_2$: C, 70.29; H,

6.29; N, 10.93. Found: C, 70.39; H, 6.54; N, 11.13. X-ray crystallographic data is in supporting information.

1-Azidomethyl-2-azabicyclo[2.1.1]hexane-2-carboxylic acid benzyl ester 70



The mesylate **68** (183 mg, 0.56 mmol) was dissolved in dry DMF (4 ml) under a nitrogen atmosphere. Sodium azide (146 mg, 2.25 mmol) was added to the solution. The mixture was heated at 40°C for 48 h. The solution was washed with ammonium chloride (2 × 5 ml) and water (2 × 4 ml). The organic layer was dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield **70** (130 mg, 0.48 mmol, 85 % yield) as a yellow oil. (R_f 0.74 in diethyl ether saturated with NH_3).

δ_H (250 MHz, $CDCl_3$): 1.51 (dd, J = 4.6, 1.8 Hz, 2 H, H_{5s}, H_{6s}), 1.91-1.95 (m, 2 H, H_{5a}, H_{6a}), 2.75-2.77 (m, 1 H, H_4), 3.48 (s, 2 H, H_{3x}, H_{3n}), 4.02 (s, 2 H, $C\underline{H}_2N_3$), 5.13 (s, 2 H, $C\underline{H}_2Ph$), 7.27-7.37 (m, 5 H, Ph). δ_C (62.9 MHz, $CDCl_3$): 34.79 (C_4), 42.25 (C_5, C_6), 52.11 (C_3), 52.81 ($\underline{C}H_2N_3$), 66.91 ($\underline{C}H_2Ph$), 72.79 (C_1), 128.35, 128.43, 129.21 (5 × aryl CH), 137.21 (aryl C), 156.15 (C=O). ν_{max} (CH_2Cl_2): 2090 (N_3), 1690 (C=O) cm^{-1}. $^m/_z$ (%): 273 (MH^+, 100), 266 (4), 140 (3), 74 (4). $C_{14}H_{17}N_4O_2$ [MH^+] requires $^m/_z$ 273.1352; observed 273.1352.

1-Imidazol-1-ylmethyl-2-azabicyclo[2.1.1]hexane-2-carboxylic acid benzyl ester 71

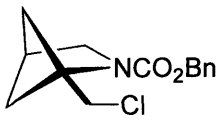
Imidazole (199 mg, 2.92 mmol) was dried by azeotropic distillation with benzene. *tert*-Butyllithium (1.43 ml, 1.57 M in hexanes, 2.92 mmol) in dry acetonitrile (5 ml) was then added and the mixture stirred for 15 min, forming a white precipitate. The mesylate **68** (733 mg, 2.25 mmol) was dissolved in dry acetonitrile (8 ml) and was added dropwise and the mixture was heated at 40°C for 96 h. After basification with gaseous ammonia and removal of the solvent under reduced pressure, the mixture was introduced on to silica and washed with diethyl ether to give the chloro compound **72** (27 mg, 0.81 mmol, 36 % yield) as a pale yellow oil. (R_f 0.78 in diethyl ether saturated with NH_3). Further elution in dichloromethane gave the cyclic urethane **73** (19 mg, 0.14 mmol, 6 % yield) as a cream solid. (R_f 0.66 in diethyl ether saturated with NH_3). Eluting with 9:1 dichloromethane: methanol saturated with NH_3, to give **71** (285 mg, 0.96 mmol, 43 % yield) as a white oil. (R_f 0.15 in diethyl ether saturated with NH_3).

δ_H (250 MHz, $CDCl_3$): 1.46 (dd, J = 4.5, 1.7 Hz, 2 H, H_{5s}, H_{6s}), 1.66-1.70 (m, 2 H, H_{5a}, H_{6a}), 2.69-2.71 (m, 1 H, H_4), 3.48 (s, 2 H, H_{3x}, H_{3n}), 4.76 (s, 2 H, $C\underline{H}_2N$), 5.13 (s, 2 H, $C\underline{H}_2Ph$),

7.09 (bs, 2 H, heterocycle), 7.25-7.33 (m, 5 H, Ph), 7.55 (bs, 1 H, heterocycle). δ_C (62.9 MHz, $CDCl_3$): 34.18 (C_4), 42.19 (C_5, C_6), 48.11 ($\underline{C}H_2N$), 53.23 (C_3), 67.07 ($\underline{C}H_2Ph$), 73.37 (C_1), 127.67, 128.23, 128.48, 128.69, 128.96, 129.37 (5 × aryl CH, 3 × heterocycle), 137.04 (aryl C), 156.76 (C=O). ν_{max} (CH_2Cl_2): 1690 (C=O) cm^{-1}. $^m/_z$ (%): 298 (MH^+, 100), 230 (18), 159 (21), 91 (62), 69 (26). $C_{17}H_{20}N_3O_2$ [MH^+] requires $^m/_z$ 298.1554; observed 298.1555.

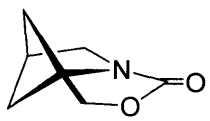
The synthesis of the chloro compound **72** was found to be a by-product due to methanesulfonyl chloride present in the starting material. In another experiment, dry imidazole (48 mg, 0.70 mmol) in dry acetonitrile (4 ml) was added to the mesylate **68** (175 mg, 0.54 mmol) in dry acetonitrile (5 ml), followed by dry triethylamine (0.11 ml, 0.81 mmol). After heating at 60°C for 96 h, the mixture was worked up and chromatographed as above to give the cyclic urethane **73** (27 mg, 0.19 mmol, 36 % yield) and **71** (69 mg, 0.14 mmol, 27 % yield). In this experiment the chloro compound **72** was not obtained. An improved method for the synthesis and spectral data for the cyclic urethane **73** is shown subsequently on page 117.

1-Chloromethyl-2-azabicyclo[2.1.1]hexane-2-carboxylic acid benzyl ester 72



δ_H (250 MHz, $CDCl_3$): 1.45 (dd, J = 4.8, 1.9 Hz, 2 H, H_{5s}, H_{6s}), 1.97-2.01 (m, 2 H, H_{5a}, H_{6a}), 2.69-2.71 (m, 1 H, H_4), 3.42 (s, 2 H, H_{3x}, H_{3n}), 4.20 (s, 2 H, $C\underline{H}_2Cl$), 5.19 (s, 2 H, $C\underline{H}_2Ph$), 7.20-7.34 (m, 5 H, Ph). δ_C (62.9 MHz, $CDCl_3$): 34.37 (C_4), 42.32 (C_5, C_6), 44.49 ($\underline{C}H_2Cl$), 53.49 (C_3), 66.87 ($\underline{C}H_2Ph$), 73.52 (C_1), 128.32, 128.45, 128.89 (5 × aryl CH), 137.22 (aryl C), 156.18 (C=O). ν_{max} (CH_2Cl_2): 2950m (C-H), 1700s (C=O), 1410m, 1360m, 1320w, 1110s cm^{-1}. $^m/_z$ (%): 288 (MNa^+, 6), 266 (MH^+, 8), 222 (28), 149 (18), 91 (100). $C_{14}H_{17}NO_2Cl$ [MH^+] requires $^m/_z$ 266.0948; observed 266.0948.

3-Oxa-5-azatricyclo[5.1.1.$0^{1,5}$]nonan-4-one 73 from 65

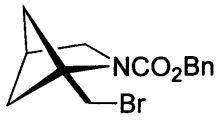


The alcohol **65** (891 mg, 4.18 mmol) was dissolved in dry dichloromethane (10 ml) under an atmosphere of nitrogen. Methanesulfonyl chloride (0.34 ml, 4.39 mmol) was added dropwise followed by dry triethylamine (1.16 ml, 8.36 mmol). The reaction was then heated to 30°C for 24 h. The solution was filtered to remove triethylamine hydrochloride and washed with dry dichloromethane (10 ml). The

solution was then washed with water (2 × 10 ml) and then saturated sodium hydrogen carbonate (20 ml). The organic 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 7:3 petroleum ether (b.p. 40-60°C): diethyl ether saturated with NH_3 (R_f 0.38) to give **73** (509 mg, 3.64 mmol, 88 % yield) as a cream solid. A sample was recrystallised to afford cream crystals for X-ray crystal determinations (m.p. 29.5-31.5°C).

δ_H (250 MHz, $CDCl_3$): 1.62 (dd, J = 4.7, 1.8 Hz, 2 H, H_{5s}, H_{6s}), 1.91-1.95 (m, 2 H, H_{5a}, H_{6a}), 2.88-2.91 (m, 1 H, H_4), 3.25 (s, 2 H, H_{3x}, H_{3n}), 4.21 (s, 2 H, $C\underline{H}_2O$). δ_C (62.9 MHz, $CDCl_3$): 40.02 (C_4), 43.62 (C_5, C_6), 47.44 (C_3), 66.44 ($\underline{C}H_2O$), 74.49 (C_1), 157.23 (C=O). ν_{max} (CH_2Cl_2): 1745 (N-C=O) cm^{-1}. $^m/_z$ (%): 140 (MH^+, 100), 97 (6). $C_7H_{10}NO_2$ [MH^+] requires $^m/_z$ 140.0711; observed 140.0711. X-ray crystallographic data is in supporting information.

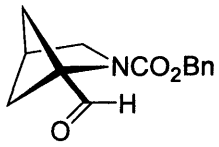
1-Bromomethyl-2-azabicyclo[2.1.1]hexane-2-carboxylic acid benzyl ester 74



The alcohol **64** (50 mg, 0.20 mmol) was dissolved in dry dichloromethane (5 ml) under a nitrogen atmosphere. TPP (212 mg, 0.81 mmol) and then carbontetrabromide (288 mg, 0.87 mmol) were added slowly to the suspension. The reaction mixture was heated to 25°C for 10 min and then left to stir at room temperature for 24 h. The solid was filtered and washed successively in dry dichloromethane (50 ml) and then dry diethyl ether (20 ml). The organic solvent was removed to give the crude product, which was purified by flash chromatography, eluting with 1:1 petroleum ether (b.p. 40-60°C): diethyl ether saturated with NH_3 (R_f 0.23) to give **74** (50 mg, 0.16 mmol, 80 % yield) as a yellow oil.

δ_H (250 MHz, $CDCl_3$): 1.50 (dd, J = 4.7, 1.9 Hz, 2 H, H_{5s}, H_{6s}), 1.90-194 (m, 2 H, H_{5a}, H_{6a}), 2.65-2.68 (m, 1 H, H_4), 3.44 (s, 2 H, H_{3x}, H_{3n}), 4.05 (s, 2 H, $C\underline{H}_2Br$), 5.06 (s, 2 H, $C\underline{H}_2Ph$), 7.24-7.26 (m, 5 H, Ph). δ_C (62.9 MHz, $CDCl_3$): 33.74 ($\underline{C}H_2Br$), 33.44 (C_4), 43.24 (C_5, C_6), 53.26 (C_3), 66.54 ($\underline{C}H_2Ph$), 73.19 (C_1), 128.32, 128.39, 128.89 (5 × aryl CH), 137.21 (aryl C), 156.83 (C=O). ν_{max} (CH_2Cl_2): 1690 (C=O) cm^{-1}. $^m/_z$ (%): 332 (MNa^+, 6), 310 (MH^+, 100), 266 (22), 91 (4). $C_{14}H_{17}NO_2{}^{79}Br$ [MH^+] requires $^m/_z$ 310.0442; observed 310.0442 and 312.0423.

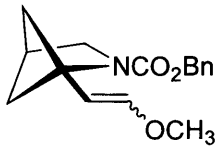
1-Formyl-2-azabicyclo[2.1.1]hexane-2-carboxylic acid benzyl ester 76



Dimethyl sulphoxide (0.09 ml, 1.37 mmol) in dry dichloromethane (5 ml) was added slowly dropwise to a solution of oxalyl chloride (0.06 ml, 0.69 mmol) in dry dichloromethane (5 ml) that had been cooled to -78°C in a dry ice and acetone bath, under nitrogen. Once the addition was complete, the reaction was stirred for 30 min at -78°C. The alcohol **64** (67 mg, 0.27 mmol) was dissolved in dry dichloromethane (5 ml) and added dropwise to the mixture and stirred for a further 15 min. Dry triethylamine (0.23 ml, 1.65 mmol) in dry dichloromethane (5 ml) was added dropwise and the reaction mixture was warmed to room temperature with stirring for 90 min. To the crude product dichloromethane (2 ml) was added. The product was then washed and extracted with water (2 × 10 ml) and saturated sodium hydrogen carbonate (5 × 15 ml). The organic layer was dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield **76** (60 mg, 0.24 mmol, 90 % yield) as a pale yellow oil. (R_f 0.82 in diethyl ether saturated with NH_3).

δ_H (250 MHz, $CDCl_3$): 1.65 (dd, J = 4.7, 1.9 Hz, 2 H, H_{5s}, H_{6s}), 2.10-2.14 (m, 2 H, H_{5a}, H_{6a}), 2.81-2.83 (m, 1 H, H_4), 3.43 (s, 2 H, H_{3x}, H_{3n}), 5.16 (s, 2 H, $C\underline{H}_2Ph$), 7.30-7.36 (m, 5 H, Ph), 9.87 (s, 1 H, $\underline{H}C{=}O$). δ_C (62.9 MHz, $CDCl_3$): 35.43 (C_4), 41.96 (C_5, C_6), 52.67 (C_3), 67.92 ($\underline{C}H_2Ph$), 76.37 (C_1), 128.45, 128.63, 128.88 (5 × aryl CH), 136.51 (aryl C), 194.34 (2 × C=O). ν_{max} (CH_2Cl_2): 1735 (HC=O), 1680 (C=O) cm^{-1}. $^m/_z$ (%): 246 (MH^+, 100), 202 (7), 102 (4). $C_{14}H_{16}NO_3$ [MH^+] requires $^m/_z$ 246.1130; observed 246.1130.

1-(2-Methoxy-vinyl)-2-azabicyclo[2.1.1]hexane-2-carboxylic acid benzyl ester 77

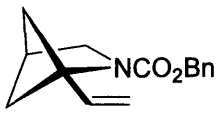


Potassium tertiary-butoxide (143 mg, 1.27 mmol) was stirred in dry THF (2 ml) under an argon atmosphere at 0°C. (Methoxymethyl)-triphenylphosphonium chloride (437 mg, 1.27 mmol) was then added followed by dry THF (2 ml). The bright red mixture was stirred for 2 h at 0°C under an atmosphere of argon. The aldehyde **76** (298 mg, 1.21 mmol) was dissolved in dry THF (4 ml) and added to the reaction mixture at 0°C. The mixture was stirred for 20 h under an argon atmosphere. Ether saturated with water (6 ml) was added at room temperature and stirred for 10 min. Water (4 ml) was then added and stirred for a further 10 min. The organic layer was separated and the aqueous layer extracted with diethyl ether (5 × 10 ml). The organic layers were combined, washed in brine (5 ml), dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield **77** (550

mg, 2.01 mmol, 166 % yield) as an orange oil. (R_f 0.38, 0.30, 0.10 in 1:1 petroleum ether (b.p. 40-60°C): diethyl ether saturated with NH_3). Compound **77** was obtained as *cis* and *trans* isomers, which includes rotamers of each. The crude product was not purified using by flash chromatography as it was found to be unstable.

δ_H (250 MHz, $CDCl_3$): 1.61 (dd, J = 4.9, 3.1 Hz, 2 H, H_{5s}, H_{6s}), 1.81-1.85 (m, 2 H, H_{5a}, H_{6a}), 2.95-2.97 (m, 1 H, H_4), 3.32 (s, 2 H, H_{3x}, H_{3n}), 3.41 (s, 3 H, $OC\underline{H}_3$), 5.12-5.16 (m, 1 H, olefinic), 5.16-5.21 (m, 2 H, $C\underline{H}_2Ph$), 5.48 (d, J = 12.8 Hz, 1 H, olefinic), 5.91 (d, J = 6.8 Hz, 1 H, olefinic), 6.39 (d, J = 12.8 Hz, 1 H, olefinic), 6.48-6.52 (m, 1 H, $\underline{H}C$=C), 7.17-7.31 (m, 5 H, Ph). $^m/_z$ (%): 273 (MH^+, 100).

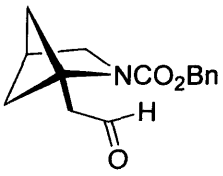
1-Vinyl-2-azabicyclo[2.1.1]hexane-2-carboxylic acid benzyl ester 78



Potassium tertiary-butoxide (123 mg, 1.09 mmol) was stirred in dry THF (2 ml) under an argon atmosphere at 0°C. Methyltriphenylphosphonium bromide (390 mg, 1.09 mmol) was then added followed by dry THF (2 ml). The bright yellow mixture was stirred for 2 h at 0°C under an atmosphere of argon. The aldehyde **76** (255 mg, 1.04 mmol) was dissolved in dry THF (3 ml) and added to the reaction mixture at 0°C. The mixture was stirred for 20 h under an argon atmosphere. Ether saturated with water (6 ml) was added at room temperature and stirred for 10 min. Water (2 ml) was then added and stirred for a further 10 min. The organic layer was separated and the aqueous layer extracted with diethyl ether (5 × 10 ml). The organic layers were combined, dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography, eluting with 1:1 petroleum ether (b.p. 40-60°C): diethyl ether saturated with NH_3 (R_f 0.59) to give **78** (160 mg, 0.65 mmol, 63 % yield) as a yellow oil.

δ_H (250 MHz, $CDCl_3$): 1.56 (dd, J = 4.9, 3.1 Hz, 2 H, H_{5s}, H_{6s}), 1.80-1.84 (m, 2 H, H_{5a}, H_{6a}), 2.63-2.65 (m, 1 H, H_4), 3.41 (s, 2 H, H_{3x}, H_{3n}), 5.03-5.23 (m, 4 H, ($C\underline{H}_2Ph$, $\underline{H}C$=$C\underline{H}$), 6.48-6.19 (m, 1 H, $\underline{H}C$=C), 7.18-7.31 (m, 5 H, Ph). δ_C (62.9 MHz, $CDCl_3$): 34.14 (C_4), 40.03 (C_5, C_6), 52.76 (C_3), 66.78 ($\underline{C}H_2Ph$), 74.50 (C_1), 115.29 ($H_2\underline{C}$=C), 128.52, 128.74, 128.86 (5 × aryl CH), 131.27 (C=$\underline{C}$H), 136.04 (aryl C), 156.15 (C=O). ν_{max} (CH_2Cl_2): 1690 (C=O) cm^{-1}. $^m/_z$ (%): 243 (MH^+, 52), 200 (15), 183 (53), 141 (20), 91, (100). $C_{15}H_{17}NO_2$ [MH^+] requires $^m/_z$ 243.1259; observed 243.1259.

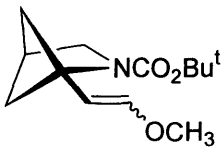
1-(2-Oxo-ethyl)-2-azabicyclo[2.1.1]hexane-2-carboxylic acid benzyl ester 80



The vinyl ether **77** (23 mg, 0.08 mmol) was dissolved in dry toluene (3 ml) and the solvent removed under reduced pressure. The residue was dissolved in 1M HCl (6 ml) and washed with petroleum ether (b.p. 40-60°C) (2 × 2 ml). The aqueous layer was basified with ammonium hydroxide (5 ml) and extracted with dichloromethane (5 × 5 ml). The organic layers were combined, dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography, eluting with 1:1 petroleum ether (b.p. 40-60°C): diethyl ether saturated with NH_3 (R_f 0.24) to give **80** (10 mg, 0.03 mmol, 46 % yield) as a yellow oil.

δ_H (250 MHz, $CDCl_3$): 2.67-3.06 (m, 4 H, H_{5s}, H_{6s}, H_{5a}, H_{6a}), 3.24-3.38 (m, 3 H, H_{3x}, H_{3n}, H_4), 4.93 (bs, 1 H, H_7), 5.12 (s, 2 H, $C\underline{H}_2Ph$), 4.93 (d, J = 7.8 Hz, 1 H, H_7), 7.28-7.41 (m, 5 H, Ph), 9.62 (d, J = 7.8 Hz, 1 H, $\underline{H}C{=}O$). δ_C (62.9 MHz, $CDCl_3$): 31.35 (C_4), 34.48 (C_5, C_6), 36.60 (C_7), 45.39 (C_3), 66.91 ($\underline{C}H_2Ph$), 76.68 (C_1), 128.14, 128.56, (5 × aryl CH), 156.58, 190.11 (2 × C=O). ν_{max} (CH_2Cl_2): 2910w (C-H), 1720s (C=O), 1670s (C-O), 1510m, 1230m, 1150m cm^{-1}. $^m/_z$ (%): 260 (MH^+, 100), 216 (22) 91(3). $C_{15}H_{18}NO_3$ [MH^+] requires $^m/_z$ 260.1287; observed 260.1287.

1-(2-Methoxy-vinyl)-2-azabicyclo[2.1.1]hexane-2-carboxylic acid *tert*-butyl ester 84

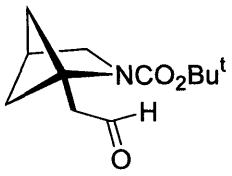


Potassium tertiary-butoxide (1.11 g, 9.94 mmol) was stirred in dry THF (6 ml) under an argon atmosphere at 0°C. (Methoxymethyl)triphenyl-phosphonium chloride (3.41 g, 9.94 mmol) was then added followed by dry THF (3 ml). The bright red mixture was stirred for 2 h at 0°C under an atmosphere of argon. The aldehyde **161** (1.75 g, 8.28 mmol) was dissolved in dry THF (10 ml) and added to the reaction mixture at 0°C. The mixture was stirred for 20 h under an argon atmosphere. Ether saturated with water (10 ml) was added at room temperature and stirred for 10 min. Water (10 ml) was then added and stirred for a further 10 min. The organic layer was separated and the aqueous layer extracted with diethyl ether (8 × 10 ml). The organic layers were combined, washed in brine (10 ml), dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield **84** (3.57 g, 14.91 mmol, 180 % yield) as an orange oil. (R_f 0.72, 0.31, 0.10 in 1:1 petroleum ether (b.p. 40-60°C): diethyl ether saturated with NH_3). Compound **84** was obtained as *cis* and *trans*

isomers, which includes rotamers of each. The crude product was not purified using by flash chromatography as it was found to be unstable.

δ_H (250 MHz, $CDCl_3$): 1.49 (bs, 9 H, 3 × CH_3), 1.61 (dd, J = 4.6, 1.6 Hz, 2 H, H_{5s}, H_{6s}), 1.81-1.85 (m, 2 H, H_{5a}, H_{6a}), 2.65-2.68 (m, 1 H, H_4), 3.44 (s, 2 H, H_{3x}, H_{3n}), 3.57 (s, 3 H, $OC\underline{H}_3$), 5.10 (d, J = 6.9 Hz, 1 H, olefinic), 5.51 (d, J = 12.9 Hz, 1 H, olefinic), 5.91 (d, J = 6.9 Hz, 1 H, olefinic), 6.36 (d, J = 12.9 Hz, 1 H, olefinic), 6.60 (d, J = 12.5 Hz, 1 H, olefinic).

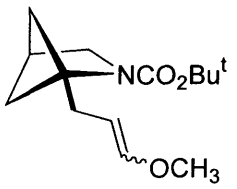
1-(2-Oxo-ethyl)-2-azabicyclo[2.1.1]hexane-2-carboxylic acid *tert*-butyl ester 86



The vinyl ether **84** (3.57 g, 14.90 mmol) was dissolved in dry toluene (20 ml) and the solvent removed under reduced pressure. The residue was dissolved in 1M HCl (18 ml) and washed with petroleum ether (b.p. 40-60°C) (2 × 5 ml). The aqueous layer was basified with ammonium hydroxide (15 ml) and extracted with dichloromethane (5 × 15 ml). The organic layers were combined, dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography, eluting with 1:1 petroleum ether (b.p. 40-60°C): diethyl ether saturated with NH_3 (R_f 0.57 in diethyl ether saturated with NH_3) to give **86** (0.30 g, 1.34 mmol, 16 % yield) as a pale yellow oil.

δ_H (250 MHz, $CDCl_3$): 1.45 (bs, 9 H, 3 × CH_3), 2.62-3.13 (m, 4 H, H_{5s}, H_{6s}, H_{5a}, H_{6a}), 3.28-3.32 (m, 3 H, H_{3x}, H_{3n}, H_4), 4.73 (bs, 1 H, H_7), 5.87-5.90 (m, 1 H, H_7), 9.63 (d, J = 8.1 Hz, 1 H, $\underline{H}C$=O). δ_C (62.9 MHz, $CDCl_3$): 28.16 (3 × $\underline{C}H_3$), 31.42 (C_4), 34.55 (C_5, C_6), 36.57 (C_7), 44.96 (C_3), 65.75 (C_1), 79.51 ($\underline{C}(CH_3)_3$), 169.2, 190.10 (2 × C=O). ν_{max} (CH_2Cl_2): 3400w, 2900w (C-H), 1710s (C=O), 1670s (C=O), 1500s, 1215m, 1150m cm^{-1}. $^m/_z$ (%): 226 (MH^+, 100).

1-(3-Methoxy-allyl)-2-azabicyclo[2.1.1]hexane-2-carboxylic acid *tert*-butyl ester 87

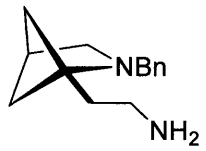


Potassium tertiary-butoxide (90 mg, 0.80 mmol) was stirred in dry THF (2 ml) under an argon atmosphere at 0°C. (Methoxymethyl)triphenyl-phosphonium chloride (274 mg, 0.80 mmol) was then added followed by dry THF (3 ml). The bright red mixture was stirred for 2 h at 0°C under an atmosphere of argon. The aldehyde **86** (150 mg, 0.67 mmol) was dissolved in dry THF (3 ml) and added to the reaction mixture at 0°C. The mixture was stirred for 20 h under an argon atmosphere. Ether saturated with water (2 ml) was added at room temperature and stirred for 10 min. Water (2 ml) was then added and stirred for a further 10 min. The organic

layer was separated and the aqueous layer extracted with diethyl ether (3 × 5 ml). The organic layers were combined, washed in brine (1 ml), dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield **87** (261 mg, 1.03 mmol, 154 % yield) as an orange oil. (R_f 0.89, 0.79, 0.32 in diethyl ether saturated with NH_3). Compound **87** was obtained as *cis* and *trans* isomers, which includes rotamers of each. The crude product was not purified using by flash chromatography as it was found to be unstable.

δ_H (250 MHz, $CDCl_3$): 1.24 (bs, 9 H, 3 × CH_3), 2.25-2.82 (m, 4 H, H_{5s}, H_{6s}, H_{5a}, H_{6a}), 3.18-3.20 (m, 1 H, H_4), 3.38 (s, 2 H, H_{3x}, H_{3n}), 3.59 (s, 3 H, $OC\underline{H}_3$), 4.90 (dd, J = 11.3, 6.2, 1 H, olefinic), 5.36 (d, J = 12.0 Hz, 1 H, olefinic), 5.66-5.71 (m, 1 H, olefinic), 5.82 (d, J = 6.2 Hz, 1 H, olefinic), 6.08-6.12 (m, 1 H, olefinic), 6.45 (d, J = 12.0 Hz, 1 H, olefinic).

