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The synthesis of analogues of mecamylamine

Trinity College Dublin

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
Declaration

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work. Due acknowledgements and references are given to the work of others.

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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 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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>5-HT</td>
<td>serotonin</td>
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<tr>
<td>ACh</td>
<td>acetylcholine</td>
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<tr>
<td>AChBP</td>
<td>acetylcholine binding protein</td>
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<tr>
<td>AD</td>
<td>Alzheimer's Disease</td>
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<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
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<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
</tr>
<tr>
<td>BBB</td>
<td>blood brain barrier</td>
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<tr>
<td>bPhIDDB</td>
<td>N,N-dodecane-1,12-diyl-bis-3-picolinium dibromide</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>DA</td>
<td>dopamine</td>
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<tr>
<td>DALYs</td>
<td>disability adjusted life years</td>
</tr>
<tr>
<td>DAT</td>
<td>dopamine transporter protein</td>
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<tr>
<td>DBU</td>
<td>1,8-diazabicycloundec-7-ene</td>
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<tr>
<td>DHβE</td>
<td>dihydro-β-erythroidine</td>
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<tr>
<td>DIAD</td>
<td>diisopropyl azodicarboxylate</td>
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<tr>
<td>DID</td>
<td>“drinking in the dark”</td>
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<tr>
<td>DMPK</td>
<td>drug metabolism and pharmacokinetics</td>
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<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
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<tr>
<td>DSM</td>
<td>diagnostic and statistics manual of mental disorders</td>
</tr>
<tr>
<td>EAS</td>
<td>electrophilic aromatic substitution</td>
</tr>
<tr>
<td>ECD</td>
<td>extracellular domain</td>
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<tr>
<td>ELIC</td>
<td><em>Erwinia chrysanthemi</em> pentameric ligand gated ion channel</td>
</tr>
<tr>
<td>EM</td>
<td>electron microscopy</td>
</tr>
<tr>
<td>EMCDDA</td>
<td>European Monitoring Centre for Drugs and Drug Addiction</td>
</tr>
<tr>
<td>EWG</td>
<td>electron withdrawing group</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drugs Administration</td>
</tr>
<tr>
<td>FST</td>
<td>forced swim test</td>
</tr>
<tr>
<td>GABA</td>
<td>γ-amino butyric acid</td>
</tr>
<tr>
<td>GLIC</td>
<td><em>Gloeobacter violaceus</em> pentameric ligand gated ion channel</td>
</tr>
<tr>
<td>H₂SO₄</td>
<td>sulfuric acid</td>
</tr>
<tr>
<td>HCN</td>
<td>hydrogen cyanide</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Name</td>
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<td>--------------</td>
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<tr>
<td>HMBC</td>
<td>heteronuclear multiple bond correlation</td>
</tr>
<tr>
<td>HSQC</td>
<td>heteronuclear single quantum coherence</td>
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<tr>
<td>IC₅₀</td>
<td>half maximal inhibitory concentration</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
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<tr>
<td>KOH</td>
<td>potassium hydroxide</td>
</tr>
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<td>KSCN</td>
<td>potassium thiocyanate</td>
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<td>LDA</td>
<td>lithium diisopropylamine</td>
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<td>MA</td>
<td>mecamylamine</td>
</tr>
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<td>MAO</td>
<td>monoamine oxidase</td>
</tr>
<tr>
<td>MDD</td>
<td>Major Depressive Disorder</td>
</tr>
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<td>MeLi</td>
<td>methylolithium</td>
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<td>MLA</td>
<td>methyllycaconitine</td>
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<tr>
<td>MPEP</td>
<td>2-methyl-6-(phenylethynyl)pyridine</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>MW</td>
<td>microwave</td>
</tr>
<tr>
<td>MWC</td>
<td>Monod-Wyman-Changeux</td>
</tr>
<tr>
<td>NA</td>
<td>norepinephrine/noradrenaline</td>
</tr>
<tr>
<td>NAc</td>
<td>nucleus accumbens</td>
</tr>
<tr>
<td>NRTs</td>
<td>nicotine replacement therapies</td>
</tr>
<tr>
<td>nAChR</td>
<td>nicotinic acetylcholine receptor</td>
</tr>
<tr>
<td>NaH</td>
<td>sodium hydride</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>sodium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>NaOH</td>
<td>sodium hydroxide</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
</tr>
<tr>
<td>NMJ</td>
<td>neuromuscular junction</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>n.O.e</td>
<td>Nuclear Overhauser Effect</td>
</tr>
<tr>
<td>PD</td>
<td>Parkinson's Disease</td>
</tr>
<tr>
<td>PDC</td>
<td>pyridium dichromate</td>
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<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PNS</td>
<td>peripheral nervous system</td>
</tr>
<tr>
<td>PTSA</td>
<td>para-toluene sulfonic acid</td>
</tr>
<tr>
<td>SAR</td>
<td>structure activity relationship</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>SNRI</td>
<td>serotonin/noradrenaline re-uptake inhibitor</td>
</tr>
<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>TBA</td>
<td>tetra-n-butylammonium</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-n-butylammonium fluoride</td>
</tr>
<tr>
<td>tBuOK</td>
<td>potassium tert-butoxide</td>
</tr>
<tr>
<td>TCA</td>
<td>tricyclic anti-depressant</td>
</tr>
<tr>
<td>THC</td>
<td>tetrahydrocannabinol</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TiCl₄</td>
<td>titanium tetrachloride</td>
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<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMD</td>
<td>transmembrane domain</td>
</tr>
<tr>
<td>TMPH</td>
<td>2,2,6,6-tetramethylpiperidin-4-yl-heptanoate</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TOCSY</td>
<td>Total Correlation Spectroscopy</td>
</tr>
<tr>
<td>Trp</td>
<td>tryptophan</td>
</tr>
<tr>
<td>TS</td>
<td>Tourette Syndrome</td>
</tr>
<tr>
<td>TST</td>
<td>tail suspension test</td>
</tr>
<tr>
<td>VTA</td>
<td>ventral tegmental area</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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</table>
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. 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). 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. 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. 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.

![Figure 1-1](image-url)

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-excitable region of muscle fiber plasma membrane responsible for initiation of action potentials across the muscle's surface, ultimately causing the muscle to contract. 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.
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 \((\alpha_1)\_2(\beta_1)(\gamma)\) 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 (α2-α6) and β (β2-β4) subunits, homomer α
subunits ($\alpha^7$ and $\alpha^9$) and $\alpha$ 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. 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.

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

Ligand binding sites are located at the junction or intersection between two distinct subunits in the receptor. The subunits concerned must consist of an $\alpha$-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 α7 nAChRs the binding site would be located at the junction of two α subunits. This results in variable numbers of binding sites found on a receptor depending upon its composition of subunits. For example, the homomeric α7 nAChRs would have 5 binding sites whereas a heteromeric receptor e.g. (α4)2(β2), 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 αxβy, 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 (α4)2(β2), More complex combinations containing three (α3β4α5) or four subunits (α3β2β4α5) have been immunisolated from the brain.

![Figure 1-5 nAChRs subunits](http://pubs.niaaa.nih.gov)

**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., 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. 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. 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 α1 ECD was identified as a complex with α-bungarotoxin, a competitive nAChR antagonist. 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.

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 αTrp-149 residue. 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. These findings were subsequently supported by the works of Brejc *et al.* and Smit and co-workers who solved crystal structures of AChBPs cloned from the snail *Lymnaea stagnalis*, (Figure 1-6). These structures revealed an 'aromatic box' or 'cage' within the binding pocket which contained a number of tyrosine and tryptophan residues.
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.\textsuperscript{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-\(\alpha\) subunit interface deep within the subunit interfaces of the AChBP, in a region in which the amino acid sequence is conserved in nAChRs.
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. Several studies have since been carried out investigating the binding interactions of channel blockers. These include many well known nAChR inhibitors such as phencyclidine, hexamethonium, amantidine and QX222, 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.
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 Iml, 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 α7 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.\(^{39}\)
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).\textsuperscript{40,41}
The activity of the receptor in the absence of an agonist has been previously demonstrated in agreement with the MWC model.\textsuperscript{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.\textsuperscript{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. 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. 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, while alcohol related problems cost approximately 3.7 billion euro in 2007. Addictive behaviour relating to gambling and overeating 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.

Dopamine (DA) and the mesolimbic pathway have been shown to be a common factor for the reinforcing properties of most addictive drugs. 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
Introduction

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).]

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. 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. 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.
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. 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. 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).
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 \( \gamma \)-aminobutyric 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\textsuperscript{62,63} Opiates act on $\mu$ 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 \textit{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.\textsuperscript{64,65}

\subsection*{1.2.2.4 Amphetamines.}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1-16.png}
\caption{Structures of a selection of amphetamine drugs.}
\end{figure}

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).\textsuperscript{66-69}
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$_A$. Human clinical studies utilising PET and a DA receptor radio-ligand $[^{11}]$Craclopride 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. Ethanol consumption in rats has also been shown to inhibit NMDA receptors both directly (by acting upon NMDA
receptors) and indirectly via GABA<sub>A</sub> activation, which account for its sedative effects. 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. Similarly it was observed that the re-uptake of extracellular norepinephrine was inhibited by ethanol.

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. The positive reinforcement hypothesis proposes that substance dependence and drug cravings are a result of a desire for reward initiated by a drug stimulus.

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. 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. Drug withdrawal produces many physical and psychological effects including depression, anxiety, irritability, sweating, tremor, insomnia, hallucinations and anorexia. These symptoms lead to negative reinforcement, whereby drug administration will alleviate an aversive state.

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. 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. 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.

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. 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. 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. 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).
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. 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. 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. Figures released by the World Health Organisation (WHO) state that tobacco was responsible for 100 million deaths in the 20th century 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. On average, smokers die 13 to 14 years earlier than non-smokers due to smoking related disease and approximately half of all tobacco users will die as a direct result of smoking. 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. 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.

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. 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
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MA, is regulated by neuronal nAChRs. A complementary study also utilising Wistar rats has shown that treatment with non-competitive MA or the competitive selective α4β2 antagonist dihydro-β-erythroidine (DHβE), (Figure 1-19), resulted in a dose dependent reduction of nicotine self-administration. 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.

Classically it has been thought that high affinity nAChRs containing the β2 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. Picotto et al. found that nicotine self-administration and nicotine induced DA striatal transmission are completely unobserved in β2 subunit knockout mice. Interestingly a more recent study by Levin et al. concluded that the effects of nicotine administration in α7 knockout mice were not initially observed as in the case of the β2. However over a longer period of time the α7 knockout mice developed an emergent decline in nicotine consumption. In addition, radio-labelled [3H]nicotine, [3H]epibatidine and [3H]cystine binding are not detected in most brain regions of β2 or α4 knockout mice. A reduction in nicotine sensitivity has also been observed in α5 knockout mice. Interestingly, it was found that α5 nAChR subtypes are not involved in the rewarding effects of nicotine, instead, α5 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. In 2012, Leslie and co-workers investigated the high affinity selective α3β4 antagonist AT-1001, (Figure 1-19), and found that it significantly reduced nicotine self-administration in rats thus demonstrating the α3β4 subtypes involvement in drug seeking behaviour. Obviously the situation is complex but some compounds such as varenicline, bupropion and MA have anti-addictive properties, (Figure 1-20).
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. Varenicline has shown high affinity toward the α4β2 nAChRs where it acts as a partial agonist and as a potent full agonist at α7 nAChRs. It also acts upon α3β4, α3β2 and α6 containing receptor subtypes although with considerably less potency. 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. Bupropion exerts its anti-depressant action via dual dopamine and norepinephrine re-uptake inhibition. It also acts as a non-competitive nAChR antagonist and blocks nicotine action on a number of receptor subtypes including α3β2, α4β2, α7 and α3β4.
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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. 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 varenicline 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 bupropion 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.
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. 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. According to tentative estimates published by the WHO there were approximately 15.9 million cocaine users across the globe in 2008. 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 α7 nAChRs in the VTA induced by methyllycaconitine (MLA), a selective α7 nAChR antagonist, resulted in the attenuation of the reward facilitating effect of systemic cocaine. A later study carried out by Zoli and co-workers determined that the inhibition of α7 and β2 subunits decreased cocaine induced DA response. Administration of MLA, (Figure 1-21) the α7 selective antagonist and β2 selective antagonist DHβE were ineffective when individually co-administered with cocaine. However, dual administration with cocaine significantly reduced cocaine elicited DA release. These findings suggest that the α7 and β2 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. 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. Encouragingly, MA has also produced a reduction in cue-induced cravings in human cocaine addicts.

![Figure 1-21: Structures of nAChR antagonists MLA and MRZ 2/621.](image)

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. In 2011 approximately 17.4 million people in the U.S. required treatment for an alcohol abuse problem. It is estimated that there are in the region of 140 million people suffering from alcoholism across the globe.

Ethanol has been shown to activate the mesolimbic dopaminergic system via excitation of DA neurons in the VTA. Once again nAChRs seem to play a role in the addictive process. Typically, ethanol consumption is higher in smokers than in non-smokers and ethanol dependence is estimated to be 10 times more common among smokers. 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. Several animal studies have reported a marked reduction in self-administration of ethanol upon treatment with MA. In addition administration of MA in ethanol dependent mice produced an attenuation in the symptoms of withdrawal.
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.\textsuperscript{134} In human clinical studies MA was shown to diminish the euphoric and stimulant effects of ethanol\textsuperscript{135,136} and was also found to reduce the self-reported desire to consume ethanol in healthy male and female non-smoking social drinkers.\textsuperscript{136}

In 2007 Steensland \textit{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 α2β4 nAChR subtypes may be involved in ethanol dependence.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 α3β4 sites. Hence it was suggested that α3β4 subtypes may be implicated in drug seeking behavior.\textsuperscript{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.](image)

### 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.\textsuperscript{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. 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.

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, such as serotonin (5-HT) and noradrenaline (NA) in the brain. 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. 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.

![Structures of neurotransmitters](image-url)
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 amitryptiline, desipramine and trimipramine, an imipramine metabolite. 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. 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.

![Diagram of early anti-depressants]

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
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into the nerve terminal by binding to their respective transporter proteins.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\%.\textsuperscript{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.\textsuperscript{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.\textsuperscript{142,154} Mirtazapine is classified as a NA and specific serotonergic anti-depressant. It exerts its action by blocking α2-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.\textsuperscript{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.\textsuperscript{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.

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.\textsuperscript{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, and 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.\textsuperscript{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 \textit{et al.}\textsuperscript{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 \textit{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

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{structures.png}
\caption{Structures of anti-depressants fluoxetine and mirtazapine.}
\end{figure}
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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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 \textit{in vitro} study of antagonistic effect on nAChRs present in rat hippocampal slices.\textsuperscript{168} A similar study performed by Hennings \textit{et al.} investigating the ability of a group of TCAs and SSRIs, (Figure 1-27), to inhibit nAChR in rat hippocampal slices and utilising MA as a reference, found noteworthy levels of antagonism in all cases, while desipramine and nisoxetine produced significant levels of inhibition which match that of MA, Table 1-1.\textsuperscript{169}

\begin{table}[h]
\centering
\caption{Inhibition of nAChRs by selected TCAs and SSRIs.}
\begin{tabular}{llll}
\hline
 & IC\textsubscript{50} (\textmu M) & Conc. range (\textmu M) & Threshold\textsuperscript{*} conc. (\textmu M) \\
\hline
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 \\
\hline
\end{tabular}
\textsuperscript{*} The lowest concentration that produced significant inhibition.
\end{table}

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.\textsuperscript{165} Similarly to MA, bupropion is a potent nAChR antagonist and is currently marketed for smoking cessation.\textsuperscript{36,170}
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. 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. In 1967 Seligman first described the learned helplessness theory. 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). 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.

Epidemiological studies have confirmed that psychiatric patients were considerably more likely to smoke than those who did not suffer a mental disorder. 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. Interestingly, the administration of transdermal nicotine to non-smoking depressed patients in a double-blind, placebo-controlled trial produced a significant reduction in symptoms. 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.

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. In 2009 Andreasen et al. 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.\textsuperscript{188,189} Hence prolonged nicotine exposure could in fact act as an antagonist, preventing further receptor activation \textit{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.\textsuperscript{190} The three principal characteristics of PD are rigidity, bradykinesia and the presence of a tremor at rest.\textsuperscript{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. Studies have also shown that the disease is more prevalent in men than in women. While the average age of onset of this disorder is estimated to be in the early-to-mid 60s.

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 mortem examinations of the affected brains. 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 stratum of PD affected patients. The administration of L-Dopa (a precursor of DA which crosses the BBB) to PD sufferers gave dramatic effects, lessening the symptoms of bradykinesia. 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. 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.

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. 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. Several epidemiological studies have revealed that there is a marked decreased in occurrence of PD among smokers. Administration of nicotine to PD affected rats significantly reduced L-Dopa induced dyskinesias. Additionally, two acetylcholinesterase inhibitors namely donepezil and rivastigmine, (Figure 1-28), have been shown to help alleviate the symptoms of PD related dementia. 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.
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. 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. The disease was named after a German psychiatrist, Alois Alzheimer who first described that disorder in 1906. In 2006 the estimated global prevalence of AD was 26.6 million. 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.

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. A reduction in cholinergic activity is a marked characteristic of
AD. Acetylcholinesterase inhibitors such as donepezil, galantamine and rivastigmine 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. 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. In a more recent study, AD affected mice receiving chronic nicotine showed a significant reduction in the density of β-amyloid plaques.

Studies have shown that nicotine and nicotinic agonists at α4β2 and α7 nAChRs improve learning and memory. Imaging studies utilising isotopic ligands 125I-α-bungarotoxin and 3H-cytisine to radiolabel α7 and α4β2 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. These receptors have been shown to be involved in long term potentiation (LTP), which is involved in the cellular mechanism of memory and learning. Animal studies investigating the effects of the partial agonist AR-R17779, (Figure 1-29), which is selective for α7 nAChRs displayed an improvement in scopolamine-induced deficits in social recognition. The α7 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. AZD-0328 entered phase II clinical trials in 2008, unfortunately the drug was not expected to meet its targets and was subsequently discontinued.

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. 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. 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. A review of prevalence studies of the disorder has identified significant disparity in differing populations.

Exceptionally high rates of tobacco smoking have been recorded in schizophrenic patients. 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. 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. 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. Furthermore, a study employing magnetic resonance spectroscopy identified increased levels of choline in schizophrenic patients compared with healthy volunteers.

α7 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 α7 nAChR may be responsible for the auditory sensory gating deficit characterised in schizophrenia patients. Post mortem examinations of the frontal cortex of schizophrenic patients revealed a 40% reduction of α7 nAChR subunits when directly compared to normal healthy brains in age matched controls. These findings maintain the supposition that a deficit of the nAChR α7 subunit in the frontal cortex might be involved in the
Introduction

A double-blind placebo-controlled clinical trial investigating the effects of varenicline, an α7 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.\(^\text{238}\)

A number of current treatments in clinical use for the treatment of symptoms of schizophrenia are active at α7 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 α7 nAChRs.\(^\text{239}\) GTS-21, (Figure 1-30), an alkaloid derived from anabaseine found in marine worms is a partial agonist at the α7 nAChR and a weak competitive antagonist at α4β2 and 5-HT3 receptors. This compound has been shown to improve auditory gating in mice via α7 nAChR activation.\(^\text{240}\) 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.\(^\text{241}\) Galantamine, (Figure 1-30), is a reversible competitive cholinesterase inhibitor\(^\text{242}\) which is used in the treatment of Alzheimer's disease.\(^\text{236}\) It has also been shown to act as a positive modulator at α7 nAChRs.\(^\text{243}\) 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/D\(_2\) antagonist) and galantamine exhibited an improvement in cognition, attention and delayed memory.\(^\text{244}\)
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 childhood 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.

Although its pathogenesis is not yet known, studies suggest that nicotine may aid the reduction of symptoms of TS. Sanberg et al. 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. 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. 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.

Figure 1-30: Therapies investigated for the treatment of schizophrenia.
found that while it was well tolerated in patients, MA it did not appear to be an effective treatment for the symptoms of TS.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{252} In 2002 the rights were sold to Targacept who in conjunction with AstraZeneca investigated its activity as a treatment for MDD.\textsuperscript{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. 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. Administration of MA to male Wistar rats two hours after receiving a dose of nicotine induces withdrawal-like symptoms.

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. 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. MA also reduced self-administration in rats who consumed greater than 65% of their daily fluid intake as ethanol. 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.

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. In addition, MA has shown to reduce the symptoms of TS in a human clinical study.

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. 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. 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. 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. 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.

In 1962 by Stone et al.\textsuperscript{261} reported a more comprehensive library of MA analogues with associated \textit{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 \textit{et al.}\textsuperscript{260} it was observed that compounds lacking alkyl substitution at positions 2 and 3 displayed a lower activity than the
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).

