The Functionalisation of 2-Azanorbornanes and Approaches to Novel Epibatidine Analogues

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by

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Statement

The accompanying thesis submitted for the degree of Ph.D. entitled 'The Functionalisation of 2-Azanorbornanes and Approaches to Novel Epibatidine Analogues' is based on work conducted by the author in the Department of Chemistry at the University of Leicester mainly during the period between October 2003 and September 2006. All the work in this thesis is original unless indicated otherwise in the text or references. None of the work has been submitted for another degree in this or any other university.

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I could not have completed this thesis without the support of my family and I dedicate it to my Mum, Dad and my brother.

Abstract

The functionalisation of 2-Azanorbornanes and Approaches to Novel Epibatidine analogues

By Richard White

Epibatidine (*exo*-2-(6-chloro-3-pyridyl)-7-azabicyclo[2.2.1]heptane) is an alkaloid found on the skin of the Ecuadorian poison-dart frog *Epipedobates tricolor*. It has extremely high affinity for nicotinic acetylcholine receptors and is a potent analgesic but it can not be used therapeutically as it is highly toxic. A wide range of epibatidine analogues and isomers has been produced in order to identify compounds with medicinal potential and to help elucidate the nicotinic pharmacophore. This thesis describes synthetic routes to novel epibatidine analogues, in particular, derivatives based on the 2-azabicyclo[2.2.1]heptane (2-azanorbornane) molecular framework.

A general method for the synthesis of 7-functionalised 2-azanorbornanes has been devised. Bromination of *N*-benzyl-2-azanorborn-5-ene and treatment of the resulting tricyclic salt with hydride occurs with skeletal rearrangement to give *N*-benzyl-7-bromo-2-azanorbornane. Nucleophilic substitution reactions of this compound were found to occur with retention of configuration, consistent with neighbouring group participation of the bicyclic nitrogen lone pair. Heterocycles have been introduced at the 7-position of 2-azanorbornanes and manipulation of the stereochemistry at this position gave the novel epibatidine analogues isoepiboxidine and isoepibatidine. Both have very high affinity for nicotinic receptors; isoepibatidine is equipotent with epibatidine.

The synthesis of fluorinated 2-azanorbornanes was investigated leading to the synthesis of a fluorinated isoepibatidine molecule (*syn*-7-(6-chloro-pyridin-3-yl)-*exo*-6-fluoro-2-azabicyclo--[2.2.1]heptane). In addition, a novel rearrangement was discovered which results in functionalisation of the bridgehead position (C1) of 2-azanorbornanes.

An oxidation-reduction strategy of *anti*-7-hydroxy-2-azanorbornanes gave the corresponding *syn*-alcohols and the introduction of pyridine moieties gave ether-linked nicotinic receptor ligands with the general structure 7-(pyridinyloxy)-2-benzyl-2-azabicyclo[2.2.1]heptane. Routes have also been devised to novel isotropane-based epibatidine analogues; chloropyridine heterocycles have been introduced to the 8-positions of the 2-azabicyclo[3.2.1]octane and 3-azabicyclo[3.2.1]octane frameworks.

Abbreviations

AChBP	Acetylcholine binding-protein
°C	Degrees Celsius
COD	Cyclooctadiene
COSY	Correlation spectroscopy
cm^{-1}	Per centimetre
CNS	Central nervous system
DAST	(Diethylamino)sulfur trifluoride
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless enhancement by polarisation transfer
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
EI	Electron impact
FAB	Fast atom bombardment
g	Grams
GC	Gas chromatography
GCMS	Gas chromatography mass spectrometry
h	Hours
Hz	Hertz
IR	Infra-red
M	Molar
M^+	Molecular ion
mCPBA	Meta-chloroperoxybenzoic acid
MHz	Megahertz
ml	Millilitre
mm	Millimetre
mmol	Millimoles
mol^{-1}	Per mole
nAChR	Nicotinic acetylcholine receptor
NGP	Neighbouring group participation
MS	Mass spectrometry
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy

PDC	Pyridinium dichromate
PET	Positron emission tomography
PNS	Peripheral nervous system
ppm	Parts per million
RT	Room temperature
QSAR	Quantitative structure activity relationship
SAR	Structure activity relationship
TBAF	Tetrabutylammonium fluoride
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography

Contents

Statement i

Acknowledgements ii

Abstract iii

Abbreviations iv

Chapter 1: Introduction 1

1.1 The nicotinic acetylcholine receptor 2

1.2 Naturally-occurring nicotinic receptor agonists 3

1.3 Epibatidine 5

1.4 The nicotinic pharmacophore 7

1.5 Epibatidine analogues 10

1.5.1 Alternative heterocycles 11

1.5.2 The azabicyclo[2.2.1]heptane framework 12

1.5.3 Higher analogues of epibatidine 13

1.5.4 Smaller azabicyclic frameworks 15

1.5.5 Heteroatom incorporation 16

1.5.6 Epibatidine analogues with ether linkages 17

1.6 7-Substituted 2-azabicyclo[2.2.1]heptanes 18

1.6.1 The proposed route to 7-substituted 2-azabicyclo[2.2.1]heptanes 20

Chapter 2: Functionalisation of the 7-position of 2-azanorbornanes and approaches to isoepiboxidine 22

2.1 Synthesis of 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene 23

2.2 Bromination of 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene 23

2.3 Nucleophilic ring opening of aziridinium salts 24

2.4 Substitution at the 7-position of 2-azabicyclo[2.2.1]heptanes 26

2.4.1 Determination of C7 stereochemistry in substitution products 27

2.4.2 Neighbouring group participation in 2-azabicyclo[2.2.1]heptanes 28

2.5 Epimerisation at the 7-position of 2-azabicyclo[2.2.1]heptanes 30

2.6 Construction of the methylisoxazole heterocycle 33

Chapter 3: Approaches to isoepibatidine 37

3.1 Introduction 38

3.2 Suzuki cross-coupling reactions 38

3.3 Cross-coupling to *anti*-7-bromo-2-boc-2-azabicyclo[2.2.1]heptane 41

3.4		Synthesis of isoepibatidine	44
Chapter 4:		**Epibatidine analogues with ether-linkages**	46
4.1		Nicotinic ligands with ether-linkages	47
4.2		Target selection	49
4.3		Approaches to 7-keto-2-azabicyclo[2.2.1]heptanes	50
4.4		The reduction of 7-keto-2-azabicyclo[2.2.1]heptanes	51
4.5		Facial selectivity in 7-norbornanones and related systems	53
	4.5.1	Discussion of facial selectivity in 7-keto-2-azabicyclo[2.2.1]heptanes	54
4.6		Pyridyl derivatives of 7-hydroxy-2-azabicyclo[2.2.1]heptane	56
	4.6.1	Approaches to pyridyl derivatives of *anti*-7-hydroxy-2-azabicyclo[2.2.1]heptane	56
	4.6.2	Approaches to pyridyl derivatives of *syn*-7-hydroxy-2-azabicyclo[2.2.1]heptane	57
		4.6.2.1 2-Pyridyl and 4-pyridyl derivatives of *syn*-7-hydroxy-2-azabicyclo[2.2.1]heptane	57
		4.6.2.2 Routes to 3- pyridyl derivatives of *syn*-7-hydroxy-2-azabicyclo[2.2.1]heptane	58
4.7		Attempted synthesis of a conformationally restricted analogue of isoepibatidine	59
Chapter 5:		**Fluorinated analogues of epibatidine**	62
5.1		Introduction	63
5.2		Fluorinated analogues of epibatidine	63
5.3		Fluorinated 2-azabicyclo[2.2.1]heptanes	64
5.4		6-*exo* Fluorinated analogues of isoepibatidine	66
	5.4.1	Synthesis of *exo*-6-fluoro-2-azabicyclo[2.2.1]heptanes	66
	5.4.2	Substitution reactions of dibromo-2-Cbz-2-azabicyclo[2.2.1]heptane	67
	5.4.3	Coupling reactions of *exo*-6-fluoro-*anti*-7-bromo-2-azabicyclo[2.2.1]heptanes	68
5.5		3-Substituted 1-azatricyclo[2.2.1.$0^{2,6}$]heptanes	70
5.6		Attempted routes to 3-Fluorinated 2-azabicyclo[2.2.1]heptanes	72
5.7		Routes to 1-substituted 2-azabicyclo[2.2.1]heptanes	74
	5.7.1	Attempted routes to 6-fluoro-2-azabicyclo[2.2.1]hept-5-enes	74
	5.7.2	Rearrangement reactions of 6-keto-2-azabicyclo[2.2.1]heptanes	75

5.8 Routes to 7-fluorinated 2-azabicyclo[2.2.1]heptanes 80

Chapter 6: Approaches to isotropane analogues of epibatidine 82

6.1 Introduction 83

6.2 Analogues of epibatidine based on 3-azabicyclo[3.2.1]octane 84

6.2.1 Synthesis of 8-hydroxy-3-benzyl-3-azabicyclo[3.2.1]octane 84

6.2.2 Synthesis of 8-bromo-3-azabicyclo[3.2.1]octanes 84

6.2.3 Attempted substitution reactions of 8-bromo-3-azabicyclo[3.2.1]octanes 86

6.2.4 Attempted synthesis of *syn*-8-(6-Chloro-pyridin-3-yl)-3-azabicyclo[3.2.1]octane 86

6.3 Analogues of epibatidine based on 2-azabicyclo[3.2.1]octane 88

6.3.1 Synthesis of 2-benzyl-2-azabicyclo[2.2.2]hept-5-ene 89

6.3.2 Synthesis of 8-bromo-2-benzyl-2-azabicyclo[3.2.1]octane 89

6.3.3 Synthesis of homoisoepibatidine 90

Chapter 7: Nicotinic receptor binding studies 93

7.1 Nicotinic receptor binding assays 94

7.2 The nicotinic receptor affinities of isoepibatidine and the isoepiboxidines 94

7.3 The nicotinic receptor affinities of pyridyl-ether analogues of epibatidine 97

Chapter 8: Experimental 99

Appendix I: Crystal structure data 149

Appendix II: Selected ^{13}C NMR spectra 154

Appendix III: Publications 157

References 174

Chapter 1

Introduction

1.1 The nicotinic acetylcholine receptor

Nicotinic acetylcholine receptors (nAChRs) are vital for neurotransmission and have many biological roles; they are ligand-gated ion channels and are part of the superfamily of neurotransmitter receptors that includes the γ-aminobutyric acid ($GABA_A$), glycine and serotonin (5-HT) receptors. The discovery and study of the alkaloids nicotine (**1**) and muscarine (**2**) resulted in the division of nicotinic receptors into two principal classes, the muscle and neuronal types (Fig. 1.10). Muscarine binds to the muscle nAChR, which is found at the neuromuscular junction and mediates muscle contraction; nicotine acts at the neuronal type which is found in autonomic ganglia and in the brain. Nicotinic receptors are pivotal in the initiation of muscle contraction and in autonomic neurotransmission, but have a more regulatory role in the central and peripheral nervous systems, where they are widespread but in relative low abundance.[1,2]

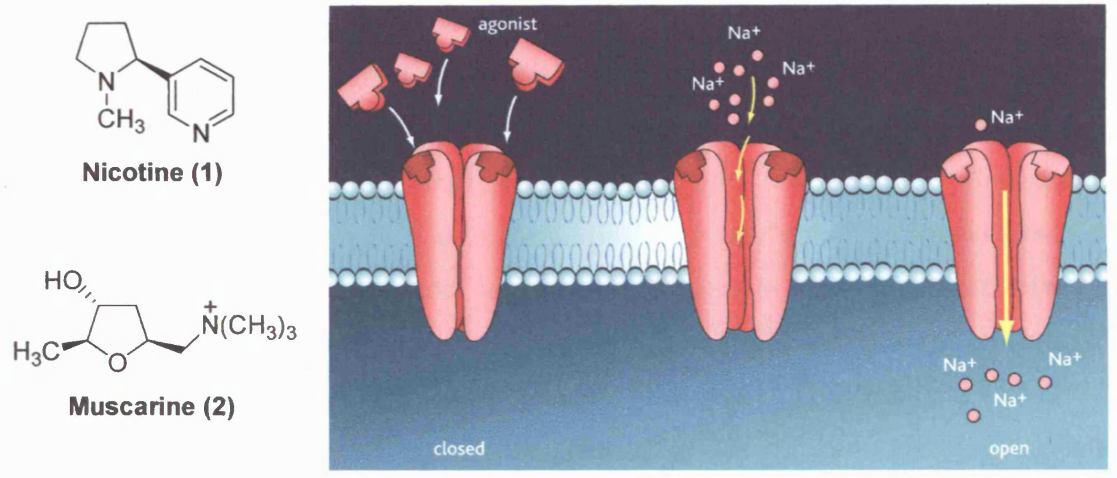


Fig. 1.10 The nicotinic receptor,[3] nicotine and muscarine.

Nicotinic receptors are cell membrane-spanning pentameric ion-channels; five subunits combine to form the nAChR, a trans-membrane protein with a cation-conducting water-filled pore.[4] Each subunit comprises an extra-cellular domain, which contains the acetylcholine binding site, four hydrophobic membrane-spanning domains and an intra-cellular loop. A range of different subunits are known to exist, they combine in various combinations to give the distinct nAChR subtypes. The subunit composition of muscle nAChRs is $(\alpha 1)_2(\beta 1)\delta\varepsilon$;[5] neuronal nAChRs, however, are much more diverse but are assembled from only α and β subunits; twelve mammalian neuronal nAChR subunits have been discovered (α2-α10; β2-4).[6] Despite the plethora of potential subunit permutations, only a small number of neuronal nAChR subtypes are known. These include $(\alpha 4)_2(\beta 2)_3$ which is the most abundant nAChR in the CNS, $(\alpha 7)_5$ and $(\alpha 3)_2(\beta 4)_3$ which is prevalent in autonomic ganglia;[4] these receptors are

usually referred to as the α4β2, α7, and α3β4 subtypes respectively. The physiological and pharmacological roles of the different receptor subtypes are poorly understood but are the subject of intense research efforts.[7]

The neurotransmitter acetylcholine (**3**; Fig. 1.20) is the endogenous agonist for the nAChR. Upon agonist binding the receptor undergoes a conformational change from the resting, closed state to an open state, through which the cations of sodium, potassium and calcium can be conducted. There are other naturally-occuring nicotinic agonists which have particular relevance to this study.

1.2 Naturally-occurring nicotinic receptor agonists

A large range of compounds that interact with nicotinic receptors has been discovered.[8] Agonists and competitive antagonists bind to sites at the interface of α and β subunits; there are two binding sites per receptor.[4] Non-competitive antagonists and positive allosteric modulators act at sites distinct from the agonist binding site and will not be discussed here. Agonists can loosely be termed 'activators' as they show a higher affinity for the open state of the nAChR causing influx of cations (principally sodium) into the cell. The resulting depolarisation of the cell leads to neurotransmission. The binding of antagonists does not cause such changes as they do not show preference in binding to the closed/open states. The potency of an agonist depends on two factors: affinity (how well it binds to the receptor) and efficacy (the tendency, once bound to cause the channel to open).[2] The affinity of a compound is indicated by its K_i, which is an equilibrium-based term derived from how well a labelled nicotinic ligand, such as tritium-labelled nicotine, is displaced from the receptor by the ligand under investigation; low K_i values indicate high affinity.[9] Efficacy is quantified as the percentage of the maximum response a ligand can achieve and gives rise to the terms full-agonist, partial-agonist and antagonist. The EC_{50} value gives an indication of the functional potency of a substance, and is the dose required to give 50% of the maximum response. However, the affinity and efficacy values for any particular compound are not absolute as there are discrepancies due to the exact origins of the receptors being used and variations in experimental procedures.[7] The binding, efficacy and potency figures quoted in this thesis are not definitive; they are intended to give an indication of biological properties and to illustrate trends.

The first naturally occurring nicotinic receptor agonist to consider is acetylcholine (**3**), the ester product of acetate and choline. It is a neurotransmitter and mediates the transmission of nerve signals across synapses; it binds with high affinity (K_i ~ 10 nM) at α4β2 nAChRs.[1] Acetylcholine is released by the presynaptic membrane and diffuses to the postsynaptic

membrane where two molecules bind to each nicotinic receptor. The subsequent channel opening and influx of sodium ions causes depolarisation of the postsynaptic membrane triggering an action potential.[10]

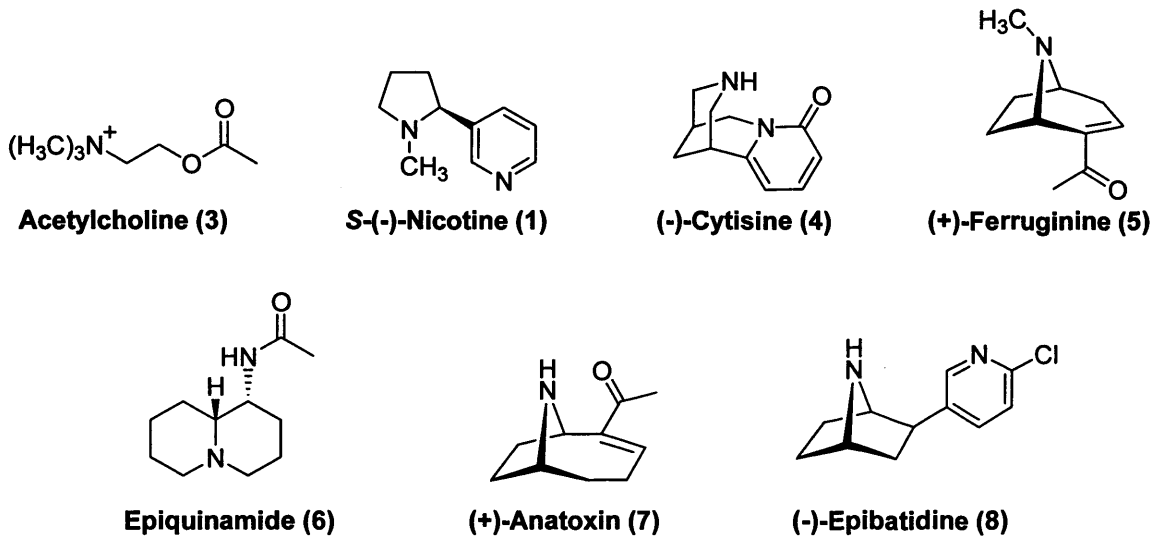


Fig. 1.20 Some naturally-occurring nicotinic agonists. The naturally-occurring enantiomers are shown where appropriate.

Nicotine (**1**) consists of a pyridine ring linked to a pyrrolidine ring, it acts at the nAChR and indeed, gives the receptor its name; like acetylcholine, nicotine binds with high affinity (K_i = 1-11 nM) to α4β2 receptors.[1] Nicotine is the addictive component of tobacco but it also has some beneficial properties, including cognitive enhancement, analgesia, neuroprotection and anxiolytic properties.[11] The incidence of Parkinson's disease in smokers is twofold less than in non-smokers and evidence suggests that smokers are also less likely to suffer from Alzheimer's. It is thought that nicotine combats these neurodegenerative diseases by activating nicotinic receptors that mediate dopamine release in the CNS.[2] Nicotine can increase alertness and enhance learning and memory; it is also known to have antinociceptive (pain killing) effects, although antinociception in mammals is of short duration and is attenuated with repeated dosing. Despite these properties, nicotine is not used therapeutically for various reasons, including its addictive nature and the adverse effects it has on autonomic function.[4]

Cytisine (**4**) is a natural product found in plants of the *leguminosae* family, such as laburnum; it also binds with high affinity (K_i ~1 nM) to α4β2 receptors, akin to acetylcholine and nicotine.[1] The rigid structure of cytisine has led to its use as a research tool, particularly as a template for modelling nicotinic ligands. The efficacy of cytisine is dependent on the identity of the β–subunit that forms the binding site. For instance, cytisine shows full efficacy

at β4-containing subtypes but greatly reduced efficacy at β2-containing nAChRs. This is in contrast to many nicotinic agonists and emphasises the importance of the β-subunit in determining agonist-nAChR interactions,[1] it also helps to illustrate the distinction between affinity and efficacy.

Ferruginine (**5**) is unusual in that the naturally occurring (+)-enantiomer has an extremely low affinity for α4β2 receptors (K_i = 7600 nM) but the unnatural (-)-enantiomer has 60-fold higher affinity.[12] Epiquinamide (**6**), a quinolizidine alkaloid found recently on the skin of an Ecuadorian frog (see Section 1.3), is selective for β2-containing subtypes and more detailed pharmacological characterisation of this compound is being undertaken.[13]

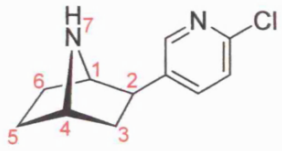
Anatoxin A (**7**) is an extremely potent nicotinic agonist and has higher affinity (K_i = 0.34 nM) for the α4β2 subtype than nicotine (K_i ~ 1 nM). It is a product of the freshwater blue-green algae *Anabaena flosaquae* and is a semi-rigid azabicyclononene; the natural (+)-enantiomer is much more potent than the (-)-enantiomer. Anatoxin A has been used to study nicotinic currents in brain neurons and nAChR-mediated dopamine release.[1,4,7] Epibatidine (**8**), like anatoxin A, is azabicyclic and it is the most potent nicotinic agonist yet discovered.

1.3 Epibatidine

Epibatidine (**8**) was first isolated in 1974 from the skin of the Ecuadorian poison-dart frog *Epipedobates tricolor* (Fig 1.30); in 1992 analytical techniques, particularly NMR, became sensitive enough to elucidate the structure.[14] Epibatidine or *exo*-2-(6-chloro-3-pyridyl)-7-azabicyclo[2.2.1]heptane (**8**) is composed of a 2-azanorbornane bicycle attached to a chloropyridine heterocycle, an unusual structure for an alkaloid natural product.

In 1994 the first total synthesis of epibatidine was achieved, allowing its absolute stereochemistry to be determined.[15] Approaching 100 syntheses of epibatidine have been published to date (SciFinder Scholar, 2006) and current efforts are focussed on enantioselective preparations. Recent examples include the total syntheses by Aggarwal,[16] Ley,[17] and Takemoto.[18] Before synthetic routes to epibatidine were developed, detailed pharmacological study of the compound was not possible since a particularly epibatidine-laden frog will possess only about 1 μg of the substance. Frogs kept in captivity do not harbour epibatidine at all,[14] and therefore it is thought that *Epipedobates tricolor* receives epibatidine, or an epibatidine precursor, from an unidentified arthropod present in its diet.[8] In addition, the frog is now very rare and collection has been outlawed since 1984 by the international treaty for the protection of endangered species.[19]

Pharmacological characterisation indicated that epibatidine binds with exceptionally high affinity (K_i = 19 pM) at α4β2 nAChRs, and with approximately tenfold lower affinity at α3β2 (K_i = 230 pM) and α3β4 (K_i = 380 pM). The functional potency of epibatidine is also extremely high at these receptor subtypes with EC_{50} values typically in the sub-micromolar range - only at α7 and muscle nAChRs are the EC_{50} values in the low micromolar range.[1] Unlike anatoxin and nicotine, the two enantiomers of epibatidine show similar biological activities ((-)-**8** K_i = 0.045 nM; (+)-**8** K_i = 0.058 nM; measured at rat brain membranes),[20] the naturally occurring (-)-enantiomer has marginally higher affinity for all nAChR subtypes.[21,22]



Epibatidine (8)

Fig. 1.30 Epibatidine (**8**) with atom numbering; Epipedobates tricolor (www.anaesthetist.com).

Epibatidine was found to be a potent analgesic,[14] having antinociceptive activity 200 times greater than morphine in the hot-plate test, and to be effective against a range of pain types.[7] In contrast to epibatidine, morphine acts at opioid receptors the more usual site of action for an analgesic.[2] Many nicotinic agonists have some degree of antinociceptive activity but the discovery of the potent analgesic properties of epibatidine renewed interest in the role of nAChRs in pain transmission and as targets for painkillers. Exactly how nicotinic agonists mediate pain relief is unclear although it is known to involve both peripheral and central nicotinic receptors and α4β2 nAChRs are thought to have an important role.[4,23]

The potency of epibatidine made it the source of much pharmacological interest. However, its high activity and lack of receptor-subtype selectivity result in epibatidine being extremely toxic; it protects *Epipedobates tricolor* from potential predators.[7] Epibatidine cannot be used therapeutically: the antinociceptive effects of epibatidine decay substantially in the first thirty minutes after administration and toxic side effects are seen at doses similar to those required for analgesic activity. These include reduction in body temperature and locomotor activity, disruption of motor coordination, hypertension, convulsions and respiratory distress. Epibatidine is acutely lethal at doses six times higher than the fully efficacious antinociceptive dose; repeated administration at doses in the antinociceptive range is also lethal.[4]

Although there are inherent problems in using epibatidine medicinally, the study of the compound has inspired a large amount of research into the synthesis of epibatidine analogues

as potential therapeutic agents. In addition to analgesia, nicotinic receptors have been implicated in numerous other diseases and conditions (see Section 1.5). When selecting target structures as possible drug candidates, it is desirable to have a good knowledge of drug-binding site interactions and how the structure of a compound affects its activity.

1.4 The nicotinic pharmacophore

A pharmacophore is considered to be the minimal structural features necessary for a compound to bring about a pharmacological response, that is, to behave as an agonist, partial agonist or competitive antagonist.[24] The nicotinic pharmacophore is not well defined; the compounds already considered begin to give an indication of the wide range of structural types that can mediate nicotinic activity. The situation is further complicated by the multiple subtypes of nAChRs and the range of different allosteric receptor conformations.

Knowledge of the nAChR binding site was attained only recently and is discussed below. Prior to these developments, binding models were based purely on the binding affinities of known nicotinic ligands and are limited in view of the fact that they do not take efficacy, that is, if the compound is an agonist, partial agonist or anatagonist, into account. The $\alpha4\beta2$ subtype is by far the most abundant receptor in the CNS; the pharmacophore of this receptor type is the only one to receive concerted attention and will be considered here.[24]

The Sheridan pharmacophore was first proposed in 1986 when few nicotinic ligands were known and understanding of the nAChR subtypes was poor. The Sheridan model attempts to define the optimum distances between three pharmacophoric elements (Fig. 1.40A).[25] Once the structure of epibatidine was determined it was found to be compatible with the Sheridan model. As further nicotinic agonists were evaluated, a parabolic relationship between affinity and inter-nitrogen distance ($X\text{-}N^+$) was shown to exist (Fig. 1.40B), a low energy conformation of epibatidine possesses the optimum inter-nitrogen distance, 5.5 Å.[26] Recent developments (see below) have indicated that this distance is not representative of the active conformations of nicotinic ligands. An improved, four-point binding model was postulated (Fig. 1.40C), this pharmacophore defines the distance between two binding site elements. A modified version of this model also includes the 'aryl centroid' present in the Sheridan model (Fig. 1.40D). These binding models do not account for the binding of all ligands and there remains a need for multiple pharmacophores. Some binding models have also been investigated which include the coordination of a water molecule between the ligand and the binding site.[24]

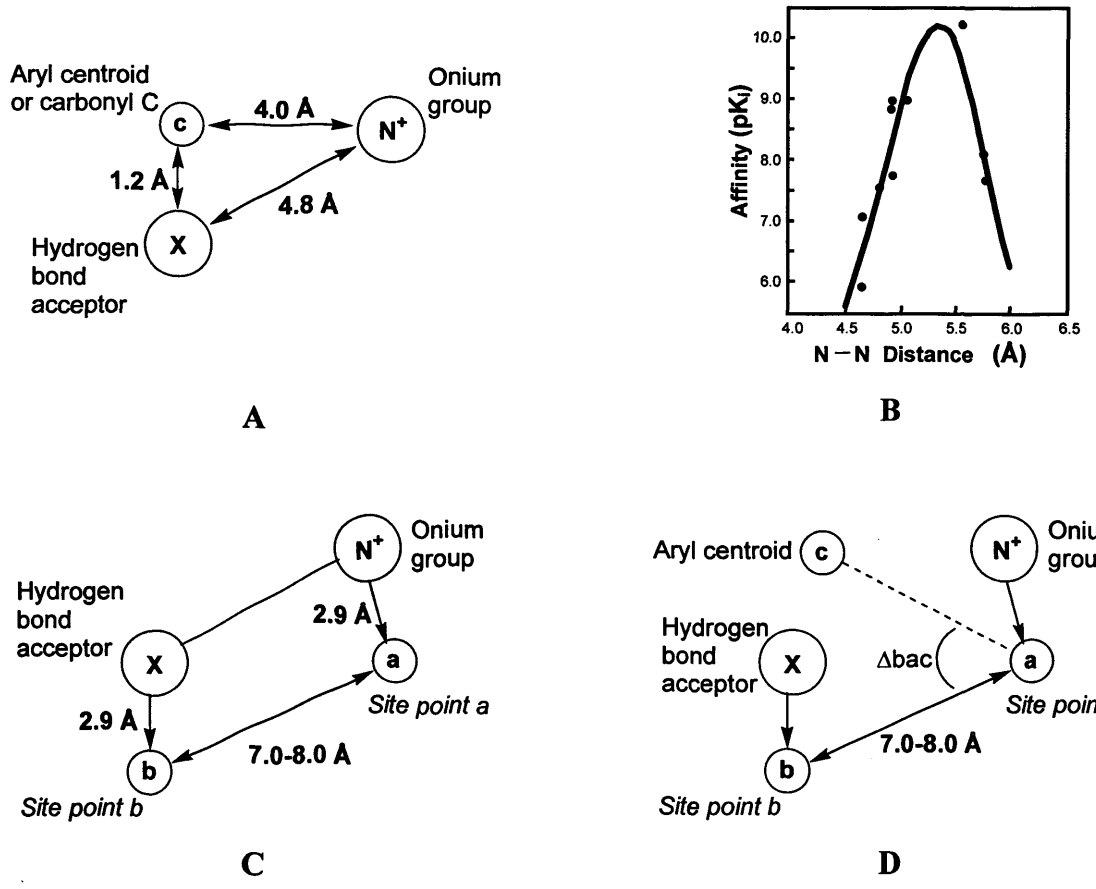


Fig. 1.40 Nicotinic pharmacophore models. A: The Sheridan pharmacophore; B: The relationship of inter-nitrogen distance to nicotinic affinity; C and D: 4-point binding models.[24] For epibatidine: N^+/onium group = the bicyclic nitrogen; X/hydrogen bond acceptor = pyridyl nitrogen; c/aryl centroid = the centre of the pyridine ring. Site point a and site point b are points in space.

The synthesis and discovery of new nAChR ligands has gone hand-in-hand with increased understanding of the nicotinic pharmacophore;[27,28] as the pharmacological properties of new compounds are determined their structures are fitted to existing binding models, which are then refined. Some compounds have been synthesised for the principal purpose of probing the nicotinic pharmacophore. Acetylcholine, and to a lesser extent nicotine and epibatidine, have a plethora of low energy conformations and rigid analogues of these compounds have been produced in attempts to determine their active conformations.[27,29-32]

Key to understanding the nicotinic pharmacophore is the elucidation of the receptor structure, particularly the extra-cellular domain and the agonist binding site. No X-ray or NMR data on the nAChR have been reported, although the muscle nAChR has been examined by electron microscopy at low resolution (4.6 Å).[33] In 2001 the crystal structure of a ACh-binding protein (AChBP) from *Lymnaea stagnalis* (a snail) was obtained at atomic resolution, allowing the features of an ACh binding pocket to be determined for the first time.[34,35] Since this breakthrough, crystal structures of snail AChBP with nicotine and carbamylcholine bound have been determined.[36] In 2005, the crystal structure of an

epibatidine-bound AChBP from *Aplysia californica* (another snail) was published by Hansen *et al.*[37] The binding mode of epibatidine to AChBP was found to be similar to that for nicotine with an inter-nitrogen distance of 4.5 Å observed for both ligands. The pyridyl nitrogen forms hydrogen bonds to two amino acid residues via a solvent molecule; the bicyclic nitrogen is bound by two hydrogen bonds and the aromatic chlorine makes polar contacts with the carbonyl oxygens of two amino acids (Fig. 1.41).[37]

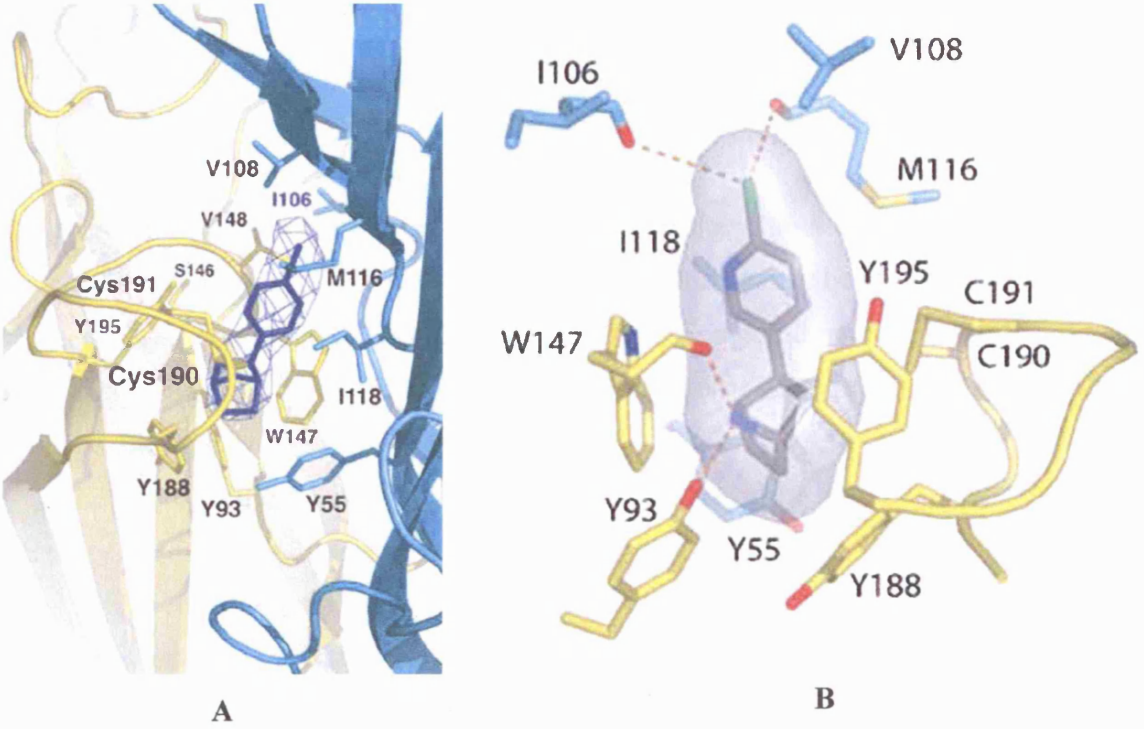


Fig. 1.41 The crystal structure of epibatidine bound to *A*-AChBP. A: The electron density map of epibatidine (blue) is shown. B: An expanded view with hydrogen bonding; the molecular surface of epibatidine is shown in grey.[37] C/Cys: cysteine; I: isoleucine; M: methionine; V: valine; W: tryptophan; Y: tyrosine.

The agonist binding sites of nAChRs have high amino acid sequence homology (40-60%) with the AChBPs,[6] and this together with electron microscopy have helped to confirm the structural similarity between AChBPs and nAChRs.[38] These new findings are facilitating computational studies including modelling of nicotinic receptor subtypes, docking experiments and quantitative structure activity relationship (QSAR) studies,[6,39-44] that are beginning to aid rational nACh drug design.[6] As understanding of the nicotinic pharmacophore and the nAChR binding site increases, it will begin to have greater influence on the design of novel nicotinic agonists and epibatidine analogues. Ideally, an individual pharmacophore model for each nAChR subtype will direct the search for subtype-selective analogues of epibatidine. Most epibatidine analogues that have been synthesised to date are the result of making structural changes to compounds with known nicotinic activity.

1.5 Epibatidine analogues

Many novel nicotinic ligands have been and continue to be synthesised, the principal aim being to produce compounds that have therapeutic potential. A plethora of diseases and conditions are candidates for treatment with agents that act at nAChRs. As has already been alluded to, Alzheimer's and Parkinson's disease are associated with a decrease in neuronal nAChR density.[7] The antinociceptive properties of epibatidine suggest that there is scope for the use of nAChR agonists/epibatidine analogues as analgesics.[4] Other conditions that could potentially be treated with nAChR agonists include schizophrenia, Tourette's syndrome, attention deficit hyperactivity disorder, familial frontal lobe epilepsy, depression, anxiety and compounds may find use as smoking cessation agents.[5,7,45] A recent patent even describes how nicotinic agonists could be used to improve joint lubrication.[46] Some of these applications are considered to be speculative and future drugs may be used to augment current therapies rather than replace them. Compounds to treat pain and neurodegenerative diseases such as Parkinson's and Alzheimer's are probably the most likely near-term applications of novel nAChR ligands.[7]

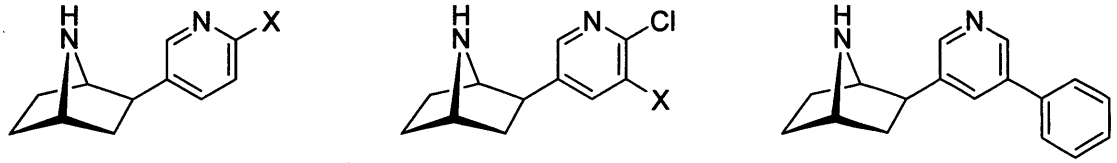
The major challenge is to synthesise compounds that show improved receptor subtype selectivity, leading to an improved separation of activity and toxicity. That is, produce novel agents which have therapeutic properties without significant side effects.[7] Agonists or competitive antagonists that show nAChR subtype selectivity can also be used as research tools to further our understanding of the roles and locations of the receptor subtypes.[1] Indeed, since the first division of acetylcholine receptors into the muscarinic and nicotinic types, the discovery and synthesis of new nicotinic agents has gone hand-in-hand with increased understanding of receptor structures and functions.

The quest for novel epibatidine analogues is directed towards the synthesis of therapeutically and scientifically valuable substances. However, many of these compounds, akin to epibatidine, are toxic and have the potential to be misused. Therefore, some of the interest in these compounds lies in their ability to harm and hence, their ease of preparation and the regulation of precursor availability.

Many analogues of epibatidine have been developed with these aims in mind; a selection will be discussed here. Particular consideration will be given to the influence of structural features on pharmacological properties, *i.e.* structure activity relationships (SARs). Taking epibatidine as a starting point, various structural aspects have been altered to give a multitude of novel molecules.

1.5.1 Alternative heterocycles

Perhaps the simplest change that can be made to the structure of epibatidine (**8**) is to exchange the chlorine for an alternative atom; a range of 6-substituted deschloro-epibatidine analogues have been synthesised and their pharmacological properties determined. The chlorine atom has been replaced by hydrogen, fluorine and bromine. Despite the differing sizes of these substituents in relation to chlorine, the resulting compounds **9a-c** have binding affinities (K_i) for neuronal nAChRs similar to those of epibatidine. The chlorine atom is required for the exquisite properties of epibatidine but the functional potencies of **9a-c** are also high, being greater than nicotine but reduced in comparison to epibatidine. In contrast, when a methyl substituent (**9g**), amino groups (**9d-e**) or strongly electron-withdrawing groups (**9f**) are present, both the binding affinity and potency are greatly reduced.[27,47] This is probably due to the reduced basicity of the pyridine nitrogen and therefore its ability to act as a hydrogen bond acceptor. With the exception of **9d,e** all the deschloro analogues behaved as agonists and none of these compounds showed improved receptor subtype selectivity.[47]



9a, X = H
b, X = F
c, X = Br
d, X = NH_2
e, X = $N(CH_3)_2$
f, X = CF_3SO_3
g, X = CH_3

10a, X = Cl
b, X = F
c, X = Br
d, X = I
e, X = NH_2
f, X = Ph
g, X = N_3

11

Fig. 1.50 Alterations to the chloropyridine ring of epibatidine.

A range of epibatidine analogues with an additional 5'-substituent (**10a-g**) have also been synthesised. These compounds have binding affinities for the α4β2 receptor very similar to that of epibatidine (even when a phenyl ring is attached).[27,48] suggesting that the nature of the substituent at this position is not important for binding. However, the bulk of the group at the 5'-position does affect the efficacy of the compound; **10f**, has much lower antinociceptive activity and functional potency than epibatidine and **10a-e,g**.[49] Indeed, when the chlorine of **10f** is replaced with H the resulting compound (**11**) shows only antagonistic properties at nAChRs.[50] Derivatives of **11** have been produced and progress has been made towards subtype-selective novel nicotinic antagonists.[51-54]

Bioisoteric heterocycles have been substituted into the structure of epibatidine with the aim of improving receptor subtype selectivity and elucidating structure activity

relationships.[27] Most notable among this class of epibatidine analogues is epiboxidine (**12a**), which contains a methylisoxazole moiety and was first synthesised by the Daly group in 1997. Epiboxidine has approximately ten-fold lower affinity and antinociceptive activity than epibatidine but has an improved activity/toxicity ratio.[55] The analogues containing an unsubstituted isoxazole (**12b**) and the 3-phenylisoxazole (**12c**) have also been studied; **12b** has a two-fold lower affinity than epiboxidine (**12a**), whilst the bulkier **12c** has a much lower affinity.[27] The 2-thiazolyl and 4-pyrazolyl analogues **12d** and **12e** also have very low affinities for nAChRs,[56] whilst the pyrimidine analogue (**12f**) shows high affinity for nAChRs ($K_i \sim 0.31$ nM *cf.* epibatidine 0.18 nM).[27]

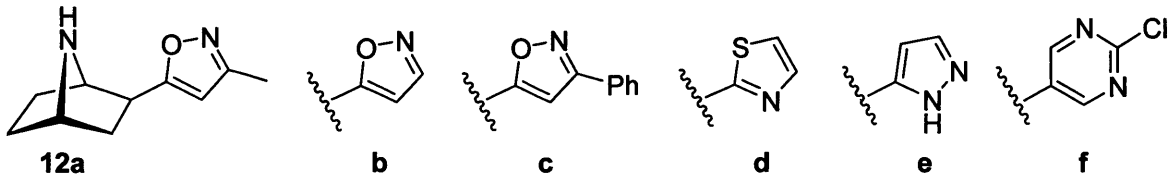


Fig. 1.51 Epibatidine analogues bearing bioisoteric heterocycles.

Some of the heterocyclic variants discussed here have been substituted into the structure of nicotine, replacing the pyridine ring, to give analogue molecules. For example, the methylisoxazole analogue of nicotine, ABT-418, was developed by Abbott laboratories as an antinociceptive agent.[57] In general, when alterations to the pyridyl ring of nicotine are made, the same trends described above for epibatidine are observed.[58]

1.5.2 The azabicyclo[2.2.1]heptane framework

Compounds have been made in which the bicyclo[2.2.1]heptane framework is retained but the positions of the nitrogen atom and heterocycle have been altered. *endo*-Epibatidine (**13**) has a relatively low affinity for nAChRs as might be expected due to the increased inter-nitrogen distance.[58] Analogues in which the heterocycle is attached to the bridgehead position of the 7-azabicyclo[2.2.1]heptane system, **14** and **15**, have been synthesised, and although these compounds have N-N distances close to that of epibatidine, both have low affinity and activity at neuronal nAChRs.[30,59]

Previous work at Leicester on 2-azabicyclo[2.2.1]heptanes led to the synthesis of the *endo*-5- and 6-chloropyridyl analogues of epibatidine **16** and **17** using a strategy based on Heck coupling reactions; both compounds have been shown to possess binding affinities and potencies very similar to epibatidine.[58,60] In contrast, the corresponding *exo*-5- and 6-analogues **18** and **19** have low affinities for nAChRs, again, a consequence of increased inter-nitrogen distance.[58,61,62]

The 1-azabicyclo[2.2.1]heptane system has also been investigated; **20** has been used as a tool for probing the nicotinic pharmacophore[28,32] and is receiving current interest as a potential α7 selective agonist.[63]

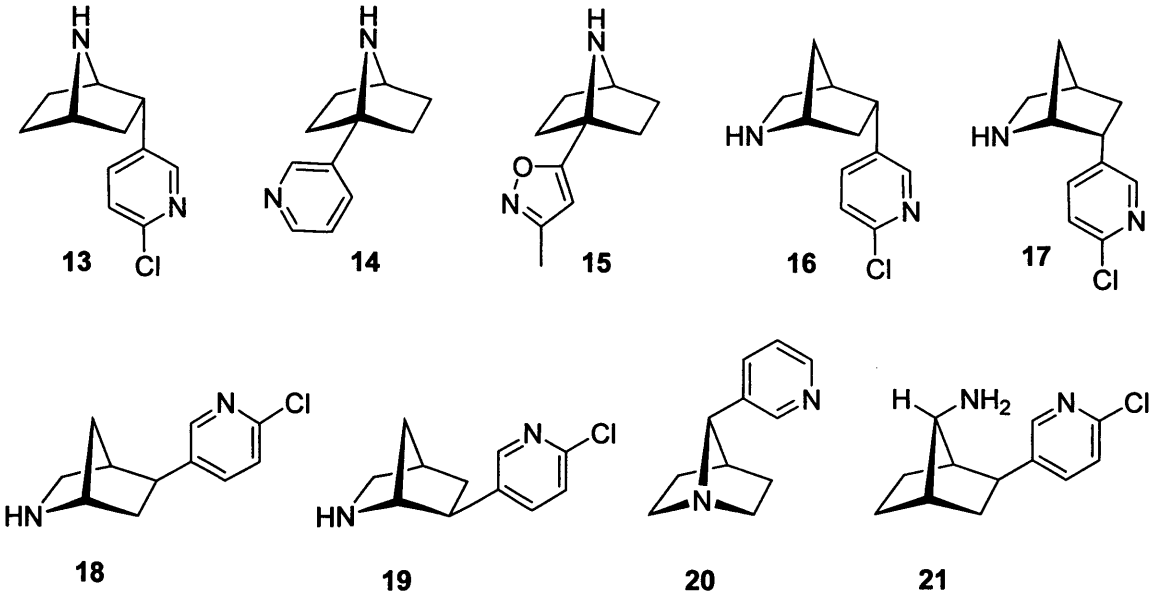


Fig. 1.52 Analogues based on the azabicyclo[2.2.1]heptane framework.

Carroll has recently investigated the possibility of positioning an amine group at C7 of the norbornane framework; **21** has similar properties to nicotine but ~10-fold lower receptor affinity. Hence, the location of the bicyclic nitrogen in epibatidine is of utmost importance. Attachment of a benzyl group to the amine functionality of **21** results in extremely low affinity.[64] However, *N*-substitution in epibatidine itself is tolerated to a limited extent in that *N*-methylation has little effect on nicotinic affinity and pharmacological properties.[27] In fact, *N*-methyl epibatidine has now been found on the skin of *Epipedobates tricolor*.[11] The introduction of larger *N*-substituents, even ethyl, causes marked reductions in nicotinic affinity.[27,65]

1.5.3 Higher analogues of epibaidine

Epibatidine analogues containing larger azabicyclic frameworks have also been synthesised. Homoepibatidine (**22**) and dihomoepibatidine (**23**) were first produced at Leicester and are based on the 8-azabicyclo[3.2.1]octane and 9-azabicyclo[4.2.1]nonane frameworks respectively. (-)-Homoepibatidine (**22**) binds with high affinity to nAChRs (rat brain membrane preparation) (K_i = 0.3 nM; *cf.* (-)-epibatidine K_i = 0.1 nM, (-)-nicotine K_i = 7.8 nM); the larger, less strained dihomoepibatidine (**23**) binds with lower affinity K_i = 2.85 nM.[66] The synthesis of homoepiboxidine (**24**) was published very recently and is the methylisoxazole equivalent of homoepibatidine (**22**). Homoepiboxidine has affinity for α4β2

receptors comparable with epiboxidine (**12a**) but has lower affinity for α3-containing receptors. Homoepiboxidine also has functional activity similar to epiboxidine yet is less active as an analgetic.[65]

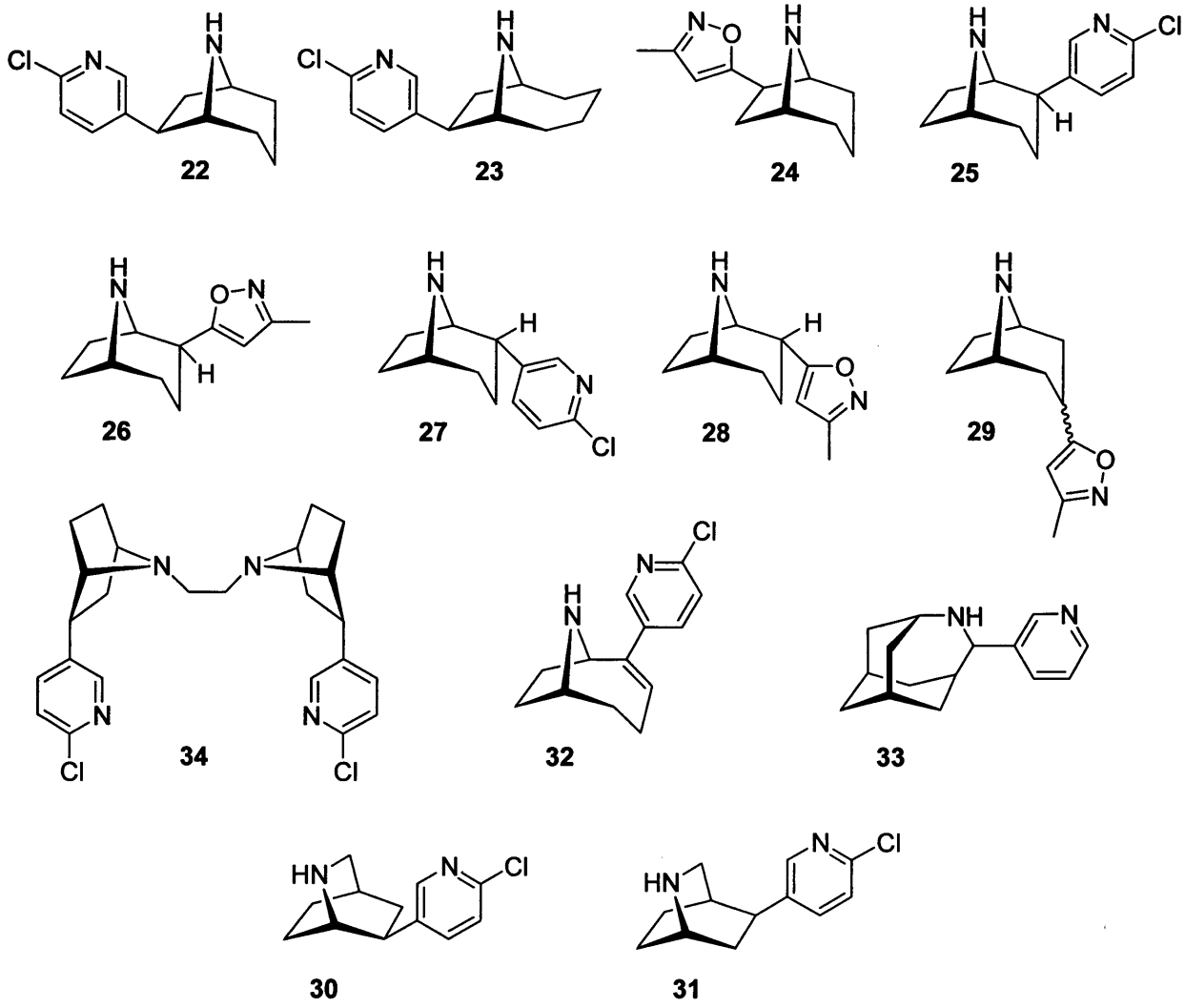


Fig. 1.53 Higher analogues of epibatidine.

Trudell and co-workers have produced a range of epibatidine analogues based on the 8-azabicyclo[3.2.1]octane framework but in which the heterocycle is attached to the propano[3] bridge rather than the ethano[2] bridge.[67-69] The 2-substituted compounds **25** and **26** have high, but reduced affinity for nAChRs in comparison to homoepibatidine (**22**) and homoepiboxidine (**24**). When the configuration at the 2-position is altered, as in **27** and **28**, or when the heterocycle is at the 3-position (**29**) very low affinities for nicotinic receptors are observed.[27,67-69] The 2-azabicyclo[2.2.2]octane system has also been investigated and compounds **30** and **31** have receptor affinities comparable to homoepibatidine (**22**). The vicinal analogue **30** is about one-quarter as potent as epibatidine as an analgesic; however, the distal analogue **31** has very low antinociceptive activity.[27,70]

Gallagher and co-workers produced UB-165 (**32**) a hybrid of epibatidine (**8**) and anatoxin A (**7**).[71] The nicotinic affinity of UB-165 is intermediate to those of the parent compounds and shows a similar lack of selectivity between α4β2, α3β4 and α7 receptor subtypes.[52] Work on UB-165 analogues continues to be published, particularly concerning alternative heterocycles and their effect on biological properties.[12,72]

Epibatidine analogues based on the bulky and unusual azahomoadamantane ring system have also been synthesised; **33** binds to α7 nAChRs with affinity comparable to that of nicotine. Unlike most of the analogues already considered, the *N*-methyl derivative of **33** shows extremely low affinity.[73] This may be due to the relatively close proximity of the two nitrogen centres; the methyl group is able to disrupt the interaction of the heterocycle with the receptor binding site.

The effect of linking two molecules of epibatidine by oligo-methylene chains of varying lengths has recently been reported. Compound **34** shows similar low nanomolar affinities to epibatidine at a range of nAChRs but, significantly, has low affinity and weak partial agonist properties at α3β4 receptors. This slight improvement in selectivity may result in decreased toxicity and bivalent ligands are believed to warrant further study.[74]

During the course of this Ph.D. study a patent was published which includes a large number of epibatidine homologues;[75] it will be considered in Chapter 6.

1.5.4 Smaller azabicyclic frameworks

Some epibatidine analogues are based on smaller, less sterically demanding and more strained azabicyclic frameworks such as the 2-azabicyclo[2.1.1]hexane (**35-36**), 2-azabicyclo[2.2.0]-hexane (**37-38**) and pyrrolizidine (**39-40**) frameworks. Piotrowski succeeded in positioning the chloropyridyl heterocycle at the 1-position of the 2-azabicyclo[2.1.1]hexane system (**35**)[76] and recent work at Leicester has also led to isoxazole incorporation at this position (**36**).[77] Disappointingly, **36**, and some chain extended variants of this molecule, have very low affinities for α4β2 and α3β4 receptors.[78]

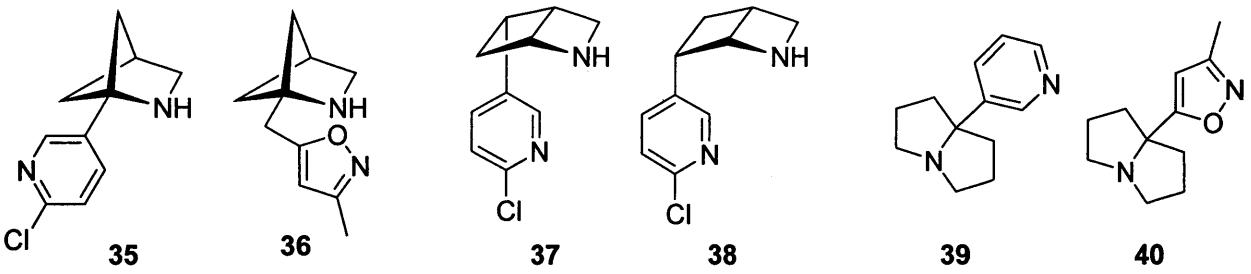
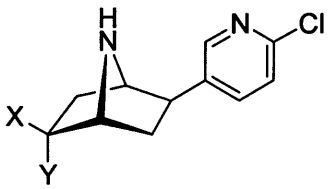


Fig. 1.54 Smaller azabicyclic epibatidine analogues.

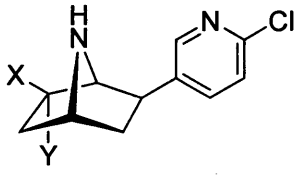
The Krow group has produced 2-azabicyclo[2.2.0]hexane-based epibatidine analogues (**37-38**). The *endo*-isomers **37** and **38** show moderately high affinity for nAChRs but do not demonstrate antinociceptive properties.[79] Various heterocycles have been attached to the 5-position of the pyrrolizidine (1-azabicyclo[3.3.0]octane) framework, **39-40**. These molecules are considered to be hybrids of the two enantiomers of nicotine and their symmetry means that the stereochemical issues associated with nicotine do not have to be considered. The pyrrolizidine analogues **39** and **40** retain high nAChR affinity and show marginally increased α4β2 affinity in comparison to the analogous pyrrolidine (nicotine analogue) compounds.[58]

1.5.5 Heteroatom incorporation

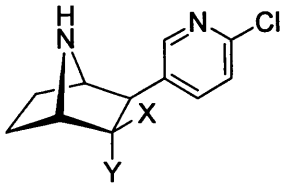
All the analogues of epibatidine considered so far retain an unfunctionalised azabicycle. Investigations into the effects of heteroatom incorporation into the bicyclic core have been undertaken in the hope that favourable interactions will form within the binding site of the receptor, resulting in improved nAChR subtype selectivity. Kozikowski has published the syntheses of hydroxylated analogues of epibatidine (**41-43**) and the carbonyl compounds **44a-b**.[80,81]



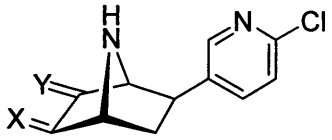
41a: X = OH, Y = H
41b: X = H, Y = OH



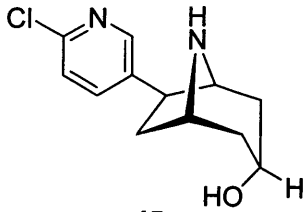
42a: X = OH, Y = H
42b: X = H, Y = OH



43a: X = OH, Y = H
43b: X = H, Y = OH



44a: X = O, Y = H_2
44b: X = H_2, Y = O



45

Fig. 1.55 Hydroxylated analogues of epibatidine.

These molecules were tested against a range of receptor subtypes; all had reduced affinity compared to epibatidine but moving the hydroxyl group around the molecule did have a profound effect on binding strength. The 3-*exo*-OH and 5-*endo*-OH compounds (**43a** and **41b**) had extremely low receptor affinities (low μM range) whilst the others had moderately high affinity (low nM range). Hence, the 3-*exo* and 5-*endo*-positions of epibatidine were least tolerant of the presence of an OH group. The carbonyl compounds **44a** and **44b** had very low

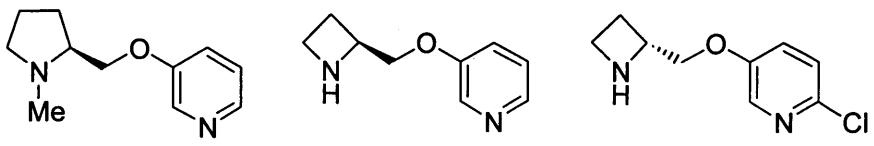
binding affinities. None of the epibatidine analogues **41-44** showed improved subtype selectivity.[81]

A hydroxylated analogue of homoepibatidine, **45**, has also been prepared; this compound has been pharmacologically evaluated and binds to nAChRs with affinity comparable to nicotine. Compound **45** showed no significant improvement in receptor selectivity.[82] Fluorine has also been introduced to the azabicycle of epibatidine and these analogues will be discussed in Chapter 5. It is not yet clear whether heteroatom incorporation is a valid strategy in the design of potent subtype-selective nicotinic agonists.

1.5.6 Epibatidine analogues with ether linkages

Epibatidine analogues containing a 3-pyridyl ether moiety and lacking a bicycle are structurally distinct from the compounds already discussed. Certain compounds of this class, such as **46-48** (Fig. 1.56), have very high affinity for nAChRs (A-84543 (**46**) K_i = 0.15 nM; A-85380 (**47**) K_i = 0.05 nM; ABT-594 (**48**) K_i = 0.04 nM).[83,84] Additionally, these compounds show higher selectivity for α4β2 receptors than, but are not as potent as, epibatidine.[58] ABT-594, also known as Tebanicline (**48**), is the most famous amongst these compounds; Abbott (the pharmaceutical company) chose this compound for development on the basis of screens for analgesic properties.[83] The improved separation of antinociceptive effects and nicotinic side-effects[4] allowed **48** to enter phase II clinical trials as a broad-scope analgesic in the late 1990s. However, ABT-594 has been shown to have analgesic and toxic effects resembling those of epibatidine and nicotine[85] and it is now known that clinical trials were ceased due to gastrointestinal side-effects.[86] Abbott are developing second-generation derivatives of ABT-594 the structures of which are not in the public domain.

The discovery of this new structural class of nicotinic ligand has led to synthetic endeavours towards novel ether-containing molecules in the hope of finding compounds with high nicotinic affinity and improved receptor sub-type selectivity. Developments in this area are discussed in Chapter 4.



A-84543 (46) **A-85380 (47)** **ABT-594 (48)**

Fig. 1.56 3-Pyridyl ether analogues.

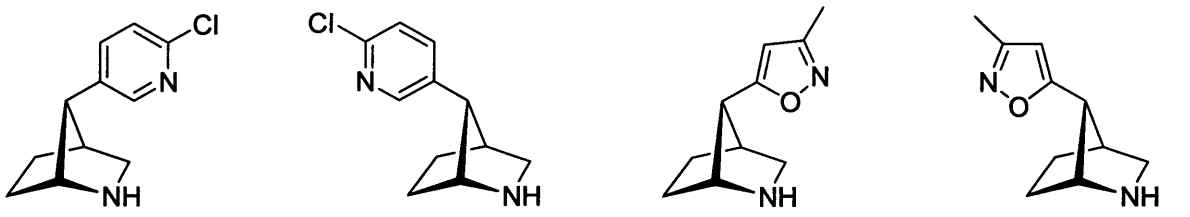
This review of epibatidine analogues is not exhaustive but gives an indication of the structural features that can be manipulated, and how these changes affect pharmacological properties. The race to produce therapeutic compounds that act at neuronal nAChRs is intensifying and there is increasing desire to elucidate the structure and function of nAChR subtypes. Hence, syntheses of novel epibatidine analogues continue to be published.

1.6 7-Substituted 2-azabicyclo[2.2.1]heptanes

The major aim of this study was to synthesise epibatidine analogues based on the 2-azanorbornane framework with a heterocycle attached to the methano-bridge (7-position). Interest in the chloropyridyl and methylisoxazole heterocycles remains particularly high; a large proportion of recently published analogues contain them (see Section 1.5). Hence, compounds **49-52** (Fig. 1.60) were particularly attractive targets; they are isomers of epibatidine (**8**) and epiboxidine (**12a**), in which the positions of the bicyclic nitrogen atom and the heterocycle have been switched. This has implications in terms of inter-nitrogen distances which will be very similar to that of epibatidine. Indeed, molecular modelling indicated that the *syn* derivatives **49** and **51** have low energy conformations with inter-nitrogen distances of 4.5 and 4.4 Å respectively (epibatidine: 4.5 Å).[a] It was hoped, therefore, that **49** and **51** would show high affinity for nicotinic receptors; the *anti* compounds **50** and **52** have larger N-N distances (5.9 and 5.6 Å respectively) and were not expected to have such high affinity. Inter-nitrogen distances were used throughout this study to predict and rationalise the observed nicotinic receptor affinities. This approach is reasonable for the derivatives discussed in this thesis as they have structures similar to that of epibatidine and the recent epibatidine-bound AChBP crystal structure confirms the active conformation of epibatidine. However, there are limitations to the inter-nitrogen distance approach; not all nicotinic ligands fit the hypothesis and for molecules which are more structurally distinct from epibatidine the approach is less valid.

Regardless of how tightly **49-52** bind to nicotinic receptors, 7-heterocycle-substituted 2-azabicyclo[2.2.1]heptanes represent a novel class of epibatidine analogue. Their synthesis will serve to further the series of 2-azabicyclo[2.2.1]heptane analogues discussed in section 1.5.2 and comparisons of the pharmacological properties of **49-52** with those of existing molecules will contribute to our understanding of the nicotinic pharmacophore.

[a] See Chapter 8 for details regarding molecular modelling techniques.



***syn*-isoepibatidine (49)** ***anti*-isoepibatidine (50)** ***syn*-isoepiboxidine (51)** ***anti*-isoepiboxidine (52)**

Fig. 1.60 7-Heterocycle 2-azabicyclo[2.2.1]heptanes; a 7-heterocycle 7-azabicyclo[2.2.1]heptane.

The chemistry of 2-azanorbornanes has been the subject of much research[87] and continues to draw attention. 2-Azanorbornanes have been used as a rigid molecular scaffold for the construction of other biologically active molecules; for example, as conformationally restricted proline and glutamic acid analogues.[88,89] The introduction of substituents to the 7-position of 2-azabicyclo[2.2.1]heptanes is not straightforward and has received little attention. Hodgson has developed a radical rearrangement of 7-azanorbornadienes to 2-azanorbornenes, which has led to the synthesis of a limited number of 7-substituted 2-azanorbornenes.[90-95] The radical addition of thiols to **53** was found to give rearranged 7-substituted 2-azanorbornene products (**54**) exclusively via the mechanism shown in Fig. 1.61.[90,92] During the course of this Ph.D. study (2005) the analogous addition of alkyl radicals to a derivative of **53** was also reported to give rearrangement thus leading to 7-alkyl 2-azanorbornenes.[93,95]

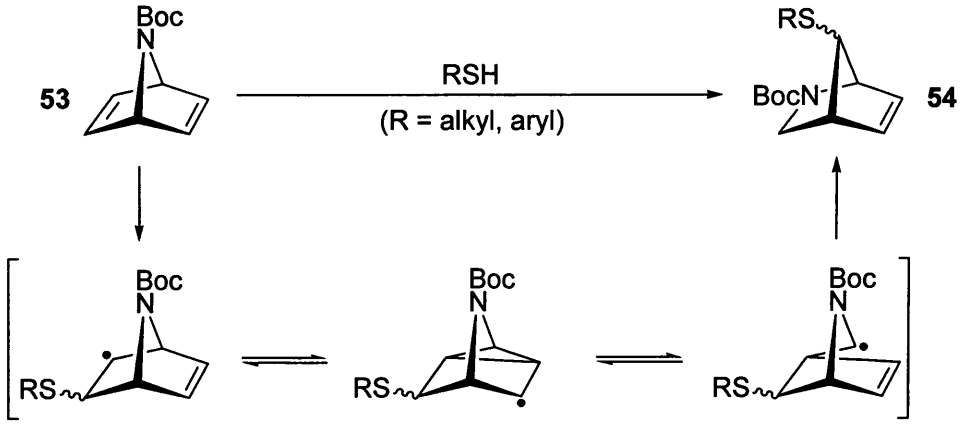


Fig. 1.61 The radical rearrangement of 2-azanorbornanes.[90,93]

Hodgson and co-workers have applied the radical rearrangement of 7-azanorbornanes to an alternative synthesis of the highly potent epibatidine isomer **17** (Fig. 1.52).[91] More recently, progress towards the epibatidine analogue targets of this study (e.g. **49**) was alluded to. Thus, the epoxide **55** was treated with 4-$MeOC_6H_4MgBr$ and subsequent desulfonylation gave **56**. Preparation of the corresponding xanthate, followed by radical-catalysed deoxygenation and concomitant rearrangement then gave the *syn*-7-substituted 2-azanorbornane product **57**.

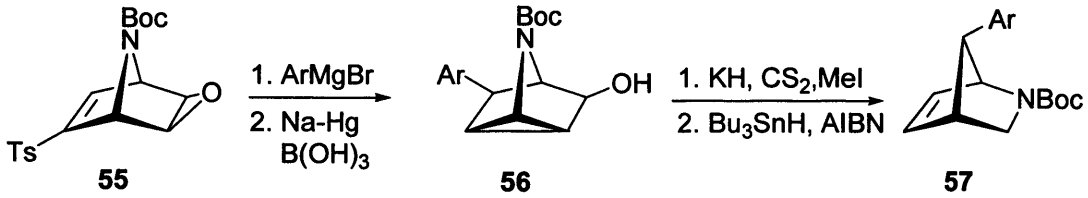


Fig. 1.62 A radical-rearrangement route to *syn*-7-aryl-2-azanorbornanes; Ar = 4-$MeOC_4H_6MgBr$.[94]

We wished to devise practical methods to functionalise the 7-position of 2-azanorbornanes and to introduce heterocycles. Manipulation of the C7 stereochemistry was of utmost importance, since the *syn*- compounds **49** and **51** were expected to have nicotinic activity whilst the corresponding *anti*- compounds **50** and **52** were not. The synthetic route envisaged is outlined below.

1.6.1 The proposed route to 7-substituted 2-azabicyclo[2.2.1]heptanes

Bromination of 2-azabicyclo[2.2.1]hept-5-ene derivatives (e.g. **58**) is known to bring about skeletal rearrangement to give rearranged products (e.g. **59**; Fig. 1.63). Thus, neighbouring group participation (NGP) by the bicyclic nitrogen results in the opening of the bromonium intermediate (**60**) to give **61**; attack of the bromide counter-ion on **61** yields **59** (Fig. 1.60).[96] Recent publications by Sosonyuk and co-workers have demonstrated that in certain cases, when R is alkyl, the tricyclic salts (**61**) are favoured in the equilibrium between **61** and **59**. These salts are stable and can be isolated.[97,98]

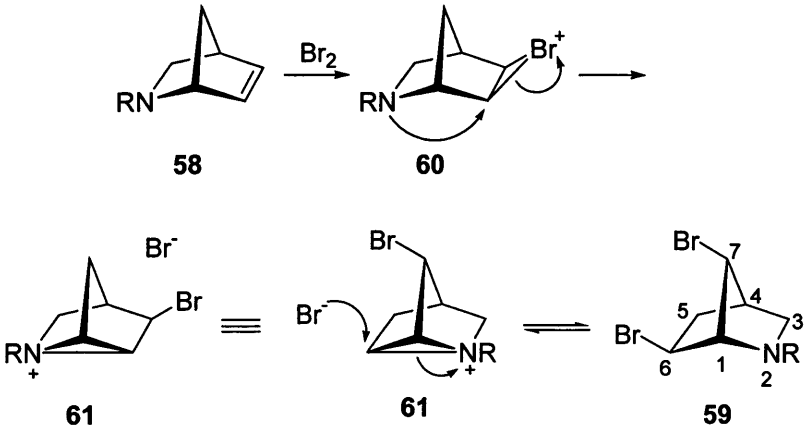
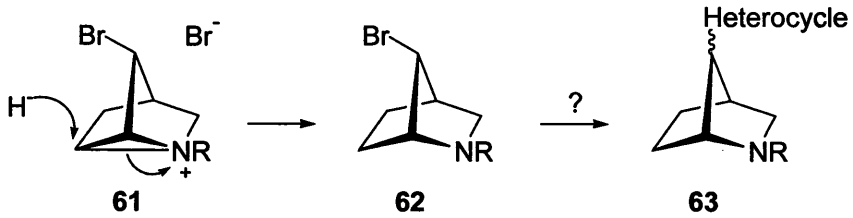


Fig. 1.63 Bromination of 2-azabicyclo[2.2.1]hept-5-ene derivatives.

As the equilibrium between **61** and **59** suggests, the aziridinium ring of **61** can be opened by nucleophiles including alcohols and amines.[99] Subsequent removal of the 7-bromine allowed a range of 6-substituted 2-azabicyclo[2.2.1]heptanes to be accessed.[100] In order to produce 7-substituted systems the opposite must be achieved: the aziridinium

functionality should be removed leaving the 7-bromine in place. To this end, attempts will be made to treat azaniotricyclic salts (**61**) with hydride to give **62** (Fig. 1.64).

With the 7-bromo-2-azabicyclo[2.2.1]heptane compound **62** in hand, functional group interconversions will be undertaken. However, substitution reactions at the 7-position of norbornanes are unfavourable[101,102] and may prove to be equally problematic in azanorbornanes.



61 **62** **63**

Fig. 1.64 The proposed route to 7-substituted 2-azabicyclo[2.2.1]heptanes.

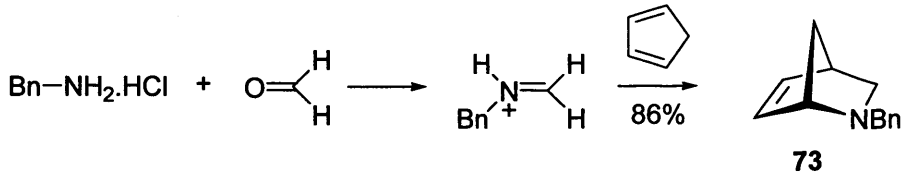
Heterocycles will be assembled at the 7-position or introduced using cross-coupling reactions (**62** to **63**). The stereochemistry at the 7-position must be manipulated so that the both the *syn*-7- and *anti*-7- series of derivatives can be accessed. Results in these areas are discussed in Chapters 2 and 3. Chapter 4 concerns the synthesis of epibatidine analogues containing ether-linkages, Chapter 5 describes research into the incorporation of fluorine into the 2-azanorbornane skeleton and studies into the synthesis of isotropane-based analogues of epibatidine are discussed in Chapter 6.

Chapter 2

Functionalisation of the 7-position of 2-azanorbornanes and approaches to isoepiboxidine

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

The 2-azanorbornane system was used extensively in these studies and the key precursor, **73**, was formed through a well-known aqueous aza Diels-Alder reaction (Fig. 2.10). Under Mannich conditions, benzylamine hydrochloride and formaldehyde react *in situ* to give an iminum salt which undergoes a 4π + 2π cycloaddition with cyclopentadiene to give 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene (**73**).[103,104]



73

Fig. 2.10 Aza Diels-Alder reaction to form 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene (**73**).

The product of the cycloaddition, **73**, is conveniently *N*-benzyl protected; conversion to an alternate *N*-protecting group by hydrogenation followed by re-protection will be shown to be straightforward. The benzyl protecting group preserves the basicity of the nitrogen atom, which is well placed to anchimerically assist reactions in the ring system, an important feature in the context of this thesis. It is also notable that, unlike some other *N*-protecting groups, an alkyl group such as benzyl allows nitrogen inversion. Nitrogen inversion is rapid in **73** and is therefore not generally a concern, although it can result in reactions giving a mixture of isomers.[105] The double bond in **73** will enable functionalisation and subsequent heterocycle incorporation.

The yield of **73** was 86%, ^{1}H NMR analysis and comparison to literature data[104] indicated that no further purification was required.

This reaction is not enantioselective but this is not a concern as a racemic mixture of an epibatidine analogue could be resolved at a suitable later stage if desired or required. Additionally, the two enantiomers of epibatidine itself have similar biological properties and therefore racemic mixtures were targeted.[22] The discussion in the remainder of this thesis concerns racemic mixtures of compounds.

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

As previously described, bromination of 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene (**73**) occurs with rearrangement (see Section 1.6.1). The benzyl protecting-group maintains the nucleophilicity of the nitrogen atom allowing it to form the aziridinium salt **74** which can be attacked by the bromide counter-ion to establish the equilibrium between **74** and **75** (Fig. 2.20). A two-step bromination procedure of **73** has been developed recently by Sosonyuk *et*

al.. This gives quantitative yields, improving on the previously described methodology reported by Pombo-Villar *et al.* whose procedure involved adding the alkene **73** drop-wise to a solution of bromine and gave a yield of 82%.[106]

Treatment of the alkene **73** with two equivalents of bromine gives a tricyclic salt with a tribromide counter-ion (**76**); addition of a second equivalent of the alkene **73** essentially converts the counter-ion to monobromide.[97,98] It is not clear why this procedure gives improved yields but it is likely to be solvent-related as the first step is carried out in DCM and the second in acetonitrile. Previously published bromination methods gave poorer yields, principally due to the formation of side-products.[106]

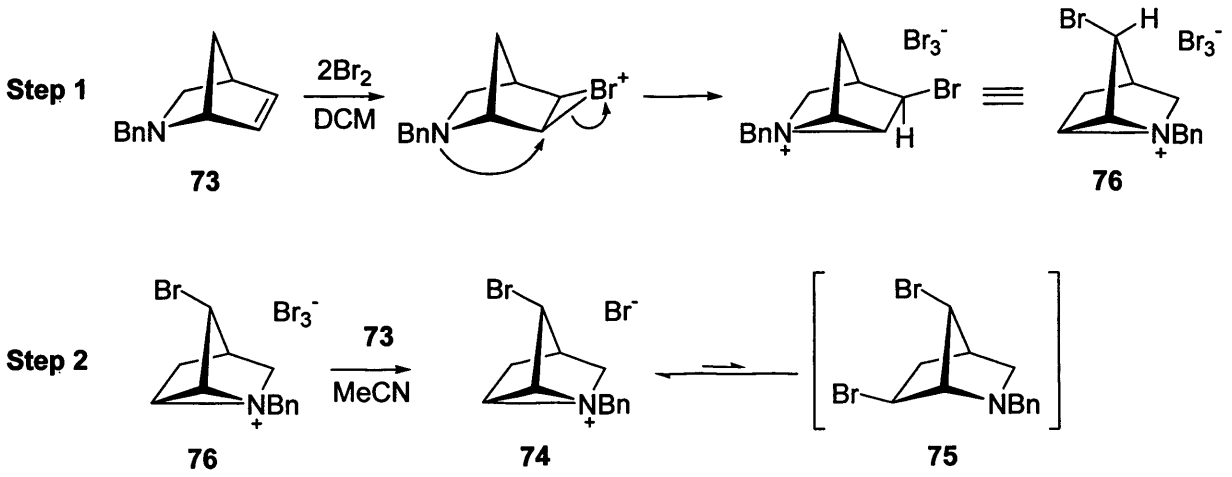


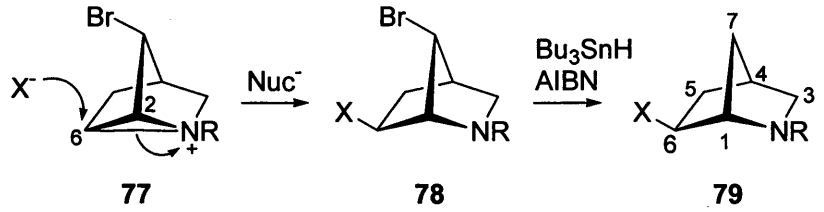
Fig. 2.20 The two-step bromination of 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene (**73**).[97,98]

The quantitative yields reported by Sosonyuk *et al.* were found to be reproducible. However, there was no evidence that the tricyclic product **74** was in equilibrium with the bicycle **75**. There was little difference in the ^{1}H NMR spectra of compounds **74** and **76**, indicating that any equilibrium between **74** and **75** is overwhelmingly in favour of **74**. Both tricyclic compounds **74** and **76** were found to be stable; ^{1}H NMR indicated no degradation after storage at ~5 °C for three months. This is contrary to the observations of Sosonyuk *et al.* who suggest that the nitrogen atom of **74** is able to eliminate HBr from **74** causing degradation via an unstable olefinic intermediate.[97,98]

2.3 Nucleophilic ring-opening of aziridinium salts

The equilibrium of **74** and **75** (Fig. 2.20) involves attack of the bromide counter-ion on the three-membered ring. Although the bicyclic tautomer (**75**) was not observable, this equilibrium has been studied in related systems and demonstrates the potential of the aziridinium functionality to be opened by nucleophiles. Bulanov *et al.* have reported that

nucleophilic attack is at the 6-position rather than the 2-position, probably due to the closer proximity of the bulky bromine atom to the 2-position.[97,98] A recent publication indicates that a variety of O, N, S and C nucleophiles can intercept the tricycle **77**, to give 6-substituted 7-bromo-2-azabicyclo[2.2.1]heptanes (e.g. **78**). Radical-mediated removal of the 7-bromine atom provides a route to 6-substituted 2-azabicyclo[2.2.1]heptanes (**79**).[100]



77 **78** **79**

Fig. 2.30 Nucleophilic ring opening of the aziridinium ring in 1-alkyl-1-azoniatricyclo[2.2.1.$0^{2,6}$]heptanes.[100]

In order to access 7-substituted 2-azabicyclo[2.2.1]heptanes attempts were made to open the aziridinium ring of **74** using hydride (Fig. 2.31). The use of sodium borohydride in methanol resulted in solvolysis rather than hydride addition; methanol opened the aziridinium ring to give **80** as the only isolable product (17% yield). A switch of solvent to diethyl ether with only a catalytic amount of methanol gave no discernable reaction.

