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# Synthesis of mecamylamine analogues



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

By  
David Mangan B.A. (Mod.)

Under the supervision of  
Dr. Mike Southern

School of Chemistry  
Trinity College Dublin  
Dublin

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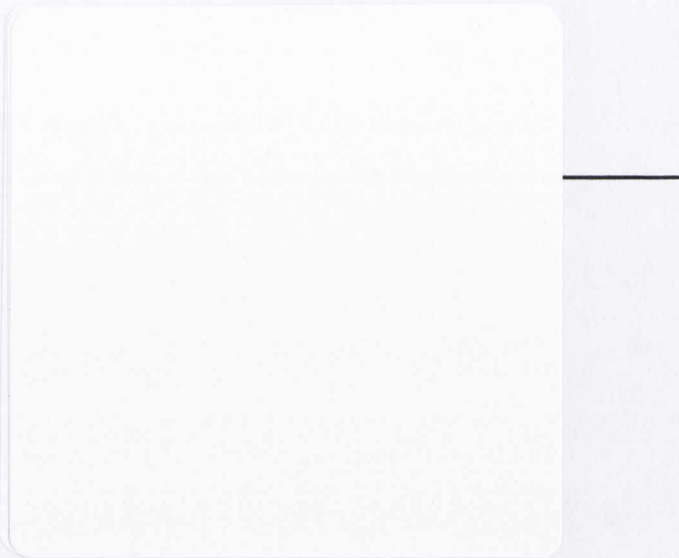




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David Mangan

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*To my parents Peter and Dee,  
to whom I owe everything*

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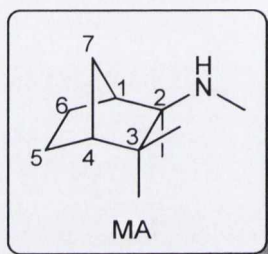
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## Abstract

This project was concerned with the synthesis of structural analogues of the neuronal nicotinic acetylcholine receptor (nAChR) antagonist mecamylamine (MA). MA was used clinically as an antihypertensive compound since the 1950s but has more recently been investigated for its therapeutic potential as an anti-addictive and antidepressant compound. Unfortunately MA is viewed as unsuitable for clinical use in this regard due to its non-specific activity at various nAChRs subtypes and it was hoped that by making subtle changes to the molecular structure of MA a novel compound could be found that would display higher selectivity thereby enhancing the therapeutic potential of the parent compound.



It was our intention to synthesise a range of MA analogues in order to probe the pharmacological space around the MA skeleton and which would form the basis for a structure activity relationship (SAR) study for MA at the receptors of interest. In order to synthesise the required analogue series a novel synthetic route to the parent compound was devised that would allow the selective functionalisation of the 2 and 3 positions. This route was initially employed to successfully prepare mecamylamine itself. Subsequently nine novel MA analogues exhibiting modification at position 2 and/or 3 were prepared and have been submitted for assessment of antagonistic activity at nAChRs - the results are eagerly awaited.

Further modifications to the MA framework required the development of new synthetic methodology beyond that employed for the synthesis of our initial series. These ultimately lead to the synthesis of both 5- and 6-substituted MA analogues that could be further developed to extensively probe the effect of substitution at these positions. The attempted synthesis of a 5,6-disubstituted MA analogue was abandoned prior to completion.



## Abbreviations

|              |                                                                  |
|--------------|------------------------------------------------------------------|
| 5-HT         | serotonin                                                        |
| A-AChBP      | <i>aplysia californica</i> acetylcholine binding protein         |
| Ach          | acetylcholine                                                    |
| AChBP        | acetylcholine binding protein                                    |
| AD           | Alzheimer's disease                                              |
| bPiDDb       | <i>N,N</i> -dodecane-1,12-diyl-bis-3-picolinium dibromide        |
| BTMPS        | <i>bis</i> -(2,2,6,6-tetramethyl-4-piperidiny)-sebacate          |
| CDC          | Centers for Disease Control and Prevention                       |
| CHF          | congestive heart failure                                         |
| CNS          | central nervous system                                           |
| COX          | cyclo-oxygenase                                                  |
| CSCB         | Centre for Synthesis and Chemical Biology                        |
| DA           | dopamine                                                         |
| DAT1         | dopamine transporter protein                                     |
| DBU          | 1,8-diazabicycloundec-7-ene                                      |
| DEPT         | distortionless enhancement by polarization transfer              |
| DH $\beta$ E | dihydro- $\beta$ -erythroidine                                   |
| DID          | "drinking in the dark" (paradigm)                                |
| DMPK         | drug metabolism and pharmacokinetics                             |
| DMPU         | 1,3-dimethyltetrahydropyrimidin-2(1H)-one                        |
| DMSO         | dimethylsulfoxide                                                |
| DSM          | diagnostic and statistics manual of mental disorders             |
| ECD          | extracellular domain                                             |
| ELIC         | <i>erwinia chrysanthemi</i> pentameric ligand gated ion channel  |
| EMCDDA       | European Monitoring Centre for Drugs and Drug Addiction          |
| FDA          | Food and Drug Authority                                          |
| fMRI         | functional magnetic resonance imaging                            |
| FST          | forced swim test                                                 |
| GABA         | $\gamma$ -amino butyric acid                                     |
| GLIC         | <i>gloeobacter violaceus</i> pentameric ligand gated ion channel |

|                  |                                            |
|------------------|--------------------------------------------|
| GPCR             | G-protein coupled receptor                 |
| HEK              | human embryonic kidney                     |
| HMBC             | heteronuclear multiple bond coherence      |
| HMPA             | hexamethylphosphoramide                    |
| HPLC             | high performance liquid chromatography     |
| HRMS             | high resolution mass spectrometry          |
| HSQC             | heteronuclear single quantum coherence     |
| IC <sub>50</sub> | half maximal inhibitory concentration      |
| LDA              | lithium diisopropylamine                   |
| LSD              | <i>d</i> -lysergic acid diethylamide       |
| MA               | mecamylamine                               |
| MDMA             | 3,4-methylenedioxymethamphetamine          |
| MLA              | methyllycaconitine                         |
| MRI              | magnetic resonance imaging                 |
| MW               | microwave                                  |
| MWC              | Monod-Wyman-Changeux                       |
| NA               | noradrenaline                              |
| NAc              | nucleus accumbens                          |
| NAcD             | National Advisory Committee on Drugs       |
| nAChR            | nicotinic acetylcholine receptor           |
| NaHMDS           | sodium bis(trimethylsilyl)amide            |
| NMR              | nuclear magnetic resonance                 |
| NMRI             | Naval Medical Research Institute           |
| nOe              | nuclear Overhauser effect                  |
| NRT              | nicotine replacement therapy               |
| NSAIDs           | non-steroidal anti-inflammatory drugs      |
| PD               | Parkinson's disease                        |
| PET              | positron emission tomography               |
| PFC              | prefrontal cortex                          |
| PNS              | peripheral nervous system                  |
| PTSA             | para-toluene sulfonic acid                 |
| SAR              | structure activity relationship            |
| SNRI             | serotonin/noradrenaline reuptake inhibitor |

|                  |                                              |
|------------------|----------------------------------------------|
| SSRE             | selective serotonin reuptake enhancer        |
| SSRIs            | selective serotonin reuptake inhibitor       |
| TFA              | trifluoroacetic acid                         |
| THF              | tetrahydrofuran                              |
| TLC              | thin layer chromatography                    |
| TMD              | transmembrane domain                         |
| TMPH             | 2,2,6,6-tetramethylpiperidin-4-yl-heptanoate |
| TOCSY            | total correlation spectroscopy               |
| TS               | Tourette's Syndrome                          |
| TST              | tail suspension test                         |
| VTa              | ventral tegmental area                       |
| WHO              | World Health Organisation                    |
| $\alpha$ -BTX    | $\alpha$ -bungarotoxin                       |
| $\alpha$ -CtxMII | $\alpha$ -conotoxin MII                      |



# **Chapter 1**

## **Introduction to nicotinic acetylcholine receptor**

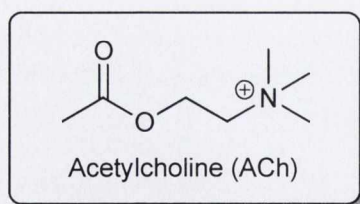
# **1 Introduction to nicotinic acetylcholine receptors**

## **1.1 Nicotinic acetylcholine receptors**

Nicotinic acetylcholine receptors (nAChRs) are located throughout the human body and have been implicated in a wide range of neurobiological disorders including addiction, depression, schizophrenia, Alzheimer's, Parkinson's, Tourette syndrome and pain. Modulators of these receptors possess therapeutic potential across these fields. The synthesis of highly selective nAChR antagonists or agonists is of great interest to the biomedical scientific community at large and forms the basis of this thesis work.

### **1.1.1 Classification**

Acetylcholine (ACh) was first discovered by Henry Dale in 1913.<sup>1</sup> It is produced by the enzyme choline acetyltransferase and is active in both the central nervous system (CNS) and the peripheral nervous system (PNS). Acetylcholine receptors (AChRs) are membrane bound proteins that were originally isolated in 1972<sup>2, 3</sup>. They consist of two broad receptor families – the muscarinic, metabotropic G protein-coupled AChRs and the nicotinic, ligand gated ion channel AChRs. The nAChRs are located in the PNS at neuromuscular junctions and in the autonomic nervous system but are also found extensively within the CNS. It is neuronal nAChRs that are of paramount interest to this study.



**Figure 1-1 The neurotransmitter acetylcholine**

With the advent of the molecular biology revolution of the late 1980s and early 1990s, Heineman, Ballivet, Claudio, Patrick and co-workers<sup>4-7</sup> managed to elucidate the genes coding for nAChRs which lead to the cloning and expression of these receptors from a variety of

species. This allowed the complete classification of the nAChR family. Neuronal nAChRs are composed of combinations of  $\alpha$  ( $\alpha 2$ - $\alpha 6$ ) and  $\beta$  ( $\beta 2$ - $\beta 4$ ) subunits, homomers of  $\alpha$  subunits ( $\alpha 7$  and  $\alpha 9$ ) and  $\alpha$  subunit heteromers ( $\alpha 9$  and  $\alpha 10$ ). The  $\alpha 8$  subunit identified in avian brain has not yet been identified in mammals. Five muscular subunit types ( $\alpha 1$ ,  $\beta 1$ ,  $\gamma$ ,  $\delta$ ,  $\epsilon$ ) that make up the neuromuscular junction have also been identified in the mammalian genome. Figure 1-2 shows how broadly the various assemblies of nAChRs are distributed throughout the human brain.

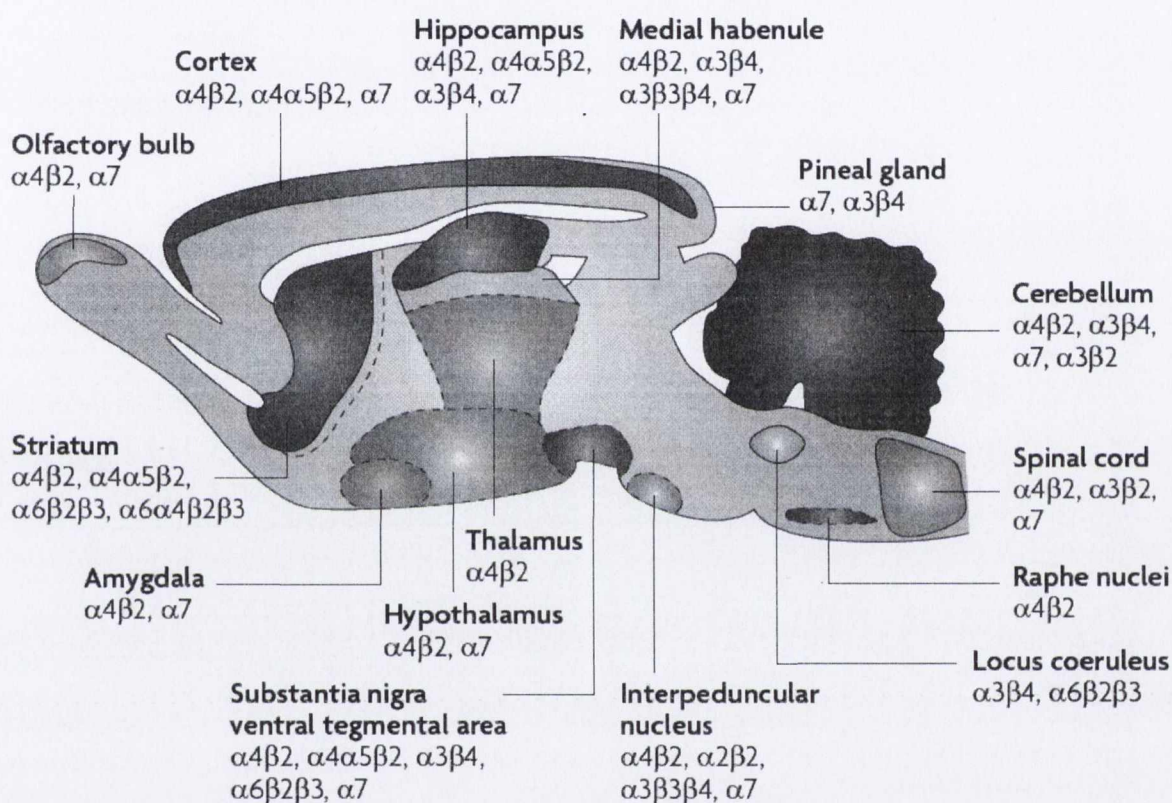


Figure 1-2 Distribution of nAChR subtypes throughout the brain (extract from Taly, A.; Corringer, P.-J.; Guedin, D.; Lestage, P.; Changeux, J.-P. *Nat. Rev. Drug. Discov.* 2009, 8, 733-750<sup>8</sup>)

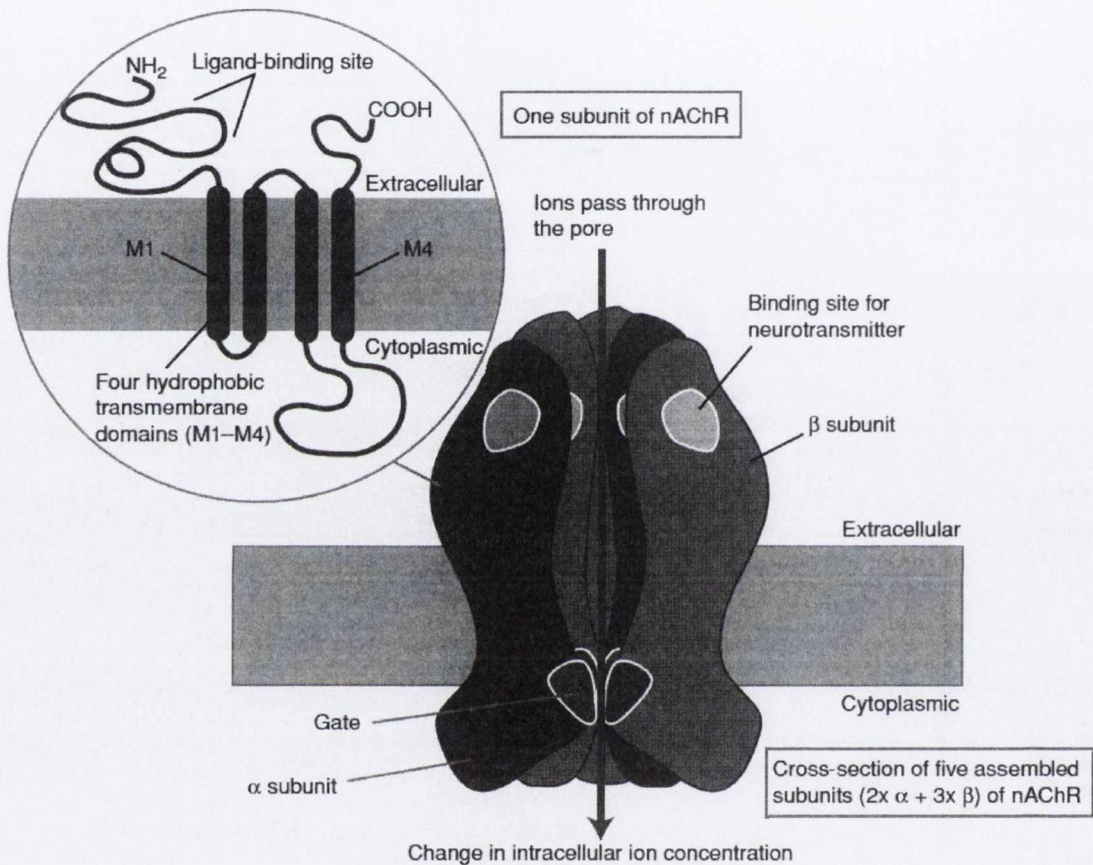
### 1.1.2 Receptor structure

Structurally, these receptors are pentameric ligand gated ion channels. (Figure 1-3) Each of the 5 subunits is a protein comprised of:

- i) a long *N*-terminal extracellular domain, which is involved in binding to neurotransmitter ligands,



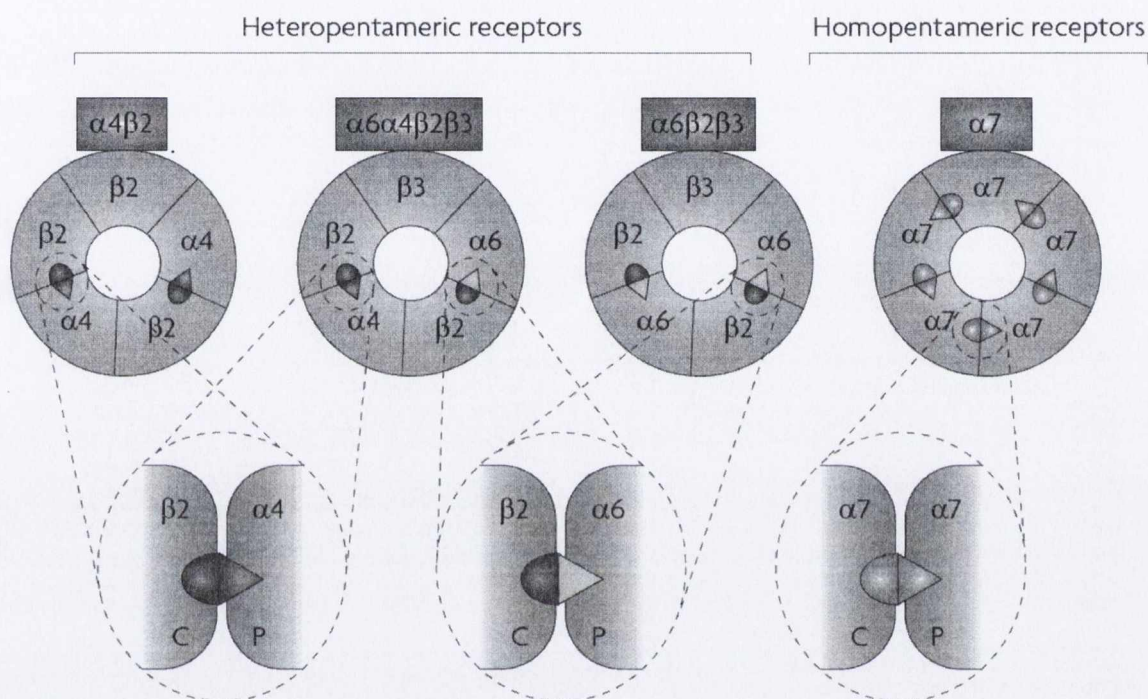
- ii) four hydrophobic transmembrane domains designated M1, M2, M3 and M4,
- iii) a long cytoplasmic loop between M3 and M4, and other shorter loops connecting the domains. It is the M2 domain of the five subunits that together form the wall of the ion channel. Charged amino acids line the gate region and select the ions that can pass through into the cell.



**Figure 1-3 Structure of nicotinic acetylcholine receptors (extract from Bate, L.; Gardiner, M. *Expert Reviews in Molecular Medicine* 1999, 1, 1-22)<sup>9</sup>**

There are a variable number of orthosteric binding sites located in the extracellular domain (ECD) depending on the subunits present in a given receptor (Figure 1-4). These binding sites lie at the interface between an  $\alpha$ -type subunit (usually described as the ‘principal component’) and a non- $\alpha$ -type subunit (the ‘complementary component’)<sup>10</sup>, except in homomeric nAChRs such as  $\alpha 7$  nAChRs. This allows for the number of binding sites to be anywhere between two (as in the muscle type  $(\alpha 1)_2\beta 1\gamma\delta$ ) to five (as in the homomeric  $\alpha 7$  receptor).

The ‘accessory’ subunit can also play a role. For example, the receptor shown on the left in Figure 1-4 is more precisely described as  $(\alpha 4)_2(\beta 2)_3$  as opposed to  $(\alpha 4)_3(\beta 2)_2$ . It has been shown that these two receptors have distinct pharmacological profiles and in fact the former displays much higher agonist sensitivity than the latter.<sup>11, 12</sup> In this way, the accessory subunit can act as a modulator of receptor function.



**Figure 1-4 nAChRs orthosteric binding sites** (extract from Corringer, P.-J.; Galzi, J.-L.; Eisele, J.-L.; Bertrand, S.; Changeux, J.-P.; Bertrand, D. *Journal of Biological Chemistry* 1995, 270, 11749-11752)<sup>13</sup>

### 1.1.3 Atomic structure and crystallography

As membrane bound proteins, analysis of these receptors by X-ray diffraction directly was extremely difficult, and as such, a number of alternative approaches have been attempted. In 2001, Brejc *et al.* solved the X-ray structure of the ECD homologue using acetylcholine binding proteins (AChBPs).<sup>12</sup> These are water soluble proteins similar to the nAChR ECD that were initially cloned from the snail, *Lymnaea stagnalis*.<sup>14, 15</sup>

In 2003, the first images of the transmembrane domain of a nAChR appeared. A study undertaken by Miyazawa *et al.* combining electron microscopy with computational methods



provided an accurate picture of the transmembrane pore and the gating mechanism.<sup>16</sup> In 2007, an X-ray structure of the ECD of the mouse nAChR  $\alpha 1$  subunit was solved as a monomeric complex with the competitive antagonist,  $\alpha$ -bungarotoxin ( $\alpha$ -BTX).<sup>17</sup> This X-ray structure can be successfully superimposed on the structure obtained from the AChBP, thereby validating the use of AChBP as a reliable template of the mammalian ECD of these receptors. More recently two bacterial homologues of nAChRs have been cloned and expressed in human embryonic kidney (HEK) 293 cells and *Xenopus* oocytes. Crystal structures of *Gloeobacter violaceus* pentameric ligand gated ion channel (GLIC)<sup>18, 19</sup> and *Erwinia chrysanthemi* pentameric ligand gated ion channel (ELIC)<sup>20</sup> have both been solved aiding our ever-improving understanding of the atomic structure of these receptors. The latter two examples are significantly closer in structure to mammalian nAChRs than any previous homologues lacking only the *N*-terminal  $\alpha$ -helix and the extended cytoplasmic loop between M3 and M4.

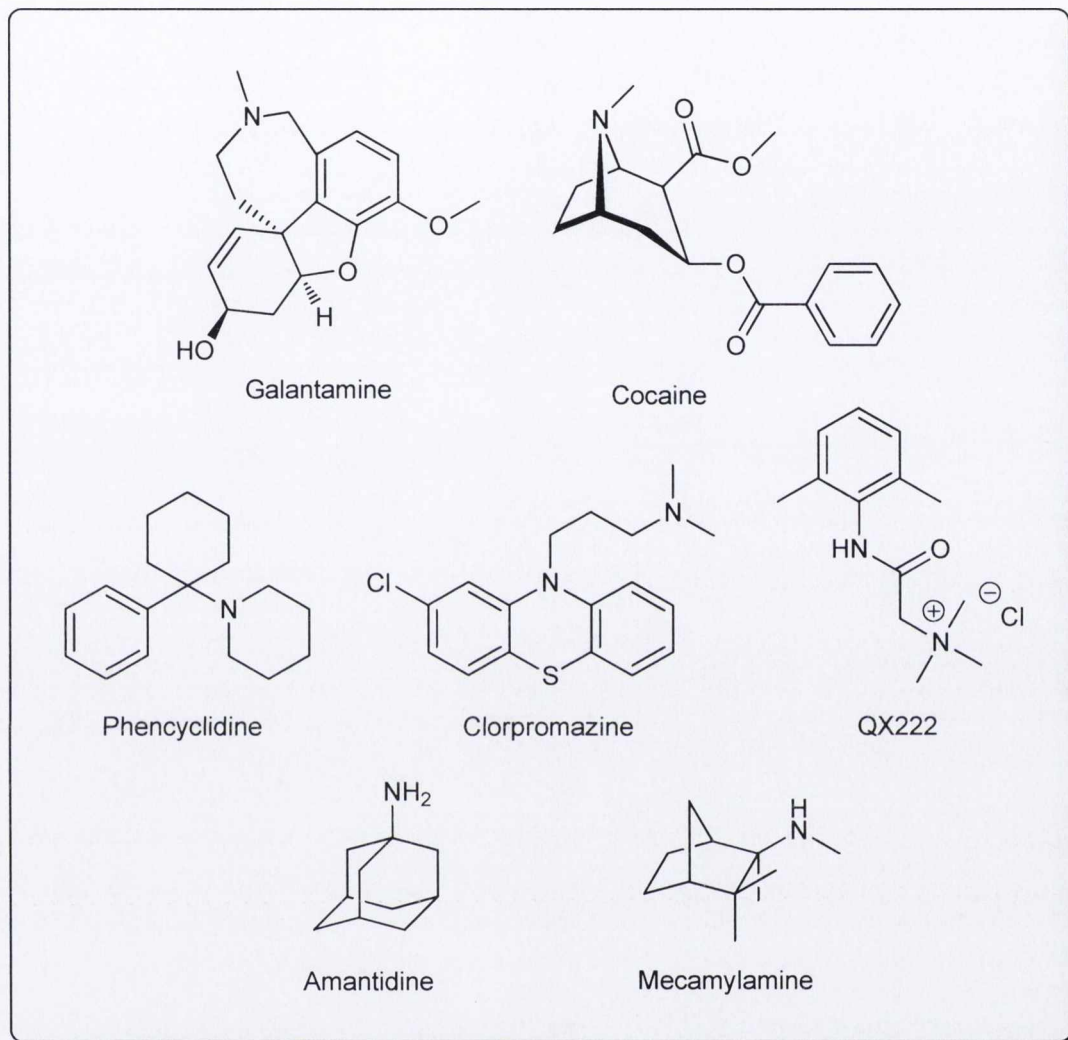
#### 1.1.4 Ligand interactions

The binding of nicotine based ligands at the orthosteric site is now reasonably well understood. Two excellent studies undertaken by Hansen *et al.*<sup>21</sup> and Taylor and co-workers<sup>22</sup> managed to solve crystal structures for another AChBP, this time cloned from the saltwater mollusk, *Aplysia californica* (A-AChBP) complexed to a number of agonists and antagonists. The binding pocket was shown to contain an 'aromatic box' formed by a number of tyrosine and tryptophan residues. Surprisingly, this was predicted in a computational study carried out by Zhong and co-workers<sup>23</sup> that showed strong  $\pi$ -cation interactions between these amino acid residues and the quaternary ammonium of the endogenous ligand long before any crystal structure data was available.

A number of other binding sites removed from the orthosteric binding site have also been identified. These allosteric sites have been shown to be able to moderate ion channel activity by binding ligands that do not compete with known orthosteric binders like acetylcholine, nicotine or  $\alpha$ -BTX. The non competitive ligands galantamine (a positive allosteric modulator<sup>24</sup>) and cocaine (a negative allosteric modulator<sup>25</sup>)(Figure 1-5) have been found to bind at the same site in A-AChBP.<sup>26</sup> The principal face of the binding pocket is in this case provided by a non  $\alpha$ -subunit. This site, highlighted in Figure 1-6, is found deep within the



subunit interfaces in a region in which the amino acid sequence is conserved in nAChRs. It is therefore highly likely that this is a binding site for allosteric modulators in nAChRs.



**Figure 1-5 Selection of allosteric nAChR ligands**

Finally, channel blockers, including phencyclidine,<sup>27</sup> amantidine,<sup>28</sup> QX222,<sup>29</sup> (Figure 1-5) are among the best characterised non-competitive ligands. These compounds sterically occlude the TM pore preventing ionic flux. The site at which these ligands bind within the TMD was first identified<sup>30</sup> by Giraudat *et al.* using radiolabeled [<sup>3</sup>H]chlorpromazine which was shown to compete with compounds previously established as channel blockers. Isotopic labeling studies suggest that the nonselective nAChR antagonist mecamylamine also binds at this site.<sup>31</sup>

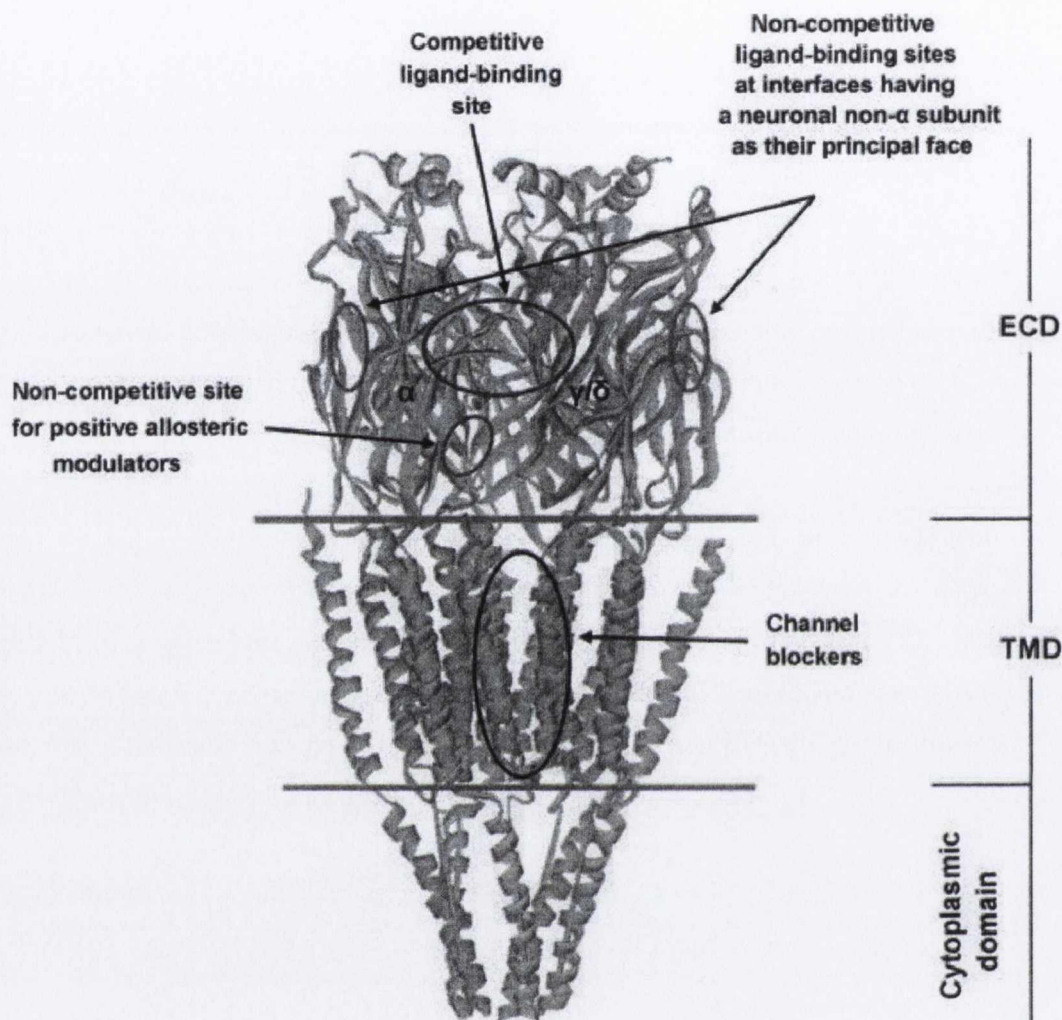


Figure 1-6 Binding sites in the nAChR (extract from Zouridakis, M.; Zisimopoulou, P.; Poulas, K.; Tzartos, S. J. *IUBMB Life* 2009, 61, 407-423)<sup>32</sup>

In 2005 Taly *et al.* elegantly modeled the gating mechanism of the ion channel computationally.<sup>33</sup> This group was the first to propose the quaternary twist mechanism which competently explains how the ion channel opens and closes. In a broader pharmacological sense, the currently accepted MWC model (originally proposed by Jacques Monod, Jeffries Wyman, and Jean-Pierre Changeux)<sup>18</sup> that describes channel opening in the nAChR has surprisingly changed very little since its proposal in 1965<sup>34, 35</sup> when only the crudest of biophysical data was available.



The latest extension to the model<sup>19</sup> applies this hypothesis to membrane bound proteins and is outlined below. It states that these receptors exist in different interchangeable states *in the absence of any regulator*. The ratio of the different conformational states is determined by thermal equilibrium and they are classified as active or open (A), resting or closed (R) and desensitised (either fast onset (I) or slow onset (D)). In reality, the regulators merely shift the equilibrium toward one state or another but phenomenologically, it appears as if the agonist *provokes* the conformational transition.

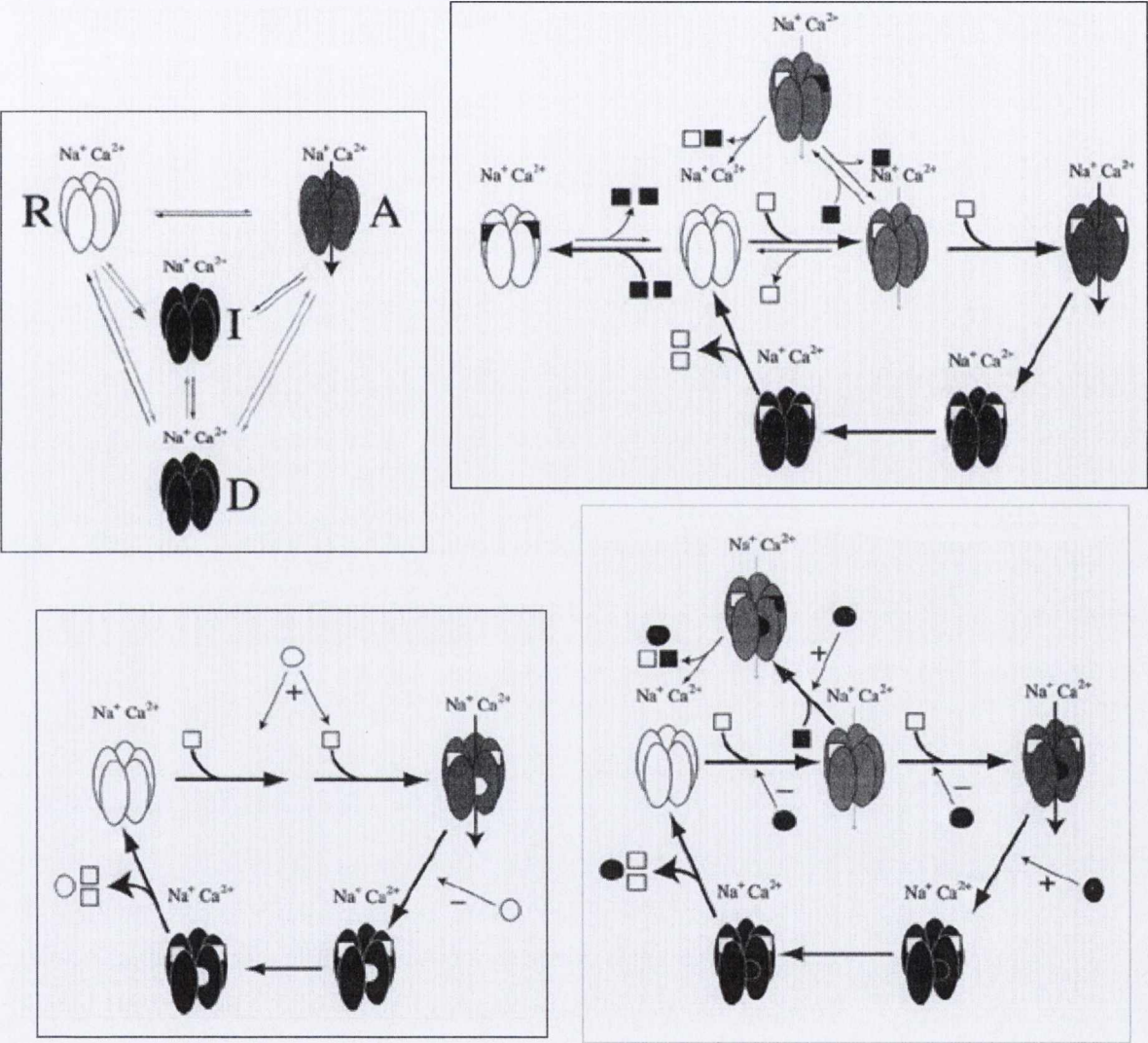


Figure 1-7 MWC model describing conformational change in nAChRs (extract from Jensen, A. A.; Frolund, B.; Liljefors, T.; Krogsgaard-Larsen, P. *J. Med. Chem.* 2005, 48, 4705-4745)<sup>36</sup>



In Figure 1-7 we can see the 3 distinct receptor states – white for resting, grey for active and black for desensitised. Predominant pathways are shown in black. Firstly, in the red box, nAChR behavior in the absence of a modulator is shown.<sup>37</sup> In the blue box, white and black squares represent agonist ligands and competitive antagonist ligands respectively. In the green box, the white circles represent positive allosteric modulators that can have two effects – either aiding agonist binding or inhibiting desensitisation of the active state. Finally in the yellow box, black circles represent negative modulators which can produce the opposite effects.

An interesting feature of nAChRs is the phenomenon of agonist-induced up-regulation of the receptor<sup>38</sup> that contrasts to the more traditional agonist-induced downregulation as seen with GPCRs. It is possible that this neuroadaptation is produced as a result of agonist induced desensitisation of nAChRs.

## 1.2 nAChR antagonist applications: addiction

### 1.2.1 Neurochemistry

What is addiction? It has been described as a primary chronic, neurobiological disease with genetic, psychosocial and environmental factors influencing its development and manifestations. It is characterised in the diagnostic and statistics manual of mental disorders (DSM IV) by behaviours that include one or more of the following; craving, impaired control, drug overuse, compulsive use or continuous use despite harm.<sup>39</sup> The obvious agents of concern include alcohol, nicotine, opiates and cocaine and amphetamine based stimulants. However, it is noteworthy that other non-substance related addictions, such as gambling, have also been documented.<sup>40</sup>

What do we know about the neurochemical processes of addiction in general? The mesolimbic pathway and mesocortical pathway are two major dopamine pathways that have been hypothesised to play a role in the biological mechanisms of addiction.<sup>41-43</sup> The mesolimbic pathway links the ventral tegmental area (VTA) to the nucleus accumbens (NAc) while the mesocortical pathway links the VTA to the prefrontal cortex (PFC). These pathways form the brain's reward circuitry. (Figure 1-8)

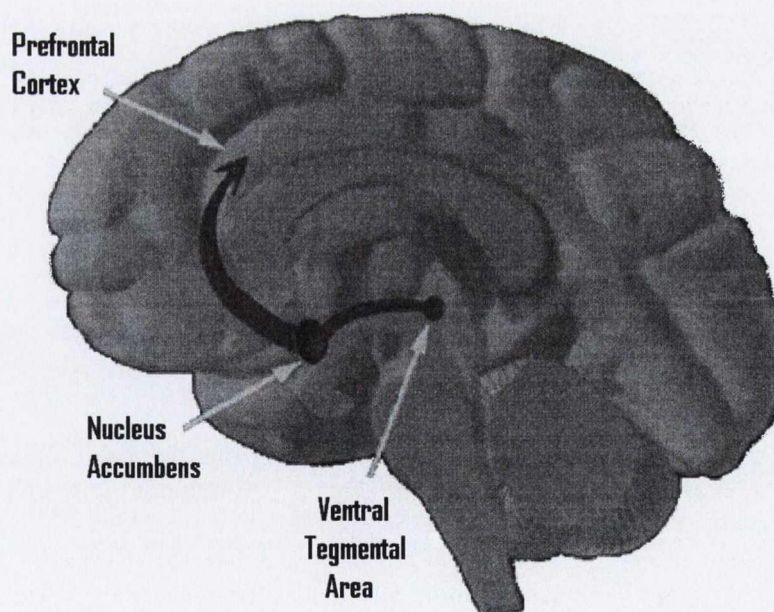


Figure 1-8 Reward circuitry of the human brain (extract from <http://www.nida.nih.gov>)<sup>44</sup>

In order to understand addiction on a neurobiological level, it is necessary to elucidate the mechanism of action of known addictive drugs. While the specific site or mechanism of action may differ, all known recreational drugs have the common effect that they increase levels of dopamine (DA) in the NAc resulting in pleasurable sensations.<sup>45</sup> This can occur directly or indirectly. It is worth noting however that it is not known how or why increased levels of DA cause this pleasurable response.

#### 1.2.1.1 Common recreational drugs and their effects

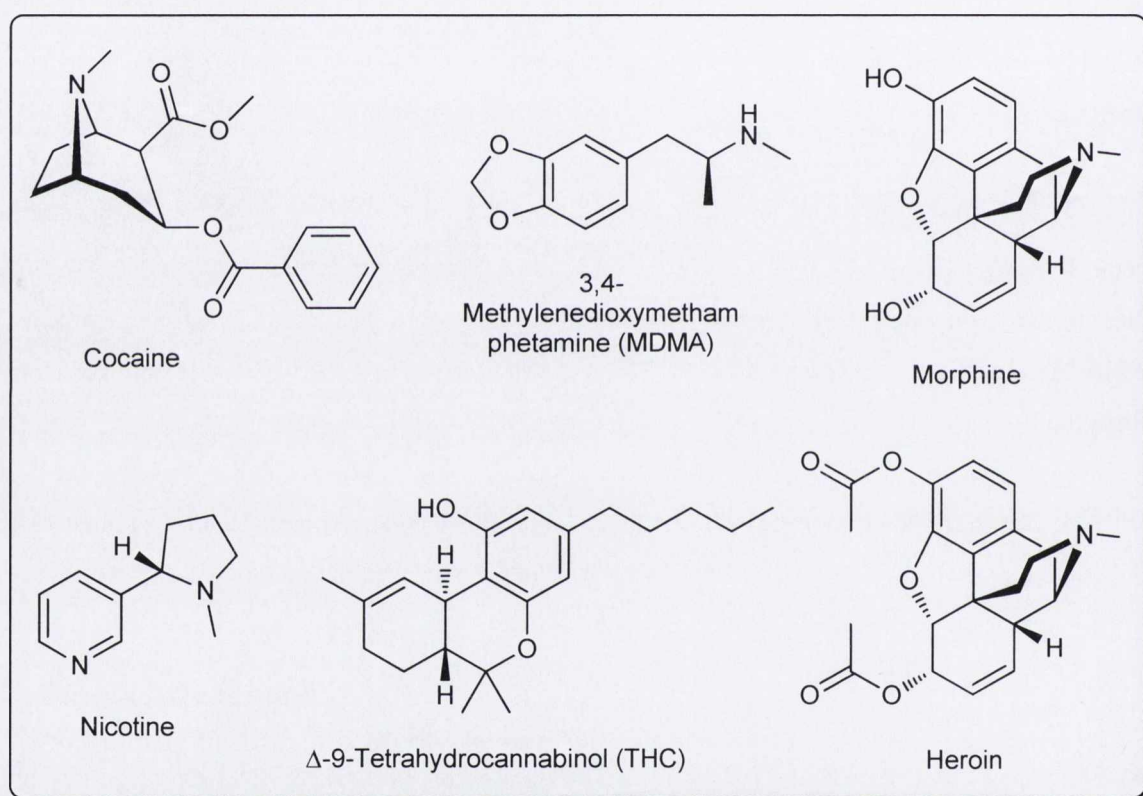
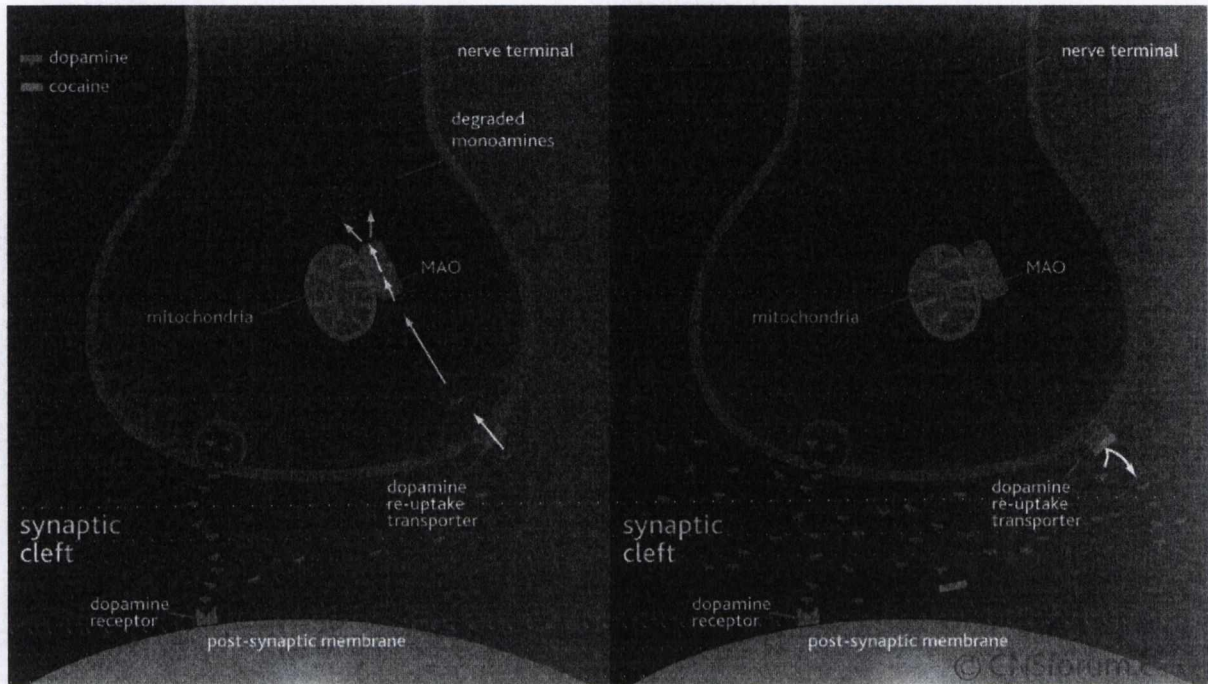


Figure 1-9 Common drugs of abuse

The process by which cocaine binds to the DA transporter protein, DAT1, is now very well understood.<sup>46, 47</sup> (Figure 1-10) DA released during neural signaling is normally recycled *via* DAT1. This transporter binds the neurotransmitter and pumps it out of the synaptic cleft back into the presynaptic neuron, where it is taken up into storage vesicles. Cocaine binds tightly to DAT1 forming a complex that blocks the transporter's function resulting in an



accumulation of DA in the synaptic cleft. It is the increased and prolonged levels of DA that are responsible for causing the pleasurable “high” associated with cocaine use.



**Figure 1-10 Action of cocaine on the dopamine transporter (extract from the image bank at [www.cnsforum.com](http://www.cnsforum.com))**

Heroin is a pro-drug for the systemic delivery of morphine. It is known that heroin, when taken orally, undergoes extensive first-pass metabolism *via* deacetylation.<sup>48</sup> When the drug is injected however, it avoids this first-pass effect, rapidly crossing the blood-brain barrier due to the presence of the acetyl groups, which render this compound much more lipid-soluble than morphine itself.<sup>49</sup> Morphine then binds presynaptically to  $\gamma$ -amino butyric acid (GABA) inhibitory neurons in the VTA and as a result, DA levels in the NAc become elevated. Morphine and cannabinoids also act directly on opioid receptors in the NAc.<sup>43, 50</sup>

As the only synthetically produced recreational drug shown in Figure 1-9, MDMA is generally produced for illicit trade racemically. It has been documented however that the S(+) enantiomer of MDMA shown in Figure 1-9 is more active than its R(-) antipode.<sup>51</sup> Amphetamines tend to be somewhat similar in structure to DA and have the ability to enter the pre-synaptic dopaminergic neuron, causing the release of endogenous DA intracellularly which is expelled *via* a DA transporter protein into the synaptic cleft. In addition, amphetamines can

bind to and inhibit monoamine oxidase (MAO), an enzyme involved in the degradation of DA. Lastly, amphetamines can bind to a DA reuptake transporter and cause it to act in reverse, pumping dopamine into the synaptic cleft.<sup>52-54</sup>

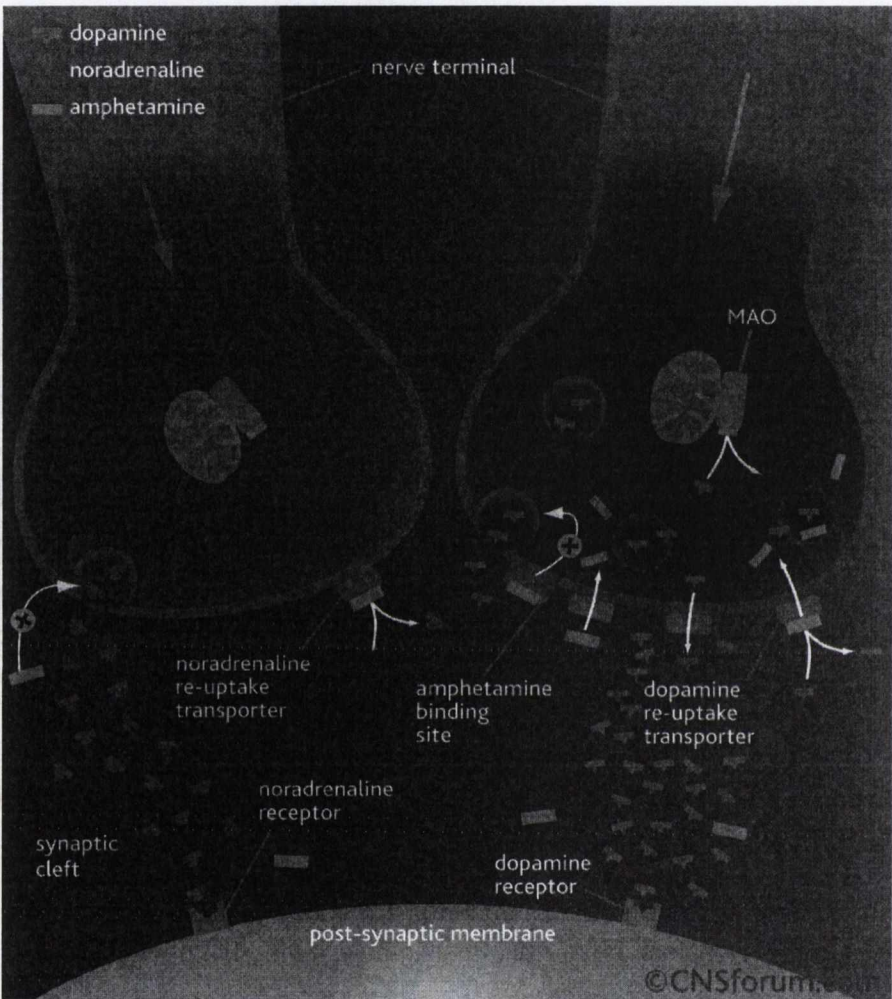


Figure 1-11 Biological action of amphetamines (extracted from the image bank at [www.cnsforum.com](http://www.cnsforum.com))

Nicotine activates VTA DA neurons directly *via* stimulation of nAChRs on those neurons and indirectly *via* stimulation of nAChRs on glutamatergic nerve terminals that innervate the DA cells.<sup>55</sup> Alcohol primarily acts as a positive allosteric modulator of GABA<sub>A</sub>, an inhibitory neurotransmitter.<sup>56</sup> It has been proposed that the action of alcohol on GABAergic transmission reduces the action of GABA in the VTA causing an increase in the release of DA in the NAc. Alcohol may also inhibit glutamatergic (excitatory neurotransmitter) terminals that



innervate NAc neurons eliciting widespread sensitisation to endogenous glutamate. A number of other neural substrates have been implicated in the action of alcohol on the human brain.<sup>57</sup> Figure 1-12 summarises these effects.

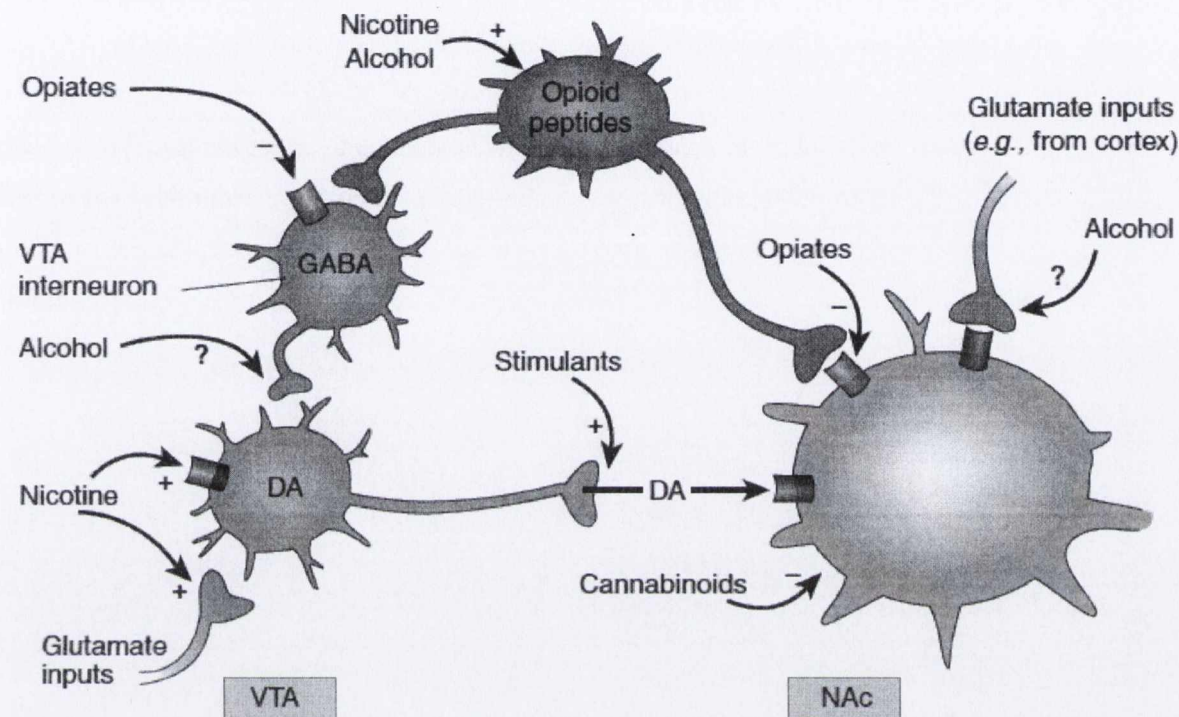


Figure 1-12 Common recreational drugs effecting a release of DA in the NAc (extract from Nestler, E. J. *Nat Neurosci* 2005, 8, 1445-1449)

### 1.2.1.2 Theories of addiction

Due to the fact that the mesolimbic pathway has been so heavily implicated in the reward process it is also thought to be vital in the addictive process.<sup>58</sup> This hypothesis has been tested by both the administration of DA antagonists or the formation of lesions in the NAc, both of which result in the attenuation of the rewarding effects of nicotine and other drugs of abuse.<sup>59, 60</sup> The hypothesis that dependence develops as a result of this recurrent drive for reward is known as positive reinforcement.<sup>61, 62</sup>

Unfortunately this is too simplistic a view to take with reference to addiction. It is a fact that the human body has a natural tendency to maintain homeostasis, and the central nervous



system is no exception. Chronic elevation of DA levels will eventually result in the down regulation of DA receptors producing less excitable post synaptic neurons. This reduced responsiveness of the brain's reward pathways contributes to anhedonia, an inability to feel pleasure.<sup>63</sup> There is then a requirement for an increased level of DA to maintain the same electrical activity and it is this requirement that is the basis of physiological tolerance.<sup>64</sup> At this stage, a decrease in the reinforcing properties of the drug is observed which means positive reinforcement does not provide a complete explanation for addiction.

It is known that long term drug use often results in aversive psychological and physiological effects if intake is withheld, thus resulting in continued use as a means to avoid the aversive consequences of drug withdrawal<sup>65</sup>. This theory is known as negative reinforcement. Increased heart rate and/or blood pressure, sweating and tremor are common signs of withdrawal. More serious symptoms include confusion, seizures, and visual hallucinations.<sup>66</sup>

Although positive and negative reinforcement theories provide insight into the initiation and maintenance of compulsive drug use respectively, they fail to account for other aspects of addiction. A relapse for example is the resumption of drug seeking and drug taking after a prolonged period of abstinence when acute withdrawal symptoms have long since dissipated.<sup>67</sup> Where is the driving force coming from in this case? There is no unifying theory of addiction which can account for all aspects of the disease. In some cases genetic factors<sup>68</sup> have been hypothesised to play a role but it is thought by many that complicated long-term neuroadaptations in the mesocorticolimbic system underlie the transition to drug dependence and cycles of relapse.

### **1.2.2 Nicotine addiction**

Nicotine addiction is the largest cause of preventable mortality on the planet. Although tobacco deaths rarely make headlines, it is estimated that tobacco kills one person every six seconds, mainly from cancer, heart disease, stroke and chronic obstructive pulmonary disease.<sup>69</sup> These medical conditions are all thought to arise as a result of the mode of administration - smoking. Some sources would suggest that we have made huge strides in combating tobacco related illness, at least in developed countries. In Britain in 2008 just 22% of men smoked,<sup>70</sup> compared with 65% in 1948.<sup>71</sup> While in the United States, the Centers for Disease Control and

Prevention (CDC) reported in 2009 that the death rate from lung cancer in men had fallen by 2% per year since 1999 and was no longer increasing in women.<sup>72</sup>

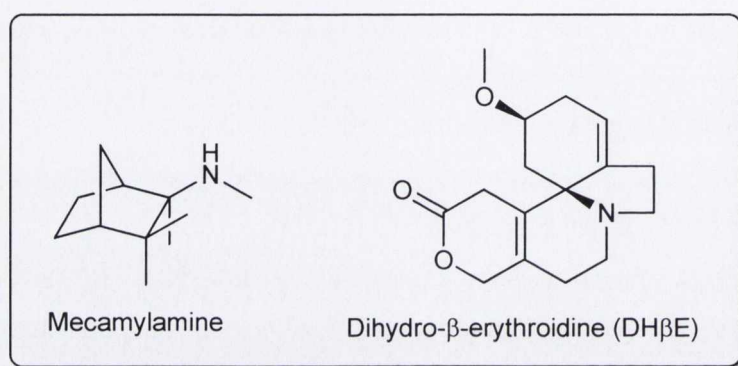
However, the trend of a decline in smoking in the West has not occurred elsewhere. 1.2 billion people (40% of men and 10% of women) are smokers.<sup>73</sup> In fact both the production and consumption of cigarettes in developing countries are increasing at a rate of approximately 1% per year.<sup>74</sup> A recent report by the World Health Organisation (WHO) warns that tobacco killed 100 million people in the 20<sup>th</sup> century and unless current trends are reversed tobacco will kill 1 billion people in the 21<sup>st</sup> century. It is currently estimated that 5.4 million people die annually worldwide as a result of tobacco related diseases and it is predicted to rise to over 8.3 million deaths per year by 2030.<sup>75</sup> Despite recent advances and new pharmacotherapies available relapse rate remain unacceptably high.<sup>76</sup>

Nicotine addiction is perhaps the most researched of all substance dependence cases and is believed to manifest itself solely by chronically elevating DA levels in the NAc. How exactly is this brought about? It has been shown that local injections of nicotine or other nAChR agonists into the VTA affect DA release in the NAc while direct injections of nicotine into the NAc produce a much lower response.<sup>77, 78</sup> This confirms that nAChRs in the VTA can clearly produce a downstream effect in the NAc. Nicotine or other nAChR agonists have also been shown to have an effect at GABA neurons.<sup>79</sup> The nAChRs that are associated with GABA neurons rapidly desensitise resulting in an overall excitation of the DA pathway due to the removal of the inhibitory effect of the GABA neurons on DA release. These effects occur on a sub-minute timescale. It has been shown that upon smoking, inhaled nicotine enters the brain within seconds, reaching maximal concentrations within 2 minutes.<sup>80, 81</sup>

A number of studies have directly implicated nAChRs as vital to the addictive process. It has been shown that Wistar rats pretreated with either the non specific nAChR antagonist MA, or the selective  $\alpha 4\beta 2$  antagonist DH $\beta$ E display a marked decrease in nicotine self administration tests.<sup>82</sup> Complementing this research is a study by Piciotto and co-workers which showed that nicotine self-administration and nicotine-elicited dopamine striatal release is abolished in  $\beta 2$  subunit knockout mice.<sup>83</sup> In a separate study Salas and co-workers showed  $\beta 4$ ,  $\alpha 2$  and  $\alpha 5$  subunit knockout mice displayed decreased signs of nicotine withdrawal symptoms.<sup>84, 85</sup> Jackson and co-workers attempted to differentiate between different types of withdrawal symptoms and found that  $\beta 2$  subunit knockout mice exhibit a loss of the affective signs while  $\alpha 5$  and  $\alpha 7$  knockout mice display a loss in some of the physical signs of nicotine



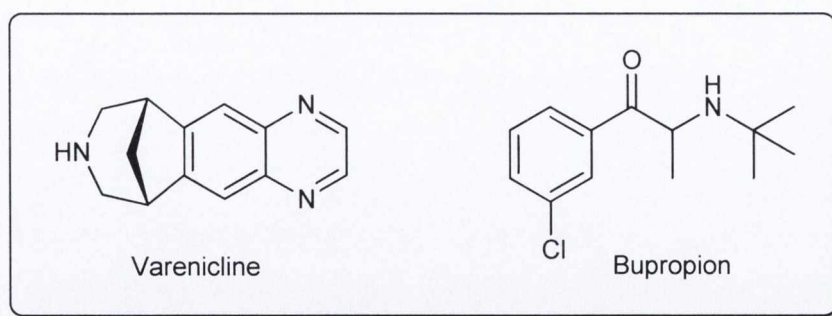
withdrawal.<sup>86</sup> In 2005, Maskos *et al.* documented an excellent study in which  $\beta 2$  knockout mice were injected with a lentiviral vector that re-expressed the  $\beta 2$  subunit selectively in the VTA. The behavior of these mice shifted from nicotine non self administrators to self administrators.<sup>87</sup> In 2007, Exley and co-workers reported that  $\alpha 6$  containing receptors seem to dominate the nicotine controlled release of DA in the NAc.<sup>88</sup> This would imply that these receptors, which up until now have received little attention, may play a central role in addiction.



**Figure 1-13 Nonselective nAChR antagonist, MA and  $\alpha 4\beta 2$  selective antagonist, DH $\beta$ E**

Unsurprisingly, a number of modulators of these receptors have been studied with a view to finding an effective treatment for nicotine addiction. The most notable example to date is varenicline.<sup>89</sup> Varenicline was approved by the FDA in May 2006 and launched in August 2006. It is sold by Pfizer under the trade name Chantix in the USA and Champix in Europe and other countries. It is a partial agonist at  $\alpha 4\beta 2$  nAChRs and a full agonist at  $\alpha 7$  nAChRs. Partial agonists are expected to exhibit a dual action by sufficiently stimulating  $\alpha 4\beta 2$  nAChR mediated dopamine release to reduce craving when quitting and by inhibiting nicotine reinforcement when smoking.<sup>90</sup>





**Figure 1-14 Clinical smoking cessation therapies: varenicline and bupropion**

The notion that a partial agonist would exhibit clinical efficacy initially came from a study by Rose and Levin<sup>91</sup> who showed that in initial small clinical trials using transdermal nicotine and oral MA, this combination achieved higher abstinence rates than did nicotine replacement therapy (NRT) alone.<sup>92</sup> However, the major practical challenge of maintaining a narrow agonist:antagonist ratio while administering two separate compounds with different pharmacokinetic and metabolic profiles remained.

In 1997 the FDA approved the use of bupropion, a compound initially marketed as an antidepressant under the trade name Wellbutrin, as a smoking cessation aid under the trade name Zyban sold by GlaxoSmithKline. Bupropion is a dopamine and norepinephrine reuptake inhibitor.<sup>93</sup> It also acts as an antagonist at  $\alpha 3\beta 4$  nAChRs.<sup>27</sup> These features allow bupropion to artificially increase DA levels thereby attenuating nicotine withdrawal symptoms while also antagonising nAChRs much like a partial agonist. Interestingly, Zyban is sold as a racemic mixture as the activities of the enantiomers were found to be the same.<sup>94</sup>

Two randomized, double-blind, placebo-controlled trials were conducted between June 2003 and April 2005 with a 12-week treatment period involving 1027 and 1025 patients to evaluate the smoking cessation therapeutics available on the market.<sup>95, 96</sup> The efficacy of varenicline was compared to bupropion and a placebo. The results of these studies are outlined in Table 1-1.

**Table 1-1: Performance of varenicline and bupropion in smoking cessation clinical trial**

| <i>1025 member trial group</i>                           | <b>Varenicline</b> | <b>Bupropion</b> | <b>Placebo</b> |
|----------------------------------------------------------|--------------------|------------------|----------------|
| <b>Abstinence rate after 12 weeks (% of trial group)</b> | 43.9               | 29.8             | 17.6           |
| <b>Abstinence rate after 24 weeks (% of trial group)</b> | 29.7               | 20.2             | 13.2           |
| <b>Abstinence rate after 52 weeks (% of trial group)</b> | 23.0               | 14.6             | 10.3           |
| <i>1027 member trial group</i>                           | <b>Varenicline</b> | <b>Bupropion</b> | <b>Placebo</b> |
| <b>Abstinence rate after 12 weeks (% of trial group)</b> | 44.0               | 29.5             | 17.7           |
| <b>Abstinence rate after 52 weeks (% of trial group)</b> | 21.9               | 16.1             | 8.4            |

What is immediately apparent is the fact that Varenicline is vastly superior to the placebo in these trials and also appears more effective than bupropion. These results need to be taken in context however. After continuous use of varenicline over a 12 week period the majority of subjects had not managed to quit smoking.<sup>97</sup> The considerable drop in continued abstinence between weeks 12 and 52 would indicate that there is more to treating nicotine addiction than the simple return to normal levels of receptor expression that is seen as traditional withdrawal. Simply put, varenicline is not the ‘cure’ that Pfizer currently attempt to market it as. These results are encouraging but surely more effective novel compounds will improve upon these results in the years to come. What these results do prove beyond doubt is that nAChR modulators can provide viable therapeutic options.



### 1.2.3 Other addictions

Unfortunately, reliable data on the illicit drug trade is not easy to obtain. If marijuana, heroin, LSD (*d*-lysergic acid diethylamide) and amphetamine use were legal, information on the number and types of user, trends in patterns of use, and the long term effects of the various drugs on users could be easily accessed, as it is for tobacco. Because use of these drugs is illegal we have statistics on arrests, convictions and quantities of drugs seized rather than statistics on the extent, frequency and quantity of drug use in the drug market. The official data that does exist paints a grim picture. The National Household Survey on Drug Abuse measures the prevalence, and attempts to correlate trends of drug use in the United States. In 2001, it found that approximately 3.1 million Americans (1.4%) 12 years and older had used heroin at least once in their lifetime.<sup>98</sup> In 2006, there were 91,000 persons aged 12 or older who had used heroin for the first time within the past 12 months.<sup>99</sup> This problem is clearly not being dealt with. According to the 2005 annual report of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), the number of people in Ireland being treated for cocaine-related problems is rising sharply. The report states that the number of treatment admittants citing cocaine as their main problem drug increased from 83 in 1998 to 308 in 2003 – a rise of 400%.<sup>100</sup> A report released on January 25<sup>th</sup> 2008 by the National Advisory Committee on Drugs (NACD) states that the percentage of people in Ireland who have taken cocaine at least once in their lives has increased from 3% in 2003 to 5% in 2008.<sup>101</sup> The most recent report from the EMCDDA outlines the prevalence of use for a number of illicit drug substances at least once in a European adult's lifetime.<sup>102</sup>



Table 1-2: Illicit drug use statistics from the 2009 EMCDDA annual report

|                                                        | Cannabis | Cocaine | Ecstasy | Amphetamines | Opioids |
|--------------------------------------------------------|----------|---------|---------|--------------|---------|
| Number of users<br>(millions)                          | 74       | 13      | 10      | 12           | 1.5     |
| Percentages of<br>European adults<br>(15-64 years old) | 22       | 3.9     | 3.1     | 3.5          | 0.5     |

As stated earlier in this section it is a commonly held belief that there is, at least to some extent, a common neurobiological process to all addictions regardless of the substance in question. This then poses the question can we treat different addiction types in the same way?

1.2.3.1 Ethanol

It has been known for some time now that, as for nicotine, direct injection of ethanol into the NAc does not result in DA release response.<sup>103</sup> However ethanol can activate nAChRs in the VTA and raise the level of DA in the NAc in much the same way as nicotine albeit to lesser extent.<sup>104</sup> A recent study by Kamens and co-workers has shown that nAChR  $\alpha 7$  subunit knockout mice do not consume ethanol to the same extent as their wild-type counterparts.<sup>105</sup> Interestingly, they found that deletion of the  $\beta 2$  subunit had no effect in this study when compared to wild type mice. Independently, Lof and co-workers found that the nAChR antagonists MA and  $\alpha$ -CtxMII were able to block the presentation of cue-induced alcohol cravings in mice.<sup>106</sup> These are cravings observed in response to an external cue such as an audio tone or light change, that an animal has been conditioned to associate with drug administration. A separate animal model known as “drinking in the dark” (DID) is used to study binge-drinking behavior in mice. In a study undertaken by Hendrickson and co-workers, MA was found to dose-dependently reduce ethanol consumption.<sup>107</sup>

This is all encouraging as it implies that nAChR modulators can play a role in combating ethanol addiction. Varenicline, having already received full FDA approval would be

an attractive compound to investigate in this regard. In 2007 Varenicline was employed in a study by Steensland and co-workers to investigate its effect in three different animal models of drinking.<sup>108</sup> In all three models they found that Varenicline had the ability to reduce ethanol consumption and ethanol seeking behavior.

Finally in 2009, McKee and co-workers carried out a study on human subjects.<sup>109</sup> This double-blind, placebo-controlled investigation examined the effect of varenicline on alcohol self-administration in twenty non-alcohol-dependent heavy drinkers who were daily smokers. Varenicline was administered for seven days before a 'priming' dose of alcohol was administered. A self-administration period immediately followed during which participants could choose to consume up to 8 additional drinks. On average, those treated with varenicline, consumed less than half the alcohol of that consumed by those in the placebo group. Although the study was carried out with a small group size, the results are certainly impressive and further research in this area is clearly warranted.

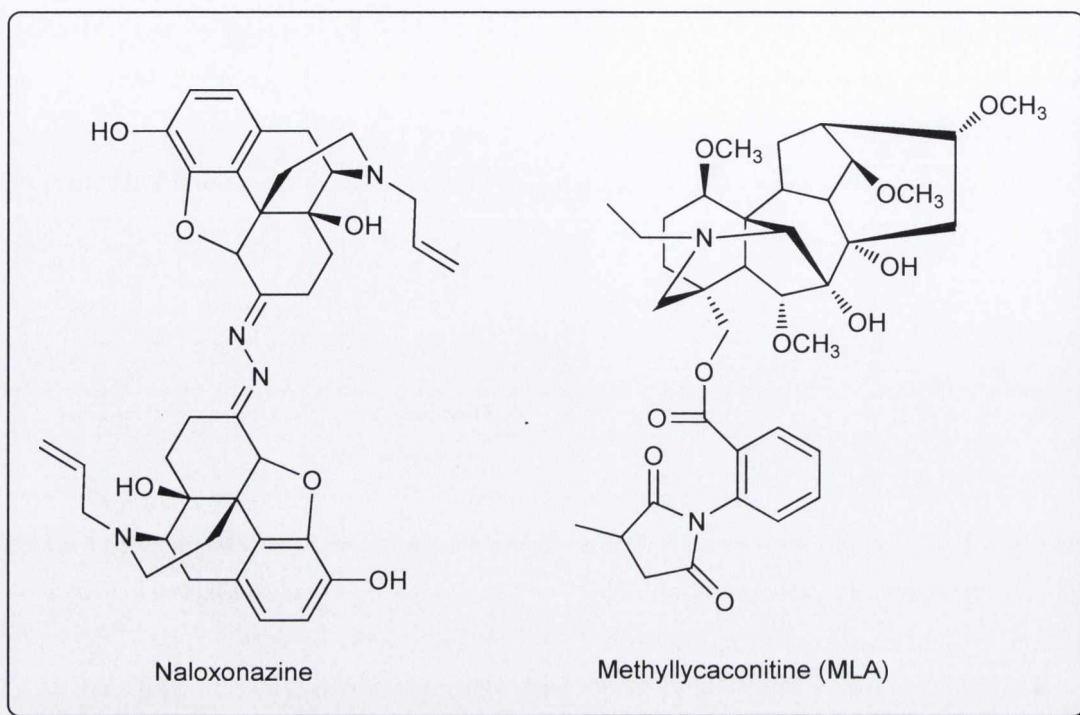
#### 1.2.3.2 Cocaine

The cocaine elicited increase of DA levels in the NAc is well documented.<sup>110, 111</sup> Unsurprisingly perhaps, nAChRs are again involved in the reward, reinforcement and addictive processes. This was elucidated by Zachariou and co-workers using the condition place preference paradigm in mice.<sup>112</sup> This research group was able to show that a two-fold increase in cocaine dosage was needed to condition a place preference when a low dose of MA was co-administered with the stimulant. A similar result was achieved if mice lacking the  $\beta 2$  subunit were employed in the test.<sup>112</sup>

Zanetti and co-workers have ascertained that both  $\alpha 7$  and  $\beta 2$  subunits are necessary to produce a cocaine elicited DA response.<sup>113</sup> They have shown that administration of MA with cocaine inhibits the normal DA release response in mice while administration of the selective  $\alpha 7$  subunit receptor antagonist methyllycaconitine (MLA) (Figure 1-15) does not. MLA does inhibit the cocaine elicited DA response in  $\beta 2$  subunit knockout mice which would seem to adequately validate their initial claim.

MA has also been shown to reduce self administration of cocaine but importantly not food in rats.<sup>114</sup> Perhaps more impressively, it has also been reported to reduce cue-induced cocaine cravings in human cocaine addicts.<sup>115</sup>





**Figure 1-15  $\mu$ 1 opioid receptor antagonist, naloxonazine and the  $\alpha$ 7 nicotinic acetylcholine receptor antagonist, methyllycaconitine (MLA)**

### 1.2.3.3 Cannabis, opioids and amphetamines

In 1997 a publication in *Science* by Tanda and co-workers suggested that a  $\mu$ 1 opioid receptor was responsible for the both cannabinoid elicited and heroin elicited release of DA in the NAc.<sup>50</sup> They were able to show that administration of the  $\mu$ 1 opioid receptor antagonist naloxonazine (Figure 1-15) was able to block the action of cannabinoids and heroin on DA transmission.

It has been shown however, by Solinas and co-workers that nAChRs also play a role.<sup>116</sup> Systemic administration of the selective  $\alpha$ 7 nicotinic acetylcholine receptor antagonist MLA, (Figure 1-15) but not the selective  $\alpha$ 4 $\beta$ 2 nAChR antagonist DH $\beta$ E, (Figure 1-13) produced a number of effects in rats including reduction in self administration of a cannabinoid CB1 receptor agonist and reduction in the THC-induced DA elevation in the shell of the NAc. It should be noted that these research findings are in no way mutually exclusive with those published a decade earlier.



Glick and co-workers reported in 2002 that a number of nAChR antagonists including MA were able to bring about a reduction in self administration of both morphine and amphetamines in rats.<sup>117</sup> They have proposed that it is the effect of these antagonists at  $\alpha 3\beta 4$  nAChRs that brings about this effect. Unfortunately there are no known antagonists that are highly selective for this receptor subtype which precludes absolute confirmation of their claim.

It can be seen through numerous pharmacological and genetic studies that neuronal nAChRs have a key role to play in each stage of the addiction process. These receptors have been heavily implicated in inducing the rewarding effects associated with recreational drug use, which aids reinforcement of these habits. Sensitisation and withdrawal are two other facets of this disease that also appear to be mediated largely by these widely dispersed multifunctional receptors. The nAChR modulators varenicline and bupropion that are currently marketed as smoking cessation treatments provide excellent proof of concept for a therapeutic agent with a similar pharmacological profile that could target a range of addictive disorders.