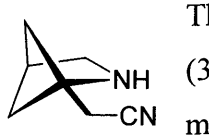
2-(2-Benzyl-2-azabicyclo[2.1.1]hex-1-yl)-ethylamine 108



The nitrile **57** (20 mg, 0.09 mmol) was dissolved in dry THF (2 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (14 mg, 0.37 mmol) in dry THF (2 ml). The mixture was heated at 65°C for 24 h under an atmosphere of nitrogen. The reaction mixture was cooled and quenched with water-saturated ether. The slurry was filtered through celite and the solvent removed under reduced pressure to yield **108** (18 mg, 0.08 mmol, 90 % yield) as a yellow oil. (R_f 0.17 in 9:1 diethyl ether: methanol saturated with NH_3).

δ_H (300 MHz, $CDCl_3$): 1.52-1.70 (m, 4 H, H_{5s}, H_{6s}, H_{5a}, H_{6a}), 1.85 (t, J = 9.0 Hz, 2 H, H_7), 2.21 (bs, 2 H, NH_2), 2.62 (s, 3 H, H_3, H_4), 2.82 (t, J = 9.0 Hz, 2 H, $C\underline{H}_2NH_2$), 3.65 (s, 2 H, $C\underline{H}_2Ph$), 7.21-7.45 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$): 34.32 (C_7), 36.61 (C_4), 39.23 (C_5, C_6), 55.47 (C_3), 55.47 ($\underline{C}H_2NH_2$), 57.41 ($\underline{C}H_2Ph$), 72.48 (C_1), 128.40, 128.67, 129.46 (5 × aryl CH), 140.10 (aryl C). ν_{max} (CH_2Cl_2): 3410w (N-H), 3020m (C-H), 2910m (C-H), 2820m (C-H), 1430m, 1260s, 710br cm^{-1}. $^m/_z$ (%): 217 (MH^+, 61), 188 (100), 110 (31), 91 (83). $C_{14}H_{21}N_2$ [MH^+] requires $^m/_z$ 217.1705; observed 217.1705.

(2-Azabicyclo[2.1.1]hex-1-yl)-acetonitrile 114

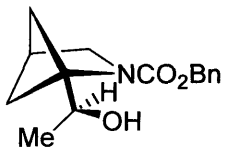


The cyclic carbamate **73** (20 mg, 0.14 mmol) was dissolved in dry acetonitrile (3 ml) under an atmosphere of nitrogen. Potassium cyanide (37 mg, 0.57 mmol) and 18-crown-6 (6 mg, 0.02 mmol) were added to the solution. The mixture was heated at 80°C for 168 h. The reaction mixture was triturated with ether. The

solid filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography, eluting with 9:1 diethyl ether: methanol saturated with NH_3, (R_f 0.14) to give **114** (12 mg, 0.09 mmol, 70 % yield) as a yellow oil.

δ_H (300 MHz, $CDCl_3$): 1.40 (dd, J = 4.4, 1.8 Hz, 2 H, H_{5s}, H_{6s}), 1.77-1.81 (m, 2 H, H_{5a}, H_{6a}), 2.10 (bs, 1 H, NH), 2.79 (s, 2 H, H_7), 2.81-2.83 (m, 1 H, H_4), 3.07 (s, 2 H, H_{3x}, H_{3n}). δ_C (75.5 MHz, $CDCl_3$): 22.21 (C_7), 37.43 (C_4), 42.03 (C_5, C_6), 49.54 (C_3), 65.07 (C_7), 117.14 (CN). ν_{max} (CH_2Cl_2): 3430w (N-H), 3020m (C-H), 1420m, 1260s cm^{-1}. $^m/_z$ (%): 123 (MH^+, 33), 114 (100), 96 (32), 79 (29).

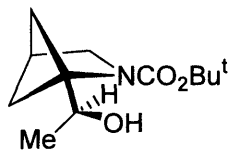
1-(1-Hydroxy-ethyl)-2-azabicyclo[2.1.1]hexane-2-carboxylic acid benzyl ester 119



The alkene **78** (531 mg, 2.18 mmol) was dissolved in dry THF (8 ml) that had been cooled to -78°C in a dry ice and acetone bath, under nitrogen. BH_3.THF complex (1M, 11 ml, 10.90 mmol) was injected dropwise, the solution was allowed to warm to room temperature overnight. The reaction was quenched by sequential addition of water (1 ml), sodium hydroxide (6M, 2.55 ml, 15.20 mmol) and hydrogen peroxide (30 %w.v., 2.55 ml, 21.80 mmol). The reaction mixture was then stirred for a further 30 min after which the solvent was removed under reduced pressure. The white residue was partitioned between dichloromethane (15 ml) and water (10 ml) and the organic layers were washed with water (10 ml) and brine (10 ml). The organic 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 6:4 petroleum ether (b.p. 40-60°C): diethyl ether saturated with NH_3, (R_f 0.72 diethyl ether saturated with NH_3) to give racemic **119** (38 mg, 0.14 mmol, 7 % yield) as a white solid.

δ_H (250 MHz, $CDCl_3$): 1.20 (d, J = 6.6 Hz, 3 H, CH_3), 1.43-1.46 (m, 2 H, H_{5s}, H_{6s}), 1.73-1.76 (m, 1 H, H_{5a}/H_{6a}), 1.83-1.86 (m, 1 H, H_{5a}/H_{6a}), 2.65-2.67 (m, 1 H, H_4), 3.40 (s, 2 H, H_{3x}, H_{3n}), 4.23 (q, J = 6.6 Hz, 1 H, C<u>H</u>OH), 4.99 (bs, 1 H, OH), 5.07 (s, 2 H, C<u>H</u>$_2$Ph), 7.19-7.29 (m, 5 H, Ph). δ_C (62.9 MHz, $CDCl_3$): 19.18 (CH_3), 33.09 (C_4), 38.88 (C_5/C_6), 41.87 (C_5/C_6), 52.55 (C_3), 64.92 (C_7), 66.78 (CH_2Ph), 78.71 (C_1), 127.79, 128.00, 128.49 (5 × aryl CH), 137.39 (aryl C), 156.18 (C=O). ν_{max} (CH_2Cl_2): 3400br (O-H), 2960s (C-H), 1660s (C=O), 1460s, 1360s, 1130s cm^{-1}. $^m/_z$ (%): 262 (MH^+, 4), 218 (35), 132 (4), 91 (100). $C_{15}H_{20}NO_3$ [MH^+] requires $^m/_z$ 262.1443; observed 262.1443.

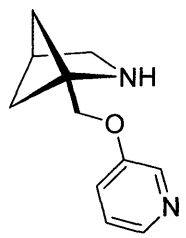
1-(1-Hydroxy-ethyl)-2-azabicyclo[2.1.1]hexane-2-carboxylic acid *tert*-butyl ester 120



The alkene **202** (90 mg, 0.43 mmol) was dissolved in dry THF (4 ml) that had been cooled to -78°C in a dry ice and acetone bath, under nitrogen. BH_3.THF complex (1M, 2.15 ml, 2.15 mmol) was injected dropwise, the solution was allowed to warm to room temperature overnight. The reaction was quenched by sequential addition of water (0.5 ml), sodium hydroxide (6M, 0.5 ml, 3 mmol) and hydrogen peroxide (30 %w.v., 0.5 ml, 4.30 mmol). The reaction mixture was then stirred for a further 30 min after which the solvent was removed under reduced pressure. The white residue was partitioned between dichloromethane (15 ml) and water (5 ml) and the organic layers were washed with water (5 ml) and brine (5 ml). The organic 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 1:1 petroleum ether (b.p. 40-60°C): diethyl ether saturated with NH_3 (R_f 0.93 diethyl ether saturated with NH_3) to give racemic **120** (6 mg, 0.03 mmol, 6 % yield) as a white solid.

δ_H (250 MHz, $CDCl_3$): 1.19 (d, J = 6.6 Hz, 3 H, CH_3), 1.41 (bs, 9 H, 3 × CH_3), 1.41-1.45 (m, 2 H, H_{5s}, H_{6s}), 1.70-1.73 (m, 1 H, H_{5a}/H_{6a}), 1.78-1.81 (m, 1 H, H_{5a}/H_{6a}), 2.61-2.63 (m, 1 H, H_4), 3.30 (s, 2 H, H_{3x}, H_{3n}), 4.17 (q, J = 6.6 Hz, 1 H, C<u>H</u>OH), 5.20 (bs, 1 H, OH). δ_C (75.5 MHz, $CDCl_3$): 19.15 (CH_3), 28.55 (3 × <u>C</u>H_3), 32.99 (C_4), 39.03 (C_5/C_6), 41.84 (C_5/C_6), 52.94 (C_3) 65.10 (C_7), 76.59 <u>C</u>$(CH_3)_3$), 79.89 (C_1), 156.18 (C=O). ν_{max} (CH_2Cl_2): 3400br (O-H), 2980s (C-H), 1680s (C=O), 1440m, 1380m cm^{-1}. $^m/_z$(%): 228 (MH^+, 5), 225 (100), 168 (51), 130 (165), 96 (52). $C_{12}H_{22}NO$ [MH^+] requires $^m/_z$ 228.1600; observed 228.1599.

1-(Pyridin-3-yloxymethyl)-2-azabicyclo[2.1.1]hexane 138

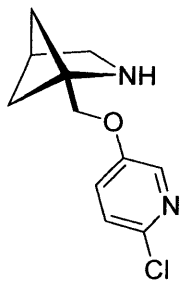


Compound **140** (101 mg, 0.31 mmol) was dissolved in dry dichloromethane (6 ml) and stirred under a nitrogen atmosphere. TMSI (222 µl, 1.56 mmol) was added and stirred for 7 min followed by hydrofluoroboric acid-diethyl ether complex (46 µl, 0.62 mmol) stirring for a further 6 min. The reaction mixture was quenched with water (200 µl) and the solvent removed under reduced pressure. Water (5 ml) was added and the solution washed with petroleum ether (b.p. 40-60°C) (3 × 3 ml). The solution was neutralised with solid potassium carbonate and the product extracted with dichloromethane (5 × 10 ml). The organic layer was dried with

anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield **138** (48 mg, 0.25 mmol, 81 % yield) as a yellow oil.

δ_H (300 MHz, $CDCl_3$): 1.37 (dd, J = 4.4, 2.0 Hz, 2 H, H_{5s}, H_{6s}), 1.70-1.74 (m, 2 H, H_{5a}, H_{6a}), 2.76-2.78 (m, 1 H, H_4), 3.01 (s, 2 H, H_{3x}, H_{3n}), 4.16 (s, 2 H, $C\underline{H}_2O$), 7.12-7.15 (m, 2 H, heterocycle), 8.12-8.15 (m, 1 H, heterocycle), 8.23-8.25 (m, 1 H, heterocycle). δ_C (75.5 MHz, $CDCl_3$): 37.77 (C_4), 40.65 (C_5, C_6), 48.73 (C_3), 68.32 ($\underline{C}H_2O$), 68.89 (C_1), 120.90, 123.71, 138.07, 142.14 (4 × heterocycle), 154.95 (heterocycle C–O). ν_{max} (CH_2Cl_2): 3500w (N-H), 3000s (C-H), 2950s (C-H), 1420s, 1160s, 900s, 690br cm^{-1}. $^m/_z$ (%): 191 (MH^+, 32), 154 (8), 109 (12), 96 (50). $C_{11}H_{15}N_2O$ [MH^+] requires $^m/_z$ 191.1184; observed 191.1184.

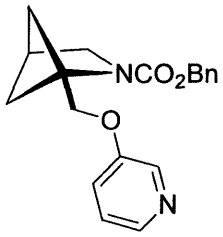
1-(6-Chloro-pyridin-3-yloxymethyl)-2-azabicyclo[2.1.1]hexane 139



Compound **141** (57 mg, 0.16 mmol) was dissolved in dry dichloromethane (4 ml) and stirred under a nitrogen atmosphere. TMSI (113 µl, 0.79 mmol) was added and stirred for 7 min followed by hydrofluoroboric acid-diethyl ether complex (24 µl, 0.31 mmol) stirring for a further 6 min. The reaction mixture was quenched with water (100 µl) and the solvent removed under reduced pressure. Water (10 ml) was added and the solution washed with petroleum ether (b.p. 40-60°C) (5 × 5 ml). The solution was neutralised with solid potassium carbonate and the product extracted with dichloromethane (5 × 10 ml). The organic layer was dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield **139** (30 mg, 0.13 mmol, 83 % yield) as a bright yellow oil.

δ_H (300 MHz, $CDCl_3$): 1.41 (dd, J = 4.5, 1.6 Hz, 2 H, H_{5s}, H_{6s}), 1.72-176 (m, 2 H, H_{5a}, H_{6a}), 2.78-2.80 (m, 1 H, H_4), 3.05 (s, 2 H, H_{3x}, H_{3n}), 4.18 (s, 2 H, $C\underline{H}_2O$), 7.14-7.18 (m, 2 H, heterocycle), 8.00 (bs, 1 H, heterocycle). δ_C (75.5 MHz, $CDCl_3$): 37.68 (C_4), 40.59 (C_5, C_6), 48.76 (C_3), 68.48 ($\underline{C}H_2O$), 69.10 (C_1), 124.39, 124.92, 136.77 (3 × heterocycle), 142.76 (heterocycle C–Cl), 154.19 (heterocycle C–O). ν_{max} (CH_2Cl_2): 3490w (N-H), 3020s (C-H), 2990s (C-H), 2300m, 1420s, 1260s, 900s, 750br (C-Cl) cm^{-1}. $^m/_z$ (%): 225 (MH^+, 100), 130 (68), 96 (57). $C_{11}H_{14}N_2OCl$ [MH^+] requires $^m/_z$ 225.0794; observed 225.0794.

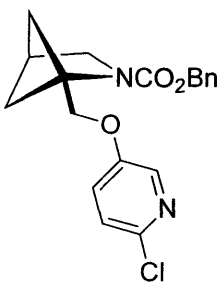
1-(Pyridin-3-yloxymethyl)-2-azabicyclo[2.1.1]hexane-2-carboxylic acid benzyl ester 140



The alcohol **64** (50 mg, 0.20 mmol) was dissolved in dry THF (1 ml) under an atmosphere of nitrogen. 3-Hydroxypyridine (58 mg, 0.61 mmol) dissolved in dry THF (1 ml), TPP (69 mg, 0.26 mmol) dissolved in dry THF (2 ml) and DEAD (0.04 ml, 0.26 mmol) were added to the reaction. The mixture was heated at 65°C for 48 h. The crude product was purified by flash chromatography, eluting with 6:4 petroleum ether (b.p. 40-60°C): diethyl ether saturated with NH_3 (R_f 0.50 in diethyl ether saturated with NH_3) to give **140** (14 mg, 0.04 mmol, 22 % yield) as a yellow oil.

δ_H (300 MHz, $CDCl_3$): 1.44 (dd, J = 4.6, 1.8 Hz, 2 H, H_{5s}, H_{6s}), 2.04-2.08 (m, 2 H, H_{5a}, H_{6a}), 2.73-2.75 (m, 1 H, H_4), 3.45 (s, 2 H, H_{3x}, H_{3n}), 4.52 (bs, 2 H, $C\underline{H}_2O$), 5.03 (s, 2 H, $C\underline{H}_2Ph$), 7.07 (d, J = 2.5 Hz, 2 H, heterocycle), 7.18-7.31 (m, 5 H, Ph), 8.12 (t, J = 3.6 Hz, 1 H, heterocycle), 8.22 (s, 1 H, heterocycle). δ_C (75.5 MHz, $CDCl_3$): 34.26 (C_4), 41.37 (C_5, C_6), 52.32 (C_3), 66.28 ($\underline{C}H_2Ph$), 66.29 ($\underline{C}H_2O$), 72.04 (C_1), 120.64, 123.68, 138.37, 142.10 (4 × heterocycle), 127.95, 128.03, 128.48 (5 × aryl), 136.62 (aryl C), 155.02 (C=O), 155.72 (heterocycle C–O). ν_{max} (CH_2Cl_2): 2900w (C-H), 1730s (C=O), 1220w, 1060w cm^{-1}. $^m/_z$ (%): 325 (MH^+, 100), 230 (60), 186 (21), 91 (30). $C_{19}H_{21}N_2O_3$ [MH^+] requires $^m/_z$ 325.1552; observed 325.1552.

1-(6-Chloro-pyridin-3-yloxymethyl)-2-azabicyclo[2.1.1]hexane-2-carboxylic acid benzyl ester 141

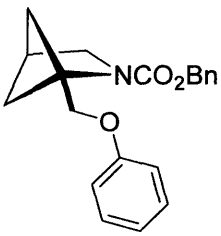


The alcohol **64** (50 mg, 0.20 mmol) was dissolved in dry THF (3 ml) under an atmosphere of nitrogen. 2-Chloro-5-hydroxypyridine (29 mg, 0.22 mmol) dissolved in dry THF (3 ml), TPP (69 mg, 0.26 mmol) dissolved in dry THF (2 ml) and DEAD (0.04 ml, 0.26 mmol) were added to the reaction. The mixture was heated at 65°C for 48 h. The crude product was purified by flash chromatography, eluting with 6:4 petroleum ether (b.p. 40-60°C): diethyl ether saturated with NH_3 (R_f 0.76 in diethyl ether saturated with NH_3) to give **141** (20 mg, 0.06 mmol, 27 % yield) as a bright yellow oil.

δ_H (300 MHz, $CDCl_3$): 1.46 (dd, J = 4.5, 1.8 Hz, 2 H, H_{5s}, H_{6s}), 2.02-2.06 (m, 2 H, H_{5a}, H_{6a}), 2.75-2.77 (m, 1 H, H_4), 3.50 (s, 2 H, H_{3x}, H_{3n}), 4.51 (bs, 2 H, $C\underline{H}_2O$), 5.03 (s, 2 H, $C\underline{H}_2Ph$), 7.09 (s, 2 H, heterocycle), 7.19-7.29 (m, 5 H, Ph), 7.97 (s, 1 H, heterocycle). δ_C (75.5 MHz, $CDCl_3$): 34.44 (C_4), 41.47 (C_5, C_6), 52.28 (C_3), 67.30 ($\underline{C}H_2Ph$), 67.34 ($\underline{C}H_2O$), 71.23 (C_1),

124.19, 124.43, 137.21 (3 × heterocycle), 127.93, 128.08, 128.53 (5 × aryl), 136.57 (aryl C), 142.52 (heterocycle C–Cl), 154.23 (C=O), 155.67 (heterocycle C–O). ν_{max} (CH_2Cl_2): 3040m (C-H), 1690s (C=O), 1560w, 1410m, 1350w, 1250m, 1030m, 700br (C-Cl) cm^{-1}. $^m/_z$ (%): 359 (MH^+, 40), 230 (100), 220 (22), 91 (68). $C_{19}H_{20}N_2O_3Cl$ [MH^+] requires $^m/_z$ 359.1162; observed 359.1162.

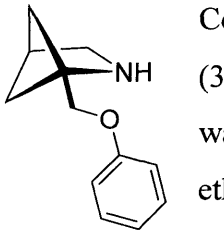
1-Phenoxymethyl-2-azabicyclo[2.1.1]hexane-2-carboxylic acid benzyl ester 142



The alcohol **64** (400 mg, 1.62 mmol) was dissolved in dry THF (4 ml) under an atmosphere of nitrogen. Phenol (198 mg, 2.10 mmol) dissolved in dry THF (4 ml), TPP (551 mg, 2.10 mmol) dissolved in dry THF (4 ml) and DEAD (0.33 ml, 2.10 mmol) were added to the reaction. The mixture was heated at 65°C for 48 h. The crude product was purified by flash chromatography, eluting with 6:4 petroleum ether (b.p. 40-60°C): diethyl ether saturated with NH_3 (R_f 0.91 in diethyl ether saturated with NH_3) to give **142** (113 mg, 0.34 mmol, 22 % yield) as a brown oil.

δ_H (300 MHz, $CDCl_3$): 1.50 (dd, J = 4.7, 1.7 Hz, 2 H, H_{5s}, H_{6s}), 2.14-2.18 (m, 2 H, H_{5a}, H_{6a}), 2.79-2.81 (m, 1 H, H_4), 3.52 (s, 2 H, H_{3x}, H_{3n}), 4.56 (bs, 2 H, $C\underline{H_2}O$), 5.12 (s, 2 H, $C\underline{H_2}Ph$), 6.81-6.98, 7.18-7.42 (m, 10 H, 2 × Ph). δ_C (75.5 MHz, $CDCl_3$): 34.24 (C_4), 41.39 (C_5, C_6), 52.39 (C_3), 64.43 ($\underline{C}H_2Ph$), 64.43 ($\underline{C}H_2O$), 72.55 (C_1), 114.54, 120.71, 121.07, 125.96, 127.97, 128.39, 129.40 (10 × aryl), 136.78 (aryl C), 155.68 (C=O), 158.83 (aryl C–O). ν_{max} (CH_2Cl_2): 2970m (C-H), 1690s (C=O), 1600m (Ph), 1490m (Ph), 1410m, 1350m, 1240s, 1130s (C-O), 1040m cm^{-1}. $^m/_z$ (%): 324 (MH^+, 15), 280 (100), 140 (16) 91 (49). $C_{20}H_{22}NO_3$ [MH^+] requires $^m/_z$ 324.1599; observed 324.1599.

1-Phenoxymethyl-2-azabicyclo[2.1.1]hexane 143

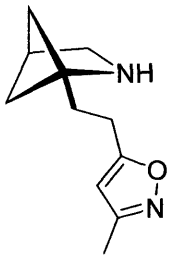


Compound **142** (110 mg, 0.34 mmol) was dissolved in dry dichloromethane (3 ml) and stirred under a nitrogen atmosphere. TMSI (242 µl, 1.70 mmol) was added and stirred for 7 min followed by hydrofluoroboric acid-diethyl ether complex (51 µl, 0.68 mmol) stirring for a further 6 min. The reaction mixture was quenched with water (200 µl) and the solvent removed under reduced pressure. Water (3 ml) was added and the solution washed with petroleum ether (b.p. 40-60°C) (3 × 1 ml). The solution was neutralised with solid potassium carbonate and

the product extracted with dichloromethane (6 × 5 ml). The organic layer was dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield **143** (56 mg, 0.29 mmol, 87 % yield) as an orange oil.

δ_H (300 MHz, $CDCl_3$): 1.36 (dd, J = 4.4, 1.4 Hz, 2 H, H_{5s}, H_{6s}), 1.69-1.73 (m, 2 H, H_{5a}, H_{6a}), 2.73-2.75 (m, 1 H, H_4), 3.00 (s, 2 H, H_{3x}, H_{3n}), 4.12 (s, 2 H, $C\underline{H}_2O$), 6.82-6.89 (m, 3 H, Ph), 7.17-7.23 (m, 2 H, Ph). δ_C (75.5 MHz, $CDCl_3$): 37.69 (C_4), 40.72 (C_5, C_6), 48.85 (C_3), 68.45 ($\underline{C}H_2O$), 68.77 (C_1), 114.55, 120.86, 129.44 (5 × aryl), 158.87 (aryl C–O). ν_{max} (CH_2Cl_2): 3500w (N-H), 2880w (C-H), 1590w (Ph), 1490w (Ph), 1050w cm^{-1}. $^m/_z$ (%): 190 (MH^+, 100), 173 (16), 107 (21), 96 (64). $C_{12}H_{16}NO$ [MH^+] requires $^m/_z$ 190.1231; observed 190.1231.

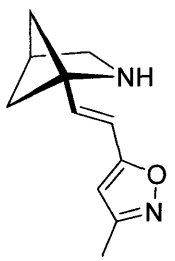
1-[2-(3-Methyl-isoxazol-5-yl)-ethyl]-2-azabicyclo[2.1.1]hexane 156



Compound **158** (10 mg, 0.02 mmol) was stirred in a solution of 3M HCl (2 ml) made *in situ* (dry ethanol (0.43 ml), dry ethyl acetate (1.2 ml) and acetyl chloride (0.36 ml) at 0°C for 1 h. The reaction mixture was washed with diethyl ether (3 × 0.5 ml) and then evaporated to dryness to give the hydrochloride salt of **156** (8 mg, 0.02 mmol, 99 % yield).

δ_H (300 MHz, D_2O): 1.49 (dd, J = 6.1, 2.2 Hz, 2 H, H_{5s}, H_{6s}), 1.83-1.87 (m, 2 H, H_{5a}, H_{6a}), 2.10 (s, 3 H, CH_3), 2.42 (t, J = 7.8 Hz, 2 H, H_7), 2.71-2.73 (m, 1 H, H_4), 2.78 (t, J = 7.8 Hz, 2 H, H_8), 3.24 (s, 2 H, H_{3x}, H_{3n}), 6.01 (s, 1 H, =CH). $^m/_z$ (%): 193 (MH^+, 100), 176 (35) 164 (19), 91 (19). $C_{11}H_{17}N_2O$ [MH^+] requires $^m/_z$ 193.1340; observed 193.1340.

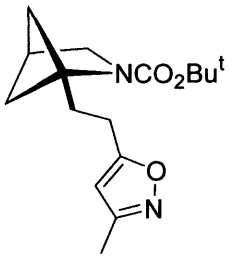
1-[2-(3-Methyl-isoxazol-5-yl)-vinyl]-2-azabicyclo[2.1.1]hexane 157



Compound **159** (5 mg, 0.02 mmol) was stirred in a solution of 3M HCl (2 ml) made *in situ* (dry ethanol (0.43 ml), dry ethyl acetate (1.2 ml) and acetyl chloride (0.36 ml) at 0°C for 1 h. The reaction mixture was washed with diethyl ether (3 × 0.5 ml) and then evaporated to dryness to give the hydrochloride salt of **157** (4 mg, 0.02 mmol, 97 % yield).

δ_H (300 MHz, D_2O): 1.95-2.16 (m, 4 H, H_{5s}, H_{6s}, H_{5a}, H_{6a}), 2.04 (s, 3 H, CH_3), 2.31-2.33 (m, 1 H, H_4), 2.88-2.92 (m, 2 H, H_{3x}, H_{3n}), 6.08 (s, 1 H, =CH), 6.28 (d, J = 16.0 Hz, 1 H, H_8), 6.46 (d, J = 16.0 Hz, 1 H, H_7). δ_C (75.5 MHz, D_2O): 10.35 (CH_3), 25.69 (C_4), 37.76 (C_5, C_6), 44.24 (C_3), 102.95 (=$\underline{C}$H), 113.04 (C_8), 141.20 (C_7). $^m/_z$ (%): 191 (MH^+, 60), 174 (52), 136 (40), 105 (42), 88 (100).