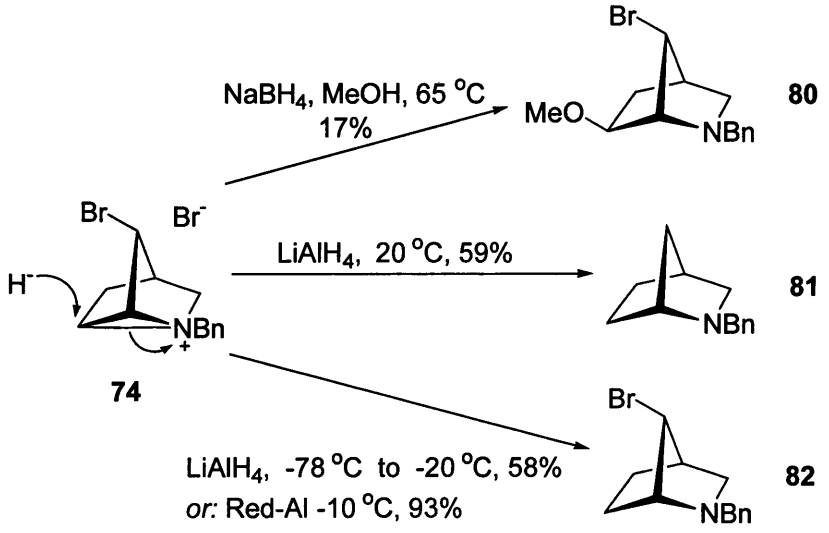


Fig. 2.31 Reaction of hydride with 1-benzyl-1-azoniatricyclo[2.2.1.$0^{2,6}$]heptane.

As $NaBH_4$ did not give the desired product, $LiAlH_4$ was used as the hydride source. At room temperature $LiAlH_4$ gave the defunctionalised compound, **81** (59%) in which the aziridinium ring had been opened but the 7-bromine substituent had also been removed. This compound (**81**) had been made at Leicester previously and confirmation of its formation was

by comparison to earlier spectra.[107] The conditions were changed: the reaction of **74** with $LiAlH_4$ was started at –78 °C and allowed to warm to –20 °C over one hour. The reaction was quenched at -20 °C and this resulted in ring opening with retention of the bromine atom at the 7- position (**82**)(58% yield). A recent patent indicated that hydride addition can also be achieved using Red-Al;[108] following this procedure gave **82** in an improved 93% yield. For more detailed discussion of this patent see Chapter 4.

2-Benzyl-2-azabicyclo[2.2.1]hept-5-ene (**73**) is observed as a side-product in the reaction of **74** with $LiAlH_4$ or Red-Al, typically in ~10% yield by ^1H NMR. A possible explanation of the formation of **73** is shown in Fig. 2.32. This involves hydride attack at the 2-position of the tricycle **74** to give the *exo*-5-bromo compound **83**; Bulanov *et al.* have reported that nucleophilic attack is only at the 6- position. Elimination of HBr from **83** would result in the formation of the alkene **73**.

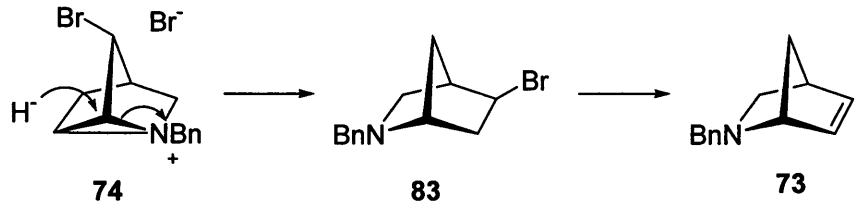
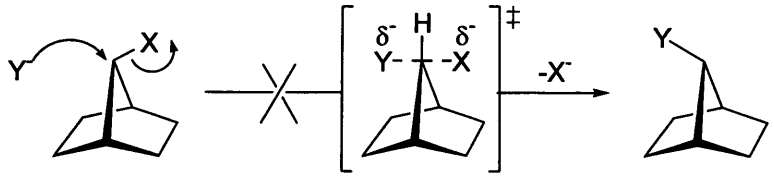


Fig. 2.32 Possible mechanism of side-product (**73**) formation.

In conclusion, through the two-step bromination of a 2-benzyl-2-azabicyclo[2.2.1]heptane and opening of the resulting aziridinium salt with hydride, the 7-position of the 2-azabicyclo[2.2.1]heptane ring system was selectively functionalised in good overall yield.

2.4 Substitution at the 7-position of 2-azabicyclo[2.2.1]heptanes

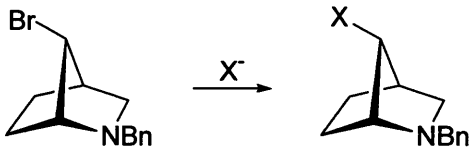
With the *anti*-7-bromo compound **82** in hand, nucleophilic substitution at the 7-position of 2-azanorbornanes could now be investigated. Substitution reactions at the 7-position of bicyclo[2.2.1]heptanes (norbornanes) are disfavoured due to angle constraints and steric factors.[101,102] The transition states for both S_N1 and S_N2 reactions ideally have 120° bond angles but the rigid bicycle in **84** prevents this bond angle being achieved at the 7-position (C_1-C_7-C_4 = 93°) (Fig. 2.40). In addition, the approach of the nucleophile is hindered by the *exo*-2- and *exo*-3-protons. The reactivity of the 7- position of norbornanes can be increased by the presence of carbonyl groups at the 2- and 3- positions, apparently due to electric field effects.[102,109]



84

Fig. 2.40 The 7- position of norbornanes (e.g. **84**) is unreactive towards nucleophiles X = leaving group, Y = nucleophile.

The 7-position of 2-azabicyclo[2.2.1]heptanes (azanorbornanes) was expected to be similarly unreactive towards nucleophiles in this study but *anti*-7-bromo-2-benzyl-2-azabicyclo[2.2.1]-heptane (**82**) was found to participate in substitution reactions (Fig. 2.41). A range of nucleophiles were successfully introduced to **82** but relatively harsh conditions were required (100 °C, 24 h, DMF). Similar conditions have been used in the electric-field-facilitated substitution reactions of 1,2-diketo-7-bromo-norbornanes.[102,109]



82	LiCl	**85**	X = Cl	77%
	LiOH	**86**	X = OH	56%
	KCN	**87**	X = CN	66%
	Imidazole/BuLi	**88**	X = Imidazole	53%

Fig 2.41 Nucleophilic substitution reactions of **82** occur with retention of configuration.

The use of Cl^-, HO^-, NC^- and the imidazoyl anion as nucleophiles gave the compounds **85**, **86**, **87** and **88** respectively; the introduction of a cyano- group was particularly satisfying as heterocycles can be built up from it. The removal of the bromine atom to give **81** (Fig. 2.31) by hydride ion is also an example of nucleophilic substitution at the 7-position.

As indicated in Fig. 2.41, the *anti*-stereochemistry at the 7-position was maintained in the products of the nucleophilic substitution reactions, this was verified by COSY and NOESY NMR experiments (Section 2.4.1). None of the corresponding *syn*- compounds were observed.

2.4.1 Determination of C7 stereochemistry in substitution products

Detailed NMR studies confirmed the *anti*-7-stereochemistry in all of the substitution products **85-88**. Discussion of the 2D NMR analysis of the alcohol **86** follows, in order to demonstrate how the 7- position configuration was determined in **85-88**.

Signals in the ^{1}H NMR spectrum of **86** could be assigned unambiguously; COSY and NOESY experiments were performed in order to glean further information regarding the spatial relationships of protons. The 2D NOESY spectrum of **86** is shown in Fig. 2.42.

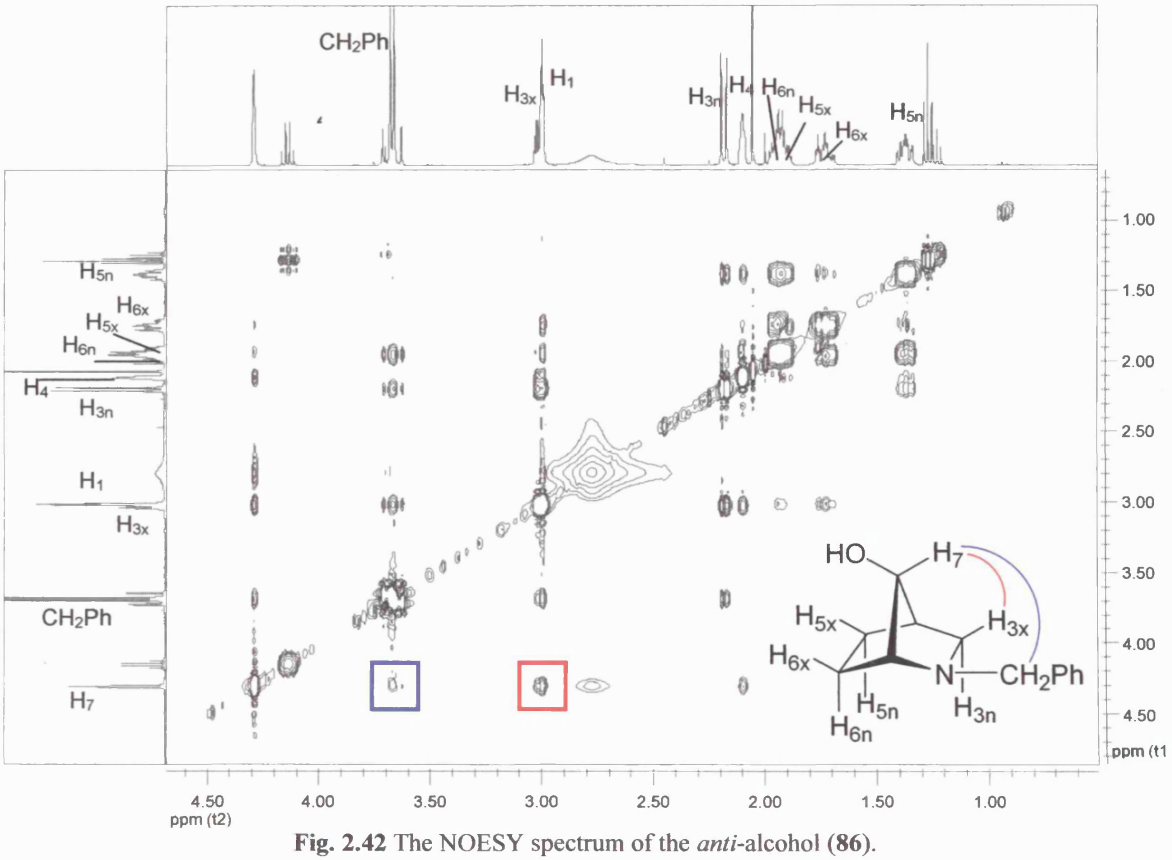


Fig. 2.42 The NOESY spectrum of the *anti*-alcohol (**86**).

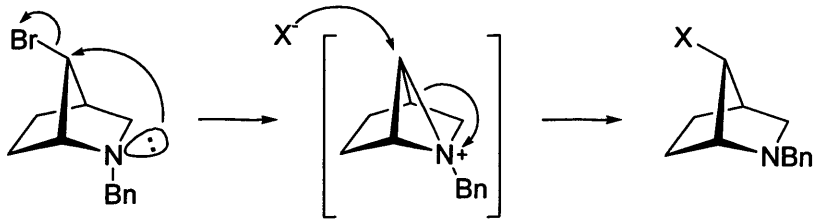
The NOESY spectrum of the alcohol **86** showed cross-peaks between H_7 and H_3(*exo*) (red) and also to the methylene protons of the inverting benzyl group (blue). ^{1}H-^{1}H COSY analysis of **86** showed 'W' couplings (~1Hz) between H_7 and the *endo*- protons in positions 5- and 6-. This spectroscopic information is compatible only with the hydroxyl group being *anti*- to the bicyclic nitrogen atom.

Similar, detailed 2D NMR analysis of compounds **85**, **87** and **88** indicated that all the substitution reactions studied occur with complete retention of stereochemistry.

2.4.2 Neighbouring group participation in 2-azabicyclo[2.2.1]heptanes

The unexpected substitution at the 7- position of **82** and the retention of configuration are consistent with neighbouring group participation (NGP) by the bicyclic nitrogen atom (Fig. 2.43). Anchimeric assistance by the nitrogen lone pair aids the loss of bromide from the 7-position and results in the formation of the non-classical cation **89**; nucleophilic attack on this

intermediate must be *anti* to the nitrogen atom. Essentially, a double inversion of configuration at C7 gives the substituted product **90** with retention of stereochemistry.



82 **89** **90**

Fig. 2.43 Neighbouring group participation in **82** gives retention of configuration.

A recent patent describes an alternative procedure (1-methyl-2-pyrrolidinone/water rather than LiOH) for the synthesis of the hydroxyl compound **86** from **82**, but claims the *syn*-7-configuration for the product; no spectroscopic data were given.[108] In our hands this alternative procedure gave only *anti*-**86**; the spectra of the product were identical to those for **86** synthesised using LiOH. For a more detailed discussion of this patent see Chapter 4. The use of 1-methyl-2-pyrrolidinone/water as an efficient source of nucleophilic oxygen was first reported by Hutchins and Taffer in 1982.[110]

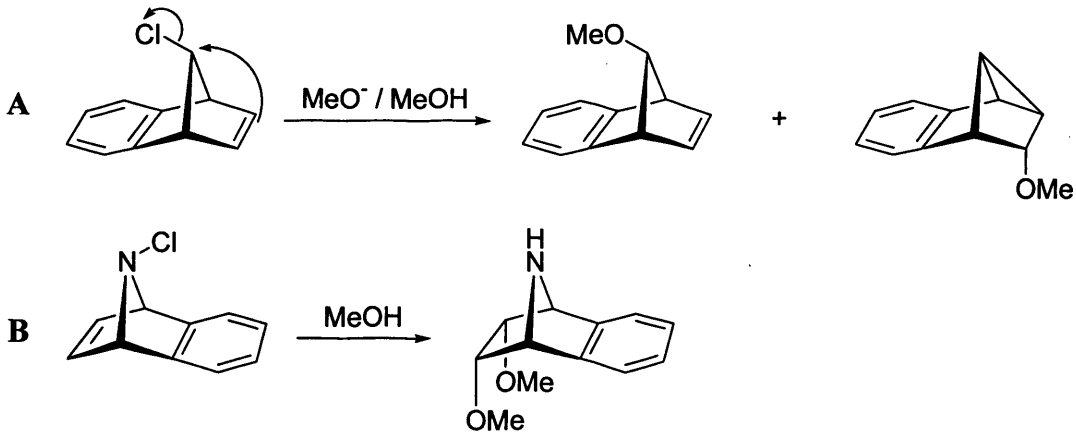


Fig. 2.44 Neighbouring group participation in norbornanes and 7-azanorbornanes.[111,114]

The participation of 2-position electrons in reactions at the 7-position of bicyclo[2.2.1]heptanes is not without precedent. Reactions of norbornanes and azanorbornanes involving NGP are well documented; these bicyclic systems often exhibit unusual chemistry, for example, simple substitution reactions can be disfavoured due to the need to pass through highly strained transition states (see Fig. 2.40). Norbornenes in particular have been used for many years as tools for probing reaction mechanisms as their rigid

framework has allowed fundamental questions regarding reactivity and stereochemistry to be tackled. For example, participation by π bonds in norbornenes facilitates the loss of a 7-position substituent giving rise to unexpected solvolysis products (Fig. 2.44A).[111-113] Similar π-participation is observed in the loss of chloride from the 7-position of 7-azabicyclo[2.2.1]heptane derivatives. Here nitrogen inversion becomes an important factor, the product shown in Fig. 2.44B can only form when the *N*-Cl is *anti-* to the participating π bond (as shown).[114]

In 2-azabicyclo[2.2.1]heptanes the nitrogen lone pair is able to overlap with areas of developing positive charge, as described in Section 2.2; in this example the nitrogen lone pair opens a bromonium ion causing skeletal rearrangement.[98] Similar opening of 5-/6-position epoxides in the 2-azabicyclo[2.2.1]heptane system has also been studied.[115]

Participation of the bicyclic-nitrogen lone-pair in reactions at the 7-position of 2-azanorbornanes is a novel observation. It clearly adds to the body of work in the literature regarding NGP in norbornanes and azanorbornanes and increases understanding of NGP and rearrangements in 2-azanorbornanes.

To summarise, the presence of the nitrogen atom in the bicycle facilitates substitution at the 7-position. However, the associated retention of stereochemistry may cause difficulties in synthesising compounds with a heterocycle *syn-* to the nitrogen atom, that is, epibatidine analogues with appropriate inter-nitrogen distances.

2.5 Epimerisation at the 7-position of 2-azabicyclo[2.2.1]heptanes

It was postulated in Section 1.6 that for a 7-heterocycle-substituted 2-azabicyclo-[2.2.1]heptane to have nicotinic activity the heterocycle must be *syn-* to the bicyclic nitrogen, due to the inter-nitrogen distance requirements of the nicotinic pharmacophore. Substitution reactions at the 7-position of azanorbornanes were shown to occur with complete retention of configuration, giving only the *anti*-7- products **85-88**. There was clearly a need to epimerise in order to access the potentially active *syn*-7-compounds.

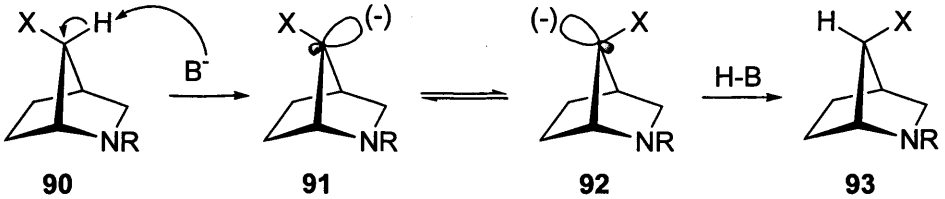


Fig. 2.50 Base-induced epimerisation of 7-substituted 2-azanorbornanes, B^- = base.

A 7-position substituent capable of stabilising a negative charge α to it will lower the pK_a of the 7-position proton. Treatment with an appropriate base would give the anion **91** which has the potential to invert (**91** to **92**); protonation would yield the epimerised *syn*-product **93**. 7-Norbonyl anions have been produced and studied,[116,117] and inversion of the 7-position carbanion of 2-azanorbornanes is analogous to nitrogen inversion in 7-azanorbornanes, a well documented process.[114]

Some total syntheses of epibatidine involve an epimerisation step, for example, Fletcher *et al.* obtained a mixture of the *endo*- and *exo*- epimers **94** and **95** (Fig. 2.51). Treatment of **94** with potassium *tert*-butoxide at 100 °C for 30 hours gave a mixture containing 50% **95**; the anion formed during this reaction is stabilised by resonance into the pyridyl system.[15] Epimerisation at the 7-position of norbornanes involves inversion at the more strained one-atom bridge but is precedented; Buske and Ford demonstrated that epimerisation at the 7-position of the ester **96** is possible. Compound **96** was treated with sodium methoxide in methanol and HMPA and the equilibrium between **96** and **97** was achieved after 165 hours at 65°C (K_{eq} = **96/97** = 0.73).[118]

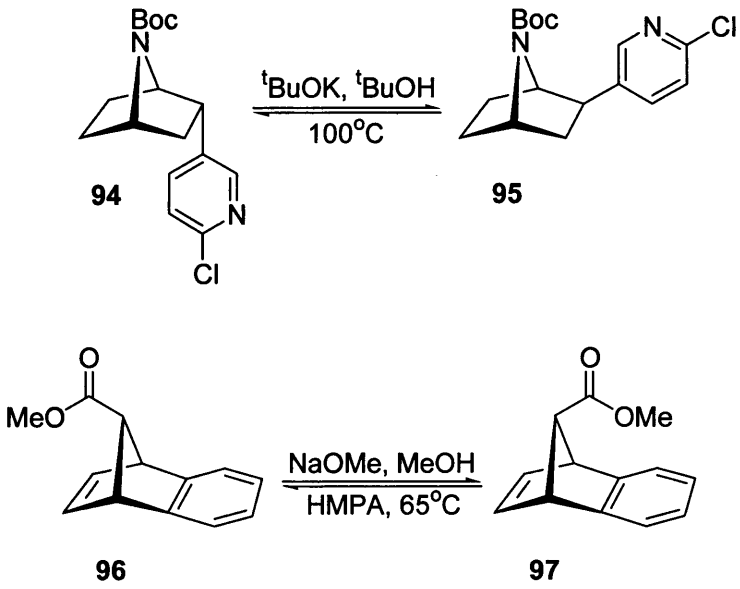
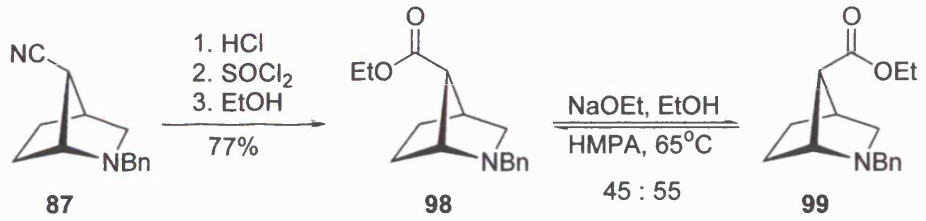


Fig. 2.51 Literature examples of epimerisation.[15,118]

In our studies, the cyano compound **87** was hydrolysed and the resulting acid converted to the ester **98** in 77% overall yield (Fig. 2.52). The *anti*-ester (**98**) was subjected to conditions similar to those described by Buske and Ford, *i.e.* sodium ethoxide in ethanol and HMPA at reflux. The use of ethoxide was necessitated by the ethyl ester; the products of ester exchange reactions would be observed in the presence of alternative alkoxide bases.

Equilibrium between the two esters **98/99** (45:55) was achieved within 24 hours, as determined by gas chromatography. The epimers were separable by column chromatography (87% total isolated yield) and detailed NMR analysis established the *syn*-ester (**99**) as the major isomer. Fig. 2.52 shows the 2D NOESY spectrum of the major (*syn*-) epimer **99**. The cross peak between the *anti*-7-position proton and H_{5exo} and H_{6exo} is indicated; there is no interaction between H_7 and H_{3x}. These data confirm that the ester group is *syn*- to the bicyclic nitrogen; hence NOESY experiments allow clear determination of C7 stereochemistries.



87 98 99

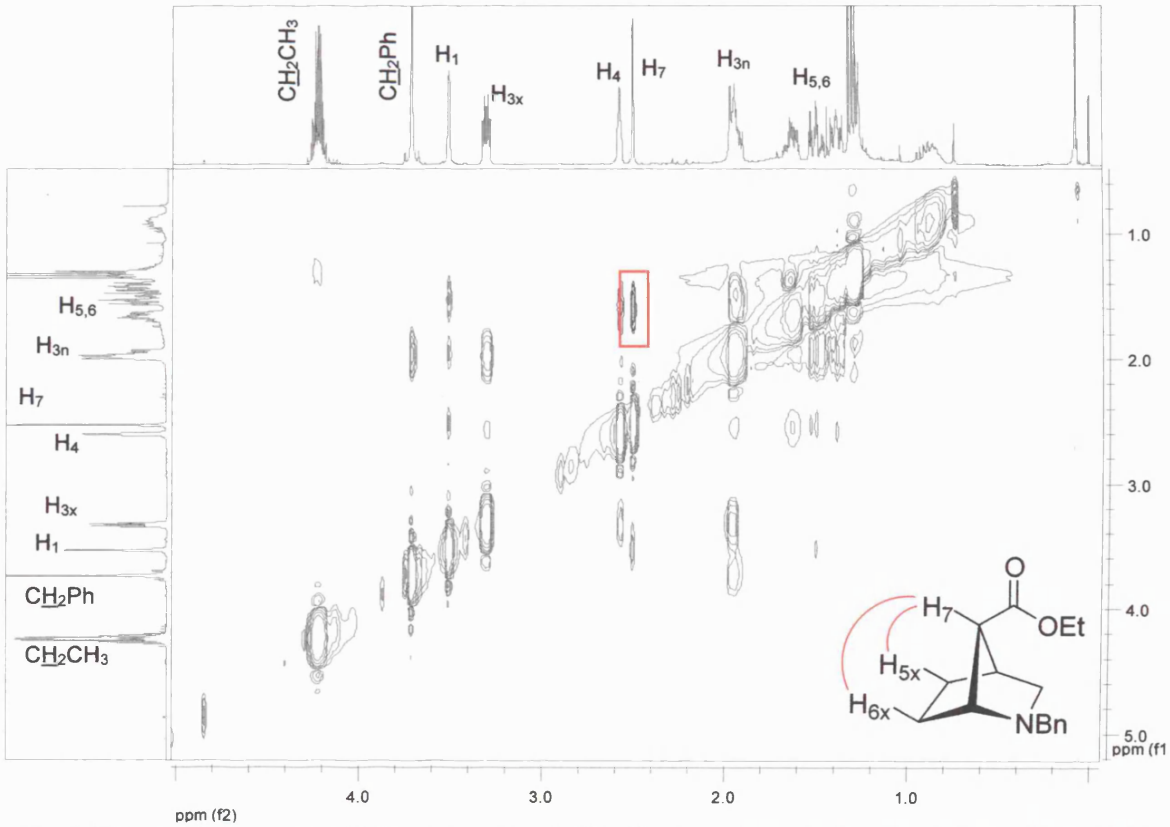


Fig. 2.52 Epimerisation of *anti*-2-benzyl-2-azabicyclo[2.2.1]heptane-7-carboxylic acid ethyl ester (**98**) and the NOESY spectrum of **99**.

Following the successful conversion of **98** to **99** and subsequent analogous interconversions of 7-heterocycle-substituted 2-azanorbornanes (see Section 3.3) the mechanism of epimerisation (Fig. 2.50) was re-evaluated. Epimerisation via a ring opening/closing mechanism is feasible. Base-induced ring-opening of **93** could occur via the mechanism shown in Fig. 2.53 to give a monocyclic intermediate which could then close to

give the epimerised product **93**. A similar mechanism could be involved in the epimerisation of **94** to **95** (Fig. 2.51) and would help to explain how butoxide is able to remove the relatively non-acidic pyridylic proton of **94**.

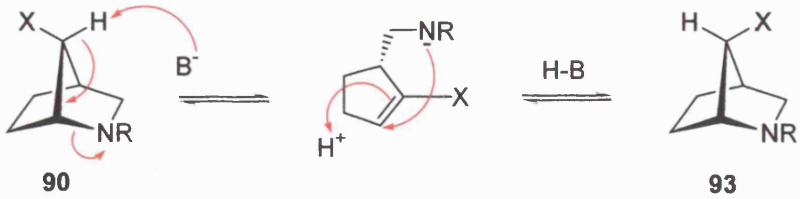


Fig. 2.53 Alternative epimerisation mechanisms.

The epimerisation of the *anti*-hydroxy compound **86** (Fig. 2.54) has also been explored (see Chapter 4). The finding that epimerisation can be achieved at the 7-position of 2-azanorbornanes is crucial and allows access to the novel *syn*-7- 2-azabicyclo[2.2.1]heptane derivatives.

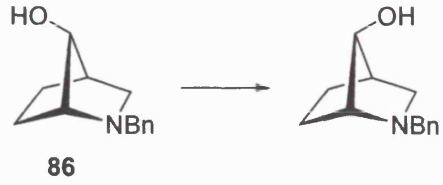
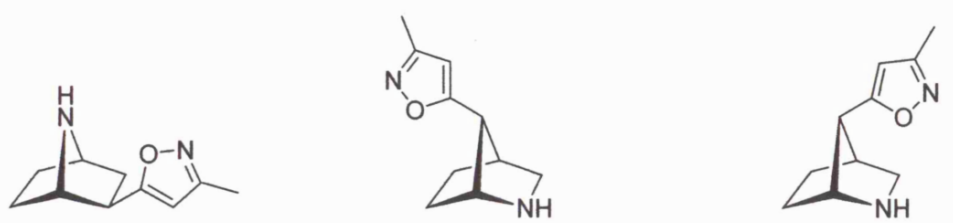


Fig. 2.54 Epimerisation of *anti*-7-hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (**86**) (see Chapter 4).

2.6 Construction of the methylisoxazole heterocycle

The methylisoxazole heterocycle has been used successfully as a bioisosteric replacement of chloropyridine in many nicotinic receptor ligands (see Section 1.5.1). Most notable among these compounds is epiboxidine (**12a**) an analogue of epibatidine in which the chloropyridyl moiety has been replaced by methylisoxazole. As previously explained, epiboxidine is only 5-10 times less potent than epibatidine but less toxic.[55] The success of the methylisoxazole heterocycle and the fact that it can be readily built up from an ester functionality led to the selection of the isoepiboxidines (**51** and **52**) as the first target compounds. The isoepiboxidines are isomers of epiboxidine (**12a**) in which the heterocycle and bicyclic nitrogen have switched positions.



epiboxidine (**12a**) *anti*-isoepiboxidine (**52**) *syn*-isoepiboxidine (**51**)

Fig. 2.60 Epiboxidine and the isoepiboxidines.

The methylisoxazole heterocycle can be readily obtained from an ester group (Fig. 2.61). The *syn*- ethyl ester (**99**) was reacted with the dianion of acetoxime (formed *in situ* from acetoxime and *n*-butyllithium); subsequent treatment with acid gave the heterocycle-bearing compound (**100**) in 36% yield. The methylisoxazole heterocycle formation reaction gives notoriously poor yields, typically 20 to 50%.[55,65,77] A possible explanation for this concerns the dianion of acetoxime. After deprotonation of the oxime oxygen, a proton is removed from either the methyl group *syn* or *anti* to the oxygen (Fig. 2.61). Addition of the *syn* anion to **99** would give **101**, while the *anti* anion would give **102**. The *syn*-oxime **101** appears well positioned to attack the ketone, leading to **100**. But in the *anti*-oxime **102**, the greater distance between the oxygen atom of the oxime and the carbonyl carbon may prohibit cyclisation. Hence the formation of *syn* and *anti* oximes as intermediates in the formation of methylisoxazole may explain why yields above 50% are rarely reported for reactions of this type.

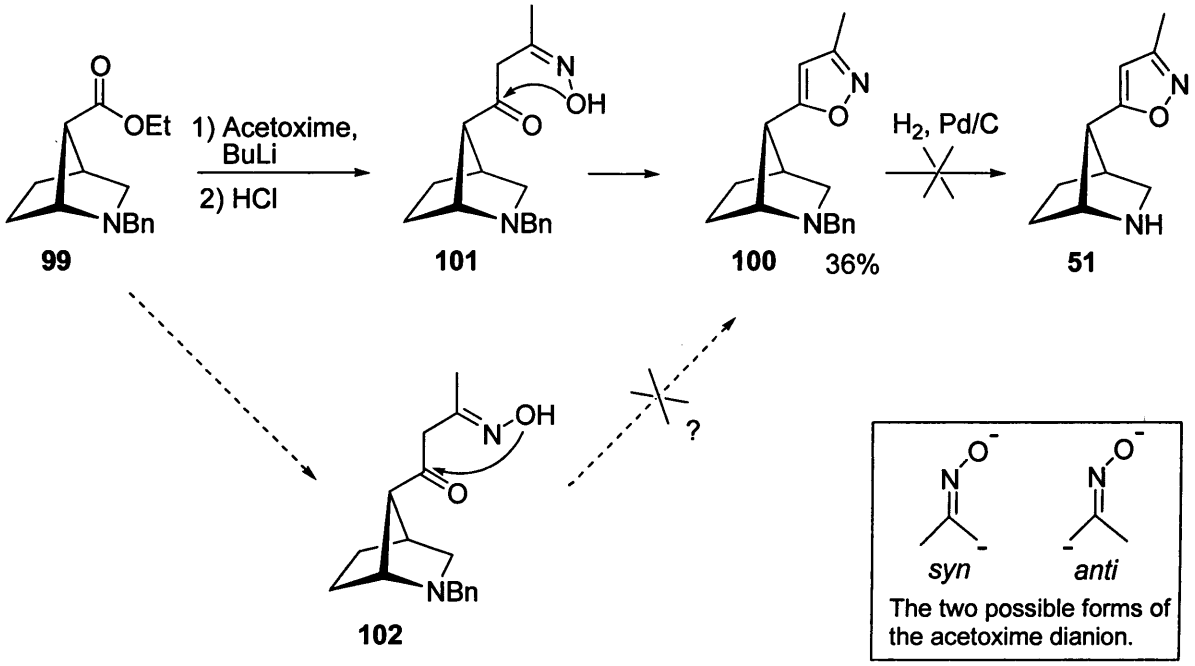


Fig. 2.61 Methylisoxazole construction and a mechanistic hypothesis to explain low yields.

Palladium-catalysed hydrogenation of **100** to give the de-protected *syn*-isoepiboxidine (**51**) was unsuccessful; de-benzylation was accompanied by reduction of the heterocycle. Addition of quinoline to attenuate the activity of the catalyst did not alter the outcome of the reaction. Similar reduction of the methylisoxazole substituent under these conditions was observed by the Daly group in their recent publication of the synthesis of homoepiboxidine.[65]

To circumvent heterocycle degradation, previous syntheses of methylisoxazole-bearing compounds have involved deprotection/reprotection strategies. Hence, the *anti*- ester **98** was de-benzylated and re-protected with a Boc group in 43% overall yield (Fig. 2.62). Heterocycle

formation proceeded smoothly (48%, based on recovered starting material) and subsequent acid-catalysed de-protection gave *anti*-isoepiboxidine (**52**). A non-aqueous source of HCl (ethanol and acetyl chloride in ethyl acetate) was used to remove the Boc group from **105** since de-protection with trifluoroacetic acid gave poor yields.

An unexpected observation removed the need to re-protect with Boc. Thus methylisoxazole formation was found to be successful even when the bicyclic nitrogen was not protected; the 24% yield for this direct conversion (**103** to **52**) is comparable with the route *via* **104** and **105** (30%). Prior to this finding, protection of the secondary amino-nitrogen was thought to be an essential requirement; the demonstration of the direct conversion (**103** to **52**) is a significant observation that is expected to have wider application.

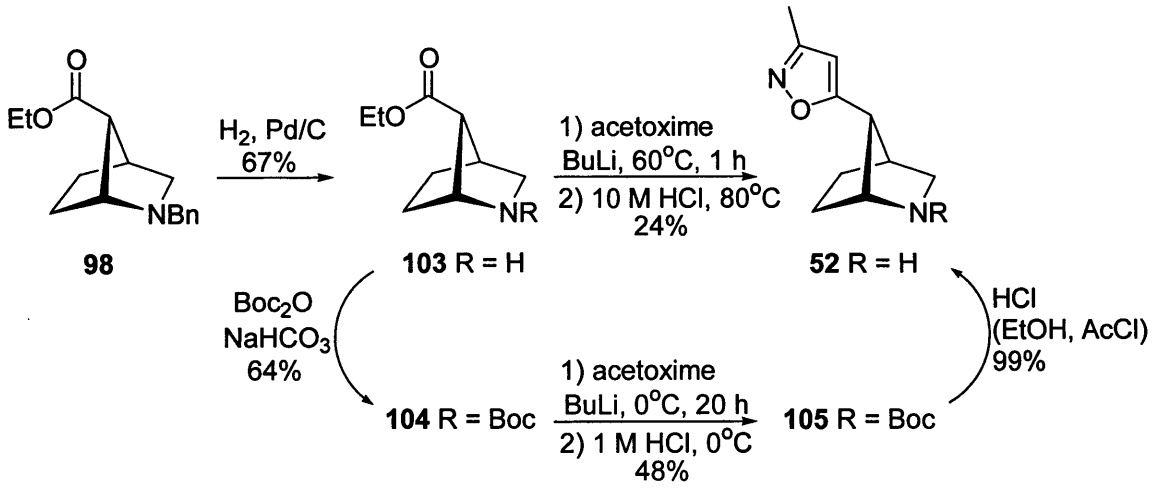


Fig. 2.62 The synthesis of *anti*-isoepiboxidine.

syn-Isoepiboxidine (**51**) was produced analogously (Fig. 2.63), the direct conversion from the de-benzylated *syn*- ester (**106**) proceeded in 26% yield, the de-/re-protection route via **107** and **108** gave an overall yield of 33%.

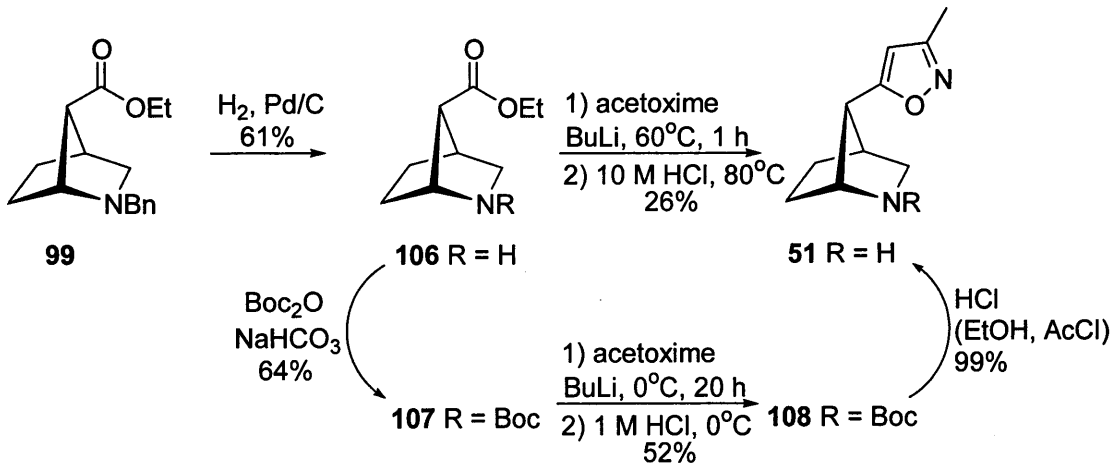


Fig. 2.63 The synthesis of *syn*-isoepiboxidine (**51**).

In conclusion, this Chapter has described a protocol for the functionalisation of the 7-position of 2-azanorbornanes. Nucleophilic substitution reactions of *anti*-7-bromo-2-benzyl-2-azanorbornane (**82**) have been shown to occur with retention of configuration. Functional group interconversions gave esters which were epimerised under basic conditions allowing the *syn*-7-series of molecules to be accessed. Construction of the methylisoxazole heterocycle, which was possible even when the bicyclic nitrogen was not protected, gave *anti*- and *syn*-isoepiboxidine.

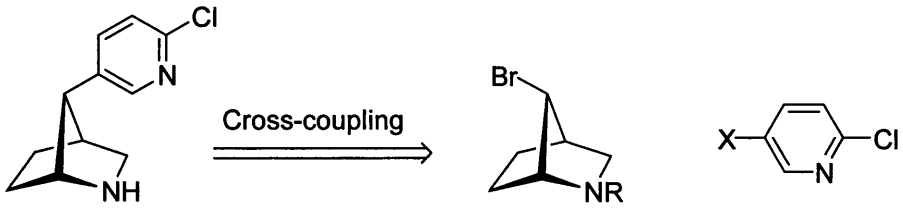
The syntheses of the isoepiboxidines were published, along with the general route to *anti*- and *syn*-7-substituted 2-azabicyclo[2.2.1]heptanes in *The Journal of Organic Chemistry*.[119] Nicotinic receptor binding data have been obtained for *anti*- and *syn*-isoepiboxidine and are discussed in Chapter 7.

Chapter 3

Approaches to isoepibatidine

3.1 Introduction

Following the successful synthesis of the isoepiboxidines (Chapter 2) attention was shifted to the chloropyridyl-bearing isoepibatidine **49**. The rationale for targeting this compound was discussed in detail in Section 1.6. Construction of the isoepiboxidines involved building up the methylisoxazole heterocycle from an ester precursor; for isoepibatidine, direct coupling of the chloropyridine moiety was envisioned (Fig. 3.10). Metal-catalysed cross-coupling reactions have been used previously in total syntheses of epibatidine and its analogues.[15,60-62] For instance, Heck reactions were used to access 5- and 6- chloropyridyl-substituted 2-azabicyclo[2.2.1]heptanes, which are potent isomers of epibatidine (Fig 1.52).[60-62]



49 **119** **118**

Fig. 3.10 The proposed route to *syn*-isoepibatidine (**49**).

A suitable metal-catalysed coupling procedure was sought for the attachment of a chloropyridyl derivative **118** to an *anti*-7-bromo compound **119**. Cross-coupling reactions of sp^3 hybridised centres are not well established but recent advances have been made. We wished to use Suzuki-type methodology to couple a pyridyl boronic acid (**118**) to **119**. Some of the developments that made this approach possible are reviewed below.

3.2 Suzuki cross-coupling reactions

The Suzuki coupling reaction was first published in 1979 and has since found wide application; it involves palladium(0)-catalysed coupling of a halide or triflate to an organoboron compound. The general catalytic cycle (Fig. 3.20) consists of an oxidative addition of 1-alkenyl, 1-alkynyl, allyl, benzyl or aryl halides to a Pd(0) complex to give a stable *trans*-σ-palladium(II) complex. Transmetallation with an organoboron species followed by reductive elimination gives the coupled product. Transmetallation is aided by the presence of a base, which is thought to form a reactive boronate species with the organoboron compound.[120]

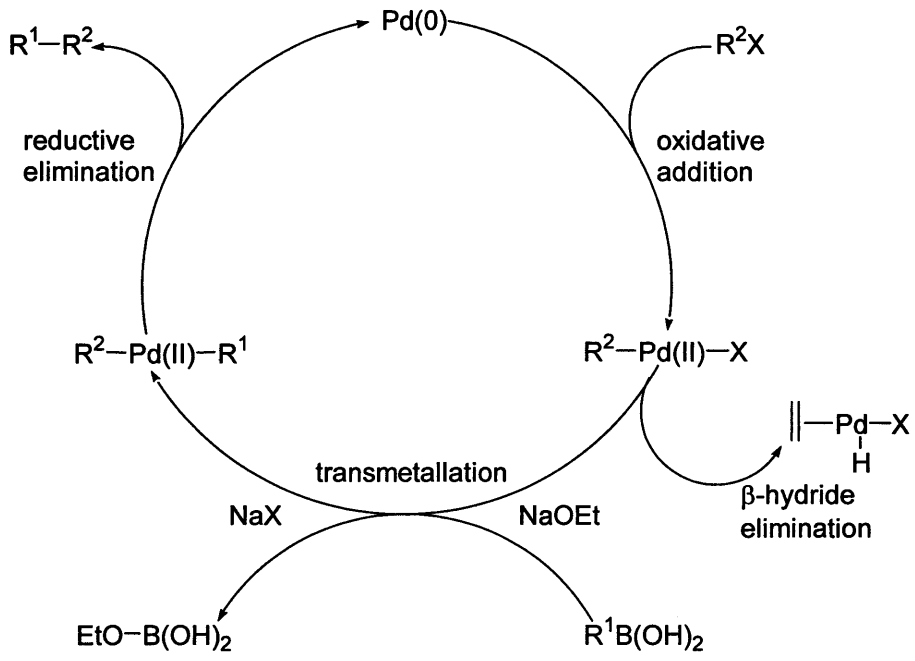
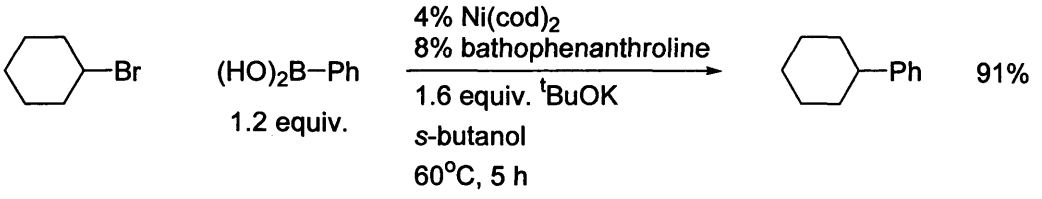


Fig. 3.20 The general catalytic cycle for Suzuki cross-coupling reactions.[120]

Traditionally, applications of the Suzuki reaction involve the coupling of sp^2 halides to sp^2 organoboron compounds. Until relatively recently, the coupling of alkyl halides with β-hydrogens was rare in Suzuki reactions, the main reason for this being that β-hydride elimination becomes feasible and competes with transmetallation. In addition, oxidative addition (usually the rate limiting step) of unactivated halides is slow. Pioneering studies by Suzuki, in which long-chain primary alkyl iodides were coupled to alkyl boranes indicated that Pd-catalysed coupling of sp^3 alkyl halides was possible and that β-hydride elimination can be overcome.[121] This work has been developed to include magnesium, tin, silicon and zirconium couplings and the range of alkyl halides has been extended, particularly in terms of increased functional group tolerance.[122,123] However, only very recently have methods been developed allowing the use of unactivated *secondary* alkyl halides, an important step in broadening the application of the Suzuki reaction.

In 2004 Zhou and Fu published the first examples of Suzuki cross-couplings of unactivated secondary alkyl bromides and iodides.[123] These couplings involve a nickel(0) catalyst; optimum conditions for these reactions are shown in Fig. 3.21 and give yields in the 50-90% range. Even slight deviations from the 'standard' procedure tend to reduce yields substantially. An illustrative selection of these coupling reactions is tabulated (Fig. 3.21). Most of these examples involve a phenyl boronic acid but the successful introduction of thiophene (Entry B) suggested that certain heterocyclic couplings are viable. In addition, coupling of the boronic acid in Entry E to bromine rather than chlorine (dimerisation)

indicates that the reaction is selective for sp^3 carbon atoms. However, the secondary alkyl halides used lack functionality; a footnote in the paper states that 'reactions of functionalised alkyl electrophiles proceed in lower yield'.[123]



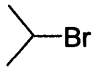
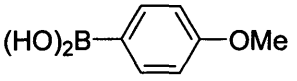
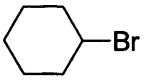
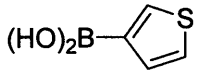
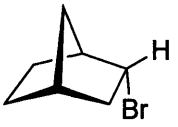
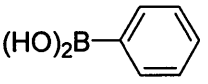
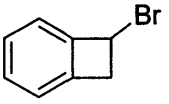
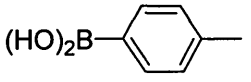
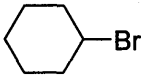
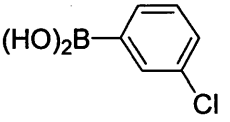
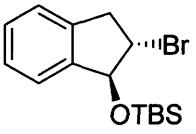
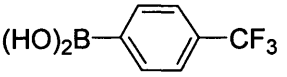
	R_{alkyl}-Br	$(HO)_2B$-R	Yield (%)
A			68
B			63
C			71
D			90
E			75
F			63

Fig. 3.21 Suzuki cross-coupling of unactivated secondary alkyl bromides.[123]

Zhou and Fu do not specifically address the issue of stereochemistry, but in Entry C (Fig. 3.21) the *exo* product is formed, that is, inversion of configuration occurs. In Entry F, retention of configuration is observed as the *trans* product is produced.[123] These findings could indicate that the thermodynamic products were produced, either during the coupling reaction or by epimerisation of the initial product by the tertiary butoxide present in the reaction mixture.

3.3 Cross-coupling to *anti*-7-bromo-2-Boc-2-azabicyclo[2.2.1]heptane

The procedure for the Suzuki coupling of unactivated secondary alkyl bromides recently developed by Zhou and Fu[123] (above) was applied to the coupling of heterocycles to the 7-position of the 2-azanorbornane framework. The heterocycle degradation observed when attempting to de-benzylate the methylisoxazole derivative (**100**; Fig. 2.61) prompted a change of protecting group prior to attempting the coupling reactions. The 7-bromo compound **82** was de-benzylated then re-protected with Boc to give **121**, which was used as the substrate for all cross-coupling reactions.

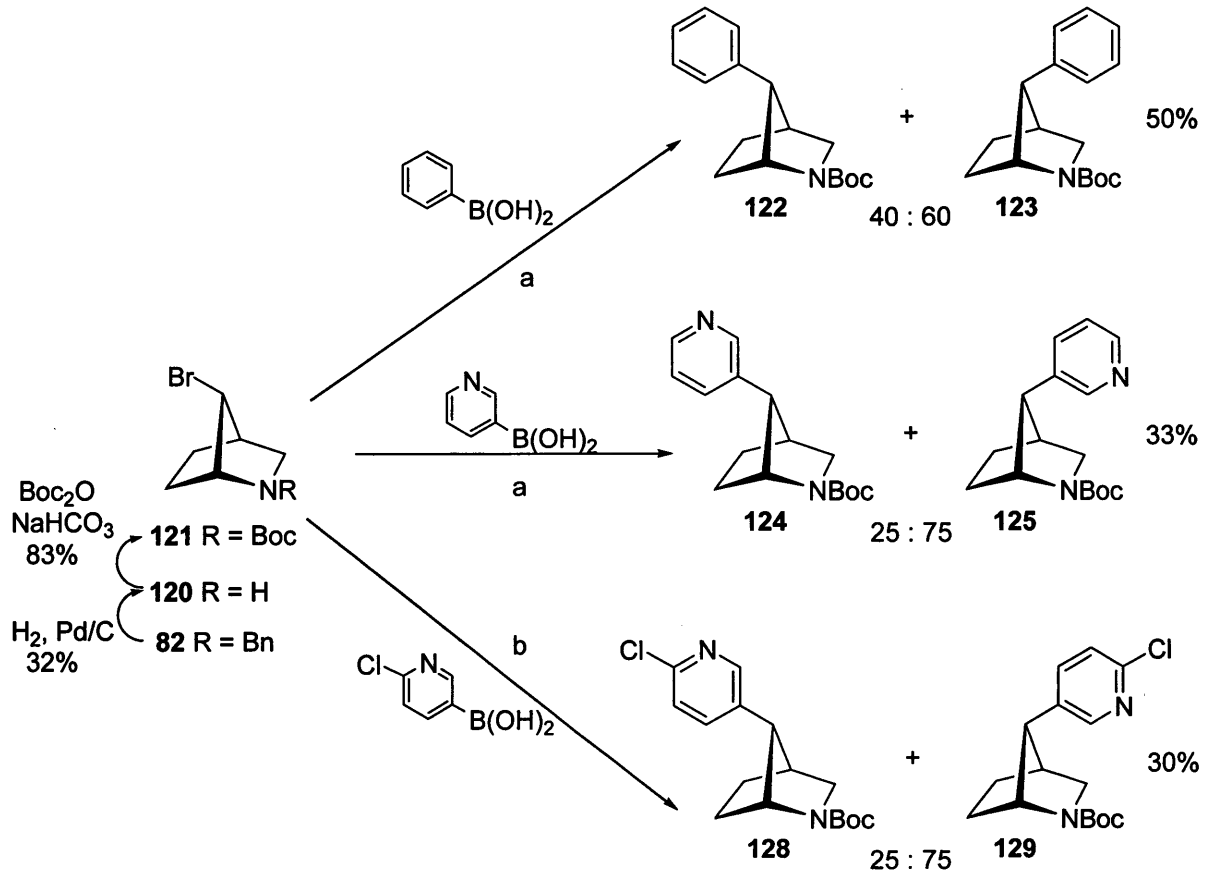
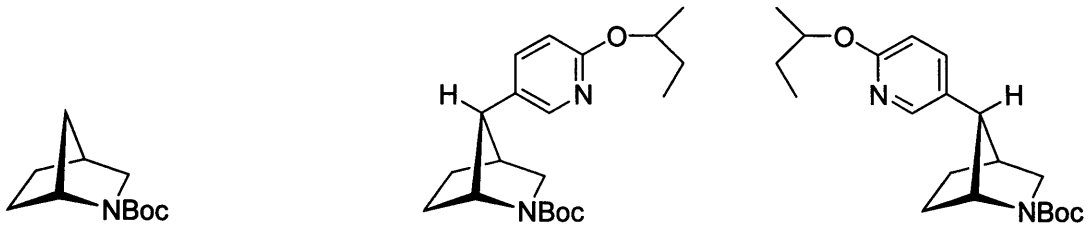


Fig. 3.30 Cross-coupling reactions at the 7-position of *anti*-7-bromo-2-Boc-2-azabicyclo[2.2.1]heptane (**121**). Conditions: $Ni(cod)_2$, bathophenanthroline, ^tBuOK, *s*-butanol. a: 100 °C, 48 h. b: 50 °C, 12 h.

Initial attempts to couple to **121** were made using benzyl boronic acid and the same conditions described by Zhou and Fu[123] The reaction gave some of the coupled product but in low yield. Hence, the temperature was increased from 60 °C to 100 °C and an isolated yield of 50% was achieved after 48 hours. It was clear that a mixture of the *anti* and *syn* products (**122** and **123**) had been obtained, (40:60) but the two isomers could not be separated and the identity of the major epimer could not be determined at this stage. Having established that the Suzuki coupling reaction tolerated the presence of the Boc group, the coupling of pyridyl

boronic acids was undertaken. 3-Pyridyl boronic acid was coupled to **121** using the same conditions as in the coupling of benzene boronic acid; after 48 hours a 33% isolated yield of the combined *anti* and *syn* products **124** and **125** was obtained. The epimer ratio was 25:75, but again, separation and identification of the major epimer was not possible at this stage. Attempts were then made to couple the all-important 4-chloro-3-pyridyl boronic acid to **121**. As in the couplings described above, an adapted procedure involving a temperature of 100 °C rather than 60 °C was implemented but this gave rise to solvolysis - the unwanted products **126** and **127** were formed (Fig. 3.31). These compounds were not isolated but were observed by mass spectrometry and as a broad quartet (~5.1 δ) in the crude ^{1}H NMR spectrum corresponding to the methine protons of the ether group. Coupling had clearly occurred but the high temperature used and the presence of potassium tertiary butoxide had resulted in substitution of the chlorine substituent for a secondary butyl-ether group. The conditions of the coupling reaction were altered. The temperature was reduced to 50 °C and after 12 hours **128** and **129** (25:75) were produced in a combined, isolated yield of 30%; there was no observable solvolysis.



130 **126** **127**

Fig. 3.31 By-products from Suzuki coupling-reactions.

The coupling reactions discussed above, and those in the remainder of this thesis, involved significantly higher catalytic loadings than in the original procedure, typically ~20-30% rather than 4%. As the reactions were performed on relatively small scales, this was principally to make experimental procedures easier, in terms of weighing reasonable amounts of material. Where yields for coupling reactions were low, the molar amount of catalyst was not limiting, that is, a catalytic cycle was established. The yields were generally in line with those reported by Zhou and Fu in view of their observation that reactions of functionalised alkyl electrophiles give lower yields. The three coupling reactions (Fig. 3.30) consistently gave the defunctionalised **130** as a by-product, typically in approximately 20% yield.

The mixture of *syn* and *anti* chloropyridyl derivatives **129** and **128** was subjected to very careful flash chromatography and a small sample of the major epimer was isolated (the minor epimer could not be isolated). 2D NMR experiments were performed as in Chapter 2 and, most notably, NOE interactions were seen between H_7 and the *exo* hydrogens at H_5 and

H_6 (shown in Fig. 3.32). This indicated that in the major epimer the heterocycle was *syn* to the bicyclic nitrogen and this was confirmed by X-ray crystallography (Fig. 3.32). Careful analysis of the 2D NMR spectra of the mixtures of **122/123** and **124/125**, and comparison to the 2D spectra of the chloropyridyl derivatives **128** and **129**, allowed the major epimers in the coupling reactions of 3-pyridyl and benzene boronic acids to be established. Again, the *syn* epimers **123** and **125** were the major products (Fig. 3.30).

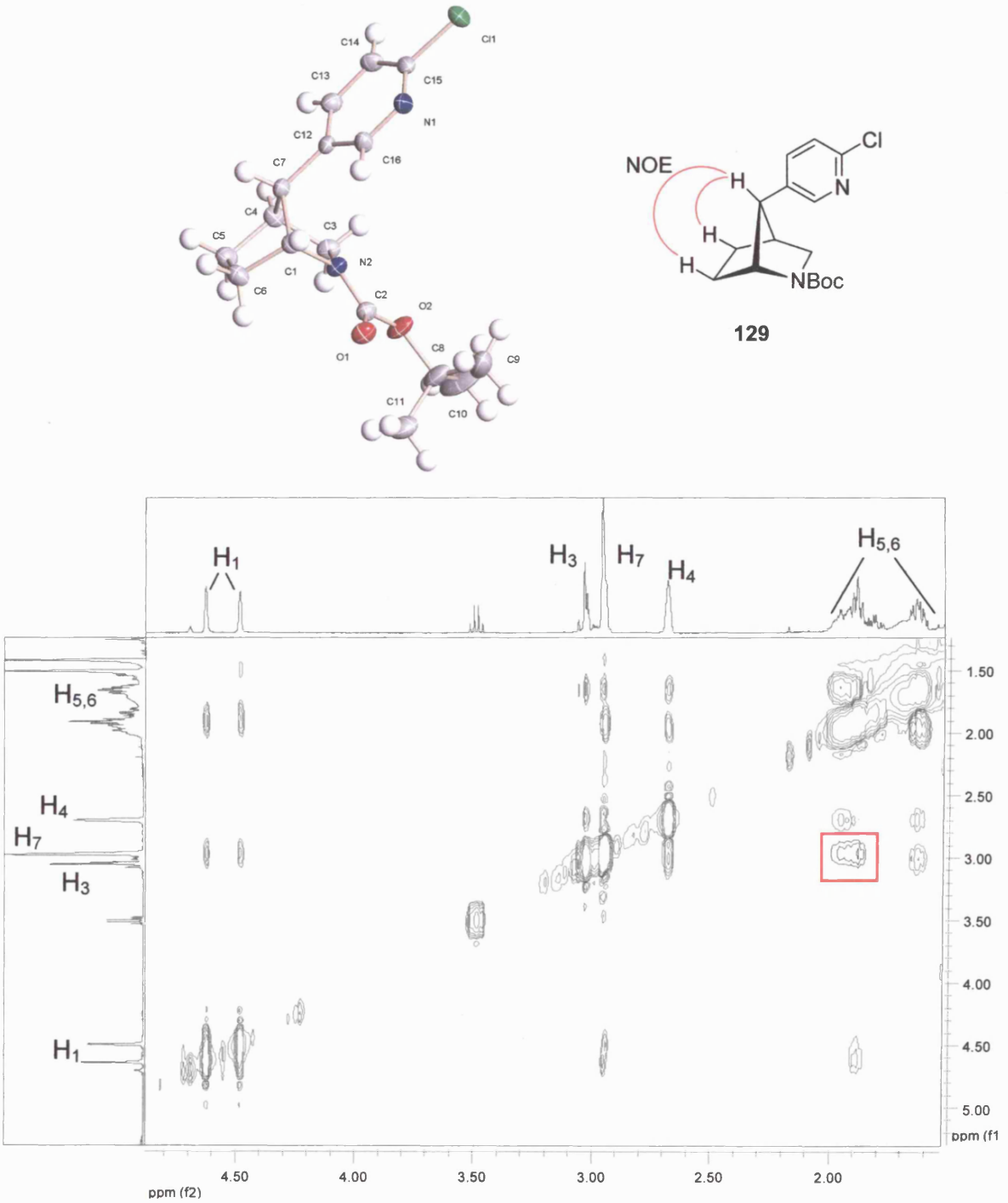


Fig. 3.32 Confirmation of the stereochemistry of **129** by X-ray crystallography and 2D NOESY experiments. [For crystallographic data see Appendix I]

The issue of stereochemistry in this Suzuki-coupling methodology was alluded to in Section 3.2. The formation of *syn* and *anti* products could arise during the coupling reaction itself or alternatively, in a subsequent base-catalysed epimerisation step, in which case the *syn* epimers **123**, **125** and **129** would appear to be more thermodynamically stable than the corresponding *anti* derivatives. Attempts were made to prevent epimerisation, in the hope of obtaining a pure sample of the *anti* chloropyridyl compound **128**: the coupling of the chloropyridyl boronic acid to **121** was attempted at 0 °C. On cooling, the purple colour (which indicates the presence of the active catalytic-complex) dissipated leaving a colourless solution; only unchanged starting material was obtained. A coupling reaction at room temperature was stopped after three hours; the crude ^{13}C NMR spectrum showed ~10% conversion and the *anti* epimer **128** as the major product (*anti*: *syn*; ~75:25). Interestingly, when this mixture was treated with strong base (^{t}BuOK/BuOH) the ratio reversed in favour of the *syn* epimer (*anti*: *syn*; ~25:75). This is consistent with the hypothesis that the Suzuki methodology gives thermodynamic mixtures of epimeric products. This could be by retention of configuration at the 7-position followed by a base-catalysed epimerisation step but a coupling reaction in which tertiary butoxide was replaced with potassium carbonate was ineffective, giving no conversion. Hence, a pure sample of the *anti* derivative, **128**, was not forthcoming.

In summary, development of the Suzuki-coupling procedure described by Zhou and Fu[123] allows the introduction of pyridine derivatives at the 7-position of 2-azanorbornanes. Notably, we have extended the range of heterocyclic derivatives that can be coupled beyond thiophene and indole, and shown that certain functional groups, *e.g.* the carbamate of the Boc protecting-group, are tolerated. The yields for these transformations are reasonable and, gratifyingly, the inherent epimerisation provides access to the desired *syn*-7-series of compounds.

3.4 Synthesis of isoepibatidine

The difficulties encountered when attempting to separate the Boc-protected epimers **128** and **129** prompted their deprotection as a mixture. **128** and **129** (25:75) were stirred in a non-aqueous source of HCl (Fig. 3.40) to give the hydrochloride salts of *anti*- and *syn*-isoepibatidine (**50** and **49**). Fortuitously, the HCl salt of *syn*-isoepibatidine (**49**) was found to be more soluble in DCM than the HCl salt of **50**; a solid-liquid extraction was undertaken and gave a pure sample of **49** (46% recovery from the initial mixture of **49** and **50**). The *anti*-isomer **50** could not be completely separated from **49**. In view of earlier difficulties regarding the separation of epimers, this method was acceptable; not least because it allowed the more important *syn*-compound (**49**) to be isolated.

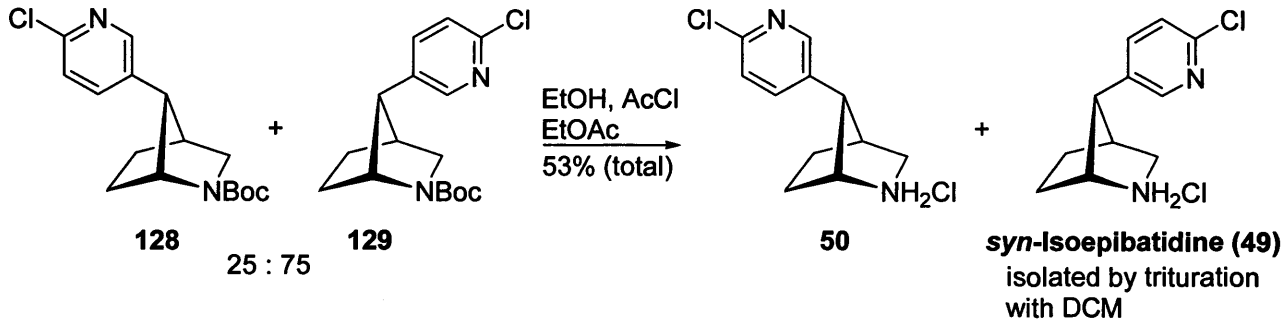


Fig. 3.40 The synthesis and isolation of *syn*-isoepibatidine (**49**).

This Chapter has described how a recently reported Suzuki coupling procedure was developed to allow the introduction of pyridine heterocycles to the 7-position of 2-azanorbornanes. This led to the successful preparation and isolation of *syn*-isoepibatidine (**49**). The synthesis of the isoepibatidines was published in *Organic Letters*.[124] Nicotinic binding data have been obtained for *syn*-isoepibatidine and are discussed in Chapter 7.

Chapter 4

Epibatidine analogues with ether-linkages

4.1 Nicotinic ligands with ether-linkages

Since the identification of ABT-594 (**48**) in 1998, the production of nicotinic agents containing ether functionalities has been a growth area. As described previously (see Section 1.5.6), ABT-594 is a potent and subtype selective nicotinic agonist, showing high affinity for α4β2 receptors and reduced affinity for the α3β4 subtype in comparison to epibatidine. It entered phase II clinical trials as an analgesic[83,125] but was abandoned recently due to side-effects.[86] However, interest in this class of compound continues, not least because the introduction of ether-linkages has been one of the few fruitful avenues in the search for receptor subtype selective molecules.

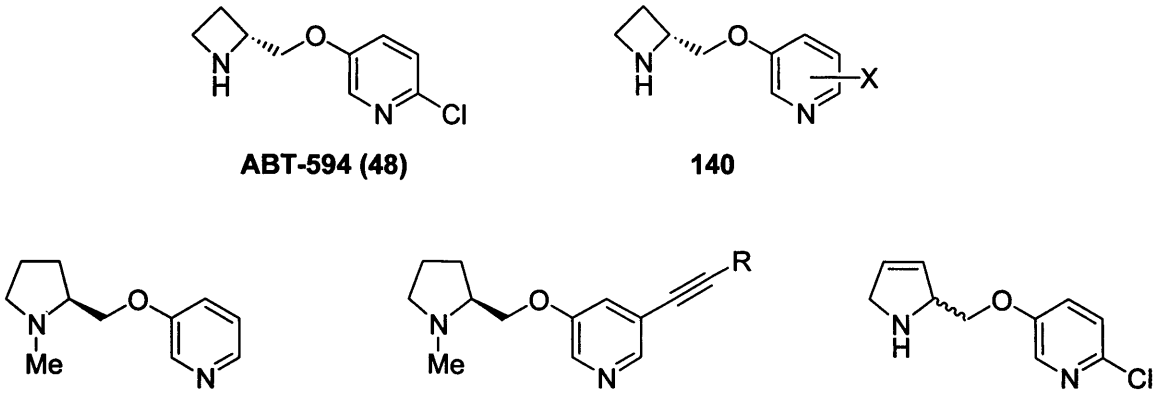


Fig. 4.10 Selected examples of nicotinic ligands with ether-linkages.[126-128]

Analogues of ABT-594 (**48**) have been made in which the chlorine atom was absent and various groups were positioned around the pyridine ring (e.g. **140**). Similar structure activity relationships (SAR) were reported to those observed for epibatidine (see Section 1.5.1): no increases in receptor binding-affinity were attained and substituents at the 5'-position were tolerated best.[126] Kozikowski and co-workers further developed the concept of introducing 5'-substituents; they investigated the selectivity exhibited by compounds with the general structure **141**. The variable group (R) was phenyl, a primary alkyl-fluoride or a primary alkyl-alcohol; all of the derivatives tested had significantly improved α4β2/α3β4 selectivity compared to their parent structure (**46**).[127] Compounds have been produced in which the azetidine ring of ABT-594 was replaced with the unsaturated 3-pyrroline heterocycle; **142** was found to have favourable analgesic properties, being approximately two-fold less potent than ABT-594. In addition to these advances, which have been published in the open literature, Abbott is developing second-generation versions of ABT-594. The structures of these molecules are not available.

All the examples above are based on aza*mono*cycles; this Chapter explores the concept of attaching an aza*bicycle* to a pyridine heterocycle via an ether-linkage. The biological properties of ABT-594 and related compounds were unexpected: the azabicyclic moiety of epibatidine and its isomers was thought to be an essential requirement for potent nicotinic activity. By creating hybrids of ABT-594 and epibatidine, we hoped to achieve the selectivity demonstrated by the ether-linked analogues and also maintain the exquisite affinity resulting from the azabicycle of epibatidine. Additionally, the binding of ether-linked derivatives to nicotinic receptors is now being elucidated through docking to homology models and an understanding of how these structures give rise to selectivity is being established.[43] The synthesis of a new class of selective nicotinic ligands would greatly aid these SAR studies.

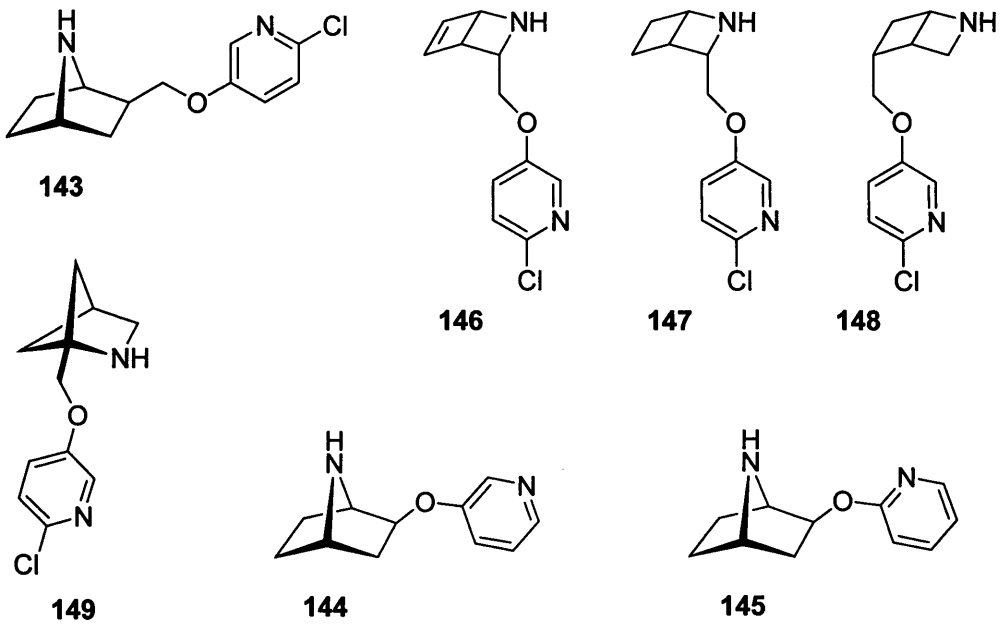


Fig. 4.11 Nicotinic ligands with an ether-linkage to an azabicycle.[79,129,130]

In the literature there is a very limited range of nicotinic ligands which combine a pyridyl-ether moiety with an azabicycle (Fig. 4.11). Trudell and co-workers produced an analogue of epibatidine in which a pyridyl ether moiety is attached to the *exo*-2-position of the 7-azanorbornane framework (**143**). This derivative exhibited low affinity (740 nM) for α4β2 receptors compared to (±)-epibatidine (0.14 nM) leading to the postulation that the structural features of ABT-594 and epibatidine could not be combined to give highly active compounds.[129] However, **143** does not have the same atom connectivity (N-N) as ABT-594 and in 2006 Mu *et al.* published the syntheses and receptor binding affinities of **144** and **145**. These derivatives (**144** and **145**) also had greatly reduced affinities in comparison to epibatidine, K_i = 17.4 nM and 620 nM respectively (epibatidine: 0.053 nM).[131]

Ether-linked epibatidine analogues with smaller azabicycles have been produced. The 2-azabicyclo[2.2.0]hexane derivatives (**146**, **147** and **148**) produced by Krow are structurally similar to ABT-594; but these compounds had only moderate binding affinities at α4β2 receptors; K_i = 14, 2.3 and 12 nM respectively ((±)-epibatidine, K_i = 0.043 nM).[79] Recently at Leicester, research into the manipulation of substituents at the neopentyl position of the methanoproline bicyclic framework has been undertaken. Mitsunobu coupling reactions led to the production of 2-azabicyclo[2.1.1]hexane pyridyl ethers (e.g. **149**).[77,130] **149** was designed as a potential nicotinic agonist with a structure very similar to that of compounds with known high activity (Fig. 4.10). However, receptor binding assays have now established that it has very low affinity for the α4β2 and α3β4 subtypes.[78]

Despite this poor track record in combining the molecular features of epibatidine and ABT-594, it was suspected that certain molecular architectures would allow the pyridyl and bicyclic nitrogen atoms to assume spatial relationships conducive to high nicotinic affinity.

4.2 Target selection

The importance of inter-nitrogen distance for nicotinic receptor binding has already been discussed extensively. The active conformation of epibatidine has N-N of ~4.5 Å and other nicotinic agonists, including ABT-594, assume conformations that give similar N-N distances.[37,43] With this in mind the structures shown in Fig. 4.20 were selected as targets.

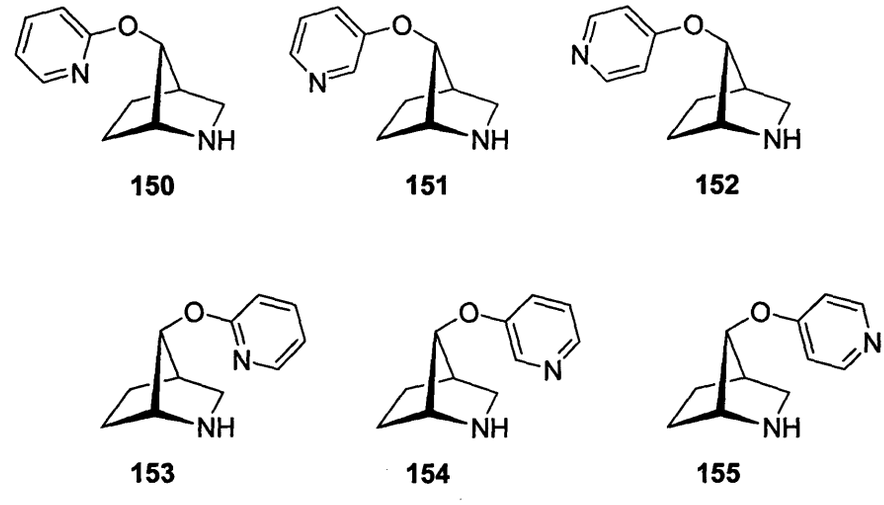
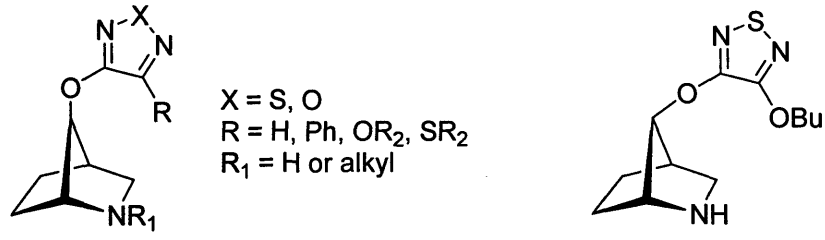


Fig. 4.20 Target compounds: hybrids of epibatidine and ABT-594.

Preliminary molecular modelling indicated that a number of these structures have low energy conformations with appropriate inter-nitrogen distances (~4.5–5.0 Å). It was reasoned that producing compounds with 2-, 3- and 4-pyridines, with both *syn*- and *anti*- C7

configuration, would maximise the chance of achieving nicotinic receptor affinity. However, of the compounds **150-155, 154** was thought the most likely to have activity as it has the same atom connectivity (N to N) as ABT-594 and *syn*-7-stereochemistry. Further discussion of the molecular modelling of **150-155** can be found in Chapter 7. The absence of a chlorine atom in **150-155** is not expected to influence nicotinic receptor affinity greatly and so is not a concern. In epibatidine, the removal of the chlorine atom has little effect on nicotinic receptor affinity but does reduce functional potency.[27]

The structures in Fig. 4.20 are novel targets but a relevant patent by Mitch and Quimby[108] came to our attention as we were publishing the syntheses of the isoepiboxidines.[119] This patent describes how compounds with the general structure **156** (e.g. **157**) could be used as selective muscarinic receptor antagonists. But it contains significant stereochemical oversights: all of the stereoisomers of **156** are claimed but the synthetic route used is similar to that which we developed for the synthesis of the isoepiboxidines (Chapter 2) and clearly gives *anti*- derivatives only. No spectroscopic or receptor binding data were given for these compounds.[108]



156 **157**

Fig. 4.21 Compounds included in a patent by Mitch and Quimby.[108]

Production of the *syn*- series of compounds **153, 154** and **155** requires manipulation of the C7 stereochemistry. The following Sections describe how *anti*-7-hydroxy-2-azabicyclo-[2.2.1]heptane (**86**) can be converted to the *syn*-alcohol precursor **158**.

4.3 Approaches to 7-keto-2-azabicyclo[2.2.1]heptanes

The epimerisation of the *anti*-alcohol **86** has been explored; we wished to reverse the 7-position configuration via an oxidation-reduction strategy.

Equilibrium between an alcohol and the corresponding ketone can be established using the conditions of the Oppenauer oxidation and the Meerwein-Ponndorf-Verley reaction. Typically, an alcohol is treated with aluminium isopropoxide and acetone; this procedure has been applied to the racemisation of secondary alcohols.[132,133] Attempts were made to

epimerise the *anti*-alcohol **86** using this method but were unsuccessful; only unchanged starting material was isolated (Fig. 4.30).

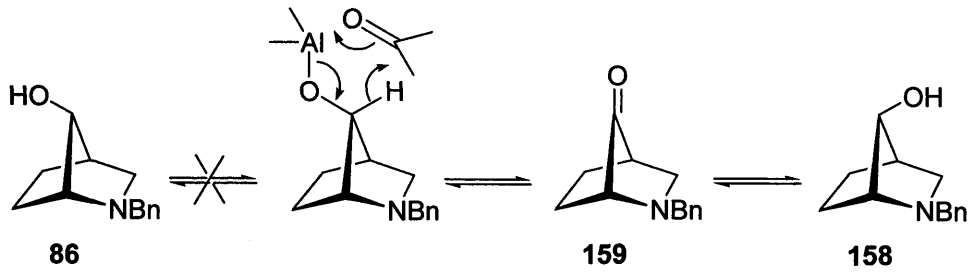


Fig. 4.30 Attempted epimerisation of **86** using the Oppenauer oxidation.

