NEW ASPECTS OF ACID-CATALYSED CYCLISATIONS

ABDUL HADI ALDMAIRI

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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)

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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.

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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-trisubstetuted 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

I would like to thank ‘my Boss’ Professor David W Knight for his great support and wisdom throughout my studies at Cardiff University. I have ever never seen like his beautiful mind.

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I would also like to say a BIG thank you to my wife FATMA and my son ZIAD for their love and support throughout my life.

Table of Contents

Abbreviations and acronyms

Ac	acetyl
app.	apparent
aq.	aqueous
Ar	aromatic
Bn	benzyl
b.p.	boiling point
br	broad
Bu	butyl
COSY	correlation spectroscopy
CI	chemical ionisation
d	doublet
DCM	dichloromethane
dd	double doublet
dt	double triplet
DEPT	Distortionless Enhancement by Polarization Transfer
DMF	dimethylformamide
DMSO	dimethylsulfoxide
e.e.	enantiomeric excess
EI	electron ionisation
eq.	equivalent(s)
ES	electrospray

ether	diethyl ether
Et	ethyl
Δ	heat
h	hour(s)
HRMS	high resolution mass spectrometry
Hz	hertz
IR	infra-red
J	coupling constant
m	multiplet
M	molar
Me	methyl
MHz	megahertz
μmol	micromole(s)
ml	millilitre(s)
mmol	millimole(s)
m.p.	melting point
MS	mass spectrometry
Ms	methane sulfonyl
NMR	nuclear magnetic resonance
NOSEY	nuclear Overhauser enhancement spectroscopy
Ns or nosyl	*p*-nitrobenzenesulphonyl
o	*ortho*

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.**).

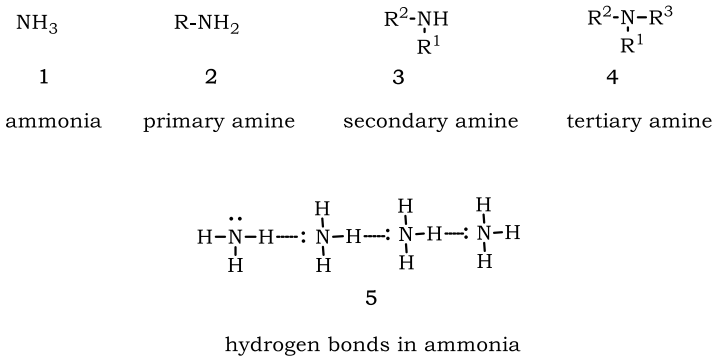

Fig. 1.1.

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.**).

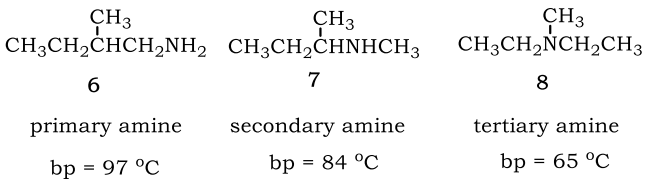

Fig. 1.2.

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 methylamine as the lone pair of electrons on the nitrogen are conjugated to the π-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]

	NH_3	CH_3-NH_2	$(CH_3)_2NH$	$(CH_3)_3N$	$PhCH_2NH_2$	Ph-NH_2
	5	9	10	11	12	13
pK_a	9.27	10.62	10.64	9.76	9.34	4.63

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]

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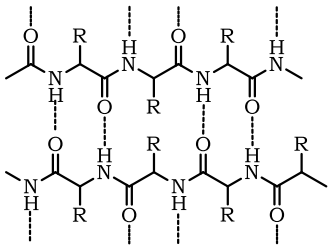

Fig. 1.4. Hydrogen bond proposed by Huggins

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.**).

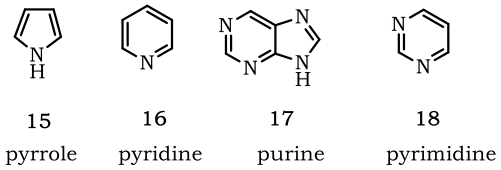

Fig. 1.5.

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.**).

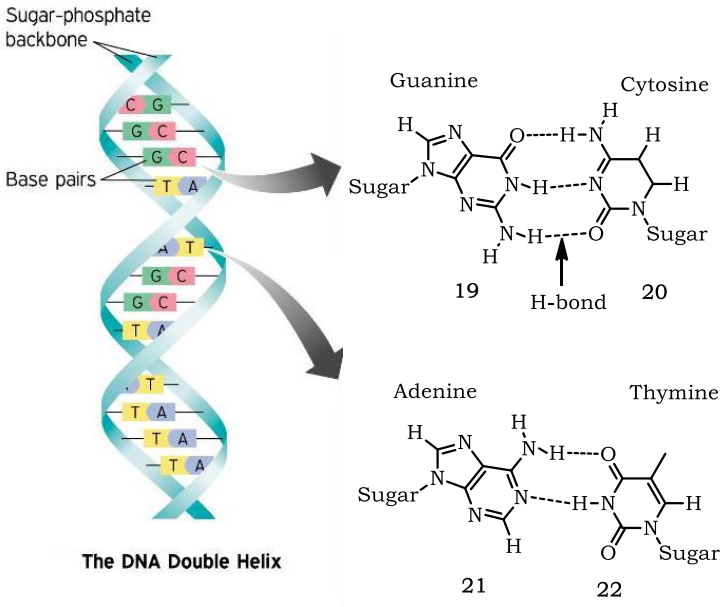

Fig. 1.6.

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]

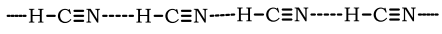

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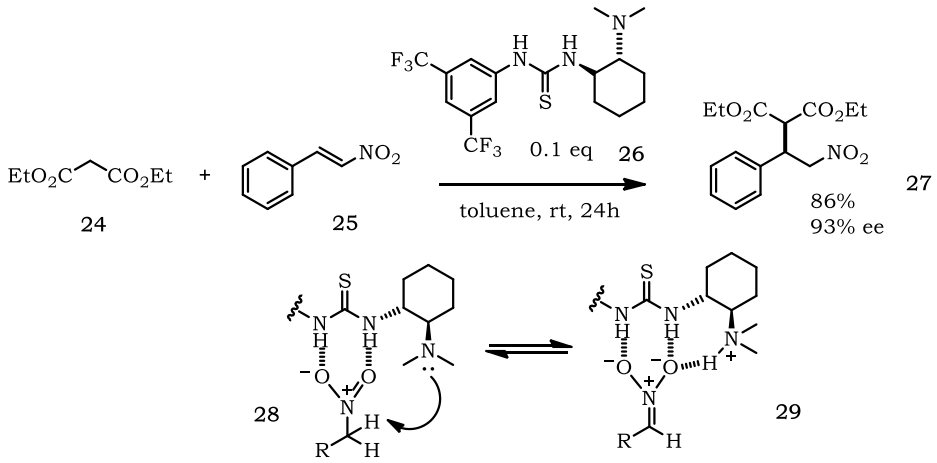
Fig. 1.7.

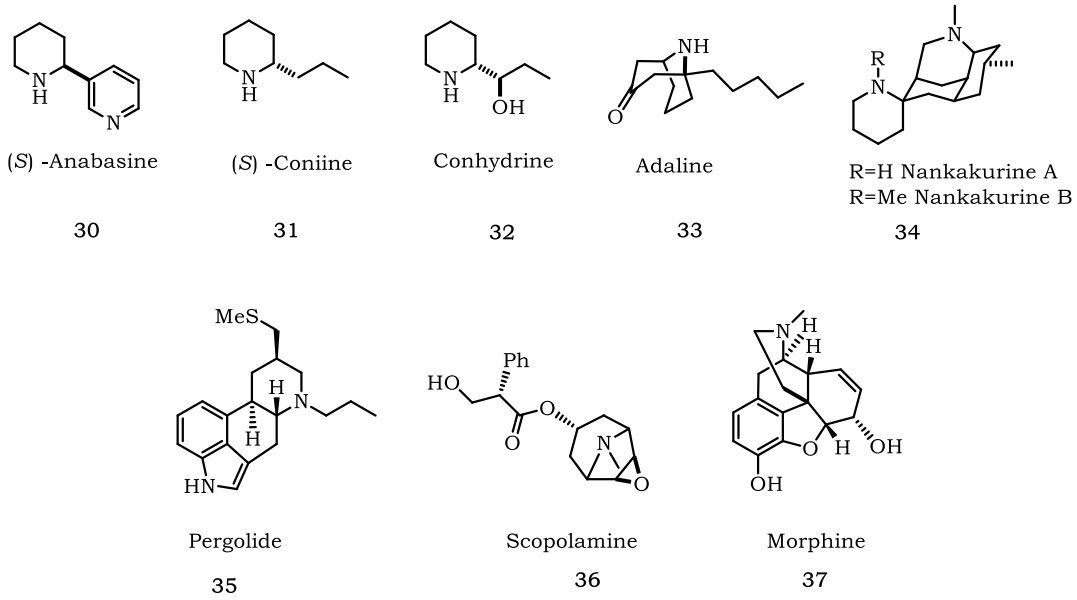
Nitro groups can also participate in intermolecular and intramolecular hydrogen bonding. Takemoto *et al.* reported novel, catalysed Michael reactions between malonates **24** and nitroolefins **25**. In this reaction, the thiourea catalyst seems to interact with the nitro group, facilitating formation 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.[4] Anabasine **30** is a piperidine alkaloid found in the *Nicotiana tabacum*.[5] Conine **31** and conhydrine **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.[6] 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.[7] *Spiro*-alkaloid nankakurine **34** induced secretion of neurotrophic factors in human astrocytoma cells at a concentration of 1 μM.[8] Pergolide **35** is a dopamine receptor agonist used in some countries for the treatment of Parkinson's disease.[9] Scopolamine **36** is a tropane alkaloid drug with muscarinic antagonist effects.[10] Morphine **37** is the gold standard of analgesics used to relieve intense pain. The legal medicinal use of morphine[11] in the United States of America exceeds 80,000 kg/year **(Scheme 1.2.)**.



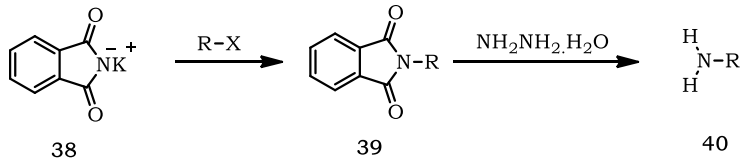
Scheme 1.2.

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:

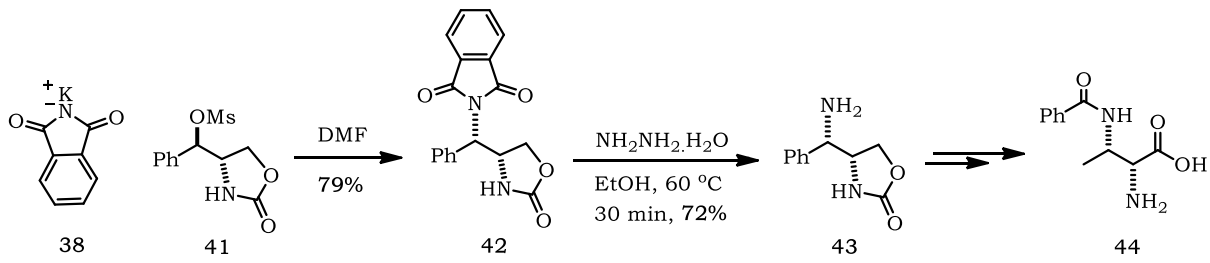
1- **Gabriel synthesis**:

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[12] **(Scheme 1.3.)**.



Scheme 1.3.

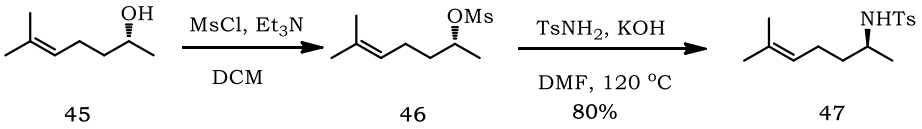
During synthetic studies by Rossi *et al.*, *β*-benzoylamino phenylalanine **44,** the secondary alcohol of an enantiopure oxazolidinone was mesylated then the sulfonate ester group of **41** was displaced with potassium phthalimide to give **42**. Deprotection of the phthalimide without destruction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



Scheme 1.4.

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.[14] This is illustrated by the reaction of potassium

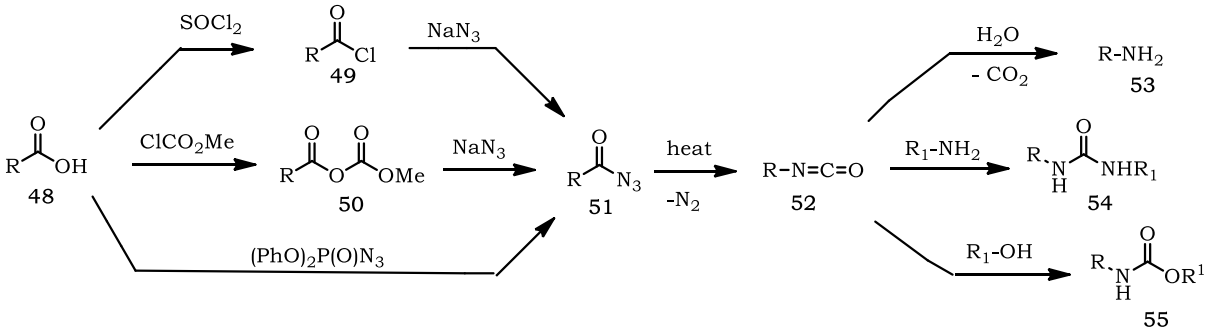
tosylamide which was prepared by heating 1.5 equivalents each of KOH and *p*-toluenesulfonamide in DMF. Following complete dissolution of the base, one equivalent of mesylate **46** prepared from commercial (*R*)-alcohol **45** is added, in DMF. Purification of the reaction mixture obtained after one 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.

3- **Curtius Rearrangement**:

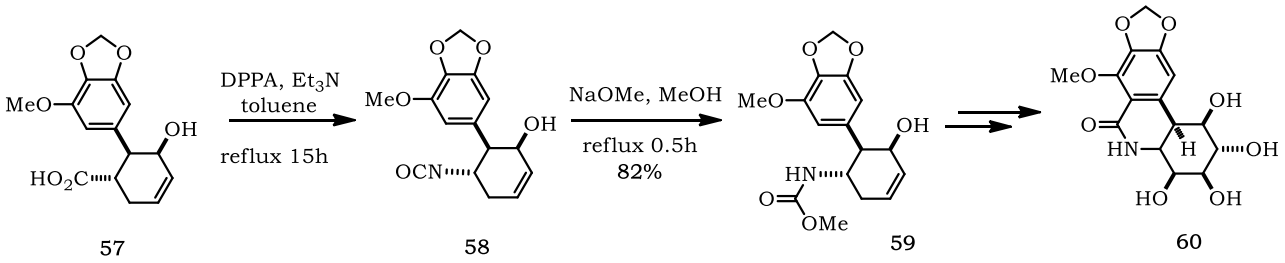
The thermal decomposition of acyl azides **51** to produce an isocyanate **52** is known as the Curtius rearrangement.[15] These intermediate isocyanates **52** may be isolated, or their corresponding hydrolysis products may be obtained directly. If the reaction is carried out in the presence of water,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



Scheme 1.6.

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

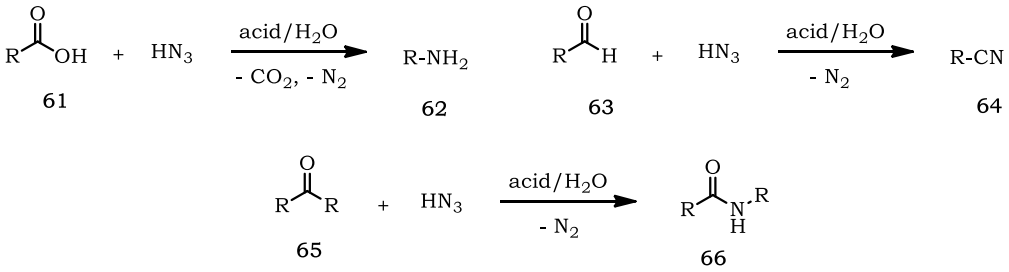
intermediate **58** that required further treatment with NaOMe/MeOH to generate the corresponding carbamate **59** in 82% overall yield (**Scheme 1.7.**).[16]



Scheme 1.7.

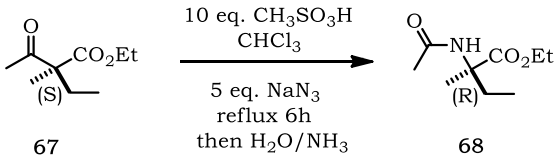
4- **Schmidt Reaction**:

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 N_2, 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.**).



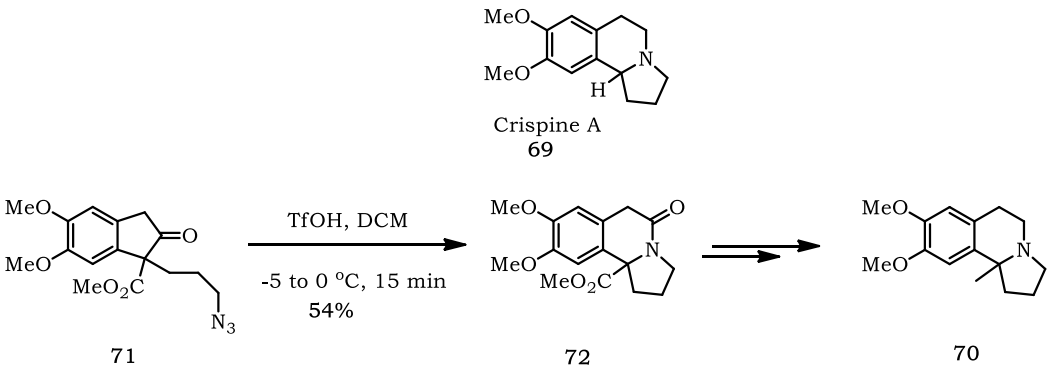
Scheme 1.8.

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.**).[17]



Scheme 1.9.

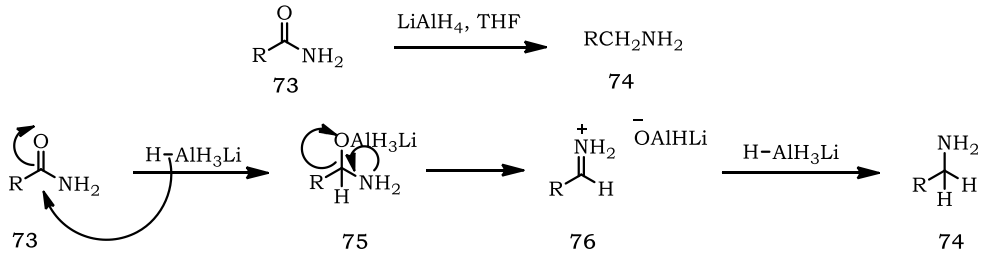
Kumar *et al.* report the synthesis of the methyl analogue **70** of crispine A **69** *via* an intramolecular Schmidt reaction. The indolizidine alkaloid known as crispine A, was isolated from carduus crispus, an European biennial introduced in North America having flower heads, and was found to exhibit significant antitumor activity against many human cancer lines.[18] The intramolecular Schmidt reaction of azido-ketone **71** was successfully achieved using triflic acid (TfOH) at -5 to 0 ^oC and the resultant cyclized product **72** was isolated in 54% yield (**Scheme 1.10.**).[19]



Scheme 1.10.

5- **Amide reduction**:

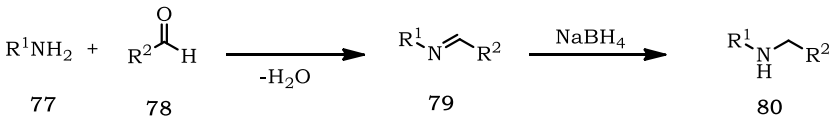
An amide [*e.g.* **73**] can be reduced to the corresponding amine **74** by lithium aluminum hydride ($LiAlH_4$) and many related hydride sources (**Scheme 1.11.**).



Scheme 1.11

6- **Imine reduction**:

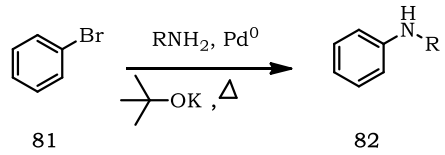
Reductive amination is another technique to alkylate amines. It consists of two subsequent reactions: first condensation of an amine **77** with an aldehyde **78** or a ketone to give an imine **79** with elimination of water then reduction of the imine **79** to the corresponding amine **80** (**Scheme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



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.**).[20]

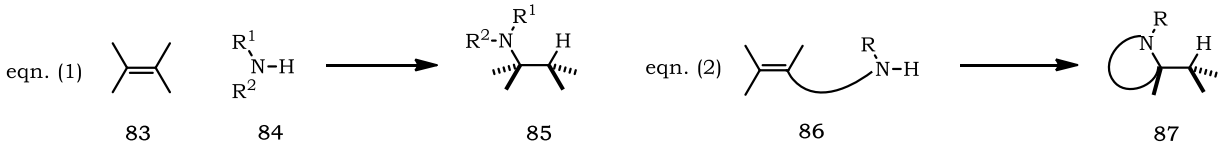


Scheme 1.13.

8- Hydroamination reaction:

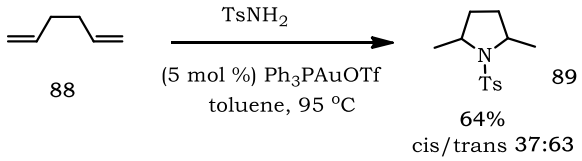
Hydroamination is a highly atom-economical process in which an amine N–H functionality is added across an unsaturated carbon–carbon linkage. This potentially highly useful process can give access to various nitrogen-containing compounds and fine chemicals of many structural types as well as naturally 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.**).[21]



Scheme 1.14.

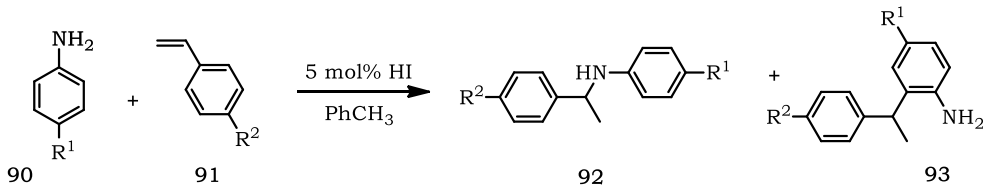
The intermolecular hydroamination of a 1,5-diene **88** by $TsNH_2$ could be followed by a second intramolecular hydroamination to produce pyrrolidines **89** in an one-pot operation. A mixture of *cis* and *trans* products (37:63) was isolated in 64% yield with the use of four equivalents of the 1,5-diene **88** in toluene with a catalytic amount of $Ph_3PAuOTf$ (5 mol%) (generated by mixing equal equivalents of Ph_3PAuCl and AgOTf) at 95 °C for 15 h (**Scheme 1.15.**).[22]



Scheme 1.15.