### 1.3 nAChR antagonist applications: depression

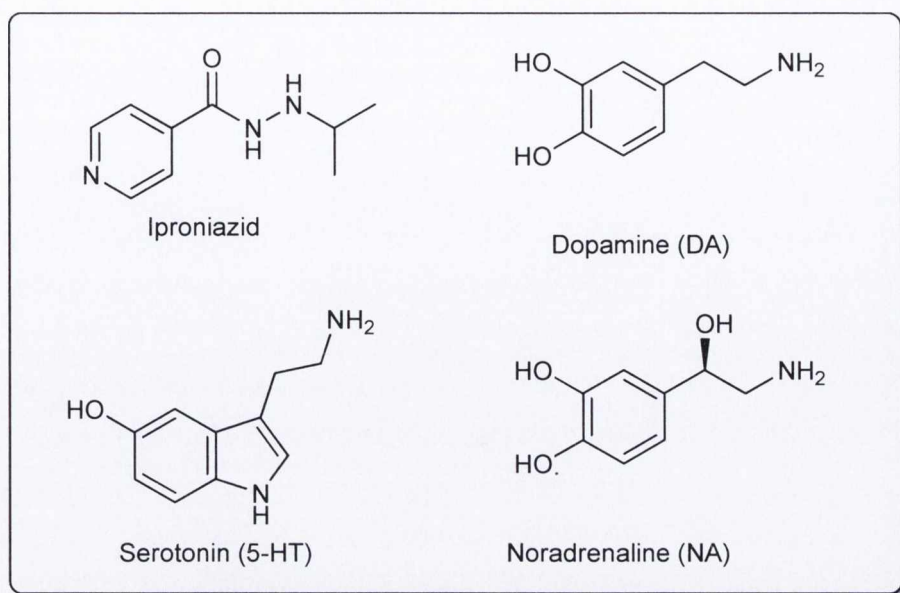
DSM IV has classified major depression as a mental disorder which can present many symptoms including an all-encompassing low mood accompanied by low self-esteem, loss of interest or pleasure in normally enjoyable activities, weight loss, insomnia, fatigue, diminished ability to think or concentrate or suicidal thoughts.<sup>39</sup>

Major depression is the leading cause of disability in the U.S. for ages 15-44.<sup>118</sup> It is a disease that affects approximately 14.8 million American adults, or about 6.7 percent of the U.S. population aged 18 and older in a given year.<sup>119</sup> Over the last 40 years, study after study has shown that major depressive disorder is the main attributable cause of more than half of all suicides.<sup>120-122</sup> Interestingly, in the U.S. major depression is approximately twice as prevalent in women compared to men but the suicide rate in women is approximately 25% of that in men.<sup>123, 124</sup> It has been documented that in Europe in 2004, at least 21 million adults were suffering with depression resulting in an estimated annual cost burden of 118 billion euro.<sup>125</sup> While it has been shown that major depressive disorder can develop at any age, the median age of onset is 32.<sup>126</sup>

#### 1.3.1 Monoamine hypothesis

Over half a century ago, antidepressants were discovered in a serendipitous manner. In 1954, it was observed that some treatments for tuberculosis were exerting a beneficial effect in patient's sense of well-being.<sup>127, 128</sup> These results lead to the discovery of iproniazid as the first antidepressant.<sup>129</sup> Soon after, a completely new approach to treating depression was exposed: the monoamine theory of depression or biogenic amine hypothesis.<sup>130-132</sup> In its contemporary formulation, the monoamine hypothesis postulates that a deficiency of certain neurotransmitters, namely serotonin (5-HT), noradrenaline (NA) and DA, is responsible for the corresponding features of depression. NA may be related to alertness and energy as well as anxiety, attention, and interest in life. A lack of serotonin is linked to anxiety, obsessions, and compulsions while DA is known to play a central role in attention, motivation, pleasure, and reward, as well as interest in life.<sup>133</sup>





**Figure 1-16 A selection of endogenous neurotransmitters and iproniazid, the first clinical anti-depressant**

For more than four decades, major depression has been treated with compounds that either inhibit monoamine reuptake or inhibit their metabolism. Unfortunately, it has been established that the tricyclic antidepressants and monoamine oxidase inhibitors have limited safety in overdose (deliberate or accidental) or are burdened with potentially fatal side-effect profiles that lead to frequent noncompliance.<sup>134, 135</sup> The newer selective serotonin reuptake inhibitors (SSRIs) and serotonin/noradrenaline reuptake inhibitors (SNRIs) are currently the most common treatment for major depression.<sup>136</sup> Although these compounds are safer in overdose and present a better side-effect profile, they lack efficacy in patients with extremely severe depression and some side effects are unavoidable. In particular they have been associated with high incidences of sexual dysfunction and nausea.<sup>137</sup>

While the monoamine deficiency hypothesis is the most commonly used explanation for the depressive state there is a considerable body of experimental evidence that is not explained by this concept.<sup>138</sup> Gjerris and co-workers have found that levels of 5-HT in the spinal fluid of unmedicated depressed patients to be elevated to 2-4 times normal levels.<sup>139</sup> Tryptophan hydroxylase is an enzyme involved in the synthesis of 5-HT. AGN2979 is an inhibitor of this enzyme and yet displays antidepressive properties in rodent models.<sup>140</sup> In addition, the potent centrally active monoamine reuptake inhibitor EXP561 was completely devoid of antidepressant activity in humans despite exceptional results in pre-clinical animal models.<sup>141, 142</sup> It should also be noted that a delay of approximately two weeks in therapeutic



effect is often observed with anti-depressants, especially SSRIs. It has been proposed that slow changes in neuroplasticity could in fact be directly responsible for observed anti-depressant effects.<sup>143</sup>

Perhaps the most interesting contradictions to this theory are the pharmacological profiles of some readily available antidepressants in clinical use. Tianeptine was originally developed by Survector and is marketed under a number of tradenames including Stablon, Coaxial and Tatinol. Tianeptine acts to induce neuroplastic changes that enhance the functional responsiveness of DA D<sub>2</sub> and D<sub>3</sub> receptors but surprisingly is also a potent selective serotonin reuptake enhancer (SSRE) working in the exact opposite way to traditional selective serotonin reuptake inhibitors (SSRIs).<sup>144</sup> Opipramol, which is marketed as Insidon, Pramolan, Ensidon and Oprimol, is a member of the tricyclic antidepressant family. Interestingly, it has been documented that opipramol possesses no reuptake inhibiting processes.<sup>145</sup>

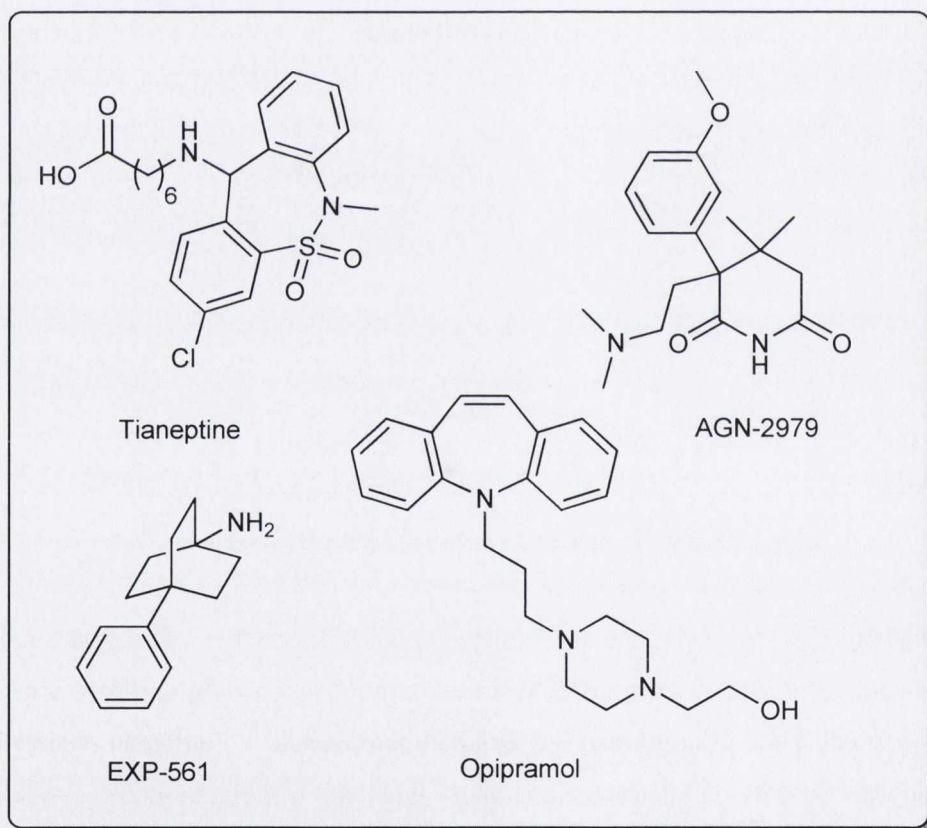


Figure 1-17 Clinically available anti-depressants that do not support the monoamine hypothesis

### 1.3.2 nAChRs and depression

It has become evident over the last 25 years that a function shared by many antidepressants is inhibition of nAChRs. Classic tricyclic antidepressants including imipramine (Antidepressin),<sup>146, 147</sup> nortriptyline (Sensoval), amitriptyline (Elavil),<sup>148, 149</sup> and desipramine (Norpramin)<sup>150</sup> as well as newer, more selective monoamine reuptake inhibitors including fluoxetine (Prozac),<sup>151</sup> sertraline (Zoloft), paroxetine (Seroxat), nefazodone (Serzone),<sup>152</sup> bupropion (Wellbutrin, Zyban),<sup>153</sup> nisooxetine, citalopram (Celexa), nomifensine (Merital),<sup>154</sup> and GBR-12909<sup>155</sup> are all active as nAChR antagonists. Generally, it has been found that the concentrations of antidepressants that inhibit nAChRs are consistently in the low micromolar range. While the prominent monoaminergic effects of these drugs occur at much lower concentrations, it has been argued that concentrations required to inhibit nAChRs are comparable to the antidepressant concentrations accumulated in the brain at about the time that these drugs become therapeutically active.<sup>156</sup>

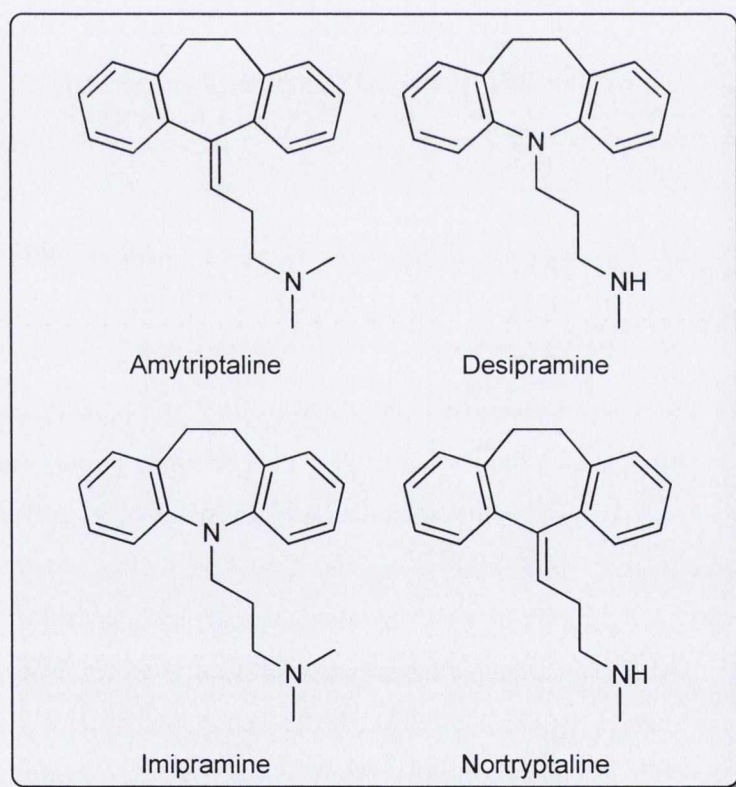
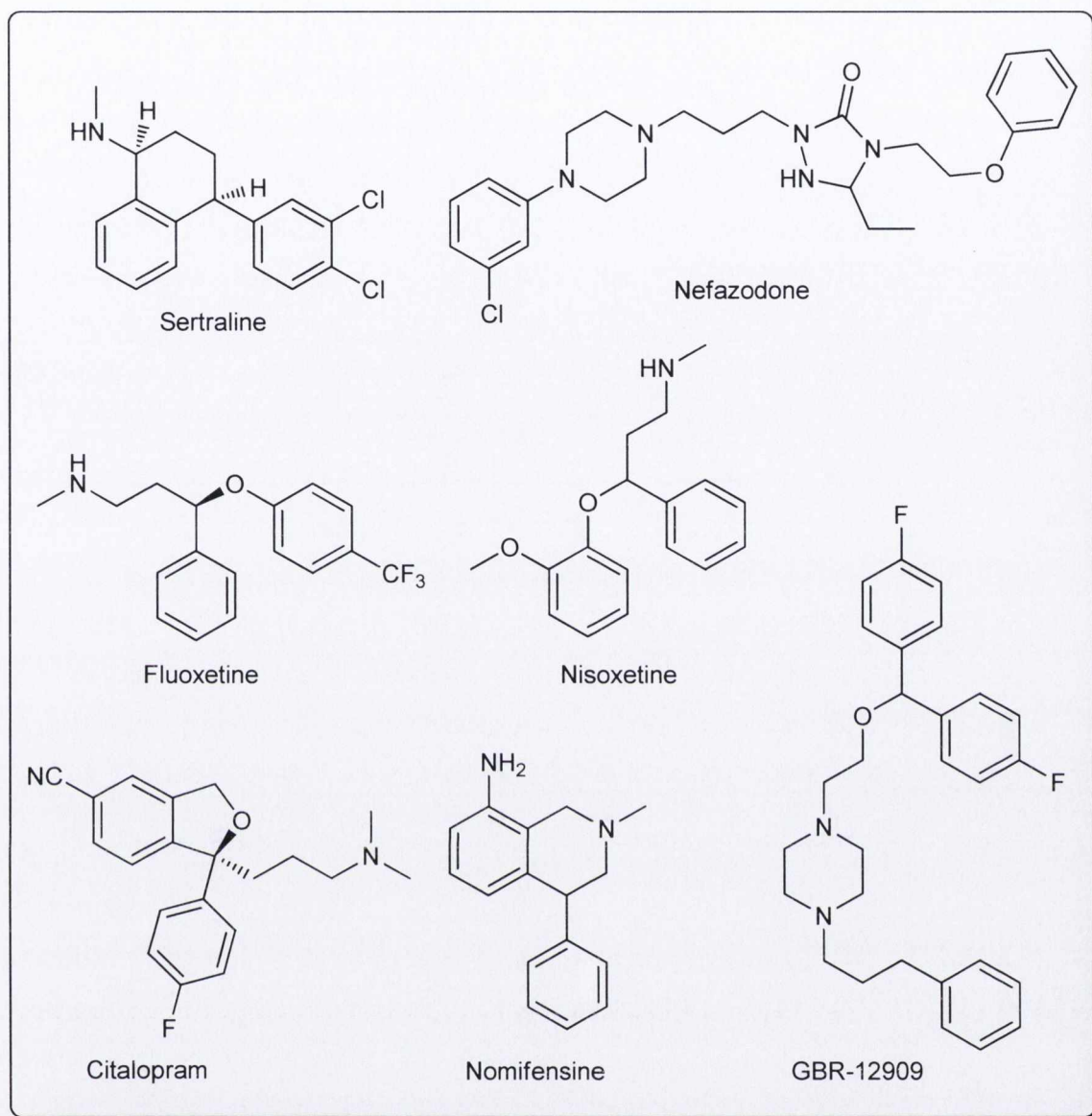


Figure 1-18 Classic tricyclic antidepressants that are known to act as nAChR antagonists

Many studies have highlighted a link between nicotine and depression. Epidemiological research carried out at the end of the 20<sup>th</sup> century found that the rate of smoking is much higher among depressed patients than among non-depressed individuals<sup>157</sup> and smokers are more likely than nonsmokers to experience depression in their lifetimes.<sup>158, 159</sup> Brown and co-workers report that smoking cessation often precipitates depression<sup>160</sup> while in a recent study, McClernon and co-workers have shown that transdermal nicotine patches improve mood in non-smoking depressed patients.<sup>161</sup> Taking these findings into account, it has been hypothesised that nicotine has antidepressant effects and that smoking is an attempt to self-medicate the depressive symptoms.<sup>162</sup>





**Figure 1-19 Selective monoamine reuptake inhibitors that also act as nAChR antagonists**

Indeed, antidepressant-like effects of acute nicotine treatment have been reported in rats<sup>163, 164</sup> and antidepressant-like properties of a number of nAChR agonists have been shown in the learned helplessness paradigm.<sup>165</sup> The learned helplessness paradigm, initially described by Seligman,<sup>166</sup> induces a pseudo-depressed “helpless” state and measures the effect of various stimuli or medication on this. It is the most widely used animal model for depression.<sup>167</sup> An extension of this paradigm is the forced swim test (FST).<sup>168, 169</sup> In this model, animals are subjected to two trials during which they are forced to swim in a cylinder filled with water from

which they cannot escape. The first trial lasts 15 minutes. After 24-hours, a second trial is performed that lasts 5 minutes. The time that the test animal spends without moving in the second trial is measured. This immobility time is decreased by antidepressants. Various nAChR agonists have also been shown to display antidepressant properties in the forced swim test in rats (rFST)<sup>170, 171</sup> and mice (mFST).<sup>172</sup> It should be noted however that the validity of the FST as a purely depressive model has been questioned. It has been argued that immobility during forced swimming reflects effects of learning and memory rather than effects of despair or depression or that immobility during forced swimming is not a failure of coping but instead reflects a relatively successful coping strategy that employs energy conserving behaviors.<sup>173</sup>

How can we reconcile this data with the fact that so many known antidepressants are antagonists at nAChRs and that it was reported in 1972 by Janowski and co-workers that increased cholinergic tone was associated with depressive symptoms in humans?<sup>174</sup>

The most obvious danger with comparing data from different model tests is the simple fact that these tests may display vastly different sensitivity to pharmacological manipulation. Another explanation for the contradictory effects of nicotine across rodent models is that nicotine leads to desensitisation and inactivation of nAChRs in addition to activation.<sup>175</sup> The balance between nAChR activation and desensitisation may differ with the mode of administration and genetic background and account for the differential effects of nicotine in these behavioral assays.<sup>176</sup>

In an attempt to overcome these limitations, Andreassen and co-workers carried out an excellent study in 2009.<sup>177</sup> They systematically characterised the effect of nicotinic agonists and antagonists in the same species, strain and sex, namely female, Naval Medical Research Institute (NMRI) mice, in the mFST and another well established depressive animal model test, the mouse tail suspension test (mTST).<sup>178</sup> Interestingly, they found that all centrally active nAChR antagonists tested showed antidepressant-like profiles, whereas the agonists were devoid of antidepressant-like effects. It should be noted however, that in the mFST there was a slight anti-depressive effect at the highest dose of nicotine. This can possibly be attributed to nAChR inactivation *via* desensitisation as discussed earlier. Andreassen and co-workers also attempted to quantify the level of anti-depressant efficacy induced and found that the nAChR antagonists tested (MLA, DH $\beta$ E and MA) produced effects comparable to two antidepressants currently in clinical use, namely the SSRI citalopram and the NRI reboxetine. In fact MA



outperformed both of these compounds along with all of the agonists and antagonists tested in this study.

The fact that MLA and DH $\beta$ E (Figure 1-20) were able to produce the desired effect when administered alone albeit to a lesser extent than MA shows that both  $\alpha 7$  and  $\alpha 4\beta 2$  nAChRs are involved in depression. This result confirmed earlier findings that the antidepressive effects of MA were attenuated in both  $\alpha 7$  and  $\beta 2$  nAChR subunit knockout mice.<sup>179</sup> I believe this data firmly implies that research into antagonism of central nAChRs could lead to novel antidepressant therapeutics.

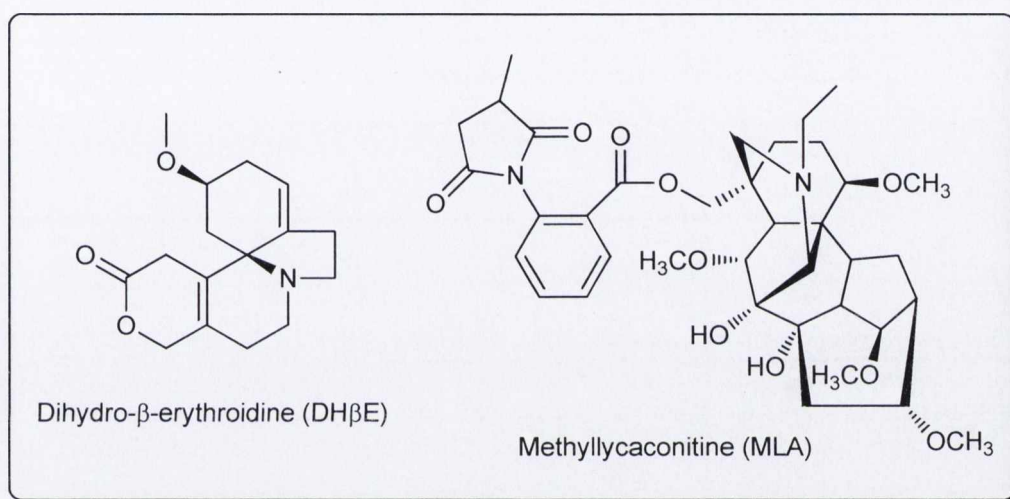


Figure 1-20 Selective nAChR ligands

### 1.3.3 nAChRs and Tourette's syndrome

There is an interesting parallel to consider to the involvement of nAChRs in depression which relates to Tourette's Syndrome (TS). Towards the end of the 20<sup>th</sup> century, a number of findings indicated that nicotine may be able to play a role in reducing the overt symptoms of TS.<sup>180, 181</sup> Discussion on the nature of the influence of nicotine on the disease was widespread and the familiar activation vs. desensitisation hypothesis was raised.<sup>182</sup> Sanberg and co-workers showed that MA produced a positive effect on TS symptoms in a clinical study on 13 human subjects<sup>183</sup> thereby proving antagonists and not agonists to be the therapeutic target of choice. Unfortunately a larger, follow-up, placebo controlled study indicated that MA itself would not



be successful as a monotherapy in the treatment on TS but nevertheless recommended further research in the area.<sup>184</sup>

## 1.4 nAChR agonist applications

It should come as no surprise that nAChRs are involved in many different neurological diseases given their distribution throughout the entire human brain. They have been implicated most heavily as already discussed in addiction and depression but their involvement in schizophrenia, Parkinson's, Alzheimer's, epilepsy and pain all warrant brief mention.

### 1.4.1 Alzheimer's

Alzheimer's (AD) is a CNS disease that was first described by a German psychiatrist, Alois Alzheimer, in 1906.<sup>185</sup> It is characterised by progressive cognitive decline, accompanied by a loss of neurons and synapses in the basal forebrain, cerebral cortex and hippocampus.<sup>186</sup> A substantial reduction in both muscarinic and nAChR expression has also been documented.<sup>187</sup> In 2006 the worldwide prevalence of AD was 26.6 million but by 2050 prevalence is expected to quadruple which will mean an unsettling 1 in 85 persons worldwide will be living with the disease.<sup>188</sup>

It has been shown that acute nicotine administration can improve the performance of AD patients in cognitive tasks.<sup>189</sup> Three dose strengths were employed in this study and only the medium strength dose produced the enhancement in cognition. The higher strength dose may have produced an overall inhibitory effect *via* desensitisation of the nAChRs. It would have been interesting to assess the effect of long-term nicotine exposure at the high dose strength in view of the agonist induced upregulation known to occur with nAChRs. Unfortunately this was not investigated. Complementing these findings however is the study carried out by Newhouse and co-workers in 1994 using healthy patients which shows that administration of MA can produce measurable and significant cognitive impairment similar to deficits seen in dementing illnesses, and that there is an age-related increase in sensitivity to nicotinic blockade.<sup>190</sup>

More recently, the  $\alpha 7$  nAChR subtype has been specifically implicated in learning and memory function.<sup>191, 192</sup> These attributes are obviously central to AD. It has also been shown that a loss of  $\alpha 7$  nAChRs in the hippocampus (an area known to be involved in memory) appears to correlate with advanced stages of this disease.<sup>193</sup> Given these findings it is

unsurprising that AR-R17779, a selective partial agonist at  $\alpha 7$  nAChRs improved scopolamine-induced deficits in social recognition and also improved the 24-hour memory retention interval in unimpaired animals. In addition, repeated doses of this compound were found to enhance long-term learning and memory.<sup>194</sup>

Research is ongoing in this area with a number of partial agonists targeted at AD currently in phase II clinical trials including SSR-180711,<sup>195</sup> developed by Sanofi-Aventis and AZD-0328, developed by AstraZeneca.<sup>196</sup>

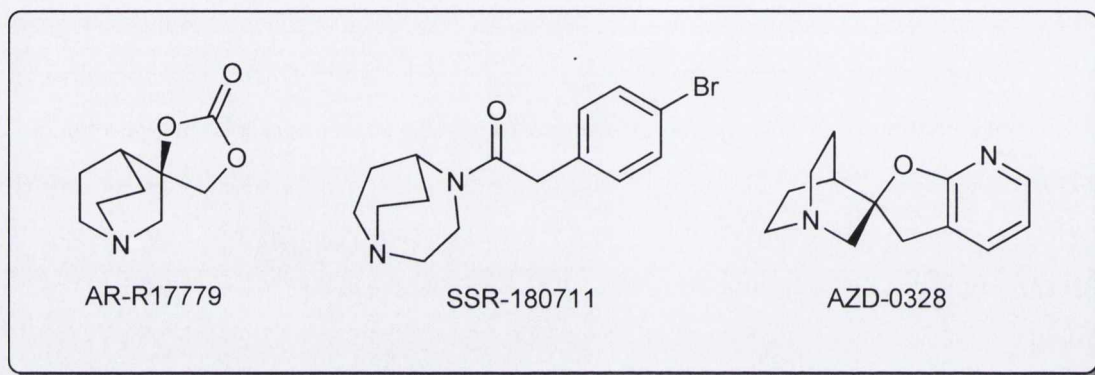


Figure 1-21 Potential nAChR agonist therapeutics for the treatment of Alzheimer's

### 1.4.2 Schizophrenia

DSM IV describes Schizophrenia as a mental disorder characterised by abnormalities in the perception or expression of an individual's reality. Common symptoms include hallucinations, delusions, disorganised speech, catatonic behavior, fatigue, or lack of emotion coupled with lack of interest or ability in social interaction.<sup>39</sup> The prevalence of schizophrenia is estimated at 0.4-0.6% although large variations from this were observed in different geographical regions.<sup>197, 198</sup> An interesting study ranging over two decades in the London district of Camberwell, found the incidence of schizophrenia in people of Afro-Caribbean origin to be between four and eight times that of their Caucasian counterparts.<sup>199</sup> The average age of onset in men is 18 and in women is 25.<sup>200</sup>

The more obvious symptoms of schizophrenia are clearly the unwanted hallucinations and delusions but cognitive symptoms such as the inability to focus attention often couple these.<sup>201</sup> In fact, this deficit is increasingly perceived as central to the disease as it pre-dates the



onset of the more overt psychotic symptoms.<sup>202</sup> Impaired attention and focus in schizophrenic patients is caused by defective sensory gating, which is known to be controlled by nAChRs.<sup>203,</sup><sup>204</sup> Further evidence to support this comes from two separate studies carried out by Adler and co-workers who have shown that both acute nicotine administration<sup>205</sup> as well as smoking cigarettes<sup>206</sup> transiently normalizes deficits in auditory sensory gating.

More recently a number of findings have specifically implicated  $\alpha 7$  nAChRs. A decrease in the density of  $\alpha 7$  nAChRs in the hippocampus of schizophrenic patients has been documented<sup>207</sup> while in animal models, inbred mice that possess lower levels of  $\alpha 7$  nAChRs have displayed poor sensory gating responses.<sup>208</sup> As such it is unsurprising that a number of compounds in clinical use that are known to possess agonistic ability at  $\alpha 7$  nAChRs have also produced inhibitory effects of schizophrenic symptoms. Clozapine is an antipsychotic that is usually only used for treatment resistant schizophrenia.<sup>209</sup> It has been shown to normalize auditory gating in mice *via* stimulation of  $\alpha 7$  nAChRs.<sup>210</sup> Tropicisetron is an anti-nausea medication, whose primary pharmacological profile is as a 5-HT<sub>3</sub> antagonist, also behaves as a partial agonist at  $\alpha 7$  nAChRs and has been shown to reduce the sensory gating deficit associated with schizophrenia.<sup>211</sup> GTS-21 is derived from an alkaloid found in marine worms that is a partial agonist at  $\alpha 7$  nAChRs. It has been shown to significantly improve memory and attention in a number of testing paradigms and also to reduce deficits in sensory gating and is currently undergoing phase II clinical trials.<sup>212</sup>

Finally, galantamine is an acetylcholinesterase inhibitor that also acts as a positive allosteric modulator at  $\alpha 7$  nAChRs.<sup>213</sup> A 2002 case study showed that co-administration of galantamine with a number of other anti-psychotics already being administered produced a marked improvement in the negative symptoms of schizophrenia. Moreover, discontinuation of galantamine produced remission and a return of all previous negative symptoms.<sup>214</sup>

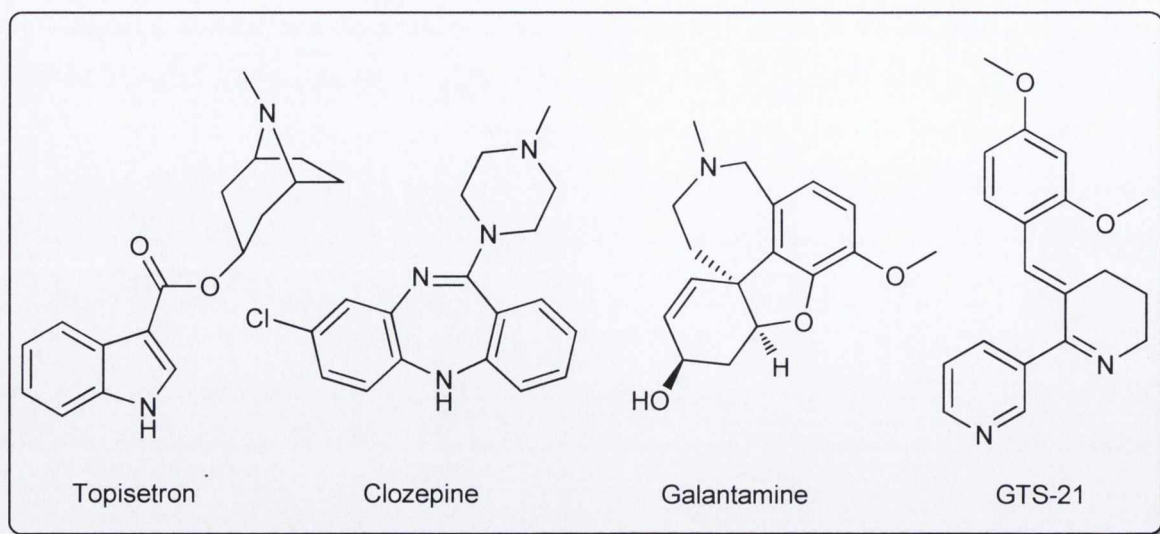


Figure 1-22 Potential nAChR agonist therapeutics for the treatment of schizophrenia

### 1.4.3 Parkinson's disease

Parkinson's disease (PD) is a common progressive bradykinetic disorder that is characterised by the presence of severe pars-compacta nigral cell loss, and accumulation of aggregated  $\alpha$ -synuclein in specific brain stem, spinal cord, and cortical regions.<sup>215</sup> The cardinal signs of PD as opposed to a number of other Parkinsonian-type disease are rest tremor, bradykinesia, rigidity and loss of postural reflexes.<sup>216</sup> PD affects 1-2% (depending on geographical region) of the global population over 60 years of age<sup>217, 218</sup> and the average age of onset is around 60 years of age.<sup>219</sup>

PD was first described by James Parkinson in 1817<sup>220</sup> although it was not until the 1960s that the discovery was made that dopamine concentrations are markedly decreased in the striatum of afflicted patients.<sup>221</sup> The central administration of L-Dopa, a prodrug of DA, was found to alleviate the akinesia associated with the disease<sup>222</sup> and within a few years an oral administration became available.<sup>223, 224</sup> Remarkably, L-Dopa is still the drug of choice used to combat the symptoms of PD today, although it is usually co-administered with L-Dopa decarboxylase inhibitors such as carbidopa<sup>225</sup> and benserazide.<sup>226</sup> These enzymatic inhibitors help to prevent the metabolism of L-Dopa before it can cross the blood brain barrier to reach the dopaminergic neurons. Catechol O-methyltransferase inhibitors such as entacapone can further prevent enzymatic degradation.<sup>227</sup>



While most therapeutics to date have focused on the dopaminergic system, the cholinergic system is also clearly involved in PD.<sup>228</sup> Acetylcholinesterase inhibitors like Donepezil<sup>229</sup> and Rivastigmine<sup>230</sup> have been FDA approved for use in Alzheimer's but have also been shown to exert positive effects in PD induced dementia.<sup>231, 232</sup>

It has been suggested that nAChRs may provide a novel therapeutic target. Nicotine has been shown to protect against degeneration in two separate PD model studies.<sup>233, 234</sup> In addition, Allam and co-workers have compiled a review which demonstrates the inverse association between smoking and PD.<sup>235</sup> Given that nAChRs can positively affect the cognitive aspects of PD and knowing that these receptors facilitate DA release being located presynaptically on mesolimbic and nigrostriatal DA neurons,<sup>55</sup> this might suggest an all encompassing treatment role for nAChR agonists, partial agonists or positive allosteric modulators. This is certainly an exciting prospect.

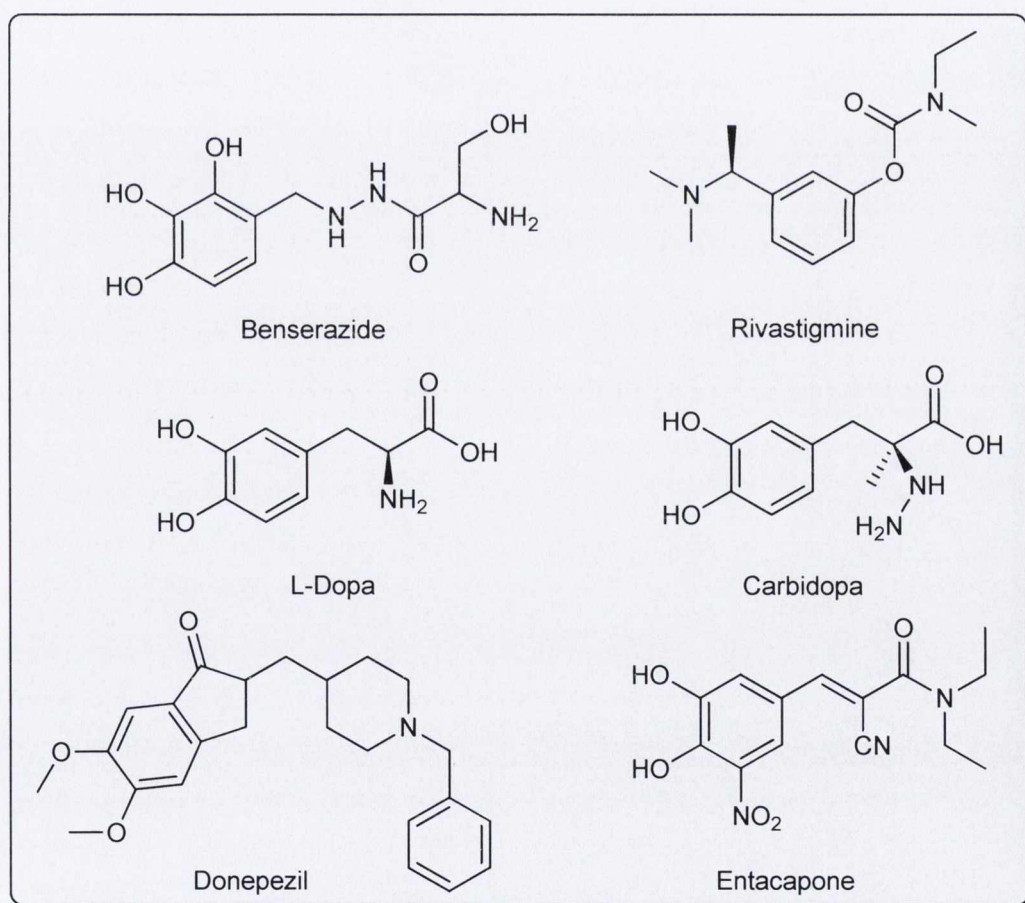


Figure 1-23 Potential nAChR agonist therapeutics for the treatment of Parkinson's



#### 1.4.4 Analgesia

Current pharmacological therapies for pain management come primarily from two classes of compounds, namely non-steroidal anti-inflammatory drugs (NSAIDs)<sup>236</sup> and opioids.<sup>237</sup> Unfortunately, the unavoidable addictive nature of opioids is well known<sup>238</sup> and the use of NSAIDs carries risks due to their extensive side effect profile.<sup>239</sup> The inhibition of COX-1 by NSAIDs is known to cause gastrointestinal problems<sup>240</sup> while the link between congestive heart failure (CHF) and NSAID use has also been demonstrated.<sup>241</sup> The search for an alternative to these therapeutic classes is of great interest to the pharmaceutical industry and it may be that nAChRs modulators can provide a solution.

The antinociceptive (pain reducing) effects of nicotine have long been documented.<sup>242</sup> In animal models,  $\alpha 4$  and  $\beta 2$  knock-out mice exhibit the reduction of nicotine-elicited antinociception.<sup>243</sup> Complementing this, a separate study has shown that  $\alpha 4$  hypersensitive knock-in mice exhibit hypersensitivity to nicotine in the hot-plate assay.<sup>244</sup> Great excitement greeted the discovery of epibatidine, a compound isolated from a small amphibian, *Epipedobates tricolor*, found in the Ecuadorian rainforest.<sup>245</sup> It was observed to have a dramatic antinociceptive effect in the hot plate and tail flick assays and appeared to be approximately 200 times more active than morphine.<sup>246</sup> Moreover, rather than acting at the opioid receptors, it emerged that this compound was acting at nAChRs as its antinociceptive effect could be blocked by the action of MA. It was also found that epibatidine was approximately 120 times more potent than nicotine in analgesic terms and more importantly produced a much longer duration of action.<sup>247</sup> Epibatidine itself is far too toxic to be used in clinical practice (it was one of the active ingredients used in a dart poison by the native Ecuadorian inhabitants) but it provides proof of concept for a potent nAChR agonist.<sup>248</sup> ABT-594 was the first nAChR ligand to undergo phase II clinical trials for analgesic activity. Despite promising early results, this compound could not be developed further due to adverse side effects, most commonly nausea.<sup>249</sup> Two other compounds, A-366833 and ABT-894 were later developed with improved selectivity for the  $\alpha 4\beta 2$  nAChR as it was believed the side effects associated with ABT-594 arose from its activity at ganglionic  $\alpha 3\beta 4$  nAChRs.<sup>250</sup> Unfortunately these compounds failed to perform well in clinical trials and were abandoned.

More recently antagonists at  $\alpha 9\alpha 10$  nicotinic acetylcholine receptors have received attention for their potential antinociceptive effects.<sup>251-253</sup> Increasing interest in this line of

research would indicate that a potential alternative to opioid and NSAID medication may be developed clinically in the near future.

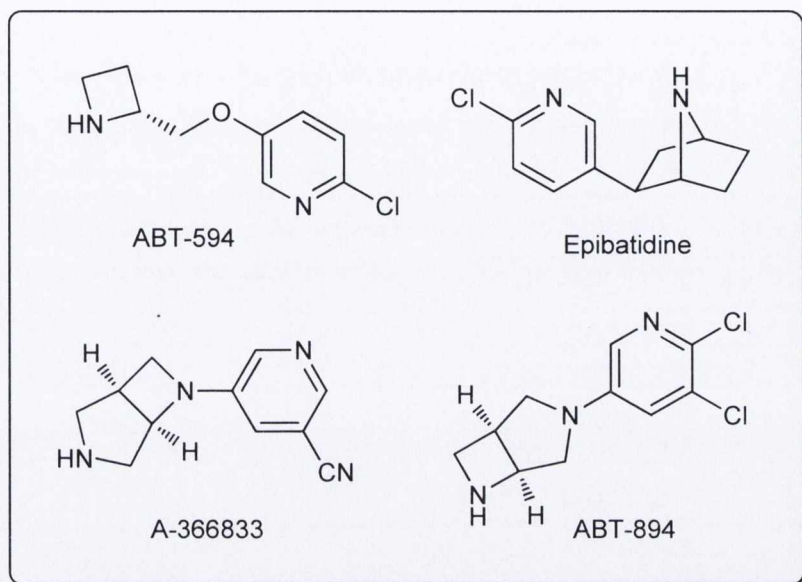


Figure 1-24 Potential nAChR agonist analgesic therapeutics



## 1.5 Mecamylamine

### 1.5.1 History

As can be seen from the work previously described nAChRs make an attractive target for a drug discovery investigation. Antagonists of these receptors could potentially find use as an anti-addictive therapeutic or antidepressant while an agonist could prove useful in the treatment of Parkinson's, Alzheimer's, Schizophrenia or as a novel analgesic.

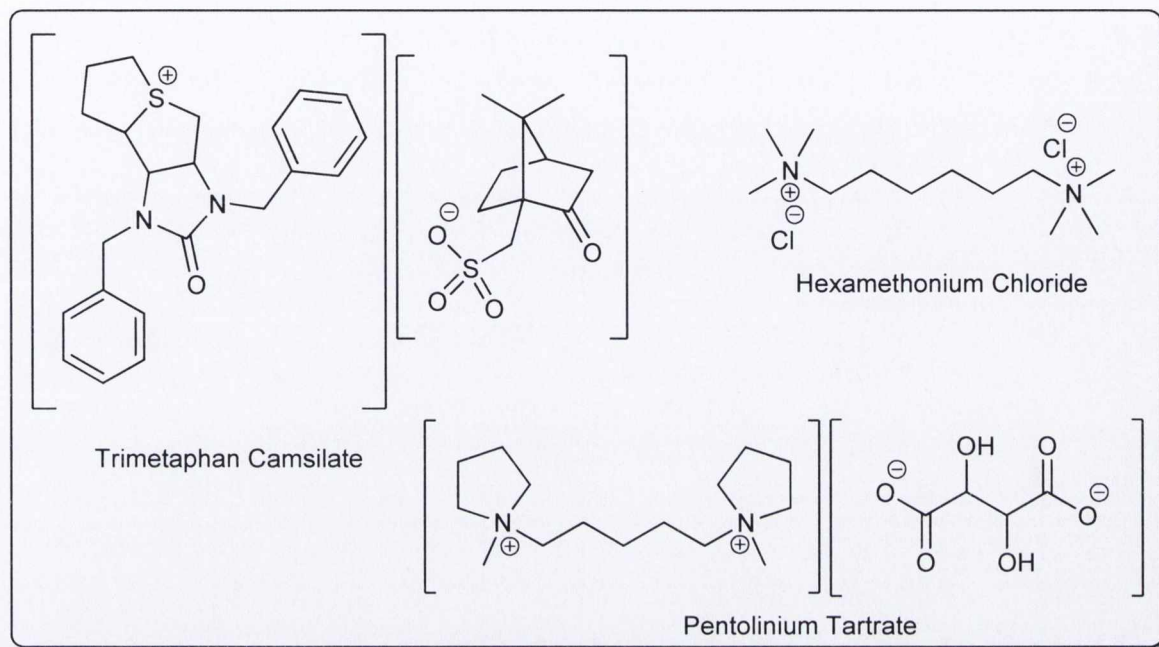
A compound that stimulated our interest was MA. This compound was previously employed as an anti-hypertensive but has subsequently been shown to possess other exciting properties, described below. MA was first introduced in the 1950s as an anti-hypertensive drug under the tradename Inversine.<sup>254</sup> It was the first useful ganglionic blocking agent that did not contain hypervalent heteroatoms.<sup>255</sup> This means that unlike trimetaphan, hexamethonium chloride and pentolinium tartrate (Figure 1-25) which are poorly absorbed from the gastrointestinal tract and do not cross the blood brain barrier, MA is readily absorbed and easily crosses the blood brain barrier where it acts as a non-specific nAChR antagonist at an allosteric site.<sup>256, 257</sup>

MA has a long standing history of wide clinical use. Between 1954 and 1984, Merck distributed both 10 mg and 2.5 mg tablets for the treatment of hypertension. The 10-mg tablet was discontinued in March 1984. Unfortunately, MA distribution statistics are not available for the period of greatest drug usage as an antihypertensive agent (1954 to 1960). However, from 1961 until 1996, Merck distributed approximately 41.5 million and 7 million of the 2.5 mg and 10 mg tablets, respectively.<sup>258</sup> In 1996 Merck sold the Inversine label to Layton Bioscience and in 2002 it was purchased by Targacept. Inversine was on sale in the US until September 2009, when it was discontinued due to declining sales.<sup>259</sup>

This widespread clinical use of MA surpasses the requirement of phase IV clinical trials. For instance, it is known that MA does not inhibit the hERG ion channel that contributes to the electrical activity of the heart, an important 'antitarget' for all drug development studies. In addition MA is known to be sufficiently resistant to metabolism by the cytochrome P450 superfamily to allow excellent bioavailability. While it cannot be guaranteed that a structural analogue of MA will retain these druglike qualities to the same extent as the parent compound,



it does suggest that a close analogue will display a somewhat similar positive pharmacokinetic profile.



**Figure 1-25 Traditional ganglionic blocking agents**

### 1.5.2 Potential therapeutic uses

In addition to the extensive use of MA in humans and its excellent bioavailability, MA has been mentioned many times in the discussion on the applications of nAChR modulators and it is deemed appropriate to collate those instances here.

- The combination of MA and NRT produces better abstinence rates for smoking cessation in human clinical trials than NRT alone.<sup>92</sup>
- MA reduces cue-induced cocaine cravings in humans.<sup>115</sup>
- Wistar rats pretreated with MA display marked reductions in nicotine self administration tests.<sup>82</sup>
- MA blocks the presentation of cue-induced alcohol cravings in mice.<sup>106</sup>

- MA dose-dependently reduces ethanol consumption in a binge-drinking model for mice.<sup>107</sup>
- Co-administration of MA with cocaine inhibits the normal DA release response in mice.<sup>113</sup>
- A two-fold increase in the cocaine dosage administered to mice was needed to condition a place preference when a small dose of MA was co-administered with the stimulant.<sup>112</sup>
- MA produces a reduction in self administration of cocaine in rats.<sup>114</sup>
- MA produces a reduction in self administration of both morphine and amphetamines in rats.<sup>117</sup>
- MA outperforms two clinically used anti-depressants, namely citalopram (Celexa) and riboxetin (Edronax) in two well established animal anti-depression models.<sup>177</sup>
- The antidepressive effects of MA were attenuated in  $\alpha 7$  and  $\beta 2$  knock-out mice.<sup>179</sup>

In addition:

- In a small human clinical study, MA produced a positive effect on TS symptoms.<sup>183</sup>
- In a specific case study involving two patients suffering with co-morbid bipolar disorder, MA produced a positive mood stabilising effect.<sup>260</sup>
- MA also displays anti-seizure effects in mice.<sup>261</sup>

MA clearly has extensive therapeutic potential as an anti-addictive or anti-depressive agent but is unfortunately hindered by unwanted side effects including constipation, urinary retention, dryness of the mouth and skin and loss of visual accommodation in some patients.<sup>262</sup> It is thought that these ganglionic side effects are brought about by the non-specific nature of this compound and that a structural analogue may target a neuronal subtype of this receptor specifically, thereby producing only the desired anti-addictive or anti-depressive effect.



### 1.5.3 Structure activity relationship studies

Despite the long standing interest in MA as a drug, receptor pharmacology workhorse and potential anti-addictive or anti-depressant agent, remarkably few SAR studies have been performed. Initially only non-specific studies were carried out as the existence of nAChR subtypes was not yet known. These investigations were simple *in vivo* studies such as that carried out by Stone *et al*<sup>263</sup>, in which the compounds that were synthesised were tested for their ability to protect against convulsions in mice induced by a standard nicotine injection. Analysis of the effects of compounds on the different neuronal subtypes has only become possible recently.

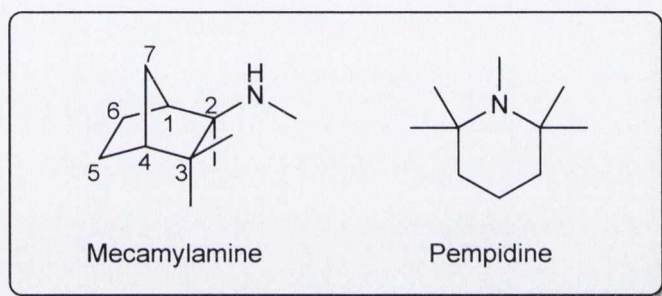


Figure 1-26 MA and pempidine

In 1960, Corne and co-workers proposed the importance of alkyl substitution around the amine moiety.<sup>264</sup> A total of four structural isomers of MA were prepared lacking substitution at either or both of the 2- and 3- positions and the activity of these compounds when tested on pre-ganglionically stimulated nictitating membrane was only 4 to 7% of that of hexamethonium. They also investigated a newly discovered closely related structure known to possess ganglionic blocking activity, pempidine.<sup>265</sup> (Figure 1-26) Intensive research into pempidine revealed that it exhibited approximately twice the antagonistic activity of MA at neuromuscular junctions and it was this fact that precluded pempidine becoming the pharmacological ‘workhorse’ that MA has been over the last 50 years.<sup>266, 267</sup>

In 1962 a much more extensive study was carried out by Stone *et al*.<sup>263</sup> Evaluation of the compounds synthesised in this study was performed by measuring the ability of a compound to protect against nicotine induced convulsions in mice, for its ability to dilate the pupils of the mice and for its ability to diminish the contractions of the cat nictitating



membrane induced by both pre- and post-ganglionic nerve stimulation. This produced a number of interesting findings:

Amine alkylation – MA and its dimethyl amino analogue proved to be the most active members of 15 isomers synthesised. Increased steric bulk produced a drop in activity. The greatest drop in activity was observed when branched alkyl groups, cyclohexyl, benzyl, phenylethyl and phenylpropyl were appended to the nitrogen.

Alkyl substitution at position 2 and 3 – the earlier work of Corne and co-workers was validated through the testing of a larger series of analogues. Compounds lacking alkyl substitution at positions 2 and 3 displayed lower activity. However as the length of the alkyl chain inserted at the 2- position increased, this produced a corresponding decrease in antagonistic activity. Increasing the length of the alkyl substitution at position 3 was not investigated.

Methylene bridge – a number of analogues were also synthesised lacking the methylene bridgehead. These compounds displayed vastly reduced activity.

Geometrical isomerism – the *endo* and *exo* (with respect to the amine functionality) analogue pairs **1-4** shown in Figure 1-27 were synthesised. In each case the *exo* isomer proved to be the more active compound. Unfortunately, the most active compounds, MA and its dimethyl amino analogue could not be synthesised in an *endo* configuration.

Optical isomerism – the *d*- optical isomer of MA was isolated and displayed activity approximately equal to that of the racemic mixture.

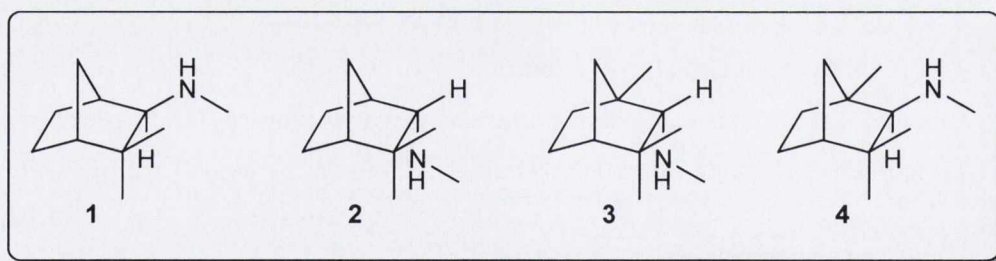


Figure 1-27 *exo* and *endo* analogue pairs synthesised by Stone *et al*<sup>263</sup>.

In 1970 Wragg and co-workers verified that the bridgehead methylene group was required for activity by synthesising a number of analogues lacking this structural feature, none of which displayed activity higher than one tenth that of MA.<sup>268</sup>

In 1971 Herr and co-workers used a microbial oxidation protocol employing *Sporotrichum sulfurescens* in a fermentation process with *N*-benzoylmecamylamine.<sup>269</sup> This

produced a mixture of products from which a number of useful compounds were isolated. This allowed the group to synthesise the MA analogues shown. (Figure 1-28) The activity of these compounds was assessed by measuring their ability to lower the blood pressure of renal hypertensive (Goldblatt) rats.

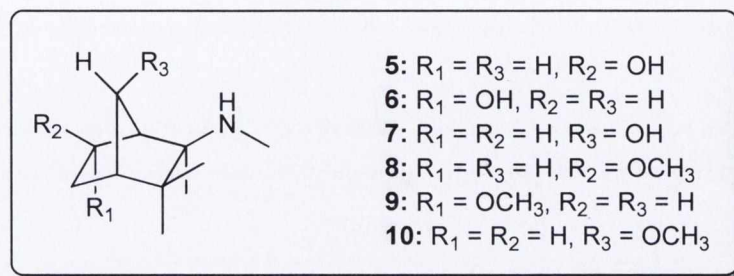


Figure 1-28 Extract from M. E. Herr, H. C. Murray and G. S. Fonken, *J Med Chem*, 1971, 14, 842-845.

Interestingly, they found that compounds **8**, **9** and **10** all displayed similar anti-hypertensive activity to the parent compound.

May and colleagues published the most comprehensive SAR study on MA to date in 1991.<sup>270</sup> However, despite synthesising a large number of novel analogues they succeeded mainly in reproducing the earlier SAR conclusions. However, two particularly noteworthy findings were documented. They investigated the effect of incorporating a phenyl group at position 3 by testing compound **11** (Figure 1-29) which surprisingly proved to be an agonist. This is particularly encouraging as it suggests that subtle changes to the structure of MA can switch its modulatory effect from negative to positive. This is an exciting prospect considering the many applications of nAChR agonists outlined in Section 1.3. They also tested the compound **12** structurally similar to *endo*-MA **13** which proved to be only slightly less potent than MA. Their attempts to synthesise *endo*-MA itself were unsuccessful. The activity of these compounds was assessed by measuring their ability to antagonise the effect of nicotine to decrease spontaneous activity and the antinociceptive effect of nicotine in mice.



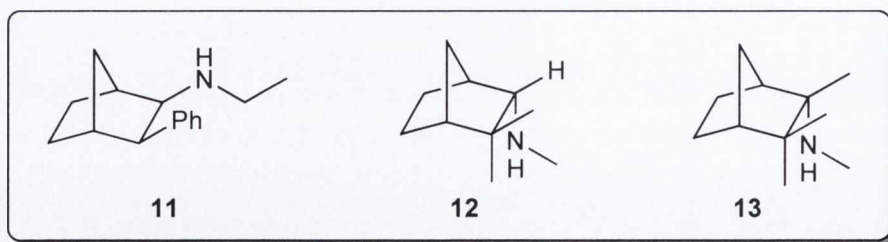


Figure 1-29 Fencamphamine 11, a lower homologue of *endo*-MA 12 and *endo*-MA 13

In addition, separation of the enantiomers of MA *via* resolution using *S*-(+)-10-camphorsulfonic acid was achieved and analysis showed that both enantiomers displayed similar activity. The biological test results obtained also added weight to the conclusion drawn by Stolerman<sup>271</sup> that MA exerts its effects through noncompetitive antagonism.

Towards the end of the 1980s and early 1990s characterisation of the subtypes of the nAChRs became possible<sup>272</sup> which paved the way for cloning specific subtypes for biological testing.<sup>273</sup> In 2001 Papke and co-workers carried out an excellent study on the effects of MA on human nAChR subtypes.<sup>274</sup> They tested both enantiomers of MA and the racemate as inhibitors of human  $\alpha 3\beta 4$ ,  $\alpha 3\beta 2$ ,  $\alpha 7$ , and  $\alpha 4\beta 2$  nAChRs, as well as mouse adult type muscle  $\alpha 1\beta 1\delta \epsilon$  nAChRs.

Table 1-3 IC<sub>50</sub> values for MA and its enantiomers at nAChR subtypes

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

This work was able to show that the selectivity of MA for neuronal type nAChRs over muscle type nAChRs is based largely on the fact that dissociation from the receptor once the antagonist is bound occurs much more rapidly in the case of muscle type nAChRs. More specifically they found that *S*-(+)-MA dissociated more slowly from neuronal nAChRs when compared to its enantiomer. Furthermore it was found that muscle-type receptors appeared to



be somewhat more sensitive to *R*-(-)-MA. Together these findings clearly indicate that *S*-(+)-MA is the more promising potential therapeutic agent. To date no extensive study has been carried out testing a range of MA analogues for activity on the variety of nAChR subtypes now available.

#### 1.5.4 Recent developments

In the last few years research into the identification of potent, but more importantly selective nAChR ligands has intensified and a number of research groups are looking to the past for inspiration. 2,2,6,6-tetramethylpiperidin-4-yl-heptanoate (TMPH)<sup>275, 276</sup> is a pempidine analogue while tinuvin 770 (BTMPS)<sup>277, 278</sup> shares strong structural similarities with a pempidine dimer. (Figure 1-30) Both display selective central nAChR antagonism. In 2007 a series of epibatidine analogues were synthesised by Bunelle and co-workers and found that both enantiomers of **14** shown in Figure 1-30 exhibited potency and toxicity comparable to the parent compound.<sup>279</sup> Dr. Peter Crooks at the University of Kentucky has contributed greatly to this area. Also in 2007, Crooks and co-workers reported the synthesis of N,N-dodecane-1,12-diyl-bis-3-picolinium dibromide (bPiDDB), a novel nAChR antagonist inspired by hexamethonium and displaying almost equipotent efficacy with MA for the inhibition of nicotine elicited DA release as evidenced by *in-vivo* microdialysis studies.<sup>280</sup> It is only recently however that MA has been readdressed from a medicinal chemistry perspective. In early 2010 Crooks and colleagues synthesised a number of MA dimers and trimers and reported tMecBPY as their most active compound,<sup>281</sup> (Figure 1-30) an interesting finding considering that previous SAR studies indicated that increased *N*-alkyl substitution brought about a reduction in antagonistic activity.

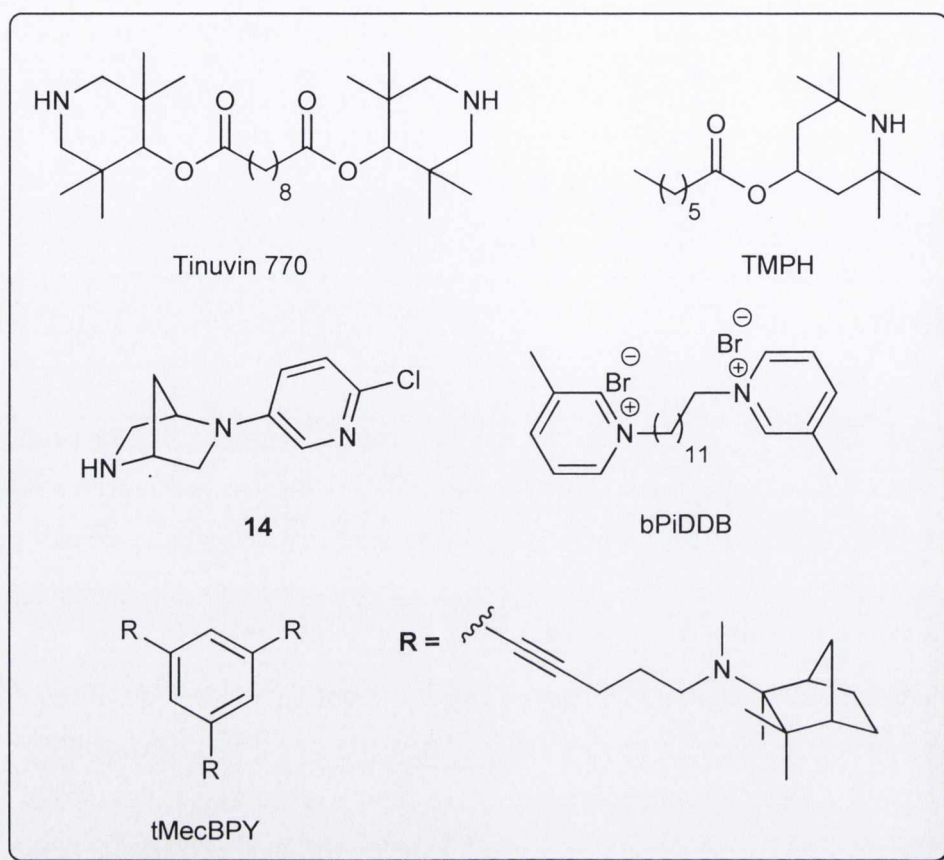


Figure 1-30 Recent MA, epibatidine and pempidine analogues

The goal of this project is to probe the pharmacological space around the basic [2.2.1] bicyclo framework of MA, a compound that has clearly been neglected in this regard since the most recent SAR study carried out by Suchocki *et al.* in 1991. All of the compounds synthesised in this, the most extensive study of its type related to mecamylamine, were assessed for biological activity in an indirect *in vivo* manner discussed above. The developments of modern molecular biology have provided the platform for the *in vitro* assessment of novel bioactive compounds as antagonists or agonists at a range of isolable nAChR subtypes.

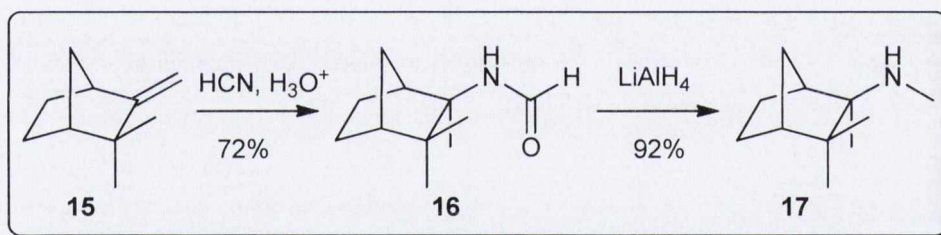
It is our objective to systematically synthesise a range of MA analogues and test these compounds for antagonist or agonist activity on a range of available nAChR subtypes.

## 1.6 Synthetic strategy

The aim of this project was to develop a novel approach to the synthesis of MA in order to prepare a range of analogues to probe the pharmacological space around the [2.2.1] system and quantitatively measure the effect of substitution on the MA framework through *in-vitro* testing at nAChR subtypes.

### 1.6.1 Previous syntheses

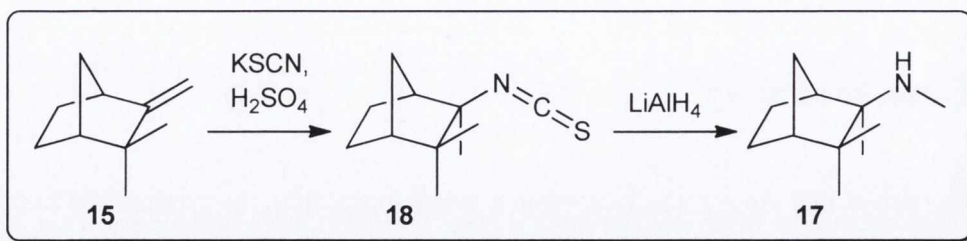
MA was originally synthesised in 1956 by Stein *et al.* via a two step synthesis from camphene **15**. (Scheme 1-1) Regrettably, the first step requires the use of the highly toxic reagent HCN. Nevertheless this is a very direct, high yielding synthesis albeit somewhat limited in its scope.



Scheme 1-1 Original synthesis of MA

Astonishingly, it was not until 2010 that Crooks and co-workers published a modified version of this synthesis that avoided the use of HCN.<sup>281</sup> Camphene **15** was again used as the starting material and treatment with H<sub>2</sub>SO<sub>4</sub>/KSCN afforded isothiocyanate **18** shown in Scheme 1-2. The isothiocyanate can be reduced with lithium aluminium hydride to yield the desired secondary amine, MA **17**. Unfortunately, no yields were published with these results.



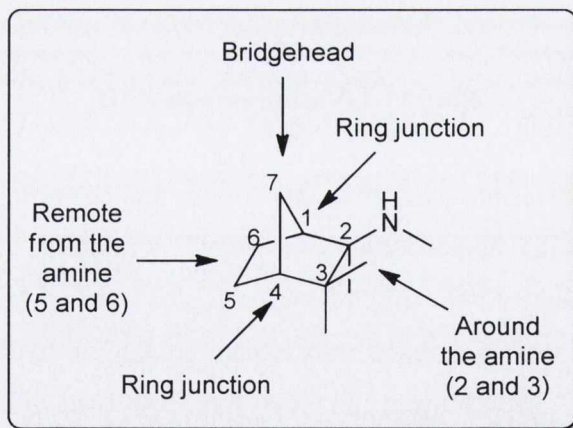


**Scheme 1-2 Modified MA synthesis reported by Crooks and co-workers**

Unfortunately, these syntheses are of no use to our purposes as they lack the opportunity to increase diversity in the system. It is possible to hydrolyse the formamide **16** or isothiocyanate **18** under basic conditions to yield the primary amine which can then be alkylated but this is woefully inadequate in terms of SAR development. A novel approach was necessary.

### 1.6.2 Position 2 and 3

Analysis of the structure of MA, reveals different areas that could be modified (ideally in an individual and sequential manner). (Figure 1-31)

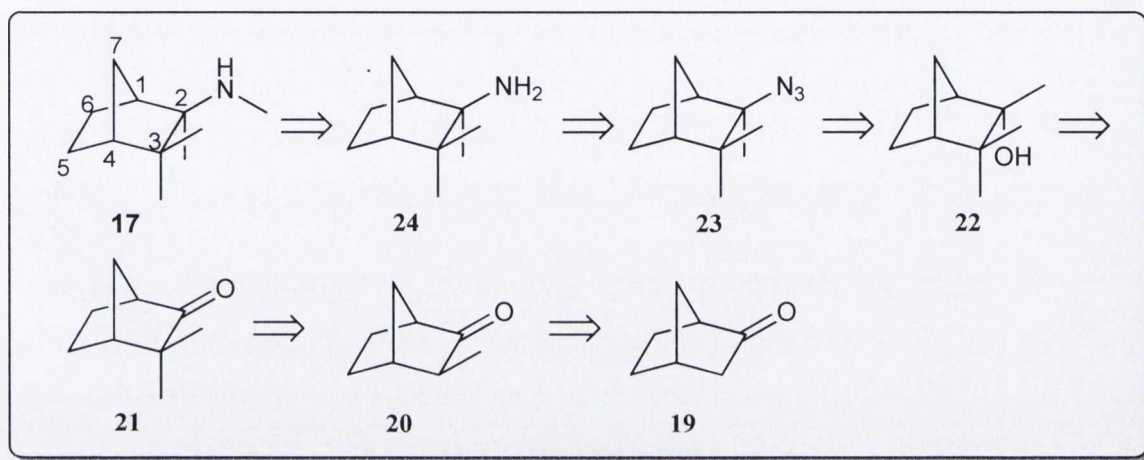


**Figure 1-31 Regions of the MA skeleton that could be addressed**

Our initial aim was to devise a synthesis that would allow the study of systems differing “around the amine” (positions 2 and 3) but naturally we wanted to develop a general protocol that could be expanded to cover the various other regions in the future.

#### 1.6.2.1 *exo*-Mecamylamine analogues

The first synthetic targets that we wished to access were analogues of MA that displayed diversity in positions 2 and 3. (Scheme 1-3) In order to achieve this, the retrosynthesis of MA shown below was devised.



Scheme 1-3 Retrosynthesis of MA

The methylated amine **17** could be derived from the primary amine **24** via reductive amination. It was envisaged that the primary amine would be derived from the azide **23** using a reductive protocol. Catalytic hydrogenation, the Staudinger reduction or a reduction employing lithium aluminium hydride were all potential candidates for this step. The azide **23** could be formed from the alcohol **22** via an  $S_N1$  reaction. The high stereoselectivity of this step is ensured by 1,3 and 1,5 steric interactions due to the presence of the axial hydrogen substituents, the so-called “picket fence” effect.<sup>282</sup> This effect dictates that all electrophiles and nucleophiles must add to the [2.2.1] bicyclo system from the *exo* face. Alcohol **22** could be derived from the ketone **21** by addition of methylmagnesium bromide or methyllithium. The stereoselectivity of this step is again governed by the picket fence effect. The dimethylated ketone **21** could be formed from the commercially available reagent norcamphor **19** via two successive  $\alpha$ -methylations using simple enolate chemistry. Bredt’s rule outlines the steric constraints that ensure only the desired enolate can form despite the presence of an  $\alpha$ -proton at position 1.<sup>283, 284</sup>

This synthetic route is concise and uncomplicated yet facilitates the formation of two new stereocentres and the stereoselective incorporation of 4 new alkyl groups. It was hoped that this general approach would enable the facile synthesis of a library of analogues with a variety of substitutions at position 2 and 3 of MA. The use of well established synthetic transformations that would tolerate alkyl substituents larger than methyl was deemed essential.

Examining each reaction in turn proved encouraging. In 1962, Corey and co-workers had described the picket fence effect relating to enolates of norcamphor in their reported synthesis of the natural product  $\beta$ -santalene.<sup>285</sup> (Figure 1-32) More recently, more convenient commercially available reagents have also been used to carry out transformations of this type.<sup>286</sup>

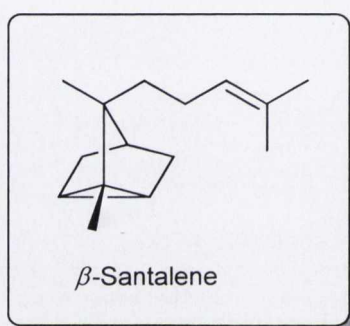
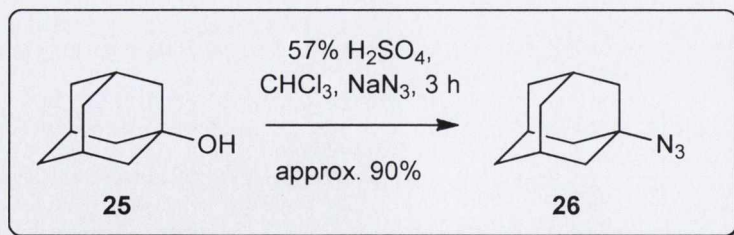


Figure 1-32  $\beta$ -santalene, synthesised by Corey and co-workers in 1962

A potentially problematic synthetic step that was identified was the azide formation reaction. Sazaki and co-workers had demonstrated that adamantan-1-ol **25** could be converted to 1-azidoadamantane **26** via an  $S_N1$  process using sodium azide and sulphuric acid.<sup>287</sup> (Scheme 1-4)



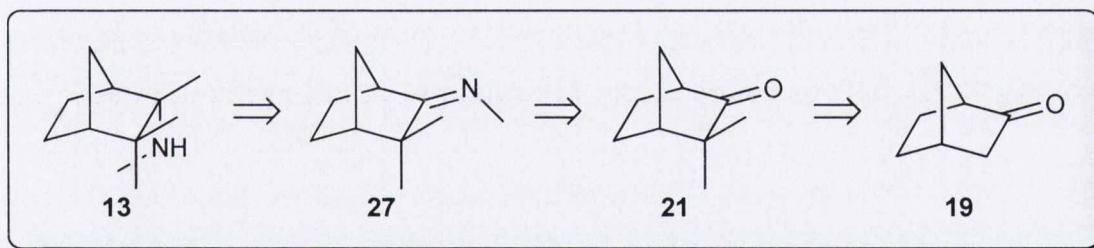
Scheme 1-4 Synthesis of 1-azidoadamantane from adamantan-1-ol



This approach was favoured because of the similarities evident between adamantane and the [2.2.1] bicyclo structure. Other groups had successfully used this process to introduce azide functionality at a tertiary centre in a number of different systems.<sup>288, 289</sup> However, it was apparent that possible complications could arise from the fact that the tertiary alcohol **22** would form a nonclassical carbocation liable to undergo both Wagner-Meerwein and Nametkin rearrangements.<sup>290</sup> It was hoped that the azide nucleophile could trap the carbonium ion formed before these potential rearrangements could intervene. Numerous “azide clock” experiments have shown that the interception of carbocations by azides tend to be diffusion controlled<sup>291</sup> and as such, it was hoped that formation of a tertiary cation would facilitate the desired reaction.

#### 1.6.2.2 *endo*-Mecamylamine

The synthesis of *endo*-MA **13** was also set as a somewhat ambitious but necessary target to fully explore the pharmacophore of this molecule. Despite previous attempts,<sup>263, 270</sup> no group had successfully synthesised this molecule. The retrosynthesis shown below (Scheme 1-5) outlines our intended approach.



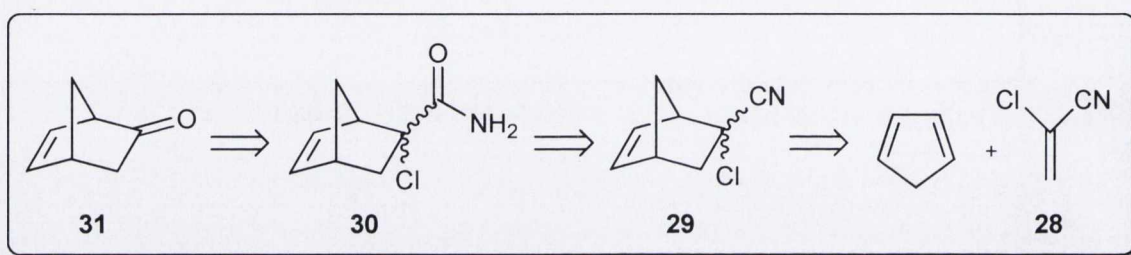
Scheme 1-5 Retrosynthesis of *endo*-MA

We envisaged that the desired amine could be derived from the imine **27** via a 1,2 organometallic addition. The imine could be formed from the ketone **21** in a condensation reaction with methylamine while the dimethylated ketone **21** could be formed as before from the commercially available reagent, norcamphor **19**.

### 1.6.3 Position 5 and 6

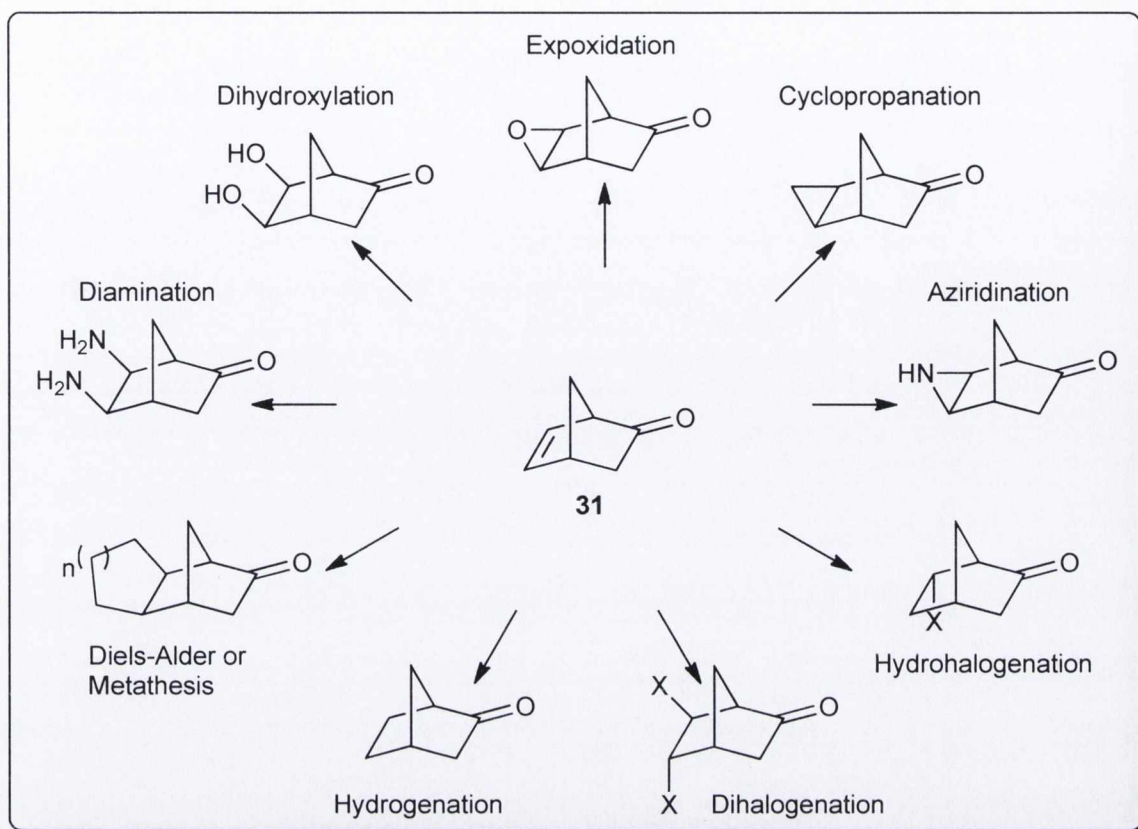
#### 1.6.3.1 Bicyclo[2.2.1]hept-5-en-2-one (31)

Having addressed the 2- and 3- positions of the MA framework, we considered how we might adapt this methodology to facilitate the synthesis of other analogues outlined in Figure 1-31. In 1968 Freeman and co-workers had shown that norbornenone **31** could be synthesised from cyclopentadiene and a ketene equivalent **28**.<sup>292</sup> This reaction displayed its robustness in 1982 when it was used in the total synthesis of brefeldin-A on a 300 g scale.<sup>293</sup>



Scheme 1-6 Retrosynthesis of norbornenone

Retrosynthetically, (Scheme 1-6) norbornenone **31** can be derived directly from the  $\alpha$ -chloronitrile mixture **29** under basic hydrolysis conditions although the intermediate  $\alpha$ -chlorocarboxamide mixture **30** can be isolated if desired. This may be of use as the resolution of **30** into its enantiomers has been documented.<sup>294</sup> The  $\alpha$ -chloronitrile mixture **29** can be formed from the Diels-Alder cyclisation of cyclopentadiene and  $\alpha$ -chloroacrylonitrile **28** in a 4:1 mixture of *exo:endo* diastereomers with respect to the chlorine substituent. The olefin moiety is a functional handle that can be exploited to introduce a wide range of functionality into the [2.2.1] bicycle framework. (Scheme 1-7)



**Scheme 1-7 Potential functionalisation of olefin moiety**

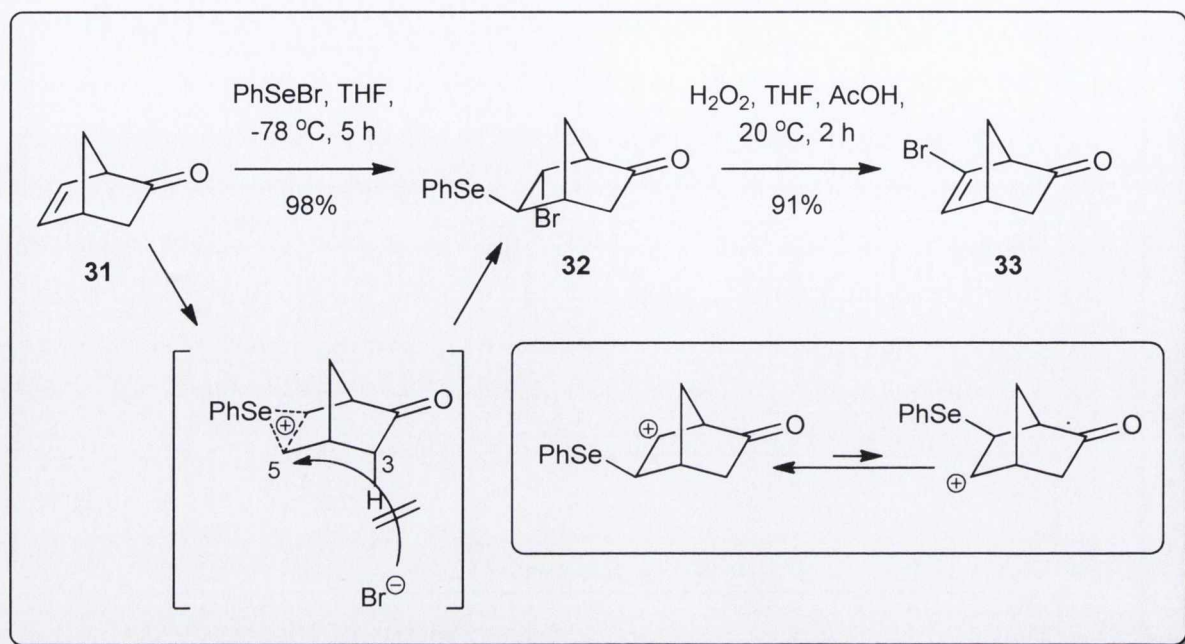
Obviously these are just some of the compounds that could be synthesised by quickly exploiting the alkene. One can imagine subsequent transformations such as opening the epoxide with a variety of nucleophiles or eliminating the dihalogenated species to provide a vinyl halide and open up whole new vistas of palladium chemistry. The sheer number of synthetic manipulations possible would excite most organic chemists!

Our intention was to then use our newly optimised synthetic route to install the standard MA functionality at positions 2 and 3 and test these compounds so as to ascertain the effects of various substitution motifs relative to the parent compound. Obviously some of the more labile 5- and 6-substituted moieties would require protection.

#### 1.6.3.2 6-substituted mecamylamine

In 1989 Lal and co-workers successfully synthesised 6-bromobicyclo[2.2.1]hept-5-en-2-one (**33**) from norbornenone **31** in 2 steps and an impressive 89% yield.<sup>295</sup> (Scheme 1-8)



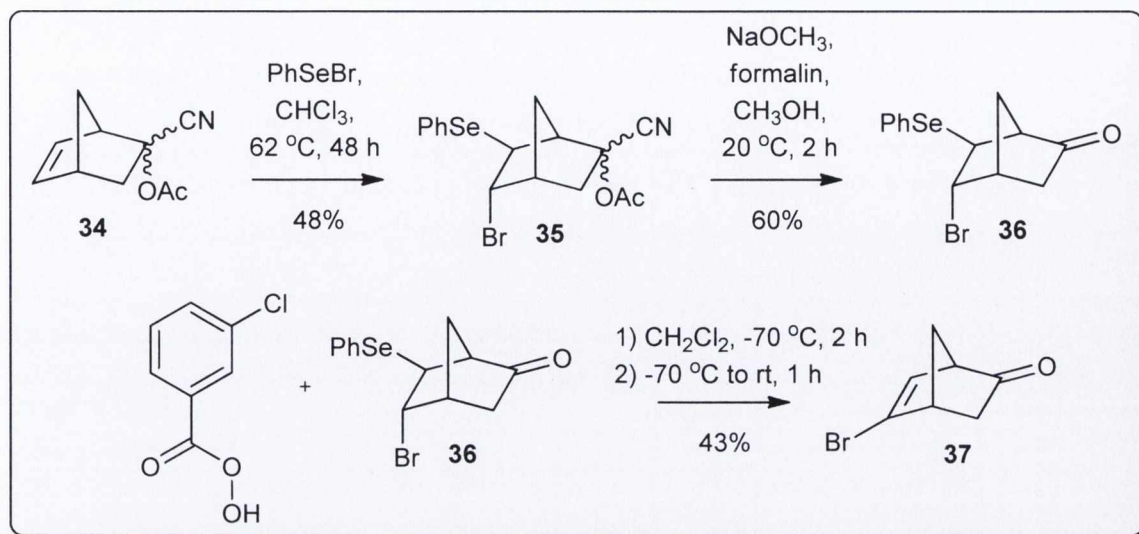


Scheme 1-8 Synthesis of 6-bromobicyclo[2.2.1]hept-5-en-2-one (33)

According to the authors, the quantitative regioselectivity observed in the addition step arose as a result of the steric effect of the 3-*endo* hydrogen substituent preventing the bromide ion from attacking the 5 position. An alternative theory proposed by Carrupt *et al.* suggested that the homoconjugative effect of the carbonyl group stabilises the intermediate cation at position 6 but not position 5 in the limiting cases.<sup>296</sup> Obviously the Curtin-Hammett principle would refute this latter argument. In any case, we decided that this would be an excellent starting point for our investigations into a 6-substituted MA analogue.

