NEW ASPECTS OF ACID-CATALYSED CYCLISATIONS

ABDUL HADI ALDMAIRI

A Thesis Submitted for the Degree of Doctor of Philosophy

At
Cardiff University

2014
Declaration
This work has not previously been accepted in substance for any degree and is not being concurrently submitted for candidature for any degree.

Signed …………………………………………………… (Abdul Hadi Admairi)

Date…………………………………………………………

STATEMENT 1
This thesis is the result of my own investigations, except where otherwise stated. Other sources are acknowledged by footnotes giving explicit references. A bibliography is appended.

Signed …………………………………………………… (Abdul Hadi Admairi)

Date…………………………………………………………

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Signed …………………………………………………… (Abdul Hadi Admairi)

Date…………………………………………………………
Abstract

This thesis describes the use of both sulfuric acid and triflic acid, to promote hydroamination and hydroalkoxylation cyclisations for the formation of N- and O-heterocycles.

Chapter 2 describes the synthesis of 2,2,6-trisubstituted piperidine. A wide range of protecting groups has been employed in the cyclisation. A new, general and flexible method for the highly enantioselective synthesis of chiral piperidine and spiro-piperidine has been developed. The main advantages of this synthetic method lie in the readily availability of the precursors. There is no reason why this reaction cannot find further application in natural product synthesis.

Chapter 3 describes a miscellany of cascade and transannular cyclizations. The hydroamination has also been used to form the sterically crowded bridged isoquinuclidines through a transannular cyclisation, which would have rearranged to the less hindered products.

We have also applied acid-catalyzed intramolecular cascade methodology to the synthesis of polycyclic hydroquinolines.

Oxygen-centered transannular cyclisation has been compared with nitrogen-based examples, by acid-catalyzed hydroalkoxylation cyclisation to give only the sterically crowded bridged cineoles.

Chapter 4 describes a new discovery of a novel $N$-to-$O$ transfer reaction.
Acknowledgements

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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>app.</td>
<td>apparent</td>
</tr>
<tr>
<td>aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aromatic</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>b.p.</td>
<td>boiling point</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>CI</td>
<td>chemical ionisation</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>dd</td>
<td>double doublet</td>
</tr>
<tr>
<td>dt</td>
<td>double triplet</td>
</tr>
<tr>
<td>DEPT</td>
<td>Distortionless Enhancement by Polarization Transfer</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>e.e.</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>electron ionisation</td>
</tr>
<tr>
<td>eq.</td>
<td>equivalent(s)</td>
</tr>
<tr>
<td>ES</td>
<td>electrospray</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>ether</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Δ</td>
<td>heat</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>IR</td>
<td>infra-red</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>M</td>
<td>molar</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz</td>
</tr>
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</tr>
<tr>
<td>ml</td>
<td>millilitre(s)</td>
</tr>
<tr>
<td>mmol</td>
<td>millimole(s)</td>
</tr>
<tr>
<td>m.p.</td>
<td>melting point</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>Ms</td>
<td>methane sulfonyl</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOSEY</td>
<td>nuclear Overhauser enhancement spectroscopy</td>
</tr>
<tr>
<td>Ns or nosyl</td>
<td>p-nitrobenzenesulphonyl</td>
</tr>
<tr>
<td>o</td>
<td>ortho</td>
</tr>
</tbody>
</table>
p. page

$p$ para

Ph phenyl

q quartet

r.t. room temperature

s singlet

t triplet

td triple doublet

THF tetrahydrofuran

TfOH/triflic acid trifluoromethanesulfonic acid

TLC thin layer chromatography

Ts toluenesulfonyl
Chapter 1

Introduction
Chapter 1

Introduction:

Nitrogen plays a central role in determining the properties of very many organic compounds, usually by reason of its ability to form strong hydrogen bonds. This is true despite the many chemical forms which a nitrogen atom can adopt (Fig. 1.1).

<table>
<thead>
<tr>
<th>Chemical Form</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH₃</td>
<td><img src="NH%E2%82%83.png" alt="Structure" /></td>
</tr>
<tr>
<td>R-NH₂</td>
<td><img src="R-NH%E2%82%82.png" alt="Structure" /></td>
</tr>
<tr>
<td>R²-NH</td>
<td><img src="R%C2%B2-NH.png" alt="Structure" /></td>
</tr>
<tr>
<td>R²-N-R³</td>
<td><img src="R%C2%B2-N-R%C2%B3.png" alt="Structure" /></td>
</tr>
</tbody>
</table>

![Fig. 1.1.](ammonia-hydrogen-bonds.png)

Because primary amines have two N-H bonds, hydrogen bonding is more significant in such compounds than in secondary amines. Tertiary amines cannot form hydrogen bonds between each other because they do not have a hydrogen attached to the nitrogen. Consequently, if one compares amines with the same molecular weight and similar structures, it is found that primary amines have higher boiling points than secondary amines and secondary amines have higher boiling points than tertiary amines (Fig. 1.2).

![Fig. 1.2.](amines-boiling-points.png)

Because groups attached to the nitrogen atom that are electron donating increase the basicity (increase pKa), dimethylamine is more basic than methylamine and both compounds are more basic than simple ammonia. Attaching a phenyl group to the ammonia molecule dramatically decreases
its basic properties due to resonance of the nitrogen lone pair with the benzene ring; aniline is much less basic than methyleamine as the lone pair of electrons on the nitrogen are conjugated to the \(\pi\)-electrons of the aromatic ring and are therefore less available for acid-base chemistry. Electron donating substituents can enhance basicity by pushing electron density toward nitrogen, enabling the nitrogen to share its lone pair of electrons more readily, but the aromatic ring will still serve as an electron sink by resonance, pulling electron density away from nitrogen and thereby reducing its ability to coordinate its lone pair electrons. Based on the electronic factors, tertiary amines should be more basic when compared to secondary amines the fact that the nitrogen atom is now highly sterically crowded, however, this is not usually the case. The addition of the third methyl group results in a slight decrease in basicity. This reduction in pKa is a result of steric factors (Fig. 1.3).\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>(\text{NH}_3)</th>
<th>(\text{CH}_3\text{-NH}_2)</th>
<th>(\text{(CH}_3\text{)}_2\text{NH})</th>
<th>(\text{(CH}_3\text{)}_3\text{N})</th>
<th>(\text{PhCH}_2\text{NH}_2)</th>
<th>(\text{Ph-}\text{-NH}_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(pK_a)</td>
<td>9.27</td>
<td>10.62</td>
<td>10.64</td>
<td>9.76</td>
<td>9.34</td>
<td>4.63</td>
</tr>
</tbody>
</table>

Fig. 1.3.

Amide groups are the key defining structural features in peptides, proteins and enzymes and form hydrogen bonds, which are very important in determining the secondary and tertiary structure of such compounds. Huggins in 1936 expected the importance of the hydrogen bond to be “… the most fruitful applications of hydrogen-bridge theory will be to a better understanding of the nature and behaviour of complicated organic substances such as gels, protein, starch, sugar, and other carbohydrates, chlorophyll, haemoglobin and related substances” (Fig. 1.4).\(^2\)

Fig. 1.4. Hydrogen bond proposed by Huggins
Nitrogen can also be inside or part of an aromatic system. The lone pair electrons of nitrogen in pyrrole 15 are part of the aromatic system but can still form hydrogen bonds. In pyridine 16, the lone pair of electrons are not part of the aromatic system and hence is better at forming hydrogen bonds. Substituted purines 17 and pyrimidines 18 are very important units in nucleic acids (found in DNA and RNA) in which hydrogen bonding determines the structures and is also a key element in the formation and especially the structure of DNA, a building block of life (Fig. 1.5.).

![Fig. 1.5.](image)

In a DNA helix, each purine (Adenine A or Guanine G) is bonded specifically to one pyrimidine (Thymine T or Cytosine C) by two or three hydrogen bonds respectively. The hydrogen bonds are of two kinds: one links an amine to a carbonyl group and the other links an amine to an imine (Fig. 1.6.).

![Fig. 1.6.](image)
A hydrogen attached to carbon is not expected to form hydrogen bonds. If, however, the carbon atom is sufficiently polarized by attachment to one or more electronegative atoms, the hydrogen in question may become loosely enough bound to serve as a bridge. This seems to be the case in the HCN molecule, in which the nitrogen is connected by a hydrogen bridge to an electronegative atom in another molecule.²

---H-C\text{EN}---H-C\text{EN}---H-C\text{EN}---H-C\text{EN}---

23

Fig. 1.7.

Nitro groups can also participate in intermolecular and intramolecular hydrogen bonding. Takemoto et al. reported novel, catalysed Michael reactions between malonates 24 and nitroolefins 25. In this reaction, the thiourea catalyst seems to interact with the nitro group, facilitating formation of the corresponding nitronate which could be produced from the nitroalkane with the bifunctional thiourea 26 via hydrogen-bonding activation and subsequent deprotonation by the neighboring tertiary amino group (see structures 28 and 29) (Scheme 1.1.).³

Scheme 1.1.

Therefore, it is not surprising that pharmaceuticals usually contain multiple nitrogen atoms, the positions of which are usually primarily responsible for the observed bioactivity of many drugs and natural products. The piperidine structural is a ubiquitous ring feature of numerous naturally
occurring alkaloids. Anabasine 30 is a piperidine alkaloid found in the *Nicotiana tabacum*. Conine 31 and conhydride 32 are poisonous alkaloids found in poison hemlock *Conium maculatum*. Conine 31 was the first of the alkaloids to be synthesized by Albert Ladenburg in 1886. Adaline alkaloid 33 acts as part of the defence system of the European ladybird, *adalia bipunctata*. This alkaloid is proven feeding deterrents to spiders and ants. Spiro-alkaloid nankakurine 34 induced secretion of neurotrophic factors in human astrocytoma cells at a concentration of 1 μM. Pergolide 35 is a dopamine receptor agonist used in some countries for the treatment of Parkinson's disease. Scopolamine 36 is a tropane alkaloid drug with muscarinic antagonist effects. Morphine 37 is the gold standard of analgesics used to relieve intense pain. The legal medicinal use of morphine in the United States of America exceeds 80,000 kg/year (Scheme 1.2.).

Hence, it is hardly surprising that there has been enormous interest in the development of many methods for the synthesis of carbon-nitrogen bonds.
Carbon-nitrogen bond synthesis:

1- Gabriel synthesis:

The preparation of primary amines 40 from the corresponding alkyl halides, in which potassium phthalimide 38 is first alkylated, is known as the Gabriel synthesis\textsuperscript{12} (Scheme 1.3.).

![Scheme 1.3.](image)

During synthetic studies by Rossi et al., β-benzoylamino phenylalanine 44, the secondary alcohol of an enantiopure oxazolidinone was mesylated then the sulfonate ester group of 41 was displaced with potassium phthalimide to give 42. Deprotection of the phthalimide without destruction of the oxazolidinone ring was achieved by treating 42 with dilute hydrazine to give the free amine 43 (Scheme 1.4.).\textsuperscript{13}

![Scheme 1.4.](image)

2- Yields from nucleophilic substitution of ammonia are often poor as the product, a primary amine, is itself a nucleophile, which is usually more reactive than ammonia itself and can therefore react with more alkyl halide. The result is mixtures containing primary, secondary and tertiary amines and even quaternary ammonium salts, hence the value of the Gabriel synthesis (see above).

This can be avoided by using another simple method for carbon-nitrogen formation: an $S_N2$ reaction for the conversion of alcohols into tosylamides.\textsuperscript{14} This is illustrated by the reaction of potassium...
tosylamide which was prepared by heating 1.5 equivalents each of KOH and p-toluenesulfonamide in DMF. Following complete dissolution of the base, one equivalent of mesylate 46 prepared from commercial (R)-alcohol 45 is added, in DMF. Purification of the reaction mixture obtained after one hour gave the desired tosylamide 47 in 80% yield with an enantiomeric excess of 94% (Scheme 1.5). Hence, by lowering the reactivity of the amine nitrogen, a single S_N2 displacement can be efficiently achieved.

![Scheme 1.5.](image)

3- Curtius Rearrangement:

The thermal decomposition of acyl azides 51 to produce an isocyanate 52 is known as the Curtius rearrangement.\(^\text{15}\) These intermediate isocyanates 52 may be isolated, or their corresponding hydrolysis products may be obtained directly. If the reaction is carried out in the presence of water, an amine or an alcohol, the corresponding amine 53, urea 54 and carbamate 55 are formed, respectively (Scheme 1.16.).

![Scheme 1.6.](image)

Kim et al. used a key carbamate intermediate during their total synthesis of Pancratistatin 60 via a Curtius rearrangement of the corresponding carboxylic acid 57 induced by diphenylphosphoryl azide (DPPA) in refluxing toluene, to give a rather stable isocyanate
intermediate 58 that required further treatment with NaOMe/MeOH to generate the corresponding carbamate 59 in 82% overall yield (Scheme 1.7.).

Scheme 1.7.

4- Schmidt Reaction:

The Schmidt reaction is similar to the Curtius rearrangement, except that in this reaction the azide is protonated and hence it proceeds via different intermediates. The acid-catalysed reaction of hydrazoic acid with electrophiles, such as carbonyls, tertiary alcohols or alkenes is known as the Schmidt reaction. After a rearrangement and extrusion of N₂, amines, nitriles, amides or imines are produced, respectively. Aliphatic carboxylic acids 61 give amines 62 more easily than aromatic examples which need very strong acid catalysts; aldehydes 63 and ketones 65 react faster than carboxylic acids to give nitriles 64 and amides 66, respectively (Scheme 1.8.).

Scheme 1.8.

Tanaka and Suemune developed a practical procedure for the synthesis of various chiral disubstituted amino acids, from the β-keto ester 67, which was subjected to the Schmidt reaction to give the N-acetyl α-amino acid 68 without loss of the optical activity (Scheme 1.9.).
Kumar et al. report the synthesis of the methyl analogue 70 of crispine A 69 via an intramolecular Schmidt reaction. The indolizidine alkaloid known as crispine A, was isolated from carduus crispus, an European biennial introduced in North America having flower heads, and was found to exhibit significant antitumor activity against many human cancer lines. The intramolecular Schmidt reaction of azido-ketone 71 was successfully achieved using triflic acid (TfOH) at -5 to 0 °C and the resultant cyclized product 72 was isolated in 54% yield (Scheme 1.10.).

5- Amide reduction:

An amide [e.g. 73] can be reduced to the corresponding amine 74 by lithium aluminum hydride (LiAlH₄) and many related hydride sources (Scheme 1.11.).
6- **Imine reduction:**

Reductive amination is another technique to alkylate amines. It consists of two subsequent reactions: first condensation of an amine $77$ with an aldehyde $78$ or a ketone to give an imine $79$ with elimination of water then reduction of the imine $79$ to the corresponding amine $80$ (Scheme 1.12.).

\[
\begin{align*}
R^1NH_2 + R^2CHO &\rightarrow R^1N\equiv R^2 + H_2O \\
&\xrightarrow{NaBH_4} R^1NH_2 + R^2CO
\end{align*}
\]

**Scheme 1.12.**

7- **Buchwald-Hartwig cross-coupling:**

In addition to many rearrangement methods toward C-N bond formation, nitrogen insertion reactions have increasingly been developed. In Buchwald-Hartwig cross-couplings, palladium(0) catalyses C-N bond formation between an aryl halide and an amine in the presence of base (Scheme 1.13.).

\[
\begin{align*}
\text{Br} \quad \text{R}NH_2, \text{Pd}^0 &\rightarrow R^1N\equiv R^2 \quad \text{OK, }\Delta
\end{align*}
\]

**Scheme 1.13.**

8- **Hydroamination reaction:**

Hydroamination is a highly atom-economical process in which an amine N–H functionality is added across an unsaturated carbon–carbon linkage. This potentially highly useful process can give access to various nitrogen-containing compounds and fine chemicals of many structural types as well as naturally occurring alkaloid skeletons. Recently, there has been much interest in alkene hydroamination. The addition of an amine N–H $84$ functionality to unsaturated an carbon–carbon bond, either in an intermolecular [eqn. (1)] or intramolecular $86$ [eqn. (2)] fashion, generates amines
in a waste-free, highly atom-economical manner starting from simple and inexpensive precursors (Scheme 1.14.).

**Scheme 1.14.**

The intermolecular hydroamination of a 1,5-diene 88 by TsNH$_2$ could be followed by a second intramolecular hydroamination to produce pyrrolidines 89 in an one-pot operation. A mixture of *cis* and *trans* products (37:63) was isolated in 64% yield with the use of four equivalents of the 1,5-diene 88 in toluene with a catalytic amount of Ph$_3$PAuOTf (5 mol%) (generated by mixing equal equivalents of Ph$_3$PAuCl and AgOTf) at 95 °C for 15 h (Scheme 1.15.).

**Scheme 1.15.**

### 8.1. Intermolecular Acid-Catalyzed Hydroamination of Alkenes

Marcseková and Doye found that substituted anilines 90 reacted with olefins 91 in the presence of catalytic amounts of aqueous hydrogen iodide to give a mixture of the corresponding hydroamination and hydroarylation products, 92 and 93, respectively. Electron-withdrawing substituents on the aniline ring increase the overall yield of the reaction and favoured the formation of the hydroamination products 92 (Scheme 1.16. and Table 1.1.).
Table 1.1. Examples of hydroamination/hydroarylation of simple olefins with hydrogen iodide

<table>
<thead>
<tr>
<th>Anilines 90 R¹</th>
<th>Olefin 91 R²</th>
<th>Temperature / °C</th>
<th>Time / h</th>
<th>Ratio of 92:93</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>5</td>
<td>4</td>
<td>3:2</td>
<td>98</td>
</tr>
<tr>
<td>Cl</td>
<td>H</td>
<td>35</td>
<td>24</td>
<td>2:3</td>
<td>86</td>
</tr>
<tr>
<td>H</td>
<td>Me</td>
<td>135</td>
<td>24</td>
<td>5:4</td>
<td>80</td>
</tr>
</tbody>
</table>

Hartwig reported that additions of aliphatic amines to olefins in the presence of acid do not occur under mild conditions, presumably because the amine will be very largely protonated. The intermolecular additions of sulfonamides to alkenes catalyzed by triflic acid which were subsequently discovered by Hartwig are summarized in Scheme 1.17. The addition of p-toluenesulfonamide TsNH₂ 94 to norbornene occurred within hours at room temperature to form the exo-addition product in 91% yield, while the addition of TsNH₂ to cyclohexene and cyclooctene occurred within a day at 85 °C in 58% and 86% isolated yield (Scheme 1.17.).²⁵
The presence of the acid makes this kind of hydroamination related to the Ritter reaction, an old method where aliphatic or aromatic nitriles 98 are used as a nitrogen nucleophile to react with alkenes 99 or tertiary alcohols 102 under acidic conditions to give $N$-tert-alkylamides (Scheme 1.18.).

\[ \text{Ph} = \text{N} \xrightarrow{\text{H}_2\text{SO}_4} \xrightarrow{\text{H}_2\text{O}} \xrightarrow{70\%} \xrightarrow{\text{Lewis acid}} \xrightarrow{R^3 R^1 R^2} \]

**Scheme 1.18.**

The mechanism of the Ritter reaction has been thoroughly studied. When an alkene 99 is used, the carbocation 104 is generated by protonation of the double bond. The cation is then attacked by the nitrogen atom of the nitrile to form nitrilium ion 105, which is then hydrolysed to produce the observed $N$-alkyl carboxamide (Scheme 1.19.).

\[
\begin{align*}
\text{Ph} & \xrightarrow{\Phi} \xrightarrow{\text{N=CN}} \xrightarrow{105} \xrightarrow{106} \xrightarrow{\text{H}_2\text{O}} \xrightarrow{\Phi} \xrightarrow{107}
\end{align*}
\]

**Scheme 1.19.**

The intramolecular Ritter reaction has been used by Compernolle et al. for the synthesis of a potential dopamine receptor ligand 110. A six membered lactam ring was formed upon treatment of the tertiary benzylic alcohol 108 with methanesulfonic acid. The benzylic carbocation thus generated was captured by the nitrogen of the cyano group (Scheme 1.20.).

\[
\begin{align*}
\text{Ph} & \xrightarrow{\Phi} \xrightarrow{\text{HC} = \text{CN}} \xrightarrow{107} \xrightarrow{\Phi} \xrightarrow{110}
\end{align*}
\]

**Scheme 1.20.**
Obviously, there is a basic incompatibility between an amine and an acid catalyst due to rapid salt formation and therefore the trend in reactivity is an increase in catalytic efficiency with decreasing anion coordination ability OTf$^- < \text{NTf}_2^-$. Both hydroamination 113 and ortho-hydroarylation 114 products are formed using 5 mol % of TfOH and HNTf$_2$. These observations are consistent with the intermediacy of a stabilized carbenium ion and suggest that these transformations proceed along a reaction pathway similar to that of acid-catalyzed hydration, where either the heteroatom or the aromatic ring can act as the nucleophile (Scheme 1.21.).

Scheme 1.21.

8.2.1 Intramolecular Acid-Catalyzed Hydroamination of Alkenes

Intramolecular hydroamination is of great interest, because nitrogen-containing heterocycles could be synthesized from amino olefins using such a reaction. The first examples of Brønsted acid-catalyzed intramolecular hydroaminations were reported contemporaneously by Hartwig and Knight. Aminoalkenes 117 bearing an electron-withdrawing group at the nitrogen atom led to pyrrolidines and piperidines 118 in generally excellent yields in the presence of a substoichiometric amount of triflic acid in hot toluene (Scheme 1.22.). Lactams ($X = O$) were also prepared under the same reaction conditions starting from amides. In the case of using sulfuric acid as catalyst, yields were generally lower. In a proposed mechanism, the alkenyl tosylamide is protonated first at the tosylamide group, the proton is then transferred intramolecularly to the double bond, and finally, the resulting carbenium ion is trapped by the sulfonamide, which regenerates a proton, rendering the
process catalytic in acid. The regiochemistry of this process is determined mostly by the stability of the carbenium ion intermediate; thus, most of these transformations are overall unfavourable 5-endo-trig cyclisations, according to Baldwin’s rules. Hartwig evaluated acid-catalyzed reactions of the aliphatic substrate Entry 2: both substrates underwent the acid catalyzed cyclization to form the formal Markovnikov cyclization product. The very electron deficient alkene [Entry 3] did not react, presumably because the low Lewis basicity of the double bond makes it less susceptible to protonation. Reactions that would form three- or four-membered rings did not occur because of rapid decomposition of the allylic amine precursors under the strongly acidic conditions. In addition, the six-membered ring Entry 4 was formed by a formal 6-endo-trig cyclization in excellent yield; prolonged heating was necessary to complete the reaction in the presence of sulfuric acid as the catalyst. Entry 5 which could form a seven-membered ring through an intermediate with benzylic stabilization or a six-membered ring through an unstabilized intermediate, gave the six-membered ring by an overall 6-exo-trig process. Substrates containing the p-nitrophenylsulfonyl group [e.g. Entry 6] gave the cyclization products in excellent yields. Lactams [Entry 7] were obtained in essentially quantitative yield when the reaction were conducted in the presence of stoichiometric amount of triflic acid. A stoichiometric amount of acid was required because the protonated N-alkyl amide product is too weakly acidic to initiate cyclization of a second starting benzamide.

![Scheme 1.22.](image-url)
Table 1.2. Selected Examples of Acid-Catalyzed Intramolecular Hydroamination of Protected Alkenylamines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n)</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Product</td>
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<td><img src="image2.png" alt="Product2" /></td>
<td><img src="image3.png" alt="Product3" /></td>
<td><img src="image4.png" alt="Product4" /></td>
<td><img src="image5.png" alt="Product5" /></td>
<td><img src="image6.png" alt="Product6" /></td>
<td><img src="image7.png" alt="Product7" /></td>
</tr>
<tr>
<td>Yield %</td>
<td>83</td>
<td>95</td>
<td>0</td>
<td>83</td>
<td>51</td>
<td>96</td>
<td>99</td>
</tr>
</tbody>
</table>

8.2.2 Acid-Catalysed Hydroamination Reactions in the Knight Group

Amjad and Knight group found the exposure of the \((E)\)-homoallylic sulfonamides 119 to iodocyclisation conditions in the presence of a proton source gave the thermodynamically more stable 2,5-	extit{cis} diastereoisomers 122, whereas exposure to excess iodine in the presence of potassium carbonate showed a distinct preference for the formation of the 2,5-	extit{trans} isomers 121. These results were thought to be due to an initial cyclisation via a chair-like transition state conformation 120, which leads to the 2,5-	extit{trans} isomers 121, and which can then be followed by proton-induced cycloreversion and re-closure and hence equilibrium towards, and eventually only, the more thermodynamically stable 2,5-	extit{cis} isomers 122 (Scheme 1.23.).

![Scheme 1.23.](image8.png)
The stereochemical outcomes appear to follow largely the chair-like conformation 120, wherein the sp\(^3\)-bonded group (R\(^2\)) adopts an equatorial position during the initial cyclisation, under basic conditions, hence leading to kinetic products, the 2,5-\textit{trans} isomers 121. Omission of the base leads to only the 2,5-\textit{cis} isomers 122. The pathways were proven by exposing a 2,5-\textit{trans}-pyrrolidine 121 to a mixture of hydrogen iodine and iodine, when conversion into the \textit{cis}-isomer 122 occurred rapidly. Acid-catalysed cyclo-reversion and equilibration to the thermodynamically more stable \textit{cis}-isomers 122 then follows (Scheme 1.24).\(^{31}\)

![Scheme 1.24.](image)

Amjad observed another significant feature during extensions of this methodology to the formation of highly substituted proline analogues 123, which, in extreme cases, required prolonged exposure to large excesses of iodine in order to achieve complete conversion into the desired iodopyrrolidines 124 (Fig. 1.8). When such cyclisations were carried out in the absence of base, the products 125 were sometimes accompanied by small amounts of the de-iodopyrrolidines. It was reasoned that one possibility was that direct acid-catalysed cyclisation was occurring to a limited extent to give the unexpected products 125.

![Fig. 1.8.](image)
When these ideas were extended to alkyne systems, new and efficient approaches to dihydroiodo and iodopyrroles were found via 5-endo-dig cyclisations. However, when such cyclisations were carried out without any base present, a mixture of iodopyrroles and pyrroles were formed (Scheme 1.25).32

\[
\begin{align*}
\text{Scheme 1.25.}
\end{align*}
\]

It was assumed that the hydrogen iodide HI produced in the initial stages of iodopyrrole formation was the acid which was causing cyclisation to give the pyrroles 128. This led to the development of new acid-catalysed approaches to pyrroles. All of this led to the idea of using acid-catalysed cyclizations to form saturated N-heterocycles, especially pyrrolidines and piperidines. The prenyl amino esters 129 was synthesised to test this, the idea being that if this did not undergo smooth cyclisation, then the idea was not viable, because the cyclization should involve a relatively stabilized tertiary carbenium ion 130 (Scheme 1.26.).

\[
\begin{align*}
\text{Scheme 1.26.}
\end{align*}
\]

In the event, Haskins and Knight, prepared pyrrolidine derivatives by using trifluoromethanesulfonic acid CF₃SO₃H (triflic acid, TfOH) as a catalyst in excellent yields.33 Both prenyl derivatives 132 underwent rapid and very clean cyclisation when exposed to 0.4 equivalents of triflic acid at 0 °C to give essentially quantitative yields of the pyrrolidines 133. In contrast, the cinnamyl derivatives 136 required slightly more demanding conditions (0.6 eq. TfOH, 25 °C, 4.5
h). Understandably, cyclisation of the corresponding crotly analogue 134 required heating to reflux to achieve complete reaction; the excellent yields of the resulting pyrrolidines 132 were, however, obtained. Spiro-Pyrrolidines can also be prepared using this chemistry: the ylidene cyclohexane derivative 138 gave an excellent return of the expected product 139 under the mildest set of conditions, indicating again the intermediacy of a tertiary carbenium ion (Scheme 1.27.).

![Scheme 1.27.](image)

The Knight group has had a longstanding interest in 5-endo-trig cyclisations. Almost simultaneously to the study of Schlummer and Hartwig\(^\text{34}\), Haskins and Knight demonstrated that triflic acid was an excellent catalyst for inducing overall 5-endo-trig cyclisation of homoallylic sulfonamides to give pyrrolidines. They applied this methodology to the synthesis of polycyclic compounds through a cationic cascade terminated by a sulfonamide group. For instance, geranyl derivative 140 underwent rapid cyclisation at 0 °C to give 90% isolated yield of the trans-annulated pyrrolidine 141, as a 3:2 epimeric mixture at the amino ester stereogenic centre. This assignment of structure was confirmed by a single crystal X-ray crystallographic determination of a separated sample of the major isomer of the glycine derivative (Scheme 1.28.).

![Scheme 1.28.](image)
In plants, monoterpenes with ten carbons (C10) such as pinene are biosynthesized in the plastid from the C5 intermediates isopentenyl diphosphate (IPP) 145 and dimethylallyl diphosphate (DMAPP) 146 generated via the deoxyxylulose-5-phosphate (DXP) 144 pathway. Geranyl diphosphate synthase (GPPS) carries out a head-to-tail condensation of IPP 145 and DMAPP 146 to produce geranyl diphosphate (GPP, C10) 147, which is, in turn, cyclized by pinene synthase (PS) to produce either $\alpha$- or $\beta$-pinene 148, 149 (Scheme 1.29.).

The pinene synthase cyclization mechanism of geranyl diphosphate GPP 147 to $\alpha$- or $\beta$-pinene 148, 149 is shown in (Scheme 1.30.).

When Haskins attempted to extend acid-catalysed hydroamination chemistry to the synthesis of piperidines, she claimed that formation of such six-membered rings is particularly disfavoured. For example, exposure of the homoprenyl derivative of alaninate 153 to triflic acid gave only the pyrrolidine 154 (cis:trans ~ 3:2); isolated yield was in excess of 90%, although the less stable secondary carbocation was involved. The tertiary carbocation would give the piperidine product 155 through an overall 6-endo-trig process, which is favoured according to Baldwin’s rules whereas secondary ion would give the pyrrolidine ring 154, which would occur through an overall 5-exo-trig process, which is also favoured by Baldwin’s rules (Scheme 1.31.).
However, Haskins prepared the indolic terpene alkaloid $\alpha$-cyclopiazonic acid 155 in 11 steps; the key step is a carbocationic cascade, terminated by a 4-nitrosulfonamide group and initiated by benzylic carbocation formation directly from the intermediate 158. Clearly the benzylic carbocation 158 was not generated by double bond protonation, but rather by protonation of the benzylic alcohol to produce the benzylic carbocation 158 (Scheme 1.32).^36

![Scheme 1.31.](image)

Scheme 1.31.

The cyclization reaction was carried out on the tert-butyldiphenylsilyl (TBDPS) protected alcohol 160 with one equivalent of triflic acid for one hour at room temperature. Both the deprotection and the cascade cyclization were carried out in one step to generate the tetracyclic system 161 in 74% yield (Scheme 1.33).

![Scheme 1.32.](image)

Scheme 1.32.

![Scheme 1.33.](image)

Scheme 1.33.
Conclusion

From the previously reported work of Hartwig and Knight, the acid-catalysed hydroamination reaction is a powerful method for the synthesis of nitrogen containing heterocycles. Both sulphuric acid and triflic acid are effective catalysts in these cyclizations with some limitations of using sulphuric acid in the case of cinnamyl alkene derivatives. New synthetic routes to such a wealthy of structures are always desirable, especially when new stereogenic centres are introduced in a controlled way. This potential is explored in the following chapter.
References


32 Knight, D. W.; Sharland, C. M. *Synlett* **2003**, 2258.


Chapter 2

Acid-catalysed synthesis of piperidines
Chapter 2

Acid-catalysed synthesis of piperidines

Introduction:

The importance of the piperidine ring in natural products and the successful results of using acid-catalysed hydroamination reactions to synthesize pyrrolidines made us think in a logical way to extend this methodology toward piperidine synthesis. Piperidine syntheses have been studied extensively, as the development of new drugs containing six-membered ring heterocycles becomes more and more common. The synthesis of piperidines using very common C-N bond-formation is well known along with many rearrangements and ring expansions, which have also been extensively studied, but many strategies are less common and are often used only in a few particular cases rather than as a general method.¹

Piperidine synthesis

Watson and colleagues noted that a substructure search of the piperidine ring using the electronic version of the Drug Data Report (MDL Drug Data Report) which includes data from July 1988 through to December 1998 revealed over 12,000 discrete piperidine entities that have been mentioned in clinical or preclinical studies.² There are many different methods that have been used to construct piperidine rings and these have been reviewed.¹ General and popular strategies include nucleophilic substitutions, reductive amination and the reaction of amines with alkenes and alkynes.

1. Nucleophilic substitution

Nucleophilic substitution is a reliable method of making piperidines. It is often used as the final step, followed by deprotection of the functional groups present, if necessary. The main difficulty with this type of cyclisation compared to intermolecular nucleophilic substitution is the choice of the correct concentration of reagents. A too dilute reaction mixture gives a slow reaction and, if the reaction mixture is too concentrated or the intramolecular nucleophilic substitution is too slow,
polymerisation can occur. Halides, mesylates or tosylates are most commonly used as the leaving groups to form piperidines via intramolecular cycloaddition.\textsuperscript{3} The chloride 162 has been used by Hanessian \textit{et al} in the synthesis of enantiomerically pure 2,3-piperidines (Scheme 2.1). Ring-closure using \textit{tert}-BuOK as the base afforded the piperidine 163 in 45–55% yield. Oxidative cleavage, followed by reduction, afforded the target compound 164 in 62% yield (Scheme 2.1).

Scheme 2.1

Reaction of bis-tosylates with primary amines is also known in the literature and has been used more commonly from bis-mesylates/ tosylates than halogens. Kurth and co-workers\textsuperscript{5} cyclised the bis-tosylate 165 using an excess of benzylamine at 85 °C. The reaction occurred in 90% yield and gave only the \textit{anti}-piperidine 166 (Scheme 2.2).

Scheme 2.2

2. Reductive amination

One of the most common methods for the synthesis of piperidines, if not the mostly widely used, is reductive amination. Indeed, piperidines can be synthesised from 1,5-amino-aldehydes in a one-pot procedure in the case of secondary amines or a two-pot procedure for primary amines. The two-step process involves the formation of an imine intermediate, followed by its reduction. Urban \textit{et al}.,\textsuperscript{6} achieved the conjugate addition of the \(\beta\)-keto-amide 167 with acrolein to afford the desired aldehyde 168 in 99% yield (Scheme 2.3). These workers found, however, that complete conversion of 168 into
a mixture of aminals 169 occurred on storage over several hours. Reduction of the amino-aldehyde 168 or the aminals 169 with LiAlH₄ resulted in a reductive cyclisation, yielding the racemic alcohol 170 (Scheme 2.3).

![Scheme 2.3](image)

3. Reaction of amines with alkenes and alkynes

3.1. Michael addition

Michael addition plays an important role in the synthesis of piperidines. Control of the stereoselectivity is the main difficulty in this type of cyclisation. Armstrong et al.⁷ in their approach towards the synthesis of cylindrospermopsin, synthesised the first piperidine intermediate 172 via a Michael addition reaction. Treatment of the compound 171 with a catalytic amount of p-TsOH in refluxing benzene gave the more stable N-Cbz-protected-2,6-cis-piperidine 172, as a single diastereoisomer in 74% yield (Scheme 2.4).

![Scheme 2.4](image)

Carretero et al. converted α,β-unsaturated sulfone 173 via a one-pot deprotection/Michael addition sequence into the piperidines 174 and 175 (Scheme 2.5). Complete N-Boc deprotection by treatment with trifluoroacetic acid afforded quantitatively the corresponding ammonium salt which, after isolation, was redissolved in THF, cooled to -78 °C and treated with ten equivalents of Et₃N. The cyclization was complete in less than 30 min at -78 °C, giving piperidines 174 and 175 as a mixture
of cis and trans isomers in quantitative yield. The diastereoselectivity is affected by the substituent on nitrogen: the mechanistic rationales suggest an equilibrium between conformers 176 and 177 exists, disfavoring 176 due to 1,3-diaxial interactions between the substituents.8,9

![Scheme 2.5](image)

### 3.2. Electrophile-Induced Cyclizations

Deziel developed catalytic asymmetric syntheses of piperidines by using catalytic amounts of chiral C2-symmetric arylselenium triflate 179 to give diastereomERICALLY pure trans-2,3-disubstituted piperidine 181 in 89% yield with an excellent 92% ee (Scheme 2.6).9,10

![Scheme 2.6](image)

### 4. Formation of Lactams

MaGee et al.11 developed a convenient and general method for the synthesis of piperidinone lactams via the intramolecular trapping of ketenes. Refluxing the ethoxyalkyne 182 in xylene afforded the desired piperidinone 184 in 81% yield. This reaction is believed to proceed via the ketene 183, which cyclises spontaneously under the reaction conditions (Scheme 2.7).
5. Ring Expansion

Cossy observed the enantioselective ring expansion of pyrrolidines in the presence of trifluoroacetic anhydride and subsequent treatment with Et$_3$N to give piperidines typically with ~97% ee.$^{12}$ Trans-3-Hydroxy-2-phenylpiperidine 188 was stereospecifically formed from chiral 2-hydroxymethylpyrrolidine 185b. On the other hand, the diastereomeric pyrrolidine derivative 186a did not rearrange to cis-3-hydroxy-2-phenylpiperidine 187. This was taken as evidence for a tight ion pair mechanism, in which the initially formed trifluoroacetate undergoes substitution reaction with concomitant formation of the aziridinium ions 186a and 186b. Due to steric hindrance in the tight ion pair, attack of trifluoroacetate on the aziridinium ion 186a is strongly disfavored as compared to the isomeric 186b (Scheme 2.8).$^{13,9}$

6. Aza-Prins piperidine synthesis$^{14}$

The synthesis of piperidines was investigated by Martin and co-workers. Their strategy consisted of allowing homoallylic tosylamides to react with aldehydes in the presence of FeCl$_3$ or FeBr$_3$. 

Scheme 2.7

Scheme 2.8
Homoallylic tosylamide 190 led preferentially to trans-2,4-disubstituted piperidines 192 (Scheme 2.9).\(^{15}\)

![Scheme 2.9](image)

The diastereoselectivity is influenced by the geometry of the intermediate iminium cation. The \(E\)-iminium ion (precursor of the 2,4-trans product through cyclization via a chair-like transition state, followed by equatorial trapping of the resulting carbocation by \(X^-\)) is more stable than the \((Z)\)-iminium ion by 0.78–1.77 kcal/mol, except when \(R\) is a benzyl group (Scheme 2.10).\(^{16}\)

![Scheme 2.10](image)

7. Reduction of pyridines

The synthesis of piperidines from pyridines is a well-known transformation and shown to be a very important synthetic tool for the preparation of 3,4,5-trisubstituted piperidine derivatives.\(^{17}\) Access to piperidines containing a quaternary carbon via the reduction of pyridines is, however, not known in the literature for obvious reasons. The outcome of partially reducing pyridines is normally formation of 1,4-dihydro products.\(^{18}\) The Birch reduction of pyridines forms 1,4-dihydropyridines
that must be either stabilized by an electron-withdrawing group on nitrogen or transformed in situ, presumably to prevent autoxidation.\textsuperscript{19} The full reduction of pyridines to piperidines using hydrogen can be achieved using different catalysts such as Pd/C, PtO\textsubscript{2} or Rh/C. The full reduction of 2,4-pyridines \textsuperscript{197} has been studied by Steiner \textit{et al.} who found the best result in terms of diastereoselectivity to be using one equivalent of NaOH. They were able to efficiently scale up the reduction of the pyridine \textsuperscript{197} to the desired \textit{syn} 2,4-disubstituted piperidine \textsuperscript{198}, in 95\% yield, which contained only 3\% of the \textit{anti}-diastereoisomer (\textbf{Scheme 2.11}).\textsuperscript{20}

\begin{center}
\textbf{Scheme 2.11}
\end{center}

8. \textbf{Metal-catalyzed hydroamination}

Metal-catalyzed hydroamination of simple olefins is one of the most important strategies to prepare nitrogen-containing molecules.\textsuperscript{21, 22} It has been reported that gold(I)-catalyzed intramolecular hydroamination of tosylated amino olefins \textsuperscript{199} and \textsuperscript{201} is a very effective pyrrolidine synthesis. Several \textit{N}-tosylated olefins were efficiently cyclized to afford pyrrolidines \textsuperscript{200} and \textsuperscript{202} in toluene with a catalytic amount of Ph\textsubscript{3}PAuOTf (5 mol\%) (generated by mixing equal equivalents of Ph\textsubscript{3}PAuCl and AgOTf) (\textbf{Scheme 2.12}).\textsuperscript{23}

\begin{center}
\textbf{Scheme 2.12}
\end{center}

A gold-catalyzed methodology involving a favoured 6-\textit{endo}-dig cyclization has been applied to obtain dendrobate alkaloid (+)-241D \textsuperscript{206}, which has been isolated from the methanolic skin extracts
of the Panamanian poison frog *Dendrobates speciosus* and has shown to be a non-competitive blocker of acetylcholine to ganglionic nicotinic receptor channels. The gold-catalyzed intramolecular cyclisation of this intermediate β-amino ynone derivative 203 using PPh₃AuCl in the presence of a silver salt in 1,2-dichloroethane at room temperature gave, in one hour, the expected enantiopure 4-pyridinone 204 in good yield. With this chiral synthon 204 in hand, the synthesis of dendrobate alkaloid (+)-241 D 206 was completed. Thus, acid-catalyzed removal of the Boc-protecting group was achieved before catalytic hydrogenation of the thus generated 2,3-dihydropyridone 205 gave a unique cis-diastereoisomer in 78% isolated yield (Scheme 2.13).

![Scheme 2.13](image)

Takaki *et al.* reported investigations into FeCl₃-catalyzed intramolecular hydroamination, in which they found that the iron activity was superior to that of other conventional transition-metal catalysts. The compatibility of FeCl₃.6H₂O (10 mol %) with various types of amino-olefins was investigated under the optimized conditions in air. In these cases of the 2,2-disubstituted amino-olefins 207 and 209 were smoothly transformed into the corresponding pyrrolidine 208 and 210 in quantitative yield within two hours in 1,2-dichloroethane at 80 °C under air (Scheme 2.14).

![Scheme 2.14](image)
In the same report, consistent with 6-endo-trig cyclisations being unfavourable according to Baldwin’s rules,\textsuperscript{27} when Takaki \textit{et al.} attempted to extend this methodology to the synthesis of piperidine derivatives, not surprisingly, they found that the construction of five-membered rings was more favorable than of six-membered rings under these conditions. Treatment of 2,2-dimethyl-1-(4-toluenesulfonylamino)hex-5-ene 211 with FeCl$_3$·6H$_2$O gave pyrrolidine 212 in 72\% yield, together with 2-methylpiperidine 213 (24\%). On the other hand, 2,2-dimethyl-5-phenyl-1-(4-toluenesulfonylamino)pent-4-ene 214 produced 2-phenylpiperidine 215 in 94\% yield through 6-endo-trig cyclization, but no 2-benzylpyrrolidine was detected (Scheme 2.15); presumably, a stabilized benzylic carbenium ion is involved in this case.

![Scheme 2.15](image)

These piperidine syntheses become limited however when a quaternary carbon is present at the centre which is undergoing nucleophilic attack, which generally fail when applied to tertiary electrophiles. Haskins and Knight found that exposure of homoprenyl derivative of alaninate 217 to triflic acid gave only pyrrolidine 218 (cis/trans ~3:2) in 88\% overall yield despite the implication that a less stable secondary carbocation is involved. The formation of piperidine 216 is particularly disfavoured in this case. Similarly, treatment of the cyclohexenyl sulfonamide 220 with catalytic amounts of triflic acid did not give the expected spiro-piperidine 219 but rather the piperidine/pyrrolidine ring system 221. This result was unexpected as the cyclisation appears to proceed \textit{via} a less stable secondary carbocation intermediate. The major diastereoisomer of pyrrolidine 221, with the cyclohexyl and methyl ester substituent \textit{cis} to one another, was confirmed by X-ray crystallographic analysis (Scheme 2.16).\textsuperscript{28}
Haskins confirmed the structure of pyrrolidine 218 by constructing it through a different route, which had also been developed in the group (Scheme 2.17). Amino acid alanine ester was converted into the corresponding benzyl imine 222. The imine acts as a protecting group for the next step of the synthesis following the method developed by the Stork group. Imine 222 was deprotonated with LDA and then reacted with 1-bromo-4-methyl-2-pentene 224, which was prepared by S_N2’ reaction of the alcohol 226.

Subsequent hydrolysis of the imine and reprotction of the resulting amine 225 yields the cyclisation substrate. Iodocyclization of sulfonamide 227 under basic conditions gave an iodopyrrolidine 228 (2,5-trans : 2,5-cis 4:1) which was deiodinated by hydrogenolysis to yield the corresponding pyrrolidine 218. This pyrrolidine showed the same spectroscopic data as those displayed by the acid-catalyzed cyclization product, although the diastereomeric ratios were different (Scheme 2.18).
It becomes clear that pyrrolidine 218 was formed in the acid-catalysed cyclization rather than the expected piperidine 216 (Scheme 2.16). This finding was particularly unexpected especially when compared with Hartwig’s piperidine synthesis. In 2002, he published a paper which reported that two piperidines 230 and 232 synthesized by overall 6-endo- and 6-exo- reaction using 0.2 equivalent of triflic acid in toluene at 100 °C. The cyclisation of sulfonamide 229 occurs via a benzylic carbocation rather than the corresponding and much less stabilized secondary carbocation intermediate. The cyclisation of sulfonamide 231 by contrast occurs via such a less stable secondary carbocation rather than the isomeric benzylic carbocation, the low yield 51% suggesting that this cyclisation is not especially a favoured one. It would be interesting to see what other products were formed in this reaction, particularly if these include the corresponding azepane ring. It is noted that sulfonamide 231 did not give any product when sulfuric acid was used as a catalyst, neither the piperidine nor the azepane (Scheme 2.19).

Just before my arrival in Cardiff, a French Erasmus student, Alexis Dupauw, was visiting the group for three months and began a study of the unexpected inability to form piperidines by acid-catalysed cyclisations (Scheme 2.20), which became my starting point.
His chosen unsaturated sulfonamide 236 was readily prepared from commercially-available ketone 233 by sequential oxime formation 234, reduction to the corresponding amine 235 and, finally, \(N\text{-tosylation}\) by \(para\)-methylbenzene sulfonyl chloride in the presence of triethylamine. Each of these three steps gave essentially quantitative yields (Scheme 2.20). At this time, it had been discovered by Henderson, another member of the group, that concentrated sulfuric acid could equally well be used in place of triflic acid, thereby both reducing costs significantly and also providing a much more ‘certain’ acid quality, as the sulfuric acid was sourced from a 1.5 L bottle whereas the extremely hygroscopic triflic acid came in relatively expensive 10 ml batches. Older samples were undoubtedly contaminated with varying levels of water. The major drawback with the use of concentrated sulfuric acid is its high viscosity, which meant that it was quite difficult to measure accurately a small quantity while keeping it dry. It was also essentially insoluble in the usual solvent for these acid-catalysed cyclisations, dichloromethane.

![Scheme 2.20](image)

All of Alexis’ experiments were carried out using concentrated sulfuric acid, c.H\(_2\text{SO}_4\). The idea was the same as for the initial pyrrolidine synthesis (Scheme 1.27): protonation of the alkene group in unsaturated amine 236 should provide predominantly or only the tertiary carbenium ion 238, leading to the piperidine 237 (Scheme 2.21).

![Scheme 2.21](image)
In one of his attempts to form piperidine 237, treatment of the sulfonamide 236 with 0.2 equivalents of c.H₂SO₄ gave only the piperidine 237! Alexis tried many times to repeat the cyclisation to give the piperidine 237, but was unable to do so, despite working carefully. It was at this point that the present project began. In this extended study, pyrrolidine 239 was the only product that could be found after 60 minutes of exposing sulfonamide 236 to catalytic amounts of pure concentrated sulfuric acid, c.H₂SO₄, at room temperature, 20 °C, which formally involved formation of a secondary carbenium ion. This result was unexpected as the cyclisation appears to proceed via a less stable secondary carbocation intermediate but did confirm the original findings made by Haskins (Scheme 2.22).

Scheme 2.22

The evidence of cyclisation came from, mainly, ¹H NMR analysis of the crude product.

i) The disappearance of =CH proton and NH₉s proton at (δ_H = 4.91, 4.21 ppm respectively; Fig. 2.1) confirmed the full conversion of sulfonamide 236 into a cyclic product. ii) The peak corresponding to NCH proton was distinguishable among the reactant sulfonamide 236 (δ_H = 3.41 – 3.01 ppm) and both piperidine 237 (δ_H = 4.45 – 4.55 ppm), pyrrolidine 239 (δ_H = 3.66 – 3.32 ppm) products (Fig. 2.2 and 2.3). iii) Clearly, the methyl peaks on double bond =C(CH₃)₂ in sulfonamide 236 (δ_H = 1.51 and 1.45 ppm, Fig. 2.1) completely have disappeared to give four peaks as doublet related to isopropyl CH(CH₃)₂ in pyrrolidine 239 cis/trans 1.4:1 (Fig. 2.2) and two sharp singlets in piperidine 237 (Fig. 2.3).
Figure 2.1 $^1$H NMR spectrum of sulfonamide 236 in CDCl$_3$ (400 MHz).

Figure 2.2 $^1$H NMR spectrum of pyrrolidine 239 in CDCl$_3$ (400 MHz)
Figure 2.3 $^1$H NMR spectrum of $N$-tosyl piperidine 237 in CDCl$_3$ (400 MHz).

By repeating the reaction, as can be seen in Table 2.1, sulfonamide 236 was completely converted into pyrrolidine 239 after one hour at 20 °C (entry 1). There were no products after three hours at -30 °C (entry 2). There was still present about 75% of the starting material, sulfonamide 236 after two hours at -30 °C (entry 3). After 90 minutes of reaction at -10 °C, there was still present 53% of the sulfonamide 236 and pyrrolidine 239 started to appear in the reaction mixture with 35% piperidine 237 (entry 4). The best result was after 60 minutes at 0 °C with 2% pyrrolidine 239 and 73% piperidine 237 as a major product present in the reaction mixture but still ca. 25% of starting material 236 (entry 5). When the reaction was left for just 6 minutes at room temperature 20 °C, there was still 48% starting material 236, but with 45% pyrrolidine 239 and 7% piperidine 237 (entry 6). Alexis’ original result (the $^1$H NMR which appeared as Fig. 2.3) could never be repeated despite many attempts, clearly there must be a very small “window” of acid concentration and reaction temperature. The reasonable result obtained in entry 5 allowed the separation by simple crystallization of a good sample of the desired piperidine 237; its $^1$H NMR spectrum is reproduced in
**Fig. 2.3.** The observed NCH resonance at $\delta_H = 4.45 - 4.55$ ppm allowed for its easy quantification in mixtures with sulfonamide 236 and pyrrolidine 239 (Fig. 2.1 and 2.2).

**Table 2.1** c,H$_2$SO$_4$, DCM, percentages as determined from $^1$H NMR spectra integration depending on NCH proton, with N-Ts as a protecting group.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time / min</th>
<th>Temperature °C</th>
<th>SM 236 : Pip 237: Py 239</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>20</td>
<td>0 : 0 : 100</td>
</tr>
<tr>
<td>2</td>
<td>180</td>
<td>-30</td>
<td>100 : 0 : 0</td>
</tr>
<tr>
<td>3</td>
<td>120</td>
<td>-30</td>
<td>75 : 18 : 7</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>-10</td>
<td>53 : 35 : 12</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>0</td>
<td>25 : 73 : 2</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>20</td>
<td>48 : 7 : 45</td>
</tr>
</tbody>
</table>

Extra evidence of cyclisation came from $^{13}$C NMR: sulfonamide 236 showed one quaternary carbon on double bond at 132.5 ppm and two methylene carbons at 37.3 and 24.2 ppm. Piperidine 237 showed one quaternary carbon near to nitrogen at 58.2 ppm and three methylene carbons at 41.0, 30.2 and 15.3 ppm. Pyrrolidine 239 showed no quaternary carbon on the center of the reaction, two methylene carbons and three methine carbons two of them near to nitrogen and another related to isopropyl group CH(CH$_3$)$_2$ ; as can be seen in **Table 2.2**.
Table 2.2 Some peaks from $^{13}$C NMR spectra of sulfonamide 236, piperidine 237 and pyrrolidine 239.

<table>
<thead>
<tr>
<th>$^{13}$C NMR ppm</th>
<th>$^{13}$C NMR ppm</th>
<th>$^{13}$C NMR ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cq</td>
<td>$=\text{C(CH}_3)_2$ : 132.5</td>
<td>NCq : 58.2</td>
</tr>
<tr>
<td>CH</td>
<td>$=\text{CH}$ : 123.7</td>
<td>NCH : 50.6</td>
</tr>
<tr>
<td>CH$_2$</td>
<td>2 x CH$_2$ : 37.3, 24.2</td>
<td>3 x CH$_2$ : 41.0, 30.2, 15.3</td>
</tr>
</tbody>
</table>

The above evidence suggest that piperidine 237 is unstable under such acidic conditions. This conversion could possibly occur through a series of equilibria, where piperidine 237 is the kinetic product and pyrrolidine 239 the thermodynamic product (Scheme 2.23). We suggest this involves a new type of piperidine rearrangement. This rearrangement could be taking place because of steric hindrance in the suggested conformation of N-tosyl 2,2,6-trimethylpiperidine 237a (Scheme 2.23).

![Scheme 2.23](image)

The structure of piperidine 237 was confirmed by X-ray crystallographic analysis: the methyl substituent was found to be in an axial orientation (Fig 2.4). It seems to be the same in solution: the 6-H resonates at $\delta_H = 4.45 - 4.55$ ppm in deuterated chloroform, CDCl$_3$, as a broad resonance with a peak width at half height of $\omega_{1/2} < \text{ca. } 16-17$ Hz. As this already contains a quartet of $J = 6.9$ Hz, due
to coupling with the 6-methyl group, the presence of a large, *trans*-diazial coupling of *ca.* 12-14 Hz is not possible. The broadened apparent pentet must be from a fifth coupling of *ca.* 6.9 Hz to one of the protons at the 5-position of the piperidine ring. The remaining proton must have a small coupling constant to the 6-H (*< ~ 3 Hz*) resulting in only peak broadening. With no large coupling, 6-H cannot be an axial proton and the 6-methyl group therefore must be axial.

**Figure 2.4** The X-ray structure of piperidine 237. Full crystallographic data is included in Appendix 1.

In 2,6-dimethylpiperidines Chow *et al.*[^31] found that the favoured structure was where the α-methyl groups were in an axial orientation (**Figure 2.5**) to avoid the interaction between the oxygen of the acyl group and the α-equatorial methyl, if they were so positioned.

**Figure 2.5** Structures of axial and equatorial of 2,6-dimethylpiperidine 241a,b

Equatorially substituted 2-piperidines are well recognized to be less stable than their axially substituted isomers due to A[^14] strain so *N*-Boc piperidines 242a would be expected to undergo conformational equilibration to 242b (**Figure 2.6**).[^32]
This phenomenon seems to be the same in N-tosyl-2,2,6-trimethylpiperidine 237. The interaction between the oxygen atoms of the tosyl group and the α-equatorial methyl in 237a is severe and thus the favoured structure is 237b, where the single α-methyl group is in an axial orientation (Figure 2.7).

The reason behind using a tosyl group (Ts) as a protecting group was its high stability, which makes it compatible with a wide variety of reactions conditions. Although the tosyl group is very useful when carrying out reactions under harsh conditions, unfortunately, it is this very stability that makes it very difficult to remove without disrupting other sensitive functionalities in the molecule. Most detosylation reactions require some very harsh reducing conditions often based upon a single electron transfer mechanism. The electron source for this process is usually lithium or sodium in liquid ammonia. Electrons will attack the sulfur atom of the sulfonamide 243a which breaks the molecule into two parts 244a and 245 then the resulting sulfanyl radical 244a is further reduced with another electron to the corresponding anion 244b (Figure 2.8).\textsuperscript{33}
Although this radical reaction is very demanding in the synthesis of sensitive natural products, it has been used many times during such total syntheses. For example, removal of the $N$-tosyl protecting group in sulfonamide 246 was accomplished by treatment with lithium in ammonia which did not affect any stereo-centers or the alkene and hydroxyl group during a total synthesis of Fawcettimine 248 (Scheme 2.24).\textsuperscript{34}

Since it has been found $N$-tosyl-2,2,6-trimethylpiperidine 237 was rapidly converted into the corresponding isopropyl pyrrolidine 239 under hydroamination conditions (Scheme 2.22), it was important to investigate if other piperidines would undergo the same rearrangement. In the present study, 2,2-dimethylpiperidine sulfonamide 249 was synthesized by acid catalyzed hydroamination reaction in the presence of 0.6 equivalent of sulfuric acid in just 50 minutes at room temperature ($20^\circ$C) in an excellent yield of 98%. The evidence of cyclisation came from $^1$H NMR analysis. The disappearance of olefinic proton $=\text{CH}$ and $\text{NHT} \text{s}$ proton at $\delta_H = 4.91$, 4.60 ppm respectively confirmed the full conversion of sulfonamide 249 into a cyclic product. The two methyl peaks on double bond $=\text{C(CH}_3)_2$ in sulfonamide 249 at $\delta_H = 1.58$ and 1.46 ppm have moved to the high field as
a sharp singlet at 1.18 ppm. $^{13}$C NMR spectra of piperidine 250 showed a quaternary carbon at 57.9 ppm (NCq) with four CH$_2$ carbons at 43.7, 41.3, 26.2 and 20.5 ppm. Piperidine 250 showed no rearrangement to 2-isopropyl-1-tosylpyrrolidine 251 even after exposure to 0.4 equivalent of triflic acid for 18 hours at room temperature (20 °C). A trace of pyrrolidine 251 appeared after sulfonamide 249 was refluxed with 0.5 equivalent of triflic acid for 1.5 hours in toluene (110 °C). Nearly 80% of piperidine 250 rearranged to pyrrolidine 251 after 25 hours of reaction with 0.5 equivalent of triflic acid in toluene (110 °C), as judged by the appearance of isopropyl CH(CH$_3$)$_2$ due to pyrrolidine 251 in $^1$H NMR spectra (Scheme 2.25).

![Scheme 2.25](image)

Scheme 2.25

Piperidine 250 was synthesized stating from prenyl bromide 252. Treatment of the anion of acetonitrile at -70 °C with prenyl bromide 252 by an S$_N$2 reaction resulted in the formation of 5-methyl-4-hexene nitrile 253. Reduction of this nitrile by LiAlH$_4$ gave the corresponding amine 254. Finally $N$-tosylation using tosyl chloride in the presence of triethylamine in dichloromethane gave the desired sulfonamide 249. All of these reactions proceeded in essentially quantitative yields (Scheme 2.26). This all seems consistent with the idea of steric hindrance causing the forgoing rearrangement (Scheme 2.23).

![Scheme 2.26](image)

Scheme 2.26
Recently, Saikia et al. also synthesized 2,2-dimethylpiperidine 250 by acid-catalyzed hydroamination reaction in the presence of boron trifluoride–diethyl ether as a Lewis acid in good yield (82%) (Scheme 2.27).36

![Scheme 2.27](image)

We confirmed the structure of piperidine 250 by X-ray crystallography. Full crystallographic data is included in the Appendix 2.

![Figure 2.9](image)

**Figure 2.9** The X-ray structure of piperidine 250.

Due to the limitations seen with tosyl (Ts) as a protecting group for the production of 2,2,6-trimethylpiperidine, a new protecting group was needed. In the case of the acid-catalyzed cyclisation reaction, the protecting group obviously should be stable to strong acid. Para-nitrobenzenesulfonyl (p-nosyl; Ns) ia an analogue of the tosyl (Ts) protecting group, but can be readily removed. The nosyl group is more electron withdrawing than the tosyl protecting group, which could offer more benefit to the reaction as the lone pair of the nitrogen is less available, then protonation is more likely to occur on the dipole bond. On the other hand, the nitrogen-hydrogen bond will be weaker and more likely to cleave, which should help the cyclisations. Nosylation of an amine is a relatively simple
reaction and 4-nosyl chloride is a commercially available compound which reacts with an amine in the presence of triethylamine. Nosyl deprotection can be achieved by using sulfide anions which perform an ipso-attack on the benzene ring generating Meisenheimer complexes 257, 37 which is stabilised by the electron withdrawing of the nitro group. This intermediate decomposes to the aryl sulphide 258, the liberated amine 259 and sulphur dioxide. A variety of sulphides have been used by Fukuyama 38 for this denosylation reaction, including potassium thiophenolate and lithium thioglycolate (Figure 2.10).

![Figure 2.10](image)

Using nosyl (Ns) as a protecting group did not give better results (Scheme 2.32): as can be seen in Table 2.3, when nosyl sulfonamide 260 was treated with 0.5 equivalents of c.H₂SO₄ gave only pyrrolidines 269 after one hour at room temperature (entry 1). After 60 minutes of reaction at 0 °C, there was still 48% of the starting material 260 present and pyrrolidine 262 starts to appear in the reaction mixture 6% with 46% piperidine 261 (entry 2). The best result was after 180 min at 0 °C with 19% pyrrolidine 262 and 66% piperidine 261 as a major product, which was isolated by crystallization (entry 3). When the reaction has been left for just twenty minutes at room temperature (20 °C) there was still 13% starting material, but with 78% pyrrolidine 262 (entry 4).

![Scheme 2.28](image)
Table 2.3 c. H₂SO₄, DCM, percentages as determined from ¹H NMR spectra integration depending on NCH proton, N-Ns as a protecting group.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time / min</th>
<th>Temperature °C</th>
<th>SM 260 : Pip 261 : Py 262</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>20</td>
<td>0 : 0 : 100</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>0</td>
<td>48 : 46 : 6</td>
</tr>
<tr>
<td>3</td>
<td>180</td>
<td>0</td>
<td>15 : 66 : 19</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>20</td>
<td>13 : 9 : 78</td>
</tr>
</tbody>
</table>

The structure of piperidine 261 was confirmed by X-ray crystallographic analysis: the methyl substituent is in axial orientation once again (Fig 2.11).

Figure 2.11 ¹H NMR spectrum of N-nosyl piperidine 261 in CDCl₃ (400 MHz) with the X-ray structure. Full crystallographic data is included in the Appendix 3.
Steric hindrance is the key reason behind the Ts- and Ns- substituted piperidine sulfonamides rearrangements to pyrrolidines as the tosyl and nosyl groups are bulky groups. It seemed reasonable that if the steric bulk of the tosyl and nosyl groups was playing a role in the favoured synthesis of pyrrolidines over the piperidines then surely changing the bulk of the nitrogen protecting group to a smaller size could improve the chance of achieving a piperidine synthesis. Alternative protecting groups were therefore tried. Methanesulfonyl (mesylate, Ms), was chosen due to its chemical similarity to the tosyl and nosyl protecting groups. The mesylate belongs to the sulfonamide family of protecting groups but has less steric hindrance and is less electron withdrawing than the tosyl. The mesyl sulfonamide 263 was prepared in the same manner starting from the amine 235 (Scheme 2.29).

Unfortunately, after more than four attempts of cyclisation in different conditions of time and sulfuric acid equivalents, methanesulfonamide 263 gave neither piperidine 264 nor pyrrolidine 265 when treated with c.H₂SO₄. In fact all that was observed was starting sulfonamide 263 and some amine 235, where the methanesulfonyl group had been removed, thus making it a totally inappropriate protecting group for this type of acid-induced hydroamination reaction (Scheme 2.30).
Amides

The amide functionality is ubiquitous in life, as proteins play a crucial role in virtually all biological processes such as enzymatic catalysis, transport/storage, antibodies and mechanical support. In bio-system, protein synthesis involve a sequence of amide bond formation between two α-amino acids in very complex sequence of every protein. A deep analysis of the Comprehensive Medicinal Chemistry database revealed that the carboxamide group appears in more than 25% of known drugs. This can be expected, since carboxamides are neutral, stable and have both hydrogen-bond accepting and donating properties. Amides can participate in hydrogen bonding with water and other protic solvents; the oxygen and nitrogen atoms can accept hydrogen bonds from water and the N-H hydrogen atoms can donate H-bonds. The strongly electron withdrawing nature of the carbonyl group by resonance allows for delocalization of the lone pair electrons of nitrogen, which limits the ability of the nitrogen atom to coordinate with electrophiles and also reduces the electrophilic nature of the carbonyl in amides (Fig 2.12).

Fig 2.12

Trifluoroacetamide

Because of trifluoroacetamide stability to acidic conditions and the ease in which it may be removed under mildly basic condition, the trifluoroacetamide is one of the most useful protecting group. For example, it has been used by Snider in a martinellie acid total synthesis. The alcohol reacted with trifluoroacetic anhydride TFAA and triethylamine in dichloromethane to provide trifluoroacetamide. Hydrolysis of trifluoroacetamide with potassium carbonate in methanol provided pure product in 95% yield (Scheme 2.31).
Generally, trifluoroacetamide is stable to acidic conditions such as trifluoroacetic acid (TFA) and single electron reducing agents like sodium/anthracene, which makes the trifluoroacetamide group one of the more useful amides as a protecting group. In addition, the ease in which trifluoroacetamide may be removed under mildly basic conditions can be an additional advantage. Acetamide 272 was prepared starting from the amine 235 and trifluoroacetic anhydride in the presence of pyridine in dichloromethane. Unfortunately, the trifluoroacetamide group was found to be unstable to our acidic hydroamination conditions. After exposure of trifluoroacetamide 272 to catalytic amount of sulphuric acid for 10 minute at 0 °C, the only product which could be seen was the deprotected amine and there was no trace of any piperidine 273 (Scheme 2.32).

Scheme 2.32

Acetamide and Benzamide:

The acetamide and benzamide amine protecting groups have been widely used in synthesis because they offer the advantage of excellent stability to a wide range of conditions. The simplest
Methodology for acetamide and benzamide preparation reacts the amine with a carboxylic acid anhydride or carboxylic acid chloride and a base. Generally, acetamide and benzamide deprotection requires harsh conditions than trifluoroacetamide such as refluxing in aqueous solutions of HCl for long periods (8-72 hours), which was not always compatible with sensitive functionality.\textsuperscript{41}

**Acetamide:**

Jackson\textsuperscript{42} achieved an enantioselective cyclisation towards \(N\)-acetyl protected 5,5-dimethylproline methyl ester \(276\) from \(N\)-protected prenylglycines \(274\). After four hours of reaction with 20\% triflic acid in toluene at 100 °C, acetamide \(274\) cyclised to the dimethylproline \(275\) in quantitative yield (96\%). Acid catalysed hydrolysis of the protected proline \(275\) then afforded pure 5,5-dimethylproline \(276\) in 90\% yield and 98\% ee after chromatography (Scheme 2.33).

![Scheme 2.33](image)

Acetamide \(277\) was prepared from the amine \(235\) and acetic anhydride in the presence of pyridine in dichloromethane. After five attempts of cyclisation under different conditions of time and temperature. After 50 min of reaction with c.H\(_2\)SO\(_4\) at room temperature, acetamide \(277\) converted to piperidine \(278\) in 85\% yield. After one hour of reaction at the same condition, a trace of starting material was observed in \(^1\)H NMR spectra and \(^{13}\)C NMR spectra showed a quaternary carbon at 70.7 ppm (NCq, 2-C), methine carbon at 45.1 ppm (CHN, 6-CH) and three CH\(_2\) carbons (43.3, 37.3, 20.6 ppm). After one hour of reaction with 0.5 equivalent of triflic acid at room temperature, the acetamide \(277\) did decomposed to starting amine \(235\), where the protecting group had been removed (Scheme 2.34).
Hartwig et al. found, acetamide 279 did not undergo cyclization reaction to pyrrolidine 280 even after heating in toluene for 24 hours at 100 °C with 20% TfOH. They proposed that the higher Lewis basicity of the amide 279 prevented the reaction. The protonated carbonyl is apparently not acidic enough to transfer its proton to the olefin (Scheme 2.35).