As the one-step epimerisation of the *anti*- alcohol **86** had failed, it was converted into the ketone **159** using a Swern oxidation. The use of Jones and Dess-Martin conditions was unsuccessful, as was use of PDC. Protecting-group inter-conversions were straightforward and the Boc and Cbz protected alcohols **161** and **162** were converted to the corresponding ketones using the same methodology; yields for these transformations were mediocre. Column chromatography of the ketones **159**, **163** and **164** had a detrimental effect on the appearance of the ^{1}H NMR spectra. This may be attributable to the formation of hydrates and acetals.

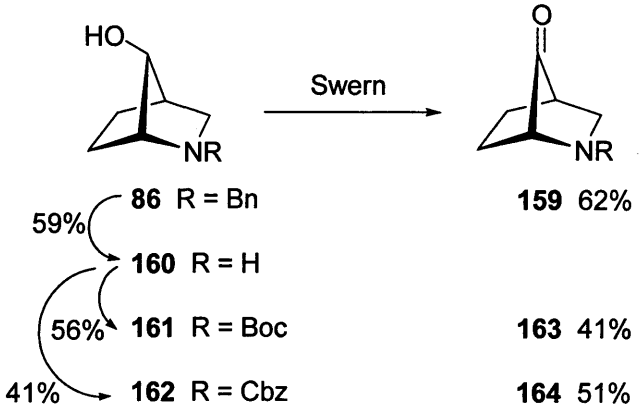


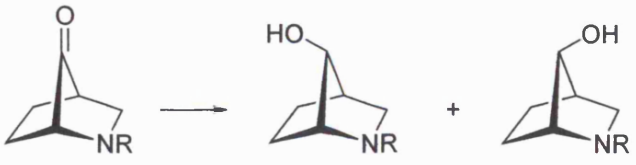
Fig. 4.31 Synthesis of 7-keto-2-azabicyclo[2.2.1]heptanes.

4.4 The reduction of 7-keto-2-azabicyclo[2.2.1]heptanes

The ketones **159**, **163** and **164** were treated with sodium borohydride (Fig. 4.40); it was hoped that in addition to the initial *anti*-alcohols, the *syn*-alcohols would also be obtained. The facial selectivity of borohydride attack was found to be largely dependent on the nature of the *N*-protecting group. Reaction of the benzyl-protected **159** gave a mixture of the alcohols **86** and **158**, with the *syn*- alcohol **158** as the major product (95:5). These epimers were separable, with difficulty, by column chromatography. Interestingly, similar reaction of the *N*-Boc and

N-Cbz-protected ketones **163** and **164** with $NaBH_4$ appeared to give only the *anti*-7- alcohols **161** and **162**.

Epimer ratios were determined by ^1H NMR peak integrations and epimer identification was by 2D NOESY experiments as described in Chapter 2. For additional stereochemical verification, the 3,5-dinitrobenzoate of **158** was prepared; a crystal of this derivative was obtained and an X-ray structure confirmed the *syn* configuration of the 7-substituent (Fig. 4.40).



159	R = Bn	**86**	5 : 95	**158**
163	R = Boc	**161**	100 : 0	**165**
164	R = Cbz	**162**	100 : 0	**166**

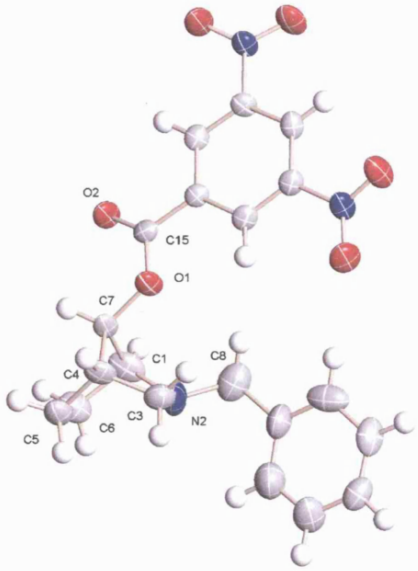


Fig. 4.40 Preliminary findings into the facial selectivity of 7-keto-2-azabicyclo[2.2.1]heptanes and the X-ray crystal structure of the 3,5-dinitrobenzoate of **158**. [For crystallographic data see Appendix I].

These initial findings regarding facial selectivity on 7-keto-2-azanorbornanes were explored further by B. Pibworth, as part of a final-year undergraduate project at Leicester.[134] The range of hydride sources was extended and the alcohol epimer-ratios were accurately determined by GCMS and GC. The principal results of this study are summarised in Fig. 4.41. Most notably, the facial selectivity does not change significantly when either $LiAlH_4$ or Red-Al is used in place of $NaBH_4$. The reaction of the *N*-Boc protected ketone (**163**) with $NaBH_4$ gives a ratio of 92:8 *anti*:*syn*; the presence of the *syn* epimer was not detected in the preliminary study due to broad overlapping signals in the ^1H NMR spectrum.

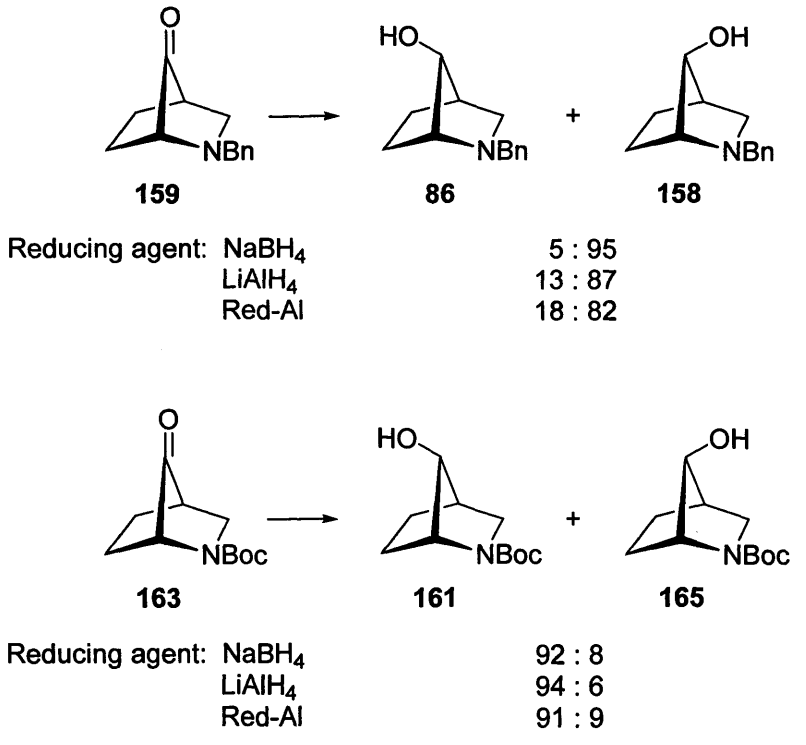


Fig. 4.41 Further studies on the facial selectivity in the reduction of 7-keto-2-azabicyclo[2.2.1]heptanes.[134]

To summarise, oxidation of the *N*-benzyl-protected *anti*-alcohol **86**, followed by reduction of the resulting ketone with $NaBH_4$ affects the epimerisation of **86** to the desired *syn*-alcohol **158**. It is clear that when the bicyclic nitrogen is *N*-benzyl-protected, attack on the 7-ketone is predominantly *anti* to the protecting-group. This selectivity is reversed when a carbamate protecting-group is present. Possible reasons for these preferences are discussed below, in the context of published work on facial selectivity in 7-norbornanones and related systems.

4.5 Facial selectivity in 7-norbornanones and related systems

The facial selectivity of attack on carbonyl groups in rigid molecular frameworks has been studied extensively and is an issue of some complexity.[135-138] The adamantane ring system and norbornanes in particular, have been used as tools to probe the facial selectivity of reactions. It is well established that 2-norbornanones preferentially react with nucleophiles on the *exo* face of the ring system.[135] The facial selectivity of 7-norbornanones has also been studied, most notably by Mehta and Le Noble, and some illustrative examples from these investigations are presented below.

Attack of both sodium borohydride and methyl Grignard on 7-norbornenone (**166**) occurs preferentially from the face of the ketone adjacent to the double bond, giving the *anti*-alcohol (**168**) as the major product (Fig. 4.50A).[138,139] The argument that this is reasonable on

steric grounds can be made: the double bond might be expected to provide less hindrance to nucleophile approach than the *exo* hydrogens on the opposite side of the molecule. However, when **166** is treated with C_2F_5MgBr a complete reversal of selectivity is observed; clearly the electronic nature of the attacking nucleophile is also a factor.[138]

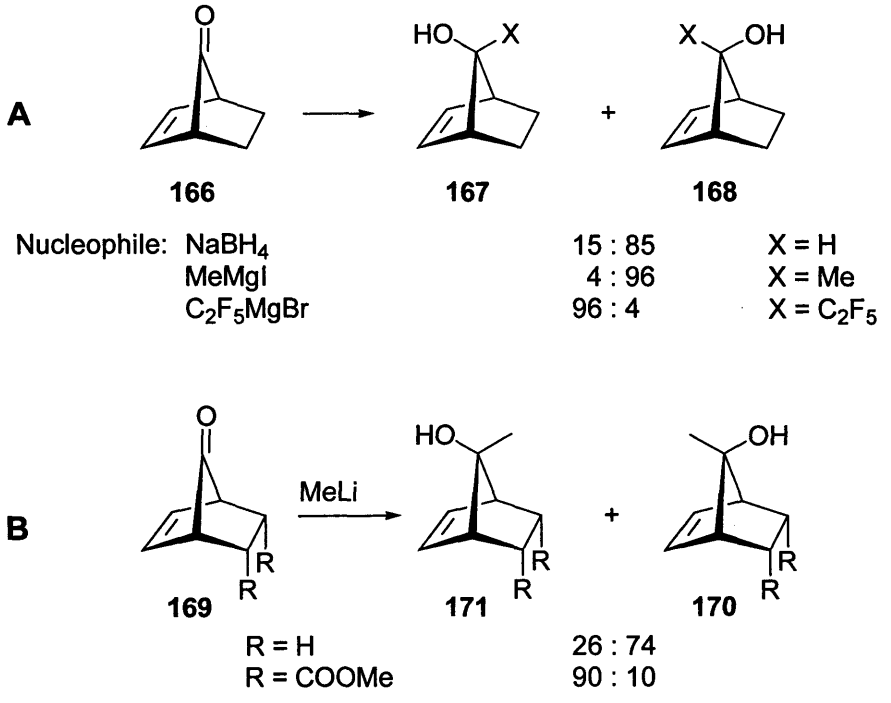


Fig 4.50 Selected literature examples of facial selectivity in 7-norbornanones.[138-140]

Electronic substituent effects have been investigated extensively by Mehta and co-workers. For example, in the reaction of **169** with methyl lithium, the R groups can have no significant steric influence but their nature has a profound effect on facial selectivity (Fig. 4.50B). When R = H nucleophilic attack is preferentially from over the double bond to give **170** as the major product but when R is an electron-withdrawing group, such as methyl ester, then the selectivity is reversed yielding **171** predominantly. It is thought that electronic substituent effects may effect facial selectivity through hyperconjugative stabilisation of the transition state, distortion of the bicycle or pyrimidalisation of the ketone. There is no real consensus on how these different factors combine to influence facial selectivity.[141] For discussion of how 7-norbornanones have been used as sterically unbiased probes see the review by Kaselj *et al.*[136]

4.5.1 Discussion of facial selectivity in 7-keto-2-azabicyclo[2.2.1]heptanes

Whilst the facial selectivity of 7-norbornanones has been considered relatively extensively (see above), our studies are the first into the facial selectivity of 7-keto-2-azanorbornanes.

Some possible explanations for the selectivity observed in this system will be discussed, starting with the *N*-benzyl-protected ketone **159**.

Sodium borohydride and other hydride reagents attack **159** *anti* to the bicyclic nitrogen (see Section 4.4). The first rationale for this observation is a relatively simple steric argument. An *N*-alkyl group in a 2-azanorbornane molecule can assume either an *exo* or *endo* configuration; from previous work at Leicester, the *exo* invertomer is known to be more thermodynamically stable and hence predominates at equilibrium.[142] Attempts were made to determine the invertomer ratio of **159** but kinetic protonation experiments were inconclusive. Addition of trifluoro acetic acid to an NMR sample of **159** gave complex spectra with an abundance of overlapping signals; accurate peak integrations could not be obtained but there appeared to be predominantly one invertomer (>80-90%). Low temperature (-60 °C) NMR studies did not resolve the two invertomers. However, it is reasonable to assume that the *exo* invertomer will be more abundant. With the benzyl group in **159** *exo* it is clear that the *anti* face of the ketone will be more sterically accessible for the attacking species (Fig. 4.51A). Alternatively, neighbouring group participation (NGP) may explain the *anti* attack. The ability of the nitrogen lone pair to displace an *anti*-7-nucleofuge was discussed in Chapter 2 (see Section 2.4.2). Similar participation in the ketone, **159**, would lead to a tricyclic intermediate **172**. Hydride attack on **172** would give the *syn*-alcohol (**158**) (Fig. 4.51B).

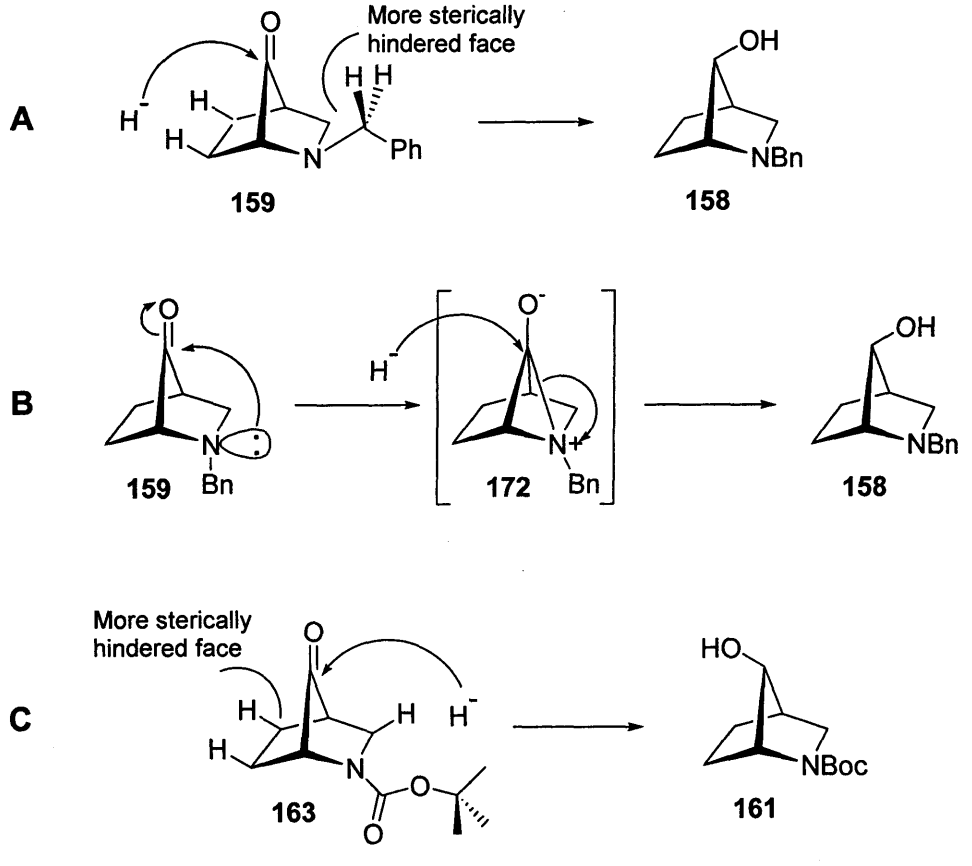


Fig. 4.51 Explanations of facial selectivity in 7-keto-2-benzyl-2-azanorbornanes.

Nucleophilic attack on 7-keto-2-Boc-2-azanorbornanes is principally at the carbonyl face adjacent to the protecting-group. Again, steric arguments can be made: the carbamate group is planar due to electron delocalisation; this is likely to result in the *syn* face of the ketone being more sterically accessible (Fig. 4.51C). Another hypothesis is that the approach of the attacking species may be directed by the Boc group. That is, coordination of the hydride reagent to the carbamate functionality may occur, increasing the probability of *syn* attack. The electron withdrawing nature of the Boc protecting-group can also be considered; Mehta showed that electron withdrawing groups at the 2- and 3- positions of 7-norbornanones cause increased *syn* attack (Fig 4.50B).[140] This could similarly be the case in 7-keto-2-azanorbornanes.

The true underlying factors controlling the facial selectivity of 7-keto-2-azanorbornanes are likely to be no less complex than those influencing the selectivity of 2-norbornanones and warrant further investigation.

4.6 Pyridyl derivatives of 7-hydroxy-2-azabicyclo[2.2.1]heptane

With the *anti* and *syn* alcohols **86** and **158** in hand, routes to their pyridyl derivatives were explored. We wished to attach 2- 3- and 4- pyridines for reasons explained previously (see Section 4.2); the following sections describe the syntheses of these compounds.

4.6.1 Approaches to pyridyl derivatives of *anti*-7-hydroxy-2-azabicyclo[2.2.1]heptane

The 2-pyridyl derivative **173** was produced by nucleophilic displacement of chloride from 2-chloropyridine using KO^{t}Bu as base (65%). The 3-pyridyl compound **174** could not be accessed by a similar method. The 3-position of pyridines is not reactive with nucleophiles and predictably, when **86** is treated with 2-chloro-5-iodopyridine, displacement of chloride, rather than iodide occurs.

Hence, compound **174** was approached using Mitsunobu methodology; reaction of the alcohol **86** with 3-hydroxypyridine gave **174** (30%). The 4-pyridyl derivative **175** was made in an analogous fashion using 4-hydroxypyridine (29%). The debenzylations of **173**, **174** and **175** were effected by hydrogenolysis using palladium on carbon as catalyst. Reduction of the pyridine heterocycles is competitive with debenzylation, resulting in only modest yields for these transformations (and those in Sections 4.6.2.1 and 4.6.2.2).

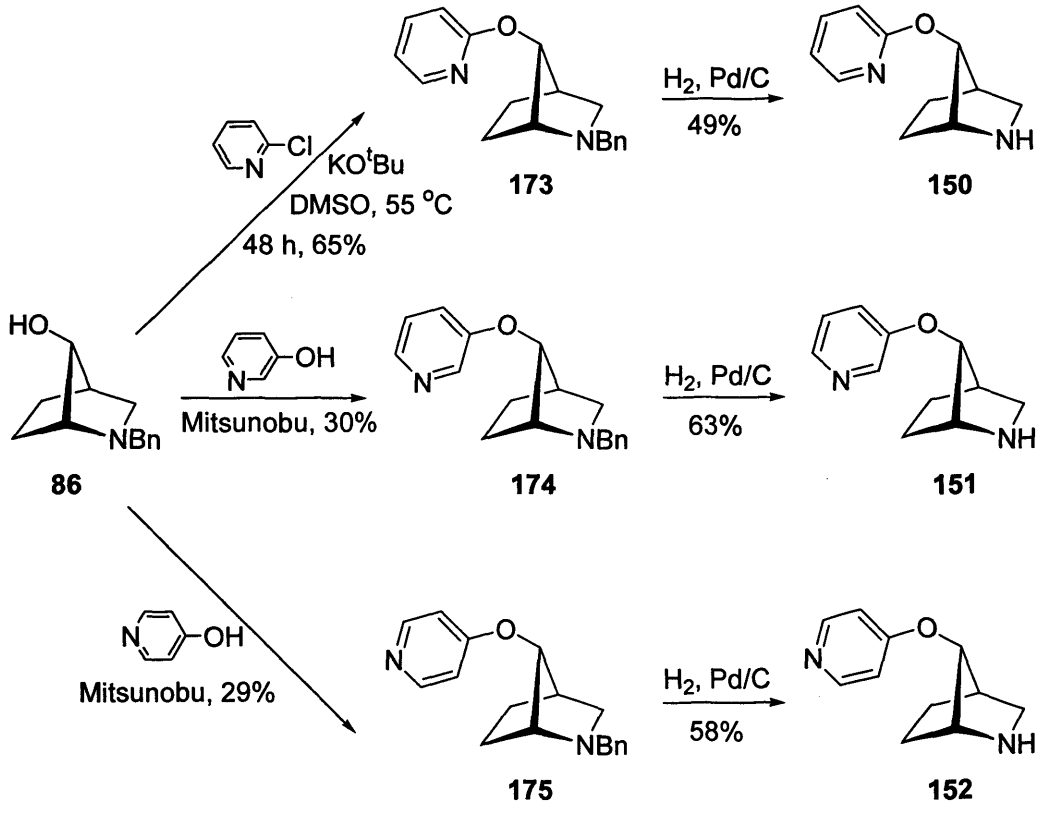


Fig. 4.60 The syntheses of pyridyl derivatives of *anti*-7-hydroxy-2-azabicyclo[2.2.1]heptane.

4.6.2 Approaches to pyridyl derivatives of *syn*-7-hydroxy-2-azabicyclo[2.2.1]heptane

The following discussion concerns the production of the *syn* pyridyl derivatives **153, 154** and **155**. This involved methodology similar to that employed for the synthesis of the *anti* compounds (above). However, certain changes were necessary in order to overcome problems associated with the *syn*-7- configuration.

4.6.2.1 2-Pyridyl and 4-pyridyl derivatives of *syn*-7-hydroxy-2-azabicyclo[2.2.1]heptane

The 2- and 4- pyridyl compounds **176** and **177** were produced by nucleophilic displacements of chloride from 2-chloropyridine and 4-chloropyridine hydrochloride respectively, in reasonable yields. Notably, the debenzylation of **177** went with excellent yield, in contrast to the moderate yields attained for the other ether-linked analogues.

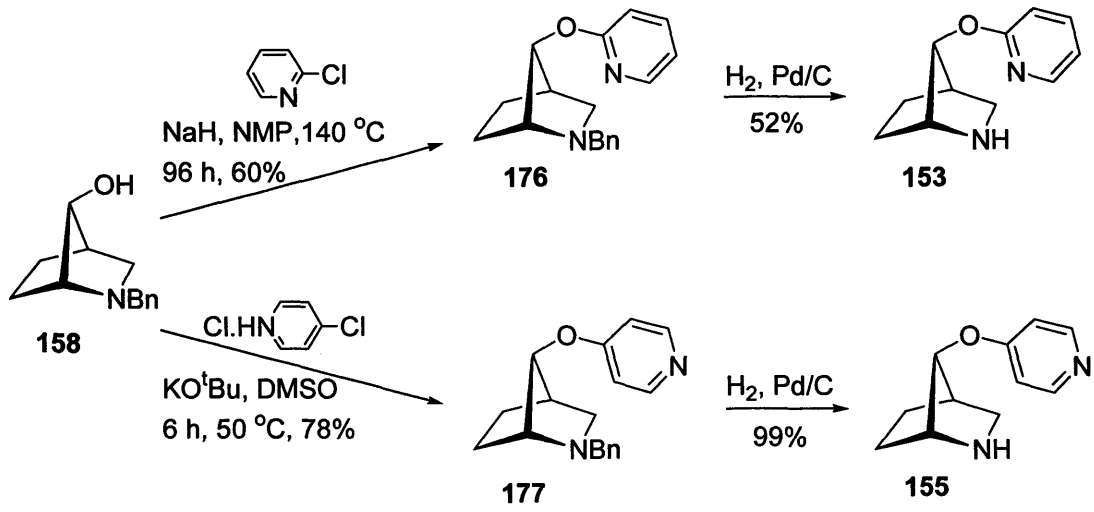


Fig. 4.61 Syntheses of 2-pyridyl and 4-pyridyl derivatives of *syn*-7-hydroxy-2-azabicyclo[2.2.1]heptane.

4.6.2.2 Routes to 3- pyridyl derivatives of *syn*-7-hydroxy-2-azabicyclo[2.2.1]heptane

Nucleophilic displacement is not easily achieved for the *anti*-3-pyridyl compound **174** so alternative routes were sought to the *syn* derivative **154**. The Mitsunobu procedure used earlier to produce **174** and **175** was implemented but was unsuccessful, giving only unreacted starting material. Indeed, attempts to couple 2-hydroxypyridine and 4-hydroxypyridine to the *syn*-alcohol (**158**) also failed. It is likely, therefore, that the Mitsunobu reactions of the *anti*-alcohol **86** are enabled by neighbouring group participation of the bicyclic nitrogen lone-pair (see Section 2.4.2).

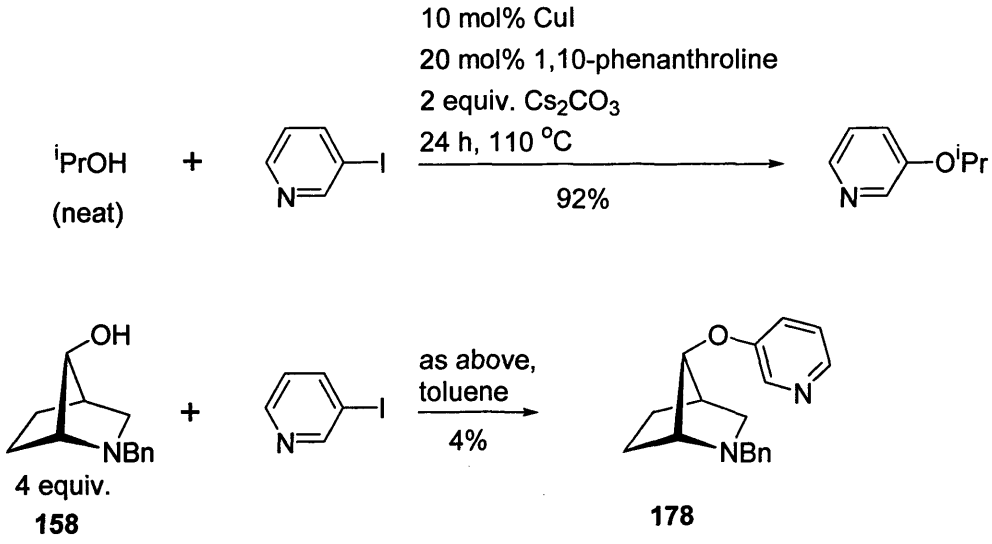


Fig. 4.62 A copper-catalysed pyridine coupling.[143]

A recent copper-catalysed coupling published by Buchwald and co-workers describes the coupling of aryl iodides to aliphatic alcohols.[143] One particular example from this work is the coupling of 3-iodopyridine to isopropyl alcohol (Fig. 4.62). Although the yield for this

reaction is excellent, the alcohol is used as the solvent. A procedure is described for when using the alcohol neat is not practical; it involves two equivalents of the alcohol and a small amount of toluene as the solvent (0.5 ml toluene/1 mmol of substrate).[143] This method was adapted for use with the *syn*-alcohol **158**: four equivalents of **158** were used and the reaction mixture was mobilised with the minimum volume of toluene (1 ml). After 96 hours at 110 °C **178** was obtained in only 4% yield and the excess alcohol (**158**) was not easily recovered.

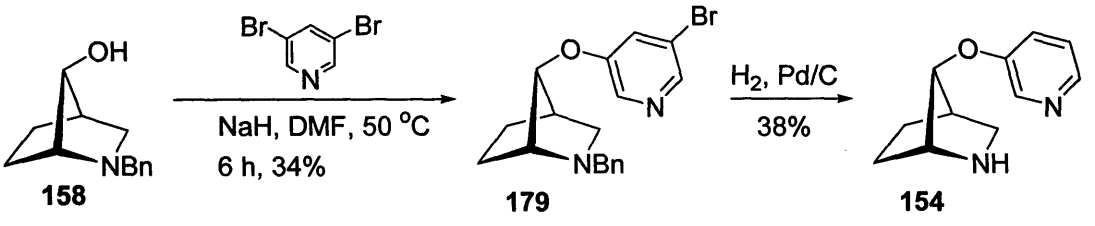


Fig. 4.63 The synthesis of the 3- pyridyl derivative of *syn*-7-hydroxy-2-azabicyclo[2.2.1]heptane (**154**).

Recent syntheses of receptor subtype selective nicotinic agents with 5'-substituted pyridine rings have involved nucleophilic attack of an alcohol on 3,5-dibromopyridine, allowing later elaboration at the 5'- position.[127] The presence of bromine atoms at the 3- and 5- positions of pyridine activates these positions sufficiently for nucleophilic displacement to occur. Hence, **158** was treated with sodium hydride and 3,5-dibromopyridine to give **179** (34%) (Fig. 4.63). Careful simultaneous removal of the benzyl protecting-group and the superfluous bromine substituent under hydrogenolytic conditions gave the elusive *syn*- 3-pyridyl derivative **154** (38%).

To summarise, an oxidation/reduction strategy facilitated the epimerisation of the *anti*-alcohol **86** to the *syn*-alcohol **158** and procedures have been developed to access their 2-, 3- and 4- pyridyl derivatives **150-155**. These six epibatidine/ABT-594 hybrids have been assessed for their nicotinic receptor binding affinities and preliminary results are discussed in Chapter 7.

4.7 Attempted synthesis of a conformationally restricted analogue of isoepibatidine

Conformationally restricted nicotinic ligands have been produced principally to probe the nicotinic pharmacophore and generally have low nicotinic receptor affinities compared to their parent structures.[27,29-32] Very recently, a restricted analogue of epibatidine has been discovered on the skin of *Epipedobates tricolor* by Daly and co-workers; the frog is also known as the Phantasmal poison-arrow frog and the new compound has been dubbed 'phantasmidine'. Only a partial structure of phantasmidine has been published (**180**) but the remainder of the molecule resembles epibatidine.[11] In view of the active conformation of

epibatidine, the probable structures of phantasmidine are **181** and **182**. The ether-linkage rigidifies the compound and results in a fixed inter-nitrogen distance (Fig. 4.70).

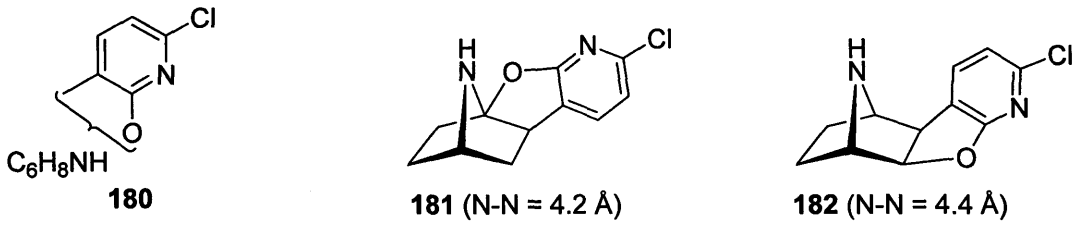


Fig. 4.70 Probable structures of phantasmidine.

We considered the possibility of producing isomers of phantasmidine; routes were sought towards the conformationally restricted isoepibatidine analogue **183**. Structure **183** has an N-N distance of 4.1 Å and is an attractive target in terms of potential nicotinic activity. The successful synthesis of this 'isophantasmidine' would also add to our understanding of the nicotinic pharmacophore.

The strategy implemented to access **183** is outlined in Fig. 4.71 and involved the coupling of a hydroxy pyridine to **184** followed by oxidation of the amine to an imine. It was hoped that the hydroxyl group would attack the imine resulting in ring closure. Before trying to couple a pyridyl derivative to **184**, attempts to couple 2-hydroxy benzene boronic acid (**185**) were made. The Suzuki methodology used to access isoepibatidine (Chapter 3) was unsuccessful; only unreacted starting material was obtained. Coupling of the Boc-protected boronic acid (**186**) also failed.

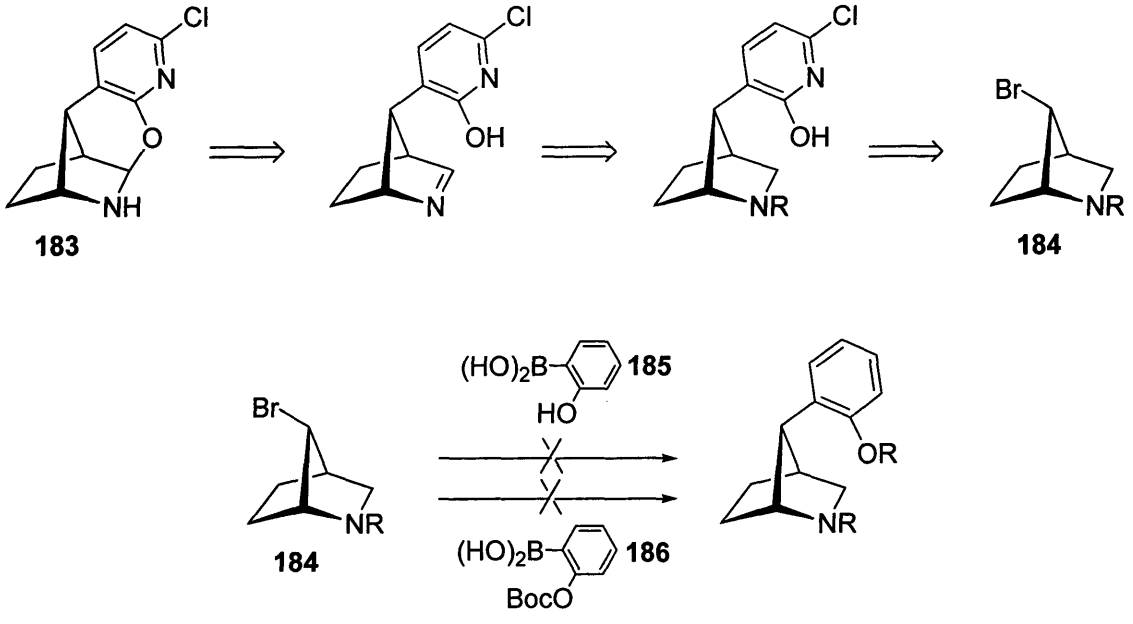


Fig. 4.71 The synthetic strategy towards an isophantasmidine. Suzuki-coupling conditions as in Fig. 3.30.

Although these attempts to produce isophantasmidines were unsuccessful, it is likely that the publication of the structure and biological properties of phantasmidine will renew interest in the synthesis of rigid molecules as potent nicotinic agonists.

Chapter 5

Fluorinated analogues of epibatidine

5.1 Introduction

As the most electronegative element, fluorine has unique chemical properties and is present in a large proportion of currently used drugs.[144] The incorporation of fluorine atoms into molecules can lead to profound changes to their biological properties.[145,146] Fluorination affects the lifetime of a drug; positioning fluorine atoms at metabolically labile sites of a molecule increases its metabolic stability by retarding oxidation by enzymes such as cytochrome P450.[145] The presence of fluorine also increases the lipophilicity of a compound which contributes to the bio-availability of a drug by influencing its ability to penetrate cell membranes.[146] This is particularly relevant in the context of this study as CNS-acting compounds must pass the blood-brain barrier. Fluorination can also affect how a molecule interacts with the target protein; the substitution of fluorine for hydrogen has little steric effect (Van der Waals radii: F = 1.35 Å; H = 1.20 Å) but often has a profound influence on the binding of a ligand with its target. The general increase in lipophilicity resulting from fluorine substitution often gives rise to a non-specific increase in affinity. More importantly, the electronegative nature of fluorine can significantly alter the pK_a of other functionalities, in particular by altering the acidity and basicity of groups within the molecule. This often results in changes to ligand-protein interactions and also influences bioavailability by altering the polarity of the molecule. In addition, fluorine is also able to form polar interactions in protein binding-sites (*e.g.* to a carbonyl oxygen).[146]

5.2 Fluorinated analogues of epibatidine

A range of epibatidine analogues containing fluorinated heterocycles has been produced, particularly for use in Positron Emission Tomography (PET) (see Section 1.5.1)[147] but examples of analogues with fluorinated azabicycles are fewer in number.

The work of Kozikowski and co-workers, in which hydroxylated epibatidines have been produced, was discussed in Section 1.5.5;[80] these studies have been extended to give the fluorinated compounds **196** and **197** (Fig. 5.20).[81] Fluorination of the azabicyclic core of epibatidine can be considered to be more synthetically challenging than introducing fluorinated heterocycles and, to the best of our knowledge, these are the only examples in the literature of epibatidine analogues with fluorinated azabicycles. Kozikowski's syntheses of **196** and **197** are outlined in Fig. 5.20. Reductive Heck coupling of the chloropyridyl moiety to **198** gave **199** and **200**; subsequent conversion to the corresponding alcohols with $NaBH_4$, treatment with DAST and de-protection of the bicyclic nitrogen with TFA yielded the fluorinated epibatidines **196** and **197**.[80,81]

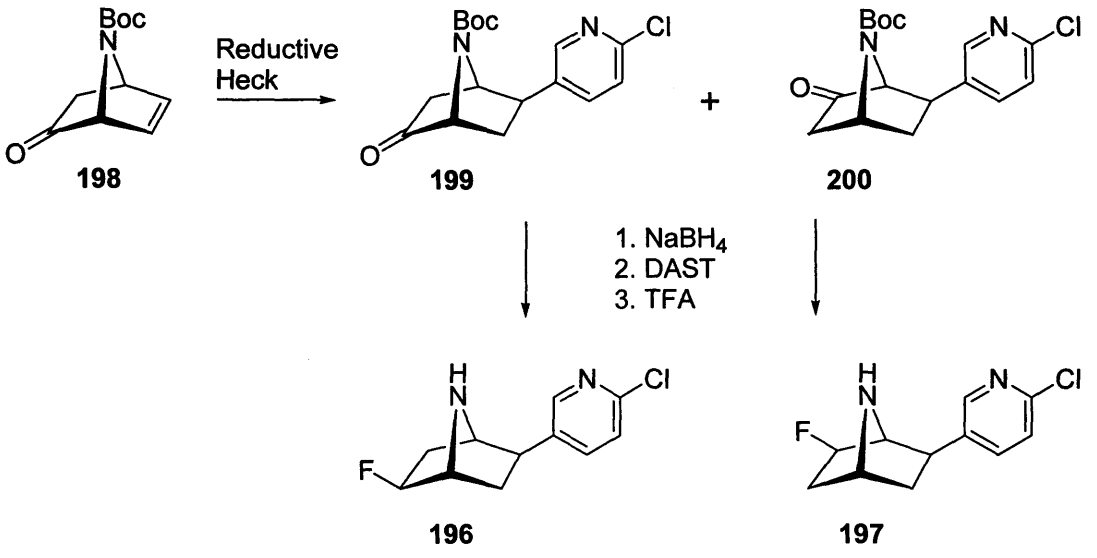


Fig. 5.20 The synthesis of fluorinated analogues of epibatidine.[80,81]

Nicotinic receptor affinity studies of **196** and **197** at a range of receptor subtypes indicated binding affinities lower than those of epibatidine but still in the low nM range ($K_i \approx 0.2$–10 nM; epibatidine $K_i \approx 0.03$–0.2 nM). The *exo*-6-fluoro derivative **197** showed higher affinities at all subtypes compared to **196**; both **196** and **197** showed similar selectivity profiles to epibatidine. Both compounds are currently being explored in brain imaging (PET) studies.[81]

The relative lack of fluorinated-azabicyclic epibatidine analogues in the literature, the demonstration (above) by Kozikowski that fluorinated epibatidines can retain nicotinic receptor affinity, and the hope of achieving receptor sub-type selectivity, led us to the investigation of the synthesis of fluorinated 2-azanorbornanes.

5.3 Fluorinated 2-azabicyclo[2.2.1]heptanes

The only known examples of directly-fluorinated 2-azanorbornanes were produced in the following study by Toyota *et al.*.[148,149] Molecular fluorine was added to 2-azabicyclo[2.2.1]hept-5-en-ones as part of a program to produce fluorinated carbocyclic nucleosides. Fluorination of **201** gave the *exo*-5,6-difluoro compound **202** as the major product as well as the minor products **203**, **204** and **205** (Fig. 5.30). The authors suggest that the trifluoride **205** is formed from the rearranged product **204**.[148,149]

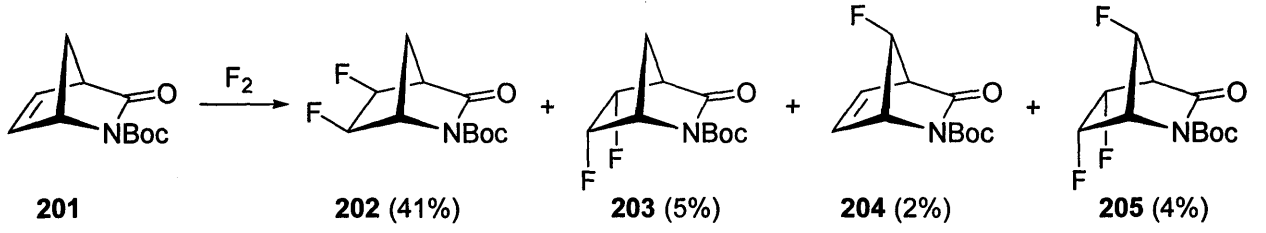


Fig. 5.30 The fluorination of the 2-azabicyclo[2.2.1]hept-5-en-one (**201**).[148,149]

We wished to devise methods for the controlled introduction of fluorine atoms to the 2-azanorbornane framework. There are two basic strategies to produce organofluorine molecules, the building-block method and the fluorination method (of which the work of Toyota *et al.* (Fig. 5.30) is an example).[150] The building block method was considered for fluorinated 2-azanorbornanes. An aza-Diels-Alder approach similar to that described in Chapter 2 would require fluorinated cyclopentadiene and/or a fluorinated dienophile (Fig. 5.31). Difluoromethanimine (**206**) can be produced by hydrolysing **207** with wet triethylamine but it is unstable and must be handled at pressures below 5 mmHg;[151] hence, attempts to synthesise this compound and react it with cyclopentadiene were not made. There are reports of highly fluorinated cyclopentadienes[152] but examples of monofluorinated derivatives are fewer in number.[153-155] 5-Fluorinated cyclopentadiene (**208**) has been prepared by treating cyclopentadienylthallium (**209**) with selectfluor (**210**) and can be trapped by certain dienophiles to give substituted norbornenes (*e.g.* **211**) in low yields (Fig. 5.31). All the norbornanes produced by this method had fluorine at the *syn*-7-position.[153] This method was not developed for the synthesis of 2-azanorbornanes (*e.g.* **212**).

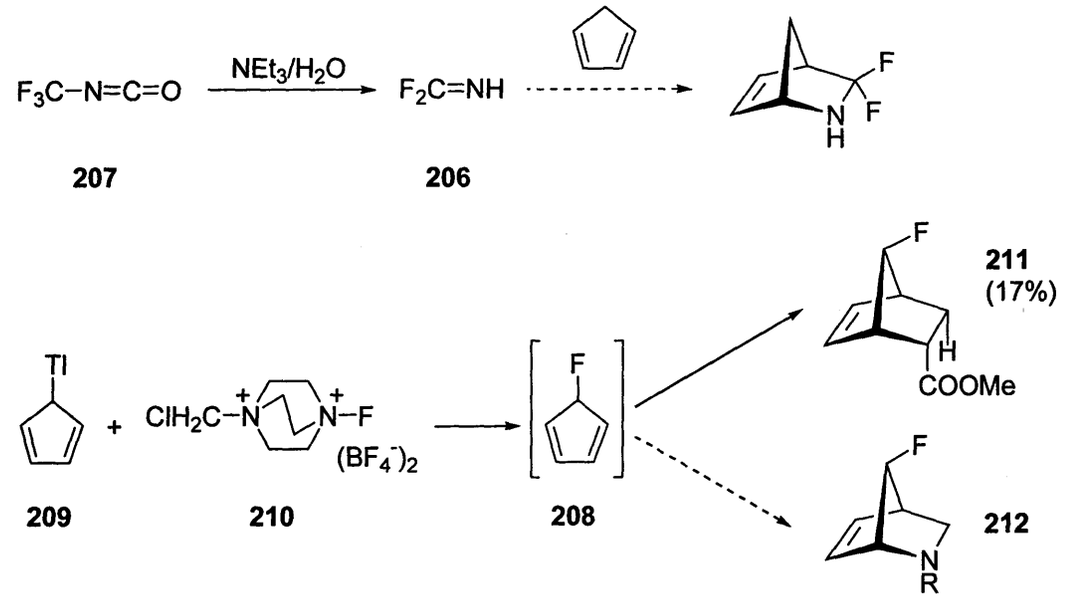


Fig. 5.31 Literature syntheses of difluoromethanimine and 5-fluorocyclopentadiene. Potential building-block routes to fluorinated 2-azanorbornanes.[151,153]

Whilst it would be possible to investigate these building-block approaches, it was decided that using fluorination methods would allow greater control and access to a larger range of fluorinated 2-azanorbornanes. The remainder of this Chapter concerns investigations into the incorporation of fluorine at various positions of the 2-azanorbornane framework.

5.4 6-*exo* Fluorinated analogues of isoepibatidine

Fluorinated epibatidine analogues with an *exo*-6-fluoro moiety (the fluorinated isoepibatidine **213** in particular) were targeted. It was envisaged that fluoride could be incorporated at the 6-position by treating the tricyclic salt **61** with fluoride; following the route to isoepibatidine described in Chapter 3 would give **213** via **214** (Fig. 5.40).

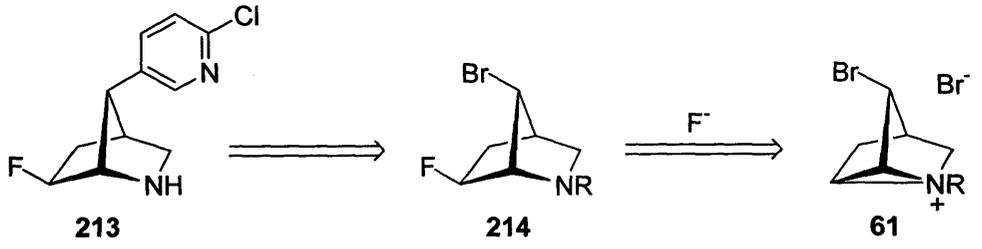


Fig. 5.40 Retrosynthesis of *exo*-6-fluoro-isoepibatidine.

5.4.1 Synthesis of *exo*-6-fluoro-2-azabicyclo[2.2.1]heptanes

In Chapter 2 it was described how the tricyclic salt **74** could be intercepted with hydride; in order to access *exo*-6-fluoro-2-azanorbornanes similar interception of **74** with fluoride was implemented. Reaction of **74** with potassium fluoride in acetonitrile gave **215** in good yield (84%). The *exo*- configuration of the 6-fluorine was confirmed by detailed NMR analysis. Most notably, 2D COSY experiments indicated 'W' coupling between H_{6endo} and H_{7anti} (~1.3 Hz).

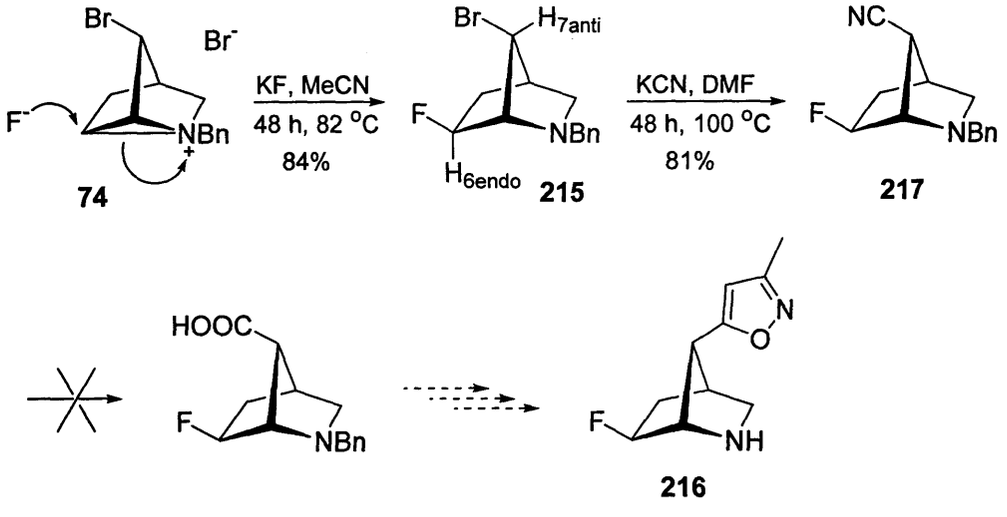


Fig. 5.41 Reaction of KF with 3-bromo-1-benzyl-1-azoniatricyclo[2.2.1.$0^{2,6}$]heptane bromide (**74**) and the attempted synthesis of *exo*-6-fluoro-*syn*-isoepiboxidine (**216**).

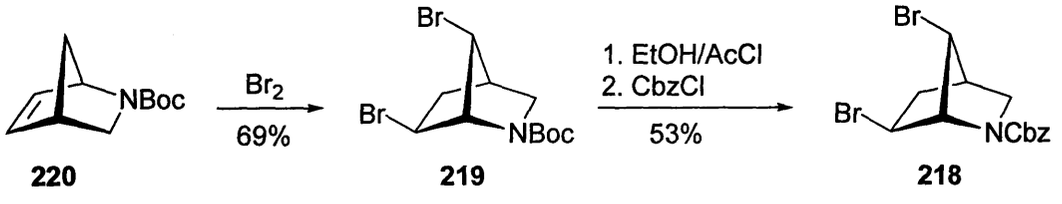
Before attempting Suzuki coupling-reactions, that is, the production of the fluorinated isoepibatidine **213**, the synthesis of the fluorinated isoepiboxidine **216** was considered. We wished to follow a synthetic route analogous to that described in Chapter 2. Nucleophilic substitution of the 7-bromine in **215** with potassium cyanide proceeded smoothly (81%).

Despite neighbouring group participation of the bicyclic nitrogen with nucleofuges at C6 being a lower energy process than participation at C7, **217** was the only product isolated: no displacement of the C6 fluorine was observed.

However, hydrolysis of the nitrile **217** was unsuccessful; when **217** was treated with either HCl or NaOH only unidentifiable mixtures of products were obtained. It was clear, from ^{19}F NMR, that displacement of fluoride was occurring under the reaction conditions. The protecting-group of **217** was changed to Boc (47% overall) but base-catalysed hydrolysis and esterification of this compound was also unsuccessful. Due to these problems, and as increased attention was attached to the chloropyridyl heterocycle, attention was shifted away from the synthesis of **216** and towards the original target, namely the fluorinated isoepibatidine **213**.

5.4.2 Substitution reactions of dibromo-2-Cbz-2-azabicyclo[2.2.1]heptane

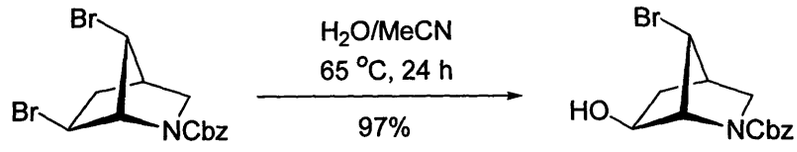
Although opening the three-membered ring of **74** with fluoride allowed the *exo*-6-fluoro compound **215** to be accessed, attempts to introduce nucleophiles to the 6-position of the Cbz-protected dibromide **218** were also made. Initial results[156] regarding the nucleophilic substitution reactions of the Cbz-protected compound **218** were alluded to in the publication of the synthesis of the isoepiboxidines; it was reported that displacement of the 6-Br in **218** could not be achieved.[61] More recently, Krow and co-workers have observed that certain analogous substitution reactions of the Boc-protected dibromide **219** do occur.[157,158] Hence, verification of our initial results was sought.



220 **219** **218**

Fig. 5.42 Synthesis of *anti*-7-*exo*-6-dibromo-2-azabicyclo[2.2.1]heptane 2-carboxylic acid benzyl ester (**218**).

The Cbz-protected dibromide **218** was synthesised as follows (Fig. 5.42). *N*-Boc-2-azanorbornene (**220**) was prepared using a known procedure involving an aza-Diels-Alder reaction, analogous to that described in Chapter 2, followed by protection of the bicyclic nitrogen with Boc (22% overall).[104,159] Bromination of **220** gave **219**, which was deprotected and reprotected with Cbz yielding **218** (Fig 5.42). More usually, **218** might be prepared from *N*-Cbz-2-azanorborn-5-ene[156] but a copious quantity of the Boc-protected alkene precursor **220** was available.



218 **221**

Fig. 5.43 Synthesis of *anti*-7-bromo-*exo*-6-hydroxy-2-Boc-2-azabicyclo[2.2.1]heptane (**221**). Reactions of **221** with other nucleophiles (CN^-, N_3^- and F^-) were unsuccessful.

The substitution reactions of the Cbz-protected dibromide **218** were investigated. The carbamate nitrogen participates in additions to *N*-alkoxycarbonyl-2-azanorborn-5-enes.[115] Hence, it was hoped that the bicyclic nitrogen of **218** would assist the loss of the *exo*-6-bromine resulting in nucleophilic substitution with retention of configuration. Treatment of **218** with a 1:1 mixture of water and acetonitrile at 65 °C gave the hydroxylated product **221** (97%) (Fig. 5.43); the analogous reaction of the Boc-protected dibromide **219** also occurs but at room temperature.[158] Further substitution reactions on **218** were attempted but disappointingly, and perhaps surprisingly, were unsuccessful. Treatment of **218** with sodium azide, fluoride and cyanide failed to give the corresponding substituted products in either acetonitrile or DMF. Decomposition occurred prior to any substitution and there was an indication that degradation of the starting material occurred more readily in the presence of NaN_3 compared to NaCN or NaF (60-100 °C compared to 160 °C). Therefore, the substitution reactions of **218** and **219** can not yet be generalised or rationalised and are receiving further attention.[157,158]

5.4.3 Coupling reactions of *exo*-6-fluoro-*anti*-7-bromo-2-azabicyclo[2.2.1]heptanes

The Suzuki coupling procedure described in Chapter 3 was implemented to access the fluorinated isoepibatidine **213**. In order to minimise the number of steps in the synthetic scheme to **213** attempts were made to couple benzene and pyridyl boronic acids to the *N*-benzyl-protected precursor **215** (Fig. 5.44). However, these reactions gave only unreacted starting material and unidentifiable compounds; it was evident from NMR analysis of the crude reaction mixtures that no incorporation of the boronic acids was taking place. Although a degree of functional-group tolerance for this Suzuki protocol was demonstrated in Chapter 3, this clearly does not extend to tolerance of the tertiary amine in **215**. Hence, the benzyl group of **215** was removed and replaced with Boc to give **222** (28% overall). The coupling reactions of **222** with benzene, pyridyl and chloropyridyl boronic acids were more successful; results

similar to those described for the non-fluorinated compounds (Fig. 3.30, Chapter 3) were observed (Fig. 5.44).

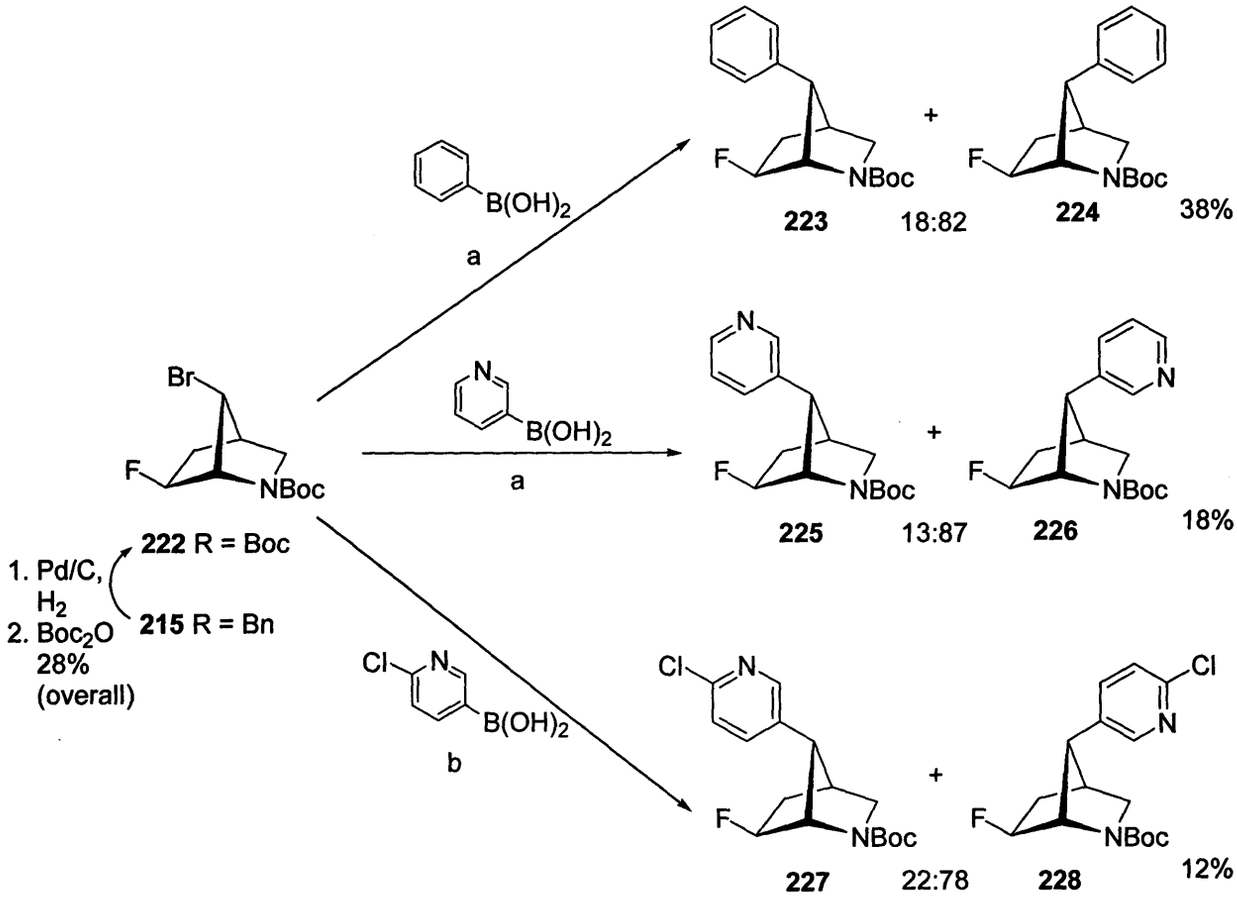
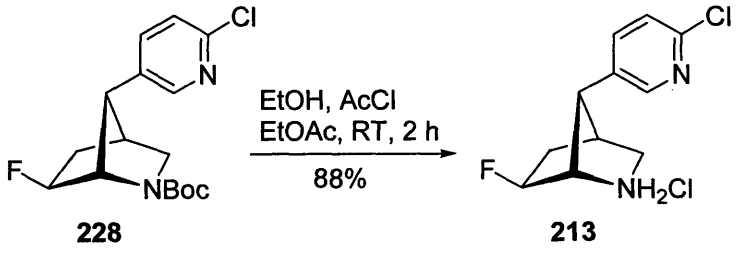


Fig. 5.44 The Suzuki coupling reactions of *anti*-7-bromo-*exo*-6-fluoro-2-Boc-2-azabicyclo[2.2.1]heptane (**222**). Conditions: $Ni(cod)_2$, bathophenanthroline, ^tBuOK, *s*-butanol, a: 100 °C, 48 h; b: 40 °C 24 h.[123]

The same conditions described in Fig 3.30 were used: refluxing conditions for the coupling of benzene and pyridyl boronic acids and 40 °C for the chloropyridyl boronic acid to avoid solvolysis (see Fig. 3.31). Again, mixtures of *anti* and *syn* epimers were formed but the presence of the *exo*-6-fluorine shifted the epimer ratios in favour of the *syn* compounds (**224, 226** and **228**); epimer ratios were determined by integration of NMR signals, particularly ^{19}F. The yields for the coupling reactions are significantly reduced in comparison to the non-fluorinated series of reactions (*cf.* Fig. 3.30). It seems apparent that, as alluded to by Zhou and Fu,[123] their coupling procedure, whilst being ground-breaking in terms of the couplings that can be achieved, has limited functional-group tolerance. Additionally, it was shown in Fig. 5.41 that the *exo*-6-fluorine was unstable to acidic and basic conditions. Hence, the presence of ^tBuOK in the coupling reactions was potentially also a factor contributing to their low yields (Fig. 5.44).

The minor (*anti*) epimers (**223**, **225** and **227**) could not be isolated pure but this was deemed to be of minor importance due to the greater significance attached to the *syn* derivatives. The C7 stereochemistry of the major products from the coupling reactions was determined by NOESY NMR analysis as described in Section 3.3; most notably, cross-peaks were observed between H_7 and H_{5exo}.

The Boc-protected compound **228** was deprotected with a non-aqueous source of HCl (Fig. 5.45) to give the target compound **213**, which was isolated and characterised as its hydrochloride salt (see Section 5.5).



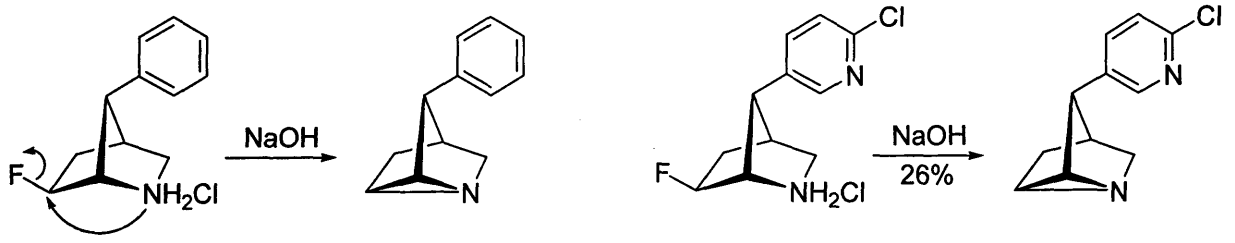
228 **213**

Fig. 5.45 Synthesis of *exo*-6-fluoro-*syn*-isoepibatidine (**213**).

The nicotinic receptor binding-affinity of *exo*-6-fluoro-isoepibatidine (**213**) has been assessed and is discussed in Chapter 7.

5.5 3-Substituted 1-azatricyclo[2.2.1.$0^{2,6}$]heptanes

The fluorinated compound **213** is stable as its hydrochloride salt but on treatment with base was found to lose HF to give the tricyclic compound **229** (Fig.5.50). This transformation was originally observed serendipitously when attempts were made to basify the hydrochloride salt of the phenyl derivative **230**; the only product isolated was the tricyclic compound **231**. A more controlled reaction of the chloropyridyl derivative **213** with sodium hydroxide gave **229** (26%).



230 **231** **213** **229**

Fig. 5.50 Formation of 3-substituted 1-azatricyclo[2.2.1.$0^{2,6}$]heptanes.

There are a limited number of literature examples of 3-substituted 1-azatricyclo[2.2.1.$0^{2,6}$]heptanes (Fig. 5.51). Raasch demonstrated that bromination of the azanorbornene **232** followed by treatment of the resulting dibromide **233** with tertiary butoxide gave the tricyclic product **234**, in an analogous fashion to the transformation of **213** to **229** (Fig. 5.50).[96] This work was extended by Nagaev *et al.* who achieved the transformation of **232** to **234** directly using a source of Br^+ (the use of Cl^+ or I^+ gave the corresponding chloro and iodo derivatives respectively). It was also shown that **234** could be ring-opened by a range of nucleophiles in the presence of H_2SO_4 (*e.g.* **234** to **235**).[160] Malpass and co-workers at Leicester described an alternative route to a 3-substituted 1-azatricyclo[2.2.1.$0^{2,6}$]heptane which involved skeletal rearrangements due to π-participation in the loss of nucleofuges from the bicyclic nitrogen atom (Fig. 5.51). Exposure of the *N*-chloro derivative **236** to alumina caused rearrangement to give **237** which rearranged further when treated with MeOH and $AgNO_3$ yielding the tricyclic compound **238**.[161]

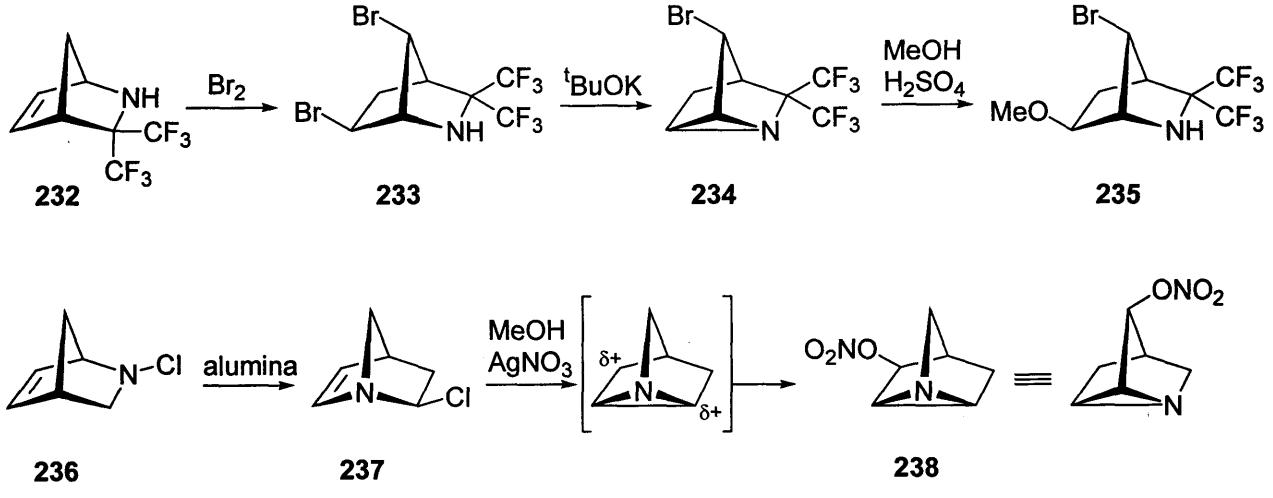


Fig. 5.51 Literature examples of 3-substituted 1-azatricyclo[2.2.1.$0^{2,6}$]heptanes.[96,160,161]

The presence of these 3-substituted 1-azatricyclo[2.2.1.$0^{2,6}$]heptanes in the literature and careful NMR analysis enabled the structural assignment of **229** and **231**. The ^{1}H NMR spectrum of **229** is shown in Fig 5.52.

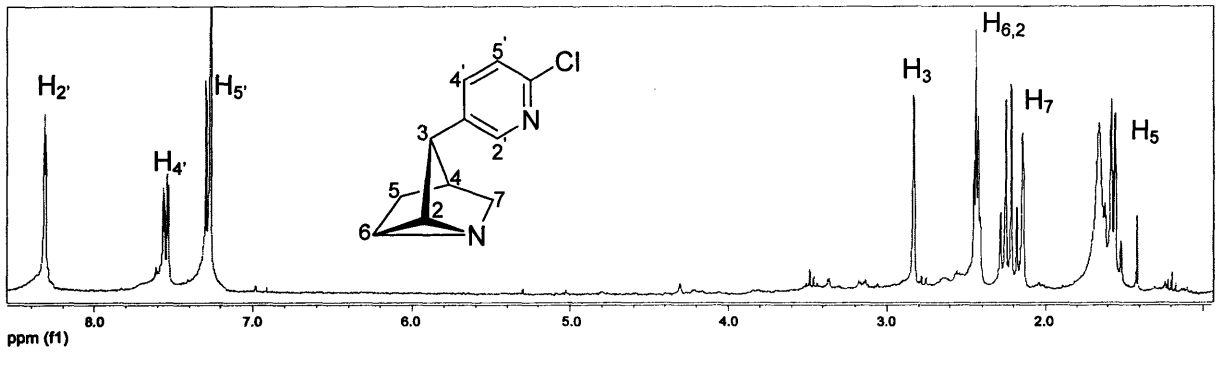
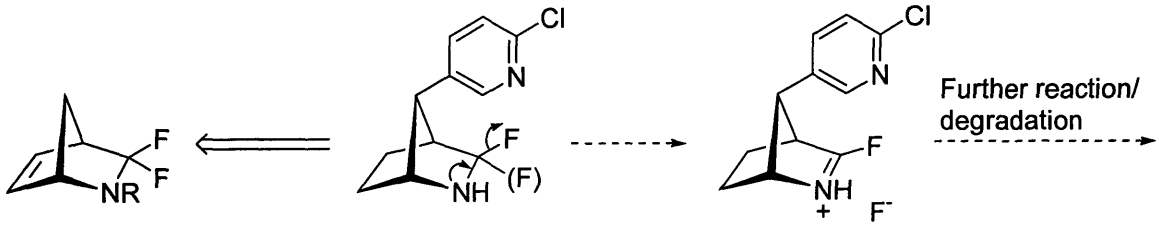


Fig. 5.52 ^{1}H NMR spectrum of *syn*-3-(6-Chloro-pyridin-3-yl)-1-azatricyclo[2.2.1.$0^{2,6}$]heptane (**229**).

The tricyclic epibatidine analogue **229** has not been assessed for its nicotinic receptor affinity but it will be interesting to investigate the effect on receptor binding of substituting a tertiary for a secondary amine. Particularly as in **229** only minor changes to the relative orientations of the pharmacophoric elements of isoepibatidine have been made. Additionally, the aziridine functionality of **229** has the potential to be opened within the binding site, resulting in irreversible binding and thus could show value in the labelling of nicotinic receptors.

5.6 Attempted routes to 3-Fluorinated 2-azabicyclo[2.2.1]heptanes

3-Fluorinated 2-azabicyclo[2.2.1]heptanes were targeted, in particular, 3-fluoro-isoepibatidines (e.g. **239**). Positioning fluorine atoms at the 3-position of the 2-azanorbornane framework is likely to result in a pronounced reduction of the basicity of the bicyclic nitrogen-atom and hence, to have a profound effect on nicotinic-receptor binding. We had concerns about the stability of 3-fluorinated 2-azanorbornanes since there are few literature examples of α-fluoroamines and those that have been produced are typically used as fluorinating agents.[162] If compounds such as **239** could be produced there is a distinct possibility that loss of fluoride could occur, leading to intermediates such as **240** and subsequent degradation (Fig. 5.60). Indeed, α,α-difluoroamines (*e.g.* **239**) are considered to exist predominantly in their eliminated forms (*e.g.* **240**).[163] It was hoped that careful protecting-group manipulation and handling the final products (secondary amines) as salts would avoid this problem.



239 **240**

Fig. 5.60 3-Fluoro-isoepibatidine and its potential route of degradation.

2-Azabicyclo[2.2.1]hept-5-en-3-one (**241**) is commercially available and was chosen as the starting point in the quest for 3-fluorinated 2-azanorbornanes (Fig. 5.61). Benzylation of **241** gave the tertiary amide **242** in modest yield. There are very few examples in the literature involving the conversion of the carbonyl of amides to *gem*-difluorides. However, a recent patent describes how this transformation can be effected in a range of different amides; a representative example is shown in Fig. 5.61. Treatment of the lactam **243** with oxalyl chloride gives the *gem*-dichloride **244** which is converted to the *gem*-difluoride **245** using

sodium fluoride.[162] The same methodology was applied to **242** but with no success, neither the difluoride **246** or the corresponding dichloride precursor were isolable; only starting material (**241**) (~ 2% recovery) and an unidentifiable mixture of decomposition products was obtained.

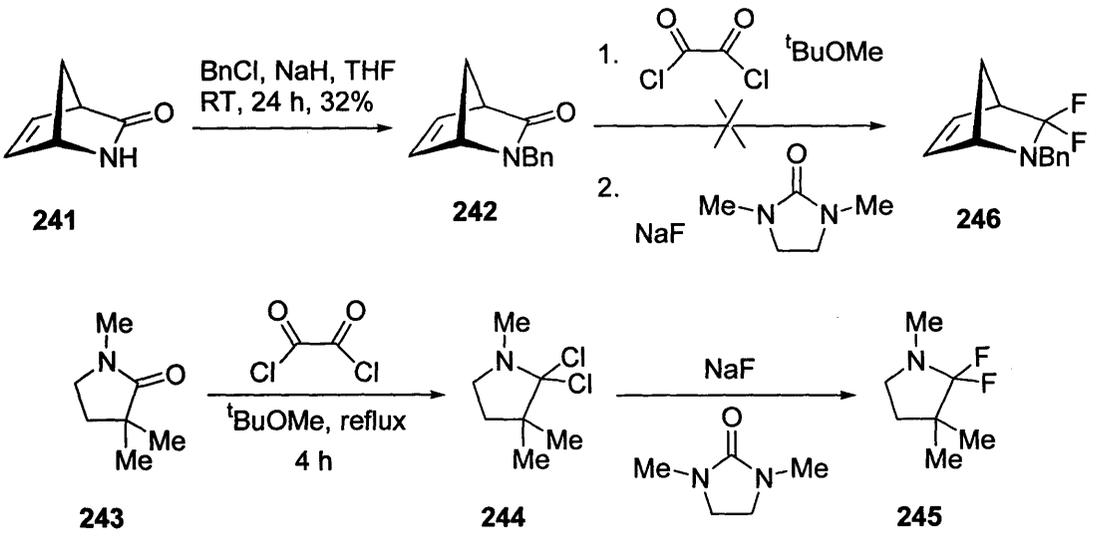


Fig. 5.61 A representative example from a patent which describes methodology for the conversion of amides to α-fluoroamines.[162] The attempted conversion of 2-benzyl-2-azabicyclo[2.2.1]hept-5-en-3-one (**242**) to the corresponding *gem*-difluoride (**246**).

Following the failure of the route via the *gem*-dichloride other approaches were considered and a ring opening/closing strategy was envisioned. Hence, **242** was treated with $LiAlH_4$ to give the ring opened alcohol **247** (Fig. 5.62). Attempts were made to oxidise **247** to **248** with the Swern reaction and Dess-Martin periodinane but they appeared to cause decomposition only. It had been hoped that treatment of the aldehyde **248** with DAST would give the *gem*-difluoride **249** which could then be reacted with base to produce the ring-closed 2-azanorbornane **250**.

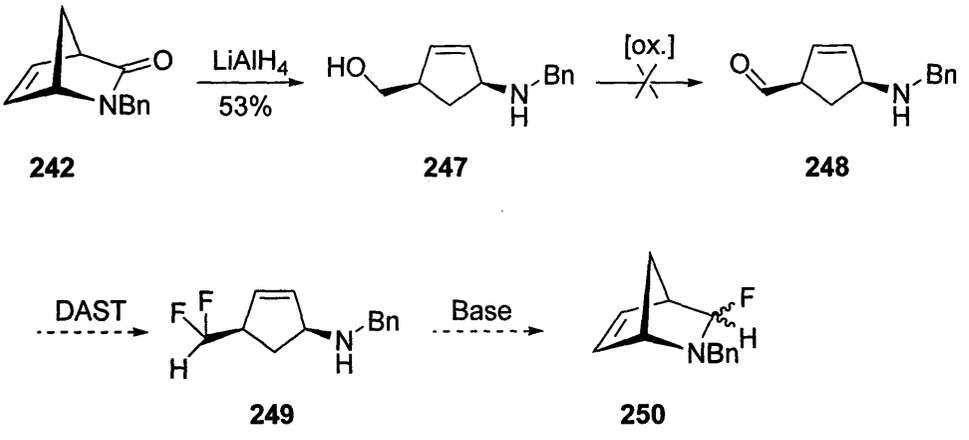
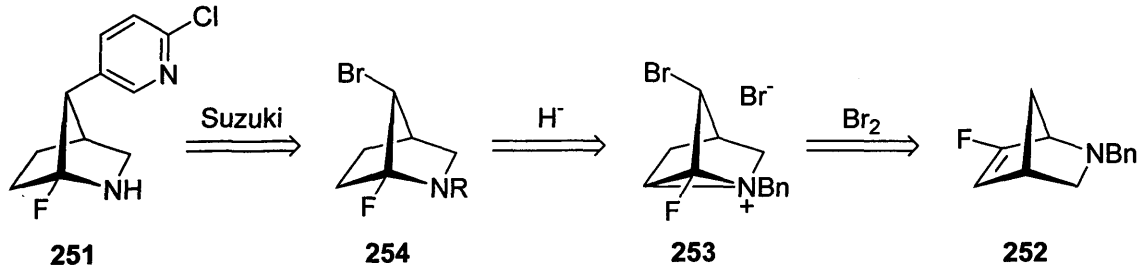


Fig. 5.62 The attempted incorporation of fluorine at the 3-position of 2-azanorbornanes via a ring opening/closing strategy.

The difficulties experienced in producing 3-fluorinated 2-azanorbornanes, their anticipated instability and the potential for overly-convoluted synthetic routes led to the suspension of these endeavours. Thus, attention was shifted to more fruitful areas.

5.7 Routes to 1-substituted 2-azabicyclo[2.2.1]heptanes

The incorporation of fluorine at the bridgehead position (C1) of 2-azanorbornanes was investigated next. There are very few examples of 1-substituted 2-azanorbornanes in the literature; it is not straightforward to access this class of compound and devising methods of incorporating groups at the bridgehead position is an attractive challenge. In particular, the 1-fluorinated isoepibatidine **251** was targeted; again, the close proximity of the fluorine atom to the bicyclic nitrogen was expected to have a significant effect on its pK_a.



251 **254** **253** **252**

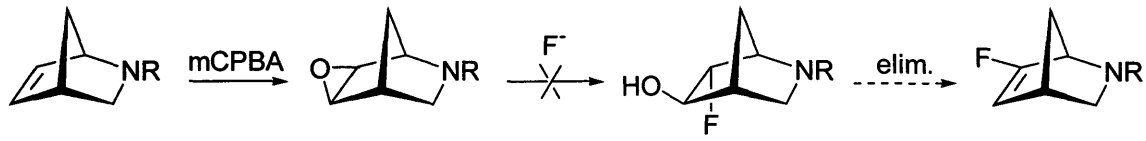
Fig. 5.70 The proposed route to 1-fluoro-isoepibatidine.

The retrosynthesis of **251** is outlined in Fig. 5.70; a synthetic scheme analogous to that described in Chapters 2 and 3 for isoepibatidine was envisioned. Bromination of the fluoroalkene **252** would give the tricyclic salt **253** which could be opened with hydride and the resulting 7-bromo-1-fluoro-2-azanorbornane **254** would then be subjected to a Suzuki cross-coupling reaction yielding 1-fluoro-isoepibatidine **251**. Hence, attempts were made to produce the fluoroalkene precursor **252**.

5.7.1 Attempted routes to 6-fluoro-2-azabicyclo[2.2.1]hept-5-enes

Efforts were made to produce the fluoroalkene **252** via an epoxide (Fig. 5.71). The *N*-Boc-protected alkene **220** was made using a known procedure which involved an aza-Diels-Alder reaction to give 2-azanorbornene which was treated with Boc_2O (22% overall).[159] Reaction of **220** with mCPBA gave the epoxide **255a** (56%); only *exo* attack occurs giving the *exo* epoxide exclusively. The *N*-Cbz-protected epoxide **255b** had been made previously at Leicester by C. D. Cox[159] and a sample was available. The *N*-benzyl-protected epoxide was not produced as mCPBA is known to react with the bicyclic nitrogen lone-pair of 2-

azanorbornanes to give *N*-oxides, which can undergo Meisenheimer rearrangements and Cope eliminations.[164]



220 R = Boc, R = Cbz | **255a**, **255b** | **256a**, **256b** | **257a**, **257b**

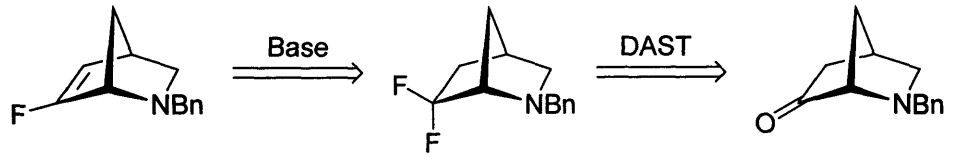
Fig. 5.71 The attempted synthesis of fluoroalkenes.