<table>
<thead>
<tr>
<th>Compound</th>
<th>R1</th>
<th>R2</th>
<th>Nicotine convulsions ED50 mg/kg</th>
<th>Pupil dilation ED10 mg/kg</th>
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</thead>
<tbody>
<tr>
<td>6</td>
<td>H</td>
<td>H</td>
<td>2.8</td>
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<tr>
<td>7</td>
<td>H</td>
<td>H</td>
<td>0.78</td>
<td>1.3</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
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<td>1.6</td>
</tr>
<tr>
<td>9</td>
<td>H</td>
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<td>6.4</td>
<td>7.5</td>
</tr>
<tr>
<td>10</td>
<td>H</td>
<td>(CH2)2CH3</td>
<td>toxic</td>
<td>toxic</td>
</tr>
<tr>
<td>11</td>
<td>H</td>
<td>(CH2)4CH3</td>
<td>11.0</td>
<td>13.5</td>
</tr>
<tr>
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<td>H</td>
<td>CH(CH3)2</td>
<td>4.9</td>
<td>5.2</td>
</tr>
<tr>
<td>13</td>
<td>H</td>
<td>CH2CH=CH2</td>
<td>5.8</td>
<td>8.5</td>
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<td>43.0</td>
</tr>
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<td>H</td>
<td>C6H13</td>
<td>24.0</td>
<td>40.0</td>
</tr>
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<td>H</td>
<td>C6H5CH2</td>
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<tr>
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<td>H</td>
<td>C6H5(CH2)3</td>
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<td>20</td>
<td>CH2CH3</td>
<td>CH2CH3</td>
<td>3.2</td>
<td>3.8</td>
</tr>
</tbody>
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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 Wragg 262 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 sulphurescens 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).
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.\textsuperscript{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 \textit{endo} position and enantiomers of both \textit{endo} and \textit{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 \textit{endo} analogues proved to be only slightly less potent that their \textit{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 \textit{R} and \textit{S} enantiomers of MA displayed a similar potency to the racemate. This result in conjunction with previous work by Suchocki \textit{et al.}\textsuperscript{265} in 1990 and Stolerman \textit{et al.}\textsuperscript{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.

\begin{figure}[h]
\centering
\includegraphics[width=0.2\textwidth]{phenyl_ma_analogue.png}
\caption{Figure 1-35: Phenyl MA analogue producing stimulant effects.\textsuperscript{264}}
\end{figure}

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.\textsuperscript{267,268} In 2001 Shytle and co-workers examined the effects of MA on human nAChR subtypes. They tested both \textit{R} and \textit{S} enantiomers of MA and the
racemate as antagonists of human α3β4, α3β2, α7, and α4β2 nAChRs, in addition to mouse adult type muscle α1β1δε nAChRs expressed in Xenopus oocytes, shown in Table 1-2.\textsuperscript{250}

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Racemic MA (nM)</th>
<th>R-(-)-MA (μM)</th>
<th>S-(+)-MA (nM)</th>
</tr>
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<tbody>
<tr>
<td>α3β4</td>
<td>640-90</td>
<td>420-50</td>
<td>640-200</td>
</tr>
<tr>
<td>α4β2</td>
<td>2.5-0.6</td>
<td>1.7-0.5</td>
<td>3.2-0.5</td>
</tr>
<tr>
<td>α3β2</td>
<td>3.6-1.2</td>
<td>3.2-0.6</td>
<td>3.7-0.8</td>
</tr>
<tr>
<td>α7</td>
<td>6.9-1.6</td>
<td>5.8-2.2</td>
<td>4.6-1.2</td>
</tr>
</tbody>
</table>

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.
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) 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.

In 2007 Crooks and co-workers 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 it 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 stratial 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. 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.

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. 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. In September 2012 Targacept announced its intention to pursue MA as a treatment for overactive bladder.

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 (3μM) employing oocytes expressing the low sensitivity α4β2 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).

![Proposed alterations to the structure of MA.](Figure 1-38)

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 1956 and the methodology was later published in 1962. This route involved a short and efficient two-step procedure from cheap and commercially available camphene (Scheme 1-1). However the reliance on camphene 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.
Introduction

**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 H\(_2\)SO\(_4\) 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.\

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 \( \alpha \)-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 \textit{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 \textit{exo} face. Treatment of ketone \( 37 \) with either methylmagnesium bromide or methyllithium generated alcohol \( 38 \). Again the addition is governed by the "picket fence" effect\(^{279}\) forming the isomer shown. Treatment of alcohol \( 38 \) with \( \text{H}_2\text{SO}_4 \) and sodium azide in \( \text{CH}_3\text{Cl} \) formed the \textit{exo} azide \( 39 \) (picket fence) via the \( 3^\circ \) 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 \textit{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)
Preliminary testing of compounds 41-48 by electrophysiological measurements at a single concentration (3 μM) employing oocytes expressing the low sensitivity α4β2 nAChR indicated that all compounds retained antagonistic character but differed in their activity. Oocytes expressing the α4β2 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).
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.](image)

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.
Preliminary in vivo testing was performed by electrophysiological measurements at a single concentration (3 μM) employing oocytes expressing the low sensitivity α4β2 nAChR. 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 μM ACh. A response of 100% refers to 0% inhibition. A response of 0% refers to 100% inhibition or a complete blockade of the receptor.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Response to 100 μM ACh</th>
</tr>
</thead>
<tbody>
<tr>
<td>- -</td>
<td>100%</td>
</tr>
<tr>
<td>7 (MA)</td>
<td>33%</td>
</tr>
<tr>
<td>41</td>
<td>74%</td>
</tr>
<tr>
<td>42</td>
<td>18%</td>
</tr>
<tr>
<td>43</td>
<td>Error - results pending</td>
</tr>
<tr>
<td>44</td>
<td>22%</td>
</tr>
<tr>
<td>45</td>
<td>22%</td>
</tr>
<tr>
<td>46</td>
<td>23%</td>
</tr>
<tr>
<td>47</td>
<td>0%</td>
</tr>
<tr>
<td>48 (Endo-MA)</td>
<td>18%</td>
</tr>
</tbody>
</table>

Figure 2-2: Results of initial in vitro biological testing at α4β2 nAChR subtypes.
Chapter 2

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.

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.

![Diagram of compound](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Response to 100 μM Nicotine</th>
</tr>
</thead>
<tbody>
<tr>
<td>- -</td>
<td>100%</td>
</tr>
<tr>
<td>7 (MA)</td>
<td>6.3%</td>
</tr>
<tr>
<td>41</td>
<td>4.6%</td>
</tr>
<tr>
<td>42</td>
<td>12.0%</td>
</tr>
<tr>
<td>43</td>
<td>9.6%</td>
</tr>
<tr>
<td>44</td>
<td>9.0%</td>
</tr>
<tr>
<td>45</td>
<td>12.4%</td>
</tr>
<tr>
<td>46</td>
<td>9.4%</td>
</tr>
<tr>
<td>47</td>
<td>13.7%</td>
</tr>
<tr>
<td>48 (Endo-MA)</td>
<td>13.8%</td>
</tr>
</tbody>
</table>

Figure 2-3: Results of second in vitro biological testing at α3β4 nAChR subtypes.
Chapter 2

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 μM of nicotine. These cells express mainly α3β4 and α7 subtypes. The responses mediated by α7 receptor subtypes are very fast and therefore we are reasonably confident that responses mediated by α3β4 receptor subtype are those recorded by these methods. Responses were observed via fluo-3, a highly specific fluorescent Ca^{2+} probe. 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 α4β2 subtypes with the triethyl derivative, compound 47 being the most active, the situation is reversed at α3β4 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.

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.

Fortunately, a synthesis of ketones 56 and 57 had been reported by Hori et al.\textsuperscript{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).

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).
Chapter 2

A solution of ethyllithium was prepared \textit{in situ} by treating bromoethane with 2 equivalents of \textit{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 \textit{in situ} was the best option.

Having prepared the tertiary alcohols we turned our attention to azide formation. Although all the alcohols were treated with 50% H$_2$SO$_4$ 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.
Chapter 2

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.

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.

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 CH$_2$Cl$_2$ 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 CH$_2$Cl$_2$ and diethyl ether.
2.1.2 Synthesis of endo-mecamylamine analogues.

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 α4β2 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.\textsuperscript{286} and Moss et al.\textsuperscript{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\textsubscript{2}Cl\textsubscript{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 α4β2 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.](image)

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.](image)

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).
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 methyllithium 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$_2$Cl$_2$ and diethyl ether, (Scheme 2-15).

Scheme 2-14: Attempted synthesis of amine 82.

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).

\[ \text{Figure 2-7: Targeting position 2 on the MA skeleton.} \]

2.2.1 Synthesis of an aromatic MA analogue.

\[ \text{Figure 2-8: Proposed Aromatic MA target and stimulant prepared by Suchocki et al.}^{264} \]

It was clear from the work of Suchocki et al.,\textsuperscript{264} that the introduction of an aromatic species could have 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% \(\text{H}_2\text{SO}_4\) and an excess of sodium azide in \(\text{CHCl}_3\) 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 \(\text{CH}_2\text{Cl}_2\) 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 \(\text{HCl}\) 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 \(\alpha3\beta4\) nAChR receptor subtypes expressed in SH-SY5Y cells in the presence of 100 \(\mu\text{M}\) of nicotine. A response of 28.1% was observed when cells pretreated with phenyl substituted analogue 87 were treated with 100 \(\mu\text{M}\) of nicotine. This analogue produced the lowest antagonistic response during testing of the library against the \(\alpha3\beta4\) nAChR. Unfortunately, the compound has not been tested at the \(\alpha4\beta2\) 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.
Chapter 2

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).

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).
2.3.1 Amine Functionalisation.

As previously mentioned (section 1.5.3), SAR studies of MA performed by Stone et al.\textsuperscript{261} and Suchocki et al.\textsuperscript{264} had shown that MA analogues with more sterically demanding N-alkyl substitution than methyl produced a reduction in \textit{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-workers\textsuperscript{272} 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 \textit{N}-substituted MA analogues.

2.3.2 Alkyl alterations to the amine.

Previous reports have implied that increased steric bulk around the amine moiety hinders antagonistic activity. As technology now allows us to test individual \textit{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 \textit{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. 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 generated new compounds with variable pK<sub>a</sub> 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). Its major advantages over the azide-alkyne Huisgen cycloadditions include lower reactions 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. 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.
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.

![Scheme 2-19: Azide-alkyne copper catalysed click synthesis of triazoles 93-96.](image)

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.
Initial attempts involved a traditional 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 preformed 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, the amine salt was generated by a H$_3$PO$_4$ 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% H$_2$SO$_4$ 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.](image)

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

<table>
<thead>
<tr>
<th>Amine</th>
<th>Reagents</th>
<th>Time</th>
<th>Temp</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>Glyoxal, NH₄Cl, Formaline</td>
<td>24 hrs</td>
<td>90 °C</td>
<td>Starting material</td>
</tr>
<tr>
<td>40</td>
<td>Glyoxal, NH₄Cl, Formaline, 10% H₂SO₄</td>
<td>19 hrs</td>
<td>90 °C</td>
<td>Starting material</td>
</tr>
<tr>
<td>40</td>
<td>Glyoxal, NH₄Cl, Formaline, 10% H₂SO₄</td>
<td>68 hrs</td>
<td>90 °C</td>
<td>Starting material</td>
</tr>
</tbody>
</table>

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.
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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. 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

Targets

![Figure 3-1: Targeting positions 5 and 6 on the MA skeleton.](image)

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 μM of nicotine. 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. performed a series of molecular docking studies investigating the binding of MA at α4β2 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).
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.

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

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.](image)
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. 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).

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 CH₂Cl₂ 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).
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$_2$SO$_4$ 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$_2$SO$_4$ 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.](image)

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

<table>
<thead>
<tr>
<th>Lewis acid</th>
<th>Nucleophilic azide</th>
<th>Time monitored</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF$_3$.Et$_2$O</td>
<td>TMS-N$_3$</td>
<td>20 hours</td>
<td>No reaction observed</td>
</tr>
<tr>
<td>TiCl$_4$</td>
<td>TMS-N$_3$</td>
<td>19 hours</td>
<td>No reaction observed</td>
</tr>
<tr>
<td>TiCl$_4$</td>
<td>TMS-N$_3$</td>
<td>5 hours</td>
<td>Protecting group removed</td>
</tr>
<tr>
<td>SnCl$_4$</td>
<td>TMS-N$_3$</td>
<td>2 hours</td>
<td>No reaction observed</td>
</tr>
<tr>
<td>TMS-OTf</td>
<td>TMS-N$_3$</td>
<td>3 hours</td>
<td>No reaction observed</td>
</tr>
<tr>
<td>TiCl$_3$</td>
<td>TBA-N$_3$</td>
<td>22 hours</td>
<td>No reaction observed</td>
</tr>
</tbody>
</table>

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 CH$_2$Cl$_2$ in the presence of TiCl$_3$. 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 recyclication or if it was formed at all.
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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).

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.](image)

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 CH₂Cl₂ 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).
Once again the azide formation proved problematic. Concentrations of H₂SO₄ of up to and including 65% in combination with sodium azide and CHCl₃ returned only starting material. However, if a slightly higher concentration of 70% H₂SO₄ 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 3-9: Synthesis of the exo benzyl protected tertiary alcohol 120.

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.**

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.
Fortunately, the formation of benzyne and its Diels-Alder reaction with cyclopentadiene has been reported by Goll and Fillion.\textsuperscript{298} Benzyne was generated \textit{in situ} by treating anthranillic acid 134 with 1.2 molar equivalents of isobutyl nitrite at 50 °C until the expulsion of N$_2$ and CO$_2$ 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).
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 CH₂Cl₂ 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).
Once again the azide formation would prove troublesome. Treatment of tertiary alcohol 131 with 50% H$_2$SO$_4$ 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$_2$SO$_4$, 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-Meerwien rearrangements in previous work and they were often easily isolated and occurred at higher acid concentrations.
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Whether the Wagner-Meervien 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.

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 Konaka\(^\text{299}\) (mono nitration) and Tanida \textit{et al.}\(^\text{300}\) (dinitration). Tanida \textit{et al.}\(^\text{300}\) published a procedure for the installation of a second nitro group \textit{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 \textit{ortho} to a nitro group during EAS chemistry; however, examples of this occurring in benzonorbornene derivatives have been reported in the literature.\(^\text{300,301}\) After some adjustment of the sequence of the reactions the following strategy was devised.

Terabe and Konaka\(^\text{299}\) 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 \textit{para} to each bridgehead. Utilising the procedure published by Tanida \textit{et al.}\(^\text{300}\) the installation of a second nitro group \textit{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 $\text{H}_2\text{SO}_4$ 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 °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 $\text{H}_2\text{SO}_4$ with a mixture of nitric acid in $\text{H}_2\text{SO}_4$ for 30 minutes at approximately 0 °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 desire ketone 145 in 29% yield.
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, tBuOK 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).

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.

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$_2$SO$_4$ 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$_2$SO$_4$ 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, the unsubstituted azide 154 was successfully formed, (Scheme 3-19). Firstly, the diazonium salts were formed using NaN$_2$ 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 α4β2 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.](image)

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\(_2\)Cl\(_2\) 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.](image)

3.3 Alkyl substitution at positions 5 and 6.

3.3.1 Synthesis of tricyclic MA analogue.

![Figure 3-10: Proposed alkyl tricyclic target.](image)

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 Stothers\textsuperscript{303} 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).

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\% H\textsubscript{2}SO\textsubscript{4} and an excess of sodium azide in CHCl\textsubscript{3} 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).
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.
3.4 Selective functionisation of positions 5 and 6 via vinyl bromide synthesis.

![Figure 3-11: Structures of 5 and 6 vinyl bromides.](image)

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.
Chapter 3

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. Treatment of norbornenone 168 with phenylselenyl 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.](image)

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% \( \text{H}_2\text{SO}_4 \) and an excess of sodium azide in \( \text{CHCl}_3 \) 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 \textbf{174} with tributylphosphine in anhydrous tetrahydrofuran for 4 hours followed by the addition of H$_2$O and stirring overnight gave the expected amine \textbf{175} and tributylphosphine oxide, (Scheme 3-25). Despite multiple attempts to remove the tributylphosphine oxide \textit{via} column chromatography, amine \textbf{175} remained contaminated and the crude mixture was employed in the next step. Amine \textbf{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 CH$_2$Cl$_2$ to give the free amine \textbf{165} in 28% yield, (Scheme 3-25).
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.\textsuperscript{305} Treatment of norbornene 168 with trimethylorthoformate and p-toluene sulfonic 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 CH\textsubscript{2}Cl\textsubscript{2} at -78 °C, then warming to room temperature overnight generated the necessary seleno-ether.

3.4.2. Selective synthesis of 6 vinyl bromide MA 166.
The acetal protecting group was removed \textit{in situ} by stirring in a 98:2 mixture of THF:H$_2$O 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.](image)

The initial methylation proceeded under the conditions described in the synthesis of the 6 vinyl bromide 165, using NaHMDS as the base at -30 °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 \textit{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 °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.

1) NaHMDS, THF,
-78 °C to -30 °C, 2 h
2) CH₃I, -30 °C, 30 min

52%

1) NaHMDS, THF,
-78 °C to -30 °C, 2 h
2) CH₃I, -30 °C, 30 min

Scheme 3-27: Steric congestion prevents second methylation.
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

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

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 Tam\textsuperscript{306} 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)\textsubscript{2}, PPh\textsubscript{3}, 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.
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% Pd$_2$(dba)$_3$, 3.3 molar equivalents of KF, 1.1 molar equivalent of phenylboronic acid and replacing P(i-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% Pd$_2$(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.
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.

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.
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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. \(N,5\text{-endo},6,6\text{-tetramethyloctahydro}-1H-4,7\text{-methanoinden}-5\text{-amine} 157\) is currently undergoing investigation at \(\alpha\beta2\) receptor subtypes and the results are eagerly awaited.
Chapter 4

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

Targets

[Diagram of alterations to position 7]

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).

[Diagram of proposed targets]

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. 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.

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

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 ZnI₂ 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. 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 $S_N1$ heterolyses of the chloride compared with those of the bicyclo[2.2.1]heptane analogues.

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

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). 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 ZnI₂ 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.**

<table>
<thead>
<tr>
<th>ZnI₂ eq.</th>
<th>Furan eq.</th>
<th>Temp</th>
<th>Time</th>
<th>Additional Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1.5</td>
<td>25 °C</td>
<td>5 days</td>
<td>-</td>
<td>38%</td>
</tr>
<tr>
<td>0.5</td>
<td>2</td>
<td>70 °C</td>
<td>4 hrs</td>
<td>M.W. irradiation</td>
<td>37%</td>
</tr>
<tr>
<td>0.75</td>
<td>2.5</td>
<td>30 °C</td>
<td>5 days</td>
<td>sealed flask</td>
<td>77%</td>
</tr>
<tr>
<td>0.75</td>
<td>2.5</td>
<td>30 °C</td>
<td>5 days</td>
<td></td>
<td>93%</td>
</tr>
</tbody>
</table>

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 ZnI₂ 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.](image)

<table>
<thead>
<tr>
<th>Base</th>
<th>Temp,</th>
<th>Time</th>
<th>Additional Conditions</th>
<th>Results</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃ONa</td>
<td>20°C</td>
<td>3.5 hrs</td>
<td>-</td>
<td>Incomplete</td>
<td>50%</td>
</tr>
<tr>
<td>CH₃ONa</td>
<td>20°C</td>
<td>3.0 hrs</td>
<td>Distilled methanol</td>
<td>Incomplete</td>
<td>48%</td>
</tr>
<tr>
<td>CH₃ONa</td>
<td>35°C</td>
<td>6.0 hrs</td>
<td>-</td>
<td>Incomplete</td>
<td>28%</td>
</tr>
<tr>
<td>CH₃ONa</td>
<td>35°C</td>
<td>28.0 hrs</td>
<td>-</td>
<td>Incomplete</td>
<td>37%</td>
</tr>
<tr>
<td>CH₃ONa</td>
<td>70°C</td>
<td>22.5 hrs</td>
<td>Heated at reflux</td>
<td>Incomplete</td>
<td>43%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>temperature</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH₃ONa</td>
<td>20°C</td>
<td>3.0 hrs</td>
<td>Formalin</td>
<td>Full conversion</td>
<td>59%</td>
</tr>
</tbody>
</table>

The unsaturated ketone 199 is volatile (b.p. 79-80 °C/10 Torr) 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).
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).

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. 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% H₂SO₄ 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% H₂SO₄ 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-Meerwien product was formed.

Scheme 4-9: Attempted synthesis of azide 204.
Table 4-3: Attempted azide formation - further investigation of acid concentrations.

<table>
<thead>
<tr>
<th>H₂SO₄ Conc.</th>
<th>Time</th>
<th>Product isolated</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 %</td>
<td>25 hrs</td>
<td>Starting materials</td>
</tr>
<tr>
<td>55 %</td>
<td>23 hrs</td>
<td>Starting materials</td>
</tr>
<tr>
<td>60 %</td>
<td>23 hrs</td>
<td>Starting materials</td>
</tr>
<tr>
<td>65 %</td>
<td>23 hrs</td>
<td>Starting materials</td>
</tr>
<tr>
<td>70 %</td>
<td>1 hr</td>
<td>Rearrangement</td>
</tr>
<tr>
<td>75 %</td>
<td>1 hr</td>
<td>Rearrangement</td>
</tr>
<tr>
<td>80 %</td>
<td>45 mins</td>
<td>Rearrangement</td>
</tr>
<tr>
<td>85 %</td>
<td>45 mins</td>
<td>Rearrangement</td>
</tr>
<tr>
<td>Conc.</td>
<td>15 mins</td>
<td>Rearrangement</td>
</tr>
</tbody>
</table>

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% H₂SO₄ at a room temperature of approximately 15 °C gave no reaction after 23 hours. However, when the reaction was repeated at a room temperature of approximately 26 °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% H₂SO₄ at lower temperatures. At -25 °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 °C, after 27 hours no reaction was observed. Finally, the alcohol was treated with 40% H₂SO₄ and warmed to 30 °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.

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. 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.

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.](image)

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.](image)

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).
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).

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.

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).
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$_2$Cl$_2$ 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).
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.
Chapter 4

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.
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.

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. 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.](image)

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$_2$O 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.](image)

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.](image)

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 α4β2 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.](image)
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.](image)

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.](image)

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).
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 $^1$H 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: $^1$H NMR spectra of triazole 93.
<table>
<thead>
<tr>
<th>Carbon (ppm)</th>
<th>Type</th>
<th>Proton (ppm)</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>CH₃ (s)</td>
<td>0.42</td>
<td>13</td>
</tr>
<tr>
<td>2.0</td>
<td>CH₃ (s)</td>
<td>1.18</td>
<td>9</td>
</tr>
<tr>
<td>2.6</td>
<td>CH₂ (m)</td>
<td>1.45-1.82</td>
<td>5</td>
</tr>
<tr>
<td>2.1</td>
<td>CH₃ (s)</td>
<td>1.75</td>
<td>10</td>
</tr>
<tr>
<td>2.6</td>
<td>CH₂ (m)</td>
<td>1.45-1.82</td>
<td>6</td>
</tr>
<tr>
<td>2.2</td>
<td>CH₃ (s)</td>
<td>0.53</td>
<td>8</td>
</tr>
<tr>
<td>3.0</td>
<td>CH₂ (m)</td>
<td>1.45-1.82 and 2.25</td>
<td>7</td>
</tr>
<tr>
<td>4.6</td>
<td>q</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>5.5</td>
<td>CH (br s)</td>
<td>2.85</td>
<td>1</td>
</tr>
<tr>
<td>5.7</td>
<td>CH (br s)</td>
<td>1.94</td>
<td>4</td>
</tr>
<tr>
<td>7.3</td>
<td>q</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>12.8</td>
<td>CH (s)</td>
<td>7.70</td>
<td>11</td>
</tr>
<tr>
<td>14.3</td>
<td>q</td>
<td>-</td>
<td>12</td>
</tr>
</tbody>
</table>

Figure 6-3: HSQC experiment displaying $^1$H 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.