Benzamide:

We were inspired by the successful example of a Brønsted acid-catalyzed intramolecular hydroamination reaction, which was reported by Schlummer and Hartwig, in which lactams 282 were prepared after refluxing for 30 hours in toluene in the presence of stoichiometric amounts of triflic acid. These reactions were faster with the branched substrates 282b (Scheme 2.36). This extraordinarily surprising stability of lactams 282 gave us the idea of using benzamide as a protecting group.
The benzamide 285 was formed by reacting the benzyol chloride with the amine 235. An additional equivalent of pyridine was required to trap the formed HCl and to avoid conversion of the amine into its unreactive HCl salt. Seventy percent of benzamide 285 reacted with 0.5 equivalent of triflic acid at 20 °C to give piperidine 286 after 10 min in good yield 60%. It is expected that some deprotection was happened and the resulting amine was lost during the work up (Scheme 2.37). $^{13}$C NMR spectra of piperidine 286 showed a quaternary carbon at 70.8 ppm (NCq, 2-C), methine carbon at 45.7 ppm (CHN, 6-CH) and three CH$_2$ carbons (36.8, 24.7, 20.7 ppm). It has noticed in $^{13}$C NMR spectra that the quaternary carbon (NCq) in piperidine acetamide 278 and benzamide 286 is shifted to the down field (ca. 71 ppm) comparing to the same quaternary in piperidine sulfonamide 237, 250 and 261 (NCq, ca. 58 ppm).

\[
\begin{align*}
\text{NH}_2 & \quad \text{PhCOCl} & \quad \text{NHCOPh} \\
\text{pyridine, DCM} & \quad \text{EtOH, DCM} & \\
235 & \quad 285 & \quad 286
\end{align*}
\]

Scheme 2.37

**Methyl carbamate (Moc) and Benzyl carbamate (Cbz or Z):**

Methyl carbamate and benzyl carbamate groups can easily be formed from amines. Both methyl chloroformate ClCO$_2$Me and benzyl chloroformate ClCO$_2$CH$_2$Ph are commercially available and can simply react with an amine in the presence of base.

**Benzyl carbamate**

The first “modern” protecting group was the benzyloxycarbonyl (Z), which was developed in 1932 by Bergmann and Zervas.$^{44}$ Benzyloxycarbonyl fits with the main characteristics associated with a protecting group: (1) it is easily introduced into the functional group; (2) it is stable to a broad range of reaction conditions; and (3) it is safely removed at the end of the synthetic process or when the functional group requires manipulation.$^{45}$
Benzyl carbamate cleaves by catalytic hydrogenolysis\textsuperscript{46} and can be readily cleaved under acidic condition: acetic acid\textsuperscript{47}, triflic acid\textsuperscript{48}, methanesulfonic acid\textsuperscript{49} and trifluoroacetic acid.\textsuperscript{50} The expected mechanism of acidic benzylloxycarbonyl deprotection is that carbamate \textsuperscript{287} becomes protonated to trigger loss of benzylic cation \textsuperscript{289}, which results in the carbamic acid \textsuperscript{290} then decarboxylation of this gives the free amine \textsuperscript{291} (Fig 2.13).

![Chemical structure](image)

Fig 2.13

When Hartwig\textsuperscript{43} tried to examine the stability of benzyl carbamates to acidic conditions, he found that amide \textsuperscript{292} did not undergo acid-catalysed hydroamination reaction even after heating in toluene for 24 hours at 100 °C with 20% TfOH; the same result was obtained with sulfuric acid (Scheme 2.38).

![Chemical structure](image)

Scheme 2.38

Obviously, benzylloxycarbonyl is quite unlikely to be stable in such strong acidic conditions, but the wide usage of this important protecting group encouraged us to try it, especially as the amine \textsuperscript{235} had already been prepared in large quantity. In the present project, benzyl carbamate \textsuperscript{294} was prepared by reaction of the amine \textsuperscript{235} with benzyl carbonochloridate (Scheme 2.39).

![Chemical structure](image)

Scheme 2.39
After seven minutes of reaction with catalytic amount of sulfuric acid at room temperature benzamide 294 gave the piperidine 295 (71%) and no rearrangement to pyrrolidine nor the starting benzyl carbamate 294 were observed just simple filtration over silica was needed (Scheme 2.40).

![Scheme 2.40](image)

Both $^1$H and $^{13}$C NMR spectra support the successful synthesis of piperidine 295; as can be seen from Fig 2.14, starting material 294 had clearly disappeared. Most obvious was the disappearance of the olefinic $=CH$ at 5.10 ppm and NH proton at 3.70 – 3.53 ppm, with the appearance of the NCH of piperidine 295 at 4.35 – 4.25 ppm and OCH$_2$Ph protons showing clear AB coupling system after cyclisation at $\delta_H$ 5.07 (d, $J = 12.5$, 1H, OCH$_A$H$_B$) and 5.02 (d, $J = 12.5$, 1H, OCH$_A$H$_B$). $^{13}$C NMR showed a quaternary carbon next to the nitrogen atom at 54.4 (NCq, 2-C), NCH (6-C) carbon at 48.3 ppm, and three CH$_2$ carbons on the piperidine ring at 39.2, 28.3 and 14.7 ppm (Fig 2.14).

![Fig 2.14](image)
Methyl carbamate Moc

Methyl carbamate can be cleaved by many methods, one widely used method employs trimethylsilyl iodide, TMSI. This electron rich carbamate is cleaved preferentially by running the reaction in refluxing dichloromethane with 2.2 equivalent of TMSI. The resulting product 297 was isolated in 95% yield; this step was used during a strychnine total synthesis (Scheme 2.41).\textsuperscript{51}

![Scheme 2.41](image)

The effect of protecting group on acid-catalysed cyclisation reaction was studied widely in Knight’s group. When Haskins in Knight’s group heated Moc protected substrates 298 with two equivalents of triflic acid at 25 °C after two hours pyrrolidine 299 was formed in reasonable yield (69%) (Scheme 2.42).\textsuperscript{52}

![Scheme 2.42](image)

In the present study, piperidine 301 was successfully synthesized after 55 min at room temperature with a catalytic amount of sulfuric acid (87% yield); no rearrangement to pyrrolidine nor the starting carbamate 300 were observed. The reactions did not require any chromatography as the reaction proceeded cleanly. The same piperidine carbamate gave an excellent yield 96% when triflic acid was used (0.4 equivalent) with somewhat less time (30 min) at the same temperature 20 °C (Scheme 2.43).
From the appearance of the $^1$H-NMR spectrum of 2,2,6-trimethylpiperidine carbamate 301, clearly a single conformation at ambient temperature can be seen. The 6-H resonates at $\delta_H 4.24 – 4.17$ (pentet, $J = ca. 6.9 \text{ Hz}$) in appearance exactly as the $N$-tosyl analogue. With no large coupling, 6-H cannot be in an axial position and the 6-methyl group therefor once again has an axial orientation, which is the same in the case of benzyl 2,2,6-trimethylpiperidine carboxylate (Fig 2.14a) where the 6-H resonates at $\delta_H 4.35 – 4.25$ (br. pentet, $J = ca. 6.9 \text{ Hz}$).

![Image of chemical structures](image)

**Fig 2.15**

The generality of this chemistry was next tested by using substituents that were somewhat less able to provide stabilisation of a positive charge, such as cinnamyl and crotyl. After much experimentation, the best conditions were found for both cinnamyl and crotyl. Cinnamyl ketone 303 was synthesized by refluxing ethyl acetoacetate 302 with cinnamyl chloride in tetrahydrofuran in the presence of potassium carbonate $\text{K}_2\text{CO}_3$ for 20 hours (55% yield). This was then converted into the oxime 304 by a standard oximation reaction then reduced by $\text{LiAlH}_4$ to give the amine 305. Finally, carbamate was added by using methyl chloroformate in the presence of triethyl amine; all of these reactions proceeded in good yields. The cyclisation reaction of cinnamyl carbamate 306 was carried out with 0.5 equivalent of sulphuric acid at room temperature for 20 hours (Scheme 2.44).
Two possible carbenium ions can form from carbamate 306; however the benzylic carbenium ion 306a is much more likely to form than the isomeric 306b due to the stabilisation afforded by the phenyl group, resulting in the exclusive formation of piperidine 307 after 20 hours of reaction using 0.5 equivalent of sulphuric acid at ambient temperature, which were the optimum condition found. The $^1$H NMR spectrum showed no starting material was present. Benzylic carbocation 306a would give the desired piperidine product 307 through an overall 6-endo-trig process, which is favoured according to Baldwin’s rules; whereas secondary ion 306b would give the pyrrolidine ring 308, which would occur through an overall 5-exo-trig process, which is also favoured by Baldwin’s rules (Scheme 2.45).

A single isomer was formed and identified by a clear, rather high field methyl doublet at $\delta_H$ 0.70 ($J = 7.1$ Hz, 3H) and two low field resonance at $\delta_H$ 4.51 – 4.42 and $\delta_H$ 5.41 ppm both integrating for one proton. The one resonating at $\delta_H$ 4.51 – 4.42 was the same in its appearance as all of the above 6-H resonances at $\delta_H$ 4.51 – 4.42 ($app. br. pentet, J = ca. 7$ Hz). The resonance at $\delta_H$ 5.41 was narrower.
and appeared as a broadened apparent doublet ($J = ca. 5.2$ Hz). This proton had, more important for comparison purposes with width at half height of $\omega_{1/2} = 10.4$ Hz, which clearly excluded the presence of a large trans-diaxial coupling constant and hence placed the 6-phenyl group also in an axial position implying a 2,6-cis geometry for the 2-methyl-6-phenylpiperidine carboxylate 307a obtained.

A trans-configuration would place one of the protons α-to the nitrogen atom in an axial position (Fig 2.16 and 2.17).

**Figure 2.16**

[Diagram showing structures 307a and 307b]

**Figure 2.17** $^1$H NMR spectrum of 2-methyl-6-phenylpiperidine 307a, 6-CH proton width at half height of $\omega_{1/2} = 10.4$ Hz, in CDCl$_3$ (500 MHz).
Even with the likely distortion of the ring due to the single axial substituent, it is surely very likely that a single large coupling constant would be evident in the resonance of one of these protons. Presumably, the phenyl ring would be positioned at the angle shown above 307a, otherwise it would begin to interact sterically with the methyl group protons. Hence, the 2-methyl group is positioned over the face of phenyl group, which may explain its rather high chemical shift at $\delta_H$ 0.75 ppm. Further, the 3-equatorial proton is adjacent to the edge of the 6-phenyl group which would account for its low field position at $\delta_H$ 2.40 ppm, relative to remaining methylene protons, where it appears as a broadened doublet ($J = 7.2$ Hz), due to a single large germinal coupling with H$_{3ax}$. Prolonged exposure to 0.4 equivalent of triflic acid at 20 °C for 20 hours caused significant (ca. 30%) conversion into what appeared to be isomeric pyrrolidines although this was not confirmed. In any event, this observation shows the importance of stopping the acid–catalysed cyclisation immediately it is completed.

Crotyl oxime 309 was prepared starting from acetone oxime 308 in THF with n-butyllithium in hexane: the mixture was cooled to -78 °C, a solution of crotyl chloride 309 in THF was added dropwise. This was followed by LiAlH$_4$ reduction to the amine 311 and finally the carbamate group was added.$^{54}$ The cyclisation reaction of crotyl carbamate 312 was carried out with 0.5 equivalent of triflic acid at 40 °C for 3.5 hours to give pyrrolidine 313 (98%, cis:trans 1:1 ratio). In $^1$H NMR of the resonance at ca. $\delta_H$ 1.01 ppm (d, $J = 6.0$ Hz, 3H, CH$_3$) another methyl triplet at 0.75 (t, $J = 7.0$ Hz, 3H, CH$_3$) related to the other methyl. In $^{13}$C NMR, two methine groups (CHN) at $\delta_C$ 60.3 and 53.8 ppm, three methylene groups at $\delta_C$ 37.0, 28.8 and 25.6 ppm (Scheme 2.46).

![Scheme 2.46](image-url)
Secondary carbenium ions are more challenging to form than tertiary or benzylic examples. There are two possible secondary carbenium ions that can form from carbamate 312; these are both equally likely to form (Scheme 2.51). Trapping the secondary carbenium ion 312a will form pyrrolidine 313 through a formally overall 5-exo - process. Carbenium ion 312b would form the 6-membered piperidine ring 314, through an overall 6-endo process. Such cyclisations involving secondary carbenium ion will require higher temperatures and longer reaction time than those having tertiary carbenium or benzylic ions. Both the pyrrolidine 313 and piperidine 314 would have been formed through a secondary carbenium ion. After extensive experimentation, complete conversion to a reasonably clean pyrrolidine 313 occurred in refluxed dichloromethane after 3.5 hours with 0.5 equivalent of triflic acid (Scheme 2.47).

![Scheme 2.47](image)

The absence of 2,6-dimethylpiperidine carboxylate 314 was confirmed by the preparation of an authentic sample of cis-dimethylpiperidine carboxylate 316. The carbamate was added smoothly to commercial available cis-2,6-dimethylpiperidine 315 in quantative yield. The resonance at δH 4.30 – 4.16 ppm in 1H NMR of dimethylpiperidine 316 related to two protons on carbons near to nitrogen (NCH, 2H) and a sharp doublet at δH 1.10 (d, J = 7.1, 6H, 2 x CH3) related to two methyl groups. In 13C NMR spectra the resonance at δC 46.0 (2 x CHN, 2- and 6-CH) related to two methine groups, 30.0 (2 x CH2, 3- and 5-CH2), 20.8 (2 x CH3), 13.7 (4-CH2) ppm (Scheme 2.48).

![Scheme 2.48](image)
In view of the successful cyclisations of the prenyl derivatives, it was expected that it might well be possible to apply this methodology to the synthesis of spiro-piperidines, as this would also involve highly stabilised tertiary alkyl carbenium ions related to ion 238 (p. 37). Cyclohexylidene carboxylic acid 318 was prepared, using the Wittig reaction of cyclohexanone 317 with (4-carboxybutyl)triphenylphosphonium bromide using sodium hydride in THF (Scheme 2.49).55

![Scheme 2.49](image)

5-Cyclohexylidenepentanoic acid 318 was transformed into cyclohexylidene carbamate 319 through a Curtius sequence by heating a solution of the acid 318, diphenylphosphoryl azide (DPPA) and triethylamine under reflux for 1 h, followed by addition of methanol with catalytic amount of copper(II) chloride CuCl₂, and further heating of this mixture under reflux for 1 h (Scheme 2.50).56

![Scheme 2.50](image)

The spiro-piperidine 320 was successfully synthesized after 30 min at 0 °C with 0.4 equivalent of triflic acid (95% yield); no rearrangement to pyrrolidine nor the starting carbamate 319 were observed. The reactions did not require any chromatography as the reaction proceeded cleanly. From the appearance of the ¹H-NMR spectrum, CH₂ near to nitrogen resonates at δH 3.47 ppm as a triplet (t, J = 6.0, 2H, CH₂N). From ¹³C NMR spectrum a quaternary carbon came at δH 59.0 ppm and NCH₂ at 51.8 ppm (Scheme 2.51).

![Scheme 2.51](image)
The successful synthesis of spiro-piperidine 320 should lead to be attempted in natural product spiro-cycles such as the azaspirocyclic alkaloids isolated from the skin extracts of the neotropical frog *Dendrobates spiro-piperidine* “histrionicotoxin” 321 and nankakurine 34, a member of the Lycopodium alkaloid family that was isolated from the club moss *Lycopodium lucidulum*. It should also include rings that contain heteroatoms such as spiro-tetrahydropyran 322 and spiro-tetrahydrofuran 323, which are useful for treating HIV infection and AIDS (Scheme 2.52).

Scheme 2.52

The retrosynthetic analysis of nankakurine 34 A and B leads to core of the luciduline 326, which syntheses have been reported (Scheme 2.53). The search for a general strategy to access Lycopodium alkaloids has led Overman to suggest the asymmetric total syntheses of nankakurines 34 from luciduline 326. A few years later, the hypothesis became reality by Waters, who accomplished the total syntheses of the Lycopodium alkaloids nankakurines 34 A and B in 6 and 7 steps, respectively, via a sequence that passes through a third Lycopodium alkaloid, luciduline 326. Retrosynthetic analysis of nankakurine 34 shows that the spiro-piperidine core could be generated by acid-catalysed hydroamination from carbamate 324 (Scheme 2.53).
The suggested acid-catalysed hydroamination synthesis of nankakurines 34 A and B starting from luciduline 326 can be achieved similar to spiro-piperidine 320 (Scheme 2.54). Luciduline carboxylic acid 325 could prepare by using the Wittig reaction followed by Curtius reaction to carbamate 324, then acid-catalysed hydroamination to aza-spiro-lycopodium alkaloid 327 finally, carbamate deprotection to nankakurines 34 A by TMSI or by lithium aluminium hydride to nankakurines 34B (Scheme 2.54).

Scheme 2.54

Asymmetric Synthesis of 2,2,6-trimethylpiperidine

In organic synthesis, stereoselective construction of a chiral carbon atom adjacent to the ring nitrogen atom in 2-substituted piperidines has a special importance in total synthesis. The interest in the synthesis of substituted piperidines with stereo- and enantioselective manner have been increased. Developing a feasible and highly stereoselective route to synthesize piperidine with C-2 stereogenic center away from ring closing metathesis is a very big challenge. The optically pure 2-substituted piperidine skeleton has been used as a bulding block in the synthesis of biologically active medicinal drugs and is observed in a wide range of natural products and medicinal drugs (Scheme 1.2).
Hodgson et al.\textsuperscript{66} reported the asymmetric synthesis of $\alpha$-alkylated aldehydes 331 using terminal epoxide 328 and examined the enamine derived from this and lithium 2,2,6-trimethylpiperidide 329. They found that the latter formed the corresponding enamine in good yield, and was bulky enough to avoid potentially competing allylic alcohol/amino alcohol formation. The enamine underwent effective C-alkylation to generate $\alpha$-alkylated aldehydes 331. By contrast, the enamine derived from lithium 2,2,6,6-tetramethylpiperidine (LTMP) was slow to react, affording the $\alpha$-methylated aldehyde in only 30% yield (Scheme 2.55).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {C\textsubscript{4}H\textsubscript{9}O};
\node (b) at (2,0) {C\textsubscript{4}H\textsubscript{9}O};
\node (c) at (2,1) {C\textsubscript{4}H\textsubscript{9}O};
\draw (a) -- (b);
\draw (b) -- (c);
\node [below] at (1,-0.5) {THF, 1 h};
\node [left] at (0,0.5) {Li\textsuperscript{+}N;};
\end{tikzpicture}
\end{center}

\textbf{Scheme 2.55}

To ascertain how effective 2,2,6-trimethylpiperidine (TriMP) would be in a chiral context, Hodgson synthesized (R)-2,2,6-trimethylpiperidine 335 (>99.5:0.5 e.r.) by copper-catalyzed Grignard ring opening of enantiopure (R)-2-substituted aziridine 332 followed by formal intramolecular hydroamination reaction, a simple example of a Markovnikov type reaction of a terminal olefin 334 with a mercury(II) chloride. The amine was converted to its hydrochloride salt by the addition of hydrochloric acid in ether (2 M) to form the trimethylpiperidine salt, which re-crystallized in ethanol then the salt was dissolved in aqueous NaOH solution (3 M) to afford (R)-2,2,6-trimethylpiperidine (57%). N-Boc protected aziridine 332 itself was synthesized starting from racemic epoxide 336 using tert-butyl carbamate as the nucleophile, catalyzed by the chiral Co(III) complex called (R,R)-(−)-$N,N'$-bis(3,5-di-tert-butyrsalicylidene)-1,2-cyclohexanedianinocobalt [AKR] (Scheme 2.56).
Scheme 2.56

When methyl enamine (R)-330 was used as a single enantiomer in alkylations with ethyl iodide and allyl bromide, the corresponding α-alkylated aldehydes were formed in satisfactory e.r. values (88:12 e.r. and 84:16 e.r., respectively), with the sense of asymmetric induction as shown in Scheme 2.57. Workup after enamine alkylation using AcOD/NaOAc/D$_2$O showed no deuterium incorporation, indicating that no loss of enantiointegrity occurred during hydrolysis.

Scheme 2.57

In the present study, (S)-2,2,6-trimethylpiperidine 344 was synthesized starting from (S)-alaninol 338 which was N-protected selectivity over oxygen by using methyl chloroformate ClCO$_2$Me. The direct reaction of N-protected amino alcohol 339 with the Hata$^{67}$ reagent (diphenyl disulfide and tributylphosphine), used under the modified conditions (76 °C, for 72 h), afforded the desired phenyl sulfide 340 in low yield (28%).$^{68}$ The oxidation with aqueous hydrogen peroxide was carried out on phenyl sulfide 340 at 40 °C in methanol with two equivalent of 30% aqueous hydrogen peroxide H$_2$O$_2$ and a catalytic amount of sodium tungstate dehydrate Na$_2$WO$_4$.H$_2$O to give sulfone 341 in good yield (88%)$^{69}$ (Scheme 2.58).
Scheme 2.58

Prenyl bromide was added to sulfone 341 by using n-BuLi in tetrahydrofuran at -78 °C to give an inseparable mixture of isomers 342. The acid-catalysed cyclization reaction of sulfone 342 with sulfuric acid gave pure (S)-2,2,6-trimethyl-5-(phenylsulfonyl)piperidine 343 after two hours of reaction at ambient temperature in excellent yield of 98% then, followed desulfonylation reaction by magnesium in cold dry methanol to give (S)-trimethylpiperidine 344 (Scheme 2.59).

Scheme 2.59

The intermediate sulfone 343 was observed as a single enantiomer. In $^1$H NMR, the 6-H resonates at δ_H 4.59 (qd, J = 6.9, 4.4 Hz, NCH) ppm in deuterated chloroform, CDCl$_3$, as this already contains a quartet of J = 6.9 Hz, due to coupling with the 6-methyl group. With no large coupling, 6-H cannot be an axial proton and the 6-methyl group therefore once again has an axial orientation, which is the same in the case of benzyl 2,2,6-trimethylpiperidine carboxylate (Fig 2.14a) and 2,2,6-trimethylpiperidine carbamate (Fig 2.15). Only one large coupling was observed for 5-H (343A), which resonates at δ_H 3.18 (ddd, J = 10.8, 7.6, 4.4 Hz, 1H, PhSO$_2$CH) ppm. If 6-proton was axial (343B) we would expect two large coupling constants (Figure 2.18).
Conclusion

The acid-catalysed cyclisation we have developed appears to offer a very fast route to substituted piperidines. The reaction proceeds quickly in good yields and the starting materials can readily be prepared from ketone in just three steps. We have been able to prepare a range of piperidines using this technique, included one hindered spiro compound and one highly enantioselective chiral piperidine.

2,2,6-Trisubstituted piperidine underwent rearrangement to the corresponding pyrrolidine by using sulfonamide as the $N$-protecting group. A wide range of alternative protecting groups has also been employed in the cyclisation, thus solving the problem incurred in rearrangement to pyrrolidine. This problem has been solved by changing the protection group to carbamate and benzyloxycarbonyl which allowed 2,2,6-trimethylpiperidine to be isolated cleanly without any visible traces of pyrrolidine, thus solving another problem incurred in deprotection the sulfonamide products. The deprotection of sulfonamide protecting groups required very harsh chemistry comparing to carbamate. In the light of the result obtained when nosyl as a protecting group was used, it would be rewarding to use the nosyl group over tosyl.

The concentrated sulfuric acid could equally well be used in place of triflic acid, thereby both reducing costs significantly and also providing a much more ‘certain’ acid quality. The major drawback with the use of concentrated sulfuric acid is its high viscosity, which meant that it was quite difficult to measure accurately a small quantity while keeping it dry. Although its availability and lower price gave sulfuric acid an advantageous cyclizing agent, over triflic acid, when using sulfuric acid as catalyst yields were generally lower. Triflic acid is relatively easier to handle, but it is not easy to keep it dry.

A new, general and flexible method for the highly enantioselective synthesis of chiral piperidine has been developed. The main advantages of this synthetic method lie in the readily availability of the precursors. There is no reason why this reaction cannot find further application in natural product synthesis. The compatibility of applying the acid-catalysed methodology to related polyene cascade cyclisations and other bicyclic system syntheses will be focused on in the next chapter.
References


Chapter 3

Acid-catalyzed cyclisations in synthesis
Chapter 3

Acid-catalyzed cyclisations in synthesis

3.1. Introduction

Cascade reactions and transannular cyclizations are sophisticated methods for the construction of polycyclic natural products and molecules of theoretical and structural interest. An enormous variety of polyene systems and heterocyclic medium ring compounds with a wide range of functional groups has been reported to undergo these fascinating processes for modern synthetic chemistry. Such an intramolecular cyclization is largely dependent on the nature of the reaction, reactivity of the two end groups, and geometrical features of the reacting ring molecules.¹ Both cascade and transannular cyclizations require a suitable conformation of substrates and prudent selection of functional groups. Multiple fused and bridged ring systems formed by cascade and transannular cyclizations are widespread in natural products and regularly shown to exhibit biological activity against a wide variety of human diseases.²

3.2. Cascade cyclisations

Cascade reactions are one of the most fascinating branches of organic chemistry, and one which has been the subject of intense research in recent years, as witnessed by the number of reviews that have appeared covering various aspects of these reactions. The remarkable benefits of cascade reactions are well established, having been recounted on numerous occasions, and include economies of time, labor, resource management, and waste generation.³ Perhaps the first example of a noticeable beautiful total synthesis is that of the alkaloid tropinone 346 reported as early as 1917 by Robinson. It also demonstrates a cascade reaction, in which one molecule of succindialdehyde 347, methylamine 348, and either acetone dicarboxylic acid 349 or dicarboxylate react together to afford the natural substance in a simple one-pot procedure. Two consecutive
Mannich reactions are involved in this cascade reaction, the first one in an intermolecular and the second one in an intramolecular fashion (Scheme 3.1).\(^4\)

![Scheme 3.1](image)

Lanosterol 357 is a tetracyclic triterpenoid all steroids are derived from. Lanosterol formation in animals and fungi proceeds via chair-boat-chair conformation of (3S)-epoxidosqualene 356, in a cascade cyclization which is activated by an acid-catalyzed cascade reaction. During this reaction the oxirane ring opens with participation by a neighboring π-bond. The cyclization proceeds to give a protosteryl cation, which then undergoes a series of 1,2-methyl and hydride shifts with proton elimination to yield the lanosterol skeleton and is then elaborated into cholesterol 358 (Scheme 3.2).\(^5\)

![Scheme 3.2](image)
Perhydroquinoline alkaloids are varied in structure and have provided challenging targets for total synthesis. Luciduline 326, a \textit{cis}-perhydroquinoline alkaloid, is isolated from \textit{Lycopodium lucidulum}. Comins \textit{et al.} have published a total synthesis of (+)-luciduline. The key steps are intramolecular Diels-Alder reaction and subsequent reduction leading to 361, which after \textit{retro}-Mannich ring opening is converted to enecarbamate 362 (Scheme 3.3).

In summary, the asymmetric synthesis of (+)-luciduline 326 has been accomplished from readily available materials in 14 steps (10\% overall) with a high degree of stereocontrol. Completion of the synthesis requires a novel tandem cationic alkylation/reduction cyclization reaction (Scheme 3.4).

Acid-mediated cyclization of isoxazolone 364 was examined using 98\% aq. H$_2$SO$_4$ in toluene at 2°C for two hours. Isoxazolone 364 would cyclise \textit{via} its tautomer, the major product being isoxazolone 366 (62\% yield) accompanied by its \textit{cis}-fused epimer 364 (10\% yield). This unexpected preference for ring closure \textit{via} acid-catalyst hydroamination reaction is of synthetic interest (Scheme 3.5).
Scheme 3.5

Structure confirmation of *trans* product 366 was confirmed by catalytic hydrogenation ([PtO$_2$], AcOH/AcOEt 3:1, 20 °C) to perhydroquinoline 370 (17% yield). The multistep transformation is believed to proceed *via* intermediates 368a,b in a reaction sequence involving hydrogenolysis of the nitrogen-oxygen N-O bond, tautomerism, decarboxylation, and stereoselective hydrogenation from the β-face (Scheme 3.6).$^9$

Scheme 3.6

The first total synthesis of nankakurines B 34b was accomplished by Overman in 2008 *via* an acid-catalysed cascade reaction. The desired nitrogen-terminated aza-Prins bis-cyclization could be realized by reaction of the methyl carbamate 371 with one equivalent of paraformaldehyde and 20 equivalent of TFA at room temperature in chloroform. The yield of this reaction was low (20%) and the amount of 373 was 20 mg; after two additional reductive steps nankakurines B 34b was prepared. $^1$H and $^{13}$C NMR spectra of this product were quite different from those reported for nankakurine A.$^{10}$ confirming that the initial structural assignment for this alkaloid was incorrect.
The total syntheses of (+)-nankakurine B 34b was accomplished in 14 steps (5 mg, 16% overall yield) (Scheme 3.7). 

Scheme 3.7

Cationic polyene cyclisations may be used to synthesize two, three, four or even five rings in one step reactions. Although the first example of acid-catalyzed intramolecular hydroamination reaction was reported by Hartwig, the acid-catalyzed cyclizations which have been developed in Knight’s group offer a very wide range of routes to highly substituted pyrrolidines and piperidines, not only single saturated nitrogen containing heterocyclic compounds including very hindered spiro ones, but also polycyclic compounds. Haskins applied acid-catalyzed intramolecular hydroamination methodology to the synthesis of polycyclic compounds through a cationic cascade terminated by a sulfonamide group. Cationic polyene cyclisations have been previously used in the biomimetic synthesis of steroid skeleton for several years but not with nitrogen groups as terminators. When the geranyl sulfonamides 374 were treated with 0.4 equivalent of triflic acid under the midest set of reaction conditions (15 minutes at 0 °C), these underwent rapid cyclisation to give ca. 90% isolated yields of the trans-annulated pyrrolidines 375, both as 3:2 mixtures, epimeric at the amino ester stereogenic centre. This assignment of structure was confirmed by a single crystal X-ray crystallographic determination of a separated sample of the major isomer of the glycine derivative 375. Sulfonamides 376 cyclized under the same conditions of the bicyclic systems 375 in 86% yield as 3:3:1:1 mixture of diastereoisomers 377. The tetracyclic compounds 379 were formed as a gross mixture of diastereoisomers in 80% yield. As expected, the yield of such reactions decreases as the number of rings formed increased (Scheme 3.8).
In the present study, it was decided to see if such methodology would be extended to the formation of piperidine rings by using cascade cyclisations. Geranyl amine 382 was prepared starting from commercial available geranyl acetone 380, supplied as a mixture of cis- (approximately 35%) and trans- isomers, (neryl acetone and geranyl acetone) by the usual conversion into the corresponding oxime 381 then reduction with lithium aluminum hydride to give geranyl amine 382. No attempt to separate the isomers was undertaken at any point in the synthesis, because it was considered that both of the cis- and trans-isomers would give the same carbocation intermediates in acid-catalysed reaction, if successful (Scheme 3.9).

Finally, N-tosylation by para-methylbenzene sulfonyl chloride in the presence of triethylamine gave the sulfonamide 383. Tosyl geranyl sulfonamide 383 was treated with a catalytic amount of sulfuric acid in dichloromethane. After 1.5 h of the reaction at 0 °C, a $^1$H NMR spectrum showed that the resonances corresponding to the two olefinic protons ($\delta_H 4.91 – 4.71$ ppm) had disappeared, whereas the NH proton ($\delta_H 4.52$ ppm) did not disappear. However, two of the three methyl singlets
which had been on double bonds (1.45, 1.83 ppm) moved to the upfield to appear as two singlets at δH 1.10, 0.79 ppm, which suggest formation of the half cyclic compound 384. There was no trace of the expected bicyclic compound 385 as 1H NMR data showed a clear spectrum between δH 4.50 - 4.00 ppm, where the NCH proton was to be found in piperidine 237, at 4.45 - 4.55 ppm. The 13C NMR spectrum enhanced this theory as two quaternary carbons appeared at δC 136.3 and 127.2 ppm, due to quaternary carbons on a double bond and a quaternary carbon at high field δC 34.9 ppm (sp^3 quaternary carbon). The same result has been noticed after 1.5 hours of reaction at room temperature (Scheme 3.10).

The structure of the half cyclic sulfonamide 384 was confirmed by preparing an authentic sample starting from β-ionone 386. The known reduction of β-ionone 386 with catechol borane in tetrahydrofuran gave the ketone 387 in good yield (80%). Classical oximation reaction of this ketone 387 produced the oxime 388, which was reduced to the amine 389 by lithium aluminium hydride in tetrahydrofuran. Finally, N-tosylation by tosyl chloride in the presence of triethylamine gave the corresponding sulfonamide 384b, which showed the same analytical and spectroscopic data as the sample obtained from the acid cyclisation (384a). Consistent with this, sulfonamide
384b did not undergo the acid-catalysed cyclisation to give the bicycle 385 even after 24 hours of reaction with concentrated sulfuric acid at room temperature in dichloromethane (Scheme 3.11).

![Scheme 3.11](image)

_N-Nosylation by nosyl chloride in the presence of triethylamine gave the sulfonamide 390. It was hoped that the electron-withdrawing effect of the nitrophenyl group might weaken the N-H bond sufficiently to encourage the cascade cyclisation. Nosyl geranyl sulfonamide 390 was treated with catalytic amounts of sulfuric acid in dichloromethane and, after 1.5 h of reaction at 0 °C, the partially cyclised sulfonamide 391 was the major product. Its structure was confirmed by comparison with the authentic sulfonamide 384; the ^1^H NMR spectrum showed that the resonances corresponding to two olefinic protons at δ_H 5.03 – 4.87 ppm had disappeared, but the NH at 4.66 ppm proton did not disappear. Two of three methyl singlets on double bond at (δ_H 1.54, 1.48 ppm) moved to the upfield to appear as two singlets at δ_H 0.79 and 0.78 ppm. The minor compounds were the spiro-pyrrolidines 392 (only trace <5%), which suggestion depended on NMR spectra. In the ^1^H NMR spectrum, a methine proton peak near to nitrogen atom as a multiplet at δ_H 3.54 – 3.46 ppm and methyl peaks as doublets at δ_H 1.10 and 0.81 ppm, which fits with pyrrolidine 262. From ^13^C NMR spectrum, a quaternary carbon at δ_C 60.0 ppm represents a spiro atom near to nitrogen, another sp^3^ quaternary carbon at high field δ_C 35.9 ppm and NCH peak at δ_C 51.9 ppm._
The same result has been noticed after two hours of reaction at room temperature, but the ratio of spiro-pyrrolidines 392 did not increased (Scheme 3.12).

![Scheme 3.12](image)

It would be ambitious but feasible to form two rings in a single step. Similarly, carbamate 393 was prepared by the reaction of amine 382 with methyl chloroformate in the presence of triethylamine in dichloromethane. Geranyl carbamate 393 was treated with catalytic amount of concentrated sulfuric acid in dichloromethane; after one hour of the reaction, a $^1$H NMR spectrum showed that the resonances corresponding to olefinic protons at $\delta_H 5.10 - 4.96$ ppm had disappeared, and no starting material was present the NH proton at $\delta_H 4.66$ ppm had disappeared at the end of the reaction. As usual, CH proton near to nitrogen moved to downfield $\delta_H 4.08 - 3.99$ ppm. The singlets at $\delta_H 1.60$ and 1.50 ppm representing the three methyl groups on double bonds moved further upfield to $\delta_H 1.25$ and 0.80 ppm and the complexity of the spectrum increased. In the $^{13}$C NMR spectrum, three quaternary carbons at $\delta_C 156.1, 59.6, 34.1$ ppm, five CH$_2$ signals $\delta_C 41.7, 39.4, 25.0, 19.9, 14.4$ were visible as a major isomer (ratio 6:1). Infrared spectroscopy showed an absorption band at $\nu/cm^{-1} 1701$ due to carbonyl carbamate confirmed the stability of protecting group. A very good yield was obtained (80%) which made us believe the hydroquinoline 394 had been formed (Scheme 3.13).
Scheme 3.13

The structure could be derived from chair transition state 393a, where the geometry of the double bond in the starting material, causes the ring junction to be trans-geometry. Surprisingly, the $^1$H NMR spectrum showed no diastereoisomers (depending on methyl resonances), but $^{13}$C NMR spectrum showed minor isomer (6:1 ratio) (Scheme 3.14). In the piperidine syntheses discussed in chapter 2, the methyl orientation was axial.

Scheme 3.14

Benzyl geranyl carbamate 395 reacted after one hour of the reaction in ice to give the hydroquinoline 396 (70% yield). The benzylxoycarbonyl protecting group had unexpected stability to this such strong acidic conditions to show OCH$_2$Ph protons as a clear AB coupling system after cyclisation [$\delta_H$ 4.99 – 4.94 (d, $J = 12.7$ Hz, 1H, OCH$_A$H$_B$), 4.90 (d, $J = 12.7$ Hz, 1H, OCH$_A$H$_B$)]. $^{13}$C NMR also showed a quaternary carbon next to the nitrogen atom at $\delta_C$ 59.9 (NCq), NCH (6-C) carbon at 48.7 ppm, and six CH$_2$ carbons $\delta_C$ 66.1 (OCH$_2$, Cbz group), 41.8, 39.4, 23.1, 19.9 and 14.8 ppm (Scheme 3.15). Infrared spectroscopy showed an absorption band at (υ/cm$^{-1}$ 1694) due to carbonyl carbamate confirmed the stability of protecting group. Although we have no X-ray evidence to confirm the stereochemistry of this bicyclic product, it is expected to be the same as that obtained from the cyclisation of piperidines where the methyl orientation was axial.
In view of this success in hydroquinoline synthesis, we then focussed on the more extended farnesyl derivatives. It would be worth trying to build three rings in a single step, after first preparing more simple bicyclic system. (E,E)-Farnesyl acetone 400 was obtained from commercially available farnesol 397 through alkylation of farnesyl bromide 398, which was prepared by bromination of the alcohol 397 with phosphorus tribromide, with methyl acetoacetate and subsequent Krapcho decarboxylation (Scheme 3.16).²

The carbamate 403 was prepared in exactly the same manner from (E,E)-farnesyl acetone 400 through oximation to 401 then lithium reduction to amine 402 and finally carbamate addition to give carbamate 403 (Scheme 3.17).
The carbamate 403 was transformed after one hour of reaction with half an equvalent of triflic acid at room temperature in dichloromethane, into what appeared to be the perhydro azaphenanthrene derivative 404, in 75% yield. The NMR spectra were very complex due to the nature of the tricyclic product and to the presence of five stereogenic centres and hence a possible 32 diastereoisomers. There could be many other side products like methyl groups migration products. The proposed structure 404 is somewhat tentative. The complete disappearance of all olefinic resonances in the $^1$H NMR spectra of the products provided good indication of a successful cascade, although the complexity of the spectra in which all resonances except those associated with the methyl carbamate and CH proton next to nitrogen appeared at ca. 3.5 and 4.4 ppm, respectively provided neither structural proof nor definite isomer ratios. Although probably correct, this possible approach to the azaphenanthrene skeleton requires more optimisation, especially to try and control the stereoselectivity as well as to carry out separation and more complete characterisation of those isomers, which are formed.

![Reaction Scheme](image)

**Scheme 3.18**

### 3.3. Transannular Cyclisations

Transannular cyclization, the formation a new ring across an existing one, is an advanced method for the construction of polycyclic natural products and molecules of theoretical and structural interest. Like other such intramolecular cyclisations, transannular cyclizations are largely dependent on the nature of the reaction conditions, reactivity of the two end groups, and geometrical features of the reacting ring molecules.\(^\text{18}\)
The known alkaloids library contains a huge number of azabicyclo compounds. Cocaine 405 was first isolated by Niemann in 1860 from the leaves of the Peruvian *Erythroxylon coca* plant. Epibatidine 406, a novel class of amphibian alkaloid, was first isolated by Daly and co-workers at the National Institutes of Health in a trace amount from the skin of the Ecuadorian poison frog, *Epipedobates tricolor*, of the family Dendrobatidae. Tropane 407 is a bicyclic amine that has a pyrrolidine and a piperidine ring sharing a common nitrogen atom and two carbon atoms. Tropane alkaloids such as tropinone 346 are characteristic of a class of ca. 200 alkaloids. (Fig 3.1)

Fig 3.1

The isoquinuclidine 408 (2-azabicyclo[2.2.2]octane) ring system, a semi-rigid boat form of the piperidine ring, is present in natural products possessing interesting pharmacological properties such as the alkaloids of *Dioscorea hispida*, typified by dioscorine 415. Dioscorine, an alkaloid found in the tropical yam, has been shown to be a toxic central nervous system depressant and a modulator of the nicotinic acetylcholine receptor. The biosynthesis of the isoquinuclidine moiety dioscorine suggested that nicotinic acid 409 is reduced to 3,6-dihydronicotinic acid 410, which reacts with the keto group of a branched 8-carbon unit derived from acetic acid 411 affords compound 412. Decarboxylation, shift of a double bond in the dihydropyridine ring, and further reduction of the ring yields 413. An aldol condensation then leads to 414 which contains the isoquinuclidine ring system. Decarboxylation, N-methylation, and lactone formation then afford dioscorine 415 (Scheme 3.19).
Scheme 3.19

In the present project, the rearrangement of piperidine (tosyl and nosyl) to pyrrolidines described in the second chapter of this thesis and the difficulties of carrying out cascade reactions using the same nitrogen protecting groups led to a question. Does this always have to be the case? Can the synthesis of bridged compounds through transannular hydroaminations be achieved and, if so, what would be the optimum nitrogen protecting group?

Commercially available (+/-)-limona ketone, (4-methylcyclohex-3-enyl)acetone, 416, was converted into sulfonamide 419. The reduction of oxime 417 to amine 418 gave a mixture of isomers. No attempt to separate the isomers was undertaken at any point in the synthesis. It was considered that both of the cis- and trans-isomers would give the same carbocation intermediate in an acid-catalysed reaction (Scheme 3.20).

Scheme 3.20

The acid-catalyzed hydroamination cyclisation of sulfonamide 419 was carried out and monitored by TLC and $^1$H NMR. The cyclisation reaction of sulfonamide 419 with concentrated sulfuric acid in dichloromethane at ice temperature, after four hours of reaction, a $^1$H NMR
spectrum showed no starting sulfonamide 419: both peaks related to the olefinic proton =CH at δH 5.19 ppm and the NH proton at δH 4.51 ppm had disappeared suggesting complete reaction to give only the sterically crowded bridged piperidine 420 as a single diastereoisomer (Scheme 3.21).

Scheme 3.21

A simple flask to flask recrystallization of isoquinuclidine sulfonamide 420 gave colourless crystals m.p. 112 – 114 °C (Fig 3.2). In the 1H NMR spectrum, one methine proton next to nitrogen at δH 4.20 (NCH) was obvious and distinct upfield shifts of the methyl group to get two methyl peaks one as a doublet at δH 1.41 ppm and another as singlet 1.10 ppm, together with separation of protons into much more complex patterns, was suggestive of a cyclic structure. The 13C NMR spectrum also supported the proposed structure: one quaternary carbon at (NCq : 55.2 ppm) atom, two CH carbons at (NCH : 57.0 and CH : 31.5 ppm) and four CH2 carbons at (36.7, 30.1, 26.4, 19.2 ppm) (Table 3.1).

Fig 3.2 1H NMR spectrum of isoquinuclidine sulfonamide 420 in CDCl3 (400 MHz) with the X-ray structure. Full crystallographic data is included in the Appendix 4.
After one hour of reaction of sulfonamide 419 with a catalytic amount of sulphuric acid at 0 °C there was no evidence of formation of the alternative secondary carbocation product 421, which would have resulted in the less hindered cyclization. However, the rearranged product was fully formed after five hours of reaction with concentrated sulphuric acid at ambient temperature 20 °C (Scheme 3.22).

Scheme 3.22

Evidence for this complete rearrangement came from $^1$H NMR analysis, which showed the complete disappearance of the olefinic proton in precursors 419, two methine protons next to nitrogen [$\delta_H$ 3.61 (d, $J = 3.9$ Hz, NCH), 3.56 – 3.47 (m, NCH) ppm] and distinct upfield shifts of the methyl groups which appeared as doublets at $\delta_H$ 1.10 and 0.81 ppm, together with separation of protons into much more complex patterns, suggestive of a cyclic structure, while the $^{13}$C NMR spectrum also supported the proposed structure four CH carbons at (2 x NCH 60.2, 55.3 and 2 x CH : 37.6 and 33.6 ppm) and three CH$_2$ carbons at (2 x CH$_2$ 21.5 and 19.2 ppm) (Table 3.1).

<table>
<thead>
<tr>
<th>$^{13}$C NMR ppm</th>
<th>420</th>
<th>421</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cq</td>
<td>NCq : 55.2</td>
<td>-</td>
</tr>
<tr>
<td>CH</td>
<td>NCH : 57.0, CH : 31.5</td>
<td>2 x NCH 60.2 and 55.3, 2 x CH : 37.6 and 33.6</td>
</tr>
<tr>
<td>CH$_2$</td>
<td>36.7, 30.1, 26.4 and 19.2</td>
<td>2 x CH$_2$ 21.5 and 19.2</td>
</tr>
</tbody>
</table>

Table 3.1 Some peaks from $^{13}$C NMR spectra of azabicyclo 420 and rearranged azabicyclo 421, after ignoring tosyl group.
The nosylation of amine 418 with nosyl chloride in the presence of triethylamine in dichloromethane gave the nosyl-sulfonamide 422 in very good yield (85%) (Scheme 3.23).

![Scheme 3.23](image)

**Scheme 3.23**

The use of nosyl group in these acid-catalysed cyclisation reactions has no marked effect on the rearrangement reaction. Exactly like tosyl sulfonamide 419, the nosyl sulfonamide 422 after four hours of reaction with concentrated sulphuric acid at 0 °C gave the tertiary carbocation product 423, which was distinguished in its $^1$H NMR spectrum with the peak at $\delta_H$ 4.20 ppm representing a proton next to nitrogen (NCH), a methyl doublet at $\delta_H$ 1.41 (d, $J = 7.2$, CH$_3$) ppm and a methyl singlet at $\delta_H$ 1.14 ppm. $^{13}$C NMR spectrum also supported this structure: one quaternary carbon at $\delta_C$ 56.1 (NCq), two CH carbons at $\delta_C$ 57.0 (NCH) and 31.8 ppm and four CH$_2$ carbons at ($\delta_C$ 36.2, 30.6, 26.3 and 19.4) (Scheme 3.24 and Fig 3.3).

![Scheme 3.24](image)

**Scheme 3.24**

After just one hour of reaction with concentrated sulphuric acid at 20 °C, the nosyl sulfonamide 422 gave the alternative secondary carbocation product 424, the less hindered product. In the $^1$H NMR spectrum of this thermodynamic product 424, there were two proton peaks represent protons near to nitrogen at $\delta_H$ 3.71 (dd, $J = 12.9, 6.3$ Hz, NCH) and 3.40 – 3.23 (m, 1H, NCH) ppm and two methyl peaks as doublet at $\delta_H$ 1.41 (d, $J = 6.6$ Hz) and 0.91 (d, $J = 6.4$ Hz) ppm. $^{13}$C NMR spectrum also did confirm this structure: no quaternary carbon was present in the area between 50 – 70 ppm, four CH carbons at $\delta_C$ 65.3 (NCH), 60.6 (NCH), 38.9 (CH) and 36.8 (CH) ppm and three CH$_2$ carbons at $\delta_C$ 37.4, 27.6 and 25.0 ppm were identified (Scheme 3.24 and Fig 3).
Scheme 3.2

Fig 3.4 $^1$H and $^{13}$C NMR spectra of rearranged azabicyclo 424:

a) decoupled $^{13}$C; b) DEPT CH, CH$_3$ positive; CH$_2$ negative c) proton.

Fig 3.3 $^1$H and $^{13}$C NMR spectra of azabicyclo 423: a) decoupled $^{13}$C;

b) DEPT CH, CH$_3$ positive; CH$_2$ negative c) proton.
The structure of the thermodynamic azabicyclo product 424 was confirmed by X-ray crystallography (Fig 3.5).

Fig 3.5 The X-ray structure of rearranged azabicyclo 424. Full crystallographic data is included in the Appendix 5.

Although the rearrangement of piperidine to pyrrolidine of the N-tosyl 419 and N-nosyl 422 sulfonamides is a great discovery, we did control it by using carbamate as a protecting group. The carbamate 425 did cyclize after one hour of reaction with half an equivalent of concentrated sulfuric acid at room temperature to give a single product 426 in excellent yield (92%) (Scheme 3.25). The complete disappearance of the olefinic resonance and NH proton in the ¹H NMR spectra of the product provided good indications of a successful cyclisation, although the complexity of the spectra in which all resonances except those associated with the methyl carbamate at δ_H 3.49 ppm and the CH proton next to nitrogen appearing at δ_H 4.57 – 4.46 ppm provided some structural proof. The most compelling evidence for the structure 426 came from very detailed analyses of the ¹³C NMR spectrum: one quaternary carbon at δ_C 61.0 (NCq), two CH carbons at δ_C 56.5 (NCH) and 31.3 (CH) and four CH₂ carbons at δ_C = 38.4, 30.1, 26.7 and 19.8 ppm, generally similar to 423.

\[\text{Scheme 3.25}\]
In this extended study of the piperidine/pyrrolidine rearrangement, sulphonamide 429 was prepared starting from commercially available 4-methylcyclohexenyl methanol 427, which was tosylated then the sulfonamide group introduced by an $S_N2$ reaction.\textsuperscript{25} This is illustrated by the reaction of potassium tosylamide, which was prepared by heating 1.5 equivalents each of potassium hydroxide and $p$-toluenesulfonamide in DMF. Following complete dissolution of the base, one equivalent of tosylate 428 was added and the mixture heated to 120 °C. Purification of the reaction mixture obtained after one hour gave the desired tosylamide 429 in 89% yield (Scheme 3.26).

![Scheme 3.26](image)

Tosylamide 429 did cyclise to give only the tertiary carbocation product 430 after three hours of reaction with concentrated sulfuric acid at ambient temperature in 94% yield. There was no evidence of formation of the alternative secondary carbocation product 431, which would have resulted in this less hindered product, even after 20 hours with half equivalent of the acid (Scheme 3.27). In particular, no methyl doublet was visible around $\delta_H$ 1.0 ppm in the $^1$H-NMR spectrum of the crude product, which was very pure and crystallized by itself and the structure was confirmed by X-ray crystallography. Full crystallographic data is included in the Appendix 6.

![Scheme 3.27](image)

Similarly, sulphonamide 435 was prepared starting from commercially available cyclohexenyl methanol 432, which was tosylated then the sulfonamide group introduced by an $S_N2$ reaction.\textsuperscript{25} This is illustrated, as above, by the reaction of potassium tosylamide, which was prepared by
heating 1.5 equivalents each of potassium hydroxide and \( p \)-toluenesulfonamide in DMF. Following complete dissolution of the base, one equivalent of mesylate 433 was added and the mixture heated to 120\(^\circ\) C for 1 h. Purification of the reaction mixture obtained after one hour gave the desired tosylamide 434 in 88% yield (Scheme 3.28).

![Scheme 3.28](image)

Treatment of the cyclohexenyl sulfonamide 434 with a catalytic amount of sulfuric acid gave the pyrrolidine ring system 435. This result was expected as either cyclisation would proceed via very similar secondary carbocation intermediate (Scheme 3.29).

![Scheme 3.29](image)

The structure of pyrrolidine 435 was confirmed by constructing it through a different route, which had also been developed in the group (Scheme 2.17).\(^{26}\) Iodocyclization of sulfonamide 434 under acidic conditions gave an iodopyrrolidine 436 which was deiodinated by hydrogenolysis to yield the corresponding pyrrolidine 435. This pyrrolidine showed the same spectroscopic data as those displayed by the sulfuric acid-catalyzed cyclization product (Scheme 3.30).

![Scheme 3.30](image)
Fig 3.4 $^1$H NMR spectrum of the iodopyrrolidine 436 with the X-ray structure. Full crystallographic data is included in the Appendix 7.

Fig 3.3 $^1$H NMR spectrum of azabicyclo 435.
The possibility of designing a “one-pot” sequence for the construction of highly complex molecules is a major driving force for many research programs. Tandem reaction and multistep one-pot reactions allow construction of complex structures in one step to decrease the need for a purification steps and shorten syntheses to save money on chemicals and time in research. Moreover, tandem process is an attractive choice from a green chemistry point of view. Indeed, tandem reactions have attracted the attention of organic chemists for many reasons: 1- rapid increase in complexity; 2- powerful tool for construction of polycyclic systems; 3- many reactions can be applied; 4- selectivity can be controlled by conformation or by using catalyst.

Veselovskii et al. found that when an equimolar mixture of myrcene 437 and methylvinyl ketone 438 was applied to the usual chromatographic grade silica gel, SiO₂, the [4+2] cycloaddition occurred effectively in the absence of any solvents and produced the anticipated Diels-Alder product 439 after heating at 50 °C for five hours.

The resulted ketone 439 was converted into the oxime 440 which was reduced by lithium aluminum hydride to amine 441. The reduction of oxime 440 to amine 441 gave mixture of isomers. No attempt to separate the isomers was undertaken. It was considered that both isomers would give the same carbocation intermediate in acid-catalysed reaction and then perhaps polycyclic structure by multiple cyclisations (Scheme 3.31).

![Scheme 3.31](image)

Carbamate 442 was prepared by the reaction of amine 441 with methyl chloroformate in the presence of triethylamine in dichloromethane. Carbamate 442 was treated with a catalytic amount of concentrated sulfuric acid in dichloromethane. After one hour of the reaction, a ¹H NMR
spectrum showed that the resonances corresponding to olefinic protons at $\delta_H 5.28$ and $5.10$ ppm had disappeared, whereas the NH proton at $\delta_H 4.58$ ppm did not disappear at the end of the reaction. The CH proton next to nitrogen at $\delta_H 3.67 - 3.60$ ppm, the methoxy methyl group were still visible at $\delta_H 3.64$ ppm. In the $^{13}$C NMR spectrum, three quaternary carbons were visible at $\delta_C 156.6 : C=O$, 133.7 and 127.1 ppm (Scheme 3.32).

Hence, only cyclisation to give the bicycle 443 had occurred, without any involvement of the carbamate 445 to give polycycles 444 and 446 (Scheme 3.33).

3.4 Cyclisations of highly methylated cyclopentenyl carbamates and sulfonamides

Focussing on a transannular cyclisation, what about transannular reactions involving five-membered rings?

Fortunately, from another project running in the group, Dr. Ian King had available a substantial supply of aldehyde 447 which was converted to the oxime 448 then into amine 449 by the standard lithium aluminium hydride reaction. The achievement of 2,2,6-trimethylpiperidine carbamate synthesis without any traces of pyrrolidine rearranged compound led us to try using carbamate as a protecting group instead of sulfonamide. In the light of the result obtained when carbamate as a
protecting group was used, it should be rewarding to use it. Finally, carbamate was added to the amine 449 by using methyl chloroformate in the presence of triethylamine; all of these reactions proceeded in good yields (Scheme 3.34).

The cyclisation reaction of the carbamate 450 was carried out under different conditions of time and temperature.

After four hours of reaction with one equivalent of triflic acid at room temperature carbamate 450 gave only bicyclo product 451 an inseparable 3:1 mixture of diastereoisomers. The $^1$H NMR spectrum showed that the resonances corresponding to olefinic proton at $\delta_H 5.12$ had disappeared, and no starting material was present the NH proton at $\delta_H 4.82$ ppm had disappeared at the end of the reaction. As usual, CH$_2$ protons next to nitrogen moved to $\delta_H 3.41 – 3.28$ ppm. The singlet at $\delta_H 1.51$ ppm representing the methyl group on double bond moved further upfield to $\delta_H 1.35$ and 1.25 ppm for diastereoisomers and the complexity of spectrum increased. In the $^{13}$C NMR spectrum, three quaternary carbons at $\delta_C 156.8$ (C=O), 74.8 (NCq) and 46.0 ppm, four CH$_2$ signals $\delta_C 49.1$ (NCH$_2$), 43.2, 29.9 and 28.8 ppm were visible as a major isomer. Infrared spectroscopy showed an absorption band at $\nu/cm^{-1}$ 1701 due to carbonyl carbamate confirmed the stability of protecting group. A quantitative yield was obtained (98%) which made us believe the bicyclo 451 had been formed (Scheme 3.35).
Whereas, the reaction with 0.5 equivalent of triflic acid at 80 °C gave only the Wagner-Meerwein product 452 after two hours of reaction a $^1\text{H}$ NMR spectrum showed that the resonance corresponding to the olefinic proton had disappeared, but the NH proton did not disappear. However, the $^{13}\text{C}$ NMR spectrum enhanced this theory as two quaternary carbons appeared at $\delta_C$ 142.1 and 129.8 ppm, due to quaternary carbons on a double bond and a quaternary carbon at high field $\delta_C$ 46.9 ppm (sp$^3$ quaternary carbon). The cyclisation reaction of the carbamate 450 was also carried out with a catalytic amount of concentrated sulphuric acid at room temperature for four hours to give a mixture of bicyclo 451 and the Wagner-Meerwein product 452 (Scheme 3.36).

Scheme 3.36

An alternative literature approval is that nitrile 456 can be prepared via “abnormal” Beckmann reaction.$^{29}$ Commercial available D-camphor 453 was converted into the corresponding oxime 454. Under basic conditions of triethylamine, the hydroxyl group was converted into a good leaving group by reaction with tosyl chloride. From the oxime toluenesulphonate 455, the inseparable “abnormal” Beckmann inseparable nitriles 456 and 457 were prepared. The seco-nitrile products rather than the normal lactam product of a Beckmann rearrangement were showed infrared band at 2251 cm$^{-1}$ due to nitrile presence; in the $^1\text{H}$ NMR spectrum, the olefinic proton at $\delta_H$ 5.23 (t, $J = 1.2$ Hz, 1H, =CH) ppm and three methyls at $\delta_H$ 1.60, 1.06 and 0.84 ppm. In in $^{13}\text{C}$ NMR spectrum, clearly nitrile carbon appeared at $\delta_C$ 119.3 ppm (Scheme 3.37).

Scheme 3.37
The abnormal Beckmann nitriles 457 and 458 were then reduced by lithium aluminum hydride to the corresponding amines 459. No attempt to separate the isomers was undertaken at any point in the synthesis, because it was considered that both of the isomers would give the same carbocation intermediates in acid-catalysed reaction (Scheme 3.38).

![Scheme 3.38](image)

After the reaction of amine 459 with tosyl chloride in the presence of triethylamine during the chromatography purification the sulfonamide 460 was separated. After three hours of reaction with concentrated sulfuric acid at ice temperature sulfonamide 460 cyclised to the azabicyclo[3.2.1]octane 461 as a mixture 1:1 with rearranged sulfonamide 462, which would have resulted in the Wagner-Meerwein rearrangement. The azabicyclo[3.2.1]octane 461 was separated by simple crystallisation; the $^{13}$C NMR spectrum showed a quaternary carbon next to nitrogen (NCq) at $\delta_{C}$ 53.7 ppm and four CH$_2$ carbons at $\delta_{C}$ 39.2 (NCH$_2$), 33.3, 27.3 and 27.0 ppm. After four hours of reaction with concentrated sulfuric acid at room temperature sulfonamide 460 gave only the Wagner-Meerwein product 462 (Fig 3.5); a $^1$H NMR spectrum showed that the resonance corresponding to the olefinic proton had disappeared, but the NH proton at 4.17 (t, $J$ = 5.7 Hz) ppm did not disappear (Scheme 3.39).

![Scheme 3.39](image)
The logical explanation of these abnormal products is as follows: the generation of the initial carbocation 460a was achieved by the acid, which was trapped by the lone pair of electrons on nitrogen to form the transannular product 461. At the same time the initial carbocation 460a has a tendency to rearrange to a thermodynamically more stable structure via a [1,2]-methyl shift to form a new carbocation 460b, which could end with the Wagner-Meerwein product 462 or fused cyclic product 463 (Scheme 3.40).

![Scheme 3.40](image)

The isomeric nitrile 465 was prepared in a similar way. The difficulties of the classic Beckmann reaction (strongly acidic conditions or using pyridine with sulphonate esters) led Anilkumar and Chandrasekhar to develop relatively simple and mild conditions for this rearrangement. The camphor oxime 454 was converted into the corresponding ethyl carbonate 464 relatively simply and in high yield, via treatment with ethyl chloroformate in dichloromethane, in the presence of one equivalent of triethylamine at room temperature. The “abnormal” Beckmann rearrangement was catalysed by boron trifluoride etherate to give the less sterically crowded nitrile 465, which was then reduced by lithium aluminum hydride to the corresponding amine 466 (Scheme 3.41).^30

![Scheme 3.41](image)
In the event, despite many attempts, both carbamate 467 and sulfonamide 468 were rearranged to give only the Wagner-Meerwein products 452 and 462 respectively, the structure of which were confirmed by comparison with previous data (Scheme 3.42 and Fig 3.5).

Scheme 3.42

![Scheme 3.42](image)

Fig 3.5 $^1$H NMR spectrum of the Wagner-Meerwein sulfonamide 462.

Doubtless, 5,5-transannular cyclisation can be included in this acid-catalysed hydroamination chemistry, but not without much more experimentation.
3.5 Acid-catalysed Hydroalkoxylation Cyclisations

One of the most straightforward synthetic approaches to substituted tetrahydrofurans and tetrahydropyrans oxygen heterocycles is intramolecular hydroalkoxylation of unsaturated alcohols. In particular, the intramolecular addition of the O–H bond across the unactivated C=C bond have drawn wide attention due to their high atom economy and synthetic efficiency. Recently, it was reported that intramolecular hydroalkoxylation of unactivated olefins could be promoted by Brønsted acid with varying degrees of success.\(^{31}\) Dunach and Coulombela reported that in the presence of a catalytic amount of triflic acid, substituted tetrahydrofurans and tetrahydropyrans have been efficiently and selectively synthesized from the corresponding unsaturated alcohols. Moreover, such triflic acid-catalysed cyclisations can also be run in the absence of solvent, avoiding the use of large excess of protic acid which is used to effect this transformation. 6-Methyl-5-hepten-2-ol 469 gave tetrahydropyran 470 in the presence of a catalytic amount of triflic acid, in good isolated yield (80%). They noted that the cyclisation of the alcohol 469 could be effected in the absence of solvent with 1 mol% of TfOH and the reaction was completed after 2 hours at 80 °C. Under the same conditions, the cyclisation of alcohol 471 afforded exclusively the corresponding tetrahydropyran isomer 472 after 1 h reaction, together with some polymers with an isolated yield of 21%. A terminal monosubstituted olefin 473 could also be cyclised and the 5-membered cyclic ether 474 was the only product obtained in quantitative yield according to GC analysis. The isolation of this volatile compound after extraction and distillation gave an isolated yield of 39% (Scheme 3.43).\(^{32}\)

\[
\text{Scheme 3.43}
\]
Linares-Palomino et al. found that chlorosulfonic acid is an efficient agent for cascade hydroalkoxylation cyclizations with internal nucleophilic termination, in a similar manner that is well-established with tetrahydrofurans and tetrahydropyran formations. The cyclization of alcohol 477 mainly yielded the trans-fused octahydrobenzopyran 478 after 10 min at room temperature with 5 equivalents of chlorosulfonic acid in 2-nitropropane; the ratio decreased to cis/trans 1:2.5 if the reaction was left for longer (Scheme 3.44).  

Scheme 3.44

The monoterpene 1,8-cineole 480, eucalyptol, is a major component of essential oils from *Eucalyptus bractea poly*. 1,8-Cineole has a characteristic fresh and camphoraceous fragrance and pungent taste, so it is used for flavouring of foods and cosmetics. 1,8-Cineole 480 is used in pharmaceutical preparations to treat coughs, muscular pain, neurosis, rheumatism, asthma and urinary stones. It should also be mentioned that 1,8-cineole 480 and 1,4-cineole 481 have important phytotoxic properties which could render them various practical applications. General synthesis of 1,8-cineole 480 and 1,4-cineole 481 is by isomerization of α-terpineol 479 catalyzed by acid. Lana, et al. reported the application of heteropoly acid H₃PW₁₂O₄₀ (PW), as homogeneous and solid acid catalysts for the isomerization of α-terpineol 479 to cineoles 480 and 481 (Scheme 3.45).  

Scheme 3.45
In order to compare oxygen-centered transannular cyclisation with our nitrogen-based examples, commercially available limona ketone, (4-methylcyclohex-3-enyl)acetone, 416 was converted into alcohol 482, followed by acid-catalyzed hydroalkoxylation cyclisation to give only the stericly crowded bridged 1,3-dimethyl-2-oxabicyclo[2.2.2]octane 483 after three hours of reaction with catalytic amount of sulphuric acid at 32 °C. In the \( ^1H \) NMR spectrum, the proton next to oxygen at \( \delta_H \) 3.93 (OCH) ppm was obvious and distinct upfield shifts of the methyl group resulted in the appearance of two methyl peaks, one as a doublet at \( \delta_H \) 1.10 ppm and another as a singlet 0.96 ppm, together with separation of other protons into much more complex patterns, suggestive of a cyclic structure. The \( ^{13}C \) NMR spectrum also supported the proposed structure: one quaternary carbon at (OCq : 69.1 ppm), two CH carbons at OCH : 73.1 and CH : 29.7 ppm and four CH\(_2\) carbons at 32.6, 32.1, 26.5, 19.7 ppm; there was no evidence of formation of the alternative secondary carbocation product 484, which would have resulted in the less hindered cyclization, but two doublet methyl groups and two OCH resonances. An unsurprising result: there was no rearranged product after 3 hours of reaction with a catalytic amount of sulphuric acid in DCM at 32 °C (Scheme 3.46).

![Scheme 3.46](image)

The presence of the (4-methylcyclohex-3-enyl)methanol 427 in our chemical list was worthy to try the cyclisation reaction. When the alcohol 427 was heated with a catalytic amount of sulfuric acid for 1.5 hours at 35 °C, it gave oxabicyclo-octane 485 in an excellent yield of 92%. Infrared data showed the absence of the alcohol functional group. The \( ^1H \) NMR spectrum showed the
disappearance of the olefinic proton. In the $^{13}$C NMR spectrum one quaternary carbon was clearly at OCq 68.1 ppm.

As the rearrangement was in our minds during the whole time, there was no evidence of formation of the alternative secondary carbocation product 486, which would have resulted in this less hindered product (Scheme 3.47).

![Scheme 3.47](image)

During her laboratory work on acid-catalyzed intramolecular hydroamination reactions, A. Nazer, a six months exchange student in the Knight group, has synthesized dimethyl 3-methylcyclopentene dicarboxylate 488 which was followed, in this study, by Krapcho decarboxylation to 3-methylcyclopentene carboxylate 489 then LiAlH$_4$ reduction to free alcohol 490, which gave the hydroalkoxylation product, 1-methyl-2-oxabicyclo[2.2.1]heptane 491, after 1.5 hours of reaction with catalytic amount of sulphuric acid at 35 °C. The complete disappearance of the olefinic resonance proton in the $^1$H NMR spectra of the products provided good indications of successful cyclisation. The most compelling evidence for the structure 491 came from detailed analyses of the $^{13}$C NMR spectrum: one quaternary carbon at $\delta_C$ 78.2 (OCq) ppm, one CH carbon at $\delta_C$ 38.4 ppm, four CH$_2$ carbons at $\delta_C$ 76.6 (OCH$_2$), 42.2, 36.1 and 28.8 ppm and one methyl carbon at 26.9 ppm (Scheme 3.48).

![Scheme 3.48](image)
Conclusion

The acid-catalysed hydroamination and hydroalkoxylation we have developed appears to offer an excellent route to synthesise substituted bicyclic-compounds. The hydroamination has also been used to form sterically crowded, bridged alkaloid structures, exemplified by a new route to isoquinuclidines, through a transannular cyclisation, which can undergo rearrangement to the less hindered products. Some optimisation studies have revealed how these cyclisations can be controlled to give single products.

In a preliminary study, we have also applied acid-catalyzed intramolecular cascade methodology to the synthesis of polycyclic perhydroquinolines. This initial work will require additional study of a number of related reactions before the methodology is completely defined, but the initial results do look promising.

Oxygen-centered transannular cyclisations have been compared with nitrogen-based examples, by intramolecular, acid-catalyzed hydroalkoxylation reactions, which give only sterically crowded bridged 1,4-cineoles.

The competition between these types of hydroamination and hydroalkoxylation and the rearrangement of the resulting N-heterocycles to O-heterocycles will be featured in the next Chapter.
References


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Chapter 4

A Novel $N$-to-$O$ Rearrangement
A Novel N-to-O Rearrangement

Introduction:

Nitrogen and oxygen are the atoms of life, from water H₂O and urea NH₂CONH₂ to DNA helix. It is not surprising to say most natural products are nitrogen or oxygen containing compounds. Saturated oxygen and nitrogen heterocycles occur widely as components of natural products. Tetrahydropyran (six-membered saturated O-containing ring) are components of monoterpenoid cineol 492, tetrahydrofurans (five-membered saturated O-containing ring) are components of spirocyclic ether theaspirane 493, pyrrolidine (five-membered saturated N-containing ring) is a component of nicotine 494 and piperidine (six-membered saturated N-containing ring) is a component of poisonous alkaloid coniine 31. Both dihydrofuran and piperidine are components of an important natural product morphine 37 (Fig. 4.1).

