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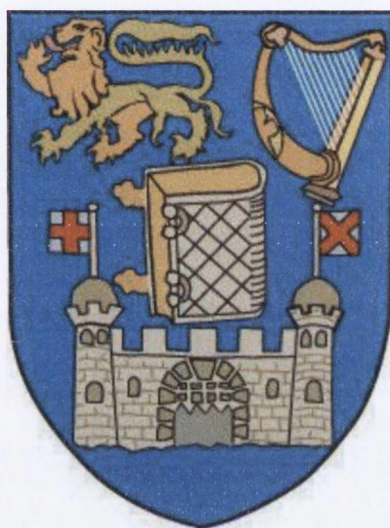
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The synthesis of analogues of mecamylamine



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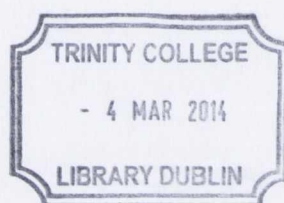
A thesis submitted to the University of Dublin for the degree of Doctor of
Philosophy

by

Neasa Mc Nabola

Under the supervision of Prof. Mike Southern

July 2013



Thesis 10235

Declaration

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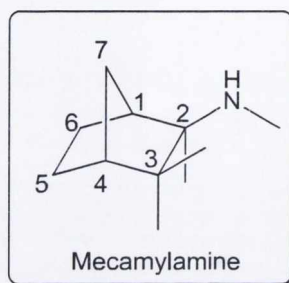
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Abstract

The project aims to develop structural analogues of mecamlamine (MA) a non-selective neuronal nicotinic acetylcholine receptor antagonist.



The anti-hypertensive drug MA (Inversine®) has been investigated for and shown anti-addictive and anti-depressive properties, in both human subjects and animal models. Due to its restrictive synthesis, structure-activity relationship studies (SAR) on MA have been very limited to date. Previous work within the group developed a novel synthetic route to the parent compound which allowed for the selective functionalisation of the 2 and 3 positions. The work herein describes a number of modifications of MA at positions 2,3 and around the amine. Further alterations to the bicyclic framework were investigated, namely functionalisation of positions 5 and 6 and the bridgehead position 7. In addition ring expanded [2.2.2]bicyclic systems were also investigated.

Abbreviations

5-HT	serotonin
ACh	acetylcholine
AChBP	acetylcholine binding protein
AD	Alzheimer's Disease
AIDS	acquired immunodeficiency syndrome
ATP	adenosine triphosphate
BBB	blood brain barrier
bPiDDb	N,N-dodecane-1,12-diyl-bis-3-picolinium dibromide
CNS	central nervous system
DA	dopamine
DALYs	disability adjusted life years
DAT	dopamine transporter protein
DBU	1,8-diazabicycloundec-7-ene
DH β E	dihydro- β -erythroidine
DIAD	diisopropyl azodicarboxylate
DID	“drinking in the dark”
DMPK	drug metabolism and pharmacokinetics
DMSO	dimethylsulfoxide
DSM	diagnostic and statistics manual of mental disorders
EAS	electrophilic aromatic substitution
ECD	extracellular domain
ELIC	<i>Erwinia chrysanthemi</i> pentameric ligand gated ion channel
EM	electron microscopy
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EWG	electron withdrawing group
FDA	Food and Drugs Administration
FST	forced swim test
GABA	γ -amino butyric acid
GLIC	<i>Gloeobacter violaceus</i> pentameric ligand gated ion channel
H ₂ SO ₄	sulfuric acid
HCN	hydrogen cyanide

HMBC	heteronuclear multiple bond correlation
HSQC	heteronuclear single quantum coherence
IC ₅₀	half maximal inhibitory concentration
IR	infrared
KOH	potassium hydroxide
KSCN	potassium thiocyanate
LDA	lithium diisopropylamine
MA	mecamylamine
MAO	monoamine oxidase
MDD	Major Depressive Disorder
MeLi	methyllithium
MLA	methyllycaconitine
MPEP	2-methyl-6-(phenylethynyl)pyridine
MS	mass spectrometry
MW	microwave
MWC	Monod-Wyman-Changeux
NA	norepinephrine/noradrenaline
NAc	nucleus accumbens
NRTs	nicotine replacement therapies
nAChR	nicotinic acetylcholine receptor
NaH	sodium hydride
NaHMDS	sodium bis(trimethylsilyl)amide
NaOH	sodium hydroxide
NMDA	<i>N</i> -methyl-D-aspartate
NMJ	neuromuscular junction
NMR	nuclear magnetic resonance
n.O.e	Nuclear Overhauser Effect
PD	Parkinson's Disease
PDC	pyridium dichromate
PET	positron emission tomography
PNS	peripheral nervous system
PTSA	para-toluene sulfonic acid
SAR	structure activity relationship

SNRI	serotonin/noradrenaline re-uptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TBA	tetra-n-butylammonium
TBAF	tetra-n-butylammonium fluoride
<i>t</i> BuOK	potassium <i>tert</i> -butoxide
TCA	tricyclic anti-depressant
THC	tetrahydrocannabinol
THF	tetrahydrofuran
TiCl ₄	titanium tetrachloride
TLC	thin layer chromatography
TMD	transmembrane domain
TMPPH	2,2,6,6-tetramethylpiperidin-4-yl-heptanoate
TMS	trimethylsilyl
TOCSY	Total Correlation Spectroscopy
Trp	tryptophan
TS	Tourette Syndrome
TST	tail suspension test
VTa	ventral tegmental area
WHO	World Health Organisation

Chapter 1

**Introduction to our biological
target: nicotinic acetylcholine
receptors**

1.Introduction to our biological target: Nicotinic Acetylcholine Receptors.

1.1 Nicotinic Acetylcholine Receptors.

This project is concerned with the preparation of novel ligands targeting nicotinic acetylcholine receptors (nAChRs). nAChRs are ligand gated ion channels located throughout the human body.¹ These receptors have been implicated in an extensive range of neurobiological disorders such as depression, schizophrenia, Alzheimer's and Parkinson's disease and are heavily involved in the mechanisms of addiction due to their ability to control the release of dopamine (the “reward chemical”) in the nucleus accumbens (NAc).² The long term aim of this project is to provide new treatments or insights into these conditions. Our primary interest is in addiction and our lead compound mecamylamine (MA), an nAChR antagonist, is a well known treatment for hypertension and has more recently been shown to have interesting anti-addictive properties.³ The primary target of MA is the nAChRs and a discussion of these is essential.

1.1.1 Receptor history and classification.

Acetylcholine (ACh) was first identified in 1914 by Henry Hallett Dale by its actions on heart tissue.⁴ It was confirmed as a neurotransmitter by Otto Loewi, who in his most famous experiment, took fluid expelled from the vagus nerve of one frog heart and administered it to another, which slowed the second heart proving that synaptic signalling uses chemical messengers, (Figure 1-1). He initially gave it the name Vagusstoff because it was released from the vagus nerve, it was later shown to be acetylcholine.⁵

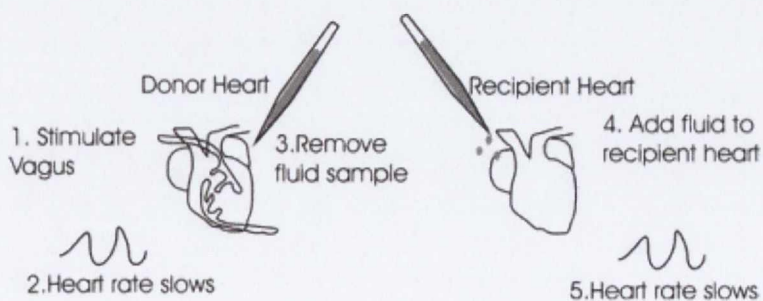


Figure1-1: Experiment of Otto Loewi (extract from Erol Basar, *Brain-Body-Mind in the Nebulous Cartesian System: A Holistic Approach by Oscillations*, Springer New York, 2011, Pg 42).⁵

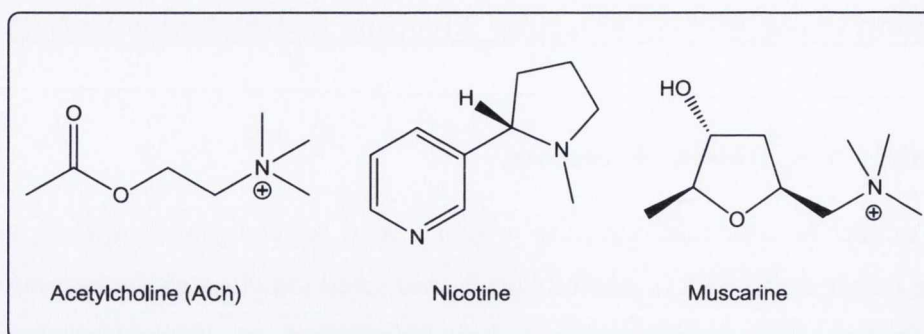


Figure 1-2: Structures of AChR agonists acetylcholine, nicotine and muscarine.

It was subsequently discovered that ACh has a wide variety of activities around the body that are mediated by two main classes of receptor. ACh receptors are categorised into two broad families namely muscarinic (mAChRs) and nicotinic (nAChRs). mAChRs are metabotropic G-coupled receptors which operate *via* a second messenger system and are stimulated by muscarine, nAChRs are ligand-gated ion channels which are activated by nicotine. ACh has functions in both the central nervous system (CNS) and the peripheral nervous system (PNS). The nAChRs located in the PNS and are associated with standard synaptic transmission in the somatic and autonomic nervous systems at the post synaptic side of the neuromuscular junction (NMJ) and in the autonomic nervous system but are also found to a great extent within the CNS, (Figure 1-3). The NMJ is the synapse of the axon terminal of a motorneuron with the end plate of the muscle. It is a highly-excitabile region of muscle fiber plasma membrane responsible for initiation of action potentials across the muscle's surface, ultimately causing the muscle to contract.⁶⁻⁸ The neuronal subtype of nAChRs are of principal interest to this study because of their implication in a wide range of diseases and disorders, including addiction.

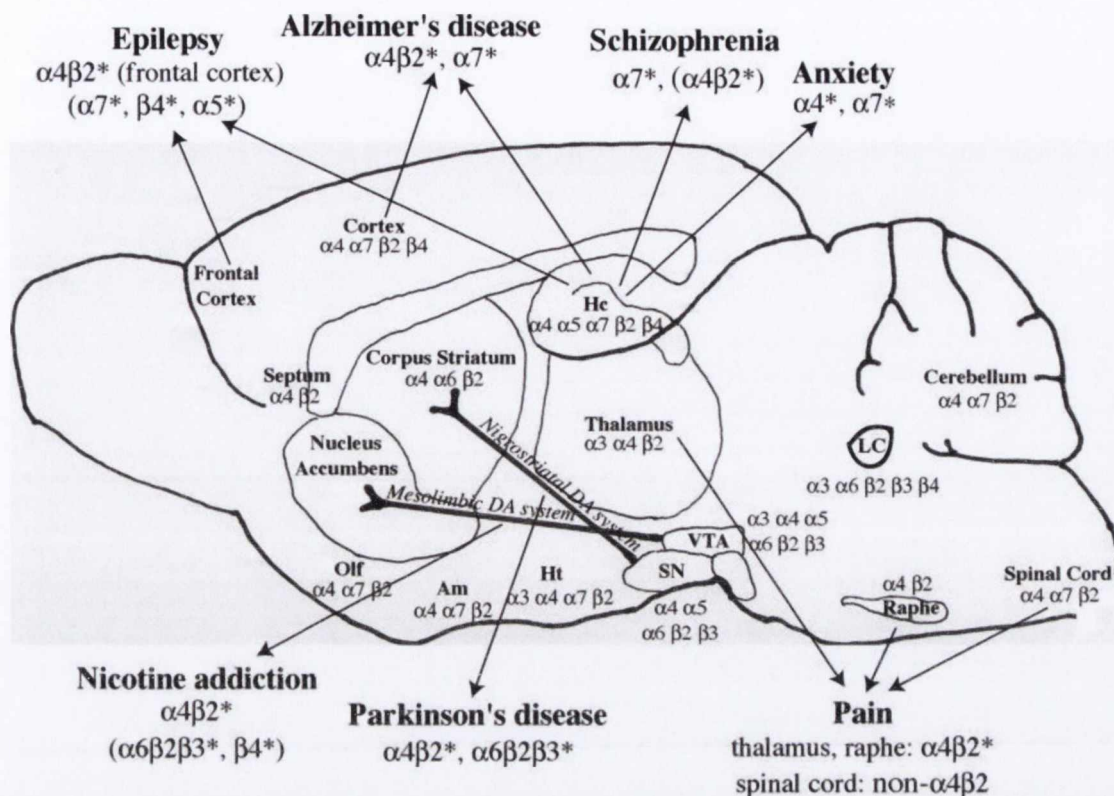


Figure 1-3: Distribution of nAChR subtypes throughout the brain (extract from A. A. Jensen, B. Frolund, T. Liljefors and P. Krosgaard-Larsen, *Journal of Medicinal Chemistry*, 2005, 48, 4705).⁹

1.1.2 Receptor Structure.

ACh receptors are ligand-gated ion channels comprised of five protein subunits denoted α , β , γ , δ and ϵ which constitute the NMJ. These muscle type receptors are found in either the embryonic form composed of $(\alpha 1)_2(\beta 1)(\delta)(\gamma)$ or the adult form composed of $(\alpha 1)_2(\beta 1)(\delta)(\epsilon)$. The neuronal variants operating in the CNS are comprised of combinations of $\alpha 1$ - $\alpha 10$, $\beta 2$ - $\beta 4$ subunits. Each of the five protein subunits consists of a long *N*-terminal extracellular domain, four hydrophobic transmembrane domains M1-M4, a long cytoplasmic loop which connects M3 and M4, while shorter loops connect the other domains, (Figure 1-4).^{10,11}

There has been a significant advancement with regards to receptor structure in the last 10-20 years following the work of Ballivet, Claudio, Patrick, Noda and Sumikawa *et al.* who, through the techniques of molecular biology, elucidated the primary structure of the subunits of the nAChRs. Their work led to the cloning of these receptors from various species, which in turn allowed for complete classification of the nAChR family.¹²⁻¹⁶ Neuronal nAChRs are composed of heteromeric combinations of α ($\alpha 2$ - $\alpha 6$) and β ($\beta 2$ - $\beta 4$) subunits, homomer α

subunits ($\alpha 7$ and $\alpha 9$) and α subunit heteromers ($\alpha 9$ and $\alpha 10$). The $\alpha 8$ subunit has been identified in avian tissues and has not yet been observed in mammals.¹⁷ Figure 1-3 illustrates the distribution and variants of different subtypes of the nAChR in the brain and the disorders with which they are associated.

nAChRs exist in at least three conformational states which control channel gating: resting, activated, and desensitised states. Desensitisation refers to a reversible reduction in response during prolonged agonist exposure. An agonist binds the receptor and triggers a response. Upon binding of a ligand, conformational changes occur in the receptor which ultimately controls the channel gating.¹⁸

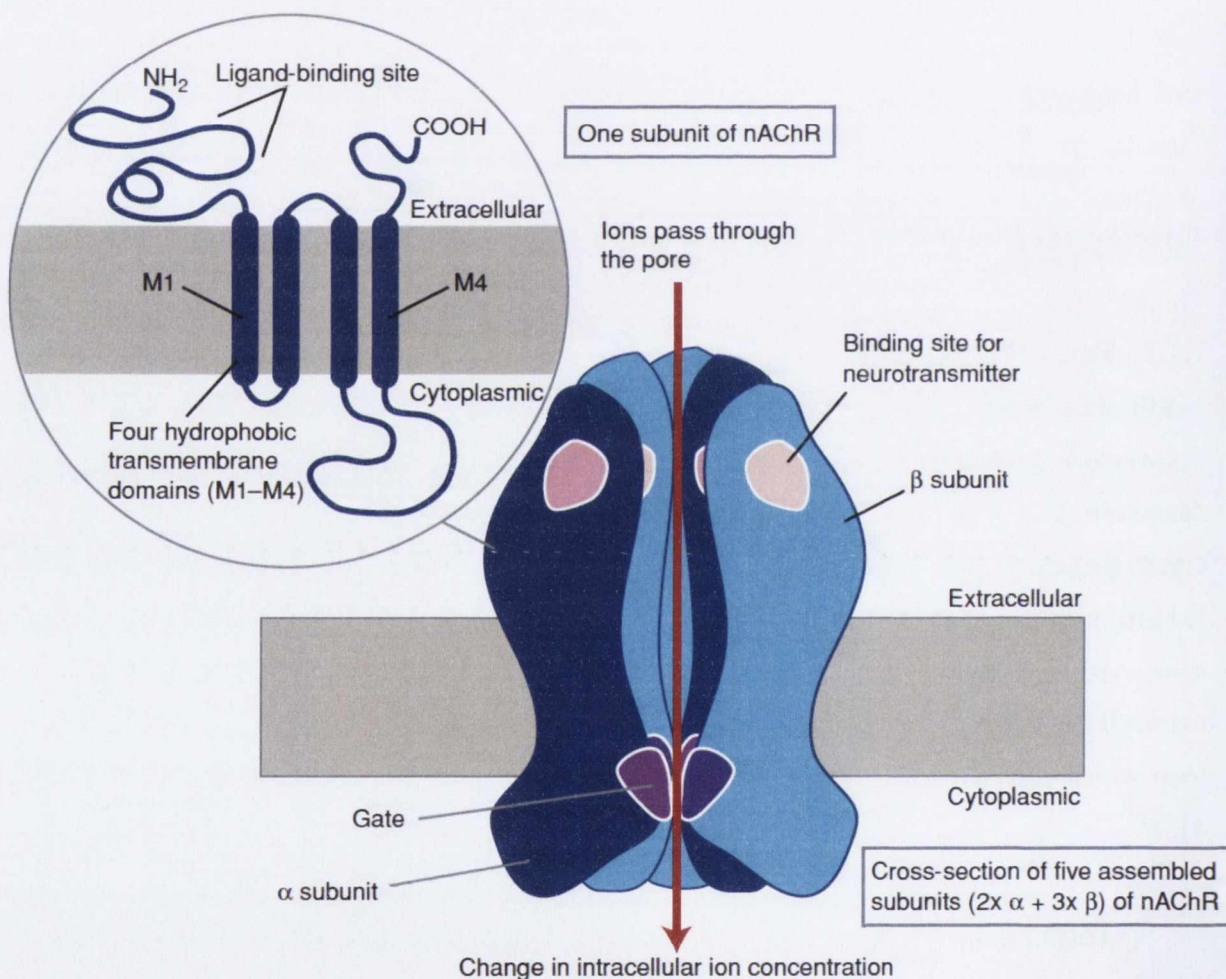


Figure 1-4: Structure of nicotinic acetylcholine receptors (extract from L. Bate, M. Gardiner, *Expert Rev. Mol. Med.*, 1999, 1, 1-22).¹⁹

Ligand binding sites are located at the junction or intersection between two distinct subunits in the receptor. The subunits concerned must consist of an α -type subunit which is

referred to as the ‘principal component’ and a non- α -type subunit named the ‘complementary component’. In the case of homomeric nAChRs such as $\alpha 7$ nAChRs the binding site would be located at the junction of two α subunits.¹⁰ This results in variable numbers of binding sites found on a receptor depending upon its composition of subunits. For example, the homomeric $\alpha 7$ nAChRs would have 5 binding sites whereas a heteromeric receptor e.g. $(\alpha 4)_2(\beta 2)_3$ would have just 4, (Figure 1-5). It is important to note that due to a variation in the numbers of subunits present in a given receptor, it is insufficient to simply describe these as $\alpha\beta\gamma$, although this is common and gives an indication of the classification. The receptor exemplified in Figure 1-5 on the right should be described more precisely as $(\alpha 4)_2(\beta 2)_3$. More complex combinations containing three $(\alpha 3\beta 4\alpha 5)$ or four subunits $(\alpha 3\beta 2\beta 4\alpha 5)$ have been immunoisolated from the brain.²⁰

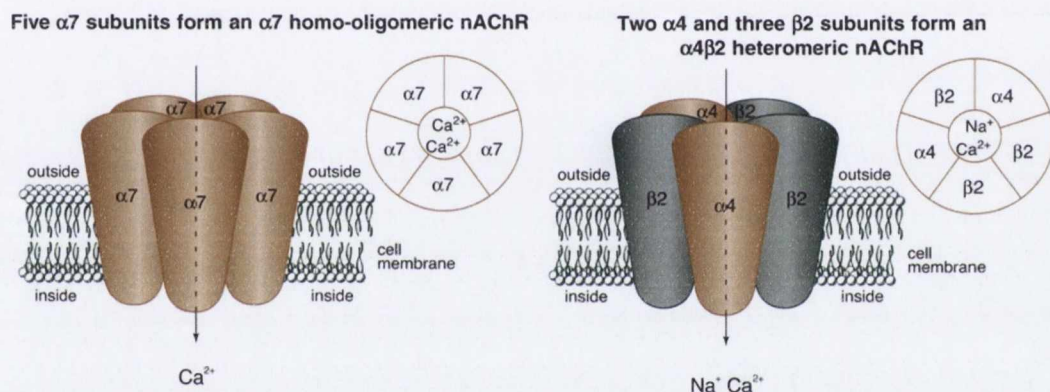


Figure 1-5 nAChRs subunits (extract from <http://pubs.niaaa.nih.gov>).²¹

1.1.3 Receptor three-dimensional structure.

Significant efforts have been made in recent years to fully elucidate the three-dimensional structures of nAChRs through the use of X-ray crystallography and electron microscopy (EM). As a result our knowledge of nAChR structure and its relation to function has greatly increased. Initial structural information was revealed by Brejc *et al.*,²² who elucidated the X-ray crystal structure of a homologue of the nAChR extracellular domain (ECD) through the use of acetylcholine binding protein (AChBP), in this instance cloned from the snail *Lymnaea stagnalis*. These AChBPs align with the ECD and therefore act as structural homologues of the nAChR ECD.²³ In 2005 Urwin developed a model for nAChRs in the

closed state through electron microscopy (EM) studies of the structure of the *Torpedo marmorata* nAChR in combination with the structure of AChRBPs.²⁴ The atomic model provides a comprehensive description of the receptor in its closed state and has disclosed detailed information regarding ligand-binding and the intracellular domains. Later in 2007, the X-ray structure of the mouse nAChR $\alpha 1$ ECD was identified as a complex with α -bungarotoxin, a competitive nAChR antagonist.²⁵ More recently the crystal structures of two prokaryotic pentameric ligand gated ion channels which are homologous with human nAChRs have been solved. Crystal structures of *Gloeobacter violaceus* pentameric ligand-gated ion channel (GLIC) and *Erwinia chrysanthemi* pentameric ligand-gated ion channel (ELIC) have been examined in both the open and closed states which could provide structural insight into the mechanisms of opening of the ion channel pore.²⁶⁻²⁸

1.1.4 nAChR-Ligand interaction and binding.

In recent years, great advancements have been made in the comprehension of ligand interaction and binding with regards nAChRs. In 1998 Zhong *et al.* found that ACh binds tightly to its receptors due to a cation- π interaction between the quaternary ammonium portion of the ligand and the indole ring of a specific tryptophan in the receptor namely TrpB or α Trp-149 residue.²⁹ Later works revealed that the high affinity nicotine displays for neuronal subtypes over their muscle counterparts is also the result of a strong cation- π interaction to the TrpB amino acid residue. This key interaction is absent in the case of muscle type nAChRs resulting in a radical reduction in affinity.³⁰ These findings were subsequently supported by the works of Brejc *et al.*³¹ and Smit and co-workers³² who solved crystal structures of AChBPs cloned from the snail *Lymnaea stagnalis*, (Figure1-6). These structures revealed an 'aromatic box' or 'cage' within the binding pocket which contained a number of tyrosine and tryptophan residues.

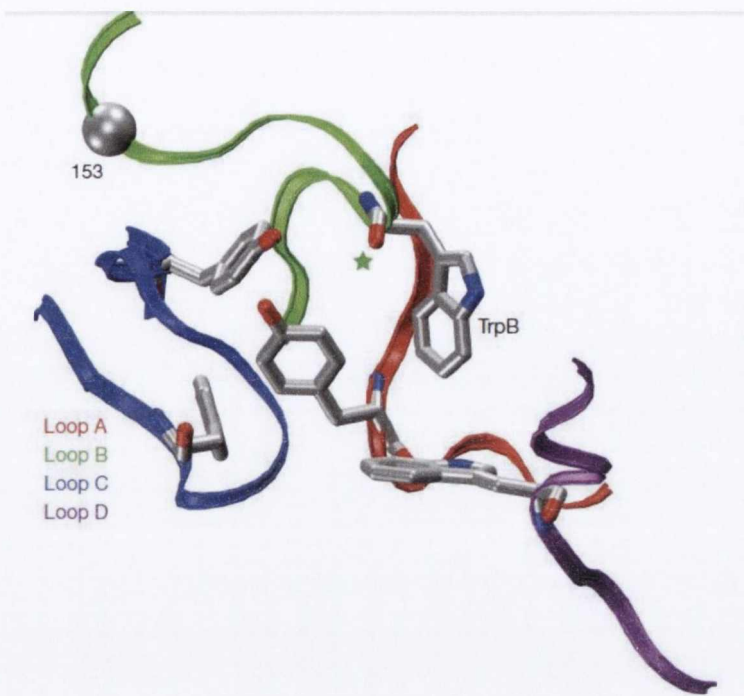


Figure 1-6:The binding site of AChBP (extract from X. Xiu, N. L. Puskar, J. A. P. Shanata, H. A. Lester and D. A. Dougherty, *Nature*, 2009, 458, 534 - 538).³⁰

Allosteric binding sites (different modulatory binding sites to the active site) have been shown to modulate neuronal nAChR function. These allosteric sites are targeted by ligands which do not compete with orthosteric binders such as ACh. Hansen *et al.*³³ conducted an excellent study investigating the binding sites of a number of non-competitive nAChR ligands including galantamine and cocaine, (Figure 1-7). Utilising AChBP cloned from the mollusk *Aplysia californica*, X-ray structures of ligand bound AChBPs were studied exposing the binding site. Both cocaine and galantamine were found to bind at the same location, a non- α subunit interface deep within the subunit interfaces of the AChBP, in a region in which the amino acid sequence is conserved in nAChRs.

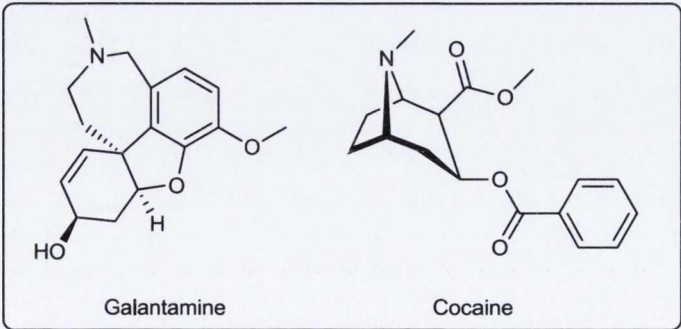


Figure 1-7: Non-competitive nAChR ligands cocaine and galantamine.

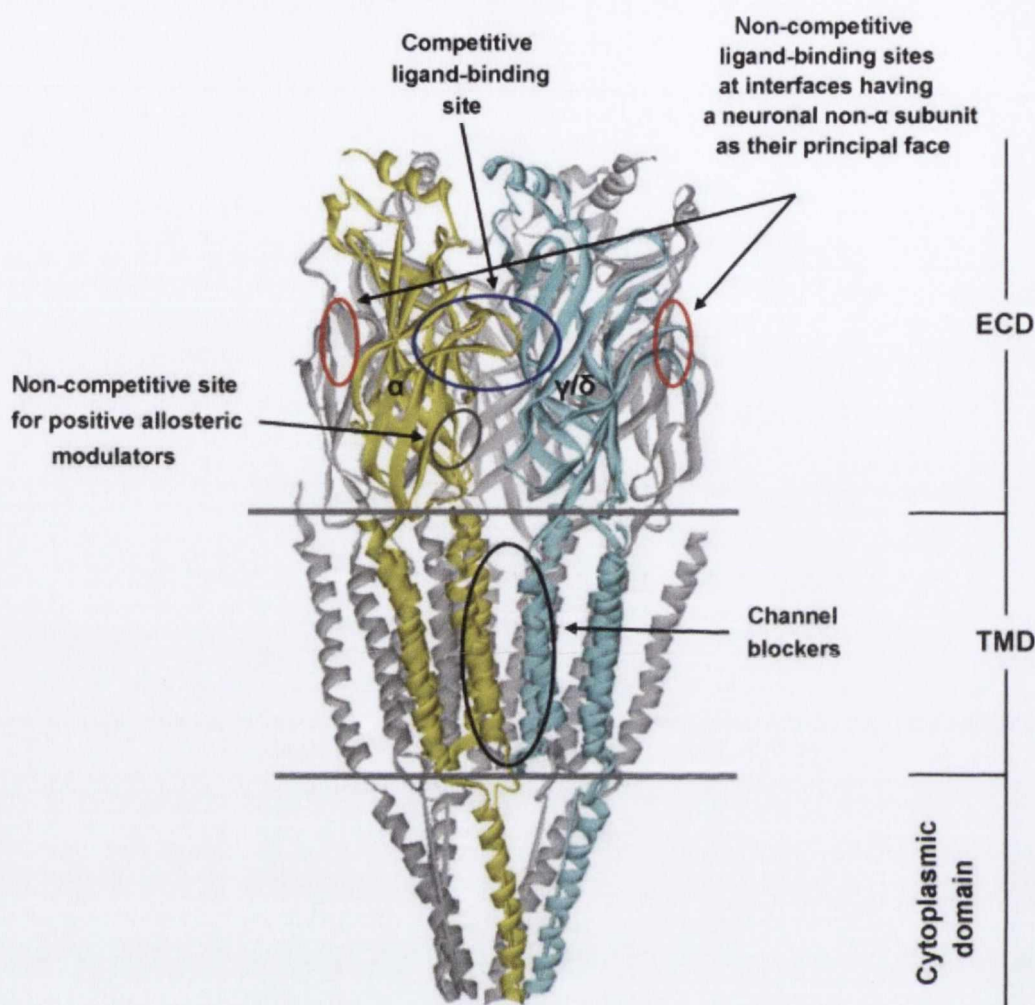


Figure 1-8: Binding sites in the nAChR (extract from Zouridakis, M.; Zisimopoulou, P.; Poulas, K.; Tzartos, S. J. *IUBMB Life* 2009, 61, 407-423).³⁴

In 1986 Giraudat *et al.* undertook an excellent study which first identified the site whereupon channel blocking non-competitive ligands bind within the transmembrane domain. Giraudat achieved this *via* radiolabeled [^3H]chlorpromazine which was shown to compete with phencyclidine, a previously confirmed channel blocker.³⁵ Several studies have since been carried out investigating the binding interactions of channel blockers. These include many well known nAChR inhibitors such as phencyclidine,³⁶ hexamethonium, amantidine³⁷ and QX222,³⁸ which have all been characterised as non-competitive ligands, (Figure 1-9). These compounds operate as channel blockers obstructing the channel pore thus preventing the passage of ions across the cell membrane.

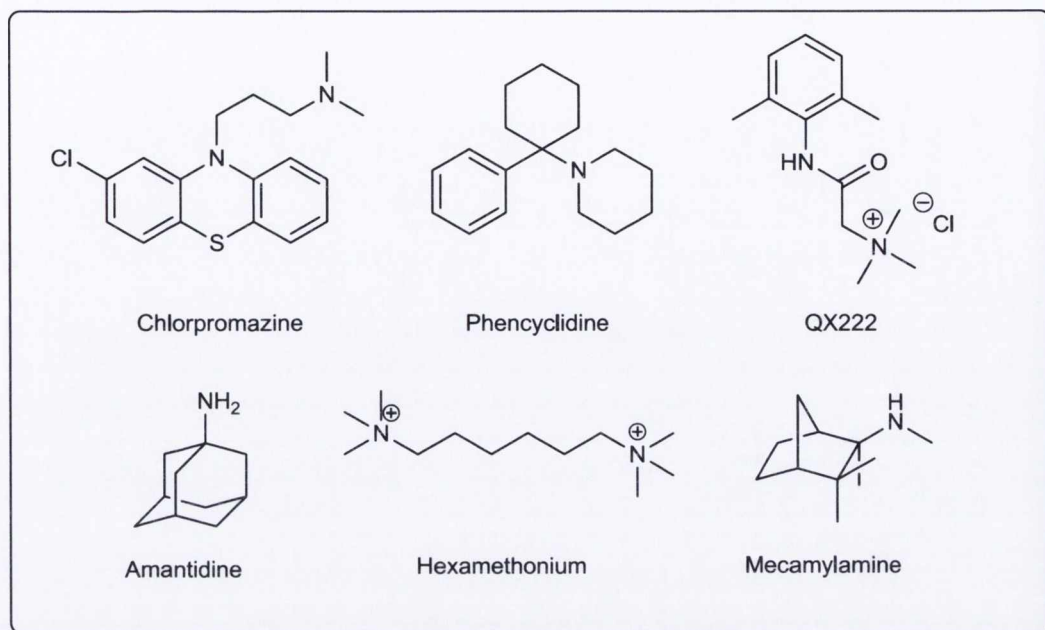


Figure 1-9: Selection of nAChR ligands.

1.1.5 Channel opening and conformational transitions.

Comparison studies of the crystal structures of ligand free AChBP and the corresponding agonist bound AChBPs revealed significant conformational changes in the nAChR-ECD which occur upon agonist binding. Utilising the AChBP from *Aplysia californica* complexed with agonist epibatidine and antagonist α -conotoxin ImI, Hansen *et al.* obtained crystal structures of the complexes which revealed marked rearrangements in the C loop, depicted in Figure 1-10, which differ greatly upon binding of an agonist or antagonist.¹⁸ These structures provide the basis to further define conformational changes occurring at the ligand binding domain of nAChRs. In 2005, Taly *et al.* prepared a three-dimensional model of the $\alpha 7$ nAChR. Analysis suggested channel opening is achieved predominantly by a global symmetrical twist of the quaternary structure of the receptor with opposing rotations for the upper and lower domains.³⁹

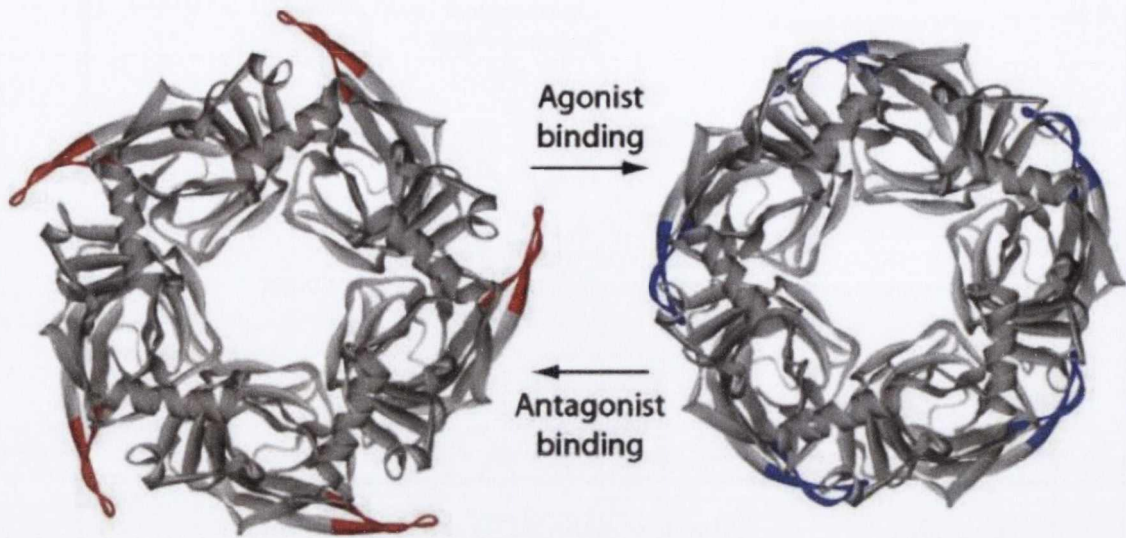


Figure 1-10: Conformation changes observed in C loop upon agonist or antagonist binding (extract from S. Hansen, G. Sulzenbacher, T. Huxford, P. Marchot, P. Taylor and Y. Bourne, *EMBO J.*, 2005, 24, 3635–3646).¹⁸

In 1965 the Monod-Wyman-Changeux model (MWC) was devised to describe allosteric signalling. It states that receptors exist in at least three different interchangeable states in the absence of an agonist. These states are categorised as active or open state (A), resting or closed state (R) and desensitised which is divided into either a fast onset (I) or slow onset state (D). The equilibrium between two states is determined by the difference in free energy of the two states and the kinetic rate for the transition from one state to another is determined by the energy barrier between the two states, activation occurs *via* a rapid transient process while desensitisation of the receptor occurs much more slowly. Once the receptor has reached the desensitised state it has been proposed that it returns to the resting state *via* the active state in such a rapid manner that it does not induce a channel opening response (Figure 1-11, I).^{40,41}

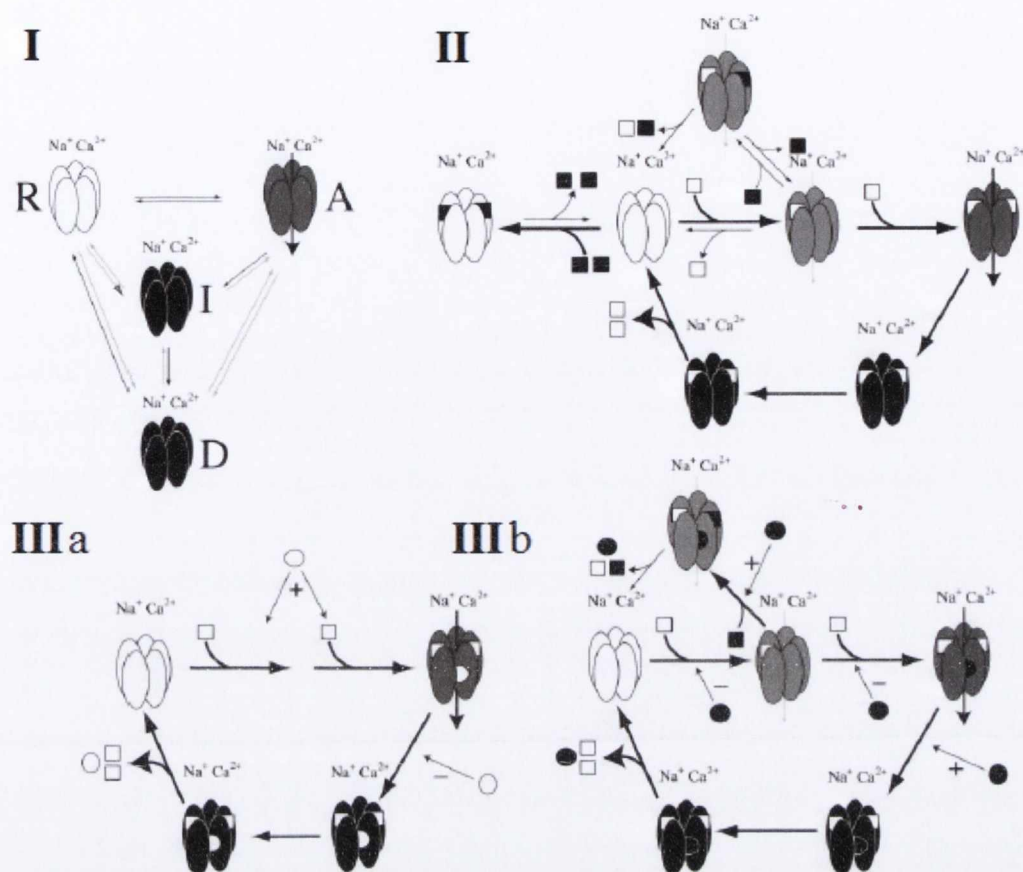


Figure 1-11 MWC model depicting conformational change in nAChRs (extract from Jensen, A. A.; Frolund, B.; Liljefors, T.; Krogsaard-Larsen, P. *J. Med. Chem.* 2005, 48, 4705-4745).⁹

The activity of the receptor in the absence of an agonist has been previously demonstrated in agreement with the MWC model.⁴² In Figure 1-11 the three receptor states are depicted as the following; resting state (white), grey active state (grey) and desensitised state (black). Figure 1-11, II depicts the binding of agonists and competitive antagonists illustrated as squares, to the orthosteric sites present on nAChRs. Agonists display a greater affinity for the active state than for the resting state while antagonists have higher affinities for resting receptor states. Figure 1-11, IIIa illustrates positive allosteric modulators in the form of white circles. These allosteric ligands modulate nAChR signalling by aiding agonist binding or inhibiting desensitisation of the active state. Negative modulators shown in IIIb produce the opposite effect.⁹

1.2 Potential Disease Targets of nAChRs: Addiction.

1.2.1 Addiction.

Addiction is defined by the American Academy of Pain Medicine as a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations.⁴³ As described by the diagnostic and statistics manual of mental disorders 4th edition, addiction presents itself as a combination of behaviours which include drug cravings, lack of control over drug use, development of a tolerance towards the drug, drug withdrawals and compulsive use or continuous use despite harm.⁴⁴ Addiction is a major health problem in contemporary society, it encompasses a vast variety of substances including, nicotine, alcohol, illicit and prescription drugs. Not only does addiction create a deeply negative effect within society it also has huge financial repercussions in terms of health care. It is estimated that providing health services to smokers costs approximately one billion euros each year in Ireland,⁴⁵ while alcohol related problems cost approximately 3.7 billion euro in 2007.⁴⁶ Addictive behaviour relating to gambling⁴⁷ and overeating^{48,49} have also been well documented.

1.2.2 The "reward circuits" of the brain – the dopaminergic pathways.

The brain's reward circuit is a collection of brain regions which regulate behavior by inducing pleasurable effects. It is comprised of two dopaminergic tracts; the mesolimbic and the mesocortical pathways. The mesolimbic pathway begins in the ventral tegmental area (VTA) of the midbrain which then connects to the nucleus accumbens (NAc), and the hippocampus and the amygdala. The mesocortical pathway also begins in the VTA and projects to the prefrontal cortex. These are key components which are involved in the regulation of the reward response and high levels of nAChRs are expressed in these areas.^{50,51}

Dopamine (DA) and the mesolimbic pathway have been shown to be a common factor for the reinforcing properties of most addictive drugs.⁵² Although the dopaminergic tracts are recognised as major elements in addiction the mechanism is still not fully understood on a neurobiological level. It is therefore helpful to delineate the mechanism of action of known addictive drugs. Drugs of abuse are highly diverse and have different acute mechanisms of

action. While the target site or mechanism of action may differ, most addictive drugs of abuse have the common effect that they increase levels of extracellular DA in the limbic regions which include the NAc, resulting in pleasurable sensations, (Figure 1-12).

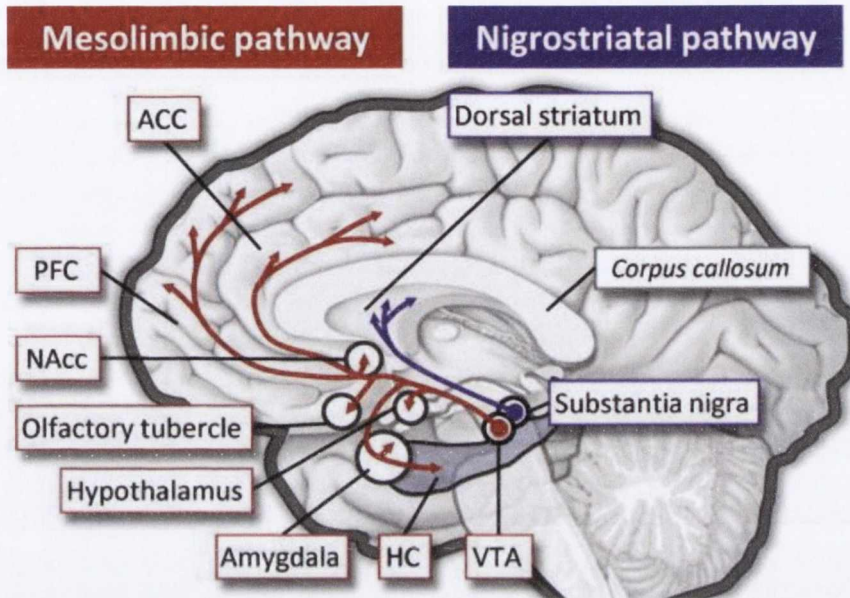


Figure 1-12: Representation of the mesolimbic pathway (extract from L. Perogamvros and S. Swartz, *Neurosci. Biobehav. Rev.*, 2012, 36, 1934-1951).⁵³

1.2.2.1 Nicotine.

Nicotine addiction has repeatedly been concurrent with DA release in the NAc. Within the mesolimbic pathway, nicotine stimulates nAChRs on neurons of the VTA that project to the NAc and release DA, resulting in positive reinforcement.^{54,55} Recent studies of human smokers have shown changes in DA concentration through the use of [¹¹C] carbon radiolabelling which was monitored *via* positron emission tomography (PET). These studies have supported the connection between nicotine addiction and the release of DA in the mesolimbic pathway.⁵⁶ The key to this mechanism seems to be the control of DA release in the NAc by nAChRs in the VTA. As mentioned the action of nicotine in the VTA stimulates DA release in the NAc but it is important to note that the direct introduction of nicotine to the NAc has little effect on DA levels.

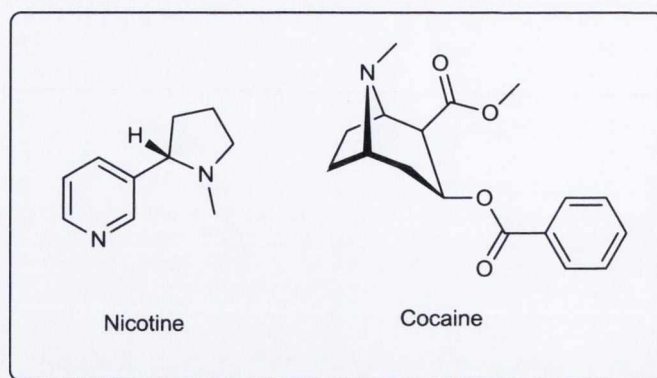


Figure 1-13: Structures of addictive substances nicotine and cocaine.

1.2.2.2 Cocaine.

A study on genetically modified mice, who possessed a mutant dopamine transporter (DAT) has suggested that the presynaptic DAT is the primary target for cocaine's action.⁵⁷ DAT mediates re-uptake of DA from the synaptic cleft and thereby controls the termination of dopaminergic signaling. This transporter binds the extracellular DA and actively pumps it out of the synaptic cleft across the cell membrane. Once inside the presynaptic neuron DA is deposited into storage vesicles.⁵⁸ Cocaine exerts its action by binding to the DAT transporter forming a complex that renders it incapable of performing its function resulting in a prolonged increase in concentration of DA in the synaptic cleft. Cocaine exerts its euphoric effects *via* increased and prolonged levels of extracellular DA brought about by this delay in the termination of dopaminergic transmission, (Figure 1-14).^{59,60}

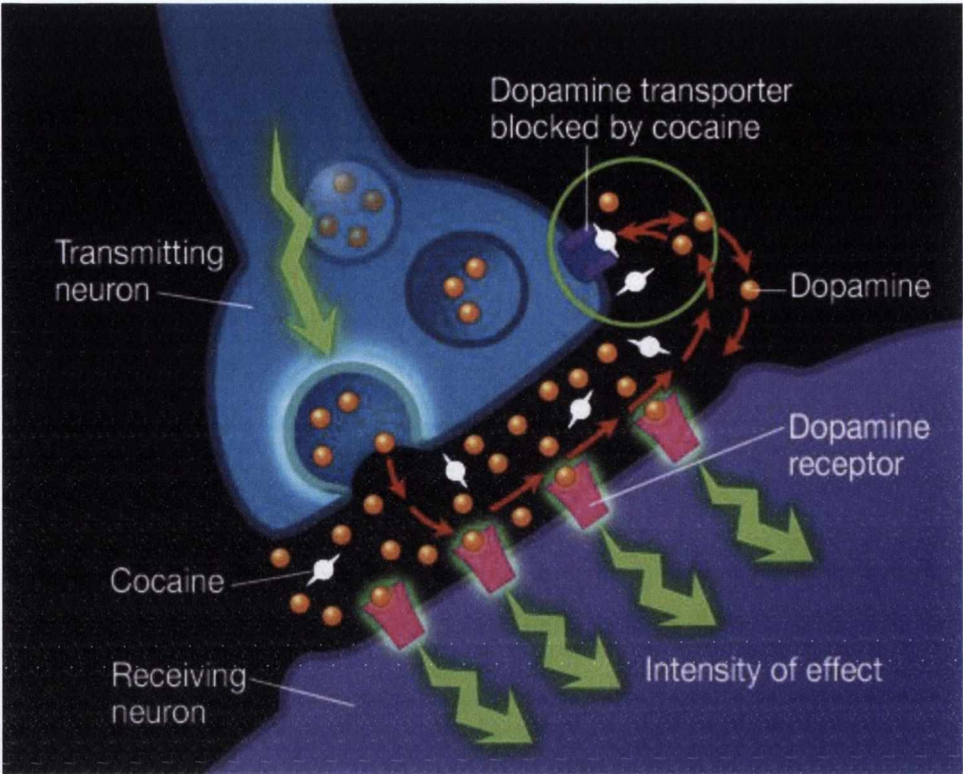


Figure 1-14: Mechanism of action of cocaine (extract from <http://m.drugabuse.gov/publications/research-reports/cocaine-abuse-addiction/how-does-cocaine-produce-its-effects>).⁶¹

1.2.2.3 Opiates - Morphine and Heroin.

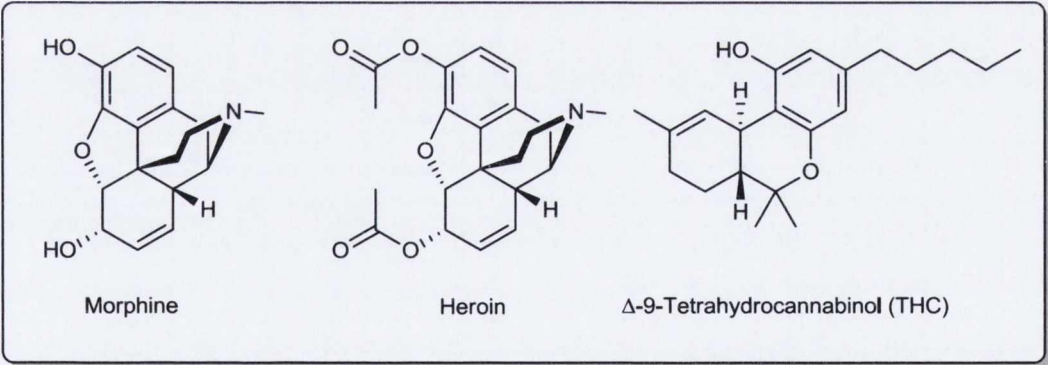


Figure 1-15: Structures of addictive opioid and cannabinoid drugs.

Morphine is a highly addictive and potent opiate analgesic medicine. Administered intravenously morphine crosses the blood brain barrier (BBB) where it binds to presynaptic γ -amino butyric acid (GABA) inhibitory neurons in the VTA. Opiates inhibit these receptors which indirectly increase DA levels in the NAc by preventing the inhibition of dopaminergic

neurons within the VTA. Morphine and cannabinoids such as THC, the major active component of cannabis, also act upon opioid receptors in the NAc.^{62,63} Opiates act on μ receptors on presynaptic GABAergic neurons which inhibits synaptic transmission. Heroin is the 3,6-diacetyl ester of morphine and functions as a prodrug. Injection of the drug avoids first pass metabolism to morphine *via* deacetylation, instead the presence of the diacetyl ester groups increase its lipophilicity and allows it to rapidly cross the BBB, conferring heroin with a greater potency than morphine itself.^{64,65}

1.2.2.4 Amphetamines.

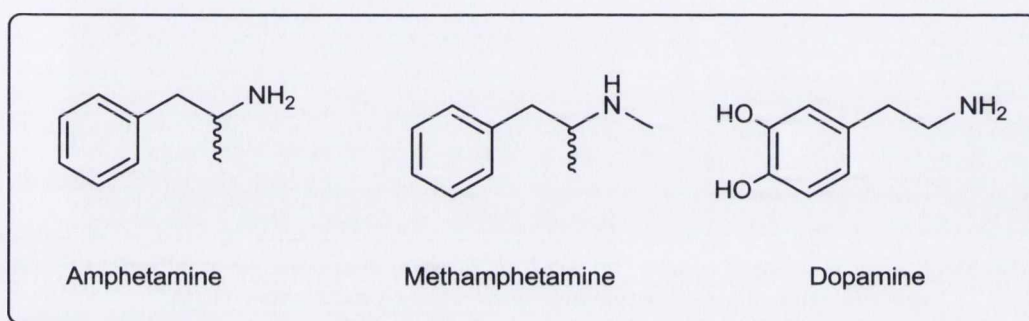


Figure 1-16: Structures of a selection of amphetamine drugs.

Amphetamines are a class of addictive drugs which are similar in structure to DA, (Figure 1-16). They include amphetamine and methamphetamine among others. Like all drugs of abuse amphetamines exert their action by increasing the concentrations of extracellular DA in the brain. Amphetamine can enter the pre-synaptic dopaminergic neuron and induce the release of DA from storage vesicles, which release DA into the nerve terminal. In addition, amphetamine can inhibit monoamine oxidase (MAO), an enzyme in dopaminergic neurons which is involved in the degradation of DA. Finally, amphetamine can bind to the dopamine re-uptake transporter, reversing its action resulting in the transport of DA out of the nerve terminal and into the synapse, (Figure 1-17).⁶⁶⁻⁶⁹

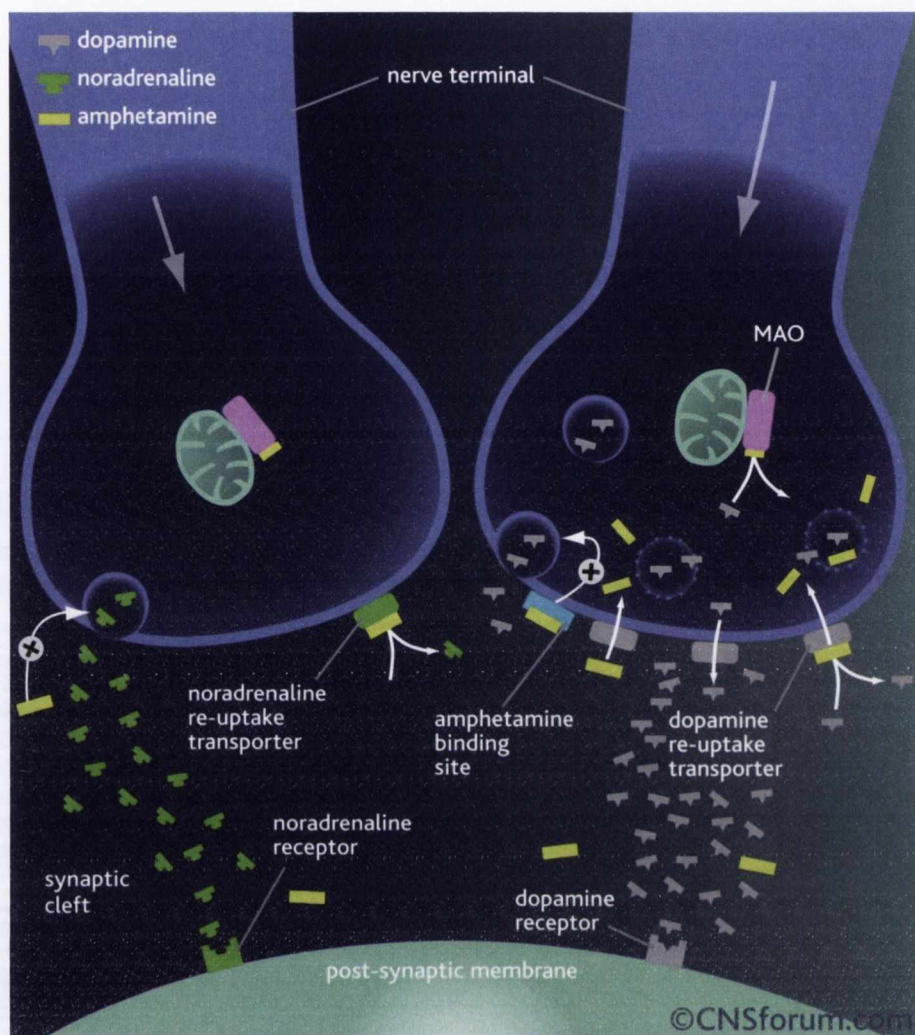


Figure 1-17: Representation of amphetamine mode of action
(extract from http://www.cnsforum.com/imagebank/item/Drug_amphet_high/default.aspx).⁷⁰

1.2.2.5 Ethanol.

The neurological mechanisms that account for alcoholism are poorly understood and a number of neural pathways have been implicated in alcohol addiction. Ethanol is a small molecule and has been shown to act on many different areas within the brain. Ethanol has been shown to act as a positive allosteric modulator of the inhibitory neurotransmitter GABA_A.⁷¹ Human clinical studies utilising PET and a DA receptor radio-ligand [¹¹C]raclopride have shown that the administration of ethanol promotes DA release in the NAc. It is believed that ethanol does not act on DA receptors directly but rather by potentiation of GABA_A receptor function which reduces GABA action in the VTA. This inhibitory action would result in an increase of DA release in the NAc.⁷² Ethanol consumption in rats has also been shown to inhibit NMDA receptors both directly (by acting upon NMDA

receptors) and indirectly *via* GABA_A activation, which account for its sedative effects.⁷³ It is proposed that alcohol exerts stimulant activity by increasing extracellular norepinephrine. A human clinical study has shown that ethanol increases plasma concentrations of norepinephrine by inhibiting its clearance or re-uptake.⁷⁴ Similarly it was observed that the re-uptake of extracellular norepinephrine was inhibited by ethanol.⁷⁵

1.2.3 Theories of the mechanisms of addiction - The reward pathway.

As the mesolimbic pathway has proven to be heavily involved in the reward process it has been implicated in the mechanisms of addiction. While this area remains somewhat ambiguous, research is making progress in understanding molecular and cellular effects of the common effects of addictive substances. As mentioned in the previous section all drugs of addiction evoke DA transmission in the NAc. Furthermore, several illicit drugs have been shown to activate the endogenous opioid and cannabinoid systems within the mesolimbic pathway, which adds to the possibility of a shared mechanism of action.⁷⁶ The positive reinforcement hypothesis proposes that substance dependence and drug cravings are a result of a desire for reward initiated by a drug stimulus.⁷⁷

Chronic drug use will result in continual elevation of DA concentration. The consequences of this are down regulation of DA receptors, contributing to sensitisation and a state of anhedonia.⁷⁸ As a direct result of this the affected individual will require greater quantities of the stimulant in order to maintain these elevated levels of DA. Down regulation of DA receptors and receptors associated with the primary drug target forms the basis of physiological tolerance, reduced drug responsiveness with repeated exposure.^{79,80} Drug withdrawal produces many physical and psychological effects including depression, anxiety, irritability, sweating, tremor, insomnia, hallucinations and anorexia.⁸¹ These symptoms lead to negative reinforcement, whereby drug administration will alleviate an aversive state.⁸²

More recently additional brain regions have been identified that interact with the VTA and the NAc and are involved in the reward process. The hippocampus and amygdala as well as sections of the prefrontal cortex have a contribution to the addiction process. As these brain regions are involved in memory function it has been proposed that some aspect of addiction may involve powerful-circuitry memories.^{51, 76, 82-84} This could help to explain drug relapse, the resumption of drug use and drug seeking behaviour after a prolonged period of abstinence

when associated withdrawal symptoms have passed.⁸⁵ In fact, learned behaviour has been implicated in the mechanisms of addiction. It has been proposed that addictive behaviours are learned in a similar way to normal motivated learning, (Figure 1-18). The development of an addiction is initiated by repeated social use, which leads to habitual use and often repeated relapse due to environmental stressors or cues. At this stage the addicted individual acts compulsively, without making a conscious decision. The behaviour is now learned and is carried out without continual decision making, in a similar manner to opening the refrigerator door when hungry.⁸⁶

Recent research in preclinical models of addiction has identified an impairment in connections from the prefrontal cortex to the NAc. For example, repeated nicotine and cocaine self-administration results in the down regulation of the glutamate-cysteine exchanger in the NAc, this results in glutamate depletion, reducing synaptic plasticity making the re-modelling of the learned addiction behaviour more difficult.⁸⁷ *N*-Acetylcysteine, a prodrug of cysteine, activates the reduced number of exchanger proteins thus increasing glutamate concentrations in the locality. It has also been shown to reduce cocaine seeking behaviour in rats.⁸⁸ In addition, a double-blind placebo-controlled study investigating the effects of *N*-acetylcysteine in cocaine dependent patients found that *N*-acetylcysteine reduced both the desire to use and the interest in cocaine measured by physiological response to cues.⁸⁹ While these theories provide insight into the mechanism of addiction there is still much that remains ambiguous.

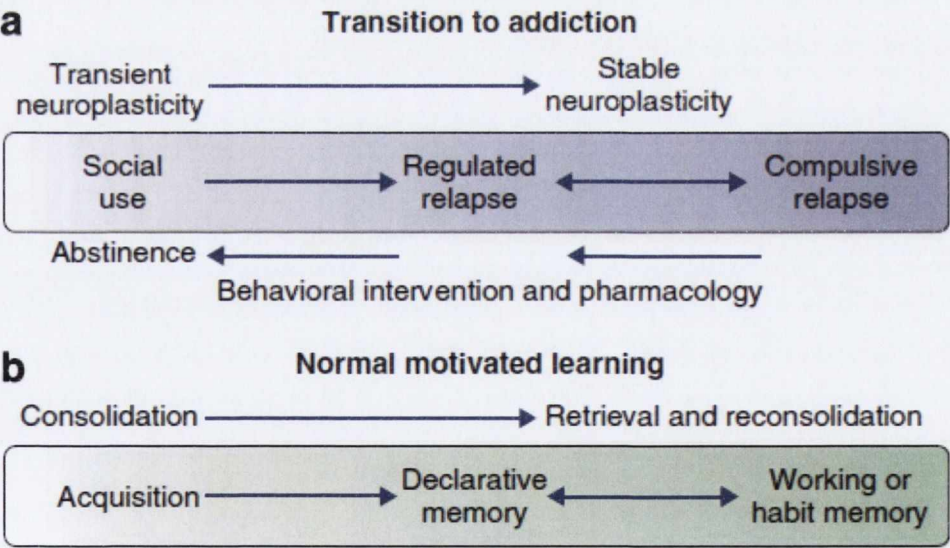


Figure 1-18: Motivated learning compared to development of addiction (extract from P. W. Kalivas and C. O'Brien, *Neuropsychopharmacology*, 2008, 33, 166-180).⁸⁶

1.2.4 Nicotine addiction.

Nicotine is one of the most commonly used addictive substances and is associated with the leading cause of preventable death. Currently, there are an estimated 1.3 billion smokers across the world, a shocking 84% of them in developing countries.⁹⁰ On a global scale, tobacco use is responsible for more than 5 million deaths each year, and current trends indicate that tobacco use will lead to more than 8 million deaths annually by 2030.⁹¹ In the United States, smoking is responsible for approximately one in five deaths per annum which equals 443,000 deaths per year. An estimated 49,000 of these smoking-related deaths are the result of second-hand smoke exposure.⁹² Figures released by the World Health Organisation (WHO) state that tobacco was responsible for 100 million deaths in the 20th century⁹³ and a recent report has warned that unless current trends are reversed tobacco use may kill more than 1 billion people in the 21st century.⁹⁴ On average, smokers die 13 to 14 years earlier than non-smokers due to smoking related disease⁹⁵ and approximately half of all tobacco users will die as a direct result of smoking.⁹³ Disturbingly in Ireland figures show that the occurrence of tobacco related cancer are rising, according to the National Cancer Registry the risk of developing lung cancers will increase by 59% for men and 136% for woman by 2020.⁹⁶ Despite recent advances in the development of new pharmacological therapies for nicotine addiction the rate of relapse in affected individuals remains alarmingly high. During the past two decades, rates of successful smoking cessation aided by nicotine replacement therapies in controlled clinical trials appear to be declining.⁹⁷

Extensive research has been undertaken in the area of nicotine dependence in both human and animal clinical studies, however the complete picture is not yet known. It is known that nicotine directly activates VTA DA neurons *via* activation of nAChRs on those neurons resulting in the release of DA in the NAc. Nicotine also stimulates presynaptic nAChRs on glutamatergic nerve terminals, increasing the concentration of Glutamate within the VTA resulting in the activation of DA neurons.^{54,55,98} A number of studies have directly implicated nAChRs as an integral part of the process of nicotine addiction but the evidence is sometimes contradictory and probably indicates that a number of processes are involved. The administration of the nAChR antagonist MA to male Wistar rats chronically treated with nicotine produced marked withdrawal effects as well as a reduction in DA release in the NAc. This adds weight to the argument that nicotine withdrawal, in this case modulated by systemic

MA, is regulated by neuronal nAChRs.⁹⁹ A complementary study also utilising Wistar rats has shown that treatment with non-competitive MA or the competitive selective $\alpha 4\beta 2$ antagonist dihydro- β -erythroidine (DH β E), (Figure 1-19), resulted in a dose dependent reduction of nicotine self-administration.¹⁰⁰ The mGluR5 antagonist, 2-methyl-6-(phenylethynyl)pyridine (MPEP), (Figure 1-19) also achieved a reduction in the self-administration of nicotine addiction rats, thus supporting evidence that nicotine action at glutamatergic neurons increases DA release adding to DA mediated nicotine dependence.¹⁰¹

Classically it has been thought that high affinity nAChRs containing the $\beta 2$ subtype are those influential in nicotine addiction. However, the use of knockout mice has identified a number of other nAChR receptor subtypes involved in the addiction process. Piciotto *et al.* found that nicotine self-administration and nicotine induced DA striatal transmission are completely unobserved in $\beta 2$ subunit knockout mice.¹⁰² Interestingly a more recent study by Levin *et al.* concluded that the effects of nicotine administration in $\alpha 7$ knockout mice were not initially observed as in the case of the $\beta 2$. However over a longer period of time the $\alpha 7$ knockout mice developed an emergent decline in nicotine consumption.¹⁰³ In addition, radio-labelled [³H]nicotine, [³H]epibatidine and [³H]cystine binding are not detected in most brain regions of $\beta 2$ or $\alpha 4$ knockout mice.¹⁰⁴ A reduction in nicotine sensitivity has also been observed in $\alpha 5$ knockout mice.¹⁰⁵ Interestingly, it was found that $\alpha 5$ nAChR subtypes are not involved in the rewarding effects of nicotine, instead, $\alpha 5$ nAChRs regulate the reward-inhibiting effects that counter the reward-facilitating effects of nicotine, thus helping to control the concentration of nicotine that induces a reward response.¹⁰⁶ In 2012, Leslie and co-workers investigated the high affinity selective $\alpha 3\beta 4$ antagonist AT-1001, (Figure 1-19), and found that it significantly reduced nicotine self-administration in rats thus demonstrating the $\alpha 3\beta 4$ subtypes involvement in drug seeking behaviour.¹⁰⁷ Obviously the situation is complex but some compounds such as varenicline, bupropion and MA have anti-addictive properties, (Figure 1-20).

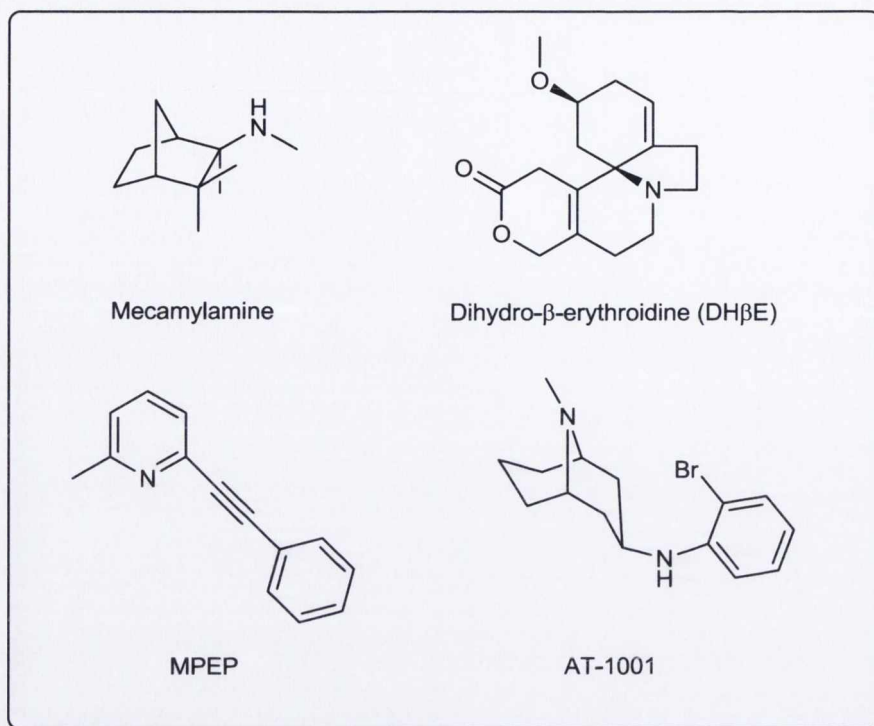


Figure 1-19: Structures of nAChR and mGluR5 antagonist.

1.2.4.1 Current therapeutics available.

Varenicline has proven to be an effective and successful treatment for nicotine addiction. Marketed by Pfizer under the trade names Champix and Chantix, in Europe and the US respectively, it was approved by the FDA in May 2006.¹⁰⁸ Varenicline has shown high affinity toward the $\alpha 4\beta 2$ nAChRs where it acts as a partial agonist and as a potent full agonist at $\alpha 7$ nAChRs. It also acts upon $\alpha 3\beta 4$, $\alpha 3\beta 2$ and $\alpha 6$ containing receptor subtypes although with considerably less potency.¹⁰⁹ As a partial agonist it both reduces the cravings for, and decreases the pleasurable effects of, nicotine if consumed.

Bupropion was initially researched and marketed as an anti-depressant, but was subsequently found to be effective as a smoking cessation aid. In 2007 it was approved for use as a smoking cessation therapy by the FDA and was marketed by Glaxosmithkline under the trade name Zyban.¹¹⁰ Bupropion exerts its anti-depressant action *via* dual dopamine and norepinephrine re-uptake inhibition.¹¹¹ It also acts as a non-competitive nAChR antagonist and blocks nicotine action on a number of receptor subtypes including $\alpha 3\beta 2$, $\alpha 4\beta 2$, $\alpha 7$ ¹¹² and $\alpha 3\beta 4$.³⁶

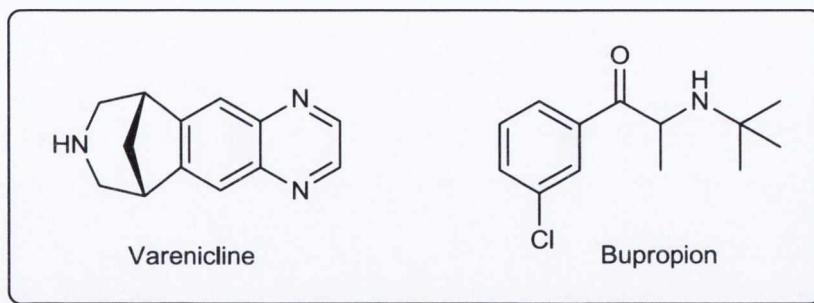


Figure 1-20: Structures of smoking cessation therapies varenicline and bupropion.

In 2006, prior to FDA approval, a randomised, double-blind, placebo-controlled phase III clinical trial with 1027 participants was conducted over a 12-week treatment period.¹¹³ The objective was to determine the efficacy and safety of varenicline for smoking cessation compared with bupropion and a placebo. Varenicline significantly out-performed both bupropion and the placebo in terms of abstinence from smoking. During the last 4 weeks of treatment, i.e. weeks 9-12, 43.9% of participants receiving varenicline were continuously abstinent from smoking compared with 17.6% who received the placebo and 29.8% of those receiving bupropion. During the last four weeks of treatment and a follow up period from weeks 9-24, 29.7% of participants in the varenicline group remained abstinent compared with 13.2% receiving placebo and 20.2% receiving bupropion. After 52 weeks of treatment, 23% receiving varenicline group were continuously abstinent while only 10.3% in placebo group and 14.6% in the bupropion group remained so. The continued decline in abstinence observed from weeks 12-52 is a stern reminder of the complexity of addiction. Perhaps combinational therapies addressing multiple targets may provide a more advantageous approach. Other considerable shortcomings include the many and, in some instances severe side effects associated with these drugs. Adverse effects associated with varenicline¹¹⁴ include nausea, abnormal dreams, insomnia, taste perversion, flatulence, dyspepsia, constipation and headache. Serious psychiatric adverse effects have been linked with varenicline; these include behavioural changes, depressed mood and suicidal thoughts and behaviours. Adverse effects associated with bupropion¹¹⁴ include insomnia, dry mouth, headache, nausea and anxiety. The most shocking side effects associated with bupropion since its release include seizures and psychiatric disorders. Observational studies of bupropion have suggested that the frequency of seizures occurs in approximately 0.1–0.4% of recipients. In 2009 the FDA reported an association between bupropion use for smoking cessation and neuropsychological disorders such as suicidal thoughts and tendencies and the ideation of suicidal behaviour.¹¹⁵

While great strides have been made in the field of pharmacological therapies beyond simple nicotine replacement therapies (NRTs), there still remains the grave issue of serious and in some cases life threatening side effects. The role of selectivity in anti-addiction pharmaceuticals is crucial in order to provide safer and more effective treatments. MA has shown anti-addictive properties against a range of addictive compounds, including nicotine, morphine and ethanol among others. It is our hope that by probing the structure of MA we may discover a more selective and more efficacious treatment for addiction.

1.2.5 Cocaine addiction.

Unfortunately cocaine use and dependence has become a common and substantial health problem. In 2009, it has been estimated that approximately 43% of all drug related emergency hospital admissions in the U.S. was due to cocaine use.¹¹⁶ However, there has been a noted improvement in the prevalence of cocaine dependence in the United States. Between 2006 and 2011, the number of individuals exhibiting cocaine dependence declined from 1.7 million to 0.8 million.¹¹⁷ According to tentative estimates published by the WHO there were approximately 15.9 million cocaine users across the globe in 2008.¹¹⁸ To date the FDA has not approved any pharmacotherapies for cocaine abuse.

It has long been speculated that cocaine's blockade of the DAT transporter is integral to its rewarding and hence intensely addictive effects, however, evidence suggests that nAChRs may have some involvement in the process. In 2000, Panagis *et al.* found that blockade of the $\alpha 7$ nAChRs in the VTA induced by methyllycaconitine (MLA), a selective $\alpha 7$ nAChR antagonist, resulted in the attenuation of the reward facilitating effect of systemic cocaine.¹¹⁹ A later study carried out by Zoli and co-workers determined that the inhibition of $\alpha 7$ and $\beta 2$ subunits decreased cocaine induced DA response.¹²⁰ Administration of MLA, (Figure 1-21) the $\alpha 7$ selective antagonist and $\beta 2$ selective antagonist DH β E were ineffective when individually co-administered with cocaine. However, dual administration with cocaine significantly reduced cocaine elicited DA release. These findings suggest that the $\alpha 7$ and $\beta 2$ subunits are necessary in the production of cocaine induce DA release. The pre-treatment of adult male Swiss mice with either MA or the non-selective antagonist MRZ 2/621, (Figure 1-21) significantly reduced cocaine self-administration. In fact, no self-administration was observed in MA treated mice and the effects were not dependant on dosage.¹²¹ Administration

of MA also prevents an increase in the frequency of self-administration in rats, a trait which is a principal characteristic of addiction in humans.¹²² Encouragingly, MA has also produced a reduction in cue-induced cravings in human cocaine addicts.¹²³

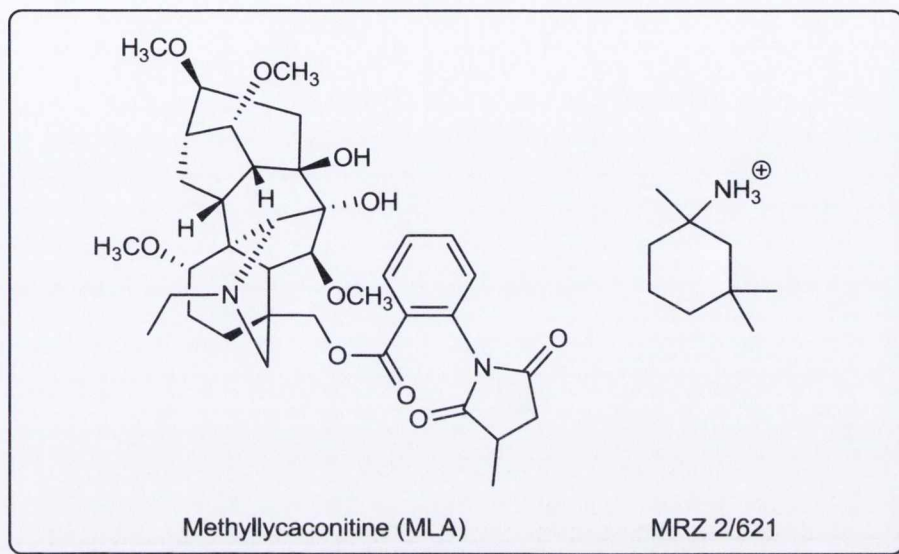


Figure 1-21: Structures of nAChR antagonists MLA and MRZ 2/621.

1.2.6 Ethanol addiction.

According to the WHO alcohol abuse is the third largest risk factor in the global burden of disease and is responsible for 2.5 million deaths each year.¹²⁴ In 2011 approximately 17.4 million people in the U.S. required treatment for an alcohol abuse problem.¹²⁵ It is estimated that there are in the region of 140 million people suffering from alcoholism across the globe.¹²⁶

Ethanol has been shown to activate the mesolimbic dopaminergic system *via* excitation of DA neurons in the VTA.¹²⁷ Once again nAChRs seem to play a role in the addictive process. Typically, ethanol consumption is higher in smokers than in non-smokers¹²⁸ and ethanol dependence is estimated to be 10 times more common among smokers.¹²⁹ It is postulated that many drug users are smokers to enhance pleasurable effects. Larson *et al.* showed that ethanol consumption increases the concentration of extracellular ACh in the VTA of the rat and suggested that this interaction with nAChRs may be the cause of the increased DA transmission in the NAc.¹³⁰ Several animal studies have reported a marked reduction in self-administration of ethanol upon treatment with MA.^{131,132} In addition administration of MA in ethanol dependent mice produced an attenuation in the symptoms of withdrawal.¹³³

The “drinking in the dark” (DID) paradigm is used as a model of binge-drinking behaviour in mice. Utilising this model Hendrickson and co-workers found that MA dose-dependently reduced ethanol consumption while the peripheral antagonist hexamethonium produced no noteworthy effect.¹³⁴ In human clinical studies MA was shown to diminish the euphoric and stimulant effects of ethanol^{135,136} and was also found to reduce the self-reported desire to consume ethanol in healthy male and female non-smoking social drinkers.¹³⁶

In 2007 Steensland *et al.* investigated the effects of varenicline in the modulation of ethanol consumption and ethanol seeking behaviour in rats employing three different animal models of drinking. Encouragingly, ethanol seeking and consumption was reduced in all three models, which implies that $\alpha 2\beta 4$ nAChR subtypes may be involved in ethanol dependence.¹³⁷

Following these findings further investigation was undertaken to investigate whether varenicline would reduce alcohol consumption and cravings in humans. In a double-blind, placebo-controlled study comprising of twenty non-alcohol dependent heavy smokers, varenicline significantly reduced alcohol self-administration compared to the placebo.¹³⁸ Participants were treated with varenicline for seven days prior to a priming dose of alcohol. Participants were subsequently allowed to self-administer for a period of two hours thereafter and could consume up to an additional 8 drinks. On average, those receiving varenicline consumed less than half of the alcohol consumed by those in the placebo group. Collectively these findings heavily implicate nAChRs in the process of ethanol dependence and further research in this area could warrant potential novel treatments for the disorder.

1.2.7 Cannabis, opioids and amphetamine addictions.

A recent report published by EMCDDA outlines the prevalence of illicit drug use in European adults who have engaged in illegal drug use at least once in their lifetime.¹³⁹ Cannabis is by far the most commonly used illegal substance in Europe. Based on surveys carried out between 2001 and 2009 it is estimated that 78 million Europeans have used cannabis, 12.5 million have taken amphetamines and 1.3-1.4 million have partaken in opioid use.

In studies of morphine and methamphetamine self-administration in rats, co-administration of other nAChR antagonists such as dextromethorphan and 18-

methoxycoronaridine, (Figure 1-22), with MA diminished self-administration at doses that were ineffective if administered alone. At present only one common action exhibited by MA, 18-methoxycoronaridine and dextromethorphan has been identified, antagonism at $\alpha 3\beta 4$ sites. Hence it was suggested that $\alpha 3\beta 4$ subtypes may be implicated in drug seeking behavior.¹⁴⁰

Collectively these works clearly demonstrate that neuronal nAChRs play an influential role in the addiction process. Their involvement in the reward system has been heavily documented in all drugs of abuses and the use of nAChR modulators such as varenicline and bupropion to ease addictive behaviours highlights the potential therapeutic benefit of nAChR antagonists or partial agonists.

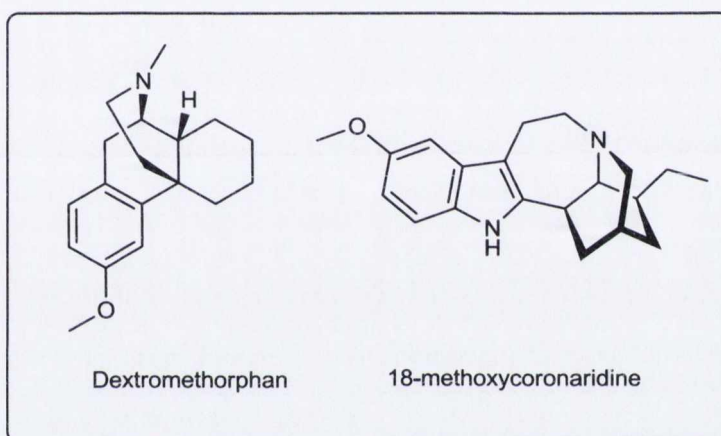


Figure 1-22: Structures of nAChR receptor antagonists.

1.3 Potential disease targets of nAChRs: Depression.

1.3.1 Depression.

DSM IV has classified major depression as a mental disorder which can present many symptoms including an all-encompassing low mood accompanied by low self-esteem, loss of interest or pleasure in normally enjoyable activities, weight loss, insomnia, fatigue, diminished ability to think or concentrate or suicidal thoughts.⁴⁴ According to the WHO, depression is classed as the leading cause of disability affecting as many as 350 million people across the world, meaning it is more common than heart disease or AIDS. It is a major contributor to the global burden of disease as measured by the disability adjusted life years or DALYs; to be more precise it is the sum of years of potential life lost due to premature mortality and the

years of productive life lost due to disability.¹⁴¹ The disease greatly reduces quality of life and creates economic problems incurred through employment losses and health-care costs. There is an increased occurrence of suicide among depressed patients and the disease also affects cardiovascular health. As a result it has been predicted that by the year 2020, depression will become the second leading cause of death after cardiovascular disease.¹⁴²

1.3.2 The Monoamine hypothesis and the development of anti-depressants.

The monoamine hypothesis proposes that the symptoms of depression are related to a deficiency of neurotransmitters, (Figure 1-23), such as serotonin (5-HT) and noradrenaline (NA) in the brain.¹⁴³ The theory was arrived at somewhat serendipitously during the 1950s when certain medicines were monitored for their ability to effect the moods of patients being treated for other ailments. For example, an American biochemist Bernard Brodie found that reserpine (a blood pressure medicine) often triggered depression as a side effect. Reserpine was also shown to deplete the brain's stores of NA and 5-HT.¹⁴⁴ Concurrently iproniazid, the first monoamine oxidase inhibitor, was being investigated for anti-tubercular activity in a group of 92 terminally ill tuberculous patients. It was noted that the moods of the patients were elevated and a small group exhibited levels of mania.¹⁴⁵

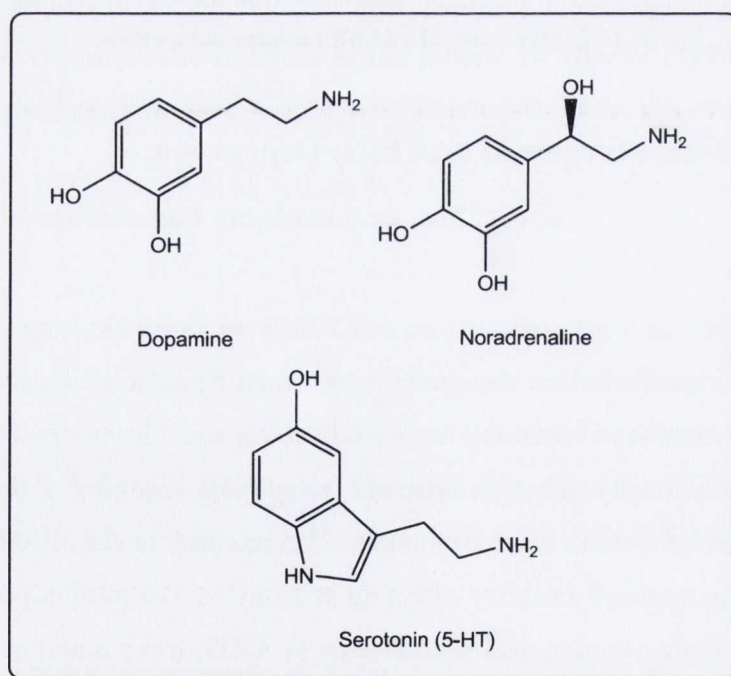


Figure 1-23: Structures of neurotransmitters.

After the discovery of monoamine oxidase inhibitors came another chance discovery, the tricyclic anti-depressants (TCAs). The anti-depressive action of imipramine, the first TCA, was discovered by Roland Kuhn while investigating the compound as a potential treatment for schizophrenia. It was first marketed in 1959 and became an established treatment for MDD. During the 1960s an array of TCA were developed displaying modifications at the dibenzazepine core, these include amiptryptiline, desipramine and trimipramine, an imipramine metabolite.¹⁴⁶ Unfortunately the use of TCAs gave rise to a wide range of side effects including hypotension, drowsiness, reduced gut motility, urinary retention, blurred vision, nausea, anorexia, stomatitis, fatigue and headache.¹⁴⁷ TCAs have a narrow therapeutic index which has resulted in both intentional and unintentional poisoning. The grave fatality associated with these drugs has been well documented and their cardiovascular and neurological toxicity has resulted in their decline as a contemporary treatment for major depression.¹⁴⁸

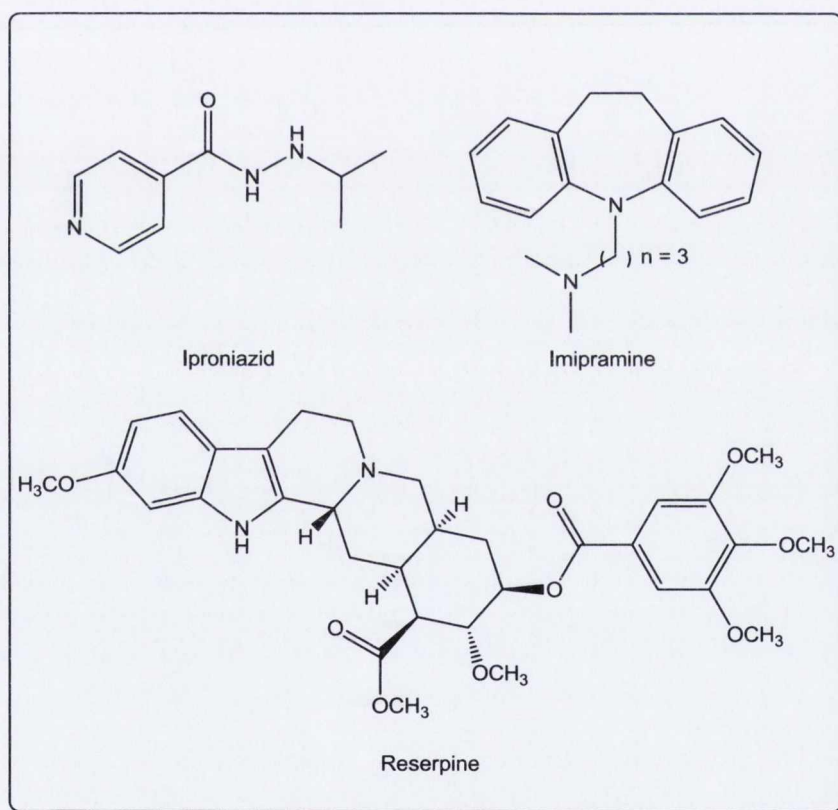


Figure 1-24: Structures of early anti-depressants.

Selective serotonin reuptake inhibitors (SSRIs) and selective noradrenaline reuptake inhibitors (SNRIs) are the most commonly prescribed treatment for MDD at present. These anti-depressants exert their action by preventing the re-uptake of extracellular 5-HT and NA

into the nerve terminal by binding to their respective transporter proteins.^{149,150} MDD is described as a distinct change in mood accompanied by several other psychophysiological changes which last for a period of at least 2 weeks including disturbances in sleep, reduced appetite, or sexual desire, anhedonia and suicidal thoughts or tendencies.¹⁵¹ The first SSRI marketed was fluoxetine (Prozac®), it was introduced to the market in 1988 and quickly became the most commonly prescribed anti-depressant, (Figure 1-22). Prozac, and other SSRIs exhibit a considerably more favourable side effect profile, with a safer overdose risk, reduced cardiovascular side effects and a greater ease of tolerability and therefore patient compliance, than that of their TCA counterparts. After the success of Prozac which has been used to treat over 54 million patients, many new SSRIs were developed during the following decade.^{152,153} The pharmaceutical market for anti-depressants became awash with SSRIs and as a result it virtually eliminated the market for older anti-depressants like the TCAs. Unfortunately as with the TCAs there are a great many negative aspects associated with SSRIs as a treatment for MDD. For instance, it is estimated that approximately 40% of patients prescribed SSRIs do not receive therapeutic relief from the symptoms of depression. This observation was based on the percentage of patients who did not achieve a 50% reduction in depressive symptoms following 6–8 weeks of treatment. Another rather worrying aspect of the SSRIs is that of efficacy. Approximately only 35–45% of patients taking these anti-depressants become totally free of symptoms or reach a remission from the disease; SSRIs achieved 35% remission rate while the SNRI venlafaxine achieved 45%.¹⁵⁴ A meta analysis of the efficacy and tolerability of TCAs and SSRIs found TCAs to be more effective than SSRIs, however, more patients receiving TCAs stopped treatment due to adverse side effects.¹⁵⁵

The most recent generation of anti-depressants are the SNRIs, these drugs have been shown to be superior to SSRIs in preventing the recurrence of depressive episodes in patients suffering from major depression and are often prescribed to patients who failed to respond to SSRI treatment. While these clinical results are promising, there are still populations of patients that do not adequately respond to SSRI or SNRI treatment.^{142,154} Mirtazapine is classified as a NA and specific serotonergic anti-depressant. It exerts its action by blocking α_2 -adrenergic receptors to enhance adrenergic and serotonergic neurotransmission. Unlike SSRI and SNRI anti-depressants, Mirtazapine, (Figure 1-25), has no activity as a re-uptake inhibitor. Comparative studies have shown that Mirtazapine is a more efficacious treatment for the symptoms of depression than other SSRIs and SNRIs including duloxetine and fluoxetine.^{156,157} Interestingly, Mirtazapine has recently been investigated as a potential anti-

addiction therapy and has shown promise as a treatment for alcohol, cocaine, methamphetamine and opioid addictions.¹⁵⁸ It is important to note that the symptoms of depression differ greatly among patients and the fact that there are large percentages of patients who do not receive therapeutic benefit from clinical anti-depressants would imply that it may not be a singular disease. It is possible that the pathology of depression differs from person to person and hence there may be no single all encompassing treatment for the disorder.