A HMBC (heteronuclear multiple bond correlation) experiment was preformed. 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>
<thead>
<tr>
<th>H Signal</th>
<th>Correlation</th>
<th>C Signal</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>3 bond correlation</td>
<td>C3</td>
</tr>
<tr>
<td>H1</td>
<td>3 bond correlation</td>
<td>C5</td>
</tr>
<tr>
<td>H4</td>
<td>3 bond correlation</td>
<td>C6</td>
</tr>
<tr>
<td>H10</td>
<td>3 bond correlation</td>
<td>C3</td>
</tr>
</tbody>
</table>

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).
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 \textit{exo} position, (Figure 6-7).

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 F<sub>254</sub> silica gel plates. Visualisation was by UV light, KMn<sub>O</sub><sub>4</sub>, 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. <sup>1</sup>H 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)

![Chemical structure](image)

**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 <i>n</i>-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.

\[ ^1H \text{ NMR (CDCl}_3, 400 MHz): \delta (ppm) \]
1.10 (3H, d, J = 7.5 Hz, Hg), 1.46-1.63 (3H, m, Hsa, H6a, H7a), 1.81-1.98 (4H, m, Hsb, Haa, H3, H7b), 2.35-2.40 (1H, m, H4), 2.58-2.64 (1H, m, H1).

\[ ^13C \text{ NMR (CDCl}_3, 100 MHz): \delta (ppm) \]
14.1 (Cg), 23.7 (C6), 27.9 (C5), 34.4 (C7), 41.4 (C3), 48.2 (C4), 49.5 (C1), 221.0 (q, C2).

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

HRMS: \( m/z \text{- CI) Calculated for C}_{8}H_{13}O (M+H)^+ 125.0966, \text{ found 125.0970.} \)

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
Experimental

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, Rf = 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 13C NMR data reported in the literature.312

1H NMR (CDCl3, 400 MHz): δ (ppm) 1.06 (3H, s, H9), 1.08 (3H, s, H8), 1.44-1.53 (2H, m, H6a, H7a), 1.54-1.59 (1H, m, H5a), 1.77-1.93 (2H, m, H5b, H6b), 1.97-2.03 (1H, m, H7b), 2.31-2.35 (1H, m, H4), 2.55-2.58 (1H, m, H1).

13C NMR (CDCl3, 100 MHz): δ (ppm) 21.1 (C9), 22.7 (C8), 22.9 (C9), 24.2 (C6), 34.6 (C7), 45.8 (C4), 46.6 (q, C3), 49.7 (C1), 222.5 (q, C2).

IR νmax (cm⁻¹): 2966, 2874, 1739, 1464, 1290, 1153, 949, 748.
HRMS: (m/z - EI) Calculated for C9H14O (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 NH₄Cl (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 Rₚ = 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.^[13] 113-115 °C).

^1H NMR (CDCl₃, 600 MHz): δ (ppm) 0.94 (3H, s, H₉), 0.98 (3H, s, H₈), 1.14-1.20 (1H, m, H₇₉), 1.23 (3H, s, H₁₀), 1.30-1.41 (2H, m, H₅₉, H₆₉), 1.71-1.77 (3H, m, H₇₈, H₄, H₂₈), 1.83-1.92 (1H, m, H₅₈), 1.96-2.00 (1H, m, H₁).

^13C NMR (CDCl₃, 150 MHz): δ (ppm) 20.7 (C₃), 21.3 (C₃), 23.5 (C₆), 25.9 (C₁₀), 26.6 (C₈), 34.3 (C₇), 41.6 (q, C₃), 49.3 (C₄), 50.5 (C₁), 78.4 (q, C₂).

IR νₘₐₓ (cm⁻¹): 3422, 2928, 2872, 1476, 1372, 1295, 1086, 927.
HRMS: (m/z - EI) Calculated for C₁₀H₁₈O (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 HN₃ was prepared by carefully adding a solution of 50% H₂SO₄ (20 mL) to a suspension of NaN₃ (5.00 g, 77.8 mmol) in CHCl₃ (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 CH₂Cl₂ (2 x 30 mL). The combined organic extracts were washed with 5% aqueous NaHCO₃ solution (30 mL), dried over magnesium sulfate, filtered, and the
Experimental

Volatile compounds 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 colorless oil (2.40 g, 13.4 mmol, 56%).

^1H NMR (CDCl_3, 400 MHz): δ (ppm) 0.93 (3H, s, H9), 1.05 (3H, s, H8), 1.11-1.17 (1H, app d, J = 10.1 Hz, H7a), 1.26-1.35 (4H, m, H10, H5a), 1.42-1.50 (2H, m, H6), 1.55-1.63 (1H, m, H5b), 1.76-1.80 (1H, m, H4), 1.99-2.05 (1H, m, H7b), 2.11-2.14 (1H, m, H1).

^13C NMR (CDCl_3, 100 MHz): δ (ppm) 16.9 (C10), 22.6 (C6), 23.0 (C9), 23.3 (C5), 26.4 (C8), 34.4 (C7), 43.8 (q, C3), 48.3 (C1), 49.3 (C4), 72.5 (q, C2).

IR v_max (cm^-1): 2963, 2874, 2081, 1454, 1255, 1071, 801.

HRMS: (m/z - Cl) Calculated for C_{10}H_{23}N_4 (M+H-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-
Experimental

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 (lit14168-169 °C).

1H NMR (CDCl3, 400 MHz): δ (ppm) 0.93 (3H, s, Hg), 1.00 (3H, s, H9), 1.07-1.13 (4H, m, H10, H7b), 1.23-1.33 (1H, m, H5a), 1.33-1.43 (1H, m, H6a), 1.50-1.66 (2H, m, H3b, H6b), 1.71-1.76 (1H, m, H1), 1.80-1.85 (1H, m, H4), 1.91-1.97 (1H, m, H7b).

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

IR νmax (cm−1): 3387, 2953, 2870, 1464, 1386, 1258, 1127, 806, 743.

HRMS: (m/z - El) 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, Rf = 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, H8a), 1.39-1.67 (5H, m, H5a, H6a, H7a, H3, H8b), 1.78-1.88 (3H, m, H3b, H6b, H7b), 2.44-2.47 (1H, m, H4), 2.52-2.56 (1H, m, H1).
$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ (ppm) 12.6 (C$_9$), 21.9 (C$_8$), 23.7 (C$_3$), 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 $\nu_{\text{max}}$ (cm$^{-1}$): 2959, 2877, 1740, 1626, 1458, 1172, 1027.

HRMS: (m/z - EI) Calculated for C$_9$H$_{14}$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 (9.50 g, 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%).

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (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): $\delta$ (ppm) 8.2 (C$_{11}$), 8.6 (C$_9$), 22.6 (C$_{10}$), 23.0 (C$_4$), 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 $\nu_{\text{max}}$ (cm$^{-1}$): 2965, 2878, 1734, 1467, 1379, 1059.

HRMS: (m/z - EI) Calculated for C$_{11}$H$_{15}$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, Rf = 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, H7a), 1.21-1.36 (4H, m, H6a, H8a, H10a), 1.59-1.74 (6H, m, H5b, H7b, H8b, H10b, H12), 1.76-1.83 (1H, m, H6b), 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 νmax (cm⁻¹): 3515, 2962, 2879, 1463, 1377, 1127, 984.
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), NaN₃ (9.70 g, 149.0 mmol), 60% H₂SO₄ (30 mL) and CHCl₃ (120 mL) to yield a pale yellow oil which was further purified by column chromatography (100% hexane, Rₛ = 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%).

\(^1\)H NMR (CDCl₃, 400 MHz): \(\delta\) (ppm) 0.80 (3H, t, \(J = 7.4\) Hz, H₁₁), 0.84 (3H, app t, \(J = 7.4\) Hz, H₉), 0.98 (3H, app t, \(J = 7.4\) Hz, H₁₃), 1.16-1.21 (IH, m, H₇₆), 1.25-1.65 (8H, m, H₅, H₆, H₈₈, H₁₀, H₁₂₉), 1.70-1.94 (4H, m, H₈₉, H₇₈, H₄, H₁₂₈), 2.36-2.40 (1H, m, H₁).

\(^13\)C NMR (CDCl₃, 100 MHz): \(\delta\) (ppm) 9.0 (C₁₁), 9.1 (C₁₃), 9.7 (C₆), 21.5 (C₁₀), 22.0 (C₅), 23.4 (C₈), 25.1 (C₁₂), 26.3 (C₈), 33.8 (C₇), 44.3 (C₁), 46.0 (C₄), 50.2 (q, C₃), 76.7 (q, C₂).

IR \(\nu_{\text{max}}\) (cm⁻¹): 2964, 2881, 2091, 1464, 1270, 901, 881.

HRMS: \((m/z - \text{EI})\) Calculated for C₁₃H₂₃N (M-N₂)⁺ 193.1830, found 193.1835.
Experimental

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%).

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (ppm) 0.79 (3H, t, $J = 7.4$ Hz, H$_9$), 0.85 (3H, app t, $J = 7.4$ Hz, H$_{10}$), 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): $\delta$ (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 $\nu_{\text{max}}$ (cm$^{-1}$): 3363, 2960, 2877, 1462, 1376, 802, 732.

HRMS: (m/z - EI) Calculated for C$_{13}$H$_{25}$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, H₇a), 1.26-1.96 (9H, m, H₅, H₆, H₈, H₁₀a, H₁₂), 2.12-2.24 (2H, m, H₄, H₁₀b), 2.48-2.56 (1H, m, H₇b), 2.65-2.77 (4H, m, H₁, H₁₄), 8.39 (1H, br s, H₁₅a), 9.01 (1H, br s, H₁₅b).
$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ (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 $\nu_{max}$ (cm$^{-1}$): 2981, 2892, 1589, 1476, 1379, 1150, 944.

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

6.3.12 3-endo-Ethyl-3-methylbicyclo[2.2.1]heptan-2-one$^{315}$ (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%).

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (ppm) 0.91 (3H, app t, $J = 7.5$ Hz, H$_{10}$), 1.02 (3H, s, H$_s$), 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): $\delta$ (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$_2$).
Experimental

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

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

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

![Image of the molecular structure](image)

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%).

\(^1\)H NMR (CDCl\(_3\), 400 MH): \( \delta \) (ppm)

0.87 (3H, app t, \( J = 7.5 \text{ Hz}, \text{H}_{10} \)), 0.92 (3H, s, \text{H}_8), 1.13-1.20 (1H, m, \text{H}_{7a}), 1.24 (3H, s, \text{H}_{11}), 1.25-1.34 (3H, m, \text{H}_{5a}, \text{H}_{6a}, \text{H}_9), 1.48-1.59 (1H, m, \text{H}_{9b}), 1.59-1.67 (1H, m, \text{H}_{6b}), 1.67-1.73 (1H, m, \text{H}_7), 1.78-1.90 (2H, m, \text{H}_{5b}, \text{H}_4), 1.95-2.00 (1H, m, \text{H}_9).

\(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) (ppm)

9.4 (C\(_{10}\)), 20.9 (C\(_3\)), 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 \( \nu_{\text{max}} \) (cm\(^{-1}\)): 3468, 2961, 2936, 2876, 1462, 1375, 1089, 941.

HRMS: \((m/z - \text{Cl})\) Calculated for C\(_{11}\)H\(_{21}\)O (M+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), H$_2$SO$_4$ (55%, 20 mL), NaN$_3$ (10.00 g, 153.8 mmol) and CHCl$_3$ (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%).

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (ppm) 0.87 (3H, app t, $J = 7.5$ Hz, H$_{10}$), 1.04 (3H, s, H$_8$), 1.12-1.18 (1H, m, H$_{7a}$), 1.21-1.32 (2H, m, H$_{9a}$, H$_{5a}$), 1.35 (3H, s, H$_{11}$), 1.41-1.52 (4H, m, H$_6$, H$_{5b}$, H$_{9b}$), 1.86-1.91 (1H, m, H$_4$), 1.96-2.02 (1H, m, H$_7b$), 2.11 (1H, br s, H$_1$).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ (ppm) 10.0 (C$_{10}$), 16.9 (C$_{11}$), 21.4 (C$_8$), 23.25 (C$_6$), 23.34 (C$_3$), 27.8 (C$_9$), 34.7 (C$_7$), 46.6 (C$_4$), 47.6 (q, C$_3$), 49.2 (C$_1$), 73.8 (q, C$_2$).

IR $\nu_{max}$ (cm$^{-1}$): 2958, 2875, 2096, 1458, 1373, 1189, 1028.

HRMS: $(m/z - ES)$ Calculated for C$_{11}$H$_{20}$N (M+H-N$_2$)$^+$ 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%).

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (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): $\delta$ (ppm) 10.1 (C$_{10}$), 20.7 (C$_5$), 22.2 (C$_{11}$), 23.1 (C$_3$), 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 $\nu_{max}$ (cm$^{-1}$): 3378, 2962, 2930, 2878, 1461, 1378, 1158.

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

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

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 CH$_2$Cl$_2$ (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).

$^1$H NMR (CD$_3$OD, 400 MHz): δ (ppm) 0.93 (3H, app t, $J = 7.5$ Hz, H$_{10}$), 1.15 (3H, s, H$_8$), 1.31-1.46 (6H, m, H$_{11}$, H$_{7a}$, H$_{5a}$, H$_{9a}$), 1.54-1.75 (4H, m, H$_6$, H$_{5b}$, H$_{9b}$), 1.94-2.00 (1H, m, H$_{7b}$), 2.00-2.05 (1H, m, H$_4$), 2.45 (1H, br s, H$_1$), 2.66 (3H, s, H$_{12}$).

$^{13}$C NMR (CD$_3$OD, 100 MHz): δ (ppm) 8.2 (C$_{10}$), 14.0 (C$_{11}$), 18.0 (C$_{8}$), 21.5 (C$_6$), 22.7 (C$_3$), 26.5 (C$_9$), 27.3 (C$_{12}$), 32.8 (C$_7$), 43.7 (C$_1$), 46.88 (C$_4$), 46.92 (q, C$_3$), 70.0 (q, C$_2$).

IR $\nu_{\text{max}}$ (cm$^{-1}$): 3360, 2953, 2884, 1458, 1381, 1342, 1112, 915.

HRMS: (m/z - ES) Calculated for C$_{12}$H$_{24}$N (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%).

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) (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): \(\delta\) (ppm)

- 8.9 (C\(_8\)), 9.8 (C\(_{10}\)), 21.3 (C\(_{12}\)), 21.5 (C\(_6\)), 23.3 (C\(_3\)), 26.5 (C\(_9\)), 30.1 (C\(_{11}\)), 34.4 (C\(_7\)), 45.6 (C\(_3\)), 46.0 (C\(_1\)), 47.7 (C\(_4\)), 81.0 (C\(_2\)).

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

HRMS: (m/z - EI) Calculated for C\(_{12}\)H\(_{22}\)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\(_2\)SO\(_4\) (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%).

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) (ppm)

- 0.98 (3H, app t, \(J = 7.7\) Hz, H\(_{10}\)), 0.87 (3H, t, \(J = 7.5\) Hz, H\(_{12}\)), 1.06 (3H, s, H\(_8\)), 1.14-1.19 (1H, m, H\(_1\)), 1.68
Experimental

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): $\delta$ (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 $\nu_{\text{max}}$ (cm$^{-1}$): 2965, 2880, 2091, 1465, 1379, 1269, 1076, 901.

HRMS: (m/z - ES) Calculated for C$_{12}$H$_{22}$N (M+H-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).

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (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): $\delta$ (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).
Experimental

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

HRMS: $(m/z - \text{ES})$ Calculated for C$_{12}$H$_{24}$N (M+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$_2$Cl$_2$ (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).

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (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): $\delta$ (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$_2$).
Experimental

IR $\nu_{\text{max}}$ (cm$^{-1}$): 3361, 2953, 2885, 2744, 1459, 1381, 1151, 1113, 916.
HRMS: $(m/z - \text{ES})$ Calculated for C$_{11}$H$_{17}$O (M+H)$^+$ 165.1279, found 165.1279.

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$_2$O (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%).

$^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ (ppm) 1.44-1.67 (8H, m, H$_{7a}$, H$_{6a}$, H$_{6b}$, H$_{5a}$, H$_{1'a}$, H$_{1'b}$, H$_{2'a}$, H$_{2'b}$), 1.67-1.80 (4H, m, H$_{1'c}$, H$_{1'd}$, H$_{2'c}$, H$_{2'd}$), 1.80-1.92 (2H, m, H$_{7b}$, H$_{5b}$), 2.25-2.27 (1H, m, H$_{d}$), 2.56-2.59 (1H, m, H$_{1}$).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ (ppm) 23.8 (C$_{5}$), 25.5 (C$_{6}$), 26.4 (C$_{2}$), 26.8 (C$_{2'}$), 32.8 (C$_{1'}$), 36.0 (C$_{7}$), 36.5 (C$_{1'}$), 46.5 (C$_{4}$), 49.9 (C$_{1}$), 59.0 (q, C$_{3}$), 224.5 (q, C$_{2}$).

IR $\nu_{\text{max}}$(cm$^{-1}$): 2951, 2873, 1736, 1449, 911.
HRMS: $(m/z - \text{ESI})$ Calculated for C$_{11}$H$_{17}$O (M+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%).

_1^H NMR (CDCl₃, 400 MHz): δ (ppm) 1.21-1.26 (4H, m, H_7a, H_8), 1.26-1.42 (3H, m, H_6a, H_5b, H_{1'a}), 1.42-1.54 (3H, m, H_{1'b}, H_{1'c}, H_{2'a}), 1.55-1.72 (6H, m, H_{5b}, H_{7b}, H_{1'd}, H_{2'b}, H_{2'c}, H_{2'c}), 1.82-1.90 (2H, m, H_{4'}, H_{6b}), 1.99-2.03 (1H, m, H_1).

_13^C NMR (CDCl₃, 100 MHz): δ (ppm) 21.6 (C_6), 23.4 (C_{2'}), 23.5 (C_{2'}), 23.8 (C_3), 26.9 (C_8), 30.4 (C_{1'}), 35.36 (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 C_{12}H_{20}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'-cyclopentan]-2-ol 58 (0.50 g, 2.78 mmol), NaN$_3$ (1.26 g, 19.4 mmol), 50% H$_2$SO$_4$ (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%).

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (ppm)

1.19 (1H, app dt, $J$ = 9.9, 1.4 Hz, H$_{7a}$), 1.30-1.55 (11H, m, H$_8$, H$_{1'a}$, H$_{1'b}$, H$_{5a}$, H$_{5b}$, H$_{1'c}$, H$_{2'a}$, H$_{2'b}$, H$_2$), 1.55-1.68 (3H, m, H$_{6a}$, H$_{6b}$, H$_{2'd}$), 1.74-1.84 (1H, m, H$_{1'd}$), 1.87-1.91 (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): $\delta$ (ppm)

18.7 (C$_8$), 22.6 (C$_6$), 23.4 (C$_2'$), 23.5 (C$_2$), 23.6 (C$_5$), 31.8 (C$_{1'}$), 35.3 (C$_7$), 35.5 (C$_{1''}$), 45.8 (C$_4$), 48.4 (C$_1$), 57.1 (q, C$_3$), 72.1 (q, C$_2$).

IR $\nu_{\text{max}}$ cm$^{-1}$: 2957, 2875, 2080, 1456, 1254, 1071.

HRMS: (m/z - EI) Calculated for C$_{12}$H$_{19}$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%).

$^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ (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$_{5b}$, H$_{1'a}$, H$_{1'c}$, H$_{2'a}$, H$_{2'b}$, H$_{2'c}$, H$_{2'd}$), 1.71-1.78 (1H, m, H$_1$), 1.82-1.88 (3H, m, H$_1$, H$_4$, H$_7$).

$^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta$ (ppm) 22.6 (C$_3$), 23.1 (C$_2$), 23.4 (C$_2'$), 24.0 (C$_6$), 24.2 (C$_8$), 31.4 (C$_1$), 33.9 (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 $\nu_{\text{max}}$ cm$^{-1}$: 3351, 2949, 2872, 1456, 1372, 804.

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

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

![Diagram](image-url)
Experimental

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).

IH NMR (CDCl₃, 600 MHz): δ (ppm) 1.27-1.43 (5H, m, H₇a, H₅a, H₇a'), 1.44-1.57 (5H, m, H₆a, H₆b, H₂a, H₂b, H₁'d), 1.62-1.86 (4H, m, H₅b, H₂'c, H₂'d, H₁'b), 1.94-2.17 (3H, m, H₄, H₁'e, H₁'d), 2.29-2.37 (1H, m, H₄), 2.39-2.46 (1H, m, H₁), 2.61-2.71 (3H, br s, H₉), 8.24 (1H, br s, H₁0a), 9.15 (1H, br s, H₁0b).

I3C NMR (CDCl₃, 150 MHz): δ (ppm) 17.4 (C₈), 22.0 (C₂'), 22.1 (C₅), 22.5 (C₆), 23.4 (C₂'), 28.6 (C₉), 31.6 (C₁'), 33.4 (C₁'), 34.8 (C₇), 43.8 (C₁), 44.5 (C₄), 57.3 (q, C₃), 69.2 (q, C₄).

IR νmax cm⁻¹: 2955, 2733, 1462, 1431, 1398, 1108, 1036.