![Fig. 4.1](image)

It is known that many functional groups are unstable in acidic conditions especially in strong acid like sulfuric acid and super acids like trifluoromethanesulfonic acid CF₃SO₃H (triflic acid, TfOH), but we have got good evidence that the carboxylic acid ester in sulfonamide 495 was stable for four hours in triflic acid at 60 °C to give pyrrolidine 496 in an excellent yield of 91% (Scheme 4.1).¹

![Scheme 4.1](image)
A tandem dehydration-THP cleavage-intramolecular hydroalkoxylation addition used to synthesize the aza-spiropyran 500 started from the Grignard addition of maleimide 497. Treatment of the THP-protected 4-hydroxybutyl magnesium bromide with maleimide 497 at \(-20^\circ C\) for 2.5 h afforded \(N,O\)-acetal 498 as an epimeric mixture in 7:1 ratio and with a combined yield of 89%. Exposure of the diastereomeric mixture of the \(N,O\)-acetal 499 to acidic conditions of \(p\)-toluene sulfonic acid TsOH as a catalyst in dichloromethane at room temperature for half an hour resulted in the formation of the desired functionalized aza-spiropyran derivative 500 as a single diastereomer in quantitative yield. It could be seen clearly in this reaction that there is stability associated with some of the functional groups to the acidic conditions, but with the exception of the THP-ether group. However, the resulting alcohol undergoes smooth cyclisation (Scheme 4.2).\(^2\)

Scheme 4.2

Haskins in the Knight Group studied the limitation of functional groups to acid catalysed-hydroamination reactions. The functionalised amino-ester precursors allyl \(CH_2CH=CH_2\) and sulfonyl \(CH_2SO_2Ph\) in sulfonamides 501 and 503 underwent smooth cyclisation to give the hoped-for \(spiro\)-pyrrolidines 502 and 504 upon exposure to sub-stoichiometric amounts of triflic acid in ice-cold chloroform. Both products were isolated as 3:1 mixtures of only two diastereomers in unoptimised isolated yields about 70% (Scheme 4.3).\(^1\)

Scheme 4.3
Aldehyde 505 is also able to survive the acidic reaction conditions and undergoes smooth cyclisation to give the corresponding pyrrolidine 506 in excellent yield (95%). The unprotected alcohol in precursor 507 competed with the sulfonamide as a trap for the carbocation to give 1:1 mixture of pyrrolidine 508 and tetrahydropyran 509 (Scheme 4.4).

Scheme 4.4

To incorporate alcohol groups in a controlled way was clearly a challenge, to this methodology, however, as almost all protecting groups for these are acid-sensitive. To mask the useful hydroxyl group, we expected benzyl ether (OBn) and para-methoxybenzyl ether (OPMB) unlikely to survive in such acidic conditions. Trimethylsilyl ether OSi(CH₃)₃ and t-butyldimethylsilyl ether were also unlikely to survive at 20 °C. We then realised that perhaps acetate groups would indeed survive as the foregoing esters were not affected by the strong acid. We found benzyloxy carbonyl CO₂CH₂Ph survives in acidic condition at 20 °C (see p. 57 and 59) and CO₂Me as well. It may be possible therefore to protect the hydroxyl group OH by acetate formation as ester groups are stable to the present acidic conditions (Scheme 4.5).

Scheme 4.5

a) c. H₂SO₄, 55 min, 87%
b) 0.4 eq. TFOH, 30 min, 96%
Preparation the cyclisation precursors

Cyanoester derivatives 511 can be prepared from cyanoacetate 510 and allylic halides in reasonably good yields (55%). The prenyl bromide used was not completely pure, due to its sensitive nature; this could result in lower yield. In the case of using pure alkyl halide the yield was much better (74%) (Fig. 4.2).

![Fig. 4.2](attachment:image)

In all cases there was also formed double alkylated product 512 (ca. 20%), which was used in future to synthesise spiro-products (Scheme 4.6). The two product were separated by using column chromatography.

![Scheme 4.6](attachment:image)

Prenyl cyanoacetate 511 was reduced by lithium aluminium hydride to γ-amino alcohol 513. By selective addition of CO₂Me to the more nucleophilic nitrogen over oxygen, unsaturated amino-alcohol 514 was synthesized. Now the reactant was ready to test both the protected alcohol stability to acid and to find out which nucleophile (i.e. NH or OH) would trap the carbenium ion, generated when the substrate 514 is exposed to acid (Scheme 4.7).

![Scheme 4.7](attachment:image)
In the event, when the alcohol group was blocked as the corresponding acetate 515, then only the piperidine 516 was formed after one hour of reaction at room temperature with a catalytic amount of sulfuric acid in an excellent yield of 93%. The products did not require any chromatographic purification as the reaction proceeded very cleanly. Infrared spectroscopy showed the absence of NH absorption and the presence of two carbonyl groups at $\nu$/cm$^{-1}$ 1701 and 1730 due to carbamate carbonyl and acetate carbonyl, respectively, confirmed the stability of the acetate protecting group. So, acetate is suitable to protect alcohol groups in this chemistry a very useful finding. Both $^1$H and $^{13}$C NMR spectra support the successful synthesis of piperidine 516; as can be seen from Fig 4.3, starting material 515 had clearly disappeared. Most obvious was the disappearance of the olefinic =CH at $\delta$H 5.02 ppm and NH proton at $\delta$H 4.94 ppm and the appearance of two ABX systems. Four methyls could be seen clearly; methoxy methyl at $\delta$H 3.55 ppm, methyl acetyl at $\delta$H 1.91 ppm and two methyls on quaternary carbons at $\delta$H 1.35 and 1.23 ppm. The $^{13}$C NMR spectrum showed a quaternary carbon next to a nitrogen atom at $\delta$C 54.8 ppm and four CH$_2$ carbons, one next to oxygen at $\delta$C 66.4 ppm and three on the piperidine ring at $\delta$C 43.1 (NCH$_2$), 36.2 and 21.3 ppm (Scheme 4.8, Table 4.1 and Fig 4.3).

![Scheme 4.8](image)

However, we were very much excited to know what would happen when we attempt to cyclise the free amino-alcohol 514, especially as this had not been tried before in the literature. It was clear that cyclisation had occurred after four hours of reaction at ice temperature with a catalytic amount of sulfuric acid in excellent yield (93%), as the olefinic =CH at 5.02 ppm had disappeared. Surprisingly, the NH proton at $\delta$H 4.60 ppm was still visible in a product with a most interesting
$^1$H NMR spectrum (Fig 4.4). It was to our great surprise that the product clearly did not contain any piperidine residue and it was equally clear that the product was tetrahydropyran 517! By analysing the $^1$H NMR and $^{13}$C NMR spectra, we confirmed that tetrahydropyran 517 was formed. As can be seen from Fig 4.4, starting material 514 had clearly disappeared; the $^{13}$C NMR showed a quaternary carbon next to the oxygen atom at $\delta$C 71.3 ppm and four CH$_2$ carbons one next to an oxygen at 64.3 ppm, one next to nitrogen at $\delta$C 43.1, and two others at 35.1 and 23.7 ppm (Scheme 4.9, Table 4.1).

![Scheme 4.9](image)

**Table 4.1** $^{13}$C NMR spectra of piperidine 516 and tetrahydropyran 517.

| $^{13}$C NMR ppm | Cq | CH | CH$_2$ | CH$_3$
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMe$_2$CO$_2$Me</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ac-C=O : 171.0</td>
<td></td>
<td></td>
<td>OCH$_2$ : 66.4</td>
<td>OCH$_3$ : 51.9</td>
</tr>
<tr>
<td>C=O : 156.9</td>
<td></td>
<td></td>
<td>NCH$_2$ : 43.1</td>
<td>Ac-CH$_3$ : 27.9</td>
</tr>
<tr>
<td>NCq : 54.8</td>
<td></td>
<td></td>
<td>36.2 and 21.3</td>
<td>24.5 and 20.8</td>
</tr>
<tr>
<td>C=O : 157.2</td>
<td></td>
<td></td>
<td>OCH$_2$ : 64.3</td>
<td>OCH$_3$ : 52.1</td>
</tr>
<tr>
<td>NCq : 71.3</td>
<td></td>
<td></td>
<td>NCH$_2$ : 43.1</td>
<td>29.2 and 23.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>35.1 and 23.7</td>
<td></td>
</tr>
</tbody>
</table>

The reactions involved are overall 6-endo-trig cyclisations and the intermediate carbocation is the same in both cases. A simple energy minimisation experiment performed using the programme Chem3D Pro calculated the total energy for tetrahydropyran 517 is 19.51 kcal/mol which is very close to piperidine 518 total energy 19.36 kcal/mol (Scheme 4.10).

![Scheme 4.10](image)
The reactions are remarkably clean: the NMR spectra shown below were obtained from *crude* products.

![NMR spectra of piperidine and tetrahydropyran](image)

Fig 4.3 $^1$H and $^{13}$C NMR spectra of piperidine 516:

- a) proton,
- b) decoupled $^{13}$C,
- c) DEPT CH$_2$ positive; CH, CH$_3$ negative.

Fig 4.4 $^1$H and $^{13}$C NMR spectra of tetrahydropyran 517:

- a) proton,
- b) decoupled $^{13}$C,
- c) DEPT CH$_2$ positive; CH, CH$_3$ negative.
We then hydrolysed the acetate with potassium carbonate to make an authentic sample of piperidine methanol 518 and treated the resulting alcohol 518 with acid, when it rearranged to the initial tetrahydropyran 517 after 20 hours of reaction at ambient temperature (Scheme 4.11). This appears to be a new rearrangement reaction!

![Scheme 4.11](image)

The structure of piperidine methanol 518 was confirmed by NMR ($^1$H, $^{13}$C, COSY) spectroscopy, infra-red spectroscopy, and mass spectrometry analysis (Table 4.2, Fig 4.5 and Fig 4.6). In its $^1$H NMR spectrum, methyl acetyl at $\delta_H$ 1.91 ppm had disappeared and a new hydroxyl proton was visible also at $\delta_H$ 1.91. Methylene protons next to the hydroxyl group were moved to the upfiled (Table 4.2). The $^{13}$C NMR spectrum showed a quaternary carbon next to a nitrogen atom at $\delta_C$ 55.1 ppm and four CH$_2$ carbons, one next to oxygen at $\delta_C$ 65.2 ppm and three on the piperidine ring one next to a nitrogen atom at $\delta_C$ 42.7 (NCH$_2$) and two others at 38.0 and 20.8 ppm. Three methyls could be seen clearly; methoxy methyl at $\delta_C$ 51.9 ppm and two other methyls on quaternary carbons at $\delta_C$ 27.6 and 24.8 ppm. (Scheme 4.8, Table 4.2 and Fig 4.3).

**Table 4.2** $^1$H and $^{13}$C NMR spectrum of piperidine 518.

<table>
<thead>
<tr>
<th>$^{13}$C NMR ppm</th>
<th>OCH$_2$</th>
<th>NCH$_2$</th>
<th>CH$_2$</th>
<th>CH</th>
<th>CH$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^1$H NMR ppm</td>
<td>65.2</td>
<td>42.7</td>
<td>38.0</td>
<td>36.8</td>
<td>20.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>$^1$H NMR ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.46 (dd)</td>
</tr>
<tr>
<td>3.42–3.38 (m)</td>
</tr>
</tbody>
</table>
In the $^1$H $^{13}$C COSY spectrum (Fig 4.5 and Table 4.2), the left side of Fig 4.5 shows the 1-D $^{13}$C NMR spectrum (DEPT CH$_2$ right; CH and CH$_3$ left), and the top of the spectrum shows the 1-D $^1$H NMR spectrum. The three cross peaks arising from the methyl groups are the easiest to identify. In the lower left of the COSY spectrum, we see a cross peak between the two methylene protons (the integral of resonance at $\delta_H$ 3.46 and 3.42 – 3.38 ppm) whose resonance is the carbon next to oxygen at $\delta_C$ 65.2 ppm. The cross peak between the carbon (6-C) next to nitrogen at $\delta_C$ 42.7 ppm resonates the two protons whose appearance is as doublets of doublets at $\delta_H$ 3.62 and 3.12 ppm. The cross peak between the methine proton is the carbon (5-C) at $\delta_C$ 36.8 ppm. We expect the cross peak between the carbon (3-C) at $\delta_C$ 38.0 ppm is the two protons whose resonance is the multiplet at $\delta_H$ 1.58 – 1.43 ppm. In the upper right of the COSY spectrum, we see a cross peak correlating the resonance of the methylene protons (both multiplet $\delta_H$ 1.22 – 1.07 and 1.71 – 1.59 ppm) is the carbon (4-C) at $\delta_C$ 20.8 ppm (Table 4.2 and Fig 4.5).
By analysing the $^1$H$^1$H COSY spectrum (Fig 4.6) we determined that there were two ABX systems. Tracing from the multiplet at $\delta_H$ 1.85 – 1.79 ppm, the methine proton at the carbon (5-C), is coupled not only to the 6-CH$_2$N at ($\delta_H$ 3.62 and 3.12 ppm protons) and CH$_2$O protons in the left at ($\delta_H$ 3.46 and 3.42 – 3.38 ppm), but also to the 4-CH$_2$ protons. Now we can confirm the multiplet at $\delta_H$ 1.58 – 1.43 ppm is the two protons whose carbon is the carbon (3-C) at $\delta_C$ 38.0 ppm.

While the initial piperidine protected alcohol 516 had a formula of C$_{12}$H$_{21}$NO$_4$, the piperidine methanol 518 showed m/z = 201.1365 for the formula C$_{10}$H$_{19}$NO$_3$ [M]$^+$. This was confirmed by high resolution measurements and so confirmed the piperidine methanol 518. Also, infrared spectroscopy showed the presence of hydroxyl group absorption at $\nu$/cm$^{-1}$ 3416 and the presence of the carbamate group at $\nu$/cm$^{-1}$ 1684.
Sulfonamide 519 was prepared after selective addition of tosyl to nitrogen over oxygen in a similar way to that described in Scheme 4.7, but at -78 °C. Then tetrahydropyran 520 formed from sulfonamide 519 in quantitative yield after just one hour of reaction with concentrated sulfuric acid at ice temperature. There was no trace of any piperidine 521; the NH proton was still visible and there were three sharp methyl singlets related to methyl tosyl at δ_H 2.34 ppm and two methyl groups on quaternary carbon at δ_H 1.02 and 1.00 ppm in ^1H NMR spectrum. When the alcohol group was protected as the corresponding acetate 522, then only the piperidine 523 was formed at room temperature, which was distinguished by its ^1H and ^13C NMR spectra. In ^1H NMR, both olifinic proton (=CH) at δ_H 4.98 – 4.87 ppm and NH proton at δ_H 4.79 ppm had disappeared to confirm the complete reaction. Four methyl signals could be seen clearly; aryl methyl at δ_H 2.27 ppm, methyl acetyl at δ_H 1.91 ppm and two methyls on quaternary carbon at δ_H 1.25 and 1.03 ppm. The stability of acetate was confirmed by infrared spectroscopy, which showed an absorption band at υ/cm⁻¹ 1737 due to the carbonyl group, again showing the stability of this protecting group. The ^13C NMR showed a quaternary carbon next to the nitrogen atom at δ_C 57.8 ppm and four CH₂ carbons one next to oxygen at δ_C 65.9 ppm and three on the piperidine ring at δ_C 45.4 (NCH₂), 39.8 and 23.2 ppm. Moreover, we were delighted to find that there was no rearrangement to pyrrolidine 524, where an isopropyl group was not seen in the NMR spectra (no isopropyl group). When the acetate was hydrolysed and the resulting alcohol 521 was treated with acid, it rearranged to the initial tetrahydropyran 520 (Scheme 4.12).
The same chemistry was repeated to synthesize more substituted tetrahydropyran derivatives and piperidine derivatives. The particular starting materials were chosen, first because they are commercially available and further to test the pattern of this chemistry upon the reaction conditions. Prenyl cyanoacetate 523 was synthesized smoothly in excellent yield (95%), and was used directly without further purification to give amino-alcohol 524 after lithium aluminium hydride reduction, then carbamate was added at nitrogen at ice temperature to give the N-protected amino-alcohol 525 (Scheme 4.13).

Scheme 4.13

When the free amino-alcohol 514 was exposure to a catalytic amount of concentrated sulfuric acid for two hours at 0 °C in dry dichloromethane, $^1$H NMR analysis of the crude reaction mixture suggested that the product of the reaction was the tetrahydropyran 526, which did not need any purification. It was clear that the cyclisation had occurred in an excellent yield of 98%. This was believed due to the disappearance of the olefinic $\equiv$CH at $\delta_H$ 5.15 ppm, but the NH proton at 4.73 ppm was still visible and the appearance of a new singlet at 1.13 ppm which is characteristic of six protons of the two methyls at the 6-position of the tetrahydropyran 526 ring. The $^1$H NMR spectrum of the product also revealed another singlet at $\delta_H$ 0.80 ppm which is characteristic of the three protons of the methyl in the 3-position of the product 526. The $^{13}$C NMR spectrum revealed a quaternary carbon next to the oxygen at $\delta_C$ 71.3 ppm and four CH$_2$ carbons one next to oxygen at $\delta_C$ 68.5 ppm, one next to nitrogen at 47.3 and two on the ring at 32.1 and 27.1 ppm (Scheme 4.14).

Scheme 4.14
In the event, when the alcohol group was blocked as the corresponding acetate \textbf{527}, then only the piperidine \textbf{528} was formed after one hour of reaction at ambient temperature in an excellent yield of 97\%. The products did not require any chromatographic purification as the reaction proceeded very cleanly. Infrared spectroscopy showed the absence of NH absorption and the presence of the carbonyl group at $\nu$/cm\(^{-1}\) 1699. Both \(^1\)H and \(^{13}\)C NMR spectra support the successful synthesis of piperidine \textbf{528}; starting material \textbf{527} had clearly disappeared. Most obvious was the disappearance of the olefinic $=$CH at $\delta_H$ 5.07 ppm and NH proton at $\delta_H$ 4.91 ppm, with the appearance of two AB systems one next to oxygen at $\delta_H$ 3.75 and another next to nitrogen at 3.31 (d, $J = 13.9$ Hz, 1H, NCH\textsubscript{A}H\textsubscript{B}) and 2.96 (d, $J = 13.9$ Hz, 1H, NCH\textsubscript{A}H\textsubscript{B}). Five methyls could be seen clearly; methoxy methyl at $\delta_H$ 3.54 ppm, methyl acetyl at $\delta_H$ 1.99 ppm and two methyls on quaternary carbon at $\delta_H$ 1.33 and 1.30 ppm and tinaly a singlet at $\delta_H$ 0.88 ppm which is characteristic of three protons in the 5-position. The \(^{13}\)C NMR showed four quaternary carbons: two of these in the downfield at $\delta_C$ 171.1 and 157.0 ppm, one next to the nitrogen atom at $\delta_C$ 55.0 ppm and anther quaternary at the 5-position of the ring at 34.4 ppm. Four CH\textsubscript{2} carbons were present, one next to oxygen at $\delta_C$ 70.2 ppm and three on the piperidine ring at $\delta_C$ 47.6 (NCH\textsubscript{2}), 36.4 and 28.1 ppm. When the acetate was hydrolysed in piperidine \textbf{528}, the resulting alcohol \textbf{529} showed the appearance of hydroxyl proton at 1.84 ppm as a broad singlet and a clear AB system next to oxygen at 3.48 and 2.83 (both d, $J = 14.1$ Hz, 1H) ppm. When the alcohol \textbf{529} was treated with acid, it rearranged to the initial tetrahydropyran \textbf{526} after 18 h at room temperature (Scheme 4.15).

\begin{center}
\textbf{Scheme 4.15}
\end{center}
Benzyl bromide was added to ethyl cyanoacetate in the presence of sodium hydride in dimethylformamide to give 530, then prenyl cyanoacetate 531 was synthesized smoothly in excellent yield (93%), which used directly without further perfection to give amino-alcohol 532 after lithium aluminium hydride reduction. Then the carbamate was added at nitrogen at ice temperature to give the N-protected amino-alcohol 533 (Scheme 4.16).

Scheme 4.16

However, when the alcohol group was protected as the corresponding acetate 534, then only the piperidine 535 was formed after one hour of reaction at room temperature with catalytic amount of sulfuric acid in excellent yield of 98%. The crude reaction mixture did require some chromatography as it showed some impurity; it could be because the starting reactant was not pure enough. Both $^1$H and $^{13}$C NMR spectra supported the successful synthesis of piperidine 535; starting material 534 had clearly disappeared. Most obvious was the disappearance of the olefinic proton at $\delta_H$ 5.19 ppm and NH proton at $\delta_H$ 4.78 ppm, with the appearance of two new AB systems. The $^{13}$C NMR showed a quaternary carbon next to the nitrogen at $\delta_C$ 55.3 ppm and four CH$_2$ carbons one next to oxygen at $\delta_C$ 67.3 ppm and three on the piperidine ring at $\delta_C$ 46.4 (NCH$_2$), 41.2 and 38.2 ppm. The acetate was hydrolysed in piperidine 535, and subsequent rearrangement of the resulting alcohol 536 gave the tetrahydropyran 537 which was also synthesized starting from amino-alcohol 533 after one hour of reaction at room temperature (98%) (Scheme 4.17).
Scheme 4.17

The double alkylated product 512 was reduced by lithium aluminium hydride to a mino-alcohol 538, then selective addition of tosyl to nitrogen over oxygen gave the N-tosyl free alcohol 539, which was subject to catalytic amount of sulfuric acid in dry dichloromethane to synthesis spiro-product 540 after just one hour of reaction at ice temperature in 97% isolated yield. Infrared spectroscopy showed the absence of NH absorption or alcohol. $^1$H NMR spectrum supported the successful synthesis of the product 540. Starting material 539 had clearly disappeared. This was confirmed by disappearance of the olefinic protons at δ$_H$ 5.02 ppm and the NH proton at δ$_H$ 4.94 ppm, and the appearance of two AB systems. The $^{13}$C NMR showed a quaternary carbon next to the oxygen at δ$_C$ 71.8 ppm, a quaternary carbon next to the nitrogen at δ$_C$ 58.2 and spiro-quaternary carbon at 32.9 ppm. Six CH$_2$ carbons one next to oxygen at δ$_C$ 67.9 ppm, one next to nitrogen at δ$_C$ 49.1 ppm and four on the rings at δ$_C$ 37.9, 31.7, 28.5 and 28.1 ppm, which are compatible with $^{13}$C NMR data for tetrahydropyran 520 and piperidine 523 (Scheme 4.18).
The generality of the new rearrangement was next tested by using substituent such as cinnamyl. Cinnamyl cyanoacetate 542 was synthesized by reaction of ethyl cyanoacetate 510 in the presence of sodium hydride with cinnamyl chloride 541 in DMF. The double alkylated product 543 was present. The two products were separated by using column chromatography (Scheme 4.19).

\[
\text{NC} \quad \text{CO}_2\text{Et} \quad \text{Ph} \quad \text{Ph} \quad \text{Cl} \quad \text{NaH, DMF} \quad \text{NC} \quad \text{CO}_2\text{Et} \quad \text{Ph} \quad \text{Ph} \\
510 \quad 541 \quad 542 \quad 543
\]

**Scheme 4.19**

Cinnamyl cyanoacetate 542 was then converted into the amino-alcohol 544 by a standard lithium aluminium hydride reduction. Finally, carbamate was added by using methyl chloroformate in the presence of triethylamine at ice temperature; all of these reactions proceeded in good yields. The cyclisation reaction of cinnamyl carbamate 545 was carried out with 0.5 equivalent of triflic acid at room temperature after six hours of reaction some starting material (ca. 20%) was still noticeable, which could be seen in the \(^1\)H NMR spectrum by the presence of olefinic protons at 7.12 and 6.35 ppm. After 20 hours of reaction with 0.5 equivalent of triflic acid at ambient temperature, no starting material could be seen and tetrahydropyran 546 was formed as an approximately 2:1 mixture of diastereoisomers, but was accompanied by extensive decomposition and multiple peaks from unidentified products. The ratio was measured according to the integration of methoxy in the protecting group, but a pure sample of the tetrahydropyran 546 was not separable (Scheme 4.20).

\[
\text{Ph} \quad \text{NC} \quad \text{CO}_2\text{Et} \quad \text{LiAlH}_4 \quad \text{THF} \quad \text{H}_2\text{N} \quad \text{OH} \quad \text{ClICO}_2\text{Me} \quad \text{Et}_3\text{N}, 0^\circ\text{C} \quad \text{DCM} \\
542 \quad 544 \quad 545 \quad 0.5 \text{ eq. TIOH} \quad \text{CH}_2\text{Cl}_2, 20^\circ\text{C}, 20\text{h} \quad \text{Ph} \quad \text{O} \quad \text{NHCO}_2\text{Me} \\
2:1 \quad 546
\]

**Scheme 4.20**
Alcohol 545 was protected and then subjected to 0.5 equivalent of triflic acid at room temperature; no starting material could be seen after six hours in the $^1$H NMR spectrum and piperidine 548 was formed as an approximately 1:1 mixture of diastereoisomers. The $^1$H NMR spectrum also showed some impurities which could be removed by column chromatography. The ratio was measured according to the integration of methoxy function in the $N$-protecting group. Analysis of the $^{13}$C NMR data showed a new CH peak at 776 ppm, a characteristic shift for a carbon next to nitrogen (Scheme 4.21).

![Scheme 4.21](image)

By comparison to the prenyl derivatives, the cinnamyl derivatives required more time to obtain both phenyltetrahydropyran and phenylpiperidine. In the case of alcohol cyclisation, the reaction was very slow and resulted in extensive decomposition. The previous results in Chapter 2 lead us to assume that the cyclisation of crotyl derivative would probably not be useful to try using this methodology, so this particular cyclisation was not attempted in this time.

We found in Chapter 2 (p.50), the steric hindrance was the key reason behind the tosyl and nosyl substituted piperidine rearrangements to pyrrolidines as the tosyl and nosyl groups are bulky groups. To study the effect of sulfonamide on this new $N$- to $O$-rearrangement, sulfonamide 549 was synthesized from amino alcohol 544 (Scheme 4.22).

![Scheme 4.22](image)
Surprisingly, sulfonamide free alcohol 549 underwent smooth cyclization in 0.5 equivalent of triflic acid after one hour at room temperature to give (6-phenyl-1-tosylpiperidin-3-yl)methanol 550 as a 2:1 mixture of diastereoisomers which were not separated. NMR analysis was used to confirm the structures of the diastereoisomers. The $^1$H NMR spectrum showed no starting material was present by the disappearance of the olefinic protons at $\delta_H 5.87$ and 5.58 and the NH proton at $\delta_H 4.70$ ppm with the increasing in the complexity of the spectrum. Two new low field resonances were visible at $\delta_H 5.21$ (d, $J = 4.8$ Hz, 1H, 6-H) and 5.05 (t, $J = 4.5$ Hz, 1H, 6-H) ppm both integrating for one proton for each isomer (Fig 4.7a). The resonance at $\delta_H 5.21$ was narrower and appeared as an apparent doublet ($J = 4.8$ Hz) with width at half height of $\omega_{1/2} = 10.7$ Hz. The resonance at $\delta_H 5.05$ appeared as apparent triplet ($J = 4.5$ Hz) with width at half height of $\omega_{1/2} = 11.0$ Hz (Fig 4.7a expansion). The $^{13}$C NMR spectrum confirmed the piperidine 550 structure; resonances at $\delta_C 56.4$ and 54.9 (2 x CHN, major/minor) were related to two methine carbons. The structure of tetrahydropyran 551 was excluded, as the literature survey$^4$ showed that methine carbon in 2-phenyl tetrahydropyran was expected to be at ca. $>80$ ppm in $^{13}$C NMR spectrum. The structure of piperidine 550 was confirmed by cyclisation of O-protected sulfonamide 552 reaction to piperidine 553 which gave an identical spectra to the piperidine prepared starting from free alcohol 549, except for a slight difference in the ratio of stereoisomers (Scheme 4.23).

![Scheme 4.23](image-url)
The double cinnamyl product 543 was reduced by lithium aluminium hydride to amino-alcohol 554, then selective addition of CO$_2$Me to nitrogen over oxygen gave N-protected free alcohol 555, which was subject to catalytic amount of sulfuric acid in dry dichloromethane to synthesis spiro-product 556 after 24 hours of reaction at 37 °C as a 3:1 mixture of diastereoisomers which were not separated. $^1$H NMR spectrum supported the successful synthesis of the product 556. Starting material had clearly disappeared. This confirmed by disappearance of the olefinic protons and the NH proton (Scheme 4.24). The $^{13}$C NMR of spiro[5.5]undecane 556 was compatible with $^{13}$C NMR for tetrahydropyran 546 and piperidine 548 in Scheme 4.20 and Scheme 4.21.

Scheme 4.24
Following these successful results, a logical extension of this methodology was its application to some pyrrolidines and tetrahydrofurans syntheses and the pattern of this rearrangement. Therefore, the cyclisation precursor was prepared from the reaction of 3-chloro-2-methylprop-1-ene 557 with ethyl cyanoacetate 510 in the presence of sodium hydride in DMF. The double alkylated product 559 was separated by using column chromatography (Scheme 4.25).

![Scheme 4.25](image)

The cyanoacetate 558 was reduced by lithium aluminium hydride to \(\gamma\)-amino alcohol 560. By selective addition of \(\text{CO}_2\text{Me}\) to nitrogen over oxygen unsaturated amino-alcohol 561 was synthesized. (Scheme 4.26).

![Scheme 4.26](image)

Thus tetrahydrofuran 562 was formed in an excellent total yield of 97% after just one hour of reaction with concentrated sulfuric acid at ice temperature, by overall 5-exo-trig cyclisation according to Baldwin’s rules. In \(^1\text{H NMR}\), there was no trace of starting material 561: both olefinic protons \(=\text{CH}_2\) at \(\delta_H \) 4.81 and 4.73 ppm had disappeared to confirm the complete reaction. There was no trace of any pyrrolidine 563 as NH proton was still visible in the \(^1\text{H NMR}\) spectrum and there were three sharp methyl singlets related to methyl carbamate at \(\delta_H \) 3.60 ppm and two methyl groups on quaternary carbon at \(\delta_H \) 1.23 and 1.12 ppm. The \(^{13}\text{C NMR}\) showed a quaternary carbon next to the oxygen atom at \(\delta_C \) 80.9 ppm and three \(\text{CH}_2\) carbons one next to oxygen at \(\delta_C \) 69.9 ppm, one next to nitrogen at \(\delta_C \) 45.4 (NCH\(_2\)) and another on the ring at 42.7 ppm.
When the alcohol group was protected as the corresponding acetate 564, then only the pyrrolidine 565 was formed in quantitative yield at room temperature, which was distinguished by its $^1$H and $^{13}$C NMR spectra. In $^1$H NMR, the NH proton at $\delta_H$ 4.92 ppm and olefinic protons $=\text{CH}_2$ at $\delta_H$ 4.75 and 4.67 ppm had completely disappeared to confirm the complete reaction. The $^{13}$C NMR showed a quaternary carbon next to the nitrogen atom at $\delta_C$ 60.9 ppm and three CH$_2$ carbons one next to oxygen at $\delta_C$ 65.8 ppm and two on the pyrrolidine ring at $\delta_C$ 50.6 (NCH$_2$) and 44.7 ppm. When the acetate was hydrolysed and the resulting alcohol 563 was treated with acid, it rearranged to the initial tetrahydrofuran 562 in an excellent yield of 97% (Scheme 4.27).

![Scheme 4.27](image)

Fig 4.8 $^1$H and $^{13}$C NMR spectra of tetrahydrofuran 562 a) decoupled $^{13}$C, b) proton.
Sulfonamide 566 was prepared by selective addition of tosyl to nitrogen over oxygen in a similar way to that described before. When sulfonamide 566 was subjected to catalytic amounts of sulfuric acid in dry dichloromethane the starting material disappeared after just one hour of reaction at 0 °C. Thus tetrahydrofuran 567 was formed as a mixture with ca. 20% of pyrrolidine 568 and excellent total yield of 97%. The ratios were measured from the integrals of the 1H NMR resonances corresponding to the tosyl group. There was no trace of any starting material 566 as the olefinic protons at δH 4.76 and 4.67 ppm had disappeared. There were two methyl singlets related to methyl tosyl ca. 2.34 ppm in 1H NMR spectrum. The key quaternary carbon (OCq) at δC 81.0 ppm related to tetrahydrofuran 567 and another small quaternary carbon (NCq) at δC 65.0 ppm referred to pyrrolidine 568 (Scheme 4.28).

![Scheme 4.28](image)

Pure pyrrolidine 568 was synthsized after the alcohol group was protected as the corresponding acetate 569, then only the pyrrolidine 570 was formed at ice temperature in quantitive yield, which was distinguished by its 1H and 13C NMR spectra. In 1H NMR, all NH proton at δH 4.95 ppm and olifinic protons =CH2 at δH 4.72 and 4.61 ppm had disappeared, which confirmed the complete reaction. Then the acetate group was hydrolysed and pyrrolidine methanol 568 was formed. The 13C NMR showed a quaternary carbon next to the nitrogen atom at δC 65.5 ppm and three CH2 carbons one next to oxygen at δC 64.4 ppm and two on the pyrrolidine ring at δC 51.8 (NCH2) and 45.6 ppm. One CH carbon at 38.0 ppm (Fig 4.9 and Scheme 4.29).

![Scheme 4.29](image)
Spirocyclic Frameworks

Spirocyclic framework structures have a well-defined three-dimensional spatial arrangement that exhibit specificity of action with biological receptors and enzymes. We had seen that double addition occurred when ethyl cyanoacetate reacted with alkyl halide 557 (Scheme 4.25), so that double alkylated products 559 was also isolated. The advantage of these double reactions was taken the two compounds were separated by column chromatography and gave a chance to investigate the compatibility of dual acid-catalysed cyclization reactions. The double alkylated product 559 was reduced by lithium aluminium hydride to amino-alcohol 569, then selective addition of tosyl to nitrogen over oxygen gave N-tosyl free alcohol 570, which was subjected to a catalytic amount of sulfuric acid in dry dichloromethane to synthesise spiro-product 571 after just one hour of reaction at room temperature in quantitative yield. Infrared spectroscopy showed no NH absorption or the
presence of alcohol. A $^1$H NMR spectrum confirmed the successful synthesis of the oxazaaspiro[4.4]nonane 571. As can be seen in Fig 4.10; starting material 570 had clearly disappeared. This was confirmed by disappearance of the NH proton at δ_H 5.12 ppm, olefinic protons at δ_H 4.90 and 4.76 ppm and of the hydroxyl proton at 2.29 ppm. The $^{13}$C NMR showed a quaternary carbon next to the oxygen at δ_C 80.2 ppm, a quaternary carbon next to the nitrogen at δ_C 64.8 and spiro-quaternary carbon at 48.5 ppm. Four CH$_2$ carbons one next to oxygen at δ_C 75.6 ppm, one next to nitrogen at δ_C 59.2 ppm and two on the rings at δ_C 52.7 and 49.7 ppm. Five methyl groups were present at δ_C 29.2, 29.1, 29.0, 28.3, 21.5 ppm (Fig 4.10, Scheme 4.30 and Table 4.3).

Scheme 4.30

Fig 4.10 $^1$H and decoupled $^{13}$C NMR spectra of oxazaaspiro[4.4]nonane 568
The *spiro*-structure was confirmed by NMR (\(^1\)H, \(^{13}\)C, COSY) spectroscopy, infrared spectroscopy, and mass spectrometry analysis. The \(^{13}\)C NMR data obtained were consistent with the published data by Chuan He *et. al.*\(^6\), who reported that gold(I) catalyzed intramolecular hydroamination/hydroalkoxylation of olefin 570 to give oxa-azaspiro 571 after ten hours of reaction with a catalytic amount of Ph\(_3\)PAuOTf (generated by mixing equal equivalents of Ph\(_3\)PAuCl and AgOTf) at 85 °C in toluene (Scheme 4.31 and Table 4.3).

![Scheme 4.31](image)

**Table 4.3** \(^{13}\)C NMR spectra of oxa-azaspiro 571.

<table>
<thead>
<tr>
<th>(^{13})C ppm</th>
<th>Cq</th>
<th>CH</th>
<th>OCH(_2)</th>
<th>NCH(_2)</th>
<th>CH(_2)</th>
<th>CH(_3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chuan He</td>
<td>142.9 and 137.9</td>
<td>129.4 (2 x CH)</td>
<td>75.4</td>
<td>59.1</td>
<td>52.5</td>
<td>48.5</td>
</tr>
<tr>
<td></td>
<td>(OCq) : 80.2</td>
<td>(127.3 (2 x CH))</td>
<td>(59.2)</td>
<td>(48.5)</td>
<td>(21.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(NCq) : 64.7</td>
<td>(spiro Cq) : 49.4</td>
<td>(52.7)</td>
<td>(48.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D. W. Knight</td>
<td>142.8 and 138.1</td>
<td>129.4 (2 x CH)</td>
<td>75.6</td>
<td>59.2</td>
<td>52.7</td>
<td>48.5</td>
</tr>
<tr>
<td></td>
<td>(OCq) : 80.2</td>
<td>(127.3 (2 x 2H))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(NCq) : 64.8</td>
<td>(spiro Cq) : 49.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A small sample of the amino-alcohol 569 (ca. 200 mg) was also converted into the carbamate 572 as protecting group. Cleanly, the synthesis of oxa-azaspiro[4.4]nonane 573 was achieved by double acid-catalysed cyclization reactions after one hour of reaction with catalytic amount of sulfuric acid at room temperature in quantitative yield. The $^{13}$C NMR showed a quaternary carbon next to the oxygen at $\delta$C 79.9 ppm, a quaternary carbon next to the nitrogen at $\delta$C 60.3 and spiro-quaternary carbon at 48.2 ppm. Four $\text{CH}_2$ carbons one next to oxygen at $\delta$C 75.8 ppm, one next to nitrogen at $\delta$C 58.2 ppm and two on the rings at $\delta$C 50.7 and 50.0 ppm. Five methyl groups were present at 51.4 (OCH$_3$), 29.4, 28.8, 27.2 and 26.8 ppm (Scheme 4.32). As can be seen in Table 4.4, the $^{13}$C NMR of spiro-nonane 573 was compatible with $^{13}$C NMR for tetrahydrofuran 562 and pyrrolidine 563.

![Scheme 4.32](image)

Table 4.4 $^{13}$C NMR spectra of tetrahydrofuran 562, pyrrolidine 563 and spiro[4.4]nonane 573.

<table>
<thead>
<tr>
<th>$^{13}$C NMR ppm</th>
<th>Cq</th>
<th>CH$_2$</th>
<th>CH$_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Structure" /></td>
<td>C=O : 157.2 OCq : 80.9</td>
<td>OCH$_2$ : 69.9 NCH$_2$ : 44.1 42.7</td>
<td>OCH$_3$ : 52.8 28.7 and 27.7</td>
</tr>
<tr>
<td><img src="image" alt="Structure" /></td>
<td>C=O : 157.5 NCq : 60.9</td>
<td>OCH$_2$ : 64.8 NCH$_2$ : 50.5 29.8</td>
<td>OCH$_3$ : 51.8 25.6 (2 x CH$_3$)</td>
</tr>
<tr>
<td><img src="image" alt="Structure" /></td>
<td>C=O : 153.8 OCq : 79.9 NCq : 60.3 $spiro$-Cq : 48.2</td>
<td>OCH$_2$ : 75.8 NCH$_2$ : 58.2 50.7 and 50.0</td>
<td>OCH$_3$ : 51.8 29.4, 28.8, 27.2 and 26.8</td>
</tr>
</tbody>
</table>
Transannular Cyclisations

Amino-alcohol 574 was the target to study the transannular N vs O cyclisation. A standard disconnection of the required cyclopentene ring 575 indicated that a route employing Grubbs’ metathesis would be suitable chemistry to start from relatively simple starting materials. Substituted oxa- and aza-bicyclo compounds can be made, showing the wide range application of this chemistry, starting from alkyl halides 577 and 578 (Scheme 4.33).

![Scheme 4.33](image)

It was decided to first focus on a simplified model, with the transannular precursor simplified to a methyl group. Synthesising this methyl model 558 was achieved as before (Scheme 4.25), followed a second allylation by allyl bromide 577 in the presence of sodium hydride to give substituted cyanoacetate 579 (87%). It is known that, Grubbs’ catalyst is a ruthenium carbene complex and there are three generations of the reagent available, which are compatible with a wide range of solvents. Grubbs’ second generation catalyst had been available within the group, so a simple ring closing metathesis using this catalyst was used to form the cyclopentene ring 580, which was then reduced by lithium aluminium hydride to the amino-alcohol 581 (Scheme 4.34).

![Scheme 4.34](image)

Sulfonamide 582 was prepared by selective addition of tosyl to nitrogen over oxygen in a similar way as described before. When sulfonamide 582 was subjected to a catalytic amount of sulfuric acid in dry dichloromethane, the starting material disappeared after just one hour of reaction at
ambient temperature. Thus oxabicyclo 583 was formed as a mixture with azabicyclo 584 as an inseparable mixture (3:1) in an excellent total yield of (92%). There was good evidence for the presence of rearrangement to azabicyclo 585 < 5%, which would have been formed through a less stable secondary carbenium ion. The evidence came mainly from the $^1$H NMR spectrum; there was no trace of any starting sulfonamide 582 as the olefinic proton at $\delta_H$ 5.06 ppm had disappeared. The resonances corresponding to the tosyl group about $\delta_H$ 7.00 – 7.70 ppm and the broad methyl singlet related to methyl tosyl ca. 2.34 ppm suggested the presence of three compounds. A methyl doublet at $\delta_H$ 1.48 ppm referred to the rearranged compound 585. The key quaternary carbon (OCq) at ca. 87.0 ppm related to oxabicyclo 583, another small quaternary carbon (NCq) at ca. 71.0 ppm referred to azabicyclo 584, NCH carbon was present ca. 45.0 ppm. Further studies would be necessary to confirm this result (Scheme 4.35).

Scheme 4.35

After the alcohol group was protected as the corresponding acetate 587, then only the azabicyclo 587 was formed at room temperature in an excellent yield (95%), which was distinguished by its $^1$H and $^{13}$C NMR spectra. In $^1$H NMR, all olefinic proton at $\delta_H$ 5.09 and NH proton at $\delta_H$ 4.99 ppm had disappeared to confirm the complete reaction. The $^{13}$C NMR showed a quaternary carbon next to the nitrogen at $\delta_C$ 70.8 ppm, another quaternary carbon at $\delta_C$ 46.8 ppm and five CH$_2$ carbons, one next to oxygen at $\delta_C$ 65.5 ppm, one next to nitrogen (NCH$_2$) at $\delta_C$ 58.5 ppm. Clearly, three CH$_2$ carbons could be seen; one between two quaternaries at $\delta_C$ 49.0 and and two others at 36.1, 32.1 ppm. Three methyl carbons close to each other were at 21.5, 20.7 and 19.4 ppm (Scheme 4.36).
A pure authentic sample of pyrrolidine 584 (Scheme 4.35) was synthesized after the alcohol group was deprotected. The $^1$H NMR showed a new ABX system reflected the coupling between OCH$_2$ protons with hydroxyl group at $\delta_H$ 3.35 (dd, $J = 8.5, 3.2$ Hz, 1H) and 3.27 (dd, $J = 8.5, 1.4$ Hz, 1H). The $^{13}$C NMR showed a quaternary carbon next to the nitrogen at $\delta_C$ 70.9 ppm, another quaternary carbon at $\delta_C$ 49.2 ppm. The CH$_2$ carbon next to oxygen was at $\delta_C$ 64.4 ppm, which showed no big difference comparing with CH$_2$ carbon next to oxygen in protecting alcohol 587 at $\delta_C$ 65.5 ppm. There were two methyl carbons at 21.5 and 19.5 ppm. Treatment of cyclic free methanol 584 with concentrated sulfuric acid gave similar result to that reaction reported above (Scheme 4.34) for the sample prepared by cyclisation of the sulfonamide 582 (Scheme 4.37).

This obstacle of equilibrium could be avoided by changing the size of the ring to cyanocyclohexene 588. It is expected the best way to prepare ethyl cyanocyclohexene carboxylate 588 by Grubbs metathesis. Initially, a standard disconnection of the required methyl cyclohexene ring 588 indicated that a route employment Grubbs’ metathesis would be suitable chemistry to start from a relatively simple starting materials. This methodology requires five steps to end with cyanocyclohexene 588 (Scheme 4.38).
It was previously described by Zhu et al. a procedure in which isoprene 591 was used to trap the methylidene cyanoacetate generated in situ in a Diels–Alder process with the assistance of copper(II) acetate monohydrate. In light of this, cyanocyclohexene carboxylate 588 was prepared in one step practical reaction by this methodology. Heating ethyl cyanoacetate, isoprene 591 and two equivalent of paraformaldehyde in the presence copper(II) acetate monohydrate at 80 °C in toluene-acetic acid 1:1 gave methyl cyanocyclohexene carboxylate 588 in excellent yield 94% (Scheme 4.39).

Scheme 4.39

Sulfonamide 591 was prepared after selective addition of tosyl to nitrogen over oxygen. The cineol framework 592 could be formed from in excellent yield (91%) after just one hour of reaction with concentrated sulfuric acid at ice temperature. In 1H NMR spectrum, the NH proton was still visible and there were two sharp methyl singlets related to methyl tosyl at δH 2.25 ppm and one methyl group on quaternary carbon at δH 0.90 ppm. The 13C NMR showed two quaternary carbons; one next to the oxygen atom (OCq) at δC 69.1 ppm and another at 32.4 ppm. Six CH2 carbons one next to oxygen at δC 71.7 ppm one next to nitrogen at δC 49.4 ppm, four on the rings, which showed a plane of symmetry at δC 32.1 (2 x CH2), 28.0 (2 x CH2) ppm (Scheme 4.40).

Scheme 4.40

When the alcohol group was protected as the corresponding acetate 594, then only the azabicyclo-octane 595 was formed at room temperature, which was distinguished by its 1H and 13C NMR
spectra. In $^1$H NMR, both olefinic proton (=CH) at $\delta_H$ 5.14 ppm and NH proton at $\delta_H$ 4.98 ppm had disappeared to confirm complete reaction. Three methyl signals could be seen clearly; aryl methyl at $\delta_H$ 2.36 ppm, methyl acetyl at $\delta_H$ 2.01 ppm and one methyl on quaternary carbon at $\delta_H$ 1.27 ppm. The stability of acetate was confirmed by infrared spectroscopy, which showed an absorption band at $\nu/cm^{-1}$ 1740 due to the carbonyl group, again showing the stability of this protecting group. The $^{13}$C NMR showed a quaternary carbon next to the nitrogen atom at $\delta_C$ 55.2 ppm and another at 34.0 ppm. Six CH$_2$ carbons one next to oxygen at $\delta_C$ 69.4 ppm, one next to nitrogen at $\delta_C$ 53.8 and four the rings at $\delta_C$ 33.0 (2 x CH$_2$), 27.1 (2 x CH$_2$) ppm (Scheme 4.41).

Scheme 4.41

Carbamate 596 was prepared from amino-alcohol 591. Then cineole framework 597 could be formed in quantitative yield (98%) after just one hour of reaction with concentrated sulfuric acid at room temperature. In $^1$H NMR spectrum the NH proton was still visible and there were two sharp methyl singlets related to methyl carbamate at $\delta_H$ 3.61 ppm and one methyl group on quaternary carbon at $\delta_H$ 1.02 ppm (Fig 4.9). The $^{13}$C NMR showed three quaternary carbons; a carbonyl carbon at $\delta_C$ 157.2 ppm, one next to the oxygen atom (OCq) at $\delta_C$ 68.9 ppm and another at 33.0 ppm. Six CH$_2$ carbons one next to oxygen at $\delta_C$ 71.7 ppm one next to nitrogen at $\delta_C$ 47.1 ppm, four on the rings, which showed a plane of symmetry at $\delta_C$ 32.1 (2 x CH$_2$), 27.8 (2 x CH$_2$) ppm. Two methyl carbamate (OCH$_3$) was at $\delta_C$ 52.1 ppm and one methyl carbon on quaternary carbon at $\delta_C$ 26.3 ppm (Scheme 4.42 and Fig 4.9).

Scheme 4.42
In the $^1$H $^{13}$C correlation spectrum (Fig 4.9), the left side of Fig 4.9 shows the 1-D $^{13}$C NMR spectrum (DEPT CH$_2$ right; CH and CH$_3$ left), and the top of the spectrum shows the 1-D $^1$H NMR spectrum. The two cross peaks arising from the methyl groups are the easiest to identify. In the lower left of the COSY spectrum, we see a cross peak between the two methylene protons (the integral of resonance at $\delta_H$ 3.71 – 3.49 ppm) whose resonance is the carbon next to oxygen at $\delta_C$ 71.7 ppm. The cross peak between the carbon next to nitrogen at $\delta_C$ 47.1 ppm resonates the two protons whose appearance is as doublets at $\delta_H$ 2.89 (d, $J = 6.5$ Hz, 2H) ppm. In the upper right of the COSY spectrum, a cross peak correlating the resonance of the methylene protons (both multiplet $\delta_H$ 1.79 – 1.67 (m, 2H, CH$_2$) and 1.57 – 1.40 (m, 6H, 3 x CH$_2$) ppm are the carbons at $\delta_C$ 32.1 (2 x CH$_2$) and 27.8 (2 x CH$_2$) ppm (Fig 4.11).

![Fig 4.11 $^1$H $^{13}$C COSY analysis oxabicyclo-octane 597.](image-url)
The oxabicyclo-octane 597 was very pure and crystallized by itself and the structure was confirmed by X-ray crystallography (Fig 3.12).

![Fig 3.12 The X-ray structure of oxabicyclo-octane 597. Full crystallographic data is included in the Appendix 8.](image)

When the alcohol group was protected as the corresponding acetate 598, then only the azabicyclo-octane 599 was formed at room temperature, which was confirmed by its $^1$H NMR spectrum. Both olefinic proton (=CH) and NH proton had disappeared to confirm the complete reaction. Three methyl signals could be seen; methoxy methyl at $\delta_H$ 3.55 ppm, methyl acetyl at $\delta_H$ 1.97 ppm and one methyl on quaternary carbon at $\delta_H$ 1.42 ppm. (Scheme 4.43).

![Scheme 4.43](image)

This chemistry showed variety in application, both cineol 597 and isoquinuclidine 599 frameworks were synthesized in excellent yields by acid-catalysed transannular cyclizations.
Cascade cyclisations

As hydroquinolines were studied before in Chapter 3, it was decided to see if such methodology would be extended to the formation of six membered rings by using cascade cyclisations.

Geranyl cyanoacetate 601 was synthesized by refluxing ethyl cyanoacetate 510 with geranyl bromide 600 in ethanol in the presence of potassium carbonate for 20 hours (75% yield),\(^{10}\) which was then reduced by LiAlH\(_4\) to give the amino-alcohol 602 (Scheme 4.44).

```
\[
\begin{array}{c}
\text{NC} & \text{CO}_2\text{Et} \\
\text{\textbf{510}} & \text{EtOH,reflux} \\
\end{array}
\quad
\begin{array}{c}
\text{Br} \\
\text{\textbf{600}} \\
\end{array}
\xrightarrow{\text{K}_2\text{CO}_3} \\
\begin{array}{c}
\text{CO}_2\text{Et} \\
\text{\textbf{601}} \\
\end{array}
\quad
\begin{array}{c}
\text{CN} \\
\text{\textbf{601}} \\
\end{array}
\xrightarrow{\text{LiAlH}_4} \\
\begin{array}{c}
\text{OH} \\
\text{\textbf{602}} \\
\end{array}
\end{array}
\]
```

Scheme 4.44

Finally, carbamate was added the amino-alcohol 602 by using methyl chloroformate in the presence of triethylamine. Unusually, the reaction mixture was left stirring overnight, then chromatographic purification showed a trace of cyclic carbamate 604 as a side product (ca. 2%). The structure of cyclic carbamate 604 was deduced by \(^1\)H and \(^{13}\)C NMR spectroscopy. In the \(^1\)H NMR spectrum, an NH proton at \(\delta_H\) 5.08 ppm and two olefinic protons at \(\delta_H\) 5.06 – 4.95 ppm were visible. There were two ABX systems. The \(^{13}\)C NMR spectrum showed five CH\(_2\) carbons: one next to oxygen at \(\delta_C\) 70.2 ppm, one next to nitrogen atom at \(\delta_C\) 45.3 ppm and three CH\(_2\) carbons next to double bonds at \(\delta_C\) 39.7, 27.3 and 26.5 ppm (Scheme 4.45).

```
\[
\begin{array}{c}
\text{\textbf{602}} \\
\end{array}
\xrightarrow{\text{ClCO}_2\text{Me}} \\
\begin{array}{c}
\text{\textbf{603}} \\
\end{array}
\quad
\begin{array}{c}
\text{\textbf{604}} \\
\end{array}
\end{array}
\]
```

Scheme 4.45

It was perhaps fortunate that the cyclic carbamate 607 was not similarly formed during the preparation of carbamate 605, or during the acid-catalysed cyclisations. Carbamate free alcohol 605 clearly could be converted into cyclic carbamate 607 under acidic conditions (Fig 3.13).
Having separated the cyclic carbamate by-product 604, the cyclisation reaction of geranyl carbamate 603 was carried out with a catalytic amount of sulfuric acid at room temperature for one hour. Cascade reaction showed the same chemistry; the octahydro chromene skeleton 608 was synthesized directly from free alcohol 603 in an excellent yield of 90% as a mixture of major and minor isomers. The $^1$H NMR spectrum showed that the resonances corresponding to the two olefinic protons had disappeared, whereas the NH proton did not disappear. The singlets at $\delta_H 1.68$ and 1.61 ppm representing the three methyl groups on double bonds moved further upfield as two isomers (ratio 2:1) were formed and the complexity of spectrum increased. In the $^{13}$C NMR spectrum, a major isomer showed three quaternary carbons at $\delta_C 157.2$ (C=O), 74.7 (OCq), and 34.0 ppm, six CH$_2$ signals $\delta_C 64.0$ (OCH$_2$), 42.4 (NCH$_2$), 41.5, 40.0, 23.6 and 21.1 ppm and two CH carbons at $\delta_C 52.9$ and 38.8 ppm (Scheme 4.46).
The structure could be derived from chair transition state, where the geometry of the double bond in the starting material, causes the ring junction likely to be trans-fused and the side chain up or down. This seems to be consistent with the MM2 energies calculated using the CS Chem3D Pro program (Fig 3.14). This information allows us to envisage a double-chair conformation for the trans-fused isomer 608B, where the side chain is equatorial, but more investigations are needed to confirm the detailed structures of the two products.

After the alcohol group was protected as the corresponding acetate 609, then only the perhydroquinoline 610 was formed by one hour of reaction with a catalytic amount of sulfuric acid in a very good isolated yield of 84%. This was distinguished by its $^1$H and $^{13}$C NMR spectra. In the $^1$H NMR, all olefinic protons at $\delta_H$ 5.09 – 4.96 ppm and NH proton at 4.90 ppm had disappeared with a trace of an unidentified compound formed at less than 10%. Three singlets at $\delta_H$ 1.61 and 1.53 ppm representing three methyl groups on double bonds moved further upfield to be as six singlets as two isomer (ratio 2:1) were formed, the complexity of spectrum increased. In the $^{13}$C NMR spectrum, a major isomer showed a quaternary carbon next to nitrogen at $\delta_C$ 60.9 ppm, sp$^3$ quaternary carbon at 34.2 ppm, two CH carbons 51.9 and 34.2 ppm and six CH$_2$ carbons at $\delta_C$ 66.8 (OCH$_2$), 44.3 (NCH$_2$), 41.2, 38.5, 32.8 and 22.9 ppm (Scheme 4.47).
Thus, octahydro-chromene and perhydroquinoline skeletons were synthesized directly from the corresponding geranyl amino-alcohols in excellent yields after only one hour of reaction with catalytic amounts of sulfuric acid.

Conclusions:

The novel rearrangement was first discovered using the amino-alcohol 514 and works with both carbamate and tosylate derivatives, which rearranged to the initial tetrahydropyran 517 after reaction with the acid at ambient temperature (Scheme 4.48). However, when the alcohol is blocked by acetylation, the corresponding piperidines 516 are formed. Significantly, these reactions also showed that an acetyl group was suitable as an alcohol protecting group in this type of chemistry.

The inclusion of additional substituents ($R = \text{CH}_3$ and $\text{CH}_2\text{Ph}$) has no obvious affect on the reactions (Scheme 4.49).
Exactly the same occurred with the corresponding five-membered rings (Scheme 4.50).

Surprisingly, sulfonamide free alcohol 549 gave piperidine 550. This structure was confirmed by O-protected sulfonamide reaction which gave identical spectra to that piperidine starting from free alcohol (Scheme 4.51).

The synthesis of spiro-compounds was achieved by double acid-catalysed cyclization reactions (Scheme 4.52).
The transannular example showed only a trace of rearrangement to the $O$-heterocyclic product 593 under the previous conditions (18 hours at room temperature) **Scheme 4.48**.

**Scheme 4.52**

Formation of the half-cyclised sulfonamide 384 (p. 82) showed that steric factors probably play an important role in these cyclisations. However, the cascade example was successful with the carbamate derivative 603, which cyclized smoothly, again showing the utility of acetate protection, to give both bicyclic systems 608 and 610 (**Scheme 4.54**). A few studies on the $N \rightarrow O$-rearrangement gave mixed results and were not clean.

**Scheme 4.53**

**Scheme 4.54**
**Future work:**

1. **Amino acid derivatives:**

The cyclohexenes 616 derived from dehydroalanine 614 by Diles-Alder cyclisation should cyclise to give the proline homologues 617 which may well undergo subsequent rearrangement to the O-heterocycles 618, following reduction (Scheme 4.55). The incorporation of more substituents and examination of many different ring sizes could open up useful new routes to a whole series of proline analogues.

![Scheme 4.55](image)

2. **Hydrothiolation vs hydroamination**

Related competitions between sulphur and nitrogen nucleophiles could also open up new approaches to many saturated heterocyclic systems.

![Scheme 4.56](image)

As two differing structures can thus be obtained from a single precursor, these strategies should find many applications in efficient and flexible heterocyclic synthesis.
There are also many opportunities to modify the nature of the acid catalyst used. In particular, the use of solid phase super acids such as Nafion-H offers the prospect of developing a flow system for carrying out this type of cyclisation chemistry. As yet, no Lewis acids have been tested in place of triflic or sulfuric acids; there are many types of such catalysts which have at least the required level of acidity. If successful, these too could be used in potentially very efficient flow systems and hence contribute to the conversion of this methodology into very environmentally friendly chemistry, despite the fact that it relies on very powerfully acidic conditions.

References

Chapter 5

Experimental
5.1 General experimental details

Reagents were obtained from Aldrich, Alfa Aesar, Lancaster, Fluka and Strem chemical suppliers and used as received unless otherwise specified. Solvents and reagents were purified according to the procedures of Perrin, Armarego and Perrin. \(^1\) Dichloromethane and toluene were dried by refluxing over, and distilling from, calcium hydride. Ethanol was dried by refluxing over magnesium, followed by distillation. Anhydrous diethyl ether and tetrahydrofuran were obtained by refluxing over sodium with sodium benzophenone ketyl as indicator, followed by distillation. “Petrol” refers to petroleum ether b.p. 40 - 60 °C, “ether” refers to diethyl ether.

All aqueous solutions were saturated unless otherwise stated. All non-aqueous reactions were, unless otherwise stated, conducted using oven or flame-dried glassware and under an atmosphere of dry nitrogen. “Dried” refers to the addition of dried magnesium sulfate (MgSO\(_4\)) to remove trace amounts of water at the work-up stage. “Filtered” refers to the removal of solid residues by gravity filtration of organic solutions through filter paper. “Evaporated” refers to the distillation of volatiles using a Büchi rotary evaporator attached to a 20 L Charles Austen pump at approx. 8 mbar, heated with a water bath typically between 20 and 40 °C. “Degassed” refers to bubbling nitrogen gas through the solvent for 30 minutes.

Solid carbon dioxide and an acetone bath (-78 °C) or an ice-water bath (0 - 5 °C) were used to obtain low temperatures; “r.t.” stands for room temperature; “b.p.” stands for boiling point; “m.p.” stands for melting point. Heated reactions were conducted in a stirred oil bath heated on a magnetically stirred hotplate.

All reactions were followed and monitored by TLC, \(^1\)H NMR, \(^13\)C NMR and mass spectrometry as appropriate. TLC analysis refers to analytical thin layer chromatography, using aluminium-backed plates coated with Merck Kieselgel 60 GF254. Product spots were viewed either by the quenching of UV fluorescence, or by staining with a solution of 2% aqueous potassium permanganate.
Column chromatography refers to flash column chromatography using head pressure by means of compressed air according to the procedure of Still,\(^2\) and using Merck Kieselgel 60 H silica or Matrix silica 60. Melting points were recorded using a Kofler Heated Stage Micro Melting Point apparatus and are uncorrected. Infra-red spectra were recorded in the range 4000-600 cm\(^{-1}\) using a Shimadzu 8400S series FTIR instrument, a diamond prism supported by a ZnSe lens, a solution in CDCl\(_3\). All absorptions are quoted in wave numbers (cm\(^{-1}\)).

\(^1\)H NMR spectra (\(\delta_H\)) were recorded using an Avance Bruker DPX 400 (400 MHz). \(^13\)C NMR spectra (\(\delta_H\)) were recorded using an Avance Bruker DPX 400 (500 MHz), with \(^13\)C NMR spectra (\(\delta_C\)) recorded at 125 MHz unless otherwise stated. Spectra were obtained as dilute solutions in deuterated chloroform, unless otherwise stated, in which case spectra were obtained in dilute solutions of fully deuterated dimethyl sulfoxide (DMSO-\(d_6\)). The chemical shifts were recorded relative to residual chloroform (7.26 or 77.0 ppm) as an internal standard unless otherwise stated, in which case chemical shifts were recorded relative to partially deuterated dimethyl sulfoxide (2.50 or 39.52).\(^3\) Abbreviations used for the multiplicities are s (singlet), d (doublet), t (triplet), q (quartet), br. (broad), dd (doublet of doublets), dt (doublet of triplets), td (triplet of doublets), m (unresolved multiplet), app. (apparent) or as a combination of these multiplicities. All coupling constants (\(J\)) are recorded in Hertz (Hz). Assignments were made on the basis of chemical shift and coupling constant data using DEPT-90, DEPT-135, COSY, NOESY, HSQC and HMBC experiments where required.

Mass spectrometric data were determined using a Waters GCT Premier instrument using electron ionisation (EI) unless otherwise stated, in which case mass spectrometric data were determined using a Waters LCT Premier XE instrument (LRMS) or Agilent 5975C Series GC/MSD (GC-MS) using pressure chemical ionisation (APCI) or electrospray ionisation (ES) as indicated. High
resolution mass spectrometric data were determined with the molecular formula corresponding to the observed signal using the most abundant isotopes of each element.

A literature reference associated with the title of compound means it is not a novel compound and any data recorded in this thesis matches well with those reported in the associated references, unless otherwise stated.

5.2 General Procedures

**General Procedure A: Amine Protection by Ts, Ns, CO₂Me and Cbz (PG).⁴**

The amine (1.0 eq.) was dissolved in dry dichloromethane (1 ml mmol⁻¹) and the solution cooled in ice-water. Triethylamine (1.1 eq.) and the PG. chloride (1.1 eq.) were added sequentially. The resulting mixture was allowed to warm to room temperature over 2 h then quenched with water (1 ml mmol⁻¹) and 2M hydrochloric acid (1 ml mmol⁻¹). The aqueous phase was extracted with dichloromethane (3 x 1 ml mmol⁻¹). The combined organic extracts were washed with brine (0.5 ml mmol⁻¹) then dried, filtered and concentrated under reduced pressure to yield the crude product which was purified by filtration through a pad of silica gel or, if necessary, by column chromatography (gradient elution of silica gel with 0 - 100% dichloromethane in hexanes) to give the pure title compound.

**General Procedure B: Acid Catalyst Cyclization Reactions with sulfuric acid H₂SO₄.**

The starting compound (1.00 mmol) was taken up in anhydrous dichloromethane (5 ml) and the solution was cooled in ice-water. Concentrated sulfuric acid (0.3 - 0.5 eq.) was then added. The completed reaction was quenched with saturated aqueous potassium carbonate (5 ml). The separated aqueous layer was extracted with dichloromethane (2 x 5 ml) and the combined organic extracts were dried, filtered and evaporated to yield the product.
General Procedure C: Reductions of oximes or cyanoacetates to the corresponding amines or amino-alcohols using lithium aluminium hydride; typical method.

The oxime or cyanoacetate (19 mmol, 1.0 eq.) was dissolved in dry tetrahydrofuran (30 ml) and the solution added dropwise to a stirred suspension of lithium aluminium hydride (0.76 g, 20 mmol, 1.1 eq. or 0.86 g, 45.5 mmol, 2.5 eq. in the case of a cyanoacetate, or as stated in an individual experiment) in tetrahydrofuran (20 ml) cooled in ice-water. The suspension was then refluxed for 3 h and subsequently cooled in an ice-water bath. When it was cold, water (5 ml) and 15% aqueous NaOH (5 ml) were added sequentially and the resulting mixture then stirred for one hour. The precipitated salts were then filtered off and washed with tetrahydrofuran (40 ml). The combined filtrates were concentrated and the liquid residue extracted with dichloromethane (2 x 10 ml). The combined extracts were dried and concentrated to give the amine or amino-alcohol, which was typically sufficiently pure to be used immediately in a subsequent step.

Solvent quantities were scaled in line with foregoing quantities for different scales of reaction.

5.3. Experimental Procedures

6-Methylhept-5-en-2-one oxime 234

\[
\begin{align*}
\text{233} & \xrightarrow{\text{NH}_2\text{OH.HCl, NaOAc, EtOH}} \text{234} \\
& \quad \text{Ketone} \quad \text{Hydroxylamine hydrochloride}\n\end{align*}
\]

To a solution of the ketone 233 (2.52 g, 20 mmol, 1.0 eq) and hydroxylamine hydrochloride (2.09 g, 30 mmol, 1.5 eq) in ethanol (30 ml) was added sodium acetate (1.0 g, 12.2 mmol) in one portion. The reaction mixture was heated at 40 °C for 2 h and then concentrated on a rotary evaporator. The residue was partitioned between ether (50 ml) and water (10 ml). The separated organic layer was dried and evaporated to give the oxime 234 (2.70 g, 95%) as a 3:1 mixture of isomers and as a colourless liquid which was used directly in the next step. All data obtained were
in accordance with those previously reported in the literature:δH 9.75 – 8.00 (br. s, NOH), 5.30–5.00 (m, 1H, =CH), 2.24 – 2.10 (m, 4H, 2 × CH2), 1.91 (2 x s, 3H, E:Z isomers 3:1 ratio, CH3),
1.70 (s, 3H, CH3), 1.63 (s, 3H, CH3). δC 158.7 (Cq), 132.7 (Cq), 122.8 (CH), 35.8 (CH2), 25.7 (CH3), 25.0 (CH2), 17.6 (CH3), 13.5 (CH3).

* 3:1 ratio determined after expansion of the apparent singlet.

6-Methylhept-5-en-2-amine 235

By general procedure C, the oxime 235 (2.70 g, 19 mmol, 1.0 eq.) was reduced using lithium aluminium hydride (0.38 g, 20 mmol, 1.1 eq.) to give the amine 236 (2.20 g, 90%) as a clear oil, which was used directly in the next step. All data obtained were in accordance with those previously reported in the literature:δH 5.10 – 5.00 (m, 1H, =CH), 2.85 (app. sext, 1H, J = ca. 6.5 Hz, NCH), 2.10 – 1.89 (m, 2H, CH2), 1.60 (s, 3H, CH3), 1.57 (s, 3H, CH3), 1.40 – 1.20 (m, 2H, CH2), 0.95 (d, 3H, J = 6.3 Hz, CH3). δC 133.2 (Cq), 124.2 (CH), 46.6 (NCH), 35.9 (CH2), 25.7 (CH2), 25.0 (CH3), 21.0 (CH3), 17.7 (CH3).