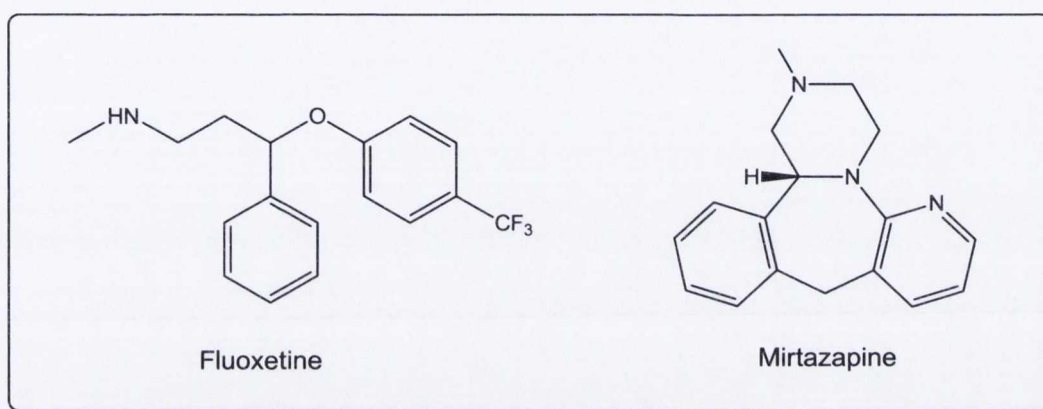


Figure 1-25: Structures of anti-depressants fluoxetine and mirtazapine.

While the monoamine hypothesis is the most popular neurophysiological explanation of the mechanisms of depression there are some discrepancies and contradictions which challenge the theory.¹⁵⁹ One such instance is that it often takes from two up to three weeks after commencing treatment for any anti-depressive effect to be observed, especially in the case of SSRIs. According to the monoamine hypothesis, an increase in levels of neurotransmitters in the brain should provide relief from symptoms of depression. Stahl proposed that the delayed therapeutic effects of SSRIs may be due to a delay in neurochemical adaptations.¹⁴⁹ For example, the number of receptors in depressed patients are lower than in healthy patients, the administration of SSRIs and SNRIs increase the concentrations of neurotransmitters in the synapse. This leads to an increase in the number of receptors over a period of time, which could explain the delay in symptomatic relief. Santarelli *et al.*¹⁶⁰ suggested that this delay in therapeutic effect was due to slow neurochemical and structural changes within the brain and that anti-depressants may exert their activity *via* neurogenesis in the hippocampus. Mice administered with various anti-depressants including the SSRI fluoxetine have shown an increase in neurogenesis in the dentate gyrus of the hippocampus. Irradiation of the hippocampus region of the brain prevented the neurogenic and behavioural

effects of two anti-depressants fluoxetine and imipramine. In 2011, Surget *et al.* demonstrated that chronic stress in mice reduces hippocampus neurogenesis and that treatment with SSRI fluoxetine reverses this effect. It was also observed that in both irradiated and non-irradiated mice corticotropin releasing factor 1 (involved in stress response circuits) antagonist SSR125543 also reversed the reduction in neurogenesis in mice exposed to chronic mild stress.¹⁶¹

Another contradiction to the theory which cannot be overlooked is that there are many examples of anti-depressants currently in clinical use whose pharmacological profiles do not fit the monoamine hypothesis. Tianeptine, (Figure 1-26), is a clinically used anti-depressant which exerts its anti-depressive action by modulation and repair of damage done to brain structure and neuroplasticity by chronic stress and mood disorders such as depression. It also enhances DA release in the nucleus accumbens. It shows no affinity for neurotransmitter receptors and does not inhibit monoamine oxidase A or B. Tianeptine has been shown to decrease extracellular levels of 5-HT and also reduces the number of transporter sites in the dorsal raphe nucleus.¹⁶² A multinational double-blind study comprised of 387 patients suffering from depression or bipolar disorder compared the efficacy and safety of anti-depressant tianeptine with the SSRI fluoxetine. The study was conducted over a six week period and results showed tianeptine to be equivalent to fluoxetine in both efficacy and safety profile.¹⁶³

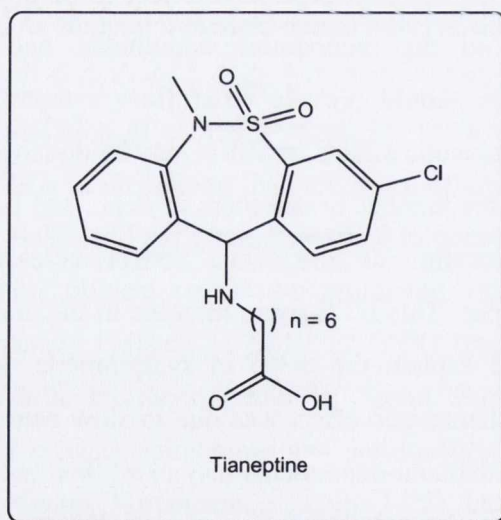


Figure 1-26: Structure of anti-depressant tianeptine.

1.3.3 Depression and the Mesolimbic Pathway.

The mesolimbic pathway is associated with the rewarding effects of food, sex, and drugs of abuse. Given that the major symptoms of depression include a marked disinterest in anything pleasurable, reduced motivation (often an aversion to activity), and reduced energy levels, it was proposed by Nestler *et al.* that the dopaminergic mesolimbic system plays an important role in the pathophysiology and symptomatology of depression.¹⁶⁴ It would be of great interest therefore, to carry further research into potential new anti-depressants which exert their function on the dopaminergic region of the brain, thus providing a novel treatment which could be useful as a monotherapy or in combination with SSRIs or SNRIs.

Despite advances in drug discovery anti-depressants are still hampered by multiple inadequacies that need to be addressed. It is clear that there is an immense need for a more selective and efficient treatment for the symptoms of depression. TCAs have been crippled by dangerous and often fatal side effects. While SSRIs and SNRIs do possess anti-depressant activity, however, they are not effective for all patients. New anti-depressants with distinct mechanisms of action are greatly needed. The majority of recent research in this field has focused mainly on studies of current commercial SSRI anti-depressant drugs. Nevertheless, in order to probe the mechanisms of depression and develop more selective anti-depressants, the depressive states of patients should be more thoroughly studied. Importantly, we still do not fully understand the pathophysiology of the disease. Given that many patients do not respond to SSRIs or SNRIs, it certainly indicates that there is scope for the development of new anti-depressants that may interact with other neurotransmitter systems namely DA, in isolation or in combination with 5-HT or NA.

1.3.4 nAChRs, Nicotine and their role in Depression.

One common trait shared by the vast majority of clinically useful anti-depressants is the inhibition of nAChRs. Tricyclic anti-depressants, SSRIs and SNRIs are all antagonists of nAChRs. While the monoamine hypothesis is still the most commonly accepted theory to explain the mechanisms of depression there is mounting evidence that other factors are also important, in particular the ability of SSRIs to increase neurogenesis. It has also been proposed that hypercholinergic neurotransmission is associated with depressive moods and

may be mediated through excessive nAChR activation and that it is by inhibition of these receptors that anti-depressants exert part of their activity.¹⁶⁵

Over the past twenty to thirty years many independent studies have been carried out investigating the antagonistic potential of classic TCAs. Both imipramine and desipramine, (Figure 1-27), were shown to potently inhibit nicotine induced ATP secretion from bovine chromaffin cells,¹⁶⁶ while amitriptyline, (Figure 1-27) also produced a blockage of the ion channel which was monitored by the decrease in amplitude of end plate potential at the NMJ of frog skeletal muscle.¹⁶⁷ In more recent years selective monoamine re-uptake inhibitors have been also shown to inhibit nAChRs. Interestingly, fluoxetine (Prozac) displayed a very similar level of inhibition to MA in an *in vitro* study of antagonistic effect on nAChRs present in rat hippocampal slices.¹⁶⁸ A similar study performed by Hennings *et al.* investigating the ability of a group of TCAs and SSRIs, (Figure 1-27), to inhibit nAChRS in rat hippocampal slices and utilising MA as a reference, found noteworthy levels of antagonism in all cases, while desipramine and nisooxetine produced significant levels of inhibition which match that of MA, Table 1-1.¹⁶⁹

Table 1-1: Inhibition of nAChRs by selected TCAs and SSRIs.

	IC ₅₀ (μM)	Conc. range (μM)	Threshold* conc. (μM)
Mecamylamine	0.19	0.1-10	0.3
Fluoxetine	0.57	0.1-10	1
Desipramine	0.36	0.3-10	0.3
Nisoxetine	0.59	0.1-10	0.3
Citalopram	0.93	0.1-30	1
Nomifensine	1.84	0.1-10	3

* The lowest concentration that produced significant inhibition.

One very interesting example is bupropion, an atypical anti-depressant which displays a weak re-uptake potential on both DA and NA while having no notable effect on the reuptake of 5-HT.¹⁶⁵ Similarly to MA, bupropion is a potent nAChR antagonist and is currently marketed for smoking cessation.^{36,170}

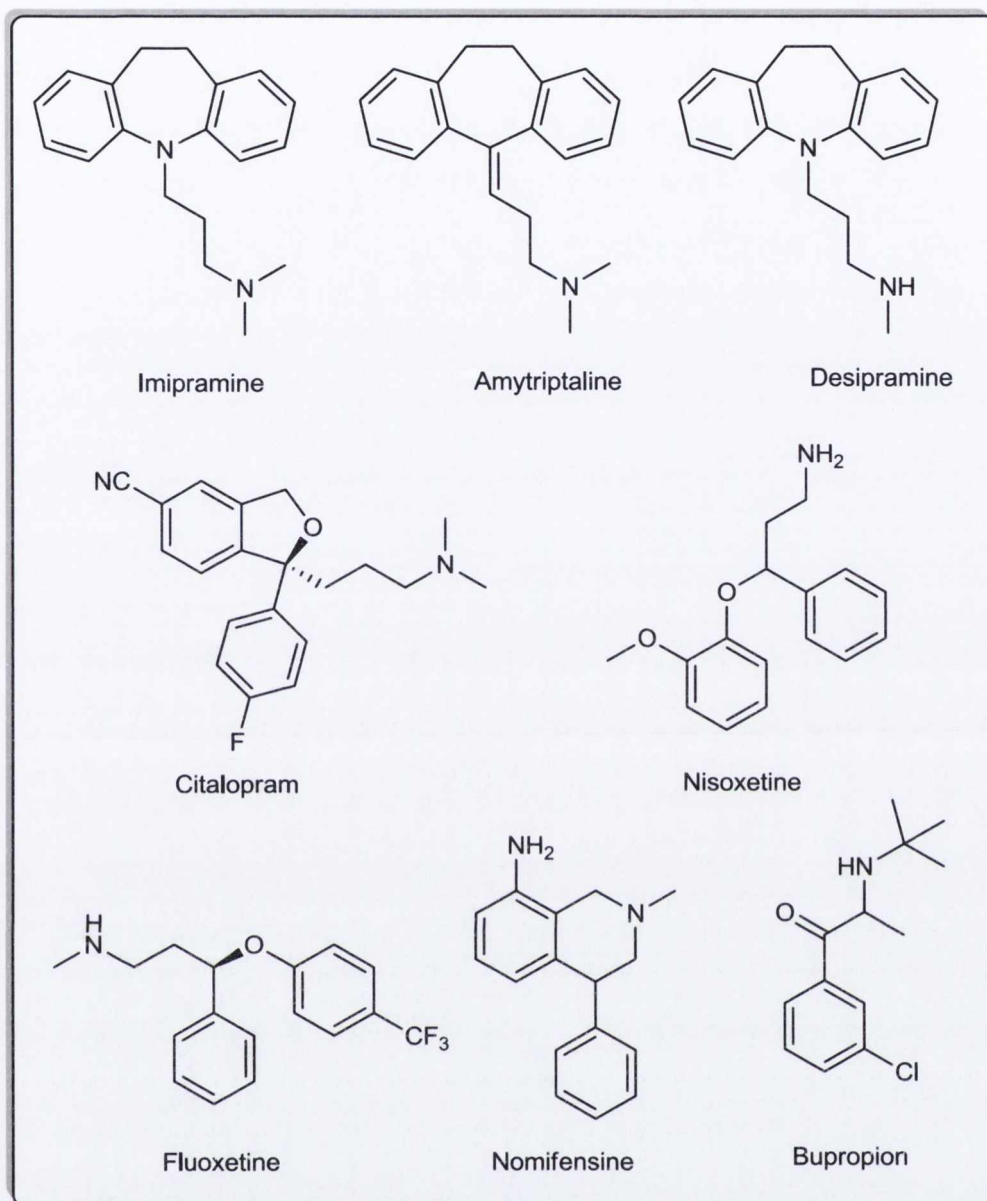


Figure 1-27: A selection of anti-depressants which inhibit nAChRs.

1.3.5 Nicotine and depression, the cholinergic theory?

Nicotine has a long-standing clinical association with depression. Several animal studies have been conducted which have shown an irrefutable association between nicotine and depression.^{171,172} A study investigating the effects of nAChR agonists SIB-1508Y and nicotine in comparison with clinically used anti-depressants imipramine, and fluoxetine, has shown reduced learned helplessness in the learned helplessness rat model of depression.¹⁷³ In 1967 Seligman first described the learned helplessness theory.^{174,175} In the learned

helplessness experiment an animal is induced into a helpless state which is a mimic of clinical depression, by repeatedly exposing the animal to an adverse stimulus which it cannot escape. Once the animal exhibits the “helpless” behaviour the effect of various stimuli or medication can be investigated in order to reverse this condition. The theory was further developed to a somewhat more humane method, namely the forced swim test (FST).¹⁷⁶ In this model, animals, usually rodents, are subjected to two trials during which they are forced to swim in a container filled with water. The first trial is carried out over a period of 15 minutes and after 24 hours, a second 5 minute trial is performed. The test animal eventually ceases all attempts to struggle or swim and remains motionless, the time the animal remains in this state is recorded. All anti-depressants reduce the time that the test animal remains motionless. This is currently the most commonly used model for animal depression. However, this model has not been free from controversy. Criticisms of the test refer to its dissimilarity of depression in humans. Short-term stress applied to normal rodents differs greatly from human depression and the ability of anti-depressants to produce a rapid response after single doses marks a complete contrast with the requirement of chronic anti-depressants' use in order to generate a therapeutic response in humans.¹⁷⁷

Epidemiological studies have confirmed that psychiatric patients were considerably more likely to smoke than those who did not suffer a mental disorder.¹⁷⁸ Several works have identified an association between nicotine dependence and depression. In cross sectional studies a greater prevalence of major depression was found in smokers when compared with never-smokers, and nicotine dependent smokers are more than twice as likely as non-dependent smokers to have suffered major depression.^{179,180,181} Interestingly, the administration of transdermal nicotine to non-smoking depressed patients in a double-blind, placebo-controlled trial produced a significant reduction in symptoms.¹⁸² Taking these findings into account, it has been hypothesised that nicotine has anti-depressant effects and that smoking is an attempt to self-medicate the depressive symptoms.^{183,184}

This poses a great contradiction due to the fact that many known anti-depressants are nAChRs antagonists. It has also been postulated that increased cholinergic activity is associated with symptoms of depression. This hypothesis was inspired by reports that cholinesterase inhibitors induced depressive symptoms.^{185,186} In 2009 Andreasen *et al.*,¹⁸⁷ carried out an excellent study encompassing a wide range of nicotinic agonist and antagonists. In order to fully investigate whether the anti-depressant-like effect of nAChR modulation is

induced by activation, desensitisation or inhibition of central nAChRs they systematically compared the effects of non-selective and selective nicotinic agonists and antagonists in two different tests for anti-depressant activity. Tests were carried out utilising female medical research institute mice in both the FST and the tail suspension test (TST). Interestingly, results confirmed absolutely no anti-depressant activity for any of the nAChR agonists tested. Comparatively, all centrally active nAChR antagonists tested showed anti-depressant-like profiles. Encouragingly, further examination of the results revealed that MA proved to be more efficacious than two anti-depressants currently in clinical use, namely the SSRI citalopram and the NRI reboxetine. One explanation for this discrepancy in the literature is that different animal model tests may display vastly different sensitivity to pharmacological manipulation. Another important observation is that exposure to nicotine leads to desensitisation and inactivation of nAChRs in addition to activation. Desensitisation is a reversible state in which the receptor displays a reduction in response during a period of prolonged agonist application, receptors subsequently recover after agonist removal.^{188,189} Hence prolonged nicotine exposure could in fact act as an antagonist, preventing further receptor activation *via* desensitisation. Collectively, these findings suggest that further research into antagonism of central nAChRs may well produce novel anti-depressant therapeutics.

1.4 Other nAChR therapeutic applications.

Nicotinic acetylcholine receptors have been implicated in an array of diseases and disorders of the central nervous system. As previously discussed they are heavily involved in mechanisms of addiction and depression but there is also evidence to support their involvement in a number of other serious conditions including Tourette Syndrome, Alzheimer's and Parkinson's diseases and schizophrenia.

1.4.1 Parkinson's disease.

Parkinson's disease (PD) is a slowly progressive neurodegenerative disorder that is characterised by massive cell death of DA neurons within the substantia nigra, in particular affecting the ventral component of the pars compacta.¹⁹⁰ The three principal characteristics of PD are rigidity, bradykinesia and the presence of a tremor at rest.¹⁹¹ The prevalence of PD in persons 65 years of age has been calculated to be approximately 1.8%, which increases to

2.6% for those aged 85 to 89 years.¹⁹² Studies have also shown that the disease is more prevalent in men than in women.¹⁹³ While the average age of onset of this disorder is estimated to be in the early-to-mid 60s.¹⁹⁴

In 1817 James Parkinson first described PD as a "Shaking Palsy." Later, in 1919 Konstantin Tretiakoff reported that the substantia nigra was the main cerebral structure affected by the disease in post mortum examinations of the affected brains.¹⁹⁵ It wasn't until the late 1950s that DA was discovered to play a role in the symptomology of the disease, largely due to the work of Arvid Carlsson. Hornykiewicz later discovered a major depletion of DA in the striatum of PD affected patients.¹⁹⁶ The administration of L-Dopa (a precursor of DA which crosses the BBB) to PD sufferers gave dramatic effects, lessening the symptoms of bradykinesia.¹⁹⁷ The most common treatment of PD today is a combination therapy consisting of L-Dopa and L-Dopa decarboxylase inhibitors for example carbidopa, (Figure 1-28), which is given prior to L-Dopa and does not cross the BBB, inhibiting only peripheral dopa decarboxylation.¹⁹⁸ This enzyme is found in the liver, intestines, kidneys as well as the brain and hence without enzymatic inhibitors 95% of the dosage of L-Dopa is metabolised before it crosses the BBB. These inhibitors prevent the metabolism of L-Dopa in the peripheral system, hence enhancing the therapeutic benefits of L-Dopa.¹⁹⁹

Although L-Dopa remains the most successful therapy to date, it is limited by debilitating side effects such as dyskinesias and unfortunately only provides symptomatic relief but does not prevent disease progression.^{200,201} The nicotinic cholinergic system is one that is becoming an attractive target for further investigation due to increasing evidence of the involvement of nAChRs in PD and its presence in the striatal dopaminergic system.²⁰² Several epidemiological studies have revealed that there is a marked decreased in occurrence of PD among smokers.^{203,204} Administration of nicotine to PD affected rats significantly reduced L-Dopa induced dyskinesias.²⁰⁵ Additionally, two acetylcholinesterase inhibitors namely donepezil and rivastigmine, (Figure 1-28), have been shown to help alleviate the symptoms of PD related dementia.^{206,207} To conclude, the connection between nicotine and a reduced risk of development of PD in conjunction with the presence of nAChRs in the dopamine rich striatal region suggest that a nAChR agonist may prove to be an appealing novel treatment for PD.

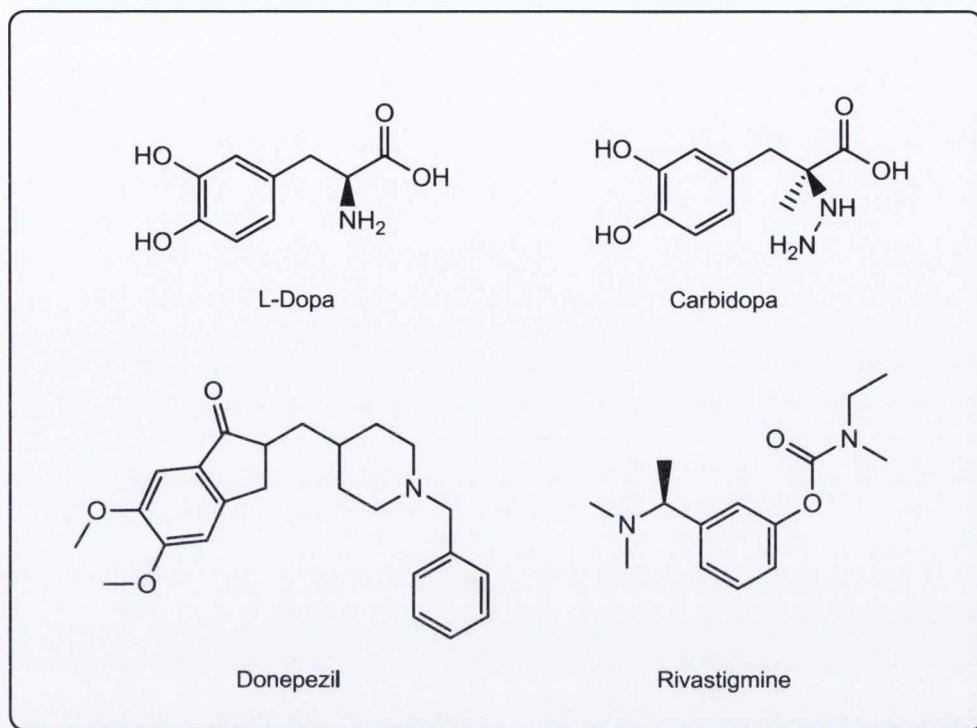


Figure 1-28: Current therapeutics for the treatment of PD.

1.4.2 Alzheimer's Disease.

Alzheimer's Disease (AD) is a progressive neurodegenerative disease of the CNS characterised by gradual cognitive decline, due to destruction of nerve cells and neural connections in the cerebral cortex of the brain and a significant loss of brain mass.²⁰⁸ AD is currently the most common cause of age related dementia and the prevalence of the disease increases with age. According to a 2012 report published by the Alzheimer's Association, AD affected approximately 5.4 million Americans in 2012. Of those suffering from the disease 4% were over 65 years of age, 6% were 65 to 74 years, 44% were 75 to 84 years and 46% were 85 years or older.²⁰⁹ The disease was named after a German psychiatrist, Alois Alzheimer who first described that disorder in 1906.²¹⁰ In 2006 the estimated global prevalence of AD was 26.6 million.²¹¹ Disturbingly the prevalence of the disease is increasing, it is estimated that the number of people affected by the disease will double every 20 years reaching approximately 81.1 million by the year 2040.²¹²

The cause of AD is not known however, it is characterised by the formation of lesions of β -amyloid plaques and neurofibrillary tangles as well as a reduction in cholinergic activity and reduced brain mass.²¹³ A reduction in cholinergic activity is a marked characteristic of

AD.²¹⁴ Acetylcholinesterase inhibitors such as donepezil,²¹⁵ galantamine²¹⁶ and rivastigmine²¹⁷ have all been approved for the management of the symptoms of AD. Nicotine has also been shown to help improve cognitive function in AD affected patients. Patients receiving the transdermal nicotine patch were found to have significantly improved performance in attention tasks in a double-blind placebo-controlled study.²¹⁸ Newhouse *et al.* studied the effects of nAChR antagonist MA on normal healthy patients. Administration of the antagonist resulted in significant cognitive impairment which were observably similar to symptoms of dementia. It was also noted that there is an age-related increase in sensitivity to nicotinic blockade.²¹⁹ In a more recent study, AD affected mice receiving chronic nicotine showed a significant reduction in the density of β -amyloid plaques.²²⁰

Studies have shown that nicotine and nicotinic agonists at $\alpha 4\beta 2$ and $\alpha 7$ nAChRs improve learning and memory.^{221,222} Imaging studies utilising isotopic ligands ¹²⁵I- α -bungarotoxin and ³H-cytisine to radiolabel $\alpha 7$ and $\alpha 4\beta 2$ nAChRs, have elucidated the high density locations of these receptors in the hippocampus region of the brain, an area which has important memory and learning functions.²²³ These receptors have been shown to be involved in long term potentiation (LTP), which is involved in the cellular mechanism of memory and learning.²²⁴ Animal studies investigating the effects of the partial agonist AR-R17779, (Figure 1-29), which is selective for $\alpha 7$ nAChRs displayed an improvement in scopolamine-induced deficits in social recognition.²²⁵ The $\alpha 7$ nAChR selective agonist AZD-0328, (Figure 1-29), developed by AstraZeneca has been shown to augment the release of cortical dopamine and improve learning and attentional processes in animal studies.²²⁶ AZD-0328 entered phase II clinical trials in 2008, unfortunately the drug was not expected to meet its targets and was subsequently discontinued.²²⁷

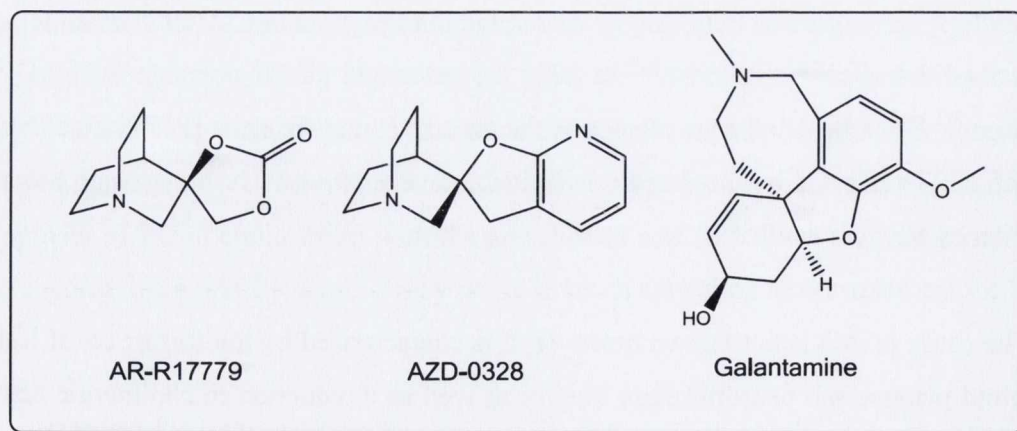


Figure 1-29: nAChR agonists and acetylcholinesterase inhibitors investigated as treatments for AD.

1.4.3 Schizophrenia.

Schizophrenia is described by the DSM IV as a chronic, debilitating mental disorder characterised by perturbations in cognition which include delusions, hallucinations, disorganised speech, catatonic behaviour, apathy and poor social functioning.⁴⁴ The prevalence of schizophrenia has been estimated to affect approximately 0.33 - 0.72% of the population and no significant differences have been observed in the occurrence of the disorder among men and women.²²⁸ However, the age of onset of the schizophrenia differs depending on gender, the average age for men is 18 while on average symptoms appear in women at 25.²²⁹ A review of prevalence studies of the disorder has identified significant disparity in differing populations.²³⁰

Exceptionally high rates of tobacco smoking have been recorded in schizophrenic patients.²³¹ De Leon and Diaz conducted a thorough analysis of epidemiological data of populations of patients who smoke from various different countries across the globe. Their results revealed extraordinarily high rates of smoking among schizophrenic patients and found the average current smoking rate to be 62% of schizophrenic patients. It was also observed that patients with schizophrenia are approximately 5.3 times more likely to be current smokers than those in the general population.²³² One of the many theories proposed to explain the high rates of tobacco consumption is due to an attempted "self-medication," in which schizophrenic patients manage their symptoms by compensating for deficits in cholinergic transmission.²³³ Disturbances in cholinergic transmission have been implicated in schizophrenia. Post mortem examinations of patients have reported elevated levels of choline acetyltransferase in several areas of the brain including the hippocampus and NAc.²³⁴ Furthermore, a study employing magnetic resonance spectroscopy identified increased levels of choline in schizophrenic patients compared with healthy volunteers.²³⁵

$\alpha 7$ nAChRs have recently been implicated in the symptoms of schizophrenia. A series of human and animal investigations has suggested that altered expression and function of the $\alpha 7$ nAChR may be responsible for the auditory sensory gating deficit characterised in schizophrenia patients.²³⁶ Post mortem examinations of the frontal cortex of schizophrenic patients revealed a 40% reduction of $\alpha 7$ nAChR subunits when directly compared to normal healthy brains in age matched controls.²³⁷ These findings maintain the supposition that a deficit of the nAChR $\alpha 7$ subunit in the frontal cortex might be involved in the

pathophysiology of schizophrenia. A double-blind placebo-controlled clinical trial investigating the effects of varenicline, an $\alpha 7$ nAChR agonist, on the symptoms of smoking and non-smoking schizophrenic patients found that varenicline produced a reduction in the sensory gating deficit in schizophrenic patients.²³⁸

A number of current treatments in clinical use for the treatment of symptoms of schizophrenia are active at $\alpha 7$ nAChRs. Clozapine, (Figure 1-30), an atypical antipsychotic drug, normalises deficient inhibitory auditory processing in schizophrenic patients has been shown to do so in mice by means of a activation of $\alpha 7$ nAChRs.²³⁹ GTS-21, (Figure 1-30), an alkaloid derived from anabaseine found in marine worms is a partial agonist at the $\alpha 7$ nAChR and a weak competitive antagonist at $\alpha 4\beta 2$ and 5-HT₃ receptors. This compound has been shown to improve auditory gating in mice *via* $\alpha 7$ nAChR activation.²⁴⁰ Its clinical use as a potential treatment for the symptoms of schizophrenia was examined in a double-blind phase II clinical trial. Thirty-one schizophrenic patients received either GTS-21 at two different doses or a placebo. No significant improvement between the placebo and GTS-21 was observed at the lower dosage. However at higher dosage patients displayed an improvement in negative symptoms that are generally resistant to treatment with dopamine antagonistic antipsychotic drugs.²⁴¹ Galantamine, (Figure 1-30), is a reversible competitive cholinesterase inhibitor²⁴² which is used in the treatment of Alzheimer's disease.²³⁶ It has also been shown to act as a positive modulator at $\alpha 7$ nAChRs.²⁴³ Recently it has been investigated as a potential therapy for schizophrenic patients. In a combination study, schizophrenic patients receiving risperidone, (Figure 1-30), were treated with galantamine or placebo. Patients who received a combination treatment of risperidone (a 5-HT/D₂ antagonist) and galantamine exhibited an improvement in cognition, attention and delayed memory.²⁴⁴

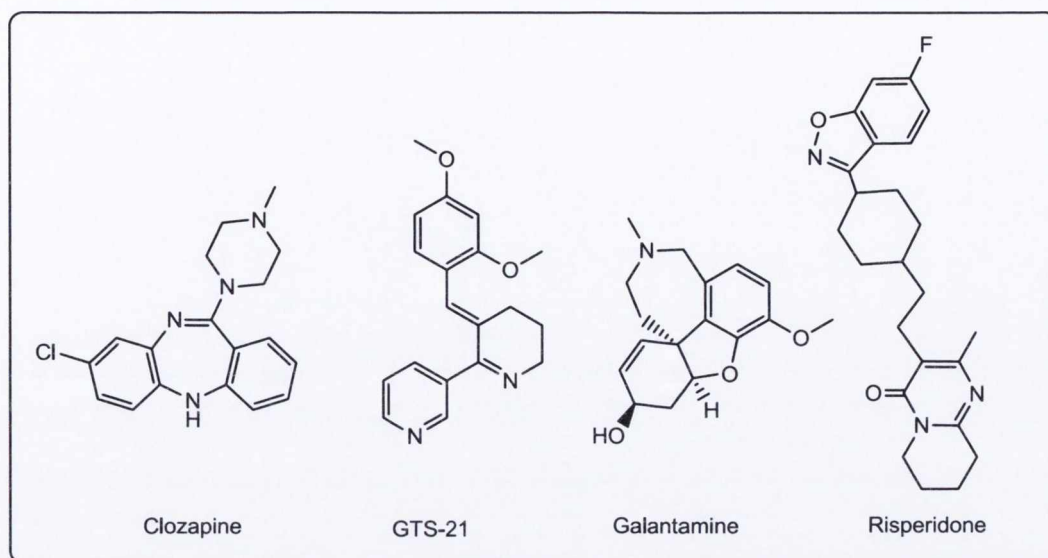


Figure 1-30: Therapies investigated for the treatment of schizophrenia.

1.4.4 Tourette syndrome.

Tourette syndrome (TS) is a neurological disorder characterised by repetitive, involuntary movements and vocalisations called tics that first manifest in childhood²⁴⁵ and is classified by the DSM-IV as a disorder displaying multiple motor tics, and at least one phonic tic, which are present for more than one year.⁴⁴

Although its pathogenesis is not yet known, studies suggest that nicotine may aid the reduction of symptoms of TS. Sanberg *et al.*²⁴⁶ conducted a series of human clinical trials which demonstrated that nicotine gum increased the efficacy of haloperidol, a typical treatment for Tourettes and a DA receptor antagonist. Administration of nicotine gum alone resulted in a decrease in the frequency of tics however, the benefits were short lived as the gum was only effective during chewing. In order to lengthen the duration of action, a combination therapy consisting of transdermal nicotine and haloperidol, was shown to radically reduced the frequency and severity of symptoms when compared to haloperidol alone.²⁴⁷ A clinical study conducted on 13 TS patients showed that the treatment with MA produced a reduction in the severity of both motor and vocal symptoms, evaluated using the Yale Global Tic Severity Scale.²⁴⁸ Interestingly, it was also noted that patients reported an improvement in mood which included both a reduction in aggression and irritability. Unfortunately, a larger double-blind placebo-controlled trial consisting of 61 patients investigating the potential of MA as a monotherapy for the treatment of Tourette syndrome

found that while it was well tolerated in patients, MA it did not appear to be an effective treatment for the symptoms of TS.²⁴⁹

1.5 Mecamylamine. (MA)

1.5.1 A brief history.

MA (Inversine ®) is a non-selective, nicotinic acetylcholine receptor (nAChR) antagonist. Our interest in MA was prompted by the broad potential therapeutic range of the drug. It has previously been employed as an anti-hypertensive treatment and research has shown other applications in many diseases.

MA was the first orally available anti-hypertensive agent and was developed by Merck in the 1950s as a ganglionic blocker with clinically significant hypotensive actions. It was used in millions of subjects prior to the development of β blockers. The major advantages of MA as a therapeutic agent include exceptional oral efficacy, extremely high absorption from the gastrointestinal tract, rapid onset and long duration of action.²⁵⁰ One of the foremost advantages MA possessed over other anti-hypertensive medicines at the time such as trimethaphan, hexamethonium and pentolinium was its excellent bioavailability. While other anti-hypertensives were not absorbed well from the gastrointestinal tract, MA was almost completely absorbed. An important aspect of our interest is that MA readily crosses the blood brain barrier (BBB) where it acts as an antagonist at nAChRs.²⁵¹

MA was first marketed by Merck in 1954 and was distributed in both 2.5 mg and 10 mg tablets. In 1984 the 10 mg tablet was discontinued. Although the distribution statistics of MA during its greatest period of drug usage (1954-1960) are unavailable it is known that by the end of MAs commercial lifespan with Merck & Co more than 50 million tablets had been sold between 1966 and 1998.²⁵¹ In 1998 Merck ceased production of MA and sold the manufacturing rights to Layton Bioscience Inc., who in 2000, reintroduced the 2.5 mg tablet as a treatment for moderately severe to severe hypertension.²⁵² In 2002 the rights were sold to Targacept who in conjunction with AstraZeneca investigated its activity as a treatment for MDD.^{253,254}

1.5.2 Therapeutic effects of Mecamylamine.

Interest in MA waned after the introduction of alternative anti-hypertensive medication. However in recent years curiosity regarding this potential therapeutic agent has been reinvigorated because of the research which has indicated its broad therapeutic potential which comprises a vast and varied list of diseases including addiction and depression.

Human studies have shown that the combinative treatment of MA with the nicotine patch have a substantial improvement in rates of abstinence for smoking cessation versus that of the nicotine patch alone. In a study of 48 volunteers, the abstinence rate of those who received the combination treatment was 37.5% compared with 4.2% of those who received the nicotine patch alone.²⁵⁵ The administration of MA with other anti-addictive compounds, such as bupropion, as a combination treatment to nicotine addicted rats showed a significant decrease in the level of nicotine self-administration.²⁵⁶ Administration of MA to male Wistar rats two hours after receiving a dose of nicotine induces withdrawal-like symptoms.²⁵⁷

It has been reported that low doses of MA significantly reduce cue-induced craving and the desire to use cocaine in human cocaine addicts. Participants were required to abstain from smoking 9.5 hours prior to testing. It was also observed during testing that in addition to reducing cocaine craving, MA also produced a moderate reduction in tobacco withdrawal before cocaine cue testing. This was noted by a reduction in the levels of self-reported tobacco withdrawal.¹²³ MA perfused directly into the VTA of Wistar rats *via* reversed microdialysis antagonised the nicotine evoked release of DA in the NAc and a significant reduction in self-administration was observed.¹³² MA also reduced self-administration in rats who consumed greater than 65% of their daily fluid intake as ethanol.¹³¹ MA has been shown to inhibit the place preference (associative learning mechanism) of morphine addicted rats, also the administration of MA reduces the effects of alcohol on the mesolimbic dopamine system.²⁵⁸

Furthermore, several studies have reported that MA reduces craving and the rewarding effects of alcohol. Test subjects pre-treated with MA two hours prior to alcohol ingestion showed reduced alcohol breath levels and reduced the stimulant effect compared to subjects who had received a placebo. It was proposed by Bacher *et al.* that MA may have the ability to

modify both the pharmacokinetic profile and the rewarding effects of alcohol.²⁵⁹ In addition, MA has shown to reduce the symptoms of TS in a human clinical study.²⁴⁸

MA has shown significant anti-depressant-like effects, and with less negative effects on locomotor activity than two clinically used anti-depressants, namely citalopram (Celexa) and riboxetin (Edronax) in two well established animal anti-depression models; the forced swim test and the tail suspension test.¹⁸⁷ Encouragingly, (*S*)-(+)-mecamylamine entered Phase III clinical trials as a nAChR modulator as an adjunct treatment with citalopram, for MDD. MA was well tolerated in both acute and chronic toxicity tests, displayed no mutagenic potential, and possessed pharmacokinetic properties suitable for development.²⁵³ Unfortunately, in 2012 the clinical trial was terminated as MA had failed to meet its primary targets. While patient self-reporting can be somewhat unreliable this result emphasises the need for a more selective analogue.

MA undoubtedly has a great therapeutic potential as an anti-addictive or anti-depressive therapy. However, due to its non-selective activity at the neuronal nAChRs subtypes, it has been hindered by unacceptable and potentially dangerous side effects including, constipation, nausea, hypotension, anxiety, palpitations, urinary retention, dryness of skin and mouth, mydriasis and blurred vision.²⁵⁹ It is postulated that structural analogues may be more selective towards one neuronal subtype which would in turn reduce unwanted side effects while maintaining the anti-addictive or anti-depressive effects.

1.5.3 Structure-activity relationship studies.

Previous syntheses have been quite restrictive in terms of systematic SAR so the development of a new synthetic route that would allow the systematic analysis of the pharmacological space around the structure of this interesting molecule was extremely attractive. It is rather astounding that given the long standing pharmacological history of MA relatively few SAR studies have been performed. In 1960 Corne *et al.*²⁶⁰ undertook a study which signified the importance of alkyl substitution at the amine position for antagonist activity and duration of action. Three analogues of MA in which some degree of methyl substitution at the 2 and 3 positions was absent, (Figure 1-31), were tested on pre-ganglionically stimulated nictitating cat membrane. The antagonist activity of these

compounds ranged from 15 to 35% of that of hexamethonium, while the parent compound MA boasted an activity of 120%. Two analogues lacking methyl substitution at positions 2 and 3 with substitution at position 1 and 7 reduced activity further to 5-7%. It was noted that removal of a methyl group from the 2 or 3 position resulted in a pronounced decrease in antagonist activity, likewise the absence of the methyl group at the amine produced a dramatic fall in blocking action.

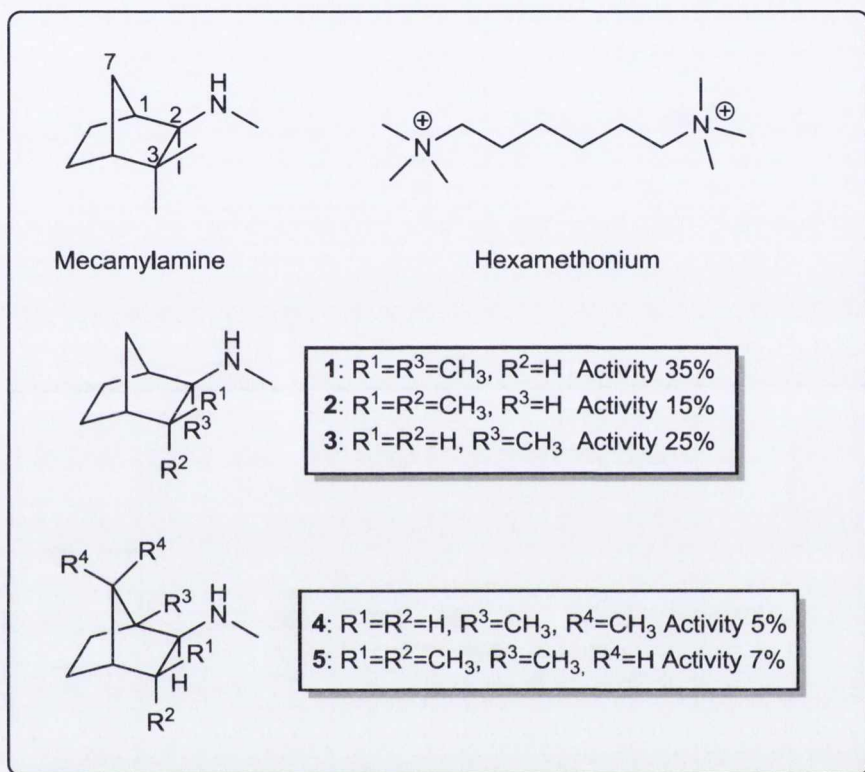


Figure 1-31: Structures of MA, hexamethonium and MA analogues reported by Corne *et al.*²⁶⁰

In 1962 by Stone *et al.*²⁶¹ reported a more comprehensive library of MA analogues with associated *in vivo* testing. The antagonistic potential was assessed based on their ability to prevent convulsions in mice due to a standard intravenous dose of nicotine and for their ability to lessen the contractions of cat nictitating membrane induced by both pre- and post-ganglionic nerve stimulation. The optimal time for measuring the effect of said analogues was calculated based on ability to dilate the pupils of the mice. The results of said study produced a considerably more detailed pharmacophore for antagonistic activity at the nAChR.

In agreement with the work performed by Corne *et al.*²⁶⁰ it was observed that compounds lacking alkyl substitution at positions 2 and 3 displayed a lower activity than the

parent compound MA. It was also observed that increasing the length of the alkyl chain at position 2 to that of an ethyl or propyl group resulted in a decrease in activity; however, increasing the length of alkyl substitution at position 3 was not examined. The methylene group also acts as an activity enhancing group. A multitude of analogues devoid of the methylene bridge were synthesised. These compounds produced a drastic reduction in activity, (one important example) notably a congener of MA with complete alkyl substitution at positions 2 and 3 but lacking the methylene bridge displayed a significant drop in activity.

Investigation of the effect of alkyl and aryl substitution at the amine positions delivered somewhat varied results. Highest activity was achieved by substitution of one (MA) or two methyl groups at the amine. Increasing the size of the alkyl substituent at the amine position produced a decrease in activity, branched groups such as the cyclohexyl, benzyl, phenethyl and phenylpropyl groups produced the greatest deterioration in activity, (Figure 1-32).

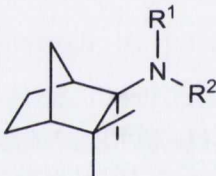
	Nicotine convulsions ED ₅₀ mg/kg	Pupil dilation ED ₁₀ mg/kg
6: R ¹ =H, R ² =H	2.8	5.2
7: R ¹ =H, R ² =CH ₃ (MA)	0.78	1.3
8: R ¹ =H, R ² =CH ₂ CH ₃	1.3	1.6
9: R ¹ =H, R ² =(CH ₂) ₂ CH ₃	6.4	7.5
10: R ¹ =H, R ² =(CH ₂) ₃ CH ₃	toxic	toxic
11: R ¹ =H, R ² =(CH ₂) ₄ CH ₃	11.0	13.5
12: R ¹ =H, R ² =CH(CH ₃) ₂	4.9	5.2
13: R ¹ =H, R ² =CH ₂ CH=CH ₂	5.8	8.5
14: R ¹ =H, R ² =(CH ₂) ₂ C(CH ₃) ₃	26.5	43.0
15: R ¹ =H, R ² =C ₆ H ₁₃	24.0	40.0
16: R ¹ =H, R ² =C ₆ H ₅ CH ₂	48.0	83.0
17: R ¹ =H, R ² =C ₆ H ₅ CH ₂ CH ₂	15.0	36.0
18: R ¹ =H, R ² =C ₆ H ₅ (CH ₂) ₃	45.0	37.0
19: R ¹ =CH ₃ , R ² =CH ₃	0.71	1.5
20: R ¹ =CH ₂ CH ₃ , R ² =CH ₂ CH ₃	3.2	3.8

Figure 1-32: MA analogues with alterations to the methyl amine, extract from Stone *et al.*²⁶¹

Two separate sets of *endo* and *exo* analogues were prepared and tested, (Figure 1-33). In each case the *exo* isomer produced a higher degree of activity than that of the corresponding

endo one. The *d*- optical isomer of MA was also examined against the corresponding racemate. It produced activity approximately equal to the racemate thus suggesting that optical isomerism does not play a significant role in determining the degree of activity.

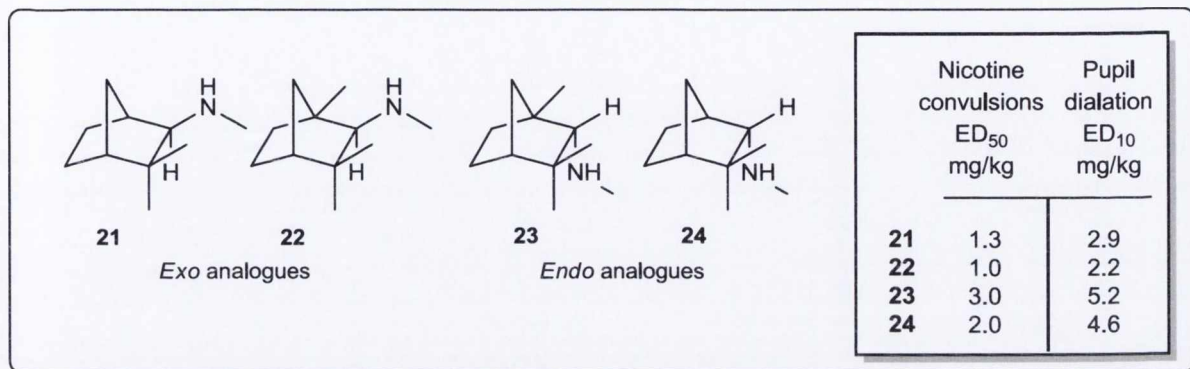


Figure 1-33: Structures of *exo* and *endo* analogues reported by Stone *et al.*²⁶¹

In 1970, Hunt and Wragg²⁶² confirmed the necessity of the bridgehead methylene group towards activity by synthesising a number of monocyclic analogues which omitted the bridgehead, these results were in agreement with the findings of Stone *et al.*²⁶¹ It was observed that none of the monocyclic analogues displayed ganglion blocking activity higher than one tenth that of MA.

In 1971, Herr *et al.*²⁶³ produced a number of alcohol and methoxy substituted analogues of MA illustrated in Figure 1-34. This was achieved through the fermentation of *N*-benzoylmecamylamine by *Sporotrichum sulfurescens* which produced a mixture of microbial oxidation metabolites in which either the 6 or 7 positions had been oxygenated. The activity of these compounds was determined by measuring their ability to lower the blood pressure of renal hypertensive Goldbatt rats against that of the parent compound MA.

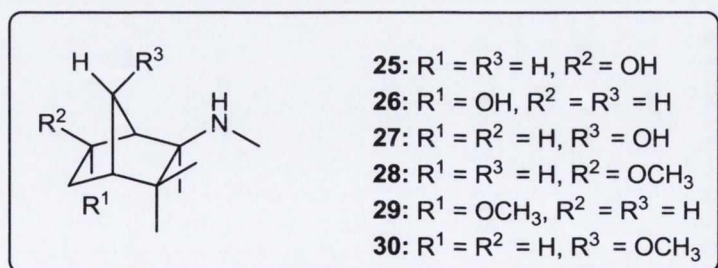


Figure 1-34: (extract from M. E. Herr, H. C. Murray and G. S. Fonken, *J. Med. Chem.*, 1971, 14, 842-845).²⁶³

Compounds **28**, **29** and **30** displayed anti-hypertensive activity equal to that of the parent compound MA, while alcohols **25**, **26** and **27** exhibited lower activity. It was proposed that this reduction in activity was due to decreased lipophilicity of the OH isomers over the corresponding methoxy derivatives.

In 1991 Suchocki *et al.*²⁶⁴ generated the most extensive study at the time. A library was prepared including nine analogues of MA in which the number and arrangement of methyl groups were altered. Activity was tested by measuring the analogues ability to antagonise nicotine induced antinociception, using the tail flick method. Four of these analogues were synthesised with the amine moiety in the *endo* position and enantiomers of both *endo* and *exo* analogues of MA were also prepared. Three N-substituted pyridinyl and one analogue with a phenyl substitution at position 3 and were also investigated. Results verified those of Corne and Stone, with those lacking methyl substitution at positions 2 and 3 displaying a decrease in activity. The *endo* analogues proved to be only slightly less potent than their *exo* counterparts. The N-substituted pyridinyl compounds displayed low levels of antagonist activity, indicating that increased steric hinderance at the amine moiety is detrimental towards antagonist activity. One intriguing result was that of the phenyl substituted compound **31** which acted as a stimulant, (Figure 1-35). Both *R* and *S* enantiomers of MA displayed a similar potency to the racemate. This result in conjunction with previous work by Suchocki *et al.*²⁶⁵ in 1990 and Stolerman *et al.*²⁶⁶ in 1983 in which it was noted that the antagonistic effect of MA was not overcome by increasing the dose of nicotine, confirms that MA acts through non-competitive antagonism.

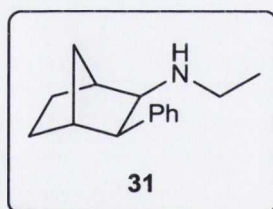


Figure 1-35: Phenyl MA analogue producing stimulant effects.²⁶⁴

It is important to note that the tests carried out up until this point did not allow analysis of activity at different receptor subtypes due to a lack of technology. As cloning and expression technologies improved activity at individual nAChRs became possible, allowing more specific biological testing.^{267,268} In 2001 Shytle and co-workers examined the effects of MA on human nAChR subtypes. They tested both *R* and *S* enantiomers of MA and the

racemate as antagonists of human $\alpha 3\beta 4$, $\alpha 3\beta 2$, $\alpha 7$, and $\alpha 4\beta 2$ nAChRs, in addition to mouse adult type muscle $\alpha 1\beta 1\delta \epsilon$ nAChRs expressed in *Xenopus* oocytes, shown in Table 1-2.²⁵⁰

Table 1-2: IC_{50} values for MA and its enantiomers at nAChR subtypes.²⁵⁰

Receptor	Racemic MA	R-(-)-MA	S-(+)-MA
$\alpha 3\beta 4$	640-90 nM	420-50 nM	640-200 nM
$\alpha 4\beta 2$	2.5-0.6 μ M	1.7-0.5 μ M	3.2-0.5 μ M
$\alpha 3\beta 2$	3.6-1.2 μ M	3.2-0.6 μ M	3.7-0.8 μ M
$\alpha 7$	6.9-1.6 μ M	5.8-2.2 μ M	4.6-1.2 μ M

The selectivity of MA for neuronal nAChR was noted in terms of slow recovery rates from MA-induced inhibition. Results showed that the selectivity of MA for neuronal type nAChRs over that of muscle type nAChRs is due to a slow dissociation from the receptor once the antagonist is bound, while in the case of the muscle type nAChRs dissociation occurs much more rapidly producing only transient inhibition. Interestingly it was observed that the S-(+)-MA enantiomer dissociated more slowly from neuronal nAChRs than the R-(-)-MA enantiomer. In addition it was noted that muscle-type receptors displayed a greater sensitivity to R-(-)-MA. These findings suggest that S-(+)-MA would deliver a more preferable therapy to R-(-)-MA with regards superior selectivity towards neuronal nAChRs and greater efficacy.

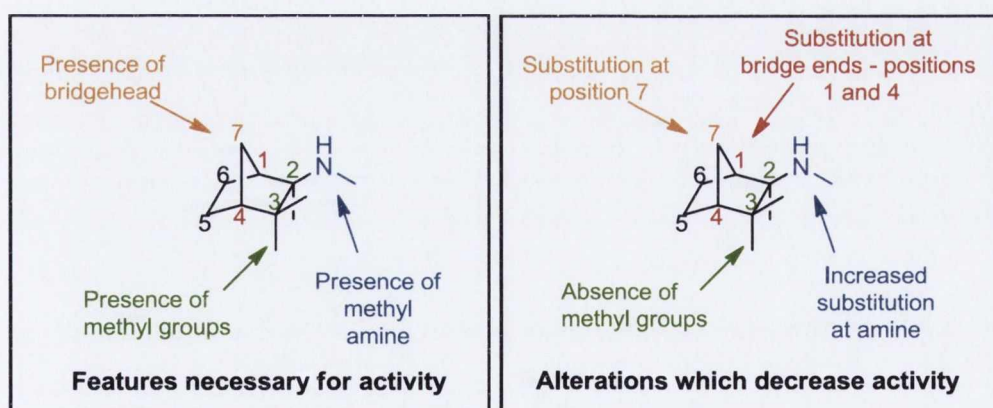


Figure 1-36: Summary of features which increase and decrease activity.

1.5.4 Recent developments.

In recent years interest in the development of more potent and select nAChR antagonists has been rekindled. A pempidine analogue, 2,2,6,6-tetramethylpiperidin-4-yl-heptanoate (TMPH)²⁶⁹ was reported in 2005 to display neuronal nAChR antagonism. A pempidine dimer analogue tinuvin 770, was investigated for its effect on nicotine self-administration in Wistar rats. A dose of 1mg/kg per day results in near elimination of self-administration while no obvious side effects were observed.²⁷⁰

In 2007 Crooks and co-workers²⁷¹ reported a novel antagonist of nAChRs *N,N*-dodecane-1,12-diyl-bis-3-picolinium dibromide (bPiDDB). The bis-azaaromatic quaternary ammonium compound enters the brain *via* the choline transporter. Microdialysis demonstrated that it inhibited nicotine induced dopamine release in the rat NAc. Results of these experiments revealed that bPiDDB exhibited similar antagonistic activity to that of MA with regards to its ability to inhibit nicotine induced dopamine release. In 2010, Crooks reported a number of MA dimers and trimers which were also investigated for their capacity to inhibit nicotine induced dopamine release. A MA trimer analogue, (Figure 1-37), proved to be their most active compound displaying up to 73% inhibition of nicotine evoked DA release in rat striatal slices at 100 nM. Interestingly these compounds did not inhibit nicotine induced dopamine release completely unlike its parent compound MA itself indicating that the trimer is acting only at a selection of the nAChR subtypes.²⁷² In 2011, Crooks and co-workers also reported a preclinical evaluation of a bPiDDB analogue bPiDI which inhibited dopamine release by 53-57%. Once again they postulated that the reduction in inhibition in comparison to that of the parent compound MA (which displayed >90% inhibition) was as a result of a higher selectivity towards a subtype of nAChRs.²⁷³

In 2002 Targacept purchased the rights to MA, later in 2009 a double-blind, placebo-controlled phase IIb trial was conducted in patients with MDD as an adjunct treatment with citalopram.²⁵³ The results of these trials demonstrated the combination treatment to be superior to that of the placebo which led to a licence agreement with AstraZeneca. The following year, AstraZeneca and Targacept commenced a phase III trial of MA cleverly dubbed the Renaissance Program. Unfortunately in 2011 the trials were ceased and Targacept announced

that the primary endpoint for phase III had not been met.²⁵⁴ In September 2012 Targacept announced its intention to pursue MA as a treatment for overactive bladder.²⁷⁴

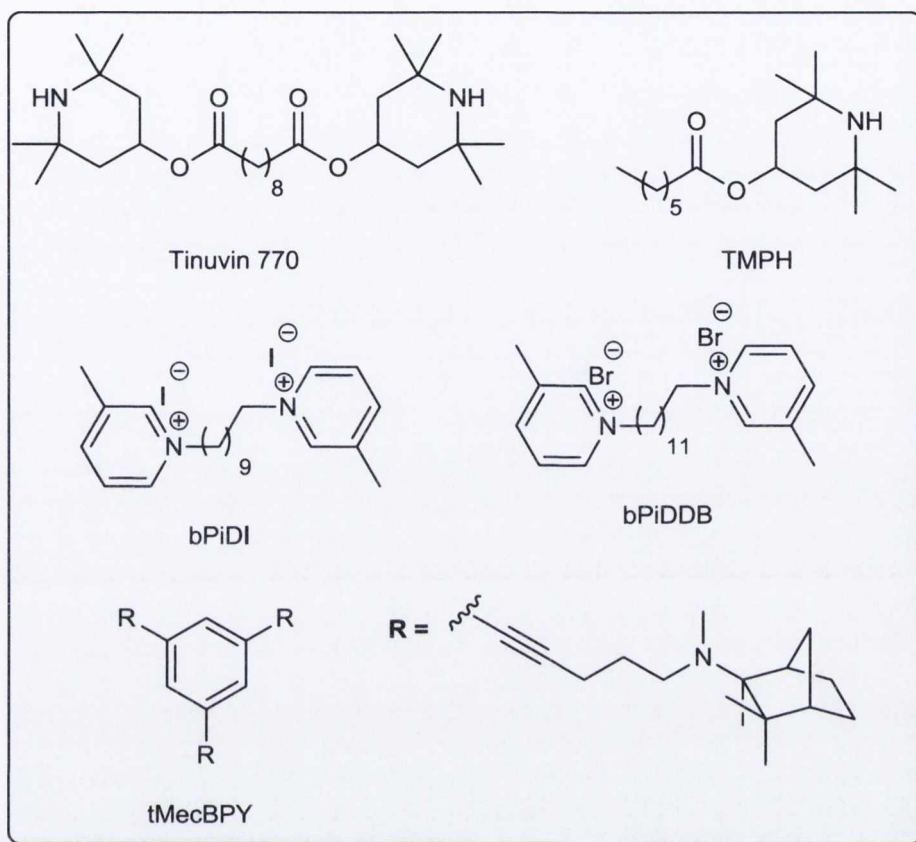


Figure 1-37: Recently developed nAChR antagonists.^{272,273}

The development of a more thorough and extensive, in-depth SAR study is an important aspect and one of the key tasks associated with this project. Due to previous restrictive syntheses, work completed in this area still remains somewhat preliminary. As outlined in section 1.6 (synthetic strategy) a novel route designed and carried out within our research group by Dr. David Mangan has allowed us to install a variety of modifications in a controlled and sequential approach, thus permitting us to investigate the pharmacological space around the [2.2.1]bicyclo skeleton of MA. All analogues synthesised in this study were submitted for biological assessment for antagonistic activity through *in vitro* testing at nAChR subtypes. These tests were performed by electrophysiological measurements at a single concentration (3 μ M) employing oocytes expressing the low sensitivity $\alpha 4\beta 2$ nAChR, a subtype which has been implicated in the addiction process.

1.6 Synthetic strategy.

The main objective of this project was to synthesise a library of analogues by making structural changes to the molecular skeleton of MA, in order to probe the pharmacological space around the molecule and to discover a molecule that is more effective than MA. The aim was to make systematic changes in the areas shown, Figure 1-38, and to investigate the effects of these alterations on antagonism *via in-vitro* testing at nAChR subtypes.

Analysis of the structure of MA depicts a multitude of potential areas of the parent compound which can be investigated, (Figure 1-38).

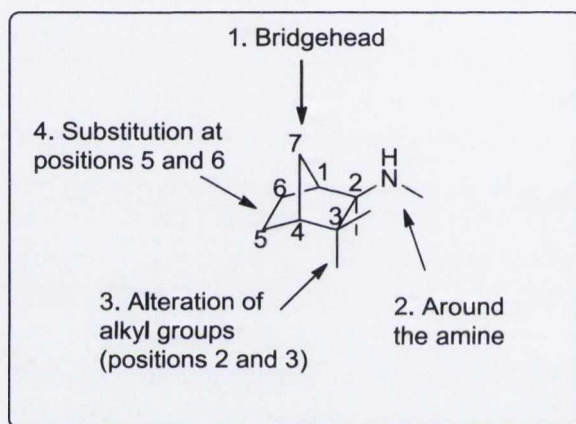
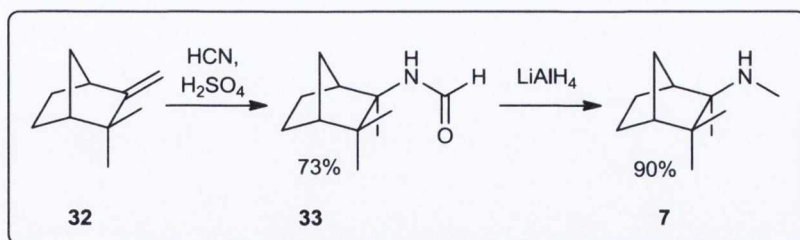


Figure 1-38: Proposed alterations to the structure of MA.

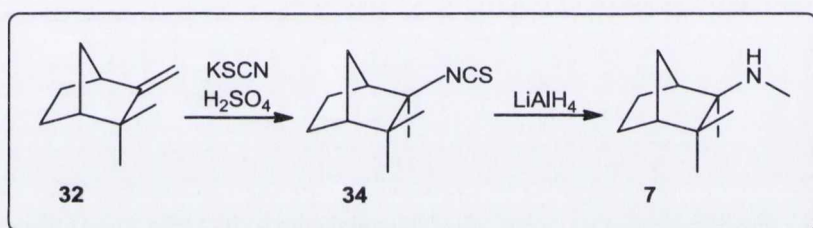
1.6.1 Previously developed synthetic routes towards mecamylamine.

Previous syntheses including previous work carried out within the group is described below. MA was first synthesised by Stone *et al.* in 1956²⁷⁵ and the methodology was later published in 1962.²⁶¹ This route involved a short and efficient two-step procedure from cheap and commercially available camphene (Scheme 1-1). However the reliance on camphene **32** in the synthesis limits its suitability with regards to the production of analogues. Although the route is direct and excellent for the synthesis of MA, it limits the scope for alterations to the molecule.



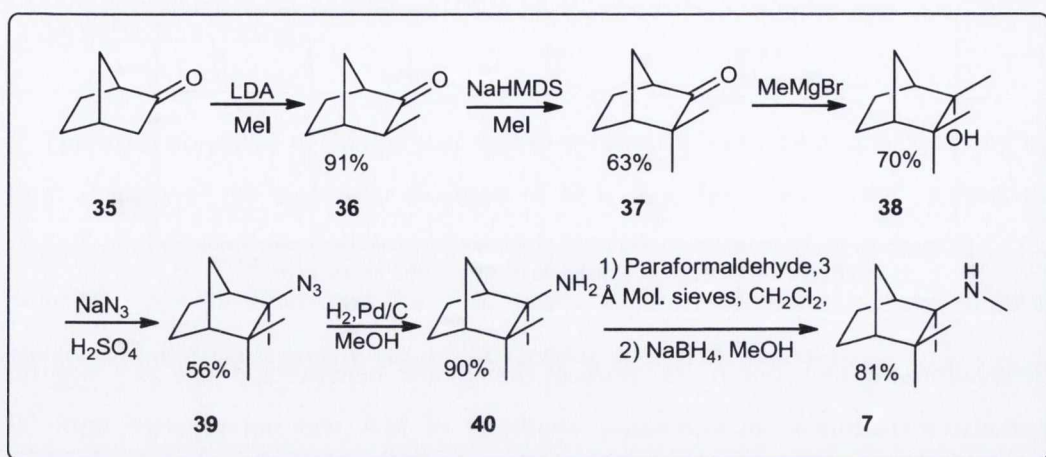
Scheme 1-1: Original synthesis of MA, 1962 Stone *et al.* ²⁶¹

It is surprising that, due to its apparent therapeutic benefits and sale as a significant anti-hypertensive treatment, an alternative synthesis of MA was not reported until 2010. Crooks and co-workers developed a synthetic strategy once again starting from camphene **32** but which avoided the use of HCN.²⁷² Treatment of camphene with H₂SO₄ and KSCN (Scheme 1-2) furnished the isothiocyanate **34** which was subsequently reduced with lithium aluminium hydride forming MA, unfortunately no yields were reported.



Scheme 1-2: MA synthesis published by Crooks and co-workers.²⁷²

As these synthetic routes provided little freedom for structural modification around the [2.2.1] core, it was necessary to develop a new synthetic strategy in order to achieve our goals of SAR development. Previous work carried out within the research group by Dr. David Mangan developed a novel route to MA which allows for diversification in positions 2 and 3 in addition to alteration of the amine substituent, (Scheme 1-3).



Scheme 1-3: Novel synthesis of MA developed by Dr. D. Mangan.²⁷⁶

Scheme 1-3 illustrates the new route generating MA as an example. Substitution of the electrophiles and nucleophiles permitted the synthesis of the structures described in Figure 1-39. Direct α -methylation of commercially available norcamphor **35** affords the methylated and dimethylated ketones **36** and **37** *via* enolate formation. Methylation occurred exclusively at the 3 position as Bredt's rule indicates that enolate formation at position 1 is highly undesirable hence only the desired enolate can form.^{277,278} Although not relevant to the synthesis of MA it is important to note that the alkylations occur from the *exo* face due to the "picket fence" effect.²⁷⁹ If different alkylating agents are used then the order of addition is important with the second agent ending up in the *exo* face. Treatment of ketone **37** with either methylmagnesium bromide or methyl lithium generated alcohol **38**. Again the addition is governed by the "picket fence" effect²⁷⁹ forming the isomer shown. Treatment of alcohol **38** with H_2SO_4 and sodium azide in CH_3Cl formed the *exo* azide **39** (picket fence) *via* the 3° cation. Reduction with lithium aluminium hydride or by catalytic hydrogenation converted azide **39** to the corresponding amine **40**. Finally the methyl functionality at the amine is installed *via* reductive amination. This novel synthetic route allows for a vast range of alterations to the parent compound, with readily available starting materials and high yields, it stands as an excellent foundation for the development of an extensive and comprehensive SAR study.

Using this procedure, Dr. Mangan synthesised a library of analogues which involved the substitution of 1, 2 or 3 methyl groups for ethyl groups in positions 2 and 3. A series of substitutions at the amine position were also undertaken (Figure 1-39)

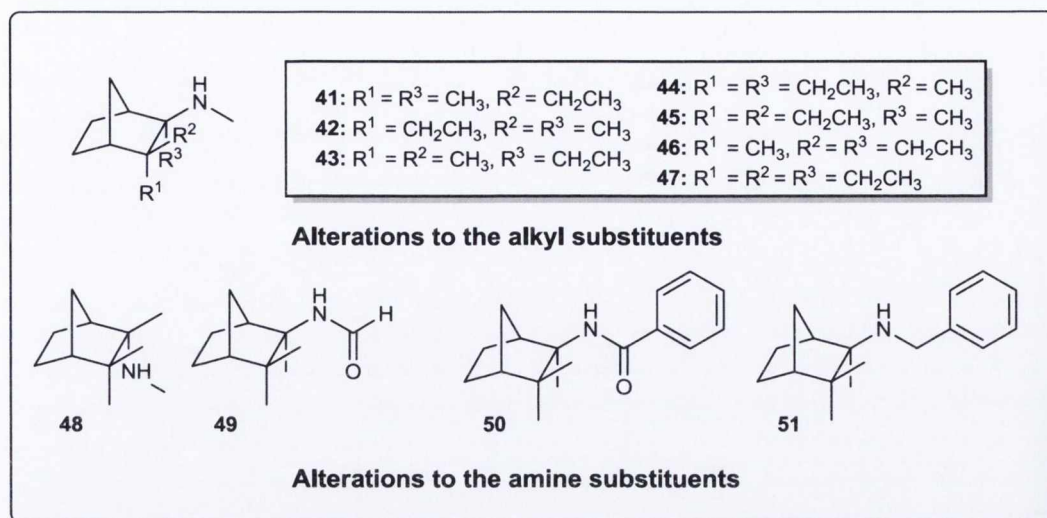
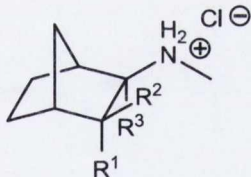


Figure 1-39: Library of analogues prepared by Dr. Mangan.

Preliminary testing of compounds **41-48** by electrophysiological measurements at a single concentration (3 μM) employing oocytes expressing the low sensitivity $\alpha 4\beta 2$ nAChR indicated that all compounds retained antagonistic character but differed in their activity. Oocytes expressing the $\alpha 4\beta 2$ nAChR were treated with 100 μM ACh, which activated the ion channels and allowed the passage of sodium ions. An electrical response is measured and this measurement is compared to the change in electrical response in the presence of an antagonist. The activity of each compound in the presence of 100 μM ACh was compared to the response elicited by 100 μM ACh alone, (Figure 1-40).²⁸⁰



Compound	Response to 100 μM ACh
--	100%
7 (MA)	33%
41	74%
42	18%
43	Error - results pending
44	22%
45	22%
46	23%
47	0%
48 (Endo-MA)	18%

7: $R^1 = R^2 = R^3 = \text{CH}_3$
41: $R^1 = R^3 = \text{CH}_3, R^2 = \text{CH}_2\text{CH}_3$
42: $R^1 = \text{CH}_2\text{CH}_3, R^2 = R^3 = \text{CH}_3$
43: $R^1 = R^2 = \text{CH}_3, R^3 = \text{CH}_2\text{CH}_3$
44: $R^1 = R^3 = \text{CH}_2\text{CH}_3, R^2 = \text{CH}_3$
45: $R^1 = R^2 = \text{CH}_2\text{CH}_3, R^3 = \text{CH}_3$
46: $R^1 = \text{CH}_3, R^2 = R^3 = \text{CH}_2\text{CH}_3$
47: $R^1 = R^2 = R^3 = \text{CH}_2\text{CH}_3$

Figure 1-40: Results of initial testing on $\alpha 4\beta 2$ nAChR subtypes.²⁸⁰

Gratifyingly, initial tests gave very encouraging results with most compounds displaying activity greater than MA. Compound **47** displayed the best activity - complete blockade of the receptor. Interestingly the diastereoisomer *endo* MA showed more potent activity than MA. Compound **41** was the least potent antagonist in the series, less so than MA.

1.6.2 Targets discussed in Chapter 2; Alterations to positions 2 and 3.

This chapter will discuss further alterations to positions 2 and 3 and alterations at the amine. Encouraged by the promising biological activity exhibited by the ethyl substituted systems we decided to explore this area further by restricting the ability of the alkyl substituents to rotate. We envisioned the introduction of a 5 or 6 membered ring at the 3 position coupled with methyl or ethyl substitution at position 2, illustrated in Figure 1-41. A continued investigation of *endo*-MA analogues and a variety of alkyl and aryl alterations of the amine are detailed in this chapter. These alterations and the chemistry employed to achieve our synthetic goals will be discussed thoroughly in chapter 2.

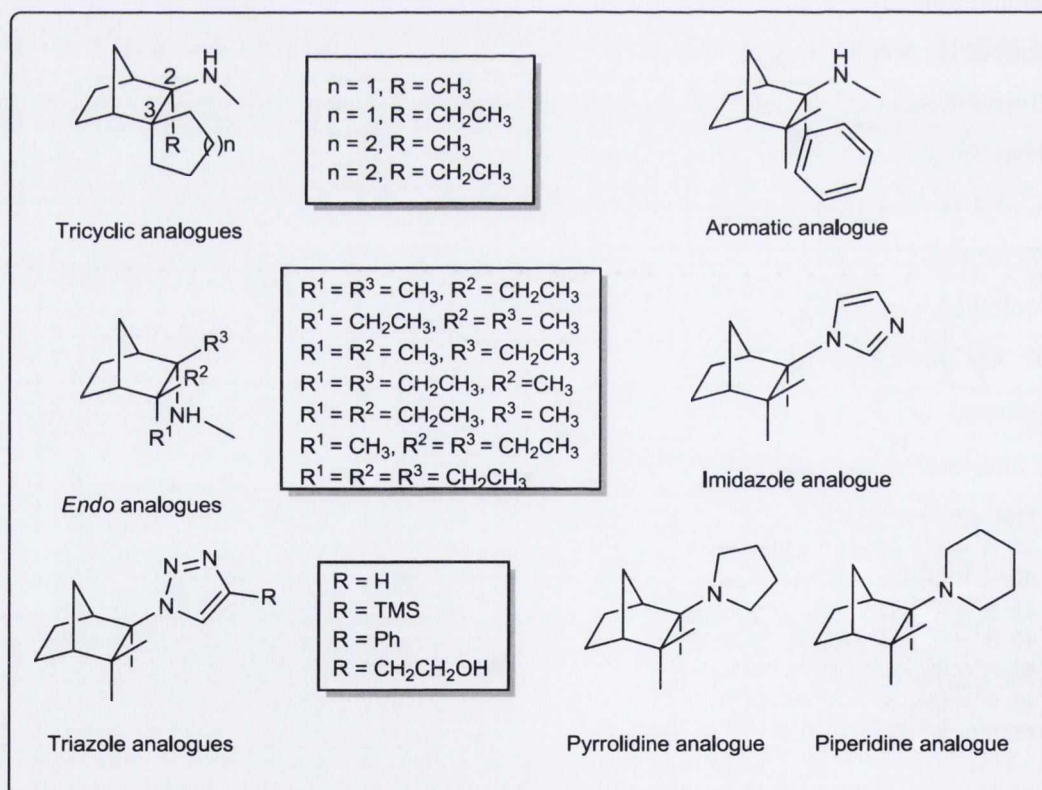


Figure 1-41: Proposed structural analogues discussed in chapter 2.

1.6.3 Targets discussed in Chapter 3; Alterations to positions 5 and 6.

Chapter 3 describes the work designed to introduce diversity at the 5 and 6 positions including saturated and unsaturated ring systems, 5,6 di-substituted and selective 5 or 6 substituted compounds. Our specific targets are depicted in Figure 1-42.

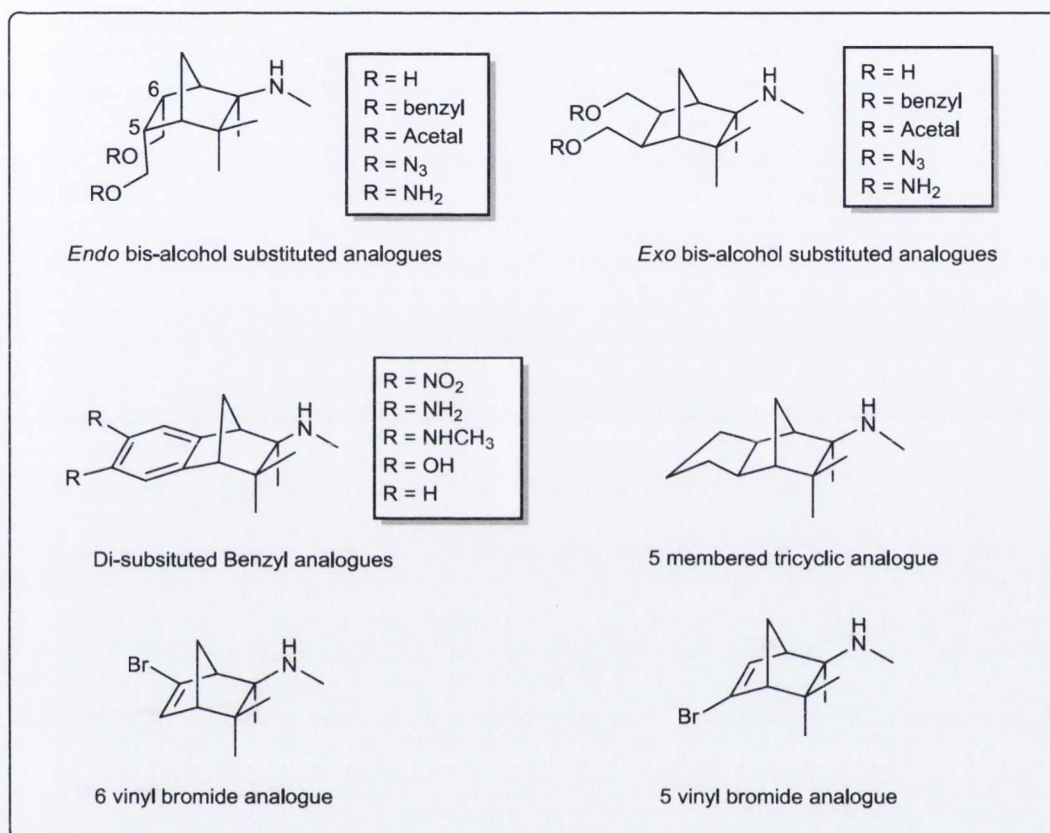


Figure 1-42: Proposed structural analogues discussed in chapter 3.

1.6.4 Targets discussed in Chapter 4; Alterations to position 7.

Chapter 4 describes attempts to make alterations to the bridgehead, including expansion of the bicyclic system and the incorporation of a heteroatom, illustrated in Figure 1-43. All appropriate background information and chemistry will be discussed in the appropriate chapters.

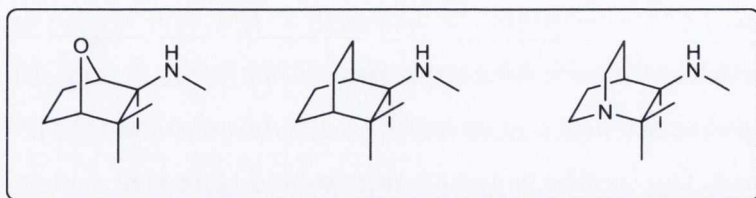


Figure 1-43: Proposed structural analogues discussed in chapter 4.

Chapter 2

Diversity in positions 2 and 3

2. Diversity in positions 2 and 3.

Targets

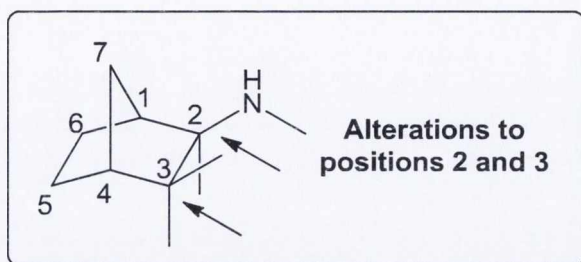
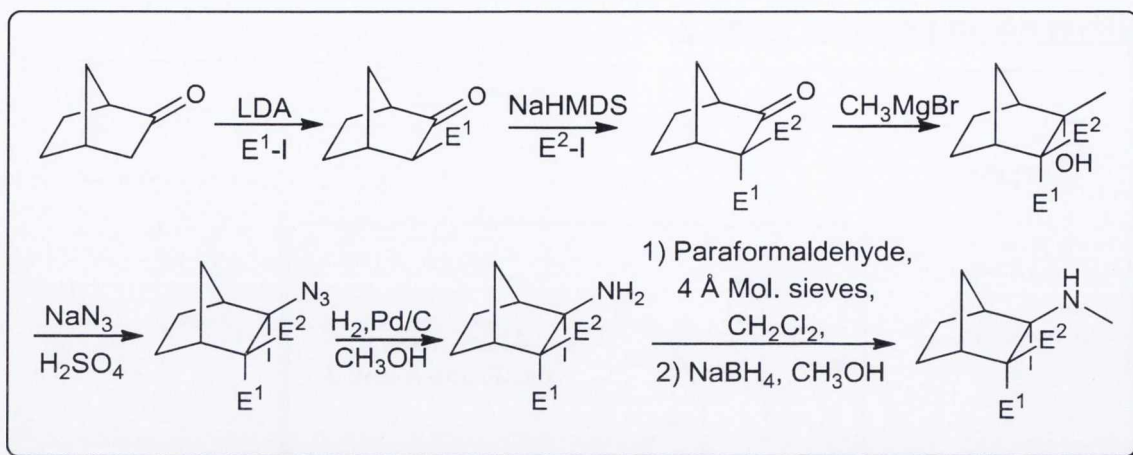


Figure 2-1: Targeting positions 2 and 3 on the MA skeleton.

This chapter describes the attempts to introduce diversity at positions 2 and 3 of the MA framework, (Figure 2-1), these include modifications to the alkyl substituents at these positions but also alterations to the amine moiety. The main areas of interest to us are described below:

2.1. Alterations at position 3.

As briefly described in section 1.6.1, Dr. Mangan prepared a small compound library by the stereoselective and regioselective installation of ethyl groups at the 2 and 3 positions. This was achieved by exchanging methyl for ethyl substituents at pre-determined steps within the previously developed route shown in Scheme 2-1. Due to the "picket fence" effect, nucleophiles and electrophiles attack preferentially from the *exo* face. This natural attribute allowed for complete stereocontrol during alkylation of the enolates and the ethyl groups could be selectively installed in either the *endo* or *exo* position. The "picket fence" effect also accounted for the *exo* selectivity of the azide addition.



Scheme 2-1: Novel synthesis of MA allowing for complete regioselectivity of substituents, developed by Dr. Mangan.²⁷⁶

Preliminary *in vivo* testing was performed by electrophysiological measurements at a single concentration (3 μ M) employing oocytes expressing the low sensitivity $\alpha 4\beta 2$ nAChR.²⁸⁰ The results for the first 8 compounds are displayed in Figure 2-2. Due to an error compound **43** was not tested *via* this method. Compounds were tested in the presence of 110 μ M ACh. A response of 100% refers to 0% inhibition. A response of 0% refers to 100% inhibition or a complete blockade of the receptor.

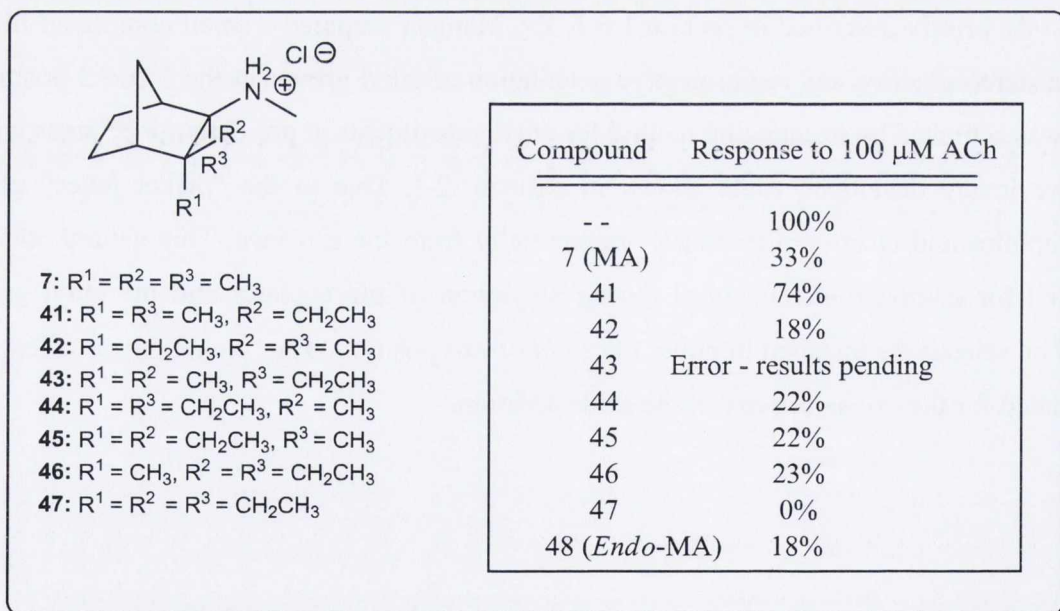


Figure 2-2: Results of initial *in vitro* biological testing at $\alpha 4\beta 2$ nAChR subtypes.²⁸⁰

It can be seen that the triethyl analogue **47** had the greatest antagonistic activity with a complete blockade of the receptor at the concentration tested, (Figure 2-2). While this work was ongoing Targacept began phase III clinical trials investigating the potential of MA as a treatment for major depressive disorder. The move to phase III trials prompted us to re-synthesise compound **47** in order to assess its anti-depressant activity in the somewhat crude FST. Results were unclear, during the control experiment mice swam for 178 seconds on average. However, upon administration of compound **47** this period was reduced to an average of 170 seconds.²⁸¹

There are numerous factors which could affect testing results such as the time between administration of the compound and initiation of the experiment. Too little time means the drug has not yet reached its target and too lengthy a wait could mean metabolism of the compound before the test takes place. As discussed in section 1.3.5, the FST is by no means a perfect model for depression. However some interesting observations were noted during the FST. Compound **47** displayed characteristics of an anxiolytic compound. We did not pursue this with any vigour and our instincts were proven to be correct when the trial failed.

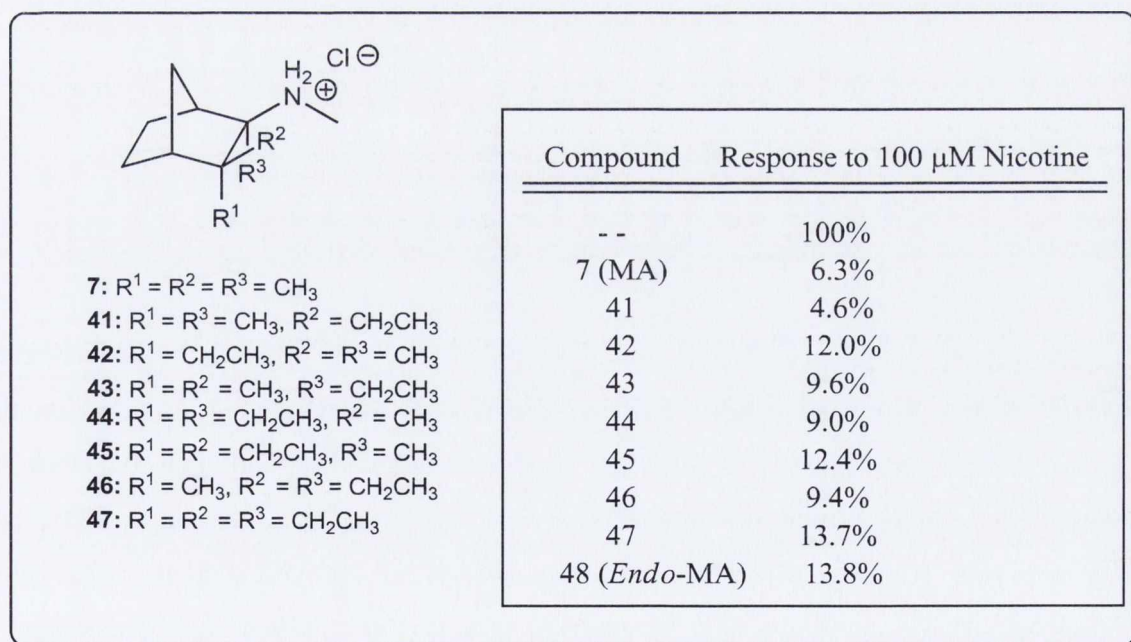


Figure 2-3: Results of second *in vitro* biological testing at $\alpha 3\beta 4$ nAChR subtypes.²⁸²

We were keen to assess the effects of these compounds on another ion channel subtype, (Figure 2-3). In a second *in vitro* test the compounds were tested for their ability to antagonise nAChRs expressed in SH-SY5Y cells in the presence of 100 μ M of nicotine. These cells express mainly $\alpha 3\beta 4$ and $\alpha 7$ subtypes. The responses mediated by $\alpha 7$ receptor subtypes are very fast and therefore we are reasonably confident that responses mediated by $\alpha 3\beta 4$ receptor subtype are those recorded by these methods.²⁸³ Responses were observed *via* fluo-3, a highly specific fluorescent Ca^{2+} probe.²⁸⁴ Once again a response of 100% refers to 0% inhibition. The results show an interesting trend, (Figure 2-3). While all the new compounds except one were more active than MA against $\alpha 4\beta 2$ subtypes with the triethyl derivative, compound **47** being the most active, the situation is reversed at $\alpha 3\beta 4$ with compound **47** 0.1% away from the worst compound *endo*-MA **48**. Although deeper testing is required these results are pleasing.

2.1.1. Synthesis of the Tricyclic Analogues.

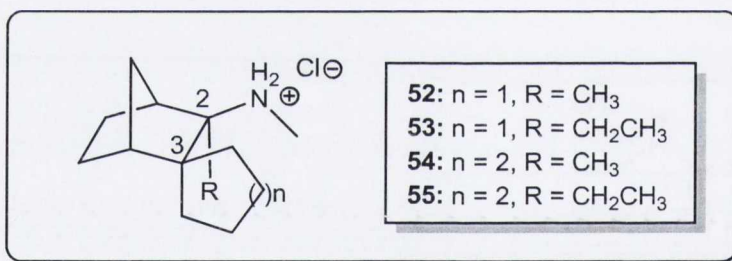
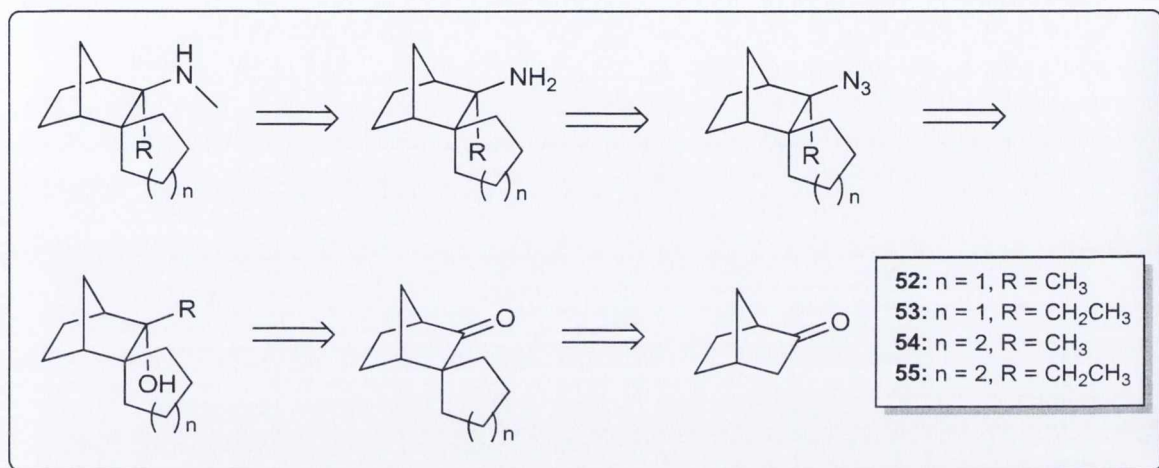


Figure 2-4: Proposed tricyclic MA analogues.