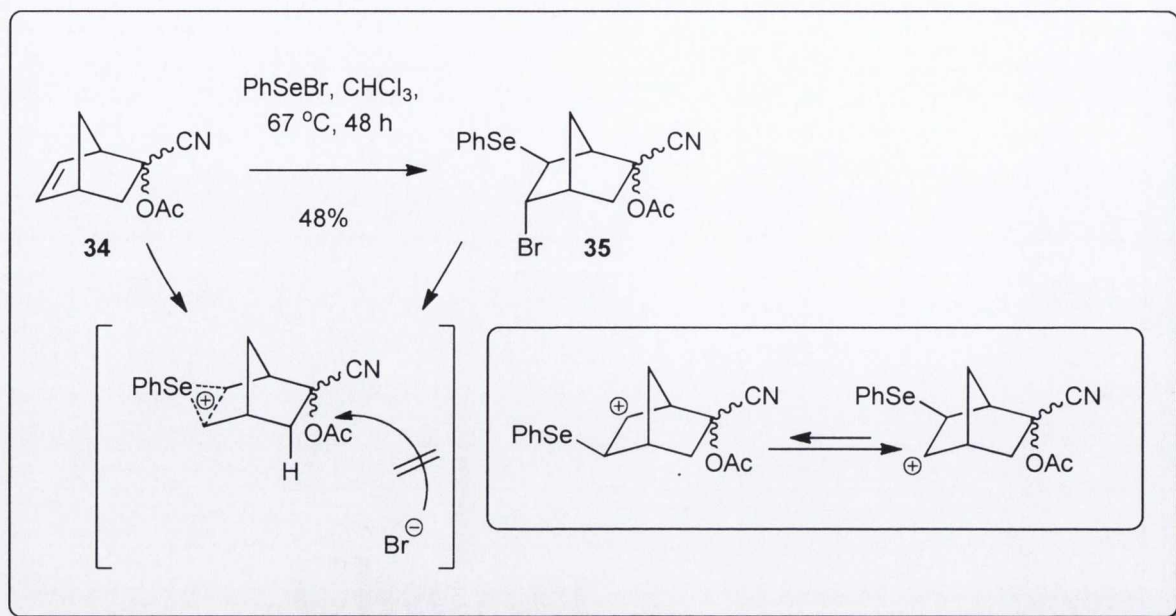
#### 1.6.3.3 5-substituted mecamylamine

We also believed that this chemistry could be adapted to synthesise a 5-substituted analogue. Carrupt *et al.* had reported the synthesis of ketone **37** in 1989. (Scheme 1-9) Unfortunately the yield obtained for the 3 steps from the  $\alpha$ -acetoxynitrile **34** to the desired ketone **37** was only 12%. This was deemed to not be a viable synthetic strategy considering that the dienophile required (1-cyanovinyl acetate) is roughly six times more expensive than chloroacrylonitrile and ketone **37** would be required in multigram quantities.



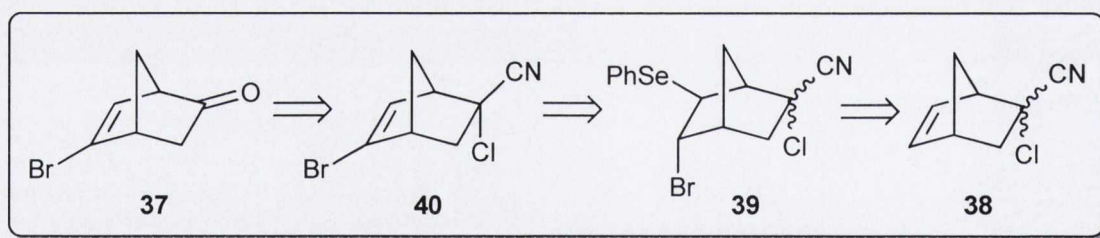
Scheme 1-9 Synthesis of ketone 37

We envisaged a strategy in which phenylselenenyl bromide would add directly to the  $\alpha$ -chloronitrile **38** (Scheme 1-11). It was thought that this substrate should display similar regioselectivity in the addition process to the  $\alpha$ -acetoxynitrile **34**. (Scheme 1-10) Whether the selectivity for this reaction arises from steric aspects (due to the relatively bulky substituent now occupying the 2-*endo* position) or electronic effects (replacement of the homoconjugative M+ effect of the carbonyl with the weakly inductive withdrawing I- effect of the cyano and acetoxo functionalities) is unclear (Scheme 1-10). However, it seems plausible to suggest that at least the relative contribution of the electronic effects is lessened here compared to the 6-bromo analogous case. (Scheme 1-8)



Scheme 1-10 Synthesis of 5-bromo carbonitrile mixture **35**

It was hoped that it would then be possible to perform the standard  $\text{H}_2\text{O}_2$  oxidative cleavage on the product **39** followed by hydrolysis of the  $\alpha$ -chloronitrile **40** to generate the required ketone **37**. (Scheme 1-11) It was thought that by using the methodology previously optimised for the formation of ketone **33**, ketone **37** could be obtained with a minimum of effort.

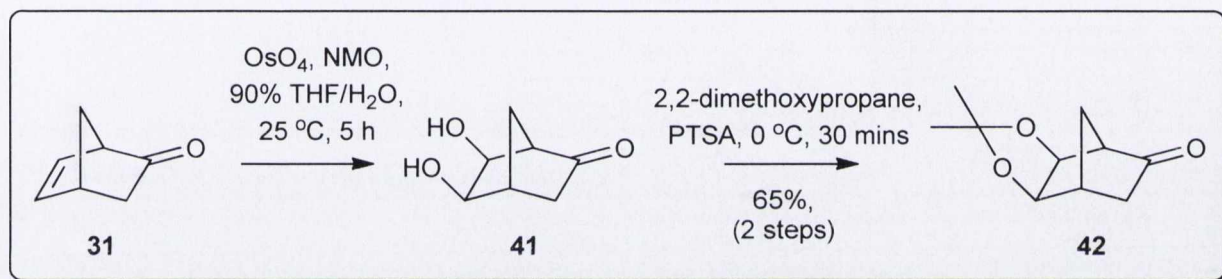


Scheme 1-11 Retrosynthesis of ketone **37**



#### 1.6.3.4 5,6-disubstituted Mecamylamine

Another interesting reaction sequence that came to our attention was carried out by Wang *et al.* in 2001.<sup>297</sup> While working on a drug discovery project for Abbott, a dihydroxylation and subsequent isopropylidene diol protection was implemented on norbornenone **31**. (Scheme 1-12) The two steps were accomplished in an acceptable 65% yield and it was thought that the sequence was well suited to our purposes. Evidently the picket fence effect proved sufficient to induce complete facial selectivity for the dihydroxylation step to form diol **41** as no chiral ligands were employed. In addition we suspected that the isopropylidene protection would serve adequately in the enolate mediated alkylations and the 1,2 Grignard addition that would ensue.



Scheme 1-12 Dihydroxylation of norbornenone **31** and isopropylidene protection of the resulting diol

#### 1.6.4 Isotopic labeling

A potentially important aspect to the synthetic strategy governing position 2 and 3 of the MA skeleton is the ability to incorporate isotopically labeled atoms. With respect to the synthesis of MA itself, between one and four labeled methyl groups could be introduced. <sup>13</sup>C labeled iodomethane is readily available and could be used directly for the enolate mediated alkylation reactions. Halogen lithium exchange would provide a facile route to <sup>13</sup>CH<sub>3</sub>Li required for the alcohol formation step while <sup>13</sup>CH<sub>2</sub>O (required for *N*-methylation) is also commercially available.

The possibility of synthesising <sup>13</sup>C enriched bioactive molecules is of great interest to a number of fields including neuroscience, psychiatry, medicinal chemistry and pharmacology. Owing to the fact that carbon-13 possesses a spin quantum number of 1/2, <sup>13</sup>C magnetic

resonance imaging (MRI)<sup>298</sup> or functional magnetic resonance imaging (fMRI) could be employed to observe the distribution and accumulation of MA itself or an analogue in various brain tissue in a completely non-invasive manner in either humans or animals. This type of study may be able to further elucidate the mechanism by which MA exerts its anti-addictive or anti-depressive effects. It would also be possible to directly monitor the metabolism and excretion of this compound in real time.

Another opportunity for neuroimaging would be presented by the successful incorporation of <sup>11</sup>C radiolabeled isotopes into the MA framework. Unlike carbon-13 which is a stable non-radioactive isotope, carbon-11 decays by positron emission with a half life of approximately 20 minutes. As such, the range of chemistry that can be used to introduce a <sup>11</sup>C radiolabeled group into any molecule is limited by the duration of the reaction required to insert the radiotracer and also by the limited number of <sup>11</sup>C radiolabeled reagents available. The main source of carbon-11 available is <sup>11</sup>CO<sub>2</sub> which is synthesised in a cyclotron. This can be rapidly converted to <sup>11</sup>CH<sub>4</sub> or more commonly <sup>11</sup>CH<sub>3</sub>OH, which allows the synthesis of <sup>11</sup>C-iodomethane by treatment with HI.<sup>299</sup>

To perform the final methylation in the synthesis of MA and future analogues, it may be possible to react iodomethane with amine **24** directly using simple S<sub>N</sub>2 chemistry and yet avoid the unwanted over alkylation through extensive optimisation of this reaction. If this were possible, positron emission tomography (PET) studies could be carried out using the <sup>11</sup>C isotopically labeled product. Carbon-11 decays by emitting positrons which travel a very short distance before encountering an electron resulting in an annihilation event which produces two photons travelling in opposite directions. By detecting these photons, it is possible to build a 3-d image of the radioisotope concentration in a subject.<sup>300</sup> This poses an exciting prospect for the direct imaging of nAChRs by any selective MA analogues produced, as following a preliminary study by Debruyne *et al.*,<sup>301</sup> a successful <sup>11</sup>C radiolabeled MA PET study was carried out by Sobrio *et al.* using male Sprague-Dawley rats and rhesus monkeys.<sup>302</sup>

## **Chapter 2**

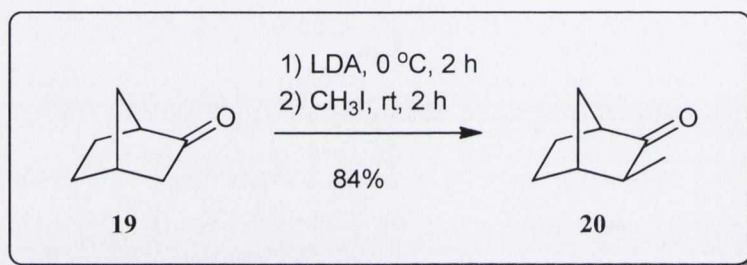
### **Synthesis of mecamlamine**



## 2 Novel synthesis of mecamylamine

### 2.1 3-Methyl-bicyclo[2.2.1]heptan-2-one (20)

The aim of this project was to prepare structural analogues of MA. In order to achieve this, it was necessary to devise a new synthetic route (Scheme 1-3). In order to develop the route it was deemed prudent to initially prepare MA itself. The first synthetic step in our proposed synthesis was the alkylation of norcamphor **19** (Scheme 2-1). This was achieved by treatment with lithium diisopropylamine (LDA) at 40 °C followed by the addition of iodomethane.

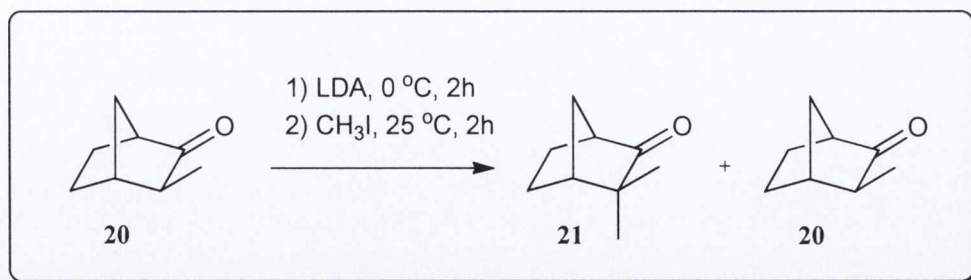


Scheme 2-1 Monomethylation of ketone 19

This furnished ketone **20** with a yield of 84%, which is consistent with literature precedent.<sup>286</sup> The crude product was isolated as a brown oil which could be columned on silica gel to yield a pale yellow oil. However, these oils were indistinguishable by <sup>1</sup>H NMR spectroscopic analysis and it was shown that the crude product could be used in subsequent reactions without affecting the purity or yield of the product and as a result, purification in this step was deemed unnecessary.

### 2.2 3,3-Dimethyl-bicyclo[2.2.1]heptan-2-one (21)

The second methylation was attempted under the same reaction conditions employed for the first methylation, as described by Posner and co-workers.<sup>286</sup> Unfortunately, the result was incomplete methylation, yielding an approximate 6:1 ratio of ketones **21:20**. (Scheme 2-2) Repeated attempts produced the same result.



**Scheme 2-2 Methylation of ketone 20**

To add to this complication, the two ketones displayed the same  $R_f$  by TLC analysis and unsurprisingly proved inseparable on silica gel or alumina. In addition, their respective boiling points were too close to be separated by K ugelrohr distillation.

An extensive search of the literature revealed a number of groups claiming to have employed this chemistry without difficulty.<sup>303, 304</sup> Frustrated by this lack of reproducibility, a series of experiments were devised in an attempt to improve the ratio of ketone **21** over the starting material ketone **20**, or at the very least to clearly identify whether it was the deprotonation or alkylation which was the problematic step in the overall reaction. Table 2-1 elaborates on the findings. Unfortunately, no useful trends emerged. Varying these parameters seemed to produce only small and sometimes inconsistent results.

Table 2-1 Alkylation of ketone 20

| LDA<br>Molar<br>Eqs. | CH <sub>3</sub> I<br>Molar<br>Eqs. | Deprotonation<br>Temp. (°C) | Alkylation<br>Temp. (°C) | Deprotonation<br>Time<br>(Hours) | Alkylation<br>Time<br>(Hours) | Ratio of<br>21:20<br>Obtained |
|----------------------|------------------------------------|-----------------------------|--------------------------|----------------------------------|-------------------------------|-------------------------------|
| 1.25                 | 3                                  | 0                           | 20                       | 1                                | 1.5                           | 6.1                           |
| 2                    | 5                                  | 0                           | 20                       | 1                                | 1.5                           | 5.9                           |
| 3                    | 5                                  | 0                           | 20                       | 1                                | 1.5                           | 6.3                           |
| 1.25                 | 3                                  | 0                           | 20                       | 2                                | 2                             | 5.7                           |
| 1.25                 | 3                                  | 0                           | 20                       | 3                                | 3                             | 6.3                           |
| 1.25                 | 3                                  | -78                         | -78                      | 2                                | 2                             | 0.9                           |
| 1.25                 | 3                                  | -78                         | 0                        | 2                                | 2                             | 6.2                           |

1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU)<sup>305</sup> is a relatively non-toxic alternative to the co-solvent/additive hexamethylphosphoramide (HMPA) which has been shown to aid in reactions of this type.<sup>306, 307</sup> (Figure 2-1) Unfortunately, addition of DMPU to the reaction medium in this case produced no observable effect.

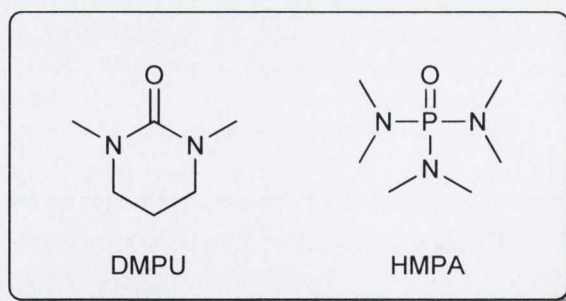
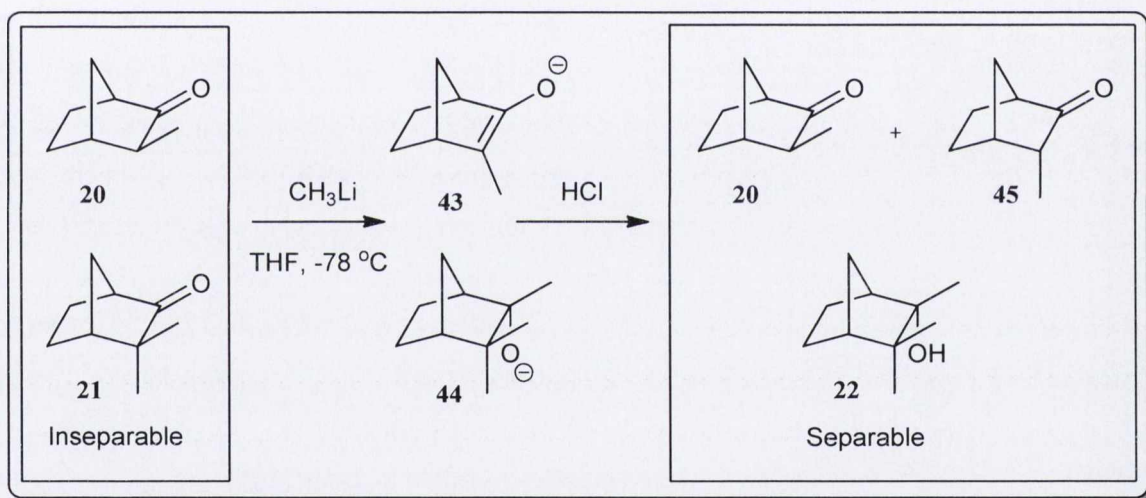


Figure 2-1 Polar, aprotic, organic co-solvents



### 2.3 2,3,3-Trimethyl-bicyclo[2.2.1]heptan-2-ol (**22**)

It was hypothesised that the required separation of these compounds could be achieved by attempting to form the alcohol **22** from the crude mixture of ketones. (Scheme 2-3) It was hoped that the organometallic reagent would preferentially deprotonate the monoalkylated species as opposed to undergoing addition to the carbonyl moiety. If the enol **43** was formed it was likely that in the absence of any electrophiles it would simply be protonated under aqueous workup conditions to reform ketone **20** (or more likely ketone **45**). It was envisaged that alcohol **22** derived from the desired 1,2 addition to the dimethyl ketone **21** would be easily separated from ketone **20** by flash chromatography. Methyl lithium was chosen over methylmagnesium bromide as the organometallic component in an effort to favour enolate formation over 1,2 addition.

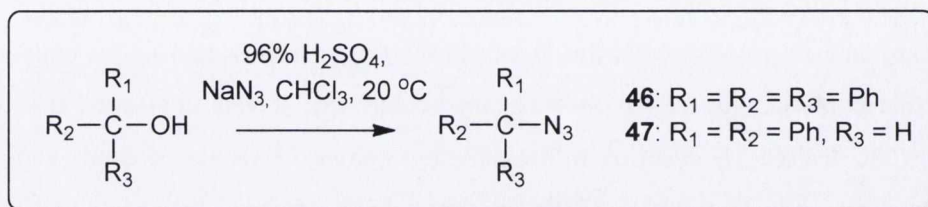


Scheme 2-3 Organometallic addition to the inseparable ketone mixture of **20** and **21**

Gratifyingly, this approach proved successful, proving that it was possible to form alcohol **22** in 2 steps and 55% yield from the monoalkylated ketone **20**. It was envisaged that this approach could be used to form a range of trialkylsubstituted alcohols.

## 2.4 2-Azido-2,3,3-trimethyl-bicyclo[2.2.1]heptanes (23)

To convert the alcohol **22** to the desired azide **23** required the use of hydrazoic acid ( $\text{HN}_3$ ) which was formed *in situ* by the dropwise addition of sulfuric acid to a suspension of sodium azide in chloroform as described originally by Arcus and co-workers to synthesise the azides **46** and **47**.<sup>308</sup> (Scheme 2-4)

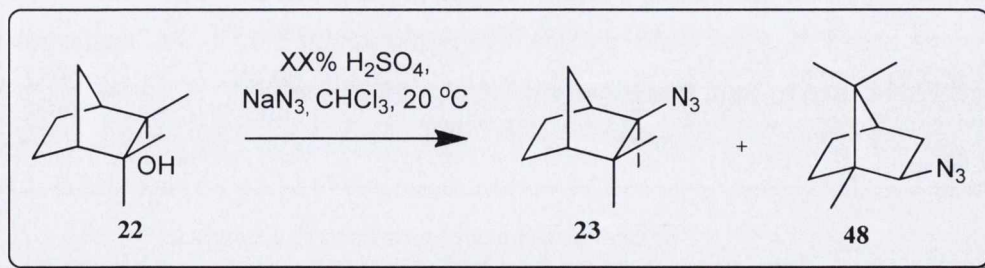


Scheme 2-4 Transformation of benzylic alcohols to azides as described by Arcus and co-workers.<sup>308</sup>

Early attempts to optimise this reaction were hindered by the unexpected volatility of the azide product. The expected product could not be observed by  $^1\text{H}$ -NMR spectroscopy as it was being removed in the course of evaporating reaction solvent. Once identified, this problem was avoided by removing the solvent at 0-10  $^\circ\text{C}$  on a standard rotary evaporator.

A number of experiments were devised to optimise clean azide formation. The results are summarised in Table 2-2. It was found that the dependence of the reaction rate on alcohol concentration in the organic phase was largely insignificant when compared to the effect of the concentration of sulfuric acid used. It was also apparent that stirring speed was an important parameter. This is perhaps unsurprising considering the biphasic nature of the reaction medium. As such all optimisation experiments were carried out at maximum stirring speed in an effort to enforce pseudo-homogeneity on the system.

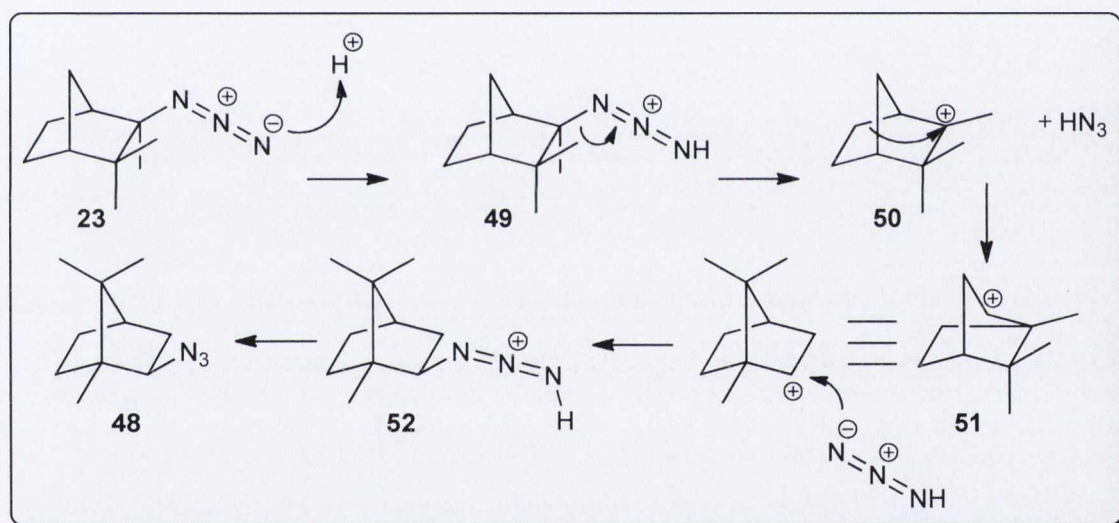
Table 2-2 Optimisation of azide formation





| Sulfuric Acid Conc.<br>% (M) | Alcohol Conc.<br>(M) | Time<br>(Hours) | Product Distribution (%) |     |     |
|------------------------------|----------------------|-----------------|--------------------------|-----|-----|
|                              |                      |                 | 22                       | 23  | 48  |
| 75% (13.8)                   | 0.33                 | 3               | 0                        | 0   | 100 |
| 50% (9.2)                    | 0.33                 | 4               | 0                        | 100 | 0   |
| 50% (9.2)                    | 0.06                 | 4               | 0                        | 100 | 0   |
| 40% (7.4)                    | 0.33                 | 24              | 100                      | 0   | 0   |

Although it was found that a 100% sulfuric acid solution facilitates the conversion of alcohol **22** to the desired azide **23** within minutes this was not the reaction condition of choice. Exposure of azide **23** to the acidic reaction medium allows formation of **48**. We believe this compound to be the Wagner-Meerwein rearranged azide. (Scheme 2-5) The structure has been tentatively assigned by 2d-NMR spectroscopy.



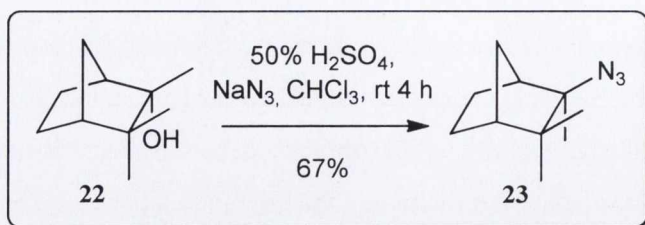
Scheme 2-5 Wagner-Meerwein rearrangement of azide **23**

These types of rearrangements have been previously documented,<sup>309</sup> with a protonated alcohol acting as the leaving group and trapping of the cation formed by the acetate anion. This rearrangement is believed to be an analogous case. It was vital therefore to closely monitor azide formation by <sup>1</sup>H NMR spectroscopy and quench the reaction as soon as conversion to the desired product **23** was complete as it was not possible to separate azide **23** from the rearranged product **48** by chromatographic means. Complete conversion of **22** to **48** was achieved by stirring for 3h at



room temperature with 75% H<sub>2</sub>SO<sub>4</sub>. The synthetic value of this rearrangement was unfortunately limited because the hydrocarbon skeleton and stereochemistry produced was the same as that found in commercially available isobornyl structures.<sup>310</sup>

Optimal yields of azide **23** were obtained with the reaction conditions outlined in Scheme 2-6.

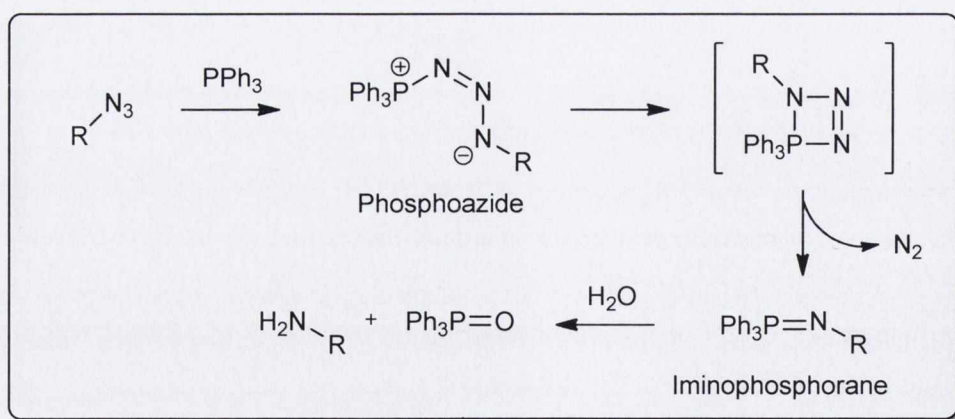


Scheme 2-6 Synthesis of azide **23** from alcohol **22**

## 2.5 2,3,3-Trimethyl-bicyclo[2.2.1]heptan-2-amine (**24**)

### 2.5.1 Staudinger reduction

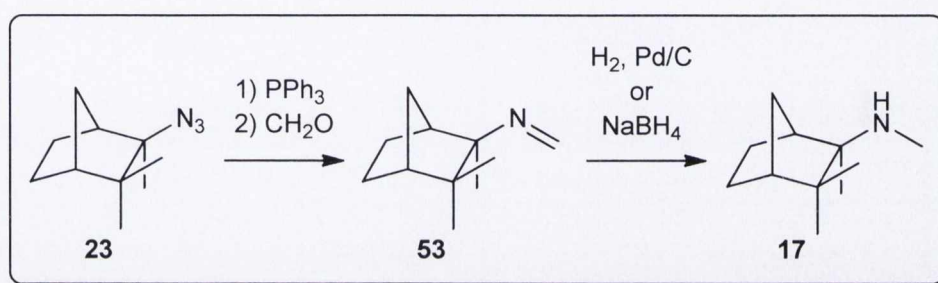
There are numerous methods to effect the reduction of azide **23** to yield the primary amine **24** including catalytic hydrogenation, the Staudinger reduction and reduction by lithium aluminium hydride. The preferred option was the Staudinger reduction as this would employ conditions least likely to affect other functional groups in future, more complex, MA analogue syntheses.



Scheme 2-7 Staudinger Reduction

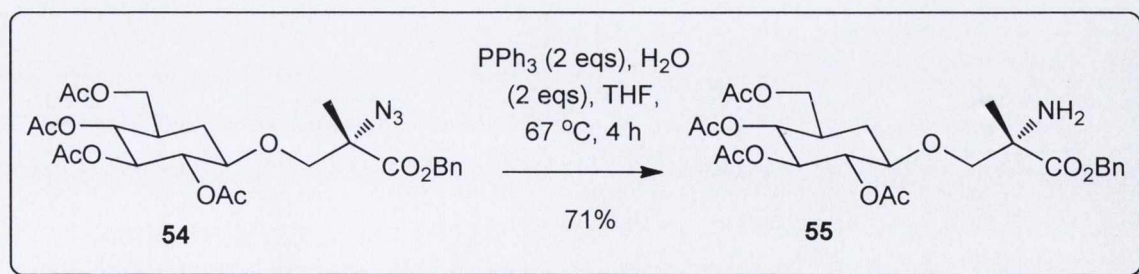
The Staudinger reduction (Scheme 2-7) has been a reliable and versatile method for reducing azides to amines since its discovery by Staudinger and Meyer in 1919.<sup>311</sup> It is accepted that the phosphoazide formed by attack of the trialkylphosphine on the azide is rapidly converted to the iminophosphorane by extrusion of N<sub>2</sub>. The iminophosphorane can then be attacked by H<sub>2</sub>O to yield the amine and PPh<sub>3</sub>O.

In addition, we felt that it might be possible to convert the tertiary azide **23** to the desired methylated amine **53** via an aza-Wittig reaction<sup>312</sup> and subsequent *in situ* reduction. (Scheme 2-8) If possible, this would provide a shorter synthetic route to MA and other *N*-functionalised analogues.



Scheme 2-8 Aza-Wittig reaction

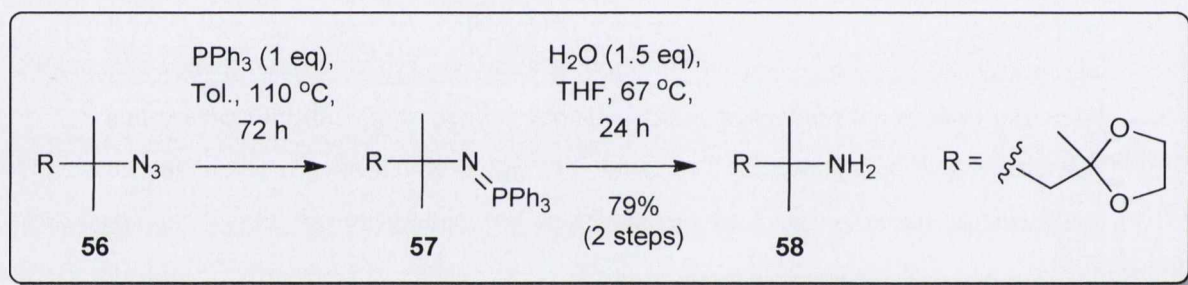
There are numerous examples of Staudinger reductions of primary azides in the literature<sup>313-315</sup> but tertiary azide reductions of this type are much less common. Indeed in 1985 Knouzi *et al.* illustrated their resistance to reduction by demonstrating that it was possible to reduce a primary or secondary azide selectively in the presence of a tertiary azide.<sup>316</sup> However, in 2003, Avenoza and co-workers reported the transformation of **54** to **55** shown in Scheme 2-9 as a key step in their synthesis of a glycoaminoacid building block.<sup>317</sup>



Scheme 2-9 Tertiary azide Staudinger reduction



It was thought that it should be possible to employ these reaction conditions for the required reduction. Unfortunately, even after heating at reflux for 48 hours no conversion from azide **23** to amine **24** was observed by analysis of the  $^1\text{H}$  NMR spectroscopic data. Discouraged, other examples in the literature were sought and it was discovered that a more complete translation of a paper published in French by Vaultier *et al*<sup>318</sup> provided a valuable piece of information that had been originally overlooked. This group had achieved the transformation shown in Scheme 2-10 but noted in their appendices that this example alone out of seven compounds surveyed required a different synthetic approach. For the six less hindered azides studied it was reported that triphenylphosphine and  $\text{H}_2\text{O}$  could be added to the reaction simultaneously with no effect on conversion or yield. Surprisingly, this group found that for the hindered azide **56** shown in Scheme 2-10, the iminophosphorane **57** had to be formed quantitatively before the addition of  $\text{H}_2\text{O}$  in order to achieve the desired transformation to amine **58**.



Scheme 2-10 Two step conversion of hindered tertiary azide

By applying this approach, it was possible to convert azide **23** into an intermediate organophosphorane complex by heating in THF at reflux for 72 hours or in toluene at reflux for 24 h as evidenced by  $^1\text{H}$  and  $^{31}\text{P}$  NMR spectroscopy. Surprisingly, addition of  $\text{H}_2\text{O}$  at this stage did not furnish the desired amine **24** and in fact, a slow conversion of the intermediate organophosphorane back to azide **23** was observed. This result was perplexing as it was clearly impossible for an iminophosphorane to revert to an azide. The simplest conclusion that could be drawn from this was that the intermediate organophosphorane complex formed was not the desired iminophosphorane.

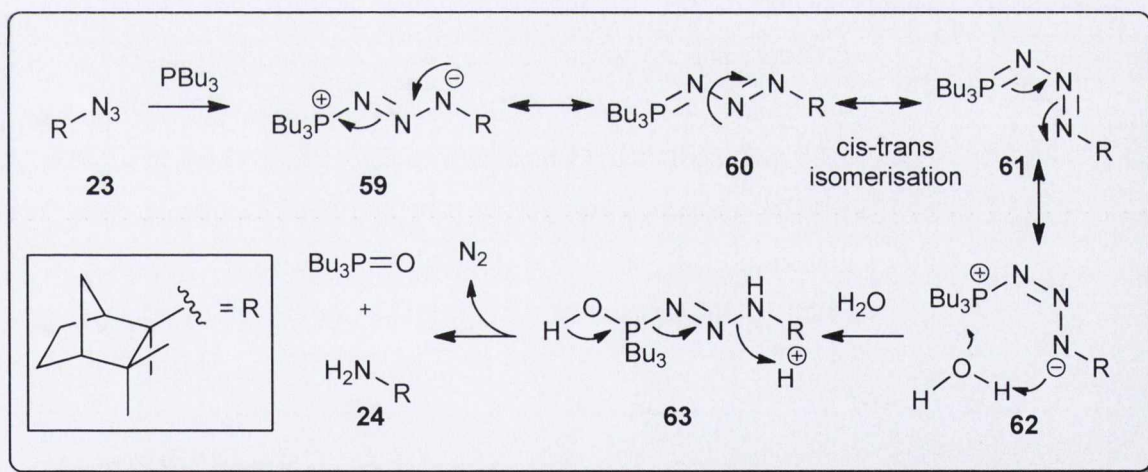
It is known that tributylphosphine reacts more rapidly in the Staudinger reduction than triphenylphosphine<sup>319</sup> and it was deemed prudent to attempt this reaction with the more reactive trialkylphosphine. Gratifyingly, the azide was converted to an intermediate organophosphorane



complex as evidenced by marked shifts in the  $^{31}\text{P}$  NMR spectrum that was believed to be the required iminophosphorane in only 4 hours at room temperature. Addition of  $\text{H}_2\text{O}$  after this time facilitated the conversion to the desired amine **24**.

During the development and optimisation of this reaction an interesting observation was made. While carrying out the Staudinger reduction on a very small scale, it was noticed that upon addition of  $\text{H}_2\text{O}$  to the iminophosphorane formed with tributylphosphine, a small amount of gas was evolved. This was surprising because if the normal reaction mechanism was operating one would expect  $\text{N}_2$  extrusion to occur prior to the addition of water. Analysis of NMR data had indicated that a new phosphorous species had been formed but this new finding precluded the possibility that this phosphorous species could be the desired iminophosphorane. We offer a tentative explanation of these experimental findings, although further experimental investigation is required.

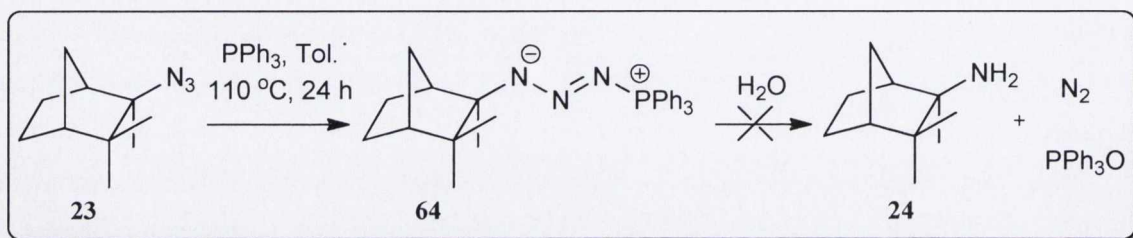
We tentatively propose that in this case the stable intermediate observed is the phosphoazide **59** and not the iminophosphorane. It is hypothesised that the steric constraints around position 2 of azide **23** are too great to allow cyclisation of the four membered ring required for iminophosphorane formation.



Scheme 2-11 Proposed alternative mechanism for the Staudinger reduction

Perhaps in this specific case, collapse of the phosphoazide and loss of  $\text{N}_2$  cannot occur spontaneously. It is conceivable that the trans phosphoazide **59** could extrude nitrogen upon exposure to  $\text{H}_2\text{O}$  without forming a cyclic system or perhaps a molecule of  $\text{H}_2\text{O}$  is required to act as a bridge between the nucleophilic nitrogen and electrophilic phosphorous atoms in the cis phosphoazide **62**. (Scheme 2-11) The resulting six membered transition state would alleviate the

need to form a relatively congested 4-membered ring containing the bicyclic [2.2.1] system and the bulky tributylphosphine substituent. A facile proton transfer in **63** would result in N<sub>2</sub> extrusion and formation of the observed reaction products and would explain the gas evolved upon addition of H<sub>2</sub>O to the intermediate organophosphorane complex. Although applied to a different system, this may also explain the reversion observed upon addition of H<sub>2</sub>O to the organophosphorane complex formed with triphenylphosphine now believed to be **64**. (Scheme 2-12) It is plausible that the steric (or electronic) demand in the triphenyl case is too great to allow even the six membered, H<sub>2</sub>O bridged transition state to form.



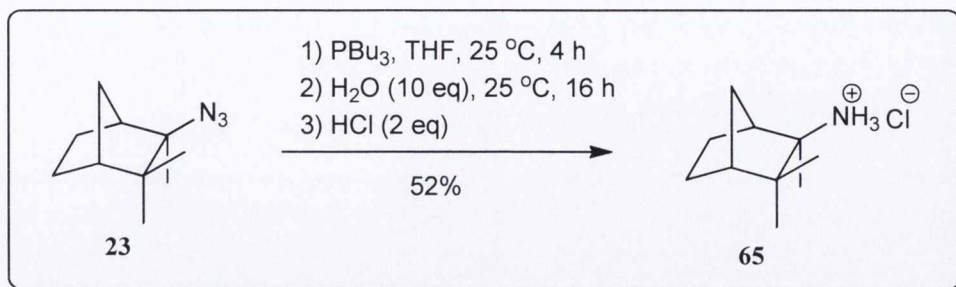
**Scheme 2-12 Failed attempt to form desired amine **24** using triphenylphosphine**

Further evidence supporting the proposed mechanism for the alternative Staudinger reduction pathway observed for this substrate is provided by the failure of the intermediate phosphorous compound formed (using either tributylphosphine or triphenylphosphine) to undergo the attempted Aza-Wittig process upon addition of formaldehyde. This reaction clearly requires the iminophosphorane.

Returning to the synthesis of MA, although the desired amine **24** was formed cleanly in this reaction, isolating the product proved problematic. A number of methods for the removal of tributylphosphine oxide have been described in the literature. The tendency of tributylphosphine oxide to co-elute with the amine product on either silica gel or alumina precluded the use of chromatographic techniques as outlined by Mio and co-workers in their 1991 synthesis of (+)-hydantocidin (**3**).<sup>320</sup> The distillation protocol described by Boyer and Woodyard<sup>321</sup> also proved unsuitable as the free amine decomposed at a temperature below its boiling point, while attempts to distil tributylphosphine oxide from the hydrochloride salt of the amine also proved unsuccessful. Precipitation of the amine hydrochloride salt **65** in diethyl ether was found to remove a considerable portion of the tributylphosphine oxide to leave a tacky white solid. Solubility tests showed that acetone dissolved the remaining tributylphosphine oxide but also dissolved a significant amount of the product. However, it was discovered that butan-2-one was



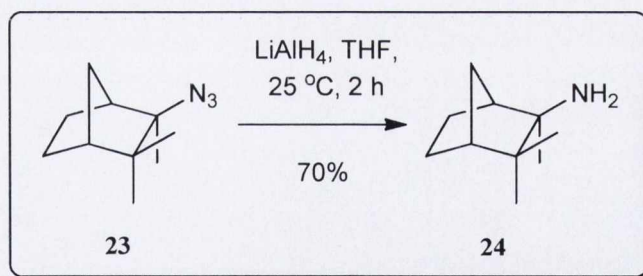
sufficiently polar to dissolve the tributylphosphine oxide but not the hydrochloride salt **65**. Washing the mixture of tributylphosphine oxide and **65** with butan-2-one allowed the isolation of the product in 52% yield. (Scheme 2-13)



Scheme 2-13 Staudinger reduction of azide **23**

### 2.5.2 Lithium aluminium hydride

Reports of reductions of azides by lithium aluminium hydride are widespread in the literature<sup>322-324</sup> and predictably, this approach proved successful, furnishing the desired amine **24** in 70% yield after purification by flash chromatography on silica gel. (Scheme 2-14) As alluded to earlier, this technique would be unsuitable for analogous azides bearing sensitive functional groups.



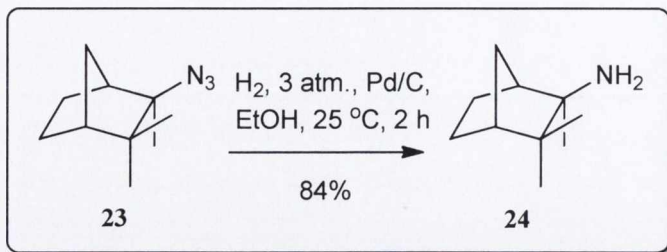
Scheme 2-14  $\text{LiAlH}_4$  reduction of azide **23**

### 2.5.3 Hydrogenation

The reduction of azides by catalytic hydrogenation is well documented<sup>325-327</sup> and this approach proved the most straightforward of the three alternatives examined. The desired amine **24** was obtained in 84% yield and no purification beyond removal of the catalyst by filtration was



required. (Scheme 2-15) This reductive protocol is perhaps not quite as selective as the Staudinger reduction but the higher yields obtained and more importantly, its ease of implementation ensured that this would be the method of choice for future syntheses where appropriate.

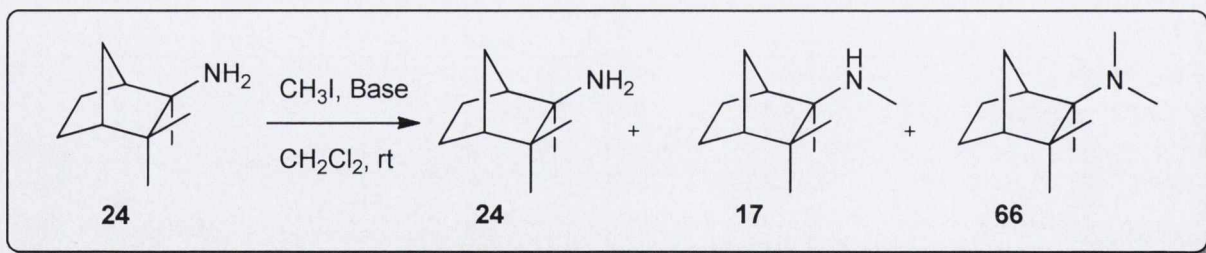


Scheme 2-15 Catalytic hydrogenation of azide **23**

#### 2.5.4 N,2,3,3-Tetramethylbicyclo[2.2.1]heptan-2-amine (**17**)

#### 2.5.5 S<sub>N</sub>2 amine alkylation

The final synthetic step in the synthesis of MA involved methylation of the amine moiety. The large steric contribution of the substituted [2.2.1]bicyclo system on the reactivity of azide **23** had already been demonstrated in the previous transformation and it was thought that it might be possible to exploit this in the methylation step. (Scheme 2-16) It was thought that the secondary amine **17** might be too sterically hindered to undergo a second methylation forming the unwanted tertiary amine **66**.



Scheme 2-16 The possibility of over alkylation of amine **24**

A number of experiments were devised to explore this possibility.

Table 2-3 details the results.

Table 2-3 Optimisation of alkylation of amine 10

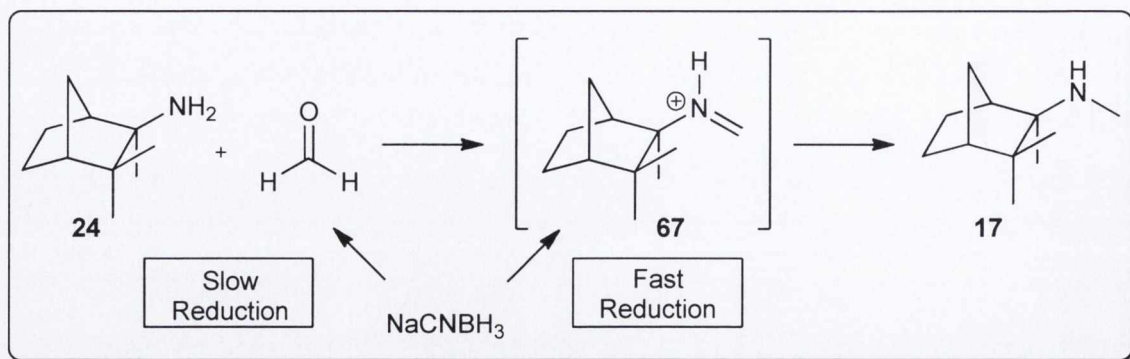
| CH <sub>3</sub> I Molar<br>Equivalence | Base                             | Starting material / Product Ratio Obtained |      |      |
|----------------------------------------|----------------------------------|--------------------------------------------|------|------|
|                                        |                                  | 24                                         | 17   | 66   |
| 2                                      | K <sub>2</sub> CO <sub>3</sub>   | 1                                          | 0.08 | 0.05 |
| 8                                      | K <sub>2</sub> CO <sub>3</sub>   | 1                                          | 0.1  | 0.6  |
| 1.1                                    | Et <sub>3</sub> N                | 1                                          | 0    | 0    |
| 5                                      | Et <sub>3</sub> N                | 0.33                                       | 1    | 0.58 |
| 1.1                                    | Et( <i>i</i> -Pr) <sub>2</sub> N | 1                                          | 0.4  | 0.09 |
| 2                                      | <i>t</i> -BuOK                   | 0                                          | 0.1  | 1    |
| 1.05                                   | DBU                              | 1                                          | 0.3  | 0.08 |
| 1.1                                    | DBU                              | 1                                          | 0.58 | 0.18 |
| 1.5                                    | DBU                              | 1                                          | 0.9  | 0.6  |
| 2                                      | DBU                              | 0.34                                       | 0.9  | 1    |
| 2.5                                    | DBU                              | 0.12                                       | 0.9  | 1    |
| 1.05 <sup>a</sup>                      | DBU                              | 1                                          | 0.11 | 0.07 |
| 1.05 <sup>b</sup>                      | DBU                              | 1                                          | 0.14 | 0.06 |
| 1.05                                   | None                             | 1                                          | 0.47 | 0.26 |

All reactions were carried out at a concentration of 0.2M with respect to **24** for 24h at room temperature. <sup>a</sup>0.04M with respect to **10**. <sup>b</sup>Reaction performed at 0°C.

As can be seen from the table, this approach failed to provide any encouraging potential reaction conditions and this avenue of investigation was abandoned.

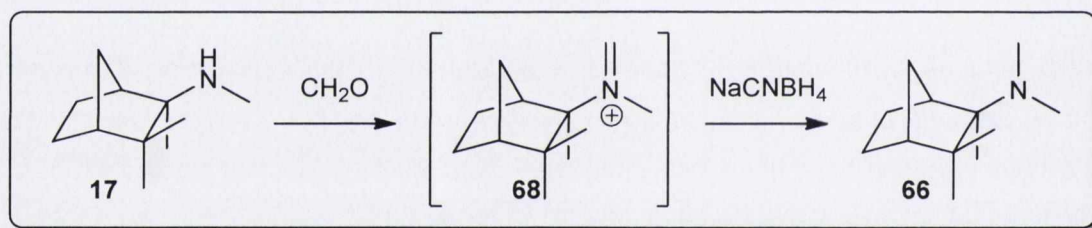
### 2.5.6 Reductive amination

Reductive amination provides a method that usually allows mono-methylation without the complication of over alkylation of amines. Sodium cyanoborohydride (NaCNBH<sub>3</sub>) is traditionally the favoured reagent for carrying out transformations of this type as it allows synthesis of the desired monoalkylated amines in a 'one pot' process.<sup>328</sup> In this case the iminium ion formed **67** would usually be reduced at a much higher rate than the aldehyde (formaldehyde) present which permits the possibility of having all reagents present *in situ*. (Scheme 2-17)



**Scheme 2-17** Proposed reductive amination of amine **24** with sodium cyanoborohydride

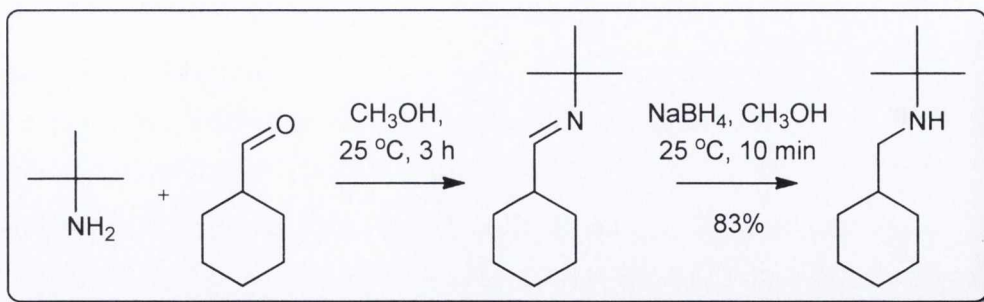
Unfortunately, upon attempting this reaction, a mixture of the mono- and dialkylated amines was obtained. It would seem that the formation of the unwanted iminium ion **68** shown in Scheme 2-18 occurs readily as the over alkylated amine **66** is observed even when 1 equivalent of formaldehyde is used.



**Scheme 2-18** Over alkylation observed with  $\text{NaCNBH}_3$

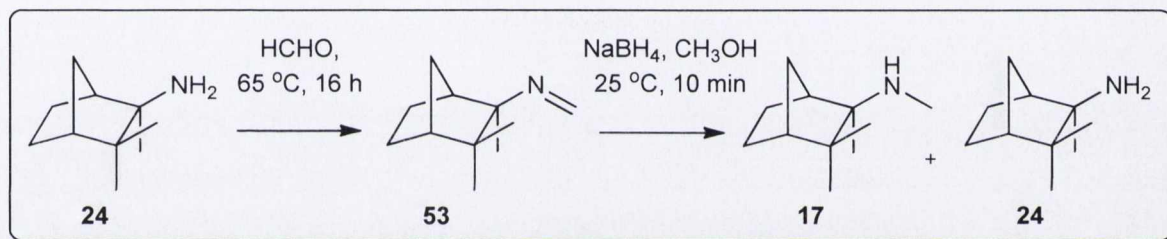
A problem of this nature was encountered by Abdel-Magid in co-workers in a systematic study carried out in 1996.<sup>329</sup> This group was investigating the chemistry of sodium triacetoxyborohydride ( $\text{NaBH}(\text{OAc})_3$ ), a reagent exhibiting similar reactivity to sodium cyanoborohydride but possessing a better toxicity profile. They found that a number of primary amines would undergo over alkylation when exposed to an aldehyde and sodium triacetoxyborohydride. To circumnavigate this problem a traditional stepwise reductive amination was carried out on a range of amines with impressive results. An example is shown in Scheme 2-19.





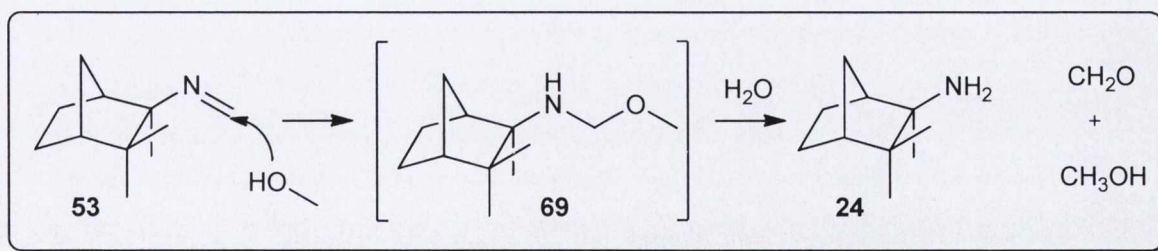
Scheme 2-19 Extract from A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff and R. D. Shah, *The Journal of Organic Chemistry*, 1996, 61, 3849-3862 (Table 5, entry 3)

This approach was attempted for the methylation of amine **24** and quantitative conversion to the imine **53** was confirmed by <sup>1</sup>H NMR spectroscopy. Disappointingly, the reduction of imine **53** by sodium borohydride as described by Abdel-Magid and colleagues lead to the formation of a mixture of the desired methylated amine **17** and amine **24**, the hydrolysis product of the imine.



Scheme 2-20 Attempted reductive amination of amine **24**

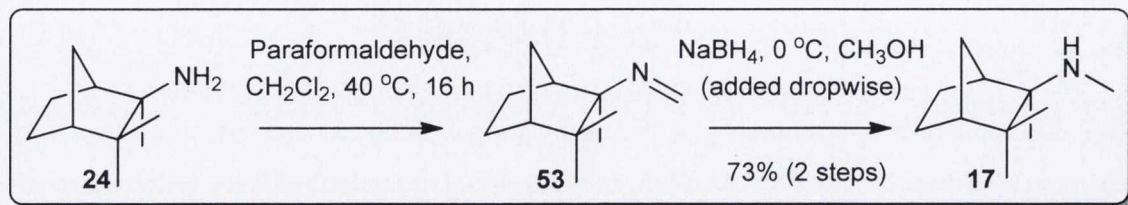
It was tentatively proposed that the imine **53** was reacting with methanol to form the N,O-acetal **69** which was then hydrolysed to amine **24** during workup. (Scheme 2-21)



Scheme 2-21 Imine hydrolysis in the presence of CH<sub>3</sub>OH and NaBH<sub>4</sub>

As the primary amine **24** and secondary amine **17** were inseparable by flash chromatography, quantitative reduction of imine **53** was deemed essential. To circumnavigate this

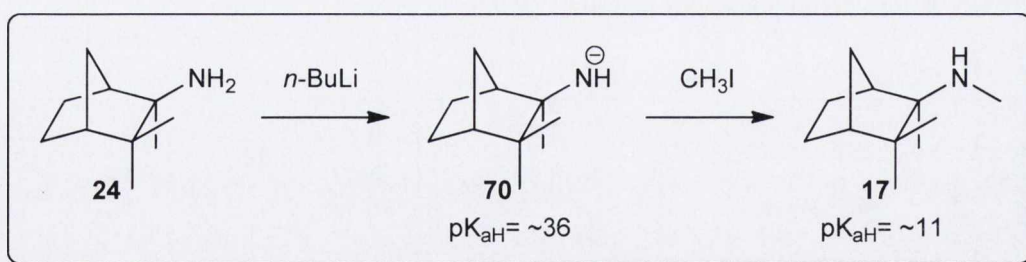
problem, imine formation was carried out in an aprotic solvent. Quantitative conversion to the desired imine **53** was confirmed by  $^1\text{H}$  NMR analysis before the addition of sodium borohydride followed by methanol dropwise to the cooled ( $0\text{ }^\circ\text{C}$ ) reaction mixture. Dichloromethane and cyclohexane were both screened for this purpose. Dichloromethane was found to facilitate much cleaner amine formation and gratifyingly, after the addition of sodium borohydride and methanol, no further purification was required. (Scheme 2-22)



Scheme 2-22 Successful reductive amination of amine **24** to yield MA

### 2.5.7 Deprotonation and subsequent alkylation

It was envisaged that the problem of over-alkylation could also be overcome by quantitatively deprotonating amine **24** prior to exposure to 1 equivalent of a methylating agent such as iodomethane. This approach should furnish the desired monoalkylated amine **17** as the nucleophilicity of the lithium amide species **70** generated would be far superior to the methylated amine **17** formed during the reaction. (Scheme 2-23)

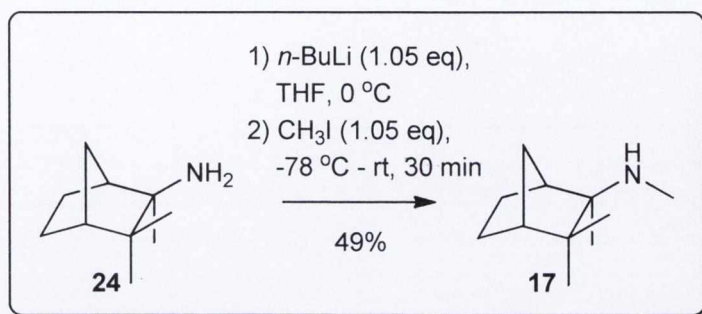


Scheme 2-23 Deprotonation - alkylation approach to methylation of amine **24**

This reaction was carried out and the desired amine **17** obtained in 49% yield. (Scheme 2-24) Clearly this method would not be suitable for more complex analogues but the overall short reaction time associated with this procedure would allow incorporation of an isotopically labeled



$^{11}\text{C}$  methyl substituent, useful for PET imaging. The advantages of this have been discussed in detail in section 1.6.4. It is worth noting that introduction of  $^{11}\text{C}$  would not be possible using the reductive amination method as the imine formation requires longer reaction times and moreover the synthesis of the required  $^{11}\text{C}$  labeled formaldehyde has not been reported to date.



Scheme 2-24 Monomethylation of amine **24** furnishing MA *via* a deprotonation protocol

## 2.6 Conclusion

A novel route to mecamylamine was developed. This route has the potential to allow the stereoselective installation of alkyl groups of varying length at position 2 and 3 of the MA framework. In the case of the azide reduction step, three alternative methods were investigated that each have their own advantages such as ease of implementation / purification in the case of hydrogenation or the high chemoselectivity obtained in the case of the Staudinger reduction. The methodology developed could now be exploited to synthesise a range of MA analogues displaying structural diversity at the position 2 and 3 which will be necessary for a comprehensive SAR study.

On a side note, this methodology will allow the facile incorporation of up to four  $^{13}\text{C}$  labels. A viable method for the introduction of a  $^{11}\text{C}$  radiolabeled methyl substituent that provides the potential for PET imaging studies was also developed.



# **Chapter 3**

## **Diversity in position 2 and 3**

### 3 Diversity in position 2 and 3

#### 3.1 Targets

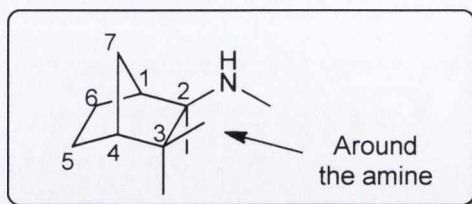


Figure 3-1 Targeting position 2 and 3 on the MA skeleton

This chapter describes the attempts to introduce diversity at the position 2 and 3 of the MA skeleton. We considered that there were 3 important issues:

1. The effect of stereoselective and regioselective installation of non methyl groups at the 2 and 3 positions would be assessed. The simplest way to achieve this would be to exchange methyl for ethyl substituents at strategic points within the previously developed route as shown in Figure 3-2. It was envisaged that the “picket fence effect” could be exploited to control the stereochemistry of  $R_1$  and  $R_2$  by varying their order of addition to the MA framework.

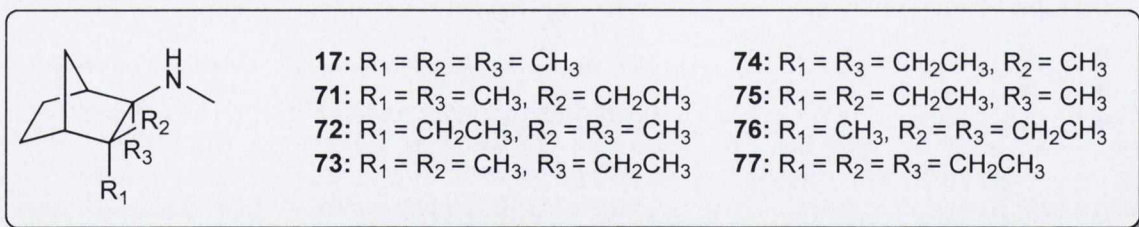


Figure 3-2 Initial MA analogue targets

2. Investigation of the *exo*-amine / *endo*-methyl relationship in MA would be performed by the synthesis of *endo*-MA **13** (Figure 3-3). This would clearly require significant expansion of the previously developed chemistry.

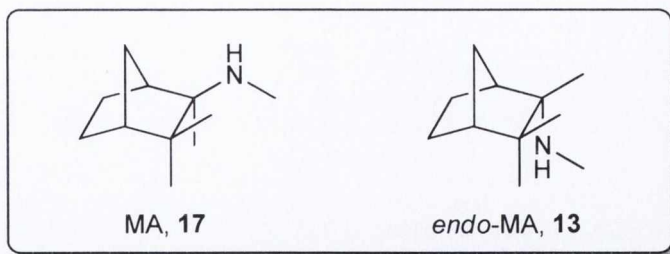


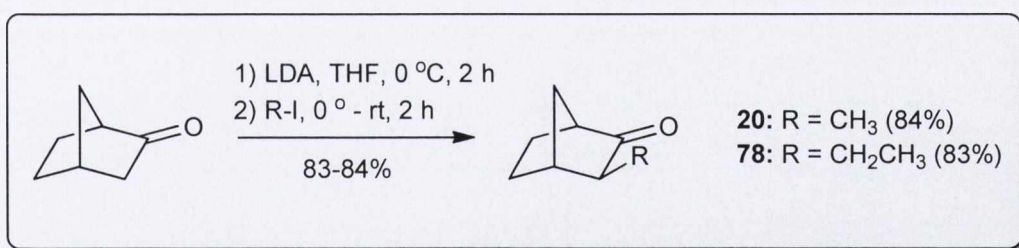
Figure 3-3 MA and *endo*-MA

3. The effect of alkyl substitution on the amine moiety would be briefly investigated. Although previous SAR studies have concluded that increasing steric bulk at this position by *N*-alkylation produces a drop in antagonistic activity *in vivo*,<sup>263, 270</sup> analogues of this type have not been tested for their affinity for nAChR subtypes *in vitro*. It is conceivable that a reduction in IC<sub>50</sub> values could be acceptable if a significant increase in selectivity for a nAChR subtype was observed.

## 3.2 Synthesis of basic 2 and 3 alkyl substituted analogues

### 3.2.1 Ketone synthesis

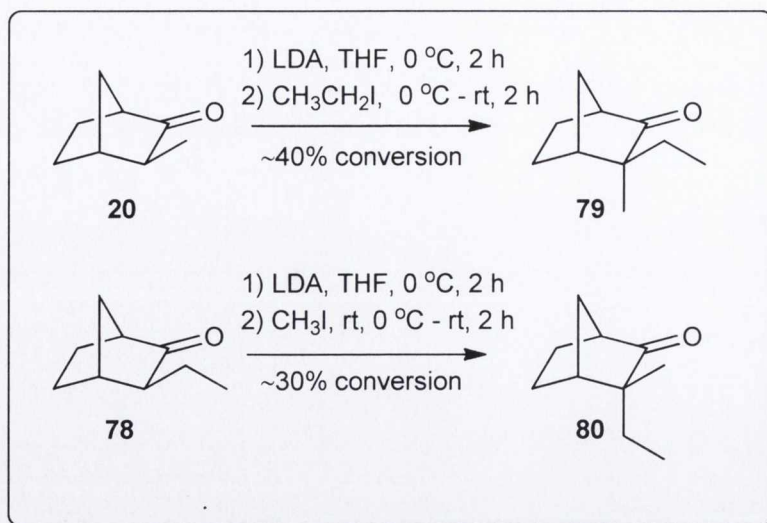
The synthesis of the two required monoalkylated ketones (**20** and **78**) was carried out pursuant with the methodology employed in the synthesis of MA. (2.1)



Scheme 3-1 Synthesis of monoalkylated ketones **20** and **78**

The synthesis of the required dialkylated ketones proved problematic. The conversion of mono to dialkylated ketone could be estimated from <sup>1</sup>H NMR spectroscopic analysis of the crude product obtained and this was shown to be unacceptably low. (Scheme 3-2) As such, the formation of the *bis*-ethylated ketone **83** was not attempted.





Scheme 3-2 Attempted LDA mediated formation of dialkylated ketones 79 and 80

As was found during the synthesis of MA, the mono and dialkylated ketones were inseparable by chromatographic means. Again, variation of the reaction conditions failed to improve the conversions obtained. It was concluded that the methodology employed in the synthesis of MA would evidently not provide a general method for the synthesis of analogous compounds and an alternative method would have to be devised.

The literature evidence pertaining to the alkylation of ketone **20** *via* LDA mediated enolate formation<sup>286</sup> was set aside as it had already been shown to be irreproducible in our hands. The focus of investigation was instead centered on Corey's early work in this area relating to the synthesis of  $\beta$ -santalene itself and a diastereomer of the parent compound published in 1962.<sup>285</sup> The ketones (**81** and **82**) shown in Figure 3-4 had been synthesised as required intermediates in the total syntheses.

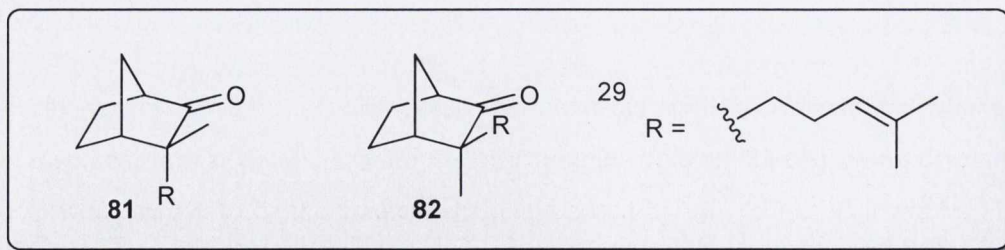
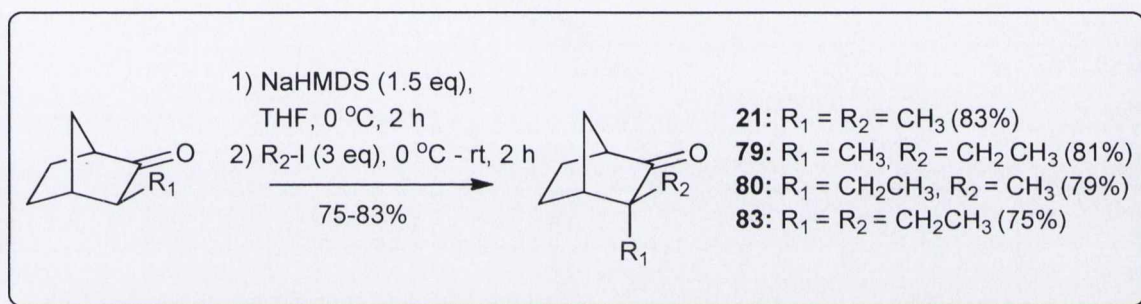


Figure 3-4 Extract from E. J. Corey, R. Hartmann and P. A. Vatakencherry, *Journal of the American Chemical Society*, 1962, 84, 2611-2614, Fig 1.

Corey and colleagues had used sodium amide or sodium triphenylmethane to carry out the deprotonations required for the substituted ketone syntheses. Although LDA was first prepared by Hammell and Levine at the University of Pittsburgh in 1950,<sup>330</sup> it remained in relative obscurity<sup>331</sup> until 1967 when a report by Creger highlighted the advantages of LDA as a highly reactive base.<sup>332</sup> As such, it was assumed that these bases were employed as the standard powerful non-nucleophilic bases available at the time. The basicity of these reagents was not stronger than that of LDA ( $pK_a$  of triphenylmethane is approximately 31) but it was hypothesised that the counterion might play a role.

The use of sodium bis(trimethylsilyl)amide (NaHMDS) in place of LDA was investigated as Krotz *et al.*<sup>333</sup> had employed this reagent to successfully effect a similar transformation and gratifyingly, this facilitated the stereoselective incorporation of either methyl or ethyl substituents to furnish the desired compounds (**21**, **79**, **80**, **83**) in good yield. (Scheme 3-3)



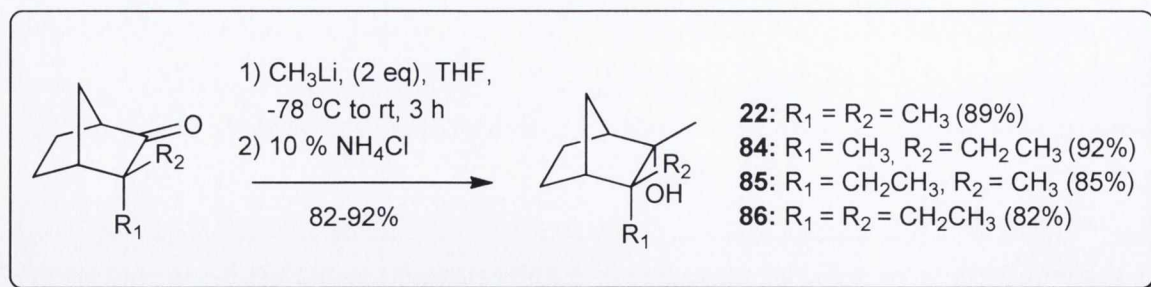
**Scheme 3-3 Successful NaHMDS mediated formation of dialkylated ketones**

This approach requires purification by flash chromatography to remove byproducts arising from the use of NaHMDS but the benefit of clean conversion far outweighs the added inconvenience associated with isolation of the desired products.

### 3.2.2 Alcohol synthesis

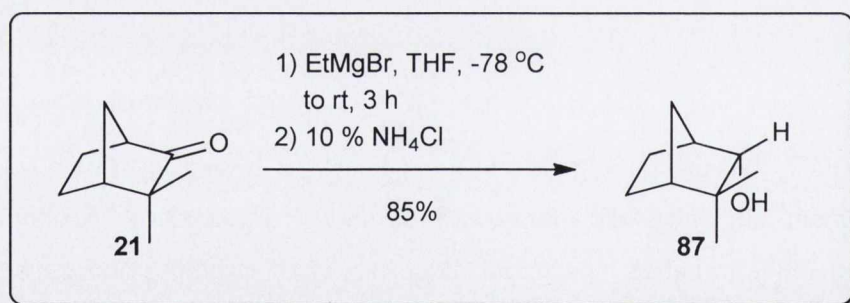
Installation of methyl substituents at position 2 to form **22**, and **84-86** was achieved in a facile manner using the methodology developed for the synthesis of MA. (Scheme 3-4)





Scheme 3-4 Synthesis of MA analogue alcohol precursors

The next synthetic targets required were alcohols substituted with an ethyl group at position 2. We were somewhat surprised to find that the price per mole of ethyllithium was approximately 7 times that of methyllithium.<sup>310</sup> It was thought that the equivalent Grignard reagent could be employed to carry out the desired transformation. However, an unexpected experimental result was obtained when attempting this reaction in practice. (Scheme 3-5) A single product was obtained after allowing the reaction to warm from  $-78\text{ }^\circ\text{C}$  to room temperature over 3 hours, the structure of which was tentatively assigned as that of **87** by 2d-NMR spectroscopy. A review of the literature revealed that in 1974, Vaughan *et al.* had carried out the same reaction with this substrate under slightly different conditions and reported a similar result.<sup>334</sup> This group had attempted the 1,2 addition process at room temperature and had obtained the desired tertiary alcohol **88** as a minor product. It was reasoned therefore that the hydride transfer process was favoured over nucleophilic addition to the carbonyl moiety.

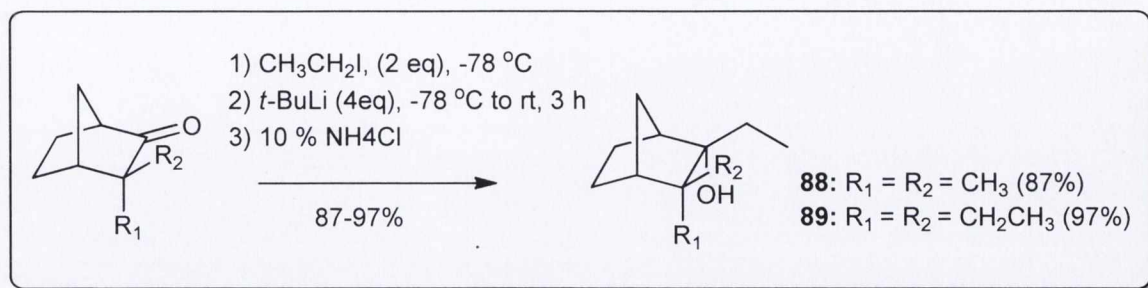


Scheme 3-5 Unexpected hydride transfer observed with ethylmagnesium bromide

It would have been economically challenging to use the commercially available ethyllithium solution on the large scale required for multiple analogue syntheses. The preparation of ethyllithium using an analogous procedure for methyllithium from iodomethane<sup>335</sup> or bromomethane<sup>336</sup> and lithium metal was attempted but failed to perform the required 1,2 addition

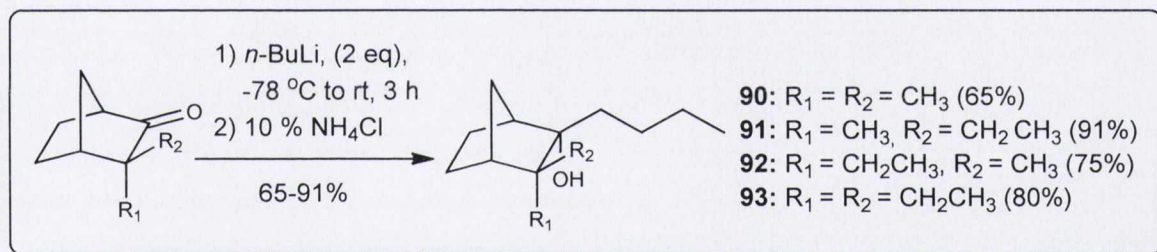


on a simple model compound. Gratifyingly, halogen lithium exchange using iodoethane and *tert*-butyllithium (which is the same price per mole as methylolithium<sup>310</sup>) generated the required ethyllithium *in situ* and this method facilitated the synthesis of the tertiary alcohols **88** and **89** shown in Scheme 3-6.



Scheme 3-6 Ethyllithium *in situ* formation via halogen lithium and 1,2 addition

The synthesis of a number of other tertiary alcohols (**90-93**) was also accomplished with a view to further broadening the SAR analysis at position 2 in the future. (Scheme 3-7)

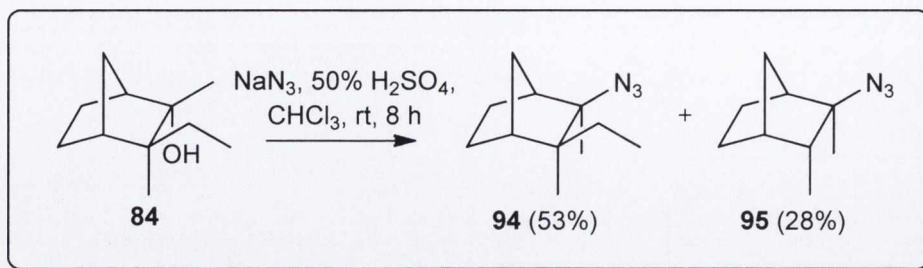


Scheme 3-7 Alcohols possessing a butyl substituent at the 2 position

### 3.2.3 Azide synthesis

Despite the success of the route to prepare MA and our ability to avoid the Wagner-Meerwein rearrangement in that case, the synthesis of analogues of azide **23** displaying diversity at position 2 or 3 would prove to be the greatest challenge posed by this project as a whole. The reaction shown in Scheme 3-8 was the first transformation of this type that was investigated. The course of the reaction was monitored by  $^1\text{H}$  NMR spectroscopy and it was found that a reaction duration of twice that for alcohol **22** was required for this substrate in order for the starting material **84** to be completely consumed. A side product was formed simultaneously with the

desired product but fortunately this could be removed by flash chromatography. The structure of this side product was tentatively assigned as **95** by 2d-NMR spectroscopy. Unfortunately it was not possible to acquire an accurate mass spectral analysis for azide **95** despite employing a wide range of mass spectrometry techniques.

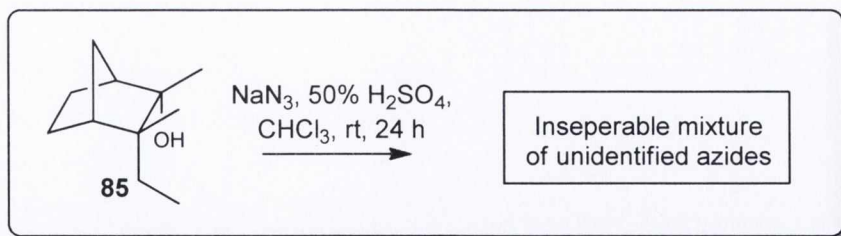


Scheme 3-8 Synthesis of azide **94**

No precedent for the formation of **95** by a reaction of this type was found in the literature. Interestingly, it was found that prolonged exposure to the acidic reaction medium eventually decomposed both azides but did not induce a Wagner-Meerwein rearrangement analogous to that observed in the case of trimethyl azide **23** in either compound. Nevertheless, the desired azide **94** had been synthesised and could be isolated in acceptable yield.

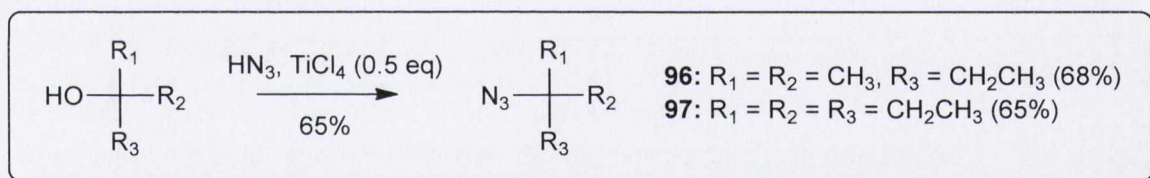
Unfortunately, the attempted synthesis of the expected azide from alcohol **85** did not proceed as desired. (Scheme 3-9)  $^1\text{H}$  NMR spectroscopy was used to monitor the disappearance of alcohol **85** but disappointingly, at least 4 distinct compounds were observed forming throughout the course of the reaction. These compounds proved to be inseparable by flash chromatography and no individual compounds, desired or otherwise could be isolated. A large number of optimisation reactions were carried out varying all parameters in the reaction. As was the case with the synthesis of azide **23**, the only factor found to greatly affect the reaction was the concentration of sulfuric acid employed. Unfortunately, while changing this parameter brought about large changes in the rate of formation of the products it did not affect the ratios of the compounds obtained.