N-(6-Methylhept-5-en-2-yl)-4-methyl benzenesulfonamide 236

By general procedure A, p-tosyl chloride (2.10 g, 11.0 mmol, 1.1 eq.) was added to the amine 235 (1.20 g, 10.0 mmol, 1.0 eq.) and Et3N (1.25 ml, 11.0 mmol) to give the sulfonamide 236 as a clear oil (2.1 g, 75%). All data obtained were in accordance with those previously reported in the literature:δH 7.74 – 7.64 (m, 2H), 7.27 – 7.21 (m, 2H), 4.91 - 4.85 (m, 1H, =CH), 4.21 (d, J = 8.1 Hz, NH), 3.41 – 3.01 (m, 1H, NCH), 2.36 (s, 3H, ArCH3), 1.92 – 1.86 (m, 2H, CH2), 1.51 (s, 3H,
CH₃), 1.45 (d, J = 1.3 Hz, 3H, CH₃), 1.30 (dt, J = 7.7, 6.5 Hz, 2H, CH₂), 0.97 (d, J = 6.5 Hz, 3H, CH₃). δc 154.6 (Cq), 143.3 (Cq), 132.5 (Cq), 129.2 (2 x CH), 126.3 (2 x CH), 123.7 (CH), 50.6 (NCH), 37.3 (CH₂), 26.6 (ArCH₃), 24.2 (CH₂), 21.7 (CH₃), 21.4 (CH₃), 17.5 (CH₃). IR (neat) ν/cm⁻¹: 3282, 2970, 2924, 1599, 1303, 1150. HRMS (EI) m/z calculated for C₁₅H₂₃NO₂S [M]+ = 281.1450; found: 281.1443.

1-Toluenesulfonyl-2,2,6-trimethylpiperidine 237

By general procedure B, to sulfonamide 236 (140 mg, 0.5 mmol) in dry dichloromethane (10 ml) under nitrogen, concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for one hour at 0 °C to give the piperidine 237 (105 mg, 75% after crystallization in dichloromethane/hexanes) as sharp, colourless crystals, m.p. 82 – 83°C. δH 7.74 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 8.2 Hz 2H), 4.45 – 4.55 (m, 1H, NCH), 2.41 (s, 3H, ArCH₃), 1.84 – 1.75 (m, 2H), 1.70 – 1.65 (m, 1H), 1.53 (s, 3H, CH₃), 1.32 (d, J = 6.9 Hz, 3H, CH₃), 1.45 – 1.35 (m, 3H, CH₂ and CH), 1.07 (s, 3H, CH₃). δc 142.2 (Cq), 140.0 (Cq), 129.4 (2 x CH), 126.2 (2 x CH), 58.2 (Cq, 2-C), 51.3 (NCH, 6-CH), 41.0 (CH₂), 30.9 (ArCH₃), 30.2 (CH₂), 29.6 (CH₃), 22.6 (CH₃), 22.6 (CH₃), 15.3 (CH₂). IR (neat) ν/cm⁻¹: 2936, 2873, 1599, 1465, 1321, 1158, 1141, 1095. HRMS (EI) m/z calculated for C₁₅H₂₃NO₂S [M]+ = 281.1450; found: 281.1453.

(Cis and trans)-2-Isopropyl-5-methyl-1-tosylpyrrolidine 239
By general procedure B, to sulfonamide 236 (88 mg, 0.3 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (2 drops) was added and the resulting mixture stirred for 1 h at 20 °C to give the pyrrolidine 239 (82 mg, 93%) (1.4:1 ratio) as a colourless oil. All data obtained were in accordance with those previously reported in the literature.\(^8\) Major-2-isopropyl-5-methylpyrrolidine: δ\(_H\) 7.62 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 3.66 – 3.62 (m, 1H, NCH), 3.32 (dd, J = 12.4, 7.0 Hz, 1H, NCH), 2.30 (s, 3H, Ar-CH\(_3\)), 2.03 – 1.93 (m, 1H, CH), 1.85 – 1.78 (m, 2H, CH\(_2\)), 1.58 – 1.51 (m, 1H, CH), 1.37 – 1.29 (m, 1H, CH), 1.14 (d, J = 6.4 Hz, 3H, CH\(_3\)), 0.74 (d, J = 7.0 Hz, 3H, CH\(_3\)), 0.50 (d, J = 6.8 Hz, 3H, CH\(_3\)).

Minor-2- isopropyl-5-methylpyrrolidine: δ\(_H\) 7.63 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 4.06 – 3.98 (m, 1H, NCH), 3.66 – 3.62 (m, 1H, NCH), 2.33 (s, 3H, Ar-CH\(_3\)), 1.67 – 1.62 (m, 1H, CH), 1.58 – 1.51 (m, 1H, CH), 1.48 – 1.39 (m, 2H, CH\(_2\)), 1.33 – 1.25 (m, 1H, CH), 1.20 (d, J = 6.4 Hz, 3H, CH\(_3\)), 0.88 (d, J = 6.9 Hz, 3H, CH\(_3\)), 0.82 (d, J = 6.7 Hz, 3H, CH\(_3\)).

5-Methyl-4-hexenenitrile 253\(^9\)

\[\begin{align*}
\text{CH}_{3}\text{CN} & \quad \text{n-BuLi} \quad \text{85\%} \\
\text{Br} & \quad \text{252} & \quad \text{253}
\end{align*}\]

n-Butyllithium (12.8 ml of a 1.6 M solution in hexanes, 20.0 mmol, 1.05 eq) was added via syringe to a solution of acetonitrile (0.86 g, 20 mmol, 1.05 eq) in dry tetrahydrofuran (50 ml) at -70 °C. After stirring the mixture at -70 °C for 15 min, the bromide 252 (2.90 g, 19 mmol, 1.0 eq) in dry tetrahydrofuran (25 ml) was added. The mixture was stirred at -50 °C for 0.5 h and at room temperature for a further 2 h. Saturated aqueous ammonium chloride (50 ml) was added and the resulting mixture extracted with ether (3 x 10 ml). The combined organic extracts were dried, filtered and evaporated to yield the nitrile 253 (1.90 g, 85%) as a yellowish oil. All data obtained were in accordance with those previously reported in the literature.\(^9\) δ\(_H\) 5.16 – 4.97 (m, 1H, =CH), 2.27 (t, J = 6.6 Hz, 2H, CH\(_2\)), 2.22 (q, J = 6.9 Hz, 2H, CH\(_2\)), 1.65 (s, 3H, CH\(_3\)), 1.58 (s, 3H, CH\(_3\)). δ\(_C\) 135.8 (Cq), 122.4 (=CH), 119.6 (CN), 25.7 (CH\(_3\)), 24.1 (CH\(_2\)), 17.9 (CH\(_2\)), 17.8 (CH\(_3\)).
5-Methylhex-4-en-1-amine 254

By general procedure C, 5-methyl-4-hexene nitrile 253 (1.90 g, 17 mmol, 1.0 eq.) was reduced using lithium aluminium hydride (0.76 g, 20 mmol, 1.1 eq.) to give the amine 254 (1.57 g, 83%) as a clear oil, which was used directly in the next step. All data obtained were in accordance with those previously reported in the literature: $^8$ δ_H 5.04 – 5.10 (m, 1H, =CH), 2.69 – 2.44 (m, 2H, CH₂N), 1.90 – 2.08 (m, 2H, CH₂), 1.63 (s, 3H, CH₃), 1.53 (s, 3H, CH₃), 1.21 – 1.10 (m, 2H, CH₂). δ_C 132.2 (Cq), 122.9 (=CH), 42.8 (CH₂N), 30.3 (CH₂), 25.6 (CH₂), 17.8 (CH₃), 17.6 (CH₃).

N-(5-Methylhex-4-en-1-yl)-4-methyl benzenesulfonamide 249$^{10}$

By general procedure A, p-tosyl chloride (2.10 g, 11.0 mmol, 1.1 eq.) was added to the amine 254 (1.10 g, 10.0 mmol, 1.0 eq.) and Et₃N (1.25 ml, 11.0 mmol, 1.1 eq.) to give the sulfonamide 249 as a clear oil (1.19 g, 46%). All data obtained were in accordance with those previously reported in the literature: $^8$ δ_H 7.68 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 8.2 Hz, 2H), 4.91 (t, J = 7.2 Hz, 1H, =CH), 4.60 (t, J = 6.1 Hz, 1H, NH), 2.85 (td, J = 7.2, 6.1 Hz, 2H, CH₂N), 2.36 (s, 3H, ArCH₃), 1.95 – 1.79 (m, 2H, CH₂), 1.58 (s, 3H, CH₃), 1.46 (s, 3H, CH₃), 1.41 (p, J = 7.2 Hz, 2H, CH₂). δ_C 143.3 (Cq), 137.1 (Cq), 132.7 (Cq), 129.6 (2 x CH), 127.1 (2 x CH), 124.0 (=CH), 42.9 (CH₂N), 29.6 (CH₂), 25.6 (ArCH₃), 25.0 (CH₂), 21.5 (CH₃), 17.6 (CH₃). IR (neat) μ/cm$^{-1}$: 3287, 2928, 2257, 1599, 1323, 1157, 1094, 907, 814. HRMS (El) m/z calculated for C$_{14}$H$_{21}$NO$_2$S [M]$^+$ = 267.1293; found: 267.1287.
**2,2-Dimethyl-1-tosylpiperidine 250**

![Chemical Reaction Diagram](image)

By general procedure B, to sulfonamide 249 (112 mg, 0.42 mmol, 1.0 eq) in dry dichloromethane (10 ml) under nitrogen, concentrated sulfuric acid (25 mg, 0.25 mmol, 0.6 eq) was added and the resulting mixture stirred for 50 min at room temperature to give the piperidine 250 (110 mg, 98%) as yellowish crystals, m.p. 66 – 67 °C. All data obtained were in accordance with those previously reported in the literature: \(^8\) \(\delta_H\) 7.64 – 7.53 (m, 2H), 7.23 – 7.10 (m, 2H), 3.40 (t, \(J = 6.0\) Hz, 2H, CH\(_2\)N), 2.31 (s, 3H, Ar CH\(_3\)), 1.61 – 1.42 (m, 4H, 2 x CH\(_2\)), 1.35 (t, \(J = 6.7\) Hz, 2H, CH\(_2\)), 1.18 (s, 6H, 2 x CH\(_3\)). \(\delta_C\) 142.5 (Cq), 140.5 (Cq), 129.4 (2 x CH), 126.9 (2 x CH), 57.9 (Cq, 2-C), 43.7 (CH\(_2\)N), 41.3 (CH\(_2\)), 26.2 (ArCH\(_3\)), 26.2 (CH\(_2\)), 21.4 (2 x CH\(_3\)), 20.5 (CH\(_2\)). IR (neat) \(\nu/cm^{-1}\): 2930, 2866, 1599, 1454, 1157, 1319, 1139, 943, 814, 673. HRMS (EI) \(m/z\) calculated for C\(_{14}\)H\(_{21}\)NO\(_2\)S [M]\(^+\) = 267.1293; found: 267.1287.

**2-Isopropyl-1-tosylpyrrolidine 251**

![Chemical Reaction Diagram](image)

The sulfonamide 249 (0.14 g, 0.5 mmol) was dissolved in dry toluene (10 ml) and to this triflic acid (76 mg, 46 \(\mu\)l, 0.5 mmol) was added and the resulting solution stirred for 25 h at 110 °C. The reaction was allowed to cool and was then quenched with saturated aqueous potassium carbonate (10 ml). The quenched solution was then separated and the aqueous layer was extracted with ether (3 x 10 ml). The combined organic solutions were dried and evaporated to give the pyrrolidine 251 as a yellow oil (113 mg, 81%). All data obtained were in accordance with those previously reported in the literature: \(^{11}\) \(\delta_H\) 7.74 (d, \(J = 8.3\) Hz, 2H), 7.52 (d, \(J = 8.3\) Hz, 2H), 3.70 (dt, \(J = 8.1\),
5.1 Hz, 1H, NCH), 3.25 – 3.21 (m, 2H, NCH₂), 2.24 (s, 3H, ArCH₃), 2.16 – 2.15 (m, 1H, CH), 1.85 (p, J = 6.9 Hz, 2H, CH₂), 1.65 – 1.54 (m, 2H, CH₂), 0.85 (d, J = 6.0 Hz, 3H, CH₃), 0.81 (d, J = 6.8 Hz, 3H, CH₃).

*N-(6-Methylhept-5-en-2-yl)-4-nitrobenzenesulfonamide 260*

![Chemical structure](image)

By general procedure A, *p*-nitrobenzenesulfonyl chloride (1.24 g, 5.62 mmol, 1.7 eq.) was added to the amine **235** (0.40 g, 3.3 mmol, 1.0 eq.) and Et₃N (0.8 ml, 4.0 mmol, 1.2 eq.) to give the nosyl derivative **260** (0.50 g, 50%), as a clear oil. δH 8.37 – 8.19 (m, 2H), 8.07 – 7.94 (m, 2H), 4.91 (d, J = 8.3 Hz, NH), 4.91 – 4.62 (m, 1H, =CH), 3.50 – 3.11 (m, 1H, NCH), 1.93 – 1.68 (m, 2H), 1.56 (s, 3H), 1.44 (d, J = 1.3 Hz, 3H), 1.34 (dt, J = 7.7, 6.6 Hz, 2H), 1.01 (d, J = 6.6 Hz, 3H). δc 149.8 (Cq), 147.3 (Cq), 132.7 (Cq), 128.2 (2 x CH), 124.3 (2 x CH), 122.7 (CH), 50.3 (CH), 37.3 (CH₂), 25.6 (CH₃), 24.2 (CH₂), 21.7 (CH₃), 17.6 (CH₃). IR (neat) ν/cm⁻¹: 3295, 2967, 2922, 2855, 1607, 1530, 1350, 1306, 1160, 1092. HRMS (EI) m/z calculated for C₁₄H₂₀N₂O₄S [M]+ = 312.1144; found: 312.1138.

1-(4-Nitrophenylsulfonyl)-2,2,6-trimethylpiperidine 261

![Chemical structure](image)

By general procedure B, to sulfonamide **260** (125 mg, 0.4 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for three hours at 0 °C to give the piperidine **261** (76 mg, 61% after crystallization from dichloromethane/hexanes) as sharp, yellowish crystals, m.p. 124 – 127°C. δH 8.13 (d, J = 8.0 Hz, NCH₃), 8.11 (d, J = 8.0 Hz, 2H, =CH), 7.87 – 7.83 (m, 2H), 7.48 – 7.46 (m, 2H), 7.36 (d, J = 8.0 Hz, CH₃), 4.91 (d, J = 8.0 Hz, =CH), 3.50 – 3.11 (m, 1H, NCH), 2.16 – 1.68 (m, 2H), 1.56 (s, 3H), 1.44 (d, J = 1.3 Hz, 3H), 1.34 (dt, J = 7.7, 6.6 Hz, 2H), 1.01 (d, J = 6.6 Hz, 3H). δc 133.1 (Cq), 132.7 (Cq), 128.2 (2 x CH), 124.3 (2 x CH), 122.7 (CH), 50.3 (CH), 37.3 (CH₂), 25.6 (CH₃), 24.2 (CH₂), 21.7 (CH₃), 17.6 (CH₃). IR (neat) ν/cm⁻¹: 3295, 2967, 2922, 2855, 1607, 1530, 1350, 1306, 1160, 1092. HRMS (EI) m/z calculated for C₁₅H₂₂N₂O₄S [M]+ = 326.1295; found: 326.1292.
(2H), 7.82 (d, \( J = 8.0 \) Hz, 2H), 4.40 – 4.34 (m, 1H, NCH), 1.74 – 1.60 (m, 1H), 1.60 – 1.50 (m, 2H), 1.45 – 1.38 (m, 2H), 1.36 (s, 3H, CH₃), 1.32 (d, \( J = 7.0 \) Hz, 3H, CH₃), 1.26 – 1.14 (m, 1H), 1.07 (s, 3H, CH₃), \( \delta_C \) 151.2 (Cq), 149.3 (Cq), 127.4 (2 x CH), 124.2 (2 x CH), 58.3 (Cq, 2-C), 52.3 (NCH, 6-CH), 41.0 (CH₂), 30.9 (CH₃), 30.6 (CH₂), 29.0 (CH₃), 23.6 (CH₃), 15.3 (CH₂).

IR (neat) \( \nu/cm^{-1} \): 2978, 2942, 2868, 1604, 1524, 1346, 1167, 1134, 1095, 1034, 747. HRMS (APCI) \( m/z \) calculated for \( C_{14}H_{21}N_2O_4S \) [M+H]+ = 313.1222; found: 313.1221.

\((\text{Cis and trans})\) - 2-Isopropyl-5-methyl-1-(4-nitrophenylsulfonyl)pyrrolidine 262

By general procedure B, to sulfonamide 260 (145 mg, 0.5 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for 2 hours at 20 °C to give the pyrrolidine 262 (137 mg, 94%) \((\text{cis:trans} \ 2:1 \ \text{ratio})\) as a colourless oil. Cis-2-isopropyl-5-methylpyrrolidine: \( \delta_H \) 8.31 – 8.19 (m, 2H), 7.98 – 7.93 (m, 2H), 4.09 (dt, \( J = 11.9, 5.8 \) Hz, 1H, 2-H), 3.79 – 3.72 (m, 1H, 5-H), 2.36 – 2.32 (m, 1H), 2.31 – 2.23 (ddt, \( J = 13.8, 6.9, 4.6 \) Hz, 1H), 1.91 – 1.87 (m, 1H), 1.56 – 1.48 (m, 1H), 1.44 (ddt, \( J = 13.8, 7.0, 4.6 \) Hz, 1H), 1.20 (d, \( J = 6.4 \) Hz, 3H, CH₃), 0.81 (d, \( J = 4.9 \) Hz, 3H, CH₃), 0.47 (d, \( J = 6.9 \) Hz, 3H, CH₃). \( \delta_C \) 149.6 (Cq), 148.3 (Cq), 128.7 (CH), 128.0 (2 x CH), 124.2 (2 x CH), 65.2 (NCH), 58.4 (NCH), 32.8 (CH₂), 29.7 (CH), 23.4 (CH₂), 21.2 (CH₃), 19.8 (CH₃), 15.3 (CH₃).

Trans-2- isopropyl-5-methylpyrrolidine: \( \delta_H \) 8.34 – 8.28 (m, 2H), 8.09 – 8.04 (m, 2H), 3.68 – 3.58 (m, 1H, 2-CH), 3.37 (dd, \( J = 12.5, 7.0 \) Hz, 1H), 2.06 – 2.00 (m, 1H), 1.87 – 1.81 (m, 1H), 1.71 (ddd, \( J = 8.6, 5.2, 2.7 \) Hz, 1H), 1.68 – 1.59 (m, 1H), 1.26 (d, \( J = 6.9 \) Hz, 3H, CH₃), 0.79 (dd, \( J = 6.8, 5.0 \) Hz, 1H), 0.92 (d, \( J = 6.9 \) Hz, 3H, CH₃), 0.86 (d, \( J = 6.7 \) Hz, 3H, CH₃). \( \delta_C \) 150.0 (Cq), 144.0 (Cq), 128.7 (CH), 128.0 (2 x CH), 124.2 (2 x CH), 67.9 (NCH), 57.8 (NCH), 31.9 (CH₂), 31.4 (CH), 25.4 (CH₂), 21.2 (CH₃), 20.0 (CH₃), 15.3 (CH₃).
**N-(6-Methylhept-5-en-2-yl)methanesulfonamide 263**

\[
\begin{array}{c}
\text{235} \\
\text{NH}_2 \quad \text{MsCl, Et}_3\text{N} \quad \text{DCM} \\
\text{263} \\
\end{array}
\]

By general procedure A, methanesulfonyl chloride (0.63 g, 5.5 mmol, 1.1 eq.) was added to the amine 235 (0.60 g, 5.0 mmol, 1.0 eq.) and Et₃N (0.6 ml, 5.5 mmol, 1.1 eq.) to give the *N*-mesyl derivative 263 as a clear oil (0.70 g, 68%). All data obtained was in accordance with that previously reported: δH 5.17 – 4.99 (m, 1H, =CH), 4.89 – 4.67 (m, 1H, NH), 3.11 – 2.98 (m, 1H, NCH), 2.98 (s, 3H, Ms-CH₃), 2.23 – 1.91 (m, 2H, CH₂), 1.87 – 1.69 (m, 2H, CH₂), 1.67 (d, J = 1.5 Hz, 3H, CH₃), 1.64 (s, 3H, CH₃), 1.41 (d, J = 6.2 Hz, 3H, CH₃).

**N-(6-Methylhept-5-en-2-yl)-2,2,2-trifluoroacetamide 272**

\[
\begin{array}{c}
\text{235} \\
\text{NH}_2 \quad \text{F₃C} \quad \text{O} \quad \text{O} \quad \text{CF}_₃ \quad \text{pyridine, DCM} \\
\text{272} \\
\end{array}
\]

A solution of the amine 235 (0.60 g, 5.0 mmol, 1.0 eq.), trifluoroacetic anhydride (0.73 g, 5.5 mmol, 1.1 eq.) and pyridine (0.6 ml, 5.5 mmol, 1.1 eq.) in dry dichloromethane (10 ml) was stirred for 6 h at room temperature. The mixture was quenched with water (5 ml). The separated aqueous layer was extracted with dichloromethane (2 x 5 ml) and the combined organic solutions were washed with saturated aqueous copper(II) sulfate (5 ml) and water (5 ml) then dried and concentrated to give the trifluoroacetamide 272 as a clear oil (0.70 g, 68%). δH 6.88 - 6.67 (m, 1H, NH), 5.10 – 4.50 (m, 1H, =CH), 3.99 – 3.51 (m, 1H, NCH), 1.95 – 2.05 (m, 2H, CH₂), 1.60 (s, 3H, CH₃), 1.51 (s, 3H, CH₃), 1.50 – 1.45 (m, 2H, CH₂), 1.14 (d, J = 6.7 Hz, 3H, CH₃). δC 156.6 (q, J = 36.6 Hz, Cq), 132.8 (Cq), 123.0 (=CH), 115.9 (q, J = 288.0 Hz, CF₃), 46.3 (NCH), 35.9 (CH₂), 25.6 (CH₃), 24.4 (CH₂), 20.1 (CH₃), 17.5 (CH₃). IR (neat) v/cm⁻¹: 3293, 2978, 2924, 1699, 1557, 1182, 723. HRMS (EI) m/z calculated for C₁₀H₁₆F₃NO [M]+ = 223.1184; found: 223.1179.
N-(6-Methylhept-5-en-2-yl)acetamide 277

\[
\begin{align*}
\text{NH}_2 & \quad \text{CH}_3\text{COCl, Et}_3\text{N} \quad \text{DCM} \quad \text{NHCOCH}_3 \\
\end{align*}
\]

By general procedure A, acetyl chloride (0.43 g, 5.5 mmol, 1.1 eq.) was added to the amine 235 (0.60 g, 5.0 mmol, 1.0 eq.) and Et\(_3\)N (0.6 ml, 5.5 mmol) to give the acetamide 277 as a clear oil (0.5 g, 63%). \(\delta_H\) 6.25 (d, \(J = 8.7\) Hz, 1H, NH), 5.10 – 4.89 (m, 1H, =CH), 3.97 – 3.73 (m, 1H, NCH), 1.96 – 1.90 (m, 2H, CH\(_2\)), 1.88 (s, 3H, COCH\(_3\)), 1.59 (s, 3H, CH\(_3\)), 1.51 (s, 3H, CH\(_3\)), 1.47 – 1.28 (m, 2H), 1.04 (d, \(J = 6.6\) Hz, 3H, CH\(_3\)). \(\delta_C\) 169.5 (Cq), 131.7 (Cq), 123.6 (=CH), 44.9 (NCH), 36.7 (CH\(_2\)), 25.5 (CH\(_3\)), 24.6 (CH\(_2\)), 23.2 (CH\(_3\)), 20.9 (CH\(_3\)), 20.7 (CH\(_3\)). IR (neat) \(\nu/cm^{-1}\): 3269, 2969, 2928, 1722, 1640, 1549, 1441, 1373, 1284. HRMS (EI) \(m/\text{z}\) calculated for C\(_{10}\)H\(_{19}\)NO [M]\(^+\) = 169.1467; found: 169.1463.

1-Acetyl-2,2,6-trimethylpiperidine 278

\[
\begin{align*}
\text{NHCOCH}_3 & \quad \text{COCH}_3 \\
\end{align*}
\]

By general procedure B, to the amide 277 (151 mg, 0.9 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for 50 min at room temperature to give the piperidine 278 as a colourless oil (149 mg, 99%). \(\delta_H\) 3.94 – 3.79 (m, 1H, NCH), 1.87 (s, 3H, Ac-CH\(_3\)), 1.45 – 1.24 (m, 6H, 3 x CH\(_2\)), 1.10 (d, \(J = 6.4\) Hz, 3H, CH\(_3\)), 1.04 (s, 3H, CH\(_3\)), 1.03 (s, 3H, CH\(_3\)). \(\delta_C\) 169.6 (C=O), 70.7 (Cq, 2-C), 45.1 (NCH, 6-CH), 43.3 (CH\(_2\)), 37.3 (CH\(_2\)), 29.2 (Ac-CH\(_3\)), 23.4 (CH\(_3\)), 21.0 (2 x CH\(_3\)), 20.6 (CH\(_2\)). IR (neat) \(\nu/cm^{-1}\): 3293, 2964, 2934, 2870, 1672, 1549, 1448, 1373, 1259, 1161, 1089, 1012, 910, 796, 731. HRMS (EI) \(m/\text{z}\) calculated for C\(_{10}\)H\(_{19}\)NO [M]\(^+\) = 169.1467; found: 169.1466.
**N-(6-Methylhept-5-en-2-yl)benzamide 285**

![N-(6-Methylhept-5-en-2-yl)benzamide 285](image)

By general procedure A, benzoyl chloride (0.77 g, 5.5 mmol, 1.1 eq.) was added to the amine 235 (0.60 g, 5.0 mmol, 1.0 eq.) and Et₃N (0.6 ml, 5.5 mmol, 1.1 eq.) to give the benzamide 285 (0.83 g, 72%) as a clear oil.

δH 7.74 – 7.59 (d, J = 7.1, 2H), 7.44 – 7.37 (m, 1H), 7.43 – 7.23 (m, 2H), 6.35 (br. s, 1H, NH), 5.07 (br. t, J = 7.1, =CH), 4.26 – 4.00 (m, 1H, NCH), 2.01 (dt, J = 10.6, 7.1 Hz, 2H, CH₂), 1.60 (d, J = 1.4 Hz, 3H, CH₃), 1.51 (s, 3H, CH₃), 1.48 - 1.52 (m, 2H, CH₂), 1.16 (d, J = 6.5 Hz, 3H, CH₃). δC 135.1 (Cq), 132.2 (Cq), 131.2 (CH), 128.5 (2 x CH), 126.8 (2 x CH), 123.8 (CH), 45.7 (CH), 36.9 (CH₂), 25.7 (CH₃), 24.70 (CH₂), 21.0 (CH₃), 17.7 (CH₃). IR (neat) υ/cm⁻¹: 3320, 2967, 2931, 1716, 1640, 1578, 1541, 1491, 1450, 1276, 1161, 910, 723. HRMS (APCI) m/z calculated for C₁₅H₂₂NO [M+H]⁺ = 232.1701; found: 232.1712.

**1-Benzoyl-2,2,6-trimethylpiperidine 286**

![1-Benzoyl-2,2,6-trimethylpiperidine 286](image)

By general procedure B, to the amide 285 (0.23 g, 1 mmol) in dry dichloromethane (10 ml) under nitrogen triflic acid (76 mg, 46 µl, 0.5 mmol, 0.5 eq) was added and the resulting mixture stirred for 10 min at room temperature to give the piperidine 286 as a colourless oil (138 mg, 60%). δH 7.65 (dd, J = 6.9, 2.2 Hz, 2H), 7.41 – 7.36 (m, 1H), 7.36 – 7.29 (m, 2H), 4.20 – 4.05 (m, 1H, NCH), 1.49 – 1.44 (m, 4H, 2 x CH₂), 1.39 – 1.33 (m, 2H, CH₂), 1.16 (d, 3H, J = 6.5 Hz, CH₃), 1.12 (s, 3H, CH₃), 1.11 (s, 3H, CH₃). δC 166.9 (C=O), 131.2 (CH), 128.5 (2 x CH), 127.0 (2 x CH), 70.8 (Cq, 2-C), 45.7 (NCH, 6-CH), 36.8 (CH₂), 29.4 (Ac-CH₃), 25.7 (CH₃), 24.7 (CH₂) 21.0 (2 x CH₃), 20.7 (CH₂). IR (neat) υ/cm⁻¹: 3302, 2963, 2930, 1717, 1603, 1578, 1537, 1491, 1271, 1160, 910, 731. HRMS (APCI) m/z calculated for C₁₅H₂₂NO [M+H]⁺ = 232.1701; found: 232.1701.
Benzyl \textit{N-(6-methylhept-5-en-2-yl)}carbamate \textbf{294}

\[
\begin{align*}
\text{Benzyl} & \quad \text{N} \quad \text{C} \\
\text{NH}_{2} & \quad \text{C}_{\text{bzCl}}, \text{Et}_{3}\text{N} \\
\text{DCM} & \quad \text{NH}_{\text{C}z} \\
\text{235} & \quad \text{294}
\end{align*}
\]

By general procedure A, benzyl chloroformate (0.95 g, 5.5 mmol, 1.1 eq.) was added to the amine \textbf{235} (0.60 g, 5.0 mmol, 1.0 eq.) and Et\textsubscript{3}N (0.6 ml, 5.5 mmol, 1.1 eq.) to give the \textit{Z-carbamate} \textbf{294} as a clear oil (0.90 g, 70%). \(\delta\)\textsubscript{H} 7.37 – 7.20 (m, 5H), 5.15 – 4.90 (m, 4H), 3.70 – 3.53 (m, 1H, NCH), 2.00 – 1.87 (m, 2H, CH\textsubscript{2}), 1.64 (s, 3H, CH\textsubscript{3}), 1.54 (s, 3H, CH\textsubscript{3}), 1.42 – 1.28 (m, 2H, CH\textsubscript{2}), 1.05 (d, \(J = 7.1\), 3H, CH\textsubscript{3}). \(\delta\)\textsubscript{C} 156.1 (Cq, C=O), 137.3 (Cq), 128.4 (2 x CH), 127.9 (CH), 127.7 (2 x CH), 123.9 (=CH), 66.5 (OCH\textsubscript{2}Ph), 48.3 (NCH), 39.2 (CH\textsubscript{2}), 29.7 (CH\textsubscript{3}), 28.3 (CH\textsubscript{2}), 27.8 (CH\textsubscript{3}), 21.9 (CH\textsubscript{3}). IR (neat) \(\nu/cm^{-1}\): 2967, 2936, 1696, 1456, 1329, 1290, 1148, 1062, 773, 696. HRMS (EI) \(m/z\) calculated for C\textsubscript{16}H\textsubscript{23}NO\textsubscript{2} [M]\textsuperscript{+} = 261.1729; found: 261.1730.

\textbf{Benzyl 2,2,6-trimethylpiperidine-1-carboxylate} \textbf{295}

\[
\begin{align*}
\text{HN} & \quad \text{c.}\text{H}_{2}\text{SO}_{4} \\
\text{CO}_{2}\text{CH}_{3}\text{Ph} & \quad 20^\circ\text{C}, \text{CH}_2\text{Cl}_2, \\
\text{3min, 71%} & \quad \text{N} \quad \text{CO}_{2}\text{CH}_{2}\text{Ph} \\
\text{294} & \quad \text{295}
\end{align*}
\]

By general procedure B, to carbamate \textbf{294} (130 mg, 0.5 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for 3 min at room temperature to give the \textit{piperidine} \textbf{295} as a colourless oil (92 mg, 71%). \(\delta\)\textsubscript{H} 7.32 – 7.27 (m, 4H), 7.25 – 7.20 (m, 1H), 5.07 (d, \(J = 12.5\), 1H, OCH\textsubscript{A}H\textsubscript{B}), 5.02 (d, \(J = 12.5\), 1H, OCH\textsubscript{A}H\textsubscript{B}), 4.35 – 4.25 (m, 1H, NCH), 1.76 – 1.54 (m, 3H), 1.50 – 1.47 (m, 2H, CH\textsubscript{2}), 1.41 (s, 3H, CH\textsubscript{3}), 1.40 – 1.37 (m, 1H), 1.32 (s, 3H, CH\textsubscript{3}), 1.13 (d, \(J = 6.9\) Hz, 3H, CH\textsubscript{3}). \(\delta\)\textsubscript{C} 156.1 (Cq), 137.2 (Cq), 128.5 (2 x CH), 127.8 (2 x CH), 127.7 (CH), 66.4 (OCH\textsubscript{2}), 54.4 (Cq, 2-C), 48.3 (NCH, 6-CH), 39.2 (CH\textsubscript{2}), 29.8 (CH\textsubscript{3}), 28.3 (CH\textsubscript{2}), 27.8 (CH\textsubscript{3}), 21.9 (CH\textsubscript{3}), 14.7 (CH\textsubscript{2}). IR (neat) \(\nu/cm^{-1}\): 2967, 2935, 1695, 1496, 1456, 1329, 1300, 1148, 1063, 1049, 1028, 696. HRMS (APCI) \(m/z\) calculated for C\textsubscript{16}H\textsubscript{23}NO\textsubscript{2} [M]\textsuperscript{+} = 261.1729; found: 261.1732.
Methyl 6-methylhept-5-en-2-ylcarbamate 300

\[ \text{NH}_2 \xrightarrow{\text{ClCO}_2\text{Me, Et}_3\text{N}} \text{NHCO}_2\text{Me} \]

By general procedure A, methyl chloroformate (1.50 ml, 20 mmol) was added to the amine 235 (2.20 g, 17.5 mmol) and Et\textsubscript{3}N (2.5 ml, 22 mmol) to give the carbamate 300 as a clear oil (0.61 g, 38%). \( \delta^H \) 5.05 - 4.95 (m, 1H, =CH), 4.75 (\textit{br.} s, 1H, NH), 3.50 – 3.60 (m, 1H, NCH), 3.59 (s, 3H, OCH\textsubscript{3}), 1.94 (\textit{app.} q, 2H, \( J = 7.5 \text{ Hz, CH}_2 \)), 1.61 (s, 3H, CH\textsubscript{3}), 1.52 (s, 3H, CH\textsubscript{3}), 1.42 – 1.30 (m, 2H, CH\textsubscript{2}), 1.06 (d, 3H, \( J = 6.0 \text{ Hz, CH}_3 \)). \( \delta^C \) 156.3 (C=O), 131.8 (Cq), 123.5 (=CH), 51.6 (OCH\textsubscript{3}), 46.7 (NCH), 36.9 (CH\textsubscript{2}), 25.4 (CH\textsubscript{3}), 24.4 (CH\textsubscript{2}), 21.0 (CH\textsubscript{3}), 17.4 (CH\textsubscript{3}). IR (neat) \( \upsilon/cm^-1: \) 3374, 2967, 2915, 1723, 1527, 1441, 1234, 885. HRMS (EI) \( m/z \) calculated for C\textsubscript{10}H\textsubscript{19}NO\textsubscript{2} [M]+ = 185.1416; found: 185.1414.

Methyl 2,2,6-trimethylpiperidine-1-carboxylate 301

\[ \text{NHCO}_2\text{Me} \xrightarrow{\text{H}_2\text{SO}_4, \text{DCM}} \text{CO}_2\text{Me} \]

By general procedure B, to methyl carbamate 300 (180 mg, 1.41 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for 50 min at room temperature to give the piperidine 301 (157 mg, 87%) as a colourless oil. \( \delta^H \) 4.24 – 4.17 (m 1H, NCH), 3.55 (s, 3H, OCH\textsubscript{3}), 1.71 – 1.60 (m, 4H, 2 × CH\textsubscript{2}), 1.55 – 1.45 (m, 2H, CH\textsubscript{2}), 1.42 (s, 3H, CH\textsubscript{3}), 1.25 (s, 3H, CH\textsubscript{3}), 1.10 (d, 3H, \( J = 6.9 \text{ Hz, CH}_3 \)). \( \delta^C \) 156.8 (C=O), 54.1 (Cq, 2-C), 51.6 (CH\textsubscript{3}O), 48.1 (NCH, 6-CH), 39.0 (CH\textsubscript{2}), 29.5 (CH\textsubscript{3}), 28.2 (CH\textsubscript{2}), 27.7 (CH\textsubscript{3}), 21.8 (CH\textsubscript{3}), 14.6 (CH\textsubscript{2}). IR (neat) \( \upsilon/cm^-1: \) 2949, 2872, 1701, 1438, 1342, 1332, 1303, 1288, 1148, 1192. HRMS (APCI) \( m/z \) calculated for C\textsubscript{10}H\textsubscript{20}NO\textsubscript{2} [M+H]+ = 186.1494; found: 186.1493.
A mixture of ethyl acetoacetate 302 (5.12 g, 40 mmol, 1.0 eq.), cinnamyl chloride (6.10 g, 40 mmol, 1.0 eq.), anhydrous potassium carbonate (6.63 g, 40 mmol, 1.0 eq.) and ethanol (50 ml) was refluxed overnight. The solvent was removed by atmospheric distillation. The residue was diluted with water (20 ml) and extracted with ether (2 × 20 ml). The combined organic layers were washed with water (3 × 5 ml), brine (3 × 5 ml), then dried and evaporated. The crude product was separated by silica gel column chromatography (eluting silica gel with 0 - 10% dichloromethane in hexanes) to give the ketone 303 (3.83 g, 55% yield) as a yellow oil. All data obtained were in accordance with those previously reported in the literature: δ_H 7.35 – 7.13 (m, 4H), 7.10 – 7.05 (m, 1H), 6.40 (d, J = 15.6, 1H, =CH), 6.20 (dt, J = 15.6, 6.8, 1H, =CH), 2.50 (t, J = 6.8, 2H, 3-CH_2), 2.41 (app. q, J = 6.8, 2H, 4-CH_2), 2.02 (s, 3H, CH_3). δ_C 207.7 (C=O), 137.5 (Cq), 130.8 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.0 (CH), 127.1 (CH), 126.0 (CH), 43.1 (CH_2), 29.9 (CH_3), 27.1 (CH_2).

To a solution of ketone 303 (3.80 g, 22 mmol, 1.0 eq) and hydroxylamine hydrochloride (2.09 g, 30 mmol, 1.4 eq) in ethanol (30 ml) was added sodium acetate (1.0 g, 12.2 mmol) in one portion. The reaction mixture was heated at 40 °C for 2 h and then concentrated on a rotary evaporator. The residue was partitioned between ether (50 ml) and water (10 ml). The separated organic layer was dried. Evaporation provided the oxime 304 (3.70 g, 90%) as a 2:1 mixture of isomers as a
thick yellow liquid, which was used directly in the next step. All data obtained were in accordance with those previously reported in the literature: \( ^{14} \delta H 7.41 (br. s, NOH), 7.26 – 7.15 (m, 4H), 7.12 – 7.06 (m, 1H), 6.36 – 6.26 (m, 1H, =CH), 6.10 (dt, J = 15.8, 6.7 Hz, 1H), 2.37 – 2.29 (m, 2H), 2.29 – 2.23 (m, 2H), 1.83 (s, 2H, CH\textsubscript{3}, major isomer), 1.79 (s, 1H, CH\textsubscript{3}, minor isomer). \( \delta C \) 140.8 (Cq), 137.6 (Cq), 132.5 (CH), 129.0 (CH), 128.3 (2 x CH), 126.9 (CH), 126.0 (2 x CH), 45.6 (CH\textsubscript{2}), 41.8 (CH\textsubscript{2}), 38.2 (CH\textsubscript{3}).

### 6-Phenylhex-5-en-2-amine 305\textsuperscript{15}

![Diagram]

By general procedure C, the oxime 304 (3.70 g, 19.5 mmol) was reduced using lithium aluminium hydride (0.38 g, 20 mmol) to give the amine 305 (2.40 g, 70%) as thick yellow oil, which was sufficiently pure to be used directly in the next step. All data obtained were in accordance with those previously reported in the literature: \( ^{15} \delta H 7.28 – 7.15 (m, 4H), 7.14 – 7.06 (m, 1H), 6.31 (dt, J = 15.7, 1.5 Hz, 1H, =CH), 6.12 (dt, J = 15.7, 6.8 Hz, 1H, =CH), 2.80 – 2.71 (m, 1H, NCH), 2.22 – 2.07 (m, 2H, CH\textsubscript{2}), 1.42 (td, J = 7.9, 6.4 Hz, 2H, CH\textsubscript{2}), 1.01 (d, J = 6.3 Hz, 3H, CH\textsubscript{3}).

### Methyl (6-phenylhex-5-en-2-yl)carbamate 306

![Diagram]

By general procedure A, methyl chloroformate (0.75 ml, 10 mmol, 1.5 eq.) was added to the amine 305 (1.10 g, 6.85 mmol, 1.0 eq.) and Et\textsubscript{3}N (1.25 ml, 11 mmol, 1.2 eq.) to give the carbamate 306 as a clear oil (0.72 g, 48%). \( \delta H 7.31 – 7.16 (m, 4H), 7.14 – 7.10 (m, 1H), 6.32 (d, J \)
= 15.9 Hz, 1H, =CH), 6.20 – 6.05 (m, 1H, =CH), 4.45 (br. s, 1H, NH), 3.76 – 3.64 (m, 1H, NCH),
3.58 (s, 3H, OCH3), 2.19 (td, J = 8.5, 5.4 Hz, 2H, CH2), 1.53 (td, J = 8.5, 4.2 Hz, 2H, CH2), 1.10
(d, J = 6.5 Hz, 3H, CH3). δc 156.4 (Cq), 137.7 (Cq), 130.4 (CH), 129.8 (CH), 128.5 (2 x CH),
126.9 (CH), 126.0 (2 x CH), 51.9 (OCH3), 46.9 (NCH), 36.9 (CH2), 29.5 (CH2), 21.3 (CH3). IR
(neat) υ/cm⁻¹: 3323, 2934, 1696, 1520, 1449, 1248, 1192, 1072, 909, 723, 694. HRMS (EI) m/z
calculated for C14H19NO2 [M]+ = 233.1416; found: 233.1414.

**Methyl cis-2-methyl-6-phenylpiperidine-1-carboxylate 307**

By general procedure B, to carbamate 306 (233 mg, 1.0 mmol) in dry dichloromethane (10 ml)
under nitrogen concentrated sulfuric acid (50 mg, 0.5 mmol) was added and the resulting mixture
stirred for 20 h at room temperature to give the piperidine 307 as a colourless oil (203 mg, 87%).
δH 7.30 – 7.20 (m, 4H), 7.17 – 7.06 (m, 1H), 5.41 (br. d, J = ca. 5.2, 1H, 6-H), 4.51 – 4.42 (m, 1H,
2-H), 3.70 (s, 3H, OCH3), 2.37 (dd, J = 11.5, 2.0 Hz, 1H), 1.83 – 1.61 (m, 3H, CH2 and CH), 1.52
– 1.45 (m, 1H), 1.46 – 1.39 (m, 1H), 0.75 (d, J = 7.1 Hz, 3H, CH3). δc 157.2 (C=O), 142.5 (Cq),
128.1 (2 x CH), 126.6 (2 x CH), 126.4 (CH), 52.7 (NCH, 6-CH), 51.6 (OCH3), 46.9 (NCH, 2-CH),
30.5 (CH2), 27.0 (CH2), 20.5 (CH3), 15.0 (CH2). IR (neat) υ/cm⁻¹: 2934, 2859, 1693, 1531, 1445,
1361, 1330, 1248, 1094, 1068, 1028. HRMS (EI) m/z calculated for C14H19NO2 [M]+ = 233.1416;
found: 233.1413.
To a solution of acetone oxime 308 (0.73 g, 10 mmol, 1.0 eq) in dry tetrahydrofuran (20 ml), maintained under a nitrogen atmosphere, was added dropwise n-butyl lithium (13.2 ml of a 1.55 M solution in hexanes, 20 mmol, 2.0 eq). The mixture was cooled to -78 °C, and a solution of crotyl chloride 309 (0.90 g, 10 mmol, 1.0 eq) in dry tetrahydrofuran (10 ml) was added dropwise. Stirring was continued for 2 h, then the solution was allowed to warm to room temperature and was stirred for a further two hours. The mixture was then poured into ice-cold water, the organic layer was separated, and the aqueous layer extracted with dichloromethane (3 x 20 ml). The combined organic solutions were dried and the solvents evaporated to give the oxime 310 (1.01 g, 80%) as a mixture of isomers (2:1) as a yellow liquid, which was sufficiently pure to be used directly in the next step: δH 9.19 (br. s, 1H, NOH), 5.49 – 5.07 (m, 2H, 2 x =CH), 2.31 (dt, J = 8.8, 6.8 Hz, 2H, CH2), 2.21 – 1.95 (m, 2H, CH2), 1.75 (s, 1H, CH3, minor isomer), 1.74 (s, 2H, CH3, major isomer), 1.54 (d, J = 6.2, 3H, 7-CH3). δC 158.5 (Cq), 130.0 (=CH), 125.7 (=CH), 28.5 (CH2), 28.3 (CH2), 20.0 (CH3, isomers), 19.9 (CH3, isomers), 17.8 (CH3). IR (neat) ν/cm⁻¹: 3246, 2920, 2885, 1663, 1441, 1370, 1330. HRMS (EI) m/z calculated for C7H13NO [M]+ = 127.0997; found: 127.0998.

Hept-5-en-2-amine 311

Using general procedure C, the foregoing oxime 310 (1.01 g, 7.9 mmol, 1.0 eq.) was reduced by lithium aluminium hydride (0.19 g, 20 mmol, 1.2eq.) to give the amine 311 (0.65 g, 73%) as a
clear oil, which was sufficiently pure to be used directly in the next step. All data obtained were in accordance with those previously reported in the literature: $^{16} \delta_H 5.40 - 5.15$ (m, 2H, 2 x =CH), 2.78 – 2.70 (m, 1H, NCH), 2.01 – 1.80 (m, 2H, CH$_2$), 1.50 (s, 3H, CH$_3$), 1.33 – 1.16 (m, 2H, CH$_2$), 0.96 (d, J = 6.2, 3H, 7-CH$_3$). $\delta_C$ 131.0 (=CH), 125.0 (=CH), 46.5 (NCH), 39.9 (CH$_2$), 29.5 (CH$_2$), 23.9 (CH$_3$), 17.9 (CH$_3$).

**Methyl hept-5-en-2-ylcarbamate 312**

![Chemical diagram]

By general procedure A, methyl chloroformate (0.47 g, 5 mmol, 1.0 eq.) was added to the amine 311 (0.56 g, 5.5 mmol, 1.0 eq.) and Et$_3$N (0.62 ml, 5.5 mmol, 1.1 eq.) to give the carbamate 312 as a clear oil (0.57 g, 72%). $\delta_H 5.40 - 5.15$ (m, 2H, 2 x =CH), 4.40 (br. s, 1H, NH), 3.61 – 3.54 (m, 1H, NCH), 3.54 (s, 3H, OCH$_3$), 2.01 – 1.80 (m, 2H, CH$_2$), 1.50 (d, J = 4.9 Hz, 3H, CH$_3$), 1.39 – 1.33 (m, 2H, CH$_2$), 0.96 (d, J = 6.2 Hz, 3H, 7-CH$_3$). $\delta_C$ 156.4 (C=O), 130.4 (=CH), 125.4 (=CH), 51.8 (OCH$_3$), 46.7 (NCH, 2-CH), 37.0 (CH$_2$), 29.0 (CH$_2$), 21.2 (CH$_3$), 17.8 (CH$_3$). IR (neat) $\nu$/cm$^{-1}$: 3327, 2966, 2931, 1695, 1531, 1450, 1352, 1250, 1192, 1078, 964, 777. HRMS (EI) $m/z$ calculated for C$_9$H$_{17}$NO$_2$ [M]$^+$ = 171.1259; found: 171.1258.

**Methyl (cis/trans) 2-ethyl-5-methylpyrrolidine-1-carboxylate 313**

![Chemical diagram]

To a stirred solution of the carbamate 312 (171 mg, 1.0 mmol) in dry dichloromethane (10 ml) under nitrogen, cooled in an ice-water bath, was added triflic acid (76 mg, 46 µl, 0.5 mmol, 0.5 eq). The resulting mixture stirred was stirred at 40 °C for 3.5 hours to give the pyrrolidines 313.
(cis:trans 1:1 ratio) (167 mg, 98%) as a colourless oil, which was not separable into its two components.

*Trans*-2-ethyl-5-methylpyrrolidine: $\delta$H 3.90 – 3.80 (m, 1H), 2.64 – 3.60 (m, 1H), 3.60 (s, 3H, OCH$_3$), 1.99 – 1.91 (m, 2H, CH$_2$), 1.77 – 1.70 (m, 2H, CH$_2$), 1.56 – 1.50 (m, 1H), 1.17 – 1.07 (m, 1H), 1.01 (d, $J = 6.0$ Hz, 3H, CH$_3$), 0.75 (t, $J = 7.0$ Hz, 3H, CH$_3$). $\delta$C 156.1 (C=O), 60.3 (NCH), 53.8 (NCH), 52.1 (OCH$_3$), 37.0 (CH$_2$), 28.8 (CH$_2$), 25.6 (CH$_2$), 22.7 (CH$_3$), 12.2 (CH$_3$).

*Cis*-2-ethyl-5-methylpyrrolidine: $\delta$ 3.90 – 3.80 (m, 1H), 2.64 – 3.60 (m, 1H), 3.60 (s, 3H, OCH$_3$), 1.99 – 1.91 (m, 2H, CH$_2$), 1.77 – 1.70 (m, 2H, CH$_2$), 1.56 – 1.50 (m, 1H), 1.17 – 1.07 (m, 1H), 1.07 (d, $J = 6.0$ Hz, 3H), 0.77 (t, $J = 7.0$ Hz, 3H). $\delta$C 155.2 (C=O), 60.0 (NCH), 53.0 (NCH), 52.0 (OCH$_3$), 36.9 (CH$_2$), 30.0 (CH$_2$), 23.4 (CH$_2$), 22.7 (CH$_3$), 11.2 (CH$_3$). IR (neat) $\nu$/cm$^{-1}$: 2967, 2935, 1690, 1533, 1454, 1379, 1250, 1163, 1097, 1040, 912, 775, 731, 638. HRMS (EI) m/z calculated for C$_9$H$_{17}$NO$_2$ [M]$^+ = 171.1259$; found: 171.1262.

**Methyl cis-2,6-dimethylpiperidine-1-carboxylate 316**

![Chemical structure](image)

By general procedure A, methyl chloroformate (0.37 ml, 5.0 mmol, 1.0 eq.) was added to commercial *cis*-2,6-dimethylpiperidine 315 (Aldrich; 0.56 g, 5.0 mmol, 1.0 eq.) and Et$_3$N (0.62 ml, 5.5 mmol, 1.1 eq.) to give the *piperidine carbamate* 316 (0.85 g, 100%) as a clear oil. All data obtained were in accordance with those previously reported in the literature: $\delta$H 4.30 – 4.16 (m, 2H), 3.62 (s, 3H, OCH$_3$), 1.75 – 1.60 (m, 1H), 1.60 – 1.43 (m, 4H, 2 x CH$_2$), 1.38 (dp, $J = 12.6$, 3.5 Hz, 1H), 1.10 (d, $J = 7.1$, 6H, 2 x CH$_3$). $\delta$C 156.3 (C=O), 52.2 (OCH$_3$), 46.0 (2 x NCH, 2- and 6-CH), 30.0 (2 x CH$_2$, 3- and 5-CH$_2$), 20.8 (2 x CH$_3$), 13.7 (4-CH$_2$). IR (neat) $\nu$/cm$^{-1}$: 2969, 2937, 1691, 1441, 1400, 1344, 1311, 1275, 1255, 1192, 775. HRMS (EI) m/z calculated for C$_9$H$_{17}$NO$_2$ [M]$^+ = 171.1259$; found: 171.1258.
5-Cyclohexylidenepentanoic acid 318\textsuperscript{18}

A mixture of (4-carboxybutyl)triphenylphosphonium bromide (5.32 g, 12 mmol, 4.0 eq) in dry tetrahydrofuran (20 ml) and cyclohexanone 317 (300 mg, 3.0 mmol, 1.0 eq) in dry tetrahydrofuran (10 ml) was treated with sodium hydride (288 mg, 12 mmol, 4.0 eq) in dry THF (10 ml) under nitrogen, and the resulting orange mixture was stirred at room temperature for 6 h. The reaction was quenched with water (20 ml) and acidified to pH 2 using 10% hydrochloric acid. The separated aqueous layer extracted with ether (3 x 30 ml). The combined organic layers were washed with brine (5 ml), dried and evaporated to afford the acid 318 (215 mg, 42%) as an oil, which was used without further purification in the next step. All data obtained were in accordance with those previously reported in the literature:\textsuperscript{19} $\delta$H 11.00 (br. s, 1H, COOH), 4.97 (t, $J = 7.3$, Hz, 1H, =CH), 2.28 (t, $J = 7.5$ Hz, 2H, CH$_2$), 2.05 – 2.01 (m, 2H, CH$_2$), 2.00 (t, $J = 6.9$ Hz, 2H, CH$_2$), 1.96 (t, $J = 7.4$ Hz, 2H, CH$_2$), 1.60 (app. p, $J = 7.4$ Hz, 2H, CH$_2$), 1.51 – 1.37 (m, 6H, 3 x CH$_2$).

$\delta$C 179.7 (Cq, COOH), 141.0 (Cq), 119.9 (=CH), 37.2 (CH$_2$), 33.3 (CH$_2$), 28.7 (2 x CH$_2$), 27.8 (CH$_2$), 26.9 (CH$_2$), 26.3 (CH$_2$), 25.0 (CH$_2$).

Methyl (4-cyclohexylidenebutyl)carbamate 319\textsuperscript{20}

Diphenylphosphoryl azide (DPPA) (0.24 ml, 1.16 mmol, 1.0 eq) and triethylamine (0.15 ml, 0.16 mmol, 1.0 eq) were added to a solution of the acid 318 (195 mg, 1.16 mmol, 1.0 eq) in dry toluene (10 ml) and the mixture was refluxed for 1 h then cooled. Copper(II) chloride (10 mg, 0.1 mmol)
and dry methanol (10 ml) were then added. The mixture was refluxed for a further 1 h then cooled and concentrated \textit{in vacuo}. The solid residue was dissolved in ether (30 ml) and the resulting solution successively washed with saturated aqueous sodium bicarbonate (10 ml) and water (10 ml). The solution was then dried, filtered and evaporated to give the crude product which was purified by column chromatography (eluting silica gel with 0 - 100% dichloromethane in hexanes) to give the carbamate 319 (42 mg, 18\%) as colourless oil: $\delta$H 4.97 (br. t, $J$ = 7.4 Hz, 1H, =CH), 4.61 (br. s, 1H, NH), 3.59 (s, 3H, OCH$_3$), 3.10 (t, $J$ = 6.8 Hz, 2H, CH$_2$), 2.10 – 1.90 (m, 6H, 3 x CH$_2$), 1.50 – 1.35 (m, 8H, 4 x CH$_2$). $\delta$C 156.6 (C=O), 140.6 (Cq), 120.0 (=CH), 52.0 (OCH$_3$), 40.7 (CH$_2$), 37.2 (CH$_2$), 37.2 (CH$_2$), 33.2 (CH$_2$), 30.3 (CH$_2$), 28.7 (CH$_2$), 28.6 (CH$_2$), 25.0 (CH$_2$). IR (neat) $\nu$/cm$^{-1}$: 3325, 2924, 2852, 1705, 1531, 1446, 1384, 1255, 1190, 1026, 777. HRMS (EI) m/z calculated for C$_{12}$H$_{21}$NO$_2$ [M]$^+$ = 211.1572; found: 211.1576.

**Methyl 1-azaspiro[5.5]undecane-1-carboxylate 320**

To a stirred solution of the carbamate 319 (21 mg, 0.05 mmol) in dry dichloromethane (10 ml) under nitrogen, cooled in an ice-water bath, was added triflic acid acid (3 mg, 1.8 µl, 0.02 mmol, 0.4 eq). The resulting mixture stirred was stirred at 0 °C for 0.5 h to give spiro-piperidine 320 (20 mg, 95\%) as a clear, colourless oil. $\delta$H 3.50 (s, 3H, OCH$_3$), 3.47 (app. t, $J$ = 6.0, 2H, CH$_2$N), 3.40 – 3.30 (m, 2H, CH$_2$), 2.47 – 2.40 (m, 2H, CH$_2$), 1.58 – 1.47 (m, 4H, 2 x CH$_2$), 1.47 – 1.32 (m, 8H, 4 x CH$_2$). $\delta$C 156.4 (C=O), 58.9 (Cq), 51.8 (OCH$_3$), 40.7 (CH$_2$), 33.0 (CH$_2$), 31.0 (CH$_2$), 25.5 (CH$_2$), 23.5 (CH$_2$), 22.8 (2 x CH$_2$), 21.9 (CH$_2$), 17.12 (CH$_2$). IR (neat) $\nu$/cm$^{-1}$: 2924, 2859, 1719, 1441, 1377, 1293, 1190, 1140, 1082, 1066, 760. HRMS (APCI) m/z calculated for C$_{12}$H$_{21}$NO$_2$ [M]$^+$ = 211.1572; found: 211.1569.
(S)-Methyl N-(1-hydroxypropan-2-yl)carbamate 339

\[
\text{OH} \quad \text{ClCO}_2\text{Me} 
\]
\[
\text{NH}_2 \quad \text{Et}_3\text{N, DCM} 
\]
\[
\text{OH} \quad \text{NHCO}_2\text{Me} 
\]

By general procedure A, methyl chloroformate (2.83 ml, 36.6 mmol, 1.1 eq.) was added to the (S)-(+)-alaninol 338 (2.50 g, 33.3 mmol, 1.0 eq.) and Et\textsubscript{3}N (3.5 ml, 36.6 mmol, 1.1 eq.) at –20 °C to give the carbamate 339 as a clear oil (2.70 g, 61%), which was sufficiently pure to be used directly in the next step. \( \delta_H \) 5.41 – 5.17 (m, 1H, NH), 3.85 – 3.69 (m, 1H), 3.63 (s, 3H, OCH\textsubscript{3}), 3.60 – 3.53 (m, 1H), 3.47 (dd, \( J = 10.6, 5.1 \text{ Hz} \), 2H, OCH\textsubscript{2}), 1.12 (d, \( J = 6.6 \text{ Hz} \), 3H). \( \delta_C \) 157.3 (C=O), 65.7 (OCH\textsubscript{2}), 51.5 (OCH\textsubscript{3}), 48.8 (NCH), 16.6 (CH\textsubscript{3}). IR (neat) \( \nu/cm^-1 \): 3393, 3311, 2972, 2942, 1712, 1532, 1454, 1260, 1190, 1193, 1097, 1074, 1053, 993, 779. HRMS (EI) \textit{m/z} calculated for C\textsubscript{5}H\textsubscript{11}NO\textsubscript{3} \([M]^+\) = 133.0739; found: 133.0738.

(S)-(++)-Methyl N-(1-(phenylthio)propan-2-yl)carbamate 340

\[
\text{OH} \quad \text{PhSSPh} \quad \text{Bu}_3\text{P, THF} 
\]
\[
\text{NHCO}_2\text{Me} \quad \text{PhS} \quad \text{NHCO}_2\text{Me} 
\]

A solution of carbamate 339 (2.70 g, 20.3 mmol, 1.0 eq.), diphenyl disulfide (13.30 g, 3.0 eq.) and tributylphosphine (16.40 g, 4.0 eq.) in dry tetrahydrofuran (50 ml) under nitrogen was refluxed for 72 h. The cooled mixture was diluted with ether (50 ml) and washed with 2 M sodium hydroxide (20 ml) and brine then dried. After evaporation, the crude product was purified by column chromatography (eluting silica gel with 0 - 100% dichloromethane in hexanes) to give the sulfide 340 (1.30 g, 28%) as a colourless oil: \( [\alpha]^{20}\text{D} +20.0 \) (c 1.0 g/100 ml, CH\textsubscript{3}OH); \( \delta_H \) 7.23 (d, \( J = 7.6 \text{ Hz} \), 2H), 7.14 (t, \( J = 7.6 \text{ Hz} \), 2H), 7.02 (t, \( J = 7.6 \text{ Hz} \), 1H), 4.78 – 4.59 (m, 1H, NH), 3.80 – 3.69 (m, 1H, NCH), 3.48 (s, 3H, OCH\textsubscript{3}), 3.01 (dd, \( J = 14.1, 6.1 \text{ Hz} \), 1H, PhSH\textsubscript{A}H\textsubscript{B}), 2.81 (dd, \( J = 14.1, 6.1 \text{ Hz} \), 1H, PhSH\textsubscript{B}H\textsubscript{A}), 2.18 (dd, \( J = 14.1, 6.1 \text{ Hz} \), 1H, PhSH\textsubscript{B}H\textsubscript{A}), 2.15 (dd, \( J = 14.1, 6.1 \text{ Hz} \), 1H, PhSH\textsubscript{B}H\textsubscript{A}).
6.0 Hz, 1H, PhSCH₂H₃), 1.09 (d, J = 6.6 Hz, 3H, CH₃). δC 156.1 (C=O), 135.9 (Cq), 129.3 (2 x CH), 128.8 (2 x CH), 126.1 (CH), 51.9 (OCH₃), 46.5 (NCH), 40.2 (PhSCH₂), 19.8 (CH₃). IR (neat) v/cm⁻¹: 3312, 2971, 1710, 1583, 1514, 1481, 1452, 1439, 1348, 1327, 1242, 1192, 1053, 1024, 779, 737. HRMS (EI) m/z calculated for C₁₁H₁₅NO₂S [M⁺] = 225.0824; found: 225.0825.

**(S)-(-)-Methyl N-(1-(phenylsulfonyl)propan-2-yl)carbamate 341**

Phenyl sulphide 240 (1.30 g, 5.0 mmol, 1.0 eq) and sodium tungstate (15 mg, 0.05 mmol) were added to methanol (10 ml) at 40 ºC. After the resulting mixture was stirred for 2 minutes, 30% aqueous hydrogen peroxide (1.80 ml, 15.0 mmol, 3.0 eq) was added dropwise. After 3 h, the mixture was diluted with saturated aqueous sodium thiosulfate (5 ml) and the bulk of the solvents evaporated. The residue was extracted with dichloromethane (3 x 10 ml) and the combined extracts dried, filtered through a bed of silica gel and evaporated to give the sulfone 341 (1.30 g, 88% yield) as a colourless oil: [α]D²⁰ -8.89 (c 0.9 g/100 ml, CH₃OH); δH 7.87 (d, J = 7.5 Hz, 2H), 7.61 (d, J = 7.5 Hz, 1H), 7.50 (t, J = 7.5 Hz, 2H), 5.14 (br. s, 1H, NH), 4.02 – 3.96 (m, 1H, NCH), 3.51 (s, 3H, OCH₃), 3.42 (dd, J = 14.3, 5.5 Hz, 1H, PhSO₂CH₂H₃), 3.15 (dd, J = 14.3, 5.5 Hz, 1H, PhSO₂CH₂H₃), 1.31 (d, J = 6.8 Hz, 3H, CH₃). δC 155.8 (C=O), 139.9 (Cq), 133.8 (CH), 129.4 (2 x CH), 127.9 (2 x CH), 52.0 (OCH₃), 43.6 (NCH), 24.3 (PhSO₂CH₂), 20.5 (CH₃). IR (neat) v/cm⁻¹: 3362, 2976, 1699, 1528, 1447, 1304, 1254, 1178, 1101, 1084, 1053, 779, 737. HRMS (EI) m/z calculated for C₁₁H₁₅NO₂S [M⁺] = 257.0722; found: 257.0727.
A solution of the phenyl sulfone 341 (1.30 g, 5 mmol, 1.0 eq.) in dry tetrahydrofuran (10 ml) at -78 °C was treated with n-butyl lithium (4.24 ml, of a 2.5 M solution in hexanes, 10.5 mmol, 2.1 eq). After stirring for 0.5 h, a solution of prenyl bromide (0.72 ml, 5.5 mmol 1.1 eq.) in tetrahydrofuran (5 ml) was added. The cooling bath was removed and the reaction mixture was stirred for 3 h then diluted with ether (50 ml). The resulting solution was washed with water (10 ml). The separated aqueous phase was extracted with ether (2 x 20 ml) and the combined organic solutions washed sequentially with 10% hydrochloric acid (20 ml), 5% aqueous sodium bicarbonate (20 ml) and brine (20 ml), then dried, filtered and evaporated. Separation of the residue on silica gel using 50:50 hexanes/dichloromethane gave the homologated sulfone 342 (0.89 g, 54%) as a yellow oil and a 2:1 mixture of diastereoisomers, which were not separated.

The major isomer showed: δH 7.95 – 7.82 (m, 2H), 7.67 – 7.60 (m, 1H), 7.60 – 7.46 (m, 2H), 5.37 (d, J = 8.6 Hz, 1H, NH), 4.81 – 4.92 (m, 1H, =CH), 4.36 – 4.2 (m, 1H, NCH), 3.60 (s, 3H, OCH3), 3.30 (dt, J = 7.9, 6.4 Hz, 1H, PhSO₂CH), 2.52 – 2.23 (m, 2H, CH₂), 1.54 (s, 3H, CH₃), 1.47 (s, 3H, CH₃), 1.37 (d, J = 7.0 Hz, 3H). δC 156.0 (C=O), 139.4 (Cq), 133.7 (CH), 129.2 (2 x CH), 128.3 (2 x CH), 119.4 (=CH), 67.1 (NCH), 52.0 (OCH₃), 46.2 (PhSO₂CH), 25.6 (CH₃), 24.2 (CH₂), 17.8 (CH₃), 17.6 (CH₃).

The minor isomer showed: δH 7.95 – 7.82 (m, 2H), 7.67 – 7.60 (m, 1H), 7.60 – 7.46 (m, 2H), 6.0 (d, J = 8.6 Hz, 1H, NH), 4.81 – 4.92 (m, 1H, =CH), 4.22 – 4.18 (m, 1H, NCH), 3.68 (s, 3H, OCH₃), 3.21 (dt, J = 7.9, 6.4 Hz, 1H, PhSO₂CH), 2.52 – 2.23 (m, 2H, CH₂), 1.67 (s, 3H, CH₃), 1.40 (s, 3H, CH₃), 1.37 (d, J = 7.0 Hz, 3H). δC 156.0 (C=O), 136.0 (Cq), 133.7 (CH), 129.2 (2 x CH), 128.3 (2 x CH), 119.4 (=CH), 66.4 (NCH), 50.0 (OCH₃), 46.2 (PhSO₂CH), 25.6 (CH₃), 24.2 (CH₂), 17.8 (CH₃), 17.6 (CH₃).
CH), 128.3 (2 x CH), 118.3 (=CH), 68.4 (NCH), 52.0 (OCH₃), 47.0 (PhSO₂CH), 26.1 (CH₂), 25.6 (CH₃), 17.8 (CH₃), 17.6 (CH₃).

The whole sample showed IR (neat) \( \text{\textit{\nu}} / \text{cm}^{-1} \): 3370, 2972, 1715, 1512, 1447, 1302, 1248, 1178, 1101, 1084, 1070, 914, 727. HRMS (APCI) \( m/z \) calculated for C₁₆H₂₄NO₄S [M+H]⁺ = 326.1426; found: 326.1428.

(6S)-(-)-Methyl-2,2,6-trimethyl-5-(phenylsulfonyl)piperidine-1-carboxylate 343

By general procedure B, to carbamate 342 (163 mg, 0.5 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (3 drops) was added and the mixture stirred for 2 h at room temperature to give the piperidine 343 (159 mg, 98%) as a colourless oil: \([\alpha]_{D}^{20} -23.33 (c 0.6 \text{ g/100 ml, CH₃OH})\); \( \delta_H \) 7.67 (d, \( J = 7.8 \text{ Hz, 2H} \)), 7.44 (t, \( J = 8.6, 1.3 \text{ Hz, 1H} \)), 7.40 – 7.22 (m, 2H), 4.59 (qd, \( J = 6.9, 4.4 \text{ Hz, 1H, 6-H} \)), 3.43 (s, 3H, OCH₃), 3.18 (ddd, \( J = 10.8, 7.7, 4.4 \text{ Hz, 1H, PhSO₂CH} \)), 2.02 (ddddd, \( J = 13.8, 11.2, 7.5, 4.1 \text{ Hz, 1H} \)), 1.93 – 1.83 (m, 1H), 1.35 – 1.28 (m, 2H), 1.24 (d, \( J = 6.9 \text{ Hz, 3H, CH₃} \)), 1.20 (s, 3H, CH₃), 1.10 (s, 3H, CH₃). \( \delta_C \) 155.6 (C=O), 138.7 (Cq), 133.9 (CH), 129.3 (2 x CH), 128.4 (2 x CH), 61.7 (NCH), 54.2 (Cq), 52.1 (OCH₃), 47.2 (PhSO₂CH), 36.0 (CH₂), 29.1 (CH₃), 27.3 (CH₃), 18.9 (CH₃), 15.9 (CH₂). IR (neat) \( \text{\textit{\nu}} / \text{cm}^{-1} \): 2964, 1697, 1514, 1446, 1338, 1305, 1084, 1070, 727, 690. HRMS (EI) \( m/z \) calculated for C₁₆H₂₃NO₄S [M]⁺ = 325.1348; found: 325.1336.
(S)-Methyl 2,2,6-trimethylpiperidine-1-carboxylate 344$^{23}$

A mixture of substrate 344 (137 mg, 0.42 mmol) and magnesium (146 mg, 6.0 mmol) in dry methanol (10 ml) was stirred for 20 h at room temperature. The reaction mixture was poured into cold 0.5 N HCl (10 ml) and extracted with dichloromethane (3 x 15 ml). The combined organic layers were washed with saturated aqueous sodium bicarbonate (5 ml), then dried, filtered, and evaporated to give piperidine 344 (64 mg, 82%) as colourless oil. All data obtained were in accordance with those previously reported in the piperidine 301 (p. 169).

