Synthesis of Analogues of Epibatidine based on the 2-azabicyclo[2.2.1]heptane system

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By

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Statement

The concomitant thesis submitted for the degree of PhD under the title constitutes work conducted by the author in the Department of Chemistry at the University of Leicester fundamentally during the period of time from January 2014 to November 2017. The work involved here is original otherwise indicated in the text or references. To the best of my knowledge, no one has been submitted this work for another degree in this or any other universities.

Signed…Huda Ismail Al-Rubaye… Date…21/03/2018…

TO

My father soul

Mother

Sisters & brothers

Abstract

Synthesis of Analogues of Epibatidine based on the 2-azabicyclo[2.2.1] heptane system

By Huda Ismail Al-Rubaye

Epibatidine (*exo*-2-(6-chloro-3-pyridyl)-7-azabicyclo[2.2.1]heptane) is an alkaloid isolated from the skin of the Ecuadorian poison frog. It has been known since 1992 and has high binding affinity for nicotinic acetylcholine receptors. Many studies have reported epibatidine to possess analgesic properties, but it is also toxic even in low doses, thus, it cannot be used therapeutically. A wide range of epibatidine analogues have been studied in the hope of reducing their toxicity, and hence exploiting their therapeutic potential

A general method for the synthesis of *anti*-7-functionalised 2-benzyl-2-azabicyclo[2.2.1]heptane has been employed. Aza Diels-Alder reaction was used successfully to construct the rigid protected amine 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene skeleton. Bromination of 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene gives a reactive tricyclic salt, which in turn undergoes skeletal rearrangement with hydrid to obtain *anti*-7-bromo-2-benzyl-2-azabicyclo[2.2.1]heptane. Nucleophilic substitution reaction at C-7 of this compound found to be occur with retention of configuration, consistent with neighbouring group participation of the bicyclic nitrogen lone pair.

An oxidation-reduction strategy facilitated the epimerisation at the C-7 of 2-azabicyclo[2.2.1]heptane, heterocycles have been introduced at this position to give the ether linkage nicotinic receptor ligands with general structure 7-(pyridyloxy)-2-benzyl-2-azabicyclo[2.2.1]heptane. Mitsunobu chemistry has been utilised to synthesis a range of pyridyl ether compounds. Methylisoxazole heterocycle has also been synthesised and incorporated to open the way to some analogues.

The synthesis of fluorinated analogues of 2-azabicyclo[2.2.1]heptane has been investigated using nucleophilic fluorinating agent, diethylaminosulphur trifluoride, DAST. Moreover, fluorination of all alcohols is consistent with S_N2 attack, whilst fluorination of ketones gave geminal difluorides with the 6-*oxo* isomer being assisted by neighbouring group participation.

A range of different 5- and 6-chloropyridyl-substituted-2-azabicyclo[2.2.1]heptane derivatives have been constructed. The 5- and 6-chloropyridyl derivatives were synthesised *via* nucleophilic attack of lithiated-chloropyridine onto the appropriate

azabicyclic ketone. Dehydration of the adduct gave an olefin. ^{1}H, ^{13}C and ^{19}F NMR spectroscopy was used to characterise these compounds.

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Special thanks to my family, Mum, sisters & brothers, especially Dr. Zainab. For their wholehearted support and encouragement in my study, I would like to dedicate this thesis to them.

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Abbreviations

nAChR	Nicotinic acetylcholine receptor
mAChR	Muscarinic acetylcholine receptor
CNS	Central nervous system
AChBP	Acetylcholine-binding protein
IR	Infra-red
COSY	Correlation spectroscopy
NOESY	Nuclear Overhauser effect spectroscopy
^{o}C	Degrees celsius
cm $^{-1}$	wave numbers
AD	Alzheimer's disease
Å	Angstrom
Me	Methyl
MeOH	Methanol
DAST	Diethyl amino sulfur trifluoride
PDC	Pyridinium dichromate
DCM	Dichloromethane
THF	Tetrahydrofurane
RT	Room temperature
SAR	Structure activity relationship
TLC	Thin layer chromatography
h	Hours
Hz	Hertz
ml	Milliliter
mmol	Millimoles
MS	Mass spectroscopy
M^{+}	Molecular ion
NGP	Neighbouring group participation
pH	Potential of hydrogen (-log[H^{+}])
g	Grams

M	Molar
DIAD	Diisopropyl azodicarboxylate
PPh_3	Triphenyl phosphine
mg	Milligram
DMSO	Dimethylsulfoxide
DMF	Dimethyl formamide
Boc	*Tert*-Butyloxycarbonyl protecting group
MHz	Megahertz
NMP	1-Methyl-2-pyrrolidone
m.p.	Melting point
NMR	Nuclear magnetic resonance
K_i	Binding affinity constant
hv	Irradiation with light
lit.	Literature
i.p.	Intraperitoneal injection

Chapter 1

Introduction

1. Introduction

1.1 Neuronal Nicotinic Acetylcholine Receptors

The first neurotransmitter to be discovered was acetylcholine ACh (**1**) and this compound is produced by the enzyme choline acetyltransferase which utilizes acetyl-CoA and choline as substrates for its formation. Acetylcholine receptors in the mammalian central nervous system CNS can be divided into muscarinic receptors (mAChRs) and nicotinic receptors (nAChRs). The former (mAChRs) have the ability to bind to the natural alkaloid muscarine (**2**) and are found in the CNS, glands, heart and smooth muscle while the latter (nAChRs) bind to the natural alkaloid nicotine (**3**) and are mainly found in the nervous system. However, both receptors stimulate ion channels and play a significant role in mediating neuromuscular and autonomic transmission.[1] Although, the molecular structure of these two types of receptors are similar, they have different biological function when activated and further agonists from natural sources have played key role in the development of different approaches towards synthetic agonists to mimic the effects of ACh as a neurotransmitter.[1]

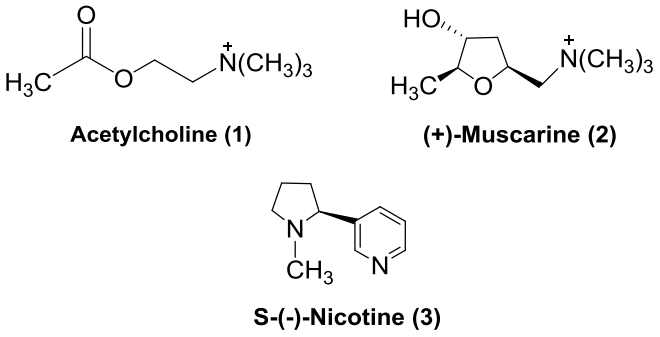


Fig. 1.1 The structure of Ach and the alkaloids nicotine and muscarine.

Nicotinic acetylcholine receptors (nAChRs) are a set of ligand-gated ion channels that play a vital role in different biological activities, in particular, those related to central nervous system (CNS) functions. Several studies have revealed that nicotine and it analogues show potent biological activity in mammals by modification of (nAChRs) which, in addition, regulates the release of other important neurotransmitters. In recent decades, researchers have shown an increasing interest in the neurobiology and pharmacology of nicotine and related (nAChRs) agonists and antagonists that has led renewed interest in drug discovery for the treatment of Parkinson's and Alzheimer's (AD)

diseases, schizophrenia, attention deficit/hyperactivity and Tourette's syndrome. Moreover, some drugs are also being developed for the treatment of tobacco addiction and anesthetic agents.[2, 3]

Nicotine (a plant alkaloid) has a wide range of biological activities, some beneficial, some not so (**Table**. **1**). Its activity is mostly based on its ability to selectively activate nAChR subtypes present in the body. Several studies have reported that the interaction of nicotine with nAChRs leads to nicotine addiction.[1, 4, 5]

Table 1: Major pharmacological effects of nicotine.[1]

Harmful effects	Beneficial effects
Addiction	Cognitive enhancement
Hypothermia	Anxiolytic
Seizures	Antipsychotic
Hypertension	Neuroprotection
Emetic	Cerebrovasodilation
Respiratory failure	Analgesia

Recent developments in the field of nicotinic agonists have led to improvements in memory function.[3] Whilst, nicotinic antagonists have been shown to have a correlation between a decrease in nicotinic receptors density and cognitive dysfunction.[3] A large and growing body of research has investigated the structure of neuronal nAChR agonists and antagonists, which, based on pharmacological precedent, may represent novel targets for a wide variety of therapeutic benefits for the treatment of different neurological disease states.

1.2 The structure and action of nicotinic acetylcholine receptor subunits

The neuronal nAChRs are a major class of transmitter receptor as well as part of the superfamily of ligand gated ion channels (LGIC) which includes those activated by serotonin (5HT3), γ-aminobutyric acid (GABA) $_{A, C}$ and glycine.[6, 7] The nAChRs isolated from the *Electrophorus* fish or electric organ of the torpedo ray are well characterized and distributed throughout the peripheral and CNS,[8] and are analogous to those found in mammalian skeletal muscle. In addition, they are pharmacologically and functionally

diverse.[9] Recent studies have confirmed that peripheral nAChRs are composed of an ion channel surrounded by a ring of five protein subunits including two α and one each of β, ϒ and δ. It is predicted that each subunit consists of four domains which are helix transmembrane spanning regions, M_1-M_4, where there regions, shape the cavity of the channel. The channel opens allowing diffusion of cations into the cell and this depolarises the post synaptic membrane, which induces an action potential, propagating the signal and resulting in an antinociceptive response (**Fig.1.2)**.[10] The unique pentameric structure concept has the potential for producing a myriad of neuronal nAChRs subunits combinations consisting of both homomeric (contain only α subunits) and heteromeric (contain α and β subunits). Moreover, the eleven neuronal nAChRs subunits found in mammalian species have been identified and shown to include eight α (α2-α9) and three β (β2-β4) components (**Fig.1.2**).[5, 11, 12]

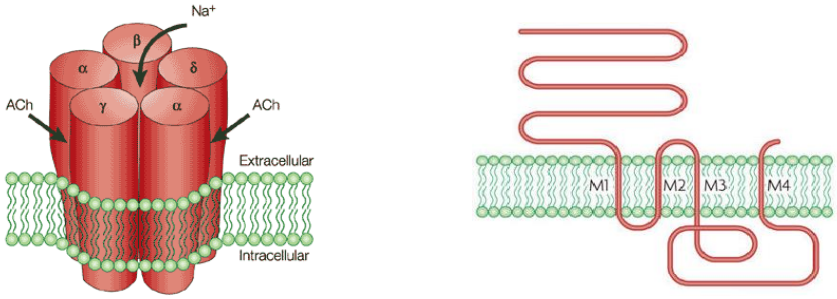


Fig. 1.2 The structure of nicotinic receptor channel.[13]

Although, the qualitative relationships of most nAChRs in the brain is still under study and not defined, the most abundant subtypes have been found to be α4β2 and α7, where the α4β2 subtype is suggested to have two α4- and three β2- subunits and the homogenous α7 is composed of five α7 units. Presently, the function of these two nAChRs receptors is not well understood, although studies have shown that these nAChRs receptors are associated with cognitive function.[5]

The subunits that make up muscle nAChRs consists of two α1 subunits and one each of δ, β1 and either γ and ε. Nevertheless, the diversity associated with neuronal nAChRs is more than that of muscle nAChRs because the subunits combinations in neuronal nAChRs consist of only protein subunits α and β, and many complex combinations are possible.[14]

The significant pentameric structure of the neuronal nAChR synthetically leads to a large number of nAChR subtypes, which based on pharmacological findings represent a novel

target for a wide range of therapeutic agents. It is important to note, that many recently characterized nAChR agonists are very different from (-)-nicotine in terms of their pharmacological properties and side effects because of their nAChR subtype selectivity.[5]

1.3 Epibatidine

In 1974, Daly and Myers at the National Institutes of Health in South America first isolated a trace amount of the natural alkaloid epibatidine from the skin of the Ecuadorian poison frog (*Epipedobates tricolor*) (**Fig. 1.3**). During their research they collected approximately 60 mg of a complex mixture of alkaloids from a total of 750 frogs of which the most active component was epibatidine.[14]

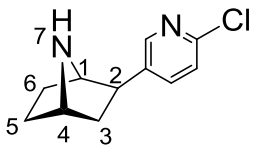


Fig. 1.3 *Epipedobates tricolor* poison frog (http:/img.photobucket.com) **Epibatidine (4)**

The structure of epibatidine was not fully elucidated until 1992 with the aid of NMR spectroscopy and other analytical techniques and the structure of the novel alkaloid was reported as (1*R*, 2*R*, 4*S*)-*exo*-2-(6-chloro-3-pyridyl)-7-azabicyclo [2.2.1] heptane.[15] This unique structure consists of a 7-azabicyclo[2.2.1]heptane (7-azanorbornane) structure, with an *exo*-oriented 5-(2-chloropyridyl) ring. In addition, the structure of nicotine (**3**) is similar to that of epibatidine: both possess a pyridine ring attached by the carbon atom, but in epibatidine the five membered ring is part of the 7-azabicyclic skeleton. Thus, with this structural resemblance it is perhaps not surprising that studies have shown that epibatidine is a much more potent analgesic, 200 times more potent than morphine and 30 times more potent than nicotine due to its high binding affinity towards the α4β2 subtype nAChR. However, lack of selectivity of epibatidine towards nAChRs subtype and its high toxicity prevent it exploration as a potential therapeutic agent.[16]

Of the possible two stereoisomers *exo*- and *endo*-, only *exo*-epibatidine has been found to be active. Additionally for this isomer,[15] which can exist as (+)- or *R*-epibatidine and (-)- or *S*-epibatidine, there is little difference in pharmacological activity between the (+)-

enantiomer and (-)-enantiomer (K_i = 0.026 nM and K_i = 0.018 nM respectively). The advances in the synthesis of epibatidine isomers and analogues provides an opportunity to explore more about this exceptional compound.[15] Since its discovery, epibatidine has been studied by researchers to develop novel epibatidine analogues which are more nAChRs subtypes specific and thus may potentially have lower toxicity.

1.3.1 Epibatidine and analgesia

Epibatidine is most useful as a pain reliever,[17] however, it is not selective. This has been clearly established by the fact that epibatidine, like nicotine, has high binding affinity to the α4β2 subtypes in the central nervous system. Epibatidine acts as an agonist and desensitizes the receptor to further stimuli. In other word, the analgesia effect of epibatidine is not blocked by the potent opiate antagonist naloxone, suggesting a therapeutic action different from that of morphine. Therefore, there is the possibility that epibatidine can be used as an effective treatment for severe pain without addiction. However, the toxicity of epibatidine at a dose higher than 5μg kg^{-1} i.p. causes respiratory paralysis, hypertension, seizures and some times death.[17]

The biological activity of epibatidine has encouraged scientists to develop new synthetic approaches which offer an important advantage in describing the pharmacology of the compound.[17] The antinociceptive effect has been measured only in rodents using a hotplate experiment and at 2.5μg kg^{-1} i.p., the compound shows significant analgesia; this effect was found to be 200-300 times higher than nicotine.[17] Other studies using different techniques, such as a footshock vocalization assay, show that epibatidine is approximately equal-active and equal-efficacious with morphine, except in some cases, where it was found to be less active. Furthermore, because of the dangerous side effects of epibatidine, there have been no reports of the use of the compound as an antinociceptive agent in humans.[17]

1.4 Alkaloids

Alkaloids are basic compounds containing at least one nitrogen atom which are found mainly in plants and less commonly in insects, amphibians and fungi. They are characterised by their powerful pharmacological action, ranging from poisonous to having medicinal value. Spectroscopic and chromatographic analysis contributed to the development of the chemistry of alkaloids in the 20th century. Nearly 12,000 natural products had been identified and the first synthetic alkaloid, Coniine, was prepared in 1886 by Albert Ladenburg.[18] Coniine is an extremely poisonous alkaloid that can be extracted from the seeds of hemlock (*Conium maculactum*) where less than 200 mg can be fatal. The mechanism of action involves disruption of the nervous system leading to failure of the respiratory system and eventually to death (**Fig. 1.4**). Alkaloids are also identified by their wide structural diversity constituting of monocyclic and multicycle molecules; epibatidine is a unique alkaloid possessing the 7-azabicyclic[2.2.1]heptane backbone attached to a chloropyridyl substituent.[18]

Fig. 1.4 Coniine and poison hemlock flower (http://www.piercecountyweedboard.org).

1.4.1 Examples of alkaloids extracted from plants

Most alkaloids that have been identified to date have been extracted from plants (leaves, seeds and roots) and the majority of these compounds have pharmacological properties. Examples include quinine, reserpine, cocaine and 1-hydroxytropacocaine.

Quinine is extracted from the bark of the cinchona tree and has a 1-azabicyclo[2.2.2]octane template (**Fig. 1.5**).[19] The total synthesis of quinine was first published in 1944 and the compound itself was the only efficient treatment for malaria until recent develpoments in the drug industry. Quinine has an intense bitter taste and is added in trace amount to make tonic water.[19]

Fig. 1. 5 Quinine structure and the cinchona tree (https://commons.wikimedia.org).

Reserpine, an indole natural product with a series of connecting ring systems (non bicyclic), was isolated from the roots of the Indian plants *Rauwolfia serpentine* and was first synthesized in 1956 by Woodward (**Fig. 1.6**). It has been used for the treatment of psychiatric disease and high blood pressure. Recently, it has been found that reserpine therapy has a positive impact on mental health.[20]

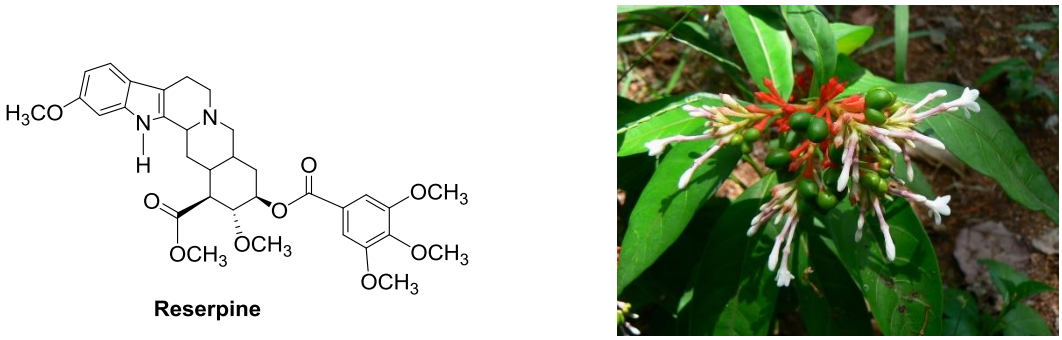


Fig. 1.6 Reserpine structure and *Rauwolfia serpentine* (https://www.flickr.com/photos).

Both cocaine and 1-hydroxytropacocaine (**Fig. 1.7**) are tropane alkaloids having a 8-azabicyclo[3.2.1]octane template they can be extracted in small amounts from the leaves of the plant *Erthroxylom coca* and in larger amounts from *Erythroxylum novogranatense*. Cocaine is powerful stimulant with addictive effects due to the fact that it blocks the metabolism of dopamine resulting in high population of this neurotransmitter in the nervous system. 1-Hydroxytropacocaine belongs to the calystegine family of alkaloids which are known to have diverse roles in the rhizosphere ecology such as glycosidase inhibitory function.[1, 21]

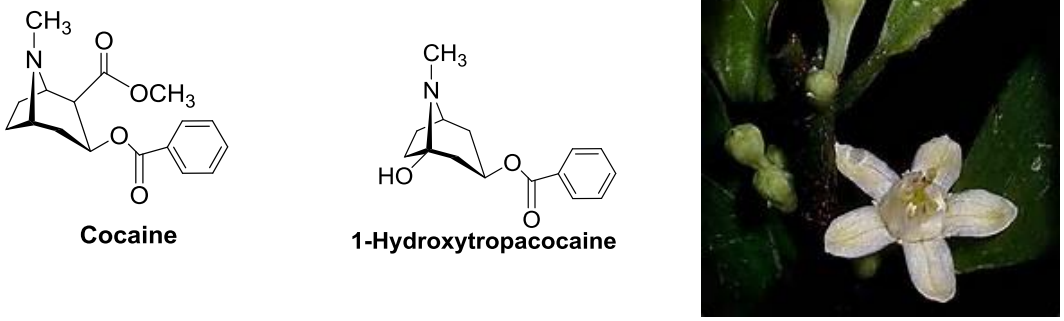


Fig. 1.7 Cocaine structure and *Erthroxylom coca* (http://www.uniprot.org).

1.4.2 Alkaloids from frogs

A wide range of natural products isolated from the skin of amphibians have been documented,[22, 23] one of which is epibatidine. Many of these compounds are metabolites secreted onto the surface of the frog skin and play a primary role in chemical defence. It is worth mentioning that the native Indians in America used these metabolites from frog skin on their hunting weapons, an example of such metabolites are pumiliotoxin A and batrachotoxine A.

Pumiliotoxin A is typically extracted in a small amount from the skin of the poison frog *Dendrobates pumilio* (**Fig.1.8**). The structure of Pumiliotoxin A consists of a 6-alkylidiendolizidine ring moiety and a dose of 20 μg can lead to death. The compound is found to be incompatible with muscle contraction by affecting sodium channels, resulting in partial paralysis or death. Alkaloids similar in structure to pumiliotoxin have also been reported in poison ants.[23, 24]

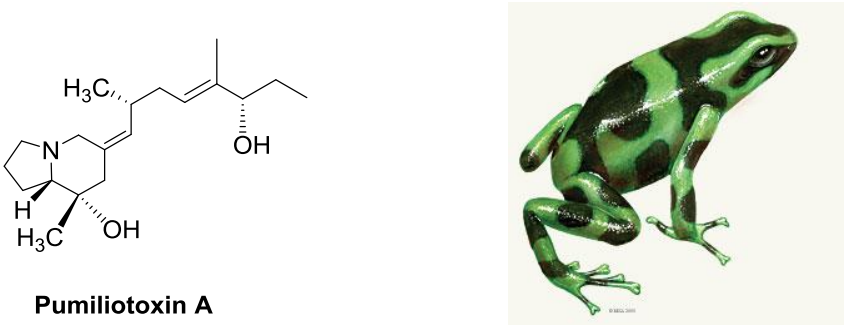
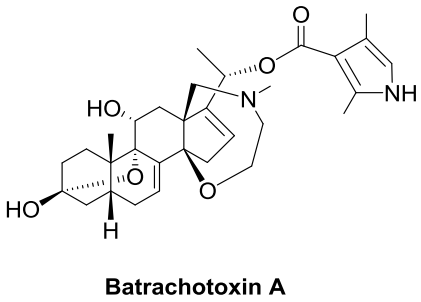


Fig. 1.8 The structure of Pumiliotoxin A and *Dendrobates pumilio* frog (http://www.ryanphotographic.com).

Batrachotoxin A is an extremely toxic steroidal natural product that can be found on the skin of the poison frog *Phyllobates aurotaenia* (**Fig. 1.9**). The toxin has no effect on skin

but is fatal in very low concentrations (two parts per billion) in the bloodstream. It affects the peripheral nervous system by binding to sodium-ion channels, thus resulting in a conformational change thereby forcing the channel to remain open leading to failure in nervous function and ultimately paralysis.[25]



Batrachotoxin A

Fig. 1.9 Batrachotoxin A and phyllobates aurotaenia frog (http://www.ryanphotographic.com).

1.5 The nicotinic pharmacophore concept

A pharmacophore is a collection of electrostatic, steric (distance) and hydrophobic properties responsible for the pharmacological interaction of a certain part of a molecule with its receptor. Much of the research conducted in this area has concentrated on the high affinity α4β2 type neuronal nAChRs, due to the fact that they are the most abundant nACh receptors in the mammalian brain. Consequently, pharmacophores of this receptor type have been previously formulated and analysed.[26, 27, 28] Beer and Reich [26] proposed the first nicotinic pharmacophore model and it stated that the nicotinic agonist requires two important structural elements: a hydrogen bond accepter site (*e.g.* carbonyl O atom or pyridine N atom) and a positive charge centre (*e.g.* protonated nitrogen). The hydrogen bond formation with the receptor was found to be 5.9 Å from the cationic core, a distance known as the inter-nitrogen distance, where the epibatidine analogues contain a pyridine nitrogen.[26]

The Sheridan *et al.* model uses a three-dimensional molecular arrangement with respect to the key structural features (**Fig. 1.10**), containing the centre of a hydrophobic atom (dummy atom) which is the point used to form the hydrogen bond. Also, in this model, an aromatic ring with a nitrogen lone pair of electron represents the hydrogen bond acceptor and the basic aliphatic nitrogen (onium group) represents the cationic centre. Moreover, for nicotine, the dummy atom can be considered the centre of the pyridine ring.[29] In 1986, Sheridan first designed this model on four ligands when a knowledge of

functional nAChR receptor was poor and only a few nicotinic ligands were known.[26, 27, 30]

Glennon and Dukat proposed a parabolic relationship between the affinity and inter-nitrogen distance as shown in (**Fig.1.10**). They did this by examining the receptor affinity and inter-nitrogen distance of ten nicotinic ligands. Epibatidine was one of the ten ligands they employed and was found to possess an optimal distance of 5.5 Å with a low energy conformation. Nevertheless, the argument over which active conformation of epibatidine is responsible for binding to the receptor still remains.[27] The model optimized by Oleson *et al.* dismissed the inter-nitrogen distance and proposed that the pharmacophore model should measure the distance between *site point a* and *site point b* on the receptor (**Fig. 1.10**), with a proposed optimum distance of 7.3 to 8.0 Å on the receptor between site points.[26]

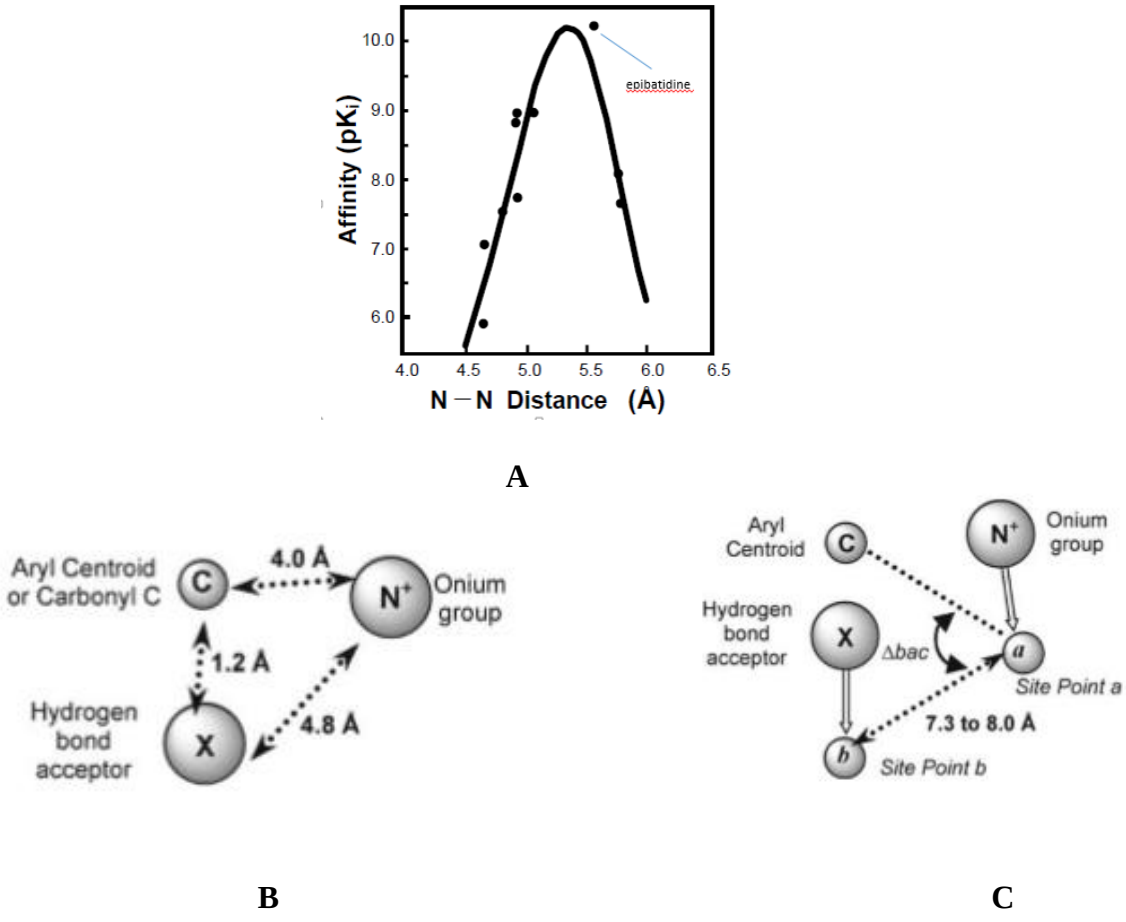


Fig. 1.10 Nicotinic pharmacophore models. A: The relation between the affinity and N-N distance, B: Suggested Sheridan *et al.* model and C: The improved Olesene *et al.* model.[26]

The elucidation of the receptor structure, in particular the agonist binding sites and the extra-cellular domain is the key to understanding the nicotinic pharmacophore. Brejc *et al.*, obtained the crystal structure of acetylcholine-binding protein (AChBP), a soluble protein found in the snail, *Lymnaea stagnalis*, using atomic resolution technique, thus revealing the features of an ACh binding site at the subunit interface for the first time.[31] More recently, in 2005 another crystal structure of an epibatidine-bound AChBP isolated from the snail *Aplysia californica* has been characterized. The mode of binding of the first ligand epibatidine-A-AChBP was found to be somewhat similar to nicotine-L-AChBP, having similar N-N distances of 4.5 Å and 4.4 Å, respectively. Due to this similarity, the hydrogen bonds present in both ligand complexes are also analogues, also the pyridyl N-atom forms hydrogen bonds with two amino acids (Ile118 and Trp147) *via* a solvent molecule and the bridge ring amine binds to the carbonyl oxygen of Trp147 and Tyr93. However, the large bridge ring of epibatidine and its aromatic chloride contributes to the compound having a higher affinity to A-AChBP than nicotine (**Fig. 1.11**).[32]

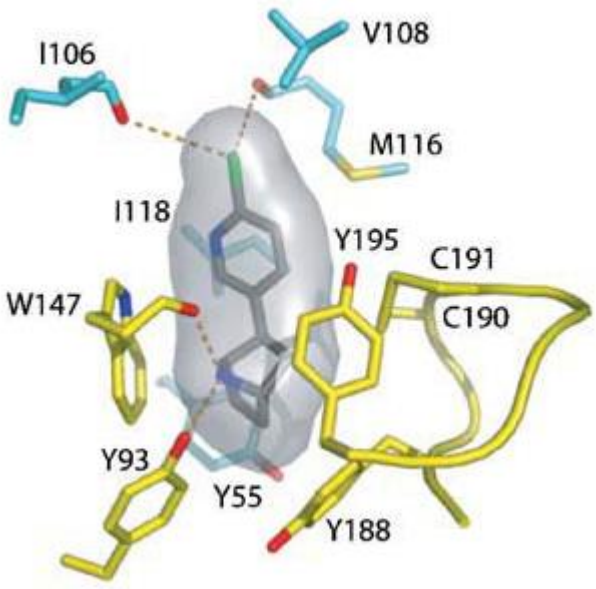


Fig. 1.11 An expanded view of the crystal structure of epibatidine bound to A-AChBP subunit with hydrogen bounding; the grey shape belong to the molecular surface of epbatidine; amino acids, W: tryptophan; C: cysteine; I: isoleucine; M: methionine; Y: tyrosine; V; valine.[32]

Various nicotinic ligands have been investigated for improved pharmacophore modelling architecture. Recently, research showed that utilizing scanning electron microscopy helps to examine the muscle nAChR at resolution 4.6 Å.[33, 34] The agonist binding sites of nAChRs have high amino acids sequence homology (40% - 60%),[35] and this together with

the data interpretation obtained with electron microscopy help to confirm that AChBPs and AChRs are similar in structure.[36] With the help of computational research, superpositionings of novel nicotinic ligands and calculation of the N-N distance can be determined.[36, 37, 38] These pharmacophore approaches give a better clue for synthesizing novel nAChR binding ligands which enabled accurate prediction of nicotinic receptor interactions. Due to the challenges associated with the pharmacophore methods, this limits its capability to reach full potential in drug discovery.

1.6 The total synthesis of epibatidine

The novel analgesic alkaloid epibatidine has grabbed the attention of chemists in the field of organic chemistry since its structure elucidation and the discovery of its high binding affinity as an agonist at nicotinic acetylcholine receptors (nAChRs) in the central nervous system. This activity is attributed to the unique ring nature of the 7-azabicyclo [2.2.1] heptane structure.

Several synthetic routes to epibatidine have been reported especially based on three strategies of constructing the significant azabicyclo[2.2.1]heptane ring system.[39, 40, 41, 42, 43, 44, 45]

1- The tropane route: using aldol chemistry

It has been found that a simple and versatile method for the construction of the basic skeleton of epibatidine is *via* the tropane retrosynthetic route shown in (**Fig. 1.12**). In this route the [2.2.1]azabicyclo skeleton is produced in the form of (**5**) from an adol reaction of ketoester (**7**) which in turn can be accessed from the oxidative cleavage of the enol silane (**8**) itself produced from the readily available tropane derivative (**9**). Subsequently the 2-substituted pyridine could be introduced by addition of an organometallic reagent (**6**) to the α, β unsaturated ester (**5**) giving (**4**). This approach allows enantioselective access to epibatidine, as shown below (**Fig. 1.12**).[40]

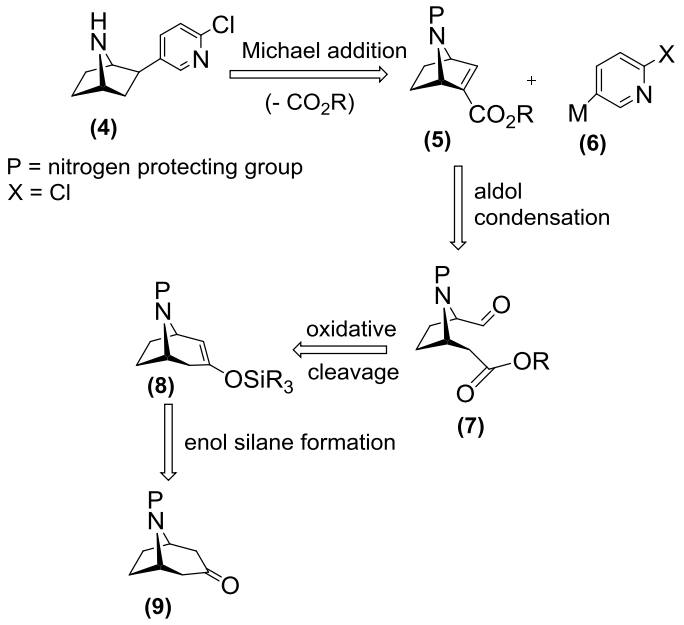


Fig. 1.12 The tropane retrosynthetic route.

2 - The cycloaddition reaction of *N*-protected pyrroles with activated dienophiles.

The Diels-Alder cycloaddition reaction has been reported to be a successful approach to the synthesis of epibatidine and has the benefit of being the shortest synthetic approach to produce the 7-azabicyclo[2.2.1] heptane framework. The Diels-Alder approach employs an ethynyl sulfone as the dienophile (**10**) and *N*-protected pyrrole as the diene (**11**). The cycloaddition is followed by the chemospecific hydrogenation to give (**12**) and subsequent addition of the organolithium reagent (**13**) produced from 5-bromo-2-methoxypyridine. The desulfonylation step to give (**14**) proved problematic, because the target compound (**14**) was produced together with by-product (**15**) (**Fig. 1.13**).[40] The next step of this reaction involved conversion the methoxypyridine (**14**) to the desired chloropyridine under Vilsmeier conditions which was accompanied by exchange of nitrogen protecting groups due to Boc removal, followed by *N*-formylation. Finally, compound (**4**) was produced by heating with dilute hydrochloric acid to give the pure alkaloid (**Fig. 1.13**).

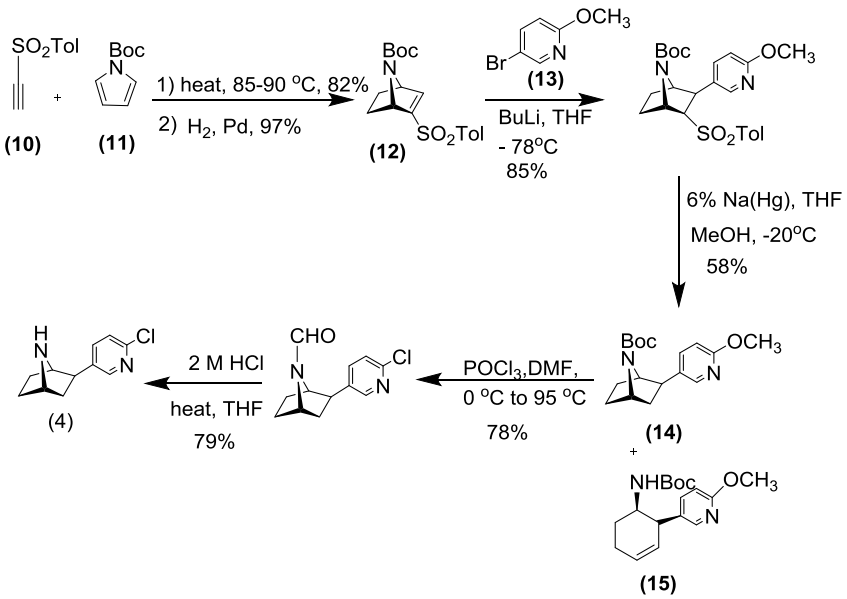


Fig. 1.13 The cycloaddition route.

3 – The ring contraction of the tropinone structure *via* a Favorskii rearrangement.[39]

An alternative method widely used to construct the 7-azabicyclol2.2.1]heptane ring is a Favorskii rearrangement (**Fig. 1.14**). Here a *N*-protected tropinone (**16**) was reacted with cupric bromide to produce the monobromide intermediate (**17**), which was subjected to the Favorskii rearrangement using sodium methoxide to yield the anticipated ester (**18**) stereoselectively in 56% overall yield. This was then followed by a reductive Heck reaction to introduce the chloropyridyl ring (**19**) in 56% yield. Conversion of (**19**) to epibatidine (**4**) was straightforward by radical decarboxylation in 83% yield.[45]

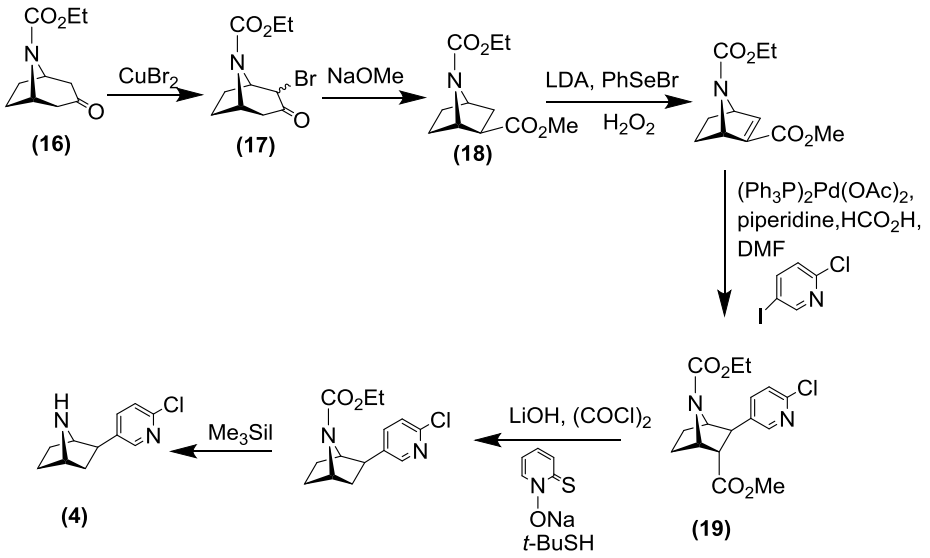


Fig. 1.14 Synthesis of Epibatidine *via* Favorskii reaction.

In summary, many approaches to the total synthesis of the alkaloid epibatidine have been reported. Nevertheless, these remarkable and novel methods established for the construction of the 7-azabicyclo[2.2.1]heptane core have the potential for synthesis of epibatidine analogues which can be further evaluated for analgesic activity.

1.7 Selected Epibatidine analogues

After the discovery of epibatidine, different ligands for nAChRs have been synthesised with the aim to decrease the toxicity of the ligand and at the same time maintaining the potency to receptor subtype. The main drawbacks of using epibatidine as a potential analgesic drug is the lack of marked selectivity for neuronal nAChR subtypes. Nevertheless, epibatidine is used as a model structure for the design and development of compounds which have tight binding affinity and lower toxicity as subtype-specific nAChR ligands. Potential compounds then can be used for treating a plethora of diseases that mediate neurotransmitter activity such as Parkinson's disease, Alzheimer's disease and schizophrenia which are associated with a reduction in neuronal nAChR density. As a result, interest in the 7-azabicyclo [2.2.1] heptane (7-azanorbornane) ring structure has increased dramatically. Likewise, epibatidine behaves as a powerful antinociceptive agent with non-opioid analgesics, due to the different components of its molecular skeleton, the 7-azabicyclo[2.2.1] heptane system and the pyridine ring.[7]

There are several structural aspects that can be altered in the construction of epibatidine analogues, and this usually involves manipulation of the stereochemistry of epibatidine, the azanorbornane ring and using bioisosteric rings (rings that produce similar biological properties without causing significant changes in the chemical structure) instead of the chloropyridine ring. Particular modifications should improve selectivity towards receptor sub-type whilst maintaining potency, in other words undertake a structure activity relationship (SAR) study.

Analogues with ether linkage are described in more detail in chapter 2.

1.7.1 7-Azabicyclo[2.2.1]heptane analogues

The first and the easiest modification that can be done to the epibatidine structure (**4**) is to change the substituent on the 2′-chloropyridine ring to produce different analogues whilst maintaining the 7-azabicyclo[2.2.1]heptane skeleton. Herein, replacing the 2`-chlorine (K_i = 30 pM for α4β2 subtype) with the smaller atoms such as hydrogen (K_i =

8.5 pM for α4β2 subtype) and fluorine (K_i = 9.2 pM for the same subtype) or with larger atoms such as iodine (**4d**) or bromine (**4c**) atoms (K_i = 10 pM) had similar effect on binding affinity (**Fig. 15**).[46]

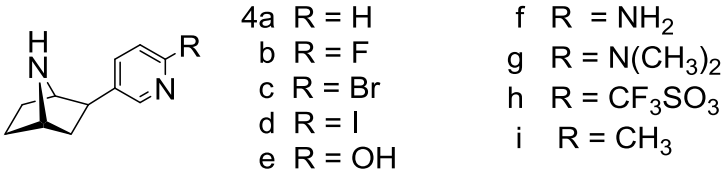


Fig. 1.15 Structure of epibatidine and analogues.

Carroll (2004) has synthesized many derivatives of epibatidine with different groups at the 2-position of the pyridine ring and measured the binding affinities for different neuronal nAChR subtypes combinations (α2β2, α3β2, α4β2, α2β4, α3β4 and α4β4). All these derivatives showed different binding affinity values (K_i) with the exception of **4f** and **4g (Fig. 1.15)**. For example, the range of binding affinities of **4a-d** is between K_i values of 0.026 nM to 0.070 nM. In contrast, ligands **4e-g** showed weak binding affinity when compared to epibatidine; **4f** (2′- amino group) with a K_i value of 1.3nM, **4g** has a greater binding affinity value than **4e** (2′- hydroxyl group), which has K_i value of 107 nM. Finally, the 2′-*N*,*N*-dimethylamino analogue **4g** was reported to have much weaker affinity, K_i value of 26.4 nM when compared to (-)-epibatidine K_i value of 0.026nM.[47]

Spang *et al.* have studied the structure-activity relationship (SAR) of the alkaloid epibatidine and analogues toward nAChRs receptors (**Fig. 1.16**), they examined the role of the chlorine atom in the pyridyl part through the preparation of dechloroepibatidine (DCIEPB). The study demonstrated that both enantiomers (+) - and (-) - DCIEPB have a weaker efficacy for α3β4 and α4β2 sub-types. While, the homomeric nAChR α7 showed variable efficacy for both enantiomers (**Table 1.2**).[48]

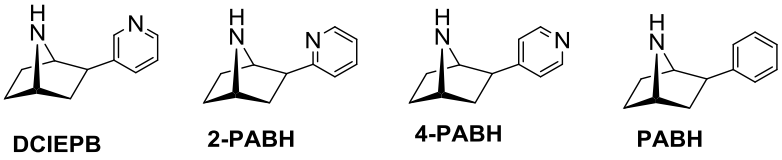


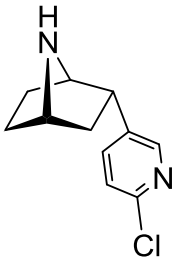
Fig. 1.16 The epibatidine analogues.

Table 1.2 Comparative efficiency data

	EC_{50} (μM). Assay used rat cDNA injected into *Xenopus oocytes*		
Ligands	**α4β2**	**α3β4**	**α7**
(+)-epibatidine	0.021 (100)	0.036 (100)	2.5 (60)
(-)-epibatidine	0.023 (100)	0.019 (100)	2.03 (90)
(+)-DCIEPB	0.93 (120)	0.51 (100)	2.25 (110)
(-)-DCIEPB	2.8 (80)	0.25 (100)	4.6 (110)
(+)-2PABH	32	207	48
(-)-2PABH	67.5	738	32.5
4PABH	21	100	0.5

The synthesis of 2-PABH involved changing the position of the pyridine nitrogen from the *meta* to the *ortho* position with respect to the bicycle attachment, which led to a decreased inter-nitrogen distance and a changed spatial orientation of the pyridine nitrogen. This led to a decreased affinity and efficacy (how the analogue activates a particular subtype) of the receptor sub-types, while (-)-2-PABH only was a full agonist at α7. 4-PABH was synthesised to have the pyridine nitrogen located in the *para* position, and PABH was obtained when the nitrogen is removed. Both compounds have decrease activity on α4β2 and α7sub-types, however, these molecules acts as agonists at the α3β4 sub-types. These findings suggest that the aromatic nitrogen in the *meta* position is necessary for activating the α4β2 sub-types but not necessary for activation of the α3β4 sub-types.[47]

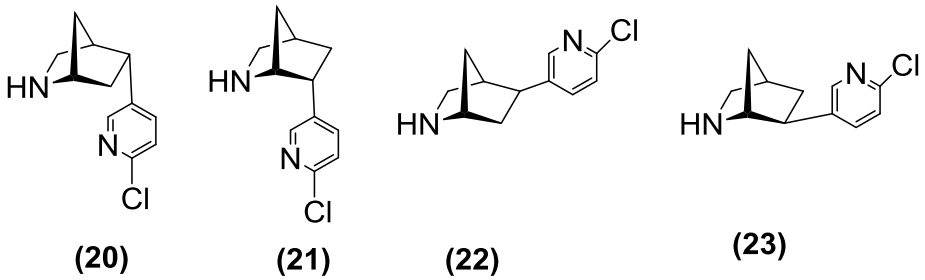
The (±) *endo*-isomer of epibatidine where the orientation of the chloropridyl ring has been changed from *exo* to *endo* was also investigated. The biological assays revealed that there was a decrease in the binding affinity receptor sub-types (K_i = 7.6 nM). This was attributed to the large inter-nitrogen distance (5.93 Å) between the nitrogen chloropridyl ring and that of azabicyclic ring (optimal inter-nitrogen distance (5.5 Å).[49]



(±)-*endo*-epibatidine

1.7.2 2-Azabicyclo[2.2.1]heptane analogues

Many ligands have been synthesised where the orientation of the nitrogen in the bicyclo[2.2.1]heptane has been altered to the 2-position. Work done at the University of Leicester on the 2-zabicyclo[2.2.1]heptane framework led to the synthesis of *endo*-5- (**20**) and *endo*-6-(6-chloro-3′-pyridyl) (**21**) analogues. Both ligands were constructed using an effective Heck coupling reaction and showed high binding affinity for α4β2 with a K_i value of 0.056 nM for (**20)** and 0.045 nM for (**21**). Furthermore, the compounds showed high selectivity toward α4β2 sub-types compared to α7. In comparison, the corresponding stereoisomers *exo*-5 (**22**) and *exo*-6-(6- chloro-3′-pyridyl) (**23**) analogues were shown to possess low binding affinities for both α4β2 and α7 sub-types (K_i > 38 nM). This outcome was expected due to the increased inter-nitrogen distance between the nitrogen of the chloropyridyl ring and that of the azabicyclic ring.[50]



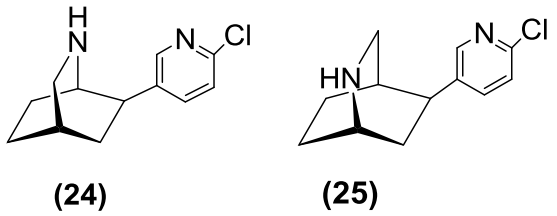
(20) **(21)** **(22)** **(23)**

Fig. 1.17 Analogues based on 2-azabicyclo[2.2.1]heptane.

As the nitrogen atom in the bicyclic system has been changed from 2- to the 7- position, it is suggested to be asymmetric leading to potential enantioselectivity at the receptor site, and this increases the possibility of the synthesis of epibatidine analogues with high selectivity while maintaining the potency. Further research conducted showed the synthesis of *endo*-6-(6-chloro-3′-pyridyl) analogue (**21**) using a radical method (see section 1.8)[51, 52]

1.7.3 2-Azabicylo[2.2.2]octane analogues

Another modification of epibatidine is the synthesis of analogues containing a larger azabicyclic skeleton and examples include homoepibatidine 2′-(chloro-5′-pyridyl)-2-azabicyclo[2.2.2]octanes (**24**) and (**25**), both of which have a methylene group added between the 7-aza group and the bridgehead. Generally, the vicinal analogue (**24**) has low affinity (K_i = 0.47 nM) compared to epibatidine and the distal analogue (**25**) possess very low antinociceptive activity (K_i = 0.34 nM).[47, 53]

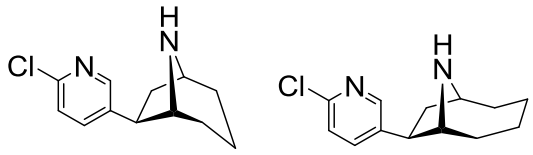


(24) **(25)**

Fig. 1.18 Analogues based on 2-azabicyclo[2.2.2]octane.

1.7.4 8-Azabicyclo[3.2.1]octane and 9-azabicyclo[4.2.1]nonane analogues

Two epibatidine analogues based on a higher azabicyclic ring framework were synthesised at the University of Leicester[54] including homoepibatidine (**26**) which was based on the tropane 8-azabicyclo[3.2.1]octane and *bis*-homoepibatidine (**27**) based on the homotropane 9-azabicyclo[4.2.1]nonane (**Fig. 1.19**).[55] The binding affinity data reported for the enantiomer (-)-homoepibatidine and (+)-homoepibatidine were K_i values of 0.13 nM and 0.35 nM for nicotinic receptors, respectively. This affinity was reported to be about 10-fold higher than that of nicotine. In contrast, (±)-*bis*-homoepibatidine (**27**) was reported to have a low affinity to nAChRs (K_i = 1.25 nM) due to an increased flexibility in the bicyclic ring to four-carbon atoms.[55]



(26) **(27)**

Fig. 1.19 The structures of (±)-homoepibatidine and (±)-*bis*-homoepibatidine.