**Scheme 3-9 Attempted azide formation from alcohol 85**

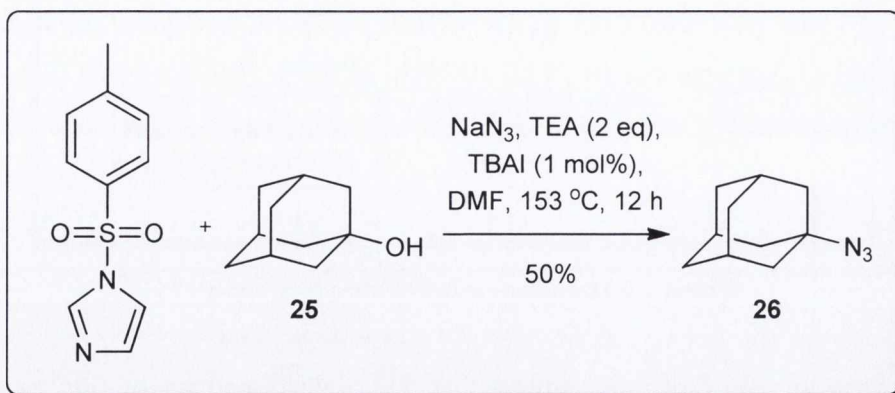
A review of the literature showed that  $S_N1$  transformations of this type had been successfully carried out in a variety of ways. It was hoped that formation of the required carbocation by an alternative method might prevent the unwanted rearrangements occurring. In 1984, Hassner and co-workers<sup>337</sup> described a Lewis acid mediated approach for converting allylic, benzylic and tertiary alcohols into the corresponding azides. In Scheme 3-10, formation of two of the tertiary azides synthesized (**96** and **97**) are shown. A hydrazoic acid solution in chloroform was successfully produced and isolated as described by the authors but treatment of alcohol **22** with this solution and titanium tetrachloride failed to promote the desired reaction. After 72 hours, the reaction was abandoned.



**Scheme 3-10** Extract from Hassner, A.; Fibiger, R.; Andisik, D. *The Journal of Organic Chemistry* 1984, 49, 4237-4244, Table IV, entries 9 and 10

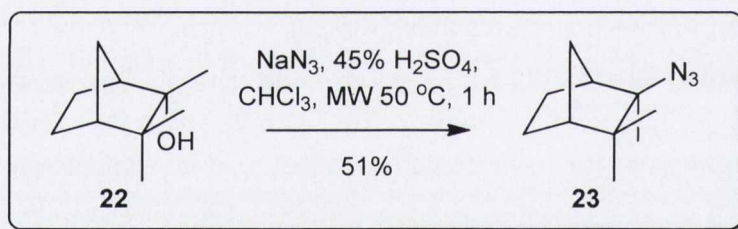
Rad and co-workers<sup>338</sup> described a general procedure for the conversion of alcohols to azides using tosylimidazole. 1-Azidoadamantane **26** was synthesised using this methodology (Scheme 3-11). These reaction conditions were also applied to alcohol **22** but disappointingly, no conversion was observed after 48 hours.





Scheme 3-11 Extract from M. Rad, S. Behrouz and A. Khalafi-Nezhad, *Tet. Lett.*, 2007, 3445-3449, Table 6, entry 10

It was envisaged that a microwave assisted synthesis might facilitate azide formation at a lower acid concentration and that this could aid in avoiding the troublesome competing rearrangements. Encouraging preliminary results showed that it was possible to promote the synthesis of azide **23** using a 45% sulfuric acid aqueous phase at  $50\text{ }^\circ\text{C}$  in the microwave in 1 hour.

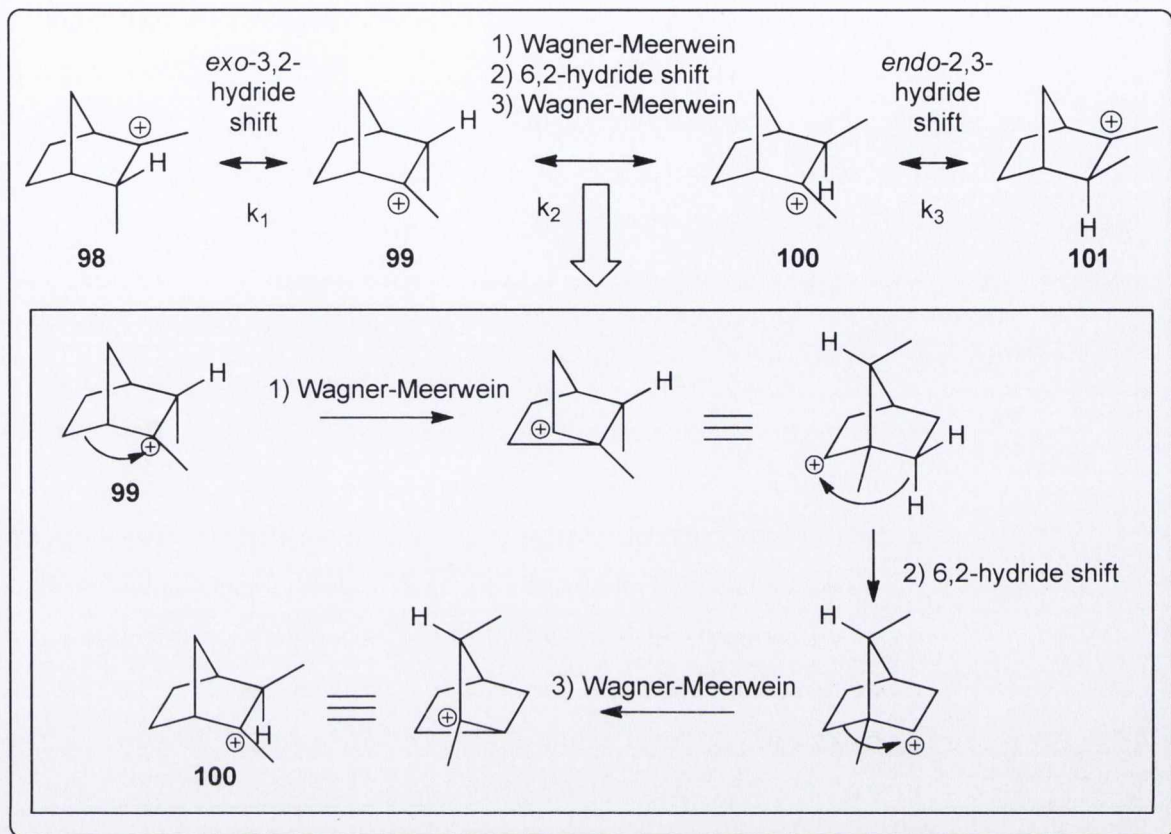


Scheme 3-12 Microwave assisted synthesis of azide **23**

Regrettably, when alcohol **85** was exposed to the same reaction conditions, the familiar undesired rearrangements contrived to produce the same ratio of products as was observed in the previous experiments.

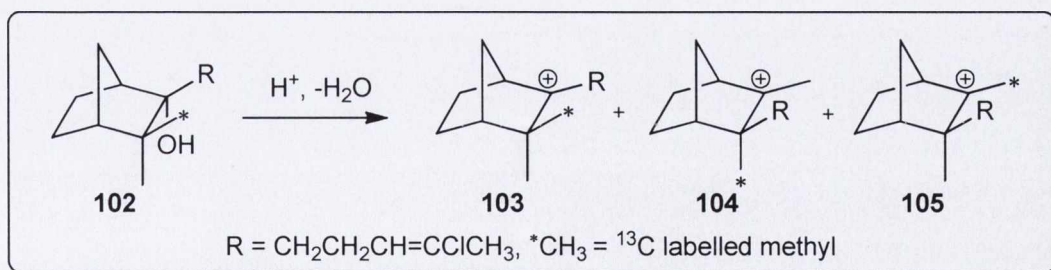
Having failed to facilitate the desired conversion of alcohol **85** to its corresponding azide cleanly, we turned our attention to an interesting study focusing on norbornyl cations carried out by Sorensen and co-workers.<sup>290</sup> This group attempted a kinetic analysis of the conversion between possible norbornyl cationic species **98-101** shown in Scheme 3-13. Their findings indicated that the rate of interconversion of **98** to **99** is significantly faster than the rate of interconversion of **99** to **100** which is moderately faster than the rate of interconversion of **100** to **101**. To summarise;  $k_1$

$\gg k_2 > k_3$ . This group also suggested that **98** or **99** are more thermodynamically stable species than **100** or **101**.



Scheme 3-13 Rearrangements associated with the norbornyl cation

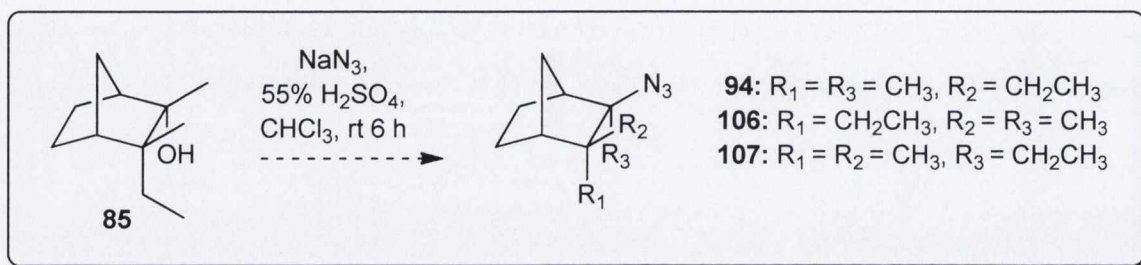
In 1983, Baldwin and co-workers<sup>307</sup> demonstrated rearrangements of this type with alkyl shifts in place of the hydride shifts. They demonstrated the formation of 3 distinct cations **103-105** from the alcohol **102** shown in Scheme 3-14.



Scheme 3-14 Various carbocations generated under acidic conditions from alcohol **102**



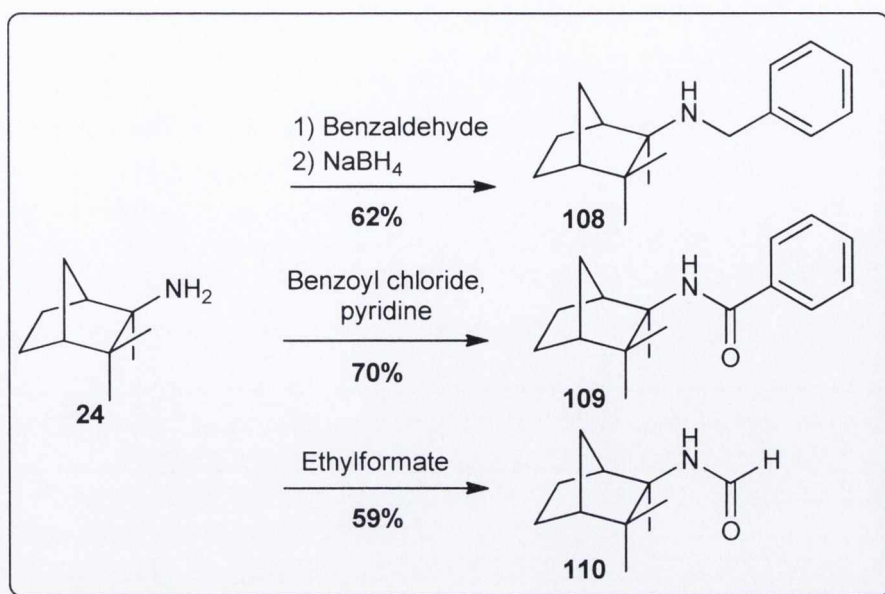
It was therefore hypothesised that formation of the carbocation derived from alcohol **85** could generate the useful isomeric products **106-108** shown in Scheme 3-15. In addition however, Wagner-Meerwein rearrangements analogous to that which formed azide **48** (Table 2-2) or unexpected rearrangements analogous to that which facilitated formation of azide **95** (Scheme 3-8) could produce an array of structurally related undesired compounds. Even so, it was hypothesised that if the various products formed could be separated, then the azides required for the SAR study of MA could be obtained, albeit in low yield.



Scheme 3-15 Potentially useful rearranged products from azide formation reaction

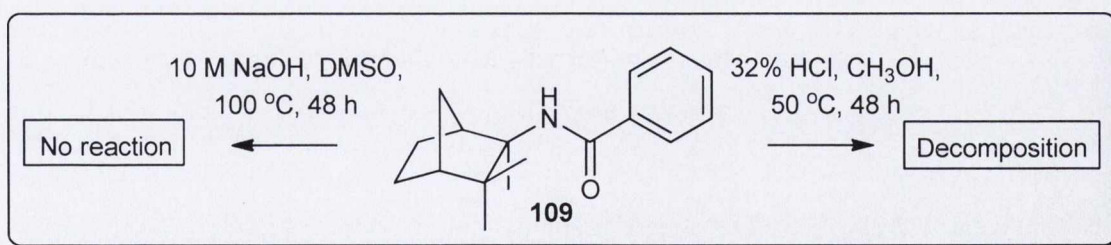
The starting material, alcohol **85**, was observed to be completely consumed after 6 hours after treatment with sodium azide and 55%  $\text{H}_2\text{SO}_4$  (Scheme 3-15) to generate a mixture of azide compounds. The major problem with isolation of the azides formed was their extreme lack of polarity. An  $R_f$  value of approximately 0.6 in 100% hexane was recorded by TLC analysis for the spot pertaining to the mixture. It was believed that derivatising the azides might provide a means for their separation by chromatography. The azide mixture was reduced by catalytic hydrogenation to yield a mixture of their respective amines. Unfortunately, the separation of these amines proved impossible as they tended to 'drag' on silica gel and co-elute. Deactivating the silica failed to improve the separation. This was unsurprising given that the mixture was thought to contain a number of isomers with subtle structural differences. It was thought that if the basicity of the amines could be temporarily masked, separation of the mixture might be possible. It was decided that protection and deprotection reactions should be optimised for amine **24** initially before applying the methodology to the more precious amine mixture derived from the azide mixture formed from alcohol **85** as shown in Scheme 3-15.





Scheme 3-16 Protection of amine 24

From the small selection of protecting groups screened (Scheme 3-16), the *N*-benzoyl amine **109** was found to run reasonably well on silica gel exhibiting a sharp spot with an  $R_f$  value of 0.15 in 95:5 hexane:EtOAc. Frustratingly however, cleavage of the benzoyl protecting group provided its own challenge. Basic hydrolysis failed to facilitate any conversion from the amide **109** while acid hydrolysis caused decomposition prior to cleavage of the *N*-benzoyl group. (Scheme 3-17) The possibility of performing a reduction to furnish the *N*-benzyl amine **108** which could presumably be converted back to amine **24** *via* catalytic hydrogenation was considered but subsequently disregarded as being too low yielding given that it was suspected less than 20% yield of any individual azide had been formed from alcohol **85**.



Scheme 3-17 *N*-benzoyl cleavage attempts in **109** proved unsuccessful

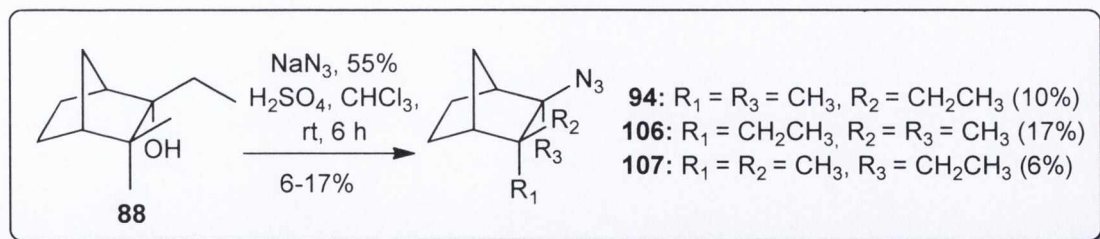
It was thought that the most desirable option would be the direct separation of the azide mixture which would preclude resorting to labor intensive and time consuming derivatisation.

Around this time, the School of Chemistry in Trinity College acquired high performance liquid chromatography (HPLC) equipment with preparative capability. The separation of the azide mixture derived from alcohol **85** was attempted initially by reverse phase and later by normal phase HPLC on an analytical scale without success despite testing a range of solvent systems in over 20 runs.

Finally, in an effort to categorically rule out the notion of direct separation of the azide mixture formed from alcohol **85**, we considered using a huge quantity of silica gel. To this end, a 500 mg sample of the mixture was loaded onto a 600 mL silica gel column and a mobile phase of 100% hexane was employed. As the mixture was eluted a number of fractions were collected despite the fact that TLC analysis could not differentiate between the fractions. However,  $^1\text{H}$  NMR spectroscopic analysis of these fractions showed that although no pure compounds had been isolated, the ratio of products in each fraction was noticeably different. It was thought that this separation effect could be exploited to isolate the products cleanly after a number of repeated chromatographic runs. Unfortunately this approach proved unsuccessful in this case due to the presence of an inseparable unidentified side product in the reaction. It was believed that this side product was analogous to azide **95** that was formed from alcohol **84** (Scheme 3-8). However it was hypothesised that this method could be used to separate other mixtures of this type.

Alcohol **88** was exposed to the same azide formation conditions in the hope that the use of a different substrate would also form the desired azide compounds. Gratifyingly, the azide mixture derived from alcohol **88** was found to be separable after repeated separation attempts by flash chromatography employing a large excess of silica gel. (Scheme 3-18) Evidently, the inseparable undesired side product formed on exposing alcohol **84** to the azide formation conditions is not formed in the case of alcohol **88**. This woefully inelegant, cumbersome and low yielding approach was seen as the only viable option for the synthesis of the azides required to carry out the complete SAR study of MA. Approximately 15 chromatographic runs were carried out on a 1200 mL silica gel column to separate the mixture obtained from 2 g of alcohol **88**. After each chromatographic run, 3 to 5 fractions were analyzed by  $^1\text{H}$  NMR spectroscopy to ascertain their composition and identify any clean fractions. This process was made considerably less wasteful by the fact that the same column could be used repeatedly and the column eluent was constantly recycled. Overall the purification process could be completed in about 5 days.





Scheme 3-18 Synthesis of azides **94**, **106** and **107**

The unambiguous assignment of these isomeric structures was of paramount importance. This was achieved by performing a complete systematic NMR analysis similar to that outlined in section 5.1. Such an undertaking for each compound proved extremely timeconsuming but undoubtedly necessary.



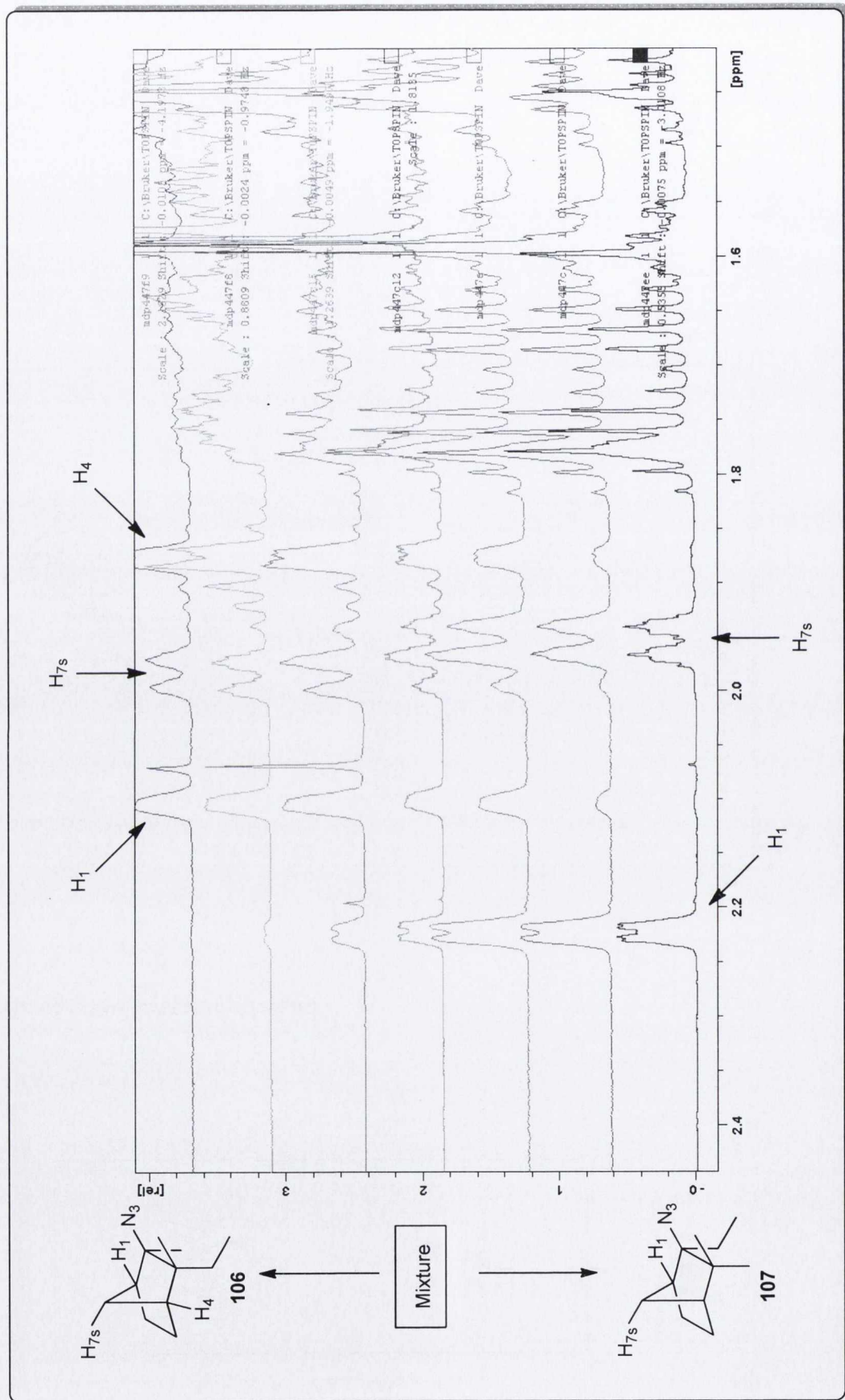
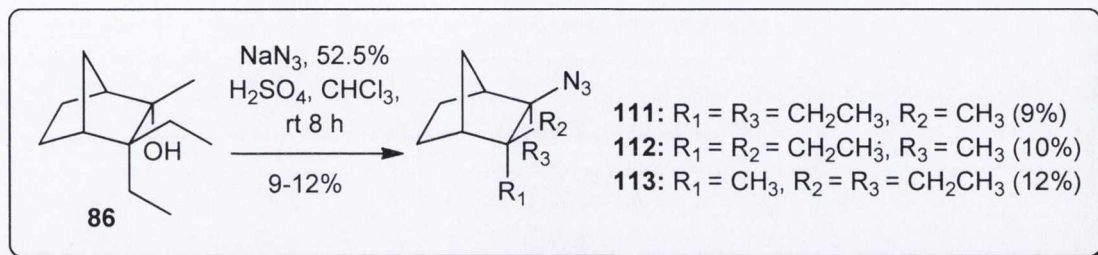


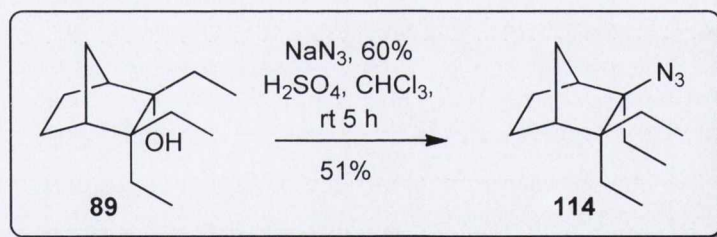
Figure 3-5 Gradual purification of 106 and 107 achieved by multiple chromatographic separations on silica gel eluting with 100% hexane

A similar approach was used to obtain a number of the other azides required for this series of analogues. Alcohols **86** and **88** were screened in the azide formation reaction in an attempt to ascertain which would provide the azide mixture most amenable to separation. Eventually, it was found that alcohol **86** was able to furnish the required azides cleanly albeit in very low yields. (Scheme 3-19)



Scheme 3-19 Synthesis of azides 111-113

The final azide necessary to complete the required series was obtained from alcohol **89**. (Scheme 3-20) This transformation, like that which forms azide **23**, is greatly simplified by the fact that the 2, 3 alkyl shifts that are known to occur do not affect the final structure of the compound while an unidentified rearranged azide analogous to azide **95** (Scheme 3-8) proved separable by flash chromatography.



Scheme 3-20 Synthesis of azide 114

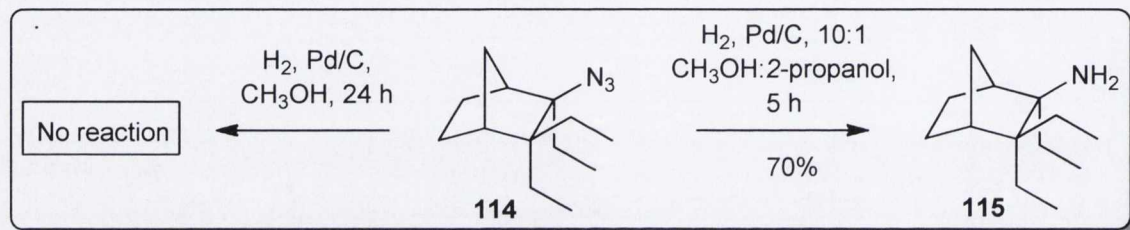
Although the isolation of the individual azides required to complete this series of analogues proved troublesome it was fervently hoped that the separation of isomers formed in future analogue syntheses will prove simpler as any compounds substituted with a heteroatom should possess a lower  $R_f$  value.

Having prepared and isolated the required azides we turned our hand to the synthesis of the corresponding amines.



### 3.2.4 Amine synthesis

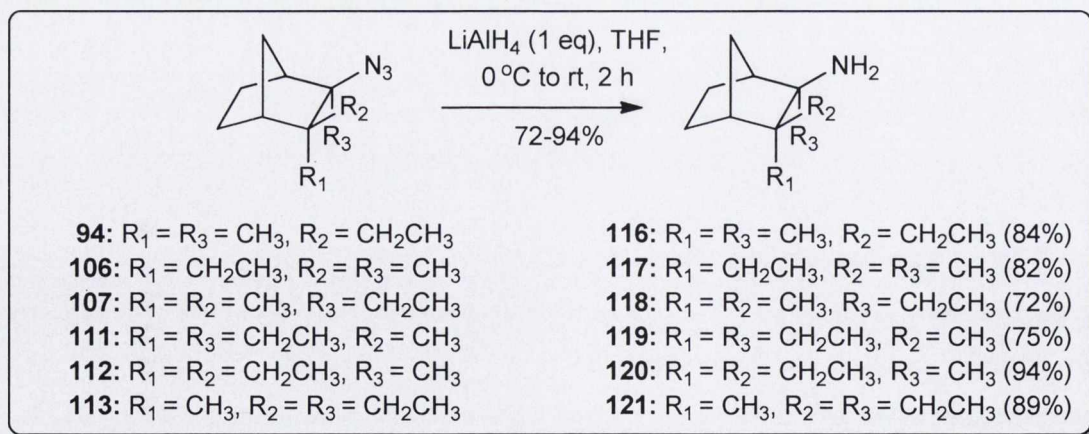
As stated in section 1.5.3, catalytic hydrogenation was found to be the preferred method for azide reduction and it was envisaged that the newly generated azide series would be reduced in this way. Reduction of azide **114** was attempted as shown in Scheme 3-21 but no reaction was observed. Satisfyingly, it was discovered that the lack of solubility of the substrate in methanol was the source of the problem and that performing the reduction in a methanol/isopropanol solvent mixture facilitated the formation of amine **115**.



Scheme 3-21 Synthesis of amine **113** from azide **112**

Disappointingly, the attempted reduction of azide **94** by this method resulted in decomposition of the substrate. Varying the solvent did not affect the reaction outcome. Considering that catalytic hydrogenation is regarded as one of the 'mildest' methods of reduction available, the decomposition that was observed was both frustrating and inexplicable.

Thankfully, it was found that the reduction of all azides synthesised including azide **94** could be accomplished cleanly with the use of lithium aluminium hydride. (Scheme 3-22)

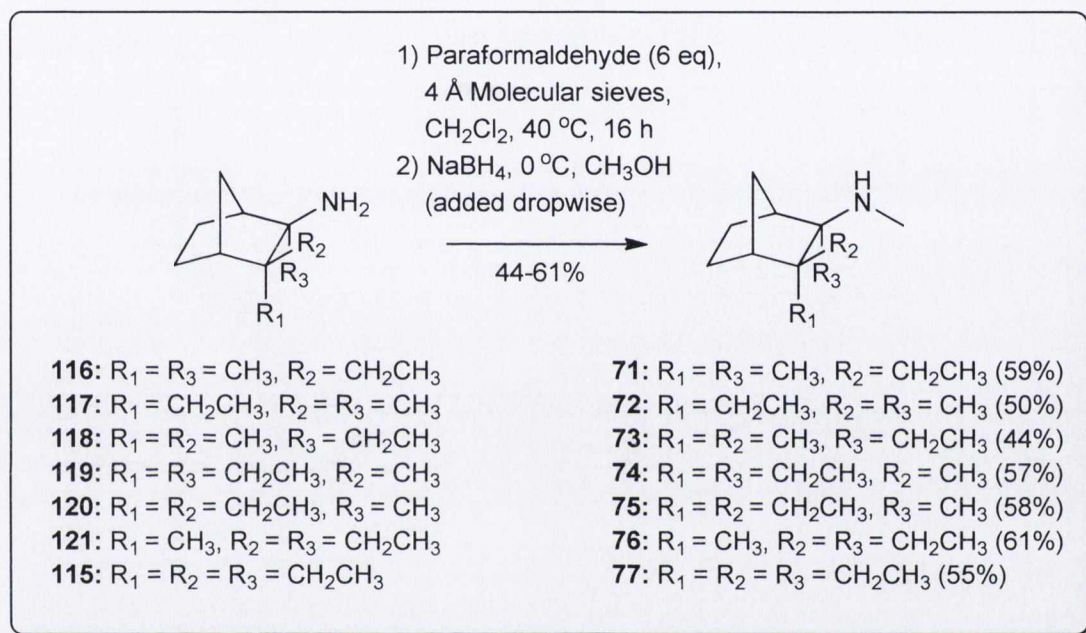




Scheme 3-22 Synthesis of amines 116-131 from the corresponding azides

### 3.2.5 Methylated amine synthesis

Thankfully, the final synthetic step in the synthesis of the desired MA analogue series, methylation of the amine was successfully carried out by employing the reductive amination methodology previously described in section 1.6.2. (Scheme 3-23)



Scheme 3-23 Synthesis of methylated amines 71-77

## 3.3 Synthesis of *endo*-mecamylamine

### 3.3.1 Imine precursor (27)

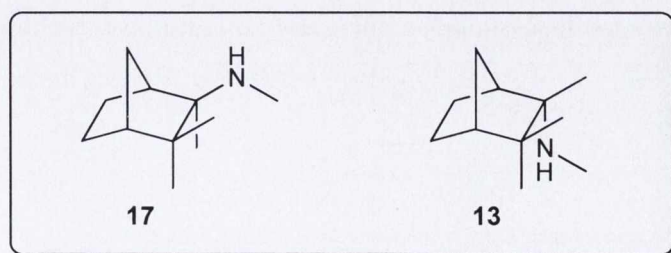
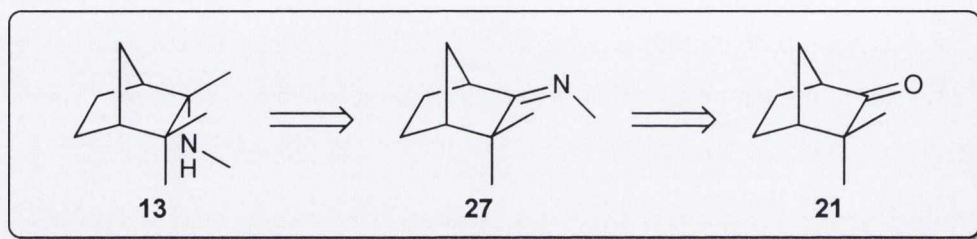


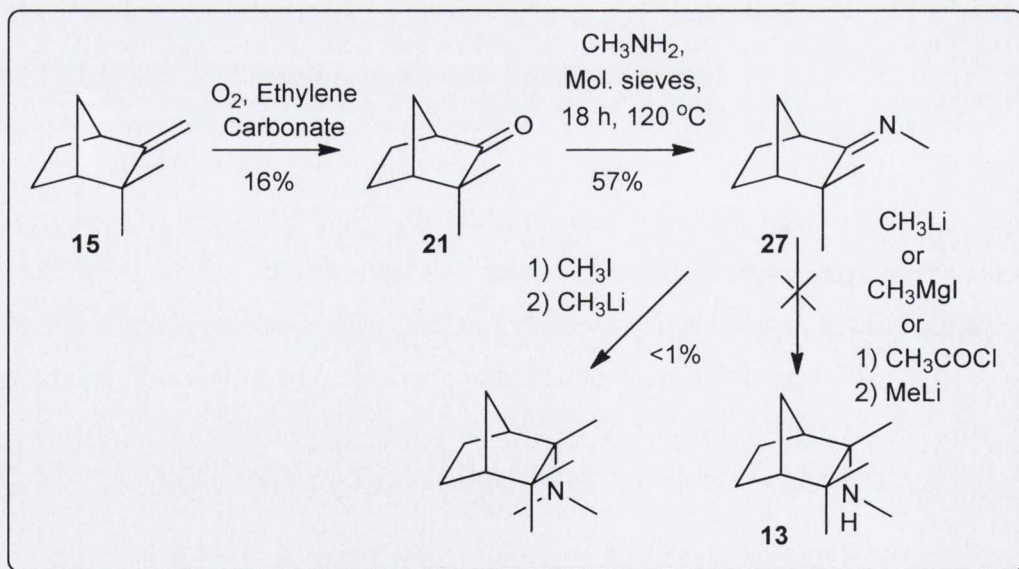
Figure 3-6 MA and *endo*-MA

The final compound required to complete our initial series would allow us to examine the *endo* / *exo* relationship of the methyl and methyl amino groups in MA **17**. To this end, it was deemed necessary to prepare *endo*-MA **13**. The simplest way to prepare **13** would be to add a methyl group to the preformed imine **27** in a manner which is dictated by the “picket fence” effect. (Scheme 3-24)



Scheme 3-24 Preparation of *endo*-MA

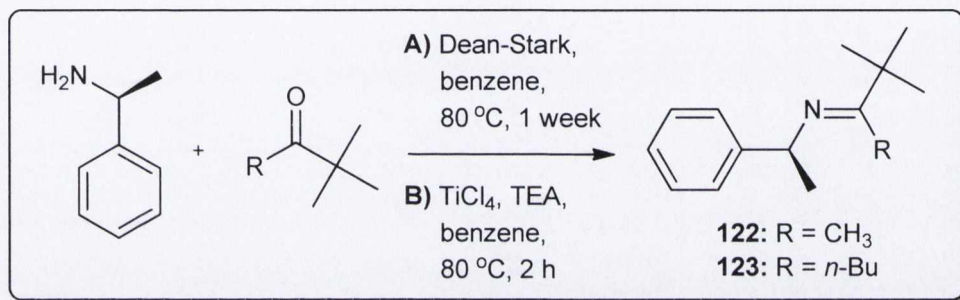
As such, the first challenge would be to obtain the required imine **27**. Suchocki *et al.*<sup>270</sup> reported the synthesis of the **27** by bubbling methylamine gas through a solution of ketone **21** for 18 hours but were unable to force the formation of the required amine **13** from the imine **27**. (Scheme 3-25)



Scheme 3-25 Attempts by Suchocki *et al.* to synthesise *endo*-MA<sup>270</sup>

It was our intention to employ a strong Lewis acid to greatly increase the electrophilicity of ketone **21** thereby promoting imine formation. It was hoped that this would substantially increase the rate of reaction and reduce the waste associated with bubbling a gaseous reagent through a system over 18 hours.

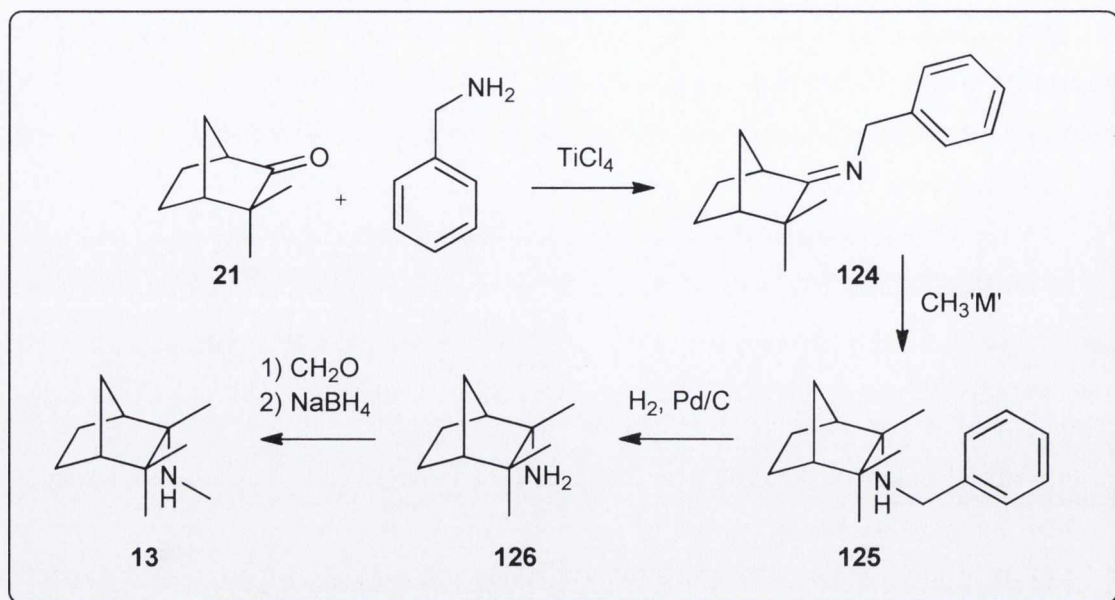
A review of the literature showed that the hindered imine **122** shown in Scheme 3-26 could be synthesised *via* the azeotropic removal of water by heating a solution in benzene at reflux for 1 week.<sup>339</sup> However, by modifying the original titanium chloride mediated procedure of Weingarten *et al.*<sup>340</sup> the synthesis of this compound had been achieved by Moss and co-workers in 86% yield in 2 hours.<sup>341</sup> The latter group also achieved the synthesis of the more sterically demanding imine **123** (Scheme 3-26) in 80% yield albeit in a slightly longer 16 hours.



Scheme 3-26 Synthesis of hindered imines

Initial attempts to synthesise the required imine **27** involved bubbling gaseous methylamine through a solution of ketone **21** and titanium tetrachloride but unfortunately this proved unsuccessful. It was thought that the volatility of the methylamine (boiling point -6 °C) prevented significant solvation of the gas in the reaction solvent. An alternative approach would be required.

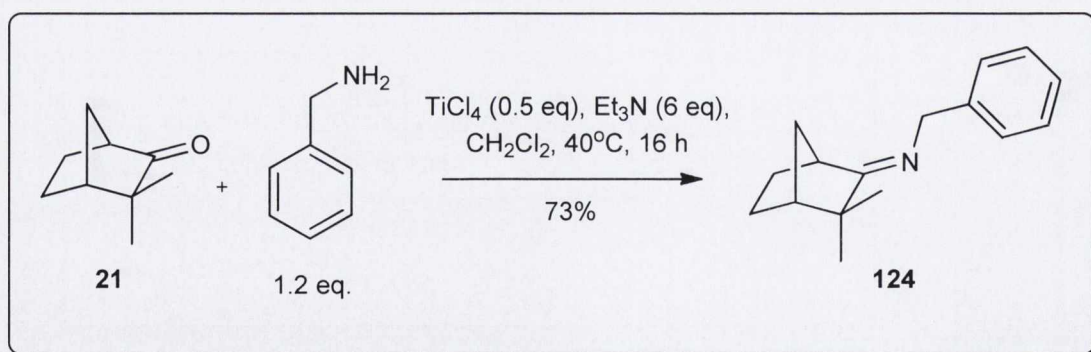




Scheme 3-27 Proposed alternative route to *endo*-MA x

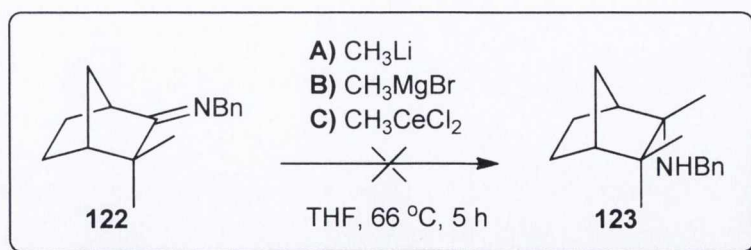
To circumnavigate the problems associated with the use of a gaseous reagent, it was proposed that the *N*-benzylimine **124** be synthesised in place of imine **27**. This compound could then undergo the proposed 1,2 addition with an organometallic reagent to generate the amine **125** and subsequent cleavage of the benzyl function by catalytic hydrogenation would furnish **126** which could be converted to *endo*-MA *via* reductive amination. (Scheme 3-27)

The required imine **124** was synthesised in an acceptable 73% yield validating the methodology outlined by Moss and co-workers.<sup>341</sup> (Scheme 3-28)



Scheme 3-28 Synthesis of imine **124**

Unfortunately, attempts to promote 1,2 addition to the imine using  $\text{CH}_3\text{CeCl}_2$ , methyllithium or methylmagnesium bromide were unsuccessful as shown in Scheme 3-29.



Scheme 3-29 Attempts to promote 1,2 addition to imine **122**

A strong colour change was observed however upon addition of the organometallic species to **124** in each case which was believed to denote a facile deprotonation at the benzylic position. Such a deprotonation would presumably prevent the desired 1,2 addition process occurring.  $\text{pK}_a$  data for a benzylic alkyl imine could not be found but Bordwell reports the  $\text{pK}_a$  of imine **127** shown in as 24.3 in DMSO, adding weight to the deprotonation diagnosis.<sup>342</sup>

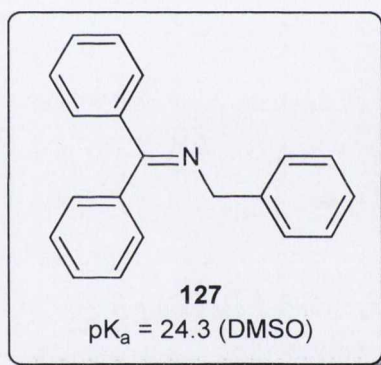
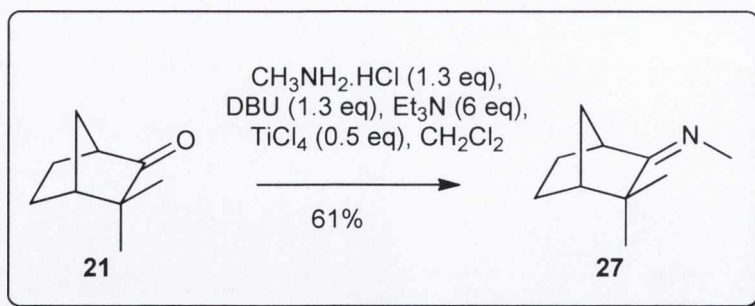


Figure 3-7 Extract from Bordwell, F. G. *Accounts of Chemical Research* 1988, 21, 456-463, Table II

Although the preparation of imine **124** would not prove synthetically use itself, this investigation had categorically shown that the imine formation methodology was sound confirming that loss of methylamine by evaporation had prevented the formation of imine **27**. A procedure was developed that allowed formation of the desired imine. (Scheme 3-30)



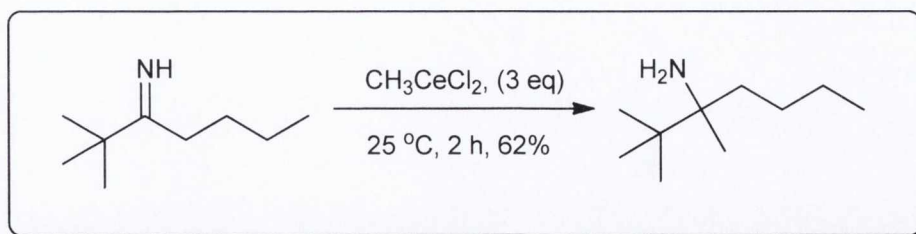
Scheme 3-30 Synthesis of imine **27**

The reaction was carried out in a sealed tube and all additions were made *via* syringe through a thick septum. It was found that the order of addition of reagents was vitally important. 1,8-Diazabicycloundec-7-ene (DBU) was added to the methylamine hydrochloride salt in dichloromethane and stirred until the insoluble hydrochloride salt was no longer visible. At this point, triethylamine, followed by titanium chloride was added. It was necessary to bring this mixture to reflux before adding ketone **21**. It was presumed that this facilitates a ligand exchange process with the titanium chloride. Gratifyingly, this procedure furnished the required imine **27** without the need for any purification beyond filtration through celite.

### 3.3.2 *N*,2-*exo*-,3,3-Tetramethylbicyclo[2.2.1]heptan-2-amine (**13**)

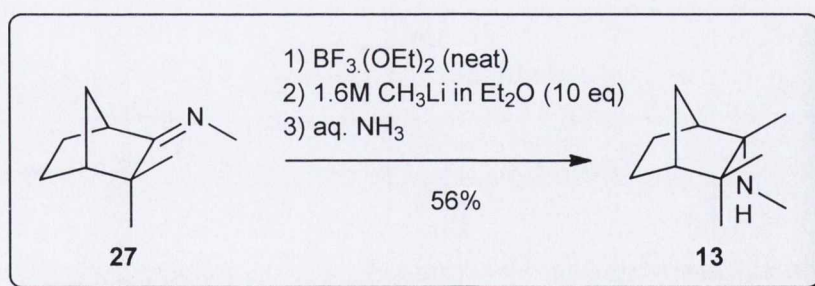
Once imine **27** was formed, we intended to use an organocerium reagent to carry out the attack on the evidently unreactive imine. Organocerium chemistry was pioneered by Imamoto who prepared the first series of organocerium reagents and examined their properties in the 1980s.<sup>343</sup> Advances throughout the 1990s have shown that it is possible to use these reagents to perform synthetic transformations which are not feasible for organolithium or Grignard reagents.<sup>344</sup> Examples in the literature include organocerium additions to oxazolidines,<sup>345</sup> hydrazones,<sup>346</sup> imines<sup>347</sup> and interestingly, hindered ketimines.<sup>348</sup> An example from the latter group is shown. (Scheme 3-31)





Scheme 3-31 An extract from E. Ciganek, *The Journal of Organic Chemistry*, 1992, 57, 4521-4527, Table II, entry 1

We were encouraged by this particular example and felt we should be able to reproduce this with respect to our system. Unfortunately, the addition of  $\text{CH}_3\text{CeCl}_2$  to imine **27** did not furnish *endo*-MA as expected. Heating a solution of imine **27** in tetrahydrofuran at reflux with  $\text{CH}_3\text{Li}$  or  $\text{CH}_3\text{MgBr}$  also proved unsuccessful validating the work of Suchocki *et al.*<sup>270</sup> It was hypothesised that a Lewis acid might again provide the solution by increasing the electrophilicity at the imine carbon through coordination by the nitrogen atom. The use of a 1M solution of titanium chloride in dichloromethane proved unsuccessful but addition of neat boron trifluoride etherate [ $\text{BF}_3 \cdot (\text{OEt})_2$ ] to imine **27** caused a crystalline substance to form which displayed very broad peaks in the  $^1\text{H}$  NMR spectrum. This solid was believed to be a boron – nitrogen complex and if this proved to be the case it would be more amenable to attack by an organometallic reagent. Addition of methyllithium to the complex produced effervescence which ceased after approximately 10 equivalents had been added. Addition of concentrated  $\text{NH}_3$  to the reaction mixture was required to liberate the desired amine **13** and allow its isolation as a white solid after precipitating the hydrochloride salt in diethyl ether. (Scheme 3-32)



Scheme 3-32 Synthesis of *endo*-MA

The requirement for a large excess of methyllithium was not investigated further. It was tentatively proposed that the organolithium initially acts as a base at either the *N*-methyl group or

at the coordinating ethyl substituents liberating methane before performing the desired 1,2 addition to the imine.

### 3.4 Further amine functionalisation

#### 3.4.1 *N*-Alkylation

As stated in section 1.5.3, previous SAR studies of MA had shown a decrease in *in vivo* antagonistic activity for MA analogues with increased *N*-alkyl substitution.<sup>263, 270</sup> It is worth noting that assessment of these *N*-alkyl substituted compounds at individual receptor subtypes was not possible when these SAR studies were performed. It was thought therefore that a decrease in IC<sub>50</sub> values for an *N*-alkyl analogue would be acceptable if a considerable increase in selectivity for a nAChR subtype was obtained. As such it was deemed that a very brief investigation into substitution at this position was warranted. Throughout the course of this project a number of *N*-substituted MA analogues had already been synthesised as a byproduct of other synthetic investigations. (Figure 3-8)

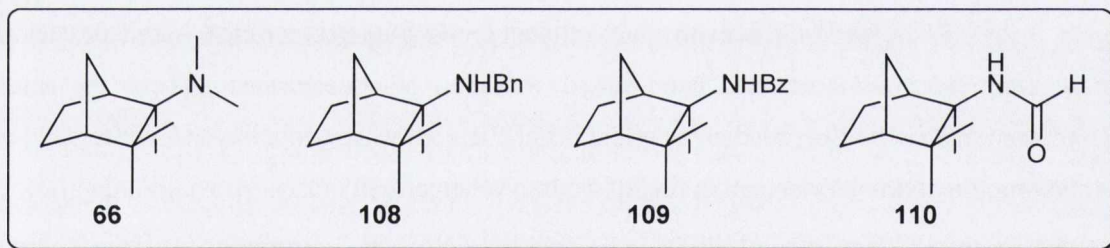
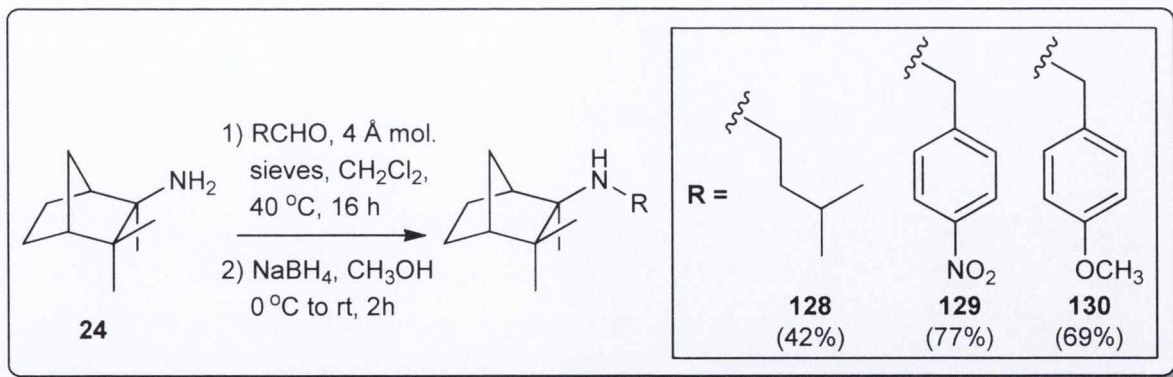


Figure 3-8 Previously synthesised *N*-substituted MA analogues

To further complement this analogue series the compounds shown in Scheme 3-33 were also prepared pursuant with the methodology employed for the synthesis of the methylated amines 71-77 (Scheme 3-23). It was thought that the testing of analogues containing electron poor (**129**) and electron rich (**130**) aromatic rings would provide informative results when combined with the previously synthesised *N*-benzyl analogue **108**.

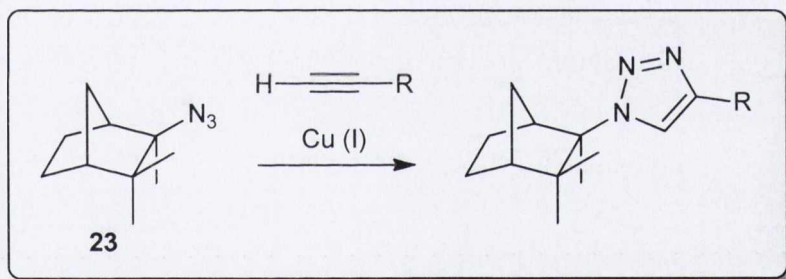




Scheme 3-33 Synthesis of various *N*-substituted MA analogues

### 3.4.2 Click chemistry

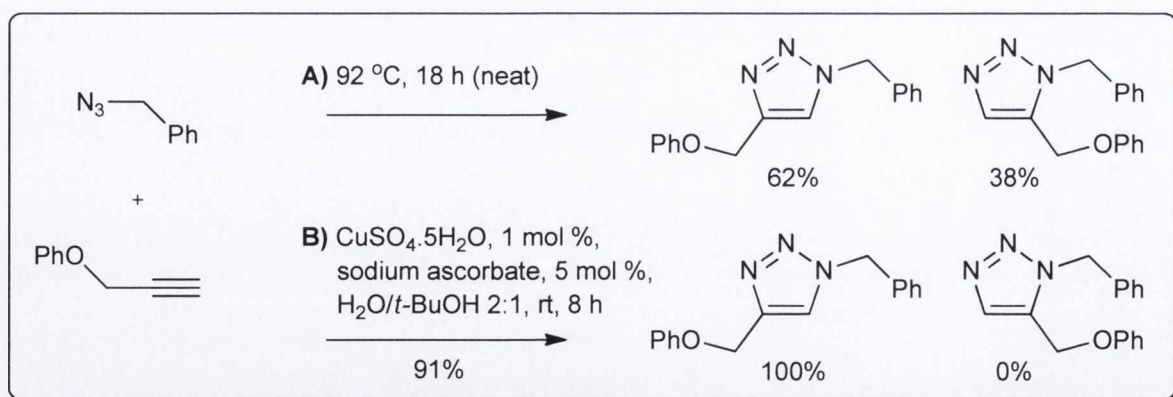
In an effort to broaden the scope of the SAR study of MA, the possibility of using “click chemistry” to synthesise a number of MA analogues containing a triazole moiety was investigated. It was thought that this reaction, if successful, would allow the rapid facile synthesis of a small library of triazole based MA analogues. (Scheme 3-34)



Scheme 3-34 Click chemistry potential

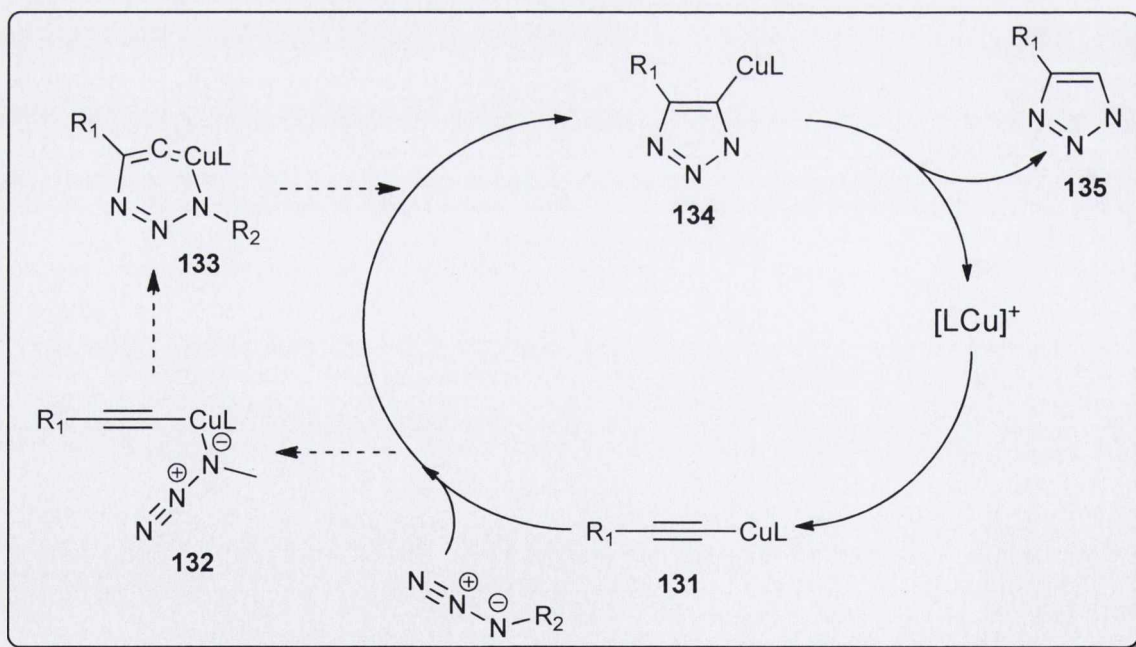
There are a number of examples of reactions of this type in the literature. Sharpless and co-workers describe the original copper catalysed general protocol under thermal conditions<sup>349</sup> while large rate enhancements have been reported with microwave assisted synthesis.<sup>350, 351</sup> Sharpless in particular is a vocal advocate of the benefits of this reaction and while presenting a keynote lecture at the 8<sup>th</sup> Tetrahedron Symposium in Berlin in 2007 remarked that this transformation undoubtedly had not received the attention it deserved by synthetic organic chemists. Azide-alkyne Huisgen cycloadditions generally do proceed without a copper catalyst albeit at a far lower rate and in a non regioselective manner. A comparison of the copper catalysed and non catalysed reactions are shown in Scheme 3-35.<sup>349</sup>





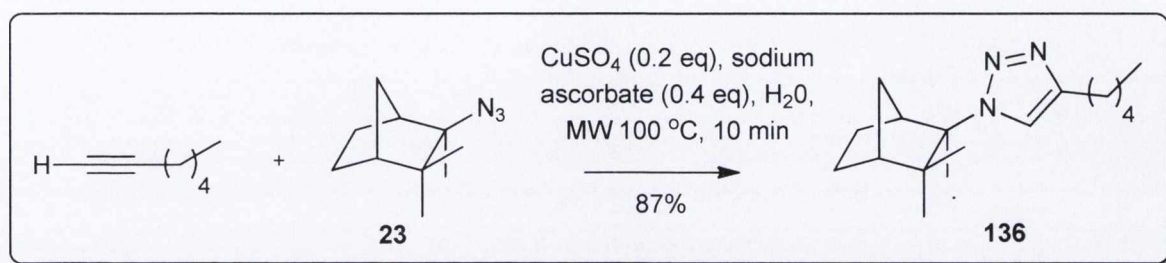
Scheme 3-35 Comparison of copper catalyzed and non catalyzed 1,3-dipolar cycloadditions

The proposed catalytic cycle for this reaction is outlined in Scheme 3-36. The initial step is formation of the copper acetylide. As expected, no reaction is observed under these conditions with internal alkynes although work undertaken by Yamamoto and colleagues has provided access to 1,4,5 trisubstituted triazoles using bimetallic catalysis.<sup>352</sup> Extensive density functional theory calculations offer compelling evidence which strongly disfavors the concerted [2+3] cycloaddition (**131** to **134** directly) and points to a stepwise, annealing sequence *via* **132** and **133**.<sup>353</sup>



Scheme 3-36 Catalytic cycle for Cu(I)-catalysed azide-alkyne "click reaction"

Although it was decided that the priority for this project should be completion of the basic syntheses outlined in section (1.6.2), proof of concept for the future synthesis of this analogue series was obtained by preparing triazole **136** in 87% yield under the conditions outlined in Scheme 3-37.



Scheme 3-37 Synthesis of triazole **136** from azide **23**

### 3.5 Conclusion

Gratifyingly, the synthetic goals outlined in section 3.1 were achieved. The desired analogue series composed of compounds **71-77** was successfully synthesised albeit with modifications to the methodology originally developed for the synthesis of MA itself **17**.

In addition, the synthesis of *endo*-MA **13**, a novel compound despite previous attempts by others was achieved. These compounds (**13**, **17** and **71-77**) have been submitted for *in-vitro* biological testing in order to ascertain their activity at the  $\alpha 4\beta 2$ ,  $\alpha 3\beta 4$  and  $\alpha 7$  nAChR subtypes and will form the basis of our initial SAR investigation into MA. These tests are currently underway and the results are eagerly awaited.

Diversification in the form of *N*-functionalisation was also briefly examined. A small series of *N*-functionalised MA analogues was synthesised in a facile manner and will be assessed for nAChR antagonistic activity in the near future. The possibility of replacing the *N*-methyl moiety in MA with a triazole function using “click chemistry” was briefly addressed. The synthesis of a single triazole based analogue **136** from heptyne and azide **23** provided proof of concept for the development of an analogue series that could be quickly synthesised by simply varying the alkyne in this highly versatile reaction.

We await the biological analysis data before deciding on the direction of the project in this area.

# **Chapter 4**

## **Diversity in position 5 and 6**



## 4 Diversity in position 5 and 6

### 4.1 Targets

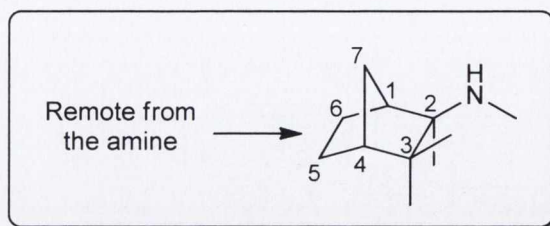


Figure 4-1 Targeting position 5 and 6 of the MA skeleton

Having developed the methodology to make alterations at positions 2 and 3 of MA, our attention turned to the other side of the molecule, namely the 5 and 6 position. The installation of a bromine atom, which could act as the functional handle at the 5 or 6 position was deemed advantageous. Further selective functionalisation at the 5 or 6 position *via* Pd(0) mediated coupling reactions or bromine metal exchange offered the potential for diverse further functionalisation.

As such the initial synthetic targets would be the 5-bromo and 6-bromo analogues of norbornenone shown in Figure 4-2. It was thought that application of the synthetic methodology previously developed to ketones **33** and **37** would provide access to the required 5- and 6-substituted MA analogues.

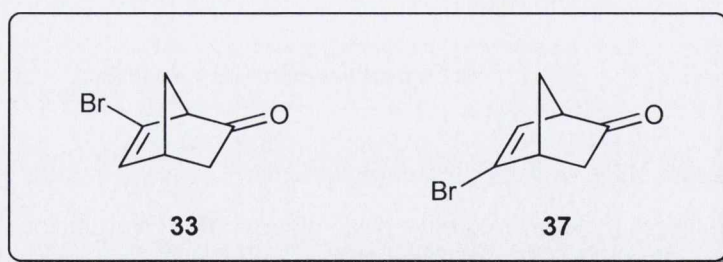
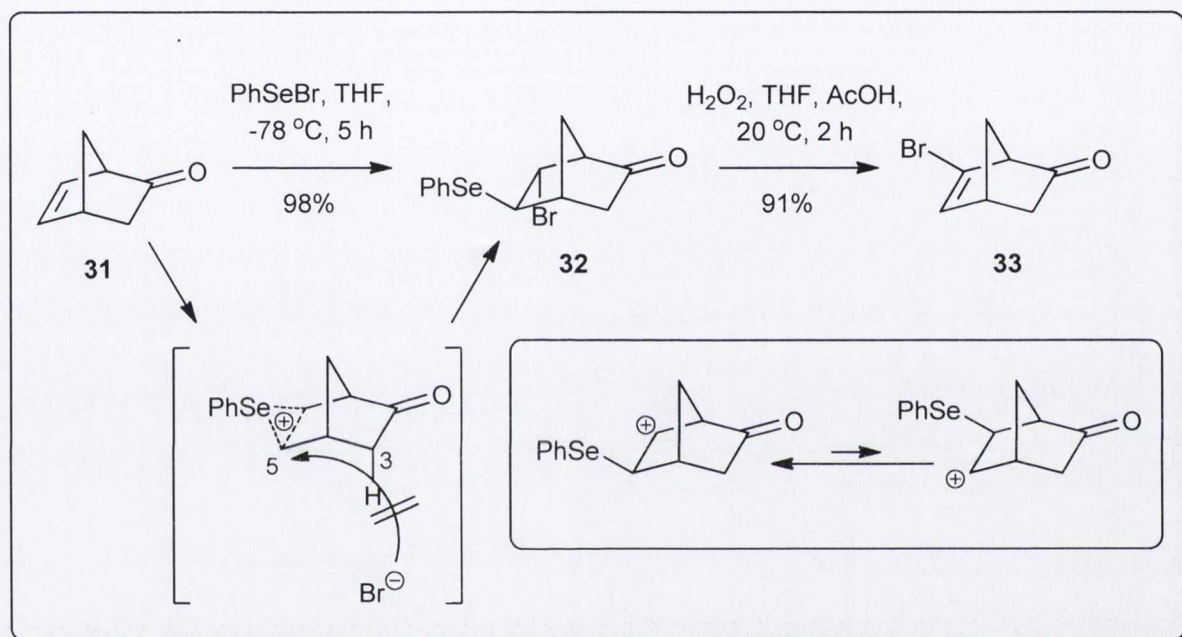


Figure 4-2 Initial synthetic targets for the synthesis of 5- and 6- substituted MA analogues

## 4.2 6-substituted mecamylamine analogue

### 4.2.1 6-Bromobicyclo[2.2.1]hept-5-en-2-one (33)

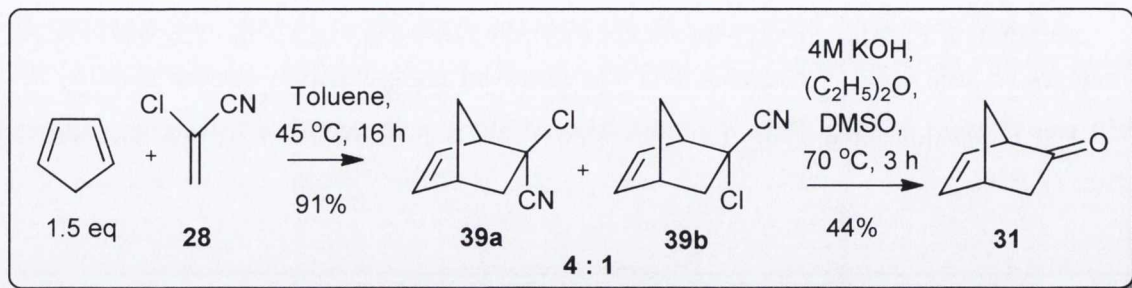
Lal and co-workers had previously reported the synthesis of **33** from norbornenone **31** in an impressive 89% yield.<sup>295</sup> (Scheme 4-1) The observed regioselectivity for the addition to the olefin was thought to arise from a combination of steric and electronic effects as outlined in section 1.6.3.1.



Scheme 4-1 Synthesis of ketone **33** by Lal and co-workers

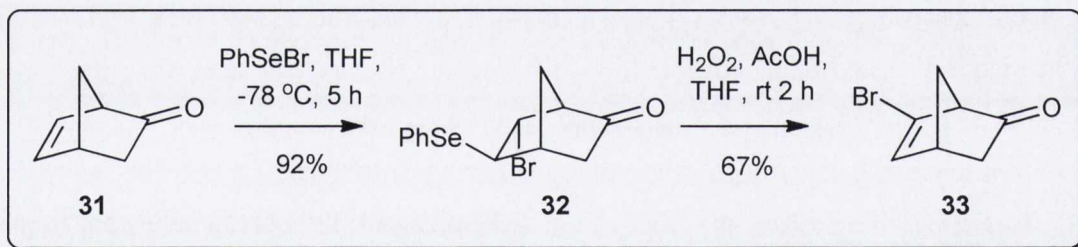
To attempt to reproduce the work of Lal and colleagues, it would be necessary to prepare norbornenone **31**. The first step of this synthesis was the Diels-Alder reaction of the ketene equivalent  $\alpha$ -chloroacrylonitrile **28** and cyclopentadiene. This was carried out without difficulty and yields comparable to those reported in the literature were obtained.<sup>294</sup> (Scheme 4-2) An excess of cyclopentadiene was employed to ensure complete consumption of the significantly more expensive dienophile component. Purification of the  $\alpha$ -chloronitrile mixture **39** by flash chromatography removed the unreacted cyclopentadiene giving the two diastereomers in a ratio of 4:1 in favour of the *endo*-carbonitrile. Hydrolysis of the 4:1 mixture of  $\alpha$ -chloronitrile diastereomers was achieved by heating in DMSO with 4 M KOH at 70 °C for 3 hours. The desired ketone **31** was produced cleanly but the yields were hampered by the volatility of the product. A

yield of approximately 70% was estimated (by  $^1\text{H}$  NMR spectroscopic analysis when compared to an internal standard) when the diethyl ether used to extract the compound from the reaction medium was not evaporated to dryness.



Scheme 4-2 Synthesis of norbornenone 31

The next step was the selective installation of the bromine at the 6 position using the methodology developed by Saloman and Lal.<sup>295</sup> Pleasingly, after treatment of the olefin **31** with phenylselenenyl bromide in THF at -78 °C the expected seleno-ether **32** was isolated in 92% yield following purification by flash chromatography. (Scheme 4-3) Analysis of the spectral data confirmed the complete regioselectivity obtained in this reaction. Treatment of selenide **32** with hydrogen peroxide and acetic acid in THF at room temperature facilitated syn-elimination to furnish the desired vinyl bromide **33** in 67% yield after purification by flash chromatography.

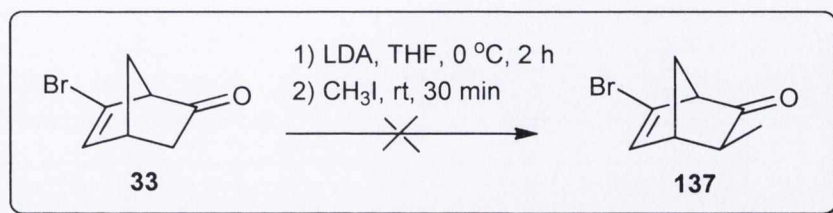


Scheme 4-3 Synthesis of vinyl bromide 33



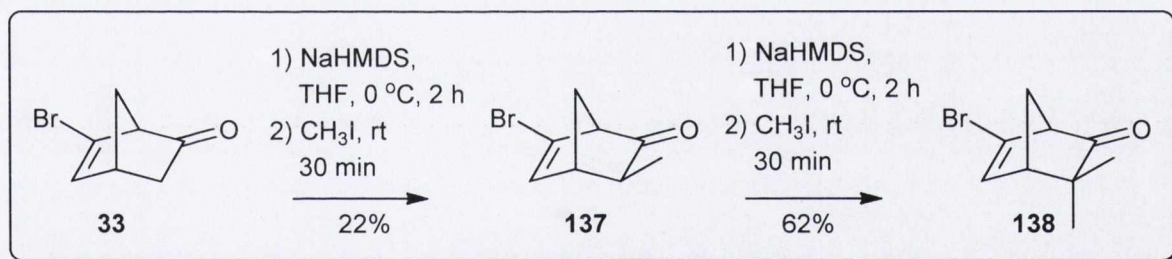
#### 4.2.2 6-Bromo-3,3-dimethylbicyclo[2.2.1]hept-5-en-2-one (138)

The next step was the enolate mediated methylation of ketone **33**. Initial attempts employed LDA as the base followed by treatment with iodomethane. (Scheme 4-4) Analysis of the  $^1\text{H}$  NMR spectral data showed the appearance of unidentified peaks in the olefin region of the  $^1\text{H}$  NMR spectrum of the crude product.



Scheme 4-4 Attempted formation of ketone **137** using LDA to form the required enolate

It was found that replacing LDA with NaHMDS afforded the desired ketone **137**, albeit in low (22%) yield. (Scheme 4-5) The second methylation to generate **138** was achieved using the same NaHMDS/ $\text{CH}_3\text{I}$  protocol and proceeded with a significantly higher yield than the previous step. (Scheme 4-5)

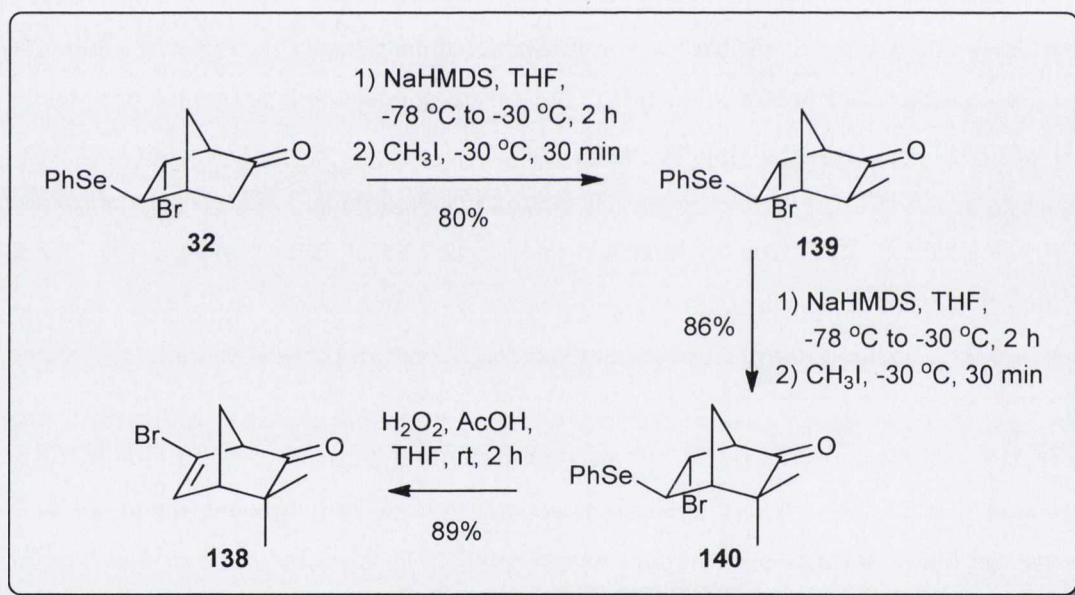


Scheme 4-5 Synthesis of ketone **138**

Although we were able to form and isolate ketone **138**, the low yield was deemed to be unacceptable, especially considering the relatively long synthetic route. It was known that the formation of ketone **137** from ketone **33** did not proceed cleanly and it was estimated from the  $^1\text{H}$  NMR spectrum of the crude product that approximately 30% of the mass recovered was attributed to side products which were later separated by flash chromatography. The low yield was mainly caused however by the volatility of the vinyl bromide **137**. It was hypothesised that it might be possible to carry out the necessary methylation reactions before the deselenation was performed.

It was postulated that the 'anti' conformation assumed by the substituents at position 5 and 6 of bromoseleno-ether **32** should preclude the possibility of elimination of HBr *via* an E2 reaction.

A modification to the reaction conditions employed for the NaHMDS mediated alkylations of 2- and 3-substituted MA analogues (Scheme 3-3) was required however, as it was found that prolonged exposure of seleno-ether **32** to an excess of iodomethane at 0 °C resulted in decomposition. This was thought to be brought about by methylation of the selenium. However it was found that quenching the reaction at -30 °C once the desired methylation of the enolate was complete provided the desired ketone **139** in 80% yield after purification by flash chromatography. (Scheme 4-6) The second methylation was carried out in a similar manner affording dimethyl ketone **140** in 86% yield following purification by column chromatography. Deselenation was achieved using the conditions described above to facilitate the formation of vinyl bromide **138** in 89% yield after purification by flash chromatography.

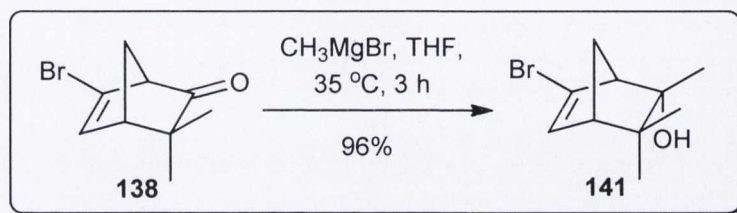


Scheme 4-6 Improved synthesis of ketone **138**



### 4.2.3 6-Bromo-2-*exo*-,3,3-trimethylbicyclo[2.2.1]hept-5-en-2-ol (141)

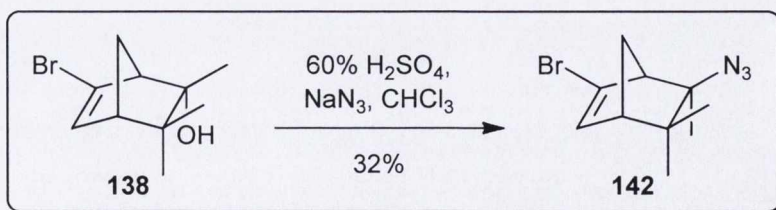
As it was postulated that methyllithium might in this case facilitate lithium bromide exchange reactions, methylmagnesium bromide was successfully employed in place of methyllithium to carry out attack at the carbonyl to form the desired tertiary alcohol **141** in 96% yield which was used without further purification. (Scheme 4-7) Fortunately, none of the hydride transfer product that had been observed with the analogous use of ethylmagnesium bromide as discussed in Section 2.2.3 was obtained.



Scheme 4-7 Synthesis of alcohol **141**

#### 4.2.3.1 6-Azido-2-bromo-5,5,6-*endo*-trimethylbicyclo[2.2.1]hept-2-ene (142)

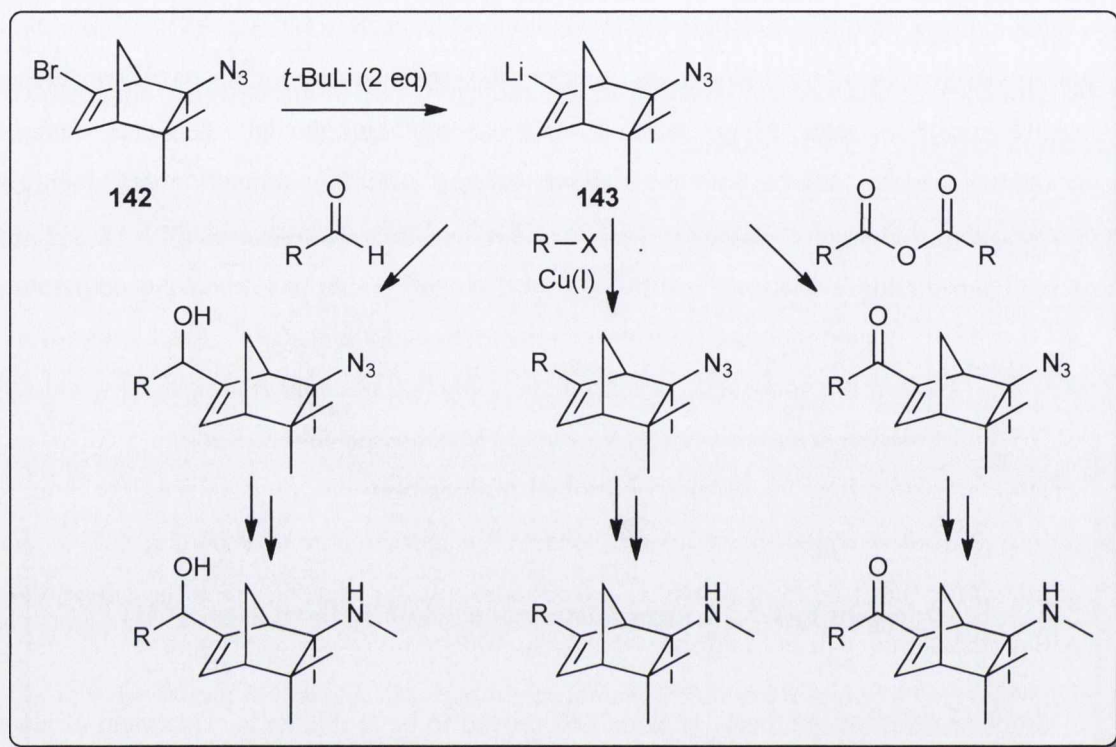
Unfortunately, the synthesis of azide **142** proved to be problematic. Treatment of alcohol **141** with 60% sulfuric acid and sodium azide in chloroform gave the desired azide product in only 32% yield. Although the yield was low, fortuitously, the desired azide could be easily separated from the unidentified side products. As was found with earlier attempts to optimise azide formation, varying the reaction conditions did not affect the ratio of products obtained and no improvement on the yield of azide **142** was achieved.