(E/Z)-6,10-Dimethylundeca-5,9-dien-2-one oxime 381

To a solution of (E/Z 35:65)-geranyl acetone 380 (Aldrich, 3.90 g, 20 mmol, 1.0 eq) and hydroxylamine hydrochloride (2.09 g, 30 mmol, 1.5 eq) in ethanol (30 ml) was added sodium acetate (1.00 g, 12.2 mmol) in one portion. The reaction mixture was heated at 40 °C for 2 h and then concentrated on a rotary evaporator. The residue was partitioned between ether (150 ml) and water (50 ml). The separated organic layer was dried. Evaporation provided the oxime 381 (3.10 g, 74%) as an inseparable 2:1 mixture of E/Z isomers as a colourless liquid, which was pure enough and which was used directly in the next step. $\delta_H$ (selected resonances) 5.10–4.90 (m, 2H, =CH), 2.14 – 2.21 (m, 6H, 3x CH$_2$), 1.75 (s, 2H, CH$_3$, E-isomer), 1.75 (s, 1H, CH$_3$, Z-isomer), 1.65 (s, 3H, CH$_3$), 1.53 (s, 3H, CH$_3$). Major (E)-isomer $\delta_C$ 158.1 (Cq, C=NOH), 136.2 (Cq), 131.3 (Cq), 124.2 (=CH), 123.3 (=CH), 39.6 (CH$_2$), 36.1 (CH$_2$), 28.8 (CH$_2$), 25.7 (CH$_3$), 25.0 (CH$_2$), 17.6 (CH$_3$), 15.95 (CH$_3$). Minor (Z)-isomer $\delta_C$ 158.6 (C=NOH), 136.4 (Cq), 131.6 (Cq), 124.2 (=CH), 123.6 (=CH), 43.7 (CH$_2$), 31.9 (CH$_2$), 28.9 (CH$_2$), 22.4 (CH$_3$), 22.2 (CH$_2$), 20.0 (CH$_3$), 17.6 (CH$_3$).$^{24}$
6,10-Dimethylundeca-5,9-dien-2-amine 382

Using general procedure C, the foregoing oxime 381 (3.10 g, 14.8 mmol, 1.0 eq.) was reduced by lithium aluminium hydride (0.76 g, 20 mmol, 1.4 eq.) to give the amine 382 (2.85 g, 99%) as a clear oil. \( \delta_H \) 5.10 - 4.96 (m, 2H, \( 2 \times =CH \)), 2.85 (sext, 1H, \( J = 6.3 \) Hz, NCH), 2.00 – 1.85 (m, 6H, CH$_2$), 1.80 – 1.70 (m, 2H, CH$_3$), 1.60 (s, 3H, CH$_3$), 1.55 (s, 3H, CH$_3$), 1.35 – 1.28 (m, 2H, CH$_2$), 0.98 (d, 3H, \( J = 6.4 \) Hz, CH$_3$). The sample was >95% pure and was used immediately in the next step.

(E/Z)-N-(6,10-Dimethylundeca-5,9-dien-2-yl)-4-methylbenzenesulfonamide 383

By general procedure A, \( p \)-tosyl chloride (1.0 g, 5.5 mmol, 1.1 eq.) was added to the amine 382 (1.0 g, 5.0 mmol, 1.0 eq.) and Et$_3$N (0.6 ml, 5.5 mmol, 1.1 eq.) to give the sulfonamide 383 (0.84 g, 47%) as a thick, clear oil (2:1 mixture of isomers). \( \delta_H \) 7.56 (d, \( J = 8.2 \) Hz, 2H), 7.12 (d, \( J = 8.2 \) Hz, 2H), 4.91 – 4.78 (m, 1H, =CH), 4.71 (br. t, \( J = 7.0 \) Hz, 1H, =CH), 4.52 (d, \( J = 8.1 \) Hz, 1H, NH), 3.15 – 3.01 (m, 1H, NCH), 2.20 (s, 3H, ArCH$_3$), 1.86 – 1.74 (m, 2H, CH$_2$), 1.74 – 1.66 (m, 2H, CH$_2$), 1.66 – 1.85 (m, 2H, CH$_2$), 1.45 (s, 3H, CH$_3$), 1.40 (s, 1H, CH$_3$, Z-isomer), 1.38 (s, 3H, CH$_3$), 1.29 (s, 2H, CH$_3$, E-isomer), 1.23 – 1.09 (m, 2H, CH$_2$), 0.82 (d, \( J = 6.5 \) Hz, 3H, CH$_3$). E-isomer: \( \delta_C \) 143.1 (Cq), 138.3 (Cq), 135.9 (Cq), 131.5 (Cq), 129.6 (2 x CH), 127.1 (2 x CH), 124.2 (=CH), 123.1 (=CH), 49.8 (NCH), 39.6 (CH$_2$), 37.7 (CH$_2$), 26.5 (CH$_2$), 24.0 (CH$_3$), 21.6 (CH$_2$), 17.7 (CH$_3$), 16.0 (CH$_3$), 14.1 (CH$_3$). Z-isomer: \( \delta_C \) 131.7 (Cq), 123.4 (=CH), 39.7 (CH$_2$), 21.7 (CH$_3$)-only 4 distinct peaks.

The whole sample showed IR (neat) \( \upsilon/cm^{-1} \): 3296, 2969, 2930, 1599, 1321, 1158, 1091, 814, 661. HRMS (EI) \( m/z \) calculated for C$_{20}$H$_{31}$NO$_2$S [M]$^+$ = 349.2076; found: 349.2078.
4-Methyl-N-(4-(2,6,6-trimethylcyclohex-1-en-1-yl)butan-2-yl)benzenesulfonamide 384

By general procedure B, to sulfonamide 383 (200 mg, 0.6 mmol) in dry dichloromethane (10 ml) under nitrogen, concentrated sulfuric acid (2 drops) was added and the mixture stirred for 1 h at 0 °C to give the sulfonamide 384 as a colourless oil (190 mg, 95%). \( \delta H \) 7.52 (d, \( J = 8.2 \text{ Hz}, 2\text{H} \)), 7.66 (d, \( J = 8.2 \text{ Hz}, 2\text{H} \)), 4.71 (d, \( J = 8.4 \text{ Hz}, 1\text{H}, \text{NH} \)), 3.27 – 2.95 (m, 1H, NCH), 2.34 (s, 3H, ArCH\(_3\)), 1.87 – 1.72 (m, 3H, CH and CH\(_2\)), 1.72 – 1.63 (m, 1H), 1.48 – 1.40 (m, 2H, CH\(_2\)), 1.39 (s, 3H, CH\(_3\)), 1.35 – 1.24 (m, 4H, 2 x CH\(_2\)), 1.10 (d, \( J = 6.6 \text{ Hz}, 3\text{H}, \text{CH}_3\)), 0.79 (s, 3H, CH\(_3\)), 0.78 (s, 3H, CH\(_3\)). \( \delta C \) 143.1 (Cq), 138.4 (Cq), 136.3 (Cq), 129.6 (2 x CH), 127.2 (Cq), 127.1 (2 x CH), 50.8 (NCH), 39.8 (CH\(_2\)), 37.9 (CH\(_2\)), 34.9 (Cq), 32.7 (CH\(_2\)), 28.5 (2 x CH\(_3\)), 24.8 (CH\(_2\)), 21.6 (CH\(_3\)), 21.4 (CH\(_3\)), 19.7 (CH\(_3\)), 19.5 (CH\(_2\)). IR (neat) \( \nu / \text{cm}^{-1} \): 3296, 2969, 2930, 1599, 1321, 1158, 1091, 814, 661. HRMS (EI) m/z calculated for C\(_{20}\)H\(_{31}\)NO\(_2\)S [M]\(^+\) = 349.2076; found: 349.2076.

4-(2,6,6-Trimethylcyclohex-1-en-1-yl)butan-2-one 387

To a 2 M solution of borane in THF (10 ml, 20 mmol) under nitrogen and cooled in ice-water was added a solution of catechol (2.20 g, 20 mmol) in dry THF (10 ml) over 0.5 h with efficient stirring. The reaction mixture was then stirred without cooling for 1 h, before recooling in ice-cold water. A solution of \( \beta \)-ionone 386 (1.92 g, 10 mmol) in dry THF (50 ml) was added. The resulting solution is stirred for 1 h at room temperature and then quenched by the addition of acetone (20 ml), followed by saturated aqueous ammonium chloride (10 ml). The resulting mixture was
extracted with dichloromethane (2 x 25 ml) and the combined extracts dried and concentrated to
give the ketone 387 (1.56 g, 80%) as a clear oil, which was used directly in the next step. All data
obtained were in accordance with those previously reported in the literature: \[\delta_H 2.45 \text{(app. dt, } J = 8.2, 7.5 \text{ Hz, 1H)}, 2.23 - 2.13 \text{(m, 1H)}, 2.10 \text{(s, 3H, CH}_3\text{)}, 1.87 - 1.76 \text{(m, 4H, 2 x CH}_2\text{)}, 1.52 \text{(s, 3H, CH}_3\text{)}, 1.37 - 1.28 \text{(m, 4H, 2 x CH}_2\text{)}, 0.88 \text{(s, 6H, 2 x CH}_3\text{).}

4-(2,6,6-Trimethylcyclohex-1-en-1-yl)butan-2-one oxime 388

To a solution of the ketone 387 (1.56 g, 8.0 mmol) and hydroxylamine hydrochloride (1.04 g, 15
mmol) in methanol (30 ml) was added sodium acetate (1.00 g, 12.2 mmol) in one portion. The
reaction mixture was heated at 40 °C for 2 h and then concentrated on a rotary evaporator. The
residue was partitioned between ether (50 ml) and water (10 ml). The separated organic layer was
dried and evaporated to give the oxime 388 (1.20 g, 71%) as a 2:1 mixture of isomers and as a
colourless liquid, which was used directly in the next step: \[\delta_H 2.22 - 2.13 \text{(m, 2H, CH}_2\text{)}, 2.12 -
2.03 \text{(m, 2H, CH}_2\text{)}, 1.87 \text{(s, 2H, isomer)}, 1.82 \text{(s, 1H, isomer)}, 1.53 - 1.50 \text{(m, 2H, CH}_2\text{)}, 1.37 -
1.26 \text{(m, 2H, CH}_2\text{)}, 0.89 \text{(s, 6H, 2 x CH}_3\text{).}

Major isomer \[\delta_C 157.2 \text{(Cq)}, 136.7 \text{(Cq)}, 133.5 \text{(Cq)}, \]
40.7 \text{(CH}_2\text{)}, 39.8 \text{(CH}_2\text{)}, 34.9 \text{(Cq)}, 32.7 \text{(CH}_2\text{)}, 28.5 \text{(2 x CH}_3\text{)}, 25.4 \text{(CH}_2\text{)}, 23.3 \text{(CH}_3\text{), 19.7
}(\text{CH}_3\text{)}, 19.5 \text{(CH}_2\text{).}

Minor isomer \[\delta_C 39.9 \text{(CH}_2\text{)}, 32.8 \text{(CH}_2\text{)}, 28.4 \text{(CH}_3\text{), 19.8 \text{(CH}_2\text{); only four
distinct peaks.

The whole sample showed IR (neat) \[\nu/cm^{-1}: 3366, 2955, 2928, 2903, 1512, 1470, 1445, 1362,
1260, 1096. \text{HRMS (EI) } m/z \] calculated for C\text{13H}_{25}\text{NO} [M]^+ = 209.1780; found: 209.1783.
4-(2,6,6-Trimethylcyclohex-1-en-1-yl)butan-2-amine 389

![Chemical structure](image)

By general procedure C, the oxime 388 (1.2 g, 5.7 mmol) was reduced using lithium aluminium hydride (0.38 g, 10 mmol) to give the amine 389 (1.00 g, 89%) as a clear oil, which was used directly in the next step. δH 2.81 (m, 1H, NCH), 1.99 – 1.84 (m, 4H, 2 x CH₂), 1.53 (s, 3H, CH₃), 1.50 – 1.44 (m, 2H, CH₂), 1.37 – 1.30 (m, 4H, 2 x CH₂), 1.02 (d, J = 6.3 Hz, 3H, CH₃), 0.91 (s, 6H, 2 x CH₃). δC 137.1 (Cq), 126.7 (Cq), 47.9 (NCH), 40.7 (CH₂), 39.9 (CH₂), 34.9 (Cq), 32.7 (CH₂), 28.5 (2 x CH₃), 25.4 (CH₂), 23.3 (CH₃), 19.7 (CH₃), 19.5 (CH₂). IR (neat) ν/cm⁻¹: 3264, 2963, 2926, 2866, 1458, 1375, 908. HRMS (APCI) m/z calculated for C₁₃H₂₆N [M+H]⁺ = 196.2065; found: 196.2058.

4-Methyl-N-(4-(2,6,6-trimethylcyclohex-1-en-1-yl)butan-2-yl)benzenesulfonamide 384

![Chemical structure](image)

By general procedure A, p-tosyl chloride (1.00 g, 5.5 mmol, 1.1 eq.) was added to the amine 389 (1.00 g, 5.1 mmol, 1.0 eq.) and Et₃N (0.6 ml, 5.5 mmol) to give the sulfonamide 384 (1.50 g, 84%) as a thick, clear oil, which showed ¹H and ¹³C resonances completely identical to the sample obtained from the partial cyclisation reaction (p.184).
N-(6,10-Dimethylundeca-5,9-dien-2-yl)-4-nitrobenzenesulfonamide 390

By general procedure A, p-nitrobenzenesulfonyl chloride (1.24 g, 5.6 mmol, 1.1 eq.) was added to the amine 382 (1.00 g, 5.0 mmol, 1.0 eq.) and Et$_3$N (0.6 ml, 5.5 mmol) to give the sulfonamide 390 (1.00 g, 54%) as yellow oil (2:1 mixture of isomers). $\delta$H 8.31 (d, $J = 8.2$ Hz, 2H), 7.95 (d, $J = 8.2$ Hz, 2H), 5.03 – 4.91 (m, 1H, =CH), 4.87 (t, $J = 5.7$ Hz, 1H, =CH), 4.66 (d, $J = 7.8$ Hz, 1H, NH), 3.41 – 3.22 (m, 1H, NCH), 2.01 – 1.90 (m, 2H, CH$_2$), 1.90 – 1.70 (m, 4H, 2 x CH$_2$), 1.60 (s, 3H, CH$_3$), 1.54 (s, 1H, CH$_3$, Z-isomer), 1.52 (s, 3H, CH$_3$), 1.48 (s, 3H, CH$_3$), 1.44 (s, 2H, CH$_3$, E-isomer), 1.40 – 1.29 (m, 2H, CH$_2$), 1.02 (d, $J = 6.6$ Hz, 3H, CH$_3$). E-isomer: $\delta$C 149.9 (Cq), 147.3 (Cq), 136.5 (Cq), 131.7 (Cq), 131.5 (Cq), 128.2 (2 x CH), 124.3 (2 x CH), 124.1 (=CH), 123.3 (=CH), 50.5 (NCH), 39.6 (CH$_2$), 37.7 (CH$_2$), 26.8 (CH$_2$), 26.7 (CH$_3$), 24.0 (CH$_2$), 23.3 (CH$_3$), 21.8 (CH$_3$), 17.6 (CH$_3$), 16.0 (CH$_3$). Z-isomer: $\delta$C 131.8 (Cq), 123.4 (=CH), 37.9 (CH$_2$), 26.7 (CH$_2$)-only four distinct peaks.

The whole sample showed IR (neat) $\nu$/cm$^{-1}$: 3281, 2968, 2858, 1530, 1433, 1306, 1092, 852, 750, 687. HRMS (EI) m/z calculated for C$_{19}$H$_{28}$N$_2$O$_4$S [M]$^+$ = 380.1770; found: 380.1763.

4-Nitro-N-(4-(2,6,6-trimethylocyclohex-1-en-1-yl)butan-2-yl)benzenesulfonamide 391 and 2,6,6,10-Tetramethyl-1-((4-nitrophenyl)sulfonyl)-1-azaspiro[4.5]decane 392

By general procedure B, to sulfonamide 390 (235 mg, 0.62 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (3 drops) was added and the reaction stirred for 1.5 h at
0 °C to give the sulfonamide 391 and Spiro-pyrrolidine 392 (total 218 mg, 93%) as a colourless oil.

Sulfonamide 391 δH 8.41 (d, J = 8.2 Hz, 2H), 8.17 (d, J = 8.2 Hz, 2H), 5.10 (d, J = 8.2 Hz, 1H, NH), 3.43 – 3.24 (m, 1H, NCH), 1.95 – 1.73 (m, 4H, 2 x CH₂), 1.48 – 1.40 (m, 2H, CH₂), 1.46 (s, 3H, CH₃), 1.40 - 1.33 (m, 4H, 2 x CH₂), 1.10 (d, J = 6.6 Hz, 3H, CH₃), 0.88 (s, 3H, CH₃), 0.86 (s, 3H, CH₃). δC 149.9 (Cq), 147.3 (Cq), 135.9 (Cq), 128.2 (2 x CH), 127.6 (Cq), 124.4 (2 x CH), 51.4 (NCH), 39.6 (CH₂), 37.9 (CH₂), 34.9 (Cq), 32.6 (CH₂), 28.5 (CH₃), 24.8 (CH₂), 21.7 (CH₃), 19.7 (CH₂), 19.3 (2 x CH₃).

Spiro-pyrrolidine 392: δH 3.54 – 3.43 (m, 1H, NCH), 1.10 (d, J = 5.7 Hz, 3H, CH₃), 0.81 (d, J = 5.5 Hz, 3H, CH₃); only 3 distinct peaks. δC 67.8 (NCq), 51.9 (NCH), 37.0 (CH₂), 35.9 (Cq), 36.0 (CH₂); only 5 distinct peaks.

The whole sample showed IR (neat) υ/cm⁻¹: 3281, 2922, 1705, 1532, 1354, 1165, 1091, 914, 855, 737. HRMS (EI) m/z calculated for C₁₉H₂₉N₂O₄S [M⁺] = 211. 1572; found: 211. 1576.

Methyl 6,10-dimethylundeca-5,9-dien-2-ylcarbamate 393

By general procedure A, methyl chloroformate (0.75 ml, 12 mmol, 1.3 eq.) was added to the foregoing amine 382 (1.95 g, 10 mmol, 1.0 eq.) and Et₃N (2.5 ml, 22 mmol, 1.2 eq.) to give the carbamate 393 as a clear oil (0.71 g, 28%). δH 5.10 – 4.96 (m, 2H, 2 × =CH), 4.66 (br. s, 1H, NH), 3.60 (sext, 1H, J = 6.3 Hz, NCH), 3.52 (OCH₃), 2.00 – 1.85 (m, 6H, 3 x CH₂), 1.60 (s, 3H, CH₃), 1.50 (s, 6H, 2 x CH₃), 1.42 – 1.30 (m, 2H, CH₂), 1.06 (d, 3H, J = 6.7 Hz, CH₃). δC 156.4 (CO₂), 135.7 (Cq), 131.5 (Cq), 124.3 (=CH), 123.5 (=CH), 51.8 (OCH₃), 47.0 (NCH), 39.6 (CH₂), 31.9 (CH₂), 26.7 (CH₂), 25.6 (CH₃), 24.4 (CH₂), 23.3 (CH₃), 17.6 (CH₃), 15.9 (CH₃).
Z-isomer: δ\text{C} 131.6 (Cq), 124.4 (=CH), 32.1 (CH\text{2}), 24.5 (CH\text{2})- only four distinct peaks.

IR (neat) \nu/cm\text{⁻¹}: 3333, 2970, 2931, 1695, 1531, 1450, 1375, 1252, 1078, 777. HRMS (EI) m/z calculated for C\text{15}H\text{27}NO\text{2} [M]\text{+} = 253. 2042; found: 253. 2036.

Methyl 2,5,5,8a-tetramethyloctahydroquinoline-1(2H)-carboxylate 394

\[
\begin{array}{c}
\text{H}_2\text{SO}_4 \\
\text{1 h, 20 °C, CH}_2\text{Cl}_2 \\
393 \\
\end{array}
\rightarrow
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{CO}_2\text{Me} \\
394 \\
\end{array}
\]

By general procedure B, to the carbamate 393 (140 mg, 0.6 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for 1 h at room temperature to give the octahydroquinoline 394 (112 mg, 80%) as a colourless oil and an inseparable 6:1 mixture of diastereoisomers. The major diastereoisomer showed: δ\text{H} 4.08 – 3.99 (m, 1H, NCH), 3.61 (dd, J = 9.7, 4.1 Hz, 1H), 3.56 (s, 3H, OCH\text{3}), 3.09 (dtd, J = 13.1, 3.5, 1.6 Hz, 1H), 1.89 (ddd, J = 19.3, 9.8, 4.8 Hz, 1H), 1.80 – 1.69 (m, 1H), 1.57 – 1.51 (m, 1H), 1.42 (dq, J = 5.5, 3.2 Hz, 2H), 1.36 – 1.32 (m, 1H), 1.32 – 1.29 (m, 1H), .25 (s, 3H, CH\text{3}), 1.20 (d, J = 6.5, 3H, CH\text{3}), 1.18 – 1.01 (m, 1H), 0.82 (s, 6H, 2 x CH\text{3}), 0.73 (dd, J = 8.9, 5.1 Hz, 1H). δ\text{C} 156.1 (Cq), 59.6 (Cq), 51.7 (OCH\text{3}), 48.6 (CH), 46.5 (CH), 41.7 (CH\text{2}), 39.4 (CH\text{2}), 34.1 (Cq), 31.8 (CH\text{3}) 25.0 (CH\text{2}), 21.6 (CH\text{3}), 20.6 (CH\text{3}), 19.9 (CH\text{2}), 19.7(CH\text{3}), 14.4 (CH\text{2}).

The minor diastereoisomer could be characterized by δ\text{C} 53.6 (Cq), 37.1 (CH\text{2}), 36.4 (CH\text{2}), 38.3 (CH\text{3}), 36.9 (CH\text{3}), 19.9 (CH\text{2}), 13.6 (CH\text{3}).

The whole sample showed IR (neat) \nu/cm\text{⁻¹}: 2937, 1701, 1693, 1512, 1344, 1244, 1087, 987, 775. HRMS (EI) m/z calculated for C\text{15}H\text{27}NO\text{2} [M]\text{+} = 253. 2042; found: 253. 2042.
Benzyl (6,10-dimethylundeca-5,9-dien-2-yl)carbamate 395

![Chemical structure](image)

By general procedure A, benzyl chloroformate (0.95 g, 5.5 mmol, 1.1 eq.) was added to the amine 382 (1.00 g, 5.0 mmol, 1.0 eq.) and Et₃N (0.6 ml, 5.5 mmol) to give the Z-carbamate 395 as a clear oil (0.88 g, 52%). δH 7.30 – 7.19 (m, 5H), 5.02 – 4.91 (m, 4H, 2 x =CH, OCH₂), 4.54 (br. d, J = 13.3 Hz, 1H, NH), 3.64 – 3.50 (m, 1H, NCH), 2.07 – 1.81 (m, 6H, 3 x CH₂), 1.60 (s, 3H, CH₃), 1.49 (s, 3H, CH₃), 1.48 (s, 3H, CH₃), 1.42 – 1.29 (m, 2H, CH₂), 1.07 (d, J = 5.1 Hz, 3H, CH₃). δC 154.5 (CO₂), 136.4 (Cq), 136.0 (Cq), 131.1 (Cq), 128.4 (2 x CH), 127.9 (2 x CH), 124.2 (CH), 123.3 (2 x CH), 66.4 (OCH₂), 46.9 (NCH), 39.6 (CH₂), 37.5 (CH₂), 26.6 (CH₂), 25.6 (CH₃), 24.2 (CH₂), 21.2 (CH₃), 17.6 (CH₃), 15.8 (CH₃). IR (neat) ν/cm⁻¹: 3337, 2969, 2920, 1696, 1526, 1452, 1244, 1060, 1028, 735, 698. HRMS (EI) m/z calculated for C₂₁H₃₁NO₂ [M]⁺ = 329.2355; found: 329.2347.

Benzyl 2,5,5,8a-tetramethyloctahydroquinoline-1(2H)-carboxylate 396

![Chemical structure](image)

By general procedure B, to Z-carbamate 395 (165 mg, 0.5 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the reaction mixture was stirred for 1 h at 0 °C to give the octahydroquinoline 396 (116 mg, 70%) as a colourless oil. δH 7.29 – 7.18 (m, 4H), 7.24 – 7.21 (m, 1H), 4.99 – 4.94 (d, J = 12.7 Hz, 1H, OCH₃H₈), 4.90 (d, J = 12.7 Hz, 1H, OCH₃H₈), 4.08 – 4.00 (m, 1H, NCH), 3.09 (ddt, J = 13.1, 3.5, 1.6 Hz, 1H), 1.89 – 1.77 (m, 2H, CH₂), 1.67 (ddd, J = 10.6, 7.7, 4.6 Hz, 2H, CH₂), 1.42 (d, J = 5.8 Hz, 2H, CH₂), 1.40
– 1.31 (m, 2H, CH₂), 1.22 (s, 3H, CH₃), 1.16 (d, J = 6.9 Hz, 3H, CH₃), 1.04 – 0.96 (m, 1H), 0.84 – 0.77 (m, 1H), 0.75 (s, 6H, 2 x CH₃). δC 156.2 (Cq), 136.7 (Cq), 128.5 (CH), 128.4 (2 x CH), 127.9 (2 x CH), 66.1 (OCH₂), 59.9 (Cq), 48.7 (NCH), 41.8 (CH₂), 39.4 (CH₂), 34.2 (Cq), 33.0 (CH₃) 23.1 (CH₂), 21.0 (CH₃), 19.6 (CH₃), 19.9 (CH₂), 19.7(CH₃), 14.8 (CH₂). IR (neat) v/cm⁻¹: 2872, 2855, 1694, 1552, 1393, 912, 731. HRMS (EI) m/z calculated for C₂₁H₃₁NO₂ [M⁺] = 329.2355; found: 329.2348.

(2E,6E)-1-Bromo-3,7,11-trimethyldodeca-2,6,10-triene 398²⁷

\[ \text{OH} \quad \xrightarrow{\text{PBr₃, Py}} \quad \text{Br} \]

To a stirred solution of (E,E)-farnesol 397 (2.20 g, 10 mmol) in petroleum ether (10 ml) was added phosphorus tribromide (2.71 g, 10 mmol). The resulting solution was stirred at 0 °C for 1 h. The mixture was treated with cold brine (5 ml) and extracted with ether. The organic extracts dried and concentrated to give crude farnesyl bromide 398 (2.79 g, 98%) which was used without any purification. All data obtained were in accordance with those previously reported in the literature:²⁷ δH 5.42 (t, J = 8.5 Hz, 1H, =CH), 5.14 – 4.98 (m, 2H, 2 x =CH), 4.09 (d, J = 7.0 Hz, 2H, CH₂Br), 2.30 – 1.97 (m, 8H, 4 x CH₂), 1.77 (s, 3H, CH₃), 1.66 (s, 6H, 2 x CH₃), 1.59 (d, J = 3.8 Hz, 3H, CH₃).

(4E,8E)-Methyl 2-acetyl-5,9,13-trimethyldodeca-4,8,12-trienoate 399²⁸

\[ \text{Br} \quad \xrightarrow{\text{OOCOMe, NaH, DMF}} \quad \text{O}_2\text{O} \]

(2E,6E)-1-Bromo-3,7,11-trimethyldodeca-2,6,10-triene 398

(4E,8E)-Methyl 2-acetyl-5,9,13-trimethyldodeca-4,8,12-trienoate 399
A 60% dispersion of sodium hydride in mineral oil (0.42 g, 10.5 mmol) was washed with hexanes (3 x 10 ml) and suspended in dry DMF (50 ml). Methyl acetoacetate (1.16 ml, 10.8 mmol) was added dropwise. After 0.5 h, the resulting solution was treated with farnesyl bromide 398 (2.79 g, 9.8 mmol) and stirred for 4 h. The reaction mixture was quenched with water (10 ml) and extracted with ether (3 x 30 ml). The combined organic extracts were dried and concentrated. Column chromatography (dichloromethane/ hexanes, 1:19) of the crude afforded the acetoacetate 399 (2.27 g, 72%) as a colourless oil. All data obtained were in accordance with those previously reported in the literature: 28 ΔH 5.10 – 4.88 (m, 3H), 3.66 (s, 3H), 3.37 (dt, J = 7.6, 4.5 Hz, 1H), 2.49 (t, J = 7.4 Hz, 2H), 2.15 (s, 3H), 2.10 - 1.98 (m, 5H), 1.98 - 1.90 (m, 3H), 1.61 (d, J = 1.1 Hz, 3H), 1.56 (s, 3H), 1.54 (s, 3H), 1.51 (s, 3H).

(5E,9E)-6,10,14-Trimethylpentadeca-5,9,13-trien-2-one 400 29

The foregoing acetoacetate 399 (2.27 g, 7.0 mmol) in dimethyl sulfoxide/water (50 ml : 0.5 ml) containing sodium chloride NaCl (1.0 g, 17 mmol ) was refluxed for 3 h. Cold water (10 ml) was added and the resulting mixture extracted with ether (3 x 30 ml). The combined organic layers were dried and concentrated to yield the ketone 400 (1.80 g, 64%) as a colourless oil. All data obtained were in accordance with those previously reported in the literature: 30 ΔH 5.10 – 4.93 (m, 3H, 3 x =CH), 2.36 (dd, J = 11.1, 7.3 Hz, 2H), 2.24 – 2.13 (m, 2H, CH2), 2.05 (s, 3H, CH3), 2.01 – 1.93 (m, 4H, 2 x CH2), 1.93 – 1.84 (m, 4H, 2 x CH2), 1.61 (s, 6H, 2 x CH3), 1.53 (s, 6H, 2 x CH3). ΔC 158.3 (C=O), 136.3 (Cq), 135.3 (Cq), 131.3 (Cq), 124.9 (=CH), 124.0 (=CH), 122.5 (=CH), 39.63 (CH2), 36.2 (CH2), 29.8 (CH2), 26.61 (CH2), 24.9 (CH3), 24.7 (CH2), 24.8 (CH2), 23.4 (CH3), 17.7 (CH3), 16.1 (CH3), 13.3 (CH3).
(5E,9E)-6,10,14-Trimethylpentadeca-5,9,13-trien-2-one oxime 401

\[ \text{400} \xrightarrow{\text{NH}_2\text{OH.HCl}} \text{401} \]

To a solution of ketone 400 (1.80 g, 6.9 mmol, 1.0 eq) and hydroxylamine hydrochloride (0.70 g, 10 mmol, 1.4 eq) in methanol (30 ml) was added sodium acetate (1.0 g, 12.2 mmol) in one portion. The reaction mixture was heated at 40 °C for 2 h and then concentrated on a rotary evaporator. The residue was partitioned between ether (50 ml) and water (10 ml). The separated organic layer was dried. Evaporation provided the oxime 401 (1.90 g, 100%) as a 2:1 mixture of isomers as a colourless liquid which was used directly in the next step: \( \delta^{1}H \) 5.10 – 4.90 (m, 3H, =CH), 2.20 – 2.10 (m, 2H, CH\_2), 2.14 – 2.21 (m, 10H, 5 x CH\_2), 1.77 (s, 2H, CH\_3, isomer), 1.75 (s, 1H, CH\_3, isomer), 1.65 (s, 6H, 2 x CH\_3), 1.53 (s, 6H, 2 x CH\_3).

(5E,9E)-6,10,14-Trimethylpentadeca-5,9,13-trien-2-amine 402

The oxime 401 (1.90 g, 6.8 mmol, 1.0 eq.) was dissolved in dry tetrahydrofuran (30 ml) and the solution added dropwise to a suspension of lithium aluminium hydride (0.38 g, 10 mmol, 1.4 eq.) in tetrahydrofuran (20 ml) at 0 °C. The suspension was then refluxed for 3 h and subsequently cooled to 0 °C. When it was cold, water (5 ml) and 15% aqueous NaOH (5 ml) were added sequentially and the resulting mixture then stirred for one hour. The precipitated salts were then filtered off and washed with tetrahydrofuran (40 ml). The combined filtrate was concentrated, then the liquid residue extracted with dichloromethane (2 x 20 ml) and the combined extracts dried and
concentrated to give the amine 402 (1.20 g, 67%) as a yellow oil which was used directly in the next step. δ_H 5.10 - 4.96 (m, 3H, 3 x =CH), 2.88 – 2.80 (m, NCH), 2.00 – 1.85 (m, 10H, 5 x CH₂), 1.6 (s, 6H, 2 x CH₃), 1.55 (s, 6H, 2 x CH₃), 1.35 - 1.28 (m, 2H, CH₂), 1.01 (d, 3H, J = 4.4 Hz, CH₃). δ_C 135.1 (Cq), 135.0 (Cq), 131.5 (Cq), 125.0 (=CH), 124.3 (=CH), 123.5 (=CH), 46.7 (NCH), 39.7 (2 x CH₂), 31.9 (CH₂), 26.7 (CH₂), 25.6 (CH₃), 24.4 (2 x CH₂), 23.3 (2 x CH₃), 17.7 (CH₃), 15.9 (CH₃). IR (neat) υ/cm⁻¹: 3462, 2971, 2936, 1740, 1705, 1445, 1244, 1084, 1049, 912.

HRMS (AP) m/z calculated for C₁₈H₃₄N [M+H]^+ = 264.2691; found: 264.2696.

**Methyl ((5E,9E)-6,10,14-trimethylpentadeca-5,9,13-trien-2-yl)carbamate 403**

By general procedure A, methyl chloroformate (0.38 ml, 5 mmol, 1.1 eq.) was added to the amine 402 (1.20 g, 4.5 mmol, 1.0 eq.) and Et₃N (0.6 ml, 5.5 mmol, 1.2 eq.) to give the carbamate 403 (0.80 g, 55%) as a clear oil. δ_H 5.21 – 5.02 (m, 3H, 3 x =CH), 4.53 (br. d, J = 6.6 Hz, 1H, NH), 3.77 – 3.68 (m, 1H, NCH), 3.66 (s, 3H, OCH₃), 2.16 - 1.98 (m, 10H, 5 x CH₂), 1.70 (s, 6H, 2 x CH₃), 1.62 (s, 6H, 2 x CH₃), 1.50 - 1.41 (m, 2H, CH₂), 1.15 (d, J = 6.4 Hz, 3H, CH₃). δ_C 156.4 (Cq), 135.7 (Cq), 135.4 (Cq), 131.5 (Cq), 125.0 (=CH), 124.3 (=CH), 123.5 (=CH), 51.8 (OCH₃), 47.0 (NCH), 39.7 (2 x CH₂), 31.9 (CH₂), 26.7 (CH₂), 25.6 (CH₃), 24.4 (2 x CH₂), 23.3 (2 x CH₃), 17.7 (CH₃), 15.9 (CH₃). IR (neat) υ/cm⁻¹: 3323, 2965, 2926, 2963, 1710, 1532, 1451, 1377, 1248, 1078. HRMS (EI) m/z calculated for C₂₀H₃₅N₂O₂ [M]^+ = 321.2668; found: 321.2674.
Methyl 3,4a,7,7,10a-pentamethyldodecahydrobenzo[f]quinoline-4(4aH)-carboxylate 404

To the foregoing carbamate 403 (161 mg, 0.5 mmol) in anhydrous dichloromethane (10 ml), cooled in an ice bath was added triflic acid (3 mg, 1.8 µl, 0.02 mmol, 0.4 eq), and the reaction mixture was stirred without cooling for one hour. The reaction was quenched by the addition of saturated aqueous potassium carbonate (2 ml). The separated organic layer was dried and evaporated to give the cyclised product 404 (120 mg, 75%) as a colourless oil. δH (whole sample) 4.39 – 1.34 (s, m, 1H, NCH), 3.56 (s, 3H, OCH3), 1.72 – 1.63 (m, 2H, CH2), 1.47– 1.52 (m, 4H, 2 x CH2), 1.36 – 1.23 (m, 4H, 2 x CH2), 1.19 – 1.10 (m, 6H, 3 x CH2), 0.87 (s, 3H, CH3), 0.86 (s, 3H, CH3), 0.85 (s, 3H, CH3), 0.84 (d, J = 6.8 Hz, 3H, CH3), 0.79 (s, 3H, CH3).

The whole sample showed IR (neat) υ/cm⁻¹: 2934, 2872, 1701, 1528, 1452, 1252, 1084, 908, 722. HRMS (EI) m/z calculated for C20H35NO2 [M]^+ = 321.2668; found: 321.2666.

1-(4-Methylcyclohex-3-en-1-yl)ethanone oxime 417

To a solution of commercial (+/-) limona ketone 416 (2.76 g, 20 mmol, 1.0 eq) and hydroxylamine hydrochloride (2.09 g, 30 mmol, 1.5 eq) in methanol (30 ml) was added sodium acetate (1.00 g, 12.2 mmol) in one portion. The reaction mixture was heated at 40 °C for 2 h and then concentrated on a rotary evaporator. The residue was partitioned between ether (50 ml) and water (10 ml). The separated organic layer was dried and evaporated to give the E-oxime 417 (3.00 g, 97%) as a colourless oil, which was used directly in the next step. All data obtained were in accordance with
those previously reported in the literature: 31 δH 5.10 – 5.18 (m, 1H, =CH), 3.24 (pent, J = 7.0 Hz, 1H), 2.18 – 2.03 (m, 1H), 1.85 – 1.76 (m, 4H, 2 x CH2), 1.76 – 1.65 (m, 1H), 1.62 (s, 3H, CH3), 1.40 (s, 3H, CH3), 1.36 – 1.25 (m, 1H).

1-(4-Methylcyclohex-3-en-1-yl)ethanamine 418

\[
\text{H} \quad \text{LiAlH}_4 \quad \text{THF} \quad \text{H} \quad \text{NH}_2
\]

By general procedure C, the oxime 417 (3.0 g, 19.6 mmol) was reduced using lithium aluminium hydride (0.76 g, 20 mmol) to give the amine 418 (2.60 g, 96%) as a clear oil and an inseparable 1:1 mixture of diastereoisomers, which was used directly in the next step: Diastereoisomer A - δH 5.28 (t, J = 10.0 Hz, H, =CH), 2.75 – 2.66 (m, 1H, NCH), 1.94 – 1.86 (m, 4H, 2 x CH2), 1.66 (s, 3H, CH3), 1.33 – 1.36 (m, 2H, CH2), 1.37 (dddt, J = 8.9, 8.4, 6.8, 5.7 Hz, 1H), 1.02 (d, J = 7.2, 3H). δC 134.0 (Cq), 120.0 (=CH), 51.0 (NCH), 40.8 (CH), 30.4 (CH2), 27.7 (CH2), 25.4 (CH2), 23.4 (CH3), 20.3 (CH3). Diastereoisomer B - δH 2.66 – 2.58 (m, 1H, NCH), 1.30 (dddt, J = 8.9, 8.4, 6.8, 5.7 Hz, 1H) only 2 distinct peaks. δC 120.6 (=CH), 41.0 (CH), 28.0 (CH2); only 3 distinct peaks. IR (neat) υ/cm⁻¹: 3279, 2887, 2855, 1659, 1437, 1377, 1153, 951. HRMS (ES) m/z calculated for C9H18N [M+H]+ = 140.1439; found: 140.1440.

4-Methyl-N-(1-(4-methylcyclohex-3-en-1-yl)ethyl)benzenesulfonamide 419

\[
\text{H} \quad \text{NH}_2 \quad \text{TsCl, Et}_3\text{N} \quad \text{DCM} \quad \text{H} \quad \text{NH}_2
\]

By general procedure A, p-tosyl chloride (1.00 g, 5.5 mmol, 1.1 eq.) was added to the amine 418 (0.70 g, 5.0 mmol, 1.0 eq.) and Et3N (0.62 ml, 5.5 mmol) to give the sulfonamide 419 (1.28 g,
87%) as a clear oil and as an inseparable 1:1 mixture of diastereoisomers. Diastereoisomer A - δH 7.69 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 5.19 (br. s, 1H, =CH), 4.51 – 4.42 (m, 1H, NH), 3.21 – 3.11 (m, 1H, NCH), 2.35 (s, 3H, ArCH3), 2.01 - 1.82 (m, 4H, 2 x CH2), 1.53 (s, 3H, CH3), 1.40 (dd, J = 7.0, 4.2 Hz, 1H), 1.28 – 0.98 (m, 1H), 0.89 (d, J = 6.7 Hz, 3H). δC 143.2 (Cq), 138.30 (Cq), 134.0 (Cq), 129.5 (CH), 127.0 (CH), 120.0 (=CH), 53.8 (NCH), 39.7 (CH), 30.1 (CH2), 27.8 (CH2), 25.2 (CH2), 23.3 (CH3), 21.4 (CH3), 18.8 (CH3). Diastereoisomer B: δH 0.88 (d, J = 6.7 Hz, 3H) - only 1 distinct peak. δC 133.9 (Cq), 53.7 (NCH), 39.5 (CH), 29.9 (CH2), 27.5 (CH2), 25.0 (CH2) - only 6 distinct peaks. The whole sample showed IR (neat) υ/cm⁻¹: 3289, 2920, 1599, 1433, 1321, 1159, 1089, 914, 814, 731, 665. HRMS (ES) m/z calculated for C₁₆H₂₄NO₂S [M+H]^+ = 294.1528; found: 294.1514.

1,3-Dimethyl-2-tosyl-2-azabicyclo[2.2.2]octane 420

By general procedure B, to sulfonamide 419 (117 mg, 0.4 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added, and the mixture stirred for 4 h at 0 °C to give the bicyclo-octane 420 (111 mg, 95%) as a colourless crystals, m.p. 112 – 114 °C. δH 7.78 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 4.14 (qd, J = 6.4, 3.7 Hz, 1H, NCH), 2.43 (s, 3H, Ar CH3), 1.98 – 1.89 (m, 1H), 1.89 – 1.81 (m, 1H), 1.78 (s, 1H), 1.71 – 1.66 (m, 1H), 1.65 – 1.58 (m, 1H), 1.45 (d, J = 6.4 Hz, 3H, CH3), 1.19 (s, 3H, CH3). δC 142.5 (Cq), 140.9 (Cq), 129.5 (2 x CH), 127.0 (2 x CH), 57.0 (NCH), 55.2 (Cq), 36.7 (CH2), 31.5 (CH), 30.1 (CH2), 26.4 (CH2), 26.3 (CH3), 22.2 (CH3), 21.4 (CH3), 19.2 (CH2). IR (neat) υ/cm⁻¹: 2930, 1597, 1456, 1329, 1311, 1076, 1160, 1078, 980, 878, 739. HRMS (EI) m/z calculated for C₁₆H₂₃NO₂S [M]^+ = 293.1450; found: 293.1448.
(1R,4S,5R,7R)-4,7-Dimethyl-6-tosyl-6-azabicyclo[3.2.1]octane 421

By general procedure B, to sulfonamide 419 (127 mg, 0.5 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the mixture stirred for 5 h at 20 °C to give the [3.2.1]-azabicyclo-octane 421 (122 mg, 96%) as a colourless oil. δH 7.58 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 3.61 (d, J = 3.9 Hz, 1H, NCH), 3.56 – 3.47 (m, 1H, NCH), 2.28 (s, 3H, ArCH3), 2.13 (app. s, 1H), 1.98 (app. s, 1H), 1.82 (d, J = 4.0 Hz, 1H), 1.41 – 1.37 (m, 2H, CH2), 1.31 – 1.26 (m, 1H), 1.21 (d, J = 6.8 Hz, 3H, CH3), 1.15 – 1.08 (m, 1H), 0.88 (ddd, J = 11.4, 10.1, 5.1 Hz, 1H), 0.83 (d, J = 6.3 Hz, 3H, CH3), 0.71 (dd, J = 6.8, 3.9 Hz, 1H). δC 143.1 (Cq), 139.1 (Cq), 129.5 (2 x CH), 127.0 (2 x CH), 60.2 (NCH), 55.3 (NCH), 37.6 (CH), 33.6 (CH), 31.4 (CH2), 26.3 (CH3), 21.5 (CH2), 21.0 (CH3), 19.2 (CH2). IR (neat) ν/cm⁻¹: 2957, 2930, 1458, 1333, 1155, 1091, 812. HRMS (ES) m/z calculated for C16H24NO2S [M+H]+ = 294.1528; found: 294.1524.

N-(1-(4-Methylcyclohex-3-en-1-yl)ethyl)-4-nitrobenzenesulfonamide 422

By general procedure A, p-nitrobenzenesulfonyl chloride (1.24 g, 5.5 mmol, 1.1 eq.) was added to the amine 418 (0.70 g, 5.0 mmol, 1.0 eq.) and Et3N (0.62 ml, 5.5 mmol) to give the Ns-sulfonamide 422 (1.39 g, 85%) as a yellow oil and as an inseparable 1:1 mixture of diastereoisomers. Diastereoisomer A δH 8.41 (d, J = 8.0 Hz, 2H), 8.13 (d, J = 8.0 Hz, 2H), 5.12 (br. s, 1H, =CH), 5.09 – 4.84 (m, 1H, NH), 3.36 – 2.96 (m, 1H, NCH), 2.00 – 1.79 (m, 4H, 2 x CH2), 1.50 (s, 3H, CH3), 1.29 – 1.12 (m, 2H, CH2), 0.99 (d, J = 6.7 Hz, 3H, CH3). δC 149.9 (Cq), 198
147.5 (Cq), 134.1 (Cq), 128.2 (2 x CH), 124.3 (2 x CH), 119.5 (=CH), 54.5 (NCH), 39.6 (CH), 30.0 (CH₂), 27.9 (CH₂), 27.5 (s), 25.3 (CH₂), 23.3 (CH₃), 19.2 (CH₃). Diastereoisomer B: δH 0.90 (d, J = 6.7 Hz, 3H) - only 1 distinct peak. δC 149.9 (Cq), 147.2 (Cq), 134.1 (Cq), 128.2 (2 x CH), 124.3 (2 x CH), 119.4 (=CH), 54.3 (NCH), 39.4 (CH), 29.8 (CH₂), 27.5 (CH₂), 25.1 (CH₂), 23.3 (CH₃), 19.1 (CH₃).

The whole sample showed IR (neat) υ/cm⁻¹: 3327, 2930, 1529, 1433, 1351, 1310, 1165, 1092, 914, 852, 736. HRMS (ES-VE) m/z calculated for C₁₅H₁₉N₂O₄S [M+H]^+ = 323.1066; found: 323.1077.

1,3-Dimethyl-2-(4-nitrophensylsulfonyl)-2-azabicyclo[2.2.2]octane 423

By general procedure B, to Ns-sulfonamide 422 (131 mg, 0.4 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the reaction stirred for 4 h at 0 °C to give the azabicyclo-octane 423 (126 mg, 96%) as yellowish crystals, m.p. 155 – 158°C. δH 8.31 – 8.19 (m, 2H), 8.06 – 7.96 (m, 2H), 4.23 – 4.01 (m, 1H, NCH), 1.84 (ddd, J = 11.2, 5.9, 2.5 Hz, 1H), 1.72 – 1.65 (m, 1H), 1.65 – 1.58 (m, 1H), 1.41 (d, J = 7.2, 3H, CH₃), 1.32 – 1.16 (m, 2H, CH₂), 1.14 (s, 3H, CH₃). δC 150.0 (Cq), 140.9 (Cq), 128.5 (2 x CH), 124.1 (2 x CH), 57.0 (NCH), 56.1 (Cq), 36.2 (CH₂), 31.8 (CH), 30.6 (CH₂), 26.4 (CH₃), 26.3 (CH₂), 21.4 (CH₃), 19.4 (CH₂). IR (neat) υ/cm⁻¹: 2938, 1525, 1338, 1302, 1161, 1085, 983, 910, 855. HRMS (EI) m/z calculated for C₁₅H₂₀N₂O₄S [MI]^+ = 324.1144; found: 324.1146.
(1R,4S,5R,7R)-4,7-Dimethyl-6-((4-nitrophenyl)sulfonyl)-6-azabicyclo[3.2.1]octane 424

By general procedure B, to sulfonamide 422 (142 mg, 0.44 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the reaction stirred for 1 h at 20 °C to give the [3.2.1]-azabicyclo-octane 424 (132 mg, 93%) as yellowish crystals m.p. 174 – 177 °C. δH 8.34 – 8.28 (m, 2H), 7.99 – 7.95 (m, 2H), 3.71 (dd, J = 12.9, 6.3 Hz, 1H, NCH), 3.40 – 3.23 (m, 1H, NCH), 1.96 (d, J = 3.3 Hz, 1H), 1.65 (dd, J = 4.7, 2.6 Hz, 1H), 1.58 – 1.53 (m, 1H), 1.53 – 1.45 (m, 2H, CH2), 1.41 (d, J = 6.6 Hz, 3H, CH3), 1.35 – 1.30 (m, 1H), 1.30 – 1.25 (m, 1H), 1.25 – 1.22 (m, 1H), 0.91 (d, J = 6.4 Hz, 3H, CH3). δC 150.0 (Cq), 140.9 (Cq), 124.0 (2 x CH), 124.1 (2 x CH), 65.3 (NCH), 60.6 (NCH), 38.9 (CH), 37.4 (CH2), 36.8 (CH), 27.6 (CH2), 25.0 (CH3), 19.4 (CH3), 15.6 (CH3). IR (neat) υ/cm⁻¹: 2934, 1525, 1348, 1306, 1157, 1090, 855. HRMS (EI) m/z calculated for C15H20N2O4S [M]+ = 324.1144; found: 324.1142.

Methyl (1-(4-methylcyclohex-3-en-1-yl)ethyl)carbamate 425

By general procedure A, methyl chloroformate (0.38 ml, 5 mmol, 1.0 eq.) was added to the amine 418 (0.70 g, 5.0 mmol, 1.0 eq.) and Et3N (0.62 ml, 5.5 mmol) to give the carbamate 425 (0.76 g, 77%) as a clear oil and as an inseparable 1:1 mixture of diastereoisomers. Diastereoisomer A δH 5.27 (br. s, 1H, =CH), 5.09 – 4.84 (m, 1H, NH), 3.35 – 3.29 (m, 1H, NCH), 3.25 (s, 3H, OCH3), 2.06 – 1.80 (m, 4H, 2 x CH2), 1.79 – 1.60 (m, 1H), 1.53 – 1.42 (m, 1H), 1.31 – 1.08 (m, 4H, 2 x CH2), 1.08 (d, J = 6.7 Hz, 3H, CH3). δC 156.7 (Cq), 133.9 (Cq), 120.0 (=CH), 51.6 (OCH3), 50.7

200
Diastereoisomer B \( \delta_H \) 1.00 (d, \( J = 6.7 \text{ Hz} \), 3H, CH) - only 1 distinct peak. \( \delta_C \) 133.8 (Cq), 50.6 (NCH), 39.3 (CH), 30.2 (CH\(_2\)), 28.0 (CH\(_2\)), 25.7 (CH\(_2\)) - only 7 distinct peaks. The whole sample showed IR (neat) \( \nu/cm^{-1} \): 3337, 2933, 1694, 1531, 1452, 1252, 1105, 1167, 912, 777. HRMS (EI) \( m/z \) calculated for \( C_{11}H_{19}NO_{2} \) [M]\(^{+}\) = 197.1416; found: 197.1407.

**Methyl 1,3-dimethyl-2-azabicyclo[2.2.2]octane-2-carboxylate 426**

![Chemical Structure](image)

By general procedure B, to the carbamate 425 (100 mg, 0.6 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for 1 h at room temperature to give the bicyclo-octane 426 (92 mg, 92%) as a colourless oil. \( \delta_H \) 4.51 - 4.44 (m, 1H, NCH), 3.49 (s, 3H, OCH\(_3\)), 1.72 (dd, \( J = 8.3, 4.0 \text{ Hz} \), 1H), 1.66 - 1.48 (m, 2H, CH\(_2\)), 1.46 - 1.37 (m, 2H, CH\(_2\)), 1.32 - 1.15 (m, 4H, 2 x CH\(_2\)), 1.06 (s, 3H, CH\(_3\)), 0.97 (d, \( J = 6.7 \text{ Hz} \), 3H, CH\(_3\)). \( \delta_C \) 156.8 (C=O), 61.0 (NCq) 56.5 (NCH), 51.7 (OCH\(_3\)), 38.4 (CH\(_2\)), 31.3 (CH), 30.8 (CH\(_3\)), 30.1 (CH\(_2\)), 26.7 (CH\(_2\)), 19.9 (CH\(_3\)), 19.8 (CH\(_2\)). IR (neat) \( \nu/cm^{-1} \): 2928, 2862, 1694, 1528, 1452, 1260, 910, 730. HRMS (EI) \( m/z \) calculated for \( C_{11}H_{19}NO_{2} \) [M]\(^{+}\) = 197. 1416; found: 197. 1411.

**((4-Methylocyclohex-3-en-1-yl)methyl methanesulfonate 428**

![Chemical Structure](image)

To a stirred solution of the alcohol 427 (1.26 g, 10.0 mmol) in pyridine (10 ml), tosyl chloride (1.91 g, 10 mmol) was added. After 2 h the reaction mixture was diluted with H\(_2\)O (10 ml),
acidified to pH 4 with HCl (5%) and extracted with dichloromethane (3 × 15 ml). The combined organic layers were washed with water (2 × 5 ml), brine (2 × 5 ml) then dried and evaporated to give the *tosylate 428* (2.80 g, 100%), which was used without further purification. δ_H 7.69 (d, _J_ = 8.3 Hz, 2H), 7.26 (d, _J_ = 8.3 Hz, 2H), 5.18 (br. s, 1H, =CH), 3.80 (d, _J_ = 6.7 Hz, 2H, OCH_2_), 2.35 (s, 3H, ArCH_3_), 2.12 – 1.98 (m, 1H, CH), 1.98 – 1.81 (m, 3H, CH and CH_2_), 1.80 – 1.62 (m, 2H, CH_2_), 1.56 (s, 3H, CH_3_), 1.37 – 1.21 (m, 1H, CH). δ_C 144.8 (Cq), 133.9 (Cq), 129.8 (2 x CH), 127.8 (2 x CH), 119.0 (=CH), 74.4 (OCH_2_), 36.3 (ArCH_3_), 34.0 (CH), 28.8 (CH_2_), 27.7 (CH_2_), 24.9 (CH_2_), 21.4 (CH_3_).

4-Methyl-N-(4-methylcyclohex-3-en-1-ylmethyl)benzenesulfonamide 429

Potassium hydroxide (0.67 g, 12 mmol) was dissolved in DMF (20 ml) at 120 °C and tosylamide (1.71 g, 10 mmol) was added to the resulting solution. After 0.5 h, a solution of the *tosylate 428* (2.80 g, 10 mmol) in DMF (20 ml) was added. After 1 h the reaction mixture was cooled, diluted with water (10 ml) and extracted with ether (4 × 15 ml). The combined organic layers were washed with water (3 × 5 ml), brine (3 × 5 ml) then dried and evaporated. The crude product was purified by silica gel column chromatography (eluting silica gel with 0 - 100% dichloromethane in hexanes) to give the *sulfonamide 429* (2.48 g, 89%) as a clear oil. δ_H 7.77 – 7.58 (m, 2H), 7.37 – 7.13 (m, 2H), 5.21 – 5.16 (m, 1H, =CH), 5.09 (t, _J_ = 6.2 Hz, 1H, NH), 2.80 – 2.62 (m, 2H, NCH_2_), 2.33 (s, 3H, ArCH_3_), 2.00 – 1.87 (m, 1H), 1.83 – 1.74 (m, 2H, CH_2_), 1.69 – 1.59 (m, 1H), 1.65 – 1.61 (m, 1H, CH), 1.60 – 1.52 (m, 1H), 1.52 – 1.48 (m, 3H, CH_3_), 1.21 – 1.04 (m, 1H). δ_C 143.2 (Cq), 137.3 (Cq), 134.0 (Cq), 129.7 (2 x CH), 127.0 (2 x CH), 119.7 (=CH), 48.4 (NCH_2_), 33.5 (CH), 29.2 (2 x CH_2_), 27.8 (CH_2_), 23.4 (CH_3_), 21.5 (CH_3_). IR (neat) _υ_/cm⁻¹: 3269, 2924, 1437, 1323, 1160, 1096, 814. HRMS (El) _m/z_ calculated for C_15_ H_21_ NO_2_ S [M]^+ = 279.1293; found: 279.1293.
1-Methyl-2-tosyl-2-azabicyclo[2.2.2]octane 430

By general procedure B, to sulfonamide 429 (180 mg, 0.64 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added, the reaction stirred for 3 h at 20 °C to give the azabicyclo-octane 430 (169 mg, 94%) as a colourless crystals, m.p. 135 – 138 °C. δH 7.71 – 7.58 (m, 2H), 7.20 (d, J = 7.1 Hz, 2H), 3.52 (d, J = 2.5 Hz, 2H, NCH2), 2.35 (s, 3H, ArCH3), 1.83 (dd, J = 5.9, 3.0 Hz, 1H, CH), 1.70 – 1.60 (m, 2H, CH2), 1.53 – 1.40 (m, 4H, 2 x CH2), 1.34 – 1.25 (m, 2H, CH2), 1.23 (s, 3H, CH3). δC 142.1 (Cq), 140.3 (Cq), 129.4 (2 x CH), 127.0 (2 x CH), 54.6 (Cq), 52.7 (CH2N), 34.7 (2 x CH2), 26.4 (CH3), 25.9 (CH), 24.6 (2 x CH2), 21.5 (CH3). IR (neat) ο/cm⁻¹: 2920, 1454, 1329, 1158, 1094, 816. HRMS (EI) m/z calculated for C15H21NO2S [M]+ = 279.1293; found: 279.1292.

Cyclohex-3-en-1-ylmethyl methanesulfonate 433

To a stirred solution of the alcohol 432 (1.12 g, 10.0 mmol) in pyridine (10 ml), methanesulfonyl chloride (1.14 g, 10 mmol) was added dropwise. After 2 h the reaction mixture was diluted with water (10 ml), acidified to pH 4 with HCl (5%) and extracted with dichloromethane (3 × 15 ml). The combined organic layers were washed with water (2 × 5 ml), brine (2 × 5 ml), then dried and evaporated to give the mesylate 433 (1.90 g, 100%). The product was used directly without further purification. δH 5.71 – 5.46 (m, 2H, 2 x =CH), 4.04 (d, J = 6.6 Hz, 2H, OCH2), 2.95 (s, 3H, Ms-CH3), 2.04 – 1.98 (m, 4H, 2 x CH2), 1.81 – 1.70 (m, 2H, CH2), 1.41 – 1.23 (m, 1H, CH). δC 127.1 (=CH), 125.0 (=CH), 74.0 (OCH2), 37.0 (CH), 33.3 (Ms-CH3), 27.5 (CH2), 25.2 (CH2), 24.0 (CH2).
Potassium hydroxide (0.67 g, 12 mmol) was dissolved in DMF (20 ml) at 120 °C and tosylamide (2.00 g, 12 mmol) was added to the resulting solution. After 0.5 h, a solution of the foregoing mesylate 433 (1.90 g, 10 mmol) in DMF (20 ml) was added. After 1 h, the reaction mixture was cooled, diluted with water (10 ml) and extracted with ether (4 × 15 ml). The combined organic layers were washed with water (3 × 5 ml), brine (3 × 5 ml) then dried and evaporated. The crude product was purified by silica gel column chromatography (eluting silica gel with 0 - 100% dichloromethane in hexanes) to give the sulfonamide 434 (2.30 g, 88%) as a clear oil. δH 7.78 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 5.63 – 5.58 (m, 2H, NCH2), 5.18 (br. s, 1H, NH), 2.83 (t, J = 6.2 Hz, 2H, CH2), 2.43 (s, 3H, ArCH3), 2.15 – 2.10 (m, 1H, CH), 2.10 – 1.89 (m, 2H, CH2), 1.83 – 1.50 (m, 3H, CH and CH2), 1.33 – 1.03 (m, 1H, CH). δC 143.3 (Cq), 137.1 (Cq), 129.7 (2 x CH), 127.0 (2 x CH), 125.4 (2 CH), 48.5 (NCH2), 33.7 (CH), 29.1 (CH2), 26.0 (CH2), 24.3 (CH2), 21.4 (CH3). IR (neat) ν/cm⁻¹: 3281, 2916, 1431, 1306, 1094, 814. HRMS (EI) m/z calculated for C14H19NO2S [M]+ = 265.1137; found: 265.1135.

6-Tosyl-6-azabicyclo[3.2.1]octane 435

By general procedure B, to sulfonamide 434 (284 mg, 1.07 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (50 mg, 0.5 mmol) was added and the resulting mixture stirred for 20 h at 20 °C. The crude product was purified by silica gel column chromatography (eluting silica gel with 0 - 100% dichloromethane in hexanes) to give the azabicyclo-octane 435.
(207 mg, 73%) as a yellow oil. \( \delta_H \) 7.65 (d, \( J = 8.2 \) Hz, 2H), 7.22 (d, \( J = 8.2 \) Hz, 2H), 4.09 – 3.98 (m, 1H, NCH), 3.21 (dd, \( J = 9.4 \), 5.4 Hz, 1H, NCH\(_A\)H\(_B\)), 3.18 (dd, \( J = 9.4 \), 2.4 Hz, 1H, NCH\(_A\)H\(_B\)), 2.35 (s, 3H, ArCH\(_3\)), 2.28 (br. s, 1H, CH), 1.83 – 1.77 (m, 1H, CH), 1.68 – 1.57 (m, 1H, CH), 1.57 – 1.47 (m, 1H, CH), 1.47 – 1.35 (m, 1H, CH), 1.30 – 1.25 (m, 1H, CH), 1.22 – 1.10 (m, 2H, CH\(_2\)), 1.18 (d, \( J = 5.4 \) Hz, 1H). \( \delta_C \) 142.9 (Cq), 136.3 (Cq), 129.6 (2 x CH), 127.1 (2 x CH), 58.2 (NCH), 52.3 (NCH\(_2\)), 37.4 (CH\(_2\)), 35.1 (CH), 32.0 (CH\(_2\)), 30.2 (CH\(_2\)), 21.5 (ArCH\(_3\)), 18.5 (CH\(_2\)). IR (neat) \( \nu/cm^{-1} \): 2934, 1454, 1331, 1158, 1091, 814. HRMS (EI) \( m/z \) calculated for C\(_{14}\)H\(_{19}\)NO\(_2\)S \([M]^+\) = 265.1137; found: 265.1138.

(1S,4S,5S)-4-Iodo-6-tosyl-6-azabicyclo[3.2.1]octane 437

\[
\begin{array}{c}
\text{(NHTs)} \\
\text{434} \xrightarrow{3 \text{ eq. } I_2, \text{ DCM}} \\
\text{T}^8 \\
\text{436}
\end{array}
\]

To a stirred solution of the sulfonamide 434 (240 mg, 0.9 mmol, 1.0 eq.) in dry dichloromethane (20 ml) was added iodine (0.69 g, 2.7 mmol, 3.0 eq.) at 0 \( ^\circ \)C. The reaction was then stirred without cooling for 36 h. The mixture was then quenched with saturated aqueous sodium thiosulfate (10 ml) and the resulting mixture extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried, filtered and the solvent evaporated to yield the crude product, which was purified by column chromatography (eluting silica gel with 0 - 100% dichloromethane in hexanes) to give the iodo-azabicyclo-octane 436 (0.32 g, 91%) as sharp, colourless crystals m.p. 116 – 118 \( ^\circ \)C; \( \delta_H \) 7.47 (d, \( J = 8.0 \) Hz, 2H), 7.09 (d, \( J = 8.0 \) Hz, 2H), 4.27 (t, \( J = 4.2 \) Hz, 1H, NCH), 3.93 (t, \( J = 5.0 \) Hz, 1H, CHI), 3.06 (d, \( J = 9.7 \) Hz, 1H, NCH\(_A\)H\(_B\)), 3.03 – 2.98 (m, 1H, NCH\(_A\)H\(_B\)), 2.20 (s, 3H, ArCH\(_3\)), 2.13 – 2.08 (m, 2H, CH\(_2\)), 2.08 – 2.03 (m, 1H, CH), 1.68 (dd, \( J = 15.9 \), 5.2 Hz, 1H, CH), 1.57 (td, \( J = 13.5 \), 5.3 Hz, 1H, CH), 1.29 – 1.22 (m, 1H, CH), 0.90 (dt, \( J = 11.8 \), 5.2 Hz, 1H, CH). \( \delta_C \) 143.5 (Cq), 135.4 (Cq), 129.8 (2 x CH), 127.0 (2 x CH), 62.6 (NCH), 52.9 (NCH\(_2\)), 34.4
(CH), 34.2 (CH₂), 31.0 (CH), 29.6 (CH₂), 26.1 (CH₂), 21.5 (ArCH₃). IR (neat) v/cm⁻¹: 2945, 1597, 1445, 1342, 1159, 1024, 980, 903, 814, 667. HRMS (EI) m/z calculated for C₁₄H₁₈NO₂S [M]+ = 391.0103; found: 391.0093.

6-Tosyl-6-azabicyclo[3.2.1]octane 435

The iodobicyclo-octane 436 (70 mg, 0.18 mmol) was dissolved in dry methanol (5 ml). Triethylamine (0.2 ml) was added followed by 10% palladium on active carbon (50 mg). The resulting mixture was stirred under a hydrogen atmosphere for 20 h, then filtered and concentrated in vacuo. The residue was dissolved in dichloromethane (10 ml) and washed with saturated aqueous potassium carbonate (5 ml) before being dried, filtered and evaporated to yield the azabicyclo-octane 435 (43 mg, 90%) as a colourless oil, which showed the same analytical data as the sample obtained from the acid catalysed cyclisation above (p. 204).

1-(4-(4-Methylpent-3-en-1-yl)cyclohex-3-en-1-yl)ethanone 439

Myrcene 437 (1.36 g, 10 mmol, 1.0 eq) and methyl vinyl ketone 438 (0.70 g, 10 mmol, 1.0 eq) was applied to the usual chromatographic grade silica gel (1.50 g). The mixture was heated at 50 °C for 5 h. The silica was then washed with ether (3 x 10 ml) and the combined filtrates concentrated to give the ketone 439 (1.66 g, 80%) as a clear oil. All data obtained were in accordance with those previously reported in the literature: δH 5.20 (d, J = 3.7 Hz, 1H, =CH), 4.92 (tdd, J = 6.9, 2.6, 1.3 Hz, 1H, =CH), 2.41 – 2.30 (m, 1H, CH), 2.00 (s, 3H, COCH₃), 1.91 – 1.78 (m, 8H, 4 x CH₂), 1.21 – 1.25 (m, 2H, CH₂), 1.51 (s, 3H, CH₃), 1.43 (s, 3H, CH₃).
(E)-1-(4-(4-Methylpent-3-en-1-yl)cyclohex-3-en-1-yl)ethanone oxime 440

\[
\text{\begin{align*}
\text{Ketone} & \quad \text{NH}_2\text{OH}\cdot\text{HCl} \quad \text{MeOH/H}_2\text{O} \\
\text{439} & \quad \text{440} \\
\text{96\%}
\end{align*}}
\]

To a solution of ketone 440 (1.66 g, 8 mmol, 1.0 eq) and hydroxylamine hydrochloride (0.70 g, 10 mmol, 1.25 eq) in methanol (30 ml) was added sodium acetate (1.0 g, 12.2 mmol) in one portion. The reaction mixture was heated at 40 °C for 2 h and then concentrated on a rotary evaporator. The residue was partitioned between ether (50 ml) and water (10 ml). The separated organic layer was dried. Evaporation provided the oxime 440 (1.70 g, 96%) as a colourless liquid which was used directly in the next step. \(\delta_H 9.50 - 9.25 (br. s, 1H, NOH), 5.33 (br. s, 1H, =CH), 5.02 (tdd, J = 6.9, 2.6, 1.3 Hz, 1H, =CH), 2.39 - 2.24 (m, 1H, CH), 2.03 - 1.91 (m, 8H, 4 x CH\text{2}), 1.91 - 1.85 (m, 2H, CH\text{2}), 1.81 (s, 3H, CH\text{3}), 1.61 (s, 3H, CH\text{3}), 1.53 (s, 3H, CH\text{3}).