Research carried out by Trudell *et al.* has produced new homologues (**28**) and (**29**) which were synthesised based on the 8-azabicyclo[3.2.1]octane skeleton. However, due to the heterocycle orientation to the 3-carbon bridge of the azabicycle system, very weak

affinity (for compound **28** K_i = 4800 nM) and (for compound **29** K_i = 1.04 nM) was observed in comparison to epibatidine (K_i = 0.79 nM).[56, 57, 58]

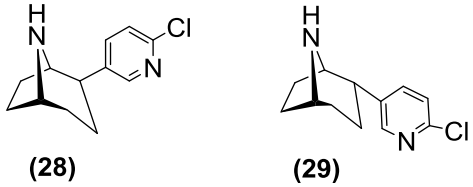


Fig. 1.20 The structures of higher homologues.

The work of Gallagher *et al.* included a natural product (+)-anatoxine-a (**30**) and hybrid molecule of epibatidine UB-165 (**31**) based on the 9-azabicyclo[4.2.1]nonane skeleton. The binding affinity of UB-165 (**31**) at both sub-types α4β2 (K_i = 0.27 nM) and α3β4 (K_i = 6.5 nM) were found to be in-between those of epibatidine (**4**) and antitoxin-a (**30**), however, UB-165 (**31**) lacked selectivity between the two receptors. A wide range of UB-165 (**31**) analogues have been synthesised, these compounds have been replaced by other aromatic ring and tested against α4β2, α3β4 and α7 receptors. The result obtained showed that 3′-phenyl analogue has no activity against any of the tested receptors while the 4′-phenyl analogue showed selectivity against the α7 receptor.[59, 60]

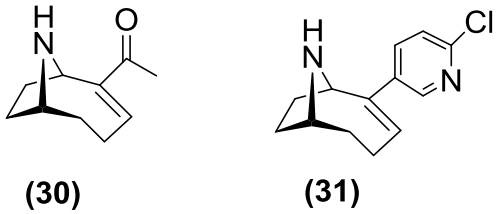
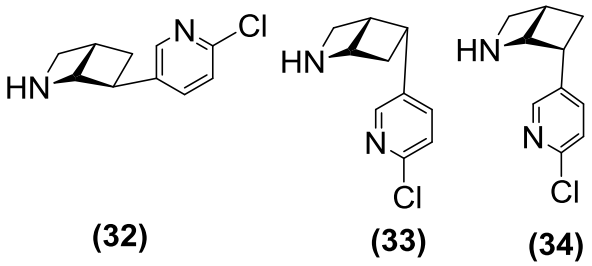


Fig. 1.21 The structures of anatoxin-a and UB-165.

1.7.5 2-Azabicyclo[2.2.0]hexane analogues and 2-azabicyclo[2.1.1]hexane analogues

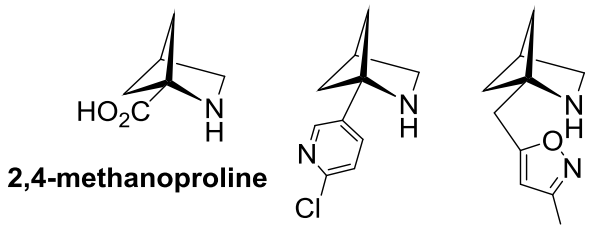
Additional work by the Krow group led to the synthesis of epibatidine analogues which have a more strained rigid skeleton such as the *exo*-6- (**32**), *endo*-5 (**33)** and *endo*-6-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.0]hexane (**34**). These compounds were produced *via* reductive Heck coupling reactions of 2-azabicyclo[2.2.0]hex-5-ene compounds. Weak binding affinity for *exo*-6 (**32**), *endo*- 5 (**33**) and *endo*- 6 (**34**) isomers for nAChRs was reported, with K_i values of 3.9, 5.0 and 39.0 nM, respectively.[61]



(32) **(33)** **(34)**

Fig. 1.22 The structures of smaller epibatidine analogues (2-azabicyclo[2.2.0]hexane).

Patel at the University of Leicester succeeded in attaching heterocycles to the 1-position of the 2-azabicyclo[2.1.1]hexane skeleton starting with the nonproteinogenic amino acid 2,4-methanoproline which was isolated and identified from the seeds of *Ateleia Herbert smithii* in 1880.[62, 63, 64] The compounds (**35**) and (**36**) are examples of the system synthesised by Patel in which the heteroaromatic rings are indirectly or directly incorporated at the C-1-position. However, for compound (**36**) and other carbon chain variants, no significant binding affinity was recorded in human brain for α4β2 and α3β4 nAChR sub-types.



2,4-methanoproline **(35)** **(36)**

Fig. 1.23 The structures of smaller epibatidine analogues (2-azabicyclo[2.1.1]hexane).

1.7.6 Bioisoteric ring incorporation

Another change to the epibatidine structure involves the replacement of the chloro-pyridine ring of epibatidine (**4**) with a bioisoteric system to improve the pharmacological properties and receptor subtype selectivity. Epiboxidine (**37**) has emerged, in which the 2-chloro-pyridine moiety of the epibatidine (**4**) has been exchanged for a 3-methylisoxazole ring. Compound (**37**) turned out to have 10-fold weaker binding affinity than (**4**) at nAChRs subtypes, in particular α4β2 and α7 with K_i values of 0.24 nM and 7.30 nM, respectively. The compound (**37**) was confirmed to have tighter affinity for α4β2 nAChRs, however, compound (**38**) were shown to have weaker affinity for both α4β2 and α7 subtypes but showed a degree of selectivity between both receptors (as discussed previously in section 1.3.1) . It was also observed that (**38)** exhibits weaker

binding affinity for α4β2 with a K_i value of 50 nM, when compared to (**4**) (K_i = 0.050 nM). In addition, the quaternary salt (**39**) was prepared and tested to investigate the function of the dimethylammomium group on binding affinity to α4β2 and α7 subtypes and the corresponding selectivity. Compound (**39**) was designed to have a charged nitrogen on its skeleton, thus enhancing its interaction with both receptor subtypes (K_i = 13.30 nM (α4β2) and 1.6 nM (α7)) and it also showed a better α4β2/ α7 selectivity ratio of 0.12 when compared to (**37**) where the corresponding ratio is 30. More so, compound (**39**) has tight binding affinity of 1.60 nM for α7 receptor compared to 7.30 nM for compound (**37**) (**Fig. 1.24**).[65]

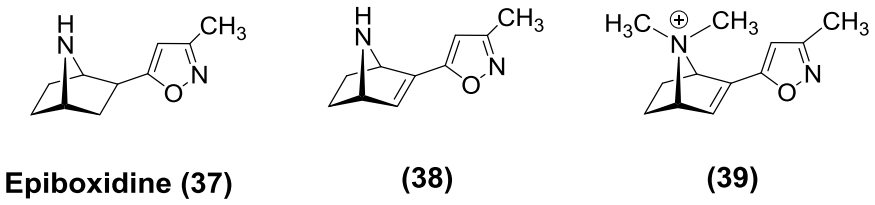


Fig. 1.24 The structure of epiboxidine derivatives.

As a part of ongoing interest in nicotinic ligands with enhanced subtype selectivity, *syn*-isoepibatidine (**40**), syn-isoepiboxidine (**41**) (**Fig. 1.25**) and the corresponding *anti*-isomers have been previously synthesized at Leicester.[66]

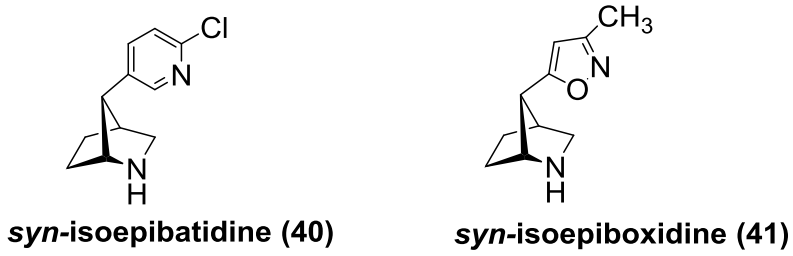


Fig. 1.25: The structure of *syn*-isoepibatidine and *syn*-isoepiboxidine.

In these compounds, the key features of epibatidine (**4**) are retained but the position of the heterocyclic moiety and the azabicyclo[2.2.1] heptane are simply reversed. Interestingly, the *syn* compounds (**40**) and (**41**) show tight binding affinity which was attributed to the inter nitrogen distance 4.5 Å and 4.4 Å, respectively, similar to that of epibatidine at 4.5 Å. Hence, *syn* and *anti*-7 derivatives of 2-azabicyclo [2.2.1] heptane, including (**40)** have been synthesized using a metal-catalysed coupling reaction (**Fig. 1.26**). The *anti*-isomer is formed at C-7 as long as neighbouring group participation by the 2-azabicyclo [2.2.1] heptane nitrogen takes place. Such a structure allows smooth

exchange of the bromine by a different range of other nucleophilic groups and at the same time prevents direct S_N2 substitution with inversion of configuration, thereby obtaining the *syn*-isomer as precursors for metal-catalysed coupling reaction.[66]

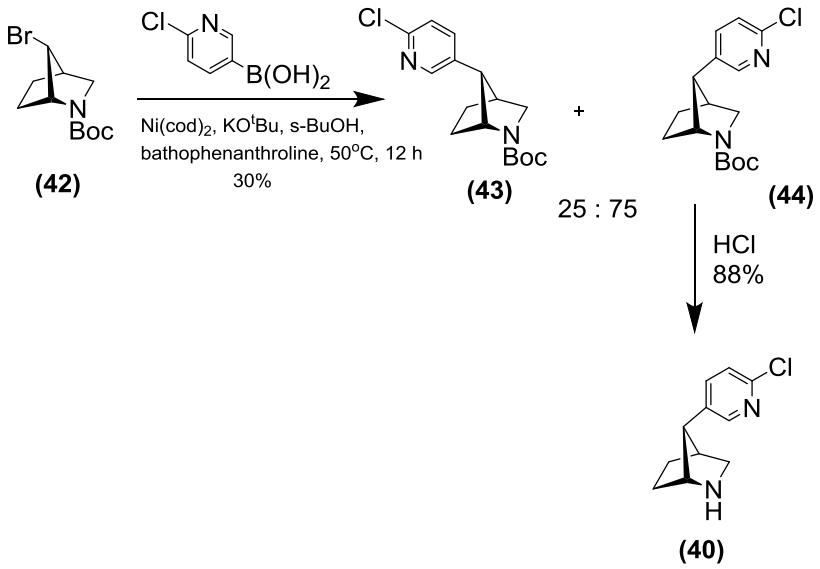


Fig. 1.26 The synthesis route of *syn*-isoepibatidine.

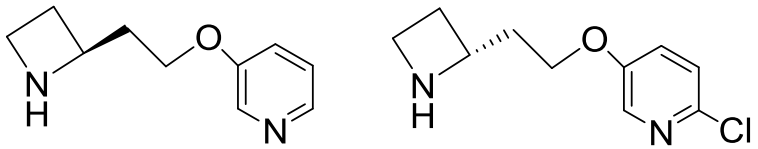
The *syn*-isoepibatidine (**40**) was prepared from the readily available intermediate (**42**) which was coupled with 4-chloro-3-pyridyl boronic acid. The temperature was reduced to 50 ^oC for 12h to avoided loss of the pyridyl chlorine to get the desired product (**40**). Although, the mixture of *N*-protected products (**43**) and **(44)** was not easy to separate, the major *syn*-epimer (**44**) was isolated by chromatography. Removal of the *N*-Boc group was straightforward using acetyl chloride in ethanol/ethyl acetate to give *syn*-isoepibatidine **(40)** as the hydrochloride salt in 88% yield.[66]

The major challenge is to synthesise such compounds that show improved receptor subtype selectivity and lower toxicity. However, many of epibatidine analogues are toxic and have the potential to be misused. Therefore, various structural aspects have been altered to produce more novel epibatidine analogues.

1.7.7 Epibatidine analogues with ether linkages

In 1998, Hollyday *et al.* documented a novel series of 3-pyridyl ether linkaged compounds without a bicycle which possess a high degree of analgesic action in comparison to epibatidine through binding to neuronal nAChRs (particularly at the α4β2 subtype) in rodent brains. Specifically, the compounds A-85380 (**45**) and Tebanicline also called ABT-594 (**46**) are examples of 3-pyridyl ether linkages that have been structurally

characterized to contain an azatidine ring moiety and chloro substituent for the latter compound. The potent analgesic activity of both (**45**) and (**46**) against α4β2 sub-type was measured and the compounds found to have binding affinity of K_i value 0.052 nM and 0.04 nM, respectively, compared to that of (**4**) which has a K_i value of 0.043 nM (**Fig. 1.27**).[67, 68] In addition, (**45**) and (**46**) showed enhanced selectivity for the α4β2 sub-type.[49, 69] Compound (**46**) is the most important analogue among this set of compounds, because it has potent antinociceptive effects and has less peripheral side effects when compared to (**4**) which allowed this compound to enter phase II clinical trials in humans conducted by Abbott (the pharmaceutical company).[70]



A-85380 (45) **ABT-594 (46)**

Fig. 1.27 The structure of ether -linkage of epibatidine analogues.

The design of epibatidine analogues with ether linkages encouraged researchers to move forward to the synthesise of new ether containing molecules with the hope of finding analogues with reduce toxicity and have high nicotinic affinity. Progress in this field will be demonstrated in more detail in chapter 2.

1.8 Background of substitution of 2-azabicyclo[2.2.1]heptane at C7

2-Azanorbornane derivatives have received much interest in the field of medicinal chemistry and many of these compounds have been recorded. This unique structural moiety is considered the foundation of some biologically active molecules, examples of such compounds include conformationally restricted bicyclic proline derivatives and glutamic acid derivatives.[71, 72] It is not straightforward to attach substituents at the 7-position of 2-azabjcyclo[2.2.1]heptane, so the synthesis of such compounds is limited. Hodgson *et al.* have employed efficient methodologies to construct this ring system, including a radical cyclisation and rearrangement processes to convert 7-azanorbornadienes to 2-azanorbornanes.[73, 51, 74, 75, 76] The mechanism involves radical addition of aryl or alkyl thiols to 7-azabicyclo[2.2.1]heptadiene (**47**) resulting in the rearrangement of 7-thio 2-azanorbornene compound (**48**) (**Fig. 1.28**).[74, 76]

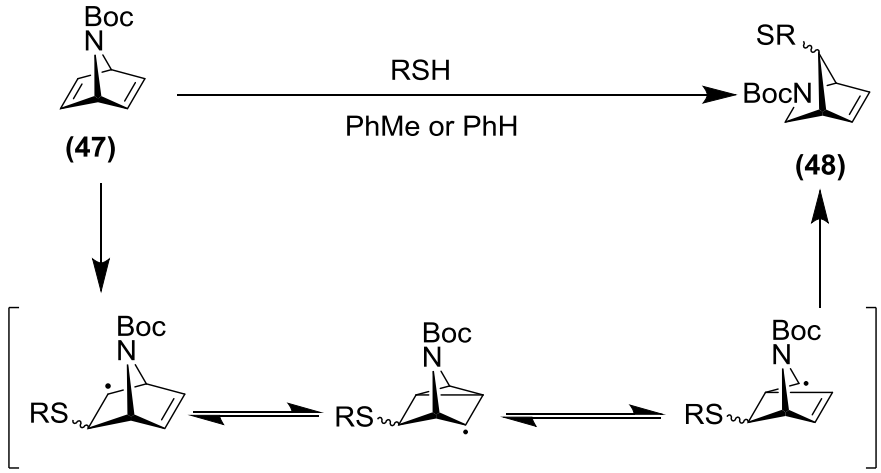


Fig. 1.28 The radical rearrangement of 2-aza-bicyclo[2.2.1]hept-5-enes.

Further work done by Hodgson *et al.* include the synthesis of the analogue *endo*-6-(6-chloropyridin-3-yl)-2-azabicyclo[2.2.1]heptane (**21**) *via* the radical rearrangement and the compound was shown to have high binding affinity for α4β2 sub-type (K_i = 0.032 n M). This makes the analogue (**21**) one of the few compounds possessing high binding affinity similar to epibatidine (**4**) (K_i = 0.04 nM) for the same receptor (**Fig. 1.17**).[51]Another alternative radical reaction applied by Hodgson to give epibatidine analogues was *via* the reaction between the epoxide (**50**) and 4-$MeOC_6H_4MgBr$, followed by desulfonylation to obtain (**51**). Then, compound (**51**) underwent radical-catalysed deoxygenation with a tandem rearrangement, which ultimately led to *syn*-7-substituted 2-azabicyclo[2.2.1]hept-5-ene (**52**) (**Fig. 1.29**).[77]

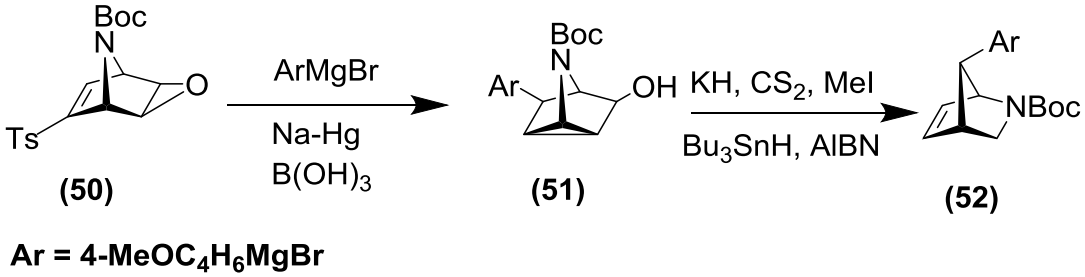


Fig. 1.29 A radical-rearrangement approach to *syn*-7-aryl-2-azanorbornanes.

Furthermore, the incorporation of heterocycles in the construction of nicotinic ligands aims to achieve high activity. Presently, the work described in the second chapter of this thesis describes the manipulation of the C7 stereochemistry to vary the flexibility of the azabicylic template and various approaches will be employed to incorporate functional groups at many positions of the 2-azabicyclo[2.2.1]heptane system with the expectation of different binding properties at the nicotinic receptor.

1.8.1 Our approach of substitution 2-azabicyclo[2.2.1]heptane at C7

Sosonyuk *et al.* reported that electrophilic addition to the double bond in compound (**53**) such as a bromination reaction yields rearranged products if R is an alkyl group.[78] The key feature of the rearrangement is the neighbouring group participation involving the electrons of the bicyclic nitrogen leading to rearrangement of the intermediate (**54**) to give (**55**), followed by addition of the bromide counter-ion to give (**56**) as shown in (**Fig. 1.30**). The equilibrium between (**55**) and (**56**) was shown to be biased toward the tricyclic salts (**55**); these salts were obtained in good quantitative yields and could be isolated with high stability (**Fig. 1.30**).[79, 78]

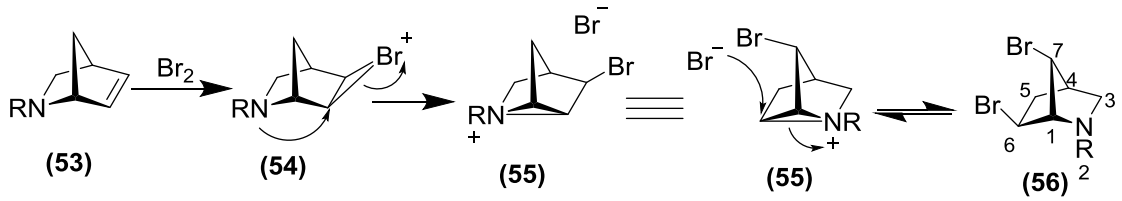


Fig. 1.30 Rearrangement products by bromination of 2-azabicyclo[2.2.1]hept-5-ene compounds.

Furthermore, it has been established that aziridinium salts such as (**55**) are worthy reagents in organic chemistry, because of the possibility of nucleophilic ring opening by amines and alcohols.[77] Hence such rearrangement allows the introduction of a wide range of nucleophilic substituents at the 6-position of 2-azabicyclo[2.2.1]heptane and effective removal of the 7-bromide.[80] The aim of this project is to produce *anti*-7- and *syn*-7-substituted systems and it can be achieved by losing the functionalization of aziridinium salts leaving the 7-bromine in place. From this point, treating (**57**) with hydride was to be carried out with expectation of forming (**58**), which would be needed to reach the target (**Fig. 1.31**) which is an important outcome on the way to the target analogues.

To get access to the next set of products *i.e.* the *anti*-7- derivatives (**59**) and *syn*-7-derivatives (**60**) (**Fig. 1.31**), the bromide group will be substituted resulting in the introduction of the heterocycles at the 7-position.

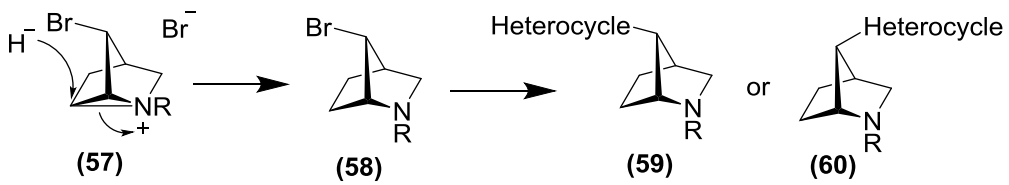
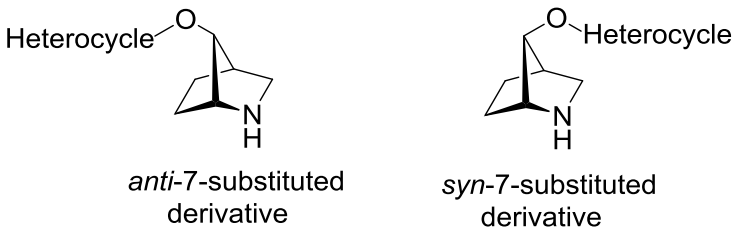


Fig. 1.31 The suggested route to synthesis 7-subsitetuted 2-azanorbornanes.

The big challenge of this approach is that the substitution at C7 of 2-azabicyclo[2.2.1]heptanes is unfavourable and potentially problematic. The outcomes of this approach will be discussed in more detail in chapter 2. The next area that was investigated during the research, reported in chapter 3, is the incorporation of a fluorine substituent into the 2-azabicyclo[2.2.1]heptane system to access fluorinated derivatives of *syn*-epibatidine. Finally, chapter 4 explained this fluorination work to investigate the synthesis of 5-ene and 6-ene (2′-chloro-5′-pyridyl) 2-azanorbornane system.

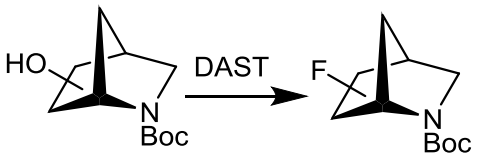
1.9 Aims of the project

The aims of this research project are to initially carry out the synthesis of novel epibatidine analogues which are potentially more specific with respect to binding to nAChRs subtypes and display lower toxicity. In particular, derivatives based on the 2-azabicyclo[2.2.1]heptane molecular framework which has been previously utilised for the *syn*-epibatidine analogue will be targeted. Generally, the synthesis of analogues substituted at the 7-position of 2-azabicyclo[2.2.1]heptane has been devised. Bromination of 2-benzyl-2-azabicyclo[2.2.1]-5-ene and treatment of the resulting tricyclic salt with hydride occurs with skeletal rearrangement to give 2-benzyl-7-bromo-2-azabicyclo[2.2.1]heptane. Nucleophilic substitution reactions of this compound were found to occur with retention of configuration, consistent with neighbouring group participation of the nitrogen lone pair to obtained alcohol compound. Once this has been established, the next stage includes introducing heterocycle moieties at the 7-position of 2-azabicyclo[2.2.1]heptane and manipulation of the stereochemistry at this position to give the novel ether-linked analogues as shown below.

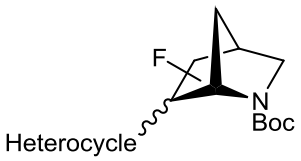


With the heterocycle strategically attached to the C-7 position and linked by O atom, the ideal inter-nitrogen distance could be attained within the nicotinic acetylcholine pharmacophore. It also offers the chance to adjust this inter-nitrogen distance by extension of the chain and by incorporation of other atoms.

The next stage is synthesis the fluorinated 2-azanorbornane which can be accessed using DAST as a fluoride source. This also work will determine that NGP is taking place in these a set of reactions. The mechanistic findings discussed in this chapter warrant further investigation and can potentially be applied to the synthesis of further fluorinated epibatidine analogues.



The final part of this work is the synthesis of *exo*-6- and *exo*-5- chloropyridyl regioisomers *via* adaptions to the DAST reactions described in chapter 3.



Chapter 2

Functionalisation of the 7-position of 2-azabicyclo[2.2.1]heptane and synthesis epibatidine analogues with ether linkages

2.1 Methods of construction of the 2-azabicyclo[2.2.1]heptane framework

A variety of synthetic routes to 2-azabicyclo[2.2.1]heptane compounds have been reported based on different strategies for construction of the bicyclic ring. These strategies fall into three main areas: intramolecular ring closure; rearrangement and Diels-Alder cycloaddition. Each of these strategies is discussed in the following pages.

2.1.1 Intramolecular ring closure

In this strategy the key step of the synthesis of the bicyclic system is the ring-closure reaction, which occurs by a stereospecific intramolecular nucleophilic substitution (which is favoured) of one or two leaving groups on a monocyclic staring material. Newman *et al.* reported the synthesis of a meperidine analogue using the latter approach in their syntheses (**Fig. 2.1**).[81]

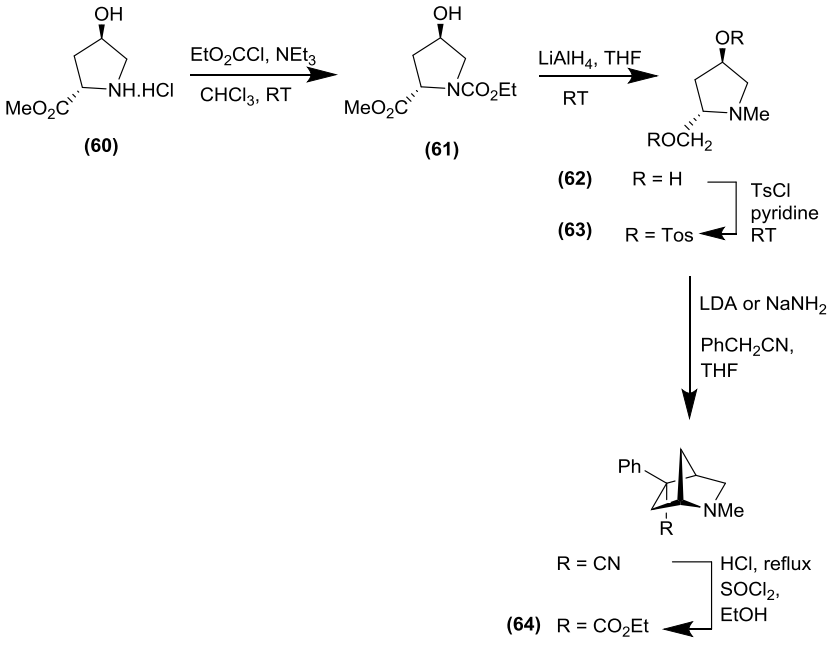


Fig. 2.1 The synthetic route of meperidine analogue.

Meperidine possesses analgesic effects similar to morphine, by acting as an agonist at the μ-opioid nicotinic receptor and shares some structural features with cocaine as a drug discrimination model of drug behavioural effects.[82]

In the reported syntheses *trans*-L-hydroxyproline methyl ester (**60**), which is synthesised from commercially available *trans*-L-hydroxyproline, was first protected as its ethyl carbamate derivative (**61**) using ethyl chloroformate and trimethylamine. The ester and the carbamate groups in (**61**) were then reduced with lithium aluminium hydride to give

the diol product (**62**). Tosylation of the two alcohols group in pyridine gave (**63**) in overall yield 18% (over three steps from **61**). Using this method it was possible to use the carbanion from phenyl acetonitrile (using either LDA or $NaNH_2$) to carry out a double substitution reaction of both tosyl groups to give the bicyclic product in 38% yield. Finally, hydrolysis of the nitrile group in acidic medium followed by esterification formed the meperidine derivative (**64**).

2.1.2 Rearrangement

Malpass *et al.* based their synthesis of the 2-azabicyclo[2.2.1]hept-5-ene framework on a cycloaddition/rearrangement approach (**Fig. 2.2**),[83] which contained four sequential steps. The first step involved the reaction of cyclopentadiene with chlorosulfonyl isocyanate leading to a single N-chloro- derivative (β-lactam) (**65**) *via* cycloaddition. Interestingly, (**65**) after 5 hours at room temperature underwent rearrangement to give (**66**) and this was followed by removal of the N-chlorosulphonyl group using sodium sulphite to give 3-*oxo*-2-azabicyclo[2.2.1]hept-5-ene (**67**). Finally, reduction with lithium aluminium hydride afforded 2-azabicyclo[2.2.1]hept-5-ene (**68**) (overall yield 22%).

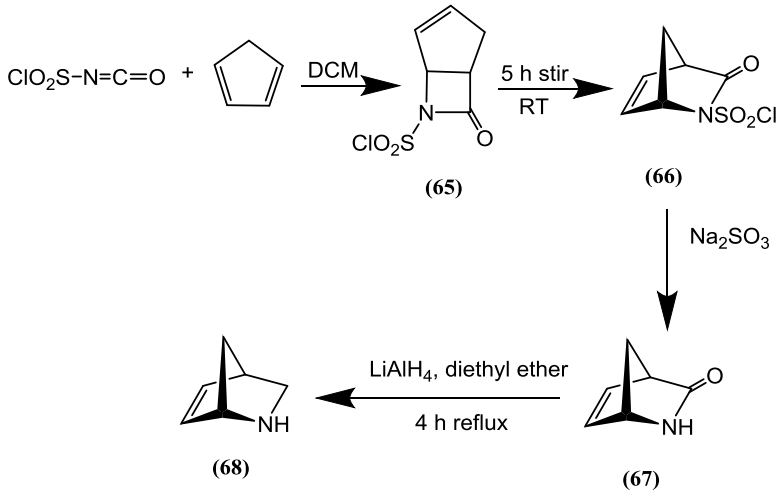


Fig. 2.2 Synthesis 2-azabicyclo[2.2.1]hept-5-ene *via* a cycloaddition/rearrangement approach**.**

2.1.3 Diels-Alder Cycloaddition

Grieco *et al.* adopted an efficient method to construct the 2-azabicyclo[2.2.1]heptane ring based on a cyclocondensation reaction of simple unactivated iminium salts with dienes in water.[84] There are many examples of the [4+2] cyclocondensation of cyclopentadiene with various iminium ions as shown in (**Fig. 2.3**).[85]

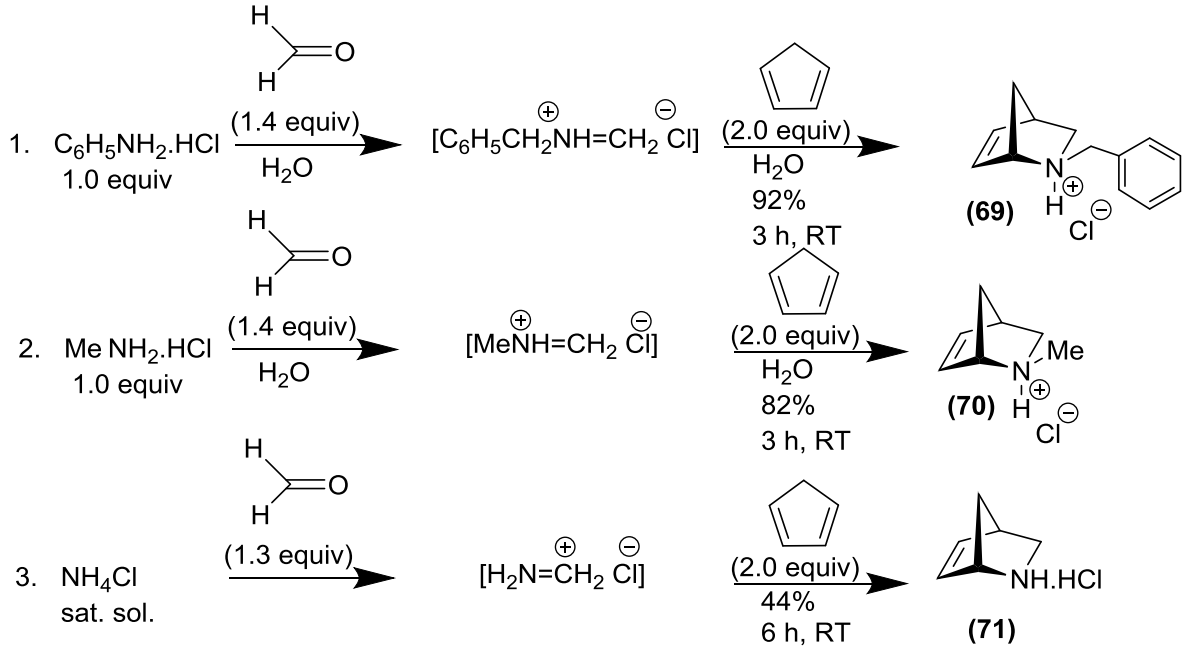


Fig. 2.3 Aza Diels-Alder reaction of various imines with cyclopentadiene.

In the reaction of benzylamine hydrochloride and formaldehyde the reactive intermediate benzyliminium hydrochloride was generated in *situ* (**entry 1**), and this then underwent an aza Diels-Alder cycloaddition reaction with freshly cracked cyclopentadiene. The reaction was carried out at room temperature and stirred vigorously for 3 hours to give (**69**) in excellent yield 92% after neutralization. The second reaction (**entry 2**) shows the formation of the corresponding *N*-methyl bicycle (**70**) which was generated from methylamine hydrochloride, but in slightly lower yield (82%) because of the higher volatility of the product. In similar fashion, the 2-azabicycle (**71**) was generated from ammonium chloride with a significantly lower yield.

The asymmetric version of the aza Diels-Alder reaction involving a nitrogen atom in the dienophile or diene has proved a useful tool for the enantioselective synthesis of a large number of interesting compounds. Grieco created a chiral iminium ion through the reaction of (-)-α-methylbenzylamine hydrochloride with formaldehyde, and this

intermediate reacted with freshly distilled cyclopentadiene over 20 hours at 0 °C. Interestingly, two diastereoisomers (**72**) and (**73**) were formed in 86% yield and a 1: 4 ratio (**Fig. 2.4**).[85]

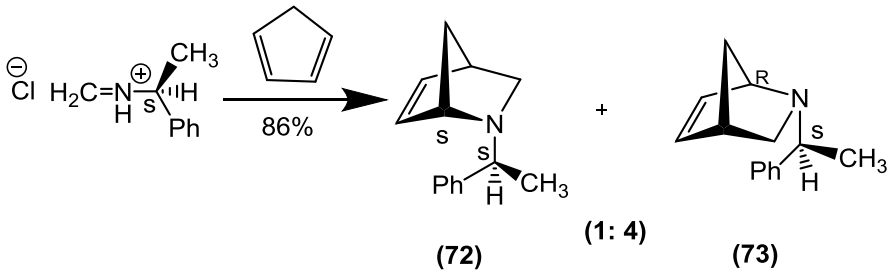


Fig. 2.4 Diels-Alder reaction involving an optically iminium ion.

Further work reported by Loh *et al.* included a Lewis acid-mediated aza Diels-Alder reaction for the synthesis novel epibatidine analogues (**Fig. 2.5**).[86] The reaction of (-)-α-methylbenzylamine with 6-chloro-3-pyridinecarboxyaldehyde generated an iminium ion, which was subsequently activated by the Lewis acid aluminium chloride and trimethylamine complex. Cyclopentadiene was added in dry conditions with shaking and sonication at 0-5 °C for 2-3 days to afford the bicyclic product (**74**) in a poor yield (28%) but with excellent diastereoselectivity. There are many syntheses reported in the literature that have applied an asymmetric aza Diels-Alder approach where carbon 3 has been functionalised to other 2-azabicyclo[2.2.1]heptane molecules, for example, an ester group.[87] The 2-azanorbornane system will be used extensively in this project.

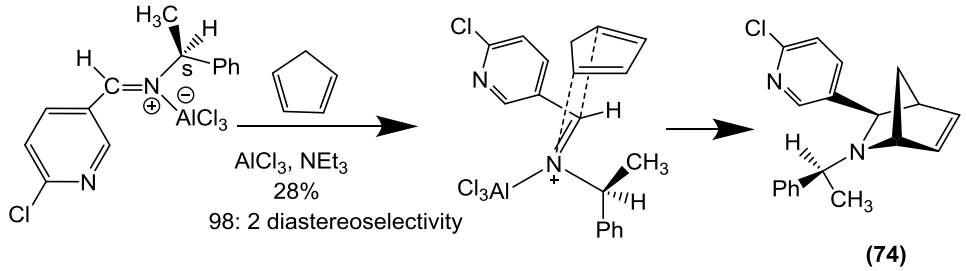


Fig. 2.5 Diels-Alder reaction of 6-chloro-3-pyridinecarboxyaldehyde and imine with cyclopentadiene.[86]

In summary, the aza Diels-Alder reaction has played a powerful role in the synthesis of natural products However, the development of asymmetric, in particular catalytic, enantioselective aza Diels-Alder reactions remains challenging, and will no doubt see enormous advances in the future.[88]

The rest of this Chapter will discuss the work that was carried out as part of this PhD project in regards to the synthesis of novel ether-linked epibatidine analogues. The

approach taken for the synthesis of the 2-azanorbornane system was based on the aza Diels-Alder reactions discussed above.

2.2 Synthesis of 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene

An important aspect of this first step is that cyclopentadiene (**74**) must be freshly cracked before the reaction is conducted. This is because (**74**) undergoes dimerization at 25 ^{o}C to produce dicyclopentadiene (**75**) in a well-known Diels-Alder reaction, where one cyclopentadiene molecule acts as the diene component and the other one acts as the dienophile (**Fig. 2.6**). The distillate cyclopentadiene was collected at 39-40 ^{o}C into a receiver flask cooled to -10 ^{o}C (dry ice/acetone bath) to prevent re-dimerization. The cyclopentadiene is popularly used as a precursor for the synthesis of the azabicyclic template.[89]

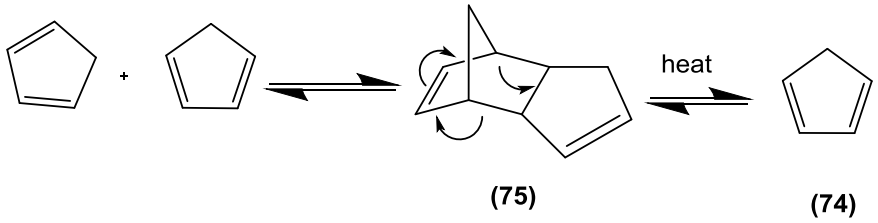


Fig. 2.6 Retro Diels-Alder reaction to produce cyclopentadiene.

The next step was the synthesis of the 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene (**76**) and is illustrated in (**Fig. 2.7**).[89, 90] Generally, an activated imine (electron-poor) is required to react with electron-rich dienes. However, in 1986, Larsen and Grieco[91] first documented that a simple unactivated iminium salt, generated in *situ* from formaldehyde and a primary alkylamine HCl salt under Mannich conditions, underwent a facile aza Diels-Alder ($4\pi + 2\pi$) reaction with a variety of dienes in water at ambient temperature. To exemplify their finding they reported the syntheses of compound (**76**) from benzylamine HCl, formaldehyde and cycloaddition as shown below.

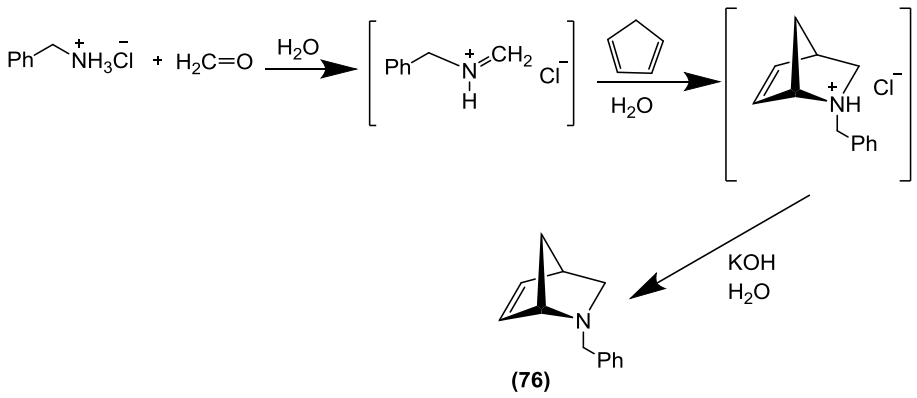


Fig. 2.7 Synthesis of 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene through aqueous hetero Diels-Alder reaction.

It seems that the approach taken by Larsen and Grieco applied features of green chemistry in their synthesis:

1- The reaction is run at atmospheric pressure and ambient temperature in water.
2- The whole synthesis is carried out in one pot without the need for isolating and purifying the intermediate iminium salt.
3- The transformation is quantitative and affords selectivity a single product (although it is a racemic mixture).
4- Less toxic starting material (natural sources), but at present there are supplied from the petrochemical industry.

In the work carried out for this thesis the reaction shown in (**Fig. 2.7**) was repeated and obtained (**76**) in 81% after 9 hours stirring at room temperature. The ^{1}H NMR spectrum of 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene (**76**) (**Fig. 2.8**) showed a doublet of doublets at δ 1.40ppm for H_{7a} (J = 2, 8 Hz), a doublet at δ 1.63ppm for H_{7s} (J = 8 Hz) and a doublet of doublets at 1.50 ppm for H_{3n} (J = 2, 9 Hz). The data indicates that H_{7a} couples with H_{3n} because both have the same small coupling constant due to 'W' coupling. The ^{1}H NMR also showed geminal coupling between protons H_{7a} and H_{7s} (J = 8 Hz), and H_{3x} and H_{3n} (J = 9 Hz). Furthermore, the two protons in the CH_2Ph group were not equivalent because the molecule contains a chiral center that means the two protons are in different magnetic environments (diastereotopic), showing a doublet each at δ 3.32 ppm and δ 3.56 ppm. Finally, H_5 was identified as a doublet of doublets at 6.63 ppm which showed vicinal interaction with H_6 in ^{1}H-^{1}H COSY experiments.

Comparison of the above ^{1}H NMR analysis data with literature data revealed that no further purification was required.[89]

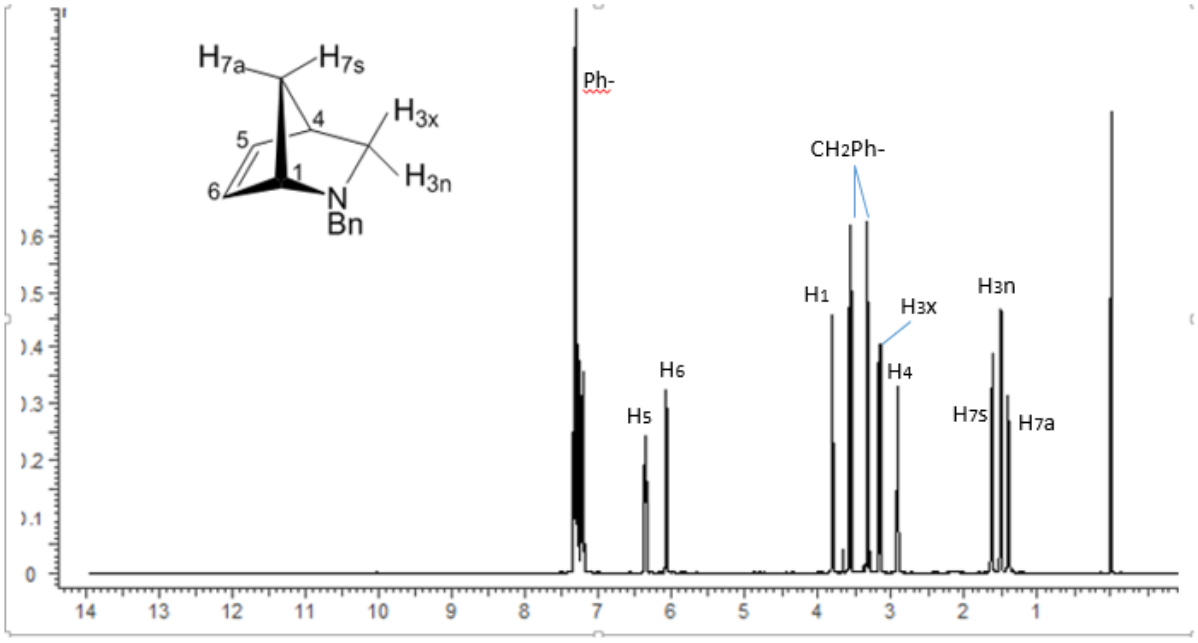


Fig. 8 The ^{1}H NMR spectrum of the 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene (**76).**

The purpose of protecting the secondary amine is to retain functionality which exists in epibatidine (**1**) and its analogues and prevent any unwanted side reactions. The benzyl group ($PhCH_2$-) was chosen as the protecting group because it preserves the basicity and nucleophilicity of the nitrogen atom which will be used in subsequent steps involving neighbouring group participation (NGP). Additionally, de-protection of the benzyl group is relatively straightforward *via* hydrogenation. Interestingly, alkyl protecting group such as benzyl group in rigid systems shows rapid nitrogen inversion in (**76**) but this was not a concern here.[92]

2.3 Electrophilic addition of bromine to the 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene (76)

As previously discussed (see section 1.7.1), the bromination of 2-benzyl-2-azabicyclo [2.2.1]hept-5-ene (**76**) affords rearrangement products. The key feature of the rearrangement is neighbouring group participation by the 2-azanorbornyl nitrogen; σ and π electrons have the ability to promote displacement of the leaving groups from nitrogen and at the 7- or 6-position of the 2-azanorbornane system. Surprisingly, it had been noticed that the nitrogen atom can participate in displacement of a nucleofuge from carbon. In addition, the nitrogen lone pair can also overlap with the core of developing positive charge during electrophilic additions to the double bond leading to another

skeletal rearrangement.[81,93] The bromination of (**76**) was originally developed by Sosonyuk *et al*. and occurs into two steps (**Fig. 2.9**), the first step involving the formation of the tribromide salt (**77**) and the second step involving addition of another equivalent of the alkene (**76**) to give the monobromide (**78**) which is isolated in quantitative yield. It should be noted that (**78**) is in equilibrium with the ring opened form (**79**) formed by nucleophilic attack of the bromide on the aziridine.[79]

In their work Sosonyuk reported that when (**76**) was treated with 2 equivalents of bromine it unexpectedly gave a product containing four bromine atoms; subsequent analysis showed that it was a quaternary ammonium salt containing a tribromide counter-ion and a three-membered aziridine ring (**77**). Sosonyuk demonstrated that addition of a second equivalent of the alkene **(76**) essentially converts (**77**) to the corresponding monobromide salt (**78**) in 100% yield. This product is isolated as pale yellow crystals, stable in storage for one year at ~ 4 ^{o}C.

We repeated the reactions reported by Sosonyuk and were also able to isolate first the tribromide (**77**) and then the bromide (**78**) in quantitative yield. In our hands both compounds proved to be stable on storage which slightly disagrees with the previous report that (**78**) degrades upon storage, presumably *via* the ring opened form (**79**).[79, 80]

It is not clear why this protocol gives improved yields but it is likely to be solvent-related as the first step is carried out in dichloromethane and the second in acetonitrile. Previously published bromination methods gave poor yields, principally due to the formation of side products.[79]

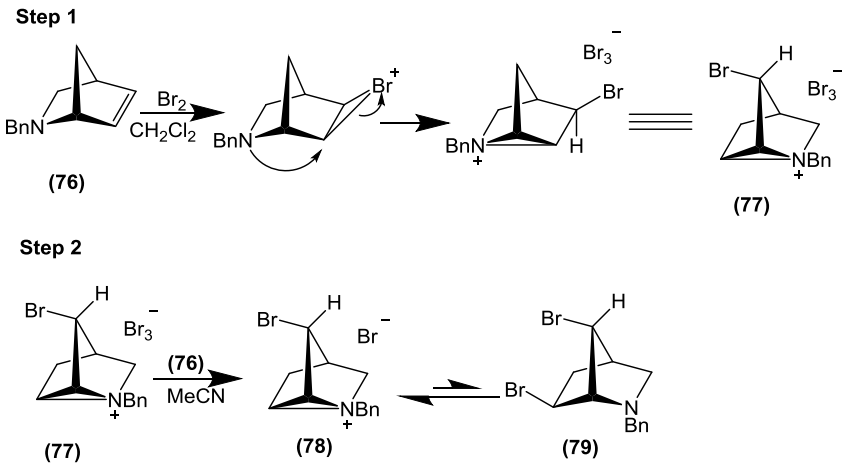


Fig. 2.9 The two-step bromination of 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene.

The ^{1}H NMR spectrum of 3-bromo-1-benzyl-1-azoniatricyclo[2.2.1.$0^{2,6}$]heptane tribromide (**77**) showed the disappearance of the double bond signals present in compound (**76**). Additionally the two new H_5 hydrogens in compound (**77**) were non-equivalent and observed as shifted to δ 2.42 ppm and δ 2.58 ppm. In addition, the ^{1}H NMR spectrum showed a broad singlet at 4.63 ppm for a H_3 that refers to the atom at C_3 (see the numbering of tricyclic compound at the beginning of experimental chapter). Furthermore, the ^{1}H NMR and ^{13}C spectrum of (**78**) shows some of the same set of signals as the ^{1}H NMR spectrum of (**77**), which led us to conclude that any equilibrium between (**78**) and (**79**) is largely biased to favour (**78**).

2.4 Ring opening of aziridinium salts by nucleophilic attack

In recent decades, it has been understood that aziridinium salts are worthy reagents in organic synthesis, because of the possibility of nucleophilic opening of their rings.[78] Bulanov *et al.* as reported that nucleophilic ring opening of the aziridine in compound (**78**) occurs at 6-position rather than the 2-position. The selectivity of this attack can be attributed to the bulky bromine atom hindering reaction at the 2-position.[79,80] Further work done by Bulanov reported that opening in 1-alkyl-3-bromo-1-azoniatricyclo[2.2.1.$0^{2,6}$]heptane (**80**) takes place with a variety of nucleophiles to achieve various 6-substituted 7-bromo-2-azabicyclo[2.2.1]heptanes involving the formation of new C-O, C-N, C-S and C-C bonds (**Fig. 2.10**). It has also been shown that the 7-bromine atom can be reduced *via* radical-mediated reduction with butylstannane.[94]

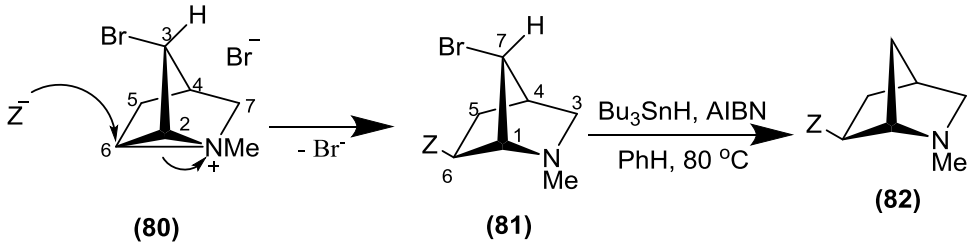


Fig. 2.10 Nucleophilic opening of aziridine ring in 1-alkyl-3-bromo-1-azoniatricyclo[2.2.1.$0^{2,6}$]heptane.[93]

Previous research carried out by White at the University of Leicester[76] investigated the reductive opening of the aziridine ring in (**78**) by different reducing agents as a source of hydride ion. Sodium borohydride in methanol was first investigated but did not give the desired compound, instead solvolysis took place to give a poor yield of (**83**) in which the solvent (methanol) had opened the aziridine directly (**Fig. 2.11**). Attempting the same

reaction but with diethyl ether as the solvent and using a small amount of methanol as a catalyst produced no easily discernible reaction.