HRMS: (m/z - ESI) Calculated for C₁₅H₂₄N (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%).

\[ ^1H \text{NMR (CDCl}_3, 600 \text{ MHz): } \delta (\text{ppm}) \]

- 1.22-1.40 (2H, m, \( H_{2a}, H_{3a} \)), 1.40-1.56 (7H, m, \( H_{7a}, H_{6a}, H_{1a}, H_{1b}, H_{1c}, H_{1d}, H_{2b} \)), 1.59-1.71 (4H, m, \( H_{5a}, H_{3b}, H_{2'a}, H_{2'b} \)), 1.72-1.79 (1H, m, \( H_{5b} \)), 1.82-1.90 (1H, m, \( H_{6b} \)), 1.90-1.95 (1H, m, \( H_{7b} \)), 2.55-2.58 (1H, m, \( H_{1} \)), 2.59-2.62 (1H, m, \( H_{4} \)).

\[ ^{13}C \text{NMR (CDCl}_3, 150 \text{ MHz): } \delta (\text{ppm}) \]

- 22.3 (C\(_2\)), 22.4 (C\(_2\)), 22.7 (C\(_5\)), 24.7 (C\(_6\)), 25.8 (C\(_2\)), 30.3 (C\(_1\)), 30.4 (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 \( \nu_{\text{max}} \text{ cm}^{-1} \): 2928, 2856, 1736, 1448, 1091, 768.

HRMS: \( (m/z - \text{El}) \) 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%).

\[ ^1H \text{NMR (CDCl}_3, 600 \text{ MHz): } \delta (\text{ppm}) \]

- 1.08 (1H, dt, \( J = 12.9, 2.9 \text{ Hz}, H_{1'b} \)), 1.12-1.26 (6H, m, \( H_{2'a}, H_{2'b}, H_{8}, H_{7a} \)), 1.30-1.39 (3H, m,
Experimental

$^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta$ (ppm) 21.1 (C$_6$), 23.3 (C$_5$), 23.7 (C$_2$), 24.1 (C$_2'$), 25.3 (C$_8$), 26.2 (C$_2'$), 30.2 (C$_1'$), 33.2 (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 $\nu_{\text{max}}$ cm$^{-1}$: 3451, 2925, 2854, 1447, 1124, 923.

HRMS: (m/z - El) Calculated for C$_{13}$H$_{22}$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$_2$SO$_4$ (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%).

$^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ (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$_4$).

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**13C NMR** (CDCl₃, 150 MHz): δ (ppm)  
16.6 (C₆), 23.1 (C₅), 23.2 (C₃), 23.7 (C₂⁻), 24.1 (C₂), 25.9 (C₂⁻), 32.1 (C₁), 32.8 (C₁), 34.6 (C₇), 41.9 (C₄), 47.1 (q, C₃), 48.6 (C₁), 74.2 (q, C₂).

IR νₑₐₓ cm⁻¹: 2926, 2857, 2082, 1448, 1260, 1102.

HRMS: (m/z - ESI) Calculated for C₁₃H₂₂N (M+H - N₂)⁺ 192.1752, found 192.1754.

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

![Diagram of 2-Methylspiro[bicyclo[2.2.1]heptane-3,1'-cyclohexan]-2-amine](image)

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** (CDCl₃, 600 MHz): δ (ppm)  
1.08-1.42 (7H, m, H₅₉a, H₆₆a, H₇₇a, H₁₆a, H₁₇b, H₂₈a, H₂₉b), 1.46-1.59 (5H, m, H₅₉b, H₆₈b, H₁₇c, H₂₈c, H₂₉d), 1.59 (3H, s, H₅), 1.60-1.68 (3H, m, H₁₆d, H₂₈c, H₂₉d), 1.77-1.80 (1H, m, H₁₁), 1.81-1.85 (1H, m, H₇b), 2.30-2.33 (1H, m, H₄).

**13C NMR** (CDCl₃, 150 MHz): δ (ppm)  
22.5 (C₆), 22.9 (C₅), 23.7 (C₃), 23.9 (C₂⁻), 25.4 (C₂), 26.1 (C₂⁻), 32.0 (C₁), 32.1 (C₁), 34.2 (C₇), 41.9 (C₄), 45.6 (q, C₃), 52.3 (C₁), 64.4 (q, C₂).

IR νₑₐₓ cm⁻¹: 3300, 2921, 2856, 1447, 1374, 829.

HRMS: (m/z - ESI) Calculated for C₁₃H₂₄N (M+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 CH₂Cl₂ (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).

$^1$H NMR (CDCl₃, 600 MHz): δ (ppm) 1.14-1.39 (7H, m, H₈, H₇a, H₁′ₐ, H₂′ₐ, H₂′₋), 1.36-1.72 (9H, m, H₅ₐ, H₅ₖ, H₆ₐ, H₆ₖ, H₁′ₖ, H₂′ₖ, H₂′₉, H₂′ₐ, H₂′₉), 1.77-1.85 (1H, m, H₁′ₚ), 2.14-2.21 (1H, m, H₁′ₚ), 2.29-2.36 (1H, m, H₇ₕ), 2.38-2.42 (1H, m, H₁), 2.52-2.55 (1H, m, H₄), 2.64-2.72 (3H, m, H₉), 8.24 (1H, br s, H₁₀ₐ), 9.00 (1H, br s, H₁₀ₙ).

$^{13}$C NMR (CDCl₃, 150 MHz): δ (ppm) 15.5 (C₈), 22.5 (C₅), 23.3 (C₆), 23.5 (C₂′), 23.9 (C₂′), 25.5 (C₂′), 29.0 (C₉), 31.2 (C₁′), 31.8 (C₁′), 34.5 (C₇), 41.7 (C₄), 44.5 (C₁), 47.8 (q, C₃), 71.8 (q, C₂).

IR vₘₐₓ cm⁻¹: 2926, 2748, 1593, 1465, 1386, 1117, 996.

HRMS: (m/z - ESI) Calculated for C₁₄H₂₆N (M+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, Rf = 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%).

$^1$H 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, H$_{1' a}$), 1.30-1.39 (2H, m, H$_{5a}$, H$_{6a}$), 1.40-1.38 (2H, m, H$_{2'a}$, H$_{1'b}$), 1.49-1.67 (8H, m, H$_{8a}$, H$_{8b}$, H$_{1'c}$, H$_{2'c}$, H$_{2'd}$, H$_{7b}$, H$_{5b}$), 1.68-1.75 (1H, m, 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 (C$_2$), 23.4 (C$_2$), 23.7 (C$_3$), 30.2 (C$_8$), 30.6 (C$_1$), 34.2 (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 $\nu_{\text{max}}$ cm$^{-1}$: 3485, 2954, 2873, 1462, 1291, 982.

HRMS: (m/z - EI) Calculated for C$_{13}$H$_{22}$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'-cyclopentan]-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%).

\(^1\)H NMR (CDCl₃, 600 MHz): \( \delta \) (ppm) 0.98 (3H, t, \( J = 7.5 \) Hz, \( H_9 \)), 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, \( H_{pd} \)), 1.86 (1H, app d, \( J = 10.1 \) Hz, \( H_{7b} \)), 1.89-1.92 (1H, m, \( H_4 \)), 2.29-2.31 (1H, m, \( H_1 \)).

\(^1\)C NMR (CDCl₃, 150 MHz): \( \delta \) (ppm) 9.3 (\( C_9 \)), 22.1 (\( C_2' \)), 23.0 (\( C_9 \)), 23.1 (\( C_2' \)), 23.3 (\( C_5 \)), 25.4 (\( C_8 \)), 31.0 (\( C_1' \)), 35.0 (\( C_7 \)), 35.2 (\( C_1' \)), 44.4 (\( C_1 \)), 44.9 (\( C_4 \)), 58.8 (q, \( C_3 \)), 75.3 (q, \( C_2 \)).

IR \( \nu_{max} \) cm\(^{-1} \): 2963, 2876, 2091, 1454, 1258, 881.

HRMS: (m/z - ESI) Calculated for \( C_{13}H_{22}N \) (M+H-N\(_2\))^⁺ 192.1752, found 192.1759.
6.3.33 2-Ethylidenespiro[bicyclo[2.2.1]heptane-3,1'-cyclopentane]. (65)

\[ \text{Experimental} \]

\[ \text{1H NMR (CDCl}_3, 400 MHz): \delta \text{ (ppm)} \]
1.17-1.33 (2H, m, H\text{6a}, H\text{7a}), 1.38-1.48 (2H, m, H\text{5a}, H\text{1a}), 1.49-1.74 (13H, m, H\text{5b}, H\text{6b}, H\text{7b}, H\text{6}, H\text{7}, H\text{1b}, H\text{1c}, H\text{1d}, H\text{2a}, H\text{2b}, H\text{2c}, H\text{2d}), 1.91-1.95 (1H, m, H\text{4}), 2.93-2.97 (1H, m, H\text{3}), 5.02 (1H quartet, \( J = 6.6 \text{ Hz} \), H\text{9}).

\[ \text{13C NMR (CDCl}_3, 100 MHz): \delta \text{ (ppm)} \]
14.4 (C\text{9}), 24.1 (C\text{5}), 25.6 (C\text{2'}), 26.2 (C\text{2'}), 28.9 (C\text{6}), 36.5 (C\text{1'}), 38.1 (C\text{7}), 40.7 (C\text{1}), 42.1 (C\text{1'}), 47.3 (C\text{4}), 54.8 (q, C\text{3}), 109.1 (C\text{8}), 157.6 (q, C\text{2}).

IR \( \nu_{\text{max}} \text{ cm}^{-1} \): 2951, 2866, 1452, 1289, 811.

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

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

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

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (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, $H_{5a}$, $H_{5b}$, $H_{6a}$, $H_{6d}$, $H_{1'a}$, $H_{1'b}$, $H_{1'c}$, $H_{1'd}$, $H_{2'a}$, $H_{2'b}$, $H_{2'c}$, $H_{2'd}$, $H_{8a}$, $H_{8b}$), 1.83-1.90 (3H, m, $H_1$, $H_4$, $H_7b$).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ (ppm)

9.2 (C$_9$), 22.3 (C$_5$), 23.3 (C$_8$), 23.4 (C$_6$), 23.79 (C$_2$), 23.80 (C$_2'$), 30.6 (C$_1'$), 34.0 (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 $\nu_{\text{max}}$ cm$^{-1}$: 3289, 2948, 2873, 1463, 1377, 947, 806.

HRMS: (m/z – El) Calculated for C$_{13}$H$_{23}$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$_2$Cl$_2$ (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.

$^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ (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, $H_{5a}$, $H_{5b}$, $H_{6a}$, $H_{6b}$, $H_8$, $H_{1'a}$, $H_{1'b}$, $H_{1'c}$, $H_{2'a}$, $H_{2'b}$, $H_{2'c}$, $H_{2'd}$), 1.99 (1H, br s, $H_4$), 2.04-2.12 (1H, m, $H_{1'd}$), 2.52
Experimental

(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): \(\delta\) (ppm) 9.6 (C\(_9\)), 22.2 (C\(_3\)), 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 \(\nu_{\text{max}}\) cm\(^{-1}\): 2950, 1594, 1456, 1416, 1107, 1101, 907.

HRMS: \(m/z\) - ESI Calculated for C\(_{14}\)H\(_{26}\)N (M+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%).

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) (ppm)

0.95 (3H, t, \(J = 7.4\) Hz, \(H_6\)), 0.98-1.07 (1H, m, \(H_{1'd}\)), 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, \(H_4\)).
Experimental

Experimental

$^{13}$C NMR (CDCl$_3$, 100 MHz): δ (ppm)

9.0 (C$_9$), 21.4 (C$_6$), 23.2 (C$_5$), 23.8 (C$_2$'), 24.0 (C$_2$'), 26.3 (C$_2$'), 28.3 (C$_8$), 30.3 (C$_1$'), 32.2 (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 $\nu_{max}$ cm$^{-1}$: 3494, 2926, 2854, 1466, 1128, 966.

HRMS: $\langle m/z - El \rangle$ Calculated for C$_{14}$H$_{24}$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$_2$SO$_4$ (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%).

$^1$H NMR (CDCl$_3$, 400 MHz): δ (ppm)

0.95 (3H, t, $J = 7.4$ Hz, H$_9$), 1.12-1.25 (4H, m, H$_{7a}$, H$_{1'a}$, H$_{2'a}$, H$_{2'b}$), 1.26-1.39 (3H, m, H$_{5a}$, H$_{6a}$, H$_{1'b}$), 1.41-1.70 (8H, m, H$_{5b}$, H$_{6b}$, H$_{8a}$, H$_{1'c}$, H$_{2'c}$, H$_{2'd}$, H$_{2'e}$, H$_{2'f}$), 1.73-1.88 (3H, m, H$_{7b}$, H$_{8b}$, 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$_5$), 23.1 (C$_3$), 23.6 (C$_2$'), 24.1 (C$_2$'), 26.0 (C$_2$'), 31.2 (C$_1$'), 32.8 (C$_1$'), 34.3 (C$_7$), 41.4 (C$_4$), 44.7 (C$_1$), 49.1 (q, C$_3$), 77.8 (q, C$_2$).
Experimental

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

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

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

![Chemical Structure](image)

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%).

$^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ (ppm) 0.92 (3H, t, $J = 7.5$ Hz, H$_9$), 1.05-1.43 (8H, m, H$_{5a}$, H$_{6a}$, H$_{7a}$, H$_{1'a}$, H$_{1'b}$, H$_{2'a}$, H$_{2'b}$, H$_2'$c), 1.44-1.78 (9H, m, H$_{3b}$, H$_{6b}$, H$_{8a}$, H$_{8b}$, H$_1'$c, H$_1$'d, H$_2''d$, H$_2''e$, 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): $\delta$ (ppm) 9.1 (C$_9$), 23.1 (C$_3$), 23.2 (C$_2$), 23.8 (C$_6$), 24.3 (C$_2'$), 26.2 (C$_2''$), 26.7 (C$_8$), 31.1 (C$_1'$), 32.1 (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 $\nu_{\text{max}}$ cm$^{-1}$: 3342, 2923, 2857, 1451, 831.

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

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Experimental

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 CH₂Cl₂ (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).

\[ ^1H \text{NMR (CDCl}_3, 600 \text{MHz): } \delta (\text{ppm}) \]

1.16 (3H, t, \( J = 7.3 \text{ Hz}, H_9 \)), 1.18-1.28 (4H, m, \( H_{6a}, H_{7a}, H_{1'a}, H_{2'a} \)), 1.35-1.84 (12H, m, \( H_{5a}, H_{5b}, H_{6b}, H_{8a}, H_{8b}, H_{1'c}, H_{2'b}, H_{2'c}, H_{2'd}, H_{2'e}, H_{2'f}, H_{1'g}, H_{1'd} \)), 2.36-2.41 (1H, m, \( H_{1'd} \)), 2.50-2.56 (2H, m, \( H_4, H_7b \)), 2.63-2.66 (1H, m, \( H_1 \)), 2.69 (3H, app t, \( J = 5.4 \text{ Hz}, H_{10} \)), 8.56 (1H, br s, \( H_{11a} \)), 8.91 (1H, br s, \( H_{11b} \)).

\[ ^13C \text{NMR (CDCl}_3, 150 \text{MHz): } \delta (\text{ppm}) \]

9.4 (C₉), 21.0 (C₈), 22.1 (C₅), 23.4 (C₂), 23.5 (C₆), 23.7 (C₂'), 25.7 (C₂'), 30.0 (C₁₀), 31.6 (C₁'), 31.7 (C₇'), 34.3 (C₇), 42.1 (C₄), 45.3 (C₁), 48.5 (q, C₃), 74.8 (q, C₂).

IR \( \nu_{\text{max}} \text{ cm}^{-1} \): 2931, 1586, 1452, 1411, 922.

HRMS: \( (m/z - \text{ESI}) \) Calculated for C₁₄H₂₃ (M-NH₂CH₃)⁺ 191.1800, found 191.1808.
Experimental

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 methylolithium 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, H₇a), 1.35 (3H, s, H₁₀), 1.40 (3H, s, H₁₁), 1.42-
Experimental

1.61 (4H, m, H₅a, H₆a, H₈a, H₈b), 1.76-1.80 (1H, m, H₇b), 1.81-1.88 (1H, m, H₅b), 1.90-1.96 (1H, m, H₆b), 2.09-2.12 (1H, m, H₄), 2.14-2.18 (1H, m, H₃), 2.65-2.69 (3H, m, H₁₂), 8.26-8.38 (1H, br s, H₁₁a), 9.27-9.37 (1H, br s, H₁₁b).

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

IR v_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 µL, 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).
Experimental

$^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ (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$_{11}$), 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): $\delta$ (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 $\nu_{\text{max}}$ (cm$^{-1}$): 2956, 2882, 2713, 1467, 1390, 1138, 1087, 921.

HRMS: (m/z - ESI) Calculated for C$_{12}$H$_{24}$N (M+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%).

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (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, 190
Experimental

H$_1$), 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$_5$), 22.4 (C$_6$), 23.7 (C$_3$), 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 $v_{	ext{max}}$ cm$^{-1}$: 3460, 2943, 2871, 1048, 703.

HRMS: (m/z - EI) Calculated for C$_{15}$H$_{20}$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$_2$SO$_4$ (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%).

$^1$H NMR (CDCl$_3$, 400 MHz): δ (ppm) 0.84 (3H, s, H$_o$), 1.23-1.34 (5H, m, H$_8$, H$_{5a}$, H$_{2a}$), 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$_{7a}$), 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$_4$), 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,
Experimental

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

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

HRMS: (m/z - El) 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%).

\(^1\)H NMR (CDCl₃, 400 MHz): \( \delta \) (ppm) 0.88 (3H, s, H₉), 1.25-1.34 (5H, m, H₈, H₇a, H₅a), 1.55-1.81 (3H, m, H₃b, H₆a, H₆b), 1.82-1.85 (1H, m, H₄), 1.23-1.29 (1H, app d, \( J = 10.4 \) Hz, H₇b), 2.47-2.52 (1H, m, H₁), 7.17-7.23 (1H, m, H₁₃), 7.29-7.37 (4H, m, H₁₁, H₁₂).

\(^{13}\)C NMR (CDCl₃, 100 MHz): \( \delta \) (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 \( \nu_{\text{max}} \) cm⁻¹: 3328, 2926, 1597, 1643, 766, 705.

HRMS: (m/z - El) 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 (0.05 g, 0.21 mmol, 50%). M.p. 175-180 °C (decomposes).

$^1$H NMR (CDCl₃, 600 MHz): δ (ppm)

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$^{13}$C NMR (CDCl₃, 150 MHz): δ (ppm)

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

HRMS: (m/z - ESI) Calculated for C$_{16}$H$_{24}$N (M+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), trimethylsilylethylene (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$_2$O 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%).

$^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ (ppm)

0.52 (3H, s, H$_5$), 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): $\delta$ (ppm)

22.0 (C$_5$), 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$_{12}$).
Experimental

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

HRMS: (m/z - El) Calculated for C$_{12}$H$_{19}$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%).

$^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ (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$_{6a}$), 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$_{15}$), 7.45 (2H, app t, $J = 7.6$ Hz, H$_{13}$), 7.89 (2H, d, $J = 7.6$ Hz, H$_{14}$), 7.92 (1H, s, H$_{11}$).

$^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta$ (ppm) 22.2 (C$_9$), 22.7 (C$_5$), 23.0 (C$_{10}$), 24.6 (C$_8$), 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 $\nu_{\text{max}}$ (cm$^{-1}$): 3138, 2963, 2884, 1481, 1229, 1021, 762.
Experimental

HRMS: (m/z - ESI) Calculated for C\textsubscript{18}H\textsubscript{24}N\textsubscript{3} (M+H)\textsuperscript{+} 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 (0.20 g, 1.12 mmol), 3-butyn-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\textsubscript{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%).

\(^1\text{H NMR}\) (CDCl\textsubscript{3}, 600 MHz): \(\delta\) (ppm) 0.54 (3H, s, H\textsubscript{9}), 1.15 (3H, s, H\textsubscript{3}), 1.44 (1H, app d, \(J = 10.5\) Hz, H\textsubscript{7a}), 1.49 (1H, m, H\textsubscript{5a}) 1.60 (1H, m, H\textsubscript{6a}) 1.65 (3H, s, H\textsubscript{10}), 1.71 (1H, m, H\textsubscript{5b}), 1.76 (1H, m, H\textsubscript{6b}), 1.93 (1H, br s, H\textsubscript{4}), 2.26 (1H, app d, \(J = 10.5\) Hz, H\textsubscript{7b}), 2.81 (1H, br s, H\textsubscript{1}), 2.98 (2H, dt, \(J = 5.7, 2.0\) Hz, H\textsubscript{13}), 3.98 (2H, t, \(J = 5.7\) Hz, H\textsubscript{14}), 7.57 (1H, s, H\textsubscript{11}).

\(^{13}\text{C NMR}\) (CDCl\textsubscript{3}, 150 MHz): \(\delta\) (ppm) 22.0 (C\textsubscript{6}), 22.6 (C\textsubscript{5}), 22.9 (C\textsubscript{10}), 24.5 (C\textsubscript{6}), 26.1 (C\textsubscript{5}), 28.5 (C\textsubscript{13}), 36.1 (C\textsubscript{7}), 46.5 (q, C\textsubscript{3}), 48.4 (C\textsubscript{1}), 50.7 (C\textsubscript{4}), 61.8 (C\textsubscript{14}), 72.5 (q, C\textsubscript{2}), 120.8 (C\textsubscript{11}), 143.5 (q, C\textsubscript{12}).

IR \(\nu\textsubscript{max}\) (cm\textsuperscript{-1}): 3342, 2980, 1663, 1386, 1051, 809.

HRMS: (m/z - ESI) Calculated for C\textsubscript{14}H\textsubscript{24}N\textsubscript{3}O (M+H)\textsuperscript{+} 250.1919, found 250.1926.
Experimental

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, Rf = 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.

\( ^1H \text{ NMR (CDCl}_3, 400 MHz): \delta \) (ppm)

<table>
<thead>
<tr>
<th>( \delta )</th>
<th>0.42 (9H, s, H\text{13}), 0.53 (3H, s, H\text{8}), 1.18 (3H, s, H\text{9}), 1.45-1.82 (8H, m, H\text{10}, H\text{5a}, H\text{5b}, H\text{6a}, H\text{6b}, H\text{7a}), 1.94 (1H, br s, H\text{4}), 2.25 (1H, app d, J = 10.5 Hz, H\text{7b}), 2.85 (1H, br s, H\text{1}), 7.70 (1H, s, H\text{11}).</th>
</tr>
</thead>
</table>

\( ^13C \text{ NMR (CDCl}_3, 100 MHz): \delta \) (ppm)

<table>
<thead>
<tr>
<th>( \delta )</th>
<th>1.0 (C\text{13}), 22.0 (C\text{9}), 22.6 (C\text{5}), 23.1 (C\text{10}), 24.6 (C\text{6}), 26.2 (C\text{8}), 36.0 (C\text{7}), 46.6 (q, C\text{3}), 48.5 (C\text{1}), 50.7 (C\text{4}), 73.3 (q, C\text{2}), 128.3 (C\text{11}), 142.6 (q, C\text{12}).</th>
</tr>
</thead>
</table>

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

HRMS: \( (m/z - \text{ESI}) \) Calculated for C\text{15}H\text{28}N\text{3}Si (M+H\text{)}^+ 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.° 73-74 °C).