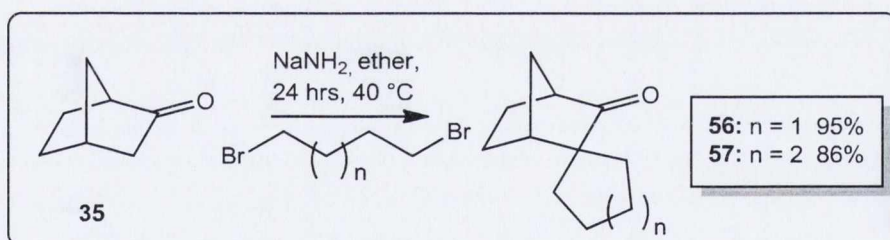
Promising biological activity exhibited by the methyl and ethyl substituted analogues prepared by Dr. Mangan, in particular the triethyl MA analogue **47**, highlighted the importance of alkyl substitution at positions 2 and 3. In order to expand upon this work we wanted to investigate further the introduction of a third ring system, (Figure 2-4). The introduction of a 5 or 6 membered ring at the 3 position would provide a greater insight into the aliphatic substitution required for receptor recognition and binding. The significance of the ethyl chain at position 2 would also be probed by synthesising 5 and 6 member ring analogues with a methyl or ethyl substituent at the 2 position.

We planned to exploit the same general synthetic procedure employed in the bicyclic systems, shown in Scheme 2-2. If this approach were to be successful then we would have to prepare the appropriate ketones.



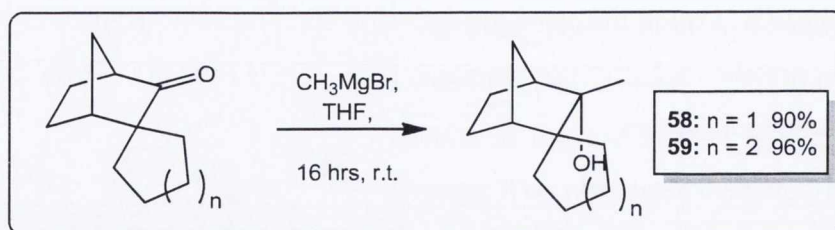
Scheme 2-2: Retrosynthesis of tricyclic MA analogues.

Fortunately, a synthesis of ketones **56** and **57** had been reported by Hori *et al.*²⁸⁵ A mixture of norcamphor **35**, an excess of sodium amide and either 1,4-dibromobutane or 1,5-dibromopentane in anhydrous ether at 40 °C for 24 hours gave the desired 5 membered and 6 membered tricyclic systems **56** and **57** in excellent yields of 95% and 86%, respectively, (Scheme 2-3). Gratifyingly, in our hands, yields were considerably higher than those reported (63% and 54%, respectively).



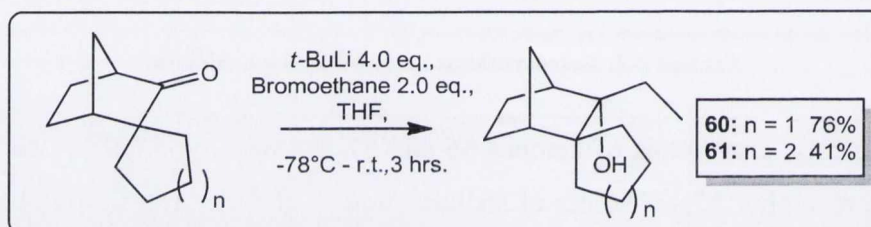
Scheme 2-3: Synthesis of spironorcamphors.

Treatment of ketones **56** and **57** with methylmagnesium bromide gave the expected 5 membered and 6 membered alcohols **58** and **59** in excellent yields of 90% and 96%, respectively, after purification, (Scheme 2-4).



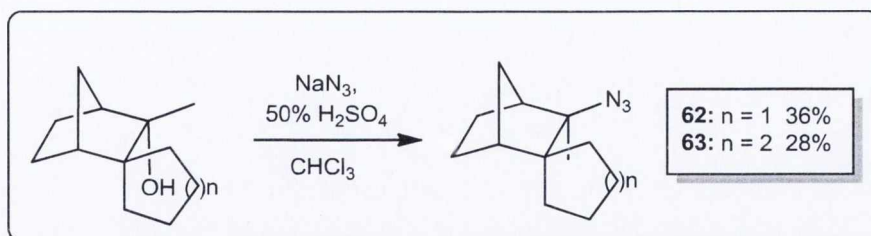
Scheme 2-4: Addition of a methyl substituent at position 2 using Grignard reagents.

A solution of ethyllithium was prepared *in situ* by treating bromoethane with 2 equivalents of *tert*-butyllithium at -78°C , to this was added ketones **56** and **57** which gave the expected alcohols **60** and **61** in 76% and 41% yield, respectively, (Scheme 2-5). Ethyllithium was employed at this stage because previous attempts within the group to add the ethyl group to [2.2.1] ketones had shown that ethyllithium prepared *in situ* was the best option.

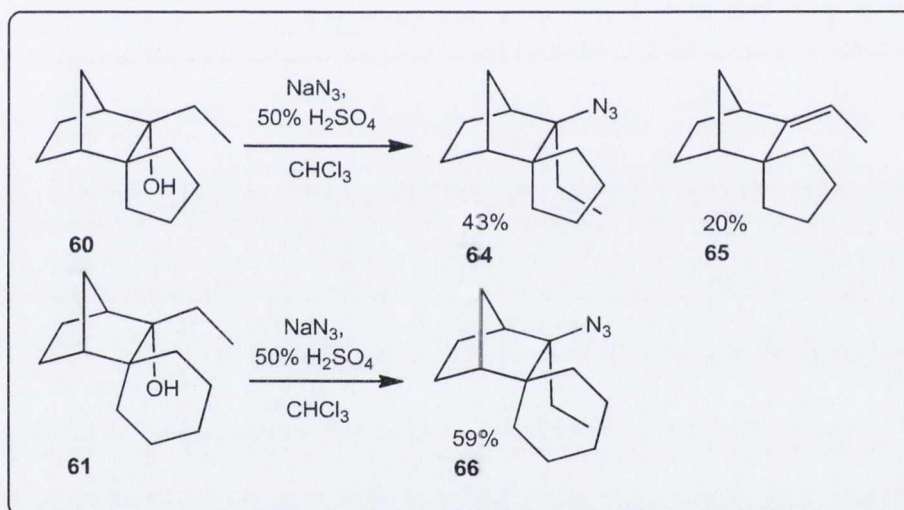


Scheme 2-5: Addition of an ethyl substituent at position 2 using organolithium reagents.

Having prepared the tertiary alcohols we turned our attention to azide formation. Although all the alcohols were treated with 50% H_2SO_4 and an excess of sodium azide, the reaction times and reaction profile varied, (Scheme 2-6). The methyl substituted alcohols **58** and **59** were prone to Wagner-Meerwein rearrangement and the reactions were carefully monitored by NMR spectroscopy and terminated as soon as a trace of the Wagner-Meerwein product was observed. In the case of the 5 membered methyl substituted alcohol **58** the reaction was terminated after 2 hours. Azide **62** had been formed in 36% yield and we were pleased to isolate the starting material in 61% yield after work-up and purification. The 6 membered methyl substituted alcohol **59** the reaction was terminated after 6 hours. The desired azide **63** was isolated in 28% yield and 60% starting material was recovered after purification.

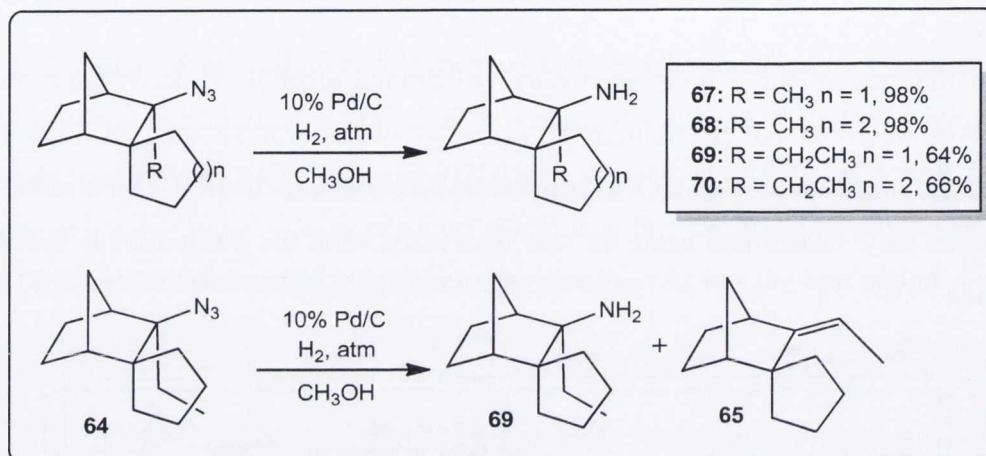
Scheme 2-6: Synthesis of azides **62** and **63**.

In the case of the 5 membered ethyl substituted alcohol **60** no Wagner-Meerwein product was observed but in addition to azide **64** which was isolated in 43% yield an unexpected elimination product **65** was isolated in 20% yield, (Scheme 2-7). Formation of the 6 membered ethyl substituted azide **66** was uneventful with the desired azide recovered in 59% yield.

Scheme 2-7: Synthesis of azides **64**, **65** and side-product **66**.

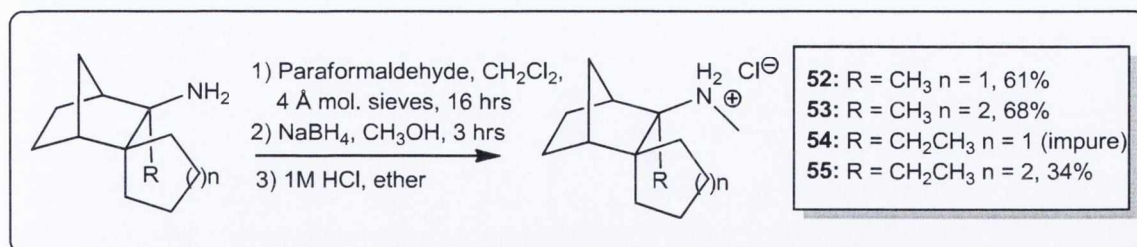
The next step in the synthetic sequence was the reduction of the azides to the corresponding amines. This was achieved by exposure of the azides to hydrogen in the presence of 10% palladium on charcoal, (Scheme 2-8). Once again ring size and substitution at position 2 affected the course of the reaction. In the case of both methyl substituted azides **62** and **63** the reaction proceeded in the expected manner with amines **67** and **68** isolated in near quantitative yields. However in the case of the ethyl substituted systems yields were considerably lower. In the case of the 5 membered azide **64** the amine **69** was recovered in 64% yield but once again a similar unexpected elimination product **65** was observed in 19% yield, (Scheme 2-8). Elimination under acidic conditions is understandable, but the

elimination under neutral hydrogenation conditions was surprising. It is difficult to rationalise why the elimination should only occur in the 5 membered ethyl substituted case. The 6 membered ethyl substituted amine **70** was isolated in 66% yield but the elimination product was not observed. In both cases starting material was not recovered.

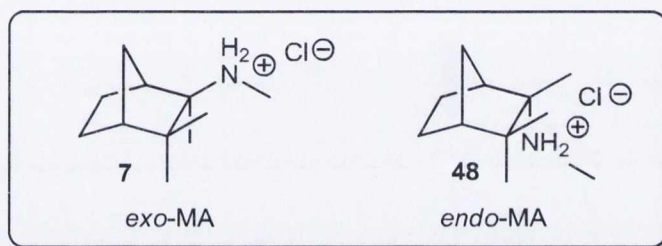


Scheme 2-8: Synthesis of amines **67**, **68**, **69**, **70** and side-product **65**.

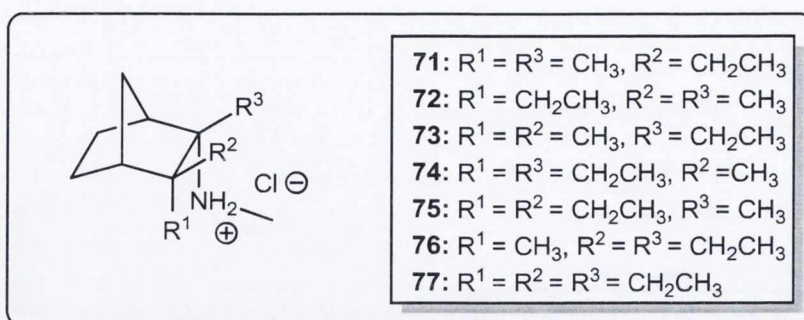
The final step was methylation of the amine. The method we chose was a 2 step reductive amination. The amines **67**, **68**, **69** and **70** were treated with paraformaldehyde and 4 Å molecular sieves in CH₂Cl₂ at reflux temperature until NMR analysis of the reaction mixture indicated complete formation of the imine (approximately 16 hours), (Scheme 2-9). The imines were not isolated but were treated directly with sodium borohydride and methanol. After isolation of the amines treatment with a solution of 1M HCl in diethyl ether gave the expected hydrochloride salts, (Scheme 2-9). Once again the amines behaved differently, the methyl substituted amines performed well and the hydrochloride salts of the 5 membered system **52** was isolated in 61% yield and the 6 membered methyl substituted hydrochloride salt **53** was formed in 68% yield. Yet again, the ethyl substituted systems were more problematic with the 5 membered compound more so. Although we are confident we formed the 5 membered ethyl substituted salt **54** by analysis of both NMR spectroscopy and MS spectrometry, we were unable to obtain the compound in pure form with decomposition and contamination of other similar compounds always being a problem. In the case of the 6 membered ethyl substituted hydrochloride salt **55** some decomposition also occurred but we were able to isolate the desired material in 34% yield after recrystallisation from CH₂Cl₂ and diethyl ether.

Scheme 2-9: Synthesis of tricyclic analogues *via* reductive amination.

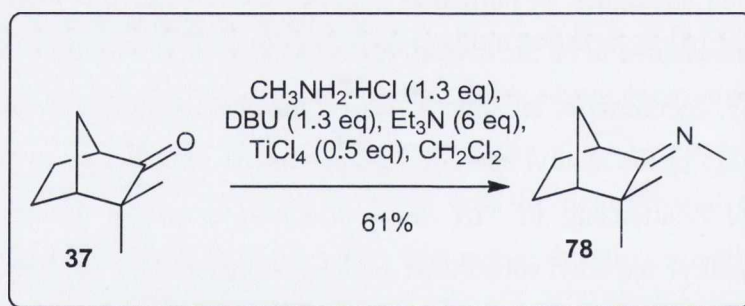
2.1.2 Synthesis of *endo*-mecamylamine analogues.

Figure 2-5: Structures of *exo*-MA and *endo*-MA.

As previously described in section 1.6.1, *endo*-MA displayed superior activity than its *exo* counterpart (Figure 2-5) in preliminary *in vitro* biological testing at $\alpha 4\beta 2$ nAChR subtypes. Combined with the encouraging results returned from the initial series of methyl and ethyl substituted analogues, in particular the triethyl substituted compound **47**, the most logical step forward seemed to be the investigation of these alkyl variations combined with an *endo* amine moiety. Synthesis of an *endo* series (Figure 2-6) would allow us to compare the *endo/exo* relationship of the methyl and ethyl groups in MA. Further investigation of the *exo*-amine/*endo*-methyl relationship in MA would be performed by the synthesis of *endo*-analogues of the methyl and ethyl substituted analogues prepared by Dr. Mangan.

Figure 2-6: Proposed *endo*-MA analogues.

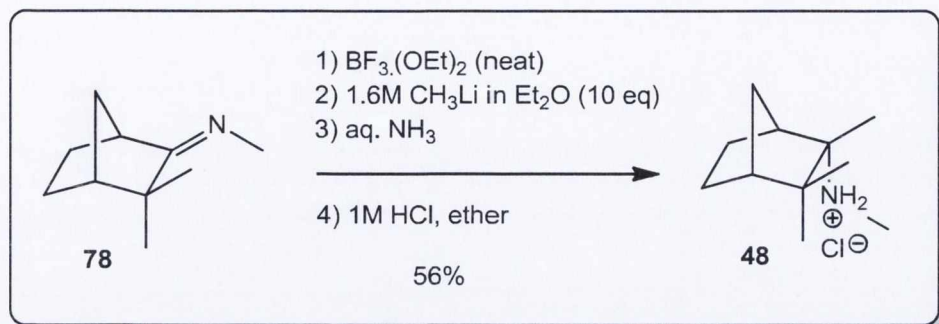
Previous work in the research group by Dr. Mangan involved the synthesis of methylated imine **77** by modification of synthetic routes devised by Suchocki *et al.*²⁸⁶ and Moss *et al.*²⁸⁷ The initial step involves the formation of an imine from the corresponding dimethyl ketone **37**, (Scheme 2-10). 1,8-Diazabicycloundec-7-ene (DBU) was added to ground and dessicated methylamine hydrochloride salt in anhydrous CH_2Cl_2 and stirred for approximately 5 minutes until the insoluble hydrochloride salt was no longer visible. Once the salt had been deprotonated, a large excess of triethylamine was added, followed by titanium (IV) chloride at which point a blood red colour was observed. The mixture was heated at reflux temperature prior to the addition of ketone **37** in order to facilitate ligand exchange between the titanium (IV) chloride and triethylamine. The imine **78** was isolated cleanly without need for further purification after filtration through a thick pad of silica.



Scheme 2-10: Conditions for formation of methylated imine, prepared by Dr. Mangan.

The next step in the synthetic sequence was the addition of methyllithium to the imine. This was achieved by adding neat boron trifluoride etherate to imine **78**. The Lewis acid presumably formed a complex with the imine moiety. A large excess of methyllithium was required to achieve the addition and effervescence was observed during addition. The *endo* amine **48** was isolated cleanly after aqueous work-up using concentrated ammonia and the

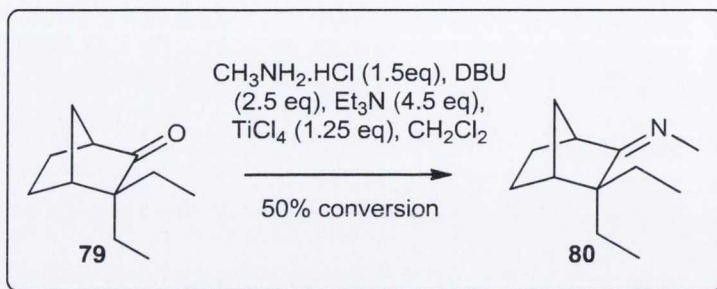
hydrochloride salt was formed by addition of a 1M solution of HCl in diethyl ether, (Scheme 2-11).



Scheme 2-11: Reduction of imine **78** to the desired *endo*-MA, prepared by Dr. Mangan.

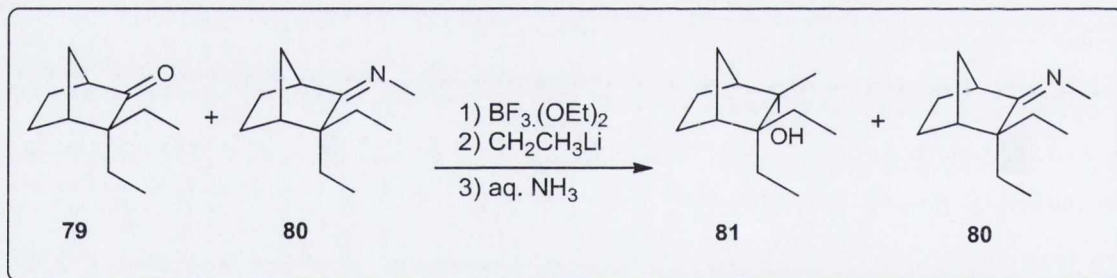
We intended to exploit this methodology to generate a library of *endo* analogues with methyl and ethyl substitution at positions 2 and 3, (Figure 2-6). At this time we had received the results of *in vitro* testing at the $\alpha 4\beta 2$ nAChR subtypes in which the *exo* triethyl substituted compound **47** had displayed the best activity. It was for this reason that we chose the corresponding *endo* triethyl compound **77** as our first synthetic target in this series. Unfortunately, the initial imine formation proved problematic and we were unable to force its formation to completion, (Scheme 2-12). Employing the conditions developed by Dr. Mangan a 50% conversion to the desired imine was achieved. We then sought to optimise the imine formation. Our first alteration to the procedure involved increasing reaction time from 16 hours to 4 days and with close monitoring by NMR spectroscopy. During this time conversion failed to increase beyond 50% and after approximately 24 hours at 40 °C decomposition of both the imine **80** and the ketone precursor **79** had commenced. As longer reaction times seemed to promote decomposition we decided to increase the number of molar equivalents of reagents in an individual fashion. Titanium tetrachloride was increased to 1.8 molar equivalents, DBU was increased to 3.5 molar equivalents and methylamine hydrochloride was increased to 2.5 molar equivalents; however, no increase in conversion was observed. In order to ensure no trace of water was present in the reaction 4 Å molecular sieves were added but, again, no change in the conversion was observed. We thought that perhaps the methylamine was a little volatile and was being lost, so to assess if this was the case an additional equivalent of methylamine hydrochloride and DBU were added after approximately 16 hours reaction; yet again, no improvements were observed. We believe that the difficulties

encountered in the imine formation were due to increased steric bulk imposed by the ethyl groups. As the conversion could not be improved and the imine could not be purified due to its instability in the presence of water the mixture of imine **80** and ketone **79** was employed in the following step.



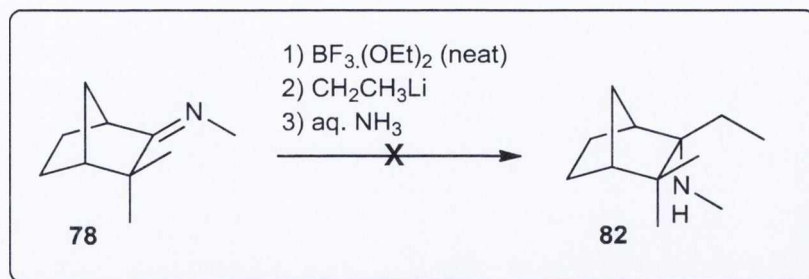
Scheme 2-12: Formation of methylated imine.

The next step involved the addition of an organolithium reagent, (Scheme 2-13). Due to the problems encountered during imine formation we chose to employ methyllithium over ethyllithium in our initial attempts. Treatment of the mixture of imine **80** and ketone **79** with neat boron trifluoride etherate and methyllithium pursuant with the methodology developed by Dr. Mangan, returned a mixture of unreacted imine and methylated alcohol **81**, (Scheme 2-13).

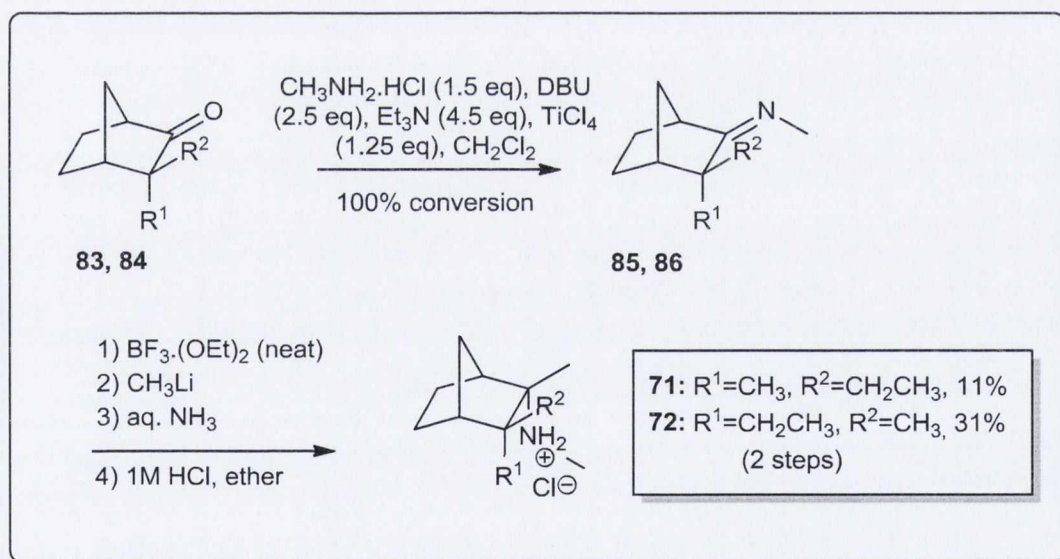


Scheme 2-13: Attempted addition of MeLi to imine **80**.

Having failed to isolate the desired amine we wanted to assess the steric restraints in the reaction so we turned our attention to the less bulky imine **78** which we had previously prepared. Treatment of dimethylated imine **78** with boron trifluoride etherate and ethyllithium for 6 hours returned the unreacted imine after work-up, (Scheme 2-14).

Scheme 2-14: Attempted synthesis of amine **82**.

To finalise our investigation into the steric demands of the reaction we attempted to prepare the two mono ethyl targets illustrated in Scheme 2-15. Gratifyingly the imine formation for both ketones **83** and **84** proceeded smoothly and extremely high conversion was achieved, although slight contamination was present, purification at this point was not possible. Treatment of the crude imines **85** and **86** with boron trifluoride etherate and methyl lithium gave *endo* analogues after work-up. The hydrochloride salts **71** and **72** were formed by treatment with a 1M solution of HCl in diethyl ether and were purified *via* recrystallisation using CH_2Cl_2 and diethyl ether, (Scheme 2-15).

Scheme 2-15: Synthesis of *endo* MA analogues.

2.2 Alterations to position 2.

This section describes attempts to synthesise analogues of MA with differing functionality at position 2 of the parent compound, (Figure 2-7).

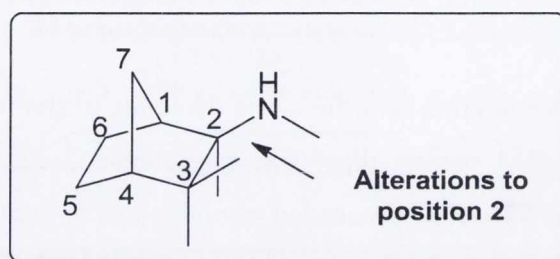


Figure 2-7: Targeting position 2 on the MA skeleton.

2.2.1 Synthesis of an aromatic MA analogue.

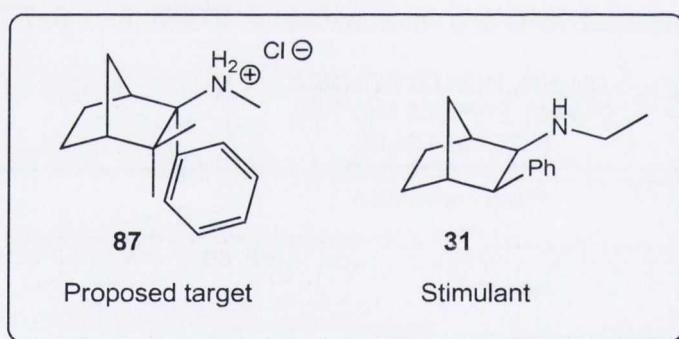
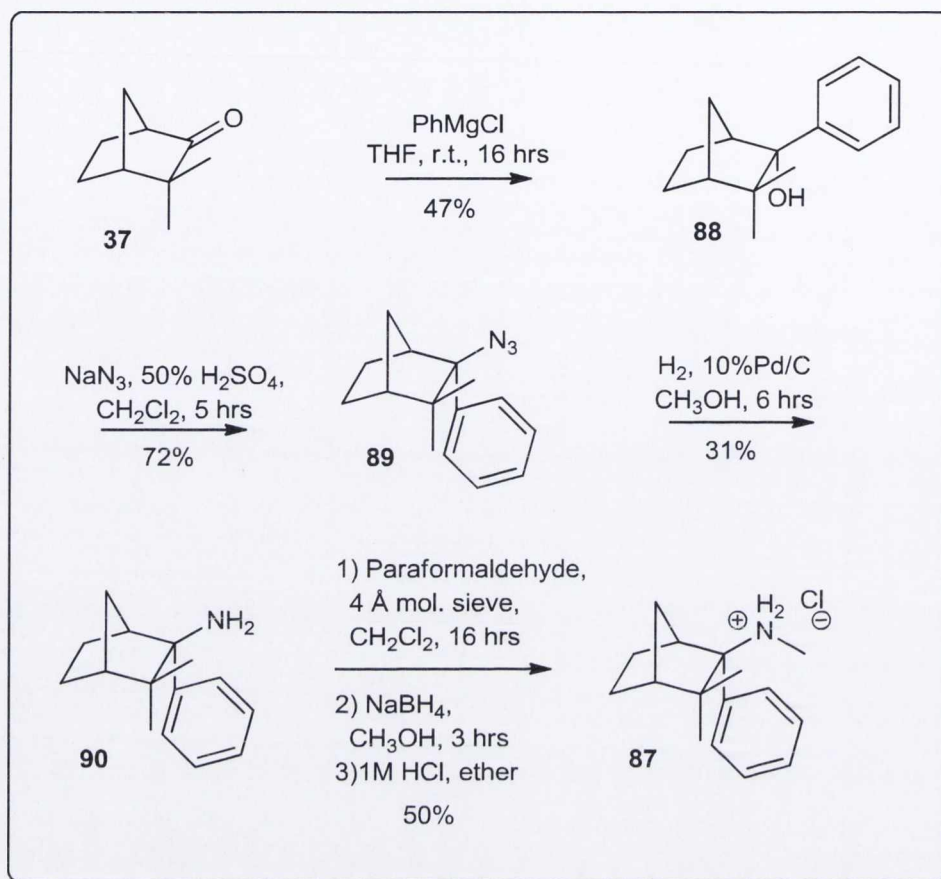


Figure 2-8: Proposed Aromatic MA target and stimulant prepared by Suchocki *et al.*²⁶⁴

It was clear from the work of Suchocki *et al.*,²⁶⁴ that the introduction of an aromatic species could have had a dramatic effect on activity. Suchocki showed that a phenyl substituted analogue **31** (Figure 2-8), had stimulant effects. Considering the lack of general SAR information on the MA structure we thought that the installation of a phenyl group at the 2 position (compound **87**) would be an interesting compound to investigate, (Figure 2-8).

The first step in the synthetic sequence was the installation of the phenyl ring using a Grignard reagent. Treatment of ketone **37** with an excess of phenylmagnesium chloride in

anhydrous tetrahydrofuran for 16 hours gave the expected alcohol **87** in a disappointing 47% yield after purification, (Scheme 2-16). With the tertiary alcohol in hand we turned our attention towards azide formation. Treatment of alcohol **88** with 50% H_2SO_4 and an excess of sodium azide in CHCl_3 for 5 hours furnished the desired azide **89** in 72% yield after purification, (Scheme 2-16). The reaction proceeded smoothly and none of the problematic Wagner-Meerwein product was observed. Azide **89** was exposed to hydrogen in the presence of 10% palladium on charcoal, (Scheme 2-16). Unfortunately, the amine **90** was isolated in a low 31% yield. The final step in our synthetic sequence involved the treatment of amine **90** with paraformaldehyde and 4 Å molecular sieves in anhydrous CH_2Cl_2 at reflux temperature for 16 hours which furnished the desired imine, (Scheme 2-16). Again the reaction was monitored by NMR analysis to ensure complete consumption of amine **90**. The imine was not isolated and was treated directly with sodium borohydride in methanol. After work-up the amine was treated with a solution of 1M HCl in diethyl ether to furnish the expected hydrochloride salt **87** in a reasonable yield of 50%, (Scheme 2-16). This compound has been evaluated against $\alpha 3\beta 4$ nAChR receptor subtypes expressed in SH-SY5Y cells in the presence of 100 μM of nicotine.²⁸² A response of 28.1% was observed when cells pretreated with phenyl substituted analogue **87** were treated with 100 μM of nicotine. This analogue produced the lowest antagonistic response during testing of the library against the $\alpha 3\beta 4$ nAChR. Unfortunately, the compound has not been tested at the $\alpha 4\beta 2$ nAChR subtype. It is important to note that while a drop in antagonistic activity is potentially undesirable, these modifications could be increasing the selectivity for one receptor subtype over another. It is necessary to perform further testing at other nAChR subtypes in order to ascertain whether an increase in selectivity has been accomplished.



Scheme 2-16: Synthesis of aromatic MA-analogue 87.

2.3 Alterations to the amine.

This section describes the attempts to synthesise analogues of MA with differing functionality at the amine position, (Figure 2-9).

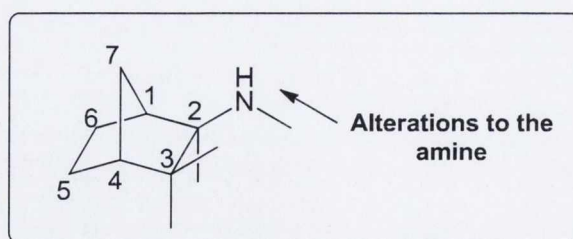


Figure 2-9: Targeting the amine moiety.

2.3.1 Amine Functionalisation.

As previously mentioned (section 1.5.3), SAR studies of MA performed by Stone *et al.*²⁶¹ and Suchocki *et al.*²⁶⁴ had shown that MA analogues with more sterically demanding *N*-alkyl substitution than methyl produced a reduction in *in vivo* antagonist activity. However, the compounds in these SAR studies were tested by observing the ability to dilate pupils, reduce nicotine induced convulsions and reduce contractions in cat nictitating membrane. The testing of antagonistic activity at individual receptor subtypes was not possible at the time these studies were reported. It is also noteworthy that dimers and trimers of MA prepared by Crooks and co-workers²⁷² displayed high levels of activity when investigated for their ability to inhibit nicotine induced DA release in rat striatal slices. It is clear that further investigation in this area is required because advancements in cloning technologies have allowed individual subtypes to be investigated. We therefore endeavoured to synthesise a small but diverse library of *N*-substituted MA analogues.

2.3.2 Alkyl alterations to the amine.

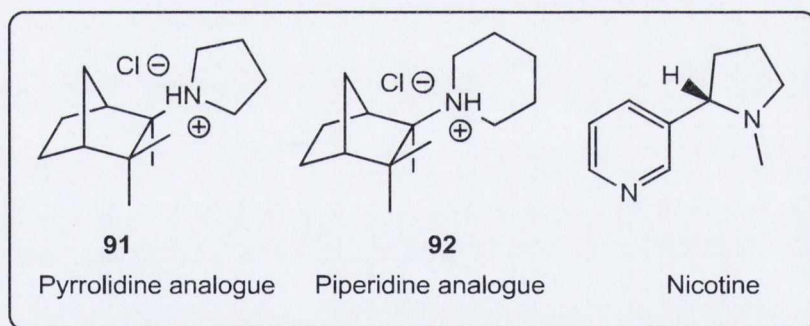
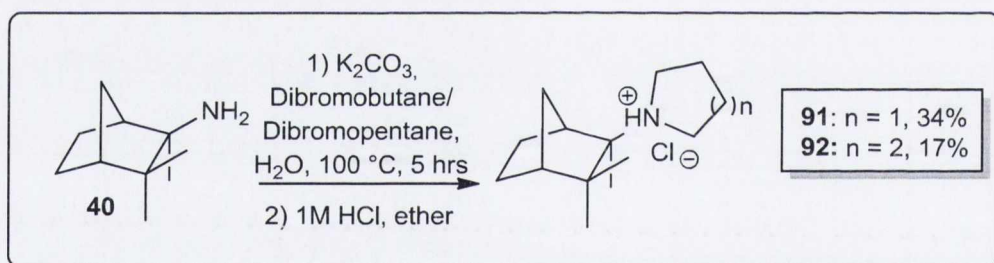


Figure 2-10: Proposed alkyl alterations to MA and nicotine comparison.

Previous reports have implied that increased steric bulk around the amine moiety hinders antagonistic activity. As technology now allows us to test individual nAChR receptor subtypes, it would be prudent to re-examine the alteration of alkyl substitutions at the amine. The preparation of 5 and 6 membered *N*-heterocyclic derivatives would be interesting. Especially when the presence of a pyrrolidine group in the structure of nicotine is considered, (Figure 2-10).

Fortunately, the microwave assisted aqueous *N*-heterocyclisation of primary amines has been reported by Ju and Varma.²⁸⁸ We planned to exploit this methodology to prepare both pyrrolidine and piperidine analogues of MA. Treatment of amine **40** with 1.1 equivalents of potassium carbonate and 1.1 equivalents of either dibromobutane or dibromopentane in water at 100 °C for 30 minutes under microwave irradiation furnished the desired tertiary amines **91** and **92** albeit in extremely low yields. Reaction times were investigated in order to improve mass return; however, we failed to isolate the desired products in crude yields greater than 10%. Also, many decomposition products contaminated the material and attempts to purify *via* column chromatography were fruitless. It was found that conventional heating afforded superior yields than microwave irradiation in this case, which was thought to be due to the decomposition of material. A suspension of amine **40**, 1.1 equivalents of potassium carbonate and either dibromobutane or dibromopentane in water heated at reflux temperature for 5 hours furnished the desired tertiary amines **91** and **92** after work-up. The hydrochloride salts were formed by treatment with a solution of 1M HCl in diethyl ether and were purified *via* repeated trituration with diethyl ether, (Scheme 2-17).



Scheme 2-17: Synthesis of *N*-heterocyclic MA analogues.

2.3.3 Amine Functionalisation *via* Click Chemistry.

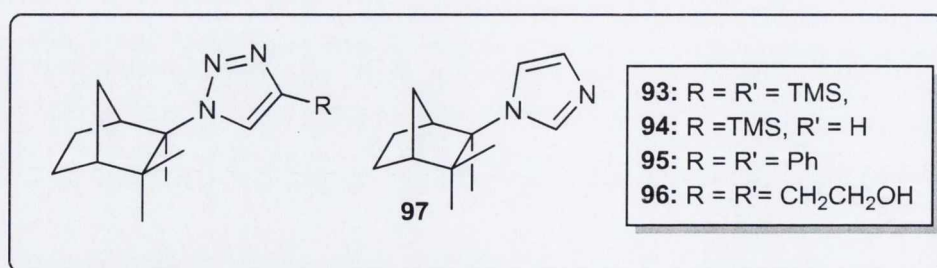
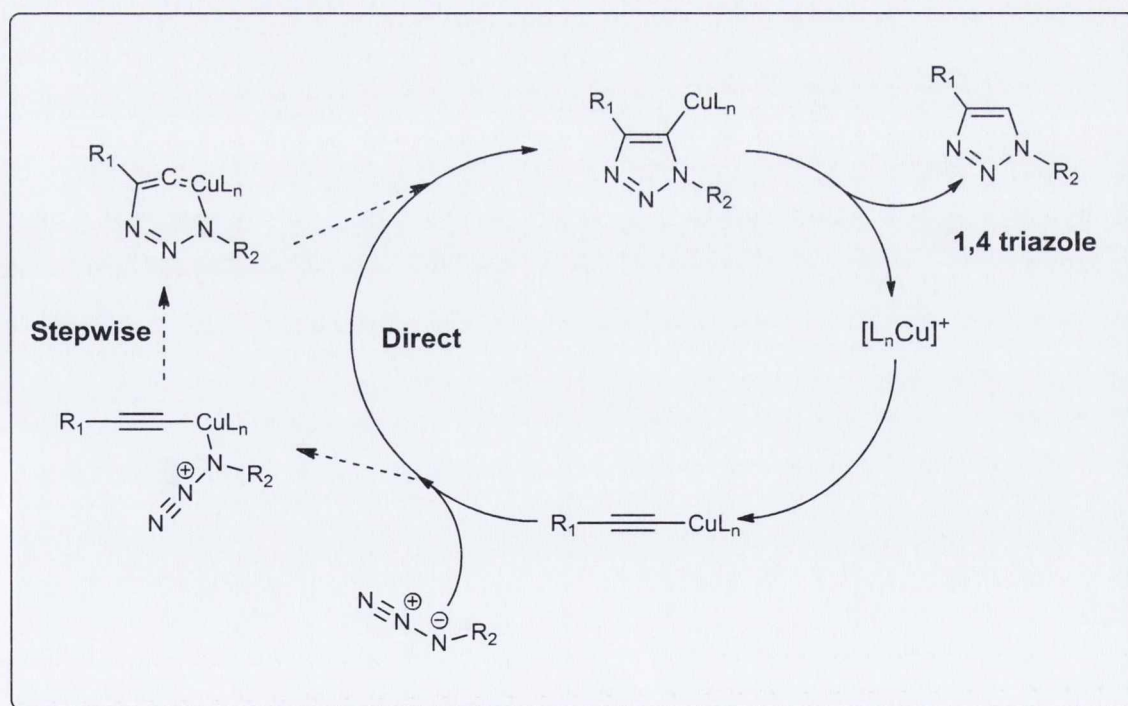


Figure 2-11: Proposed triazole and imidazole MA structures.

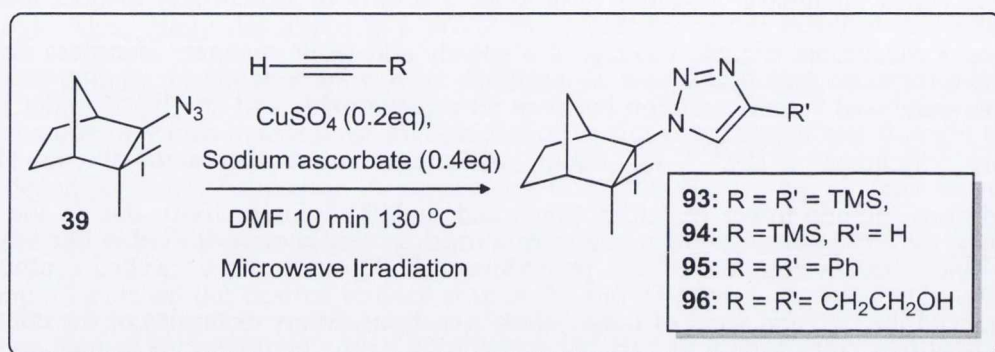
Alterations of the amine moiety would probe the H-bond relationship with the receptor. Installing imidazoles or triazoles would generate new compounds with variable pK_a profiles. We wanted to synthesise a small library of aromatic variants which contain triazole or imidazole moieties, (Figure 2-11).

The generation of an azide in our novel synthetic route gave us the advantage of employing "click chemistry" in order to produce a library of structurally distinct analogues containing a substituted triazole moiety, in a speedy and facile manner. Sharpless described the copper-catalysed "click" reaction between an organic azide and an alkyne under thermal conditions, (Scheme 2-18).²⁸⁹ Its major advantages over the azide-alkyne Huisgen cycloadditions include lower reaction times and higher regioselectivity due to the use of copper. Since the development of this procedure in 2002, microwave assisted synthesis has also enhanced the rate and yield of these "click" reactions. Many examples of the microwave assisted synthesis have been described in the literature.²⁹⁰ It was our intention to synthesise a small library of substituted triazole analogues by exploiting these methodologies and with the assistance of microwave irradiation.



Scheme 2-18: Catalytic cycle for Cu-catalysed azide-alkyne click reaction.²⁸⁹

The proposed catalytic cycle for this reaction is outlined in Scheme 2-18. The initial step is formation of the copper acetylide. As expected, no reaction is observed under these conditions with internal alkynes. Extensive density functional theory calculations performed by Himo *et al.* strongly disfavoured a concerted [2+3] cycloaddition mechanism and suggested a stepwise mechanism which proceeds *via* a six membered copper-containing intermediate.²⁹¹



Scheme 2-19: Azide-alkyne copper catalysed click synthesis of triazoles **93**–**96**.

Four triazole analogues were selected purposefully with a view towards installing differing functionality on the triazole component. Treatment of azide **39** with the appropriate terminal alkyne, 0.2 equivalents of copper sulfate and 0.4 equivalents of sodium ascorbate in DMF at 130 °C for 10 mins under microwave irradiation furnished the desired triazole analogues **93**, **94**, **95** and **96**. An unsubstituted triazole analogue **94** was isolated in a 29% yield *via* the corresponding silyl alkyne, aromaticity was introduced by means of a phenyl substituted triazole **95** in 64% yield and an alcohol substituted analogue **96** was also isolated in 47% yield. A trimethylsilyl protected triazole **93** was also isolated in 17% yield, (Scheme 2-19). This compound was isolated only once when the TMS protecting group failed to eliminate during the work-up.

2.3.4 Attempted synthesis of the imidazole analogue.

An imidazole substituted analogue we wanted to investigate is illustrated in Figure 2-12.

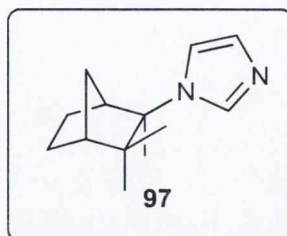


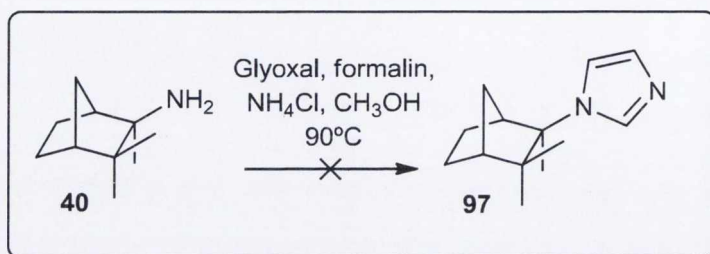
Figure 2-12: Proposed imidazole substituted MA target analogue.

Initial attempts involved a traditional²⁹² approach using glyoxal, an ammonium source, formaldehyde and amine **40**, (Scheme 2-20). Treatment of amine **40** with 1 equivalent of glyoxal, ammonium chloride and formalin in methanol heated at reflux temperature for 24 hours returned mostly starting material but with a small quantity of other material, (Scheme 2-10). Analysis of the NMR spectral information associated with the crude reaction mixture displayed promising signals in the imidazole. Unfortunately, this material could not be isolated. Instead n.O.e. and selective TOCSY experiments were performed on the crude reaction mixture in order to determine if imidazole formation had occurred at the amine **40**. Unfortunately, analysis showed that these signals in the imidazole region were not connected to the MA skeleton. Table 2-1 shows alterations to the reaction conditions. Regrettably, only the starting material and unsubstituted imidazole were recovered from the reaction mixture after work-up.

Utilising a procedure reported for the synthesis of *tert*-butyl imidazole *via* a similarly hindered reagent,²⁹³ the amine salt was generated by a H₃PO₄ solution in water at pH 2. The amine salt, glyoxal and formalin were heated to 95 °C in water for 1 hour upon which time a solution of ammonium chloride was added dropwise. The reaction continued at 95 °C for a further two hours. Disappointingly, the amine **40** was returned once again after work-up and unsubstituted imidazole was formed.

In a final attempt to force the formation of the imidazole moiety at amine **40** we decided to proceed in a stepwise manner. Firstly, amine **40** was treated with glyoxal and 50% H₂SO₄ in methanol heated at reflux temperature for 24 hours. Then ammonium acetate and formalin were added and heating was continued at reflux temperature for a further 24 hours. We hoped that, by treating the amine with glyoxal before addition of ammonium acetate, the imine would form at the correct amine, making the glyoxal unavailable to reaction with

ammonium acetate and avoiding the formation of the unsubstituted imidazole. Frustratingly only starting material was recovered from the reaction mixture affirming our previous worry that imidazole formation at the correct amine **40** could not be forced due to the steric congestion from positions 2 and 3.

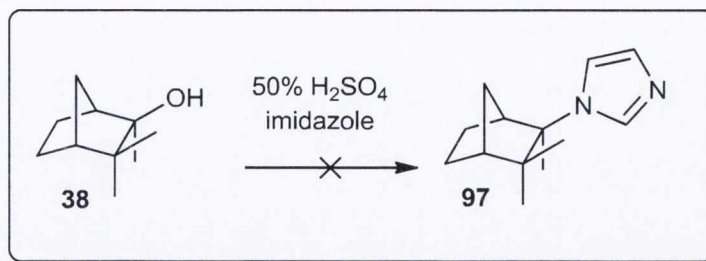


Scheme 2-20: Attempted synthesis of imidazole substituted MA.

Table 2-1: Attempts to force the formation of MA imidazole.

Amine	Reagents	Time	Temp	Results
40	Glyoxal, NH ₄ Cl, Formaline	24 hrs	90 °C	Starting material
40	Glyoxal, NH ₄ Cl, Formaline, 10% H ₂ SO ₄	19 hrs	90 °C	Starting material
40	Glyoxal, NH ₄ Cl, Formaline, 10% H ₂ SO ₄	68 hrs	90 °C	Starting material

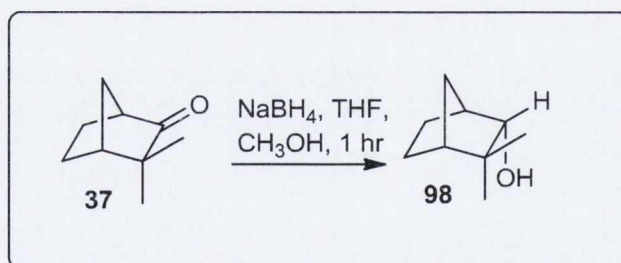
A final attempt to generate the analogue from the tertiary alcohol **38** was investigated by generation of a carbocation at position 2. It was somewhat hopeful that a small portion of the imidazole would remain unprotonated in solution and would be available to attack the carbocation at position 2. Alcohol **38** was treated with 50% H₂SO₄ and an excess of imidazole in chloroform, (Scheme 2-11). The reaction was closely monitored by NMR spectroscopy and t.l.c. analysis over a period of four hours at which time NMR analysis of the crude mixture revealed approximately 50% of the material appeared to have undergone a Wagner-Meerwein rearrangement and none of the desired imidazole substituted product had formed.



Scheme 2-21: Attempted S_N1 synthesis of imidazole analogue *via* carbocation formation.

Although it would deviate from the devised structure we thought it might be possible to form an imidazole based structure if we were willing to sacrifice a methyl group. The tertiary centre severely limits the scope of possible reactions, while a secondary alcohol lacking the C2 methyl would allow for a range of functional group conversions such as the Mitsunobu or even S_N2 nucleophilic attack to be attempted. First we had to prepare the appropriate secondary alcohol **98**.

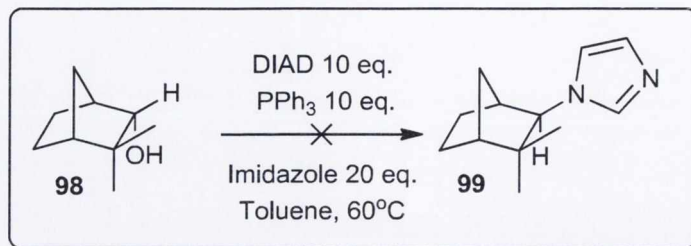
Treatment of dimethylated ketone **37** with an excess of sodium borohydride in a mixture of tetrahydrofuran and methanol gave the expected *endo* secondary alcohol **98** after work-up without the need for further purification, (Scheme 2-22). Once again the selectivity observed during this reaction was due to the "picket fence" effect which prevents attack from the lower face.



Scheme 2-22: Synthesis of the *endo*-alcohol **98**.

With the secondary alcohol **98** in hand we turned our attention towards generating the desired imidazole-MA **99** analogue by employing Mitsunobu chemistry. We intended to employ a methodology reported by Kim *et al.*²⁹⁴ who developed the Mitsunobu alkylation of imidazole using primary and secondary alcohols. With a pK_a of 14.5 imidazole is considerably less reactive than typical Mitsunobu nucleophiles and harsh conditions were employed to try to force the reaction. Alcohol **98**, 10 molar equivalents of triphenyl phosphine, DIAD and 20

molar equivalents of the imidazole nucleophile were heated at 60 °C in toluene for 24 hours, (Scheme 2-23). Unfortunately, only starting material was recovered after work-up.



Scheme 2-23: Conditions for the attempted Mistunobu reaction.

At this point we decided to abandon the pursuit of the imidazole analogue as it was deemed to be an unfeasible target due to high steric congestion. We decided that our efforts would be better put to use in other areas of amine functionalisation.

2.4. Conclusions.

While some difficulty was experienced largely due to steric hindrance and instability, many of the synthetic targets outlined in this chapter were prepared. A library of tricyclic analogues (compounds **52-55**) was successfully synthesised but, unfortunately, one of the series was lost to decomposition. A small library of broadly substituted triazole analogues (compounds **93-96**) was achieved; however, the attempted synthesis of an imidazole substituted MA analogue **97** could not be realised due to the steric congestion surrounding the amine moiety. An aromatic analogue **87** was successfully prepared. Alkyl modifications at the amine were achieved and both pyrrolidine **91** and piperidine **92** MA analogues were isolated successfully. Some difficulty was experienced during the attempted synthesis of a library of differently substituted alkyl *endo*-MA analogues but two analogues **71** and **72** were isolated. Unfortunately, the *endo* analogue **77** of the triethyl compound **47** (which had performed best in earlier testing) could not be isolated; however, the remaining two *endo* compounds **71** and **72** will still provide a comparison against their *exo* counterparts. We were able to determine the steric restraints associated with formation of the *endo* products. The compounds prepared will be assessed for activity at nAChR subtypes.

Chapter 3

Diversity in positions 5 and 6

3. Diversity in Positions 5 and 6.

Targets

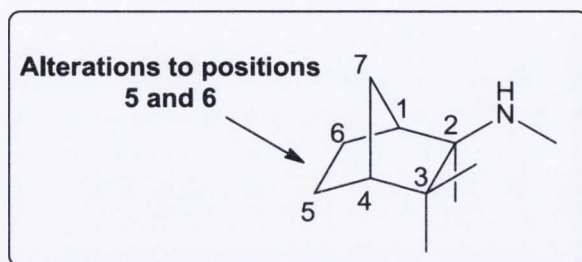


Figure 3-1: Targeting positions 5 and 6 on the MA skeleton.

Having prepared a library of analogues with alterations at positions 2 and 3 of MA, we turned our attention to the opposite side of the molecule, positions 5 and 6, (Figure 3-1). Little work has been reported with respect to this portion of the molecule. We wanted to probe the effects of substitution in this area so we tried to develop synthetic routes to 5,6 disubstituted systems and selective 5 or 6 substituted systems that would, ideally, allow for a variety of functionalisation. As previously mentioned in section 1.5.4., Crooks *et al.* successfully synthesised a series of MA dimers and trimers displaying inhibition of nicotine induced dopamine release of up to 73% in the presence of 10 μ M of nicotine.²⁷² These compounds were linked *via* long alky chains at the amine position which implies that entry to the pore occurs with the amine orientated towards the extracellular face of the ion channel. If this is the case then interaction of the [2.2.1]bicyclic system with the ion channel is clearly of paramount importance. Arias *et al.*²⁹⁵ performed a series of molecular docking studies investigating the binding of MA at $\alpha 4\beta 2$ nAChR subtypes. It was suggested that protonated *S*-(+)-MA interacted with a domain close to the extracellular edge of the TMD, the mouth of the ion channel. Alterations to positions 5 and 6 could provide more insight to the mode of binding, (Figure 3-2).

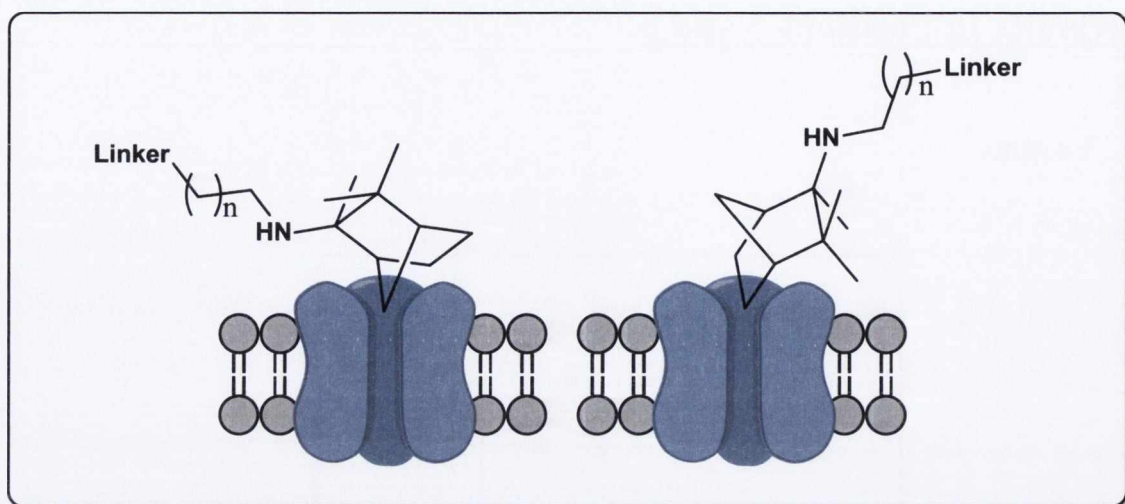


figure 3-2: Proposed orientation of binding of MA at nAChR.

With this in mind we chose a number of alterations which we believed would deliver a range of structural diversity. These alterations are shown in Figure 3-3 and discussed below.

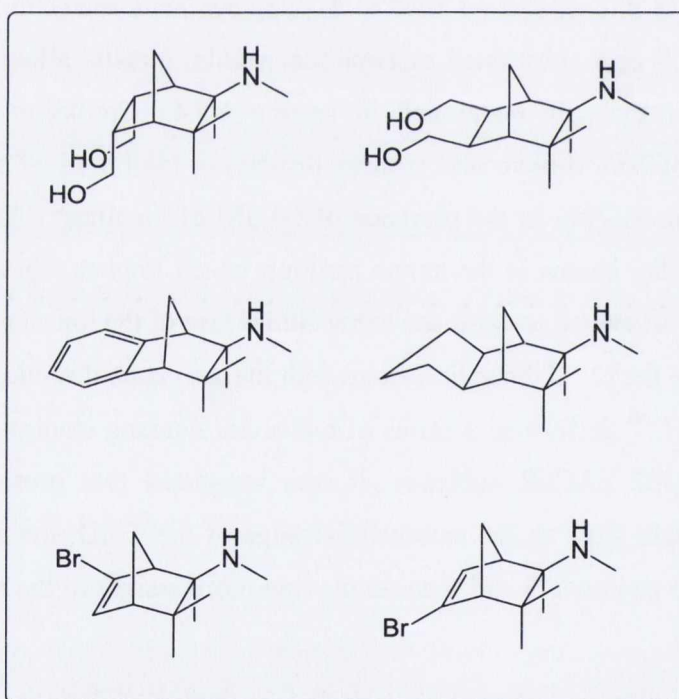


Figure 3-3: Proposed analogues containing substitution at positions 5 and 6.

3.1. Insertion of alcohol functionality.

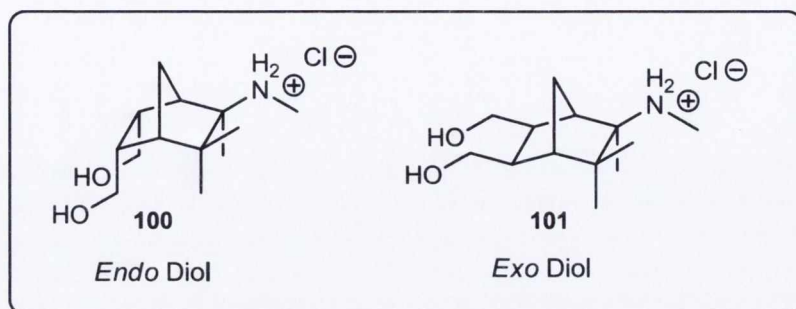


Figure 3-4: Proposed *endo* and *exo* MA diol targets.

The successful insertion of an alcohol moiety (Figure 3-4) would also provide a functional handle to introduce further functionality at those positions. As well as the expected protections and oxidative manipulations, Appel or Mitsunobu reactions would allow a range of possibilities, (Figure 3-5).

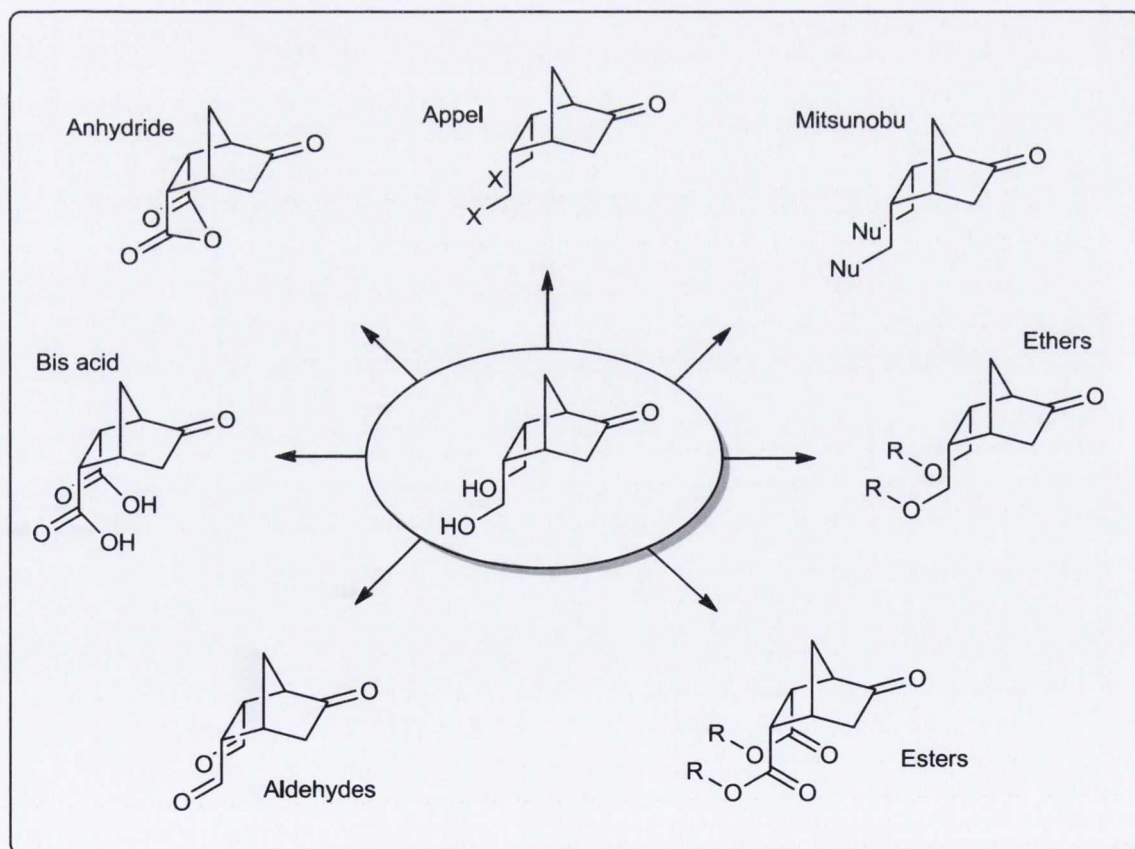
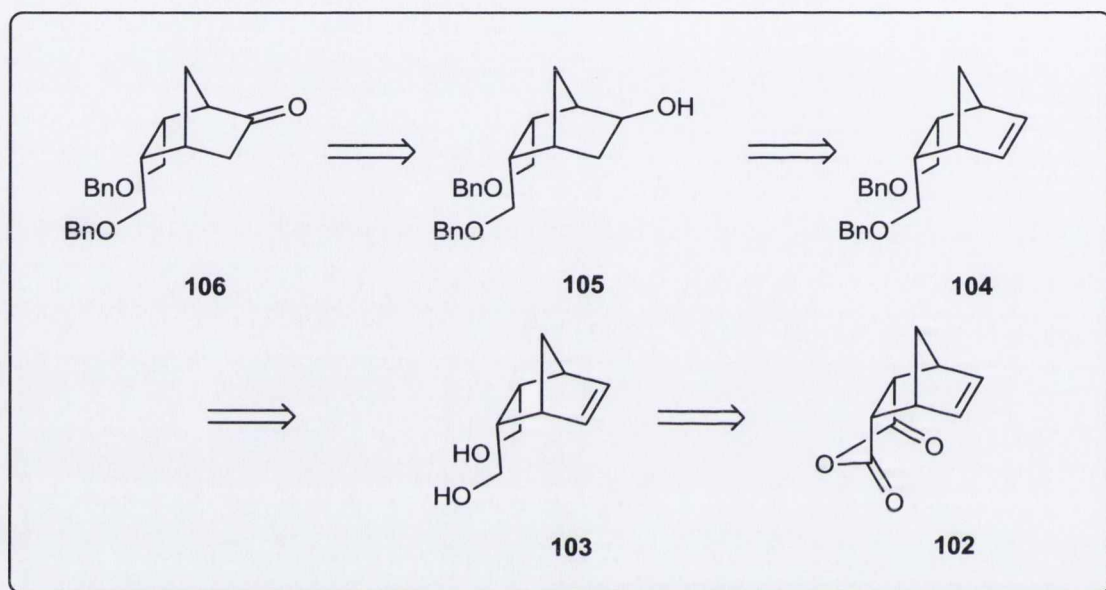


Figure 3-5: Potential modifications to the proposed diol targets.

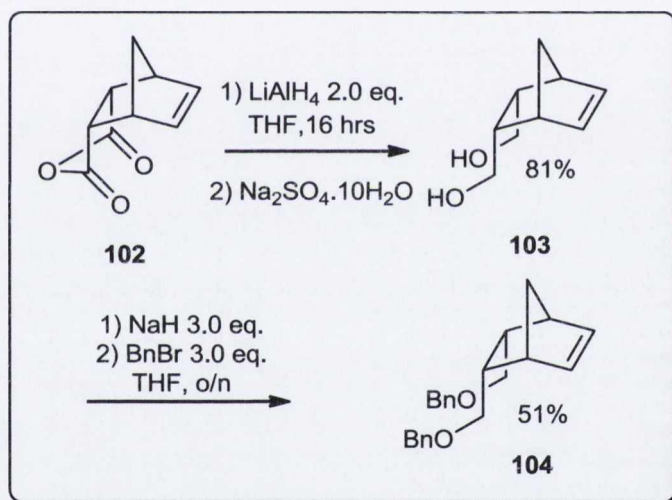
3.1.1 Attempted synthesis of *endo* diol MA analogue.

We intended to employ the same general procedure utilised in the syntheses of MA analogues. In order for this approach to be successful we would have to prepare the appropriate ketones containing the suitably protected alcohols at positions 5 and 6. Retrosynthesis of the necessary ketone is described in Scheme 3-1.



Scheme 3-1: Retrosynthesis of [2.2.1] bicyclic ketone containing protected alcohol moieties.

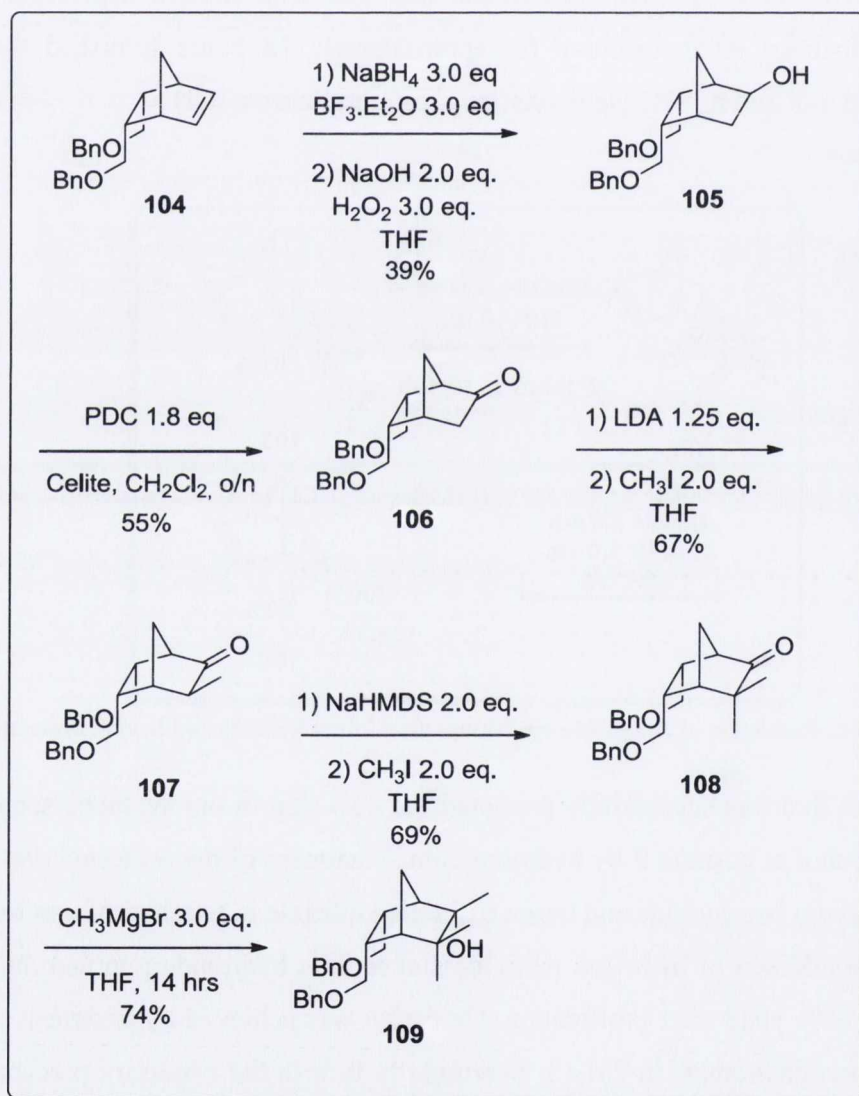
An ideal precursor to this route was *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride **102**, a cheap and commercially available material. Reduction of anhydride **102** using lithium aluminium hydride in anhydrous tetrahydrofuran for 16 hours gave the expected diol **103** albeit in meagre yields after work-up and purification. Poor mass return was attributed to a difficulty in extracting the material from the thick slurry formed during aqueous quenching of excess lithium aluminium hydride. Yields were unacceptably low in the first step of a lengthy synthesis, ranging from 48%-57%. Zhang *et al.*²⁹⁶ reported yields of 95% but using a non-aqueous work-up. While no further details were supplied, we employed the standard non-aqueous work-up for lithium aluminium hydride reactions, sodium sulfate decahydrate and the yield improved to 81%. Treatment of the diol **103** with sodium hydride and benzyl bromide in anhydrous tetrahydrofuran for approximately 18 hours furnished the desired benzyl protected diol **104** in 51% yield after purification, (Scheme 3-2).²⁹⁷



Scheme 3-2: Reduction of anhydride *via* lithium aluminium hydride and benzyl protection.

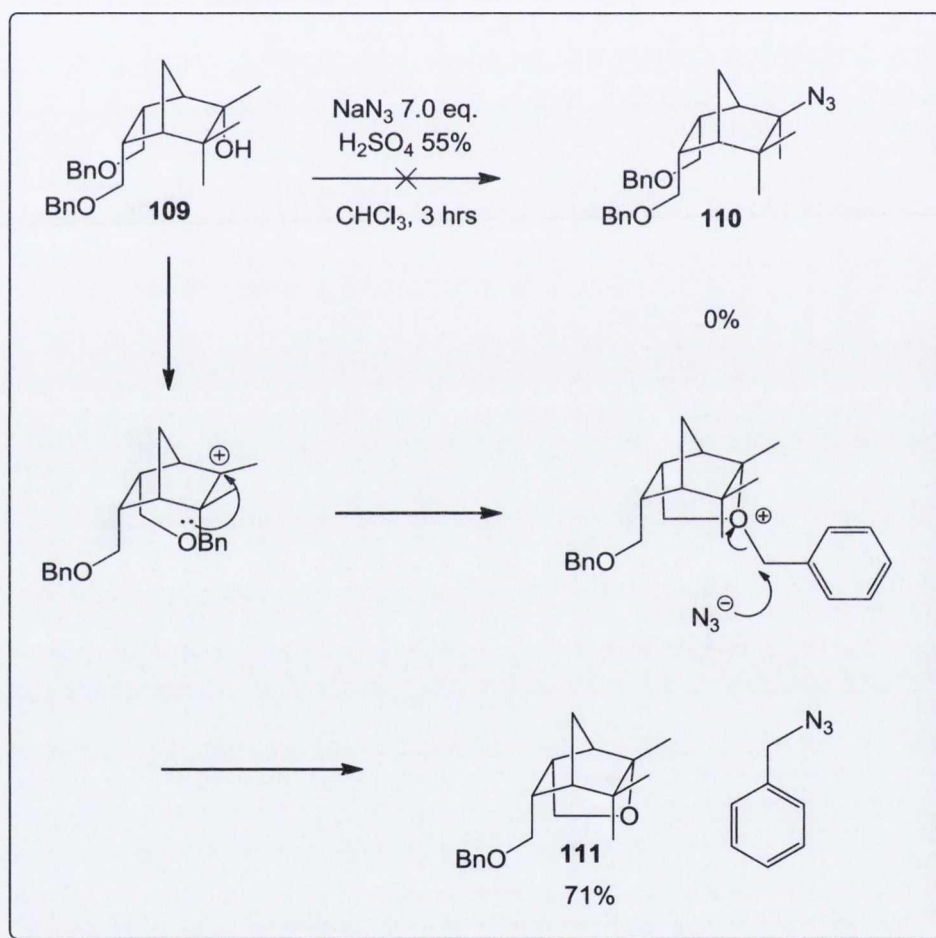
Once the diol was successfully protected the next step in our synthetic sequence was to install an alcohol at position 2 by hydroboration. Treatment of the protected diol **104** with an excess of sodium borohydride and boron trifluoride etherate in tetrahydrofuran for 3 hours, followed by the addition of hydrogen peroxide and sodium hydroxide returned the expected alcohol **105** in 39% yield after purification. Oxidation was achieved by treatment of alcohol **105** with pyridine dichromate in CH_2Cl_2 overnight to furnish the necessary precursor ketone **106** in 55% yield after purification, (Scheme 3-3). With the necessary ketone **106** successfully prepared we planned to continue our synthesis in a similar manner to that previously

developed. Treatment of ketone **106** with 1.25 molar equivalents of freshly prepared LDA followed by 2 molar equivalents of iodomethane furnished the expected mono methylated ketone **107** in 67% yield after acidic work-up. Treatment of the mono methylated ketone **107** with 2 molar equivalents of NaHMDS followed by 2 molar equivalents of iodomethane gave the desired dimethylated ketone **108** in 69% yield after purification. The next step involved the introduction of a third methyl group using a Grignard reagent. Treatment of ketone **108** with an excess of methylmagnesium bromide in tetrahydrofuran at room temperature for 14 hours afforded the expected tertiary alcohol **109** in 74% yield after purification, (Scheme 3-3).



Scheme 3-3: Synthesis of *endo* trimethylated alcohol **109**.

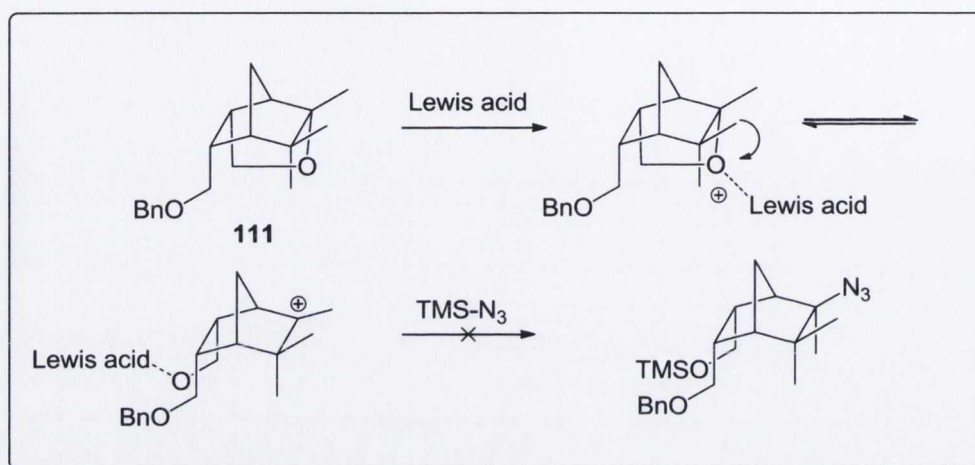
The next step in the sequence involved the insertion of the azide moiety at position 2 and this proved to be problematic. Treatment of alcohol **109** with 55% H_2SO_4 and an excess of sodium azide in CHCl_3 for 3 hours returned the ring closed product **111** in 71% yield after purification, (Scheme 3-4). In previous work we had been able to control rearrangements by altering the acid concentration. Unfortunately, in this case it did not eradicate the problem, at concentrations of up to 50% H_2SO_4 no reaction took place and only starting material was recovered from the reaction mixture. After 3 hours reaction at concentrations higher than 50% the starting material had been consumed and the cyclic ether formed in 71% yield.



Scheme 3-4: Formation of cyclic ether **111**.

Although we were disappointed with the formation of the cyclic ether we thought we might still be able to exploit it in our synthetic strategy and even enhance the previous route by permitting a selective deprotection of the alcohol in position 6. We hoped that treatment of the cyclic ether with a strong Lewis acid might open the ether ring to reveal a cation at

position 2 which could be intercepted by an azide to give the azide **110**. Clearly, we could not employ sodium azide because of insolubility in solvents compatible with Lewis acids so we employed TMS azide in its place, (Scheme 3-5). Frustratingly, after multiple attempts (Table 3-1), only the tricyclic material was recovered from the reaction mixture.

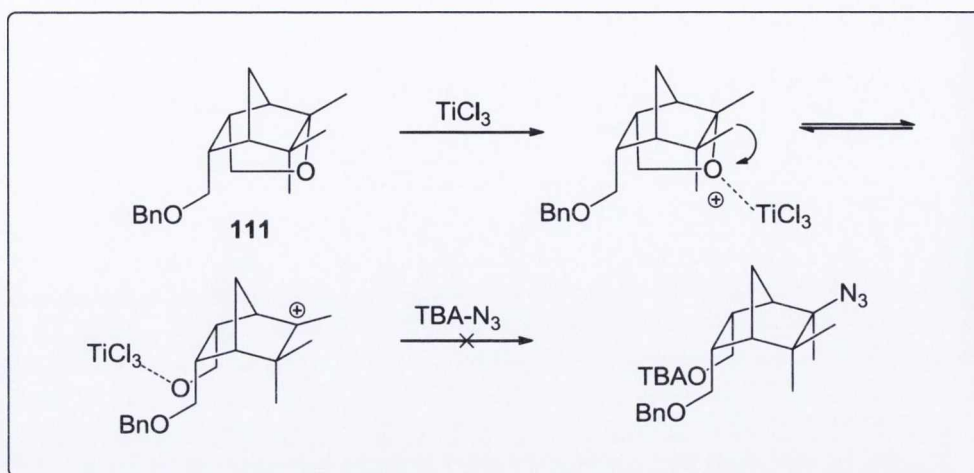


Scheme 3-5: Attempt to ring open cyclic ether **111**.

Table 3-1: attempted formation of azide **110** by ring opening cyclic ether **111**.

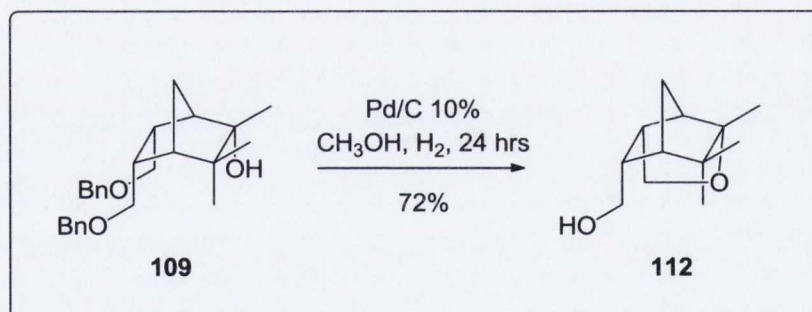
Lewis acid	Nucleophilic azide	Time monitored	Outcome
BF ₃ .Et ₂ O	TMS-N ₃	20 hours	No reaction observed
TiCl ₄	TMS-N ₃	19 hours	No reaction observed
TiCl ₄	TMS-N ₃	5 hours	Protecting group removed
SnCl ₄	TMS-N ₃	2 hours	No reaction observed
TMS-OTf	TMS-N ₃	3 hours	No reaction observed
TiCl ₃	TBA-N ₃	22 hours	No reaction observed

In order to ascertain whether the azide was not sufficiently nucleophilic we attempted to prepare tetra-*n*-butylammonium azide by treating TMS-azide with one molar equivalent of tetra-*n*-butylammonium fluoride. This mixture was added to a solution of cyclic ether **111** in anhydrous CH₂Cl₂ in the presence of TiCl₃. Unfortunately only cyclic ether **111** was isolated after work-up, (Scheme 3-6). In this short study we were not able to ascertain whether the lifetime of the cation was too short due to recyclisation or if it was formed at all.



Scheme 3-6: Attempted formation of TBA-azide.

It seemed that the ring opening route would be fruitless so we decided to try and prevent its formation by changing protecting groups from benzyl to more robust methyl groups. Rather than prepare the methyl protected diol from scratch we decided to remove the benzyl protecting groups and then re-protect the alcohols as methyl ethers. Removal of the benzyl groups was attempted by exposure to hydrogen in the presence of 10% palladium on charcoal at atmospheric pressure. Unfortunately, much to our dismay, a ring closing reaction took place and the expected triol was not isolated. Instead a similar cyclisation occurred and cyclic ether **112** was isolated in 72% yield after work-up, (Scheme 3-7).



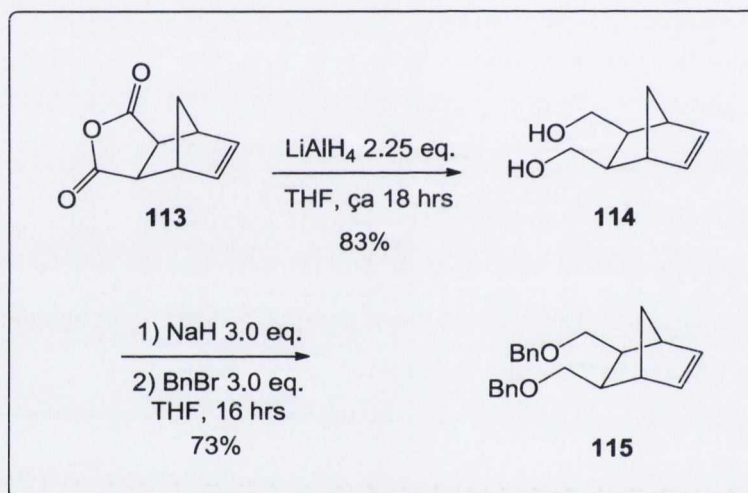
Scheme 3-7: Spontaneous ring closure during catalytic hydrogenation.

From analysing the structure of tertiary alcohol **109** it was evident that the orientation of the benzyl ether at the 6 position was ideal for interception of the tertiary cation, (Scheme 3-4). We were interested in both *endo* and *exo* isomers so we decided to focus on the *exo* derivative to try and develop the methodology. To do this we planned to use the same route

but switch from *cis*-5-norbornene-2,3-*endo*-dicarboxylic anhydride **104** to *cis*-5-norbornene-2,3-*exo*-dicarboxylic anhydride **113**.

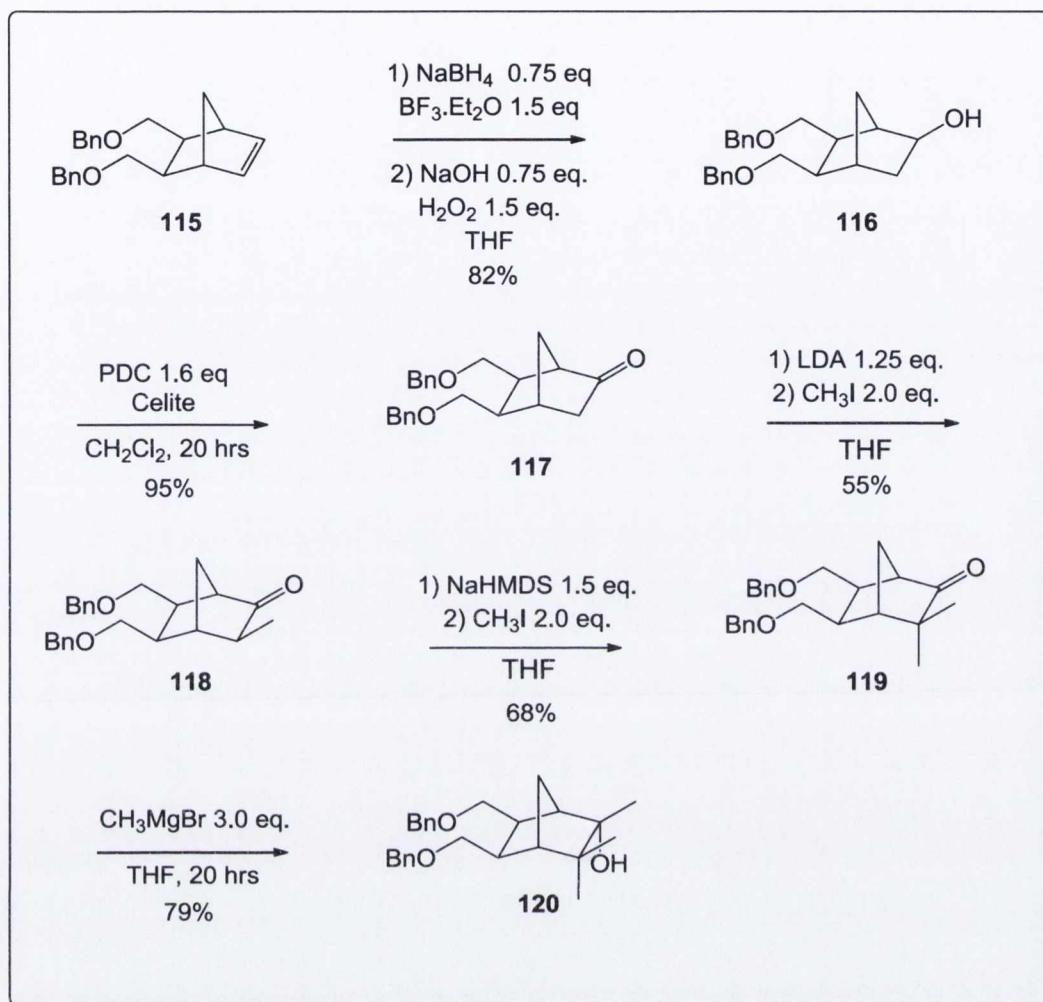
3.1.2 Attempted synthesis of *exo* diol MA analogue.

Treatment of *exo* anhydride **113** with lithium aluminium hydride in tetrahydrofuran for 18 hours gave the expected *exo* diol **114** in excellent yields of 83% after non-aqueous work-up and purification. Treatment of diol **114** with 3 molar equivalents of sodium hydride for 1 hour followed by the addition of 3 molar equivalents of benzyl bromide gave the benzyl protected ether **115** in 73% yield, (Scheme 3-8).

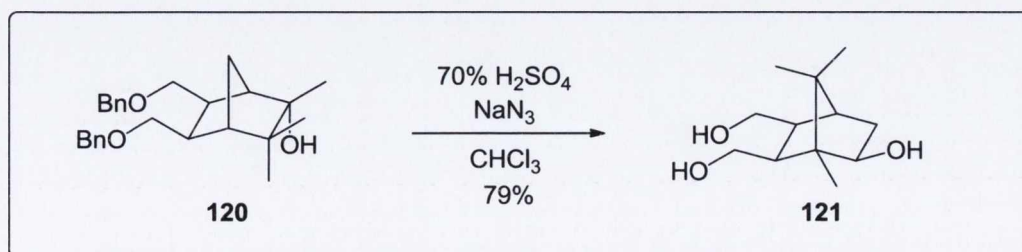


Scheme 3-8: Synthesis of benzyl protected *exo* diol.

In accordance with the methodology previously described at the beginning of this chapter, hydroboration of the protected *exo* diol **115** furnished the desired alcohol **116** in excellent yields of 82% after purification. Treatment of alcohol **116** with pyridinium dichromate in anhydrous CH_2Cl_2 gave ketone **117** in 95% yield after purification, (Scheme 3-9). Alkylations were achieved using LDA and iodomethane in the first step with 55% yield after purification and NaHMDS was employed in the second alkylation generating the expected dimethylated ketone **119** in 68% yield after purification. Treatment of ketone **119** with an excess of methylmagnesium bromide in anhydrous tetrahydrofuran for 20 hours gave the expected tertiary alcohol **120** in 79% yield after purification, (Scheme 3-9).

Scheme 3-9: Synthesis of the *exo* benzyl protected tertiary alcohol 120.

Once again the azide formation proved problematic. Concentrations of H_2SO_4 of up to and including 65% in combination with sodium azide and CHCl_3 returned only starting material. However, if a slightly higher concentration of 70% H_2SO_4 was employed then the Wagner-Meerwein rearranged product was isolated in 66% yield, (Scheme 3-10). Unfortunately, none of the desired azide was isolated.



Scheme 3-10: Formation of the Wagner-Meerwein product 121.

Due to the problems described we decided to focus on another approach, namely the installation of an aromatic moiety at the 5,6 positions.