White next investigated the use of $LiAlH_4$ as a source of hydride ion at room temperature for 24 hours. However, this resulted in reductive cleavage of the C-Br bond leading to compound (**84**). Lowering the temperature of this reaction (initial addition of reducing agent at -78 ^oC and then allowed to warm to -20 ^oC) did successfully produce the target compound (**85**) in 58% yield. Furthermore, a patent has reported that by applying the same procedure but using Red-Al as a reducing agent also produces (**85**) in improved yield (93%).[95]

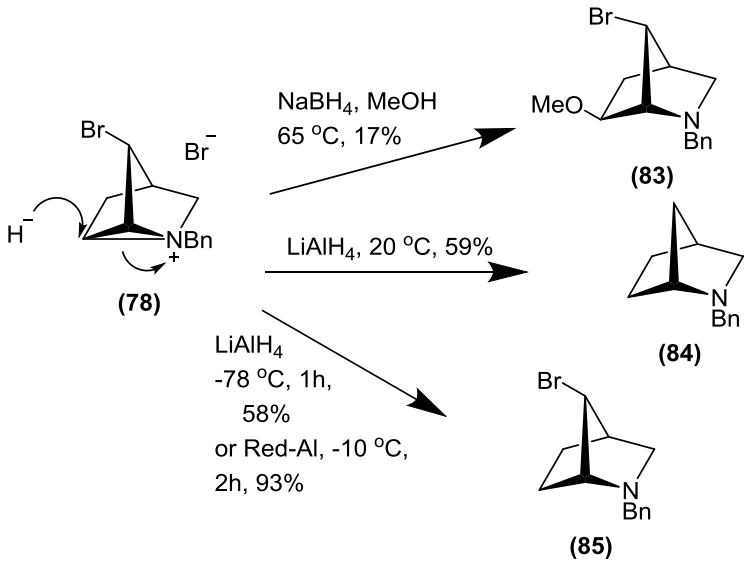


Fig. 2.11 Reduction of 1-alkyl-3-bromo-1-azoniatricyclo[2.2.1.$0^{2,6}$]heptane with hydride.[77]

In order to reach the target, (**78**) was treated with lithium aluminium hydride to generate *anti*-7-bromo compound (**85**). The synthesis of (**85**) was conducted at -78 ^oC (**Fig. 2.11**), then the mixture allowed to warm to -20 ^oC to afford (**85**) as a pale yellow oil in 67% yield after purification using flash chromatography. This yield compares favourably to that reported by White (58%). In contrast when we employed Red-Al for the reduction,[95] we isolated the product in only 58% yield, as compared to the 94% yield reported by White. The ^1H NMR analysis of the crude product showed approximately ~ 10% of 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene (**76**) as a side-product. A suggested explanation of the formation of (**76**) is shown in (**Fig. 2.12)** where the hydride ion attacks the 2-position of the salt (**78**) leading to formation *exo*-5-bromo compound (**86**) followed by elimination of HBr to generate (**76**). It should be noted that this proposal goes against the reports from Bulanov *et al.* who suggested that nucleophilic attack only occurs at 6-position.[94]

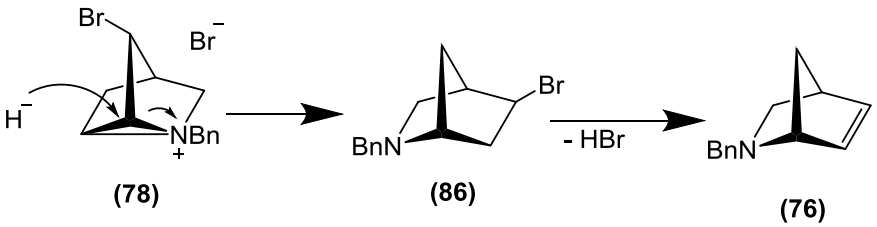


Fig. 2.12 The proposal mechanism of side-product formation (**76**).

The ^{1}H NMR spectrum for *anti*-7-bromo-2-benzyl-2-azabicyclo[2.2.1]heptane (**85**) showed that the sigma bond between C_6 and nitrogen was no longer present. Also, the signal for H_6 is no longer a singlet with an integral of one but a 2H with chemical shift at δ 1.69-1.89 ppm. Verification of the *anti*-configuration was done using ^{1}H-^{1}H COSY and ^{1}H-^{1}H NOESY experiments, the NOESY spectrum of the (**85**) showed cross peaks between H_{7s} with H_{3exo} and H_{7s} with methylene protons of the benzyl group. Similarly, ^{1}H-^{1}H COSY analysis of (**85**) showed 'W' coupling between H_{7s} and H_{5endo}. This spectroscopic information confirmed the bromine atom at 7-position being *anti*- to the bicyclic nitrogen atom.

2.5 Nucleophilic substitution at C-7 of 2-azanorbornane

On completion of the synthesis of (**85**) the next step in the route would involve nucleophilic displacement of the bromide from the 7-position. Direct S_N2 substitution at the 7-position is difficult in simple norbornanes due to angle constraints and steric factors. The sp^2 hybridization at C_7 in the transition state for the both S_N1 and S_N2 mechanisms should ideally have (C_1-C_7-C_4) bond angles of 120^o but the rigid bicyclic system prevents this bond angle being achieved at the 7-position (the bond angle in the bicycle is 93^o). In addition, the nucleophilic substitution is hindered by the *exo*-5-and *exo*-6 substituents. The nucleophilic substitution at C7 can be enhanced by the presence of a carbonyl group at the 2- and/or 3-positions (*e.g.* the corresponding 2,3-diketone) due to the electronic effect that is produced by the carbonyl group.[96]

Despite these potential issues with norbornanes, Malpass *et al.*[80] have reported that the corresponding S_N2 substitution reaction can take place in 2-azanorbornane systems albeit at a relatively slow rate even when elevated temperatures are employed. A variety of nucleophilic reagents have been employed in this reaction to produce compounds (**87**), (**88**), (**89**), and (**90**) as shown in **(Fig. 2.13)**. All of substitution reactions take place with retention of configuration at C7 which has been established by full characterisation

(COSY and NOESY NMR) of the products. It should be noted that the finding that these reactions take place with retention of stereochemistry is at odds with a patent [95] that describes the formation of the *syn*-isomer of (**87**) using the H_2O / NMP protocol. However, no spectroscopic data was presented in this patent casting so doubt on the *syn*-stereochemical assignment of the product.

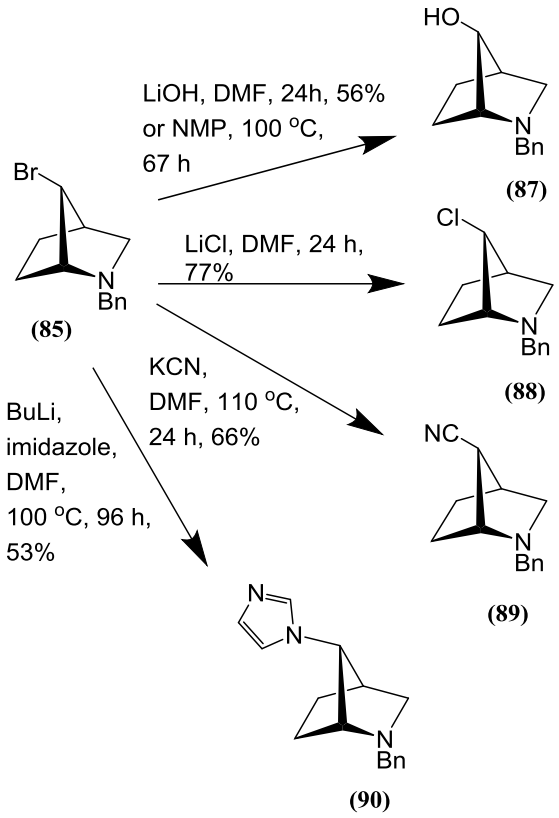


Fig 2.13 Range of nucleophilic substitution reaction of (**85**) at C7 occur with retention of configuration.[79]

In the course of this project a displacement reaction using polar aprotic solvent 1-methyl-2-pyrrolidinone (NMP) (containing 15% v/v of water) [97] was employed to replace the bromide group with a hydroxyl functionality. The conditions were slightly changed; compared to the work of White, the reaction was conducted at 108 °C (as opposed to 100 °C) and stirred for 82 h (rather than 67h) to give optimum conversion (**Fig. 2.14**). The crude product did not contain any unreacted starting material (from the TLC analysis and ^{1}H NMR) and was purified using flash chromatography to give (**87**) as pale yellow oil in excellent yield 80%.

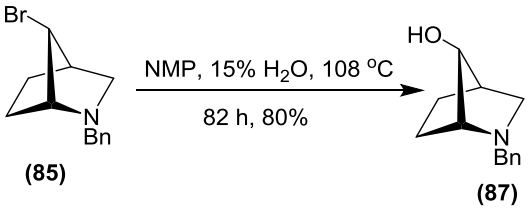
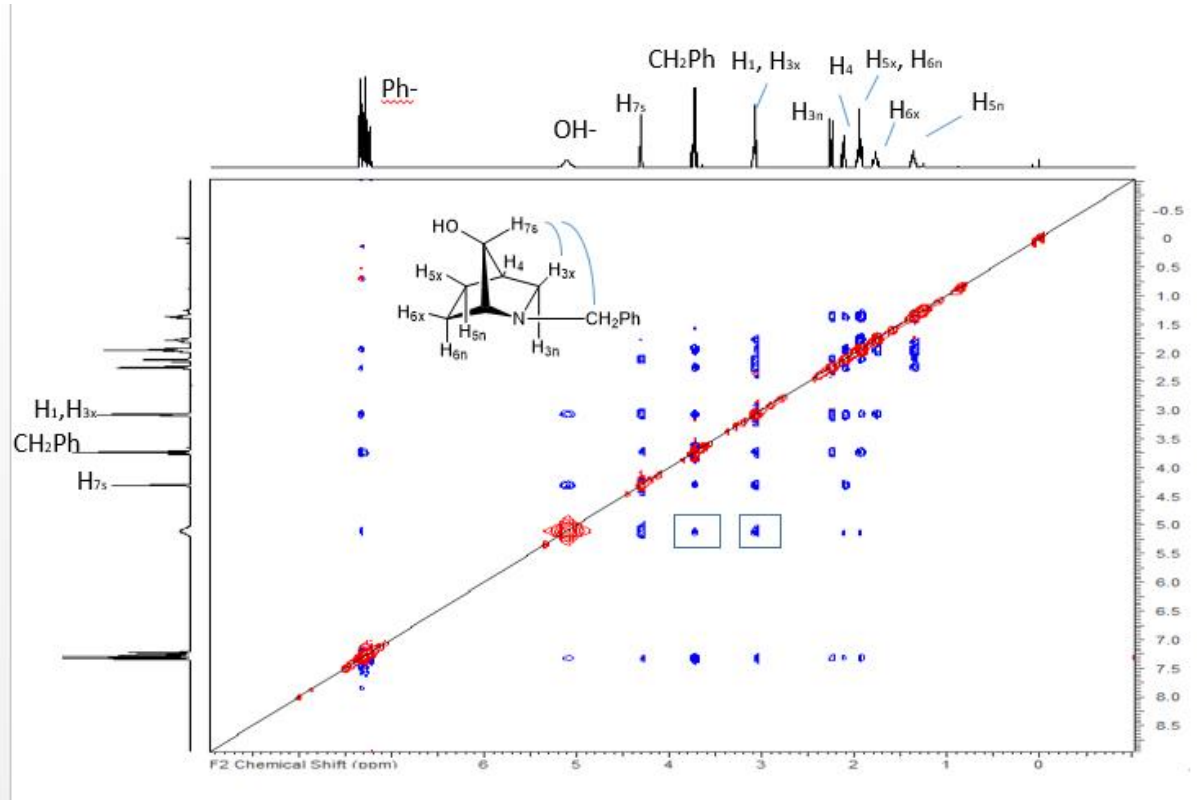


Fig 2.14 Formation of *anti*-7-hydroxy-2-azabicylic[2.2.1]heptane (**87**).

Synthesis of compound (**87**) from (**85**) occurred with retention of configuration at C7. The ^{1}H NMR spectrum showed similar data to compound (**85**) except the signal for H_7 is at δ 4.31 ppm due to the greater deshielding of the OH substituent compared to the bromide. The *anti*-stereochemistry of the alcohol at C7 was fully characterized by 2D NMR spectroscopic analysis. Thus, the NOESY spectrum of (**87**) showed the cross peaks between H_7 and of the following signals H_{3exo} and methylene protons of the benzyl group. Additionally, ^{1}H-^{1}H COSY analysis of (**87**) showed 'W' coupling between H_{7s} with H_{5endo}.

Fig. 2.15 NOESY spectrum for *anti*-7-hydroxy-2-azabicyclo[2.2.1]heptane (**87**).



2.6 Neighbouring group participation

In order to account for the retention in configuration in the reaction of (**85**) to give (**87**) the role of neighbouring group participation in 2-azanorbornane system needs to be considered. Neighbouring group participation is the process where by some substituents may exhibit their influence in a reaction through being bonded or partially bonded to the reaction centre, leading to the lowering of the transition state. This behaviour is well-known neighbouring group participation.[98, 99] If the transition state of a rate-determining step is lowered, this will result in an acceleration of the reaction rate, and then the neighbouring group is said to be supplying anchimeric assistance.[100] Additionally, the phrase 'intramolecular catalyst' has been applied when the neighbouring group can be 'regenerated' in the product of this type of reaction.[98]

It is possible for the neighbouring group participation (NGP) or neighbouring group effect to influence various reactions in organic chemistry,[92,101, 102, 103] where this influence can be seen in the rate or the stereochemistry of a reaction, while there is no actual change on the neighbouring group itself during the reaction (**Fig. 2.16**).

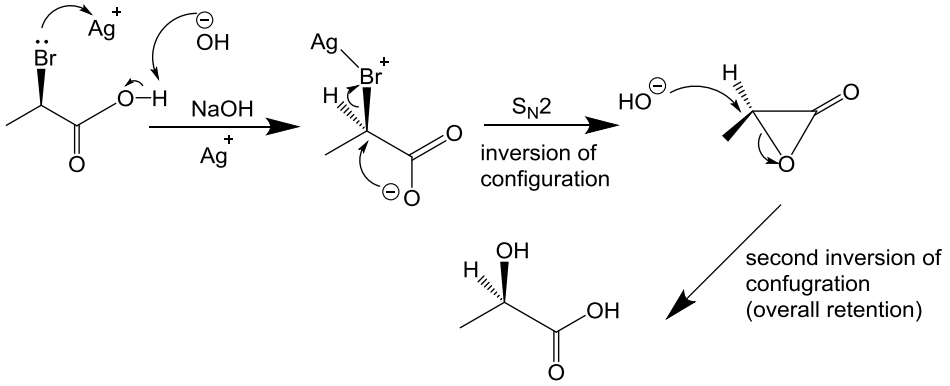


Fig. 2.16 Literature example of neighbouring group participation (NGP); the carboxylate ion acts as an NGP that forms a three-membered ring intermediate followed by ring opening by the hydroxide nucleophile in a second S_N2 step.[101]

Again, neighbouring group participation is involved, but this time *via* a lone pair of electrons that can be used to form unusual bicyclic intermediates. The crucial and unexpected nucleophilic substitution at C7 whilst maintaining the 7-stereochemistry of (**85**) occurs with anchimeric assistance by the nitrogen lone pair which can participate in the displacement of the bromide (leaving group) from C7. This leads to the formation of an unusual cation (**91**) and the subsequent S_N2 attack by the nucleophile. This must be

anti to the nitrogen atom to give (**92**), with overall retention of the configuration (**Fig. 2.17**).

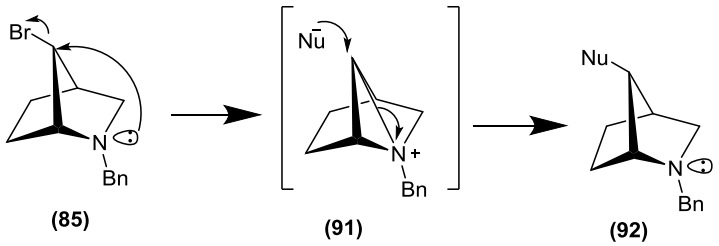


Fig. 2.17 Retention stereochemistry of (**85)** suggests neighbouring group participation.

Further evidence that the neighbouring group has an effect in norbornanes is the observation that π electrons can facilitate the loss of substituents at C7 (tosylates and brosylates) leading to the formation a range of unusual solvolysis products with overall retention of stereochemistry (**Fig. 2.18**).[102, 104,]

A similar π-participation has been observed is the loss of the chloride ion from 7-chloro-azanorbornenes, allowing an overall retention of stereochemistry.

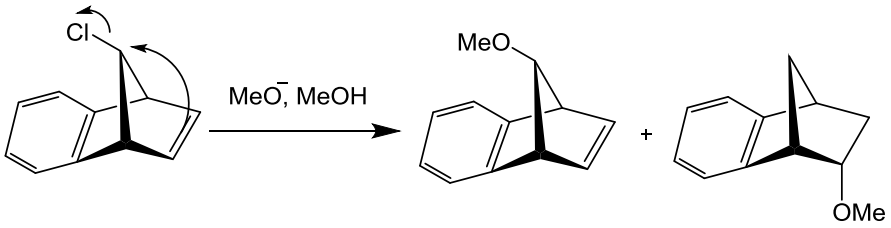


Fig 2.18 Literature example of NGP in 7-norbornanes.[80]

More usually, the lone pair of the nitrogen of 2-azabicyclo[2.2.1]heptanes can stabilise a developing positive charge through electrophilic addition to the π-bond, which leads to skeletal rearrangement (as illustrated in section 2.3); the bromonium ion is ring-opened by the lone pair of the nitrogen, allowing for skeletal rearrengment.[79, 80] The concept of NGP is expected to play a significant role in the fluorination reactions of 2-azanorbornanes with hydroxyl functionality at the 5-*exo* and 6-*exo* positions (as described in chapter 3).

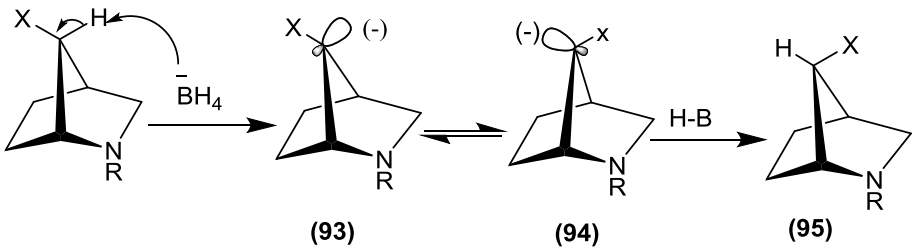
In summary, the neighbouring group participation phenomenon as facilitated by the nitrogen lone pair in reaction at the C7 of 2-azanorbornanes has been considered an important observation. It has obviously led to an increased understanding of the role of NGPs in the rearrangement of 2-azanorbornanes. However, the retention of *anti*-7

stereochemistry has clearly been more energetically demanding, which may cause difficulties in synthesising analogues of epibatidine with a heterocycle attached the *syn*-7 position to the amine nitrogen that have the potential for a high binding affinity to nAChR ligands.

2.7 Epimerisation at the C7 of 2-azanorbornanes

It has been postulated in section 1.7.6 that for an ideal N-N distance requirement in the nicotinic pharmacophore, the 7-heterocyclic compound of 2-azabicyclo[2.2.1]heptane must be *syn* to the bicyclic nitrogen. All the substituents based on *anti*-7- derivatives (**87-90**) resulted in an overall retention of configuration at C7, so there is clearly a need to epimerise at this position in order to access the potentially *syn*-7-derivatives.

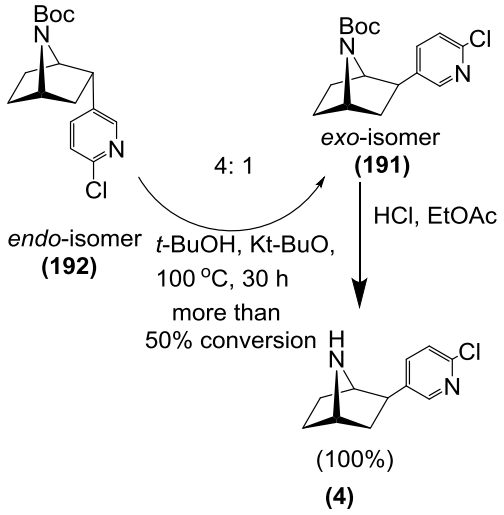
The presence of the substituents at C7 is considered to be a key feature in stabilising the negative charge α to it and will lower the pKa of the 7-position. In this case, the epimerization will proceed on addition of the appropriate base, leading to the anion (**93**), then allowing for the inversion of (**93**) to (**94**); the last step is protonation to give the final epimerised *syn*-compound (as shown in Fig. 2.19). The inversion of 7-norbonyl anions is found to be similar to that in 2-azanorbornanes, and has been well documented.[105, 106]



2.19

Epimerisation of 7-substiituted 2-azabicyclo[2.2.1]heptane, B^- = base.

Fletcher *et al.* have reported a number of total synthesis of 7-protected epibatidine that involved an epimerisation step; they obtained a mixture of two epimers (*exo*- and *endo*-) (**191**) and (**192**) (see section 4.2 and Fig. 4.2 for further details). The *endo*-isomer was epimerised successfully by utilizing potassium tert-butoxide for 30 h at 100 ^oC to obtain the *exo*-epimer (**191**) in more than 50% yield based on (**192**). In this example, it was clear that the existence of resonance in the pyridyl ring helps to stabilise the negative charge of the anion formed during the reaction as shown below (more details in chapter 4 section 4.2).[107]



Similarly, an inversion at C7 in the norbornene skeleton is possible at a more strained bridgehead, with a resulting mixture of *anti*- and *syn*-7-carbomethoxy-benzonorbornadiene (**96**) and (**97**). Treatment of (**96**) with sodium methoxide in methanol and HMPA can allow an equilibrium to occur between (**96**) and (**97**) at 65 °C after 165 h (K_{eq} = (**96**)/(**97**) = 0.73) (**Fig. 2.20**).[108]

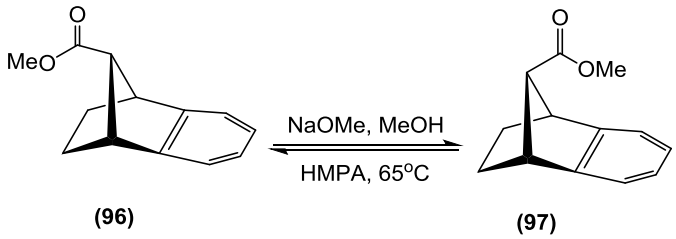


Fig. 2.20 A literature example of epimerisation at the C7 of norbornenes.

From the findings above it has been deduced that epimerisation of the *anti*-OH derivative (**87**) should be investigated (**Fig. 2.21**). The inversion at the 7-position of 2-azabicyclo[2.2.1] can only be achieved with difficulty in order to access the potential *syn*-7-dervitive, 2-azabicyclo[2.2.1]heptane.

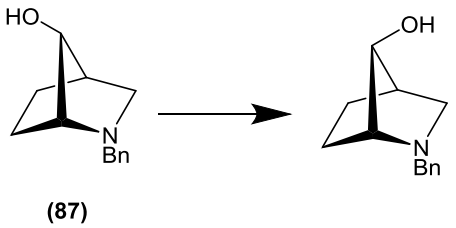


Fig 2.21 Epimerisation of *anti*-7-hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane.

2.8 The Mitsunobu reaction

The Mitsunobu reaction is well known in organic chemistry and was first described almost sixty years ago.[109] It allows the conversion of primary and secondary alcohols to a variety of functional groups under mild conditions, such as an esters, phenyl ethers, and thioethers *via* oxidation-reduction condensation.[101]

The general reaction is illustrated in (**Fig. 2.22**), in which the acidic compound (H-Nu) and alcohol (R-OH) have been condensed to produce the product (R-Nu), while the formation of a new bond from a combination of the oxidation of triphenylphosphine into phosphine oxide and reduction of diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIED) into the corresponding hydrazine.

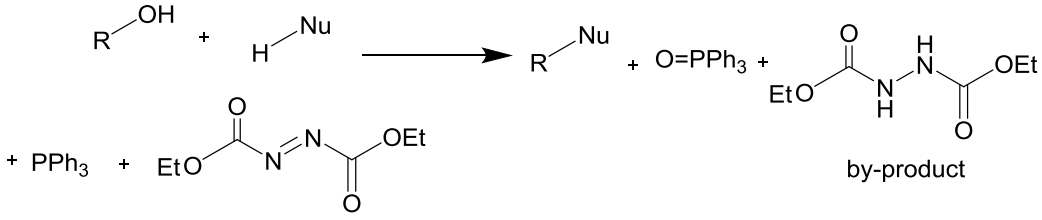


Fig 2.22 General Mitsunobu reaction.

2.8.1 How does the Mitsunobu reaction work?

The Mitsunobu mechanism proceeds through four main steps *via* the condensation reaction of alcohols using PPh_3 and DIAD (as shown in Fig. 2.23), in which the phosphine adds to the weak N=N double bond to form an anion stabilized by one of the ester groups. The second step, including removal of the proton from the acid (H-Nu), leads to the generation of the salt and Nu^-, to allow its reaction. The third step involves activation of the alcohol to form an activated oxyphosphonium ion. Finally, the Nu^- is replaced *via* an S_N2 reaction with a resulting inversion of configuration.[101]

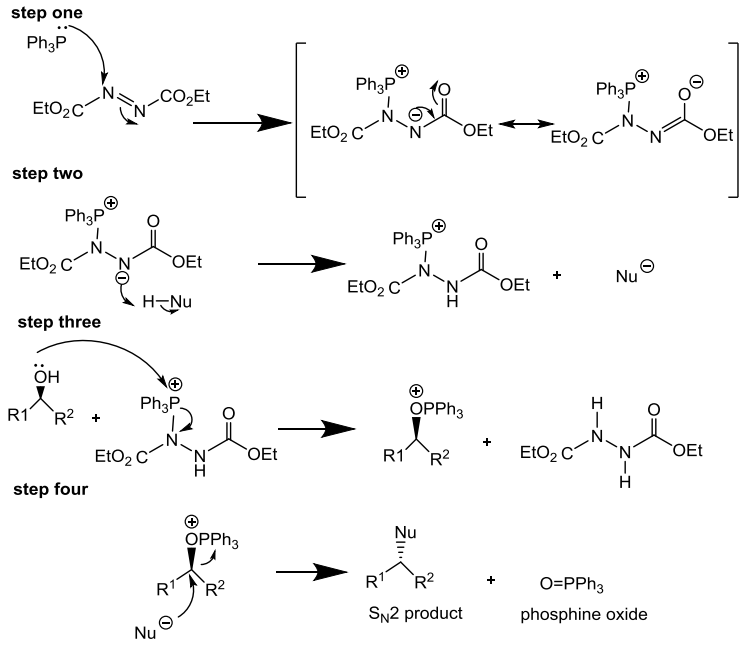


Fig 2.23 General Mitsunobu reaction mechanism.

2.9 Background on nicotinic ligands with ether linkages

The discovery of ABT-594 (**46**) in the Abbott laboratories in 1998[68] has led to the synthesis of a range of nicotinic ligands containing the 3-pyridyl ether functional moiety (as illustrated in section 1.6.7). Tebanicline (ABT-594) was the first series of nicotinic agonists that entered human clinical trials as potent analgesics, but was subsequently withdrawn due to significant side effects.[68] Using the Mitsunobu protocol is the key to forming an ether linkage for epibatidine analogues by using an appropriate 3-pyridinol and a primary alcohol.[110]

The azetidine ring and the chloro substituent are considered to be the key structural elements in producing the potent analgesic activity of compound (**46**).[111] It has been found to possess a high binding affinity for nAChRs (K_i = 0.04 ± 0.03 nM),[68] where ABT-594 was 180-fold less potent than (±)-epibatidine in activating peripheral skeletal muscle-type nAChRs.[111]

Additionally, ABT-594, has been reported to possess similar analgesic and toxic effects to (±)-epibatidine and nicotine in rats. However, it has been confirmed to be selective to neuronal nAChRs, and has been found to have a nicotine-type dependence liability. This led to the understanding that ABT-594 does not have a significantly improved safety

window over other nicotinic agonists. Furthermore, it was found to have a greater binding affinity to α3β4 subtypes than α4β2 subtypes, which is believed to be the cause of gastrointestinal side effects. After clinical trials in humans, it was dropped from further development due to the unfavourable side effects reported.[70]

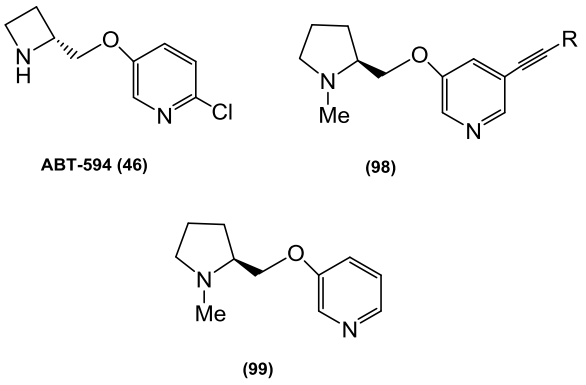


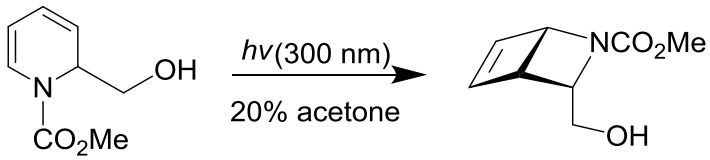
Fig. 2.22 Examples of ligands with etheral-bonds.

Further work by Kozikowski *et al.* produced analogues of ABT-594 in which the different groups (phenyl, primary alkyl-fluoride and primary alkyl-alcohol) were substituted at the C5 position of the pyridine ring.[112] They investigated the apparent selectivity for nAChRs presented by ligands with the general structure of (**98**); all high-affinity compounds tested have shown significantly improved selectivity between the α4β2 and α3β4 subtypes in comparison to the parent compound (**99**).

In this chapter, the concept of combining an azabicyclic system with a pyridine heterocycle *via* an ether linkage has been investigated. These derivatives, which represent a hybrid structure of ABT-594 and related compounds, have been found to possess unexpected biological activity that was deduced from molecular docking studies. It revealed that the azabicyclic moiety is essential to potential nicotinic activity. Thus, in the design of epibatidine analogues, we hoped to generate an appropriate inter-nitrogen distance and achieve the desired selectivity *via* ether linked analogues. Furthermore, the molecular docking study to homology models elucidated how the ether linked analogues dock to nicotinic receptors, and increased knowledge as to how these ligands give rise to their selectivity is being established that will lead to their improved safety in therapeutic applications.[110]

Krow *et al.* have synthesised ether-bonded ABT-594 analogues with smaller azabicyclic frameworks. Stereoselective photochemical ring closure of a suitable 1,2-dihydropyridine

has been used to produce 3-*endo*-(6-chloro-3-pyridoxy-methyl-2-azabicyclo[2.2.0]hex-5-ene (**100**) and 3-*endo*, 5-*endo*-6-chloro-3-pridoxy)-methyl-2-azabicyclo[2.2.1]hexane (**101**) and (**102**), respectively (**Fig. 2. 23**).[113]



According to the Mitsunobu coupling reaction protocol, the respective 2-azabicyclo[2.2.0]hexane alcohol was coupled with 2-chloro-5-hydroxypyridine to obtain the targets (**100**-**102**); this class of ligand was found to possess less binding affinity to α4β2 receptors (**100**) K_i = 14 nM, (**101**) K_i = 2.3 nM, (**102**) K_i = 12 nM) than ABT-594 or epibatidine.[113]

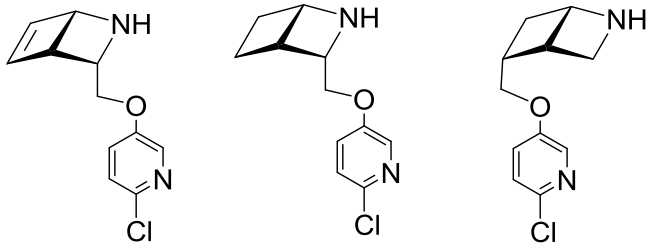
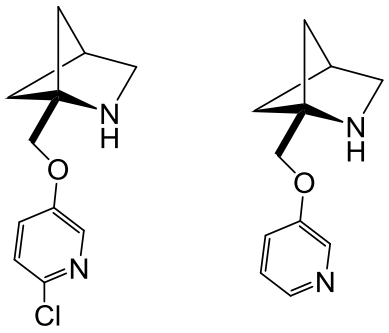


Fig. 2.23 Selected nicotinic ligand based on 2-azabicyclo[2.2.0]heptane.

Previous reseach carried by Malpass and Patel at University of Leicester investigated the synthesis of epibatidine analogue pyridyl ethers *via* the Mitsunobu coupling reaction; based on a methanoproline bicyclic framework, (**103**) and (**104**) have been synthesised[114] in which the 2-chloro-5-pyridyl-ether heterocycles and the 3-pyridyl-ether were attached to the neopentyl position of the 2-azabicyclo[2.1.1]hexane framework. Additionally, the structural features are compact due to the existence of the rigid azabicyclo system. However, compounds (**103**) and (**104**) were designed as good targets, since these molecules feature an increase in flexibility (as they have a chain containing two atoms, C and O) in the bridge between the heterocycle and the 2-azabicyclo[2.1.1]hexane system. It was anticipated that these compounds would be potential nicotinic ligands for the nAChR in comparison to compounds with known high activities (**Figs. 2.22** and **2.23**).

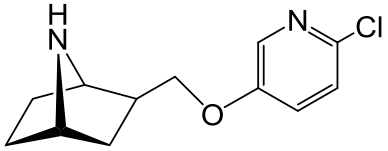
Unexpectedly, the receptor binding assay revealed that (**103**) and (**104**) had very low affinities for the α4β2 and α3β4 nAChR subtypes.[62, 114]



(103) **(104)**

Fig. 2.24 Examples of nicotinic ligands of pyridyl ether based on the 2-azabicyclo[2.1.1]hexane system.

In the literature, there are few examples of nicotinic ligands in which the bicyclic structure of epibatidine is combined with the pyridyl-ether heterocycle. Compound (**105**) has been produced by Tudell *et al.*, which represents a hybrid structure of epibatidine and ABT-594 in which a pyridyl ether moiety is attached to the *exo*-2-position of the 7-azacyclo[2.2.1]heptane system. The ligand exhibited much weaker binding affinity (K_i = 740 nM) than epibatidine, nicotine and ABT-594. These biological findings led to the deduction that the structural features that lead to the potency in epibatidine and ABT-594 could not be combined.[77]



(105)

2.10 Synthesis of pyridyl ether derivatives of *anti*-7-hydroxy-2-azabicyclo[2.2.1] heptane

The targets for synthesis of pyridyl ether derivatives of *anti*-7-hydroxy-2-azabicyclo[2.2.1]heptane are (**107**), (**109**) and (**111**). These have 2-, 3- and 4-pyridine heterocycles attached to the *anti*-7-position of the 2-azabicyclo[2.2.1]heptane framework, therefore constituting epibatidine analogues. In the synthesis of these derivatives, the objective is to increase the degree of flexibility when docking with nicotinic receptors by

increasing the chain length. Additionally, the active minimum energy conformation of epibatidine has a calculated N-N distance of 4.5 Å which is in the acceptable range of other nicotinic ligands, including ABT-594.[9, 110] In this range of compounds, having an oxygen atom in the bridge between the heterocycle and the bicyclic system is assumed to give a higher degree of flexibility once bound to the receptor, unlike the conventional compounds that have heterocycles attached directly to the bicycle (**Fig. 2.26**).

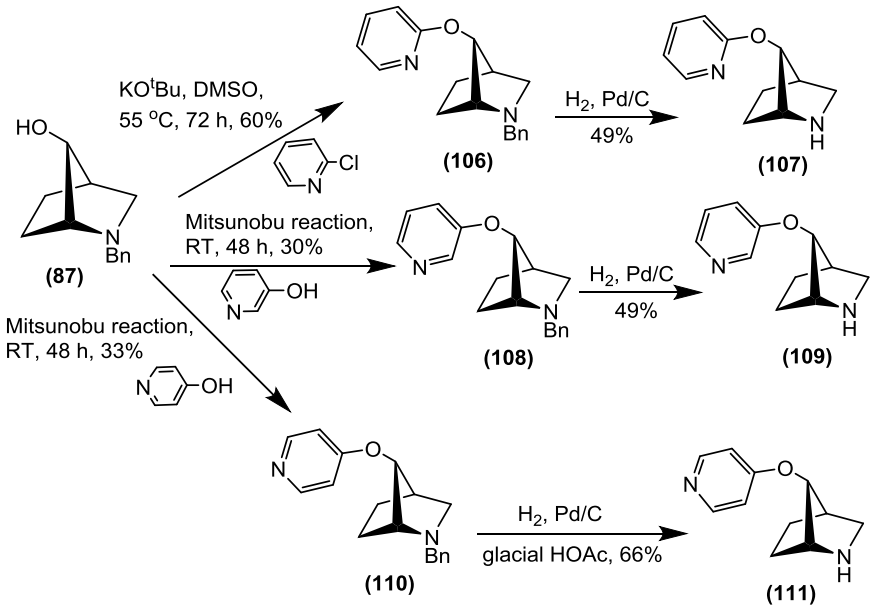


Fig. 2.26 Synthetic approaches to pyridyl-ether ligands of *anti*-7-hydroxy-2-azabicyclo[2.2.1]heptane.

2.10.1 Synthesis of the target compound (107)

To the best of our knowledge, only (**106**) was synthesised by nucleophilic displacement because there is stable resonance forms with negative charge on N atom which facilitates nucleophilic aromatic substitution, to activate the 2-position of pyridine towards the nucleophiles. (**106**) was produced by nucleophilic substitution of the chloride from 2-chloropyridine utilizing the base KO^{t}Bu in a 60% yield (**Fig. 2.26**). Compound (**106**) was fully characterised by ^{1}H-NMR and 2D-NMR spectroscopy. The H_7 signal was observed as a broad singlet at 5.24 δ and the pyridyl protons $H_{3`}$ as a doublet at 6.69 δ, $H_{5`}$ at 6.84 δ, $H_{4`}$ at 7.63 δ and $H_{6`}$ at 8.16 δ with all signals appearing as a doublet of doublet of doublets.

The removal of the *N*-benzyl protecting group from (**106**) to form a secondary amino-alcohol (**107)** by hydrogenolysis using palladium on carbon as a catalyst under hydrogen gas, was successful on the first attempt. The reaction was conducted in dry methanol

stirring for 24 h at ambient temperature in a 49% yield. From the ^{1}H-NMR spectrum, the absence benzyl protons confirmed the production of (**107**).

2.10.2 Mitsunobu coupling on *anti*-7-alcohol

We expected that the 3-pyridyl derivative (**108**) could not be obtained using the same methodology because the 3-position of the pyridine ring is not reactive towards nucleophiles. For example, in the treatment of (**87**) with 2-chloro-5-iodopyridine, the nucleophilic replacement of chloride instead of iodide occurs.To gain access to the next set of compounds (**108-111**) (**Fig. 2.26**), we had to employ the Mitsunobu coupling reaction with the key alcohol (**87**). It was then followed by the removal of the protecting group on treatment with palladium on carbon as a catalyst to obtain (**109**) and (**111**).

The attempt at the Mitsunobu reaction was successful, alcohol (**87**) was coupled with 3-hydroxypyridine to produce (**108**) in a 30% yield, whilst (**110)** was produced in the same fashion using 4-hydroxypyridine (33%). In both the synthesis of (**108**) and (**110**), DIAD was used as the Mitsunobu reagent rather than DEAD, which is the more conventional reagent.[101] DIAD was considered a safer reagent because it is not carcinogenic or explosive like DEAD. Despite the poor yields of 30% and 33%, respectively, we successfully synthesised (**108**) and (**110**). These Mitsunobu reactions occur with retention of configuration which are consistent with neighbouring group participation by the nitrogen lone pair (see section 2.6). The results from early work by White in the Mitsunobu coupling reaction using DEAD as a reagent gave similar results, obtaining a 30% yield for (**108**) and 29% for (**110**).

The deprotection of the *N*-benzyl group from the heterocycle product (**108**) was achieved again to give (**109**) in a 49% yield under one atmosphere of hydrogen, but many attempts to deprotect the nitrogen in (**110**) using palladium-catalysed hydrogenation were not successful. Another attempt was made to deprotect (**110**) by applying extra pressure (40 psi) overnight (**Fig. 2.27**). This also proved to be unsuccessful, leading to the recovery of the starting material. Selective removal of the *N*-benzyl protecting group has been found to be difficult, as reduction of the heterocycles can also occur under these conditions. Finally, a third and successful method was carried out in an acidic medium by adding glacial acetic acid 20% prior to work-up and monitoring the reaction *via* TLC and ^{1}H-NMR analysis.[115] This gave the required *N*-benzyl deprotecting nitrogen product (**111**) in a reasonable yield of 66%.

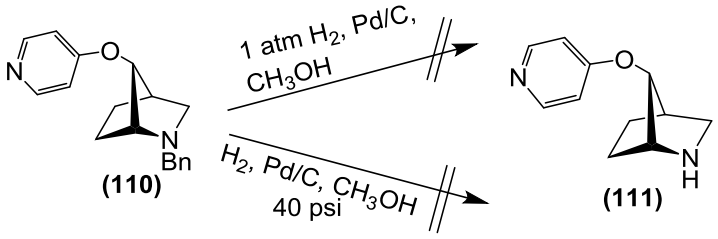


Fig. 2.27 Attempts to deprotect the *N*-benzyl group.

Acetic acid has been found to facilitate the removal of *N*-benzyl protecting groups because the hydrogenolysis of more polarized σ bonds is easier than that for nonpolarized bonds. Additionally, the Bn-N bond can be polarized by protonation of the non-pyridine N atom, leading to the Bn-N bond becoming more electrophilic for the surface hydride attack in hydrogenolysis (**Fig. 2.26**). The ^{1}H-NMR spectrum indicated that the aromatic protons had been removed, confirming the formation of both (**109**) and (**111**). The removal of the benzyl groups of (**106**), (**108**) and (**110**) has been found to be effected by the hydrogenolysis using palladium on carbon as a catalyst, and it is clear that this is competitive with the cleavage of pyridine heterocycles, leading to reasonable yields for these transformations.

2.11 Background on the construction of the methylisoxazole heterocycle

Epibatidine analogues have been synthesised that maintain the 7-azabicyclo[2.2.1]heptane molecule but contain a bioisosteric replacement in place of the chloropyridyl ring in the hope of improving the subtype selectivity. One unique analogue is (±)-epiboxidine (**37**), in which the chloropyridyl ring is replaced by methylisoxazole (see section 1.7.6). As previously demonstrated, epiboxidine has been found to have a 10-fold weaker binding affinity, but is less toxic, than epibatidine (**4**) because of its reduced potency. The University of Leicester[79] has experience with the construction of methylisoxazole from the ethyl ester (**Fig. 2.29**) through the work of Malpass *et al.* The *anti*- (**112**) and *syn*-isoepiboxidines (**113**) are analogues of epiboxidine (**37**) in which the methylisoxazole heterocycles have switched position (**Fig. 2.28**).

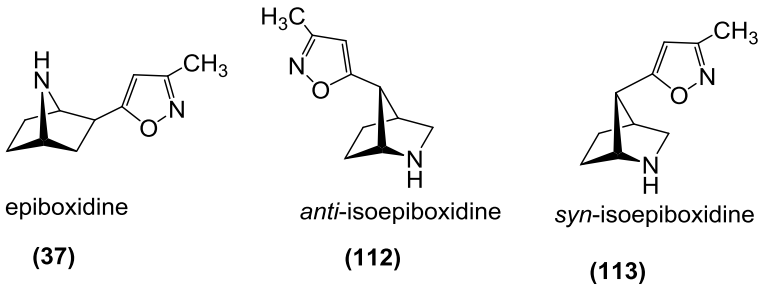


Fig. 2.28 Epioxidine and its analogues.

Malpass *et al.* reported the formation of *anti*- and *syn*-isoepiboxidine (starting from (**114**) and (**115**)) in a 24% yield and a 26% yield respectively, without need to protect the bicyclic nitrogen first (**Fig. 2.29**), leading to a reduction in the number of steps involved. Before this finding, it was thought that the protection of the secondary amino-nitrogen was a necessary feature for the synthesis of methylisoxazole products. The biological assays of both isomers indicated that they exhibit antinociceptive activity, where the *syn*-isomer (**113**) has been found to have about 13 times weaker affinity than epibatidine, but had a high affinity for α4β2 (K_i = 0.67 nM) and a low affinity for α3β4 (K_i = 9.51 nM), while the *anti*-isomer (**112**) did not show any activity for either the α4β2 and α3β2 sub-types, even at K_i =1000 nM; this was attributed to the increased N-N distance.[80]

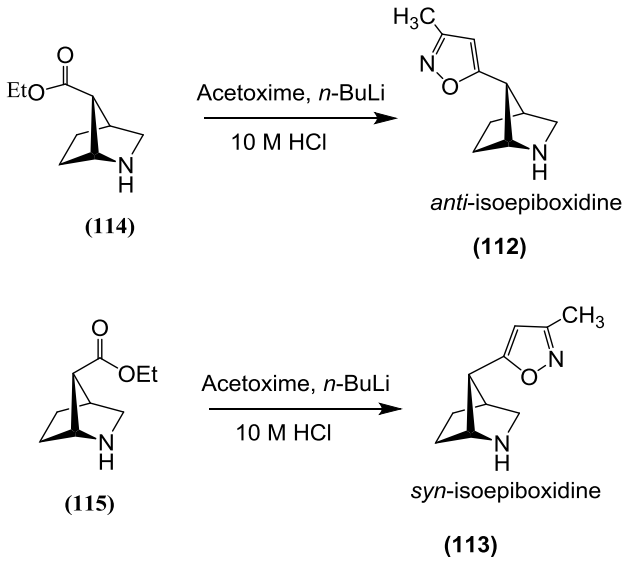


Fig. 2.29 The synthesis of *anti*- and *syn*-isoepiboxidine.

2.12 Construction of the 5-methyl-3-isoxazolol ring

In recent years, the chemistry of the 3-isoxazole moiety has seen increasing interest because it can be found in many naturally occurring compounds which have been useful

in medicine and agriculture. For example, the alkaloid muscimol (**116**) is active *in vivo*, mimicking the neurotransmitter γ-aminobutyric acid (GABA).[116] Another example of a biologically active molecule is 5-methyl-3-hydroxyisoxazolol (**117**), commercially available under the names Hymexazol and Tachigaren, which is used as a soil fungicide and a growth promoter. [116, 117, 118]

The most common and economical method by which to synthesise 5-methyl-3-isoxazolol (**117**) is by the cyclization of β-ketoester or diketene with hydroxylamine. In some cases, this method is not efficient when 2-unsubsitituted β-ketoesters are used because the formation of undesirable 5-methyl-3-isoxazolone (**118**) is favoured. However, it has been claimed that (**117**) cannot be produced by the above method. As a result, these compounds are usually made from substituted β-ketoesters or by using altogether different methods. Jacquir *et al.* studied the reaction of hydroxylamine with β-ketoesters in alkaline media extensively, leading to the formation of (**117**) in a few cases. They explained that the rapid acidification of the reaction mixture with a large amount of hydrochloric acid is essential requirement in the formation of (**117**). Additionally, they found that at pH 3-5, slow addition of hydrochloric acid led to the production of the unrequired 5-methyl-3-isoxazolones (**118**).[116]

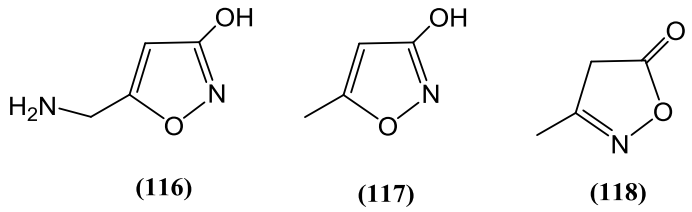


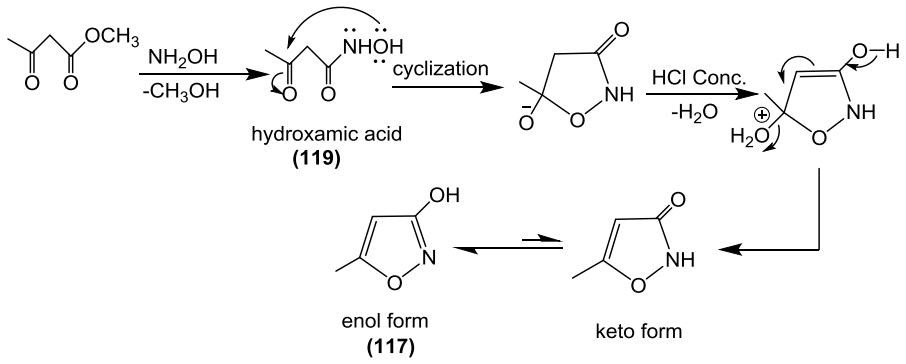
Fig. 2.30 Compounds with 3-isoxazolol molecule and 3-isoxazolone.

2.12.1 Mechanism of 5-methyl-3-isoxazolol synthesis

Jacobsen *et al.*'s protocol was adopted for the synthesis of (**117**).[116, 119, 120] The pH of the reaction mixture should be constant at around 10.0 (± 0.2), as monitored using a pH meter, using an alkaline medium (2 M sodium hydroxide). The mixture was poured into a large amount of concentrated hydrochloric acid (150 ml). This methodology does, however, lead to the formation 3-methyl-5-isoxazolone (**118**) as a by-product in addition to the major product, 5-methyl-3-isoxazolol (**117**). Jacobsen *et al.* suggested that the formation of hydroxamic acid (**119**) and the oxime (**120**) as intermediates for the synthesis of (**117**) and (**118**), respectively (**Fig. 2.31**), although the intermediates were neither isolated nor

observed in any manner. Jacobsen suggested two possible pathways for the formation of these particular products. The first major pathway demonstrated that the direct reaction between the β-ketoester with hydroxylamine led to the formation of the hydroxamic acid (**119**), which in turn underwent cyclization to produce (**117**), where any equilibrium is overwhelmingly in favour of the enol form (**117**). The second minor pathway demonstrated that the recombination of the β-ketoester with hydroxylamine to give the oxime (**120**). Cyclization would occur from (**120**) and hence treatment with concentrated acid would eventually produce (**118**) (**Fig. 2.31**).

First pathway



Second pathway

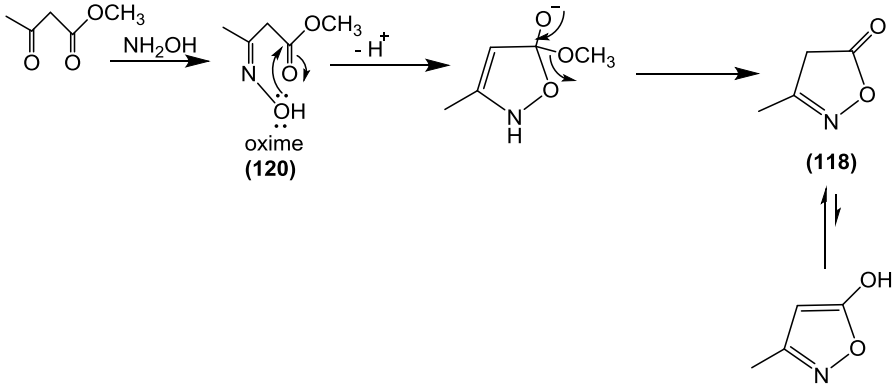


Fig. 2.31 The suggested mechanisms for the syntheses of 3-isoxazolol (**117**) and 3-isoxazolone (**118**).