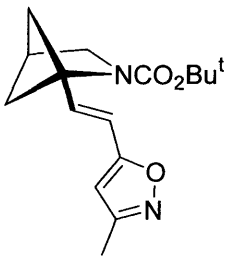
1-[2-(3-Methyl-isoxazol-5-yl)-ethyl]-2-azabicyclo[2.1.1]hexane-2-carboxylic acid *tert*-butyl ester 158



Compound **159** (65 mg, 0.22 mmol) was dissolved in dry methanol (6 ml) and stirred under a nitrogen atmosphere. Potassium azodicarboxylate was added (130 mg, 0.67 mmol), followed by glacial acetic acid (77 µl, 1.34 mmol). The reaction mixture was heated at reflux for 48 h. The reaction mixture was quenched with water (1 ml) and neutralised with saturated sodium hydrogen carbonate (3 ml). The organic layer was separated and the aqueous layer extracted with dichloromethane (3 × 10 ml). The organic layers were combined, dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography, eluting with 6:4 petroleum ether (b.p. 40-60°C): diethyl ether saturated with NH_3 (R_f 0.45 in 1:1 petroleum ether (b.p. 40-60°C): diethyl ether saturated with NH_3) to give **158** (22 mg, 0.07 mmol, 34 % yield) as a yellow oil.

δ_H (300 MHz, $CDCl_3$): 1.39 (bs, 9 H, 3 × CH_3), 1.49 (dd, J = 4.6, 1.9 Hz, 2 H, H_{5s}, H_{6s}), 1.62-1.66 (m, 2 H, H_{5a}, H_{6a}), 2.18 (s, 3 H, CH_3), 2.41-2.44 (m, 2 H, H_7), 2.63-2.65 (m, 1 H, H_4), 2.74-2.77 (m, 2 H, H_8), 3.32 (s, 2 H, H_{3x}, H_{3n}), 5.77 (s, 1 H, =CH). δ_C (75.5 MHz, $CDCl_3$): 11.41 (CH_3), 23.31 (C_7), 28.56 (3 × $\underline{C}H_3$), 29.91 (C_8), 33.87 (C_4), 43.00 (C_5, C_6), 52.92 (C_3), 73.17 (C_1), 79.30 ($\underline{C}(CH_3)_3$), 101.48 (=$\underline{C}$H), 173.17 (C=O). $^m/_z$ (%): 293 (MH^+, 5), 225 (12), 193 (100). $C_{16}H_{25}N_2O_3$ [MH^+] requires $^m/_z$ 293.1865; observed 293.1865.

1-[2-(3-Methyl-isoxazol-5-yl)-vinyl]-2-azabicyclo[2.1.1]hexane-2-carboxylic acid *tert*-butyl ester 159

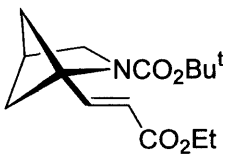


Using the procedure described by Daly *et al.*,[76] a solution of *tert*-butyllithium (1.42 ml, 1.57 M in hexanes, 2.23 mmol) was added dropwise over 10 min to a solution of acetoxime (109 mg, 1.49 mmol) in dry THF (1 ml) under an argon atmosphere at 0°C. After stirring for 2 h at 0°C, a solution of the ethyl ester **160** (209 mg, 0.74 mmol) in dry THF (3 ml) was added over 10 min. The reaction mixture was stirred under argon at 0°C for 20 h. The reaction mixture was then added to a vigorously stirred solution of 1M HCl (10 ml) over 40 min. This mixture was neutralized using sodium hydrogen carbonate and extracted with dichloromethane (8 × 50 ml). The organic layers were combined, dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography, eluting with 1:1 petroleum ether (b.p. 40-

60°C): diethyl ether saturated with NH_3 (R_f 0.55 in diethyl ether saturated with NH_3) to give **159** (65 mg, 0.22 mmol, 30 % yield) as a pale yellow oil.

δ_H (300 MHz, $CDCl_3$): 1.39 (bs, 9 H, 3 × CH_3), 1.60 (dd, J = 4.5, 2.1 Hz, 2 H, H_{5s}, H_{6s}), 1.87-1.91 (m, 2 H, H_{5a}, H_{6a}), 2.21 (s, 3 H, CH_3), 2.70-2.72 (m, 1 H, H_4), 3.40 (s, 2 H, H_{3x}, H_{3n}), 5.95 (s, 1 H, =CH), 6.21 (d, J = 16.2 Hz, 1 H, H_8), 6.98 (d, J = 16.2 Hz, 1 H, H_7). δ_C (75.5 MHz, $CDCl_3$): 11.42 (CH_3), 28.48 (3 × $\underline{C}H_3$), 34.08 (C_4), 44.04 (C_5, C_6), 52.23 (C_3), 72.69 (C_1), 79.72 ($\underline{C}(CH_3)_3$), 101.49 (=$\underline{C}$H), 114.57 (C_8), 134.93 (C_7), 159.87 (C=O). $^m/_z$ (%): 291 (MH^+, 100), 235 (100), 191 (10). $C_{16}H_{23}N_2O_3$ [MH^+] requires $^m/_z$ 291.1708; observed 291.1708.

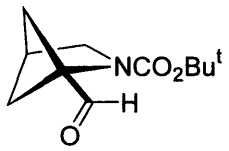
1-(2-Ethoxycarbonyl-vinyl)-2-azabicyclo[2.1.1]hexane-2-carboxylic acid *tert*-butyl ester 160



(Ethoxycarbonylmethyl)triphenylphosphonium bromide (612 mg, 1.43 mmol) was stirred in dry THF (2 ml) that had been cooled to -78°C in a dry ice and acetone bath, under an argon atmosphere. *tert*-Butyllithium (0.89 ml, 1.6 M in hexanes, 2.86 mmol) was added and the bright yellow mixture was stirred for 20 min at -78°C under an atmosphere of argon. The aldehyde **161** (200 mg, 0.94 mmol) was dissolved in dry THF (3 ml) and added to the reaction mixture at -78°C. The mixture was stirred for 20 h under an argon atmosphere. The reaction mixture was quenched with a solution of saturated ammonium chloride (3 ml). The organic layer was separated and the aqueous layer extracted with diethyl ether (3 × 10 ml). The organic layers were combined, dried with 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 saturated with NH_3 (R_f 0.55 in 1:1 petroleum ether (b.p. 40-60°C): diethyl ether saturated with NH_3) to give **160** (90 mg, 0.32 mmol, 34 % yield) as a pale yellow oil.

δ_H (300 MHz, $CDCl_3$): 1.22 (t, J = 7.2 Hz, 3 H, $CH_2\underline{CH_3}$), 1.36 (bs, 9 H, 3 × CH_3), 1.60 (dd, J = 4.5, 1.8 Hz, 2 H, H_{5s}, H_{6s}), 1.83-1.87 (m, 2 H, H_{5a}, H_{6a}), 2.69-2.71 (m, 1 H, H_4), 3.38 (s, 2 H, H_{3x}, H_{3n}), 4.13 (q, J = 7.2 Hz, 2 H, $C\underline{H_2}CH_3$), 5.75 (d, J = 15.9 Hz, 1 H, H_8), 7.38 (d, J = 15.9 Hz, 1 H, H_7). δ_C (75.5 MHz, $CDCl_3$): 14.26 (CH_3), 28.39 (3 × $\underline{C}H_3$), 34.28 (C_4), 44.08 (C_5, C_6), 52.11 (C_3), 60.34 ($\underline{C}H_2O$), 71.92 (C_1), 79.95 ($\underline{C}(CH_3)_3$), 119.93 (C_8), 145.46 (C_7), 156.28, 166.34 (2 × C=O). ν_{max} (CH_2Cl_2): 2940m (C-H), 1660s (C=O), 1400m, 1360w, 1160w, 1120m, 740m cm^{-1}. $^m/_z$ (%): 282 (MH^+, 62), 258 (12), 226 (22), 182 (32). $C_{15}H_{24}NO_4$ [MH^+] requires $^m/_z$ 282.1705; observed 282.1705.

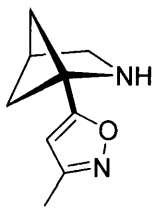
1-Formyl-2-azabicyclo[2.1.1]hexane-2-carboxylic acid *tert*-butyl ester 161



Dimethyl sulphoxide (0.48 ml, 6.79 mmol) in dry dichloromethane (2 ml) was added slowly dropwise to a solution of oxalyl chloride (0.23 ml, 3.39 mmol) in dry dichloromethane (5 ml) that had been cooled to -78°C in a dry ice and acetone bath, under nitrogen. Once the addition was complete, the reaction was stirred for 30 min at -78°C. The alcohol **65** (271 mg, 1.27 mmol) was dissolved in dry dichloromethane (6 ml) and added dropwise to the mixture and stirred for a further 15 min. Dry triethylamine (1.14 ml, 8.15 mmol) in dry dichloromethane (2 ml) was added dropwise and the reaction mixture was warmed to room temperature with stirring for 90 min. To the crude product dichloromethane (2 ml) was added. The product was then washed and extracted with water (3 × 10 ml) and saturated sodium hydrogen carbonate (3 × 10 ml). The organic layer was dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield **161** (260 mg, 1.23 mmol, 97 % yield) as a pale yellow oil. (R_f 0.70 in diethyl ether saturated with NH_3).

δ_H (300 MHz, $CDCl_3$): 1.46 (bs, 9 H, 3 × CH_3), 1.65 (dd, J = 4.5, 1.9 Hz, 2 H, H_{5s}, H_{6s}), 2.07-2.11 (m, 2 H, H_{5a}, H_{6a}), 2.80-2.82 (m, 1 H, H_4), 3.47 (s, 2 H, H_{3x}, H_{3n}), 9.79 (s, 1 H, HC=O). δ_C (75.5 MHz, $CDCl_3$): 28.16 (3 × CH_3), 34.99 (C_4), 41.25 (C_5, C_6), 52.23 (C_3), 76.02 (C_1), 81.10 ($C(CH_3)_3$), 194.04 (2 × C=O). ν_{max} (CH_2Cl_2): 3405w, 2950w (C-H), 1720s (C=O), 1670s (C=O), 1505m, 1230m, 1150m cm^{-1}. $^m/_z$ (%): 212 (MH^+, 100), 170 (20), 156 (100), 112 (3), 102 (12). $C_{11}H_{18}NO_3$ [MH^+] requires $^m/_z$ 212.1286; observed 212.1286.

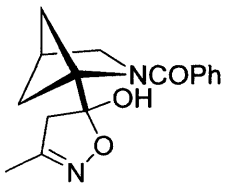
1-(3-Methyl-isoxazole-5-yl)-2-azabicyclo[2.1.1]hexane 163



Compound **165** (20 mg, 0.07 mmol) was stirred in 6M HCl (10 ml) and heated to reflux for 48 h. The reaction mixture was washed with diethyl ether (3 × 0.5 ml) and then evaporated to dryness to give the hydrochloride salt of evaporated to dryness to give the hydrochloride salt of **163** (14 mg, 0.07 mmol, 99 % yield).

δ_H (300 MHz, D_2O): 1.84-1.98, 2.08-2.26 (m, 4 H, H_{5s}, H_{6s}, H_{5a}, H_{6a}), 1.97 (s, 3 H, CH_3), 2.46-2.48 (m, 1 H, H_4), 2.81-2.85 (m, 2 H, H_{3x}, H_{3n}), 6.04 (s, 1 H, =CH). δ_C (75.5 MHz, D_2O): 10.39 (CH_3), 25.40 (C_4), 38.99 (C_5, C_6), 44.45 (C_3), 68.82 (C_1), 101.56 (=CH), 155.81 (C_7). $^m/_z$ (%): 165 (MH^+, 100).

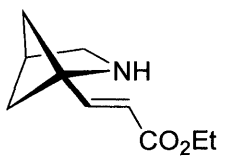
[1-(5-Hydroxy-3-methyl-4,5-dihydro-isoxazol-5-yl)-2-azabicyclo[2.1.1]hex-2-yl]phenyl-methanone 165



Using the procedure described by Daly *et al.*,[76] a solution of *tert*-butyllithium (0.96 ml, 2.4 M in hexanes, 2.31 mmol) was added dropwise over 10 min to a solution of acetoxime (169 mg, 2.31 mmol) in dry THF (1 ml) under an argon atmosphere at 0°C. After stirring for 2 h at 0°C, a solution of the ester **47** (300 mg, 1.16 mmol) in dry THF (3 ml) was added over 10 min. The reaction mixture was stirred under argon at 0°C for 20 h. The reaction mixture was then added to a vigorously stirred solution of 1M HCl (10 ml) over 40 min. This mixture was neutralized using sodium hydrogen carbonate and extracted with dichloromethane (5 × 50 ml). The organic layers were combined, dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography, eluting with 1:1 petroleum ether (b.p. 40-60°C): diethyl ether saturated with NH_3 (R_f 0.15 in diethyl ether saturated with NH_3) to give **165** (67 mg, 0.23 mmol, 61 % yield, based on recovered **47**) as a colourless oil. A small sample was recrystallised from diethyl ether for X-ray crystal determinations. (m.p. 111.5-112.5°C).

δ_H (300 MHz, $CDCl_3$): 1.52 (dd, J = 9.9, 7.5 Hz, 1 H, H_{5s}/H_{6s}), 1.63 (dd, J = 9.9, 7.5 Hz, 1 H, H_{5s}/H_{6s}), 1.94 (s, 3 H, CH_3), 2.05 (dd, J = 3.3, 1.5 Hz, 1 H, H_{5a}/H_{6a}), 2.13 (dd, J = 3.3, 1.2 Hz, 1 H, H_{5a}/H_{6a}), 2.71-2.73 (m, 1 H, H_4), 3.04 (AB, J = 14.4, 2 H, H_8), 3.35-3.45 (m, 2 H, H_{3x}, H_{3n}), 7.31-7.39, 7.45-7.49 (m, 5 H, Ph), 7.84 (bs, 1 H, OH). δ_C (75.5 MHz, $CDCl_3$): 13.23 (CH_3), 33.03 (C_4), 39.79 (C_5/C_6), 41.07 (C_5/C_6), 49.00 (C_8), 56.87 (C_3), 78.82 (C_1), 104.82 (N=C-CH_3), 127.21, 128.45 (5 × aryl CH), 130.48 (=CH), 136.00 (aryl C), 155.77 (C_7), 172.24 (C=O). ν_{max} (CH_2Cl_2): 3060br (O-H), 2960br (C-H), 1620s (C=O), 1430s, 1330m cm^{-1}. $^m/_z$ (%): 287 (MH^+, 6), 269 (100), 148 (19), 105 (20). $C_{16}H_{19}N_2O_3$ [MH^+] requires $^m/_z$ 287.1395; observed 287.1395. X-ray crystallographic data is in supporting information.

3-(2-Azabicyclo[2.1.1]hex-1-yl)-acrylic acid ethyl ester 168

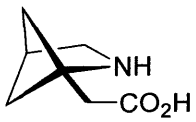


The ethyl ester **160** (10 mg, 0.03 mmol) was stirred in a solution of 3M HCl (2 ml) made *in situ* (dry ethanol (0.43 ml), dry ethyl acetate (1.2 ml) and acetyl chloride (0.36 ml) at 0°C for 1 h. The reaction mixture was washed with diethyl ether (3 × 0.5 ml) and then evaporated to dryness to

give the hydrochloride salt of **168** (8 mg, 0.03 mmol, 99 % yield).

δ_H (300 MHz, D_2O): 0.99 (t, J = 7.2 Hz, 3 H, $CH_2C\underline{H}_3$), 1.60 (d, J = 6.3 Hz, 2 H, H_{5s}, H_{6s}), 1.98-2.02 (m, 2 H, H_{5a}, H_{6a}), 2.70 (bs, 1 H, H_4), 3.21 (s, 2 H, H_{3x}, H_{3n}), 3.93 (q, J = 7.2 Hz, 2 H, $C\underline{H}_2CH_3$), 5.75 (d, J = 16.0 Hz, 1 H, H_8), 7.38 (d, J = 16.0 Hz, 1 H, H_7). δ_C (75.5 MHz, D_2O): 13.24 (CH_3), 36.00 (C_4), 40.78 (C_5, C_6), 49.56 (C_3), 62.18 ($\underline{C}H_2O$), 71.53 (C_1), 125.22 (C_8), 138.28 (C_7). ν_{max} (CH_2Cl_2): 3360br (N-H), 2940m (C-H), 1660br (C=O), (C=C), 1410m, 1320m, 1210m, 1160m, 1120m, 740s cm^{-1}. $^m/_z$ (%): 182 (MH^+, 100), 165 (31), 136 (30), 119 (51). $C_{10}H_{16}NO_2$ [MH^+] requires $^m/_z$ 182.1181; observed 182.1181.

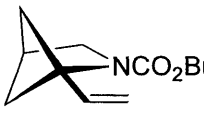
(2-Azabicyclo[2.1.1]hex-1-yl)-acetic acid 187



The nitrile **69** (40 mg, 0.15 mmol) was dissolved in 8M HCl (8 ml). The reaction mixture was heated to 90°C for 72 h. The reaction was monitored using mass spectroscopy. The crude product was purified by using a Dowex ion exchange column to give **187** (21 mg, 0.15 mmol, 100 % yield) as a white residue, which crystallised as fine needles (m.p. dec. 42-45°C).

δ_H (400 MHz, $CDCl_3$): 1.63 (dd, J = 6.1, 2.3 Hz, 2 H, H_{5s}, H_{6s}), 1.88-1.92 (m, 2 H, H_{5a}, H_{6a}), 2.62-2.64 (m, 1 H, H_4), 3.01 (s, 2 H, H_{3x}, H_{3n}), 3.26 (s, 2 H, $C\underline{H}_2CO$), 9.41 (bs, 2 H, NH, OH). δ_H (300 MHz, D_2O): 1.60 (dd, J = 6.0, 2.0 Hz, 2H, H_{5s}, H_{6s}), 2.02-2.06 (m, 2H, H_{5a}, H_{6a}), 2.85-2.87 (m, 1H, H_4), 3.00 (s, 2H, H_{3x}, H_{3n}), 3.38 (s, 2H, $C\underline{H}_2CO$). δ_C (300 MHz, D_2O): 34.48 (C_7), 36.02 (C_4), 39.88 (C_5, C_6), 49.77 (C_3), 69.58 (C_1), 173.05 (C=O). $^m/_z$ (%): 142 (MH^+, 100), 83 (28), 74 (50). $C_7H_{12}NO_2$ [MH^+] requires $^m/_z$ 142.0868; observed 142.0868.

1-Vinyl-2-azabicyclo[2.1.1]hexane-2-carboxylic acid *tert*-butyl ester 202

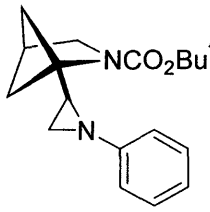


Potassium tertiary-butoxide (111 mg, 0.99 mmol) was stirred in dry THF (2 ml) under an argon atmosphere at 0°C. Methyltriphenylphosphonium bromide (355 mg, 0.99 mmol) was then added followed by dry THF (2 ml). The bright yellow mixture was stirred for 2 h at 0°C under an atmosphere of argon. The aldehyde **161** (200 mg, 0.94 mmol) was dissolved in dry THF (3 ml) and added to the reaction mixture at 0°C. The mixture was stirred for 20 h under an argon atmosphere. Ether saturated with water (2 ml) was added at room temperature and stirred for 10 min. Water (3 ml) was then added and stirred for a further 10 min. The organic layer was separated and the

aqueous layer extracted with diethyl ether (3 × 2 ml). The organic layers were combined, dried with 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 saturated with NH_3 (R_f 0.63 in 1:1 petroleum ether (b.p. 40-60°C): diethyl ether saturated with NH_3) to give **202** (84 mg, 0.40 mmol, 42 % yield) as a yellow oil.

δ_H (250 MHz, $CDCl_3$): 1.37 (bs, 9 H, 3 × CH_3), 1.54 (dd, J = 4.3, 1.7 Hz, 2 H, H_{5s}, H_{6s}), 1.78-1.82 (m, 2 H, H_{5a}, H_{6a}), 2.61-2.63 (m, 1 H, H_4), 3.34 (s, 2 H, H_{3x}, H_{3n}), 5.01-5.03 (m, 1 H, $\underline{H}_2C$=CH), 5.06 (s, 1 H, $\underline{H}_2C$=CH), 6.38-6.43 (m, 1 H, H_2C=C$\underline{H}$). δ_C (75.5 MHz, $CDCl_3$): 28.51 (3 × $\underline{C}H_3$), 33.61 (C_4), 43.59 (C_5, C_6), 52.39 (C_3), 73.71 (C_1), 79.24 ($\underline{C}(CH_3)_3$), 114.03 ($H_2\underline{C}$=C), 136.29 (C=$\underline{C}$H), 136.01 (aryl C), 156.08 (C=O). ν_{max} (CH_2Cl_2): 2980s (C-H), 1700br (C=O), (C=C), 1420s, 1360s, 1320s, 1120s cm^{-1}. $^m/_z$ (%): 210 (MH^+, 45), 118 (50), 110 (35), 93 (100).

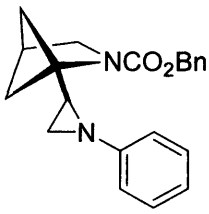
1-(1-Phenyl-aziridin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylic acid *tert*-butyl ester 203



The alkene **202** (66 mg, 0.31 mmol) was dissolved in dry dichloromethane (2 ml) and stirred under a nitrogen atmosphere in a reactivial. Phenyl azide (45 mg, 0.38 mmol) was added to the reaction. The mixture was heated at 90°C for 96 h. The crude product was purified by flash chromatography, eluting with 1:1 petroleum ether (b.p. 40-60°C): diethyl ether saturated with NH_3 (R_f 0.57) to give **203** (44 mg, 0.14 mmol, 46 % yield) as a yellow oil. A small sample was recrystallised from diethyl ether to form yellow crystals for X-ray crystal determination. (m.p. 59-60°C).

δ_H (300 MHz, $CDCl_3$): 1.22 (dd, J = 10.3, 7.2 Hz, 1 H, H_{5s}/H_{6s}), 1.39 (bs, 9 H, 3 × CH_3), 1.64 (dd, J = 9.9, 6.7 Hz, 1 H, H_{5s}/H_{6s}), 1.81 (dd, J = 7.0, 2.9 Hz, 1 H, H_{5a}/H_{6a}), 2.00 (dd, J = 6.3, 2.8 Hz, 1 H, H_{5a}/H_{6a}), 2.12 (d, J = 6.4 Hz, 1 H, *cis* H_8), 2.18 (d, J = 3.5 Hz, 1 H, *trans* H_8), 2.65-2.67 (m, 1 H, H_4), 2.90-2.94 (m, 1 H, H_7), 3.37-3.39 (m, 2 H, H_{3x}, H_{3n}), 6.88-6.92, 7.12-7.19 (m, 5 H, Ph). δ_C (75.5 MHz, $CDCl_3$): 28.61 (3 × $\underline{C}H_3$), 32.78 (C_8), 33.66 (C_4), 39.36 (C_5/C_6), 39.66 (C_7), 42.76 (C_5/C_6), 53.27 (C_3), 79.38 (C_1), 120.43, 122.23, 128.87 (5 × aryl CH). ν_{max} (CH_2Cl_2): 3020s (C-H), 2960s (C-H), 1690m (C=O), 1420m, 1260s, 1110w, 900s, cm^{-1}. $^m/_z$ (%): 301 (MH^+, 100), 245 (50), 201 (10), 91 (43). $C_{18}H_{25}N_2O_2$ [MH^+] requires $^m/_z$ 301.1916; observed 301.1916. X-ray crystallographic data is in supporting information.

1-(1-Phenyl-aziridin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylic acid benzyl ester 204

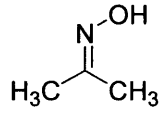


The alkene **78** (57 mg, 0.23 mmol) was dissolved in dry dichloromethane (2.5 ml) and stirred under a nitrogen atmosphere in a reactivial. Phenyl azide (33 mg, 0.28 mmol) was added to the reaction. The mixture was heated at 100°C for 72 h. The crude product was purified by flash chromatography, eluting with 1:1 petroleum ether (b.p. 40-60°C): diethyl ether saturated with NH_3 (R_f 0.48) to give **204** (61 mg, 0.16 mmol, 72 % yield) as a yellow oil.

δ_H (300 MHz, $CDCl_3$): 1.33 (dd, J = 10.1, 7.0 Hz, 1 H, H_{5s}/H_{6s}), 1.72 (dd, J = 10.1, 7.0 Hz, 1 H, H_{5s}/H_{6s}), 1.89 (dd, J = 7.0, 2.9 Hz, 1 H, H_{5a}/H_{6a}), 2.09 (dd, J = 7.0, 2.9 Hz, 1 H, H_{5a}/H_{6a}), 2.12 (d, J = 6.3 Hz, 1 H, *cis* H_8), 2.21 (d, J = 3.4 Hz, 1 H, *trans* H_8), 2.75-2.77 (m, 1 H, H_4), 3.07 (bs, 1 H, H_7), 3.54-3.58 (m, 2 H, H_{3x}, H_{3n}), 5.13 (AB, J = 18.4, 2 H, $C\underline{H}_2Ph$), 6.91-7.00, 7.18-7.49 (m, 10 H, 2 × Ph). δ_C (75.5 MHz, $CDCl_3$): 32.59 (C_8), 33.76 (C_4), 39.10 (C_7), 39.60 (C_5/C_6), 42.54 (C_5/C_6), 53.04 (C_3), 66.45 ($\underline{C}H_2Ph$), 74.39 (C_1), 120.44, 122.30, 127.88, 128.43, 128.89 (10 × aryl CH), 136.94 (aryl C), 154.44 (aryl C-N), 156.08 (C=O). ν_{max} (CH_2Cl_2): 3020m (C-H), 1690w (C=O), 1420m, 1260s, 740br cm^{-1}. $^m/_z$ (%): 335 (MH^+, 56), 291 (30), 274 (59), 196 (76), 185 (100), 91 (65). $C_{21}H_{23}N_2O_2$ [MH^+] requires $^m/_z$ 335.1759; observed 335.1759.

Synthesis of Reagents

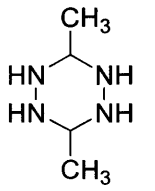
Acetoxime



Following the literature procedure,[186,187] hydroxylamine hydrochloride (5 g, 77.50 mmol) was dissolved in water (10 ml) and cooled to 0°C. Sodium hydroxide (3 g, 75 mmol) was dissolved in water (10 ml) and added dropwise at 0°C. Acetone (6 g, 103 mmol) was added dropwise to the mixture , where the temperature was not allowed to exceed 8°C. This was left to stand for 3 h to crystallise. The crude mixture was filtered and recrystallised using petroleum ether (b.p. 60-80°C). The product was obtained as white crystals (2.31 g, 32 mmol, 41 % yield).

$^{m}/_{z}$: 74 (MH^+).