8.1. Intermolecular Acid-Catalyzed Hydroamination of Alkenes: [23]

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.**).[24]

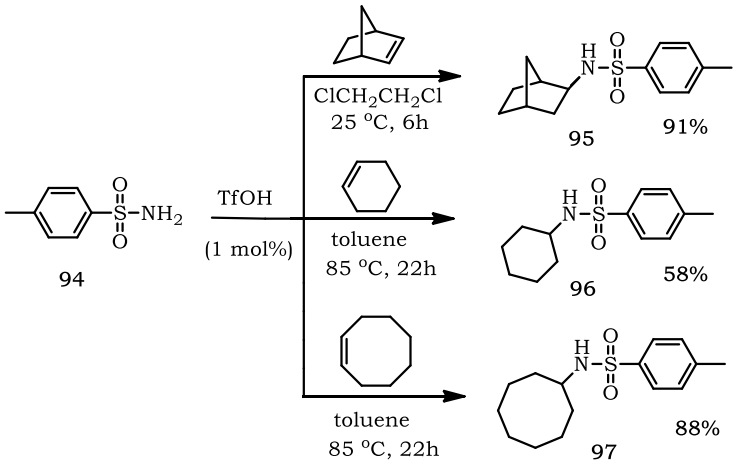


Scheme 1.16.

Table 1.1. Examples of hydroamination/hydroarylation of simple olefins with hydrogen iodide

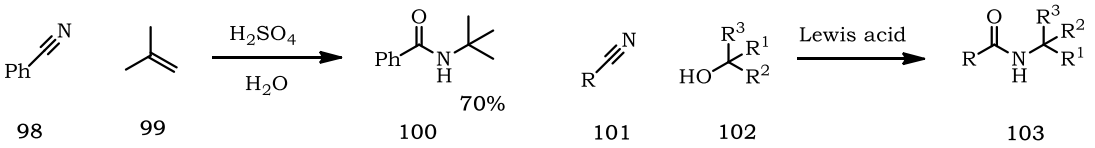
	Anilines 90 R^1 =	**Olefin 91** R^2 =	**Temperature / °C**	**Time / h**	**Ratio of 92:93**	**Yield / %**
1	H	H	5	4	3:2	98
2	Cl	H	35	24	2:3	86
3	H	Me	135	24	5:4	80

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 $TsNH_2$ **94** to norbornene occurred within hours at room temperature to form the *exo*-addition product in 91% yield, while the addition of $TsNH_2$ to cyclohexene and cyclooctene occurred within a day at 85 °C in 58% and 86% isolated yield (**Scheme 1.17.**).[25]



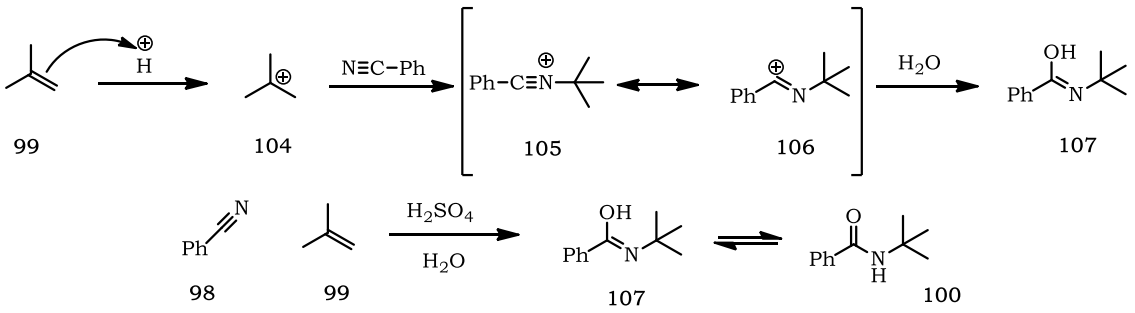
Scheme 1.17.

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.**).[26]



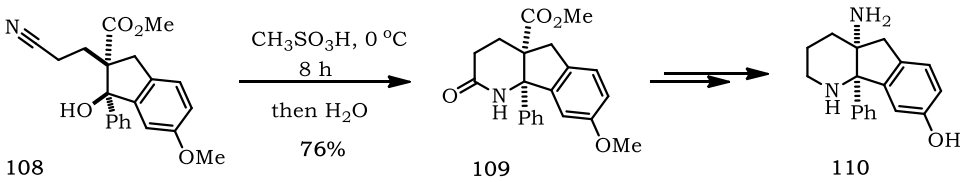
Scheme 1.18.

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.**).



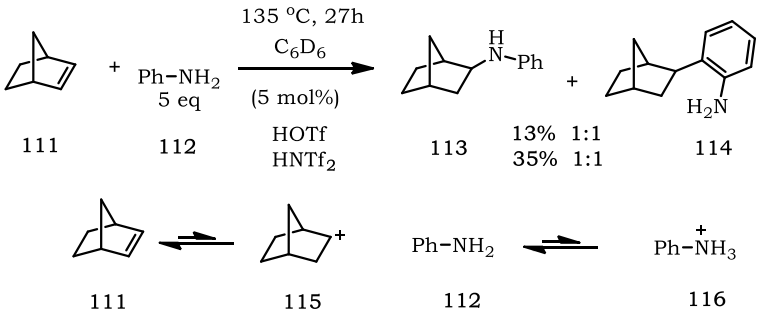
Scheme 1.19.

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.**).[27]



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 $OTf^- < NTf_2^-$. 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.**).[28]

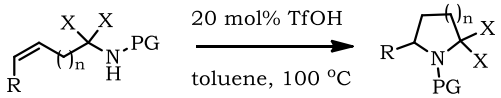


Scheme 1.21.

8.2.1 Intramolecular Acid-Catalyzed Hydroamination of Alkenes[29]

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.[30] 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

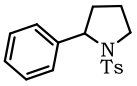
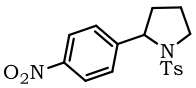
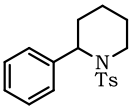
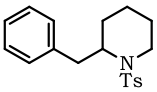
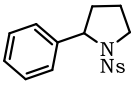
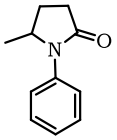
process catalytic in acid. The regiochemistry of this process is determined mostly by the stability of the carbenium ion intermediate; thus, most of these transformations are overall unfavourable 5-*endo*-trig cyclisations, according to Baldwin's rules. Hartwig evaluated acid-catalyzed reactions of the 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.



117 118

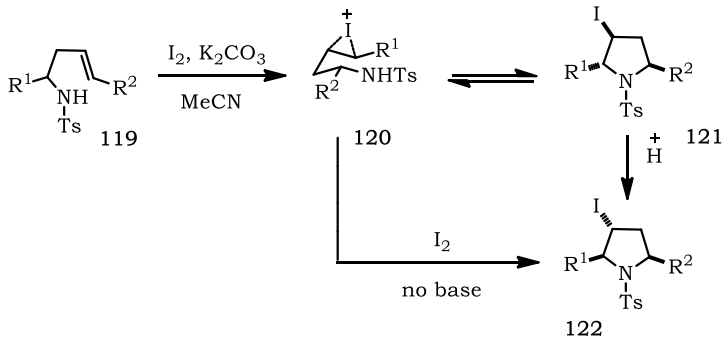
Scheme 1.22.

Table 1.2. Selected Examples of Acid-Catalyzed Intramolecular Hydroamination of Protected Alkenylamines.

Entry	**1**	**2**	**3**	**4**	**5**	**6**	**7**
n	1	2	1	2	3	2	2
Product 118							
Yield %	83	95	0	83	51	96	99

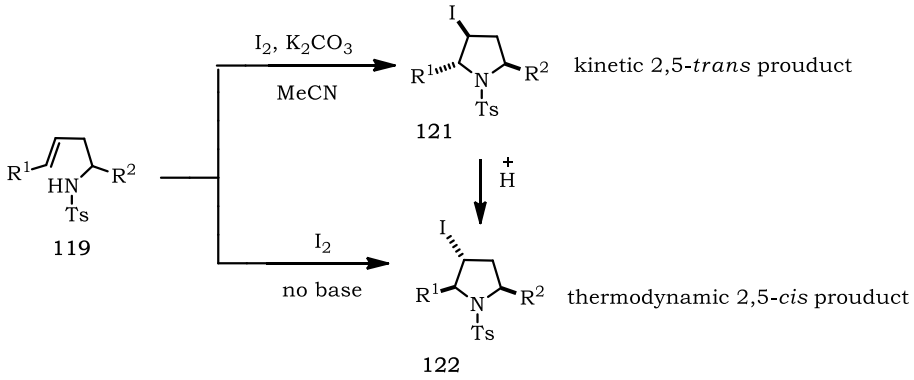
8.2.2 Acid-Catalysed Hydroamination Reactions in the Knight Group

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-*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-*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-*trans* isomers **121**, and which can then be followed by proton-induced cyclo-reversion and re-closure and hence equilibrium towards, and eventually only, the more thermodynamically stable 2,5-*cis* isomers **122** (**Scheme 1.23.**).



Scheme 1.23.

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-*trans* isomers **121**. Omission of the base leads to only the 2,5-*cis* isomers **122**. The pathways were proven by exposing a 2,5-*trans*-pyrrolidine **121** to a mixture of hydrogen iodine and iodine, when conversion into the *cis*-isomer **122** occurred rapidly. Acid-catalysed cyclo-reversion and equilibration to the thermodynamically more stable *cis*-isomers **122** then follows (**Scheme 1.24.**).[31]



Scheme 1.24.

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.**

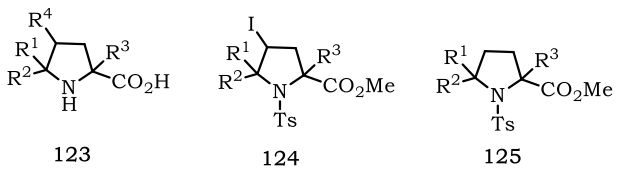
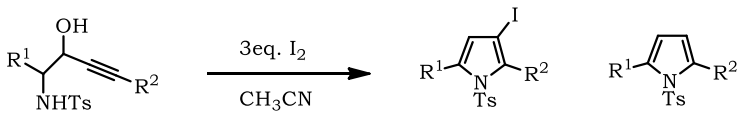


Fig. 1.8.

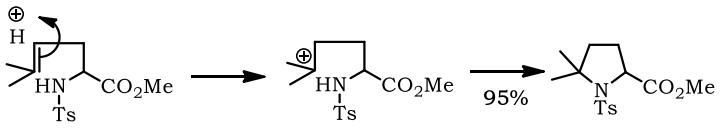
When these ideas were extended to alkyne systems, new and efficient approaches to dihydroiodo and iodopyrroles were found *via* 5-*endo*-dig cyclisations. However, when such cyclisations were carried out without any base present, a mixture of iodopyrroles and pyrroles were formed (**Scheme 1.25.**).[32]



126 127 128

Scheme 1.25.

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.**).

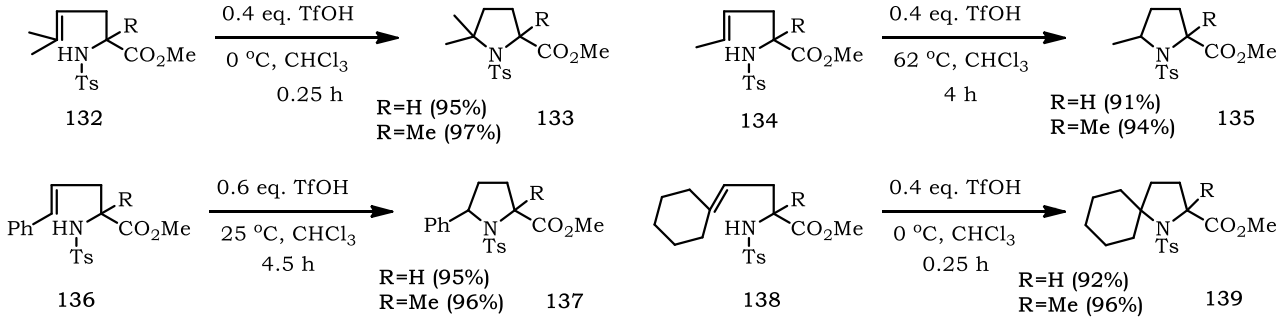


129 130 131

Scheme 1.26.

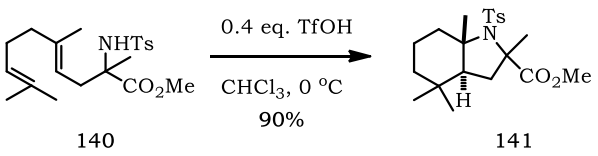
In the event, Haskins and Knight, prepared pyrrolidine derivatives by using trifluoromethanesulfonic acid CF_3SO_3H (triflic acid, TfOH) as a catalyst in excellent yields.[33] Both prenyl derivatives **132** underwent rapid and very clean cyclisation when exposed to 0.4 equivalents of triflic acid at 0 ^oC 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 crotyl analogue **134** required heating to reflux to achieve complete reaction; the excellent yields of the resulting pyrrolidines **132** were, however, obtained. S*piro*-Pyrrolidines can also be prepared using this chemistry: the ylidenecyclohexane 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.).**



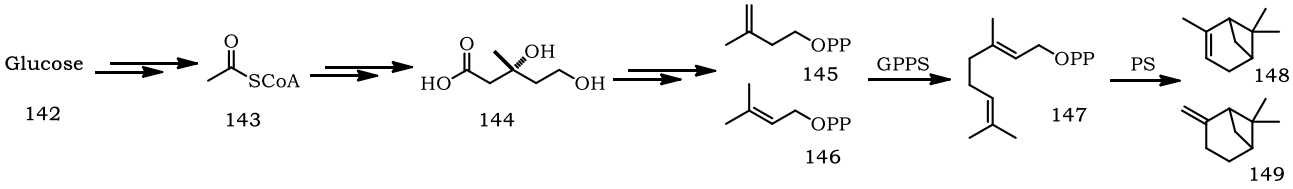
Scheme 1.27.

The Knight group has had a longstanding interest in 5-*endo*-trig cyclisations. Almost simultaneously to the study of Schlummer and Hartwig[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.**).



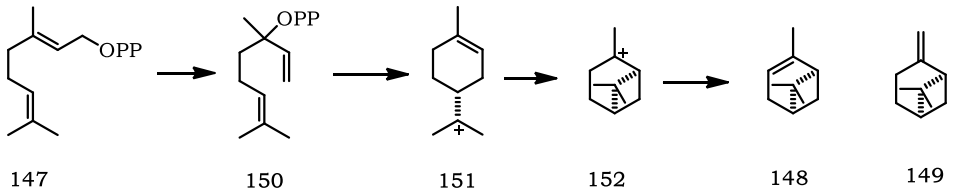
Scheme 1.28.

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 *α*- or *β*-pinene **148, 149** (**Scheme 1.29.**).



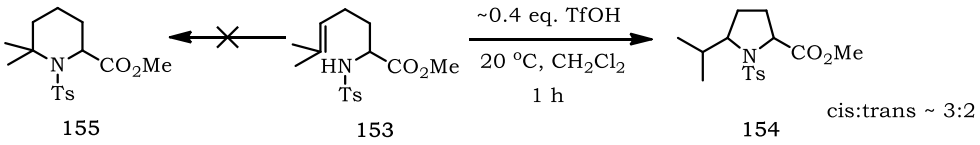
Scheme 1.29.

The pinene synthase cyclization mechanism of geranyl diphosphate GPP **147** to *α*- or *β*-pinene **148**, **149** is shown in (**Scheme 1.30.**).[35]



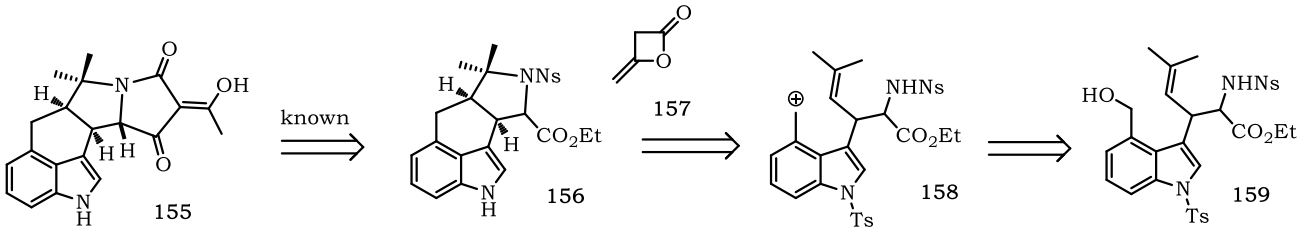
Scheme 1.30.

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.).**



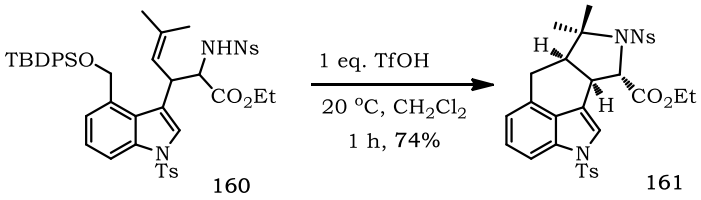
Scheme 1.31.

However, Haskins prepared the indolic terpene alkaloid *α*-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 1.32.

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 1.33.

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.

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Chapter 2

Acid-catalysed synthesis of piperidines

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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 has 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]

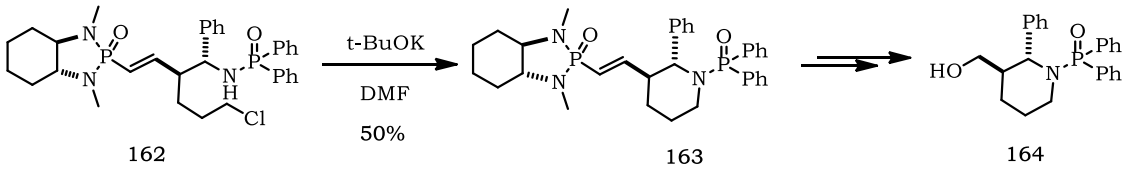
Piperdine synthesis

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

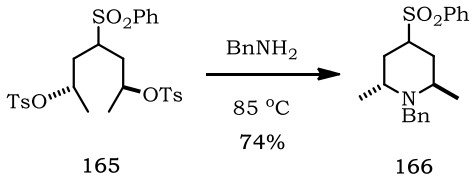
Nucleophilic substitution is a reliable method of making piperidines, It is often used as the final step, followed by deprotection of the functional groups present, if necessary. The main difficulty with this type of cyclisation compared to intermolecular nucleophilic substitution is the choice of the 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.[3] The chloride **162** has been used by Hanessian *et al*[4] in the synthesis of enantiomerically pure 2,3-piperidines (**Scheme 2.1**). Ring-closure using *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[5] cyclised the *bis*-tosylate **165** using an excess of benzylamine at 85 ^{o}C. The reaction occurred in 90% yield and gave only the *anti*-piperidine **166 (Scheme 2.2).**

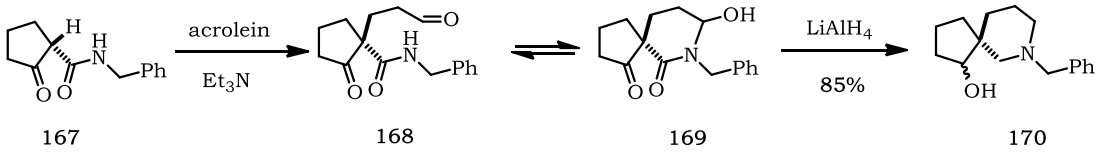


Scheme 2.2

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 *et al*.[6] achieved the conjugate addition of the *β*-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 $LiAlH_4$ resulted in a reductive cyclisation, yielding the racemic alcohol **170 (Scheme 2.3).**



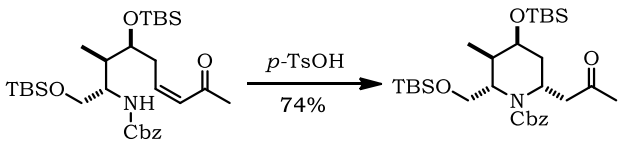
167 168 169 170

Scheme 2.3

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**).

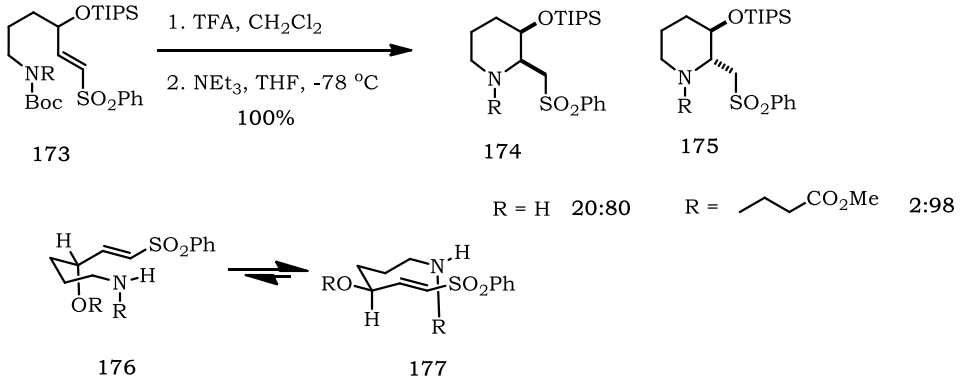


171 172

Scheme 2.4

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 Et_3N. The cyclization was complete in less than 30 min at -78 °C, giving piperidines **174** and **175** as a mixture

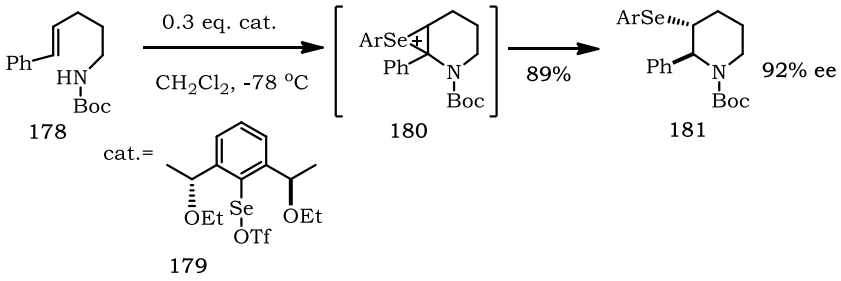
of *cis* and *trans* isomers in quantitative yield. The diastereoselectivity is affected by the substituent on nitrogen: the mechanistic rationales suggest an equilibrium between conformers **176** and **177** exists, disfavoring **176** due to 1,3-diaxial interactions between the substituents.[8, 9]



Scheme 2.5

3.2. Electrophile-Induced Cyclizations

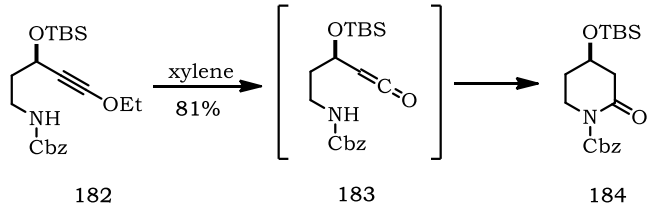
Deziel developed catalytic asymmetric syntheses of piperidines by using catalytic amounts of chiral C_2-symmetric arylselenium triflate **179** to give diastereomerically pure *trans*-2,3-disubstituted piperidine **181** in 89% yield with an excellent 92% ee (**Scheme 2.6**). [9, 10]



Scheme 2.6

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**).