The reaction was carried out at pH 10.0 (± 0.2) as monitored by a pH meter for 30 min, after which the mixture was poured into strong, ice-cold acid and left overnight at room temperature for optimum conversion. The products were isolated by using continuous extraction with dichloromethane. The ^{1}H-NMR and TLC analysis of the crude product showed the presence of the two compounds, where the ratio of these two compounds was

measured from the peak integrals (~33:67, **118**:**117**). The crude products were purified using a flash chromatography column to give (**117**) as a white crystalline solid in a 22% yield and (**118**) in 10% yield. On another note, the purity of (**117**) was that its m.p. was 85-86 ^{o}C, consistent with the literature where a m.p. of 84-85 ^{o}C was reported.[119]

The compounds were fully characterised by ^{1}H-NMR spectroscopy and X-ray crystallography to confirm the structure of (**117**) (**Fig 2.32**). Also, infra-red spectroscopy confirmed the presence of a carbonyl group *via* the presence of a vibrational feature at 1795 cm^{-1} for (**118**). All the data was found to be consistent with those in the literature.[119, 121]

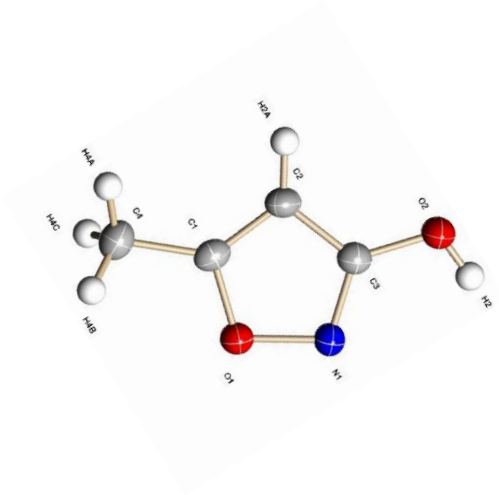


Fig. 2.32 The X-ray crystal structure for 3-isoxazolol (**117**).

It seemed likely that the outcome of the reaction greatly depends upon a number of factors, one of which was the precise pH of the reaction mixture; otherwise, many possible routes could be occur, leading to a reduction in the yield of (**117**). Additionally, adding excess concentrated hydrochloric acid to the reaction mixture, with the subsequent rapid acidification, was crucial because any decrease in the amount of hydrochloric acid would lead to a reduction in the chance to achieve a high yield of (**117**); all these reasons give a possible explanation for the low yield of 5-methyl-3-isoxazolol (**117**) at 22%, which is in contrast with the yield reported in literature (70% yield).[116] However, the optimization of this step was not critical to the next steps in the project.

2.13 Synthesis of target compound (121)

Hence, compounds (**108**) and (**110**) have been approached successfully by applying the Mitsunobu coupling reaction for the reasons demonstrated previously (see Sections 2.9.1 and 2.9.2). It was anticipated that the heterocycle would attach to the C7 position of the *anti*-alcohol. Once again, with the *anti*-alcohol (**87**) and 5-methyl-3-isoxazolol in hand, the novel species (**121**) was produced in an analogous fashion as described in (**Fig. 2.33**) using DIAD as the Mitsunobu reagent in a 15% yield. The crude product showed a lot of spots, as detected by TLC analysis, which made product purification very difficult, which in itself can lead to a lower yield. The desired product (**121**) was isolated by running it twice through flash column chromatography due to the impurities generated throughout the reaction. Once again the Mitsunobu reaction of the *anti*-alcohol (**87**) is enabled by neighbouring group participation (NGP) by the bicyclic nitrogen lone pair with overall retention of stereochemistry (as previous discussed in section 2.9.2).

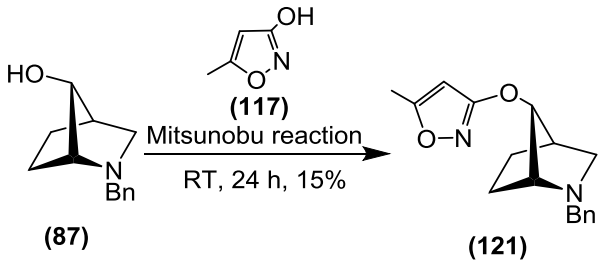
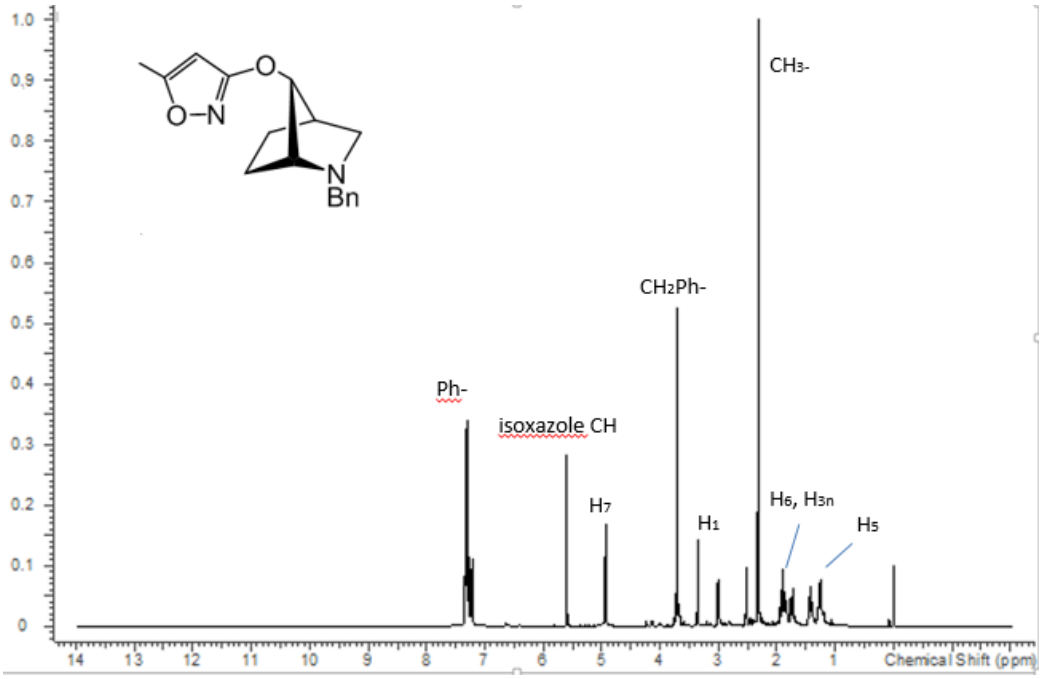


Fig. 2.33 The synthesis of (**121**) using the Mitsunobu reaction.

The structure of (**121**) was assigned by ^{1}H-NMR and ^{1}H-^{1}H COSY NMR experiments; the three protons of the methyl group appeared as a doublet at 2.31 δ and showed a vicinal coupling to the isoxazole CH (< 1 Hz). The associated ^{1}H-NMR data are shown in (**Fig. 2.34**).

Fig. 2.34 ^{1}H-NMR spectrum of (**121**)



It was deduced that the Mitsunobu coupling reaction has been used effectively in order to produce a range of epibatidine analogue ligands (**108**), (**110**) and (**121**). These promising ligands offer a good opportunity to enhance the nicotinic receptor affinity, these structures have low energy conformations with appropriate inert-nitogen distances similar to the 5.5 Å of epibatidine. Further discussion of the synthesis of *anti*-pyridyl dervatives can be found in section 2.10.2.

2.13.1 Attempted deprotection of the *N*-benzyl protecting group of (121)

De-benzylation of the heterocyclic product (**121**) to form the target (**122**) was attempted by palladium-catalysed hydrogenation (**Fig. 2.35**). This proved unsuccessful, and the attempt was accompanied by a mixture of uncharacterised products. It is noteworthy that the selective removal of the benzyl group is difficult because the isoxazole ring undergoes reduction under these conditions. A similar observation of the reduction of 5-methyl-3-isoxazolol reported by Daly *et al.* that failed to produce homoepiboxidine, whilst products arising due to isoxazole cleavage were obtained under the same conitions.[122]

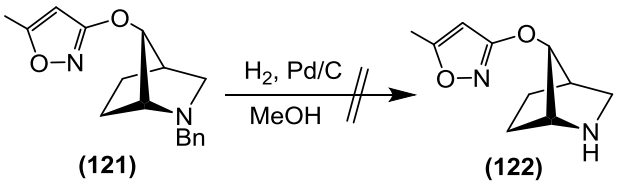


Fig. 2.35 Attempt at catalytic hydrogenation of the methylisoxazole derivative.

In summary, the Mitsunobu coupling protocol was effectively conducted in order to synthesise a range of *anti*-7-pyridyl and *anti*-7-isoxazole derivatives (**108**, **110** and **121**, respectively) with retention of configuration. These compounds have an etheral-linkage (have a longer side-chain containing one oxygen atom) which makes the molecule more flexible; these modifications may enhance the biological activity.

The manipulation of the C7 stereochemistry is an essential requirement of the synthesis of the *syn*-products (**142**), (**144**) and (**145**). The next sections will discuss the conversion of *anti*-7-hydroxy-2-azabicyclo[2.2.1]heptane to the *syn*-alcohol precursor.

2.14 Synthesis of 7-keto-2-azabicyclo[2.2.1]heptane (Swern oxidation)

The epimerization of *anti*-7-hydroxy-2-azabicyclo[2.2.1]heptane (**87**) was investigated in the hope of reversing the C7 configuration from the *anti*- to *syn*-configuration *via* an oxidation-reduction strategy**.**

In order to establish the equilibrium between the oxidation of the alcohols and the reduction of the ketones, the mild conditions of the Oppenauer oxidation and the Meerwein-Ponndorf-Verley (MPV) reduction were used, which are both efficient reactions and highly selective. Traditionally, the racemisation of secondary alcohols can be achieved by treating the alcohol with aluminium (ш) isopropoxide (catalyst) in the presence of the corresponding ketones (**Fig. 2.36**).[123, 124]

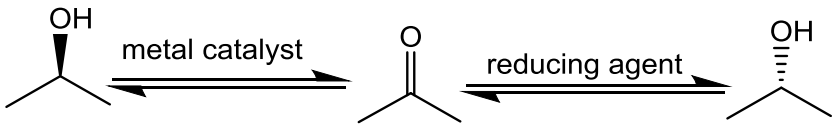
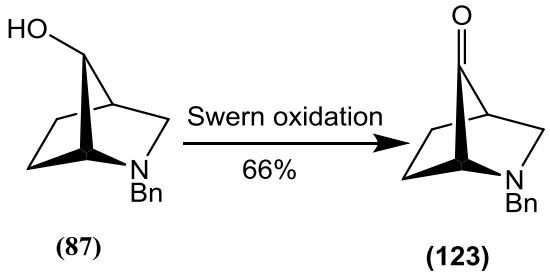


Fig. 2.36 The racemization of a secondary alcohol with a metal catalyst.

Many attempts were undertaken by White at the University of Leicester[76] to epimerise the *anti*-7-hydroxy-2-azabicyclo[2.2.1]heptane (**87**) using the Oppenauer oxidation protocol, but it proved unsuccessful with only recovered *anti*-alcohol being producded. With this failed attempt, the Swern oxidation was examined in order to achieve the corresponding ketone and this had more success.

The oxidation reaction (Swern) is carried out at -78 ^{o}C by using oxalyl chloride in DMSO in the presence of triethylamine base under dry conditions and a good yield of the ketone (**123**) was recorded after the reaction was complete (66%). The crude product was not purified by column flash chromatography because it is not stable on silica. This may be due to the formation of hydrates and acetals (**Fig. 2.37**). Infra-red spectroscopy confirmed the presence of a carbonyl group at 1712 cm^{-1}.



(87) **(123)**

Fig. 2.37 The Swern reaction to approach the 7-keto-2-benzyl-2-azabicyclo[2.2.1]heptane.

2.15 Reduction of 7-keto-2-benzyl-2-azabicyclo[2.2.1]heptane

In order to synthesise the last series of *syn*-derivatives, the ketone (**123**) was treated with the reducing agent sodium borohydride. Interestingly, the facial selectivity of borohydride attack of the ketone benzyl-protected gave a mixture of the *anti*-alcohol (**87**) in addition to the desired *syn*-alcohol (**124**). The epimer ratio was determined by ^{1}H NMR peak integration (6: 94), the crude product was purified using flash column chromatography in order to obtain the two epimers that were separable with difficulty and then fully characterized by ^{1}H NMR and 2D-NMR experiments. Analysis of the NMR data indicated that H_{3n} was identified by 'W' coupling to H_{7a} and no significant coupling interaction was seen between H_7 and H_4 confirming that the H_7 was *anti*- and the hydroxyl group was *syn*. Additionally, the physical state for (**124**) was solid which allowed crystal formation from diethyl ether and subsequent X-ray crystallography confirmed our assignments and made identification unambiguous (**Fig. 2.38**). Whilst, White needed to prepare the 3,5-dinitrobenzoate derivative of (**124**) to confirm the *syn*-configuration.

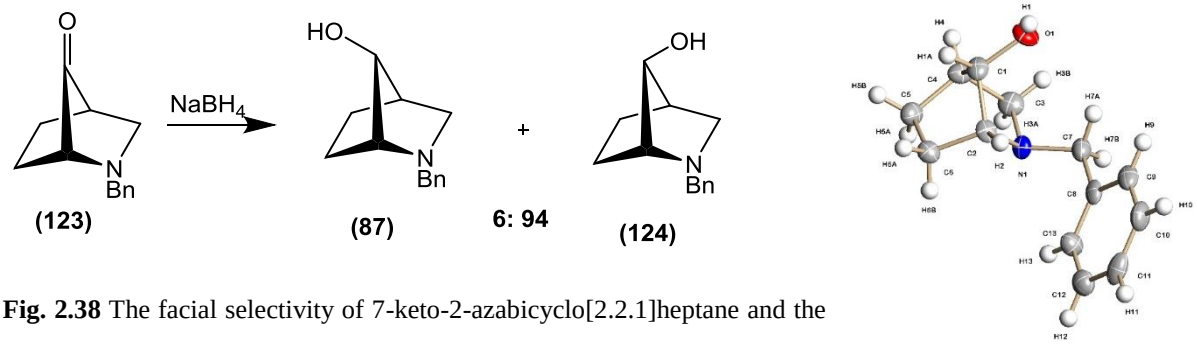


Fig. 2.38 The facial selectivity of 7-keto-2-azabicyclo[2.2.1]heptane and the X-ray crystal structure of *syn*- 7-hydroxy-2-azabiyclo[2.2.1]heptane.

The facial selectivity of nucleophilic attack on 7-keto-2-azabicyclo[2.2.1]heptane (**123**) has been investigated in more details by B. Pibworth at the University of Leicester with a range of reducing agents using Boc and Bn as protecting groups.[77] The preliminary findings of this study regarding found no significant changes in the epimer ratios when either Red-Al or $LiAlH_4$ is used instead of $NaBH_4$ (details summarised in Fig. 2.39). In contrast, in the case of treating the *N*-Boc protected compound (**125**) with $NaBH_4$, the results were 92:8 *anti*:*syn*. In this study, the epimer ratios have been accurately measured by GC-MS and GC; the *syn*-epimer cannot be detected in this study because of the broad overlapping ^{1}H-NMR signals.

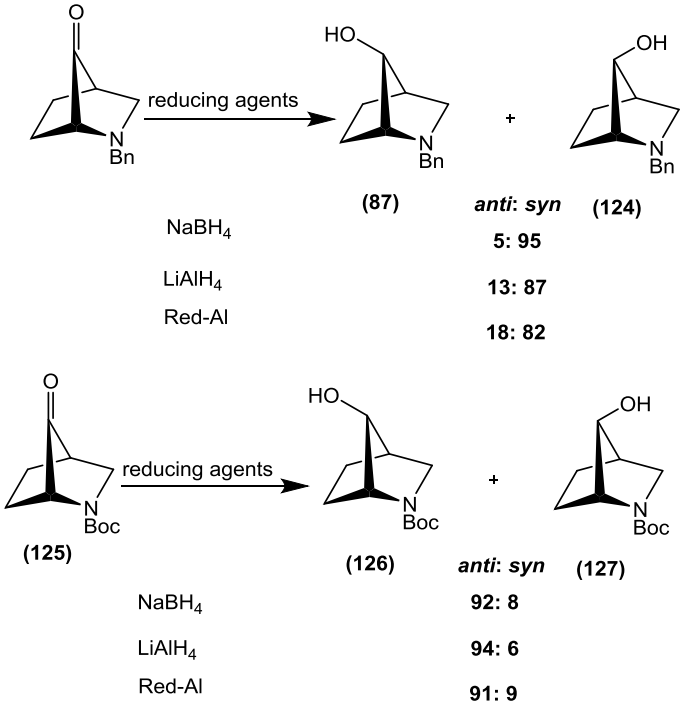


Fig. 2.39 Selected examples of the *anti*-face attack in the reduction of 7-keto-2-azabiclclo[2.2.1]heptane.[77]

In conclusion, the epimerisation of *anti*-7-hydroxy-2-azabicyclo[2.2.1]heptane (**87**) to the corresponding *syn*-7-hydroxy-2-azabicyclo[2.2.1]heptane (**124**) can be achieved by

oxidising (**87**), followed by reduction of the resulting ketone with sodium borohydride. Most notably, the selective attack on the *anti*-face of 7-keto-2-azabiclclo[2.2.1]heptane to the protecting group was considered to be most likely, but the opposite was found to occur with a carbamate protection group. Factors controlling the stereoselectivity in this reduction and the nature of the *N*-protecting group are discussed below.

2.16 Research on facial selectivity of the reduction in 7-norbornenones and related systems

In rigid systems, the facial selectivity of the attack on carbonyl functional groups has been investigated extensively and acts as an important stereoelectronic probe in numerous organic reactions.[125, 126] It has been reported that the $LiAlH_4$ reduction of 2-norbornanones can occur through intermolecular hydride attack (nucleophile) on the *exo* face of the ring system to give 2-hydroxynorbornanes *exo*- and *endo*-isomers in a ratio 9: 91, respectively (**Fig. 2.40**).[125]

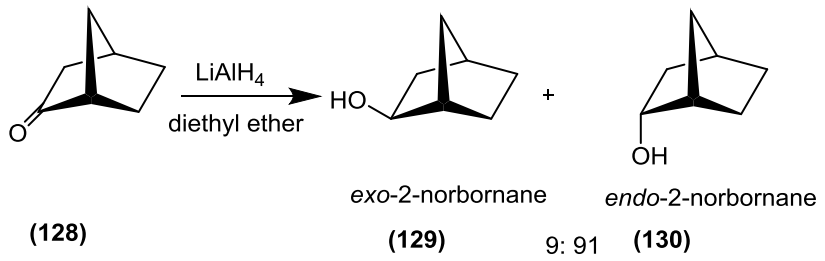


Fig. 2.40 Literature example of facial selectivity in 2-norbornenones.[125]

In further studies by Mehta, Le Noble and Giddings the facial selectivity of the reaction of 7-norbornanones *via* attack of either sodium borohydride or Grignard reagent (CH_3MgBr) on the face of the carbonyl functional group adjacent to the double bond of the rigid molecule has been well established, leading to alcohol (**133**) being the main product (**Fig. 2.41**).[127, 128, 129] These intriguing results have been interpreted in terms of steric factors; the presence of the double bound might provide less steric hindrance to nucleophilic attack than the *exo*-hydrogens on the opposite side of the molecule. Surprisingly, this result is reversed when the ketone (**131**) reacts with an organometallic reagent (C_2F_5MgBr), where it is clear that the face-selective reaction of (**131**) proceeds predominantly from the *syn*- face of the double bond to furnish a 96:4 mixture of alcohols, where this behaviour has been attributed in this instance to the electronic nature of the attacking anion on the carbonyl group.[126]

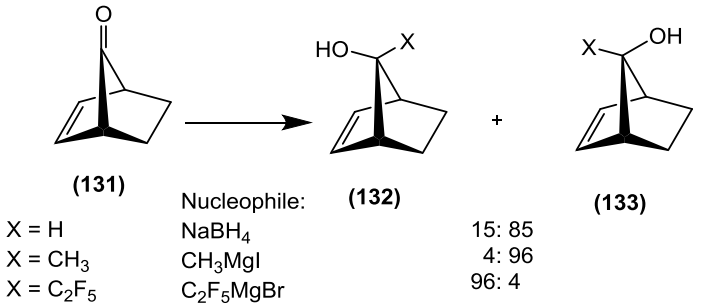


Fig. 2.41 Literature example of facial selectivity of 7-norbornones.[126]

A more notable variation in the facial selectivity regards the electronic *endo*-substituent effects on the C2 and C3 positions, as explored by Mehta *et al.* For instance, when (**134**) is treated with methyl lithium, the C2, C3 *endo*-substituted groups (R) – which can have no significant steric influence have electronic effects on facial selectivity (**Fig. 2.42**). Mehta *et al.* observed that when R_1 and R_2 = H, the preferred addition of the nucleophile is from the *anti*-face of the molecule to furnish (**135**) as the major product in a ratio of 74:26, with (**136**). When R_1 and R_2 = $COOCH_3$, which have an electron-withdrawing nature then the opposite is observed, predominantly furnishing (**136**) as the major product (*syn*-face attack). It may be noted that the long-range electronic substituent effects and ground state conformational stability probably effect facial selectivity in nucleophilic carbonyl additions through hyperconjugative stabilisation of the transition state. However, there is still a great deal of debate as to how these many factors combine to influence facial selectivity.[130]

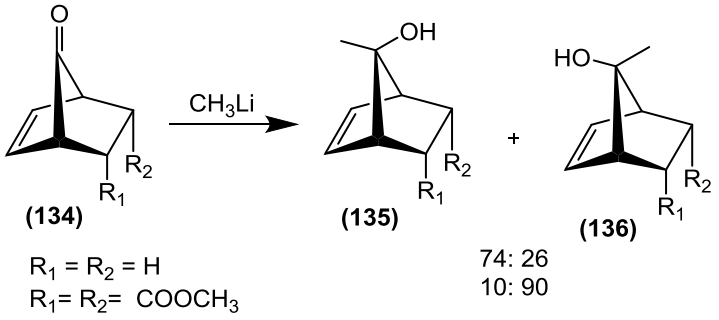
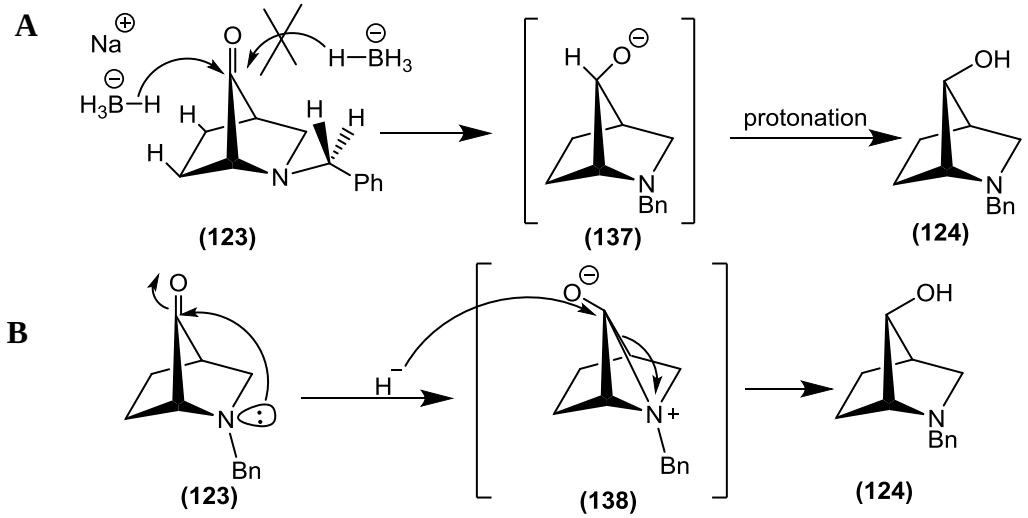


Fig 2.42 Literature example of facial selectivity of C2, C3 *endo*-substituted 7-norbornenones.[127]

2.16.1 Discussion of facial selectivity in 7-keto-2-azabicyclo[2.2.1]heptane

The University of Leicester has experience in the facial selectivity of 7-keto-azanorbornanes *via* White,[77] the first system was examined with the *N*-benzyl-protected ketone (**123**), giving some indication for the selectivity observed in this system, which was the mirror image of our work. Sodium borohydride and other reducing agents

introduce the hydride anion which attacks the carbonyl group (**123**) *anti* to the *N*-benzyl protecting group. The developing negative charge on the oxygen is protonated by the alcohol (a protic solvent); the negative ion formed (**137**) is protonated to give the corresponding alcohol (**Fig. 2.43 A**). The first reasonable explanation is simply one of a steric argument. Malpass *et al.* attempted to determine the invertomer ratio of 2-azanorbornane using NMR,[131] where according to this study the configuration of the *N*-alkyl protecting group in 2-azanorbrnane can be assumed to be *endo* or *exo*; the study revealed that the *exo* invertomer was found to be more thermodynamically stable than the *endo* invertomer, and hence the former predominates at equilibrium. Further kinetic protonation experiments have been undertaken by White in the hope of determining the invertomer ratio of (**123**), but the results were disappointing. Attempts to add trifluoroacetic acid to the NMR sample of (**123**) led to an ambiguous spectrum with a lot of overlapping signals, making it impossible to determine an accurate peak integration, from which it was deduced that there is one predominant invertomer (> 80-90%). Another attempt was made using low temperature NMR (-60 ^{o}C), but again the spectra of each of the invertomers could not be separately resolved. Nevertheless, logical thinking suggests that the *exo* invertomer will be the major product, hence it is clear that the reaction with attacking nucleophiles will proceed predominantly *via* the sterically accessible *anti*-face of the ketone. Another explanation, the presence of neighbouring group participation (NGP) could explain the *anti*-face attack. The nitrogen lone pair has the ability to overlap with the centre of an *anti*-7-nucleofuge (see section 2.6) in the same way that nitrogen lone pair participation in the ketone led to the tricyclic intermediate (**138**); hydride attack on (**138**) would then produce (**124**) (**Fig. 2.43 B**).



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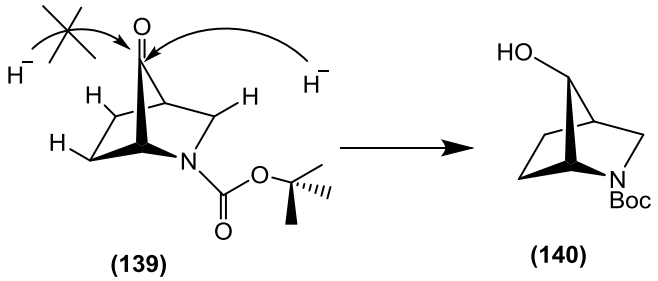


(139) **(140)**

Fig. 2.43 Proposed explanations for *anti*-face selectivity in 7-keto-2-azabicyclo[2.2.1]heptane.

White also investigated the influence of the *N*-Boc group in 2-azabornane in facial selectivity. Once more, a steric argument can be established, because the carbamate group is planar due to electron delocalisation, and thus nucleophilic attack on 7-keto-2-Boc-azabiyclo[2.2.1]heptane takes place from the *syn*-face of the molecule as it is more sterically accessible (**Fig. 2.43 C**). In addition, the carbamate group will coordinate with the hydride, increasing the probability of *syn* attack. Furthermore, Mehta *et al.* noted that the electron withdrawing nature of the substituents on the C2 and C3 of 7-norbornenones could increase the chance of *syn* attack (**Fig. 2.42**)[127] This would be similar in manner to 7-keto-2-Boc-azabiyclo[2.2.1]heptane.

In summary, the most important features that control the stereochemistry of 2-norbornenones and 7-keto-2-azabicyclo[2.2.1]heptane have been investigated. These features constitute an effective and convenient set of explanations for intermolecular hydride attack on the carbonyl group of both 2-norbornenones and 7-keto-2-azabicyclo[2.2.1]heptane but with some complexity, so further investigation is required to understand the remaining issues.

2.17 Synthesis of pyridyl ethers derivatives of *syn*-7-hydroxy-2-azabicyclo[2.2.1] heptane

The following section will discuss the formation of pyridyl ether derivatives of *syn*-7-hydroxy-2-azabicyclo[2.2.1]heptane, namely (**142**) and (**144**), by using similar methodologies to those described for the formation the *anti*-derivatives (see sections 2.91 and 2.9.2). These have 2- and 4-pyridine heterocycles attached to the *syn*-7-position of 2-azabicyclo[2.2.1]heptane, which can be obtained in a straightforward manner; we faced difficulties in attaching the 3-pyridine heterocycle to the *syn*-7-position, which required some changes in order to overcome some of the problems associated with the stereochemistry of the *syn*-7-position.

2.17.1 Synthesis of targets (142) and (144)

Only (**141**) and (**143**) were synthesised by nucleophilic substitution of the chloride from 2-chloropyridine and 4-chloropyridine hydrochloride utilizing the base NaH and KO^{t}Bu, obtaining moderate yields of 53% and 72%, respectively (**Fig. 2.44**). Interestingly, the removal of the benzyl group of (**141**) occurred smoothly in very good yield (86%) whereas, in contrast with (**143**), the debenzylation was carried out successfully in an acidic medium by adding glacial acetic acid 20% prior to work-up and monitoring the reaction *via* TLC and ^{1}H-NMR (to understand the role of the acid, see section 2.9.2). This gave the required *N*-benzyl deprotecting nitrogen product (**144**) in a reasonable yield of 68%. The ^{1}H-NMR spectrum of (**142**) showed evidence of all the characteristic signals of the 2-azabicyclo[2.2.1]heptane framework; a multiplet for H_5, H_6 and H_{3n}, broad singlets for H_4, H_1 and H_7, and a broad doublet of doublets for H_{3x}. Also, the spectrum showed the proton signals arising from the pyridine ring; a doublet of doublets for $H_{3`}$ and $H_{6`}$, and a doublet of doublets of doublets for $H_{5`}$ and $H_{4`}$ all at distinctive chemical shifts.

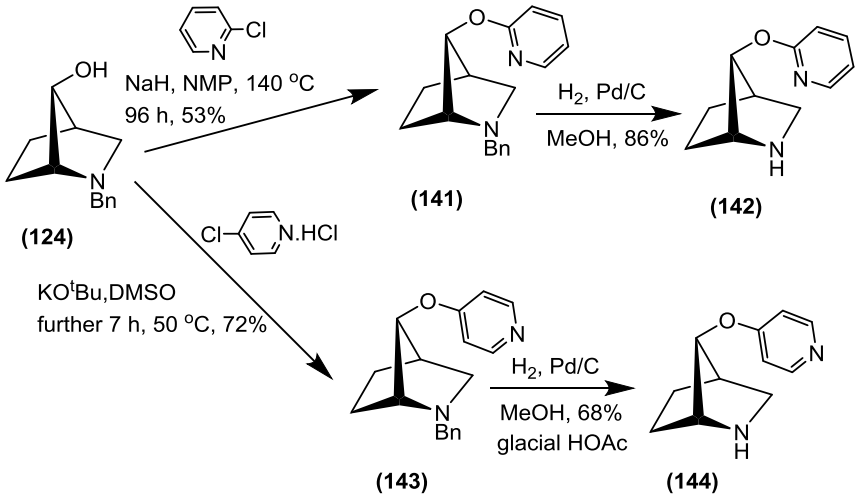
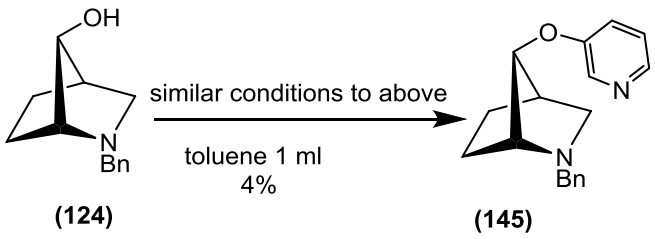


Fig. 2.44 Synthetic approaches to pyridyl-ether ligands of *syn*-7-hydroxy-2-azabicyclo[2.2.1]heptane.

2.17.2 Approaches to synthesis of 3-pyridyl derivatives of *syn*-7-hydroxy-2-azabicyco[2.2.1]heptane

Nucleophilic displacement has been found to make it difficult to achieve the *anti*-3-pyridyl derivative (**108**) because the 3-position of pyridine ring is not reactive towards the nucleophiles. Thus, an alternative methodology was attempted to gain the *syn*-3-

pyridyl derivatives (**145**). Buchwald *et al.* demonstrated the coupling of aryl iodides with aliphatic alcohols *via* a copper-catalysed system.[132] This work described the coupling of 3-iodopyridine to isopropyl alcohol to generate the alkyl aryl ether in excellent yield (92%). This method was applied with the neat alcohol used as a solvent in high concentrations (2 equivalents) and these was not found to be practical (**Fig. 2.45**). Buchwald *et al.* found that the method become more efficient when toluene was used as solvent in small amounts (0.5 ml/1 mmol substrate) in order to maintain a highly active catalytic system. Thus, the methodology has been adopted for the synthesis of *syn*-3-pyridyl derivatives, which involves four equivalents of *syn*-alcohol (**124**) with a small volume of toluene (1 ml) as a solvent. This heterogeneous mixture was stirred for four days at an elevated temperature of 110 ^{o}C to give (**145**) in very low yield (4%), which was difficult to recover from the starting material. Compound (**145**) was confirmed by the absence of an alcoholic peak both in its ^{1}H-NMR and IR spectra, and accurate mass spectroscopy indicated a molecular weight of 281.1658 g/mol [MH^{+}].



(124) **(145)**

Fig 2.45 Copper-catalysed coupling of the pyridine ring.[132]

Further work was completed by Wei *et al.* to synthesise more selective nicotinic ligands with the introduction of the bromide ion at the C5 position of the pyridyl ring. In this reaction 3,5-dibromopyridine was used as a reagent with two bromide atoms substituted onto the C3 and C5 of the pyridine ring, making these sites more active towards the nucleophilic substitutions that would take place; the alcohol (nucleophile) will attack the 3,5-dibromopyridine and as a result the 5`-position will be available. Herein, this method has been adopted to synthesise (**146**), where the *syn*-alcohol was treated with 3,5-dibromopyridine and sodium hydride, after which the reaction mixture was stirred for 6 hours at 50 ^{o}C to obtain (**146**) in a 25% yield (**Fig. 2.46**).[112] Accurate mass analysis confirmed the expected relative mass of (**146**) (359.0764 [MH^{+}]). The compound was characterised by ^{1}H-NMR spectroscopy that showed evidence of all the characteristic signals of the 2-azabicyclo[2.2.1]heptane system; multiplets for H_5, H_6 and Ph at 1.36-

1.78 δ and 7.10-7.25 δ, respectively, a broad singlet for H_4, H_1 and H_7 at 2.38 δ, 3.24 δ and 4.35 δ, respectively, a doublet for H_{3n} at 2.60 δ, a doublet of triplets for H_{3x} at 3.04 δ, and a AB system for CH_2Ph at 3.79 δ. It also shows a multiplet for each of the pyridyl protons signals at 7.34-7.36 δ and 8.18-8.24 δ, respectively.

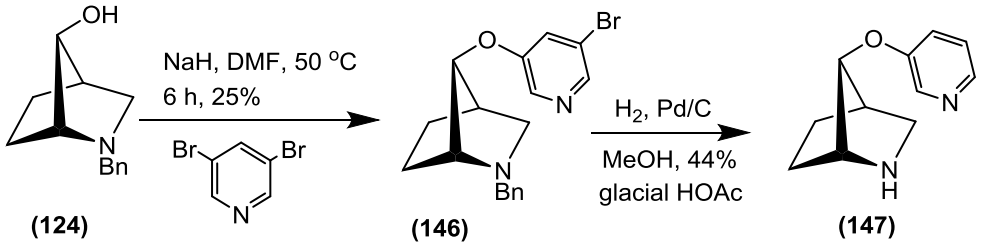


Fig. 2.46 Synthesis of 3-pyridyl-ether ligand of *syn*-7-hydroxy-2-azabicyclo[2.2.1]heptane.

Removal of the *N*-benzyl protecting group was carried out by acidifying the reaction mixture in order to facilitate debenzylation. Bizarrely, the ^{1}H-NMR and mass spectrum of the product revealed the absence of the bromine atom from the pyridyl ring suggesting that it was reduced under hydrogenolytic conditions; the *syn*-3-pyridyl product (**147**) was produced in a 44% yield, which was a similar outcome to White.

2.17.3 Attempts to synthesise the *syn*-3-isoxazole derivative (148)

Previous work has described the successful synthesis of the *anti*-3-isoxazole derivative (**121**) by applying the Mitsunobu coupling reaction. The possibility of incorporating the 5-methyl-3-isoxazolol with the *syn*-alcohol (**124**) in a similar method (**Fig. 2.47**) was considered. The reaction was attempted by changing the temperature and extending the reaction time in the hope of attaining the product, but unfortunately there was no evidence in the associated ^{1}H-NMR spectrum and mass analysis of the expected compound. It is likely that only the Mitsunobu coupling reactions of the *anti*-alcohol (**87**) were enabled by neighbouring group participation of the lone-pair of the bicyclic nitrogen (see section 2.12).

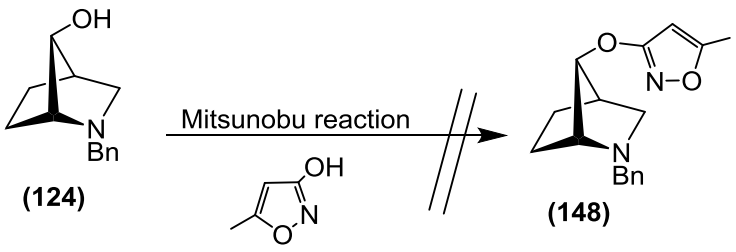


Fig. 2.47 Attempt to synthesise the *syn*-isoxazole derivative.

To summarize, the basic methodology of our route has established the functionalisation of the 7-position of the 2-azabicyclo[2.2.1]heptane ring system. We have demonstrated that the nucleophilic displacement reactions of *anti*-7-bromo-2-azabicyclo[2.2.1]heptane (**85**) are possible with such a rigid molecule with complete retention of the configuration. An oxidation-reduction protocol has been applied, which enabled the epimerisation of the *anti*-alcohol (**87**) to the *syn*-alcohol (**124**). Both alcohols underwent appropriate procedures in order to access their *anti*- and *syn*-derivatives. The successful synthesis of the 5-methyl-3-isoxazolol ring was expected to allow the incorporation of the heterocyclic substituent, giving the *anti*-3-isoxazolol derivative.

Chapter 3

Fluorinated analogues of 2-azabicyclo[2.2.1]heptane system

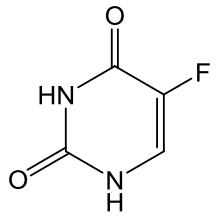
3.1 Fluorine in medicinal chemistry

A series of epibatidine analogues containing fluorine atom have been created in the hope of reducing toxicity but maintaining high antinociceptive activity. Despite that fluorine is largely absent in natural products and biological process, it still plays an important role in pharmaceuticals and agrochemicals, in addition to material science. Herein the question arises, why the fluorine atom? Fluorine is one of the smallest atoms in the periodic table with a very high electronegativity, which gives a large number of drugs containing one or more such atoms unique chemical properties. Fluorinated compounds can potentially affect a number of variables, such as the pKa of neighbouring groups, particularly by altering the acidity and basicity of substituted groups within the molecule. Another impact is represented by the associated dipole moment, lipophilicity, metabolic stability, and bioavailability.[133]

The inclusion of a fluorine atom can modify the drug disposition in terms of electron distribution, which results in effects on absorption and metabolism. Additionally, presenting a fluorine atom at the site of a metabolic attack of a drug molecule can affect the lifetime of a drug by increasing its metabolic stability through retarding oxidation by cytochrome P450 enzymes (liver enzymes).[134] Furthermore, the presence of fluorine close to a basic group reduces its basicity, and will improve the lipophilicity of the drug, resulting in better penetration of cell membranes, and thus increased bioavailability.[135] As above, a change in pKa has a strong effect on its binding affinity (ligand-protein interactions) which in turn affects bioavailability by changing the polarity of the molecule.[135]

3.2 Fluorinated epibatidine analogues

A range of fluorine-containing drugs have been synthesised. For example, 5-fluorouracil (**149**) has been used widely in the treatment of a range of cancers, the mechanism of its action as an anticancer agent being based on the inhibition of thymidylate synthase, which is an enzyme used as a target in cancer chemotherapeutic agents. Over the past 30 years, an increased understanding of the significant antitumor inhibiting activity of 5-FU has led to the development of this area of research to produce more effective chemotherapy and tumour-selective analogues.[136]



5-Fluorouracil (149)

Further work completed by Dolle *et al.* has included different epibatidine analogues containing fluorinated heterocycles, and the synthesis of an ^{18}F-labelled derivative used in Positron Emission Tomography (PET) as radiotracers also has been documented. Currently PET is an advanced technology that produces a three-dimensional image of functional processes *in vivo*. It is widely used for studying the binding affinity of agonists and antagonist to receptors in various CNS disorders (see section 1.6.1).[137, 138]

There are few derivatives of epibatidine with a fluorinated norbornane core that have been produced. For example, it has been postulated that the introduction of a polar group such as a hydroxyl might improve binding affinity and subtype selectivity.[139] Moreover, these hydroxylated epibatidines have been extended to give the fluorinated compounds (**153**) and (**154**) (**Fig. 3.1**). A reductive Heck coupling strategy was used in the synthesis *via* coupling of the chloropyridyl moiety with (**150**) to give the ketones (**151**) and (**152**). There were subsequent by converted to the corresponding alcohols using $NaBH_4$, followed by reaction with DAST to introduce the fluorine substituent. Finally, de-protection of the secondary amine with TFA, generated the 5-*exo* and 6-*exo* fluorine-substituted epibatidine analogues.[139, 140]

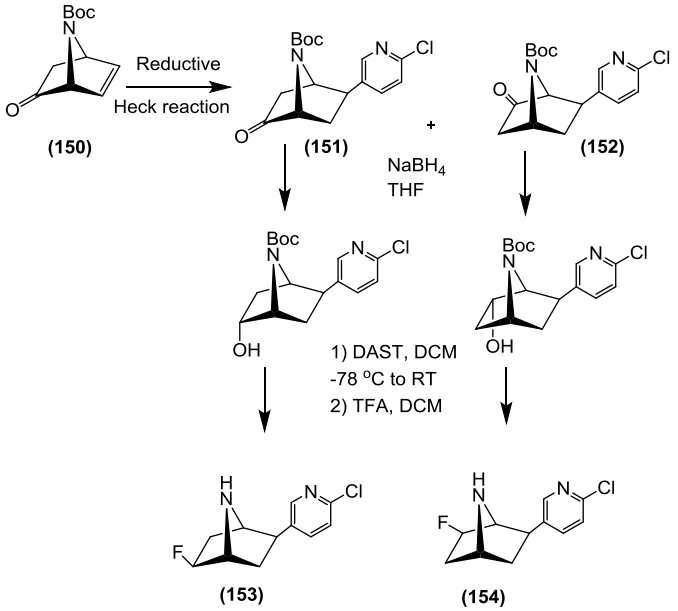
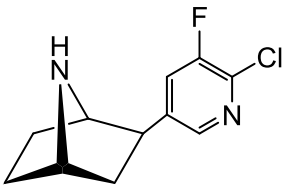


Fig 3.1 Literature example of synthesis of 5-*exo*- and 6-*exo*- fluorinated analogues of epibatidine.[139, 140]

The binding affinity studies of (**153**) and (**154**) at the α2β2, α2β4, α3β2, α3β4, α4β2 and α4β4 receptor subtypes were found to be very high for all receptor subtypes. Due to a high binding affinity for both compounds, the researchers indicated that they were planning to explore these compounds in brain imaging (PET).[140]

Research has been done by Abdrakhmanova *et al.* to introduce an analogue of epibatidine in which there is a fluoro substituent at the 3`-position of pyridine ring. Biological tests of this molecule on the three nACh receptors α4β2, α3β4 and α7 have revealed that this unique structure led to an increase in efficacy in binding to α4β2 versus α3β4 nAChRs, and significantly improved selectivity. Interestingly, compound (**155**) has been found to behave as a full agonist on the α4β2 receptor, in contrast with epibatidine which has been found to be only a partial agonist on the same receptor.[141]



(155)

The multitude of effects that have been mentioned above means that epibatidine specialists in the field of fluorine chemistry have been actively investigating methods to

incorporate fluorine into small organic molecules for many years. Furthermore, commercially available fluorine sources and the successful progress of bench stable reagents has brought the expansion of fluorine chemistry into the organic synthesis community, which has further led to an acceleration in the discovery of new fluorination methods, and consequently in methods for the asymmetric introduction of fluorine.[133,142,143] Finally, asymmetric synthesis (enantioselective) using catalytic methods is an important method by which to achieve pharmaceuticals, for each enantiomer of a molecule can have a different biological activity.

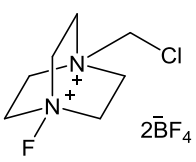
3.3 Background to fluorinating agents

During this century, the progress in introducing the fluorine atom into organic molecules has been slow because of the challenges associated with the reactivity profile and hazards associated with the use of elemental fluorine and hydrogen fluoride. Despite these problems, some remarkable breakthroughs have emerged, where synthetic chemists have sought to develop specialised fluorination technologies and reagents. In 1896, methyl fluoroacetate was synthesised by reacting methyl iodoacetate with silver fluoride, the synthesis of which heralded the beginnings of modern fluoro-organic chemistry.[144] Generally, two main types of fluorinating agents have been developed, nucleophilic and electrophilic donors, which are good source of the ionic forms of fluorine; nucleophilic reagents donate F^- and electrophilic reagents donate F^+.

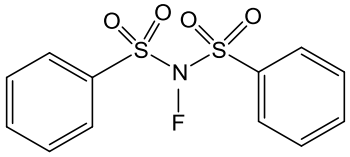
3.3.1 Electrophilic fluorinating reagents

Commercially, there are a few examples of highly oxidizing fluorinating reagents available, such as hypofluorite, fluorine gas and fluoroxysulphates. However, these have proved to be challenging to use because of being strong oxidising reagents and having a high toxicity which has prevented their reactions from being performed without appropriate precautions and specialised equipment.[133] The next breakthrough in electrophilic fluorination was the discovery of easily handled and much safer alternatives to the reagents used previously with structures such as Selectfluor (**156**) and *N*-fluorobenzenesulfoimide (NFSI) (**157**). These reagents have also shown a small amount of selectivity towards certain compounds, while with the previous reagents this selectivity could not be achieved at all. Additionally, NFSI allows the fluorination of carbanionic nucleophiles and neutral molecules ranging from slightly activated aromatic derivatives to strong reactive vinyllithium and aryl compounds in good yields.[133] Selectfluor's

properties include the fact that it is a commercially available, easy to handle, transportable, site-selective fluorinating agent which is a less toxic, less aggressive electrophilic fluorinating reagent, and is a high melting point solid which is soluble in polar solvents such as water and acetonitrile.[145, 146]



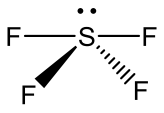
Selectfluor
(156)



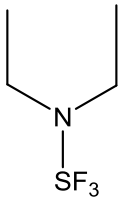
N-fluorobenzene-sulfoimide (NFSI)
(157)

3.3.2 Nucleophilic fluorinating reagents

The fluoride anion F^- is the least nucleophilic of the halides because of its small size and therefore low polarizability. However, replacement by fluorine in alkyl halides can be achieved using the F^- anion. In the past, workers in the field of fluorine chemistry have used hydrogen fluoride and simple fluoride salts, such as potassium and sodium fluoride as a source of F^-.[144, 147] Nevertheless, despite the dual reactivity profile and the low solubility of the fluoride anion, some remarkable breakthroughs regarding nucleophilic fluorinating reagents have emerged.[142] Sulphur tetrafluoride (**158**) has been synthesised to be a selective fluorinating reagent which can be used in conjunction with a Lewis acid activator or liquid HF to convert alcohols and the carbonyl products to the respective mono- and difluorinated compounds.[145, 146]



Sulfur tetrafluoride
(158)



(DAST)
(159)

Another example of a nucleophilic fluorinating reagent is diethylaminosulphur trifluoride (DAST) (**159**) which is a mild reagent, highly volatile, easily to handle, bench-stable and commercially available. DAST is useful in the conversion of hydroxyl groups to aliphatic alcohols to fluorine in good yields.[148, 149] The mechanism proceeds *via* nucleophilic attack of the alcohol onto sulphur from which fluoride is released, which in turn can act as a

nucleophile to replace the activated hydroxyl group (**Fig. 3.2**), with the ensuing inversion (S_N2) or cationic rearrangements (S_N1) being dependent on the structure of the substrate.[150]

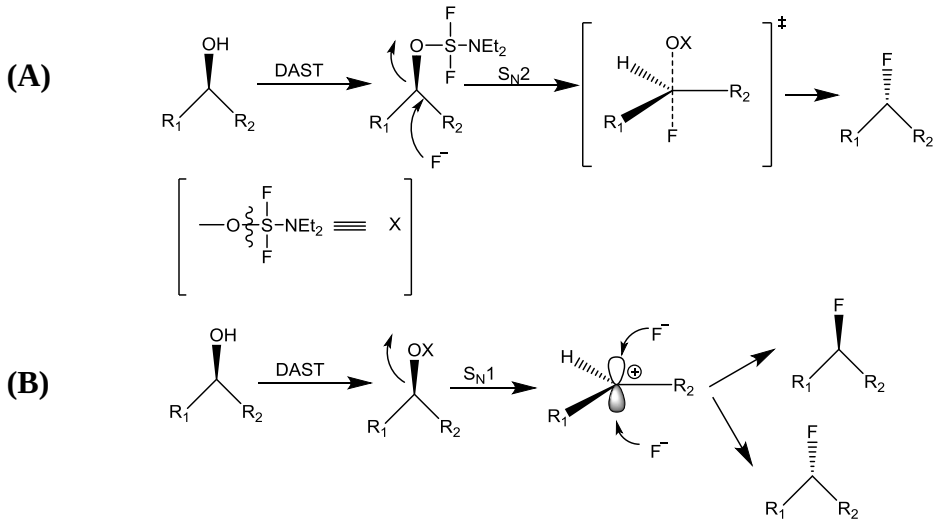


Fig. 3.2 The two pathways of nucleophilic fluorination using DAST (**158**), **(A)** one single compound with inversion of stereochemistry **(B)** a mixture of compounds with retention and inversion of stereochemistry (S_N1).

DAST has also been found useful in converting carbonyl groups in aldehydes and ketones into geminal difluorides.[151] Furthermore, the stereoselective access to vicinal difluoroalkanes has been investigated, which proceeds in two steps: epoxide ring-opining with hydrogen fluoride, whilst the second step is treatment of the resultant fluorohydrin with DAST.[152] Over the last few years, DAST has become very widely employed for the introduction of fluorine into sugar molecules in order to probe the metabolism of drugs.[144, 153]

3.4 Deoxyfluorination of 2-azanorbornane with DAST

The concept of neighbouring group participation through the lone pair of nitrogen in the displacement of a leaving group (see section 2.6) is expected to make a remarkable contribution to the fluorination of 2-azanorbornane with a hydroxyl functionality at the 6-*exo*-position using DAST. It is noteworthy that this project uses DAST as the fluorinating reagent (source of nucleophilic fluorine). It should be noted that if R = H, the final product shows complete retention of its configuration (blue arrows) and the fluorination reaction occurs *via* rearrangement (red arrows) with (NGP and S_N2 resulting in overall retention of configuration (**Fig. 3.3**). Whilst, if R = chloropyridine (bioisosteric ring), the bridgehead will change from C7 to C5 to achieve *syn*-isoepibatidine (**40**) (rearranged product).