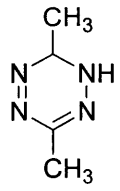
3,6-Dimethyl-[1,2,4,5]tetrazinane



Following the literature procedure,[95,96] acetaldehyde (22 g, 0.49 mol) was dissolved in ethanol (15 ml) and stirred at 0°C. Hydrazine hydrate (25 g, 0.49 mol) was dissolved in ethanol (15 ml) and added slowly. The mixture was left to for 2 h to crystallise. The product filtered and obtained as yellow crystals (27.88 g, 0.48 mol, 96 % yield). (m.p. 59-60°C). (Literature m.p. 60°C).[95,96]

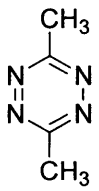
δ_H (250 MHz, $CDCl_3$): 1.85-1.90 (m, 6 H, 2 × CH_3), 4.91 (bs, 4 H, 4 × NH). $^{m}/_{z}$: 117 (MH^+).

3,6-Dimethyl-1,6-dihydro-[1,2,4,5]tetrazine



Following the literature procedure,[95,96] 3,6-Dimethyl-[1,2,4,5]tetrazinane (7.05 g, 60.70 mmol) was added to a solution of 3.3 % sodium hydroxide (93 g) and stirred. Platinum oxide (0.1 g) was added and oxygen gas bubbled through the solution. The reaction was stirred for 20 h while oxygen was bubbled through. A saturated solution of ammonium chloride (100 ml) was added and extracted using diethyl ether (5 × 100 ml). The organic layers were combined, dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The product was obtained as yellow crystals (1.46g, 13.02 mmol, 21 % yield). $^{m}/_{z}$: 113 (MH^+).

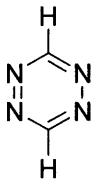
3,6-Dimethyl-[1,2,4,5]tetrazine



Following the literature procedure,[95,96] 3,6-Dimethyl-1,6-dihydro-[1,2,4,5]tetrazine (1.46 g, 13 mmol) was dissolved in water (200 ml) and sodium nitrite (0.34 g, 4.93 mmol) added. The mixture was stirred at 0°C and glacial acetic acid (20 ml) added. The solution was stirred at 0°C for 2 h, the colour changed from yellow to a red colour. The mixture was basified with calcium carbonate and brine (30 ml) added. The solution was extracted using diethyl ether until the aqueous layer was colourless. The organic layers were combined, dried with anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The product was obtained as pink crystals (0.44 g, 0.40 mmol, 31 % yield). (m.p. 72-73°C). (Literature m.p. 72°C).[95,96]

δ_H (250 MHz, $CDCl_3$): 2.96-3.02 (m, 6H, 2 × CH_3). $^m/_z$: 111 (MH^+).

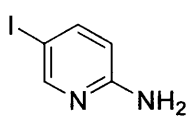
[1,2,4,5]Tetrazine



Following the literature procedure,[97] hydrazine hydrate (41.30 g, 0.82 mol) was added to formamidine acetate (41.10 g, 0.39 mol) in methanol (60 ml) at 0°C. Glacial acetic acid (4 × 20 ml) was added at 0°C over a period of 1 h. Sodium nitrite (50.90 g, 0.73 mol) was added in small portions keeping the temperature below 10°C. The mixture was stirred for 1 h at 0°C and then a further 2 h at room temperature. Solid sodium hydrogen carbonate (80 g) and water (200 ml) were added and the resulting suspension was stirred for 30 min. Undissolved sodium hydrogen carbonate was filtered off and the filtrate was extracted with dichloromethane (10 × 20 ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (3 × 10 ml), water (50 ml) and were dried over $CaCl_2$. The solvent filtered and was removed under reduced pressure to a volume of 50 ml. The crude product was purified by flash chromatography, eluting with diethyl ether. The product was obtained as red crystals (0.44 g, 5.36 mmol, 2 % yield). (m.p. 94-95°C). (Literature m.p. 94-95°C).[97]

δ_H (250 MHz, $CDCl_3$): 2.09-2.14 (m, 2 H, 2 × H). $^m/_z$: 83 (MH^+).

2-Amino–5-iodo-pyridine

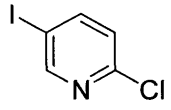


Following the literature procedure,[77,188] 2-aminopyridine (15 g, 0.16 mol), periodic acid (25 g, 0.03 mol) and iodine (16.18 g, 0.06 mol) were dissolved in a mixture of glacial acetic acid (300 ml) water (60 ml) and concentrated

H_2SO_4 (12 M, 9.5 ml) and stirred for 4 h at 80°C. After cooling the mixture was poured into a solution of saturated $Na_2S_2O_3$ (300 ml) and water (240 ml) to remove unreacted iodine. The solution was extracted with diethyl ether (3 × 300 ml), until the aqueous layer was colourless. The organic layers were combined, washed with sodium hydroxide solution (1M, 3 × 100 ml), dried with anhydrous potassium carbonate, filtered and the solvent removed under reduced pressure. The product was obtained as a yellow solid (38 g, 0.17 mol, 33 % yield).

δ_H (250 MHz, $CDCl_3$): 6.35 (d, J = 9.0 Hz, 1 H), 7.62 (dd, J = 9.0, 2.5 Hz, 1 H), 8.19 (d, J = 2.5 Hz, 1 H), 4.90 (bs, 2 H, NH_2).

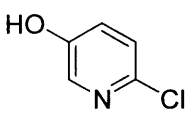
2-Chloro-5-iodo-pyridine



Following the literature procedure,[77,188] 2-amino-5-iodopyridine (35 g, 0.16 mol) was dissolved in concentrated HCl (12 M, 100 ml) to form an orange mixture at 0°C. Sodium nitrite (9.87 g, 0.14 mol) was added in portions over 2 h at 0°C and was stirred overnight at room temperature. The reaction mixture was poured into water (100 ml) and heated over a steam bath. The mixture was filtered to collect the yellow solid that formed. The product was re-crystallised from 2:1 ethanol : water to yield a crude product, which was purified by flash chromatography, eluting with petroleum ether (b.p. 40-60°C). The product was obtained as yellow crystals (8.66 g, 0.03 mol, 23 % yield). (m.p. 98-99°C). (Literature m.p. 99°C).[77,188]

δ_H (250 MHz, $CDCl_3$): 7.12 (d, J = 8.0 Hz, 1 H, H_3), 7.89 (dd, J = 8.0, 2.5 Hz, 1 H, H_4), 8.59 (d, J = 2.5 Hz, 1 H, H_6). δ_C (62.9 MHz, $CDCl_3$): 126.2, 146.8, 155.7 (C-H), 90.7 (C-I), 151.0 (C-Cl).

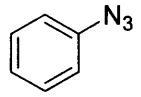
2-Chloro-5-hydroxy-pyridine



Following the literature procedure,[189] 2-chloro-5-iodo-pyridine (2.23 g, 9.32 mmol) was dissolved in dry THF (20 ml) and cooled to –78°C under an atmosphere of argon. A solution of *tert*-butyllithium (4.12 ml, 2.5 M in hexanes, 10.30 mmol) was added over a period of 20 min and the solution changed from yellow to dark orange. Trimethylborate (1.16 ml, 10.30 mmol) was added slowly over a period of 10 min, where the solution changed to a deep red colour. The mixture was stirred vigorously and taken to –10°C. Glacial acetic acid (0.8 ml, 14 mmol) and hydrogen peroxide

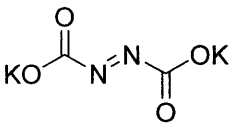
(30 %w.v., 1.5 ml, 9.32 mmol) were added and stirred for 30 min. The mixture was filtered and the crude product was purified by flash chromatography, eluting with 2:1 petroleum ether (b.p. 40-60°C): diethyl ether (R_f 0.53) to give (0.05 g, 0.37 mmol, 4 % yield) as a yellow crystals. δ_H (250 MHz, $CDCl_3$): 7.17-7.22 (m, 1 H, H_3), 7.46-7.50 (m, 1 H, H_4), 8.19 (s, 1 H, H_6).

Phenyl azide



Following the literature procedure,[180] a mixture of concentrated HCl (12 M, 14 ml) and water (75 ml) were stirred at -10°C. Phenyl hydrazine (8.87 g, 0.08 mol) was added over a period of 10 min and phenyl hydrazine hydrochloride formed as a white solid. The temperature was taken to 0°C and diethyl ether (25 ml) was added. Sodium nitrite (6.22 g, 0.09 mol) in water (10 ml) was added dropwise, keeping the temperature below 5°C. The mixture was steam distilled and the yellow distillate (80 ml) was collected. The organic layer was separated and the aqueous layer was extracted with diethyl ether (20 ml). The organic fractions were combined and washed with sodium hydroxide (2 M, 2 × 20 ml), dried using anhydrous calcium chloride and filtered. The crude compound was purified under vacuum distillation, behind an explosive proof-screen as phenyl azide may explode under reduced pressure. From the distillate solvent removed under reduced pressure leaving a yellow residue. The yellow residue was purified using azeotropic distillation, using a water bath at 87°C. The phenyl azide distilled at 55-56°C and was obtained as a yellow oil (2.87 g, 0.02 mol, 30 % yield). Phenyl azide was stored in the fridge in a sealed glass vial under nitrogen.

Potassium azodicarboxylate



Following the literature procedure,[77,190] Potassium hydroxide (25 g) in water (25 ml) was degassed and nitrogen bubbled through the solution at 0°C. This solution was added to azodicarbonamide (10.03 g, 0.08 mol) dropwise and ammonia gas evolved. After no evolution of ammonia gas, the yellow solid was filtered under nitrogen allowing minimal contact with air (CO_2) as possible. The solid was dissolved in cold water (30 ml) and poured into ethanol (175 ml), where a solid precipitate formed immediately. The solid was filtered and dried in a vacuum. The product was obtained as a bright yellow solid (15.08 g, 0.07 mol, 90 % yield).

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Appendix

Achievements

Presentations

24th June 2004, University of Sheffield
Royal Society of Chemistry
Organic Division Heterocyclic Group
19th Postgraduate Symposium in Heterocyclic Chemistry
Title: Nicotinic Acetylcholine Receptor Ligands from 2,4-Methanoproline

Poster Presentations

15th December 2003, GlaxoSmithKline, Harlow
Royal Society of Chemistry
Bio-Organic Postgraduate Symposium

1st April 2004, University of Leicester
Royal Society of Chemistry
AstraZeneca, Perkin Division, Younger Members Symposium

25th to 29th August 2004, Turin, Italy
'Set for Europe' Younger European Chemists' Conference

Publications

November 2003
Journal of Organic Chemistry, **2003**, *68*, 9348-9355

JOC Article

Modification of 1-Substituents in the 2-Azabicyclo[2.1.1]hexane Ring System; Approaches to Potential Nicotinic Acetylcholine Receptor Ligands from 2,4-Methanoproline Derivatives

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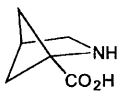
Received August 15, 2003

Successful nucleophilic substitution at a methylene attached to the bridgehead (1-) position of the 2-azabicyclo[2.1.1]hexane ring system opens the way to construction of novel derivatives having a wider range of functional groups attached to the 1-position via a methylene "spacer" (including the β-amino acid homologue of 2,4-methanoproline) and provides access to epibatidine analogues containing heterocyclic substituents and also to further homologation at the 1-position. Displacements with loss of a nucleofuge (e.g., loss of mesylate anion from the 1-mesyloxymethyl derivative) require thermal activation but proceed without the rearrangement initially anticipated in such a strained bicyclic ring system. A novel tricyclic carbamate intermediate **17** has been isolated; nucleophilic attack on **17** leads directly to the isolation of N-deprotected substitution products (with concomitant decarboxylation).

Introduction

There has been substantial recent interest in the 2-azabicyclo[2.1.1]hexane ring system, which forms the basis for the nonproteinogenic amino acid 2,4-methanoproline.[1] Early synthetic routes to the ring system were



2,4-methanoproline

based on photochemical intramolecular [2 + 2] cycloaddition strategies,[2] and there have been recent reports of alternative approaches, from 2-azabicyclo[2.2.0]hexane derivatives,[3] 3-halomethyl-1-aminocyclobutanes,[1,4] and *cis*-cyclobutene dicarboxylic anhydrides[5] so that the azabicyclic framework itself is now readily available.

Considerable recent effort has led to a significant widening of the range of methods for functionalization of the 2- and 5-/6-positions of the 2-azabicyclo[2.1.1]-hexane ring system.[3,5] In particular, Krow has recently introduced attractive approaches to 5(6)-*syn,anti*-difunctional derivatives[3a] and to control of lithiation at the 1- and 3-positions of *N*-Boc-2-azabicyclo[2.1.1]hexane leading to aldehydes and esters.[6] Other alternatives to the carboxylic acid group at the 1-position include nitriles[1] and pyridine derivatives,[2d] and hydride reduction of the cyano group[1] has been reported. However, we are not aware of any reports of displacement reactions at the 1-methylene position apart from replacement of a tosyl group by hydride in our own work (Scheme 1) in which we examined formal dyotropic rearrangements of *N*-chloro-derivatives of this strained ring system together with study of the elevated nitrogen inversion barrier.[7] The need to extend the range of functionalization at the 1-position is made more urgent by intense current activity in the construction of analogues of epibatidine[8] in the search for high affinity and high subtype selectivity

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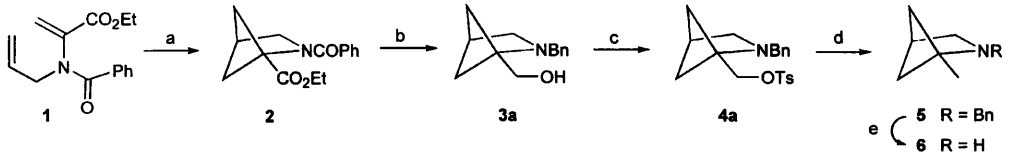
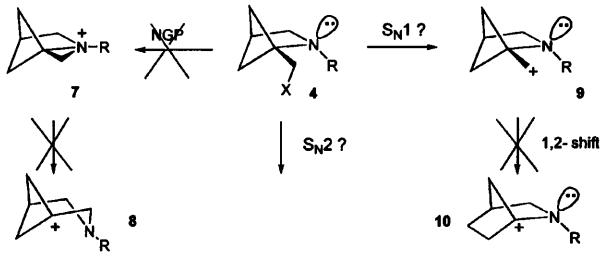
SCHEME 1[a]



[a] Reagents: (a) 254 nm (cf. ref 2a); (b) $LiAlH_4/Et_2O$, reflux (94%); (c) TsCl/pyridine, 4 °C (86%); (d) $LiAlH_4$/THF, reflux (92%); (e) H_2/Pd (100%).

at the nicotinic acetylcholine receptor (nAChR).[9] We have described epibatidine isomers[10] and homologues based on azabicyclic alternatives to the 7-azabicyclo[2.2.1]heptane skeleton[11] that have high affinity at the nicotinic acetylcholine receptor (nAChR), and modeling studies suggest that attachment of a heterocyclic substituent separated by one or more methylene spacers at the 1-position of 2-azabicyclo[2.1.1]hexane should also provide appropriate N–N distances and orientation for effective interaction at the receptor. Although Piotrowski has utilized the photochemical route to produce 2-azabicyclo[2.1.1]hexane derivatives having pyridine substituents directly attached to the 1-position,[2d] we were anxious to widen the range of potential nAChR agonists by extending the chain length and the range of available attached heterocycles[12] at the 1-position. We here describe successful substitution reactions at the 1-methylene position, opening the way to the isolation of useful intermediates for further elaboration. Manipulation of *N*-protecting groups is also described together with a convenient refinement of the substitution process that involves participation by *N*-alkoxycarbonyl protecting groups.

SCHEME 2



Discussion

Scheme 1 summarizes the preparation of **2** from *N*-benzoyl *N*-allyldehydroalanine ethyl ester **1** using the reliable photolytic approach originally established by Pirrung[2a] and Clardy and Hughes[2b,c] and includes our earlier conversion of the 1-ethoxycarbonyl group into methyl via the tosylate **4a** (by displacement using the sterically undemanding hydride ion).[7] This proceeded efficiently to give **5** and hence the secondary amine **6** (via hydrogenolysis), which provided the *N*-chloroamine with sodium hypochlorite solution.[7] We did not expect to be able to achieve ready S_N2 displacement of a leaving group at the hindered ("pseudo-neopentyl") 1-methylene group in **4** using other, more sterically demanding nucleophiles.

Some possible substitution pathways from **4** are shown in Scheme 2. Any thought of a "double displacement" leading to substitution via neighboring group participation of the amino-nitrogen lone pair is unlikely on the basis of the orientation of the lone pair and the strain in intermediate **7** (although this strain could, in principle, be released by C–N bond cleavage to **8** to yield 3-azabicyclo[3.1.1]heptane isomers). We did not expect to achieve useful S_N1 substitution in view of the propensity of the strained azabicyclo[2.1.1]hexane system for skeletal rearrangement or fragmentation.[7] However, further consideration is justified when the limited options for rearrangement of the primary carbocation **9** are considered. The strained rearranged bridgehead cation **10** should be intrinsically inaccessible; resonance stabilization by the (almost orthogonal) nitrogen lone pair is clearly impossible, and the electronegative nitrogen would further destabilize the hypothetical cation **10**.

Initial scoping studies were carried out starting with the readily available *N*-benzyl-protected alcohol **3a** in order to establish whether displacement reactions were feasible. Conversion of **3a** into the mesylate **11a** (88%) was followed by successful but slow displacement with KCN in the presence of 18-crown-6 at 80 °C, giving the

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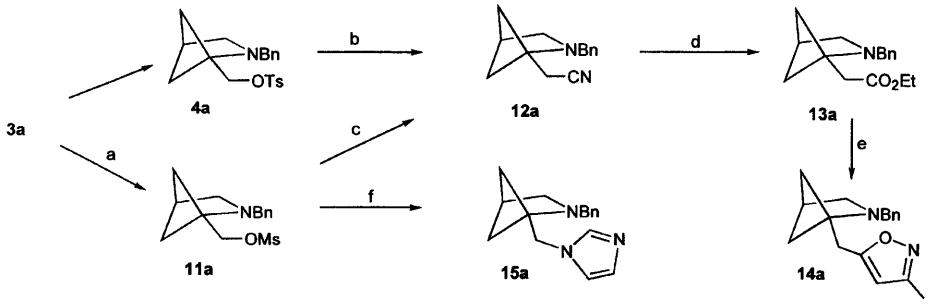
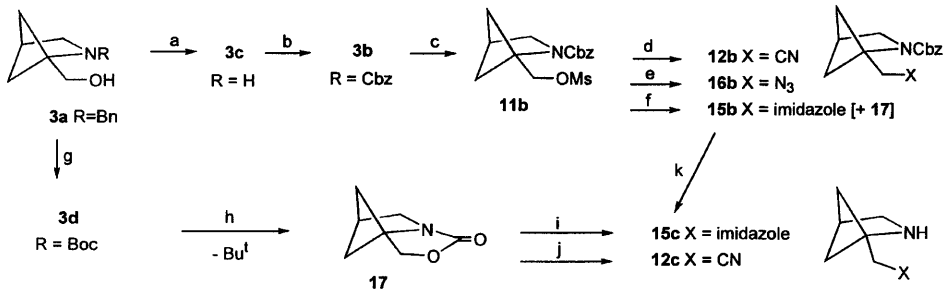
SCHEME 3[a]



[a] Reagents: (a) $MsCl/CH_2Cl_2$ (88%); (b) KCN, 18-crown-6, CH_3CN, 80 °C, 48 h (65%); (c) as (b), 60 °C (78%); (d) (i) H^+/H_2O, (ii) $SOCl_2$, (iii) EtOH (32%); (e) (i) acetoxime, BuLi, (ii) concentrated HCl, 90 °C; (f) imidazole/NEt_3/acetonitrile, 90 °C, 48 h (29%).

SCHEME 4[a]



[a] Reagents: (a) H_2/Pd (100%); (b) BnOCOCl, pH 7–8 (40%); (c) $MsCl/CH_2Cl_2/NEt_3$ (80%); (d) KCN, 18-crown-6, CH_3CN, 80 °C, 48 h (78%); (e) NaN_3, DMF (85%); (f) imidazole/BuLi/CH_3CN (**15b**, 43%; **17**, 6%;); (g) H_2/Pd/C/MeOH, $(Boc)_2O$ (60%); (h) $MsCl/CH_2Cl_2/NEt_3$ (88%); (i) as (f) (40%); (j) as (d) (55%); (k) TMSI, HBF_4, CH_2Cl_2 (90%).

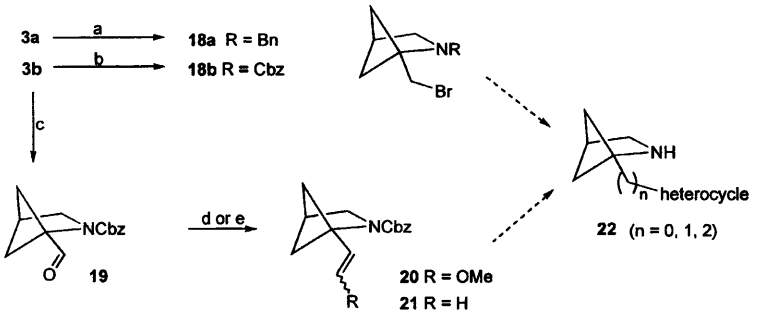
nitrile **12a** in 63% yield (Scheme 3; yields are not optimized). The use of mesylate proved slightly more effective than the conversion via the tosylate **4a**. Acid hydrolysis/esterification of **12a** gave the ester **13a**. Conversion into the methylisoxazole[12a] **14a** was attempted despite the potential for competing pathways based, for example, on enolization of **13a**, and a sample of **14a** was isolated in very low yield (as shown by signals at δ 5.96 and 2.26, corresponding to the lone isoxazole proton and the methyl group, respectively). This is not a practical preparative route but was our first example of a heterocyclic derivative of the title ring system attached to the 1-position by a methylene "spacer". The synthesis of a second example was achieved by treatment of **11a** with imidazole in the presence of triethylamine, giving **15a** directly in 29% yield and demonstrating that the direct displacement approach is also effective using a nitrogen nucleophile. The conditions for the substitution reactions are suggestive of S_N2 reactivity (the methylene bridges of the azabicyclic system clearly offer less steric hindrance than a normal neopentyl system), but we have no further evidence, as yet, concerning the balance between S_N2 and S_N1.

Having established the validity of the basic approach in Scheme 3 in the *N*-benzyl-protected (a) series, we explored the use of *N*-alkoxycarbonyl groups to protect the nitrogen, i.e., the (b) series shown in Scheme 4. The use of *N*-alkoxycarbonyl instead of *N*-benzoyl in the initial photochemical reaction has been used by Piotrowski to produce 1-aryl and 1-pyridyl 2-azabicyclo-[2.1.1]hexane derivatives,[2d] but in our hands the yields of photoadducts using the benzyloxycarbonyl (Cbz) group were poor. We therefore chose to debenzylate **3a** and reprotect the secondary amine **3c** with the Cbz (**3b**) and Boc (**3d**) groups.[13]

Scheme 4 shows the preparation of the *N*-protected derivative **3b** and conversion into the mesylate **11b** together with further substitution reactions. Nucleophilic displacement on **11b** using cyanide ion gave the nitrile **12b** in 78% yield. An X-ray crystal determination confirmed the retention of the 2-azabicyclo[2.1.1]hexane core of **12b**. Spectroscopic comparisons and protonation studies within the *N*-Bn and *N*-Cbz series eliminated any possibility of isomeric 3-azabicyclo[3.1.1]heptane derivatives derived from the hypothetical intermediate **8**. Further chemical interconversions confirmed the absence of rearrangement in both series; for example, reduction of the cyanomethyl derivative **12a** gave a primary amine attached to the 1-position by a bismethylene chain. Treatment of **11b** with azide ion provided the azide **16b** (85% yield), and use of the imidazole anion gave **15b** together with a minor product that was identified as the cyclic carbamate **17** (6% yield). The products **15b** and **17** were also formed (27% and 36%, respectively) using imidazole and triethylamine to displace the mesyl group. Clearly the cyclic carbamate **17** is formed by NGP of the benzyloxycarbonyl oxygen with loss of benzyl, and predictably, it was produced more efficiently under similar reaction conditions via loss of *tert*-butyl from the *N*-Boc-

(13) *N*-Boc- and *N*-Cbz derivatives of the parent 2-azabicyclo[2.1.1]-hexane derivatives have been described.[3a,6]

SCHEME 5[a]



[a] (a) $SOBr_2$ (77%); (b) CBr_4/PPh_3 (80%); (c) Swern oxidation (90%); (d) **(20)** methoxymethylenetriphenylphosphorane; (e) **(21)** methylenetriphenylphosphorane 63%.

protected derivative **3d**. This observation raises the possibility of wider involvement of the carbonyl of the Cbz protecting group in other displacements in Scheme 4, although the fact that corresponding reactions in the *N*-Bn and *N*-Cbz series require similar temperatures and reaction times weakens the case for wider NGP by the carbonyl group. More detailed kinetic investigations will be required to clarify this issue. Nucleophilic attack at the 1-methylene position of **17** by the imidazolyl anion required more vigorous conditions than for the mesylate **11b** but provided the *N*-deprotected compound **15c** directly (with concomitant decarboxylation) in good yield; the identical secondary amino-compound **15c** was also formed by *N*-deprotection of **15b** using TMSI. Similar treatment of **17** with cyanide ion gave **12c**. The value of **17** as a convenient direct source of *N*-deprotected 1-functionalized derivatives of the 2-azabicyclo[2.1.1]hexane ring system is under continuing study.

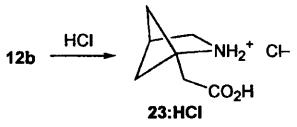
The potential for synthesis of a wider range of derivatives of this ring system is illustrated in Scheme 5. The bromo-derivative **18a** was isolated from treatment of **3a** with thionyl bromide (77%) and **18b** was accessible from **3b** using CBr_4/PPh_3 (80%); these compounds will form the basis for coupling chemistry. Swern oxidation of **3b** provided the aldehyde **19**, which was converted into the mixture of vinyl ethers **20** and the alkene **21** using established Wittig methodology.[14] The vinyl ethers **20** are precursors of systems containing pendant heterocycles including diazenes[14] and were isolated in acceptable purity, although they were not amenable to chromatographic purification.[16] Pyridyl derivatives **22** should be accessible from the alkenes using reductive Heck chemistry[15] and from halo-derivatives (e.g., **18**) via coupling reactions. These intermediates are currently forming the basis for the synthesis of target compounds having a wider range of nitrogen heterocycles attached to the 1-position by methylene chains of varying lengths. Such derivatives should allow systematic investigation of the effects of the key N–N distances (secondary N/heterocyclic N) and orientation on nAChR subtype selectivity.

(14) For typical procedures, see ref 12c. For the preparation of **20** we used potassium *tert*-butoxide in place of LDA.

(15) See refs 10b and 11 for typical reductive Heck procedures and references to the work of other groups.

(16) The purity of **20** was estimated to be greater than 90% by NMR. The spectra were complicated further owing to the presence not only of *cis/trans* isomers but also of slow rotation about the C-N bond. Spectra of many *N*-alkoxycarbonylamines in this work showed the effects of slow rotation (cf. ref 11).