Scheme 4-8 Synthesis of azide **142**

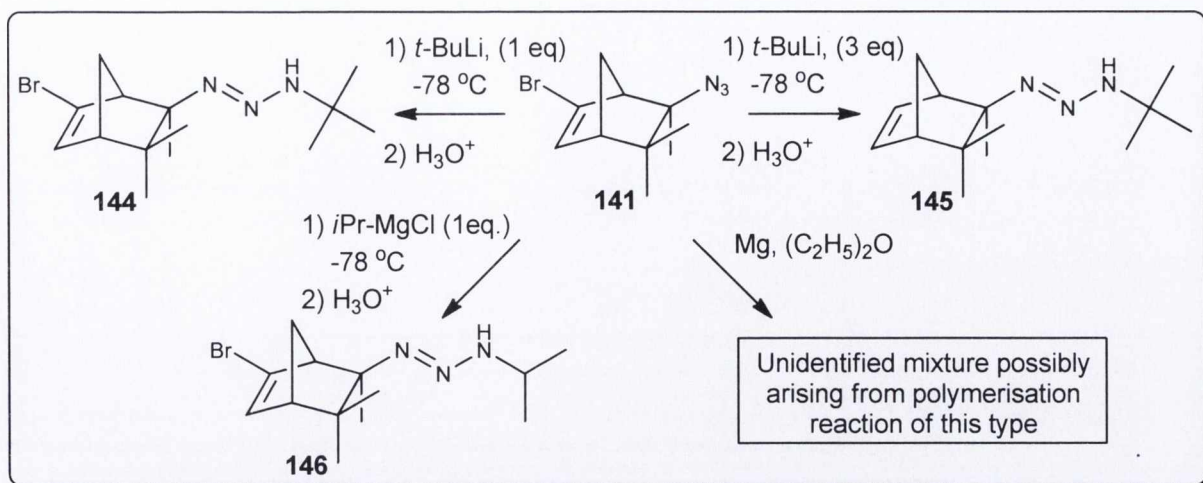


Azide **142** was viewed as a key intermediate and a number of synthetic strategies could be envisaged by exploiting the vinyl bromide moiety. One such strategy was that of bromine lithium exchange<sup>354</sup> to form the lithiated species **143** (Scheme 4-9) which could then be exposed to a wide range of electrophiles.



Scheme 4-9 Functionalisation through halogen lithium exchange

The 6-substituted analogues of azide **142** shown in Scheme 4-9 could then be reduced and methylated to form the corresponding MA analogues. In practice however, this proved impossible. Surprisingly, addition of *tert*-butyllithium to azide **142** at low temperature resulted in nucleophilic addition of the organolithium to the azide moiety generating a 1,3-triazarene species. Perhaps even more surprising was the experimental finding that this addition process was favoured over halogen lithium exchange and was complete within 1 minute at  $-78\text{ }^{\circ}\text{C}$ . This was proven by treating the azide **142** with either 1 equivalent of *tert*-butyllithium or 3 equivalents of *tert*-butyllithium in THF at low temperature. (Scheme 4-10) Analysis of the reaction mixtures indicated that the addition of 1 equivalent of *tert*-butyllithium cleanly gave the triazarene **144** whereas the use of 3 equivalents of *tert*-butyllithium produced triazarene **145**, the product of azide addition and reduction of the carbon bromine bond (after protic workup).

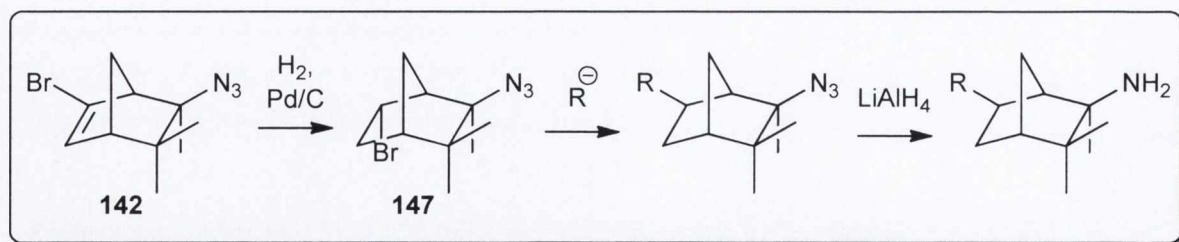


Scheme 4-10 Organometallic addition to azide moiety in azide 141

This reaction has been previously reported by Smith *et al.*<sup>355</sup> but seems to have received very little attention. The authors report that it is possible to reduce the 1,3-triazarene product formed to liberate the amine but this was not considered at this point due to the presence of the sensitive vinyl bromide. Formation of the corresponding Grignard reagent *via* isopropyl magnesium chloride (*i*Pr-MgCl)<sup>356</sup> using Knochel's methodology was attempted. However, once again addition of the organometallic to the azide was observed to form **146**. (Scheme 4-10) Finally, an attempt to form the desired Grignard species directly *via* insertion using magnesium turnings produced a complicated mixture which presumably arose from intermolecular addition reactions.

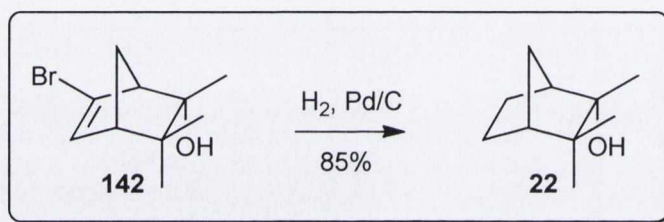
Next the possibility of reducing the olefin moiety in this compound to generate an alkyl bromide **147** which could undergo an S<sub>N</sub>2 reaction was considered. (Scheme 4-11) It was hoped that the bulky nature of the bromide and the heterogeneous nature of the catalyst would prevent insertion of palladium into the carbon bromine bond. It was thought that the olefin could be reduced under hydrogen gas at atmospheric pressure selectively as it was known that hydrogenation of azide **23** (Scheme 2-15) required higher pressures (3 atm.). Substitution of the bromide followed by reductive amination would then furnish a 6-substituted MA analogue.





Scheme 4-11 Alternative synthetic route to 6-substituted MA analogues

As azide **142** was considered to be a precious compound, the reduction was attempted on the readily available vinyl bromide **141**. (Scheme 4-12) Perhaps unsurprisingly, although the olefin can be reduced in 1 hour complete reduction of the carbon bromine bond also occurred with the saturated alcohol **22** obtained in 85% yield. (Scheme 4-12)



Scheme 4-12 Attempted formation of alkyl bromide 147

#### 4.2.3.1 6-Bromo-*N*,2-*endo*-,3,3-tetramethylbicyclo[2.2.1]hept-5-en-2-amine (**149**)

Given the problems associated with azide **142** it was thought prudent to alter the strategy and reduce the azide prior to manipulation of the vinyl bromide. In fact this late stage diversification would provide an overall more efficient approach to analogue generation.

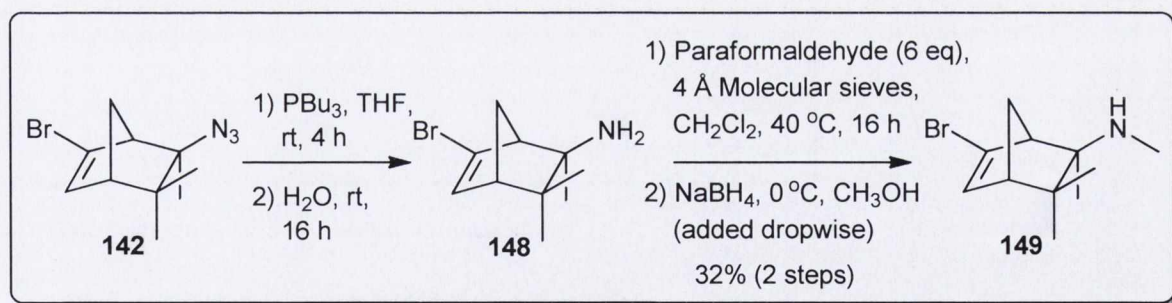
The general nature and robustness of the lithium aluminium hydride mediated azide reduction had been shown in section 2.2.5. This method had generated the 2- and 3- substituted amine series **113-119** in good yield and often without the need for extensive purification. Unfortunately, the vinyl bromide motif in azide **142** was shown to be unstable to reduction by lithium aluminium hydride in THF at low temperature.

It was hypothesised that the Staudinger reduction would selectively reduce the azide moiety in the presence of the vinyl bromide to furnish the amine **148**. (Scheme 4-13) Reductive amination of amine **148** would furnish a synthetically useful MA analogue **149**. The reduction was carried out as previously (Section 2.1.5.1) employing tributylphosphine in place of the more



common triphenylphosphine and adding the water after reaction of the phosphine and azide was complete. Unfortunately the purification technique previously optimised for the synthesis of MA did not suffice in this case. The hydrochloride salt of amine **148** exhibited an unusual solubility profile and was found to be somewhat soluble in every organic solvent tested including diethyl ether and even hexane. Assimilating this information and recalling the difficulties associated with the attempted chromatographic separation of tributylphosphine oxide, an alternative purification technique was employed. The hydrochloride salt of amine **148** was purified directly by flash chromatography using an eluent gradient ranging from 50:50 hexane:EtOAc to 50:50 EtOAc:methanol. Under these conditions, a clean fraction containing tributylphosphine oxide eluted first. A second fraction isolated contained a 4:1 mixture of the desired amine hydrochloride salt and tributylphosphine oxide. The highly polar conditions necessary to elute the salt from the column dissolved a significant amount of silica gel but this was subsequently removed by simply dissolving the desired compound in dichloromethane and performing a filtration.

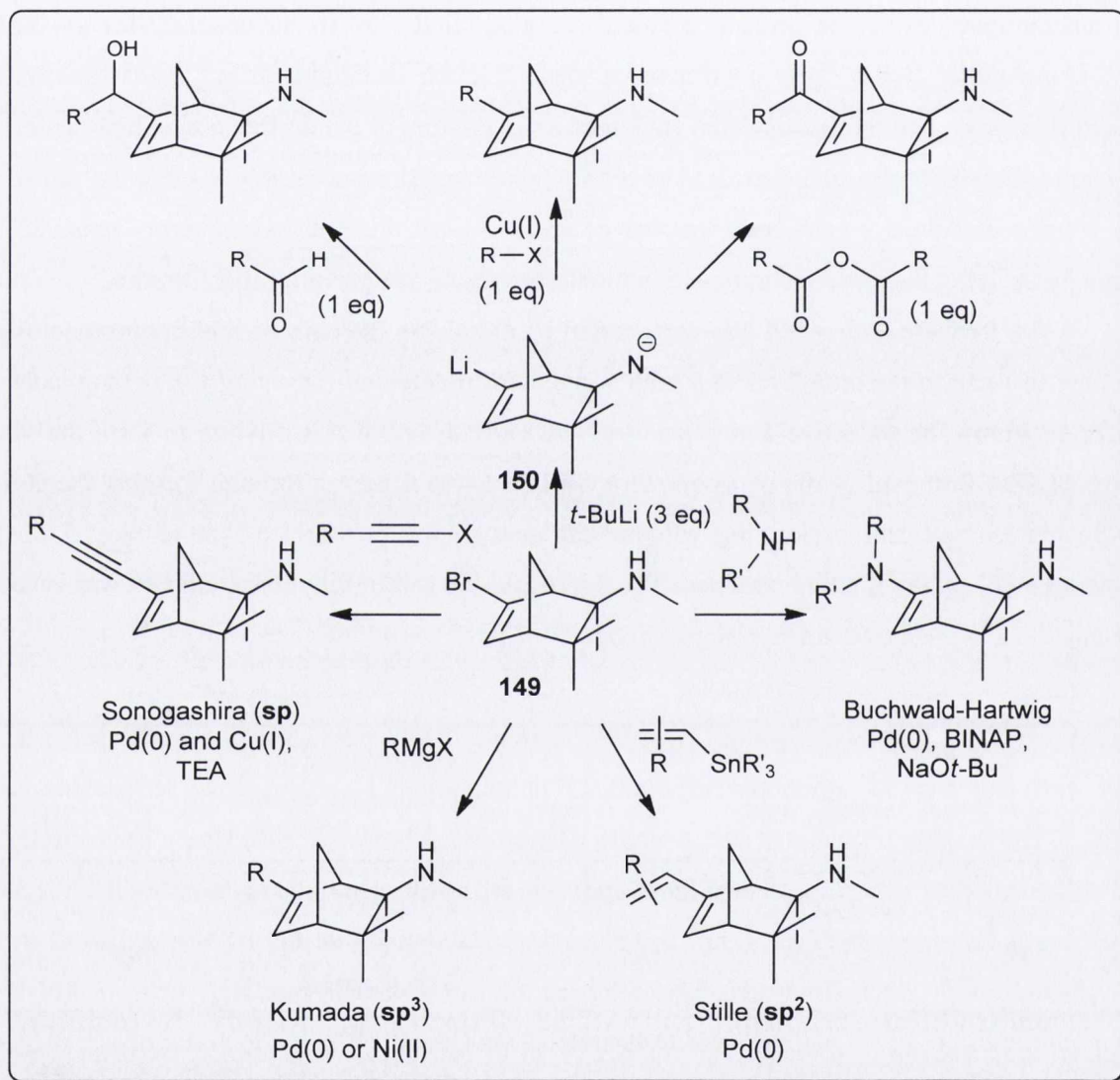
The freebase amine **148** was regenerated by dissolving the amine/tributylphosphine oxide mixture in dichloromethane, washing with sodium hydroxide and removing the organic solvent under vacuum. The reductive amination step was carried out on this mixture to form the vinyl bromide **149**. Removal of the phosphorous by-product was achieved through forming the amine hydrochloride salt and performing column chromatography (similar to that employed in the previous step) on the mixture obtained. The hydrochloride salt of vinyl bromide **149** was isolated cleanly in 32% yield over the two steps. (Scheme 4-13)



Scheme 4-13 Synthesis of vinyl bromide **149**

This final compound can be assessed for biological activity itself, while the vinyl bromide provides a powerful functional handle which can hopefully be exploited to prepare a library of structurally diverse analogues. Scheme 4-14 outlines some of the possible transformations. The *bis*-lithiated species **150** could be formed by the addition of 3 equivalents of *tert*-butyllithium to

vinyl bromide **149**. The addition of 1 equivalent of an electrophile should react preferentially at the carbanion at position 6 while the addition of 2 equivalents of electrophile should form the 6-,*N*-disubstituted analogues where possible. In certain cases protection of the nitrogen would be required. As a representative example, four metal catalysed cross coupled products are also shown. Clearly this is not an exhaustive list. Hiyama couplings using organosilanes, Suzuki couplings using boronic esters, or a range of other coupling reactions could be performed.



Scheme 4-14 Synthetic modifications to vinyl bromide **149**

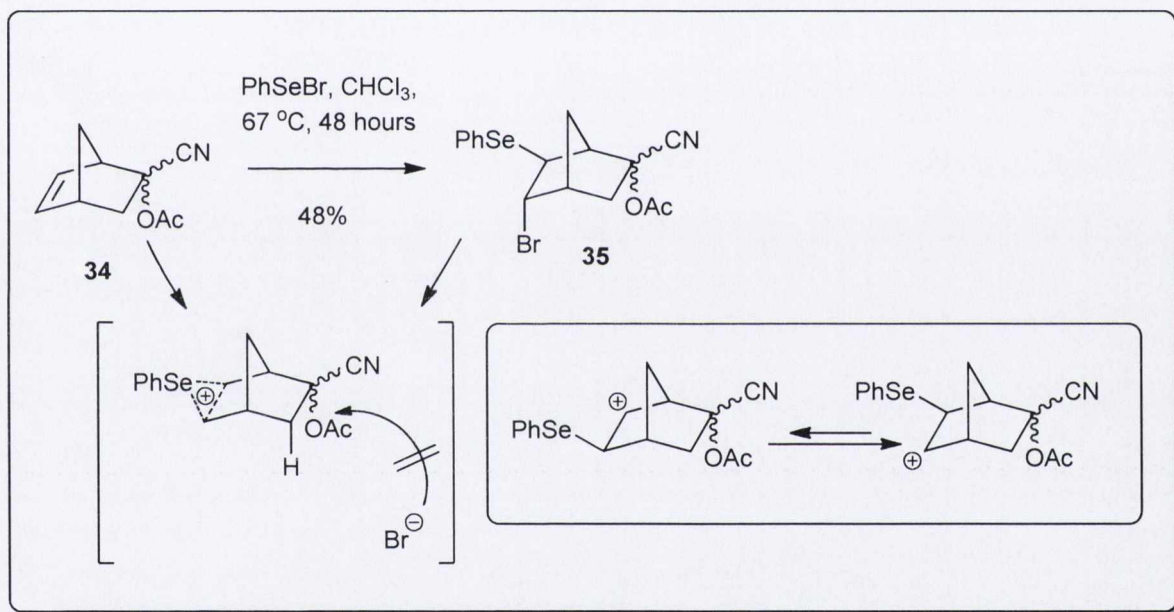
Elaboration of vinyl bromide **149** will be investigated in due course.



### 4.3 5-substituted mecamylamine analogue

#### 4.3.1 Addition of PhSeBr to 2-chlorobicyclo[2.2.1]hept-5-ene-2-carbonitrile (39)

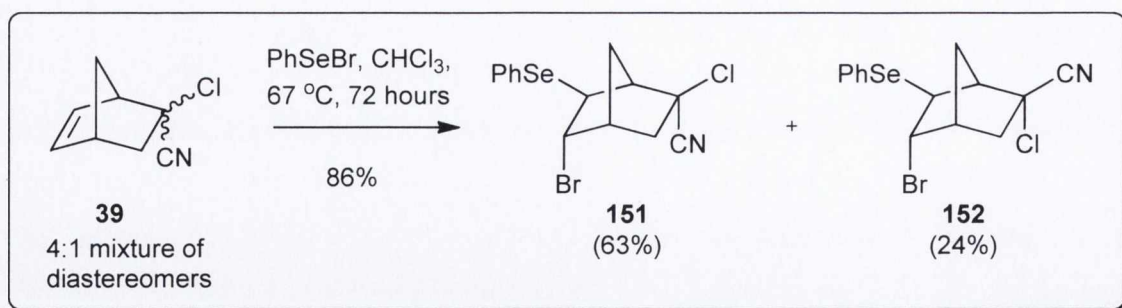
Having successfully synthesised a 6-bromo MA analogue with complete regio-control, we turned our attention to the synthesis of a 5-substituted MA analogue. As discussed in Section 1.6.3.3 it was thought that the methodology employed in the synthesis of vinyl bromide **33** could be adapted to furnish the 5-bromo version of this compound **37** by performing the addition of phenylselenenyl bromide directly on the  $\alpha$ -chloronitrile mixture **39**. It was hoped that the regiocontrol observed in the case of addition of phenylselenenyl bromide to olefin **34** (Scheme 4-15) could be reproduced for our system.



Scheme 4-15 Addition of PhSeBr to  $\alpha$ -acetoxynitrile mixture **34**

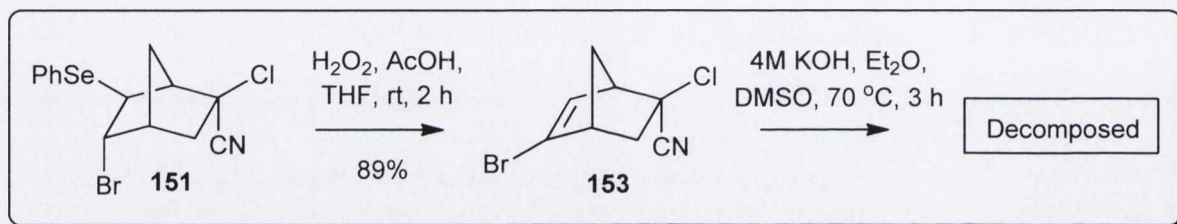
Thankfully, 100% regioselectivity was observed for the addition of phenylselenenyl bromide to the  $\alpha$ -chloronitrile mixture **39** over 3 days heating at reflux in chloroform and the *exo* and *endo* isomers (**151** and **152** respectively) were separated by column chromatography as it was thought that optimisation of the subsequent reactions would be simplified by using a single diastereomeric material rather than the mixture of diastereomers.





Scheme 4-16 Synthesis of seleno-ethers 151 and 152

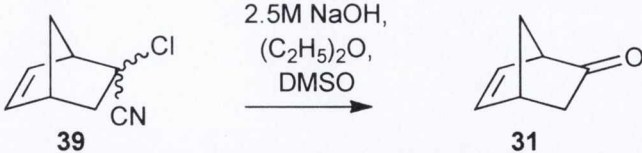
The oxidative cleavage conditions used for the synthesis of **33** and **138** provided the vinyl bromide **153** in excellent yield. (Scheme 4-17) However, attempts to hydrolyse the chlorocyano moiety employing potassium hydroxide in DMSO (as previously) resulted in decomposition.



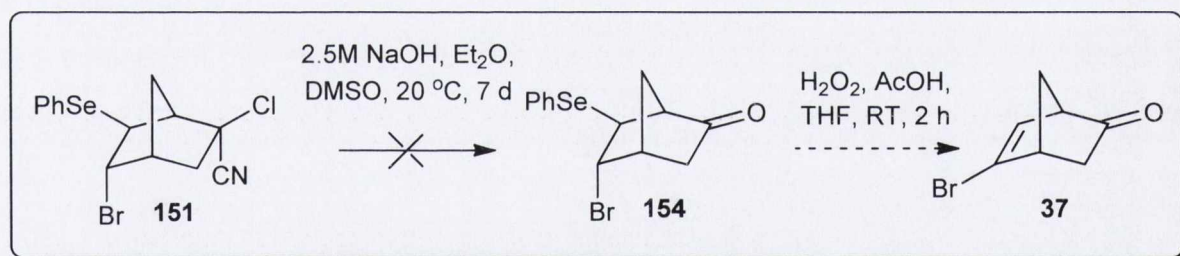
Scheme 4-17 Synthesis of vinyl bromide 153

Rather than waste vinyl bromide **153**, a number of optimisation reactions were carried out on the simple derivative mixture **39** in an effort to deduce the mildest conditions required for the hydrolysis reaction. (Table 4-1) 2.5M NaOH was chosen as the basic component as Plettner *et al.* had shown this milder base to effect the desired conversion by heating at 70 °C for 4 hours.<sup>294</sup>

Table 4-1 Optimisation of  $\alpha$ -chloronitrile hydrolysis

|  |                                                                 |
|------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| Temperature                                                                        | Time required for complete conversion of <b>39</b> to <b>31</b> |
| 20 °C                                                                              | ~7 days                                                         |
| 30 °C                                                                              | 30 hours                                                        |
| 40 °C                                                                              | 7 hours                                                         |
| 50 °C                                                                              | 3 hours                                                         |

Unfortunately even employing the mildest hydrolysis conditions decomposed vinyl bromide **153** before hydrolysis was complete. It was thought that it might be possible to hydrolyse  $\alpha$ -chloronitrile **151** and perform the oxidative cleavage on the ketone product **154** to afford the desired vinyl bromide **37**. (Scheme 4-18) Perhaps unsurprisingly, the selenide **151** was not stable to the required hydrolysis conditions and this approach was abandoned.

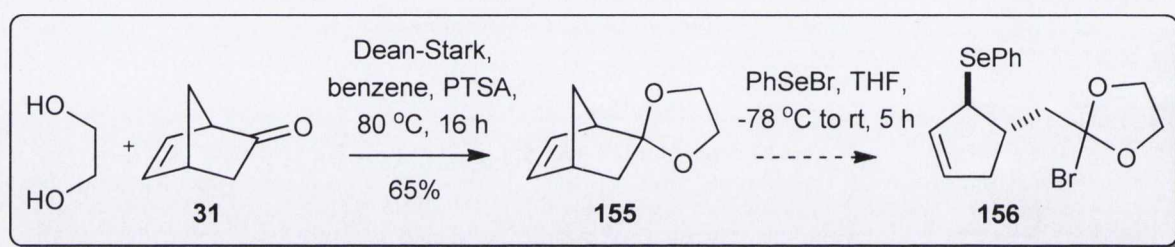


Scheme 4-18 Attempted alternative synthesis of ketone **37**

#### 4.3.2 Addition of PhSeBr to spiro[bicyclo[2.2.1]hept[5]ene-2,2'-[1,3]dioxolane] (**155**)

It was clear that the problems with the previous strategy arose from the harsh conditions required to hydrolyse the chlorocyano moiety to form the corresponding ketone. Clearly it was necessary to employ a masked version of the ketone that would still prevent the attack of bromine

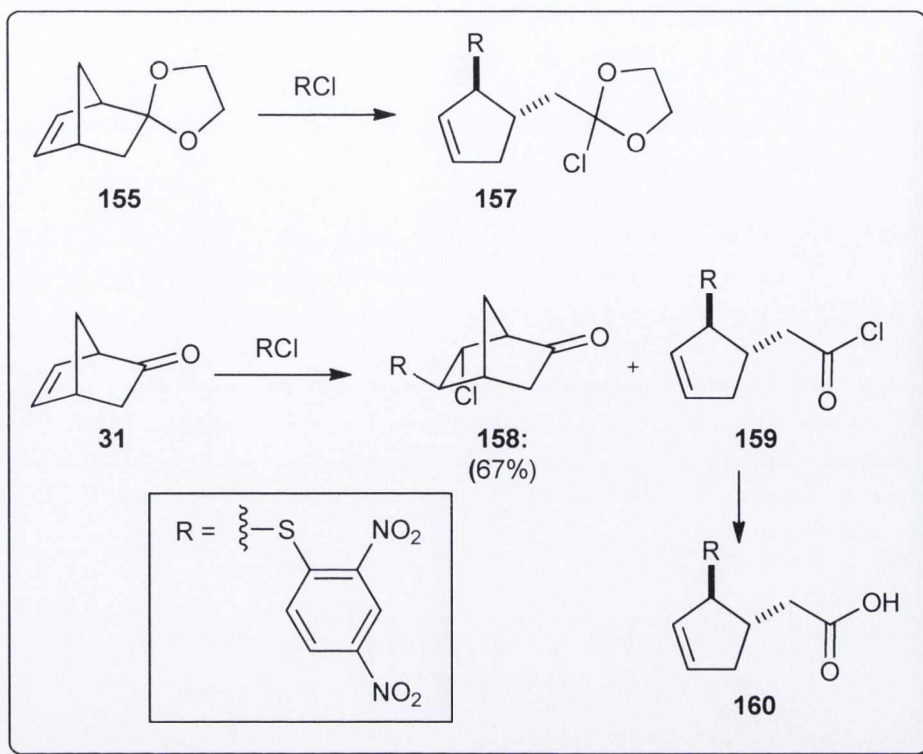
at the 6 position upon exposure to phenylselenenyl bromide but was also easily removed. It was decided to employ a cyclic acetal such as **155**. (Scheme 4-19) It was thought that the cyclic nature of this compound would provide increased stability over an acyclic acetal. Hydrolysis to regenerate the ketone moiety should proceed readily in mild aqueous acid when required. The synthesis of **155** has been described by a number of groups including Charlton,<sup>357</sup> Monti<sup>358</sup> and Meinwald<sup>359</sup> and co-workers and its preparation was achieved by heating a solution of ketone **31** and ethylene glycol with a catalytic amount of *para*-toluene sulfonic acid (PTSA) in benzene at reflux overnight under Dean-Stark conditions. Unfortunately, attempted addition of phenylselenenyl bromide to this compound resulted in a complicated mixture of products.



Scheme 4-19 Failure of PhSeBr to add as desired to acetal **155**

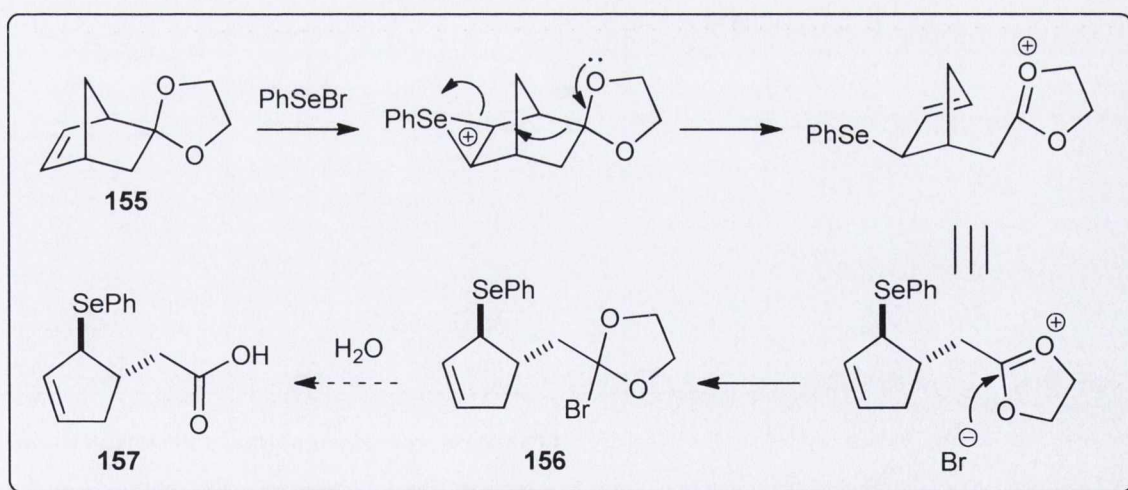
It was hypothesised that this reaction resulted in the formation of compound **156** (analysis of <sup>1</sup>H NMR data clearly shows a disubstituted olefin) among other unwanted products in a similar manner to that reported by Vogel and co-workers.<sup>360</sup> They reported that the addition of 2,4-dinitrobenzenesulfonyl chloride (DNBSCl) to **155** resulted solely in the formation of **157**. (Scheme 4-20) The reactivity profile of DNBSCl can be considered somewhat similar to that of phenylselenenyl bromide as it was also shown by Carrupt *et al.*<sup>296</sup> that DNBSCl adds to **31** in a similar fashion to phenylselenenyl bromide generating ketone **158** in 67% yield. (Scheme 4-20)





Scheme 4-20 DNBSCl additions to acetal **155** and ketone **31**

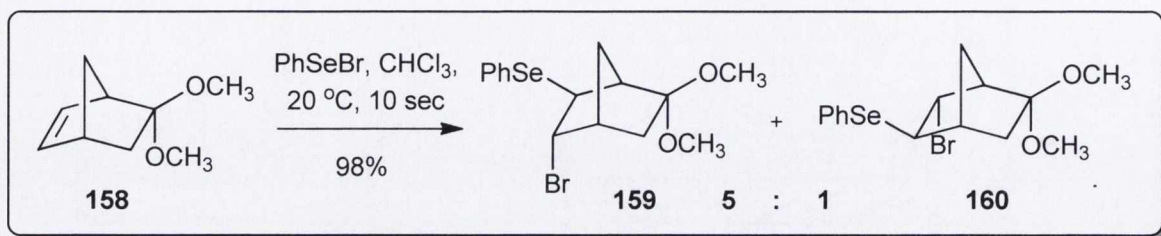
The proposed mechanism for the rearrangement is outlined in Scheme 4-21. It is thought that aqueous workup (in the presence of a small amount of selenic acid) hydrolyses the acetal **156** generating the acyl bromide which is quickly converted to the carboxylic acid **157**.



Scheme 4-21 Proposed mechanism for the rearrangement observed upon addition of PhSeBr to acetal **155**

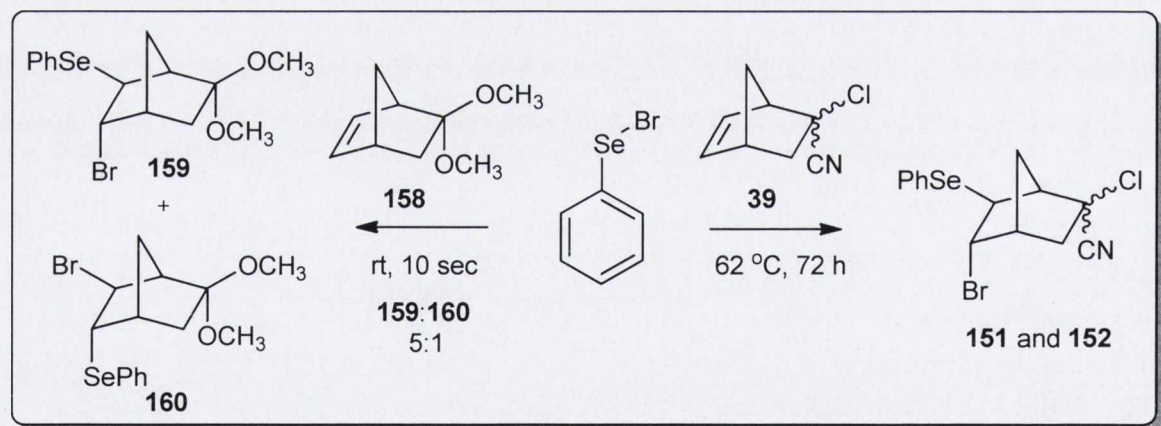
### 4.3.3 Addition of PhSeBr to 5,5-dimethoxybicyclo[2.2.1]hept-2-ene (158)

The dimethyl acetal **158** had also been shown to undergo an addition reaction with phenylselenenyl bromide to yield an approximately 5:1 mixture of regioisomers.<sup>360</sup> This was considered a promising avenue of investigation for our purposes.



Scheme 4-22 Addition of PhSeBr to dimethyl acetal **158**

The rate of reaction reported for the addition of phenylselenenyl bromide to the dimethyl acetal **158** was much faster compared to the same addition with the  $\alpha$ -chloronitrile mixture of **136** and **136** considering the similar structural and electronic effects of these substituents. (Scheme 4-23) As such it was thought to be necessary to cool the reaction significantly to enhance the regioselectivity of the process.

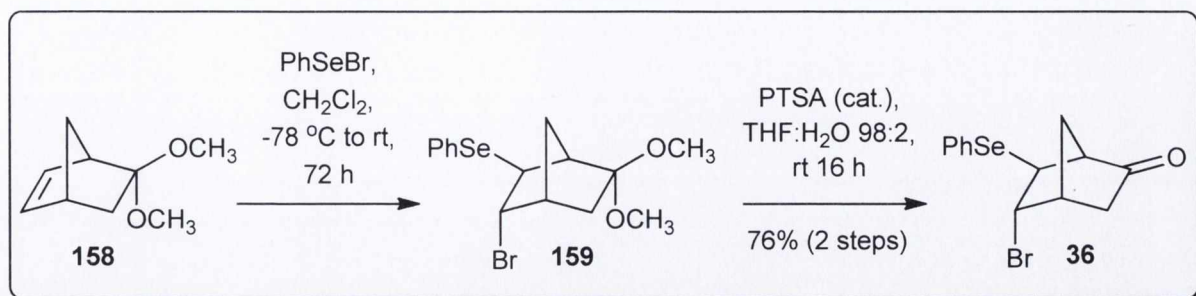


Scheme 4-23 Rate variation in PhSeBr additions

The formation of **159** was attempted with phenylselenenyl bromide. As expected, it was found that extremely stringent anhydrous conditions were required in order to prevent hydrolysis of the acetal moiety. In order to maximize the effect of the previously reported modest regioselectivity,<sup>360</sup> the reaction was allowed to slowly warm from -78 °C to ambient temperature



over 3 days. Gratifyingly, the synthesis of **159** was achieved with complete regioselectivity and the regeneration of the ketone to give **36** was accomplished by stirring a solution of acetal **159** in 'wet' THF overnight with a catalytic amount of PTSA. (Scheme 4-24)

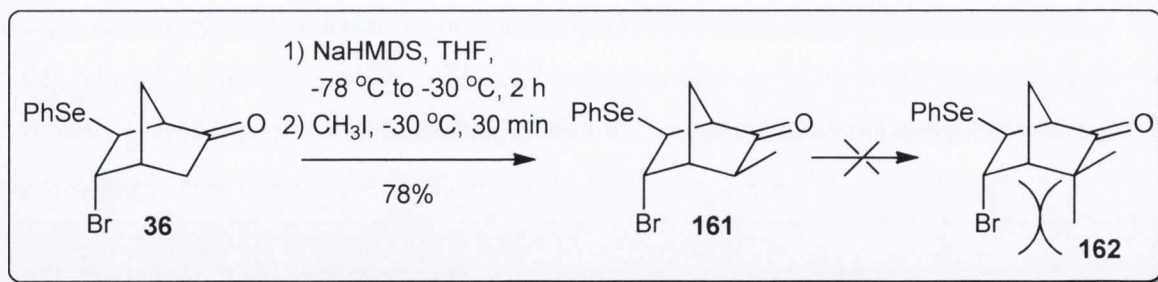


Scheme 4-24 Synthesis of ketone **161**

#### 4.3.4 5-Bromo-3,3-dimethylbicyclo[2.2.1]hept-5-en-2-one (**166**)

Applying the insight gained from the previous synthesis of the 6-bromo analogue, it was decided to carry out the enolate mediated methylation reactions prior to the oxidative cleavage of the aryl selenide moiety. The first methylation employing NaHMDS and iodomethane at -30 °C afforded the desired mono methyl ketone **161** in good yield. (Scheme 4-25) However, the formation of the dimethyl ketone **162** proved problematic. The conditions previously optimised for this transformation that had furnished the required dimethyl ketone **140** in the synthesis of the 6-bromo analogue did not suffice in this case. In fact no product was formed under the previously optimised conditions. Prolonging the duration of the methylation step resulted in the familiar decomposition brought about by alkylation of the seleno-ether. It was hypothesised that the large bromine substituent occupying the 5-*endo* position was causing the problem. In this case the first methylation to form **161** could proceed relatively easily because the methyl group can easily attack the enolate from the *exo* face. However, attempts to install the second methyl group *via* reaction on the *exo* face would force the previously installed methyl group into an *endo* orientation as the sp<sup>2</sup> enolate carbon becomes a tetrahedral sp<sup>3</sup> centre. This can clearly cause a large steric interaction creating a high energy of activation barrier for the process.

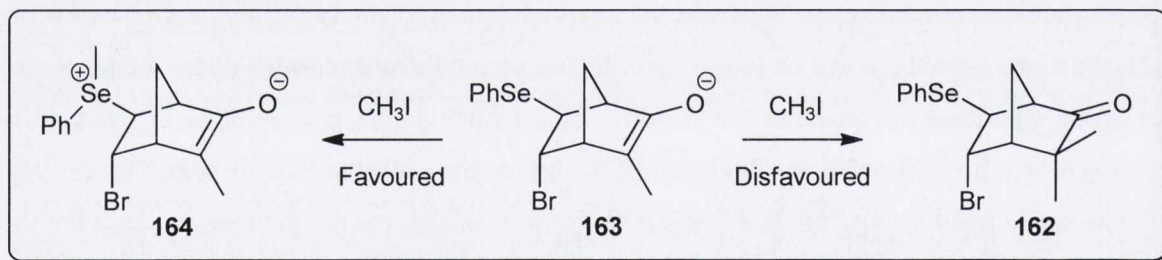




Scheme 4-25 Attempted methylations of ketone 36

An MM2 energy minimization calculation was performed on ketones **162** and **140** in an effort to explore the relevant interactions. As can be seen from

Figure 4-3 the dihedral angles for the bromine-carbon bonds in **162** are larger than those calculated for **140**. It is believed that this is a result of the steric interaction between the 5-*endo* bromine and 3-*endo* methyl substituents in **162**. It was postulated that the favoured process upon exposure of the enolate of **161**, namely **163**, to iodomethane was methylation of the seleno-ether to form **164** and not the desired methylation of the enolate. (Scheme 4-26) As such, an alternative approach would be required.



Scheme 4-26 Competing reactions of enolate 163 upon exposure to iodomethane

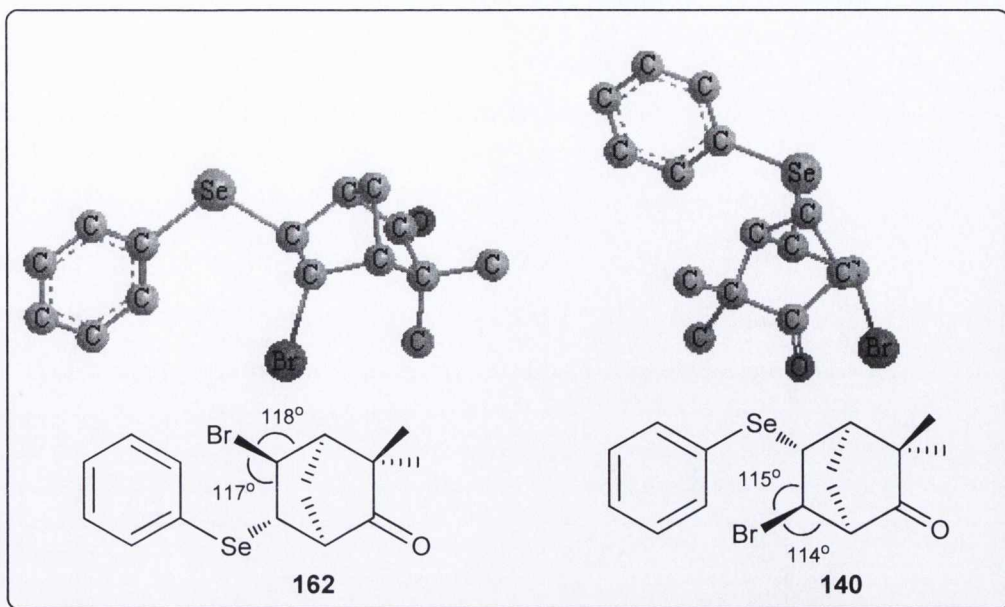
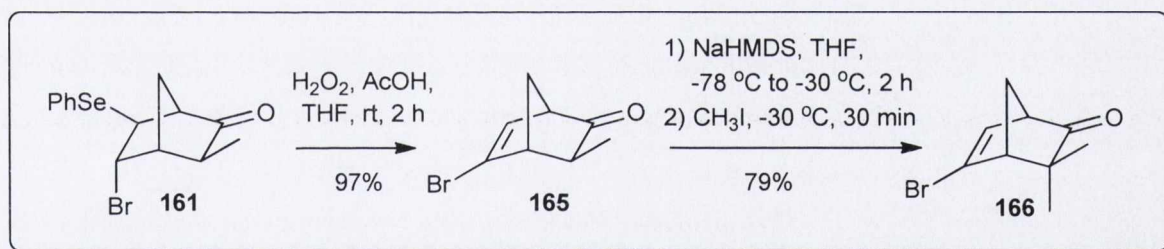


Figure 4-3 Simple (Chemdraw) MM2 energy minimized structures of ketones 162 and 140

It was proposed that carrying out the oxidative cleavage of the seleno-ether in **161** to form vinyl bromide **165** would remove the steric interaction arising from the 5-endo bromine substituent. Gratifyingly, this proved to be the case and the methylation of vinyl bromide **165** furnished ketone **166** in good yield. (Scheme 4-27)



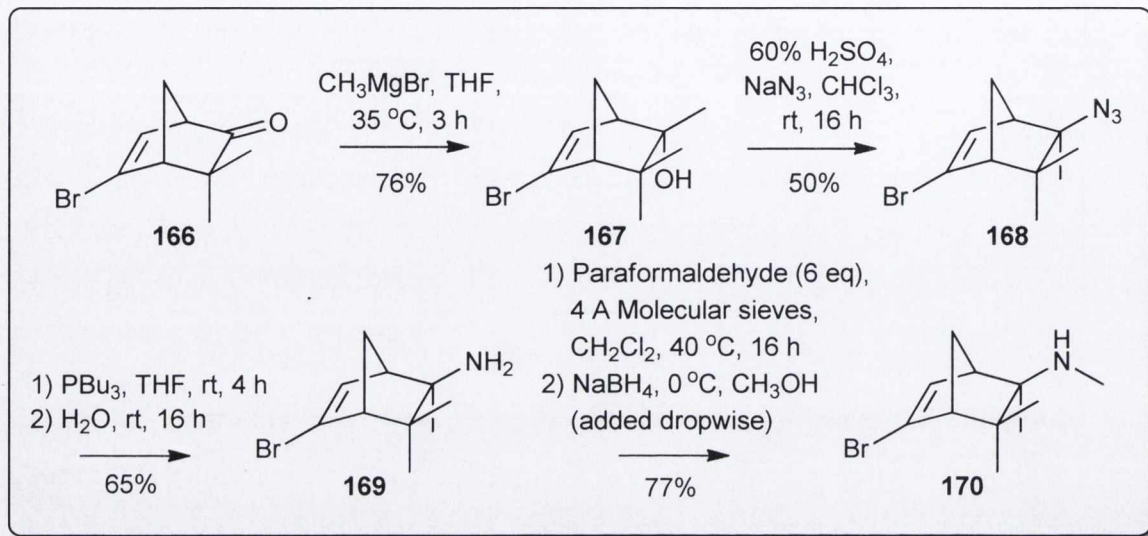
Scheme 4-27 Synthesis of ketone 166

#### 4.3.5 5-Bromo-*N*,2-*endo*-,3,3-tetramethylbicyclo[2.2.1]hept-5-en-2-amine (170)

The synthetic manipulations required to convert ketone **166** into the desired 5-bromo MA analogue were achieved using the same methodology that had been employed in the synthesis of the 6-bromo MA analogue **149** with little difference. (Scheme 4-28) Thankfully, the yield obtained for the azide formation reaction was marginally higher for the 5-bromo alcohol **167**



compared to its 6-bromo counterpart. In addition it was possible to isolate amine **169** cleanly despite the fact that precisely the same purification techniques were employed as were attempted unsuccessfully in the case of the 6-bromo analogous case.



Scheme 4-28 Synthesis of 5-bromo MA analogue 170

As was the case with the 6-bromo MA analogue **149**, amine **170** can be assessed for biological activity itself, while the vinyl bromide moiety present provides a powerful functional handle which can hopefully be exploited to prepare a library of structurally diverse analogues. As such, the synthetic developments outlined in Scheme 4-14 will also find use with vinyl bromide **170**.

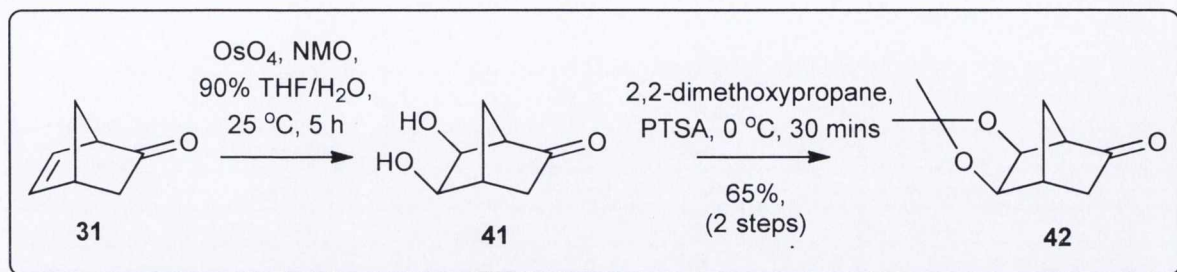
## 4.4 5,6-disubstituted analogues

### 4.4.1 5-*exo*,6-*exo*-Dihydroxybicyclo[2.2.1]heptan-2-one (**41**)

The synthetic route developed to prepare the 5- and 6-bromo MA analogues necessitated the formation of alkene **31**. Clearly the alkene itself offers vast potential for further development. Scheme 1-7) It was decided to focus on a 5,6-disubstitution by forming the diol **41**. The diol itself may have a considerably altered drug metabolism and pharmacokinetic (DMPK) profile from the parent compound MA but can easily be masked as a variety of esters. In addition from a chemical perspective the diol could be further developed.

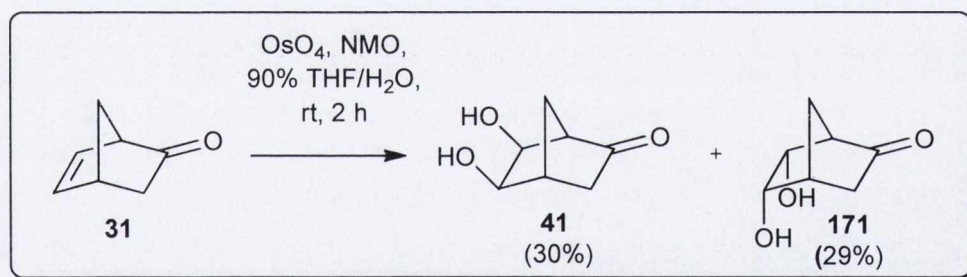


A survey of the literature indicated that Wang and co-workers had previously prepared the diol of interest to this project by osmium tetroxide mediated dihydroxylation. The authors state that this reaction should be stirred for 5 hours at room temperature to effect complete conversion and that quantitative facial selectivity for the *exo* isomer is observed. (Scheme 4-29)



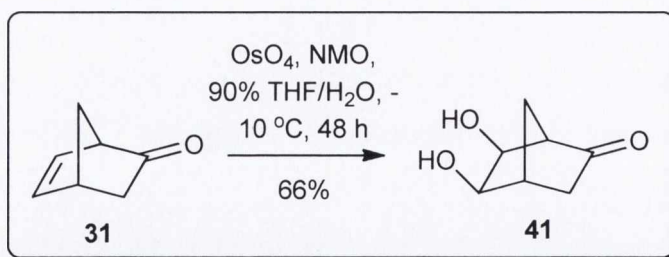
Scheme 4-29 Extract from Wang, G. T.; Wang, S.; Chen, Y.; Gentles, R.; Sowin, T. *The Journal of Organic Chemistry* 2001, 66, 2052-2056

However, in our hands we were unable to reproduce these results. TLC analysis showed that no starting material remained after only 2 hours and that worryingly, a mixture of products had been obtained. Separation of the major products was achieved *via* flash chromatography on silica gel and **41** and **171** were characterised as the *exo* and *endo* dihydroxy isomers respectively.  $^1\text{H}$  NMR spectroscopic analysis of the crude product showed that the ratio of **41**:**171** obtained was approximately 50:50.



Scheme 4-30 Isolated yields of ketones **41** and **171** obtained from dihydroxylation of ketone **31**

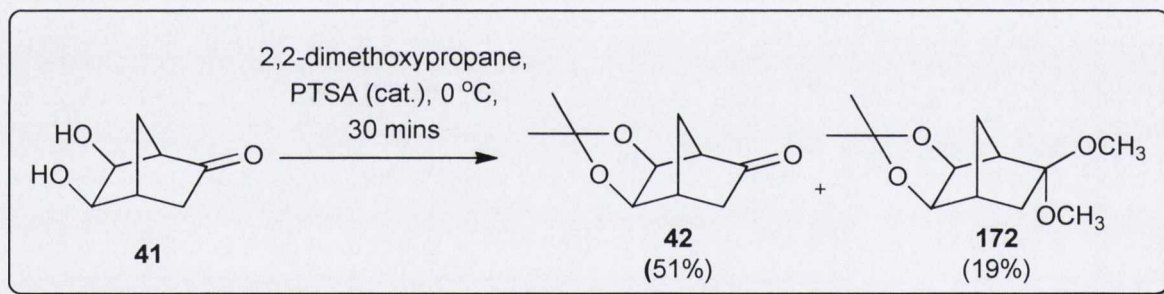
As no facial selectivity was observed in this reaction, the possibility of attempting a Sharpless Asymmetric Dihydroxylation<sup>361, 362</sup> was considered but it was deemed prudent to first investigate the racemic  $\text{OsO}_4$  method further. Surprisingly, the reaction did proceed with complete facial selectivity when stirred for 2 days at  $-10\text{ }^{\circ}\text{C}$  forming the desired diol **41** as a white solid in 66% yield after purification by flash chromatography on silica gel. (Scheme 4-31)



Scheme 4-31 Facial selective synthesis of diol **41**

#### 4.4.2 5-*exo*,6-*exo*-(Isopropylidenedioxy)bicyclo[2.2.1]-heptan-2-one (**42**)

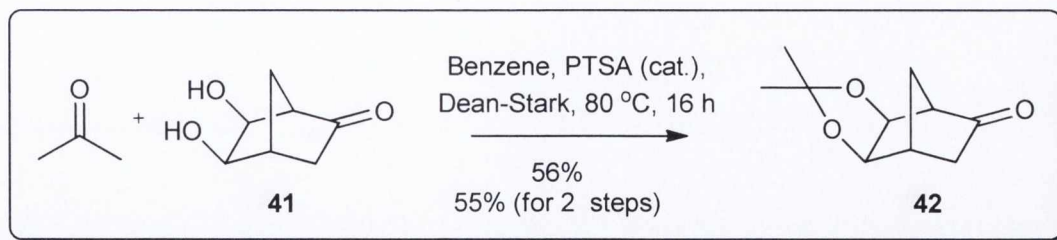
The isopropylidene protection of diol **41** was also described by Wang *et al*<sup>297</sup>. Frustratingly however, the protection of diol **41** also did not proceed as documented. Diol **41** was stirred for 30 minutes at  $0^\circ\text{C}$  and after workup, analysis of the  $^1\text{H}$  NMR data indicated that two major products were formed during reaction. (Scheme 4-32) These were the desired acetal **42** and also the corresponding dimethyl acetal **172**.



Scheme 4-32 Attempted synthesis of ketone **42**

During the transacetalisation reaction involving 2,2-dimethoxypropane, 2 equivalents of methanol are liberated for each diol **41** that is protected. The acid catalyst present could facilitate acetal formation while the excess of 2,2-dimethoxypropane employed could act as a dehydrating agent. It was thought that it should be possible to selectively hydrolyse the dimethyl acetal **172** to regenerate the ketone **42** but this would not be an efficient method to synthesise **42** in the future. Instead, the desired isopropylidene protected diol was synthesised using the procedure of Schurig *et al*<sup>363</sup> by heating a solution of the diol and acetone in benzene at reflux overnight under Dean-Stark conditions.



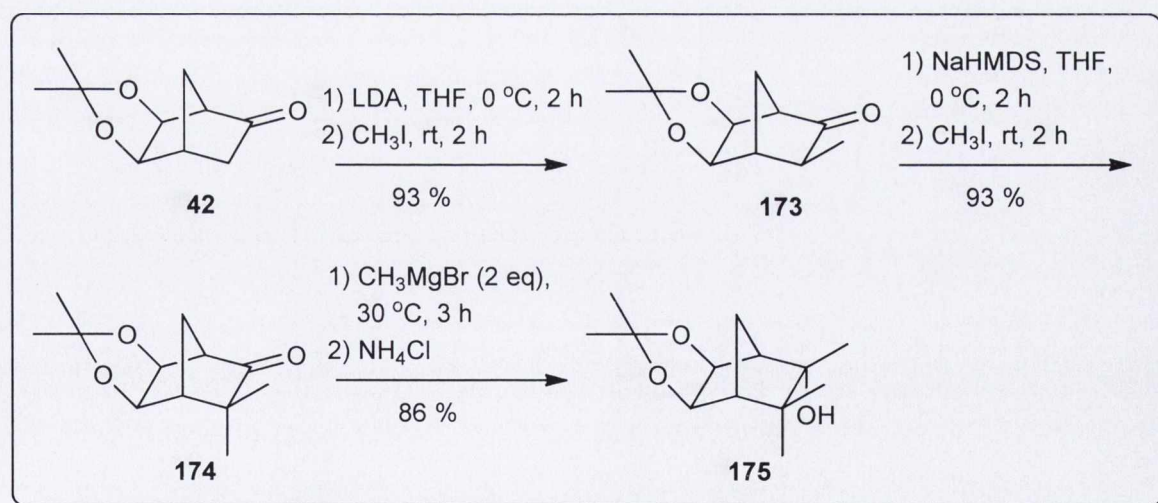


Scheme 4-33 Synthesis of ketone 42

Gratifyingly it was found that this procedure could be applied to the crude product obtained from the dihydroxylation process. This was seen as advantageous as purification of the acetal **42** was a far simpler prospect than purification of the highly polar diol **41**. A yield of 55% for the two steps was considered acceptable.

#### 4.4.3 2-*exo*-,3,3-Trimethyl-5-*exo*,6-*exo*-(isopropylidenedioxy)bicyclo[2.2.1]heptan-2-ol (**175**)

The formation of the alcohol **175** was achieved without difficulty by employing the previously described conditions used to prepare alcohol **141** or **167**. (Section 2.2.1) The only slight modification made was to employ 10%  $\text{NH}_4\text{Cl}$  in place of  $\text{HCl}$  during each of the three workup procedures in an effort to ensure the survival of the cyclic acetal. This proved to be the case and all reactions proceeded cleanly. Of the 3 novel compounds prepared, only the dimethyl ketone **174** required purification by flash chromatography on silica gel.

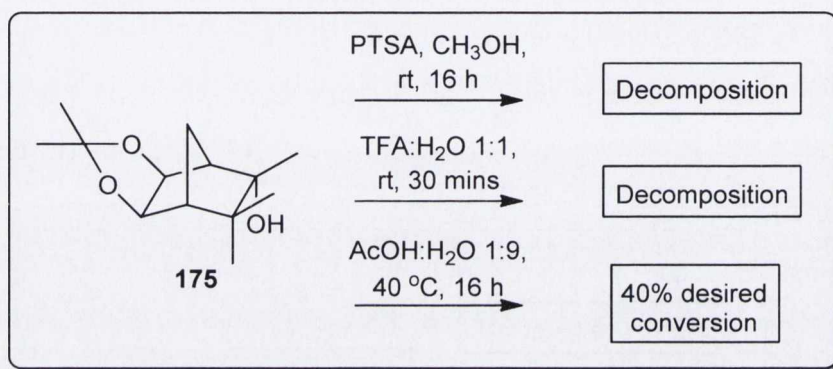


Scheme 4-34 Synthesis of alcohol 175



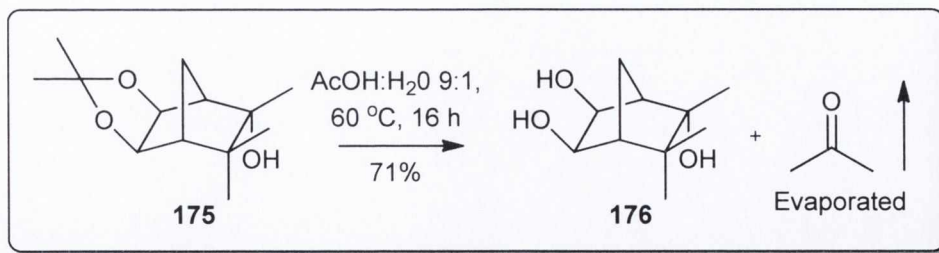
#### 4.4.4 Isopropylidene deprotection

The next step was the substitution of the alcohol for an azide. It was expected that the 1,3 dioxolane in **175** would be quickly hydrolysed to the diol but we were less sure how the triol generated would behave with respect to potential rearrangements. It was deemed necessary to isolate and characterise the triol **176** in order to provide a clean sample that would allow the disappearance of the triol to be monitored by  $^1\text{H}$  NMR spectroscopy. A number of acetal deprotection conditions were investigated.



Scheme 4-35 Screening acetal deprotection strategies

The combinations of PTSA in methanol or TFA in  $\text{H}_2\text{O}$  proved unsuccessful as analysis of the reaction mixture showed decomposition of the triol product **176** was occurring before hydrolysis of the acetal was complete. This information was a little concerning as it suggested that the undesired acid catalysed rearrangements were facile in the extreme. It was thought that the 1.75 M acetic acid solution seemed more promising. Unfortunately, after stirring for a further 24 hours a conversion of only 50% was obtained. Increasing the reaction temperature to 50 °C and stirring for a further 24 hours resulted in a conversion of 65% but by this time the appearance of rearrangement products was evident. Thankfully it was found that by heating this reaction to 50 °C while leaving the flask open to the atmosphere, the removal of the acetone formed by the hydrolysis could drive the reaction to completion in 20 hours. (Scheme 4-36) The triol **176** was obtained in 71% yield after purification by flash chromatography by employing this approach.

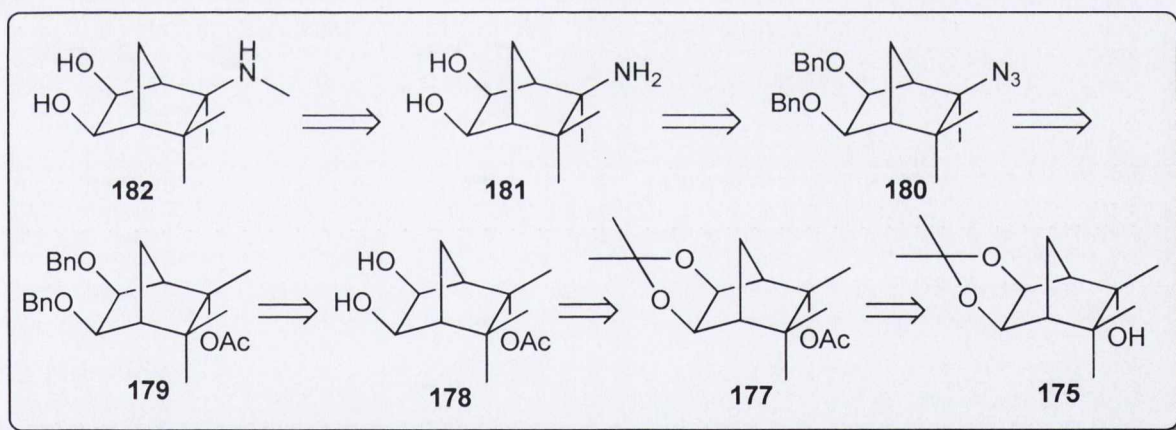


Scheme 4-36 Formation of triol **176**

## 4.4.5 Diol protection

### 4.4.5.1 *bis*-Benzyl ether

The test reactions performed to investigate the deprotection of acetal **175** had already illustrated that triol **176** was unstable in less acidic media than that required to facilitate the azide formation. A protection strategy would be necessary to successfully furnish the desired azide. Our initial strategy was to protect the secondary hydroxyl groups as benzyl ethers. The retrosynthetic analysis shown in Scheme 4-37 outlines the proposed approach.



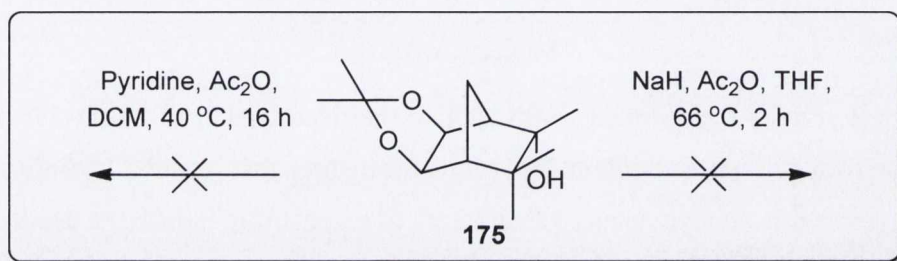
Scheme 4-37 Retrosynthesis of 5,6-disubstituted MA analogue **182**

In order to exchange the isopropylidene protecting group for another motif that would withstand the concentrated acidic medium required for the azide formation, the alcohol at position 2 would require temporary protection as shown in Scheme 4-37. It was thought that it should be possible to cleave the 1,3 dioxolane in **177** without hydrolysing the ester function to afford the 1,2 diol **178**. This compound could be *bis*-benzylated to provide **179**. It was hoped that **179** could be used directly in the azide formation reaction as hydrolysis of the ester may occur under the



reaction conditions. If this proved not to be the case, basic hydrolysis would reliably furnish the required alcohol. An advantage of this method would be the possibility of removing the benzyl protecting groups and reducing the azide simultaneously by catalytic hydrogenation of azide **180**. Reductive amination of **181** would reliably yield the 5,6-dihydroxy MA analogue **182**.

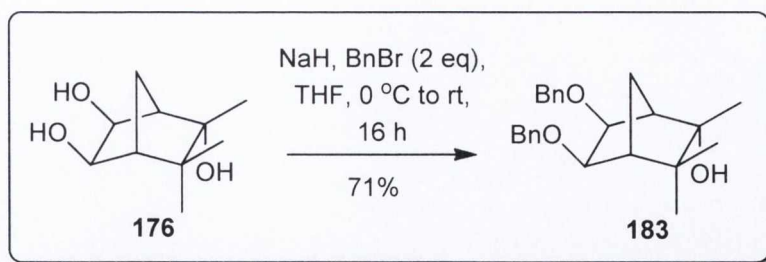
Fortunately, protection of the tertiary alcohol proved to be difficult. Employing acetic anhydride and pyridine in dichloromethane at reflux for 16 hours failed to produce any of the desired acetate **177**. The use of sodium hydride to deprotonate the alcohol failed to instigate a reaction with acetic anhydride, even when stirred at reflux in tetrahydrofuran for 2 hours.



**Scheme 4-38 Attempted acylation of alcohol 175**

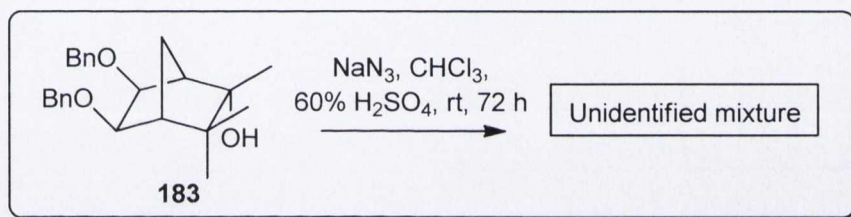
It would seem that the steric environment at the 2-*endo* position was too hindered for acylation to occur. Therefore it was thought that it should be possible to selectively *bis*-benzylate the 1,2 diol in the presence of the tertiary alcohol moiety. Gratifyingly, this was achieved using the procedure employed by both Dondoni *et al.*<sup>364</sup> and Shindo<sup>365</sup> *et al.*. Treatment of triol **176** with an excess of sodium hydride followed by addition of benzyl bromide furnished the *bis*-benzylated alcohol **183** in 71% yield after purification by flash chromatography. (Scheme 4-39)





Scheme 4-39 Synthesis of *bis*-benzyl ether **183**

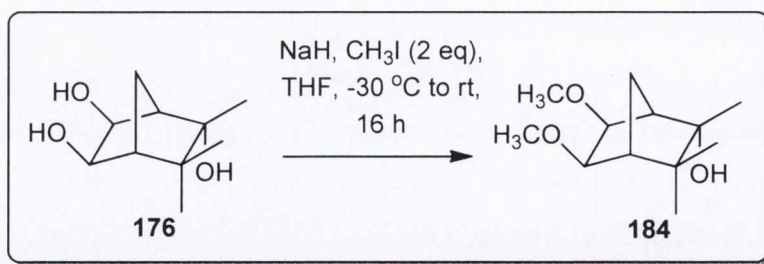
Having prepared the *bis*-benzyl ether we were in a position to attempt the azide formation. Disappointingly, it was revealed that the *bis*-benzylated diol **183** was not stable to the azide formation reaction conditions as was hoped. Exposure of a solution of alcohol **183** in chloroform to an acid strength of 60% H<sub>2</sub>SO<sub>4</sub> in the presence of NaN<sub>3</sub> resulted in the slow deprotection of alcohol **183** and subsequent decomposition.



Scheme 4-40 Attempted azide formation from the *bis*-benzylated alcohol **183**

#### 4.4.5.2 *bis*-Methyl ether

As a last resort, it was decided to attempt the synthesis of the *bis*-methyl ether **184**. Methyl ethers are considerably more resilient than benzyl ethers and it was thought that this might provide a stable substrate suitable for azide formation at position 2. A slightly modified version of the procedure used by Grieco and co-workers<sup>366</sup> to install the methyl ether protecting group in their investigation of a class of compounds known as quassinoids was employed.



Scheme 4-41 Attempted synthesis of the dimethoxy alcohol **184**

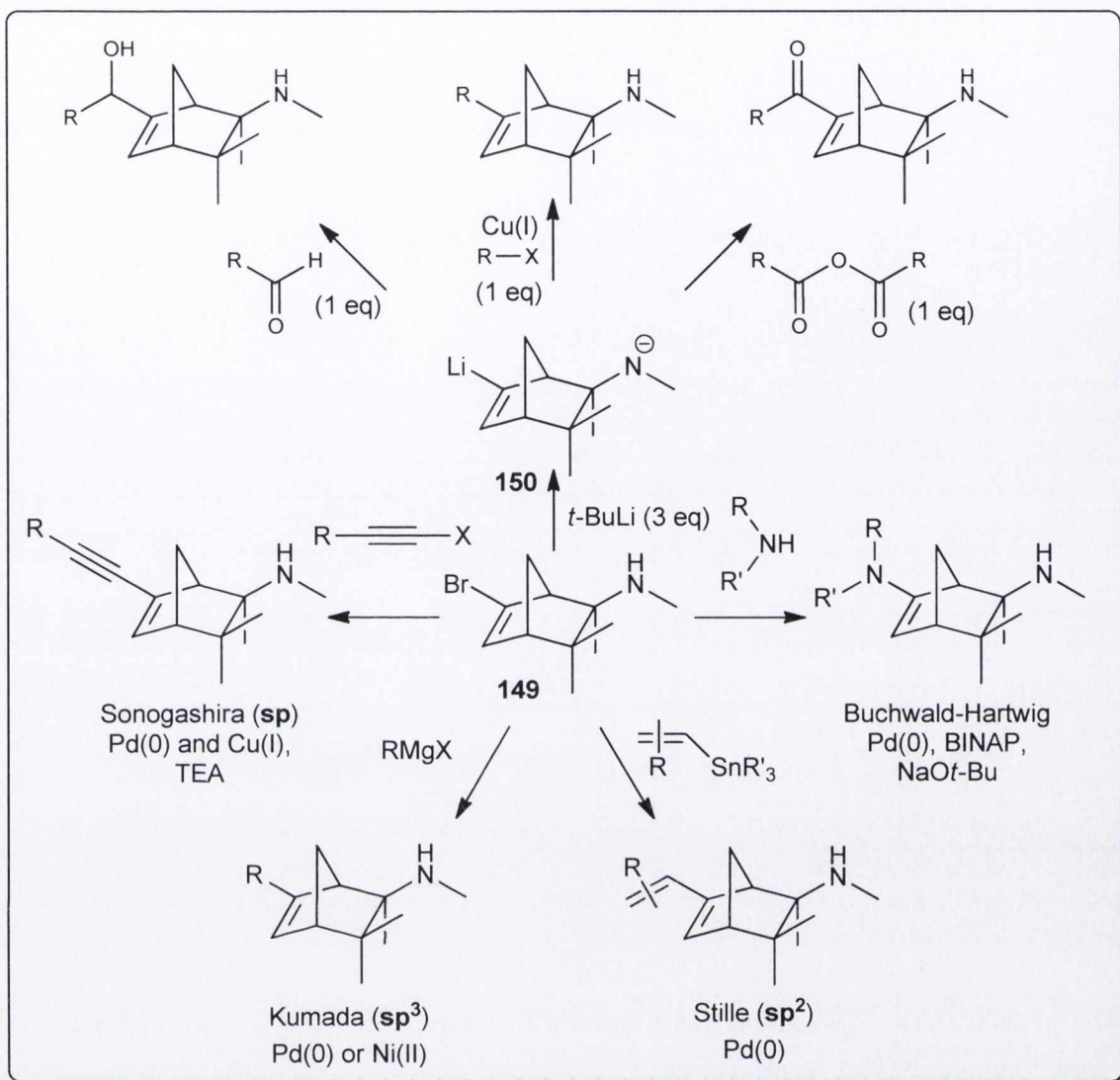
Unfortunately, the selectivity observed in the previous syntheses was not exhibited in the case iodomethane. Treatment of triol **176** with sodium hydride followed by 2 equivalents of iodomethane gave a mixture believed to contain various mono-, *bis*- and *tris*-methoxy protected compounds.

Considering the troublesome nature of the methylation coupled with the potential issues with azide formation and the pressure of time, it was deemed prudent to focus our attention elsewhere.

#### 4.4.6 Conclusions and future work

##### 4.4.6.1 5- and 6-substituted mecamlamine analogues

The synthesis of 6-bromo and 5-bromo MA analogues (**149** and **170** respectively) was accomplished. The installation of the bromine substituent with complete regioselectivity was achieved by performing an addition of phenylselenenyl bromide to norbornenone **31** and the corresponding dimethyl acetal **158** respectively. These compounds will be assessed for activity at nAChR subtypes but more importantly serve as precursors to a wide range of 5- and 6-substituted MA analogues as outlined in Scheme 4-42. In due course a small library of compounds will be prepared in order to probe the pharmacological space around position 5 and 6 on the MA skeleton.



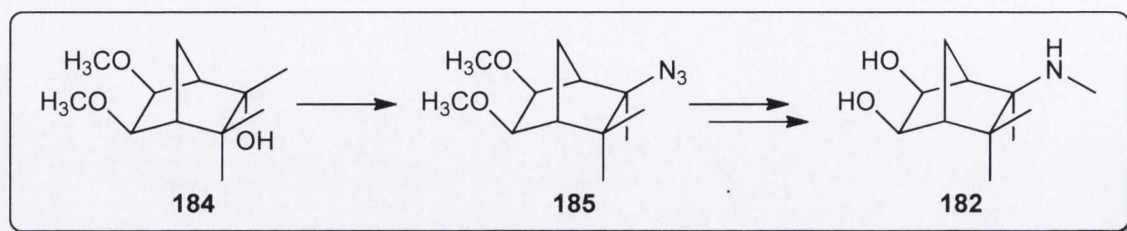
Scheme 4-42 Potential diversification of vinyl bromide **149** (or **170**)

The synthesis of a 5,6-disubstituted MA analogue in the form of diol **182** was not completed. The triol **176** was found to be unstable to the azide formation conditions. Protection of the diol moiety as a *bis*-benzyl ether did not allow us to prepare the desired azide. Limited attempts to protect the diol as a *bis*-methyl ether were unsuccessful. This synthetic target will be addressed by alternative routes in the future.



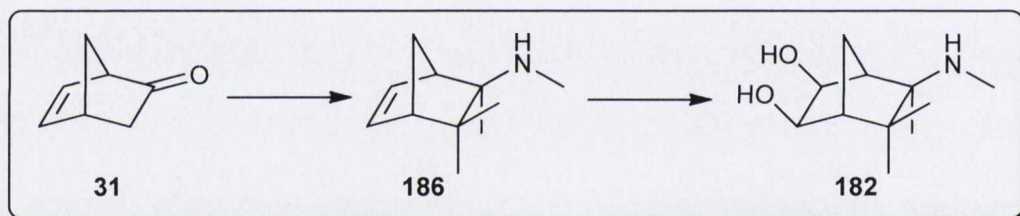
#### 4.4.6.2 5,6 disubstituted mecamlamine analogue

Uncertainty remains over the viability of forming the azide derived from alcohol **184** and also somewhat over the cleavage of the methyl ether moieties that would be necessary to successfully furnish the target analogue **182**.



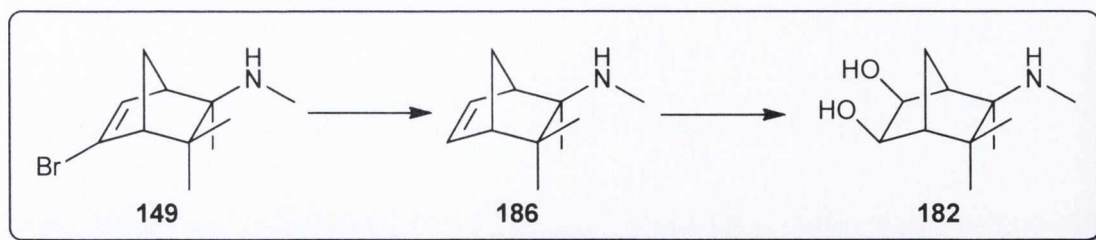
Scheme 4-43 Conversion of alcohol **184** to amine **182**

It may prove more successful to functionalise the double bond after azide formation as shown in Scheme 4-44.



Scheme 4-44 Alternative synthetic route to diol **182**

Alternatively, a longer but more reliable synthetic route to diol **182** taking advantage of the previously described synthesis of vinyl bromide **149** could be envisaged. (Scheme 4-45) Halogen lithium exchange and protonation of the resulting lithiated species would furnish the unsubstituted olefin **186**. Dihydroxylation of the product would provide the desired target amine **182**.



Scheme 4-45 Alternative synthetic route to 183

In a broader sense, it is believed that the concept of using a vinyl bromide as a pseudo protecting group for the unsubstituted olefin, which avoids the synthetic problems associated with the volatility of norbornenone **31** and also potential problems arising from the azide formation with this substrate, to be an excellent method to furnish **186** which could of course undergo the full range of synthetic manipulations outlined in Scheme 1.6.9.

#### 4.4.6.3 Therapeutic potential

Taking a long term view of this project, the ultimate goal would obviously be the synthesis of a highly selective nAChR subtype ligand that could potentially find therapeutic use. The invaluable SAR data that will be gained from the *in-vitro* assessment of the antagonistic activity of the analogue compounds synthesised in this and future projects will hopefully provide a basis for the development of a lead compound. It is an extremely satisfying feeling to have made a significant contribution to this overall process.

# **Chapter 5**

## **Experimental**



## 5 Experimental

### 5.1 $^1\text{H}$ and $^{13}\text{C}$ NMR spectra assignment

Due to the nature of this project it was essential that we were certain of the structure of the compounds that were prepared. It was our aim to unambiguously assign the proton and carbon signals in every molecule prepared. This involved numerous NMR experiments and a representative example of the analysis performed on amine **118** (Figure 5-1) is outlined below.

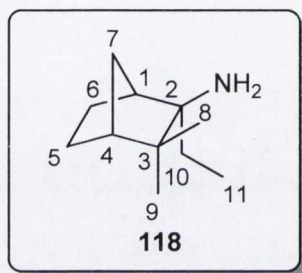


Figure 5-1 NMR assignment for amine **118**

A HSQC (heteronuclear single quantum coherence) experiment was performed (Figure 5-2). This allows the construction of a large portion of Table 5-1 which displays the direct connectivity of proton and carbon signals. The chemical shift for the quaternary carbons was taken from the standard  $^{13}\text{C}$  1-D spectrum. (

Figure 5-3) The DEPT 135 (distortionless enhancement by polarization transfer) experiment displayed on the y-axis in Figure 5-2 facilitated identification of the CH<sub>2</sub> carbon signals which were phase shifted by 180°. It was possible to distinguish between CH and CH<sub>3</sub> carbon signals from a DEPT 90 experiment (not shown). The area highlighted in Figure 5-2 is shown in greater detail in Figure 5-4 which allowed one to distinguish between the  $^1\text{H}$  signals for carbon 5 and 6 which were separated by 0.1 ppm in the  $^{13}\text{C}$  spectrum.

The information required to complete the 'position' column in Table 5-1 will be outlined in due course.