It was hoped that the epoxides **255a** and **255b** could be opened with fluoride to give the fluoro-alcohols **256a** and **256b** from which water could be eliminated to give the fluoroalkenes **257a** and **257b**. However, all attempts to open the epoxides were unsuccessful. Literature examples of opening epoxides with fluoride include the use of $BF_3.Et_2O$[165,166] and TBAF.[167] Treatment of **255a** and **255b** with $BF_3.Et_2O$ or $BF_3.Et_2O$ in the presence of KF using either toluene or diethyl ether as the solvent caused decomposition; starting material was the only identifiable product (~5% recovery). When **255b** was refluxed with TBAF in benzene or heated to 110 °C in the presence of potassium fluoride and 18-crown-6 only starting material was observed. Olah's reagent (HF-pyridine) was also unsuccessful, giving decomposition and no identifiable products.

Previous attempts at Leicester to open the epoxide **255b** with cyanide were also unsuccessful.[115] It is likely that the lack of success in opening the epoxides **255a** and **255b** is due to the unwillingness of 2-azanorbornane derivatives to undergo reactions at their *endo* face. In addition, literature examples suggest that the opening of epoxides with fluoride requires relatively harsh conditions (*e.g.* HF or refluxing $BF_3.Et_2O$).[165,166] An alternative route to the fluoroalkene **252** was therefore sought.

5.7.2 Rearrangement reactions of 6-keto-2-azabicyclo[2.2.1]heptanes

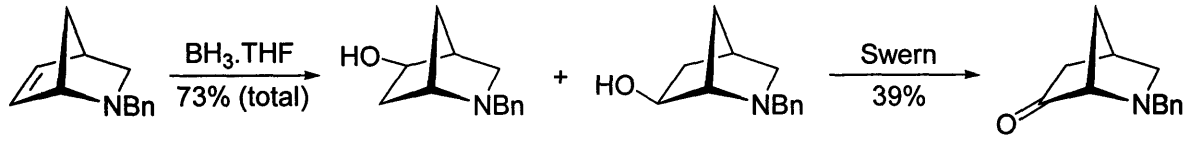
As the synthetic route to the fluoroalkene **252** outlined in Fig. 5.71 was unsuccessful an alternative strategy was devised. It was hoped that **252** could be produced by base-induced elimination of HF from the geminal-difluoride **258** which, in turn, would be accessed by treating the ketone **259** with DAST (Fig. 5.72).



252 **258** **259**

Fig. 5.72 The proposed route to 6-fluoro-2-benzyl-2-azabicyclo[2.2.1]hept-2-ene (**252**) from the ketone **259**.

Carroll and co-workers described the synthesis of **259**;[168] this existing procedure was followed. Hydroboration of 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene (**73**) gave the *exo*-5- and 6- alcohols **260** and **261** in a ratio of 21:79. The literature report indicated that only a trace amount of the *exo*-5-alcohol **260** was formed;[168] **260** was slow to elute during purification by flash chromatography and this may explain the difference in the observed product ratios. Swern oxidation of **261** afforded the ketone **259** albeit in moderate yield 39% (*cf.* 80% reported by Carroll).[168]



73 **260** 21 : 79 **261** **259**

Fig. 5.73 The synthesis of 6-keto-2-benzyl-2-azabicyclo[2.2.1]heptane (**259**).[168]

Treatment of **259** with DAST gave the expected *gem*-difluoride **258** but also the rearranged product *exo*-6,1-difluoro-2-benzyl-2-azanorbornane **262** in a 1:1 ratio (Fig. 5.74). This finding provided a fast-track method of placing a fluorine atom at the bridgehead position (C1) of the 2-azanorbornane framework. It was hypothesised initially that **262** was formed under the reaction conditions from the *gem*-difluoride **258** via the mechanism shown in Fig. 5.74. However, attempts to convert **258** to **262** failed; when **258** was refluxed in $CDCl_3$ or in DMF only unreacted starting material was observed. It is likely, therefore, that the rearrangement to **262** occurs during the reaction of the ketone **259** with DAST. The mechanism of difluoride formation from ketones using DAST is thought to involve ionic intermediates[169] and a potential mechanism which could explain the formation of **258** and **262** is outlined in Fig. 5.74. The details of this mechanism are speculative but it seems necessary for a tricyclic intermediate (*e.g.* **263**) to be involved in the rearrangement and the proposed mechanism explains the 1:1 mixture of **258** and **262**, assuming that paths a and b occur at similar rates.

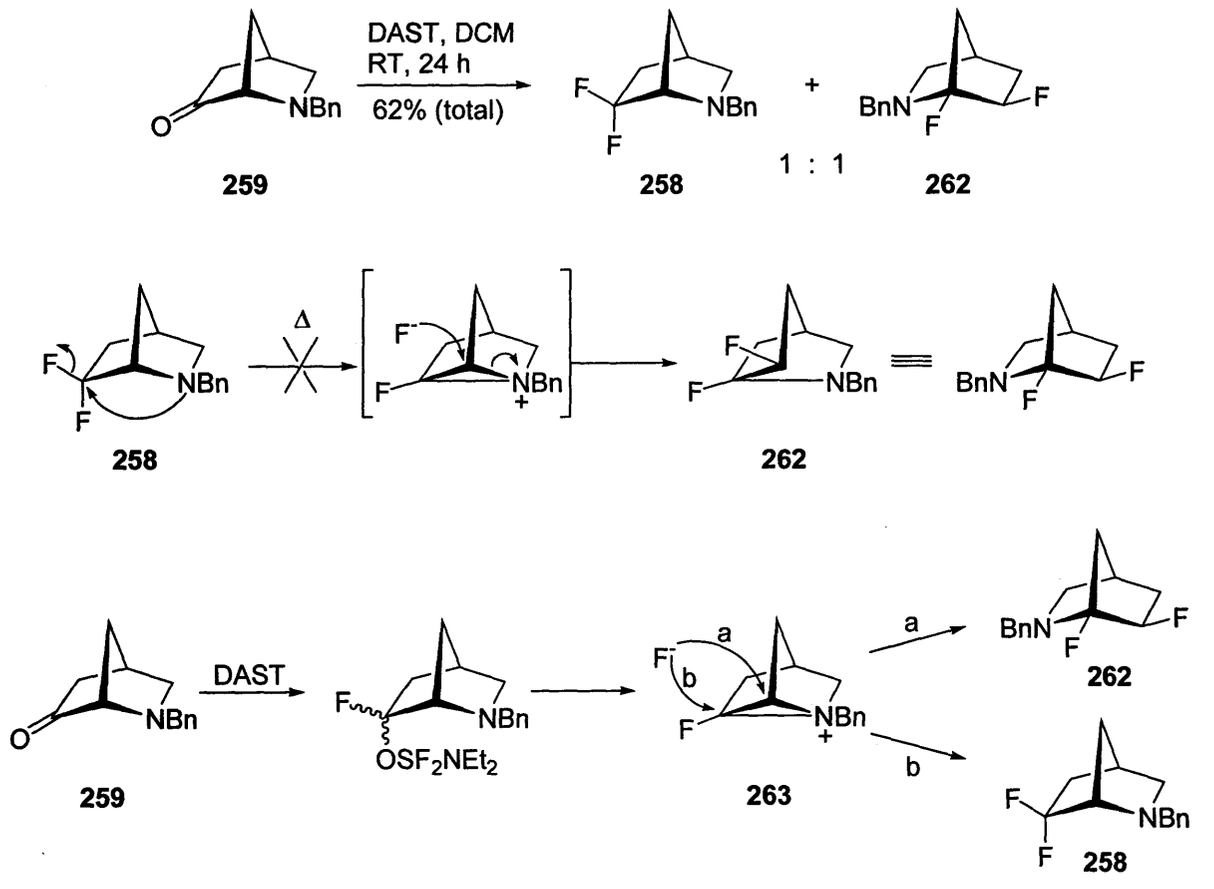
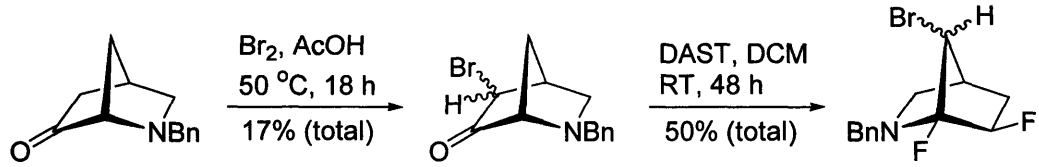


Fig. 5.74 The rearrangement of the ketone **259** when treated with DAST. The attempted conversion of **258** to **262**. A potential mechanism for the formation of the difluorides **258** and **262**.

Investigations were undertaken to establish how the DAST-induced rearrangement of **259** to **262** might be applied to the synthesis of fluorinated epibatidine analogues. Hence, the ketone **259** was treated with bromine in acetic acid and gave a mixture of *exo* and *endo* α-brominated 2-azanorbornanes **264** and **265** (~1:1). It is likely that the *exo* bromide **264** formed first, as attack on the enol of **259** would be expected to be preferentially from the *exo* face; equilibrium was then established under the reaction conditions leading to the thermodynamic mixture of **264** and **265**. The α-bromo-ketones **264** and **265** were not separated prior to reaction with DAST, as it was reasoned that subsequent Suzuki coupling-reactions were likely to give mixtures of epimers. Rearrangement of **264** and **265** occurred to give the difluorides **266** and **267** (~2:1; *syn*:*anti*); in contrast with the reaction of **259**, only ~10% of the unrearranged *gem*-difluorides were observed in the crude ^{19}F NMR. If the postulated mechanism in Fig. 5.74 is reconsidered this seems reasonable; it is likely that the presence of an α-bromine atom in the tricyclic intermediate **263** would impede opening of the aziridinium functionality via pathway-b leading to a greater proportion of rearrangement via pathway-a (*cf.* the bromination of the alkene **73** in Fig. 2.20, Chapter 2).

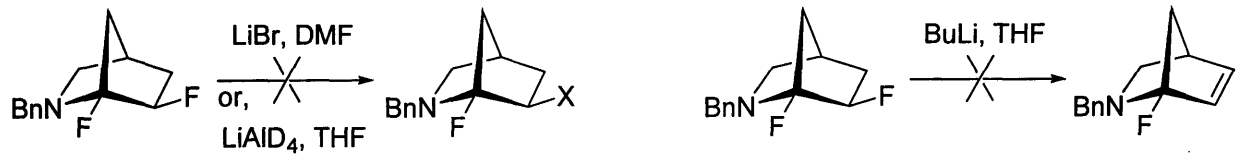


259 | **264** (*exo*)/ **265** (*endo*) (~1:1) | **266** (*syn*)/ **267** (*anti*) (~2:1)

Fig. 5.75 The synthesis of 7-bromo-*exo*-6,1-difluoro-2-benzyl-2-azabicyclo[2.2.1]heptanes **266** and **267**.

The rearrangement of **264/265** with DAST went some way to demonstrating the generality of this reaction. With precursors **266/267** in hand, protecting-group interconversion and Suzuki coupling reactions could have been undertaken. However, rather than pursuing *exo*-6,1-difluoro-isoepibatidine, attention was focused on further investigation of the novel rearrangement and associated reactions.

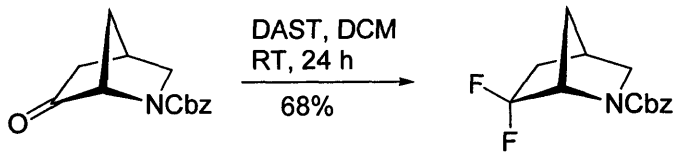
Potential transformations of the difluorides **258** and **262** were considered (Fig. 5.76). Attempts were made to displace the *exo*-6-fluorine of **262** with bromide and deuteride; reaction of **262** with LiBr in DMF or $LiAlD_4$ in THF failed to give **268**, yielding only unreacted starting material. As might be expected, loss of fluoride from the *exo*-6-position of 2-azanorbornanes is a higher energy process than the loss of bromide. The elimination of HF from **262** was also investigated, but treatment with *n*-BuLi gave decomposition to an unidentifiable mixture of products; the 1-fluorinated 2-azanorbornene **269** was not observed.



262 | **268** (R = Br or D) | **262** | **269**

Fig. 5.76 Attempted transformations of *exo*-6,1-difluoro-2-benzyl-2-azabicyclo[2.2.1]heptane (**262**).

The rearrangement of the ketone **259** was further probed and the importance of the *N*-benzyl protecting-group in this transformation was investigated. A sample of the *N*-Cbz-protected ketone **270** was available (C. D. Cox) and was treated with DAST (Fig. 5.77). The *gem*-difluoride **271** was the only observed product (68%), that is, no rearrangement occurred. The bicyclic nitrogen atom is more nucleophilic (and better able to participate in reactions at C6) when benzyl-protected compared to when Cbz-protected; this is clearly an important factor in the rearrangement of 6-keto-2-azanorbornanes to *exo*-6,1-difluoro-2-azanorbornanes.



270 **271**

Fig. 5.77 The treatment of **270** with DAST does not result in rearrangement.

The generality of the rearrangement was also investigated, in particular, it was hoped that a range of different substituents could be placed at the bridgehead position (C1) of the 2-azanorbornane framework. This position is very difficult to functionalise hence, a general route to 1-substituted 2-azanorbornanes would be extremely valuable. The synthesis of the diol **272** was considered by rearrangement of the hydrate of **259**. The ketone **259** was refluxed in a mixture of water and THF (1:1) with a catalytic amount of HCl present but only unreacted starting material was isolated; none of the rearranged hydrate **272** was observed. The treatment of **259** with PCl_5 was also studied, in the hope of positioning chlorine at C1; however, reaction in DCM, chloroform and hexane gave only a complex mixture of products. Mass spectrometry indicated that tricyclic chloride salts may have formed but attempts to purify these by chromatography and crystallisation were unsuccessful, suggesting that the products of the reaction were unstable.

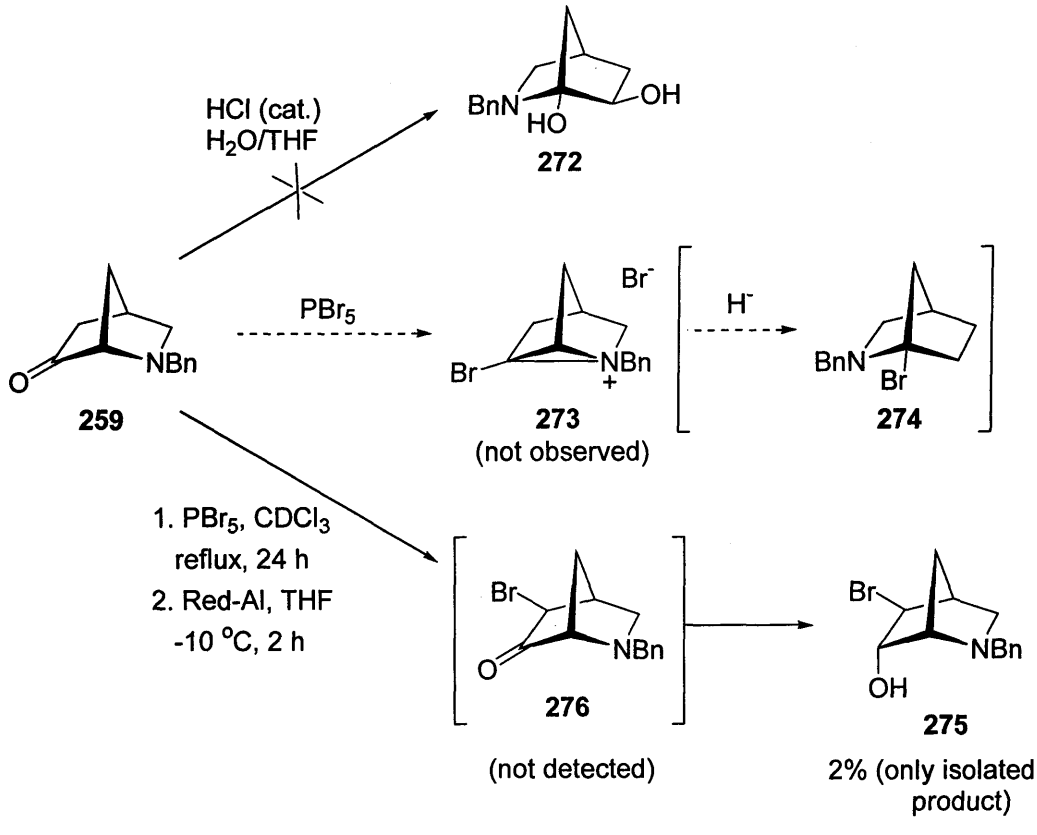


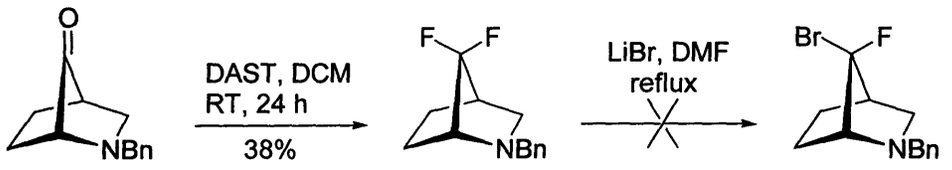
Fig. 5.78 Attempted synthesis of the diol **272** and the reactions of **259** with PBr_5.

The successful handling of certain azoniatricyclo bromide salts was discussed in Chapter 2. Hence, PBr_5 was used in place of PCl_5. It was hoped that reaction of **259** with PBr_5 would result in the formation of **273**, which could be isolated, characterised and then ring-opened with hydride (or an alternative nucleophile) to yield 1-bromo-2-azanorbornanes (*e.g.* **274**). However, after reaction of **259** with PBr_5 (in the same solvents as for PCl_5), at room temperature and at reflux, similar complex mixtures of products were obtained as in the reaction with PCl_5 and again no products could be isolated. The crude residue produced by reacting **259** with PBr_5 in $CDCl_3$ (used rather than chloroform only because a freshly distilled batch had been prepared) was treated with Red-Al in an attempt to trap any unstable tricyclic products such as **273** that may have formed. Column chromatography of the resulting residue gave the bromo-alcohol **275** as only isolable product (2% overall). It seems that in addition to the formation of unstable intermediates and products, reaction of **259** with PBr_5 is also causing α-bromination. The α-bromo-ketone **276** was not detected in the ^{1}H NMR spectrum of the crude residue probably due to its complexity and the small relative quantity of **276**. The reduction of **276** with Red-Al gave **275**; the substitution pattern of the hydroxyl and bromo substituents in **275** was determined by COSY experiments and careful analysis of coupling constants in the ^{1}H NMR spectrum.

The transformation of 6-keto-2-azanorbornanes to 1-substituted 2-azanorbornanes warrants further study but the apparent instability of the products will need to be overcome.

5.8 Routes to 7-fluorinated 2-azabicyclo[2.2.1]heptanes

In an effort to introduce fluorine to the 7-position of 2-azanorbornanes, the reaction of *N*-benzyl-7-keto-2-azanorbornane **159** with DAST was also investigated. It had been established previously (Chapter 2) that the bicyclic nitrogen lone-pair of 2-azanorbornanes is able to participate in substitution reactions at C7 as well as C6. However, treatment of **159** with DAST gave only the *gem*-difluoride **277** (38%) and no rearrangement was detected. This observation builds upon those discussed in Sections 2.4, 5.4.1 and 5.4.2 to provide further evidence that NGP of the nitrogen lone-pair with the 7-position of 2-azanorbornanes is a higher energy process than participation at the 6-position. However, it is conceivable that a tricyclic intermediate formed but was unable to react further to give rearrangement. The nucleophilic substitution of the fluorine of **277** for bromine was attempted but perhaps unsurprisingly gave no reaction. Any potential anchimeric assistance from the bicyclic nitrogen or transition-state stabilisation by the remaining fluorine atom was not enough to confer reactivity to **277**.



159 **277**

Fig. 5.80 The synthesis of 7,7-difluoro-2-benzyl-2-azabicyclo[2.2.1]heptane (**277**) and attempted substitution reactions.

This Chapter has described some exploratory work concerning the incorporation of fluorine into the 2-azanorbornane framework. Introduction of fluorine to the *exo*-6-position of the 2-azanorbornane framework was achieved by attack of fluoride on the tricyclic salt **74**. This allowed *exo*-6-fluoro-isoepibatidine to be accessed. During the course of this work loss of HF from *exo*-6-fluoro-2-azanorbornanes was observed leading to a novel tricyclic analogue of epibatidine, which has the potential to have interesting biological properties. A novel rearrangement has been discovered which leads to the functionalisation of the bridgehead position (C1) of 2-azanorbornanes. The mechanism and generality of this rearrangement have been investigated. Attempts to position fluorine at other positions of the 2-azanorbornane framework were less successful but a late precursor towards *exo*-6,1-difluoro-isoepibatidine has been synthesised. The mechanistic findings discussed in this Chapter warrant further investigation and to be applied to the synthesis of more fluorinated epibatidine analogues.

Chapter 6

Approaches to isotropane analogues of epibatidine

6.1 Introduction

Many epibatidine analogues based on the azabicyclic tropane skeleton have been produced (see Chapter 1). For example, homoepibatidine (**22**) and dihomoepibatidine (**23**) were first made at Leicester and have high affinity for nicotinic receptors; additional compounds based on **22** and **23** in which the heterocycle point-of-attachment has been altered have also been produced (Fig. 1.53). In addition, a patent filed by Breining *et al.* in 2005 described the syntheses of a large number of epibatidine analogues based on the general structure **287**; these derivatives were designed to treat pain and CNS disorders.[75]

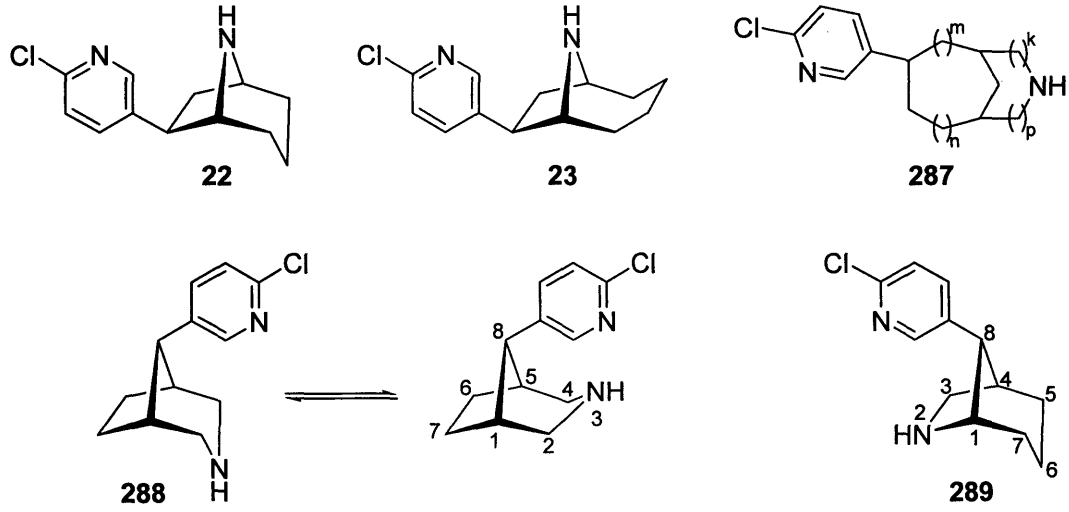


Fig. 6.10 Selected literature examples of epibatidine analogues with larger azabicyclic frameworks and isotropane-based targets (**288** and **289**). [For **287**: k, m, n and p are individually 0, 1, 2 or 3; when k + p = 1, m or n or both are greater than 0].

Although epibatidine analogues with larger azabicyclic frameworks have been reported, the heterocycle point-of-attachment is invariably on one of the larger bridges of the azabicycle, e.g. the ethano-bridge in the cases of **22** and **23**. The previous Chapters in this thesis have described the successful positioning of heterocycles at the methano-bridge of 2-azanorbornanes; hence we envisioned the introduction of heterocycles to the methano-bridges of larger, isotropane molecules. Molecular modelling suggested that *syn*-8-(6-chloro-pyridin-3-yl)-3-azabicyclo[3.2.1]octane (**288**) and *syn*-8-(6-chloro-pyridin-3-yl)-2-azabicyclo[3.2.1]-octane (**289**) were reasonable targets in terms of inter-nitrogen distances.[b] This Chapter describes routes towards the isotropane-based analogues of epibatidine **288** and **289**.

[b] The isotropane structures in this Chapter are discussed using nomenclature similar to that used for azanorbornanes in previous Chapters. That is, substituents are said to be *exo* or *endo* and *syn* or *anti* to the bicyclic nitrogen atom (Fig. 6.10). Strictly, α/β terminology might be used but was avoided in order to achieve consistency and to avoid confusion.

6.2 Analogues of epibatidine based on 3-azabicyclo[3.2.1]octane

Molecular modelling studies of **288** indicated a low energy conformation with an inter-nitrogen distance of 5.4 Å (cf. epibatidine: 4.5 Å) but if the boat conformation of **288** is specified (Fig. 6.10) the inter-nitrogen distance is reduced to 4.5 Å. The route envisioned to **288** involved the Suzuki cross-coupling of the pyridine moiety to the bromo-precursor **290**. This, in turn, could be produced by functional group inter-conversions from the known ketone **291** (Fig. 6.20).

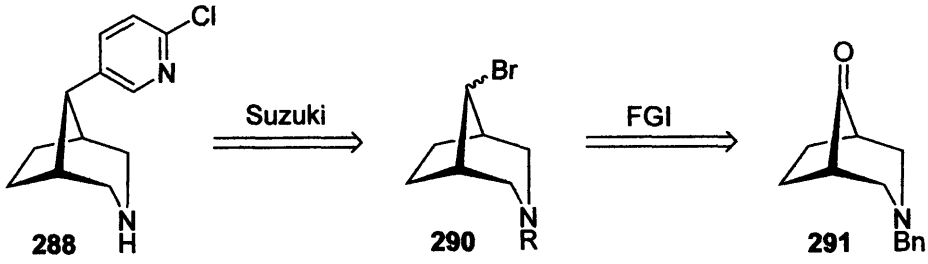


Fig. 6.20 The retrosynthesis of the isotropane-based epibatidine analogue **288**.

6.2.1 Synthesis of 8-hydroxy-3-benzyl-3-azabicyclo[3.2.1]octane

Literature procedures were followed for the synthesis of 8-hydroxy-3-benzyl-3-azabicyclo-[3.2.1]heptane (**292a**).[170,171] The 3-azabicyclo[3.2.1]octane framework was constructed using a Manich procedure; reaction of cyclopentanone, benzylamine and formaldehyde gave the ketone **291**. The low yield (4%) is consistent with the original report.[170]

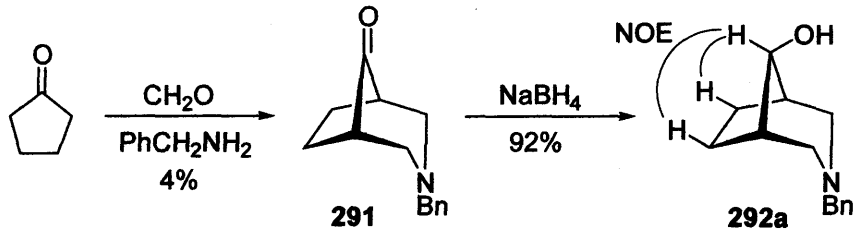


Fig. 6.21 Synthesis of 8-hydroxy-3-benzyl-3-azabicyclo[3.2.1]octane (**292a**).

Reduction of **291** with sodium borohydride occurs in good yield and gives the *syn* alcohol **292a** exclusively:[171] NOE interactions were observed between the *anti*-8- proton and those at the *exo*-6 and 7- positions. Nucleophilic attack on **291** and similar derivatives is known to occur at the *anti* face of the ketone for steric reasons;[172] *anti* attack on **291** can be equated to equatorial attack on a cyclohexanone.

6.2.2 Synthesis of 8-bromo-3-azabicyclo[3.2.1]octanes

Attempts were made to convert the alcohol **292a** to the bromide **293a**. Initially, direct methods were trialled, but both refluxing hydrobromic acid[173] and thionyl bromide gave only unchanged starting material (**292a**). Hence, **292a** was converted to the triflate **294a** using a

procedure described by Kim *et al.*[171] Reaction of **294a** with LiBr in the presence of a catalytic amount of $AlCl_3$ gave **293a** (36% overall); tosic acid could be used in place of $AlCl_3$ but no reaction occurred in the absence of acid.

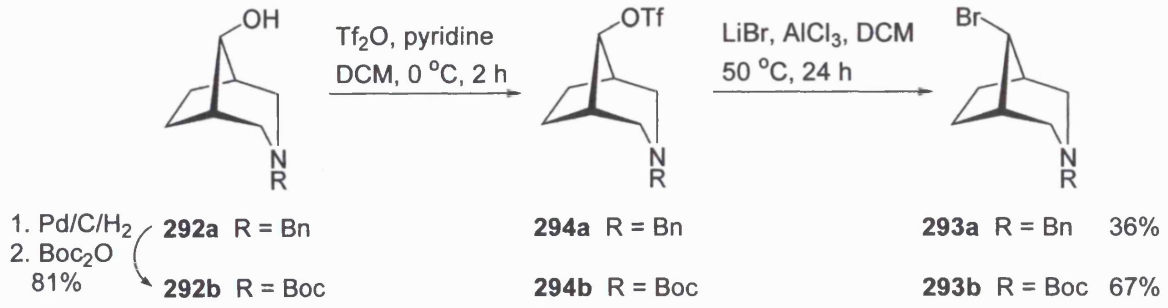


Fig. 6.22 Synthesis of the 8-bromo-3-azabicyclo[3.2.1]octanes **293a** and **293b**.

The Boc-protected bromo-compound **293b** was required as a substrate for Suzuki cross-coupling reactions. Protecting group interconversion (**292a** to **292b**) was straightforward and **293b** was accessed via the triflate **294b**, analogously to the production of **293a**, in 67% overall yield. The substitution reactions of the triflates **294a** and **294b** occurred with inversion of configuration (S_N2); only the *anti* epimers **293a** and **293b** were isolated. The C8 stereochemistry was confirmed by NOESY experiments; in particular, NOE cross-peaks were observed between H_8 and the *exo* hydrogens at C2 and C4 (Fig 6.23).

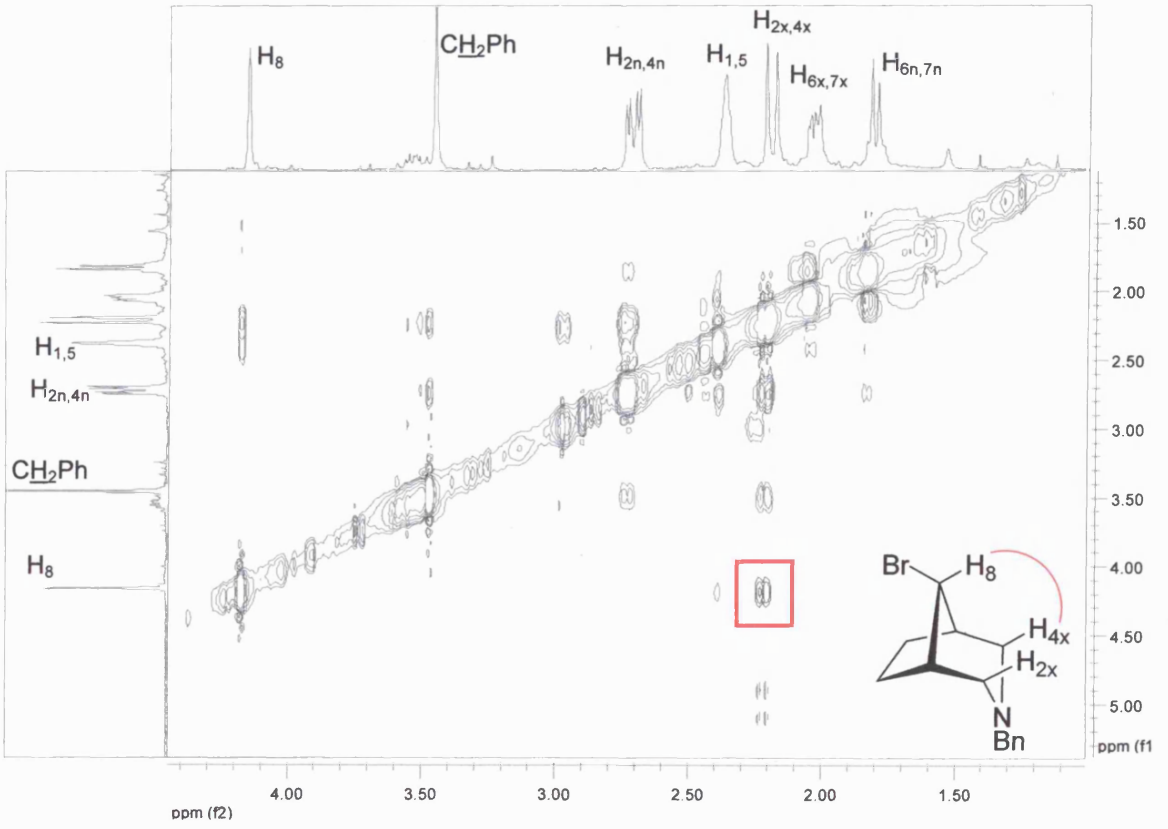


Fig 6.23 NOESY confirmation of the *anti* C8 stereochemistry of **293a**.

6.2.3 Attempted substitution reactions of 8-bromo-3-azabicyclo[3.2.1]octanes

Attempts were made to effect nucleophilic substitution reactions at the 8-position of 3-aza-bicyclo[3.2.1]octanes. It was hoped that neighbouring group participation (via **295**), akin to that observed in the substitution reactions of 7-substituted 2-azanorbornanes (Chapter 2), would be observed. The bromo-compounds **293a** and **293b** were reacted with lithium chloride in DMF and *N*-methylpyrrolidinone (NMP); for both protecting-groups (Bn and Boc) only unreacted started material was obtained (Fig. 6.24). Under refluxing conditions, decomposition to an unidentifiable mixture of products occurred prior to any substitution; the chlorinated products **296a** and **296b** were not observed. It appears that NGP in this system does not take place and that simple S_N1 and S_N2 reactions when the 7-nucleofuge is *anti* are unfavourable. It is possible that approach of a nucleophile *syn* to the bicyclic nitrogen is too sterically hindered for reaction to occur.

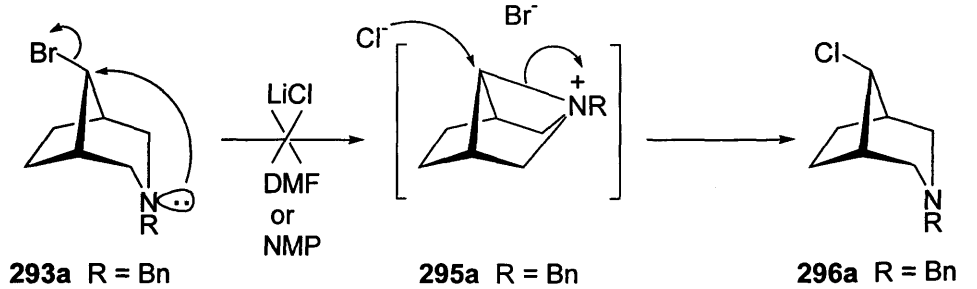


Fig. 6.24 Unsuccessful substitution reactions of the 8-bromo-3-azabicyclo[3.2.1]octanes **293a** and **293b**.

The lack of NGP in **293a** is consistent with the observations of House *et al.*; IR spectroscopy indicated that there was no appreciable participation of the amine functionality with the carbonyl group in **297** (Fig. 6.25).[174] As alluded to previously, the facial selectivity in the reduction of **291** is a result of nucleophilic attack from the least sterically hindered face of the ketone (Fig. 6.21).[172]

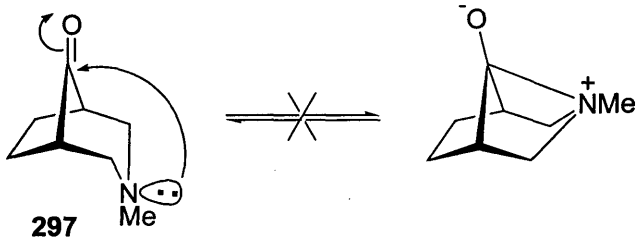


Fig 6.25 The amine functionality of **297** does not participate with the carbonyl group.[174]

6.2.4 Attempted synthesis of *syn*-8-(6-Chloro-pyridin-3-yl)-3-azabicyclo[3.2.1]octane

The Suzuki coupling procedure described in Chapter 3[123] was used to couple 4-chloro-3-pyridyl boronic acid to **293b**. Only the undesired *anti* product **298** was obtained (54% yield

based on recovered starting material); NOE interactions were observed between H_8 and the *exo* protons at the 2- and 4-positions.

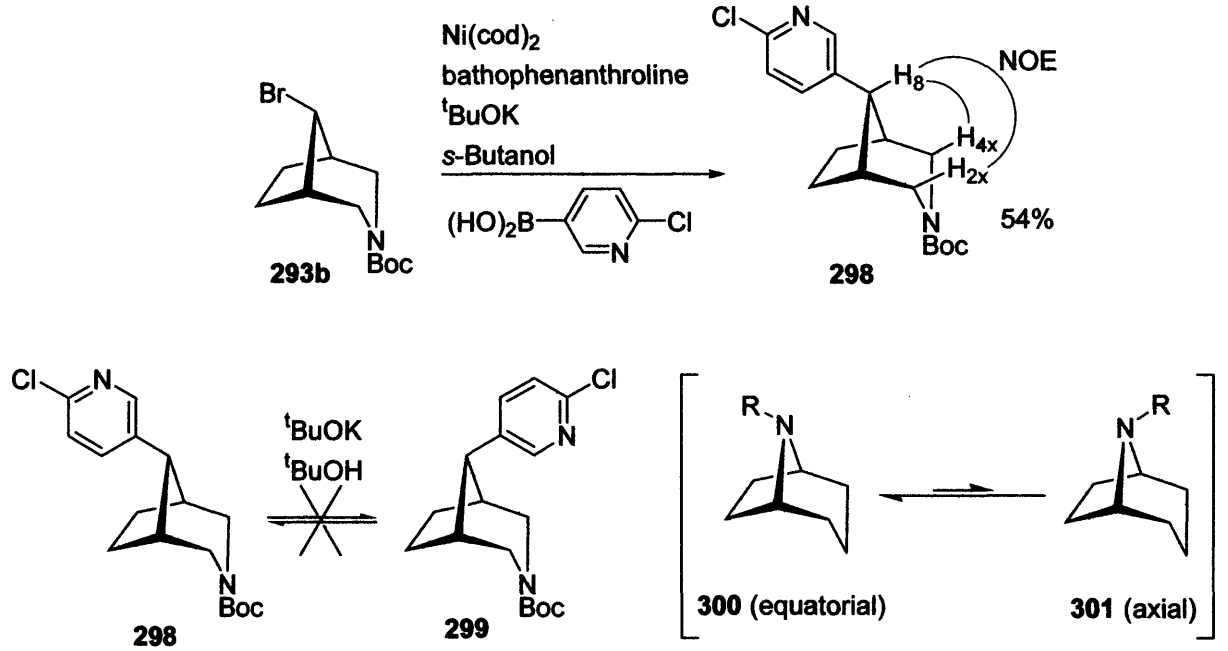


Fig 6.26 The synthesis and attempted epimerisation of *anti*-8-(6-Chloro-pyridin-3-yl)-3-boc-3-azabicyclo[3.2.1]octane (**298**). The equatorial invertomer **300** is favoured in nitrogen inversion of tropanes.[175]

As previously discussed, many syntheses of epibatidine and its analogues have involved epimerisation of the chloropyridyl moiety.[15] Attempts were made to epimerise **298** to the *syn* epimer **299**; treatment of **298** with ^{t}BuOK in refluxing ^{t}BuOH (83 °C) for 96 hours gave only unchanged starting material. This lack epimerisation (**298** to **299**), is further evidence that this cross-coupling methodology yields thermodynamic mixtures of products. It is reasonable to assume that the *anti* epimer **298** is more thermodynamically stable than **299**; interconversion of the C8 anions of **298** and **299** is analogous to nitrogen inversion in tropanes. In these equilibria the equatorial (R *syn* to ethano bridge) invertomer **300** is greatly favoured over the axial invertomer **301**.[175]

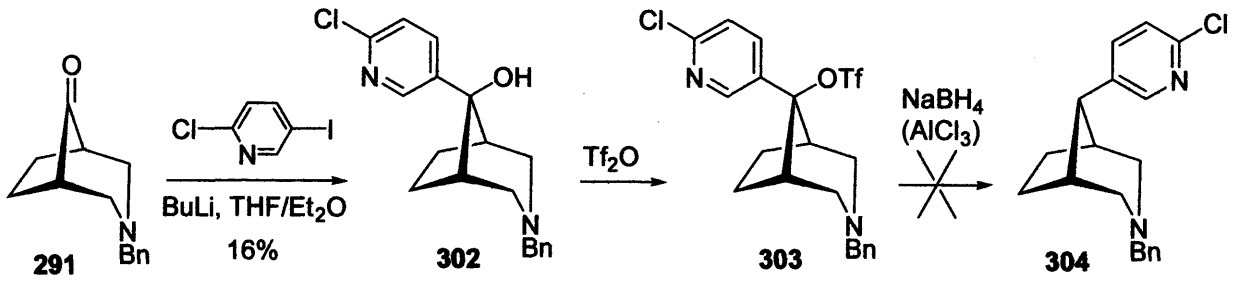
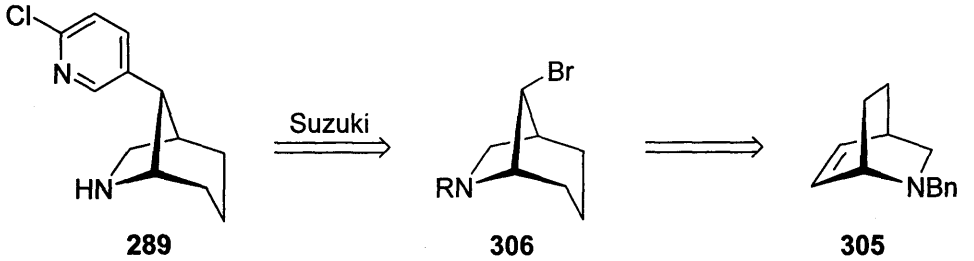


Fig. 6.27 Attempted synthesis of *syn*-8-(6-chloro-pyridin-3-yl)-3-benzyl-3-azabicyclo[3.2.1]octane (**304**).

The Suzuki-coupling approach was unsuccessful in giving the target compound **288**; an alternative route was explored (Fig 6.27). Some syntheses of epibatidine and its analogues involve addition of a lithiated pyridine to a ketone;[15] a similar tactic was envisaged in order to access **288**. The ketone **291** was reacted with chloropyridyl lithium, yielding the alcohol **302** (refluxing conditions gave only a 16% yield based on recovered starting material). The *anti* configuration of the heterocycle at C8 was not confirmed, but can be reasonably assumed based on existing knowledge of the facial selectivity in 8-keto-3-azabicyclo[3.2.1]octanes (see Section 6.2.1).[172] Conversion of **302** to the triflate **303** was successful as indicated by ^{19}F NMR (signal at -78 ppm) but the transformation to **304** could not be effected. It was hoped that inversion of configuration at C8 during displacement of the triflate with hydride would be observed, to give the *syn*-chloropyridyl derivative **304**. Treatment of **303** with sodium borohydride, with and without a catalytic amount of $AlCl_3$ present, failed to give **304**; after work up only the alcohol **302** was observed. The lack of success in achieving displacement of the triflate from **303** and the poor yield for the formation of **302** led to the prioritisation of areas that provided more positive results, in particular, the production of *syn*-8-(6-chloro-pyridin-3-yl)-2-azabicyclo-[3.2.1]octane (**289**).

6.3 Analogues of epibatidine based on 2-azabicyclo[3.2.1]octane

The isotropane analogue of epibatidine **289** is structurally similar to isoepibatidine (Chapter 3), containing just an extra methylene group. Homoepibatidine, similarly, contains an extra methylene in comparison to epibatidine and has high nicotinic affinity (Fig 1.53).[66] Molecular modelling indicated a low energy conformation of homoisoepibatidine (**289**) with an inter-nitrogen distance of 4.9 Å, which is within the range that can be expected to lead to nicotinic affinity.



289 **306** **305**

Fig. 6.30 Retrosynthesis of *syn*-8-(6-chloro-pyridin-3-yl)-2-azabicyclo[3.2.1]octane (**289**).

The structural similarity of **289** and isoepibatidine led to the implementation of a synthetic route analogous to that described in Chapters 2 and 3. That is, bromination of the alkene **305** and reaction with hydride to give the rearranged bromo-compound **306**; again, the Suzuki-coupling methodology would be used to introduce the chloropyridyl moiety (Fig 6.30).

6.3.1 Synthesis of 2-benzyl-2-azabicyclo[2.2.2]hept-5-ene

A literature aza-Diels-Alder procedure was used to give 2-benzyl-2-azabicyclo[2.2.2]hept-5-ene (**305**).[104]

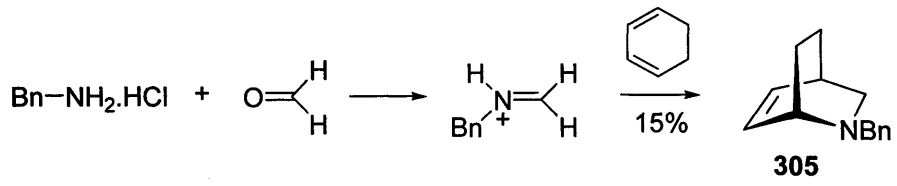


Fig. 6.31 Synthesis of 2-benzyl-2-azabicyclo[2.2.2]hept-5-ene (**305**).

The synthesis of **305** was analogous to the construction of the 2-azanorbornane framework in Chapter 2. Reaction of cyclohexadiene with the imminium ion formed from formaldehyde and benzylamine hydrochloride, gave **305** in 15% yield, after distillation.

6.3.2 Synthesis of 8-bromo-2-benzyl-2-azabicyclo[3.2.1]octane

A two-step bromination of the alkene **305** followed by treatment of the resulting tricycle with hydride, akin to that used to functionalise the 7-position of 2-azanorbornanes (Chapter 2) was envisioned. Bromination of **305** appeared to give the tricyclic salt **307** but it could not be purified, isolated or characterised, suggesting it is not particularly stable. Treatment of this crude mixture with Red-Al initially gave only a very low yield of 8-bromo-2-benzyl-2-azabicyclo-[3.2.1]octane (**308**) but the yield of **308** was increased by adaptation of the bromination/hydride procedure (Fig. 6.32).

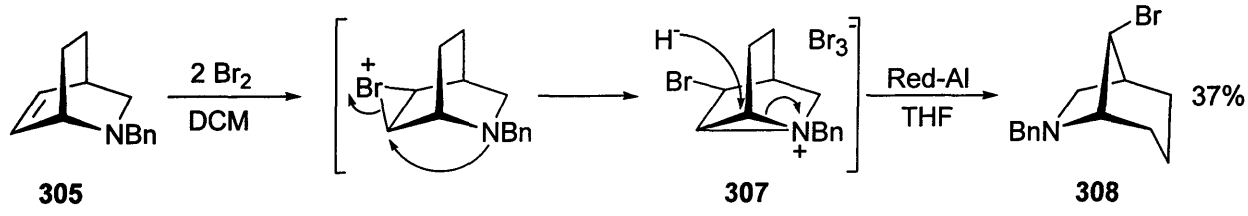


Fig. 6.32 Synthesis of 8-bromo-2-benzyl-2-azabicyclo[3.2.1]octane (**308**).

Thus, **305** was treated with two equivalents of bromine, the DCM was removed under a stream of nitrogen and the resulting residue was dissolved in THF without exposure to air. Addition of Red-Al gave **308** in 28% isolated yield (37% based on recovered starting material (**305**)). The *anti* C8 stereochemistry of **308** was confirmed by 2D NOESY experiments; most notably there were NOESY interactions between H_{3x} and H_8 (Red), and the benzyl protons and H_8 (Blue)(Fig 6.23).

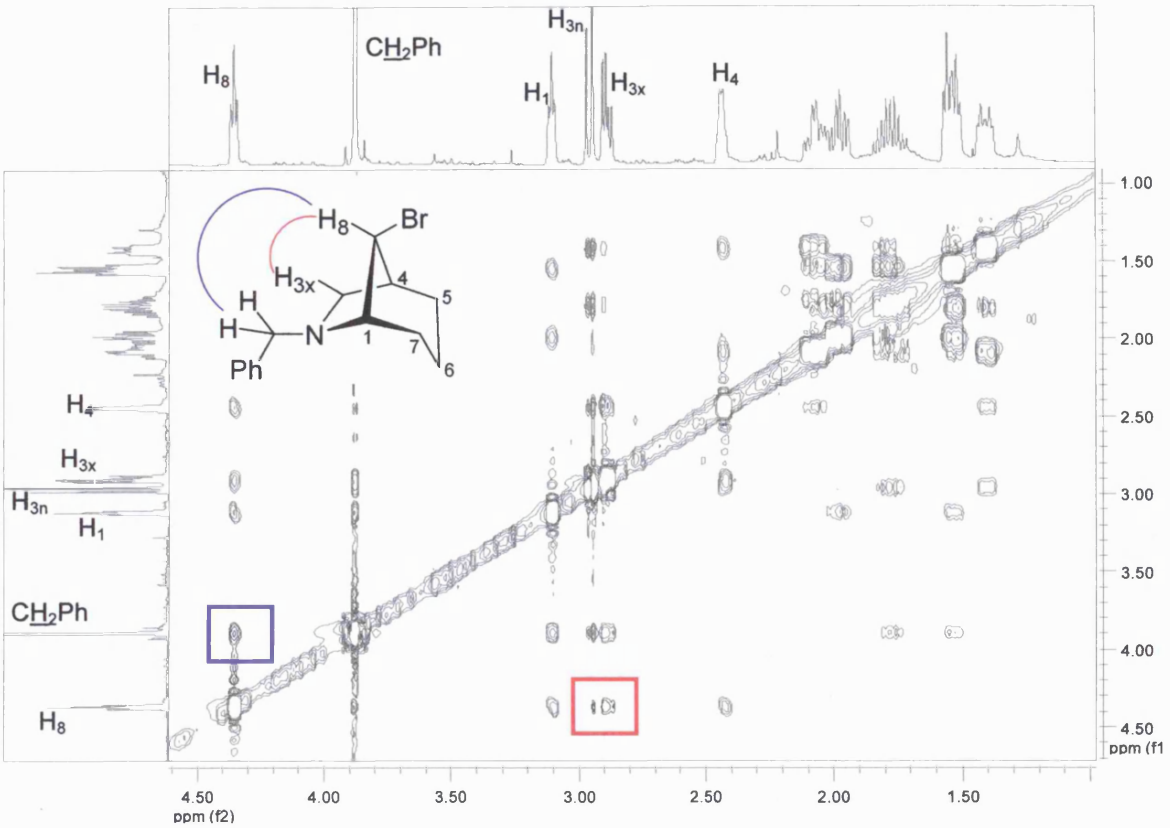
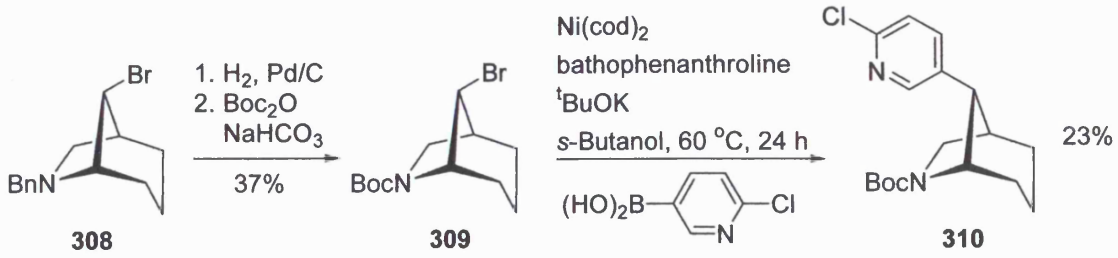


Fig 6.33 NOESY confirmation of the C8 stereochemistry of *anti*-8-bromo-2-benzyl-2-azabicyclo[3.2.1]octane (**308**).

Nucleophilic substitution reactions of **308** were not investigated as, very recently, Krow and co-workers have been studying the substitution reactions of molecules related to **308**.[157] Nucleophiles have been found to react at the 8-position of 2-azabicyclo[3.2.1]octanes with retention of configuration, due to neighbouring group participation of the bicyclic nitrogen lone-pair.[157,176]

6.3.3 Synthesis of homoisoepibatidine

The results discussed in Section 5.4.3 suggested that the Suzuki coupling-reaction is less successful with a benzyl group present. Hence, the benzyl protecting-group of **308** was removed and replaced with Boc to give **309** (Fig 6.33). The coupling methodology described in Chapter 3[123] was used to introduce the chloropyridyl heterocycle to the 8-position of **309**. The reaction proceeded in 23% yield and only one epimer of the product was observed. Detailed NMR analysis was performed and showed, fortuitously, that the desired *syn*-derivative **310** had formed.



308 **309** **310**

Fig. 6.34 The synthesis of *syn*-8-(6-Chloro-pyridin-3-yl)-2-boc-2-azabicyclo[3.2.1]octane (**310**).

The 2D NOESY spectrum of **310** is shown in Fig. 6.34. There are cross-peaks between H_8 and the *exo*-protons at the 5- and 7-positions and no cross-peaks from H_8 to H_{3x}, indicating the *syn*-stereochemistry at C_8. Again, it seems likely that the thermodynamically more favourable equatorial (in this case *syn* to the bicyclic nitrogen) product is produced, either in the coupling reaction itself or as a result of epimerisation of an initial mixture of isomeric products.

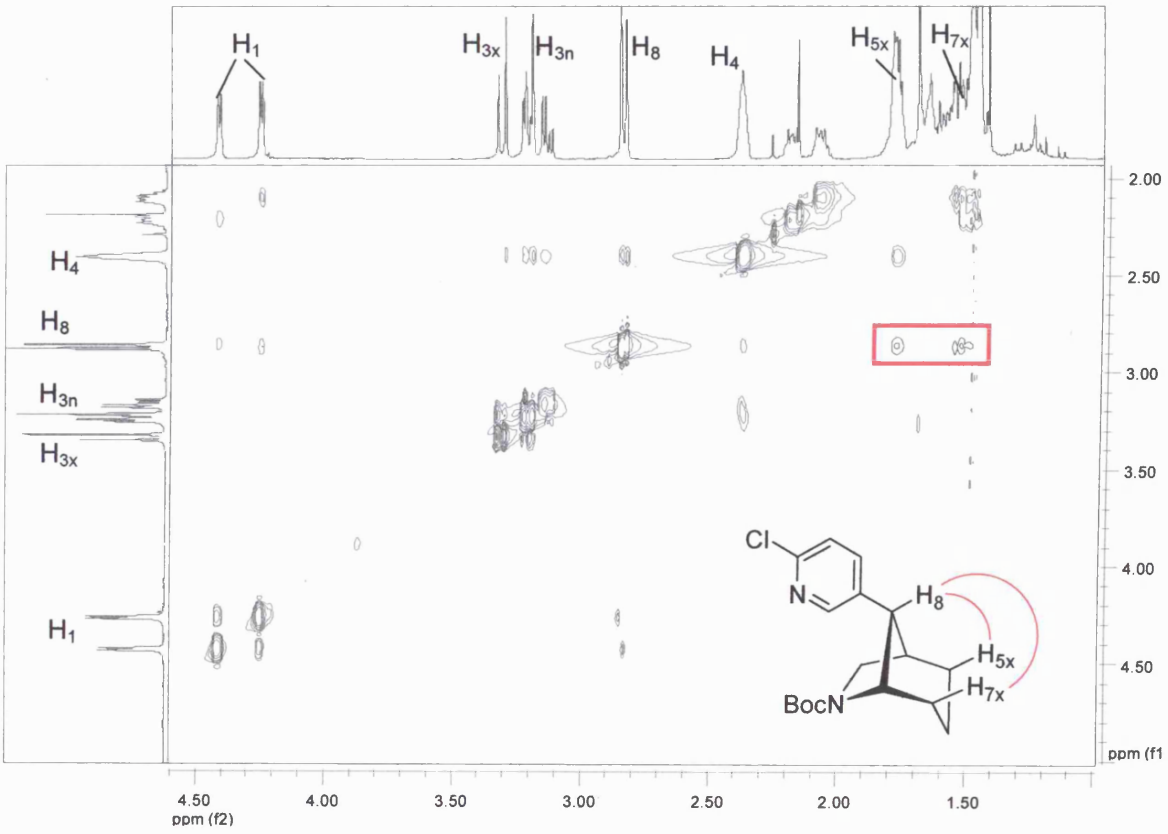
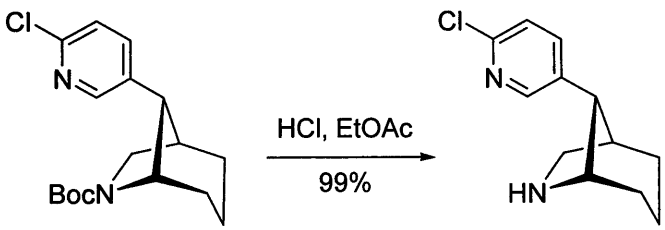


Fig. 6.35 NOESY spectrum of **310**, indicating the *syn*-8-configuration.

Compound **310** was purified then de-protected using ethanol and acetyl chloride as a non-aqueous source of HCl. Homoisoepibatidine (**289**) was isolated as a dihydrochloride salt.



310 **289**

Fig. 6.36 The synthesis of *syn*-8-(6-Chloro-pyridin-3-yl)-2-azabicyclo[3.2.1]octane (homoisoepibatidine) (**289**).

The nicotinic receptor affinity of **289** has yet to be established. Given the extremely high affinity of isoepibatidine (Chapter 7), and that the affinity of homoepibatidine is comparable to that of epibatidine,[66] **289** is expected to be a potent nicotinic ligand.

Chapter 7

Nicotinic receptor binding studies

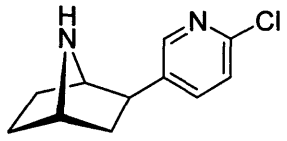
7.1 Nicotinic receptor binding assays

The target molecules synthesised in this thesis were chosen on the basis of potential nicotinic activity, as discussed in previous Chapters. Epibatidine analogues previously synthesised at Leicester were designed to have a rigid azabicyclic framework and a freely rotating heterocyclic substituent. Target compounds were selected on the basis of the distance between the bicyclic and pyridyl nitrogen atoms, which were in the appropriate range (~4-5 Å) in one or more of the structures' minimum energy conformations. These analogues, notably homoepibatidine (**22**; Fig 1.53) and the *endo*-2-azanorbornane derivatives **16** and **17** (Fig 1.52) have very high affinities for nicotinic receptors.[60,66] Hence, similar criteria were retained for the design of the target structures in this thesis. Most of the epibatidine analogues that were produced have been assessed for their nicotinic binding affinities. Competition binding assays were performed against α4β2 and α3β4 nAChR subtypes by our collaborators at Eli Lilly; full experimental details are described in Chapter 8. Although there is a wide range of nicotinic receptor subtypes in humans, assessment of binding at α4β2 and α3β4 subtypes is thought to be most informative of a compound's potential therapeutic use. The α4β2 is the most prevalent subtype in the brain and has been targeted in the treatment of a range of conditions, including pain and neurodegenerative diseases. The α3β4 receptor is principally found in autonomic ganglia and binding to this subtype is believed to be a major contributor to the toxicity of nicotinic agents.[177]

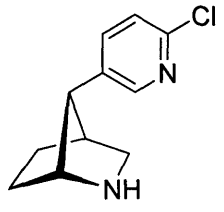
7.2 The nicotinic receptor affinities of isoepibatidine and the isoepiboxidines

The nicotinic receptor binding data for *syn*-isoepibatidine (**49**), the isoepiboxidines (**51** and **52**) and *exo*-6-fluoro-isoepibatidine (**213**) are presented on the following page. The most notable figures are those for isoepibatidine (**49**) which indicate that it is an extremely potent nicotinic receptor ligand. It has higher nicotinic receptor affinity than previously synthesised epibatidine isomers and has binding affinities at both α4β2 and α3β4 subtypes very similar to those of epibatidine (K_i = 0.0785 and 0.16 nM; cf. epibatidine: K_i = 0.0558 and 0.191). Isoepibatidine shows no improvement in subtype selectivity compared to epibatidine. The methylisoxazole-bearing *syn*-isoepiboxidine (**51**) also has high affinity for both receptor subtypes, about ten-fold lower than epibatidine; this modest reduction in affinity and the slight improvement in subtype selectivity mirrors the properties of epiboxidine.[55] Both the *syn* analogues **49** and **51** have calculated inter-nitrogen distances close to that of epibatidine (4.5 and 4.4 Å respectively; cf. 4.5 Å for epibatidine). In contrast, the two major minimum energy conformations of *anti*-isoepiboxidine (**52**) have N-N distances of 5.6 and 5.8 Å, which are not within the range typical of nicotinic receptor ligands and indeed, **52** showed no affinity for

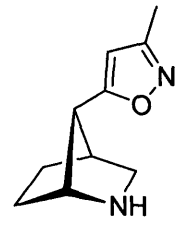
either nAChR subtype at 1000 nM. Although nicotinic pharmacophore models have increased in sophistication over recent years (see Section 1.4), inter-nitrogen distances are still used extensively in recent reports of novel nicotinic agents in order to predict whether compounds will exhibit nicotinic receptor affinity. However, there are limitations to the approach; N-N distances are a relatively crude and indirect way of predicting or rationalising the interaction of a ligand with nAChRs. As might be expected, many other, less well understood factors are also involved and some active compounds have N-N distances outside the 'ideal' range.[24]



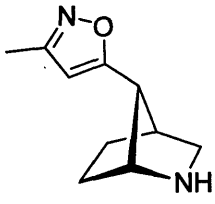
Epibatidine (8)



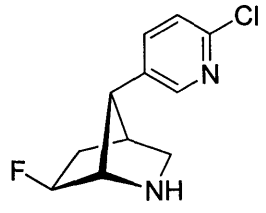
***syn*-Isoepibatidine (49)**



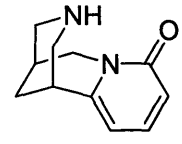
***syn*-Isoepiboxidine (51)**



***anti*-Isoepiboxidine (52)**



***exo*-6-Fluoro-**
-*syn*-isoepibatidine (213)



Cytisine (4)

Compound	Calculated N-N distances (Å)[a]		K_i (nM)[d]		α3β4/α4β2
	N-N[b]	N-N[c]	α4β2	α3β4	
(±)-(**8**)	4.5	5.5	0.0558 (±0.0056)	0.191 (±0.0075)	3.42
(±)-(**49**)	4.5	5.2	0.0785 (±0.0062)	0.16 (±0.0019)	2.05
(±)-(**51**)	4.4	4.8	0.763 (±0.092)	9.51 (±0.428)	12.5
(±)-(**52**)	5.6	5.8	ne at 1000 nM	ne at 1000 nM	-
(±)-(**213**)	4.5	5.2	66.4	ne at 1000 nM	>15.1
Cytisine (**4**)	-	-	2.59 (±0.202)	525 (±6.32)	203

Fig. 7.20 Nicotinic receptor binding affinities of **49**, **51-52** and **213**.

[a] Calculated N-N distances for free amines using Spartan Pro; equilibrium geometry by Hartree-Fock, 6-31G*.

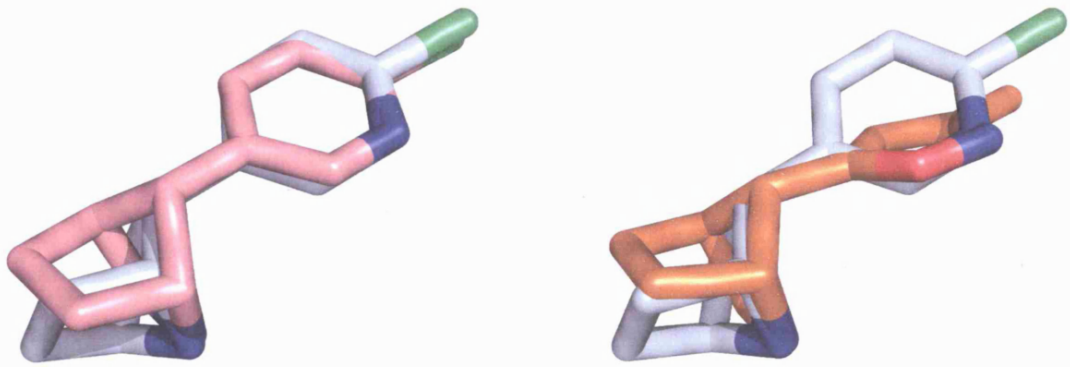
[b] Minimum energy conformation.

[c] After 180° rotation about the C-heterocycle bond.

[d] Values are geometric means of at least three experiments, standard error is given in parantheses (ne = no effect).

The recent publication of the crystal structure of an epibatidine-bound ACh binding-protein indicated the active conformation of epibatidine and hence revealed the active inter-nitrogen distance to be 4.5 Å.[37] This finding has arguably increased the credibility of using an N-N distance approach in designing nicotinic agents, certainly for structures that are closely related to epibatidine. The compounds described in this thesis and those previously produced at Leicester are generally isomers or homologues of epibatidine and those with N-N distances of ~4.5 Å invariably have high nicotinic affinity.

It seems that the 'simple' switch of the positions of the heterocycle point-of-attachment and the bicyclic nitrogen of epibatidine (**8**) to give isoepibatidine (**49**) has little effect on nicotinic receptor affinity. Indeed, the superposition of epibatidine (active conformation; taken from the crystal structure published by Hansen *et al.*[37]) and isoepibatidine (energy minimised) shows excellent overlap of the two structures (Fig. 7.21A). The superposition of epibatidine and isoepiboxidine also shows how the two compounds might behave similarly in the receptor binding-site (Fig 7.21B).



A **B**

Fig. 7.21 A: Superposition of epibatidine (**8**) (grey) and *syn*-isoepibatidine (**49**) (pink). B: Superposition of epibatidine (**8**) (grey) and *syn*-isoepiboxidine (**51**) (orange).

The fluorinated isoepibatidine **213** had only modest affinity at the α4β2 receptor. This was disappointing in that the fluorinated epibatidine molecules produced by Kozikowski and co-workers have K_i values in the low nM range (see Section 5.2).[81] However, the lower affinity of **213** by no means indicates that all fluorinated isoepibatidines will have similar properties.

Although binding data for the *syn*-isoepibatidines (**49**), the fluorinated analogue **213** and the isoepiboxidines (**51** and **52**) have been obtained and the subtype-selectivity of these compounds has, to some extent, also been elucidated, more detailed pharmacological

evaluation has not taken place. Hence, the compounds can only be assumed to be agonists based on their structural similarity to epibatidine.

7.3 The nicotinic receptor affinities of pyridyl-ether analogues of epibatidine

The compounds discussed above, whilst having very high nicotinic affinities, show no real improvement in receptor subtype selectivity in comparison to epibatidine. Some molecules with ether-linkages have demonstrated improved discrimination between subtypes (see Section 1.5.6); perhaps the most notable member of this class of compound, ABT-594 (**48**), showed promise as an analgesic and progressed to phase II clinical trials.[85,86] The concept of attaching an azabicycle to a pyridyl moiety via an ether linkage was discussed in Chapter 4 along with descriptions of the syntheses of **150-155**.

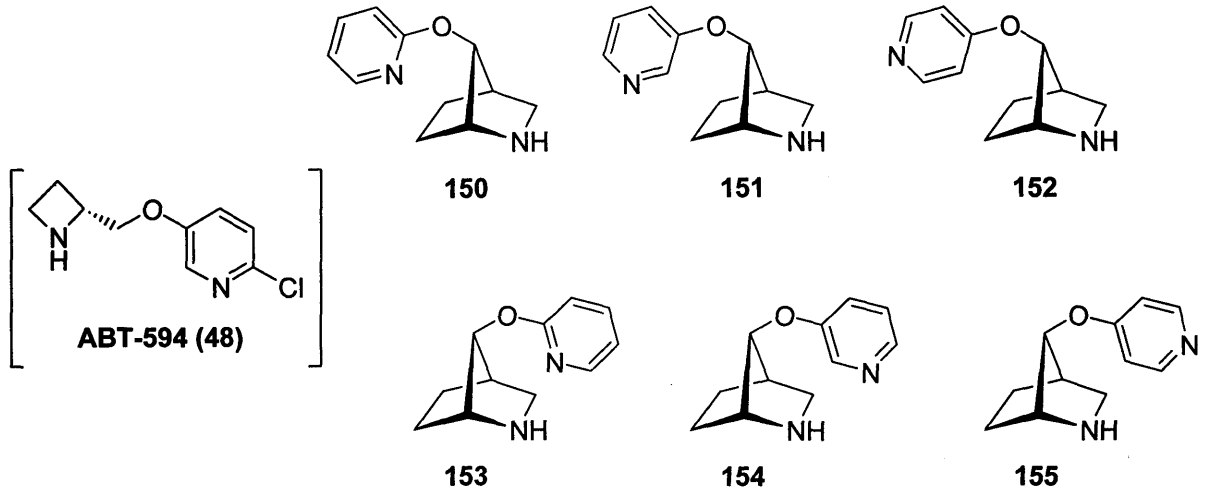
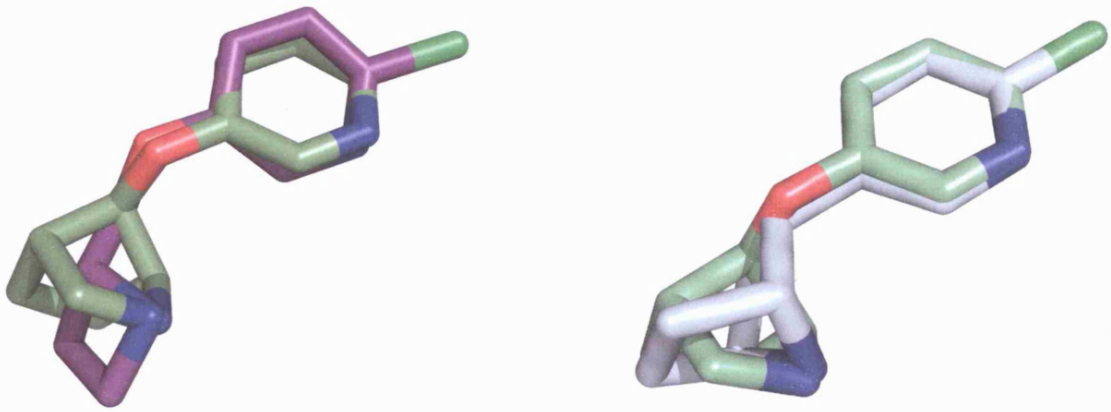


Fig. 7.30 Hybrids of epibatidine and ABT-594.

Nicotinic binding assays of **150-155** have been carried out, again at Eli Lilly, against α4β2 and α3β4 subtypes but only preliminary results have been obtained, which require verification. Initial indications are that **151**, **152**, **153** and **155** have very low affinities for both receptor subtypes. Compound **154** has a *syn*-7- configuration and the same atom connectivity (N-N) as ABT-594 (**48**) and it appears to have very similar receptor binding properties to ABT-594 (**48**). This has implications on the possible active conformation of ABT-594 and the superposition of **48** and **154** (Fig. 7.31A; both energy minimised) shows good overlap of the two structures. Similarly, the superposition of epibatidine (**8**) (active conformation[37]) and **154** (energy minimised) shows excellent overlap (Fig. 7.31B). The *anti*-7-(pyridinyl-2-yloxy)-derivative **150** also showed high affinity for the α4β2 receptor (K_i in low nM range). This molecule, at first examination, appears to have N-N distances beyond the range usually

expected to give nicotinic affinity (~4.5-5.0 Å) but further molecular modelling indicated a low energy conformation with N-N distances within the desired range. The pharmacological properties of **150** are currently under further investigation.



A B

Fig. 7.31 A: Superposition of *syn*-7-(pyridin-3-yloxy)-2-azabicyclo[2.2.1]heptane (**154**) (green) and ABT-594 (**48**) (purple). B: Superposition of epibatidine (**8**) (grey) and *syn*-7-(pyridin-3-yloxy)-2-azabicyclo[2.2.1]heptane (**154**) (green).

Some of the binding data discussed have been published in *Bioorganic and Medicinal Chemistry Letters*.[178]

This Chapter has indicated that the target structures, which were selected on the basis of their potential nicotinic activity, do indeed have high affinities for nAChRs. Notably, isoepibatidine is almost as potent as epibatidine and preliminary data regarding the ether-linked analogues suggest that some have both high affinity and improved receptor subtype selectivity. These findings will also contribute to greater understanding of structure activity relationships and the nicotinic pharmacophore.

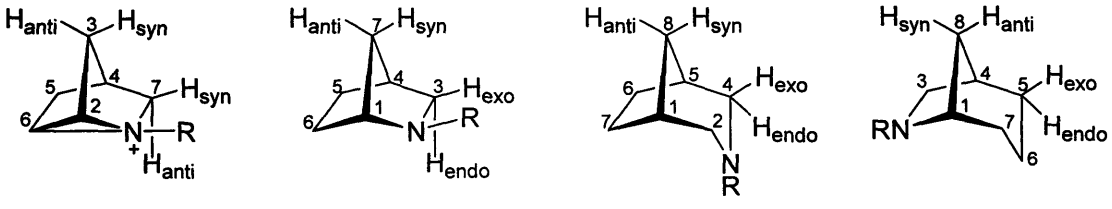
The previous chapters described the journey (including detours) to the targeted nicotinic agents. The majority of these studies involved 2-azanorbornanes, a molecular framework that continues to provide a source of mechanistic and synthetic interest and challenges. It is hoped that the contents of this thesis will contribute to the improved understanding of 2-azanorbornane chemistry.

Chapter 8

Experimental

This Chapter contains the experimental procedures and spectroscopic data for the compounds discussed in the previous Chapters. When experiments were repeated the most successful is recorded.

NMR spectra were recorded using Bruker ARX 250, DPX 300 and DRX 400 spectrometers. Chemical shifts are expressed in p.p.m. (δ) relative to the internal standard tetramethylsilane (TMS) or $CFCl_3$ in ^{19}F NMR spectra. Signal characteristics are described using standard abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Signal multiplicities in ^{13}C NMR were determined by DEPT experiments. The numbering of bicyclic and tricyclic compounds is as follows.



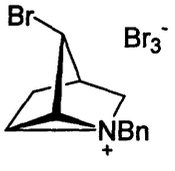
IR spectra were obtained using a PerkinElmer Spectrum One FT-IR spectrometer as films; band intensities are described as follows: s (strong), m (medium), w (weak). Mass spectra were recorded using a Micromass Quattro L.C. Triple Quadropole spectrometer (ionisation by electrospray). Accurate masses were measured on a Kratos Concept 1H Sector mass spectrometer with ionisation by fast atom bombardment (FAB) or electron impact (EI). Mass spectra are recorded in units of mass relative to charge ($^{m}/_{z}$). Where only low resolution mass spectrometry data is given the compound was not suitable for accurate mass determination. Melting points were determined using a Kofler hot stage apparatus.

All reactions were carried out in oven-dried glassware under dry nitrogen unless stated otherwise. Reagents were supplied by Aldrich, Lancaster and Strem. Solvents were distilled by standard methods[179] or dried using an Innovative Technology Inc. Pure Solv solvent purification station. 'Petrol' refers to petroleum ether 40-60. Removal of solvents *in vacuo* was done using a Buchi rotary evaporator followed by a high vacuum pump. Solvents for chromatography were routinely basified with ammonia. Thin-layer chromatography was conducted on silica plates (Merck Kieselgel 60-254). Flash chromatography was carried out using silica gel (Fisher 60).

2-Benzyl-2-azabicyclo[2.2.1]hept-5-ene (73)

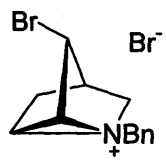
Using the procedure described by Grieco *et al.*,[104] formaldehyde (6.3 ml 37% aqueous solution, 84 mmol) was added to a solution of benzylamine hydrochloride (8.6 g, 60 mmol) in water (24 ml). Freshly distilled cyclopentadiene (9.9 ml, 120 mmol) was added; the flask was stoppered tightly and stirred vigorously at 20 °C for 9 h. The reaction mixture was poured into water (50 ml) and washed with diethyl ether:hexane 1:1 (4 × 20 ml). The aqueous phase was basified by addition of solid potassium hydroxide (4.1 g); then extracted with diethyl ether (3 × 60 ml). The combined diethyl ether extracts were dried over anhydrous $MgSO_4$ and then filtered; the solvents were removed *in vacuo* to give **73** as a pale yellow oil (9.57 g, 51.7 mmol, 86%). R_f (1:1, diethyl ether:petrol) 0.35. δ_H (250 MHz, $CDCl_3$) 1.40 (dd, J = 2, 8 Hz, 1H, H_{7a}), 1.52 (dd, J = 2, 9 Hz, 1H, H_{3n}), 1.63 (d, J = 8 Hz, 1H, H_{7s}), 2.92 (brs, 1H, H_4), 3.16 (dd, J = 3, 9 Hz, 1H, H_{3x}), 3.33 (d, J = 13 Hz, 1H, CH_2Ph), 3.57 (d, J = 13 Hz, 1H, CH_2Ph), 3.81 (d, J = 2 Hz, 1H, H_1), 6.08 (dd, J = 2, 6 Hz, 1H, H_6), 6.37 (ddd, J = 1, 3, 6 Hz, 1H, H_5), 7.21 (m, 5H, Ph). δ_C (62.9 MHz, $CDCl_3$) 43.9 (C_4), 48.1 (C_7), 52.5 (C_3), 59.1 (CH_2Ph), 64.3 (C_1), 130.9 (C_6), 136.2 (C_5), 126.7, 128.1, 128.6 (5 × aryl CH), 140.0 (aryl C). ν_{max} 2992s, 2872s, 1504m, 1463m, 1375m, 1242m, 1202s cm^{-1}. $^m/_z$ $C_{13}H_{15}N$ [M^+] requires 185.12045; observed 185.12052.