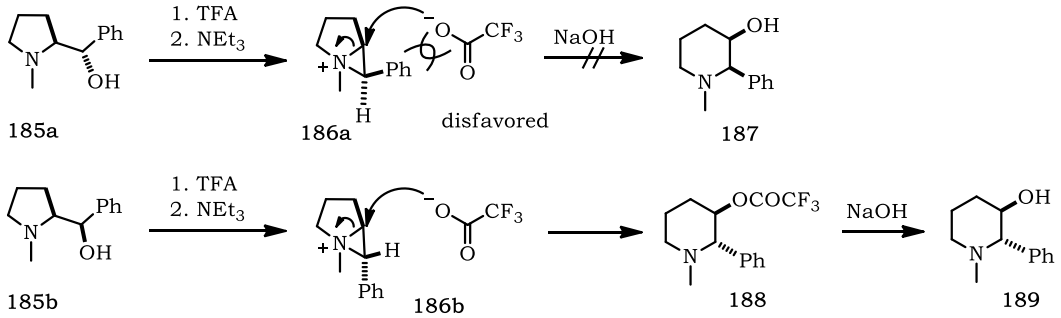


182 183 184

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_3N 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]

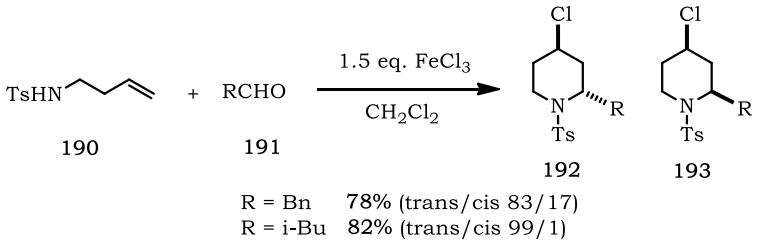


Scheme 2.8

6. Aza-Prins piperidine synthesis [14]

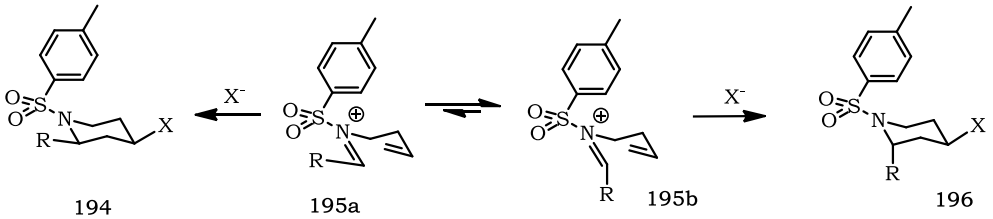
The synthesis of piperidines was investigated by Martin and co-workers. Their strategy consisted of allowing homoallylic tosylamides to react with aldehydes in the presence of $FeCl_3$ or $FeBr_3$.

Homoallylic tosylamide **190** led preferentially to *trans*-2,4-disubstituted piperidines **192** (**Scheme 2.9**).[15]



Scheme 2.9

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]



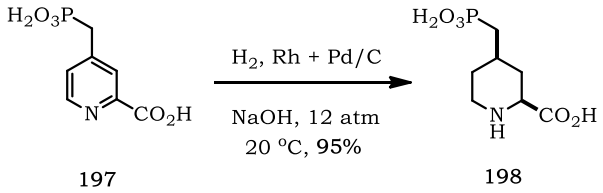
R	$E_{Z\text{-iminium}}$-$E_{E\text{-iminium}}$ (Kcal/mol)
Me	-0.78
i-Pr	-1.25
Bn	+0.37

Scheme 2.10

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

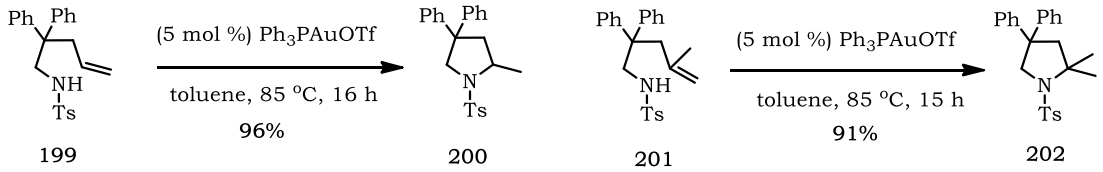
that must be either stabilized by an electron-withdrawing group on nitrogen or transformed *in situ*, presumably to prevent autoxidation.[19] The full reduction of pyridines to piperidines using hydrogen can be achieved using different catalysts such as Pd/C, PtO_2 or Rh/C. The full reduction of 2,4-pyridines **197** has been studied by Steiner *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 **197** to the desired *syn* 2,4-disubstituted piperidine **198**, in 95% yield, which contained only 3% of the *anti*-diastereoisomer (**Scheme 2.11**).[20]



Scheme 2.11

8. Metal-catalyzed hydroamination

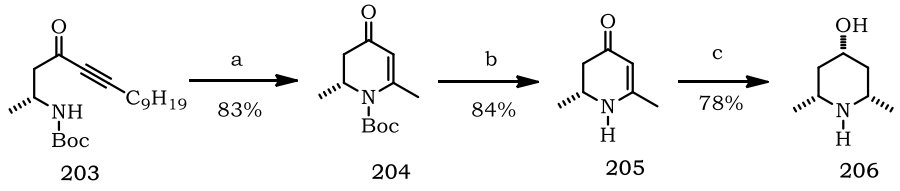
Metal-catalyzed hydroamination of simple olefins is one of the most important strategies to prepare nitrogen-containing molecules.[21, 22] It has been reported that gold(I)-catalyzed intramolecular hydroamination of tosylated amino olefins **199** and **201** is a very effective pyrrolidine synthesis. Several *N*-tosylated olefins were efficiently cyclized to afford pyrrolidines **200** and **202** in toluene with a catalytic amount of $Ph_3PAuOTf$ (5 mol%) (generated by mixing equal equivalents of Ph_3PAuCl and AgOTf) (**Scheme 2.12**).[23]



Scheme 2.12

A gold-catalyzed methodology involving a favoured 6-*endo*-dig cyclization has been applied to obtain dendrobate alkaloid (+)-241D **206,** which has been isolated from the methanolic skin extracts

of the Panamanian poison frog *Dendrobates specious*[24] and has shown to be a non-competitive blocker of acetylcholine to ganglionic nicotinic receptor channels.[25] The gold-catalyzed intramolecular cyclisation of this intermediate *β*-amino ynone derivative **203** using PPh_3AuCl 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-catayzed 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**).

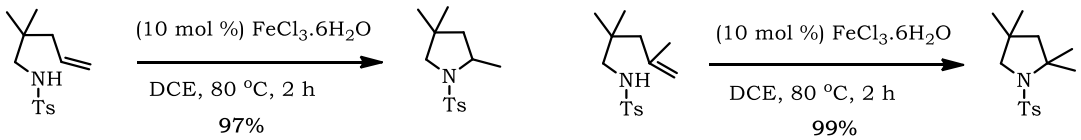


203 204 205 206

(a) (5 mol%) PPh_3AuCl , (5 mol%) $AgSbF_6$, DCE, rt, 1 h.
(b) HCl (3 N), MeOH, rt, 18 h.
(c) 10% Pd/C, H_2, MeOH, rt, 72h.

Scheme 2.13

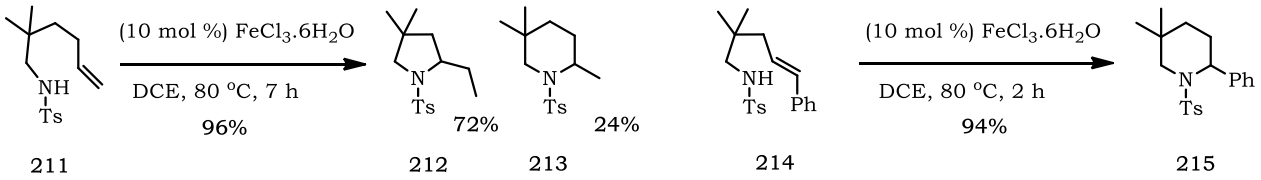
Takaki *et al.* reported investigations into $FeCl_3$-catalyzed intramolecular hydroamination, in which they found that the iron activity was superior to that of other conventional transition-metal catalysts. The compatibility of $FeCl_3.6H_2O$ (10 mol %) with various types of amino-olefins was investigated 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 ^oC under air (**Scheme 2.14**).[26]



207 208 209 210

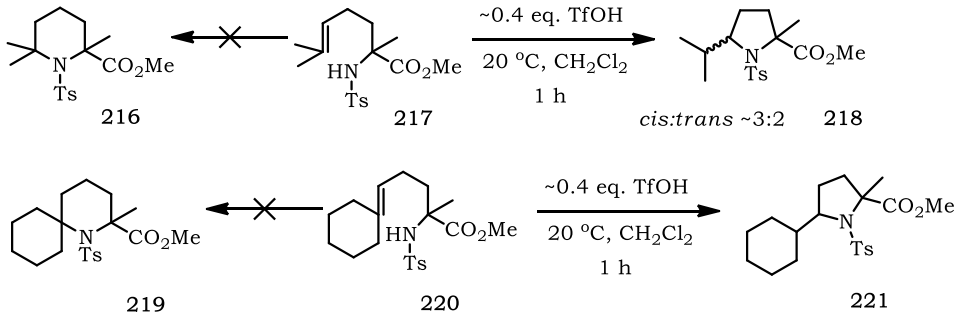
Scheme 2.14

In the same report, consistent with 6-*endo*-trig cyclisations being unfavourable according to Baldwin's rules,[27] when Takaki *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 $FeCl_3 \cdot 6H_2O$ 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.



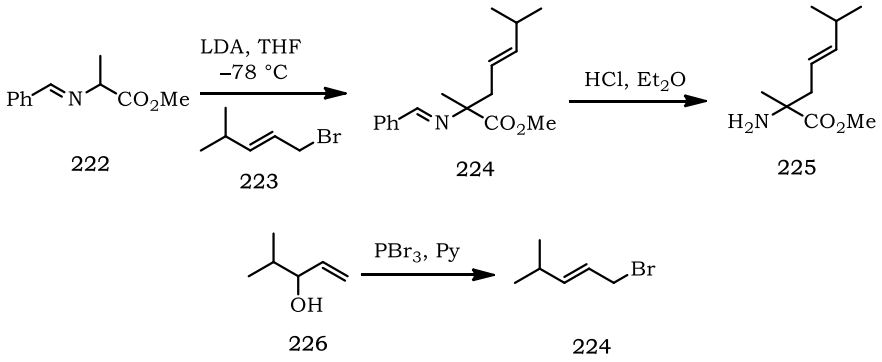
Scheme 2.15

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 *via* a less stable secondary carbocation intermediate. The major diasteroisomer of pyrrolidine 2**21,** with the cyclohexyl and methyl ester substituent *cis* to one another, was confirmed by X-ray crystallographic analysis (**Scheme 2.16**).[28]



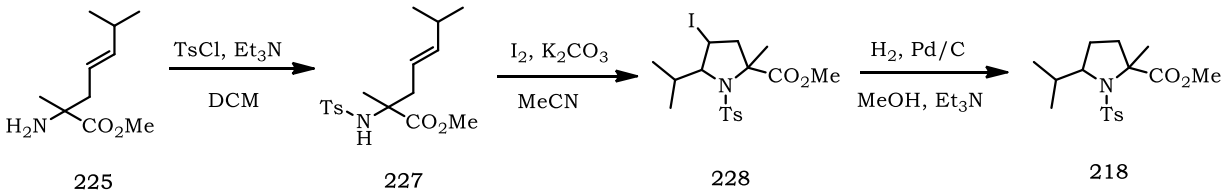
Scheme 2.16

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.[29] 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**.



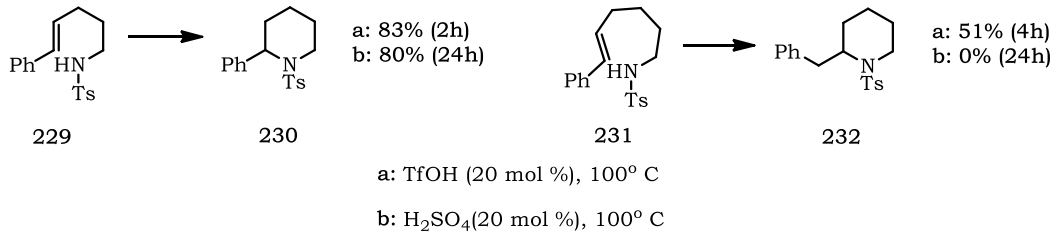
Scheme 2.17

Subsequent hydrolysis of the imine and reprotection 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**).[30]



Scheme 2.18

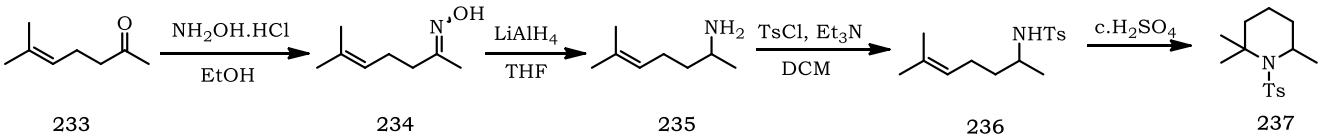
It becomes clear that pyrrolidine **218** was formed in the acid-catalysed cyclization rather than the expected piperidine **216** (**Scheme 2.16**). This finding was particularly unexpected especially when compared with Hartwig's piperidine synthesis. In 2002, he published a paper which reported that 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 ^{o}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**).



Scheme 2.19

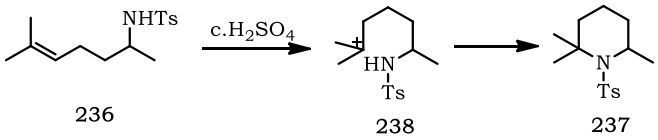
Just before my arrival in Cardiff, a French Erasmus student, Alexis Dupauw, was visiting the group for three months and began a study of the unexpected inability to form piperidines by acid-catalysed cyclisations (**Scheme 2.20**), which became my starting point.

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*-tosylation by *para*-methylbenzene sulfonyl chloride in the presence of triethylamine. Each of these three steps gave essentially quantitive 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.



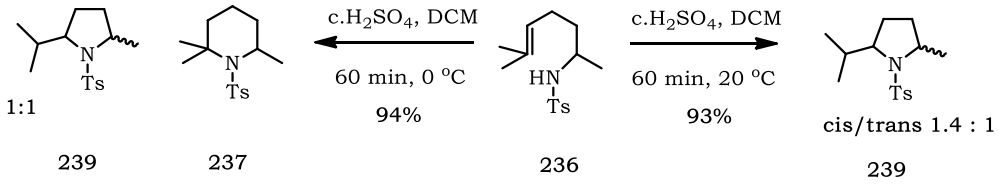
Scheme 2.20

All of Alexis' experiments were carried out using concentrated sulfuric acid, c.H_2SO_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

In one of his attempts to form piperidine **237**, treatment of the sulfonamide **236** with 0.2 equivalents of c.H_2SO_4 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.H_2SO_4, at room temperature, 20 ^oC, 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 N<u>H</u>Ts 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 NC<u>H</u> 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(CH_3)$_2$ 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(C*H*$_3$)$_2$ in pyrrolidine **239** *cis/trans* 1.4:1 (**Fig. 2.2**) and two sharp singlets in piperidine **237** (**Fig. 2.3**).

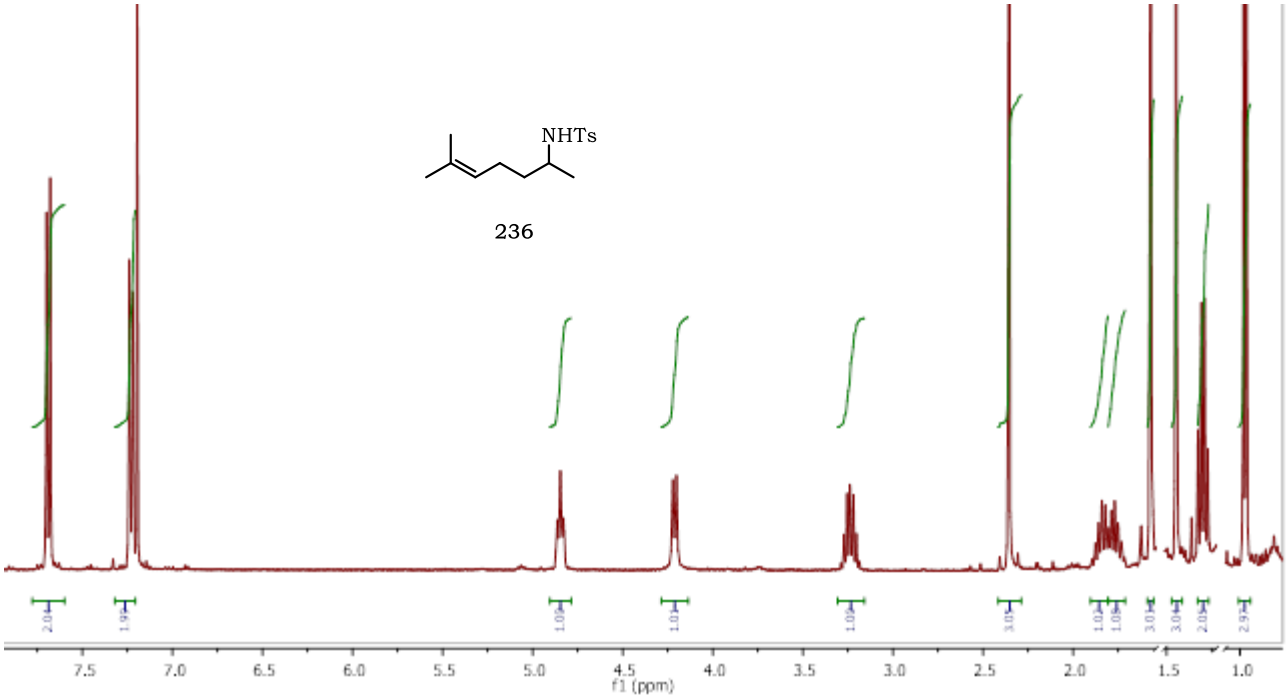


Figure 2.1 ^{1}H NMR spectrum of sulfonamide **236** in $CDCl_3$ (400 MHz).

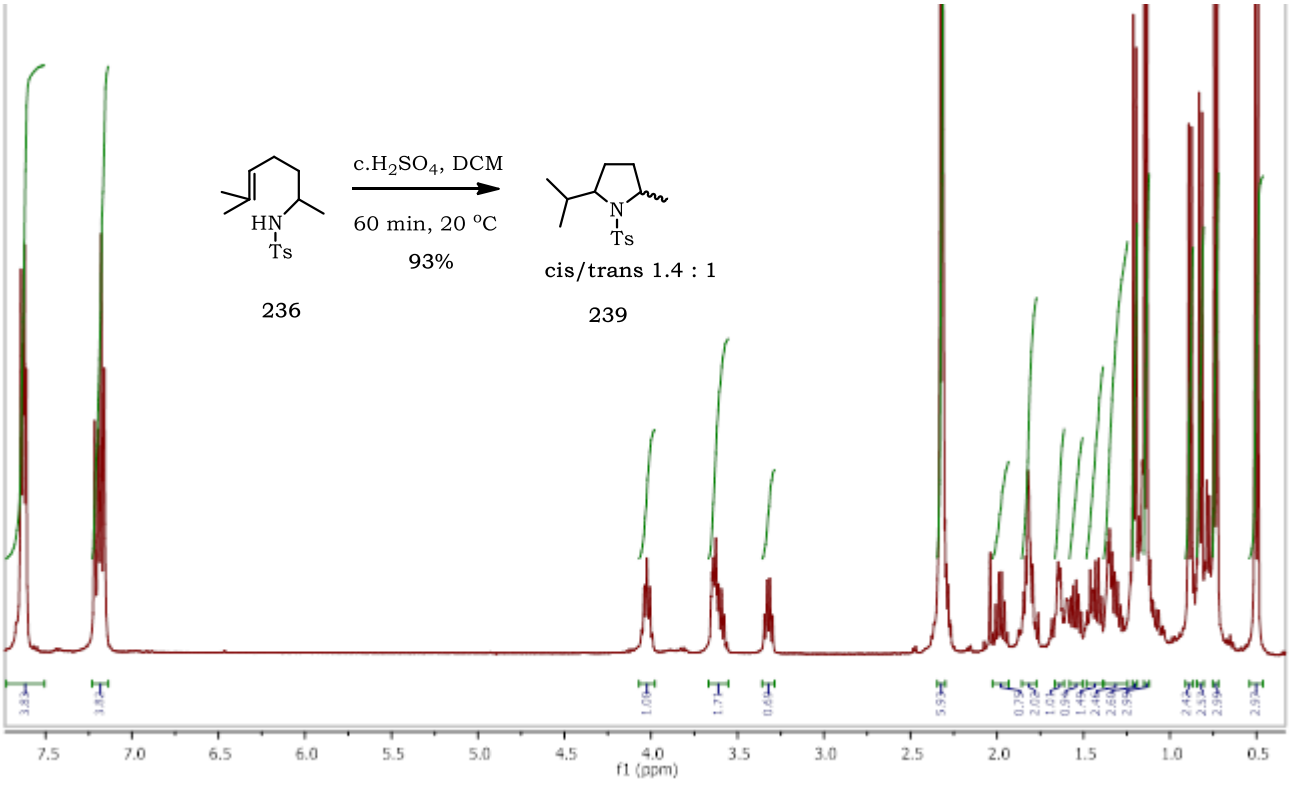


Figure 2.2 ^{1}H NMR spectrum of pyrrolidine **239** in $CDCl_3$ (400 MHz)

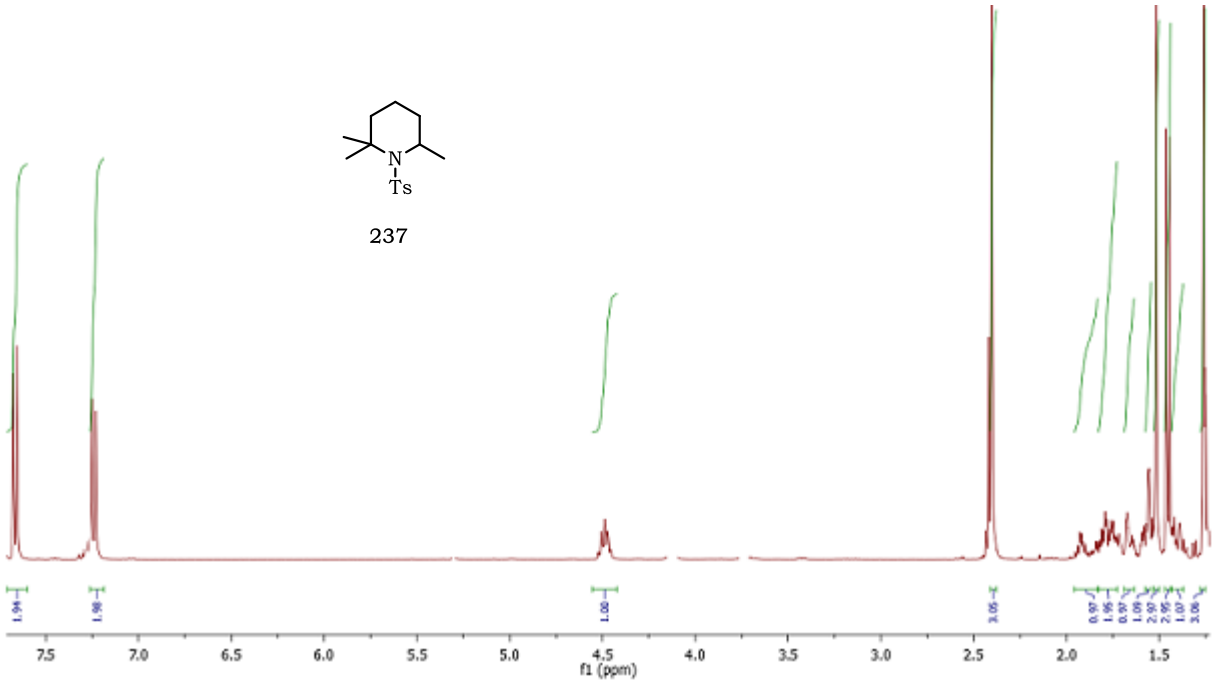


Figure 2.3 ^{1}H NMR spectrum of *N*-tosyl piperidine **237** in $CDCl_3$ (400 MHz).