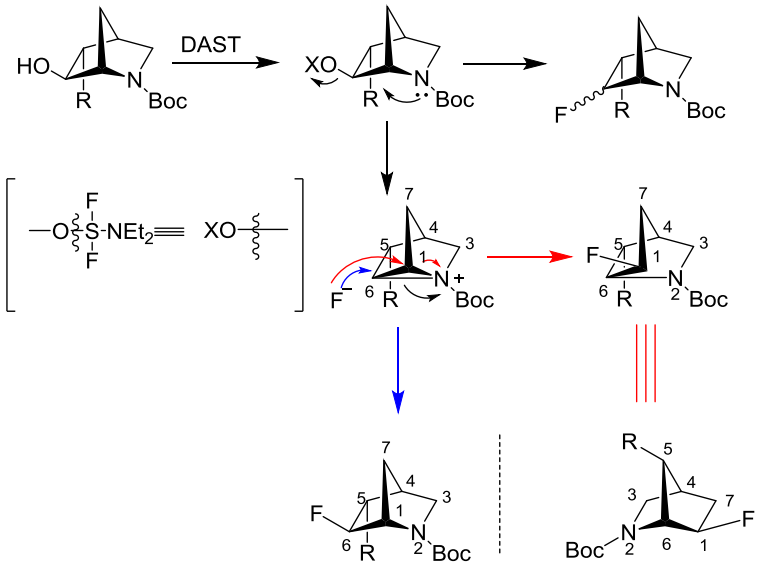


Fig. 3.3 Predicted mechanism of 6-exo-2-azabicyclo[2.2.1]heptane with DAST (**158**).

3.5 Retrosynthetic analysis

A first set of six oxygen-containing products as shown in (**Fig. 3.4**) was designed. To gain access to those compounds, a retrosynthetic analysis on one of these targets was conducted to choose the most efficient methodology and starting materials; this retrosynthetic analysis is outlined in (**Fig. 3.5**).

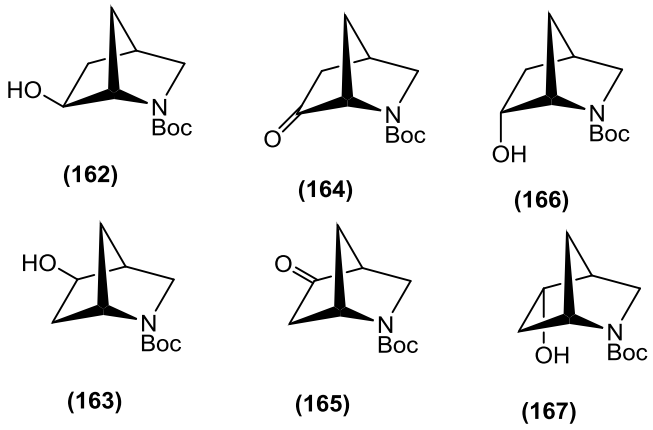


Fig. 3.4 The fluorination of the first set (six hydroxyl-containing compounds) which is investigated in this chapter**.**

The first step in the analysis is the Diels-Alder reaction using cyclopentadiene (**74**), which is the most commonly employed protocol for norbornanes and related systems,[154, 155] where (**74**) undergoes a 4π + 2π cycloaddition with an imine chloride to form the azabicyclic template (**160**). The analysis shows that after a series of hydroboration/oxidation steps, through the oxidation/reduction strategy the six intermediate compounds can be achieved from precursor (**161**). Also, it has been shown that the applicability of the hydroboration/oxidation protocol performed can generate only one set of intermediates with the hydroxyl functionalities at the 5- and 6-position, even though this pathway is non-regioselective in our system.

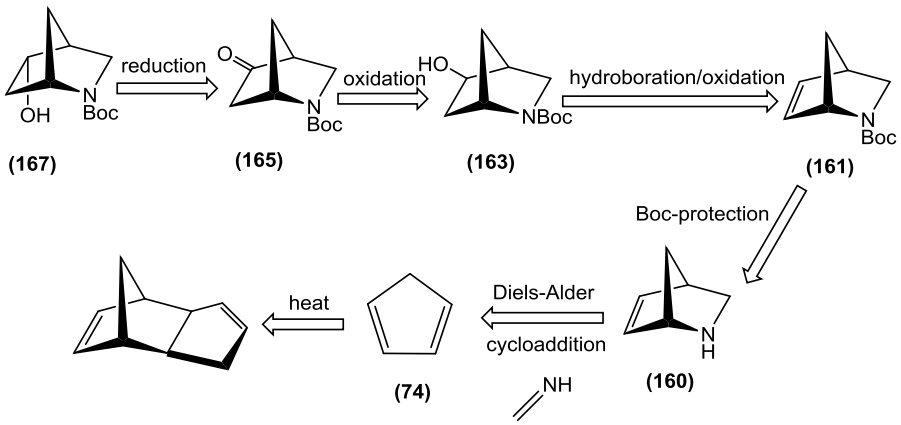


Fig. 3.5 The retrosynthetic analysis of the 2-Boc-5-*endo*-hydroxy-2-azabicyclo[2.2.1]heptane**.**

3.6 Our synthetic routes to epibatidine analogues

The experimental routes to the synthesis of 2-Boc-2-azabicyclo[2.2.1]heptane (**161**) have been adapted from the Grieco protocol (as shown in Fig. 2.3). Treatment with ammonium chloride in formaldehyde occurred smoothly, leading to the synthesis of the bicyclic

amine (**160**) over 48 hours stirring at RT as the HCl salt. The free amine was obtained by neutralisation with sodium hydroxide in a low yield of 30% after a few attempts. These results suggested that dimerization of cyclopentadiene (**74**) to dicyclopentadiene is a side reaction that occurs which resulted in the drop the yield of (**160**) (**Fig. 3.6**). This reaction is based on a literature procedure where the yield has been reported after optimization as 47% by carrying out the reaction at 4-6 ºC for 64 hours.[156]

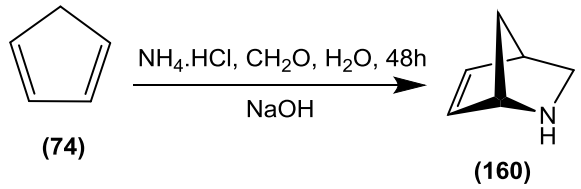


Fig. 3.6 Formation of 2-azabicyclo[2.2.1]hept-5-ene (**160**).

Theoretically, in this reaction there are two pathways that occuring equally, leading to two forms of the product. Nevertheless, only one product can be observed, and (**160 a**) and (**160 b**) are actually enantiomers and therefore have identical ^{1}H-NMR signals (**Fig. 3.7**). All enantiomers have been synthesised in this project, including (**16 a**) and (**16 b**) which were not separated; on this basis, all compounds will be racemic mixtures. The reasoning for not resolving enantiomers is that it is not necessary to investigate the concept of neighbouring group participation taking place during the fluorinating step (more details in section 2.6).

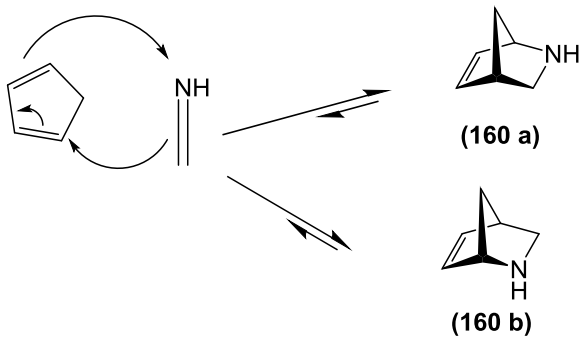


Fig. 3.7 The 4π + 2π Diels-Alder cycloaddition to form a racemic mixture.

The crude product was a yellow oil and, upon characterisation by ^{1}H-NMR, was found to be sufficiently pure to be used in the next step without further purification.

Due to the reactive nature of the secondary amine, the free amine was protected with di-*tert*- butyl dicarbonate or a Boc group.[157]Additionally, the purpose of the protection process is to retain the amine functionality of (**160**) but suppress undesired side reactions

which could be induced in subsequent steps. The reaction was based on the unpublished work of a project student.[156] The protection reaction was carried out under basic conditions at RT for 27 h and the product purified by flash chromatography to produce (**161**) in a reasonable yield of 48% (**Fig. 3.8**). This result was significantly less than those documented in literature, which was 91%.[157]

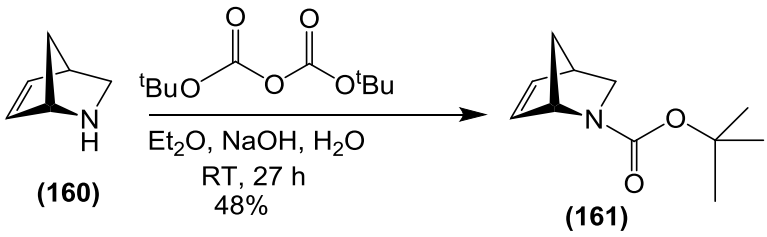
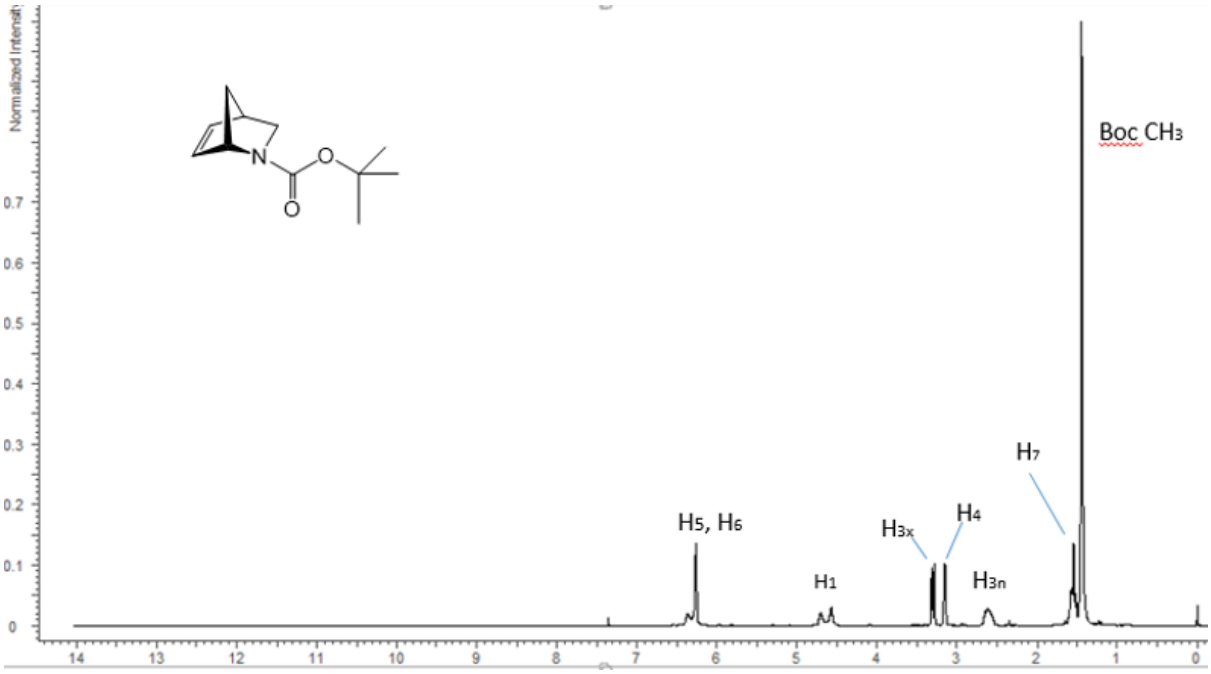


Fig. 3.8 Synthesis of 2-Boc-2-azabicyclo[2.2.1]hept-5-ene.

The ^{1}H-NMR spectrum of (**161**) (**Fig. 3.9**) revealed the presence of two rotamers in a ratio of (~ 41:59) which was measured by integration of the signals for the two rotamers. Thus, some signals in the ^{1}H-NMR spectra appear to be doubled due to restricted C-N bond rotation in the carbamate protecting group on the nitrogen.

Fig. 3.9 ^{1}H-NMR signals for (**161**).



3.7 Synthesis of alcohols (162) and (163)

In order to establish the methodology to gain access to the two hydroxyl-containing compounds (**162**) and (**163**), the hydroboration/oxidation reaction was first attempted with the alkene (**161**).[158] The hydroboration/oxidation reaction is commonly used in organic chemistry to efficiently convert an alkene into an alcohol. It is known to be an *anti*-Markovnikov reaction, with the hydroxyl group attaching to the less-substituted carbon of the reacting olefin and often shows high regioselectively. The big challenge in this step is that although alkene (**161**) is not symmetrical, being 1, 2-disubstituted control of the regiochemistry will be difficult. It is likely that the reaction will be non-regioselective leading to both (**162**) and (**163**), which means the both ends have an equal chance of forming alcohols (**162**) and (**163**) (see Fig. 3.10).

The borane-tetrahydrofuran complex was chosen for the hydroboration step, where the reaction was carried out under dry conditions at -78 ^{o}C, after which the temperature was allowed to warm to 0 ^{o}C. After three hours, the reaction mixture was quenched by water and sodium hydroxide solution in order to destroy any excess reagent. A mixture of sodium hydroxide and hydrogen peroxide was then used in the oxidation step, in which C-B bonds are oxidised to C-O bonds and which produced the alcohols. Interestingly, the lack of regioselectivity of this reaction is due to the fact the double bond although not

symmetric, is nevertheless 1,2-disubstituted, making the two regiomers equally likely. There is however some stereocontrol in that the *exo*-alcohols (**162**) and (**163**) are preferentially formed (**Fig. 3.11**).

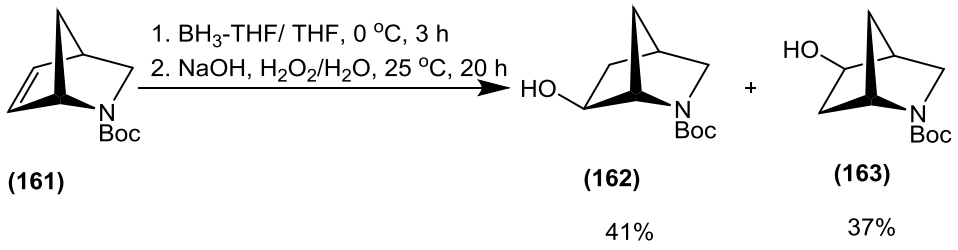


Fig. 3.10 The overall synthesis of 6-hydroxy-*exo*- and 5-hydroxy-*exo*-2-azabornane.

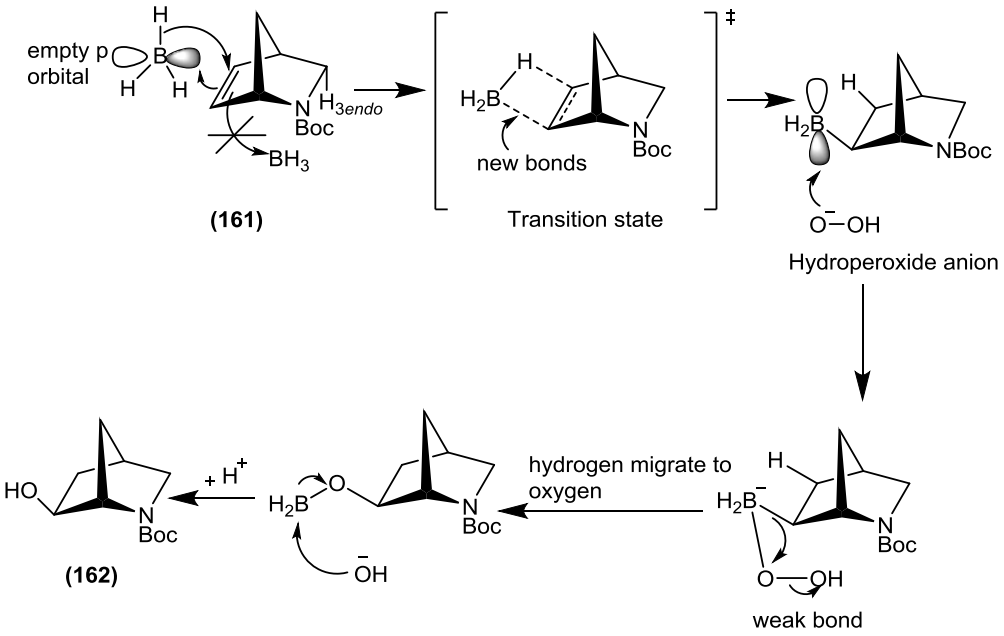


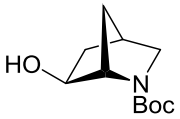
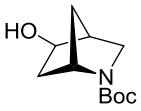
Fig. 3.11 The hydroboration/oxidation mechanism of (**162**); an identical mechanism can be suggested for the synthesis of (**163**).

The alcohols were separated on the column. The isolated alcohols (**162**) and (**163**) were each produced as a white solid in 41% and 37% yields for the 6-*exo* and 5-*exo*-compounds, respectively, confirming the reaction is non-regioselective. Furthermore, when the sodium perborate tetrahydrate was used as an oxidising agent in the oxidation step instead of hydrogen peroxide, the yields of both isolated isomers were found to be higher than those reported in the literature, at 24% for (**162**) and 19% for (**163**).[155]

Both (**162**) and (**163**) were observed as two rotamers by ^{1}H-NMR in a ratio of ~50: 50, (determined by the integration of the rotameric signals, H_1) and fully characterised by ^{1}H-

NMR and ^{1}H-^{1}H COSY. The signal H_{5n} for (**163**) was identified by 'W' coupling to H_{7s} and no significant coupling interaction has been seen between H_5 and H_4 confirming that H_5 was the *endo*-configuration and the hydroxy group was in the *exo*-configuration. Also, NOESY NMR spectroscopy was used to determine the nuclei that are close in space and hence whether the compound has an *exo*- or *endo*-stereochemistry. The spectrum shows a strong nOe (nuclear Overhauser effect) between H_{5n} and H_{6n}. This determined the stereochemistry to be *exo*-configuration from these proton correlations and from the ^{1}H-NMR.

Table 1: ^{1}H-NMR signals

	 **(162)**	 **(163)**
Signal	δ (ppm)	δ (ppm)
H_1	4.02 and 4.06 brs	4.13 and 4.25 brs
H_{3exo}	3.11-3.16 m	3.18-3.21 m
H_{3endo}	2.77 and 2.48 brs	280 and 2.87 d
H_4	2.51 brs	2.45 brs
H_{5exo} and Boc CH_3	1.44 and 1.46 brs	4.03 (H_{5exo}) d
H_{5endo}	1.49-1.57 brs	-
H_{6endo}	3.95 brs	2.01-2.08 m
H_{6exo}	-	1.46-1.47 m
H_{7a}	1.80-1.88 m	1.52-.58 m
H_{7s}	1.47-1.76 m	1.73-1.82 m
Boc CH_3	-	1.45 brs

3.8 Synthesis of the alcohols (168) and (167)

Initially we sought to establish the methodology to gain access to the two last compounds where the hydroxyl groups were in the *endo*-configuration (**Fig. 3.11**). The ketones (**164**) and (**165**) were synthesised from (**162**) and (**163**) as described in section 4.3 and we then employed a procedure by which to reduce ketones to the corresponding *endo*-alcohols (**166**) and (**167**) as shown in (**Fig. 3.9**).

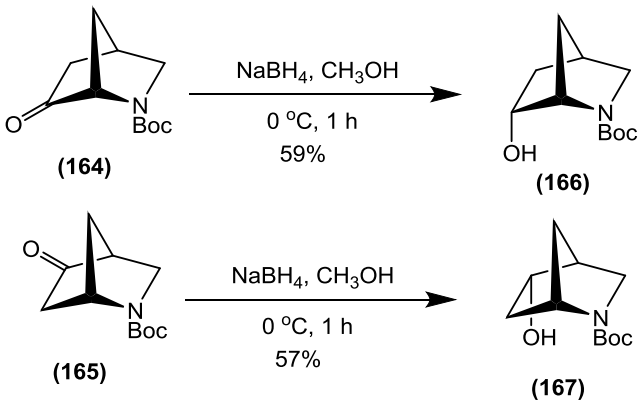


Fig. 3.9 The overall synthesis of 6-hydroxy-*endo*- and 5-hydroxy-*endo* 2-azabornane (yields are those of isolated compounds).

Sodium borohydride was chosen as a reducing reagent as it is very effective for the reduction the ketones to *endo*-alcohols, and is a safe, easy to handle, non-bulky reducing reagent. Selective attack on the ketone from the *exo*-face leading to the *endo*-configuration can be rationalised in a similar meaner to the stereoselective *exo*-hydroboration, and is due to steric hinderence by the H_{5endo} and H_{6endo} hydrogens, section 3.7). In the first step of the mechanism, an oxyanion will be produced which can stabilise the electron-deficient borane molecule by adding to its empty *p*-orbital. Finally, the reaction was quenched with saturated ammonium chloride, releasing the alcohol (**Fig. 3.12**).

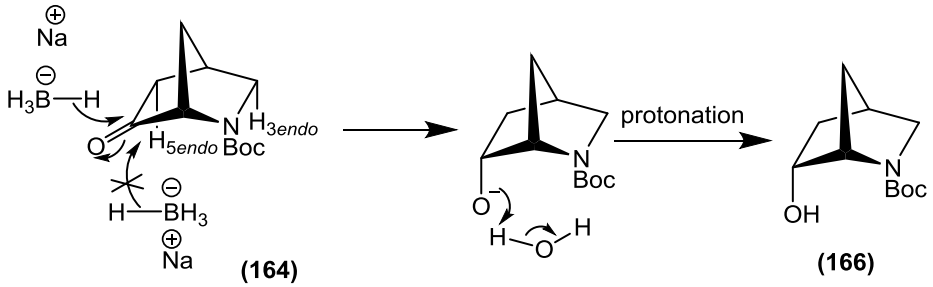


Fig. 3.12 The suggested reduction mechanism of (**164**). A similar mechanism can be proposed for the synthesis of (**165**).

The crude products for both reactions were purified using flash chromatography to gain each of the pure alcohols to allow attempted crystallisation. Only (**166**) allowed crystal formation from hexane, and subsequent X-ray crystallography analysis (**Fig. 3.13**) confirmed the assignments and made identification unambiguous. Furthermore, the degree of purity found for each of the two isomers was comparable to those found in the literature (m.p. (**166**) lit.: [155] 70.5-72.5 ^{o}C, found 69.3-71.3 ^{o}C, and m.p. (**167**) lit.:[155] 110.5-112.5 ^{o}C, found 99.3-100.3 ^{o}C). The two isomers where fully characterised by 2D-NMR. The *endo*-orientation of the hydroxyl group in (**166**) was confirmed by observation of 'W' coupling between H_{7s} and H_{5n} and geminal coupling between H_{5exo} and H_{5endo}. Also, the NOESY NMR spectrum shows a strong nOe between H_{5exo} and H_{6exo} and H_{7a} with H_{5exo}. This determined the stereochemistry to be that of the *endo*-configuration from these proton correlations and from the ^{1}H-NMR.

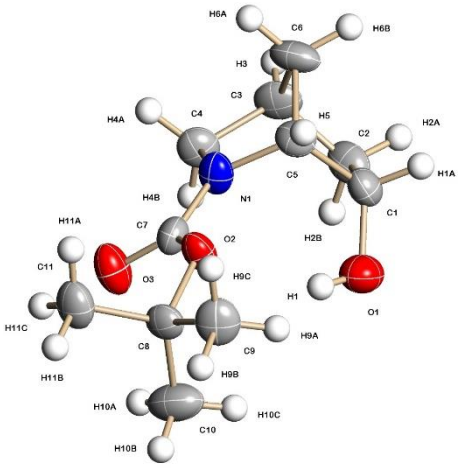
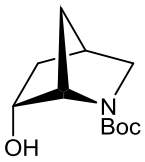
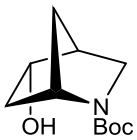


Fig.3.13 The crystal structure of 6-*endo*-hydroxyl (**166**).

Fig.3.14 ^{1}H-NMR signal; two rotamers in a ratio of ~50:50

	 **(166)**	 **(167)**
Signal	δ (ppm)	δ (ppm)
H_1	4.19 brs	4.07 and 4.19 brs
H_{3exo}	3.35 brs	3.68 t
H_{3endo}	3.09 d	3.14 t
H_4	2.31 brs	2.58 brs
H_{5exo}	2.04 brs	4.03 (H_{5exo}) d
H_{5endo}	1.08 d	-
H_{6endo}	-	1.29-1.40 m
H_{6exo}	4.24 brs	2.01-2.06 m
H_{7a}	1.49-1.52 m	1.47-1.51 m
H_{7s}	1.61 d	1.61-1.73 m
Boc CH_3	1.47 brs	1.46 brs

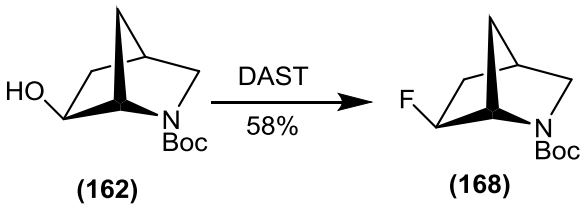
3.9 Fluorination of hydroxyl-containing compounds using DAST

The first goal of this chapter was to obtain the six hydroxyl-containing compounds (**Fig. 3.4**), and all compounds have been fully characterised due to the understanding of the mechanistic pathways of their formation. The second goal concerns the investigation of the outcome of their fluorination with DAST using the procedure described by Middleton where DAST (**74**) was added drop-wise to the starting material under an inert atmosphere at -78 ^{o}C using dry dichloromethane. After that, the reaction mixture was allowed to warm to room temperature and stirred overnight.[148] Another aim of this chapter is to determine if neighbouring group participation has been involved in the reaction by assigning the stereochemistry of the products (see section 2.6).

3.9.1 Fluorination of 2-Boc-6-*exo*-hydroxy-2-azabicyclo[2.2.1]heptane (162)

The reaction of the 6-*exo*-hydroxy compound (**162**) with the fluorinating agent DAST is considered to be very important evidence by which to determine whether neighbouring group participation (NGP) was involved during the fluorination step. Theoretically, the arrangement of the *exo*-hydroxyl group and amine functionality on the other side in the azanorbornane framework is ideal, allowing an S_N2 reaction to occur by replacement of the hydroxyl group by the lone pair of nitrogen after the conversion of the hydroxyl group to a good leaving group (see section 3.4, Fig. 3.3). If this hypothesis is confirmed, the resulting fluorinated product should see its *exo*-stereochemistry retained after the nucleophile (fluoride) will attack in the second S_N2 reaction.

The first successful attempt was carried out using two equivalents of DAST (**74**) to complete the conversion of the alcohol (**162**) to its fluorinated derivative. The crude product was purified using column chromatography to gain a 58% yield, whilst the literature report for this reaction was indicated a very low yield (<17%) by using a range of equivalents of DAST with the formation of by-products (**Fig. 3.15**).[156]



(162) **(168)**

Fig. 3.15 The overall synthesis of 2-Boc-6-*exo*-fluoro-2-azabicyclo[2.2.1]heptane (yield of isolated compound).

Compound (**168**) was fully characterised by ^{1}H-NMR and 2D-NMR experiments. The *exo*-orientation of the fluoride was confirmed by the observation of a strong nOe (nuclear Overhauser effect) between H_{5endo} and H_{6endo}. Also, the interaction between H_{7a} and H_{6endo} has been found, significantly, to be very weak. These outcomes led to the conclusion that no 6-*endo*-fluoride was produced, which implies the involvement of the lone pair on the nitrogen during the reaction leading to the replacement the hydroxyl group (good leaving group) in the first S_N2 reaction (**Fig. 3.16**). The second S_N2 step of the mechanism includes aziridinium ion as an intermediate which is then attacked by the nucleophile (fluoride), resulting in an overall retention of stereochemistry. Furthermore, ^{19}F[H]-NMR revealed the presence of fluoride at chemical shifts of -164.32 ppm ($^2J_{HF}$ = 225.8 Hz).

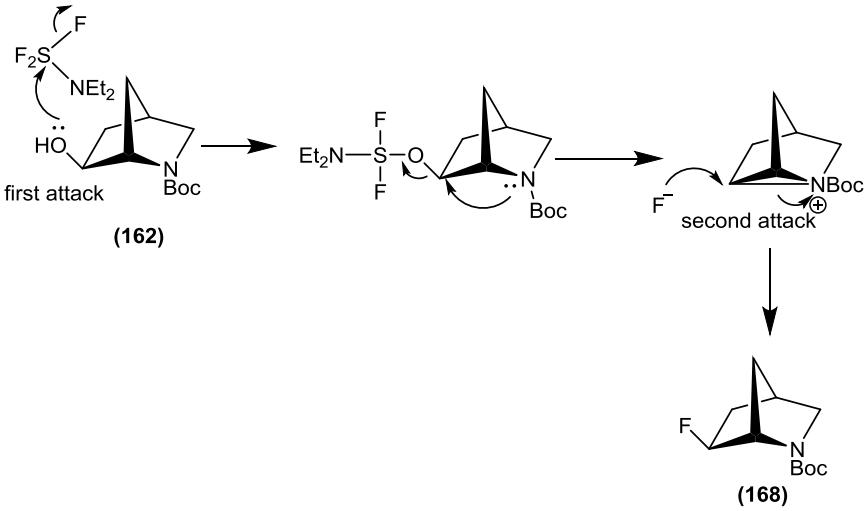


Fig. 3.16 The suggested stereoselective fluorination mechanism for the formation of (**168**).

3.9.2 Fluorination of 2-Boc-5-*exo*-hydroxy-2-azabicyclo[2.2.1]heptane (163)

Because of the encouraging result obtained from the fluorination of 2-Boc-6-*exo*-hydroxy-2-azabicyclo[2.2.1]heptane (**162**), attempts were made to fluorinate the 5-*exo*-hydroxyl analogue (**163**) in an identical manner. The crude product was purified using column chromatography and the isolated product characterised by ^{1}H-NMR and 2D-NMR experiments as the 5-*endo*-fluoride (**169**), leading to the conclusion that S_N2 attack takes place from the backside by the nucleophile (fluoride) to displace the hydroxyl group (leaving group), causing an inversion of configuration and a yield of 22%. However, this latter finding (the low yield) is consistent with the concept of there being no neighbouring group participation, and also that the *exo*-configuration of the hydroxyl group (leaving group) is not in the ideal position to facilitate its replacement by the lone pair of the nitrogen (**Fig. 3.17**).

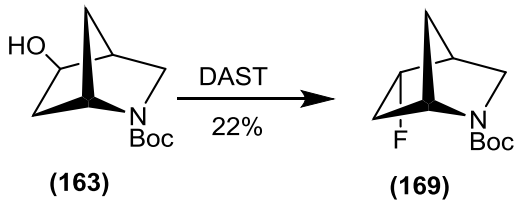


Fig. 3.17 The overall synthesis of 2-Boc-5-*endo*-fluoro-2-azabicyclo[2.2.1]heptane (yield of isolated compound).

Compound (**169**) was fully characterised by ^{1}H-NMR and 2D-NMR experiments. The *endo*-orientation of the fluoride was confirmed by the observation of a vicinal interaction between H_{5exo} and H_{6exo} and no significant interaction between H_{5exo} and H_4, confirming

that the fluoride was in the 5-*endo* configuration. Furthermore, ^{19}F[H]-NMR revealed the presence of fluoride at chemical shifts of -191.26 ppm ($^{2}J_{HF}$ = 45.2 Hz).

3.9.3 Fluorination of 6-*oxo* and 5-*oxo* 2-azanorbornane

As the synthetic route for the fluorination of 6-*exo*-hydroxy (**168**) outlined in (**Figs. 3.15**) was successful, the next step involved the fluorination of the ketones to achieve the geminal-difluorides (**170**) and (**171**) using DAST, as documented in the literature (see section 3.3.2). Both (**164**) and (**165**) were treated with four equivalents of DAST to ensure the total conversion of the fluorinated compounds by applying the same procedure described to synthesise (**168**) (**Fig. 3.18**). In each case the expected difluorinated compounds **(170**) and (**171**) was isolated in moderate yields.

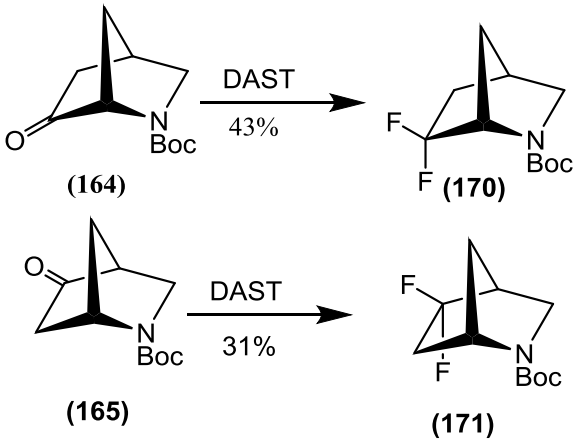


Fig.3.18 The overall synthesis of 2-Boc-6, 6-difluoro-2-azabicyclo[2.2.1]heptane and 2-Boc-5,5-difluoro-2-azabicyclo[2.2.1]heptane (yields of isolated compounds).

A proposed mechanism to explain the formation of the isolated product (**170**) with a tricyclic intermediate (**173**) involved is shown in (**Fig. 3.19**). The NGP of the nitrogen lone pair of (**164**) is suspected to increase the rate of the reaction by displacing the leaving group at the 6-position**.**

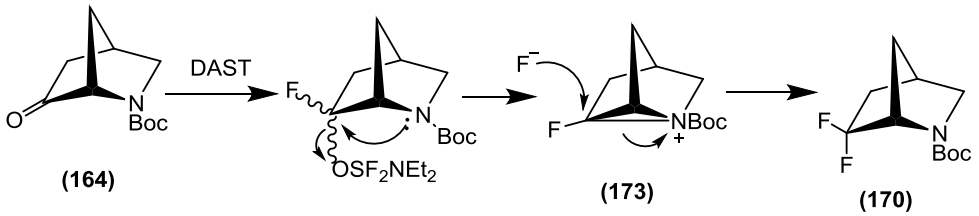


Fig.3.19 The proposed mechanism for the rearrangement of ketone (**164**) when treated with DAST**.**

The literature reports that when the benzyl-N-protected ketone (**174**) was treated with DAST, the ensuing reaction resulted in the expected geminal-difluoride (**176**), together

with the rearranged product (**177**) in a 1: 1 ratio *via* the mechanism shown in (**Fig. 3.20**). Additionally, attempts were made by heating in $CDCl_3$ to convert (**176**) to (**177**), but ultimately failed with the recovery of the starting material.[77] In our case with the Boc protected analogues (**164**) and (**165**) we saw no evidence of the corresponding rearrangement products analogues to (**177**).

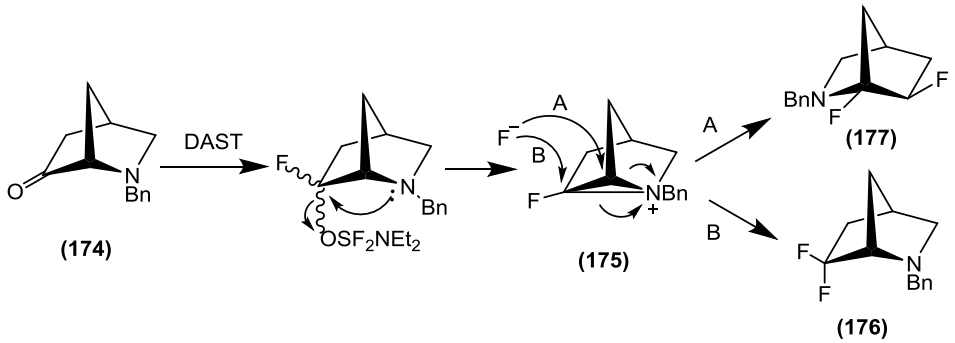


Fig. 3.20 The literature-suggested mechanism for the formation of difluoride (**177**) and (**176**).

Both crude were purified using column chromatography, and the assignment of the two compounds was achieved *via* 2D-NMR experiments and the comparison of the assigned spectra with those reported in the literature.[77] Indeed, (**170**) was identified as a geminal-difluoride by the observation of a strong nOe between H_{5exo} and H_{5endo}, H_{5exo} and H_{7a}, H_{7s}. Also, nOe interactions were seen between H_{3endo} and H_{5endo}. Furthermore, ^{19}F-NMR recorded for (**170**) revealed the presence of a difluoride at a chemical shift of -91.5 and -92.5 ppm (2×doublet, $^2J_{F\text{-}F}$ = 220.8 Hz), -113.9 and -114.5 ppm (2×doublet,$^2J_{F\text{-}F}$ = 220.4 Hz), and for (**171**) at chemical shifts of 89.0 and -89.7 ppm (2×doublet, $^2J_{F\text{-}F}$ = 226.1 Hz) and -108.8 and -109.4 ppm (2×doublet,$^2J_{F\text{-}F}$ = 226.5 Hz). These outcomes led to the conclusion that the geminal-difluoride was produced at C6 and C5 with no rearrangement detected.

3.9.4 Fluorination of 6-*endo* and 5-*endo*-hydroxyls (166) and (167)

The next two experiments attempted the fluorination of the *endo*-alcohols (**166**) and (**167**) and were conducted by applying an identical procedure to that of the fluorination of the 6-*exo*-isomer (**168**). As the result, the fluorination of the 6-*endo*-alcohol (**166**) gave an isolated product in a poor yield 6% (**Fig. 3.21**). After 2D-NMR analysis, the isolated product was found to be identical to the product obtained from the fluorination of (**162**), which is the 6-*exo*-fluoride (**168**). It is likely that the S_N2 attack took place from the backside by the nucleophile (fluoride) to displace the leaving group, causing an inversion

of configuration. However, this latter finding (the low yield) is consistent with the concept of no neighbouring group participation, whilst the *endo*-configuration of the hydroxyl group (leaving group) is not in the ideal position to facilitate its replacement by the lone pair of the nitrogen. These finding are consistent with those reported in the literature.[156]

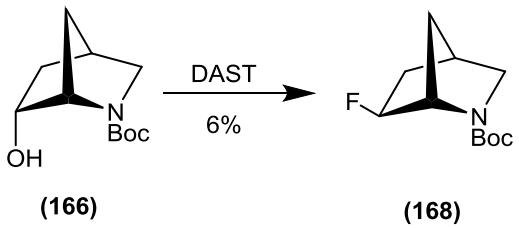


Fig. 3.21 The overall reaction describing the fluorination of 6-*endo*-alcohol (**166**).

Attempts were conducted to fluorinate the 5-*endo*-alcohol (**167**). The ^{1}H-NMR spectra for the resulting crude product was not pure enough, which unfortunately gave very unclear outcomes. The crude product was purified in the hope of obtaining a pure product, but only 6% of a product (**178**) could be isolated, and it was not considered pure enough for reliable characterisation (**Fig. 3.22**). However, ^{19}F-NMR for (**178**) indicated the presence of fluoride at chemical shifts of -166.12 ppm, while the ^{19}F-NMR for (**169**) was observed at a chemical shift of -191.26 ppm. From these findings, it can be tentatively concluded that the 5-*exo*-fluoride was obtained, again because S_N2 attack appears to take place by the backside from the nucleophile (fluoride) to displace the hydroxyl group (leaving group), causing an inversion of the configuration.

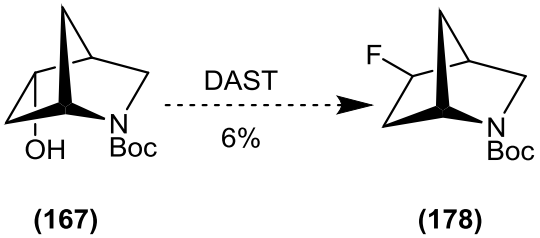


Fig. 3.22 Attempts at fluorination of the 5-*endo*-alcohol (**167**).

3.9.5 Fluorination of 7-*oxo* 2-azanorbornane

Previously, it was established that the lone pair of the nitrogen in bicyclic 2-azanorbornane had the ability to participate in the substitution reaction at C6 as well as C7 (see chapter 2). From this observation, efforts have been made to introduce fluorine at the 7-position of the 2-azabicyclo[2.2.1]heptane system. Nevertheless, the reaction of

7-keto-2-benzyl-2-azabicyclo[2.2.1]heptane with DAST was also investigated. Essentially, the same procedure as described in section 3.6.3 and 3.6.4 was repeated, but this time using four equivalents of DAST to ensure complete conversion to the final product. As expected, treatment of (**123**) (whose synthesis is described in chapter 2) with DAST gave only the *gem*-difluoride (**179**) in a 20% yield, and no rearrangement was observed. This outcome gave further evidence that the neighbouring group participation of the nitrogen lone pair at the C7 position can be considered a high energy process, far more so than at the 6-position. Additionally, White, in his thesis had been attempting the nucleophilic substitution of the fluorine for the bromine in the *gem*-difluoride (**179**), but there was no reaction and this led to the conclusion that the tricyclic intermediate had formed but was unable to react further to give rearrangement (**Fig. 3.24**). In our case the crude product (**179**) was purified using flash chromatography and fully characterised by 2D-NMR. In addition, (**179**) was identified as the geminally difluorinated analogue through the presence of difluoride at chemical shifts of -131.5 (doublet, $^{2}J_{F\text{-}F}$ = 200.4 Hz) and -128.6 ppm (doublet, $^{2}J_{F\text{-}F}$ = 200.2 Hz).

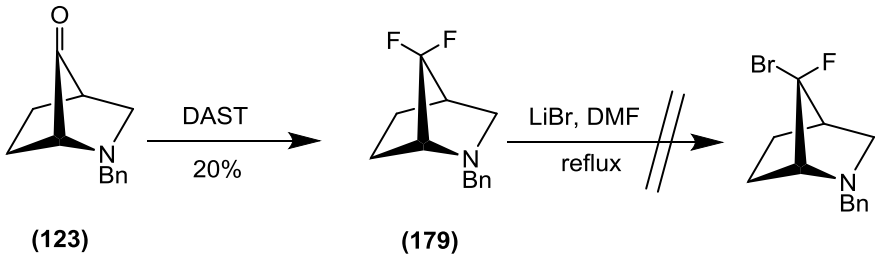


Fig. 3.24. The synthesis of 7, 7-difluoride-2-benzyl-2-azabicyclo[2.2.1]heptane (**179**) and the literature-attempted substitution reaction.

3.9.6 Fluorination of *anti*-7 and *syn*-7-alcohols (87) and (124)

In an effort to introduce the fluorine to the *anti*-7-position of 2-azanorbornane, the reaction of *anti*-7-hydroxy-2-benzyl-2-azabicyclo[2.2.2]heptane (**87**) with DAST was also investigated. Previously, it has been established that the lone pair of the nitrogen bicyclic species 2-azanorbornane (see section 3.6.4) has the ability to participate in substitution reaction at C7. Importantly, however, in our work treatment of (**87**) with DAST gave the fluorinated product (**180**). This outcome gave further evidence as to the neighbouring group participation of the nitrogen lone pair at the C7 position; also, the *anti*-configuration of the hydroxyl group (leaving group) is in the ideal position to facilitate its replacement by the lone pair of the nitrogen. This potential anchimeric

assistance from the bicyclic nitrogen led to the formation of (**180**) in a good yield of 63% with retention of configuration (more details in sections (**2.5** and **2.6**)) (**Fig. 3.25**).

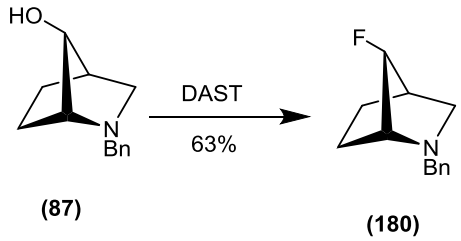


Fig. 3.25 The synthesis of *anti*-7-fluoro-2-benzyl-2-azabicyclo[2.2.1]heptane (**180**).

The *anti*-stereochemistry of (**180**) was fully characterized by 2D-NMR spectroscopic analysis. Thus, the NOESY spectrum of the *anti*-7-fluoro compound (**180**) showed the nOe (nuclear Overhauser effect) between H_7 and of the following signals H_{3exo} and H_4. Additionally, ^1H-^1H COSY analysis of (**87**) showed 'W' coupling between H_{7s} with H_{6n}. This spectroscopic information confirmed the configuration of *anti*-7-fluoro compound (**180**).

Attempts at the fluorination of the *syn*-alcohol (**124**) proceeded in a similar manner. The isolated product was characterised by 2D-expermints and it was found that the compound was identical to the one obtained from the fluorination of (**87**), which leads to the conclusion that S_N2 attack is taking place so as to cause an inversion of configuration (**Fig. 3.26**). Nevertheless, in this case we have no neighbouring group participation as the leaving group is not in the ideal *anti*-configuration to facilitate its displacement by the lone pair of the nitrogen (see sections 2.5 and 2.6).

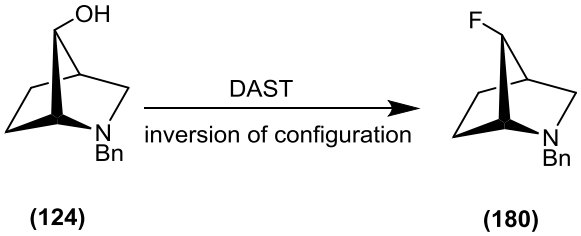


Fig. 3.26 Attempted synthesis for the fluorination of *syn*-7-alcohol (**124**).

3.10 Alteration of N-protection group

N-deprotection of the key alcohol (**87**) has also been investigated. This was based upon results from the published literature in terms of deprotecting the benzyl amines using ammonium formate and 10% Pd-C in neutral conditions.[159]

Removal of the *N*-benzyl group using the palladium activated carbon catalyst (10%) produced the secondary amino product (**181**) in a 51% yield. The structure of (**181**) was confirmed by the absence of aromatic protons in the associated ^{1}H-NMR spectrum. The following attempt to re-protect the nitrogen was straightforward using a *tert*-butyloxycarbonyl group (Boc). This gave the required 2-azanorbornane-protecteed nitrogen product (**182**) in a 90% yield (**Fig. 3.27**).

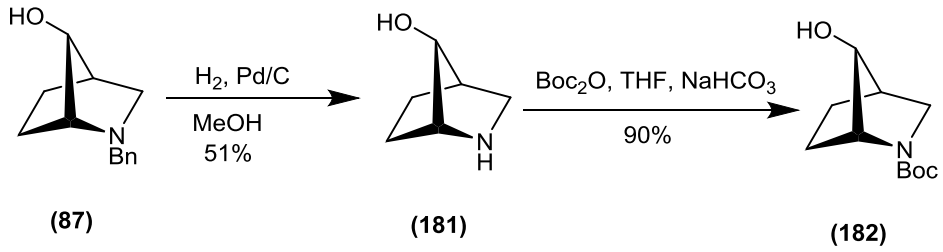
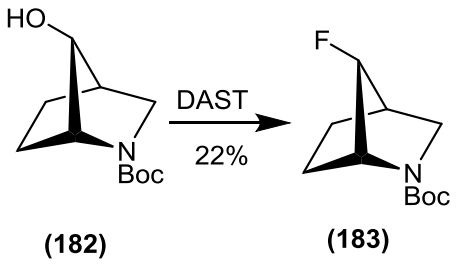


Fig. 3.27 The removal of the *N*-benzyl group of *anti*-alcohol (**87**) then re-protection to produce *anti*-7-hydroxy-2-Boc-2-azabiyclo[2.2.1]heptane (**182**).

The ^{1}H-NMR spectrum of the alcoholic compound (**182**) showed a singlet at a chemical shift of 1.44 ppm and 1.46 ppm, which indicated the presence of the Boc group; also, signal duplication indicated there is slow rotation of N-CO. Additionally, IR spectra showed a peak for the hydroxyl group (OH) at 3406 cm^{-1} for **(182)**.

3.10.1 Fluorination of *anti*-7-hydroxy-2-Boc-2-azabiyclo[2.2.1]heptane (182).

Because of the encouraging results obtained from the fluorination of *anti*-7-hydroxy-2-benzyl-2-azabicyclo[2.2.2]heptane (**87)**, attempts were made to fluorinate *anti*-7-hydroxy-2-Boc-2-azabicyclo[2.2.2]heptane (**182**) in an identical manner as (**87**). The crude product was purified using column chromatography and the isolated product was fully characterised by ^{1}H-NMR and 2D-NMR experiments which confirmed the configuration of *anti*-7-fluoro compound (**183**). Additionally, ^{19}F-NMR revealed the presence of fluoride at chemical shifts of -203.13 ppm ($^{2}J_{HF}$ = 52.7 Hz).



(182) **(183)**

Fig. 3.28 The synthesis of *anti*-7-fluoro-2-Boc-2-azabicyclo[2.2.1]heptane (**183**).

In conclusion, this chapter has described the basic methodology of our general approach to the 2-azanorbornane ring system. The introduction of fluorine to the 5- and 6-positions of the 2-azanorbornane ring system was investigated, where the fluorination of 6-*exo*-alcohol (**162**) was achieved by nucleophilic attack (F^-) on the intermediate (aziridinium salt), which then allowed *exo*-6-fluoro-2-Boc-2-azabicyclo[2.2.1]heptane (**168**) to be accessed through an overall retention of stereochemistry (**Fig. 3.16**). Also, this reaction gives evidence of the neighbouring group participation (NGP) of the nitrogen lone pair in the reaction leading to the fluorination product (**168**), and in the same manner the fluorinated products (**180**) and (**183**) were achieved. Also, the NGP involved in the formation geminal difluorides (**179**), (**170**) and (**171**) was observed through the fluorination of the ketones (**123**), (**164**) and (**165**), respectively.

Chapter 4

Synthesis of 5- and 6-(2'-chloro-3'-pyridyl)-2-Boc-2-azabicyclo[2.2.1]hept-5-ene

4.1 Synthesis of *exo*-6- and *exo*-5- chloropyridyl-substituted azanorbornanes from 6-keto and 5-keto precursors

Our successful route to synthesize natural products containing the N-protected 2-azabicyclo[2.2.1]heptane ring system, to which is attached a 5-lithio substituent of 2-chloropyridine, was through nucleophilic attack on a suitable ketone.[160, 53] We performed a retrosynthetic analysis on alkene (**184**) to determine an appropriate reaction protocol and starting materials (**Fig 4.1**).

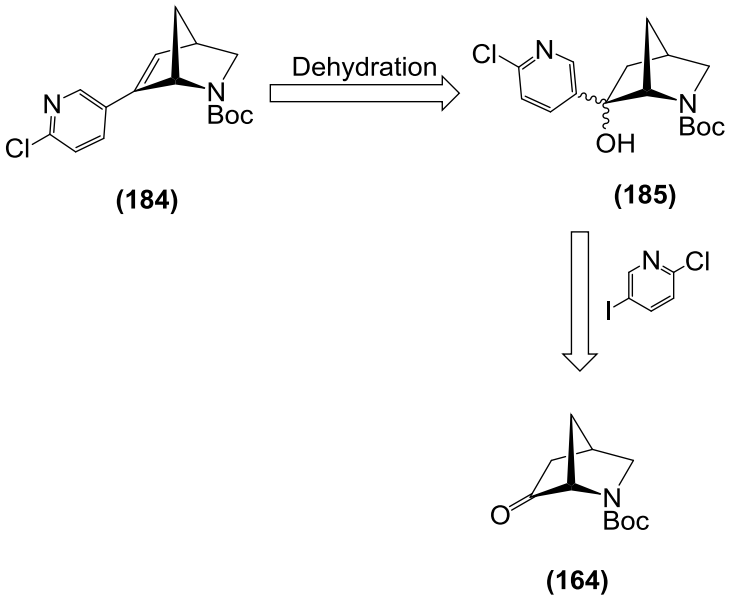


Fig. 4.1 The retrosynthetic analysis to 6-(2'-chloro-3'-pyridinyl)-2-Boc-2-azabicyclo [2,2,1]hept-5-ene (**184**).

The retrosynthetic analysis indicated that ketones were suitable precursors for the synthesis of 6-chloropyridyl-substituted azabicyclo[2.2.1]hept-5-ene (**184**) by nucleophilic attack. It has been shown that the metalation of 2-chloro-5-iodopyridine using n-BuLi at -70 ^{o}C afford a 5-lithio-2-chloropyridyl anion that would be used to attack the ketone, resulting in the formation of a tertiary alcohol. Methods to eliminate the hydroxyl group were next considered to give an olefin; however, hydration of the olefin using hydroboration/oxidation methods were not successful.