3-Bromo-1-benzyl-1-azoniatricyclo[2.2.1.0^{2,6}]heptane tribromide (76)



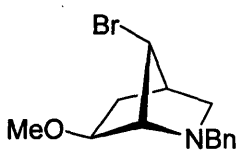
Using the procedure described by Sosonyuk *et al.*,[98] 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene (**73**) (12.03 g, 64.9 mmol) was dissolved in dry DCM (120 ml). Bromine (6.0 ml, 129.5 mmol) was added drop-wise at –78 °C. The mixture was stirred as the temperature rose to 20 °C. Removal of the solvents *in vacuo* gave **76** as an orange oil (32.80 g, 64.9 mmol, 100%). δ_H (250 MHz, $CDCl_3$) 2.39 (d, J = 13.5 Hz, 1H, H_{5s}), 2.54 (d, J = 13.5 Hz, 1H, H_{5a}), 2.89 (brs, 1H, H_4), 3.37 (d, J = 9.2 Hz, 1H, H_{7a}), 3.73 (d, J = 9.2 Hz, 1H, H_{7s}), 4.24 (d, J = 4.2 Hz, 1H, H_6), 4.28 (d, J = 4.2 Hz, 1H, H_2), 4.68 (brs, 1H, H_3), 5.08 (brs, 2H, CH_2Ph), 7.45-7.61 (m, 5H, Ph). δ_C (62.9 MHz, $CDCl_3$) 31.1 (CH_2Ph), 37.6 (C_4), 43.9 (C_2), 46.0 (C_6), 47.1 (C_3), 56.1 (C_7), 56.7 (C_5), 128.3 (Aryl C), 130.1, 131.0, 131.1 (5 × aryl CH). ν_{max} 3053s, 3050w, 2307w, 1432w, 1280s, 923m cm^{-1}. $C_{13}H_{15}NBr$ [M^+] requires 264.03879; observed 264.03874.

3-Bromo-1-benzyl-1-azoniatricyclo[2.2.1.$0^{2,6}$]heptane bromide (74)



Using the procedure described by Sosonyuk *et al.*,[98] 3-bromo-1-benzyl-1-azoniatricyclo[2.2.1.$0^{2,6}$]heptane tribromide (**76**) (32.80 g, 64.9 mmol) was dissolved in dry acetonitrile (100 ml). This solution was cooled to 0 °C and stirred vigorously under nitrogen whilst 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene **73** (12.06 g, 65.0 mmol) in dry acetonitrile (60 ml) was added drop-wise. After warming to 20 °C, the solvents were removed *in vacuo* yielding **74** as pale yellow crystals (22.3 g, 64.6 mmol, 100%). m.p. 128-130 °C. δ_H (250 MHz, $CDCl_3$) 2.42 (brs, 2H, H_5), 2.83 (brs, 1H, H_4), 3.41 (d, J = 8.9 Hz, 1H, H_{7a}), 3.94 (d, J = 8.9 Hz, 1H, H_{7s}), 4.32 (d, J = 4.4 Hz, 1H, H_6), 4.42 (d, J = 4.4 Hz, 1H, H_2), 4.86 (brs, 1H, H_3), 5.34 (s, 2H, CH_2Ph), 7.42-7.73 (m, 5H, Ph). δ_C (62.9 MHz, $CDCl_3$) 30.9 (CH_2Ph), 37.6 (C_4), 44.5 (C_2), 44.8 (C_6), 46.2 (C_3), 55.1 (C_7), 55.3 (C_5), 129.4 (Aryl C), 129.5, 130.3, 131.1 (5 × aryl CH). ν_{max} 3049s, 3003w, 2318w, 1426m, 1278m, 898m cm^{-1}. $^m/_z$ $C_{13}H_{15}NBr$ [M^+] requires 264.03879; observed 264.03884.

7-Bromo-6-methoxy-2-benzyl-2-azabicyclo[2.2.1]heptane (80)



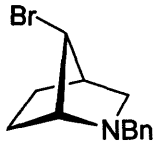
3-Bromo-1-benzyl-1-azoniatricyclo[2.2.1.$0^{2,6}$]heptane bromide (**74**) (0.1449 g, 0.42 mmol) was dissolved in dry methanol (2 ml) and sodium borohydride (8.8 mg, 0.23 mmol) was added slowly with stirring and cooling with ice. The reaction mixture was refluxed under nitrogen for 0.5 h then water (3 ml) was added. This mixture was extracted with diethyl ether (4 × 2.5 ml); the combined diethyl ether extracts were dried over anhydrous $MgSO_4$ then filtered. The solvents were removed *in vacuo* yielding **80** as a pale yellow oil (18.6 mg, 0.07 mmol, 17%). δ_H (250 MHz, $CDCl_3$) 2.02 (m, 1H, H_{5n}), 2.12 (m, 1H, H_{5x}), 2.56 (brs, 2H, H_{3n}, H_4), 2.63 (brs, 1H, H_{3x}), 3.30 (s, 3H, MeO), 3.33 (brs, 1H, H_1), 3.77 (brs, 1H, H_6), 3.81 (brs, 2H, CH_2Ph), 4.14 (brs, 1H, H_7), 7.24 (m, 5H, Ph). ν_{max} 3065s, 3020m, 2304w, 1433m, 1267m, 1116w, 900w cm^{-1}. $^m/_z$ 279 (MH^+).

2-Benzyl-2-azabicyclo[2.2.1]heptane (81)

Lithium aluminium hydride (0.145 g, 3.82 mmol) then 3-bromo-1-benzyl-1-azoniatricyclo[2.2.1.$0^{2,6}$]heptane bromide (**74**) (0.0925 g, 0.27 mmol) were placed in the reaction flask and held under nitrogen. Dry THF (5 ml) was added slowly. The reaction mixture was stirred under nitrogen at 60 °C for 24 h. Excess lithium aluminium hydride was quenched by adding water-saturated diethyl ether. The resulting mixture was filtered and the residue washed with DCM. All solvents were removed *in vacuo* yielding **81** as a yellow oil (29 mg, 0.16 mmol, 59%). R_f (7:3, petrol: diethyl ether) 0.68. [The

spectra were identical to those of an existing sample of **81**]. δ_H (250 MHz, $CDCl_3$) 1.22-1.88 (m, 6H, H_{5x}, H_{5n}, H_{6x}, H_{6n}, H_{7s}, H_{7a}), 2.24 (d, J = 9.1 Hz, 1H, H_{3n}), 2.35 (brs, 1H, H_4), 2.78 (ddd, $J \approx$ 9.1, 3.5, 3.5 Hz, 1H, H_{3x}), 3.21 (brs, 1H, H_1), 3.63 (brs, 2H, CH_2Ph), 7.29 (m, 5H, Ph). ν_{max} 3065s, 2980w, 2295w, 1425m, 1259m, 911w cm^{-1}. $^m/_z$ $C_{13}H_{18}N$ [MH^+] requires 188.14392; observed 188.14398.

anti-7-Bromo-2-benzyl-2-azabicyclo[2.2.1]heptane (82)



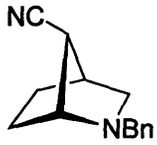
Lithium aluminium hydride (0.53 g, 13.97 mmol) and 3-bromo-1-benzyl-1-azoniatricyclo[2.2.1.$0^{2,6}$]heptane bromide **74** (3.056 g, 8.85 mmol) were cooled to –78 °C under nitrogen in a dry flask. Dry THF (100 ml) was added with stirring and the mixture allowed to warm to –20 °C over a period of 1 h followed by addition of water-saturated diethyl-diethyl ether until effervescence stopped. The mixture was filtered, the residue was washed with DCM and, after drying with anhydrous $MgSO_4$, the solvents were removed *in vacuo* to give crude **82**. Purification by flash chromatography (petrol: diethyl ether, 7:3) gave a pale yellow oil (1.359 g, 5.11 mmol, 58%). R_f (7:3, petrol: diethyl ether) 0.36. δ_H (250 MHz, $CDCl_3$) 1.42, 1.77-2.13 (m, 4H, $H_{5,6}$), 2.43 (brs, 1H, H_4), 2.47 (d, J = 9.2 Hz, 1H, H_{3n}), 2.82 (ddd, $J \approx$ 9.2, 3.3, 3.3 Hz, 1H, H_{3x}), 3.23 (brs, 1H, H_1), 3.68 (dd, J = 13.4, 17.2 Hz, 2H, CH_2Ph), 4.24 (d, J = 1.7 Hz, 1H, H_{7s}), 7.18 (m, 5H, Ph). δ_C (62.9 MHz, $CDCl_3$) 25.2, 26.7 (C_5, C_6), 44.0 (C_4), 53.4 (C_7), 58.0 (C_3), 59.0 (CH_2Ph), 64.9 (C_1), 126.9, 128.1, 128.2 (5 × aryl CH), 139.2 (aryl C). ν_{max} 3064s, 2982m, 2276w, 1504m, 1463m, 1430m, 1380w, 1279s, 1150w, 907m cm^{-1}. $^m/_z$ 266/268 (1:1) (MH^+). $C_{13}H_{16}NBr$ [M^+] requires 265.04661; observed 265.04659. Alternatively, reduction using Red-Al[108] (65+ % wt. solution in toluene, 7.65 ml, 26.0 mmol) and **74** (8.96 g, 26.0 mmol) in dry THF (225 ml) at -10 °C for 2 h gave **82** as a pale yellow oil (6.42 g, 24.1 mmol, 93%).

anti-7-Chloro-2-benzyl-2-azabicyclo[2.2.1]heptane (85)

LiCl (218 mg, 5.13 mmol) was added to a solution of 7-bromo-2-benzyl-2-azabicyclo[2.2.1]heptane (**82**) (63.7 mg, 0.24 mmol) in dry DMF (1.0 ml) in a reaction-vial. The reaction mixture was heated to 100 °C for 24 h, cooled, poured into water (2 ml) then extracted with diethyl-diethyl ether (3 × 2 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and the solvents evaporated *in vacuo* yielding **85** as a pale yellow oil (41 mg, 0.18 mmol, 77%). R_f (EtOAc:MeOH, 9:1) 0.79. δ_H (250 MHz, $CDCl_3$) 1.41, 1.80-2.08 (2 × m, 1H, 3H, $H_{5,6}$), 2.34 (brs, 1H, H_4), 2.38 (d, J = 9.2 Hz, 1H, H_{3n}), 2.85 (ddd, $J \approx$ 9.2, 3.2, 3.2 Hz, 1H, H_{3x}), 3.16 (brs, 1H, H_1), 3.66 (brs, 2H,

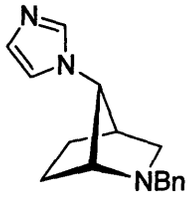
CH_2Ph), 4.20 (brs, 1H, H_{7s}), 7.27 (m, 5H, Ph). δ_C (62.9 MHz, $CDCl_3$) 24.2, 26.2 (C_5, C_6), 43.5 (C_4), 58.0 (C_3), 58.5 (CH_2Ph), 62.0 (C_7), 64.5 (C_1), 126.8, 128.1, 128.3 (5 × aryl CH), 139.1 (aryl C). ν_{max} 3064m, 2991m, 2318w, 1683s, 1500w, 1453w, 1289w, 1256s, 843w cm^{-1}. $^m/_z$ $C_{13}H_{17}NCl$ [MH^+] requires 222.10495; observed 222.10500.

***anti*-7-Cyano-2-benzyl-2-azabicyclo[2.2.1]heptane (87)**



KCN (2.36 g, 35.70 mmol) and 18-crown-6 (~ 0.1 mg) were added to 7-bromo-2-benzyl-2-azabicyclo[2.2.1]heptane (**82**) (0.765 g, 2.88 mmol) in anhydrous DMF (10 ml) and the mixture was stirred vigorously under nitrogen at 110 °C for 24 h. The reaction mixture was filtered and washed with diethyl ether; removal of solvents *in vacuo* gave a yellow oil. Purification by flash chromatography (3:7, petrol: diethyl ether) yielded **87** as a yellow oil (0.405 g, 1.91 mmol, 66%). R_f 0.32. δ_H (250 MHz, $CDCl_3$) 1.49, 1.94 (2 × m, 1H, 3H, H_5, H_6), 2.45 (d, J = 9.4 Hz, 1H, H_{3n}), 2.73 (m, 3H, H_{3x}, H_4, H_{7s}), 3.47 (brs, 1H, H_1), 3.67 (AB, J = 13.4 Hz, 2H, CH_2Ph), 7.29 (m, 5H, Ph). δ_C (62.9 MHz, $CDCl_3$) 26.2, 26.6 (C_5, C_6), 35.3 (C_7), 42.6 (C_4), 58.6 (C_3), 58.7 (CH_2Ph), 64.3 (C_1), 119.5 (CN), 127.0, 128.2, 128.3 (5 × aryl CH), 138.7 (aryl C). ν_{max} 2973s, 2874s, 2234s, 1494s, 1453s cm^{-1}. $^m/_z$ $C_{14}H_{17}N_2$ [MH^+] requires 213.13917; observed 213.13914.

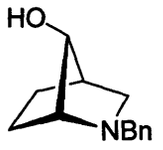
***anti*-7-(Imidazole-1-yl)-2-benzyl-2-azabicyclo[2.2.1]heptane (88)**



Butyllithium (0.31 ml, 1.6 M, 0.49 mmol) was added drop-wise to imidazole (34 mg, 0.50 mmol) in anhydrous DMF (1.5 ml) and this mixture was stirred under nitrogen at 20 °C for 0.25 h. A solution of 7-bromo-2-benzyl-2-azabicyclo[2.2.1]heptane (**82**) (103 mg, 0.39 mmol) in anhydrous DMF (4 ml) was added and after stirring under nitrogen at 100 °C for 96 h, the mixture was filtered and the residue washed with diethyl ether. The combined organic extracts were washed with water (2 × 2 ml), and the solvents removed *in vacuo*. Purification by flash chromatography (diethyl ether) gave **88** as a yellow oil (52 mg, 0.206 mmol, 53%). R_f 0.20. δ_H (250 MHz, $CDCl_3$) 1.42 (m, 1H, H_{6x}), 1.47 (m, 1H, H_{5n}), 1.68 (m, 1H, H_{5x}), 2.00 (m, 1H, H_{6n}), 2.45 (d, J = 9.4 Hz, 1H, H_{3n}), 2.81 (brs, 1H, H_4), 3.15 (ddd, $J \approx$ 9.4, 3.2, 3.2 Hz, 1H, H_{3x}), 3.63 (brs, 1H, H_1), 3.69 (brs, 2H, CH_2Ph), 4.36 (brs, 1H, H_7), 6.87 (brs, 1H, imidazole), 7.06 (brs, 1H, imidazole), 7.14 (m, 5H, Ph), 7.46 (brs, 1H, imidazole). δ_C (62.9 MHz, $CDCl_3$) 23.9, 26.6 (C_5, C_6), 41.1 (C_4), 57.9 (C_3), 58.2 (CH_2Ph), 61.6 (C_7), 62.9 (C_1), 118.5 (imidazole CH), 127.0, 128.2, 128.3 (5 × aryl CH), 129.0, 136.6 (2 × imidazole CH), 139.0 (aryl C). ν_{max} 3052m, 2972m, 2305w, 1501w,

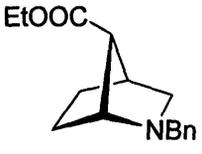
1452w, 1374w, 1265s, 1082w, 910w cm^{-1}. $^{m}/_{z}$ $C_{16}H_{20}N_3$ [MH^+] requires 254.16572; observed 254.16564.

anti-7-Hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (86)



7-Bromo-2-benzyl-2-azabicyclo[2.2.1]heptane (**82**) (110 mg, 0.41 mmol) and LiOH (173 mg, 4.1 mmol) in anhydrous DMF (8 ml) were stirred at 100 °C for 24 h. The reaction mixture was cooled, added to water (30 ml), and extracted with diethyl ether (4 × 25 ml). The combined extracts were washed with water (3 × 35 ml), dried over anhydrous $MgSO_4$ then filtered. Removal of solvents *in vacuo* gave a yellow oil which was chromatographed (9:1, EtOAc: MeOH) yielding **86** as a pale yellow oil (47 mg, 56 %). R_f 0.53. δ_H (300 MHz, $CDCl_3$) 1.34-1.43 (m, 1H, H_{5n}), 1.70-1.78 (m, 1H, H_{6x}), 1.88-2.00 (m, 2H, H_{5x}, H_{6n}), 2.11 (brs, 1H, H_4), 2.19 (d, J = 9.3 Hz, 1H, H_{3n}), 2.40 (brs, OH), 3.03 (brs, 1H, H_1), 3.05 (ddd, $J \approx$ 9.3, 3.6, 3.0 Hz, 1H, H_{3x}), 3.65, 3.70 (AB, J = 13.4 Hz, 2H, CH_2Ph), 4.29 (brs,1H, H_7), 7.21-7.35 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 22.7, 26.5 (C_5, C_6), 41.6 (C_4), 57.7, 58.1 (CH_2Ph, C_3), 62.9 (C_1), 76.3 (C_7), 126.8, 128.2, 128.5 (5 × aryl CH), 139.2 (aryl C). ν_{max} 3053m, 2970m, 2303w, 1421w, 1265s cm^{-1}. $^{m}/_{z}$ $C_{13}H_{18}NO$ [MH^+] requires 204.13884; observed 204.13886. Using the procedure described by Mitch *et al.*[108], **82** (3.06 g, 11.5 mmol) and 1-methyl-2-pyrrolidinone (containing 15% v/v H_2O; 56 ml) were stirred at 100 °C for 67 h. The reaction mixture was diluted with water (150 ml), basified with aqueous NaOH, and extracted with diethyl ether (4 × 100 ml). The combined organic extracts were washed with water (4 × 100 ml), dried over anhydrous $MgSO_4$ then filtered and evaporated to yield **86** as a yellow oil (1.54 g, 66%) showing identical NMR spectra to the sample obtained above.

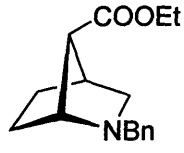
anti-2-Benzyl-2-azabicyclo[2.2.1]heptane-7-carboxylic acid ethyl ester (98)



Aqueous HCl (4 ml, 8 M) was added to 7-cyano-2-benzyl-2-azabicyclo[2.2.1]heptane (**87**) (0.309 g, 1.46 mmol) and stirred under nitrogen at 90 °C for 65 h. The mixture was evaporated to dryness; thionyl chloride (4 ml) was added then stirred at 40 °C for 6 h. The thionyl chloride was removed *in vacuo* then dry ethanol (5 ml) was added and stirred at 20 °C for 0.5 h. After removal of the solvents *in vacuo*; the resulting yellow oil was dissolved in HCl (4 ml, 1 M) and washed with DCM (3 × 4 ml). The aqueous layer was basified with ammonium hydroxide solution (8 ml, 35% ammonia) and extracted with DCM (3 × 4 ml). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of solvents *in vacuo* gave **98** as a yellow oil (0.290 g, 1.12 mmol, 77%; the sample was sufficiently pure for the epimerisation to give **99**). R_f (3:2

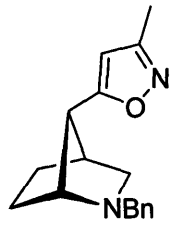
diethyl ether:petrol) 0.41. δ_H (250 MHz, $CDCl_3$) 1.24 (t, J = 7.1 Hz, 3H, CH_3), 1.40, 1.60-1.95 (2 × m, 4H, H_5, H_6), 2.40 (d, J = 9.4 Hz, 1H, H_{3n}), 2.61 (brs, 1H, H_4), 2.86 (ddd, $J \approx$ 9.4, 3.4, 3.4 Hz, 1H, H_{3x}), 2.93 (brs, 1H, H_1), 3.44 (brs, 1H, H_{7s}), 3.66, 3.74 (AB, J = 13.5 Hz, 2H, CH_2Ph), 4.13 (q, J = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 7.33 (m, 5H, Ph). δ_C (62.9 MHz, $CDCl_3$) 14.0 (CH_3), 25.5, 26.9 (C_5, C_6), 40.1 (C_4), 51.2 (C_7), 58.4 (CH_2Ph), 59.9 (C_3), 60.0 ($\underline{C}H_2CH_3$), 62.2 (C_1), 126.8, 128.2, 128.2 (5 × aryl CH), 138.9 (aryl C), 171.7 (CO_2). ν_{max} 3053s, 2982s, 2305w, 1725s, 1452m, 1370m, 1265s, 1214m, 1180m, 1043m, 896w cm^{-1}. $^m/_z$ $C_{16}H_{22}NO_2$ [MH^+] requires 260.16505; observed 260.16510.

syn-2-Benzyl-2-azabicyclo[2.2.1]heptane-7-carboxylic acid ethyl ester (99)



To *anti*-2-benzyl-2-azabicyclo[2.2.1]heptane-7-carboxylic acid ethyl ester (**87**) (3.387 g, 13.10 mmol) was added NaOEt in EtOH (0.63 M, 42 ml) and dry HMPA (0.1 ml) and the mixture was stirred at 65 °C for 24 h. After addition of the mixture to water (50 ml) and extraction with DCM (5 × 60 ml), the organic extracts were combined, dried over anhydrous $MgSO_4$ and filtered. Capillary GC analysis [25 m HP-FFAP column] indicated the presence of both **87** and **99** (anti/syn = 55:45). Chromatography (3:2 diethyl ether: petrol) yielded **87** (1.399 g; 41%), R_f 0.41 and **99** (1.56 g, 6.02 mmol, 46%), R_f 0.59. δ_H (300 MHz, $CDCl_3$) 1.28 (t, J = 7.1 Hz, 3H, CH_3), 1.32-1.54, 1.54-1.69, 1.84 (3 × m, 2H, 1H, 1H, H_5, H_6), 1.93 (d, J = 8.4 Hz, 1H, H_{3n}), 2.48 (brs, 1H, H_7), 2.55 (brs, 1H, H_4), 3.28 (ddd, $J \approx$ 8.4, 3.5, 3.5 Hz, 1H, H_{3x}), 3.48 (brs, 1H, H_1), 3.68 (brs, 2H, CH_2Ph), 4.18, 4.20 (complex - 2 overlapping dq, J = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 7.25-7.28 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 14.3 (CH_3), 23.7, 29.7 (C_5, C_6), 39.4 (C_4), 53.7 (C_7), 55.5, 56.5, 60.0 ($\underline{C}H_2CH_3$, $\underline{C}H_2Ph$, C_3), 62.7 (C_1), 126.5, 128.0 (5 × aryl CH), 140.0 (aryl C), 172.2 (CO_2). ν_{max} 2976s, 2870s, 1733s, 1453s, 1186s cm^{-1}. $^m/_z$ $C_{16}H_{22}NO_2$ [MH^+] requires 260.16505; observed 260.16509.

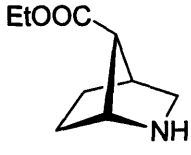
syn-2-Benzyl-7-(3-methyl-isoxazol-5-yl)-2-azabicyclo[2.2.1]heptane (100)



Using the procedure described by Badio *et al.*,[55] acetoxime (129 mg, 1.77 mmol) was dissolved in dry THF (4 ml) and held at 0 °C. Butyllithium (2.21 ml, 1.6 M, 3.53 mmol) was added and the mixture was stirred at 20 °C for 0.8 h. *syn*-2-benzyl-2-azabicyclo[2.2.1]heptane-7-carboxylic acid ethyl ester (**99**) (174 mg, 0.67 mmol) dissolved in dry THF (2 ml) was added. After stirring at 60 °C for 1 h the solvent was evaporated using nitrogen. HCl (8 ml, 10.2 M) was added and the mixture stirred at 80 °C for 4.5 h then 12 h at RT. The reaction mixture was basified with

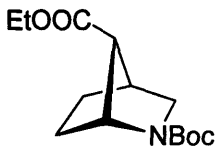
saturated $NaHCO_3$ solution (~ 15 ml) and extracted with DCM (4 × 40 ml). The organic layers were combined and removal of the solvents *in vacuo* gave an orange oil which was dissolved in HCl (1M, 3ml) and washed with diethyl ether (4 × 2 ml). The aqueous layer was basified (NH_4OH solution) and extracted with DCM (4 × 2 ml). The DCM extracts were dried over $MgSO_4$ and filtered. Flash chromatography (9:1, diethyl ether: MeOH) gave **100** as a colourless oil (65 mg, 36%), R_f 0.56. δ_H (300 MHz, $CDCl_3$) 1.45-1.62 (m, 2H, H_{5n}, H_{6x}), 1.74-1.87 (m, 1H, H_{5x}), 2.00-2.13 (m, 1H, H_{6n}), 2.02 (d, J = 9.1 Hz, 1H, H_{3n}), 2.30 (s, 3H, CH_3), 2.52 (brs, 1H, H_4), 2.88 (brs, 1H, H_7), 3.09 (ddd, $J \approx$ 9.1, 3.5, 3.5 Hz, 1H, H_{3x}), 3.46 (brs, 1H, H_1), 3.68, 3.74 (AB, J = 13.8 Hz, 2H, CH_2Ph), 6.16 (s, 1H, isoxazole CH), 7.17-7.33 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 11.5 (isoxazole CO), 24.1, 29.9 (C_5, C_6), 41.8 (C_4), 46.6 (C_7), 55.8, 56.2 (CH_2Ph, C_3), 63.0 (C_1), 102.3 (isoxazole CH), 126.6, 128.1 (5 × aryl CH), 138.8 (aryl C), 159.6, 172.3 (2 × isoxazole C). ν_{max} 2961s, 1601s, 1494m, 1418s, 1370m, 1184m, 1010m. $^m/_z$ $C_{17}H_{21}N_2O$ [MH^+] requires $^m/_z$ 269.16539; observed 269.16537.

anti-2-Azabicyclo[2.2.1]heptane-7-carboxylic acid ethyl ester (103)



A solution of *anti*-2-benzyl-2-azabicyclo[2.2.1]heptane-7-carboxylic acid ethyl ester (**98**) (1.399 g, 5.40 mmol) in dry MeOH (40 ml) was hydrogenolyzed over Pd/C (10%, 0.25 g) with stirring for 24 h. The reaction mixture was filtered through celite and the solvent removed *in vacuo* to leave a yellow oil which was chromatographed (17:3, diethyl ether: MeOH) to provide **103** (0.612 g, 3.62 mmol 67%), R_f 0.29. δ_H (300 MHz, $CDCl_3$) 1.25 (t, J = 7.1 Hz, 3H, CH_3), 1.48-1.57, 1.77-1.98 (2 × m, 2H, 2H, H_5, H_6), 2.62 (brs, 1H, H_4), 2.69 (d, J = 9.5 Hz, 1H, H_{3n}), 2.73 (brs, 1H, H_7), 3.01 (ddd, $J \approx$ 9.5, 3.0, 3.0 Hz, 1H, H_{3x}), 3.61 (brs, 1H, H_1), 4.12 (q, J = 7.1 Hz, 2H, $C\underline{H}_2CH_3$). δ_C (75.5 MHz, $CDCl_3$) 13.9 (CH_3), 26.8, 30.9 (C_5, C_6), 39.2 (C_4), 51.9 (C_3), 53.6 (C_7), 57.4 (C_1), 60.0 ($\underline{C}H_2CH_3$), 171.5 (CO). ν_{max} 3407b, 2979s, 1730s, 1541m, 1372m, 1226s, 1051m cm^{-1}. $^m/_z$ $C_9H_{16}NO_2$ [MH^+] requires 170.11810; observed 170.11811.

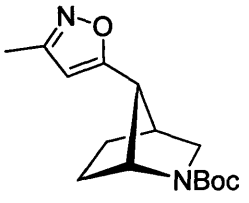
anti-2-Boc-2-azabicyclo[2.2.1]heptane-7-carboxylic acid ethyl ester (104)



anti-2-Azabicyclo[2.2.1]heptane-7-carboxylic acid ethyl ester (**103**) (103 mg, 0.61 mmol), Boc_2O (202 mg, 0.93 mmol) and $NaHCO_3$ (187 mg, 2.23 mmol) were stirred in THF (2 ml) and water (6 ml) at RT for 20 h. The reaction mixture was extracted with diethyl ether (4 × 4 ml), the organic extracts were combined, dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo*. The resulting colorless oil was chromatographed (7:3 diethyl ether:petrol) yielding **104** (105 mg,

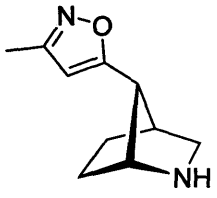
0.39 mmol, 64%), R_f 0.54. δ_H [300 MHz, $CDCl_3$; where there is signal duplication (slow N-CO rotation - ratio ~52:48) the minor rotamer signal is shown in italics] 1.27 (bt, J = 7.0 Hz, 3H, CH_3), *1.45*, 1.46 (2 × s, 9H, Boc), 1.57-1.88 (m, 4H, H_5, H_6), 2.76 (m, 2H, H_4, H_7), *3.01*, 3.07 (2 × d, J = 9.7 Hz, 1H, H_{3n}), 3.32, *3.35* (2 × brs, 1H, H_{3x}), 4.15 (bq, J = 7.0 Hz, 2H, $C\underline{H}_2CH_3$), 4.31, *4.45* (2 × brs, 1H, H_1). δ_C (75.5 MHz, $CDCl_3$) 14.1 ($CH_2\underline{C}H_3$), *25.8*, 26.0, [28.5 (Boc CH_3)] *29.1*, 29.3 (C_5, C_6), 39.1, *39.6* (C_4), *52.6*, 53.0 (C_7), 53.1, *53.7* (C_3), *57.3*, 58.1 (C_1), 60.5 ($\underline{C}H_2CH_3$), *79.2*, 79.3 (Boc C), *153.7*, 154.1 (Boc CO), 170.5 (CO). ν_{max} 2977s, 1736s, 1697s, 1408s, 1173s, 1101s, 1048s cm^{-1}. $^m/_z$ $C_{14}H_{24}NO_4$ (MH^+) requires 270.17053; observed 270.17050.

anti-7-(3-Methyl-isoxazol-5-yl)-2-Boc-2-azabicyclo[2.2.1]heptane (105)



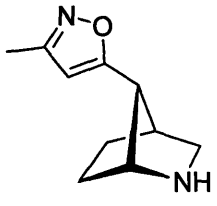
Using the procedure described by Fitch *et al.*,[65] a solution of butyllithium (0.58 ml, 1.6 M in hexanes, 0.93 mmol) was added drop-wise over 10 min to a solution of acetoxime (34 mg, 0.47 mmol) in dry THF (1 ml) under nitrogen at 0 °C. After stirring for 2 h at 0 °C a solution of *anti*-2-Boc-2-azabicyclo[2.2.1]heptane-7-carboxylic acid ethyl ester (**104**) (58 mg, 0.22 mmol) in dry THF (1 ml) was added over 10 min. The reaction mixture was stirred under nitrogen at 0 °C for 20 h then transferred to vigorously stirred HCl (1 M, 8 ml) over 40 min. This mixture was neutralized ($NaHCO_3$) and extracted with DCM (5 × 15 ml), the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo*. The resulting yellow oil was chromatographed (7:3 diethyl ether:petrol) yielding **105** (19 mg, 48% based on recovered **104**), R_f 0.21 and **104** (19 mg),. δ_H [300 MHz, $CDCl_3$; where there is signal duplication (slow N-CO rotation - ratio ~2:3) the minor rotamer signal is shown in italics] 1.47 (s, 9H, Boc), 1.60-1.86 (m, 4H, H_5, H_6), 2.28 (s, 3H, CH_3), 2.85 (brs, 1H, H_4), 3.14 (brs, 1H, H_{3n}), 3.45 (brddd, $J \approx$ 9.6, 2.7, 2.7 Hz, 1H, H_{3x}), 4.43, *4.51* (2 × brs, 1H, H_1), 5.88 (brs, 1H, isoxazole CH). δ_C (100.6 MHz, $CDCl_3$) 11.4 (isoxazole CH_3), 25.9, [28.5 (Boc CH_3),] *28.9*, 29.2 (C_5, C_6), 40.1, *40.7* (C_4), *46.0*, 46.3 (C_7), 53.2, *53.7* (C_3), *58.3*, 59.3 (C_1), 79.6 (Boc C), 102.6 (isoxazole CH), 154.2 (Boc CO), 159.7, 170.0 (2 × isoxazole C). ν_{max} 2976m, 1694s, 1406s, 1173m, 1112m cm^{-1}. $^m/_z$ $C_{15}H_{23}N_2O_3$ (MH^+) requires 279.17087; observed 279.17085.

anti-7-(3-Methyl-isoxazol-5-yl)-2-azabicyclo[2.2.1]heptane (_anti_-isoepiboxidine) (52)



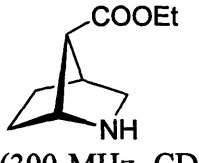
anti-2-Boc-7-(3-methyl-isoxazol-5-yl)-2-azabicyclo[2.2.1]heptane (**105**) (8.3 mg, 0.030 mmol) was stirred in a mixture of EtOH (0.435 ml), ethyl acetate (1.205 ml) and acetyl chloride (0.359 ml) at 0 °C for 1 h. The reaction mixture was evaporated to dryness to give the hydrochloride salt of **52** (6.4 mg, 99 %). Data for the free amine **52**: δ_H (300 MHz, $CDCl_3$) 1.40-1.75 (m, 4H, H_5, H_6), 1.9 (brs, NH), 2.27 (s, 3H, CH_3), 2.71 (brs, 1H, H_4), 2.77 (d, J = 9.6 Hz, 1H, H_{3n}), 3.09 (brs, 1H, H_7), 3.13 (m,1H, H_{3x}), 3.71 (brs, 1H, H_1), 5.85 (s, 1H, isoxazole CH). δ_C (75.5 MHz, $CDCl_3$) 11.4 (isoxazole CH_3), 26.8, 31.0 (C_5, C_6), 40.4, 47.2 (C_4, C_7), 52.3 (C_3), 58.7 (C_1), 102.3 (isoxazole CH), 159.6, 171.4 (2 × isoxazole C). ν_{max} 3392b, 2968s, 2876m, 1725w, 1602s, 1534m, 1415s cm^{-1}. $^m/_z$ $C_{10}H_{15}N_2O$ [MH^+] requires $^m/_z$ 179.11844; observed 179.11839.

Direct formation of _anti_-7-(3-methyl-isoxazol-5-yl)-2-azabicyclo[2.2.1]heptane (52) from 103



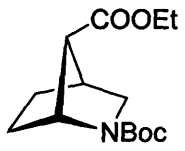
The procedure described for **105** was followed using acetoxime (76 mg, 1.04 mmol) in dry THF (3 ml), butyllithium (1.43 ml, 1.6 M, 2.29 mmol) and the _anti_-2-azabicyclo[2.2.1]heptane-7-carboxylic acid ethyl ester (**103**) (65 mg, 0.38 mmol) in dry THF (2 ml). HCl (8 ml, 10.2 M) was used in the second step and, after work-up **52** was isolated as an orange oil (28 mg). Quantitative ^1H NMR analysis gave a yield of 16.2 mg, 24%.

syn-2-Azabicyclo[2.2.1]heptane-7-carboxylic acid ethyl ester (106)



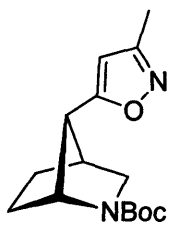
syn-2-Benzyl-2-azabicyclo[2.2.1]heptane-7-carboxylic acid ethyl ester (**99**) (1.56 g, 6.02 mmol) in dry MeOH (40 ml) was hydrogenolyzed as described for **103** to yield **106** as a yellow oil (0.625 g, 3.67 mmol 61%), R_f 0.30. δ_H (300 MHz, $CDCl_3$) 1.27 (t, J = 7.1 Hz, 3H, CH_3), 1.40-1.77 (m, 4H, H_5, H_6), 2.0 (brs NH), 2.51 (brs, 1H, H_7), 2.59 (brs, 1H, H_4), 2.61 (d, J = 9.8 Hz, 1H, H_{3n}), 3.13 (ddd, $J \approx$ 9.8, 3.1, 3.1 Hz, 1H, H_{3x}), 3.61 (brd, ≈ 2.6 Hz, 1H, H_1), 4.14 (complex 'q', J = 7.1 Hz, 2H, $C\underline{H}_2CH_3$). δ_C (75.5 MHz, $CDCl_3$) 13.9 (CH_3), 28.8, 30.8 (C_5, C_6), 40.0 (C_4), 49.8, [52.2, 52.4 (C_7), 58.27, 58.31 (C_1),] 60.0 (C_3, $\underline{C}H_2CH_3$), 172.3, 172.7 (CO). ν_{max} 3406b, 2977s, 1728s, 1542m, 1409s, 1303m, 1192m, 1037m cm^{-1}. $^m/_z$ $C_9H_{16}NO_2$ [MH^+] requires $^m/_z$ 170.11810; observed 170.11812.

syn-2-Boc-2-azabicyclo[2.2.1]heptane-7-carboxylic acid ethyl ester (107)



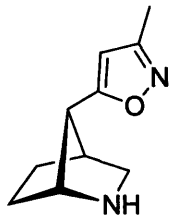
Treatment of *syn*-2-azabicyclo[2.2.1]heptane-7-carboxylic acid ethyl ester (**106**) (128 mg, 0.76 mmol) with Boc_2O (262 mg, 1.20 mmol) and $NaHCO_3$ (200 mg, 2.38 mmol), in THF (2 ml) and water (6 ml) using the method described for **104** gave **107** as a pale yellow oil (130 mg, 0.49 mmol, 64%), R_f (7:3, diethyl ether: petrol) 0.39. δ_H [300 MHz, $CDCl_3$; where there is signal duplication due to slow N-CO rotation (ratio ~45:55) the minor rotamer signal is shown in italics.] 1.24 (t, J = 7.1 Hz, 3H, CH_3), *1.44*, 1.46 (2 × s, 9H, Boc), 1.64-1.80 (m, 4H, H_5, H_6), 2.53 (brs, 1H, H_7), *2.72*, 2.75 (2 × brs, 1H, H_4), *2.94*, 3.00 (2 × d, J = 9.8 Hz, 1H, H_{3n}), 3.51 (m, 1H, H_{3x}), 4.13 (m, 2H, $C\underline{H}_2CH_3$), 4.39, *4.51* (2 × brs, 1H, H_1). δ_C (75.5 MHz, $CDCl_3$) 14.2 ($CH_2\underline{C}H_3$), 27.4, [28.5 (Boc CH_3),] 30.7 (C_5, C_6), 39.4, 40.0 (C_4), 50.6, 51.2 (C_3), 52.2, 53.0 (C_7), 58.2, 58.9 (C_1), 60.4, 60.5 ($\underline{C}H_2CH_3$), 79.0, 79.1 (Boc C), 154.2, 154.5 (Boc CO), 170.6, 170.9 (CO_2). ν_{max} 2974m, 1735s, 1696s, 1406s, 1163s, 1104s cm^{-1}. $^m/_z$ $C_{14}H_{24}NO_4$ [MH^+] requires 270.17053; observed 270.17057.

syn-7-(3-Methyl-isoxazol-5-yl)-2-Boc-2-azabicyclo[2.2.1]heptane (108)



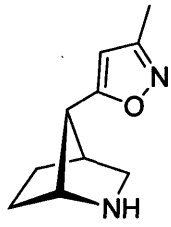
Acetoxime (74 mg, 1.01 mmol), butyllithium in hexanes (1.27 ml, 1.6 M, 2.03 mmol) and *syn*-2-Boc-2-azabicyclo[2.2.1]heptane-7-carboxylic acid ethyl ester (**107**) (133 mg, 0.49 mmol) were reacted using the procedure described for **105** to give **108** (61 mg, 52% based on recovered **107**). R_f (7:3, diethyl ether: petrol) 0.35, and recovered **107** (19 mg). δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] *1.43*, 1.47 (2 × s, 9H, Boc), 1.57-1.95 (m, 4H, H_5, H_6), *2.24*, 2.25 (2 × s, 3H, CH_3), 2.74, *2.80* (2 × brs, 1H, H_4), 2.94, *2.95* (2 × brs, 1H, H_7), *2.96*, 3.03 (2 × d, J = 10.0 Hz, 1H, H_{3n}), 3.15, *3.27* (2 × ddd, $J \approx$ 10.0, 2.7, 2.7 Hz, 1H, H_{3x}), *4.35*, 4.51 (2 × brs, 1H, H_1), 5.84, *5.91* (2 × brs, 1H, isoxazole CH). δ_C (100.6 MHz, $CDCl_3$) 11.4 (isoxazole CH_3), 28.1, [*28.5*, 28.6 (Boc CH_3)], *30.6*, 30.9 (C_5, C_6), *40.8*, 41.4 (C_4), 45.6, *46.1* (C_7), 50.1, *50.8* (C_3), *58.6*, 59.7 (C_1), *79.4*, 79.6 (Boc C), 102.1, *102.3* (isoxazole CH), 154.5 (Boc CO), 159.8, *170.2*, 170.4 (2 × isoxazole C). ν_{max} 2976s, 2359s, 1694s, 1406s, 1150s, 1112s cm^{-1}. $^m/_z$ $C_{13}H_{23}N_2O_3$ [MH^+] requires $^m/_z$ 279.17087; observed 279.17088.

syn-7-(3-Methyl-isoxazol-5-yl)-2-azabicyclo[2.2.1]heptane (_syn_-isoepiboxidine) (51)



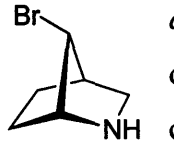
syn-2-Boc-7-(3-methyl-isoxazol-5-yl)-2-azabicyclo[2.2.1]heptane (**108**) (12.5 mg, 0.0450 mmol) was deprotected as described for compound **52**, yielding the hydrochloride salt of compound **51** (9.6 mg, 99 %). Data for the free amine **51**: δ_H (300 MHz, $CDCl_3$) 1.49-1.68 (m, 2H, H_{5n}, H_{6n}), 1.72-1.91 (m, 2H, H_{5x}, H_{6x}), 2.27 (bs, 3H, CH_3, NH), 2.66 (brs, 1H, H_4), 2.67 (d, J = 9.9 Hz, 1H, H_{3n}), 2.91 (brs, 1H, H_7), 2.99 (ddd, $J \approx$ 9.9, 3.2, 3.2 Hz, 1H, H_{3x}), 3.66 (brd, J = 2.5 Hz, 1H, H_1), 5.96 (s, 1H, isoxazole CH). δ_C (75.5 MHz, $CDCl_3$) 11.3 (isoxazole CH_3), 29.0, 31.9 (C_5, C_6), 40.8, 46.5 (C_4, C_7), 49.9 (C_3), 59.2 (C_1), 102.4 (isoxazole CH), 159.7, 171.6 (2 × isoxazole C). ν_{max} 3400b, 2966s, 2877s, 1602s, 1418s cm^{-1}. $^m/_z$ $C_9H_{16}NO_2$ [MH^+] requires 179.11844; observed 179.11842.

Direct formation of _syn_-7-(3-methyl-isoxazol-5-yl)-2-azabicyclo[2.2.1]heptane (51) from 106



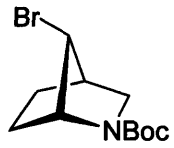
Acetoxime (72 mg, 0.99 mmol) in dry THF (3 ml) was treated with butyllithium (1.30 ml, 1.6 M, 2.08 mmol) and the _syn_-2-azabicyclo[2.2.1]heptane-7-carboxylic acid ethyl ester (**106**) (54 mg, 0.32 mmol) in dry THF (2 ml) following the procedure described for **105**. Following work-up using HCl (8 ml, 10.2 M), **51** was isolated as an orange oil (30 mg). Quantitative ^1H NMR analysis using an internal standard (DCM) gave a yield of 14.6 mg, 26%.

anti-7-Bromo-2-azabicyclo[2.2.1]heptane (120)



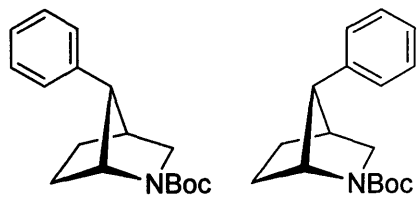
anti-7-Bromo-2-benzyl-2-azabicyclo[2.2.1]heptane (**82**) (2.80 g, 0.012 mol) in dry methanol (60 ml) was hydrogenated as described for **103**, flash chromatography (diethyl ether: methanol; 9:1) gave **120** as a colourless oil (32%). δ_H (300 MHz, $CDCl_3$) 1.42-1.63 (m, 2H, H_{5n}, H_{6n}), 1.97-2.17 (m, 2H, H_{5x}, H_{6x}), 2.40 (dd, 3.8, 3.8 Hz, 1H, H_4), 2.68 (d, 9.7 Hz, 1H, H_{3n}), 3.00 (ddd, $J \approx$ 9.7, 3.4, 3.4 Hz, 1H, H_{3x}), 3.37 (dd, J = 3.1, 3.1 Hz, 1H, H_1), 4.04 (dd, 1.5, 1.5 Hz, 1H, H_7). δ_C (75.5 MHz, $CDCl_3$) 26.5, 29.3 (C_5, C_6), 42.3 (C_4), 49.9 (C_3), 55.0 (C_7), 60.2 (C_1). ν_{max} 2976s, 2524m, 1636s, 1522m, 1421s cm^{-1}. $^m/_z$ $C_6H_{11}NBr$ [MH^+] requires 176.00749; observed 176.00751.

anti-7-Bromo-2-Boc-2-azabicyclo[2.2.1]heptane (121)



Following the procedure described for **104** using: *anti*-7-bromo-2-azabicyclo[2.2.1]heptane (**120**) (344 mg, 1.95 mmol); Boc_2O (694 mg, 3.18 mmol), $NaHCO_3$ (595 mg, 6.77 mmol); THF (4 ml), H_2O (12 ml). After reaction at RT for 72 h **121** was obtained as a white semi-solid (448 mg, 1.62 mmol, 83%) R_f (diethyl ether:petrol) 0.57. δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] 1.45 (brs, 9H, Boc), 1.04-1.88, 2.02-2.23 (2 × m, 4H, H_5, H_6), 2.57 (brs, 1H, H_4), *3.05*, 3.10 (2 × d, J = 9.6 Hz, 1H, H_{3n}), 3.34 (ddd, $J \approx$ 9.6, 3.1, 3.1 Hz, 1H, H_{3x}), 4.05 (brs, 1H, H_7), 4.05, *4.25* (2 × brs, 1H, H_1). δ_C (75.5 MHz, $CDCl_3$) 25.6, 28.1 (C_5, C_6), 28.4 (Boc CH_3), 43.0, *43.5* (C_4), 51.9 (C_7), 51.3, *52.1* (C_3), *59.7*, 60.8 (C_1), 79.7 (Boc C), 153.9 (Boc CO). ν_{max} 2977s, 1692s, 1398s, 1331m, 1304m, 1246m, 1155s, 1111s cm^{-1}. $^m/_z$ $C_{11}H_{19}NO_2Br$ [MH^+] requires 276.05992; observed 276.05987.

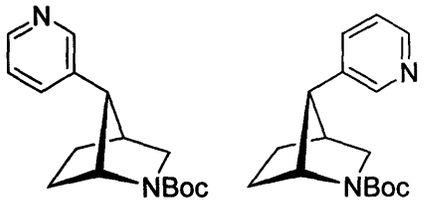
anti- and _syn_-7-phenyl-2-Boc-2-azabicyclo[2.2.1]heptane (122 and 123)



Using a procedure adapted from that described by Zhou and Fu.[123] In a glove box, $Ni(cod)_2$ (20 mg, 0.073 mmol) was placed in a two-necked flask. Bathophenanthroline (49 mg, 0.147 mmol), benzene boronic acid (57 mg, 0.467 mmol) and freshly sublimed ^{t}BuOK (103 mg, 0.918 mmol) were added, the reaction vessel was evacuated and refilled with nitrogen thrice. Dry *s*-BuOH (7 ml) was added and the reaction mixture stirred for 10 min at RT under nitrogen, the reaction mixture colour changed to deep-purple, indicating the formation of the active complex. A solution of the halide (**121**) (105 mg, 0.380 mmol) in *s*-BuOH (2 ml) was added and the resulting mixture stirred under nitrogen at reflux for 48 h, then cooled and passed through a short pad of silica. Solvents were removed *in vacuo*, the resulting residue was flash chromatographed (diethyl ether:petrol; 1:1) to give **122** and **123** as a pale yellow oil (~ 40:60; *anti*-:*syn*-)(52 mg, 0.19 mmol, 50%) R_f 0.49. δ_H [300 MHz, $CDCl_3$; the signals corresponding to the minor (*anti*-) epimer are underlined; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] 1.37, 1.45, 1.48, 1.50 (4 × brs, 9H, Boc), 1.50-1.73, 1.73-2.01 (2 × m, 4H, H_5, H_6), *2.64*, 2.65, <u>2.86</u> (3 × brs, 1H, H_4), 2.86-3.02, 3.10-3.27 (2 × m, 2H, H_{3n}, H_7), <u>3.42-3.52</u>, 3.06 (m, ddd, $J \approx$ 9.9, 2.7, 2.7 Hz, 1H, H_{3x}), <u>4.43</u>, *4.47*, <u>*4.59*</u>, 4.63 (4 × brs, 1H, H_1), 7.14-7.35 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 25.1, 25.2, 28.4, 30.8, 31.1 (C_5, C_6), 28.1, 28.2, 28.5, 28.6 (Boc CH_3), <u>*39.1*</u>, <u>39.6</u>, 41.6, *42.4* (C_4), *49.7*, 50.4, [<u>*51.9*</u>, 52.1, <u>52.3</u>, *52.5*

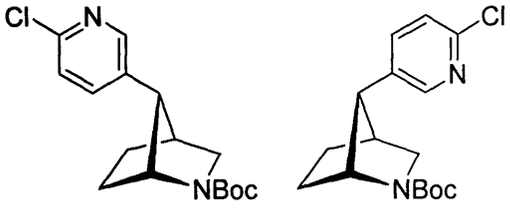
(C_7)] 53.6, *54.2* (C_3), 57.4, *58.4*, *58.6*, 59.4 (C_1), 78.8, 79.0, 79.1 (Boc C), 126.2, 126.3, 127.3, 127.5, 127.6, 128.2, 128.3, 128.4 (Ph CH), 138.1, 138.3, 138.4 (Ph C), 154.1, 154.5 (Boc CO). ν_{max} 2972s, 2879s, 1694s, 1498m, 1477m, 1407s, 1365s, 1161s, 1100s cm^{-1}. $^m/_z$ $C_{17}H_{24}NO_2$ [MH^+] requires 274.18070; observed 274.18072.

anti- and _syn_-7-(pyridin-3-yl)-2-Boc-2-azabicyclo[2.2.1]heptane (124 and 125)



The procedure described for the synthesis of **122** and **123** was followed using: $Ni(cod)_2$ (14 mg, 0.051 mmol); bathophenanthroline (34 mg, 0.102 mmol); 3-pyridyl boronic acid (43 mg, 0.35 mmol); ^{t}BuOK (145 mg, 1.29 mmol) and *anti*-7-bromo-2-Boc-2-azabicyclo[2.2.1]heptane (**121**) (80 mg, 0.29 mmol). Flash chromatography (diethyl ether) gave a mixture of **124** and **125** as a pale yellow oil (~ 25:75; *anti*-:*syn*-)(26 mg, 0.095 mmol, 33%) R_f 0.12. δ_H [300 MHz, $CDCl_3$; the signals corresponding to the minor (*anti*-) epimer are underlined; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] 1.27-2.05 (m, 4H, H_5, H_6), 1.38, 1.48, 1.50 (3 × brs, 9H, Boc), 2.71, 2.92 (2 × brs, 1H, H_4), 2.93-3.04, 3.13-3.25, 3.44-3.53 (3 × m, 3H, H_{3x}, H_{3n}, H_7), 4.48, *4.51*, *4.65*, 4.65 (4 × brs, 1H, H_1), 7.16-7.29, 7.47-7.64, 8.43-8.58 (3 × m, 4H, pyridyl). δ_C (75.5 MHz, $CDCl_3$) 24.9, 25.1, 28.0, 28.2, 28.3, 30.3, 30.7, 31.1 (C_5, C_6), 28.4, 28.6 (Boc CH_3), *39.0*, 39.5, 41.5, *42.3* (C_4), 49.6, *50.2*, 53.5, *54.0* (C_3), 49.9, 50.4 (C_7), *57.3*, *58.4*, 58.5, 59.1 (C_1), 79.2, 79.4 (Boc C), 123.3, 123.7, 135.0, 135.3, 147.7, 147.8, 148.2, 149.0, 149.3, 149.5 (pyridyl CH), 133.6, 134.0, 134.4 (pyridyl C), 154.4 (Boc CO). ν_{max} 2971m, 1690s, 1479w, 1408s, 1365m, 1148m, 1102m cm^{-1}. $^m/_z$ $C_{16}H_{23}N_2O_2$ [MH^+] requires 275.17595; observed 275.17591.

anti- and _syn_-7-(6-chloro-pyridin-3-yl)-2-Boc-2-azabicyclo[2.2.1]heptane (128 and 129)



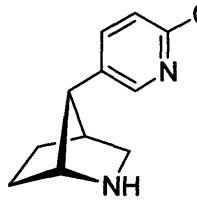
The procedure described for the synthesis of **122** and **123** was followed using: $Ni(cod)_2$ (95 mg, 0.35 mmol); bathophenanthroline (228 mg, 0.69 mmol); 4-chloro-3-pyridyl boronic acid (148 mg, 0.94 mmol); ^{t}BuOK (136 mg, 1.22 mmol) and *anti*-7-bromo-2-Boc-2-azabicyclo[2.2.1]heptane (**121**) (210 mg, 0.76 mmol) except the reaction mixture was stirred at 50 °C for 12 h rather than 100 °C for 48 h. Flash chromatography (diethyl ether) of the crude residue gave a mixture of **128** and **129** as a pale yellow oil (~ 25:75; *anti*-:*syn*-)(69 mg, 0.22 mmol, 30%) R_f 0.73. δ_H [300 MHz, $CDCl_3$; the signals corresponding to the minor (*anti*-) epimer are

underlined; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] 1.39, 1.48, 1.50 (3 × brs, 9H, Boc), 1.44-2.04 (m, 4H, H_5, H_6), 2.69, 2.91 (2 × brs, 1H, H_4), 2.95, 3.02, 3.13-3.25, 3.44-3.53 (brs, brs, m, m, 3H, H_{3x}, H_{3n}), 4.45, *4.48*, 4.61 4 × brs, 1H, H_1), 7.22-7.33 (m, 1H, $H_{5'}$), 7.47-7.60 (m, 1H, $H_{4'}$), 8.23-8.32 (m, 1H, $H_{2'}$). δ_C (75.5 MHz, $CDCl_3$) *28.1*, 28.2, *30.6*, 31.0 (C_5, C_6), 28.3, 28.5 (Boc CH_3), *39.0*, 39.4, 41.5, *42.4* (C_4), 49.1, *49.5* (C_7), 53.3, *53.8*, *49.4*, 50.0 (C_3), 57.2, *58.0*, *58.4*, 59.0 (C_1), 79.3, 79.5 (Boc C), 123.8, 123.9, 124.0 (C_5), 132.5, 132.8, 132.9 ($C_{3'}$), 138.0, 138.2 ($C_{4'}$), 148.8 ($C_{6'}$), 149.3, 149.4 ($C_{2'}$), 154.2, 154.3 (Boc CO). ν_{max} 2974m, 2878m, 2242w, 1684s,1586m, 1560m, 1462m, 1404s, 1365m cm^{-1}. Further chromatographic separation (diethyl ether) allowed the isolation of a sample of the major (*syn*-) epimer **129** as a yellow oil: δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] 1.41, 1.50 (2 × brs, 9H, Boc), 1.61-2.04 (m, 4H, H_5, H_6), 2.97, 3.03 (brs, m, 3H, H_{3x}, H_{3n}, H_7), 2.69 (brs, 1H, H_4), *4.49*, 4.63 (2 × brs, 1H, H_1), 7.26 (m, 1H, $H_{5'}$), 7.55 (m, 1H, $H_{4'}$), 8.32 (m, 1H, $H_{2'}$). δ_C (75.5 MHz, $CDCl_3$) *28.2*, 28.3, 30.7, *31.1* (C_5, C_6), 28.4, *28.6* (Boc CH_3), 41.7, *42.5* (C_4), 49.2, *49.8* (C_7), *49.5*, 50.1 (C_3), 57.4, *58.5* (C_1), *79.4*, 79.6 (Boc C), *123.9*, 124.0, *138.0*, 138.2, 149.3, *149.5* (pyridyl CH), 132.9, *133.0* (pyridyl C), 154.3 (Boc CO). ν_{max} 2970s, 2934s, 1696s, 1606m, 1488s, 1406s, 1284s cm^{-1}. $^m/_z$ $C_{16}H_{22}N_2O_2Cl$ [MH^+] requires 309.13698; observed 309.13692.

2-Boc-2-azabicyclo[2.2.1]heptane (130)

The de-functionalised by-product **130** was isolated from all cross-coupling reactions (i.e. in the preparation of **122-125**, **128** and **129**) typically in ~ 20% yield. An accurate mass determination for **130** could not be obtained but the product of de-protection was found to be 2-azabicyclo[2.2.1]heptane. δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] 1.15-1.48, 1.53-1.75 (2 × m, 6H, H_5, H_6, H_7), 1.46 (brs, 9H, Boc), 2.50 (brs, 1H, H_4), *2.93*, 3.00 (2 × brd, J = 9.5 Hz, H_{3n}), 3.23 (m, 1H, H_{3x}), *4.13*, 4.26 (2 × brs, 1H, H_1). δ_C (75.5 MHz, $CDCl_3$) 27.4, *27.5*, *30.6*, 30.9 (C_5, C_6), 28.6 (Boc CH_3), 36.9 (C_4), *37.3*, 37.8 (C_7), 52.8, *53.3* (C_3), *55.9*, 57.0 (C_1), 78.8 (Boc C). ν_{max} 2970s, 1670s, 1412m, 1102m cm^{-1}. Removal of the Boc protecting-group from **130** using the procedure described for **52** gave 2-azabicyclo[2.2.1]heptane $^m/_z$ 98 (MH^+).

syn-7-(6-Chloro-pyridin-3-yl)-2-azabicyclo[2.2.1]heptane (_syn_-isoepibatidine) (49)

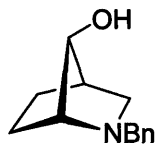


syn- and *anti*-7-(6-Chloro-pyridin-3-yl)-2-Boc-2-azabicyclo[2.2.1]heptane (**129** and **128**, 75:25) (476 mg, 1.54 mmol) were dissolved in ethyl acetate (50 ml), ethanol (10.4 ml) and acetyl chloride (8.6 ml) were added with cooling in ice, the reaction mixture was allowed to reach RT and stirred for 4 h before being evaporated to dryness. The crude mixture of epimers of isoepibatidine hydrochloride salts was subjected to a solid-liquid extraction using DCM to give a sample of pure **49** (94 mg) and a sample containing **49** and **50** (2:1, 107 mg)(53% total yield). Data for free amine of **49:** δ_H (300 MHz, $CDCl_3$) 1.24-1.50, 1.50-1.72, 1.72-1.93 (3 × m, 4H, H_5, H_6), 2.63 (brs, 1H, H_4), 2.68 (d, J = 10.1 Hz, 1H, H_{3n}), 2.76 (ddd, $J \approx$ 10.1, 2.9, 2.9 Hz, 1H, H_{3x}), 3.71 (brs, 1H, H_1), 2.89 (brs, 1H, H_7), 7.26 (s, 1H, pyridyl H_2), 7.69 (dd, J = 3.1, 0.5 Hz, 1H, pyridyl H_4), 8.36 (d, J = 2.4 Hz, 1H, pyridyl H_5). δ_C (75.5 MHz, $CDCl_3$) 29.1, 32.9 (C_5, C_6), 40.7 (C_4), 48.9 (C_3), 49.8 (C_7), 58.4 (C_1), 124.0, 138.5, 149.4 (pyridyl). $^m/_z$ 209/211 (MH^+). ν_{max} 2970s, 2750w, 2706w, 1622m, 1588w, 1561w cm^{-1}. $^m/_z$ $C_{11}H_{14}N_2Cl$ [MH^+] requires 209.08455; observed 209.08454. Tosic acid salt of **49** (white crystalline solid): m.p. 186-190 °C. Analysis: $C_{18}H_{21}N_2O_3SCl$ requires: C, 56.76; H, 5.56; N, 7.35; observed: C, 56.82; H, 5.46; N, 7.26.

7-Keto-2-benzyl-2-azabicyclo[2.2.1]heptane (159)

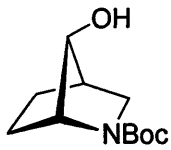
DMSO (0.19 ml, 2.80 mmol) in dry DCM (3 ml) was added drop-wise to oxalyl chloride (0.12 ml, 1.40 mmol) in dry DCM (3 ml) at -78°C and stirred under nitrogen for 0.5 h. The alcohol **86** (114 mg, 0.56 mmol) in dry DCM (3 ml) was added and the resulting mixture stirred under nitrogen at -78°C for 0.25 h, triethylamine (0.47 ml, 3.36 mmol) was added and the mixture allowed to reach RT slowly. The reaction mixture was washed with water (2 × 6 ml) then saturated $NaHCO_3$ solution (5 × 6 ml), the organic layer was dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo*, flash chromatography (diethyl ether) gave **159** as an orange oil (70 mg, 0.35 mmol, 62%) R_f 0.13. δ_H (400 MHz, $CDCl_3$) 1.67-2.15 (m, 4H, H_5, H_6), 2.05 (t, J = 4.1 Hz, 1H, H_4), 2.65 (d, J = 3.3 Hz, 1H, H_1), 2.81 (d, J = 9.3 Hz, 1H, H_{3n}), 2.99 (ddd, J = 9.3, 4.1, 2.7 Hz, 1H, H_{3x}), 3.70 (brs, 2H, CH_2Ph), 7.20-7.42 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 22.5, 23.9 (C_5, C_6), 39.6 (C_4), 55.5, [58.1 (C_1)], 59.3 (C_3, $\underline{C}H_2Ph$), 127.2, 128.4, 128.7 (Ph). ν_{max} 2960s, 1770m, 1726m, 1650m, 1494m, 1454m, 1278m cm^{-1}. $^m/_z$ $C_{13}H_{16}NO$ [MH^+] requires 202.12319; observed 202.12312.

syn-7-Hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (158)



Sodium borohydride (85 mg, 2.24 mmol) was added to 7-keto-2-benzyl-2-azabicyclo[2.2.1]heptane (**159**) (66 mg, 0.33 mmol) in dry methanol (10 ml) with cooling in ice; the reaction mixture was stirred under nitrogen at 60 °C for 48 h. Water (6 ml) was added and the resulting mixture extracted with DCM (4 × 7 ml), the combined organic extracts were dried over anhydrous magnesium sulphate, filtered and the solvents removed *in vacuo*. The crude residue contained **158** and *anti*-7-hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (**86**) (95:5 by integration of ^{1}H NMR signals). Flash chromatography (ether) gave **158** as a pale yellow oil (49 mg, 0.24 mmol, 73%). δ_H (300 MHz, $CDCl_3$) 1.25-2.00 (m, 5H, H_{3n}, H_5, H_6), 2.11 (brs, 1H, H_4), 3.00 (brs, 1H, H_1), 3.22 (ddd, J = 9.2, 3.6, 3.6 Hz, 1H, H_{3x}), 3.83 (AB, J = 9.0 Hz), 2H, CH_2Ph), 3.96 (brs, 1H, H_7), 7.18-7.42 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 20.3, 27.2 (C_5, C_6), 41.9 (C_4), 54.9, 55.0 (C_3, $\underline{C}H_2Ph$), 62.9 (C_1), 78.0 (C_7), 126.9, 128.3, 128.4 (5 × aryl CH), 139.4 (aryl C). ν_{max} 3124br, 2866s, 1668m, 1497m, 1452m, 1316s, 1278s cm^{-1}. $^m/_z$ $C_{13}H_{18}NO$ [MH^+] requires 204.13884; observed 204.13881. The 3,5-dinitrobenzoate derivative of **158** was synthesised as follows. *syn*-7-Hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (**158**) (67 mg, 0.33 mmol) was dissolved in benzene (3 ml) and 2,3-Dinitrobenzoyl chloride (165 mg, 0.72 mmol) was added. The reaction mixture was stirred vigorously at 80 °C for 4 h then diluted with water and extracted with diethyl ether; the combined extracts were washed with sodium bicarbonate solution and water, dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo*. Flash chromatography (diethyl ether: petrol; 1:1) afforded the 3,5-dinitrobenzoate derivative of **158** as yellow crystals (63 mg, 0.16 mmol, 48%). A crystal was prepared and X-ray crystallography (see appendix I) confirmed the *syn*- configuration of the derivative and hence **158**.

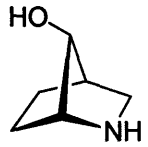
syn-7-Hydroxy-2-Boc-2-azabicyclo[2.2.1]heptane (165)



syn-7-Hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (**158**) (55 mg, 0.35 mmol) was dissolved in methanol (5 ml), palladium on carbon (10%, ~ 30 mg) was added and the reaction mixture was stirred under hydrogen for 48 h. After filtration through celite the methanol was removed *in vacuo* and the residue was dissolved in THF (2 ml) and water (6 ml). Boc_2O (150 mg, 0.69 mmol) and $NaHCO_3$ (147 mg, 1.75 mmol) were added and stirred at RT for 24 h. Then the reaction mixture was extracted with diethyl ether (6 × 6 ml), the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo* to give **165** as a yellow oil (41 mg, 0.19 mmol, 55%). δ_H

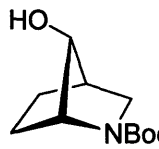
[300 MHz, $CDCl_3$; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] 1.23-1.77 (m, 4H, H_5, H_6), 1.46 (brs, 9H, Boc), 2.23 (brs, 1H, H_4), 3.05 (m, 1H, H_{3n}), 3.60 (brd, 1H, H_{3x}), 3.85, 3.94 (2 × brs, 1H, H_1), 4.00 (brs, 1H, H_7). δ_C (75.5 MHz, $CDCl_3$) 22.9, 23.7, 25.0 (C_5, C_6), 28.5 (Boc CH_3), *40.8*, 41.1 (C_4), *49.6*, 50.5 (C_3), 59.8, *60.7* (C_1), 76.0 (C_7), 79.2 (Boc C), 155.4 (Boc CO). ν_{max} 3325s, 2977m, 2951m, 2889m, 1667s, 1648s, 1482m, 1462m, 1423s, 1360s, 1334m, 1292m, 1255m, 1157s, 1127s, 1109s, 1087s cm^{-1}. $^m/_z$ $C_{11}H_{20}NO_3$ [MH^+] requires 214.14432; observed 214.14440.

anti-7-Hydroxy-2-azabicyclo[2.2.1]heptane (160)



anti-7-Hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (**86**) (1.83 g, 9.01 mmol) in dry methanol (40 ml) was hydrogenated as described for **103**, flash chromatography to give **160** as a pale yellow oil (0.604g, 5.35 mmol, 59%), which was converted to **161** and **162** without further purification. δ_H (300 MHz, $CDCl_3$) 1.37-1.54, 1.88-2.07 (2 × m, 2H, 2H, H_5, H_6), 2.11 (brs, 1H, H_4), 2.48 (brs, NH), 2.62 (d, J = 9.8 Hz, 1H, H_{3n}), 3.00 (ddd, J = 9.8, 3.1, 3.1 Hz, 1H, H_{3x}), 3.08 (brs, 1H, H_1), 4.21 (brs, 1H, H_7). δ_C (75.5 MHz, $CDCl_3$) 25.9, 29.9 (C_5, C_6), 40.4 (C_4), 49.8 (C_3), 58.0 (C_1), 77.3 (C_7). ν_{max} 3359s, 2955s, 1623m, 1395m, 1172s, 1111s cm^{-1}. $^m/_z$ 114 (MH^+).

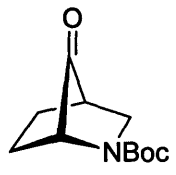
anti-7-Hydroxy-2-Boc-2-azabicyclo[2.2.1]heptane (161)



anti-7-Hydroxy-2-azabicyclo[2.2.1]heptane (**160**) (404 mg, 3.58 mmol) was treated with Boc_2O (1.091 g, 5.00 mmol) and $NaHCO_3$ (862 mg, 10.26 mmol), in THF (9 ml) and water (27 ml) using the method described for **104**. Flash chromatography (diethyl ether) gave **161** as a white crystals (430 mg, 2.02 mmol, 56%). Alternatively, treatment of 7-keto-2-Boc-2-azabicyclo[2.2.1]heptane (**163**) (40 mg, 0.19 mmol) with sodium borohydride (55 mg, 1.45 mmol) in dry methanol (2 ml) for 96 h followed by dilution with water and extraction into DCM gave **161** and *syn*-7-hydroxy-2-Boc-2-azabicyclo[2.2.1]heptane (**165**) (92:8) (33 mg, 0.15 mmol, 82%). m.p 63-66 °C. R_f 0.32. δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] *1.439*, 1.444 (2 × brs, 9H, Boc), 1.56-1.80, 1.88-2.03, 2.04-2.20 (3 × m, 1H, 2H, 1H, H_5, H_6), 2.28 (brs, 1H, H_4), *2.96*, 3.03 (2 × d, 9.8 Hz, 1H, H_{3n}), 3.31 (ddd, J = 9.8, 3.1, 3.1 Hz, 1H, H_{3x}), 3.87, *3.97* (2 × brs, 1H, H_1), 4.15 (brs, 1H, H_7). δ_C (75.5 MHz, $CDCl_3$) 24.9, *25.1*, *27.5*, 27.7 (C_5, C_6), 28.5 (Boc CH_3), 40.6, *41.0* (C_4), 50.9, *51.6* (C_3), *58.0*, 59.0 (C_1), *75.9*, 76.0 (C_7), 79.3 (Boc C), 154.7 (Boc CO). ν_{max}

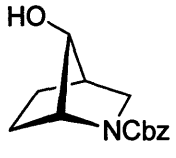
3455m, 2971s, 1659s, 1423s, 1366s, 1229s, 1217 cm^{-1}. $^m/_z$ $C_{11}H_{20}NO_3$ [MH^+] requires 214.14432; observed 214.14437.

7-Keto-2-Boc-2-azabicyclo[2.2.1]heptane (163)



The procedure described for **159** was followed, using *anti*-7-hydroxy-2-Boc-2-azabicyclo[2.2.1]heptane (**161**) (126 mg, 0.59 mmol), DMSO (0.20 ml, 2.95 mmol), oxalyl chloride (0.13 ml, 1.48 mmol), triethylamine (0.49 ml, 3.54 mmol) and dry DCM (16 ml, total) to give **163** as an orange oil (51 mg, 0.24 mmol, 41%). δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] 1.46, 1.48 (2 × brs, 9H, Boc), 1.66-2.09 (m, 4H, H_5, H_6), 2.32 (brs, 1H, H_4), 3.39 (m, 1H, H_{3x}), 3.57 (m, 1H, H_{3n}), 3.92, *4.06* (2 × brs, 1H, H_1). δ_C (75.5 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), 128.8, 130.9 (C_7). ν_{max} 3340m, 3237m, 2976w, 1653s, 1420m, 1401m cm^{-1}. $^m/_z$ $(M-55)^+$ 156.

***anti*-7-Hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylic acid benzyl ester (162)**

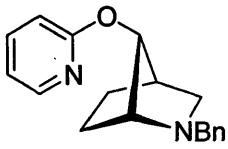


Adapted from a procedure described by Malpass *et al.*[77] Benzyl chloroformate (47 µl, 56 mg, 0.23 mmol) was added to *anti*-7-hydroxy-2-azabicyclo[2.2.1]heptane (**160**) (26 mg, 0.23 mmol) in water (5 ml), the pH was adjusted to 12.6 with NaOH solution. The reaction mixture was stirred for 72 h, then diluted with water (5 ml) and extracted with DCM (5 × 20 ml), the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo*. The resulting residue was flash chromatographed (diethyl ether) to give **162** as a colourless oil (23 mg, 0.094 mmol, 41%). R_f 0.30. Alternatively treatment of 7-keto-2-azabicyclo[2.2.1]heptane-2-carboxylic acid benzyl ester (**164**) (14 mg, 0.06 mmol) with sodium borohydride (28 mg, 0.74 mmol) in dry methanol (2 ml) for 96 h followed by dilution with water and extraction into DCM gave **162** (11 mg, 0.04 mmol, 75%). δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] 1.36-1.44, 1.60-1.75, 1.97 (3 × m, 1H, 1H, 2H, H_5, H_6), 2.27 (brs, 1H, H_4), *3.04*, 3.07 (2 × d, J = 5.9 Hz, 1H, H_{3n}), 3.56 (m, 1H, H_{3x}), 3.96, *4.00* (2 × brs, 1H, H_1), 4.11 (brs, 1H, H_7), 5.09 (m, 2H, $C\underline{H}_2Ph$), 7.25-7.35 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 24.9, *25.0*, *27.4*, 27.8 (C_5, C_6), 40.3, *40.7* (C_4), 51.29, *51.34* (C_3), *58.6*, 58.9 (C_1), *66.5*, 66.7 ($C\underline{H}_2Ph$), *75.6*, 75.8 (C_7), 127.7, 127.8, 128.4 (5 × aryl CH), 136.7 (aryl C), *154.4*, 155.0 (CO). ν_{max} 3406s, 2944s, 2884s, 1678s, 1498m, 1428s, 1361s, 1300s, 1247m, 1213m cm^{-1}.

7-Keto-2-azabicyclo[2.2.1]heptane-2-carboxylic acid benzyl ester (164)

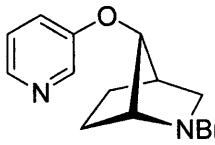
The procedure described for **159** was followed, using *anti*-7-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylic acid benzyl ester (**162**) (39 mg, 0.16 mmol), DMSO (0.053 ml, 0.80 mmol), oxalyl chloride (0.035 ml, 0.40 mmol), triethylamine (0.134 ml, 0.96 mmol) and dry DCM (7 ml, total) to give **164** as a brown oil (20 mg, 0.08 mmol, 51%). δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] 1.32-2.29 (m, 5H, H_4, H_5, H_6), 3.06-3.18 (m, 1H, H_{3n}), 3.56-3.72 (m, 1H, H_{3x}), 3.90 (m, 1H, H_1), 5.12 (m, 2H, $C\underline{H}_2Ph$), 7.26-7.36 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) *25.9*, 26.0, 28.8, *29.0* (C_5, C_6), *41.0*, 41.7 (C_4), 52.16, *52.24* (C_3), 57.6, *58.1* (C_1), 66.6, *66.7* ($\underline{C}H_2Ph$), 127.6, 127.8, 128.4 (5 × aryl CH), 136.7 (aryl C), 155.2, *155.4* (CO). ν_{max} 3410m, 2962s, 1792m, 1700s, 1420s, 1261s, 1108s cm^{-1}. $^m/_z$ 246 (MH^+).

***anti*-7-(Pyridin-2-yloxy)-2-benzyl-2-azabicyclo[2.2.1]heptane (173)**



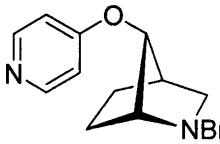
anti-7-Hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (**86**) (162 mg, 0.796 mmol) was dissolved in anhydrous DMSO (10 ml), potassium tertiary butoxide (116 mg, 1.034 mmol) was added and stirred under nitrogen at RT for 0.5 h. Then 2-chloropyridine (0.1 ml, 1.057 mmol) was added and the mixture was stirred for a further 48 h at 55 °C. The reaction was quenched with water (10 ml) and extracted with ethyl acetate; the organic extracts were combined and dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo*. The crude residue was flash chromatographed (diethyl ether) to give **173** as a pale yellow oil (144 mg, 0.51 mmol, 65%). δ_H (300 MHz, $CDCl_3$) 1.35-1.47, 1.72-1.97 (2 × m, 1H, 3H, H_5, H_6), 2.33 (d, J = 9.1 Hz, 1H, H_{3n}), 2.48 (brs, 1H, H_4), 3.08 (ddd, J = 9.1, 3.1, 3.1 Hz, 1H, H_{3x}), 3.34 (brs, 1H, H_1), 3.76 (brs, 2H, $C\underline{H}_2Ph$), 5.24 (brs, 1H, H_7), 6.69 (d, J = 8.3 Hz, 1H, $H_{3'}$), 6.84 (dd, J = 7.1, 5.0 Hz, 1H, $H_{5'}$), 7.18-7.49 (m, 5H, Ph), 7.53 (ddd, J = 8.3, 7.1, 1.8 Hz, 1H, $H_{4'}$), 8.17 (dd, J = 5.0, 1.8 Hz, 1H, $H_{6'}$). δ_C (75.5 MHz, $CDCl_3$) 24.4, 26.7 (C_5, C_6), 39.9 (C_4), 57.7 (C_3), 58.4 ($\underline{C}H_2Ph$), 61.3 (C_1), 79.1 (C_7), 111.0 ($C_{3'}$), 116.7 ($C_{5'}$), 126.7, 128.1, 128.5 (5 × aryl CH), 138.4 ($C_{4'}$), 139.7 (aryl C), 147.1 ($C_{6'}$), 163.6 ($C_{2'}$). ν_{max} 2970m, 2834m, 1589m, 1568m, 1469s, 1429s, 1285s, 1269s, 1250s cm^{-1}. $^m/_z$ $C_{18}H_{21}N_2O$ [MH^+] requires 281.16539; observed 281.16532.

***anti*-7-(Pyridin-3-yloxy)-2-benzyl-2-azabicyclo[2.2.1]heptane (174)**



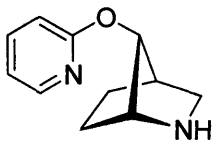
Using a procedure adapted from that described by Krow *et al.*[79] A solution of *anti*-7-Hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (**86**) (108 mg, 0.53 mmol) in dry THF (4 ml) was added to 3-hydroxypyridine (61 mg, 0.64 mmol) and triphenylphophine (180 mg, 0.69 mmol). This mixture was stirred under nitrogen at 5 °C and DEAD (123 mg, 0.71 mmol) in dry THF (2 ml) was added drop-wise. The reaction mixture was allowed to reach RT and stirred under nitrogen for 48 h, it was then evaporated to dryness. The resulting residue was dissolved in aqueous HCl (1M), washed with diethyl ether, basified with ammonium hydroxide solution and extracted with DCM. The organic extracts were combined and dried over anhydrous $MgSO_4$, filtered and reduced *in vacuo*; the crude product was flash chromatographed (diethyl ether) to give **174** as a pale yellow oil (44 mg, 0.16 mmol, 30%). R_f 0.38. δ_H (300 MHz, $CDCl_3$) 1.38-1.48 (m, 1H, H_{6n}), 1.66-1.79 (m, 1H, H_{6x}), 1.87-2.04 (m, 2H, H_5), 2.29 (d, J = 9.3 Hz, 1H, H_{3n}), 2.43 (brs, 1H, H_4), 3.13 (ddd, J = 9.3, 3.4, 3.4 Hz, 1H, H_{3x}), 3.33 (brs, 1H, H_1), 3.73 (AB, J = 13.4 Hz, 2H, $C\underline{H}_2Ph$), 4.71 (brs, 1H, H_7), 7.14-7.37 (m, 7H, Ph, $H_{4'}$, $H_{5'}$), 8.20 (brd, J = 4.9 Hz, 1H, $H_{6'}$), 8.34 (brs, 1H, $H_{2'}$). δ_C (75.5 MHz, $CDCl_3$) 23.1, 26.8 (C_5, C_6), 39.8 (C_4), 57.3 (C_3), 61.0 (C_1), 81.3 (C_7), 121.8, 123.7, [126.9, 128.3, 128.5 (5 × aryl CH)], 138.7, [139.1 (aryl C)], 142.2 (4 × pyridyl CH), 154.3 (pyridyl C). ν_{max} 2970m, 1576s, 1474s, 1431m, 1269s, 1230s cm^{-1}. $^m/_z$ $C_{18}H_{21}N_2O$ [MH^+] requires 281.16539; observed 281.16546.