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 ^{o}C (entry 1). There were no products after three hours at -30 ^{o}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 ^{o}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

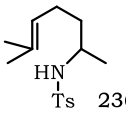
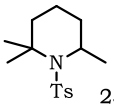
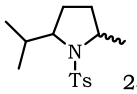
Fig. 2.3. The observed NCH resonance at δ_H = 4.45 – 4.55 ppm allowed for its easy quantification in mixtures with sulfonamide **236** and pyrrolidine **239** (**Fig. 2.1** and **2.2**).

Table 2.1 c.H_2SO_4, DCM, percentages as determined from ^{1}H NMR spectra integration depending on NC<u>H</u> proton, with N-Ts as a protecting group.

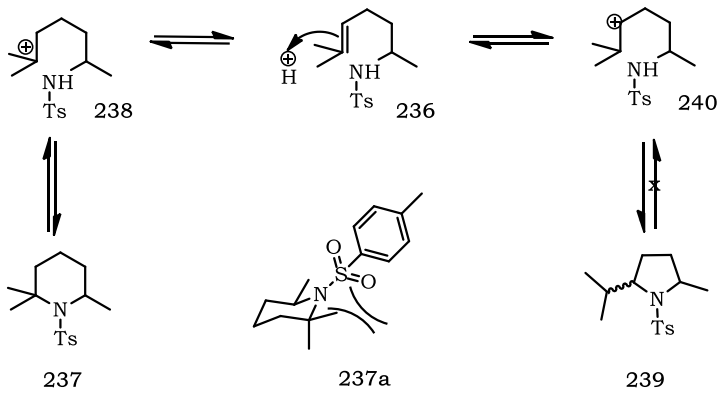
Entry	Time / min	Temperature ^oC	SM **236 :** Pip **237**: Py **239**
1	60	20	0 : 0 : 100
2	180	-30	100 : 0 : 0
3	120	-30	75 : 18 : 7
4	90	-10	53 : 35: 12
5	60	0	25 : 73 : 2
6	6	20	48 :7: 45

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 <u>CH</u>$(CH_3)_2$; 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.**

^{13}C NMR ppm	 236	 237	 239
Cq	=<u>C</u>$(CH_3)_2$: 132.5	NCq : 58.2	-
CH	=CH : 123.7 NCH : 50.6	NCH : 51.3	2 x NCH, <u>CH</u>$(CH_3)_2$
CH_2	2 x CH_2 : 37.3, 24.2	3 x CH_2 : 41.0, 30.2, 15.3	2 x CH_2

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

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 δ_H = 4.45 – 4.55 ppm in deuterated chloroform, $CDCl_3$, as a broad resonance with a peak width at half height of $\omega_{1/2}$ < *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*-diaxial 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.

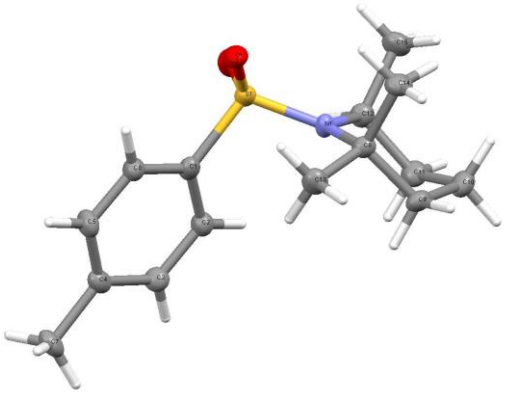
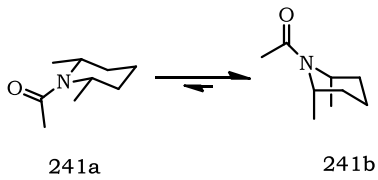


Figure 2.4 The X-ray structure of piperidine **237.** Full crystallographic data is included in **Appendix 1**.

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.



241a 241b

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 $A^{1,3}$ strain so *N*-Boc piperidines **242a** would be expected to undergo conformational equilibration to **242b** (**Figure 2.6**). [32]

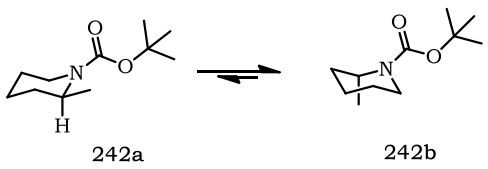


Figure 2.6

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**).

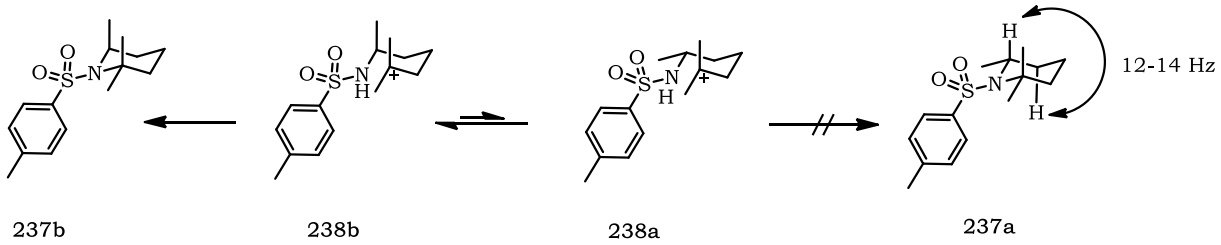


Figure 2.7

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 sulfonyl radical **244a** is further reduced with another electron to the corresponding anion **244b** (**Figure 2.8**).[33]

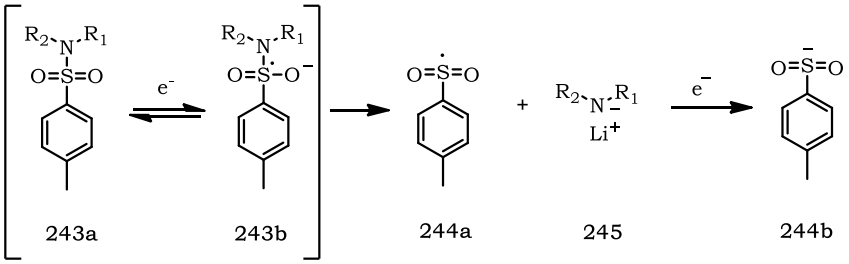
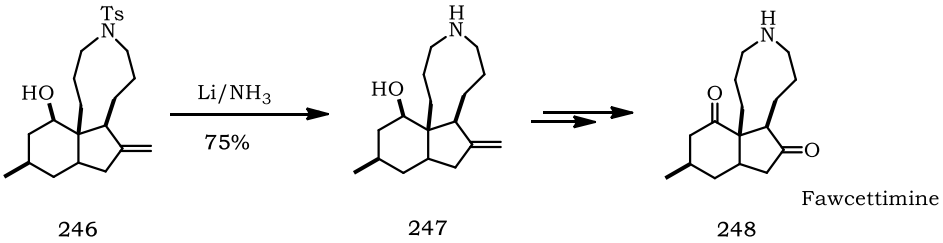


Figure 2.8

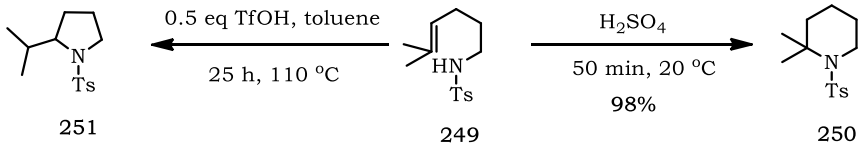
Although this radical reaction is very demanding in the synthesis of sensitive natural products, it has been used many times during such total syntheses. For example, removal of the *N*-tosyl protecting group in sulfonamide **246** was accomplished by treatment with lithium in ammonia which did not affect any *stero*-centers or the alkene and hydroxyl group during a total synthesis of Fawcettimine **248** (**Scheme 2.24**).[34]



Scheme 2.24

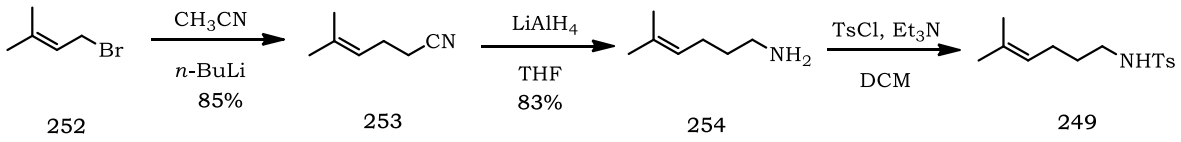
Since it has been found *N*-tosyl-2,2,6-trimethylpiperidine **237** was rapidly converted into the corresponding isopropyl pyrrolidine **239** under hydroamination conditions (**Scheme 2.22**), it was important to investigate if other piperidines would undergo the same rearrangement. In the present study, 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 °C) in an excellent yield of 98%. The evidence of cyclisation came from ^{1}H NMR analysis. The disappearance of olefinic proton =C<u>H</u> and N<u>H</u>Ts proton at δ_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 =C$(CH_3)_2$ in sulfonamide **249** at δ_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 ^1H NMR spectra (**Scheme 2.25**).



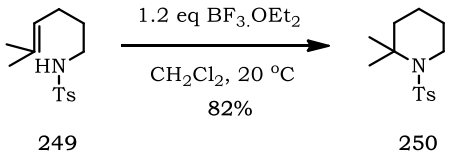
Scheme 2.25

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_N2 reaction resulted in the formation of 5-methyl-4-hexene nitrile **253**.[35] 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 quantitive yields (**Scheme 2.26**). This all seems consistent with the idea of steric hindrance causing the forgoing rearrangement (**Scheme 2.23**).



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]



249 250

Scheme 2.27

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

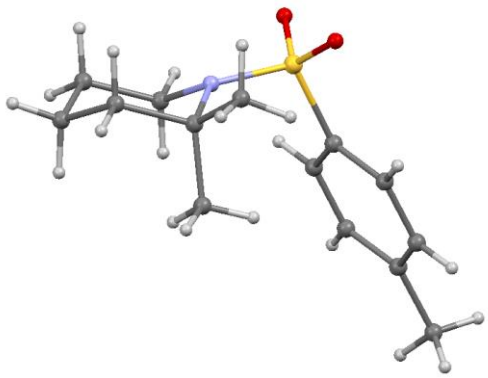


Figure 2.9 The X-ray structure of piperidine **250.**

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**).

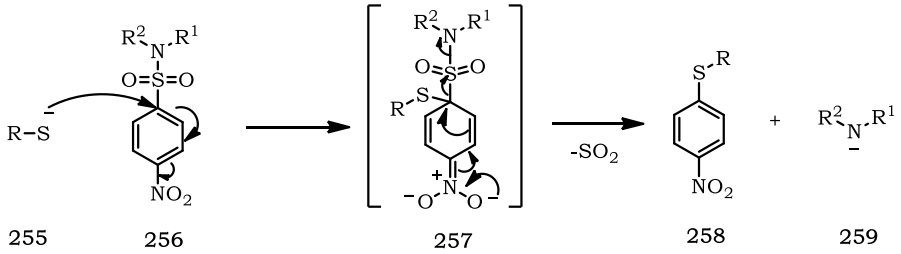
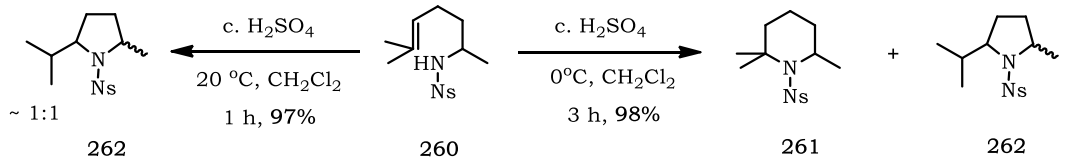


Figure 2.10

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.H_2SO_4 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 ^oC) there was still 13% starting material, but with 78% pyrrolidine **262** (entry 4).



Scheme 2.28

Table 2.3 c.H_2SO_4, DCM, percentages as determined from ^{1}H NMR spectra integration depending on NC<u>H</u> proton, *N*-Ns as a protecting group.

Entry	Time / min	Temperature ^oC	SM **260** : Pip **261 :** Py **262**
1	60	20	0 : 0 : 100
2	60	0	48 : 46 : 6
3	180	0	15 : 66 : 19
4	20	20	13 : 9 : 78

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

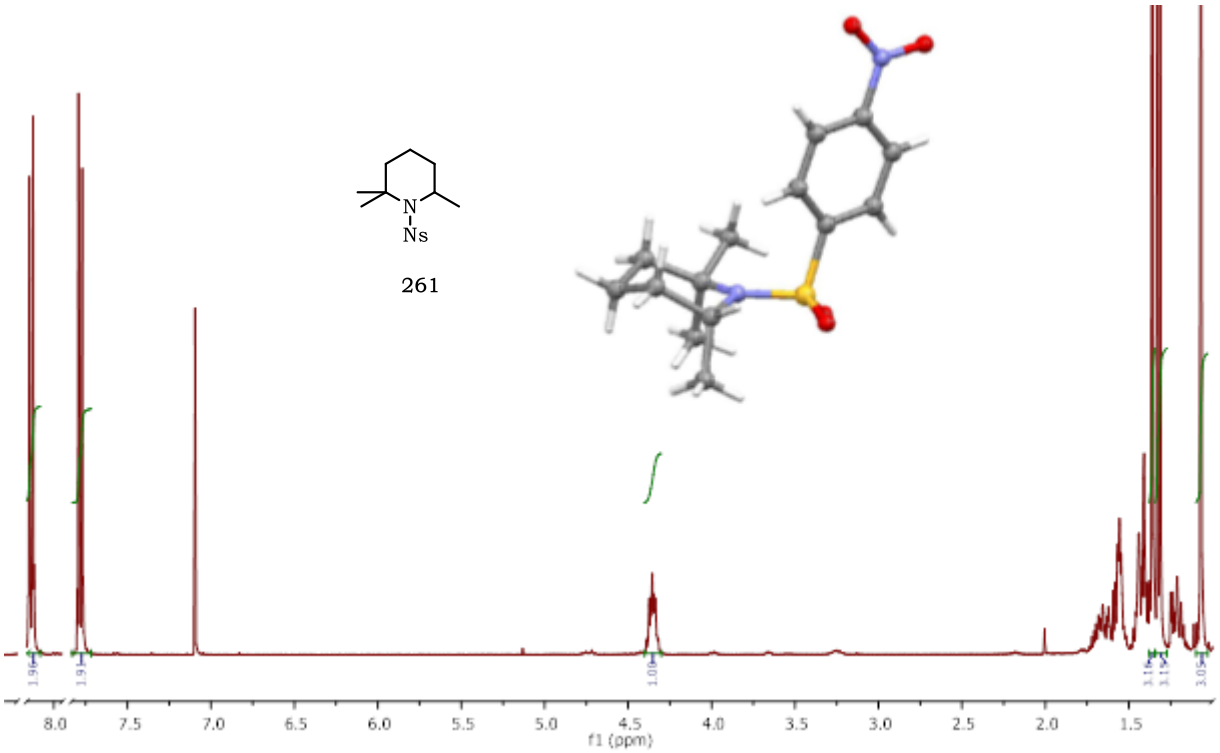
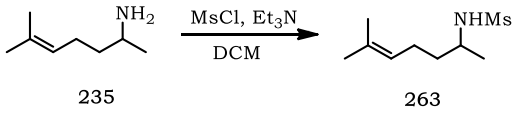


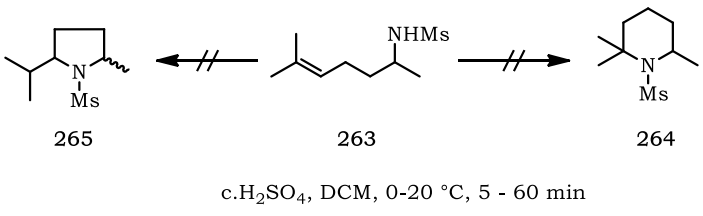
Figure 2.11 ^{1}H NMR spectrum of *N*-nosyl piperidine **261** in $CDCl_3$ (400 MHz) with the X-ray structure**.** Full crystallographic data is included in the **Appendix 3**.

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**).



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.H_2SO_4. 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**).



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)**.[39]

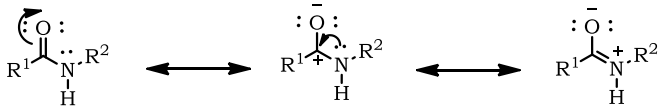
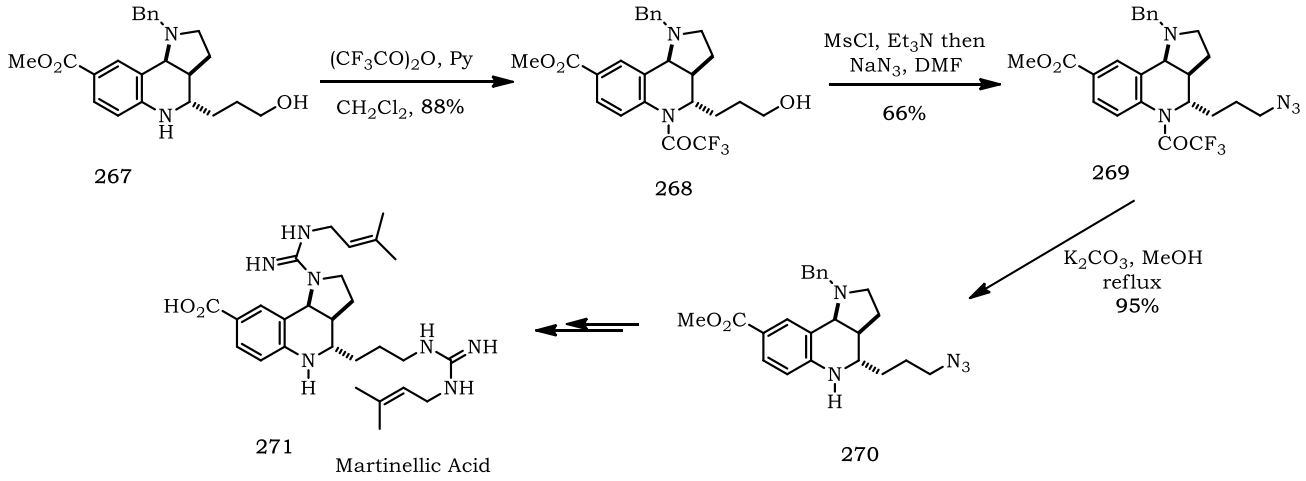


Fig 2.12

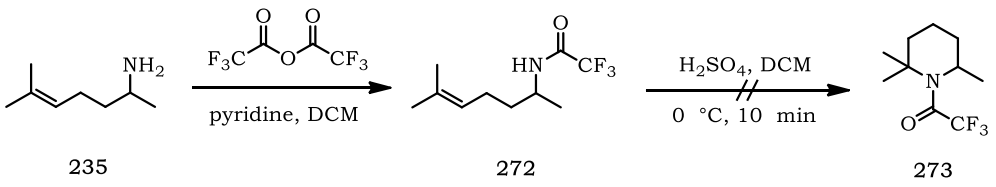
Trifluoroacetamide

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 martinellic acid total synthesis. The alcohol **267** reacted with trifluoroacetic anhydride TFAA and triethylamine in dichloromethane to provide trifluoroacetamide **268**. Hydrolysis of trifluoroacetamide **269** with potassium carbonate in methanol provided pure product **270** in 95% yield (**Scheme 2.31**).[40]



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 ^{o}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

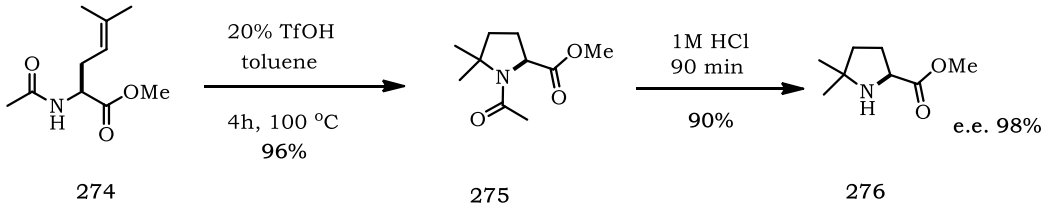
Acetamide and Benzamide:

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.[41]

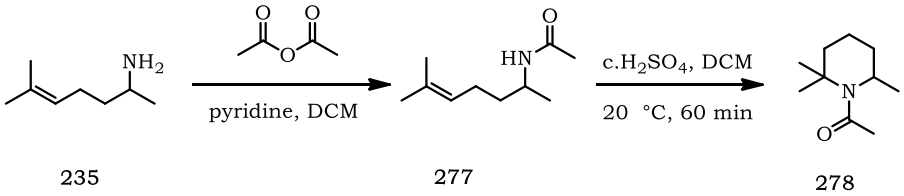
Acetamide:

Jackson[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 ^{o}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**).



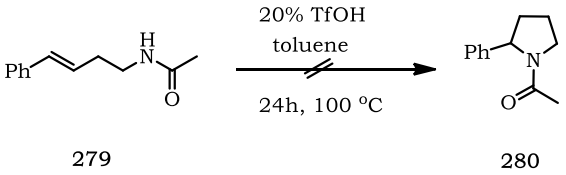
Scheme 2.33

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_2SO_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**).



Scheme 2.34

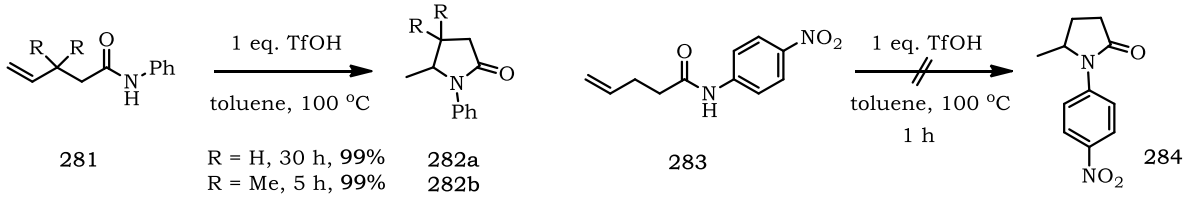
Hartwig[43] *et al.* found, acetamide **279** did not undergo cyclization reaction to pyrrolidine **280** even after heating in toluene for 24 hours at 100 ºC with 20% TfOH. They proposed that the higher Lewis basicity of the amide **279** prevented the reaction. The protonated carbonyl is apparently not acidic enough to transfer its proton to the olefin (**Scheme 2.35**).