1-(4-(4-Methylpent-3-en-1-yl)cyclohex-3-en-1-yl)ethanamine 441

\[
\text{\begin{align*}
\text{Oxime} & \quad \text{LiAlH}_4 \\
\text{440} & \quad \text{441} \\
\text{THF} & \quad \text{88\%}
\end{align*}}
\]

According to general procedure C, the oxime 440 (1.70 g, 7.7 mmol, 1.0 eq.) was reduced using lithium aluminium hydride (0.38 g, 10 mmol, 1.3 eq.) to give the amine 441 (1.40 g, 88%) as a yellow oil as an inseparable 1:1 mixture of diastereoisomers, which was used directly in the next step. Diastereoisomer A \(\delta_H 5.31 (app. br. s, 1H, =CH), 5.05 - 4.98 (m, 1H, =CH), 2.74 - 2.66 (m, 1H, NCH), 2.00 (dd, J = 18.0, 11.5 Hz, 2H, CH\text{2}), 1.90 (dt, J = 14.5, 8.9 Hz, 2H, CH\text{2}), 1.68 (dd, J = 10.6, 5.7, Hz, 2H, CH\text{2}), 1.61 (s, 3H, CH\text{3}), 1.53 (s, 3H, CH\text{3}), 1.38 - 1.22 (m, 4H, 2 x CH\text{2}), 1.22 - 1.08 (m, 1H, CH), 0.98 (d, J = 3.2 Hz, 3H, CH\text{3}). Diastereoisomer B \(\delta_H 2.66 - 2.56 (m, 1H, NCH), 1.00 - 0.99 (m, 1H, CH), 1.01 (d, J = 3.2 Hz, 3H, CH\text{3}) - only 3 distinct peaks.
Methyl (1-(4-(4-methylpent-3-en-1-yl)cyclohex-3-en-1-yl)ethyl)carbamate 442

By general procedure A, methyl chloroformate (0.76 ml, 10 mmol, 1.5 eq.) was added to the amine 441 (1.40 g, 6.8 mmol, 1.0 eq.) and Et₃N (1.2 ml, 11 mmol, 1.6 eq.) to give the carbamate 442 (1.47 g, 82%) as a clear oil as an inseparable 1:1 mixture of diastereoisomers.

Diastereoisomer A δH 5.28 (d, J = 12.2 Hz, 1H, =CH), 5.01 (t, J = 6.9 Hz, 1H, =CH), 4.61 (d, J = 8.1 Hz, 1H, NH), 3.65 – 3.59 (m, 1H, NCH), 3.58 (s, 3H, OCH₃), 2.05 – 1.94 (m, 3H, CH and CH₂), 1.93 – 1.84 (m, 3H, CH and CH₂), 1.67 (dd, J = 21.6, 8.2 Hz, 2H, CH₂), 1.60 (s, 3H, CH₃), 1.52 (s, 3H, CH₃), 1.27 – 1.09 (m, 1H, CH), 1.08 – 1.05 (d, J = 4.1 Hz, 3H, CH₃). δC 156.6 (CO₂), 137.6 (Cq), 131.3 (Cq), 124.3 (=CH), 119.6 (=CH), 53.4 (OCH₃), 50.8 (NCH), 39.6 (CH), 37.7 (CH₂), 28.6 (CH₂), 28.4 (CH₂), 27.6 (CH₂), 25.6 (CH₃), 24.8 (CH₂), 17.6 (CH₃).

Diastereoisomer B δH 1.04 (d, J = 4.1 Hz, 3H, CH₃) only 1 distinct peak. δC 137.8 (Cq), 120.0 (=CH), 120.6 (=CH), 120.5 (=CH), 51.8 (OCH₃), 50.7 (NCH), 39.5 (CH), 37.5 (CH₂), 28.2 (CH₂) - only 9 distinct peaks.

Methyl ([(S)-1-[(S)-8,8-dimethyl-1,2,3,4,5,6,7,8-octahydropyrene-2-yl]ethyl)carbamate 443

By general procedure B, to the carbamate 442 (160 mg, 0.6 mmol) in dry dichloromethane (10 ml) under nitrogen, concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for 0.5 h at room temperature to give the carbamate 443 (157 mg, 98%) as a
colourless oil as an inseparable 1:1 mixture of diastereoisomers; $\delta_H$ 4.58 (d, $J = 7.5$ Hz, 1H, NH), 3.67 – 3.60 (m, 1H, NCH), 3.64 (s, 3H, OCH$_3$), 1.98 – 1.89 (m, 2H, CH$_2$), 1.87 – 1.78 (m, 2H, CH$_2$), 1.75 – 1.63 (m, 2H, CH$_2$), 1.63 – 1.53 (m, 2H, CH$_2$), 1.51 – 1.47 (m, 1H, CH), 1.17 – 1.06 (m, 4H, 2 x CH$_2$), 0.99 (s, 6H, 2 x CH$_3$), 0.97 (d, $J = 2.1$ Hz, 3H, CH$_3$). $\delta_C$ 156.6 (CO$_2$), 133.7 (Cq), 127.1 (Cq), 53.4 (OCH$_3$), 50.8 (NCH), 40.4 (CH$_2$), 40.2 (CH$_2$), 39.7 (CH), 28.3 (2 x CH$_2$), 28.2 (2 x CH$_2$), 27.3 (CH$_3$), 27.1 (CH$_3$), 19.30 (CH$_3$).

2-(2,2,3-Trimethylcyclopent-3-en-1-yl)acetaldehyde oxime 448

![Chemical structure](image)

To a solution of the aldehyde 447 (1.50 g, 10 mmol, 1.0 eq) and hydroxylamine hydrochloride (1.40 g, 20 mmol, 2 eq) in ethanol (30 ml) was added sodium acetate (1.0 g, 12.2 mmol). The reaction mixture was heated at 40 °C for 3 h and then concentrated on a rotary evaporator. The residue was partitioned between ether (50 ml) and water (10 ml). The separated organic layer was dried and evaporated to give the oxime 448 (1.53 g, 92%) as a colourless liquid, which was used directly in the next step. All data obtained were in accordance with those previously reported in the literature: $\delta_H$ 9.72 (s, 1H, NOH), 5.16 (t, $J = 1.3$ Hz, 1H, =CH), 2.46 (ddd, $J = 15.5$, 4.3, 2.0 Hz, 1H, CH), 2.37 – 2.27 (m, 2H, CH$_2$), 2.21 (ddddd, $J = 12.1$, 10.2, 6.0, 3.2 Hz, 1H, CH), 1.86 – 1.78 (m, 1H, CH), 1.54 (d, $J = 1.6$ Hz, 3H, CH$_3$), 0.93 (s, 3H, CH$_3$), 0.72 (s, 3H, CH$_3$). $\delta_C$ 202.7 (C=N), 147.9 (Cq), 121.53 (CH), 46.9 (Cq), 45.1 (NCH$_2$), 44.1 (CH), 35.5 (CH$_2$), 25.6 (CH$_3$), 20.1 (CH$_3$), 12.5 (CH$_3$).
2-(2,2,3-Trimethylcyclopent-3-en-1-yl)ethanamine 449

Following general procedure C, the oxime 448 (1.50 g, 9.0 mmol) was reduced using lithium aluminium hydride (0.38 g, 10 mmol) to give the amine 449 as a clear oil (1.10 g, 80%). All data obtained were in accordance with those reported for a sample of the amine prepared by reduction of the nitrile 456.

Methyl (2-(2,2,3-trimethylcyclopent-3-en-1-yl)ethyl)carbamate 450

By general procedure A, methyl chloroformate (0.7 ml, 8.9 mmol) was added to the amine 449 (1.10 g, 7.2 mmol) and Et$_3$N (1 ml, 8.8 mmol) at 0°C. The mixture was then stirred for 1 h at room temperature to give the carbamate 450 (1.39 g, 91%) as a colourless oil. $\delta^H$ 5.12 (s, 1H,=-CH), 4.82 (br. s, 1H, NH), 3.56 (s, 3H, OCH$_3$), 3.21 – 3.19 (m, 1H, CH), 3.15 – 3.10 (m, 1H, CH), 2.25 – 2.19 (m, 1H, CH), 1.84 – 1.78 (m, 1H, CH), 1.73 – 1.70 (m, 1H, CH), 1.62 – 1.60 (m, 1H, CH), 1.51 (s, 3H, CH$_3$), 1.41 (dd, $J$ = 11.2, 10.1 Hz, 1H), 0.93 (s, 3H, CH$_3$), 0.69 (s, 3H, CH$_3$). $\delta^C$ 157.1 (C=O), 148.4 (Cq), 121.5 (=CH), 51.8 (OCH$_3$), 47.4 (CH), 46.8 (Cq), 40.6 (NCH$_2$), 35.4 (CH$_2$), 30.5 (CH$_2$), 25.7 (CH$_3$), 19.6 (CH$_3$), 12.5 (CH$_3$). IR (neat) u/cm$^{-1}$: 3333, 2955, 1697, 1526, 1445, 1377, 1256, 1194, 912. HRMS (EI) $m/z$ calculated for C$_{12}$H$_{21}$NO$_2$ [M]$^+$ = 211.1572; found: 211.1575.
Methyl 6,6,6a-trimethylhexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate 451

To a stirred solution of the carbamate 450 (211 mg, 1 mmol) in dry dichromethane (10 ml) under nitrogen, cooled in an ice-water bath, was added triflic acid (150 mg, 1 mmol). The resulting mixture stirred was stirred at 20 °C for 4 hours to give the bicycle 451 (207 mg, 98%) as a colourless oil (3:1).

Major product : \( \delta^1H \) 3.56 (s, 3H, OCH\(_3\)), 3.41 – 3.28 (m, 2H, NCH\(_2\)), 2.38 – 2.29 (m, 2H, CH\(_2\)), 1.89 – 1.82 (m, 2H, CH\(_2\)), 1.78 – 1.66 (m, 1H, CH), 1.45 (ddd, \( J = 8.7, 7.2, 4.5 \) Hz, 2H, CH\(_2\)), 1.35 (s, 3H, CH\(_3\)), 1.07 (s, 3H, CH\(_3\)), 0.88 s, 3H, CH\(_3\)). \( \delta^1C \) 156.8 (C=O), 74.8 (Cq), 54.1 (CH), 51.8 (OCH\(_3\)), 49.1 (NCH\(_2\)), 46.0 (Cq), 43.2 (CH\(_2\)), 29.9 (CH\(_2\)), 28.8 (CH\(_2\)), 25.9 (CH\(_3\)), 24.8 (CH\(_3\)), 22.2 (CH\(_3\)).

Minor product : \( \delta^1H \) 3.74 – 3.68 (m, 2H, NCH\(_2\)), 3.60 (s, 3H, OCH\(_3\)), 1.25 (s, 3H, CH\(_3\)), 0.98 (s, 3H, CH\(_3\)), 0.82 (s, 3H, CH\(_3\)). \( \delta^1C \) 158.8 (C=O), 74.0 (Cq), 55.8 (CH), 51.5 (OCH\(_3\)), 49.9 (NCH\(_2\)), 46.9 (Cq), 38.8 (CH\(_2\)), 32.3 (CH\(_2\)), 28.5 (CH\(_2\)), 26.4 (CH\(_3\)), 25.0 (CH\(_3\)), 23.6 (CH\(_3\)).

IR (neat) \( \nu/cm^{-1} \): 2957, 2868, 1700, 1530, 1445, 1255. HRMS (APCI) \( m/z \) calculated for C\(_{12}\)H\(_{21}\)NO\(_2\) [M-H]\(^+\) = 210.1494; found: 210.1497.

Methyl (2-(2,3,3-trimethylcyclopent-1-en-1-yl)ethyl)carbamate 452

To a stirred solution of the carbamate 450 (211 mg, 1 mmol) in dry toluene (10 ml) under nitrogen, cooled in an ice-water bath, was added triflic acid (76 mg, 0.5 mmol, 0.5 eq). The resulting mixture stirred was stirred at 80 °C for 2 hours to give the carbamate 452 (203 mg, 96%)
as a colourless oil. $\delta_H$ 4.56 (s, 1H, NH), 3.57 (s, 3H, OCH$_3$), 3.17 – 3.12 (m, 2H, NCH$_2$), 2.19 – 2.2 (m, 4H, 2 x CH$_2$), 1.54 (t, $J = 3.8$ Hz, 2H, CH$_2$), 1.43 (s, 3H, CH$_3$), 0.89 (s, 6H, 2 x CH$_3$). $\delta_C$ 157.0 (C=O), 142.1 (Cq), 129.8 (Cq), 51.9 (OCH$_3$), 46.9 (Cq), 49.3 (NCH$_2$), 38.8 (CH$_2$), 32.3 (CH$_2$), 29.2 (CH$_2$), 26.4 (3 x CH$_3$).

By general procedure B, to the carbamate 450 (211 mg, 1 mmol) in dry dichloromethane (10 ml) concentrated sulfuric acid (4 drops) was added and the resulting mixture was stirred for 4 h at 20°C to give the bicycle 451 (96 mg, 45%) and the carbamate 452 (92 mg, 44%) 3:2 as colourless oils, which were purified by column chromatography (eluting silca gel with 0 - 100% dichloromethane in hexanes). All data obtained were in accordance with those reported above.

**((1S,4R)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one oxime 454**

To a solution of camphor 453 (3.10 g, 20 mmol, 1.0 eq) and hydroxylamine hydrochloride (2.09 g, 30 mmol, 1.5 eq) in ethanol and water (1:1, 30 ml) was added sodium acetate (1.0 g, 12.2 mmol). The reaction mixture was heated at 40 °C for 18 h and then concentrated on a rotary evaporator. The residue was partitioned between ether (50 ml) and water (10 ml). The separated organic layer was dried and evaporated to give the oxime 454 (3.10 g, 93%) as a colourless liquid. All data obtained were in accordance with those previously reported in the literature: $\delta_H$ 9.62 (s, 1H, NOH), 2.51 – 2.44 (m, 1H, CH), 2.00 – 1.94 (m, 1H, CH), 1.83 (t, $J = 4.4$ Hz, 1H), 1.74 (ddd, $J = 11.5$, 7.6, 4.1 Hz, 1H), 1.66 – 1.58 (m, 1H, CH), 1.42 – 1.35 (m, 1H, CH), 1.15 (ddd, $J = 9.4$, 8.1, 4.2 Hz, 1H), 0.93 (s, 3H, CH$_3$), 0.83 (s, 3H, CH$_3$), 0.72 (s, 3H, CH$_3$). $\delta_C$ 169.6 (C=N, Cq), 51.8
(Cq), 48.3 (Cq), 43.8 (CH), 33.1 (CH2), 32.7 (CH2), 27.3 (CH2), 19.8 (CH3), 18.5 (CH3), 11.1
(CH3). IR (neat) ν/cm⁻¹: 3298, 2959, 2876, 1740, 1448, 907. HRMS (El) m/z calculated for
C10H17NO [M]+ = 167.1310; found: 167.1311.

2-(2,2,3-Trimethylcyclopent-3-en-1-yl)acetonitrile 456

2-(2,2-Dimethyl-3-methylene cyclopentyl)acetonitrile 457

The oxime 454 (2.80 g, 16.7 mmol) was dissolved in dry dichloromethane (30 ml) and the
solution cooled in ice-water. Triethylamine (2.0 ml, 20 mmol) and tosyl chloride (3.81 g, 20
mmol) were added sequentially. The resulting mixture was allowed to warm to room temperature
overnight then quenched with water (20 ml). The separated aqueous phase was extracted with
dichloromethane (3 x 20 ml). The combined organic extracts were washed with brine (5 ml),
dried, filtered and concentrated to yield the crude nitriles which were purified by column
chromatography (eluting silica gel with 0 - 100% dichloromethane in hexanes) to give an
inseparable mixture of the nitriles 456 and 457 (1.80 g, 72%) as a colourless oil. All data obtained
were in accordance with those previously reported in the literature:36 nitrile 456 δH 5.23 (t, J = 1.2
Hz, 1H, =CH), 2.44 – 2.37 (m, 1H, CH), 2.35 – 2.27 (m, 1H, CH), 2.22 – 2.11 (m, 1H, CH), 2.04
– 1.97 (m, 1H, CH), 1.60 (s, 3H, CH3), 1.06 (s, 3H, CH3), 0.84 (s, 3H, CH3). δC 147.4 (Cq), 121.1
(=CH), 119.3 (CN), 47.5 (Cq), 46.2 (CH), 37.0 (CH2), 22.9 (CH3), 19.8 (CH3), 17.9 (CH2), 12.4
(CH3).

nitriles 457 (<5%) δH 4.91 (d, J = 12.2 Hz, 1H, =CHA), 4.85 – 4.76 (m, 1H, =CHB), 0.98 (s, 3H,
CH3), 0.89 (s, 3H, CH3). δC 161.2 (=Cq), 104.1 (=CH2), 118.3 (CN), 46.5 (Cq), 45.2 (CH), 38.7
(CH2), 28.8 (CH2), 21.8 (CH2), 19.7 (CH3), 12.0 (CH3).
2-(2,2,3-Trimethylcyclopent-3-en-1-yl)ethanamine 458 and 2-(2,2-dimethyl-3-methylenecyclopentyl)ethanamine 259

Following general procedure C, the nitriles 256 and 457 (1.80 g, 12 mmol, 1.0 eq.) was reduced using lithium aluminium hydride (0.57 g, 15 mmol, 1.25 eq.) to give the amines 458 and 459 (1.40 g, 76%) as a yellow oil, which was used directly in the next step. All data obtained were in accordance with those previously reported in the literature: amine 258 δ_H 5.14 (t, J = 1.3 Hz, 1H, =CH), 2.73 – 2.65 (m, 1H, CH), 2.63 – 2.54 (m, 1H, CH), 2.25 – 2.14 (m, 1H, CH), 1.80 – 1.64 (m, 2H, CH_2), 1.53 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.69 (s, 3H, CH_3). δ_C 151.0 (Cq), 121.6 (=CH), 48.0 (CH), 46.8 (Cq), 41.5 (NCH_2), 35.5 (CH_2), 34.3 (CH_2), 25.8 (CH_3), 19.8 (CH_3), 12.5 (CH_3). Amine 259 δ_H 4.77 – 4.66 (m, 1H, =CH_2), 0.98 (s, 3H, CH_3), 0.97 (s, 3H, CH_3) only 3 distinct peaks.

4-Methyl-N-(2-(2,2,3-trimethylcyclopent-3-en-1-yl)ethyl)benzenesulfonamide 460

By general procedure A, tosyl chloride (2.10 g, 11 mmol) was added to the above amine (1.40 g, 9.1 mmol) and Et_3N (1.5 ml, 12.1 mmol) at 0 °C. The mixture was then stirred for 1 h at room temperature to give the sulfonamide 460 (2.58 g, 92%) as a colourless oil. All data obtained were in accordance with those previously reported in the literature: δ_H 7.68 (d, J = 7.6 Hz, 2H), 7.24 (d, J = 7.6 Hz, 2H), 5.10 (s, 1H,=CH), 4.28 (s, 1H, NH), 3.05 – 2.91 (m, 1H, CH), 2.89 – 2.75 (m, 1H, CH), 2.36 (s, 3H, Ar-CH_3), 2.15 – 2.09 (m, 1H, CH), 1.74 – 1.58 (m, H, CH), 1.51 (s, 3H, CH_3), 1.34 (dd, J = 11.7, 10.1 Hz, 1H), 0.83 (s, 3H, CH_3), 0.62 (s, 3H, CH_3). δ_C 148.4 (Cq), 143.4
(Cq), 137.4 (Cq), 129.6 (2 x CH), 127.2 (2 x CH), 121.6 (=CH), 48.0 (CH), 46.8 (Cq), 42.5 (NCH₂), 35.5 (CH₂), 30.3 (CH₂), 25.8 (CH₃), 21.4 (CH₃), 19.8 (CH₃), 12.5 (CH₃).

IR (neat) ν/cm⁻¹: 3277, 2955, 2930, 2866, 1435, 1323, 1092, 910, 813. HRMS (EI) m/z calculated for C₁₇H₂₅NO₂S [M]⁺ = 307.1606; found: 307.1599.

6,6,6a-Trimethyl-1-tosyloctahydrocyclopenta[b]pyrrole 457

By general procedure B, to the sulfonylamine 456 (185 mg, 0.6 mmol) in dry dichloromethane (10 ml) concentrated sulfuric acid (3 drops) was added and the resulting mixture was stirred for 3 h at 0 °C to give sulfonylamine 462 as a mixture 1:1 with azabicyclo-octane 457 (86 mg, 46%), which separated after crystallization in dichloromethane/hexanes as colourless crystals m.p. 124 – 126 °C.  δ₁H 7.68 – 7.64 (d, J = 7.9 Hz, 2H), 7.25 (d, J = 7.9 Hz, 2H), 3.19 – 3.03 (m, 2H, NCH₂), 2.44 (dt, J = 14.8, 5.7 Hz, 1H), 2.36 (s, 3H, Ar-CH₃), 2.18 – 2.06 (m, 2H, CH₂), 1.94 – 1.83 (m, 4H, 2 x CH₂), 1.32 (s, 3H, CH₃), 1.18 (s, 3H, CH₃), 0.87 (s, 3H, CH₃).  δ₁C 143.4 (Cq), 139.2 (Cq), 129.8 (2 x CH), 127.1 (2 x CH), 53.7 (NCq), 39.2 (NCH₂), 33.3 (CH₂), 27.3 (CH₂), 27.0 (CH₂), 21.5 (CH₃), 19.7 (CH₃), 17.3 (CH₃), 15.3 (CH₃).  IR (neat) ν/cm⁻¹: 2951, 2926, 1655, 1329, 1094, 910. HRMS (EI) m/z calculated for C₁₇H₂₅NO₂S [M]⁺ = 307.1606; found: 307.1599.

4-Methyl-N-(2-(2,3,3-trimethylcyclopent-1-en-1-yl)ethyl)benzenesulfonamide 462

By general procedure B, to the sulfonamide 460 (260 mg, 0.85 mmol) in dry dichloromethane (10 ml) concentrated sulfuric acid (3 drops) was added and the resulting mixture was stirred for 4 h at 20 °C to give the sulfonamide 462 (252 mg, 97%) as a colourless oil.  δ₁H 7.62 – 7.56 (d, J = 8.1 Hz,
2H), 7.15 (d, \( J = 8.1 \) Hz, 1H), 4.17 (t, \( J = 5.7 \) Hz, 1H, NH), 2.88 – 2.74 (m, 2H, NCH\(_2\)), 2.28 (s, 3H, Ar-CH\(_3\)), 2.07 – 1.96 (m, 2H, CH\(_2\)), 1.84 – 1.80 (m, 2H, CH\(_2\)), 1.41 – 1.34 (m, 2H, CH\(_2\)), 1.30 (s, 3H, CH\(_3\)), 0.79 (s, 6H, 2 x CH\(_3\))

\((1S,4R)-1,7,7\text{-Trime}thylbicyclo[2.2.1]heptan-2-one O-ethoxycarbony1 oxime 464\textsuperscript{38}\)

![Diagram](image)

The oxime 454 (3.2 g, 19 mmol) was dissolved in dry dichloromethane (40 ml) and the solution cooled in ice-water to 0 °C. Triethylamine (2 ml, 20 mmol) and ethyl chloroformate (2.17 g, 20 mmol) were added sequentially. The resulting mixture was allowed to warm to room temperature over night then quenched with water (20 ml). The aqueous phase was extracted with dichloromethane (3 x 20 ml). The combined organic extracts were washed with brine (5 ml), dried, filtered and concentrated to yield the oxime ethyl carbonate 464 (4.50 g, 99%) as a colourless oil. \( \delta \)\(^H\) 4.21 (q, \( J = 7.1 \) Hz, 2H, OCH\(_2\)), 2.61 – 2.54 (m, 1H, CH), 2.11 – 2.09 (m, 1H, CH), 1.86 (t, \( J = 4.4 \) Hz, 1H), 1.74 (ddd, \( J = 11.5, 7.6, 4.1 \) Hz, 1H), 1.66 – 1.58 (m, 1H, CH), 1.42 – 1.35 (m, 1H, CH), 1.29 (t, \( J = 7.1 \) Hz, 3H, CH\(_3\)), 1.20 (ddd, \( J = 9.4, 8.1, 4.2 \) Hz, 1H), 0.93 (s, 3H, CH\(_3\)), 0.84 (s, 3H, CH\(_3\)), 0.72 (s, 3H, CH\(_3\)). \( \delta \)\(^C\) 177.2 (C=N, Cq), 154.2 (C=O), 64.3 (OCH\(_2\)), 53.0 (Cq), 48.6 (Cq), 43.3 (CH), 34.7 (CH\(_2\)), 32.4 (CH\(_2\)), 27.0 (CH\(_2\)), 19.4 (CH\(_3\)), 18.4 (CH\(_3\)), 14.3 (CH\(_3\)), 11.1 (CH\(_3\)). IR (neat) \( \nu/cm^{-1} \): 2961, 2876, 1770, 1447, 1361, 997, 984.

\(2-\text{(2,2,4-Trimethylcyclopent-3-en-1-yl)acetonitrile 465}\textsuperscript{38}\)

![Diagram](image)

The oxime carbonate 464 (4.50 g, 18.8 mmol) was treated with boron trifluoride etherate (2 M solution, 10 ml, 20 mmol) under nitrogen at ice temperature. The resulting solution is stirred for 6
h at room temperature and then quenched by the addition of water (20 ml), then the solution was extracted with dichloromethane (3 x 20 ml). The combined extracts were dried and concentrated to give the nitrile 465 (2.67 g, 95%) as a clear oil, which was used directly in the next step. All data obtained were in accordance with those previously reported in the literature: \( \delta^H \) 5.11 (s, 1H, =CH), 2.40 – 2.33 (m, 1H, CH), 2.32 – 2.26 (m, 1H, CH), 2.23 – 2.16 (m, 1H, CH), 2.10 – 2.01 (m, 1H, CH), 1.90 – 1.85 (m, 1H, CH), 1.49 (s, 3H, CH\(_3\)), 0.95 (s, 3H, CH\(_3\)), 0.73 (s, 3H, CH\(_3\)). \( \delta^C \) 147.8 (Cq), 121.0 (=CH), 119.7 (CN), 46.8 (Cq), 46.1 (CH), 35.5 (CH\(_2\)), 25.7 (CH\(_3\)), 19.5 (CH\(_3\)), 18.0 (CH\(_2\)), 12.5 (CH\(_3\)). IR (neat) \( \nu/cm^{-1} \): 2965, 2251, 1703, 1616, 912. HRMS (ES) \( m/z \) calculated for C\(_{10}\)H\(_{16}\)N [M+H]\(^+\) = 150.1283; found: 150.1285.

2-(2,2,4-Trimethylcyclopent-3-en-1-yl)ethanamine 466

By general procedure C, the nitrile 465 (2.64 g, 17.7 mmol) was reduced using lithium aluminium hydride (0.76 g, 20 mmol) to give the amine 466 (2.50 g, 92%) as a yellow oil. \( \delta^H \) 5.15 (s, 1H, =CH), 2.71 (ddd, \( J = 12.2, 9.5, 5.1 \) Hz, 1H, CH), 2.59 (ddd, \( J = 12.2, 9.0, 6.6 \) Hz, 1H, CH), 2.23 – 2.15 (m, 1H, CH), 1.81 – 1.75 (m, 1H, CH), 1.74 – 1.59 (m, 2H, CH\(_2\)), 1.53 (s, 3H, CH\(_3\)), 1.41 – 1.29 (m, 1H, CH), 0.91 (s, 3H, CH\(_3\)), 0.70 (s, 3H, CH\(_3\)). \( \delta^C \) 148.7 (Cq), 121.6 (=CH), 48.0 (CH), 46.8 (Cq), 41.6 (NCH\(_2\)), 35.6 (CH\(_2\)), 34.4 (CH\(_2\)), 25.8 (CH\(_3\)), 19.7 (CH\(_3\)), 12.6 (CH\(_3\)). IR (neat) \( \nu/cm^{-1} \): 3281, 2953, 2932, 1651, 1445, 1375, 1360, 1072, 1015, 910. HRMS (ES) \( m/z \) calculated for C\(_{10}\)H\(_{20}\)N [M+H]\(^+\) = 154.1596; found: 154.1592.
Methyl (2-(2,2,4-trimethylcyclopent-3-en-1-yl)ethyl)carbamate 467

By general procedure A, methyl chloroformate (0.7 ml, 8.9 mmol) was added to the amine 466 (1.00 g, 6.5 mmol) and Et₃N (1 ml, 8.8 mmol) at 0 °C. The mixture was then stirred for 1 h at room temperature to give the carbamate 467 (1.12 g, 88%) as a colourless oil. δH 5.15 (s, 1H, =CH), 4.71 (br. s, 1H, NH), 3.60 (s, 3H, OCH₃), 3.18 (dt, J = 14.3, 7.0 Hz, 1H, CH), 3.14 – 3.02 (m, 1H, CH), 2.28 – 2.18 (m, 1H, CH), 1.83 – 1.73 (m, 1H, CH), 1.73 – 1.63 (m, 1H, CH), 1.53 (s, 3H, CH₃), 1.44 – 1.31 (m, 1H, CH), 0.89 (s, 3H, CH₃), 0.67 (s, 3H, CH₃). δC 157.1 (C=O), 148.5 (Cq), 121.5 (=CH), 51.9 (OCH₃), 47.7 (Cq), 46.8 (CH), 40.6 (NCH₂), 35.4 (CH₂), 28.3 (CH₂), 25.7 (CH₃), 19.7 (CH₃), 12.5 (CH₃). HRMS (EI) m/z calculated for C₁₂H₂₁NO₂ [M]+ = 211.1572; found: 211.1571.

4-Methyl-N-(2-(2,2,4-trimethylcyclopent-3-en-1-yl)ethyl)benzenesulfonamide 468

By general procedure A, tosyl chloride (1.96 g, 10 mmol) was added to the amine 466 (1.00 g, 6.5 mmol) and Et₃N (1.5 ml, 12.1 mmol) at 0 °C. The mixture was then stirred for 1 h at room temperature to give the sulfonamide 468 (1.80 g, 90%) as a colourless oil. δH 7.68 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 8.2 Hz, 2H), 5.09 (s, 1H, =CH), 4.71 (s, 1H, NH), 2.99 – 2.88 (m, 1H, CH), 2.88 – 2.76 (m, 1H, CH), 2.36 (s, 3H, Ar-CH₃), 2.13 – 2.05 (m, 1H, CH), 1.70 – 1.58 (m, 3H, CH and CH₂), 1.49 (s, 3H, CH₃), 1.31 (ddddd, J = 12.4, 10.2, 8.1, 4.6 Hz, 1H, CH), 0.82 (s, 3H, CH₃), 0.59 (s, 3H, CH₃). δC 148.4 (Cq), 143.3 (Cq), 137.1 (Cq), 129.7 (2 x CH), 127.1 (2 x CH), 121.3 (=CH), 47.4 (CH), 46.8 (Cq), 42.7 (NCH₂), 35.1 (CH₂), 30.1 (CH₂), 25.6 (CH₃), 21.5 (CH₃), 19.6
(CH₃), 12.5 (CH₃). IR (neat) v/cm⁻¹: 3279, 2963, 1699, 1448, 1327, 1094, 815. HRMS (ES) m/z calculated for C₁₇H₂₄NO₂S [M⁺] = 306.1528; found: 306.1527.

**Methyl (2-(2,3,3-trimethylcyclopent-1-en-1-yl)ethyl)carbamate 452**

![Methyl (2-(2,3,3-trimethylcyclopent-1-en-1-yl)ethyl)carbamate 452](image)

To a stirred solution of the carbamate 467 (211 mg, 1 mmol) in dry dichloromethane (10 ml) under nitrogen, cooled in an ice-water bath, was added sulfuric acid (3 drops). The resulting mixture stirred was stirred at 20 °C for 4 hours to give the carbamate 452 (200 mg, 95%) as a colourless oil. All data obtained were in accordance with those reported above.

**4-Methyl-N-(2-(2,3,3-trimethylcyclopent-1-en-1-yl)ethyl)benzenesulfonamide 462**

![4-Methyl-N-(2-(2,3,3-trimethylcyclopent-1-en-1-yl)ethyl)benzenesulfonamide 462](image)

By general procedure B, to the sulfonamide 468 (120 mg, 0.39 mmol) in dry dichloromethane (10 ml) concentrated sulfuric acid (3 drops) was added and the resulting mixture was stirred for 4 h at 20 °C to give the sulfonamide 462 (109 mg, 91%) as a colourless oil. All data obtained were in accordance with those reported above.

**1-(4-Methylcyclohex-3-en-1-yl)ethanol 482**

Following general procedure C, reduction of the ketone 416 (0.70 g, 5 mmol, 1.0 eq.) using lithium aluminum hydride (0.38 g, 10 mmol, 2.0 eq.) and a 1 h reflux period gave the alcohol 482 (623 mg, 89%) as a clear oil and as an inseparable 1:1 mixture of diastereoisomers.

*Diastereoisomer A* δH 5.37 – 5.22 (m, 1H, =CH), 3.64 – 3.55 (m, 1H, CH), 2.12 – 1.98 (m, 1H,...
CH), 1.99 – 1.86 (m, 3H, CH and CH$_2$), 1.71 (app. d, $J = 14.8$ Hz, 1H, CH), 1.58 (s, 3H, CH$_3$), 1.47 – 1.38 (m, 1H, CH), 1.12 (d, $J = 7.1$ Hz, 3H, CH$_3$). $\delta$C 134.0 (Cq), 120.2 (=CH), 71.7 (OCH), 41.1 (CH), 30.8 (CH$_2$), 28.0 (CH$_2$), 25.4 (CH$_2$), 23.4 (CH$_3$), 20.8 (CH$_3$). Diastereoisomer B $\delta$H 3.54 – 3.49 (m, 1H, CH) - only 1 distinct peak. $\delta$C 134.0 (Cq), 120.1 (=CH), 71.6 (OCH), 41.0 (CH), 30.8 (CH$_2$), 27.0 (CH$_2$), 24.9 (CH$_2$), 23.4 (CH$_3$), 20.6 (CH$_3$). The whole sample showed IR (neat) $\nu$/cm$^{-1}$: 3351, 2916, 1448, 1375, 1072, 1017, 912. HRMS (EI) $m/z$ calculated for C$_9$H$_{14}$O [M]$^+$ = 122.1096; found: 122.1090.

1,3-Dimethyl-2-oxabicyclo[2.2.2]octane 483

By general procedure B, to alcohol 482 (153 mg, 1.09 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (50 mg, 0.5 mmol) was added, the mixture stirred for 3 h at 32 °C to give the oxabicyclo-octane 483 (135 mg, 88%) as a pale yellow oil. $\delta$H 3.93 (q, $J = 6.3$ Hz, 1H, OCH), 1.86 – 1.78 (m, 1H, CH), 1.70 – 1.65 (m, 1H, CH), 1.62 – 1.53 (m, 3H, CH and CH$_2$), 1.49 – 1.41 (m, 2H, CH$_2$), 1.41 – 1.36 (m, 2H, CH$_2$), 1.10 (d, $J = 6.3$ Hz, 3H, CH$_3$), 0.96 (s, 3H, CH$_3$). $\delta$C 73.1 (OCH), 69.1 (Cq), 32.6 (CH$_2$), 32.1(CH$_2$), 29.7 (CH), 27.1 (CH$_3$), 26.5 (CH$_2$), 20.8 (CH$_3$), 19.7 (CH$_2$). IR (neat) $\nu$/cm$^{-1}$: 2986, 2912, 2888, 1713, 1458, 1373, 1209, 1055, 957. HRMS (EI) $m/z$ calculated for C$_9$H$_{16}$O [M]$^+$ = 140.1201; found: 140.1206.

1-Methyl-2-oxabicyclo[2.2.2]octane 485

By general procedure B, to commercially available (4-methylcyclohex-3-enyl)methanol 427 (Aldrich, 155 mg, 1.23 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated
sulfuric acid (50 mg, 0.5 mmol) was added and the reaction stirred for 1.5 h at 35 °C to give the oxabicyclo-octane 485 (143 mg, 92%). δH 3.81 (app. dd, J = 2.9, 1.5 Hz, 2H, CH2), 1.70 (dd, J = 1.1, 1.1 Hz, 4H, 2 x CH2), 1.56 (br. s, 2H, CH2), 1.54 – 1.45 (m, 2H, CH2), 1.15 (d, J = 8.2 Hz, 1H), 0.96 (s, 3H, CH3). δC 70.1 (OCH2), 68.1 (Cq), 32.9 (2 x CH2), 27.1 (CH3), 24.9 (CH), 24.8 (2 x CH2). IR (neat) v/cm⁻¹: 2924, 2864, 1377, 1262, 1093, 910. HRMS (EI) m/z calculated for C8H14O [M]+ = 126.1045; found: 126.1044.

**Methyl 3-methylcyclopent-3-ene carboxylate 489**

![Diagram](attachment:488_489.png)

The cyclopentene 488 (0.40 g, 2.00 mmol) in dimethyl sulfoxide/water (10 ml : 0.5 ml) containing sodium chloride (0.20 g, 3.4 mmol) was refluxed for 3 h. Cold water was added (3 ml) to the cooled mixture and the resulting mixture extracted with ether (3 x 10 ml). The combined organic extracts were washed with water (3 x 10 ml) then dried and concentrated to yield the ester 489 (0.20 g, 72%) as a colourless oil. δH 5.20 – 5.11 (m, 1H, =CH), 3.61 (s, 3H, OCH3), 3.15 – 3.00 (m, 1H, CH), 2.59 – 2.48 (m, 3H, CH and CH2), 2.47 – 2.35 (m, 1H, CH), 1.63 (s, 3H, CH3). δC 176.6 (Cq, CO2), 138.6 (Cq), 122.4 (=CH), 51.6 (OCH3), 42.2 (CH), 40.2 (CH2), 36.4 (CH2), 16.1 (CH3). All data obtained were in accordance with those previously reported in the literature.40

**(3-Methylcyclopent-3-en-1-yl)methanol 490**

![Diagram](attachment:489_490.png)

Following general procedure C, reduction of the ester 489 (0.20 g, 1.4 mmol, 1.0 eq.) using lithium aluminum hydride (0.19 g, 5 mmol) and a 1 h reflux period gave the alcohol 490 (126 mg,
78%) as a clear oil. $\delta_H$ 5.14 (t, $J = 1.6$ Hz, 1H, =CH), 3.46 (d, $J = 6.8$ Hz, 2H, OCH$_2$), 2.49 – 2.42 (m, 1H, CH), 2.39 – 2.33 (m, 1H, CH), 2.33 – 2.30 (m, 1H, CH), 2.09 (s, 1H, OH), 2.04 – 1.93 (m, 2H, CH$_2$), 1.63 (d, $J = 0.9$ Hz, 3H, CH$_3$). $\delta_C$ 139.2 (Cq), 123.1 (=CH), 67.3 (OCH$_2$), 40.1 (CH), 49.9 (CH$_2$), 35.7 (CH$_2$), 16.5 (CH$_3$).

1-Methyl-2-oxabicyclo[2.2.1]heptane 491

By general procedure B, to alcohol 490 (83 mg) in dry dichloromethane (5 ml) under nitrogen, concentrated sulfuric acid (2 drops) was added, the reaction stirred for 1.5 h at 35 °C to give 491 (70 mg, 84%). $\delta_H$ 3.70 (d, $J = 6.7$ Hz, 1H, OCH$_A$CH$_B$), 3.49 (d, $J = 6.7$ Hz, 1H, OCH$_A$CH$_B$), 2.33 (s, 1H), 1.64 (s, 1H), 1.60 (s, 2H), 1.50 (d, $J = 2.4$ Hz, 1H), 1.48 (s, 1H), 1.40 (d, $J = 2.4$ Hz, 1H), 1.36 (s, 1H), 1.32 (s, 3H, CH$_3$). $\delta_C$ 78.2 (OCq), 76.6 (OCH$_2$), 42.2 (CH$_2$), 38.4 (CH), 36.1 (CH$_2$), 28.8 (CH$_2$), 26.9 (CH$_3$).
Typical Procedure D: The preparation of substituted ethyl 2-cyanoacetates\textsuperscript{41}

To sodium hydride (60\% dispersion in mineral oil, 0.80 g, 20 mmol, 1.0 eq.) was added dry DMF (20 ml) under nitrogen and the suspension then cooled to 0 °C. To the suspension was slowly added ethyl cyanoacetate (6.80 g, 60 mmol, 3.0 eq.) in DMF (10 ml). After 15 min, an alkyl halide (20 mmol, 1.0 eq.) were added dropwise \textit{via} syringe to the solution. The resulting reaction mixture was allowed to stir at 0 °C for 3 h, then quenched with water (30 ml) and diluted with ether (30 ml). The aqueous layer was removed and the organic layer was washed twice with brine (5 ml). The combined aqueous and brine layers were then extracted three times with ether (3 x 30 ml). All the combined organic extracts were then dried and the solvent was removed. The residue was purified by column chromatography on silica gel eluting with ether/hexanes (1:99). Other mono-substituted cyanoacetates were obtained in a similar manner.

General Procedure E: Alcohol protection by acetate formation\textsuperscript{42}

A solution of the alcohol (1.0 mmol), acetic anhydride (0.1 ml, 1.1 mmol) and pyridine (0.1 ml) in dry dichloromethane (10 ml) was stirred for 6 h at room temperature. The mixture was quenched with water (5 ml) and extracted with dichloromethane (2 x 5 ml). The combined organic extracts were washed with a saturated aqueous copper(II) sulfate (5 ml), water (5 ml) then dried and concentrated to give the protected alcohol.
Ethyl 2-cyano-5-methylhex-4-enoate 511 and

Ethyl 2-cyano-5-methyl-2-(3-methylbut-2-en-1-yl)hex-4-enoate 512

By typical procedure D, to sodium hydride (60% dispersion in mineral oil, 1.20 g, 30 mmol, 1.0 eq.) in DMF (25 ml) under nitrogen at 0 °C was slowly added ethyl cyanoacetate 510 (4.40 g, 20 mmol, 2.0 eq.) in DMF (20 ml). After 15 min, prenyl bromide (1.49 g, 10 mmol, 1.0 eq.) was added. The usual work-up then gave the monosubstituted cyanoacetate 511 (1.00 g, 55%) and disubstituted cyanoacetate 512 (0.50 g, 20%) as colourless oils, which were separated by column chromatography.

Monosubstituted product 511: δ_H 4.90 (br. t, J = ca. 7.1 Hz, 1H, =CH), 3.97 (q, J = 7.1 Hz, 2H, OCH_2), 3.26 (t, J = 6.5 Hz, 1H), 2.42 (dd, J = 7.3 Hz, 6.5, 2H), 1.49 (d, J = 0.9 Hz, 3H, CH_3), 1.42 (app. s, 3H, CH_3), 1.07 (t, J = 7.1 Hz, 3H, CH_3). δ_C 165.7 (C=O), 137.3 (Cq), 117.0 (=CH), 116.3 (CN), 62.5 (OCH_2), 37.7 (CH), 28.4 (CH_2), 25.6 (CH_3), 17.7 (CH_3), 13.8 (CH_3). IR (neat) υ/cm^-1: 2982, 2932, 2255, 1743, 1445, 1371, 1195, 1030, 908. HRMS (EI) m/z calculated for C_{10}H_{15}NO_2 [M]^+ = 181.1103; found: 181.1105.

Disubstituted product 512 δ_H 5.13 (br. t, J = 7.6 Hz, 2H, 2 x =CH), 3.97 (q, J = 7.2 Hz, 2H, OCH_2), 2.62 (dd, J = 14.2, 6.6 Hz, 2H), 2.45 (dd, J = 7.7, 6.6 Hz, 2H) 1.63 (s, 6H, 2 x CH_3), 1.60 (s, 6H, 2 x CH_3), 1.27 (t, J = 7.2 Hz, 3H, CH_3). δ_C 168.7 (C=O), 137.3 (Cq), 119.6 (CN), 116.8 (2 x =CH), 62.1 (OCH_2), 49.7 (Cq), 35.0 (2 x CH_2), 25.6 (2 x CH_3), 17.8 (2 x CH_3), 13.8 (CH_3).
2-(Aminomethyl)-5-methylhex-4-en-1-ol 513

Using general procedure C, the cyanoacetate 511 (4.18 g, 23.1 mmol) was reduced by lithium aluminium hydride (0.95 g, 25 mmol) to give the amino-alcohol 513 (2.60 g, 72 %) as a yellow oil, which was sufficiently pure to use directly in the next step. δ\textsubscript{H} 4.66 – 4.57 (m, 1H, =CH), 3.31 – 3.23 (m, 1H), 3.15 – 3.06 (m, 1H), 2.53 (ddd, J = 12.2, 3.7, 1.1 Hz, 1H), 2.29 – 2.19 (m, 1H), 2.18 – 2.05 (m, 2H), 1.46 – 1.38 (m, 1H), 1.23 (s, 3H, CH\textsubscript{3}), 1.10 (s, 3H, CH\textsubscript{3}). δ\textsubscript{C} 132.7 (C\textsubscript{q}), 121.8 (=CH), 67.6 (OCH\textsubscript{2}), 46.2 (NCH\textsubscript{2}), 41.9 (CH), 27.7 (CH\textsubscript{2}), 25.4 (CH\textsubscript{3}), 17.5 (CH\textsubscript{3}). IR (neat) υ/cm\textsuperscript{-1}: 3323, 2967, 2913, 2856, 1451, 1377, 1038, 910. HRMS (EI) m/z calculated for C\textsubscript{8}H\textsubscript{17}NO [M]\textsuperscript{+} = 143.1310; found: 143.1310.

Methyl 2-(hydroxymethyl)-5-methylhex-4-en-1-ylcarbamate 514

By general procedure A, methyl chloroformate (1.0 ml, 12.7 mmol) was added to the amino-alcohol 513 (1.80 g, 12.6 mmol, 1.0 eq.) and Et\textsubscript{3}N (2.5 ml, 22 mmol, 1.2 eq.) to give the N-protected amino-alcohol 514 (1.80 g, 71%) as a colourless oil. δ\textsubscript{H} 5.19 (br. s, 1H, NH), 5.16 – 5.04 (m, 1H, =CH), 3.68 (s, 3H, OCH\textsubscript{3}), 3.60 (dd, J = 6.6, 6.2 Hz, 1H), 3.50 – 3.38 (m, 1H), 3.37 – 3.21 (m, 2H), 3.21 – 3.09 (m, 1H), 2.03 – 1.86 (m, 2H), 1.74 (s, 3H, CH\textsubscript{3}), 1.63 (s, 3H, CH\textsubscript{3}). δ\textsubscript{C} 158.3 (C=O), 133.2 (C\textsubscript{q}), 121.7 (=CH), 62.9 (CH\textsubscript{2}OH), 52.2 (OCH\textsubscript{3}), 41.9 (CH), 41.6 (NCH\textsubscript{2}), 27.5 (CH\textsubscript{2}), 25.6 (CH\textsubscript{3}), 17.6 (CH\textsubscript{3}). IR (neat) υ/cm\textsuperscript{-1}: 3343, 2934, 1700, 1526, 1449, 1256, 1194, 1034, 910. HRMS (EI) m/z calculated for C\textsubscript{10}H\textsubscript{17}NO\textsubscript{2} [M]\textsuperscript{+} = 183.1269; found: 183.1258.
2-(Methoxycarbonylaminomethyl)-5-methylhex-4-en-1-yl acetate 515

Using general procedure E, the alcohol 514 (201 mg, 1.0 mmol) was converted into the corresponding acetate 515 (243 mg, 100%), a colourless oil. $\delta^H$ 5.02 (dd, $J = 11.6, 10.0$ Hz, 1H, =CH), 4.94 (br. s, 1H, NH), 4.15 (dd, $J = 6.8, 4.4$ Hz, 1H), 3.95 – 3.85 (m, 1H), 3.52 (s, 3H, OCH$_3$), 3.27 – 3.12 (m, 1H), 3.04 (dt, $J = 13.7, 7.3$ Hz, 1H), 2.00 (s, 3H, Ac-CH$_3$), 1.96 – 1.93 (m, 2H), 1.89 – 1.74 (m, 1H), 1.64 (s, 3H, CH$_3$), 1.53 (s, 3H, CH$_3$). $\delta^C$ 171.2 (Ac-CO), 157.1 (CO), 133.9 (Cq), 120.9 (=CH), 64.8 (OCH$_2$), 52.0 (OCH$_3$), 42.2 (NCH$_2$), 39.0 (CH), 37.9 (Ac-CH$_3$), 27.7 (CH$_2$), 22.2 (CH$_3$), 20.8 (CH$_3$).

Methyl 5-(acetoxymethyl)-2,2-dimethylpiperidine-1-carboxylate 516

By general procedure B, to the protected amino-alcohol 515 (243 mg, 1.0 mmol) in dry dichloromethane (10 ml) concentrated sulfuric acid (3 drops) was added and the resulting mixture stirred for 1 h at 20 °C to give the piperidine 516 (225 mg, 93%) as a colourless oil. $\delta^H$ 3.85 (dd, $J = 11.0, 5.7$ Hz, 1H), 3.75 (dd, $J = 11.0, 8.0$ Hz, 1H), 3.65 – 3.59 (m, 1H), 3.55 (s, 3H, OCH$_3$), 2.90 (dd, $J = 13.6, 8.8$ Hz, 1H), 1.91 (s, 3H, Ac-CH$_3$), 1.65 – 1.52 (m, 1H), 1.52 – 1.36 (m, 2H, CH$_2$), 1.35 (s, 3H, CH$_3$), 1.23 (s, 3H, CH$_3$) 1.17 – 1.05 (m, 2H, CH$_2$). $\delta^C$ 171.0 (Ac-C=O), 156.9 (C=O), 66.4 (OCH$_2$), 54.8 (NCq), 51.9 (OCH$_3$), 43.1 (CH$_2$N), 36.2 (CH$_2$), 33.8 (CH), 27.9 (CH$_3$), 24.5 (CH$_3$), 21.3 (CH$_2$), 20.8 (CH$_3$).
Methyl (6,6-dimethyltetrahydro-2H-pyran-3-yl)methylcarbamate 517

By general procedure B, to the N-protected amino-alcohol 514 (136 mg, 0.7 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for 4 h at 0 °C to give the tetrahydropyran 517 as a colourless oil (127 mg, 93%). δH 4.60 (app. br. s, NH, 1H), 3.66 (dd, J = 3.9, 1.9 Hz, 1H), 3.65 (s, 3H, OCH3), 3.62 (dd, J = 4.1, 1.9 Hz, 1H), 3.09 - 2.92 (m, 2H, CH2N), 1.91 (m, 1H), 1.70 - 1.60 (m, 2H) 1.43 - 1.29 (m, 2H), 1.16 (s, 3H, CH3), 1.12 (s, 3H, CH3). δC 157.2 (C=O), 71.3 (OCq), 64.3 (OCH2), 52.1 (OCH3), 43.1 (CH2N), 36.2 (CH), 35.1 (CH2), 29.2 (CH3), 23.7 (CH2), 23.3 (CH3). IR (neat) ν/cm−1: 3329, 2970, 2930, 1701, 1533, 1452, 1247, 1084, 1009. HRMS (EI) m/z calculated for C10H19NO3 [M]+ = 201.1365; found: 201.1370.

Methyl 2,2-dimethyl-5-(hydroxymethyl)piperidine-1-carboxylate 518

To a solution of the acetoxyethyl piperidine 516 (122 mg, 0.5 mmol) in undried methanol (5 ml) was added potassium carbonate (400 mg, 2.9 mmol). The mixture was stirred for 20 h at room temperature. The solvent was evaporated and the residue diluted with water (5 ml) and extracted with dichloromethane (3 x 5 ml). The combined organic extracts were dried and concentrated to give the piperidine-methanol 518 (92 mg, 91%) as a colourless oil. δH 3.62 (dd, J = 13.7, 4.6 Hz, 1H), 3.58 (s, 3H, OCH3), 3.46 (dd, J = 10.8, 5.6 Hz, 1H), 3.42 – 3.38 (m, 1H, CH), 3.12 (dd, J = 13.7, 7.6 Hz, 1H), 1.91 (br. s, 1H, OH), 1.85 – 1.79 (m, 1H, CH), 1.71 – 1.59 (m, 1H, CH), 1.58 – 1.43 (m, 2H, CH2), 1.39 (s, 3H, CH3), 1.30 (s, 3H, CH3), 1.22 – 1.07 (m, 1H, CH). δC 157.2
(C=O), 65.2 (OCH₂), 55.1 (NCq), 51.9 (OCH₃), 42.7 (CH₂N), 38.0 (CH₂), 36.8 (CH), 27.6 (CH₃), 24.8 (CH₃), 20.8 (CH₂). IR (neat) υ/cm⁻¹: 3416, 2947, 2930, 1684, 1539, 1440, 1381, 1157, 1022.

HRMS (EI) m/z calculated for C₁₀H₁₉NO₃ [M]⁺ = 201.1365; found: 201.1368.

**Methyl (6,6-dimethyltetrahydro-2H-pyran-3-yl)methylcarbamate 517**

![Chemical Structure](attachment:structure.png)

By general procedure B, to the alcohol 518 (60 mg, 0.3 mmol) in dry dichloromethane (10 ml) concentrated sulfuric acid (12 mg, 0.12 mmol) was added and the resulting mixture stirred for 20 h at 20 °C to give the tetrahydropyran 517 as (57 mg, 95%) as a colourless oil, which exhibited spectroscopic and analytical data identical to those reported above for a sample of the same tetrahydropyran prepared by direct cyclisation of the alcohol 514.

**N-(2-(Hydroxymethyl)-5-methylhex-4-en-1-yl)-4-methylbenzenesulfonamide 519**

![Chemical Structure](attachment:structure.png)

By general procedure A, tosyl chloride (553 mg, 3.0 mmol) was added to the amino-alcohol 513 (0.41 g, 2.9 mmol) and Et₃N (0.5 ml, 4.4 mmol) at -78 °C. The mixture was then stirred for 1 h as it warmed to room temperature to give the sulfonamide 519 (0.60 g, 70%) as a colourless oil. δH 7.71 – 7.62 (m, 2H), 7.25 (d, J = 8.0 Hz, 2H), 5.02 (br. s, 1H, NH), 4.94 (td, J = 7.3, 1.4 Hz, 1H, =CH), 3.64 (dd, J = 11.0, 4.0 Hz, 1H), 3.46 (dd, J = 11.0, 7.1 Hz, 1H), 2.99 (dd, J = 12.9, 3.9 Hz, 1H), 2.88 – 2.78 (m, 1H), 2.36 (s, 3H, ArCH₃), 1.84 – 1.78 (m, 2H), 1.69 (br. s, 1H, OH), 1.66 – 1.62 (m, 1H), 1.60 (d, J = 0.9 Hz, 3H, CH₃), 1.49 (s, 3H, CH₃). δC 143.1 (Cq), 136.4 (Cq), 133.7 (Cq), 129.5 (2 x CH), 126.8 (2 x CH), 120.9 (CH), 64.2 (OCH₂), 44.9 (NCH₂), 40.6 (CH), 27.2 (CH₂), 25.5 (ArCH₃), 21.3 (CH₃), 17.6 (CH₃).
N-((6,6-Dimethyltetrahydro-2H-pyran-3-yl)methyl)-4-methylbenzenesulfonamide 520

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\text{By general procedure B, to the } N\text{-tosyl alcohol } 519 \text{ (100 mg, 0.3 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for 1 h at } 0 ^\circ C \text{ to give the tetrahydropyran } 520 \text{ (97 mg, 97%) as a colourless oil. } \delta H \\
7.68 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 4.37 (t, J = 6.5 Hz, 1H, NH), 3.82 – 3.75 (m, 1H), 3.61 (ddd, J = 11.9, 4.1, 1.7 Hz, 1H), 3.23 (dd, J = 11.8, 8.8 Hz, 1H), 3.05 – 2.99 (m, 1H), 2.37 (s, 3H, ArCH$_3$), 1.82 – 1.74 (m, 1H, CH), 1.65 – 1.57 (m, 2H, CH$_2$), 1.47 – 1.39 (m, 2H, CH$_2$), 1.12 (s, 3H, CH$_3$), 1.07 (s, 3H, CH$_3$). \delta C 144.1 (Cq), 129.5 (2 x CH), 127.0 (2 x CH), 71.4 (OCq) 64.7 (OCH$_2$), 45.3 (NCH$_2$), 39.7 (CH), 38.6 (CH$_2$), 34.7 (CH$_2$), 28.3 (ArCH$_3$), 22.7 (CH$_3$), 21.5 (CH$_3$). IR (neat) $\nu$/cm$^{-1}$: 3220, 2974, 2930, 1454, 1325, 1090, 912. HRMS (EI+) $m/z$ calculated for C$_{15}$H$_{23}$NO$_3$NaS [M+Na]$^+$ = 320.1296; found: 320.1285.

5-Methyl-2-((4-methylphenylsulfonamido)methyl)hex-4-en-1-yl acetate 522

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\text{By procedure E, the alcohol } 519 \text{ (297 mg, 1.0 mmol) was converted into the corresponding acetate } 522 \text{ (339 mg, 100%), a colourless oil. } \delta H 7.72 – 7.62 (m, 2H), 7.24 (d, J = 8.0 Hz, 2H), 4.98 – 4.87 (m, 1H, =CH), 4.79 (t, J = 6.1 Hz, 1H, NH), 4.01 (dd, J = 11.4, 4.3 Hz, 1H), 3.90 – 3.75 (m, 1H), 2.87 (ddd, J = 12.5, 6.9, 5.4 Hz, 1H), 2.77 (dt, J = 13.2, 6.7 Hz, 1H), 2.16 (s, 3H, ArCH$_3$), 1.93 (s, 3H, AcCH$_3$), 1.93 – 1.86 (m, 2H), 1.80 – 1.69 (m, 1H), 1.61 (d, J = 0.7 Hz, 3H, CH$_3$), 1.48 (s, 3H, CH$_3$). \delta C 171.1 (C=O), 143.4 (Cq), 134.5 (Cq), 129.7 (2 x CH), 127.1 (2 x CH), 120.5 (=CH), 64.6 (OCH$_2$), 44.2 (NCH$_2$), 38.7 (CH), 27.6 (CH$_2$), 25.7 (ArCH$_3$), 22.1 (CH$_3$), 21.5 (CH$_3$), 20.8 (CH$_3$). IR (neat) $\nu$/cm$^{-1}$: 3285, 2969, 1732, 1599, 1447, 1327, 1240, 1092, 1033, 910. HRMS (EI) $m/z$ calculated for C$_{17}$H$_{25}$NNaO$_4$S [M+Na]$^+$ = 362.1402; found: 362.1400.
Methyl 5-(acetoxymethyl)-2,2-dimethylpiperidine-1-carboxylate 523

\[
\begin{align*}
\text{Ac} & \quad \text{Ts} \\
\text{NH} & \quad \text{Ts} \\
\text{H} & \quad \text{OAc}
\end{align*}
\]

By general procedure B, to the protected amino-alcohol 522 (280 mg, 0.8 mmol) in dry dichloromethane (10 ml) concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture was stirred for 1 h at 20° C to give the piperidine 523 as a colourless oil (269 mg, 96%). δ\text{H} 7.58 – 7.47 (m, 2H), 7.16 – 7.06 (m, 2H), 3.86 (dd, \( J = 11.1, 5.4 \) Hz, 1H), 3.82 – 3.77 (m, 1H), 3.75 (dd, \( J = 11.1, 8.0 \) Hz, 1H), 2.82 (dd, \( J = 13.3, 9.8 \) Hz, 1H), 2.27 (s, 3H, Ar\text{CH}_3), 1.91 (s, 3H, CO\text{CH}_3), 1.90 – 1.77 (m, 1H), 1.51 (dddd, \( J = 13.3, 8.3, 4.0 \) Hz, 1H), 1.46 – 1.37 (m, 1H), 1.33 (dt, \( J = 13.3, 4.5 \) Hz, 1H), 1.25 (s, 3H, CH_3), 1.23 – 1.12 (m, 1H), 1.03 (s, 3H, CH_3). δ\text{C} 170.9 (C=O), 142.8 (Cq), 140.1 (Cq), 129.4 (2 x CH), 127.0 (2 x CH), 65.9 (OCH_2), 57.8 (NCOq), 45.4 (NCH_2), 39.8 (CH_2), 35.7 (CH), 28.7 (Ar\text{CH}_3), 23.2 (CH_2), 23.0 (Ac-CH_3), 21.4 (CH_3), 20.8 (CH_3). IR (neat) \text{υ/cm}^{-1}: 2928, 1737, 1454, 1321, 1228, 1089, 910. HRMS (ES) \text{m/z} calculated for C_{17}H_{26}NO_4S [M+H]^+ = 340.1583; found: 340.1585.

6,6-Dimethyl-1-tosylpiperidine-3-methanol 521

\[
\begin{align*}
\text{Ac} & \quad \text{Ts} \\
\text{NH} & \quad \text{Ts} \\
\text{H} & \quad \text{OH}
\end{align*}
\]

To a solution of acetoxyethyl piperidine 523 (240 mg, 0.7 mmol) in undried methanol (5 ml) was added potassium carbonate (200 mg, 1.5 mmol). The reaction was stirred for 18 h at room temperature. The solvent was removed and the residue was diluted with water (5 ml) and extracted with dichloromethane (3 x 5 ml). The combined organic layers were dried and concentrated to give the piperidine 521 (201 mg, 97%) as a colourless oil. δ\text{H} δ 7.65 – 7.59 (m, 2H), 7.19 (d, \( J = 7.8 \) Hz, 2H), 3.81 (dddd, \( J = 13.0, 4.0, 0.8 \) Hz, 1H), 3.48 (dd, \( J = 8.8, 2.9 \) Hz, 2H), 3.00 (dd, \( J = 13.0, 9.3 \) Hz, 1H), 2.34 (s, 3H, Ar\text{CH}_3), 2.01 (br. s, 1H, OH), 1.84 – 1.70 (m, 1H), 1.59 (dq, \( J =
}
13.3, 4.3 Hz, 1H), 1.51 – 1.35 (m, 2H), 1.30 (s, 3H, CH₃), 1.23 (ddd, J = 10.2, 8.0, 4.4 Hz, 1H), 1.12 (s, 3H, CH₃). δC 142.5 (Cq), 139.6 (Cq), 129.2 (2 x CH), 126.7 (2 x CH), 64.3 (OCH₂), 57.7 (NCq), 45.2 (NCH₂), 39.5 (CH₂), 38.4 (CH), 28.2 (CH₃), 23.3 (CH₃), 22.5 (CH₂), 21.2 (CH₃). IR (neat) v/cm⁻¹: 3489, 2926, 1454, 1317, 1089, 1016, 914. HRMS (EI) m/z calculated for C₁₅H₂₃NO₅S [M]+ = 297.1399; found: 297.1388.

*N-*((6,6-Dimethyltetrahydro-2H-pyran-3-yl)methyl)-4-methylbenzenesulfonamide 520

By general procedure B, to the alcohol 521 (103 mg, 0.35 mmol) in dry dichloromethane (10 ml) concentrated sulfuric acid (12 mg, 0.12 mmol) was added and the resulting mixture stirred for 18 h at 20 °C to give the tetrahydropyran 520 (98 mg, 97%) as a colourless oil, which exhibited spectroscopic and analytical data identical to those reported for a sample of the tetrahydropyran prepared by cyclisation of the alcohol 519.

**Ethyl 2-cyanopropanoate 522**

By typical procedure C, to potassium hydroxide (1.12 g, 20 mmol, 1.0 eq.) in ethanol (20 ml) under nitrogen at 0 °C was slowly added ethyl cyanoacetate 510 (2.27 g, 20 mmol, 1.0 eq.). After 15 min, methyl iodide (2.84 g, 20 mmol, 1.0 eq.) was added to give the cyanopropanoate 522 (2.14 g, 84%) as colourless oil. All data obtained were in accordance with those previously reported in the literature:δH 4.28 (q, J = 7.1 Hz, 2H, OCH₂), 3.56 (q, J = 7.4 Hz, 1H, CH), 1.63 (d, J = 7.4 Hz, 3H, CH₃), 1.34 (t, J = 7.1 Hz, 3H, CH₃). δC 166.5 (CO₂), 117.3 (CN), 62.8 (OCH₂), 31.5 (CH), 15.3 (CH₃), 13.9 (CH₃).
**Methyl 2-cyano-2,5-dimethylhex-4-enoate 523**

\[
\begin{align*}
\text{NC} & \quad \text{CO}_2\text{Et} \quad \xrightarrow{\text{NaH, THF}} \quad \text{NC} \\
\text{522} & \quad \text{CO}_2\text{Et} \quad \xrightarrow{\text{Br} \quad 95\%} \\
\end{align*}
\]

By typical procedure D, to sodium hydride (60% dispersion in mineral oil, 0.40 g, 10 mmol, 1.0 eq.) in dry tetrahydrofuran (20 ml) under nitrogen at 0 °C was slowly added methyl cyanoacetate 522 (1.10 g, 10 mmol, 1.0 eq.) in dry tetrahydrofuran (10 ml). After 15 min, prenyl bromide (1.50 g, 10 mmol, 1.0 eq.) was added to give the cyanoacetate 523 (1.71 g, 95%) as a colourless oil. \(\delta H\) 5.11 (dd, \(J = 7.6, 6.2\) Hz, 1H, =CH), 4.23 – 4.11 (m, 2H, OCH\(_2\)), 2.56 (dd, \(J = 14.2, 7.6\) Hz, 1H, 3-H\(_\alpha\)), 2.42 (dd, \(J = 14.2, 7.6\) Hz, 1H, 3-H\(_\beta\)), 1.70 (s, 3H, CH\(_3\)), 1.59 (s, 3H, CH\(_3\)), 1.50 (d, \(J = 2.9\) Hz, 3H), 1.23 (t, \(J = 4.7\), 3H, CH\(_3\)). \(\delta C\) 169.3 (C=O), 137.9 (Cq), 120.1 (CN), 116.5 (=CH), 62.6 (OCH\(_2\)), 44.0 (Cq), 36.6 (CH\(_2\)), 25.9 (CH\(_3\)), 22.6 (CH\(_3\)), 18.1 (CH\(_3\)), 13.7 (CH\(_3\)). IR (neat) \(\nu/cm^{-1}\): 2986, 2247, 1786, 1717, 1452, 1381, 1236, 1190, 1122, 1111, 1016, 914. HRMS (El) \(m/z\) calculated for C\(_{11}\)H\(_{17}\)NO\(_2\) [M]\(^+\) = 195.1259; found: 195.1259.