***anti*-7-(Pyridin-4-yloxy)-2-benzyl-2-azabicyclo[2.2.1]heptane (175)**



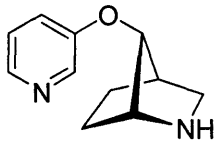
The procedure described for **174** was followed using *anti*-7-hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (**86**) (230 mg, 1.13 mmol), THF (10 ml), 4-hydroxypyridine (128 mg, 1.35 mmol), triphenylphosphine (459 mg, 1.75 mmol) and DEAD (261 mg, 1.50 mmol in THF (2 ml)). Flash chromatography of the crude residue (diethyl ether) gave **175** as a yellow oil (91 mg, 0.325 mmol, 29%). R_f 0.28. δ_H (300 MHz, $CDCl_3$) 1.30-1.47, 1.64-1.77, 1.84-2.04 (3 × m, 1H, 1H, 2H, H_5, H_6), 2.27 (d, J = 9.2 Hz, 1H, H_{3n}), 2.44 (brs, 1H, H_4), 3.12 (ddd, J = 9.2, 3.5, 3.5 Hz, 1H, H_{3x}), 3.34 (brs, 1H, H_1), 3.71 (AB, J = 13.3 Hz, 2H, $C\underline{H}_2Ph$), 4.71 (brs, 1H, H_7), 6.84 (d, J = 6.2 Hz, 2H, $H_{3'}$, $H_{5'}$), 7.28-7.36 (m, 5H, Ph), 8.38 (d, J = 6.2 Hz, 2H, $H_{2'}$, $H_{6'}$). δ_C (75.5 MHz, $CDCl_3$) 22.9, 26.7 (C_5, C_6), 39.6 (C_4), 57.0, 57.4 (C_3, $\underline{C}H_2Ph$), 60.8 (C_1), 80.7 (C_7), 110.7 ($C_{3'}$, $C_{5'}$), 128.2, 128.3, 128.4 (5 × aryl CH), 138.9 (aryl C), 150.7 ($C_{2'}$, $C_{6'}$), 164.1 ($C_{4'}$). ν_{max} 2971m, 1592m, 1569m, 1496m, 1454m, 1366m, 1279m, 1229m, 1210s cm^{-1}. $^m/_z$ $C_{18}H_{21}N_2O$ [MH^+] requires 281.16539; observed 281.16534.

anti-7-(Pyridin-2-yloxy)-2-azabicyclo[2.2.1]heptane (150)



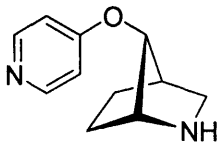
anti-7-(Pyridin-2-yloxy)-2-benzyl-2-azabicyclo[2.2.1]heptane (**173**) (154 mg, 0.550 mmol) was dissolved in dry methanol and stirred with Palladium on carbon (10%, ~ 40 mg) under an atmosphere of hydrogen. After 24 h the reaction mixture was filtered through celite; after reduction *in vacuo* the crude residue was flash chromatographed (9:1; diethyl ether: methanol) to give **150** as an orange oil (52 mg, 0.27 mmol, 49%). R_f 0.28. δ_H (300 MHz, $CDCl_3$) 1.43-1.62, 1.88-2.03 (2 × m, 2H, 2H, H_5, H_6), 2.46 (brs, 1H, H_4), 2.70 (d, J = 9.7 Hz, 1H, H_{3n}), 3.44 (brs, 1H, H_1), 3.19 (ddd, J = 9.7, 3.0, 3.0 Hz, 1H, H_{3x}), 5.09 (brs, 1H, H_7), 6.72 (d, J = 8.4 Hz, 1H, $H_{3'}$), 6.86 (ddd, J = 6.3, 5.1, 0.8 Hz, 1H, $H_{5'}$), 7.56 (ddd, J = 8.4, 6.3, 1.4 Hz, 1H, $H_{4'}$), 8.15 (dd, J = 5.1, 1.4 Hz, 1H, $H_{6'}$). δ_C (75.5 MHz, $CDCl_3$) 26.0, 28.3 (C_5, C_6), 38.1 (C_4), 49.0 (C_3), 56.3 (C_1), 80.1 (C_7), 111.0 ($C_{3'}$), 117.0 ($C_{5'}$), 138.6 ($C_{4'}$), 146.9 ($C_{6'}$), 163.2 ($C_{2'}$). ν_{max} 2958m, 2727w, 1597s, 1571m, 1473s, 1435s, 1374m, 1276m, 1250m, 1237m cm^{-1}. $^m/_z$ $C_{11}H_{15}N_2O$ [MH^+] requires 191.11844; observed 191.11846.

anti-7-(Pyridin-3-yloxy)-2-azabicyclo[2.2.1]heptane (151)



The procedure described for **150** was followed using _anti_-7-(pyridin-3-yloxy)-2-benzyl-2-azabicyclo[2.2.1]heptane (**174**) (230 mg, 0.82 mmol). The crude product was flash chromatogaphed (9:1; diethyl ether: methanol) to give **151** as a yellow oil (98 mg, 0.52 mmol, 63%). δ_H (300 MHz, MeOD) 1.69-1.84, 2.00-2.18 (2 × m, 1H, 3H, H_5, H_6), 2.80 (brs, 1H, H_4), 3.25 (d, J = 11.2 Hz, 1H, H_{3n}), 3.55 (ddd, J = 11.2, 3.0, 3.0 Hz, 1H, H_{3x}), 4.11 (brs, 1H, H_1), 5.07 (brs, 1H, H_7), 7.45 (dd, J = 8.5, 4.6 Hz, 1H, $H_{5'}$), 7.70 (ddd, 8.5, 2.6, 1.1 Hz, 1H, $H_{6'}$), 8.24 (d, J = 4.6 Hz, 1H, $H_{4'}$), 8.40 (d, J = 2.6 Hz, 1H, $H_{2'}$). δ_C (75.5 MHz, MeOD) 24.6, 25.6 (C_5, C_6), 38.5 (C_4), 49.5 (C_3), 58.3 (C_1), 81.3 (C_7), 124.3 ($C_{6'}$), 126.2 ($C_{5'}$), 139.3 ($C_{2'}$), 143.7 ($C_{4'}$). ν_{max} 2951m, 1580s, 1476m, 1420m, 1255m cm^{-1}. $^m/_z$ $C_{11}H_{15}N_2O$ [MH^+] requires 191.11844; observed 191.11846.

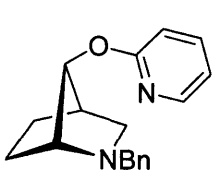
anti-7-(Pyridin-4-yloxy)-2-azabicyclo[2.2.1]heptane (152)



The procedure described for **150** was followed using _anti_-7-(pyridin-4-yloxy)-2-benzyl-2-azabicyclo[2.2.1]heptane (**175**) (50 mg, 0.179 mmol). The crude product was flash chromatogaphed (9:1; diethyl ether: methanol) to give **152** as a yellow oil (20 mg, 0.11 mmol, 58%).δ_H (300 MHz, $CDCl_3$) 1.26-1.67 (m, 4H, H_5, H_6), 2.49 (brs, 1H, H_4), 2.80 (brd, J = 9.7 Hz, 1H, H_{3n}), 3.10-3.26 (m, 1H, H_{3x}), 3.49 (brs, 1H, H_1), 4.69 (brs, 1H, H_7), 6.88 (d, J = 5.2 Hz, 2H, $H_{3'}$, $H_{5'}$), 8.43 (d, J = 5.2 Hz, 2H, $H_{2'}$,

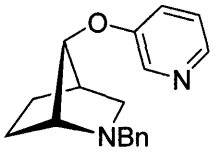
$H_{6'}$). δ_C (75.5 MHz, $CDCl_3$) 26.1, 29.6 (C_5, C_6), 38.5 (C_4), 49.3 (C_3), 56.2 (C_1), 82.0 (C_7), 110.8 ($C_{3'}$, $C_{5'}$), 151.2 ($C_{2'}$, $C_{6'}$), 164.2 ($C_{4'}$). ν_{max} 2943w, 1568s, 1470m, 1450m, 1250m cm^{-1}. $^m/_z$ $C_{11}H_{15}N_2O$ [MH^+] requires 191.11844; observed 191.11840.

syn-7-(Pyridin-2-yloxy)-2-benzyl-2-azabicyclo[2.2.1]heptane (176)



syn-7-Hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (**158**) (0.655g, 3.23 mmol) was dissolved in dry _N_-methyl pyrrolidinone (40 ml); 2-chloropyridine (0.75 ml, 0.90 g, 7.93 mmol) and sodium hydride (60% dispersion, 2.19 g) were added and the reaction mixture was stirred under nitrogen at 140 °C for 96 h. The reaction was quenched by the addition of water (30 ml) and extracted into ethyl acetate; the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvents removed _in vacuo_. The crude product was flash chromatographed (1:1; diethyl ether: petrol) to give **176** as an orange oil (0.546 g, 1.99 mmol, 60%). δ_H (300 MHz, $CDCl_3$) 1.36-1.50, 1.62-1.83 (2 × m, 1H, 3H, H_5, H_6), 2.45 (brs, 1H, H_1), 2.68 (d, J = 8.9 Hz, 1H, H_{3n}), 3.14 (ddd, J = 8.9, 2.6, 2.6 Hz, 1H, H_{3x}), 3.30 (brs, 1H, H_1), 3.89 (AB, J = 13.7 Hz, 2H, $C\underline{H}_2Ph$), 5.03 (brs, 1H, H_7), 6.84 (m, 2H, $H_{3'}$, $H_{5'}$), 7.14-7.32 (m, 5H, Ph), 7.56 (ddd, J = 7.3, 7.3, 2.0 Hz, 1H, $H_{4'}$), 8.15 (dd, J = 5.0, 2.0 Hz, 1H, $H_{6'}$). δ_C (75.5 MHz, $CDCl_3$) 25.0, 26.5 (C_5, C_6), 40.0 (C_4), 58.3 (C_3), 60.0 ($\underline{C}H_2Ph$), 61.6 (C_1), 80.8 (C_7), 111.3 ($C_{3'}$), 116.6 ($C_{5'}$), 123.3, 126.5, 128.0 (5 × aryl CH), 138.5 ($C_{4'}$), 140.7 (aryl C), 146.9 ($C_{6'}$), 163.6 ($C_{2'}$). ν_{max} 2971m, 2858m, 1596m, 1569m, 1469s, 1432s, 1367s, 1229s, 1216s cm^{-1}. $^m/_z$ $C_{18}H_{21}N_2O$ [MH^+] requires 281.16539; observed 281.16531.

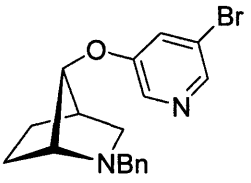
syn-7-(Pyridin-3-yloxy)-2-benzyl-2-azabicyclo[2.2.1]heptane (178)



Using a procedure adapted from that described by Wolter _et al._[143] Toluene (1 ml) was added to the _syn_-7-hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (**158**) (470 mg, 2.32 mmol) followed by copper iodide (137 mg, 0.72 mmol), 1,10-phenanthroline (250 mg, 1.39 mmol), caesium carbonate (1.000 g, 2.96 mmol) and 3-iodopyridine (115 mg, 0.56 mmol). This heterogeneous mixture was stirred at 110 °C for 96 h then filtered through silica with rinsing with (ethyl acetate: methanol; 9:1); the solvents were removed _in vacuo_ and the crude residue was flash chromatographed (diethyl ether) to give **178** as a yellow oil (24 mg, 0.084 mmol, 4%). R_f 0.27. δ_H (300 MHz, $CDCl_3$) 1.47-2.00 (m, 4H, H_5, H_6), 2.50 (brs, 1H, H_4), 2.80 (m, 1H, H_{3n}), 3.15 (ddd, J = 9.2, 3.0, 3.0 Hz, 1H, H_{3x}), 3.33 (brs, 1H, H_1), 3.95 (brs, 2H, $C\underline{H}_2Ph$), 4.44 (brs, 1H, H_7), 7.17-7.37 (m, 7H, Ph, $H_{4'}$, $H_{5'}$), 8.26 (dd, J = 4.3, 1.5 Hz, 1H, $H_{6'}$), 8.39 (d, J = 2.6

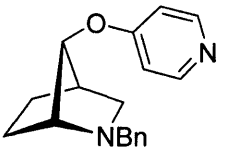
Hz, 1H, $H_{2'}$). δ_C (75.5 MHz, $CDCl_3$) 24.9, 26.2 (C_5, C_6), 40.1 (C_4), 57.9, 59.9 (C_3, $\underline{C}H_2Ph$), 61.3 (C_1), 83.4 (C_7), 122.0, 123.9 [128.2, 128.5 (5 × aryl CH), 138.6 (aryl C)], 148.9 (4 × pyridyl CH). $^m/_z$ $C_{18}H_{21}N_2O$ [MH^+] requires 281.16539; observed 281.16534.

syn-7-(5-Bromo-pyridin-3-yloxy)-2-benzyl-2-azabicyclo[2.2.1]heptane (179)



Using a procedure adapted from that described by Wei *et al.*[127] Sodium hydride (24 mg, 60% suspension in mineral oil, 0.60 mmol) was added to a solution of *syn*-7-hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (**158**) (93 mg, 0.49 mmol) in anhydrous DMF (7 ml). This mixture was stirred under nitrogen at RT for 2 h prior to the addition of 3,5-dibromopyridine (142 mg, 0.60 mmol); the temperature was raised to 50 °C and stirred for a further 6 h. The reaction mixture was diluted with water (5 ml) and extracted with ethyl acetate; the combined organic extracts were dried over anhydrous magnesium sulphate, filtered and the solvents removed *in vacuo*. The resulting residue was flash chromatographed (diethyl ether) to give the alcohol **158** (28 mg) and **179** (38 mg, 0.11 mmol, 34% based on recovered starting material). δ_H (300 MHz, $CDCl_3$) 1.31-1.84 (m, 4H, H_5, H_6), 2.40 (brs, 1H, H_4), 2.62 (d, J = 9.3 Hz, 1H, H_{3n}), 3.05 (ddd, J = 9.3, 2.9, 2.9 Hz, 1H, H_{3x}), 3.22 (brs, 1H, H_1), 3.81 (AB, J = 13.4 Hz, 2H, $C\underline{H}_2Ph$), 4.37 (brs, 1H, H_7), 7.13-7.27 (m, 5H, Ph), 7.37 (m, 1H, pyridyl), 8.24 (m, 2H, pyridyl). δ_C (75.5 MHz, $CDCl_3$) 24.9, 26.2 (C_5, C_6), 40.1 (C_4), 57.7, 59.7 (C_3, $\underline{C}H_2Ph$), 61.3 (C_1), 83.8 (C_7), 120.3 (pyridyl C), 124.8 (pyridyl CH), 126.7, 128.2, 128.3 (5 × aryl CH), 137.1, 143.1 (2 × pyridyl CH), 154.8 (pyridyl C). $^m/_z$ $C_{18}H_{20}N_2OBr$ [MH^+] requires 359.07590; observed 359.07592.

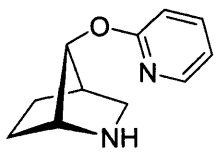
syn-7-(Pyridin-4-yloxy)-2-benzyl-2-azabicyclo[2.2.1]heptane (155)



Potassium *tert*-butoxide (128 mg, 1.14 mmol) was added to a solution of *syn*-7-hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (**158**) (87 mg, 0.43 mmol) in anhydrous DMSO (7 ml) and stirred under nitrogen at RT for 0.5 h. 4-Chloropyridine hydrochloride (73 mg, 0.49 mmol) was added and the temperature was raised to 50 °C. The reaction mixture was stirred for a further 6 h, then quenched with water (5 ml) and extracted with diethyl ether. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and solvents removed *in vacuo* to give **155** as a pale yellow oil (94 mg, 0.34 mmol, 78%). δ_H (300 MHz, $CDCl_3$) 1.45-1.56, 1.59-1.86 (2 × m, 1H, 3H, H_5, H_6), 2.49 (brs, 1H, H_4), 2.74 (d, J = 9.1 Hz, 1H, H_{3n}), 3.11 (ddd, J = 9.1, 2.9, 2.9 Hz, 1H, H_{3n}), 3.30 (brs, 1H, H_1), 3.86 (AB, J = 13.7 Hz, 2H, $C\underline{H}_2Ph$), 4.48 (brs, 1H, H_7), 6.88 (dd, J = 5.0,

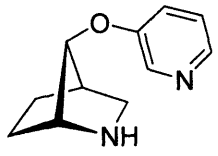
1.5 Hz, 2H, pyridyl), 7.17-7.34 (m, 5H, Ph), 8.45 (d, J = 5.0 Hz, 2H, pyridyl). δ_C (75.5 MHz, $CDCl_3$) 24.9, 26.6 (C_5, C_6), 40.1 (C_4), 57.9 (C_3), 60.0 ($\underline{C}H_2Ph$), 61.1 (C_1), 82.7 (C_7), 110.9 (pyridyl CH), 126.6, 128.2, 128.3 (5 × aryl CH), 151.2 (pyridyl CH), 164.3 (pyridyl C). ν_{max} 2969m, 1594s, 1563m, 1496m, 1451m, 1417m, 1366m, 1302m, 1279s cm^{-1}. $^m/_z$ $C_{18}H_{21}N_2O$ [MH^+] requires 281.16539; observed 281.16546.

syn-7-(Pyridin-2-yloxy)-2-azabicyclo[2.2.1]heptane (153)



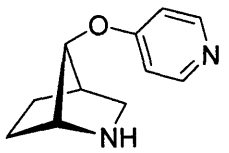
The procedure described for **150** was followed using _syn_-7-(pyridin-2-yloxy)-2-benzyl-2-azabicyclo[2.2.1]heptane (**176**) (298 mg, 1.064 mmol) to give **153** as a pale yellow oil (106 mg, 0.558 mmol, 52%). δ_H (300 MHz, $CDCl_3$) 1.38-1.91 (m, 4H, H_5, H_6), 2.43 (brs, 1H, H_4), 2.72 (d, J = 9.6 Hz, 1H, H_{3n}), 3.28 (ddd, J = 9.6, 3.2, 3.2 Hz, 1H, H_{3x}), 3.44 (brd, J = 2.3 Hz, 1H, H_1), 5.02 (brs, 1H, H_7), 6.75 (d, J = 7.2 Hz, 1H, $H_{3'}$), 6.88 (dd, J = 7.2, 5.0 Hz, 1H, $H_{5'}$), 7.57 (ddd, J = 7.2, 7.2, 1.6 Hz, 1H, $H_{4'}$), 8.15 (dd, J = 5.0, 1.6 Hz, 1H, $H_{6'}$). δ_C (75.5 MHz, $CDCl_3$) 25.3, 27.6 (C_5, C_6), 38.7 (C_4), 49.6 (C_3), 57.5 (C_1), 79.9 (C_7), 111.3 ($C_{3'}$), 116.9 ($C_{5'}$), 138.6 ($C_{4'}$), 146.8 ($C_{6'}$), 163.3 ($C_{2'}$). ν_{max} 2951m, 1598m, 1570m, 1470s, 1432s, 1367m, 1311m, 1271s, 1252s, 1144m cm^{-1}. $^m/_z$ $C_{11}H_{15}N_2O$ [MH^+] requires 191.11844; observed 191.11838.

syn-7-(Pyridin-3-yloxy)-2-azabicyclo[2.2.1]heptane (154)



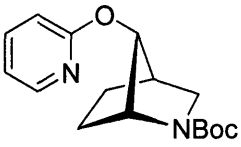
syn-7-(5-bromo-pyridin-3-yloxy)-2-benzyl-2-azabicyclo[2.2.1]heptane (**179**) (38 mg, 0.11 mmol) was dissolved in dry methanol (10 ml) and reduced using 10% palladium on charcoal (~ 10 mg) under an atmosphere of hydrogen. After stirring for 6 h the reaction mixture was filtered through celite; the methanol was removed _in vacuo_ and the residue flash chromatographed (eluting with diethyl ether followed by 7:3 diethyl ether: methanol) to give **154** as a yellow oil (8 mg, 38 %). δ_H (300 MHz, $CDCl_3$) 1.43-1.82 (m, 4H, H_5, H_6), 2.3 (NH), 2.42 (brs, 1H, H_4), 2.71 (d, J = 9.6 Hz, 1H, H_{3n}), 3.25 (ddd, J = 9.6, 2.9, 2.9 Hz, 1H, H_{3x}), 3.39 (brd, J = 2.6 Hz, 1H, H_1), 4.44 (brs, 1H, H_7), 7.19-7.29 (m, 2H, 2 × pyridyl), 8.23 (dd, J = 4.4, 1.8 Hz, 1H, pyridyl), 8.36 (d, J = 2.6 Hz, 1H, pyridyl). δ_C (75.5 MHz, $CDCl_3$) 25.4, 27.9 (C_5, C_6), 38.7 (C_4), 49.5 (C_3), 57.4 (C_1), 82.4 (C_7), 122.0, 123.8, 138.5, 142.4 (4 × pyridyl CH), 154.3 (pyridyl C). ν_{max} 2949m, 1575s, 1475m, 1424s, 1371m, 1269s, 1232s, 1189w cm^{-1}. $^m/_z$ $C_{11}H_{15}N_2O$ [MH^+] requires 191.11844; observed 191.11843.

syn-7-(Pyridin-4-yloxy)-2-azabicyclo[2.2.1]heptane (155)



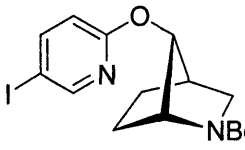
The procedure described for **150** was followed using *syn*-7-(pyridin-2-yloxy)-2-benzyl-2-azabicyclo[2.2.1]heptane (**177**) (72 mg, 0.26 mmol) to give **155** as a yellow oil (49 mg, 99%). δ_H (300 MHz, $CDCl_3$) 1.41-1.82 (m, 4H, C_5, C_6), 2.45 (brs, 1H, H_4), 2.74 (d, J = 9.9 Hz, 1H, H_{3n}), 3.24 (ddd, J = 9.9, 2.6, 2.6 Hz, 1H, H_{3x}), 3.43 (brs, 1H, H_1), 4.47 (brs, 1H, H_7), 6.86 (dd, J = 4.7, 1.5 Hz, 2H, pyridyl), 8.43 (dd, J = 4.7, 1.5 Hz, 2H, pyridyl). δ_C (75.5 MHz, $CDCl_3$) 25.2, 27.7 (C_5, C_6), 38.6 (C_4), 49.4 (C_3), 57.3 (C_1), 81.8 (C_7), 110.7 (pyridyl CH), 151.0 (pyridyl CH), 164.1 (pyridyl C). ν_{max} 2972w, 2879w, 1592s, 1569m, 1499m, 1419m, 1277s, 1211s, 1151w cm^{-1}. $^m/_z$ $C_{11}H_{15}N_2O$ [MH^+] requires 191.11844; observed 191.11844.

***anti*-7-(Pyridin-2-yloxy)-2-Boc-2-azabicyclo[2.2.1]heptane**



The procedure describe for **176** was followed using *anti*-7-hydroxy-2-Boc-2-azabicyclo[2.2.1]heptane (**161**) (14 mg, 0.066 mmol), *N*-methyl pyrrolidinone (8 ml), 2-chloropyridine (0.0.15 ml, 18 mg, 0.159 mmol) and sodium hydride (60% dispersion, 39 mg). The crude product was flash chromatographed (1:1; diethyl ether: petrol) to give the title compound as a beige semi-solid (14 mg, 0.049 mmol, 74%) R_f(diethyl ether) 0.72. δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] 1.46 (brs, 9H, Boc), 1.62-2.04 (m, 4H, H_5, H_6), 2.61 (brs, 1H, H_4), *3.04*, 3.13 (2 × d, J = 9.9 Hz, 1H, H_{3n}), 3.44 (m, 1H, H_{3x}), 4.20, *4.34* (2 × brs, 1H, H_1), *5.06*, 5.09 (2 × brs, 1H, H_7), 6.71 (d, J = 8.4 Hz, 1H, $H_{3'}$), 6.89 (m, 1H, $H_{5'}$), 7.57 (m, 1H, $H_{4'}$), 8.15 (m, 1H, $H_{6'}$). δ_C (75.5 MHz, $CDCl_3$) 25.5, *25.7*, *28.0*, 28.3 (C_5, C_6), 28.5 (Boc CH_3), 38.9, *39.3* (C_4), 50.5, *51.3* (C_3), *56.4*, 57.5 (C_1), *79.1*, 79.3 (Boc C), 111.1 ($C_{3'}$), 117.1 ($C_{5'}$), 138.7 ($C_{4'}$), 147.0 ($C_{6'}$), 154.7 (Boc CO), 163.0 ($C_{2'}$). ν_{max} 2963m, 1683s, 1590m, 1568m, 1471s, 1429s, 1399s, 1366s cm^{-1}. $^m/_z$ $C_{16}H_{23}N_2O_3$ [MH^+] requires 291.17087; observed 291.17083.

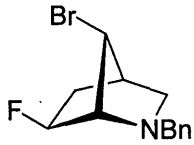
***anti*-7-(5-Iodo-pyridin-2-yloxy)-2-Boc-2-azabicyclo[2.2.1]heptane**



anti-7-Hydroxy-2-Boc-2-azabicyclo[2.2.1]heptane (**161**) (52 mg, 0.24 mmol) was dissolved in dry DMF (10 ml), 2-chloro-5-iodopyridine (68 mg, 0.28 mmol) and ^{t}BuOK (52 mg, 0.46 mmol) were added and the reaction mixture was stirred under nitrogen at RT for 3 h. Water (10 ml) was added and the mixture was extracted with diethyl ether, the organic extracts were combined, dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo*. Flash chromatography of the

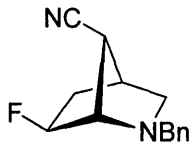
crude residue (diethyl ether: petrol; 1:1) gave the title compound as a yellow oil (72 mg, 0.17 mmol, 72%). R_f 0.59. δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] 1.30-1.54, [1.46 (brs, 9H, Boc)], 1.60-1.83, 1.83-2.04 (3 × m, 1H, 1H, 2H, H_5, H_6), 2.60 (brs, 1H, H_4), *3.05*, 3.13 (2 × d, J = 9.8 Hz, 1H, H_{3n}), 3.45 (brd, J = 9.8 Hz, 1H, H_{3x}), 4.18, *4.32* (2 × brs, 1H, H_1), *4.99*, 5.02 (2 × brs, 1H, H_7), 6.56 (d, J = 8.6 Hz, 1H, $H_{3'}$), 7.78 (dd, J = 8.6, 2.0 Hz, 1H, $H_{4'}$), 8.34 (d, J = 2.0 Hz, 1H, $H_{6'}$). δ_C (75.5 MHz, $CDCl_3$) 25.5, *25.6*, *27.9*, 28.1 (C_5, C_6), 28.5 (Boc CH_3), 38.7, *39.2* (C_4), 50.4, *51.2* (C_3), *56.2*, 57.3 (C_1), 78.6 (C_7), 82.7 (Boc C), 113.4 (pyridyl CH), 146.5 (pyridyl CH), 152.8 (pyridyl CH), *153.9*, 154.5 (Boc CO), 162.3 (pyridyl C). ν_{max} 2975m, 1687s, 1576m, 1557w, 1457m, 1404s, 1352s, 1278s cm^{-1}. $^m/_z$ $C_{16}H_{20}N_3$ [MH^+] requires 417.06752; observed 417.06755.

anti-7-Bromo-_exo_-6-fluoro-2-benzyl-2-azabicyclo[2.2.1]heptane (215)



Potassium fluoride (13.62 g, 234 mmol) and 18-crown-6 (~ 20 mg) were added to a suspension of 3-bromo-1-benzyl-1-azoniatricyclo[2.2.1.$0^{2,6}$]-heptane bromide (**74**) (15.41 g, 44.7 mmol) in dry acetonitrile (125 ml). After vigorous stirring at reflux under nitrogen for 48 h the reaction mixture was diluted with water then extracted with DCM, the organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo*. The resulting residue was crystallised from diethyl ether/ethyl acetate to give **215** as an orange oil (10.62 g, 37.4 mmol, 84%). δ_H (300 MHz, $CDCl_3$) 1.97-2.13 (m, 1H, H_{5n}), 2.17-2.42 (m, 1H, H_{5x}), 2.43 (d, J = 8.7 Hz, 1H, H_{3n}), 2.53 (ddd, J = 8.7, 6.0, 3.0 Hz, 1H, H_{3x}), 2.57 (brs, 1H, H_4), 3.36 (brd, J = 3.7 Hz, 1H, H_1), 3.72 (AB, J = 13.4 Hz, 2H, $C\underline{H}_2Ph$), 4.11 (brs, 1H, H_7), 4.86 (dddd, J = 54.8, 7.2, 1.3, 1.3 Hz, 1H, H_{6n}), 7.18-7.34 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 36.1 (d, J = 20 Hz, C_5), 43.3 (C_4), 48.3 (C_7), 55.8 (C_3), 59.7 ($\underline{C}H_2Ph$), 65.9 (d, J = 22 Hz, C_1), 93.0 (d, J = 195 Hz, C_6), 127.2, 128.3, 128.4 (5 × aryl CH), 138.4 (aryl C). δ_F (282.3 MHz, $CDCl_3$) -63.8 (ddd, 54, 34, 12 Hz). ν_{max} 2978m, 2874m, 2801m, 1494m, 1455m, 1439m, 1374m, 1354m, 1311w, 1269w, 1122s cm^{-1}. $^m/_z$ 284/286 (MH^+).

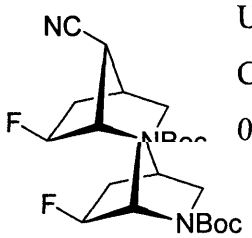
anti-7-Cyano-_exo_-6-fluoro-2-benzyl-2-azabicyclo[2.2.1]heptane (217)



Potassium cyanide (2.18 g, 33.5 mmol) and 18-crown-6 (~ 10 mg) were added to a solution of *anti*-7-bromo-*exo*-6-fluoro-2-benzyl-2-azabicyclo[2.2.1]heptane (**215**) (907 mg, 3.19 mmol) in dry DMF (40 ml). After stirring under nitrogen at 100°C for 48 h the reaction mixture was cooled and passed

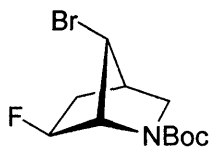
through a pad of silica, solvents were removed *in vacuo*, the resulting residue was flash chromatographed (diethyl ether) to give **217** as a pale yellow oil (595 mg, 2.59 mmol, 81%). R_f 0.69. δ_H (300 MHz, $CDCl_3$) 1.98-2.24 (m, 2H, H_{5x}, H_{5n}), 2.48 (brs, 2H, H_{3x}, H_{3n}), 2.71 (brs 1H, H_7), 2.83 (brs, 1H, H_4), 3.59 (brd, J = 3.2 Hz, 1H, H_1), 3.67 (AB, J = 13.4 Hz, 2H, $C\underline{H}_2Ph$), 4.85, 4.87 (2 × dddd, $J \approx$ 53.0, 6.5, 1.4, 1.4 Hz, 1H, H_{6n}), 7.18-7.36 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 32.6 (C_7), 36.4 (d, J = 21 Hz, C_5), 41.2 (C_4), 57.0 (C_3), 59.2 ($\underline{C}H_2Ph$), 66.4 (d, J = 24 Hz, C_1), 92.1 (d, J = 193 Hz, C_6), 118.1 (CN), 127.4, 128.3, 128.4 (5 × aryl CH), 137.9 (aryl C). δ_F (282.3 MHz, $CDCl_3$) –164.2 (ddd, J = 55, 18, 18 Hz). ν_{max} 2976m, 2939m, 2871m, 2236m, 1495m, 1453m, 1440m, 1375m, 1357m, 1337m, 1310m, 1240w, 1206w cm^{-1}. $^m/_z$ $C_{14}H_{15}N_2O$ [M^+] requires 230.12193 observed 230.12197.

***anti*-7-Cyano-*exo*-6-fluoro-2-Boc-2-azabicyclo[2.2.1]heptane**



Using a procedure adapted from that described by Malpass *et al.*[77] *anti*-7-Cyano-*exo*-6-fluoro-2-benzyl-2-azabicyclo[2.2.1]heptane (**217**) (59 mg, 0.257 mmol), Boc_2O (143 mg, 0.655 mmol) and $NaHCO_3$ (104 mg, 1.24 mmol) were dissolved in dry methanol (10 ml). 10% Paladium on carbon (~ 250 mg) was added, the atmosphere was changed to hydrogen (ballon fitted) and the reaction mixture was stirred vigorously for 72 h then filtered through celite. Methanol was removed *in vacuo*, the resulting residue was flash chromatographed (diethyl ether) to give the title compound as a colourless oil (29 mg, 0.121 mmol, 47%), R_f 0.38. δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] 1.46 (brs, 9H, Boc), 2.05-2.37 (m, 2H, H_{5x}, H_{6n}), 2.80 (brs, 1H, H_7), 2.91 (m, 1H, H_{3n}), 2.99 (brs, 1H, H_4), 3.25 (ddd, J = 9.9, 2.6, 2.6 Hz, 1H, H_{3x}), 4.55, 4.69, 4.88 (3 × brs, 2H, H_1, H_{6n}), δ_C (75.5 MHz, $CDCl_3$) 28.3 (Boc CH_3), 35.4 (C_7), 36.4 (d, J = 22 Hz, C_5), 40.3 (C_4), 49.8 (C_3), 61.1 (d, J = 27 Hz, C_1), 81.2 (Boc C), 90.7 (d, J = 198 Hz, C_6), 116.4 (CN), 153.1 (Boc CO). δ_F (282.3 MHz, $CDCl_3$) -161.8. $^m/_z$ $C_{12}H_{18}N_2O_2F$ [MH^+] requires 241.13523 observed 241.13527.

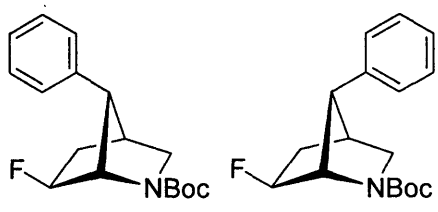
***anti*-7-Bromo-*exo*-6-fluoro-2-Boc-2-azabicyclo[2.2.1]heptane (222)**



Palladium on carbon (10%, ~ 250 mg) was added to *anti*-7-cyano-*exo*-6-fluoro-2-benzyl-2-azabicyclo[2.2.1]heptane (**215**) (3.18g, 11.20 mmol) dissolved in methanol (50 ml) in a high pressure reaction vessel and stirred under hydrogen (20 bar) for 24 h. The reaction mixture was filtered through celite, the methanol removed *in vacuo* and the resulting residue dissolved in THF (30 ml) and water (90

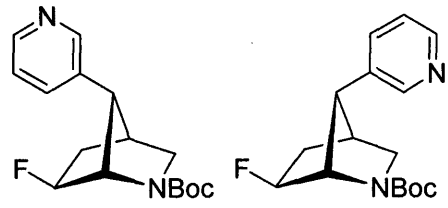
ml); Boc_2O (4.88 g, 22.4 mmol) and $NaHCO_3$ (3.90 g, 46.4 mmol) were added and the mixture stirred at RT for 24 h. The reaction mixture was extracted with diethyl ether, the organic extracts combined and dried over $MgSO_4$, filtered and the solvents removed *in vacuo* the crude product was flash chromatographed (petrol:diethyl ether, 3:1) to give **222** as a colourless oil (0.911 g, 3.10 mmol, 28%) R_f 0.29. δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] 1.46 (brs, 9H, Boc), 2.05-2.18 (m, 1H, H_{5n}), 2.30-2.53 (m, 1H, H_{5x}), 2.74 (brs, 1H, H_4), 2.94 (brd, J = 9.6 Hz, 1H, H_{3n}), 3.25 (ddd, J = 9.6, 3.4, 3.4 Hz, 1H, H_{3x}), 4.04 (brs, 1H, H_7), 4.37, *4.49* (2 × brs, 1H, H_1), 4.57-4.72, 4.72-4.88 (2 × m, 1H, H_{6n}). δ_C (75.5 MHz, $CDCl_3$) 28.3 (Boc C), 36.1 (d, J = 20 Hz, C_5), 42.7 (C_4), 47.3 (C_7), 49.3 (C_3), 61.8 (d, J = 23 Hz, C_1), 80.8 (Boc C), 91.6 (d, J = 201 Hz, C_6). δ_F (282.3 MHz, $CDCl_3$) *-162.2*, -161.6. ν_{max} 2976m, 2896w, 1683s, 1483m, 1456m, 1393s, 1365s, 1330m, 1293m, 1268m, 1250m, 1227m, 1154s, 1102s cm^{-1}. $^m/_z$ $C_{11}H_{18}NO_2FBr$ [MH^+] requires 294.05049; observed 294.05054.

***anti-* and *syn*-7-phenyl-*exo*-6-fluoro-2-Boc-2-azabicyclo[2.2.1]heptane (223 and 224)**



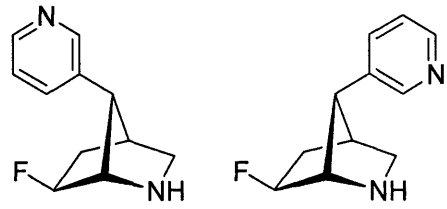
The procedure described for the synthesis of **122** and **123** was followed using: $Ni(cod)_2$ (23 mg, 0.084 mmol); bathophenanthroline (56 mg, 0.168 mmol); benzene boronic acid (60 mg, 0.492 mmol); ^{t}BuOK (66 mg, 0.588 mmol) and *anti*-7-bromo-*exo*-6-fluoro-2-Boc-2-azabicyclo[2.2.1]heptane (**222**) (103 mg, 0.350 mmol). Flash chromatography (diethyl ether:petrol, 1:1) gave a mixture of **223** and **224** as a pale yellow oil (~ 18:82; *anti-*:*syn-*, from ^{19}F peak integration)(39 mg, 0.134 mmol, 38% by ^{19}F internal standard). **224**: δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] 1.31, 1.43 (2 × s, 9H, Boc), 1.80-2.10 (m, 2H, H_{5x}, H_{5n}), 2.62 (brs, 1H, H_4), 2.64, *2.72* (2 × d, J = 9.9 Hz, 1H, H_{3n}), *2.81*, 2.90 (2 × m, 1H, H_{3x}), 3.26 (brs, 1H, H_7), 4.49, *4.67* (2 × brs, 1H, H_1), 4.72, 4.80 (2 × dddd, J = 54.1, 6.3, 2.5, 2.5 Hz, 1H, H_{6n}), 7.12-7.27 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) *28.3*, 28.5 (Boc CH_3), 38.6 (d, J = 20 Hz, C_5), 39.7, *40.5* (C_4), 48.0, [48.2 (C_7)], *48.8* (C_3), *60.1*, 60.4 (2 × d, J = 91 Hz, C_1), *79.7*, 80.0 (Boc C), 91.3, *91.5* (2 × d, J = 203 Hz, C_6), 127.5, 127.6, 128.5 (5 × aryl CH), 136.9 (aryl C), 154.4 (Boc CO). δ_F (282.3 MHz, $CDCl_3$) *-164.4*, -163.7. $^m/_z$ $C_{17}H_{23}NO_2F$ [MH^+] requires 292.17128; observed 292.17122. **223** (was not isolable): δ_F (282.3 MHz, $CDCl_3$) *-162.6*, -161.9.

anti- and _syn_-7-(pyridin-3-yl)-_exo_-6-fluoro-2-Boc-2-azabicyclo[2.2.1]heptane (225 and 226)



The procedure described for the synthesis of **122** and **123** was followed using: $Ni(cod)_2$ (25 mg, 0.091 mmol); bathophenanthroline (61 mg, 0.184 mmol); 3-pyridyl boronic acid (47 mg, 0.382 mmol); ^tBuOK (64 mg, 0.570 mmol) and *anti*-7-bromo-*exo*-6-fluoro-2-Boc-2-azabicyclo[2.2.1]-heptane (**222**) (104 mg, 0.354 mmol). Flash chromatography (diethyl ether) gave a mixture of **225** and **226** as a pale yellow oil (only **226** was characterisable, deprotection to (see below) indicated: ~ 13:87; *anti-*:*syn-*, from ^{19}F peak integration)(18 mg, 0.062 mmol, 18%). **226**: δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] 1.39, *1.50* (2 × s, 9H, Boc), 1.90-2.14 (m, 2H, H_{5x}, H_{5n}), 2.76 (brs, 1H, H_4), 2.76-3.08 (m, 2H, H_{3x}, H_{3n}), 3.34 (brs, 1H, H_7), 4.60, *4.76* (2 × brs, 1H, H_1), 4.82, 4.91 (2 × dddd, J = 53.4, 6.3, 2.1, 2.1 Hz, 1H, H_{6n}), 7.25 (m, 1H, $H_{5'}$), 7.56 (m, 1H, $H_{4'}$), 8.50 (m, 1H, $H_{6'}$), 8.54 (m, 1H, $H_{2'}$). δ_C (75.5 MHz, $CDCl_3$) *28.3*, 28.5 (Boc CH_3), 38.5 (d, J = 25 Hz, C_5), 39.6, *40.3* (C_4), 46.1, *46.6* (C_7), *47.8*, 48.6 (C_3), *59.8*, 60.2 (2 × d, J = 81 Hz, C_1), *80.1*, 80.4 (Boc C), *91.0*, 91.3 (2 × d, J = 193 Hz, C_6), 123.4, [132.5, 132.7 (pyridyl C)], 135.0, 135.1, 148.19, 148.28, 149.3, 149.5 (4 × pyridyl CH), 154.2, *154.5* (Boc CO). δ_F (282.3 MHz, $CDCl_3$) *-164.4*, -163.7. ν_{max} 2975m, 1691s, 1480m, 1399s, 1366s, 1267m, 1147s, 1105m cm^{-1}. $^m/_z$ $C_{16}H_{22}N_2O_2F$ [MH^+] requires 293.16653; observed 293.16645. **225** (was not isolable): δ_F (282.3 MHz, $CDCl_3$) *-162.0*, -161.3.

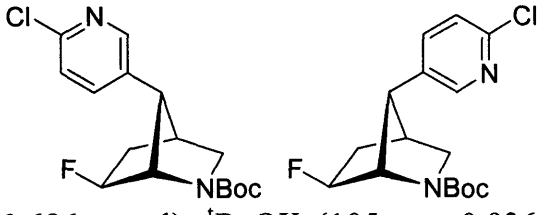
anti- and _syn_-7-(pyridin-3-yl)-_exo_-6-fluoro-2-azabicyclo[2.2.1]heptane



Ethanol (2.6 ml) then acetyl chloride (2.1 ml) were added to a solution of *anti-* and *syn*-7-(pyridin-3-yl)-*exo*-6-fluoro-2-Boc-2-azabicyclo[2.2.1]heptane (**225** and **226**) (15 mg, 0.051 mmol) in ethyl acetate (7ml) with stirring and cooling in ice. The reaction mixture was allowed to reach RT then evaporated to dryness to give the dihydrochloride salts of the title compounds (13 mg 96 %) (~ 13:87; *anti-*:*syn-*, from ^{19}F peak integration). Data for dihydrochloride salt of *syn*-7-(pyridin-3-yl)-*exo*-6-fluoro-2-azabicyclo[2.2.1]heptane. δ_H (300 MHz, CD_3OD) 2.12-2.30 (m, 1H, H_{5x}), 2.30-2.44 (m, 1H, H_{5n}), 3.08-3.24 (m, 2H, H_{3x}, H_{3n}), 3.51 (brs, 1H, H_4), 3.96 (brs, 1H, H_7), 4.95 (brd, J = 2.8 Hz, 1H, H_1), 5.26 (dd, J = 50.7, 6.4 Hz, 1H, H_{6n}), 8.17 (dd, J = 7.9, 5.6 Hz, 1H, $H_{5'}$), 8.78 (d, J = 7.9 Hz, 1H, $H_{6'}$*), 8.89 (d, J = 5.6 Hz, 1H, $H_{4'}$*), 9.09 (brs, 1H, $H_{2'}$), *denotes interchangeable

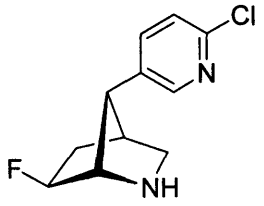
assignments. δ_C (75.5 MHz, CD_3OD) 38.2 (C_4), 38.4 (d, J = 22 Hz, C_5), 48.2 (C_3), 48.5 (C_7), 62.7 (d, J = 29 Hz, C_1), 90.2 (d, J = 189 Hz, C_6), 128.9, [136.4 (pyridyl C)], 142.2, 143.1, 148.2 (4 × pyridyl CH). δ_F (282.3 MHz, CD_3OD) -172.7. $^m/_z$ $C_{13}H_{15}NOBr$ [MH^+] requires 193.11410; observed 193.11405. *anti*-7-(Pyridin-3-yl)-*exo*-6-fluoro-2-azabicyclo[2.2.1]heptane (was not isolable): δ_F (282.3 MHz, $CDCl_3$) -170.4.

anti- and _syn_-7-(6-chloro-pyridin-3-yl)-_exo_-6-fluoro-2-Boc-2-azabicyclo[2.2.1]heptane (227 and 228)



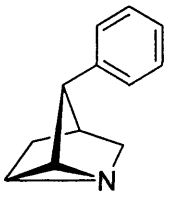
The procedure described for the synthesis of **122** and **123** was followed using: $Ni(cod)_2$ (30 mg, 0.109 mmol); bathophenanthroline (75 mg, 0.226 mmol); 4-chloro-3-pyridyl boronic acid (108 mg, 0.686 mmol); ^{t}BuOK (105 mg, 0.936 mmol) and *anti*-7-bromo-*exo*-6-fluoro-2-Boc-2-azabicyclo[2.2.1]heptane (**222**) (154 mg, 0.524 mmol) except reaction mixture stirred at 40 °C for 24 h rather than 100 °C for 48 h. Flash chromatography (diethyl ether:petrol, 1:1) gave a mixture of **227** and **228** as a pale yellow oil (~22:78; *anti-*:*syn-*, from ^{19}F peak integration)(20 mg, 0.062 mmol, 12%). **228**: δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] 1.41, 1.50 (2 × brs, 9H, Boc), 1.89-2.13 (m, 2H, H_{5x}, H_{5n}), 2.73 (brs, 1H, H_4), *2.78*, 2.86 (2 × d, J = 9.9 Hz, H_{3n}), 2.91 (m, 1H, H_{3x}), 3.28 (brs, 1H, H_7), *4.56*, 4.72 (2 × brs, 1H, H_1), 4.82, 4.88 (2 × dddd, J = 53.4, 6.3, 2.4, 2.4 Hz, 1H, H_{6n}), 7.27, 7.30 (2 × d, J = 8.4 Hz, 1H, $H_{5'}$), 7.51, 7.53 (2 × dd, 8.4, 2.4 Hz, 1H, $H_{4'}$), 8.30, 8.31 (2 × d, J = 2.4 Hz, 1H, $H_{2'}$). δ_C (75.5 MHz, $CDCl_3$) 28.3, 28.5 (Boc CH_3), 38.5 (d, J = 21 Hz, C_5), 39.7, *40.5* (C_4), *45.5*, 46.1 (C_7), *47.8*, 48.5 (C_3), 59.9, 60.2 (2 × d, J = 97 Hz, C_1), 80.3, 80.6 (Boc C), 91.0, 91.3 (2 × d, J = 194 Hz, C_6), 124.1, 124.2 [131.7 (pyridyl C)], 137.9, 138.1, 149.1, 149.3 (3 × pyridyl CH), 154.1, 154.4 (Boc CO). δ_F (282.3 MHz, $CDCl_3$) *-164.4*, -163.7. ν_{max} 2976m, 1690s, 1587w, 1563w, 1464m, 1392s, 1366s, 1333m, 1289m, 1257m, 1171m, 1146s, 1102s cm^{-1}. $^m/_z$ $C_{16}H_{21}N_2O_2ClF$ [MH^+] requires 327.12756; observed 327.12747. **227** (was not isolable): δ_F (282.3 MHz, $CDCl_3$) -161.7, *-160.9*.

syn-7-(6-Chloro-pyridin-3-yl)-_exo_-6-fluoro-2-azabicyclo[2.2.1]heptane (213)



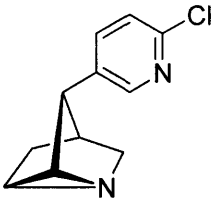
syn-7-(6-Chloro-pyridin-3-yl)-_exo_-6-fluoro-2-Boc-2-azabicyclo[2.2.1]-heptane (**228**) was dissolved in ethanol (0.52 ml) and ethyl acetate (1.43 ml). Acetyl chloride (0.43 ml) was added with cooling in ice and the reaction mixture was stirred at RT for 2 h. The solvents were removed _in vacuo_ to give the hydrochloride salt of **213** as a white solid (14 mg (by NMR integration against an internal standard) 88%). Data for hydrochloride salt of **213**: δ_H (300 MHz, CD_3OD) 1.92-2.29 (m, 2H, H_{5x}, H_{5n}), 2.96 (brs, 1H, H_4), 3.20-3.30 (m, 2H, H_{3x}, H_{3n}), 3.65 (brs, 1H, H_7), 4.69 (brd, J = 3.2 Hz, 1H, H_1), 5.12 (dddd, J = 51.2, 6.0, 2.0, 2.0 Hz, 1H, H_{6n}), 7.48 (brd, J = 8.5 Hz, 1H, $H_{5'}$), 7.89 (brdd, J = 8.5, 2.6 Hz, 1H, $H_{4'}$), 8.42 (brd, J = 2.6 Hz, 1H, $H_{2'}$). δ_C (75.5 MHz, CD_3OD) 38.3 (C_4), 38.5 (C_5), 48.15 (C_7), 48.18 (C_3), 62.7 (d, J = 28.7 Hz, C_1), 90.4 (d, J = 187.9 Hz, C_6), 126.3 ($C_{5'}$), 130.9 ($C_{3'}$), 141.5 ($C_{4'}$), 148.4 ($C_{6'}$), 150.1 ($C_{2'}$). δ_F (282.3 MHz, CD_3OD) -172.9. $^m/_z$ $C_{11}H_{13}N_2ClF$ [MH^+] requires 227.07513; observed 227.07506.

syn-3-Phenyl-1-azatricyclo[2.2.1.0^{2,6}]heptane (231)



syn-7-Phenyl-_exo_-6-fluoro-2-Boc-2-azabicyclo[2.2.1]heptane (**230**) was deprotected as described for **52**. The crude residue was dissolved in ammonium hydroxide solution and extracted with DCM; the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvents removed _in vacuo_. The only product observed was **231**. δ_H (300 MHz, $CDCl_3$) 1.56 (AB, J = 11.2 Hz, 2H, H_5), 2.17, 2.39 (2 × m, 2H, 2H, H_2, H_6, H_7), 2.49 (d, J = 3.7 Hz, 1H, H_4), 2.88 (brs, 1H, H_3), 7.22-7.36 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 32.8, [33.2 (C_5)], 34.5, 35.2 (C_2, C_4, C_6), 48.6 (C_3), 51.9 (C_7), 126.5, 128.0, 128.2 (5 × aryl), 139.8 (aryl C). $^m/_z$ (MH^+) 171.

syn-3-(6-Chloro-pyridin-3-yl)-1-azatricyclo[2.2.1.0^{2,6}]heptane (229)



The hydrochloride salt of _syn_-7-(6-chloro-pyridin-3-yl)-_exo_-6-fluoro-2-azabicyclo[2.2.1]heptane (**213**) (12 mg) was stirred in sodium hydroxide solution (1 M, 3 ml) for 5 h. The reaction mixture was extracted with DCM; the organic extracts were combined and dried over anhydrous $MgSO_4$, filtered and the solvents removed _in vacuo_. The crude residue was flash chromatographed (19:1; diethyl ether: methanol) to give **229** (2.4 mg, 0.012 mmol, 26% isolated yield). R_f 0.35. δ_H (300 MHz, $CDCl_3$) 1.59 (AB, J = 12.0 Hz, 2H, H_5), 2.16 (brs, 1H, H_4), 2.23 (AB, J = 10.5 Hz, 2H, H_7), 2.45 (m, 2H, H_2, H_6), 2.84 (brs, 1H, H_3), 7.28 (d, J = 8.2 Hz, 1H, $H_{5'}$), 7.55 (dd,

J = 8.2, 2.6 Hz, 1H, $H_{4'}$), 8.31 (d, J = 2.6 Hz, 1H, $H_{2'}$). δ_C (100.6 MHz, $CDCl_3$) 32.7, [33.2 (C_5)], 34.2, 35.1 (C_2, C_4, C_6), 45.7 (C_3), 52.0 (C_7), 123.8 ($C_{5'}$), 134.2 (pyridyl C), 138.3 ($C_{4'}$), 149.3 ($C_{2'}$), 149.8 (pyridyl C). $^m/_z$ $C_{11}H_{12}N_2Cl$ [MH^+] requires 207.06890; observed 207.06886.

2-Boc-2-azabicyclo[2.2.1]hept-5-ene (220)

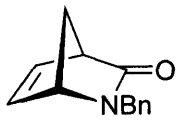
Based on the procedure described by Cox.[159] Aqueous formaldehyde solution (37%, 10 ml, 0.120 mol) was added to ammonium chloride (14.2 g, 0.265 mol) in water (100 ml) and stirred for 0.5 h, freshly distilled cyclopentadiene (19 ml, 0.230 mol) was added. The reaction mixture stirred at RT for 21 h then washed with diethyl ether (3 × 20 ml), basified with NaOH to pH 10 and extracted with DCM (4 × 20 ml). The organic extracts were evaporated to dryness and the resulting residue was dissolved in THF (20 ml) and water (60 ml), Boc_2O (13.5 g, 0.062 mol) and sodium bicarbonate (14.22 g, 0.169 mmol) were added. The mixture was stirred at RT for 24 h then extracted with diethyl ether (4 × 30 ml), the combined organic layers were dried over $MgSO_4$, filtered and the solvents removed *in vacuo* to give **220** as a pale yellow oil (10.06 g, 51.6 mmol, 22%). δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] 1.44 (brs, 9H, Boc), 1.47-1.63 (m, 2H, H_{7s}, H_{7a}), 2.62 (m, 1H, H_4), 3.16 (brs, 1H, H_{3n}), 3.30 (dd, J = 9.1, 3.0 Hz, 1H, H_{3x}), 4.58, *4.71* (2 × brs, 1H, H_1), 6.27 (brs, 1H, H_5), 6.28, 6.38 (2 × brs, 1H, H_6). δ_C (75.5 MHz, $CDCl_3$) 28.5 (Boc CH_3), 42.9, *43.4* (C_4), 45.9, *46.3* (C_3), *59.9*, 61.1 (C_1), 79.0 (Boc C), 133.7, 134.4 (C_5, C_6). ν_{max} 2978m, 1810w, 1691s, 1478m, 1455m, 1365s, 1308m, 1249m, 1212m cm^{-1}. $^m/_z$ 196 $(MH)^+$.

6-Boc-3-oxa-6-azatricyclo[3.2.1.$0^{2,4}$]octane (255a)

mCPBA (7.48 g, 70% maximum, 30.4 mmol maximum) was added to a solution of **220** (4.89 g, 25.1 mmol) in dry DCM (50 ml). After stirring under nitrogen at RT for 48 h the reaction mixture was washed with sodium bicarbonate solution (2 × 20 ml) then water (2 × 20 ml), the organic layer was dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo*. The resulting residue was flash chromatographed (diethyl ether) to give **255a** as a yellow oil (2.94 g, 13.9 mmol, 56%). R_f 0.63. δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] 1.17-1.20, 1.43-1.65 (2 × m, 2H, H_{7s}, H_{7a}), 1.46 (brs, 9H, Boc), 2.77 (brd, J = 1.4 Hz, 1H, H_4), 2.89-3.05 (m, 1H, H_{3n}),

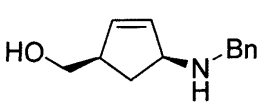
3.15-3.27 (m, 2H, H_{3x}, H_5), 3.41 (m, 1H, H_6), 4.30, *4.45* (2 × brs, 1H, H_1). δ_C (75.5 MHz, $CDCl_3$) *25.6*, 25.9 (C_7), 28.4 (Boc CH_3), 37.3, *37.9* (C_4), 46.7, *47.0* (C_3), 49.2, 49.4 (C_5, C_6), *56.5*, 57.6 (C_1), 79.6 (Boc C), 154.8 (Boc CO). ν_{max} 2976m, 1683s, 1479m, 1403s, 1364s, 1254m, 1176m, 1156s cm^{-1}. $^m/_z$ $C_{11}H_{18}NO_3$ [MH^+] requires 212.12867; observed 212.12863.

2-Benzyl-2-azabicyclo[2.2.1]hept-5-en-3-one (242)



Using a procedure adapted from that described by Buston *et al.*[180] 2-azabicyclo[2.2.1]hept-5-en-3-one (**241**) (80 mg, 0.733 mmol) was dissolved in dry THF (10 ml), sodium hydride (60%, 91 mg, 2.28 mmol) was added and stirred under nitrogen at RT for 0.5 h. Benzyl bromide (0.2 ml, 1.69 mmol) was added and the reaction mixture was stirred under nitrogen at RT for a further 24 h. Addition of ammonium hydroxide solution was followed by extraction with diethyl ether, the combined organic extracts were washed with water then dried over anhydrous $MgSO_4$, filtered and solvents removed *in vacuo*. The residue was flash chromatographed (diethyl ether: petrol; 1:1) to give **242** as a colourless oil (47 mg, 0.236 mmol, 32%). R_f 0.17. δ_H (300 MHz, $CDCl_3$) 2.08, 2.30 (2 × ddd, J = 7.6, 1.9, 1.9 Hz, 1H, 1H, H_{7s}, H_{7a}), 3.39 (brd, J = 1.9 Hz, 1H, H_4), 3.97, [4.04 (brdd, J = 1.9, 1.9 Hz, 1H, H_1)], 4.46 (2 × d, 1H, 1H, $C\underline{H}_2Ph$), 6.56, 6.57 (2 × d, J = 1.9 Hz, 1H, 1H, H_5, H_6), 7.16-7.35 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 47.9 (C_7), 53.7 (C_4), 58.3 ($\underline{C}H_2Ph$), 62.6 (C_1), 127.5, 128.3, 128.5 (5 × aryl CH), 136.4 (aryl C), 137.3, 139.5 (C_5, C_6), 179.9 (C_3). ν_{max} 3006w, 1697s, 1558m, 1496m, 1454m, 1391m, 1355m, 1305m, 1230m cm^{-1}. $^m/_z$ $C_{13}H_{14}NO$ [MH^+] requires 200.10754; observed 200.10752.

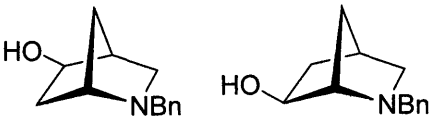
(4-Benzylamino-cyclopent-2-enyl)-methanol (247)



Lithium aluminium hydride (42 mg, 1.11 mmol) was added to a solution of 2-benzyl-2-azabicyclo[2.2.1]hept-5-en-3-one (**242**) (44 mg, 0.221 mmol) in dry THF (5 ml) with cooling in ice. The reaction mixture was allowed to reach RT and stirred under nitrogen for 4 h; then quenched with ether saturated with water (~ 5 ml) followed by water (~ 5 ml) and extracted with DCM. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo* to give **247** (24 mg, 53%) in high enough purity for further reactions. δ_H (300 MHz, $CDCl_3$) 1.59 (d, J = 13.4 Hz, 1H, H_{5s}), 2.19 (ddd, J = 13.4, 8.8, 6.7 Hz, 1H, H_{5a}), 2.94 (brd, J = 8.8 Hz, 1H, H_1), 3.3 (NH, OH), 3.61 (t, J = 3.0 Hz, 2H, $C\underline{H}_2OH$), 3.70 (ddd, J = 6.7, 1.5, 1.5 Hz, 1H, H_4), 3.78 (AB, J = 12.9 Hz, 2H, $C\underline{H}_2Ph$), 5.90 (brs, 2H, H_2, H_3), 7.21-7.35 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 34.4 (C_5), 45.8 (C_1), 50.8 ($\underline{C}H_2Ph$), 60.0 (C_4), 62.1 ($\underline{C}H_2OH$), 126.2, 127.2, 127.5 (5

× aryl CH), 131.7, 135.4 (C_2, C_3), 138.3 (aryl C). $^m/_z$ $C_{13}H_{18}NO$ [MH^+] requires 204.13884; observed 204.13889.

exo-5- and _exo_-6-Hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (260 and 261)

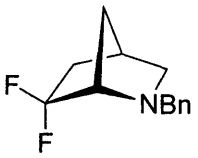


Following the procedure described by Carroll *et al.*[168] Borane-THF complex (1M, 28.9 ml, 28.9 mmol) was added drop-wise to a solution of 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene (**73**) (3.60 g, 19.5 mmol) in dry THF (40 ml) at 0 °C under N_2 and stirred for 2 h. THF:water (1:1; 20 ml) was added, followed by NaOH solution (3M, 6 ml), then H_2O_2 (30%, 7 ml) the temperature was raised to 40 °C and the reaction mixture was stirred for a further 1.5 h. Potassium carbonate (1.8 g) was added, the THF was removed *in vacuo* and the residue was extracted with DCM; the combined organic extracts were washed with water and dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo*. Flash chromatography (diethyl ether) gave *exo*-6-hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (**261**) (2.252 g, 11.09 mmol, 57%) R_f 0.64; and *exo*-5-hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (**260**) (0.576 g, 2.84 mmol, 15%) R_f 0.32 as pale yellow oils. Data for *exo*-5-hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (**260**): δ_H (300 MHz, $CDCl_3$) 1.16 (brd, J = 14.0 Hz, 1H, H_{6x}), 1.59 (m, 2H, H_{7s}, H_{7a}), 1.90 (d, J = 9.9 Hz, 1H, H_{3n}), 2.15-2.25 (m, 2H, H_4, H_{6n}), 2.2 (OH), 2.66 (dd, J = 9.9, 4.4 Hz, 1H, H_{3x}), 3.13 (brd, J = 1.5 Hz, 1H, H_1), 3.48 (AB, J = 13.4 Hz, 2H, $C\underline{H}_2Ph$), 3.81 (ddd, J = 7.0, 1.2, 1.2 Hz, 1H, H_{5n}), 7.11-7.27 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 32.2 (C_7), 38.6 (C_6), 45.6 (C_4), 54.5 (C_3), 58.3 ($\underline{C}H_2Ph$), 59.4 (C_1), 73.2 (C_5), 126.7, 128.2, 128.5 (5 × aryl CH), 139.5 (aryl C). ν_{max} 3320m, 2963s, 1495m, 1453s, 1368s, 1325s, 1211s, 1113s, 1045s, 1008s cm^{-1}. $^m/_z$ $C_{14}H_{18}N$ [MH^+] requires 204.13884; observed 204.13877. Data for *exo*-6-hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (**261**): δ_H (300 MHz, $CDCl_3$) 1.31 (dddd, J = 13.2, 4.4, 2.1, 0.6 Hz, 1H, H_{5x}), 1.53 (brs, 2H, H_{7s}, H_{7a}), 1.81 (dd, J = 13.2, 7.0 Hz, 1H, H_{5n}), 2.38 (brs, 1H, H_4), 2.48 (ddd, J = 8.8, 3.2, 2.6 Hz, 1H, H_{3x}), 2.99 (brs, 1H, H_1), 3.31 (d, J = 8.8 Hz, 1H, H_{3n}), 3.67 (brs, 2H, $C\underline{H}_2Ph$), 4.05 (brd, J = 6.7 Hz, 1H, H_{6n}), 7.19-7.36 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 31.1 (C_7), 36.5 (C_4), 40.3 (C_5), 58.6 (C_3), 59.5 ($\underline{C}H_2Ph$), 65.6 (C_1), 72.5 (C_6), 126.7, 128.2, 128.5 (5 × aryl CH), 139.9 (aryl C). ν_{max} 3348m, 2963s, 1495m, 1453s, 1368s, 1330s, 1229m cm^{-1}. $^m/_z$ $C_{13}H_{18}NO$ [MH^+] requires 204.13884; observed 204.13890.

6-Keto-2-benzyl-2-azabicyclo[2.2.1]heptane (259)

Following the procedure described by Carroll *et al.*[168] Trifluoroacetyl anhydride (2.3 ml, 16.5 mmol) in dry DCM (7 ml) was added to a solution of DMSO (1.56 ml, 22.2 mmol) in dry DCM (11.5 ml) under nitrogen at -78 °C and stirred for 10 min. *exo*-6-Hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (**261**) (2.252 g, 11.09 mmol) was added in dry DCM (7 ml) and the reaction mixture was stirred for a further 30 min. Triethylamine (9.2 ml) was added and the reaction mixture was allowed to reach RT overnight; addition of water (15 ml) was followed by extraction into DCM. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo*; the residue was flash chromatographed (petrol: diethyl ether; 6:4) to give **259** as a pale yellow oil (0.880 g, 4.38 mmol, 39%). δ_H (300 MHz, $CDCl_3$) 1.65-1.75, 1.94 (m, ddd, J = 10.5, 4.4, 2.3 Hz, 2H, 1H, H_{5n}, H_{7s}, H_{7a}), 2.05 (dd, J = 9.1, 1.5 Hz, 1H, H_{3n}), 2.19 (ddd, J = 17.8, 4.4, 1.8 Hz, 1H, H_{5x}), 2.64 (brs, 1H, H_4), 3.21 (brs, 1H, H_1), 3.30 (ddd, J = 9.1, 2.9, 2.0 Hz, 1H, H_{3x}), 3.59 (AB, J = 13.7 Hz, 2H, C$\underline{H}_2$Ph), 7.20-7.36 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 35.6 (C_4), 36.7 (C_7), 44.2 (C_5), 55.9 (C_3), 57.4 ($\underline{C}H_2$Ph), 66.8 (C_1), 127.0, 128.3, 128.5 (5 × aryl CH), 136.8 (aryl C), 208.1 (C_6). ν_{max} 2973m, 1734s, 1494m, 1453m, 1407m, 1370m, 1209m, 1184m, 1159m cm^{-1}. $^m/_z$ $C_{13}H_{16}NO$ [MH^+] requires 202.12319; observed 202.12314.

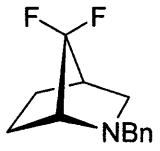
***exo*-6,1-Difluoro-2-benzyl-2-azabicyclo[2.2.1]heptane (262) and 6,6-difluoro-2-benzyl-2-azabicyclo[2.2.1]heptane (258)**



DAST (0.18 ml, 1.37 mmol) was added to a solution of 6-keto-2-benzyl-2-azabicyclo[2.2.1]heptane (**259**) (55 mg, 0.274 mmol) in dry DCM (4 ml) and stirred under nitrogen at RT. After 24 h, the reaction mixture was quenched by the addition of $NaHCO_3$ solution (5 ml) and extracted with DCM. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo*. The crude product residue was flash chromatographed (19:1; petrol: diethyl ether) to give **262** (19 mg, 0.085 mmol, 31%, R_f 0.17) and **258** (19 mg, 0.085 mmol, 31%, R_f 0.09) as colourless oils. Data for *exo*-6,1-difluoro-2-benzyl-2-azabicyclo[2.2.1]heptane (**262**): δ_H (300 MHz, $CDCl_3$) 1.87-2.22 (m, 5H, H_{3n}, H_{5x}, H_{5n}, H_{7s}, H_{7a}), 2.26 (brs, 1H, H_4), 3.32 (m, 1H, H_{3x}), 3.43, 4.20 (2 × d, J = 13.2 Hz, 1H, 1H, C$\underline{H}_2$Ph), 4.95 (dd, J = 56.4, 6.4 Hz, 1H, H_{6n}), 7.20-7.34 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 31.1 (d, J = 5.3 Hz, C_4), 36.0 (d, J = 14.3 Hz, C_7), 38.8 (dd, J = 20.4, 5.3 Hz, C_5), 52.4 ($\underline{C}H_2$Ph), 58.7 (d, J = 5.3 Hz, C_3), 87.3 (dd, J = 196.9, 30.2 Hz, C_6), 127.0, 128.0, 128.3 (5 × aryl CH), 138.9 (aryl C). δ_F (282.3 MHz, $CDCl_3$) -180.3 (d, J = 24.8 Hz, F_1), -174.7 (dddd,

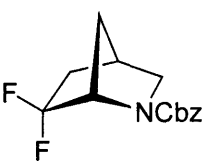
J = 75.9, 43.4, 24.8, 4.6 Hz, F_{6x}). ν_{max} 2883m, 1494m, 1454m, 1431m, 1378m, 1346m, 1295m, 1260m, 1231s, 1161s, 1136s cm^{-1}. $^m/_z$ $C_{13}H_{15}NF_2$ [MH^+] requires 223.11726; observed 223.11732. Data for 6,6-difluoro-2-benzyl-2-azabicyclo[2.2.1]heptane (**258**): δ_H (300 MHz, $CDCl_3$) 1.61-1.86 (m, 3H, H_{5n}, H_{7s}, H_{7a}), 1.94-2.18 (m, 1H, H_{5x}), 2.47 (d, J = 9.0 Hz, 1H, H_{3n}), 2.50 (brs, 1H, H_4), 2.84 (ddd, J = 9.0, 5.6, 2.9 Hz, 1H, H_{3x}), 3.25 (brs, 1H, H_1), 3.86 (AB, J = 13.7 Hz, 2H, $C\underline{H}_2Ph$), 7.20-7.38 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 34.5 (d, J = 3.6 Hz, C_7), 36.6 (dd, J = 3.6, 3.6 Hz, C_4), 41.4 (dd, J = 20.3, 23.9 Hz, C_5), 57.3 (C_3), 58.6 (d, J = 3.6 Hz, $\underline{C}H_2Ph$), 64.5 (dd, J = 28.7, 19.1 Hz, C_1), 126.8, 128.2 (5 × aryl CH), 139.6 (aryl C). δ_F (282.3 MHz, $CDCl_3$) -111.8 (d, J = 223.5 Hz), -86.0 (d, J = 223.5 Hz). ν_{max} 2968w, 2913w, 2843m, 1492m, 1452m, 1440m, 1369m, 1336s, 1230s cm^{-1}. $^m/_z$ 223 (MH^+).

7,7-Difluoro-2-benzyl-2-azabicyclo[2.2.1]heptane (277)



DAST (0.22 ml, 1.70 mmol) was added to a solution of 7-keto-2-benzyl-2-azabicyclo[2.2.1]heptane (**159**) (68 mg, 0.34 mmol) in dry DCM (5 ml) and stirred under nitrogen at RT. After 24 h the reaction mixture was quenched by the addition of $NaHCO_3$ solution (5 ml) and extracted with DCM. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo*. The crude product residue was flash chromatographed (3:1; petrol: diethyl ether) to give **277** as a yellow oil (29 mg, 0.13 mmol, 38%). R_f 0.57. δ_H (300 MHz, $CDCl_3$) 1.48-1.58, 1.81-1.96 (2 × m, 1H, 3H, H_5, H_6), 2.20 (dd, J = 3.8, 3.8 Hz), 2.72 (brd, J = 9.1 Hz, 1H, H_{3n}), 2.90 (brs, 1H, H_1), 2.98 (m, 1H, H_{3x}), 3.80 (AB, J = 13.4 Hz, $C\underline{H}_2Ph$), 7.20-7.37 (m, 5H, Ph). δ_C [75.5 MHz, $CDCl_3$; * denotes interchangeable assignments] 25.0, (d, J = 6.0 Hz, C_5*), 26.4 (d, 4.8 Hz, C_6*), 39.9 (dd, J = 19.1, 19.1 Hz, C_4), 57.4 (d, J = 7.2 Hz, C_3), 59.4 ($\underline{C}H_2Ph$), 59.8 (dd, J = 20.3, 18.0 Hz, C_1), 126.9, 128.3, 128.4 (5 × aryl CH), 139.3 (aryl C). δ_F (282.3 MHz, $CDCl_3$) -131.4 (d, J = 200.4 Hz), -128.5 (d, J = 200.4 Hz). ν_{max} 2985m, 2865m, 1495m, 1454m, 1353s, 1327m, 1288m, 1248m, 1201s, 1173s, 1149s cm^{-1}. $^m/_z$ $C_{13}H_{16}NF_2$ [MH^+] requires 224.12508; observed 224.12510.

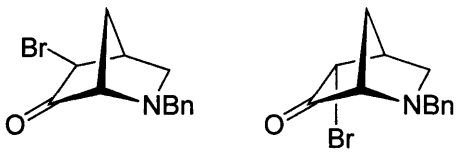
6,6-Difluoro-2-azabicyclo[2.2.1]heptane 2-carboxylic acid benzyl ester (271)



6-Keto-2-azabicyclo[2.2.1]heptane 2-carboxylic acid benzyl ester (**270**) (43 mg, 0.176 mmol) (sample obtained from C. D. Cox) was dissolved in dry DCM (4 ml), DAST (0.1 ml, 0.76 mmol) was added and the reaction mixture was stirred under nitrogen at RT for 24 h. Sodium bicarbonate solution (5 ml) was added and extracted with DCM, the combined organic extracts were dried

over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo*. The crude product was flash chromatographed (diethyl ether: petrol) to give **271** as a yellow oil (32 mg, 0.120 mmol, 68%). R_f 0.25. δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] 1.68-1.92, 2.03-2.23 (2 × m, 3H, 1H, H_5, H_7), 2.65 (brs, 1H, H_4), 3.13, 3.17 (2 × brd, J = 9.7 Hz, 1H, H_{3n}), 3.44 (ddd, J = 9.7, 2.5, 2.5 Hz, 1H, H_{3x}), 4.31, *4.41* (2 × brs, 1H, H_1), 5.15 (brs, 2H, $C\underline{H}_2Ph$), 7.26-7.43 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 35.2, *35.8* (C_4), *35.5*, 36.1 (C_7), 40.3, 40.4 (2 × dd, J = 27, 27 Hz, C_5), 50.9 (C_3), 59.4, 59.8, 60.1, 60.4 (C_1), *66.9*, 67.0 ($\underline{C}H_2Ph$), 127.78, 127.93, 128.42 (5 × aryl CH), 136.6 (aryl C), *154.8*, 155.0 (CO). δ_F (282.3 MHz, $CDCl_3$) *-114.13*, -113.84 (2 × d, J = 220.0 Hz), *-91.98*, -91.96 (2 × d, J = 220.0 Hz).

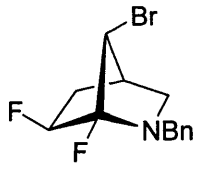
exo- And _endo_-5-bromo-6-keto-2-benzyl-2-azabicyclo[2.2.1]heptane (264 and 265)

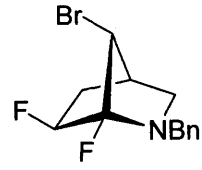


Bromine (0.6 ml, 11.7 mmol) was added to a stirred solution of 6-keto-2-benzyl-2-azabicyclo[2.2.1]heptane (**259**) (226 mg, 1.124 mmol) in acetic acid (20 ml) dropwise at 0 °C. The temperature was raised to 50 °C and the reaction mixture was stirred under nitrogen for 18 h then cooled, washed with DCM, basified with NaOH (soln.) and extracted into ethyl acetate. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo* yielding the *exo*-bromo-compound **264** R_f 0.50 and the *endo*-bromo-compound **265** (~1:1, 52 mg, 0.186 mmol, 17%) R_f 0.21 which were deemed pure enough for further reaction. Flash chromatography (diethyl ether: petrol; 1:1) allowed pure samples of **264** and **265** to be isolated for separate characterisation. *exo*-5-Bromo-6-keto-2-benzyl-2-azabicyclo[2.2.1]heptane (**264**): δ_H (400 MHz, $CDCl_3$) 2.03 (brd, J = 11.1 Hz, 1H, H_{7s}), 2.15 (d, J = 10.1 Hz, 1H, H_{3n}), 2.31 (dd, J = 11.1, 1.3 Hz, 1H, H_{7a}), 2.78 (brs, 1H, H_4), 3.35 (brs, 1H, H_1), 3.40 (dd, J = 10.1, 3.4 Hz, 1H, H_{3x}), 3.58 (AB, J = 13.5 Hz, 2H, $C\underline{H}_2Ph$), 3.66 (brd, J = 3.1 Hz, 1H, H_{5n}), 7.25-7.35 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 34.0 (C_7), 44.5 (C_4), 47.6 (C_5), 54.6, 57.1 (C_3, $\underline{C}H_2Ph$), 65.9 (C_1), 127.3, 128.4, 128.5 (5 × aryl CH), 138.0 (aryl C) $^m/_z$ $C_{13}H_{15}NOBr$ [MH^+] requires 280.03370; observed 280.03371. *endo*-5-Bromo-6-keto-2-benzyl-2-azabicyclo[2.2.1]heptane (**265**): δ_H (300 MHz, $CDCl_3$) 1.92 (brd, J = 11.1 Hz, 1H, H_{7a}), 2.27 (brd, J = 11.1 Hz, 1H, H_{7s}), 2.77 (brd, J = 9.6 Hz, 1H, H_{3n}), 2.90 (brs, 1H, H_4), 3.19 (brd, J = 9.6 Hz, 1H, H_{3x}), 3.30 (brs, 1H, H_1), 3.60 (AB, J = 13.5 Hz, 2H, $C\underline{H}_2Ph$), 4.46 (d, J = 4.3 Hz, 1H, H_{5x}), 7.25-7.38 (m, 5H, Ph). δ_C (100.6 MHz, $CDCl_3$) 35.2 (C_7), 42.8 (C_4), 50.6, [55.0 (C_5)], 56.4 (C_3, $\underline{C}H_2Ph$), 64.9 (C_1), 127.2, 128.4, 128.6 (5 × aryl CH), 198.8 (C_6).

ν_{max} 2874w, 1739s, 1494m, 1454m, 1371m, 1317w, 1257m, 1194m, 1147m, 1072m cm^{-1}. $^{m}/_{z}$ $C_{13}H_{15}NOBr$ [MH^{+}] requires 280.03370; observed 280.03368.