The recent interest in 2,4-methanoproline[1] led us to synthesize the novel homologue, the *β*-amino acid **23**, by hydrolysis of the 1-cyanomethyl derivative **12b**. The crude hydrochloride salt **23**·HCl was isolated directly in good yield and ion-exchange chromatography provided the crystalline amino acid **23**. Derivatization and further chemistry of **23** is under continuing study.



Conclusions

Nucleophilic substitution has been successfully demonstrated (without rearrangement) at a methylene group attached to the 1-position of the 2-azabicyclo[2.1.1]hexane ring system and has led to the isolation of a broad selection of novel substituted derivatives. The work has demonstrated that a wide range of 1-substituted intermediates having different chain lengths are accessible, including heterocyclic derivatives that have significance as potential ligands for the nAChR. The methodology will also be applicable to precursors bearing substituents in the azabicyclic core.

Experimental Section

NMR spectra were recorded in $CDCl_3$ using tetramethylsilane as internal standard. Routine mass spectra were measured using electrospray, and accurate mass measurements were made using FAB. All reactions were performed in oven-dried glassware under dry nitrogen (or argon where stated). Commercially available solvents were purified and dried, when necessary, prior to use. "Ether" refers to diethyl ether and "petrol" to petroleum ether, bp 40–60 °C, unless indicated otherwise.

Flash chromatography was carried out using silica gel (60) unless stated otherwise. Thin-layer chromatography was conducted on silica 60-254 plates. Chromatography solvents were routinely saturated with ammonia gas for amine (and *N*-protected amine) separations.

***N*-Benzoyl-*N*-allyldehydroalanine Ethyl Ester, 1.** Allylamine (9.38 mL, 125 mmol) was added dropwise to a stirred solution of ethyl pyruvate (13.7 g, 125 mmol) in toluene (150 mL), and stirring was continued for 3 h at room temperature. The organic layer was separated, and the aqueous layer was extracted with toluene (3 × 150 mL). The combined organic layers were dried with $MgSO_4$ and filtered. Distilled triethylamine (19.5 mL, 140 mmol) was added under nitrogen,

followed by dropwise addition of benzoyl chloride (16.3 mL, 140 mmol) over 15 min. After the mixture stirred overnight, the triethylamine hydrochloride was filtered off, and the solvent was evaporated to give crude **1** (42.91 g). A sample (18.36 g) was chromatographed (3:7 ether/petrol; R_f 0.19), yielding **1** as a pale yellow oil (6.53 g, 47%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.17 (t, J = 7.0 Hz, 3H), 4.07 (q, J = 7.0 Hz, 2H), 4.31 (bd, J = 6.0 Hz, 2H), 5.20 (ddt, J = 10.0, 1.5, 1.0 Hz), 5.24 (ddt, J = 17.0, 1.5, 1.5 Hz), 5.51 (bs, 1H), 5.92 (ddt, J = 17.0, 10.0, 6.0 Hz, 1H), 6.07 (bs, 1H), 7.26–7.52 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.8 (CH_3), 51.8, 61.4, 117.8, 121.8 (CH_2), 127.9, 130.0, 132.8 (CH), 135.6 (C), 140.6 (C), 163.7, 170.6 (C). ν_{max} ($CDCl_3$): 1702 1652, 1625, cm^{-1}. *m/z*: 260.12865; $C_{15}H_{18}NO_3$ [MH$^+$] requires 260.12867.

2-Benzoyl-2-azabicyclo[2.1.1]hexane-1-carboxylic Acid Ethyl Ester, 2. These methods were based on the work of Pirrung[2a] and Clardy.[2b,c] Compound **1** (1.0–1.5% in dry benzene containing 0.2% acetophenone) was photolyzed in quartz tubes in a Rayonet reactor (254 nm, 40 h) to give crystalline **2**, mp 105.5–106.5 °C, in 65% yield after chromatography (1:1 ether/petrol). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.31 (t, J = 7.0 Hz, 3H), 1.81 (dd, J = 5.0, 2.0 Hz, 2H), 2.19 (m, 2H), 2.81 (m, 1H), 3.56 (bs, 2H), 4.28 (q, J = 7.0 Hz, 2H), 7.36–7.52, 7.71–7.79 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.4 (CH_3), 35.7 (CH), 42.2, 55.5, 61.4 (CH_2), 70.7 (C), 128.7, 128.8, 131.7 (CH), 135.0 (C), 168.8, 174.2 (C=O). ν_{max} ($CDCl_3$): 1733, 1652 cm^{-1}. *m/z*: 260.12862; $C_{15}H_{18}NO_3$ [MH$^+$] requires 260.12867. Further crystallization from ether gave an analytical sample, mp 106.5–107 °C. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 68.48; H, 6.61; N, 5.40. Found: C, 68.42; H, 6.65; N, 5.43. X-ray crystallographic data for **2** are recorded in Supporting Information.

Photolysis of a 1.5% solution of **1** in acetone (254 nm, 60h) followed by filtration through silica (7:3 petrol/ether) gave material, mp 106–107 °C, in ca. 40% yield; although the yield was lower, this method was readily adaptable to production of **2** on a multigram scale because yields were more consistent and the chromatographic separation was simpler.

(2-Benzyl-2-azabicyclo[2.1.1]hex-1-yl)methanol, 3a. The ester **2** (2.32 g, 8.95 mmol) in dry THF (20 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (1.358 g, 35.78 mmol) in dry THF (40 mL). The mixture was heated at 68 °C for 36 h, cooled, and quenched with water-saturated ether. The slurry was filtered through Celite, and the solvent was removed under reduced pressure prior to chromatographic purification. The less polar impurities were eluted with ether and the product was then flushed off the column with 9:1 ether: methanol (saturated with NH_3, R_f 0.10) to give crystalline **3a** (1.75 g, 96%), mp 58–59 °C after recrystallization from petrol. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.62 (bs, 4H), 2.60 (bs OH), 2.66 (bs, 1H), 2.67 (bs, 2H), 3.69 (bs, 2H), 3.79 (bs, 2H), 7.20–7.44 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 37.2 (CH), 38.2 (CH_2), 55.8 (CH_2), 57.9 (CH_2), 61.9 (CH_2), 74.3 (C), 127.4, 128.8, 129.0 (CH), 139.8 (C). *m/z*: 204.13884; $C_{13}H_{18}NO$ [MH$^+$] requires 204.13885. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 77.06; H, 8.41; N, 6.88.

1-Hydroxymethyl-2-azabicyclo[2.1.1]hexane-2-carboxylic Acid Benzyl Ester, 3b. Following the procedure of Cox,[17] **3c** (0.908 g, 8.03 mmol) was dissolved in distilled water (10 mL) and cooled to 0 °C. Aqueous sodium hydroxide (12 M, 2.5 mL) was added dropwise, and when addition was halfway through (pH 12), the simultaneous addition of benzyl chloroformate (2.97 mL, 20.81 mmol) was begun. Addition of the sodium hydroxide was finished just after that of the benzyl chloroformate, and stirring was continued at 0 °C for 15 min and then at room temperature for 24 h. Distilled water (10 mL) was added to the reaction mixture. The organic layer was run off, and the aqueous layer was extracted with CH_2Cl_2 (6 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. Chromatography (7:3 petrol/ether saturated with NH_3, R_f 0.17) gave **3b** (0.884 g, 45%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.57 (dd, J = 4.8, 1.8 Hz, 2H), 1.79 (m, 2H), 2.77–2.79 (m, 1H), 3.46 (s, 2H), 3.95 (d, J = 7.0 Hz, 2H), 4.60 (bs, 1H), 5.14 (s, 2H), 7.26–7.38 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 34.7 (CH), 42.1, 52.4, 61.9, 67.1 (CH_2), 74.9 (C), 128.2, 128.4, 128.9 (CH), 137.0 (C), 156.0 (C=O). ν_{max} ($CDCl_3$): 3420, 1684 cm^{-1}. *m/z*: 248.12867; $C_{14}H_{18}NO_3$ [MH$^+$] requires 248.12866.

(2-Azabicyclo[2.1.1]hex-1-yl)-methanol, 3c. Compound **3a** (768 mg, 3.78 mmol) in dry methanol (20 mL) was hydrogenated using 10% Pd/C (250 mg) at room temperature for 24 h. Ammonia gas was bubbled through the solution, which was filtered through Celite. The solid was washed with methanol saturated with NH_3 (100 mL), and the combined methanol extracts were evaporated under reduced pressure to yield **3c** (427 mg, 100%) as a yellow oil. (R_f 0.10 in 6:4 ether/methanol saturated with NH_3). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.53 (dd, J = 4.4, 1.8 Hz, 2H), 1.86 (m, 2H), 2.79 (m, 1H), 3.05 (m, 2H), 3.74 (s, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 37.1 (CH), 39.8, 48.5, 62.2 (CH_2), 70.6 (C). ν_{max} ($CDCl_3$): 3375, 1650, 1638 cm^{-1}. *m/z*: 114.09181; $C_6H_{12}NO$ [MH$^+$] requires 114.09189.

1-Hydroxymethyl-2-azabicyclo[2.1.1]hexane-2-carboxylic Acid *tert*-Butyl Ester, 3d, from 3a. Compound **3a** (60 mg, 0.295 mmol) was stirred in dry methanol (1 mL) with (10%) Pd/C (250 mg) and Boc_2O (45 mg, 0.206 mmol) at room temperature for 24 h. The mixture was filtered through Celite, and the solid was washed with ethyl acetate saturated with NH_3 (30 mL) and methanol saturated with NH_3 (30 mL). The combined organic layers were evaporated under reduced pressure, and the product was chromatographed (7:3 petrol/ether saturated with NH_3, R_f 0.58) to give **3d** (38 mg, 60% yield) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.48 (s, 9H), 1.56 (dd, J = 4.6, 1.8 Hz, 2H), 1.76 (m, 2H), 2.75 (m, 1H), 3.37 (s, 2H), 3.93 (d, J = 7.0 Hz, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 29.0 (CH_3), 34.7 (CH), 42.2, 52.9, 62.2 (CH_2), 74.6 (C), 80.3 (C), 156.2 (C). *m/z*: 214.14432; $C_{11}H_{20}NO_3$ [MH$^+$] requires 214.14429.

Toluene-4-sulfonic Acid (2-Benzyl-2-azabicyclo[2.1.1]-hex-1-ylmethyl) Ester, 4a. A solution of the alcohol **3a** (2.03 g; 10 mmol) in dry pyridine (50 mL) was cooled in an ice bath, and tosyl chloride (3.81 g; 20 mmol) was added portionwise so that the temperature did not exceed 10 °C. The mixture was left overnight at 4 °C, poured into ice water, and basified with aqueous NH_3. The resulting yellowish solid was slurried and filtered twice more with ice water (2 × 100 mL). The solid was dried under vacuum to afford the tosylate **4a** (3.08 g; 86%), which was used without further purification. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.52 (m, 2H), 1.68 (m, 2H), 2.43 (s, 3H), 2.65 (m, 3H), 3.58 (bs, 2H), 4.18 (s, 2H), 7.2–7.3 (m, 7H), 7.75 (d, J = 8 Hz, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 22.0 (CH_3), 37.2 (CH), 38.4, 56.9, 58.1, 69.8 (CH_2), 70.9 (C), 127.2, 128.3, 128.6, 128.9, 130.2 (CH), 133.3, 139.9, 145.2 (C). ν_{max} (CH_2Cl_2): 1598 cm^{-1}. *m/z*: 358.14769; $C_{20}H_{24}NO_3S$ [MH$^+$] requires 358.14764. X-ray crystallographic data for **4a** are recorded in Supporting Information.

2-Benzyl-1-methyl-2-azabicyclo[2.1.1]hexane, 5. A solution of **4a** (3.00 g, 8.4 mmol) in dry THF (80 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (1.60 g, 40 mmol) in dry THF (120 mL) and heated overnight under reflux. After careful decomposition of the excess $LiAlH_4$ using water-saturated ether, the mixture was filtered, dried with $MgSO_4$, and evaporated under vacuum to yield **5** as a pale yellow oil (1.44 g, 91%). An analytical sample was obtained by chromatography on alumina (ether). ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.29 (s, 3H), 1.41–1.62 (m, 4H), 2.55 (brs, 1H), 2.59 (brs, 2H), 3.60 (s, 2H), 7.13–7.44 (m, 5H). ^{13}C NMR (15 MHz, $CDCl_3$): δ 17.7 (CH_3), 36.6 (CH), 40.8, 56.0, 57.9 (CH_2), 70.1 (C), 126.8,

(17) Cox, C. D. PhD Thesis, University of Leicester, 2000. We thank Caroline Cox for a synthesis of **18b** and the corresponding iodo-derivative. Details of coupling investigations will be reported in due course. We also acknowledge her additional assistance with the optimization of yields for compounds **2**, **3a**, and **4a**.

128.4, 128.9 (CH), 140.6 (C). Anal. Found: C, 83.04; H, 9.17; N, 7.36. $C_{13}H_{17}N$ requires C, 83.37; H, 9.15; N, 7.48.

1-Methyl-2-azabicyclo[2.1.1]hexane Hydrochloride, 6·HCl, and Picrate Salt of 6. A solution of **5** (0.48 g, 2.57 mmol) in ethanol (15 mL) was hydrogenated over 10% Pd/C (0.14 g) for 24 h. The reaction mixture was filtered through Celite, and dry HCl gas was passed through the cooled filtrate. Removal of solvent left a dark oil, which was dissolved in the minimum of CH_2Cl_2 and treated with ether to precipitate the hydrochloride salt. This was filtered and dried under vacuum to afford **6**·HCl, which was used without further purification. ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.70 (s, 3H), 1.83 (brs, 4H), 2.78 (brs (1H), 3.30–3.48 (m, 2H), 9.88 (brs, exch. 2 × NH). Solutions of the free amine **6** were prepared as required by dissolution of the salt in water and basification with 2 M aqueous NaOH. The free amine was then extracted into ether (or an alternative solvent such as a low-boiling chlorofluorocarbon) and dried by passage through a short column of $MgSO_4$. ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.70 (s, 3H), 1.83 (brs, 4H), 2.78 (brs, 1H), 3.30–3.48 (m, 2H), 9.88 (brs, NH). The hydrochloride **6**·HCl was hygroscopic, and a solution of **6** in ether was used to prepare an analytical sample of **6** as the picrate salt. A solution of the free amine was concentrated carefully under reduced pressure and treated with a dry, saturated solution of picric acid in ether until no further precipitate appeared. The supernatant was removed from the precipitate, which was washed with a small aliquot of cold, dry ether. The precipitate was recrystallized from 80% ethanol/water, filtered, and dried under vacuum to afford the picrate salt of **6** as a yellow crystalline solid, mp 166–172 °C (dec). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.22 (bd, J = 4 Hz, 2H), 1.38 (s, 3H), 1.55 (bd, 2H), 2.03 (brs, NH), 2.64 (m, 1H), 2.97 (brs, 2H). Anal. Found: C, 44.09; H, 4.32; N, 17.02. $C_{12}H_{14}N_4O_7$ requires C, 44.18; H, 4.33; N, 17.17.

1-Methanesulfonic Acid (2-Benzyl-2-azabicyclo[2.1.1]-hex-1-ylmethyl) Ester, 11a. Methanesulfonyl chloride (0.726 mL, 9.39 mmol) was added dropwise to a solution of the alcohol **3a** (1.74 g, 8.53 mmol) in dry CH_2Cl_2 (15 mL) followed by dry triethylamine (2.38 mL, 17.06 mmol). The reaction was heated at 30 °C for 20 h, filtered to remove triethylamine hydrochloride, and washed with distilled water (2 × 25 mL) and finally with saturated $NaHCO_3$ (30 mL). The organic layer was dried with anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to yield **11a** (2.10 g, 88%) as a brown oil, which was used without further purification. (R_f 0.29 in ether saturated with NH_3). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.61 (dd, J = 4.6, 1.4 Hz, 2H), 1.71 (m, 2H), 2.65 (s, 3H), 2.92 (s, 3H), 3.65 (s, 2H), 4.38 (s, 2H), 7.1–7.4 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 36.7 (CH), 37.4 (CH_3), 38.1 (CH_2), 56.4 (CH_2), 57.6 (CH_2), 68.4 (CH_2), 70.8 (C), 126.9, 128.2, 128.5 (CH), 139.3 (C). ν_{max} ($CDCl_3$): 3430, 1638, 1628 cm^{-1}. m/z: 282.11639 (MH^+); $C_{14}H_{20}NO_3S$ [MH^+] requires 282.11644.

1-Methanesulfonyloxymethyl-2-azabicyclo[2.1.1]hexane-2-carboxylic Acid Benzyl Ester, 11b. Compound **3b** (606 mg, 2.45 mmol) in CH_2Cl_2 (10 mL) was treated with methanesulfonyl chloride (0.209 mL, 2.695 mmol) and dry triethylamine (0.683 mL, 4.9 mmol) using the procedure for **11a** and gave **11b** (0.670 g, 81%) as a pale yellow oil (R_f 0.76 in 4:1 petrol/ether saturated with NH_3). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.47 (dd, J = 4.0, 1.7 Hz, 2H), 1.94 (m, 2H), 2.74 (m, 1H), 2.92 (s, 3H), 3.42 (s, 2H), 4.76 (s, 2H), 5.02 (s, 2H), 7.2–7.4 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 34.7 (CH), 37.3 (CH_3), 41.5, 52.2, 66.6, 68.6 (CH_2), 69.7 (C), 127.9, 128.0, 128.5 (CH), 136.3 (C), 155.6 (C). ν_{max} ($CDCl_3$): 1750, 1685, 1636 cm^{-1}. m/z: 326.10622; $C_{15}H_{20}NO_5S$ [MH^+] requires 326.10620.

(2-Benzyl-2-azabicyclo[2.1.1]hex-1-yl)-acetonitrile, 12a. Potassium cyanide (1.47 g, 22.51 mmol) and 18-crown-6 (0.238 g, 0.90 mmol) were added to a solution of mesylate **11a** (1.58 g, 5.63 mmol) in dry acetonitrile (8 mL). The mixture was heated at 60 °C for 72 h, cooled, triturated with ether, and filtered, and the solvent was removed under reduced pressure. Chromatography (4:1 petrol/ether saturated with NH_3, R_f 0.77) gave **12a** (0.778 g, 65%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.68 (dd, J = 4.6, 1.6 Hz, 2H), 1.79 (m, 2H), 2.70 (bs, 5H), 3.64 (s, 2H), 7.22–7.47 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.0 (CH_2), 36.5 (CH), 39.4 (CH_2), 55.9 (CH_2), 57.9 (CH_2), 68.4 (C), 117.4 (CN), 127.0, 128.3, 128.5 (CH), 139.2 (C). m/z: 213.13917; $C_{14}H_{17}N_2$ [MH^+] requires 213.13918.

1-Cyanomethyl-2-azabicyclo[2.1.1]hexane-2-carboxylic Acid Benzyl Ester, 12b. The mesylate **11b** (350 mg, 1.08 mmol) in dry acetonitrile (5 mL) was reacted with KCN (280 mg, 4.30 mmol) and 18-crown-6 (4.4 mg, 0.165 mmol). After 48 h of heating at 60 °C and workup as described for **12a**, the solid product was chromatographed (7:3 petrol/ether saturated with NH_3, R_f 0.23) to give **12b** (215 mg, 78%); a small sample was recrystallized from ether for CHN analysis and X-ray determinations, mp 86.5–88.0 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.51 (dd, J = 4.7, 1.95 Hz, 2H), 1.92 (m, 2H), 2.72–2.75 (m, 1H), 3.24 (s, 2H), 3.42 (s, 2H), 5.04 (s, 2H), 7.12–7.29 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.6 (CH_2), 34.1 (CH), 42.9, 52.3, 66.5 (CH_2), 68.2 (C), 117.2 (CN), 127.6, 127.9, 128.4 (CH), 136.3 (C), 155.8 (C). m/z: 257.12900; $C_{15}H_{17}N_2O_2$ [MH^+] requires 257.12905. Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.39; H, 6.54; N, 11.13. X-ray crystallographic data for **12b** are recorded in Supporting Information.

(2-Azabicyclo[2.1.1]hex-1-yl)-acetonitrile, 12c. The carbamate **17** (20 mg, 0.144 mmol) was reacted with KCN (37 mg, 0.57 mmol) and 18-crown-6 (6 mg, 0.023 mmol) in dry acetonitrile (3 mL) and heated at 80 °C for 168 h. After workup as described for **12a**, chromatography (9:1 ether/methanol saturated with NH_3, R_f 0.14) yielded **12c** as a yellow oil (12 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (dd, J = 4.38, 1.77 Hz, 2H), 1.79 (m, 2H), 2.10 (bs, NH), 2.79 (m, 2H), 2.81 (m, 1H), 3.07 (s, 2H). ^{13}C NMR (75.8 MHz, $CDCl_3$): δ 22.0 (CH_2), 37.2 (CH), 41.8, 49.3 (CH_2), 64.9, 116.9 (C). m/z: 123 (MH^+).

(2-Benzyl-2-azabicyclo[2.1.1]hex-1-yl) Acetic Acid Ethyl Ester, 13a. The nitrile **12a** (0.691 g, 3.25 mmol) was heated in 8 N HCl (5 mL) at 90 °C for 96 h. After cooling and evaporation to dryness under reduced pressure, thionyl chloride (4 mL, 54.37 mmol) was added. The mixture was heated to 40 °C for 5 h and evaporated to dryness, and absolute ethanol (5 mL) was added. The mixture was stirred at room temperature for 15 min and evaporated to dryness, and the solid remaining was dissolved in 1 N HCl (5 mL). After washing with ethyl acetate (2 × 5 mL), the aqueous layer was basified with ammonium hydroxide and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were dried with anhydrous $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Chromatography (7:3 petrol/ether saturated with NH_3, R_f 0.43) gave **13a** (0.296 g, 35%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.25 (t, J = 7.0 Hz, 3H), 1.66 (dd, J = 4.6, 1.6 Hz, 2H), 1.70 (m, 2H), 2.68 (s, 2H), 3.66 (s, 2H), 3.73 (m, 1H), 4.14 (q, J = 7.0 Hz, 2H), 7.18–7.45 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.2 (CH_3), 36.4 (CH), 37.2 (CH_2), 39.6 (CH_2), 57.4 (CH_2), 60.3 (CH_2), 69.7 (C), 128.1, 128.2, 128.6 (CH), 140.0 (C), 171.1 (C=O). ν_{max} ($CDCl_3$): 1732 cm^{-1}. m/z: 260.16500; $C_{16}H_{22}NO_2$ [MH^+] requires 260.16505.

2-Benzyl-1-(3-methylisoxazolyl-5-ylmethyl)-2-azabicyclo[2.1.1]hexane, 14a. Butyllithium (1.57 M solution; 800 μL) was added to acetone oxime (13.2 mg, 0.18 mmol) in THF (580 μL). The solution was heated at 60 °C for 5 min in a sealed reacti-vial. A solution of the ester **13a** (40 mg, 0.15 mmol) in THF (240 mL) was injected, and the mixture was stirred at 60 °C for 45 min. Concentrated HCl (800 mL) was added, and the solution was heated in the sealed reacti-vial at 100 °C for 3 h. After neutralization with aqueous $NaHCO_3$ and extraction with ethyl acetate (3 × 8 mL), the organic layers were combined, dried over anhydrous $MgSO_4$, and filtered, and the solvent removed under reduced pressure to yield a brown oil, which was chromatographed (7:3 ether/petrol, R_f 0.35) to give an impure sample of **14a** (10 mg) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.44–1.63 (m, 4H), 2.26 (s, 3H), 2.58–

2.63 (m, 3H), 3.10 (s, 2H), 3.68 (s, 2H), 5.96 (s, 1H), 7.2–7.4 (m, 5H). *m/z*: 269 (MH^+). Yields from later attempts to produce **14a** were low and variable, and alternative approaches to this compound are under study.

2-Benzyl-1-imidazol-1-ylmethyl-2-azabicyclo[2.1.1]hexane, 15a. The mesylate **11a** (100 mg, 0.355 mmol) was dissolved in dry acetonitrile (3 mL), and imidazole (24 mg, 0.355 mmol; dried by azeotropic distillation with benzene prior to use) was added, followed by dry triethylamine (54 μL, 0.39 mmol). After heating at 90 °C for 48 h, the mixture was cooled and basified with gaseous NH_3 before removal of the solvent under reduced pressure. The crude product was purified by flash chromatography (4:1 petrol/ether saturated with NH_3, R_f 0.45) to give **15a** (26 mg, 29%) as a colorless oil. ^1H NMR (250 MHz, $CDCl_3$): δ 1.49 (m, 2H), 1.60 (dd, J = 4.6, 1.5 Hz, 2H), 2.63 (m, 1H), 2.69 (s, 2H), 3.74 (s, 2H), 4.19 (s, 2H), 6.95 (s, 1H), 7.06 (s, 1H), 7.26–7.40 (m, 5H), 7.50 (s, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 36.0 (CH), 38.2 (CH_2), 47.7 (CH_2) 55.9 (CH_2), 57.9 (CH_2), 72.5 (C), 119.9, 127.1, 128.4, 128.5, 129.1 137.7 (CH), 139.2 (C). ν_{max} ($CDCl_3$): 1676 cm^{-1}. *m/z*: 254.16572 (MH^+); $C_{16}H_{20}N_3$ [MH^+] requires 254.16573.

A similar reaction using butyllithium instead of triethylamine (following the procedure described below for **15b**) gave **15a** in improved yield (35%).

Reaction of Mesylate 11b with Imidazole; Formation of 1-Imidazol-1-ylmethyl-2-aza-bicyclo[2.1.1]hexane-2-carboxylic Acid Benzyl Ester, 15b and 17. Imidazole (199 mg, 2.92 mmol) was dried by azeotropic distillation with benzene. Butyllithium (1.57 M in hexanes, 1.434 mL) in dry acetonitrile (5 mL) was then added, and the mixture was stirred for 15 min, forming a white precipitate. The mesylate **11b** (733 mg, 2.25 mmol) in dry acetonitrile (8 mL) was added dropwise, and the mixture was heated at 40 °C for 96 h. After basification with gaseous NH_3 and removal of solvent under reduced pressure, the mixture was introduced onto silica and washed with ether. Further elution (CH_2Cl_2) gave the cyclic urethane **17** (19 mg, 6% yield), and elution with 5% methanol/CH_2Cl_2 (saturated with NH_3) gave the imidazole derivative **15b** (285 mg, 43%). ^1H NMR (250 MHz, $CDCl_3$): δ 1.46 (dd, J = 4.5, 1.7 Hz, 2H), 1.68 (m, 2H), 2.70 (m, 1H), 3.48 (s, 2H), 4.76 (s, 2H), 5.13 (s, 2H), 7.09 (bs, 2H), 7.25–7.33 (m, 5H), 7.55 (bs, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 33.8 (CH), 41.8, 47.7, 52.8, 66.7 (CH_2), 73.0 (C), 127.2, 127.8, 128.1, 128.3, 128.5, 128.9 (CH), 136.6 (C), 156.4 (C). ν_{max} (CH_2Cl_2): 1690 cm^{-1}. *m/z*: 298.15555; [MH^+] requires 298.15544.