**2-(Aminomethyl)-2,5-dimethylhex-4-en-1-ol 524**

\[
\begin{align*}
\text{NC} & \quad \text{CO}_2\text{Et} \quad \xrightarrow{\text{LiAH}_3, \text{THF}} \\
\text{523} & \quad \text{H}_2\text{N} \quad \text{CO}_2\text{Et} \quad \xrightarrow{} \quad \text{OH} \\
\text{524} & \\
\end{align*}
\]

Following general procedure C, the cyano-hexenoate 523 (1.70 g, 8.7 mmol, 1.0 eq.) was reduced using lithium aluminium hydride (0.76 g, 20 mmol) to give the amino-alcohol 524 (1.30 g, 94%) as a colourless oil, which was of sufficient purity to be used directly in the next step. \(\delta H\) 5.14 – 5.05 (m, 1H, =CH), 3.50 – 3.42 (m, 2H, OCH\(_2\)), 2.73 (d, \(J = 12.5\) Hz, 1H, NCH\(_A\)H\(_B\)), 2.63 (d, \(J = 12.5\) Hz, 1H, NCH\(_A\)H\(_B\)), 2.57 – 2.52 (br. s, 3H, NH\(_2\), OH), 1.99 (dd, \(J = 14.4, 8.0\) Hz, 1H, =CCH\(_A\)H\(_B\)), 1.90 (dd, \(J = 14.4, 7.4\) Hz, 1H, =CCH\(_A\)H\(_B\)), 1.65 (d, \(J = 0.7\) Hz, 3H, CH\(_3\)), 1.53 (s, 3H, CH\(_3\)), 0.75 (s, 3H, CH\(_3\)). \(\delta C\) 133.7 (Cq), 119.7 (=CH), 72.3 (OCH\(_2\)), 67.9 (NCH\(_2\)), 51.1 (CH\(_2\)), 38.6 (Cq), 33.4 (CH\(_2\)), 26.0 (CH\(_3\)), 25.6 (CH\(_2\)), 19.8 (CH\(_3\)), 17.8 (CH\(_3\)).
Methyl (2-(hydroxymethyl)-2,5-dimethylhex-4-en-1-yl)carbamate 525

\[
\begin{align*}
\text{H}_3\text{N} & \quad \text{OH} \\
\text{ClCO}_2\text{Me} & \quad \text{Et}_3\text{N}, 0^\circ \text{C} \\
& \quad \text{DCM} \\
\rightarrow & \quad \text{O} \quad \text{N} \\
\text{H}_3\text{N} & \quad \text{OH}
\end{align*}
\]

By general procedure A, methyl chloroformate (0.94 g, 10 mmol, 1.2 eq.) was added to the amino-alcohol 524 (1.25 g, 8 mmol, 1.0 eq.) and Et\(_3\)N (1.25 ml, 11 mmol, 1.3 eq.) to give the \(N\)-protected amino-alcohol 525 (1.54 g, 90%) as a colourless oil. \(\delta_H 5.29 \ (br. \ s, \ 1H, \text{NH}), 5.15 – 5.10 \ (m, \ 1H, =\text{CH}), 3.66 \ (s, \ 3H, \text{OCH}_3)), 3.23 \ (dd, \ J = 11.7, \ 7.0 \text{ Hz}, \ 1H), 3.21 \ (dd, \ J = 11.7, \ 7.0 \text{ Hz}, \ 1H), 3.07 \ (dd, \ J = 14.3, \ 6.7 \text{ Hz}, \ 1H), 2.99 \ (dd, \ J = 14.3, \ 6.7 \text{ Hz}, \ 1H), 1.91 \ (d, \ J = 7.7 \text{ Hz}, \ 2H, \text{CH}_2), 1.70 \ (s, \ 3H, \text{CH}_3), 1.60 \ (s, \ 3H, \text{CH}_3), 0.79 \ (s, \ 3H, \text{CH}_3). \ \delta_C 158.6 \ (\text{C}=\text{O}), 134.1 \ (\text{Cq}), 119.2 \ (=\text{CH}), 67.1 \ (\text{CH}_2\text{OH}), 52.4 \ (\text{OCH}_3), 46.4 \ (\text{NCH}_2), 40.3 \ (\text{Cq}), 33.3 \ (\text{CH}_2), 26.0 \ (\text{CH}_3), 19.2 \ (\text{CH}_3), 17.8 \ (\text{CH}_3). \ \text{IR (neat) \upsilon/cm}^{-1}: 3331, 2964, 2928, 1696, 1527, 1454, 1194, 1141, 777, 731. \ \text{HRMS (EI) m/z calculated for C}_{11}\text{H}_{19}\text{NO}_2 [\text{M-H}_2\text{O}]^+ = 197.1416; \text{found: 197.1422.}

Methyl (3,6,6-trimethyltetrahydro-2H-pyran-3-ylmethyl)carbamate 526

\[
\begin{align*}
\text{H}_3\text{N} & \quad \text{OH} \\
\text{CO}_2\text{Me} & \quad \text{c}_\text{H}_2\text{SO}_4 \\
& \quad \text{CH}_2\text{Cl}_2, 0^\circ \text{C, 2h} \\
\rightarrow & \quad \text{O} \quad \text{N} \\
\text{H}_3\text{N} & \quad \text{OH}
\end{align*}
\]

By general procedure B, to the \(N\)-protected amino-alcohol 525 (160 mg, 0.74 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for 2 h at 0 °C to give the tetrahydropyran 526 as a colourless oil (156 mg, 98%). \(\delta_H 4.73 \ (br. \ s, \text{NH, 1H}), 3.60 \ (s, \ 3H, \text{OCH}_3), 3.33 – 3.24 \ (m, \ 2H), 3.22 \ (dd, \ J = 11.9, \ 4.8 \text{ Hz}, \ 1H), 2.98 \ (dd, \ J = 13.8, \ 6.1 \text{ Hz}, \ 1H), 1.55 – 1.41 \ (m, \ 2H), 1.41 – 1.26 \ (m, \ 2H), 1.13 \ (s, \ 6H, 2 \times \text{CH}_3), 0.80 \ (s, \ 3H, \text{CH}_3). \ \delta_C 157.5 \ (\text{C}=\text{O}), 71.3 \ (\text{OCq}), 68.5 \ (\text{OCH}_2), 52.1 \ (\text{OCH}_3), 47.3 \ (\text{CH}_2\text{N}), 33.7 \ (\text{Cq}), 32.1 \ (\text{CH}_2), 29.1 \ (\text{CH}_2), 27.1 \ (\text{CH}_3), 25.4 \ (\text{CH}_3), 21.3 \ (\text{CH}_3). \ \text{IR (neat) \upsilon/cm}^{-1}: 3354, 2931, 1705, 1537, 1452, 1367, 1074, 1011, 916, 829. \ \text{HRMS (EI) m/z calculated for C}_{11}\text{H}_{21}\text{NO}_3 [\text{M}]^+ = 215.1521; \text{found: 215.1518.}
2-(Methoxycarbonylaminomethyl)-2,5-dimethylhex-4-en-1-yl acetate 527

By general procedure E, the alcohol 525 (180 mg, 0.8 mmol) was reacted with acetic anhydride (0.1 ml, 1.1 mmol) to give the protected alcohol 527 (215 mg, 100%) as a colourless oil. $\delta_H$ 5.07 (t, $J = 7.8$ Hz, 1H, -$\equiv$CH), 4.91 (br. s, 1H, NH), 3.82 (d, $J = 11.2$ Hz, 1H), 3.75 – 3.70 (m, 1H), 3.59 (s, 3H, OCH$_3$), 3.09 – 3.03 (m, 1H), 2.99 (dd, $J = 13.8$, 6.3 Hz, 1H), 2.02 (s, 3H, COCH$_3$), 1.93 – 1.90 (m, 2H), 1.65 (s, 3H, CH$_3$), 1.54 (s, 3H, CH$_3$), 0.76 (s, 3H, CH$_3$). IR (neat) $\nu$/cm$^{-1}$: 3360, 2968, 1699, 1531, 1456, 1369, 1240, 1037, 910, 777.

Methyl 5-(acetoxymethyl)-2,2,5-trimethylpiperidine-1-carboxylate 528

By general procedure B, to the protected amino-alcohol 527 (190 mg, 0.74 mmol) in dry dichloromethane (10 ml) concentrated sulfuric acid (2 drops) was added and the resulting mixture stirred for 1 h at 20 $^\circ$C to give the piperidine 528 (184 mg, 97%) as a colourless oil. $\delta_H$ 3.75 (app. d, $J = 1.9$ Hz, 2H, OCH$_2$), 3.54 (s, 3H, OCH$_3$), 3.31 (d, $J = 13.9$ Hz, 1H, NCH$_A$H$_B$), 2.96 (d, $J = 13.9$ Hz, 1H, NCH$_A$H$_B$), 1.99 (s, 3H, COCH$_3$), 1.53 – 1.45 (m, 1H), 1.45 – 1.40 (m, 1H), 1.39 – 1.34 (m, 1H), 1.33 (s, 3H, CH$_3$), 1.30 (s, 3H, CH$_3$), 1.30 – 1.28 (m, 1H), 0.88 (s, 3H, CH$_3$). $\delta_C$ 171.1 (Me-C=O), 157.0 (CO$_2$), 70.2 (OCH$_2$), 55.0 (NCq), 51.9 (OCH$_3$), 47.6 (CH$_2$N), 36.4 (CH$_2$), 34.4 (Cq), 28.1 (CH$_2$), 25.9 (CH$_3$), 25.8 (CH$_3$), 22.8 (CH$_3$), 20.8 (CH$_3$). IR (neat) $\nu$/cm$^{-1}$: 2962, 1742, 1699, 1526, 1442, 1379, 1138, 1035, 910, 775. HRMS (ES) $m/z$ calculated for C$_{13}$H$_{23}$NO$_4$Na [M+Na]$^+$ = 280.1525; found: 280.1534.
**Methyl 5-(hydroxymethyl)-2,2,5-trimethylpiperidine-1-carboxylate 529**

![Chemical Structure]

To a solution of acetoxyethyl piperidine 528 (150 mg, 0.6 mmol) in undried methanol (5 ml) was added potassium carbonate (200 mg, 1.45 mmol). The reaction was stirred for 24 h at room temperature. The solvent was removed and the residue was diluted with water (5 ml) and extracted with dichloromethane (3 x 5 ml). The combined organic layers were dried and concentrated to give the *piperidinemethanol* 529 (126 mg, 98%) as a colourless oil. δ^H^ 3.56 (s, 3H, OCH₃), 3.48 (d, J = 14.1 Hz, 1H), 3.35 (d, J = 11.0 Hz, 1H), 3.22 (d, J = 11.0 Hz, 1H), 2.83 (d, J = 14.1 Hz, 1H), 1.84 (br. s, 1H, OH), 1.63 – 1.53 (m, 1H), 1.40 (ddd, J = 10.3, 6.6, 3.3 Hz, 1H), 1.34 (s, 3H, CH₃), 1.32 (app. t, J = 3.3 Hz, 1H), 1.29 (s, 3H, CH₃), 1.20 (ddd, J = 14.0, 6.6, 4.0 Hz, 1H), 0.87 (s, 3H, CH₃). δ^C^ 157.7 (C=O), 69.4 (OCH₂), 55.1 (NCq), 52.0 (OCH₃), 47.2 (CH₂N), 36.5 (CH₂), 36.1 (Cq), 27.9 (CH₂), 26.1 (CH₃), 25.9 (CH₃), 22.5 (CH₂). IR (neat) ν/cm⁻¹: 3447, 2932, 2870, 1682, 1440, 1364, 1275, 1190, 1154, 1049. HRMS (EI) m/z calculated for C₁₁H₂₁NO₃ [M]^+ = 215.1521; found: 215.1521.

**Methyl ((3,6,6-trimethyltetrahydro-2H-pyran-3-yl)methyl)carbamate 526**

![Chemical Structure]

By general procedure B, to the alcohol 529 (54 mg, 0.25 mmol) in dry dichloromethane (10 ml) concentrated sulfuric acid (12 mg, 0.12 mmol) was added and the resulting mixture stirred for 4 h at 20 °C to give the *tetrahydropyran* 526 as (52 mg, 96%) as a colourless oil, which exhibited spectroscopic and analytical data identical to that reported for a sample of the same tetrahydropyran prepared by direct cyclisation of the alcohol 525.
Methyl 2-cyano-3-phenylpropanoate 530

By general procedure D, to sodium hydride (60% dispersion in mineral oil, 0.80 g, 20 mmol, 1.0 eq.) in DMF (20 ml) under nitrogen at 0 °C was slowly added ethyl cyanoacetate 510 (6.80 g, 60 mmol, 3.0 eq.) in DMF (10 ml). After 15 min, benzyl bromide (3.42 g, 20 mmol, 1.0 eq.) was added to give the cyanophenylpropanoate 530 (3.30 g, 87%) as a colourless oil. All data obtained were in accordance with those previously reported in the literature: δH 7.44 – 7.24 (m, 5H), 4.25 (q, J = 7.1 Hz, 2H, OCH2), 3.75 (dd, J = 8.4, 5.8 Hz, 1H), 3.30 (dd, J = 13.8, 5.8 Hz, 1H, PhCHAHB), 3.21 (dd, J = 13.8, 8.4 Hz, 1H, PhCHABH), 1.29 (t, J = 7.1 Hz, 3H, CH3). δC 165.5 (C=O), 135.4 (Cq), 130.0 (CH), 129.0 (CH), 128.8 (CH), 128.6 (CH), 127.8 (CH), 116.2 (CN), 62.9 (OCH2), 39.6 (CH), 35.8 (CH2), 13.9 (CH3).

IR (neat) υ/cm⁻¹: 3032, 2988, 2251, 1720, 1456, 1260, 1198, 1030. HRMS (APCI) m/z calculated for C12H14NO2 [M+H]+ = 204.1025; found: 204.1019.

Methyl 2-benzyl-2-cyano-5-methylhex-4-enoate 531

By typical procedure D, to sodium hydride (60% dispersion in mineral oil, 0.40 g) in DMF (20 ml) under nitrogen at 0 °C was slowly added ethyl cyanoacetate 530 (1.90 g, 10 mmol) in DMF (10 ml). After 15 min, prenyl bromide (1.50 g, 10 mmol) was added dropwise to give the cyanoacetate 531 (2.40 g, 93%) as a colourless oil. δH 7.44 – 7.09 (m, 5H), 5.15 (br. t, J = 7.5 Hz, 1H, =CH), 4.05 (q, J = 7.1 Hz, 2H, OCH2), 3.12 (d, J = 13.5 Hz, PhCHAHB), 3.00 (d, J = 13.5 Hz,
PhCH$_2$H$_2$), 2.65 (dd, $J = 14.1$, 7.7 Hz, 1H, =CHCH$_2$H$_2$), 2.49 (dd, $J = 14.1$, 7.3 Hz, 1H, =CHCH$_2$H$_2$), 1.68 (s, 3H, CH$_3$), 1.59 (s, 3H, CH$_3$), 1.07 (t, $J = 7.1$ Hz, 3H, CH$_3$). δc 168.5 (CO$_2$), 137.9 (Cq), 134.4 (Cq), 129.9 (2 x CH), 128.8 (2 x CH), 127.74 (CH), 119.0 (CN), 116.43 (=CH), 62.5 (OCH$_2$), 51.5 (Cq), 42.4 (CH$_2$), 36.1 (CH$_2$), 25.9 (CH$_3$), 18.1 (CH$_3$), 13.9 (CH$_3$). IR (neat) υ/cm$^{-1}$: 2984, 2251, 2240, 1738, 1230, 910. HRMS (EI) m/z calculated for C$_{17}$H$_{21}$NO$_2$ [M]$^+$ = 271.1572; found: 271.1568.

**2-(Aminomethyl)-2-benzyl-5-methylhex-4-en-1-ol 532**

By general procedure C, reduction of the foregoing cyanoacetate 531 (2.37 g, 8.7 mmol) using lithium aluminium hydride (0.76 g, 20 mmol) gave the amino-alcohol 532 (1.90 g, 93%) as a colourless oil. δ$_H$ 7.23 – 7.06 (m, 5H), 5.22 – 5.14 (m, 1H, =CH), 3.52 – 3.48 (m, 2H, OCH$_2$), 2.79 – 2.73 (m, 1H), 2.71 (d, $J = 7.5$ Hz, 1H), 2.67 (d, $J = 7.5$ Hz, 1H), 2.60 (br. s, 3H, NH$_2$, OH), 2.46 (dd, $J = 13.4$, 3.5 Hz, 1H), 1.92 (dd, $J = 13.7$, 7.7 Hz, 1H, =CCH$_2$H$_2$), 1.83 (dd, $J = 13.7$, 5.8 Hz, 1H, =CCH$_2$H$_2$), 1.68 (d, $J = 1.0$ Hz, 3H, CH$_3$), 1.53 (s, 3H, CH$_3$). δc 137.9 (Cq), 134.0 (Cq), 130.5 (2 x CH), 128.0 (2 x CH), 126.1 (CH), 119.4 (=CH), 68.0 (OCH$_2$), 49.2 (NCH$_2$), 41.9 (Cq), 39.0 (CH$_2$), 30.7 (CH$_2$), 26.1 (CH$_3$), 18.0 (CH$_3$). IR (neat) υ/cm$^{-1}$: 3387, 2916, 1452, 1063, 1032. HRMS (EI) m/z calculated for C$_{15}$H$_{23}$NO [M]$^+$ = 233.1780; found: 233.1782.
Methyl (2-(hydroxymethyl)-2,5-dimethylhex-4-en-1-yl)carbamate 533

By general procedure A, methyl chloroformate (0.94 g, 10 mmol, 1.2 eq.) was added to the amino-alcohol 532 (1.87 g, 8.0 mmol, 1.0 eq.) and Et$_3$N (1.25 ml, 11 mmol, 1.3 eq.) to give the N-protected amino-alcohol 533 (1.65 g, 71%) as a colourless oil. $\delta$H 7.31 – 7.07 (m, 5H), 5.30 – 5.14 (m, 1H), 4.76 (br. s, NH), 3.62 (s, 3H, OCH$_3$), 3.24 – 3.19 (m, 1H), 3.17 (app. s, 2H, OCH$_2$), 2.89 (dd, $J = 14.6$, 5.9 Hz, 1H), 2.65 (d, $J = 13.3$ Hz, 1H), 2.40 (d, $J = 13.3$ Hz, 1H), 1.70 (s, 3H, CH$_3$), 1.69 (d, $J = 7.9$ Hz, 2H), 1.53 (s, 3H, CH$_3$). δC 137.6 (Cq), 135.0 (Cq), 130.5 (2 x CH), 128.1 (2 x CH), 126.2 (CH), 118.8 (=CH), 65.1 (CH$_2$OH), 52.5 (CH$_3$O), 45.1 (Cq), 44.3 (NCH$_2$), 38.7 (CH$_2$), 30.1 (CH$_2$), 26.2 (CH$_3$), 18.1 (CH$_3$). IR (neat) $\nu$/cm$^{-1}$: 3367, 2955, 1699, 1526, 1454, 1385, 1244, 1260, 1031, 909. HRMS (AP) $m/z$ calculated for C$_{17}$H$_{25}$NO$_3$ [M+H]$^+$ = 292.1913; found: 292.1916.

2-Acetyloxymethyl-2-benzyl-1-methoxycarbonylamino-5-methylhex-4-ene 534

By procedure E, but for 16 h, the alcohol 533 (180 mg, 0.8 mmol) was converted into the corresponding acetate 534 (215 mg, 100%), a colourless oil. $\delta$H 7.26 – 7.12 (m, 4H), 7.06 (d, $J = 7.0$ Hz, 1H), 5.19 (br. t, $J = 7.0$ Hz, 1H, =CH), 4.78 (br. s, 1H, NH), 3.83 (d, $J = 11.3$ Hz, 1H, CH$_3$H$_8$OAc), 3.73 (d, $J = 11.3$ Hz, 1H, CH$_3$H$_8$OAc), 3.58 (s, 3H, OCH$_3$), 3.13 (d, $J = 6.5$ Hz, 2H, NCH$_2$), 2.58 (d, $J = 4.7$ Hz, 2H, CH$_2$), 2.04 (s, 3H, Ac-CH$_3$), 1.89 (d, $J = 7.3$ Hz, 2H, CH$_2$), 1.69 (s, 3H, CH$_3$), 1.52 (s, 3H, CH$_3$). δC 166.7 (Ac-CO), 157.2 (CO$_2$), 136.8 (Cq), 135.0 (Cq), 130.4 (2 x CH), 128.3 (2 x CH), 126.5 (CH), 118.3 (=CH), 66.8 (OCH$_2$), 52.1 (OCH$_3$), 45.0 (NCH$_2$), 41.8 (Cq), 39.1 (CH$_2$), 31.0 (CH$_2$), 26.1 (CH$_3$), 22.1 (CH$_3$), 20.9 (COCH$_3$).
Methyl 5-(acetoxyethyl)-5-benzyl-2,2-dimethylpiperidine-1-carboxylate 535

By general procedure B, to the protected amino-alcohol 534 (191 mg, 0.6 mmol) in dry dichloromethane (10 ml) concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for 1 h at 20 °C to give the piperidine 535 (187 mg, 98%) as a colourless oil. δH 7.37 – 6.67 (m, 5H), 3.76 (d, J = 11.1 Hz, 1H, CHAHB1Ac), 3.65 (d, J = 11.1 Hz, 1H, CHAHB2Ac), 3.56 (s, 3H, OCH3), 3.28 (d, J = 14.1 Hz, 1H, NCHAHb), 3.18 (d, J = 14.1 Hz, 1H, NCHAHb), 2.64 (d, J = 13.4 Hz, 1H, PhCHAHb), 2.52 (d, J = 13.4 Hz, 1H, PhCHAHb), 2.03 (s, 3H, Ac-CH3), 1.44 – 1.38 (m, 2H), 1.31 (s, 6H, 2 x CH3), 1.18 – 1.11 (m, 2H, CH2). δC 171.1 (Ac-CO), 157.1 (CO2), 137.0 (Cq), 132.2 (CH), 130.4 (2 x CH), 128.1 (2 x CH), 67.3 (OCH2), 55.3 (NCq), 52.1 (OCH3), 46.4 (CH2N), 41.2 (CH2), 38.2 (CH2), 36.3 (Cq), 26.0 (CH3), 25.7 (CH3), 25.7 (CH2), 20.9 (CH3).

Methyl 5-benzyl-2,2-dimethyl-5-hydroxymethylpiperidine-1-carboxylate 536

To a solution of the acetoxyethyl piperidine 535 (165 mg, 0.5 mmol) in undried methanol (5 ml) was added potassium carbonate (200 mg, 1.45 mmol). The mixture was stirred for 20 h at room temperature. The solvent was removed and the solution was diluted with water (5 ml) and extracted with dichloromethane (3 x 5 ml). The combined organic layers were dried and concentrated to give the piperidine methanol 536 (142 mg, 99%) as a colourless oil. δH 7.34 – 6.71 (m, 5H), 3.59 (s, 3H, OCH3), 3.49 (d, J = 14.2 Hz, 1H), 3.33 – 3.27 (m, 1H), 3.20 (dd, J = 11.2,
5.7 Hz, 1H), 3.00 (d, J = 14.2 Hz, 1H), 3.00 (d, J = 14.2 Hz, 1H), 2.67 (d, J = 13.2 Hz, 1H), 2.46 (d, J = 13.2 Hz, 1H), 2.22 (br. s, 1H, OH), 1.50 – 1.41 (m, 2H, CH₂), 1.37 (t, J = 4.2 Hz, 2H, CH₂), 1.30 (s, 3H, CH₃), 1.27 (s, 3H, CH₃). δc 157.6 (Cq, CO₂), 147.6 (Cq), 130.5 (2 x CH), 127.9 (2 x CH), 126.1 (CH), 66.4 (OCH₂), 55.3 (NCq), 52.4 (OCH₃), 47.0 (CH₂N), 40.4 (CH₂), 39.1 (Cq), 26.3 (CH₂), 26.1 (CH₃), 25.9 (CH₃), 22.5 (CH₂).

3-Benzyl-6,6-dimethyl-3-(methoxycarbonylaminomethyl)-tetrahydro-2H-pyran 537

By general procedure B, to the N-protected amino-alcohol 533 (170 mg, 0.6 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for 1 h at 20 °C to give the tetrahydropyran 537 as a colourless oil (167 mg, 98%). δH 7.27 – 7.09 (m, 4H), 7.05 (d, J = 7.1 Hz, 1H), 4.55 (br. s, NH, 1H), 3.56 (s, 3H, OCH₃), 3.38 (d, J = 12.1 Hz, 1H), 3.28 (d, J = 12.1 Hz, 1H), 3.21 (dd, J = 14.0, 6.7 Hz, 1H), 2.95 (dd, J = 14.0, 5.4 Hz, 1H), 2.56 (d, J = 13.6 Hz, 1H), 2.46 (d, J = 13.6 Hz, 1H), 1.51 – 1.37 (m, 4H), 1.11 (s, 3H, CH₃), 1.09 (s, 3H, CH₃). δc 158.0 (C=O), 137.6 (Cq), 130.1 (2 x CH), 128.1 (2 x CH), 126.3 (CH), 71.3 (OCq), 66.6 (OCH₂), 52.1 (OCH₃), 44.8 (CH₂N), 40.5 (CH₂), 37.0 (Cq), 31.9 (CH₂), 27.0 (CH₃), 26.7 (CH₂), 25.4 (CH₃). IR (neat) υ/cm⁻¹: 3335, 2931, 1705, 1520, 1452, 1244, 1074, 1030, 1074, 909. HRMS (EI) m/z calculated for C₁₇H₂₅NO₃ [M]+ = 291.1834; found: 291.1830.
2-(Aminomethyl)-5-methyl-2-(3-methylbut-2-en-1-yl)hex-4-en-1-ol 538

Using general procedure C, the cyanoacetate 512 (0.50 g, 2 mmol) was reduced by lithium aluminium hydride (0.19 g, 5 mmol) to give the amino-alcohol 538 (0.40 g, 94%) as a clear oil. δH 5.08 (t, J = 7.3 Hz, 2H, 2 x =CH), 3.51 (s, 2H, OCH2), 3.72 (s, 2H, NCH2), 2.68 – 2.53 (br. s, 3H OH and NH2), 2.07 (dd, J = 8.0, 7.3 2H, 2 x CH), 1.92 (dd, J = 8.0, 7.3 2H, 2 x CH), 1.65 (s, 6H, 2 x CH3), 1.54 (s, 6H, 2 x CH3). δC 133.7 (2 x Cq), 119.6 (2 x =CH), 70.9 (OCH2), 49.3 (NCH2), 41.8 (Cq), 30.9 (2 x CH2), 26.1 (2 x CH3), 17.8 (2 x CH3). IR (neat) υ/cm\(^{-1}\): 3308, 2972, 2916, 2859, 1452, 1379, 1049. HRMS (APCI) m/z calculated for C13H26NO [M+H]+ = 212.2014; found: 212.2012.

N-(2-(Hydroxymethyl)-5-methyl-2-(3-methylbut-2-en-1-yl)hex-4-en-1-yl)-4-methylbenzenesulfonamide 539

By general procedure A, tosyl chloride (362 mg, 1.9 mmol) was added to the amino-alcohol 538 (0.40 g, 1.9 mmol) and Et3N (0.5 ml, 4.4 mmol) at -78 °C. The mixture was then stirred for 1 h at room temperature to give the sulfonamide 539 (0.52 g, 75%) as a colourless thick oil. δH 7.62 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 5.02 (t, J = 7.3 Hz, 2H, 2 x =CH) 4.94 (t, J = 6.4 Hz, 1H, NH), 3.51 (s, 2H, OCH2), 3.72 (d, J = 6.4, 2H, NCH2), 2.40 (s, 3H, ArCH3), 1.94 (dd, J = 7.5, 7.3 Hz, 2H), 1.86 (dd, J = 7.5, 7.3 Hz, 2H), 1.62 (s, 6H, 2 x CH3), 1.52 (s, 6H, 2 x CH3). δC 143.1 (Cq), 136.4 (Cq), 133.3 (Cq), 129.4 (2 x CH), 126.7 (2 x CH), 118.3 (2 x CH), 66.3 (OCH2), 47.6
(NCH2), 42.3 (Cq), 30.1 (2 x CH2), 25.8 (ArCH3), 21.2 (2 x CH3), 17.6 (2 x CH3). IR (neat) v/cm-1: 3506, 3295, 2982, 2924, 1452, 1331, 1092, 912. HRMS (ES) m/z calculated for C20H30NO3S [M-H]+ = 364.1946; found: 364.1933.

3,3,9,9-Tetramethyl-8-tosyl-2-oxa-8-azaspiro[5.5]undecane 540

By general procedure B, to the N-tosyl alcohol 539 (143 mg, 0.39 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for 1 h at 0 °C to give the oxa-azaspiro 540 as a colourless oil (139 mg, 97%). δH 7.60 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.2 Hz, 2H), 3.40 (d, J = 13.2 Hz, 1H), 3.36 (d, J = 12.0 Hz, 1H), 3.25 (d, J = 12.0 Hz, 1H), 3.06 (d, J = 13.2 Hz, 1H), 2.31 (s, 3H, Ar-CH3), 1.62 (dt, J = 5.8, 4.6 Hz, 1H, CH), 1.48 – 1.43 (m, 1H, CH), 1.43 – 1.36 (m, 4H, 2 x CH2), 1.34 (dt, J = 5.8, 4.6 Hz, 1H, CH), 1.29 (s, 3H, CH3), 1.28 – 1.21 (m, 1H, CH), 1.12 (m, 6H, 2 x CH3), 1.08 (s, 3H, CH3), 0.73 – 0.81 (m, 2H, CH2). δC 142.7 (Cq), 139.8 (Cq), 129.4 (2 x CH), 127.3 (2 x CH), 71.8 (OCq), 67.9 (OCH2), 58.2 (NCq), 49.1 (NCH2), 37.9 (CH2), 32.9 (Cq), 31.7 (CH2), 28.5 (CH2), 28.1 (CH2), 27.3 (ArCH3), 24.9 (2 x CH3), 22.6 (2 x CH3). IR (neat) v/cm-1: 2972, 2930, 2861, 1454, 1327, 1221, 1150, 1090, 906, 729. HRMS (EI) m/z calculated for C20H31NO3S [M]+ = 365.2025; found: 365.2022.

Methyl (E)-2-cyano-5-phenylpent-4-enoate 54246

A mixture of ethyl cyanoacetate 510 (4.60 g, 40 mmol, 1.2 eq.), cinnamyl chloride 541 (5.17 g, 33.3 mmol, 1.0 eq.), potassium carbonate (5.50 g, 40 mmol, 1.2 eq.) and sodium chloride (0.50 g)
in ethanol (50 ml) was refluxed overnight. The solvent was removed and the residue was taken up in ether (50 ml) and the solution washed with water (10 ml). The extracts were dried, concentrated and the residue purified by column chromatography on silica gel eluting with ether/hexanes (1:99) to give the cyanoacetate 542 (4.30 g, 56% yield) as a colourless oil. δH 7.32 – 7.23 (m, 4H), 7.21 – 7.14 (m, 1H), 6.50 (dt, J = 13.5, 4.3 Hz, 1H, =CH), 6.10 (d, J = 13.5 Hz, 1H, =CH), 4.19 (q, J = 6.9 Hz, 2H, OCH2), 3.54 (dd, J = 7.1, 6.3 Hz, 1H), 2.77 (dd, J = 7.1, 4.3 Hz, 2H, CH2), 1.23 (t, J = 6.9 Hz, 3H, CH3). δC 165.5 (CO), 135.8 (Cq), 135.0 (=CH), 128.6 (2 x =CH), 126.5 (2 x =CH), 116.2 (CN), 62.9 (OCH2), 37.9 (CH), 33.3 (CH2), 14.1 (CH3). IR (neat) υ/cm⁻¹: 2984, 2251, 1741, 1449, 1256, 1200, 1026, 966. HRMS (EI) m/z calculated for C14H15NO2 [M]+ = 229.1103; found: 229.1108.

(\textit{E})-2-(Aminomethyl)-5-phenylpent-4-en-1-ol 544

\[
\text{CO}_2\text{Et} \quad \text{Ph} \quad \text{Ph} \\
\text{542} \quad \text{LiAlH}_4 \quad \text{THF} \quad \text{H}_2\text{N} \quad \text{OH} \quad \text{544}
\]

Reduction of the foregoing cyanoacetate 542 (4.30 g, 18.8 mmol, 1.0 eq.) using lithium aluminium hydride (0.95 g, 25 mmol, 2 eq.) as described in general procedure C gave the amino-alcohol 544 (2.30 g, 61 %) as a yellow oil. δH 6.87 – 6.70 (m, 4H), 6.70 – 6.62 (m, 1H), 5.85 (d, J = 15.8 Hz, 1H, =CH), 5.66 – 5.59 (m, 1H, =CH), 3.29 (dd, J = 8.4, 3.5 Hz, 1H, OCH\textsubscript{A}CH\textsubscript{B}), 3.22 – 3.20 (dt, J = 4.5, 2.0 Hz, 2H, NCH\textsubscript{2}), 3.13 (dd, J = 8.4, 5.7 Hz, 1H, OCH\textsubscript{A}CH\textsubscript{B}), 2.57 – 2.53 (m, 1H), 2.23 (dd, J = 12.3, 8.7 Hz, 2H, CH\textsubscript{2}), 1.94 (br. s, 3H, OH and NH\textsubscript{2}). δC 136.7 (Cq), 128.5 (=CH), 127.9 (2 x =CH), 127.9 (=CH), 127.1 (=CH), 126.0 (2 x =CH), 68.6 (OCH2), 44.5 (NCH2), 42.4 (CH), 33.4 (CH2). IR (neat) υ/cm⁻¹: 3356, 3254, 2922, 1597, 1448, 1028, 964. HRMS (EI) m/z calculated for C12H17NO [M]+ = 291.1310; found: 291.1309.
**Methyl (2-(hydroxymethyl)-4-methylpent-4-en-1-yl)carbamate 545**

By general procedure A, methyl chloroformate (1.0 ml, 12.7 mmol) was added to the amino-alcohol 544 (1.17 g, 9 mmol) and Et₃N (2.5 ml, 22 mmol) to give the N-protected amino-alcohol 545 (1.20 g, 71%) as a colourless oil. δH 7.30 – 7.12 (m, 4H), 7.12 (dd, J = 13.3, 6.1 Hz, 1H, =CHAr), 6.35 (d, J = 15.8 Hz, 1H, =CH), 6.09 (dt, J = 15.8, 7.4 Hz, 1H, =CH), 5.08 (br. s, 1H, NH), 3.60 (s, 3H, OCH₃), 3.42 (dd, J = 11.3, 6.5 Hz, 1H, OCHₐCHₐ), 3.30 – 3.25 (m, 1H, OCHₐCHₐ), 3.18 – 3.11 (m, 2H, NCH₁), 2.19 – 2.17 (m, 1H, CH), 2.09 – 2.06 (m, 1H, CH), 1.78 – 1.67 (br. s, 1H, OH), 1.63 – 1.52 (m, 1H, CH). δC 158.4 (C=O), 137.3 (Cq), 132.0 (=CH), 128.3 (2 x =CH), 126.03 (2 x =CH), 127.9 (=CH), 127.2 (=CH), 62.6 (OCH₂), 52.4 (OCH₃), 41.6 (CH), 41.5 (NCH₂), 32.7 (CH₂). IR (neat) v/cm⁻¹: 3343, 2928, 1696, 1523, 1449, 1255, 1192, 1028, 966. HRMS (EI) m/z calculated for C₁₄H₁₇NO₂ [M-H₂O]^+ = 231.1259; found: 231.1250.

**(E)-2-((Methoxycarbonylamino)methyl)-5-phenylpent-4-en-1-yl acetate 547**

By general procedure E, the alcohol 545 (249 mg, 1.0 mmol) was reacted with acetic anhydride (0.1 ml, 1.1 mmol) for 17 h at room temperature to give the acetate 547 (291 mg, 100%) as a colourless oil. δH 7.31 – 7.21 (m, 4H), 7.17 – 7.11 (m, 1H), 6.36 (d, J = 12.3 Hz, 1H, =CH), 6.14 – 6.06 (m, 1H, =CH), 4.92 (br. s, 1H, NH), 4.11 (dd, J = 11.3, 4.6 Hz, 1H, OCHₐCHA), 3.98 – 3.96 (m, 1H, OCHₐCHA), 3.59 (s, 3H, OCH₃), 3.21 – 3.16 (m, 1H, NCHₐCHA), 3.08 (dd, J = 14.0, 6.6 Hz, 1H, NCHₐCHA), 2.20 (dd, J = 6.7, 5.0 Hz, 2H, CH₂), 2.01 (s, 3H, COCH₃), 1.67 – 1.60 (m,
The protected amino-alcohol 547 (267 mg, 0.92 mmol) under nitrogen was dissolved in dichloromethane (10 ml) and to this triflic acid (76 mg, 46 µl, 0.5 mmol) was added. The resulting mixture stirred for 6 h at 20 °C. The reaction was allowed to cool and was then quenched with saturated aqueous potassium carbonate (10 ml) and extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried and evaporated to give the piperidine 251 (224 mg, 84%) as a yellow oil and as a 1:1 ratio of stereoisomers, which were not separated.

The first isomer: δH 7.31 – 7.21 (m, 4H), 7.17 – 7.11 (m, 1H), 5.30 (t, J = 4.7 Hz, 1H, NCH), 4.09 – 4.01 (m, 1H, CH), 3.99 (dd, J = 10.5, 7.2 Hz, 1H, CH), 3.64 (s, 3H, OCH3), 3.25 – 3.13 (m, 1H, CH), 2.98 (dd, J = 11.0, 4.2 Hz, 1H, CH), 2.38 – 2.31 (m, 1H, CH), 1.98 (s, 3H, Ac-CH3), 1.93 – 1.83 (m, 2H, CH2), 1.81 – 1.75 (m, 1H, CH), 1.48 – 1.40 (m, 1H, CH). δC 171.1 (Ac-CO), 157.2 (C=O), 142.0 (Cq) 128.8 (2 x =CH), 126.9 (=CH), 126.6 (2 x =CH), 64.9 (OCH2), 52.9 (NCH), 52.1 (OCH3), 42.1 (NCH2), 32.5 (CH), 28.5 (CH2), 23.9 (CH2), 20.9 (Ac-CH3).

The second isomer: δH 4.88 (br. s, 1H), 3.90 (dd, J = 11.3, 6.2 Hz, 11H), 3.66 (m, 3H, OCH3), 1.96 (s, 3H, Ac-CH3) only 4 distinct peaks. δC 171.1 (Ac-CO), 156.7 (C=O), 140.0 (Cq) 128.7 (2 x =CH), 128.1 (=CH), 126.2 (2 x =CH), 64.5 (OCH2), 52.1 (NCH), 52.1 (OCH3), 43.0 (NCH2), 38.2 (CH), 28.5 (CH2), 20.9 (Ac-CH3), 23.8 (CH2).
The whole sample showed: IR (neat) $\nu$/cm$^{-1}$: 2945, 2860, 1728, 1699, 1529, 1447, 1190, 1034, 912, 735. HRMS (El) $m/z$ calculated for $C_{16}H_{21}NO_4 [M]^+ = 291.1471$; found: 291.1479.

$(E)$-N-(2-(Hydroxymethyl)-5-phenylpent-4-en-1-yl)-4-methylbenzenesulfonamide 549

![Chemical structure](image)

By general procedure A, tosyl chloride (496 mg, 2.6 mmol) was added to the amino-alcohol 544 (0.50 g, 2.6 mmol) and Et$_3$N (0.5 ml, 4.4 mmol) at -78 °C. The mixture was then stirred for 1 h as it warmed to room temperature to give the sulfonamide 549 (0.76 g, 85%) as a colourless oil. $\delta$H 7.26 – 7.22 (d, $J = 8.3$ Hz, 2H), 6.83 – 6.77 (m, 6H), 6.71 (dd, $J = 9.5, 6.8$ Hz, 1H), 5.87 (d, $J = 15.7$ Hz, 1H, =CH), 5.58 (dt, $J = 15.7, 7.5$ Hz, 1H, =CH), 4.70 (t, $J = 6.4$ Hz, 1H, NH), 3.27 (dd, $J = 9.7, 5.4$ Hz, 1H, OCH$_A$CH$_B$), 3.15 – 3.08 (m, 1H, OCH$_A$CH$_B$), 2.63 – 2.56 (m, 1H, NCH$_A$CH$_B$), 2.51 – 2.43 (m, 1H, OCH$_A$CH$_B$), 1.92 (s, 3H, Ar-CH$_3$), 1.65 (dd, $J = 12.9, 7.5, 6.5$ Hz, 2H, CH$_2$), 1.40 – 1.30 (m, 1H, CH). $\delta$C 143.4 (Cq), 137.2 (Cq), 136.9 (Cq), 132.3 (CH), 129.8 (2 x CH), 128.5 (2 x CH), 127.2 (2 x CH), 127.1 (CH), 126.1 (CH), 126.0 (OCH$_2$), 44.6 (NCH$_2$), 40.6 (CH), 32.4 (CH$_2$), 21.5 (ArCH$_3$). IR (neat) $\nu$/cm$^{-1}$: 3520, 3290, 2924, 1598, 1321, 1091, 1070, 968. HRMS (ES) $m/z$ calculated for $C_{19}H_{23}NNaO_3S [M+Na]^+ = 368.1296$; found: 368.1294.

6-Phenyl-1-tosylpiperidine-3-methanol 550

![Chemical structure](image)

To a stirred solution of the sulfonamide 549 (173 mg, 0.5 mmol) in dry dichloromethane (10 ml) under nitrogen, cooled in an ice-water bath, was added triflic acid (38 mg, 23 µl, 0.25 mmol). The resulting solution was stirred at 20 °C for 1 h to give the piperidine 550 (170 mg, 98%) as a colourless oil and as a 2:1 ratio of stereoisomers, which were not separated.
Major isomer: $\delta_H$ 7.52 (d, $J = 8.3$ Hz, 2H), 7.19 – 7.12 (m, 5H), 6.96 – 6.92 (m, 2H), 5.05 (t, $J = 4.5$ Hz, 1H, 6-H), 3.70 – 3.66 (m, 2H, OCH$_2$), 3.15 – 3.09 (dd, $J = 8.3$, 5.6 Hz, 2H, NCH$_2$), 2.59 (dd, $J = 14.2$, 11.8 Hz, 1H), 2.33 (s, 3H, Ar-CH$_3$), 1.97 (td, $J = 10.4$, 4.4 Hz, 2H, CH$_2$), 1.70 (br. s, 1H, OH), 1.63 – 1.53 (m, 2H, CH$_2$). $\delta_C$ 143.0 (Cq), 139.0 (Cq), 129.7 (2 x CH), 129.5 (2 x CH), 128.6 (CH), 128.5 (CH), 127.0 (CH), 126.9 (CH), 126.8 (CH), 62.2 (OCH$_2$), 56.4 (NCH), 41.9 (NCH$_2$), 35.4 (CH), 25.8 (CH$_2$), 21.5 (Ar-CH$_3$), 20.8 (CH$_2$).

The minor isomer was identified by: $\delta_H$ 7.70 (d, $J = 8.3$ Hz, 2H), 7.19 – 7.12 (m, 7H), 5.21 (d, $J = 4.8$ Hz, 1H, 6-H), 3.92 (dd, $J = 14.2$, 4.2, 1H), 3.39 (dd, $J = 11.3$, 5.6 Hz, 2H), 2.34 (s, 3H, Ar-CH$_3$), 3.24 (dd, $J = 10.8$, 5.4 Hz, 1H), 2.21 – 2.15 (m, 1H), 1.47 – 1.40 (m, 2H, CH$_2$), 1.34 – 1.27 (m, 1H), 0.98 (tt, $J = 13.2$, 6.5 Hz, 1H). $\delta_C$ 66. (OCH$_2$), 54.9 (NCH), 44.2 (NCH$_2$), 37.4 (CH), 26.8 (CH$_2$), 22.0 (CH$_2$), 21.5 (Ar-CH$_3$).

The whole sample showed IR (neat) $\nu$/cm$^{-1}$: 3530, 2926, 2859, 1452, 1334, 1329, 1155, 1090, 907. HRMS (EI) $m/z$ calculated for C$_{19}$H$_{23}$NO$_3$S [M]$^+$ = 345.1399; found: 345.1396.

(E)-2-((4-Methylphenylsulfonamido)methyl)-5-phenylpent-4-en-1-yl acetate 552

![Reaction scheme]

Following general procedure E, reaction between the alcohol 549 (346 mg, 1.0 mmol) and acetic anhydride (0.1 ml, 1.1 mmol) gave the acetate 552 (388 mg, 100%) as a colourless oil. $\delta_H$ 7.64 (d, $J = 8.2$ Hz, 2H), 7.25 – 7.20 (m, 6H), 7.18 – 7.11 (m, 1H), 6.32 (d, $J = 15.8$ Hz, 1H, =CH), 6.05 – 5.93 (m, 1H, =CH), 4.77 (t, $J = 6.8$ Hz, 1H, NH), 4.08 (dd, $J = 11.7$, 4.3 Hz, 1H), 3.95 – 3.88 (m, 1H), 2.91 (ddd, $J = 12.4$, 6.8, 5.4 Hz, 1H), 2.82 (dt, $J = 13.1$, 6.5 Hz, 1H), 2.34 (s, 3H, Ac-CH$_3$), 2.19 – 2.14 (m, 2H, CH$_2$), 1.96 (s, 3H, Ar-CH$_3$), 1.95 – 1.87 (m, 1H). $\delta_C$ 156.4 (C=O, Cq), 143.6 (Cq), 137.4 (Cq), 133.9 (Cq), 132.9 (CH), 129.7 (2 x CH), 128.6 (2 x CH), 127.4 (CH), 127.1...
CH), 126.3 (CH), 126.1 (CH), 64.0 (OCH\textsubscript{2}), 43.8 (NCH\textsubscript{2}), 38.5 (CH), 32.5 (CH\textsubscript{2}), 21.5 (Ar-CH\textsubscript{3}), 21.0 (Ac-CH\textsubscript{3}). IR (neat) \(\nu/cm^{-1}\): 3298, 2958, 1740, 1599, 1327, 1238, 1096, 970. HRMS (E) \(m/z\) calculated for C\textsubscript{21}H\textsubscript{25}NO\textsubscript{4}SNa \[M+Na]^+ = 410.1402; found: 410.1392.

### 5-Acetoxymethyl-2-phenyl-1-tosylpiperidine 553

![5-Acetoxymethyl-2-phenyl-1-tosylpiperidine 553](image)

To a stirred solution of the protected amino-alcohol 552 (388 mg, 1.0 mmol) in dry dichloromethane (10 ml) under nitrogen, cooled in an ice-water bath, was added triflic acid (61 mg, 37 \(\mu\)l, 0.5 mmol). The resulting mixture stirred was stirred at 20 °C for 30 min to give the piperidine 553 (358 mg, 92%) as a colourless oil, consisting of a 2:1 ratio of stereoisomers.

**Major isomer** : \(\delta_H\) 7.54 (d, \(J = 7.8\) Hz, 2H), 7.26 – 7.14 (m, 7H), 4.97 (t, \(J = 4.6\) Hz, 1H, 6-H), 3.80 (dd, \(J = 11.0, 6.1\) Hz, 1H), 3.61 (dd, \(J = 11.0, 9.0\) Hz, 1H), 3.45 (dd, \(J = 13.7, 3.5\) Hz, 1H), 3.34 (dd, \(J = 13.7, 3.8\) Hz, 1H), 2.33 (s, 3H, Ac-CH\textsubscript{3}), 2.24 – 2.18 (m, 1H), 2.00 (s, 3H, Ar-CH\textsubscript{3}), 1.96 – 1.92 (m, 2H, CH\textsubscript{2}), 1.66 – 1.50 (m, 2H, CH\textsubscript{2}). \(\delta_C\) 170.7 (C=O), 143.2 (Cq), 139.2 (Cq), 137.5 (Cq), 129.7 (CH), 129.5 (CH), 128.7 (CH), 128.5 (CH), 127.0 (CH), 126.8 (CH), 126.8 (CH), 64.6 (OCH\textsubscript{2}), 56.9 (NCH), 43.2 (NCH\textsubscript{2}), 32.6 (CH), 26.3 (CH\textsubscript{2}), 21.5 (Ar-CH\textsubscript{3}), 21.1 (CH\textsubscript{2}), 20.9 (Ac-CH\textsubscript{3}).

**Minor isomer** \(\delta_H\) 7.67 (d, \(J = 8.3\) Hz, 2H), 7.20 – 7.12 (m, 7H), 5.22 (d, \(J = 4.8\) Hz, 1H, 6-H), 3.90 (dd, \(J = 14.4, 4.2\) Hz, 1H), 3.74 (dd, \(J = 11.2, 5.3\) Hz, 1H), 3.53 (d, \(J = 8.2\) Hz, 1H), 3.50 (d, \(J = 8.2\) Hz, 1H), 2.36 (s, 3H, Ac-CH\textsubscript{3}), 2.25 – 2.17 (m, 1H, CH), 1.57 – 1.49 (m, 2H, CH\textsubscript{2}), 1.29 (ddd, \(J = 13.7, 9.0, 4.4\) Hz, 1H), 1.03 (ddd, \(J = 13.5, 13.3, 3.4\) Hz, 1H). \(\delta_C\) 170.7 (C=O), 143.2 (Cq), 138.2 (Cq), 138.0 (Cq), 129.7 (2 x CH), 129.5 (CH), 128.7 (2 x CH), 127.0 (2 x CH), 126.8 (2 x CH), 66.3 (OCH\textsubscript{2}), 54.7 (NCH), 44.3 (NCH\textsubscript{2}), 34.5 (CH), 26.5 (CH\textsubscript{2}), 22.2 (CH\textsubscript{2}), 21.5 (Ar-CH\textsubscript{3}), 21.1 (CH\textsubscript{2}), 20.9 (Ac-CH\textsubscript{3}).
The whole sample showed IR (neat) $\nu$/cm$^{-1}$: 2928, 1738, 1452, 1334, 1236, 1159, 1092, 907. HRMS (EI) $m/z$ calculated for C$_{21}$H$_{25}$NO$_4$S [M]$^+$ = 387.1504; found: 387.1487.

(E-6-Phenyl-1-tosylpiperidin-3-yl)methanol 550

To a solution of foregoing acetoxymethyl piperidine 553 (350 mg, 0.9 mmol) in undried methanol (5 ml) was added potassium carbonate (200 mg, 1.5 mmol). The reaction was stirred for 17 h at room temperature. The solvent was removed and the residue was diluted with water (5 ml) and extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried and concentrated to give the piperidine methanol 550 (305 mg, 98%) as a colourless oil, which exhibited spectroscopic and analytical data identical to those reported above for a sample of the piperidine methanol 550 prepared by cyclisation of the amino-alcohol 549, except for a slight difference in the ratio of stereoisomers (p. 246).

Ethyl 2-cyano-4-methylpent-4-enoate 558 and

Ethyl 2-cyano-4-methyl-2-(2-methylallyl)pent-4-enoate 559

By typical procedure D, to sodium hydride (60% dispersion in mineral oil, 0.40 g, 10 mmol, 1.0 eq.) in DMF (20 ml) under nitrogen at 0 °C was slowly added ethyl cyanoacetate 510 (2.20 g, 20 mmol, 2.0 eq.) in DMF (10 ml). After 15 min, 3-chloro-2-methylprop-1-ene 557 (0.90 g, 10 mmol, 1.0 eq.) was added to give, after the usual work-up and chromatographic separation, the cyanopentenoates 558 (1.10 g, 69%) and 559 (0.44 g, 20%) as colourless oil.
Ethyl 2-cyano-4-methylpent-4-enoate 558: \( \delta_H 4.90 \) (\(app.\) s, 1H, =CH\(_A\)), 4.83 (\(app.\) s, 1H, =CH\(_B\)), 4.20 (q, \(J = 7.1\) Hz, 2H, OCH\(_2\)), 3.58 (dd, \(J = 8.7, 6.2\) Hz, 1H), 2.58 (qd, \(J = 14.5, 7.5\) Hz, 2H, CH\(_2\)), 1.73 (s, 3H, CH\(_3\)), 1.26 (t, \(J = 7.1\) Hz, 3H, CH\(_3\)). \( \delta_C 165.8 \) (C=O, Cq), 139.3 (Cq), 116.2 (CN), 114.8 (CH\(_2\)), 62.9 (OCH\(_2\)), 37.7 (CH), 36.4 (CH\(_2\)), 21.9 (CH\(_3\)), 14.0 (CH\(_3\)). IR (neat) \( \nu/cm^{-1}\): 2984, 2251, 1722, 1457, 1370, 1260, 1202, 1022, 902. HRMS (ES) \( m/z \) calculated for C\(_9\)H\(_{12}\)NO\(_2\) [M-H]+ = 166.0868; found: 166.0868.

Ethyl 2-cyano-4-methyl-2-(2-methylallyl)pent-4-enoate 559: \( \delta_H 4.90 \) (\(app.\) s, 2H, 2 x =CH\(_A\)), 4.82 (\(app.\) s, 2H, 2 x =CH\(_B\)), 4.17 (q, \(J = 7.1\) Hz, 2H, OCH\(_2\)), 2.62 (d, \(J = 14.0\) Hz, 2H, 2 x CH), 2.43 (d, \(J = 14.0\) Hz, 2H, 2 x CH), 1.78 (s, 6H, 2 x CH\(_3\)), 1.24 (t, \(J = 7.1\) Hz, 3H, CH\(_3\)). \( \delta_C 168.6 \) (C=O), 139.2 (2 x Cq), 119.3 (CN, Cq), 116.4 (2 x =CH), 62.6 (OCH\(_2\)), 48.3 (Cq), 45.7 (2 x CH\(_2\)) 23.0 (2 x CH\(_3\)), 13.8 (CH\(_3\)).

2-(Aminomethyl)-4-methylpent-4-en-1-ol 560

Following general procedure C, the cyanoacetate 558 (1.67 g, 10 mmol, 1.0 eq.) was reduced using lithium aluminium hydride (0.76 g, 20 mmol, 2.0 eq.) to give the amido-alcohol 560 (1.19 g, 92%) as a clear oil, which was used directly in the next step. \( \delta_H 4.58 \) (d, \(J = 13.2\) Hz, 1H, =CH\(_A\)), 4.53 (s, 1H, =CH\(_B\)), 3.59 – 3.56 (m, 2H, OCH\(_2\)), 3.42 (dd, \(J = 10.7, 7.6\) Hz, 1H, NCH\(_A\)H\(_B\)), 2.85 (ddd, \(J = 12.3, 3.5, 1.4\) Hz, 1H, NCH\(_AH\)B), 2.54 (d, \(J = 3.8\) Hz, 2H, CH\(_2\)), 2.48 (br. s, 3H, NH\(_2\), OH), 1.72 - 165 (m, 1H), 1.55 (s, 3H, CH\(_3\)). \( \delta_C 143.5 \) (Cq), 112.0 (=CH\(_2\)), 67.9 (OCH\(_2\)), 46.4 (NCH\(_2\)), 39.0 (CH), 38.1 (CH\(_2\)), 22.1 (CH\(_3\)).
Methyl (2-(hydroxymethyl)-4-methylpent-4-en-1-yl)carbamate 561

By general procedure A, methyl chloroformate (1.0 ml, 12.7 mmol) was added to the amino-alcohol 560 (1.17 g, 9.0 mmol) and Et₃N (2.5 ml, 22 mmol) to give the N-protected amino-alcohol 561 (1.20 g, 71%) as a colourless oil. δH 5.08 (br. s, 1H, NH), 4.81 (app. s, 1H, =CH_A), 4.73 (d, J = 0.8 Hz, 1H, =CH_B), 3.70 (s, 3H, OCH₃), 3.60 (ddd, J = 11.2, 7.1, 3.9 Hz, 1H), 3.40 (ddd, J = 10.5, 10.1, 5.2 Hz, 2H), 3.30 (t, J = 6.6 Hz, 1H), 3.11 (dt, J = 14.3, 6.4 Hz, 1H), 2.03 (dd, J = 13.5, 7.0 Hz, 1H), 1.96 (t, J = 6.6 Hz, 1H), 1.90 – 1.85 (m, 1H), 1.73 (s, 3H, CH₃). δC 158.4 (C=O), 143.3 (Cq), 112.4 (=CH₂), 62.9 (CH₂OH), 52.3 (OCH₃), 41.2 (NCH₂), 38.9 (CH), 37.5 (CH₂), 22.1 (CH₃). IR (neat) ν/cm⁻¹: 3329, 2928, 1695, 1525, 1444, 1377, 1257, 1194, 1033, 891. HRMS (ES) m/z calculated for C₉H₁₈NO₃ [M+H]^+ = 188.1287; found: 188.1281.

Methyl ((5,5-dimethyltetrahydrofuran-3-yl)methyl)carbamate 562

By general procedure B, to the N-protected amino-alcohol 561 (116 mg, 0.62 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for 1 h at 0 °C to give the tetrahydrofuran 562 as a colourless oil (112 mg, 97%). δH 4.80 (br. s, NH, 1H), 3.88 (dd, J = 8.8, 7.3 Hz, 1H), 3.60 (s, 3H, OCH₃), 3.47 (dt, J = 14.5, 7.2 Hz, 1H), 3.21 – 3.05 (m, 2H), 2.50 (dt, J = 14.5, 7.4 Hz, 1H), 1.85 (dd, J = 12.4, 8.2 Hz, 1H), 1.34 (dt, J = 9.2, 7.3 Hz, 1H), 1.23 (s, 3H, CH₃), 1.12 (s, 3H, CH₃). δC 157.2 (C=O), 80.9 (OCq), 69.9 (OCH₂), 52.8 (OCH₃), 44.1 (CH₂N), 42.7 (CH₂), 40.4 (CH), 28.7 (CH₃), 27.7 (CH₃). IR (neat) ν/cm⁻¹: 3327, 2969, 2932, 1701, 1537, 1449, 1368, 1192, 1146, 775. HRMS (ES) m/z calculated for C₉H₁₈NO₃ [M+H]^+ = 188.1287; found: 188.1283.
2-((Methoxycarbonylamino)methyl)-4-methylpent-4-en-1-yl acetate 564

\[
\text{\begin{align*}
\text{OH} & \quad \text{OAc} \\
561 & \quad \text{Py, CH}_2\text{Cl}_2 \\
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me}
\end{align*}}
\]

By general procedure E, the alcohol 561 (187 mg, 1.0 mmol) was converted into the acetate 564 (229 mg, 100%), a colourless oil. \(\delta_H 4.92 \ (br. \ s, \ 1H, \ \text{NH}), \ 4.75 \ (app. \ s, \ 1H, =\text{CH}_A), \ 4.67 \ (app. \ s, \ 1H, =\text{CH}_B), \ 4.09 \ (dd, \ J = 11.3, \ 3.5 \ Hz, \ 1H), \ 3.87 \ (dd, \ J = 11.3, \ 5.5 \ Hz, \ 1H), \ 3.59 \ (s, \ 3H, \ \text{OCH}_3), \ 3.25 - 3.17 \ (m, \ 1H), \ 3.02 - 2.94 \ (m, \ 1H), \ 2.01 \ (s, \ 3H, \ \text{Ac-CH}_3), \ 1.99 - 1.93 \ (m, \ 2H, \ \text{CH}_2), \ 1.67 \ (s, \ 3H, \ \text{CH}_3), \ \delta_C 172.2 \ (\text{Ac-CO}), \ 157.7 \ (\text{C}=\text{O}), \ 133.9 \ (\text{Cq}), \ 112.9 \ (=\text{CH}_2), \ 64.8 \ (\text{OCH}_2), \ 52.1 \ (\text{OCH}_3), \ 42.2 \ (\text{NCH}_2), \ 37.9 \ (\text{CH}_2), \ 36.1 \ (\text{CH}), \ 22.1 \ (\text{Ac-CH}_3), \ 20.8 \ (\text{CH}_3).\)

Methyl 4-(acetoxymethyl)-2,2-dimethylpyrrolidine-1-carboxylate 565

\[
\text{\begin{align*}
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
564 & \quad \text{CH}_2\text{Cl}_2, \ 20 ^\circ \text{C, 1h} \\
\text{NH} & \quad \text{NH}
\end{align*}}
\]

By general procedure B, to the protected amino-alcohol 564 (200 mg, 0.9 mmol) in dry dichloromethane (10 ml) concentrated sulfuric acid (2 drops) was added and the resulting mixture stirred for 1 h at 20 °C to give the pyrrolidine 565 (197 mg, 99%) as a colourless oil. \(\delta_H 4.02 \ (dd, \ J = 10.9, \ 5.9 \ Hz, \ 1H), \ 3.87 \ (dd, \ J = 11.2, \ 3.7 \ Hz, \ 1H), \ 3.60 \ (d, \ J = 14.7 \ Hz, \ 1H), \ 3.55 \ (s, \ 3H, \ \text{OCH}_3), \ 2.99 \ (t, \ J = 10.4 \ Hz, \ 1H), \ 2.51 - 2.36 \ (m, \ 1H), \ 1.97 \ (s, \ 3H, \ \text{Ac-CH}_3), \ 1.87 - 1.76 \ (m, \ 1H), \ 1.50 \ (dt, \ J = 24.1, \ 12.1 \ Hz, \ 1H), \ 1.41 \ (s, \ 3H, \ \text{CH}_3), \ 1.25 \ (d, \ J = 15.7 \ Hz, \ 3H, \ \text{CH}_3), \ \delta_C 170.8 \ (\text{Ac-CO}), \ 154.4 \ (\text{Cq}, \ \text{CO}), \ 65.8 \ (\text{OCH}_2), \ 60.9 \ (\text{NCq}), \ 51.6 \ (\text{OCH}_3), \ 50.6 \ (\text{CH}_2\text{N}), \ 44.7 \ (\text{CH}_2), \ 34.6 \ (\text{CH}), \ 27.3 \ (\text{Ac-CH}_3), \ 25.5 \ (\text{CH}_3), \ 20.8 \ (\text{CH}_3), \ \text{IR (neat) w/cm}^{-1}: \ 2961, \ 1743, \ 1699, \ 1445, \ 1233, \ 1190, \ 1111, \ 1084, \ 1033. \ \text{HRMS (EI) m/z calculated for C}_{13}\text{H}_{23}\text{NO}_2 [\text{M}]^{+} = 229.1314; \ \text{found: 229.1316.}
Methyl 2,2-dimethyl-4-(hydroxymethyl)pyrrolidine-1-carboxylate 563

\[
\text{Methyl 2,2-dimethyl-4-(hydroxymethyl)pyrrolidine-1-carboxylate 563}
\]

To a solution of the acetoxymethyl pyrrolidine 565 (170 mg, 0.74 mmol) in undried methanol (5 ml) was added potassium carbonate (200 mg, 1.5 mmol). The reaction was stirred for 18 h at room temperature. The solvent was removed and the residue was diluted with water (5 ml) extracted with dichloromethane (3 x 5 ml). The combined organic layers were dried and concentrated to give the pyrrolidine 563 (131 mg, 95%) as a colourless oil. $^1$H 3.61 (d, $J = 11.0$ Hz, 2H, OCH$_2$), 3.60 (s, 3H, OCH$_3$), 3.04 (t, $J = 10.1$ Hz, 1H), 2.43 – 2.29 (m, 1H), 1.83 (dd, $J = 11.7$, 6.2 Hz, 1H), 1.73 (br. s, 1H, OH), 1.62 – 1.45 (m, 1H), 1.43 (s, 3H, CH$_3$), 1.34 (t, $J = 11.1$ Hz, 1H), 1.29 (s, 3H, CH$_3$). $^1$C 64.8 (OCH$_2$), 60.9 (NCq), 51.8 (OCH$_3$), 50.5 (CH$_2$N), 37.6 (CH), 29.8 (CH$_2$), 25.6 (2 x CH$_3$).

Methyl ((5,5-dimethyltetrahydrofuran-3-yl)methyl)carbamate 562

\[
\text{Methyl ((5,5-dimethyltetrahydrofuran-3-yl)methyl)carbamate 562}
\]

By general procedure B, to the alcohol 563 (90 mg, 0.5 mmol) in dry dichloromethane (10 ml) concentrated sulfuric acid (12 mg, 0.12 mmol) was added and the resulting mixture stirred for 20 h at 20$^\circ$ C to give the tetrahydrofuran 562 as (87 mg, 97%) as colourless oil, which exhibited spectroscopic and analytical data identical to that reported above for a sample of the tetrahydrofuran prepared by cyclisation of the alcohol 561.
**N-(2-(Hydroxymethyl)-4-methylpent-4-en-1-yl)-4-methylbenzenesulfonamide 566**

\[ \begin{align*}
\text{OH} & \quad \text{TsCl} \\
\text{N} & \quad \text{Et}_3\text{N}, 0^\circ\text{C} \\
\text{CH}_2\text{Cl}_2 \\
\text{NH} & \quad \text{T}\text{s} \\
\end{align*} \]

By general procedure A, tosyl chloride (553 mg, 3.0 mmol) was added to the amino-alcohol 560 (0.28 g, 2.2 mmol) and Et\(_3\)N (0.5 ml, 4.4 mmol) at 0 °C. The mixture was then stirred for 1 h at room temperature to give the sulfonamide 566 (0.52 g, 83%) as a colourless oil. \(\delta_H\) 7.72 (d, \(J = 7.9\) Hz, 2H), 7.32 (d, \(J = 7.9\) Hz, 2H), 5.44 (t, \(J = 3.8\) Hz, 1H, NH), 4.76 (td, \(J = 1.4, 0.9\) Hz, 1H, =CH), 4.67 (d, \(J = 0.9\) Hz, 1H, =CH), 3.70 (d, \(J = 11.0\) Hz, 1H, OCH\(_A\)CH\(_B\)), 3.52 (d, \(J = 11.0\) Hz, 1H, OCH\(_A\)CH\(_B\)), 3.05 (dd, \(J = 11.7, 3.8\) Hz, 1H, NCH\(_A\)CH\(_B\)), 2.88 (dd, \(J = 11.7, 3.8\) Hz, 1H, NCH\(_A\)CH\(_B\)), 2.44 (s, 3H, ArCH\(_3\)), 1.93 – 1.88 (m, 3H, CH and CH\(_2\)), 1.65 (s, 3H, CH\(_3\)). \(\delta_C\) 143.4 (Cq), 142.8 (Cq), 137.0 (Cq), 129.8 (CH), 129.7 (CH), 127.0 (CH), 112.6 (=CH\(_3\)), 64.0 (OCH\(_2\)), 44.8 (NCH\(_2\)), 37.9 (CH), 37.4 (CH\(_2\)), 22.0 (ArCH\(_3\)), 21.5 (CH\(_3\)). IR (neat) \(\nu/cm^{-1}\): 3520, 3281, 2922, 1599, 1445, 1319, 1092, 893. HRMS (APCI) \(m/z\) calculated for C\(_{14}\)H\(_{22}\)NO\(_3\)S [M+H]\(^+\) = 284.1320; found: 284.1316.

**N-((5,5-Dimethyltetrahydrofuran-3-yl)methyl)-4-methylbenzenesulfonamide 567**

\[ \begin{align*}
\text{OH} & \quad \text{c.H}_2\text{SO}_4 \\
\text{N} & \quad \text{CH}_2\text{Cl}_2, 0^\circ\text{C}, 1\text{h} \\
\text{NH} & \quad \text{T}\text{s} \\
\text{NHTs} & \quad \text{T}\text{s} \\
\text{OH} & \quad \text{T}\text{s} \\
\end{align*} \]

By general procedure B, to the N-tosyl alcohol 566 (120 mg, 0.4 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for 1 h at 0° C to give the tetrahydrofuran 567 as inseparable mixture with ca. 20% of pyrrolidine 568 as a colourless oil (116 mg, total 97%).

The tetrahydrofuran 567: \(\delta_H\) 7.65 (d, \(J = 8.2\) Hz, 2H), 7.22 (d, \(J = 8.2\) Hz, 2H), 4.95 (t, \(J = 6.3\) Hz, 1H, NH), 3.78 (dd, \(J = 9.5, 7.2\) Hz, 1H), 3.35 (dd, \(J = 9.5, 3.7\) Hz, 1H), 2.85 – 2.79 (m, 2H, 254
NCH₂, 2.48 – 2.39 (m, 1H), 2.34 (s, 3H, ArCH₃), 1.82 – 1.71 (m, 2H, CH₂), 1.13 (s, 3H, CH₃), 1.05 (s, 3H, CH₃). δc 14.5 (Cq), 136.9 (Cq), 129.8 (2 x CH), 127.2 (2 x CH), 81.0 (OCq), 69.7 (OCH₂), 46.3 (NCH₂), 42.7 (CH₂), 40.0 (CH), 29.2 (ArCH₃), 27.6 (CH₃), 21.5 (CH₃). IR (neat) υ/cm⁻¹: 3266, 2971, 2930, 2868, 1599, 1456, 1329, 1091, 910. HRMS (APCI) m/z calculated for C₁₄H₂₂NO₃S [M+H]⁺ = 284.1320; found: 284.1320.

4-Methyl-2-((4-methylphenylsulfonamido)methyl)pent-4-en-1-yl acetate 569

By general procedure E, the alcohol 566 (283 mg, 1.0 mmol) was reacted with acetic anhydride (0.1 ml, 1.1 mmol) for 19 h to give the acetate 569 (325 mg, 100%) as a colourless oil. δH 7.66 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 4.95 (br. s, 1H, NH), 4.72 (s, 1H, =CH), 4.61 (d, J = 0.8 Hz, 1H, =CH), 4.05 (dd, J = 11.4, 3.6 Hz, 1H, CH), 3.83 – 3.77 (m, 1H, CH), 2.90 – 2.84 (m, 1H, CH), 2.76 (dt, J = 12.9, 4.3 Hz, 1H, CH), 2.36 (s, 3H, ArCH₃), 1.96 (s, 3H, AcCH₃), 1.59 (s, 3H, CH₃). δc 171.1 (C=O), 143.4 (Cq), 142.1 (Cq), 129.7 (2 x CH), 127.1 (2 x CH), 113.1 (=CH₂), 64.5 (OCH₂), 44.1 (NCH₂), 37.6 (CH₂), 35.9 (CH), 22.0 (Ar-CH₃), 22.5 (Ac-CH₃), 20.7 (CH₃). IR (neat) υ/cm⁻¹: 3283, 2961, 2934, 2872, 1738, 1647, 1599, 1446, 1369, 1027, 1238, 1094, 1038, 899, 814. HRMS (ES) m/z calculated for C₁₆H₂₄NO₄S [M+H]⁺ = 326.1426; found: 326.1425.