3.2 Introduction of Aromaticity at positions 5 and 6.

3.2.1 Attempted synthesis of an aromatic tricyclic MA analogue.

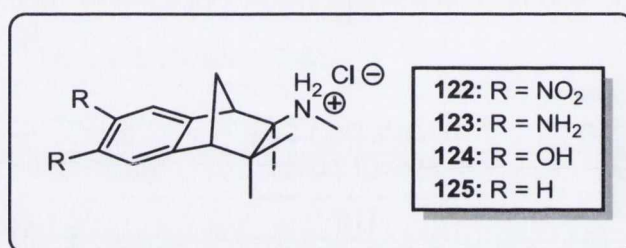
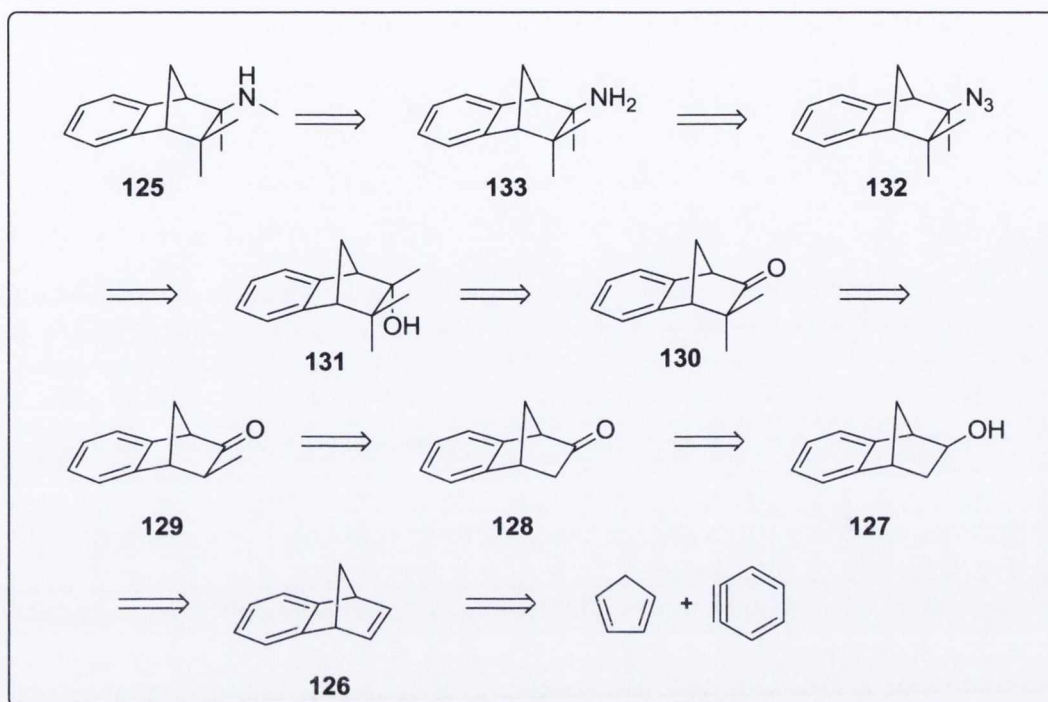


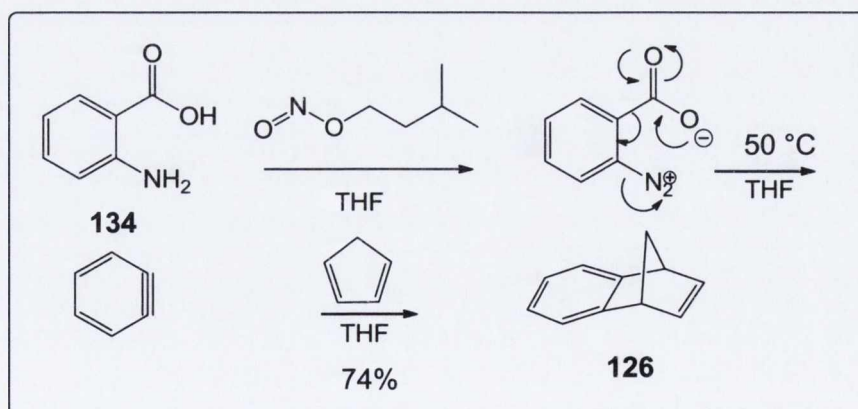
Figure 3-6: Proposed aromatic targets.

Initially we envisioned the synthesis of our aromatic target shown in Figure 3-6 to be pursuant with the methodology described in section 2.1, Scheme 2-1. In order to employ this approach we would have to prepare the appropriate [2.2.1] framework, **126**, followed by manipulation of the alkene and exploitation of the ketone as shown in Scheme 3-11.

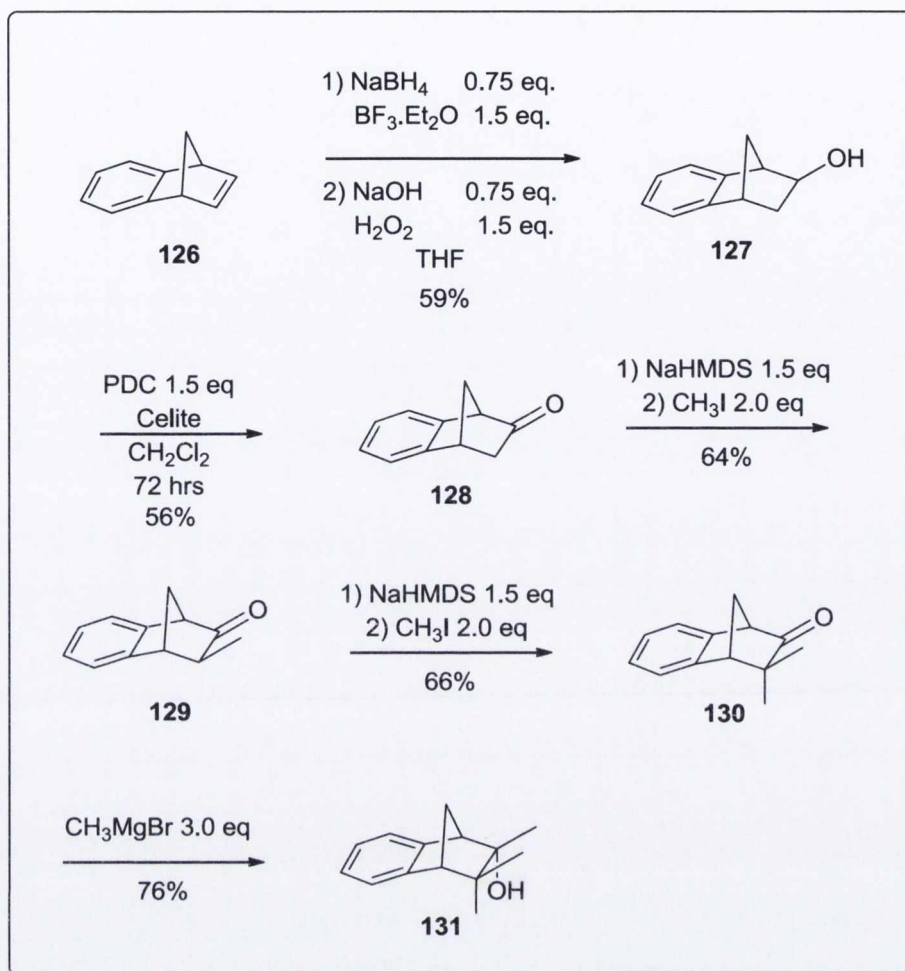


Scheme 3-11: Retrosynthesis of proposed aromatic target 125.

Fortunately, the formation of benzyne and its Diels-Alder reaction with cyclopentadiene has been reported by Goll and Fillion.²⁹⁸ Benzyne was generated *in situ* by treating anthranillic acid **134** with 1.2 molar equivalents of isobutyl nitrite at 50 °C until the expulsion of N₂ and CO₂ had ceased. Then, three molar equivalents of freshly distilled cyclopentadiene were employed to ensure total consumption of the benzyne and was later removed *via* column chromatography to furnish adduct **126** in 74% yield after purification, (Scheme 3-12).

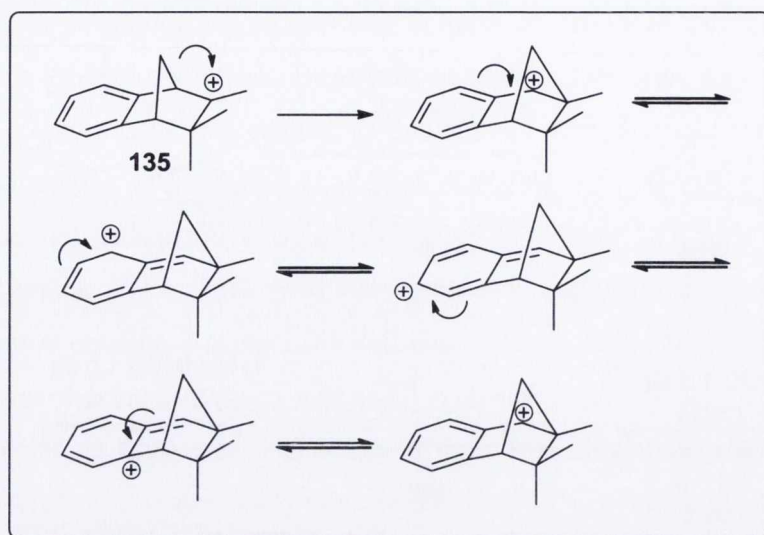
Scheme 3-12: Formation of 1,4-dihydro-1,4-methanonaphthalene *via* benzyne Diels-Alder mechanism.

With our basic framework successfully in hand we set about the development of the alkene by means of hydroboration. Treatment of adduct **126** with an excess of sodium borohydride and boron trifluoride etherate in anhydrous tetrahydrofuran for 3 hours formed the alkyl borane complex and subsequent addition of NaOH and hydrogen peroxide furnished the expected alcohol **127** in 59% yield. Oxidation of alcohol **127** with PDC in CH_2Cl_2 overnight gave ketone **128** in 56% yield after purification. Unfortunately the installation of the methyl group at position 2 using LDA and iodomethane, was unsatisfactory with a 37% yield. As this was the fourth step in a lengthy synthetic route the use of other bases was investigated. Replacing LDA with NaHMDS in the initial alkylation reaction dramatically improved mass return to a synthetically more satisfactory 64% in the first instance and 66% in the second alkylation. Treatment of the dimethylated ketone **130** with an excess of methylmagnesium bromide in anhydrous tetrahydrofuran for 3 hours afforded the expected tertiary alcohol **131** in 76% yield after purification, (Scheme 3-13).



Scheme 3-13: Synthesis of alcohol 131.

Once again the azide formation would prove troublesome. Treatment of tertiary alcohol **131** with 50% H_2SO_4 and an excess of sodium azide in CHCl_3 for 20 minutes resulted in rapid decomposition. In order to try and control this we varied the concentrations of H_2SO_4 , which had circumvented some problems. However, even at concentrations as low as 30% an unrecognisable decomposed product was isolated, (Scheme 3-14). We had previously experienced Wagner-Meerwein rearrangements in previous work and they were often easily isolated and occurred at higher acid concentrations.



Scheme 3-14: Proposed formation of benzylic cation.

Whether the Wagner-Meerwein rearrangement or the tentatively proposed rearrangement, (Scheme 3-14), occurred we thought that the addition of an EWG to the aromatic ring would help, (Figure 3-7). It should both reduce the migratory aptitude of the aromatic ring and also disfavour the formation of the benzylic cation. We thought that a nitro group would be ideal as the EWG due to their versatility later in the synthesis. Analysing the structure of the product showed that a single nitro group might not be sufficient. Looking at cation **135** we can see that the suspected rearrangement would give a benzylic cation *para* to the nitro group maximising the destabilising effect of the nitro group, (Scheme 3-14). However, if a 1,2 methyl shift occurred then rearrangement would form a benzylic cation *meta* to the nitro so the destabilised effect would be reduced, (Scheme 3-15). We also had no reason to believe we could install the nitro with any degree of regiocontrol.

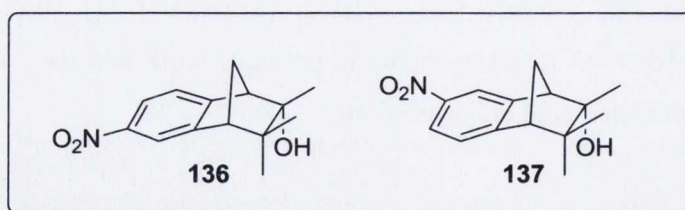
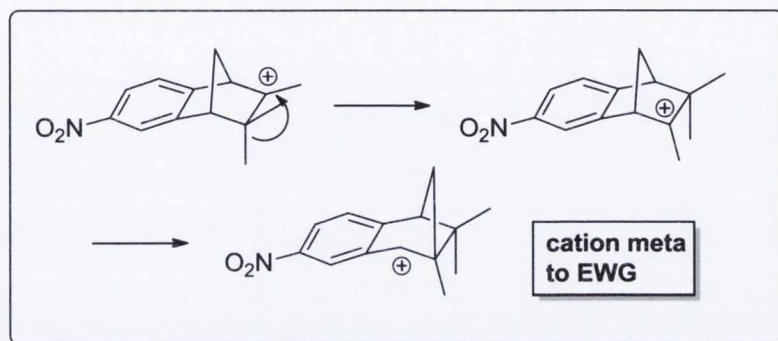


Figure 3-7: Proposed mixture of isomers as a result of mono nitration.

To circumvent both these potential problems we thought that preparation of a dinitro compound would be a sensible option. The introduction of nitro groups would provide

another functional handle which we could exploit to further functionalise the molecule at a later stage in the synthesis. It is also important to note that the troublesome rearrangement may still occur regardless of the substitution of the aromatic ring, (Scheme 3-15).

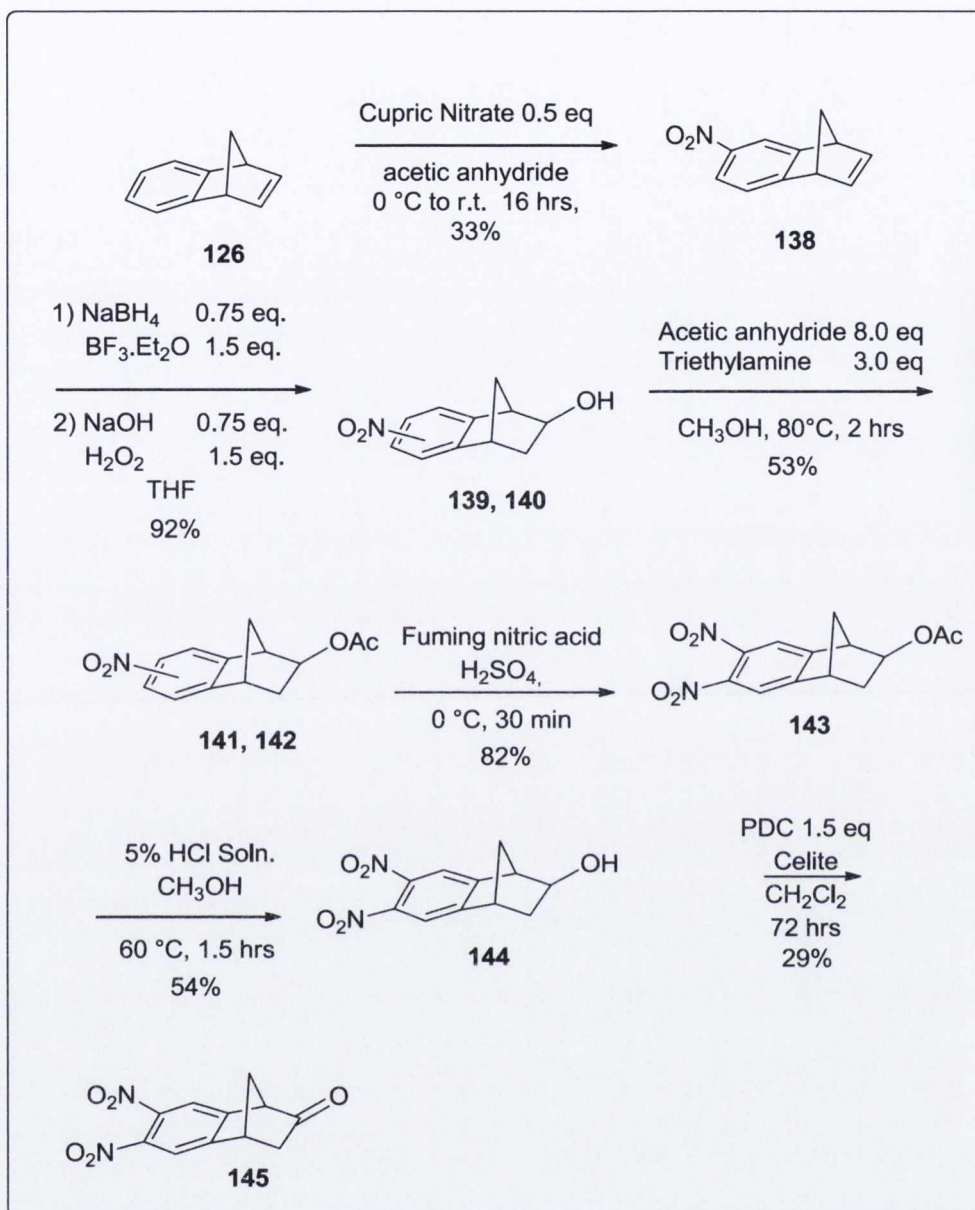


Scheme 3-15: Proposed 1,2 methyl shift and subsequent formation of benzillic cation.

Fortunately the nitration of similar systems has been reported by Terabe and Konaka²⁹⁹ (mono nitration) and Tanida *et al.*³⁰⁰ (dinitration). Tanida *et al.*³⁰⁰ published a procedure for the installation of a second nitro group *ortho* to the first group using a solution of fuming nitric acid in concentrated sulfuric acid, (Scheme 3-16). The regiochemistry of the nitration is interesting as it is extremely unusual for substitution to occur *ortho* to a nitro group during EAS chemistry; however, examples of this occurring in benzonorborene derivatives have been reported in the literature.^{300,301} After some adjustment of the sequence of the reactions the following strategy was devised.

Terabe and Konaka²⁹⁹ have reported the direct nitration of the Diels-Alder product **126** by treatment with an excess of cupric nitrate in acetic anhydride at -5°C overnight, (Scheme 3-16). Exploiting this methodology the mononitrated compound **138** was isolated in 33% yield after purification. The next step involved the hydroboration of the nitrated compound carried out in the same manner as previously described using an excess of sodium borohydride, boron trifluoride etherate, hydrogen peroxide and NaOH to generate a mixture of structural isomers **139** and **140** in excellent yields 92%, (Scheme 3-16). The installation of a second nitro group at this stage would produce a single isomer which would contain a nitro group *para* to each bridgehead. Utilising the procedure published by Tanida *et al.*³⁰⁰ the installation of a second nitro group *ortho* to the first group was achieved using a solution of fuming nitric acid in concentrated sulfuric acid, (Scheme 3-16). Firstly, due to the use of

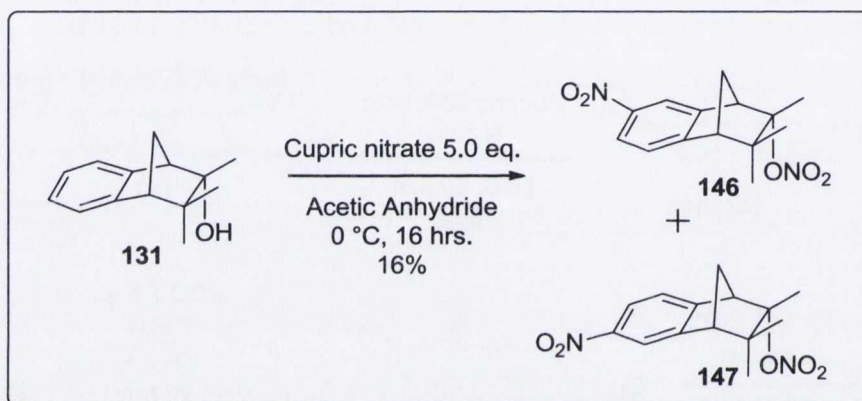
concentrated H_2SO_4 the alcohol would need to be protected as the acetate, in order to prevent elimination of the alcohol group and the generation of the cation at position 2. Treatment of alcohols **139** and **140** with an excess of triethylamine in acetic anhydride at $80\text{ }^\circ\text{C}$ for 2 hours gave the expected acetates **141** and **142** in 53% yield after purification. Once the alcohols were successfully protected the second nitro group could be installed. Treatment of a solution of acetates **141** and **142** in concentrated H_2SO_4 with a mixture of nitric acid in H_2SO_4 for 30 minutes at approximately $0\text{ }^\circ\text{C}$ furnished the desired dinitro compound **143** in 82% yield. Removal of the acetate protecting group was achieved by treatment of acetate **143** with a 5% solution of HCl in methanol heated at reflux temperature for 1.5 hours which gave the expected alcohol **144** in 54% yield. Oxidation to the desired ketone **145** was accomplished with PDC in accordance with the methodology used in the previous unsubstituted case giving the desired ketone **145** in 29% yield.



Scheme 3-16: Synthesis of 6,7-Dinitro-3,4-dihydro-1,4-methanonaphthalen-2(1H)-one.

Having prepared the dinitro compound **145** we turned our attention towards the installation of the two methyl groups at position 3. Treatment of dinitro ketone **145** with LDA followed by iodomethane in anhydrous tetrahydrofuran led to complete consumption of the starting material but none of the expected product was formed. In fact we were unable to identify any portions of the starting material during analysis of the spectroscopic data obtained from the crude reaction product - decomposition had occurred. Frustratingly, the dinitro ketone **145** proved highly unstable towards treatment with base. We wondered if

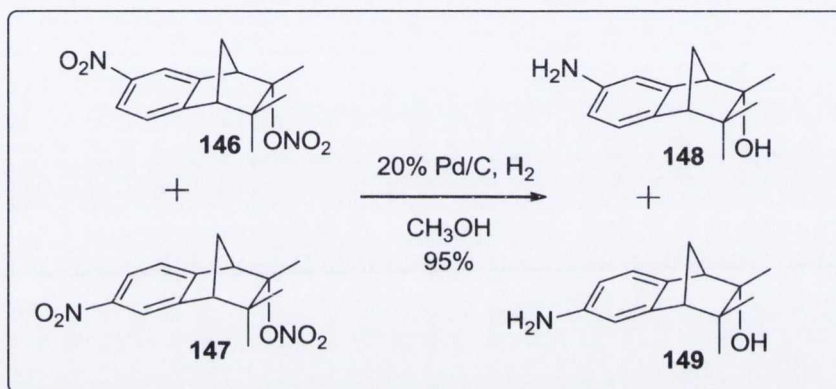
alternative and/or bases weaker than LDA might be compatible with the reaction. A range of bases including LDA, NaHMDS, *t*BuOK and NaH were investigated unfortunately decomposition occurred in all cases. Likewise, addition of these bases at lower temperatures than -10 °C resulted in the immediate formation of an insoluble brown tarry resin with no recognisable signals in the spectral data. Although we were disappointed, we thought we could circumvent the problem by introducing the nitro group at a later stage in the synthesis. Exposing the tertiary alcohol **131** to the nitration conditions would avoid exposing the dinitro compound to basic conditions, (Scheme 3-17).



Scheme 3-17: Synthesis of nitrate isomers.

We intended to install a nitro group onto the aromatic ring of the tertiary alcohol **131** using the same methodology employed for the initial nitration of adduct **126**. Gratifyingly, treatment of tertiary alcohol **131** with cupric nitrate in acetic anhydride at 0 °C for 16 hours furnished a mixture of nitro aromatics **146** and **147** albeit in a combined low yield of 16%. The alcohol moiety also underwent nitration to form a nitrate group at position 2. Unfortunately we were unable to introduce the second nitro group. Treatment of the nitro aromatic mixture to standard nitration conditions of nitric acid in H₂SO₄ resulted in decomposition. We were worried that 50% of the material did not have an electron withdrawing group *para* to the bridgehead α to position 2 and that a 1,2 methyl shift could occur in the case of the other isomer, but we hoped that the presence of one electron withdrawing group would be sufficient to prevent the problematic rearrangement during azide formation. Initially we employed the nitrate mixture directly in the azide formation; however, even at high concentrations of H₂SO₄ the nitrate group failed to eliminate and the starting

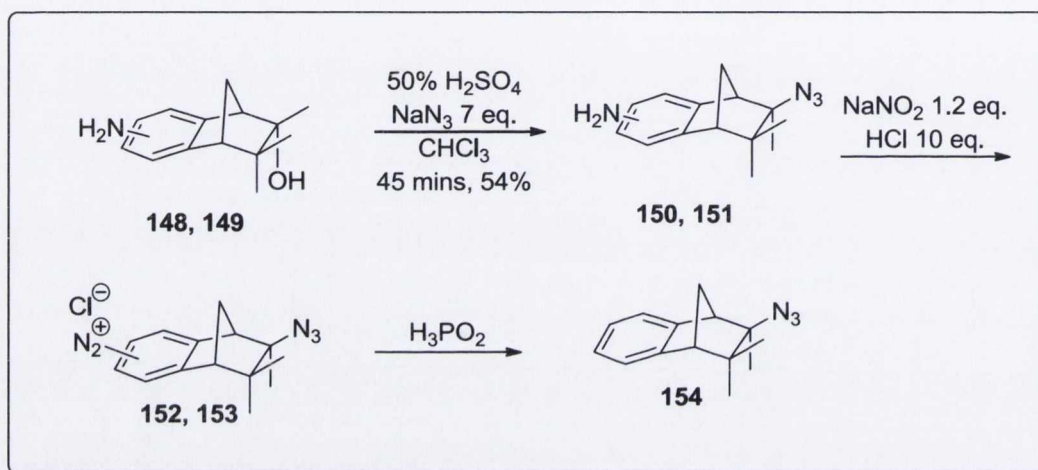
material was recovered from the reaction. Next we decided to employ hydrogenation to cleave the nitrate group. Exposure of nitrates **146** and **147** to hydrogen in the presence of 20% palladium on charcoal under a hydrogen at atmospheric overnight gave the desired amino alcohols **148** and **149** in 95% crude yield, (Scheme 3-18). Unfortunately, the amino alcohol products **148** and **149** were not stable and could not be purified by column chromatography, it was continued in the next synthetic step without further purification.



Scheme 3-18: Cleavage of the nitrate group *via* hydrogenation.

With the amino alcohols **148** and **149** in hand we turned our attention towards the azide formation. We expected that the amine group would become protonated upon exposure to H_2SO_4 and although only withdrawing by induction would deactivate the aromatic ring sufficiently to prevent rearrangement promoted. Treatment of amino alcohols **148** and **149** with 50% H_2SO_4 and an excess of sodium azide in CHCl_3 for 45 mins furnished the desired azides **150** and **151** in 54% crude yield, (Scheme 3-19). Unfortunately, the azides were also unstable; however, attempts were made to purify it *via* column chromatography but this decomposed the material further. As our desired target seemed within reach we decided to continue our synthesis using the crude material. Although we were interested in both substituted and unsubstituted aromatic analogues because our material was a mixture of isomers and due to the difficulty encountered with decomposition we decided to remove the amino groups. This would generate a single isomer and we hoped the unsubstituted compound would be more stable. Deamination was successful and using a procedure reported by Kronblum and Iffland,³⁰² the unsubstituted azide **154** was successfully formed, (Scheme 3-19). Firstly, the diazonium salts were formed using NaNO_2 and HCl at -5°C . The diazonium

salts **152** and **153** were not isolated but were treated directly with hypophosphinic acid which gave the unsubstituted ring **154** in 28% crude yield. Much to our dismay, the unsubstituted azide was also unstable and readily decomposed, (see Figure 3-8). At this point, it was decided that due to the instability of the aromatic compounds our efforts would be put to better use in other areas of substitution.



Scheme 3-19: Formation of the un-substituted azide **154**.

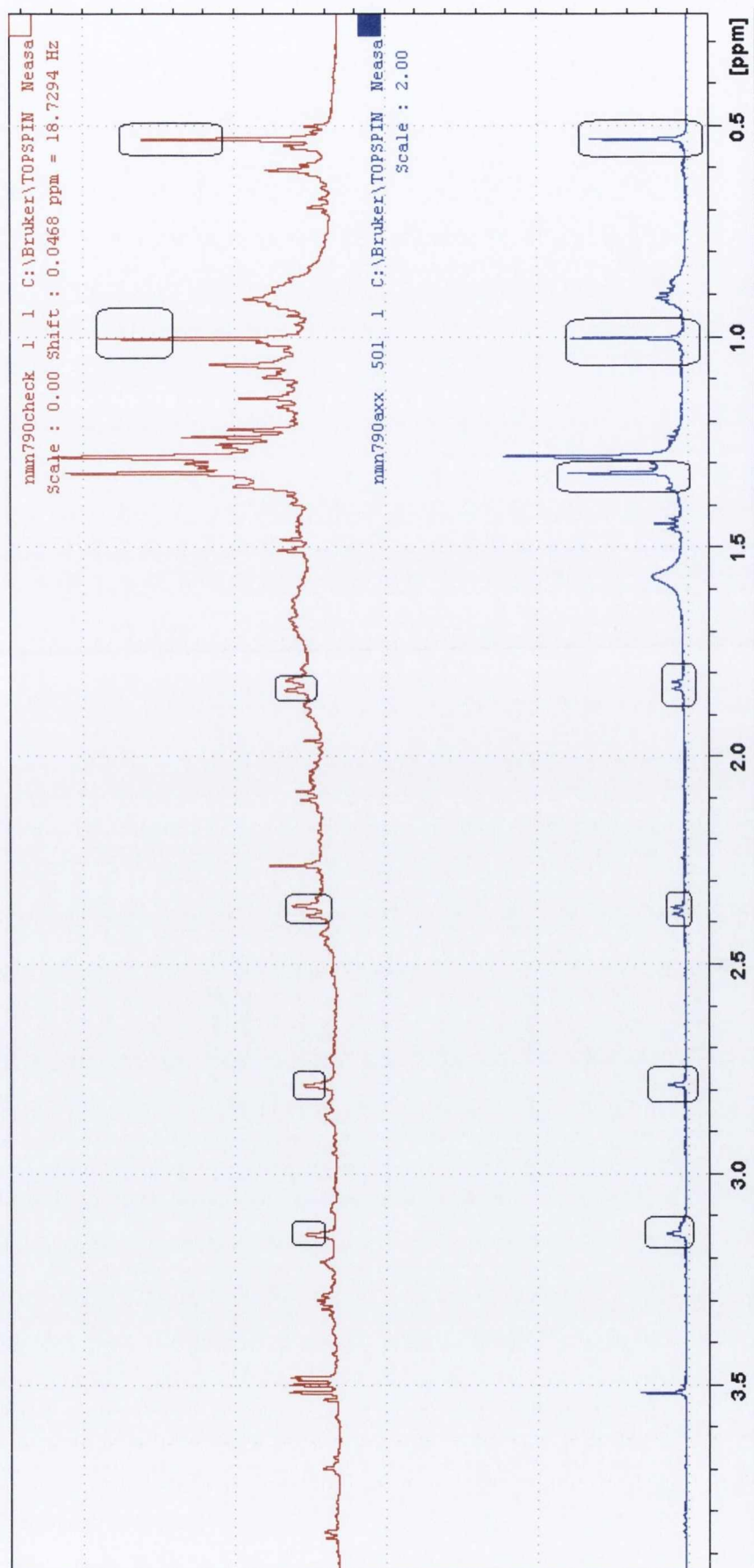


Figure 3-8: NMR data depicting decomposition of azide 154 (Product peaks are highlighted).

3.2.2 Synthesis of aromatic tricyclic *endo* MA analogue.

The *endo* analogue of MA was more potent at the $\alpha 4\beta 2$ receptor than the parent *exo* MA. Due to the stability issues associated with the synthesis of the *exo* aromatic derivative we turned our attention toward the *endo* aromatic derivative. After achieving some success with our *endo* MA analogues described in section 2.1.2., we decided to employ these methods with dimethylated ketone **130** in order to isolate an analogue containing the fused aromatic ring, (Figure 3-9). While the compound would not be a direct comparison to the parent *exo*-MA, it could still provide much needed insight to the effects of 5 and 6 substitution and of course the effects of aromaticity within the molecule.

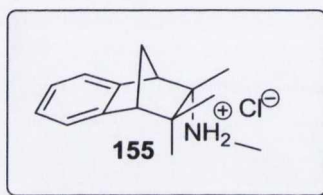
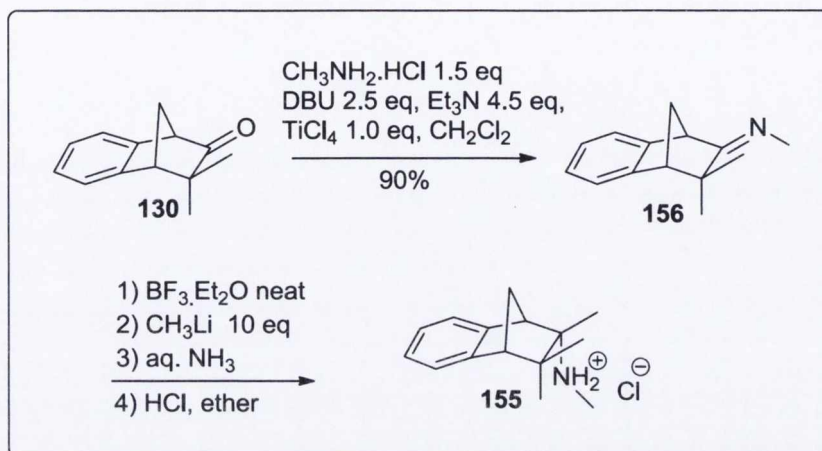


Figure 3-9: Proposed *endo* aromatic target.

We were able to exploit the ketone **130** prepared for the *exo* compound. The next step was imine formation. 1,8-Diazabicycloundec-7-ene (DBU) was added to ground and dessicated methylamine hydrochloride salt in anhydrous CH_2Cl_2 and stirred for approximately 5 minutes, (Scheme 3-20). Triethylamine (4.5 molar eq.) was subsequently added, followed by titanium tetrachloride (1.0 molar eq.) and the resulting mixture was heated at reflux temperature prior to addition of ketone **130**. The expected imine **156** was isolated cleanly *via* filtration through a thick pad of silica in an excellent yield of 90%, (Scheme 3-20). Treatment of imine **156** with boron trifluoride etherate (1.5 eq.) and methyllithium (5.0 eq.) formed the desired *endo* amine but, unfortunately, the crude reaction mixture contained numerous by-products. The hydrochloride salt **155** was formed by treating the free amine with a solution of 1M HCl in diethyl ether, (Scheme 3-20), in order to attempt purification *via* recrystallisation however exposure to acid resulted in rapid decomposition. Attempts to purify the free base by column chromatography produced much the same effects. Once again instability was observed and NMR spectral analysis indicated a similar decomposition pattern to that observed in the case of the tertiary alcohol **131** and the tertiary azide **154**. Due to the seemingly inherent issues with

the stability of aromatics we decided to focus our efforts in other areas of substitution at the 5 and 6 positions of the [2.2.1] bicyclic core.



Scheme 3-20: Synthesis of the *endo* aromatic MA analogue 155.

3.3 Alkyl substitution at positions 5 and 6.

3.3.1 Synthesis of tricyclic MA analogue.

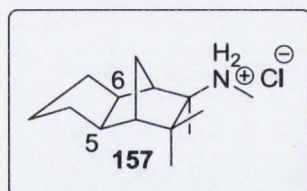
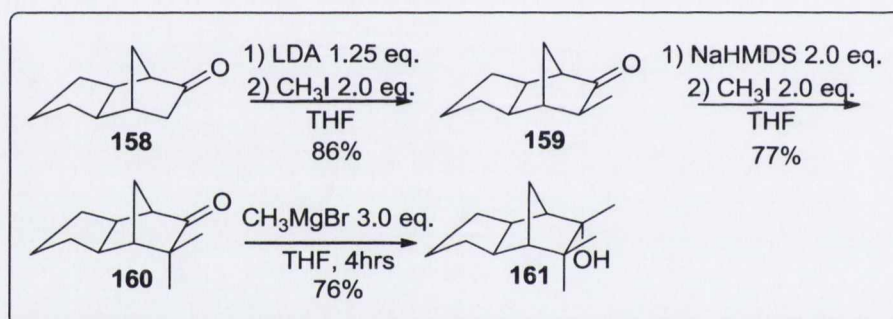


Figure 3-10: Proposed alkyl tricyclic target.

An alternative method to install substitution at positions 5 and 6, (Figure 3-10), was developed from the commercially available ketone **158**. The most problematic step in our previous synthetic efforts has been the formation of the azide. In this case the bridgehead shift observed in the aromatic substituted system should not be a problem. However Wagner-Meerwein rearrangements and alkyl migrations were still a possible problem.

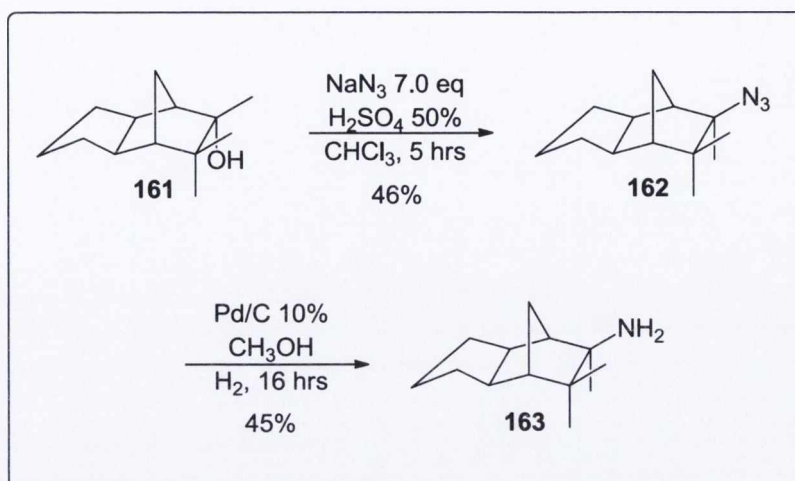
A study of NMR spectral DATA by Dawson and Stothers³⁰³ has shown that the exact conformation of the 5 membered alkyl ring fused to positions 5 and 6 is that depicted in Figure 3-10.

We planned to exploit the same methodology previously employed in the preparation of MA analogues. The first two steps involved the introduction of methyl groups to position 2 by enolate formation using LDA as the base in the first alkylation and NaHMDS in the second, followed by treatment with iodomethane in each case. Alkylation proceeded smoothly and cleanly, often without the need for further purification, with 86% yield in the first step and 77% yield for the second alkylation. Treatment of ketone **160** with an excess of methylmagnesium bromide (3.0 molar eq.) in anhydrous tetrahydrofuran for 4 hours gave the expected alcohol **161** in 76% yield after purification, (Scheme 3-21).



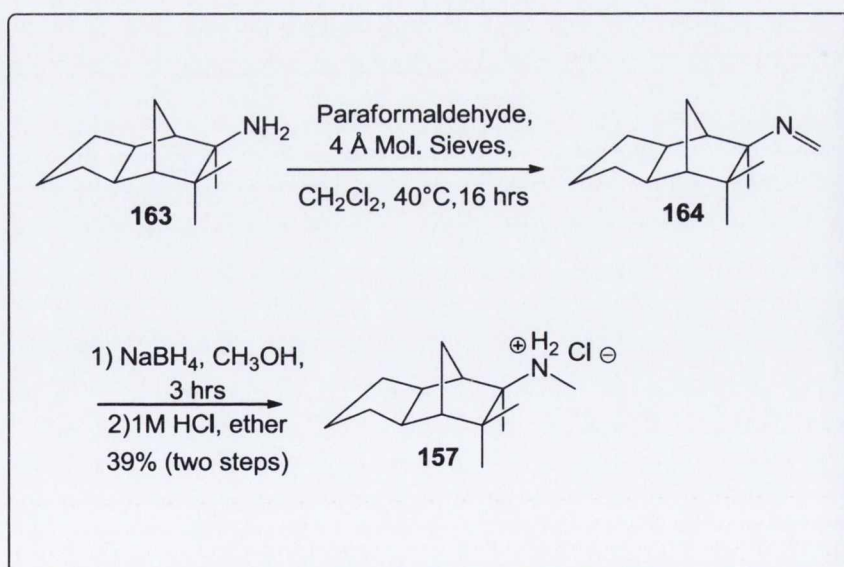
Scheme 3-21: Synthesis of 5-*exo*,6,6-trimethyloctahydro-1H-4,7-methanoinden-5-ol.

The next step in our synthetic sequence was the troublesome azide formation. Fortunately, formation of the azide proceeded smoothly and no rearranged side products were observed. Treatment of alcohol **161** with 50% H₂SO₄ and an excess of sodium azide in CHCl₃ for 5 hours furnished the desired azide **162** in 46% yield after purification, (Scheme 3-22). With the azide in hand we focused our efforts on its reduction to the primary amine **163**. This was achieved by exposure of azide **162** to hydrogen in the presence of 10% palladium on charcoal, with amine **163** being isolated in a 45% yield after work-up, (Scheme 3-22).



Scheme 3-22: Synthesis of 5-endo,6,6-trimethyloctahydro-1H-4,7-methanoinden-5-amine.

The final step involved the methylation of the primary amine **163** which was achieved in a two step process by reductive amination. Amine **163** was treated with paraformaldehyde and 4 Å molecular sieves in CH₂Cl₂ at reflux temperature until NMR spectral analysis of the reaction mixture indicated complete formation of the imine **164** (approximately 16 hours). The imine was not isolated but was treated directly with sodium borohydride and methanol. After isolation of the amine it was treated with a solution of 1M HCl in diethyl ether which gave the expected hydrochloride salt **157** cleanly in 39% yield, (Scheme 3-23). This compound has been submitted for testing at α4β2 receptor subtypes and the results are eagerly awaited.



Scheme 3-23: Two-step reductive amination forming amine 157.

3.4 Selective functionalisation of positions 5 and 6 *via* vinyl bromide synthesis.

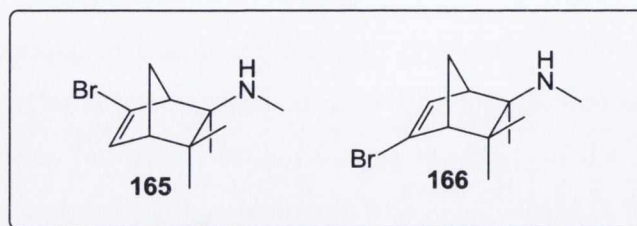


Figure 3-11: Structures of 5 and 6 vinyl bromides.

The vinyl bromides **165** and **166** have previously been prepared (selectively as individual compounds) by Dr. David Mangan, (Figure 3-11). These compounds could provide a means of introducing varied functionalisation selectively at the 5 or 6 position. Unfortunately, due to time constraints Dr. Mangan was unable to investigate the vinyl bromides in order to synthesise a library of analogues with differing functionality at either positions 5 or 6. This functionality can be manipulated using numerous methods including Pd(0) mediated coupling reactions or bromine lithium exchange to furnish selective functionalisation at the 5 or 6 position, a selection of possible methods are illustrated in Figure 3-12. Indeed the use of a vinyl bromide as a pseudo protecting group for the unsubstituted olefin could also be a means to a variety of other alterations including epoxidation, aziridination, dihydroxylation and Diels-Alder reactions among many others. Protection of the olefin moiety as a vinyl bromide is necessary due to the use of strong acids in our synthetic route, which would protonate the alkene.

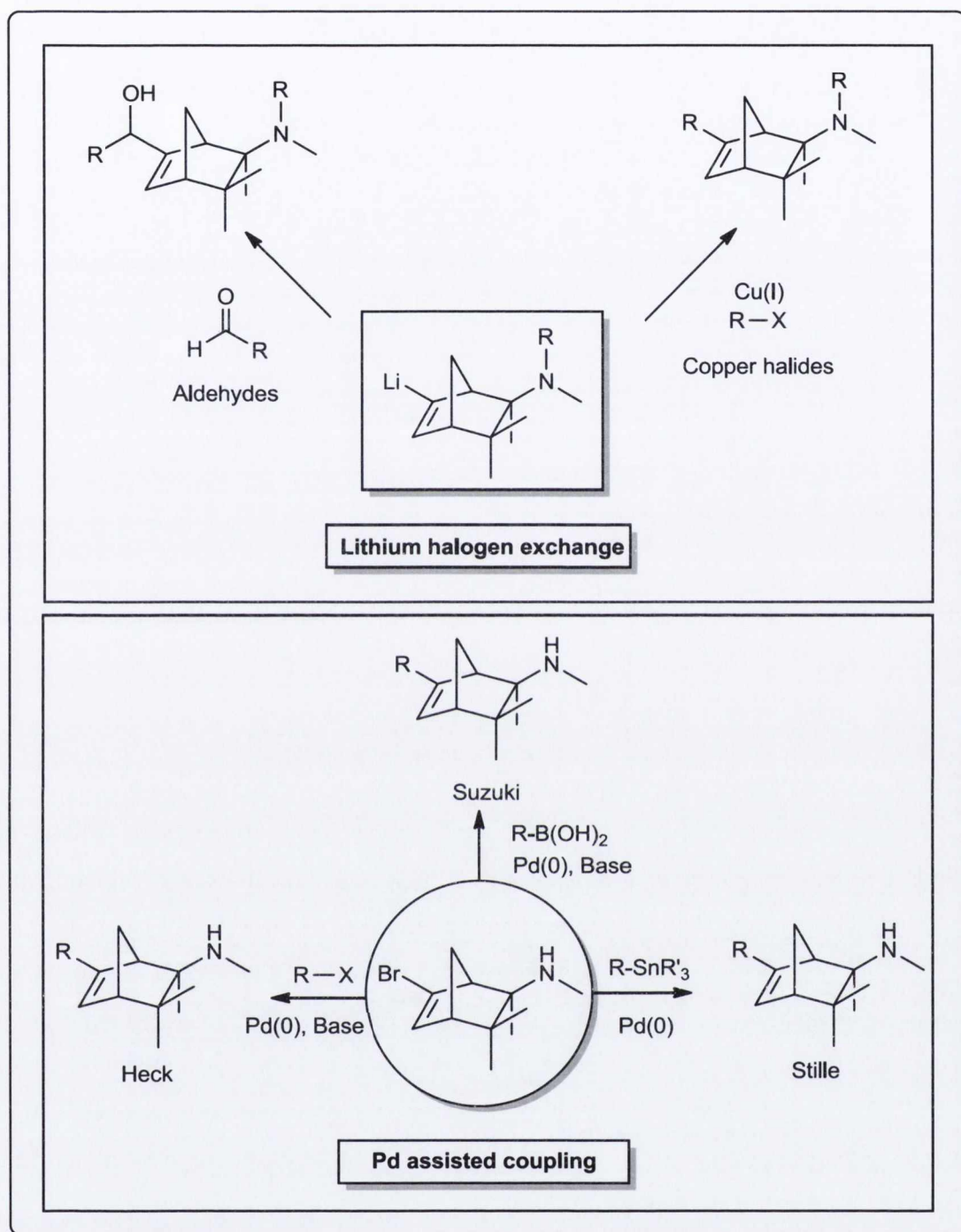
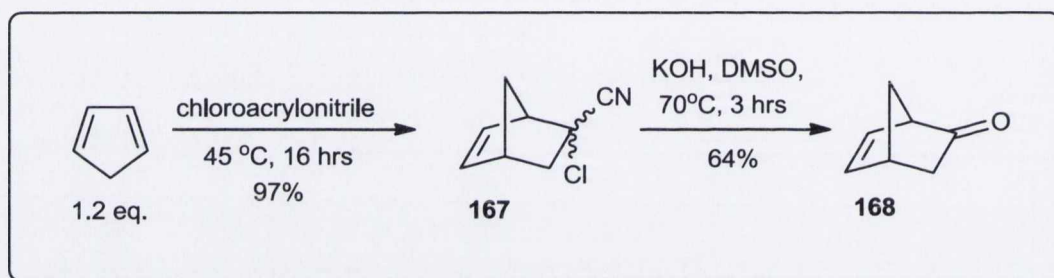


Figure 3-12: Potential functionalisation *via* lithium halogen exchange and palladium assisted coupling.

The selective synthetic route developed within our research group for the synthesis of both 5 and 6 vinyl bromide MA analogues by Dr. David Mangan are shown in the following sections. Unfortunately Dr. Mangan only prepared the two vinyl bromides in very small quantities. More of each compound was prepared using his route.

3.4.1. Selective synthesis of 6 vinyl bromide MA 165.

The initial step in this synthesis was the Diels-Alder addition of cyclopentadiene and α -chloroacrylonitrile furnishing compound **167** in 97% yield. Subsequent hydrolysis using 4M KOH in DMSO at 70 °C for 3 hours gave norbornenone **168** in 64% yield without the need for further purification, (Scheme 3-24). The next step was the selective installation of bromine at the 6 position using methodology developed by Lal and Salomon.³⁰⁴ Treatment of norbornenone **168** with phenylselenenyl bromide in THF at -78 °C for 5 hours gave the seleno-ether **169** in a disappointing 19% yield, (Scheme 3-25).

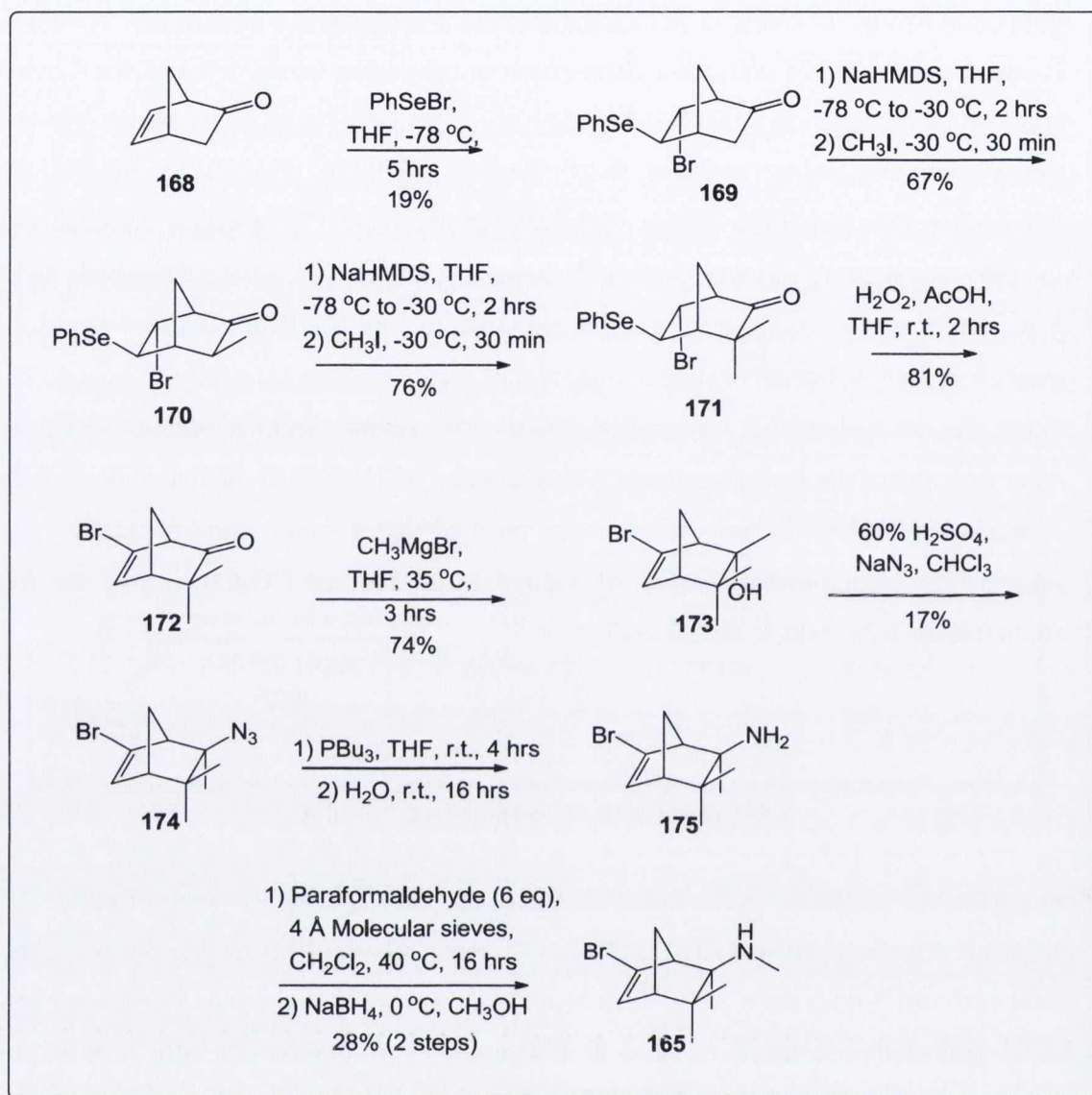


Scheme 3-24: Synthesis of norbornenone **168**.

Modifications to our standard alkylation reactions were necessary to isolate the desired mono and bis methylated ketones **170** and **171**. LDA was replaced with NaHMDS and the reaction took place at lower temperatures than -30 °C with shorter reactions times of 30 mins after the addition of iodomethane in order to avoid decomposition of the starting material. This decomposition was found to be due to the prolonged exposure of seleno-ether **170** to an excess of iodomethane, brought about by methylation of the selenium. Oxidation of selenide **171** with hydrogen peroxide and acetic acid in THF at room temperature facilitated *syn*-elimination to furnish the expected vinyl bromide **172** in 81% after purification, (Scheme 3-25).

Treatment of vinyl bromide **172** with methylmagnesium bromide (3.0 molar eq.) for 3 hours at 35 °C gave the expected alcohol **173** in 74% yield. Treatment of alcohol **173** with 60% H₂SO₄ and an excess of sodium azide in CHCl₃ gave azide **174** in a disappointing 17% yield, (Scheme 3-25). It was necessary to employ a Staudinger reduction to reduce the azide without affecting the vinyl bromide. Our usual reduction methods of lithium

aluminium hydride or catalytic hydrogenation were incompatible with the vinyl bromides. Treatment of azide **174** with tributylphosphine in anhydrous tetrahydrofuran for 4 hours followed by the addition of H₂O and stirring overnight gave the expected amine **175** and tributylphosphine oxide, (Scheme 3-25). Despite multiple attempts to remove the tributylphosphine oxide *via* column chromatography, amine **175** remained contaminated and the crude mixture was employed in the next step. Amine **175**, paraformaldehyde and 4 Å molecular sieves were heated at reflux temperature until NMR spectral analysis of the reaction mixture indicated complete formation of the imine (approximately 16 hours). The imine was not isolated but was treated directly with sodium borohydride and methanol. After isolation of the amine treatment with a solution of 1M HCl in diethyl ether gave the expected hydrochloride salt which was purified by column chromatography and subsequently partitioned a solution of sodium hydroxide and CH₂Cl₂ to give the free amine **165** in 28% yield, (Scheme 3-25).

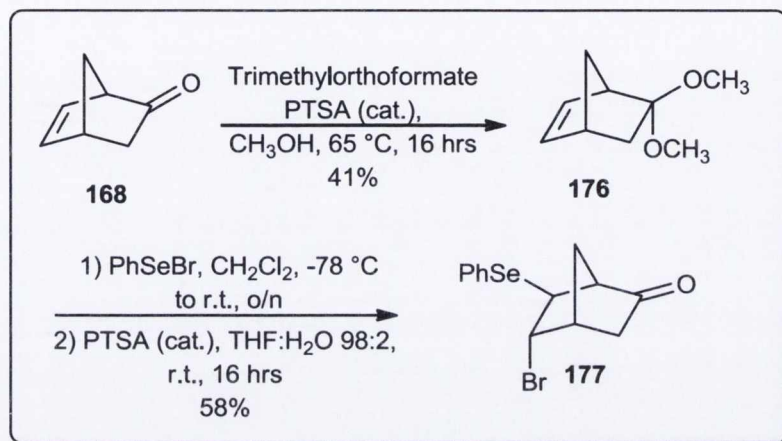


Scheme 3-25: Selective synthesis of 6 vinyl bromide MA 165.

3.4.2. Selective synthesis of 6 vinyl bromide MA 166.

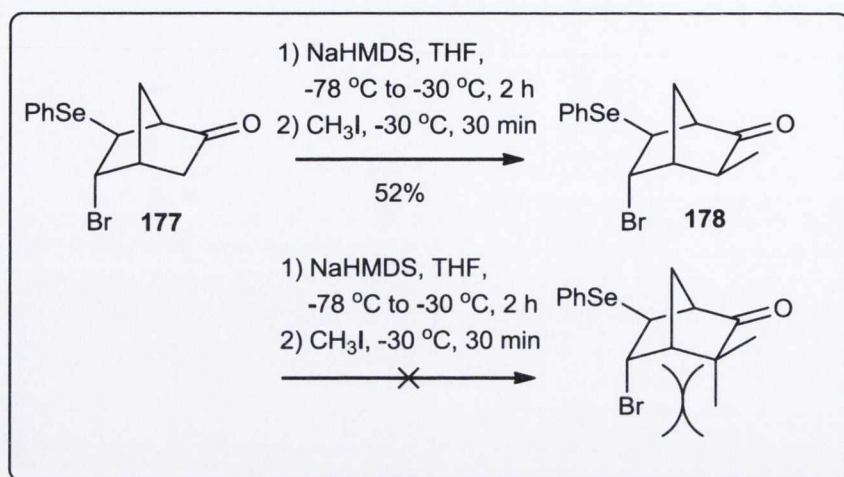
In order to achieve selectivity at position 5, it was necessary to synthesise dimethyl acetal **176** which had been shown by Carrupt and Vogel to undergo reaction with phenylselenium bromide with a high degree of selectivity.³⁰⁵ Treatment of norbornene **168** with trimethylorthoformate and *p*-toluenesulfonic acid monohydrate in anhydrous methanol at 65 °C for 16 hours gave the dimethyl acetal **176** in 41% yield, (Scheme 3-26). Treatment of the protected ketone with phenylselenium bromide in anhydrous CH₂Cl₂ at -78 °C, then warming to room temperature overnight generated the necessary seleno-ether.

The acetal protecting group was removed *in situ* by stirring in a 98:2 mixture of THF:H₂O in the presence of catalytic PTSA which gave the desired seleno-ether **177** in 58% yield, (Scheme 3-26).

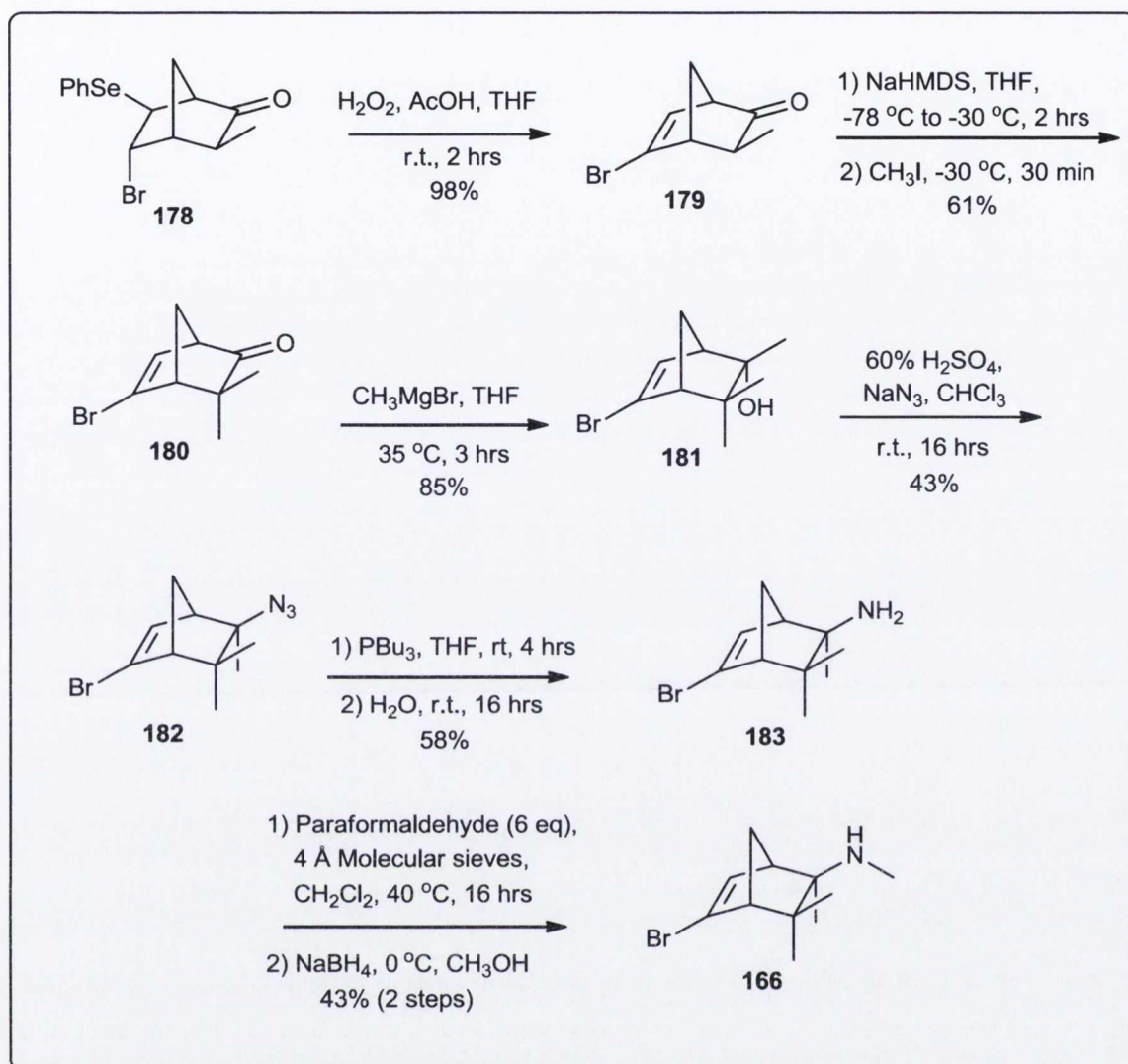


Scheme 3-26: synthesis of seleno ether **177**.

The initial methylation proceeded under the conditions described in the synthesis of the 6 vinyl bromide **165**, using NaHMDS as the base at $-30\text{ }^\circ\text{C}$, (Scheme 3-27). The second methylation was problematic due to a steric clash between the bromine at position 5 and the first methyl group. It was therefore necessary to remove the phenylselenium moiety prior to installation of the second alkyl group, (Scheme 3-27). This was achieved by oxidation of the selenide **178** with hydrogen peroxide and acetic acid in THF at room temperature which facilitated *syn*-elimination to furnish the expected vinyl bromide **179** in 98% after purification, (Scheme 3-28). The second methyl group was installed under the conditions described in the synthesis of the 6 vinyl bromide **165**, using NaHMDS as the base at $-30\text{ }^\circ\text{C}$ to give the dimethylated ketone **180** in 61% yield, (Scheme 3-28). The remaining synthetic steps proceeded pursuant with the methodology described in the synthesis of the 6 substituted vinyl bromide MA analogue to yield the desired 5 vinyl bromide MA **166**, (Scheme 3-28).



Scheme 3-27: Steric congestion prevents second methylation.

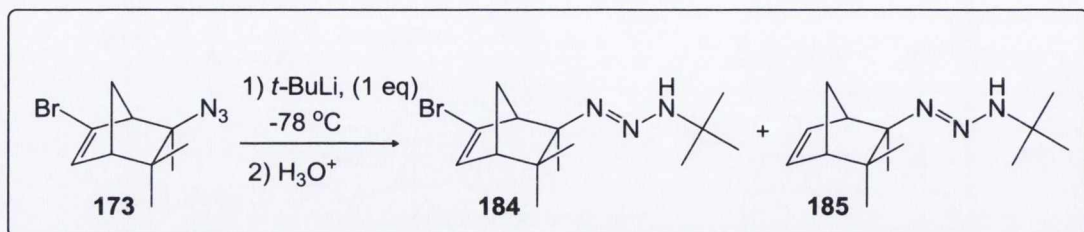


Scheme 3-28: Selective synthesis of 5 vinyl bromide MA 166.

3.4.3 Introduction of functionality utilising 5 and 6 vinyl bromides.

Dr. Mangan had previously attempted to introduce some functionality to the vinyl bromides. Dr. Mangan focused on functionalising the azides, but unfortunately, limited time meant that his efforts were unsuccessful. Treatment of azide **173** with *tert*-butyllithium generated 1,3-triazarene products **184** and **185**, (Scheme 3-29). While exposure to Grignard reagents either decomposed the material or produced similar undesired triazarenes. It appeared that the most sensible option was to investigate the final

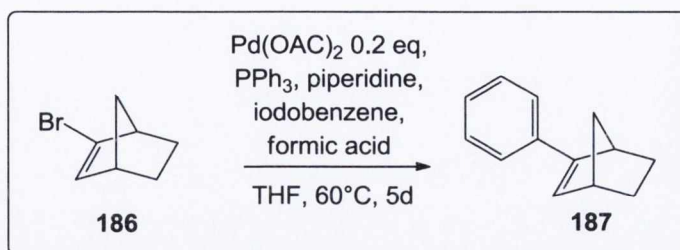
compounds **165** and **166**. We planned to treat these amines to similar metal exchange conditions to avoid the formation of unwanted side products associated with the azides.



Scheme 3-29: Formation of triazarene products.

If we were going to employ anion chemistry we would first need to protect the amine. It seems that steric constraints at the 2 and 3 positions of the MA skeleton made this extremely difficult. A variety of protecting groups and conditions were investigated including boc, tosyl and benzyl, protection. Similar difficulties were experienced during previous attempts to protect the tertiary alcohol **109** in the *endo*-diol series. All attempts to protect the amine element resulted in the return of starting material or, more disturbingly, decomposition of the material.

As the amine seemed to be extremely hindered we hoped that we would be able to employ the unprotected compound in palladium(0) mediated coupling reactions. Prior to investigating any palladium chemistry on our precious compounds, it was deemed prudent to test conditions on a structure similar to our bicyclic vinyl bromides rather than risking the loss of precious material. Mayo and Tam³⁰⁶ reported a Heck type hydrophenylation of bicyclic alkenes. Employing this methodology we repeated the reported synthesis of 2-phenylbicyclo[2.2.1]hept-2-ene **187**, (Scheme 3-30). Treatment of 2-bromobicyclo[2.2.1]hept-2-ene **186** with Pd(OAc)₂, PPh₃, iodobenzene, piperidine and formic acid in anhydrous tetrahydrofuran for 5 days at 60 °C gave the expected 2-phenylbicyclo[2.2.1]hept-2-ene **187**.



Scheme 3-30: Synthesis of 2-phenylbicyclo[2.2.1]hept-2-ene.³⁰⁶

We employed the same with the 5 and 6 MA vinyl bromide analogues, **166** and **165**, respectively. The reaction was monitored over a period of 5 days but, unfortunately, no reaction was observed and only starting material was recovered. The coupling of a vinyl bromide and an aryl halide is a slightly unusual example under Heck conditions so we decided to employ standard Suzuki coupling conditions instead.

Treating 5 vinyl bromide **166** with 0.5% $\text{Pd}_2(\text{dba})_3$, 3.3 molar equivalents of KF, 1.1 molar equivalent of phenylboronic acid and replacing $\text{P}(t\text{-Bu})_3$ with 1.2% PPh_3 with a reaction time of 20 hrs returned only the unreacted starting material. Disappointed we attempted a Stille coupling using tributylphenylstannane. Treatment of 6 vinyl bromide **165** with 5 mol% triphenylarsine, 5 mol% $\text{Pd}_2(\text{dba})_3$ and 1.2 molar equivalents of tributylphenylstannane in anhydrous tetrahydrofuran with a reaction time of 18 hours at 60 °C returned only starting material.

Having had no success in the palladium assisted coupling reactions we turned our attention to halogen metal exchange. Initially, we decided to take a chance and try to force the bromine metal exchange using the unprotected secondary amine. Amine **166** was treated with 4 molar equivalents of *tert*-butyllithium at -78 °C followed by an addition of 4 molar equivalents of benzaldehyde; however, only starting material was recovered. It was postulated that the exchange could not occur due to the deprotonation of the secondary amine, depicted in Figure 3-13.

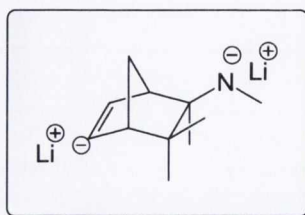


Figure 3-13: Lithium bromine exchange and deprotonation of secondary amine.

Dr. Mangan had previously synthesised the saturated dimethyl MA analogue **188**, Figure 3-14. Using the corresponding dimethyl vinyl bromide analogue would prevent deprotonation of the secondary amine and would hopefully allow halogen metal exchange to take place.

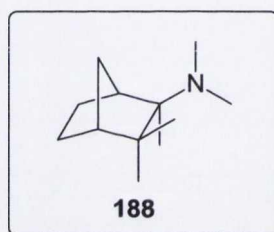
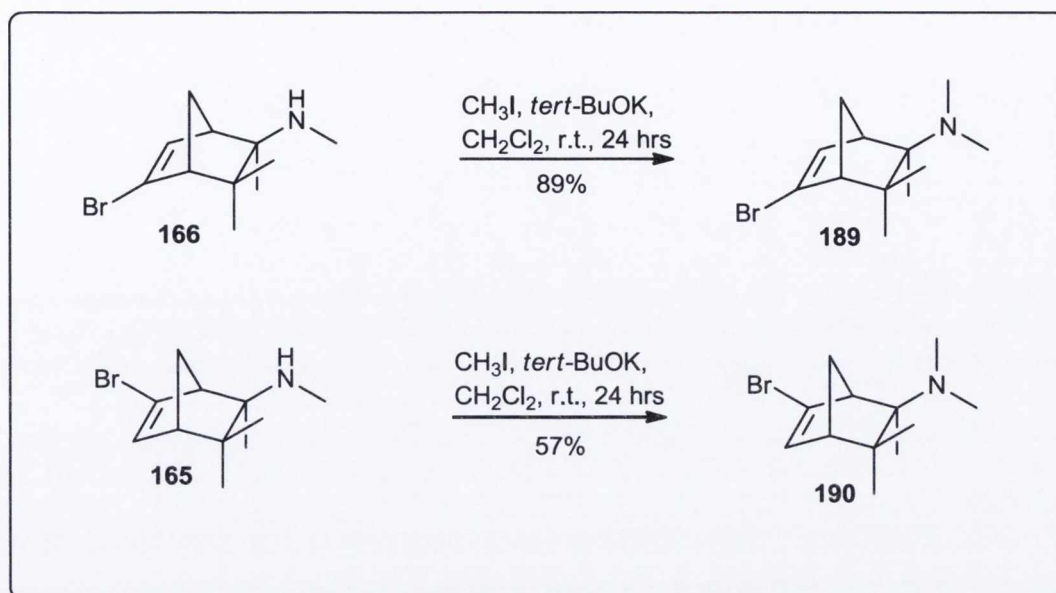
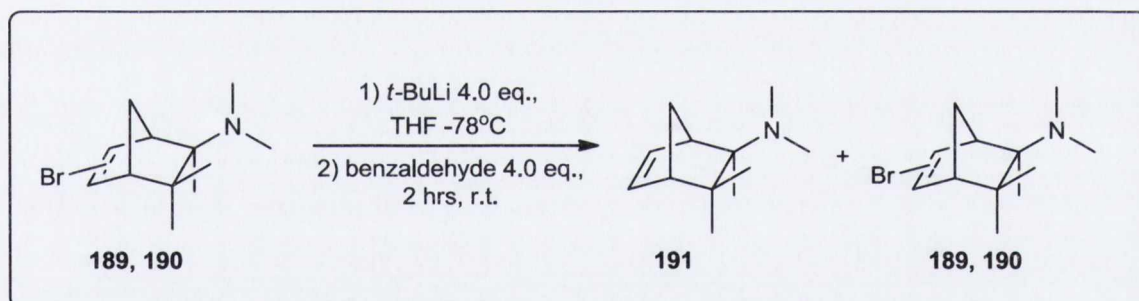


Figure 3-14: *N,N,2-endo-3,3-Pentamethylbicyclo[2.2.1]heptan-2-amine* synthesised by Dr. Mangan.

Treatment of amines **165** and **166** with 2.5 molar equivalents of iodomethane and potassium *tert*-butoxide for 24 hours gave the desired tertiary amines **189** and **190** in 89% and 57% crude yields, respectively, (Scheme 3-31). Unfortunately, these compounds were highly unstable and purification at this stage was not possible, instead they were used directly in the following step.

Scheme 3-31: Synthesis of dimethylated amines, **189** and **190**.

Treatment of amines **189** and **190** with 4 molar equivalents of *tert*-butyllithium at -78°C followed by 4 molar equivalents of benzaldehyde with stirring for 2 hours at room temperature returned a small amount of starting material and alkene **191**, (Scheme 3-32).

Scheme 3-32: Attempted lithium bromine exchange using tertiary amines **189** and **190**.

While the majority of material had decomposed it appeared that bromine metal exchange had occurred but attack at the carbonyl of benzaldehyde had not taken place. Instead, upon aqueous work-up the vinyl anion was quenched. Encouraged, we attempted to prove that metal exchange occurred by the addition of trimethylsilylchloride in place of benzaldehyde in order to trap the anion. Unfortunately, after work-up it was revealed that a complete decomposition of the material had taken place and no starting material remained. Unfortunately, the dimethyl amines **189** and **190** proved to be too unstable to be synthetically useful. The long syntheses, troublesome reaction profiles and stability issues

meant that we decided our time could be employed more effectively considering other positions to alter, namely position 7.

3.5 Conclusions.

Frustratingly, little success was achieved in our attempts to further functionalise the MA skeleton at positions 5 and 6. Despite a number of synthetic strategies only the alkyl analogue **157** was successfully isolated.

The main synthetic obstacles faced were the formation of the azide coupled with the steric congestion at positions 2 and 3. While alkyl substitution at the 5 and 6 positions gave no problem in terms of rearrangement or decomposition, introduction of a suitably positioned heteroatom, an aromatic ring or alkene led to rapid decomposition or rearrangement. Deactivation of the aromatic ring allowed for the formation of the azide; however, the product itself and the compounds associated with subsequent steps in our synthetic route were unstable. Likewise, attempts to isolate an *endo* aromatic analogue **155** resulted in decomposition of the material.

Unfortunately, simple attempts to protect the 5 and 6 vinyl bromides were unsuccessful, presumably due to steric congestion around the amines **165** and **166** and this hindered halogen metal exchange. Palladium coupling was unsuccessful but only limited conditions were attempted. *N*,5-*endo*,6,6-tetramethyloctahydro-1H-4,7-methanoinden-5-amine **157** is currently undergoing investigation at $\alpha 4\beta 2$ receptor subtypes and the results are eagerly awaited.

Chapter 4

Diversity in position 7

4. Diversity in position 7: Alterations to the bridgehead.

Targets

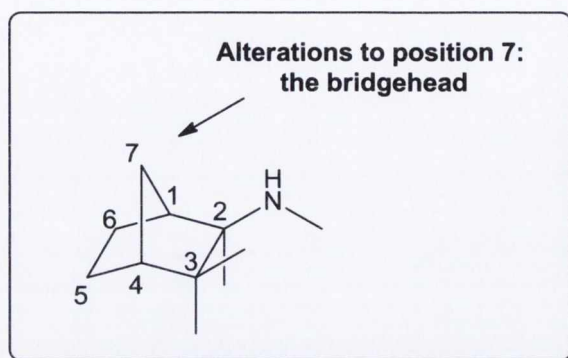


Figure 4-1: Targeting position 7 on the MA skeleton.

Having utilised the methodology to generate a broad range of alterations at positions 2 and 3 of MA, and investigating potential synthetic routes toward diversity at positions 5 and 6, our attention turned to the final section of the molecule, namely the bridgehead position, (Figure 4-1). We were particularly interested in two key alterations, insertion of a heteroatom to the [2.2.1] bicyclic framework and expansion of the bridgehead to generate a [2.2.2] bicyclic system, (Figure 4-2).

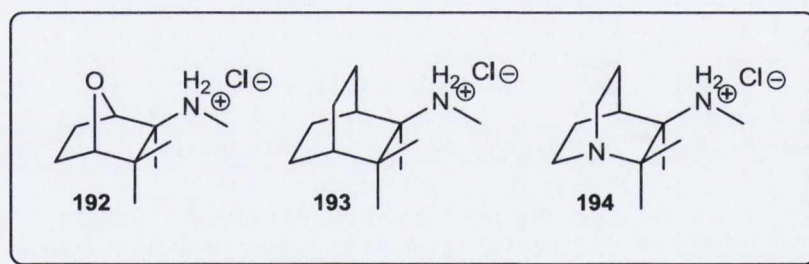


Figure 4-2: Proposed targets containing alterations to position 7.

As previously mentioned in chapter 3, Crooks *et al.* successfully synthesised a series of MA dimers and trimers displaying inhibition of nicotine induced dopamine release of up to 73% in the presence of 10 μM of nicotine.²⁷² These compounds were linked *via* long alkyl chains at the amine position which implies that entry to the pore occurs with the amine orientated towards the extracellular face of the ion channel. This is fully discussed in chapter 3, the proposed orientation is illustrated in Figure 4-3. Alterations to position 7 could have a

dramatic effect on interaction with the ion channel and also provide more insight to the mode of binding.

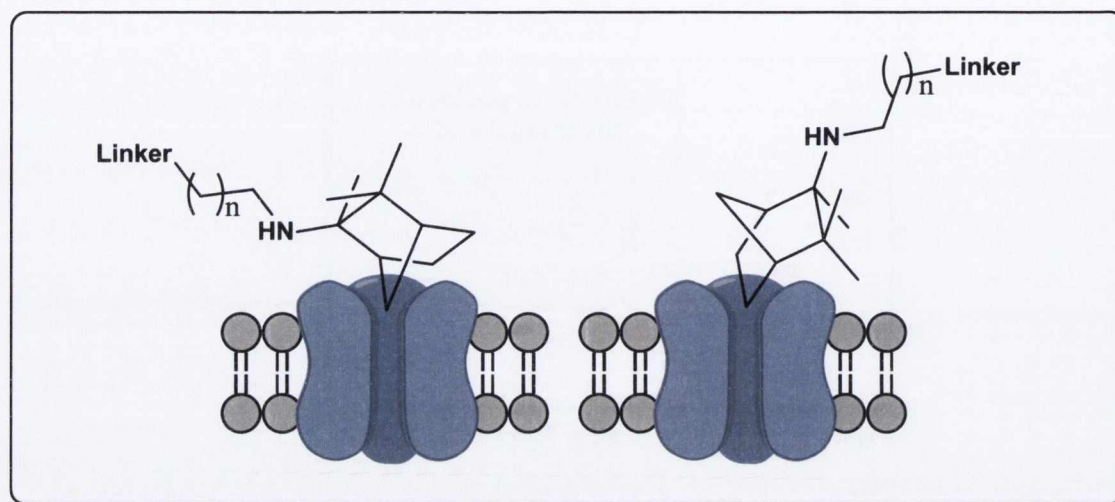


figure 4-3: Proposed orientation of binding of MA at nAChR.

4.1 Introduction of a heteroatom to the bridgehead of [2.2.1]system.

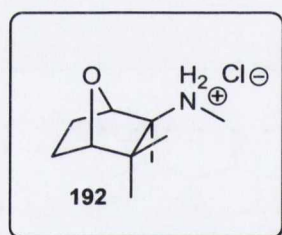


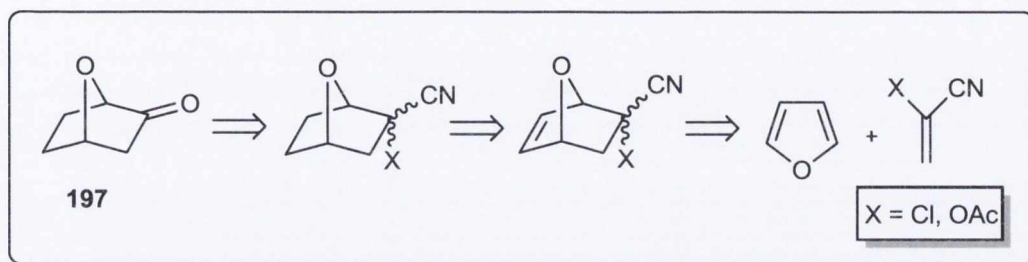
Figure 4-4: Proposed 7-oxa-bicyclo MA target.

Introduction of a heteroatom to the molecular skeleton of MA, (Figure 4-4), would allow us to investigate the effect of hydrogen bond acceptors and donors at the binding pocket, permitting a further exploration of the pharmacological space around the molecule.

4.1.1 Attempted synthesis of 7-oxa[2.2.1]bicyclo MA analogue.

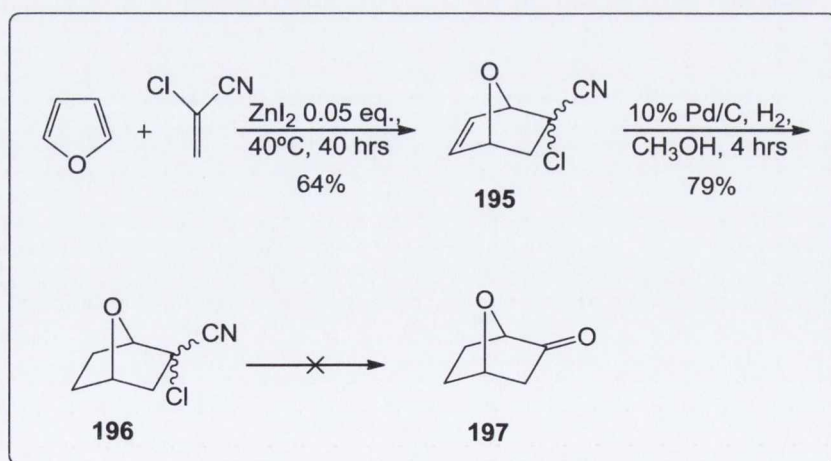
Once again we hoped that we could exploit previously developed chemistry for this task. A survey of the literature indicated that the synthesis of the oxygen containing species

such as **197** would be simpler, (see Scheme 4-1), so we made that our first target. It was envisaged that the introduction of a heteroatom to the MA skeleton could be achieved utilising a Diels-Alder approach. Initially attempts were made to synthesise the appropriate ketone **197** using 2-chloroacrylonitrile as illustrated in Scheme 4-1.



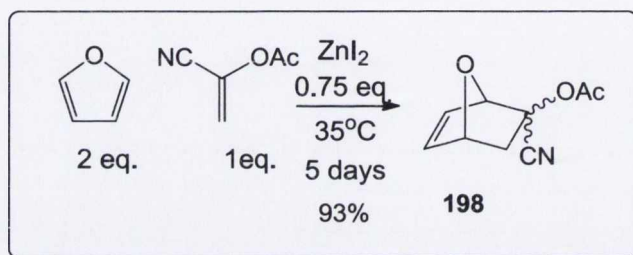
Scheme 4-1: Retrosynthesis of 7-oxabicyclo[2.2.1]heptan-2-one.

Furan and α -chloro acrylonitrile were stirred with ZnI_2 as a catalyst, at 45 °C for 48 hours to yield an *exo* and *endo* mixture of Diels-Alder adduct **195** in 64% yield after purification.³⁰⁷ Exposure of adduct **195** to hydrogen in the presence of 10% palladium on charcoal for 4 hours gave **196** in 79% yield after work-up, (Scheme 4-2). Attempts to hydrolyse the cyano group proved problematic. Treatment of chloronitrile **196** with 4M KOH in DMSO at 70 °C for 24 hours gave only a mixture of *exo* and *endo* α -chloro amides. Upon further investigation of the literature it was discovered that due to the inductive effect of the ethereal bridge, the carbonitrile hydrolysis becomes competitive and even faster than the chloride solvolysis thus invoking a retarded $\text{S}_{\text{N}}1$ heterolyses of the chloride compared with those of the bicyclo[2.2.1]heptane analogues.³⁰⁸



Scheme 4-2: Initial route investigated for the synthesis of 7-Oxa bicyclo ketone.

A simple adaptation of the initial approach by switching the chloride for an acetate would allow access to the desired ketone **197**, (Scheme 4-3).³⁰⁹ Our next step was to optimise the Diels-Alder reaction between furan and α -acetoxy acrylonitrile, as shown in Scheme 4-3 and Table 4-1. The best results were obtained when α -acetoxyacrylonitrile was treated with an excess of furan (2.5 molar equivalents) and ZnI_2 catalyst (0.75 molar equivalents) in a sealed reaction flask at 30 °C for 5 days. A 1:4 mixture of stereoisomers was noted with an excellent yield of 93%.



Scheme 4-3: Conditions for the Diels-Alder reaction.

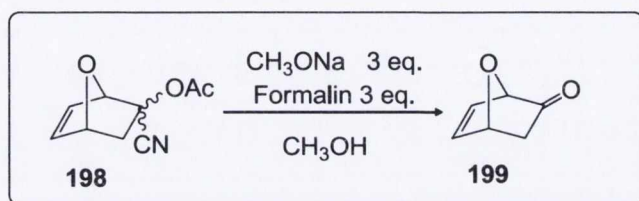
Table 4-1: Optimisation of the Diels-Alder reaction.

ZnI ₂ eq.	Furan eq.	Temp	Time	Additional Conditions	Yield
0.5	1.5	25 °C	5 days	-	38%
0.5	2	70 °C	4 hrs	M.W. irradiation	37%
0.75	2.5	30 °C	5 days	-	77%
0.75	2.5	30 °C	5 days	sealed flask	93%

In order to reduce the reaction time the use of microwave irradiation was investigated. In the best result treatment of α -acetoxy acrylonitrile with 2.0 molar equivalents of furan and 0.5 molar equivalents of ZnI_2 under microwave irradiation at 70 °C for 4 hours gave the expected adduct **198** in 37% isolated yield. Presumably longer reaction times would drive the reaction to full conversion but considering only small quantities could be irradiated at a time it seemed more sensible to continue our synthesis *via* conventional heating.

The next step was the hydrolysis of the cyano group. Treatment of **198** with sodium methoxide in methanol generated a mixture of the expected ketone **199** but the reaction had

not gone to completion. A short study was undertaken to optimise the hydrolysis and achieve a full conversion to the ketone **199**, (Scheme 4-4 and Table 4-2). Although different conditions were employed it was not until the addition of formalin, a cyanide anion trap, that the reaction went to completion.

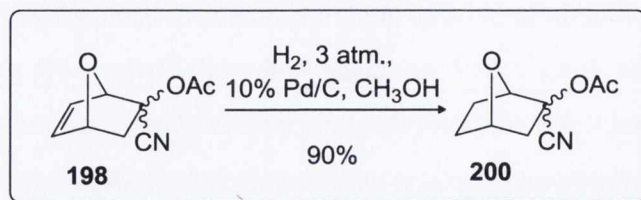


Scheme 4-4: Hydrolysis of cyano acetate **198** to form ketone **199**.

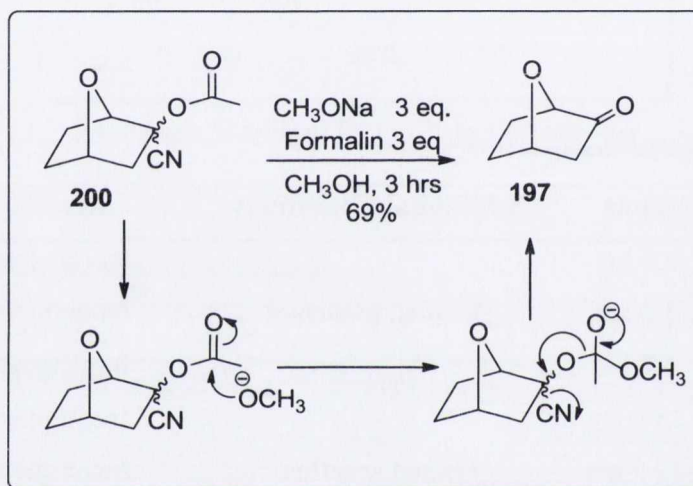
Table 4-2: Optimisation of the hydrolysis of adduct **198**.

Base	Temp.	Time	Additional Conditions	Results	Yield
CH ₃ ONa	20°C	3.5 hrs	-	Incomplete	50%
CH ₃ ONa	20°C	3.0 hrs	Distilled methanol	Incomplete	48%
CH ₃ ONa	35°C	6.0 hrs	-	Incomplete	28%
CH ₃ ONa	35°C	28.0 hrs	-	Incomplete	37%
CH ₃ ONa	70°C	22.5 hrs	Heated at reflux temperature	Incomplete	43%
CH ₃ ONa	20°C	3.0 hrs	Formalin	Full conversion	59%

The unsaturated ketone **199** is volatile (b.p. 79-80 °C/10 Torr)³⁰⁸ and significant losses were observed during the removal of ether after work-up and therefore could not be purified by column chromatography. Attempts to purify the crude reaction mixture by distillation were also unsuccessful. It was deemed more practical to hydrogenate the adduct **198** prior to hydrolysis. Exposure of adduct **198** to 3 atm of hydrogen in the presence of 10% palladium on charcoal gave the expected cyano acetate mixture **200** in 90% yield after work-up (Scheme 4-5).

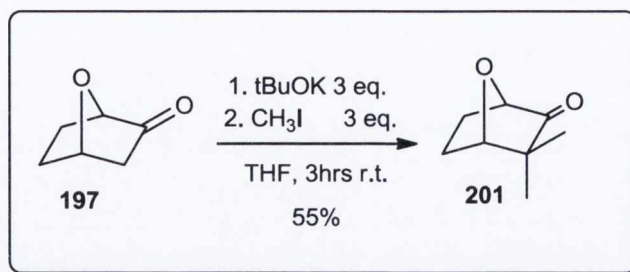
Scheme 4-5: Hydrogenation of Diels-Alder adduct **198** to give **200**.

Exploiting the previously optimised conditions, treatment of cyano acetate mixture **200** with sodium methoxide (3.0 molar eq.) and formalin (3.0 molar eq.) in methanol for 3 hours at 25 °C gave the desired ketone **197** in 69% yield after purification, (Scheme 4-6).

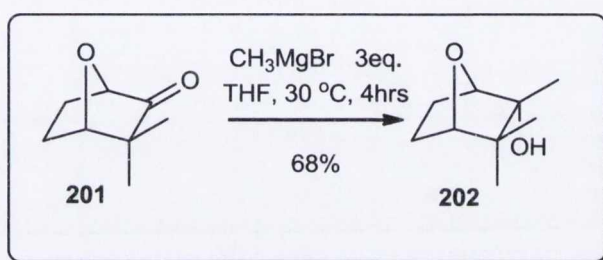


Scheme 4-6: Mechanism for the hydrolysis of the aceto group.

The next step involved the introduction of the two methyl substituents at position 3 of the [2.2.1] bicyclic core. A review of the literature indicated that both methyl substituents could be introduced to the ketone **197** in a single step.³¹⁰ Treatment of ketone **197** with of potassium *tert*-butoxide (3.0 molar eq.) and iodomethane (3.0 molar eq.) in anhydrous tetrahydrofuran for 3 hours gave the dimethylated ketone **201** in 55% crude yield, (Scheme 4-7). Unfortunately the compound was unstable to purification by column chromatography and multiple attempts to purify the material resulted in decomposition. The ketone was employed without purification in the next step.

Scheme 4-7: Installation of methyl groups to form ketone **201**.

Treatment of the crude ketone **201** with methylmagnesium bromide (3.0 molar eq.) for 3 hours gave the expected tertiary alcohol **202** in 68% yield after purification, (Scheme 4-8).

Scheme 4-8: Synthesis of trimethyl alcohol **202** using a Grignard reagent.

Once again the formation of the azide would prove troublesome and the desired azide **204** was not isolated, (Scheme 4-9). Treatment of alcohol **202** with 70% H_2SO_4 and an excess of sodium azide for 4 hours gave a rearranged product **203** in 83% yield after purification, (Scheme 4-10). Varying the acid concentrations had proved successful previously so in order to determine whether the desired azide **204** could be formed before rearrangement took place further investigation of the acid concentrations was undertaken, (Table 4-3). The alcohol **202** was surprisingly stable to acidic conditions and it was found that treatment with 60% H_2SO_4 in the presence of sodium azide with reaction times of up to 24 hours returned only starting material. It was noted that once the acid concentration was increased to 65-70 % rearrangement started to occur and the undesired Wagner-Meerwein product was formed.

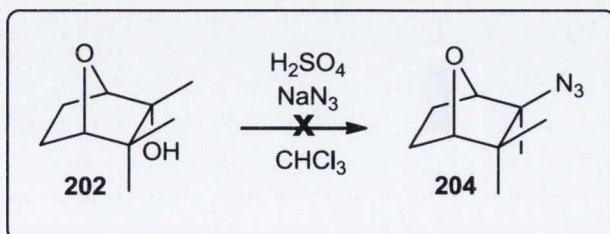
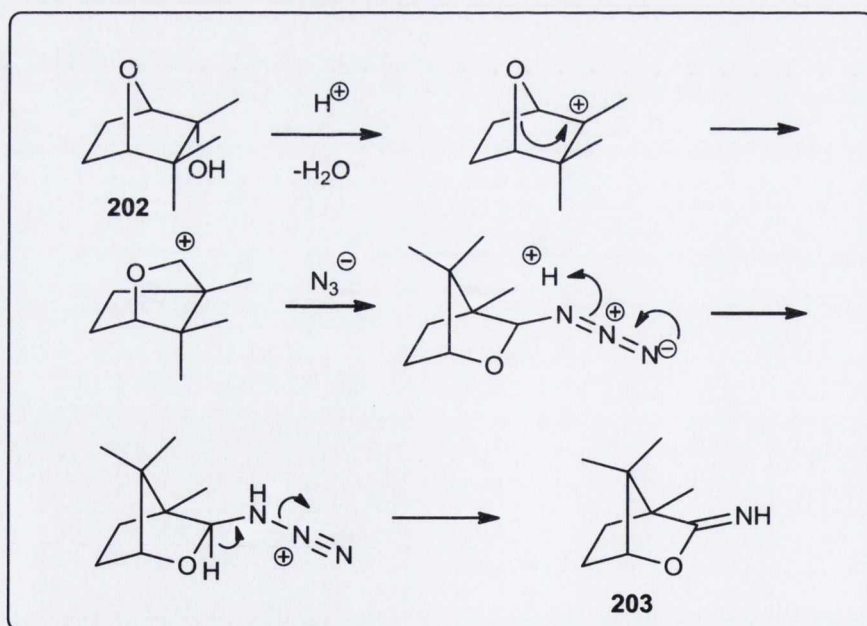
Scheme 4-9: Attempted synthesis of azide **204**.