In another experiment, dry imidazole (48 mg, 0.699 mmol) in dry acetonitrile (4 mL) was added to **11b** (175 mg, 0.538 mmol) in dry acetonitrile (5 mL), followed by dry triethylamine (0.112 mL, 0.807 mmol). After heating at 60 °C for 96 h, the mixture was worked up and chromatographed as above to give the cyclic urethane **17** (27 mg, 36%) and **15b** (69 mg, 0.232 mmol, 27%). An improved method and spectral data for **17** are given below.

1-Imidazol-1-ylmethyl-2-azabicyclo[2.1.1]hexane, 15c, from 17. Compound **17** (34 mg, 0.24 mmol) in dry DMF (3 mL) was added to a solution of the imidazolyl anion [prepared from imidazole (34 mg, 0.24 mmol) and butyllithium (1.57 M, 0.202 mL) in dry DMF (2 mL) as described in the previous procedure]. The mixture was heated at 90 °C for 144 h and chromatographed (9:1 CH_2Cl_2/methanol saturated with NH_3) to give some unchanged **17** and **15c** (22 mg, 55% yield, 69% conversion) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 1.48 (dd, J = 4.4, 1.8 Hz, 2H), 1.75 (m, 2H), 2.85 (m, 1H), 3.10 (s, 2H), 4.38 (s, 2H), 6.87 (bs, 1H), 6.98 (bs, 1H), 7.55 (bs, 1H). Shifts varied and showed broadening, possibly associated with traces of moisture and slow rotation of the imidazole ring. ^{13}C NMR (75.8 MHz, $CDCl_3$): δ 37.0 (CH), 40.7, 48.7, 49.4 (CH_2), 69.8 (C), 119.4, 129.2, 137.2 (CH). *m/z*: 163.11095; $C_9H_{13}N3$ [MH^+] requires 163.11092.

1-Imidazol-1-ylmethyl-2-azabicyclo[2.1.1]hexane, 15c, from 15b. To **15b** (57 mg, 0.19 mmol) in dry CH_2Cl_2 (1.5 mL) was added TMSI (136 μL, 0.96 mmol). After 7 min of stirring, HF–ether complex (29 μL, 0.38 mmol) was added, and stirring was continued for a further 6 min. Water (200 μL) was added, and the solvent was removed under reduced pressure. Additional water (0.5 mL) was added, and the solution was washed with petrol (2 × 2 mL). The aqueous solution was neutralized with solid K_2CO_3 and extracted with CH_2Cl_2 (5 × 5 mL). The organic layer was dried with anhydrous $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Chromatography (95:5 CH_2Cl_2/methanol saturated with NH_3, R_f 0.14) gave **15c** (27 mg, 87%) as a yellow oil.

1-Azidomethyl-2-azabicyclo[2.1.1]hexane-2-carboxylic Acid Benzyl Ester, 16b, from 11b. Sodium azide (146 mg, 2.25 mmol) was added to a solution of **11b** (183 mg, 0.56 mmol) in dry DMF (4 mL), and the mixture was heated at 40 °C for 48 h. After washing with aqueous NH_4Cl (2 × 5 mL) and distilled water (2 × 4 mL), the organic layer was dried with anhydrous $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to yield **16b** (130 mg, 85%) as a yellow oil, which was not purified further (R_f 0.74 in ether saturated with NH_3). ^1H NMR (250 MHz, $CDCl_3$): δ 1.51 (dd, J = 4.6, 1.84 Hz, 2H), 1.93 (m, 2H), 2.76 (m, 1H), 3.48 (s, 2H), 4.02 (s, 2H), 5.13 (s, 2H), 7.27–7.37 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 34.2 (CH), 41.7, 51.6, 52.3, 66.4 (CH_2), 72.2 (C), 127.7, 127.9, 128.7 (CH), 136.7 (C), 155.6 (C). ν_{max} (CH_2Cl_2): 2090, 1690 cm^{-1}. *m/z*: 273.13515; $C_{14}H_{17}N_4O_2$ [MH^+] requires 273.13522.

3-Oxa-5-aza-tricyclo[5.1.1.0^{1,5}]nonan-4-one, 17, from 3d. Methanesulfonyl chloride (0.340 mL, 4.39 mmol) was added dropwise to **3d** (0.891 g, 4.39 mmol) in dry CH_2Cl_2 (10 mL) followed by dry triethylamine (1.16 mL, 8.36 mmol), and the mixture was heated at 30 °C for 24 h. Triethylamine hydrochloride was filtered off and washed with dry CH_2Cl_2 (10 mL). The organic extracts were washed with distilled water (2 × 10 mL) and saturated $NaHCO_3$ (20 mL), dried with anhydrous $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. Chromatography (7:3 petrol/ether saturated with NH_3, R_f 0.17) yielded **17** (0.509 g, 88%) as a cream solid, mp 29.5–31.5 °C. ^1H NMR (250 MHz, $CDCl_3$): δ 1.62 (dd, J = 4.7, 1.8 Hz, 2H), 1.93 (m, 2H), 2.88–2.91 (m, 1H), 3.25 (s, 2H), 4.21 (s, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 40.1 (CH), 42.6, 47.0, 66.4 (CH_2), 73.9 (C), 156.7 (C). ν_{max} (CH_2Cl_2): 1745 cm^{-1}. *m/z*: 140.07115; $C_7H_{10}NO_2$ [MH^+] requires 140.07109.

2-Benzyl-1-bromomethyl-2-azabicyclo[2.1.1]hexane, 18a. Thionyl bromide (34 mg, 13μL, 164 mmol) was added to a solution of **3a** (28.0 mg, 138 mmol) in $CDCl_3$ (1 mL) in an NMR tube, which was shaken and left for 17 h. NH_3(g) was bubbled through the reaction mixture until the pH was alkaline, the ammonium bromide salt was filtered off, and the solvent was removed under reduced pressure. Chromatography (3:1 petrol/ether R_f 0.29) gave **18a** (28.3 mg, 106 mmol, 77%) as a colorless oil. ^1H NMR (250 MHz, $CDCl_3$): δ 1.68 (bs, 4H), 2.63 (bs, 1H), 2.68 (bs, 2H), 3.63 (bs, 4H), 7.20–7.48 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 35.9 (CH), 32.8, 39.2, 39.2, 55.6, 57.7 (CH_2) 71.6 (C), 126.8, 128.2, 128.8 (CH), 139.5 (C). *m/z*: 266.05444 & 268.05252; $C_{13}H_{17}N^{79}Br$ [MH^+] requires 266.05452.

1-Bromomethyl-2-azabicyclo[2.1.1]hexane-2-carboxylic Acid Benzyl Ester, 18b. Triphenylphosphine (212 mg, 0.81 mmol) was added to a solution of **3b** (50 mg, 0.20 mmol) in dry CH_2Cl_2 (5 mL) followed by slow addition of CBr_4 (288 mg, 0.87 mmol). After heating at 25 °C for 10 min, the mixture was stirred at room temperature for 24 h. The mixture was filtered, and the solids were washed successively with dry CH_2Cl_2 (50 mL) and ether (20 mL). Chromatography (1:1 petrol/ether saturated with NH_3, R_f 0.23) gave **3b** (50 mg, 80%) as a yellow oil. ^1H NMR (250 MHz, $CDCl_3$): δ 1.50 (dd, J = 4.7, 2.0 Hz, 2H), 1.90–194 (m, 2H), 2.65–2.68 (m, 1H), 3.44 (s, 2H), 4.05 (s, 2H), 5.06 (s, 2H), 7.24–7.26 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 32.7 (CH_2), 33.4 (H), 42.8, 53.2, 66.5 (CH_2), 72.6 (C), 127.8, 127.9, 128.4 (CH), 136.7, 155.8 (C). ν_{max} (CH_2Cl_2): 1690 cm^{-1}. *m/z*: 310.04427 and 312.04235; $C_{14}H_{17}NO_2{}^{79}Br$ [MH^+] requires 310.04422. Treatment of **3b** with

$SOBr_2$ following the procedure of Cox[17] also produced **18**, but the method above was more successful.

1-Formyl-2-azabicyclo[2.1.1]hexane-2-carboxylic Acid Benzyl Ester, 19. DMSO (0.097 mL, 1.38 mmol) in dry CH_2Cl_2 was added dropwise to a solution of oxalyl chloride (0.060 mL, 0.69 mmol) in dry CH_2Cl_2 (5 mL) at −78 °C. The mixture was stirred for 30 min at −78°C after completion of the addition. A solution of **3b** in dry CH_2Cl_2 (5 mL) was added dropwise, and the mixture was stirred for a further 15 min at −78°C. Triethylamine (0.230 mL, 1.65 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise, and the reaction mixture was warmed to room temperature with stirring for 90 min. CH_2Cl_2 (2 mL) was added, and the mixture was washed with water (2 × 10 mL) and saturated aqueous $NaHCO_3$ (5 × 15 mL). The organic extracts were dried with anhydrous $MgSO_4$ and filtered, and the solvent removed under reduced pressure to yield **19** (60 mg, 90%) as a pale yellow oil (R_f 0.82 in ether saturated with NH_3). ^1H NMR (250 MHz, $CDCl_3$): δ 1.65 (dd, J = 4.7, 1.95 Hz, 2H), 2.12 (m, 2H), 2.82 (m, 1H), 3.43 (s, 2H), 5.16 (s, 2H), 7.30−7.36 (m, 5H), 9.87 (s, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 35.0 (CH), 41.5, 52.3, 67.5, (CH_2), 76.3 (C), 128.0, 128.2, 128.5 (CH), 136.1 (C), 194.0 (C). ν_{max} (CH_2Cl_2): 1735, 1680 cm^{-1}. *m/z*: 246.11302; $C_{14}H_{16}NO_3$ [MH^+] requires 246.11296.

1-(2-Methoxy-vinyl)-2-azabicyclo[2.1.1]hexane-2-carboxylic Acid Benzyl Ester, 20. Potassium *tert*-butoxide (143 mg, 1.28 mmol) was stirred in dry THF (2 mL) at 0 °C under an argon atmosphere. (Methoxymethyl)triphenylphosphonium chloride (437 mg, 1.28 mmol) was then added, followed by dry THF (2 mL). The bright red mixture was stirred for 2 h at 0 °C under argon. Compound **19** in dry THF (4 mL) was added at 0 °C, and the mixture was stirred for 20 h under argon. Water-saturated ether (6 mL) was added at room temperature, and the mixture was stirred for 10 min followed by more water (4 mL) and stirring (10 min). The organic layer was separated, and the aqueous layer was extracted with ether (5 × 10 mL). The combined organic layers were washed with brine (5 mL), dried with anhydrous $MgSO_4$, and filtered, and the solvent removed under reduced pressure to yield the mixture of *cis* and *trans* stereoisomers **20** as an orange oil that still contained some triphenylphosphine oxide. The crude product was unstable and was not purified by chromatography. ^1H NMR (250 MHz, $CDCl_3$): δ (both stereoisomers showed slow N-CO rotation) 1.61 (dd, J = 4.93, 3.10 Hz, 2H), 1.83 (m, 2H), 2.96 (m, 1H), 3.32 (s, 2H), 3.41 (s, 3H), 5.12 (m, 1H), 5.19 (m, 2H), 5.48 (d, J = 13.1 Hz, 1H), 5.91 (d, J = 6.9 Hz, 1H), 6.39 (d, J = 12.9 Hz, 1H), 6.50 (m, 1H), 7.17−7.31 (m, 5H, Ph). *m/z*: 273 (MH^+).

1-Vinyl-2-azabicyclo[2.1.1]hexane-2-carboxylic Acid Benzyl Ester, 21. Potassium *tert*-butoxide (0.123 g, 1.09 mmol) was stirred in dry THF (2 mL) under argon at 0 °C. Methyltriphenylphosphonium bromide (0.390 g, 1.09 mmol) was added, followed by dry THF (2 mL). The bright yellow mixture was stirred for 2 h at 0 °C under argon. A solution of **19** in dry THF (3 mL) was added at 0 °C, and the mixture was stirred for 20 h under argon. The workup procedure followed that described for **20**, but the product was chromatographed (1:1 petrol/ether saturated with NH_3, R_f 0.59) to give **21** (0.16 g, 63%) as a yellow oil. ^1H NMR (250 MHz, $CDCl_3$): δ 1.56 (dd, J = 4.9, 3.1 Hz, 2H), 1.82 (m, 2H), 2.64 (m, 1H), 3.41 (s, 2H), 5.05 (m, 4H), 6.50 (m, 1H), 7.18−7.31 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 30.0 (CH), 43.6, 52.2, 66.2 (CH_2), 74.1 (C), 114.9 (CH_2), 127.7, 128.1, 128.3 (CH), 135.5 (CH), 137.1 155.9 (C). ν_{max} (CH_2Cl_2): 1690 cm^{-1}. *m/z*: 243.12593; $C_{15}H_{17}NO_2$ [MH^+] requires 243.12592.

(2-Azabicyclo[2.1.1]hex-1-yl)-acetic Acid, 23. The nitrile **12b** (40 mg, 0.156 mmol) was dissolved in 8 N HCl (8 mL), and the mixture was heated to 90 °C for 72 h. The reaction was monitored using mass spectroscopy, and when hydrolysis was complete, the product was evaporated to dryness under reduced pressure to give **23**·HCl as a white residue in quantitative yield. ^1H NMR (300 MHz, D_2O): δ 1.60 (dd, J = 6.0, 2.0 Hz, 2H), 2.04 (m, 2H), 2.86 (m, 1H), 3.00 (s, 2H), 3.38 (s, 2H). ^{13}C NMR (75.8 MHz, D_2O): δ 34.5 (C_7), 36.0 (C_4), 39.9 ($C_{5/6}$), 49.8 (C_3), 69.6 (C_1), 173.1 (C=O). A small amount of **23**·HCl was passed down a Dowex ion exchange column to give a sample of **23**, which crystallized as fine needles (dec 42−45 °C). ^1H NMR (300 MHz, D_2O): δ 1.54 (dd, J = 6.1, 2.3 Hz, 2H), 1.97 (m, 2H), 2.72 (m, 1H), 2.84 (s, 2H), 3.35 (s, 2H). *m/z*: 142.08680; $C_7H_{12}NO_2$ [MH^+] requires 142.08689.

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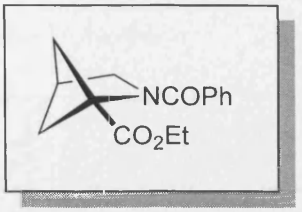
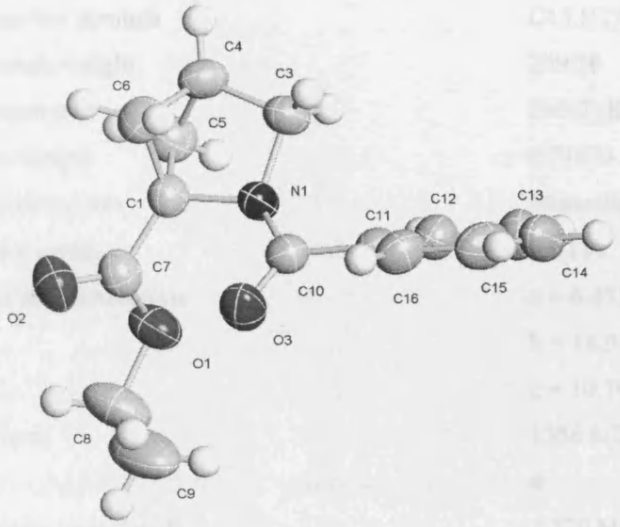
Supporting Information Available: Spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035199N

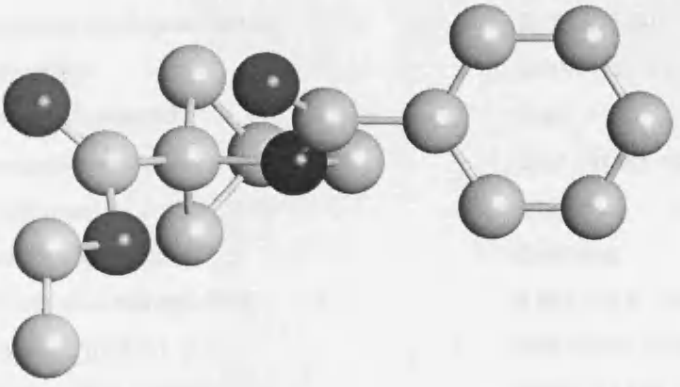
X-ray Crystallography Data

X-ray crystal structure of **47**





molecular structure showing the atom label scheme and 50% displacement ellipsoids



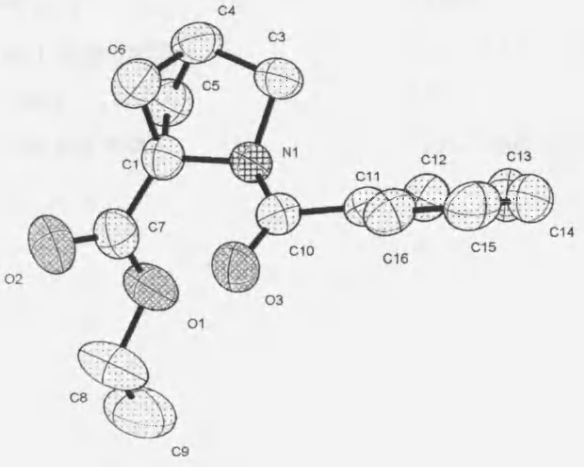


Table 1. Crystal data and structure refinement for 03059.

Identification code	03059	
Empirical formula	C15 H17 N O3	
Formula weight	259.30	
Temperature	290(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 6.8510(6) Å	α= 90°.
	b = 18.9429(16) Å	β= 104.3690(10)°.
	c = 10.7912(9) Å	γ = 90°.
Volume	1356.6(2) $Å^3$	
Z	4	
Density (calculated)	1.270 Mg/m^3	
Absorption coefficient	0.089 mm^{-1}	
F(000)	552	
Crystal size	0.30 x 0.28 x 0.19 mm^3	
Theta range for data collection	2.15 to 25.00°.	
Index ranges	-8<=h<=8, -22<=k<=22, -12<=l<=12	
Reflections collected	9762	
Independent reflections	2385 [R(int) = 0.0285]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Empirical	
Max. and min. transmission	0.962 and 0.768	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2385 / 0 / 173	
Goodness-of-fit on F^2	1.072	
Final R indices [I>2sigma(I)]	R1 = 0.0505, wR2 = 0.1461	
R indices (all data)	R1 = 0.0651, wR2 = 0.1555	
Largest diff. peak and hole	0.429 and -0.256 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 03059. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	6264(2)	7503(1)	2402(2)	52(1)
O(1)	4893(3)	6064(1)	1959(2)	72(1)
O(2)	7319(3)	5952(1)	928(2)	81(1)
O(3)	4519(3)	7340(1)	365(2)	70(1)
C(1)	7523(3)	6870(1)	2452(2)	54(1)
C(3)	7610(3)	7990(1)	3319(2)	61(1)
C(4)	9417(3)	7507(1)	3683(2)	62(1)
C(5)	8418(4)	6810(1)	3905(2)	64(1)
C(6)	9553(3)	7197(1)	2392(2)	68(1)
C(7)	6574(4)	6257(1)	1668(2)	60(1)
C(8)	3768(5)	5510(2)	1168(3)	98(1)
C(9)	2282(5)	5222(2)	1706(4)	131(2)
C(10)	4940(3)	7706(1)	1324(2)	52(1)
C(11)	3935(3)	8397(1)	1380(2)	51(1)
C(12)	3161(3)	8570(1)	2408(2)	62(1)
C(13)	2147(4)	9196(1)	2406(3)	77(1)
C(14)	1959(4)	9658(1)	1421(3)	81(1)
C(15)	2746(4)	9500(1)	409(3)	76(1)
C(16)	3698(3)	8859(1)	368(2)	65(1)

Table 3. Bond lengths [Å] and angles [°] for 03059.

N(1)-C(10)	1.342(3)
N(1)-C(1)	1.470(2)
N(1)-C(3)	1.493(3)
O(1)-C(7)	1.318(3)
O(1)-C(8)	1.448(3)
O(2)-C(7)	1.198(3)
O(3)-C(10)	1.219(2)
C(1)-C(7)	1.487(3)
C(1)-C(6)	1.539(3)
C(1)-C(5)	1.540(3)
C(3)-C(4)	1.511(3)
C(4)-C(5)	1.532(3)
C(4)-C(6)	1.536(3)
C(8)-C(9)	1.402(4)
C(10)-C(11)	1.488(3)
C(11)-C(16)	1.377(3)
C(11)-C(12)	1.383(3)
C(12)-C(13)	1.374(3)
C(13)-C(14)	1.358(4)
C(14)-C(15)	1.366(4)
C(15)-C(16)	1.385(4)
C(10)-N(1)-C(1)	121.97(17)
C(10)-N(1)-C(3)	124.87(17)
C(1)-N(1)-C(3)	102.67(15)
C(7)-O(1)-C(8)	115.4(2)
N(1)-C(1)-C(7)	116.48(17)
N(1)-C(1)-C(6)	101.46(16)
C(7)-C(1)-C(6)	124.23(19)
N(1)-C(1)-C(5)	100.31(16)
C(7)-C(1)-C(5)	121.94(18)
C(6)-C(1)-C(5)	86.36(17)
N(1)-C(3)-C(4)	97.46(16)
C(3)-C(4)-C(5)	101.15(18)
C(3)-C(4)-C(6)	103.05(17)
C(5)-C(4)-C(6)	86.73(18)
C(4)-C(5)-C(1)	81.83(15)
C(4)-C(6)-C(1)	81.74(17)

O(2)-C(7)-O(1)	124.5(2)
O(2)-C(7)-C(1)	123.9(2)
O(1)-C(7)-C(1)	111.44(19)
C(9)-C(8)-O(1)	111.9(3)
O(3)-C(10)-N(1)	122.70(19)
O(3)-C(10)-C(11)	121.35(18)
N(1)-C(10)-C(11)	115.90(18)
C(16)-C(11)-C(12)	119.6(2)
C(16)-C(11)-C(10)	119.45(19)
C(12)-C(11)-C(10)	120.92(19)
C(13)-C(12)-C(11)	119.8(2)
C(14)-C(13)-C(12)	120.5(3)
C(13)-C(14)-C(15)	120.4(2)
C(14)-C(15)-C(16)	120.0(2)
C(11)-C(16)-C(15)	119.7(2)

Symmetry transformations used to generate equivalent atoms:

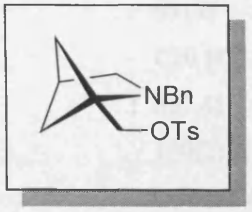
Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 03059. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	52(1)	45(1)	53(1)	-6(1)	2(1)	3(1)
O(1)	81(1)	65(1)	73(1)	-18(1)	24(1)	-18(1)
O(2)	94(1)	65(1)	86(1)	-17(1)	31(1)	9(1)
O(3)	75(1)	73(1)	54(1)	-13(1)	1(1)	14(1)
C(1)	53(1)	48(1)	57(1)	1(1)	10(1)	7(1)
C(3)	59(1)	55(1)	61(1)	-9(1)	1(1)	-4(1)
C(4)	51(1)	65(1)	62(1)	0(1)	-1(1)	-3(1)
C(5)	63(1)	62(1)	62(1)	6(1)	3(1)	6(1)
C(6)	58(1)	69(2)	78(2)	0(1)	17(1)	3(1)
C(7)	69(2)	50(1)	59(1)	0(1)	15(1)	7(1)
C(8)	121(2)	88(2)	83(2)	-28(2)	20(2)	-41(2)
C(9)	108(3)	132(3)	164(4)	-60(3)	57(3)	-57(2)
C(10)	46(1)	55(1)	52(1)	-2(1)	9(1)	0(1)
C(11)	41(1)	50(1)	56(1)	-1(1)	3(1)	0(1)
C(12)	57(1)	61(1)	66(1)	0(1)	12(1)	5(1)
C(13)	70(2)	79(2)	75(2)	-14(1)	8(1)	20(1)
C(14)	71(2)	59(2)	98(2)	-11(1)	-9(2)	16(1)
C(15)	67(2)	65(2)	84(2)	20(1)	-5(1)	3(1)
C(16)	54(1)	72(2)	62(1)	8(1)	5(1)	3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 03059.

	x	y	z	U(eq)
H(3A)	7071	8106	4044	73
H(3B)	7901	8419	2909	73
H(4)	10641	7666	4300	74
H(5A)	7448	6848	4421	77
H(5B)	9339	6418	4170	77
H(6A)	10637	6861	2438	81
H(6B)	9479	7541	1715	81
H(8A)	3137	5701	330	118
H(8B)	4688	5140	1058	118
H(9A)	2898	5043	2544	196
H(9B)	1609	4844	1175	196
H(9C)	1321	5581	1768	196
H(12)	3326	8263	3099	74
H(13)	1585	9304	3084	92
H(14)	1292	10084	1436	97
H(15)	2642	9823	-253	92
H(16)	4176	8741	-340	77

X-ray crystal structure of **50**



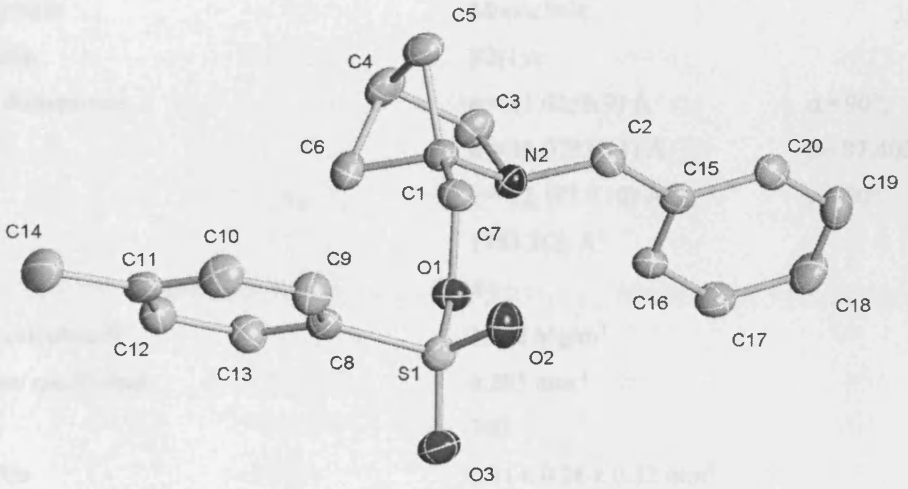


fig shows the atom label scheme and 50% displacement ellipsoids. Hydrogen atoms are omitted for clarity

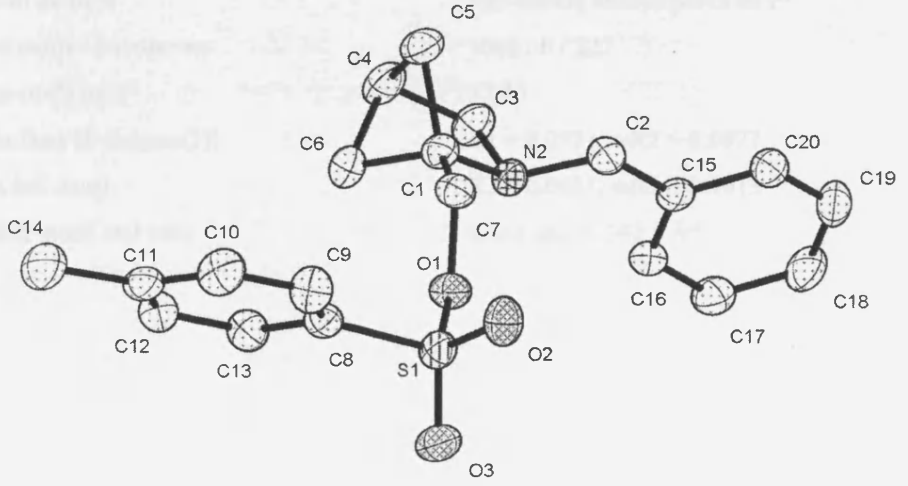


Table 1. Crystal data and structure refinement for 03133.