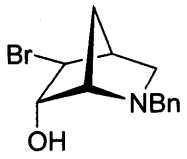
syn-7-Bromo-_exo_-6,1-difluoro-2-benzyl-2-azabicyclo[2.2.1]heptane (266) and _anti_-7-bromo-_exo_-6,1-difluoro-2-benzyl-2-azabicyclo[2.2.1]heptane (267)





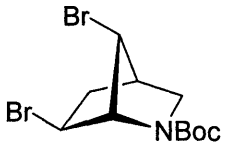
DAST (0.20 ml, 1.02 mmol) was added to a solution of *exo*- and *endo*-5-bromo-6-keto-2-benzyl-2-azabicyclo[2.2.1]heptane (**264** and **265**) (~1:1) (52 mg, 0.186 mmol) in dry DCM (5 ml) and stirred under nitrogen at RT. After 48 h, the reaction mixture was quenched by the addition of $NaHCO_3$ solution (5 ml) and extracted with DCM. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo*. The crude product residue was flash chromatographed (diethyl ether: methanol; 9:1) to give an inseparable mixture of **266** and **267** (~2:1 *syn*: *anti*) (28 mg, 0.093 mmol, 50%). δ_H [300 MHz, $CDCl_3$; the signals corresponding to the minor (*anti*) epimer are underlined] 1.96-2.39, 2.44, 2.50-2.74 (m, brs, m, 4H, H_{3n}, H_4, H_{5x}, H_{5n}), 3.25, [3.48, 3.58 (2 × d, J = 13.3 Hz, J = 13.8 Hz, 1H, H_7)], 3.65 (2 × m, 1H, H_{3x}), 4.18-4.33 (m, 2H, CH_2Ph), 4.85, 5.04 (2 × m, 1H, H_{6n}), 7.22-7.39 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 36.7 (dd, J = 21.5, 5.6 Hz, C_5), 36.9, [37.3 (dd, J = 20.5, 5.4 Hz, C_5)], 37.7 (C_4), 49.1 (dd, J = 15.5, 2.3 Hz, C_7), 50.11 (dd, J = 15.3, 3.0 Hz, C_7), 51.14, 52.3 (CH_2Ph), 55.9, 56.0 (2 × d, J = 4.6 Hz, C_3), 85.0 (dd, J = 201.8, 28.9 Hz, C_6), 86.0 (dd, J = 205.2, 27.3 Hz, C_6), 127.1, 127.3, 127.6, 128.1, 128.4 (5 × aryl CH), 137.6, 138.5 (aryl C). δ_F (282.3 MHz, $CDCl_3$) -182.62 (d, J = 23.9 Hz), -181.34 (d, J = 22.8 Hz), -175.26 (d, J = 22.8 Hz), -173.76 (d, J = 23.9 Hz). ν_{max} 3030w, 2984w, 2924w, 2869w, 1604w, 1495m, 1455m, 1439m, 1368m, 1347m, 1320m, 1295m, 1266m, 1224m, 1187m, 1164m cm^{-1}. $^{m}/_{z}$ $C_{13}H_{14}NF_2Br$ [M^{+}] requires 301.02777; observed 301.02781. The mixture of **266** and **267** contained ~10% (by ^{19}F NMR signal integrations) of the unrearranged products *exo*-5-bromo-6,6-difluoro-2-benzyl-2-azabicyclo[2.2.1]heptane and *endo*-5-bromo-6,6-difluoro-2-benzyl-2-azabicyclo[2.2.1]heptane. δ_F [282.3 MHz, $CDCl_3$; the minor epimer is underlined] -111.89 (d, J = 221.7 Hz), -109.00 (d, J = 223.8 Hz), -87.30 (d, J = 223.8 Hz), -85.98 (d, J = 221.7).

exo-5-Bromo-_endo_-6-hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (275)



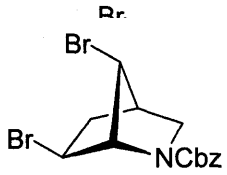
Phosphorus pentabromide (163 mg, 0.379 mmol) was added to a solution of 6-keto-2-benzyl-2-azabicyclo[2.2.1]heptane (**259**) (38 mg, 0.189 mmol) in dry $CDCl_3$ (5 ml); the reaction mixture was stirred under nitrogen at reflux for 24 h then quenched with water (5 ml) and extracted into ethyl acetate. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo*. The resulting residue was dissolved in dry THF (4 ml), Red-Al (65+ % wt. solution in toluene, 0.06 ml, 0.20 ml) was added and the mixture was stirred at -10 °C for 2h. Sodium bicarbonate solution (4 ml) was then added and extracted into ethyl acetate. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo*; flash chromatography of the crude residue gave **275** as the only isolated product (1.2 mg, 0.0043 mmol, 2%). δ_H (400 MHz, $CDCl_3$) 1.85 (ddd, J = 11.0, 4.2, 2.0 Hz, 1H, H_7), 2.05 (d, J = 11.0 Hz, 1H, H_7), 2.63 (brs, 1H, H_4), 2.54 (dd, J = 10.5, 3.9 Hz, 1H, H_{3x}), 2.80 (brd, J = 10.5 Hz, 1H, H_{3n}), 3.27 (brs, 1H, H_1), 3.58 (brs, 1H, H_{5n}), 3.72 (AB, J = 12.9 Hz, 2H, $C\underline{H_2}Ph$), 4.23 (m, 1H, H_{6x}), 7.25-7.36 (m, 5H, Ph). $^m/_z$ 282/284 (1:1) [MH^+].

***anti*-7-_exo_-6-Dibromo-2-Boc-2-azabicyclo[2.2.1]heptane (219)**



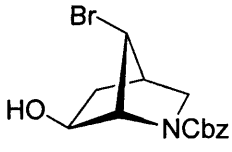
Using a procedure adapted from that described by Sosonyuk *et al.*,[98] 2-Boc-2-azabicyclo[2.2.1]hept-5-ene (**220**) (575 mg, 2.95 mmol) was dissolved in dry DCM (6 ml). Bromine (0.27 ml, 5.9 mmol) was added drop-wise at –78 °C. The mixture was stirred as the temperature rose to 20 °C. Removal of the solvents *in vacuo* gave a residue which was dissolved in dry acetonitrile (3 ml). This solution was cooled to 0 °C and stirred vigorously under nitrogen whilst more **220** (575 mg, 2.95 mmol) in dry acetonitrile (3 ml) was added drop-wise. After warming to 20 °C, the solvents were removed *in vacuo*; flash chromatography (petrol: ether; 9:1) gave starting material (**220**) (305 mg) and **219** as a colourless oil (1.057 g, 2.98 mmol, 69% based on recovered starting material). δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] *1.44*, 1.47 (2 × brs, 9H, Boc), 2.41 (ddd, J = 13.7, 8.2, 1.2 Hz, 1H, H_{5n}), 2.55-2.76 (m, 2H, H_4, H_{5x}), 2.94-3.06 (m, 1H, H_{3n}), 3.34 (ddd, J = 9.9, 2.9, 2.9 Hz, 1H, H_{3x}), 3.90-4.05 (m, 1H, H_{6n}), 4.10 (brs, 1H, H_7), 4.37, *4.49* (2 × brs, 1H, H_1). δ_C (100.6 MHz, $CDCl_3$) 28.3 (Boc CH_3), 39.1 (C_5), 43.1 (C_4), 44.6, *45.1* (C_6), 47.7 (C_7), 49.4, *50.1* (C_3), *62.9*, 64.9 (C_1), 81.0 (Boc C). ν_{max} 2977m, 1694s, 1587w, 1477m, 1456m, 1386s, 1366s, 1330m, 1298m, 1249m, 1228m, 1152s, 1101s cm^{-1}. $^m/_z$ $C_{11}H_{17}NO_2Br_2$ [M^+] requires 352.96260; observed 352.96258.

anti-7-_exo_-6-Dibromo-2-azabicyclo[2.2.1]heptane 2-carboxylic acid benzyl ester (218)



anti-7-_exo_-6-Dibromo-2-Boc-2-azabicyclo[2.2.1]heptane (**219**) (384 mg, _anti_-7-_exo_-6-Dibromo-2-Boc-2-azabicyclo[2.2.1]heptane (**219**) (384 mg, 1.082 mmol) was dissolved in a mixture of ethyl acetate (4 ml) and ethanol (2 ml) after cooling to 0 °C acetyl chloride (2 ml) was added. The temperature was allowed to reach RT and the reaction mixture was stirred for 3 h before the solvents were removed *in vacuo*. The resulting residue was dissolved in water (14 ml); benzylchloroformate (0.30 ml, 1.468 mmol) was added and the pH was adjusted to ~ 11 with NaOH (aqueous). After stirring at RT for 2 h the reaction mixture was extracted into DCM; the organic extracts were combined, dried over anhydrous $MgSO_4$, filtered and reduced *in vacuo*. The crude residue was flash chromatographed (ether: petrol; 1:1) yielding **218** as a colourless oil (223 mg, 0.574 mmol, 53%). δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N-CO rotation (ratio ~40:60), the minor rotamer signal is shown in italics.] 2.36 (dd, J = 14.0, 8.2 Hz, 1H, H_{5n}), 2.56 (brd, J = 14.0 Hz, 1H, H_{5x}), 2.77 (brs, 1H, H_4), 3.02-3.10 (m, 1H, H_{3n}), 3.37 (brd, J = 9.7 Hz, 1H, H_{3x}), 3.99 (m, 1H, H_{6n}), 4.07 (brs, 1H, H_7), 4.43, *4.50* (2 × brs, 1H, H_1), 5.09-5.21 (m, 2H, $C\underline{H}_2Ph$), 7.28-7.42 (m, 5H, Ph). δ_C (100.6 MHz, $CDCl_3$) 39.1 (C_5), 44.1, *44.6* (C_4), 47.4 (C_7), 49.8 (C_3), *55.2*, 55.4 (C_6), *63.8*, 64.3 (C_1), 67.5 ($\underline{C}H_2Ph$), 128.0, 128.9, 129.4 (5 × aryl CH), 136.1 (aryl C). ν_{max} 2952w, 2892w, 1698s, 1498w, 1444m, 1408m, 1355m, 1329m, 1313m, 1258m, 1225m, 1210m, 1098m cm^{-1}. Alternatively, **218** can be made by brominating 2-azabicyclo[2.2.1]hept-5-ene 2-carboxylic acid benzyl ester.[156] Bromine (0.25 ml, 4.87 mmol) was added drop-wise to a solution of 2-azabicyclo[2.2.1]hept-5-ene 2-carboxylic acid benzyl ester (1.00 g, 4.37 mmol) in dry DCM (25 ml). After stirring for 24 h the reaction mixture was washed with sodium thiosulfate solution (20 ml), dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo* to give **218** (1.47 g, 3.78 mmol, 86%).

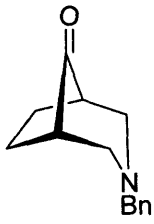
anti-7-Bromo-_exo_-6-hydroxy-2-azabicyclo[2.2.1]heptane 2-carboxylic acid benzyl ester (221)



anti-7-_exo_-6-Dibromo-2-azabicyclo[2.2.1]heptane 2-carboxylic acid benzyl ester (**218**) (13.3 mg, 0.034 mmol) was stirred in a mixture of water (2 ml) and acetonitrile (2 ml) at 65 °C for 24 h. Then the acetonitrile was removed *in vacuo* and the remaining mixture extracted with diethyl ether. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo*. Flash chromatography (petrol: ether; 3:1) of the crude residue gave **221** as a pale yellow oil (10.8 mg, 0.033 mmol, 97%). δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N-CO rotation (ratio ~30:70), the minor rotamer signal is shown

in italics.] 2.07-2.30 (m, 2H, H_{5n}, H_{5x}), 2.36, *2.41* (2 × d, J = 11.0 Hz, 1H, OH), 2.77 (brs, 1H, H_4), 3.02 (brd, J = 9.4 Hz, 1H, H_{3n}), 3.31 (brd, J = 9.4 Hz, 1H, H_{3x}), 4.31, *4.37* (2 × brs, 1H, H_1), 4.07 (brs, 1H, H_7), 4.98 (m, 1H, H_{6n}), 5.06-5.21 (m, 2H, $C\underline{H}_2Ph$), 7.29-7.40 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) *38.8*, 39.0 (C_5), 42.7, *43.2* (C_4), 49.6, *49.8* (C_3), *49.4*, 49.6 (C_7), *62.7*, 63.0 (C_1), *67.1*, 67.3 ($\underline{C}H_2Ph$), *74.1*, 74.5 (C_6), 128.1, 128.2, 128.5 (5 × aryl CH), 136.2 (aryl C). ν_{max} 3427w, 2947w, 1695s, 1498w, 1417s, 1358s, 1329m, 1265m, 1224m cm^{-1}. $^m/_z$ $C_{14}H_{17}NO_3Br$ [MH^+] requires 326.03918; observed 326.03911.

8-Keto-3-benzyl-3-azabicyclo[3.2.1]octane (291)



Using the procedure described by Lowe *et al.*[170] Benzylamine hydrochloride (55 g, 0.38 mol), cyclopentanone (27 ml, 25.7 g, 0.31 mol), and formaldehyde (37%, 150 ml, 0.74 mol) were dissolved in glacial acetic acid (200 ml) and stirred at 80 °C for 15 h. The reaction mixture was concentrated *in vacuo*, taken into water and washed with diethyl ether; the aqueous layer was basified with sodium carbonate then extracted with DCM. The combined organic extracts were reduced *in vacuo*, the residue was dissolved in ethanol (150 ml) and acetic anhydride (50 ml) and stirred at RT for 2 h, then HCl (12 M, 50 ml) was added and the mixture was stirred for a further 12 h. The reaction mixture was concentrated, taken into water and washed with DCM, basified with sodium carbonate and extracted with DCM, the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and solvents removed *in vacuo*. Flash chromatography (petrol: diethyl ether; 3:1) gave **291** as a yellow oil (1.705 g, 7.9 mmol, 3%). R_f 0.36. δ_H [300 MHz, $CDCl_3$; * and # indicate interchangeable assignments] 1.82 (m, 2H, H_{6n}, H_{7n}),# 2.04 (m, 2H, H_{6x}, H_{7x}),# 2.13 (m, 2H, H_1, H_5), 2.51 (d, J = 10.8 Hz, 2H, H_{2x}, H_{4x}),* 2.94 (dd, J = 10.8, 3.1 Hz, H_{2n}, H_{4n}),* 3.57 (s, 2H, $C\underline{H}_2Ph$), 7.21-7.40 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 22.7 (C_6, C_7), 45.4 (C_1, C_5), 60.2 ($\underline{C}H_2Ph$), 61.7 (C_2, C_4), 127.2, 128.3, 128.6 (5 × aryl CH), 138.8 (aryl C), 220.1 (C_8). ν_{max} 2939m, 2792m, 1750s, 1674m, 1495m, 1453m, 1360m, 1345m, 1271m cm^{-1}. $^m/_z$ $C_{14}H_{18}NO$ [MH^+] requires 216.13884; observed 216.13877.

***syn*-8-Hydroxy-3-benzyl-3-azabicyclo[3.2.1]octane (292a)**

Using the procedure described by Kim *et al.*[171] 8-Keto-3-benzyl-3-azabicyclo[3.2.1]octane (**291**) (0.972 g, 4.52 mmol) was dissolved in dry methanol (15 ml) and stirred at 0 °C under nitrogen. Sodium borohydride (243 mg, 6.42 mmol) was added, the temperature was allowed to reach RT slowly and the reaction mixture was stirred for a further 24 h. Water (20 ml) was added and extracted

with DCM, the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo*. Trituration with petrol gave **292a** as a white semi-solid (905 mg, 4.17 mmol, 92%). δ_H (300 MHz, $CDCl_3$) 1.54 (m, 2H, H_{6n}, H_{7n}), 1.73 (m, 2H, H_{6x}, H_{7x}), 1.85 (brs, 2H, H_1, H_5), 2.33 (dd, J = 10.7, 3.3 Hz, 2H, H_{2n}, H_{4n}), 2.52 (brd, J = 10.7 Hz, 2H, H_{2x}, H_{4x}), 3.42 (brs, 2H, $C\underline{H}_2Ph$), 3.83 (t, J = 4.7 Hz, 1H, H_8), 7.17-7.26 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 25.3 (C_6, C_7), 38.5 (C_1), 52.1 (C_2, C_4), 62.2 ($\underline{C}H_2Ph$), 72.6 (C_8), 127.3, 128.4, 128.6 (5 × aryl CH), 139.5 (aryl C). ν_{max} 3299m, 2936s, 2812s, 1493m, 1453s, 1387m, 1341m, 1277m cm^{-1}. $^m/_z$ $C_{14}H_{20}NO$ [MH^+] requires 218.15449; observed 218.15449. Analysis: $C_{14}H_{19}NO$ requires: C, 77.48; H, 8.70; N, 6.46; observed: C, 77.56; H, 8.70; N, 6.53.

syn-8-Hydroxy-3-Boc-3-azabicyclo[3.2.1]octane (292b)

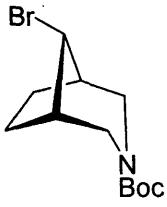
syn-8-Hydroxy-3-benzyl-3-azabicyclo[3.2.1]octane (**292a**) (35 mg, 0.164 mmol) was dissolved in dry methanol (4 ml) and palladium on carbon (10%, ~ 50 mg) was added. The reaction mixture was stirred under hydrogen for 24 h then filtered through celite, the filtrate was evaporated to dryness and the residue was dissolved in water (7.5 ml) and THF (2.5 ml). Boc_2O (72 mg, 0.33 mmol) and $NaHCO_3$ (55 mg, 0.66 mmol) were added. This mixture was stirred at RT for 24 h then extracted with diethyl ether, the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo* to give **292b** as a white solid (30 mg, 0.132 mmol, 81%). δ_H [300 MHz, $CDCl_3$; * indicates an interchangeable assignment] 1.46 (brs, 9H, Boc), 1.43-1.75 (m, 4H, H_6, H_7), 1.99 (m, 2H, H_1, H_5), 3.80, 3.38 (2 × brd, J = 12.3 Hz, 1H, 1H, H_{2x}, H_{4x}),* 3.54, 3.67 (2 × brd, J = 12.3 Hz, 1H, 1H, H_{2n}, H_{4n}),* 4.03 (t, J = 4.9 Hz, 1H, H_8). δ_C (75.5 MHz, $CDCl_3$) 23.15, 23.23 (C_6, C_7), 27.5 (Boc CH_3), 36.5, 36.6 (C_1, C_5), 42.3, 43.2 (C_2, C_4), 70.8 (C_8), 78.2 (Boc C), 155.4 (Boc CO). ν_{max} 3415m, 2938m, 1666s, 1418s, 1365s, 1249s cm^{-1}. $^m/_z$ $C_{12}H_{22}NO_3$ [MH^+] requires 228.15997; observed 228.15990.

anti-8-Bromo-3-benzyl-3-azabicyclo[3.2.1]octane (293a)

Using a procedure adapted from that described by Kim *et al.*[171] *syn*-8-Hydroxy-3-benzyl-3-azabicyclo[3.2.1]octane (**292a**) (318 mg, 1.465 mmol) was dissolved in dry DCM (10 ml), pyridine (1.2 ml, 14.7 mmol) and Tf_2O (0.74 ml, 4.40 mmol) were added and the mixture was stirred under nitrogen at 0 °C for 2 h. Sodium bicarbonate solution was added and extracted with DCM, the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo* to give the triflate (**294a**): δ_H (300 MHz, $CDCl_3$) 1.69, 1.97 (2 × m, 2H, 2H, H_6, H_7), 2.31 (brs,

2H, H_1, H_5), 2.58 (m, 4H, H_2, H_4), 3.56 (brs, 2H, C$\underline{H}_2$Ph), 4.99 (t, J = 5.0 Hz, 1H, H_8), 7.14-7.40 (m, 5H, Ph). δ_F (282.3 MHz, $CDCl_3$) -75.3. The triflate was dissolved in dry DMF (10 ml), lithium bromide (1.116 g, 12.8 mmol) and aluminium chloride (102 mg, 0.765 mmol) were added and the reaction mixture was stirred at 50 °C under nitrogen for 24 h. Sodium bicarbonate solution was added and extracted with DCM, the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo*. Flash chromatography (petrol: diethyl ether; 1:1) gave **293a** as a yellow oil (149 mg, 0.532 mmol, 36%). R_f 0.60. δ_H (300 MHz, $CDCl_3$) 1.82 (d, J = 7.1 Hz, 2H, H_{6n}, H_{7n}), 2.05 (m, 2H, H_{6x}, H_{7x}), 2.21 (d, J = 11.5 Hz, 2H, H_{2x}, H_{4x}), 2.37 (brs, 2H, H_1, H_5), 2.72 (dd, J = 11.5, 4.4 Hz, 2H, H_{2n}, H_{4n}), 3.45 (brs, 2H, C$\underline{H}_2$Ph), 4.16 (brs, 1H, H_8), 7.19-7.27 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 26.5 (C_6, C_7), 44.7 (C_1, C_5), 60.3 (C_2, C_4), 61.5 (C$\underline{H}_2$Ph), 63.0 (C_8), 126.9, 128.2, 128.6 (5 × aryl CH), 139.0 (aryl C). ν_{max} 2943s, 2794s, 1454s, 1364s, 1265m, 1217m cm^{-1}. $^m/_z$ 280/282 (1:1) (MH^+).

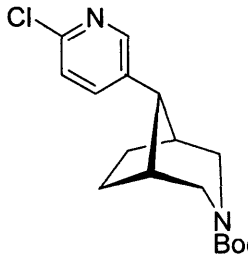
***anti*-8-Bromo-3-Boc-3-azabicyclo[3.2.1]octane (293b)**



Using a procedure adapted from that described by Kim *et al.*[171] *syn*-8-Hydroxy-3-Boc-3-azabicyclo[3.2.1]octane (**292b**) (223 mg, 0.982 mmol) was dissolved in dry DCM (10 ml), pyridine (0.8 ml, 9.8 mmol) and Tf_2O (0.5 ml, 2.95 mmol) were added and the mixture was stirred under nitrogen at 0 °C for 2 h. Sodium bicarbonate solution was added and extracted with DCM, the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo* to give the triflate (**294b**): δ_H [300 MHz, $CDCl_3$; * indicates interchangeable assignments] 1.40 (s, 9H, Boc), 1.54-1.77 (m, 4H, H_6, H_7), 2.22-2.35 (m, 2H, H_1, H_5), 3.14, 3.24 (2 × brd, J = 12.3 Hz, 1H, 1H, H_{2x}, H_{4x}),* 3.63, 3.78 (2 × brd, J = 12.3 Hz, 1H, 1H, H_{2n}, H_{4n}),* 4.96 (t, J = 5.2 Hz, 1H, H_8). δ_F (282.3 MHz, $CDCl_3$) -75.1. The triflate was dissolved in dry DMF (10 ml), lithium bromide (842 mg, 9.69 mmol) and aluminium chloride (67 mg, 0.502 mmol) were added and the reaction mixture was stirred at 50 °C under nitrogen for 24 h. Sodium bicarbonate solution was added and extracted with DCM, the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo*. Flash chromatography (petrol: diethyl ether; 3:1) gave **293b** as a white solid (190 mg, 0.655 mmol, 67%). m.p. 60-62 °C. δ_H [300 MHz, $CDCl_3$] 1.12-1.74 (m, 4H, H_6, H_7), 1.38 (brs, 9H, Boc), 2.03, 2.36 (2 × m, 1H, 1H, H_1, H_5), 2.86 (m, 2H, H_{2x}, H_{4x}), 3.77, 3.93 (2 × brd, J = 12.5 Hz, 1H, 1H, H_{2n}, H_{4n}), 4.17 (brs, 1H, H_8). δ_C (75.5 MHz, $CDCl_3$) 25.3 (C_6, C_7), 28.4 (Boc CH_3),

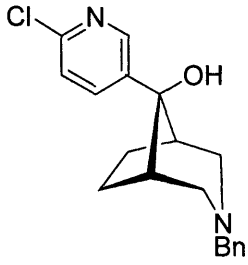
43.8 (C_1, C_5), 50.9, 51.8 (C_2, C_4), 60.9 (C_8), 79.8 (Boc C). ν_{max} 2969m, 1689s, 1456m, 1417s, 1364s, 1326m, 1247m, 1218m cm^{-1}. $^m/_z$ 290/292 (1:1) (MH^+).

anti-8-(6-Chloro-pyridin-3-yl)-3-Boc-3-azabicyclo[3.2.1]octane (298)



The Suzuki coupling procedure described for **122** and **123** was used with: *anti*-8-Bromo-3-Boc-3-azabicyclo[3.2.1]octane (**293b**) (76 mg, 0.262 mmol), $Ni(cod)_2$ (24 mg, 0.087 mmol), bathophenanthroline (58 mg, 0.174 mmol), 4-chloro-3-pyridyl boronic acid (54 mg, 0.343 mmol), potassium *tert*-butoxide (49 mg, 0.437 mmol) and s-butanol (13 ml). After 24 h at 60 °C the reaction was stopped and the crude residue flash chromatographed (3:1; petrol: diethyl ether) to give **293b** (29 mg) and **298** as a white solid (28 mg, 0.087 mmol, 33%; 54% based on recovered starting material). m.p. 100-102 °C. R_f 0.21. δ_H (300 MHz, $CDCl_3$) 1.48 (brs, 9H, Boc), 1.61 (brs, 4H, H_6, H_7), 2.49, 2.54 (2 × brs, 2H, H_1, H_5), 2.91 (brs, 1H, H_{8s}), 3.00, 3.08 (2 × brd, J = 12.3 Hz, 2H, H_{2x}, H_{4x}), 3.94, 4.08 (2 × brd, J = 12.3 Hz, 2H, H_{2n}, H_{4n}), 7.27 (d, J = 8.2 Hz, 1H, $H_{5'}$), 7.52 (dd, J = 8.2, 2.6 Hz, 1H, $H_{4'}$), 8.28 (d, J = 2.6 Hz, 1H, $H_{2'}$). δ_C (75.5 MHz, $CDCl_3$) 25.6, 25.8 (C_6, C_7), 28.4 (Boc CH_3), 39.2 (C_1, C_5), 50.2 (C_8), 51.3, 52.3 (C_2, C_4), 79.6 (Boc C), 123.8 ($C_{5'}$), 136.9 ($C_{4'}$), 148.1 ($C_{2'}$), 149.2 (pyridyl C), 155.9 (Boc CO). ν_{max} 2965m, 2934m, 2867m, 1687s, 1586w, 1560w, 1466m, 1420s, 1389m, 1361m, 1318m, 1284m, 1238s, 1220m, 1158s, 1105s cm^{-1}. $^m/_z$ $C_{17}H_{24}N_2O_2Cl$ [MH^+] requires 323.15263; observed 323.15265.

anti-8-(6-Chloro-pyridin-3-yl)-_syn_-8-hydroxy-3-benzyl-3-azabicyclo[3.2.1]octane (302)



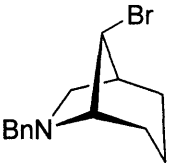
Using a procedure adapted from that described by Fletcher *et al.*[15] Butyllithium (1.6 M, 0.183 ml, 0.292 mmol) was added to a solution of 2-chloro-3-iodopyridine (70 mg, 0.292 mmol) in dry diethyl ether (6 ml) and dry THF (3 ml) at -78 °C under nitrogen. The reaction mixture was stirred for 0.5 h then a solution of 8-keto-3-benzyl-3-azabicyclo[3.2.1]octane (**291**) (64 mg, 0.298 mmol) in diethyl ether (4 ml) was added and stirred at reflux for 48 h. Saturated ammonium chloride solution (3 ml) then water (10 ml) were added to quench the reaction mixture, which was then extracted into ethyl acetate. The organic extracts were combined, dried over $MgSO_4$, filtered and the solvents removed *in vacuo*. The crude residue was flash chromatographed (diethyl ether: petrol; 1:1) to give the ketone **291** (37 mg, R_f 0.65) and **302** as an orange oil (9 mg, 0.026 mmol, 16% based on recovered starting material). R_f 0.31. δ_H [300 MHz, $CDCl_3$; * denotes interchangeable

assignments] 1.40, 1.88 (2 × m, 2H, 2H, H_6, H_7), 2.38 (brs, 2H, H_1, H_5), 2.64 (dd, J = 10.6, 3.4 Hz, 2H, H_{2n}, H_{4n}),* 2.87 (d, J = 10.6 Hz, 2H, H_{2x}, H_{4x}),* 3.62 (brs, 2H, $C\underline{H}_2Ph$), 7.21-7.39 (m, 6H, Ph, $H_{5'}$), 7.78 (dd, J = 8.2, 2.6 Hz, 1H, $H_{4'}$), 8.48 (d, J = 2.6 Hz, 1H, $H_{2'}$). δ_C (75.5 MHz, $CDCl_3$) 25.4 (C_6, C_7), 41.8 (C_1, C_5), 53.6 (C_2, C_4), 61.7 ($\underline{C}H_2Ph$), 124.1 ($C_{5'}$), 126.8, 128.2, 128.6 (5 × aryl CH), 136.6 ($C_{4'}$), 139.5 (aryl C), 147.5 ($C_{2'}$), 150.5 (pyridyl C). ν_{max} 2924s, 1598m, 1565m, 1453m, 1394m, 1359m cm^{-1}. $^m/_z$ $C_{19}H_{22}N_2OCl$ [MH^+] requires 329.14207; observed 329.14213.

2-Benzyl-2-azabicyclo[2.2.2]oct-5-ene (305)

Using the procedure described by Larsen *et al.*,[103] 1,3-cyclohexadiene (26 ml, 0.27 mol) was added to a mixture of benzylamine hydrochloride (17.67 g, 0.14 mol) and aqueous formaldehyde (37%, 16 ml) in water (54 ml). The reaction mixture was stirred under nitrogen at 60 °C for 48 h then cooled and diluted with water (70 ml), washed with diethyl ether: petrol (1:1), basified with sodium hydroxide (~ 17 g) and extracted with diethyl ether. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo*. Distillation (1 mm Hg) of the crude residue gave **305** as a colourless oil (4.23 g, 0.021 mol, 15%). b.p. 105-110 °C. δ_H [300 MHz, $CDCl_3$; * indicates an interchangeable assignment] 1.15-1.34, 1.52-1.63, 1.92-2.03 (3 × m, 2H, 1H, 1H, H_7, H_8), 1.97-2.13 (m, 1H, H_{3n}),* 2.48 (m, 1H, H_4), 3.48 (AB, J = 13.2 Hz, 2H, $C\underline{H}_2Ph$), 3.00 (dd, J = 9.8, 2.0 Hz, 1H, H_{3x}),* 3.34 (m, 1H, H_1), 6.27 (m, 1H, H_6), 6.42 (m, 1H, H_5), 7.18-7.37 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 22.1, 26.8 (C_7, C_8), 30.9 (C_4), 51.2 (C_1), 55.5 (C_3), 62.0 ($\underline{C}H_2Ph$), 126.7, 128.1, 128.8 (5 × aryl CH), 131.7 (C_6), 133.4 (C_5), 139.8 (aryl C). ν_{max} 3027w, 2941s, 1495m, 1453s, 1347m, 1168w, 1132m cm^{-1}. $^m/_z$ $C_{14}H_{18}N$ [MH^+] requires 200.14392; observed 200.14386.

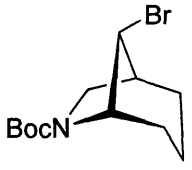
***anti*-8-Bromo-2-benzyl-2-azabicyclo[3.2.1]octane (308)**



2-Benzyl-2-azabicyclo[2.2.2]oct-5-ene (**305**) (128 mg, 0.641 mmol) was dissolved in dry DCM (4 ml) and stirred under nitrogen at -78 °C; bromine (0.059 ml, 1.282 mmol) was added drop-wise. The reaction mixture was allowed to reach RT over 1 h then evaporated to dryness with a stream of nitrogen followed by a high vacuum pump, without exposure to air. The residue was dissolved in dry THF (10 ml) and Red-Al (65% solution, 0.38 ml, 1.292 mmol) was added; the mixture was stirred at RT under nitrogen for 15 h. Saturated sodium bicarbonate solution (12 ml) then brine (12 ml) were added and extracted with ethyl acetate, the combined organic

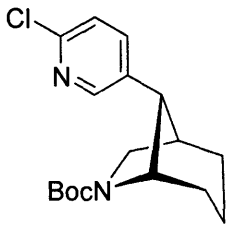
extracts were combined and dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo*. Flash chromatography (petrol: diethyl ether; 3:1) gave starting material (**305**) (29 mg) and **308** as a yellow oil (51 mg, 0.182 mmol, 28% (37% based on recovered **305**)). R_f 0.60. δ_H (300 MHz, $CDCl_3$) 1.38-1.47 (m, 1H, H_{5n}), 1.49-1.59 (m, 2H, H_{6x}, H_{7n}), 1.72-1.85 (m, 1H, H_{6n}), 1.94-2.13 (m, 2H, H_{5x}, H_{7x}), 2.40 (brd, J = 4.1 Hz, 1H, H_4), 2.86 (ddd, J = 9.6, 5.3, 1.1 Hz, 1H, H_{3x}), 2.93 (d, 9.6 Hz, 1H, H_{3n}), 3.08 (t, J = 4.7 Hz, 1H, H_1), 3.85 (brs, 2H, CH_2Ph), 4.32 (t, J = 4.9 Hz, 1H, H_8), 7.24-7.43 (m, 5H, Ph). δ_C (75.5 MHz, $CDCl_3$) 17.9 (C_6), 25.0, 25.2 (C_5, C_7), 40.0 (C_4), 53.2 (C_8), 55.8 (C_3), 59.7 ($\underline{C}H_2Ph$), 61.4 (C_1), 126.9, 128.2 (5 × aryl CH), 139.3 (aryl C). ν_{max} 2941s, 2862m, 1494m, 1453s, 1372m, 1331m, 1272m, 1216s cm^{-1}. $^m/_z$ $C_{14}H_{18}NBr$ [MH^+] requires 279.06226; observed 279.06211.

anti-8-Bromo-2-Boc-2-azabicyclo[3.2.1]octane (309)



anti-8-Bromo-2-benzyl-2-azabicyclo[3.2.1]octane (**308**) (141 mg, 0.50 mmol) was de-benzylated in methanol (10 ml) with 10% palladium on charcoal (~ 20 mg) under an atmosphere of hydrogen. After vigorous stirring for 3 h, the reaction mixture was filtered through celite and the methanol was removed *in vacuo*. The resulting residue (97 mg) was dissolved in THF (5 ml) and water (15 ml); Boc_2O (251 mg, 1.15 mmol) and $NaHCO_3$ (170 mg, 2.02 mmol) were added and stirred at RT for 24 h. The reaction mixture was extracted with diethyl ether, the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvents removed *in vacuo* to give **309** as a yellow oil (53 mg, 0.183 mmol, 37%). δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] 1.39, 1.40 (2 × brs, 9H, Boc), 1.44-1.82, 1.88-2.12 (2 × m, 4H, 2H, H_5, H_6, H_7), 2.36 (brs, 1H, H_4), 3.24-3.44 (m, 2H, H_{3x}, H_{3n}), 3.99, 4.10 (2 × brt, J = 4.7 Hz, 1H, H_1), 4.16 (brd, J = 4.5 Hz, 1H, H_8). δ_C (75.5 MHz, $CDCl_3$) 17.0 (C_6), 23.3, 24.0, 24.8 (C_5, C_7), 28.5 (Boc CH_3), 37.8, *38.5* (C_4), 48.8, *49.5* (C_3), 51.3 (C_8), *56.2*, 56.8 (C_1), 79.6 (Boc C).

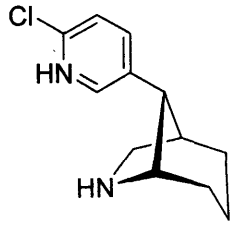
syn-8-(6-Chloro-pyridin-3-yl)-2-Boc-2-azabicyclo[3.2.1]octane (310)



The Suzuki coupling procedure described for **122** and **123** was used with: *anti*-8-Bromo-3-Boc-2-azabicyclo[3.2.1]octane (**309**) (53 mg, 0.183 mmol); $Ni(cod)_2$ (22 mg, 0.080 mmol); bathophenanthroline (51 mg, 0.153 mmol); 4-chloro-3-pyridyl boronic acid (38 mg, 0.241 mmol); potassium *tert*-butoxide (38 mg, 0.339 mmol) and s-butanol (10 ml). After 24 h at 60 °C the reaction was stopped and the crude residue flash chromatographed (3:1;

petrol: diethyl ether) to give **310** as a pale yellow solid (13.3 mg, 0.041 mmol, 23%). m.p. 97-99 °C. δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N-CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] 1.34-1.65, [1.40, 1.42 (2 × brs, 9H, Boc)], 1.72, 1.97-2.16 (3 × m, 3H, 2H, 1H, H_5, H_6, H_7), 2.32 (brs, 1H, H_4), 2.78 (d, J = 6.4 Hz, 1H, H_8), 3.04-3.27 (m, 2H, H_{3x}, H_{3n}), 4.18, *4.34* (2 × d, J = 4.7 Hz, 1H, H_1), *7.18*, 7.19 (2 × d, J = 8.2 Hz, 1H, $H_{5'}$), 7.35, *7.36* (2 × dd, J = 8.2, 2.6 Hz, 1H, $H_{4'}$), *8.16*, 8.17 (2 × d, J = 2.6 Hz, 1H, $H_{2'}$). δ_C (75.5 MHz, $CDCl_3$) 18.0, *18.1* (C_6), 28.5, 28.6 (Boc CH_3), 30.2, 30.3, 31.8, 31.9 (C_5, C_7), 40.6, *41.8* (C_4), 48.0, *48.4* (C_3), *50.5*, 51.3 (C_8), *56.8*, 57.8 (C_1), *79.5*, 79.6 (Boc C), *124.0*, 124.1 ($C_{5'}$), 136.8, *136.9* ($C_{4'}$), 148.6, *148.7* ($C_{2'}$), 149.5 (pyridyl C), *153.8*, 153.9 (Boc CO). ν_{max} 2974m, 2938m, 2878m, 1687s, 1584w, 1568m, 1458m, 1388s, 1364s, 1340m, 1325m, 1273m, 1255m, 1208m, 1175m, 1145m, 1135m, 1105s cm^{-1}. $^m/_z$ $C_{17}H_{24}N_2O_2Cl$ [MH^+] requires 323.15263; observed 323.15255.

syn-8-(6-Chloro-pyridin-3-yl)-2-azabicyclo[3.2.1]octane dihydrochloride (289)



syn-8-(6-Chloro-pyridin-3-yl)-2-Boc-2-azabicyclo[3.2.1]octane (**310**) (9.3 mg, 0.029 mmol) was dissolved in ethanol (1 ml) and ethyl acetate (2.9 ml); acetyl chloride (0.9 ml) was added with cooling in ice. The reaction mixture was stirred at RT for 2 h then was evaporated to dryness; the crude residue was triturated with $CDCl_3$ to give the hydrochloride salt of **289** as a white powder (7.5 mg, 99%). m.p. 150-155 °C (decomp.). δ_H (300 MHz, CD_3OD) 1.59-2.08 (m, 6H, H_5, H_6, H_7), 3.08 (brs, 1H, H_4), 3.24-3.36 (m, 3H, H_1, H_{3x}, H_{3n}), 4.83 (brs, 1H, H_8), 7.48 (d, J = 8.5 Hz, 1H, $H_{5'}$), 7.88 (dd, J = 8.5, 2.5 Hz, 1H, $H_{4'}$), 8.39 (d, J = 2.5 Hz, 1H, $H_{2'}$). δ_C (75.5 MHz, CD_3OD) 18.0 (C_6), 30.3, 31.6 (C_5, C_7), 39.3 (C_4), 48.7 (C_3), 51.5 (C_8), 63.0 (C_1), 126.2 ($C_{5'}$), 135.4 ($C_{3'}$), 140.5 ($C_{4'}$), 148.6 ($C_{2'}$), 150.6 ($C_{6'}$). ν_{max} 2943s, 1641m, 1599s, 1586s, 1553m, 1472s, 1423m, 1373s, 1294m cm^{-1}. $^m/_z$ $C_{12}H_{16}N_2Cl$ [MH^+] requires 223.10020; observed 223.10025.

Membrane Preparation

Cell pastes from large-scale production of HEK-293 cells expressing cloned human nAChR were homogenized in 4 volumes of buffer (50 mM Tris.HCl, 150 mM NaCl and 5 mM KCl, pH 7.4). The homogenate was centrifuged twice (40,000 g, 10 minutes, 4 °C) and the pellets re-suspended in 4 volumes of Tris.HCl buffer after the first spin and 8 volumes after the second spin. The re-suspended homogenate was centrifuged (100 g, 10 minutes, 4 °C) and the supernatant kept and re-centrifuged (40,000 g, 20 minutes, 4 °C). The pellet was re-suspended

in Tris.HCl buffer supplemented with 10% w/v sucrose. The membrane preparation was stored in 1ml aliquots at -80 °C until required. The protein concentration of the membrane preparation was determined using a BCA protein assay reagent kit.

Nicotinic Receptor Radioligand Binding Scintillation Proximity Assay (SPA)

SPA radioligand binding assays were performed in 96 well plates in a final volume of 250µl Tris-HCl buffer (50 mM Tris-HCl, 150 mM NaCl, 5 mM KCl, pH 7.4) using the following conditions: [^{3}H]-epibatidine (53 Ci/mmol; Amersham) - α4β2 = 1 nM, α3β4 = 2 nM; WGA-coated PVT SPA beads (Amersham) - α4β2 = 1 mg/well, α3β4 = 1.5 mg/well; membrane protein = 30 µg/well for both assay types. Non-specific binding (<10% for both assay types) was determined using 10 µM epibatidine. Reactions were allowed to equilibrate for 2-4 h at RT prior to reading on a Trilux Scintillation counter (Perkin Elmer). Data were analyzed using a standard 4 parameter logistic equation (Multicalc, Perkin Elmer) to provide IC_{50} values that were converted to K_i values using the Cheng-Prusoff equation.[9]

Molecular modeling

Molecular models were determined using the Spartan Pro program; equilibrium geometries were calculated with the Hartree-Fock, 6-31G* method. The superpositions in Chapter 7 were produced with the 'Fit' function of the PyMOL software package.

Appendix I

Crystal structure data

Crystal data and structure refinement for 129

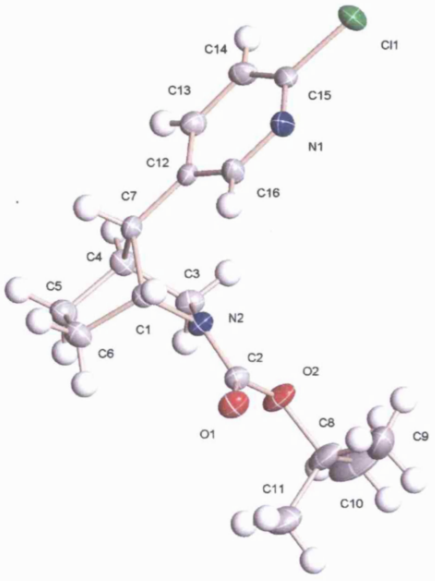


Figure shows 50% displacement ellipsoids.

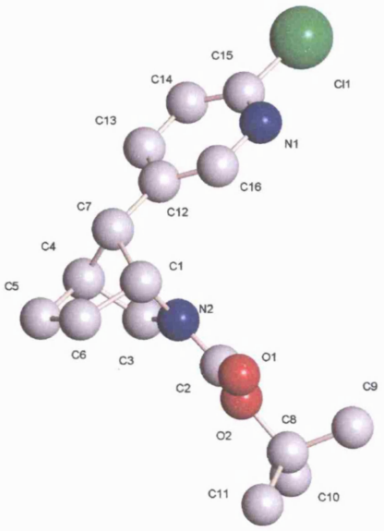
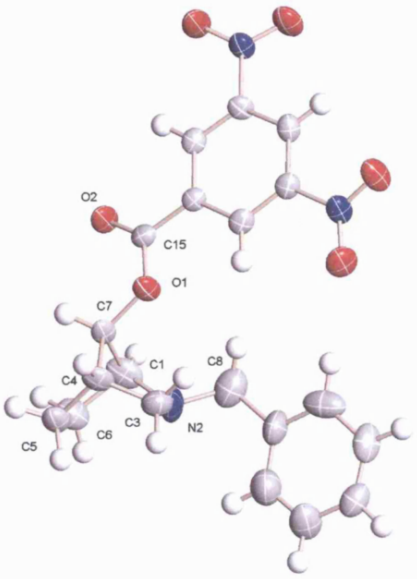


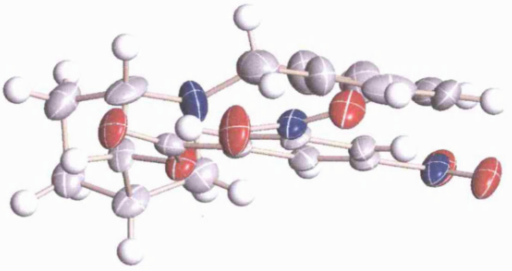
Figure shows the molecular structure as arbitrary spheres, H atoms omitted for clarity.

Empirical formula	C16 H21 Cl N2 O2	
Formula weight	308.80	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 13.2093(17) Å	α= 90°.
	b = 6.6337(9) Å	β= 105.829(3)°.
	c = 18.646(3) Å	γ = 90°.
Volume	1571.9(4) $Å^3$	
Z	4	
Density (calculated)	1.305 Mg/m^3	
Absorption coefficient	0.249 mm^{-1}	
F(000)	656	
Crystal size	0.21 x 0.04 x 0.04 mm^3	
Theta range for data collection	1.69 to 25.00°.	
Index ranges	-15<=h<=15, -7<=k<=7, -22<=l<=22	
Reflections collected	9626	

Independent reflections	2770 [R(int) = 0.0565]
Completeness to theta = 25.00°	100.0 %
Absorption correction	Empirical
Max. and min. transmission	0.981 and 0.767
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2770 / 0 / 193
Goodness-of-fit on F^2	0.851
Final R indices [I>2sigma(I)]	R1 = 0.0426, wR2 = 0.0737
R indices (all data)	R1 = 0.0752, wR2 = 0.0804
Largest diff. peak and hole	0.325 and -0.232 e.$Å^{-3}$

Crystal data and structure refinement for the 3,5-dinitrobenzoate of 158





Figures show 50% displacement ellipsoids.

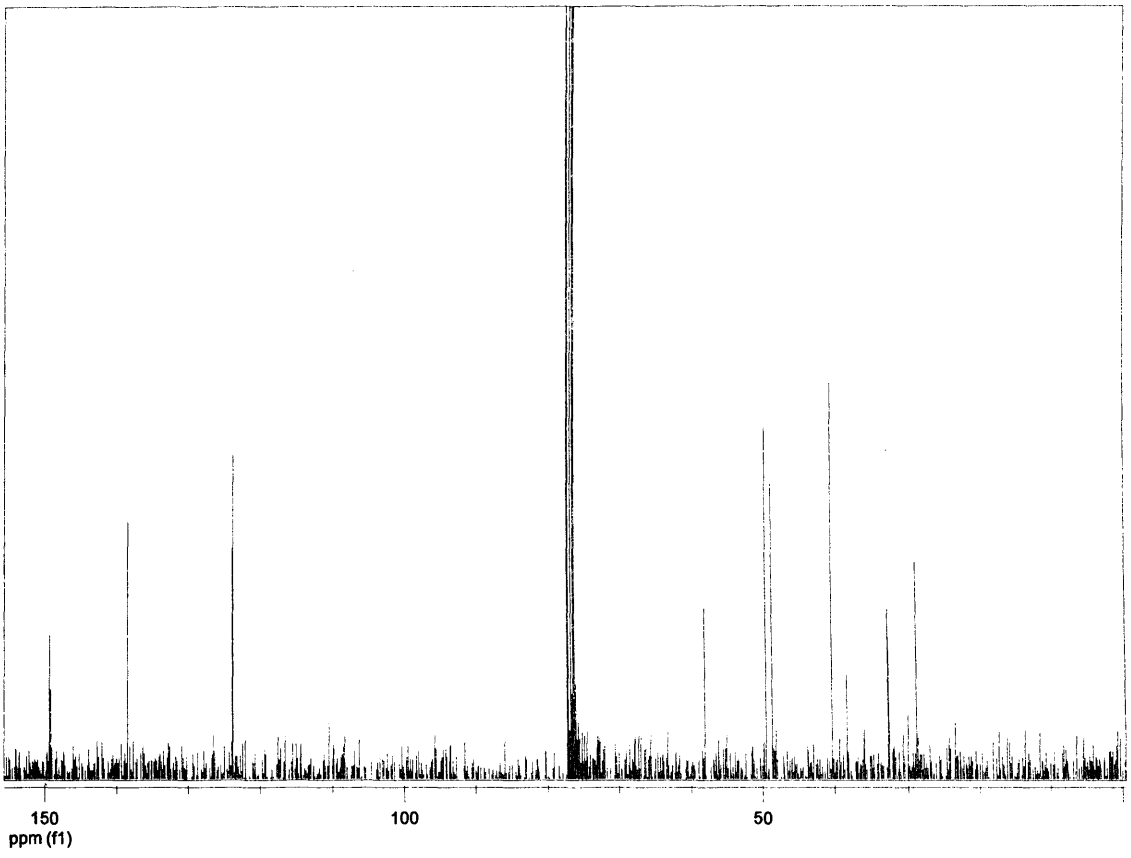
Empirical formula	C20 H19 N3 O6	
Formula weight	397.38	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.013(3) Å	α= 76.674(7)°.
	b = 11.227(5) Å	β= 84.349(7)°.
	c = 12.175(5) Å	γ = 84.149(7)°.
Volume	925.2(7) $Å^3$	
Z	2	
Density (calculated)	1.426 Mg/m^3	
Absorption coefficient	0.107 mm^{-1}	
F(000)	416	
Crystal size	0.32 x 0.11 x 0.08 mm^3	
Theta range for data collection	1.72 to 25.00°.	
Index ranges	-8<=h<=8, -13<=k<=13, -14<=l<=14	
Reflections collected	6517	
Independent reflections	3212 [R(int) = 0.0684]	
Completeness to theta = 25.00°	98.4 %	

Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3212 / 0 / 262
Goodness-of-fit on F^2	1.010
Final R indices [I>2sigma(I)]	R1 = 0.1142, wR2 = 0.2749
R indices (all data)	R1 = 0.1993, wR2 = 0.3233
Largest diff. peak and hole	0.611 and -0.417 e.$Å^{-3}$

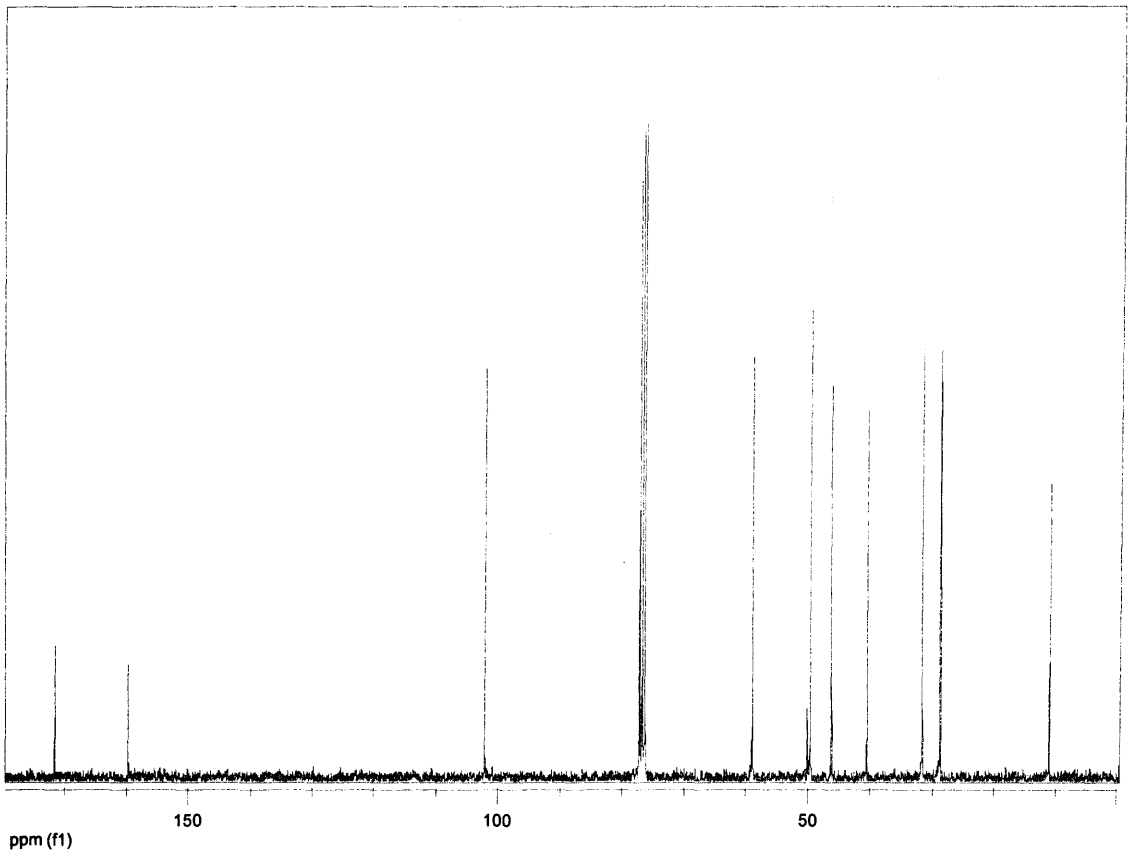
Appendix II

Selected ^{13}C NMR spectra

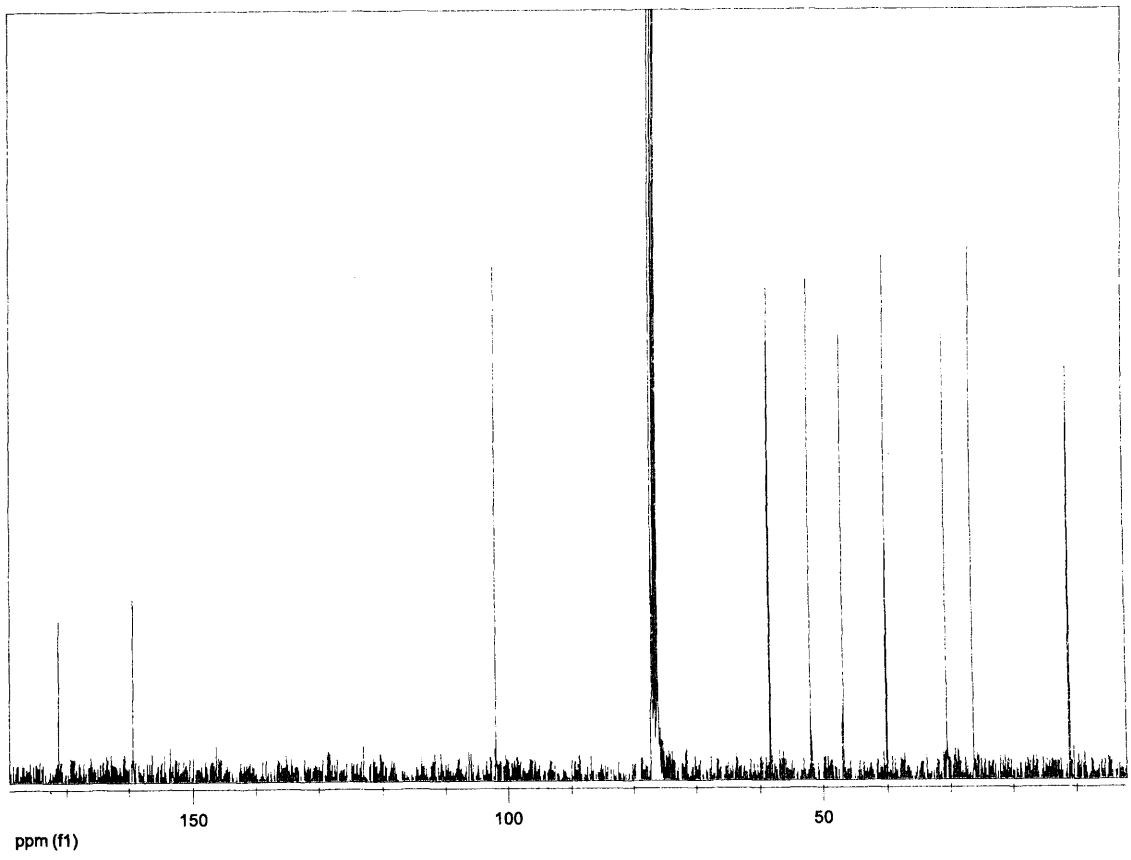
Isoepibatidine (49)



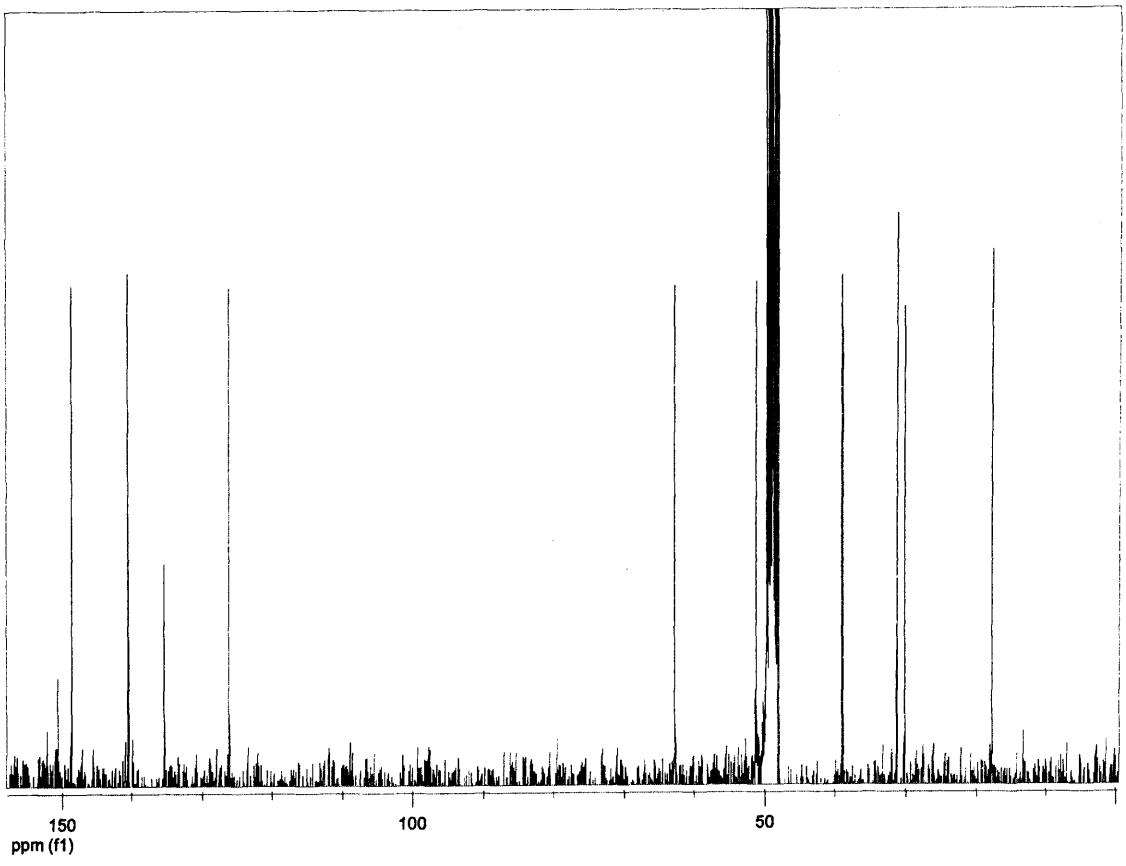
syn-Isoepiboxidine (51)



***anti*-Isoepiboxidine (52)**



***syn*-8-(6-Chloro-pyridin-3-yl)-2-azabicyclo[3.2.1]octane (289)**



Appendix III

Publications

- 7-Substituted 2-Azabicyclo[2.2.1]heptanes as Key Intermediates for the Synthesis of Novel Epibatidine Analogues; Synthesis of *syn* and *anti*-Isoepiboxidine. Malpass, J. R.; White, R. *J. Org. Chem.* **2004**, *69*, 5328-5334.

- Approaches to Syn-7-Substituted 2-Azanorbornanes as Potential Nicotinic Agonists; Synthesis of syn- and anti-Isoepibatidine. Malpass, J. R.; Handa, S.; White, R. *Org. Lett.* **2005**, *7*, 2759-2762.

- Epibatidine isomers and analogues: Structure-activity relationships. White, R.; Malpass, J. R.; Handa, S.; Baker, S. R.; Broad, L. M.; Folly, L.; Mogg, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5493-5497.

JOC*Article*

7-Substituted 2-Azabicyclo[2.2.1]heptanes as Key Intermediates for the Synthesis of Novel Epibatidine Analogues; Synthesis of *syn*- and *anti*-Isoepiboxidine

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Received May 1, 2004

Neighboring group participation by the 2-nitrogen in *anti*-7-bromo-2-benzyl-2-azabicyclo[2.2.1]-heptane allows ready nucleophilic substitution at the 7-position by C, N, O, and halogen nucleophiles and opens the way to a range of novel 7-substituted 2-azabicyclo[2.2.1]heptanes. Conversion of an *anti*-7-ethoxycarbonyl group into a methylisoxazole ring provides *anti*-isoepiboxidine, a conversion that is possible even without protection of the secondary bicyclic nitrogen. Successful base-induced epimerization α to the carbonyl of the *anti*-7-ethoxycarbonyl derivative gives the *syn*-stereoisomer and hence *syn*-isoepiboxidine.

Introduction

Interest in the 7-azabicyclo[2.2.1]heptane (7-azanorbornane) ring system has increased dramatically since the discovery of epibatidine **1a**, a natural product with unusually high activity at the nicotinic acetylcholine receptor (nAChR).[1] Intense synthetic interest has led to a large number of approaches to **1a**, together with an ever-increasing variety of analogues bearing different heterocycles;[2] prominent among these is epiboxidine **2a** in which replacement of the chloropyridyl substituent by methylisoxazole leads to high nAChR affinity but lower toxicity compared to **1a**.[2a] Homologous systems showing high nAChR affinity include homoepibatidine **1b**,[3] and interest in the methylisoxazole substituent has been further reinforced by the very recent report of the potent nAChR agonist homoepiboxidine **2b** by the Daly group.[4] The emphasis in the search for therapeutically useful compounds is now on high nAChR subtype selectivity.[5] We have recently reported analogues based on the more highly strained 2-azabicyclo[2.1.1]hexane ring system[6a] together with epibatidine isomers **3**–**6** in which the heterocycle is attached to the 5- and 6-positions of 2-azanorbornane.[6b-d] Compounds **3** and **4** have shown sufficient promise in this and other work[6b,e,f] to encourage us to explore routes to the remaining 2-azanorbornane derivatives *syn*-**7** and *anti*-**7** in which the positions of the bicyclic nitrogen and the heterocycle of **1a** have simply

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(1) (a) Spande, T. F.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3475–3478. For leading references to epibatidine analogue synthesis, see: (b) Carroll, F. I.; Lee, J. R.; Navarro, H. A.; Ma, W.; Brieaddy, L. E.; Abraham, P.; Damaj, M. I., Martin, B. R. *J. Med. Chem.* **2002**, *45*, 4755–4761. (c) Wei, Z.-L.; George, C.; Kozikowski, A. P. *Tetrahedron Lett.* **2003**, *44*, 3847–3850.

(2) Recent examples of alternative heterocycles incorporated into the epibatidine framework and into analogues include the following. (a) Methylisoxazole: Badio, B.; Garraffo, H. M.; Plummer, C. V.; Padgett, W. L.; Daly, J. W. *Eur. J. Pharmacol.* **1997**, *321*, 189–194. (b) Isoxazoles: Silva, N. M.; Tributino, J. L. M.; Miranda, A. L. P.; Barreiro, E. J.; Fraga, C. A. M. *Eur. J. Med. Chem.* **2002**, *37*, 163–169. (c) Pyridazines: Che, D.; Wegge, T.; Stubbs, M.; Seitz, G.Meier, H.; Methfessel, C. *J. Med. Chem.*, **2001**, *44*, 47–57. (d) Substituted pyridines: Carroll, F. I.; Lee, J. R.; Navarro, H. A.; Ma, W.; Brieaddy, L. E.; Abraham, P.; Damaj, M. I., Martin, B. R. *J. Med. Chem.* **2002**, *45*, 4755–4761. Avalos, M.; Parker, M. J.; Maddox, F. N.; Carroll, F. I.; Luetje, C. W. *J. Pharmacol. Exp. Ther.* **2002**, *302*, 1246–1252. Carroll, F. I.; Lee, J. R.; Navarro, H. A.; Brieaddy, L. E.; Abraham, P.; Damaj, M. I.; Martin, B. R. *J. Med. Chem.* **2001**, *44*, 4039–4041. (e) 6-Chloropyridazin-3-yl derivatives: Toma, L.; Quadrelli, P.; Bunnelle, W. H.; Anderson, D. J.; Meyer, M. D.; Cignarelli, G.; Gelain, A.; Barlocco, D. *J. Med. Chem.* **2002**, *45*, 4011–4017. (f) See also: Gohlke, H.; Schwarz, S.; Gündisch, D.; Tilotta, M. C.; Weber. A.; Wegge, T.; Seitz, G. *J. Med. Chem.* **2003**, *46*, 2031–2048 for recent work on 3D QSAR analysis in the design of heterocyclic substituents for high nAChR subtype selectivity in epibatidine analogues and homologues.

(3) (a) Malpass, J. R.; Hemmings, D. A.; Wallis, A. L.; Fletcher, S.; Patel, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1044–1050. Malpass, J. R.; Hemmings, D. A.; Wallis, A. L. *Tetrahedron Lett.* **1996**, *37*, 3911–3914. (b) Xu, R.; Bai, D. L.; Chu, G. H.; Tao, J. N.; Zhu, X. Z. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 279–282. Bai, D. L.; Xu, R.; Chu G. H.; Zhu, X. Z. *J. Org. Chem.* **1996**, *61*, 4600–4606.

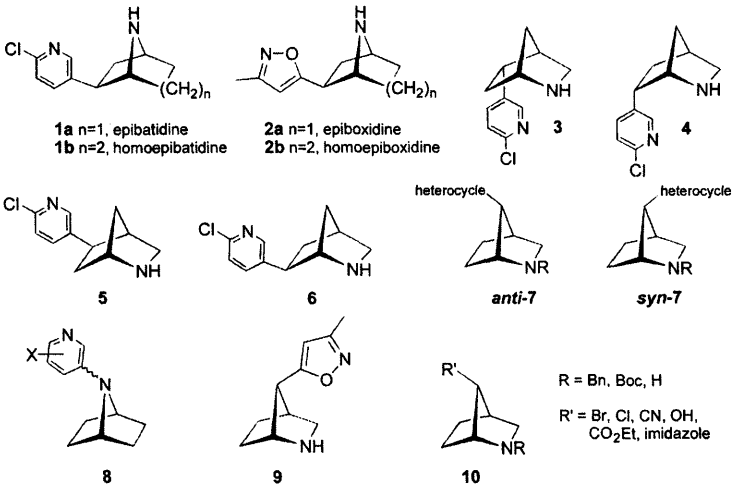
(4) Fitch, R. W.; Pei, X.-F.; Kaneko, Y.; Gupta, T.; Shi, D.; Federova, I.; Daly, J. W. *Bioorg. Med. Chem.* **2004**, *12*, 179–190.

(5) For leading reviews and references to nAChR affinities, see: (a) Carroll, F. I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1889–1896. (b) Bunnelle, W. H.; Dart, M. J.; Schrimpf, M. R. *Curr. Top. Med. Chem.* **2004**, *4*, 299–334. (c) Astles, P. C.; Baker, S. R.; Boot, J. R.; Broad, L. M.; Dell, C. P.; Keenan, M. *Curr. Drug Targets: CNS Neurol. Disord.* **2002**, *1*, 337–348. (d) Tønder, J. E.; Olesen, P. H. *Curr. Med. Chem.* **2001**, *8*, 651–674. (e) Lloyd, G. K.; Williams, M. *J. Pharmacol. Exp. Ther.* **2000**, *292*, 461–467. (f) Curtis, L.; Chiodini, F.; Spang, J. E.; Bertrand, S.; Patt, J. T.; Westera, G.; Bertrand, D. *Eur. J Pharmacol.* **2000**, *393*, 155–163. (g) Tønder, J. E.; Hansen, J. B.; Begtrup, M.; Petterson, I.; Rimvall. K.; Christensen, B.; Ehrbar, U.; Olesen, P. H. *J. Med. Chem.* **1999**, *42*, 4970–4980. (h) Holladay, M. W.; Dart M. J.; Lynch, J. K. *J. Med. Chem.* **1997**, *40*, 4169–4194.

(6) (a) Malpass, J. R.; Patel, A. B.; Davies, J. W.; Fulford, S. Y. *J. Org. Chem.* **2003**, *68*, 9348–9355. (b) Cox, C. D.; Malpass, J. R.; Rosen, A.; Gordon, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2372–2379. (c) Malpass, J. R.; Cox, C. D. *Tetrahedron* **1999**, *55*, 11879–11888. (d) Malpass, J. R.; Cox, C. D. *Tetrahedron Lett.* **1999**, *40*, 1419–1422. (e) Dart, M. J.; Wasicak, J. T.; Ryther, K. B.; Schrimpf, M. R.; Kim, K. H.; Anderson, D. J.; Sullivan, J. P.; Meyer, M. D. *Pharm. Acta Helv.* **2000**, *74*, 115–123. (f) Hodgson, D. M.; Maxwell, C. R.; Wisedale, R.; Matthews, I. R.; Carpenter, K. J.; Dickenson, A. H.; Wonnacott, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3150–3158. Hodgson, D. M.; Maxwell, C. R.; Matthews, I. R. *Synlett* **1998**, *12*, 1349–1350.

10.1021/jo0492564 CCC: $27.50
Published on Web 07/03/2004

CHART 1



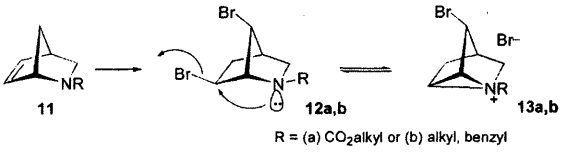
been reversed.[7] Although 7-substituted-7-azabicyclo[2.2.1]-heptyl (7-azanorbornyl) derivatives **8** have been reported recently,[8] we are not aware of any compounds having heterocycles directly attached to the 7-position of 2-azanorbornanes.

We chose *syn*-isoepiboxidine **9** as our first target. We demonstrate here that this and related 7-substituted-2-azanorbornanes are available by way of the key *anti*-7-substituted intermediates **10**. Neighboring group participation by the 2-azanorbornyl nitrogen is the key to displacements from the 7-position, extending its established role in the loss of 6-substituents. Epimerization at the 7-position [e.g., for the ester **10** (R = CO_2Et)] provides the essential first entry into the 7-*syn* series and hence a route to **9**.

Discussion

Neighboring group participation by σ and π bonds is a key feature of the rearrangement chemistry of bicyclo-[2.2.1]heptanes (norbornanes), and similar participation has also been established in the chemistry of azanorbornanes and -enes; σ or π electrons can participate in displacement of a nucleofuge from nitrogen in the 2-[9] or the 7-position[10] of the azanorbornane skeleton. More usually, nitrogen is seen to participate in the displacement of leaving groups from carbon,[9,11] and the nitrogen lone pair can also overlap with centers of developing positive charge during electrophilic addition to double bonds, leading again to skeletal rearrangement.[11,12] Such involvement of *N*-acyl and *N*-alkoxycarbonyl nitrogen in skeletal rearrangement is well established during electrophilic addition to derivatives of the 2-azanorborn-5-ene system **11**,[12] leading for example to dibromo derivatives such as **12a**.[12b] In the case of *N*-alkyl derivatives, the pioneering work of Raasch[11] has been developed, leading to isolation of the aziridinium intermediates **13b** during bromination.[13a] Indeed when R is alkyl, the equilibrium shown in Scheme 1 is biased completely in favor of the aziridinium salt **13b** with none of the dibromide **12b**.

SCHEME 1



We had hoped that addition of nucleophiles to the *N*-ethoxycarbonyl derivative **12a** ⇌ **13a** might allow interception of a small equilibrium concentration of **13a** (effectively achieving substitution at the 6-position), but we were unable to demonstrate any replacement of the 6-bromine in **12a**,[14a] despite the fact that carbamate

(7) Clearly, the N–N distances and orientation will be important in determining the binding ability of these ligands. Compounds **3** and **4** show much higher affinities and subtype selectivity than **5** and **6**,[6b] and it is reasonable to expect *syn*-**7** to be a better ligand than *anti*-**7**.

(8) Cheng, J.; Zhang, C.; Stevens, E. D.; Izenwasser, S.; Wade, D.; Chen, S.; Paul, D.; Trudell, M. L. *J. Med. Chem.* **2002**, *45*, 3041–3047. In addition, 7-substituted 1-azabicyclo[2.2.1]heptanes have been reported: Ullrich, T.; Binder, D.; Pyerin, M. *Tetrahedron Lett.* **2002**, *43*, 177–179.

(9) (a) Davies, J. W.; Malpass J. R.; Walker, M. P. *J. Chem. Soc., Chem. Commun.* **1985**, 686–687. (b) Durrant, M. L.; Malpass J. R.; Walker, M. P. *J. Chem. Soc., Chem. Commun.* **1985**, 687–688 and references to earlier work.

(10) Durrant, M. L.; Malpass J. R. *Tetrahedron* **1995**, *51*, 7063–7076. Davies, J. W.; Durrant, M. L.; Naylor, A.; Malpass, J. R. *Tetrahedron* **1995**, *51*, 8655–8664.

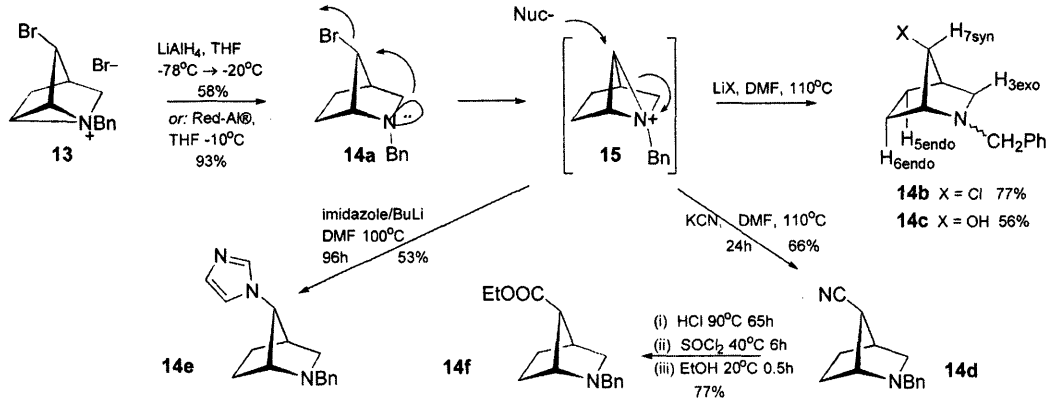
(11) Raasch, M. S. *J. Org. Chem.* **1975**, *40*, 161–172.

(12) (a) For work in the 2-azabicyclo[2.2.1]hept-5-ene-3-one system, see: Faith, W. C.; Booth, C. A.; Foxman, B. M.; Snider, B. B. *J. Org. Chem.* **1985**, *50*, 1983–1985. Evans, C.; McCague, R.; Roberts, S. M.; Sutherland, A. G. *J. Chem. Soc., Perkin Trans. 1* **1991**, 656–657. Palmer, C. F.; McCague, R. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2977–2978. (b) Bromination of *N*-ethoxycarbonyl-2-azanorborn-5-ene also proceeds smoothly with rearrangement to give **12a** (R = CO_2CH_2-Ph): Cox, C. D. PhD thesis, University of Leicester, 2000.

(13) (a) Sosonyuk, S. E.; Bulanov, M. N.; Leshcheva, I. F.; Zyk, N. V. *Russ. Chem. Bull.* **2002**, *51*, 1254–1261. For other azatricyclene intermediates, see: Portoghese, P. S.; Sepp, D. T. *Tetrahedron* **1973**, *29*, 2253–2256 and ref 9. (b) A 6-methoxy derivative was isolated on treatment of **13** (R = Me) with sodium methoxide in MeOH (ref 12a). A very recent paper from the same group has widened the range of nucleophiles: Bulanov, M. N.; Sosonyuk, S. E.; Zyk, N. V.; Zefirov, N. S. *Russ. J. Org. Chem.* **2003**, *39*, 415–421.

(14) (a) Barth, G. S.; (b) Fulford, S. Y.; (c) Rimmington, S. Unpublished work, University of Leicester.

SCHEME 2



nitrogen participates during additions to *N*-alkoxycarbonyl-2-azanorborn-5-enes and also electrophilic ring opening of the derived *exo*-5,6-epoxides.[14b] However, interception of **13** using a wider range of nucleophiles is possible in the *N*-alkyl series and has been used to make 6-substituted 2-azabicyclo[2.2.1]heptanes following reductive removal of the 7-substituent.[13b]

We were concerned to do the opposite: to remove the 6-substituent and introduce a range of functional groups at the 7-position. Treatment of **13b** (R = Bn) with hydride allows effective removal of the 6-bromine yielding the 7-bromo derivative **14a** (Scheme 2). At low temperature (−78 °C followed by warming to −20 °C over 1 h), $LiAlH_4$ gave **14a** in 58% yield after chromatography on silica.[15] The use of Red-Al[16] is preferable.

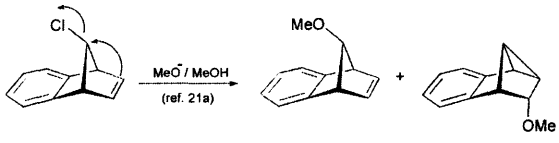
Nucleophilic substitution at the 7-position of **14a** was then attempted, despite the fact that direct (S_N2) substitution is difficult to achieve at this position in simple norbornanes.[17] The key substitution reactions occurred at elevated temperatures (ca. 100 °C). Thus, treatment of **14a** with LiCl in DMF gave the chloro analogue **14b** in 77% yield (Scheme 2),[18] and LiOH in DMF provided **14c** in 56% yield.[16b]

All of the substitutions based on **14a** occurred with complete retention of configuration at C-7. For example, the *anti* stereostructure of **14b** was confirmed by COSY experiments that identified "W" coupling between H_{7syn} and H_{5endo}/H_{6endo}.[19] In addition, NOE interactions were seen between H_{7syn} and H_{3exo} and between the CH_2 of the inverting *N*-benzyl group and both H_{7syn} and H_{6endo}. Similar reaction of **14a** with KCN in DMF yielded **14d** in 66% yield, and use of the imidazolyl anion followed the same pathway, producing **14e** in 53% yield. Here, the protons H_{5exo} and H_{6exo} appeared ca. 0.5 ppm upfield of the corresponding signals in **14b–d**, shielded by the ring current of the *anti* imidazole ring.