Table 4-3: Attempted azide formation - further investigation of acid concentrations.

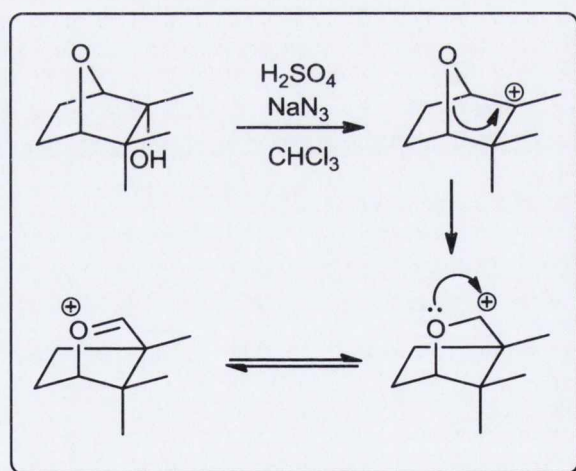
H ₂ SO ₄ Conc.	Time	Product isolated
50 %	25 hrs	Starting materials
55 %	23 hrs	Starting materials
60 %	23 hrs	Starting materials
65 %	23 hrs	Starting materials
70 %	1 hr	Rearrangement
75 %	1 hr	Rearrangement
80 %	45 mins	Rearrangement
85 %	45 mins	Rearrangement
Conc.	15 mins	Rearrangement

The compound was unstable towards column chromatography and despite multiple attempts to isolate the rearranged product resulted in the isolation of decomposed material. A relatively pure sample was isolated by preparative t.l.c.. Analysis of the spectral data indicated that rearrangement had occurred but the product was unexpected. The proposed product **203** and its formation is shown in Scheme 4-10. It is unsurprising that this structure is sensitive to silica.

**Scheme 4-10: Mechanism of the Wagner-Meerwein rearrangement and decomposition of resulting azide.**

Temperature in the laboratory varied considerably on a day to day basis and this was extremely influential in the rate of the rearrangement reaction. For example, the initial test reaction using 65% H_2SO_4 at a room temperature of approximately $15\text{ }^\circ\text{C}$ gave no reaction after 23 hours. However, when the reaction was repeated at a room temperature of approximately $26\text{ }^\circ\text{C}$ the rearranged product was generated in just 3 hours. In order to fully examine and hopefully exploit the role of temperature in the reaction, it was repeated with 66% H_2SO_4 at lower temperatures. At $-25\text{ }^\circ\text{C}$ the acid layer remained frozen and no reaction took place after 48 hours. The reaction was repeated at a temperature range of -5 to $0\text{ }^\circ\text{C}$, after 27 hours no reaction was observed. Finally, the alcohol was treated with 40% H_2SO_4 and warmed to $30\text{ }^\circ\text{C}$, no reaction was observed after 49 hours.

The main problem with this approach in this case was the stabilisation of the cation formed upon rearrangement by the adjacent oxygen atom, (Scheme 4-11). Thus interception of the initial cation by azide is unlikely. If this approach was unsuccessful in the case of the oxygen series then it is highly likely that similar problems would be encountered with the corresponding amine series so we decided to abandon this approach. However, it could be possible to prepare these compounds using approaches similar to those developed for the synthesis of epibatidine. Instead we turned our attention to the expanded [2.2.2]bicyclic systems.



Scheme 4-11: Cation stabilisation by oxonium ion formation.

4.2 Expansion of the bridgehead.

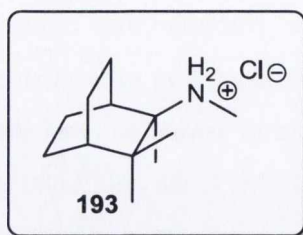
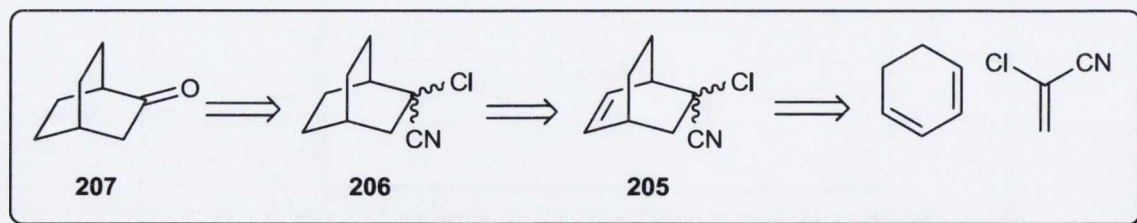


Figure 4-5: Proposed target.

Expanding the skeleton to a [2.2.2]bicyclic system such as compound **193**, (Figure 4-5), would give us the opportunity to examine the importance of the bridgehead position with regards potency. The work of Wragg and co-workers has shown that a rigid system is required when they synthesised a number of analogues lacking this structural feature, none of which displayed activity higher than one tenth that of MA.²⁶⁰ However, they were unable to assess the effects of the addition of an extra carbon. Expanding the bridgehead to a two carbon chain would provide an interesting comparison to the parent compound MA. It would also introduce a degree of symmetry meaning the *endo* and *exo* conformations are structurally equivalent.

4.2.1 Synthesis of a [2.2.2]bicyclo MA analogue.

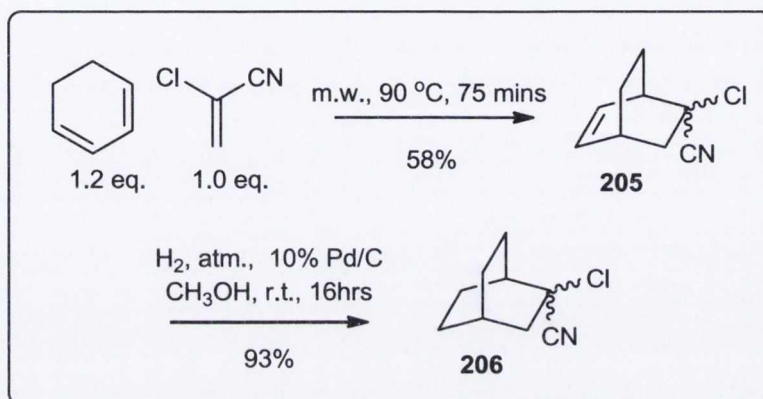
It seemed sensible to employ a variant of the previously developed route *via* the appropriate ketone **207**, as shown in Scheme 4-12.



Scheme 4-12: Retrosynthesis of Ketone **207**.

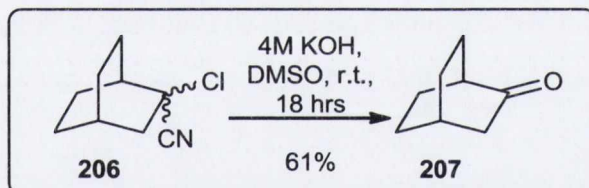
The first step in the synthesis was the Diels-Alder reaction of 2-chloroacrylonitrile and 1,3-cyclohexadiene. Microwave irradiation proved a useful tool in the promotion of the Diels-

Alder reaction. Treatment of 2-chloroacrylonitrile with 1.2 molar equivalents of 1,3-cyclohexadiene (neat) under microwave irradiation at 90 °C for 75 minutes gave the expected product **205** in 58% yield after purification. Exposure of the Diels-Alder adduct **205** to hydrogen in the presence of 10% palladium on charcoal furnished the saturated 2-chloro-carbonitrile **206** in 93% yield, (Scheme 4-13).



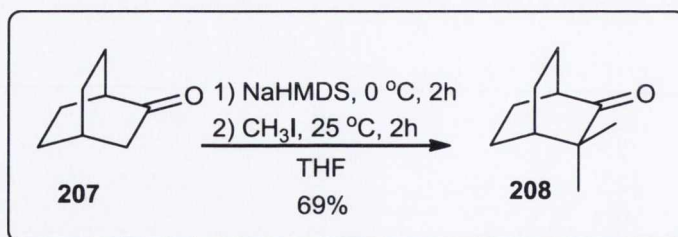
Scheme 4-13: Synthesis of chloro-nitrile **206**.

The next step was the hydrolysis of chloro-nitrile **206** achieved by treatment of **206** with 4M KOH in DMSO at room temperature for 18 hours which gave the expected ketone **207** in 61% yield after purification, (Scheme 4-14).

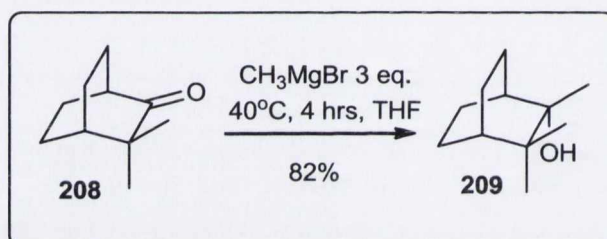


Scheme 4-14: Hydrolysis of the chloro-carbonitrile **206**.

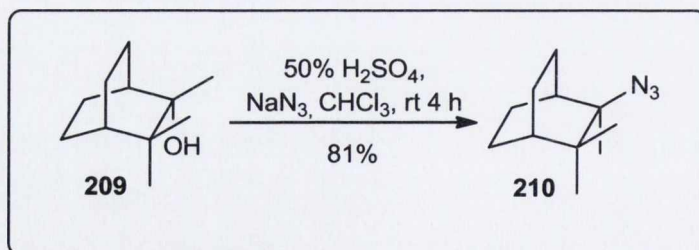
Fortunately, both methyl substituents could be introduced to the bicyclic framework in one step. Treatment of ketone **207** with 2 molar equivalents of NaHMDS at -78°C, warmed to room temperature and stirred for 2 hours, followed by the addition of 2 molar equivalents of iodomethane for 2 hours at room temperature gave the desired dimethylated ketone **208** in 69% yield after purification, (Scheme 4-15).

Scheme 4-15: Conditions for dimethylation of ketone **207**.

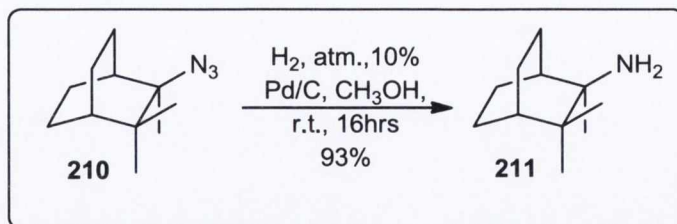
The third methyl substituent was installed at position 2 in accordance with our previous synthetic route using Grignard reagents. Treatment of ketone **208** in anhydrous THF with an excess of methylmagnesium bromide at 40 °C for 4 hours gave the tertiary alcohol **209** very cleanly and without the need for further purification in a good yield of 82%, (Scheme 4-16).

Scheme 4-16: Installation of third methyl substituent *via* Grignard chemistry.

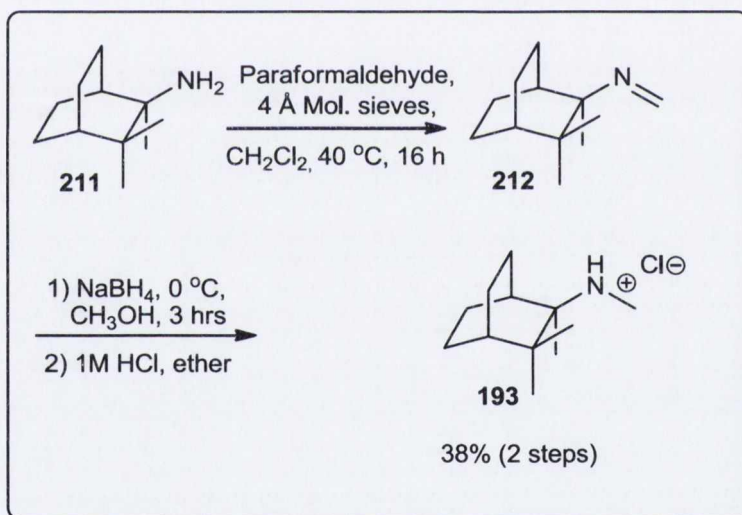
We were delighted that the azide formation proceeded smoothly. Treatment of alcohol **209** with 50% H₂SO₄ and an excess of sodium azide for 4 hours gave azide **210** in 81% yield after purification, (Scheme 4-17). A complete conversion to the azide was observed at this time and none of the undesired and troublesome Wagner-Meerwein side product was detected in the reaction mixture.

Scheme 4-17: S_N1 azide formation.

Exposure of azide **210** to hydrogen in the presence of 10% palladium on charcoal gave the expected amine **211** in 93% yield after work-up, (Scheme 4-18).

Scheme 4-18: Catalytic hydrogenation of azide **210** to amine **211**.

The final synthetic step involved the methylation of the amine by means of a two-step reductive amination methodology previously described in section 2.1.1. The amine **211** was treated with paraformaldehyde and 4 Å molecular sieves in CH_2Cl_2 heated at reflux temperature until NMR spectral analysis of the reaction mixture indicated complete formation of the imine **212** (approximately 16 hours). The imine was not isolated but was treated directly with sodium borohydride and methanol. Treatment of the free amine with a solution of 1M HCl in diethyl ether gave the expected hydrochloride salt **193** in 38% yield, (Scheme 4-19).

Scheme 4-19: Reductive amination to form *N*,2-endo-3,3-tetramethyl-bicyclo[2.2.2]octan-2-amine.

4.3. Introduction of a heteroatom combined with ring expansion.

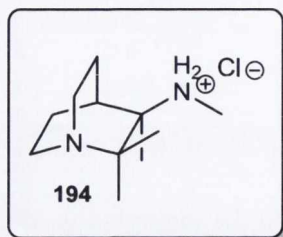
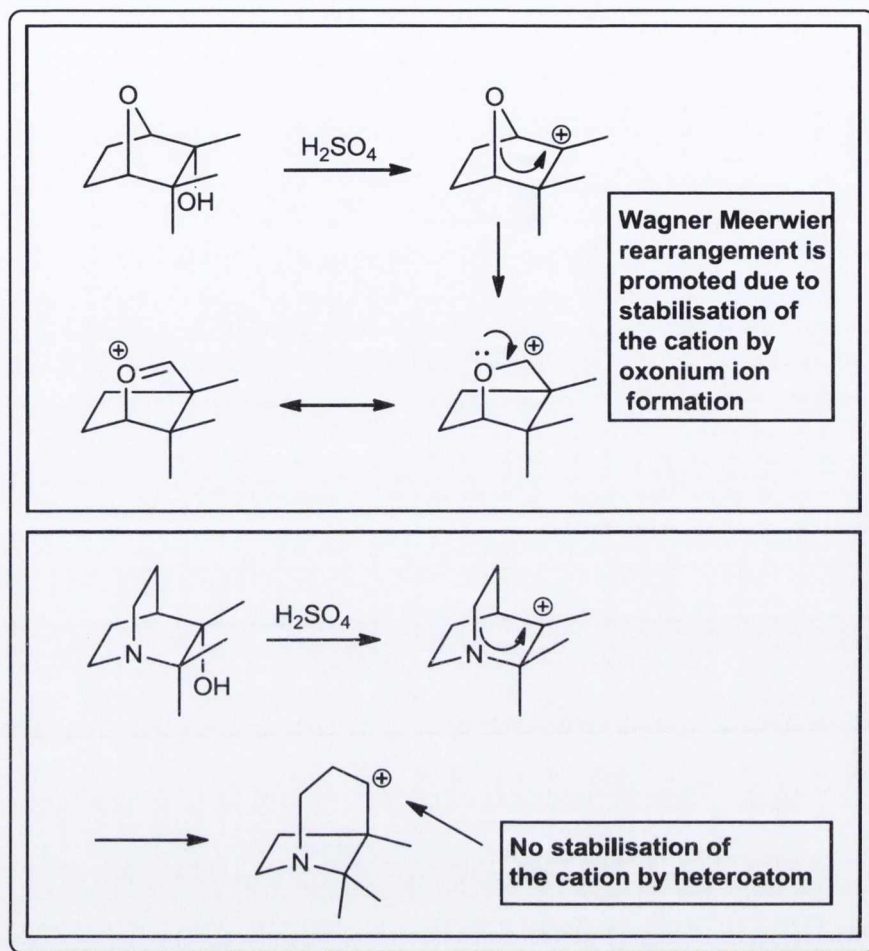


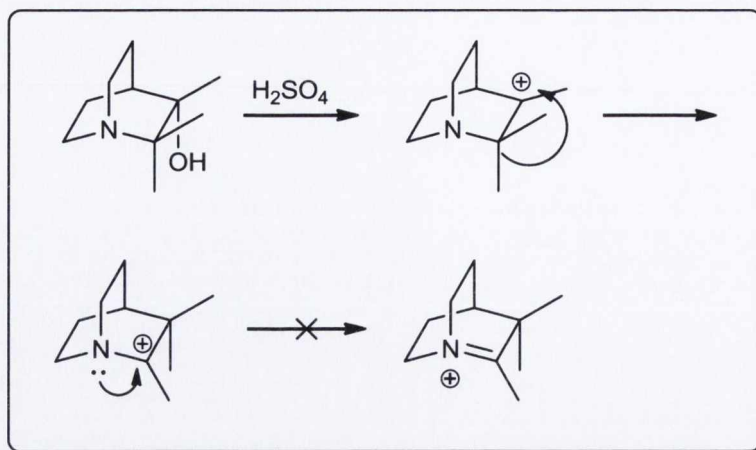
Figure 4-6: Proposed Quinuclidine type MA analogue.

Following the success of our bridgehead expansion we turned our attention once more to the introduction of a heteroatom to the bicyclic framework, (see compound **194**, Figure 4-6). The previous attempts had proved fruitless due to the stabilisation afforded by the oxygen atom in the 7-oxa example. Examining the [2.2.2]bicyclic system indicated that we could possibly install a nitrogen at the ring junction. The commercially available 3-quinuclidone provided a promising precursor which we hoped would comply with our synthetic route.



Scheme 4-20: Comparing Wagner-Meerwein rearrangements in the 7-oxa and quinuclidine systems.

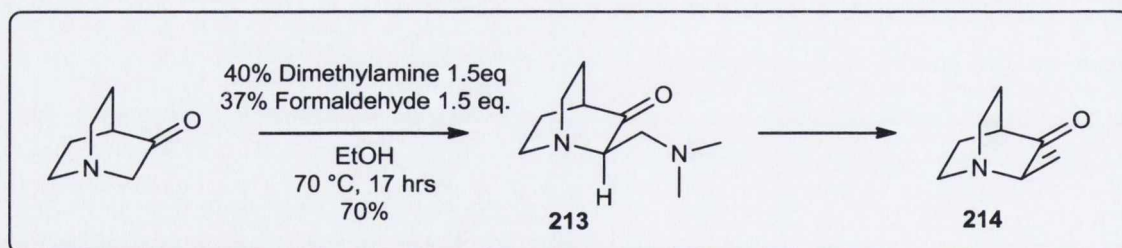
At first glance one might envisage issues with complications arising from 1,2 methyl shifts, (Scheme 4-20). However in this case methyl shifts should be disfavoured because the lone pair of the nitrogen is unable to associate with the vacant p orbital of the cation, (Scheme 4-20). Not only is the stabilisation of the lone pair unavailable but the inductive effect of the nitrogen on the cation should further disfavour methyl shifts, (Scheme 4-21). It is also important to note that under acidic conditions the nitrogen would be protonated, meaning the lone pair would not be available to interact with any cations formed during the reaction.



Scheme 4-21: Cation stabilisation by nitrogen not possible.

4.3.1 Attempted synthesis of quinuclidine MA analogue.

Although we had been unsuccessful preparing the [2.2.1] systems to include extra heteroatoms we saw the opportunity using the [2.2.2] system. Although limited in scope it seemed like an attractive molecule to prepare and compare to MA. Our first attempt to synthesise the quinuclidine analogue in accordance with our previous synthetic route (section 2.1, Scheme 2-1) resulted in failure. Methylation *via* enolate formation resulted in rapid decomposition of the starting material. We postulated that the problem was due to the methylation of the nitrogen atom generating a quaternary ammonium salt, meaning that typical alkylating agents could not be used for this series.

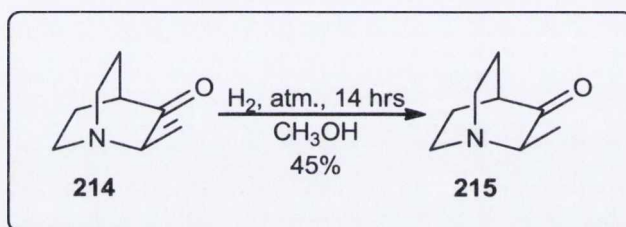


Scheme 4-22: Mannich reaction.

Clearly we had to alter our initial strategy; fortunately, investigation of the literature revealed that the first methyl group could be installed in a two-step process.³¹¹ Treatment of 3-quinuclidone with aqueous dimethylamine (1.5 molar eq.) and formaldehyde (1.5 molar eq.) in ethanol at 70 °C for 17 hours afforded the Mannich base. Upon evaporation of the solvents

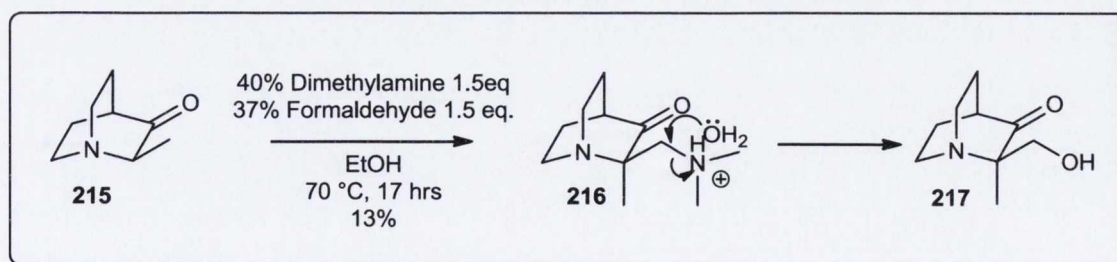
at reduced pressure deamination occurred to form the crude 2-methylene-3-quinuclidinone **214** in a good yield of 70%, (Scheme 4-22). This compound was unstable towards column chromatography and was employed in the next step without further purification.

The second step involved the reduction of the alkene by catalytic hydrogenation. Exposure of alkene **214** to hydrogen in the presence of 10% palladium on charcoal gave the desired 3-methylquinuclidin-2-one **215** in a disappointing yield of 45% after purification, (Scheme 4-23).



Scheme 4-23: Saturation of alkene **214** via catalytic hydrogenation.

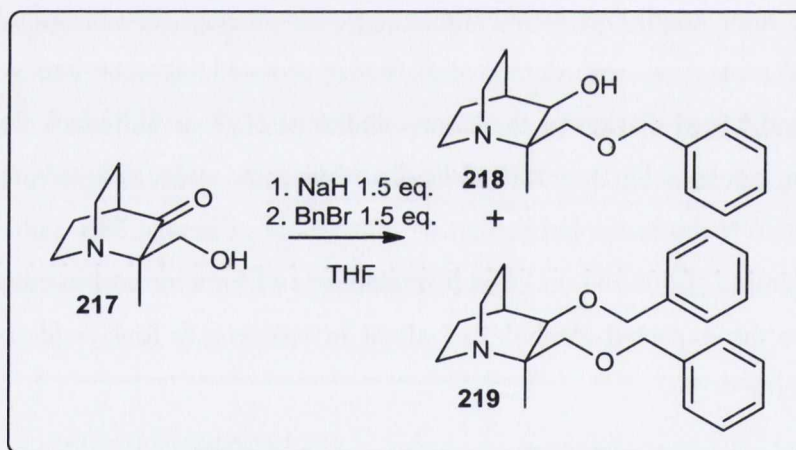
As the Mannich conditions had allowed us to access the mono methylated ketone **215**, we hoped that the same conditions would furnish an *endo*-methyl, *exo*-methanol substituted product **216**. In the previous step deamination under reduced pressure had generated the alkene **214**. We had hoped that under the same conditions H_2O would attack the protonated amine **215** forming alcohol **217**. Removal of the dimethylamine under reduced pressure would drive the equilibrium towards alcohol formation. Treatment of ketone **215** with an excess of aqueous dimethylamine (1.5 molar eq.) and formaldehyde (1.5 molar eq.) in ethanol at 70°C for 19 hours gave the expected alcohol **217** albeit in worryingly low yields of 13% after purification, (Scheme 4-24).



Scheme 4-24: Synthesis of **217** via Mannich conditions.

In order to install the third methyl substituent using Grignard reagents, the alcohol moiety would first need to be protected. Frustratingly, the compound proved to be extremely

unstable towards treatment with base, leading to decomposition during the attempted protection of the alcohol moiety. Treatment of alcohol **217** with 1.5 molar equivalents of NaH, followed by 1.5 molar equivalents of benzyl bromide astonishingly gave an unstable mixture of a bis benzyl ether **218** and a hydroxy benzyl ether **219**, (Scheme 4-25). The mixture rapidly decomposed however crude NMR, IR and MS spectral analysis confirmed the presence of an alcohol and a hydroxy benzyl ether. Although uncharacteristic of the reagent, it appears that the NaH had reduced the carbonyl. No starting material was recovered from the reaction mixture and the desired ketone was not observed. In fact no carbonyl signals were observed in both the IR and NMR spectral data. Attempts to install the third methyl group by treating the unprotected alcohol **217** with methylmagnesium bromide led to complete decomposition of the starting material. We then considered reduction of the alcohol at position 2 prior to installation of the third methyl group. The first step in this approach was an attempted tosylation of alcohol **217** which resulted in decomposition of the starting material. Due to time constraints and synthetic issues associated with the proposed route we decided to terminate our interest in this molecule.



Scheme 4-25: Attempted benzyl protection.

4.4. Conclusions.

We were able to make some alterations to position 7 of the MA skeleton. Bridgehead expansion *via* the synthesis of an expanded [2.2.2]bicyclo analogue **193** was accomplished and will undergo *in vitro* biological testing at $\alpha 4\beta 2$ receptor subtypes. Unfortunately, our attempts to introduce a heteroatom to the bicyclic framework of MA could not be realised due to the

proposed formation of an oxonium ion during the azide formation and the incompatibility of quinuclidone with our synthetic route.

Chapter 5

Future Work

5.1 Future Work.

The library of structural analogues of MA prepared during the course of this project have been submitted for *in vitro* biological testing at $\alpha 4\beta 2$ and $\alpha 3\beta 4$ nAChR subtypes. These results are eagerly awaited and the data they provide along with future works will help to form the basis of a more in depth SAR study of MA. Depending on the outcome of these biological tests there are an array of modifications which could be investigated for antagonistic activity in the hopes of developing a lead compound with therapeutic application.

Firstly, combining alterations which have shown increased antagonistic activity or selectivity for one receptor subtype over another could be investigated. For example, the preparation of an analogue possessing the triethyl substituents at positions 2 and 3 with other modifications such as the 5 membered alkyl ring at positions 5 and 6 or in combination with the triazole moieties or the ring expanded [2.2.2] bicyclo analogue could lead to greater selectivity, (Figure 5-1). Again these proposed modifications are hypothetical and depend on the results of *in vitro* testing.

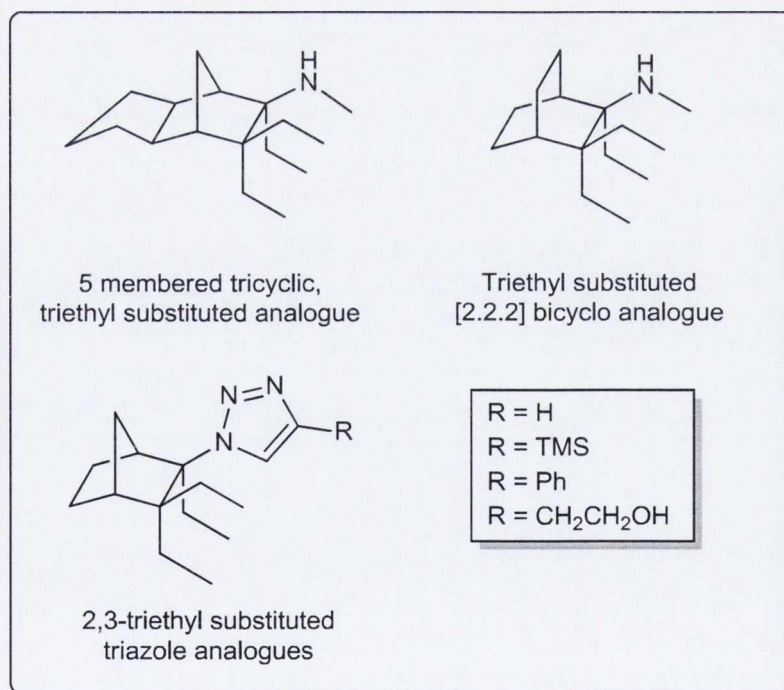


Figure 5-1: Potential targets possessing combined alterations.

Some success was achieved in the synthesis of a library of *endo*-MA analogues. This area could be investigated further, again depending on the results of biological testing, by synthesising *endo* analogues of those which had performed well during *in vitro* testing. These could include *endo* analogues of the spirocyclic series as well as the analogue containing a 5 membered alkyl ring at positions 5 and 6, (Figure 5-2).

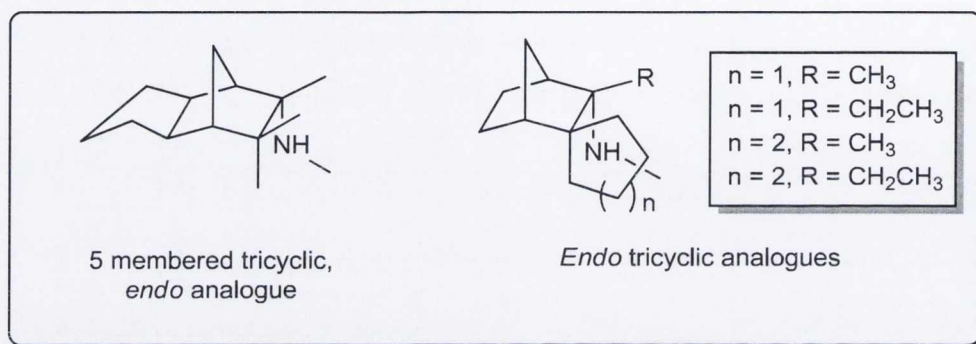


Figure 5-2: Potential *endo* target analogues.

The successful synthesis of an aromatic analogue **87** opens up the possibility of a wide range of analogues by functionalising the phenyl ring by means of EAS chemistry, (Figure 5-3).

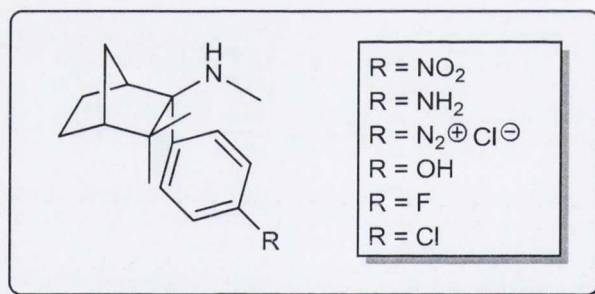


Figure 5-3: Potential analogues which can be achieved using EAS chemistry.

If the triazole analogues were to perform well during testing further substitution in this area would be investigated and a larger library would be prepared. Regioselectivity could be switched from 1,4 to 1,5 by employing a ruthenium catalyst instead of copper. Tetrazoles could be investigated by microwave assisted synthesis using the azide generated during the synthesis of MA and a carbonitrile, (Figure 5-4).

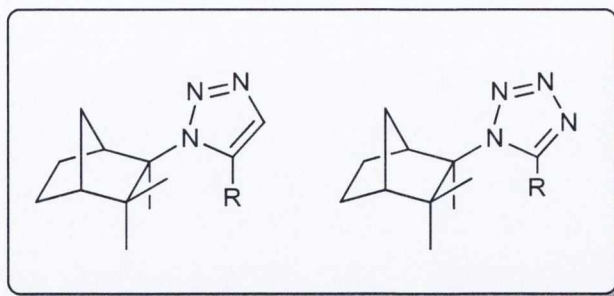


Figure 5-4: Altering triazole regioselectivity and introducing a tetrazole to MA.

While much difficulty was encountered during the numerous attempts to functionalise positions 5 and 6 of the MA framework we believe that substitution may be possible by employing palladium assisted coupling at a different point in the synthesis. Introduction of aromaticity or heteroatoms have been problematic when introduced before the installation of the azide moiety; however, alkyl substitution at the 5 and 6 positions underwent azide formation without difficulty. Employing palladium assisted coupling to the vinyl bromides prior to azide formation may circumvent this problem if coupled with alkyl substituents.

The 5,6 substituted diol series may still be synthetically useful by exchanging the alcohol moieties for chlorine atoms. This alteration could provide a means of avoiding ring closure during the attempted azide formation. Different functionality could be introduced at a later stage in the synthesis under Mitsunobu conditions.

In conclusion, the goal of this project was to prepare a library of structurally distinct analogues which possessed greater antagonistic activity and selectivity than the parent compound MA. While some difficulty was encountered during the course of this project a library of analogues was prepared displaying a wide range of diversity in the in areas outlined in section 1.6, Figure 1-38. The SAR data obtained from *in vitro* assessment of antagonistic activity of these compounds at different nAChR subtypes will help to create a more thorough pharmacophore. It is our hope that these works and future projects will lead to the development of a lead compound possessing therapeutic benefit for the treatment of addiction.

Chapter 6

Experimental

Experimental.

6.1 ^1H and ^{13}C NMR spectra assignment.

Due to the nature of this project it was of the utmost importance to determine the exact structure of each of the compounds prepared. In order to unambiguously assign the proton and carbon spectral data obtained for each compound numerous NMR experiments were performed. An example of the techniques used and their in-depth analysis is outlined below, (Figure 6-1, Figure 6-2 and Table 6-1).

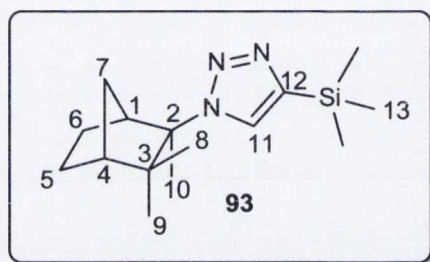


Figure 6-1: Triazole 93.

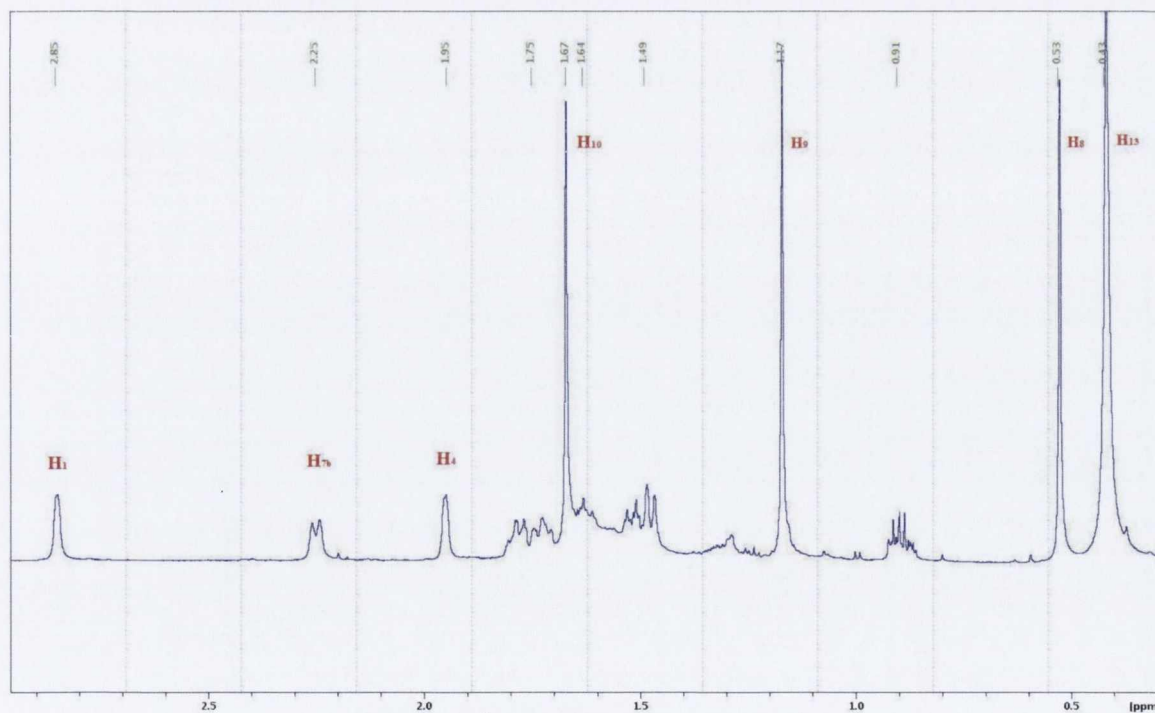
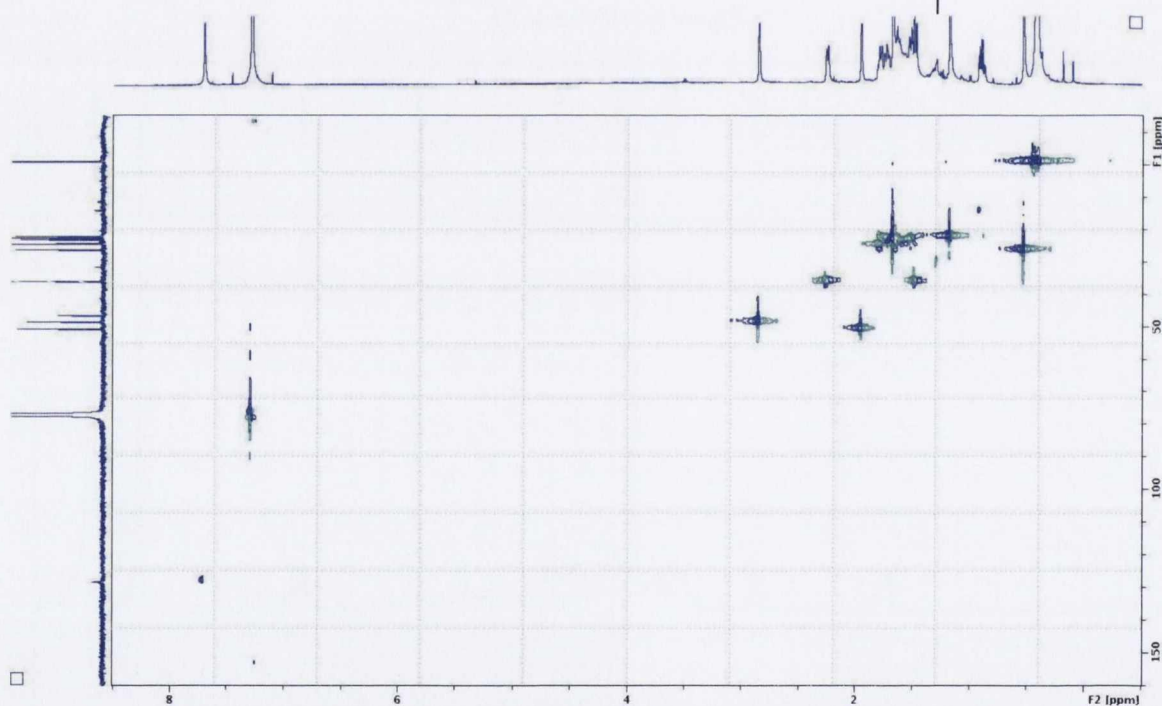


Figure 6-2: ^1H NMR spectra of triazole 93.

Table 6-1: Assignment of triazole 93.

Carbon (ppm)	Type	Proton (ppm)	Position
1.0	CH ₃ (s)	0.42	13
22.0	CH ₃ (s)	1.18	9
22.6	CH ₂ (m)	1.45-1.82	5
23.1	CH ₃ (s)	1.75	10
24.6	CH ₂ (m)	1.45-1.82	6
26.2	CH ₃ (s)	0.53	8
36.0	CH ₂ (m)	1.45-1.82 and 2.25	7
46.6	q	-	3
48.5	CH (br s)	2.85	1
50.7	CH (br s)	1.94	4
73.3	q	-	2
128.3	CH (s)	7.70	11
142.6	q	-	12

Figure 6-3: HSQC experiment displaying ^1H on x-axis and ^{13}C on y-axis.

A HSQC (heteronuclear single quantum coherence) experiment displays the correlation between carbon and proton signals which are directly attached, (Figure 6-3). This experiment allowed for the completion of Table 6-1 once the proton signals had been

identified using the HMBC experiment described in the following section. The chemical shift for the quaternary carbons was taken from the standard ^{13}C 1-D spectrum (Figure 6-4) and the HMBC (Figure 6-5) experiment in the case of C2 which was less visible due to signal broadening.

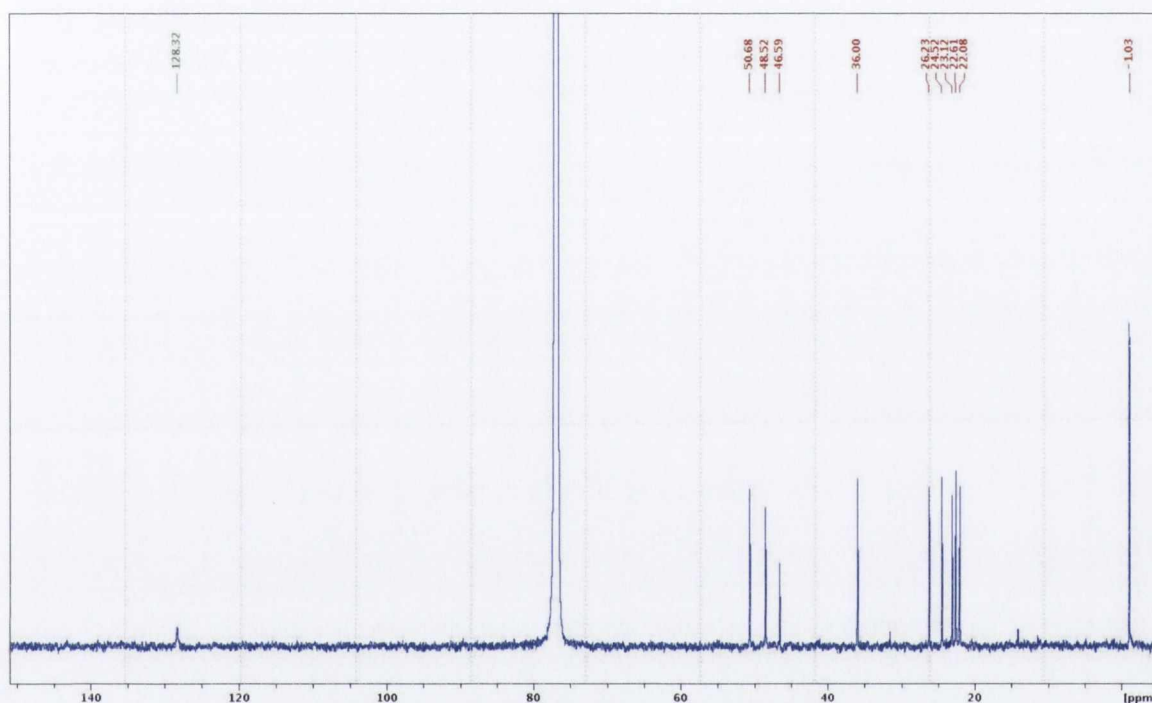


Figure 6-4: ^{13}C NMR spectrum of triazole 93.

A HMBC (heteronuclear multiple bond correlation) experiment was performed. HMBC responses are generally strongest between atoms separated by three bonds, (Figure 6-5). This experiment was the most useful tool in our analysis and allows us to identify the majority of the signals in our compounds. To begin, H1 and H4 can be identified based on their correlation to quaternary carbon C3, at 73.3 ppm and 46.6 ppm respectively. An interaction was observed between the quaternary C3 and the CH at 2.85 ppm implying the signal at 2.85 is H1. H4 is then identified as the CH at position 1.94 ppm. An interaction between H1 at 2.85 ppm and a carbon signal at 22.6 ppm can be identified as C5. In the same manner C6 can be identified by the interaction between H4 at 1.94 ppm and the carbon signal at 24.6 ppm. The remaining CH_2 was attributed to position 7. It is also possible to differentiate methyl groups H8 and H9 from H10 using the HMBC experiment. An interaction is observed between the methyl group H10 and the quaternary C3 at 46.6 ppm. Similarly the remaining two methyl groups H8 and H9 display an interaction with the quaternary C2 at 73.3 ppm although an

unambiguous assignment of the *endo* (H9) and *exo* (H8) methyls is not possible at this point. This is summarised in Table 6-2.

Table 6-2: Summary of correlations identified using HMBC experiment.

H Signal	Correlation	C Signal
H1	3 bond correlation	C3
H1	3 bond correlation	C5
H4	3 bond correlation	C6
H10	3 bond correlation	C3

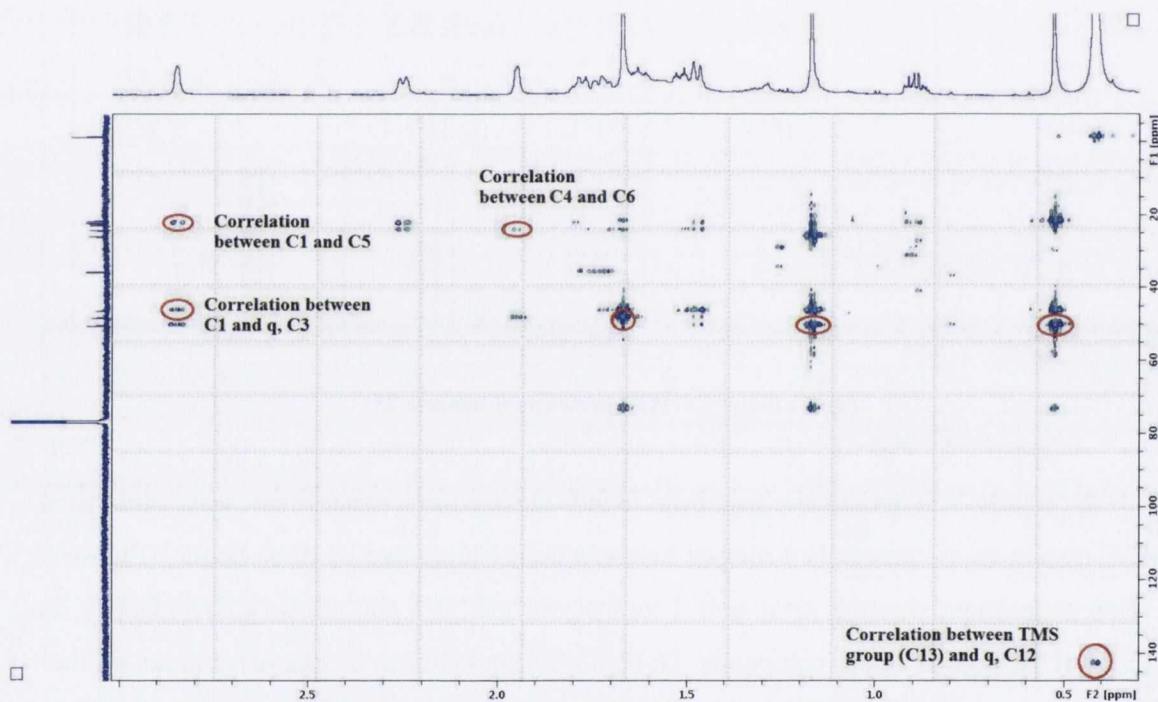


Figure 6-5: HMBC experiment displaying ^1H on x-axis and ^{13}C on y-axis.

In order to determine the *endo* (H9) and *exo* (H8) methyl groups a series of nOe (nuclear Overhauser effect) experiments were performed in order to analyse the 'through space' interactions between these methyl groups and the bridgehead position 7, (Figure 6-6).

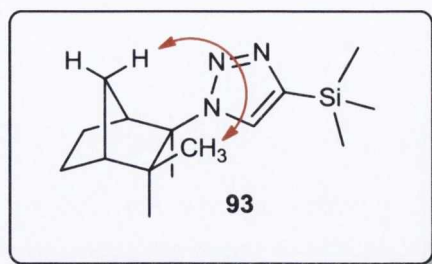


Figure 6-6: nOe response between H7 and H8.

The irradiation of the methyl group at 0.53 ppm confirms the earlier assignment of H4 at 1.94 ppm and a visible response at position 2.25 ppm which corresponds to position 7 unambiguously identifies the methyl group as H8 which is in the *exo* position, (Figure 6-7).

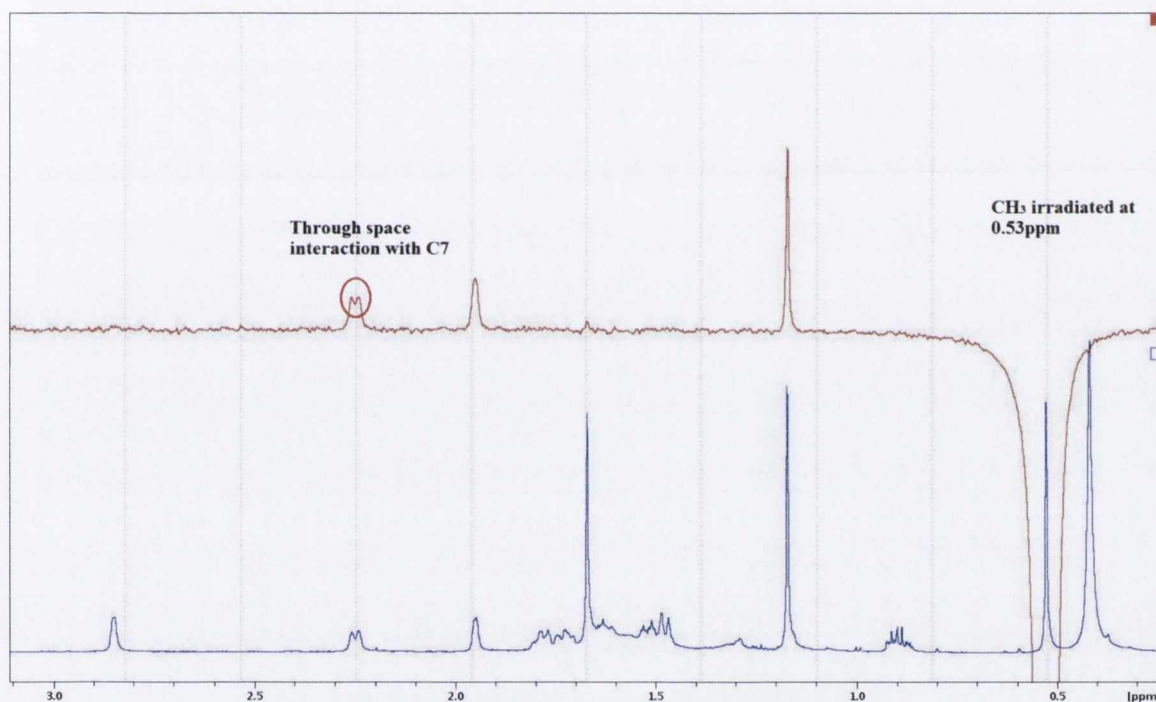


Figure 6-7: nOe experiment overlapping ^1H NMR spectrum.

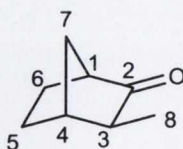
This approach was applied when assigning the structure of each of the compounds. Due to the regioselectivity observed in our synthetic route analysis of the stereochemistry of the alkyl substituents at positions 3 was normally carried out once in the series for either the azide, amine or methylated amine of each analogue.

6.2 General.

All commercial chemicals were obtained from Sigma-Aldrich or TCI and were used without further purification. Toluene, dichloromethane and triethylamine were distilled over calcium hydride and stored under argon prior to use. THF and diethyl ether were distilled over sodium-benzophenone ketyl radical and stored under argon. Chromatographic columns were run using Silica gel 60 (230-400 mesh ASTM). Solvents for synthetic purposes were used at GPR grade. Analytical TLC was performed using Merck Kieselgel 60 F₂₅₄ silica gel plates. Visualisation was by UV light, KMnO₄, or phosphomolybdic acid staining. Proton and carbon nuclear magnetic resonance (NMR) spectra were recorded on: Bruker Avance III 400 MHz, Bruker DPX400 400 MHz and Bruker Avance II 600 MHz spectrometers. Shifts are referenced to the internal solvent signals. ¹H NMR spectra were recorded at 400.23 MHz, 400.13 MHz and 600.13 MHz, respectively. Carbon NMR spectra were recorded at 100.64 MHz, 100.61 MHz and 150.9 MHz, respectively. Chemical shifts are reported in ppm relative to tetramethylsilane and coupling constants (*J*) are quoted in Hertz. Electrospray mass spectra were recorded on a Mass Lynx NT V 3.4 on a Waters 600 controller connected to a 996 photodiode array detector with methanol as carrier solvent. Electron impact mass spectra were determined on a Quatro-II mass spectrometer. Chemical ionisation mass spectra were recorded on a Waters GCT Premier mass spectrometer. Melting points were determined using an Electrothermal IA9000 digital melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer.

6.3 Synthesis of compounds described in chapter 2.

6.3.1 3-*exo*-Methylbicyclo[2.2.1]heptan-2-one. (36)



General Procedure A

To a solution of distilled diisopropylamine (11.70 mL, 82.61 mmol) in anhydrous THF (60 mL) at -78 °C was added a solution of *n*-butyllithium (2.5M in hexanes, 31.80 mL, 79.43

mmol). The reaction mixture was allowed to warm to room temperature and a solution of bicyclo[2.2.1]heptan-2-one **35** (7.00 g, 63.5 mmol) in anhydrous THF (40 mL) was added dropwise. After stirring for 2 hrs, the solution was cooled to 0 °C and iodomethane (5.90 mL, 95.3 mmol) was added dropwise. The solution was stirred for 2 hrs at room temperature and a solution of 1M HCl (100 mL) was added. The mixture was extracted with diethyl ether (2 x 40 mL), the combined organic layers were washed with brine (40 mL) and dried over magnesium sulfate. The mixture was filtered before the volatiles were removed at reduced pressure to yield 3-methyl-bicyclo[2.2.1]heptan-2-one **36** as a yellow oil (7.10 g, 57.2 mmol 91%). The ketone was used without further purification.

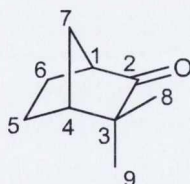
^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.10 (3H, d, $J = 7.5$ Hz, H_8), 1.46-1.63 (3H, m, H_{5a} , H_{6a} , H_{7a}), 1.81-1.98 (4H, m, H_{5b} , H_{6b} , H_3 , H_{7b}), 2.35-2.40 (1H, m, H_4), 2.58-2.64 (1H, m, H_1).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 14.1 (C_8), 23.7 (C_6), 27.9 (C_5), 34.4 (C_7), 41.4 (C_3), 48.2 (C_4), 49.5 (C_1), 221.0 (q, C_2).

IR ν_{max} (cm^{-1}): 2960, 2876, 1736, 1460, 1083, 937, 850.

HRMS: (m/z - CI) Calculated for $\text{C}_8\text{H}_{13}\text{O}$ ($\text{M}+\text{H}^+$) 125.0966, found 125.0970.

6.3.2 3,3-Dimethylbicyclo[2.2.1]heptan-2-one. (37)



General Procedure B

A solution of 3-*exo*-methylbicyclo[2.2.1]heptan-2-one **36** (4.44 g, 39.7 mmol) in THF (20 mL) was added to a solution of sodium bis(trimethylsilyl)amide (1.9M in THF, 31.30 mL, 59.48 mmol) in anhydrous THF (80 mL) at -78 °C. The reaction was allowed to warm slowly

to room temperature. After stirring for 2 hrs, the reaction mixture was cooled to 0 °C before iodomethane (3.70 mL, 59.5 mmol) was added dropwise. The cooling bath was removed and stirring was continued for 2 hrs at room temperature. 1M HCl (70 mL) was added. The mixture was extracted with diethyl ether (2 x 30 mL), the combined organic extracts were washed with brine (30 mL), dried over magnesium sulfate, filtered and the volatiles removed at reduced pressure to give a pale yellow oil. The crude reaction product was purified by column chromatography (97:3 hexane: ethyl acetate, R_f = 0.2) to yield 3,3-dimethylbicyclo[2.2.1]heptan-2-one **37** as a yellow oil (3.35 g, 24.24 mmol, 63%). The spectroscopic analysis is consistent with the ^{13}C NMR data reported in the literature.³¹²

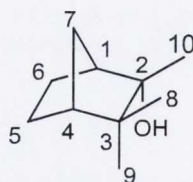
^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.06 (3H, s, H_9), 1.08 (3H, s, H_8), 1.44-1.53 (2H, m, H_{6a} , H_{7a}), 1.54-1.59 (1H, m, H_{5a}), 1.77-1.93 (2H, m, H_{5b} , H_{6b}), 1.97-2.03 (1H, m, H_{7b}), 2.31-2.35 (1H, m, H_4), 2.55-2.58 (1H, m, H_1).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 21.1 (C_9), 22.7 (C_8), 22.9 (C_5), 24.2 (C_6), 34.6 (C_7), 45.8 (C_4), 46.6 (q, C_3), 49.7 (C_1), 222.5 (q, C_2).

IR ν_{max} (cm^{-1}): 2966, 2874, 1739, 1464, 1290, 1153, 949, 748.

HRMS: (m/z - EI) Calculated for $\text{C}_9\text{H}_{14}\text{O}$ (M)⁺ 138.1045, found 138.1044.

6.3.3 2-*exo*-3,3-Trimethylbicyclo[2.2.1]heptan-2-ol. (**38**)



General Procedure C

A solution of 3,3-dimethylbicyclo[2.2.1]heptan-2-one **37** (4.30 g, 31.2 mmol) in anhydrous THF (30 mL) was added dropwise to a solution of methylmagnesium bromide (3M in diethyl ether, 20.8 mL, 62.3 mmol) in anhydrous THF (40 mL) at -78 °C. The reaction mixture was then warmed to 40 °C and heating was continued for 4 hrs. The reaction mixture was allowed

to cool to room temperature before 10% aqueous NH_4Cl (60 mL) was added. The mixture was extracted with diethyl ether (2 x 30 mL), the combined organic layers were washed with water (30 mL), brine (30 mL) and dried over magnesium sulfate before being filtered. The volatiles were removed at reduced pressure and the resultant pale yellow oil was purified by column chromatography (97:3 hexane:ethyl acetate, (9:1 hexane:ethyl acetate $R_f = 0.3$)) to yield 2-*exo*-3,3-trimethylbicyclo[2.2.1]heptan-2-ol **38** as a white solid (3.40 g, 22.1 mmol, 70%). M.p. 117-120 °C (lit.³¹³ 113-115 °C).

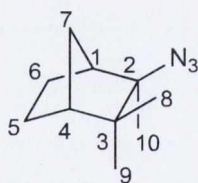
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 0.94 (3H, s, H_9), 0.98 (3H, s, H_8), 1.14-1.20 (1H, m, H_{7a}), 1.23 (3H, s, H_{10}), 1.30-1.41 (2H, m, H_{5a} , H_{6a}), 1.71-1.77 (3H, m, H_{7b} , H_4 , H_{6b}), 1.83-1.92 (1H, m, H_{5b}), 1.96-2.00 (1H, m, H_1).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 20.7 (C_5), 21.3 (C_9), 23.5 (C_6), 25.9 (C_{10}), 26.6 (C_8), 34.3 (C_7), 41.6 (q, C_3), 49.3 (C_4), 50.5 (C_1), 78.4 (q, C_2).

IR ν_{max} (cm^{-1}): 3422, 2928, 2872, 1476, 1372, 1295, 1086, 927.

HRMS: (m/z - EI) Calculated for $\text{C}_{10}\text{H}_{18}\text{O}$ (M)⁺ 154.1358, found 154.1353.

6.3.4 2-Azido-2-*endo*-3,3-trimethylbicyclo[2.2.1]heptane. (39)



General Procedure D

A solution of HN_3 was prepared by carefully adding a solution of 50% H_2SO_4 (20 mL) to a suspension of NaN_3 (5.00 g, 77.8 mmol) in CHCl_3 (100 mL) at 0 °C. To this was slowly added 2-*exo*-3,3-trimethylbicyclo[2.2.1]heptan-2-ol **38** (4.00 g, 25.9 mmol). After stirring for 4 hrs at room temperature in a stoppered vessel, ice-cold water (30 mL) was added. The mixture was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with 5% aqueous NaHCO_3 solution (30 mL), dried over magnesium sulfate, filtered, and the

volatiles were removed at reduced pressure to give a yellow oil. Purification by column chromatography (100% hexane, $R_f = 0.7$) gave 2-azido-2,3,3-trimethylbicyclo[2.2.1]heptane **39** as clear colourless oil (2.40 g, 13.4 mmol, 56%).

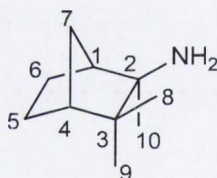
^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 0.93 (3H, s, H_9), 1.05 (3H, s, H_8), 1.11-1.17 (1H, app d, $J = 10.1$ Hz, H_{7a}), 1.26-1.35 (4H, m, H_{10} , H_{5a}), 1.42-1.50 (2H, m, H_6), 1.55-1.63 (1H, m, H_{5b}), 1.76-1.80 (1H, m, H_4), 1.99-2.05 (1H, m, H_{7b}), 2.11-2.14 (1H, m, H_1).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 16.9 (C_{10}), 22.6 (C_6), 23.0 (C_9), 23.3 (C_5), 26.4 (C_8), 34.4 (C_7), 43.8 (q, C_3), 48.3 (C_1), 49.3 (C_4), 72.5 (q, C_2).

IR ν_{max} (cm^{-1}): 2963, 2874, 2081, 1454, 1255, 1071, 801.

HRMS: (m/z - CI) Calculated for $\text{C}_{10}\text{H}_{23}\text{N}_4$ ($\text{M}+\text{H}-\text{N}_2$) $^+$ 154.1596, found 154.1608.

6.3.5 2-endo-3,3-Trimethylbicyclo[2.2.1]hept-2-ylamine (**40**)



General Procedure E

To a solution of 2-azido-2-endo-3,3-trimethylbicyclo[2.2.1]heptane **39** (0.30 g, 1.72 mmol), in methanol (20 mL) palladium on charcoal (0.03 g, 10% w/w) was added. The reaction vessel was evacuated and filled with hydrogen. The reaction mixture was stirred vigorously under a blanket of hydrogen at atmospheric pressure overnight. The reaction mixture was filtered through celite, dried over magnesium sulfate and filtered before the volatiles were removed at reduced pressure. The free amine was isolated by the addition of a 1M solution of NaOH. It was extracted with ethyl acetate (2 x 20 mL) and dried over magnesium sulfate and filtered before the volatiles were removed at reduced pressure to yield 2,3,3-

trimethylbicyclo[2.2.1]hept-2-ylamine **40** as a white solid (0.24 g, 1.56 mmol, 90%). M.p. 110 °C -112 °C (Sublimes). M.p. HCl salt 166-167 °C (lit³¹⁴ 168-169 °C).

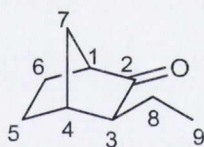
¹H NMR (CDCl₃, 400 MHz): δ (ppm) 0.93 (3H, s, H₈), 1.00 (3H, s, H₉), 1.07-1.13 (4H, m, H₁₀, H_{7a}), 1.23-1.33 (1H, m, H_{5a}), 1.33-1.43 (1H, m, H_{6a}), 1.50-1.66 (2H, m, H_{5b}, H_{6b}), 1.71-1.76 (1H, m, H₁), 1.80-1.85 (1H, m, H₄), 1.91-1.97 (1H, m, H_{7b}).

¹³C NMR (CDCl₃, 100 MHz): δ (ppm) 22.8 (C₁₀), 23.0 (C₆), 23.1 (C₈), 23.6 (C₅), 25.9 (C₉), 34.0 (C₇), 42.5 (q, C₃), 49.9 (C₁), 52.1 (C₄), 59.5 (q, C₂).

IR ν_{max} (cm⁻¹): 3387, 2953, 2870, 1464, 1386, 1258, 1127, 806, 743.

HRMS: (*m/z* - EI) Calculated for C₁₀H₁₉N (M)⁺ 153.1517, found 153.1510.

6.3.6 3-*exo*-Ethylbicyclo[2.2.1]heptan-2-one³¹⁵ (**220**)



Prepared as per general procedure A using norcamphor **35** (8.00 g, 71.5 mmol), diisopropylamine (13.00 mL, 92.91 mmol), *n*-butyllithium (2.5M solution in hexanes, 36.00 mL, 89.40 mmol), iodoethane (1.70 mL, 3.32 g, 27.3 mmol) and THF (100mL) to yield a yellow oil which was purified by column chromatography (9:1 hexane: ethyl acetate, *R_f* = 0.45) to yield 3-*exo*-ethylbicyclo[2.2.1]heptan-2-one **220** as a pale yellow oil (7.96 g, 57.6 mmol, 81%).

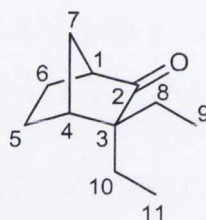
¹H NMR (CDCl₃, 400 MHz): δ (ppm) 1.01 (3H, app t, *J* = 7.1 Hz, H₉), 1.22-1.32 (1H, m, H_{8a}), 1.39-1.67 (5H, m, H_{5a}, H_{6a}, H_{7a}, H₃, H_{8b}), 1.78-1.88 (3H, m, H_{5b}, H_{6b}, H_{7b}), 2.44-2.47 (1H, m, H₄), 2.52-2.56 (1H, m, H₁).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 12.6 (C_9), 21.9 (C_8), 23.7 (C_5), 27.6 (C_6), 34.5 (C_7), 38.4 (C_4), 49.3 (C_1), 55.4 (C_3), 220.5 (q, C_2).

IR ν_{max} (cm^{-1}): 2959, 2877, 1740, 1626, 1458, 1172, 1027.

HRMS: (m/z - EI) Calculated for $\text{C}_9\text{H}_{14}\text{O}$ (M^+) 138.1045, found 138.1042.

6.3.7 3,3-Diethylbicyclo[2.2.1]heptan-2-one (221)



Prepared as per general procedure B using 3-*exo*-ethylbicyclo[2.2.1]heptan-2-one **220** (9.50g, 67.9 mmol), sodium bis(trimethylsilyl)amide (1.9M solution in THF, 71.00 mL, 135.72 mmol), iodoethane (10.80 mL, 135.72 mmol) and THF (100 mL) to yield a pale yellow oil which was purified by column chromatography (9:1 hexane: ethyl acetate, R_f = 0.54) to yield 3,3-diethylbicyclo[2.2.1]heptan-2-one **221** as a clear oil (7.10 g, 42.7 mmol, 63%).

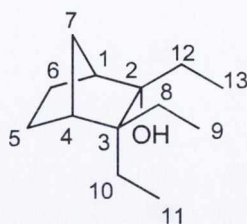
^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 0.87 (3H, app t, J = 7.5 Hz, H_{11}), 0.91 (3H, t, J = 7.5 Hz, H_9), 1.19-1.30 (1H, m, H_{10a}), 1.41-1.77 (7H, m, H_{5a} , H_{5b} , H_{6a} , H_{7a} , H_8 , H_{10b}), 1.80-1.90 (1H, m, H_{6b}), 1.97-2.03 (1H, m, H_{7b}), 2.30 (1H, br s, H_4), 2.52-2.57 (1H, m, H_1).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 8.2 (C_{11}), 8.6 (C_9), 22.6 (C_{10}), 23.0 (C_5), 23.5 (C_8), 25.7 (C_6), 34.7 (C_7), 43.6 (C_4), 50.6 (C_1), 52.9 (q, C_3), 222.3 (q, C_2).

IR ν_{max} (cm^{-1}): 2965, 2878, 1734, 1467, 1379, 1059.

HRMS: (m/z - EI) Calculated for $\text{C}_{11}\text{H}_{18}\text{O}$ (M^+) 166.1358, found 166.1358.

6.3.8 2-*exo*-3,3-Triethylbicyclo[2.2.1]heptan-2-ol (222)



General Procedure F

To a solution of bromoethane (7.50 mL, 88.3 mmol) in anhydrous THF (60 mL) was added a solution of *tert*-butyllithium (1.7 M in pentane, 104.00 mL, 176.58 mmol) at -78 °C. The reaction mixture was stirred for 10 mins before a solution of 3-diethylbicyclo[2.2.1]heptan-2-one **221** (6.09 g, 36.7 mmol), in anhydrous THF (5 mL) was added. The reaction mixture was allowed to warm to room temperature and was stirred for 3 hrs upon which time a saturated solution of sodium bicarbonate (20 mL) was added. The mixture was extracted with diethyl ether (2 x 40 mL), the combined organic layers were washed with brine (35 mL) and dried over magnesium sulfate before being filtered. The volatiles were removed at reduced pressure to afford a pale yellow oil which was purified by column chromatography (9:1 hexane:ethyl acetate, R_f = 0.48) to yield 2-*exo*-3,3-triethylbicyclo[2.2.1]heptan-2-ol **222** as a clear oil (4.45 g, 22.7 mmol, 62%).

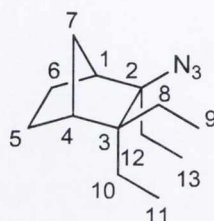
¹H NMR (CDCl₃, 400 MHz): δ (ppm) 0.84 (3H, app t, *J* = 7.2 Hz, H₁₁), 0.84 (3H, app t, *J* = 7.19 Hz, H₉), 0.94 (3H, t, *J* = 7.4 Hz, H₁₃), 1.05-1.10 (1H, m, H_{7a}), 1.21-1.36 (4H, m, H_{5a}, H_{6a}, H_{8a}, H_{10a}), 1.59-1.74 (6H, m, H_{5b}, H_{7b}, H_{8b}, H_{10b}, H₁₂), 1.76-1.83 (1H, m, H_{6b}), 1.98-2.03 (1H, m, H₄), 2.19-2.24 (1H, m, H₁).

¹³C NMR (CDCl₃, 100 MHz): δ (ppm) 8.5 (C₁₃), 9.4 (C₉), 9.9 (C₁₁), 20.8 (C₆), 21.8 (C₈), 22.8 (C₅), 24.0 (C₁₀), 29.1 (C₁₂), 34.2 (C₇), 45.0 (C₄), 45.6 (C₁), 47.8 (q, C₃), 81.2 (q, C₂).

IR $\nu_{\max}$ (cm⁻¹): 3515, 2962, 2879, 1463, 1377, 1127, 984.

HRMS: (m/z - EI) Calculated for $C_{13}H_{24}O$ (M)⁺ 196.1827, found 196.1831.

6.3.9 2-Azido-2-*endo*-3,3-triethylbicyclo[2.2.1]heptanes (**223**)



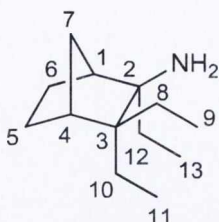
Prepared as per general procedure D using 2-*exo*-3,3-triethylbicyclo[2.2.1]heptan-2-ol **222** (4.20 g, 21.4 mmol), NaN_3 (9.70 g, 149.0 mmol), 60% H_2SO_4 (30 mL) and $CHCl_3$ (120 mL) to yield a pale yellow oil which was further purified by column chromatography (100% hexane, R_f = 0.65) to yield 2-azido-2-*endo*-3,3-triethylbicyclo[2.2.1]heptane **223** as a clear colourless oil (2.72 g, 12.3 mmol, 57%).

1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.80 (3H, t, J = 7.4 Hz, H_{11}), 0.84 (3H, app t, J = 7.4 Hz, H_9), 0.98 (3H, app t, J = 7.4 Hz, H_{13}), 1.16-1.21 (1H, m, H_{7a}), 1.25-1.65 (8H, m, H_5 , H_6 , H_{8a} , H_{10} , H_{12a}), 1.70-1.94 (4H, m, H_{8b} , H_{7b} , H_4 , H_{12b}), 2.36-2.40 (1H, m, H_1).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 9.0 (C_{11}), 9.1 (C_{13}), 9.7 (C_9), 21.5 (C_{10}), 22.0 (C_6), 23.4 (C_5), 25.1 (C_{12}), 26.3 (C_8), 33.8 (C_7), 44.3 (C_1), 46.0 (C_4), 50.2 (q, C_3), 76.7 (q, C_2).

IR ν_{max} (cm^{-1}): 2964, 2881, 2091, 1464, 1270, 901, 881.

HRMS: (m/z - EI) Calculated for $C_{13}H_{23}N$ ($M-N_2$)⁺ 193.1830, found 193.1835.

6.3.10 2-*endo*-3,3-Triethylbicyclo[2.2.1]heptan-2-amine (224)

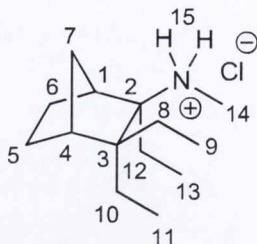
Prepared as per general procedure E using 2-azido-2-*endo*-3,3-triethylbicyclo[2.2.1]heptane **223** (1.50 g, 6.78 mmol), palladium on charcoal (0.15 g, 10% w/w) and a 10:1 methanol:isopropanol solution (22 mL) in a reinforced glass vessel, fitted with a protective metal jacket, attached to a hydrogen gas cylinder at 3 atm pressure with a reaction time of 5 hrs to yield 2-*endo*-3,3-triethylbicyclo[2.2.1]heptan-2-amine **224** as a clear oil (0.36 g, 18.4 mmol, 27%).

^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 0.79 (3H, t, $J = 7.4$ Hz, H_9), 0.85 (3H, app t, $J = 7.4$ Hz, H_{11}), 0.91 (3H, app t, $J = 7.4$ Hz, H_{13}), 1.01-1.09 (1H, m, H_{7a}), 1.16-1.70 (8H, m, H_5 , H_6 , H_8 , H_{10a} , H_{12a}), 1.74-1.90 (4H, m, H_1 , H_4 , H_{10b} , H_{12b}), 1.90-1.97 (1H, m, H_{7a}).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 8.8 (C_{13}), 9.2 (C_9), 10.7 (C_{11}), 21.5 (C_8), 22.3 (C_5), 23.5 (C_6), 25.3 (C_{10}), 27.3 (C_{12}), 33.4 (C_7), 46.7 (C_1), 48.8 (q, C_3), 49.3 (C_4), 62.8 (q, C_2).

IR ν_{max} (cm^{-1}): 3363, 2960, 2877, 1462, 1376, 802, 732.

HRMS: (m/z - EI) Calculated for $\text{C}_{13}\text{H}_{25}\text{N}$ (M) $^+$ 195.1987, found 195.1982.

6.3.11 2-*endo*-3,3-Triethyl-*N*-methylbicyclo[2.2.1]heptan-2-amine (47)

General Procedure G

Into an oven dried RBF under an argon atmosphere and fitted with a reflux condenser was added 2-*endo*-3,3-triethylbicyclo[2.2.1]heptan-2-amine **224** (0.15 g, 0.76 mmol), paraformaldehyde (0.10 g 2.69 mmol) and activated 4 Å molecular sieves (0.12 g). Anhydrous CH₂Cl₂ (10 mL) was then added and the reaction was heated at reflux temperature for 16 hrs. After this time, an *in situ* ¹H NMR sample was taken to confirm quantitative conversion to the imine was complete. The reaction was cooled to -10 °C and sodium borohydride (0.13 g, 3.42 mmol) was added. Anhydrous methanol (1.50 mL) was added dropwise and the reaction was allowed to warm to room temperature with continuous stirring over 1 hr and then stirred at room temperature for a further 2 hrs. The reaction mixture was filtered to remove the 4 Å molecular sieves and the unreacted paraformaldehyde. The residue was washed with CH₂Cl₂ (50 mL) and the combined filtrate extracted with a solution of aqueous NaOH (2M, 30 mL). The organic solvent was dried over magnesium sulfate and removed under vacuum to give the *N*-methylated amine as a tacky solid. This product was re-dissolved in anhydrous diethyl ether (5 mL) and a solution of hydrogen chloride (2M in diethyl ether, 1.00 mL, 2.00 mmol) was added. The diethyl ether was removed under vacuum to yield the desired HCl salt of 2-*endo*-3,3-triethyl-*N*-methylbicyclo[2.2.1]heptan-2-amine **47** as a white solid (0.13 g, 0.53 mmol, 66%). M.p. 140-150 °C (decomposes).

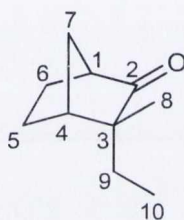
¹H NMR (CDCl₃, 400 MHz): δ (ppm) 0.90 (3H, t, *J* = 7.5 Hz, H₁₃), 0.96 (3H, app t, *J* = 7.1 Hz, H₁₁), 1.15 (3H, t, *J* = 7.3 Hz, H₉), 1.19-1.26 (1H, m, H_{7a}), 1.26-1.96 (9H, m, H₅, H₆, H₈, H_{10a}, H₁₂), 2.12-2.24 (2H, m, H₄, H_{10b}), 2.48-2.56 (1H, m, H_{7b}), 2.65-2.77 (4H, m, H₁, H₁₄), 8.39 (1H, br s, H_{15a}), 9.01 (1H, br s, H_{15b}).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 9.6 (C_9), 10.0 (C_{11}), 10.1 (C_{13}), 21.4 (C_8), 21.7 (C_5), 23.1 (C_{12}), 23.9 (C_6), 24.0 (C_{10}), 30.6 (C_{14}), 34.6 (C_7), 46.18 (C_4), 46.24 (C_1), 51.3 (q, C_3), 75.6 (q, C_2).

IR ν_{max} (cm^{-1}): 2981, 2892, 1589, 1476, 1379, 1150, 944.

HRMS: (m/z - EI) Calculated for $\text{C}_{14}\text{H}_{27}\text{N}$ (M) $^+$ 209.2143, found 209.2144.

6.3.12 3-*endo*-Ethyl-3-methylbicyclo[2.2.1]heptan-2-one³¹⁵ (**225**)



Prepared as per general procedure B using 3-*exo*-ethylbicyclo[2.2.1]heptan-2-one **220** (2.70 g, 21.7 mmol), sodium bis(trimethylsilyl)amide (1.9M solution in THF, 21.70 mL, 43.47 mmol), THF (30 mL) and iodomethane (2.70 mL, 43.4 mmol) to yield a pale yellow oil which was purified by column chromatography (9:1 hexane:ethyl acetate, R_f = 0.53) to yield 3-*exo*-methyl-3-ethylbicyclo[2.2.1]heptan-2-one **225** as a clear oil (2.55 g, 16.8 mmol, 77%).

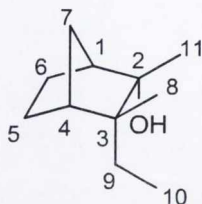
^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 0.91 (3H, app t, J = 7.5 Hz, H_{10}), 1.02 (3H, s, H_8), 1.31-1.39 (1H, m, H_{9a}), 1.43-1.56 (3H, m, H_{6a} , H_{7a} , H_{9b}), 1.58-1.66 (1H, m, H_{5a}), 1.68-1.75 (1H, m, H_{5b}), 1.80-1.89 (1H, m, H_{6b}), 1.93-1.98 (1H, m, H_{7b}), 2.29-2.32 (1H, m, H_4), 2.57-2.60 (1H, m, H_1).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 8.3 (C_{10}), 18.7 (C_8), 23.1 (C_5), 24.9 (C_6), 27.0 (C_9), 34.8 (C_7), 43.6 (C_4), 50.1 (q, C_3), 50.2 (C_1), 223.1 (q, C_2).

IR $\nu_{\max}$ (cm^{-1}): 2960, 2926, 1739, 1456, 1257, 1012, 791.

HRMS: (m/z - ES) Calculated for $\text{C}_{10}\text{H}_{17}\text{O}$ ($\text{M}+\text{H}$)⁺ 153.1279, found 153.1283.

6.3.13 3-endo-Ethyl-2-exo-3-dimethylbicyclo[2.2.1]heptan-2-ol (**226**)



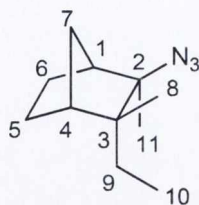
Prepared as per general procedure C using 3-endo-ethyl-3-methylbicyclo[2.2.1]heptan-2-one **225** (5.32 g, 34.9 mmol), methylmagnesium bromide (3M in diethyl ether, 23.30 mL, 69.89 mmol) and THF (50 mL) to yield a pale yellow oil which was purified by column chromatography (9:1 hexane:ethyl acetate, R_f = 0.26) to yield 3-endo-ethyl-2-exo-3-dimethylbicyclo[2.2.1]heptan-2-ol **226** as a clear oil. (5.04 g, 29.9 mmol, 86%).

^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 0.87 (3H, app t, J = 7.5 Hz, H_{10}), 0.92 (3H, s, H_8), 1.13-1.20 (1H, m, H_{7a}), 1.24 (3H, s, H_{11}), 1.25-1.34 (3H, m, H_{5a} , H_{6a} , H_{9a}), 1.48-1.59 (1H, m, H_{9b}), 1.59-1.67 (1H, m, H_{6b}), 1.67-1.73 (1H, m, H_{7b}), 1.78-1.90 (2H, m, H_{5b} , H_4), 1.95-2.00 (1H, m, H_1)

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 9.4 (C_{10}), 20.9 (C_5), 21.5 (C_8), 23.1 (C_6), 25.9 (C_9), 26.5 (C_{11}), 34.1 (C_7), 44.2 (q, C_3), 46.9 (C_4), 50.7 (C_1), 78.9 (q, C_2).

IR $\nu_{\max}$ (cm^{-1}): 3468, 2961, 2936, 2876, 1462, 1375, 1089, 941.

HRMS: (m/z - CI) Calculated for $\text{C}_{11}\text{H}_{21}\text{O}$ ($\text{M}+\text{H}$)⁺ 169.1592, found 169.1602.

6.3.14 2-Azido-3-*endo*-ethyl-2-*endo*-3-dimethylbicyclo[2.2.1]heptane (227)

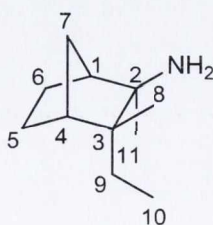
Prepared as per general procedure D using 2-*exo*-ethyl-3,3-dimethylbicyclo[2.2.1]heptan-2-ol **226** (9.80 g, 50.4 mmol), H₂SO₄ (55%, 20 mL), NaN₃ (10.00 g, 153.8 mmol) and CHCl₃ (150 mL) with reaction time of 6 hrs to yield 2-azido-3-*endo*-ethyl-2-*endo*-3-dimethylbicyclo[2.2.1]heptanes **227** as a clear oil after multiple column chromatography separations (100% hexane, *R_f* = 0.62) (0.18 g, 0.93 mmol, 2%).

¹H NMR (CDCl₃, 400 MHz): δ (ppm) 0.87 (3H, app t, *J* = 7.5 Hz, H₁₀), 1.04 (3H, s, H₈), 1.12-1.18 (1H, m, H_{7a}), 1.21-1.32 (2H, m, H_{9a}, H_{5a}), 1.35 (3H, s, H₁₁), 1.41-1.52 (4H, m, H₆, H_{5b}, H_{9b}), 1.86-1.91 (1H, m, H₄), 1.96-2.02 (1H, m, H_{7b}), 2.11 (1H, br s, H₁).

¹³C NMR (CDCl₃, 100 MHz): δ (ppm) 10.0 (C₁₀), 16.9 (C₁₁), 21.4 (C₈), 23.25 (C₆), 23.34 (C₅), 27.8 (C₉), 34.7 (C₇), 46.6 (C₄), 47.6 (q, C₃), 49.2 (C₁), 73.8 (q, C₂).

IR ν_{max} (cm⁻¹): 2958, 2875, 2096, 1458, 1373, 1189, 1028.

HRMS: (*m/z* - ES) Calculated for C₁₁H₂₀N (M+H-N₂)⁺ 166.1596, found 166.1590.

6.3.15 3-*endo*-Ethyl-2-*endo*-3-dimethylbicyclo[2.2.1]heptan-2-amine (228)

General Procedure H

To a suspension of lithium aluminium hydride powder (0.65 g, 1.72 mmol) in anhydrous THF (10 mL) was added a solution of 2-azido-3-*endo*-ethyl-2-*endo*-3-dimethylbicyclo[2.2.1]heptane **227** (0.17 g, 0.86 mmol) in anhydrous THF (10 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 hrs. The reaction was cooled to 0 °C before a solution of NaOH (2M, 10 mL) was added slowly. After stirring for 30 minutes at room temperature, the mixture was extracted using diethyl ether (2 x 20 mL), washed with brine (10 mL), dried over magnesium sulfate, filtered and concentrated to yield a clear viscous oil. The crude oil was filtered through a pad of silica to yield 2-*endo*-3,3-trimethylbicyclo[2.2.1]heptan-2-amine **228** as a clear colourless oil (107 mg, 0.64 mmol, 74%).

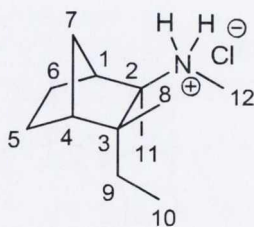
^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 0.84 (3H, t, $J = 7.3$ Hz, H_{10}), 0.97 (3H, s, H_8), 1.12 (3H, s, H_{11}), 1.08-1.14 (1H, m, H_{7a}), 1.16-1.57 (6H, m, H_5 , H_6 , H_9), 1.81-1.86 (2H, m, H_1 , H_4), 1.89-1.96 (1H, m, H_{7b}).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 10.1 (C_{10}), 20.7 (C_8), 22.2 (C_{11}), 23.1 (C_5), 24.1 (C_6), 27.6 (C_9), 34.3 (C_7), 45.9 (q, C_3), 47.0 (C_4), 52.3 (C_1), 60.9 (q, C_2).

IR ν_{max} (cm^{-1}): 3378, 2962, 2930, 2878, 1461, 1378, 1158.

HRMS: (m/z - ES) Calculated for $\text{C}_{11}\text{H}_{20}\text{N}$ ($\text{M}-\text{H}$) $^-$ 166.1596, found 166.1598.

6.3.16 3-*endo*-Ethyl-*N*-2-*endo*-3-trimethylbicyclo[2.2.1]heptan-2-amine (42)



Prepared as per general procedure G using 3-*endo*-ethyl-2-*endo*-3-dimethylbicyclo[2.2.1]heptan-2-amine **228** (70 mg, 0.4 mmol), paraformaldehyde (45 mg, 1.5 mmol), activated 4 Å molecular sieves (100 mg), anhydrous CH₂Cl₂ (10 mL), sodium borohydride (75 mg, 1.89 mmol) and anhydrous methanol (1.0 mL) to yield a clear colourless viscous oil. This oil was dissolved in anhydrous diethyl ether (1.0 mL) and hydrogen chloride solution (2M in diethyl ether, 500 µL, 1.0 mmol) was added. The desired HCl salt of 3-*endo*-ethyl-*N*-2-*endo*-3-trimethylbicyclo[2.2.1]heptan-2-amine **42** was obtained by filtration and dried under vacuum to yield a white solid (59 mg, 0.3 mmol, 65%). M.p. 160-165 °C (decomposes).

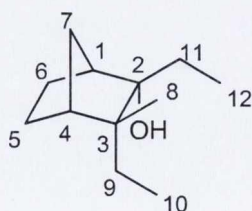
¹H NMR (CD₃OD, 400 MHz): δ (ppm) 0.93 (3H, app t, *J* = 7.5 Hz, H₁₀), 1.15 (3H, s, H₈), 1.31-1.46 (6H, m, H₁₁, H_{7a}, H_{5a}, H_{9a}), 1.54-1.75 (4H, m, H₆, H_{5b}, H_{9b}), 1.94-2.00 (1H, m, H_{7b}), 2.00-2.05 (1H, m, H₄), 2.45 (1H, br s, H₁), 2.66 (3H, s, H₁₂).

¹³C NMR (CD₃OD, 100 MHz): δ (ppm) 8.2 (C₁₀), 14.0 (C₁₁), 18.0 (C₈), 21.5 (C₆), 22.7 (C₅), 26.5 (C₉), 27.3 (C₁₂), 32.8 (C₇), 43.7 (C₁), 46.88 (C₄), 46.92 (q, C₃), 70.0 (q, C₂).

IR ν_{max} (cm⁻¹): 3360, 2953, 2884, 1458, 1381, 1342, 1112, 915.

HRMS: (*m/z* - ES) Calculated for C₁₂H₂₄N (M+H)⁺ 182.1909, found 182.1916.

6.3.17 3-*endo*-Ethyl-2-*exo*-3-methylbicyclo[2.2.1]heptan-2-ol (**229**)



Prepared as per general procedure F using 3-*endo*-ethyl-3-methylbicyclo[2.2.1]heptan-2-one **225** (5.00 g, 32.9 mmol), bromoethane (4.40 mL, 59.2 mmol), a solution of *tert*-butyllithium (1.7M in pentane, 69.60 mL, 118.4 mmol) and anhydrous THF (100 mL) with a reaction time

of 3 hrs. Purification by column chromatography (9:1 hexane:ethyl acetate, R_f = 0.54) gave 3-*endo*-ethyl-2-*exo*-3-methylbicyclo[2.2.1]heptan-2-ol **229** as a clear colourless oil (3.67 g, 20.1 mmol, 61%).

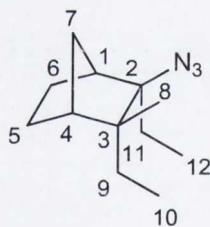
^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 0.87 (3H, app t, J = 7.4 Hz, H_{10}), 0.95 (3H, s, H_8), 0.95 (3H, app t, J = 7.4 Hz, H_{12}), 1.14 (1H, app d, J = 10.5 Hz, H_{7a}), 1.23-1.35 (3H, m, H_{5a} , H_{6a} , H_{9a}), 1.55-1.62 (3H, m, H_{9b} , H_{11a} , H_{11b}), 1.63-1.69 (2H, m, H_{5b} , H_{7b}), 1.80-1.85 (2H, m, H_4 , H_{6b}), 2.20-2.23 (1H, m, H_1).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 8.9 (C_8), 9.8 (C_{10}), 21.3 (C_{12}), 21.5 (C_6), 23.3 (C_5), 26.5 (C_9), 30.1 (C_{11}), 34.4 (C_7), 45.6 (q, C_3), 46.0 (C_1), 47.7 (C_4), 81.0 (q, C_2).

IR ν_{max} (cm^{-1}): 3494, 2962, 2937, 1463, 1380, 1093, 985.