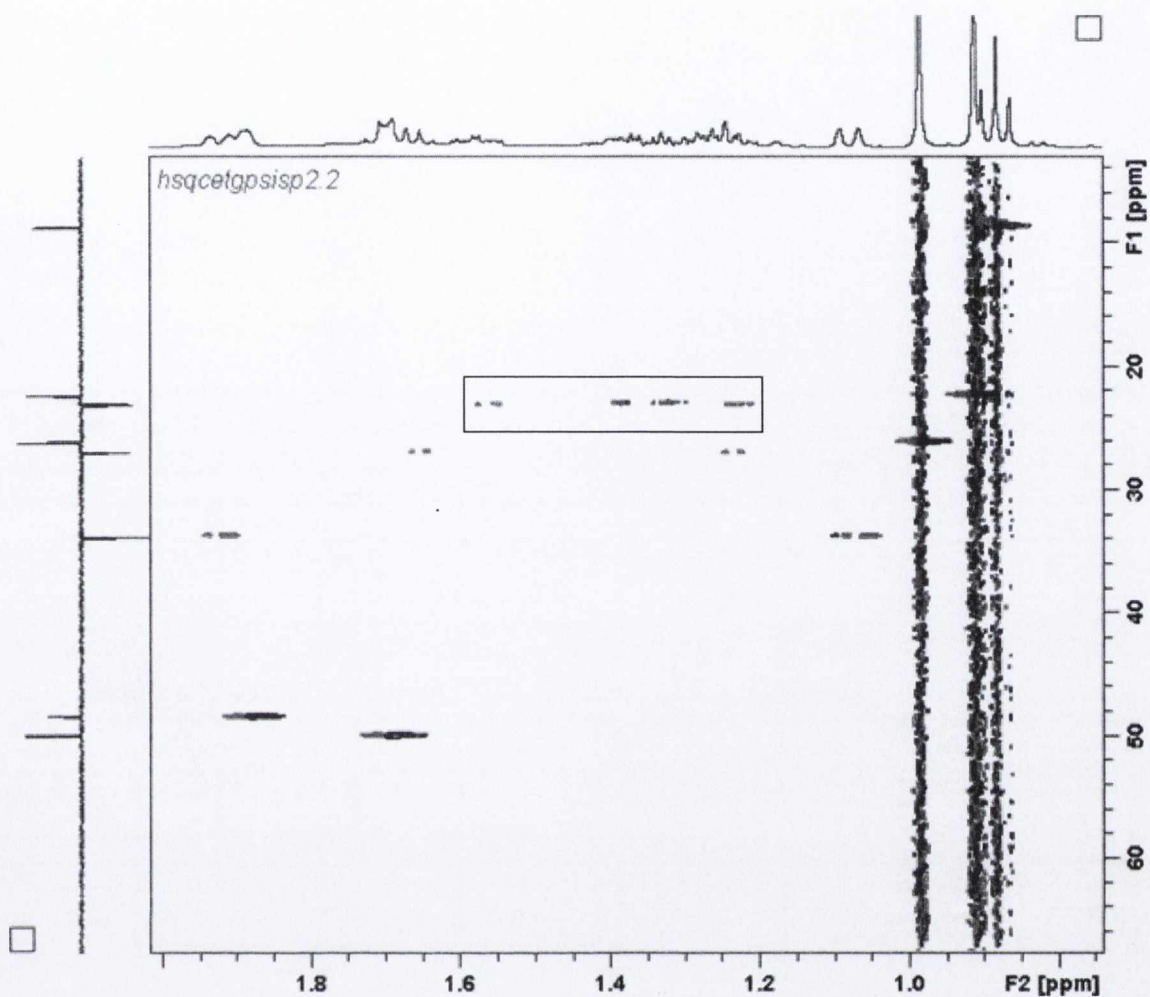


Figure 5-2 HSQC experiment:  $^1\text{H}$  NMR on x axis and DEPT 135 on y-axis

Table 5-1 Complete NMR assignment of amine 118

| Carbon (ppm) | Type    | Proton (ppm)            | Position |
|--------------|---------|-------------------------|----------|
| 8.9          | CH3 (t) | 0.88                    | 11       |
| 22.4         | CH3 (s) | 0.91                    | 9        |
| 23.0         | CH2 (m) | 1.29-1.40               | 6        |
| 23.1         | CH2 (m) | 1.19-1.27 and 1.54-1.62 | 5        |
| 26.2         | CH3 (s) | 0.99                    | 8        |
| 27.0         | CH2 (m) | 1.20-1.27 and 1.62-1.70 | 10       |
| 33.8         | CH2 (m) | 1.04-1.11 and 1.89-1.96 | 7        |
| 43.0         | q       |                         | 3        |
| 48.5         | CH (m)  | 1.86-1.90               | 1        |
| 50.1         | CH (m)  | 1.68-1.72               | 4        |
| 61.5         | q       |                         | 2        |

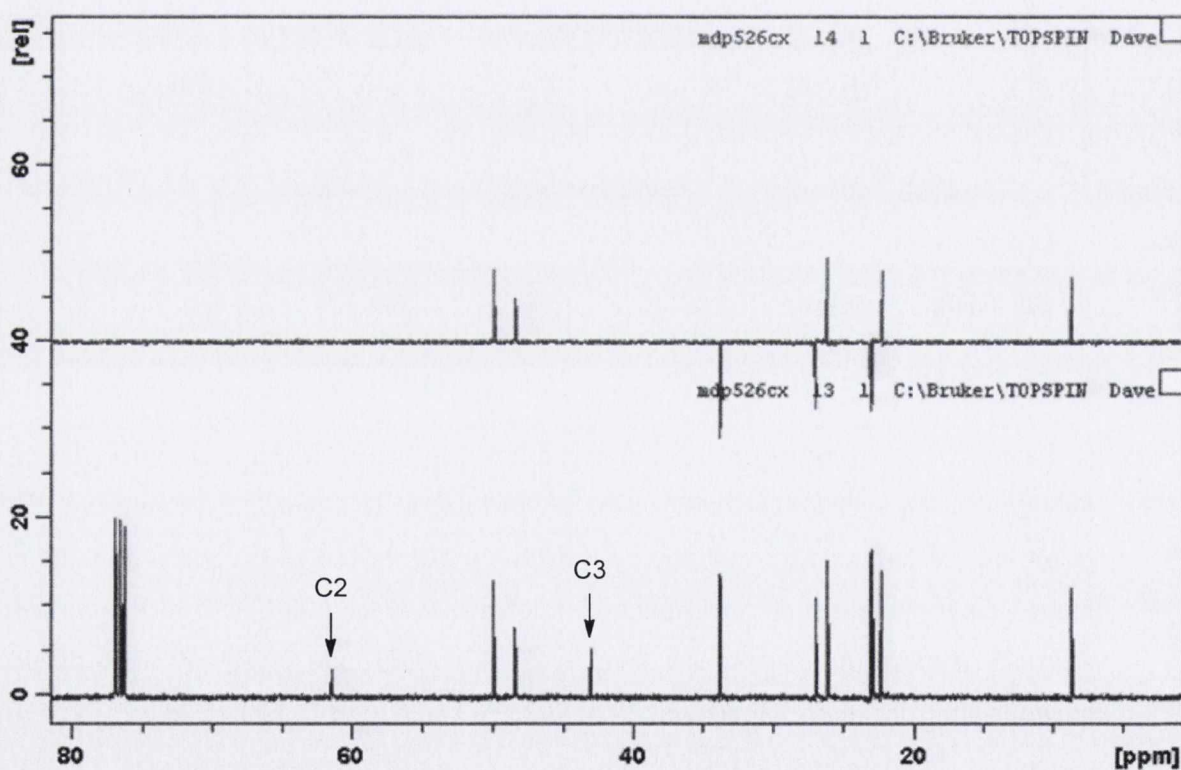


Figure 5-3 13C and DEPT 135 experiments for amine x



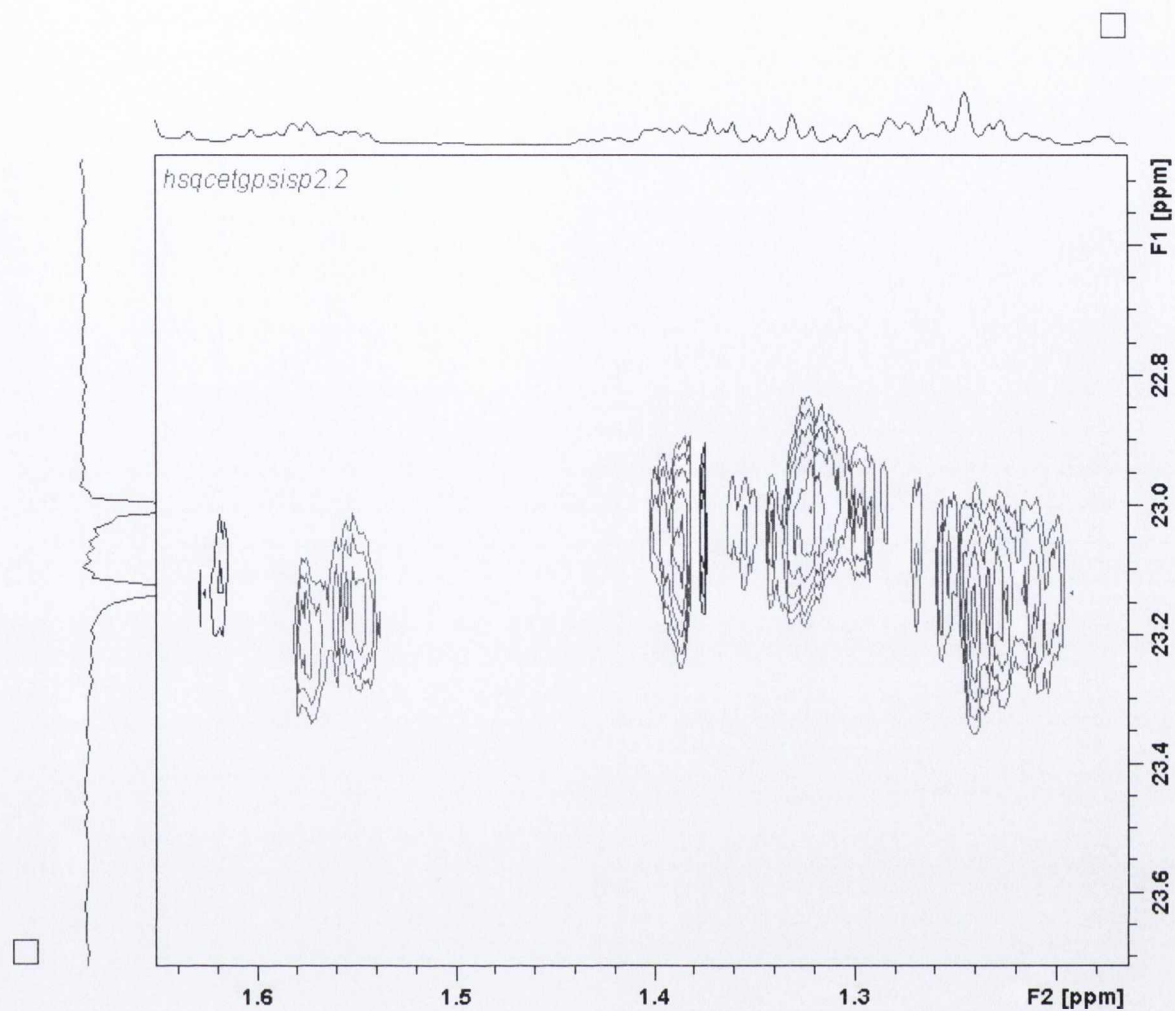


Figure 5-4 Magnification of a portion of the HSQC response for amine 118

A TOCSY (total correlation spectroscopy) experiment was performed to analyse the interactions between protons on adjacent carbons (or on the same carbon if the protons were diastereotopic).

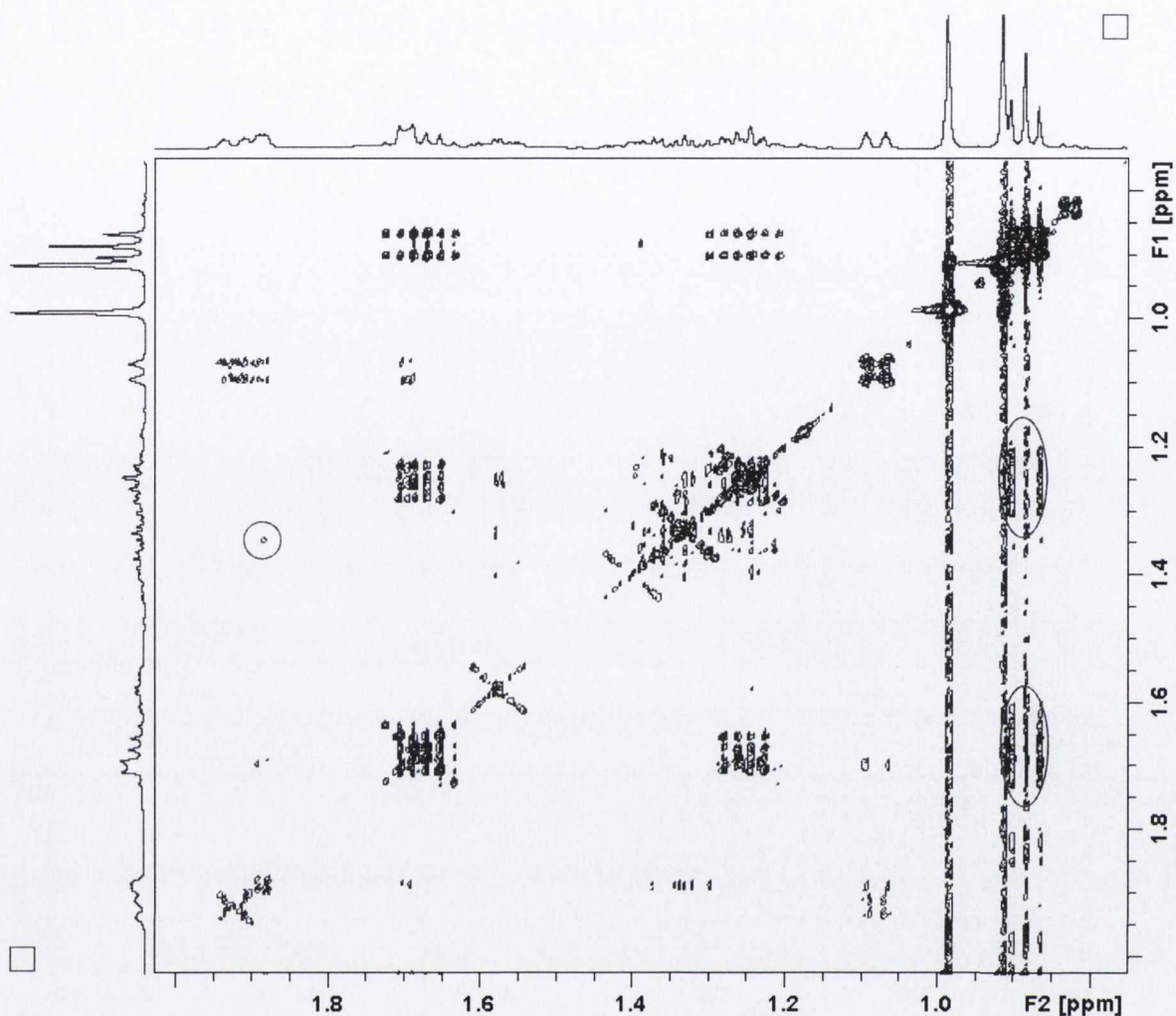


Figure 5-5 TOCSY experiment:  $^1\text{H}$  NMR on both x and y axes

The methyl triplet signal at 0.88 ppm showed a response at 1.20-1.27 ppm and 1.62-1.70 ppm which corresponds to the  $\text{CH}_2$  at 27.0 ppm. Hence, carbons 10 and 11 were assigned. Also evident, is an interaction between the CH at 1.86-1.90 ppm and the  $\text{CH}_2$  at 1.29-1.40 although unambiguous assignment of these signals was not yet possible. As a result, a HMBC (heteronuclear multiple bond coherence) experiment was performed to analyse long range carbon-

hydrogen interactions in an attempt to characterise the relevant CH position.

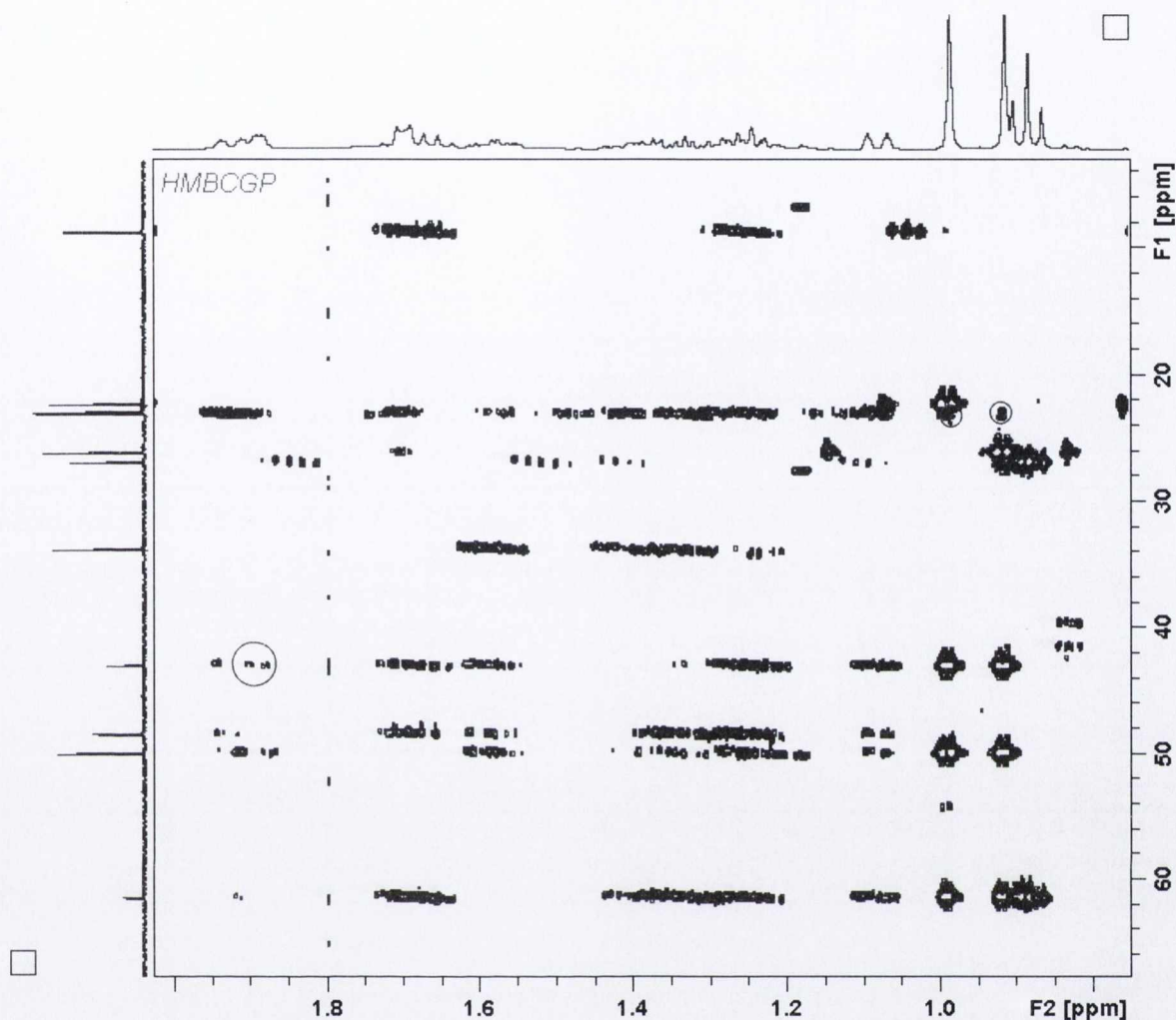


Figure 5-6 HMBC experiment on amine x:  $^1\text{H}$  NMR on x axis and  $^{13}\text{C}$  NMR on y axis

An interaction was observed between the quaternary carbon 3 and the CH at 1.86-1.90 ppm. HMBC responses are generally strongest between atoms separated by three bonds, implying the CH in question is at position 1. The TOCSY interaction (Figure 5-5) observed for this signal implies that the  $\text{CH}_2$  at 1.29-1.40 ppm is at position 6. A number of the remaining signals could also be identified at this point. The second CH (51.1 ppm) was assigned to position 4. It was thought to be highly likely that carbons 5 and 6 would have very similar chemical shifts allowing the  $\text{CH}_2$  at 23.1 ppm to be assigned to position 5. Further evidence to support this claim was available from the HMBC experiment (Figure 5-6) which shows an interaction between both methyl singlets and the  $\text{CH}_2$  at 23.1 ppm (C5). The remaining  $\text{CH}_2$  was attributed to position 7.



In order to confirm the proposed characterisation and also to define the stereochemistry in this system, a series of nOe (nuclear Overhauser effect) experiments were performed in order to analyse the 'through space' interactions for a selected number of protons.

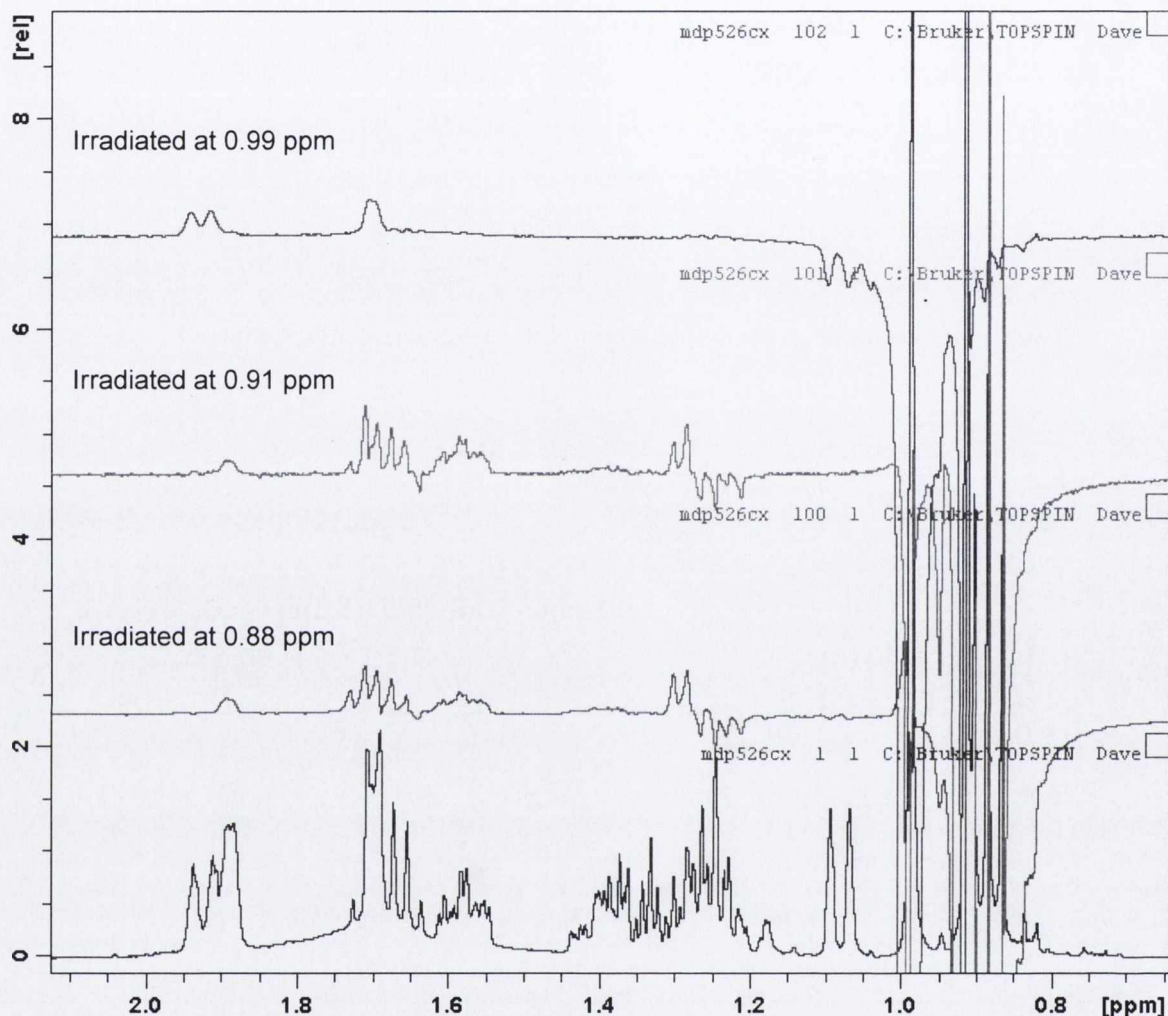


Figure 5-7 nOe experiments irradiating the methyl substituents in amine 118 and original <sup>1</sup>H NMR

In the spectrum for the experiment irradiating at 0.99 ppm, the response visible for the CH at 1.68 - 1.72 ppm confirms the earlier assignment of position 4. The response at 1.89-1.96 ppm corresponds to the interaction shown in Figure 5-8.

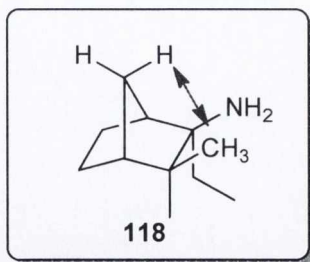


Figure 5-8 NOE response between H8 and H7b in amine **x**

This confirms the assignment of position 7 and allows unambiguous assignment of the *exo* methyl substituent. The nOe experiments irradiating the two remaining methyl groups proved to be less informative, as their chemical shifts were too close to allow selective irradiation of each signal individually. Vitally however, there was clearly no response observed with the nOe experiments irradiating at 0.91 or 0.88 ppm for the signal at 1.89-1.96 ppm, thereby confirming these substituents reside in an *endo* orientation.

This methodical approach was applied to every compound synthesised. Analysis of the stereochemistry of the alkyl substituents at positions 2 and 3 was generally carried out only for one of the azide, amine or methylated amine of each analogue as it was known that the stereochemistry was immutable throughout these transformations.

In certain cases, unambiguous stereochemical assignment was not possible. This generally arose in the case of 3,3-diethyl compounds, in which nOe analysis of the type described above was prevented by the fact that the  $^1\text{H}$  NMR signals for  $\text{CH}_2$  protons on ethyl substituents tended to give rise to overlapping multiplets that could not be selectively irradiated. In these cases, the ethyl substituents were assigned arbitrarily. The example of amine **118** is shown in Figure 5-9.

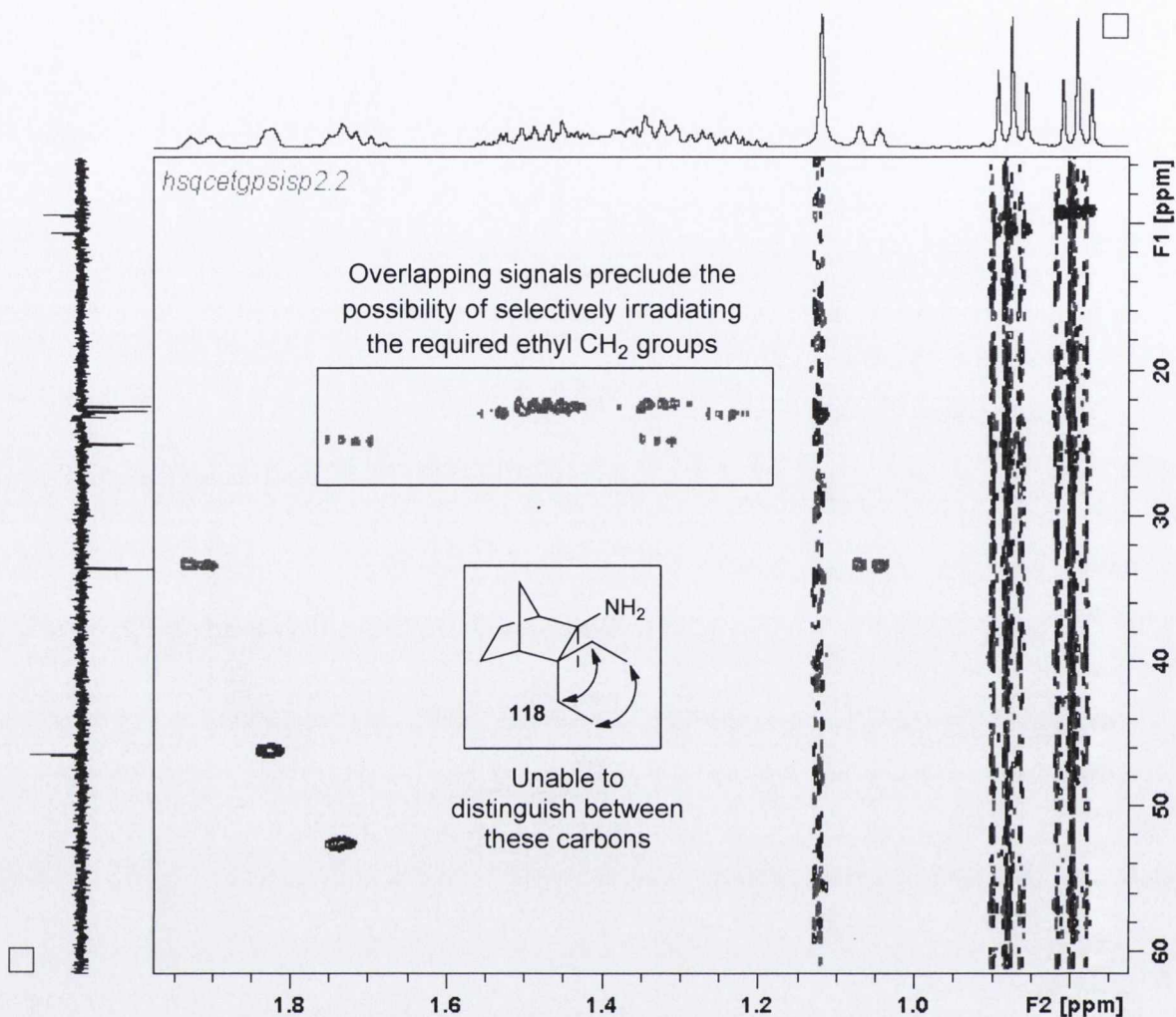


Figure 5-9 Inability to unambiguously assign NMR spectra in amine 118

## 5.2 General

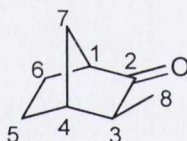
Melting points were determined using a standard melting point apparatus and are uncorrected. All aliphatic amine hydrochloride salts decomposed as opposed to melted. Decomposition temperature was judged to have been reached when the white crystals began to turn brown. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a universal ATR sampling accessory. Proton nuclear magnetic resonance (NMR) spectra were recorded on: Bruker Avance III 400 MHz, Bruker DPX400 400 MHz and Bruker Avance II 600 MHz spectrometers (<sup>1</sup>H NMR spectra were recorded at 400.23 MHz, 400.13 MHz and 600.13 MHz respectively). Chemical shifts are reported in ppm relative to tetramethylsilane and coupling constants (*J*) are quoted in Hertz. Carbon NMR spectra were recorded on the



previously mentioned instruments (100.64 MHz, 100.61 MHz & 150.9 MHz, respectively) with total proton decoupling. HSQC, HMBC, TOCSY and nOe NMR experiments were used to aid assignment of NMR peaks as discussed in section 5.1. A Waters micromass LCT-tof mass spectrometer was used in ES positive and ES negative modes for electrospray mass spectrometry. Electron impact mass spectra were determined on a Quatro-II mass spectrometer in the EI mode. Mass spectra were recorded in CSCB Trinity College Dublin. Flash chromatography was performed using Merk Kiesegel 60 (art. 9385) and aluminium oxide 90, standardized (activity II-III). Merk precoated Kiesegel 60F<sub>254</sub> and alumina (neutral, type E) were used for thin-layer chromatography and slides were visualised by UV irradiation, KMnO<sub>4</sub>, or phosphomolybdic acid staining. Tetrahydrofuran and diethyl ether were distilled over sodium-benzophenone ketyl radical before use. Dichloromethane, toluene and triethylamine were distilled from calcium hydride.

### 5.3 Synthesis of mecamylamine

#### 5.3.1 3-*exo*-Methylbicyclo[2.2.1]heptan-2-one (20)



#### General procedure A

To a solution of freshly distilled diisopropylamine (1.70 mL, 1.72 g, 11.84 mmol) in anhydrous THF (11 mL) cooled to -78 °C, a solution of 2.5 M *n*-butyllithium in hexanes (4.60 mL, 11.36 mmol) was added. The reaction mixture was allowed to warm to 0 °C. A solution of bicyclo[2.2.1]heptan-2-one **19** (1.00 g, 9.08 mmol) in anhydrous THF (2mL) was then added dropwise. After stirring for 2 hours at 0 °C, iodomethane (1.70 mL, 3.87 g, 27.30 mmol) was added dropwise. After stirring for 2 hours at room temperature, a solution of 1M HCl (8 mL) was added. The product was extracted using diethyl ether (2 x 10 mL), washed with brine (10 mL) and dried over MgSO<sub>4</sub>. The solvent was evaporated at reduced pressure to yield 3-*exo*-methylbicyclo[2.2.1]heptan-2-one **20** as a yellow oil. (0.95g, 84.4%) *R*<sub>f</sub> (10% EtOAc/hexane) 0.52.

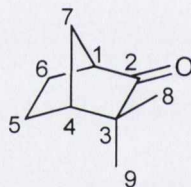
IR  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 2956, 2874, 1736, 1459, 1082, 937, 850.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 1.06 (d,  $J = 7.5$  Hz, 3H, H8), 1.43-1.56 (m, 3H, H5a, H6a, H7a), 1.77-1.91 (m, 4H, H5b, H6b, H3, H7b), 2.30-2.35 (m, 1H, H4), 2.53-2.58 (m, 1H, H1).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 13.7 ( $\text{CH}_3$ , C8), 23.3 ( $\text{CH}_2$ , C6), 27.5 ( $\text{CH}_2$ , C5), 34.0 ( $\text{CH}_2$ , C7), 41.0 ( $\text{CH}$ , C3), 47.5 ( $\text{CH}$ , C4), 49.2 ( $\text{CH}$ , C1), 220.7 (q, C2).

HRMS: ( $m/z$  - CI) calcd. for  $\text{C}_8\text{H}_{13}\text{O}$  ( $\text{M}+\text{H}$ ) $^+$  125.0966, found 125.0974.

### 5.3.2 3,3-Dimethylbicyclo[2.2.1]heptan-2-one (21)



#### General procedure B

3-*exo*-Methylbicyclo[2.2.1]heptan-2-one **20** (1.24 g, 10 mmol) was added to a solution of 1M sodium bis(trimethylsilyl)amide in THF (15.00 mL, 15.00 mmol) in anhydrous THF (12 mL) cooled to  $-78$   $^{\circ}\text{C}$ . After stirring for 2 hours at  $0$   $^{\circ}\text{C}$ , iodomethane (1.93 mL, 4.40 g, 30.98 mmol) was added dropwise. After stirring for 2 hours at room temperature, a solution of 1M HCl (8 mL) was added. The product was extracted using diethyl ether (2 x 10 mL), washed with brine (10 mL) and dried over  $\text{MgSO}_4$ . The solvent was evaporated at reduced pressure to provide a pale yellow oil which was purified by flash chromatography using 97:3 hexane:EtOAc as the eluent to yield 3,3-dimethylbicyclo[2.2.1]heptan-2-one **21** as a pale yellow oil. (1.15g, 83.1%)  $R_f$  (10% EtOAc/hexane) 0.53.



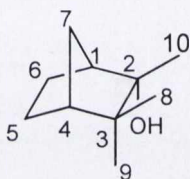
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2967, 2874, 1739, 1464, 1290, 1153, 949, 748.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 1.04 (s, 3H, H9), 1.08 (s, 3H, H8), 1.43-1.53 (m, 2H, H6a, H7a), 1.58-1.72 (m, 1H, H5a), 1.76-1.93 (m, 2H, H5b, H6b), 1.97-2.03 (m, 1H, H7b), 2.30-2.35 (m, 1H, H4), 2.53-2.58 (m, 1H, H1).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 21.5 (CH<sub>3</sub>, C9), 23.26 (CH<sub>3</sub>, C8), 23.31 (CH<sub>2</sub>, C5), 24.6 (CH<sub>2</sub>, C6), 35.1 (CH<sub>2</sub>, C7), 46.2 (CH, C4), 47.2 (q, C3), 50.2 (CH, C1), 223.3 (q, C2).

HRMS: ( $m/z$ +EI) calcd. for C<sub>9</sub>H<sub>14</sub>O (M) 138.1045, found 138.1045.

### 5.3.3 2-*exo*-,3,3-Trimethylbicyclo[2.2.1]heptan-2-ol (**22**)



#### General procedure C

3,3-Dimethylbicyclo[2.2.1]heptan-2-one **21** (0.897 g, 6.50 mmol) was added dropwise to a solution of methyllithium (1.6 M in diethyl ether, 8.13 mL, 13.00 mmol) in anhydrous THF (20 mL) at -78 °C. The reaction mixture was allowed to warm to room temperature. After 3 hours, 10% NH<sub>4</sub>Cl (20 mL) was added. The product was extracted using diethyl ether (2 x 20 mL), washed with brine (20 mL) and dried over MgSO<sub>4</sub>. The solvent was evaporated at reduced pressure to yield a pale yellow oil which was purified by flash chromatography using 98:2 hexane:EtOAc as the eluent. 2-*endo*-,3,3-Trimethylbicyclo[2.2.1]heptan-2-ol **22** was obtained as a white solid (0.89g, 89%). M.p. 118-120 °C (lit.,<sup>367</sup> 113-115°C)  $R_f$  (10% EtOAc/hexane) 0.27.

IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3411, 2929, 2871, 1473, 1371, 1295, 1087, 927

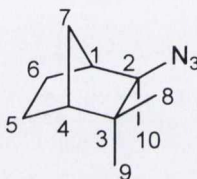
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): (ppm) 0.94 (s, 3H, H9), 0.97 (s, 3H, H8), 1.19-1.15 (m, 1H, H7a), 1.25 (s, 3H, H10), 1.30-1.36 (m, 2H,



H5a, H6a), 1.71-1.78 (m, 3H, H7s, H4, H6b), 1.85-1.90 (m, 1H, H5b), 1.97-2.01 (m, 1H, H1)  
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ (ppm) 21.1 (CH<sub>2</sub>, C5), 21.8 (CH<sub>3</sub>, C9), 24.0 (CH<sub>2</sub>, C6), 26.3 (CH<sub>3</sub>, C10), 27.0 (CH<sub>3</sub>, C8), 34.6 (CH<sub>2</sub>, C7), 42.0 (q, C3), 49.7 (CH, C4), 50.9 (CH, C1), 78.8 (q, C2).

HRMS: (*m/z* - EI) calcd. for C<sub>10</sub>H<sub>6</sub>O<sub>4</sub>N<sub>2</sub>S (M)<sup>+</sup> 154.1358, found 154.1353.

#### 5.3.4 2-Azido-2-*endo*-,3,3,-trimethyl-bicyclo[2.2.1]heptane (23)



##### General Procedure E

A solution of HN<sub>3</sub> was prepared by carefully adding a solution of 50% H<sub>2</sub>SO<sub>4</sub> (10 mL) to a solution of NaN<sub>3</sub> (2.00 g, 30.77 mmol) in CHCl<sub>3</sub> (50 mL) at 0 °C. To this was added 2-*exo*-,3,3-trimethylbicyclo[2.2.1]heptan-2-ol **22** (1.00 g, 6.49 mmol). After stirring for 4 hours at room temperature, ice-cold water (30 mL) was added. The product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 30 mL). The combined organic extracts were washed with 5% NaHCO<sub>3</sub> solution (30 mL), dried over MgSO<sub>4</sub>, and evaporated at reduced pressure to give a yellow oil which was purified by flash chromatography on silica gel using 100% hexane to yield 2-azido-2-*endo*-,3,3,-trimethylbicyclo[2.2.1]heptane **23** as pale yellow oil. (0.78 g, 67% yield) *R<sub>f</sub>* (100% hexane) 0.71.

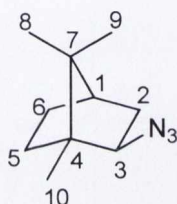
IR ν<sub>max</sub> (cm<sup>-1</sup>): 2934, 2876, 2083, 1454, 1253, 1071, 801

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 0.94 (s, 3H, H9), 1.06 (s, 3H, H8), 1.12-1.16 (m, 1H, H7a), 1.25-1.35 (m, 4H, H10, H5a), 1.41-1.51 (m, 2H, H6), 1.55-1.63 (m, 1H, H5b), 1.75-1.80 (m, 1H, H4), 1.99-2.05 (m, 1H, H7b), 2.11-2.15 (m, 1H, H1).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 17.3 ( $\text{CH}_3$ , C10), 23.1 ( $\text{CH}_2$ , C6), 23.5 ( $\text{CH}_3$ , C9), 23.7 ( $\text{CH}_2$ , C5), 26.8 ( $\text{CH}_3$ , C8), 34.8 ( $\text{CH}_2$ , C7), 43.9 (q, C3), 48.8 ( $\text{CH}$ , C1), 49.8 ( $\text{CH}$ , C4), 72.6 (q, C2).

HRMS: ( $m/z$  - ES) calcd. for  $\text{C}_{10}\text{H}_{18}\text{N}$  ( $\text{M}+\text{H}-\text{N}_2$ ) $^+$  152.1439, found 152.1443.

### 5.3.5 2-Azido-1,7,7-trimethylbicyclo[2.2.1]heptanes (**48**)



Prepared as per general procedure E using 2-*exo*-3,3-trimethylbicyclo[2.2.1]heptan-2-ol **22** (50 mg, 0.32 mmol), 75%  $\text{H}_2\text{SO}_4$  (1 mL),  $\text{NaN}_3$  (100 mg, 1.54 mmol) and  $\text{CHCl}_3$  (5 mL) with a reaction time of 3 hours to yield 2-azido-1,7,7-trimethylbicyclo[2.2.1]heptane **48** as clear oil (29 mg, 51%) without the need for further purification.  $R_f$  (100% hexane) 0.70.

IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 2959, 2930, 2877, 2101, 1456, 1375, 1013.

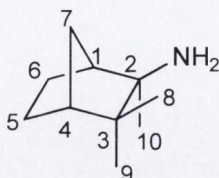
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 0.86 (s, 3H, H9), 0.97 (s, 3H, H8), 1.00 (s, 3H, H10), 1.09-1.18 (m, 2H, H5a, H6a), 1.54-1.66 (m, 2H, H5b, H6b), 1.67-1.84 (m, 3H, H1, H2), 3.49 (dd,  $J = 8.08$  Hz, 4.04 Hz, 1H, H3).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 12.2 ( $\text{CH}_3$ , C10), 19.7 ( $\text{CH}_3$ , C8), 20.1 ( $\text{CH}_3$ , C9), 27.2 ( $\text{CH}_2$ , C6), 35.5 ( $\text{CH}_2$ , C5), 37.5 ( $\text{CH}_2$ , C2), 45.5 ( $\text{CH}$ , C1), 46.8 (q, C7), 50.1 (q, C4), 70.4

(CH, C3).

HRMS: ( $m/z$  - ES) calcd. for  $C_{10}H_{18}N$  ( $M+H-N_2$ )<sup>+</sup> 152.1439, found 152.1445.

### 5.3.6 2-*endo*-,3,3-Trimethyl-bicyclo[2.2.1]heptan-2-amine (24)



*Reduction using lithium aluminium hydride:*

#### General procedure F

To a solution of 2-azido-2-*endo*-,3,3-trimethylbicyclo[2.2.1]heptane **23** (179 mg, 1 mmol) in anhydrous THF (10 mL) under an argon atmosphere cooled to 0 °C, a solution of lithium aluminium hydride (2M in THF, 400  $\mu$ L, 0.80 mmol) was added dropwise. The reaction was allowed to warm to room temperature over 2 hours. Effervescence was observed. After this time, TLC analysis showed that no starting material remained. The reaction was cooled to 0 °C and 2 M NaOH (10 mL) was added slowly. After stirring for 30 minutes at room temperature, the product was extracted using diethyl ether (2 x 10 mL), washed with brine (10 mL), dried over  $MgSO_4$  and concentrated to give a clear viscous oil. The crude oil was further purified by flash chromatography on silica gel using a 50:50 hexane:EtOAc eluent to provide 2-*endo*-,3,3-trimethyl-bicyclo[2.2.1]heptan-2-amine **24** white solid. (107 mg, 70%) M.p. 110 °C -112 °C (Sublimes)

*Reduction via Staudinger protocol:*

#### General procedure G

To a solution of 2-azido-2-*endo*-,3,3-trimethylbicyclo[2.2.1]heptane **23** (179mg, 1 mmol) in anhydrous THF (10 mL) under an argon atmosphere, tributylphosphine (375  $\mu$ L, 304 mg, 1.5 mmol) was added. The reaction was stirred for 4 hours at room temperature.  $H_2O$  (180  $\mu$ L, 10 mmol) was added and effervescence was observed. The reaction was stirred for a further 16 hours at room temperature. The organic solvent was evaporated to yield a pale yellow oil. This oil was redissolved in  $CH_2Cl_2$  (20 mL) and dried over  $MgSO_4$ . A 2 M solution of hydrogen chloride in



diethyl ether (1 mL, 2 mmol) was added to form the hydrochloride salt of the amine. The  $\text{CH}_2\text{Cl}_2$  was removed under vacuum to give a pale yellow oil which was purified by flash chromatography on silica gel using a 100% EtOAc to 50:50 EtOAc:methanol eluent gradient. After removing the column solvent under vacuum, the hydrochloride salt was extracted from 1M NaOH (15 mL) using  $\text{CH}_2\text{Cl}_2$  (2 x 15 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated to yield 2-*endo*-,3,3-trimethyl-bicyclo[2.2.1]heptan-2-amine **24** as a white solid. (88 mg, 58%) M.p. 110 °C -112 °C (Sublimes)

#### *Reduction by hydrogenation:*

##### **General Procedure H**

A hydrogenation reaction vessel was charged with azido-2-*endo*-,3,3-trimethylbicyclo[2.2.1]heptane **23** (179 mg, 1 mmol), methanol (10 mL), and 10% Pd/C (20 mg). This mixture was reacted under an atmosphere of  $\text{H}_2$  at 3 atm for 40 minutes. The catalyst was removed by filtration thorough celite and the celite was washed with  $\text{CH}_2\text{Cl}_2$  (30 mL). The hydrochloride salt was isolated by the addition of dry HCl and evaporation of solvent. M.p. 233 °C (lit.,<sup>368</sup> 243 °C) The free amine was obtained by the addition of NaOH (0.8 g, 20 mmol) and extraction with  $\text{CH}_2\text{Cl}_2$  (2 x 20 mL). The combined organic extracts were dried over  $\text{MgSO}_4$  and concentrated to yield 2-*endo*-,3,3-trimethyl-bicyclo[2.2.1]heptan-2-amine **24** as a white solid. (0.71 g, 83.3%). M.p. 110 °C -112 °C (Sublimes)

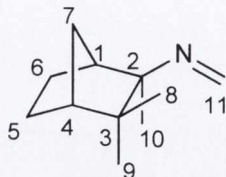
IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 2953, 2870, 1466, 1385, 1258, 1168, 806,743

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 0.93 (s, 3H, H8), 0.99 (s, 3H, H9), 1.07-1.12 (m, 4H, H10, H7a), 1.23-1.32 (m, 1H, H5a), 1.34-1.44 (m, 1H, H6a), 1.50-1.66 (m, 2H, H5b, H6b), 1.71-1.76 (m, 1H, H), 1.79-1.82 (m, 1H, H4), 1.89-1.96 (m, 1H, H7b).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 23.3 ( $\text{CH}_3$ , C10), 23.5 ( $\text{CH}_2$ , C6), 23.6 ( $\text{CH}_3$ , C8), 24.0 ( $\text{CH}_2$ , C5), 26.3 ( $\text{CH}_3$ , C9), 34.4 ( $\text{CH}_2$ , C7), 42.9 (q, C3), 50.2 (CH, C1), 52.6 (CH, C4), 59.5 (q, C2).

HRMS: ( $m/z$  - EI) calcd. for  $\text{C}_{10}\text{H}_{20}\text{N}$  ( $\text{M}+\text{H}$ )<sup>+</sup> 154.1596, found 154.1590.

### 5.3.7 2-endo-3,3-Trimethyl-N-methylenebicyclo[2.2.1]heptan-2-amine (53)



2-endo-,3,3-trimethyl-bicyclo[2.2.1]heptan-2-amine **24** (1.00 g, 6.54 mmol) was dissolved in anhydrous  $\text{CH}_2\text{Cl}_2$  (20 mL). Paraformaldehyde (1.18 g, 39.25 mmol) and 4Å molecular sieve pellets (1 g) were added. The reaction mixture was refluxed at 40 °C for 12 hours under an argon atmosphere. After this time, the molecular sieves and any unreacted paraformaldehyde were removed by filtration. The residue was washed with  $\text{CH}_2\text{Cl}_2$  (40mL). The washings were combined and the solvent evaporated at reduced pressure to yield 2-endo-3,3-trimethyl-N-methylenebicyclo[2.2.1]heptan-2-amine **53** as a clear oil (0.98g, 91%).

IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 2934, 2867, 1647, 1460, 1095, 937, 782, 1386, 1290, 1075, 971, 878

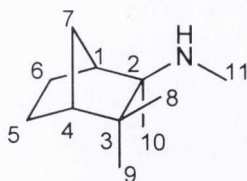
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 0.88 (s, 3H, H9), 0.94 (s, 3H, H8), 1.06 (s, 3H, H10), 1.09-1.13 (m, 1H, H7a), 1.32-1.40 (m, 1H, H5a), 1.42-1.50 (m, 1H, H6a), 1.53-1.63 (m, 1H, H6b), 1.65-1.74 (m, 1H, H5b), 1.77-1.82 (m, 1H, H4), 2.02-2.12 (m, 2H, H1, H7b), 7.32-7.45 (m, 2H, H11).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 18.3 ( $\text{CH}_3$ , C10), 23.1 ( $\text{CH}_3$ , C8), 23.3 ( $\text{CH}_2$ , C6), 23.57 ( $\text{CH}_3$ , C9), 23.62 ( $\text{CH}_2$ , C5), 27.6 ( $\text{CH}_3$ , C9), 33.9 ( $\text{CH}_2$ , C7), 43.2 (q, C3), 48.7 (CH, C4), 49.7 (CH, C1), 70.1 (q, C2), 146.5 ( $\text{CH}_2$ , C11).

HRMS: ( $m/z$  - EI) calcd. for  $\text{C}_{11}\text{H}_{20}\text{N}$  ( $\text{M}+\text{H}$ ) $^+$  166.1596, found 166.1597.



### 5.3.8 *N*,2-*endo*-,3,3-Tetramethylbicyclo[2.2.1]heptan-2-amine (17)



2-*endo*-3,3-Trimethyl-*N*-methylenebicyclo[2.2.1]heptan-2-amine **53** (1.00 g, 6.06 mmol) was added to a solution of NaBH<sub>4</sub> (345 mg, 9.09 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (20 mL) under an argon atmosphere at -78 °C. Anhydrous methanol (0.97 mL, 30.6 mmol) was added dropwise and the reaction allowed to warm to room temperature. After 1 hours, H<sub>2</sub>O (20 mL) was added and the product was extracted using CH<sub>2</sub>Cl<sub>2</sub> (2 x 20 mL). The organic extracts were combined and dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure to yield *N*,2-*endo*-,3,3-tetramethylbicyclo[2.2.1]heptan-2-amine **17** as a clear viscous oil (0.82 g, 81%).

#### *Alkylation via quantitative deprotonation and subsequent alkylation:*

A solution of *n*-butyllithium (2.5M in hexanes, 222 µL, 0.56 mmol) in anhydrous THF (2 mL) was prepared and cooled to 0 °C. To this was added a solution of 2-*endo*-,3,3-trimethylbicyclo[2.2.1]heptan-2-amine **24** (0.081 g, 0.53 mmol) in anhydrous THF (1 mL) dropwise. The reaction was cooled to -78 °C. Freshly distilled iodomethane (34 µL, 0.57 mmol) was added dropwise and the reaction allowed to warm to room temperature over 30 minutes. H<sub>2</sub>O (10 mL) was added and the product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 20 mL). The organic extracts were combined and dried over MgSO<sub>4</sub>. The solvent was evaporated at reduced pressure to yield *N*,2-*endo*-,3,3-tetramethylbicyclo[2.2.1]heptan-2-amine **17** as a clear oil. (0.44 g, 49 %).

IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2930, 2830, 1450, 1410, 1255, 1110

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 0.95 (s, 3H, H9), 1.01-1.05 (m, 4H, H8, H7a), 1.06 (s, 3H, H10), 1.23-1.32 (m, 1H, H5a), 1.33-1.47 (m, 2H, H6), 1.52-1.65 (m, 1H, H5b), 1.65-1.70 (m, 1H, H1), 1.82-1.90 (m, 1H, H7b), 2.17-2.22 (m, 1H, H4), 2.31 (s, 3H, H11).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 17.5 (CH<sub>3</sub>, C10), 22.9 (CH<sub>2</sub>, C6), 23.1 (CH<sub>3</sub>, C9),



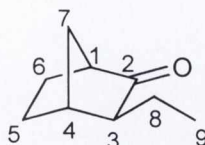
23.7 (CH<sub>2</sub>, C5), 25.1 (CH<sub>3</sub>, C8), 29.7 (CH<sub>3</sub>, C11),  
33.9 (CH<sub>2</sub>, C7), 43.4 (q, C3), 44.5 (CH, C4), 50.0  
(CH, C1), 63.3 (q, C2).

HRMS: (*m/z* - ES) calcd. for C<sub>11</sub>H<sub>22</sub>N (M+H)<sup>+</sup> 168.1752, found 168.1747.

## 5.4 Synthesis of 2- and 3-substituted MA analogues

### 5.4.1 Ketones

#### 5.4.1.1 3-*exo*-Ethylbicyclo[2.2.1]heptan-2-one (78)



Prepared as per general procedure A using freshly distilled diisopropylamine (1.70 mL, 1.72 g, 11.84 mmol), THF (11 mL), *n*-butyllithium (2.5M solution in hexanes, 4.6 mL, 11.36 mmol), bicyclo[2.2.1]heptan-2-one **19** (1.00 g, 9.08 mmol) in anhydrous THF (2 mL) and iodoethane (1.7 mL, 3.32 g, 27.3 mmol) to yield 3-*exo*-ethylbicyclo[2.2.1]heptan-2-one **78** (0.93 g, 82.6 %)  $R_f$  (10% EtOAc/hexane) 0.45.

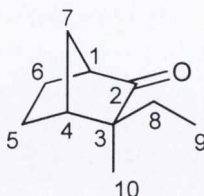
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2959, 2877, 1739, 1463, 1173, 1095, 937.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 1.0 (t,  $J$  = 7.2 Hz, 3H, H9), 1.22-1.31 (m, 1H, H8a), 1.37-1.68 (m, 5H, H5a, H6a, H7a, H3, H8b), 1.77-1.92 (3H, H5b, H6b, H7b), 2.43-2.46 (m, 1H, H4), 2.52-2.55 (m, 1H, H1).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 12.9 (CH<sub>3</sub>, C9), 22.3 (CH<sub>2</sub>, C8), 24.1 (CH<sub>2</sub>, C5), 28.0 (CH<sub>2</sub>, C6), 34.8 (CH, C7), 38.8 (CH, C4), 49.6 (CH, C1), 55.8 (CH, C3), 220.5 (q, C2).

HRMS: ( $m/z$  - ES) calcd. for C<sub>9</sub>H<sub>15</sub>O (M+H)<sup>+</sup> 139.1123, found 139.1125.

#### 5.4.1.2 3-*exo*-Ethyl,3-methylbicyclo[2.2.1]heptan-2-one (79)



Prepared as per general Procedure B using 3-*exo*-methylbicyclo[2.2.1]heptan-2-one **20** (1.76 g, 14.20 mmol), 1 M sodium bis(trimethylsilyl)amide in THF (21.3 mL, 21.3 mmol), THF 25 mL and iodoethane (3.41 mL, 6.65 g, 42.62 mmol) to yield 3-*exo*-ethyl,3-methylbicyclo[2.2.1]heptan-2-one **79** as a clear oil. (1.75 g, 81%).  $R_f$  (10% EtOAc/hexane) 0.55

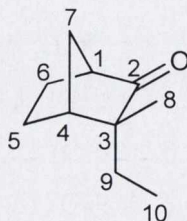
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2960, 2876, 1739, 1460, 1083, 938, 850.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 0.89 (t,  $J$  = 7.2 Hz, 3H, H9), 0.97 (s, 3H, H10), 1.33-1.53 (m, 4H, H6a, H7a, H8), 1.56-1.66 (m, 1H, H5a), 1.68-1.77 (m, 1H, H5b), 1.79-1.90 (m, 1H, H6b), 1.93-2.01 (m, 1H, H7b), 2.36 (br s, 1H, H4), 2.52-2.57 (m, 1H, H1).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 8.4 (CH<sub>3</sub>, C10), 17.9 (CH<sub>3</sub>, C9), 23.2 (CH<sub>2</sub>, C5), 25.2 (CH<sub>2</sub>, C6), 34.8 (CH<sub>2</sub>, C7), 42.8 (CH, C4), 50.1 (q, C3), 50.2 (CH, C1), 223.3 (q, C2).

HRMS: ( $m/z$  - ES) calcd. for C<sub>10</sub>H<sub>17</sub>O (M+H)<sup>+</sup> 153.1279, found 153.1279.

#### 5.4.1.3 3-*endo*-Ethyl,3-methylbicyclo[2.2.1]heptan-2-one (80)





Prepared as per general procedure B using 3-*exo*-ethylbicyclo[2.2.1]heptan-2-one **78** (2.32 g, 16.81 mmol), 1 M sodium bis(trimethylsilyl)amide in THF (25.21 mL, 25.21 mmol), THF 30 mL and iodomethane (3.14 mL, 7.16 g, 50.43 mmol) to yield 3-*exo*-methyl,3-ethylbicyclo[2.2.1]heptan-2-one **80** as a clear oil (1.99 g, 79%).  $R_f$  (10% EtOAc/hexane) 0.53

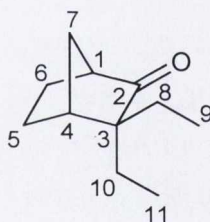
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2960, 2926, 1739, 1456, 1257, 1012, 791.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 0.91 (t,  $J$  = 7.50 Hz, 3H, H10), 1.02 (s, 3H, H8), 1.31-1.39 (m, 1H, H9a), 1.43-1.56 (m, 3H, H6a, H7a, H9b), 1.58-1.66 (m, 1H, H5a), 1.68-1.75 (m, 1H, H5b), 1.80-1.89 (m, 1H, H6b), 1.93-1.98 (m, 1H, H7b), 2.29-2.32 (m, 1H, H4), 2.57-2.60 (m, 1H, H1).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 8.3 (CH<sub>3</sub>, C10), 18.7 (CH<sub>3</sub>, C8), 23.1 (CH<sub>2</sub>, C5), 24.9 (CH<sub>2</sub>, C6), 27.0 (CH<sub>2</sub>, C9), 34.8 (CH<sub>2</sub>, C7), 43.6 (CH, C4), 50.2 (CH, C1), 50.1 (q, C3), 223.1 (q, C2).

HRMS: ( $m/z$  - ES) calcd. for C<sub>10</sub>H<sub>17</sub>O (M+H)<sup>+</sup> 153.1279, found 153.1283.

#### 5.4.1.4 3, 3-Diethylbicyclo[2.2.1]heptan-2-one (**83**)



Prepared as per general procedure B using 3-*exo*-ethylbicyclo[2.2.1]heptan-2-one **78** (1.15 g, 8.32 mmol), 1 M sodium bis(trimethylsilyl)amide in THF (12.48 mL, 12.48 mmol), THF 15 mL and iodoethane (2.00 mL, 3.90 g, 24.96 mmol) to yield 3,3-diethyl-bicyclo[2.2.1]heptan-2-one **83** as a clear oil (1.01 g, 75%).  $R_f$  (10% EtOAc/hexane) 0.54

IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2954, 2872, 1731, 1460, 1382, 1056.

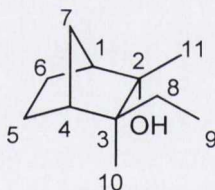
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 0.88 (t, 3H, H11), 0.92 (t, 3H, H9), 1.30-1.30 (m, 1H, H10), 1.41-1.79 (m, 7H, H5, H6, H7, H8, H10), 1.80-1.90 (m, 1H, H6), 1.98-2.04 (m, 1H, H7s), 2.30 (br s, 1H, H4), 2.52-2.57 (m, 1H, H1).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ (ppm) 7.83 (CH<sub>3</sub>, C11), 8.19 (CH<sub>3</sub>, C9), 22.2 (CH<sub>2</sub>, C10), 22.6 (CH<sub>2</sub>, C5), 23.06 (CH<sub>2</sub>, C8), 25.1 (CH<sub>2</sub>, C6), 34.2 (CH<sub>2</sub>, C7), 43.1 (CH, C4), , 50.1 (CH, C1), 52.5 (q, C3), 222.0 (q, C2).

HRMS: ( $m/z$  - Cl) calcd. for  $C_{11}H_{19}O$  (M+H)<sup>+</sup> 167.1436, found 167.1428.

### 5.4.2 Alcohols

#### 5.4.2.1 3-*exo*-Ethyl-2-*exo*-,3-dimethylbicyclo[2.2.1]heptan-2-ol (84)



Prepared as per general procedure C using 3-*exo*-ethyl,3-methylbicyclo[2.2.1]heptan-2-one **79** (4.25g, 27.92 mmol), methyllithium (1.6M in diethyl ether, 34.9 mL, 55.84 mmol) and THF (80 mL) to yield 3-*exo*-ethyl-2-*endo*-,3-dimethylbicyclo[2.2.1]heptan-2-ol **84** as a clear oil. (4.32 g, 92%).  $R_f$  (10% EtOAc/hexane) 0.29

IR  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 3455, 2953, 2875, 1454, 1370, 1292, 1199, 1148, 1003, 899, 876

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 0.86 (t, J = 7.50Hz, 3H, H9), 0.89 (s, 3H, H10), 1.11-1.16 (m, 1H, H7a), 1.25 (s, 3H, H11), 1.26-1.36 (m, 2H, H5a, H6a), 1.38 (q, J = 7.5 Hz, 2H, H8), 1.60-1.69 (m, 2H, H7b, H6b), 1.81-1.90 (m,

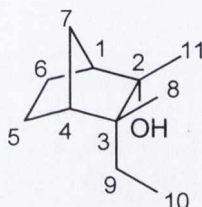
1H, H5b), 1.94-1.98 (m, 1H, H4), 2.02-2.06 (m, 1H, H1).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ (ppm)

9.7 (CH<sub>3</sub>, C9), 17.0 (CH<sub>3</sub>, C10), 20.6 (CH<sub>2</sub>, C5), 23.7 (CH<sub>2</sub>, C6), 25.3 (CH<sub>3</sub>, C11), 29.5 (CH<sub>2</sub>, C8), 34.1 (CH<sub>2</sub>, C7), 43.7 (CH, C4), 44.4 (q, C3), 50.7 (CH, C1), 79.2 (q, C2).

HRMS:(*m/z* - CI) calcd. for C<sub>11</sub>H<sub>21</sub>O (M+H)<sup>+</sup> 169.1592, found 169.1592.

#### 5.4.2.2 3-*endo*-Ethyl-2-*exo*-, 3-dimethyl-bicyclo[2.2.1]heptan-2-ol (85)



Prepared as per general procedure C using 3-*endo*-ethyl,3-methylbicyclo[2.2.1]heptan-2-one **80** (3.83 g, 25.11 mmol), methyllithium (1.6 M in diethyl ether, 31.41 mL, 50.22 mmol) and THF (75 mL) to yield 3-*endo*-ethyl-2-*exo*-,3-dimethylbicyclo[2.2.1]heptan-2-ol **85** as a clear oil. (3.59 g, 85%). *R<sub>f</sub>* (10% EtOAc/hexane) 0.26

IR ν<sub>max</sub> (cm<sup>-1</sup>): 3468, 2961, 2936, 2876, 1462, 1375, 1089, 941.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ (ppm)

0.86 (t, *J* = 7.5 Hz, 3H, H10), 0.92 (s, 3H, H8), 1.13-1.20 (m, 1H, H7a), 1.24 (s, 3H, H11), 1.25-1.34 (m, 3H, H5a, H6a, H9), 1.48-1.58 (m, 1H, H9), 1.58-1.66 (m, 1H, H6b), 1.66-1.73 (m, 1H, H7b), 1.77-1.90 (m, 2H, H5b, H4), 1.94-2.00 (m, 1H, H1).

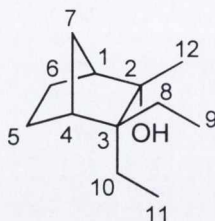
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ (ppm)

9.3 (CH<sub>3</sub>, C10), 20.9 (CH<sub>2</sub>, C5), 21.4 (CH<sub>3</sub>, C8), 23.1 (CH<sub>2</sub>, C6), 26.0 (CH<sub>2</sub>, C9), 26.5 (CH<sub>3</sub>, C11), 34.1 (CH<sub>2</sub>, C7), 46.88 (CH, C4), 44.6 (q, C3), 50.9 (CH, C1), 79.3 (q, C2).



HRMS: ( $m/z$  - CI) calcd. for  $C_{11}H_{21}O$  ( $M+H$ )<sup>+</sup> 169.1592, found 169.1602.

#### 5.4.2.3 2-*exo*-Methyl-3,3-diethyl-bicyclo[2.2.1]heptan-2-ol (**86**)



Prepared as per general procedure C using 3,3-diethylbicyclo[2.2.1]heptan-2-one **83** (3.51 g, 21.14 mmol), methyllithium (1.6 M in diethyl ether, 2.43 mL, 42.28 mmol) and THF (75 mL) to yield 2-*exo*-methyl-3,3-diethylbicyclo[2.2.1]heptan-2-ol **86** as a clear oil. (3.16 g, 82%).  $R_f$  (10% EtOAc/hexane) 0.31

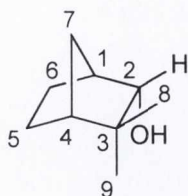
IR  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 2936, 2746, 1480, 1428, 1327, 1112, 1072

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 0.846 (t,  $J$  = 7.48 Hz, 3H, H11), 0.853 (t,  $J$  = 7.52 Hz, 3H, H9), 1.09-1.16 (m, 1H, H7a), 1.23-1.35 (m, 7H, H6a, H5a, H8a, H10a, H12), 1.58-1.71 (m, 4H, H5b, H10b, H9b, H7b), 1.83-1.88 (m, 1H, H6b), 1.91-1.93 (m, 1H, H1), 1.97-1.99 (m, 1H, H4).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 9.8 ( $\text{CH}_3$ , C9), 10.2 ( $\text{CH}_3$ , C11), 21.1 ( $\text{CH}_2$ , C6), 22.0 ( $\text{CH}_3$ , C10), 23.3 ( $\text{CH}_2$ , C5), 25.4 ( $\text{CH}_2$ , C8), 26.8 ( $\text{CH}_3$ , C12), 34.7 ( $\text{CH}_2$ , C7), 45.6 (CH, C4), 47.2 (q, C3), 51.9 (CH, C1), 80.0 (q, C2).

HRMS: ( $m/z$  - EI) calcd. for  $C_{12}H_{21}O$  ( $M-H$ )<sup>-</sup> 181.1592, found 181.1592.

#### 5.4.2.4 3,3-Dimethylbicyclo[2.2.1]heptan-2-endo-ol (**87**)



Prepared as per general procedure C using 3,3-dimethylbicyclo[2.2.1]heptan-2-one **21** (2.50 g, 18.66 mmol), ethylmagnesium bromide (3 M in diethyl ether, 15.00 mL, 45.00 mmol) and THF (30 mL) to unexpectedly yield 3,3-dimethylbicyclo[2.2.1]heptan-2-endo-ol **87** as a white solid following purification by flash chromatography on silica gel using 95:5 hexane EtOAc as eluent. (3.16 g, 82%). None of the expected 2-*exo*-ethyl-3,3-dimethylbicyclo[2.2.1]heptan-2-ol **88** was obtained.  $R_f$  (15% EtOAc/hexane) 0.35

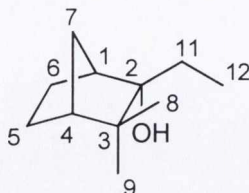
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3412, 2932, 2873, 1476, 1372, 1129, 1081.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 0.86 (s, 3H, H<sub>9</sub>), 0.99 (s, 3H, H<sub>8</sub>), 1.14-1.20 (m, 1H, H<sub>7a</sub>), 1.25-1.40 (m, 2H, H<sub>5a</sub>, H<sub>6a</sub>), 1.56-1.71 (m, 3H, H<sub>5b</sub>, H<sub>6b</sub>, H<sub>7b</sub>), 1.79 (m, 1H, H<sub>4</sub>), 2.25-2.32 (m, 1H, H<sub>1</sub>), 3.67 (d,  $J = 4.03$  Hz, 1H, H<sub>1</sub>).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 18.2 (CH<sub>2</sub>, C<sub>6</sub>), 20.1 (CH<sub>3</sub>, C<sub>9</sub>), 24.7 (CH<sub>2</sub>, C<sub>5</sub>), 30.6 (CH<sub>3</sub>, C<sub>8</sub>), 33.8 (CH<sub>2</sub>, C<sub>7</sub>), 38.1 (q, C<sub>3</sub>), 44.1 (CH, C<sub>1</sub>), 48.4 (CH, C<sub>4</sub>), 80.4 (CH, C<sub>2</sub>).

HRMS: ( $m/z$  - CI) calcd. for C<sub>9</sub>H<sub>17</sub>O (M) 141.1279, found 141.1272.

#### 5.4.2.5 2-*exo*-Ethyl-3,3-dimethylbicyclo[2.2.1]heptan-2-ol (**88**)



#### General Procedure D

A solution of ethyllithium in THF was prepared by slowly adding *tert*-butyllithium (1.7 M in pentane, 34.12 mL, 58.00 mmol) to a solution of ethylbromide (2.17 mL, 3.16 g, 29.0 mmol) in anhydrous THF (45 mL) cooled to  $-78^{\circ}\text{C}$  under an argon atmosphere. To this, a solution of 3,3-dimethylbicyclo[2.2.1]heptan-2-one **21** (2.00 g, 14.49 mmol) in THF (5 mL) was added and the reaction was allowed to warm to room temperature. After 3 hours, 10%  $\text{NH}_4\text{Cl}$  (80 mL) was added. The product was extracted using diethyl ether (2 x 80 mL), washed with brine (80 mL) and dried over  $\text{MgSO}_4$ . The solvent was evaporated at reduced pressure to yield a pale yellow oil which was purified by flash chromatography using 98:2 hexane:EtOAc as the eluent. 2-*exo*-Ethyl-3,3-dimethylbicyclo[2.2.1]heptan-2-ol **88** was obtained as a clear oil (2.05g, 87%).  $R_f$  (10% EtOAc/hexane) 0.28

IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3512, 2957, 2875, 1459, 1372, 1190, 1027.

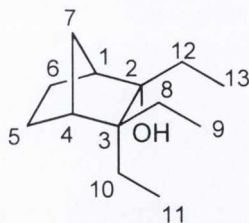
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 0.946 (s, 3H, H9), 0.948 (t,  $J = 7.53$  Hz, 3H, H11), 0.99 (s,  $\text{CH}_3$ , 3H, H8), 1.10-1.15 (m, 1H, H7a), 1.26-1.37 (m, 2H, H5a, H6a), 1.53-1.76 (m, 5H, H5b, H10, H7b, H4), 1.78-1.86 (m, 1H, H6b) 2.22 (br s, 1H, H1).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 8.4 ( $\text{CH}_3$ , C11), 20.8 ( $\text{CH}_2$ , C6), 21.4 ( $\text{CH}_3$ , C9), 23.5 ( $\text{CH}_2$ , C5), 25.9 ( $\text{CH}_3$ , C8), 28.9 ( $\text{CH}_2$ , C10), 34.0 ( $\text{CH}_2$ , C7), 42.5 (q, C3), 45.1 (CH, C1), 49.4 (CH, C4), 80.2 (q, C2).

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



#### 5.4.2.6 2-*exo*-,3,3-Triethylbicyclo[2.2.1]heptan-2-ol (**89**)



Prepared as per general procedure D using 3,3-diethylbicyclo[2.2.1]heptan-2-one **83** (2.50 g, 15.06 mmol), bromoethane (2.25 mL, 3.29 g, 30.14 mmol), *tert*-butyllithium solution (1.7 M in pentane, 35.44 mL, 60.24 mmol) to yield 2-*exo*-,3,3-triethylbicyclo[2.2.1]heptan-2-ol **89** as a clear oil (2.89 g, 97%).  $R_f$  (10% EtOAc/hexane) 0.38.

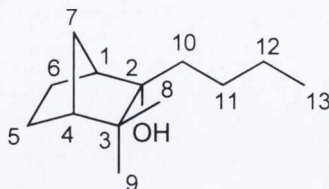
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3456, 2953, 2876, 1464, 1370, 1128.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 0.840 (t,  $J$  = 7.36 Hz, 3H, H11), 0.844 (t,  $J$  = 7.46 Hz, 3H, H9), 0.94 (t,  $J$  = 7.42 Hz, 3H, H13), 1.06-1.11 (m, 1H, H7a), 1.22-1.36 (m, 4H, H5a, H6a, H8a, H10a), 1.59-1.74 (m, 6H, H5b, H7b, H8b, H10b, H12), 1.75-1.83 (m, 1H, H6b), 1.98-2.02 (m, 1H, H4), 2.18-2.23 (m, 1H, H4).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 8.5 (CH<sub>3</sub>, C13), 9.5 (CH<sub>3</sub>, C9), 9.8 (CH<sub>3</sub>, C11), 20.1 (CH<sub>2</sub>, C6), 21.7 (CH<sub>2</sub>, C8), 22.7 (CH<sub>2</sub>, C5), 24.0 (CH<sub>2</sub>, C10), 29.1 (CH<sub>2</sub>, C12), 34.1 (CH<sub>2</sub>, C7), 45.0 (CH, C4), 45.4 (CH, C1), 47.8 (q, C3), 81.4 (q, C2).

HRMS: ( $m/z$  - CI) calcd. for C<sub>13</sub>H<sub>25</sub>O (M+H)<sup>+</sup> 197.1905, found 197.1901.

#### 5.4.2.7 2-*exo*-Butyl-3,3-dimethylbicyclo[2.2.1]heptan-2-ol (**90**)



Prepared as per general procedure C using 3,3-dimethylbicyclo[2.2.1]heptan-2-one **21** (2.00 g, 14.49 mmol), *n*-butyllithium (2.5 M in hexanes, 11.20 mL, 29.00 mmol) and THF (50 mL) to yield 2-*exo*-butyl-3,3-dimethylbicyclo[2.2.1]heptan-2-ol **90** as a clear oil. (1.85 g, 65%). *R<sub>f</sub>* (10% EtOAc/hexane) 0.35.

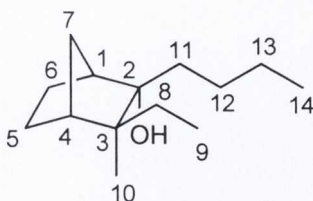
IR  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 3482, 2960, 2934, 2878, 1466, 1094, 984.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 0.91-0.96 (m, 6H, H<sub>9</sub>, H<sub>13</sub>), 0.99 (s, 3H, H<sub>8</sub>), 1.10-1.16 (m, 1H, H<sub>7a</sub>), 1.29-1.41 (m, 6H, H<sub>5a</sub>, H<sub>6a</sub>, H<sub>10a</sub>, H<sub>11a</sub>, H<sub>12</sub>), 1.47-1.56 (m, 2H, H<sub>10b</sub>, H<sub>11b</sub>), 1.65-1.72 (m, 2H, H<sub>5b</sub>, H<sub>7b</sub>), 1.72-1.75 (m, 1H, H<sub>4</sub>), 1.78-1.85 (m, 1H, H<sub>6b</sub>), 2.20-2.23 (m, 1H, H<sub>1</sub>).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 14.3 (CH<sub>3</sub>, C<sub>13</sub>), 21.4 (CH<sub>2</sub>, C<sub>6</sub>), 22.0 (CH<sub>3</sub>, C<sub>9</sub>), 23.6 (CH<sub>2</sub>, C<sub>12</sub>), 23.9 (CH<sub>2</sub>, C<sub>5</sub>), 26.4 (CH<sub>3</sub>, C<sub>8</sub>), 27.1 (CH<sub>2</sub>, C<sub>11</sub>), 34.5 (CH<sub>2</sub>, C<sub>7</sub>), 37.1 (CH<sub>2</sub>, C<sub>10</sub>), 43.0 (q, C<sub>3</sub>), 46.4 (CH, C<sub>1</sub>), 50.0 (CH, C<sub>4</sub>), 80.4 (q, C<sub>2</sub>).

HRMS: (*m/z* - Cl) calcd. for C<sub>13</sub>H<sub>25</sub>O (M) 197.1905, found 197.1898.

#### 5.4.2.8 2-*exo*-Butyl-3-*exo*-ethyl-3-methylbicyclo[2.2.1]heptan-2-ol (91)



Prepared as per general procedure C using 3-*exo*-ethyl,3-methylbicyclo[2.2.1]heptan-2-one **79** (200 mg, 1.266 mmol), *n*-butyllithium (2.5 M in hexanes, 1.01 mL, 2.53 mmol) and THF (6 mL) to yield 2-*exo*-butyl-3-*exo*-ethyl-3-methylbicyclo[2.2.1]heptan-2-ol **91** as a clear oil. (241 mg, 91%).  $R_f$  (10% EtOAc/hexane) 0.33.

IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3479, 2956, 2930, 2874, 1465, 1380, 1008.

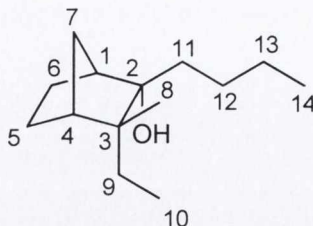
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 0.86 (t,  $J$  = 7.42 Hz, 3H, H9), 0.89 (s, 3H, H10), 0.94 (t,  $J$  = 7.16 Hz, 3H, H14), 1.07-1.11 (m, 1H, H7a), 1.28-1.41 (m, 7H, H5a, H6a, H8a, H12, H13), 1.42 (q,  $J$  = 7.42, 2H, H8), 1.50-1.68 (m, 4H, H5b, H7b, H11), 1.78-1.89 (m, 1H, H6b), 2.04-2.07 (m, 1H, H4), 2.21-2.24 (m, 1H, H1).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 10.3 (CH<sub>3</sub>, C9), 14.3 (CH<sub>3</sub>, C14), 17.5 (CH<sub>3</sub>, C10), 21.5 (CH<sub>2</sub>, C6), 23.6 (CH<sub>2</sub>, C13), 24.0 (CH<sub>2</sub>, C5), 27.1 (CH<sub>2</sub>, C12), 29.0 (CH<sub>2</sub>, C8), 34.3 (CH<sub>2</sub>, C7), 36.4 (CH<sub>2</sub>, C11), 44.1 (CH, C4), 45.9 (q, C3), 46.1 (CH, C1), 77.2 (q, C2).

HRMS: ( $m/z$  - Cl) calcd. for C<sub>14</sub>H<sub>27</sub>O (M+H)<sup>+</sup> 211.2062, found 211.2070.



#### 5.4.2.9 2-*exo*-Butyl-3-*endo*-ethyl-3-methylbicyclo[2.2.1]heptan-2-ol (**92**)



Prepared as per general procedure C using 3-*endo*-ethyl,3-methylbicyclo[2.2.1]heptan-2-one **80** (200 mg, 1.266 mmol), *n*-butyllithium (2.5 M in hexanes, 1.01 mL, 2.53 mmol) and THF (6 mL) to yield 2-*exo*-butyl-3-*endo*-ethyl-3-methylbicyclo[2.2.1]heptan-2-ol **92** as a clear oil. (198 mg, 75%).  $R_f$  (10% EtOAc/hexane) 0.30.

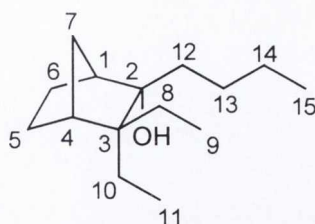
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3479, 2961, 2879, 1464, 1378, 1093, 982.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 0.87 (t,  $J$  = 7.41 Hz, 3H, H10), 0.93 (t,  $J$  = 7.10 Hz, 3H, H14), 0.94 (s, 3H, H8), 1.11-1.16 (m, 1H, H7a), 1.19-1.44 (m, 7H, H5a, H6a, H9a, H12, H13), 1.49-1.69 (m, 5H, H5b, H7b, H9b, H11), 1.77-1.85 (m, 2H, H4, H6b), 2.19-2.23 (m, 1H, H1).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 9.8 (CH<sub>3</sub>, C10), 14.3 (CH<sub>3</sub>, C14), 21.45 (CH<sub>3</sub>, C8), 21.48 (CH<sub>2</sub>, C6), 23.3 (CH<sub>2</sub>, C5), 23.6 (CH<sub>2</sub>, C13), 26.5 (CH<sub>2</sub>, C9), 27.1 (CH<sub>2</sub>, C12), 34.4 (CH<sub>2</sub>, C7), 37.7 (CH<sub>2</sub>, C11), 45.6 (q, C3), 46.7 (CH, C1), 47.6 (CH, C4), 80.9 (q, C2).

HRMS: ( $m/z$  - CI) calcd. for C<sub>14</sub>H<sub>27</sub>O (M+H)<sup>+</sup> 211.2062, found 211.2056.

#### 5.4.2.10 2-*exo*-Butyl-3,3-diethylbicyclo[2.2.1]heptan-2-ol (**93**)



Prepared as per general procedure C using 3,3-diethylbicyclo[2.2.1]heptan-2-one **83** (200 mg, 1.205 mmol), *n*-butyllithium (2.5 M in hexanes, 0.96 mL, 2.41 mmol) and THF (6 mL) to yield 2-*exo*-butyl-3,3-diethylbicyclo[2.2.1]heptan-2-ol **93** as a clear oil. (215 mg, 80%).  $R_f$  (10% EtOAc/hexane) 0.34.

IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3503, 2951, 2874, 1456, 1378, 1013.