Scheme 2.35

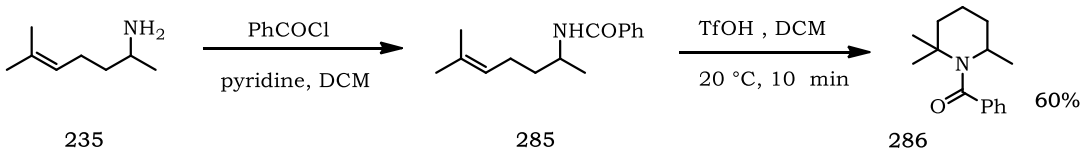
Benzamide:

We were inspired by the successful example of a Brønsted acid-catalyzed intramolecular hydroamination reaction, which was reported by Schlummer and Hartwig,[43] 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.



Scheme 2.36

The benzamide **285** was formed by reacting the benzoyl 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 ^{o}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).



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 $ClCO_2Me$ and benzyl chloroformate $ClCO_2CH_2Ph$ 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[46] and can be readily cleaved under acidic condition: acetic acid[47], triflic acid[48], methanesulfonic acid[49] and trifluoroacetic acid.[50] The expected mechanism of acidic benzyloxycarbonyl deprotection is that carbamate **287** becomes protonated to trigger loss of benzylic cation **289**, which results in the carbamic acid **290** then decarboxylation of this gives the free amine **291** (**Fig 2.13**).

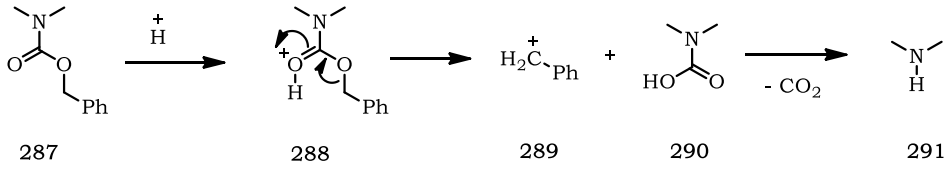
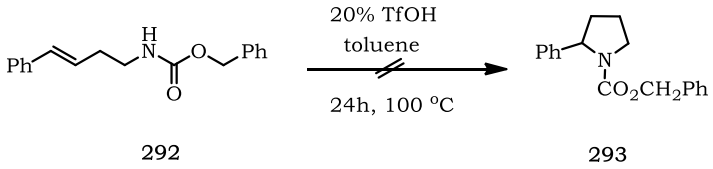


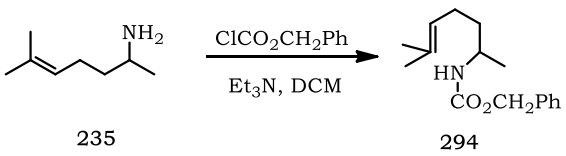
Fig 2.13

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



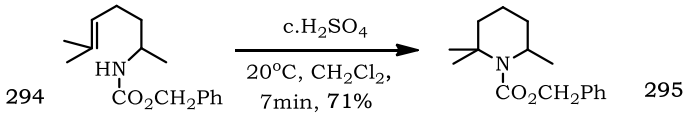
Scheme 2.38

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



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

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_2Ph protons showing clear AB coupling system after cyclisation at δ_H 5.07 (d, J = 12.5, 1H, OCH_AH_B) and 5.02 (d, J = 12.5, 1H, OCH_AH_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**).

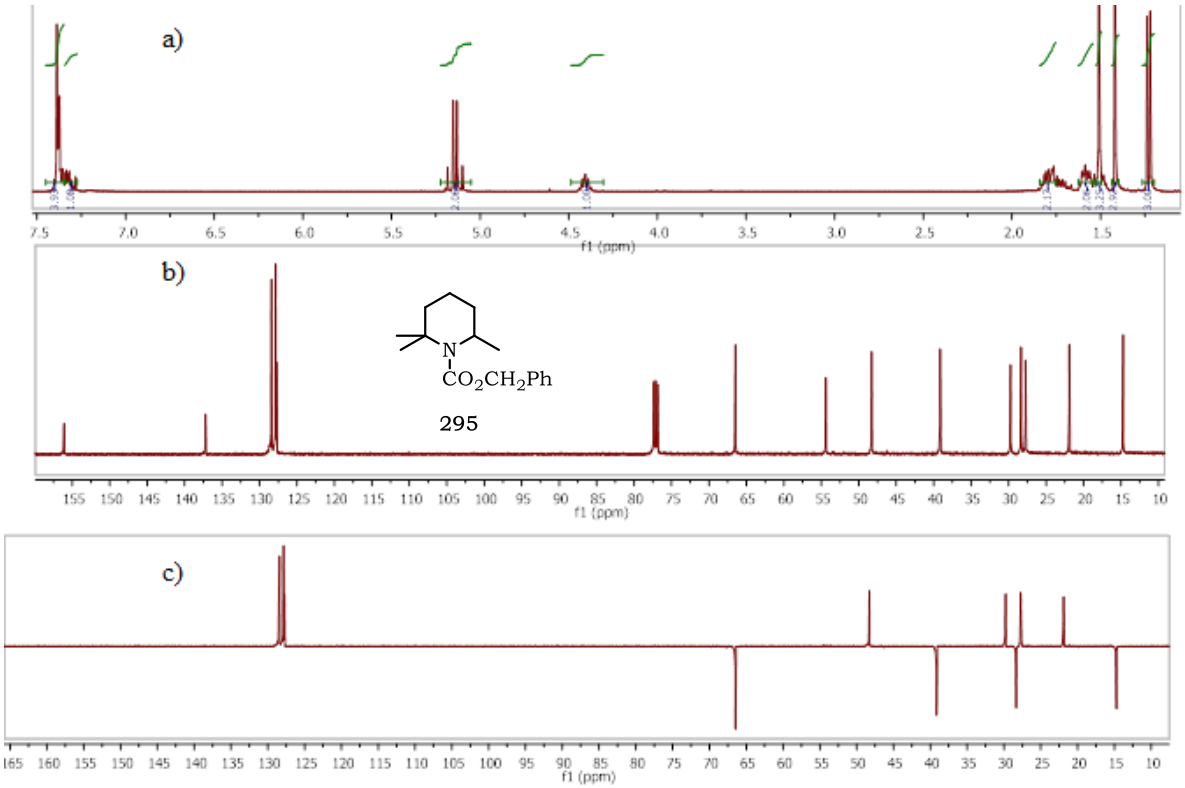
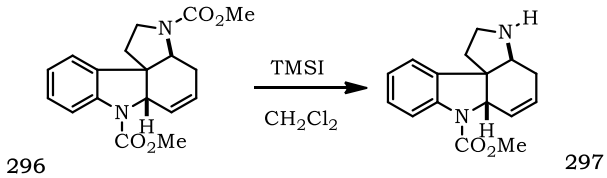


Fig 2.14 ^{1}H and ^{13}C NMR spectra of piperidine **295**: a) proton; b) decoupled ^{13}C; c) DEPT CH, CH_3 positive; CH_2 negative.

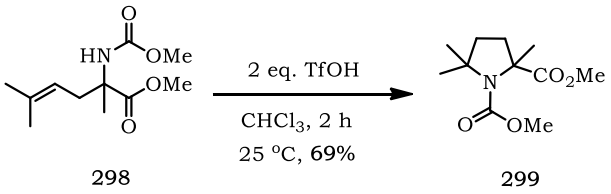
Methyl carbamate Moc

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)**.[51]



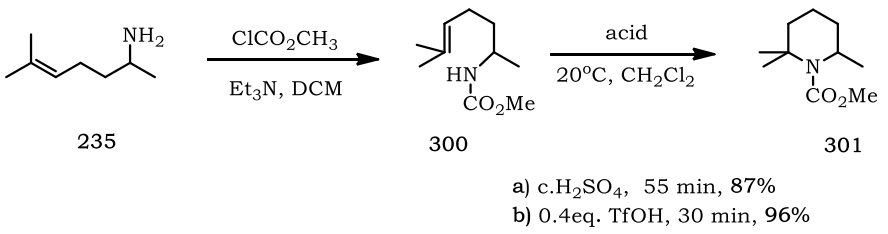
Scheme 2.41

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 ºC after two hours pyrrolidine **299** was formed in reasonable yield (69%) **(Scheme 2.42**).[52]



Scheme 2.42

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 ºC **(Scheme 2.43)**.

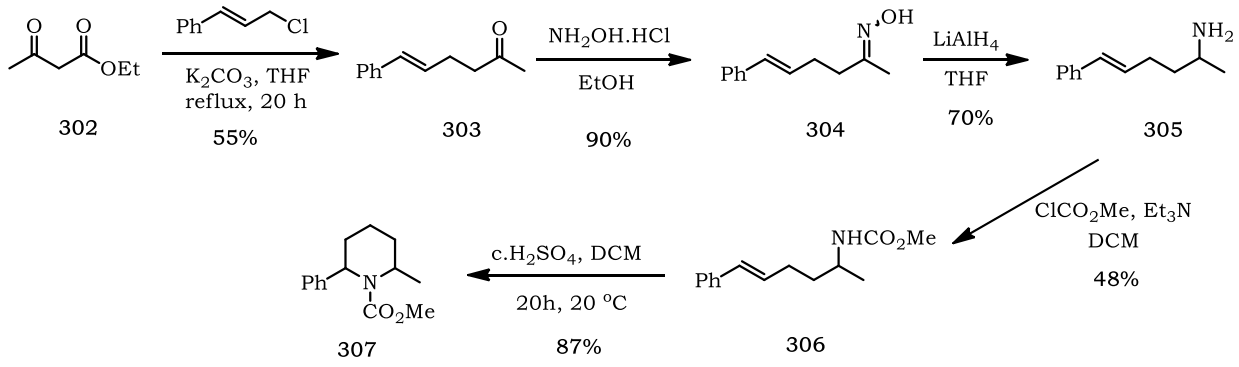


Scheme 2.43

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 δ_H 4.24 – 4.17 (pentet, J = *ca*. 6.9 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 δ_H 4.35 – 4.25 (*br*. pentet, J = *ca*. 6.9 Hz).

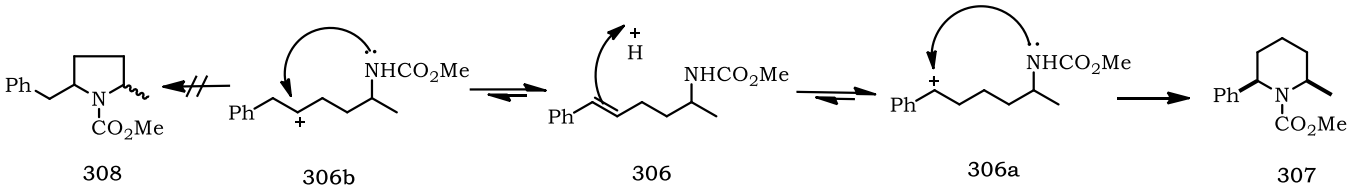
Fig 2.15

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 K_2CO_3 for 20 hours (55% yield).[53] This was then converted into the oxime **304** by a standard oximination reaction then reduced by $LiAlH_4$ 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)**.



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 condithon 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)**.



Scheme 2.45

A single isomer was formed and identified by a clear, rather high field methyl doublet at δ_H 0.70 (J = 7.1 Hz, 3H) and two low field resonance at δ_H 4.51 – 4.42 and δ_H 5.41 ppm both integrating for one proton. The one resonating at δ_H 4.51 – 4.42 was the same in its appearance as all of the above 6-H resonances at δ_H 4.51 – 4.42 (*app. br*. pentet, J = *ca*. 7 Hz). The resonance at δ_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**).

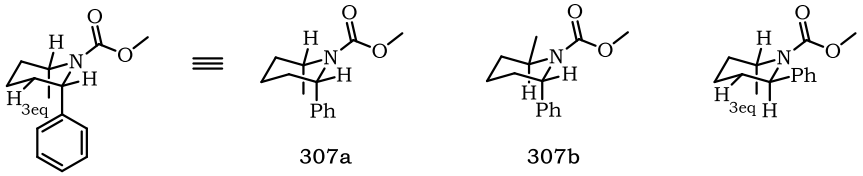


Fig 2.16

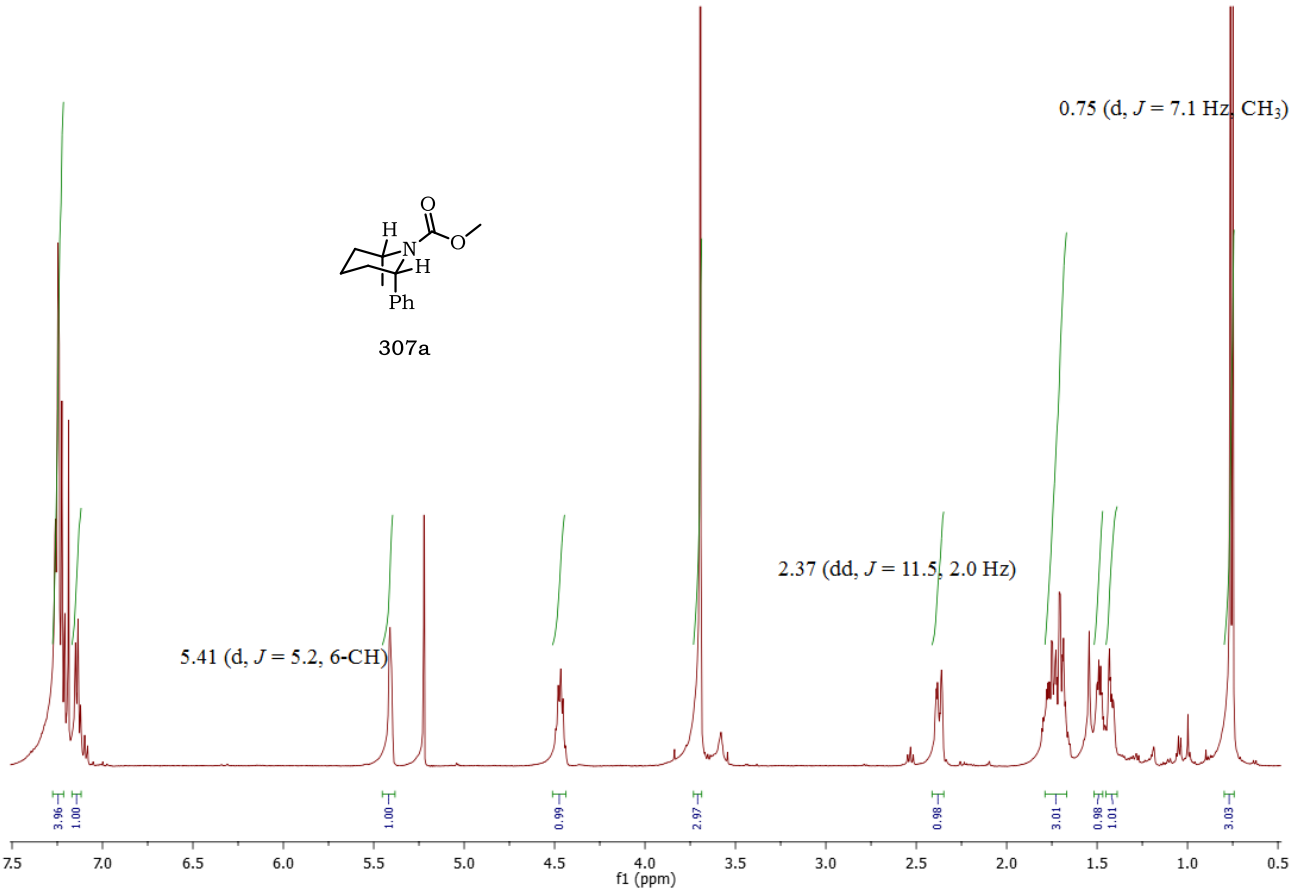
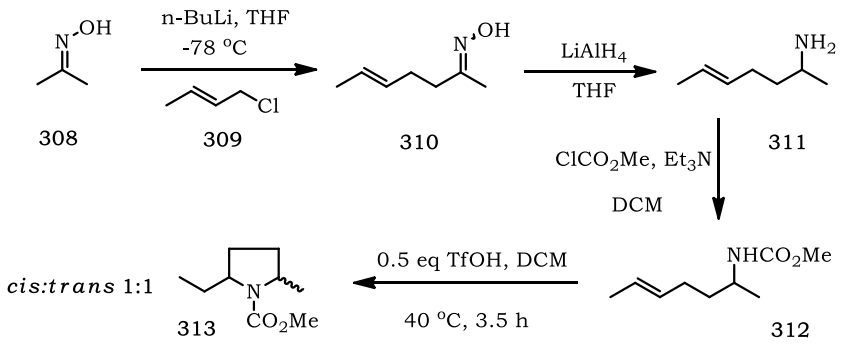


Figure 2.17 ^{1}H NMR spectrum of 2-methyl-6-phenylpiperidine **307a,** 6-CH proton width at half height of $\omega_{1/2}$ = 10.4 Hz, in $CDCl_3$ (500 MHz).

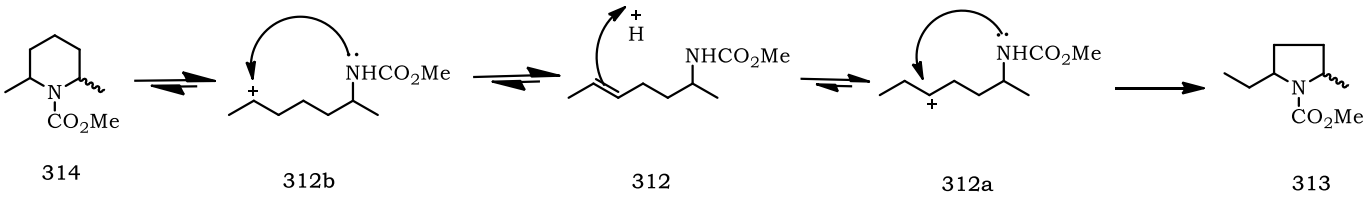
Even with the likely distortion of the ring due to the single axial substituent, it is surely very likely that a single large coupling constant would be evident in the resonance of one of these protons. Presumably, the phenyl ring would be positioned at the angle shown above **307a**, otherwise it would 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 δ_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 δ_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 ^oC 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 ^oC, 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 ^oC for 3.5 hours to give pyrrolidine **313** (98%, *cis:trans* 1:1 ratio). In ^1H NMR of the resonance at *ca*. δ_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 δ_C 60.3 and 53.8 ppm, three methylene groups at δ_C 37.0, 28.8 and 25.6 ppm (**Scheme 2.46**).



Scheme 2.46

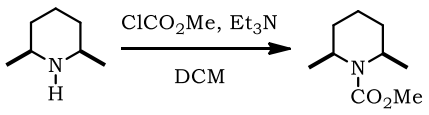
Secondary carbenium ions are more challenging to form than tertiary or benzylic examples. There are two possible secondary carbenium ions that can form from carbamate **312**; these are both equally likely to form **(Scheme 2.51).** Trapping the secondary carbenium ion **312a** will form pyrrolidine **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).**



314 312b 312 312a 313

Scheme 2.47

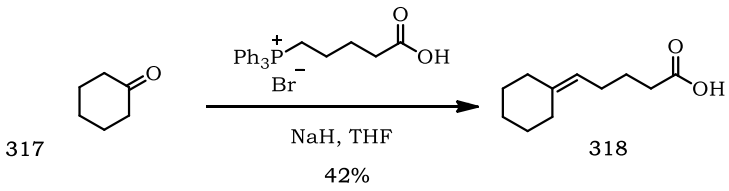
The absence of 2,6-dimethylpiperidine carboxylate **314** was confirmed by the preparation of an authentic sample of *cis*-dimethylpiperidine carboxylate **316**. The carbamate was added smoothly to commercial available *cis*-2,6-dimethylpiperidine **315** in quantative yield. The resonance at δ_H 4.30 – 4.16 ppm in ^{1}H NMR of dimethylpiperidine **316** related to two protons on carbons near to nitrogen (NCH, 2H) and a sharp doublet at δ_H 1.10 (d, J = 7.1, 6H, 2 x CH_3) related to two methyl groups. In ^{13}C NMR spectra the resonance at δ_C 46.0 (2 x CHN, 2- and 6-CH) related to two methine groups, 30.0 (2 x CH_2, 3- and 5-CH_2), 20.8 (2 x CH_3), 13.7 (4-CH_2) ppm (**Scheme 2.48**).



315 316

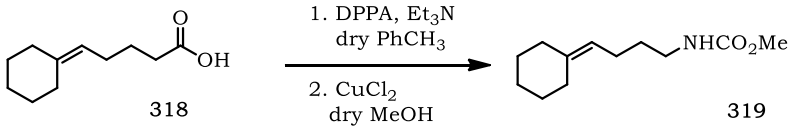
Scheme 2.48

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]



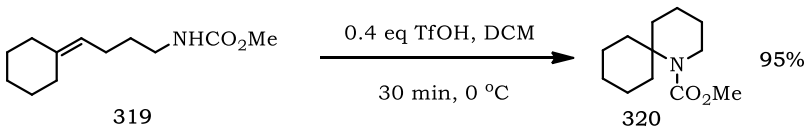
Scheme 2.49

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 $CuCl_2$, and further heating of this mixture under reflux for 1 h **(Scheme 2.50)**.[56]



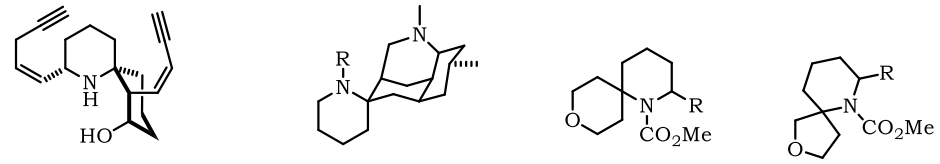
Scheme 2.50

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 ^{1}H-NMR spectrum, CH_2 near to nitrogen resonates at δ_H 3.47 ppm as a triplet (t, J = 6.0, 2H, CH_2N). From ^{13}C NMR spectrum a quaternary carbon came at δ_H 59.0 ppm and $N\underline{C}H_2$ at 51.8 ppm **(Scheme 2.51).**



Scheme 2.51

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’’[57] **321** and nankakurine **34**, a member of the Lycopodium alkaloid family that was isolated from the club moss *Lycopodium lucidulum.*[58] 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[59] **(Scheme 2.52)**.