HRMS: (m/z - EI) Calculated for $\text{C}_{12}\text{H}_{22}\text{O}$ (M) $^+$ 182.1671, found 182.1673.

6.3.18 2-Azido-2-*endo*-3-*endo*-diethyl-3-methylbicyclo[2.2.1]heptane (**230**)



Prepared as per general procedure D using 3-*endo*-ethyl-2-*exo*-3-methylbicyclo[2.2.1]heptan-2-ol **229** (3.50 g, 19.2 mmol), NaN_3 (4.99 g, 76.8 mmol), CHCl_3 (100 mL), H_2SO_4 (60%, 10 mL) with a reaction time of 4 hrs to yield a pale yellow oil which was purified by column chromatography (100% hexane, R_f = 0.65) to yield 2-azido-2-*endo*-3-*endo*-diethyl-3-methylbicyclo[2.2.1]heptane **230** as a clear oil (1.22 g, 5.88 mmol, 31%).

^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 0.98 (3H, app t, J = 7.7 Hz, H_{12}), 0.87 (3H, t, J = 7.5 Hz, H_{10}), 1.06 (3H, s, H_8), 1.14-1.19 (1H, m,

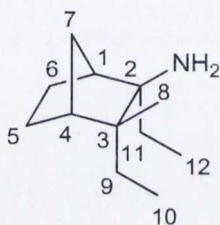
H_{7a}), 1.20-1.59 (6H, m, H_6 , H_5 , H_9), 1.61-1.72 (1H, m, H_{11a}), 1.78-1.88 (1H, m, H_{11b}), 1.88-1.95 (2H, m, H_{7b} , H_4), 2.19-2.24 (1H, m, H_1).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 9.5 (C_{12}), 9.9 (C_{10}), 21.5 (C_8), 22.7 (C_6), 23.0 (C_{11}), 23.3 (C_5), 27.3 (C_9), 34.4 (C_7), 45.2 (C_1), 46.5 (C_4), 49.7 (q, C_3), 77.2 (q, C_2).

IR ν_{max} (cm^{-1}): 2965, 2880, 2091, 1465, 1379, 1269, 1076, 901.

HRMS: (m/z - ES) Calculated for $\text{C}_{12}\text{H}_{22}\text{N}$ ($\text{M}+\text{H}-\text{N}_2$) $^+$ 180.1752, found 180.1759.

6.3.19 2-endo-3-endo-Diethyl-3-methylbicyclo[2.2.1]heptan-2-amine (231)



Prepared as per general procedure H using 2-azido-2-endo-3-endo-diethyl-3-methylbicyclo[2.2.1]heptane **230** (0.38 g, 1.84 mmol), lithium aluminium hydride powder (0.14 g, 3.68 mmol) and anhydrous THF (20 mL) to yield a clear oil which was purified by precipitation of the hydrochloride salt in anhydrous diethyl ether and subsequent filtration to yield the hydrochloride salt of 2-endo-3-endo-diethyl-3-methylbicyclo[2.2.1]heptan-2-amine **231** as white solid (0.29 g, 1.60 mmol, 87%). M.p. 140-145 °C (decomposes).

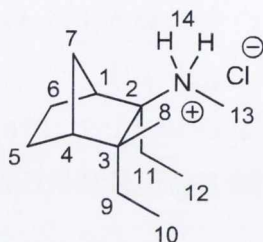
^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 0.84 (3H, t, J = 6.2 Hz, H_{10}), 1.14, (3H, t, J = 6.3 Hz, H_{12}), 1.19-1.26 (1H, m, H_{7a}), 1.27, (3H, s, H_8), 1.28-1.64 (6H, m, H_5 , H_6 , H_9), 1.66-1.98 (3H, m, H_4 , H_{11}), 2.32-2.42 (2H, m, H_1 , H_{7b}).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 9.5 (C_{12}), 9.8 (C_{10}), 20.8 (C_8), 22.6 (C_6), 23.0 (C_5), 24.0 (C_{11}), 26.8 (C_9), 34.0 (C_7), 46.0 (C_1), 46.8 (C_4), 46.9 (q, C_3), 69.8 (q, C_2).

IR $\nu_{\max}$ (cm^{-1}): 3361, 2960, 2844, 1457, 1379, 1150, 882.

HRMS: (m/z - ES) Calculated for $\text{C}_{12}\text{H}_{24}\text{N}$ ($\text{M}+\text{H}$) $^{+}$ 182.1909, found 182.1909.

6.3.20 2-endo-3-endo-Diethyl-N-3-dimethylbicyclo[2.2.1]heptan-2-amine. (44)



Prepared as per general procedure G using 2-endo-3-endo-diethyl-3-methylbicyclo[2.2.1]heptan-2-amine **231** (290 mg, 1.60 mmol), paraformaldehyde (170 mg, 5.61 mmol), activated 4 Å molecular sieves (20 mg), anhydrous CH_2Cl_2 (15 mL), sodium borohydride (281 mg, 7.20 mmol) and methanol (2 mL) to yield a clear colourless viscous oil. The HCl salt was formed on addition of a solution of hydrogen chloride (2M in diethyl ether, 1.0 mL, 2.0 mmol). The diethyl ether was removed at reduced pressure to yield the desired HCl salt of 2-endo-3-endo-diethyl-N-3-dimethylbicyclo[2.2.1]heptan-2-amine **44** as a white solid (269 mg, 1.16 mmol, 73%). M.p. 150-160 °C (decomposes).

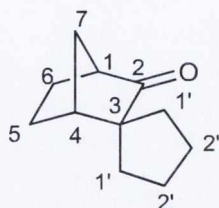
^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 0.93 (3H, app t, $J = 7.5$ Hz, H_{10}), 1.01 (3H, s, H_8), 1.14 (3H, t, $J = 7.4$ Hz, H_{12}), 1.20-1.25 (1H, m, H_{7a}), 1.31-1.53 (4H, m, H_5 , H_6), 1.54-1.65 (1H, m, H_{9a}), 1.65-1.89 (2H, m, H_{11}), 2.17-2.21 (1H, m, H_4), 2.21-2.32 (1H, m, H_{9b}), 2.52-2.60 (2H, m, H_1 , H_{7b}), 2.67 (3H, t, $J = 5.3$ Hz, H_{13}), 8.51-8.97 (2H, m, H_{14}).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 9.4 (C_{12}), 10.1 (C_{10}), 19.2 (C_8), 22.3 (C_{11}), 22.7 (C_5), 23.6 (C_6), 28.7 (C_9), 29.6 (C_{13}), 34.5 (C_7), 44.7 (C_4), 45.5 (C_1), 48.1 (q, C_3), 74.5 (q, C_2).

IR $\nu_{\max}$ (cm^{-1}): 3361, 2953, 2885, 2744, 1459, 1381, 1151, 1113, 916.

HRMS: (m/z - ES) Calculated for $\text{C}_{13}\text{H}_{26}\text{N}$ ($\text{M}+\text{H}$)⁺ 196.2065, found 196.2065.

6.3.21 Spiro[bicyclo[2.2.1]heptane-3,1'-cyclopentan]-2-one.²⁸⁵ (56)



General Procedure I

To a solution of norcamphor (2.00 g, 18.2 mmol), and 1,4-dibromobutane (6.50 mL, 54.5 mmol), in anhydrous diethyl ether (40 mL) was added sodium amide (1.77 g, 45.4 mmol). The reaction mixture was heated at reflux temperature and stirred for 24 hrs. The mixture was allowed to cool to room temperature and was diluted with cold H_2O (100 mL). The mixture was extracted with diethyl ether (2 x 50 mL), the combined organic layers were washed with brine (50 mL) and dried over magnesium sulfate before being filtered. The volatiles were removed at reduced pressure to give a pale yellow oil which was purified by column chromatography (9:1 hexane:diethyl ether, R_f = 53.3%) to yield spiro[bicyclo[2.2.1]heptane-3,1'-cyclopentan]-2-one **56** as a clear colourless oil (2.84 g, 17.3 mmol, 95%).

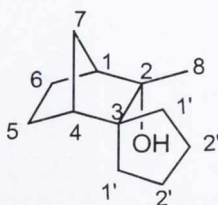
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.44-1.67 (8H, m, H_{7a} , H_{6a} , H_{6b} , H_{5a} , $\text{H}_{1'a}$, $\text{H}_{1'b}$, $\text{H}_{2'a}$, $\text{H}_{2'b}$), 1.67-1.80 (4H, m, $\text{H}_{1'c}$, $\text{H}_{1'd}$, $\text{H}_{2'c}$, $\text{H}_{2'd}$), 1.80-1.92 (2H, m, H_{7b} , H_{5b}), 2.25-2.27 (1H, m, H_4), 2.56-2.59 (1H, m, H_1).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 23.8 (C_5), 25.5 (C_6), 26.4 ($\text{C}_{2'}$), 26.8 ($\text{C}_{2'}$), 32.8 ($\text{C}_{1'}$), 36.0 (C_7), 36.5 ($\text{C}_{1'}$), 46.5 (C_4), 49.9 (C_1), 59.0 (q, C_3), 224.5 (q, C_2).

IR $\nu_{\max}$ (cm^{-1}): 2951, 2873, 1736, 1449, 911.

HRMS: (m/z - ESI) Calculated for $\text{C}_{11}\text{H}_{17}\text{O}$ ($\text{M}+\text{H}$)⁺ 165.1279, found 165.1279.

6.3.22 2-Methylspiro[bicyclo[2.2.1]heptane-3,1'-cyclopentan]-2-ol. (58)



Prepared as per general procedure C using spiro[bicyclo[2.2.1]heptane-3,1'-cyclopentan]-2-one **56** (2.30 g, 14.0 mmol), a solution of methylmagnesium bromide (3M in diethyl ether, 28.0 mL, 84.1 mmol) and anhydrous THF (40 mL) at room temperature with a reaction time of 19 hrs to yield a yellow oil which was purified by column chromatography (3:7 diethyl ether: hexane, $R_f = 0.35$) to yield 2-methylspiro[bicyclo[2.2.1]heptane-3,1'-cyclopentan]-2-ol **58** as a clear colourless oil, (2.27 g, 12.6 mmol, 90%).

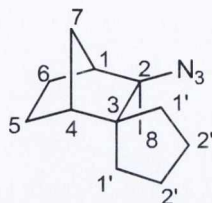
^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.21-1.26 (4H, m, H_{7a} , H_8), 1.26-1.42 (3H, m, H_{6a} , H_{5a} , $\text{H}_{1'a}$), 1.42-1.54 (3H, m, $\text{H}_{1'b}$, $\text{H}_{1'c}$, $\text{H}_{2'a}$), 1.55-1.72 (6H, m, H_{5b} , H_{7b} , $\text{H}_{1'd}$, $\text{H}_{2'b}$, $\text{H}_{2'c}$, $\text{H}_{2'd}$), 1.82-1.90 (2H, m, H_4 , H_{6b}), 1.99-2.03 (1H, m, H_1).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 21.6 (C_6), 23.4 ($\text{C}_{2'}$), 23.5 ($\text{C}_{2'}$), 23.8 (C_5), 26.9 (C_8), 30.4 ($\text{C}_{1'}$), 35.36 ($\text{C}_{1'}$), 35.37 (C_7), 46.0 (C_4), 50.7 (C_1), 55.8 (q, C_3), 78.8 (q, C_2).

IR ν_{max} (cm^{-1}): 3451, 2951, 2872, 1464, 1372, 1097, 940.

HRMS: (m/z - EI) Calculated for $\text{C}_{12}\text{H}_{20}\text{O}$ (M) $^+$ 180.1514, found 180.1523.

6.3.23 2-Azido-2-methylspiro[bicyclo[2.2.1]heptane-3,1'-cyclopentane]. (62)



Prepared as per general procedure D using 2-methylspiro[bicyclo[2.2.1]heptane-3,1'-cyclopentane]-2-ol **58** (0.50 g, 2.78 mmol), NaN_3 (1.26 g, 19.4 mmol), 50% H_2SO_4 (10 mL) and chloroform (60 mL) with a reaction time of 2 hrs to yield a yellow oil which was purified by column chromatography (100% hexane, $R_f = 65.7\%$) to yield 2-azido-2-methylspiro[bicyclo[2.2.1]heptane-3,1'-cyclopentane] **62** as a clear colourless liquid (0.21 g, 1.02 mmol, 36%).

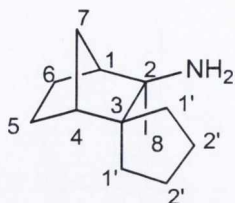
^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.19 (1H, app dt, $J = 9.9, 1.4$ Hz, H_{7a}), 1.30-1.55 (11H, m, $\text{H}_8, \text{H}_{1'a}, \text{H}_{1'b}, \text{H}_{5a}, \text{H}_{5b}, \text{H}_{1'c}, \text{H}_{2'a}, \text{H}_{2'b}, \text{H}_{2'c}$), 1.55-1.68 (3H, m, $\text{H}_{6a}, \text{H}_{6b}, \text{H}_{2'd}$) 1.74-1.84 (1H, m, $\text{H}_{1'd}$), 1.87-19.1 (1H, m, H_4), 1.94 (1H, app dt, $J = 9.9, 1.4$ Hz, H_{7b}), 2.18-2.22 (1H, m, H_1).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 18.7 (C_8), 22.6 (C_6), 23.4 ($\text{C}_{2'}$), 23.5 ($\text{C}_{2'}$), 23.6 (C_5), 31.8 ($\text{C}_{1'}$), 35.3 (C_7), 35.5 ($\text{C}_{1'}$), 45.8 (C_4), 48.4 (C_1), 57.1 (q, C_3), 72.1 (q, C_2).

IR ν_{max} cm^{-1} : 2957, 2875, 2080, 1456, 1254, 1071.

HRMS: (m/z - EI) Calculated for $\text{C}_{12}\text{H}_{19}\text{N}_3$ (M^+) 205.1579, found 205.1584.

6.3.24 2-Methylspiro[bicyclo[2.2.1]heptane-3,1'-cyclopentan]-2-amine. (67)



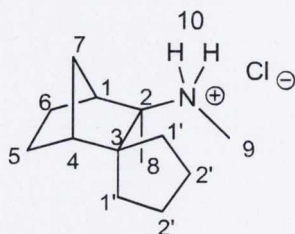
Prepared as per general procedure E using 2-azido-2-methylspiro[bicyclo[2.2.1]heptane-3,1'-cyclopentane] **62** (0.13 g, 0.63 mmol), palladium on charcoal (0.013 g, 10% w/w) and methanol (20 mL) with a reaction time of 16 hrs under a hydrogen atmosphere at atmospheric pressure to yield 2-methylspiro[bicyclo[2.2.1]heptane-3,1'-cyclopentan]-2-amine **67** as a clear colourless oil (0.11 g, 0.62 mmol, 98%).

^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.09 (3H, s, H_8), 1.17 (1H, app d, $J = 10.1$ Hz, H_{7a}), 1.28-1.68 (11H, m, H_{6a} , H_{6b} , H_{5a} , H_{5b} , $\text{H}_{1'a}$, $\text{H}_{1'b}$, $\text{H}_{1'c}$, $\text{H}_{2'a}$, $\text{H}_{2'b}$, $\text{H}_{2'c}$, $\text{H}_{2'd}$), 1.71-1.78 (1H, m, $\text{H}_{1'd}$), 1.82-1.88 (3H, m, H_1 , H_4 , H_{7b}).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 22.6 (C_5), 23.1 ($\text{C}_{2'}$), 23.4 ($\text{C}_{2'}$), 24.0 (C_6), 24.2 (C_8), 31.4 ($\text{C}_{1'}$), 33.9 ($\text{C}_{1'}$), 34.8 (C_7), 45.5 (C_4), 52.3 (C_1), 56.7 (q, C_3), 58.9 (q, C_2).

IR ν_{max} cm^{-1} : 3351, 2949, 2872, 1456, 1372, 804.

HRMS: (m/z - ESI) Calculated for $\text{C}_{12}\text{H}_{22}\text{N}$ ($\text{M}+\text{H}$) $^+$ 180.1752, found 180.1753.

6.3.25 *N*-3-dimethylspiro[bicyclo[2.2.1]heptane-3,1'-cyclopentan]-2-amine.³¹⁶ (52)

Prepared as per general procedure G using 2-methylspiro[bicyclo[2.2.1]heptane-3,1'-cyclopentan]-2-amine **67** (0.32 g 1.79 mmol), paraformaldehyde (0.29 g, 9.66 mmol), activated 4 Å molecular sieves (0.40 g), anhydrous CH₂Cl₂ (30 mL), sodium borohydride (0.30 g, 8.10 mmol) and anhydrous methanol (2 mL) to yield a pale yellow tacky solid. This product was re-dissolved in anhydrous diethyl ether (5 mL) and a solution of hydrogen chloride (2M in diethyl ether, 1.5 mL, 3.0 mmol) was added. Filtration afforded the HCl salt of *N*-3-dimethylspiro[bicyclo[2.2.1]heptane-3,1'-cyclopentan]-2-amine **52** as a white solid (0.25 g, 1.09 mmol, 61%). M.p. 170-175 °C (decomposes).

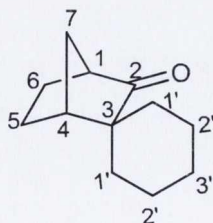
¹H NMR (CDCl₃, 600 MHz): δ (ppm) 1.27-1.43 (5H, m, H₈, H_{7a}, H_{5a}), 1.44-1.57 (5H, m, H_{6a}, H_{6b}, H_{2'a}, H_{2'b}, H_{1'a}), 1.62-1.86 (4H, m, H_{5b}, H_{2'c}, H_{2'd}, H_{1'b}), 1.94-2.17 (3H, m, H₄, H_{1'c}, H_{1'd}), 2.29-2.37 (1H, m, H_{7b}), 2.39-2.46 (1H, m, H₁), 2.61-2.71 (3H, br s, H₉), 8.24 (1H, br s, H_{10a}), 9.15 (1H, br s, H_{10b}).

¹³C NMR (CDCl₃, 150 MHz): δ (ppm) 17.4 (C₈), 22.0 (C_{2'}), 22.1 (C₅), 22.5 (C₆), 23.4 (C_{2'}), 28.6 (C₉), 31.6 (C_{1'}), 33.4 (C_{1'}), 34.8 (C₇), 43.8 (C₁), 44.5 (C₄), 57.3 (q, C₃), 69.2 (q, C₂).

IR ν_{max} cm⁻¹: 2955, 2733, 1462, 1431, 1398, 1108, 1036.

HRMS: (*m/z* - ESI) Calculated for C₁₃H₂₄N (M+H)⁺ 194.1909, found 194.1915.

6.3.26 Spiro[bicyclo[2.2.1]heptane-3,1'-cyclohexan]-2-one.²⁸⁵ (**57**)



Prepared as per general procedure I using norcamphor (2.00 g, 18.2 mmol), 1,5-dibromopentane (7.40 mL, 54.5 mmol), sodium amide (1.77 g, 45.4 mmol) and anhydrous diethyl ether (50 mL) with a reaction time of 24 hrs to yield a pale yellow oil which was purified by column

chromatography (9:1 hexane: diethyl ether, R_f = 0.47) to yield spiro[bicyclo[2.2.1]heptane-3,1'-cyclohexan]-2-one **57** as a clear colourless oil (2.76 g, 15.5 mmol, 86%).

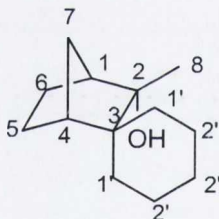
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.22-1.40 (2H, m, $\text{H}_{2'\text{a}}$, $\text{H}_{3'\text{a}}$), 1.40-1.56 (7H, m, $\text{H}_{7\text{a}}$, $\text{H}_{6\text{a}}$, $\text{H}_{1'\text{a}}$, $\text{H}_{1'\text{b}}$, $\text{H}_{1'\text{c}}$, $\text{H}_{1'\text{d}}$, $\text{H}_{2'\text{b}}$), 1.59-1.71 (4H, m, $\text{H}_{5\text{a}}$, $\text{H}_{3'\text{b}}$, $\text{H}_{2'\text{a}}$, $\text{H}_{2'\text{b}}$), 1.72-1.79 (1H, m, $\text{H}_{5\text{b}}$), 1.82-1.90 (1H, m, $\text{H}_{6\text{b}}$), 1.90-1.95 (1H, m, $\text{H}_{7\text{b}}$), 2.55-2.58 (1H, m, H_1), 2.59-2.62 (1H, m, H_4).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 22.3 ($\text{C}_{2'}$), 22.4 ($\text{C}_{2'}$), 22.7 (C_5), 24.7 (C_6), 25.8 ($\text{C}_{3'}$), 30.3 ($\text{C}_{1'}$), 30.4 ($\text{C}_{1'}$), 34.9 (C_7), 40.9 (C_4), 50.3 (C_1), 51.6 (q, C_3), 222.1 (q, C_2).

IR ν_{max} cm^{-1} : 2928, 2856, 1736, 1448, 1091, 768.

HRMS: (m/z - EI) Calculated for $\text{C}_{12}\text{H}_{18}\text{O}$ (M^+) 178.1358, found 178.1355.

6.3.27 2-Methylspiro[bicyclo[2.2.1]heptane-3,1'-cyclohexan]-2-ol (**59**)



Prepared as per general procedure C using spiro[bicyclo[2.2.1]heptane-3,1'-cyclohexan]-2-one **57** (3.30 g, 16.8 mmol), a solution of methylmagnesium bromide (3M in diethyl ether, 33.70 mL, 100.9 mmol) and anhydrous THF (50 mL) with a reaction time of 16 hrs at room temperature to yield a yellow oil which was purified by column chromatography (9:1 hexane: diethyl ether, R_f = 0.2) to yield 2-methylspiro[bicyclo[2.2.1]heptane-3,1'-cyclohexan]-2-ol **59** as a clear colourless oil (3.12 g, 16.1 mmol, 96%).

^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.08 (1H, dt, J = 12.9, 2.9 Hz, $\text{H}_{1'\text{a}}$), 1.12-1.26 (6H, m, $\text{H}_{2'\text{a}}$, $\text{H}_{2'\text{b}}$, H_8 , $\text{H}_{7\text{a}}$), 1.30-1.39 (3H, m,

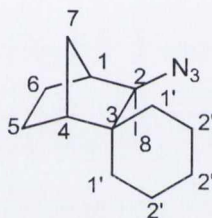
H_{6a} , H_{5a} , $H_{1'b}$), 1.40-1.53 (2H, m, $H_{1'c}$, $H_{2'c}$), 1.56-1.65 (5H, m, H_{5b} , H_{7b} , $H_{2'd}$, $H_{2'e}$, $H_{2'f}$) 1.69-1.74 (1H, m, $H_{1'd}$), 1.79-1.84 (1H, m, H_{6b}), 1.95-1.98 (1H, m, H_1), 2.30-2.33 (1H, m, H_4).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 21.1 (C_6), 23.3 (C_5), 23.7 ($\text{C}_{2'}$), 24.1 ($\text{C}_{2'}$), 25.3 (C_8), 26.2 ($\text{C}_{2'}$), 30.2 ($\text{C}_{1'}$), 33.2 ($\text{C}_{1'}$), 34.4 (C_7), 41.2 (C_4), 44.8 (q, C_3), 50.8 (C_1), 79.8 (q, C_2).

IR ν_{max} cm^{-1} : 3451, 2925, 2854, 1447, 1124, 923.

HRMS: (m/z - EI) Calculated for $\text{C}_{13}\text{H}_{22}\text{O}$ (M) $^+$ 194.1671, found 194.1662.

6.3.28 2-Azido-2-methylspiro[bicyclo[2.2.1]heptane-3,1'-cyclohexane]. (63)



Prepared as per general procedure D using 2-methylspiro[bicyclo[2.2.1]heptane-3,1'-cyclohexan]-2-ol **59** (2.97 g, 15.3 mmol), NaN_3 (6.96 g, 107.1 mmol), 50% H_2SO_4 (15 mL) and chloroform (100 mL) with a reaction time of 6 hrs to yield a yellow oil was purified by column chromatography (100% hexane, R_f = 0.5) to yield 2-azido-2-methylspiro[bicyclo[2.2.1]heptane-3,1'-cyclohexane] **63** as a clear colourless liquid (0.95 g, 4.33 mmol, 28%).

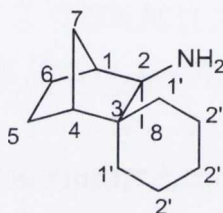
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.11-1.21 (4H, m, H_{7a} , $H_{1'a}$, $H_{2'a}$, $H_{2'b}$), 1.22-1.43 (6H, m, $H_{1'b}$, H_{5a} , H_{6a} , H_8), 1.44-1.53 (2H, m, H_{5b} , H_{6b}), 1.54-1.70 (6H, m, $H_{1'c}$, $H_{1'd}$, $H_{2'c}$, $H_{2'd}$, $H_{2'e}$, $H_{2'f}$), 1.90-1.96 (1H, m, H_{7b}), 2.09-2.13 (1H, m, H_1), 2.32-2.36 (1H, m, H_4).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 16.6 (C_8), 23.1 (C_6), 23.2 (C_5), 23.7 ($\text{C}_{2'}$), 24.1 ($\text{C}_{2'}$), 25.9 ($\text{C}_{2'}$), 32.1 ($\text{C}_{1'}$), 32.8 ($\text{C}_{1'}$), 34.6 (C_7), 41.9 (C_4), 47.1 (q, C_3), 48.6 (C_1), 74.2 (q, C_2).

IR ν_{max} cm^{-1} : 2926, 2857, 2082, 1448, 1260, 1102.

HRMS: (m/z - ESI) Calculated for $\text{C}_{13}\text{H}_{22}\text{N}$ ($\text{M}+\text{H} - \text{N}_2$) $^+$ 192.1752, found 192.1754.

6.3.29 2-Methylspiro[bicyclo[2.2.1]heptane-3,1'-cyclohexan]-2-amine. (68)



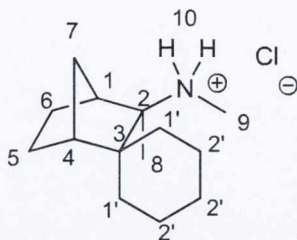
Prepared as per general procedure E using 2-azido-2-methylspiro[bicyclo[2.2.1]heptane-3,1'-cyclohexane] **63** (0.80 g, 3.65 mmol), palladium on charcoal (0.08 g, 10% w/w) and a 1:6 solution of methanol:THF (30 mL) with a reaction time of 14 hrs under a hydrogen atmosphere at atmospheric pressure to yield 2-methylspiro[bicyclo[2.2.1]heptane-3,1'-cyclohexan]-2-amine **68** as a clear colourless oil (0.69 g, 3.57 mmol, 98%).

^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.08-1.42 (7H, m, H_{5a} , H_{6a} , H_{7a} , $\text{H}_{1'a}$, $\text{H}_{1'b}$, $\text{H}_{2'a}$, $\text{H}_{2'b}$), 1.46-1.59 (5H, m, H_{5b} , H_{6b} , $\text{H}_{1'c}$, $\text{H}_{2'c}$, $\text{H}_{2'd}$), 1.59 (3H, s, H_8), 1.60-1.68 (3H, m, $\text{H}_{1'd}$, $\text{H}_{2'c}$, $\text{H}_{2'd}$), 1.77-1.80 (1H, m, H_1), 1.81-1.85 (1H, m, H_{7b}), 2.30-2.33 (1H, m, H_4).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 22.5 (C_8), 22.9 (C_6), 23.7 (C_5), 23.9 ($\text{C}_{2'}$), 25.4 ($\text{C}_{2'}$), 26.1 ($\text{C}_{2'}$), 32.0 ($\text{C}_{1'}$), 32.1 ($\text{C}_{1'}$), 34.2 (C_7), 41.9 (C_4), 45.6 (q, C_3), 52.3 (C_1), 64.4 (q, C_2).

IR ν_{max} cm^{-1} : 3300, 2921, 2856, 1447, 1374, 829.

HRMS: (m/z - ESI) Calculated for $\text{C}_{13}\text{H}_{24}\text{N}$ ($\text{M}+\text{H}$) $^+$ 194.1909, found 194.1919.

6.3.30 *N*-2-dimethylspiro[bicyclo[2.2.1]heptane-3,1'-cyclohexan]-2-amine. (53)

Prepared as per general procedure G using 2-methylspiro[bicyclo[2.2.1]heptane-3,1'-cyclohexan]-2-amine **68** (0.50 g 2.59 mmol), paraformaldehyde (0.50 g, 16.7 mmol), activated 4 Å molecular sieves (0.96 g) anhydrous CH_2Cl_2 (40 mL), sodium borohydride (0.34 g, 9.07 mmol) and anhydrous methanol (2 mL) to yield a colourless oil. This product was re-dissolved in anhydrous diethyl ether (5 mL) and a solution of hydrogen chloride (2M in diethyl ether, 1.5 mL, 3.0 mmol) was added. Filtration afforded the HCl salt of *N*-2-dimethylspiro[bicyclo[2.2.1]heptane-3,1'-cyclohexan]-2-amine **53** as a white solid (0.43 g, 1.76 mmol, 68%). M.p. 175-180 °C (decomposes).

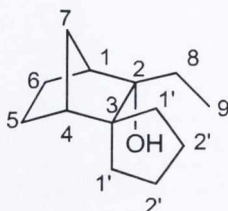
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.14-1.39 (7H, m, H_8 , H_{7a} , $\text{H}_{1'a}$, $\text{H}_{2'a}$, $\text{H}_{2'b}$), 1.36-1.72 (9H, m, H_{5a} , H_{5b} , H_{6a} , H_{6b} , $\text{H}_{1'b}$, $\text{H}_{2'c}$, $\text{H}_{2'd}$, $\text{H}_{2'e}$, $\text{H}_{2'f}$), 1.77-1.85 (1H, m, $\text{H}_{1'c}$), 2.14-2.21 (1H, m, $\text{H}_{1'd}$), 2.29-2.36 (1H, m, H_{7b}), 2.38-2.42 (1H, m, H_1), 2.52-2.55 (1H, m, H_4), 2.64-2.72 (3H, m, H_9), 8.24 (1H, br s, H_{10a}), 9.00 (1H, br s, H_{10b}).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 15.5 (C_8), 22.5 (C_5), 23.3 (C_6), 23.5 ($\text{C}_{2'}$), 23.9 ($\text{C}_{2'}$), 25.5 ($\text{C}_{2'}$), 29.0 (C_9), 31.2 ($\text{C}_{1'}$), 31.8 ($\text{C}_{1'}$), 34.5 (C_7), 41.7 (C_4), 44.5 (C_1), 47.8 (q, C_3), 71.8 (q, C_2).

IR ν_{max} cm^{-1} : 2926, 2748, 1593, 1465, 1386, 1117, 996.

HRMS: (m/z - ESI) Calculated for $\text{C}_{14}\text{H}_{26}\text{N}$ ($\text{M}+\text{H}$) $^+$ 208.2065, found 208.2069.

6.3.31 2-Ethylspiro[bicyclo[2.2.1]heptane-3,1'-cyclopentan]-2-ol. (60)



Prepared as per general procedure F using spiro[bicyclo[2.2.1]heptane-3,1'-cyclopentan]-2-one **56** (1.30 g, 7.93 mmol), bromoethane (1.20 mL, 16.2 mmol), *tert*-butyllithium (1.7M in pentane, 18.70 mL, 31.72 mmol) and anhydrous THF (25 mL) with a reaction time of 3 hrs to yield a pale yellow oil which was purified by column chromatography (1:9 diethyl ether:hexane, R_f = 0.25) to give 2-ethylspiro[bicyclo[2.2.1]heptane-3,1'-cyclopentan]-2-ol **60** as a clear colourless oil (1.17g, 6.02 mmol, 76%).

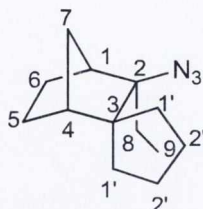
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 0.94 (3H, t, J = 7.5 Hz, H_9), 1.16-1.21 (1H, m, H_{7a}), 1.24-1.29 (1H, m, $\text{H}_{1'a}$), 1.30-1.39 (2H, m, H_{5a} , H_{6a}), 1.40-1.38 (2H, m, $\text{H}_{2'a}$, $\text{H}_{1'b}$), 1.49-1.67 (8H, m, H_{8a} , H_{8b} , $\text{H}_{1'c}$, $\text{H}_{2'b}$, $\text{H}_{2'c}$, $\text{H}_{2'd}$, H_{7b} , H_{5b}), 1.68-1.75 (1H, m, $\text{H}_{1'd}$), 1.78-1.86 (2H, m, H_4 , H_{6b}), 2.23-2.26 (1H, m, H_1).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 8.7 (C_9), 21.9 (C_6), 23.3 ($\text{C}_{2'}$), 23.4 ($\text{C}_{2'}$), 23.7 (C_5), 30.2 (C_8), 30.6 ($\text{C}_{1'}$), 34.2 ($\text{C}_{1'}$), 35.1 (C_7), 45.1 (C_1), 46.0 (C_4), 56.8 (q, C_3), 80.5 (q, C_2).

IR ν_{max} cm^{-1} : 3485, 2954, 2873, 1462, 1291, 982.

HRMS: (m/z - EI) Calculated for $\text{C}_{13}\text{H}_{22}\text{O}$ (M) $^+$ 194.1671, found 194.1674.

6.3.32 2-Azido-2-ethylspiro[bicyclo[2.2.1]heptane-3,1'-cyclopentane]. (64)



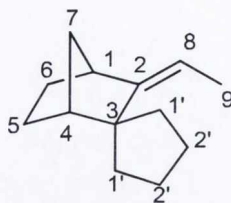
Prepared as per general procedure D using 2-ethylspiro[bicyclo[2.2.1]heptane-3,1'-cyclopentane]-2-ol **60** (0.33 g, 1.72 mmol), NaN₃ (0.56 g, 8.62 mmol), 50% H₂SO₄ (5 mL) and chloroform (30 mL) with a reaction time of 2 hrs to yield a yellow oil which was purified by column chromatography (100% hexane, R_f = 0.56) to yield 2-azido-2-ethylspiro[bicyclo[2.2.1]heptane-3,1'-cyclopentane] **64** as a clear colourless liquid (0.16 g 0.74 mmol, 43%) and an elimination side-product 2-ethylidenespiro[bicyclo[2.2.1]heptane-3,1'-cyclopentane] **65** (0.06 g, 0.34 mmol, 20%).

¹H NMR (CDCl₃, 600 MHz): δ (ppm) 0.98 (3H, t, J = 7.5 Hz, H₉), 1.23 (1H, app d, J = 10.1 Hz, H_{7a}), 1.27-1.69 (13H, m, H_{1'a}, H_{1'b}, H_{1'c}, H_{5a}, H_{5b}, H_{6a}, H_{6b}, H_{2'a}, H_{2'b}, H_{2'c}, H_{2'd}, H_{8a}, H_{8b}), 1.73-1.80 (1H, m, H_{1'd}), 1.86 (1H, app d, J = 10.1 Hz, H_{7b}), 1.89-1.92 (1H, m, H₄), 2.29-2.31 (1H, m, H₁).

¹³C NMR (CDCl₃, 150 MHz): δ (ppm) 9.3 (C₉), 22.1 (C_{2'}), 23.0 (C₆), 23.1 (C_{2'}), 23.3 (C₅), 25.4 (C₈), 31.0 (C_{1'}), 35.0 (C₇), 35.2 (C_{1'}), 44.4 (C₁), 44.9 (C₄), 58.8 (q, C₃), 75.3 (q, C₂).

IR $\nu_{\max}$ cm⁻¹: 2963, 2876, 2091, 1454, 1258, 881.

HRMS: (m/z - ESI) Calculated for C₁₃H₂₂N (M+H-N₂)⁺ 192.1752, found 192.1759.

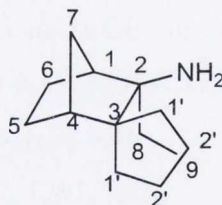
6.3.33 2-Ethylidenespiro[bicyclo[2.2.1]heptane-3,1'-cyclopentane]. (65)

^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.17-1.33 (2H, m, H_{6a} , H_{7a}), 1.38-1.48 (2H, m, H_{5a} , $\text{H}_{1'a}$), 1.49-1.74 (13H, m, H_{5b} , H_{6b} , H_{7b} , H_9 , $\text{H}_{1'b}$, $\text{H}_{1'c}$, $\text{H}_{1'd}$, $\text{H}_{2'a}$, $\text{H}_{2'b}$, $\text{H}_{2'c}$, $\text{H}_{2'd}$), 1.91-1.95 (1H, m, H_4), 2.93-2.97 (1H, m, H_1), 5.02 (1H quartet, $J = 6.6$ Hz, H_8).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 14.4 (C_9), 24.1 (C_5), 25.6 ($\text{C}_{2'}$), 26.2 ($\text{C}_{2'}$), 28.9 (C_6), 36.5 ($\text{C}_{1'}$), 38.1 (C_7), 40.7 (C_1), 42.1 ($\text{C}_{1'}$), 47.3 (C_4), 54.8 (q, C_3), 109.1 (C_8), 157.6 (q, C_2).

IR ν_{max} cm^{-1} : 2951, 2866, 1452, 1289, 811.

HRMS: (m/z - EI) Calculated for $\text{C}_{13}\text{H}_{20}$ (M) $^+$ 176.1565, found 176.1557.

6.3.34 2-Ethylspiro[bicyclo[2.2.1]heptane-3,1'-cyclopentan]-2-amine. (69)

Prepared as per general procedure E using 2-azido-2-ethylspiro[bicyclo[2.2.1]heptane-3,1'-cyclopentane] **64** (0.11 g, 0.50 mmol), palladium on charcoal (0.012 g, 10% w/w) and methanol (10 mL) with a reaction time of 14 hrs under an atmosphere of hydrogen at atmospheric pressure to yield 2-ethylspiro[bicyclo[2.2.1]heptane-3,1'-cyclopentan]-2-amine **69** as a clear colourless oil (0.06 g, 0.32 mmol, 64%).

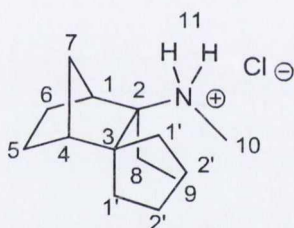
^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 0.93 (3H, t, $J = 7.5$ Hz, H_9), 1.18 (1H, app d, $J = 10.0$ Hz, H_{7a}), 1.25-1.75 (14H, m, H_{5a} , H_{5b} , H_{6a} , H_{6d} , $\text{H}_{1'a}$, $\text{H}_{1'b}$, $\text{H}_{1'c}$, $\text{H}_{1'd}$, $\text{H}_{2'a}$, $\text{H}_{2'b}$, $\text{H}_{2'c}$, $\text{H}_{2'd}$, H_{8a} , H_{8b}), 1.83-1.90 (3H, m, H_1 , H_4 , H_{7b}).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 9.2 (C_9), 22.3 (C_5), 23.3 (C_8), 23.4 (C_6), 23.79 ($\text{C}_{2'}$), 23.80 (C_2), 30.6 ($\text{C}_{1'}$), 34.0 ($\text{C}_{1'}$), 34.6 (C_7), 45.27 (C_1), 45.29 (C_4), 48.3 (q, C_3), 57.5 (q, C_2).

IR ν_{max} cm^{-1} : 3289, 2948, 2873, 1463, 1377, 947, 806.

HRMS: (m/z – EI) Calculated for $\text{C}_{13}\text{H}_{23}\text{N}$ (M^+) 193.1830, found 193.1828.

6.3.35 2-Ethyl-*N*-methylspiro[bicyclo[2.2.1]heptane-3,1'-cyclopentan]-2-amine. (54)



Prepared as per general procedure G using 2-ethylspiro[bicyclo[2.2.1]heptane-3,1'-cyclopentan]-2-amine **69** (0.07 g 0.36 mmol), paraformaldehyde (0.40 g, 1.26 mmol), activated 4 Å molecular sieves (0.15 g), anhydrous CH_2Cl_2 (15 mL), sodium borohydride (0.06 g, 1.62 mmol) and anhydrous methanol (0.5 mL) to yield a pale yellow oil. This product was re-dissolved in anhydrous diethyl ether (5 mL) and a solution of hydrogen chloride (2M in diethyl ether, 0.5 mL, 1.0 mmol) was added. Filtration afforded the HCl salt of 2-ethyl-*N*-methylspiro[bicyclo[2.2.1]heptane-3,1'-cyclopentan]-2-amine **54** as a white solid. The solid was contaminated by decomposition products and could not be purified.

^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.16 (3H, t, $J = 7.3$ Hz, H_9), 1.32 (1H, app d, $J = 11.5$ Hz, H_{7a}), 1.35-1.86 (13H, m, H_{5a} , H_{5b} , H_{6a} , H_{6b} , H_8 , $\text{H}_{1'a}$, $\text{H}_{1'b}$, $\text{H}_{1'c}$, $\text{H}_{2'a}$, $\text{H}_{2'b}$, $\text{H}_{2'c}$, $\text{H}_{2'd}$), 1.99 (1H, br s, H_4), 2.04-2.12 (1H, m, $\text{H}_{1'd}$), 2.52

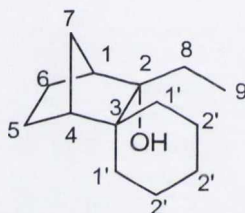
(1H, app d, $J = 11.5$ Hz, H_{7b}), 2.65 (3H, t, $J = 5.7$ Hz, H_{10}), 2.70 (1H, br s, H_1), 8.71 (1H, br s, H_{11a}), 9.02 (1H, br s, H_{11b}).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 9.6 (C_9), 22.2 (C_5), 22.4 (C_2), 22.6 (C_2'), 23.1 (C_8), 23.9 (C_6), 29.5 (C_{10}), 31.4 ($C_{1'}$), 34.0 ($C_{1'}$), 34.6 (C_7), 44.8 (C_1), 45.8 (C_4), 57.9 (q, C_3), 72.3 (q, C_2).

IR ν_{max} cm^{-1} : 2950, 1594, 1456, 1416, 1107, 1101, 907.

HRMS: (m/z - ESI) Calculated for $\text{C}_{14}\text{H}_{26}\text{N}$ ($\text{M}+\text{H}$) $^+$ 208.2065, found 208.2051.

6.3.36 2-Ethylspiro[bicyclo[2.2.1]heptane-3,1'-cyclohexan]-2-ol. (61)



Prepared as per general procedure F using spiro[bicyclo[2.2.1]heptane-3,1'-cyclohexan]-2-one **57** (0.80 g, 4.49 mmol), bromoethane (0.65 mL, 8.97 mmol), a solution of *tert*-butyllithium (1.7M in pentane, 10.50 mL, 17.96 mmol) and anhydrous THF (65 mL) to yield a pale yellow oil which was purified by column chromatography (1:9 diethyl ether: hexane, $R_f = 0.38$) to yield 2-ethylspiro[bicyclo[2.2.1]heptane-3,1'-cyclohexan]-2-ol **61** as a clear colourless oil (0.42g, 2.02 mmol, 41%).

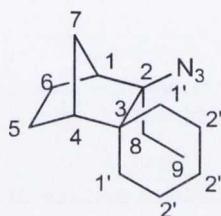
^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 0.95 (3H, t, $J = 7.4$ Hz, H_9), 0.98-1.07 (1H, m, $H_{1'a}$), 1.09-1.32 (3H, m, H_{7a} , $H_{2'a}$, $H_{2'b}$), 1.32-1.48 (4H, m, H_{5a} , H_{6a} , $H_{1'b}$, $H_{1'c}$), 1.49-1.69 (8H, m, H_{5b} , H_{8a} , H_{8b} , H_{7b} , $H_{2'c}$, $H_{2'd}$, $H_{2'e}$, $H_{2'f}$), 1.74-1.82 (2H, m, H_{6b} , $H_{1'd}$), 2.23-2.26 (1H, m, H_1), 2.26-2.32 (1H, m, H_4).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 9.0 (C_9), 21.4 (C_6), 23.2 (C_5), 23.8 ($\text{C}_{2'}$), 24.0 ($\text{C}_{2'}$), 26.3 ($\text{C}_{2'}$), 28.3 (C_8), 30.3 ($\text{C}_{1'}$), 32.2 ($\text{C}_{1'}$), 34.3 (C_7), 41.8 (C_4), 45.1 (C_1), 45.9 (q, C_3), 81.7 (q, C_2).

IR ν_{max} cm^{-1} : 3494, 2926, 2854, 1466, 1128, 966.

HRMS: (m/z - EI) Calculated for $\text{C}_{14}\text{H}_{24}\text{O}$ (M) $^+$ 208.1827, found 208.1822.

6.3.37 2-Azido-2-ethylspiro[bicyclo[2.2.1]heptane-3,1'-cyclohexane]. (66)



Prepared as per general procedure D using 2-ethylspiro[bicyclo[2.2.1]heptane-3,1'-cyclohexan]-2-ol **61** (0.42 g, 2.02 mmol), NaN_3 (0.91 g, 13.9 mmol), 50% H_2SO_4 (5 mL) and chloroform (50 mL) with a reaction time of 6 hrs to yield a yellow oil was purified by column chromatography (100% hexane, R_f = 0.46) to yield 2-azido-2-ethylspiro[bicyclo[2.2.1]heptane-3,1'-cyclohexane] **66** as a colourless liquid (0.28 g, 1.20 mmol, 59%).

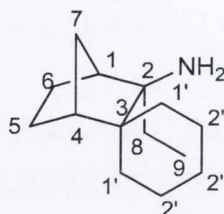
^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 0.95 (3H, t, J = 7.4 Hz, H_9), 1.12-1.25 (4H, m, H_{7a} , $\text{H}_{1'a}$, $\text{H}_{2'a}$, $\text{H}_{2'b}$), 1.26-1.39 (3H, m, H_{5a} , H_{6a} , $\text{H}_{1'b}$), 1.41-1.70 (8H, m, H_{5b} , H_{6b} , H_{8a} , $\text{H}_{1'c}$, $\text{H}_{2'c}$, $\text{H}_{2'd}$, $\text{H}_{2'e}$, $\text{H}_{2'f}$), 1.73-1.88 (3H, m, H_{7b} , H_{8b} , $\text{H}_{1'd}$), 2.21-2.24 (1H, m, H_1), 2.37-2.41 (1H, m, H_4).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 9.5 (C_9), 22.6 (C_6), 23.0 (C_8), 23.1 (C_5), 23.6 ($\text{C}_{2'}$), 24.1 ($\text{C}_{2'}$), 26.0 ($\text{C}_{2'}$), 31.2 ($\text{C}_{1'}$), 32.8 ($\text{C}_{1'}$), 34.3 (C_7), 41.4 (C_4), 44.7 (C_1), 49.1 (q, C_3), 77.8 (q, C_2).

IR $\nu_{\max}$ cm^{-1} : 2926, 2858, 2091, 1452, 1270, 1135, 878.

HRMS: (m/z - ESI) Calculated for $\text{C}_{14}\text{H}_{24}\text{N}$ ($\text{M}+\text{H}-\text{N}_2$)⁺ 206.1909, found 206.1903.

6.3.38 2-Ethylspiro[bicyclo[2.2.1]heptane-3,1'-cyclohexan]-2-amine. (70)



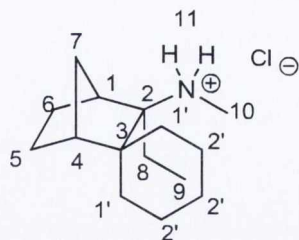
Prepared as per general procedure E using 2-azido-2-ethylspiro[bicyclo[2.2.1]heptane-3,1'-cyclohexane] **66** (0.24 g, 1.15 mmol), palladium on charcoal (0.02 g, 10% w/w) and methanol (10 mL) with a reaction time of 12 hrs under a hydrogen atmosphere at atmospheric pressure to yield 2-ethylspiro[bicyclo[2.2.1]heptane-3,1'-cyclohexan]-2-amine **70** as a clear colourless oil (0.15 g, 0.73 mmol, 66%).

^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 0.92 (3H, t, $J = 7.5$ Hz, H_9), 1.05-1.43 (8H, m, H_{5a} , H_{6a} , H_{7a} , $\text{H}_{1'a}$, $\text{H}_{1'b}$, $\text{H}_{2'a}$, $\text{H}_{2'b}$, $\text{H}_{2'c}$), 1.44-1.78 (9H, m, H_{5b} , H_{6b} , H_{8a} , H_{8b} , $\text{H}_{1'c}$, $\text{H}_{1'd}$, $\text{H}_{2'd}$, $\text{H}_{2'e}$, $\text{H}_{2'f}$), 1.79-1.85 (1H, m, H_{7b}), 1.89 (1H, br s, H_4), 2.34 (1H, br s, H_1).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 9.1 (C_9), 23.1 (C_5), 23.2 ($\text{C}_{2'}$), 23.8 (C_6), 24.3 ($\text{C}_{2'}$), 26.2 ($\text{C}_{2'}$), 26.7 (C_8), 31.1 ($\text{C}_{1'}$), 32.1 ($\text{C}_{1'}$), 34.2 (C_7), 41.8 (C_1), 48.4 (C_4), 46.4 (q, C_3), 62.5 (q, C_2).

IR $\nu_{\max}$ cm^{-1} : 3342, 2923, 2857, 1451, 831.

HRMS: (m/z - ESI) Calculated for $\text{C}_{14}\text{H}_{26}\text{N}$ ($\text{M}+\text{H}$)⁺ 208.2065, found 208.2067.

6.3.39 2-Ethyl-*N*-methylspiro[bicyclo[2.2.1]heptane-3,1'-cyclohexan]-2-amine. (55)

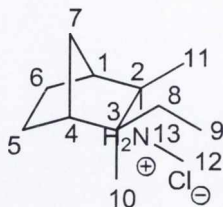
Prepared as per general procedure G using 2-ethylspiro[bicyclo[2.2.1]heptane-3,1'-cyclohexan]-2-amine **70** (0.13 g 0.63 mmol), paraformaldehyde (0.70 g, 2.19 mmol), activated 4 Å molecular sieves (0.20 g), anhydrous CH_2Cl_2 (20 mL), sodium borohydride (0.11 g, 2.84 mmol) and anhydrous methanol (1 mL) to yield a clear colourless oil. This product was dissolved in anhydrous diethyl ether (3 mL) and a solution of hydrogen chloride (2M in diethyl ether, 0.5 mL, 1.0 mmol) was added. Filtration afforded the HCl salt of 2-ethyl-*N*-methylspiro[bicyclo[2.2.1]heptane-3,1'-cyclohexan]-2-amine **55** as a white solid (0.47 g, 1.82 mmol, 34%), M.p. 170-180 °C (decomposes).

^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.16 (3H, t, $J = 7.3$ Hz, H_9), 1.18-1.28 (4H, m, H_{6a} , H_{7a} , $\text{H}_{1'a}$, $\text{H}_{2'a}$), 1.35-1.84 (12H, m, H_{5a} , H_{5b} , H_{6b} , H_{8a} , H_{8b} , $\text{H}_{1'b}$, $\text{H}_{1'c}$, $\text{H}_{2'b}$, $\text{H}_{2'c}$, $\text{H}_{2'd}$, $\text{H}_{2'e}$, $\text{H}_{2'f}$), 2.36-2.41 (1H, m, $\text{H}_{1'd}$), 2.50-2.56 (2H, m, H_4 , H_{7b}), 2.63-2.66 (1H, m, H_1), 2.69 (3H, app t, $J = 5.4$ Hz, H_{10}), 8.56 (1H, br s, H_{11a}), 8.91 (1H, br s, H_{11b}).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 9.4 (C_9), 21.0 (C_8), 22.1 (C_5), 23.4 ($\text{C}_{2'}$), 23.5 (C_6), 23.7 ($\text{C}_{2'}$), 25.7 ($\text{C}_{2'}$), 30.0 (C_{10}), 31.6 ($\text{C}_{1'}$), 31.7 ($\text{C}_{1'}$), 34.3 (C_7), 42.1 (C_4), 45.3 (C_1), 48.5 (q, C_3), 74.8 (q, C_2).

IR ν_{max} cm^{-1} : 2931, 1586, 1452, 1411, 922.

HRMS: (m/z - ESI) Calculated for $\text{C}_{14}\text{H}_{23}$ ($\text{M}-\text{NH}_2\text{CH}_3$) $^+$ 191.1800, found 191.1808.

6.3.40 3-*exo*-Ethyl-*N*-2,3-trimethylbicyclo[2.2.1]heptan-2-amine. (71)

General Procedure J

Methylamine hydrochloride (133 mg, 1.97 mmol) was ground into a fine powder and heated to 100 °C in an RBF under high vacuum to remove all traces of H₂O. A reflux condenser was fitted to the flask and the system was flushed with argon. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.50 mL, 3.28 mmol) was added and the reaction was stirred for 5 minutes. Triethylamine (0.83 mL, 5.90 mmol) was added. Titanium tetrachloride solution (1M in CH₂Cl₂, 1.65 mL, 1.65 mmol) was added and the reaction was stirred for 20 minutes at 40 °C. 3-*exo*-Ethyl-3-methylbicyclo[2.2.1]heptan-2-one **83** (200 mg, 1.31 mmol) was added slowly and the reaction turned from bright red to dark brown. After stirring at 40 °C for 16 hours, the reaction mixture was poured into diethyl ether (40 mL) and filtered through celite to remove triethylamine hydrochloride. The organic solvent was dried over magnesium sulfate and evaporated at reduced pressure to yield imine **85** as a clear viscous oil. To this, boron trifluoride diethyl etherate (250 µL, 1.97 mmol) was added dropwise. A crystalline solid formed. The reaction mixture was cooled to 0 °C and methyllithium solution (1.6M in diethyl ether, 4.10 mL, 6.55 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 1 hr. Ammonium hydroxide solution (30% in H₂O, 10 mL) was added and the mixture extracted with diethyl ether (2 x 10 mL), washed with brine (10 mL) and dried over magnesium sulfate. The organic solvent was evaporated under vacuum to yield the desired amine as a viscous oil. This product was re-dissolved in anhydrous diethyl ether (2 mL) and a solution of hydrogen chloride (2M in diethyl ether, 1.5 mL, 3.0 mmol) was added. The hydrochloride salt of 3-*exo*-ethyl-*N*-2,3-trimethylbicyclo[2.2.1]heptan-2-amine **71** was isolated by filtration and dried under vacuum to yield a white solid (27 mg, 0.1 mmol, 11%). M.p.= 154-156 °C (decomposes).

¹H NMR (CDCl₃, 600 MHz): δ (ppm) 0.90 (3H, t, *J* = 7.3 Hz, H₉), 1.26-1.30 (1H, m, H_{7a}), 1.35 (3H, s, H₁₀), 1.40 (3H, s, H₁₁), 1.42-

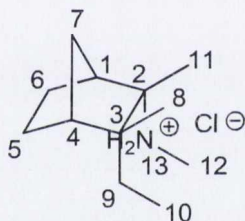
1.61 (4H, m, H_{5a}, H_{6a}, H_{8a}, H_{8b}), 1.76-1.80 (1H, m, H_{7b}), 1.81-1.88 (1H, m, H_{5b}), 1.90-1.96 (1H, m, H_{6b}), 2.09-2.12 (1H, m, H₄), 2.14-2.18 (1H, m, H₁), 2.65-2.69 (3H, m, H₁₂), 8.26-8.38 (1H, br s, H_{13a}), 9.27-9.37 (1H, br s, H_{13b}).

¹³C NMR (CDCl₃, 150 MHz): δ (ppm) 10.1 (C₉), 18.0 (C₁₀), 18.9 (C₁₁), 22.3 (C₆), 23.5 (C₅), 29.0 (C₁₂), 30.3 (C₈), 34.7 (C₇), 44.5 (C₄), 46.0 (q, C₃), 47.1 (C₁), 70.2 (q, C₂).

IR $\nu_{\max}$ (cm⁻¹): 2949, 2719, 2454, 1589, 1430, 1388, 1091.

HRMS: (m/z - ESI) Calculated for C₁₂H₂₄N (M+H) 182.1909, found 182.1903.

6.3.41 3-*endo*-Ethyl-*N*-2,3-trimethylbicyclo[2.2.1]heptan-2-amine. (72)



Prepared as per general procedure J using 3-*endo*-Ethyl-3-methylbicyclo[2.2.1]heptan-2-one **84** (200 mg, 1.31 mmol), methylamine hydrochloride (1.33 mg, 1.97 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.50 mL, 3.28 mmol), triethylamine (0.83 mL, 5.90 mmol), titanium tetrachloride solution (1M in CH₂Cl₂, 1.65 mL, 1.65 mmol) with a reaction time of 16 hrs at 40 °C to yield the desired imine **86** as a clear viscous oil. To this was added boron trifluoride diethyl etherate (250 μ L, 1.97 mmol), methyllithium solution (1.6M in diethyl ether, 4.10 mL, 6.55 mmol) to yield a clear colourless oil. This product was re-dissolved in anhydrous diethyl ether (2 mL) and a solution of hydrogen chloride (2M in diethyl ether, 1.5 mL, 3.0 mmol) was added. The hydrochloride salt of 3-*endo*-ethyl-*N*-2,3-trimethylbicyclo[2.2.1]heptan-2-amine **72** was isolated by filtration and dried under vacuum to yield a white solid. (74 mg, 0.4 mmol, 31%) M.p. = 149-150 °C (decomposes).

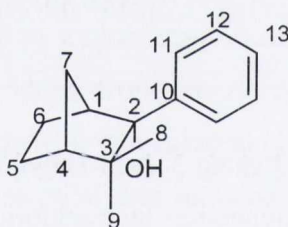
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 0.94 (3H, app t, $J = 7.1$ Hz, H_{10}), 1.07 (1H, s, H_8), 1.31-1.36 (1H, m, H_{7a}), 1.41 (3H, s, H_{11}), 1.42-1.58 (2H, m, H_{5a} , H_{6a}), 1.62-1.69 (1H, m, H_{9a}), 1.79-1.85 (2H, m, H_{5b} , H_{7b}), 1.86-1.93 (1H, m, H_{6b}), 1.96-1.99 (1H, m, H_4), 2.16-2.20 (1H, m, H_1), 2.20-2.27 (1H, m, H_{9b}), 2.69 (3H, app t, $J = 5.4$ Hz, H_{12}), 8.22-8.36 (1H, br s, H_{13a}), 9.25-9.40 (1H, br s, H_{13b}).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 9.6 (C_{10}), 19.7 (C_{11}), 21.7 (C_8), 22.6 (C_6), 23.0 (C_5), 25.9 (C_9), 28.9 (C_{12}), 34.4 (C_7), 46.1 (C_4), 46.5 (q, C_3), 46.7 (C_1), 70.3 (q, C_2).

IR ν_{max} (cm^{-1}): 2956, 2882, 2713, 1467, 1390, 1138, 1087, 921.

HRMS: (m/z - ESI) Calculated for $\text{C}_{12}\text{H}_{24}\text{N}$ ($\text{M}+\text{H}$) $^+$ 182.1909, found 182.1913.

6.3.42 3,3-Dimethyl-2-*exo*-phenylbicyclo[2.2.1]heptan-2-ol.³¹⁷ (**88**)



Prepared as per general procedure C using 3,3-dimethylbicyclo[2.2.1]heptan-2-one **37** (1.00 g, 7.25 mmol), phenylmagnesium bromide (3M in diethyl ether, 7.25 mL, 21.7 mmol) and anhydrous THF (30 mL) at room temperature with a reaction time of 16 hrs to yield a yellow oil which was purified by column chromatography (9:1 hexane: ethyl acetate, $R_f = 0.4$), to yield 3,3-dimethyl-2-*exo*-phenylbicyclo[2.2.1]heptan-2-ol **88** as a clear colourless oil, (0.73g, 3.38 mmol, 47%).

^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 0.55 (3H, s, H_9), 1.16 (3H, s, H_8), 1.42-1.49 (3H, m, H_{5a} , H_{6a} , H_{7a}), 1.82-1.87 (2H, m, H_4 , H_{5b}), 2.05-2.18 (2H, m, H_{6b} , H_{7b}), 2.67-2.71 (1H, m,

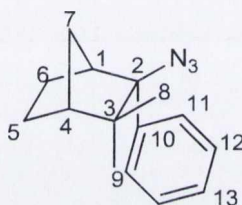
^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 7.23 (1H, t, $J = 7.3$ Hz, H_{13}), 7.33 (2H, app t, $J = 7.3$ Hz, H_{12}), 7.53 (2H, d, $J = 7.3$ Hz, H_{11}).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 21.4 (C_8), 22.4 (C_6), 23.7 (C_5), 30.2 (C_9), 36.6 (C_7), 44.5 (q, C_3), 49.0 (C_1), 49.7 (C_4), 81.7 (q, C_2), 126.4 (C_{11}), 126.5 (C_{13}), 127.6 (C_{12}), 148.1 (q, C_{10}).

IR ν_{max} cm^{-1} : 3460, 2943, 2871, 1048, 703.

HRMS: (m/z - EI) Calculated for $\text{C}_{15}\text{H}_{20}\text{O}$ (M^+) 216.1514, found 216.1517.

6.3.43 2-Azido-3,3-dimethyl-2-*endo*-phenylbicyclo[2.2.1]heptane. (89)



Prepared as per general procedure D using 3,3-dimethyl-2-*exo*-phenylbicyclo[2.2.1]heptan-2-ol **88** (0.60 g, 2.77 mmol), NaN_3 (1.26 g, 19.4 mmol), 50% H_2SO_4 (8.5 mL) and CHCl_3 (75 mL) with a reaction time of 5 hrs to yield a pale yellow oil was purified by column chromatography (100% hexane, $R_f = 0.30$) to yield 2-azido-3,3-dimethyl-2-*endo*-phenylbicyclo[2.2.1]heptane **89** as a clear colourless oil (0.48 g, 1.99 mmol, 72%).

^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 0.84 (3H, s, H_9), 1.23-1.34 (5H, m, H_8 , H_{5a} , H_{7a}), 1.53-1.81 (3H, m, H_{5b} , H_{6a} , H_{6b}), 1.83-1.88 (1H, m, H_4), 2.25 (1H, app d, $J = 10.1$ Hz, H_{7b}), 2.79-2.84 (1H, m, H_1), 7.26-7.38 (5H, m, H_{11} , H_{12} , H_{13}).

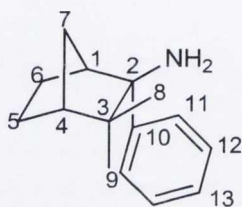
^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 23.4 (C_6), 25.1 (C_5), 27.6 (C_9), 28.2 (C_8), 35.3 (C_7), 43.8 (q, C_3), 45.5 (C_1), 50.8 (C_4), 79.7 (q,

C₂), 127.4 (C₁₃), 127.7 (C₁₂), 129.2 (C₁₁), 138.3 (q, C₁₀).

IR $\nu_{\max}$ cm⁻¹: 2938, 2086, 1242, 706.

HRMS: (m/z - EI) Calculated for C₁₅H₁₉N (M-N₂)⁺ 213.1517, found 213.1510.

6.3.44 3,3-Dimethyl-2-*endo*-phenylbicyclo[2.2.1]heptan-2-amine. (90)



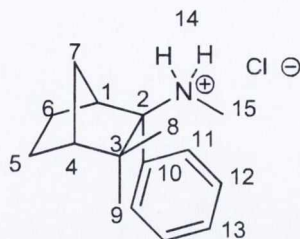
Prepared as per general procedure E using 2-azido-3,3-dimethyl-2-*endo*-phenylbicyclo[2.2.1]heptane **89** (0.40 g, 1.66 mmol), methanol (30 mL) and palladium on charcoal (0.04 g, 10% w/w) under an atmosphere of hydrogen for 6 hrs at atmospheric pressure to yield 3,3-dimethyl-2-*endo*-phenylbicyclo[2.2.1]heptan-2-amine **90** as a clear colourless oil (0.11 g, 0.51 mmol, 31%).

¹H NMR (CDCl₃, 400 MHz): δ (ppm) 0.88 (3H, s, H₉), 1.25-1.34 (5H, m, H₈, H_{7a}, H_{5a}), 1.55-1.81 (3H, m, H_{5b}, H_{6a}, H_{6b}), 1.82-1.85 (1H, m, H₄), 1.23-1.29 (1H, app d, J = 10.4 Hz, H_{7b}), 2.47-2.52 (1H, m, H₁), 7.17-7.23 (1H, m, H₁₃), 7.29-7.37 (4H, m, H₁₁, H₁₂).

¹³C NMR (CDCl₃, 100 MHz): δ (ppm) 23.9 (C₆), 25.4 (C₅), 27.5 (C₈), 28.6 (C₉), 34.8 (C₇), 43.0 (q, C₃), 49.4 (C₁), 51.0 (C₄), 67.2 (q, C₂), 125.7 (C₁₃), 127.7 (C₁₂), 128.3 (C₁₁), 147.8 (q, C₁₀).

IR $\nu_{\max}$ cm⁻¹: 3328, 2926, 1597, 1643, 766, 705.

HRMS: (m/z - EI) Calculated for C₁₅H₂₁N (M)⁺ 215.1674, found 215.1677.

6.3.45 3,3-Trimethyl-2-*endo*-phenyl-2-*exo*-methylaminobicyclo[2.2.1]heptane. (87)

Prepared as per general procedure G using 3,3-dimethyl-2-*endo*-phenylbicyclo[2.2.1]heptan-2-amine **90** (0.09 g 0.42 mmol), paraformaldehyde (0.04 g, 1.48 mmol), activated 4 Å molecular sieves (0.25 g), anhydrous CH₂Cl₂ (15 mL), sodium borohydride (0.07 g, 1.91 mmol) and anhydrous methanol (1.00 mL) to yield a viscous colourless oil. This product was re-dissolved in anhydrous diethyl ether (5 mL) and a solution of hydrogen chloride (2M in diethyl ether, 0.5 mL, 1.0 mmol) was added. Filtration afforded the HCl salt of 3,3-trimethyl-2-*endo*-phenyl-2-*exo*-methylaminobicyclo[2.2.1]heptane **87** as a white solid (0.05g, 0.21 mmol, 50%). M.p. 175-180 °C (decomposes).

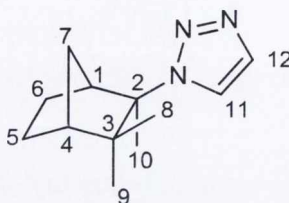
¹H NMR (CDCl₃, 600 MHz): δ (ppm) 0.89 (3H, s, H₉), 1.32-1.40 (1H, m, H_{5a}), 1.48 (1H, app d, *J* = 13.2 Hz, H_{7a}), 1.56-1.62 (1H, m, H_{5b}), 1.73-1.88 (5H, m, H₈, H_{6a}, H_{6b}), 2.01-2.04 (1H, m, H₄), 2.17-2.21 (3H, m, H₁₅), 2.78-2.84 (1H, app d, *J* = 13.2 Hz, H_{7b}), 2.89-2.82 (1H, m, H₁), 7.25-7.37 (3H, m, H_{11a}, H_{12a}, H₁₃), 7.51 (1H, app t, *J* = 7.9 Hz, H_{12b}), 7.83 (1H, d, *J* = 7.9 Hz, H_{11b}), 8.60-8.71 (1H, br s, H₁₄), 9.09-9.19 (1H, br s, H₁₄).

¹³C NMR (CDCl₃, 150 MHz): δ (ppm) 23.6 (C₆), 24.8 (C₅), 27.2 (C₈), 28.3 (C₉), 28.7 (C₁₅), 34.7 (C₇), 41.6 (C₁), 44.9 (q, C₃), 50.8 (C₄), 77.6 (q, C₂), 127.1 (C_{12a}), 128.7 (C₁₃), 129.2 (C_{12b}), 129.9 (C_{11a}), 131.7 (C_{11b}), 134.1 (q, C₁₀).

IR $\nu_{\max}$ cm^{-1} : 2948, 1394, 1012, 767, 740, 707.

HRMS: (m/z - ESI) Calculated for $\text{C}_{16}\text{H}_{24}\text{N}$ ($\text{M}+\text{H}$) $^{+}$ 230.1909, found 230.1904.

6.3.46 1-(2-*endo*-3,3-Trimethylbicyclo[2.2.1]heptan-2-yl)-1H-1,2,3-triazole. (94)



General Procedure K

A microwave reaction vessel charged with 2-azido-2-*endo*-3,3-trimethylbicyclo[2.2.1]heptane **39** (0.25 g, 1.40 mmol), trimethylsilylethyne (0.30 mL, 2.11 mmol), copper sulfate (0.07 g, 0.30 mmol) and sodium ascorbate (0.12 g, 0.60 mmol) in DMF (1.0 mL) was heated to 130 °C and was stirred vigorously for 10 minutes under microwave irradiation. After this time, the reaction mixture was diluted with H_2O and concentrated aqueous ammonia was added. The mixture was extracted using diethyl ether and was dried over magnesium sulfate to yield a brown oil. This was further purified by column chromatography (8:2 hexane:ethyl acetate, R_f = 0.3) to yield 1-(2,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)-1H-1,2,3-triazole **94** as a brown oil (0.08 g, 0.40 mmol, 29%).

^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 0.52 (3H, s, H_8), 1.16 (3H, s, H_9), 1.44 (1H, app d, J = 10.6 Hz, H_{7a}), 1.46-1.52 (1H, m, H_{5a}), 1.67-1.64 (1H, m, H_{6a}), 1.66 (3H, s, H_{10}), 1.68-1.74 (1H, m, H_{5b}), 1.75-1.80 (1H, m, H_{6b}), 1.90-1.93 (1H, m, H_4), 2.27 (1H, app d, J = 10.6 Hz, H_{7b}), 2.82-2.84 (1H, m, H_1), 7.66 (1H, app s, H_{12}), 7.71 (1H, app s, H_{11}).

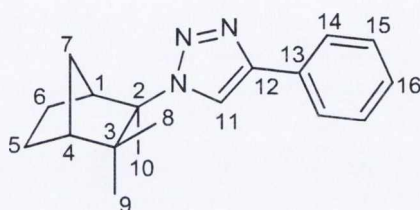
^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 22.0 (C_9), 22.5 (C_5), 22.9 (C_{10}), 24.4 (C_6), 26.0 (C_8), 35.8 (C_7), 46.4 (q, C_3), 48.4 (C_1), 50.6 (C_4), 72.2 (q, C_2), 122.1 (C_{11}), 132.0 (C_{12}).

IR $\nu_{\max}$ (cm^{-1}): 2951, 1475, 1248, 839.

HRMS: (m/z - EI) Calculated for $\text{C}_{12}\text{H}_{19}\text{N}_3$ (M)⁺ 205.1579, found 205.1580.

6.3.47 1-(2-*endo*-3,3-Trimethylbicyclo[2.2.1]heptan-2-yl)-4-phenyl-1H-1,2,3-triazole.

(95)



Prepared as per general procedure K using 2-azido-2-*endo*-3,3-trimethylbicyclo[2.2.1]heptane **39** (0.33 g, 1.70 mmol), phenylacetylene (1.00 mL, 9.10 mmol), copper sulfate (0.08 g, 0.34 mmol) and sodium ascorbate (0.13 g, 0.67 mmol) in DMF (1.00 mL) to yield a brown oil. This was further purified by column chromatography (100% hexane, R_f = 0.5) to yield 1-(2,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)-4-phenyl-1H-1,2,3-triazole **95** as a brown oil (0.29 g, 1.05 mmol, 64%).

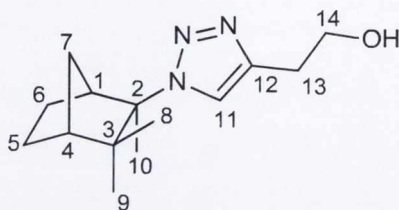
^1H NMR (CDCl_3 , 600 MHz): δ (ppm): 0.64 (3H, s, H_8), 1.21 (3H, s, H_9), 1.48 (1H, app d, J = 10.5 Hz, H_{7a}), 1.50-1.55 (1H, m, H_{5a}), 1.60-1.67 (1H, m, H_{6a}), 1.71 (3H, s, H_{10}), 1.73-1.77 (1H, m, H_{5b}), 1.78-1.84 (1H, m, H_{6b}), 1.95-1.97 (1H, m, H_4), 2.34 (1H, app d, J = 10.5 Hz, H_{7b}), 2.87-2.90 (1H, m, H_1), 7.34 (1H, t, J = 7.6 Hz, H_{16}), 7.45 (2H, app t, J = 7.6 Hz, H_{15}), 7.89 (2H, d, J = 7.6 Hz, H_{14}), 7.92 (1H, s, H_{11}).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 22.2 (C_9), 22.7 (C_5), 23.0 (C_{10}), 24.6 (C_6), 26.3 (C_8), 36.0 (C_7), 46.6 (q, C_3), 48.5 (C_1), 50.7 (C_4), 72.6 (q, C_2), 118.5 (C_{11}), 125.6 (C_{14}), 127.8 (C_{16}), 128.7 (C_{15}), 131.1 (q, C_{13}), 145.9 (q, C_{12}).

IR $\nu_{\max}$ (cm^{-1}): 3138, 2963, 2884, 1481, 1229, 1021, 762.

HRMS: (m/z - ESI) Calculated for $C_{18}H_{24}N_3$ ($M+H$)⁺ 282.1970, found 282.1971.

6.3.48 2-(1-(2-*endo*-3,3-Trimethylbicyclo[2.2.1]heptan-2-yl)-1H-1,2,3-triazol-4-yl)ethanol. (96)



Prepared as per general procedure K using 2-azido-2-*endo*-3,3-trimethylbicyclo[2.2.1]heptane **39** (0.20 g, 1.12 mmol), 3-butyne-1-ol (0.84 mL, 11.2 mmol), copper sulfate (0.06 g, 0.23 mmol) and sodium ascorbate (0.09 g, 0.46 mmol) in DMF (1.0 mL) to yield a brown oil. This was further purified by column chromatography (100% ethyl acetate, R_f = 0.6) to yield 2-(1-(2,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)-1H-1,2,3-triazol-4-yl)ethanol **96** as a brown oil (0.13 g, 0.53 mmol, 47%).

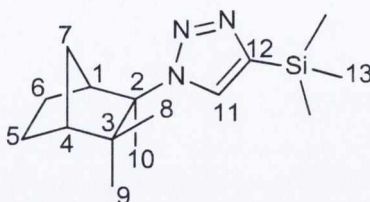
1H NMR ($CDCl_3$, 600 MHz): δ (ppm) 0.54 (3H, s, H_8), 1.15 (3H, s, H_9), 1.44 (1H, app d, J = 10.5 Hz, H_{7a}), 1.49 (1H, m, H_{5a}), 1.60 (1H, m, H_{6a}), 1.65 (3H, s, H_{10}), 1.71 (1H, m, H_{5b}), 1.76 (1H, m, H_{6b}), 1.93 (1H, br s, H_4), 2.26 (1H, app d, J = 10.5 Hz, H_{7b}), 2.81 (1H, br s, H_1), 2.98 (2H, dt, J = 5.7, 2.0 Hz, H_{13}), 3.98 (2H, t, J = 5.7 Hz, H_{14}), 7.57 (1H, s, H_{11}).

^{13}C NMR ($CDCl_3$, 150 MHz): δ (ppm) 22.0 (C_9), 22.6 (C_5), 22.9 (C_{10}), 24.5 (C_6), 26.1 (C_8), 28.5 (C_{13}), 36.1 (C_7), 46.5 (q, C_3), 48.4 (C_1), 50.7 (C_4), 61.8 (C_{14}), 72.5 (q, C_2), 120.8 (C_{11}), 143.5 (q, C_{12}).

IR ν_{max} (cm^{-1}): 3342, 2980, 1663, 1386, 1051, 809.

HRMS: (m/z - ESI) Calculated for $C_{14}H_{24}N_3O$ ($M+H$)⁺ 250.1919, found 250.1926.

6.3.49 1-(2-*endo*-3,3-Trimethylbicyclo[2.2.1]heptan-2-yl)-4-trimethylsilyl-1H-1,2,3-triazole. (93)



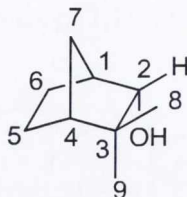
Prepared as per general procedure K using 2-azido-2-*endo*-3,3-trimethylbicyclo[2.2.1]heptane **39** (0.30 g, 1.68 mmol), trimethylsilylethyne (1.40 mL, 10.1 mmol), copper sulfate (0.08 g, 0.33 mmol) and sodium ascorbate (0.13 g, 0.67 mmol) in DMF (1.0 mL) to yield a brown oil. This was further purified by column chromatography (100% ethyl acetate, $R_f = 0.6$) to yield 1-(2,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)-4-trimethylsilyl-1H-1,2,3-triazole **93** as a white solid (0.08 g, 0.29 mmol, 17%). M.p = 72-74°C.

^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 0.42 (9H, s, H_{13}), 0.53 (3H, s, H_8), 1.18 (3H, s, H_9), 1.45-1.82 (8H, m, H_{10} , H_{5a} , H_{5b} , H_{6a} , H_{6b} , H_{7a}), 1.94 (1H, br s, H_4), 2.25 (1H, app d, $J = 10.5$ Hz, H_{7b}), 2.85 (1H, br s, H_1), 7.70 (1H, s, H_{11}).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 1.0 (C_{13}), 22.0 (C_9), 22.6 (C_5), 23.1 (C_{10}), 24.6 (C_6), 26.2 (C_8), 36.0 (C_7), 46.6 (q, C_3), 48.5 (C_1), 50.7 (C_4), 73.3 (q, C_2), 128.3 (C_{11}), 142.6 (q, C_{12}).

IR ν_{max} (cm^{-1}): 2960, 1475, 1244, 1042, 838, 757.

HRMS: (m/z - ESI) Calculated for $\text{C}_{15}\text{H}_{28}\text{N}_3\text{Si}$ ($\text{M}+\text{H}^+$) 278.2053, found 278.2045.

6.3.50 3,3-Dimethylbicyclo[2.2.1]heptan-2-*endo*-ol. (**98**)

A solution of 3,3-dimethylbicyclo[2.2.1]heptan-2-one **37** (1.30 g, 9.56 mmol) in anhydrous THF (60 mL) was added to NaBH₄ (0.72 g, 19.1 mmol) at 0 °C. To this methanol (10 mL) was added dropwise. The reaction was stirred for 1 hr at room temperature upon which time the reaction mixture was acidified with 1M HCl to a pH of 7. The aqueous layer was extracted with diethyl ether (2 x 30 mL), the combined organic layers were washed with brine (40 mL) and dried over magnesium sulfate before being filtered. The volatiles were removed under reduced pressure to yield 3,3-dimethylbicyclo[2.2.1]heptan-2-*endo*-ol **98** as a white solid (0.92 g, 6.56 mmol, 68%). M.p. 68-69 °C (Lit.³¹⁸ 73-74 °C).

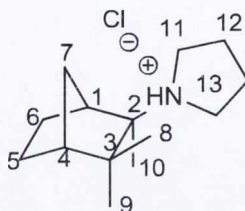
¹H NMR (CDCl₃, 400 MHz): δ (ppm) 0.88 (3H, s, H₉), 0.99 (3H, s, H₈), 1.16 (1H, app dt, *J* = 10.5, 1.7 Hz, H_{7a}), 1.25-1.40 (2H, m, H_{6a} & H_{5a}), 1.56-1.71 (3H, m, H_{5b}, H_{6b} & H_{7b}), 1.77-1.80 (1H, m, H₄), 2.26-2.30 (1H, m, H₁), 3.66 (1H, d, *J* = 4.0 Hz, H₂).

¹³C NMR (CDCl₃, 100 MHz): δ (ppm) 18.1 (C₆), 19.9 (C₉), 24.6 (C₅), 30.5 (C₈), 33.9 (C₇), 38.0 (q, C₃), 44.0 (C₁), 48.2 (C₄), 80.4 (C₂).

IR ν_{max} (cm⁻¹): 3367, 2965, 2879, 1459, 1341, 1297, 1067.

HRMS: (*m/z* – EI) Calculated for C₉H₁₆O (M)⁺ 140.1201, found 140.1203.

6.3.51 1-(2,3,3-Trimethylbicyclo[2.2.1]heptan-2-yl)pyrrolidine. (91)

**General Procedure L**

A suspension of amine **40** (0.20 g, 1.31 mmol), dibromobutane (0.18 mL, 1.44 mmol), potassium carbonate (0.20 g, 1.44 mmol) in H₂O (3 mL) was heated at reflux temperature for 5 hrs. Once cooled the reaction mixture was extracted with ethyl acetate (3 x 10 mL), dried over magnesium sulfate and filtered. The volatiles were removed at reduced pressure and the resulting brown oil was dissolved in anhydrous diethyl ether and treated with a solution of HCl in diethyl ether (1M, 2.0 mL, 2.0 mmol) to yield a brown solid **91** which was purified by repeatedly triturating with diethyl ether and then dried under vacuum (0.11 g, 0.46 mmol, 34%). M.p. = 93-95 °C (decomposes).

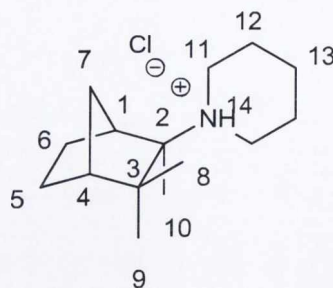
¹H NMR (CDCl₃, 600 MHz): δ (ppm) 1.05 (3H, s, H₉), 1.24 (3H, s, H₁₀), 1.27-1.32 (1H, m, H_{7a}), 1.34-1.59 (7H, m, H_{5a}, H_{5b}, H_{6a}, H_{6b}, H₈), 1.68-1.78 (1H, m, H_{12a}), 1.89-1.93 (1H, m, H₄), 1.98-2.05 (1H, m, H_{12b}), 2.12-2.19 (1H, m, H_{12c}), 2.23-2.32 (1H, m, H_{12d}), 2.38-2.43 (1H, br s, H₁), 2.83-2.89 (1H, app d, *J* = 11.4 Hz, H_{7b}), 2.95-3.08 (2H, m, H_{11a}, H_{11b}), 3.65-3.73 (1H, m, H_{11c}), 4.02-4.10 (1H, m, H_{11d}), 9.89-10.10 (1H, br s, H₁₃).

¹³C NMR (CDCl₃, 150 MHz): δ (ppm) 14.5 (C₁₀), 22.3 (C₅), 24.0 (C₉), 24.7 (C₆), 25.0 (C₁₂), 26.2 (C₁₂), 28.5 (C₈), 34.8 (C₇), 46.4 (q, C₃), 46.8 (C₁), 52.1 (C₄), 52.7 (C₁₁), 52.8 (C₁₁), 78.0 (q, C₂).

IR ν_{max} (cm⁻¹): 2946, 1474, 1384, 1339, 1083, 1039, 732.

HRMS: (*m/z* - ESI) Calculated for C₁₄H₂₆N (M+H)⁺ 208.2065, found 208.2064.

6.3.52 1-(2,3,3-Trimethylbicyclo[2.2.1]heptan-2-yl)piperidine. (92)



Prepared as per general procedure L using amine **40** (62.0 mg, 0.41 mmol), dibromopentane (0.06 mL, 0.45 mmol), potassium carbonate (62.0 mg, 0.45 mmol) in H₂O (1.5 mL) to yield 1-(2,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)piperidine as a yellow oil. This product was re-dissolved in anhydrous diethyl ether and treated with a solution of HCl (1M, 2.0 mL, 2.0 mmol) to yield a yellow solid **92** which was purified by repeatedly washing with diethyl ether and then dried at reduce pressure (24.0 mg, 0.09 mmol, 17%). M.p. = 165-166 °C (decomposes).

¹H NMR (CDCl₃, 600 MHz): δ (ppm) 1.09 (3H, s, H₉), 1.25-1.33 (4H, m, H_{7a}, H₁₀), 1.38-1.47 (2H, m, H_{5a}, H_{13a}), 1.49-1.57 (3H, m, H_{5b}, H_{6a}, H_{6b}), 1.77-1.85 (5H, m, H₈, H_{12a}, H_{12b}), 1.91-1.95 (1H, br s, H₄), 1.98-2.04 (1H, m, H_{13b}), 2.62-2.67 (1H, br s, H₁), 2.72-2.85 (2H, m, H_{11a}, H_{12c}), 2.85-2.95 (1H, m, H_{11b}), 3.19-3.27 (1H, m, H_{7b}), 3.43-3.50 (1H, m, H_{11c}), 3.50-3.60 (1H, m, H_{12d}), 3.79-3.85 (1H, m, H_{11d}), 8.59-8.81 (1H, br s, H₁₄).

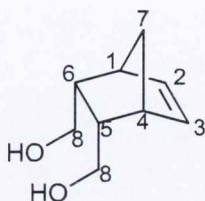
¹³C NMR (CDCl₃, 150 MHz): δ (ppm) 14.9 (C₁₀), 22.0 (C₅), 22.2 (C₁₂), 22.4 (C₁₂), 22.6 (C₁₃), 23.9 (C₉), 26.3 (C₆), 28.5 (C₈), 35.7 (C₇), 44.6 (C₁), 47.5 (q, C₃), 50.6 (C₁₁), 52.9 (C₄), 53.8 (C₁₁), 79.8 (q, C₂).

IR ν_{max} (cm⁻¹): 2933, 1458, 1388, 1113, 998.

HRMS: (m/z - ESI) Calculated for C₁₅H₂₈N (M+H)⁺ 222.2222, found 222.2226.

6.4 Synthesis of compounds described in chapter 3.

6.4.1 5-Norbornene-2-*endo*-3-*endo*-dimethanol. (103)



General Procedure M

To a suspension of LiAlH_4 (0.46 g, 12.2 mmol) in anhydrous THF (15 mL) was added slowly a solution of *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride **102** (1.00 g, 6.09 mmol) in THF (5 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was cooled to 0 °C and ground crystals of sodium sulfate decahydrate were added to remove the excess LiAlH_4 . The resulting slurry was filtered through a pad of celite and washed with THF (50 mL) and ethyl acetate (100 mL). The filtrate was dried over magnesium sulfate, filtered and concentrated to yield a pale yellow solid, which was further purified by column chromatography (85:15 hexane:ethyl acetate, $R_f = 0.2$) to yield 5-norbornene-2-*endo*-3-*endo*-dimethanol **103** as a white solid. (0.57g, 3.68 mmol, 58%) M.p. 84-86 °C (Lit.³¹⁹ 85-86 °C).

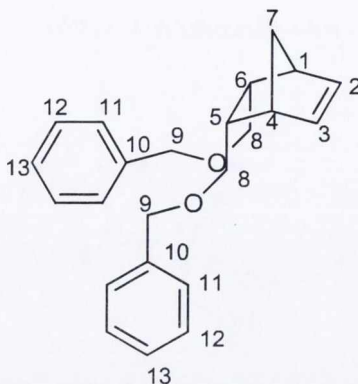
^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.39-1.47 (2H, m, H_{7a} , H_{7b}), 2.52-2.61 (2H, m, H_5 , H_6), 2.83 (2H, br s, H_1 , H_4), 3.36-3.45 (2H, m, 2H_{8a}), 3.69 (2H, dd, $J = 10.8, 2.7$ Hz, 2H_{8b}), 6.06 (2H, s, H_2 , H_3).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 45.1 (C_5 & C_6), 46.6 (C_1 & C_4), 50.0 (C_7), 63.6 (C_8), 134.9 (C_2 & C_3).

IR ν_{max} (cm^{-1}): 3233, 2939, 1347, 1018, 988, 888.

HRMS: (m/z - ESI) Calculated for $\text{C}_9\text{H}_{15}\text{O}_2$ ($\text{M}+\text{H}^+$) 155.1702, found 155.1076.

6.4.2 5,6-*endo*-Bis[(benzyloxy)methyl]bicyclo[2.2.1]hept-2-ene.²⁹⁷ (104)



General Procedure N

To a solution of 5-norbornene-2-*endo*-3-*endo*-dimethanol **103** (1.06 g, 6.87 mmol) in anhydrous THF (30 mL) was added sodium hydride (60% in mineral oil, 0.83 g, 20.6 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 1 hr upon which time benzyl bromide (2.50 mL, 20.6 mmol) was added and the reaction was stirred overnight. Water was added (20 mL) and the mixture was extracted with diethyl ether (2 x 30 mL). The combined organic layers were washed with brine (20 mL) and dried over magnesium sulfate. The solvent was filtered and removed at reduced pressure to yield a yellow oil which was purified by column chromatography (97:3 hexane:ethyl acetate, R_f = 0.25) to yield 5,6-*endo*-bis[(benzyloxy)methyl]bicyclo[2.2.1]hept-2-ene **104** as a clear colourless oil (1.18 g, 3.53 mmol, 51%).

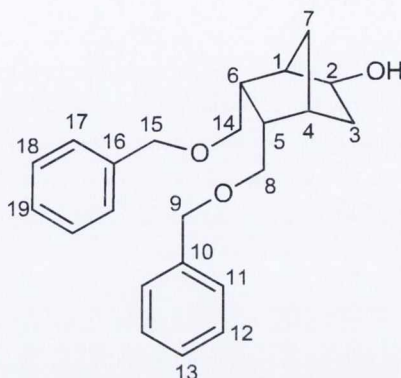
¹H NMR (CDCl₃, 400 MHz): δ (ppm) 1.35 (1H, app d, J = 8.3 Hz, H_{7a}), 1.50 (1H, app d, J = 8.3 Hz, H_{7b}), 2.52-2.59 (2H, m, H₅, H₆), 2.99 (2H, br s, H₁, H₄), 3.05-3.10 (2H, m, 2H_{8a}), 3.29-3.36 (2H, m, 2 H_{8b}), 4.43 (2H, d, J = 12.2 Hz, 2H_{9a}), 4.49 (2H, d, J = 12.2 Hz, 2H_{9b}), 6.07 (2H, s, H₃, H₂), 7.28-7.39 (10H, m, H₁₁, H₁₂, H₁₃).

¹³C NMR (CDCl₃, 100 MHz): δ (ppm) 41.9 (C₆ & C₅), 45.8 (C₁ & C₄), 47.5 (C₈), 49.4 (C₇), 73.0 (C₉), 127.5 (C₁₃), 127.6 (C₁₁), 128.3 (C₁₂), 135.3 (C₂ & C₃), 138.4 (q, C₁₀).

IR $\nu_{\max}$ (cm^{-1}): 2918, 2850, 1453, 1365, 1091, 1075, 1028.

HRMS: (m/z - ESI) Calculated for $\text{C}_{23}\text{H}_{27}\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$)⁺ 357.1831, found 357.1836.

6.4.3 5,6-*endo*-Bis[(benzyloxy)methyl]bicyclo[2.2.1]heptan-2-ol. (105)



General Procedure O

To a suspension of 5,6-*endo*-bis[(benzyloxy)methyl]bicyclo[2.2.1]hept-2-ene **104** (1.20 g, 3.59 mmol) and NaBH_4 (0.39 g, 10.8 mmol) in THF (40 mL) was added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.30 mL, 10.8 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 3 hrs, upon which time a solution of NaOH (4M, 1.80 mL, 7.18 mmol) and H_2O_2 (35% in H_2O , 1.00 mL, 10.8 mmol) were added. The mixture was stirred for 1 hr, diluted with water (100 mL), extracted with diethyl ether (2 x 50 mL), the combined organic layers were washed with brine (30 mL) and dried over magnesium sulfate. After filtration the volatiles were removed at reduced pressure to yield a yellow oil which was purified by column chromatography (85:15 hexane:ethyl acetate, R_f = 0.25) to yield 5,6-*endo*-bis[(benzyloxy)methyl]bicyclo[2.2.1]heptan-2-ol **105** as a clear colourless oil (0.49 g, 1.39 mmol, 39%).