(5,5-Dimethyl-1-tosylpyrrolidin-3-yl)methyl acetate 570

By general procedure B, to the sulfonamide 569 (292 mg, 0.9 mmol) in dry dichloromethane (10 ml) concentrated sulfuric acid (3 drops) was added and the resulting mixture was stirred for 1 h at 0°C to give the pyrrolidine 570 as a colourless oil (289 mg, 99%). δH 7.58 (d, J = 8.3 Hz, 2H),
7.14 (d, \( J = 8.3 \) Hz, 2H), 3.91 (dd, \( J = 11.0, 5.8 \) Hz, 1H), 3.74 (dd, \( J = 11.0, 7.8 \) Hz, 1H), 3.51 (dd, \( J = 11.0, 7.8 \) Hz, 1H), 2.85 (dd, \( J = 12.3, 6.5 \) Hz, 3H), 2.47 – 2.36 (m, 1H), 2.28 (s, 3H, ArCH\(_3\)), 1.90 (s, 3H, AcCH\(_3\)), 1.82 – 1.78 (m, 1H), 1.77 – 1.72 (m, 1H), 1.34 (s, 3H, CH\(_3\)), 1.30 (s, 3H, CH\(_3\)). \( \delta_c \) 170.8 (C=O), 142.8 (Cq), 138.4 (Cq), 129.4 (2 x CH), 127.3 (2 x CH), 65.4 (NCq), 65.4 (OCH\(_2\)), 52.0 (CH\(_2\)), 45.7 (CH\(_2\)), 34.8 (CH), 28.6 (AcCH\(_3\)), 28.4 (ArCH\(_3\)), 21.43 (CH\(_3\)), 20.74 (CH\(_3\)). IR (neat) \( \nu/cm^{-1} \): 29681, 2928, 2870, 1740, 1456, 1369, 1332, 1230, 1090, 1034, 912.

HRMS (ES) \( m/z \) calculated for C\(_{16}\)H\(_{24}\)NO\(_4\)S [M+H]+ = 326.1426; found: 326.1426.

(5,5-Dimethyl-1-tosylpyrrolidin-3-yl)methanol 569

To a solution of acetoxyethyl pyrrolidine 570 (270 mg, 0.83 mmol) in undried methanol (5 ml) was added potassium carbonate (200 mg, 1.5 mmol). The reaction was stirred for 18 h at room temperature. The solvent was removed and the residue was diluted with water (5 ml) and extracted with dichloromethane (3 x 5 ml). The combined organic layers were dried and concentrated to give the pyrrolidine 568 (231 mg, 98%) as a colourless oil. \( \delta_H \) 7.66 (d, \( J = 8.3 \) Hz, 2H), 7.21 (d, \( J = 8.3 \) Hz, 2H), 3.60 – 3.52 (m, 2H, 2 x CH), 3.47 (dd, \( J = 10.1, 6.6 \) Hz, 1H), 2.97 (t, \( J = 9.3 \) Hz, 1H), 2.35 (s, 3H, ArCH\(_3\)), 1.81 (dd, \( J = 12.4, 6.7 \) Hz, 1H), 1.56 (br. s, 1H, OH), 1.55 – 1.46 (m, 2H, CH\(_2\)), 1.43 (s, 3H, CH\(_3\)), 1.36 (s, 3H, CH\(_3\)). \( \delta_c \) 142.8 (Cq), 138.4 (Cq), 129.4 (2 x CH), 127.2 (2 x CH), 65.5 (NCq), 64.4 (OCH\(_2\)), 51.8 (CH\(_2\)), 45.6 (CH\(_2\)), 38.0 (CH), 28.6 (2 x CH\(_3\)), 21.5 (CH\(_3\)). IR (neat) \( \nu/cm^{-1} \): 3513, 2924, 1330, 1261, 1091, 941. HRMS (EI) \( m/z \) calculated for C\(_{14}\)H\(_{21}\)NO\(_3\)S [M]+ = 283.1242; found: 283.1236.
\[ N-((5,5-\text{Dimethyltetrahydrofuran-3-yl})\text{methyl})-4-\text{methylbenzenesulfonamide} \]

By general procedure B, to the alcohol 568 (174 mg, 0.7 mmol) in dry dichloromethane (10 ml) concentrated sulfuric acid (2 drops) was added and the resulting mixture stirred for 18 h at 20°C to give the tetrahydrofuran 567 as inseparable mixture with of pyrrolidine 568* as colourless oil (162 mg, total 93%), which exhibited spectroscopic and analytical data identical to those reported above for a sample of the tetrahydrofuran prepared by cyclisation of the alcohol 566, except for a slight difference in the ratio of the two compounds.

*The structure of pyrrolidine 568 was confirmed by different way (p. 256).

\[ \text{2-(Aminomethyl)-4-methyl-2-(2-methylallyl)pent-4-en-1-ol 569}^{47} \]

Using general procedure C, the cyanoacetate 559 (0.44 g, 2 mmol) was reduced by lithium aluminium hydride (0.19 g, 5 mmol) to give the amino-alcohol 569 (0.35 g, 96%) as a clear oil, which was used directly in the next step. \( \delta^H \) 4.88 (d, \( J = 1.2 \) Hz, 1H, 2 x =CH\(_A\)), 4.63 (app. s, 1H, 2 x =CH\(_B\)), 3.75 (t, \( J = 6.4 \) Hz, 2H, NCH\(_2\)), 3.62 (s, 2H, OCH\(_2\)), 2.90 (s, 2H, NH\(_2\)), 2.73 – 2.33 (br. s, OH), 2.17 (d, \( J = 13.6 \) Hz, 2H, 2 x CH\(_A\)), 2.12 (d, \( J = 13.6 \) Hz, 2H, 2 x CH\(_B\)), 1.55 (s, 6H, 2 x CH\(_3\)). \( \delta^C \) 142.7 (2 x Cq), 115.0 (2 x =CH\(_2\)), 70.4 (OCH\(_2\)), 67.9 (NCH\(_2\)), 49.7 (Cq), 41.8 (2 x CH\(_2\)), 25.4 (2 x CH\(_3\)).
\(N\)-(2-(Hydroxymethyl)-4-methyl-2-(2-methylallyl)pent-4-en-1-yl)-4-ethylbenzenesulfonamide

570\(^{47}\)

By general procedure A, tosyl chloride (191 mg, 1 mmol) was added to the amino-alcohol 569 (156 mg, 0.85 mmol) and Et\(_3\)N (0.2 ml) at -78 °C. The mixture was then stirred for 1 h without additional cooling to give, after the usual work-up, the sulfonamide 570 (253 mg, 88%) as a colourless oil. \(\delta_H\) 7.73 (d, \(J = 8.2\) Hz 2H), 7.34 (d, \(J = 8.2\) Hz, 2H), 5.12 (t, \(J = 6.8\) Hz, 1H, NH), 4.90 (d, \(J = 1.2\) Hz, 2H, 2 x =CH), 4.76 (d, \(J = 1.2\) Hz, 2H, 2 x =CH), 3.60 (s, 2H, OCH\(_2\)), 2.91 (d, \(J = 6.8\) Hz, 2H, NCH\(_2\)), 2.45 (s, 3H, Ar-CH\(_3\)), 2.29 (br. s, 1H, OH), 2.16 (dd, \(J = 13.8, 0.5\) Hz, 2H), 2.05 (dd, \(J = 13.8, 0.5\) Hz, 2H), 1.79 (s, 6H, 2 x CH\(_3\)). \(\delta_C\) 142.6 (Cq), 136.6 (Cq), 129.6 (2 x CH), 126.8 (2 x CH), 115.5 (2 x CH\(_2\)), 67.6 (OCH\(_2\)), 48.6 (NCH\(_2\)), 44.1 (Cq), 41.5 (2 x CH\(_2\)), 25.1 (2 x CH\(_3\)).

\textbf{3,3,8,8-Tetramethyl-7-tosyl-2-oxa-7-azaspiro[4.4]nonane 571\(^{47}\)}

By general procedure B, to the \(N\)-tosyl alcohol 570 (115 mg, 0.34 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for 1 h at 20 °C to give the \textit{oxa-azaspiro} 571 as a colourless oil (114 mg, 99%). \(\delta_H\) 7.65 (d, \(J = 8.6\) Hz 2H), 7.19 (d, \(J = 8.6\) Hz, 2H), 3.55 (d, \(J = 8.8\) Hz, 1H), 3.46 (d, \(J = 8.8\) Hz, 1H), 3.32 (d, \(J = 9.4\) Hz, 1H), 3.13 (d, \(J = 9.4\), 1H), 2.32 (s, 3H, Ar-CH\(_3\)), 1.80 (d, \(J = 1.8\) Hz, 2H), 1.63 (d, \(J = 6.9\) Hz, 2H), 1.39 (s, 3H, CH\(_3\)), 1.35 (s, 3H, CH\(_3\)), 1.12 (s, 6H, 2 x CH\(_3\)). \(\delta_C\) 142.8
(Cq), 138.1 (Cq), 129.4 (2 x CH), 127.3 (2 x CH), 80.2 (OCq), 75.6 (OCH₂), 64.8 (NCq), 59.2 (NCH₂), 52.7 (CH₂), 49.7 (Cq), 48.5 (CH₂), 29.2 (CH₃), 29.1 (CH₃), 29.0 (CH₃), 28.3 (CH₃), 21.5 (ArCH₃). IR (neat) υ/cm⁻¹: 2971, 2930, 2868, 1599, 1451, 1334, 1090, 1007, 814, 677. HRMS (EI) m/z calculated for C₁₈H₂₇NO₃S [M]⁺ = 337.1712; found: 337.1710.

Methyl (2-(hydroxymethyl)-4-methyl-2-(2-methylallyl)pent-4-en-1-yl)carbamate 572

By general procedure A, methyl chloroformate (0.1 ml, 1.2 mmol) was added to the amino-alcohol 569 (183 mg, 1 mmol) and Et₃N (2.5 ml, 22 mmol) to give the N-protected amino-alcohol 572 (231 mg, 96%) as a colourless oil. δH 5.72 (t, J = 6.4 Hz, 1H, NH), 4.90 (d, J = 0.8 Hz, 2H, 2 x =CH), 4.76 (app. s, 2H, 2 x =CH), 3.71 (s, 3H, OCH₃), 3.51 (br. s, 1H, OH), 3.41 (d, J = 6.8 Hz, 2H, OCH₂), 2.27 (d, J = 6.4 Hz, 2H, NCH₂), 2.16 (dd, J = 13.8, 1.5 Hz, 2H), 2.05 (dd, J = 13.8, 1.5 Hz, 2H), 1.79 (s, 6H, 2 x CH₃). δC 158.5 (C=O), 143.1 (2 x Cq), 115.3 (2 x CH₂), 65.4 (OCH₂), 45.9 (NCH₂), 43.7 (Cq), 41.3 (2 x CH₂), 25.4 (2 x CH₃). IR (neat) υ/cm⁻¹: 3345, 2970, 2948, 1705, 1520, 1450, 1244, 1046, 907. HRMS (EI) m/z calculated for C₁₃H₂₃NO₂ [M]⁺ = 241.1678; found: 241.1677.

Methyl 3,3,8,8-tetramethyl-2-oxa-7-azaspiro[4.4]nonane-7-carboxylate 573

By general procedure B, to the N-tosyl alcohol 572 (177 mg, 0.55 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for 1 h at 0 °C to give the oxa-azaspiro 573 as a colourless oil (172 mg, 97%). δH
3.58 (d, $J = 8.7$ Hz, 1H), 3.44 (d, $J = 8.7$ Hz, 1H), 3.43 (s, 3H, CH$_3$), 3.37 (d, $J = 10.7$ Hz, 1H), 3.16 (d, $J = 10.7$, 1H), 1.80 (d, $J = 2.8$ Hz, 2H), 1.63 (d, $J = 1.2$ Hz, 2H), 1.22 (s, 3H, CH$_3$), 1.15 (s, 3H, CH$_3$), 1.05 (s, 6H, 2 x CH$_3$). $\delta$C 153.8 (C=O, Cq), 79.9 (OCq), 75.8 (OCH$_2$), 60.3 (NCq), 58.2 (NCH$_2$), 51.4 (OCH$_3$), 50.7 (CH$_2$), 50.0 (CH$_2$), 48.2 (Cq), 29.4 (CH$_3$), 28.8 (CH$_3$), 27.2 (CH$_3$), 26.8 (CH$_3$). HRMS (APCI) $m/z$ calculated for C$_{13}$H$_{23}$NO$_3$ [M+H]$^+$ = 242.1756; found: 242.1755.

**Ethyl 2-allyl-2-cyano-4-methylpent-4-enoate 579**

By general procedure D, to sodium hydride (60% dispersion in mineral oil, 0.40 g, 10 mmol, 1 eq.) in DMF (20 ml) under nitrogen at 0 °C was slowly added cyanoacetate 558 (1.10 g, 6.6 mmol) in DMF (10 ml). After 15 min, allyl bromide 577 (1.20 g, 10 mmol) was added. To give cyanomethylpentenoate 579 (1.40 g, 84%) as a colourless oil. $\delta$H 5.90 − 5.80 (m, 1H, =CH), 5.27 (d, $J = 14.5$ Hz, 2H, =CH$_2$), 4.99 (app. s, 1H), 4.91 (app. s, 1H), 4.26 (q, $J = 6.5$ Hz, 2H, OCH$_2$), 2.72 − 2.63 (m, 2H, CH$_2$), 2.61 − 2.49 (m, 2H, CH$_2$), 1.86 (s, 3H, CH$_3$), 1.33 (t, $J = 6.5$ Hz, 3H, CH$_3$). $\delta$C 168.3 (C=O), 139.2 (Cq), 130.5 (=CH), 121.0 (=CH$_2$), 118.9 (CN, Cq), 116.3 (=CH$_2$), 62.7 (OCH$_2$), 48.8 (Cq), 44.4 (CH$_2$), 42.1 (CH$_2$), 23.0 (CH$_3$), 14.0 (CH$_3$). IR (neat) $\nu$/cm$^{-1}$: 3082, 2984, 2928, 2868, 2245, 1720, 1645, 1442, 1213, 993, 910, 733. HRMS (APCI) $m/z$ calculated for C$_{12}$H$_{18}$NO$_2$ [M+H]$^+$ = 208.1338; found: 208.1343.

**Ethyl 1-cyano-3-methylocyclopent-3-enecarboxylate 580**
A solution of the cyanoacetate 579 (0.70 g, 3.4 mmol) and Grubbs II catalyst (20 mg, 0.024 mmol) in dry dichloromethane (10 ml) was stirred at room temperature overnight. The solvent was evaporated to give the cyano pentene 580 (0.66 g, 100%) as a colourless oil. δH 5.82 – 5.69 (m, 1H, =CH), 4.20 (q, J = 6.7 Hz, 2H, OCH2), 2.98 (d, J = 9.4 Hz, 2H, CH2), 2.60 (d, J = 8.7 Hz, 1H), 2.46 (d, J = 8.7 Hz, 1H), 1.68 (s, 3H, CH3), 1.32 (t, J = 6.7 Hz, 3H, OCH3). δC 169.3 (C=O, Cq), 137.4 (Cq), 121.3 (CN, Cq), 120.9 (=CH), 62.9 (OCH2), 47.3 (CH2), 46.2 (Cq), 44.0 (CH2), 15.8 (CH3), 13.9 (CH3).

(1-(Aminomethyl)-3-methylcyclopent-3-en-1-yl)methanol 581

Following general procedure C, the cyanoacetate 580 (0.66 g, 3.4 mmol) was reduced using lithium aluminium hydride (0.38 g, 10 mmol) to give the amino-alcohol 581 (0.46 g, 96 %) as a yellow oil, which was used directly in the next step. δH 4.99 (s, 1H, =CH), 3.42 (s, 2H, OCH2), 2.71 (s, 2H, NCH2), 2.49 – 2.30 (br. s, 3H, OH and NH2), 1.99 (d, J = 11.7 Hz, 2H, CH2), 1.80 (s, 2H, CH2), 1.48 (s, 2H, CH3). δC 138.3 (Cq), 122.3 (=CH), 68.0 (OCH2), 51.7 (NCH2), 47.2 (Cq), 43.8 (CH2), 39.7 (CH2), 16.7 (CH3).

N-((1-(Hydroxymethyl)-3-methylcyclopent-3-en-1-yl)methyl)-4-methylbenzenesulfonamide 582

By general procedure A, tosyl chloride (0.66 g, 3.2 mmol) was added to the amino-alcohol 581 (0.44 g, 3.1 mmol) and Et3N (0.5 ml, 4.4 mmol) at -78 °C. The mixture was then stirred for 1 h
without additional cooling. The usual work-up then gave the sulfonamide 582 (0.61 g, 66%) as a colourless oil. δ\textsubscript{H} 7.66 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 5.34 (t, J = 6.3 Hz, 1H, NH), 5.06 (d, J = 4.5 Hz, 1H, =CH), 3.49 (d, J = 4.3 Hz, 2H, OCH\textsubscript{2}), 2.89 (dd, J = 6.3 Hz, 2H, NCH\textsubscript{2}), 2.54 – 2.41 (br, s, 1H, OH), 2.36 (s, 3H, Ar-CH\textsubscript{3}), 2.11 – 1.99 (m, 2H, CH\textsubscript{2}), 1.93 (m, 2H, CH\textsubscript{2}), 1.56 (s, 3H, CH\textsubscript{3}). δ\textsubscript{C} 143.4 (Cq), 138.3 (Cq), 137.3 (Cq), 129.7 (2 x CH), 127.0 (2 x CH), 122.1 ( =CH), 68.0 (OCH\textsubscript{2}), 49.4 (NCH\textsubscript{2}), 47.5 (Cq), 43.7 (CH\textsubscript{2}), 39.6 (CH\textsubscript{2}), 21.5 (CH\textsubscript{3}), 16.5 (CH\textsubscript{3}).

4-Methyl-N-((1-methyl-2-oxabicyclo[2.2.1]heptan-4-yl)methyl)benzenesulfonamide 583 and 1-Methyl-2-tosyl-2-azabicyclo[2.2.1]heptan-4-yl)methanol 584

By general procedure B, to the N-tosyl alcohol 582 (143 mg, 0.48 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for 1 h at 20° C to give the oxabicyclo 583 as a mixture with azabicyclo 584* as an inseparable mixture (3:1) as a colourless oil (132 mg, 92%). δ\textsubscript{H} 7.55 (d, J = 8.3 Hz, 2H), 7.14 (d, J = 8.3 Hz, 2H), 4.51 (t, J = 6.8 Hz, 1H, NH), 3.42 (s, 2H, OCH\textsubscript{2}), 2.48 (d, J = 6.9 Hz, NCH\textsubscript{2}), 2.25 (s, 3H, Ar-CH\textsubscript{3}), 1.58 (dd, J = 9.8, 4.0 Hz, 2H, CH\textsubscript{2}), 1.41 – 1.20 (m, 6H, 3 x CH\textsubscript{2}), 0.90 (s, 3H, CH\textsubscript{3}). δ\textsubscript{C} 143.5 (Cq), 136.9 (Cq), 129.8 (2 x CH), 127.0 (2 x CH), 71.7 (OCH\textsubscript{2}), 69.1 (OCq), 49.4 (NCH\textsubscript{2}), 32.4 (Cq), 32.1 (2 x CH\textsubscript{2}), 28.0 (2 x CH\textsubscript{2}), 26.3 (CH\textsubscript{3}), 21.5 (CH\textsubscript{3}).

*The structure of azabicyclo 584 was confirmed by different way (p. 264).

(3-Methyl-1-((4-methylphenylsulfonamido)methyl)cyclopent-3-en-1-yl)methyl acetate 586
By general procedure E, but with a reaction time of 19 h, the alcohol \(582\) (295 mg, 1.0 mmol) was converted into the acetate \(586\) (337 mg, 100%), a colourless oil. \(\delta_H\) 7.65 (t, \(J = 8.1\) Hz, 2H), 7.24 (d, \(J = 8.1\) Hz, 2H), 5.09 (s, 1H, =CH), 4.99 (t, \(J = 6.8\) Hz, 1H, NH), 3.93 (d, \(J = 4.9\) Hz, 1H, OCH\(_2\)CH\(_3\)), 3.89 (d, \(J = 4.9\) Hz, 1H, OCH\(_2\)CH\(_3\)), 3.62 (s, 3H, Ar-CH\(_3\)), 2.10 (s, 2H, CH\(_2\)), 2.04 (s, 2H, CH\(_2\)), 1.94 (s, 3H, Ac-CH\(_3\)), 1.58 (s, 3H, Ac-CH\(_3\)). \(\delta_C\) 171.4 (C=O), 143.3 (Cq), 138.2 (Cq), 137.1 (Cq), 129.7 (2 x CH), 127.1 (2 x CH), 121.9 (=CH), 68.2 (OCH\(_2\)), 48.5 (NCH\(_2\)), 46.0 (Cq), 39.6 (CH\(_2\)), 39.8 (CH\(_2\)), 22.1 (CH\(_3\)), 21.5 (CH\(_3\)), 20.8 (CH\(_3\)). IR (neat) \(\nu/cm^{-1}\): 3269, 2957, 2915, 1740, 1437, 1333, 1248, 1094, 1037, 814. HRMS (ES) \(m/z\) calculated for \(C_{17}H_{23}NO_4SNa\) [M+Na]\(^+\) = 360.1245; found: 360.1239.

(1-Methyl-2-tosyl-2-azabicyclo[2.2.1]heptan-4-yl)methyl acetate \(587\)

By general procedure B, to the protected amino-alcohol \(586\) (302 mg, 0.9 mmol) in dry dichloromethane (10 ml) concentrated sulfuric acid (3 drops) was added and the resulting mixture was stirred for 1 h at 20 °C to give the azabicycloheptane \(587\) as a colourless oil (287 mg, 95%). \(\delta_H\) 7.68 (d, \(J = 8.0\) Hz, 2H), 7.23 (d, \(J = 8.0\) Hz, 2H), 4.05 (s, 2H, OCH\(_2\)), 3.31 (d, \(J = 2.3\) Hz, 1H, NCH\(_2\)CH\(_3\)), 3.27 (d, \(J = 2.3\) Hz, 1H, NCH\(_2\)CH\(_3\)), 2.36 (s, 3H, Ar-CH\(_3\)), 1.99 (s, 3H, Ac-CH\(_3\)), 1.94 (d, \(J = 1.3\) Hz, 1H, CH), 1.83 – 1.77 (m, 1H, CH), 1.56 (s, 3H, CH\(_3\)), 1.53 (d, \(J = 1.3\) Hz, 1H, CH), 1.44 (d, \(J = 3.1\) Hz, 1H, CH), 1.41 (t, \(J = 3.1\) Hz, 1H, CH). \(\delta_C\) 170.5 (C=O) 143.0 (Cq), 138.2 (Cq), 129.5 (2 x CH), 127.1 (2 x CH), 70.8 (NCq), 65.5 (OCH\(_2\)), 58.5 (NCH\(_2\)), 49.0 (CH\(_2\)), 46.8 (Cq), 36.1 (CH\(_2\)), 32.1 (CH\(_2\)), 21.5 (CH\(_3\)), 20.7 (CH\(_3\)), 19.4 (CH\(_3\)). IR (neat) \(\nu/cm^{-1}\): 2937, 1740, 1339, 1240, 1094, 1034, 815. HRMS (EI) \(m/z\) calculated for \(C_{17}H_{23}NO_4S\) [M]\(^+\) = 337.1348; found: 337.1336.
To a solution of foregoing azabicycloheptane 587 (263 mg, 0.78 mmol) in undried methanol (5 ml) was added potassium carbonate (200 mg, 1.5 mmol). The reaction was stirred for 18 h at room temperature. The solvent was removed and the residue was diluted with water (5 ml) and extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried and concentrated to give the azabicyclo methanol 584 (209 mg, 91%) as a colourless oil.

δ⁴H 7.65 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 3.62 (s, 2H, NCH₂), 3.35 (dd, J = 8.5, 3.2 Hz, 1H, OCHₓCHₓB), 3.27 (dd, J = 8.5, 1.4 Hz, 1H, OCHₓCHₓB), 2.35 (s, 3H, Ar-CH₃), 1.83 – 1.74 (m, 1H, CH), 1.62 – 1.58 (m, 1H, CH), 1.56 – 1.54 (m, 1H, CH), 1.52 (s, 3H, CH₃), 1.42 (d, J = 5.2 Hz, 1H, CH), 1.38 (d, J = 2.1 Hz, 1H, CH), 1.32 – 1.29 (m, 1H, CH). δ¹C 142.9 (Cq), 138.9 (Cq), 129.5 (2 x CH), 127.1 (2 x CH), 70.9 (NCq), 64.4 (OCH₂), 58.6 (NCH₂), 49.2 (Cq), 48.6 (CH₂), 36.1 (CH₂), 31.6 (CH₂), 21.5 (CH₃), 19.5 (CH₃). IR (neat) ν/cm⁻¹: 3510, 2932, 2872, 1333, 1288, 1012, 814. HRMS (EI) m/z calculated for C₁₅H₂₁NO₃S [M]+ = 295.1242; found: 295.1239.

4-methyl-N-((1-methyl-2-oxabicyclo[2.2.1]heptan-4-yl)methyl)benzenesulfonylamine 583

By general procedure B, to the azabicyclo methanol 584 (170 mg, 0.59 mmol) in dry dichloromethane (10 ml) concentrated sulfuric acid (3 drops) was added and the resulting mixture stirred for 20 h at 20 ºC to give the oxabicycloheptane 583 (162 mg, 95%) as a colourless oil, which exhibited spectroscopic and analytical data identical to those reported above for a sample of the oxabicyclo 583 prepared by cyclisation of the alcohol 582 (p. 262).
Ethyl 1-cyano-4-methylcyclohex-3-enecarboxylate 588

A mixture of ethyl cyanoacetate 510 (4.52 g, 40 mmol), isoprene 591 (8.17 g, 120 mmol), paraformaldehyde (2.40 g, 80 mmol) and copper(II) acetate monohydrate (0.25 g, 0.125 mmol) were heated at 80 °C for 24 h in acetic acid and toluene (25 ml, 1:1). The reaction mixture was cooled to room temperature and evaporated under reduced pressure, and the oily residue taken up in ether (50 ml) and the solution washed with water (10 ml) then dried and evaporated and the residue purified by column chromatography on silica gel eluting with ether/hexanes (1:99) to give cyanoacetate 588 (3.50 g, 94%) as a colourless oil. All data obtained were in accordance with those previously reported in the literature: \( \delta^1 H 5.30 \) (t, \( J = 1.4 \) Hz, 1H, =CH), 4.21 (q, \( J = 7.1 \) Hz, 2H, OCH\(_2\)), 2.50 (d, \( J = 1.4 \) Hz, 2H, CH\(_2\)), 2.20 – 2.03 (m, 2H, CH\(_2\)), 2.01 – 1.86 (m, 2H, CH\(_2\)), 1.65 (s, 3H, CH\(_3\)), 1.26 (t, \( J = 7.1 \) Hz, 3H, CH\(_2\)). \( \delta^13 C 169.1 \) (Cq), 134.1 (Cq), 120.5 (CN), 115.9 (=CH), 62.8 (OCH\(_2\)), 42.2 (Cq), 32.5 (CH\(_2\)), 29.3 (CH\(_2\)), 26.8 (CH\(_2\)), 23.2 (CH\(_3\)), 14.0 (CH\(_3\)).

(1-(Aminomethyl)-4-methylcyclohex-3-en-1-yl)methanol 592

Following general procedure C, the cyanoacetate 588 (3.50 g, 18.1 mmol) was reduced using lithium aluminium hydride (1.52 g, 40 mmol) to give the amino-alcohol 592 (2.50 g, 89 %) as a yellowish oil, which was used directly in the next step. \( \delta^1 H 5.21 \) (d, \( J = 1.5 \) Hz, 1H, =CH), 3.48 (s, 2H, OCH\(_2\)), 3.00 – 2.84 (br. s, 3H, OH and NH\(_2\)), 2.68 (t, \( J = 8.6 \) Hz, 2H, NCH\(_2\)), 1.94 – 1.80 (m, 2H, CH\(_2\)), 1.75 – 1.63 (m, 2H, CH\(_2\)), 1.57 (s, 3H, CH\(_3\)), 1.50 – 1.43 (m, 2H, CH\(_2\)). \( \delta^13 C 133.3 \) (Cq), 118.6 (=CH), 70.2 (OCH\(_2\)), 50.3 (NCH\(_2\)), 35.8 (Cq), 31.0 (CH\(_2\)), 26.7 (CH\(_2\)), 26.3 (CH\(_2\)), 23.3 (CH\(_3\)).
**N-((1-(Hydroxymethyl)-4-methylcyclohex-3-en-1-yl)methyl)-4-methylbenzenesulfonamide**

592

By general procedure A, tosyl chloride (1.36 g, 7.7 mmol) was added to the amino-alcohol 591 (1.20 g, 7.7 mmol) and Et₃N (1 ml, 8.8 mmol) at -78 °C. The mixture was then stirred for 1 h without additional cooling to give the sulfonamide 592 (1.76 g, 74%) as a colourless oil. δH 7.67 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.3 Hz, 2H), 5.15 (d, J = 1.5 Hz, 1H, =CH), 5.10 – 4.93 (br. s, 1H, NH), 3.44 (s, 2H, OCH₂), 2.83 (d, J = 13.0 Hz, 1H), 2.73 (d, J = 13.0 Hz, 1H), 2.36 (s, 3H, Ar-CH₃), 1.94 – 1.83 (m, 2H, CH₂), 1.69 – 1.60 (m, 2H, CH₂), 1.54 (s, 3H, CH₃), 1.50 – 1.35 (m, 2H, CH₂). δC 142.6 (Cq), 136.6 (Cq), 133.5 (Cq), 129.7 (2 x CH), 127.0 (2 x CH), 118.0 (CH), 67.7 (OCH₂), 48.1 (NCH₂), 36.6 (Cq), 30.7 (CH₂), 26.9 (CH₂), 26.3 (CH₂), 23.3 (CH₃), 21.5 (CH₃). IR (neat) ν/cm⁻¹: 3505, 3295, 2926, 1452, 1327, 1094, 814. HRMS (EI) m/z calculated for C₁₆H₂₄NO₃S [M+H]+ = 310.1477; found: 310.1465.

**4-Methyl-N-((1-methyl-2-oxabicyclo[2.2.2]octan-4-yl)methyl)benzenesulfonamide 693**

By general procedure B, to the N-tosyl alcohol 592 (137 mg, 0.44 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for 1 h at 0 °C to give the oxabicyclo-octane 593 as a colourless oil (124 mg, 91%). δH 7.55 (d, J = 8.3 Hz, 2H), 7.14 (d, J = 8.3 Hz, 2H), 4.51 (t, J = 6.8 Hz, 1H, NH), 3.42 (s, 2H, OCH₂), 2.48 (d, J = 6.8 Hz, NCH₂), 2.25 (s, 3H, Ar-CH₃), 1.58 (dd, J = 9.8, 4.0 Hz, 2H, CH₂), 1.41 – 1.20 (m, 6H, 3 x CH₂), 0.90 (s, 3H, CH₃). δC 143.5 (Cq), 136.9 (Cq), 129.8 (2 x CH), 127.0
(2 x CH), 71.7 (OCH$_2$), 69.1 (OCq), 49.4 (NCH$_2$), 32.4 (Cq), 32.1 (2 x CH$_2$), 28.0 (2 x CH$_2$), 26.3 (CH$_3$), 21.5 (CH$_3$). IR (neat) $\nu$/cm$^{-1}$: 3283, 2924, 2862, 1452, 1321, 1094, 814. HRMS (EI) $m/z$ calculated for C$_{16}$H$_{24}$NO$_3$S [M+H]$^+$ = 310.1477; found: 310.1471.

(4-Methyl-1-((4-methylphenylsulfonamido)methyl)cyclohex-3-en-1-yl)methyl acetate 594

By general procedure E, the alcohol 592 (309 mg, 1.0 mmol) was converted during 18 h into the acetate 594 (351 mg, 100%), a colourless oil. $\delta$H 7.66 (d, $J = 8.1$ Hz, 3H), 7.23 (d, $J = 8.1$ Hz, 2H), 5.14 (d, $J = 1.5$ Hz, 1H, =CH), 4.98 (t, $J = 7.3$ Hz, 1H, NH), 3.88 (d, $J = 11.4$ Hz, 1H, OCH$_A$CH$_B$), 3.78 (d, $J = 11.4$ Hz, 1H, OCH$_A$CH$_B$), 2.74 (dd, $J = 7.3$, 6.8 Hz, 1H), 2.60 (dd, $J = 7.3$, 6.8 Hz, 1H), 2.36 (s, 3H, Ar-CH$_3$), 1.93 (s, 3H, Ac-CH$_3$), 1.82 (t, $J = 5.3$ Hz, 2H, CH$_2$), 1.77 – 1.71 (m, 2H, CH$_2$), 1.55 (s, 3H, CH$_3$), 1.45 – 1.40 (m, 2H, CH$_2$). $\delta$C 171.3 (C=O), 143.2 (Cq), 137.1 (Cq), 133.4 (Cq), 129.6 (2 x CH), 127.1 (2 x CH), 117.7 (=CH), 67.5 (OCH$_2$), 47.3 (NCH$_2$), 35.7 (Cq), 31.0 (CH$_2$), 26.9 (CH$_2$), 26.1 (CH$_2$), 23.2 (CH$_3$), 21.5 (CH$_3$), 20.7 (CH$_3$). IR (neat) $\nu$/cm$^{-1}$: 3286, 2934, 1732, 1327, 1236, 1092, 1036, 910. HRMS (ES) $m/z$ calculated for C$_{18}$H$_{25}$NNaO$_4$S [M+Na]$^+$ = 374.1402; found: 374.1399.

(1-Methyl-2-tosyl-2-azabicyclo[2.2.2]octan-4-yl)methyl acetate 595

By general procedure B, to the protected amino-alcohol 594 (325 mg, 0.93 mmol) in dry dichloromethane (10 ml) concentrated sulfuric acid (3 drops) was added and the resulting mixture was stirred for 1h at 20 °C to give the azabicyclo-octane 595 as a colourless oil (306 mg, 94%). $\delta$H
7.67 (d, \( J = 8.0 \) Hz, 2H), 7.24 (d, \( J = 8.0 \) Hz, 2H), 3.73 (s, 2H, OCH\(_3\)), 3.43 (s, 2H, NCH\(_2\)), 2.36 (s, 3H, Ar-CH\(_3\)), 2.01 (s, 3H, Ac-CH\(_3\)), 1.73 (s, 2H, CH\(_2\)), 1.60 (d, \( J = 9.5 \) Hz, 2H), 1.51 (s, 2H, CH\(_2\)), 1.44 – 1.34 (m, 2H, CH\(_2\)), 1.27 (s, 3H, CH\(_3\)). \( \delta \)C 171.5 (C=O) 143.4 (Cq), 139.2 (Cq), 129.5 (2 x CH), 127.0 (2 x CH), 69.4 (OCH\(_2\)), 55.2 (NCq), 53.8 (NCH\(_2\)), 34.0 (Cq), 33.0 (2 x CH\(_2\)), 27.1 (2 x CH\(_2\)), 25.4 (CH\(_3\)), 21.5 (CH\(_3\)), 20.8 (CH\(_3\)). IR (neat) \( \nu/cm^-1\): 2940, 2870, 1740, 1458, 1331, 1235, 1092, 1040, 1010, 980. HRMS (EI) \( m/z \) calculated for C\(_{18}\)H\(_{25}\)NO\(_4\)S [M]\(^+\) = 351.1504; found: 351.1491.

Methyl ((1-(hydroxymethyl)-4-methylcyclohex-3-en-1-yl)methyl)carbamate 596

By general procedure A, methyl chloroformate (0.7 ml, 8.9 mmol) was added to the amino-alcohol 591 (1.30 g, 8.4 mmol) and Et\(_3\)N (1 ml, 8.8 mmol) at 0 °C. The mixture was then stirred for 1 h at room temperature to give the carbamate 596 (1.26 g, 71%) as a colourless oil. \( \delta \)H 5.30 (s, 1H, =CH), 5.21 (d, \( J = 1.5 \) Hz, 1H, NH), 3.61 (s, 3H, OCH\(_3\)), 3.24 (d, \( J = 6.4 \) Hz, 2H, OCH\(_2\)), 3.03 – 2.89 (m, 2H, NCH\(_2\)), 1.80 (d, \( J = 2.5 \) Hz, 2H, CH\(_2\)), 1.76 – 1.65 (m, 2H, CH\(_2\)), 1.57 (s, 3H, CH\(_3\)), 1.42 (t, \( J = 6.5 \) Hz, 2H, CH\(_2\)). \( \delta \)C 158.8 (C=O, Cq), 133.2 (Cq), 118.5 (CH), 66.1 (OCH\(_2\)), 52.4 (OCH\(_3\)), 45.2 (NCH\(_2\)), 38.3 (Cq), 30.8 (CH\(_2\)), 27.0 (CH\(_2\)), 26.5 (CH\(_2\)), 23.3 (CH\(_3\)).

Methyl (1-methyl-2-oxabicyclo[2.2.2]octan-4-yl)methyl)carbamate 597

By general procedure B, to the N-protected amino-alcohol 596 (106 mg, 0.5 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for 1 h at 20 °C to give the oxabicyclo-octane 597 (104 mg, 98%)
as sharp, colourless crystals, m.p. 92 – 94 °C. δ\textsubscript{H} 4.65 (br. s, 1H, NH), 3.71 – 3.49 (m, 2H, OCH\textsubscript{2}), 3.61 (s, 3H, OCH\textsubscript{3}), 2.89 (d, J = 6.5 Hz, 2H, NCH\textsubscript{2}), 1.79 – 1.67 (m, 2H, CH\textsubscript{2}), 1.57 – 1.40 (m, 6H, 3 x CH\textsubscript{2}), 1.02 (s, 3H, CH\textsubscript{3}). δ\textsubscript{C} 157.2 (C=O, Cq), 71.7 (OCH\textsubscript{2}), 68.9 (OCq), 52.1 (OCH\textsubscript{3}), 47.1 (NCH\textsubscript{2}), 33.0 (Cq), 32.1 (2 x CH\textsubscript{2}), 27.8 (2 x CH\textsubscript{2}), 26.3 (CH\textsubscript{3}). IR (neat) \textit{μ}/cm\textsuperscript{-1}: 3335, 2930, 2862, 1722, 1694, 1545, 1447, 1192, 1117, 1047, 997. HRMS (EI) \textit{m}/\textit{z} calculated for C\textsubscript{11}H\textsubscript{19}NO\textsubscript{3} [M]\textsuperscript{+} = 213.1365; found: 213.1373.

(1-((Methoxycarbonylamino)methyl)-4-methylcyclohex-3-en-1-yl)methyl acetate 598

By general procedure B, to the alcohol 596 (213 mg, 1.0 mmol) in dry dichloromethane (10 ml) was added acetic anhydride (0.1 ml, 1.1 mmol) and pyridine (0.1 ml). The mixture was stirred 18 h at room temperature then the organic layer was washed with a saturated aqueous copper sulphate (5 ml) and water (5 ml), dried and concentrated to give the protected alcohol 598 (255 mg, 100%) as a colourless oil. δ\textsubscript{H} 5.21 (d, J = 1.5 Hz, 1H, =CH), 5.01 (br. s, 1H, NH), 3.85 (dd, J = 15.4, 9.2 Hz, 2H, OCH\textsubscript{2}), 3.59 (s, 3H, OCH\textsubscript{3}), 3.18 (dd, J = 14.0, 6.5 Hz, 1H), 3.02 (dd, J = 14.0, 6.5 Hz, 1H), 2.01 (s, 3H, Ac-CH\textsubscript{3}), 1.88 (d, J = 1.5 Hz, 2H, CH\textsubscript{2}), 1.76 – 1.72 (m, 2H, CH\textsubscript{2}), 1.58 (s, 3H, CH\textsubscript{3}), 1.48 – 1.39 (m, 2H, CH\textsubscript{2}). δ\textsubscript{C} 166.3 (C=O, Cq), 133.3 (Cq), 118.0 (CH), 67.5 (OCH\textsubscript{2}), 52.1 (OCH\textsubscript{3}), 45.6 (NCH\textsubscript{2}), 36.9 (Cq), 30.7 (CH\textsubscript{2}), 27.0 (CH\textsubscript{2}), 26.4 (CH\textsubscript{3}), 23.3 (CH\textsubscript{3}), 22.1 (CH\textsubscript{3}).

Methyl 4-(acetoxymethyl)-1-methyl-2-azabicyclo[2.2.2]octane-2-carboxylate 599
By general procedure B, to the protected amino-alcohol \(598\) (220 mg, 0.86 mmol) in dry dichloromethane (10 ml) concentrated sulfuric acid (3 drops) was added and the resulting mixture stirred for 1 h at 20° C to give the azabicyclo \(599\) (204 mg, 93%) as a colourless oil. \(\delta_H\) 3.71 (s, 2H, OCH\(_2\)), 3.55 (s, 3H, OCH\(_3\)), 3.21 (s, 2H, NCH\(_2\)), 1.97 (s, 3H, Ac-CH\(_3\)), 1.87 – 1.79 (m, 2H, CH\(_2\)), 1.51 – 1.45 (m, 6H, 3 x CH\(_2\)), 1.42 (s, 3H, CH\(_3\)). \(\delta_C\) 157.2 (C=O, Cq), 71.7 (OCH\(_2\)), 68.9 (NCH), 52.1 (OCH\(_3\)), 47.1 (NCH\(_2\)), 33.0 (Cq), 32.1 (2 x CH\(_2\)), 27.8 (2 x CH\(_2\)), 26.3 (CH\(_3\)).

IR (neat) \(\nu/cm^-1\): 2932, 2864, 1695, 1537, 1445, 1246, 1195, 1040, 912. HRMS (EI) \(m/z\) calculated for C\(_{13}\)H\(_{21}\)NO\(_4\) \([M]^+\) = 255.1471; found: 255.1460.

\((E)\)-Ethyl 2-cyano-5,9-dimethyldeca-4,8-dienoate \(601\)^{49}

A mixture of ethyl cyanoacetate \(510\) (2.26 g, 20 mmol), geranyl bromide \(600\) (2.17 g, 10 mmol), potassium carbonate (2.75 g, 20 mmol), sodium chloride (0.50 g) in ethanol (50 ml) was refluxed overnight. The solvent was removed and the residue was taken up in ether (3 x 20 ml) and the solution washed with water (10 ml). The extracts were dried, concentrated and the residue purified by column chromatography on silica gel eluting with ether/hexanes (1:99) to give the cyanoacetate \(601\) (1.86 g, 75% yield) as a colourless oil. \(\delta_H\) 5.11 (t, \(J = 7.4\) Hz, 1H, =CH), 5.01 (t, \(J = 6.6\) Hz, 1H, =CH), 4.18 (q, \(J = 7.1\), 2H, OCH\(_2\)), 3.42 (t, \(J = 6.9\) Hz, 1H, CH), 2.60 (q, \(J = 7.1\) Hz, 2H, CH\(_2\)), 2.02 – 1.94 (m, 4H, 2 x CH\(_2\)), 1.62 (s, 3H, CH\(_3\)), 1.60 (s, 3H, CH\(_3\)), 1.53 (s, 3H, CH\(_3\)), 1.25 (t, \(J = 7.1\), 3H, CH\(_3\)). \(\delta_C\) 165.9 (C=O), 141.1 (Cq), 131.7 (Cq), 123.7 (=CH), 117.3 (=CH), 116.5 (CN), 62.6 (OCH\(_2\)), 39.6 (CH\(_2\)), 37.9 (CH), 28.6 (CH\(_2\)), 26.4 (CH\(_2\)), 25.6 (CH\(_3\)) 17.6 (CH\(_3\)), 16.3 (CH\(_3\)), 14.0 (CH\(_3\)).
(E)-2-(Aminomethyl)-5,9-dimethyldeca-4,8-dien-1-ol 602

![Chemical structure](image)

The foregoing cyanoacetate 601 (1.80 g, 7.2 mmol) was dissolved in dry tetrahydrofuran (30 ml) and the solution added dropwise to a suspension of lithium aluminium hydride (0.76 g, 20 mmol) in tetrahydrofuran (20 ml) at 0 °C. The suspension was then refluxed for 3 hours subsequently cooled to 0 °C. When it was cold, water (5 ml), 15% aqueous NaOH (5 ml) were added sequentially and the resulting mixture then stirred for one hour, the precipitated salts were then filtered off and washed with tetrahydrofuran (40 ml). The combined filtrate was concentrated, then the liquid residue extracted with dichloromethane (2 x 10 ml) and the combined extracts dried and concentrated to give the amino-alcohol 602 (1.23 g, 81 %) as a yellow oil, which was used directly in the next step.

δ_H 5.07 – 4.96 (m, 2H, 2 x =CH), 3.69 (dd, J = 9.1, 7.3 Hz, 1H), 3.56 – 3.49 (m, 1H), 3.40 – 3.22 (br. s, 3H, OH and NH₂), 2.99 (d, J = 10.3 Hz, 1H), 2.70 (dd, J = 10.3 Hz, 1H), 2.01 – 1.96 (m, 1H, CH), 1.95 – 1.89 (m, 4H, 2 x CH₂), 1.85 – 1.82 (m, 2H, CH₂), 1.61 (s, 3H, CH₃), 1.53 (s, 3H, CH₃), 1.51 (s, 3H, CH₃). δ_C 136.7 (Cq), 131.4 (Cq), 124.3 (=CH), 121.9 (=CH), 62.9 (OCH₂), 46.0 (NCH₂), 41.8 (CH), 39.8 (CH₂), 27.8 (CH₂), 26.7 (CH₂), 25.7 (CH₃), 16.3 (CH₃). IR (neat) µ/cm⁻¹: 3370, 2967, 2918, 2853, 1648, 1443, 1375, 1150, 1105, 908. HRMS (EI) m/z calculated for C₁₃H₂₅NO [M⁺] = 211.1936; found: 211.1931.

(E)-Methyl (2-(hydroxymethyl)-5,9-dimethyldeca-4,8-dien-1-yl)carbamate 603 and

(E)-5-(3,7-Dimethylocta-2,6-dien-1-yl)-1,3-oxazinan-2-one 604

![Chemical structure](image)
By general procedure A, methyl chloroformate (0.25 ml, 3 mmol) was added to the amino-alcohol 602 (0.6 g, 2.9 mmol) and Et₃N (0.5 ml, 4.4 mmol) at 0 °C. The mixture was then stirred for 18 h at room temperature to give the carbamate 603 (0.66 g, 87%) as a colourless oil, with a trace of cyclic carbamate 604 (less than 2%).

Carbamate 603: δ_H 5.16 – 5.03 (m, 3H, 2 x =CH and NH), 3.61 (dd, J = 11.6, 3.9 Hz, 1H, CH), 3.45 – 3.40 (m, 1H, CH), 3.40 – 3.30 (m, 1H, CH), 3.20 – 3.11 (m, 1H, CH), 2.08 – 2.06 (m, 1H, CH), 2.05 – 1.93 (m, 6H, 3 x CH₂), 1.68 (s, 3H, CH₃), 1.61 (s, 6H, 2 x CH₃). δ_C 158.4 (C=O, Cq), 138.6 (Cq), 137.0 (Cq), 131.5 (Cq), 124.2 (=CH), 121.8 (=CH), 62.9 (OCH₂), 52.3 (OCH₃), 44.9 (NCH₂), 42.0 (CH), 27.5 (CH₂), 27.3 (CH₂), 26.6 (CH₂), 25.7 (CH₃), 17.7 (CH₃), 16.0 (CH₃).

Cyclic carbamate 604: δ_H 5.08 (s, 1H, NH), 5.06 – 4.95 (m, 2H, 2 x =CH), 4.22 – 4.17 (m, 1H, CH), 3.94 – 3.89 (m, 1H, CH), 3.32 (d, J = 11.2 Hz, 1H, CH), 3.01 – 2.95 (m, 1H, CH), 2.06 – 1.98 (m, 5H, 2 x CH₂ and CH), 1.98 – 1.88 (m, 2H, CH₂), 1.61 (s, 3H, CH₃), 1.53 (s, 6H, 2 x CH₃). δ_C 154.4 (C=O, Cq), 139.6 (Cq), 137.0 (Cq), 124.2 (=CH), 119.7 (=CH), 70.2 (OCH₂), 45.3 (NCH₂), 39.7 (CH₂), 31.7 (CH), 27.3 (CH₂), 26.5 (CH₂), 25.7 (CH₃), 17.7 (CH₃), 16.1 (CH₃).

Methyl ((5,5,8a-trimethylctahydro-2H-chromen-3-yl)methyl)carbamate 608

By general procedure B, to the N-protected amino-alcohol 603 (135 mg, 0.5 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for 1 h at 20 °C to give the trimethyloctahydro chromen 608 (122 mg, 90%) as a colourless oil and an inseparable 2:1 mixture of diastereoisomers.

The major diastereoisomer showed: δ_H 8.91 (s, 1H, NH), 3.59 (s, 3H, OCH₃), 3.28 (dd, J = 12.4, 9.8 Hz, 2H, CH₂), 2.97 (d, J = 7.0 Hz, 2H, CH₂), 1.76 (ddd, J = 11.6, 8.2, 4.1 Hz, 1H, CH), 1.61 – 1.55 (m, 1H, CH), 1.49 (ddd, J = 7.4, 6.1, 2.4 Hz, 1H, CH), 1.33 – 1.25 (m, 6H), 1.12 (s, 3H,
CH₃), 0.76 (s, 3H, CH₃), 0.65 (s, 3H, CH₃). δC 157.2 (Cq), 74.7 (OCq), 64.0 (OCH₂), 52.9 (CH), 52.0 (OCH₃), 42.4 (NCH₂), 41.5 (CH₂), 40.0 (CH₂), 38.8 (CH), 34.0 (Cq), 31.9 (CH₃) 23.6 (CH₂), 21.3 (CH₃), 21.1 (CH₂), 19.2 (CH₃).

The minor diastereoisomer could be characterized by: δH 4.87 (s, 1H, NH), 3.79 (dd, J = 12.4, 3.2 Hz, 2H, CH₂), 3.42 (d, J = 12.5 Hz, 1H, CH), 1.90 (d, J = 6.5 Hz, 1H, CH), 1.19 (s, 3H, CH₃), 0.77 (s, 3H, CH₃), 0.67 (s, 3H, CH₃). δC 75.4 (OCq), 61.4 (OCH₂), 43.7 (CH), 52.1 (OCH₃), 40.2 (CH₂), 33.2 (Cq), 30.6 (CH₃), 20.7 (CH₃), 18.7 (CH₃).

The whole sample showed IR (neat) ù/cm⁻¹: 3327, 2930, 2866, 1701, 1533, 1458, 1375, 1256, 1090, 777. HRMS (APCI) m/z calculated for C₁₅H₂₇NO₃Na [M+Na]⁺ = 292.1889; found: 292.1877.

(E)-2-(((Methoxycarbonyl)amino)methyl)-5,9-dimethyldeca-4,8-dien-1-yl acetate 609

By general procedure E, the alcohol 603 (269 mg, 1.0 mmol) was converted into the acetate 609 (302 mg, 97%), a colourless oil. δH 5.09 – 4.96 (m, 2H, 2 x =CH), 4.90 (s, 1H, NH), 4.04 (dd, J = 11.2, 4.4 Hz, 1H, CH), 3.89 (dd, J = 11.2, 6.0 Hz, 1H, CH), 3.59 (s, 3H, OCH₃), 3.18 (dd, J = 12.1, 6.0 Hz, 1H, CH), 3.10 – 3.00 (m, 1H, CH), 2.00 (s, 3H, Ac-CH₃), 1.98 – 1.89 (m, 6H, 3 x CH₂), 1.85 – 1.81 (m, 1H, CH), 1.61 (s, 3H, CH₃), 1.53 (s, 6H, 2 x CH₃). δC 154.4 (C=O, Cq), 137.1 (Cq), 136.9 (Cq), 133.5 (Cq), 126.2 (=CH), 122.3 (=CH), 66.8 (OCH₂), 53.2 (OCH₃), 44.3 (NCH₂), 42.6 (CH), 27.6 (CH₂), 27.0 (CH₂), 26.2 (CH₂), 26.0 (CH₃), 19.8 (CH₃), 17.7 (CH₃), 16.1 (CH₃).
By general procedure B, to the protected amino-alcohol 609 (291 mg, 0.93 mmol) in dry dichloromethane (10 ml) concentrated sulfuric acid (3 drops) was added and the resulting mixture stirred for 1 h at 20 °C to give the octahydroquinoline 610 (245 mg, 84%) as a colourless oil and an inseparable 2:1 mixture of diastereoisomers.

The major diastereoisomer showed: \( \delta^H \) 3.98 – 3.89 (m, 1H, CH), 3.89 – 3.79 (m, 1H, CH), 3.59 (s, 3H, OCH\(_3\)), 2.99 (ddd, \( J = 17.2, 11.3, 5.1 \) Hz, 1H, CH), 2.93 – 2.81 (m, 1H, CH), 2.77 (d, \( J = 13.3 \) Hz, 1H, CH), 2.11 – 2.02 (m, 1H, CH), 2.00 (s, 3H, AcCH\(_3\)), 1.89 (dd, \( J = 12.2, 6.0 \) Hz, 2H, CH\(_2\)), 1.63 – 1.57 (m, 2H, CH\(_2\)), 1.53 – 1.47 (m, 4H, 2 x CH\(_2\)), 0.93 (s, 3H, CH\(_3\)), 0.84 (s, 3H, CH\(_3\)), 0.75 (s, 3H, CH\(_3\)). \( \delta^C \) 171.1 (Cq), 156.5 (Cq), 66.8 (OCH\(_2\)), 60.9 (NCq), 52.2 (OCH\(_3\)), 51.9 (CH), 44.3 (NCH\(_2\)), 41.2 (CH\(_2\)), 38.5 (CH\(_2\)), 36.4 (CH), 34.2 (Cq), 32.8 (CH\(_2\)), 22.9 (CH\(_2\)), 21.3 (CH\(_3\)), 20.8 (CH\(_3\)), 19.98 (CH\(_3\)), 18.14 (CH\(_3\)).

The minor diastereoisomer could be characterized by: \( \delta^H \) 4.18 (dd, \( J = 10.8, 3.8 \) Hz, 1H, CH), 4.08 (dd, \( J = 11.2, 3.1 \) Hz, 1H, CH), 3.53 (OCH\(_3\)), 3.29 (ddddd, \( J = 11.0, 5.4, 3.6, 2.1 \) Hz, 1H, CH), 3.19 (dd, \( J = 12.4, 7.1 \) Hz, 1H, CH), 1.99 (s, 3H, AcCH\(_3\)), 1.25 (s, 3H, CH\(_3\)), 0.94 (s, 3H, CH\(_3\)), 0.80 (s, 3H, CH\(_3\)). \( \delta^C \) 157.3 (Cq), 70.3 (OCH\(_2\)), 59.3 (NCq), 45.1 (CH\(_2\)), 40.2 (CH\(_2\)), 38.3 (CH\(_2\)), 34.8 (CH\(_2\)), 19.9 (CH\(_2\)), 13.6 (CH\(_3\)).
References


Appendices
Appendices

Appendix 1: 1-Toluenesulfonyl-2,2,6-trimethylpiperidine 237

Appendix 2: 2,2-Dimethyl-1-tosylpiperidine 250

Appendix 3: 1-(4-Nitrophenylsulfonyl)-2,2,6-trimethyl piperidine 261

Appendix 4: 1,3-Dimethyl-2-tosyl-2-azabicyclo[2.2.2]octane 420

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Appendix 6: 1-Methyl-2-tosyl-2-azabicyclo[2.2.2]octane 430

Appendix 7: 4-Iodo-6-tosyl-6-azabicyclo[3.2.1]octane 436

Appendix 8: Methyl (1-methyl-2-oxabicyclo[2.2.2]octan-4-yl)methyl carbamate 597
Appendix 1

1-Toluenesulfonyl-2,2,6-trimethylpiperidine 237

m.p. 82 – 83°C

CCDC 797890
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Appendix 2

2,2-Dimethyl-1-tosylpiperidine 250

m.p. 66 – 67 °C

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Table 1. Crystal data and structure refinement for CCDC 1021610.

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<td>Independent reflections</td>
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</tr>
<tr>
<td>Completeness to theta = 67.684°</td>
<td>99.8 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Gaussian</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.990 and 0.921</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F2</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>2752 / 0 / 166</td>
</tr>
<tr>
<td>Goodness-of-fit on F2</td>
<td>1.046</td>
</tr>
<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.0327, wR2 = 0.0887</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0374, wR2 = 0.0926</td>
</tr>
<tr>
<td>Extinction coefficient</td>
<td>n/a</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.296 and -0.296 e.Å⁻³</td>
</tr>
</tbody>
</table>
Appendix 3

1-(4-Nitrophenylsulfonyl)-2,2,6-trimethyl piperidine 261

m.p. 124 – 127 °C

CCDC 797889
Table 1. Crystal data and structure refinement for CCDC 797889.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>CCDC 797889</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C14 H20 N2 O4 S</td>
</tr>
<tr>
<td>Formula weight</td>
<td>312.38</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P21/a</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 6.2943(18) Å, α = 90°.</td>
</tr>
<tr>
<td></td>
<td>b = 19.982(7) Å, β = 96.79(2)°.</td>
</tr>
<tr>
<td></td>
<td>c = 11.764(3) Å, γ = 90°.</td>
</tr>
<tr>
<td>Volume</td>
<td>1469.2(8) Å</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.412 Mg/m3</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.238 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>664</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.30 x 0.04 x 0.02 mm³</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>3.42 to 20.92°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-6≤h≤6, -18≤k≤20, -11≤l≤11</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>2647</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>1534 [R(int) = 0.0947]</td>
</tr>
<tr>
<td>Completeness to theta = 20.92°</td>
<td>98.1 %</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.9953 and 0.9320</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F2</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>1534 / 0 / 193</td>
</tr>
<tr>
<td>Goodness-of-fit on F2</td>
<td>1.164</td>
</tr>
<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.0865, wR2 = 0.1593</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.1428, wR2 = 0.1816</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.264 and -0.304 e.Å⁻³</td>
</tr>
</tbody>
</table>
Appendix 4

1,3-Dimethyl-2-tosyl-2-azabicyclo[2.2.2]octane 420

m.p. 112 – 114 °C
Table 4. Crystal data and structure refinement for dwk1016.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>dwk1016</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C16 H23 N O2 S</td>
</tr>
<tr>
<td>Formula weight</td>
<td>293.41</td>
</tr>
<tr>
<td>Temperature</td>
<td>293(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P21/a</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 15.4205(9) Å, α = 90°.</td>
</tr>
<tr>
<td></td>
<td>b = 11.3763(9) Å, β = 114.435(4)°.</td>
</tr>
<tr>
<td></td>
<td>c = 18.7020(14) Å, γ = 90°.</td>
</tr>
<tr>
<td>Volume</td>
<td>2987.0(4) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>8</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.305 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.218 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>1264</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.200 x 0.200 x 0.020 mm³</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>1.196 to 23.872°.</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-17&lt;=h&lt;=17, -12&lt;=k&lt;=12, -21&lt;=l&lt;=21</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>13023</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>4500 [R(int) = 0.0868]</td>
</tr>
<tr>
<td>Completeness to theta = 25.242°</td>
<td>83.3 %</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>4500 / 24 / 367</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>2.807</td>
</tr>
<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.2994, wR2 = 0.6171</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.3274, wR2 = 0.6287</td>
</tr>
<tr>
<td>Extinction coefficient</td>
<td>n/a</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>7.679 and -1.056 e.Å⁻³</td>
</tr>
</tbody>
</table>
Appendix 5

4,7-Dimethyl-6-((4-nitrophenyl)sulfonyl)-6-azabicyclo[3.2.1]octane 242

m.p. 174 – 177 °C

CCDC 1021607
Table 1. Crystal data and structure refinement for CCDC 1021607.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>CCDC 1021607</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C15 H20 N2 O4 S</td>
</tr>
<tr>
<td>Formula weight</td>
<td>324.39</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P 21</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 6.2309(10) Å</td>
</tr>
<tr>
<td></td>
<td>b = 10.869(3) Å</td>
</tr>
<tr>
<td></td>
<td>c = 11.970(3) Å</td>
</tr>
<tr>
<td>Volume</td>
<td>792.2(3) Å</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.360 Mg/m3</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.224 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>344</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.500 x 0.040 x 0.010 mm³</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>1.741 to 20.796°.</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>1642</td>
</tr>
<tr>
<td>Completeness to theta = 25.242°</td>
<td>58.1 %</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix-block least-squares on F2</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>1642 / 104 / 181</td>
</tr>
<tr>
<td>Goodness-of-fit on F2</td>
<td>1.240</td>
</tr>
<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.1183, wR2 = 0.2744</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.2021, wR2 = 0.3613</td>
</tr>
<tr>
<td>Absolute structure parameter</td>
<td>0.5(6)</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>1.044 and -0.576 e.Å⁻³</td>
</tr>
</tbody>
</table>
Appendix 6

1-Methyl-2-tosyl-2-azabicyclo[2.2.2]octane 430

m.p. 135 – 138 °C

CCDC 1061506
Table 1. Crystal data and structure refinement for exp_769.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>CCDC 1061506</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C15 H21 N O2 S</td>
</tr>
<tr>
<td>Formula weight</td>
<td>279.39</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>P n a 21</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>(a = 7.6489(4) , \text{Å})</td>
</tr>
<tr>
<td></td>
<td>(\alpha = 90^\circ)</td>
</tr>
<tr>
<td></td>
<td>(b = 16.1308(7) , \text{Å})</td>
</tr>
<tr>
<td></td>
<td>(\beta = 90^\circ)</td>
</tr>
<tr>
<td></td>
<td>(c = 11.3067(6) , \text{Å})</td>
</tr>
<tr>
<td></td>
<td>(\gamma = 90^\circ)</td>
</tr>
<tr>
<td>Volume</td>
<td>1395.05(12) , \text{Å}^3</td>
</tr>
<tr>
<td>(Z)</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.330 Mg/m3</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.230 mm(^{-1})</td>
</tr>
<tr>
<td>(F(000))</td>
<td>600</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.200 x 0.101 x 0.055 mm(^3)</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>3.455 to 29.574°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>(-10 \leq h \leq 7, -15 \leq k \leq 22, -15 \leq l \leq 9)</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>4434</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>2636 [(R(\text{int}) = 0.0426)]</td>
</tr>
<tr>
<td>Completeness to theta = 25.242°</td>
<td>99.4 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>1.000000 and 0.71986</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F2</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>2636 / 425 / 257</td>
</tr>
<tr>
<td>Goodness-of-fit on F2</td>
<td>1.089</td>
</tr>
<tr>
<td>Final R indices [(I &gt; 2\sigma(I))]</td>
<td>(R1 = 0.0567, , wR2 = 0.1293)</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>(R1 = 0.0745, , wR2 = 0.1410)</td>
</tr>
<tr>
<td>Absolute structure parameter</td>
<td>0.6(3)</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.460 and -0.328 e.Å(^{-3})</td>
</tr>
</tbody>
</table>
Appendix 7

4-Iodo-6-tosyl-6-azabicyclo[3.2.1]octane 436

m.p. 116 – 118 °C

CCDC 1021608
### Table 1. Crystal data and structure refinement for CCDC 1021608

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>CCDC 1021608</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C14 H18 I N O2 S</td>
</tr>
<tr>
<td>Formula weight</td>
<td>391.25</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Triclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P -1</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 7.2761(2) Å, α = 69.202(2)°.</td>
</tr>
<tr>
<td></td>
<td>b = 9.8338(3) Å, β = 80.029(2)°.</td>
</tr>
<tr>
<td></td>
<td>c = 11.1700(3) Å, γ = 80.879(2)°.</td>
</tr>
<tr>
<td>Volume</td>
<td>731.77(4) Å</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.776 Mg/m3</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>2.328 mm-1</td>
</tr>
<tr>
<td>F(000)</td>
<td>388</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.150 x 0.100 x 0.100 mm3</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>2.228 to 27.867°.</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-9&lt;=h&lt;=9, -10&lt;=k&lt;=12, -14&lt;=l&lt;=13</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>4991</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>3447 [R(int) = 0.0259]</td>
</tr>
<tr>
<td>Completeness to theta = 25.242°</td>
<td>99.1 %</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F2</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>3447 / 0 / 174</td>
</tr>
<tr>
<td>Goodness-of-fit on F2</td>
<td>1.119</td>
</tr>
<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.0385, wR2 = 0.0891</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0419, wR2 = 0.0921</td>
</tr>
<tr>
<td>Extinction coefficient</td>
<td>0.054(3)</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>1.563 and -1.267 e.Å-3</td>
</tr>
</tbody>
</table>
Appendix 8

Methyl (1-methyl-2-oxabicyclo[2.2.2]octan-4-yl)methyl)carbamate 597

m.p. 92 – 94 °C

CCDC 1021609
<table>
<thead>
<tr>
<th><strong>Identification code</strong></th>
<th>CCDC 1021609</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Empirical formula</strong></td>
<td>C22 H38 N2 O6</td>
</tr>
<tr>
<td><strong>Formula weight</strong></td>
<td>426.54</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td>293(2) K</td>
</tr>
<tr>
<td><strong>Wavelength</strong></td>
<td>1.54184 Å</td>
</tr>
<tr>
<td><strong>Crystal system</strong></td>
<td>Orthorhombic</td>
</tr>
<tr>
<td><strong>Space group</strong></td>
<td>P b c a</td>
</tr>
<tr>
<td><strong>Unit cell dimensions</strong></td>
<td>a = 9.6049(2) Å, α = 90°.</td>
</tr>
<tr>
<td></td>
<td>b = 10.7454(3) Å, β = 90°.</td>
</tr>
<tr>
<td></td>
<td>c = 22.5611(6) Å, γ = 90°.</td>
</tr>
<tr>
<td><strong>Volume</strong></td>
<td>2328.50(10) Å³</td>
</tr>
<tr>
<td><strong>Z</strong></td>
<td>4</td>
</tr>
<tr>
<td><strong>Density (calculated)</strong></td>
<td>1.217 Mg/m³</td>
</tr>
<tr>
<td><strong>Absorption coefficient</strong></td>
<td>0.717 mm⁻¹</td>
</tr>
<tr>
<td><strong>F(000)</strong></td>
<td>928</td>
</tr>
<tr>
<td><strong>Crystal size</strong></td>
<td>0.305 x 0.242 x 0.115 mm³</td>
</tr>
<tr>
<td><strong>Theta range for data collection</strong></td>
<td>3.919 to 73.920°.</td>
</tr>
<tr>
<td><strong>Index ranges</strong></td>
<td>-11&lt;=h&lt;=11, -8&lt;=k&lt;=12, -27&lt;=l&lt;=22</td>
</tr>
<tr>
<td><strong>Reflections collected</strong></td>
<td>7806</td>
</tr>
<tr>
<td><strong>Independent reflections</strong></td>
<td>2316 [R(int) = 0.0162]</td>
</tr>
<tr>
<td><strong>Completeness to theta = 67.684°</strong></td>
<td>100.0 %</td>
</tr>
<tr>
<td><strong>Refinement method</strong></td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td><strong>Data / restraints / parameters</strong></td>
<td>2316 / 0 / 139</td>
</tr>
<tr>
<td><strong>Goodness-of-fit on F²</strong></td>
<td>1.052</td>
</tr>
<tr>
<td><strong>Final R indices [I&gt;2sigma(I)]</strong></td>
<td>R₁ = 0.0465, wR₂ = 0.1283</td>
</tr>
<tr>
<td><strong>R indices (all data)</strong></td>
<td>R₁ = 0.0525, wR₂ = 0.1370</td>
</tr>
<tr>
<td><strong>Extinction coefficient</strong></td>
<td>0.00079(17)</td>
</tr>
<tr>
<td><strong>Largest diff. peak and hole</strong></td>
<td>0.283 and -0.219 e.Å⁻³</td>
</tr>
</tbody>
</table>