$^1$H NMR (CDCl₃, 400 MHz): $\delta$ (ppm) 0.88 (3H, s, H₉), 0.99 (3H, s, H₈), 1.16 (1H, app dt, $J = 10.5$, 1.7 Hz, H₇α), 1.25-1.40 (2H, m, H₆a & H₅a), 1.56-1.71 (3H, m, H₅b, H₆b & H₇b), 1.77-1.80 (1H, m, H₄), 2.26-2.30 (1H, m, H₁), 3.66 (1H, d, $J = 4.0$ Hz, H₂).

$^{13}$C NMR (CDCl₃, 100 MHz): $\delta$ (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 $v_{\text{max}}$ (cm$^{-1}$): 3367, 2965, 2879, 1459, 1341, 1297, 1067.

HRMS: $(m/z - \text{El})$ Calculated for C₉H₁₆O (M)$^+$ 140.1201, found 140.1203.
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 vaccum (0.11 g, 0.46 mmol, 34%). M.p. = 93-95 °C (decomposes).

\[\begin{align*}
\text{H NMR (CDCl}_3, 600 MHz): & \delta (ppm) \\
1.05 & (3H, s, H_9), 1.24 & (3H, s, H_{10}), 1.27-1.32 & (1H, m, H_{7a}), 1.34-1.59 & (7H, m, H_{5a}, H_{5b}, H_{6a}, H_{6b}, H_8), 1.68-1.78 & (1H, m, H_{12a}), 1.89-1.93 & (1H, m, H_4), 1.98-2.05 & (1H, m, H_{12b}), 2.12-2.19 & (1H, m, H_{12c}), 2.23-2.32 & (1H, m, H_{12d}), 2.38-2.43 & (1H, br s, H_1), 2.83-2.89 & (1H, app d, J = 11.4 Hz, H_{7b}), 2.95-3.08 & (2H, m, H_{11a}, H_{11b}), 3.65-3.73 & (1H, m, H_{11c}), 4.02-4.10 & (1H, m, H_{11d}), 9.89-10.10 & (1H, br s, H_{13}).
\end{align*}\]

\[\begin{align*}
\text{C NMR (CDCl}_3, 150 MHz): & \delta (ppm) \\
14.5 & (C_{10}), 22.3 & (C_3), 24.0 & (C_9), 24.7 & (C_8), 25.0 & (C_{12}), 26.2 & (C_{12}), 28.5 & (C_8), 34.8 & (C_7), 46.4 & (q, C_3), 46.8 & (C_1), 52.1 & (C_4), 52.7 & (C_{11}), 52.8 & (C_{11}), 78.0 & (q, C_2).
\end{align*}\]

IR \(\nu_{\text{max}}\) (cm\(^{-1}\)): 2946, 1474, 1384, 1339, 1083, 1039, 732.

HRMS: \((m/z - \text{ESI})\) Calculated for C\(_{14}\)H\(_{26}\)N (M+H)\(^+\) 208.2065, found 208.2064.
Experimental

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 redissolved 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, H₇a, H₁₀), 1.38-1.47 (2H, m, H₅a, H₁₃a), 1.49-1.57 (3H, m, H₅b, H₆a, H₆b), 1.77-1.85 (5H, m, H₈, H₁₂a, H₁₂b), 1.91-1.95 (1H, br s, H₄), 1.98-2.04 (1H, m, H₁₃b), 2.62-2.67 (1H, br s, H₁), 2.72-2.85 (2H, m, H₁₁a, H₁₂c), 2.85-2.95 (1H, m, H₁₁b), 3.19-3.27 (1H, m, H₂), 3.43-3.50 (1H, m, H₁₁c), 3.50-3.60 (1H, m, H₁₂d), 3.79-3.85 (1H, m, H₁₁d), 8.59-8.81 (1H, br s, H₁₄). |

¹³C NMR (CDCl₃, 150 MHz): δ (ppm)

| 14.9 (C₁₀), 22.0 (C₃), 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 ν₀ (cm⁻¹): 2933, 1458, 1388, 1113, 998.

HRMS: (m/z - ESI) Calculated for C₁₅H₂₉N (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 LiAlH₄ (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 LiAlH₄. 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, Rf = 0.2) to yield 5-norbornene-2-endo-3-endo-dimethanol 103 as a white solid. (0.57 g, 3.68 mmol, 58%) M.p. 84-86 °C (Lit. 319 85-86 °C).

¹H NMR (CDCl₃, 400 MHz): δ (ppm) 1.39-1.47 (2H, m, H₇α, H₇β), 2.52-2.61 (2H, m, H₅, H₆), 2.83 (2H, br s, H₁, H₄), 3.36-3.45 (2H, m, 2H₈α), 3.69 (2H, dd, J = 10.8, 2.7 Hz, 2H₈β), 6.06 (2H, s, H₂, H₃).

¹³C NMR (CDCl₃, 100 MHz): δ (ppm) 45.1 (C₅ & C₇), 46.6 (C₁ & C₄), 50.0 (C₇), 63.6 (C₈), 134.9 (C₂ & C₃).

IR ν max (cm⁻¹): 3233, 2939, 1347, 1018, 988, 888.

HRMS: (m/z - ESI) Calculated for C₉H₁₅O₂ (M+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%).

\[^1\text{H} \text{NMR (CDCl}_3, \text{400 MHz):} \delta (\text{ppm})\]

1.35 (1H, app d, \( J = 8.3 \text{ Hz, H}_7\)), 1.50 (1H, app d, \( J = 8.3 \text{ Hz, H}_7\)), 2.52-2.59 (2H, m, \( \text{H}_5, \text{H}_6\)), 2.99 (2H, br s, \( \text{H}_1, \text{H}_4\)), 3.05-3.10 (2H, m, \( 2\text{H}_{8a}\)), 3.29-3.36 (2H, m, \( 2\text{H}_{8b}\)), 4.43 (2H, d, \( J = 12.2 \text{ Hz, } 2\text{H}_{9a}\)), 4.49 (2H, d, \( J = 12.2 \text{ Hz, } 2\text{H}_{9b}\)), 6.07 (2H, s, \( \text{H}_3, \text{H}_2\)), 7.28-7.39 (10H, m, \( \text{H}_{11}, \text{H}_{12}, \text{H}_{13}\)).

\[^{13}\text{C} \text{NMR (CDCl}_3, \text{100 MHz):} \delta (\text{ppm})\]

41.9 (C\(_6\) & C\(_3\)), 45.8 (C\(_1\) & C\(_4\)), 47.5 (C\(_8\)), 49.4 (C\(_7\)), 73.0 (C\(_9\)), 127.5 (C\(_{13}\)), 127.6 (C\(_{11}\)), 128.3 (C\(_{12}\)), 135.3 (C\(_2\) & C\(_3\)), 138.4 (q, C\(_{10}\)).
Experimental

IR \( v_{\text{max}} \) (cm\(^{-1}\)): 2918, 2850, 1453, 1365, 1091, 1075, 1028.

HRMS:  \( m/z \) - ESI) Calculated for C\(_{23}\)H\(_{27}\)O\(_2\)Na (M+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 BF\(_3\).Et\(_2\)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\(_2\)O\(_2\) (35% in H\(_2\)O, 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 with 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%).

\(^1\)H NMR (CDCl\(_3\), 400 MHz):  \( \delta \) (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\(_{19}\)).

203
$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ (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 $\nu_{\text{max}}$ (cm$^{-1}$): 3380, 2960, 1453, 1365, 1090, 1072, 984.

HRMS: (m/z - ESI) Calculated for C$_{23}$H$_{28}$O$_3$Na (M+Na)$^+$ 375.1936, found 375.1933.

**6.4.4 5,6-endo-Bis[(benzyl)oxy)methyl]bicyclo[2.2.1]heptan-2-one. (106)**

![Chemical structure](image)

**General Procedure P**

To a suspension of PDC (6.83 g, 18.2 mmol) and celite (1.00 g) in anhydrous CH$_2$Cl$_2$ (90 mL) was added a solution of 5,6-endo-bis[(benzyl)oxy)methyl]bicyclo[2.2.1]heptan-2-ol 105 (3.20 g, 9.90 mmol) in CH$_2$Cl$_2$ (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$_2$Cl$_2$ (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[(benzyl)oxy)methyl]bicyclo[2.2.1]heptan-2-one 106 as a clear colourless oil (1.91 g, 5.45 mmol, 55%).
Experimental

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (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$_{ga}$, H$_{gb}$, H$_{4a}$), 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): $\delta$ (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$_{13}$), 73.4 (C$_9$), 127.61 (C$_{13}$/C$_{19}$), 127.67 (C$_{11}$/C$_{17}$), 127.7 (C$_{13}$/C$_{19}$), 127.8 (C$_{11}$/C$_{17}$), 128.4 (C$_{12}$/C$_{18}$), 128.5 (C$_{12}$/C$_{18}$), 138.1 (q, C$_{10}$/C$_{16}$), 138.2 (q, C$_{10}$/C$_{16}$), 216.6 (q, C$_2$).

IR $\nu_{\text{max}}$ (cm$^{-1}$): 2968, 2861, 1739, 1453, 1365, 1091, 1074, 998.

HRMS: ($m/z$ - ESI) Calculated for C$_{23}$H$_{26}$O$_3$Na (M+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-
Experimental

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, Rf = 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%).

$^1$H 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 (C$_{14}$/C$_{20}$), 127.65 (C$_{12}$/C$_{18}$), 127.7 (C$_{14}$/C$_{20}$), 127.80 (C$_{12}$/C$_{18}$), 128.3 (C$_{13}$/C$_{19}$), 128.4 (C$_{13}$/C$_{19}$), 138.1 (q, C$_{17}$), 138.3 (q, C$_{11}$), 219.5 (q, C$_2$).

IR $\nu_{\text{max}}$ (cm$^{-1}$): 2871, 1739, 1454, 1366, 1091, 1027, 909.

HRMS: (m/z - ESI) Calculated for C$_{24}$H$_{26}$O$_3$Na (M+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), 3.69-3.73 (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).

^13C NMR (CDCl_3, 150 MHz): δ (ppm) 22.0 (C_9), 26.4 (C_8), 36.7 (C_7), 39.7 (C_3), 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 (C_11/17), 73.4 (C_11/17), 127.4 (C_15/C_21), 127.5 (C_15/C_21), 127.67 (C_13/C_19), 127.7 (C_13/C_19), 128.2 (C_14/C_20), 128.3 (C_14/C_20), 138.18 (q, C_12/C_18), 138.2 (q, C_12/C_18),
Experimental

IR $v_{\text{max}}$ (cm$^{-1}$): 2871, 1737, 1454, 1365, 1093, 1027, 910.

HRMS: (m/z - ESI) Calculated for C$_{25}$H$_{30}$O$_3$Na (M+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%).

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (ppm)

<table>
<thead>
<tr>
<th>Proton</th>
<th>$\delta$ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H$_9$</td>
<td>0.90 (3H, s)</td>
</tr>
<tr>
<td>H$_6$</td>
<td>0.93 (3H, s)</td>
</tr>
<tr>
<td>H$_{10}$</td>
<td>1.21 (3H, s,  H$_{10}$)</td>
</tr>
<tr>
<td>H$_{11}$</td>
<td>1.33 (1H, app dt, $J = 10.7$, 1.5 Hz, H$<em>{7a}$), 1.74-1.77 (1H, m, H$<em>4$), 1.80 (1H, app d, $J = 10.7$ Hz, H$</em>{7b}$), 2.72-2.35 (2H, m, H$<em>1$, H$<em>3$), 2.50-2.75 (1H, m, H$<em>6$), 3.63-3.72 (2H, m, H$</em>{11a}$, H$</em>{7b}$), 3.75-3.83 (2H, m, H$</em>{11b}$, H$</em>{17b}$), 4.52 (H, d, $J = 13.6$ Hz, H$<em>{12a}$), 4.55 (1H, d, $J = 13.6$ Hz, H$</em>{12b}$), 4.74 (2H, s, H$<em>8$), 7.29-7.43 (10H, m, H$</em>{14}$, H$<em>{15}$, H$</em>{16}$, H$<em>{20}$, H$</em>{21}$, H$_{22}$).</td>
</tr>
</tbody>
</table>

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ (ppm)

<table>
<thead>
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<th>Carbon</th>
<th>$\delta$ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C$_{10}$</td>
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</tr>
<tr>
<td>C$_9$</td>
<td>22.2 (C$_9$)</td>
</tr>
<tr>
<td>C$_8$</td>
<td>27.4 (C$_8$)</td>
</tr>
<tr>
<td>C$_7$</td>
<td>34.6 (C$_7$)</td>
</tr>
<tr>
<td>C$_6$</td>
<td>40.7 (C$_6$)</td>
</tr>
<tr>
<td>C$_5$</td>
<td>45.7 (q, C$_5$)</td>
</tr>
<tr>
<td>C$_4$</td>
<td>45.9 (C$_4$)</td>
</tr>
<tr>
<td>C$_3$</td>
<td>50.0 (C$_4$)</td>
</tr>
<tr>
<td>C$_1$</td>
<td>54.3 (C$_1$), 208</td>
</tr>
</tbody>
</table>
Experimental

65.6 (C<sub>18</sub>), 67.1 (C<sub>17</sub>), 69.7 (C<sub>11</sub>), 73.2 (C<sub>12</sub>), 88.9 (q, C<sub>2</sub>), 127.0 (C<sub>20</sub>), 127.6 (C<sub>22</sub>), 127.7 (C<sub>16</sub>), 127.8 (C<sub>14</sub>), 128.4 (C<sub>15</sub>), 128.6 (C<sub>21</sub>), 138.7 (q, C<sub>13</sub>), 140.8 (q, C<sub>19</sub>).

IR ν<sub>max</sub> (cm<sup>-1</sup>): 3418, 2927, 1454, 1369, 1070, 1027, 999.

HRMS: (m/z - ESI) Calculated for C<sub>26</sub>H<sub>34</sub>O<sub>3</sub>Na (M+Na)<sup>+</sup> 417.2406, found 417.2403.

6.4.8 7-[(Benzyloxy)methyl]-6,6,6a-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% H<sub>2</sub>SO<sub>4</sub> (2 mL), NaN<sub>3</sub> (0.51 g, 7.81 mmol) and CHCl<sub>3</sub> (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<sub>f</sub> = 0.5) to yield 111 as a clear colourless oil (0.24 g, 0.82 mmol, 71%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 0.88 (3H, s, H<sub>9</sub>), 0.92 (3H, s, H<sub>8</sub>), 1.19 (3H, s, H<sub>10</sub>), 1.31 (1H, app dt, J = 10.5, 1.3 Hz, H<sub>12a</sub>), 1.73-1.76 (1H, m, H<sub>4</sub>), 1.79 (1H, app d, J = 10.5 Hz, H<sub>7b</sub>), 2.27-2.35 (2H, m H<sub>1</sub>, H<sub>5a</sub>), 2.49-2.56 (1H, m, H<sub>6</sub>), 3.62-3.71 (2H, m, H<sub>11a</sub>, H<sub>12a</sub>), 3.74-3.83 (2H, m, H<sub>11b</sub>, H<sub>12b</sub>), 4.52 (1H, d, J = 15.7 Hz, H<sub>13a</sub>), 4.54 (1H, d, J = 15.7 Hz, H<sub>13b</sub>), 7.28-7.39 (5H, m, H<sub>15</sub>, H<sub>16</sub>, H<sub>17</sub>).
Experimental

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ (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 $\nu_{\text{max}}$ (cm$^{-1}$): 2928, 1454, 1372, 1092, 1024, 1053, 870.

HRMS: (m/z - ESI) Calculated for C$_{19}$H$_{26}$O$_2$Na (M+Na)$^+$ 309.1831, found 309.1821.

6.4.9 (6,6,6a-Trimethylhexahydro-2H-3,5-methanocyclopenta[b]furan-7-yl)methanol. (112)

![Chemical structure]

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%).

$^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ (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): $\delta$ (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$_2$).
Experimental

IR $v_{\text{max}}$ (cm$^{-1}$): 3405, 2952, 2871, 1373, 1090, 1005.

HRMS: (m/z - ESI) Calculated for C$_{12}$H$_{21}$O$_2$ (M+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).

$^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ (ppm) 1.29 (1H, app d, $J = 8.6$ Hz, H$_7$a), 1.39 (1H, app d, $J = 8.6$ Hz, H$_7$b), 1.83-1.92 (2H, m, H$_5$, H$_6$), 2.57 (2H, br s, H$_1$, H$_4$), 3.80 (4H, m, 2H$_8$a, 2H$_8$b), 6.22 (2H, m, H$_2$, H$_3$).

$^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta$ (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 $v_{\text{max}}$ (cm$^{-1}$): 3281, 2957, 2871, 1455, 1016, 968.

HRMS: (m/z - ESI) Calculated for C$_9$H$_{13}$O$_2$ (M-H)$^-$ 153.0916 found 153.0914.
6.4.11 5,6-exo-Bis[(benzyloxy)methyl]bicyclo[2.2.1]hept-2-ene.\textsuperscript{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%).

\(\text{^1H NMR (CDCl}_3, 600 MHz): \delta \text{ (ppm)}\)

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\(_{13}\)).

\(\text{^13C NMR (CDCl}_3, 150 MHz): \delta \text{ (ppm)}\)

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 \(\nu_{\text{max}} \text{ (cm}^{-1})\): 2955, 2854, 1453, 1364, 1073, 947.

HRMS: \(\text{(m/z - ESI) Calculated for C}_{23}\text{H}_{26}\text{O}_2\text{Na (M+Na)}^+ 357.1831 \text{ found 357.1824.}\)
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), NaBH\textsubscript{4} (0.35 g, 8.98 mmol), BF\textsubscript{3}.Et\textsubscript{2}O (2.25 mL, 17.9 mmol), a solution of NaOH (4M, 2.25 mL, 8.98 mmol), H\textsubscript{2}O\textsubscript{2} (35% in H\textsubscript{2}O, 1.75 mL, 17.9 mmol) and anhydrous THF (80 mL). This was purified by column chromatography (3:2 hexane:ethyl acetate, R\textsubscript{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\%).

\begin{align*}
\text{1H NMR (CDCl}_3, 600 MHz): \delta & (ppm) \\
& 1.38-1.44 (2H, m, H\textsubscript{3a}, H\textsubscript{7a}), 1.46-1.51 (1H, m, H\textsubscript{7b}), 1.72-1.80 (1H, m, H\textsubscript{3b}), 1.80-1.88 (2H, m, H\textsubscript{5}, H\textsubscript{6}), 2.20 (1H, br s, H\textsubscript{1}), 2.29-2.32 (1H, m, H\textsubscript{4}), 3.29-3.36 (2H, m, H\textsubscript{8a}, H\textsubscript{14a}), 3.47-3.57 (2H, m, H\textsubscript{8b}, H\textsubscript{14b}), 3.89 (1H, app d, J = 6.9 Hz, H\textsubscript{2}), 4.46-4.49 (4H, m, H\textsubscript{9a}, H\textsubscript{9b}, H\textsubscript{15a}, H\textsubscript{15b}), 7.29-7.39 (10H, m, H\textsubscript{11}, H\textsubscript{12}, H\textsubscript{13}, H\textsubscript{17}, H\textsubscript{18}, H\textsubscript{19}). \\
\text{13C NMR (CDCl}_3, 150 MHz): \delta & (ppm) \\
& 29.8 (C\textsubscript{7}), 38.9 (C\textsubscript{4}), 40.3 (C\textsubscript{6}), 42.1 (C\textsubscript{3}), 44.1 (C\textsubscript{5}), 48.2 (C\textsubscript{1}), 69.9 (C\textsubscript{8}/C\textsubscript{14}), 70.4 (C\textsubscript{8}/C\textsubscript{14}), 73.1 (C\textsubscript{9}/C\textsubscript{15}), 73.2 (C\textsubscript{9}/C\textsubscript{15}), 74.7 (C\textsubscript{2}), 127.5 (C\textsubscript{13}/C\textsubscript{19}), 127.55 (C\textsubscript{13}/C\textsubscript{19}), 127.58 (C\textsubscript{11}/C\textsubscript{17}), 127.7 (C\textsubscript{11}/C\textsubscript{17}), 128.4 (C\textsubscript{12} \& C\textsubscript{18}), 138.4 (q, C\textsubscript{10}/C\textsubscript{16}), 138.5 (q, C\textsubscript{10}/C\textsubscript{16}). \\
\end{align*}

IR \nu\textsubscript{max} (cm\textsuperscript{-1}): 3380, 2858, 1453, 1366, 1069, 1027.

HRMS: (m/z - ESI) Calculated for C\textsubscript{25}H\textsubscript{28}O\textsubscript{3}Na (M+Na\textsuperscript{+}) 375.1936, found 375.1938.
Experimental

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$_2$Cl$_2$ (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%)

$^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ (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 (1OH, m, H$_{1}$, H$_{2}$, H$_{11}$, H$_{12}$, H$_{13}$, H$_{17}$, H$_{18}$, H$_{19}$).

$^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta$ (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 (C$_{11}$/C$_{17}$), 127.65 (C$_{11}$/C$_{17}$), 127.65 (C$_{13}$/C$_{19}$), 127.7 (C$_{13}$/C$_{19}$), 128.4 (C$_{12}$/C$_{18}$), 128.5 (C$_{12}$/C$_{18}$), 138.2 (q, C$_{10}$/C$_{16}$), 138.3 (q, C$_{10}$/C$_{16}$), 217.7 (q, C$_2$).