Identification code	03133	
Empirical formula	C20 H23 N O3 S	
Formula weight	357.45	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 11.0258(9) Å	α= 90°.
	b = 13.0793(11) Å	β= 97.4020(10)°.
	c = 12.1933(10) Å	γ = 90°.
Volume	1743.7(2) $Å^3$	
Z	4	
Density (calculated)	1.362 Mg/m^3	
Absorption coefficient	0.205 mm^{-1}	
F(000)	760	
Crystal size	0.31 x 0.26 x 0.12 mm^3	
Theta range for data collection	1.86 to 24.99°.	
Index ranges	-13<=h<=13, -15<=k<=15, -14<=l<=14	
Reflections collected	11191	
Independent reflections	3068 [R(int) = 0.0363]	
Completeness to theta = 24.99°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3068 / 0 / 227	
Goodness-of-fit on F^2	1.040	
Final R indices [I>2sigma(I)]	R1 = 0.0371, wR2 = 0.0977	
R indices (all data)	R1 = 0.0431, wR2 = 0.1013	
Largest diff. peak and hole	0.364 and -0.302 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 03133. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	2519(1)	-33(1)	8694(1)	26(1)
O(1)	3357(1)	620(1)	8026(1)	27(1)
O(2)	3203(1)	-397(1)	9685(1)	36(1)
O(3)	1945(1)	-742(1)	7911(1)	35(1)
N(2)	5286(1)	1602(1)	7004(1)	24(1)
C(1)	4530(2)	2090(1)	7774(1)	26(1)
C(2)	6389(2)	1099(1)	7515(1)	26(1)
C(3)	5536(2)	2503(1)	6321(2)	32(1)
C(4)	4778(2)	3309(1)	6822(2)	36(1)
C(5)	5155(2)	3136(1)	8066(2)	34(1)
C(6)	3621(2)	2693(1)	6963(2)	33(1)
C(7)	4109(2)	1410(1)	8626(1)	27(1)
C(8)	1439(2)	850(1)	9044(1)	26(1)
C(9)	1259(2)	952(1)	10134(2)	34(1)
C(10)	354(2)	1601(1)	10401(2)	39(1)
C(11)	-359(2)	2152(1)	9599(2)	33(1)
C(12)	-135(2)	2058(1)	8514(2)	34(1)
C(13)	755(2)	1408(1)	8229(2)	31(1)
C(14)	-1361(2)	2840(2)	9890(2)	49(1)
C(15)	7029(2)	507(1)	6701(1)	23(1)
C(16)	6484(2)	309(1)	5638(1)	27(1)
C(17)	7070(2)	-264(1)	4915(2)	33(1)
C(18)	8223(2)	-644(1)	5247(2)	39(1)
C(19)	8793(2)	-440(1)	6298(2)	37(1)
C(20)	8194(2)	125(1)	7016(2)	28(1)

C(1)-N(2)-C(3)	100.00(12)
N(2)-C(1)-C(7)	115.93(13)
N(2)-C(1)-C(6)	100.78(13)
C(7)-C(1)-C(6)	121.46(14)
N(2)-C(1)-C(5)	104.85(13)
C(7)-C(1)-C(5)	122.47(14)
C(6)-C(1)-C(5)	85.93(13)
N(2)-C(2)-C(15)	112.90(13)
N(2)-C(3)-C(4)	99.93(13)
C(3)-C(4)-C(5)	101.67(14)
C(3)-C(4)-C(6)	100.91(14)
C(5)-C(4)-C(6)	86.31(13)
C(4)-C(5)-C(1)	81.22(13)
C(1)-C(6)-C(4)	81.84(13)
O(1)-C(7)-C(1)	106.34(13)
C(9)-C(8)-C(13)	120.78(16)
C(9)-C(8)-S(1)	119.17(14)
C(13)-C(8)-S(1)	120.02(13)
C(8)-C(9)-C(10)	119.15(18)
C(11)-C(10)-C(9)	121.18(17)
C(10)-C(11)-C(12)	118.49(16)
C(10)-C(11)-C(14)	121.07(18)
C(12)-C(11)-C(14)	120.44(18)
C(13)-C(12)-C(11)	121.19(18)
C(12)-C(13)-C(8)	119.18(17)
C(16)-C(15)-C(20)	117.93(15)
C(16)-C(15)-C(2)	122.04(14)
C(20)-C(15)-C(2)	120.02(15)
C(17)-C(16)-C(15)	121.23(16)
C(18)-C(17)-C(16)	119.95(17)
C(17)-C(18)-C(19)	119.71(17)
C(20)-C(19)-C(18)	119.81(17)
C(19)-C(20)-C(15)	121.36(17)

Symmetry transformations used to generate equivalent atoms:

Table 3. Bond lengths [Å] and angles [°] for 03133.

S(1)-O(3)	1.4207(13)
S(1)-O(2)	1.4208(13)
S(1)-O(1)	1.5628(11)
S(1)-C(8)	1.7500(16)
O(1)-C(7)	1.4615(19)
N(2)-C(2)	1.451(2)
N(2)-C(1)	1.479(2)
N(2)-C(3)	1.489(2)
C(1)-C(7)	1.486(2)
C(1)-C(6)	1.533(2)
C(1)-C(5)	1.553(2)
C(2)-C(15)	1.504(2)
C(3)-C(4)	1.521(2)
C(4)-C(5)	1.537(3)
C(4)-C(6)	1.537(3)
C(8)-C(9)	1.375(2)
C(8)-C(13)	1.377(2)
C(9)-C(10)	1.380(3)
C(10)-C(11)	1.377(3)
C(11)-C(12)	1.383(3)
C(11)-C(14)	1.502(2)
C(12)-C(13)	1.375(2)
C(15)-C(16)	1.382(2)
C(15)-C(20)	1.385(2)
C(16)-C(17)	1.380(2)
C(17)-C(18)	1.377(3)
C(18)-C(19)	1.379(3)
C(19)-C(20)	1.377(2)
O(3)-S(1)-O(2)	119.62(8)
O(3)-S(1)-O(1)	104.36(7)
O(2)-S(1)-O(1)	109.96(7)
O(3)-S(1)-C(8)	109.71(8)
O(2)-S(1)-C(8)	108.48(8)
O(1)-S(1)-C(8)	103.48(7)
C(7)-O(1)-S(1)	117.42(10)
C(2)-N(2)-C(1)	115.63(13)
C(2)-N(2)-C(3)	113.13(13)

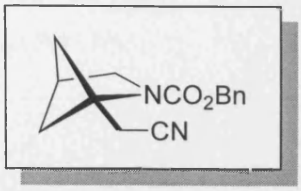
Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 03133. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

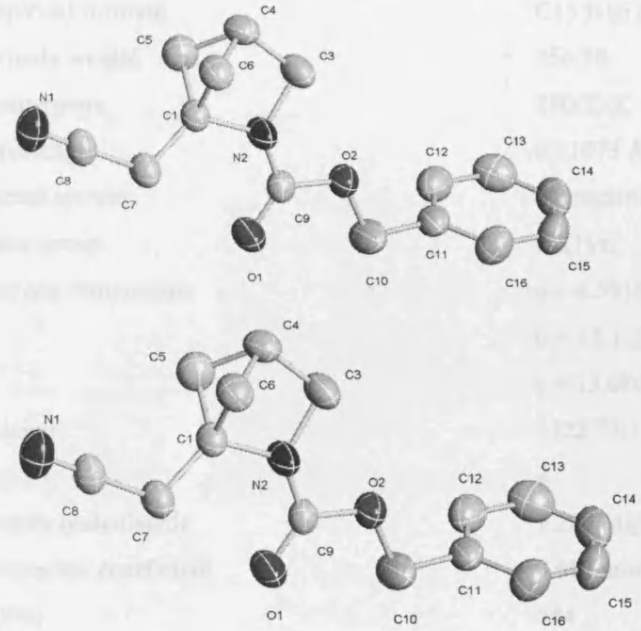
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	26(1)	25(1)	30(1)	0(1)	9(1)	0(1)
O(1)	27(1)	30(1)	27(1)	-5(1)	9(1)	-4(1)
O(2)	37(1)	37(1)	35(1)	8(1)	7(1)	8(1)
O(3)	36(1)	29(1)	43(1)	-8(1)	11(1)	-5(1)
N(2)	24(1)	23(1)	25(1)	1(1)	7(1)	1(1)
C(1)	25(1)	25(1)	30(1)	-5(1)	7(1)	-1(1)
C(2)	25(1)	29(1)	26(1)	-1(1)	3(1)	0(1)
C(3)	39(1)	24(1)	33(1)	5(1)	11(1)	0(1)
C(4)	43(1)	21(1)	44(1)	2(1)	10(1)	2(1)
C(5)	34(1)	26(1)	42(1)	-10(1)	10(1)	-3(1)
C(6)	32(1)	29(1)	38(1)	-4(1)	5(1)	7(1)
C(7)	24(1)	31(1)	26(1)	-8(1)	6(1)	-3(1)
C(8)	23(1)	24(1)	31(1)	-2(1)	8(1)	-4(1)
C(9)	37(1)	37(1)	30(1)	4(1)	10(1)	4(1)
C(10)	42(1)	41(1)	35(1)	-5(1)	18(1)	1(1)
C(11)	25(1)	26(1)	49(1)	-9(1)	12(1)	-5(1)
C(12)	29(1)	31(1)	41(1)	0(1)	2(1)	2(1)
C(13)	31(1)	35(1)	29(1)	-2(1)	6(1)	0(1)
C(14)	38(1)	42(1)	70(2)	-14(1)	18(1)	4(1)
C(15)	25(1)	18(1)	29(1)	3(1)	7(1)	-4(1)
C(16)	24(1)	24(1)	31(1)	-2(1)	2(1)	-2(1)
C(17)	36(1)	31(1)	33(1)	-7(1)	4(1)	-1(1)
C(18)	41(1)	32(1)	44(1)	-9(1)	13(1)	7(1)
C(19)	30(1)	32(1)	49(1)	3(1)	6(1)	8(1)
C(20)	28(1)	25(1)	30(1)	4(1)	2(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 03133.

	x	y	z	U(eq)
H(2A)	6175	628	8095	32
H(2B)	6956	1621	7876	32
H(3A)	5248	2392	5527	38
H(3B)	6416	2681	6415	38
H(4)	4712	4017	6512	43
H(5A)	4734	3578	8558	40
H(5B)	6048	3104	8301	40
H(6A)	2990	3073	7306	39
H(6B)	3265	2307	6300	39
H(7A)	4818	1098	9088	32
H(7B)	3625	1801	9112	32
H(9)	1750	581	10695	41
H(10)	220	1668	11152	46
H(12)	-604	2448	7955	41
H(13)	896	1346	7480	38
H(14A)	-2069	2426	10019	74
H(14B)	-1598	3316	9279	74
H(14C)	-1069	3226	10560	74
H(16)	5690	572	5400	32
H(17)	6678	-395	4188	40
H(18)	8625	-1046	4754	46
H(19)	9595	-687	6526	44
H(20)	8589	256	7742	34

X-ray crystal structure of **69**





Fig's 1 & 2 show the molecular structure with the atom label scheme and 50% displacement ellipsoids. H atoms have been omitted for clarity

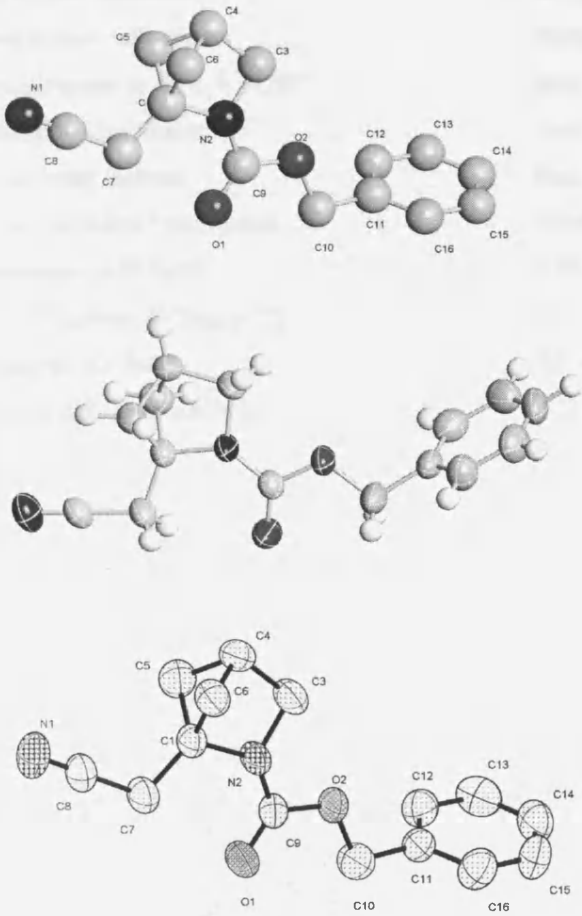


Table 1. Crystal data and structure refinement for 03056.

Identification code	03056	
Empirical formula	C15 H16 N2 O2	
Formula weight	256.30	
Temperature	290(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 8.5016(7) Å	α= 90°.
	b = 12.1227(10) Å	β= 101.2750(10)°.
	c = 13.0867(11) Å	γ = 90°.
Volume	1322.72(19) $Å^3$	
Z	4	
Density (calculated)	1.287 Mg/m^3	
Absorption coefficient	0.087 mm^{-1}	
F(000)	544	
Crystal size	0.39 x 0.35 x 0.32 mm^3	
Theta range for data collection	2.31 to 24.99°.	
Index ranges	-10<=h<=10, -14<=k<=14, -15<=l<=15	
Reflections collected	9378	
Independent reflections	2326 [R(int) = 0.0442]	
Completeness to theta = 24.99°	99.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2326 / 0 / 172	
Goodness-of-fit on F^2	1.056	
Final R indices [I>2sigma(I)]	R1 = 0.0428, wR2 = 0.1175	
R indices (all data)	R1 = 0.0523, wR2 = 0.1234	
Largest diff. peak and hole	0.223 and -0.171 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 03056. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	-152(2)	1648(1)	179(1)	75(1)
O(2)	-149(1)	3197(1)	1119(1)	52(1)
N(1)	4721(2)	-1244(1)	813(1)	72(1)
N(2)	1987(2)	2128(1)	1397(1)	57(1)
C(1)	3062(2)	1165(1)	1451(1)	45(1)
C(3)	2752(2)	2804(2)	2298(1)	63(1)
C(4)	4162(2)	2059(1)	2682(1)	56(1)
C(5)	3371(2)	911(1)	2622(1)	61(1)
C(6)	4691(2)	1750(1)	1664(1)	55(1)
C(7)	2594(2)	309(1)	609(1)	54(1)
C(8)	3790(2)	-567(1)	721(1)	53(1)
C(9)	520(2)	2254(1)	848(1)	44(1)
C(10)	-1752(2)	3398(2)	555(2)	78(1)
C(11)	-2430(2)	4362(1)	1031(1)	54(1)
C(12)	-2917(2)	4266(2)	1969(2)	65(1)
C(13)	-3620(2)	5150(2)	2373(2)	72(1)
C(14)	-3826(2)	6125(2)	1846(2)	72(1)
C(15)	-3336(3)	6233(2)	931(2)	75(1)
C(16)	-2640(2)	5362(2)	521(2)	68(1)

Table 3. Bond lengths [Å] and angles [°] for 03056.

O(1)-C(9)	1.1980(18)
O(2)-C(9)	1.3550(17)
O(2)-C(10)	1.439(2)
N(1)-C(8)	1.130(2)
N(2)-C(9)	1.3210(19)
N(2)-C(1)	1.4765(18)
N(2)-C(3)	1.4776(19)
C(1)-C(7)	1.510(2)
C(1)-C(6)	1.532(2)
C(1)-C(5)	1.535(2)
C(1)-C(4)	2.014(2)
C(3)-C(4)	1.507(2)
C(4)-C(6)	1.534(2)
C(4)-C(5)	1.541(2)
C(7)-C(8)	1.457(2)
C(10)-C(11)	1.492(2)
C(11)-C(12)	1.374(3)
C(11)-C(16)	1.378(3)
C(12)-C(13)	1.382(3)
C(13)-C(14)	1.362(3)
C(14)-C(15)	1.349(3)
C(15)-C(16)	1.371(3)
C(9)-O(2)-C(10)	114.34(12)
C(9)-N(2)-C(1)	128.85(13)
C(9)-N(2)-C(3)	126.25(13)
C(1)-N(2)-C(3)	103.21(12)
N(2)-C(1)-C(7)	115.86(13)
N(2)-C(1)-C(6)	99.86(12)
C(7)-C(1)-C(6)	123.42(13)
N(2)-C(1)-C(5)	100.98(12)
C(7)-C(1)-C(5)	124.10(14)
C(6)-C(1)-C(5)	86.54(13)
N(2)-C(1)-C(4)	78.40(9)
C(7)-C(1)-C(4)	165.72(12)
C(6)-C(1)-C(4)	48.99(9)
C(5)-C(1)-C(4)	49.25(9)
N(2)-C(3)-C(4)	97.55(13)

C(3)-C(4)-C(6)	101.84(14)
C(3)-C(4)-C(5)	102.33(14)
C(6)-C(4)-C(5)	86.24(13)
C(3)-C(4)-C(1)	80.84(10)
C(6)-C(4)-C(1)	48.89(8)
C(5)-C(4)-C(1)	48.96(9)
C(1)-C(5)-C(4)	81.79(12)
C(1)-C(6)-C(4)	82.12(12)
C(8)-C(7)-C(1)	110.35(14)
N(1)-C(8)-C(7)	179.7(2)
O(1)-C(9)-N(2)	126.24(14)
O(1)-C(9)-O(2)	122.98(14)
N(2)-C(9)-O(2)	110.76(13)
O(2)-C(10)-C(11)	108.83(14)
C(12)-C(11)-C(16)	118.30(16)
C(12)-C(11)-C(10)	120.99(17)
C(16)-C(11)-C(10)	120.67(18)
C(11)-C(12)-C(13)	120.34(17)
C(14)-C(13)-C(12)	120.04(19)
C(15)-C(14)-C(13)	120.19(18)
C(14)-C(15)-C(16)	120.31(19)
C(15)-C(16)-C(11)	120.81(19)

Symmetry transformations used to generate equivalent atoms:

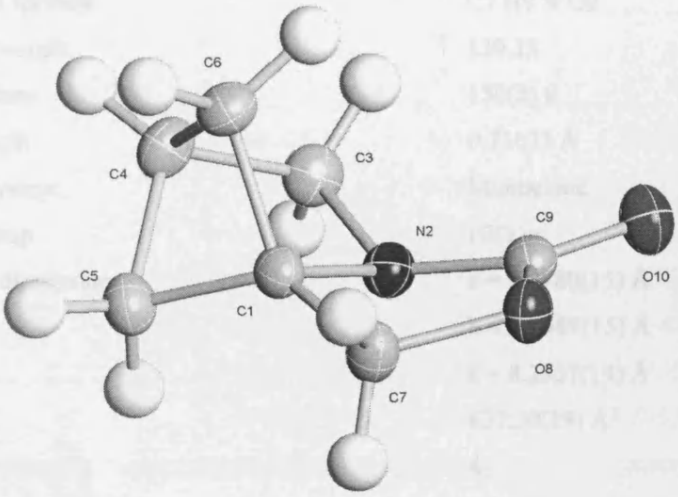
Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 03056. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	63(1)	58(1)	90(1)	-31(1)	-17(1)	16(1)
O(2)	46(1)	43(1)	65(1)	-9(1)	3(1)	12(1)
N(1)	86(1)	51(1)	82(1)	2(1)	29(1)	20(1)
N(2)	47(1)	49(1)	70(1)	-23(1)	-5(1)	14(1)
C(1)	42(1)	39(1)	52(1)	-5(1)	8(1)	6(1)
C(3)	58(1)	57(1)	69(1)	-25(1)	-1(1)	8(1)
C(4)	52(1)	59(1)	54(1)	-14(1)	-2(1)	5(1)
C(5)	70(1)	56(1)	56(1)	0(1)	12(1)	4(1)
C(6)	46(1)	54(1)	66(1)	-8(1)	10(1)	1(1)
C(7)	52(1)	45(1)	64(1)	-12(1)	9(1)	7(1)
C(8)	63(1)	40(1)	58(1)	-5(1)	18(1)	6(1)
C(9)	46(1)	35(1)	51(1)	-1(1)	11(1)	3(1)
C(10)	62(1)	75(1)	86(1)	-26(1)	-14(1)	28(1)
C(11)	43(1)	49(1)	64(1)	-9(1)	-4(1)	11(1)
C(12)	65(1)	51(1)	73(1)	4(1)	2(1)	-4(1)
C(13)	61(1)	86(2)	70(1)	-12(1)	19(1)	-4(1)
C(14)	55(1)	63(1)	96(2)	-19(1)	7(1)	16(1)
C(15)	81(1)	50(1)	90(2)	6(1)	8(1)	20(1)
C(16)	68(1)	68(1)	69(1)	7(1)	14(1)	15(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 03056.

	x	y	z	U(eq)
H(3A)	2056	2892	2817	75
H(3B)	3086	3537	2084	75
H(4)	4909	2354	3270	68
H(5A)	4117	291	2846	73
H(5B)	2397	864	2929	73
H(6A)	4782	2378	1195	66
H(6B)	5632	1254	1746	66
H(7A)	1537	-8	655	64
H(7B)	2501	660	-83	64
H(10A)	-2427	2739	587	93
H(10B)	-1735	3553	-185	93
H(12)	-2770	3589	2340	77
H(13)	-3960	5078	3020	86
H(14)	-4317	6729	2123	87
H(15)	-3474	6917	570	90
H(16)	-2299	5448	-124	81

X-ray crystal structure of **73**



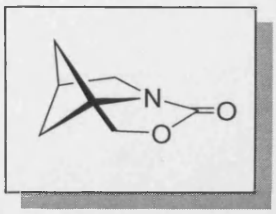
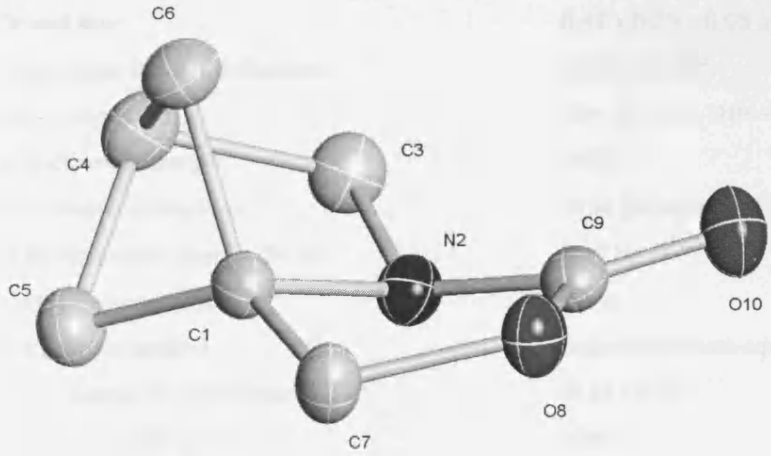


fig shows the atom label scheme and 50% displacement ellipsoids



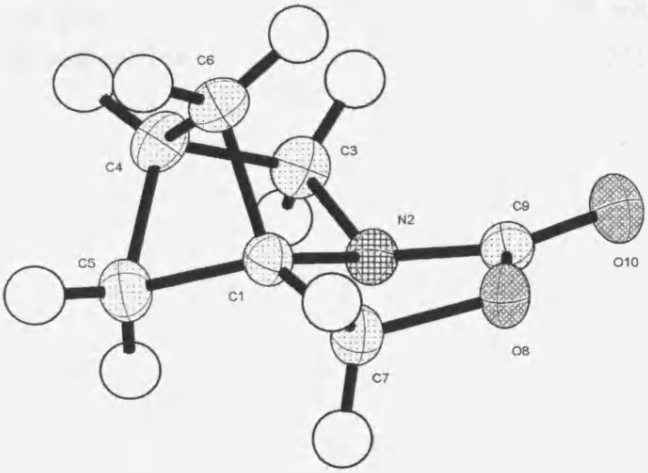


Table 1. Crystal data and structure refinement for 03147.

Identification code	03147	
Empirical formula	C7 H9 N O2	
Formula weight	139.15	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 9.0780(15) Å	α= 90°.
	b = 8.5989(15) Å	β= 97.290(3)°.
	c = 8.2307(14) Å	γ = 90°.
Volume	637.30(19) $Å^3$	
Z	4	
Density (calculated)	1.450 Mg/m^3	
Absorption coefficient	0.107 mm^{-1}	
F(000)	296	
Crystal size	0.42 x 0.25 x 0.08 mm^3	
Theta range for data collection	2.26 to 24.99°.	
Index ranges	-10<=h<=10, -10<=k<=10, -9<=l<=9	
Reflections collected	4460	
Independent reflections	1124 [R(int) = 0.0535]	
Completeness to theta = 24.99°	99.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1124 / 0 / 91	
Goodness-of-fit on F^2	1.055	
Final R indices [I>2sigma(I)]	R1 = 0.0375, wR2 = 0.0920	
R indices (all data)	R1 = 0.0398, wR2 = 0.0939	
Largest diff. peak and hole	0.214 and -0.211 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 03147. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	8047(2)	-4403(2)	2792(2)	24(1)
N(2)	7778(1)	-5509(1)	1431(1)	24(1)
C(3)	6481(2)	-6403(2)	1800(2)	30(1)
C(4)	6322(2)	-5618(2)	3429(2)	30(1)
C(5)	7959(2)	-5485(2)	4254(2)	30(1)
C(6)	6463(2)	-3889(2)	2993(2)	29(1)
C(7)	9226(2)	-3416(2)	2205(2)	29(1)
O(8)	8877(1)	-3519(1)	434(1)	29(1)
C(9)	7994(2)	-4781(2)	42(2)	25(1)
O(10)	7552(1)	-5103(1)	-1358(1)	34(1)

Table 3. Bond lengths [Å] and angles [°] for 03147.