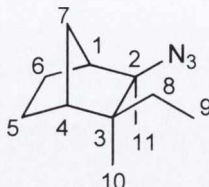
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 0.84 (t,  $J$  = 7.37 Hz, 3H, H11), 0.85 (t,  $J$  = 7.06 Hz, 3H, H9), 0.94 (t,  $J$  = 7.10 Hz, 3H, H15), 1.06-1.11 (m, 1H, H7a), 1.22-1.44 (m, 7H, H5a, H6a, H8a, H10a, H13, H14a), 1.55-1.84 (m, 8H, H5b, H6b, H7b, H8b, H10b, H12, H14b), 1.98-2.02 (m, 1H, H4), 2.18-2.23 (m, 1H, H1).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 9.9 (CH<sub>3</sub>, C9), 10.3 (CH<sub>3</sub>, C11), 14.3 (CH<sub>3</sub>, C15), 21.3 (CH<sub>2</sub>, C6), 22.1 (CH<sub>2</sub>, C8), 23.1 (CH<sub>2</sub>, C5), 23.6 (CH<sub>2</sub>, C13), 24.5 (CH<sub>2</sub>, C10), 27.0 (CH<sub>2</sub>, C14), 34.5 (CH<sub>2</sub>, C7), 37.3 (CH<sub>2</sub>, C12), 45.3 (q, C4), 46.7 (CH, C1), 48.2 (q, C3), 81.8 (q, C2).

HRMS: ( $m/z$  - CI) calcd. for C<sub>15</sub>H<sub>29</sub>O (M+H)<sup>+</sup> 225.2218, found 225.2223.

### 5.4.3 Azides

#### 5.4.3.1 2-Azido-3-*exo*-ethyl-2-*endo*-,3-dimethylbicyclo[2.2.1]heptanes (**94**)



Prepared as per general procedure E using 3-*exo*-ethyl-2-*exo*-,3-dimethylbicyclo[2.2.1]heptan-2-ol **84** (500 mg, 2.98 mmol), 50% H<sub>2</sub>SO<sub>4</sub> (10 mL), NaN<sub>3</sub> (2.40 g, 36.9 mmol) and CHCl<sub>3</sub> (50 mL) with a reaction time of 8 hours to yield 2-azido-3-*exo*-ethyl-2,3-dimethylbicyclo[2.2.1]heptanes **94** as a clear oil (304 mg, 53%) *R<sub>f</sub>* (100% hexane) 0.58 and a related azide tentatively assigned as 2-azido-2-*endo*-,3-dimethylbicyclo[2.2.1]heptane **95** as a clear oil. (140 mg, 28%) *R<sub>f</sub>* (100% hexane) 0.66.

2-azido-3-*exo*-ethyl-2-*endo*-,3-dimethylbicyclo[2.2.1]heptanes (**94**):

IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2917, 2849, 2087, 1463, 1378, 1131, 952.

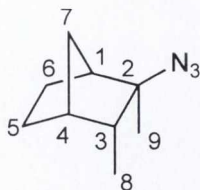
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 0.87 (s, 3H, H10), 0.88 (t, *J* = 7.38 Hz, 3H, H9), 1.11-1.14 (m, 1H, H7a), 1.28-1.35 (m, 4H, H5a, H11), 1.39-1.60 (m, 5H, H8, H6, H5b), 1.94-1.97 (m, 1H, H4), 1.98-2.02 (m, 1H, H7b), 2.15-2.18 (m, 1H, H1).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 10.1 (CH<sub>3</sub>, C9), 17.7 (CH<sub>3</sub>, C11), 19.3 (CH<sub>3</sub>, C10), 23.0 (CH<sub>2</sub>, C6) 24.2 (CH<sub>2</sub>, C5), 30.7 (CH<sub>2</sub>, C8), 34.9 (CH<sub>2</sub>, C7), 46.1 (CH, C4), 46.5 (q, C3), 48.7 (CH, C1), 73.7 (q, C2).

HRMS: (*m/z* - ES) calcd. for C<sub>11</sub>H<sub>20</sub>N (M+H-N<sub>2</sub>)<sup>+</sup> 166.1596, found 166.1596.



### 5.4.3.2 2-Azido-2-endo-,3-dimethylbicyclo[2.2.1]heptane (95)

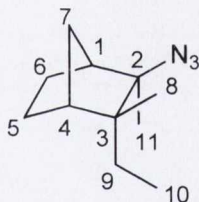


IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2965, 2879, 2082, 1458, 1261, 1111, 1079, 741.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 0.92 (d,  $J$  = 7.41 Hz, 3H, H8), 1.25 (s, 3H, H9), 1.26-1.48 (m, 5H, H7a, H5, H6), 1.77-1.83 (m, 1H H7b), 1.91-2.00 (m, 1H, H3), 2.11-2.17 (m, 2H, H4, H1).

<sup>13</sup>C NMR CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 12.13 (CH<sub>3</sub>, C8), 17.6 (CH<sub>3</sub>, C9), 20.1 (CH<sub>2</sub>, C5), 24.0 (CH<sub>2</sub>, C6), 37.2 (CH<sub>2</sub>, C7), 42.7 (CH, C4), 44.6 (CH, C3), 48.0 (CH, C1), 69.6 (q, C2).

### 5.4.3.3 2-Azido-3-endo-ethyl-2-endo-,3-dimethylbicyclo[2.2.1]heptane (106)



Prepared as per general procedure E using 2-*exo*-ethyl-3,3-dimethylbicyclo[2.2.1]heptan-2-ol **88** (2.00 g, 11.90 mmol), H<sub>2</sub>SO<sub>4</sub> (55%, 40 mL), NaN<sub>3</sub> (7.00 g, 107.7 mmol) and CHCl<sub>3</sub> (200 mL) with reaction time of 6 hours to yield 2-azido-3-*endo*-ethyl-2-*endo*-,3-dimethylbicyclo[2.2.1]heptanes **106** as a clear oil (390 mg, 17%), 2-azido-2-*endo*-ethyl-3,3-dimethylbicyclo[2.2.1]heptane **107** as a clear oil (140 mg, 6%) and 2-azido-3-*exo*-ethyl-2-*endo*-,3-dimethylbicyclo[2.2.1]heptane **94** as a clear oil (210 mg, 10%) after multiple column chromatography separations on silica gel using 100% hexane as eluent.  $R_f$  (100% hexane) 0.62.

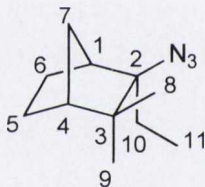
IR  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 2958, 2875, 2096, 1458, 1373, 1189, 1028.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 0.87 (t, 3H, H10), 1.04 (s, 3H, H8), 1.12-1.18 (m, 1H, H7a), 1.21-1.32 (m, 2H, H9a, H5a), 1.35 (s, CH<sub>3</sub>, H11), 1.41-1.52 (m, 4H, H6, H5b, H9b), 1.86-1.91 (m, 1H, H4), 1.96-2.02 (m, 1H, H7s), 2.11 (br s, 1H, H1).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 10.0 (CH<sub>3</sub>, C10), 16.9 (CH<sub>3</sub>, C11), 21.4 (CH<sub>3</sub>, C8), 23.25 (CH<sub>2</sub>, C6), 23.34 (CH<sub>2</sub>, C5), 27.8 (CH<sub>2</sub>, C9), 34.7 (CH<sub>2</sub>, C7), 46.6 (CH, C4), 47.6 (q, C3), 49.2 (CH, C1), 73.8 (q, C2).

HRMS: ( $m/z$  - ES) calcd. for  $\text{C}_{11}\text{H}_{20}\text{N}$  ( $\text{M}+\text{H}-\text{N}_2$ )<sup>+</sup> 166.1596, found 166.1590.

#### 5.4.3.4 2-Azido-2-*endo*-ethyl-3,3-dimethylbicyclo[2.2.1]heptanes (107)



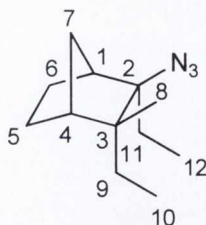
IR  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 2962, 2083, 1456, 1377, 1254, 1112, 1072.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 0.96 (s, 3H, H8), 0.98 (t,  $J = 7.38$  Hz, 3H, H11), 1.13 (s, 3H, H9), 1.16-1.21 (m, 1H, H7a), 1.30-1.83 (m, 7H, H5, H6, H10, H4), 1.93-2.00 (m, 1H, H7b), 2.21-2.25 (m, 1H, H1).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 9.6 (CH<sub>3</sub>, C11), 23.0 (CH<sub>3</sub>, C8), 22.6 (CH<sub>2</sub>, C6), 23.7 (CH<sub>2</sub>, C5), 23.9 (CH<sub>2</sub>, C10), 27.0 (CH<sub>3</sub>, C9), 34.6 (CH<sub>2</sub>, C7), 45.2 (CH, C1), 46.0 (q, C3), 49.8 (CH, C4), 76.2 (q, C2).

HRMS: ( $m/z$  - ES) calcd. for  $\text{C}_{11}\text{H}_{20}\text{N}$  ( $\text{M}+\text{H}-\text{N}_2$ )<sup>+</sup> 166.1596, found 166.1589.

#### 5.4.3.5 2-Azido-2-*endo*-,3-*endo*-diethyl-3-methylbicyclo[2.2.1]heptane (111)



Prepared as per general procedure E using 3,3-diethyl-2-*exo*-methylbicyclo[2.2.1]heptan-2-ol **86** (9.19 g, 50.49 mmol), NaN<sub>3</sub> (20.00 g, 307.69 mmol), CHCl<sub>3</sub> (200 mL), H<sub>2</sub>SO<sub>4</sub> (52.5%, 200 mL) with a reaction time of 8 hours to yield 2-azido-2-*endo*-,3-*endo*-diethyl-3-methylbicyclo[2.2.1]heptane **111** as a clear oil (0.91 g, 9%), 2-azido-3,3-diethyl-2-*endo*-methylbicyclo[2.2.1]heptane **112** as a clear oil (1.04 g, 10%), and 2-azido-2-*endo*-,3-*exo*-diethyl-3-methylbicyclo[2.2.1]heptane **113** as a clear oil (1.25 g, 12%) after multiple column chromatography separations on silica gel using 100% hexane as eluent. *R<sub>f</sub>* (100% hexane) 0.65.

2-Azido-2-*endo*-,3-*endo*-diethyl-3-methylbicyclo[2.2.1]heptane (111):

IR  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 2965, 2880, 2091, 1465, 1379, 1269, 1076, 901.

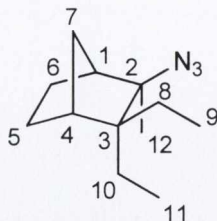
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 0.98 (t, *J* = 7.65 Hz, 3H, H12), 0.87 (t, *J* = 7.51 Hz, 3H, H10), 1.06 (s, 3H, H8), 1.14-1.19 (m, 1H, H7a), 1.20-1.59 (m, 6H, H9, H5, H6), 1.61-1.72 (m, 1H, H11a), 1.78-1.88 (m, 1H, H11b), 1.88-1.95 (m, 2H, H7b, H4), 2.19-2.24 (m, 1H, H1).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 9.5 (CH<sub>3</sub>, C12), 9.9 (CH<sub>3</sub>, C10), 21.5 (CH<sub>3</sub>, C8), 22.7 (CH<sub>2</sub>, C6), 23.0 (CH<sub>2</sub>, C11), 23.3 (CH<sub>2</sub>, C5), 27.3 (CH<sub>2</sub>, C9), 34.4 (CH<sub>2</sub>, C7), 45.2 (CH, C1), 46.5 (CH, C4), 49.7 (q, C3), 77.2 (q, C2).

HRMS: (*m/z* - ES) calcd. for C<sub>12</sub>H<sub>22</sub>N (M+H-N<sub>2</sub>)<sup>+</sup> 180.1752, found 180.1759.



#### 5.4.3.6 2-Azido-3,3-diethyl-2-endo-methylbicyclo[2.2.1]heptane (112)



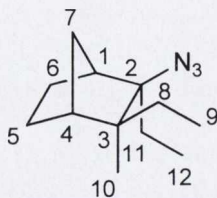
IR  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 2964, 2881, 2084, 1459, 1261, 1109, 1079, 742.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 0.79 (t,  $J = 7.50$  Hz, 3H, H11), 0.84 (t,  $J = 7.53$  Hz, 3H, H9), 1.10-1.15 (m, 1H, H7a), 1.20-1.56 (m, 10H, H12, H5, H6, H10, H8a), 1.67-1.79 (m, 1H, H8b), 1.87 (br s, 1H, H1), 1.98-2.03 (m, 1H, H7b), 2.17-2.21 (m, 1H, H4).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 9.4 ( $\text{CH}_3$ , C9), 9.9 ( $\text{CH}_3$ , C11), 17.9 ( $\text{CH}_3$ , C12), 22.5 ( $\text{CH}_2$ , C10), 23.0 ( $\text{CH}_2$ , C5), 24.0 ( $\text{CH}_2$ , C6), 26.4 ( $\text{CH}_3$ , C8), 34.5 ( $\text{CH}_2$ , C7), 46.8 (CH, C1), 48.7 (q, C3), 48.8 (CH, C4), 73.7 (q, C2).

HRMS: ( $m/z$  - EI) calcd. for  $\text{C}_{12}\text{H}_{21}\text{N}$  (M- $\text{N}_2$ ) 179.1674, found 179.1669.

#### 5.4.3.7 2-Azido-2-endo-,3-exo -diethyl-3-methylbicyclo[2.2.1]heptanes (113)



IR  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 2965, 2880, 2090, 1463, 1263, 1075, 931.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 0.88 (t,  $J = 7.60$  Hz, 3H, H9), 0.90 (s, 3H, H10), 0.99 (t,  $J = 7.50$  Hz, 3H, H12), 1.13-1.18 (m, 1H, 176

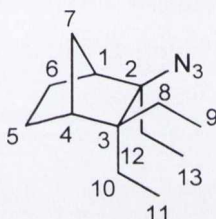
H7a), 1.27-1.68 (m, 7H, H6, H5, H8, H11a), 1.77-1.88 (m, 1H, H11b), 1.88-1.94 (m, 1H, H7b), 1.98-2.02 (m, 1H, H4), 2.26-2.30 (m, 1H, H1).

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

9.6 ( $\text{CH}_3$ , C12), 10.2 ( $\text{CH}_3$ , C9), 18.7 ( $\text{CH}_3$ , C10), 22.5 ( $\text{CH}_2$ , C6), 23.9 ( $\text{CH}_2$ , C5), 24.7 ( $\text{CH}_2$ , C11), 30.7 ( $\text{CH}_2$ , C8), 34.6 ( $\text{CH}_2$ , C7), 45.1 ( $\text{CH}$ , C1), 45.3 ( $\text{CH}$ , C4), 48.1 (q, C3), 77.1 (q, C2).

HRMS: ( $m/z$  - ES) calcd. for  $\text{C}_{12}\text{H}_{22}\text{N}_3$  ( $\text{M}+\text{H}$ ) $^+$  208.1814, found 208.1801.

#### 5.4.3.8 2-Azido-2-*endo*-,3,3-triethylbicyclo[2.2.1]heptanes (114)



Prepared as per general procedure E using 2-*exo*-,3,3-triethylbicyclo[2.2.1]heptan-2-ol **89** (500 mg, 2.55 mmol), 60%  $\text{H}_2\text{SO}_4$  (10 mL),  $\text{NaN}_3$  (2.50 g, 38.46 mmol) and  $\text{CHCl}_3$  (50 mL) with a reaction time of 5 hours to yield 2-azido-2-*endo*-,3,3-triethylbicyclo[2.2.1]heptane **114** (290 mg, 51%) after purification by flash chromatography on silica gel using 100% hexane as eluent.  $R_f$  (100% hexane) 0.65

IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 2964, 2881, 2091, 1464, 1270, 957, 881.

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

0.80 (t,  $J = 7.48$  Hz, 3H, H11), 0.84 (t,  $J = 7.48$  Hz, 3H, H9), 0.98 (t,  $J = 7.48$  Hz, 3H, H13), 1.16-1.21 (m, 1H, H7a), 1.25-1.65 (m, 8H, H5, H6, H8a, H10, H12a), 1.70-1.94 (m, 4H, H8b, H7b, H4, H12b), 2.36-2.41 (m, 1H, H1).

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

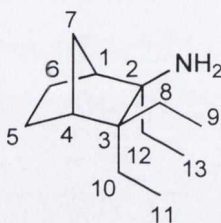
9.0 ( $\text{CH}_3$ , C11), 9.1 ( $\text{CH}_3$ , C13), 9.6 ( $\text{CH}_3$ , C9), 21.5 ( $\text{CH}_2$ , C10), 21.9 ( $\text{CH}_2$ , C6), 23.4 ( $\text{CH}_2$ , C5),

25.1 (CH<sub>2</sub>, C12), 26.3 (CH<sub>2</sub>, C8), 33.8 (CH<sub>2</sub>, C7),  
44.3 (CH, C1), 46.0 (CH, C4), 50.2 (q, C3), 76.7  
(q, C2).

HRMS: (*m/z* - ES) calcd. for C<sub>13</sub>H<sub>24</sub>N (M+H-N<sub>2</sub>)<sup>+</sup> 194.1909, found 194.1908.

## 5.4.4 Amines

### 5.4.4.1 2-*endo*-,3,3-Triethylbicyclo[2.2.1]heptan-2-amine (115)



Prepared as per general procedure H using 2-azido-2-*endo*-,3,3-triethylbicyclo[2.2.1]heptane **114** (450 mg, 2.03 mmol), 10% Pd/C (60 mg) and 10:1 methanol:isopropanol (35 mL) with a reaction time of 5 hour to 2-*endo*-,3,3-triethylbicyclo[2.2.1]heptan-2-amine **115** as a clear oil (279 mg, 70%).

IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3380, 2965, 2874, 1465, 1373, 1156, 742.

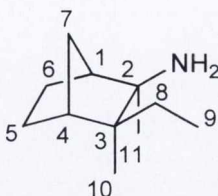
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 0.80 (t, *J* = 7.34 Hz, 3H, H9), 0.86 (t, *J* = 7.34 Hz, 3H, H11), 0.93 (t, *J* = 7.54 Hz, 3H, H13), 1.03-1.12 (m, 1H, H7a), 1.17-1.70 (m, 8H, H5, H6, H8, H10a, H12a), 1.72-1.91 (m, 4H, H1, H4, H10b, H12b), 1.91-2.007 (m, 1H, H7).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 9.2 (CH<sub>3</sub>, C13), 9.7 (CH<sub>3</sub>, C9), 11.1 (CH<sub>3</sub>, C11), 22.1 (CH<sub>2</sub>, C8), 22.7 (CH<sub>2</sub>, C5), 23.9 (CH<sub>2</sub>, C6), 25.7 (CH<sub>2</sub>, C10), 27.7 (CH<sub>2</sub>, C12), 33.9 (CH<sub>2</sub>, C7), 47.1 (CH, C1), 49.2 (q, C3), 49.3 (CH, C4), 63.5 (q, C2).



HRMS: ( $m/z$  - ES) calcd. for  $C_{13}H_{26}N$  ( $M+H$ )<sup>+</sup> 196.2065, found 196.2066.

5.4.4.2 3-*exo*-Ethyl-2-*endo*-,3-dimethylbicyclo[2.2.1]heptan-2-amine (116)



Prepared as per general procedure F using 2-Azido-3-*exo*-ethyl-2-*endo*-,3-dimethylbicyclo[2.2.1]heptane **94** (150 mg, 0.78 mmol), lithium aluminium hydride solution (2 M in THF, 500  $\mu$ L, 1 mmol) and anhydrous THF (5 mL) to yield 3-*exo*-ethyl-2-*endo*-,3-dimethylbicyclo[2.2.1]heptan-2-amine **116** as a clear oil (110 mg, 84%).

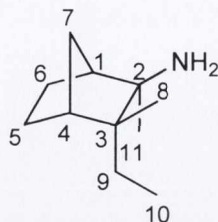
IR  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 2960, 2937, 2874, 1463, 1379, 805.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 0.83 (s, 3H, H10), 0.86 (t,  $J = 7.31$  Hz, 3H, H9), 1.02-1.10 (m, 4H, H11, H7a), 1.21-1.58 (m, 6H, H5, H6, H8), 1.73-1.79 (m, 1H, H1), 1.82-1.90 (m, 1H, H7b), 1.92 (br s, 1H, H4).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 10.6 ( $\text{CH}_3$ , C9), 19.3 ( $\text{CH}_3$ , C10), 23.6 ( $\text{CH}_3$ , C11), 23.7 ( $\text{CH}_2$ , C6), 23.9 ( $\text{CH}_2$ , C5), 29.7 ( $\text{CH}_3$ , C8), 34.4 ( $\text{CH}_2$ , C7), 45.2 (q, C3), 45.5 (CH, C4), 52.7 (CH, C1), 60.6 (q, C2).

HRMS: ( $m/z$  - ES) calcd. for  $C_{11}H_{22}N$  ( $M+H$ )<sup>+</sup> 168.1752, found 168.1751.

#### 5.4.4.3 3-*endo*-Ethyl-2-*endo*-,3-dimethylbicyclo[2.2.1]heptan-2-amine (117)



Prepared as per general procedure F using 2-azido-3-*endo*-ethyl-2-*endo*-,3-dimethylbicyclo[2.2.1]heptane **106** (100 mg, 0.52 mmol), lithium aluminium hydride solution (2 M in THF, 200  $\mu$ L, 0.40 mmol) and anhydrous THF (5 mL) to yield 3-*endo*-ethyl-2-*endo*-,3-dimethylbicyclo[2.2.1]heptan-2-amine **117** as a clear oil (71 mg, 82%).

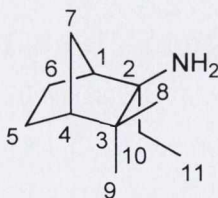
IR  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3378, 2962, 2930, 2878, 1461, 1378, 1158.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 0.84 (t,  $J = 7.25$  Hz, 3H, H10), 0.97 (s,  $J = 7.31$  Hz, 3H, H8), 1.12 (s, 3H, H11), 1.08-1.14 (m, 1H, H7a), 1.16-1.57 (m, 6H, H5, H6, H9), 1.81-1.86 (m, 2H, H1, H4), 1.89-1.96 (m, 1H, H7b).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 10.1 ( $\text{CH}_3$ , C10), 20.7 ( $\text{CH}_3$ , C8), 22.2 ( $\text{CH}_3$ , C11), 23.1 ( $\text{CH}_2$ , C5), 24.1 ( $\text{CH}_2$ , C6), 27.6 ( $\text{CH}_2$ , C9), 34.3 ( $\text{CH}_2$ , C7), 45.9 (q, C3), 47.0 (CH, C4), 52.3 (CH, C1), 60.9 (q, C2).

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

#### 5.4.4.4 2-*endo*-Ethyl-3,3-dimethylbicyclo[2.2.1]heptan-2-amine (118)



Prepared as per general procedure F using 2-azido-2-*endo*-ethyl-3,3-dimethylbicyclo[2.2.1]heptane **107** (100 mg, 0.52 mmol), lithium aluminium hydride solution (2 M in THF, 200  $\mu$ L, 0.40 mmol) and anhydrous THF (5 mL) to yield 2-azido-2-*endo*-ethyl-3,3-dimethylbicyclo[2.2.1]heptan-2-amine **118** as a clear oil (63 mg, 72%).

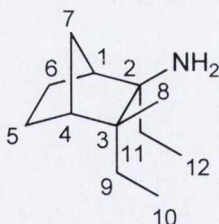
IR  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 2958, 2930, 2884, 1466, 1273, 1130, 954.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 0.88 (t,  $J = 7.57$  Hz, 3H, H11), 0.91 (s, 3H, H9), 0.99 (s, 3H, H8), 1.05-1.11 (m, 1H, H7a), 1.77-1.45 (m, 4H, H6, H5a, H10a), 1.54-1.62 (m, 1H, H5b), 1.62-1.74 (m, 2H, H4, H10b), 1.86-1.96 (m, 2H, H1, H7b).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 8.9 ( $\text{CH}_3$ , C11), 22.4 ( $\text{CH}_3$ , C9), 23.0 ( $\text{CH}_3$ , C6), 23.1 ( $\text{CH}_2$ , C5), 26.2 ( $\text{CH}_3$ , C8), 27.0 ( $\text{CH}_2$ , C10), 33.8 ( $\text{CH}_2$ , C7), 43.0 (q, C3), 48.5 (CH, C1), 50.1 (CH, C4), 61.5 (q, C2).

HRMS: ( $m/z$  - EI) calcd. for  $\text{C}_{11}\text{H}_{20}\text{N}$  ( $\text{M-H}^+$ ) 166.1596, found 166.1594.

#### 5.4.4.5 2-*endo*-,3-*endo*-Diethyl-3-methylbicyclo[2.2.1]heptan-2-amine (**119**)



Prepared as per general procedure F using 2-azido-2-*endo*-,3-*endo*-diethyl-3-methylbicyclo[2.2.1]heptane **111** (1.00 g, 4.83 mmol), lithium aluminium hydride solution (2 M in THF, 1.70 mL, 3.38 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 **119** as white solid (655 mg, 75%). M.p. 140-145  $^{\circ}\text{C}$  (decomposes).



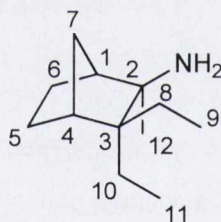
IR  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3361, 2960, 2844, 1457, 1379, 1150, 882.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 0.84 (t,  $J = 6.20$  Hz, 3H, H10), 1.14, (t,  $J = 6.30$  Hz, 3H, H12), 1.19-1.26 (m, 1H, H7a), 1.27, (s, 3H, H8), 1.28-1.64 (m, 6H, H5, H6, H9), 1.66-1.98 (m, 3H, H4, H11), 2.32-2.42 (m, 2H, H1, H7b).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 9.5 (CH<sub>3</sub>, C12), 9.8 (CH<sub>3</sub>, C10), 20.8 (CH<sub>3</sub>, C8), 22.6 (CH<sub>2</sub>, C6), 23.0 (CH<sub>2</sub>, C5), 24.0 (CH<sub>2</sub>, C11), 26.8 (CH<sub>2</sub>, C9), 34.0 (CH<sub>2</sub>, C7), 46.0 (CH, C1), 46.8 (CH, C4), 46.9 (q, C3), 69.8 (q, C2).

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

#### 5.4.4.6 3,3-Diethyl-2-*endo*-methylbicyclo[2.2.1]heptan-2-amine (120)



Prepared as per general procedure F using 2-azido 3,3-diethyl-2-*endo*-methylbicyclo[2.2.1]heptane **112** (85 mg, 0.41 mmol), lithium aluminium hydride solution (2 M in THF, 210  $\mu\text{L}$ , 0.41 mmol) and anhydrous THF (5 mL) to yield 3,3-diethyl-2-*endo*-methylbicyclo[2.2.1]heptan-2-amine **120** as a clear oil (70 mg, 94%).

IR  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 2936, 2746, 1480, 1428, 1327, 1112, 1072

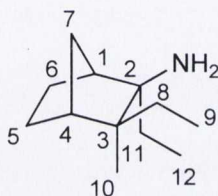
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 0.79 (t,  $J = 7.33$  Hz, 3H, H9), 0.87 (t,  $J = 7.34$  Hz, 3H, H11), 1.03-1.8 (m, 1H, H7a), 1.43 (s, 3H, H12), 1.19-1.57 (m, 7H, H6, H5, H8, H10a), 1.67-1.77 (m, 2H, H1, H10b), 1.80-1.85 (m, 1H, H4),

1.88-1.95 (m, 1H, H7b).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 9.4 ( $\text{CH}_3$ , C9), 10.6 ( $\text{CH}_3$ , C11), 23.3 ( $\text{CH}_3$ , C12), 22.5 ( $\text{CH}_2$ , C8), 22.9 ( $\text{CH}_2$ , C6), 23.3 ( $\text{CH}_2$ , C5), 25.1 ( $\text{CH}_2$ , C10), 33.7 ( $\text{CH}_2$ , C7), 46.5 ( $\text{CH}$ , C4), 47.9 (q, C3), 52.9 ( $\text{CH}$ , C1), 60.5 (q, C2).

HRMS: ( $m/z$  - ES) calcd. for  $\text{C}_{12}\text{H}_{24}\text{N}$  ( $\text{M}+\text{H}$ ) $^+$  182.1909, found 182.1907.

#### 5.4.4.7 2-endo-,3-exo-Diethyl-3-methylbicyclo[2.2.1]heptan-2-amine (121)



Prepared as per general procedure F using 2-azido-2-endo-,3-exo-diethyl,3-methylbicyclo[2.2.1]heptane **113** (400 mg, 1.93 mmol), lithium aluminium hydride solution (2 M in THF, 900  $\mu\text{L}$ , 1.80 mmol) and anhydrous THF (12 mL) to yield 2-endo-,3-exo-diethyl-3-methylbicyclo[2.2.1]heptan-2-amine **121** as a clear oil (310 mg, 89%).

IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 2960, 2930, 1465, 1377, 1054, 953, 760.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 0.878 (t,  $J = 7.36$  Hz, 3H,  $\text{H}_{12}$ ), 0.880 (s, 3H,  $\text{H}_{10}$ ), 0.92 (t,  $J = 7.25$  Hz, 3H,  $\text{H}_9$ ), 1.05-1.10 (m, 1H,  $\text{H}_{7a}$ ), 1.22-1.59 (m, 7H,  $\text{H}_6$ ,  $\text{H}_5$ ,  $\text{H}_8$ ,  $\text{H}_{11a}$ ), 1.71-1.82 (m, 1H,  $\text{H}_{11}$ ), 1.85-1.97 (m, 3H,  $\text{H}_1$ ,  $\text{H}_4$ ,  $\text{H}_{7b}$ )

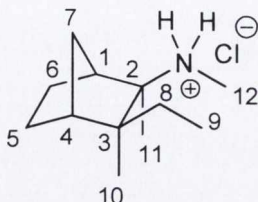
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 9.3 ( $\text{CH}_3$ , C9), 10.6 ( $\text{CH}_3$ , C12), 18.6 ( $\text{CH}_3$ , C10), 23.1 ( $\text{CH}_2$ , C6), 23.9 ( $\text{CH}_2$ , C5), 27.8 ( $\text{CH}_2$ , C11), 30.0 ( $\text{CH}_2$ , C8), 34.3 ( $\text{CH}_2$ , C7), 45.9 (q, C3), 46.0 ( $\text{CH}$ , C1), 49.2 ( $\text{CH}$ , C4), 62.8 (q, C2)

HRMS: ( $m/z$  - ES) calcd. for  $\text{C}_{12}\text{H}_{24}\text{N}$  ( $\text{M}+\text{H}$ ) $^+$  182.1909, found 182.1911.



## 5.4.5 N-Methyl amine MA analogues

### 5.4.5.1 3-*exo*-Ethyl-*N*,2-*endo*-,3-trimethylbicyclo[2.2.1]heptan-2-amine (71)



#### General Procedure I

Into an oven dried RBF under an argon atmosphere fitted with a reflux condenser, 3-*exo*-ethyl-2-*endo*-,3-dimethylbicyclo[2.2.1]heptan-2-amine **116** (120 mg, 0.62 mmol), paraformaldehyde (70 mg, 2.33 mmol) and activated molecular sieves (200 mg) were added. Anhydrous CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was then added and the reaction refluxed for 16 hours. After this time, an *in situ* <sup>1</sup>H nmr sample was taken to confirm quantitative conversion to the imine was complete. The reaction was cooled to -10 °C and sodium borohydride (110 mg, 2.91 mmol) was added. Anhydrous methanol (0.5 mL) was added dropwise and the reaction was allowed to warm to room temperature with continuous stirring over 1 hour and then stirred at room temperature for a further 2 hours. The reaction mixture was filtered to remove the molecular sieves and the unreacted paraformaldehyde. The residue was washed with CH<sub>2</sub>Cl<sub>2</sub> (30 mL) and the combined filtrate extracted with 2 M NaOH (30 mL). The organic solvent was dried over MgSO<sub>4</sub> and removed under vacuum to give the *N*-methylated amine as a tacky solid. This product was redissolved in anhydrous diethyl ether (2 mL) and a solution of hydrogen chloride (2 M in diethyl ether, 1.0 mL, 2.0 mmol) was added. Filtration afforded the HCl salt of 3-*exo*-ethyl-*N*,2-*endo*-,3-trimethylbicyclo[2.2.1]heptan-2-amine **71** as a white solid (80 mg, 59%). M.p. 150-160 °C (decomposes).

IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3359, 2953, 1457, 1370, 1150, 1112, 914, 892.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 0.94 (t, *J* = 6.95 Hz, 3H, H<sub>9</sub>), 0.98 (s, 3H, H<sub>10</sub>), 1.23-1.27 (m, 1H, H<sub>7a</sub>), 1.36 (s, 3H, H<sub>11</sub>), 1.37-1.60 (m, 4H, H<sub>5</sub>, H<sub>6</sub>), 1.78-1.90 (m, 1H, H<sub>8a</sub>), 2.03-2.14 (m, 1H, H<sub>8b</sub>), 2.20-2.23 (m, 1H, H<sub>4</sub>),

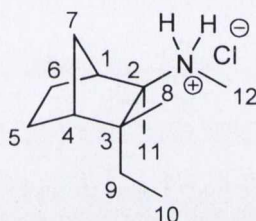


2.32-2.39 (m, 1H, H7b), 2.39-2.43 (m, 1H, H1),  
2.69 (br s, 3H, H12), 8.40 (br s, 1H, H13a), 9.04  
(br s, 1H, H13b).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 9.9 ( $\text{CH}_3$ , C<sub>9</sub>), 16.1 ( $\text{CH}_3$ , C11), 19.07 ( $\text{CH}_3$ , C10),  
23.11 ( $\text{CH}_2$ , C5), 23.5 ( $\text{CH}_3$ , C6), 28.0 ( $\text{CH}_2$ , C8),  
29.1 ( $\text{CH}_3$ , C12), 34.5 ( $\text{CH}_2$ , C7), 44.1 ( $\text{CH}$ , C4),  
44.8 ( $\text{CH}$ , C1), 47.6 (q, C3), 71.5 (q, C2)

HRMS: ( $m/z$  - ES) calcd. for  $\text{C}_{12}\text{H}_{24}\text{N}$  ( $\text{M}+\text{H}$ )<sup>+</sup> 182.1909, found 182.1901.

#### 5.4.5.2 3-endo-Ethyl-N,2-endo-,3-trimethylbicyclo[2.2.1]heptan-2-amine (72)



Prepared as per general procedure I using 3-endo-ethyl-2-endo-,3-dimethylbicyclo[2.2.1]heptan-2-amine **117** (110 mg, 0.67 mmol), paraformaldehyde (60 mg, 2.0 mmol) and activated molecular sieves (110 mg),  $\text{CH}_2\text{Cl}_2$  (10 mL) and sodium borohydride (101 mg, 2.67 mmol) to yield the desired amine as a viscous oil. This oil was dissolved in anhydrous diethyl ether (1.0 mL) and hydrogen chloride solution (2 M in diethyl ether, 800  $\mu\text{L}$ , 1.6 mmol) was added. The desired HCl salt of 3-endo-ethyl-N,2-endo-,3-trimethylbicyclo[2.2.1]heptan-2-amine **72** was obtained by filtration and dried under vacuum to yield a white solid (72 mg, 50%). M.p. 160-165 °C (decomposes).

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

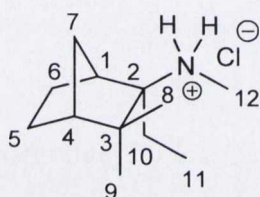
$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz):  $\delta$  (ppm) 0.93 (t,  $J$  = 7.48 Hz, 3H, H10), 1.15 (s, 3H, H8),  
185

1.31-1.46 (m, 6H, H11, H7a, H5a, H9a), 1.54-1.75 (m, 4H, H6, H5b, H9b), 1.94-2.00 (m, 1H, H7b), 2.00-2.05 (m, 1H, H4), 2.45 (br s, 1H, H1), 2.66 (s, 3H, H12).

$^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 100 MHz):  $\delta$  (ppm) 8.2 ( $\text{CH}_3$ ,  $\text{C}_{10}$ ), 14.0 ( $\text{CH}_3$ ,  $\text{C}_{11}$ ), 18.0 ( $\text{CH}_3$ ,  $\text{C}_8$ ), 21.5 ( $\text{CH}_2$ ,  $\text{C}_6$ ), 22.7 ( $\text{CH}_2$ ,  $\text{C}_5$ ), 26.5 ( $\text{CH}_2$ ,  $\text{C}_9$ ), 27.3 ( $\text{CH}_3$ ,  $\text{C}_{12}$ ), 32.8 ( $\text{CH}_2$ ,  $\text{C}_7$ ), 43.7 ( $\text{CH}$ ,  $\text{C}_1$ ), 46.88 ( $\text{CH}$ ,  $\text{C}_4$ ), 46.92 ( $\text{C}_3$ , q), 70.0 (q,  $\text{C}_2$ ).

HRMS: ( $m/z$  - ES) calcd. for  $\text{C}_{12}\text{H}_{24}\text{N}$  ( $\text{M}+\text{H}$ ) $^+$  182.1909, found 182.1916.

#### 5.4.5.3 2-*endo*-Ethyl-*N*,2,3-trimethylbicyclo[2.2.1]heptan-2-amine (73)



Prepared as per general procedure I using 2-*endo*-ethyl-3,3-dimethylbicyclo[2.2.1]heptan-2-amine **118** (60 mg, 0.36 mmol), paraformaldehyde (32.3 mg, 1.07 mmol), molecular sieves (100 mg),  $\text{CH}_2\text{Cl}_2$  (5 mL) and sodium borohydride (41 mg, 1.07 mmol) to yield the desired amine as a viscous oil. This oil was dissolved in anhydrous diethyl ether (0.5 mL) and hydrogen chloride solution (2 M in diethyl ether, 400  $\mu\text{L}$ , 0.8 mmol) was added. The desired HCl salt of 2-*endo*-ethyl-*N*,2,3-trimethylbicyclo[2.2.1]heptan-2-amine **73** was obtained by filtration and dried under vacuum to yield a white solid (34 mg, 44%). M.p. 150-155  $^\circ\text{C}$  (decomposes).

IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3360, 2950, 2761, 1596, 1513, 1381, 1370, 1092, 1000, 860.

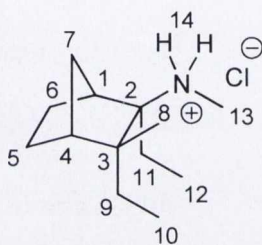
$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz):  $\delta$  (ppm) 1.00 (t,  $J$  = 6.81 Hz, 3H, H11), 1.15 (s, 3H, H8), 1.27 (s, 3H, H9), 1.30-1.74 (m, 5H, H5, H6, H7a), 1.75-2.01 (m, 3H, H10, H4), 2.06-2.14 (m, 1H, 186

H7b), 2.43 (br s, 1H, H1), 2.69 (s, 3H, H12).

$^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 100 MHz):  $\delta$  (ppm) 8.1 ( $\text{CH}_3$ , C11), 21.5 ( $\text{CH}_2$ , C10), 22.27 ( $\text{CH}_3$ , C8), 22.30 ( $\text{CH}_2$ , C5), 23.3 ( $\text{CH}_2$ , C6), 25.0 ( $\text{CH}_3$ , C9), 29.1 ( $\text{CH}_3$ , C12), 33.7 ( $\text{CH}_2$ , C7), 44.9 (q, C3), 45.7 ( $\text{CH}$ , C1), 51.9 ( $\text{CH}$ , C4), 73.2 (q, C2).

HRMS: ( $m/z$  - ES) calcd. for  $\text{C}_{12}\text{H}_{24}\text{N}$  ( $\text{M}+\text{H}$ ) $^+$  182.1909, found 182.1914.

#### 5.4.5.4 2-endo-,3-endo-Diethyl-N,3-dimethylbicyclo[2.2.1]heptan-2-amine (74)



Prepared as per general procedure I using 2-endo-,3-endo-diethyl-3-methylbicyclo[2.2.1]heptan-2-amine **119** (400 mg, 2.2 mmol), paraformaldehyde (198 mg, 6.6 mmol, molecular sieves (400 mg), anhydrous  $\text{CH}_2\text{Cl}_2$  (15 mL) and sodium borohydride (304 mg, 8.0 mmol) to yield the free amine as a viscous oil. This was purified by flash chromatography on silica gel using a 100% EtOAc to 95:5 EtOAc:methanol eluent gradient. The HCl salt was formed on addition of a solution of hydrogen chloride (2 M in diethyl ether, 2.2 mL, 4.4 mmol). The diethyl ether was removed under vacuum to yield the desired HCl salt of 2-endo-,3-endo-diethyl-N,3-dimethylbicyclo[2.2.1]heptan-2-amine **74** as a white solid (290 mg, 57%). M.p. 150-160  $^\circ\text{C}$  (decomposes).

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

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 0.93 (t,  $J$  = 7.51 Hz, 3H, H10), 1.01 (s, 3H, H8), 1.14 (t,  $J$  = 7.39 Hz, 3H, H12), 1.20-1.25 (m, 1H, 187



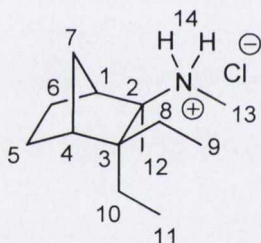
H7a), 1.31-1.53 (m, 4H, H5, H6), 1.54-1.65 (m, 1H, H9a), 1.65-1.89 (m, 2H, H11), 2.17-2.21 (m, 1H, H4), 2.21-2.32 (m, 1H, H9b), 2.52-2.60 (m, 2H, H1, H7b), 2.67 (app t, 3H, H13), 8.51-8.97 (m, 2H, H14).

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

9.4 ( $\text{CH}_3$ ,  $\text{C}_{12}$ ), 10.1 ( $\text{CH}_3$ ,  $\text{C}_{10}$ ), 19.2 ( $\text{CH}_3$ ,  $\text{C}_8$ ), 22.3 ( $\text{CH}_3$ ,  $\text{C}_{11}$ ), 22.7 ( $\text{CH}_2$ ,  $\text{C}_5$ ), 23.6 ( $\text{CH}_2$ ,  $\text{C}_6$ ), 28.7 ( $\text{CH}_2$ ,  $\text{C}_9$ ), 29.6 ( $\text{CH}_3$ ,  $\text{C}_{13}$ ), 34.5 ( $\text{CH}_2$ ,  $\text{C}_7$ ), 44.7 ( $\text{CH}$ ,  $\text{C}_4$ ), 45.5 ( $\text{CH}$ ,  $\text{C}_1$ ), 48.1 (q,  $\text{C}_3$ ), 74.5 (q,  $\text{C}_2$ ).

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

#### 5.4.5.5 3,3-Diethyl-*N*,2-*endo*-dimethylbicyclo[2.2.1]heptan-2-amine (75)



Prepared as per general procedure I was followed using 3,3-diethyl-2-*endo*-methylbicyclo[2.2.1]heptan-2-amine **120** (410 mg, 2.23 mmol), paraformaldehyde (356 mg, 11.86 mmol), molecular sieves (400 mg), anhydrous  $\text{CH}_2\text{Cl}_2$  (15 mL) and sodium borohydride (350 mg, 10.52 mmol) to yield the free amine as a low melting solid. This was purified by flash chromatography on silica gel using a 100% EtOAc to 95:5 EtOAc:methanol eluent gradient. The HCl salt was formed on addition of a solution of hydrogen chloride (2 M in diethyl ether, 2.25 mL, 4.4 mmol). The diethyl ether was removed under vacuum to yield the desired HCl salt of 3,3-diethyl-*N*,2-*endo*-dimethylbicyclo[2.2.1]heptan-2-amine **75** as a white solid (310 mg, 58%). M.p. 165-175  $^\circ\text{C}$  (decomposes).

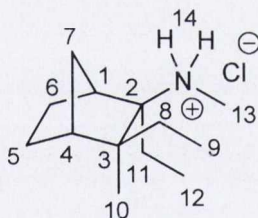
IR  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3359, 2953, 2844, 2744, 1458, 1369, 1150.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 0.92-1.00 (m, 6H, H<sub>9</sub>, H<sub>11</sub>), 1.19-1.26 (m, 1H, H<sub>7a</sub>), 1.27-1.65 (m, 9H, H<sub>5</sub>, H<sub>6</sub>, H<sub>10</sub>, H<sub>12</sub>), 1.91-2.05 (m, 2H, H<sub>8</sub>), 2.18-2.22 (m, 1H, H<sub>4</sub>), 2.34-2.41 (m, 2H, H<sub>1</sub>, H<sub>7b</sub>), 2.69 (br s, 3H, H<sub>13</sub>), 8.43 (br s, 1H, H<sub>14a</sub>), 8.98 (br s, 1H, H<sub>14b</sub>).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 9.41 ( $\text{CH}_3$ , C<sub>9</sub>), 9.44 ( $\text{CH}_3$ , C<sub>11</sub>), 16.2 ( $\text{CH}_3$ , C<sub>12</sub>), 21.6 ( $\text{CH}_2$ , C<sub>5</sub>), 22.8 ( $\text{CH}_2$ , C<sub>6</sub>), 23.1 ( $\text{CH}_2$ , C<sub>8</sub>), 23.6 ( $\text{CH}_2$ , C<sub>10</sub>), 28.7 ( $\text{CH}_3$ , C<sub>13</sub>), 34.3 ( $\text{CH}_2$ , C<sub>7</sub>), 45.3 ( $\text{CH}$ , C<sub>4</sub>), 45.6 ( $\text{CH}$ , C<sub>1</sub>), 49.9 (q, C<sub>3</sub>), 71.0 (q, C<sub>2</sub>)

HRMS: ( $m/z$  - ES) calcd. for  $\text{C}_{13}\text{H}_{26}\text{N}$  ( $\text{M}+\text{H}$ )<sup>+</sup> 196.2065, found 196.2062.

#### 5.4.5.6 2-*endo*-,3-*exo*-Diethyl-*N*,3-dimethylbicyclo[2.2.1]heptan-2-amine (76)



Prepared as per general procedure I using 2-*endo*-,3-*exo*-diethyl-3-methylbicyclo[2.2.1]heptan-2-amine **121** (400 mg, 2.2 mmol), paraformaldehyde (198 mg, 6.6 mmol, molecular sieves (400 mg), anhydrous  $\text{CH}_2\text{Cl}_2$  (15 mL) and sodium borohydride (304 mg, 8.0 mmol) to yield the free amine as a low melting solid. This was purified by flash chromatography on silica gel using a 100% EtOAc to 95:5 EtOAc:methanol eluent gradient. The HCl salt was formed on addition of a solution of hydrogen chloride (2 M in diethyl ether, 2.2 mL, 4.4 mmol). The diethyl ether was removed under vacuum to yield the desired HCl salt of 2-*endo*-,3-*exo*-diethyl-*N*,3-dimethylbicyclo[2.2.1]heptan-2-amine **76** as a white solid (310 mg, 61%). M.p. 140-150 °C. (decomposes).

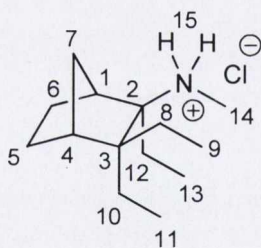
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3360, 2954, 1597, 1458, 1381, 1113, 916, 886.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ (ppm) 0.89 (t, J = 7.22 Hz, 3H, H<sub>9</sub>), 1.15 (t, 3H, H<sub>12</sub>), 1.26-1.57 (m, 9H, H<sub>10</sub>, H<sub>5</sub>, H<sub>6</sub>, H<sub>8a</sub>, H<sub>7a</sub>), 1.59-1.85 (m, 3H, H<sub>11</sub>, H<sub>8b</sub>), 1.95-2.00 (m, 1H, H<sub>4</sub>), 2.52-2.61 (m, 1H, H<sub>7b</sub>), 2.61-2.76 (m, 4H, H<sub>13</sub>, H<sub>1</sub>), 8.51-8.77 (br s, 1H, H<sub>14a</sub>), 8.87-9.10 (br s, 1H, H<sub>14b</sub>).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ (ppm) 8.9 (CH<sub>3</sub>, C12), 9.3 (CH<sub>3</sub>, C9), 20.9 (CH<sub>2</sub>, C11), 21.3 (CH<sub>3</sub>, C10), 21.8 (CH<sub>2</sub>, C6), 23.3 (CH<sub>2</sub>, C5), 27.0 (CH<sub>2</sub>, C8), 29.1 (CH<sub>3</sub>, C13), 33.8 (CH<sub>2</sub>, C7), 45.3 (CH, C1), 47.5 (CH, C4), 47.9 (q, C3), 73.8 (q, C2).

(*m/z* - ES) calcd. for C<sub>13</sub>H<sub>26</sub>N (M+H)<sup>+</sup> 196.2065, found 196.2069

#### 5.4.5.7 2-endo-3,3-Triethyl-N-methylbicyclo[2.2.1]heptan-2-amine (77)



Prepared as per general procedure I using 2-*endo*-3,3-triethylbicyclo[2.2.1]heptan-2-amine **115** (120 mg, 0.61 mmol), paraformaldehyde (110 mg, 3.66 mmol, molecular sieves (100 mg), anhydrous CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and sodium borohydride (152 mg, 4.00 mmol) to yield the free amine as a low melting solid. The HCl salt was formed on addition of a solution of hydrogen chloride (2 M in diethyl ether, 0.75 mL, 1.5 mmol). 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 **77** as a white solid (82 mg, 55%). M.p. 140-150 °C. (decomposes).

IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3360, 2952, 2886, 1457, 1343, 1150, 1112, 915.

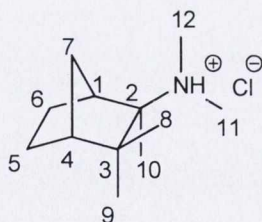
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 0.90 (t, *J* = 7.48 Hz, 3H, H13), 0.96 (t, *J* = 7.05 Hz, 3H, H11), 1.15 (t, *J* = 7.26 Hz, 3H, H9), 1.19-1.26 (m, 1H, H7a), 1.26-1.96 (m, 9H, H5, H6, H8, H10a, H12), 2.12-2.24 (m, 2H, H4, H10b), 2.48-2.56 (m, 1H, H7b), 2.65-2.77 (m, 4H, H1, H14), 8.39 (br s, 1H, H15a), 9.01 (br s, 1H, H15b).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 9.6 (CH<sub>3</sub>, C9), 10.0 (CH<sub>3</sub>, C11), 10.1 (CH<sub>3</sub>, C13), 21.4 (CH<sub>2</sub>, C8), 21.7 (CH<sub>2</sub>, C5), 23.1 (CH<sub>2</sub>, C12), 23.9 (CH<sub>2</sub>, C6), 24.0 (CH<sub>2</sub>, C10), 30.6 (CH<sub>3</sub>, C14), 34.6 (CH<sub>2</sub>, C7), 46.18 (CH, C4), 46.24 (CH, C1), 51.3 (q, C3), 75.6 (q, C2).

HRMS: (*m/z* - ES) calcd. for C<sub>14</sub>H<sub>28</sub>N (M+H)<sup>+</sup> 210.2222, found 210.2204.

#### 5.4.6 *N*-Functionalised MA analogues

##### 5.4.6.1 *N,N*,2-*endo*-,3,3-Pentamethylbicyclo[2.2.1]heptan-2-amine (**66**)



2-*endo*-,3,3-trimethyl-bicyclo[2.2.1]hept-2-amine **24** (0.081 g, 0.53 mmol) was dissolved in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a RBF under an argon atmosphere. Iodomethane (66  $\mu$ L, 1.06

mmol) was added and the reaction was stirred for 30 minutes. Potassium *t*-butoxide (0.149 g, 1.33 mmol) was then added and the reaction stirred at room temperature. After 24 hours H<sub>2</sub>O (10 mL) was added and the product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 20mL). The organic extracts were combined and dried over MgSO<sub>4</sub>. A hydrogen chloride solution (2 M in diethyl ether, 0.5 mL, 1.0 mmol) was added. The solvent was removed under reduced pressure to yield a 9:1 mixture of the hydrochloride salts of amines **66** and **17** which was purified by recrystallisation from EtOAc to yield the desired amine, *N,N*,2,3,3-pentamethylbicyclo[2.2.1]hept-2-amine **66** as a white solid (0.041 g, 35.6 %). M.p. 150-160 °C (decomposes).

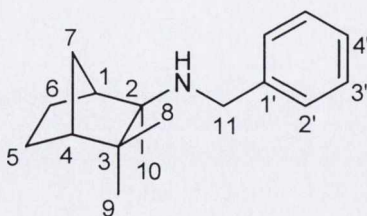
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3360, 2951, 1457, 1381, 1370, 1342, 1112, 914.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 1.05 (s, 3H, H9), 1.25-1.30 (m, 4H, H8, H7a), 1.33-1.41 (m, 1H, H5a), 1.49-1.57 (m, 3H, H6, H5b), 1.60 (s, 3H, H10), 1.89-1.93 (m, 1H, H4), 2.44-2.49 (m, 1H, H1), 2.53-2.59 (m, 1H, H7b), 2.77 (s, 3H, H11), 2.82 (s, 3H, H12).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 13.1 (CH<sub>3</sub>, C8), 22.2 (CH<sub>2</sub>, C6), 24.1 (CH<sub>3</sub>, C9), 25.1 (CH<sub>2</sub>, C6), 25.1 (CH<sub>3</sub>, C8), 28.0 (CH<sub>3</sub>, C10), 34.5 (CH<sub>2</sub>, C7), 40.7 (CH<sub>3</sub>, C12), 42.9 (CH<sub>3</sub>, C11), 45.7 (CH, C4), 46.2 (q, C3), 52.5 (CH, C1), 77.8 (q, C2).

HRMS (*m/z* –ES): Found: 182.1916 (M<sup>+</sup> + H. C<sub>12</sub>H<sub>24</sub>N Requires 182.1909)

#### 5.4.6.2 *N*-Benzyl-2-*endo*-,3,3-trimethylbicyclo[2.2.1]heptan-2-amine (**108**)



Prepared as per general procedure I using 2-*endo*-,3,3-trimethyl-bicyclo[2.2.1]hept-2-amine **24** (120 mg, 0.78 mmol), benzaldehyde (158  $\mu$ L, 166 mg, 1.56 mmol, molecular sieves (120 mg), anhydrous  $\text{CH}_2\text{Cl}_2$  (5 mL) and sodium borohydride (89 mg, 2.34 mmol) to yield *N*-benzyl-2-*endo*-,3,3-trimethylbicyclo[2.2.1]heptan-2-amine **108** as a viscous oil. (151 mg, 62%)  $R_f$  (15% EtOAc/Hexane) 0.25.

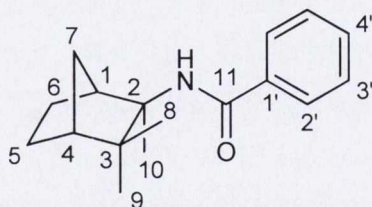
IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 2956, 2930, 2871, 1471, 1452, 1371, 1134.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 0.99 (s, 3H, H9), 1.05-1.09 (m, 1H, H7a), 1.09 (s, 3H, H8), 1.21 (s, 3H, H10), 1.26-1.35 (m, 1H, H5a), 1.28-1.35 (m, 2H, H6), 1.61-1.68 (m, 1H, H5b), 1.72 (br s, 1H, H4), 2.04-2.10 (m, 1H, H7b), 2.27 (br s, 1H, H1), 3.70-3.81 (m, 2H, H11), 7.23-7.28 (m, 1H, H4'), 7.31-7.36 (t,  $J = 7.44$  Hz, 2H, H3'), 7.39-7.44 (m, 2H, H2')

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 18.7 ( $\text{CH}_3$ , C10), 23.6 ( $\text{CH}_2$ , C5), 23.7 ( $\text{CH}_3$ , C9), 24.0 ( $\text{CH}_2$ , C6), 26.0 ( $\text{CH}_3$ , C8), 34.4 ( $\text{CH}_2$ , C7), 43.8 (q, C3), 46.5 (CH, C1), 48.0 ( $\text{CH}_2$ , C11), 50.7 (CH, C4), 63.3 (q, C2), 126.7 (CH, C4'), 128.1 (CH, C2'), 128.4 (CH, C3'), 141.6 (q, C1').

HRMS: ( $m/z$  - ES) calcd. for  $\text{C}_{17}\text{H}_{26}\text{N}$  ( $\text{M}+\text{H}$ ) $^+$  244.2065, found 244.2074.

#### 5.4.6.3 *N*-(2-*endo*-,3,3-Trimethylbicyclo[2.2.1]heptan-2-yl)benzamide (109)



To a solution of the hydrochloride salt of amine **24** (100 mg, 0.53 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (5 mL) under an argon atmosphere, pyridine (94  $\mu$ L, 92 mg, 1.17 mmol) was added. After stirring for 10 minutes at room temperature, benzoyl chloride (74  $\mu$ L, 90 mg, 0.64 mmol) was added. The



reaction was stirred for a further 16 hours. The solvent was evaporated at reduced pressure to yield a brown oil that was purified by flash chromatography on silica gel using 95:5 hexane:EtOAc as eluent to yield *N*-(2-*endo*-,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)benzamide **109** as a white solid (95 mg, 70%). M.p. 116-117 °C. *R<sub>f</sub>* (20% EtOAc/Hexane) 0.50

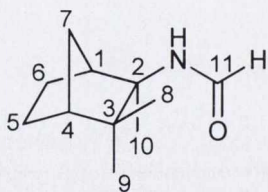
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3264, 2936, 1630, 1541, 1466, 1321, 1081, 798.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 1.10 (s, 3H, H9), 1.18-1.24 (m, 4H, H8, H7a), 1.28-1.51 (m, 2H, H5), 1.58 (s, 3H, H10), 1.61-1.73 (m, 1H, H6), 1.80-1.84 (m, 1H, H4), 1.91-1.98 (m, 1H, H7b), 2.43-2.47 (m, 1H, H1), 6.11 (br s, 1H, NH), 7.41-7.52 (m, 3H, H3', H4'), 7.71-7.75 (m, 2H, H2')

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 17.9 (CH<sub>3</sub>, C10), 23.01 (CH<sub>2</sub>, C5), 23.02 (CH<sub>3</sub>, C9), 23.3 (CH<sub>2</sub>, C6), 26.4 (CH<sub>3</sub>, C8), 34.7 (CH<sub>2</sub>, C7), 45.2 (q, C3), 49.8 (CH, C1), 50.6 (CH, C4), 64.7 (q, C2), 126.6 (CH, C2'), 128.6 (CH, C3'), 131.0 (CH, C4'), 136.7 (q, C1'), 167.3 (q, C11).

HRMS: (*m/z* - ES) calcd. for C<sub>17</sub>H<sub>24</sub>NO (M+H)<sup>+</sup> 258.1858, found 258.1848.

#### 5.4.6.4 *N*-(2-*endo*-,3,3-Trimethylbicyclo[2.2.1]heptan-2-yl)formamide (**110**)



To 2-*endo*-,3,3-trimethyl-bicyclo[2.2.1]hept-2-amine **24** (50 mg, 0.33 mmol), ethyl formate (2 mL, 1.84 g, 24.9 mmol) was added neat. A reflux condenser was fitted and the reaction mixture was heated to 50 °C. After stirring for 1 hour, the reaction mixture was allowed to cool to room

temperature before removing the volatiles at reduced pressure to yield a pale yellow solid. This solid was further purified by recrystallization from hexane/EtOAc 1:1 to yield *N*-(2-*endo*-,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)formamide **110** as a white solid. (35 mg, 59%). M.p. 200-210 °C (sublimes).  $R_f$  (50% EtOAc/Hexane) 0.33.

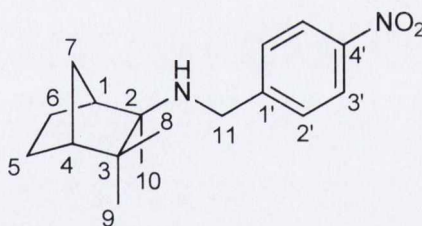
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2940, 2881, 2755, 2668, 1580, 1433, 1327, 752.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 0.96 (s, 3H, H9), 1.14-1.24 (m, 4H, H8, H7a), 1.27-1.62 (m, 7H, H5, H6, H10), 1.80-1.84 (m, 1H, H4), 2.19-2.25 (m, 1H, H7b), 2.25- 2.30 (m, 1H, H1), 8.65 (s, 1H, H11).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 18.5 (CH<sub>3</sub>, C10), 22.4 (CH<sub>3</sub>, C9), 22.5 (CH<sub>2</sub>, C5), 22.8 (CH<sub>2</sub>, C6), 24.8 (CH<sub>3</sub>, C8), 33.7 (CH<sub>2</sub>, C7), 42.3 (q, C3), 47.9 (CH, C1), 49.6 (CH, C4), 64.1 (q, C2), 167.9 (CH, C11).

HRMS: ( $m/z$  - CI) calcd. for C<sub>11</sub>H<sub>20</sub>NO (M+H)<sup>+</sup> 182.1545, found 182.1552.

#### 5.4.6.5 *N*-(4-Nitrobenzyl)-2-*endo*-,3,3-trimethylbicyclo[2.2.1]heptan-2-amine (**129**)



Prepared as per general procedure I using 2-*endo*-,3,3-trimethyl-bicyclo[2.2.1]hept-2-amine **24** (121 mg, 0.79 mmol), 4-nitrobenzaldehyde (360 mg, 2.38 mmol), molecular sieves (150 mg), anhydrous CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and sodium borohydride (89 mg, 2.34 mmol) to yield *N*-(4-nitrobenzyl)-2-*endo*-,3,3-trimethylbicyclo[2.2.1]heptan-2-amine **129** as yellow solid. (176 mg, 77%). M.p. 92-93 °C.  $R_f$  (50% EtOAc/Hexane) 0.43.

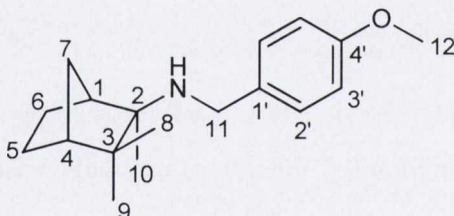
IR  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3360, 3010, 2959, 1512, 1340, 1091, 841, 736.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 0.98 (s, 3H, H9), 1.04-1.12 (m, 4H, H8, H7a), 1.16 (s, 3H, H10), 1.25-1.53 (m, 3H, H5a, H6), 1.58-1.69 (m, 1H, H5b), 1.74 (br s, 1H, H4), 2.04-2.13 (m, 1H, H7b), 2.18 (br s, 1H, H1), 3.75-3.90 (m, 2H, H11), 7.50-7.64 (m, 2H, H2'), 8.18 (d,  $J = 8.60$  Hz, 2H, H3')

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 18.6 ( $\text{CH}_3$ , C10), 23.2 ( $\text{CH}_2$ , C5), 23.3 ( $\text{CH}_3$ , C9), 23.5 ( $\text{CH}_2$ , C6), 25.5 ( $\text{CH}_3$ , C8), 34.0 ( $\text{CH}_2$ , C7), 43.5 (q, C3), 46.1 (CH, C1), 46.9 ( $\text{CH}_2$ , C11), 50.2 (CH, C4), 62.8 (q, C2), 123.0 (CH, C3'), 128.1 (CH, C2'), 146.4 (CH, C1'), 149.8 (q, C4').

HRMS: ( $m/z$  - ES) calcd. for  $\text{C}_{17}\text{H}_{25}\text{N}_2\text{O}_2$  ( $\text{M}+\text{H}$ ) $^+$  289.1916, found 289.1906.

#### 5.4.6.6 *N*-(4-Methoxybenzyl)-2-*endo*-,3,3-trimethylbicyclo[2.2.1]heptan-2-amine (130)



Prepared as per general procedure I using 2-*endo*-,3,3-trimethyl-bicyclo[2.2.1]hept-2-amine **24** (200 mg, 1.31 mmol), 4-methoxybenzaldehyde (0.477 mL, 534 mg, 3.92 mmol), molecular sieves (250 mg), anhydrous  $\text{CH}_2\text{Cl}_2$  (10 mL) and sodium borohydride (199 mg, 5.23 mmol) to yield a brown oil which was further purified by flash chromatography on silica gel using 8:2 hexane:EtOAc as the eluent to yield *N*-(4-methoxybenzyl)-2-*endo*-,3,3-trimethylbicyclo[2.2.1]heptan-2-amine **130** as a viscous yellow oil. (247 mg, 69%)  $R_f$  (50% EtOAc/Hexane) 0.40.



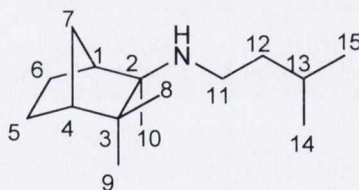
IR  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 2954, 2927, 1607, 1510, 1464, 1244, 1036.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 0.97 (s, 3H, H9), 1.03-1.09 (m, 4H, H7a, H8), 1.18 (s, 3H, H10), 1.26-1.69 (m, 4H, H5, H6), 1.69-1.73 (m, 1H, H4), 2.02-2.11 (H7), 2.23-2.28 (m, 1H, H1), 3.64 (d,  $J = 12.80$  Hz, 1H, H11a), 3.69 (d,  $J = 12.80$  Hz, 1H, H11b), 3.82 (s, 3H, H12), 6.88 (d,  $J = 8.39$  Hz, 2H, H3'), 7.32 (d,  $J = 8.39$  Hz, 2H, H2').

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 18.4 ( $\text{CH}_3$ , C10), 23.3 ( $\text{CH}_2$ , C5), 23.3 ( $\text{CH}_3$ , C9), 23.6 ( $\text{CH}_2$ , C6), 25.6 ( $\text{CH}_3$ , C8), 34.0 ( $\text{CH}_2$ , C7), 43.5 (q, C3), 45.9 (CH, C1), 46.9 ( $\text{CH}_2$ , C11), 50.2 (CH, C4), 54.8 ( $\text{CH}_3$ , C12), 62.5 (q, C2), 113.3 (ArH, C3'), 128.7 (ArH, C2'), 133.9 (q, C1'), 158.1 (q, C4').

HRMS: ( $m/z$  - ES) calcd. for  $\text{C}_{18}\text{H}_{28}\text{NO}$  ( $\text{M}+\text{H}$ ) $^+$  274.2171, found 274.2178.

#### 5.4.6.7 *N*-Isopentyl-2-*endo*-,3,3-trimethylbicyclo[2.2.1]heptan-2-amine (128)



Prepared as per general procedure I using 2-*endo*-,3,3-trimethyl-bicyclo[2.2.1]hept-2-amine **24** (100 mg, 0.65 mmol), anhydrous  $\text{CH}_2\text{Cl}_2$  (6mL), molecular sieves (100 mg), isovaleraldehyde (0.14 mL, 1.3 mmol) and sodium borohydride (0.074 g, 1.96 mmol) to yield *N*-Isopentyl-2-*endo*-,3,3-trimethylbicyclo[2.2.1]heptan-2-amine **128** as a pale yellow oil. (59 mg, 41.3 %)

IR  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 2953, 2870, 1466, 1386, 1168, 1135, 1148, 1003, 899, 876, 969, 744

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 0.88 (d,  $J=6.5\text{Hz}$ , 3H, H14), 0.89 (d,  $J = 6.5$  Hz,

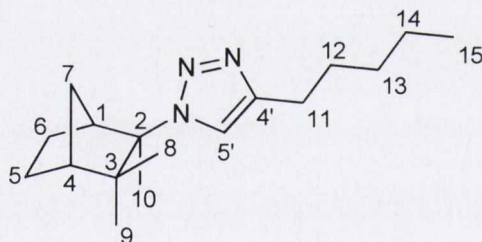
3H, H15), 0.91 (s, 3H, H9), 0.97-1.01 (m, 4H, H8, H7a), 1.04 (s, 3H, H10), 1.21-1.28 (m, 1H, H5a), 1.28-1.47 (m, 4H, H6, H12), 1.53-1.66 (m, 3H, H13, H5b, H1), 1.65-1.70 (m, 1H, H1), 1.82-1.89 (m, 1H, H7b), 2.12-2.16 (m, 1H, H4), 2.42-2.56 (m, 2H, H11).

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

18.8 ( $\text{CH}_3$ , C10), 22.6 ( $\text{CH}_3$ , C14), 23.1 ( $\text{CH}_3$ , C15), 23.4 ( $\text{CH}_2$ , C5), 23.6 ( $\text{CH}_3$ , C9), 24.3 ( $\text{CH}_2$ , C6), 25.8 ( $\text{CH}_3$ , C8), 26.5 ( $\text{CH}$ , C13), 34.4 ( $\text{CH}_2$ , C7), 40.3 ( $\text{CH}_2$ , C12), 41.9 ( $\text{CH}_2$ , C11), 43.9 (q,  $\text{C}_3$ ), 46.1 ( $\text{CH}$ , C4), 50.6 ( $\text{CH}$ , C1), 62.7 (q, C2).

HRMS: ( $m/z$  - ES) calcd. for  $\text{C}_{15}\text{H}_{30}\text{N}$  ( $\text{M}+\text{H}$ ) $^+$  224.2378, found 224.2387.

#### 5.4.6.8 4-Pentyl-1-(2-*endo*-,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)-1*H*-1,2,3-triazole (136)



A microwave reaction vessel was charged with 2-azido,2-*endo*-,3,3-trimethylbicyclo[2.2.1]heptane **23** (100 mg, 0.55 mmol), heptyne (79  $\mu\text{L}$ , 58 mg, 0.61 mmol), 0.08 M sodium ascorbate solution (2.8 mL, 0.224 mmol) and 0.04 M copper sulphate solution (2.8 mL, 0.112 mmol). The reaction mixture was heated to 100  $^{\circ}\text{C}$  and stirred vigorously for 10 minutes in the microwave. After this time, the reaction mixture was diluted with  $\text{H}_2\text{O}$  (60 mL) and concentrated aqueous ammonia (1 mL) was added. The product was extracted using diethylether (2 x 60 mL) which was dried over  $\text{MgSO}_4$ . The organic solvent was removed under vacuum to yield a brown oil. This was further purified on silica gel using 100% EtOAc as eluent to yield 4-

pentyl-1-(2-*endo*-,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)-1*H*-1,2,3-triazole **136** as a pale yellow oil. (124 mg, 82%) *R<sub>f</sub>* (100% EtOAc) 0.28.

IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2931, 1550, 1467, 1392, 1376, 1222, 1047, 1016.

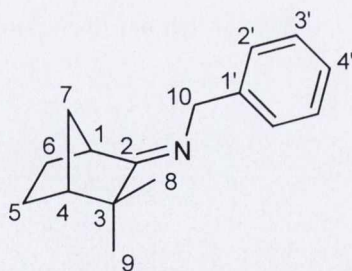
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 0.49 (s, 3H, H9), 0.88 (t, *J* = 6.72 Hz, 3H, H15), 1.09 (s, 3H, H8), 1.24-1.82 (m, 8H, H5, H6, H7a, H10), 1.84-1.88 (m, 1H, H4), 2.20-2.27 (m, 1H, H7b), 2.67 (t, *J* = 7.65 Hz, 2H, H11), 2.74-2.79 (m, 1H, H1), 7.38 (s, 1H, H5').

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 13.7 (CH<sub>3</sub>, C15), 21.6 (CH<sub>3</sub>, C8), 21.9 (CH<sub>2</sub>, C6), 22.2 (CH<sub>2</sub>, C5), 22.5 (CH<sub>3</sub>, C10), 24.1 (CH<sub>2</sub>, C14), 25.2 (CH<sub>2</sub>, C11), 25.6 (CH<sub>3</sub>, C9), 28.8 (CH<sub>2</sub>, C12), 31.0 (CH<sub>2</sub>, C13), 35.6 (CH<sub>2</sub>, C7), 46.0 (q, C3), 47.9 (CH, C1), 50.1 (CH, C4), 71.4 (q, C2), 119.2 (CH, C5'), 146.0 (q, C4').

HRMS: (*m/z* - ES) calcd. for C<sub>17</sub>H<sub>30</sub>N<sub>3</sub> (M+H)<sup>+</sup> 276.2440, found 276.2433.

#### 5.4.7 *endo*-Mecamylamine (17)

##### 5.4.7.1 *N*-(3,3-Dimethylbicyclo[2.2.1]heptan-2-ylidene)-1-phenylmethanamine (124)



To a solution of benzylamine (95  $\mu$ L, 93 mg, 0.870 mmol) and triethylamine (606  $\mu$ L, 440 mg, 4.347 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (5 mL) under an argon atmosphere cooled to 0 °C, titanium tetrachloride solution (1 M in CH<sub>2</sub>Cl<sub>2</sub>, 370  $\mu$ L, 0.370 mmol) was added slowly. The reaction was



heated to 40 °C. A solution of 3,3-dimethylbicyclo[2.2.1]heptan-2-one **21** (100 mg, 0.725 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) was then added and the reaction stirred at 40 °C for 16 hours. The reaction mixture was poured into diethyl ether (20 mL) and filtered thorough celite. The organic solvent was evaporated at reduced pressure to to yield *N*-(3,3-dimethylbicyclo[2.2.1]heptan-2-ylidene)-1-phenylmethanamine **124** as a clear oil (120 mg, 73%).

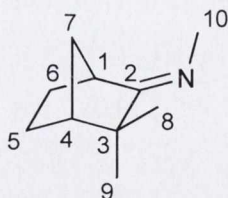
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2965, 2870, 1675, 1473, 1342, 1211, 1080, 822.

<sup>1</sup>H NR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 1.16 (s, 3H, H9), 1.18 (s, 3H, H8), 1.19-1.27 (m, 1H, H6a), 1.36-1.41 (m, 1H, H7a), 1.48-1.58 (m, 1H, H5a), 1.64-1.88 (m, 3H, H5b, H6b, H7b), 2.11-2.15 (m, 1H, H4), 3.15-3.19 (m, 1H, H10), 4.58 (d, *J* = 14.42 Hz, 1H, H10a), 4.62 (d, *J* = 14.42 Hz, 1H, H10b), 7.21-7.36 (m, 5H, H2', H3', H4')

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 23.6 (CH<sub>2</sub>, C5), 24.0 (CH<sub>3</sub>, C9), 25.6 (CH<sub>2</sub>, C6), 26.2 (CH<sub>3</sub>, C8), 36.3 (CH<sub>2</sub>, C7), 40.4 (CH, C1), 44.7 (q, C3), 46.7 (CH, C4), 56.4 (CH<sub>2</sub>, C10), 126.4 (CH, H4'), 127.3 (CH, H2'), 128.3 (CH, H3'), 188.0 (q, C2).

HRMS: (*m/z* - ES) calcd. for C<sub>16</sub>H<sub>22</sub>N (M+H)<sup>+</sup> 228.1752, found 228.1756.

#### 5.4.7.2 *N*-(3,3-Dimethylbicyclo[2.2.1]heptan-2-ylidene)methanamine (27)



Methylamine hydrochloride (640 mg, 9.48 mmol) was ground into a fine powder and heated to 100 °C in an RBF under high vacuum to remove all traces of H<sub>2</sub>O. A reflux condenser was fitted to the flask and the system flushed with argon. 1,8-Diazabicyclo[5.4.0]undec-7-ene (19.24 mmol, 200

1.406 mL, 1.434 g) was added and the reaction stirred for 5 minutes. Triethylamine (4.545 mL, 3.30 g, 32.61 mmol) was added. Titanium tetrachloride solution (1 M in CH<sub>2</sub>Cl<sub>2</sub>, 3.60 mL, 3.60 mmol) was added and the reaction was stirred for 20 minutes at 40 °C. 3,3-dimethylbicyclo[2.2.1]heptan-2-one **21** (1.00 g, 7.25 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 (200 mL) and filtered thorough celite to remove triethylamine hydrochloride. The organic solvent was dried over MgSO<sub>4</sub> and evaporated at reduced pressure to yield *N*-(3,3-dimethylbicyclo[2.2.1]heptan-2-ylidene)methanamine **27** as a clear oil (663 mg, 61%) without the need for further purification.

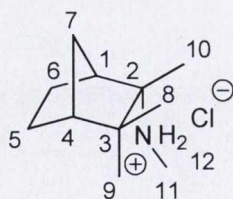
IR  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 2965, 2869, 1686, 1463, 1379, 1105, 1066.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 1.08 (s, 3H, H9), 1.09 (s, 3H, H8), 1.23-1.33 (m, 1H, H6a), 1.41-1.46 (m, 1H, H7a), 1.53-1.63 (m, 1H, H5a), 1.74-1.88 (m, 3H, H5b, H6b, H7b), 2.08-2.11 (m, 1H, H4), 3.11 (s, 3H, H10), 3.19-3.24 (m, 1H, H1).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 22.6 (CH<sub>3</sub>, C9), 22.9 (CH<sub>2</sub>, C5), 24.6 (CH<sub>2</sub>, C6), 24.7 (CH<sub>3</sub>, C8), 35.4 (CH<sub>2</sub>, C7), 38.3 (CH<sub>3</sub>, C10), 40.1 (CH, C1), 44.3 (q, C3), 46.8 (CH, C4), 189.8 (q, C2).

HRMS: (*m/z* - ES) calcd. for C<sub>10</sub>H<sub>18</sub>N (M+H)<sup>+</sup> 152.1439, found 152.1444.

#### 5.4.7.3 *N*,2-*exo*-,3,3-Tetramethylbicyclo[2.2.1]heptan-2-amine (13)



*N*-(3,3-Dimethylbicyclo[2.2.1]heptan-2-ylidene)methanamine **27** (250 mg, 1.66 mmol) was placed in a RBF with a stirring bar in the absence of any solvent under an argon atmosphere. To



this, boron trifluoride diethyl etherate (316  $\mu$ L, 354 mg, 2.49 mmol) was added dropwise. A crystalline solid formed. The reaction mixture was cooled to 0 °C and methyllithium solution (1.6 M in diethyl ether, 10.00 mL, 16.00 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 1 hour. Ammonium hydroxide solution (30% in H<sub>2</sub>O, 10 mL) was added and the product extracted with diethyl ether (2 x 10 mL), washed with brine (10 mL) and dried over MgSO<sub>4</sub>. The organic solvent was evaporated under vacuum to yield the desired amine as a viscous oil. This product was redissolved in anhydrous diethyl ether (2 mL) and a solution of hydrogen chloride (2 M in diethyl ether, 1.0 mL, 2.0 mmol) was added. The hydrochloride salt of *N*,2-*exo*-,3,3-Tetramethylbicyclo[2.2.1]heptan-2-amine **13** was isolated by filtration and dried under vacuum to yield a white solid (191 mg, 56%). M.p. 140-145 °C (decomposes).

IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3358, 2965, 1457, 1381, 1341, 1081, 912.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 1.00 (s, 3H, H8), 1.11 (CH<sub>3</sub>, 3H, H9), 1.18-1.23 (m, 1H, H7a), 1.24 (s, 3H, H10), 1.30-1.47 (m, 2H, H5a, H6a), 1.50-1.68 (m, 2H, H5b, H6b), 1.73-1.77 (m, 1H, H4), 1.82-1.89 (m, 1H, H7b), 2.14-2.18 (m, 1H, H1), 2.47 (t, *J* = 5.34 Hz, 3H, H11), 7.81 (br s, 1H, H12a), 8.98 (br s, 1H, H12b).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 18.6 (CH<sub>3</sub>, C10), 21.3 (CH<sub>3</sub>, C9), 21.4 (CH<sub>2</sub>, C6), 23.0 (CH<sub>2</sub>, C5), 27.0 (CH<sub>3</sub>, C8), 28.5 (CH<sub>3</sub>, C11), 34.3 (CH<sub>2</sub>, C7), 42.5 (q, C3), 46.0 (CH, C1), 49.2 (CH, C4), 68.0 (q, C2).

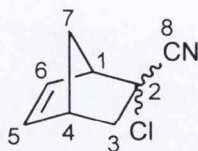
HRMS: (*m/z* - ES) calcd. for C<sub>11</sub>H<sub>22</sub>N(M+H)<sup>+</sup> 168.1752, found 168.1751.



## 5.5 5- and 6-substituted mecamylamine

### 5.5.1 6-substituted mecamylamine analogue

#### 5.5.1.1 2-Chlorobicyclo[2.2.1]hept-5-ene-2-carbonitrile (**39**)



To a solution of 2-chloroacrylonitrile **28** (1.21 mL, 1.33 g, 15.2 mmol) in toluene (3 mL) at 70 °C, freshly distilled cyclopentadiene (1.475 mL, 18.24 mmol) was slowly added. After stirring overnight at 45 °C, the solvent was removed under vacuum to yield a clear oil. Purification on silica gel using 98:2 hexane:EtOAc as eluent yielded a pale yellow oil (2.12 g, 13.83 mmol, 91%) which is 4:1 mixture of the *exo*:*endo* diastereomers of 2-chlorobicyclo[2.2.1]hept-5-ene-2-carbonitrile **39**.  $R_f$  (2% EtOAc/Hexane) 0.35.

IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3071, 2990, 2946, 2869, 2235, 1712, 1336, 1269, 766, 725.