4.2 Research on *exo*-5- and *exo*-6-substituted 2-azanorbornanes

Fletcher and co-workers successfully synthesized epibatidine by adding the 5-lithio-2-chloropyridyl anion to 7-Boc-3-oxo-2-azabicyclo[2.2.1]heptane, resulting in a 67% yield of one stereoisomer of the tertiary alcohol (**187**) (**Fig. 4.2**).[107] The next step was

dehydration, where the first reagent attempted by Fletcher was thionyl chloride, involving its conversion of the hydroxyl group to a chloride. However, the subsequent attempts to remove the chloride, *via* a one-electron process, was unsuccessful.[161]

Successful dehydration was ultimately achieved with carbon disulphide and methyl iodide in a basic medium to convert the hydroxyl group to form a stable S-methyl xanthate in a 96% yield (**188**). The ^{1}H-NMR and NOESY spectra of (**188**) confirmed the xanthate group to be in the *endo*-configuration by identification of an nOe between H_1 and $H_{6'}$ (pyridyl). Additionally, an nOe was observed between S-methyl protons and the H_{3endo} proton. Elimination of the xanthate group *via* thermolysis in toluene at 110 ^{o}C occurred smoothly to afford the alkene **(189)** in a 73% yield as the major product and (**190**) as a minor product generated from a retro Diels-Alder reaction. The vinylic proton signal of (**189**) was detected at 6.55 ppm. Saturation of the double bond using Adams' catalyst in ethyl acetate and hydrogen gas (40 psi) produced a mixture of a 1:4 of *exo*-: *endo*- isomers in a 68% yield, with the *exo*-isomer **(191)** as the preferred product being isolated in an 11% yield by flash chromatography. Alternatively, the *endo*-isomer (**192**) could be easily epimerised into the *exo*-isomer by utilising potassium *tert*-butoxide in *t*-butyl alcohol under reflux for 30 h, where the conversion ratio was found to be more than 50%. An nOe spectrum confirmed the *exo*- orientation of (**191**). An nOe between H_{2endo} and $H_{6'}$, $H_{4'}$ and H_1, H_{3endo} and H_{6endo} was observed. The *endo*- isomer was identified by observation of an nOe between H_{2exo} and H_{3exo}, and $H_{4'}$ and H_1. Finally, deprotection of the N-BOC was achieved in excellent yield for *exo*-2-(2′-chloro-5′-pyridinyl)-7-Boc-7-azabicyclo[2.2.1]heptane (**191**) using hydrochloric acid and ethyl acetate to yield a racemic mix of epibatidine.

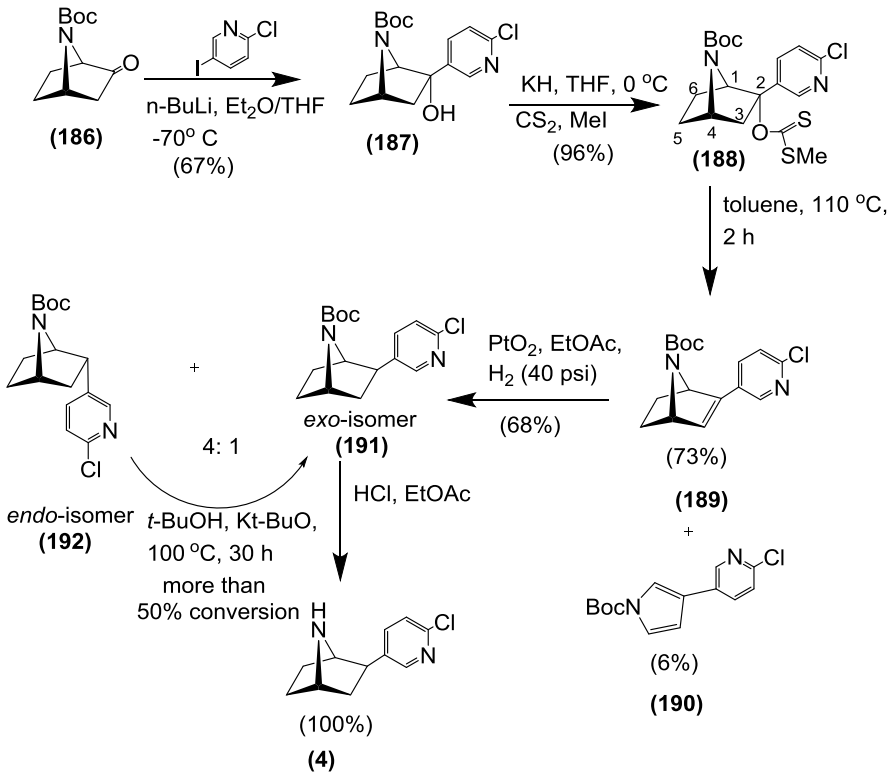


Fig. 4.2 Literature example of the synthesis of epibatidine.[107]

Another successful methodology was adopted by Cox at the University of Leicester[162] (**Fig. 4.3**) to obtain *exo*-5 and *exo*-6 *N*-protected derivatives *via* the Heck reaction[163] using an excess of 2-chloro-5-iodopyridine with $Pd(PPh_3)_4$[162] as a catalyst, where it was observed that the coupling was stereoselective for the desired *exo*-isomers, **(193)** and **(194).** The ratio of the two isomers was calculated by ^{1}H-NMR spectra and confirmed that yield of the *exo*-5 isomer (**193**) was higher than that of *exo*-6 (**194**).

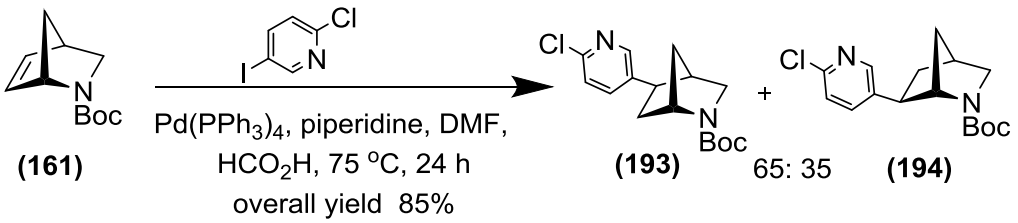


Fig. 4.3 The synthesis of *exo*-5 and 6-*exo*-2-(6′-chloro-3′-pyridyl)-2-Boc-2-azabicyclo [2.2.1]heptane (**193**) and (**194**).[162]

4.3 Synthesis of ketones (164) and (165) - Cornforth oxidation

The ketone (**198**) was first made by Carroll and co-workers,[164] as shown in (**Fig. 4.4**). The 2-(carbobenzyloxy)-2-azabicyclo[2.2.1]hept-5-ene (**195**) was synthesized *via* a hetero Diels-Alder reaction of freshly cracked cyclopentadiene (**74**) with the iminium ion

prepared from formaldehyde and ammonium chloride to give the alkene. Compound (**195**) was hydrated by oxymercuration then reduction using sodium hydride to afford the alcohols (**196**) and (**197**), which were isolated by flash chromatography and their ratio calculated as 2:1, respectively. The structural assignment of the alcohols by ^{1}H-NMR examined only the C_5-alcohol, and was not fully characterised. Oxidation of alcohol (**196**) using the Jones reagent gave the ketone (**198**).

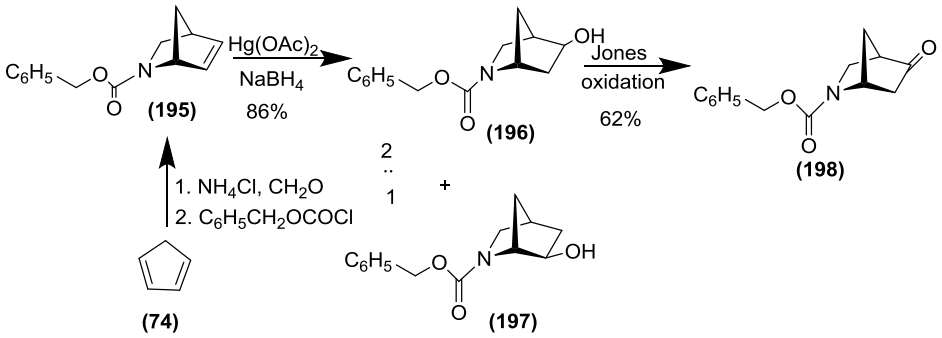


Fig. 4.4 Carroll methodologies which describe the conversion of cyclopentadiene to 2-(Carbobezyloxy)2-azabicyclo[2.2.1]heptan-5-one (**198**).[164]

In this work in order to gain access to the alcohols (**162**) and (**163**), we chose to utilise hydroboration/oxidation, as this reagent is less toxic than mercuric acetate, as discussed in more detail in Chapter 3. It is noteworthy that the hydration of the olefin (**195**) formed different ratios of regioisomers depending on which reagent was utilised.[7] For example, in the case of borane, we have an approximately equal chance of a distribution of regioisomers through the mechanism of the hydroboration/oxidation reaction (see chapter 3). By contrast, for mercuric acetate the ratio is 2:1, with a higher yield of C_5 alcohol being formed. Considering the mechanism of the reaction, the regioselectivity shown by mercuric acetate can be rationalised. In the first step of the mechanism, the mercuric acetate adds to the unsaturated bond leading to a bridged cation (**199**), followed by water attacking the C_5 atom to neutralise the positive charge. Thus, this led us to the conclusion that C_6 may be suffering from lack of electrons owing because of the electron-withdrawing effect of the carbamate group (or urethane group).

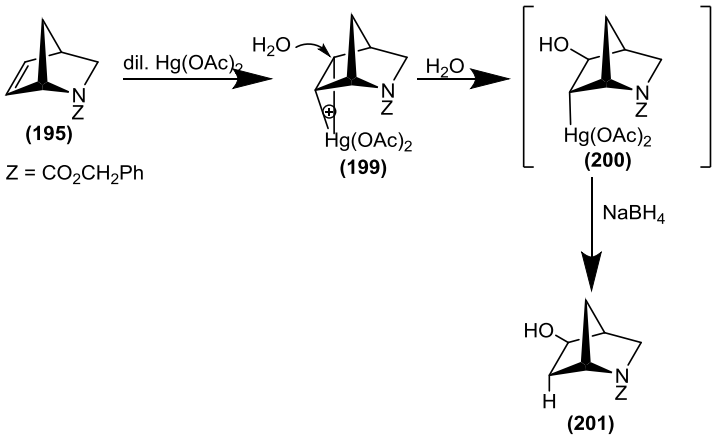


Fig. 4.5 Suggested regioselective mechanism of production of (**203**).

Steric hindrance factors may also influence the addition of borane to (**195**). However, with only slight steric differences between C_6 and C_5; this explains the almost equal distribution of regioisomers.

The next stage in the synthetic scheme was to obtain the two ketones (**164**) and **(165),** but using a different procedure from that described by Carroll. The ketones represented very valuable precursors in reaching our target, not only because we wanted to investigate the reaction conditions with metalpyridine species to build up the carbon framework, as illustrated in (**Fig. 4.6**), but also because they were essential to the investigation of their fluorination reaction (see Chapter 3). Because of the Boc protecting group in bicyclic system using di-*tert*-butyl dicarbonate, an acidic medium can be used to effect its removal. In this case a less acidic oxidising agent was needed compared with those more conventionally used by Carroll, potassium dichromate and chromium trioxide (Jones' reagent), and the presence of dilute sulphuric acid in acetone. Therefore, the Cornforth reagent (pyridinuim dichromate PDC) was used.[165, 155]

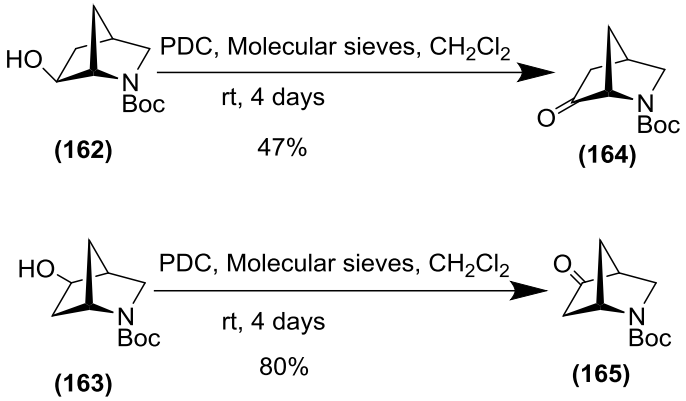


Fig. 4.6 The synthesis of ketones (**164**) and (**165**).[165, 155]

The oxidation is usually performed at ambient temperature under dry conditions for four days for both ketones. Subsequent ^{1}H-NMR and TLC confirmed that (**165**) did not contain any unreacted starting material, but for (**164**) we found there were unidentified by-products with the main product. The oxidation was accomplished in a reasonable yield (47%) for (**164**) and in excellent yield (80%) for (**165**) after purification by flash chromatography. It is worth mentioning that in literature the yield of 92% for (**165**) was much larger than that of 49% for (**164**). The samples were fully characterised by 2D-NMR spectroscopy. Indeed, the physical state of product (**164**) (solid) allowed the growth of crystals from toluene/ethyl acetate. The X-ray crystallography analysis confirmed the structural assignment for **(164)** (**Fig. 4.7**). Also, IR spectra show an extra peak assigned to a carbonyl group (C=O) at 1755 cm^{-1} for **(164)** and at 1753 cm^{-1} for **(165)**.

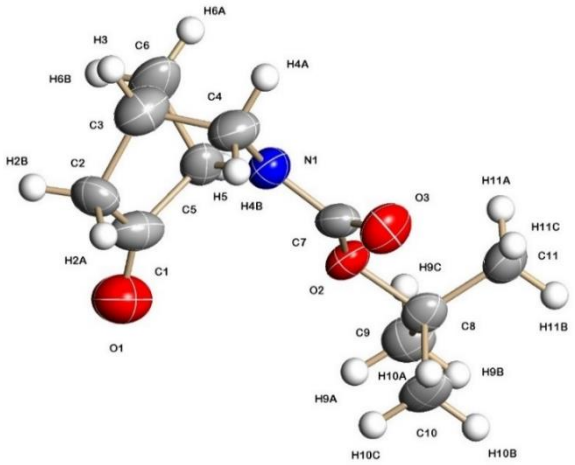


Fig. 4.7 The X-ray crystallography structure of 2-Boc-6-*oxo*-2-azabicyclo[2.2.1]heptane **(164).**

4.4 Synthesis *endo*-5- and *endo*-6-(2'-chloro-3'-pyridyl)-2-Boc-2-azabicyclo [2,2,1]heptan-6-ol (**185**) and (**202**)

In order to synthesis the targets (**185**) and (**202**), (**Fig. 4.8**), we employed the lithation of an aromatic system containing both iodine and chlorine, which occured with selective transmetallation of the iodine atom. The adducts (**185**) and (**202**) each appeared as one stereoisomer in reasonable yields of 49% and 62%, respectively. The determination of whether the 2-chloropyridyl ring was oriented *endo*- or *exo*- represented a significant challenge. As methods were considered in the synthesis of the next step to remove the hydroxyl groups by dehydration, it was clear the configurations at these positions would be lost. However, (**202**) was obtained as a white solid, which allowed crystal formation from petroleum ether/ethyl acetate for X-ray crystallography analysis, which confirmed the configuration of alcohol (**202**) (**Fig. 4.9**) and made the identification unambiguous, with an *exo*- configuration of the 2-chloropyridyl rings.

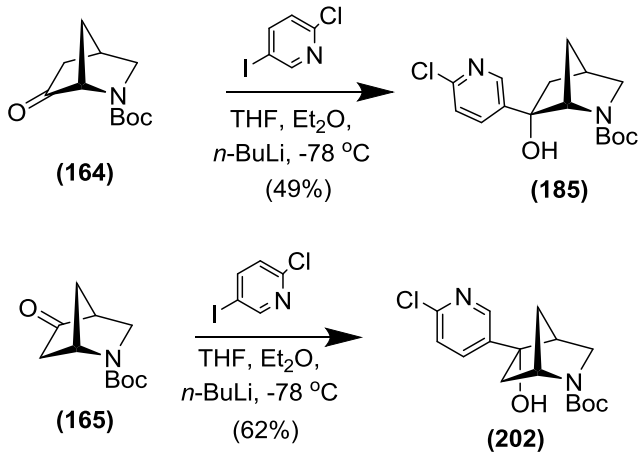


Fig. 4.8 Both adducts were fully characterised by ^{1}H-NMR and 2D-NMR spectroscopy. In the manner of (**185**), an nOe was examined between H_4, H_{3n} and the proton of hydroxyl group, confirming the hydroxyl group at the C_6 was in the *endo*-orientation and the chloropyridyl ring was *exo*. (**Table**. **1**) illustrates the proton signals for alcohols (**185**) and (**202**) to confirm that the two isomers were different products.

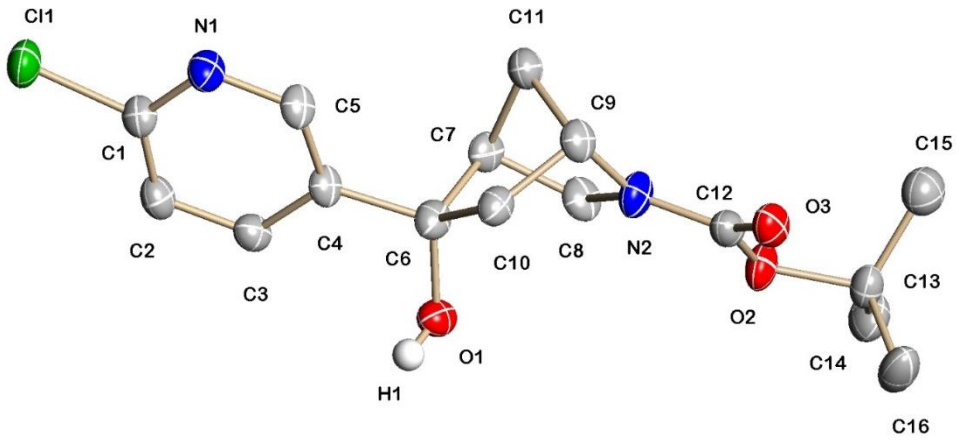
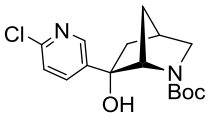
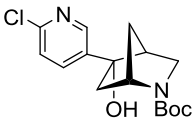


Fig. 4.9 The X-ray crystallography structure of *endo*-5-(2'-chloro-3'-pyridinyl)-2-Boc-2-azabicyclo [2,2,1]heptan-6-ol (**202**).

Table (1): ^{1}H NMR signal data

	 **(185)**	 **(202)**
	δ (ppm)	δ (ppm)
H_1	4.39 and <u>4.25</u> brs	4.21 and <u>4.30</u> brs
H_{3n}	3.20 dd	<u>2.77</u> and 2.80 brs
H_{3x}	3.42 dt	3.24 dd
H_4	2.64 brs	3.92 and <u>3.95</u> dd
H_{6x}	--	1.62-1.72 m
H_{6n}	--	1.78-1.86 m
H_{7a}	--	2.00 – 2.05 m
H_{7s}	--	2.24 – 2.29 m
$H_{5,}$ H_7	1.61-2.48 m	- -
Boc CH_3	1.49 brs	1.46 brs
-OH	3.72 brs	--
$H_{2'}$	7.30 d	7.32 d
$H_{4'}$	7.67 dd	7.82 d
$H_{5'}$	8.45 d	8.46 brs

Rotamers were observed for both (**185**) and (**202**) by ^{1}H-NMR spectroscopy, where the ratio of the two rotamers was calculated to be ~ 38:62, where the minor rotamer is underlined, and the major is in standard form.

4.5 Attempts to synthesis *syn*-7-hydroxy-7-(2′-chloro-3-pyridyl)-2-Boc-2-azabicyclo [2.2.1]heptane (203)

In an effort to attach the 2-chloropyridyl ring to the 7-position of 2-azanorbornanes, the reaction of 7-keto-2-Boc-2-azabicyclo[2.2.1]heptane (**139**) with the 5-lithiated -2-chloropyridine agent generated in *situ* from *n*-BuLi and 2-chloro-5-iodopyridine at -78 ^{o}C was also investigated. It has previously been established that the ketones (**164**) and (**165**) gave our targets (**185**) and (**202**) *via* nucleophilic attack of the carbonyl group with the lithiated derivative with the outcome of a tertiary alcohol (**Fig. 4.8**). However,

attempts to apply this protocol for the synthesis of (**203**) from (**139**) were less successful. Disappointingly, after purification by column chromatography the only compounds isolated was 2-chloro-5-iodopyridine and (**139**). This led to conclude that the lithiation step had not occured, possibly due to the presence of water (**Fig. 4.10**).

The last attempt was performed overnight at room temperature. The crude product was quite messy with overlapping signals, and where TLC analysis showed multiple spots. Nevertheless, the crude product was purified using flash column chromatography, but unfortunately no conductive evidence of the formation of (**203**) was obtained.

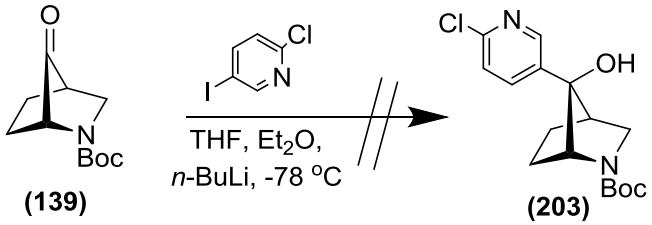


Fig. 4.10 Attempts to synthesise *syn*-7-hydroxy-7-(2′-chloro-3-pyridinyl)-2-Boc-2-azabicyclo [2.2.1]heptane (**203**).

4.6 Synthesis of the targets 5- and 6-(2'-chloro-3'-pyridyl)-2-Boc-2-azabicyclo [2,2,1]hept-5-ene (184) and (205)

Elimination of the hydroxyl group to give the olefins (**184**) and (**205**) did not occur in a straightforward manner. Regarding the 6- substituent 5-ene (**184**) synthesis, dehydration involved the conversion the hydroxyl group into an *S*-methyl (tertiary xanthate group) (**Fig. 4.11**).[166, 167] Compound (**184**) proved to have long-term stability at room temperature and could be isolated by flash chromatography. The xanthate derivative was achieved using carbon disulphide and methyl iodide in a basic medium at 0 °C with a good yield (73%) as a yellow oil. The ^{1}H-NMR and 2D-NMR assignment identified the *endo*- configuration of S-methyl which in turn confirmed the *endo*- configuration of alcohol (**185**). An nOe was detected between *S*-CH_3 protons to H_{3endo}, H_{5endo} to H_{3endo} and $H_{6'}$ to H_1. Thermolysis of the intermediate the xanthate (**204**) was conducted in toluene at 110 °C for 5 h, with the elimination proceeding smoothly to give the olefin (**184**) in a reasonable yield (49%) after flash chromatography, but only a 5% yield could be achieved for (**205**) using the same method based on the recovered starting material. Attempts to improve the yield of (**205**) by increasing the reflux time did not work. Finally, Burgess reagent (methyl N-(triethylammoniumsulphonyl) carbamate (inner salt), a selective and mild reagent, were utilized successfully for dehydration by converting the hydroxyl group

into N-carboxysulphamate ester, and the *endo*-alcohol (**202**) was reacted with Burgess' reagent under dry conditions stirring for 24 h at room temperature, with subsequent thermolysis achieving a 51% yield for (**205**).[168, 169] Key observations confirmed the presence of both regioisomers of (**184**) and (**205**), which included identification of vinylic proton signals and their respective rotamers in the range of 6.47- 6.55 δ and 6.65-6.76 δ, respectively. Finally. (**Table 2**) illustrates the proton signals and the 2D-NMR data for (**184**) and (**205**) to confirm that the two isomers were, in fact, different products.

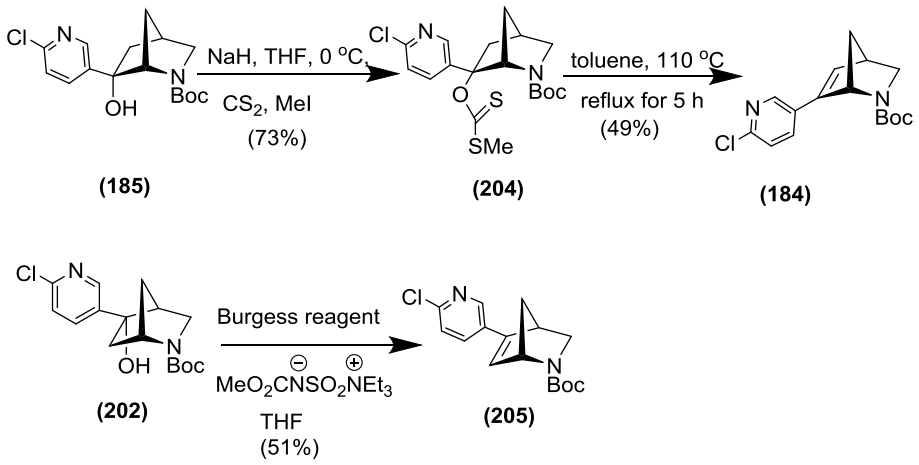


Fig. 4.11 Synthetic scheme for the formation of alkenes (**184**) and (**205**) with percentage yields for isolated products.

2D-NMR (COSY and NOESY) experiments were performed to give further information regarding the distribution and relationships of the protons. ^{1}H-^{1}H COSY analysis of (**184**) showed a signal for H_5 was identified by 'W' coupling to H_{3exo}. Furthermore, the NOESY spectrum of the same product appeared cross peak between H_1 to $H_{4'}$ and H_5 to $H_{6'}$.

With respect to the alkene (**205**), the NOESY analysis showed an interaction between H_6 to $H_{4'}$, H_6 to $H_{3'}$ and H_6 to H_1. The 2D NOESY spectrum of (**205**) is shown in (**Fig. 4.12**).

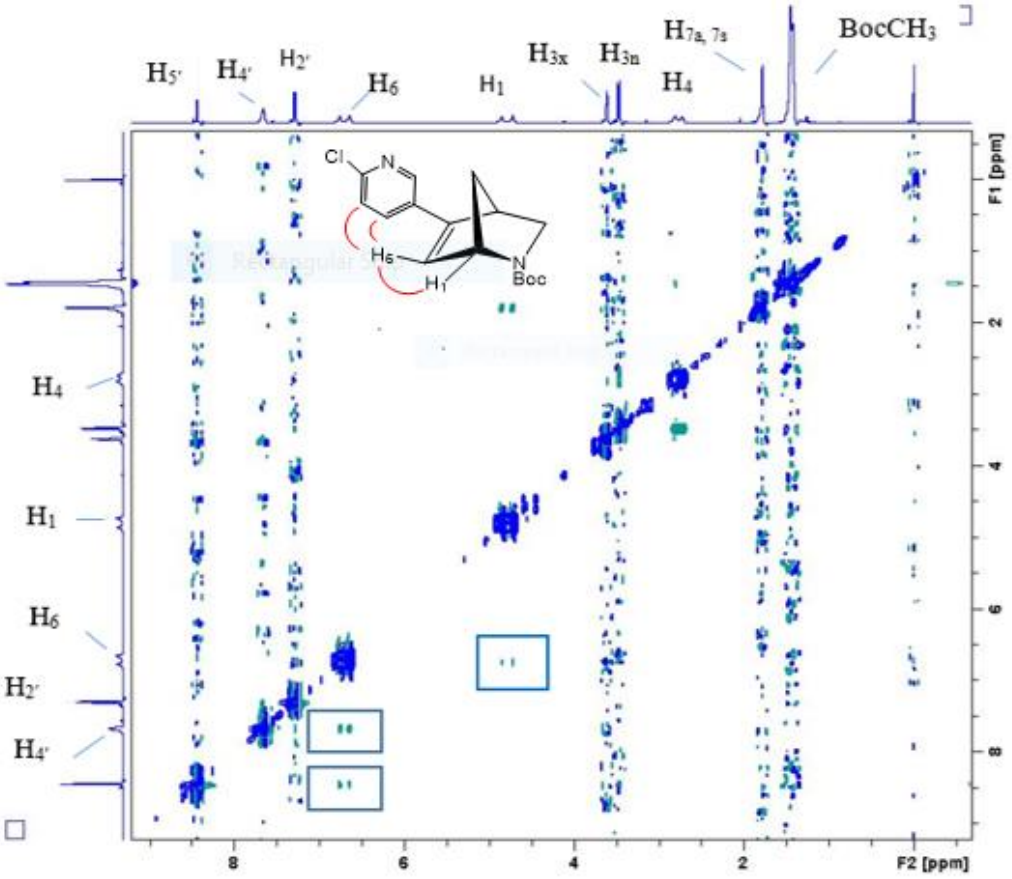
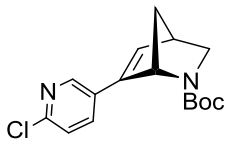
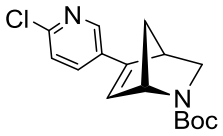


Fig. 2.12 The NOESY spectrum of the alkene (**205**).

Table (2): ^{1}H-NMR signals data of (**184**) and (**205**).

	 **(184)** **δ (ppm)**		 **(205)** **δ (ppm)**	
H_1	5.00	brs	4.37 and 4.85	brs
H_{3endo}	3.26	brs	3.47	dd
H_{3exo}	3.40	dd	3.61	brs
H_4	2.67	brs	2,81	brs
H_5	6.47 and 6.55	brs	--	
H_6	--		6.65 and 6.76	brs
$H_{7a,s}$	1.65-1.73	m	1.79	brs
Boc CH_3	1.35	brs	1.44	brs
$H_{2'}$	7.21	d	7.29	d
$H_{4'}$	7.71 and 7.74	brs	7.66	d
$H_{5'}$	8.50	brs	8.44	dd

Rotamers were observed for (**184**) by ^{1}H-NMR spectroscopy, where the ratio of the two rotamers was calculated to be ~40:60) and ~50:50, respectively; the the minor rotamer is underlined, and the major is standard.

4.7 Attempts at hydroboration/oxidation of the alkene (184)

After obtaining the alkenes (**184**) and (**205**), and understanding the mechanistic pathways of their formation by fully characterising the products, interest moved towards hydrating the alkenes.The hydroboration/oxidation reaction is an efficient procedure by which to convert the double bond to an alcohol.[170] It is known to be an *anti*-Markovnikov reaction and regioselective, with the hydroxyl group bonded to the less substituted carbon of the reacting alkene (**Fig. 4.14**).

The results from the early work of the conversion of the symmetrical alkene (**161**) into a mixture of the two stereoisomer alcohols (**162**) and (**163**) was achieved successfully *via* the hydroboration/oxidation method (see chapter 3) in an approximately equal amount. This encouraged us to apply the same method on alkene (**184**) in the hope of making the isomers (**206**) and (**207**). All attempts were disappointing, giving an uncharacterised product, even though it was purified by flash chromatography. Obviously, the presence of the hetero ring might have hindered the reaction from proceeding.

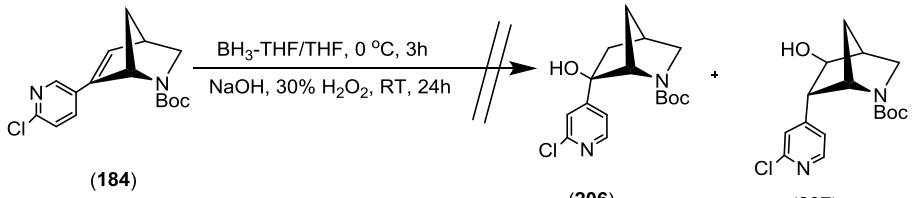


Fig. 4. **14** The attempt at hydroboration/oxidation of the alkene (**184**).

In conclusion to this chapter, the novel synthetic route described consists of three steps and results in stereoisomers in 47% (**164**), 80% (**165**), 49% (**185**), 62% (**202**), 49% (**184**), and 51% (**205**) yields of the corresponding *N*-protected azanorbornane. The importance of developing novel approaches for the preparation of epibatidine analogues with potential analgesic potency and lower toxicity (better receptor subtype selectivity) cannot be overstated. The basic methodology of our work has been established on the 2-azabicyclo[2.2.1]heptane skeleton. We have explained that the possible nucleophilic addition of 5-lithio-2-chloropyridine to appropriate ketones (5-keto and 6-keto), is the optimal method by which to attach the 2-chloropyridinyl ring in the *exo* face to the 2-azabicyclo[2.2.1]heptane core in order to generate the corresponding *endo* alcohols. Unfortunately, all attempts that were made to incorporate a 2-chloropyridyl ring at the 7-position failed, based on the amount of substrate recovered. Further transformation of the synthetic scheme involved formation of the alkenes (**184**) and (**205**) using different dehydration reagents, conversion of the tertiary alcohol to the xanthate intermediate followed by pyrolysis led to the desired alkene (**184**), but the corresponding yield for (**205**) was very poor. However, using Burgess' reagent led to successful dehydration of (**202**). Hydrogenation of (**184**) *via* the hydroboration/oxidation reaction was found not to work, and that only an unidentified product was left at the conclusion of the reaction.

Chapter 5

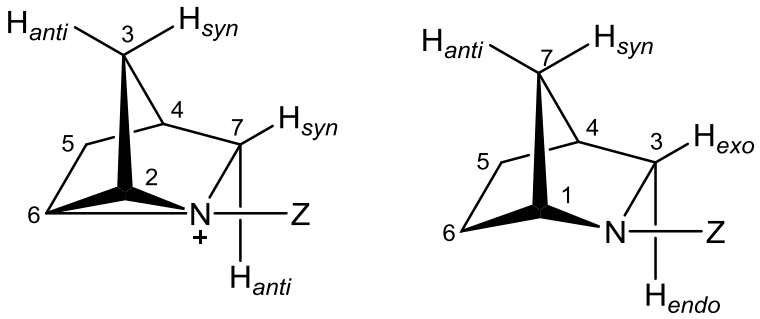
Experimental

Experimental

Reagents were obtained from Alfa Aesar, Sigma Aldrich and Fisher Scientific and were used without further purification with the exception of cyclopentadiene and methanol; cyclopentadiene which was cracked from dicyclopentadiene and used fresh for each subsequent reaction. All reactions were carried out in oven-dried glassware under dry nitrogen unless stated otherwise. 'Petroleum ether' refers to the fraction distilled over the range 40-60 ^{o}C. Removal of solvents *in vacuo* was done using a Buchi rotary evaporator followed by a high vacuum pump. Column chromatography was carried out using a Merck Kieselgel 60 (230-400 mesh). Thin-layer chromatography was conducted on standard commercial aluminium sheets pre-coated with a 0.2 mm layer of silica gel (Merck 60-245). Melting points were determined using a Griffin melting point apparatus equipped with a Fisher Scientific digital thermometer.

^{1}H-, ^{13}C- and ^{19}F-NMR spectra were recorded on Bruker DRX 300, DRX 400 and AV 500 spectrometers. Chemical shifts (δ) are expressed in parts per million (ppm). All spectra were obtained in $CDCl_3$ with tetramethylsilane (TMS) as internal references unless stated otherwise. Multiplicities are abbreviated according to: s (singlet), d (doublet), t (triplet), AB (AB-system), m (multiplet), br (broad). Signal multiplicities in ^{13}C-NMR were determined by DEPT experiments. Signals were assigned with the assistance of ^{1}H-^{1}H COSY, ^{1}H-^{1}H NOESY and ^{1}H-^{13}C HMQC spectra. The compounds were analysed by LC-MS using a Xevo QTof mass spectrometer (Waters) coupled to an Acquity LC system (Waters) using an Acquity UPLC BEH C18 column (2.1 × 500 mm, Waters). The flow rate was 0.6 ml min-1 and the gradient was as follows: 95% solvent A (0.1% formic acid in water) with 5% solvent B (0.1% formic acid in acetonitrile) was held constant for 0.5 min, followed by a linear gradient to 100% B over the next 2.1 min. After 1 min at 100% solvent B, the gradient was returned to 95% solvent A and 5% solvent B over 0.2 min. The ESI capillary voltage was 3 kV, cone voltage 30 V and collision energy 4eV. The MS acquisition rate was 10 spectra per second and m/z data ranging from 50 to 2000 Da was collected. Mass accuracy was achieved using a reference lock mass scan, once every 10 seconds. For samples analysed using ASAP (Atmospheric Solids Analysis Probe), the corona discharge pin current was 5 µA, cone voltage 30V and collision energy 4 eV. The MS acquisition rate was 5 spectra per second and m/z data ranging from 50 to 1000 Da was collected. Mass accuracy was achieved using a reference lock mass scan, once every 10 seconds in ESI mode. IR spectra were obtained on a Perkin-

Elmer spectrum One FT-IR spectrometer as a solution in dichloromethane unless stated otherwise. Band intensities are described using standard abbreviations: s (strong), m (medium), w (weak), br (broad). X-ray crystallography structures were visualised on a Bruker APEX 2000 diffractometer; Mo Ka radiation, 150 K (Oxford Cyrostream Cooler), 4 k CCD detector. The numbering of bicyclic and tricyclic products is as follows.



Formation of cyclopentadiene (74)

Dicyclopentadiene (30 ml) was cracked by heating at approximately 180 ^{o}C, using a fractional column and collecting the distillate at between 39-41^{o}C. The rate of distillation was allowed to proceed at about 2-3 drops per second, and was stopped after most of the dicyclopentadiene had been distilled. The cyclopentadiene was stored at -10 ^{o}C to prevent reformation of the dimer.

δ_H (400 MHz, $CDCl_3$) 2.97 (quintet, J = 1.4 Hz, 2H, CH_2), 6.47-6.45 and 6.55-6.58 (m, 4H, CH=CH);

Synthesis of 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene (76)

According to the procedure described by Grieco *et al*.,[84] benzyl amine (6.54 ml, 60 mmol) was added to 24 ml of HCl (2.5 M), then formaldehyde (6.3 ml, 37% aqueous solution, 84 mmol) and freshly distilled cyclopentadiene (**74**) (9.9 ml, 120 mmol) were added, respectively. The flask was stoppered tightly, and the mixture was stirred vigorously at 26 °C for 9 h. The reaction mixture was diluted with water (50 ml) and washed with diethyl ether: hexane 1:1 (4 × 20 ml). The aqueous layer was basified, using solid potassium hydroxide (4.1 g), and the basified aqueous layer extracted with diethyl ether (3 × 60 ml), after which the combined organic layer extracts were dried over anhydrous $MgSO_4$ and filtered, with the solvent then being removed under reduced pressure to obtain (**76**) as a pale yellow oil (8.9 gm, 48.232 mmol, 81%) which was converted to (**77**) without further purification.

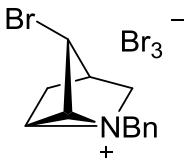
δ_H (400 MHz, $CDCl_3$) 1.40 (dd, J = 2, 8 Hz, 1H, H_{7a}), 1.50 (dd, J = 2, 9 Hz, 1H, H_{3n}), 1.63 (d, J = 8 Hz, 1H, H_{7s}), 2.91 (brs, 1H, H_4), 3.16 (dd, J = 3, 9 Hz, 1H, H_{3x}), 3.32 (d, J = 13 Hz, 1H , CH_2Ph), 3.56 (d, J = 13 Hz, 1H , CH_2Ph), 3.80 (d, J = 1.3 Hz, 1H, H_1), 6.07 (dd, J = 2, 6 Hz, 1H, H_6), 6.35 (ddd, J = 1, 3, 6 Hz, 1H, H_5), 7.20-7.35 (m, 5H, Ph).

δ_C (100.62 MHz, $CDCl_3$) 44.1 (C_4), 48.2 (C_7), 52.7 (C_3), 59.3 (CH_2Ph), 64.4 (C_1), 126.7, 128.2, 128.7 (5 × aryl CH), 131.0 (C_6), 136.3 (C_5),140.1 (aryl C).

ν_{max} (NaCl film) 2981s (C-H), 2855s (C-H), 1604w, 1494m, 1453m, 1362m, 1208s cm^{-1}.

$^{m}/_{z}$ $C_{13}H_{16}N$ [MH^+] requires 186.1283; observed 186. 1274.

Synthesis of 3-bromo-1-benzyl-1-azoniatricyclo[2.2.1.0^{2,6}]heptane tribromide (77)



According to the procedure described by Sosonyuk *et al*.,[79] 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene (**76**) (4.1 g, 22.249 mmol) was dissolved in dry DCM (40 ml), then bromine (2 ml, 43.167 mmol) was added dropwise at -78 °C with stirring and the reaction allowed to warm to 20 °C. The solvent was removed *in vacuo* to give (**77**) as an orange oil (11.18 g, 22.143 mmol, 100%).

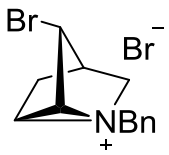
δ_H (400 MHz, $CDCl_3$) 2.42 (d, *J* = 13.3 Hz, 1H, H_{5s}), 2.58 (d, *J* = 13.3 Hz, 1H, H_{5a}), 2.94 (brs, 1H, H_4), 3.40(d, *J* = 9.2 Hz, 1H, H_{7a}), 3.66 (d, *J* = 9.2 Hz, 1H, H_{7s}), 4.18 (brd, *J* = 4.4 Hz, 1H, H_6), 4.25 (dd, *J* = 1.5, 4.4 Hz, H_2), 4.63 (brs, 1H, H_3), 5.00 (AB quartet, *J* = 13.3 Hz, 2H, CH_2Ph), 7.50-7.64 (m, 5H,Ph).

δ_C (100.62 MHz, $CDCl_3$) 31.8 (CH_2Ph), 37.7 (C_4), 44.9 (C_2), 45.3 (C_6), 46.6 (C_3), 55.6 (C_7), 55.7(C_5), 129.6 (Aryl C), 130.4, 130.5, 131.4 (5 × aryl CH).

ν_{max} (NaCl film) 3412s (C-H aromatic), 2964m (C-H), 2811m (C-H), 2539m, 1519w, 1456s, 1383w, 1263m, 699s, 733s cm^{-1}.

$^m/_z$ $C_{13}H_{15}NBr^{79}$ [M^+] requires 264.0388; observed 264.0395.

Synthesis of 3-bromo-1-benzyl-1-azoniatricyclo[2.2.1.0^{2,6}]heptane bromide (78)



According to the procedure described by Sosonyuk *et al*.,[79] 3-bromo-1-azoniatricyclo[2.2.1.0^{2,6}]heptane tribromide (**77**) (10.93 g, 21.6 mmol) was dissolved in dry acetonitrile (33.3 ml). The reaction mixture was cooled to 0 °C and stirred vigorously under nitrogen, this time 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene (**76**) (4.02 g, 21.815 mmol) in dry acetonitrile (20 ml) was added drop-wise, then the mixture allowed to warm to 20 °C. The solvent was removed *in vacuo* to afford (**78**) as a pale yellow solid (7.43 g, 21.531 mmol, 100%). m.p. 130-132 °C.

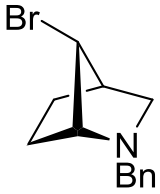
δ_H (400 MHz, $CDCl_3$) 2.42 (ABq, 2H, H_5), 2.81 (brs, 1H, H_4), 3.43 (d, *J* = 9.3 Hz, 1H, H_{7a}), 3.97 (d, *J* = 9.3 Hz, 1H, H_{7s}), 4.38 (d, *J* = 4.4 Hz, 1H, H_6), 4.41 (d, *J* = 4.4 Hz, 1H, H_2), 4.87 (brs, 1H, H_3), 5.37 (s, 2H, CH_2Ph), 7.39-7.74 (m, 5H, Ph).

δ_C (100.62) MHz $CDCl_3$) 31.1 (CH_2Ph), 37.7 (C_4), 44.4 (C_2), 45.1 (C_6), 46.6 (C_3), 55.4 (C_7), 55.6 (C_5), 129.5 (Aryl C), 129.6, 130.4, 131.2 (5 × aryl CH).

ν_{max} (NaCl solid) 3053s (C-H aromatic), 2963m (C-H), 2305w, 1457m, 1383w, 1285s, 699s, 733s cm^{-1}.

$^{m}/_{z}$ $C_{13}H_{15}NBr^{81}[M^{+}]$ requires 264.0388; observed 264.0375.

Synthesis of *anti*-7-bromo-2-benzyl-2-azabicyclo[2.2.1]heptane (85)



A degassed three-necked round-bottom flask which contained a mixture of lithium aluminium hydride (1.06 g, 27.931 mmol) and 3-bromo-1-benzyl-1-azoniatricyclo[2.2.1.$0^{2,6}$]heptane bromide (**78**) (6.11 g, 17.712 mmol) equipped with thermometer and addition funnel, was cooled to -78 °C using an acetone/dry ice bath under a nitrogen atmosphere; then dry THF (200 ml) was added drop-wise with stirring for 30 min at this temperature, then warmed to -20 °C over the duration of one hour. The reaction mixture was quenched with water-saturated diethyl ether until effervescence stopped; the solution was filtered, then the residue was washed with DCM and dried with anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude product was purified by flash chromatography (petroleum ether 40-60 ^{o}C: diethyl ether, 7:3) to give (**85**) as a pale yellow oil (3.06 g, 11.485 mmol, 67%).

δ_H (400 MHz, $CDCl_3$) 1.30-1.37, 1.69-1.89 (2× m, 4H, $H_{5,6}$), 2.30 (brs, 1H, H_4), 2.34 (d, *J* = 9.1, 1H, H_{3n}), 2.60 (dt, *J* = 9.1, 3.3Hz, 1H, H_{3x}), 3.11 (brs, 1H, H_1), 3.57 (AB quartet, *J* = 13.4, Hz, 2H, CH_2Ph), 4.13 (t, *J* = 2.7 Hz, 1H, H_{7s}), 7.10 – 7.21 (m, 5H, Ph).

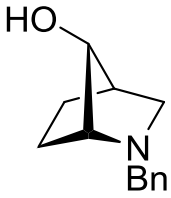
δ_C (100.62 MHz, CDCl3) 25.4, 26.8 (C_5, C_6), 44.1 (C_4), 53.6 (C_7), 58.1 (C_3), 59.2 (CH_2Ph), 65.1 (C_1), 127.0 128.4, 128.5 (5 × aryl CH) 139.2 (aryl C).

ν_{max} (NaCl film) 3085m, 2973s (C-H), 2856m (C-H), 1603w, 1494s, 1453s, 1313m, 1228m, 1154m, 788m cm^{-1}.

$^{m}/_{z}$ $C_{13}H_{17}NBr^{81}[MH^{+}]$ requires 266.0544; observed 266.0543.

Alternatively, reduction using Red-Al [95] (60 +% wt. solution in toluene, 9.2 ml, 28.0 mmol) and **3** (10.0 g, 28.0 mmol) in dry THF (245 ml) at -10 ^{o}C for 2 h to give 4 as a pale yellow oil (4.48 g, 6.856 mmol, 58%).

Synthesis of *anti*-7-hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (87)



According to the procedure described by Mitch *et al*.,[95] *anti*-7-bromo-2-benzyl-2-azabicyclo[2.2.1]heptane (**85**) (0.477 g, 1.792 mmol) was dissolved in 1-methyl-2-pyrrolidnone (containing 15% v/v H_2O: 9 ml). The mixture was stirred vigorously at 108 °C for 82 h, then water (25 ml) was poured in and the reaction basified with a solution of NaOH. The mixture was extracted with diethyl ether (4 × 15 ml), the combined organic layers was washed with water (4 × 15 ml), then dried using anhydrous $MgSO_4$; it was then filtered, then the solvent was evaporated *in vacuo*. The crude was purified by column chromatography using an eluent (ethyl acetate: methanol; 9:1) to yield (**87**) as a pale yellow oil (0.290 g, 1.43 mmol, 80%).

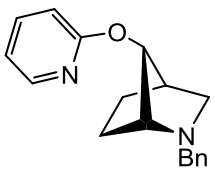
δ_H (400 MHz, $CDCL_3$) 1.34-1.40 (m, 1H, H_{5n}), 1.74-1.82 (m, 1H, H_{6X}), 1.91-1.20 (m, 2H, H_{5x}, H_{6n}), 2.12 (brs, 1H, H_4), 2.26 (d, J = 9.7 Hz, 1H, H_{3n}), 3.06-3.10 (m, 2H, $H_{1,}$ H_{3x}), 3.74 (AB quartet, J = 13.3 Hz, 2H, CH_2Ph), 4.31 (brs, 1H, H_7), 4.97 (brs, OH), 7.21 – 7.35 (m, 5H, Ph).

δ_C (100.62 MHz, $CDCl_3$) 22.2, 26.3 (C_5, C_6), 41.1 (C_4), 57.3 (CH_2Ph), 57.8 (C_3), 63.1 (C_1), 75.7 (C_7), 127.5, 128.4, 128.1 (5 × aryl CH), 137.2 (aryl C).

ν_{max} (NaCl film) 3366 brd (O-H), 3053m, 2967m (C-H), 2869m (C-H), 1495m, 1369m, 1265s cm^{-1}.

$^m/_z$ $C_{13}H_{18}NO$ [MH^+] requires 204.1388; observed 204.1389.

Synthesis of a*nti*-7-(pyridin-2-yloxy)-2-benzyl-2-azabicyclo[2,2,1]heptane (106)



To a solution of *anti*-7-hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (**87**) (137 mg, 0.67 mmol) in dry DMSO (9 ml), potassium *tert*-butoxide (99 mg, 0.88 mmol) was added and the mixture stirred under nitrogen at RT for 30 min. 2-Chloropyridine (0.08 ml, 0.85 mmol) was added and the mixture stirred for 72 h at 55 ^oC. Water (8.5 ml) was added to the reaction mixture then extracted with ethyl acetate. The combined extracts were dried over anhydrous $MgSO_4$ then evaporated *in vacuo*. The crude product was purified by column chromatography using an eluent diethyl ether to give (**106**) as a pale yellow oil (113 mg, 0.403 mmol, 60%).

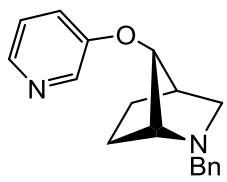
δ_H (300 MHz, $CDCl_3$) 1.39-1.45, 1.77-1.82, 1.86-1.95 (3 × m, 1H, 1H, 2H, H_5, H_6), 2.34 (d, *J* = 9.3 Hz, 1H, H_{3n}), 2.47 (brs, 1H, H_4), 3.08 (dt, *J* = 9.3, 3.3 Hz, 1H, H_{3x}), 3.34 (brs, 1H, H_1), 3.76 (AB quartet, *J* = 13.8 Hz, 2H, CH_2Ph), 5.24 (brs, 1H, H_7), 6.69 (d, *J* = 8.3 Hz, 1H, $H_{3`}$), 6.84 (ddd, *J* = 7.9, 5.1, 0.8 Hz, 1H, $H_{5`}$), 7.19-7.37 (m, 5H, Ph), 7.63 (ddd, *J* = 8.4, 7.1, 1.7 Hz, 1H, $H_{4`}$), 8.16 (ddd, *J* = 5.1, 1.7, 0.6 Hz, 1H, $H_{6`}$).

δ_C (75.5 MHz, $CDCl_3$) 24.5, 26.8 (C_5, C_6), 40.0 (C_4), 57.7 (C_3), 58.5 (CH_2Ph), 61.4 (C_1), 79.1 (C_7), 111.1 ($C_{3`}$), 116.8($C_{5`}$), 126.7, 128.2, 128.5 (5 × aryl CH), 138.5 ($C_{4`}$), 139.8 (aryl C), 147.1 ($C_{6`}$), 162.6 ($C_{2`}$).

ν_{max} (NaCl film) 2967m (C-H), 1569m, 1596m, 1432s, 1470s, 1304m (C-N), 1288s (C-O), 1057m cm^{-1}.

$^m/_z$ $C_{18}H_{21}N_2O$ [MH^+] requires 281.1654; observed 281.1647.