The *anti* stereochemistry in all of the 7-derivatives **14a–f** was confirmed by detailed spectroscopic analysis and is presumably the result of participation by nitrogen, as shown by **14a** → **15** (Scheme 2). Such involvement of the 2-nitrogen in displacements from the 7-position is clearly more energetically demanding than in displacement from the 6-position (**12** → **13**, Scheme 1) so that there was no competition during the earlier substitution at C-6 in the 6,7-dibromo compound **12b**.

Participation by the nitrogen lone pair in displacement of an *anti* substituent from C-7 is closely analogous to the involvement of π-electrons in the overall retention of stereochemistry observed in the classic studies by Cristol, Winstein, and others on the solvolysis of 7-substituted norbornenyl tosylates and brosylates[21] (e.g., Scheme 3). Similar π-participation has been observed in the loss of chloride ion from a range of *N*-chloro-7-azanorbornadienes.[10]

SCHEME 3



It is not unreasonable, in principle, that S_N2 substitution at the 7-position might proceed (with inversion), and on the basis of existing work in norbornanes[17] a slow reaction would be expected and a high temperature would

(15) Addition of $NaBH_4$ in MeOH to **13** led only to isolation of the 6-methoxy compound (17% yield).[13b] Treatment of **13** with $LiAlH_4$ at room temperature led to loss of both bromines and gave *N*-benzyl-2-azanorbornane, which was identical to a sample obtained by careful hydrogenation[14c] of **11**.

(16) (a) Mitch, C. H.; Quimby, S. J. Patent WO 00/75140 A1, 2000; US 6,559,171 B1, 2003. (b) The reaction conditions described in this patent were different to ours and were claimed to provide the 7-*endo*-hydroxy compound (OH *syn* to nitrogen). In our hands they gave only the *anti* stereoisomer, identical to our sample **14c**.

(17) (a) See: Jenkins, M. N.; Nash, J. J.; Morrison, H. *Tetrahedron Lett.* **2002**, *43*, 3773–3775 and references therein to earlier work. (b) The work in ref 17a indicates, for example, that carbonyl groups in the 2-/3-position(s) of the norbornyl skeleton can exert a significant effect on substitution at C-7.

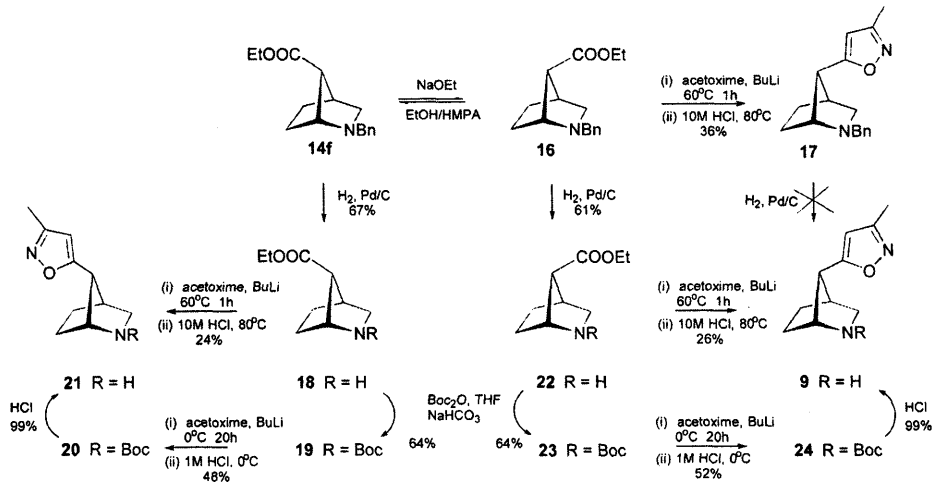
(18) Yields in these reactions have not been optimized in all cases. Typical reactions were performed on a 5–20 mmol scale but smaller-scale reactions in sealed reaction vials were effective down to a 0.1 mmol scale.

(19) See: Belkacemi, D.; Malpass, J. R. *Tetrahedron* **1993**, *40*, 9105–9116 for examples of W-coupling in 2-azanorbornanes.

(20) (a) We and others have previously exchanged *N*-benzyl for *N*-Cbz or *N*-Boc groups, e.g., ref 6a and references therein. (b) Conversion of *N*-benzyl into *N*-Boc was carried out prior to methylisoxazole formation in the recent work by Fitch et al.[4]

(21) (a) Cristol, S. J.; Nachtigall, G. W. *J. Am. Chem. Soc.* **1968**, *90*, 7132–7133; 7133–7134. (b) Tanida, H. *Acc. Chem. Res.* **1968**, *1*, 239–245. (c) Winstein, S. *J. Am. Chem. Soc.* **1961**, *83*, 1516–1517 and earlier references therein.

SCHEME 4



be required. However, our demonstration of *anti* stereochemistry for all of the derivatives **14a–f** strongly suggests that participation of the 2-nitrogen is general and provides a lower-energy alternative to S_N2 displacement for all of the nucleophilic substitutions studied. We are currently exploring alternative routes to the *syn*-7-hydroxy compound. Calculations make it clear that *syn*-7-heterocyclic derivatives will have more appropriate N–N distances for interaction with nicotinic receptors than *anti* stereoisomers, and it was thus important to achieve inversion of configuration at C-7.

The conversion of **14d** into the ester **14f** proceeded in an overall yield of 77% (Scheme 2). Crucially, epimerization of **14f** with base led to a mixture containing approximately 55% of the *syn*-epimer **16** (Scheme 4).[22,23] Base-induced epimerization at the 7-position in norbornanes is precedented[24] but is more difficult than at normal unstrained sp^3 carbon. This area is currently under active investigation, as is the influence of substituents elsewhere in the azanorbornyl ring system on the ease of bimolecular nucleophilic substitution at the 7-position.[17b]

Chromatographic separation of the stereoisomers **14f** and **16** was straightforward. The *syn*-ester **16** was converted into the *syn*-methylisoxazole derivative **17** using standard methods[2a,4] in 36% yield. However, attempts to deprotect the *N*-benzyl compound **17** by hydrogenolysis were unsuccessful (Scheme 4); not surprisingly, the methylisoxazole ring did not survive such treatment.

Our failure to obtain **9** from **17** prompted exchange of the *N*-benzyl for an *N*-alkoxycarbonyl protecting group in the 7-esters prior to heterocycle formation.[20] In the *anti* series, hydrogenolysis of **14f** gave the secondary amine **18**, which was *N*-Boc-protected to give **19** prior to heterocycle formation and *N*-deprotection of **20**; *anti*-isoepiboxidine **21** was formed in an overall yield of 30% from **18**. However, an unexpected observation avoided this reprotection/deprotection strategy and compensated for our earlier inability to enter the *N*-alkoxycarbonyl series by direct interception of **13a** (R = CO_2Alkyl) with nucleophiles. Thus, treatment of **18** with the dianion of acetoxime[2a] gave the methylisoxazole derivative *anti*-isoepiboxidine **21** directly (Scheme 4) in 24% yield. In similar fashion, debenzylation of **16** gave **22**, which was successfully converted into the target *syn*-isoepiboxidine **9** directly in 26% yield. The overall yield using the alternative 3-step procedure (via **23** and **24**) was 33%. Reported yields for the construction of methylisoxazoles are consistently low,[2a,4,6a] and mechanistic interest in this conversion[4] deserves to be extended. In the meantime, we believe that formation of the methylisoxazole ring without protection of the secondary amino-nitrogen (previously assumed to be an essential requirement) is a significant observation that will have wider application.

Further studies of substitution at the 7-position of the 2-azabicyclo[2.2.1]heptane ring system are under way. The application of coupling reactions to 7-halo compounds is being explored as a means of extending the range of available heterocyclic substituents as part of our program of synthesis of compounds having potential as high-affinity nAChR ligands.

Experimental Section

NMR spectra were recorded in $CDCl_3$ using tetramethylsilane as internal standard. Routine mass spectra were measured using electrospray and accurate mass measurements

(22) This situation is reminiscent of early syntheses of epibatidine **1a**, which gave predominantly the *endo*-stereoisomer, requiring subsequent epimerization at the 2-position of the 7-azanorbornyl ring system, for example: Fletcher, S. R.; Baker, R.; Chambers, M. S.; Herbert, R. H.; Hobbs, S. C.; Thomas, S. R.; Verrier, H. M.; Watt, A. P.; Ball, R. G. *J. Org. Chem.* **1994**, *59*, 1771–1778. For a significant improvement to the epimerization methodology for epibatidine, see: Habermann, J.; Ley, S. V.; Scott, J. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1253–1256.

(23) The methylene protons of the *syn*-ester ethyl group in **16** appeared as a complex pattern, interpreted as an overlapping pair of doublets of quartets. These complex signals collapsed to an AB pattern on double irradiation of the ester methyl triplet, confirming the diastereotopic relationship (in keeping with the position over the unsymmetrical C–N bond). The *syn*-ester **22** showed similar complexity for the methylene "quartet". The ester CH_2 protons in the *anti* isomers **14f** and **18** sit over a near-symmetrical C–C linkage and do not show diastereotopicity. In the case of **16**, the CH_2 protons of the *N*-benzyl group appear as a singlet; benzyl protons in these compounds often show accidental equivalence, and in this case this may be a consequence of the shift in the inversion equilibrium[19] towards the *endo*-*N*-benzyl invertomer as a result of steric interactions between the *exo*-invertomer and the *syn*-7 substituent.

(24) Buske, G. R.; Ford, W. T. *J. Org. Chem.* **1976**, *41*, 1998–2006.

using FAB or EI. IR spectra were measured as films. All reactions were performed in oven-dried glassware under dry nitrogen unless stated otherwise. Commercially available solvents were purified and dried, when necessary, prior to use. "Ether" refers to diethyl ether and "petrol" to petroleum ether, bp 40–60 °C.

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

3-Bromo-1-benzyl-1-azoniatricyclo[2.2.1.0^{2,6}]heptane Bromide (13). Using the procedure described by Sosonyuk et al.,[13a] 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene (**11**)[25] (12.03 g, 64.9 mmol) was dissolved in dry CH_2Cl_2 (120 mL). Bromine (6.0 mL, 129.5 mmol) was added dropwise at −78 °C. The mixture was stirred as the temperature rose to 20 °C. Evaporation in vacuo gave an orange oil, which was dissolved in dry CH_3CN (100 mL), cooled to 0 °C, and stirred vigorously while more **11** (12.06 g, 65.0 mmol) in dry CH_3CN (60 mL) was added dropwise. After warming to 20 °C, the solvents were evaporated in vacuo, yielding **13** as pale yellow crystals (22.3 g, 100%), mp 128–130 °C. [The NMR spectra are broadly similar to those described for the corresponding *N*-Me compound and the *N*-benzyl derivative having a Br_3^- counterion[13a]. δ_H (250 MHz, $CDCl_3$) 2.42 (brs, 2H), 2.83 (brs, 1H), 3.41 (d, J = 8.9 Hz, 1H), 3.94 (d, J = 8.9 Hz, 1H), 4.42 (m, 2H), 4.86 (brs, 1H), 5.34 (s, 2H), 7.42–7.73 (m, 5H). δ_C (62.9 MHz, $CDCl_3$) 30.9, 37.6, 44.5, 44.8, 46.2, 55.1, 55.3, 129.4, 129.5, 130.3, 131.1. ν_{max} 3049s, 3003w, 2318w, 1426m, 1278m, 898m cm^{-1}. *m/z* 264/266 (1:1) (M^+). $C_{13}H_{15}NBr$ [M^+] requires *m/z* 264.03879; observed 264.03884.

***anti*-7-Bromo-2-benzyl-2-azabicyclo[2.2.1]heptane (14a).** $LiAlH_4$ (0.53 g, 13.97 mmol) and **13** (3.056 g, 8.85 mmol) were cooled to −78 °C in a dry flask. Dry THF (100 mL) was added with stirring, and the mixture allowed to warm to −20 °C over a period of 1 h followed by addition of water-saturated ether until effervescence stopped. The mixture was filtered, the residue was washed with CH_2Cl_2, and after drying with $MgSO_4$ the solvents were removed in vacuo to give crude **14a**, which was chromatographed (petrol/ether 7:3; NH_3) to give a pale yellow oil (1.359 g, 58%), R_f (7:3, petrol/ether). δ_H (250 MHz, $CDCl_3$) 1.42, 1.77–2.13 (m, 4H), 2.43 (brs, 1H), 2.47 (d, J = 9.2 Hz, 1H), 2.82 (ddd, $J \approx$ 9.2, 3.3, 3.3 Hz, 1H), 3.23 (brs, 1H), 3.67, 3.69 (AB, J = 13.4 Hz, 2H), 4.24 (d, J = 1.7 Hz, 1H), 7.18 (m, 5H). δ_C (62.9 MHz, $CDCl_3$) 25.2, 26.7, 44.0, 53.4, 58.0, 59.0, 64.9, 126.9, 128.1, 128.2, 139.2. ν_{max} 3064s, 2982m, 2276w, 1504m, 1463m, 1430m, 1380w, 1279s, 1150w, 907m cm^{-1}. *m/z* 266/268 (1:1) (MH^+). $C_{13}H_{16}NBr$ [EI, M^+] requires *m/z* 265.04661; observed 265.04659.

Alternatively, reduction using Red-Al[16] (65+ wt % solution in toluene, 7.65 mL, 26.0 mmol) and **13** (8.96 g, 26.0 mmol) in dry THF (225 mL) at −10 °C for 2 h gave **14a** as a pale yellow oil (6.42 g, 24.1 mmol, 93%).

***anti*-7-Chloro-2-benzyl-2-azabicyclo[2.2.1]heptane (14b).** To a solution of **14a** (63.7 mg, 0.24 mmol) in anhydrous DMF (1.0 mL) in a reaction vial was added LiCl (217.5 mg, 5.13 mmol). The mixture was heated to 100 °C for 24 h, cooled, and poured into water (2 mL), followed by extraction with ether (3 × 2 mL). The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvents were evaporated in vacuo, yielding **14b** as a pale yellow oil (41 mg, 77%). R_f 0.79 (EtOAc/MeOH, 9:1). δ_H (250 MHz, $CDCl_3$) 1.41 (m, 1H), 1.80–2.08 (m, 3H), 2.34 (brs, 1H), 2.38 (d, J = 9.2 Hz, 1H), 2.85 (ddd, $J \approx$ 9.2, 3.2, 3.2 Hz, 1H), 3.16 (brs, 1H), 3.66 (brs, 2H), 4.20 (brs, 1H), 7.27 (m, 5H). δ_C (62.9 MHz, $CDCl_3$) 24.2, 26.2, 43.5, 58.0, 58.5, 62.0, 64.5, 126.8, 128.1, 128.3, 139.1. ν_{max} 3064m, 2991m, 2318w, 1683s, 1500w, 1453w, 1289w, 1256s, 843w cm^{-1}. *m/z* 222.10500 (MH^+); $C_{13}H_{17}NCl$ requires 222.10495.

***anti*-7-Hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (14c).** The 7-bromo compound **14a** (110 mg, 0.41 mmol) and LiOH (173 mg, 4.1 mmol) in dry DMF (8 mL) were stirred at 100 °C for 24 h. The reaction mixture was cooled, added to water (30 mL), and extracted with ether (4 × 25 mL). The combined extracts were washed with water (3 × 35 mL), dried over $MgSO_4$, and then filtered. Removal of solvents in vacuo gave a yellow oil that was chromatographed (9:1, EtOAc/MeOH, NH_3), yielding **14c** as a pale yellow oil (47 mg, 56%). R_f 0.53. δ_H (300 MHz, $CDCl_3$) 1.34–1.43 (m, 1H), 1.70–1.78 (m, 1H), 1.88–2.00 (m, 2H), 2.11 (brs, 1H), 2.19 (d, J = 9.3 Hz, 1H), 2.40 (brs, OH), 3.03 (brs, 1H), 3.05 (ddd, $J \approx$ 9.3, 3.6, 3.0 Hz, 1H), 3.65, 3.70 (AB, J = 13.4 Hz, 2H), 4.29 (brs,1H), 7.21–7.35 (m, 5H). δ_C (75.5 MHz, $CDCl_3$) 22.7, 26.5, 41.6, 57.7, 58.0, 62.9, 76.3, 126.8, 128.2, 128.5, 139.2. ν_{max} 3053m, 2970m, 2303w, 1421w, 1265s cm^{-1}. *m/z* 204.13886 (MH^+); $C_{13}H_{18}NO$ requires 204.13884.

Using the procedure described in ref 16a, **14a** (3.06 g, 11.5 mmol) and 1-methyl-2-pyrrolidinone (containing 15% v/v H_2O; 56 mL) were stirred at 100 °C for 67 h. The reaction mixture was diluted with water (150 mL), basified with aqueous NaOH, and extracted with ether (4 × 100 mL). The combined organic extracts were washed with water (4 × 100 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated to yield **14c** as a yellow oil (1.54 g, 66%) showing NMR spectra identical to those of the sample obtained above.

***anti*-7-Cyano-2-benzyl-2-azabicycl[2.2.1]heptane (14d).** KCN (2.36 g, 35.70 mmol) and 18-crown-6 (~1 mg) were added to **14a** (0.765 g, 2.88 mmol) in anhydrous DMF (10 mL), and the mixture was stirred vigorously at 110 °C for 24 h. After filtration, the solid residue was washed with ether, and the combined organic extracts were dried prior to removal of solvent in vacuo to give a yellow oil that was chromatographed (3:7 petrol/ether, NH_3), yielding **14d** as a yellow oil (0.405 g, 66%), R_f 0.32. δ_H (250 MHz, $CDCl_3$) 1.49 (m, 1H), 1.94 (m, 3H), 2.45 (d, J = 9.4 Hz, 1H), 2.73 (m, 3H), 3.47 (brs, 1H), 3.59, 3.67 (AB, J = 13.4 Hz, 2H), 7.29 (m, 5H). δ_C (62.9 MHz, $CDCl_3$) 26.2, 26.6, 35.3, 42.6, 58.6, 58.7, 64.3, 119.5, 127.0, 128.2, 128.3, 138.7. ν_{max} 2973s, 2874s, 2234s, 1494s, 1453s cm^{-1} *m/z* 213.13914; $C_{14}H_{17}N_2$ (MH^+) requires *m/z* 213.13917.

***anti*-7-(Imidazole-1-yl)-2-benzyl-2-azabicyclo[2.2.1]-heptane (14e).** Butyllithium (0.31 mL, 1.6 M in hexanes, 0.49 mmol) was added dropwise to imidazole (34 mg, 0.50 mmol) in anhydrous DMF (1.5 mL), and the mixture was stirred at 20 °C for 0.25 h. A solution of **14a** (103 mg, 0.39 mmol) in anhydrous DMF (4 mL) was added, and after stirring at 100 °C for 96 h the mixture was filtered, the residue was washed with diethyl ether, the combined organic extracts were washed with water (4 × 2 mL), and the solvents were removed in vacuo. After chromatography (ether, NH_3), **14e** was isolated as a yellow oil (52 mg, 53%), R_f 0.20. δ_H (250 MHz, $CDCl_3$) 1.42 (m, 1H), 1.47 (m, 1H), 1.68 (m, 1H), 2.00 (m, 1H), 2.45 (d, J = 9.4 Hz, 1H), 2.81 (brs, 1H), 3.15 (ddd, $J \approx$ 9.4, 3.2, 3.2 Hz, 1H), 3.63 (brs, 1H), 3.69 (brs, 2H), 4.36 (brs, 1H), 6.87 (brs, 1H), 7.06 (brs, 1H), 7.14 (m, 5H), 7.46 (brs, 1H). δ_C (62.9 MHz, $CDCl_3$) 23.9, 26.6, 41.1, 57.9, 58.2, 61.6, 62.9, 118.5, 127.0, 128.2, 128.3, 129.0, 136.6, 139.0. ν_{max} 3052m, 2972m, 2305w, 1501w, 1452w, 1374w, 1265s, 1082w, 910w cm^{-1}. *m/z* 254.16572; $C_{16}H_{20}N_3$ [MH^+] requires 254.16564.

***anti*-2-Benzyl-2-azabicyclo[2.2.1]heptane-7-carboxylic Acid Ethyl Ester (14f).** Aqueous HCl (4 mL, 8 M) was added to **14d** (0.309 g, 1.46 mmol) and stirred at 90 °C for 65 h. The mixture was evaporated to dryness; thionyl chloride (4 mL) was added, and the mixture was stirred at 40 °C for 6 h. Excess thionyl chloride was removed in vacuo, dry ethanol (5 mL) was added, and the mixture stirred at 20 °C for 0.5 h. After removal of the solvents in vacuo, the resulting yellow oil was dissolved in HCl (4 mL, 1 M) and washed with CH_2Cl_2 (3 × 4 mL). The aqueous layer was basified with ammonium hydroxide solution (8 mL, 35% ammonia) and extracted with CH_2Cl_2 (3 × 4 mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of solvents in vacuo gave **14f** as a yellow oil (0.290 g, 77%; the sample was sufficiently pure for the epimerization to give **16**). R_f 0.41 (3:2

(25) Larsen, P. A.; Grieco, P. A. *Org. Synth.* **1990**, *68*, 206–209.

ether/petrol). δ_H (250 MHz, $CDCl_3$) 1.24 (t, J = 7.1 Hz, 3H), 1.40, 1.60–1.95 (m, 4H), 2.40 (d, J = 9.4 Hz, 1H), 2.61 (brs, 1H), 2.86 (ddd, $J \approx$ 9.4, 3.4, 3.4 Hz, 1H), 2.93 (brs, 1H), 3.44 (brs, 1H), 3.66, 3.74 (AB, J = 13.5 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 7.33 (m, 5H). δ_C (62.9 MHz, $CDCl_3$) 14.0, 25.5, 26.9, 40.1, 51.2, 58.4, 59.9, 60.0, 62.2, 126.8, 128.2, 128.2, 128.4, 138.9, 171.7. ν_{max} 3053s, 2982s, 2305w, 1725s, 1452m, 1370m, 1265s, 1214m, 1180m, 1043m, 896w cm^{-1}. *m/z* 260.16510; $C_{16}H_{22}NO_2$ [MH^+] requires *m/z* 260.16505.

***syn*-2-Benzyl-2-azabicyclo[2.2.1]heptane-7-carboxylic Acid Ethyl Ester (16).** To the ester **14f** (3.387 g, 13.10 mmol) was added NaOEt in EtOH (0.63 M, 42 mL) and dry HMPA (0.1 mL), and the mixture was stirred at 65 °C for 24 h. After addition of the mixture to water (50 mL) and extraction with CH_2Cl_2 (5 × 60 mL), the organic extracts were combined, dried over anhydrous $MgSO_4$, and filtered. Capillary GC analysis [25 m HP–FFAP column] indicated the presence of both **14f** and **16** (*anti*/*syn* = 45:55). Chromatography (3:2 ether/petrol, NH_3) yielded **14f** (1.399 g; 41%), R_f 0.41, and **16** (1.56 g, 6.02 mmol, 46%), R_f 0.59. δ_H (300 MHz, $CDCl_3$) 1.28 (t, J = 7.1 Hz, 3H), 1.32–1.54, 1.54–1.69, 1.84 (3 × m, 2H, 1H, 1H), 1.93 (d, J = 8.4 Hz, 1H), 2.48 (brs, 1H), 2.55 (brs, 1H), 3.28 (ddd, $J \approx$ 8.4, 3.5, 3.5 Hz, 1H), 3.48 (brs, 1H), 3.68 (brs, 2H), 4.18, 4.20 (complex, 2 overlapping dq,[23] J = 7.1 Hz, 2H), 7.25–7.28 (m, 5H). δ_C (75.5 MHz, $CDCl_3$) 14.3, 23.7, 29.7, 39.4, 53.7, 55.5, 56.5, 60.0, 62.7, 126.5, 128.0, 140.0, 172.2. ν_{max} 2976s, 2870s, 1733s, 1453s, 1186s cm^{-1}. *m/z* 260.16509 (MH^+); $C_{16}H_{22}NO_2$ [MH^+] requires *m/z* 260.16505.

***syn*-2-Benzyl-7-(3-methyl-isoxazol-5-yl)-2-azabicyclo-[2.2.1]heptane (17).** Using the procedure described by Badio et al.,[2a] acetoxime (129 mg, 1.77 mmol) was dissolved in dry THF (4 mL) and held at 0 °C. Butyllithium (2.21 mL, 1.6 M, 3.53 mmol) was added, and the mixture was stirred at 20 °C for 0.8 h. The ester **16** (174 mg, 0.67 mmol) dissolved in dry THF (2 mL) was added. After stirring at 60 °C for 1 h the solvent was evaporated using nitrogen. HCl (8 mL, 10.2 M) was added, and the mixture was stirred at 80 °C for 4.5 h and then 12 h at room temperature. The reaction mixture was basified with saturated $NaHCO_3$ solution (~15 mL) and extracted with CH_2Cl_2 (4 × 40 mL). The organic layers were combined, and removal of the solvents in vacuo gave an orange oil that was dissolved in HCl (1 M, 3 mL) and washed with ether (4 × 2 mL). The aqueous layer was basified (NH_4OH solution) and extracted with CH_2Cl_2 (4 × 2 mL). The CH_2Cl_2 extracts were dried over $MgSO_4$ and filtered. Flash chromatography (9:1, ether/MeOH, NH_3) gave **17** as a colorless oil (65 mg, 36%), R_f 0.56. δ_H (300 MHz, $CDCl_3$) 1.45–1.62 (m, 2H), 1.74–1.87 (m, 1H), 2.00–2.13 (m, 1H), 2.02 (d, J = 9.1 Hz, 1H), 2.30 (s, 3H), 2.52 (brs, 1H), 2.88 (brs, 1H), 3.09 (ddd, $J \approx$ 9.1, 3.5, 3.5 Hz, 1H), 3.46 (brs, 1H), 3.68, 3.74 (AB, J = 13.8 Hz, 2H), 6.16 (s, 1H), 7.17–7.33 (m, 5H). δ_C (75.5 MHz, $CDCl_3$) 11.5, 24.1, 29.9, 41.8, 46.6, 55.8, 56.2, 63.0, 102.3, 126.6, 128.1, 138.8, 159.6, 172.3. ν_{max} 2961s, 1601s, 1494m, 1418s, 1370m, 1184m, 1010m. *m/z* 269.16537; $C_{17}H_{21}N_2O$ [MH^+] requires *m/z* 269.16539.

***anti*-2-Azabicyclo[2.2.1]heptane-7-carboxylic Acid Ethyl Ester (18).** A solution of **14f** (1.399 g, 5.40 mmol) in dry MeOH (40 mL) was hydrogenolyzed over Pd/C (10%, 0.25 g) with stirring for 24 h. The reaction mixture was filtered through Celite, and the solvent was removed in vacuo to leave a yellow oil that was chromatographed (17:3, ether/MeOH, NH_3) to provide **18** (0.612 g, 67%), R_f 0.29. δ_H (300 MHz, $CDCl_3$) 1.25 (t, J = 7.1 Hz, 3H), 1.48–1.57, 1.77–1.98 (2 × m, 2H, 2H), 2.62 (brs, 1H), 2.69 (d, J = 9.5 Hz, 1H), 2.73 (brs, 1H), 3.01 (ddd, $J \approx$ 9.5, 3.0, 3.0 Hz, 1H), 3.61 (brs, 1H), 4.12 (q, J = 7.1 Hz, 2H). δ_C (75.5 MHz, $CDCl_3$) 13.9, 26.8, 30.9, 39.2, 51.9, 53.6, 57.4, 60.0, 171.5. ν_{max} 3407b, 2979s, 1730s, 1541m, 1372m, 1226s, 1051m cm^{-1}. *m/z* 170.11811; $C_9H_{16}NO_2$ [MH^+] requires 170.11810.

***anti*-2-Boc-2-azabicyclo[2.2.1]heptane-7-carboxylic Acid Ethyl Ester (19).** The *anti*-ethyl ester **18** (103 mg, 0.61 mmol), Boc_2O (202 mg, 0.93 mmol), and $NaHCO_3$ (187 mg, 2.23 mmol) were stirred in THF (2 mL) and water (6 mL) at room temperature for 20 h. The reaction mixture was extracted with ether (4 × 4 mL), the organic extracts were combined, dried over anhydrous $MgSO_4$, and filtered, and the solvents were removed in vacuo. The resulting colorless oil was chromatographed (7:3 ether/petrol, NH_3) yielding **19** (105 mg, 64%), R_f 0.54. δ_H [300 MHz, $CDCl_3$; where there is signal duplication (slow N–CO rotation, ratio ~52:48) the minor rotamer signal is shown in italics] 1.27 (bt, J = 7.0 Hz, 3H), *1.45*, 1.46 (2 × s, 9H), 1.57–1.88 (m, 4H), 2.76 (m, 2H), *3.01*, 3.07 (2 × d, J = 9.7 Hz, 1H), 3.32, *3.35* (2 × brs, 1H), 4.15 (bq, J = 7.0 Hz, 2H), 4.31, *4.45* (2 × brs, 1H). δ_C (75.5 MHz, $CDCl_3$) 14.1, *25.8* & 26.0, 28.5, *29.1* & 29.3, 39.1 & *39.6*, *52.6* & 53.0, 53.1 & *53.7*, *57.3* & 58.1, 60.5, *79.2* & 79.3, *153.7* & 154.1, 170.5. ν_{max} 2977s, 1736s, 1697s, 1408s, 1173s, 1101s, 1048s cm^{-1}. *m/z* 270.17050; $C_{14}H_{24}NO_4$ (MH^+) requires 270.17053.

***anti*-2-Boc-7-(3-methyl-isoxazol-5-yl)-2-azabicyclo[2.2.1]-heptane (20).** Using the procedure described by Fitch et al.,[4] a solution of butyllithium (0.58 mL, 1.6 M in hexanes, 0.93 mmol) was added dropwise over 10 min to a solution of acetoxime (34 mg, 0.47 mmol) in dry THF (1 mL) under argon at 0 °C. After stirring for 2 h at 0 °C, a solution of the *anti*-ethyl ester **19** (58 mg, 0.22 mmol) in dry THF (1 mL) was added over 10 min. The reaction mixture was stirred under argon at 0 °C for 20 h and then transferred to vigorously stirred 1 M HCl (8 mL) over 40 min. This mixture was neutralized ($NaHCO_3$) and extracted with CH_2Cl_2 (5 × 15 mL), the combined organic extracts were dried over anhydrous $MgSO_4$ and filtered, and the solvents were removed in vacuo. The resulting yellow oil was chromatographed (7:3 ether/petrol), yielding **20** (19 mg, 48% based on recovered **19**), R_f 0.21 and **19** (19 mg). NMR signals were broadened; where there is signal duplication (slow N–CO rotation, ratio ~2:3) the minor rotamer signal is shown in italics. δ_H (300 MHz, $CDCl_3$) 1.47 (s, 9H), 1.60–1.86 (m, 4H), 2.28 (s, 3H), 2.85 (brs, 1H), 3.14 (brs, 1H), 3.45 (bddd, $J \approx$ 9.6, 2.7, 2.7 Hz, 1H), 4.43, *4.51* (2 × brs, 1H), 5.88 (brs, 1H). δ_C (100.6 MHz, $CDCl_3$) 11.4, 25.9, 28.5, *28.9* & 29.2, 40.1 & *40.7*, *46.0* & 46.3, 53.2 & *53.7*, *58.3* & 59.3, 79.6, 102.6, 154.2, 159.7, 170.0. ν_{max} 2976m, 1694s, 1406s, 1173m, 1112m cm^{-1}. *m/z* 279.17085; $C_{15}H_{23}N_2O_3$ (MH^+) requires 279.17087.

***anti*-7-(3-Methyl-isoxazol-5-yl)-2-azabicyclo[2.2.1]-heptane (21) from 20.** The ester **20** (8.3 mg, 0.030 mmol) was stirred in a mixture of EtOH (0.435 mL), ethyl acetate (1.205 mL), and acetyl chloride (0.359 mL) at 0 °C for 1 h. The reaction mixture was evaporated to dryness to give the hydrochloride salt of **21** (6.4 mg, 99%). Data for the free amine **21**: δ_H (300 MHz, $CDCl_3$) 1.40–1.75 (m, 4H), 1.9 (brs, NH), 2.27 (s, 3H), 2.71 (brs, 1H), 2.77 (d, J = 9.6 Hz, 1H), 3.09 (brs, 1H), 3.13 (m,1H), 3.71 (brs, 1H), 5.85 (s, 1H). δ_C (75.5 MHz, $CDCl_3$) 11.4, 26.8, 31.0, 40.4, 47.2, 52.3, 58.7, 102.3, 159.6, 171.4. ν_{max} 3392b, 2968s, 2876m, 1725w, 1602s, 1534m, 1415s cm^{-1}. *m/z* 179.11839; $C_{10}H_{15}N_2O$ [MH^+] requires *m/z* 179.11844.

Direct Formation of 21 from 18. The procedure described for **17** was followed using acetoxime (76 mg, 1.04 mmol) in dry THF (3 mL), butyllithium (1.43 mL, 1.6 M, 2.29 mmol), and the ester **18** (65 mg, 0.38 mmol) in dry THF (2 mL). HCl (8 mL, 10.2 M) was used in the second step, and after workup **21** was isolated as an orange oil (28 mg). Quantitative ^1H NMR analysis gave a yield of 16.2 mg, 24%.

***syn*-2-Azabicyclo[2.2.1]heptane-7-carboxylic Acid Ethyl Ester (22).** The ester **16** (1.56 g, 6.02 mmol) in dry MeOH (40 mL) was hydrogenolyzed as described for **14f** to yield **22** as a yellow oil (0.625 g, 61%), R_f 0.30. δ_H (300 MHz, $CDCl_3$) 1.27 (t, J = 7.1 Hz, 3H), 1.40–1.77 (m, 4H), 2.0 (brs NH), 2.59 (brs, 1H), 2.61 (d, J = 9.8 Hz, 1H), 2.51 (brs, 1H), 3.13 (ddd, $J \approx$ 9.8, 3.1, 3.1 Hz, 1H), 3.61 (bd, $\approx$ 2.6 Hz, 1H), 4.14 (complex "q",[23] J = 7.1 Hz, 2H). δ_C (75.5 MHz, $CDCl_3$) 13.9, 28.8, 30.8, 40.0, 49.8, 52.2 & 52.4, 58.27 & 58.31, 60.0, 172.3 & 172.7. ν_{max} 3406b, 2977s, 1728s, 1542m, 1409s, 1303m, 1192m, 1037m cm^{-1}. *m/z* 170.11812; $C_9H_{16}NO_2$ [MH^+] requires *m/z* 170.11810.

***syn*-2-Boc-2-azabicyclo[2.2.1]heptane-7-carboxylic Acid Ethyl Ester (23).** Treatment of the ester **22** (128 mg, 0.76 mmol) with Boc_2O (262 mg, 1.20 mmol) and $NaHCO_3$ (200 mg, 2.38 mmol) in THF (2 mL) and water (6 mL) using the method described for **19** gave **23** (130 mg, 64%), R_f (7:3, ether/petrol, NH_3) 0.39. δ_H [300 MHz, $CDCl_3$; where there is signal duplication due to slow N–CO rotation (ratio ~45:55) the minor rotamer signal is shown in italics.] 1.24 (t, J = 7.1 Hz, 3H), *1.44* & 1.46 (2 × s, 9H), 1.64–1.80 (m, 4H), 2.53 (brs, 1H), *2.72* & 2.75 (2 × brs, 1H), *2.94* & 3.00 (2 × d, J = 9.8 Hz, 1H), 3.51 (m, 1H), 4.13 (m, 2H), 4.39 & *4.51* (2 x brs, 1H). δ_C (75.5 MHz, $CDCl_3$) 14.2, 27.4, 28.5, 30.7, 39.4, 40.0, 50.6, 51.2, 52.2, 53.0, 58.2, 58.9, 60.4, 60.5, 79.0, 79.1, 154.2, 154.5, 170.6, 170.9. ν_{max} 2974m, 1735s, 1696s, 1406s, 1163s, 1104s cm^{-1}. *m/z* 270.17057; $C_{14}H_{24}NO_4$ [MH^+] requires *m/z* 270.17053.

***syn*-2-Boc-7-(3-methyl-isoxazol-5-yl)-2-azabicyclo[2.2.1]-heptane (24).** Acetoxime (74 mg, 1.01 mmol), butyllithium in hexanes (1.27 mL, 1.6 M, 2.03 mmol), and the ester **23** (133 mg, 0.49 mmol) were reacted using the procedure described for **20** to give **24** (61 mg, 52% based on recovered **23**), R_f (7:3, ether/petrol, NH_3) 0.35, and recovered **23** (19 mg). δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N–CO rotation (ratio ~45:55), the minor rotamer signal is shown in italics.] *1.43* & 1.47 (2 × s, 9H), 1.57–1.95 (m, 4H), *2.24* & 2.25 (2 × s, 3H), 2.74 & *2.80* (2 × brs, 1H), 2.94 & *2.95* (2 × brs, 1H), *2.96* & 3.03 (2 × d, J = 10.1 Hz, 1H), 3.15 & *3.27* (2 × ddd, $J \approx$ 9.9, 2.7, 2.7 Hz, 1H), *4.35* & 4.51 (2 × brs, 1H), 5.84 & *5.91* (2 × brs, 1H). δ_C (100.6 MHz, $CDCl_3$) 11.4, *28.5* & 28.6, *30.6* & 30.9, *40.8* & 41.4, 45.6 & *46.1*, 50.1 & *50.8*, *58.6* & 59.7, *79.4* & 79.6, 102.1 & *102.3*, 154.5, 159.8, *170.2* & 170.4. ν_{max} 2976s, 2359s, 1694s, 1406s, 1150s, 1112s cm^{-1}. *m/z* 279.17088; $C_{13}H_{23}N_2O_3$ [MH^+] requires *m/z* 279.17087.

***syn*-7-(3-Methyl-isoxazol-5-yl)-2-azabicyclo[2.2.1]-heptane (*syn*-isoepiboxidine) (9).** The *N*-Boc compound **24** (12.5 mg, 0.0450 mmol) was deprotected as described for compound **20**, yielding the hydrochloride salt of compound **9** (9.6 mg, 99%). Data for the free amine **9**: δ_H (300 MHz, $CDCl_3$) 1.49–1.68 (m, 2H), 1.72–1.91 (m, 2H), 2.27 (bs, 3H & NH), 2.66 (brs, 1H), 2.67 (d, J = 9.9 Hz, 1H), 2.91 (brs, 1H), 2.99 (ddd, $J \approx$ 9.9, 3.2, 3.2 Hz, 1H), 3.66 (bd, J = 2.5 Hz, 1H), 5.96 (s, 1H). δ_C (75.5 MHz, $CDCl_3$) 11.3, 29.0, 31.9, 40.8, 46.5, 49.9, 59.2, 102.4, 159.7, 171.6). ν_{max} 3400b, 2966s, 2877s, 1602s, 1418s cm^{-1}. *m/z* 179.11842; $C_9H_{16}NO_2$ [MH^+] requires 179.11844.

Direct Formation of 9 from 22 Acetoxime (72 mg, 0.99 mmol) in dry THF (3 mL) was treated with butyllithium (1.30 mL, 1.6 M, 2.08 mmol) and the ester **22** (54 mg, 0.32 mmol) in dry THF (2 mL) following the procedure described for **17**. Following workup using HCl (8 mL, 10.2 M), **9** was isolated as an orange oil (30 mg). Quantitative ^1H NMR analysis using an internal standard gave a yield of 14.6 mg, 26%.

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

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Approaches to Syn-7-Substituted 2-Azanorbornanes as Potential Nicotinic Agonists; Synthesis of *syn*- and *anti*-Isoepibatidine

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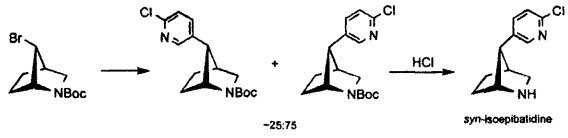
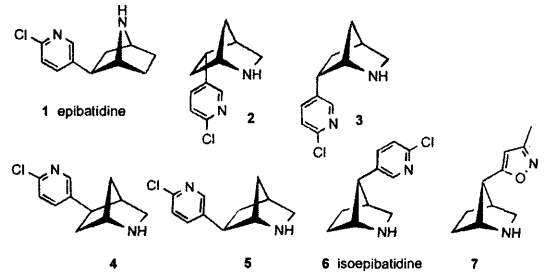
ABSTRACT



Coupling of *N*-Boc-7-bromo-2-azabicyclo[2.2.1]heptane with aryl and pyridyl boronic acids incorporates aryl and heterocyclic substituents at the 7-position and leads to a preference for syn over anti stereoisomers. Incorporation of a chloropyridyl group followed by N-deprotection gives *syn*-isoepibatidine. Facial selectivity in attack on 7-keto-2-azanorbornanes depends heavily on the N-protecting group leading to the first *syn*-7-hydroxy-2-azabicyclo[2.2.1]heptane derivative.

The discovery of epibatidine **1**, a naturally occurring derivative of the 7-azabicyclo[2.2.1]heptane (7-azanorbornane) ring system that has unusually high activity at the nicotinic acetylcholine receptor (nAChR),[1] has stimulated intense synthetic activity. The search for therapeutically useful compounds having higher nAChR subtype selectivity and lower toxicity has encouraged the synthesis of a wide range of analogues and isomers.[2]



We have been intrigued by the potential of the elusive isomer isoepibatidine **6** in which all the key features of **1** are retained but the positions of the bicyclic nitrogen and the heterocycle are simply reversed. Other epibatidine isomers **2** and **3** (having the heterocycle attached to the 5- and 6-*endo* positions of 2-azanorbornane)[3a] retain high nAChR affinity, as do many homologues and analogues.[4]

The *exo* orientation of the heterocycle in the isomers **4** and **5** leads to a much greater N–N distance and reduced nAChR affinity as anticipated.[3a]

We have recently reported the synthesis of novel syn- and anti-7-derivatives of 2-azanorbornane, including *syn*-isoepiboxidine **7** (and the anti stereoisomer) via the corre-

(1) Spande, T. F.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3475–3478. For leading references to epibatidine analogue synthesis, see: Carroll, F. I.; Lee, J. R.; Navarro, H. A.; Ma, W.; Brieaddy, L. E.; Abraham, P.; Damaj, M. I.; Martin, B. R. *J. Med. Chem.* **2002**, *45*, 4755–4761.

(2) For reviews and leading references to analogues and to nAChR affinities, see: Carroll, F. I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1889–1896. Bunnelle, W. H.; Dart, M. J.; Schrimpf, M. R. *Curr. Top. Med. Chem.* **2004**, *4*, 299–334.

(3) See: (a) Cox, C. D.; Malpass, J. R.; Rosen, A.; Gordon, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2372–2379 (**2–5**). (b) Hodgson, D. M.; Maxwell, C. R.; Wisedale, R.; Matthews, I. R.; Carpenter, K. J.; Dickenson, A. H.; Wonnacott, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3150–3158 (**3**).

(4) Malpass, J. R.; Hemmings, D. A.; Wallis, A. L.; Fletcher, S.; Patel, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1044–1050. Malpass, J. R.; Patel, A. B.; Davies, J. W.; Fulford, S. Y. *J. Org. Chem.* **2003**, *68*, 9348–9355.

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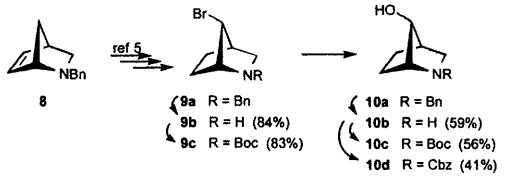
sponding 7-ethoxycarbonyl derivatives.[5] Interest in 7-substituted 2-azanorbornanes has also been extended to their use as precursors to α-kainic acids.[6] We now report the first successful direct attachment of aryl and heterocyclic rings to the 7-position of 2-azanorbornanes via metal-catalyzed coupling reactions, opening the way to *syn*-isoepibatidine **6** and a wider range of analogues.[2,7] Additionally, further investigation of the manipulation of syn/anti stereochemistry in 7-substituted 2-azanorbornanes has allowed us to resolve a disagreement over the stereochemical assignment of the 7-hydroxy compounds unambiguously.

The key anti-7-substituted intermediate **9a** is available from *N*-benzyl-2-azanorborn-5-ene **8** as described earlier.[5] The conversion of **9a** into **10a** and modification to give the *N*-Boc and *N*-Cbz examples **10c** and **10d** was achieved using standard methods[5] (Scheme 1).

Scheme 1



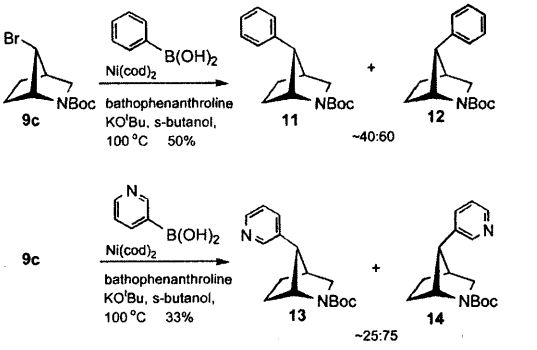
The anti stereochemistry is retained at C-7 during the substitution owing to neighboring group participation by the 2-azanorbornyl nitrogen. This allows smooth exchange of the bromine by a range of other nucleophilic groups[5] but clearly precludes direct S_N2 displacement with inversion, leading to the syn compounds which we had chosen as precursors for coupling chemistry. This is a problem since the syn-7-substituted derivatives are of much greater interest pharmacologically, bearing in mind the importance of N−N distances in achieving high nAChR affinity and the current level of understanding of the nAChR pharmacophore.[2] Our earlier synthesis of *syn*- and *anti*-isoepiboxidines involved the construction of the methylisoxazole ring in situ from a nitrile substituent via an ester group of established syn configuration.[5]

The key objective of the present work was the *direct* incorporation of pyridyl heterocycles at the 7-position of 2-azanorbornanes, preferably with control of syn stereochemistry. We hoped to use metal-catalyzed cross-coupling reactions to couple the heterocycle and the syn-bromo compound but were faced by two issues. First, studies of this type of reaction involving nonprimary sp^3 centers are in their infancy;[8] second, only the anti-7-bromo precursors **9** were available.

A significant recent report describing the coupling of nonactivated secondary bromo- and iodo- compounds with aryl boronic acids using a Ni(0) catalyst illustrates recent developments that are increasing the versatility of cross-coupling reactions substantially.[9] This work included examples of two (thiophene- and indole-based) heterocyclic boronic acids, and we applied this procedure to our more complex substrates, despite earlier observations on difficulties using functionalized alkyl electrophiles.[9]

We had intended to use the syn-7-bromo isomers of **9** as precursors but based our initial studies on the Boc-protected anti isomer **9c**, which was prepared from the readily available **9a** in 70% yield (Scheme 1). Coupling with phenylboronic acid required modification of the conditions described by Zhou and Fu.[9] A significantly higher catalyst loading was used (20 mol % instead of 4 mol %), and the low reactivity of **9c** necessitated a temperature of 100 °C for 48 h (rather than 60 °C for 5 h). Flash chromatography provided both epimers **11** and **12** in a total yield of 50%. The syn/anti ratio was 60:40 (Scheme 2).

Scheme 2



The same conditions were applied to the coupling of 3-pyridyl boronic acid with **9c** and gave **13** and **14** in a combined isolated yield of 33%. The syn epimer was again preferred (syn/anti ratio of 75:25). Yields were generally in line with those reported by Zhou and Fu.[9]

The fact that β-elimination is impossible in our system may contribute to the success of our reactions. Having demonstrated that this catalytic system can be utilized successfully with pyridyl boronic acids and functionalized secondary bromides, we applied similar conditions to the coupling of 4-chloro-3-pyridyl boronic acid[10] with **9c**. The

(5) Malpass, J. R.; White, R. *J. Org. Chem.* **2004**, *69*, 5328−5334.

(6) Hodgson D. M.; Hachisu, S.; Andrews, M. D. *Org. Lett.* **2005**, *7*, 815−817.

(7) For recent examples of alternative heterocycles incorporated into the epibatidine framework and into analogues, see leading references in: Carroll, F. I.; Ma, W.; Yokota, T.; Lee, J. R.; Brieaddy, L. E.; Navarro, H. A.; Damaj, M. I.; Martin, B. R. *J. Med. Chem.* **2005**, *48*, 1221−1228. See also citations 2 and 4 in ref 5.

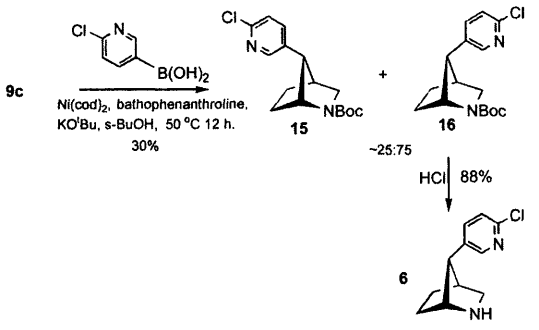
(8) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525−1532. Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674−688. Coupling of pyridylboronic acids and heteroaryl systems has been reported: Parry, P. R.; Wang, C.; Batsanov, A. S.; Bryce, M. R.; Tarbit, B. *J. Org. Chem.* **2002**, *67*, 7541−7543.

(9) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340−1341. This report concentrated on secondary alkyl halides that lacked functionality. A footnote in the paper states that "reactions of functionalized alkyl electrophiles proceed in lower yield".

(10) Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 2885−2890. This reagent is now commercially available.

isolated material contained some of the desired products, but there was also evidence of defunctionalization[11] and solvolysis (incorporation of a 2-butoxy group in place of the 2-chloropyridyl substituent). Lowering the temperature to 50 °C and the reaction time to 12 h avoided loss of the pyridyl chlorine and produced the desired **15** and **16** in an overall 30% yield (Scheme 3).

Scheme 3



The mixture of N-protected products was not easy to separate, but the major epimer **16** was isolated by careful chromatography and characterized with the aid of a crystal structure (Figure 1). Removal of the *N*-Boc group was

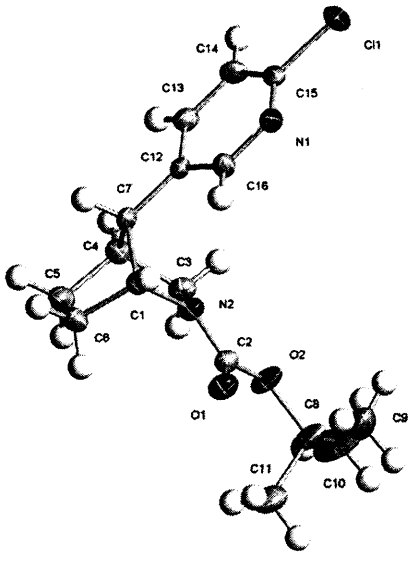


Figure 1. X-ray crystal structure of N-Boc isoepibatidine **16**.

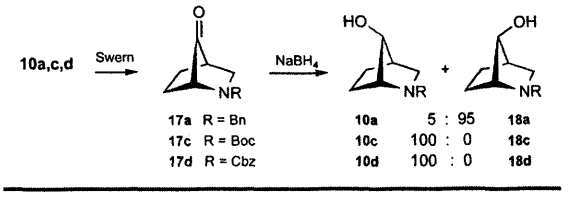
straightforward (using acetyl chloride in ethanol/ethyl acetate[5]), giving *syn*-isoepibatidine as the hydrochloride salt **6:HCl** in 88% isolated yield.

The use of strong base and elevated temperatures inevitably raised the likelihood of epimerization at the 7-position[5,12] and made the question of stereocontrol in the actual coupling reactions somewhat academic.

Nevertheless, we performed a chloropyridyl coupling at room temperature and interrupted the conversion after 3 h (ca. 10% conversion). The ratio of **15** and **16** in the isolated sample was 75 anti:25 syn. When this same mixture was treated with base (KO'Bu/BuOH) at 50 °C, the ratio reversed in favor of the syn isomer (25 anti:75 syn). This is in agreement with initial retention of configuration at C-7 followed by base-induced epimerization.

While it is now clear that syn-7 isomers of **9** are not required for synthesis of **6**, our early development work toward the syn-7-hydroxy isomers of **10** has allowed us to extend the range of syn derivatives and to resolve a recent disagreement over the orientation of the hydroxyl group.[5,13] We approached the syn-7-hydroxy compounds **18** via a simple oxidation/reduction strategy (Scheme 4).

Scheme 4



Swern oxidation of **10a,c,d** provided the corresponding 7-keto-compounds **17a,c,d**, but perversely, hydride reduction of the latter two derivatives using borohydride occurred only from the syn face, re-forming the starting compounds **10**. Fortunately, the facial selectivity was reversed in the case of the *N*-benzyl aminoketone **17a** and led to a substantial preference for the syn-hydroxy derivative **18a**.

The syn stereochemistry of **18a** was confirmed by an X-ray crystal structure of the 3,5-dinitrobenzoate derivative (Figure 2).

Standard methods allow attachment of a range of O-linked heterocycles using the oxy-anions of **10a,c,d**,[13] and it is now clear that a range of claimed syn derivatives that were synthesized as potential muscarinic antagonists[13] are in fact the anti isomers **19**. The availability of the syn compounds **18** now opens the way to the preferred range of syn derivatives **20**.

These include novel analogues of ABT-594[14] that contain the chloropyridyloxy group and have the same sequence of atoms between the two nitrogens.

(11) Quantities of defunctionalised *N*-Boc-2-azanorbornane (ca. 20%) were isolated from each of the coupling reactions.

(12) This situation recalls early syntheses of epibatidine **1** that gave predominantly the unwanted *endo* stereoisomer, requiring subsequent epimerization at the 2-position of the 7-azanorbornyl ring system, for example: Fletcher, S. R.; Baker, R.; Chambers, M. S.; Herbert, R. H.; Hobbs, S. C.; Thomas, S. R.; Verrier, H. M.; Watt, A. P.; Ball, R. G. *J. Org. Chem.* **1994**, *59*, 1771–1778. For a significant improvement to the epimerization methodology for epibatidine, see: Habermann, J.; Ley, S. V.; Scott, J. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1253–1256.

(13) Mitch, C. H.; Quimby, S. J. Patent WO 00/75140 A1, 2000; U.S. Patent 6, 559, 171 B1 2003.

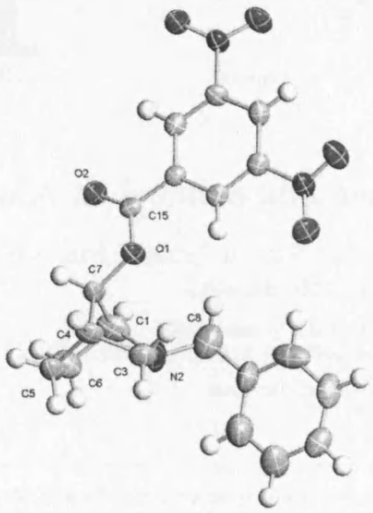
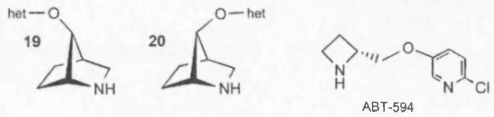


Figure 2. X-ray crystal structure of the 3,5-dinitrobenzoate of **18a**.

Syn-7 isomers have N−N distances that are more conducive to nAChR activity than the anti isomers but have less conformational freedom than ABT-594. We continue to explore this area and examine the factors that determine facial selectivity in attack on the 7-keto group.[15]



In summary, facial selectivity in attack on 7-keto-2-azanorbornanes is profoundly dependent on the N-protecting group and allows isolation and characterization of *syn*-7-hydroxy-2-azanorbornane (a precursor of novel potential nicotinic and muscarinic ligands). Significantly, we have demonstrated the first successful coupling of 4-chloro-3-pyridyl boronic acid with the functionalized secondary alkyl bromo compound **9c** and have shown that epimerization occurs under the reaction conditions. The observed thermodynamic preference for the *syn*-7-chloropyridyl derivative allows the use of the more readily accessible anti-7-bromo compound as the substrate in the synthesis of the novel epibatidine isomer *syn*-isoepibatidine **6**. This compound is a potential nicotinic agonist and will be screened for nAChR subtype selectivity. The coupling reaction itself has significance for the direct synthesis of other epibatidine analogues.

Acknowledgment. We are grateful to Dr. John Fawcett for the crystal structures and to Dr. Gerry Griffith for NMR data.

Supporting Information Available: Experimental procedures for coupling reactions and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0510365

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Epibatidine isomers and analogues: Structure–activity relationships

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Abstract—Binding affinities for a range of epibatidine isomers and analogues at the α4β2 and α3β4 nAChR subtypes are reported; compounds having similar N–N distances to epibatidine show similar, high potencies.

The remarkable affinity of epibatidine (**1**) for the nicotinic acetylcholine receptor (nAChR) is now well known.[1] Epibatidine is a potent but non-selective agonist, its pharmacological effects probably being mediated by a variety of nAChR subtypes including α7, α4β2, α3β4 and the α1β1γδ receptor at the neuromuscular junction.[2] The recognition of a wide variety of receptor subtypes has encouraged the exploration of epibatidine analogues in the hope of developing subtype-selective therapeutic compounds.[2] These compounds could then be employed as treatments for several neurological and psychiatric disorders including Parkinson's and Alzheimer's diseases, schizophrenia, chronic pain and tobacco dependence.[2] Greater subtype selectivity is likely to be associated with lower toxicity and fewer undesirable side effects.[2] The α4β2 nAChR is absent from the periphery but widely expressed within the CNS and may be a useful therapeutic target in several of the disorders described above. In contrast, activity at either the neuromuscular junction or the α3β4 ganglionic nAChR might be expected to lead to undesirable side effects. Work on defining the full role of each of the nAChR subtypes is highly dependent on the availability of subtype-specific ligands.[2]

We designed our target compounds to include: a bicyclic secondary nitrogen centre (the source of the quaternary nitrogen which is essential for binding); a freely rotating heterocyclic substituent; a rigid bicyclic framework which is capable of providing an appropriate N–N distance in one or both of the minimum-energy conformations (based on rotation about the C-pyridyl bond).[3] Our earlier work with tropanes (8-azabicyclo[3.2.1]octanes) and with 2- and 7-azabicyclo[2.2.1]heptanes (2- and 7-azanorbornanes)[4] has led us to synthesize a range of analogues and isomers based on these azabicyclic frameworks (Fig. 1). These include homoepibatidine (**2**),[5] dihomoepibatidine (**3**)[5] and isoepibatidine (**4**)[6] in which the positions of the bicyclic nitrogen and the heterocycle have been reversed. The epibatidine isomers **5** and **6**,[7] in which the bicyclic nitrogen is now in the 2-position and the 5- (or 6-)heterocyclic substituents are *endo*-, produce a calculated N–N distance in the appropriate range (Table 3).

The *exo*-isomers **7** and **8**,[7] having greater N–N distances, were included in these studies for comparison and contrast. In addition, the *syn*- and *anti*-isoepiboxidines **10** and **11**,[8] in which the chloropyridyl substituent of **4** has been replaced by a methylisoxazole ring, were synthesized in the hope of retaining potency but with lower toxicity (as reported for epiboxidine (**9**)).[9]

The synthesis and spectroscopic properties of these compounds have been published but full experimental details for *syn*-isoepibatidine (**4**) are recorded at the end of this letter since our very recent report[6] gave only a general procedure.

Activity data at the α4β2 and α3β4 receptors are listed in Table 1. Some previously published α4β2 and α7 binding data for selected compounds[7a] are included for

Keywords: Epibatidine analogues; Epibatidine isomers; nAChR affinity; Nicotinic receptor subtypes; Structure–activity relationships.
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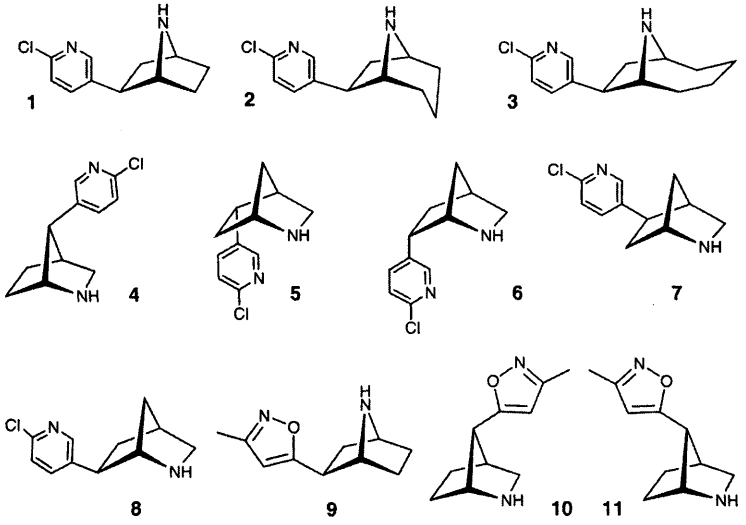


Figure 1. Epibatidine isomers and analogues.

Table 1. Inhibition of binding at human recombinant nicotinic receptors for compounds **1,2, 4–7,10** and **11**

Compound	K_i[a] (nM)		α3β4/α4β2
	α4β2	α3β4	
(±)-**1**	0.0558 (±0.0056)	0.191 (±0.0075)	3.42
(+)-**2**	0.127 (±0.011)	0.925 (±0.032)	7.28
(−)-**2**	0.343 (±0.026)	0.527 (±0.053)	1.54
(±)-**4**	0.0785 (±0.00617)	0.16 (±0.00189)	2.05
(+)-**5**	0.182 (±0.33)	0.944 (±0.058)	5.19
(−)-**5**	1.23 (±0.025)	8.73 (±0.179)	7.1
(±)-**6**	0.771 (±0.067)	2.35 (±0.122)	3.05
(±)-**7**	ne at 1000 nM	ne at 1000 nM	
(±)-**10**	0.763 (±0.092)	9.51 (±0.428)	12.5
(±)-**11**	ne at 1000 nM	ne at 1000 nM	
Cytisine	2.59 (±0.202)	525 (±6.32)	203

Preliminary data have been reported earlier.[10]

[a] Values are geometric means of at least three experiments, standard error is given in parentheses (ne = no effect).

comparison (Table 2). Differences between the K_i binding constants in Tables 1 and 2 (and early data recorded in Ref. 5) may be due to the fact that in Table 1, binding was at human recombinant nAChR, whereas the nAChR used to generate the values in Table 2 were from native rat tissue. These native receptors may be subtly different from the human recombinant nAChR in terms of their unit stoichiometry (ratio of α4 and β2 subunits) and composition (inclusion of other subunits, for example, α5).[11]

Table 2. Inhibition of binding at native rat nicotinic receptors for compounds **1**, **2** and **5–8**[7a]

Compound	α4β2 K_i[a] (nM)	α7 K_i[b] (nM)	α7/α4β2
1	(+)0.019	4.9 (±0.7) (n = 3)	258
	(−)0.020	7.0 (±1.8) (n = 4)	350
(±)-**2**	0.23	13 (n = 2)	56.5
(±)-**5**	0.056	6.3	112.5
(±)-**6**	0.045	3.9	86.7
(±)-**7**	ca. 40	3300	<87
(±)-**8**	ca. 40	1600	<42

[a] [^{3}H]Nicotine binding to rat cortical membranes.

[b] [^{125}I-α]Bungarotoxin binding to rat hippocampal membranes.

The most significant result is that isoepibatidine (**4**) is almost as potent as epibatidine ((±)-**1**). It shows similar activity to (±)-**1** at both the α4β2 and α3β4 receptors. This confirms earlier indications[5] that the unusual chemical properties[4b] of the nitrogen atom in the 7-azanorbornane ring system are not an essential factor in the unusual biological properties of **1**. Earlier results for homoepibatidine (**2**) have shown that incorporation of an extra methylene group into the 2-carbon bridge has little effect on binding affinity[5,12] (see also Table 2); thus the 7-azanorbornane system is not a pre-requisite for high activity although we have demonstrated that insertion of a second additional methylene group in dihomoepibatidine (**3**) leads to an order of magnitude reduction in activity, presumably because of the substantially greater bulk of the tetramethylene portion.[5] The new data for the enantiomers of **2** (Table 1) confirm the high

potency; the two enantiomers shows similar α4β2 selectivity.

Of the other 2-azanorbornane isomers, the *endo*-5-substituted compound **5** shows an almost 10-fold difference in the binding ability of the two enantiomers at both the α4β2 and α3β4 subtypes (Table 1), with the values for the (+)-enantiomer at the α4β2 being only 3-fold more than those for epibatidine ((±)-**1**). The enantiomers of **5** show little subtype selectivity. The K_i values for the racemic *endo*-6-substituted compound **6** are close to the average values for the enantiomers of **5** despite the difference in position of the heterocycle.

The previously accepted 'ideal' N–N distance of ca. 5.5 Å has been revised; recent X-ray studies suggest a value of 4.4–4.5 Å for the active conformation.[3b] This is in agreement with calculations for the compounds in Table 3. Interestingly, the methylisoxazole-substituted **10** is the only isomer which shows N–N distances close to the 'ideal' in both minimum energy conformations. Whatever the minor structural differences between the epibatidine isomers **1**, **4**, **5** and **6**, they all retain the key pre-requisites, including a broadly similar N–N distance, and show high potency. Significant changes are only observed when the two nitrogen centres are widely separated, as in the *exo*-isomers **7** and **8**. The *exo*-compounds are essentially inactive; the α4β2 and α3β4 data for **7** in Table 1 augment the earlier α4β2 and α7 results (Table 2).[7a]

Variation of the heterocyclic substituent has been widely investigated as a means of modifying the properties of nicotinic agonists.[2b] One of the more successful bioisosteric replacements for the chloropyridyl ring is the methylisoxazole ring, introduced by Daly in epiboxidine (**9**)[9] and, more recently, in the higher homologue homoepiboxidine.[13] We have recently reported the synthesis of the isoepiboxidine isomers **10** and **11** based on the 2-azanorbornane framework.[8] The *syn*-isomer (**10**) has approximately 13-fold weaker affinity than epibatidine at the α4β2 receptor (Table 1); this modest reduction mirrors that reported for epiboxidine (**9**).[9] The potency of **10** at the α3β4 receptor is lower but the discrimination is modest. The inactivity of the anti-isomer **11**, even at 1000 nM, is not surprising given the distance between the secondary nitrogen and the heterocycle (Table 3).

Table 3. Calculated N–N distances for amines[a]

Compound (unprotonated)	Minimum energy conformation (Å)	After 180° rotation about the C-heterocycle bond (Å)
1	4.5	5.5
2	4.6	5.6
4	4.5	5.2
5	4.8	5.9
6	4.3	5.3
7	6.4	6.6
8	5.7	6.1
10	4.4	4.8
11	5.6	5.8

[a] Calculated using Spartan Pro; equilibrium geometry by Hartree–Fock, 6-31G*.

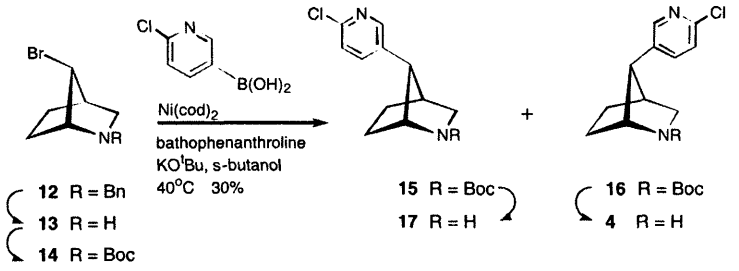
We recognise that calculated minimum energy N–N distances are a crude, indirect measure of the efficiency of interaction between the ligand and receptor and that many other factors are involved which are not yet fully understood.[3] Nevertheless, our work shows good correlations between calculated N–N distances and binding affinities for a homologue (**2**) of epibatidine, for epibatidine isomers (**4–6**) and for a variant (**10**) in which methylisoxazole replaces chloropyridine. Whilst the new compounds show similar high potency to epibatidine, there is no increase in selectivity between the α4β2 and α3β4 receptor subtypes.

Membrane preparation. Cell pastes from large-scale production of HEK-293 cells expressing cloned human α4β2 or α3β4 nAChR were homogenized in 4 volumes of buffer (50 mM Tris–HCl, 150 mM NaCl and 5 mM KCl, pH 7.4). The homogenate was centrifuged twice (40,000*g*, 10 min, 4 °C) and the pellets re-suspended in 4 volumes of Tris–HCl buffer after the first spin and 8 volumes after the second spin. The re-suspended homogenate was centrifuged (100*g*, 10 min, 4 °C) and the supernatant kept and re-centrifuged (40,000*g*, 20 min, 4 °C). The pellet was re-suspended in Tris–HCl buffer supplemented with 10% w/v sucrose. The membrane preparation was stored in 1 ml aliquots at −80 °C until required. The protein concentration of the membrane preparation was determined using a BCA protein assay reagent kit.

Nicotinic receptor radioligand binding scintillation proximity assay (SPA). SPA radioligand binding assays were performed in 96-well plates in a final volume of 250 μl Tris–HCl buffer (50 mM Tris–HCl, 150 mM NaCl, 5 mM KCl, pH 7.4) using the following conditions: [^{3}H]epibatidine (53 Ci/mmol; Amersham)-α4β2 = 1 nM, α3β4 = 2 nM; WGA-coated PVT SPA beads (Amersham)-α4β2 = 1 mg/well, α3β4 = 1.5 mg/well; membrane protein = 30 μg/well for both assay types. Non-specific binding (<10% for both assay types) was determined using 10 μM epibatidine. Reactions were allowed to equilibrate for 2–4 h at room temperature prior to reading on a Trilux Scintillation counter (Perkin Elmer). Data were analyzed using a standard 4-parameter logistic equation (Multicalc, Perkin Elmer) to provide IC_{50} values that were converted to K_i values using the Cheng–Prusoff equation.[15]

Synthesis of isoepibatidine **4**

anti-7-Bromo-2-azabicyclo[2.2.1]heptane (**13**). *anti*-7-Bromo-2-benzyl-2-azabicyclo[2.2.1]heptane **12**[6] (2.80 g, 0.012 mol) in dry MeOH (60 ml) was hydrogenolyzed using a standard procedure;[8] flash chromatography (Et_2O/MeOH; 9:1) gave **13** as a white crystalline solid (32%). δ_H (300 MHz, $CDCl_3$) 1.42–1.63 (m, 2H, H_{5n}, H_{6n}), 1.97–2.17 (m, 2H, H_{5x}, H_{6x}), 2.40 (dd, 3.8, 3.8 Hz, 1H, H_4), 2.68 (d, 9.7 Hz, 1H, H_{3n}), 3.00 (ddd, $J \approx 9.7$, 3.4, 3.4 Hz, 1H, H_{3x}), 3.37 (dd, $J = 3.1$, 3.1 Hz, 1H, H_1), 4.04 (dd, 1.5, 1.5 Hz, 1H, H_7). δ_C (75.5 MHz, $CDCl_3$) 26.5, 29.3 (C_5, C_6), 42.3 (C_4), 49.9 (C_3), 55.0 (C_7), 60.2 (C_1). ν_{max} 2976s, 2524 m, 1636 s, 1522m, 1421s cm^{-1}. *m/z* 176/178 (MH^+). $C_6H_{11}NBr$ [MH^+] requires 176.00749; observed 176.00751.



anti-2-Boc-7-bromo-2-azabicyclo[2.2.1]heptane (**14**). The procedure described for compounds **19** and **23** in Ref. 8 was followed using the *anti*-isomer **13** (344 mg, 1.95 mmol), Boc_2O (694 mg, 3.18 mmol), $NaHCO_3$ (595 mg, 6.77 mmol), THF (4 ml) and H_2O (12 ml). After reaction at rt for 72 h, **14** was obtained as a white crystalline solid (448 mg, 1.62 mmol, 83%) R_f (Et_2O/petrol; 1:1) 0.57. δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N–CO rotation (ratio ~ 45:55), the minor rotamer signal is shown in italics.] 1.45 (br s, 9H, Boc), 1.04–1.88, 2.02–2.23 (2× m, 4H, H_5, H_6), 2.57 (br s, 1H, H_4), *3.05*, 3.10 (2× d, J = 9.6 Hz, 1H, H_{3n}), 3.34 (ddd, $J \approx$ 9.6, 3.1, 3.1 Hz, 1H, H_{3x}), 4.05 (br s, 1H, H_7), 4.05, *4.25* (2× br s, 1H, H_1). δ_C (75.5 MHz, $CDCl_3$) 25.6, 28.1 (C_5, C_6), 28.4 (Boc CH_3), 43.0, *43.5* (C_4), 51.9 (C_7), 51.3, *52.1* (C_3), *59.7*, 60.8 (C_1), 79.7 (Boc C), 153.9 (Boc CO). ν_{max} 2977s, 1692s, 1398s, 1331m, 1304m, 1246m, 1155s, 1111s cm^{-1}. *m/z* 276/278 (MH^+). $C_{11}H_{19}NO_2Br$ [MH^+] requires 276.05992; observed 276.05987.

anti- and *syn*-2-Boc-7-(6-chloro-pyridin-3-yl)-2-azabicyclo[2.2.1]heptane (**15** and **16**). Procedure adapted from Ref. 14. In a glove box, $Ni(cod)_2$ (95 mg, 0.35 mmol) was placed in a two-necked flask. Bathophenanthroline (228 mg, 0.69 mmol), 4-chloro-3-pyridyl boronic acid (148 mg, 0.94 mmol) and 'BuOK (136 mg, 1.22 mmol) were added, the reaction vessel was evacuated and refilled with N_2 thrice. Dry *s*-BuOH (10 ml) was added and the mixture stirred for 10 min at rt under N_2; the colour changed to deep-purple, indicating the formation of the active complex. A solution of *anti*-**14** (210 mg, 0.76 mmol) in *s*-BuOH (2 ml) was added and the resulting mixture stirred under N_2 at 40 °C for 24 h, then cooled and passed through a short pad of silica. Solvents were removed in vacuo. Flash chromatography (Et_2O) of the crude residue gave a mixture of **15** and **16** as a pale yellow oil (~25:75; *anti*-:*syn*-) (69 mg, 0.22 mmol, 30%) R_f 0.49. δ_H [300 MHz, $CDCl_3$; signals corresponding to the minor (*anti*-) epimer are underlined; where there is signal duplication because of slow N–CO rotation (ratio ~ 45:55), the minor rotamer signal is shown in italics.] 1.39, 1.48, 1.50 (3× br s, 9H, Boc), 1.44–2.04 (m, 4H, H_5, H_6), 2.69, 2.91 (2× br s, 1H, H_4), 2.95, 3.02, 3.13–3.25, 3.44–3.53 (br s, br s, m, m, 3H, H_{3x}, H_{3n}), 4.45, *4.48*, 4.61 (4× br s, 1H, H_1), 7.22–7.33 (m, 1H, $H_{5'}$), 7.47–7.60 (m, 1H, $H_{4'}$), 8.23–8.32 (m, 1H, $H_{2'}$). δ_C (75.5 MHz, $CDCl_3$) 28.1, 28.2, *30.6*, 31.0 (C_5, C_6), 28.3, 28.5 (Boc CH_3), 39.0, 39.4, 41.5, *42.4* (C_4), 49.1, *49.5* (C_7), 53.3, *53.8*, *49.4*, 50.0 (C_3), 57.2, *58.0*, *58.4*, 59.0 (C_1), 79.3, 79.5 (Boc C), 123.8, 123.9, 124.0 (C_5), 132.5, 132.8, 132.9 ($C_{3'}$), 138.0, 138.2 ($C_{4'}$), 148.8 ($C_{6'}$), 149.3, 149.4 ($C_{2'}$), 154.2, 154.3 (Boc CO). Further chromatographic separation (Et_2O) allowed the isolation of a sample of the major (*syn*-) epimer **16** as a yellow oil: δ_H [300 MHz, $CDCl_3$; signal descriptors as described above (rotamer ratio ~ 45:55).] 1.41, 1.50 (2× br s, 9H, Boc), 1.61–2.04 (m, 4H, H_5, H_6), 2.69 (br s 1H, H_4), 2.95, 3.02 (br s, m, 3H, H_{3x}, H_{3n}, H_7), *4.48*, 4.61 (2× br s, 1H, H_1), 7.25 (m, 1H, $H_{5'}$), 7.54 (m, 1H, $H_{4'}$), 8.31 (m, 1H, $H_{2'}$). δ_C (75.5 MHz, $CDCl_3$) 28.1, 28.2, 30.6, *31.0* (C_5, C_6), 28.3, *28.5* (Boc CH_3), 41.6, *42.4* (C_4), 49.1, *49.5* (C_7), *49.4*, 50.0 (C_3), 57.3, *58.4* (C_1), *79.3*, 79.5 (Boc C), *123.8*, 123.9 ($C_{5'}$), *138.0*, 138.2 ($C_{5'}$), 149.3, *149.4* ($C_{2'}$), 132.9, *133.0* ($C_{3'}$), 154.2 (Boc CO). ν_{max} 2970s, 2934s, 1696s, 1606m, 1488s, 1406s, 1284s cm^{-1}. *m/z* 309 (MH^+). $C_{16}H_{22}N_2O_2$ [MH^+] requires 309.13698; observed 309.13692.

syn-7-(6-Chloro-pyridin-3-yl)-2-azabicyclo[2.2.1]heptane (*syn*-isoepibatidine) (**4**). A 75:25 mixture of epimers **15** and **16** (476 mg, 1.54 mmol) was dissolved in EtOAc (50 ml); EtOH (10.4 ml) and CH_3COCl (8.6 ml) were added with cooling in ice and the reaction mixture was allowed to reach rt and stirred for 4 h before being evaporated to dryness. The crude mixture of epimers of isoepibatidine–HCl salts was triturated with CH_2Cl_2 to give a sample of pure **4** (94 mg) and a sample containing **17** and **4** (2:1, 107 mg) (53% total yield). Data for free amine **4**: δ_H (300 MHz, $CDCl_3$) 1.24–1.50, 1.50–1.72, 1.72–1.93 (3× m, 4H, H_5, H_6), 2.63 (br s, 1H, H_4), 2.68 (d, J = 10.1 Hz, 1H, H_{3n}), 2.76 (ddd, $J \approx$ 10.1, 2.9, 2.9 Hz, 1H, H_{3x}), 3.71 (br s, 1H, H_1), 2.89 (br s, 1H, H_7), 7.26 (s, 1H, $H_{2'}$), 7.69 (dd, J = 3.1, 0.5 Hz, 1H, $H_{4'}$), 8.36 (d, J = 2.4 Hz, 1H, $H_{5'}$). δ_C (75.5 MHz, $CDCl_3$) 29.1, 32.9 (C_5, C_6), 40.7 (C_4), 48.9 (C_3), 49.8 (C_7), 58.4 (C_1), 124.0, 138.5, 149.4 (pyridyl). *m/z* 209/211 (MH^+). ν_{max} 2970s, 2750w, 2706w, 1622m, 1588w, 1561w cm^{-1}. *m/z* 209 (MH^+). $C_{11}H_{14}N_2Cl$ [MH^+] requires 209.08455; observed 209.08454. Tosic acid salt of **4**: mp 186–190 °C. Analysis: $C_{18}H_{21}N_2O_3SCl$ requires: C, 56.76; H, 5.56; N, 7.35; observed: C, 56.82; H, 5.46; N, 7.26.

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