*Exo* diastereomer:

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 6.42 (dd,  $J$  = 3.1, 5.7 Hz, 1H, H6), 6.12 (dd,  $J$  = 3.05, 5.7 Hz, 1H, H5), 3.51 (br s, 1H, H-1), 3.09 (br s, 1H, H4), 2.72 (dd,  $J$  = 3.7, 13.2 Hz, 1H, H3a), 1.75–1.83 (m, 2H, H7), 1.71 (dd,  $J$  = 3.7, 13.2 Hz, 1H, H3b).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 42.6 (CH, C4), 46.9 (CH<sub>2</sub>, C3), 48.5 (CH<sub>2</sub>, C7), 56.2 (CH, H1), 56.8 (q, C2), 132.5 (CH<sub>2</sub>, C6), 142.1 (CH<sub>2</sub>, C5).

*Endo* diastereomer:

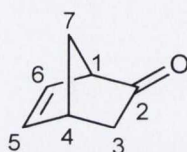
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 6.46 (dd,  $J$  = 3.0, 5.7 Hz, 1H, H6), 6.22 (dd,  $J$  = 3.0, 5.8 Hz, 1H, H5), 3.35 (br s, 1H, H1), 3.09 (br, 1H, H4), 2.36 (dd,  $J$  = 3.4, 13.2 Hz, 1H, H3a), 2.24 (dd,  $J$  = 2.7, 13.2 Hz, 1H, H3b), 1.92–1.96 (m, 2H,

H7)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 42.9 (CH, C4), 45.7 (CH<sub>2</sub>, C3), 48.5 (CH<sub>2</sub>, C7), 55.4 (CH, H1), 56.6 (q, C2), 131.9 (CH<sub>2</sub>, C6), 139.4 (CH<sub>2</sub>, C5).

HRMS: ( $m/z$  - CI) calcd. for  $\text{C}_8\text{H}_9\text{NCl}$  ( $\text{M}+\text{H}$ )<sup>+</sup> 154.0424, found 154.0428.

#### 5.5.1.2 Bicyclo[2.2.1]hept-5-en-2-one (31)



$\alpha$ -Chloronitrile mixture **39** (0.93 g, 6.0 mmol) was added to a RBF containing diethyl ether (5 mL), 4 M potassium hydroxide solution (10 mL) and DMSO (15 mL). The mixture was heated to 70 °C. After such time that TLC analysis showed complete consumption of the starting material (approximately 3 hours), the reaction was cooled to room temperature.  $\text{H}_2\text{O}$  (30 mL) was added. The product was extracted with diethyl ether (2 x 40 mL) and washed with brine (40 mL). The organic extracts were dried over  $\text{MgSO}_4$  and the organic solvent carefully removed by fractional distillation as the product is surprisingly volatile. This yielded bicyclo[2.2.1]hept-5-en-2-one **31** as a clear oil (0.286 g, 44%).  $R_f$  (10% EtOAc/Hexane) 0.29.

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

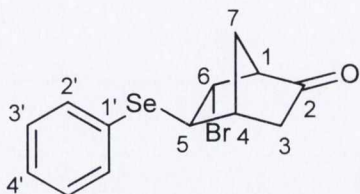
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 1.87 (dd,  $J$  = 16.5 Hz, 4.42 Hz, 1H, H3a), 1.95-2.03 (m, 2H, H3b, H7a), 2.16-2.23 (m, 1H, H7b), 3.01-3.05 (m, 1H, H1), 3.21 (m, 1H, H4), 6.12 (dd,  $J$  = 5.50 Hz, 3.85 Hz, 1H, H6), 6.58 (dd,  $J$  = 5.50 Hz, 2.73 Hz, 1H, H5).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 36.8 (CH<sub>2</sub>, C3), 39.6 (CH, C4), 50.5 (CH<sub>2</sub>, C7),

55.4 (CH, C1), 130.1 (CH, C6), 142.6 (CH, C5),  
215.9 (q, C2).

HRMS: ( $m/z$  - CI) calcd. for  $C_9H_{13}O$  ( $M+C_2H_5$ )<sup>+</sup> 137.0966, found 137.0970.

#### 5.5.1.3 6-*endo*-Bromo-5-*exo*-(phenylselanyl)bicyclo[2.2.1]heptan-2-one (32)



To a solution of phenylselenyl bromide (242 mg, 1.02 mmol) in anhydrous THF (3 mL) cooled to -78 °C under an argon atmosphere, a solution of bicyclo[2.2.1]hept-5-en-2-one **31** (105 mg, 0.98 mmol) in anhydrous THF (1 mL) cooled to -78 °C was added over 20 minutes. The reaction mixture was stirred at -78 °C for 4 hours and then allowed to warm to room temperature. The organic solvent was removed under vacuum to give a thick brown oil which was purified by flash chromatography on silica gel using a 95:5 hexane EtOAc to 8:2 hexane EtOAc eluent gradient to yield 6-bromo-5-(phenylselanyl)bicyclo[2.2.1]heptan-2-one **32** as a white solid (315 mg, 92%). M.p. 72-74 °C (lit.,<sup>295</sup> 75-77 °C)  $R_f$  (10% EtOAc/Hexane) 0.31.

IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2970, 1748, 1576, 1477, 1437, 1289, 1133.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 1.86-1.92 (m, 1H, H7a), 2.09 (dd,  $J$  = 18.37, 4.40 Hz, 1H, H3a), 2.21-2.27 (m, 1H, H7b), 2.33 (dd,  $J$  = 18.37, 5.08 Hz), 2.77-2.82 (m, 1H, H4), 2.89-2.94 (m, 1H, H1), 3.58-3.63 (m, 1H, H5), 4.27-4.31 (m, 1H, H6), 7.32-7.39 (m, 3H, H2', H4'), 7.63-7.68 (m, 2H, H3').

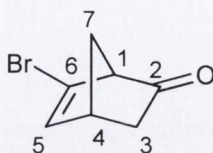
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 35.6 (CH<sub>2</sub>, C7), 42.8 (CH, C4), 44.6 (CH<sub>2</sub>, C3), 48.8 (CH, C6), 52.8 (CH, C5), 57.8 (CH, C1), 128.47 (Ar, C4'), 128.49 (q, C1'), 129.6, (Ar, C2'), 205



134.7, (Ar, C3'), 210.1 (q, C2).

HRMS: ( $m/z$  - ES) calcd. for  $C_{13}H_{13}O^{79}Br^{80}Se$  ( $M+Na$ )<sup>+</sup> 366.9213, found 366.3216.

#### 5.5.1.4 6-Bromobicyclo[2.2.1]hept-5-en-2-one (33)



#### General procedure J

To a solution of 6-bromo-5-(phenylselanyl)bicyclo[2.2.1]heptan-2-one **32** (200 mg, 0.58 mmol) and acetic acid (41  $\mu$ L, 0.72 mmol) in THF (4 mL) cooled to -10 °C, hydrogen peroxide (137  $\mu$ L, 30% solution in H<sub>2</sub>O, 41 mg, 1.2 mmol) was slowly added. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. After this time, the reaction mixture was poured into ether (20 mL) and washed with water (3 x 5 mL), saturated Na<sub>2</sub>CO<sub>3</sub> (3 x 5 mL), again with water (3 x 5 mL) and finally with brine (20 mL). The organic layer was dried of MgSO<sub>4</sub>, filtered and concentrated to give a clear oil which was purified by flash chromatography on silica gel 95:5 hexane:EtOAc as the eluent to yield 6-bromobicyclo[2.2.1]hept-5-en-2-one **33** as a clear oil (90 mg, 67%).  $R_f$  (10% EtOAc/Hexane) 0.44.

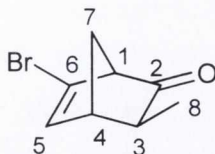
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2970, 2873, 1743, 1574, 1284, 961, 949, 828.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 2.00-2.06 (m, 3H, H7, H3a), 2.47-2.53 (m, 1H, H3b), 3.08-3.11 (m, 1H, H1), 3.26-3.30 (m, 1H, H4), 6.62 (d,  $J$  = 3.02 Hz, 1H, H5).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 36.1 (CH<sub>2</sub>, C7), 41.7 (CH, C4), 50.6 (CH<sub>2</sub>, C3), 62.9 (CH, C1), 121.3 (q, C6), 141.1 (CH, C5), 214.7, (q, C2)

HRMS: ( $m/z$  - CI) calcd. for  $C_7H_8OBr$  ( $M+H$ )<sup>+</sup> 186.9759, found 186.9773.

#### 5.5.1.5 6-Bromo-3-*exo*-methylbicyclo[2.2.1]hept-5-en-2-one (137)



Prepared as per general procedure B using bromobicyclo[2.2.1]hept-5-en-2-one **33** (1.00 g, 5.89 mmol), 1 M sodium bis(trimethylsilyl)amide in THF (8.85 mL, 8.85 mmol), THF 15 mL and iodomethane (934 1.10 mL, 17.67 mmol) to yield 6-bromo-3-methylbicyclo[2.2.1]hept-5-en-2-one **137** as a clear oil (260 mg, 22%).  $R_f$  (10% EtOAc/Hexane) 0.48.

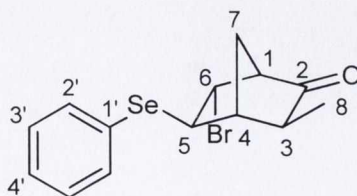
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2973, 1742, 1575, 1438, 1286, 1126, 1034, 950.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 1.12 (d,  $J$  = 7.46 Hz, 3H, H8), 2.08 (dq,  $J$  = 7.46, 3.42 Hz, 1H, H3) 2.14-2.18 (m, 1H, H7a), 2.35-2.41 (m, 1H, H7b), 2.90-2.94 (m, 1H, H4), 2.98-3.00 (m, 1H, H1), 6.62 (d,  $J$  = 3.42 Hz, 1H, H5).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 15.4 (CH<sub>3</sub>, C8), 39.3 (CH, C3), 47.0 (CH<sub>2</sub>, C7), 47.3 (CH, C4), 62.7 (CH, C1), 122.1 (q, C6), 142.1 (CH, C5), 215.1 (q, C6).

HRMS: ( $m/z$  - ES) calcd. for C<sub>8</sub>H<sub>9</sub>ONa<sup>79</sup>Br (M+Na)<sup>+</sup> 222.9734, found 222.9747.

#### 5.5.1.6 6-*endo*-Bromo-3-*exo*-methyl-5-*exo*-(phenylselanyl)bicyclo[2.2.1]heptan-2-one (139)



### General Procedure K

6-bromo-5-(phenylselanyl)bicyclo[2.2.1]heptan-2-one **32** (2.70 g, 7.76 mmol) was dissolved in anhydrous THF (20 mL) under an argon atmosphere and cooled to -78 °C. Sodium bis(trimethylsilyl)amide (1M in THF, 12.0 mL, 12 mmol) was cooled to -78 °C before being added to the reaction vessel. After stirring for 2 hours at -78 °C, the reaction was allowed to warm to -30 °C. Iodomethane (1.45 mL, 23.28 mmol) was added dropwise and the reaction was stirred for 1 hour at -30 °C. 1 M HCl (20 mL) was then added. The product was extracted using diethyl ether (2 x 30 mL), washed with brine (20 mL) and dried over MgSO<sub>4</sub>. The solvent was evaporated at reduced pressure to give a pale yellow oil which was purified by flash chromatography using 97:3 hexane:EtOAc as the eluent to yield 6-*endo*-bromo-3-*exo*-methyl-5-*exo*-(phenylselanyl)bicyclo[2.2.1]heptan-2-one **139** as a pale yellow solid. (2.25g, 80%) M.p. 73-76 °C *R<sub>f</sub>* (15% EtOAc/Hexane) 0.20.

IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2971, 1745, 1577, 1477, 1437, 1289, 1133, 1086.

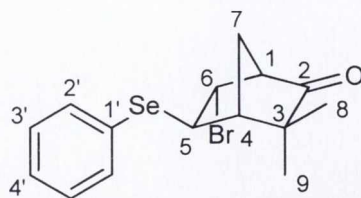
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 1.15 (d, *J* = 7.59 Hz, 3H, H8), 1.96-2.02 (m, 1H, H7a), 2.08-2.20 (m, 3H, H3, H7b), 2.45-2.48 (m, 1H, H4), 2.88-2.91 (m, 1H, H1), 3.64-3.67 (m, 1H, H5), 4.30-4.33 (m, 1H, H6), 7.32-7.39 (m, 3H, H2', H4'), 7.62-7.69 (m, 2H, H3').

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 14.5 (CH<sub>3</sub>, H8), 33.2 (CH<sub>2</sub>, C7), 48.1 (CH, C3), 48.7 (CH, C4), 49.0 (CH, C6), 53.4 (CH, C5), 57.8 (CH, C1), 128.3 (Ar, C4'), 128.6 (q, C1'), 129.5, (Ar, C2'), 134.6, Ar, C3'), 213.7 (q, C2).

HRMS: (*m/z* - EI) calcd. for C<sub>14</sub>H<sub>15</sub>O<sup>79</sup>Br<sup>80</sup>Se (M) 357.9471, found 357.9479.



5.5.1.7 **6-endo-Bromo-3,3-dimethyl-5-exo-(phenylselanyl)bicyclo[2.2.1]heptan-2-one**  
(140)



Prepared as per general procedure K using a solution of 6-*endo*-bromo-3-*exo*-methyl-5-*exo*-(phenylselanyl)bicyclo[2.2.1]heptan-2-one 139 (2.40 g, 6.70 mmol) in THF (20 mL), sodium bis(trimethylsilyl)amide (1 M in THF, 10.0 mL, 10 mmol) and iodomethane (1.25 mL, 20.1 mmol) to give a thick pale yellow oil which was absorbed onto silica and purified by flash chromatography on silica gel using a 95:5 hexane:EtOAc to 8:2 hexane:EtOAc gradient to yield 6-*endo*-bromo-3,3-dimethyl-5-*exo*-(phenylselanyl)bicyclo[2.2.1]heptan-2-one **140** as a white solid (2.14 g, 86%). M.p. 78-82 °C.  $R_f$  (15% EtOAc/Hexane) 0.30.

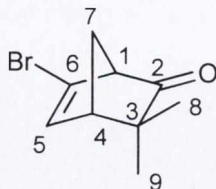
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2966, 1748, 1577, 1472, 1275, 1086, 956, 812.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 1.18 (s, 3H, H8), 1.19 (s, 3H, H9), 2.23-2.27 (m, 1H, H7a), 2.38-2.41 (m, 1H, H4), 2.86-2.90 (m, 1H, H1), 3.96-3.99 (m, 1H, H5), 4.36-4.39 (m, 1H, H6), 7.32-7.39 (m, 3H, H2', H4'), 7.60-7.66 (m, 2H, H3').

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 20.5 (CH<sub>3</sub>, C9), 24.48 (CH<sub>3</sub>, C8), 34.2 (CH<sub>2</sub>, C7), 48.2 (CH, C5), 48.4 (q, C3), 50.5 (CH, C6), 53.8 (CH, C4), 58.5 (CH, C1), 128.1 (Ar, C4'), 129.0 (q, C1'), 129.5, (Ar, C2'), 134.2, Ar, C3'), 215.6 (q, C2).

HRMS: ( $m/z$  - EI) calcd. for C<sub>15</sub>H<sub>17</sub>O<sup>80</sup>Se<sup>79</sup>Br (M) 371.9628, found 371.9619.

#### 5.5.1.8 6-Bromo-3,3-dimethylbicyclo[2.2.1]hept-5-en-2-one (138)



Prepared as per general procedure J using 6-*endo*-bromo-3,3-dimethyl-5-*exo*-(phenylselanyl)bicyclo[2.2.1]heptan-2-one **140** (3.00 g, 8.29 mmol), acetic acid (0.62 mL, 9.12 mmol), hydrogen peroxide (30% wt solution in H<sub>2</sub>O, 1.9 mL, 564 mg, 16.6 mmol) and THF 22 mL to yield 6-bromo-3,3-dimethylbicyclo[2.2.1]hept-5-en-2-one **138** as a white solid (1.59 g, 89%). M.p. 68-72 °C *R<sub>f</sub>* (10% EtOAc/Hexane) 0.41.

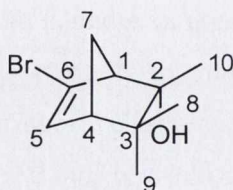
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2969, 2870, 1743, 1574, 1283, 972, 825.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 1.10 (s, 3H, H8), 1.16 (s, 3H, H9), 2.22-2.27 (m, 1H, H7a), 2.37-2.41 (m, 1H, H7b), 2.83-2.86 (m, 1H, H4), 3.05-3.08 (m, 1H, H1), 6.63 (d, *J* = 3.20 Hz, 1H, H5).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 24.3 (CH<sub>3</sub>, C8), 26.9 (CH<sub>3</sub>, C9), 42.6 (q, C3), 47.8 (CH<sub>2</sub>, C7), 51.9 (CH, C4), 63.5 (CH, C1), 120.9 (q, C6), 141.7 (CH, C5), 216.6 (q, 216.6).

HRMS: (*m/z* - EI) calcd. for C<sub>9</sub>H<sub>11</sub>O<sup>79</sup>Br (M) 213.9993, found 213.9988.

#### 5.5.1.9 6-Bromo-2-*exo*-,3,3-trimethylbicyclo[2.2.1]hept-5-en-2-ol (141)



## General Procedure L

To a stirring solution of 6-bromo-3,3-dimethylbicyclo[2.2.1]hept-5-en-2-one **138** (6.6 g, 30.7 mmol) in anhydrous THF (50 mL) at 0 °C under an argon atmosphere, methylmagnesium bromide (3 M in THF, 19.00 mL, 57.1 mmol) was added slowly. The reaction mixture was heated to 35 °C and stirred for 3 hours. After this time, TLC analysis showed no starting material remained. The reaction was cooled to 0 °C and quenched by carefully adding 1 M HCl (100 mL). The desired product was extracted using diethyl ether (2 x 100 mL) and washed with brine (100 mL). The organic extracts were dried over MgSO<sub>4</sub> and concentrated to yield 6-bromo-2-*exo*-,3,3-trimethylbicyclo[2.2.1]hept-5-en-2-ol **141** as a clear viscous oil without the need of further purification. (6.8 g, 96%) *R<sub>f</sub>* (15% EtOAc/Hexane) 0.32.

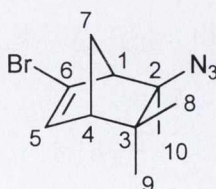
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2966, 1579, 1473, 1372, 1291, 1210, 1154, 1089, 1006, 935.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 0.93 (s, 3H, H8), 1.14 (s, 3H, H9), 1.40 (s, 3H, H10), 1.67-1.76 (m, 2H, H7), 2.42-2.47 (m, 1H, H4), 2.71-2.75 (m, 1H, H1), 6.44 (d, *J* = 3.33 Hz, 1H, H5).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 24.1 (CH<sub>3</sub>, C8), 25.8 (CH<sub>3</sub>, C10), 27.3 (CH<sub>3</sub>, C9), 44.3 (q, C3), 45.3 (CH<sub>2</sub>, C7), 56.4 (CH, C4), 63.7 (CH, C1), 81.1 (q, C2), 123.8 (q, C6), 137.8 (CH, C5).

HRMS: (*m/z* - Cl) calcd. for C<sub>10</sub>H<sub>16</sub>O<sup>79</sup>Br (M+H)<sup>+</sup> 231.0385, found 231.0379.

### 5.5.1.10 6-Azido-2-bromo-5,5,6-*endo*-trimethylbicyclo[2.2.1]hept-2-ene (142)





Prepared as per general procedure E using 6-bromo-2-*exo*-,3,3-trimethylbicyclo[2.2.1]hept-5-en-2-ol **141** (450 mg, 1.95 mmol), 60% H<sub>2</sub>SO<sub>4</sub> (25 mL), sodium azide (2.25 g, 34.6 mmol) and CHCl<sub>3</sub> (25 mL). The reaction was stirred for 8 hours and purified by flash chromatography on silica gel using 100% hexane as the eluent to yield the desired product 6-azido-2-bromo-5,5,6-*endo*-trimethylbicyclo[2.2.1]hept-2-ene **142** as a clear oil. (160 mg, 32%) *R<sub>f</sub>* (100% Hexane) 0.51.

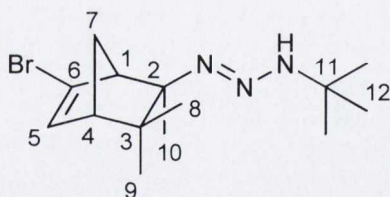
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2964, 2084, 1580, 1474, 1372, 1291, 1156, 812.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 0.93 (s, 3H, H9), 1.21 (s, 3H, H8), 1.42 (s, 3H, H10), 1.75-1.80 (m, 1H, H7a), 1.98-2.03 (m, 1H, H7b), 2.39-2.43 (m, 1H, H4), 2.75 (br s, 1H, H1), 6.39 (d, *J* = 3.27 Hz, 1H, H5).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 19.7 (CH<sub>3</sub>, C10), 26.0 (CH<sub>3</sub>, C9), 26.9 (CH<sub>3</sub>, C8), 45.6 (q, C3), 45.8 (CH<sub>2</sub>, C7), 56.3 (CH, C4), 61.9 (CH, C1), 77.2 (q, C2), 123.7 (q, C6), 139.2, (CH, C5).

HRMS: (*m/z* - EI) calcd. for C<sub>10</sub>H<sub>14</sub>N<sub>3</sub><sup>79</sup>Br (M) 255.0371, found 255.0378.

#### 5.5.1.11 1-(6-Bromo-2-*endo*-,3,3-trimethylbicyclo[2.2.1]hept-5-en-2-yl)-3-(*tert*-butyl)triaz-1-ene (**144**)



To a solution of 6-azido-2-bromo-5,5,6-*endo*-trimethylbicyclo[2.2.1]hept-2-ene **142** (50 mg, 0.20 mmol) in anhydrous THF (3 mL) cooled to -78 °C under an argon atmosphere, a solution of *tert*-butyllithium (1.7 M in pentane, 129  $\mu$ L, 0.22 mmol) was added dropwise. The reaction was allowed to warm -20 °C with continuous stirring. 'Wet ether' (10 mL) was added and reaction stirred for 10 minutes exposed to the air. H<sub>2</sub>O (10 mL) was added and the product extracted using diethyl ether (2 x 10 mL). The organic layers were washed with brine and dried over MgSO<sub>4</sub>. The

organic solvent was removed under vacuum to yield 1-(6-Bromo-2-*endo*-,3,3-trimethylbicyclo[2.2.1]hept-5-en-2-yl)-3-(*tert*-butyl)triaz-1-ene **144** as the major product of a mixture of compounds (40 mg, approx 40%).

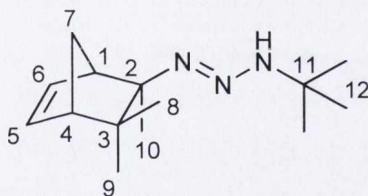
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3465, 2964, 1581, 1474, 1371, 1291, 1157, 1088, 1006.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 0.95 (s, 3H, H9), 1.01 (s, 3H, H8), 1.22 (s, 3H, H10), 1.29 (s, 3 x CH<sub>3</sub>, 9H, H12), 1.71-1.76 (m, 1H, H7a), 2.00-2.05 (m, 1H, H7b), 2.40-2.44 (m, 1H, H4), 2.88 (br s, 1H, H1), 6.40 (d, J = 3.25 Hz, 1H, H5).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 21.3 (CH<sub>3</sub>, C10), 26.0 (CH<sub>3</sub>, C9), 27.6 (CH<sub>3</sub>, C8), 29.1 (CH<sub>3</sub>, C12), 45.5 (CH<sub>2</sub>, C7), 45.7 (q, C3), 55.4 (q, C11), 56.6 (CH, C4), 61.8 (CH, C1), 71.1 (q, C2), 125.2 (q, C6), 138.3, (CH, C5).

HRMS: ( $m/z$  - ES) calcd. for C<sub>14</sub>H<sub>25</sub>N<sub>3</sub><sup>79</sup>Br (M+H)<sup>+</sup> 314.1232, found 314.1238.

#### 5.5.1.12 3-(*tert*-Butyl)-1-(2-*endo*-,3,3-trimethylbicyclo[2.2.1]hept-5-en-2-yl)triaz-1-ene (145)



To a solution of 6-azido-2-bromo-5,5,6-*endo*-trimethylbicyclo[2.2.1]hept-2-ene **142** (50 mg, 0.20 mmol) in anhydrous THF (3 mL) cooled to -78 °C under an argon atmosphere, a solution of *tert*-butyllithium (1.7 M in pentane, 471  $\mu$ L, 0.8 mmol) was added dropwise. The reaction was allowed to warm -20 °C with continuous stirring. 'Wet ether' (10 mL) was added and reaction stirred for 10 minutes exposed to the air. H<sub>2</sub>O (10 mL) was added and the product extracted using diethyl ether (2 x 10 mL). The organic layers were washed with brine and dried over MgSO<sub>4</sub>. The organic solvent was removed under vacuum to yield 3-(*tert*-Butyl)-1-(2-*endo*-,3,3-



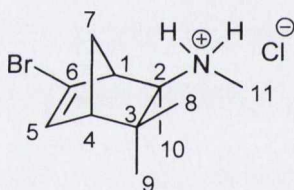
trimethylbicyclo[2.2.1]hept-5-en-2-yl)triaz-1-ene **145** as the major product of a mixture of compounds (30 mg, approx 50%).

IR  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3376, 2966, 1646, 1554, 1464, 1364, 1128, 951.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 0.87 (s, 3H, H9), 1.02 (s, 3H, H8), 1.07 (s, 3H, H10), 1.28 (s, 9H, H12), 1.71-1.76 (m, 1H, H7a), 2.00-2.05 (m, 1H, H7b), 2.40-2.44 (m, 1H, H4), 2.88 (br s, 1H, H1), 6.40 (d,  $J = 3.25$  Hz, 1H, H5).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 22.3 ( $\text{CH}_3$ , C10), 26.2 ( $\text{CH}_3$ , C9), 28.1 ( $\text{CH}_3$ , C8), 29.0 ( $\text{CH}_3$ , C12), 44.8 ( $\text{CH}_2$ , C7), 45.6 (q, C3), 54.4 (CH, C1), 55.2 (CH, C4), 56.1 (q, C11), 70.0 (q, C2), 134.5 (CH, C6), 138.9, (CH, C5).

#### 5.5.1.13 6-Bromo-*N*,2-*endo*-,3,3-tetramethylbicyclo[2.2.1]hept-5-en-2-amine (**149**)



#### 6-bromo-2,3,3-Trimethylbicyclo[2.2.1]hept-5-en-2-amine (**148**):

Prepared as per general procedure G using 6-azido-2-bromo-5,5,6-*endo*-trimethylbicyclo[2.2.1]hept-2-ene **142** (400 mg, 1.56 mmol), tributylphosphine (779  $\mu\text{L}$ , 631 mg, 3.12 mmol), THF (12 mL),  $\text{H}_2\text{O}$  (280  $\mu\text{L}$ , 15.60 mmol) and hydrogen chloride solution (2 M in diethyl ether, 2 mL, 4 mmol) to yield the hydrochloride salt of the desired amine. The majority of the tributylphosphine oxide was removed by flash chromatography on silica gel using a 50:50 EtOAc:hexane to 50:50 EtOAc:methanol eluent gradient to obtain a mixture containing a 4:1 ratio of 6-bromo-2,3,3-trimethylbicyclo[2.2.1]hept-5-en-2-amine **148** to tributylphosphine oxide. Extraction with  $\text{CH}_2\text{Cl}_2$  (2 x 20 mL) from 1 M NaOH (20 mL) furnished a mixture of the free amine and tributylphosphine oxide (160 mgs), after drying the organic solvent over  $\text{MgSO}_4$  and evaporating under vacuum.



*6-bromo-N,2,3,3-Tetramethylbicyclo[2.2.1]hept-5-en-2-amine (149):*

Prepared as per general procedure I using the mixture obtained above (150 mg), paraformaldehyde (100 mg, 3.33 mmol), molecular sieves (100 mg), anhydrous  $\text{CH}_2\text{Cl}_2$  (10 mL) and sodium borohydride (80 mg, 2.11 mmol) to yield a mixture of the desired amine and tributylphosphine. The hydrochloride salt was formed by the addition of hydrogen chloride solution (2M in diethyl ether, 750  $\mu\text{L}$ , 1.5 mmol) and evaporation of the solvent. Flash chromatography on silica gel afforded the hydrochloride salt of 6-bromo-N,2,3,3-Tetramethylbicyclo[2.2.1]hept-5-en-2-amine **149** as a white solid (140 mg, 32% (2 steps)). M.p. 207-212  $^\circ\text{C}$  (decomposes).

IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 2971, 2705, 2436, 1585, 1474, 1422, 1381, 1103, 808.

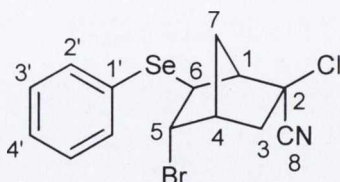
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 1.03 (s, 3H, H9), 1.39 (s, 3H, H10), 1.62 (s, 3H, H8), 1.87-1.93 (m, 1H, H7a), 2.38-2.45 (m, 1H, H7b), 2.50-2.54 (m, 1H, H4), 2.75 (s, 3H, H11), 3.04-3.08 (m, 1H, H1), 6.45 (d,  $J = 3.40$  Hz, 1H, H5).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 18.0 ( $\text{CH}_3$ , C10), 26.26 (2 x  $\text{CH}_3$ , C8, C9), 29.3 ( $\text{CH}_3$ , C11), 45.5 ( $\text{CH}_2$ , C7), 45.8 (q, C3), 56.9 ( $\text{CH}$ , C4), 58.1 ( $\text{CH}$ , C1), 70.1 (q, C2), 123.1 (q, C6), 139.2 ( $\text{CH}$ , C5).

HRMS: ( $m/z$  - ES) calcd. for  $\text{C}_{11}\text{H}_{19}\text{N}^{79}\text{Br}$  ( $\text{M}+\text{H}$ ) $^+$  244.0701, found 244.0690.

## 5.5.2 5-substituted mecamylamine analogue

### 5.5.2.1 5-*endo*-Bromo-2-*exo*-chloro-6-*exo*-(phenylselanyl)bicyclo[2.2.1]heptane-2-carbonitrile (**151**)



A 4:1 *exo*:*endo* mixture (with respect to the chlorine) of 2-chlorobicyclo[2.2.1]hept-5-ene-2-carbonitrile **39** (2.00 g, 12.99 mmol) was added to phenylselenenyl bromide (3.20 g, 13.56 mmol) in an oven dried RBF fitted with a reflux condenser. The flask and condenser were completely flushed with argon before adding anhydrous  $\text{CHCl}_3$  (15 mL). The reaction mixture was refluxed at 62 °C for 72 hour. The solvent was removed under reduced pressure to give a thick black oil which was absorbed onto silica gel and purified by flash chromatography on silica gel using 98.5:1.5 to yield 5-*endo*-bromo-2-*exo*-chloro-6-*exo*-(phenylselanyl)bicyclo[2.2.1]heptane-2-carbonitrile **151** as a white solid (3.4 g, 63%) m.p. 86-88 °C  $R_f$  (10% EtOAc/Hexane) 0.47 and 5-*endo*-Bromo-2-*endo*-chloro-6-*exo*-(phenylselanyl)bicyclo[2.2.1]heptane-2-carbonitrile **152** as a white solid. (1.2 g, 23.7%) m.p. 101-103 °C.  $R_f$  (10% EtOAc/Hexane) 0.50.

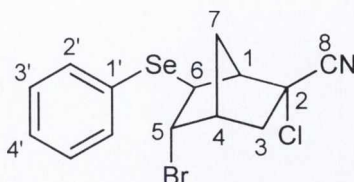
IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 2975, 2954, 2237, 1576, 1477, 1437, 1289, 748.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 2.05-2.18 (m, 2H, H7), 2.62-2.67 (m, 3H, H3, H4), 2.79-2.82 (m, 1H, H1), 3.94-3.98 (m, 1H, H6), 4.19-4.23 (m, 1H, H5), 7.34-7.40 (m, 3H, H2', H4'), 7.58-7.63 (m, 2H, H3').

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 36.0 ( $\text{CH}_2$ , C7), 42.0 ( $\text{CH}_2$ , C3), 45.1 ( $\text{CH}$ , C4), 45.6 ( $\text{CH}$ , C6), 55.5 ( $\text{CH}$ , C5), 56.4 ( $\text{CH}$ , C1), 58.5 (q, C2), 119.8 (q, C8), 128.2 (q, C1'), 128.5 (Ar, C4'), 129.6 (Ar, C2'), 134.2, (Ar, C3').

HRMS: ( $m/z$  - EI) calcd. for  $\text{C}_{14}\text{H}_{13}\text{N}^{35}\text{Cl}^{80}\text{Se}^{79}\text{Br}$  (M) 388.9085, found 388.9095.

5.5.2.2 **5-endo-Bromo-2-endo-chloro-6-exo-(phenylselanyl)bicyclo[2.2.1]heptane-2-carbonitrile (152)**



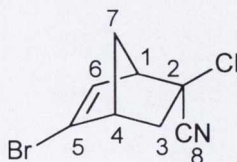
IR  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 3062, 2974, 2240, 1576, 1477, 1436, 1288, 723.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 2.04-2.10 (m, 1H, H7a), 2.15-2.22 (m, 1H, H7b), 2.33-2.41 (m, 1H, H3a), 2.67-2.72 (2H, H1, H4), 3.12 (dd,  $J = 15.15, 2.82$  Hz, H3b), 3.67-3.70 (1H, H6), 4.15-4.19 (m, 1H, H5), 7.34-7.40 (m, 3H, H2', H4'), 7.59-7.61 (m, 2H, H3').

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 34.0 ( $\text{CH}_2$ , C7), 44.0 ( $\text{CH}_2$ , C3), 45.0 (CH, C4), 47.8 (CH, C6), 54.5 (CH, C5), 57.3 (CH, C1), 57.4 (q, C2), 118.1 (q, C8), 127.8 (q, C1'), 128.6 (Ar, C4'), 129.7 (Ar, C2'), 134.4, (Ar, C3').

HRMS: ( $m/z$  - EI) calcd. for  $\text{C}_{14}\text{H}_{13}\text{N}^{35}\text{Cl}^{80}\text{Se}^{79}\text{Br}$  (M) 388.9085, found 388.9067.

5.5.2.3 **5-Bromo-2-exo-chlorobicyclo[2.2.1]hept-5-ene-2-carbonitrile (153)**



Prepared as per general procedure J using 5-bromo-2-exo-chloro-6-exo-(phenylselanyl)bicyclo[2.2.1]heptane-2-carbonitrile **151** (1.5 g, 3.86 mmol), hydrogen peroxide (872  $\mu\text{L}$ , 7.7 mmol), acetic acid (350  $\mu\text{L}$ ) and THF (12 mL) to give a yellow oil that was purified by flash chromatography on silica gel using 9:1 hexane:EtOAc as eluent to yield 5-bromo-2-exo-



chlorobicyclo[2.2.1]hept-5-ene-2-carbonitrile **153** as a white solid (805 mg, 89%). M.p. 62-64 °C.  $R_f$  (10% EtOAc/Hexane) 0.61.

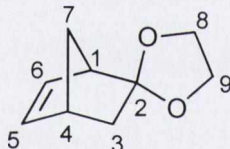
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2975, 2954, 2240, 1581, 1309, 1150, 811.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 1.80-1.85 (m, 1H, H7a), 1.92 (dd,  $J$  = 13.53, 3.66 Hz, 1H, H3a), 2.04-2.10 (m, 1H, H7b), 2.79 (dd,  $J$  = 13.53, 3.66 Hz, 1H, H3b), 3.13 (br s, 1H, H4), 3.52-3.57 (m, 1H, H1), 6.22 (d,  $J$  = 3.19 Hz).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 45.31 (CH<sub>2</sub>, C3), 48.0 (CH<sub>2</sub>, C7), 51.4 (CH, C4), 56.9 (q, C2), 57.0 (CH, C1), 120.5 (q, C8), 129.9 (q, C5), 131.3 (CH, C6)

HRMS: ( $m/z$  - EI) calcd. for C<sub>8</sub>H<sub>7</sub>N<sup>35</sup>Cl<sup>79</sup>Br (M) 230.9450, found 230.9443.

#### 5.5.2.4 Spiro[bicyclo[2.2.1]hept[5]ene-2,2'-[1,3]dioxolane] (**155**)



To a solution of bicyclo[2.2.1]hept-5-en-2-one **31** (1.00 g, 9.23 mmol) in benzene (25 mL), ethylene glycol (1.29 mL, 1.42 g, 23.08 mmol) and *p*-toluenesulfonic acid monohydrate (17 mg, 0.0923 mmol) were added. The reaction mixture was refluxed using a Dean-Stark apparatus until such time as TLC analysis indicated no starting material remained (approximately 16 hours). The reaction mixture was washed with 5% NaHCO<sub>3</sub> (3 x 10 mL). The organic solvent was carefully removed under vacuum to yield a viscous brown oil which was purified by Kugelrohr distillation (50 °C, 20 mbar) to yield Spiro[bicyclo[2.2.1]hept[5]ene-2,2'-[1,3]dioxolane] **155** as a clear oil (480 mg, 35%).  $R_f$  (10% EtOAc/Hexane) 0.39.

IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2965, 2886, 1473, 1162, 1127, 989, 860.

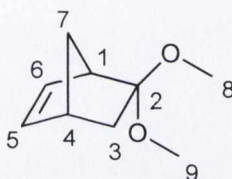
<sup>1</sup>H NMR (CD<sub>3</sub>Cl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 1.46-1.54 (m, 1H, H3a) 1.67-1.80 (m, 2H, H7), 2.18

1.86-1.94 (m, 1H, H3b), 2.68-2.73 (m, 1H, H1),  
2.86-2.90 (m, 1H, H4), 6.13 (dd,  $J = 5.56, 3.26$  Hz,  
CH, H6), 6.36 (dd,  $J = 5.56, 2.88$  Hz, CH, H5)

$^{13}\text{C}$  NMR ( $\text{CD}_3\text{Cl}_3$ , 100 MHz):  $\delta$  (ppm) 40.3 ( $\text{CH}_2$ , C3), 40.9 (CH, C4), 49.1 ( $\text{CH}_2$ , C7),  
49.4 (CH, C1), 64.3 ( $\text{CH}_2$ , C8), 64.8 ( $\text{CH}_2$ , C9),  
133.2 (CH, C6), 139.7 (CH, C5), 118.7 (q, C2)

HRMS: ( $m/z$  - ES) calcd. for  $\text{C}_9\text{H}_{13}\text{O}_2$  ( $\text{M}+\text{H}$ ) $^+$  153.0916, found 153.0917.

#### 5.5.2.5 5,5-Dimethoxybicyclo[2.2.1]hept-2-ene (158)



To a solution of bicyclo[2.2.1]hept-5-en-2-one **31** (2.26 g, 20.93 mmol) and *p*-toluenesulfonic acid monohydrate (20 mg, 0.1 mmol) in anhydrous methanol (4.5 mL) under an argon atmosphere, trimethylorthoformate (4.5 mL, 41.1 mmol) was added dropwise. The reaction mixture was heated to 65 °C and stirred for 16 hours. After this time the organic solvent was carefully removed under vacuum to yield a brown oil which was purified by flash chromatography on silica gel using 95:5 hexane:EtOAc as the eluent to yield 5,5-dimethoxybicyclo[2.2.1]hept-2-ene **158** as a clear oil. (2.19g, 68%).  $R_f$  (10% EtOAc/Hexane) 0.37.

IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 2970, 1379, 1162, 1127, 1049, 951.

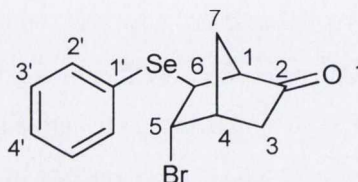
$^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz):  $\delta$  (ppm) 1.24 (dd,  $J = 11.81, 3.32$  Hz, 1H, H3a) 1.56-1.62  
(m, 1H, H7a), 1.71-1.76 (m, 1H, H7b), 1.85 (dd,  $J = 11.81, 4.04$  Hz, 1H, H3b), 2.82 (m, 1H, H1), 2.91  
(br s, 1H, H4), 3.19 (s, 3H, H8), 3.26 (s, 3H, H9),  
6.07 (dd,  $J = 5.85, 2.93$  Hz, 1H, H6), 6.28 (dd,  $J = 5.85, 2.94$  Hz, 1H, H5)



$^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 100 MHz):  $\delta$  (ppm) 39.4 ( $\text{CH}_2$ , C3), 43.0 ( $\text{CH}$ , C1), 49.8 ( $\text{CH}_2$ , C7), 50.3 ( $\text{CH}$ , C4), 50.4 ( $\text{CH}_3$ , C8), 51.1 ( $\text{CH}_3$ , C9), 134.3 ( $\text{CH}$ , C6), 140.1 ( $\text{CH}$ , C5), 112.0 (q, C2)

HRMS: ( $m/z$  - EI) calcd. for  $\text{C}_9\text{H}_{14}\text{O}_2$  (M) 154.0994, found 154.0994.

#### 5.5.2.6 5-*endo*-Bromo-6-*exo*-(phenylselanyl)bicyclo[2.2.1]heptan-2-one (36)



To a solution of phenylselenenyl bromide (18.66 g, 79.09 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (100 mL) cooled to  $-78^\circ\text{C}$ , a solution of 5,5-dimethoxybicyclo[2.2.1]hept-2-ene **158** (11.6 g, 75.3 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (20 mL) cooled to  $-78^\circ\text{C}$  was added. The reaction mixture was allowed to warm slowly from  $-78^\circ\text{C}$  to room temperature over 72 hours. 98:2 THF:  $\text{H}_2\text{O}$  (50 mL) and a few crystals of PTSA were added and the reaction mixture was stirred and left exposed to the atmosphere overnight. The organic solvents were removed under vacuum to give a thick black oil which was purified by flash chromatography on silica gel using a 98:2 to 8:2 hexane:EtOAc as eluent to yield 5-bromo-6-*exo*-(phenylselanyl)bicyclo[2.2.1]heptan-2-one **36** as a pale yellow solid (19.7 g, 76%). M.p.  $65\text{--}68^\circ\text{C}$  (lit.,<sup>296</sup>  $61\text{--}62^\circ\text{C}$ )  $R_f$  (10% EtOAc/Hexane) 0.35.

IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 2975, 1742, 1578, 1479, 1435, 1287, 1255, 1150, 1022, 930.

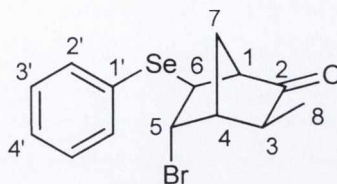
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 1.91-1.98 (m, 1H, H7a), 2.13-2.24 (m, 2H, H7b, H3a), 2.72 (dd,  $J = 18.48, 4.55$  Hz, 1H, H3a), 2.91-2.97 (m, 1H, H1), 2.69 (br s, 1H, H4), 3.43-3.47 (m, 1H, H6), 4.37-4.41 (m, 1H, H5), 7.31-7.38 (m, 3H, H2', H4'), 7.59-7.64 (m, 2H, H3').

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 35.2 ( $\text{CH}_2$ , C7), 41.0 ( $\text{CH}_2$ , C3), 43.4 ( $\text{CH}$ , C1), 47.7 ( $\text{CH}$ , C6), 55.8 ( $\text{CH}$ , C5), 57.0 ( $\text{CH}$ , C4), 128.1 (q, C1'), 128.6 (Ar, C4'), 129.6 (Ar, C2'), 134.8 (Ar, C3'), 212.4 (q, C2).



HRMS: ( $m/z$  - EI) calcd. for  $C_{13}H_{13}O^{80}Se^{79}Br$  (M) 344.9315, found 344.9320.

5.5.2.7 3-*exo*-5-*endo*-Bromo-6-*exo*-(phenylselanyl)bicyclo[2.2.1]heptan-2-one (161)



Prepared as per general procedure K using a solution of 5-bromo-6-*exo*-(phenylselanyl)bicyclo[2.2.1]heptan-2-one **36** (17.6 g, 51.16 mmol) in THF (50 mL), sodium bis(trimethylsilyl)amide (1 M in THF, 77.00 mL, 77.00 mmol) and iodomethane (9.56 mL, 21.8 g, 153.48 mmol) to give a thick pale yellow oil which was absorbed onto silica and purified by flash chromatography on silica gel using a 95:5 hexane:EtOAc to 8:2 hexane:EtOAc gradient to yield 3-*exo*-5-*endo*-bromo-6-*exo*-(phenylselanyl)bicyclo[2.2.1]heptan-2-one **161** as a white solid. (14.4 g, 78%). M.p. 69-70 °C  $R_f$  (10% EtOAc/Hexane) 0.33.

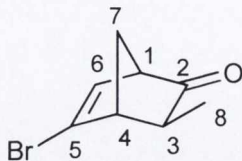
IR  $\nu_{\max}$  ( $cm^{-1}$ ): 3475, 2975, 2876, 1741, 1578, 1478, 1149, 725.

$^1H$  NMR ( $CDCl_3$ , 400 MHz):  $\delta$  (ppm) 1.15 (d,  $J$  = 7.59 Hz, 3H, H8), 1.96-2.02 (m, 1H, H7a), 2.08-2.20 (m, 3H, H3, H7b), 2.45-2.48 (m, 1H, H4), 2.88-2.91 (m, 1H, H1), 3.64-3.67 (m, 1H, H5), 4.30-4.33 (m, 1H, H6), 7.32-7.39 (m, 3H, H2', H4'), 7.62-7.69 (m, 2H, H3').

$^{13}C$  NMR ( $CDCl_3$ , 100 MHz):  $\delta$  (ppm) 14.5 ( $CH_3$ , H8), 33.2 ( $CH_2$ , C7), 48.1 ( $CH$ , C3), 48.7 ( $CH$ , C4), 49.0 ( $CH$ , C6), 53.4 ( $CH$ , C5), 57.8 ( $CH$ , C1), 128.3 (Ar, C4'), 128.6 (q, C1'), 129.5, (Ar, C2'), 134.6, Ar, C3'), 213.7 (q, C2).

HRMS: ( $m/z$  - ES) calcd. for  $C_{14}H_{15}O^{79}Br^{80}SeNa$  ( $M+Na$ ) $^+$  380.9369, found 380.9360.

### 5.5.2.8 5-Bromo-3-*exo*-methylbicyclo[2.2.1]hept-5-en-2-one (165)



Prepared as per general procedure J using 3-*exo*-5-*endo*-bromo-6-*exo*-(phenylselanyl)bicyclo[2.2.1]heptan-2-one **161**, (2.00g, 5.58 mmol), hydrogen peroxide (30% solution in H<sub>2</sub>O, 1.37 mL, 410 mg, 12.06 mmol), acetic acid (410  $\mu$ L, 7.17 mmol) and THF (15 mL) to give a brown solid that was purified by flash chromatography on silica gel using 95:5 hexane:EtOAc as eluent to yield 5-bromo-3-*exo*-methylbicyclo[2.2.1]hept-5-en-2-one **165** as a white solid (1.11 g, 97%). M.p. 70-73 °C *R<sub>f</sub>* (10% EtOAc/Hexane) 0.44.

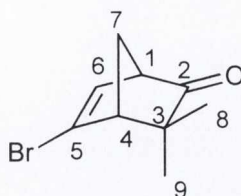
IR  $\nu_{\text{max}}$  (cm<sup>-1</sup>): 2975, 2937, 1742, 1478, 1149, 929, 726.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 1.17 (d, *J* = 7.52 Hz, 3H, H8), 2.06 (dq, *J* = 7.52, 3.34 Hz, 1H, H3), 2.10-2.16 (m, 1H, H7a), 2.26-2.32 (m, 1H, H7b), 2.82 (br s, 1H, H4), 3.00-3.04 (m, 1H, H1), 6.10-6.13 (m, 1H, H6).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 15.3 (CH<sub>3</sub>, C8), 39.2 (CH, C3), 45.9 (CH<sub>2</sub>, C7), 54.2 (CH, C4), 56.9 (CH, C1), 129.5 (CH, C6), 134.5 (q, C5), 214.8 (q, C2).

HRMS: (*m/z* - CI) calcd. for C<sub>8</sub>H<sub>10</sub>O<sup>79</sup>Br (M+H)<sup>+</sup> 200.9915, found 200.9909.

### 5.5.2.9 5-Bromo-3,3-dimethylbicyclo[2.2.1]hept-5-en-2-one (166)



Prepared as per general procedure K using 5-bromo-3-*exo*-methylbicyclo[2.2.1]hept-5-en-2-one **165** (7.50 g, 37.32 mmol) in anhydrous THF (120 mL), sodium bis(trimethylsilyl)amide (1.9M in THF, 65 mL, 143.73 mmol) and iodomethane (11.62 mL, 186.60 mmol) to yield a pale yellow oil that was purified by flash chromatography on silica gel using 95:5 hexane:EtOAc as eluent to yield 5-bromo-3,3-dimethylbicyclo[2.2.1]hept-5-en-2-one **166** as a white solid (6.3 g, 79%). M.p. 74-75 °C  $R_f$  (10% EtOAc/Hexane) 0.45.

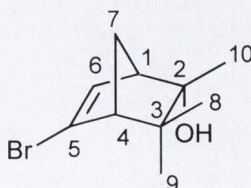
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2974, 1743, 1577, 1477, 1150, 727, 691.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 1.18 (s, 3H, H8), 1.23 (s, 3H, H9), 2.10-2.16 (m, 1H, H7a), 2.37-2.41 (m, 1H, H7b), 2.81-2.84 (br s, 1H, H4), 3.06-3.10 (m, 1H, H1), 6.17-6.21 (m, 1H, H6).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 24.0 (CH<sub>3</sub>, C9), 24.4 (CH, C8), 43.1 (q, C3), 48.1 (CH<sub>2</sub>, C7), 57.3 (CH, C1), 58.4 (CH, C4), 129.4 (CH, C6), 133.7 (q, C5), 217.5 (q, C2).

HRMS: ( $m/z$  - CI) calcd. for C<sub>11</sub>H<sub>16</sub>O<sup>79</sup>Br (M+C<sub>2</sub>H<sub>5</sub>)<sup>+</sup> 243.0385, found 243.0296.

### 5.5.2.10 5-Bromo-2-*exo*-,3,3-trimethylbicyclo[2.2.1]hept-5-en-2-ol (167)





Prepared as per general procedure L using 5-bromo-3,3-dimethylbicyclo[2.2.1]hept-5-en-2-one **166** (6.20 g, 28.84 mmol), THF (100 mL) and methylmagnesium bromide (3 M in THF, 19.3 mL, 58.0 mmol) to give a brown solid that was purified by flash chromatography on silica gel using 97:3 hexane:EtOAc as eluent to yield 5-bromo-2-*exo*-,3,3-trimethylbicyclo[2.2.1]hept-5-en-2-ol **167** as a clear viscous oil (5.1 g, 76%).  $R_f$  (20% EtOAc/Hexane) 0.43.

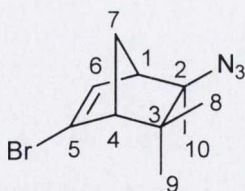
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3476, 2966, 1743, 1477, 1151, 932.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 1.06 (s, 3H, H8), 1.16 (s, 3H, H9), 1.39 (s, 3H, H10), 1.69-1.73 (m, 1H, H7a), 1.75-1.79 (m, 1H, H7b), 2.48 (br s, 1H, H4), 2.70-2.74 (m, 1H, H1), 6.29 (d,  $J = 3.34$  Hz, 1H, H6).

<sup>13</sup>C NMR (DCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 23.3 (CH<sub>3</sub>, C8), 25.4 (CH<sub>3</sub>, C10), 27.5 (CH<sub>3</sub>, C9), 45.5 (q, C3), 45.8 (CH<sub>2</sub>, C7), 57.8 (CH, C1), 62.8 (CH, C4), 80.4 (q, C2), 129.8 (q, C5), 132.8 (CH, C6).

HRMS: ( $m/z$  - Cl) calcd. for C<sub>10</sub>H<sub>14</sub><sup>79</sup>Br (M+H-H<sub>2</sub>O)<sup>+</sup> 213.0279, found 213.0280.

#### 5.5.2.11 5-Azido-2-bromo-5-*endo*-,6,6-trimethylbicyclo[2.2.1]hept-2-ene (**168**)



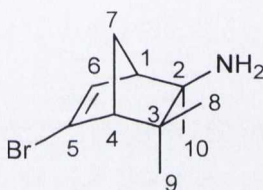
Prepared as per general procedure E using 5-bromo-2-*exo*-,3,3-trimethylbicyclo[2.2.1]hept-5-en-2-ol **167** (5.10 g, 22.08 mmol), 60% H<sub>2</sub>SO<sub>4</sub> (200 mL), sodium azide (12.50 g, 192.31 mmol) and CHCl<sub>3</sub> (200 mL). The reaction was stirred for 16 hours and purified by flash chromatography on silica gel using 100% hexane as the eluent to yield 5-Azido-2-bromo-5-*endo*-,6,6-trimethylbicyclo[2.2.1]hept-2-ene **168** and a small amount (<10%) inseparable impurity believed to be the Wagner-Meerwein rearranged azide as a clear oil. (2.88 g, 50%)  $R_f$  (100% Hexane) 0.55.

IR  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 2966, 2090, 1574, 1437, 1288, 1035, 949.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 1.07 (s, 3H, H9), 1.22 (s, 3H, H8), 1.30 (s, 3H, H10), 1.76-1.80 (m, 1H, H7a), 2.00-2.04 (m, 1H, H7b), 2.43 (br s, 1H, H4), 2.72 (br s, 1H, H1), 6.17 (d,  $J = 3.47$  Hz, 1H, H6).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (pp) 20.6 ( $\text{CH}_3$ , C10), 25.0 ( $\text{CH}_3$ , C8), 26.9 ( $\text{CH}_3$ , C9), 45.9 (q, C3), 46.0 ( $\text{CH}_2$ , C7), 55.7 (CH, C1), 62.7 (CH, C4), 71.4 (q, C2), 130.1 (q, C5), 132.3 (CH, C6).

#### 5.5.2.12 5-Bromo-2-*endo*-,3,3-trimethylbicyclo[2.2.1]hept-5-en-2-amine (169)



Prepared as per general procedure G using 5-Azido-2-bromo-5-*endo*-,6,6-trimethylbicyclo[2.2.1]hept-2-ene **168** (700 mg, 2.73 mmol) that contains approx 10% impurity, tributylphosphine (1.367 mL, 1.11 g, 5.47 mmol), THF (20 mL),  $\text{H}_2\text{O}$  (490  $\mu\text{L}$ , 27.3 mmol) and hydrogen chloride solution (2 M in diethyl ether, 2 mL, 4 mmol) to yield the hydrochloride salt of the desired amine. This was purified by flash chromatography on silica gel using 99:1 to 95:5 EtOAc:methanol as eluent. The free amine was obtained by extraction with  $\text{CH}_2\text{Cl}_2$  (2 x 20 mL) from 1 M NaOH (20 mL). The organic solvent was dried over  $\text{MgSO}_4$  and removed under vacuum to yield 5-bromo-2-*endo*-,3,3-trimethylbicyclo[2.2.1]hept-5-en-2-amine **169** as a clear viscous oil (410 mg, 65%).

IR  $\nu_{\max}$  ( $\text{cm}^{-1}$ ): 2959, 2732, 1583, 1466, 1387, 1293, 1004.

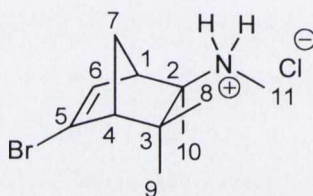


$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 1.05 (s, 3H, H9), 1.08 (s, 3H, H10), 1.39 (s, 3H, H8), 1.74-1.78 (m, 1H, H7a), 1.94-1.98 (m, 1H, H7b), 2.41 (br s, 1H, H4), 2.45 (br s, 1H, H1), 6.21 (d,  $J = 3.28$  Hz, 1H, H6).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 24.5 ( $\text{CH}_3$ , C9), 25.5 ( $\text{CH}_3$ , C10), 26.2 ( $\text{CH}_3$ , C8), 43.5 (q, C3), 45.0 ( $\text{CH}_2$ , C7), 58.4 (CH, C1), 60.2 (q, C2), 62.4 (CH, C4), 127.3 (q, C5), 133.9 (CH, C6).

HRMS: ( $m/z$  - ES) calcd. for  $\text{C}_{10}\text{H}_{17}\text{N}^{79}\text{Br}$  ( $\text{M}+\text{H}$ ) $^+$  230.0544, found 230.0546.

#### 5.5.2.13 5-Bromo-*N*,2-*endo*-3,3-tetramethylbicyclo[2.2.1]hept-5-en-2-amine (170)



Prepared as per general procedure I using 5-bromo-2-*endo*-3,3-trimethylbicyclo[2.2.1]hept-5-en-2-amine **169** (173 mg, 0.75 mmol), paraformaldehyde (135 mg, 4.5 mmol), molecular sieves (200 mg), anhydrous  $\text{CH}_2\text{Cl}_2$  (10 mL) and sodium borohydride (150 mg, 3.95 mmol) the desired amine. The hydrochloride salt of 5-bromo-*N*,2-*endo*-3,3-tetramethylbicyclo[2.2.1]hept-5-en-2-amine **170** was formed by the addition of hydrogen chloride solution (2M in diethyl ether, 750  $\mu\text{L}$ , 1.5 mmol) and evaporation of the solvent. (164 mg, 77%). M.p. 180-185  $^\circ\text{C}$  (decomposes).

IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 2928, 2733, 1587, 1478, 1427, 1383, 1103, 882.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 1.15 (s, 3H, H9), 1.29 (s, 3H, H10), 1.62 (s, 3H, H8), 1.86-1.93 (m, 1H, H7a), 1.43-1.48 (m, 1H, H7b), 2.53 (br s, 1H, H4), 2.74 (t,  $J = 4.90$  Hz, 3H, H11), 3.13 (br s, 1H, H1), 6.20 (d,  $J = 3.35$  Hz, 1H, H6).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 18.2 ( $\text{CH}_3$ , C10), 25.0 ( $\text{CH}_3$ , C9), 26.0 ( $\text{CH}_3$ , C8),

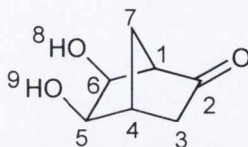


29.0 (CH<sub>3</sub>, C11), 45.0 (CH<sub>2</sub>, C7), 45.5 (q, C3), 52.0 (CH, C1), 62.9 (CH, C4), 69.4 (q, C2), 129.7 (q, C5), 131.7 (CH, C6).

HRMS: (*m/z* - ES) calcd. for C<sub>11</sub>H<sub>19</sub>N<sup>79</sup>Br (M+H)<sup>+</sup> 244.0701, found 244.0692.

### 5.5.3 5,6-disubstituted mecamylamine analogue

#### 5.5.3.1 5-*exo*,6-*exo*-Dihydroxybicyclo[2.2.1]heptan-2-one (41)



Bicyclo[2.2.1]hept-5-en-2-one **31** (500 mg, 4.63 mmol) and *N*-methylmorpholine (651 mg, 5.56 mmol) were dissolved in a THF/H<sub>2</sub>O 9/1 mixture (15 mL). The reaction vessel was cooled to -10 °C. A 4% solution of OsO<sub>4</sub> in H<sub>2</sub>O (229 μL, 0.036 mmol) was added. After stirring for 48 hours, TLC analysis showed no starting material remained. The solvents were removed under vacuum to yield a brown oil. This oil was purified on silica gel using a 75:25 EtOAc:hexane eluent to yield 5-*exo*,6-*exo*-dihydroxybicyclo[2.2.1]heptan-2-one **41** as a white solid (434 mg, 3.05 mmol, 66%). M.p. 153-156 °C *R<sub>f</sub>* (10% EtOAc/Hexane) 0.36.

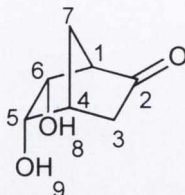
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3378, 2920, 1739, 1155, 1053, 933, 657

<sup>1</sup>H NMR ((CD<sub>3</sub>)<sub>2</sub>SO, 400 MHz):  $\delta$  (ppm) 1.55-1.60 (m, 1H, H7a), 1.711 (dd, *J* = 18.09, 4.09 Hz, 1H, H3a) 1.98-2.10 (m, 2H, H7b, H3b), 2.33 (br s, m, 1H, H1), 2.40-2.45 (m, 1H, H4), 3.68-3.73 (m, 1H, H6), 3.79-3.84 (m, 1H, H5), 4.90 (d, *J* = 5.48 Hz, 1H, H8), 4.97 (d, *J* = 5.09 Hz, 1H, H9).

<sup>13</sup>C (400 MHz, (CD<sub>3</sub>)<sub>2</sub>SO): 31.5 (CH<sub>2</sub>, C7), 41.5 (CH<sub>2</sub>, C3), 42.8 (CH, C4) 58.8 (CH, C1) 68.83 (CH, C6), 72.45 (CH, C5), 215.6 (q, C2).

HRMS: (*m/z* - ES) calcd. for C<sub>7</sub>H<sub>10</sub>O<sub>3</sub> (M+Na)<sup>+</sup> 165.0528, found 165.0520.

### 5.5.3.2 5-*endo*,6-*endo*-Dihydroxybicyclo[2.2.1]heptan-2-one (171)



Bicyclo[2.2.1]hept-5-en-2-one **31** (500 mg, 4.63 mmol) and *N*-methylmorpholine (651 mg, 5.56 mmol) were dissolved in a THF/H<sub>2</sub>O 9/1 mixture (15 mL). A 4% solution of OsO<sub>4</sub> in H<sub>2</sub>O (229 μL, 0.036 mmol) was added. After stirring for 2 hours, TLC analysis showed no starting material remained. The solvents were removed under vacuum to yield a brown oil, an equal mixture of *exo* and *endo* diastereomers. This oil was purified on silica gel using a 50:50 EtOAc:hexane eluent to yield 5-*exo*,6-*exo*-dihydroxybicyclo[2.2.1]heptan-2-one **41** as a white solid (198 mg, 1.39 mmol, 30%) and 5-*endo*,6-*endo*-Dihydroxybicyclo[2.2.1]heptan-2-one **171** as a white solid (189 mg, 1.33 mmol, 28.7%) M.p. 140-144 °C. *R<sub>f</sub>* (10% EtOAc/Hexane) 0.29.

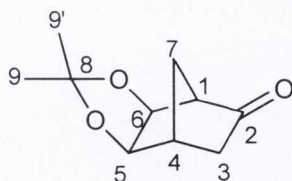
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3393, 3026, 1742, 1408, 1287, 1133, 929, 760.

<sup>1</sup>H NMR ((CD<sub>3</sub>)<sub>2</sub>SO, 400 MHz):  $\delta$  (ppm) 1.56-1.61 (m, 1H, H7), 1.701 (dd, *J* = 17.76, 4.17 Hz, 1H, H3a) 1.93-2.05 (m, 2H, H7, H3b), 2.28-2.33 (m, 1H, H4), 2.44-2.48 (m, 1H, H1), 3.46 – 3.49 (m, 1H, H6), 3.81-3.86 (m, 1H, H5), 5.09 (d, *J* = 3.96 Hz, 1H, H8), 5.05 (d, *J* = 5.09 Hz, 1H, H9)

<sup>13</sup>C NMR ((CD<sub>3</sub>)<sub>2</sub>SO, 100 MHz):  $\delta$  (ppm) 32.8 (CH<sub>2</sub>, C7), 40.3 (CH<sub>2</sub>, C3), 42.5 (CH, C4) 56.4 (CH, C1) 79.6 (CH, C5), 79.6 (CH, C6), 213.9 (q, C2)

HRMS: (*m/z* - ES) calcd. for C<sub>7</sub>H<sub>10</sub>O<sub>3</sub>Na (M+Na)<sup>+</sup> 165.0528, found 165.0529.

### 5.5.3.3 5-*exo*,6-*exo*-(Isopropylidenedioxy)bicyclo[2.2.1]-heptan-2-one (42)



5-*exo*,6-*exo*-dihydroxybicyclo[2.2.1]heptan-2-one **41** (1.00 g, 7.04 mmol) was dissolved in benzene (50 mL) in an oven dried RBF. To this was added PTSA (20 mg, 0.1 mmol) and anhydrous acetone (2.57 mL, 35.00 mmol). The reaction was refluxed for 16 hours using a Dean-Stark apparatus. The organic solvent was removed under vacuum and the thick black oil was absorbed onto silica gel. Purification by flash chromatography eluting with 9:1 hexane: EtOAc yielded 5-*exo*,6-*exo*-(isopropylidenedioxy)bicyclo[2.2.1]-heptan-2-one **42** as a white solid (722 mg, 56.3%). M.p. 79-80 °C  $R_f$  (20% EtOAc/Hexane) 0.40.

IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2981, 1747, 1377, 1152, 1049, 944.

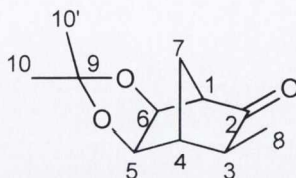
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 1.36 (s, CH<sub>3</sub>, 3H, H<sub>9</sub>), 1.53 (s, CH<sub>3</sub>, 3H, H<sub>9'</sub>), 1.66-1.76 (m, 2H, H<sub>3a</sub>, H<sub>7a</sub>), 2.07-2.21 (m, 2H, H<sub>3b</sub>, H<sub>7b</sub>), 2.73-2.78 (m, 2H, H<sub>1</sub>, H<sub>4</sub>), 4.28-4.33 (m, 1H, H-5), 4.34-4.38 (m, 1H, H-6)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 24.2 (CH<sub>3</sub>, C<sub>9</sub>), 25.3 (CH<sub>3</sub>, C<sub>9'</sub>), 31.2 (CH<sub>2</sub>, C<sub>7</sub>), 39.4 (CH<sub>2</sub>, C<sub>3</sub>), 39.5 (CH, C<sub>4</sub>) 55.4 (CH, C<sub>1</sub>) 76.9 (CH, C<sub>5</sub>), 81.3 (CH, C<sub>6</sub>), 111.3 (q, C<sub>8</sub>), 214.4 (q, C<sub>2</sub>)

HRMS: ( $m/z$  - ES) calcd. for C<sub>10</sub>H<sub>15</sub>O<sub>3</sub> (M+H)<sup>+</sup> 183.1021, found 183.1020.



5.5.3.4 **3-*exo*-Methyl-5-*exo*,6-*exo*-(Isopropylidenedioxy)bicyclo[2.2.1]heptan-2-one**  
(173)



To a solution of freshly distilled diisopropylamine (8.06 mL, 57.07 mmol) in anhydrous THF (120) cooled to -78 °C, a 2.5 M solution of *n*-butyllithium in hexane (21.4 mL, 53.51 mmol) was added. The reaction mixture was allowed to warm to 0 °C. A solution of 5-*exo*,6-*exo*-(isopropylidenedioxy)bicyclo[2.2.1]-heptan-2-one **42** (6.5 g, 35.67 mmol) in anhydrous THF (30mL) was then added dropwise. After stirring for 2 hours at 0 °C, iodomethane (6.67 mL, 107.02 mmol) was added dropwise. After stirring for 2 hours at room temperature, 10% NH<sub>4</sub>Cl (100 mL) was added. The product was extracted using diethyl ether (2 x 200mL), washed with brine (100 mL) and dried over MgSO<sub>4</sub>. The solvent was evaporated at reduced pressure to yield 3-*exo*-methyl-5-*exo*,6-*exo*-(isopropylidenedioxy)bicyclo[2.2.1]heptan-2-one **173** as a white solid. (6.5g, 93%). M.p. 77-78 °C *R<sub>f</sub>* (20% EtOAc/Hexane) 0.42.

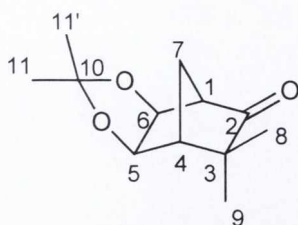
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2969, 2942, 1742, 1374, 1151, 1021, 850.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 0.96 (d, *J*=7.54 Hz, 3H, H8), 1.17 (s, 3H, H10), 1.33 (s, 3H, H10'), 1.69 (dq, *J*= 7.54, 3.5 Hz, 1H, H8) 1.59-1.64 (m, 1H, H7a), 1.88-1.94 (m, 1H, H7b), 2.25 (br s, 1H, H1), 2.51 (br s, 1H, H4), 4.10-4.13 (m, 1H, H5), 4.16-4.19 (m, 1H H6).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 14.1 (CH<sub>3</sub>, C8), 24.2 (CH<sub>3</sub>, C10), 25.3 (CH<sub>3</sub>, C10'), 28.3 (CH<sub>2</sub>, C7), 42.7 (CH<sub>2</sub>, C3), 45.7 (CH, C1) 55.2 (CH, C4) 76.7 (CH, C5), 81.5 (CH, C6), 111.2 (q, C9), 217 (q, C2)

HRMS: (*m/z* - ES) calcd. for C<sub>11</sub>H<sub>17</sub>O<sub>3</sub> (M+H)<sup>+</sup> 197.1178, found 197.1177.

### 5.5.3.5 3,3-Dimethyl-5-*exo*,6-*exo*-(isopropylidenedioxy)bicyclo[2.2.1]heptan-2-one (174)



3-*exo*-methyl-5-*exo*,6-*exo*-(isopropylidenedioxy)bicyclo[2.2.1]heptan-2-one **173** (6.4 g, 32.61 mmol) was added to a 1.9 M solution of sodium bis(trimethylsilyl)amide in THF (30.43 mL, 57.82 mmol) in anhydrous THF (120 mL) cooled to  $-78^{\circ}\text{C}$ . After stirring for 2 hours at  $0^{\circ}\text{C}$ , iodomethane (7.58 mL, 121.72 mmol) was added dropwise. After stirring for 2 hours at room temperature, 10%  $\text{NH}_4\text{Cl}$  (100 mL) was added. The product was extracted using diethyl ether (2 x 200 mL), washed with brine (100 mL) and dried over  $\text{MgSO}_4$ . The solvent was evaporated at reduced pressure to give a pale yellow oil which was purified by flash chromatography using 95:5 hexane:EtOAc as the eluent to furnish 3,3-dimethyl-5-*exo*,6-*exo*-(isopropylidenedioxy)bicyclo[2.2.1]heptan-2-one **174** as a white solid. (6.4 g, 93%). M.p.  $89-91^{\circ}\text{C}$   $R_f$  (20% EtOAc/Hexane) 0.43.

IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 2973, 1743, 1373, 1265, 1034, 945, 840.

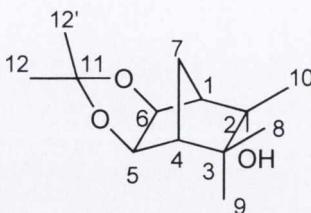
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  (ppm) 0.99 (s, 3H, H9), 1.14 (s, 3H, H8), 1.35 (s, 3H, H11), 1.51 (s, 3H, H11'), 1.86-1.91 (m, 1H, H7a), 2.06-2.11 (m, 1H, H7b), 2.36 (br s, 1H, H4), 2.70 (br s, 1H, H1), 4.27-4.31 (m, 1H, H6), 4.65-4.69 (m, 1H, H5).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  (ppm) 20.3 ( $\text{CH}_3$ , C9), 24.16 ( $\text{CH}_3$ , C8), 24.19 ( $\text{CH}_3$ , C11), 25.3 ( $\text{CH}_3$ , C11'), 28.6 ( $\text{CH}_2$ , C7), 44.6 (q, C3) 49.8 (CH, C4) 56.4 (CH, C1) 77.2 (CH, C6), 78.3 (CH, C5), 110.9 (q, C10), 218.9 (q, C2).

HRMS: ( $m/z$  - ES) calcd. for  $\text{C}_{12}\text{H}_{18}\text{O}_3$  ( $\text{M}+\text{Na}$ ) $^{+}$  233.1154, found 233.1149.



5.5.3.6 **2-*exo*-3,3-Trimethyl-5-*exo*,6-*exo*-(isopropylidenedioxy)bicyclo[2.2.1]heptan-2-ol (175)**



3,3-Dimethyl-5-*exo*,6-*exo*-(isopropylidenedioxy)bicyclo[2.2.1]heptan-2-one **174** (6.3 g, 29.96 mmol) was added dropwise to a solution of 3 M methylmagnesiumbromide in diethyl ether (15 mL, 45 mmol) in anhydrous THF (100mL) at -78 °C. The reaction mixture was allowed to warm to room temperature and then stirred at 30 °C for 3 hours. TLC analysis indicated no starting material remained after this time. The reaction mixture was cooled to -10 °C and 10% NH<sub>4</sub>Cl (100mL) was added with extreme care. The product was extracted using diethyl ether (2 x 100mL), washed with brine (100mL) and dried over MgSO<sub>4</sub>. The solvent was evaporated at reduced pressure to yield a yellow solid which was purified by flash chromatography using 50:50 hexane:EtOAc as the eluent. 2-*exo*-3,3-Trimethyl-5-*exo*,6-*exo*-(isopropylidenedioxy)bicyclo[2.2.1]heptan-2-ol **175** was obtained as a white solid (5.95 g, 86%). M.p. 145-146 °C *R<sub>f</sub>* (40% EtOAc/Hexane) 0.29.

IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3475, 2972, 1483, 1371, 1266, 1204, 1157, 1029, 881.

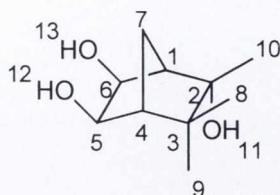
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  (ppm) 0.96 (s, 3H, H9), 1.04 (s, 3H, H8), 1.31 (s, 3H, H10), 1.34 (s, 3H, H12), 1.45-1.50 (m, 4H, H12', H7), 1.61-1.67 (m, 1H, H7), 1.85 (br s, 1H, H1), 2.09 (br s, 1H, H4), 4.54-4.58 (m, 1H, H6), 4.75-4.79 (m, 1H, H5).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  (ppm) 20.6 (CH<sub>3</sub>, C9), 24.2 (CH<sub>3</sub>, C12), 25.5 (CH<sub>3</sub>, C12'), 27.0 (CH<sub>3</sub>, C10), 27.3 (CH<sub>3</sub>, C8), 27.8 (CH<sub>2</sub>, C7), 41.1 (q, C3), 53.2 (CH, C1), 54.8 (CH, C4), 76.8 (CH, C5), 77.3 (q, C2), 77.9 (CH, C6), 108.0 (q, C11).



HRMS: ( $m/z$  - EI) calcd. for  $C_{13}H_{22}O_3$  (M) 226.1569, found 226.1558.

5.5.3.7 2-*exo*-3,3-Trimethylbicyclo[2.2.1]heptane-2,5-*exo*-6-*exo*-triol (176)



2-*exo*-3,3-Trimethyl-5-*exo*,6-*exo*-(isopropylidenedioxy)bicyclo[2.2.1]heptan-2-ol **175** (800 mg, 3.53 mmol) was added to a 9:1 acetic acid:H<sub>2</sub>O solution (15 mL) in a RBF open to the atmosphere. The reaction mixture was heated to 58 °C and stirred for 16 hours in order to facilitate the removal of acetone formed. After this time TLC analysis showed no starting material remained. The organic solvent was removed under vacuum. The residue was dissolved in EtOAc (20 mL) and dried over MgSO<sub>4</sub>. The solvent was removed under vacuum to yield a thick black oil which was purified by flash chromatography on silica gel using 100% EtOAc as the eluent to yield 2-*exo*-3,3-trimethylbicyclo[2.2.1]heptane-2,5-*exo*-,6-*exo*-triol **176** as a white solid (466 mg, 71%). M.p. 162-166 °C.  $R_f$  (100% EtOAc) 0.15.

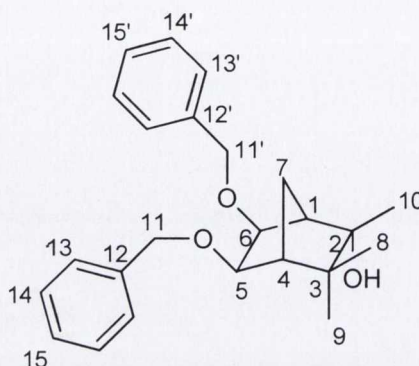
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3459, 3331, 3272, 2963, 1477, 1263, 1127, 1041.

<sup>1</sup>H NMR ((CD<sub>3</sub>)<sub>2</sub>SO, 400 MHz):  $\delta$  (ppm) 0.80 (s, 3H, H8), 0.88 (s, 3H, H9), 1.11 (s, 3H, H10) 1.36-1.43 (m, 1H, H7), 1.46-1.53 (m, 2H, H7, H4), 1.66 (br s, 1H, H1), 3.90-3.95 (m, 1H, H5), 4.09 (s, OH, H11), 4.20-4.26 (m, 1H, H6), 4.37 (d,  $J$  = 5.78 Hz, OH, H13), 4.39 (d,  $J$  = 5.03 Hz, OH, H12).

<sup>13</sup>C NMR ((CD<sub>3</sub>)<sub>2</sub>SO, 100 MHz):  $\delta$  (ppm) 21.7 (CH<sub>3</sub>, C8), 26.6 (CH<sub>3</sub>, C10), 27.5 (CH<sub>3</sub>, C9), 28.1 (CH<sub>2</sub>, C7), 41.0 (q, C3) 56.8 (CH, C4) 58.5 (CH, C1) 67.6 (CH, C6), 69.1 (CH, C5).75.96 (q, C2).

HRMS: ( $m/z$  - ES) calcd. for  $C_{10}H_{18}O_3Na$  ( $M+Na$ )<sup>+</sup> 209.1154, found 209.1161.

5.5.3.8 2-*exo*-3,3-Trimethyl-5-*exo*-,6-*exo*-bis(benzyloxy)bicyclo[2.2.1]heptan-2-ol (**183**)



2-*exo*-3,3-Trimethylbicyclo[2.2.1]heptane-2,5-*exo*-,6-*exo*-triol **176** (200 mg, 1.07 mmol) was dissolved in anhydrous THF (5 mL) and syringed into a solution of pure sodium hydride (129 mg, 5.37 mmol) in anhydrous THF (10 mL). Effervescence was observed. After stirring for 1 hour at room temperature, the reaction mixture was cooled to -78 °C. Benzyl bromide (255  $\mu$ L, 2.15 mmol) was added dropwise and the reaction allowed to warm to room temperature over 16 hours. 10%  $NH_4Cl$  (10mL) was then added slowly. The product was extracted using diethyl ether (2 x 20mL), washed with brine (10mL) and dried over  $MgSO_4$ . The solvent was evaporated at reduced pressure to yield a yellow oil which was purified by flash chromatography using 9:1 hexane:EtOAc as the eluent to yield 2-*exo*-3,3-trimethyl-5-*exo*-,6-*exo*-bis(benzyloxy)bicyclo[2.2.1]heptan-2-ol **183** as a white solid. (279 mg, 71%). M.p. 157-159 °C  $R_f$  (20% EtOAc/Hexane) 0.45.

IR  $\nu_{max}$  ( $cm^{-1}$ ): 3472, 2966, 1483, 1370, 1205, 1029, 880, 762.

$^1H$  NMR ( $CDCl_3$ , 400 MHz):  $\delta$  (ppm) 0.89 (s, 3H, H8), 1.01 (s, 3H, H9), 1.28 (s, 3H, H10), 1.57-1.64 (m, 1H, H7), 1.90 (br s, 1H, H4), 1.96-2.02 (m, 1H, H7), 2.13 (br s, 1H, H1), 4.56-4.70 (m, 4H, H11, H11') 4.02-4.08 (m, 1H, H6), 4.30-4.36 (m, 1H, H5), 7.24-7.44 (m, 10H, H13, H14, H15, H13', H14', H15')

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ (ppm)

20.6 (CH<sub>3</sub>, C8), 26.3 (CH<sub>3</sub>, C10), 26.6 (CH<sub>3</sub>, C9),  
29.3 (CH<sub>2</sub>, C7), 41.1 (q, C3) 54.0 (CH, C4) 55.5  
(CH, C4) 71.9 (CH<sub>2</sub>, C11), 72.1 (CH<sub>2</sub>, C11'), 76.6  
(CH, C5), 77.1 (q, C2), 77.6 (CH, C6), 108.0 (q,  
C11), 126.88, 126.93 (Ar, C13, C13'), 127.4, 127.5  
(Ar, C14, C14'), 127.8 (Ar, C15), 138.5, 138.6 (q,  
C12, C12').





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