IR $\nu_{max}$ (cm$^{-1}$): 2922, 2859, 1743, 1453, 1366, 1089, 1027.
Experimental

HRMS: \((m/z - \text{ESI})\) Calculated for \(\text{C}_{23}\text{H}_{26}\text{O}_{3}\text{Na} \ (\text{M}+\text{Na})^+ \ 373.1780\), 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 \(\text{117} \) (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 \(\text{118} \) as a pale yellow oil (1.60 g, 4.39 mmol, 55%).

\(^1\text{H} \text{NMR (CDCl}_3, 600 \text{ MHz}): \delta \text{ (ppm)}\)

1.10 (3H, d, \(J = 7.7 \text{ Hz}, \text{H}_8\)), 1.73 (1H, app d, \(J = 11.2 \text{ Hz}, \text{H}_7\)), 1.84 (1H, app d, \(J = 11.2 \text{ Hz}, \text{H}_7\)), 1.92-1.98 (1H, m, \text{H}_3), 2.19-2.26 (1H, m, \text{H}_3), 2.26-2.32 (1H, m, \text{H}_6), 2.39 (1H, br s, \text{H}_4), 2.55 (H, br s, \text{H}_1), 3.45-3.50 (2H, m, \text{H}_9),\text{H}_5), 3.59 (1H, dd, \(J = 9.4, 6.3 \text{ Hz}, \text{H}_{15}\)), 3.66 (1H, dd, \(J = 9.4, 5.6 \text{ Hz}, \text{H}_{9\text{b}}\)), 4.43-4.54 (4H, m, \text{H}_{10}, \text{H}_{16}), 7.29-7.40 (10H, m, \text{H}_{12}, \text{H}_{13}, \text{H}_{14}, \text{H}_{18}, \text{H}_{19}, \text{H}_{20})

\(^{13}\text{C} \text{NMR (CDCl}_3, 150 \text{ MHz}): \delta \text{ (ppm)}\)

14.0 (\text{C}_8), 29.9 (\text{C}_7), 38.7 (\text{C}_6), 44.5 (\text{C}_5), 44.9 (\text{C}_4), 48.5 (\text{C}_3), 53.2 (\text{C}_1), 69.1 (\text{C}_{15}), 69.9 (\text{C}_9), 72.9 (\text{C}_{16}), 73.2 (\text{C}_{10}), 127.43 (\text{C}_{14}/\text{C}_{20}), 127.44 (\text{C}_{12}/\text{C}_{18}), 127.51 (\text{C}_{14}/\text{C}_{20}), 127.52 (\text{C}_{12}/\text{C}_{18}), 215
Experimental

128.2 (C/13\textsubscript{19}), 128.3 (C/13\textsubscript{19}), 138.2 (q, C\textsubscript{11}/C\textsubscript{17}), 138.3 (q, C\textsubscript{11}/C\textsubscript{17}), 204.5 (q, C\textsubscript{2}).

IR $\nu_{\text{max}}$ (cm$^{-1}$): 2960, 2859, 1743, 1453, 1366, 1088, 1027.

HRMS: (m/z - ESI) Calculated for C\textsubscript{24}H\textsubscript{28}O\textsubscript{3}Na (M\textsuperscript{+}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%).

$^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ (ppm)

1.07 (3H, s, H$_9$), 1.10 (3H, s, H$_8$), 1.84 (2H, m, H$_{7a}$, H$_{7b}$), 2.19-2.29 (2H, m, H$_4$, H$_6$), 2.52-2.60 (2H, m, H$_1$, H$_3$), 3.44-3.51 (2H, m, H$_{10a}$, H$_{10b}$), 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, H$_{13}$, H$_{14}$, H$_{15}$, H$_{19}$, H$_{20}$, H$_{21}$).

$^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta$ (ppm)

21.4 (C$_9$), 23.6 (C$_8$), 30.5 (C$_7$), 38.7 (C$_3$), 39.7 (C$_6$), 47.3 (q, C$_3$), 49.8 (C$_4$), 54.0 (C$_1$), 69.4 (C$_{16}$), 70.6 (C$_{10}$), 73.0 (C$_{17}$), 73.2 (C$_{11}$), 127.59 216
**Experimental**

(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 ν<sub>max</sub> (cm<sup>-1</sup>): 2967, 2863, 1740, 1453, 1366, 1089, 1071, 1027.

HRMS: (m/z - ESI) Calculated for C<sub>25</sub>H<sub>30</sub>O<sub>3</sub>Na (M+Na)<sup>+</sup> 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<sub>f</sub> = 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%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 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, H₇α), 1.52-1.58 (1H, m, H₇β), 1.75 (1H, br s, H₄), 1.94 (1H, br s, H₁), 2.51 (1H, m, H₃), 2.77 (1H, m, H₆), 3.30-3.37 (2H, m, H₁₁α, H₁₁α), 3.52-3.58 (2H, m, H₁₁β, H₁₁β), 4.43-4.51 (4H, m, H₁₂α, H₁₂β, H₁₈α, H₁₈β), 7.28-7.39 (10H, m, H₁₄, H₁₅, H₁₆, H₂₀, H₂₁, H₂₂).
13C NMR (CDCl3, 100 MHz): \( \delta \) (ppm) 21.4 (C9), 26.6 (C10), 27.1 (C8), 30.0 (C7), 35.8 (C6), 38.5 (C5), 42.5 (q, C3), 53.3 (C4), 54.7 (C1), 70.7 (C11/C17), 71.0 (C11/C17), 72.9 (C12/C18), 73.0 (C12/C18), 78.2 (q, C2), 127.5 (C16 & C22), 127.6 (C14/C20), 127.7 (C14/C20), 128.3 (C15 & C21).

IR \( \nu_{\text{max}} \) (cm\(^{-1}\)): 3448, 2955, 1453, 1366, 1085, 1071, 1027.

HRMS: \( \text{Calc. for C}_{26}\text{H}_{33}\text{O}_{3} \text{(M-H)}^{-} 393.2430 \), 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-\textit{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\(_2\)SO\(_4\) (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\%).

\(^1\)H NMR (CDCl\(_3\), 600 MHz): \( \delta \) (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, \( J = 7.8 \text{ Hz} \), H\(_3\)).
$^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta$ (ppm) 12.1 (C$_{12}$), 20.8 (C$_8$/C$_6$), 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 $\nu_{\text{max}}$ (cm$^{-1}$): 3391, 2930, 2871, 1260, 1015, 801.

HRMS: (m/z - ESI) Calculated for C$_{12}$H$_{21}$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 $^\circ$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%).

$^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ (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): $\delta$ (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$_6$).
Experimental

IR ν_max (cm⁻¹): 3067, 2981, 2934, 1454, 1303, 1006, 829.

HRMS: (m/z - El) Calculated for C_{11}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), NaBH₄ (0.89 g, 22.8 mmol), BF₃·Et₂O (4.30 mL, 34.2 mmol), a solution of NaOH (4M, 5.70 mL, 22.8 mmol), H₂O₂ (35% in H₂O, 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. 71-74 °C).

^1H NMR (CDCl₃, 600 MHz): δ (ppm) 1.61-1.67 (1H, m, H₃a), 1.84 (1H, ddd, J = 12.7, 6.5, 2.7 Hz, H₃b), 1.91-1.95 (1H, m, H₂a), 2.12 (1H, app d, J = 9.2 Hz, H₇b), 3.27 (1H, s, H₁), 3.33-3.36 (1H, m, H₄), 4.01 (1H, app d, J = 6.7 Hz, H₂), 7.06-7.10 (2H, m, H₉, H₁₀), 7.14-7.17 (1H, m, H₈), 7.21-7.23 (1H, m, H₁₁).

^13C NMR (CDCl₃, 150 MHz): δ (ppm) 39.9 (C₃), 43.0 (C₄), 46.0 (C₇), 52.4 (C₁), 73.7 (C₂), 120.7 (C₆), 122.0 (C₁₁), 125.5 (C₁₀), 126.1 (C₀), 144.5 (q, C₆), 149.5 (q, C₅).

IR ν_max (cm⁻¹): 3338, 2968, 1469, 1043, 971.

HRMS: (m/z - El) Calculated for C_{11}H_{12}O (M)^+ 160.0888, found 160.0881.
Experimental

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 CH2Cl2 (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.\(^{322}\)

\(^1\)H NMR (CDCl\(_3\), 600 MHz): \( \delta \) (ppm)

- 1.99 (1H, dd, \( J = 17.0, 4.4 \) Hz, \( H_{3a} \)), 2.27-2.36 (2H, m, \( H_{3b} \), \( H_{7a} \)),
- 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): \( \delta \) (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 \( \nu_{max} \)(cm\(^{-1}\)): 2972, 1744, 1459, 1123, 979.

HRMS: \( (m/z - ESI) \) Calculated for C\(_{11}\)H\(_9\)O (M-H\(^-\)) 157.0653, found 157.0648.

6.4.21 3-Methyl-3,4-dihydro-1,4-methanonaphthalen-2(1H)-one. (129)
Experimental

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).

$^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ (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): $\delta$ (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 $\nu_{max}$ (cm$^{-1}$): 2967, 1743, 1459, 1123, 971.

HRMS: $^{(m/z - EI)}$ Calculated for C$_{12}$H$_{12}$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).

222
**1H NMR (CDCl$_3$, 600 MHz): $\delta$ (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, H$_{11}$, H$_{12}$), 7.25-7.29 (2H, m, H$_{10}$, H$_{13}$).

**13C NMR (CDCl$_3$, 150 MHz): $\delta$ (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 $v_{\text{max}}$ (cm$^{-1}$):** 2975, 1731, 1459, 1125, 984.

**HRMS: (m/z - El)** Calculated for C$_{13}$H$_{14}$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)

[Diagram of the molecule]

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): $\delta$ (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,
Experimental

H_4, 3.09 (1H, br s, H_1), 7.06-7.31 (4H, m, H_{11}, H_{12}, H_{13}, H_{14}).

^{13}C NMR (CDCl_3, 150 MHz): δ (ppm) 24.0 (C_9), 25.0 (C_{10}), 27.4 (C_8), 43.8 (q, C_3), 45.2 (C_7), 56.8 (C_4), 58.5 (C_1), 78.9 (q, C_2), 123.3 (C_{11}), 123.8 (C_{14}), 125.8 (C_{13}), 126.3 (C_{12}), 143.1 (q, C_6), 147.9 (q, C_5).

IR ν max (cm⁻¹): 3473, 2960, 1473, 1089, 936.

HRMS: (m/z - EI) Calculated for C_{14}H_{18}O (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 CH_2Cl_2 (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 (CDCl_3, 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, H_1, H_4), 6.78-6.83 (1H, m, H_3), 6.84-6.89 (1H, m, H_2), 7.34 (1H, d, J = 7.8 Hz, H_{11}), 7.93 (1H, dd, J = 7.8, 1.8 Hz, H_{10}), 8.04 (1H, app s, H_8).
Experimental

\(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) (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 \(v_{\text{max}}\) (cm\(^{-1}\)): 2993, 2939, 1510, 1339, 1301, 832.

HRMS: \((m/z - \text{El})\) Calculated for C\(_{11}\)H\(_9\)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-methanonaphtalene 138 (1.50 g, 8.01 mmol), NaBH\(_4\) (0.24 g, 6.01 mmol), BF\(_3\).Et\(_2\)O (1.50 mL, 12.1 mmol), a solution of NaOH (4M, 1.50 mL, 6.01 mmol), H\(_2\)O\(_2\) (35% in H\(_2\)O, 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%).

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) (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).
Experimental

$^{13}$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$_1$

IR $\nu_{\text{max}}$ (cm$^{-1}$): 3376, 2981, 1513, 1338, 1068, 1043, 971.

HRMS: (m/z - ESI) Calculated for C$_{11}$H$_{10}$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,
Experimental

$R_f = 0.45$ to yield 6- and 7-nitro-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-yl acetate $\textbf{141}$ and $\textbf{142}$ as a yellow oil (2.23g, 9.02 mmol, 53%).

$^1\text{H NMR (CDCl}_3, 600 \text{ MHz): } \delta \text{ (ppm)}$

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), 2.07-2.17 (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, $H_{14}$ 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).

$^{13}\text{C NMR (CDCl}_3, 150 \text{ MHz): } \delta \text{ (ppm)}$

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).
Experimental

IR $\nu_{\text{max}}$ (cm$^{-1}$): 2989, 1736, 1516, 1340, 1228, 1026, 821.

HRMS: (m/z - EI) Calculated for C$_{13}$H$_{13}$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)

![Chemical Structure](image)

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$_2$SO$_4$ (15 mL), was slowly added a mixture of fuming nitric acid (0.04 mL) in H$_2$SO$_4$ (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).

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (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): $\delta$ (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 $\nu_{\text{max}}$ (cm$^{-1}$): 3098, 1721, 1528, 1340, 1037, 972.

HRMS: (m/z - EI) Calculated for C$_{11}$H$_9$N$_2$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, Rf = 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. 142-143 °C).

$^{1}$H NMR (CDCl$_3$, 600 MHz): $\delta$ (ppm) 1.80-1.88 (2H, m, H$_{10}$), 2.08 (1H, m, H$_{7a}$), 2.32 (1H, app dt, J = 9.7, 1.6 Hz, H$_{7b}$), 3.47 (1H, br s, H$_{1}$), 3.54-3.57 (1H, m, H$_{4}$), 4.06-4.09 (1H, m, H$_{2}$), 7.66 (1H, s, H$_{8}$), 7.74 (1H, s, H$_{6}$).

$^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta$ (ppm) 38.4 (C$_{3}$), 43.1 (C$_{4}$), 46.9 (C$_{7}$), 52.3 (C$_{1}$), 72.0 (C$_{2}$), 117.4 (C$_{8}$), 118.8 (C$_{11}$), 141.4 (q, C$_{10}$), 141.9 (q, C$_{9}$), 150.7 (q, C$_{6}$), 156.1 (q, C$_{5}$).

IR $\nu_{\text{max}}$ (cm$^{-1}$): 3270, 2960, 1526, 1370, 1053, 966.

HRMS:  (m/z - ESI) Calculated for C$_{11}$H$_{8}$N$_{2}$O$_{5}$ (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 CH₂Cl₂ (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. 163-164 °C).

¹H NMR (CDCl₃, 600 MHz): δ (ppm) 2.07 (1H, dd, J = 17.6, 4.5 Hz, H₃α), 2.47 (1H, app dt, J = 10.3, 1.3 Hz, H₇α), 2.53 (1H, dd, J = 17.6, 4.5 Hz, H₃b), 2.66-2.72 (1H, m, H₇b), 3.83 (1H, br s, H₄), 3.93-3.96 (1H, m, H₅), 7.84 (2H, br s, H₆, H₇).

¹³C NMR (CDCl₃, 150 MHz): δ (ppm) 38.3 (C₃), 42.1 (C₁), 51.4 (C₄), 58.2 (C₇), 118.5 (C₁₁), 120.0 (C₈), 142.2 (q, C₁₀), 142.6 (q, C₉), 146.4 (q, C₅), 154.4 (q, C₆), 208.4 (q, C₂).

IR νmax (cm⁻¹): 3099, 1758, 1532, 1367, 1337, 1126, 986.

HRMS: (m/z - El) Calculated for C₁₁H₈N₂O₅ (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**

$^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ (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): $\delta$ (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**

$^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ (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$_{11}$), 8.08 (1H, s, H$_{14}$), 8.09-8.13 (1H, m, H$_{12}$).

$^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta$ (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$_{12}$), 123.1 (C$_{14}$), 147.0 (q, C$_6$), 148.0 (q, C$_5$), 150.0 (q, C$_6$).

IR $\nu_{\text{max}}$ (cm$^{-1}$): 2977, 1617, 1519, 1341, 1291, 850.

HRMS: (m/z - ESI) Calculated for C$_{14}$H$_{17}$N$_2$O$_5$ (M+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%).

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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 °C was added a solution of NaNO2 (27 mg, 0.4 mmol) in H2O (300 µL). The reaction mixture was stirred for 15 min at -5 °C, hypophosphinic acid (0.5 mL) precooled to -5 °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%).

\[\text{1H NMR (CDCl}_3, 600 \text{ MHz): } \delta (\text{ppm}) \quad 0.54 (3H, s, H_9), 1.01 (3H, s, H_8), 1.33 (3H, s, H_{10}), 1.83 (1H, app d, J = 9.6 Hz, H_{7a}), 2.73 (1H, app d, J = Hz, 9.6 Hz, H_{7b}), 2.78-2.80 (1H, m, H_4), 3.13-3.16 (1H, m, H_1), 7.10-7.13 (2H, m, H_2, H_3), 7.14-7.17 (1H, m, H_{11}/H_{14}) 7.19-7.22 (1H, m, H_{11}/H_{14}).\]

\[\text{13C NMR (CDCl}_3, 150 \text{ MHz): } \delta (\text{ppm}) \quad 19.7 (C_8), 25.5 (C_9), 26.8 (C_{10}), 44.9 (q, C_3), 45.6 (C_7), 56.1 (C_1), 56.9 (C_4), 71.6 (q, C_2), 122.6 (C_{11}/C_{14}), 123.0 (C_{11}/C_{14}), 125.5 (C_{12}/C_{13}), 125.8 (C_{12}/C_{13}), 143.6 (q, C_6), 147.6 (q, C_5).\]

IR $\nu_{\text{max}}$ (cm$^{-1}$): 2960, 2926, 2090, 1463, 1260, 1077, 799.

Due to the unstable nature of the compound mass spectral data was not obtained.
Experimental

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 CH$_2$Cl$_2$, 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%).

$^1$H NMR (CDCl$_3$, 600 MHz): δ (ppm)

- 1.21 (3H, s, H$_9$)
- 1.76 (3H, s, H$_8$)
- 2.50-2.54 (1H, m, H$_{7a}$)
- 2.55-2.59 (1H, m, H$_{7b}$)
- 3.21 (1H, br s, H$_4$)
- 3.50 (3H, m, H$_{10}$)
- 4.29 (1H, br s, H$_1$)
- 7.25 (1H, app t, J = 7.6 Hz, H$_{13}$)
- 7.28-7.33 (2H, m, H$_{12}$, H$_{14}$)
- 7.38 (1H, d, J = 7.6 Hz, H$_{11}$).

$^{13}$C NMR (CDCl$_3$, 150 MHz): δ (ppm)

- 25.4 (C$_8$)
- 26.3 (C$_9$)
- 35.2 (C$_{10}$)
- 48.88 (C$_7$)
- 48.89 (q, C$_3$)
- 50.2 (C$_1$)
- 53.7 (C$_4$)
- 123.3 (C$_{14}$)
- 124.4 (C$_{11}$)
- 127.9 (C$_{13}$)
- 128.9 (C$_{12}$)
- 135.4 (q, C$_6$)
- 147.4 (q, C$_5$)
- 200.5 (q, C$_2$).

IR $\upsilon_{\max}$ (cm$^{-1}$): 2989, 2516, 1711, 1468, 1057, 988.

HRMS: (m/z - ESI) calculated for C$_{14}$H$_{18}$N (M+H) 200.1439, found 200.1449.
6.4.35 6-exo-Methylhexahydro-1H-4,7-methanoind en-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-methanoind en-5(6H)-one 159 as a pale yellow oil (2.07 g, 12.1 mmol, 86%). The spectroscopic analysis is consistent with the 13C NMR data reported in the literature.303

1H NMR (CDCl3, 400 MHz): δ (ppm) 1.03-1.15 (5H, H_g, H_9a, H_ua), 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).

13C NMR (CDCl3, 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_3), 47.8 (C_5), 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 C_{11}H_{16}O (M)^+ 164.1201, found 164.1202.

6.4.36 6,6-Dimethylhexahydro-1H-4,7-methanoid en-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, Rf = 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.$^{303}$

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (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): $\delta$ (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 $\nu_{\text{max}}$ cm$^{-1}$: 2949, 2865, 1741, 1471, 1151, 954.

HRMS: (m/z - El) Calculated for C$_{12}$H$_{18}$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-dimethyloctahydro-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-methanoindene-5-ol \(161\) as a clear colourless oil (1.26 g, 6.51 mmol, 76%).

\[\text{\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 600 MHz): } \delta \text{ (ppm)} \]

0.86-0.98 (5H, m, H\textsubscript{9}, H\textsubscript{11a}, H\textsubscript{13a}), 1.01 (3H, s, H\textsubscript{8}), 1.19-1.34 (5H, m, H\textsubscript{7a}, H\textsubscript{10}, H\textsubscript{12a}), 1.43 (1H, app dt, \(J = 1.6, 11.1\) Hz, H\textsubscript{7b}), 1.54 (1H, br s, H\textsubscript{4}), 1.62-1.69 (1H, m, H\textsubscript{12b}), 1.75 (1H, br s, H\textsubscript{1}), 1.81-1.93 (2H, m H\textsubscript{11b}, H\textsubscript{13b}), 2.34 (1H, app quartet, \(J = 8.7\) Hz, H\textsubscript{5}), 2.49 (1H, app quartet, \(J = 8.7\) Hz, H\textsubscript{6}).

\[\text{\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 150 MHz): } \delta \text{ (ppm)} \]

21.2 (C\textsubscript{9}), 26.3 (C\textsubscript{10}), 27.0 (C\textsubscript{12}), 27.1 (C\textsubscript{8}), 28.0 (C\textsubscript{7}), 32.2 (C\textsubscript{13}), 32.5 (C\textsubscript{11}), 38.3 (C\textsubscript{6}), 40.9 (C\textsubscript{5}), 42.1 (q, C\textsubscript{3}), 54.0 (C\textsubscript{4}), 55.7 (C\textsubscript{1}), 78.3 (q, C\textsubscript{2}).

IR \(v_{\text{max}} \text{ cm}^{-1} \): 3451, 2926, 2862, 1485, 1372, 1128, 1074.