Synthesis of *anti*-7- (pyridin-3-yloxy)-2-benzyl-2-azabicyclo[2,2,1]heptane (108)



According to the procedure described by Krow *et al*.[61], a solution of *anti*-7-hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (**87**) (192 mg, 0.94 mmol) in dry THF (8 ml) was added slowly to 3-hydroxypyridine (117 mg, 1.23 mmol) and triphenylphosphine (320 mg, 1.22 mmol). The solution was stirred under nitrogen at 5 ^oC followed by addition of DIAD (0.25 ml, 1.25 mmol) in dry THF (4 ml) drop-wise. The reaction mixture allowed to reach to RT and stirred under nitrogen for 48 h. The solvent was evaporated, and the resulting residue was dissolved in aqueous HCl (1 M), washed with diethyl ether (2 × 20 ml), the aqueous layer was basified with ammonium hydroxide solution and finally extracted with DCM (4 × 20 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure, and the crude product was flash chromatographed (diethyl ether) to give (**108**) as a pale yellow oil (80 mg, 0.29 mmol, 30%).

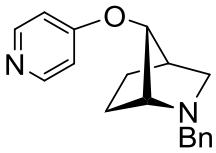
δ_H (300 MHz, CDCl3) 1.40-1.48 (m, 1H, H_{6n}), 1.70-1.78 (m, 1H, H_{6x}), 1.90-2.02 (m, 2H,H_5), 2.29 (d, *J* = 9.3 Hz, 1H, H_{3n}), 2.44 (brs, 1H, H_4), 3.13 (dt, *J* = 9.3, 3.4 Hz, 1H, H_{3x}), 3.33 (brs, 1H, H_1), 3.73 (AB quartet, *J* = 13.4 Hz, 2H, CH_2Ph), 4.71 (brs, 1H, H_7), 7.18-7.32 (m, 7H, Ph, $H_{4`}$,$H_{5`}$), 8.21 (brd, *J* = 3.7 Hz, 1H, $H_{6`}$), 8.35 (brd, *J* = 2.6 Hz, 1H, $H_{2`}$).

δ_C (75.5 MHz, CDCl3) 22.7, 26.6 (C_5, C_6), 41.6 (C_4), 57.7 (C_3), 63.0 (C_1), 81.5 (C_7), 126.9, 127.0, 128.3, 128.7 (5 × aryl CH)], 138.4 (aryl C)], 141.9 (4 × pyridyl CH), 154.6 (pyridyl C).

ν_{max} (NaCl film) 3054m, 2928m (C-H), 2964m, 1603w, 1437m, 1452m, 1265s, 1183w cm^{-1}.

m/z $C_{18}H_{21}N_2O$ [MH^+] requires 281.1654; observed 281.1653.

Synthesis of *anti*-7-(pyridin-4-yloxy)-2-benzyl-2-azabicyclo[2,2,1]heptane (110)



According to the procedure described by Krow *et al*.,[61] a solution of *anti*-7-hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (**87**) (230 mg, 1.13 mmol) in dry THF (10 ml) was added drop-wise to 4-hydroxypyridine (127 mg, 1.35 mmol) and triphenylphosphine (459 mg, 1.76 mmol). This mixture was stirred under nitrogen at 5 ^oC and a solution of DIAD (0.29 ml, 1.50 mmol) in THF (2 ml) was added drop-wise. The mixture was allowed to reach to RT slowly and stirred under nitrogen for 48 h, and the solvent was then evaporated. The resulting residue was dissolved in aqueous HCl (1 M), washed with diethyl ether (2×20 ml), basified with ammonium hydroxide solution and extracted with DCM (3×20 ml). The organic extracts were dried over anhydrous $MgSO_4$, filtered then evaporated under reduced pressure; the crude was flash chromatographed (diethyl ether) to give (**110**) as a pale yellow oil (106 mg, 0.38 mmol, 33%).

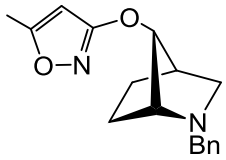
δ_H (400 MHz, $CDCl_3$) 1.32-1.40 (m, 1H, H_{6n}), 1.58-1.66 (m, 1H, H_{6x}), 1.79-1.94 (m, 2H, H_5), 2.20 (d, J = 9.5 Hz, 1H, H_{3n}), 2.37 (brs, 1H, H_4), 3.00 (dt, J = 9.5, 3.5 Hz, 1H, H_{3x}), 3.26 (brs, 1H, H_1), 3.65 (AB quartet, J = 13.4 Hz, 2H, CH_2Ph), 4.60 (brs, 1H, H_7), 6.77 (d, J = 6.3Hz, 2H, $H_{3`}$, $H_{5`}$), 7.14-7.29 (m, 5H, Ph), 8.32 (d, J = 6.3Hz, 2H, $H_{2`}$, $H_{6`}$).

δ_C (100.62 MHz, $CDCl_3$) 23.2, 26.9 (C_5, C_6), 39.9 (C_4), 57.3 (C_3), 57.7 (CH_2Ph), 61.0 (C_1), 81.0 (C_7), 110.8 ($C_{3`}$, $C_{5`}$), 126.9, 128.3, 128.5 (5 × aryl CH), 139.2 (aryl C), 151.1 ($C_{2`}$, $C_{6`}$), 164.3 ($C_{4`}$).

ν_{max} (NaCl film) 3028w, 2968m (C-H), 2848m (C-H), 1593s, 1569m, 1497s, 1372w, 1280s, 1211m, 1057m cm^{-1}.

m/z $C_{18}H_{21}N_2O$ [MH^+] requires 281.1654; observed 281.1651.

Synthesis of *anti*-7-(5-methylisoxazole-3-yl)-2-benzyl-2-azabicyclo[2.2.1]heptane (121)



According to the producer, as described by Yu,[118] to a stirred solution of *anti*-7-hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (**87**) (243.9 mg, 1.20 mmol), 5-methyl-3-isoxazolol (**117**) (99.1 mg, 1.00 mmol) and PPh_3 (393 mg, 1.5 mmol) in dry THF (20 ml) were added, followed by DIAD (0.29 ml, 1.5 mmol) drop-wise. After stirring overnight at RT, the solvent was evaporated until dryness and the residue was dissolved in ethyl acetate, the mixture solution was washed with water (2 × 20 ml) and saturated sodium chloride (2 × 20 ml), dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash chromatography of the crude residue (8:2; DCM: ethyl acetate) to give (**121**) as an orange oil (52 mg, 0.20 mmol, 15%).

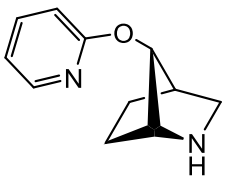
δ_H (400 MHz, $CDCl_3$) 1.18-1.47 (m, 2H, H_5), 1.68-1.95 (m, 3H, H_6, H_{3n}), 2.31 (d, J = 1.0 Hz, 3H, Me), 2.52 (brs, 1H, H_4), 3.00 (dt, J = 9.3, 3.2 Hz, 1H, H_{3x}), 3.36 (brs, 1H, H_1), 3.71 (brs, 2H, CH_2Ph), 4.93 (brs, 1H, H_7), 5.60 (d, J = 1.0 Hz, 1H, isoxazole CH), 7.19-7.34 (m, 5H, Ph).

δ_C (100.62 MHz, $CDCl_3$) 12.9 (isoxazole CH_3), 26.4, 29.2 (C_5, C_6), 39.9 (C_4), 57.5 (C_3), 58.3 (CH_2Ph), 61.1(C_1), 82.7 (C_7), 93.2 (isoxazole CH), 126.8, 128.3, 128.5 (5 × aryl CH), 139.5 (aryl C), 170.2, 171.5 (2 × isoxazole C).

ν_{max} (NaCl film) 2973m (C-H), 1736w, 1523m, 1400s, 1464s, 1304m, 1261m, 1108m cm^{-1}.

$^m/_z$ $C_{17}H_{21}N_2O_2$ [MH^+] requires 285.1603; observed 285.1608.

Synthesis of a*nti*-7-(pyridin-2-yloxy)-2-azabicyclo[2,2,1]heptane (107)



The protected amine (**106**) (195 mg, 0.70 mmol) was dissolved in dry methanol (15 ml). Palladium on charcoal (10%, 115 mg) was added under an atmosphere of hydrogen at RT. After 24 h, the reaction mixture was filtered through celite and washed with methanol (2 × 100 ml), and the solvent was removed under reduced pressure. The crude product was flash chromatographed (9:1; diethyl ether: methanol) to offer (**107**) as a red oil (65 mg, 0.34 mmol, 49 %).

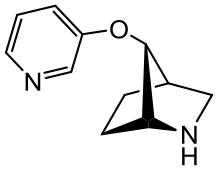
δ_H (400 MHz, $CDCl_3$) 1.66-1.70 (m, 2H, H_5), 2.04-2.11 (m, 2H, H_6), 2.80 (brs, 1H, H_4), 3.13 (d, *J* = 9. 8 Hz, 1H, H_{3n}), 3.45 (brd, *J* = 9.8 Hz, 1H, H_{3x}), 4.06 (brs, 1H, H_1), 5.32 (brs, 1H, H_7), 6.71 (d, *J* = 8.3 Hz, 1H, $H_{3`}$), 6.92 (ddd, *J* = 8.2, 5.0, 0.6 Hz, 1H, $H_{5`}$),7.59 (ddd, J = 7.2, 8.3, 1.6 Hz, 1H, $H_{4`}$), 8.15 (dd, *J* = 5.0, 1.6 Hz, 1H, $H_{6`}$).

δ_C (100.62 MHz, $CDCl_3$) 26.3, 29.3 (C_5, C_6), 38.4 (C_4), 49.5 (C_3), 56.3 (C_1), 80.8 (C_7), 111.1($C_{3`}$), 116.0 ($C_{5`}$), 138.6 ($C_{4`}$), 147.0 ($C_{6`}$), 163.5 ($C_{2`}$).

ν_{max} (NaCl film) 3348brd m (N-H), 2969m (C-H), 2873m (C-H), 1597m, 1570m, 1432s, 1471s, 1273s, 1287s, 1143m, 1059m cm^{-1}.

$^m/_z$ $C_{11}H_{15}N_2O$ [MH^+] requires 191.1184; observed 191.1183.

Synthesis of *anti*-7- (pyridin-3-yloxy)-2-azabicyclo[2,2,1]heptane (109)



The protected amine (**108**) (143 mg, 0.51 mmol) was dissolved in dry methanol (11 ml). Palladium activated on carbon (10%, 84 mg) was added under an atmosphere of hydrogen at RT. After 24 h, the mixture was filtered through celite and washed with methanol (2× 60 ml), and the solvent removed *in vacuo*. The crude product was purified by flash chromatography (9: 1-7: 3; diethyl ether: methanol), yielding (**109**) as a pale yellow oil (47 mg, 0.25 mmol, 49%).

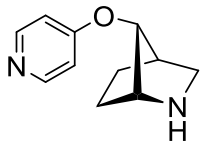
δ_H (400 MHz, $CDCl_3$) 1.59-1.70, 1.82-1.92 (2× m, 1H, 3H, H_5, H_6), 2.21 (brs, 1H, H_4), 2.36 (brs, 1H, H_{3n}), 3.07 (dt, *J* = 9.3, 3.4 Hz, 1H, H_{3x}), 3.20 (brs, 1H, H_1), 4.63 (brs, 1H, H_7), 7.13 (dd, *J* = 8.4, 4.0 Hz, 1H, $H_{5`}$), 7.22 (ddd, *J* = 8.4, 4.0, 1.4 Hz, 1H, $H_{6`}$),8.15 (brd, *J* = 4.0 Hz, 1H, $H_{4`}$), 8.29 (brd, *J* = 2.7 Hz, 1H, $H_{2`}$).

δ_C (100.62 MHz, $CDCl_3$) 22.5, 26.8 (C_5, C_6), 40.2 (C_4), 58.8 (C_3), 62.9 (C_1), 81.3 (C_7), 121.9($C_{6`}$), 123.9 ($C_{5`}$), 138.9 ($C_{2`}$), 142.5 ($C_{4`}$), 154 (pyridyl C).

ν_{max} (NaCl film) 3054m (pyridyl aromatic), 2986m (C-H), 1595w, 1343m, 1421m, 1285s cm^{-1}.

$^m/_z$ $C_{11}H_{15}N_2O$ [MH^+] requires 191.1184; observed 191.1191.

Synthesis of *anti*-7-(pyridin-4-yloxy)-2-azabicyclo[2,2,1]heptane(111)



The protected amine (**110**) (74 mg, 0.264 mmol) was dissolved in dry methanol (5 ml). Palladium activated on carbon (10%) (44 mg) was added under an atmosphere of hydrogen at RT. The mixture medium was acidified with glacial acetic acid and allowed to stir vigorously for 24 h, filtered through celite and washed with methanol (2 × 50 ml), and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (9: 1-7: 3; diethyl ether: methanol, triethyl amine), yielding (**111**) as a pale yellow oil (33 mg, 0.17 mmol, 66%).

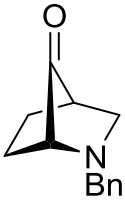
δ_H (400 MHz, $CDCl_3$) 1.43-2.01 (m, 4H, H_5, H_6), 2.51 (brs, 1H, H_4), 2.85 (brs, 1H, H_{3n}), 3.11-3.32 (m, 1H, H_{3x}), 3.56 (brs, 1H, H_1), 4.20 (brs, NH), 4.74 (brs, 1H, H_7), 6.89 (d, *J* = 5.4 Hz, 2H, $H_{5`}$, $H_{3`}$), 8.43 (brs, 2H, $H_{6`}$, $H_{2`}$).

δ_C (100.62 MHz, $CDCl_3$) 26.0, 28.5 (C_5, C_6), 38.2 (C_4), 48.8 (C_3), 56.0 (C_1), 81.5 (C_7), 110.8($C_{3`}$, $C_{5`}$), 151.1 ($C_{2`}$, $C_{6`}$), 164.0 ($C_{4`}$).

ν_{max} (NaCl film) 3054m, 2986m (C-H), 1595w, 1343m, 1421m, 1285s cm^{-1}.

$^m/_z$ $C_{11}H_{15}N_2O$ [MH^+] require191.1184; observed 191.1188.

Synthesis of 7-keto-2-benzyl-2-azabicyclo[2,2,1]heptane(123)



A mixture of anhydrous DMSO (3.70 ml, 52.14 mmol) in anhydrous DCM (50 ml) was added drop-wise with stirring to a mixture of oxalyl chloride (2.34 ml, 27.65 mmol) in anhydrous DCM (50 ml) at -78 ^oC and stirred under nitrogen for 30 min. The *anti*-alcohol (**87**) (2.222 g, 10.93 mmol) in anhydrous DCM (50 ml) was added dropwise at -78 ^oC followed by stirring for 25 minutes. This was followed by adding anhydrous triethylamine (9.2 ml, 65.72 mmol). After allowing the reaction to reach RT slowly, the mixture was washed with water (2 × 117 ml) then saturated $NaHCO_3$ solution (5 × 117 ml). The organic layer was dried with anhydrous $MgSO_4$ and the solvent evaporated in *vacuo*, to provide **(123)** as an orange oil (1.547 g, 7.69 mmol, 66%). The crude product was not purified using flash chromatography because it was not stable.

δ_H (400 MHz, $CDCl_3$) 1.61-1.67, 1.73-1.85, 1.96-2.05 (3 × m, 1H,1H, 2H, H_5, H_6), 2.20 (brs, 1H, H_4), 2.57 (d, *J* = 3.2 Hz, 1H, H_1), 2.73 (d, *J* = 9.3 Hz, 1H, H_{3n}), 2.91 (ddd, *J* = 9.3, 4.1, 1.3 Hz,1H, H_{3x}), 3.62 (brs, 2H, CH_2Ph), 7.13-7.27 (m, 5H, Ph).

δ_C (100.62 MHz, CDCl3) 22.5, 23.9 (C_5, C_6), 39.8 (C_4), 55.5 (C_3), 58.1 (C_1), 59.3 (CH_2Ph), 127.2, 128.4, 128.7 (5 × aryl CH), 138.2 (aryl C), 211.9 (C_7).

ν_{max} (NaCl film) 2970m (C-H), 1712s (C=O), 1494m, 1435m, 1369m, 1133m cm^{-1}.

$^{m}/_{z}$ $C_{13}H_{16}NO$ [MH^+] requires 202.1232; observed 202.1238.

Synthesis of *syn*-7-hydroxy-2-benzyl-2-azabycyclo[2,2,1]heptane(124)

To a solution of 7-keto-2-benzyl-2-azabicyclo[2.2.1] (**123**) (0.799 g, 3.97 mmol) in dry methanol (21 ml), sodium borohydride (1.029 g, 27.53 mmol) was added with cooling in ice. The solution was stirred under a nitrogen atmosphere at 60 ^{o}C for 48 h. The reaction was quenched with water (73 ml) and the aqueous layer extracted with DCM (4 × 85 ml). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated using a freeze dryer. The crude residue contained (**124**) and *anti*-7-hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (**87**) (94:6 by integration of ^{1}H NMR signals). Flash chromatography (diethyl ether: trimethylamine: 99.9: 0.1) gave (**124)** as a pale yellow crystal (0.58 g, 2.86 mmol, 73%). m.p. 69-71°C. The *syn*-configuration of (**124**) was confirmed by X-ray crystallography (see appendix 1).

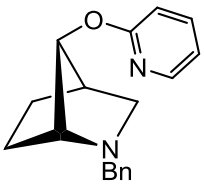
δ_H (400 MHz, $CDCl_3$). 1.19-1.40, 1.52-1.61, 1.78-1.85 (3 × m, 2H, 1H, 1H, H_5, H_6), 1.94 (d, *J* = 9.2 Hz, 1H, H_{3n}), 2.01 (brs, 1H, H_4), 3.00 (brs, OH), 3.13 (dt, *J* = 9.2, 3.7 Hz, 1H, H_{3x}), 3. 72 (AB quartet, *J* = 13.4 Hz, 2H, CH_2Ph), 3.87 (brs, 1H, H_7), 7.14-7.27 (m, 5H, Ph).

δ_C (100.62 MHz, $CDCl_3$) 20.4, 27.3 (C_5, C_6), 41.9 (C_4), 54.9 (C_3), 55.1 (CH_2Ph), 62.9(C_1), 78.1 (C_7), 126.9, 128.3, 128.4 (5 × aryl CH), 139.5 (aryl C).

ν_{max} (NaCl solid) 3419brd (OH), 2964m, 2874m (C-H), 1494w, 1454w, 1285s cm^{-1}.

$^{m}/_{z}$ $C_{13}H_{18}NO$ [MH^+] requires 204.1388; observed 204.1389.

Synthesis of *syn*-7-(pyridin-2-yloxy)-2-benzyl-2-azabicyclo[2.2.1]heptane (141)



To a stirred solution of *syn*-7-hydroxy-2-benzyl-2-azabycyclo[2,2,1] heptane(**124**) (250 mg, 1.23 mmol) in anhydrous 1-methyl-2-pyrrolidnone (16 ml), 2-chloropyridine (0.3 ml, 3.17 mmol) and sodium hydride (60% dispersion, 0.8 g) were added at 140^{o}C under an atmosphere of nitrogen and the reaction stirred for 96 h. The reaction mixture was quenched by adding water (12 ml) and extracted with ethyl acetate (3 × 10 ml), and the organic layers were dried over anhydrous $MgSO_4$, evaporated *in vacuo*. The crude product was flash chromatographed (1:1; petroleum ether b.p. 40-60 ^{o}C): diethyl ether) to afford (**141)** as a pale yellow oil (181 mg, 0.65 mmol, 53%).

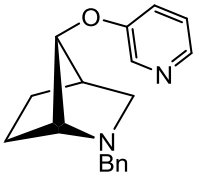
δ_H (400 MHz, $CDCl_3$) 1.59-1.75, 1.60-1.84 (2 × m, 4H, H_5, H_6), 2.38 (brs, 1H, H_4), 2.61(d, J = 8.9 Hz, 1H, H_{3n}) 3.06 (dt, J = 8.9, 2.9 Hz, 1H, H_{3x}), 3.22-3.26 (m, 1H, H_1), 3.83 (AB quartet, J = 13.7 Hz, 2H, CH_2Ph), 4.95 (brs, 1H, H_7), 6.74 (d, J = 8.4 Hz, 1H, $H_{3`}$), 6.79 (ddd, $J$ = 7.2, 5.6, 0.8 1H, $H_{5`}$), 7.08-7.38 (m, 5H, Ph), 7.51 (ddd, J = 8.4, 7.2, 1.7 Hz, 1H, $H_{4`}$), 8.08 (dd, $J$ = 5.0, 2.0 Hz, 1H, $H_{6`}$).

δ_C (100.62 MHz, $CDCl_3$) 25.1, 26.6 (C_5, C_6), 40.1 (C_4), 58.4 (C_3), 60.1 (CH_2Ph), 61.7 (C_1), 80.9 (C_7), 111.5 ($C_{3`}$), 116.7 ($C_{5`}$), 125.5, 126.5, 128.3 (5 × aryl CH), 138.6 ($C_{4`}$), 147.0 ($C_{6`}$), 163.8 (pyridyl C).

ν_{max} (NaCl film) 3025w, 2964m (C-H), 2872m (C-H), 1598m, 1570m, 1471s, 1433m, 1370w, 1265s, 1058m.

$^{m}/_{z}$ $C_{18}H_{21}N_2O$ [MH^+] requires 281.1654; observed 281.1646.

Synthesis of *syn*-7-(pyridin-3-yloxy)-2-benzyl-2-azabicyclo[2.2.1]heptane (145)



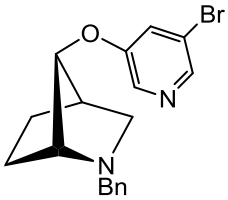
According to the procedure described by Wolter *et al*.,[132] a mixture of caesium carbonate (1000 mg, 3.07 mmol), copper iodide (123 mg, 0.65 mmol), 1,10-phenanthroline (225 mg, 1.25 mmol) and 3-iodopyridine (103.5 mg, 0.50 mmol) was added to a solution of toluene (1 ml) and *syn*-7-hydroxy-2-benzyl-2-azabycyclo[2,2,1]heptane (**124**) (423 mg, 2.08 mmol). This heterogeneous mixture was stirred at 110 ^{o}C for 96 h then filtered using sintered funnel with washing by (ethyl acetate: methanol; 9: 1), the solvents were removed *in vacuo* and the crude residue as flash chromatographed (diethyl ether) to give (**145**) as yellow oil (21 mg, 0.08 mmol, 4%).

δ_H (300 MHz, $CDCl_3$) 1.58-1.75 (m, 4H, $H_{5,}$ H_6), 2.41 (brs, 1H, H_4), 2.63 (d, *J* = 9.0 Hz, 1H, H_{3n}), 3.06 (dt, *J* = 9.0, 3 Hz, 1H, H_{3x}), 3.27 (brs, 1H, H_1), 3.87 (AB quartet, *J* = 13.6 Hz, 2H, CH_2Ph), 4.98 (brs, 1H, H_7), 7.13-7.56 (m, 7H, Ph, $H_{4`}$, $H_{5`}$), 8.05 (dd, *J* = 8.0, 1.0 Hz, 2H, $H_{6`}$ , $H_{2`}$).

δ_C (100.62 MHz, $CDCl_3$) 22.0, 29.7 (C_5, C_6), 40.3 (C_4), 58.0 (C_3), 59.7 (CH_2Ph), 62.2 (C_1), 80.2 (C_7), 128.2, 128.4, 128.5, 129.7 (5 × aryl CH), 164.3 (pyridyl C).

$^m/_z$ $C_{18}H_{21}N_2O$ [MH^+] requires 281.1654; observed 281.1658.

Synthesis of *syn*-7-(5-bromo-pyridin-3-yloxy)-2-benzyl-2-azabicyclo[2.2.1]heptane (146)



According to the procedure that described by Wei *et al*.[112] To a stirred solution of *syn*-7-hydroxy-2-benzyl-2-azabycyclo[2,2,1]heptane (**124**) (147 mg, 0.72 mmol) in dry DMF (11 ml) was added sodium hydride (60% in mineral oil, 37.9 mg, 1.58 mmol) under nitrogen for 2 h, followed by adding 3,5-dibromopyridine (224.5 mg 0.95 mmol). After being stirred at 50 ^oC for a further 6 h. The reaction mixture was diluted with water (8 ml) and extracted with ethyl acetate. The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was flash chromatographed (9: 1, diethyl ether: methanol) yielding the *syn*-alcohol (**124**) (22 mg) and (**146**) as a pale yellow oil (63 mg, 0.18 mmol, 25%).

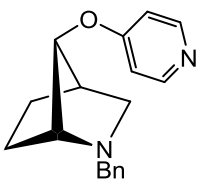
δ_H (400 MHz, $CDCl_3$) 1.36-1.78 (m, 4H, $H_{5,}$ H_6), 2.38 (brs, 1H, H_4), 2.60 (d, *J* = 9.0 Hz, 1H, H_{3n}), 3.04 (dt, *J* = 9.0, 3.2 Hz, 1H, H_{3x}), 3.24 (brs, 1H, H_1), 3.79 (AB quartet, *J* = 13.6 Hz, 2H, CH_2Ph), 4.35 (brs, 1H, H_7), 7.10-7.25 (m, 5H, Ph), 7.34-7.36 (m, 1H, pyridyl), 8.18-8.24 (m, 2H, pyridyl).

δ_C (100.62 MHz, $CDCl_3$) 22.2, 24.0 (C_5, C_6), 40.0 (C_4), 56.2 (C_3), 58.7 (CH_2Ph), 60.0 (C_1), 82.8 (C_7), 119.3 (pyridyl C), 123.9 (pyridyl CH), 125.7, 127.2, 127.3 (5 × aryl CH), 136.1, 142.1 (2× pyridyl CH), 153.9 (pyridyl C).

ν_{max} (NaCl film) 3053m (C-H aromatic), 2884m (C-H), 1574m, 1422m, 1370w, 1255s, 738s.

$^m/_z$ $C_{18}H_{20}N_2OBr^{79}$[MH^+] requires 359.0759; observed 359.0764.

Synthesis of *syn*-7-(pyridin-4-yloxy)-2-benzyl-2-azabicyclo[2.2.1]heptane (143)



Potassium *tert*-butoxide (379 mg, 3.38 mmol) was added at RT over a stirred solution prepared from *syn*-hydroxy-2-benzyl-2-azabicyclo[2.2.1] heptane (**124**) (258 mg, 1.27 mmol) in dry DMSO (21 ml) under nitrogen atmosphere for 30 min. 4-cloropyridine hydrochloride (217 mg, 1.45 mmol) was added and allowed to raise the temperature to 50 ^{o}C, after which stirring was continued for a further 7 h. The mixture was then quenched with water (21 ml) and extracted with diethyl ether (3 × 10 ml). The organic layers were dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo*. Flash chromatography (diethyl ether: triethylamine) to gave (**143)** as a pale yellow oil (250 mg, 0.89 mmol, 72 %).

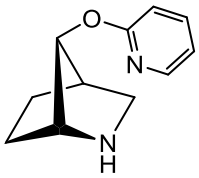
δ_H (400 MHz, $CDCl_3$) 1.33-1.39, 1.59-1.67, 1.79—1.94 (3 × m, 1H, 1H. 2H, H_5, H_6), , 2.21 (d, J = 9.4 Hz, 1H, H_{3n}), 2.37 (brs, 1H, H_4), 3.04 (dt, J = 9.4, 3.4 Hz, 1H, H_{3x}), 3.26 (brs, 1H, H_1), 3.65 (AB quartet, J = 13.4 Hz, 2H, CH_2Ph), 4.64 (brs, 1H, H_7), 6.77 (dd, J = 4.7, 1.6 Hz, 2H, pyridyl), 7.14-7.27 (m, 5H, Ph), 8.33 (dd, J = 4.7, 1.6 Hz, 2H, pyridyl).

δ_C (100.62 MHz, $CDCl_3$) 23.2, 26.9 (C_5, C_6), 40.0 (C_4), 57.3 (C_3), 57.7 (CH_2Ph), 61.0 (C_1), 81.0 (C_7), 110.8 (pyridyl CH), 125.9, 127.3, 127.4 (5 × aryl CH), 151.6 (pyridyl CH), 164.3 (pyridyl C).

ν_{max} (NaCl film) 3029, 2967m (C-H), 2870m (C-H), 1593m, 1569m, 1497s, 1453m, 1319w, 1280s, 1058m cm^{-1}.

$^{m}/_{z}$ $C_{18}H_{21}N_2O$ [MH^+] requires 281.1654; observed 281.1660.

Synthesis of *syn*-7-(pyridin-2-yloxy)-2-azabicyclo[2.2.1]heptane (142)



The protected amine (**141**) (60 mg, 0.21 mmol) was dissolved in dry methanol (6 ml). Palladium activated on carbon (10%, 35 mg) was added to the reaction flask. The mixture was allowed to stir at RT under a hydrogen atmosphere for 24 h then filtered through celite and washed with methanol (2× 50 ml), and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (9:1; diethyl ether: methanol), yielding (**142**) as a pale yellow oil (35 mg, 0.18 mmol, 86%).

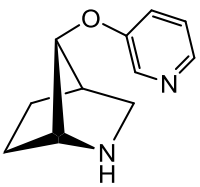
δ_H (400 MHz, $CDCl_3$) 1.65-1.99, 2.35-2.44 (2× m, 3H, 1H, H_5, H_6), 2.71 (brs, 1H, H_4), 3.28-3.31 (m, 1H, H_{3n}), 3.47 (brd, *J* = 9.9 Hz, 1H, H_{3x}), 3.71 (brs, 1H, H_1), 5.24 (brs, 1H, H_7), 6.80 (dd, *J* = 9.0, 0.6 Hz, 1H, $H_{3`}$), 6.95 (ddd, *J* = 7.5, 5.1, 0.6 Hz, 1H, $H_{5`}$),7.63 (ddd, *J* = 9.0, 7.5, 2.0 Hz, H, $H_{4`}$), 8. 16 (dd, *J* = 5.1, 2.0 Hz, 1H, $H_{6`}$).

δ_C (100.62 MHz, $CDCl_3$) 23.5, 29.7 (C_5, C_6), 39.8 (C_4), 59.8 (C_3), 66.2 (C_1), 80.4 (C_7), 111.3($C_{3`}$), 117.0 ($C_{5`}$), 139.2 ($C_{4`}$), 147.1 ($C_{6`}$), 162.6 (pyridyl C).

ν_{max} (NaCl film) 3401 brd m (N-H), 2925m (C-H), 2854m (C-H), 1598m, 1559m, 1470s, 1433s, 1317w, 1268s, 1142w cm^{-1}.

m/z $C_{11}H_{15}N_2O$ [MH^+] requires 191.1184; observed 191.1181.

Synthesis of *syn*-7-(pyridin-3-yloxy)-2-azabicyclo[2.2.1]heptane (147)



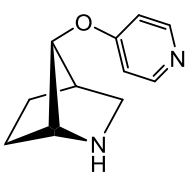
The protected amine (**146**) (43 mg, 0.12 mmol) was dissolved in dry methanol (4 ml). Palladium activated on carbon (10%, 25 mg) was added to a degassed round-bottomed flask. The mixture was acidified with glacial acetic acid and allowed to stir at RT under a hydrogen atmosphere for 24 h. The mixture was filtered through celite and washed with methanol (2 × 50 ml), and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (9:1- 7: 3; diethyl ether: methanol, triethyl amine), yielding (**147**) as a pale yellow oil (10 mg, 0.05 mmol, 44%).

δ_H (400 MHz, $CDCl_3$) 1.43-1.76 (m, 4H, H_5, H_6), 2.16 (brs, NH), 2.38 (brs, 1H, H_4), 2.62 (brs, 1H, H_{3n}), 3.48 (brs, 1H, H_{3x}), 3.69 (brs, 1H, H_1), 4.56 (brs, 1H, H_7), 7.39-7.43 (m, 2H, 2× pyridyl), 7.75-7.81 (m, 2H, 2× pyridyl).

δ_C (75.5 MHz, $CDCl_3$) 26.8, 28.6 (C_5, C_6), 39.7 (C_4), 57.2 (C_3), 61.0 (C_1), 80.7 (C_7),125.6, 127.6, 128.5, 128.7 (4 × pyridyl C-H), 151.1 (pyridyl C).

m/z $C_{11}H_{15}N_2O$ [MH^+] requires 191.1184; observed 191.1180.

Synthesis of *syn*-7-(pyridin-4-yloxy)-2-azabicyclo[2.2.1]heptane (144)



The protected amine (**143**) (33 mg, 0.12 mmol) was dissolved in dry methanol (3 ml). Palladium activated on carbon (10%, 20 mg) was added to a degassed round-bottomed flask. The mixture medium was acidified with glacial acetic acid and allowed to stir at RT under a hydrogen atmosphere for 24 h, then filtered through celite and washed with methanol (2 × 30 ml).

The solvent was removed *in vacuo*. The crude product was purified by flash chromatography (9: 1; diethyl ether: methanol, 7: 3; diethyl ether: methanol, triethyl amine), yielding (**144**) as a pale yellow oil (15 mg, 0.08 mmol, 68%).

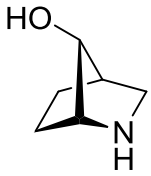
δ_H (300 MHz, $CDCl_3$) 1.26-1.81 (m, 4H, H_5, H_6), 2.47 (brs, 1H, H_4), 2.66 (d, J = 9.2 Hz, 1H, H_{3n}), 3.14 (dt, J = 9.2, 3.1 Hz, 1H, H_{3x}), 3.29 (brs, 1H, H_1), 4.50 (brs, H_7), 4.71 (brs, NH), 6.87 (dd, J = 4.9, 1.3 Hz, 2H, pyridyl), 8.43 (brs, 2H, pyridyl).

δ_C (125.77 MHz, $CDCl_3$) 24.9, 29.7 (C_5, C_6), 40.0 (C_4), 41.8 (C_3), 58.8 (C_1), 83.0 (C_7), 110.9 (pyridyl CH), 151.1 (pyridyl CH), 164.2 (pyridyl C).

ν_{max} (NaCl film) 2986m (C-H), 1505w, 1363w, 1421m, 1265s cm^{-1}.

$^m/_z$ $C_{11}H_{15}N_2O$ [MH^+] require191.1184; observed 191.1185.

Synthesis of *anti*-7-hydroxy-2-azabicyclo[2.2.1]heptane (181)



The catalyst palladium activated on carbon (10%, 230 mg) was added to degassed solution of *anti*-7-hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (**87**) (646 mg, 3.18 mmol) in dry methanol (18 ml) and stirred at RT for 24 h. After the completion of the reaction, the catalyst was removed by filtration through celite, which was then washed with methanol (4 × 20 ml) and concentrated *in vacuo*. The crude product was flash chromatographed on silica gel (9:1; diethyl ether: methanol: triethylamine) to afford (**181**) as a pale yellow oil (183 mg, 1.62 mmol, 51%).

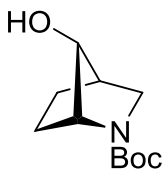
δ_H (400 MHz, $CDCl_3$) 1.40-2.05 (2 × m, 4H, H_5, H_6), 2.11 (brs, 1H, H_4), 2.63 (d, J = 9.9 Hz, 1H, H_{3n}), 2.82 (brs, 1H, NH), 3.01 (dt, J = 9.9, 3.0 Hz, 1H, H_{3x}), 3.09 (brs, 1H, H_1), 4.21 (brs, 1H, H_7).

δ_C (100.62 MHz, $CDCl_3$) 25.9, 29.8 (C_5, C_6), 40.4 (C_4), 49.7 (C_3), 58.1(C_1), 77.1 (C_7).

ν_{max} (NaCl film) 3418brd, 2924m, 1616m, 1378m, 1458m, 1170m cm^{-1}.

$^m/_z$ $C_6H_{12}NO$ [MH^+] requires 114.0919; observed 114.0922.

Synthesis of *anti*-7-hydroxy-2-Boc-2-azabicyclo[2.2.1]heptane (182)



Anti-7-hydroxy-2-azabicyclo[2.2.1]heptane (**181**) (1.0 g, 8.84 mmol) was dissolved in THF (22 ml) and water (67 ml), then treated with Boc_2O (2.7 g, 12.37 mmol) and $NaHCO_3$ (2.13g, 25.35 mmol) were stirred at RT for 24 h. The reaction mixture was extracted with diethyl ether (4 × 30 ml), and the

combined organic phase was dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. The resulting crude was chromatographed (diethyl ether) yielding (**182**) (1.70g, 8.00 mmol, 90 %) as white crystals. m.p. 68-72 °C.

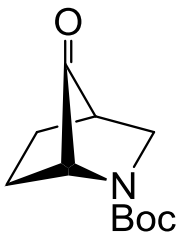
δ_H (400 MHz, $CDCl_3$); where there is signal duplication because of slow N-CO rotation (ratio ~ 38: 62), the minor rotamer signal is underlined. 1.44 (brs, 3H) and 1.46 (brs, 6H, BocCH_3), 1.59-2.03 (2 × m, 1H, 3H, H_5, H_6), 2.82 (brs, 1H, H_4), 2.96 (d, J = 9.8 Hz, 0.4H) and 3.03 (d, J = 9.8 Hz, 0.6H, H_{3n}), 3.30-3.33 (m, 1H, H_{3x}), 3.87 (brs, 0.6H) and 3.98 (brs, 0.4H, H_1), 4.15 (brs, 1H, H_7).

δ_C (100.62 MHz, $CDCl_3$) 25.1, 25.3, 27.7, 28.0 (C_5, C_6), 28.7 (Boc CH_3), 40.8, 41.1 (C_4), 50.9, 51.8 (C_3), 58.2, 59.2 (C_1), 76.0, 76.2 (C_7), 79.5 (Boc C), 154.3, 154.9 (Boc CO).

ν_{max} (NaCl solid) 3406brd m, 2977s, 1656s, 1417s, 1365s, 1244s, 1111s cm^{-1}.

$^m/_z$ $C_7H_{12}NO_3$ $[M\text{-}55]^+$ 158.

Synthesis of 7-keto-2-Boc-2-azabicyclo[2.2.1]heptane (139)



The procedure described for (**123**) was followed**,** utilizing oxalyl chloride (0.13 ml, 1.54 mmol), DMSO (0.20 ml, 2.82 mmol), *anti*-7-hydroxy-2-Boc-2-azabicyclo[2.2.1]heptane **19** (128 mg, 0.60 mmol) in dry DCM (15 ml in total) and triethylamine (0.5ml, 3.58 mmol) to yield (**139**) as a colourless oil (63 mg, 0.30 mmol, 50%).

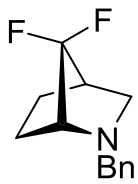
δ_H (400 MHz, $CDCl_3$); where there are rotational isomers (ratio ~ 38: 62), the rotamer signal is underlined. 1.45 (brs, 3H) and 1.47 (brs, 6H, BocCH_3), 1.70-1.81, 1.94-2.14 (2 × m, 1H, 3H, H_5, H_6), 2.21 (d, J = 3.1 Hz, 1H, H_4), 2.27-2.33 (m, 1H, H_{3x}), 2.94-3.18 (m, 1H, H_{3n}), 3.94 (brs, 0.4H) and 4.09 (brs, 0.6H, H_1),

δ_C (100.62 MHz, $CDCl_3$) 23.3, 25.3 (C_5, C_6), 28.4, 28.5 (Boc CH_3), 40.0 (C_4), 49.7 (C_3), 54.9 (C_1), 79.4, 80.3 (Boc C), 154.5, 155.1 (Boc CO), 206.3 (C_7).

ν_{max} (NaCl film) 3345brd m, 2977m, 1656s, 1477w, 1420s, 1366s, 1244s, 1111s cm^{-1}.

$^m/_z$ $C_7H_{10}NO_3$ $[M\text{-}55]^+$ 156.

Synthesis of 7, 7-difluoro-2-benzyl-2-azabicyclo[2.2.1]heptane (179)



DAST (0.48 ml, 3.63 mmol) was added drop-wise to a stirred solution of degassed 7-keto-2-benzyl-2-azabicyclo[2,2,1]heptane (**123**) (184 mg, 0.92 mmol) in dry DCM (14 ml). The reaction mixture was allowed to stir at RT for 24 h. The reaction mixture was slowly quenched with saturated $NaHCO_3$ solution (14 ml), and then extracted with DCM (4 × 15 ml). The combined organic extracts were dried using anhydrous $MgSO_4$ and filtered. The solvent was removed *in vacuo*. The crude product was chromatographed on silica gel (petroleum ether b.p. 40-60 ^oC: diethyl ether; 3:1) to give (**179**) as a brown oil (41 mg, 0.18 mmol, 20%).

δ_H (400 MHz, $CDCl_3$). 1.49-1.56, 183-196 (2 × m, 1H, 3H, H_5, H_6), 2.17-2.20 (m, 1H, H_4), 2.71 (brd, J = 9.1, 1.2 Hz, 1H, H_{3n}), 2.90 (brs, 1H, H_1), 2.93-3.02 (m, 1H, H_{3x}), 3.80 (AB quartet, J = 13.5 Hz, 2H, CH_2Ph), 7.20-7.36 (m, 5H, Ph).

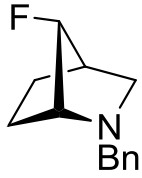
δ_C (125.7 MHz, $CDCl_3$) 25.0 (d, J = 5.0 Hz, C_5), 26.4 (d, J = 6.2 Hz, C_6), 39.9 (t, J = 19.2 Hz, C_4), 57.4 (d, J = 7.6 Hz, C_3), 59.4 (CH_2Ph), 61.0 (t, J = 18.8 Hz, C_1), 126.9, 128.3, 128.5 (5 × aryl CH), 130.7 (C_7), 139.4 (aryl C).

$^{19}F[H]$ NMR δ_F (376.4 MHz, $CDCl_3$) -131.5 (d, J = 200.4 Hz), -128.6 (d, J = 200.2 Hz).

ν_{max} (NaCl film) 2986m, 2868m, 1494m, 1453m, 1354s, 1327m, 1265m, 1201s, 1173s, 1149s cm^{-1}.

$^m/_z$ $C_{13}H_{16}NF_2$ $[MH^+]$ requires 224.1251; observed 224.1248.

Synthesis of *anti*-7-fluoro-2-benzyl-2-azabicyclo[2.2.1]heptane (180)



DAST (0.13 ml, 0.98 mmol) was added drop-wise to a stirred solution of degassed *anti*-7-hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (**87**) (99 mg, 0.49 mmol) in dry DCM (4 ml) at -78 ^oC under an atmosphere of nitrogen. The reaction mixture was allowed to warm and stir at RT for 24 h. The mixture was slowly quenched with $NaHCO_3$ solution (9 ml), and then extracted with DCM (4 × 9 ml). The combined organic extracts were dried using anhydrous $MgSO_4$ and filtered. The solvent was removed *in vacuo*. The crude product was chromatographed on silica gel (petroleum ether b.p. 40-60 ^oC: diethyl ether; 7:3) to give (**180**) as a pale yellow oil (63mg, 0.31 mmol, 63 %).

δ_H (400 MHz, $CDCl_3$). 1.40-1.46 (m, 1H, H_{5n}), 1.77-1.75 (m, 1H, H_{6x}), 1.85-2.02 (m, 2H, H_{5x}, H_{6n}), 2.20 (dd, *J* = 3.5, 9.3 Hz, 1H, H_{3n}), 2.31 (brs, 1H, H_4), 3.00-3.02 (m, 1H, H_{3x}), 3.29 (t, J = 2.6 Hz, 1H, H_1), 5.05 (d, *J* = 58.4 Hz, 1H, H_7), 3.66 (AB quartet, *J* = 13.4 Hz, 2H, CH_2Ph), 7.28-7.30 (m, 5H, Ph).

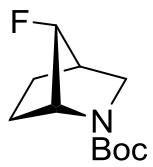
δ_C (125.7 MHz, $CDCl_3$) 22.8 (C_5), 26.6 (d, *J* = 2.8 Hz, C_6), 40.0 (d, *J* = 16.0 Hz, C_4), 56.9(d, *J* = 8.4 Hz, C_3), 57.6 (CH_2Ph), 61.9 (d, *J* = 18.7 Hz, C_1), 95.2 (d, *J* = 195.5 Hz, C_7), 126.9, 128.3, 128.4 (5 × aryl CH), 139.2 (aryl C).

$^{19}F[H]$ NMR δ_F (376.4 MHz, $CDCl_3$) -206.4 ($^2J_{HF}$ = 58.1 Hz).

ν_{max} (NaCl film) 3054m, 2979m, 2842m, 1495m, 1424m, 1279s, 1154w cm^{-1}.

$^m/_z$ $C_{13}H_{17}NF$ $[MH^+]$ requires 206.1345; observed 206.1339.

Synthesis of *anti*-7-fluoro-2-Boc-2-azabicyclo[2.2.1]heptane (183)



To a stirred solution of degassed *anti*-7-hydroxy-2-Boc-2-azabicyclo[2.2.1]heptane (**182**) (104 mg, 0.51 mmol) in dry DCM (5 ml). DAST (0.2 ml, 1.514 mmol) was added drop-wise at -78 ^oC under an atmosphere of nitrogen. The reaction mixture was allowed to warm slowly and stir at RT for 24 h. The mixture was slowly quenched with $NaHCO_3$ solution (8 ml), and then extracted with DCM (4 × 8 ml). The combined organic extracts were dried using anhydrous $MgSO_4$ and filtered. The solvent was removed *in vacuo*. The crude product was chromatographed on silica gel (petroleum ether b.p. 40-60 ^oC: diethyl ether; 3:1) to give (**183**) as a white semi oil (23mg, 0.11 mmol, 22 %).

δ_H (400 MHz, $CDCl_3$); where there are rotational isomers (ratio ~ 32: 68), the rotamer signal is underlined. 1.45 (brs, 9H, $BocCH_3$), 1.59-2.03 (m, 4H, H_5, H_6), 2.94 (brs, 1H, H_4), <u>3.01</u> (dd, *J* = 10.0, 3.7 Hz, 0.4H) and 3.08 (dd, *J* = 10.0, 3.7 Hz, 0.6H, H_{3n}), 3.31 (d, *J* = 10.0 Hz, 1H, H_{3x}), 4.04 (brs, 0.6H) and <u>4.16</u> (brs,0.4H, H_1), 4.89(d, *J* = 57.1 Hz, H_7).

δ_C (125.7 MHz, $CDCl_3$) 25.0 (d, *J* = 17.3 Hz, C_5), 27.6 (d, *J* = 30.0 Hz, C_6), 28.5 (Boc CH_3), 39.1(d, *J* = 16.3 Hz) and <u>39.6</u> (d, *J* = 16.0 Hz, C_4), 49.7 (d, *J* = 7.8 Hz) and <u>50.5</u> (d, *J* = 8.3 Hz, C_3), <u>56.0</u> (d, *J* = 21.9 Hz) and 57.2 (d, *J* = 21.5 Hz, C_1), 79.6 (d, *J* = 16.4 Hz, Boc C), 94.0 (d, *J* = 196.0 Hz, C_7), 154.5 (d, *J* = 82.7 Hz, Boc CO).

$^{19}F[H]$ NMR δ_F (376.4 MHz, $CDCl_3$) -203.13 ppm ($^2J_{HF}$ = 52.7 Hz).

ν_{max} (NaCl film) 2054m, 2986m, 1685s, 1421m, 1265s cm^{-1}.

$^{m}/_{z}$ [M-55]$^{+}$ 160.

Synthesis of 2-azabicyclo[2.2.1]hept-5-ene (160)

According to the procedure described by Cox,[162] ammonium chloride (20 g, 0.37 mol) was dissolved in water (57 ml). Aqueous formaldehyde solution (37% w/v, 39 ml, 0.48 mol) and freshly distilled cyclopentadiene (**74**) (60 ml, 0.714 mol) were added in a round-bottomed flask, the flask was stoppered and the bi-phasic mixture was stirred vigorously at RT for 48h then washed with hexane/diethyl ether 1:1 (4 × 70 ml). The orange aqueous layer was basified with NaOH solution (3.5 M, 120 ml, pH > 12) and extracted with DCM (5 × 70 ml). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo* to give (**160**) as a crude brown oil; racemic mixture 1:1 (20.130 g, 0.212 mol, 30%) which was deemed sufficiently pure for the next reaction.

δ_H (400 MHz, $CDCl_3$) 1.35-1.38 (m, 1H, H_{7s}), 1.50 (d, *J* = 2.7 Hz, 0.5H) and 1.53 (d, *J* = 1.7 Hz, 0.5H, H_{3n}), 1.57-1.62 (m, 1H, H_{7a}), 2.90 (brs, 1H, H_4),, 2.97 (d, *J* = 2.7 Hz, 0.5H) and 3.00(d, *J* = 2.7Hz, 0.5H, H_{3x}), 3.19 (ddd, *J* = 13.6, 8.7, 2.2 Hz,1H, H_1), 6.00 (ddd, *J* = 12.2, 6.2, 1.9 Hz,1H, H_6), 6.25-6.28 (m, 1H, H_5).

δ_C (100.62 MHz, $CDCl_3$) 43.5 and 43.7 (C_4), 47.9 and 48.0 (C_7), 51.9 and 52.3 (C_3), 63.6 and 63.8(C_1), 131.0 and 131.2 (C_6), 135.7 and 135.8 (C_5).

(NaCl film) ν_{max} 3418brd, 2924s, 1616m, 1458m, 1170m cm^{-1}.

Synthesis of 2-Boc-2-azabicyclo[2.2.1]hept-5-ene (161)

2-Azabicyclo[2.2.1]hept-5-ene (**160**) (15.11g, 158.8 mmol) was dissolved in diethyl ether (550 ml) and basified with 10% NaOH (116 ml). The resulting reaction mixture was stirred at RT. Boc_2O (44.0 g, 201.6 mmol) was added slowly over a period of 10 minutes until fully dissolved, and allowed to stir for 27 hours. The solid precipitate was filtered off and the separated organic layer dried over anhydrous $MgSO_4$. The drying agent was filtered off and the solvent was removed *in vacuo* to give a crude brown oil. The crude product was chromatographed on silica gel, eluting with diethyl ether: hexane 1:3 to yielding (**161**) as pale yellow oil (14.72 g, 75.4 mmol, 48%).

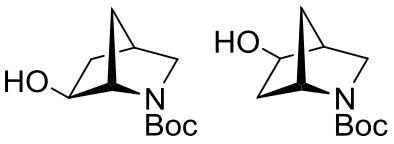
δ_H (300 MHz, $CDCl_3$); where there are rotational isomers (ratio ~41: 59), the rotamer signal is underlined. 1.44 (brs, 9H, BocCH_3), 1.50-1.57 (m, 2H, $H_{7a,}$ H_{7s}), 2.56-2.65 (m, 1H, H_{3n}), 3.56 (brs, 1H, H_4), 3.30 (dd, J = 9.1, 3.0 Hz, 1H, H_{3x}), 4.57 (brs, 0.6 H) and 4.70 (brs, 0.4 H, H_1), 6.27-6.36 (m, 2H, H_5, H_6).

δ_C (75.5 MHz, $CDCl_3$) 284 (Boc CH_3), 42.9, 43.4 (C_4), 45.9, 46.2 (C_3), 48.0 (C_7), 59.9, 61.1 (C_1), 78.9 (Boc C), 133.7, 134.3 (C_5), 136.5 (C_6), 155.8 (Boc C=O).

ν_{max} (NaCl film) 2887s, 2977s (C-H), 1694 s (C=O) cm^{-1}.

$^m/_z$ $C_{11}H_{17}NO_2$ $[M+Na]^+$ requires 218.1157; observed 218.1167.