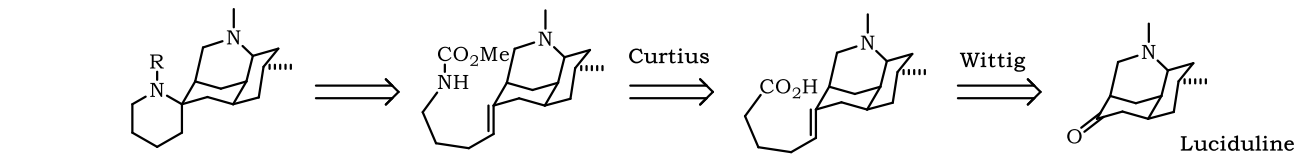
Histrionicotoxin 321

R=H Nankakurine A
R=Me Nankakurine B
34

R= H, Me and Ar
322 323

Scheme 2.52

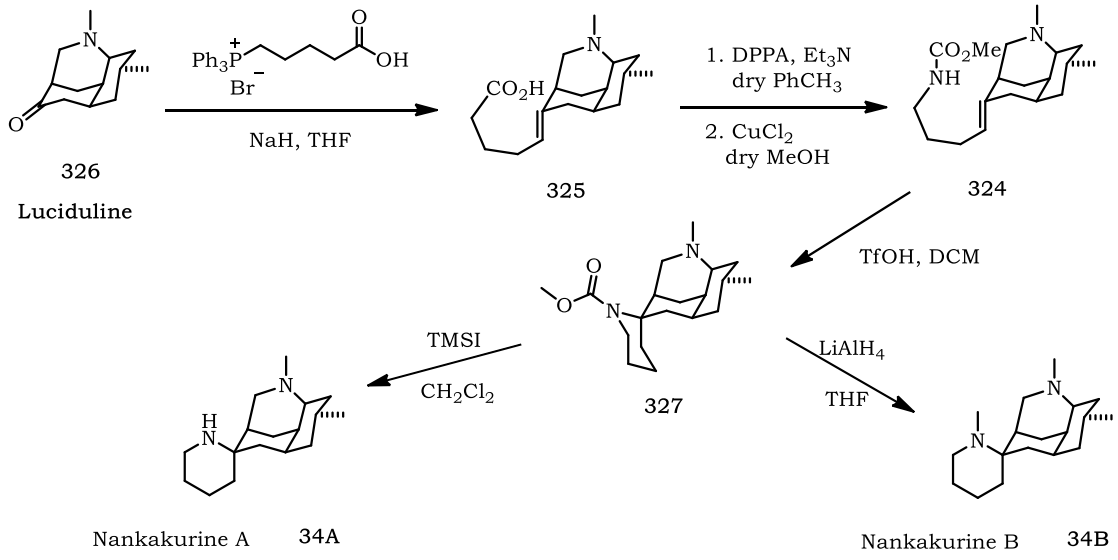
The retrosynthetic analysis of nankakurine **34** A and B leads to core of the luciduline **326,** which syntheses have been reported[60] **(Scheme 2.53)**. The search for a general strategy to access Lycopodium alkaloids has led Overman to suggest the asymmetric total syntheses of nankakurines **34** from luciduline **326.**[61] 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**.[62] Retrosynthetic analysis of nankakurine **34** shows that the *spiro*-piperidine core could be generated by acid-catalysed hydroamination from carbamate **324** (**Scheme 2.53**).



R=H Nankakurine A
R=Me Nankakurine B
34 324 325 326

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 hydroam ination to aza-*spiro*-lycopodium alkaloid **327** finally, carbamate deprotection to nankakurines **34** A by TMSI or by lithium aluminium hydride to nankakurines **34**B (**Scheme 2.54**).

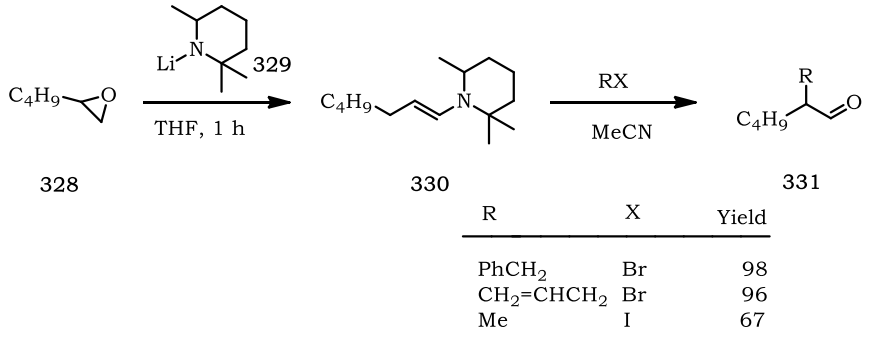


Scheme 2.54

Asymmetric Synthesis of 2,2,6-trimethylpiperidine

In organic synthesis, steroselective construction of a chiral carbon atom adjacent to the ring nitrogen atom in 2-subtituted piperidines has a special importance in total synthesis. The interest in the synthesis of substituted piperidines with stereo- and enantioselective manner have been increased.[63] 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.[64] The optically pure 2-subtituted 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.)**.[65]

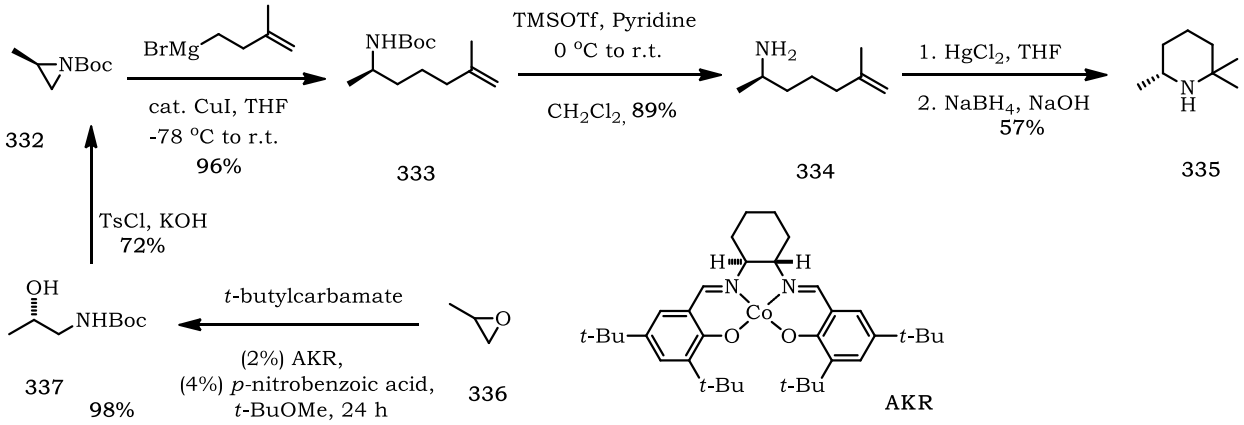
Hodgson *et. al.*[66] reported the asymmetric synthesis of α-alkylated aldehydes **331** using terminal epoxide **328** and examined the enamine derived from this and lithium 2,2,6-trimethylpiperidide **329**. They found that the latter formed the corresponding enamine in good yield, and was bulky enough to avoid potentially competing allylic alcohol/amino alcohol formation. The enamine underwent effective C-alkylation to generate α-alkylated aldehydes **331**. By contrast, the enamine derived from lithium 2,2,6,6-tetramethylpiperidine (LTMP) was slow to react, affording the α-methylated aldehyde in only 30% yield (**Scheme 2.55**).



R	X	Yield
$PhCH_2$	Br	98
CH_2=$CHCH_2$	Br	96
Me	I	67

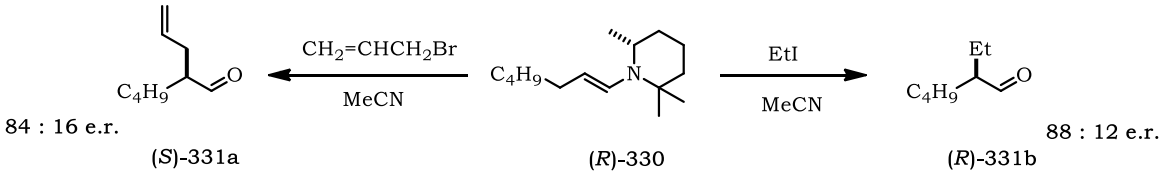
Scheme 2.55

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*-butylsalicylidene)-1,2-cyclohexanediaminocobalt [AKR] (**Scheme 2.56**).



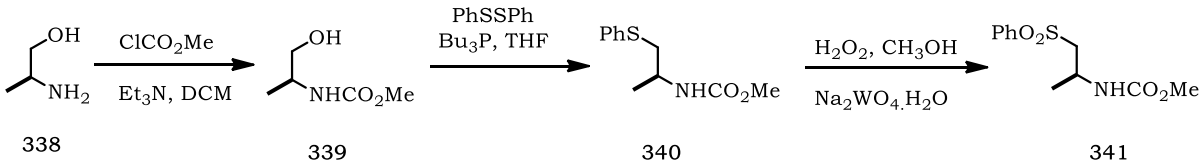
Scheme 2.56

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_2O showed no deuterium incorporation, indicating that no loss of enantiointegrity occurred during hydrolysis.



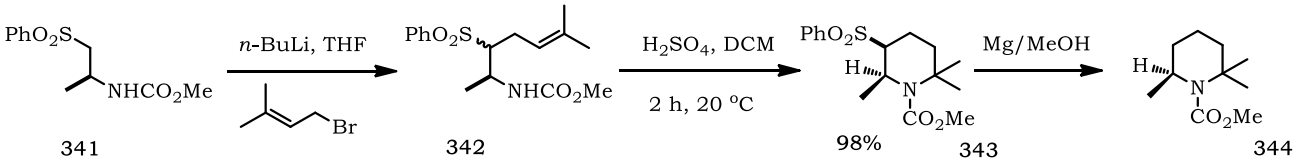
Scheme 2.57

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 $ClCO_2Me$. 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_2O_2 and a catalytic amount of sodium tungstate dehydrate $Na_2WO_4.H_2O$ 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 ^{o}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, $PhSO_2C\underline{H}$) ppm. If 6-proton was axial (**343B**) we would expect two large coupling constants (**Figure 2.18**).

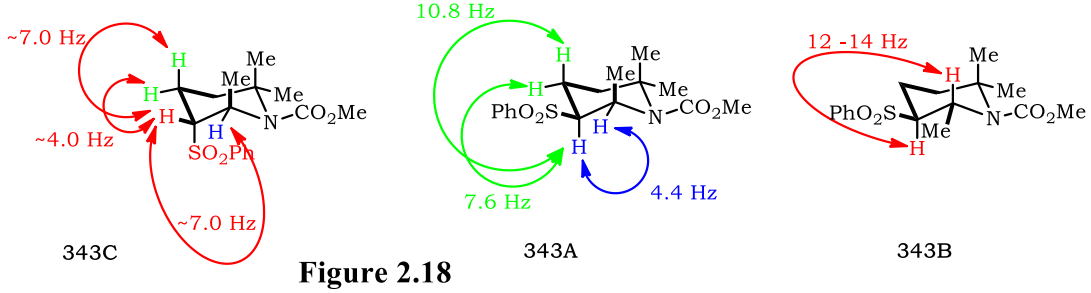


Figure 2.18

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.

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Chapter 3

Acid-catalyzed cyclisations in synthesis

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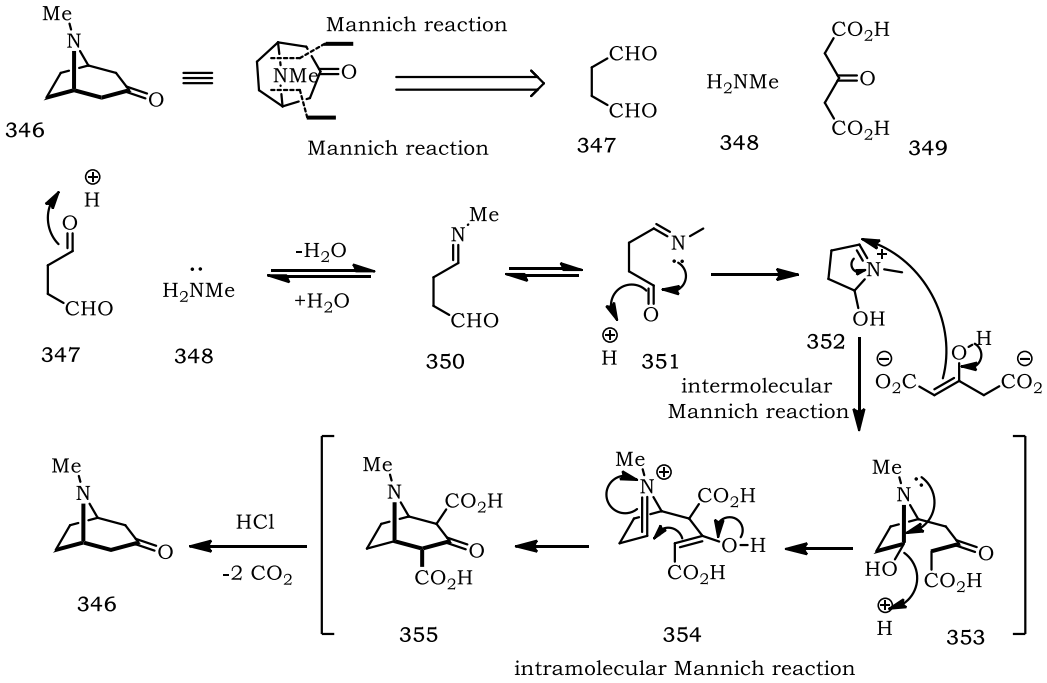
3.1. Introduction

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

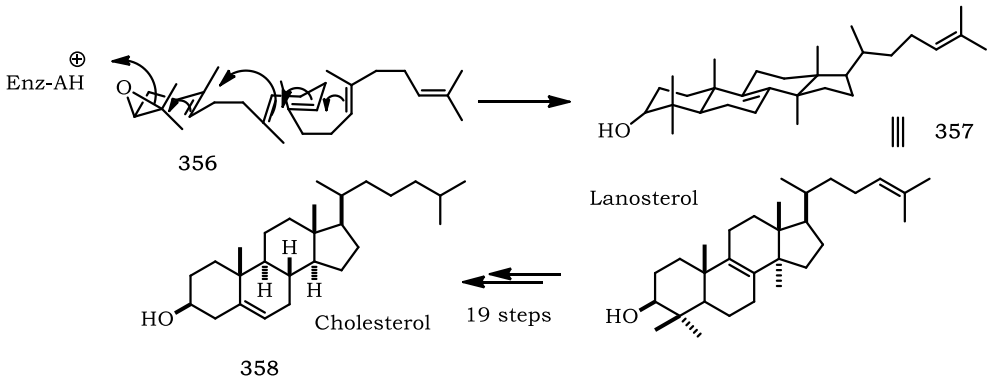
Cascade reactions are one of the most fascinating branches of organic chemistry, and one which has been the subject of intense research in recent years, as witnessed by the number of reviews that have appeared covering various aspects of these reactions. The remarkable benefits of cascade reactions are 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]



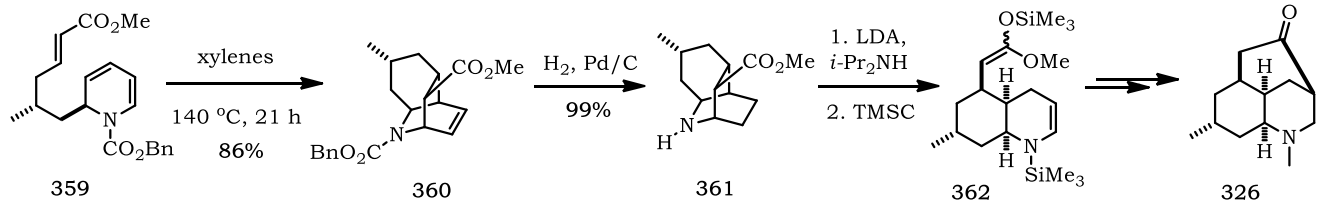
Scheme 3.1

Lanosterol **357** is a tetracyclic triterpenoid all steroids are derived from. Lanosterol formation in animals and fungi proceeds *via* chair-boat-chair conformation of (3*S*)-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]



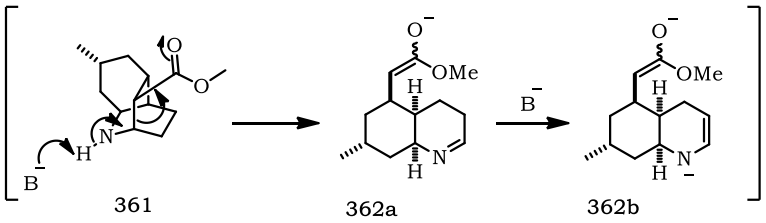
Scheme 3.2

Perhydroquinoline alkaloids are varied in structure and have provided challenging targets for total synthesis.[6] Luciduline **326**, a *cis*-perhydroquinoline alkaloid, is isolated from L*ycopodium lucidulum*.[7] Comins *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 *retro*-Mannich ring opening is converted to enecarbamate **362** (**Scheme 3.3**).[8]



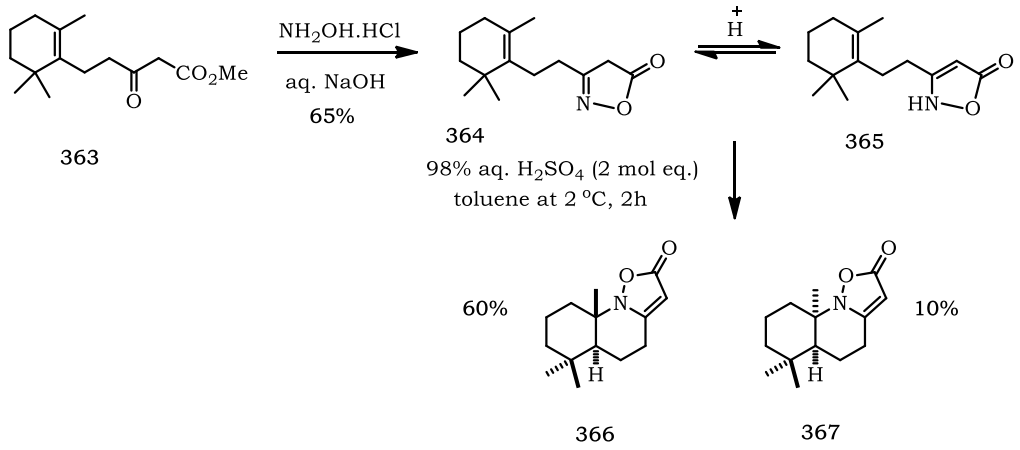
Scheme 3.3

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**).



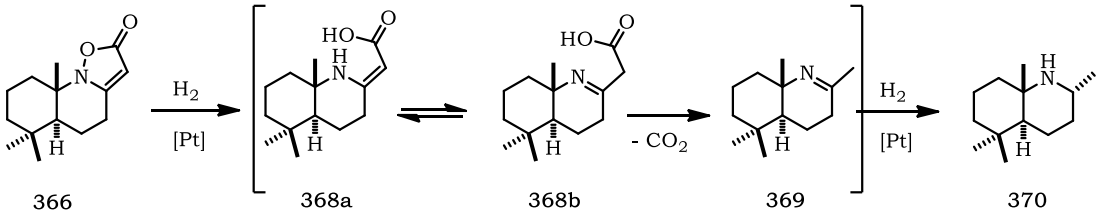
Scheme 3.4

Acid-mediated cyclization of isoxazolone **364** was examined using 98% aq. H_2SO_4 in toluene at 2 ^oC for two hours. Isoxazolone **364** would cyclise *via* its tautomer, the major product being isoxaxolone **366** (62% yield) accompanied by its *cis*-fused epimer **364** (10% yield). This unexpected preference for ring closure *via* acid-catalyst hydroamination reaction is of synthetic interest (**Scheme 3.5**).



Scheme 3.5

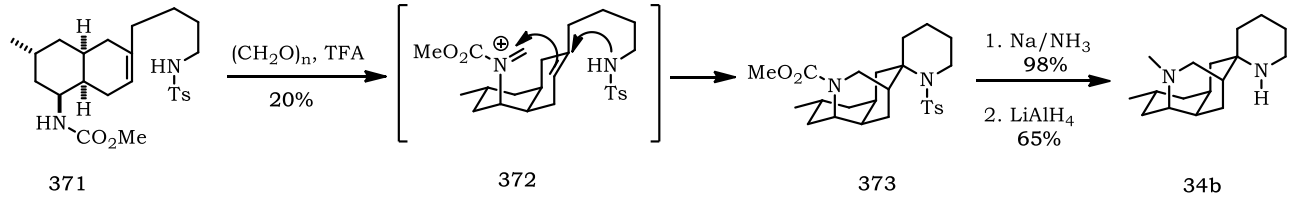
Structure confirmation of *trans* product **366** was confirmed by catalytic hydrogenation ([PtO_2], AcOH/AcOEt 3:1, 20 °C) to perhydroquinoline **370** (17% yield). The multistep transformation is believed to proceed *via* intermediates **368a,b** in a reaction sequence involving hydrogenolysis of the nitrogen-oxygem 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.

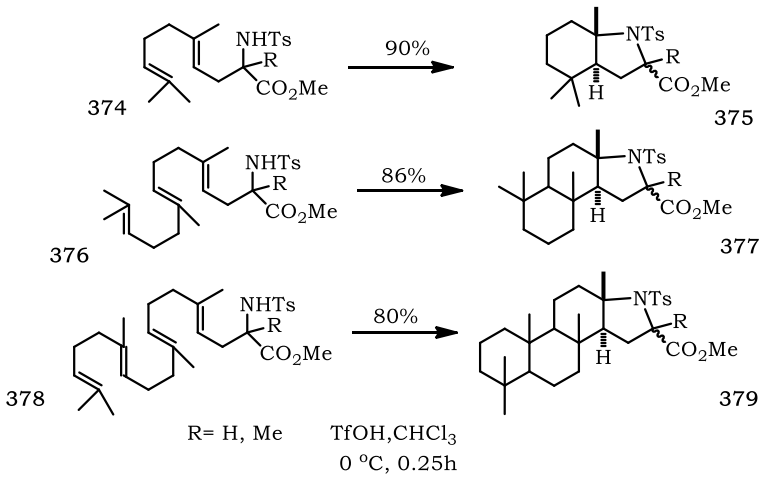
The total syntheses of (+)-nankakurine B **34b** was accomplished in 14 steps (5 mg, 16% overall yield) (**Scheme 3.7**).[11]



371 372 373 34b

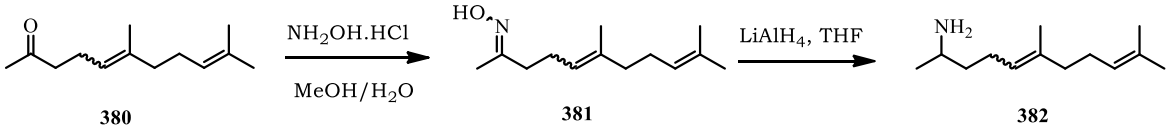
Scheme 3.7

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[12] 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 ^{o}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 diaseroisomers **377**. The tetracyclic compounds **379** were formed as a gross mixture of diaseroisomers in 80% yield. As expected, the yield of such reactions decreases as the number of rings formed increased (**Scheme 3.8**).[13]



Scheme 3.8

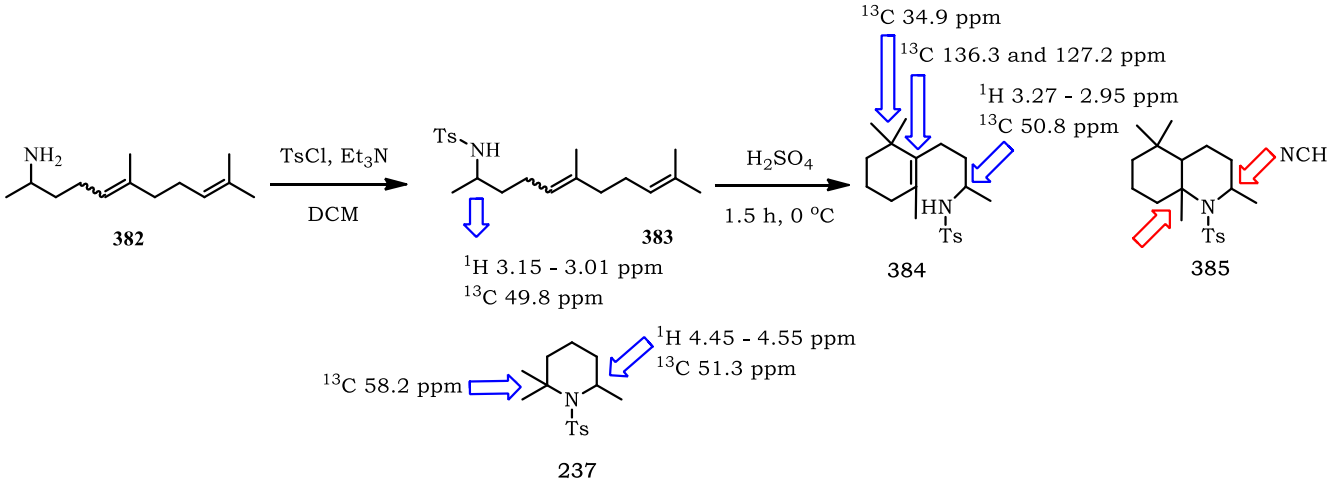
In the present study, it was decided to see if such methodology would be extended to the formation of piperidine rings by using cascade cyclisations. Geranyl amine **382** was prepared starting from commercial available geranyl acetone **380**, supplied as a mixture of *cis*- (approximately 35%) and *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)**.