HRMS: \((m/z \text{- El})\) Calculated for C\textsubscript{13}H\textsubscript{22}O (M\textsuperscript{+}) 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-methanoindene-5-ol \(161\) (1.30 g, 6.69 mmol), 55% H\textsubscript{2}SO\textsubscript{4} (8 mL), NaN\textsubscript{3} (3.00 g, 46.2 mmol) and CHCl\textsubscript{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%).
Experimental

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (ppm) 0.86-1.05 (5H, m, H$_9$, H$_{11a}$, H$_{13a}$), 1.08 (3H, s, H$_8$), 1.17-1.31 (2H, m, H$_{7a}$, H$_{12a}$), 1.33 (3H, s, H$_{10}$), 1.54-1.57 (1H, m, H$_4$), 1.68-1.96 (5H, m, H$_1$, H$_{7b}$, H$_{11b}$, H$_{12b}$, H$_{13b}$), 2.07 (1H, app quartet, $J = 8.6$ Hz, H$_6$), 2.24 (1H, app quartet, $J = 8.6$ Hz, H$_3$).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ (ppm) 17.7 (C$_{10}$), 23.1 (C$_9$), 27.1 (C$_8$), 27.4 (C$_{12}$), 28.3 (C$_7$), 32.4 (C$_{11}$), 32.6 (C$_{13}$), 40.8 (C$_6$), 41.2 (C$_5$), 44.1 (q, C$_3$), 53.6 (C$_1$), 52.4 (C$_4$), 72.5 (q, C$_2$).

IR $\nu_{max}$ cm$^{-1}$: 2948, 2865, 2084, 1460, 1252, 1081.

HRMS: (m/z - ESI) Calculated for C$_{13}$H$_{22}$N (M-N$_2$+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%).

$^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ (ppm) 0.91-0.99 (5H, m, H$_9$, H$_{11a}$, H$_{13a}$), 1.03 (3H, m, H$_8$), 1.10 (3H, s, H$_{10}$), 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, H$_4$), 1.55-1.59 (1H, m, H$_1$), 1.65-1.73 (2H, m, H$_{7b}$, H$_{12b}$), 1.79-1.91 (2H, m, H$_{11b}$).
**Experimental**

\[
^1H \text{ NMR} (\text{CDCl}_3, 600 \text{ MHz}): \delta (\text{ppm}) \\
0.91-1.03 (2H, m, H_{12a}, H_{14a}), 1.04 (3H, s, H_9), \\
1.19-1.28 (1H, m, H_{13a}), 1.32 (3H, s, H_8), 1.43 \\
(1H, \text{ app d, } J = 12.1 \text{ Hz, } H_7a), 1.50 (3H, s, H_{10}), \\
1.62 (1H, \text{ br s, } H_4), 1.69-1.76 (1H, \text{ app quintet, } J \\
= 6.2 \text{ Hz, } H_{13b}), 1.81-1.95 (2H, m, H_{12b}, H_{14b}), \\
2.07 (1H, \text{ app quartet, } J = 8.4 \text{ Hz, } H_6), 2.11 (1H, \\
br \text{ s, } H_1), 2.16 (1H, \text{ app d, } J = 12.1 \text{ Hz, } H_7b), \\
2.26 (1H, \text{ app quartet, } J = 8.6 \text{ Hz, } H_5). \\
\]

\[
^{13}C \text{ NMR} (\text{CDCl}_3, 150 \text{ MHz}): \delta (\text{ppm}) \\
23.1 (C_9), 23.1 (C_{10}), 26.4 (C_8), 27.3 (C_{12}), 27.7 \\
(C_7), 32.5 (C_1), 32.6 (C_{13}), 40.7 (C_5), 41.4 (C_6), \\
42.3 (q, C_3), 54.6 (C_4), 57.5 (C_1), 58.4 (q, C_2). \\
\]

IR \nu_{\text{max}} \text{ cm}^{-1}: 3346, 2945, 2863, 1480, 1388, 1021, 895.

HRMS: \( (m/z \text{- El}) \) Calculated for C_{13}H_{23}N (M)^+ 193.1830, found 193.1835.

6.4.40 \( N\text{-}5\text{-endo-6,6-Tetramethyloctahydro-1H-4,7-methanoinden-5-amine} \) (157)

Prepared as per general procedure G using \( 5\text{-endo-6,6-trimethyloctahydro-1H-4,7-methanoinden-5-amine} \) 163 (280 mg, 1.45 mmol), paraformaldehyde (152 mg, 5.08 mmol) and activated 4 Å molecular sieves (400 mg), CH_2Cl_2 (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 \( N\text{-}5\text{-endo-6,6-tetramethyloctahydro-1H-4,7-methanoinden-5-amine} \) 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).
Experimental

2.24 (1H, app quartet, $J = 8.4$ Hz, $H_3$), 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): $\delta$ (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 $v_{\text{max}}$ cm$^{-1}$: 2945, 2749, 1389, 1102.

HRMS: ($m/z$ - EI) Calculated for C$_{14}$H$_{25}$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:**

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (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): $\delta$ (ppm)

42.6 (C$_4$), 46.9 (C$_3$), 48.5 (C$_7$), 56.2 (C$_1$), 56.8 (q, C$_2$).
Experimental

**Endo diastereomer:**

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (ppm)

- 1.92–1.96 (2H, m, H$_7$), 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, H$_4$), 3.36 (1H, br s, H$_1$), 6.23 (1H, dd, $J$ = 5.8, 3.0 Hz, H$_5$), 6.48 (1H, dd, $J$ = 5.7, 3.0 Hz, H$_6$).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ (ppm)

- 42.9 (C$_4$), 45.7 (C$_3$), 48.5 (C$_7$), 55.4 (C$_1$), 56.6 (q, C$_2$), 131.9 (C$_6$), 139.4 (C$_5$), 120.4 (q, C$_8$).

IR $\nu_{\text{max}}$ (cm$^{-1}$): 2990, 2946, 2869, 2235, 1712, 1336, 1269, 766, 725.

HRMS: ($m/z$ - CI) Calculated for C$_8$H$_9$NCI (M+H)$^+$ 154.0424, found 154.0428.

**6.4.42 Bicyclo[2.2.1]hept-5-en-2-one. (168)**

![Bicyclo[2.2.1]hept-5-en-2-one](image)

$\alpha$-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. H$_2$O (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.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (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, H$_1$), 3.21 (1H, m, H$_4$), 6.12 (1H, dd,
Experimental

\[ J = 5.5, 3.9 \text{ Hz, H}_6, 6.58 \text{ (1H, dd, } J = 5.5, 2.8 \text{ Hz, H}_5). \]

\[ ^{13}\text{C NMR (CDCl}_3, 100 \text{ MHz): } \delta \text{ (ppm)} \]

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 \nu_{\text{max}} \text{ (cm}^{-1})$: 2973, 1737, 1322, 1122, 734, 706.

HRMS: \( (m/z \text{- Cl}) \) Calculated for C_9H_{13}O (M+C_2H_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 phenylselanyl 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. 72-74 °C (Lit.\(^{304} \) 75-77 °C). \( R_f \) (9:1 hexane: ethyl acetate) = 0.31.

\(^1\text{H NMR (CDCl}_3, 400 \text{ MHz): } \delta \text{ (ppm)} \]

1.86-1.92 (1H, m, H_2a), 2.09 (1H, dd, \( J = 18.6, \) 4.4 Hz, H_3a), 2.21-2.27 (1H, m, H_7b), 2.33 (1H, dd, \( J = 18.6, 4.4 \) 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).
Experimental

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ (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 (C$_4$), 128.49 (q, C$_1'$), 129.6, (C$_2'$), 134.7, (C$_3'$), 210.1 (q, C$_2$).

IR $\nu_{\text{max}}$ (cm$^{-1}$): 2975, 1750, 1576, 1477, 1437, 1289, 1133, 1086.

HRMS: (m/z - El) Calculated for C$_{13}$H$_{13}$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 °C, a solution of sodium bis(trimethylsilyl)amide (1.9M in THF, 10.8 mL, 20.5 mmol) pre-cooled to -78 °C was added. After stirring for 2 hrs at -78 °C, the reaction was warmed to -30 °C. Iodomethane (2.50 mL, 40.2 mmol) was added and the reaction was stirred for a further 1 hr at -30 °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. 73-76 °C.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (ppm) 1.15 (3H, d, $J = 7.5$ Hz, H$_3$), 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$_3'$).
Experimental

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ (ppm) 14.2 (C$_8$), 32.7 (C$_7$), 47.7 (C$_5$), 48.4 (C$_4$), 48.6 (C$_6$), 52.9 (C$_3$), 57.3 (C$_1$), 127.8 (C$_4'$), 128.1 (q, C$_{1'}$), 129.0, (C$_2'$), 134.2, (C$_3'$), 212.9 (q, C$_2$).

IR $\nu_{\text{max}}$ (cm$^{-1}$): 2971, 1743, 1577, 1476, 1437, 1254, 1153, 1086.

HRMS: (m/z - El) Calculated for C$_{14}$H$_{15}$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.

$^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ (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$_3$), 4.36-4.39 (1H, m, H$_6$), 7.32-7.39 (3H, m, H$_2$, H$_4'$), 7.60-7.66 (2H, m, H$_3'$).

$^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta$ (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 (C$_4'$), 128.8 (q, C$_{1'}$), 129.3 (C$_2'$), 134.0 (C$_3'$), 215.1 (q,

244
Experimental

IR $v_{\text{max}}$ (cm$^{-1}$): 2972, 1748, 1577, 1464, 1275, 1195, 956.

HRMS: ($m/z$ - EI) Calculated for C$_{15}$H$_{17}$OSeBr (M)$^+$ 371.9628, found 371.9619.

6.4.46 6-Bromo-3,3-dimethylbicyclo[2.2.1]hept-5-en-2-one. (172)

![6-Bromo-3,3-dimethylbicyclo[2.2.1]hept-5-en-2-one](image)

**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 H$_2$O, 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 Na$_2$CO$_3$ (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.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (ppm)

1.11 (3H, s, H$_8$), 1.18 (3H, s, H$_9$), 2.22-2.28 (1H, m, H$_{7a}$), 2.37-2.42 (1H, m, H$_{7b}$), 2.83-2.86 (1H, m, H$_4$), 3.05-3.08 (1H, m, H$_1$), 6.64 (1H, d, $J = 3.2$ Hz, H$_5$).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ (ppm)

23.9 (C$_8$), 26.4 (C$_9$), 42.2 (q, C$_3$), 47.2 (C$_7$), 51.4 (C$_4$), 62.9 (C$_1$), 120.4 (q, C$_6$), 141.3 (C$_5$), 216.2 (q, C$_2$).
Experimental

IR \( \nu_{\text{max}} \) (cm\(^{-1})\): 2969, 2870, 1743, 1574, 1283, 972, 825.

HRMS: \((m/z - \text{EI})\) Calculated for \(\text{C}_9\text{H}_{11}\text{OBr} \ (\text{M})^+\) 213.9993, found 213.9982.

6.4.47 6-Bromo-2-exo-3,3-trimethylbicyclo[2.2.1]hept-5-en-2-ol. (173)

![Diagram of molecule]

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.

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta \) (ppm)

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\(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta \) (ppm)

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IR \( \nu_{\text{max}} \) (cm\(^{-1})\): 3477, 2963, 1581, 1475, 1291, 1210, 1156, 1088, 1006, 935.

HRMS: \((m/z - \text{Cl})\) Calculated for \(\text{C}_{10}\text{H}_{16}\text{OBr} \ (\text{M+H})^+\) 231.0385, found 231.0379.

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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% H$_2$SO$_4$ (25 mL), sodium azide (2.86 g, 43.9 mmol) and CHCl$_3$ (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%).

$^1$H NMR (CDCl$_3$, 400 MHz): δ (ppm) 0.93 (3H, s, H$_9$), 1.21 (3H, s, H$_8$), 1.42 (3H, s, H$_{10}$), 1.75-1.80 (1H, m, H$_{7a}$), 1.98-2.03 (1H, m, H$_{7b}$), 2.39-2.43 (1H, m, H$_4$), 2.75 (1H, br s, H$_1$), 6.39 (1H, d, J = 3.3 Hz, H$_3$).

$^{13}$C NMR (CDCl$_3$, 100 MHz): δ (ppm) 19.7 (C$_{10}$), 26.0 (C$_9$), 26.9 (C$_8$), 45.6 (q, C$_3$), 45.8 (C$_7$), 56.3 (C$_4$), 61.9 (C$_1$), 77.2 (q, C$_2$), 123.7 (q, C$_6$), 139.2, (C$_5$).

IR $\nu_{\text{max}}$ (cm$^{-1}$): 2964, 2084, 1580, 1474, 1372, 1291, 1156, 812.

HRMS: $m/z$ - El) Calculated for C$_{10}$H$_{14}$N$_3$Br (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 µL, 3.05 mmol). The reaction was stirred for 4 hrs at room temperature upon which time H₂O (280 µL, 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, H₇a), 2.38-2.45 (1H, m, H₇b), 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, H₁₂a), 9.40-9.48 (1H, br s, H₁₂b).

¹³C NMR (CDCl₃, 100 MHz): δ (ppm) 18.0 (C₁₀), 26.3 (C₈), 26.3 (C₉), 29.3 (C₁₁), 45.5
Experimental

(C7), 45.8 (q, C3), 56.9 (C4), 58.1 (C1), 70.1 (q, C2), 123.1 (q, C6), 139.2 (C5).

IR νmax (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

To a solution of bicyclo[2.2.1]hept-5-en-2-one (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, Rf (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, H₃a) 1.56-1.62 (1H, m, H₇a), 1.71-1.76 (1H, m, H₇b), 1.85 (1H, dd, J = 11.8, 3.3 Hz, H₃b), 2.82 (1H, m, H₁), 2.91 (1H, br s, H₄), 3.19 (3H, s, H₅), 3.26 (3H, s, H₆), 6.07 (1H, dd, J = 5.8, 2.9 Hz, H₇), 6.28 (1H, dd, J = 5.8, 2.9 Hz, H₇)

¹³C NMR (CD₃OD, 100 MHz): δ (ppm) 39.4 (C₅), 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 νmax (cm⁻¹): 2970, 1379, 1162, 1127, 1049, 951.

HRMS: (m/z - EI) Calculated for C₅H₁₄O₂ (M)^+ 154.0994, found 154.0994.
To a solution of phenylselenyl bromide (0.80 g, 3.39 mmol) in anhydrous CH$_2$Cl$_2$ (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$_2$Cl$_2$ (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$_2$O (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. 65-68 °C (Lit. 61-62 °C).

$^1$H 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$_3$), 7.31-7.38 (3H, m, H$_2$, H$_4$O, 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$_4$), 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 $v_{max}$ (cm$^{-1}$): 2975, 1742, 1578, 1479, 1435, 1287, 1255, 1150, 1022, 930.

HRMS: (m/z - EI) Calculated for C$_{13}$H$_{13}$OSeBr (M)$^+$ 343.9315, found 343.9317.
Experimental

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, Rf = 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.

\[ 3\text{-exo-5\text{-endo-Br}} - 6\text{-exo-(phenylselanyl)bicyclo[2.2.1]heptan-2-one} \]

$^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ (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, H$_{2}$, H$_{4}$), 7.59-7.63 (2H, m, H$_{3}$).

$^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta$ (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, C$_1'$), 128.4 (C$_4'$), 129.3 (C$_2'$), 134.7 (C$_3'$), 214.8 (q, C$_2$).

IR $\nu_{\text{max}}$ (cm$^{-1}$): 2976, 1743, 1476, 1254, 1154, 906.

HRMS: (m/z - EI) Calculated for C$_{14}$H$_{15}$OSeBr (M)$^+$ 357.9471, found 357.9461.
Experimental

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, H₃), 2.06 (1H, dq, J = 7.5, 3.3 Hz, H₃), 2.10-2.16 (1H, m, H₄a), 2.26-2.32 (1H, m, H₄b), 2.82 (1H, br s, H₄), 3.00-3.04 (1H, m, H₈), 6.10-6.13 (1H, m, H₅).

^13C NMR (CDCl₃, 100 MHz): δ (ppm)
15.3 (C₅), 39.2 (C₃), 45.9 (C₇), 54.2 (C₄), 56.9 (C₁), 129.5 (C₆), 134.5 (q, C₇), 214.8 (q, C₂).

IR ν_max (cm⁻¹): 2977, 2937, 1743, 1572, 1038, 942.
HRMS: (m/z - EI) Calculated for C₈H₁₀OBr (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,
Experimental

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,
Rf = 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.

\[ ^1H \text{NMR (CDCl}_3, 600 \text{MHz): } \delta (\text{ppm}) \]
1.18 (3H, s, Hg), 1.23 (3H, s, H9), 2.23-2.27 (1H, m, H7a), 2.37-2.41 (1H, m, H7b), 2.81-2.84 (1H, br s, H4), 3.06-3.10 (1H, m, H1), 6.17-6.21 (1H, m, H6).

\[ ^13C \text{NMR (CDCl}_3, 150 \text{MHz): } \delta (\text{ppm}) \]
24.0 (C9), 24.4 (C8), 43.1 (q, C3), 48.1 (C7), 57.3 (C1), 58.4 (C4), 129.4 (C6), 133.7 (q, C5), 217.5 (q, C2).

IR v_max (cm\(^{-1}\)): 2972, 1742, 1577, 1462, 1124, 1052, 973.
HRMS: (m/z - El) Calculated for C9H11OBr (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%). \( R_f (8:2 \text{ hexane:ethyl acetate}) = 0.43 \).

\[ ^1H \text{NMR (CDCl}_3, 600 \text{MHz): } \delta (\text{ppm}) \]
1.06 (3H, s, H8), 1.16 (3H, s, H9), 1.39 (3H, s, H10), 1.69-1.73 (1H, m, H7a), 1.75-1.79 (1H, m, H7b), 2.48 (1H, br s, H4), 2.70-2.74 (1H, m, H1),
Experimental

6.29 (1H, d, J = 3.3 Hz, H₆).

$^{13}$C 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 C₁₉H₂₃Br (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, Rf = 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%).

$^1$H NMR (CDCl₃, 400 MHz): δ (ppm) 1.07 (3H, s, H₉), 1.22 (3H, s, H₆), 1.30 (3H, s, H₁₀), 1.76-1.80 (1H, m, H₇₈), 2.00-2.04 (1H, m, H₇₉), 2.43 (1H, br s, H₄), 2.72 (1H, br s, H₁), 6.17 (1H, d, J = 3.5 Hz, H₆).

$^{13}$C 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.

254
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 µL, 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 µL, 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, H₇a), 1.43-1.48 (1H, m, H₇b), 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, H₁₂a), 9.26-9.35 (1H, br s, H₁₂b).
13C NMR (CDCl3, 100 MHz): δ (ppm) 18.2 (C10), 25.0 (C9), 26.0 (C8), 29.0 (C11), 45.0 (C7), 45.5 (q, C3), 52.0 (C1), 62.9 (C4), 69.4 (q, C2), 129.7 (q, C3), 131.7 (C6).

IR v_{max} (cm\textsuperscript{-1}): 2958, 2731, 1589, 1478, 1427, 1386, 1103, 1006, 882.

HRMS: (m/z - ES) Calculated for C_{11}H_{19}NBr (M+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.\textsuperscript{107} (195)

A mixture of furan (7.00 mL, 96.3 mmol), α-chloroacrylonitrile (5.99 g, 68.8 mmol) and ZnI\textsubscript{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\textsubscript{3}, 400 MHz): δ (ppm) 1.82 (1H, app d, J = 13.1 Hz, H3\textsubscript{a} minor isomer), 2.35 (1H app d, J = 13.1 Hz, H3\textsubscript{a} major isomer), 2.49 (1H, dd, J = 13.1, 5.0 Hz, H3\textsubscript{b} major isomer), 2.85 (1H, dd, J = 13.1, 5.0 Hz, H3\textsubscript{b} minor isomer), 5.21 (1H, br s, H1 major isomer), 5.24 (1H, app d, J = 4.7 Hz H4 minor isomer), 5.26 (1H, app d, J = 4.1 Hz H4 major isomer), 5.34 (1H, br s, H1 minor isomer), 6.46 (1H, dd, J
Experimental

$= 6.1, 1.9 \text{ Hz}, \text{H}_6 \text{ minor isomer}), 6.57 (1\text{H, app d, } J = 5.6 \text{ Hz}, \text{H}_6 \text{ major isomer}), 6.67 (1\text{H, dd, } J = 6.1, 1.9 \text{ Hz}, \text{H}_5 \text{ minor isomer}), 6.73 (1\text{H, dd, } J = 5.6, 1.9 \text{ Hz}, \text{H}_5 \text{ major isomer}).$

$^13\text{C NMR (CDCl}_3, 100 \text{ MHz}): \delta (\text{ppm})$

$44.4 \text{ (C}_3 \text{ minor isomer), } 45.8 \text{ (C}_3 \text{ major isomer), }$

$51.5 \text{ (q, C}_2 \text{ minor isomer), } 53.9 \text{ (q, C}_2 \text{ major isomer), }$

$79.5 \text{ (C}_4 \text{ major isomer), } 79.7 \text{ (C}_4 \text{ minor isomer), }$

$85.0 \text{ (C}_1 \text{ minor isomer), } 87.7 \text{ (C}_1 \text{ major isomer), }$ $118.4 \text{ (CN, major isomer), } 120.1 \text{ (CN, minor isomer), } 132.2 \text{ (C}_6 \text{ minor isomer), }$

$132.6 \text{ (C}_6 \text{ major isomer), } 138.3 \text{ (C}_5 \text{ minor isomer), }$

$140.4 \text{ (C}_5 \text{ major isomer).}$

IR $v_{\text{max}} (\text{cm}^{-1})$: 3020, 2238, 1315, 1033, 1024, 905.

HRMS: ($m/z$ - El) Calculated for C$_7$H$_{11}$ClNO (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.

$^1\text{H NMR (CDCl}_3, 400 \text{ MHz): } \delta (\text{ppm})$

$1.56-1.62 (1\text{H, m, } \text{H}_{5a} \text{ B isomer}), 1.64-1.68 (1\text{H, m, } \text{H}_{5a} \text{ A isomer}), 1.90-1.82 (3\text{H, m, } \text{H}_{6a} \text{ A isomer, } \text{H}_{3b} \text{ A & B isomers}), 1.96-1.91 (1\text{H, m,}}$
Experimental

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$_{3b}$ 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, H$_1$ B isomer), 4.78 (1H, app t, $J = 5.6$ Hz, H$_4$ A isomer), 4.84–4.89 (2H, m, H$_4$ B isomer & H$_1$ A isomer).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ (ppm) 24.3 (C$_6$ A isomer), 25.9 (C$_6$ B isomer), 28.3 (C$_5$ B isomer), 29.2 (C$_5$ A isomer), 48.5 (C$_3$ A isomer), 50.8 (C$_3$ B isomer), 56.0 (q C$_2$ A isomer), 57.7 (q C$_2$ B isomer), 77.6 (C$_4$ B isomer), 78.0 (C$_4$ A isomer), 83.9 (C$_1$ A isomer), 85.9 (C$_1$ B isomer), 118.5 (CN B isomer), 119.8 (CN A isomer).