Synthesis of 2-Boc-6-hydroxy-*exo*-2-azabicyclo[2.2.1]heptane (162) and 2-Boc-5-hydroxy-*exo*-2-azabicyclo[2.2.1]heptane (163)



Borane-tetrahydrofuran complex solution (1 M, 5.8 ml, 5.80 mmol) was added drop-wise to a stirred solution of the unsaturated derivative (**161**) (1.121 g, 5.74 mmol) in dry THF (9 ml) under nitrogen, which was cooled to -78 ^oC. The reaction mixture was allowed to warm to 0 ^oC using water in an ice bath and stirred at this temperature for 3 h. The reaction mixture was quenched by the addition of water (2 ml) drop-wise and sodium hydroxide solution (3.5 M, 2 ml). Hydrogen peroxide solution (30% w/w, 2.4 ml) was added and stirred at RT for 20 h, then concentrated *in vacuo*. The resulting white slurry was diluted with diethyl ether (10 ml) and water (10 ml). The reaction mixture was washed with water (3 × 10 ml) and brine (3 × 10 ml). The aqueous layer was extracted with diethyl ether (3 × 15 ml), and the combined organic extracts were dried over anhydrous $MgSO_4$. The drying reagent was filtered off and the solvent was removed *in vacuo* to give a thick colourless oil (0.685 g). The crude product was chromatographed on silica gel, eluting with diethyl ether to give (**162**) as a white solid (305 mg, 1.43 mmol, 41%) and (**163**) also as a white solid (279 mg, 1.31 mmol, 37%); where there are rotational isomers (ratio ~ 50: 50), the rotamer signal is underlined.

(162)

m.p. 108.1-109.3 ^oC.

δ_H (400 MHz, $CDCl_3$) 1.44, 146 (brs, 10H, BocCH_3, H_{5x}), 1.49-1.57 (m, 1H, H_{5n}), 1.47-1.76 (m, 1H, H_{7s}), 1.80-1.88 (m, 1H, H_{7a}), 1.66 (brs, OH), 2.51 (brs, 1H, H_4), 2.77(brs.

0.5 H) and 2.84 (brs, 0.5 H, H_{3n}), 3.11-3.16 (m, 1H, H_{3x}), 3.95 (brs, 1H, H_{6n}), 4.02 (brs, 0.5 H) and 4.06 (brs, 0.5 H, H_1).

δ_C (100.62 MHz, $CDCl_3$) 28.5 (Boc CH_3), 33.2, 33.7 (C_7), 35.5, 36.0 (C_4), 39.1, 39.8 (C_5), 51.1, 51.8 (C_3), 60.1, 60.4 (C_1), 72.0, 72.5 (C_6), 79.4 (Boc C), 154.5 (Boc C=O).

ν_{max} (NaCl solid) 3413br m (O-H), 2887s, 2983s (C-H), 1681s (C=O) cm^{-1}.

$^m/_z$ $C_{11}H_{19}NO_3$ $[M+Na]^+$ requires 236.1263; observed 236.1271.

Elemental analysis calculated for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found C, 62.63; H, 8.66; N, 6.47.

(163)

m.p. 74.1-76.3 ^oC.

δ_H (400 MHz, $CDCl_3$) 1.45 (brs, 9H, BocCH_3), 1.46-147 (m, 1H, H_{6x}), 1.52-1.58 (m, 1H, $H_{7a/7s}$), 1.73-1.82 (m, 1H, $H_{7a/7s}$), 2.01-2.08 (m, 1H, H_{6n}), 2.11-2.17(m, OH), 2.45 (brs, 1H, H_4), 2.80 (d, *J* = 10.2 Hz, 0.5 H) and 2.87 (d, *J* = 10.2 Hz, 0.5 H, H_{3n}), 3.18-3.21 (m, 1H, H_{3x}), 4.03 (d, J = 6.2 Hz, 1H, H_{5n}), 4.13(brs, 0.5 H) and 4.25 (brs, 0.5 H, H_1).

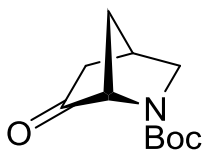
δ_C (100.62 MHz, $CDCl_3$) 28.5 (Boc CH_3), 33.6, 34.1 (C_7), 45.2 (C_6), 44.7, 45.2 (C_4), 47.7, 48.2 (C_3), 55.2, 56.2 (C_1), 72.8, 73.0 (C_5), 79.2 (Boc C), 154.5 (Boc C=O).

ν_{max} (NaCl solid) 3399 br m (O-H), 2887s, 2978s (C-H), 1674s (C=O) cm^{-1}.

$^m/_z$ $C_{11}H_{19}NO_3$ $[M+Na]^+$ requires 236.1263; observed 236.1268.

Elemental analysis calculated for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.43; N, 6.89. Found C, 61.66; H, 8.82; N, 6.68.

Synthesis of 2-Boc-6-*oxo*-2-azabicyclo[2.2.1]heptane (164)



According to the procedure described by Hrebabecky, [155] a suspension of powdered molecular sieve (4A^o, 8.314 g) and pyridinium dichromate (8.319 g, 22.133 mmol) in dry DCM (90 ml) was added to a solution of alcohol (**162**) (2.954 g, 13.850 mmol) in dry DCM (28 ml). The brown reaction mixture was stirred at RT under anhydrous conditions using a $CaCl_2$ drying tube for 4 days. The mixture was diluted with ethyl acetate; the solid was filtered off through celite and washed with ethyl acetate and the solvent removed *in vacuo*. The crude product was chromatographed on silica gel, eluting with toluene/ethyl acetate; 3:2 to give (**164**)

as a white solid (1.38 g, 6.532 mmol, 47%). X-ray crystallography (see appendix 1) confirmed the configuration of (**33**). m.p. 85.3-86.3 ^{o}C.

δ_H (400 MHz, $CDCl_3$); where there are rotational isomers (ratio ~38: 62) 1.45 (brs, 9H, BocCH_3), 1.71 (brd, *J* = 10.9 Hz, 1H, H_{7a}), 1.88-1.92 (m, 1H, H_{7s}), 1.98 (d, *J* = 4.2 Hz, 0.4 H) and 2.02 (d, *J* = 4.2 Hz, 0.6 H, H_{5n}), 2.20 (dd, *J* = 1.5, 4.2 Hz, 0.6 H) and 2.24 (dd, *J* = 1.5, 4.2 Hz, 0.4 H, H_{5x}), 2.84 (brs, 1H, H_4) , 3.18 (brs, 1H, H_{3n}), 3.45 (dt, *J* = 2.3, 9.6 Hz, 1H, H_{3x}), 4.12 (brs, 1H, H_1).

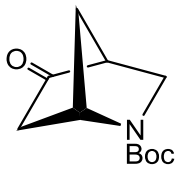
δ_C (100.61 MHz, $CDCl_3$) 28.0 (Boc CH_3), 34.2 (C_4), 36.4 (C_7), 41.6 (C_5), 50.4 (C_3), 61.3, 62.3 (C_1), 80.4 (Boc C), 154.3 (Boc C=O), 205 (C_6).

ν_{max} (NaCl solid) 2890s, 2934s (C-H), 1696s and 1755s(C=O) cm^{-1}.

$^{m}/_{z}$ $C_{11}H_{17}NO_3$ $[M+Na]^+$ requires 234.1106; observed 234.1113.

Elemental analysis calculated for $C_{11}H_{19}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found C, 62.81; H, 8.49; N, 6.75.

Synthesis of 2-Boc-5-*oxo*- 2-azabicyclo [2.2.1] heptane (165)



According to the procedure described by Hrebabecky,[155] a suspension of powdered molecular sieve (4A^{o}, 8.314 g) and pyridinium dichromate (8.076 g, 21.467 mmol) in dry DCM (90 ml) was added to a solution of alcohol (**163**) (2.925 g, 13.714 mmol) in dry DCM (28 ml). The brown reaction mixture stirred at RT under anhydrous conditions using a $CaCl_2$ drying tube for 4 days. The mixture was diluted with ethyl acetate; the solid was filtered off through celite and washed with ethyl acetate and the solvent removed *in vacuo*. The brown solid crude product was chromatographed on silica gel, eluting with toluene/ethyl acetate; 3:2 to give (**165**) as a colourless thick oil (2.310 g, 10.934 mmol, 80%).

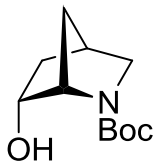
δ_H (400 MHz, $CDCl_3$); where there are rotational isomers (ratio ~50: 50). 1.46 (brs, 9H, BocCH_3), 1.95 (brs, 0.5H) and 2.00 (brs, 0.5H, H_{7a}), 2.05 (brs, 1H, H_{7s}), 2.16-2.35 (m, 2H, H_6), 2.89 (brs, 1H, H_4) 3.30-3.36 (m, 1H, H_{3n}), 3.45-3.48 (m, 1H, H_{3x}), 4.53 (brs, 0.5H) and 4.64 (brs, 0.5 H, H_1).

δ_C (100.61 MHz, $CDCl_3$) 28.5 (Boc CH_3), 37.2 and 37.6 (C_7), 45.6 (C_6), 47.1 and 47.6 (C_3), 50.3 and 51.0 (C_4), 55.3, 56.2 (C_1), 80.0 (Boc C), 154.1 (Boc C=O), 213.1 and 213.6 (C_5).

ν_{max} (NaCl film) 2977s, 2811s (C-H), 1696s and 1753s(C=O) cm^{-1}.

$^{m}/_{z}$ $C_{11}H_{18}NO_3$ [MH^+] requires 212.1287; observed 212.1283.

Synthesis of 2-Boc-6-*endo*-hydroxy- 2-azabicyclo [2.2.1] heptane (166)



To a stirred solution of protected ketone (**164**) (125 mg, 0.592 mmol) in dry methanol (3 ml), sodium borohydride was added (28 mg, 0.740 mmol) at 0 ^{o}C (ice/water bath). The mixture was stirred for 1 h and then quenched slowly with saturated ammonium chloride (3 ml). The white suspension was extracted with ethyl acetate (3 × 7 ml). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and the solvent removed *in vacuo*. The crude product was chromatographed on silica gel, eluting with ethyl acetate/hexane; 3:1 to give (**166**) as white crystal needles (74 mg, 0.347 mmol, 59%). X-ray crystallography (see appendix 1) confirmed the *endo*-configuration of (**166**). m.p. 69.3-71.3 ^{o}C.

δ_H (400 MHz, $CDCl_3$); where there are rotational isomers (ratio ~50: 50). 1.08 (d, *J* = 12.5 Hz, 1H, H_{5n}), 1.47 (brs, 9H, BocCH_3), 1.49-1.52 (m, H_{7a}), 1.61 (d, *J* = 8.8 Hz, 1H, H_{7s}), 2.04 (brs, 1H, H_{5x}), 2.31 (brs, 1H, H_4), 3.09 (d, *J* = 9.6 Hz, 1H, H_{3n}), 3.35 (brs, 1H, H_{3x}), 4.19 (brs, 1H, H_1), 4.28 (brs, 1H, H_{6x}).

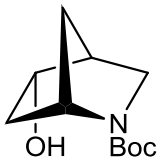
δ_C (100.61 MHz, $CDCl_3$) 28.5 (Boc CH_3), 36.5 and 36.3 (C_7), 37.3 and 37.7 (C_5), 39.2 (C_4), 52.7 and 53.2 (C_3), 60.1 and 61.2 (C_1), 73.8 (C_6), 79.3 (Boc C), 155.7 and 156.4 (Boc C=O).

ν_{max} (NaCl solid) 3413 br m (O-H), 2920s, 2850s (C-H), 1677s (C=O) cm^{-1}.

$^{m}/_{z}$ $C_{11}H_{19}NO_3$ $[M+Na]^+$ requires 236. 1263; observed 236.1272.

Elemental analysis calculated for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found C, 61.94; H, 8.98; N, 7.02.

Synthesis of 2-Boc-5-*endo*-hydroxy- 2-azabicyclo [2.2.1] heptane (167)



To a stirred solution of protected ketone (**165**) (125 mg, 0.592 mmol) in dry methanol (3 ml), sodium borohydride was added (28 mg, 0.740 mmol) at 0 ^{o}C (ice/water bath). The mixture was stirred for 1 h and then quenched slowly with saturated ammonium chloride (3 ml). The white suspension was extracted with ethyl acetate (3 × 7 ml). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and the solvent removed *in vacuo*. The crude product was chromatographed on silica gel, eluting with ethyl acetate/hexane; 3:1 to give (**167**) as a white solid (72 mg, 0.348 mmol, 57%). m.p. 99-100 ^{o}C.

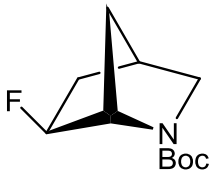
δ_H (400 MHz, $CDCl_3$); where there is rotational isomers (ratio ~50: 50), 1.29-1.40 (m, 1H, H_{6n}), 1.46 (brs, 9H, BocCH_3), 1.47-1.51 (m, H_{7a}), 1.61-1.73 (m, 1H, H_{7s}), 2.01-2.06 (m, 1H, H_{6x}), 2.33-2.45 (m, OH), 2.58 (brs, 1H, H_4), 3.14 (d, J = 10.2 Hz, 1H, H_{3n}), 3.68 (d, J = 10.2 Hz, 1H, H_{3x}), 4.07 (brs, 0.5 H) and 4.19 (brs, 0.5H, H_1), 4.38 (brs, 1H, H_{5x}).

δ_C (100.61 MHz, $CDCl_3$) 28.6 (Boc CH_3), 36.6 and 37.0 (C_7), 40.4 and 40.6 (C_6), 43.2 and 43.6 (C_4), 44.1 and 44.5 (C_3), 56.4 and 57.4 (C_1), 70.4 (C_5), 79.0 and 79.1 (Boc C), 154.2 and 154.4 (Boc C=O).

$_{Vmax}$ (NaCl solid) 3413 br m (O-H), 2978s, 2886s (C-H), 1674s (C=O) cm^{-1}.

$^{m}/_{z}$ $C_{11}H_{19}NO_3$ $[M+Na]^+$ requires 236.1263; observed 236.1278.

Synthesis of 2-Boc-*exo*-6-fluoro- 2-azabicyclo[2.2.1]heptane (168)



To a stirred solution of degassed *2*-Boc-6-hydroxy-*exo*-2-azabicyclo [2.2.1]heptane (**162**) (100 mg, 0.469 mmol) in dry DCM (5 ml) DAST (0. 12 ml, 0.938 mmol) was added drop-wise at -78 ^{o}C under a nitrogen atmosphere. The reaction mixture was allowed to warm slowly and stir at RT for 24 h. The mixture was slowly quenched with $NaHCO_3$ solution (10 ml), and then extracted with DCM (3 × 10 ml). The combined organic extracts were dried using anhydrous $MgSO_4$. The drying agent was filtered off and the solvent was removed *in vacuo*. The crude product was chromatographed on silica gel (hexane: ethyl acetate; 2:1) to give (**168**) as a pale yellow oil (64 mg, 0.297 mmol, 58%).

δ_H (400 MHz, $CDCl_3$); where there are rotational isomers (ratio ~ 38: 62), the rotamer signal is underlined, 1.37 (brs, 6H) and 1.40 (brs, 3H, BocCH_3), 1.50-1.70 (m, 3H, $H_{5x,}$

$H_{7a/7s}$), 1.74-1.83 (m, 1H, H_{5n}), 2.50 (brs, 1H, H_4), 2.68 (d, J = 8.9 Hz, 0.4H) and 2.76 (d, J = 9.3 Hz, 0.6H, H_{3n}), 3.07-3.09 (m, 1H, H_{3x}), 4.13(brs, 0.6H) and 4.26 (brs, 0.4H, H_1), 4.63 (dm, J = 54.1 Hz, 1H, H_{6n}).

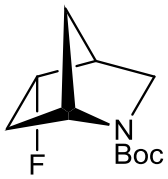
δ_C (100.62 MHz, $CDCl_3$) 27.7 (Boc CH_3), 32.5 and 33.0 (C_7), 34.2 and 34.7 (C_4), 36.6 (d, J = 9.3 Hz) and 36.9 (d, J = 9.3 Hz, C_5), 49.9 and 50.6 (C_3), 56.8 (d, J = 27.6 Hz) and 57.8 (d, J = 27.6 Hz, C_1), 78.5 and 78.8 (Boc CO), 89.4 (d, J = 31.6 Hz) and 91.3 (d, J = 31.6 Hz, C_6), 153.2 and 153.3 (Boc C).

^{19}F[H] NMR δ_F (376.4 MHz, $CDCl_3$) -164.32 ($^2J_{HF}$ = 225.8 Hz) (F_{6x}).

ν_{max} (NaCl film) 3054w, 2984w, 1687m, 1411s, 1265s. 1113w cm^{-1}.

$^m/_z$ $C_{11}H_{19}NO_2F$ $[MH]^+$ requires 216.1400; observed 216.1387

Synthesis of 2-Boc-*endo*-5-fluoro- 2-azabicyclo[2.2.1]heptane (169)



To a stirred solution of degassed 2-Boc-5-hydroxy-*exo*-2-azabicyclo [2.2.1]heptane (**163**) (100 mg, 0.469 mmol) in dry DCM (5 ml) DAST (0. 12 ml, 0.938 mmol) was added drop-wise at -78 ^oC under a nitrogen atmosphere. The reaction mixture was allowed to warm slowly and stir at RT for 24 h. The mixture was slowly quenched with $NaHCO_3$ solution (10 ml), and then extracted with DCM (3 × 10 ml). The combined organic extracts were dried using anhydrous $MgSO_4$. The drying agent was filtered off and the solvent was removed *in vacuo*. The crude product was chromatographed on silica gel (hexane: ethyl acetate; 5:1) to give (**169**) as a pale yellow oil (22 mg, 0.102 mmol, 22%).

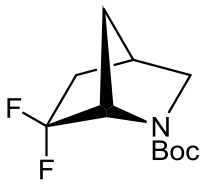
δ_H (400 MHz, $CDCl_3$); where there are rotational isomers (ratio ~ 38: 62), the rotamer signal is underlined, 1.44 (brs, 6H) and 1.47 (brs, 3H, BocCH_3), 1.61-1.73 (m, 3H, $H_{6n,}$ $H_{7a/7s}$), 1.79 (brs, 1H, H_{6x}), 2.02-2.15 (m, 1H, H_4), 3.23 (brs, 1H, H_{3n}), 3.15-3.42 (m, 1H, H_{3x}), 4.00-4.34(m, 1H, H_1), 4.84 (dd, J = 6.7, 54.2 Hz, 1H, H_{5x}).

δ_C (100.62 MHz, $CDCl_3$). 28.4 and 28.5 (Boc CH_3), 32.6 and 32.8 (C_7), 36.1 and 36.4 (C_4), 38.1 and 38.3 (C_6), 49.7 (C_3), 55.7 and 56.6 (C_1), 78.5 and 79.3 (Boc CO), 90.9 (C_5), 154.1 and 155.4 (Boc C).

^{19}F[H] NMR δ_F (376.4 MHz, $CDCl_3$) -191.26 ($^2J_{HF}$ = 45.2 Hz) (F_{5n}).

ν_{max} (NaCl film) 3054w, 2983m, 1688s, 1409m, 1265s. 1113w cm^{-1}.

Synthesis of 2-Boc-6, 6-difluoro-2-azabicyclo[2.2.1]heptane (170)



To a stirred solution of degassed *2*-Boc-6-*oxo*-2-azabicyclo[2.2.1] heptane (**164**) (46 mg, 0.218 mmol) in dry DCM (2.5 ml). DAST (0. 12 ml, 0.871 mmol) was added drop-wise at -78 ^{o}C under a nitrogen atmosphere. The reaction mixture was allowed to warm slowly and stir at RT for 24 h. The mixture was slowly quenched with $NaHCO_3$ solution (5 ml), and then extracted with DCM (3 × 5 ml). The combined organic extracts were dried using anhydrous $MgSO_4$. The drying agent was filtered off and the solvent was removed *in vacuo*. The crude product was chromatographed on silica gel (hexane: ethyl acetate; 3:1) to give **(170)** as a pale yellow oil (22 mg, 0.0943 mmol, 43%).

δ_H (400 MHz, $CDCl_3$); where there are rotational isomers (ratio ~ 38: 62), the rotamer signal is underlined. 1.46 (brs, 9H, BocCH_3), 1.76-1.86 (m, 3H, $H_{5n,}$ $H_{7a/7s}$), 2.03-2.17 (m, 1H, H_{5x}), 2.62 (brs, 1H, H_4), <u>3.04</u> (d, *J* = 9.5 Hz, 0.4H) and 3.12(d, *J* = 9.5 Hz, 0.6H, H_{3n}), 3.32-3.35 (m, 1H, H_{3x}), 4.18(brs, 0.6H) and <u>4.34</u> (brs, 0.4H, H_1).

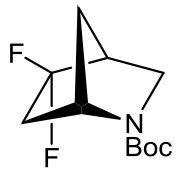
δ_C (100.62 MHz, $CDCl_3$) 28.3 and <u>28.4</u> (Boc CH_3), <u>35.2</u> and <u>35.6</u> (C_4), <u>35.9</u> and 36.1 (C_7), 40.6 and 41.1 (C_5), <u>50.4</u> and 51.0 (C_3), 59.2 (dd, *J* = 20.4, 33.7 Hz) and 60.2 (dd, *J* = 20.9, 33.3 Hz, C_1), <u>79.8</u> and 80.0 (Boc CO), 127.9 (t, *J* = 261.4 Hz, C_6), <u>154.3</u> and 154.7 (Boc C).

^{19}F[H] NMR δ_F (376.4 MHz, $CDCl_3$) -91.5 and 92.1 (2 × d, *J* = 220.8 Hz) -113.9 and -114.5 (2 × d, *J* = 220.4 Hz).

ν_{max} (NaCl film) 3055w, 2984m, 1694s, 1412s, 1340w, 1265s. 1135w, 1007w cm^{-1}.

$^{m}/_{z}$ $[M-55]^+$ 178.

Synthesis of 2-Boc-5, 5-difluoro-2-azabicyclo[2.2.1]heptane (171)



To a stirred solution of degassed *2*-Boc-5-*oxo*-2-azabicyclo[2.2.1] heptane **(165)** (65 mg, 0.308 mmol) in dry DCM (5 ml) DAST (0. 16 ml, 1.230 mmol) was added drop-wise at -78 ^{o}C under a nitrogen atmosphere. The reaction mixture was allowed to warm slowly and stir at RT for 24 h. The mixture was slowly quenched with $NaHCO_3$ solution (5 ml), and then extracted with DCM (3 × 5 ml). The combined organic extracts were dried using anhydrous $MgSO_4$. The drying agent was filtered off and the solvent was removed *in vacuo*. The crude product

was chromatographed on silica gel (hexane: ethyl acetate; 3:1) to give (**171**) as a pale yellow oil (22 mg, 0.0943 mmol, 31%).

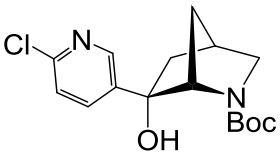
δ_H (400 MHz, $CDCl_3$); where there are rotational isomers (ratio ~ 38: 62), the rotamer signal is underlined. 1.46 (brs, 9H, BocCH_3), 1.81 (brs, 1H, H_{7s}), 1.88 (brs, 0.6H) and <u>1.90</u> (brs, 0.4H, H_{7s}), 2.03-2.19 (m, 2H, H_6), 2.78 (brs, 1H, H_4), 3.24 (brs, 1H, H_{3x}), 3.41-3.48 (m, 1H, H_{3n}), <u>4.23</u>(brs, 0.4H) and <u>4.34</u> (brs, 0.4H, H_1).

δ_C (100.62 MHz, $CDCl_3$) 28.5 (Boc CH_3), 36.3 and <u>36.7</u> (C_7), 43.9 (dd, J = 24.7, 49.5 Hz, C_6), 44.6 and 45.2 (C_3), 45.9 (dd, J = 24.2, 55.7 Hz, C_4), 55.4 and <u>56.3</u> (C_1), <u>79.8</u> (Boc CO), 128.9 (t, J = 256.0 Hz, C_5), 154.3 (Boc C).

^{19}F[H] NMR δ_F (376.4 MHz, $CDCl_3$) -89.0 and -89.7 (2 × d, J = 226.1 Hz) -108.8 and -109.4 (2 × d, J = 226.5).

ν_{max} (NaCl film) 3054s, 2987m, 1712s, 1421s, 1265s cm^{-1}.

Synthesis of *endo*-6-(2'-chloro-3'-pyridyl)-2-Boc-2-azabicyclo[2,2,1]heptan-6-ol (185)



To a stirred solution of 2-chloro-5-iodopyridine (891mg, 3.72 mmol) in THF (11ml) and diethyl ether (23 ml) at -78^{o}C under a nitrogen atmosphere *n*-butyllithium (1.6 M, 2.35 ml, 3.76 mmol) was added drop-wise and stirred for 30 min. A solution of ketone (**164**) (792 mg, 3.75 mmol) in diethyl ether (11 ml) was added drop-wise and stirring continued for 2 h, then the mixture was warmed to -50 ^{o}C and stirred at this temperature for 30 min before the reaction mixture was quenched with saturated ammonium chloride (4 ml) and warmed to RT. Water was added (4 ml) and the organic layer separated off. The aqueous layer was extracted with ethyl acetate (3× 50 ml), the organic extracts were dried over $MgSO_4$, filtered off, and evaporated. The crude product was chromatographed on silica gel (petroleum ether b.p. 40-60 ^{o}C: ethyl acetate; 8: 2 → 1: 1) to yield (**185**) (602 mg, 1.85 mmol, 49%) as a pale yellow foam.

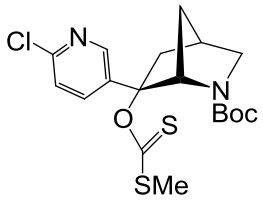
δ_H (400 MHz, $CDCl_3$); where there are rotational isomers (ratio ~ 38: 62), the rotamer signal is underlined); 1.49 (brs, 9H, BocCH_3), 1.61-2.48 (m, 4H, H_7, H_5), 2.64 (brs, 1H, H_4), 3.20 (dd, J = 9.5, 0.7 Hz, 1H, H_{3n}), 3.42 (dt, J = 9.5 Hz,1H, H_{3x}), 3.72 (brs, OH), 4.25 (brs, 0.4 H) and 4.39 (brs, 0.6 H, H_1), 7.30 (d, J = 8.4 Hz, 1H, $H_{6'}$), 7.67 (dd, J = 8.4, 2.7 Hz, 1H, $H_{4'}$), 8.45 (d, J = 8.4 Hz, 1H, $H_{3'}$).

δ_C (125.7 MHz, $CDCl_3$) 28.5 (Boc CH_3), 36.8 (C_7), 37.8 (C_4). 43.7(C_5), 52.5 (C_3), 63.8(C_1), 65.9 (C_6), 80.1 and 80.7 (Boc CO), 124.0 ($C_{3'}$), 137.1 ($C_{4'}$), 147.5 ($C_{6'}$), 149.8 and 150.3 (pyridyl C), 156.7 (Boc C).

ν_{max} (NaCl film) 3484br (-OH), 3054m (C-H), 2982s (C-H), 1682s (C=O), 1416s, 1285s, 1107m, 738br (C-Cl) cm^{-1}.

$^m/_z$ $C_{16}H_{22}N_2O_3Cl^{35}[MH]^+$ requires 325.1319; observed 325.1320.

Synthesis of *endo*-6-[(2'-chloro-3'-pyridyl)-2-Boc-2-azabicyclo[2,2,1]heptane-6-yl] S-methyl-xanthate (204)



To a stirred suspension of sodium hydride (60% in mineral oil, 81.24 mg, 3.39 mmol) in dry THF (2.5 ml) at 0 ^oC under an atmosphere of nitrogen was added drop-wise to a solution of *endo*-6-(2-chloro-5-pyridinyl)-2-Boc-2-azabicyclo[2,2,1]heptane-6-ol (**185**) (183 mg, 0.56 mmol) in 2.5 ml dry THF. The mixture reaction was allowed to stir for 20 min at RT then cooled to 0 ^oC and carbon disulphide (0.04 ml, 0.67 mmol) was added dropwise and stirred for 20 min, followed by adding methyl iodide (0.04 ml, 0.70 mmol). The cooling bath was removed, and the reaction mixture stirred for 20 min. Water was added (2 ml) to quench the reaction mixture and the solvent evaporated *in vacuo*. The crude residue was partitioned between DCM (3 × 3ml) and water (3 ml). The combined organic layers were dried over $MgSO_4$, filtered off, and evaporated. The crude product was chromatographed on silica gel (petroleum ether b.p. 40-60 ^oC: ethyl acetate; 9:1) to yield (**204**) (171mg, 0.41mmol, 73%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$); where there are rotational isomers (ratio ~ 38: 62), the rotamer signal is underlined); 1.38 (brs, 2H, $H_{7a, 7s}$), 1.45 (brs, 3H) and 1.51(brs, 6H, BocCH_3), 2.06 (d, J = 3.2 Hz, 0.4H) and 2.10(d, J = 3.4 Hz, 0.6 H, H_{5n}), 2.36 (brs, 1.8H) and 2.40 (brs, 1.2 H, Me), 2.66 (brs, 1H, H_4), 2.82-2.93 (m, H_{5x}), 3.08-3.14 (m, H_{3n}), 3.32-3.43(brs, H_{3x}), 4.33 (brs, 0.6H) and 4.41(brs, 0.4H, H_1), 7.23 (d, J = 8.4 Hz, 1H, $H_{6'}$), 7.54 (dd, J = 8.4, 2.5 Hz, 0.6H) and 7.63 (dd, J = 8.4, 2.5 Hz, 0.4H, $H_{4'}$), 8.33 (d, J = 2.5 Hz, 0.6H) and 8.35 (d, J = 2.5 Hz, 1H, $H_{3'}$).

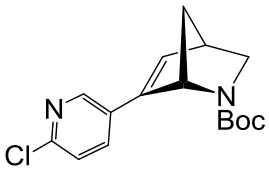
δ_C (100.61 MHz, $CDCl_3$) 19.2 and 19.5 (Me), 28.6 and 28.7 (Boc CH_3), 33.7 and 34.5 (C_7), 36.8 and 37.4 (C_4). 38.4 and 38.8(C_5), 51.8 and 52.6 (C_3), 65.3 and 66.2(C_1), 79.6

and 79.9 (Boc CO), 123.8 and 124.0 ($C_{6`}$), 137.0 and 137.2 ($C_{4`}$), 148.2 ($C_{3`}$),150.4 and 150.6 (pyridyl C), 154.4 and 154.5 (Boc C), 212.6 and 213.1 (C=S).

ν_{max} (NaCl film) 3054s (C-H), 2985s (C-H), 1711s (C=O), 1367w, 1265s, 1108w, 1155w, 738br (C-Cl) cm^{-1}.

$^{m}/_{z}$ $C_{18}H_{24}N_2O_3S_2Cl^{35}[MH]^+$ requires 415.0917; observed 415.0926.

Synthesis of 6-(2'-chloro-3'-pyridyl)-2-Boc-2-azabicyclo[2,2,1]hept-5-ene (184)



Compound (**204**) (165 mg, 0.39 mmol) was dissolved in toluene (5 ml) and heated at reflux under nitrogen atmosphere for 5h. The solvent was removed *in vacuo* and the crude chromatographed on silica gel (petroleum ether b.p. 40-60 ^{o}C: ethyl acetate; 8:2) to yield (**184**) (59 mg, 0.19 mmol, 49%) as a yellow oil.

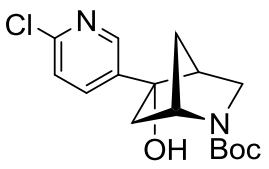
δ_H (400 MHz, $CDCl_3$); where there are rotational isomers (ratio ~ 40: 60), 1.35(brs, 9H, BocCH_3), 1.65-1.73 (m, 2H, $H_{7a/7s}$), 2.67 (brs, H_4), 3.26 (brs, 1H, H_{3n}), 3.40 (dd, *J* = 9.4, 2.9 Hz, 1H, H_{3x}) , 5.00 (brs, 1H, H_1), 6.47 (brs, 0.4H) and 6.55 (brs, 0.6H, H_5),7.21 (d, *J* = 8.3 Hz, 1H, $H_{6`}$), 7.71 (d, *J* = 8.3 Hz 0.6H) and 7.74 (d, J= 8.3 Hz, 0.4H, $H_{4`}$), 8.50 (brs, 1H, $H_{3`}$).

δ_C (100.6 MHz, $CDCl_3$) 28.5 (Boc CH_3), 36.7 and 37.4 (C_7), 37.5 and 38.0 (C_4). 46.3 and 46.9 (C_3), 61.4 and 61,6 (C_1), 83.8 (Boc CO), 122.5 and 122.6 ($C_{6`}$), 131.5 and 131.80 ($C_{4`}$), 146.9 ($C_{3`}$),149.9 (pyridyl C-Cl), 150.5 (Boc C).

ν_{max} (NaCl film) 3053m (C-H), 2928s (C-H), 1686s (C=O), 1407m, 1367s, 1265m, 1106m, 739br (C-Cl) cm^{-1}.

$^{m}/_{z}$ $C_{16}H_{20}N_2O_2Cl^{37}[MH]^+$ requires 307.1213; observed 307.1200.

Synthesis of *endo*-5-(2'-chloro-3'-pyridyl)-2-Boc-2-azabicyclo[2,2,1]heptane-6-ol (202)



To a stirred solution of 2-chloro-5-iodopyridine (405 mg, 1.69 mmol) in THF (5 ml) and diethyl ether (11 ml) at -78 ^{o}C under a nitrogen atmosphere *n*-butyllithium (1.6 M, 1.0 ml, 1.60 mmol) was added drop-wise and stirred for 30 min. A solution of ketone (**165**) (350 mg, 1.66 mmol) in diethyl ether (5 ml) was added drop-wise and stirred continuously for 2 hours at -78 ^{o}C, then warmed to -50 ^{o}C and stirring at this temperature

for 30 min before the reaction mixture was quenched with saturated ammonium chloride (2 ml) and warmed to RT. Water was added (2 ml) and the organic layer separated off. The aqueous layer was extracted with ethyl acetate (3× 20 ml), the organic extracts were dried over $MgSO_4$, filtered off, and the solvent evaporated. The crude product was chromatographed on silica gel (petroleum ether b.p. 40-60 ^oC: ethyl acetate; 8:2 → 1: 1) to yield (**202**) (334 mg, 1.03 mmol, 62%) as a white solid. A small sample was recrystallised from petroleum ether 40-60 ^oC and ethyl acetate for X-ray crystallography determination, (m.p. 130-132 ^oC).

δ_H (400 MHz, $CDCl_3$); where there are rotational isomers (ratio ~ 38: 62), the rotamer signal is underlined. 1.46 (brs, 9H, BocCH_3), 1.62-1.72(m, 1H, H_{6x}), 1.78-1.86 (m, 1H, H_{6n}), 2.00-2.05 (m, 1H, H_{7a}), 2.24-2.29 (m, 1H, H_{7s}), <u>2.77</u> (brs, 0.4H) and 2.80 (brs, 0.6H, H_{3n}), 3.24 (dd, *J* = 10.1, 3.3 Hz, 1H, H_{3x}), 3.92 (d, *J* = 1.2 Hz, 0.6H) and <u>3.95</u> (d, *J* = 1.2 Hz, 0.4H, H_4), 4.21 (brs, 0.6H) and <u>4.30</u> (brs, 0.4H, H_1), 7.32 (d, *J* = 8.4 Hz, 1H, $H_{6`}$), 7.82 (d, *J* = 7.6 Hz 1H, $H_{4`}$), 8.46 (brs, 1H, $H_{3`}$).

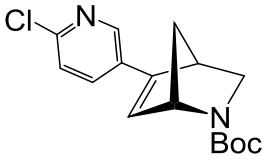
δ_C (100.6 MHz, $CDCl_3$) <u>28.5</u> and 28.6 (Boc CH_3), 37.5 and 38.1 (C_6), 45.7 and 46.2 (C_7). 46.9 and 47.6 (C_3), 47.8 and <u>48.6</u> (C_4), <u>56.8</u> and 57.8 (C_1), 77.4 (Boc CO), 124.1 ($C_{6`}$), 137.0 and <u>137.2</u> ($C_{4`}$), 142.1 (pyridyl C), 147.2 ($C_{3`}$),150.3 (pyridyl C-Cl), 154.4 (Boc C).

ν_{max} (NaCl solid) 3405 (-OH), 3054s (C-H), 2985s (C-H), 1683s (C=O), 1420s, 1285s, 1107m, 738br (C-Cl) cm^{-1}.

$^m/_z$ $C_{16}H_{22}N_2O_3Cl^{35}[MH]^+$ requires 325.1319; observed 325.1307.

Elemental analysis calculated for $C_{16}H_{21}N_2O_3$ Cl: C, 59.17; H, 6. 52; N, 8.62. Found C, 58.74; H, 6.27; N, 8.47.

Synthesis of 5-(2'-chloro-3'-pyridyl)-2-Boc-2-azabicyclo[2,2,1]hept-5-ene (205)



To a stirred solution of Burgess'reagent (700 mg, 2.94 mmol) in THF (2 ml) under a nitrogen atmosphere compound (**202**) (734 mg, 2.26 mmol) was added drop-wise, which was dissolved in THF (2 ml) and stirred continued for 24 h at RT. The reaction mixture was allowed to heat to 50 ^oC for 30 min. The reaction flask was cooled to room temperature, then quenched by the addition of water (0.6 ml), neutralised with sodium hydroxide solution. The solvent was removed under reduced pressure and the crude product was extracted with chloroform (4 × 5 ml). The organic layers were combined, dried over anhydrous

$MgSO_4$, filtered off and the solvent evaporated. The crude product was chromatographed on silica gel (petroleum ether b.p. 40-60 ^oC: ethyl acetate; 8:2) to yield (**205**) (350 mg, 1.14 mmol, 51%) as a white solid. (m.p. 122 -124 ^oC).

δ_H (400 MHz, $CDCl_3$); where there are rotational isomers (ratio ~ 50: 50), 1.44 (brs, 9H, $BocCH_3$), 1.79 (brs, 2H, $H_{7a/7s}$), 2.74 (brs, 0.5H) and 2.81 (brs, 0.5H, H_4), 3.47 (dd, *J* = 9.3, 3.0 Hz, 1H, H_{3n}), 3.61 (brs, 1H, H_{3x}) , 4.73 (brs, 0.5H) and 4.85 (brs, 0.5H, H_1), 6.65 (brs, 0.5H) and 6.76 (brs, 0.5H, H_6),7.29 (d, *J* = 8.3 Hz, 1H, $H_{6`}$), 7.66 (d, *J* = 6.3 Hz 1H, $H_{4`}$), 8.44 (dd, *J* = 2.4, 0.3 Hz, 1H, $H_{3`}$).

δ_C (100.6 MHz, $CDCl_3$) 28.6 (Boc CH_3), 44.3 and 44.6 (C_4), 46.0 and 46.4 (C_3). 47.5 and 47.7 (C_7), 60.8 and 62.0 (C_1), 79.6 (Boc CO), 124.2 ($C_{6`}$), 129.1 (129.7 and 130.5) ($C_6$), 135.2 ($C_{4`}$), 145.1 (pyridyl C), 146.4 ($C_{3`}$),150.3 (pyridyl C-Cl), 155.6 (Boc C).

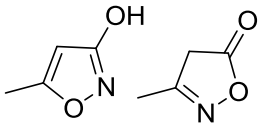
ν_{max} (NaCl solid) 3054s (C-H), 2983s (C-H), 1712S (C=O), 1683s, 1578w, 1456m, 1259m, 1106s, 739br (C-Cl) cm^{-1}.

$^m/_z$ $C_{16}H_{20}N_2O_2Cl^{35}[MH]^+$ requires 307.1213; observed 307.1221.

Elemental analysis calculated for $C_{16}H_{19}N_2O_2$ Cl: C, 62.64; H, 6. 24; N, 9.13. Found C, 59.39; H, 5.65 N, 8.62.

Synthesis of reagent

Synthesis of 5-methyl-3-isoxazolol (117) and 3-methyl-5-isoxazolone (118)



According to the procedure described by Jacobsen *et al*.,[171] hydroxylamine hydrochloride (1.4 g, 20 mmol) was dissolved in sodium hydroxide (10 ml, 2 M) to achieve a solution of pH 10. This solution was cooled to 0-5 ^oC and vigorously stirred. At this point, methyl acetoacetate (2.16 ml, 0.02 mmol) was added drop-wise over 30 min. The pH of the solution was kept at 10.0 ± 0.2 by means of the pH meter. Stirring was continued for 30 min at pH 10 and then the mixture was poured into ice-cooled concentrated HCl (15 ml) and left overnight at RT. The products were isolated by continuous extraction with DCM. Flash chromatograph (petroleum ether b.p. 40-60 ^0C: ethyl acetate, 9:1) gave a mixture of (**117**) as a white crystal and (**118**) as a yellow oil (~33:67, **17**:**18**, ^1H peak integration) (**117**: 435 mg, 4.39 mmol, 22%). (**118**: 195 mg, 1.97 mmol, 10%).

(**117**)

m.p. 85-86 ^{o}C. δ_H (400 MHz, $CDCl_3$) 2.26 (d, *J* = 0.8 Hz, 3H, CH_3), 5.60 (q, *J* = 0.9 Hz, 1H, CH), 10.79 (brs, OH). δ_C (100.62 MHz, $CDCl_3$) 12.9 (CH_3), 93.9 (CH), 170.3 (C-Me), 171.3 (C-OH).

$_{Vmax}$ (NaCl solid) 2936brd, 2662br, 1636s, 1526s, 1336m, 1246s, 1028m cm^{-1}.

$^{m}/_{z}$ $C_5H_6NO_2$ [MH^+] requires 100.0399; observed 100.0400.

(**118**)

δ_H (400 MHz, $CDCl_3$) 2.09(t, *J* = 1.6 Hz, 3H, CH_3), 3.38(s, 2H, CH_2).

δ_C (100.62 MHz, $CDCl_3$) 14.7 (CH_3), 37.1 (CH_2), 164.2 (C-Me), 176.0(C=O).

$_{Vmax}$ (NaCl film) 2184br, 1795s cm^{-1}.

$^{m}/_{z}$ $C_4H_6NO_2$ [MH^+] requires 100.0399; observed 100.0398.

Chapter 6
References

6. References

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Appendix 1

Appendix 1

7.1 Crystal data and structure refinement for (124)

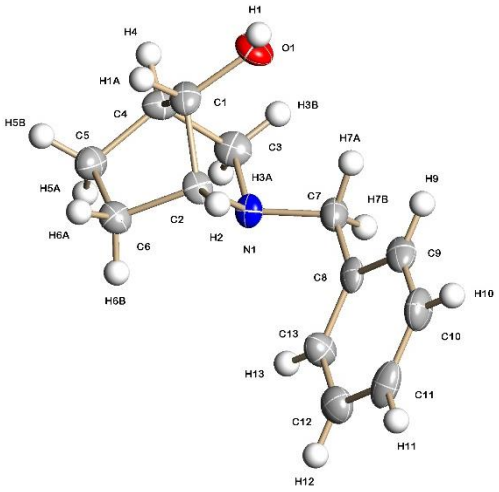

Figure shows 50% displacement ellipsoids. hydrogens have been omitted for simplicity.

R1 = 0.0831, wR2 = 0.1202.

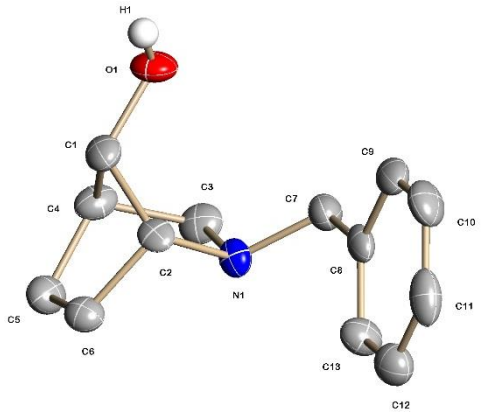

Figure shows 50% displacement ellipsoids; the

Empirical formula	C13 H17 N O	
Formula weight	203.28	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 10.771(8) Å	α= 90°.
	b = 9.893(7) Å	β= 102.831(16)°.
	c = 10.451(7) Å	γ = 90°.
Volume	1085.8(13) $Å^3$	
Z	4	
Density (calculated)	1.243 Mg/m^3	
Absorption coefficient	0.078 mm^{-1}	
F(000)	440	

Crystal size	0.16 x 0.06 x 0.03 mm^3
Theta range for data collection	1.94 to 25.99°.
Index ranges	-13<=h<=13, -12<=k<=12, -12<=l<=12
Reflections collected	8224
Independent reflections	2130 [R(int) = 0.2606]
Completeness to theta = 25.99°	100.0 %
Absorption correction	Empirical
Max. and min. transmission	0.969 and 0.407
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2130 / 0 / 138
Goodness-of-fit on F^2	0.824
Final R indices [I>2sigma(I)]	R1 = 0.0831, wR2 = 0.1202
R indices (all data)	R1 = 0.2335, wR2 = 0.1552
Extinction coefficient	0.0023(16)
Largest diff. peak and hole	0.267 and -0.285 $e.Å^{-3}$

7.2 Crystal data and structure refinement for (164)

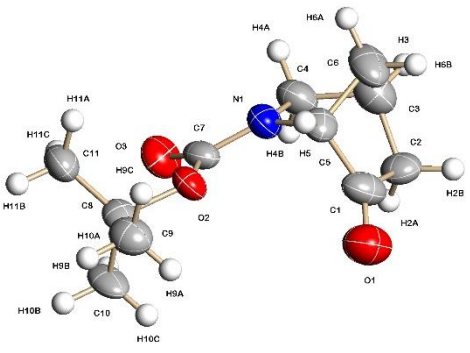

Figure shows 50% displacement ellipsoids. hydrogens have been omitted for simplicity.

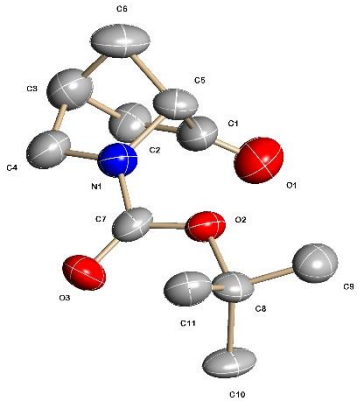

Figure shows 50% displacement ellipsoids; the

R1 = 0.1093, wR2 = 0.2536.

Empirical formula	C11 H17 N O3	
Formula weight	211.26	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 10.003(10) Å	α= 90°.
	b = 11.995(12) Å	β= 110.850(17)°.
	c = 10.157(10) Å	γ = 90°.
Volume	1139(2) $Å^3$	
Z	4	
Density (calculated)	1.232 Mg/m^3	
Absorption coefficient	0.089 mm^{-1}	
F(000)	456	
Crystal size	0.31 x 0.25 x 0.11 mm^3	
Theta range for data collection	2.45 to 24.99°.	
Index ranges	-11<=h<=11, -14<=k<=14, -12<=l<=11	
Reflections collected	8002	
Independent reflections	2006 [R(int) = 0.2988]	
Completeness to theta = 24.99°	100.0 %	
Absorption correction	Empirical	
Max. and min. transmission	0.981 and 0.169	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2006 / 0 / 139	
Goodness-of-fit on F^2	0.866	

Final R indices [I>2sigma(I)]	R1 = 0.1093, wR2 = 0.2536
R indices (all data)	R1 = 0.2152, wR2 = 0.3005
Largest diff. peak and hole	0.487 and -0.441 e.Å^{-3}

7.3 Crystal data and structure refinement for (166)

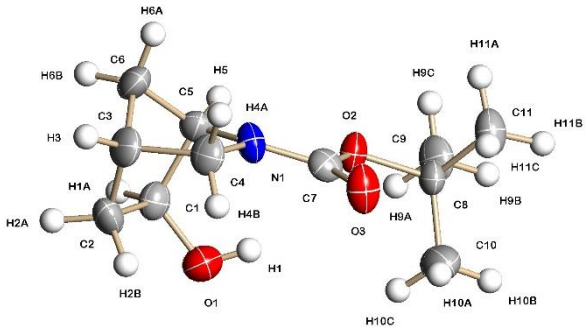

Figure shows 50% displacement ellipsoids. R1 = 0.0693, wR2 = 0.1519.

Empirical formula	C11 H19 N O3	
Formula weight	213.27	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pca2 (1)	
Unit cell dimensions	a = 9.462(3) Å	α= 90°.
	b = 11.670(3) Å	β= 90°.
	c = 10.956(3) Å	γ = 90°.
Volume	1209.8(6) Å^3	
Z	4	
Density (calculated)	1.171 Mg/m^3	
Absorption coefficient	0.084 mm^{-1}	
F(000)	464	
Crystal size	0.31 x 0.14 x 0.07 mm^3	
Theta range for data collection	1.75 to 25.00°.	

Index ranges	-11<=h<=11, -13<=k<=13, -13<=l<=13
Reflections collected	8138
Independent reflections	1124 [R (int) = 0.1100]
Completeness to theta = 25.00°	100.0 %
Absorption correction	Empirical
Max. and min. transmission	0.981 and 0.490
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1124 / 1 / 139
Goodness-of-fit on F^2	0.999
Final R indices [I>2sigma(I)]	R1 = 0.0693, wR2 = 0.1519
R indices (all data)	R1 = 0.0941, wR2 = 0.1611
Absolute structure parameter	?
Largest diff. peak and hole	0.440 and -0.198 e.$Å^{-3}$

7.4 Crystal data and structure refinement for (202)

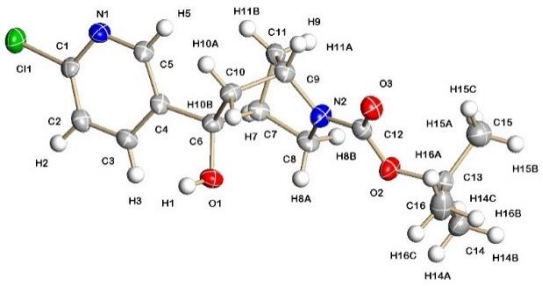

Figure shows 50% displacement ellipsoids. hydrogens have been omitted for simplicity.

R1 = 0.0893, wR2 = 0.2139.

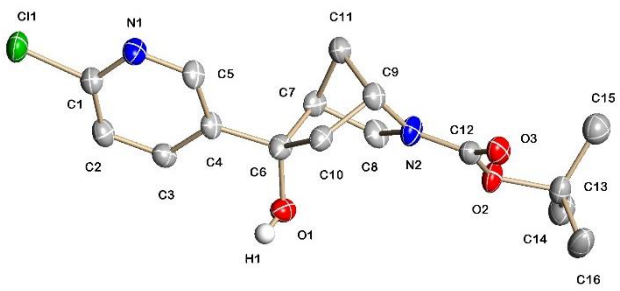

Figure shows 50% displacement ellipsoids; the

Empirical formula	C16 H21 Cl N2 O3
Formula weight	324.80
Temperature	150(2) K
Wavelength	0.71073 Å

Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 6.0583(19) Å	α= 80.023(6)°.
	b = 10.400(3) Å	β= 83.033(6)°.
	c = 12.952(4) Å	γ = 81.219(6)°.
Volume	790.5(4) $Å^3$	
Z	2	
Density (calculated)	1.365 Mg/m^3	
Absorption coefficient	0.256 mm^{-1}	
F(000)	344	
Crystal size	0.24 x 0.16 x 0.04 mm^3	
Theta range for data collection	1.60 to 25.99°.	
Index ranges	-7<=h<=7, -12<=k<=12, -15<=l<=15	
Reflections collected	6219	
Independent reflections	3058 [R(int) = 0.1543]	
Completeness to theta = 25.99°	98.5 %	
Absorption correction	Empirical	
Max. and min. transmission	0.894 and 0.255	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3058 / 0 / 202	
Goodness-of-fit on F^2	0.913	
Final R indices [I>2sigma(I)]	R1 = 0.0893, wR2 = 0.2139	
R indices (all data)	R1 = 0.1391, wR2 = 0.2390	
Largest diff. peak and hole	0.646 and -0.679 $e.Å^{-3}$	