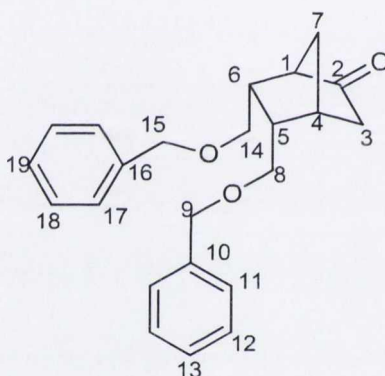
^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.15-1.22 (1H, m, H_{3a}), 1.32 (1H, app d, J = 10.1 Hz, H_{7a}), 1.74 (1H, app d, J = 10.1 Hz, H_{7b}), 1.95 (1H, ddd, J = 14.2, 6.9, 4.2 Hz, H_{3b}), 2.22-2.37 (3H, m, H_4 , H_5 , H_6), 2.39-2.42 (1H, m, H_1), 3.33 (1H, app t, J = 9.0 Hz, H_{14a}), 3.37 (1H, m, H_{8a}), 3.47-3.53 (2H, m, H_{8b} , H_{14b}), 4.43-4.52 (4H, m, H_{9a} , H_{9b} , H_{15a} , H_{15b}), 7.29-7.39 (10H, m, H_{11} , H_{12} , H_{13} , H_{17} , H_{18} , H_{19}).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 35.5 (C_3), 35.6 (C_7), 38.6 (C_5), 38.9 (C_6), 39.2 (C_1), 48.1 (C_4), 67.7 (C_8), 68.2 (C_{14}), 69.1 (C_2), 73.1 (C_9 , C_{15}), 127.5 (C_{13} , C_{19}), 127.61 (C_{13} , C_{19}), 127.63 (C_{11} , C_{17}), 127.7 (C_{11} , C_{17}), 128.3 (C_{12} , C_{18}), 128.4 (C_{12} , C_{18}), 138.4 (q, C_{10} , C_{16}), 138.5 (q, C_{10} , C_{16}).

IR ν_{max} (cm^{-1}): 3380, 2960, 1453, 1365, 1090, 1072, 984.

HRMS: (m/z - ESI) Calculated for $\text{C}_{23}\text{H}_{28}\text{O}_3\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 375.1936, found 375.1933.

6.4.4 5,6-*endo*-Bis[(benzyloxy)methyl]bicyclo[2.2.1]heptan-2-one. (106)



General Procedure P

To a suspension of PDC (6.83 g, 18.2 mmol) and celite (1.00 g) in anhydrous CH_2Cl_2 (90 mL) was added a solution of 5,6-*endo*-bis[(benzyloxy)methyl]bicyclo[2.2.1]heptan-2-ol **105** (3.20 g, 9.90 mmol) in CH_2Cl_2 (10 mL). The reaction was stirred at room temperature overnight (ca. 18 hrs) upon which time the reaction mixture was filtered through a pad of silica, washed with CH_2Cl_2 (100 mL) and dried over magnesium sulfate. After filtration the volatiles were removed at reduced pressure to yield a dark yellow oil which was purified by column chromatography (3:1 hexane:ethyl acetate, R_f = 0.31) to yield 5,6-*endo*-bis[(benzyloxy)methyl]bicyclo[2.2.1]heptan-2-one **106** as a clear colourless oil (1.91 g, 5.45 mmol, 55%).

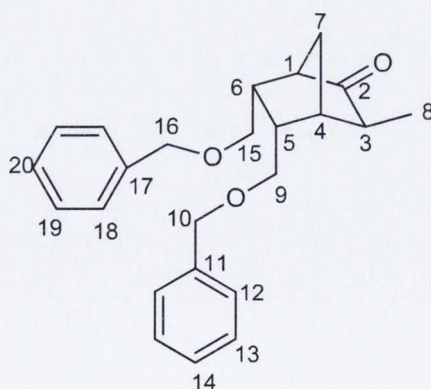
^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.73-1.82 (2H, m, H_{7a} , H_{7b}), 1.99 (1H, dd, $J = 18.1$, 4.6 Hz, H_{3a}), 2.11 (1H, dd, $J = 18.1$, 4.6 Hz, H_{3b}), 2.56-2.66 (2H, m, H_5 , H_6), 2.70-2.73 (1H, m, H_4), 2.78-2.81 (1H, m, H_1), 3.31-3.44 (3H, m, H_{8a} , H_{8b} , H_{14a}), 3.68 (1H, dd, $J = 5.8$, 9.5 Hz, H_{14b}), 4.40 (1H, d, $J = 11.8$ Hz, H_{9a}), 4.46 (1H, d, $J = 11.8$ Hz, H_{9b}), 4.46 (1H, d, $J = 11.8$ Hz, H_{15a}), 4.51 (1H, d, $J = 11.8$ Hz, H_{15b}), 7.28-7.40 (10H, m, H_{11} , H_{12} , H_{13} , H_{17} , H_{18} , H_{19}).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 37.9 (C_7), 38.0 (C_1), 39.5 (C_5), 39.8 (C_3), 39.9 (C_6), 54.2 (C_4), 67.8 (C_{14}), 68.9 (C_8), 73.3 (C_{15}), 73.4 (C_9), 127.61 ($\text{C}_{13}/\text{C}_{19}$), 127.67 ($\text{C}_{11}/\text{C}_{17}$), 127.7 ($\text{C}_{13}/\text{C}_{19}$), 127.8 ($\text{C}_{11}/\text{C}_{17}$), 128.4 ($\text{C}_{12}/\text{C}_{18}$), 128.5 ($\text{C}_{12}/\text{C}_{18}$), 138.1 (q, $\text{C}_{10}/\text{C}_{16}$), 138.2 (q, $\text{C}_{10}/\text{C}_{16}$), 216.6 (q, C_2).

IR ν_{max} (cm^{-1}): 2968, 2861, 1739, 1453, 1365, 1091, 1074, 998.

HRMS: (m/z - ESI) Calculated for $\text{C}_{23}\text{H}_{26}\text{O}_3\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 373.1780, found 373.1779.

6.4.5 5,6-endo-Bis[(benzyloxy)methyl]-3-methylbicyclo[2.2.1]heptan-2-one. (107)



Prepared as per general procedure A using 5,6-endo-

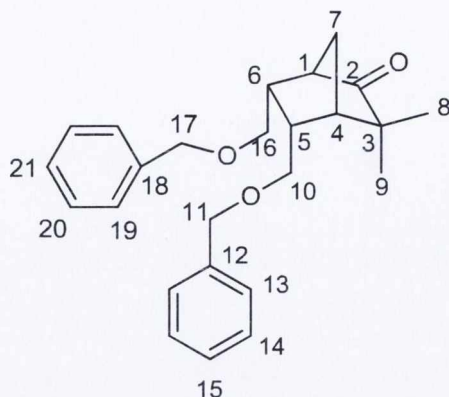
bis[(benzyloxy)methyl]bicyclo[2.2.1]heptan-2-one **106** (1.90 g, 5.42 mmol), diisopropylamine (0.98 mL, 7.05 mmol), *n*-butyllithium (2.5M solution in hexanes, 2.70 mL, 6.78 mmol), iodomethane (0.70 mL, 10.5 mmol) and THF (40 mL) to give an yellow oil which was purified by column chromatography (9:1 hexane:ethyl acetate, R_f = 0.24) to yield 5,6-*endo*-bis[(benzyloxy)methyl]-3-methylbicyclo[2.2.1]heptan-2-one **107** as a yellow oil (1.31 g, 3.59 mmol, 67%).

^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.09 (3H, d, J = 7.8 Hz, H_8), 1.62-1.68 (1H, m, H_{7a}), 1.94 (1H, app dt, J = 10.7, 1.4 Hz, H_{7b}), 2.05-2.11 (1H, m, H_3), 2.45-2.48 (1H, m, H_4), 2.53-2.65 (2H, m, H_5 , H_6), 2.65-2.68 (1H, m, H_1), 3.30-3.39 (2H, m, H_{15a} , H_{15b}), 3.39-3.49 (2H, m, H_{9a} , H_{9b}), 4.40-4.55 (4H, m, H_{10a} , H_{10b} , H_{16a} , H_{16b}), 7.29-7.41 (10H, m, H_{12} , H_{13} , H_{14} , H_{18} , H_{19} , H_{20}).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 14.1 (C_8), 35.1 (C_7), 39.6 (C_5), 40.6 (C_6), 41.6 (C_3), 44.2 (C_4), 54.4 (C_1), 67.5 (C_9), 69.1 (C_{15}), 73.2 (C_{10}), 73.4 (C_{16}), 127.62 ($\text{C}_{14}/\text{C}_{20}$), 127.65 ($\text{C}_{12}/\text{C}_{18}$), 127.7 ($\text{C}_{14}/\text{C}_{20}$), 127.80 ($\text{C}_{12}/\text{C}_{18}$), 128.3 ($\text{C}_{13}/\text{C}_{19}$), 128.4 ($\text{C}_{13}/\text{C}_{19}$), 138.1 (q, C_{17}), 138.3 (q, C_{11}), 219.5 (q, C_2).

IR ν_{max} (cm^{-1}): 2871, 1739, 1454, 1366, 1091, 1027, 909.

HRMS: (m/z - ESI) Calculated for $\text{C}_{24}\text{H}_{28}\text{O}_3\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 387.1936, found 378.1945.

6.4.6 5,6-*endo*-Bis[(benzyloxy)methyl]-3,3-dimethylbicyclo[2.2.1]heptan-2-one. (108)

Prepared as per general procedure B using 5,6-*endo*-bis[(benzyloxy)methyl]-3-methylbicyclo[2.2.1]heptan-2-one **107** (1.30 g, 3.57 mmol), sodium bis(trimethylsilyl)amide (1.9M in THF, 3.80 mL, 7.14 mmol), iodomethane (0.50 mL, 7.14 mmol) and anhydrous THF (30 mL) to yield a yellow oil which was purified by column chromatography (9:1 hexane: ethyl acetate, R_f = 0.31) to yield 5,6-*endo*-bis[(benzyloxy)methyl]-3,3-dimethylbicyclo[2.2.1]heptan-2-one **108** as a pale yellow oil (0.93 g, 2.46 mmol, 69%).

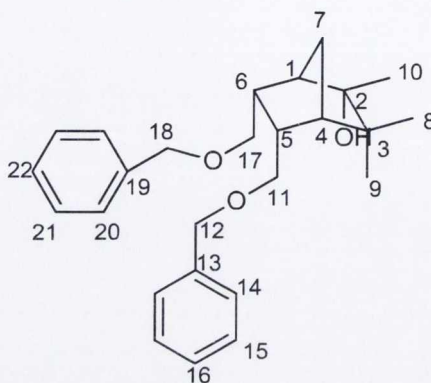
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.05 (3H, s, H_9), 1.12 (3H, s, H_8), 1.62 (1H, app d, J = 10.4 Hz, H_{7a}), 2.05 (1H, app d, J = 10.4 Hz, H_{7b}), 2.39-2.42 (1H, m, H_4), 2.68-2.73 (2H, m, H_5 , H_6), 2.78-2.80 (1H, m, H_1), 3.29-3.35 (1H, m, H_{16a}), 3.47-3.51 (1H, m, H_{16b}), 3.56-3.61 (1H, m, H_{10a}), 3.68-3.73 (1H, m, H_{10b}), 4.39-4.51 (4H, m, H_{17a} , H_{17b} , H_{11a} , H_{11b}), 7.26-7.39 (10H, m, H_{13} , H_{14} , H_{15} , H_{19} , H_{20} , H_{21}).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 22.0 (C_9), 26.4 (C_8), 36.7 (C_7), 39.7 (C_5), 42.7 (C_6), 48.3 (q, C_3), 49.8 (C_4), 54.5 (C_1), 69.4 (C_{10}), 69.7 (C_{16}), 73.2 ($\text{C}_{11/17}$), 73.4 ($\text{C}_{11/17}$), 127.4 ($\text{C}_{15/21}$), 127.5 ($\text{C}_{15/21}$), 127.67 ($\text{C}_{13/19}$), 127.7 ($\text{C}_{13/19}$), 128.2 ($\text{C}_{14/20}$), 128.3 ($\text{C}_{14/20}$), 138.18 (q, $\text{C}_{12/18}$), 138.2 (q, $\text{C}_{12/18}$),

IR ν_{max} (cm^{-1}): 2871, 1737, 1454, 1365, 1093, 1027, 910.

HRMS: (m/z - ESI) Calculated for $\text{C}_{25}\text{H}_{30}\text{O}_3\text{Na}$ ($\text{M}+\text{Na}$)⁺ 401.2093, found 401.2094.

6.4.7 5,6-endo-Bis[(benzyloxy)methyl]-2,3,3-trimethylbicyclo[2.2.1]heptan-2-ol. (109)



Prepared as per general procedure C using 5,6-endo-bis[(benzyloxy)methyl]-3,3-dimethylbicyclo[2.2.1]heptan-2-one **108** (0.90 g, 2.38 mmol), methylmagnesium bromide (3M in THF, 2.40 mL, 7.13 mmol) and anhydrous THF (30 mL) at room temperature with a reaction time of 14 hrs to yield a pale yellow oil which was purified by column chromatography (9:1 hexane:ethyl acetate, R_f = 0.4) to yield 5,6-endo-bis[(benzyloxy)methyl]-2,3,3-trimethylbicyclo[2.2.1]heptan-2-ol **109** as a clear colourless oil (0.69 g, 1.75 mmol, 74%).

^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 0.90 (3H, s, H_9), 0.93 (3H, s, H_8), 1.21 (3H, s, H_{10}), 1.33 (1H, app dt, J = 10.7, 1.5 Hz, H_{7a}), 1.74-1.77 (1H, m, H_4), 1.80 (1H, app d, J = 10.7 Hz, H_{7b}), 2.72-2.35 (2H, m, H_1 , H_5), 2.50-2.75 (1H, m, H_6), 3.63-3.72 (2H, m, H_{11a} , H_{7b}), 3.75-3.83 (2H, m, H_{11b} , H_{17b}), 4.52 (H, d, J = 13.6 Hz, H_{12a}), 4.55 (1H, d, J = 13.6 Hz, H_{12b}), 4.74 (2H, s, H_{18}), 7.29-7.43 (10H, m, H_{14} , H_{15} , H_{16} , H_{20} , H_{21} , H_{22}).

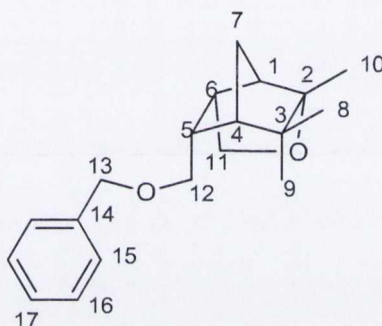
^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 20.4 (C_{10}), 22.2 (C_9), 27.4 (C_8), 34.6 (C_7), 40.7 (C_6), 45.7 (q, C_3), 45.9 (C_5), 50.0 (C_4), 54.3 (C_1),

65.6 (C₁₈), 67.1 (C₁₇), 69.7 (C₁₁), 73.2 (C₁₂), 88.9 (q, C₂), 127.0 (C₂₀), 127.6 (C₂₂), 127.7 (C₁₆), 127.8 (C₁₄), 128.4 (C₁₅), 128.6 (C₂₁), 138.7 (q, C₁₃), 140.8 (q, C₁₉).

IR $\nu_{\max}$ (cm⁻¹): 3418, 2927, 1454, 1369, 1070, 1027, 999.

HRMS: (m/z - ESI) Calculated for C₂₆H₃₄O₃Na (M+Na)⁺ 417.2406, found 417.2403.

6.4.8 7-[(Benzyloxy)methyl]-6,6a-trimethylhexahydro-2H-3,5-methanocyclopenta[b]furan. (111)



Prepared as per general procedure D 5,6-*endo*-bis[(benzyloxy)methyl]-2,3,3-trimethylbicyclo[2.2.1]heptan-2-ol **109** (0.44 g, 1.12 mmol), 55% H₂SO₄ (2 mL), NaN₃ (0.51 g, 7.81 mmol) and CHCl₃ (20 mL) with a reaction time of 3 hrs to yield a yellow oil which was purified by column chromatography (9:1 hexane:ethyl acetate, R_f = 0.5) to yield **111** as a clear colourless oil (0.24 g, 0.82 mmol, 71%).

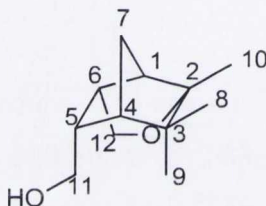
¹H NMR (CDCl₃, 400 MHz): δ (ppm) 0.88 (3H, s, H₉), 0.92 (3H, s, H₈), 1.19 (3H, s, H₁₀), 1.31 (1H, app dt, J = 10.5, 1.3 Hz, H_{7a}), 1.73-1.76 (1H, m, H₄), 1.79 (1H, app d, J = 10.5 Hz, H_{7b}), 2.27-2.35 (2H, m H₁, H_{5a}), 2.49-2.56 (1H, m, H₆), 3.62-3.71 (2H, m, H_{11a}, H_{12a}), 3.74-3.83 (2H, m, H_{11b}, H_{12b}), 4.52 (1H, d, J = 15.7 Hz, H_{13a}), 4.54 (1H, d, J = 15.7 Hz, H_{13b}), 7.28-7.39 (5H, m, H₁₅, H₁₆, H₁₇).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 20.4 (C_{10}), 22.2 (C_9), 27.3 (C_8), 34.7 (C_7), 40.7 (C_6), 45.6 (q, C_3), 45.9 (C_5), 49.9 (C_4), 54.2 (C_1), 67.0 (C_{11}), 69.6 (C_{12}), 73.2 (C_{13}), 88.9 (q, C_2), 127.6 (C_{17}), 127.8 (C_{15}), 128.4 (C_{16}), 138.6 (q, C_{14}).

IR ν_{max} (cm^{-1}): 2928, 1454, 1372, 1092, 1024, 1053, 870.

HRMS: (m/z - ESI) Calculated for $\text{C}_{19}\text{H}_{26}\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 309.1831, found 309.1821.

6.4.9 (6,6,6a-Trimethylhexahydro-2H-3,5-methanocyclopenta[b]furan-7-yl)methanol. (112)



Prepared as per general procedure E using 5,6-*endo*-bis[(benzyloxy)methyl]-2,3,3-trimethylbicyclo[2.2.1]heptan-2-ol **111** (3.48 g, 8.82 mmol), methanol (100 mL) and palladium on charcoal (0.35 g, 10% w/w) with a reaction time of 24 hrs under a hydrogen atmosphere to yield **112** as a clear colourless oil (1.25 g, 6.37 mmol, 72%).

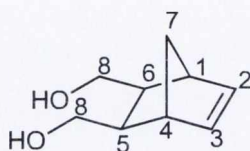
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 0.95 (6H, s, H_8 , H_9), 1.23 (3H, s, H_{10}), 1.34 (1H, app d, $J = 10.7$ Hz, H_{7a}), 1.77 (1H, br s, H_4), 1.83 (1H, app d, $J = 10.7$ Hz, H_{7b}), 2.16-2.21 (1H, m, H_5), 2.34-2.36 (1H, m, H_1), 2.52-2.58 (1H, m, H_6), 3.80-3.83 (2H, m, H_{12a} , H_{12b}), 3.87 (1H, dd, $J = 5.6, 10.7$ Hz, H_{11a}), 4.02 (1H, app t, $J = 10.7$ Hz, H_{11b}).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 20.3 (C_{10}), 22.1 (C_9), 27.3 (C_8), 34.7 (C_7), 40.2 (C_6), 45.7 (q, C_3), 48.7 (C_5), 49.5 (C_4), 54.2 (C_1), 62.1 (C_{11}), 66.7 (C_{12}), 88.9 (q, C_2).

IR $\nu_{\max}$ (cm^{-1}): 3405, 2952, 2871, 1373, 1090, 1005.

HRMS: (m/z - ESI) Calculated for $\text{C}_{12}\text{H}_{21}\text{O}_2$ ($\text{M}+\text{H}$)⁺ 197.1542, found 197.1548.

6.4.10 5-Norbornene-2-*exo*-3-*exo*-dimethanol. (114)



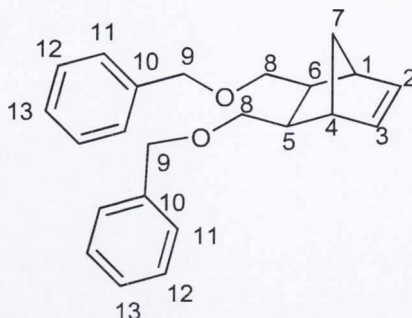
Prepared as per general procedure M using *cis*-5-norbornene-*exo*-2,3-dicarboxylic anhydride **113** (4.00 g, 24.4 mmol), LiAlH_4 (2.08 g, 54.8 mmol) in anhydrous THF (100 mL) with a reaction time of 18 hrs. The resulting slurry was filtered through a pad of celite and washed with a 1:9 methanol:ethyl acetate solution (100 mL). The filtrate was dried over magnesium sulfate, filtered and concentrated to yield a pale yellow solid, which was purified by column chromatography (100% ethyl acetate, R_f = 0.5) to yield 5-norbornene-2-*exo*-3-*exo*-dimethanol **114** as a colourless solid (3.12 g, 20.2 mmol, 83%). M.p. = 52 °C (Lit.³²⁰ 52 °C).

^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.29 (1H, app d, J = 8.6 Hz, H_{7a}), 1.39 (1H, app d, J = 8.6 Hz, H_{7b}), 1.83-1.92 (2H, m, H_5 , H_6), 2.57 (2H, br s, H_1 , H_4), 3.80 (4H, m, 2H_{8a} , 2H_{8b}), 6.22 (2H, m, H_2 , H_3).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 43.6 (C_5 , C_6), 43.9 (C_7), 45.9 (C_1 , C_4), 65.1 (C_8), 137.5 (C_2 , C_3).

IR $\nu_{\max}$ (cm^{-1}): 3281, 2957, 2871, 1455, 1016, 968.

HRMS: (m/z - ESI) Calculated for $\text{C}_9\text{H}_{13}\text{O}_2$ ($\text{M}-\text{H}$)⁻ 153.0916 found 153.0914.

6.4.11 5,6-*exo*-Bis[(benzyloxy)methyl]bicyclo[2.2.1]hept-2-ene.³²⁰ (**115**)

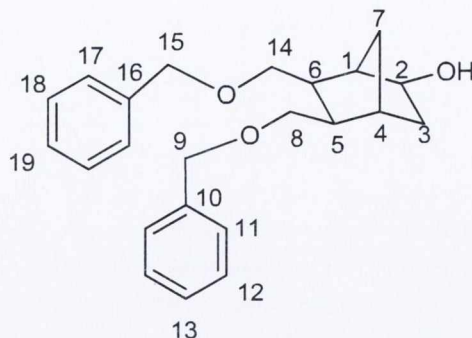
Prepared as per general procedure N using 5-norbornene-2-*exo*-3-*exo*-dimethanol **114** (3.10 g, 20.1 mmol), sodium hydride (60% in mineral oil, 2.41 g, 60.3 mmol), benzyl bromide (7.20 mL, 60.3 mmol) and anhydrous THF (50 mL) with a reaction time of 16 hrs to yield a yellow oil which was purified by column chromatography (97:3 hexane: ethyl acetate, R_f = 0.35) to yield 5,6-*exo*-bis[(benzyloxy)methyl]bicyclo[2.2.1]hept-2-ene **115** as a clear colourless oil (4.87 g, 14.6 mmol, 73%).

^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.28-1.32 (1H, m, H_{7a}), 1.48 (1H, app d, J = 9.3 Hz, H_{7b}), 1.84-1.89 (2H, m, H_5 , H_6), 2.81-2.84 (2H, m, H_1 , H_4), 3.34-3.40 (2H, m, 2H_{8a}), 3.64-3.69 (2H, m, 2H_{8b}), 4.49 (2H, d, J = 13.3 Hz, 2H_{9a}), 4.52 (2H, d, J = 13.3 Hz, 2H_{9b}), 6.18 (2H, m, J = 1.8 Hz, H_2 , H_3), 7.30-7.40 (10H, m, H_{11} , H_{12} , H_{13}).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 40.7 (C_5 & C_6), 42.8 (C_7), 44.9 (C_1 & C_4), 71.8 (C_8), 73.2 (C_9), 127.5 (C_{13}), 127.7 (C_{11}), 128.4 (C_{12}), 137.4 (C_2 & C_3), 138.6 (q, C_{10}).

IR ν_{max} (cm^{-1}): 2955, 2854, 1453, 1364, 1073, 947.

HRMS: (m/z - ESI) Calculated for $\text{C}_{23}\text{H}_{26}\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$)⁺ 357.1831 found 357.1824.

6.4.12 5,6-*exo*-Bis[(benzyloxy)methyl]bicyclo[2.2.1]heptan-2-ol. (**116**)

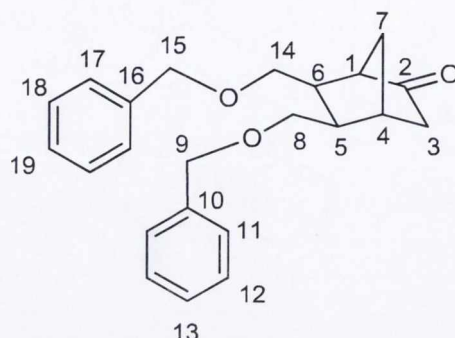
Prepared as per general procedure O using 5,6-*exo*-bis[(benzyloxy)methyl]bicyclo[2.2.1]hept-2-ene **115** (4.00 g, 11.9 mmol), NaBH₄ (0.35 g, 8.98 mmol), BF₃·Et₂O (2.25 mL, 17.9 mmol), a solution of NaOH (4M, 2.25 mL, 8.98 mmol), H₂O₂ (35% in H₂O, 1.75 mL, 17.9 mmol) and anhydrous THF (80 mL). This was purified by column chromatography (3:2 hexane:ethyl acetate, R_f = 0.35) to yield 5,6-*exo*-bis[(benzyloxy)methyl]bicyclo[2.2.1]heptan-2-ol **116** as a clear colourless oil (3.46 g, 9.82 mmol, 82%).

¹H NMR (CDCl₃, 600 MHz): δ (ppm) 1.38-1.44 (2H, m, H_{3a}, H_{7a}), 1.46-1.51 (1H, m, H_{7b}), 1.72-1.80 (1H, m, H_{3b}), 1.80-1.88 (2H, m, H₅, H₆), 2.20 (1H, br s, H₁), 2.29-2.32 (1H, m, H₄), 3.29-3.36 (2H, m, H_{8a}, H_{14a}), 3.47-3.57 (2H, m, H_{8b}, H_{14b}), 3.89 (1H, app d, *J* = 6.9 Hz, H₂), 4.46-4.49 (4H, m, H_{9a}, H_{9b}, H_{15a}, H_{15b}), 7.29-7.39 (10H, m, H₁₁, H₁₂, H₁₃, H₁₇, H₁₈, H₁₉).

¹³C NMR (CDCl₃, 150 MHz): δ (ppm) 29.8 (C₇), 38.9 (C₄), 40.3 (C₆), 42.1 (C₃), 44.1 (C₅), 48.2 (C₁), 69.9 (C₈/C₁₄), 70.4 (C₈/C₁₄), 73.1 (C₉/C₁₅), 73.2 (C₉/C₁₅), 74.7 (C₂), 127.5 (C₁₃/C₁₉), 127.55 (C₁₃/C₁₉), 127.58 (C₁₁/C₁₇), 127.7 (C₁₁/C₁₇), 128.4 (C₁₂ & C₁₈), 138.4 (q, C₁₀/C₁₆), 138.5 (q, C₁₀/C₁₆).

IR ν_{max} (cm⁻¹): 3380, 2858, 1453, 1366, 1069, 1027.

HRMS: (*m/z* - ESI) Calculated for C₂₃H₂₈O₃Na (M+Na)⁺ 375.1936, found 375.1938.

6.4.13 5,6-*exo*-Bis[(benzyloxy)methyl]bicyclo[2.2.1]heptan-2-one. (117)

Prepared as per general procedure P using 5,6-*exo*-bis[(benzyloxy)methyl]bicyclo[2.2.1]heptan-2-ol **116** (3.40 g, 9.65 mmol), PDC (5.76 g, 15.3 mmol), celite (5.00 g) in anhydrous CH_2Cl_2 (100 mL) with a reaction time of 20 hrs. The resulting pale yellow oil was purified by column chromatography (9:1 hexane: ethyl acetate, $R_f = 0.47$) to yield 5,6-*exo*-bis[(benzyloxy)methyl]bicyclo[2.2.1]heptan-2-one **117** as a clear colourless oil (3.22 g, 9.19 mmol, 95%)

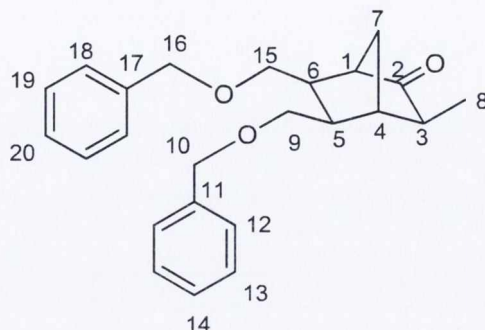
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.58-1.61 (1H, m, H_{7a}), 1.91-1.98 (2H, m, H_{3a} , H_{7b}), 2.11-2.33 (3H, m, H_{3b} , H_5 , H_6), 2.61 (1H, br s, H_1), 2.70-2.73 (1H, m, H_4), 3.45-3.51 (2H, m, H_{8a} , H_{14a}), 3.60 (1H, dd, $J = 9.5$, 6.1 Hz, H_{14b}), 3.66 (1H, dd, $J = 9.5$, 5.6 Hz, H_{8b}), 4.46 (2H, d, $J = 4.6$ Hz, H_{15}), 4.5-4.51 (2H, m, H_9), 7.29-7.39 (10H, m, H_{11} , H_{12} , H_{13} , H_{17} , H_{18} , H_{19}).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 33.2 (C_7), 38.9 (C_4), 39.2 (C_6), 43.9 (C_5), 45.5 (C_3), 53.7 (C_1), 69.2 (C_{14}), 70.1 (C_8), 73.0 (C_{15}), 73.3 (C_9), 127.6 ($\text{C}_{11}/\text{C}_{17}$), 127.65 ($\text{C}_{11}/\text{C}_{17}$), 127.65 ($\text{C}_{13}/\text{C}_{19}$), 127.7 ($\text{C}_{13}/\text{C}_{19}$), 128.4 ($\text{C}_{12}/\text{C}_{18}$), 128.5 ($\text{C}_{12}/\text{C}_{18}$), 138.2 (q, $\text{C}_{10}/\text{C}_{16}$), 138.3 (q, $\text{C}_{10}/\text{C}_{16}$), 217.7 (q, C_2).

IR ν_{max} (cm^{-1}): 2922, 2859, 1743, 1453, 1366, 1089, 1027.

HRMS: (m/z - ESI) Calculated for $C_{23}H_{26}O_3Na$ ($M+Na$)⁺ 373.1780, found 373.1795.

6.4.14 5,6-*exo*-Bis[(benzyloxy)methyl]-3-methylbicyclo[2.2.1]heptan-2-one. (118)



Prepared as per general procedure A using 5,6-*exo*-bis[(benzyloxy)methyl]bicyclo[2.2.1]heptan-2-one **117** (2.80 g, 7.99 mmol), diisopropylamine (1.45 mL, 10.4 mmol), *n*-butyllithium (2.5M solution in hexanes, 4.00 mL, 10.00 mmol), iodomethane (1.00 mL, 16.1 mmol) and THF (50 mL) to give a yellow oil which was purified by column chromatography (95:5 hexane:ethyl acetate, R_f = 0.35) to yield 5,6-*exo*-bis[(benzyloxy)methyl]-3-methylbicyclo[2.2.1]heptan-2-one **118** as a pale yellow oil (1.60 g, 4.39 mmol, 55%).

¹H NMR ($CDCl_3$, 600 MHz): δ (ppm) 1.10 (3H, d, J = 7.7 Hz, H_8), 1.73 (1H, app d, J = 11.2 Hz, H_{7a}), 1.84 (1H, app d, J = 11.2 Hz, H_{7b}), 1.92-1.98 (1H, m, H_3), 2.19-2.26 (1H, m, H_5), 2.26-2.32 (1H, m, H_6), 2.39 (1H, br s, H_4), 2.55 (H, br s, H_1), 3.45-3.50 (2H, m, H_{9a} , H_{15a}), 3.59 (1H, dd, J = 9.4, 6.3 Hz, H_{15b}), 3.66 (1H, dd, J = 9.4, 5.6 Hz, H_{9b}), 4.43-4.54 (4H, m, H_{10} , H_{16}), 7.29-7.40 (10H, m, H_{12} , H_{13} , H_{14} , H_{18} , H_{19} , H_{20})

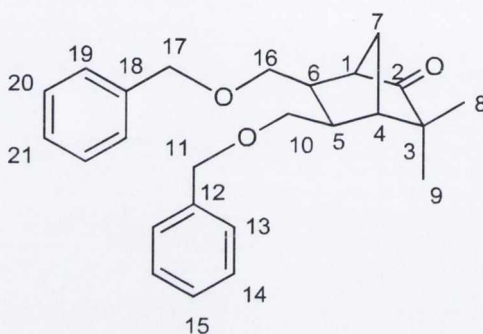
¹³C NMR ($CDCl_3$, 150 MHz): δ (ppm) 14.0 (C_8), 29.9 (C_7), 38.7 (C_6), 44.5 (C_5), 44.9 (C_4), 48.5 (C_3), 53.2 (C_1), 69.1 (C_{15}), 69.9 (C_9), 72.9 (C_{16}), 73.2 (C_{10}), 127.43 (C_{14}/C_{20}), 127.44 (C_{12}/C_{18}), 127.51 (C_{14}/C_{20}), 127.52 (C_{12}/C_{18}),

128.2 (C₁₃/C₁₉), 128.3 (C₁₃/C₁₉), 138.2 (q, C₁₁/C₁₇), 138.3 (q, C₁₁/C₁₇), 204.5 (q, C₂).

IR $\nu_{\max}$ (cm⁻¹): 2960, 2859, 1743, 1453, 1366, 1088, 1027.

HRMS: (*m/z* - ESI) Calculated for C₂₄H₂₈O₃Na (M+Na)⁺ 387.1936 found, 387.1935.

6.4.15 5,6-*exo*-Bis[(benzyloxy)methyl]-3,3-dimethylbicyclo[2.2.1]heptan-2-one. (119)



Prepared as per general procedure B using 5,6-*exo*-bis[(benzyloxy)methyl]-3-methylbicyclo[2.2.1]heptan-2-one **118** (1.56 g, 4.29 mmol), sodium bis(trimethylsilyl)amide (1.9M in THF, 3.40 mL, 6.46 mmol), iodomethane (0.55 mL, 8.58 mmol) and anhydrous THF (50 mL) to give a yellow oil which was purified by column chromatography (95:5 hexane:ethyl acetate, *R_f* = 0.23) to yield 5,6-*exo*-bis[(benzyloxy)methyl]-3,3-dimethylbicyclo[2.2.1]heptan-2-one **119** as a pale yellow oil (1.11 g, 2.93 mmol, 68%).

¹H NMR (CDCl₃, 600 MHz): δ (ppm) 1.07 (3H, s, H₉), 1.10 (3H, s, H₈), 1.84 (2H, m, H_{7a}, H_{7b}), 2.19-2.29 (2H, m, H₄, H₆), 2.52-2.60 (2H, m, H₁, H₅), 3.44-3.51 (2H, m, H_{10a}, H_{16a}), 3.59 (1H, dd, *J* = 9.4, 6.8 Hz, H_{16b}), 3.66 (1H, dd, *J* = 9.4, 6.2 Hz, H_{10b}), 4.44-4.52 (4H, m, H_{11a}, H_{11b}, H_{17a}, H_{17b}), 7.26-7.41 (10H, m, H₁₃, H₁₄, H₁₅, H₁₉, H₂₀, H₂₁).

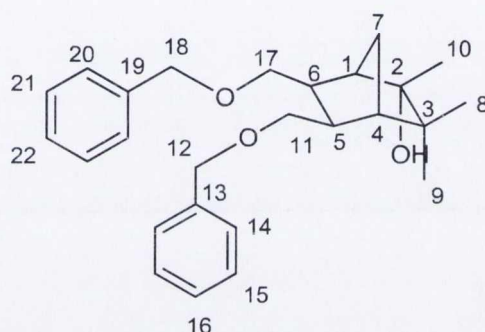
¹³C NMR (CDCl₃, 150 MHz): δ (ppm) 21.4 (C₉), 23.6 (C₈), 30.5 (C₇), 38.7 (C₅), 39.7 (C₆), 47.3 (q, C₃), 49.8 (C₄), 54.0 (C₁), 69.4 (C₁₆), 70.6 (C₁₀), 73.0 (C₁₇), 73.2 (C₁₁), 127.59

(C₁₅/C₂₁), 127.60 (C₁₃/C₁₉), 127.65 (C₁₅/C₂₁),
 127.67 (C₁₃/C₁₉), 128.4 (C₁₄/C₂₀), 128.5 (C₁₄,
 C₂₀), 138.2 (q, C₁₂/C₁₈), 138.4 (q, C₁₂/C₁₈),
 222.5 (q, C₂).

IR $\nu_{\max}$ (cm⁻¹): 2967, 2863, 1740, 1453, 1366, 1089, 1071, 1027.

HRMS: (m/z - ESI) Calculated for C₂₅H₃₀O₃Na (M+Na)⁺ 401.2093, found 401.2083.

6.4.16 5,6-*exo*-Bis[(benzyloxy)methyl]-2,3,3-trimethylbicyclo[2.2.1]heptan-2-ol. (120)



Prepared as per general procedure C using 5,6-*exo*-bis[(benzyloxy)methyl]-3,3-dimethylbicyclo[2.2.1]heptan-2-one **119** (1.10 g, 2.91 mmol), a solution of methylmagnesium bromide (3M in THF, 3.00 mL, 9.00 mmol) and anhydrous THF (30 mL) at room temperature with a reaction time of 20 hrs to yield a pale yellow oil which was purified by column chromatography (9:1 hexane:ethyl acetate, R_f = 0.28) to yield 5,6-*exo*-bis[(benzyloxy)methyl]-2,3,3-trimethylbicyclo[2.2.1]heptan-2-ol **120** as a clear colourless oil (0.91 g, 2.31 mmol, 79%).

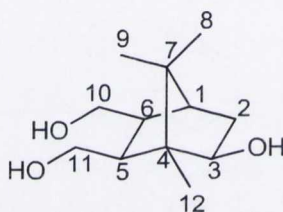
¹H NMR (CDCl₃, 400 MHz): δ (ppm) 0.99 (3H, s, H₉), 1.01 (3H, s, H₈), 1.27 (3H, s, H₁₀), 1.41 (1H, app d, J = 10.8 Hz, H_{7a}), 1.52-1.58 (1H, m, H_{7b}), 1.75 (1H, br s, H₄), 1.94 (1H, br s, H₁), 2.51 (1H, m, H₅), 2.77 (1H, m, H₆), 3.30-3.37 (2H, m, H_{11a}, H_{17a}), 3.52-3.58 (2H, m, H_{11b}, H_{17b}), 4.43-4.51 (4H, m, H_{12a}, H_{12b}, H_{18a}, H_{18b}), 7.28-7.39 (10H, m, H₁₄, H₁₅, H₁₆, H₂₀, H₂₁, H₂₂).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 21.4 (C_9), 26.6 (C_{10}), 27.1 (C_8), 30.0 (C_7), 35.8 (C_6), 38.5 (C_5), 42.5 (q, C_3), 53.3 (C_4), 54.7 (C_1), 70.7 ($\text{C}_{11}/\text{C}_{17}$), 71.0 ($\text{C}_{11}/\text{C}_{17}$), 72.9 ($\text{C}_{12}/\text{C}_{18}$), 73.0 ($\text{C}_{12}/\text{C}_{18}$), 78.2 (q, C_2), 127.5 (C_{16} & C_{22}), 127.6 ($\text{C}_{14}/\text{C}_{20}$), 127.7 ($\text{C}_{14}/\text{C}_{20}$), 128.3 (C_{15} & C_{21}).

IR ν_{max} (cm^{-1}): 3448, 2955, 1453, 1366, 1085, 1071, 1027.

HRMS: (m/z - ESI) Calculated for $\text{C}_{26}\text{H}_{33}\text{O}_3$ ($\text{M}-\text{H}$) $^-$ 393.2430, found 393.2424.

6.4.17 3-Hydroxy-4,7,7-trimethyl-bicyclo[2.2.1]heptane-5,6-diyl)dimethanol. (**121**)



Prepared as per general procedure D using 5,6-*exo*-bis[(benzyloxy)methyl]-2,3,3-trimethylbicyclo[2.2.1]heptan-2-ol **120** (50.0 mg, 0.13 mmol), NaN_3 (200 mg, 3.08 mmol), 60% H_2SO_4 (0.3 mL) and CHCl_3 (10 mL) to yield 3-hydroxy-4,7,7-trimethyl-bicyclo[2.2.1]heptane-5,6-diyl)dimethanol **121** as a colourless oil after purification by column chromatography (1:1 hexane: ethyl acetate, $R_f = 0.1$) (18.0 mg, 0.08 mmol, 66%).

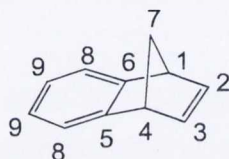
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 0.85 (3H, s, H_8/H_9), 0.92 (3H, s, H_{12}), 0.97 (3H, s, H_8/H_9), 1.18-1.22 (1H, m, H_{2a}), 1.58-1.61 (1H, m, H_1), 1.86-1.92 (1H, m, H_{2b}), 2.02-2.06 (1H, m, H_5), 2.44-2.51 (1H, m, H_6), 3.62-3.66 (1H, m, H_{10a}), 3.68-3.75 (3H, m, H_{10b} , H_{11a} , H_{11b}), 3.90 (1H, app d, $J = 7.8$ Hz, H_3).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 12.1 (C_{12}), 20.8 (C_8/C_9), 20.9 (C_8/C_9), 32.7 (C_2), 41.9 (C_6), 44.8 (C_1), 45.2 (C_5), 47.5 (q, C_7), 59.0 (q, C_4), 62.0 (C_{10}), 67.2 (C_{11}), 85.7 (C_3).

IR ν_{max} (cm^{-1}): 3391, 2930, 2871, 1260, 1015, 801.

HRMS: (m/z - ESI) Calculated for $\text{C}_{12}\text{H}_{21}\text{O}_3$ (M-H^-) 213.1491, found 213.1497.

6.4.18 1,4-Dihydro-1,4-methanonaphthalene.²⁹⁸ (126)



A 2-necked RBF fitted with a reflux condenser was charged with a solution of freshly distilled cyclopentadiene (9.20 mL, 109.4 mmol) in anhydrous THF (60 mL). The reaction mixture was warmed to 50 °C at which time solutions of anthranillic acid (5.00 g, 36.5 mmol) in THF (10 mL) and isobutyl nitrite (5.90 mL, 43.7 mmol) in THF (10 mL) were added slowly at a rate to maintain a gentle reflux. The reaction mixture continued to reflux for a further hour. Once cooled the volatiles were removed at reduced pressure and the residue was re-dissolved in diethyl ether (40 mL) and a saturated solution of sodium bicarbonate (20 mL). The mixture was extracted with diethyl ether (2 x 40 mL), dried over magnesium sulfate and filtered before the volatiles were removed at reduced pressure to yield a brown oil which was further purified by column chromatography (99:1 hexane:ethyl acetate, R_f = 0.87) to yield 1,4-dihydro-1,4-methanonaphthalene **126** as a clear colourless oil (3.82g, 26.9 mmol, 74%).

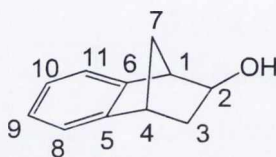
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 2.28 (1H, app d, J = 7.1 Hz, H_{7a}), 2.35 (1H, dt, J = 7.1, 1.6 Hz, H_{7b}), 3.91-3.94 (2H, m, H_1 , H_4), 6.81-6.84 (2H, m, H_2 , H_3), 6.96 (1H, d, J = 5.2 Hz, H_9), 6.97 (1H, d, J = 5.2 Hz, H_9) 7.25 (1H, d, J = 5.2 Hz, H_8), 7.26 (1H, d, J = 5.2 Hz, H_8).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 50.3 (C_1 & C_4), 70.3 (C_7), 121.6 (C_8), 124.3 (C_9), 143.5 (C_2 & C_3), 151.8 (q, C_5 & C_6).

IR $\nu_{\max}$ (cm^{-1}): 3067, 2981, 2934, 1454, 1303, 1006, 829.

HRMS: (m/z - EI) Calculated for $\text{C}_{11}\text{H}_{10}$ (M^+) 142.0783, found 142.0780.

6.4.19 1,2,3,4-Tetrahydro-1,4-methanonaphthalen-2-ol. (**127**)



Prepared as per general procedure O using 1,4-dihydro-1,4-methanonaphthalene **126** (3.24 g, 22.8 mmol), NaBH_4 (0.89 g, 22.8 mmol), $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (4.30 mL, 34.2 mmol), a solution of NaOH (4M, 5.70 mL, 22.8 mmol), H_2O_2 (35% in H_2O , 3.30 mL, 34.2 mmol) and anhydrous THF (80 mL). The product was purified by column chromatography (9:1 hexane:ethyl acetate, $R_f = 0.28$) to yield 1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-ol **127** as a white solid (2.16 g, 13.5 mmol, 59%). M.p. = 68-70 °C (Lit.³²¹ 71-74 °C).

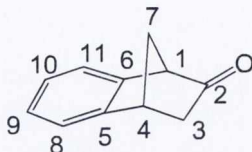
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.61-1.67 (1H, m, H_{3a}), 1.84 (1H, ddd, $J = 12.7$, 6.5, 2.7 Hz, H_{3b}), 1.91-1.95 (1H, m, H_{7a}), 2.12 (1H, app d, $J = 9.2$ Hz, H_{7b}), 3.27 (1H, s, H_1), 3.33-3.36 (1H, m, H_4), 4.01 (1H, app d, $J = 6.7$ Hz, H_2), 7.06-7.10 (2H, m, H_9 , H_{10}), 7.14-7.17 (1H, m, H_8), 7.21-7.23 (1H, m, H_{11}).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 39.9 (C_3), 43.0 (C_4), 46.0 (C_7), 52.4 (C_1), 73.7 (C_2), 120.7 (C_8), 122.0 (C_{11}), 125.5 (C_{10}), 126.1 (C_9), 144.5 (q, C_6), 149.5 (q, C_5).

IR $\nu_{\max}$ (cm^{-1}): 3338, 2968, 1469, 1043, 971.

HRMS: (m/z - EI) Calculated for $\text{C}_{11}\text{H}_{12}\text{O}$ (M^+) 160.0888, found 160.0881.

6.4.20 3,4-Dihydro-1,4-methanonaphthalen-2(1H)-one. (128)



Prepared as per general procedure P using 1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-ol **127** (2.10 g, 13.1 mmol), PDC (6.16 g, 16.4 mmol), celite (8.00 g) in anhydrous CH_2Cl_2 (100 mL) with a reaction time of 19 hrs to give a brown oil which was purified by column chromatography (9:1 hexane:ethyl acetate, $R_f = 0.51$) to yield 3,4-dihydro-1,4-methanonaphthalen-2(1H)-one **128** as a clear colourless oil (1.15 g, 7.27 mmol, 56%). The spectroscopic analysis is consistent with the ^{13}C NMR data reported in the literature.³²²

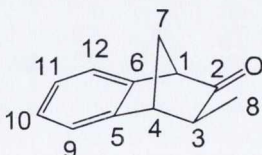
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.99 (1H, dd, $J = 17.0, 4.4$ Hz, H_{3a}), 2.27-2.36 (2H, m, H_{3b} , H_{7a}), 2.47-2.52 (1H, m, H_{7b}), 3.61 (1H, br s, H_1), 3.68-3.71 (1H, m, H_4), 7.12-7.21 (2H, m, H_9 , H_{10}), 7.28-7.32 (2H, m, H_8 , H_{11}).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 40.4 (C_3), 41.7 (C_4), 50.9 (C_7), 58.0 (C_1), 121.6 (C_8), 123.6 (C_{11}), 126.7 (C_{10}), 127.4 (C_9), 139.8 (q, C_5), 148.6 (q, C_6), 213.6 (q, C_2).

IR ν_{max} (cm^{-1}): 2972, 1744, 1459, 1123, 979.

HRMS: (m/z - ESI) Calculated for $\text{C}_{11}\text{H}_9\text{O}$ (M-H^-) 157.0653, found 157.0648.

6.4.21 3-Methyl-3,4-dihydro-1,4-methanonaphthalen-2(1H)-one. (129)



Prepared as per general procedure A using 3,4-dihydro-1,4-methanonaphthalen-2(1H)-one **128** (1.91 g, 12.1 mmol), diisopropylamine (2.20 mL, 15.7 mmol), *n*-butyllithium (2.5M solution in hexanes, 6.00 mL, 15.00 mmol), iodomethane (1.50 mL, 24.1 mmol) and THF (40 mL) to give a yellow oil which was purified by column chromatography (97:3 hexane:ethyl acetate, $R_f = 0.3$) to yield 3-methyl-3,4-dihydro-1,4-methanonaphthalen-2(1H)-one **129** as a white solid (1.33 g, 7.72 mmol, 64%). M.p. = 56 °C (Lit.³²³ 54-54.5 °C).

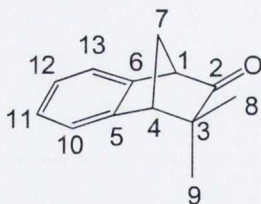
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.27 (3H, d, $J = 7.5$ Hz, H_8), 2.01-2.09 (1H, m, H_3), 2.38-2.48 (2H, m, H_{7a} , H_{7b}), 3.36 (1H, br s, H_4), 3.55 (1H, br s, H_1), 7.10-7.21 (2H, m, H_{10} , H_{11}), 7.26-7.31 (2H, m, H_9 , H_{12}).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 15.5 (C_8), 43.5 (C_3), 47.1 (C_7), 47.7 (C_4), 58.0 (C_1), 121.3 (C_9), 123.5 (C_{12}), 126.5 (C_{11}), 127.4 (C_{10}), 140.3 (q, C_6), 149.4 (q, C_5), 216.4 (q, C_2).

IR ν_{max} (cm^{-1}): 2967, 1743, 1459, 1123, 971.

HRMS: (m/z - EI) Calculated for $\text{C}_{12}\text{H}_{12}\text{O}$ (M^+) 172.0888, found 172.0881.

6.4.22 3,3-Dimethyl-3,4-dihydro-1,4-methanonaphthalen-2(1H)-one. (**130**)



Prepared as per general procedure B using 3-methyl-3,4-dihydro-1,4-methanonaphthalen-2(1H)-one **129** (1.75 g, 10.2 mmol), sodium bis(trimethylsilyl)amide (1.9M in THF, 8.00 mL, 15.2 mmol), iodomethane (1.30 mL, 2.30 mmol) and anhydrous THF (30 mL) to give a yellow oil which was purified by column chromatography (9:1 hexane:ethyl acetate, $R_f = 0.31$) to yield 3,3-dimethyl-3,4-dihydro-1,4-methanonaphthalen-2(1H)-one **130** as a white solid (1.24 g, 6.66 mmol, 66%). M.p. = 74 °C. (Lit.³²³ 76-78 °C).

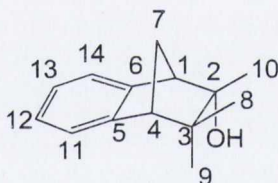
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 0.69 (3H, s, H_9), 1.30 (3H, s, H_8), 2.41 (1H, app dt, $J = 10.2, 1.5$ Hz, H_{7a}), 2.54 (1H, app dt, $J = 10.2, 1.5$ Hz, H_{7b}), 3.21-3.24 (1H, m, H_4), 3.57-3.60 (1H, m, H_1), 7.11-7.19 (2H, m, $\text{H}_{11}, \text{H}_{12}$), 7.25-7.29 (2H, m, $\text{H}_{10}, \text{H}_{13}$).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 24.3 (C_8), 25.0 (C_9), 44.5 (q, C_3), 47.9 (C_7), 52.7 (C_4), 58.2 (C_1), 123.1 (C_{10}), 123.2 (C_{13}), 126.7 (C_{12}), 126.8 (C_{11}), 139.9 (q, C_6), 148.1 (q, C_5), 218.7 (q, C_2).

IR ν_{max} (cm^{-1}): 2975, 1731, 1459, 1125, 984.

HRMS: (m/z - EI) Calculated for $\text{C}_{13}\text{H}_{14}\text{O}$ (M) $^+$ 186.1045, found 186.1048.

6.4.23 2,3,3-Trimethyl-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-ol. (131)



Prepared as per general procedure C using 3,3-dimethyl-3,4-dihydro-1,4-methanonaphthalen-2(1H)-one **130** (1.15 g, 6.17 mmol), methylmagnesium bromide (3M in THF, 6.20 mL, 18.6 mmol) and anhydrous THF (30 mL) at room temperature with a reaction time of 14 hrs to yield a pale yellow oil which was purified by column chromatography (9:1 hexane:ethyl acetate, $R_f = 0.23$) to yield 2,3,3-trimethyl-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-ol **131** as a clear colourless oil (0.95 g, 4.69 mmol, 76%).

^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 0.51 (3H, s, H_9), 1.26 (3H, s, H_8), 1.49 (3H, s, H_{10}), 1.85 (1H, app d, $J = 9.9$ Hz, H_{7a}), 2.10 (1H, app d, $J = 9.9$ Hz, H_{7b}), 2.83 (1H, br s,

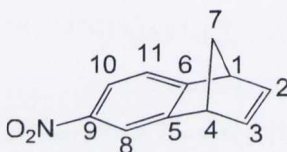
H₄), 3.09 (1H, br s, H₁), 7.06-7.31 (4H, m, H₁₁, H₁₂, H₁₃, H₁₄).

¹³C NMR (CDCl₃, 150 MHz): δ (ppm) 24.0 (C₉), 25.0 (C₁₀), 27.4 (C₈), 43.8 (q, C₃), 45.2 (C₇), 56.8 (C₄), 58.5 (C₁), 78.9 (q, C₂), 123.3 (C₁₁), 123.8 (C₁₄), 125.8 (C₁₃), 126.3 (C₁₂), 143.1 (q, C₆), 147.9 (q, C₅).

IR $\nu_{\max}$ (cm⁻¹): 3473, 2960, 1473, 1089, 936.

HRMS: (m/z - EI) Calculated for C₁₄H₁₈O (M)⁺ 202.1358, found 202.1366.

6.4.24 6-Nitro-1,4-dihydro-1,4-methanonaphthalene.²⁹⁹ (138)



General Procedure Q

To a solution of 1,4-dihydro-1,4-methanonaphthalene **126** (3.79 g, 26.7 mmol) in acetic anhydride (80 mL) was added cupric nitrate (3.23 g, 13.3 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight (ca. 16 hrs). The mixture was poured into water (100 mL), extracted with CH₂Cl₂ (2 x 40 mL), dried over magnesium sulfate and filtered. The volatiles were removed at reduced pressure and the resulting brown oil was purified by column chromatography (95:5 hexane:ethyl acetate, R_f = 0.30) to yield 6-nitro-1,4-dihydro-1,4-methanonaphthalene **138** as a pale yellow oil (1.64 g, 8.76 mmol, 33%).

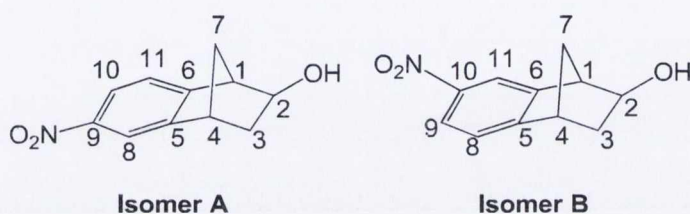
¹H NMR (CDCl₃, 400 MHz): δ (ppm) 2.33 (1H, app d, J = 7.6 Hz, H_{7a}), 2.44 (1H, app dt, J = 7.6, 1.6 Hz, H_{7b}), 3.99-3.41 (2H, m, H₁, H₄), 6.78-6.83 (1H, m, H₃), 6.84-6.89 (1H, m, H₂), 7.34 (1H, d, J = 7.8 Hz, H₁₁), 7.93 (1H, dd, J = 7.8, 1.8 Hz, H₁₀), 8.04 (1H, app s, H₈).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 49.8 (C_1), 50.0 (C_4), 69.7 (C_7), 116.0 (C_8), 120.8 (C_{10}), 120.9 (C_{11}), 141.8 (C_3), 142.7 (C_2), 144.9 (q, C_9), 153.4 (q, C_5), 159.7 (q, C_6).

IR ν_{max} (cm^{-1}): 2993, 2939, 1510, 1339, 1301, 832.

HRMS: (m/z - EI) Calculated for $\text{C}_{11}\text{H}_9\text{NO}_2$ (M^+) 187.0633, found 187.0631.

6.4.25 6-Nitro-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-ol and 7-Nitro-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-ol. (139) and (140)



Prepared as per general procedure O using 6-nitro-1,4-dihydro-1,4-methanonaphthalene **138** (1.50 g, 8.01 mmol), NaBH_4 (0.24 g, 6.01 mmol), $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.50 mL, 12.1 mmol), a solution of NaOH (4M, 1.50 mL, 6.01 mmol), H_2O_2 (35% in H_2O , 1.20 mL, 12.1 mmol) and anhydrous THF (30 mL). The product was purified by column chromatography (7:3 hexane:ethyl acetate, R_f = 0.23) to yield 6 and 7-nitro-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-ol **139** and **140** as a pale yellow oil (1.49 g, 7.29 mmol, 92%).

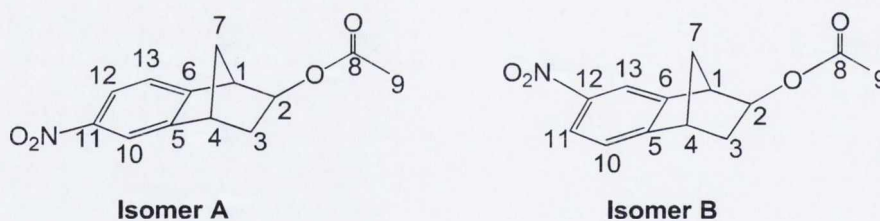
^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.72-1.89 (4H, m, H_{3a} , H_{3b} isomers A and B), 1.98-2.04 (2H, m, H_{7a} isomers A and B), 2.21-2.25 (2H, m, H_{7b} isomers A and B), 3.39 (2H, br s, H_1 isomers A and B), 3.45-3.50 (2H, m, H_4 isomers A and B), 4.00-4.06 (2H, m, H_2 isomers A and B), 7.28 (1H, d, J = 7.7 Hz, H_{11} isomer A or H_8 isomer B), 7.35 (1H, d, J = 7.7 Hz, H_{11} isomer A or H_8 isomer B), 7.99-8.07 (4H, m, H_8 , H_{10} isomer A and H_9 and H_{11} isomer B).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 38.8 (C_3 isomer A or B), 39.1 (C_3 isomer A or B), 42.9 (C_4 isomer A or B), 43.1 (C_4 isomer A or B), 46.2 (C_7 isomer A or B), 46.3 (C_7 isomer A or B), 52.2 (C_1 isomer A or B), 52.5 (C_1 isomer A or B), 72.6 (C_2 isomer A or B), 72.7 (C_2 isomer A or B), 111.6 (C_8 isomer A or C_{11} isomer B), 117.5 (C_8 isomer A or C_{11} isomer B), 121.1 (C_{11} isomer A or C_8 isomer B), 122.1 (C_{10} isomer A or C_9 isomer B), 122.5 (C_{11} isomer A or C_8 isomer B), 122.7 (C_{10} isomer A or C_9 isomer B), 146.1 (q, C_6 isomer A or B), 146.5 (q, C_9 isomer A or C_{10} isomer B), 146.9 (q, C_9 isomer A or C_{10} isomer B), 151.0 (q, C_5 isomer A or B), 152.3 (q, C_6 isomer A or B), 157.3 (q, C_5 isomer A or B).

IR ν_{max} (cm^{-1}): 3376, 2981, 1513, 1338, 1068, 1043, 971.

HRMS: (m/z - ESI) Calculated for $\text{C}_{11}\text{H}_{10}\text{NO}_3$ (M-H^-) 204.0661, found 204.0667.

6.4.26 6-Nitro-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-yl acetate and 7-nitro-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-yl acetate. (141) and (142)



To a solution of 6- and 7-nitro-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-ol **139** and **140** (3.50 g, 17.1 mmol) in acetic anhydride (15 mL) was added freshly distilled triethylamine (7.20 mL, 51.2 mmol). The reaction mixture was heated to 80 °C for 2 hrs upon which time the mixture was diluted with water (100 mL), extracted with ether (2 x 40) and dried over magnesium sulfate before being filtered. The volatiles were removed at reduced pressure to yield a brown oil which was purified by column chromatography (85:15 hexane: ethyl acetate,

$R_f = 0.45$) to yield 6- and 7-nitro-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-yl acetate **141** and **142** as a yellow oil (2.23g, 9.02 mmol, 53%).

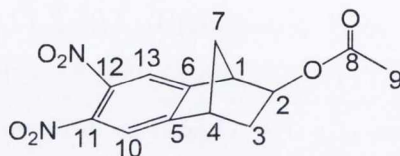
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.85-1.92 (4H, m, H_{3a} , H_{3b} isomers A and B), 2.00-2.04 (2H, app d, $J = 9.4$ Hz, H_{7a} , isomers A and B), 2.08-2.17 (8H, m, H_{7b} , H_9 isomers A and B), 3.48-3.53 (2H, m, H_4 isomers A and B), 3.54-3.57 (2H, m, H_1 isomers A and B), 4.73-4.78 (2H, m, H_2 isomers A and B), 7.31 (1H, d, $J = 8.2$ Hz, H_{13} isomer A or H_{10} isomer B), 7.42 (1H, d, $J = 8.2$ Hz, H_{13} isomer A or H_{10} isomer B), 8.00-8.08 (3H, m, H_{11} isomer A, H_{12} isomer B and H_{10} isomer A or H_{13} isomer B), 8.13 (1H, s, H_{10} isomer A or H_{13} isomer B).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 21.1 (C_9 isomer A and B), 36.2 (C_3 isomer A or B), 36.4 (C_3 isomer A or B), 42.6 (C_4 isomer A or B), 42.8 (C_4 isomer A or B), 46.7 (C_7 isomer A or B), 46.8 (C_7 isomer A or B), 49.0 (C_1 isomer A or B), 49.3 (C_1 isomer A or B), 74.5 (C_2 isomer A or B), 74.6 (C_2 isomer A or B), 115.9 (C_{10} isomer A or C_{13} isomer B), 117.8 (C_{10} isomer A or C_{13} isomer B), 121.0 (C_{13} isomer A or C_{10} isomer B), 122.1 (C_{12} isomer A or C_{11} isomer B), 122.8 (C_{12} isomer A or C_{11} isomer B), 122.9 (C_{13} isomer A or C_{10} isomer B), 144.9 (C_6 isomer A or B), 146.5 (q, C_{11} isomer A or C_{12} isomer B), 146.6 (q, C_{11} isomer A or C_{12} isomer B), 150.8 (q, C_5 isomer A or B), 150.9 (q, C_6 isomer A or B), 157.0 (q, C_5 isomer A or B), 170.5 (C_8 isomer A or B), 170.6 (C_8 isomer A or B).

IR $\nu_{\max}$ (cm^{-1}): 2989, 1736, 1516, 1340, 1228, 1026, 821.

HRMS: (m/z - EI) Calculated for $\text{C}_{13}\text{H}_{13}\text{NO}_4$ (M^+) 247.0845, found 247.0833.

6.4.27 6,7-Dinitro-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-yl acetate. (143)



To a solution of 6- and 7-nitro-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-yl acetate **141** and **142** (1.95 g, 7.86 mmol) in conc. H_2SO_4 (15 mL), was slowly added a mixture of fuming nitric acid (0.04 mL) in H_2SO_4 (4 mL) at 0 °C. The reaction mixture was stirred for 30 min upon which time it was poured onto ice (40 g), extracted with ether (2 x 40 mL) and dried over magnesium sulfate before being filtered. The volatiles were removed at reduced pressure and the resulting solid was recrystallised by a hexane, acetone and ether solution to yield 6,7-dinitro-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-yl acetate **143** as a yellow solid (1.89 g, 6.47 mmol, 82%). M.p. = 128-130 °C (Lit.³⁰⁰ 133-134 °C).

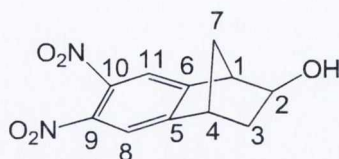
^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.90-1.97 (2H, m, H_3), 2.07-2.12 (1H, m, H_{7a}), 2.14 (3H, s, H_9), 2.20 (1H, app dt, $J = 9.8, 1.7$ Hz, H_{7b}), 3.58-3.61 (1H, m, H_4), 3.64 (1H, br s, H_1), 4.74-4.78 (1H, m, H_2), 7.67 (1H, s, H_{10}), 7.83 (1H, s, H_{13}).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 21.1 (C_9), 36.0 (C_3), 43.2 (C_4), 47.7 (C_7), 49.6 (C_1), 73.5 (C_2), 117.5 (C_{10}), 119.3 (C_{13}), 141.6 (q, C_{12}), 141.8 (q, C_{11}), 149.9 (q, C_6), 155.9 (q, C_5), 170.6 (q, C_8).

IR $\nu_{\max}$ (cm^{-1}): 3098, 1721, 1528, 1340, 1037, 972.

HRMS: (m/z - EI) Calculated for $\text{C}_{11}\text{H}_9\text{N}_2\text{O}_5$ (M-Acetyl^+) 249.0511, found 249.0601.

6.4.28 6,7-Dinitro-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-ol. (144)



To a solution of 6,7-dinitro-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-yl acetate **143** (1.80 g, 6.14 mmol), in methanol (30 mL) was added 5% HCl solution (20 mL). The reaction was heated at reflux temperature for 1.5 hrs. Methanol was removed at reduced pressure and the remaining aqueous portion was extracted with ether (3 x 30 mL). The organic layers were dried over magnesium sulfate and filtered. The volatiles were removed at reduced pressure to yield a yellow oil which was purified by column chromatography (65:35 hexane: ethyl acetate, R_f = 0.25) to yield 6,7-dinitro-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-ol **144** as a pale yellow solid (0.83 g, 3.32 mmol, 54%). M.p. = 139-140 °C (Lit.³⁰⁰ 142-143 °C).

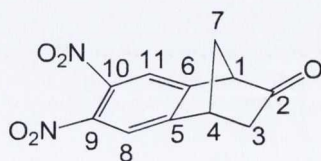
¹H NMR (CDCl₃, 600 MHz): δ (ppm) 1.80-1.88 (2H, m, H₃), 2.08 (1H, m, H_{7a}), 2.32 (1H, app dt, *J* = 9.7, 1.6 Hz, H_{7b}), 3.47 (1H, br s, H₁), 3.54-3.57 (1H, m, H₄), 4.06-4.09 (1H, m, H₂), 7.66 (1H, s, H₈), 7.74 (1H, s, H₁₁).

¹³C NMR (CDCl₃, 150 MHz): δ (ppm) 38.4 (C₃), 43.1 (C₄), 46.9 (C₇), 52.3 (C₁), 72.0 (C₂), 117.4 (C₈), 118.8 (C₁₁), 141.4 (q, C₁₀), 141.9 (q, C₉), 150.7 (q, C₆), 156.1 (q, C₅).

IR ν_{max} (cm⁻¹): 3270, 2960, 1526, 1370, 1053, 966.

HRMS: (m/z - ESI) Calculated for $C_{11}H_9N_2O_5$ (M-H)⁻ 249.0511, found 249.0503.

6.4.29 6,7-Dinitro-3,4-dihydro-1,4-methanonaphthalen-2(1H)-one. (145)



Prepared as per general procedure P using 6,7-dinitro-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-ol **144** (0.82 g, 0.34 mmol), PDC (1.92 g, 0.51 mmol), celite (2.00 g) in anhydrous CH_2Cl_2 (30 mL) with a reaction time of 72 hrs to give a white solid which was purified by recrystallisation from hexane and ether to yield 6,7-dinitro-3,4-dihydro-1,4-methanonaphthalen-2(1H)-one **145** as a white solid (0.24 g, 0.10 mmol, 29%). M.p = 161-162 °C (Lit.³⁰⁰ 163-164 °C).

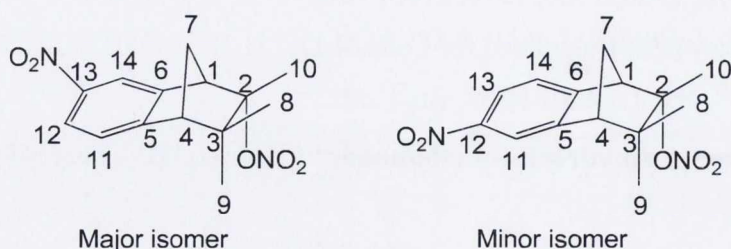
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 2.07 (1H, dd, $J = 17.6, 4.5$ Hz, H_{3a}), 2.47 (1H, app dt, $J = 10.3, 1.3$ Hz, H_{7a}), 2.53 (1H, dd, $J = 17.6, 4.5$ Hz, H_{3b}), 2.66-2.72 (1H, m, H_{7b}), 3.83 (1H, br s, H_4), 3.93-3.96 (1H, m, H_1), 7.84 (2H, br s, $\text{H}_8, \text{H}_{11}$).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 38.3 (C_3), 42.1 (C_1), 51.4 (C_4), 58.2 (C_7), 118.5 (C_{11}), 120.0 (C_8), 142.2 (q, C_{10}), 142.6 (q, C_9), 146.4 (q, C_5), 154.4 (q, C_6), 208.4 (q, C_2).

IR ν_{max} (cm^{-1}): 3099, 1758, 1532, 1367, 1337, 1126, 986.

HRMS: (m/z - EI) Calculated for $\text{C}_{11}\text{H}_8\text{N}_2\text{O}_5$ (M)⁺ 248.0433, found 248.0443.

6.4.30 2,3,3-Trimethyl-7-nitro-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-yl nitrate and 2,3,3-trimethyl-6-nitro-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-yl nitrate. (146) and (147)



Prepared as per general procedure Q using 2,3,3-trimethyl-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-ol **131** (0.49 g, 2.66 mmol), cupric nitrate (3.21 g, 13.3 mmol) and

acetic anhydride (10 mL) to yield a nitrate mixture of **146** and **147** as a pale yellow oil (0.12 g, 0.41 mmol, 16%). (95:5 hexane:ethyl acetate, $R_f = 0.3$).

Major Isomer

^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 0.69 (3H, s, H_9), 1.39 (3H, s, H_8), 1.82 (3H, s, H_{10}), 1.96-2.01 (1H, m, H_{7a}), 2.18-2.23 (1H, m, H_{7b}), 2.99 (1H, br s, H_4), 3.97 (1H, br s, H_1), 7.36 (1H, d, $J = 8.2$ Hz, H_{11}), 8.03 (1H, s, H_{14}), 8.09-8.13 (1H, m, H_{12}).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 20.6 (C_{10}), 23.6 (C_9), 27.2 (C_8), 45.6 (C_7), 46.7 (q, C_3), 55.8 (C_1), 56.3 (C_4), 95.5 (q, C_2), 118.1 (C_{14}), 122.7 (C_{12}), 123.3 (C_{11}), 144.1 (q, C_6), 147.0 (q, C_{13}), 154.0 (q, C_5).

Minor Isomer

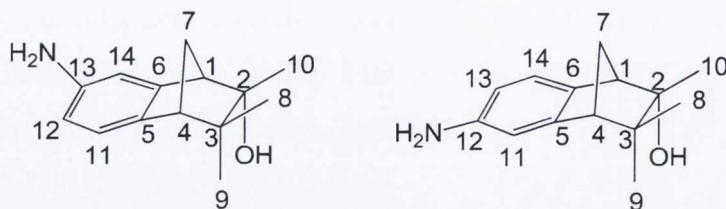
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 0.71 (3H, s, H_9), 1.39 (3H, s, H_8), 1.82 (3H, s, H_{10}), 1.96-2.01 (1H, m, H_{7a}), 2.18-2.23 (1H, m, H_{7b}), 3.01 (1H, br s, H_4), 3.98 (1H, br s, H_1), 7.33 (1H, d, $J = 8.2$ Hz, H_{14}), 8.08 (1H, s, H_{11}), 8.09-8.13 (1H, m, H_{13}).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 20.5 (C_{10}), 23.7 (C_9), 27.1 (C_8), 45.6 (C_7), 46.6 (q, C_3), 56.0 (C_1), 56.1 (C_4), 95.8 (q, C_2), 118.0 (C_{11}), 122.6 (C_{13}), 123.1 (C_{14}), 147.0 (q, C_{12}), 148.0 (q, C_5), 150.0 (q, C_6).

IR ν_{max} (cm^{-1}): 2977, 1617, 1519, 1341, 1291, 850.

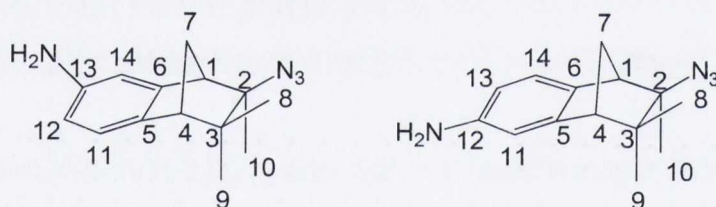
HRMS: (m/z - ESI) Calculated for $\text{C}_{14}\text{H}_{17}\text{N}_2\text{O}_5$ ($\text{M}+\text{H}^+$) 293.1137, found 293.1138.

6.4.31 6-Amino-2,3,3-trimethyl-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-ol and 7-amino-2,3,3-trimethyl-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-ol. (148) and (149)

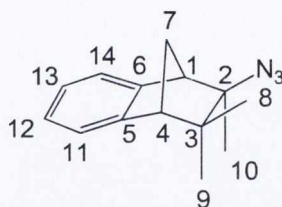


Prepared as per general procedure E using the mixture of nitrates **146** and **147** (280 mg, 0.96 mmol), palladium on charcoal (60 mg, 21% w/w) and methanol (10 mL) under a hydrogen atmosphere at atmospheric pressure with a reaction time of 19 hrs to yield an amine mixture of **148** and **149** as a yellow oil. The product was unstable towards column chromatography and was used in the next step without further purification (199 mg, 0.92 mmol, 95%).

6.3.32 3-Azido-2,2,3-trimethyl-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-amine and 2-azido-2,3,3-trimethyl-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-amine. (150) and (151)



Prepared as per general procedure D using 6 and 7-amino-2,3,3-trimethyl-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-ol **148** and **149** (180 mg, 0.83 mmol), sodium azide (380 mg, 5.85 mmol), 50% H₂SO₄ (1 mL) and CHCl₃ with a reaction time of 45 min to yield **150** and **151** as a brown oil. The product was unstable towards column chromatography and was used in the next step without further purification (108 mg, 0.45 mmol, 54%).

6.4.33 2-Azido-2,3,3-trimethyl-1,2,3,4-tetrahydro-1,4-methanonaphthalene. (**154**)

To a solution of azides **150** and **151** (80 mg, 0.3 mmol) in methanol (2 mL) and a solution of HCl (1M, 1.30 mL, 1.30 mmol) at $-5\text{ }^{\circ}\text{C}$ was added a solution of NaNO_2 (27 mg, 0.4 mmol) in H_2O (300 μL). The reaction mixture was stirred for 15 min at $-5\text{ }^{\circ}\text{C}$, hypophosphinic acid (0.5 mL) precooled to $-5\text{ }^{\circ}\text{C}$ was added and stirred a further 15 min. The mixture was then allowed to warm to room temperature and stirred for 4 hrs. A NaOH solution (2M, 5.0 mL, 5.0 mmol) was added and the mixture was extracted with diethyl ether (2 x 10 mL), dried over magnesium sulfate and filtered before the solvent was removed at reduced pressure. The yellow oil **154** obtained was unstable towards column chromatography and attempts to purify resulted in rapid decomposition of material (21.0 mg, 0.09 mmol, 28%).

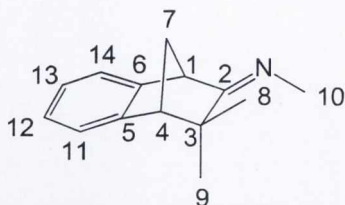
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 0.54 (3H, s, H_9), 1.01 (3H, s, H_8), 1.33 (3H, s, H_{10}), 1.83 (1H, app d, $J = 9.6\text{ Hz}$, H_{7a}), 2.73 (1H, app d, $J = \text{Hz}$, 9.6 Hz, H_{7b}), 2.78-2.80 (1H, m, H_4), 3.13-3.16 (1H, m, H_1), 7.10-7.13 (2H, m, H_{12} , H_{13}), 7.14-7.17 (1H, m, $\text{H}_{11}/\text{H}_{14}$) 7.19-7.22 (1H, m, $\text{H}_{11}/\text{H}_{14}$).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 19.7 (C_8), 25.5 (C_9), 26.8 (C_{10}), 44.9 (q, C_3), 45.6 (C_7), 56.1 (C_1), 56.9 (C_4), 71.6 (q, C_2), 122.6 ($\text{C}_{11}/\text{C}_{14}$), 123.0 ($\text{C}_{11}/\text{C}_{14}$), 125.5 ($\text{C}_{12}/\text{C}_{13}$), 125.8 ($\text{C}_{12}/\text{C}_{13}$), 143.6 (q, C_6), 147.6 (q, C_5).

IR ν_{max} (cm^{-1}): 2960, 2926, 2090, 1463, 1260, 1077, 799.

Due to the unstable nature of the compound mass spectral data was not obtained.

6.4.34 (Z)-N-3,3-Dimethyl-3,4-dihydro-1,4-methanonaphthalen-2(1H)-ylidene)methanamine. (156)



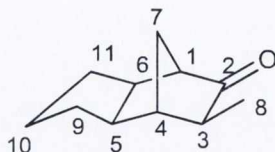
Prepared as per general procedure J using 3,3-dimethyl-3,4-dihydro-1,4-methanonaphthalen-2(1H)-one **130** (785 mg, 4.22 mmol), methylamine hydrochloride (430 mg, 6.33 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (1.20 mL, 10.6 mmol), triethylamine (4.00 mL, 18.9 mmol), titanium tetrachloride solution (1M in CH₂Cl₂, 4.30 mL, 4.30 mmol) with a reaction time of 16 hrs at 40 °C to yield (Z)-N-3,3-dimethyl-3,4-dihydro-1,4-methanonaphthalen-2(1H)-ylidene)methanamine **156** as a clear viscous oil (753 mg, 3.77 mmol, 90%).

¹H NMR (CDCl₃, 600 MHz): δ (ppm) 1.21 (3H, s, H₉), 1.76 (3H, s, H₈), 2.50-2.54 (1H, m, H_{7a}), 2.55-2.59 (1H, m, H_{7b}), 3.21 (1H, br s, H₄), 3.50 (3H, m, H₁₀), 4.29 (1H, br s, H₁), 7.25 (1H, app t, *J* = 7.6 Hz, H₁₃), 7.28-7.33 (2H, m, H₁₂, H₁₄), 7.38 (1H, d, *J* = 7.6 Hz, H₁₁).

¹³C NMR (CDCl₃, 150 MHz): δ (ppm) 25.4 (C₈), 26.3 (C₉), 35.2 (C₁₀), 48.88 (C₇), 48.89 (q, C₃), 50.2 (C₁), 53.7 (C₄), 123.3 (C₁₄), 124.4 (C₁₁), 127.9 (C₁₃), 128.9 (C₁₂), 135.4 (q, C₆), 147.4 (q, C₅), 200.5 (q, C₂).

IR ν_{max} (cm⁻¹): 2989, 2516, 1711, 1468, 1057, 988.

HRMS: (*m/z* - ESI) calculated for C₁₄H₁₈N (M+H) 200.1439, found 200.1449.

6.4.35 6-*exo*-Methylhexahydro-1H-4,7-methanoinden-5(6H)-one. (159)

Prepared as per general procedure A using tricyclo[5.2.1.0(2,6)]decan-8-one **158** (2.00 g, 13.3 mmol), diisopropylamine (2.43 mL, 17.3 mmol), a solution of *n*-butyllithium (2.5M in hexanes, 6.70 mL, 16.6 mmol), iodomethane (1.65 mL, 26.6 mmol) and anhydrous THF (55 mL) to yield a yellow oil which was purified by column chromatography (9:1 hexane: ethyl acetate, $R_f = 0.47$) to yield 6-*exo*-methylhexahydro-1H-4,7-methanoinden-5(6H)-one **159** as a pale yellow oil (2.07 g, 12.1 mmol, 86%). The spectroscopic analysis is consistent with the ^{13}C NMR data reported in the literature.³⁰³

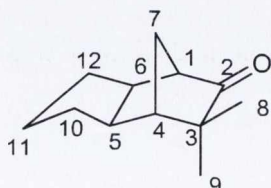
^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.03-1.15 (5H, m, H_8 , H_{9a} , H_{11a}), 1.26-1.45 (1H, m, H_{10a}), 1.67-1.69 (2H, m, H_{7a} , H_{7b}), 1.75-1.86 (2H, m, H_3 , H_{10b}), 1.93-2.03 (2H, m, H_{9b} , H_{11b}), 2.06-2.20 (3H, m, H_4 , H_5 , H_6), 2.33-2.35 (1H, m, H_1).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 14.3 (C_8), 28.1 (C_{10}), 28.5 (C_7), 31.6 (C_{11}), 32.3 (C_9), 41.6 (C_6), 46.0 (C_4), 47.7 (C_5), 47.8 (C_3), 54.2 (C_1), 221.3 (q, C_2).

IR ν_{max} cm^{-1} : 2946, 2863, 1740, 1449, 1163, 950.

HRMS: (m/z - EI) Calculated for $\text{C}_{11}\text{H}_{16}\text{O}$ (M^+) 164.1201, found 164.1202.

6.4.36 6,6-Dimethylhexahydro-1H-4,7-methanoinden-5(6H)-one. (160)



Prepared as per general procedure B using 6-*exo*-methylhexahydro-1H-4,7-methanoinden-5(6H)-one **159** (1.90 g, 11.6 mmol), sodium bis(trimethylsilyl)amide (1.9M in THF, 12.2 mL, 23.1 mmol), iodomethane (1.50 mL, 23.1 mmol) and anhydrous THF (45 mL) to yield a pale yellow oil which was purified by column chromatography (95:5 hexane: diethyl ether, R_f = 0.45) to yield 6,6-dimethylhexahydro-1H-4,7-methanoinden-5(6H)-one **160** as a yellow oil (1.59 g, 8.91 mmol, 77%). The spectroscopic analysis is consistent with the ^{13}C NMR data reported in the literature.³⁰³

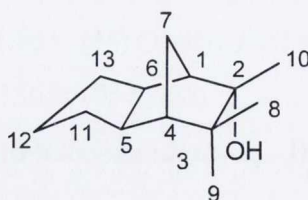
^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.03 (3H, s, H_9), 1.05-1.19 (5H, m, H_8 , H_{10a} , H_{12a}), 1.29-1.43 (1H, m, H_{11a}), 1.66-1.72 (1H, m, H_{7a}), 1.76-1.85 (2H, m, H_{7b} , H_{11b}), 1.89-2.04 (3H, m, H_4 , H_{10b} , H_{12b}), 2.12 (1H, app quartet, J = 8.6 Hz, H_6), 2.32-2.34 (1H, m, H_1), 2.64 (1H, app quartet, J = 8.6 Hz, H_5).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 21.1 (C_9), 23.8 (C_8), 28.1 (C_{11}), 28.9 (C_7), 32.1 (C_{12}), 32.3 (C_{10}), 41.7 (C_5), 42.4 (C_6), 46.6 (q, C_3), 50.4 (C_4), 55.2 (C_1), 223.1 (q, C_2).

IR ν_{max} cm^{-1} : 2949, 2865, 1741, 1471, 1151, 954.

HRMS: (m/z - EI) Calculated for $\text{C}_{12}\text{H}_{18}\text{O}$ (M^+) 178.1358, found 178.1357.

6.4.37 5-*exo*-6,6-Trimethyloctahydro-1H-4,7-methanoinden-5-ol. (**161**)



Prepared as per general procedure C using 6,6-dimethylhexahydro-1H-4,7-methanoinden-5(6H)-one **160** (1.80 g, 8.56 mmol), a solution of methylmagnesium bromide (3M in diethyl ether, 6.70 mL, 20.1 mmol) and anhydrous THF (40 mL), warmed to 40 °C with a reaction

time of 4 hrs to yield a pale yellow oil which was purified by column chromatography (95:5 hexane: ethyl acetate, $R_f = 0.12$) to yield 5-*exo*-6,6-trimethyloctahydro-1H-4,7-methanoinden-5-ol **161** as a clear colourless oil (1.26 g, 6.51 mmol, 76%).

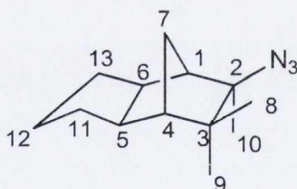
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 0.86-0.98 (5H, m, H_9 , H_{11a} , H_{13a}), 1.01 (3H, s, H_8), 1.19-1.34 (5H, m, H_{7a} , H_{10} , H_{12a}), 1.43 (1H, app dt, $J = 1.6, 11.1$ Hz, H_{7b}), 1.54 (1H, br s, H_4), 1.62-1.69 (1H, m, H_{12b}), 1.75 (1H, br s, H_1), 1.81-1.93 (2H, m H_{11b} , H_{13b}), 2.34 (1H, app quartet, $J = 8.7$ Hz, H_5), 2.49 (1H, app quartet, $J = 8.7$ Hz, H_6).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 21.2 (C_9), 26.3 (C_{10}), 27.0 (C_{12}), 27.1 (C_8), 28.0 (C_7), 32.2 (C_{13}), 32.5 (C_{11}), 38.3 (C_6), 40.9 (C_5), 42.1 (q, C_3), 54.0 (C_4), 55.7 (C_1), 78.3 (q, C_2).

IR ν_{max} cm^{-1} : 3451, 2926, 2862, 1485, 1372, 1128, 1074.

HRMS: (m/z - EI) Calculated for $\text{C}_{13}\text{H}_{22}\text{O}$ (M^+) 194.1671, found 194.1674.

6.4.38 5-Azido-5-*endo*-6,6-trimethyloctahydro-1H-4,7-methanoindene. (**162**)



Prepared as per general procedure D using 5-*exo*-6,6-trimethyloctahydro-1H-4,7-methanoinden-5-ol **161** (1.30 g, 6.69 mmol), 55% H_2SO_4 (8 mL), NaN_3 (3.00 g, 46.2 mmol) and CHCl_3 (75 mL) with a reaction time of 5 hrs to yield a yellow oil. This was purified by column chromatography (100% hexane, $R_f = 0.7$) to yield 5-azido-5-*endo*-6,6-trimethyloctahydro-1H-4,7-methanoindene **162** as a clear colourless oil (0.77g, 3.51 mmol, 46%).

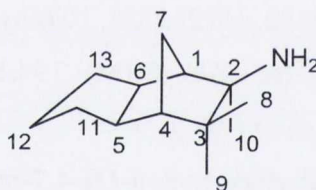
¹H NMR (CDCl₃, 400 MHz): δ (ppm) 0.86-1.05 (5H, m, H₉, H_{11a}, H_{13a}), 1.08 (3H, s, H₈), 1.17-1.31 (2H, m, H_{7a}, H_{12a}), 1.33 (3H, s, H₁₀), 1.54-1.57 (1H, m, H₄), 1.68-1.96 (5H, m, H₁, H_{7b}, H_{11b}, H_{12b}, H_{13b}), 2.07 (1H, app quartet, *J* = 8.6 Hz, H₆), 2.24 (1H, app quartet, *J* = 8.6 Hz, H₅).

¹³C NMR (CDCl₃, 100 MHz): δ (ppm) 17.7 (C₁₀), 23.1 (C₉), 27.1 (C₈), 27.4 (C₁₂), 28.3 (C₇), 32.4 (C₁₁), 32.6 (C₁₃), 40.8 (C₆), 41.2 (C₅), 44.1 (q, C₃), 53.6 (C₁), 52.4 (C₄), 72.5 (q, C₂).

IR $\nu_{\max}$ cm^{-1} : 2948, 2865, 2084, 1460, 1252, 1081.

HRMS: (m/z - ESI) Calculated for $C_{13}H_{22}N$ (M-N₂+H)⁺ 192.1752, found 192.1759.

6.4.39 5-endo-6,6-Trimethyloctahydro-1H-4,7-methanoinden-5-amine. (163)



Prepared as per general procedure E using 5-azido-5-*endo*-6,6-trimethyloctahydro-1H-4,7-methanoindene **162** (0.70 g, 3.19 mmol), methanol (20 mL) and palladium on charcoal (0.07 g, 10% w/w) under a hydrogen atmosphere at atmospheric pressure for 16 hrs to yield 5-*endo*-6,6-trimethyloctahydro-1H-4,7-methanoinden-5-amine **163** as a clear colourless oil (0.28 g, 1.44 mmol, 45%).

¹H NMR (CDCl₃, 600 MHz): δ (ppm) 0.91-0.99 (5H, m, H₉, H_{11a}, H_{13a}), 1.03 (3H, m, H₈), 1.10 (3H, s, H₁₀), 1.17-1.26 (1H, m, H_{12a}), 1.28 (1H, app d, *J* = 11.1 Hz, H_{7a}), 1.49-1.52 (1H, m, H₄), 1.55-1.59 (1H, m, H₁), 1.65-1.73 (2H, m, H_{7b}, H_{12b}), 1.79-1.91 (2H, m, H_{11b},

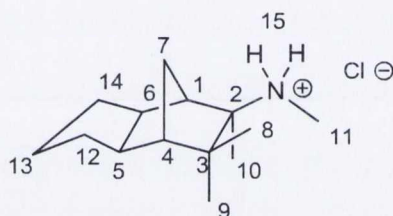
H_{13b}), 2.12 (1H, app quartet, $J = 8.6$ Hz, H₆),
2.26 (1H, app quartet, $J = 8.6$ Hz, H₅).

¹³C NMR (CDCl₃, 150 MHz): δ (ppm) 23.1 (C₉), 23.1 (C₁₀), 26.4 (C₈), 27.3 (C₁₂), 27.7 (C₇), 32.5 (C₁₁), 32.6 (C₁₃), 40.7 (C₅), 41.4 (C₆), 42.3 (q, C₃), 54.6 (C₄), 57.5 (C₁), 58.4 (q, C₂).

IR $\nu_{\max}$ cm⁻¹: 3346, 2945, 2863, 1480, 1388, 1021, 895.

HRMS: (m/z - EI) Calculated for C₁₃H₂₃N (M)⁺ 193.1830, found 193.1835.

6.4.40 *N*-5-endo-6,6-Tetramethyloctahydro-1H-4,7-methanoinden-5-amine. (157)



Prepared as per general procedure G using 5-endo-6,6-trimethyloctahydro-1H-4,7-methanoinden-5-amine **163** (280 mg, 1.45 mmol), paraformaldehyde (152 mg, 5.08 mmol) and activated 4 Å molecular sieves (400 mg), CH₂Cl₂ (30 mL) and sodium borohydride (255 mg, 6.53 mmol) to yield the desired amine as a viscous oil. This oil was dissolved in anhydrous diethyl ether (1.00 mL) and hydrogen chloride solution (2M in diethyl ether, 1.00 mL, 2.00 mmol) was added. The desired HCl salt of *N*-5-endo-6,6-tetramethyloctahydro-1H-4,7-methanoinden-5-amine **157** was obtained by filtration and dried under vacuum to yield a cream solid (154 mg, 0.61 mmol, 39%). M.p. 210-215 °C (decomposes).