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 (δ_H 4.91 – 4.71 ppm) had disappeared, whereas the NH proton (δ_H 4.52 ppm) did not disappear. However, two of the three methyl singlets

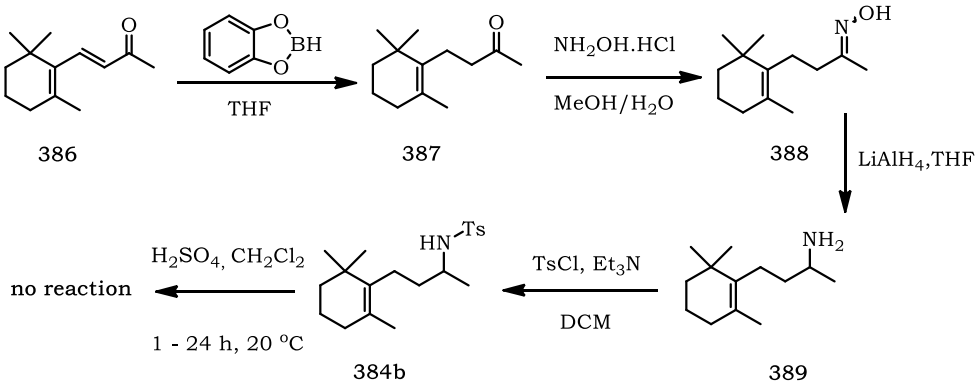
which had been on double bonds (1.45, 1.83 ppm) moved to the upfield to appear as two singlets at δ_H 1.10, 0.79 ppm, which suggest formation of the half cyclic compound **384**. There was no trace of the expected bicyclic compound **385** as ^{1}H NMR data showed a clear spectrum between δ_H 4.50 - 4.00 ppm, where the NCH proton was to be found in piperidine **237**, at 4.45 - 4.55 ppm. The ^{13}C NMR spectrum enhanced this theory as two quaternary carbons appeared at δ_C 136.3 and 127.2 ppm, due to quaternary carbons on a double bond and a quaternary carbon at high field δ_C 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)**.



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%).[14] Classical oximination 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

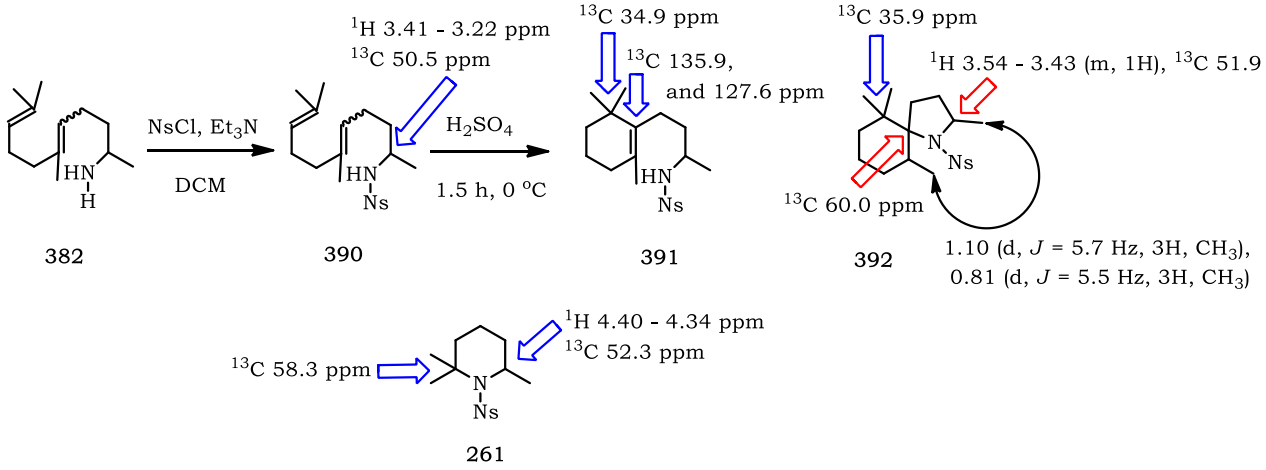
384b did not undergo the acid-catalysed cyclisation to give the bicycle **385** even after 24 hours of reaction with concentrated sulfuric acid at room temperature in dichloromethane (**Scheme 3.11)**.



Scheme 3.11

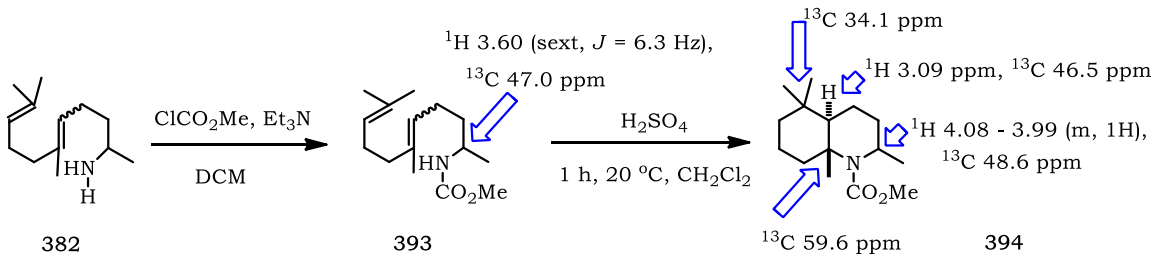
N-Nosylation by nosyl chloride in the presence of triethylamine gave the sulfonamide **390.** It was hoped that the electron-withdrawing effect of the nitrophenyl group might weaken the N-H bond sufficiently to encourage the cascade cyclisation. Nosyl geranyl sulfonamide **390** was treated with catalytic amounts of sulfuric acid in dichloromethane and, after 1.5 h of reaction at 0 ^{o}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)**.



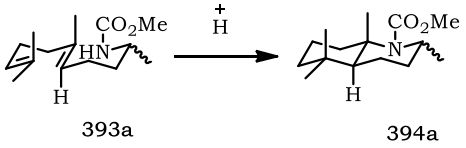
Scheme 3.12

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 δ_H 5.10 – 4.96 ppm had disappeared, and no starting material was present the NH proton at δ_H 4.66 ppm had disappeared at the end of the reaction. As usual, CH proton near to nitrogen moved to downfield δ_H 4.08 – 3.99 ppm. The singlets at δ_H 1.60 and 1.50 ppm representing the three methyl groups on double bonds moved further upfield to δ_H 1.25 and 0.80 ppm and the complexity of the spectrum increased. In the ^{13}C NMR spectrum, three quaternary carbons at δ_C 156.1, 59.6, 34.1 ppm, five CH_2 signals δ_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 υ/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)**.



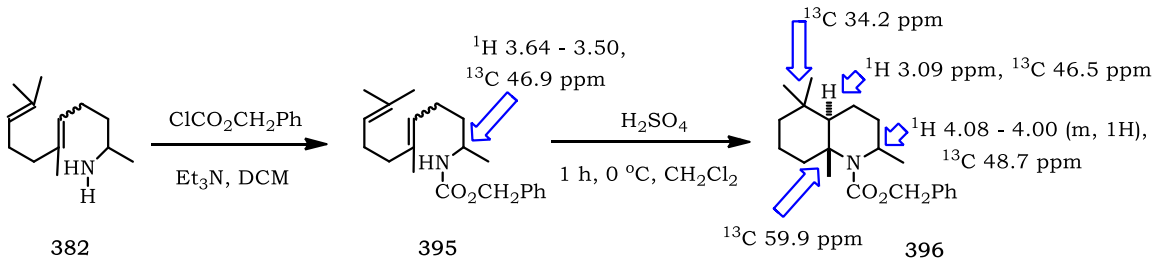
Scheme 3.13

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.



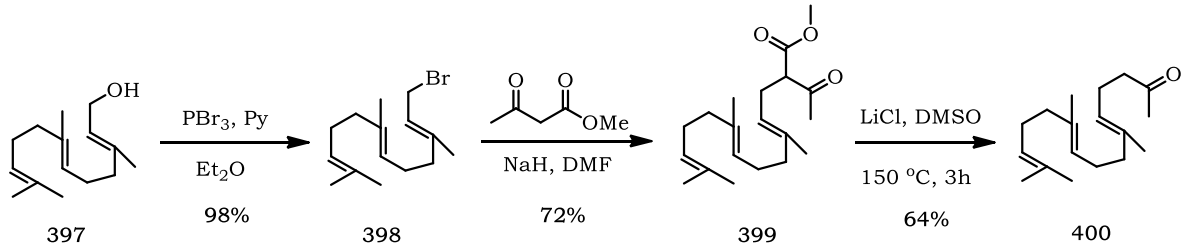
Scheme 3.14

Benzyl geranyl carbamate **395** reacted after one hour of the reaction in ice to give the hydroquinoline **396** (70% yield). The benzyloxycarbonyl protecting group had unexpected stability to this such strong acidic conditions to show OC$\underline{H_2}$Ph protons as a clear AB coupling system after cyclisation [δ_H 4.99 – 4.94 (d, *J* = 12.7 Hz, 1H, OC*H*$_A$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 δ_C 59.9 (NCq), N$\underline{C}$H (6-C) carbon at 48.7 ppm, and six $\underline{C}H_2$ carbons δ_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.



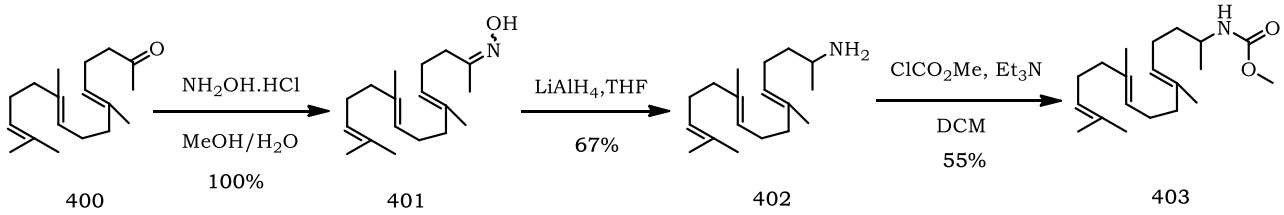
Scheme 3.15

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,[15] with methyl acetoacetate and subsequent Krapcho decarboxylation[16] (**Scheme 3.16**).[17]



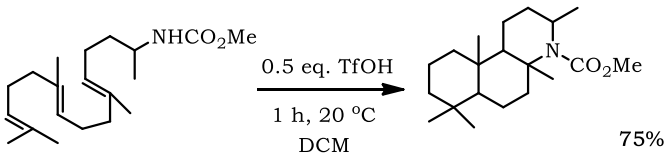
Scheme 3.16

The carbamate **403** was prepared in exactly the same manner from (*E*,*E*)-farnesyl acetone **400** through oximination to **401** then lithium reduction to amine **402** and finally carbamate addition to give carbamate **403 (Scheme 3.17).**



Scheme 3.17

The carbamate **403** was transformed after one hour of reaction with half an equevelent 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.



403 404

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.[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.[19] 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.[20] Tropane **407** is a bicyclic amine that has a pyrrolidine and a piperidine ring sharing a common nitrogen atom and two carbon atoms [*N*-methyl-8-azabicyclo[3.2.1]octane]. Tropane alkaloids such as tropinone **346** are characteristic of a class of *ca*. 200 alkaloids.[21] (**Fig 3.1**)

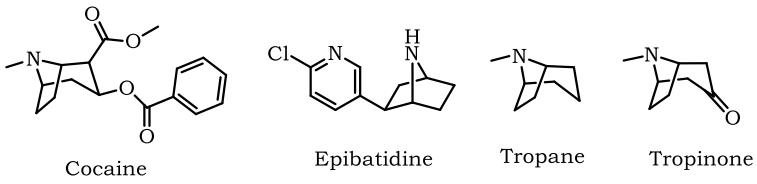
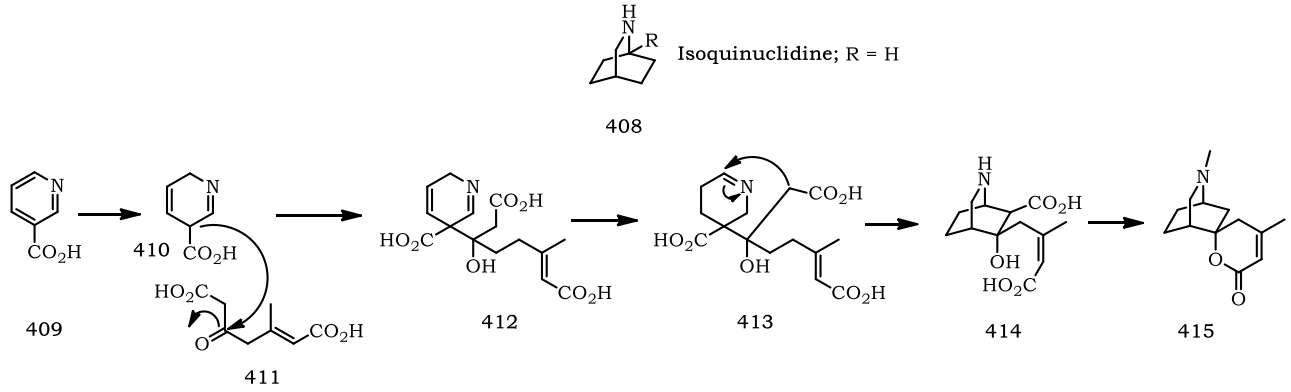


Fig 3.1

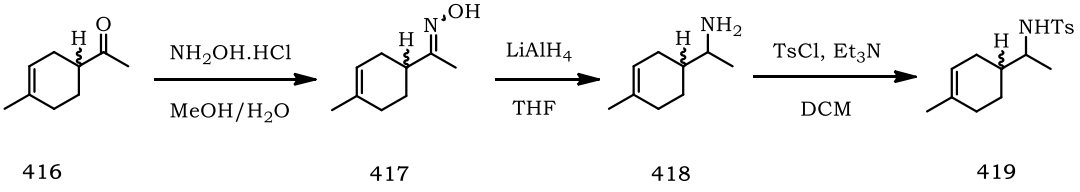
The isoquinuclidine **408** (2-azabicyclo[2.2.2]octane) ring system, a semi-rigid boat form of the piperidine ring, is present in natural products possessing interesting pharmacological properties such as the alkaloids of *Dioscorea hispida*, typified by dioscorine **415**.[22] Dioscorine, an alkaloid found in the tropical yam, has been shown to be a toxic central nervous system depressant[23] 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)**.[24]



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?

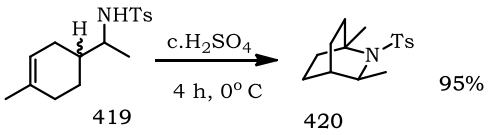
Commercially available (+/-)-limona ketone, (4-methylcyclohex-3-enyl)acetone, **416,** was converted into sulfonamide **419**. The reduction of oxime **417** to amine **418** gave a mixture of isomers. No attempt to separate the isomers was undertaken at any point in the synthesis. It was considered 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 δ_H 5.19 ppm and the NH proton at δ_H 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 ^{1}H NMR spectrum, one methine proton next to nitrogen at δ_H 4.20 (NCH) was obvious and distinct upfield shifts of the methyl group to get two methyl peaks one as a doublet at δ_H 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 ^{13}C 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 CH_2 carbons at (36.7, 30.1, 26.4, 19.2 ppm) (**Table 3.1**).

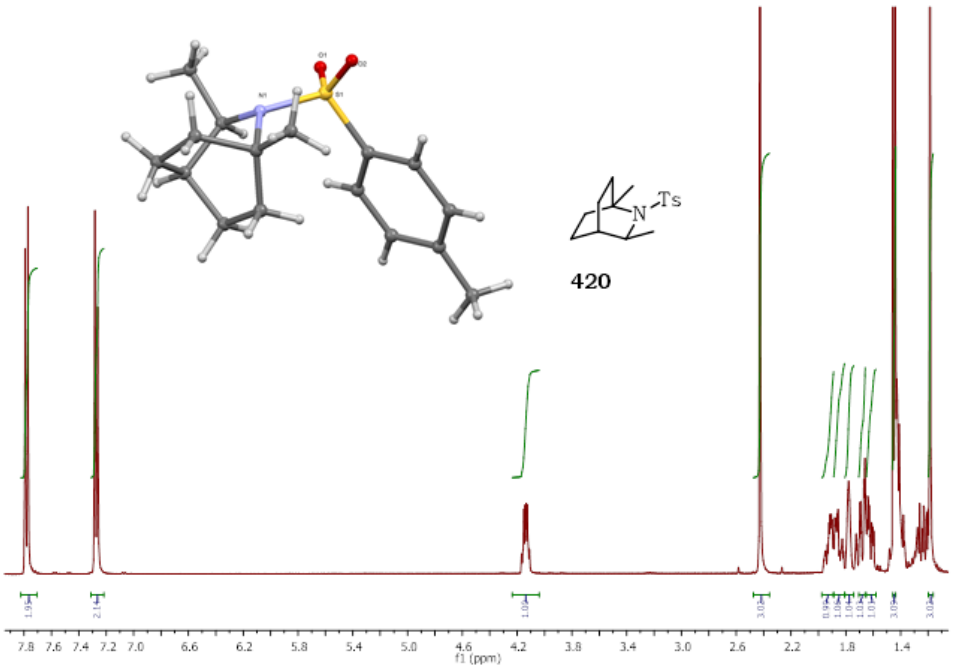
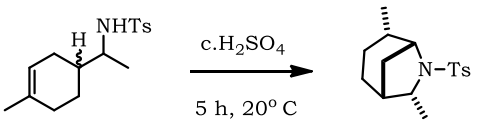


Fig 3.2 ^{1}H NMR spectrum of isoquinuclidine sulfonamide **420** in $CDCl_3$ (400 MHz) with the X-ray structure**.** Full crystallographic data is included in the **Appendix 4**.

After one hour of reaction of sulfonamide **419** with a catalytic amount of sulphuric acid at 0 ºC 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 ºC (**Scheme 3.22**).



419 421

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 [δ_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 δ_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**).

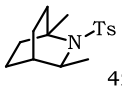
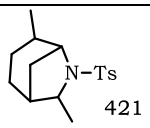
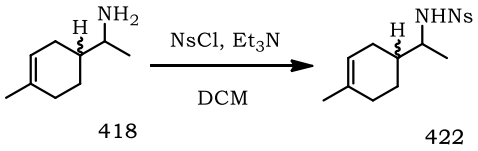
^{13}C NMR ppm	 420	 421
Cq	NCq : 55.2	-
CH	NCH : 57.0 CH : 31.5	2 x NCH 60.2 and 55.3 2 x CH : 37.6 and 33.6
CH_2	36.7, 30.1, 26.4 and 19.2	2 x CH_2 21.5 and 19.2

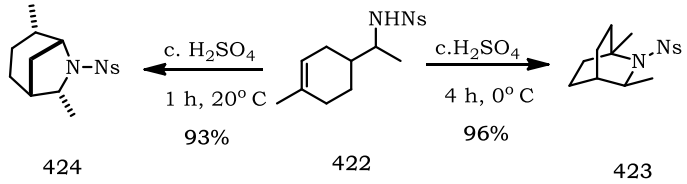
Table 3.1 Some peaks from ^{13}C NMR spectra of azabicyclo **420** and rearranged azabicyclo **421,** after ignoring tosyl group**.**

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**).



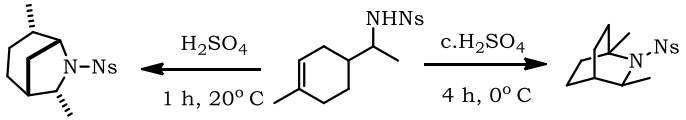
Scheme 3.23

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 ^{o}C gave the tertiary carbocation product **423**, which was distinguished in its ^{1}H NMR spectrum with the peak at δ_H 4.20 ppm representing a proton next to nitrogen (NCH), a methyl doublet at δ_H 1.41 (d, J = 7.2, CH_3) ppm and a methyl singlet at δ_H 1.14 ppm. ^{13}C NMR spectrum also supported this structure: one quaternary carbon at δ_C 56.1 (NCq), two CH carbons at δ_C 57.0 (NCH) and 31.8 ppm and four CH_2 carbons at (δ_C 36.2, 30.6, 26.3 and 19.4) (**Scheme 3.24** and **Fig 3.3**).



Scheme 3.24

After just one hour of reaction with concentrated sulphuric acid at 20 ^{o}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 δ_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 δ_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 δ_C 65.3 (NCH), 60.6 (NCH), 38.9 (CH) and 36.8 (CH) ppm and three CH_2 carbons at δ_C 37.4, 27.6 and 25.0 ppm were identified (**Scheme 3.24** and **Fig 3**).