C(1)-N(2)	1.4657(17)
C(1)-C(7)	1.4926(19)
C(1)-C(5)	1.5317(19)
C(1)-C(6)	1.5340(19)
N(2)-C(9)	1.3399(18)
N(2)-C(3)	1.4699(18)
C(3)-C(4)	1.524(2)
C(4)-C(6)	1.539(2)
C(4)-C(5)	1.557(2)
C(7)-O(8)	1.4548(17)
O(8)-C(9)	1.3631(17)
C(9)-O(10)	1.2036(16)
N(2)-C(1)-C(7)	100.29(11)
N(2)-C(1)-C(5)	100.70(11)
C(7)-C(1)-C(5)	135.31(12)
N(2)-C(1)-C(6)	101.64(11)
C(7)-C(1)-C(6)	126.26(12)
C(5)-C(1)-C(6)	86.93(11)
C(9)-N(2)-C(1)	108.69(11)
C(9)-N(2)-C(3)	128.97(12)
C(1)-N(2)-C(3)	104.01(11)
N(2)-C(3)-C(4)	96.75(11)
C(3)-C(4)-C(6)	101.73(12)
C(3)-C(4)-C(5)	102.97(11)
C(6)-C(4)-C(5)	85.88(10)
C(1)-C(5)-C(4)	81.05(10)
C(1)-C(6)-C(4)	81.56(10)
O(8)-C(7)-C(1)	102.47(10)
C(9)-O(8)-C(7)	109.40(10)
O(10)-C(9)-N(2)	129.97(13)
O(10)-C(9)-O(8)	121.64(13)
N(2)-C(9)-O(8)	108.38(11)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 03147. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	26(1)	25(1)	21(1)	-2(1)	3(1)	1(1)
N(2)	28(1)	23(1)	23(1)	-1(1)	5(1)	0(1)
C(3)	33(1)	25(1)	32(1)	0(1)	6(1)	-4(1)
C(4)	31(1)	29(1)	32(1)	0(1)	12(1)	-4(1)
C(5)	36(1)	31(1)	24(1)	3(1)	5(1)	2(1)
C(6)	27(1)	27(1)	32(1)	-3(1)	7(1)	2(1)
C(7)	30(1)	35(1)	23(1)	-3(1)	5(1)	-5(1)
O(8)	35(1)	30(1)	23(1)	1(1)	6(1)	-6(1)
C(9)	27(1)	24(1)	25(1)	-1(1)	4(1)	4(1)
O(10)	44(1)	36(1)	22(1)	-3(1)	2(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 03147.

	x	y	z	U(eq)
H(3A)	6696	-7529	1925	36
H(3B)	5602	-6239	976	36
H(4)	5510	-5988	4016	36
H(5A)	8089	-4970	5338	36
H(5B)	8550	-6452	4248	36
H(6A)	5852	-3557	1970	34
H(6B)	6386	-3155	3906	34
H(7A)	9165	-2329	2588	35
H(7B)	10228	-3832	2578	35

X-ray crystal structure of **165**

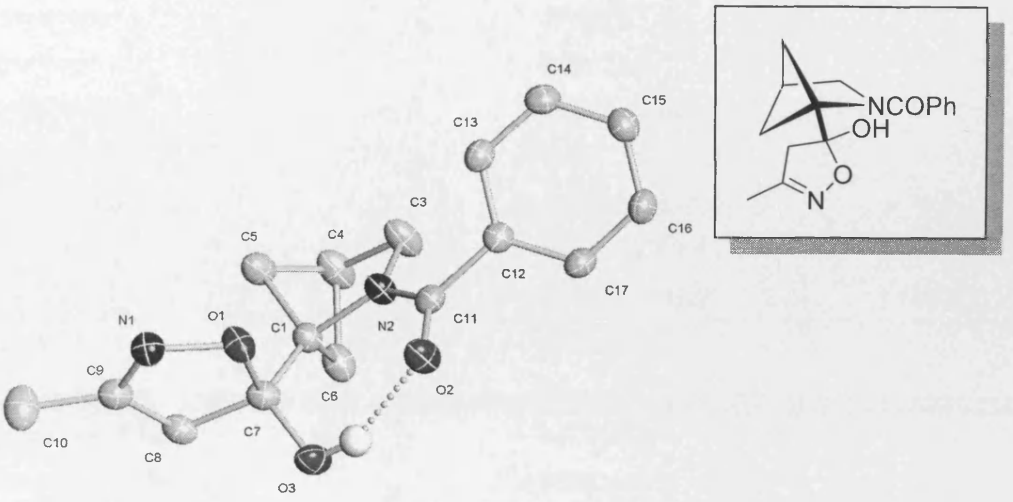


fig shows the atom label scheme and 50% displacement ellipsoids. All H atoms except for the O3-H3…H2 bond (1.849) are omitted for clarity.

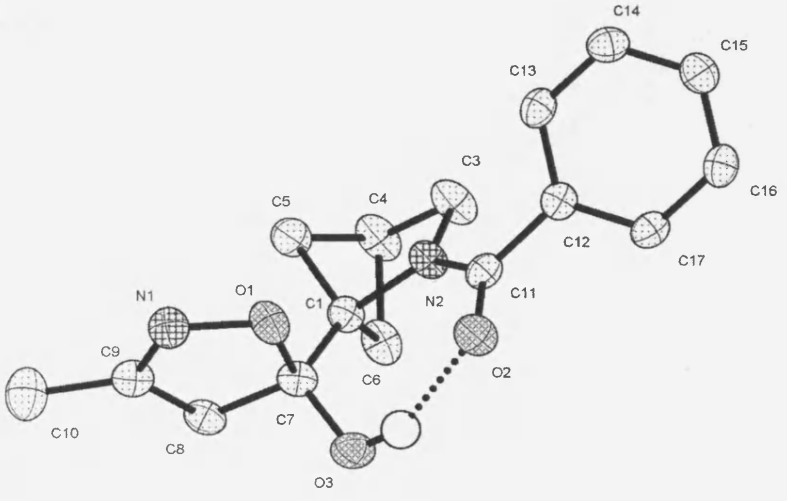


Table 1. Crystal data and structure refinement for 04172.

Identification code	04172	
Empirical formula	C16 H18 N2 O3	
Formula weight	286.32	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 10.9814(18) Å	α= 90°.
	b = 12.936(2) Å	β= 90°.
	c = 20.191(3) Å	γ = 90°.
Volume	2868.1(8) $Å^3$	
Z	8	
Density (calculated)	1.326 Mg/m^3	
Absorption coefficient	0.093 mm^{-1}	
F(000)	1216	
Crystal size	0.28 x 0.14 x 0.17 mm^3	
Theta range for data collection	2.02 to 25.00°.	
Index ranges	-12<=h<=13, -15<=k<=15, -24<=l<=24	
Reflections collected	19261	
Independent reflections	2524 [R(int) = 0.0461]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2524 / 0 / 192	
Goodness-of-fit on F^2	1.069	
Final R indices [I>2sigma(I)]	R1 = 0.0391, wR2 = 0.0868	
R indices (all data)	R1 = 0.0478, wR2 = 0.0908	
Largest diff. peak and hole	0.209 and -0.149 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 04172. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	413(1)	1661(1)	6495(1)	30(1)
N(2)	4128(1)	2215(1)	6153(1)	26(1)
O(1)	1613(1)	1494(1)	6256(1)	31(1)
O(2)	3854(1)	653(1)	5650(1)	34(1)
O(3)	2059(1)	1726(1)	5138(1)	34(1)
C(1)	3009(1)	2818(1)	5974(1)	24(1)
C(3)	4984(2)	3032(1)	6393(1)	35(1)
C(4)	4145(1)	3956(1)	6295(1)	35(1)
C(5)	2940(2)	3540(1)	6585(1)	32(1)
C(6)	3584(2)	3748(1)	5606(1)	31(1)
C(7)	1892(1)	2240(1)	5736(1)	25(1)
C(8)	755(1)	2911(1)	5689(1)	26(1)
C(9)	-51(1)	2434(1)	6194(1)	27(1)
C(10)	-1298(2)	2799(1)	6358(1)	42(1)
C(11)	4463(1)	1250(1)	5998(1)	24(1)
C(12)	5654(1)	894(1)	6278(1)	23(1)
C(13)	5873(1)	910(1)	6957(1)	27(1)
C(14)	6970(1)	557(1)	7204(1)	29(1)
C(15)	7858(1)	200(1)	6778(1)	29(1)
C(16)	7648(1)	180(1)	6102(1)	29(1)
C(17)	6541(1)	511(1)	5852(1)	26(1)

Table 3. Bond lengths [Å] and angles [°] for 04172.

N(1)-C(9)	1.275(2)
N(1)-O(1)	1.4198(17)
N(2)-C(11)	1.3376(19)
N(2)-C(3)	1.4947(19)
N(2)-C(1)	1.4998(18)
O(1)-C(7)	1.4587(18)
O(2)-C(11)	1.2403(18)
O(3)-C(7)	1.3897(18)
C(1)-C(7)	1.515(2)
C(1)-C(5)	1.549(2)
C(1)-C(6)	1.549(2)
C(1)-C(4)	2.036(2)
C(3)-C(4)	1.523(2)
C(4)-C(6)	1.544(2)
C(4)-C(5)	1.545(2)
C(7)-C(8)	1.523(2)
C(8)-C(9)	1.484(2)
C(9)-C(10)	1.485(2)
C(11)-C(12)	1.497(2)
C(12)-C(17)	1.390(2)
C(12)-C(13)	1.391(2)
C(13)-C(14)	1.382(2)
C(14)-C(15)	1.379(2)
C(15)-C(16)	1.385(2)
C(16)-C(17)	1.384(2)
C(9)-N(1)-O(1)	109.18(12)
C(11)-N(2)-C(3)	124.23(13)
C(11)-N(2)-C(1)	130.86(12)
C(3)-N(2)-C(1)	103.04(11)
N(1)-O(1)-C(7)	109.78(11)
N(2)-C(1)-C(7)	118.94(12)
N(2)-C(1)-C(5)	99.34(11)
C(7)-C(1)-C(5)	120.76(13)
N(2)-C(1)-C(6)	100.67(11)
C(7)-C(1)-C(6)	124.08(13)
C(5)-C(1)-C(6)	86.16(12)
N(2)-C(1)-C(4)	78.31(9)

C(7)-C(1)-C(4)	162.57(12)
C(5)-C(1)-C(4)	48.75(9)
C(6)-C(1)-C(4)	48.72(9)
N(2)-C(3)-C(4)	97.63(12)
C(3)-C(4)-C(6)	102.85(13)
C(3)-C(4)-C(5)	101.22(13)
C(6)-C(4)-C(5)	86.50(12)
C(3)-C(4)-C(1)	81.02(10)
C(6)-C(4)-C(1)	48.95(8)
C(5)-C(4)-C(1)	48.95(8)
C(4)-C(5)-C(1)	82.30(12)
C(4)-C(6)-C(1)	82.33(12)
O(3)-C(7)-O(1)	109.64(11)
O(3)-C(7)-C(1)	113.91(13)
O(1)-C(7)-C(1)	105.45(11)
O(3)-C(7)-C(8)	109.14(12)
O(1)-C(7)-C(8)	104.45(12)
C(1)-C(7)-C(8)	113.70(12)
C(9)-C(8)-C(7)	102.08(12)
N(1)-C(9)-C(8)	114.49(14)
N(1)-C(9)-C(10)	120.78(14)
C(8)-C(9)-C(10)	124.73(14)
O(2)-C(11)-N(2)	124.40(14)
O(2)-C(11)-C(12)	119.56(13)
N(2)-C(11)-C(12)	116.04(13)
C(17)-C(12)-C(13)	119.53(14)
C(17)-C(12)-C(11)	119.22(13)
C(13)-C(12)-C(11)	121.22(13)
C(14)-C(13)-C(12)	120.15(14)
C(15)-C(14)-C(13)	120.09(15)
C(14)-C(15)-C(16)	120.20(15)
C(17)-C(16)-C(15)	119.99(14)
C(16)-C(17)-C(12)	120.00(14)

Symmetry transformations used to generate equivalent atoms:

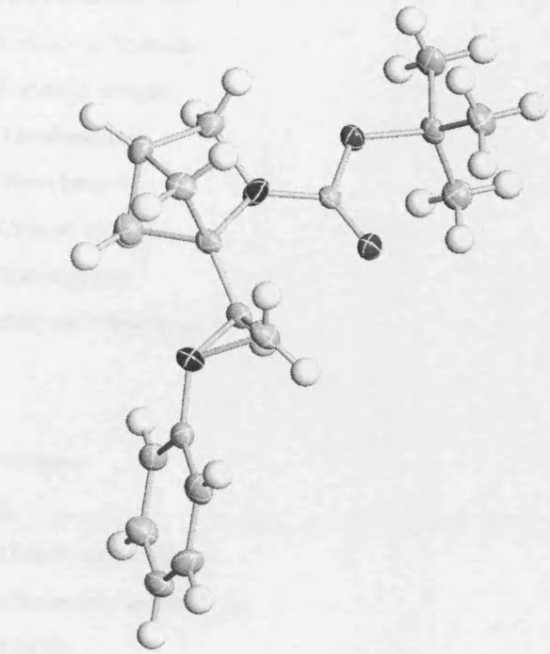
Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 04172. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

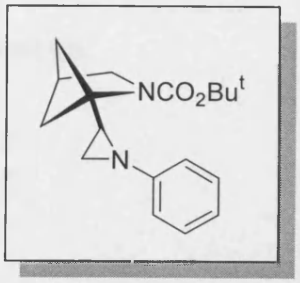
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	30(1)	28(1)	33(1)	3(1)	2(1)	0(1)
N(2)	25(1)	19(1)	33(1)	-2(1)	-4(1)	0(1)
O(1)	26(1)	28(1)	40(1)	12(1)	0(1)	0(1)
O(2)	36(1)	25(1)	41(1)	-10(1)	-7(1)	3(1)
O(3)	40(1)	32(1)	31(1)	-8(1)	-8(1)	4(1)
C(1)	26(1)	19(1)	27(1)	-1(1)	-2(1)	2(1)
C(3)	30(1)	21(1)	54(1)	-5(1)	-12(1)	-1(1)
C(4)	31(1)	18(1)	57(1)	-7(1)	-11(1)	-1(1)
C(5)	34(1)	27(1)	35(1)	-9(1)	-6(1)	5(1)
C(6)	28(1)	21(1)	44(1)	4(1)	-1(1)	0(1)
C(7)	30(1)	19(1)	26(1)	3(1)	-3(1)	-2(1)
C(8)	28(1)	23(1)	29(1)	4(1)	-6(1)	-2(1)
C(9)	32(1)	21(1)	29(1)	0(1)	-2(1)	-1(1)
C(10)	41(1)	32(1)	52(1)	9(1)	12(1)	7(1)
C(11)	29(1)	21(1)	22(1)	0(1)	4(1)	-1(1)
C(12)	27(1)	16(1)	27(1)	1(1)	1(1)	0(1)
C(13)	31(1)	23(1)	27(1)	-1(1)	5(1)	3(1)
C(14)	37(1)	26(1)	25(1)	2(1)	-3(1)	0(1)
C(15)	28(1)	25(1)	35(1)	2(1)	-2(1)	2(1)
C(16)	29(1)	25(1)	33(1)	-1(1)	7(1)	4(1)
C(17)	34(1)	21(1)	23(1)	0(1)	2(1)	1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 04172.

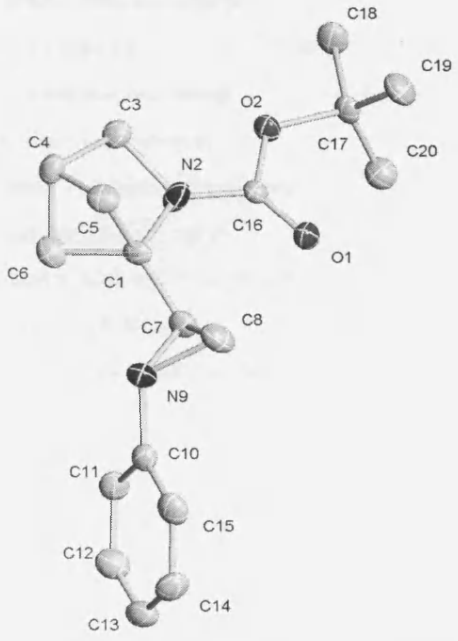
	x	y	z	U(eq)
H(3)	2633	1302	5176	51
H(3A)	5727	3077	6118	42
H(3B)	5210	2933	6864	42
H(4)	4432	4666	6412	43
H(5A)	2255	4037	6581	38
H(5B)	3019	3188	7018	38
H(6A)	4177	3562	5257	37
H(6B)	2996	4277	5453	37
H(8A)	938	3641	5799	32
H(8B)	388	2877	5242	32
H(10A)	-1649	2353	6701	62
H(10B)	-1807	2773	5960	62
H(10C)	-1258	3512	6521	62
H(13)	5267	1163	7250	33
H(14)	7113	561	7668	35
H(15)	8615	-33	6949	35
H(16)	8263	-61	5809	35
H(17)	6387	477	5389	31

X-ray crystal structure of **203**





All crystals were thin plates that could be further divided into still thinner plates. The quality of the crystals and therefore the data limited the quality of the refinement with final R1=0.10.



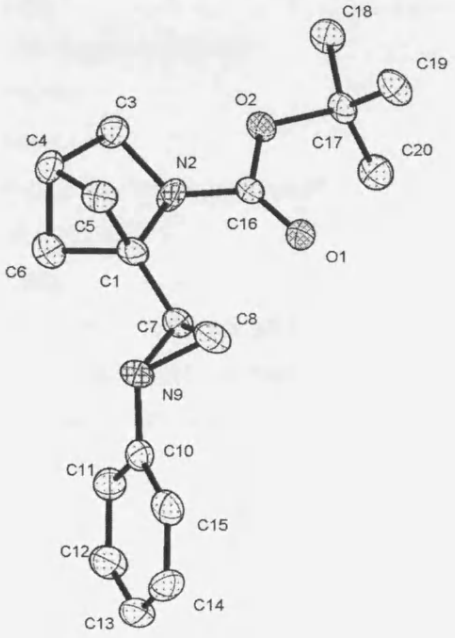


fig. shows the molecular structure with the atom label scheme and 50% displacement ellipsoids. H atoms are omitted for clarity

Table 1. Crystal data and structure refinement for 04087.

Identification code	04087	
Empirical formula	C18 H24 N2 O2	
Formula weight	300.39	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 5.699(2) Å	α= 87.927(8)°.
	b = 10.973(4) Å	β= 83.619(5)°.
	c = 13.127(5) Å	γ = 80.039(8)°.
Volume	803.5(6) $Å^3$	
Z	2	
Density (calculated)	1.242 Mg/m^3	
Absorption coefficient	0.081 mm^{-1}	
F(000)	324	
Crystal size	0.28 x 0.16 x 0.04 mm^3	
Theta range for data collection	1.56 to 24.00°.	
Index ranges	-6<=h<=6, -12<=k<=12, -15<=l<=15	
Reflections collected	5366	
Independent reflections	2499 [R(int) = 0.0871]	
Completeness to theta = 24.00°	99.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2499 / 0 / 202	
Goodness-of-fit on F^2	1.170	
Final R indices [I>2sigma(I)]	R1 = 0.1017, wR2 = 0.2993	
R indices (all data)	R1 = 0.1225, wR2 = 0.3069	
Largest diff. peak and hole	0.430 and -0.333 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 04087. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	2372(11)	1115(6)	8207(5)	22(1)
N(2)	4289(10)	1123(5)	7344(4)	28(1)
C(3)	4907(11)	-179(6)	7033(5)	26(2)
C(4)	3152(12)	-706(6)	7832(5)	28(2)
C(5)	837(11)	261(6)	7778(5)	28(2)
C(6)	3480(12)	-36(6)	8797(5)	29(2)
C(7)	1339(11)	2316(6)	8704(5)	25(1)
C(8)	-1153(12)	2941(7)	8585(5)	32(2)
N(9)	-604(9)	2243(5)	9523(4)	26(1)
O(1)	3853(8)	3165(4)	6907(3)	28(1)
O(2)	6495(7)	1700(4)	5998(3)	24(1)
C(10)	-608(11)	2934(6)	10423(5)	23(1)
C(11)	1327(12)	2735(6)	10988(5)	29(2)
C(12)	1261(13)	3357(6)	11890(5)	35(2)
C(13)	-736(13)	4188(6)	12231(5)	33(2)
C(14)	-2692(13)	4393(6)	11679(5)	34(2)
C(15)	-2646(12)	3768(6)	10781(5)	33(2)
C(16)	4755(10)	2106(6)	6767(4)	19(1)
C(17)	7377(11)	2603(6)	5250(5)	24(1)
C(18)	9364(12)	1778(6)	4587(5)	32(2)
C(19)	5399(12)	3173(7)	4617(5)	32(2)
C(20)	8419(12)	3553(6)	5773(5)	31(2)

Table 3. Bond lengths [Å] and angles [°] for 04087.

C(1)-N(2)	1.485(8)
C(1)-C(7)	1.489(9)
C(1)-C(6)	1.535(9)
C(1)-C(5)	1.547(9)
N(2)-C(16)	1.343(8)
N(2)-C(3)	1.473(8)
C(3)-C(4)	1.536(9)
C(4)-C(6)	1.532(9)
C(4)-C(5)	1.550(9)
C(7)-N(9)	1.466(8)
C(7)-C(8)	1.489(9)
C(8)-N(9)	1.461(8)
N(9)-C(10)	1.427(8)
O(1)-C(16)	1.198(7)
O(2)-C(16)	1.363(7)
O(2)-C(17)	1.480(7)
C(10)-C(11)	1.379(9)
C(10)-C(15)	1.396(9)
C(11)-C(12)	1.382(9)
C(12)-C(13)	1.373(10)
C(13)-C(14)	1.378(10)
C(14)-C(15)	1.381(10)
C(17)-C(20)	1.506(9)
C(17)-C(19)	1.509(9)
C(17)-C(18)	1.530(9)
N(2)-C(1)-C(7)	117.6(5)
N(2)-C(1)-C(6)	99.3(5)
C(7)-C(1)-C(6)	123.4(5)
N(2)-C(1)-C(5)	100.6(5)
C(7)-C(1)-C(5)	123.4(5)
C(6)-C(1)-C(5)	85.9(5)
C(16)-N(2)-C(3)	125.8(5)
C(16)-N(2)-C(1)	126.7(5)
C(3)-N(2)-C(1)	104.1(5)
N(2)-C(3)-C(4)	97.6(5)
C(6)-C(4)-C(3)	101.1(5)
C(6)-C(4)-C(5)	85.9(5)

C(3)-C(4)-C(5)	101.5(5)
C(1)-C(5)-C(4)	82.3(5)
C(4)-C(6)-C(1)	83.3(5)
N(9)-C(7)-C(8)	59.3(4)
N(9)-C(7)-C(1)	114.4(5)
C(8)-C(7)-C(1)	121.6(6)
N(9)-C(8)-C(7)	59.6(4)
C(10)-N(9)-C(8)	117.3(5)
C(10)-N(9)-C(7)	116.9(5)
C(8)-N(9)-C(7)	61.1(4)
C(16)-O(2)-C(17)	119.6(4)
C(11)-C(10)-C(15)	119.0(6)
C(11)-C(10)-N(9)	120.8(6)
C(15)-C(10)-N(9)	120.1(6)
C(10)-C(11)-C(12)	120.6(6)
C(13)-C(12)-C(11)	120.1(7)
C(12)-C(13)-C(14)	120.0(7)
C(13)-C(14)-C(15)	120.2(6)
C(14)-C(15)-C(10)	120.1(7)
O(1)-C(16)-N(2)	126.6(6)
O(1)-C(16)-O(2)	125.1(5)
N(2)-C(16)-O(2)	108.2(5)
O(2)-C(17)-C(20)	111.3(5)
O(2)-C(17)-C(19)	109.8(5)
C(20)-C(17)-C(19)	112.8(6)
O(2)-C(17)-C(18)	102.0(5)
C(20)-C(17)-C(18)	109.9(5)
C(19)-C(17)-C(18)	110.5(5)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 04087. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	21(3)	26(3)	19(3)	0(3)	4(3)	-7(3)
N(2)	30(3)	18(3)	36(3)	-1(2)	8(2)	-6(2)
C(3)	27(4)	23(3)	29(4)	-1(3)	-1(3)	-6(3)
C(4)	33(4)	19(3)	32(4)	2(3)	3(3)	-6(3)
C(5)	24(3)	33(4)	28(4)	-3(3)	-1(3)	-9(3)
C(6)	24(3)	34(4)	28(4)	5(3)	-3(3)	-5(3)
C(7)	26(3)	27(3)	21(3)	0(3)	4(3)	-7(3)
C(8)	33(4)	39(4)	22(4)	1(3)	-3(3)	0(3)
N(9)	29(3)	28(3)	19(3)	-2(2)	2(2)	-4(2)
O(1)	35(3)	22(3)	25(2)	2(2)	0(2)	0(2)
O(2)	23(2)	25(2)	21(2)	2(2)	6(2)	-4(2)
C(10)	26(3)	21(3)	23(3)	2(3)	3(3)	-6(3)
C(11)	28(4)	26(4)	28(4)	0(3)	5(3)	0(3)
C(12)	36(4)	39(4)	28(4)	-1(3)	-2(3)	-4(3)
C(13)	42(4)	33(4)	24(4)	-3(3)	5(3)	-11(3)
C(14)	35(4)	26(4)	36(4)	-7(3)	9(3)	-1(3)
C(15)	32(4)	35(4)	29(4)	5(3)	8(3)	-6(3)
C(16)	19(3)	22(3)	16(3)	0(2)	-2(2)	-4(3)
C(17)	21(3)	27(3)	21(3)	3(3)	6(3)	-5(3)
C(18)	27(4)	33(4)	31(4)	1(3)	10(3)	-3(3)
C(19)	31(4)	40(4)	23(4)	6(3)	-6(3)	-3(3)
C(20)	28(4)	34(4)	32(4)	1(3)	-1(3)	-8(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 04087.

	x	y	z	U(eq)
H(3A)	6598	-534	7111	32
H(3B)	4564	-292	6322	32
H(4)	3083	-1612	7860	34
H(5A)	404	480	7077	34
H(5B)	-557	96	8250	34
H(6A)	5168	-57	8922	35
H(6B)	2487	-248	9424	35
H(7)	2502	2866	8829	30
H(8A)	-1506	3855	8621	38
H(8B)	-2057	2578	8107	38
H(11)	2719	2164	10755	35
H(12)	2601	3209	12276	41
H(13)	-769	4623	12846	39
H(14)	-4076	4965	11918	40
H(15)	-4003	3906	10406	39
H(18A)	10624	1409	5011	47
H(18B)	10042	2278	4033	47
H(18C)	8699	1121	4294	47
H(19A)	4693	2517	4344	47
H(19B)	6058	3659	4049	47
H(19C)	4162	3714	5049	47
H(20A)	7129	4101	6172	47
H(20B)	9244	4042	5256	47
H(20C)	9561	3135	6231	47