¹H NMR (CDCl₃, 600 MHz): δ (ppm) 0.91-1.03 (2H, m, H_{12a}, H_{14a}), 1.04 (3H, s, H₉), 1.19-1.28 (1H, m, H_{13a}), 1.32 (3H, s, H₈), 1.43 (1H, app d, $J = 12.1$ Hz, H_{7a}), 1.50 (3H, s, H₁₀), 1.62 (1H, br s, H₄), 1.69-1.76 (1H, app quintet, $J = 6.2$ Hz, H_{13b}), 1.81-1.95 (2H, m, H_{12b}, H_{14b}), 2.07 (1H, app quartet, $J = 8.4$ Hz, H₆), 2.11 (1H, br s, H₁), 2.16 (1H, app d, $J = 12.1$ Hz, H_{7b}),

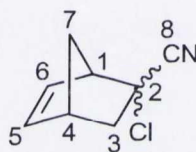
2.24 (1H, app quartet, $J = 8.4$ Hz, H_5), 2.67 (3H, app t, $J = 5.3$ Hz, H_{11}), 8.36 (1H, br s, H_{15a}), 9.08 (1H, br s H_{15b}).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 16.1 (C_8), 23.3 (C_9), 26.5 (C_{10}), 27.3 (C_{13}), 28.2 (C_7), 29.1 (C_{11}), 32.4 (C_{14}), 32.6 (C_{12}), 40.6 (C_5), 40.8 (C_6), 44.4 (q, C_3), 49.4 (C_1), 55.0 (C_4), 69.9 (q, C_2).

IR ν_{max} cm^{-1} : 2945, 2749, 1389, 1102.

HRMS: (m/z - EI) Calculated for $\text{C}_{14}\text{H}_{25}\text{N}$ (M) $^+$ 207.1987, found 207.1980.

6.4.41 2-Chlorobicyclo[2.2.1]hept-5-ene-2-carbonitrile. (167)



To a solution of 2-chloroacrylonitrile (2.50 mL, 30.4 mmol) in toluene (6 mL) at 70 °C, freshly distilled cyclopentadiene (3.00 mL, 36.5 mmol) was slowly added. After stirring overnight at 45 °C, the solvent was removed under vacuum to yield a clear oil which was purified by column chromatography (98:2 hexane:ethyl acetate, $R_f = 0.35$) to yield a colourless solid. A 4:1 ratio of the *exo:endo* diastereomers of 2-chlorobicyclo[2.2.1]hept-5-ene-2-carbonitrile **167** was noted (4.52 g, 29.4 mmol, 97%). M.p. 46–48 °C (Lit.³²⁴ 48–49 °C).

Exo diastereomer:

^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.71 (1H, dd, $J = 13.2, 3.7$ Hz, H_{3a}), 1.75–1.83 (2H, m, H_{7a}), 2.73 (1H, dd, $J = 13.2, 3.7$ Hz, H_{3b}), 3.11 (1H, br s, H_4), 3.52 (1H, br s, H_1), 6.12 (1H, dd, $J = 5.7, 3.1$ Hz, H_5), 6.42 (1H, dd, $J = 5.7, 3.1$ Hz, H_6).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 42.6 (C_4), 46.9 (C_3), 48.5 (C_7), 56.2 (C_1), 56.8 (q,

C₂), 132.5 (C₆), 142.1 (C₅), 121.5 (q, C₈).

Endo diastereomer:

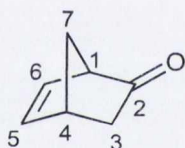
¹H NMR (CDCl₃, 400 MHz): δ (ppm) 1.92–1.96 (2H, m, H₇), 2.24 (1H, dd, *J* = 13.2, 2.7 Hz, H_{3b}), 2.38 (1H, dd, *J* = 13.2, 3.4 Hz, H_{3a}), 3.09 (1H, br s, H₄), 3.36 (1H, br s, H₁), 6.23 (1H, dd, *J* = 5.8, 3.0 Hz, H₅), 6.48 (1H, dd, *J* = 5.7, 3.0 Hz, H₆).

¹³C NMR (CDCl₃, 100 MHz): δ (ppm) 42.9 (C₄), 45.7 (C₃), 48.5 (C₇), 55.4 (C₁), 56.6 (q, C₂), 131.9 (C₆), 139.4 (C₅), 120.4 (q, C₈).

IR ν_{max} (cm⁻¹): 2990, 2946, 2869, 2235, 1712, 1336, 1269, 766, 725.

HRMS: (*m/z* - CI) Calculated for C₈H₉NCl (M+H)⁺ 154.0424, found 154.0428.

6.4.42 Bicyclo[2.2.1]hept-5-en-2-one. (168)



α-Chloronitrile mixture **167** (4.38 g, 28.5 mmol) was added to a RBF containing a potassium hydroxide solution (4M, 10 mL) and DMSO (30 mL). The mixture was heated to 70 °C. After such time that t.l.c. analysis showed complete consumption of the starting material (approximately 3 hrs), the reaction was cooled to room temperature. H₂O (30 mL) was added. The mixture was extracted with diethyl ether (2 x 30 mL) and the combined organic layers were washed with brine (10 mL). The organic extracts were dried over magnesium sulfate and the volatiles were carefully removed by fractional distillation as the product is surprisingly volatile (72–76 °C, 22 Torr).³²⁵ This yielded bicyclo[2.2.1]hept-5-en-2-one **168** as a clear oil (1.78 g, 16.5 mmol, 64%). *R_f* (9:1 hexane: ethyl acetate) = 0.29.

¹H NMR (CDCl₃, 400 MHz): δ (ppm) 1.87 (1H, dd, *J* = 16.5, 4.4 Hz, H_{3a}), 1.95–2.03 (2H, m, H_{3b}, H_{7a}), 2.16–2.23 (1H, m, H_{7b}), 3.01–3.05 (1H, m, H₁), 3.21 (1H, m, H₄), 6.12 (1H, dd,

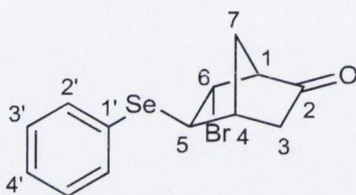
$J = 5.5, 3.9 \text{ Hz, H}_6$), 6.58 (1H, dd, $J = 5.5, 2.8 \text{ Hz, H}_5$).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 36.8 (C_3), 39.6 (C_4), 50.5 (C_7), 55.4 (C_1), 130.1 (C_6), 142.6 (C_5), 215.9 (q, C_2).

IR ν_{max} (cm^{-1}): 2973, 1737, 1322, 1122, 734, 706.

HRMS: (m/z - CI) Calculated for $\text{C}_9\text{H}_{13}\text{O}$ ($\text{M} + \text{C}_2\text{H}_5$) $^+$ 137.0966, found 137.0970.

6.4.43 6-endo-Bromo-5-exo-(phenylselanyl)bicyclo[2.2.1]heptan-2-one. (169)



To a solution of phenylselenenyl bromide (17.04 g, 72.22 mmol) in anhydrous THF (135 mL) at -78°C , a solution of bicyclo[2.2.1]hept-5-en-2-one **168** (7.80 g, 72.2 mmol) in anhydrous THF (15 mL) cooled to -78°C was added over 20 minutes. The reaction mixture was stirred at -78°C for 4 hrs and then allowed to warm slowly to room temperature. The organic solvent was removed under vacuum to give a thick brown oil which was purified by column chromatography using a gradually increasing gradient of 95:5 hexane:ethyl acetate to 8:2 hexane:ethyl acetate to yield 6-bromo-5-(phenylselanyl)bicyclo[2.2.1]heptan-2-one **169** as a white solid (4.70 g, 13.7 mmol, 19%). M.p. $72\text{--}74^\circ\text{C}$ (Lit.³⁰⁴ $75\text{--}77^\circ\text{C}$). R_f (9:1 hexane: ethyl acetate) = 0.31.

^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.86-1.92 (1H, m, H_{7a}), 2.09 (1H, dd, $J = 18.6, 4.4 \text{ Hz, H}_{3a}$), 2.21-2.27 (1H, m, H_{7b}), 2.33 (1H, dd, $J = 18.6, 4.4 \text{ Hz, H}_{3b}$), 2.77-2.82 (1H, m, H_4), 2.89-2.94 (1H, m, H_1), 3.58-3.63 (1H, m, H_5), 4.27-4.31 (1H, m, H_6), 7.32-7.39 (3H, m, H_2 , H_4'), 7.63-7.68 (2H, m, H_3').

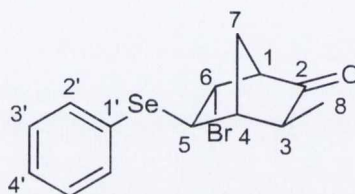
^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 35.6 (C_7), 42.8 (C_4), 44.6 (C_3), 48.8 (C_6), 52.8 (C_5), 57.8 (C_1), 128.47 ($\text{C}_{4'}$), 128.49 (q, $\text{C}_{1'}$), 129.6, ($\text{C}_{2'}$), 134.7, ($\text{C}_{3'}$), 210.1 (q, C_2).

IR ν_{max} (cm^{-1}): 2975, 1750, 1576, 1477, 1437, 1289, 1133, 1086.

HRMS: (m/z - EI) Calculated for $\text{C}_{13}\text{H}_{13}\text{OBrSe}$ (M) $^+$ 343.9315, found 343.9320.

6.4.44 6-*endo*-Bromo-3-*exo*-methyl-5-*exo*-(phenylselanyl)bicyclo[2.2.1]heptan-2-one.

(170)



General Procedure R

To a solution of 6-bromo-5-(phenylselanyl)bicyclo[2.2.1]heptan-2-one **169** (4.69 g, 13.6 mmol) in anhydrous THF (70 mL) at $-78\text{ }^{\circ}\text{C}$, a solution of sodium bis(trimethylsilyl)amide (1.9M in THF, 10.8 mL, 20.5 mmol) pre-cooled to $-78\text{ }^{\circ}\text{C}$ was added. After stirring for 2 hrs at $-78\text{ }^{\circ}\text{C}$, the reaction was warmed to $-30\text{ }^{\circ}\text{C}$. Iodomethane (2.50 mL, 40.2 mmol) was added and the reaction was stirred for a further 1 hr at $-30\text{ }^{\circ}\text{C}$. 1 M HCl (20 mL) was added and the mixture was extracted using diethyl ether (3 x 40 mL), washed with brine (20 mL) and dried over magnesium sulfate. After filtration the volatiles were evaporated at reduced pressure to give a pale yellow oil which was purified by column chromatography (97:3 hexane:ethyl acetate, R_f (85:15 hexane:ethyl acetate) = 0.20) to yield 6-*endo*-bromo-3-*exo*-methyl-5-*exo*-(phenylselanyl)bicyclo[2.2.1]heptan-2-one **170** as a pale yellow solid (3.29 g, 9.19 mmol, 67%). M.p. $73\text{--}76\text{ }^{\circ}\text{C}$.

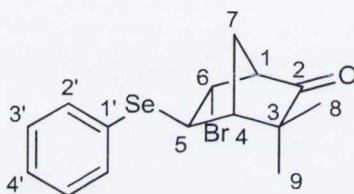
^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.15 (3H, d, $J = 7.5\text{ Hz}$, H_8), 1.95-2.02 (1H, m, H_{7a}), 2.06-2.20 (3H, m, H_{3a} , H_{3b} , H_{7b}), 2.45-2.48 (1H, m, H_4), 2.87-2.91 (1H, m, H_1), 3.63-3.67 (1H, m, H_5), 4.28-4.33 (1H, m, H_6), 7.32-7.40 (3H, m, H_2 , H_4'), 7.62-7.69 (2H, m, H_3').

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 14.2 (C_8), 32.7 (C_7), 47.7 (C_3), 48.4 (C_4), 48.6 (C_6), 52.9 (C_5), 57.3 (C_1), 127.8 ($\text{C}_{4'}$), 128.1 (q, $\text{C}_{1'}$), 129.0, ($\text{C}_{2'}$), 134.2, ($\text{C}_{3'}$), 212.9 (q, C_2).

IR ν_{max} (cm^{-1}): 2971, 1743, 1577, 1476, 1437, 1254, 1153, 1086.

HRMS: (m/z - EI) Calculated for $\text{C}_{14}\text{H}_{15}\text{OSeBr}$ (M^+) 357.9471, found 357.9461.

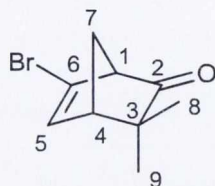
6.4.45 6-endo-Bromo-3,3-dimethyl-5-exo-(phenylselanyl)bicyclo[2.2.1]heptan-2-one.
(171)



Prepared as per general procedure R using a solution of 6-endo-bromo-3-exo-methyl-5-exo-(phenylselanyl)bicyclo[2.2.1]heptan-2-one **170** (3.27 g, 9.13 mmol) in THF (80 mL), a solution of sodium bis(trimethylsilyl)amide (1.9M in THF, 7.30 mL, 13.9 mmol) and iodomethane (1.70 mL, 27.3 mmol) to give a thick pale yellow oil which was purified by column chromatography (85:15 hexane:ethyl acetate, R_f = 0.30) to yield 6-endo-bromo-3,3-dimethyl-5-exo-(phenylselanyl)bicyclo[2.2.1]heptan-2-one **171** as a white solid (2.58 g, 6.93 mmol, 76%). M.p. 78-82 °C.

^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.18 (3H, s, H_8), 1.20 (3H, s, H_9), 2.13-2.24 (2H, m, H_{7a} , H_{7b}), 2.38-2.41 (1H, m, H_4), 2.86-2.90 (1H, m, H_1), 3.96-3.99 (1H, m, H_5), 4.36-4.39 (1H, m, H_6), 7.32-7.39 (3H, m, $\text{H}_{2'}$, $\text{H}_{4'}$), 7.60-7.66 (2H, m, $\text{H}_{3'}$).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 20.3 (C_9), 24.3 (C_8), 34.0 (C_7), 48.0 (C_5), 48.2 (q, C_3), 50.2 (C_6), 53.6 (C_4), 58.2 (C_1), 128.0 ($\text{C}_{4'}$), 128.8 (q, $\text{C}_{1'}$), 129.3 ($\text{C}_{2'}$), 134.0 ($\text{C}_{3'}$), 215.1 (q,

C₂).IR $\nu_{\max}$ (cm⁻¹): 2972, 1748, 1577, 1464, 1275, 1195, 956.HRMS: (*m/z* - EI) Calculated for C₁₅H₁₇OSeBr (M)⁺ 371.9628, found 371.9619.**6.4.46 6-Bromo-3,3-dimethylbicyclo[2.2.1]hept-5-en-2-one. (172)****General Procedure S**

To a solution of 6-*endo*-bromo-3,3-dimethyl-5-*exo*-(phenylselanyl)bicyclo[2.2.1]heptan-2-one **171** (2.57 g, 6.91 mmol), acetic acid (0.55 mL, 8.64 mmol), and THF (20 mL) cooled to -10 °C was slowly added hydrogen peroxide (30% wt solution in H₂O, 1.60 mL, 13.82 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 2 hrs. The reaction mixture was then poured into ether (20 mL) and washed with water (3 x 5 mL), saturated Na₂CO₃ (3 x 5 mL) and brine (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated to give a clear oil which was purified by column chromatography (9:1 hexane:ethyl acetate, *R_f* = 0.41) to yield 6-bromo-3,3-dimethylbicyclo[2.2.1]hept-5-en-2-one **172** as a white solid (1.20 g, 5.58 mmol, 81%). M.p. 68-72 °C.

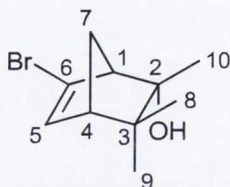
¹H NMR (CDCl₃, 400 MHz): δ (ppm) 1.11 (3H, s, H₈), 1.18 (3H, s, H₉), 2.22-2.28 (1H, m, H_{7a}), 2.37-2.42 (1H, m, H_{7b}), 2.83-2.86 (1H, m, H₄), 3.05-3.08 (1H, m, H₁), 6.64 (1H, d, *J* = 3.2 Hz, H₅).

¹³C NMR (CDCl₃, 100 MHz): δ (ppm) 23.9 (C₈), 26.4 (C₉), 42.2 (q, C₃), 47.2 (C₇), 51.4 (C₄), 62.9 (C₁), 120.4 (q, C₆), 141.3 (C₅), 216.2 (q, C₂).

IR $\nu_{\max}$ (cm^{-1}): 2969, 2870, 1743, 1574, 1283, 972, 825.

HRMS: (m/z - EI) Calculated for $\text{C}_9\text{H}_{11}\text{OBr}$ (M)⁺ 213.9993, found 213.9982.

6.4.47 6-Bromo-2-*exo*-3,3-trimethylbicyclo[2.2.1]hept-5-en-2-ol. (173)



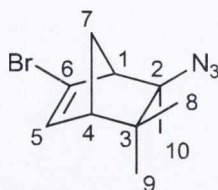
Prepared as per general procedure C 6-bromo-3,3-dimethylbicyclo[2.2.1]hept-5-en-2-one **172** (1.20 g, 5.59 mmol), methylmagnesium bromide (3M in THF, 5.60 mL, 16.8 mmol) and anhydrous THF (35 mL) heated to 35 °C with a reaction time of 3 hrs to yield 6-bromo-2-*exo*-3,3-trimethylbicyclo[2.2.1]hept-5-en-2-ol **173** as a clear viscous oil without the need of further purification (0.95 g, 4.11 mmol, 74%). R_f (85:15 hexane:ethyl acetate) = 0.32.

^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 0.92 (3H, s, H_8), 1.14 (3H, s, H_9), 1.40 (3H, s, H_{10}), 1.67-1.76 (2H, m, H_{7a} , H_{7b}), 2.42-2.47 (1H, m, H_4), 2.72-2.77 (1H, m, H_1), 6.44 (1H, d, J = 3.3 Hz, H_5).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 23.7 (C_8), 25.3 (C_{10}), 26.9 (C_9), 44.0 (q, C_3), 44.9 (C_7), 55.9 (C_4), 63.2 (C_1), 80.5 (q, C_2), 123.4 (q, C_6), 137.1 (C_5).

IR $\nu_{\max}$ (cm^{-1}): 3477, 2963, 1581, 1475, 1291, 1210, 1156, 1088, 1006, 935.

HRMS: (m/z - CI) Calculated for $\text{C}_{10}\text{H}_{16}\text{OBr}$ ($\text{M}+\text{H}$)⁺ 231.0385, found 231.0379.

6.4.48 6-Azido-2-bromo-5,5,6-*endo*-trimethylbicyclo[2.2.1]hept-2-ene. (174)

Prepared as per general procedure D using 6-bromo-2-*exo*-3,3-trimethylbicyclo[2.2.1]hept-5-en-2-ol **173** (2.03 g, 8.79 mmol), 60% H₂SO₄ (25 mL), sodium azide (2.86 g, 43.9 mmol) and CHCl₃ (50 mL) with a reaction time of 2 hrs to give a pale yellow oil. This was further purified by column chromatography (100% hexane, *R_f* = 0.51) to yield 6-azido-2-bromo-5,5,6-*endo*-trimethylbicyclo[2.2.1]hept-2-ene **174** as a clear oil (388 mg, 1.51 mmol, 17%).

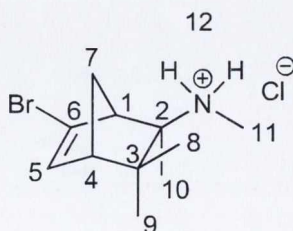
¹H NMR (CDCl₃, 400 MHz): δ (ppm) 0.93 (3H, s, H₉), 1.21 (3H, s, H₈), 1.42 (3H, s, H₁₀), 1.75-1.80 (1H, m, H_{7a}), 1.98-2.03 (1H, m, H_{7b}), 2.39-2.43 (1H, m, H₄), 2.75 (1H, br s, H₁), 6.39 (1H, d, *J* = 3.3 Hz, H₅).

¹³C NMR (CDCl₃, 100 MHz): δ (ppm) 19.7 (C₁₀), 26.0 (C₉), 26.9 (C₈), 45.6 (q, C₃), 45.8 (C₇), 56.3 (C₄), 61.9 (C₁), 77.2 (q, C₂), 123.7 (q, C₆), 139.2, (C₅).

IR ν_{max} (cm⁻¹): 2964, 2084, 1580, 1474, 1372, 1291, 1156, 812.

HRMS: (*m/z* - EI) Calculated for C₁₀H₁₄N₃Br (M)⁺ 255.0371, found 255.0378.

6.4.49 6-Bromo-2,3,3-trimethyl-2-methylaminobicyclo[2.2.1]hept-5-ene. (165)



6-Bromo-2,3,3-trimethylbicyclo[2.2.1]hept-5-en-2-amine

General Procedure T

To a solution of 6-azido-2-bromo-5,5,6-*endo*-trimethylbicyclo[2.2.1]hept-2-ene **174** (390 mg, 1.52 mmol), in anhydrous THF (10 mL) was added tributylphosphine (760 μ L, 3.05 mmol). The reaction was stirred for 4 hrs at room temperature upon which time H₂O (280 μ L, 15.6 mmol) was added and the reaction was stirred for a further 16 hrs. The organic solvent was evaporated and the resulting pale yellow oil was re-dissolved in CH₂Cl₂ (10 mL) and dried over magnesium sulfate. HCl solution (2M in diethyl ether, 2.0 mL, 4.0 mmol) was added to the free amine and the solvent was removed at reduced pressure. The majority of the tributylphosphine oxide was removed by column chromatography using a gradually increasing gradient of 50:50 hexane:ethyl acetate to 50:50 ethyl acetate:methanol to obtain a mixture containing an mixture of 6-bromo-2,3,3-trimethylbicyclo[2.2.1]hept-5-en-2-amine **175** and tributylphosphine oxide. The free amine was isolated by extraction with CH₂Cl₂ (2 x 20 mL) from 1 M NaOH (20 mL).

6-Bromo-2,3,3-trimethyl-2-methylaminobicyclo[2.2.1]hept-5-ene:

Prepared as per general procedure G using crude amine **175**, paraformaldehyde (155 mg, 5.07 mmol), 4 Å molecular sieves (200 mg), anhydrous CH₂Cl₂ (10 mL), sodium borohydride (300 mg, 7.61 mmol) and anhydrous methanol (1 mL) to yield a mixture of amine and tributylphosphine. The hydrochloride salt was formed by the addition of hydrogen chloride solution (2M in diethyl ether, 1.00 mL, 2.00 mmol) to the free amine and subsequent evaporation of the solvent. This was further purified by column chromatography to yield 6-bromo-2,3,3-trimethyl-2-methylaminobicyclo[2.2.1]hept-5-ene **165** as a white solid (131 mg, 0.46 mmol, 28% (2 steps)). M.p. 207-212 °C (decomposes).

¹H NMR (CDCl₃, 400 MHz): δ (ppm) 1.03 (3H, s, H₉), 1.39 (3H, s, H₁₀), 1.62 (3H, s, H₈), 1.87-1.93 (1H, m, H_{7a}), 2.38-2.45 (1H, m, H_{7b}), 2.50-2.54 (1H, m, H₄), 2.75 (3H, s, H₁₁), 3.04-3.08 (1H, m, H₁), 6.45 (1H, d, J = 3.4 Hz, H₅), 8.76-8.85 (1H, br s, H_{12a}), 9.40-9.48 (1H, br s, H_{12b}).

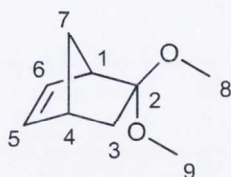
¹³C NMR (CDCl₃, 100 MHz): δ (ppm) 18.0 (C₁₀), 26.3 (C₈), 26.3 (C₉), 29.3 (C₁₁), 45.5

(C₇), 45.8 (q, C₃), 56.9 (C₄), 58.1 (C₁), 70.1 (q, C₂), 123.1 (q, C₆), 139.2 (C₅).

IR $\nu_{\max}$ (cm⁻¹): 2968, 2711, 2439, 1585, 1482, 1422, 1387, 1105, 902.

HRMS: (*m/z* - ES) Calculated for C₁₁H₁₉NBr (M+H)⁺ 244.0701, found 244.0699.

6.4.50 5,5-Dimethoxybicyclo[2.2.1]hept-2-ene.³⁰⁵ (176)



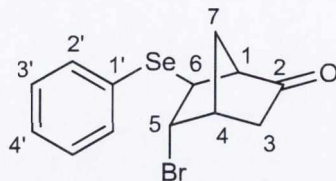
To a solution of bicyclo[2.2.1]hept-5-en-2-one **168** (12.31 g, 113.9 mmol) and *p*-toluenesulfonic acid monohydrate (108 mg, 0.60 mmol) in anhydrous methanol (100 mL) was added trimethylorthoformate (24.90 mL, 227.9 mmol). The reaction mixture was heated to 65 °C and stirred for 16 hrs. The organic solvent was removed at reduced pressure to yield a brown oil which was purified by column chromatography (95:5 hexane:ethyl acetate, *R_f* (9:1 hexane:ethyl acetate) = 0.37) to yield 5,5-dimethoxybicyclo[2.2.1]hept-2-ene **176** as a clear oil (7.22 g, 46.8 mmol, 41%).

¹H NMR (CD₃OD, 400 MHz): δ (ppm) 1.24 (1H, dd, *J* = 11.8, 3.3 Hz, H_{3a}), 1.56-1.62 (1H, m, H_{7a}), 1.71-1.76 (1H, m, H_{7b}), 1.85 (1H, dd, *J* = 11.8, 3.3 Hz, H_{3b}), 2.82 (1H, m, H₁), 2.91 (1H, br s, H₄), 3.19 (3H, s, H₈), 3.26 (3H, s, H₉), 6.07 (1H, dd, *J* = 5.8, 2.9 Hz, H₆), 6.28 (1H, dd, *J* = 5.8, 2.9 Hz, H₅)

¹³C NMR (CD₃OD, 100 MHz): δ (ppm) 39.4 (C₃), 43.0 (C₁), 49.8 (C₇), 50.3 (C₄), 50.4 (C₈), 51.1 (C₉), 112.0 (q, C₂), 134.3 (C₆), 140.1 (C₅)

IR $\nu_{\max}$ (cm⁻¹): 2970, 1379, 1162, 1127, 1049, 951.

HRMS: (*m/z* - EI) Calculated for C₉H₁₄O₂ (M)⁺ 154.0994, found 154.0994.

6.4.51 5-*endo*-Bromo-6-*exo*-(phenylselanyl)bicyclo[2.2.1]heptan-2-one. (177)

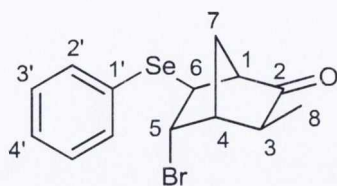
To a solution of phenylselenenyl bromide (0.80 g, 3.39 mmol) in anhydrous CH_2Cl_2 (15 mL) at -78°C , a solution of 5,5-dimethoxybicyclo[2.2.1]hept-2-ene **176** (0.50 g, 3.24 mmol) in anhydrous CH_2Cl_2 (5 mL) pre-cooled to -78°C was added. The reaction mixture was allowed to warm slowly to room temperature upon which time a solution of 98:2 THF: H_2O (10 mL) and spatula tip of PTSA crystals were added. The mixture was stirred in an open vessel overnight. The volatiles were removed under vacuum to give a thick black oil which was purified by column chromatography (9:1 hexane:ethyl acetate, $R_f = 0.35$) to yield 5-bromo-6-*exo*-(phenylselanyl)bicyclo[2.2.1]heptan-2-one **177** as a pale yellow solid (0.65 g, 1.89 mmol, 58%). M.p. $65\text{--}68^\circ\text{C}$ (Lit.³²⁶ $61\text{--}62^\circ\text{C}$).

^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.91-1.98 (1H, m, H_{7a}), 2.13-2.24 (2H, m, H_{7b} , H_{3a}), 2.72 (1H, dd, $J = 18.5, 4.6$ Hz, H_{3a}), 2.69 (1H, br s, H_4), 2.91-2.97 (1H, m, H_1), 3.43-3.47 (1H, m, H_6), 4.37-4.41 (1H, m, H_5), 7.31-7.38 (3H, m, H_2' , H_4'), 7.59-7.64 (2H, m, H_3').

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 35.2 (C_7), 41.0 (C_3), 43.4 (C_1), 47.7 (C_6), 55.8 (C_5), 57.0 (C_4), 128.1 (q, C_1'), 128.6 (C_4'), 129.6, (C_2'), 134.8, (C_3'), 212.4 (q, C_2).

IR ν_{max} (cm^{-1}): 2975, 1742, 1578, 1479, 1435, 1287, 1255, 1150, 1022, 930.

HRMS: (m/z - EI) Calculated for $\text{C}_{13}\text{H}_{13}\text{OSeBr}$ (M^+) 343.9315, found 343.9317.

6.4.52 3-*exo*-5-*endo*-Bromo-6-*exo*-(phenylselanyl)bicyclo[2.2.1]heptan-2-one. (178)

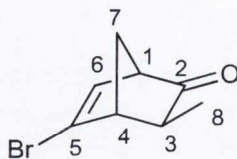
Prepared as per general procedure R using 5-bromo-6-*exo*-(phenylselanyl)bicyclo[2.2.1]heptan-2-one **177** (5.90 g, 17.1 mmol), a solution of sodium bis(trimethylsilyl)amide (1.9M in THF, 13.60 mL, 25.84 mmol), iodomethane (3.25 mL, 52.2 mmol) and anhydrous THF (80 mL) to give a thick pale yellow oil which was purified by column chromatography on (9:1 hexane:ethyl acetate, $R_f = 0.33$) to yield 3-*exo*-5-*endo*-bromo-6-*exo*-(phenylselanyl)bicyclo[2.2.1]heptan-2-one **178** as a white solid (3.18 g, 8.88 mmol, 52%). M.p. 69-70 °C.

^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.15 (3H, d, $J = 7.6$ Hz, H_8), 1.99-2.07 (2H, m, H_{7a} , H_{7b}), 2.56-2.58 (1H, m, H_4), 2.63-2.65 (1H, m, H_1), 2.75-2.80 (1H, m, H_3), 3.42-3.45 (1H, m, H_6), 4.38-4.42 (1H, m, H_5), 7.31-7.38 (3H, m, $\text{H}_{2'}$, $\text{H}_{4'}$), 7.59-7.63 (2H, m, $\text{H}_{3'}$).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 13.9 (C_8), 32.2 (C_7), 43.2 (C_3), 47.1 (C_6), 49.0 (C_4), 56.4 (C_5), 56.8 (C_1), 127.9 (q, $\text{C}_{1'}$), 128.4 ($\text{C}_{4'}$), 129.3 ($\text{C}_{2'}$), 134.7 ($\text{C}_{3'}$), 214.8 (q, C_2).

IR ν_{max} (cm^{-1}): 2976, 1743, 1476, 1254, 1154, 906.

HRMS: (m/z - EI) Calculated for $\text{C}_{14}\text{H}_{15}\text{OSeBr}$ (M^+) 357.9471, found 357.9461.

6.4.53 5-Bromo-3-*exo*-methylbicyclo[2.2.1]hept-5-en-2-one. (179)

Prepared as per general procedure S using 3-*exo*-5-*endo*-bromo-6-*exo*-(phenylselanyl)bicyclo[2.2.1]heptan-2-one **178**, (3.10 g, 8.65 mmol), hydrogen peroxide (30% solution in H₂O, 2.00 mL, 17.7 mmol), acetic acid (0.70 mL, 10.8 mmol) and THF (25 mL) to give a brown solid that was purified by column chromatography (9:1 hexane:ethyl acetate, *R_f* = 0.44) to yield 5-bromo-3-*exo*-methylbicyclo[2.2.1]hept-5-en-2-one **179** as a white solid (1.70 g, 8.46 mmol, 98%). M.p. 70-73 °C.

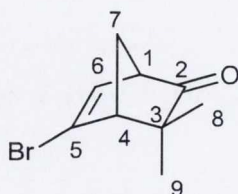
¹H NMR (CDCl₃, 400 MHz): δ (ppm) 1.18 (3H, d, *J* = 7.5 Hz, H₈), 2.06 (1H, dq, *J* = 7.5, 3.3 Hz, H₃), 2.10-2.16 (1H, m, H_{7a}), 2.26-2.32 (1H, m, H_{7b}), 2.82 (1H, br s, H₄), 3.00-3.04 (1H, m, H₁), 6.10-6.13 (1H, m, H₆).

¹³C NMR (CDCl₃, 100 MHz): δ (ppm) 15.3 (C₈), 39.2 (C₃), 45.9 (C₇), 54.2 (C₄), 56.9 (C₁), 129.5 (C₆), 134.5 (q, C₅), 214.8 (q, C₂).

IR ν_{max} (cm⁻¹): 2977, 2937, 1743, 1572, 1038, 942.

HRMS: (*m/z* - EI) Calculated for C₈H₉OBr (M)⁺ 198.9759, found 198.9768.

6.4.54 5-Bromo-3,3-dimethylbicyclo[2.2.1]hept-5-en-2-one. (180)



Prepared as per general procedure R using 5-bromo-3-*exo*-methylbicyclo[2.2.1]hept-5-en-2-one **179** (2.16 g, 10.74 mmol), a solution of sodium bis(trimethylsilyl)amide (1.9M in THF,

17.0 mL, 32.3 mmol), iodomethane (3.35 mL, 53.8 mmol) and anhydrous THF (50 mL) to give a pale yellow oil that was purified by column chromatography (9:1 hexane:ethyl acetate, $R_f = 0.45$) to yield 5-bromo-3,3-dimethylbicyclo[2.2.1]hept-5-en-2-one **180** as a white solid (1.41 g, 6.56 mmol, 61%). M.p. 74-75 °C.

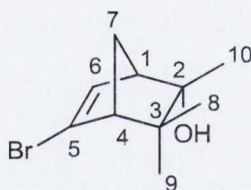
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.18 (3H, s, H_8), 1.23 (3H, s, H_9), 2.23-2.27 (1H, m, H_{7a}), 2.37-2.41 (1H, m, H_{7b}), 2.81-2.84 (1H, br s, H_4), 3.06-3.10 (1H, m, H_1), 6.17-6.21 (1H, m, H_6).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 24.0 (C_9), 24.4 (C_8), 43.1 (q, C_3), 48.1 (C_7), 57.3 (C_1), 58.4 (C_4), 129.4 (C_6), 133.7 (q, C_5), 217.5 (q, C_2).

IR ν_{max} (cm^{-1}): 2972, 1742, 1577, 1462, 1124, 1052, 973.

HRMS: (m/z - EI) Calculated for $\text{C}_9\text{H}_{11}\text{OBr}$ (M^+) 213.9993, found 213.9991.

6.4.55 5-Bromo-2-*exo*-3,3-trimethylbicyclo[2.2.1]hept-5-en-2-ol. (**181**)



Prepared as per general procedure C using 5-bromo-3,3-dimethylbicyclo[2.2.1]hept-5-en-2-one **180** (1.40 g, 6.51 mmol), a solution of methylmagnesium bromide (3M in THF, 6.50 mL, 19.5 mmol) and THF (15 mL) to yield 5-bromo-2-*exo*-3,3-trimethylbicyclo[2.2.1]hept-5-en-2-ol **181** as a clear viscous oil without the need for further purification (1.23 g, 5.33 mmol, 85%). R_f (8:2 hexane:ethyl acetate) = 0.43.

^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.06 (3H, s, H_8), 1.16 (3H, s, H_9), 1.39 (3H, s, H_{10}), 1.69-1.73 (1H, m, H_{7a}), 1.75-1.79 (1H, m, H_{7b}), 2.48 (1H, br s, H_4), 2.70-2.74 (1H, m, H_1),

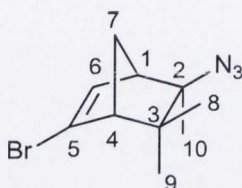
6.29 (1H, d, $J = 3.3$ Hz, H₆).

¹³C NMR (CDCl₃, 150 MHz): δ (ppm) 23.3 (C₈), 25.4 (C₁₀), 27.5 (C₉), 45.5 (q, C₃), 45.8 (C₇), 57.8 (C₁), 62.8 (C₄), 80.4 (q, C₂), 129.8 (q, C₅), 132.8 (C₆).

IR $\nu_{\max}$ (cm⁻¹): 3468, 2965, 1474, 1291, 1089, 1048, 936.

HRMS: (m/z - CI) Calculated for C₁₀H₁₄Br (M+H-H₂O)⁺ 213.0279, found 213.0280.

6.4.56 5-Azido-2-bromo-5-*endo*-,6,6-trimethylbicyclo[2.2.1]hept-2-ene. (182)



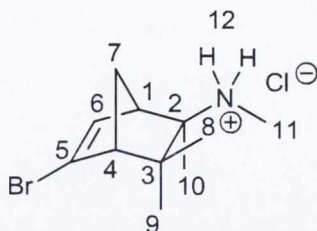
Prepared as per general procedure D using 5-bromo-2-*exo*-3,3-trimethylbicyclo[2.2.1]hept-5-en-2-ol **181** (1.22 g, 5.28 mmol), 60% H₂SO₄ (12 mL), sodium azide (2.40 g, 36.9 mmol) and CHCl₃ (30 mL) with a reaction time of 6 hrs to give a pale yellow oil which was purified by column chromatography (100% hexane, $R_f = 0.55$) to yield 5-azido-2-bromo-5-*endo*-,6,6-trimethylbicyclo[2.2.1]hept-2-ene **182** as a clear oil (579 mg, 2.26 mmol, 43%).

¹H NMR (CDCl₃, 400 MHz): δ (ppm) 1.07 (3H, s, H₉), 1.22 (3H, s, H₈), 1.30 (3H, s, H₁₀), 1.76-1.80 (1H, m, H_{7a}), 2.00-2.04 (1H, m, H_{7b}), 2.43 (1H, br s, H₄), 2.72 (1H, br s, H₁), 6.17 (1H, d, $J = 3.5$ Hz, H₆).

¹³C NMR (CDCl₃, 100 MHz): δ (pp) 20.6 (C₁₀), 25.0 (C₈), 26.9 (C₉), 45.9 (q, C₃), 46.0 (C₇), 55.7 (C₁), 62.7 (C₄), 71.4 (q, C₂), 130.1 (q, C₅), 132.3, (C₆).

IR $\nu_{\max}$ (cm⁻¹): 2964, 2086, 1582, 1437, 1260, 1072, 1006, 867.

6.4.57 5-Bromo-2,3,3-trimethyl-2-methylaminobicyclo[2.2.1]hept-5-ene. (166)

*5-Bromo-2-endo-3,3-trimethylbicyclo[2.2.1]hept-5-en-2-amine :*

Prepared as per general procedure T using 5-azido-2-bromo-5-*endo*-6,6-trimethylbicyclo[2.2.1]hept-2-ene **182** (627 mg, 2.45 mmol), tributylphosphine (1.25 mL, 4.90 mmol), THF (10 mL), H₂O (450 μ L, 24.5 mmol) and hydrogen chloride solution (2M in diethyl ether, 2 mL, 4 mmol). The hydrochloride salt was purified by column chromatography using a gradually increasing gradient of 99:1 to 95:5 EtOAc:methanol to obtain a mixture of 5-bromo-2,3,3-trimethylbicyclo[2.2.1]hept-5-en-2-amine **183** and tributylphosphine oxide. The free amine was isolated by extraction with CH₂Cl₂ (2 x 20 mL) from 1 M NaOH (20 mL).

5-Bromo-2,3,3-trimethyl-2-methylaminobicyclo[2.2.1]hept-5-ene:

Prepared as per general procedure G using crude amine **183**, paraformaldehyde (257 mg, 8.58 mmol), 4 Å molecular sieves (300 mg), anhydrous CH₂Cl₂ (20 mL), sodium borohydride (430 mg, 11.1 mmol) and anhydrous methanol (1 mL). The hydrochloride salt of 5-bromo-2,3,3-trimethyl-2-methylaminobicyclo[2.2.1]hept-5-ene **166** was formed by the addition of hydrogen chloride solution (2M in diethyl ether, 750 μ L, 1.50 mmol) to the free amine. This was further purified by column chromatography to yield 5-bromo-2,3,3-trimethyl-2-methylaminobicyclo[2.2.1]hept-5-ene **166** as a white solid (297 mg, 1.06 mmol, 43% (2 steps)). M.p. 180-185 °C (decomposes).

¹H NMR (CDCl₃, 400 MHz): δ (ppm) 1.15 (3H, s, H₉), 1.29 (3H, s, H₁₀), 1.62 (3H, s, H₈), 1.86-1.93 (1H, m, H_{7a}), 1.43-1.48 (1H, m, H_{7b}), 2.53 (1H, br s, H₄), 2.74 (1H, app t, J = 4.9 Hz, H₁₁), 3.13 (1H, br s, H₁), 6.20 (1H, d, J = 3.4 Hz, H₆), 8.96-9.06 (1H, br s, H_{12a}), 9.26-9.35 (1H, br s, H_{12b}).

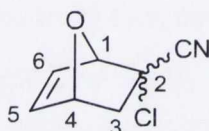
^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 18.2 (C_{10}), 25.0 (C_9), 26.0 (C_8), 29.0 (C_{11}), 45.0 (C_7), 45.5 (q, C_3), 52.0 (C_1), 62.9 (C_4), 69.4 (q, C_2), 129.7 (q, C_5), 131.7 (C_6).

IR ν_{max} (cm^{-1}): 2958, 2731, 1589, 1478, 1427, 1386, 1103, 1006, 882.

HRMS: (m/z - ES) Calculated for $\text{C}_{11}\text{H}_{19}\text{NBr}$ ($\text{M}+\text{H}$) $^+$ 244.0701, found 244.0707.

6.5 Synthesis of compounds described in chapter 4.

6.5.1 2-Chloro-2-cyano-7-oxabicyclo[2.2.1]hept-5-ene.³⁰⁷ (**195**)



A mixture of furan (7.00 mL, 96.3 mmol), α -chloroacrylonitrile (5.99 g, 68.8 mmol) and ZnI_2 (0.94 g, 2.95 mmol) were heated in a stoppered round bottomed flask at 40 °C for 40 hrs. The reaction mixture was diluted with ethyl acetate (40 mL) and the combined organic layers were washed with water (2 x 20 mL) and brine (20 mL) before being dried over magnesium sulfate. The solvent was filtered and removed under reduced pressure. The crude residue was purified by column chromatography (8:2 hexane:ethyl acetate, R_f = 0.4) to yield 2-chloro-2-cyano-7-oxabicyclo[2.2.1]hept-5-ene **195** as a pale yellow oil (6.91 g, 44.4 mmol, 64%). An inseparable 1: 1.3 ratio of isomers was noted.

^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.82 (1H, app d, J = 13.1 Hz, H_{3a} minor isomer), 2.35 (1H app d, J = 13.1 Hz, H_{3a} major isomer), 2.49 (1H, dd, J = 13.1, 5.0 Hz, H_{3b} major isomer), 2.85 (1H, dd, J = 13.1, 5.0 Hz, H_{3b} minor isomer), 5.21 (1H, br s, H_1 major isomer), 5.24 (1H, app d, J = 4.7 Hz H_4 minor isomer), 5.26 (1H, app d, J = 4.1 Hz H_4 major isomer), 5.34 (1H, br s, H_1 minor isomer), 6.46 (1H, dd, J

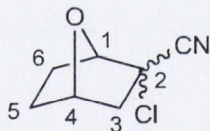
= 6.1, 1.9 Hz, H₆ minor isomer), 6.57 (1H, app d, *J* = 5.6 Hz, H₆ major isomer), 6.67 (1H, dd, *J* = 6.1, 1.9 Hz, H₅ minor isomer), 6.73 (1H, dd, *J* = 5.6, 1.9 Hz, H₅ major isomer).

¹³C NMR (CDCl₃, 100 MHz): δ (ppm) 44.4 (C₃ minor isomer), 45.8 (C₃ major isomer), 51.5 (q, C₂ minor isomer), 53.9 (q, C₂ major isomer), 79.5 (C₄ major isomer), 79.7 (C₄ minor isomer), 85.0 (C₁ minor isomer), 87.7 (C₁ major isomer), 118.4 (CN, major isomer), 120.1 (CN, minor isomer), 132.2 (C₆ minor isomer), 132.6 (C₆ major isomer), 138.3 (C₅ minor isomer), 140.4 (C₅ major isomer).

IR ν_{max} (cm⁻¹): 3020, 2238, 1315, 1033, 1024, 905.

HRMS: (*m/z* - EI) Calculated for C₇H₆ClNO (M)⁺ found Retro Diels-Alder.

6.5.2 2-Chloro-2-cyano-7-oxabicyclo[2.2.1]heptane. (196)



Prepared as per general procedure E using 2-chloro-2-cyano-7-oxabicyclo[2.2.1]hept-5-ene **195** (0.20 g, 1.29 mmol), methanol (25 mL) and palladium on charcoal (0.02 g, 10% w/w) with a reaction time of 4 hrs under an atmosphere of hydrogen at atmospheric pressure. The product was purified by column chromatography (9:1 hexane: ethyl acetate, *R_f* = 0.4) to yield 2-chloro-2-cyano-7-oxabicyclo[2.2.1]heptane **196** (0.16 g, 1.02 mmol, 79%) as a clear colourless oil. A 1:1 ratio of isomers was noted.

¹H NMR (CDCl₃, 400 MHz): δ (ppm) 1.56-1.62 (1H, m, H_{5a} B isomer), 1.64-1.68 (1H, m, H_{5a} A isomer), 1.90-1.82 (3H, m, H_{6a}, A isomer, H_{5b} A & B isomers), 1.96-1.91 (1H, m,

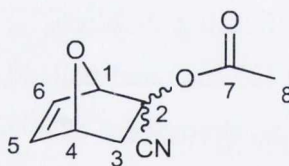
H_{6a} B isomer), 1.97 (1H, app d, $J = 13.7$ Hz, H_{3a} A isomer), 2.14 (1H, m, H_{6b} B isomer), 2.41 (1H, m, H_{6b} A isomer), 2.49 (1H, app d, $J = 13.7$ Hz, H_{3a} B isomer), 2.53 (1H, m, H_{3b} B isomer), 2.82 (1H, ddd, $J = 13.7, 5.4, 2.7$ Hz, H_{3b} A isomer), 4.75 (1H, app d, $J = 5.6$ Hz, H₁ B isomer), 4.78 (1H, app t, $J = 5.6$ Hz, H₄ A isomer), 4.84–4.89 (2H, m, H₄ B isomer & H₁ A isomer).

¹³C NMR (CDCl₃, 100 MHz): δ (ppm) 24.3 (C₆ A isomer), 25.9 (C₆ B isomer), 28.3 (C₅ B isomer), 29.2 (C₅ A isomer), 48.5 (C₃ A isomer), 50.8 (C₃ B isomer), 56.0 (q C₂ A isomer), 57.7 (q C₂ B isomer), 77.6 (C₄ B isomer), 78.0 (C₄ A isomer), 83.9 (C₁ A isomer), 85.9 (C₁ B isomer), 118.5 (CN B isomer), 119.8 (CN A isomer).

IR $\nu_{\max}$ (cm⁻¹): 2961, 2244, 1738, 1020, 930.

HRMS: (m/z - CI) Calculated for C₇H₈ClNO (M)⁺ 157.0294, found 157.0290.

6.5.3 2-Cyano-7-oxabicyclo[2.2.1]hept-5-en-yl acetate.³⁰⁸ (198)



A mixture of furan (16.50 mL, 225.00 mmol), α -acetoxyacrylonitrile (10.0 g, 90.0 mmol) and ZnI₂ (20.0 g, 62.7 mmol) were warmed in a stoppered round bottomed flask at 30 °C for 5 days. The reaction mixture was diluted with ethyl acetate (300 mL) washed with water (2 x 150 mL), brine (100 mL) and dried over magnesium sulfate before filtering. The solvent was evaporated at reduced pressure and was purified by column chromatography with 8:2 hexane: ethyl acetate ($R_f = 0.3$) as the eluent to yield 2-cyano-7-oxabicyclo[2.2.1]hept-5-en-yl acetate

198 as a clear colourless oil (14.92 g, 83.27 mmol, 93%). A ratio of 1:4 of diastereoisomers was observed.

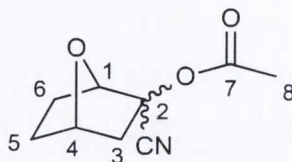
^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.75 (1H, app d, $J = 12.8$ Hz, H_{3a} major isomer), 2.08 (3H, s, H_9 major isomer), 2.20 (3H, s, H_9 minor isomer), 2.23 (1H, dd, $J = 12.8, 4.5$ Hz, H_{3a} minor isomer), 2.31 (1H, app d, $J = 12.8$ Hz, H_{3b} minor isomer), 2.75 (1H, dd, $J = 12.8, 4.5$ Hz, H_{3b} major isomer), 5.15 (1H, m, H_4 major isomer), 5.18 (1H, m, H_4 minor isomer), 5.32 (1H, s, H_1 minor isomer), 5.63 (1H, s, H_1 major isomer), 6.24 (1H, app d, $J = 6.3$ Hz, H_6 major isomer), 6.53 (1H, app d, $J = 6.3$ Hz, H_6 minor isomer), 6.67 (1H, app d, $J = 6.3$ Hz, H_5 major isomer), 6.73 (1H, app d, $J = 6.3$ Hz, H_5 minor isomer).

^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 20.4 (C_8 major isomer), 20.9 (C_8 minor isomer), 41.1 (C_3 major isomer), 41.9 (C_3 minor isomer), 71.9 (q, C_2 major isomer), 73.2 (q, C_2 minor isomer), 78.6 (C_4 minor isomer), 78.7 (C_4 major isomer), 83.4 (C_1 major isomer), 83.9 (C_1 minor isomer), 117.7 (q, CN minor isomer), 119.3 (q, CN major isomer), 131.1 (C_6 major isomer), 132.3 (C_6 minor isomer), 139.9 (C_5 major isomer), 141.1 (C_5 minor isomer), 169.2 (C_7 major isomer), 169.7 (C_7 minor isomer).

IR ν_{max} cm^{-1} : 2925, 2238, 1749, 1573, 1237, 1185, 1060, 1030.

HRMS: (m/z - CI) Calculated for $\text{C}_9\text{H}_{13}\text{N}_2\text{O}_3$ ($\text{M}+\text{NH}_4$) $^+$ 197.0926, found 197.0919.

6.5.4 2-Cyano-7-oxabicyclo[2.2.1]heptanyl acetate. (200)



Prepared as per general procedure E using 2-cyano-7-oxabicyclo[2.2.1]hept-5-en-yl acetate **198** (4.89 g, 26.9 mmol), methanol (25 mL) and palladium on charcoal (0.50 g, 10% w/w) with a reaction time of 16 hrs under 3 atm hydrogen pressure to yield 2-cyano-7-oxabicyclo[2.2.1]heptanyl acetate **200** as a yellow oil (4.45 g, 24.6 mmol, 90%). A 1:2.5 ratio of isomers was noted.

^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.56 (2H, m, H_{5a} , minor isomer & H_{6a} , major isomer), 1.75-1.81 (1H, m, H_{5a} , major isomer), 1.81-1.90 (5H, m, H_{3a} , H_{5b} , H_{6b} , major isomer & H_{5b} , H_{6b} , minor isomers), 2.15 (3H, s, H_8 , minor isomer), 2.17 (3H, s, H_8 , major isomer), 2.26 (1H, m, H_{3a} , minor isomer), 2.36 (H, app d, $J = 14.0$ Hz, H_{3b} , minor isomer), 2.67 (1H, ddd, $J = 14.0, 5.7, 2.1$ Hz, H_{3b} , major isomer), 4.69 (1H, app t, $J = 5.7$ Hz, H_4 , major isomer), 4.71 (1H, app t, $J = 5.7$ Hz, H_4 , minor isomer), 4.84 (1H, app d, $J = 5.7$ Hz, H_1 , minor isomer), 5.09 (1H, app d, $J = 5.7$ Hz, H_1 , major isomer).

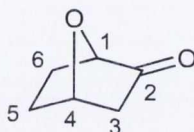
^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 20.5 (C_9 , major isomer), 20.8 (C_9 , minor isomer), 23.0 (C_5 , major isomer), 24.4 (C_6 , minor isomer), 28.2 (C_5 , minor isomer), 28.9 (C_6 , major isomer), 44.5 (C_3 , major isomer), 46.8 (C_3 , minor isomer), 74.9 (q, C_2 , major isomer), 76.0 (q, C_2 , minor isomer), 76.5 (C_4 , minor isomer), 76.7 (C_4 , major isomer), 81.7 (C_1 , major isomer), 81.8 (C_1 , minor isomer).

117.4 (q, CN, minor isomer), 118.8 (q, CN, major isomer), 169.1 (q, C₇, major isomer), 169.2 (q, C₇, minor isomer).

IR $\nu_{\max}$ (cm⁻¹): 2963, 2239, 1751, 1221, 1372, 1221, 997.

HRMS: (m/z - CI) Calculated for C₉H₁₅N₂O₃ (M+NH₄)⁺ 199.1083, found 199.1093.

6.5.5 7-Oxabicyclo[2.2.1]heptan-2-one.³²⁷ (**197**)



To a solution of 2-cyano-7-oxabicyclo[2.2.1]heptanyl acetate **200** (4.60 g, 25.4 mmol) in methanol (40 mL) was added sodium methoxide (4.10 g, 76.2 mmol). The reaction mixture was stirred at 25 °C for 2 hrs. Formalin (37%, 3.10 mL) was added and the reaction was stirred for a further hour at 25 °C. The reaction mixture was diluted with water (50 mL), extracted with CH₂Cl₂ (2 x 40 mL), washed with brine (40 mL) and dried over magnesium sulfate before being filtered. The volatiles were removed at reduced pressure. The product was purified by column chromatography (8:2 hexane: ethyl acetate, R_f = 0.3) to yield 7-oxabicyclo[2.2.1]heptan-2-one **197** as a pale yellow oil (1.97 g, 17.6 mmol, 69%).

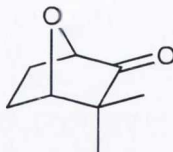
¹H NMR (CDCl₃, 400 MHz): δ (ppm) 1.66-1.75 (2H, m, H_{5a} & H_{6a}), 1.93-1.99 (2H, m, H_{5b}, H_{6b}), 2.02 (1H, app d, J = 17.7 Hz, H_{3a}), 2.44 (1H, dd, J = 17.7, 5.9 Hz, H_{3b}), 4.38 (1H, m, H₁), 4.90 (1H, m, H₄).

¹³C NMR (CDCl₃, 100 MHz): δ (ppm) 24.4 (C₆), 27.9 (C₅), 45.5 (C₃), 77.3 (C₄), 79.5 (C₁), 212.0 (q, C₂).

IR $\nu_{\max}$ (cm⁻¹): 2956, 1767, 1267, 1003, 921, 882, 772.

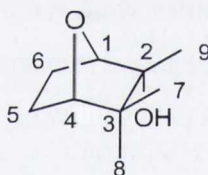
HRMS: (m/z - CI) Calculated for C₆H₉O₂ (M+H)⁺ 113.0603, found 113.0608.

6.5.6 3,3-Dimethyl-7-oxabicyclo[2.2.1]heptan-2-one. (201)



To a solution of 7-oxabicyclo[2.2.1]heptan-2-one **197** (0.10 g, 0.89 mmol) and iodomethane (0.20 mL, 2.68 mmol) in THF (10 mL) was added potassium *tert*-butoxide (0.33 g, 2.68 mmol) in THF (30 mL) at room temperature. The reaction was stirred for 3 hrs upon which time the mixture was diluted with cold water (20 mL), extracted with diethyl ether (2 x 20 mL), the combined organic layers were washed with brine (20 mL) and dried over magnesium sulfate before being filtered. The volatiles were removed under reduced pressure to yield 3,3-dimethyl-7-oxabicyclo[2.2.1]heptan-2-one **201** (0.07 g, 0.49 mmol, 55%). This compound proved unstable towards column chromatography and was used in the next step without further purification.

6.5.7 2-*endo*-3,3-Trimethyl-7-oxabicyclo[2.2.1]heptan-2-ol. (202)



Prepared as per general procedure C using 3,3-dimethyl-7-oxabicyclo[2.2.1]heptan-2-one **201** (0.40 g, 2.86 mmol), a solution of methylmagnesium bromide (3M in diethyl ether, 3.00 mL, 8.57 mmol) and THF (20 mL) to give a pale yellow oil which was purified by column chromatography (8:2 hexane: ethyl acetate, $R_f = 0.6$) to yield 2,3,3-trimethyl-7-oxabicyclo[2.2.1]heptan-2-ol **202** as a pale yellow oil (0.31 g, 1.98 mmol, 68%).

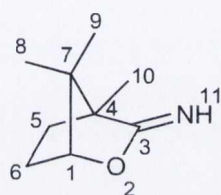
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 0.94 (3H, s, H_8), 1.09 (3H, s, H_7), 1.34 (3H, s, H_9), 1.49-1.63 (2H, m, H_{6a} , H_{5a}), 1.91 (1H, m, H_{5b}), 2.18 (1H, m, H_{6b}), 3.98 (1H, m, H_4), 4.06 (1H, m, H_1).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 20.2 (C_8), 22.7 (C_6), 24.6 (C_5), 25.6 (C_9), 26.1 (C_7), 44.6 (q, C_3), 78.8 (q, C_2), 86.6 (C_1), 88.5 (C_4).

IR ν_{max} (cm^{-1}): 3442, 2961, 2871, 1469, 1370, 1107, 1007, 930.

HRMS: (m/z - EI) Calculated. for $\text{C}_9\text{H}_{16}\text{O}_2$ (M^+) 156.1150, found 156.1146.

6.5.8 4,7,7-Trimethyl-2-oxabicyclo[2.2.1]heptan-3-imine. (203)



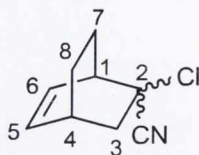
Prepared as per general procedure D using 2-*endo*-3,3-trimethyl-7-oxabicyclo[2.2.1]heptan-2-ol **202** (0.02 g, 0.12 mmol), 70% H_2SO_4 (2 mL), NaN_3 (0.05 g, 0.77 mmol) and CHCl_3 (5 mL) with a reaction time of 4 hrs to yield a yellow oil. This was purified by preparative thin layer chromatography (9:1 hexane: ethyl acetate, R_f = 0.1) to yield 4,7,7-trimethyl-2-oxabicyclo[2.2.1]heptan-3-imine **203** as pale yellow oil (0.015 g, 0.098 mmol, 83%).

^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 0.96 (3H, s, H_8/H_9), 1.23 (3H, s, H_8/H_9), 1.34 (3H, s, H_{10}), 1.72-1.81 (2H, m, H_{5a} & H_{6a}), 2.21-2.29 (1H, m, H_{5b}), 2.37-2.45 (1H, m, H_{6b}), 3.66-3.69 (1H, m, H_{11}), 3.90-3.95 (1H, m, H_1).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 19.3 (C_8/C_9), 21.3 (C_{10}), 21.6 (C_8/C_9), 31.0 (C_5), 35.2 (C_6), 43.4 (q, C_7), 47.5 (q, C_4), 80.5 (C_1), 122.5 (q, C_3).

IR ν_{max} (cm^{-1}): 2925, 1732, 1660, 1458, 909, 733.

As the imine was highly unstable and rapidly decomposed it was not possible to attain a mass spectrum of the compound.

6.5.9 2-Chlorobicyclo[2.2.2]oct-5-ene-2-carbonitrile.³²⁸ (205)

A microwave reaction vessel charged with α -chloroacrylonitrile (4.50 ml, 57.1 mmol) and 1,3-cyclohexadiene (5.50 ml, 68.6 mmol), was heated to 90 °C and was stirred vigorously for 75 minutes under microwave irradiation. The resulting brown solid was purified by column chromatography (100% CH_2Cl_2 , $R_f = 0.92$) to yield 2-chlorobicyclo[2.2.2]oct-5-ene-2-carbonitrile **205** as a white semi-solid (5.56g, 33.2 mmol, 58%).

Major isomer

^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.35 (1H, m, H_{8a}), 1.51 (1H, m, H_{7a}), 1.58 (1H, m, H_{8b}), 2.04-2.16 (2H, m, H_{3a} , H_{7b}), 2.53 (1H, dd, $J = 14.8, 2.3$ Hz, H_{3b}), 2.72-2.77 (1H, m, H_4), 3.13-3.17 (1H, m, H_1), 6.26 (1H, app t, $J = 7.23$ Hz, H_6), 6.45 (1H, app t, $J = 7.23$ Hz, H_5).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 22.22 (C_7), 22.23 (C_8), 29.5 (C_4), 41.4 (C_1), 45.1 (C_3), 56.3 (C_2), 120.5 (CN), 129.7 (C_6), 134.7 (C_5).

Minor Isomer

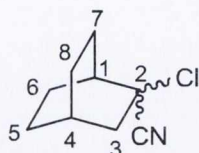
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.13-1.38 (2H, m, H_{8a} , H_{7a}), 1.34-1.71 (1H, m, H_{8b}), 2.04-2.15 (1H, m, H_{3a}), 2.22-2.28 (1H, m, H_{7b}), 2.38-2.43 (1H, app dt, $J = 14.2, 3.2$ Hz, H_{3b}), 2.71-2.77 (1H, m, C_4), 3.05-3.08 (1H, m, H_1), 6.39 (1H, app t, $J = 7.3$ Hz, H_6), 6.52 (1H, app t, $J = 7.3$ Hz, H_5).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 18.8 (C_7), 23.7 (C_8), 29.6 (C_4), 41.3 (C_1), 44.1 (C_3), 56.9 (C_2), 120.9 (q, CN), 130.9 (C_6), 136.8 (C_5).

IR $\nu_{\max}$ cm^{-1} : 2949, 2240, 1442, 960, 810, 704.

HRMS: (m/z - EI) Calculated for $\text{C}_9\text{H}_{10}\text{NCl}$ (M^+) 167.0502, found 167.0501.

6.5.10 2-Chlorobicyclo[2.2.2]octane-2-carbonitrile. (206)



Prepared as per general procedure E using 2-chlorobicyclo[2.2.2]oct-5-ene-2-carbonitrile **205** (1.00 g, 5.89 mmol), methanol (12 mL), THF (8 mL) and palladium on charcoal (0.02 g, 10% w/w) under a hydrogen atmosphere with a reaction time of 16 hrs at atmospheric pressure. Product was purified by column chromatography (97:3 hexane:ethyl acetate, R_f = 0.6) to yield 2-chlorobicyclo[2.2.2]octane-2-carbonitrile **206** as a pale yellow solid (0.94 g, 5.54 mmol, 93%). M.p. 106-108 °C (Lit.³²⁹ 108-109 °C).

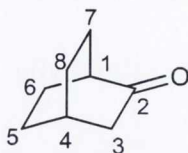
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.56-1.68 (5H, m, $\text{H}_5/\text{H}_6/\text{H}_7/\text{H}_8$), 1.78-1.85 (2H, m, H_4 , $\text{H}_5/\text{H}_6/\text{H}_7/\text{H}_8$), 2.02-2.10 (1H, m, $\text{H}_5/\text{H}_6/\text{H}_7/\text{H}_8$), 2.10-2.16 (2H, m, H_1 , $\text{H}_5/\text{H}_6/\text{H}_7/\text{H}_8$), 2.25 (1H, app d, J = 14.7 Hz, H_{3a}), 2.57 (1H, app dt, J = 14.7, 2.9 Hz, H_{3b}).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 19.8 ($\text{C}_5/\text{C}_6/\text{C}_7/\text{C}_8$), 23.0 ($\text{C}_5/\text{C}_6/\text{C}_7/\text{C}_8$), 23.4 ($\text{C}_5/\text{C}_6/\text{C}_7/\text{C}_8$), 23.5 ($\text{C}_5/\text{C}_6/\text{C}_7/\text{C}_8$), 24.5 (C_4), 36.2 (C_1), 44.4 (C_3), 58.1 (q, C_2), 121.0 (q, CN).

IR $\nu_{\max}$ cm^{-1} : 2945, 2871, 1454, 1441, 957, 814.

HRMS: (m/z - EI) Calculated for $\text{C}_9\text{H}_{12}\text{NCl}$ (M^+) 169.0658, found 169.0656.

6.5.11 Bicyclo[2.2.2]octan-2-one. (207)



To a solution of 2-chlorobicyclo[2.2.2]octane-2-carbonitrile **206** (0.80 g, 4.72 mmol) in DMSO (25 mL) was added potassium hydroxide (1.06 g, 18.9 mmol) in H₂O (5 mL). The reaction mixture was stirred at room temperature for 18 hrs. The reaction mixture was diluted with water (50 mL), extracted with ether (3 x 40 mL), washed with brine (40 mL) and dried over magnesium sulfate before being filtered. The solvent was removed at reduced pressure. The product was purified by column chromatography (98:2 hexane: ethyl acetate, R_f = 0.3) to yield bicyclo[2.2.2]octan-2-one **207** as a pale yellow oil (0.36 g, 2.89 mmol, 61%). The spectroscopic analysis is consistent with that reported in the literature.³³⁰

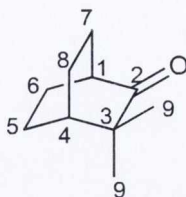
¹H NMR (CDCl₃, 600 MHz): δ (ppm) 1.58-1.68 (2H, m, H₅/H₆/H₇/H₈), 1.69-1.79 (2H, m, H₅/H₆/H₇/H₈), 1.80-1.88 (4H, m, H₅/H₆/H₇/H₈), 2.18 (1H, heptet, J = 3.0 Hz, H₄), 2.25-2.78 (3H, m, H₁, H_{3a}, H_{3b}).

¹³C NMR (CDCl₃, 150 MHz): δ (ppm) 23.4 (C₅/C₆/C₇/C₈ and C₅/C₆/C₇/C₈), 24.7 (C₅/C₆/C₇/C₈ and C₅/C₆/C₇/C₈), 27.9 (C₄), 42.4 (C₁), 44.7 (C₃), 218.5 (q, C₂).

IR $\nu_{\max}$ cm⁻¹: 2940, 2867, 1723, 1329, 1027, 859.

HRMS: (m/z - EI) Calculated for C₈H₁₂O (M)⁺ 124.0888, found 124.0891.

6.5.12 3,3-Dimethylbicyclo[2.2.2]octan-2-one. (208)



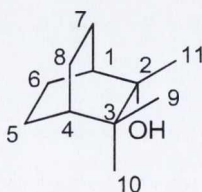
Prepared as per general procedure B using bicyclo[2.2.2]octan-2-one **207** (1.30 g, 9.42 mmol), sodium bis(trimethylsilyl)amide (1.9M in THF, 9.90 mL, 18.8 mmol), iodomethane (1.20 mL, 18.8 mmol) and anhydrous THF (45 mL) to yield a pale yellow oil which was purified by column chromatography (97:3 hexane: ethyl acetate, $R_f = 0.3$) to yield 3,3-dimethylbicyclo[2.2.2]octan-2-one **208** as a pale yellow oil (0.99 g, 6.46 mmol, 69%).

^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.16 (6H, m H_9), 1.26-1.34 (1H, m, $\text{H}_5/\text{H}_6/\text{H}_7/\text{H}_8$), 1.60-1.66 (2H, m, $\text{H}_5/\text{H}_6/\text{H}_7/\text{H}_8$), 1.69 (1H, quintet, $J = 3.0$ Hz, H_4), 1.80-1.85 (3H, m, $\text{H}_5/\text{H}_6/\text{H}_7/\text{H}_8$), 1.91-1.98 (2H, m, $\text{H}_5/\text{H}_6/\text{H}_7/\text{H}_8$), 2.23 (1H, quintet, $J = 3.0$ Hz, H_1).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 22.5 ($\text{C}_5/\text{C}_6/\text{C}_7/\text{C}_8$ and $\text{C}_5/\text{C}_6/\text{C}_7/\text{C}_8$), 23.5 ($\text{C}_5/\text{C}_6/\text{C}_7/\text{C}_8$ & $\text{C}_5/\text{C}_6/\text{C}_7/\text{C}_8$), 23.7 (C_9), 38.5 (C_4), 42.8 (C_1), 46.0 (q, C_3), 223.3 (q, C_2).

IR ν_{max} cm^{-1} : 2944, 2869, 1715, 1455, 1049, 864.

HRMS: (m/z - ESI) Calculated for $\text{C}_{10}\text{H}_{17}\text{O}$ ($\text{M}+\text{H}$) $^+$ 153.1279, found 153.1284.

6.5.13 2-*exo*-3,3-Trimethylbicyclo[2.2.2]octan-2-ol. (209)

Prepared as per general procedure C using 3,3-dimethylbicyclo[2.2.2]octan-2-one **208** (0.90 g, 5.92 mmol), a solution of methylmagnesium bromide (3M in diethyl ether, 6.00 mL, 17.8 mmol) and anhydrous THF (35 mL) warmed to 40 °C with a reaction time of 4 hrs to yield a pale yellow oil which was purified by column chromatography (9:1 hexane: diethyl ether, R_f = 0.2) to yield 2-*exo*-3,3-trimethylbicyclo[2.2.2]octan-2-ol **209** as a white solid (0.82 g, 4.87 mmol, 82%). M.p. 164-166 °C.

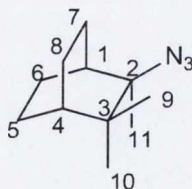
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.02 (3H, s, H_9), 1.06 (3H, s, H_{10}), 1.16-1.18 (1H, m, H_4), 1.25 (3H, s, H_{11}), 1.26-1.42 (3H, m, $\text{H}_5/\text{H}_6/\text{H}_7/\text{H}_8$), 1.43-1.70 (3H, m, H_1 , $\text{H}_5/\text{H}_6/\text{H}_7/\text{H}_8$), 1.71-1.78 (1H, m, $\text{H}_5/\text{H}_6/\text{H}_7/\text{H}_8$), 1.85-2.01 (2H, m, $\text{H}_5/\text{H}_6/\text{H}_7/\text{H}_8$).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 20.9 ($\text{C}_5/\text{C}_6/\text{C}_7/\text{C}_8$), 22.2 ($\text{C}_5/\text{C}_6/\text{C}_7/\text{C}_8$), 22.7 ($\text{C}_5/\text{C}_6/\text{C}_7/\text{C}_8$), 23.4 ($\text{C}_5/\text{C}_6/\text{C}_7/\text{C}_8$), 23.8 (C_{10}), 25.5 (C_{11}), 26.7 (C_9), 38.3 (C_4), 38.7 (q, C_3), 39.5 (C_1), 75.1 (q, C_2).

IR ν_{max} cm^{-1} : 3484, 2937, 1471, 1371, 1063, 912, 868.

HRMS: (m/z - EI) Calculated for $\text{C}_{11}\text{H}_{20}\text{O}$ (M^+) 168.1514, found 168.1511.

6.5.14 2-Azido-2-*endo*-3,3-trimethylbicyclo[2.2.2]octane. (**210**)



Prepared as per general procedure D using 2-*exo*-3,3-trimethylbicyclo[2.2.2]octan-2-ol **209** (0.29 g, 1.72 mmol), 50% H_2SO_4 (5 mL), NaN_3 (0.78 g, 12.1 mmol) and CHCl_3 (50 mL) with a reaction time of 4 hrs to yield a yellow oil which was purified by column chromatography (100% hexane, R_f = 0.55) to yield 2-azido-2-*endo*-3,3-trimethylbicyclo[2.2.2]octane **210** as colourless semi-solid (0.27 g, 1.39 mmol, 81%).

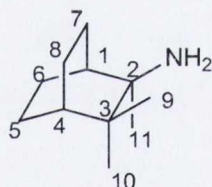
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.04 (3H, s, H_{10}), 1.09 (3H, s, H_9), 1.13-1.17 (1H, m, H_4), 1.34-1.39 (3H, m, $\text{H}_5/\text{H}_6/\text{H}_7/\text{H}_8$), 1.39-1.43 (4H, m, H_{11} , $\text{H}_5/\text{H}_6/\text{H}_7/\text{H}_8$), 1.49-1.59 (2H, m, H_1 , $\text{H}_5/\text{H}_6/\text{H}_7/\text{H}_8$), 1.65-1.78 (2H, m, $\text{H}_5/\text{H}_6/\text{H}_7/\text{H}_8$), 1.86-1.95 (2H, m, $\text{H}_5/\text{H}_6/\text{H}_7/\text{H}_8$).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 20.7 (C_{11}), 21.8 ($\text{C}_5/\text{C}_6/\text{C}_7/\text{C}_8$), 21.9 ($\text{C}_5/\text{C}_6/\text{C}_7/\text{C}_8$), 22.3 ($\text{C}_5/\text{C}_6/\text{C}_7/\text{C}_8$), 22.5 ($\text{C}_5/\text{C}_6/\text{C}_7/\text{C}_8$), 25.8 (C_9), 26.4 (C_{10}), 37.1 (C_1), 38.0 (C_4), 38.8 (q, C_3), 68.3 (q, C_2).

IR ν_{max} cm^{-1} : 2944, 2081, 1392, 1265, 1053.

HRMS: (m/z - EI) Calculated for $\text{C}_{11}\text{H}_{19}\text{N}$ ($\text{M}-\text{N}_2$) $^+$ 165.1517, found 165.1518.

6.5.15 2-endo-3,3-Trimethylbicyclo[2.2.2]octan-2-amine. (211)



Prepared as per general procedure E using 2-azido-2-endo-3,3-trimethylbicyclo[2.2.2]octane **210** (0.10 g, 0.52 mmol), methanol (5 mL) and palladium on charcoal (0.01 g, 10% w/w) under a hydrogen atmosphere at atmospheric pressure overnight to yield 2-endo-3,3-trimethylbicyclo[2.2.2]octan-2-amine **211** as a white solid (0.08 g, 0.48 mmol, 93%). M.p. 135-140 °C, (Lit.³³¹ 168 °C).

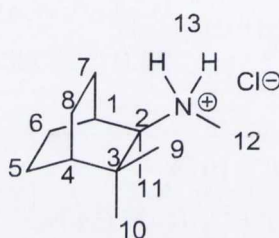
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 0.88 (3H, s, H_{10}), 0.89 (3H, s, H_9), 0.91 (3H, s, H_{11}), 0.99- 1.49 (7H, m, H_1 , $\text{H}_5/\text{H}_6/\text{H}_7/\text{H}_8$), 1.49-1.81 (3H, m, H_4 , $\text{H}_5/\text{H}_6/\text{H}_7/\text{H}_8$).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 11.4 (C_{10}), 14.1 (C_9), 22.1 ($\text{C}_5/\text{C}_6/\text{C}_7/\text{C}_8$), 22.6 (C_{11}), 22.7 ($\text{C}_5/\text{C}_6/\text{C}_7/\text{C}_8$), 29.8 ($\text{C}_5/\text{C}_6/\text{C}_7/\text{C}_8$), 31.7 ($\text{C}_5/\text{C}_6/\text{C}_7/\text{C}_8$), 36.8 (q, C_3), 38.4 (C_4), 38.8 (C_1), 41.3 (q, C_2).

IR ν_{max} cm^{-1} : 3342, 2932, 2871, 1466, 1371, 841.

HRMS: (m/z - EI) Calculated for $\text{C}_{11}\text{H}_{21}\text{N}$ (M^+) 167.1674, found 167.1680.

6.5.16 2,3,3-Trimethyl-2-methylaminobicyclo[2.2.2]octane. (193)



Prepared as per general procedure G using 2-*endo*-3,3-trimethylbicyclo[2.2.2]octan-2-amine **211** (0.06 g 0.36 mmol), paraformaldehyde (0.45 g, 1.26 mmol), activated 4 Å molecular sieves (0.15 g), anhydrous CH_2Cl_2 (10 mL), sodium borohydride (0.06 g, 1.62 mmol) and anhydrous methanol (0.5 mL) to yield a viscous colourless oil. This product was dissolved in anhydrous diethyl ether (2 mL) and a solution of hydrogen chloride (2M in diethyl ether, 0.5 mL, 1.0 mmol) was added. Filtration afforded the HCl salt of 2,3,3-trimethyl-2-methylaminobicyclo[2.2.2]octane **193** as a white solid (0.03 g, 0.14 mmol, 38%). M.p. 164–166 °C (decomposes).

^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.15 (3H, s, H_{10}), 1.21–1.24 (1H, m, H_4), 1.40–1.61 (10H, m, H_9 , H_{11} , $\text{H}_5/\text{H}_6/\text{H}_7/\text{H}_8$), 1.68–1.82 (3H, m, H_1 , $\text{H}_5/\text{H}_6/\text{H}_7/\text{H}_8$), 2.01–2.09 (1H, m, $\text{H}_5/\text{H}_6/\text{H}_7/\text{H}_8$), 2.13–2.19 (1H, m, $\text{H}_5/\text{H}_6/\text{H}_7/\text{H}_8$), 2.67 (3H, t, $J = 5.3$ Hz, H_{12}), 8.28–8.39 (1H, br s, H_{13a}), 9.12–9.22 (1H, br s, H_{13b}).

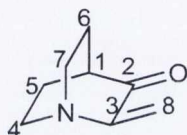
^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 19.1 (C_9), 20.4 ($\text{C}_5/\text{C}_6/\text{C}_7/\text{C}_8$), 21.5 ($\text{C}_5/\text{C}_6/\text{C}_7/\text{C}_8$), 21.6 ($\text{C}_5/\text{C}_6/\text{C}_7/\text{C}_8$), 22.0

(C₅/C₆/C₇/C₈), 25.3 (C₁₁), 26.2 (C₁₀), 27.9 (C₁₂),
32.8 (C₁), 38.1 (q, C₃), 38.4 (C₄), 65.2 (q, C₂).

IR $\nu_{\max}$ cm⁻¹: 2942, 2733, 1468, 1368, 1053.

HRMS: (m/z - ESI) Calculated for C₁₂H₂₄N (M+H)⁺ 182.1909, found 182.1911.

6.5.17 3-Methylenequinuclidin-2-one.³¹¹ (214)



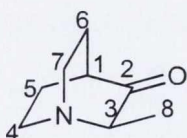
General Procedure T

To a solution of 2-quinuclidone (1.88g, 15.0 mmol) and formaldehyde (37% in H₂O, 1.85 mL, 22.5 mmol) in ethanol (8 mL) and H₂O (3 mL) was added dimethylamine (40% in H₂O, 2.55 mL, 22.5 mmol). The reaction mixture was heated at reflux temperature for 1 hr and then stirred at 70 °C for a further 17 hrs. After this time all unreacted reagents and volatiles were removed at reduced pressure to yield 3-methylenequinuclidin-2-one **214** as a brown oil which was used in the next step without further purification (1.44 g, 10.5 mmol, 69%).

IR $\nu_{\max}$ (cm⁻¹): 2950, 2872, 1715, 1693, 1251, 1054, 1021, 856.

HRMS: (m/z - ESI) Calculated for C₈H₁₂NO (M+H)⁺ 138.0919, found 138.0919.

6.5.18 3-Methylquinuclidin-2-one. (215)



Prepared as per general procedure E using 3-methylenequinuclidin-2-one **214** (2.54 g, 18.5 mmol), methanol (40 mL) and palladium on charcoal (0.26 g, 10% w/w) under a hydrogen at atmospheric pressure (ça 14 hrs) to yield a dark yellow oil. Purification by column

chromatography (93:5:2 ethyl acetate:TEA:methanol, $R_f = 0.2$) gave 3-methylquinuclidin-2-one **215** as a pale yellow oil (1.14 g, 8.33 mmol, 45%).

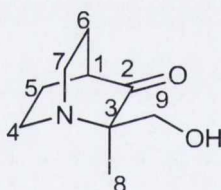
^1H NMR (CDCl_3 , 600 MHz): δ (ppm) 1.33 (3H, d, $J = 7.4$ Hz, H_8), 1.92-2.04 (4H, H_{5a} , H_{5b} , H_{6a} , H_{6b}), 2.42-2.45 (1H, m, H_1), 2.83-2.90 (1H, m, H_4 or H_7), 2.97-3.05 (1H, m, H_4 or H_7), 3.11-3.18 (2H, m, H_4 , H_7), 3.25 (1H, quartet, $J = 7.4$ Hz, H_3).

^{13}C NMR (CDCl_3 , 150 MHz): δ (ppm) 13.9 (C_8), 25.1 (C_5 or C_6), 26.5 (C_5 or C_6), 39.9 (C_1), 40.8 (C_4 or C_7), 48.7 (C_4 or C_7), 65.4 (C_3), 222.0 (q, C_2).

IR ν_{max} (cm^{-1}): 2948, 2872, 1721, 1455, 1107, 1019, 856.

HRMS: (m/z - ESI) Calculated for $\text{C}_8\text{H}_{12}\text{NO}$ ($\text{M}+\text{H}$) $^+$ 140.1075, found 140.1073.

6.5.19 3-(Hydroxymethyl)-3-methylquinuclidin-2-one. (**217**)



Prepared as per general procedure T using 3-methylquinuclidin-2-one **215** (1.70 g, 12.2 mmol), formaldehyde (37% in H_2O , 1.50 mL, 18.3 mmol) and dimethylamine (40% in H_2O , 2.10 mL, 18.3 mmol) in ethanol (20 mL) and H_2O (8 mL) heated to 70 °C for 19 hrs. Purification by column chromatography (90:5:5 ethyl acetate:TEA:methanol, $R_f = 0.1$) yielded 3-(hydroxymethyl)-3-methylquinuclidin-2-one **217** as a yellow solid (0.26 g, 1.54 mmol, 13%). M.p. = 110-112 °C.

^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.46 (3H, s, H_8), 1.96-2.14 (4H, m, H_{5a} , H_{6a} , H_{5b} , H_{6b}), 2.44-2.49 (1H, m, H_1), 2.88-2.99 (2H, m, H_7/H_4), 3.23-3.36 (2H, m, H_7/H_4), 3.69

(1H, d, $J = 11.2$ Hz, H_{9a}), 3.79 (1H, d, $J = 11.2$ Hz, H_{9b}).

¹³C NMR (CDCl₃, 100 MHz): δ (ppm) 19.5 (C₈), 25.3 (C₅/C₆), 26.5 (C₅/C₆), 40.4 (C₁), 43.7 (C₄), 43.7 (C₇), 64.3 (C₉), 68.2 (q, C₃), 221.9 (q, C₂).

IR $\nu_{\max}$ (cm⁻¹): 3410, 2942, 1711, 1454, 1380, 1249, 1073, 1017, 865.

HRMS: (m/z - ESI) Calculated for C₉H₁₆NO₂ (M+H)⁺ 170.1181, found 170.1178.

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8. Appendix.

8.1 Summary of Structure-activity relationship studies.

This section briefly describes the results of structure-activity studies which have been discussed in detail in chapter 1, section 1.5.3. The SAR information obtained from these studies has been divided into sections based on the areas investigated, a general summary is illustrated in Figure 8-6.

8.1.1 Investigation of alkyl substitution.

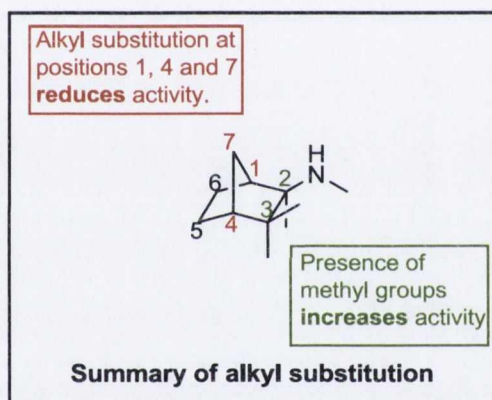


Figure 8-1: Summary of the results of investigating alkyl substitution.

Alkyl substitution has been investigated by Corne *et al.*,²⁶⁰ Stone *et al.*²⁶¹ and Suchocki *et al.*²⁶⁴ The results of their collective works are described below, (see Figure 8-1).

- Methyl groups at positions 2 and 3 are vital for activity. Removal of any of these groups results in a dramatic fall in activity.
- Alkyl substitution at positions 1, 4 or 7 all produce a reduction in antagonistic activity.

8.1.2 Investigation of substitution at the amine.

The effect of alkyl and aryl substitution at the amine has been investigated by Stone *et al.*,²⁶¹ Suchocki *et al.*,²⁶⁴ and Crooks and co-workers.²⁷² The results of their collective works are described below.

- Increasing the size of the alkyl substituent at the amine position produced a decrease in activity, branched groups such as the cyclohexyl, benzyl, phenethyl and phenylpropyl groups produced the greatest deterioration in activity.
- One (MA) or two methyl groups at the amine gave the highest activity.
- In contradiction to the works of Stone *et al.*²⁶¹ and Suchocki *et al.*,²⁶⁴ Crooks and co-workers²⁷² reported a series of MA dimers and trimers, linked at the amine by long alkyl chains, typically C₈-C₁₀. These dimers and trimers produced high levels of antagonistic activity. Their most active compound was a MA trimer illustrated in Figure 8-2.

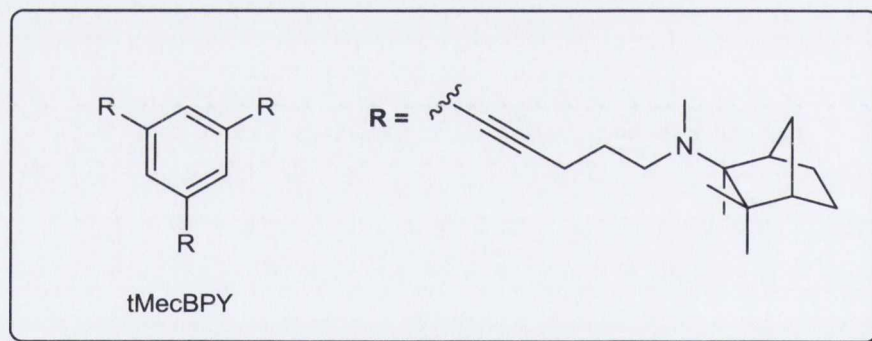


Figure 8-2: MA trimer reported by Crooks *et al.*²⁷²

8.1.3 Investigation of the amine in the *endo* and *exo* position.

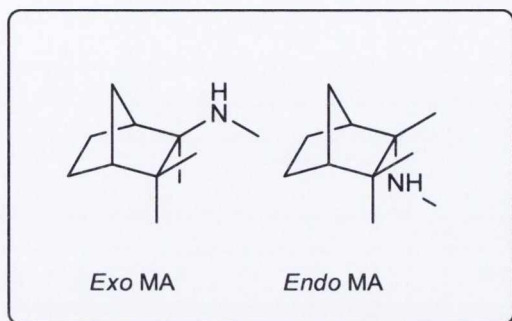


Figure 8-3: A comparison of *exo* vs. *endo* MA.

The orientation of the amine has been investigated by Stone *et al.*²⁶¹ and Suchocki *et al.*²⁶⁴ In each case the *exo* isomer produced a higher degree of activity than that of the corresponding *endo* one.

8.1.4 Investigation of the *R* and *S* enantiomers of MA against the racemate.

Stone *et al.*²⁶¹ examined the *d*- optical isomer of MA against the corresponding racemate. It produced activity approximately equal to the racemate thus suggesting that optical isomerism does not play a significant role in determining the degree of activity. Suchocki *et al.*²⁶⁴ reported that both *R* and *S* enantiomers of MA displayed a similar potency to the racemate.

8.1.5 Investigation of the importance of the bridgehead, position 7.

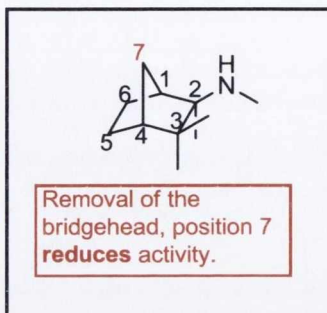


Figure 8-4: Structure of MA highlighting the bridgehead position.

Wragg and co-workers²⁶² and Stone *et al.*²⁶¹ synthesised a number of monocyclic analogues which omitted the bridgehead. A dramatic drop in activity was noted and none of the monocyclic analogues displayed ganglion blocking activity higher than one tenth that of MA.

8.1.6 Other interesting SAR results.

A phenyl substituted analogue **31** reported by Suchocki *et al.*²⁶⁴ was found to act as a stimulant at nAChR, (Figure 8-5).

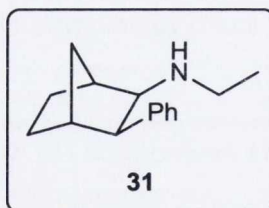


Figure 8-5: Phenyl MA analogue producing stimulant effects

The following is a general summary of the features necessary for activity and those which produced a reduction in antagonistic activity, (Figure 8-6).

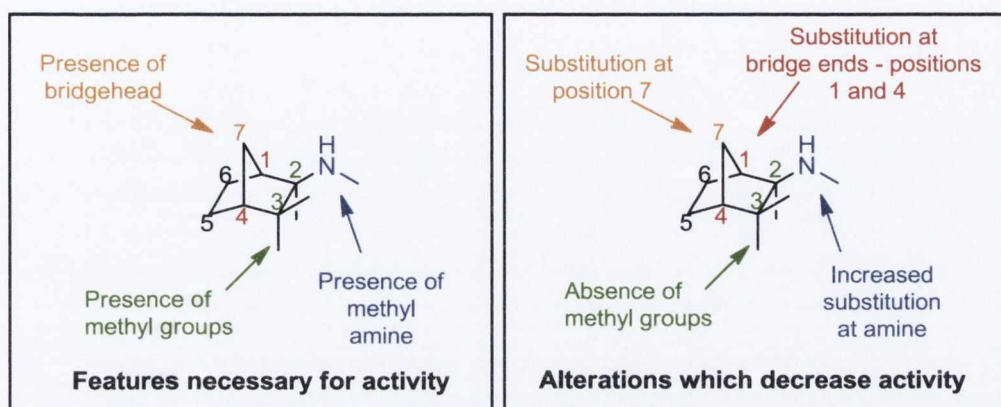
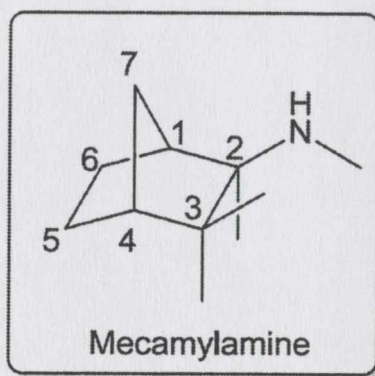


Figure 8-6: Summary of features which increase and decrease activity.

Abstract

The project aims to develop structural analogues of mecamylamine (MA) a non-selective neuronal nicotinic acetylcholine receptor antagonist.



The anti-hypertensive drug MA (Inversine®) has been investigated for and shown anti-addictive and anti-depressive properties, in both human subjects and animal models. Due to its restrictive synthesis, structure activity relationship studies (SAR) on MA have been very limited to date. Previous work within the group developed a novel synthetic route to the parent compound which allowed the selective functionalisation of the 2 and 3 positions. The work herein describes a number of modifications of MA at positions 2,3 and around the amine. Further alterations to the bicyclic framework were investigated, namely functionalisation of positions 5 and 6 and the bridgehead position 7. In addition ring expanded [2.2.2]bicyclic systems were also investigated.