IR $\nu_{\text{max}}$ (cm$^{-1}$): 2961, 2244, 1738, 1020, 930.

HRMS: (m/z - CI) Calculated for C$_7$H$_8$ClNO (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), $\alpha$-acetoxacrylonitrile (10.0 g, 90.0 mmol) and ZnI$_2$ (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.

\[ \text{1H NMR (CDCl}_3, 400 \text{ MHz): \( \delta \) (ppm)} \]

1.75 (1H, app d, \( J = 12.8 \text{ Hz, } H_{3a} \text{ major isomer} \)), 2.08 (3H, s, \( H_9 \text{ major isomer} \)), 2.20 (3H, s, \( H_9 \text{ minor isomer} \)), 2.23 (1H, dd, \( J = 12.8, 4.5 \text{ Hz, } H_{3a} \text{ minor isomer} \)), 2.31 (1H, app d, \( J = 12.8 \text{ Hz, } H_{3b} \text{ minor isomer} \)), 2.75 (1H, dd, \( J = 12.8, 4.5 \text{ Hz, } H_{3b} \text{ major isomer} \)), 5.15 (1H, m, \( H_4 \text{ major isomer} \)), 5.18 (1H, m, \( H_4 \text{ minor isomer} \)), 5.32 (1H, s, \( H_1 \text{ minor isomer} \)), 5.63 (1H, s, \( H_1 \text{ major isomer} \)), 6.24 (1H, app d, \( J = 6.3 \text{ Hz, } H_6 \text{ major isomer} \)), 6.53 (1H, app d, \( J = 6.3 \text{ Hz, } H_6 \text{ minor isomer} \)), 6.67 (1H, app d, \( J = 6.3 \text{ Hz, } H_5 \text{ major isomer} \)), 6.73 (1H, app d, \( J = 6.3 \text{ Hz, } H_5 \text{ minor isomer} \)).

\[ \text{13C NMR (CDCl}_3, 100 \text{ MHz): \( \delta \) (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 \( \nu_{\text{max}} \text{ cm}^{-1} \): 2925, 2238, 1749, 1573, 1237, 1185, 1060, 1030.

HRMS: \((m/\bar{z} - \text{Cl}) \text{ Calculated for } C_9H_{13}N_2O_3 (M+NH}_4^+ 197.0926, \text{ found } 197.0919.\)
6.5.4 2-Cyano-7-oxabicyclo[2.2.1]heptyl 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]heptyl acetate 200 as a yellow oil (4.45 g, 24.6 mmol, 90%). A 1:2.5 ratio of isomers was noted.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (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): $\delta$ (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 $\nu_{\text{max}}$ (cm$^{-1}$): 2963, 2239, 1751, 1221, 1372, 1221, 997.

HRMS: (m/z - Cl) Calculated for C$_9$H$_{15}$N$_2$O$_3$ (M+NH$_4$)$^+$ 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 CH$_2$Cl$_2$ (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%).

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ (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, H$_1$), 4.90 (1H, m, H$_4$).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ (ppm) 24.4 (C$_6$), 27.9 (C$_5$), 45.5 (C$_3$), 77.3 (C$_4$), 79.5 (C$_1$), 212.0 (q, C$_2$).

IR $\nu_{\text{max}}$ (cm$^{-1}$): 2956, 1767, 1267, 1003, 921, 882, 772.

HRMS: (m/z - Cl) Calculated for C$_9$H$_{15}$N$_2$O$_3$ (M+H)$^+$ 113.0603, found 113.0608.

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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%).

\[ ^1H \text{NMR (CDCl}_3, 600 \text{ MHz}): \delta (\text{ppm}) \]

<table>
<thead>
<tr>
<th>( \delta ) (ppm)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.94 (3H, s, ( H_b ))</td>
<td>1.09 (3H, s, ( H_7 ))</td>
</tr>
</tbody>
</table>
Experimental

\[ ^{13}\text{C NMR} \text{(CDCl}_3, 150 \text{ MHz}): \delta \text{ (ppm)} \]

\[
\begin{align*}
20.2 \text{ (C}_8 \text{)}, & \quad 22.7 \text{ (C}_6 \text{)}, \quad 24.6 \text{ (C}_5 \text{)}, \quad 25.6 \text{ (C}_9 \text{)}, \quad 26.1 \text{ (C}_7 \text{)}, \quad 44.6 \text{ (q, C}_3 \text{)}, \quad 78.8 \text{ (q, C}_2 \text{)}, \quad 86.6 \text{ (C}_1 \text{)}, \quad 88.5 \text{ (C}_4 \text{)}.
\end{align*}
\]

IR \( \nu \text{max (cm}^{-1}) \): 3442, 2961, 2871, 1469, 1370, 1107, 1007, 930.

HRMS: \((m/z - \text{ EI})\) Calculated. for C\(_9\)H\(_{16}\)O\(_2\) (M)\(^+\) 156.1150, found 156.1146.

6.5.8 4,7,7-Trimethyl-2-oxabicyclo[2.2.1]heptan-3-imine. (203)

![Diagram](Image)

Prepared as per general procedure D using 2-\textit{endo}-3,3-trimethyl-7-oxabicyclo[2.2.1]heptan-2-ol 202 (0.02 g, 0.12 mmol), 70\% H\(_2\)SO\(_4\) (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\%).

\[ ^1\text{H NMR} \text{(CDCl}_3, 600 \text{ MHz}): \delta \text{ (ppm)} \]

\[
\begin{align*}
0.96 \text{ (3H, s, H}_8\text{/H}_9 \text{)}, & \quad 1.23 \text{ (3H, s, H}_8\text{/H}_9 \text{)}, \quad 1.34 \text{ (3H, s, H}_10 \text{)}, \quad 1.72-1.81 \text{ (2H, m, H}_5\text{/H}_6 \text{)}, \quad 2.21-2.29 \text{ (1H, m, H}_5\text{)}, \quad 2.37-2.45 \text{ (1H, m, H}_6 \text{)}, \quad 3.66-3.69 \text{ (1H, m, H}_11 \text{)}, \quad 3.90-3.95 \text{ (1H, m, H}_1 \text{)}.
\end{align*}
\]

\[ ^{13}\text{C NMR} \text{(CDCl}_3, 150 \text{ MHz): \delta \text{ (ppm)} \]

\[
\begin{align*}
19.3 \text{ (C}_8\text{/C}_9 \text{)}, & \quad 21.3 \text{ (C}_10 \text{)}, \quad 21.6 \text{ (C}_8\text{/C}_9 \text{)}, \quad 31.0 \text{ (C}_5 \text{)}, \quad 35.2 \text{ (C}_6 \text{)}, \quad 43.4 \text{ (q, C}_7 \text{)}, \quad 47.5 \text{ (q, C}_4 \text{)}, \quad 80.5\text{(C}_1 \text{)}, \quad 122.5 \text{ (q, C}_3 \text{)}.
\end{align*}
\]

IR \( \nu \text{max (cm}^{-1}) \): 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.

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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% CH₂Cl₂, 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 (CDCl₃, 600 MHz): δ (ppm) 1.35 (1H, m, H₈a), 1.51 (1H, m, H₇a), 1.58 (1H, m, H₈b), 2.04-2.16 (2H, m, H₃a, H₇b), 2.53 (1H, dd, J = 14.8, 2.3 Hz, H₃b), 2.72-2.77 (1H, m, H₄), 3.13-3.17 (1H, m, H₅), 6.26 (1H, app t, J = 7.23 Hz, H₆), 6.45 (1H, app t, J = 7.23 Hz, H₅).

^13C NMR (CDCl₃, 150 MHz): δ (ppm) 22.22 (C₇), 22.23 (C₈), 29.5 (C₄), 41.4 (C₁), 45.1 (C₃), 56.3 (C₂), 120.5 (CN), 129.7 (C₆), 134.7 (C₅).

Minor Isomer

^1H NMR (CDCl₃, 600 MHz): δ (ppm) 1.13-1.38 (2H, m, H₈a, H₇a), 1.34-1.71 (1H, m, H₈b), 2.04-2.15 (1H, m, H₃a), 2.22-2.28 (1H, m, H₇b), 2.38-2.43 (1H, app dt, J = 14.2, 3.2 Hz, H₃b), 2.71-2.77 (1H, m, C₄), 3.05-3.08 (1H, m, H₁), 6.39 (1H, app t, J = 7.3 Hz, H₆), 6.52 (1H, app t, J = 7.3 Hz, H₅).

^13C NMR (CDCl₃, 150 MHz): δ (ppm) 18.8 (C₇), 23.7 (C₈), 29.6 (C₄), 41.3 (C₁), 44.1 (C₃), 56.9 (C₂), 120.9 (q, CN), 130.9 (C₆), 136.8 (C₅).
IR $u_{\text{max}}$ cm$^{-1}$: 2949, 2240, 1442, 960, 810, 704.

HRMS: (m/z - EI) Calculated for C$_9$H$_{10}$NCI (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, Rf = 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.$^\text{329}$ 108-109 °C).

$^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ (ppm) 1.56-1.68 (5H, m, H$_5$/H$_6$/H$_7$/H$_8$), 1.78-1.85 (2H, m, H$_4$, H$_5$/H$_6$/H$_7$/H$_8$), 2.02-2.10 (1H, m, H$_5$/H$_6$/H$_7$/H$_8$), 2.10-2.16 (2H, m, H$_1$, H$_5$/H$_6$/H$_7$/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): $\delta$ (ppm) 19.8 (C$_5$/C$_6$/C$_7$/C$_8$), 23.0 (C$_5$/C$_6$/C$_7$/C$_8$), 23.4 (C$_5$/C$_6$/C$_7$/C$_8$), 23.5 (C$_5$/C$_6$/C$_7$/C$_8$), 24.5 (C$_4$), 36.2 (C$_1$), 44.4 (C$_3$), 58.1 (q, C$_2$), 121.0 (q, CN).

IR $v_{\text{max}}$ cm$^{-1}$: 2945, 2871, 1454, 1441, 957, 814.

HRMS: (m/z - EI) Calculated for C$_9$H$_{12}$NCI (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, Rf = 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.^^®

\[ ^1H \text{NMR (CDCl}_3, 600 \text{MHz): } \delta \text{ (ppm)} \]

<table>
<thead>
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<th>δ (ppm)</th>
<th>Description</th>
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<td>1.58-1.68</td>
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<tr>
<td>1.69-1.79</td>
<td>(2H, m, H₅/H₆/H₇/H₈)</td>
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<tr>
<td>1.80-1.88</td>
<td>(4H, m, H₅/H₆/H₇/H₈)</td>
</tr>
<tr>
<td>2.18</td>
<td>(1H, heptet, J = 3.0 Hz, H₄)</td>
</tr>
<tr>
<td>2.25-2.78</td>
<td>(3H, m, H₁, H₃a, H₃b)</td>
</tr>
</tbody>
</table>

\[ ^13\text{C NMR (CDCl}_3, 150 \text{MHz): } \delta \text{ (ppm)} \]

<table>
<thead>
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<th>δ (ppm)</th>
<th>Description</th>
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<tbody>
<tr>
<td>23.4</td>
<td>(C₅/C₆/C₇/C₈ and C₅/C₆/C₇/C₈)</td>
</tr>
<tr>
<td>24.7</td>
<td>(C₅/C₆/C₇/C₈ and C₅/C₆/C₇/C₈)</td>
</tr>
<tr>
<td>27.9</td>
<td>(C₄), 42.4 (C₁), 44.7 (C₃), 218.5 (q, C₂).</td>
</tr>
</tbody>
</table>

IR νmax cm⁻¹: 2940, 2867, 1723, 1329, 1027, 859.

HRMS: (m/z - EI) Calculated for C₈H₁₂O (M)+ 124.0888, found 124.0891.
Experimental

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, Rf = 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 (CDCl3, 600 MHz): δ (ppm) 1.16 (6H, m, H9), 1.26-1.34 (1H, m, H5/H6/H7/H8), 1.60-1.66 (2H, m, H5/H6/H7/H8), 1.69 (1H, quintet, J = 3.0 Hz, H4), 1.80-1.85 (3H, m, H5/H6/H7/H8), 1.91-1.98 (2H, m, H5/H6/H7/H8), 2.23 (1H, quintet, J = 3.0 Hz, H1).

13C NMR (CDCl3, 150 MHz): δ (ppm) 22.5 (C5/C6/C7/C8 and C5/C6/C7/C8), 23.5 (C5/C6/C7/C8 & C5/C6/C7/C8), 38.5 (C4), 42.8 (C1), 46.0 (q, C3), 223.3 (q, C2).

IR vmax cm⁻¹: 2944, 2869, 1715, 1455, 1049, 864.

HRMS: (m/z - ESI) Calculated for C10H17O (M+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, Rf = 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.

\[ \text{H NMR (CDCl}_3, 600 MHz): \delta (ppm) \]
- 1.02 (3H, s, H₉), 1.06 (3H, s, H₁₀), 1.16-1.18 (1H, m, H₄), 1.25 (3H, s, H₁₁), 1.26-1.42 (3H, m, H₅/H₆/H₇/H₈), 1.43-1.70 (3H, m, H₁, H₅/H₆/H₇/H₈), 1.71-1.78 (1H, m, H₅/H₆/H₇/H₈), 1.85-2.01 (2H, m, H₅/H₆/H₇/H₈).

\[ \text{C NMR (CDCl}_3, 150 MHz): \delta (ppm) \]
- 20.9 (C₅/C₆/C₇/C₈), 22.2 (C₅/C₆/C₇/C₈), 22.7 (C₅/C₆/C₇/C₈), 23.4 (C₅/C₆/C₇/C₈), 23.8 (C₁₀), 25.5 (C₁₁), 26.7 (C₉), 38.3 (C₄), 38.7 (q, C₃), 39.5 (C₁), 75.1 (q, C₂).

IR \nu_{max} \text{ cm}^{-1}: 3484, 2937, 1471, 1371, 1063, 912, 868.

HRMS: (m/z - EI) Calculated for C₁₁H₂₀O (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% H₂SO₄ (5 mL), NaN₃ (0.78 g, 12.1 mmol) and CHCl₃ (50 mL) with a reaction time of 4 hrs to yield a yellow oil which was purified by column chromatography (100% hexane, Rf = 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%).

268
Experimental

$^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ (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, H$_5$/H$_6$/H$_7$/H$_8$), 1.39-1.43 (4H, m, H$_{11}$, H$_5$/H$_6$/H$_7$/H$_8$), 1.49-1.59 (2H, m, H$_1$, H$_5$/H$_6$/H$_7$/H$_8$), 1.65-1.78 (2H, m, H$_5$/H$_6$/H$_7$/H$_8$), 1.86-1.95 (2H, m, H$_5$/H$_6$/H$_7$/H$_8$).

$^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta$ (ppm)

20.7 (C$_{11}$), 21.8 (C$_5$/C$_6$/C$_7$/C$_8$), 21.9 (C$_5$/C$_6$/C$_7$/C$_8$), 22.3 (C$_5$/C$_6$/C$_7$/C$_8$), 22.5 (C$_5$/C$_6$/C$_7$/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 $v_{\text{max}}$ cm$^{-1}$: 2944, 2081, 1392, 1265, 1053.

HRMS: (m/z - El) Calculated for C$_{11}$H$_{19}$N (M-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).

$^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ (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$_1$, H$_5$/H$_6$/H$_7$/H$_8$), 1.49-1.81 (3H, m, H$_4$, H$_5$/H$_6$/H$_7$/H$_8$).
Experimental

$^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta$ (ppm) 11.4 (C$_{10}$), 14.1 (C$_9$), 22.1 (C$_5$/C$_6$/C$_7$/C$_8$), 22.6 (C$_{11}$), 22.7 (C$_5$/C$_6$/C$_7$/C$_8$), 29.8 (C$_5$/C$_6$/C$_7$/C$_8$), 31.7 (C$_5$/C$_6$/C$_7$/C$_8$), 36.8 (q, C$_3$), 38.4 (C$_4$), 38.8 (C$_1$), 41.3 (q, C$_2$).

IR $v_{\text{max}}$ cm$^{-1}$: 3342, 2932, 2871, 1466, 1371, 841.

HRMS: (m/z - EI) Calculated for C$_{11}$H$_{21}$N (M)$^+$ 167.1674, found 167.1680.

6.5.16 2,3,3-Trimethyl-2-methyaminobicyclo[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$_2$Cl$_2$ (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-methyaminobicyclo[2.2.2]octane 193 as a white solid (0.03 g, 0.14 mmol, 38%). M.p. 164-166 °C (decomposes).

$^1$H NMR (CDCl$_3$, 600 MHz): $\delta$ (ppm) 1.15 (3H, s, H$_{10}$), 1.21-1.24 (1H, m, H$_4$), 1.40-1.61 (10H, m, H$_9$, H$_{11}$, H$_5$/H$_6$/H$_7$/H$_8$), 1.68-1.82 (3H, m, H$_1$, H$_5$/H$_6$/H$_7$/H$_8$), 2.01-2.09 (1H, m, H$_5$/H$_6$/H$_7$/H$_8$), 2.13-2.19 (1H, m, H$_5$/H$_6$/H$_7$/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): $\delta$ (ppm) 19.1 (C$_9$), 20.4 (C$_5$/C$_6$/C$_7$/C$_8$), 21.5 (C$_5$/C$_6$/C$_7$/C$_8$), 21.6 (C$_5$/C$_6$/C$_7$/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_{\text{max}} \text{ cm}^{-1}: 2942, 2733, 1468, 1368, 1053.

HRMS: \(^{m/z - \text{ESI}}\) 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_{\text{max}} (\text{cm}^{-1}): 2950, 2872, 1715, 1693, 1251, 1054, 1021, 856.

HRMS: \(^{m/z - \text{ESI}}\) 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 (ca 14 hrs) to yield a dark yellow oil. Purification by column
Experimental 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%).

\[ \begin{align*}
^{1}H \text{ NMR (CDCl}_3, 600 MHz): \delta (ppm) & \quad 1.33 (3H, d, J = 7.4 Hz, H_8), 1.92-2.04 (4H, H_{5a}, H_{5b}, H_{6a}, H_{6b}), 2.42-2.45 (1H, m, H_1), 2.83-2.90 (1H, m, H_4 or H_7), 2.97-3.05 (1H, m, H_4 or H_7), 3.11-3.18 (2H, m, H_4, H_7), 3.25 (1H, quartet, } J = 7.4 Hz, H_3). \\
^{13}C \text{ NMR (CDCl}_3, 150 MHz): \delta (ppm) & \quad 13.9 (C_8), 25.1 (C_5 or C_6), 26.5 (C_5 or C_6), 39.9 (C_1), 40.8 (C_4 or C_7), 48.7 (C_4 of C_7), 65.4 (C_3), 222.0 (q, C_2).
\end{align*} \]

IR \( \nu_{\text{max}} \) (cm\(^{-1}\)): 2948, 2872, 1721, 1455, 1107, 1019, 856.

HRMS: (m/z - ESI) Calculated for \( C_9H_{12}NO \) (M+H)^+ 140.1075, found 140.1073.

6.5.19 \( 3\)-\((\text{Hydroxymethyl})\)-3-methylquinuclidin-2-one. (217)

![Chemical Structure of 3-(Hydroxymethyl)-3-methylquinuclidin-2-one](image)

Prepared as per general procedure T using 3-methylquinuclidin-2-one \( 215 \) (1.70 g, 12.2 mmol), formaldehyde (37% in \( H_2O, 1.50 \text{ mL}, 18.3 \text{ mmol} \)) and dimethylamine (40% in \( H_2O, 2.10 \text{ mL}, 18.3 \text{ mmol} \)) 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.

\[ \begin{align*}
^{1}H \text{ NMR (CDCl}_3, 400 MHz): \delta (ppm) & \quad 1.46 (3H, s, H_8), 1.96-2.14 (4H, m, H_{5a}, H_{6a}, H_{5b}, H_{6b}), 2.44-2.49 (1H, m, H_1), 2.88-2.99 (2H, m, H_7/H_4), 3.23-3.36 (2H, m, H_7/H_4), 3.69
\end{align*} \]
Experimental

(1H, d, $J = 11.2$ Hz, $H_{9a}$), 3.79 (1H, d, $J = 11.2$ Hz, $H_{9b}$).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ (ppm) 19.5 (C$_8$), 25.3 (C$_5$/C$_6$), 26.5 (C$_5$/C$_6$), 40.4 (C$_1$), 43.7 (C$_4$), 43.7 (C$_7$), 64.3 (C$_9$), 68.2 (q, $C_3$), 221.9 (q, $C_2$).

IR $\nu_{\text{max}}$ (cm$^{-1}$): 3410, 2942, 1711, 1454, 1380, 1249, 1073, 1017, 865.

HRMS: (m/z - ESI) Calculated for C$_9$H$_{10}$NO$_2$ (M+H)$^+$ 170.1181, found 170.1178.
7 References.


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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.

Alkyl substitution has been investigated by Corne et al., Stone et al. and Suchocki et al. 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.

Figure 8-1: Summary of the results of investigating alkyl substitution.
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., Suchocki et al. and Crooks and co-workers. 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. and Suchocki et al., Crooks and co-workers 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.,](image-url)
8.1.3 Investigation of the amine in the *endo* and *exo* position.

![Exo MA and Endo MA](image)

*Figure 8-3: A comparison of *exo* vs. *endo* MA.*

The orientation of the amine has been investigated by Stone *et al.* and Suchocki *et al.* 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.* 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.* 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.](image)

Wragg and co-workers\(^{262}\) and Stone \textit{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 \textit{et al.}\(^{264}\) was found to act as a stimulant at nAChR, (Figure 8-5).

![Figure 8-5: Phenyl MA analogue producing stimulant effects](image)
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.