424 422 423

Scheme 3.24

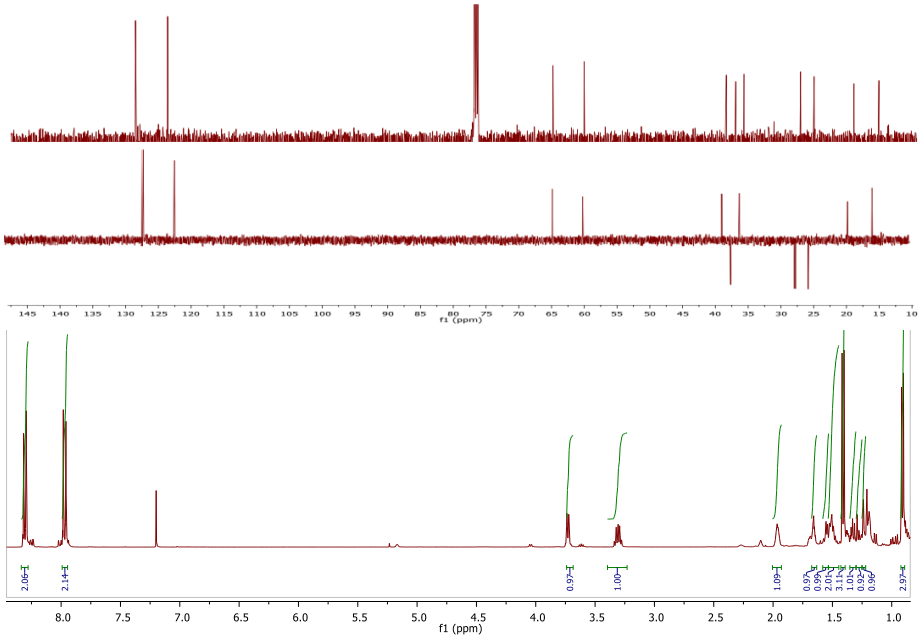


Fig 3.4 ^{1}H and ^{13}C NMR spectra of rearranged azabicyclo **424**: a) decoupled ^{13}C; b) DEPT CH, CH_3 positive; CH_2 negative c) proton.

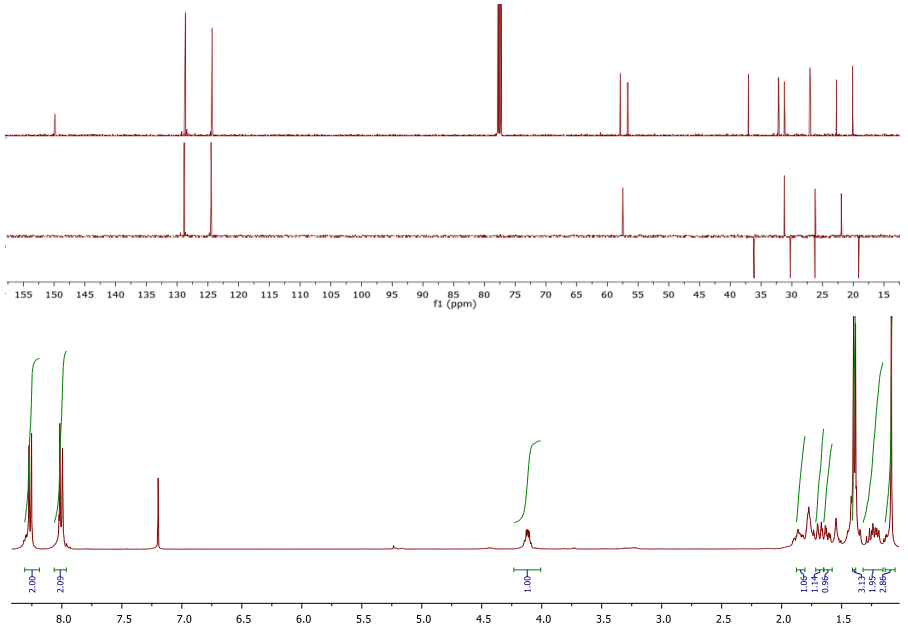
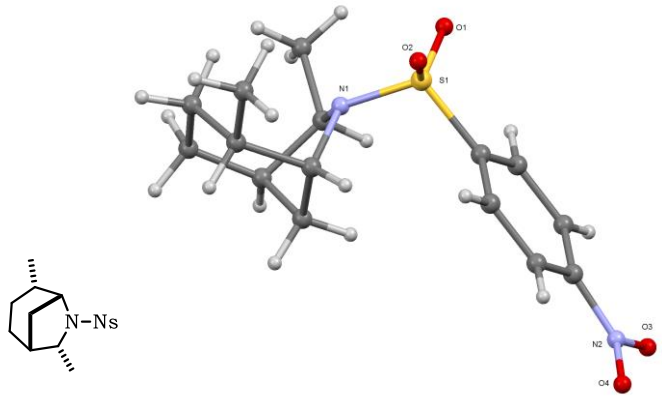


Fig 3.3 ^{1}H and ^{13}C NMR spectra of azabicyclo **423**: a) decoupled ^{13}C; b) DEPT CH, CH_3 positive; CH_2 negative c) proton.

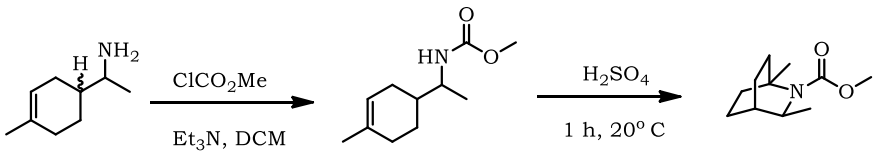
The structure of the thermodynamic azabicyclo product **424** was confirmed by X-ray crystallography (**Fig 3.5**).



424

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

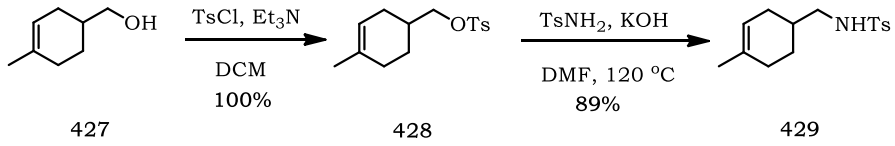
Although the rearrangement of piperidine to pyrrolidine of the *N*-tosyl **419** and *N*-nosyl **422** sulfonamides is a great discovery, we did control it by using carbamate as a protecting group. The carbamate **425** did cyclize after one hour of reaction with half an equivalent of concentrated sulfuric 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 ^{1}H 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 ^{13}C 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 CH_2 carbons at δ_C = 38.4, 30.1, 26.7 and 19.8 ppm, generally similar to **423**.



418 425 426

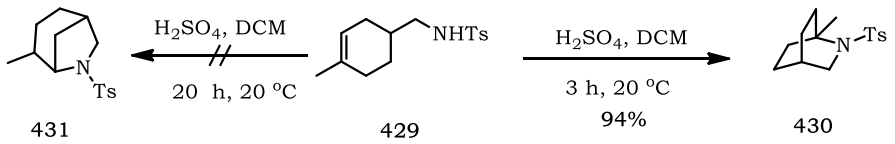
Scheme 3.25

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.[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 ^oC. Purification of the reaction mixture obtained after one hour gave the desired tosylamide **429** in 89% yield (**Scheme 3.26**).



Scheme 3.26

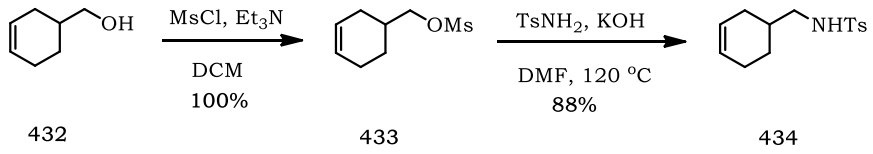
Tosylamide **429** did cyclise to give only the tertiary carbocation product **430** after three hours of reaction with concentrated sulfuric acid at ambient temperature in 94% yield. There was no evidence of formation of the alternative secondary carbocation product **431**, which would have resulted 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 δ_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

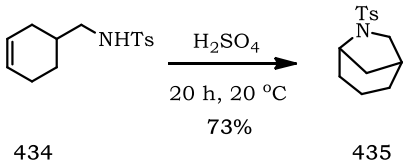
Similarly, sulphonamide **435** was prepared starting from commercially available cyclohexenyl methanol **432,** which was tosylated then the sulfonamide group introduced by an S_N2 reaction.[25] This is illustrated, as above, by the reaction of potassium tosylamide, which was prepared by

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^{o} C for 1 h. Purification of the reaction mixture obtained after one hour gave the desired tosylamide **434** in 88% yield (**Scheme 3.28**).



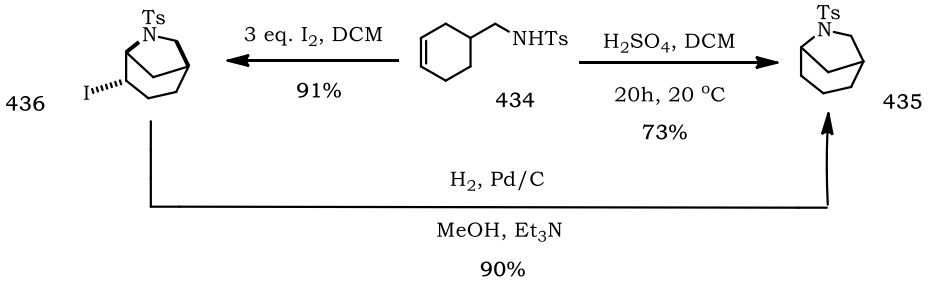
Scheme 3.28

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**).

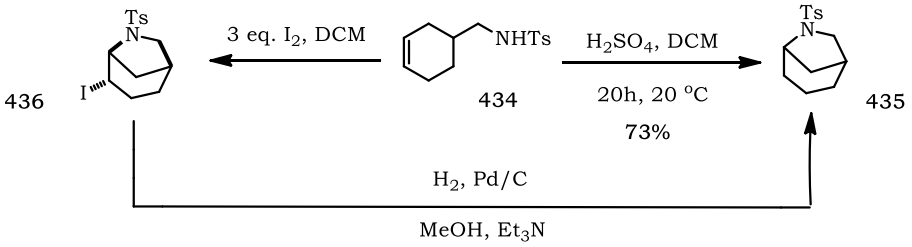


Scheme 3.29

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



Scheme 3.30

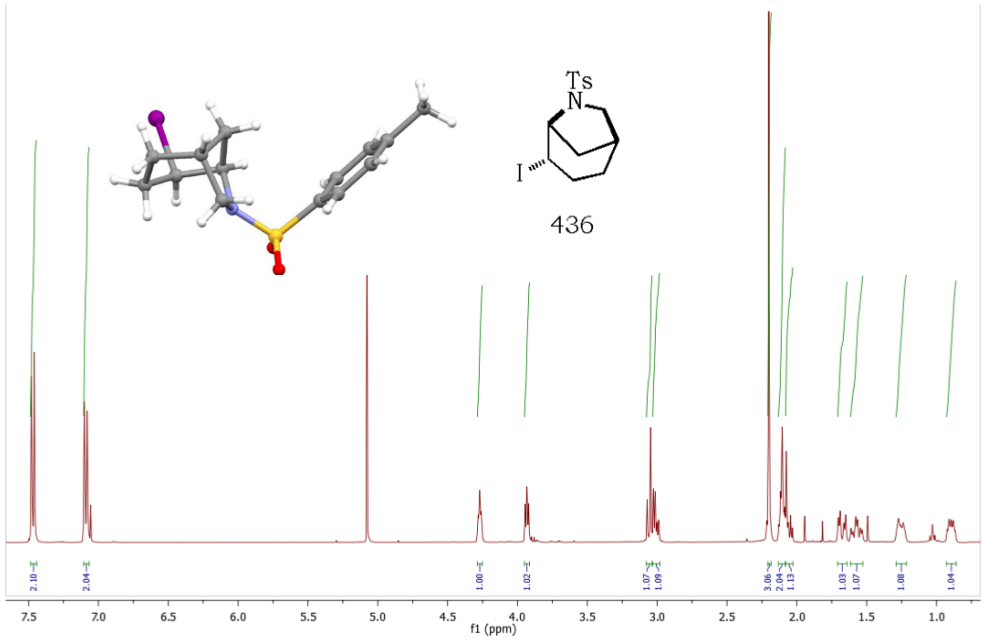


Fig 3.4 ^{1}H NMR spectrum of the iodopyrrolidine **436** with the X-ray structure**.** Full crystallographic data is included in the **Appendix 7**.

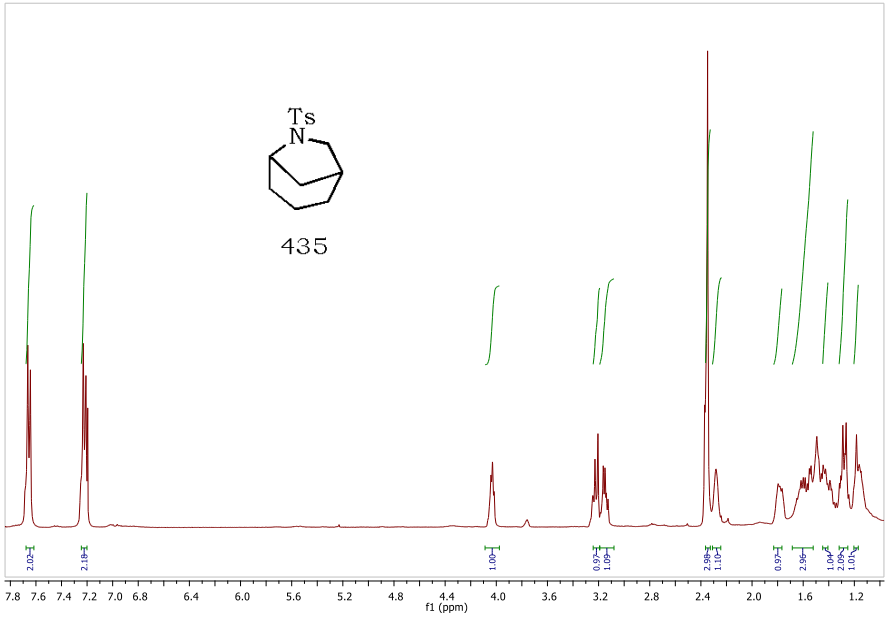
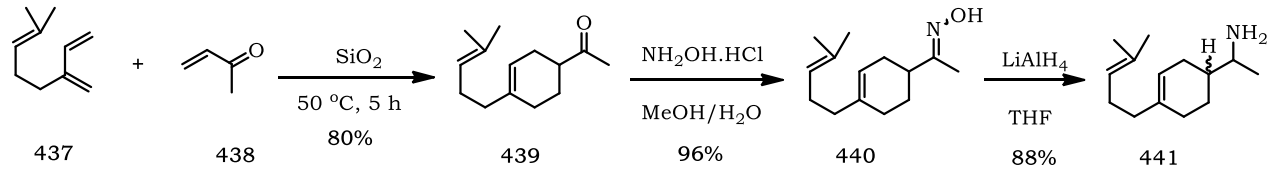


Fig 3.3 ^{1}H NMR spectrum of azabicyclo **435**.

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.[27] 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 equlmolar mixture of myrcene **437** and methylvinyl ketone **438** was applied to the usual chromatographlc grade silica gel, SiO_2, the [4+2] cycloaddition occurred effectively in the absence of any solvents and produced the anticipated Diels-Alder product **439** after heating at 50 ^oC for five hours.[28]

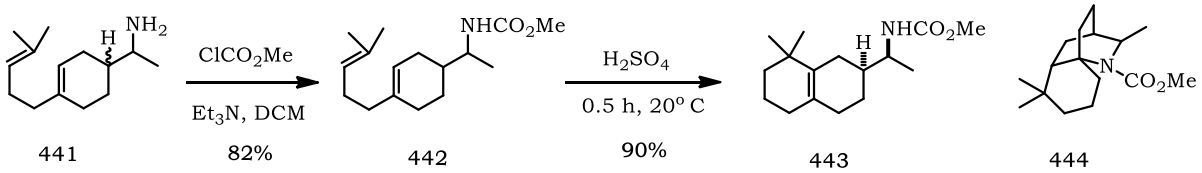
The resulted ketone **439** was converted into the oxime **440** which was reduced by lithium aluminum hydride to amine **441**. The reduction of oxime **440** to amine **441** gave mixture of isomers. No attempt to separate the isomers was undertaken. It was considered that both isomers would give the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



Scheme 3.31

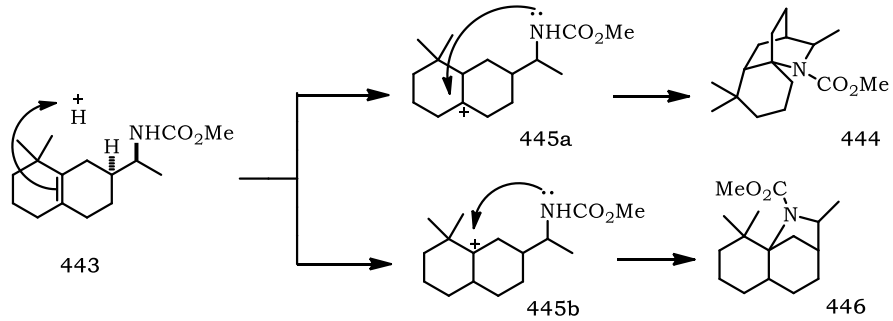
Carbamate **442** was prepared by the reaction of amine **441** with methyl chloroformate in the presence of triethylamine in dichloromethane. Carbamate **442** was treated with a catalytic amount of concentrated sulfuric acid in dichloromethane. After one hour of the reaction, a ^1H NMR

spectrum showed that the resonances corresponding to olefinic protons at δ_H 5.28 and 5.10 ppm had disappeared, whereas the NH proton at δ_H 4.58 ppm did not disappear at the end of the reaction. The CH proton next to nitrogen at δ_H 3.67 – 3.60 ppm, the methoxy methyl group were still visible at δ_H 3.64 ppm. In the ^{13}C NMR spectrum, three quaternary carbons were visible at δ_C 156.6 : C=O, 133.7 and 127.1 ppm (**Scheme 3.32)**.



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).**



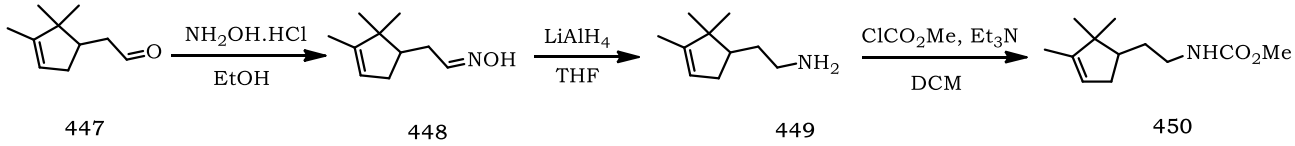
Scheme 3.33

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)**.

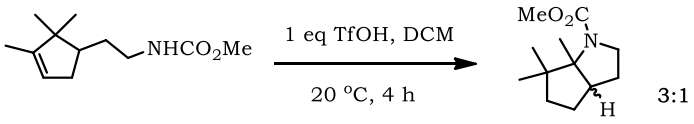


447 448 449 450

Scheme 3.34

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

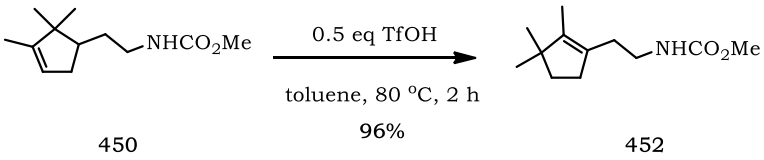
After four hours of reaction with one equivalent of triflic acid at room temperature carbamate **450** gave only bicyclo product **451** an inseparable 3:1 mixture of diastereoisomers. The ^{1}H NMR spectrum showed that the resonances corresponding to olefinic proton at δ_H 5.12 had disappeared, and no starting material was present the NH proton at δ_H 4.82 ppm had disappeared at the end of the reaction. As usual, CH_2 protons next to nitrogen moved to δ_H 3.41 – 3.28 ppm. The singlet at δ_H 1.51 ppm representing the methyl group on double bond moved further upfield to δ_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 δ_C 156.8 (C=O), 74.8 (NCq) and 46.0 ppm, four CH_2 signals δ_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 υ/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)**.



450 451

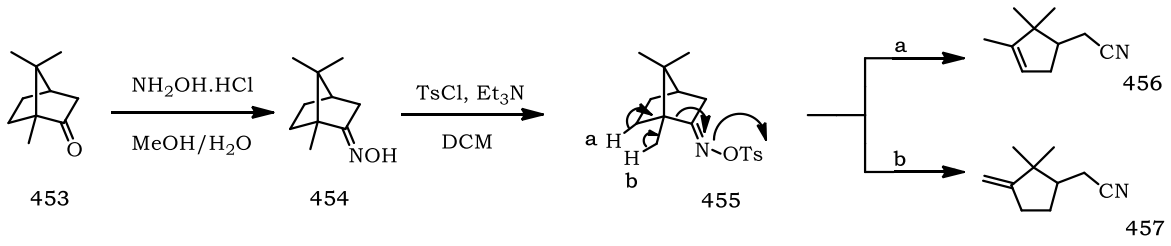
Scheme 3.35

Whereas, the reaction with 0.5 equivalent of triflic acid at 80 ^{o}C gave only the Wagner-Meerwein product **452** after two hours of reaction a ^{1}H NMR spectrum showed that the resonance corresponding to the olefinic proton had disappeared, but the NH proton did not disappear. However, the ^{13}C NMR spectrum enhanced this theory as two quaternary carbons appeared at δ_C 142.1 and 129.8 ppm, due to quaternary carbons on a double bond and a quaternary carbon at high field δ_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**).



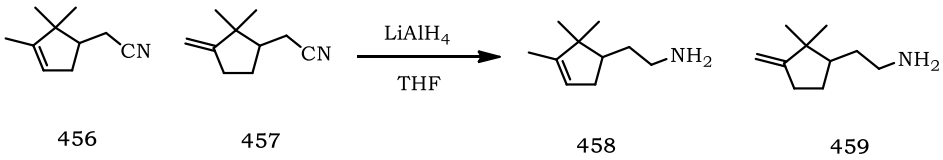
Scheme 3.36

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^{-l} due to nitrile presence; in the ^{1}H NMR spectrum, the olefinic proton at δ_H 5.23 (t, J = 1.2 Hz, 1H, =CH) ppm and three methyls at δ_H 1.60, 1.06 and 0.84 ppm. In in ^{13}C NMR spectrum, clearly nitrile carbon appeared at δ_C 119.3 ppm (**Scheme 3.37**).



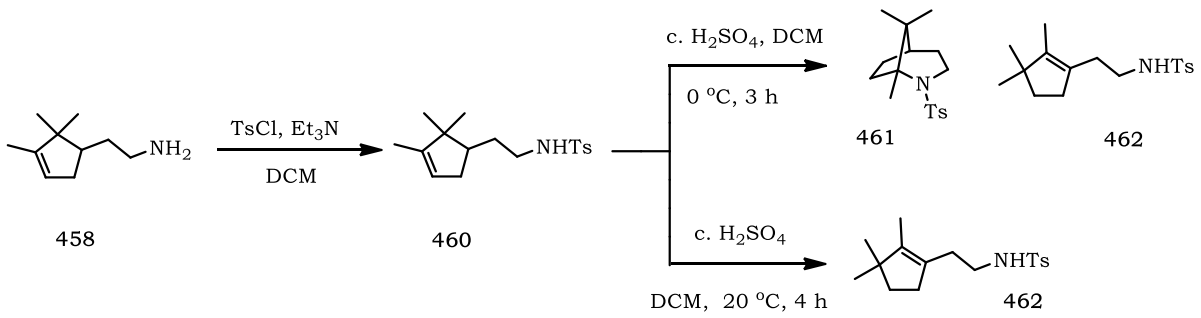
Scheme 3.37

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).**



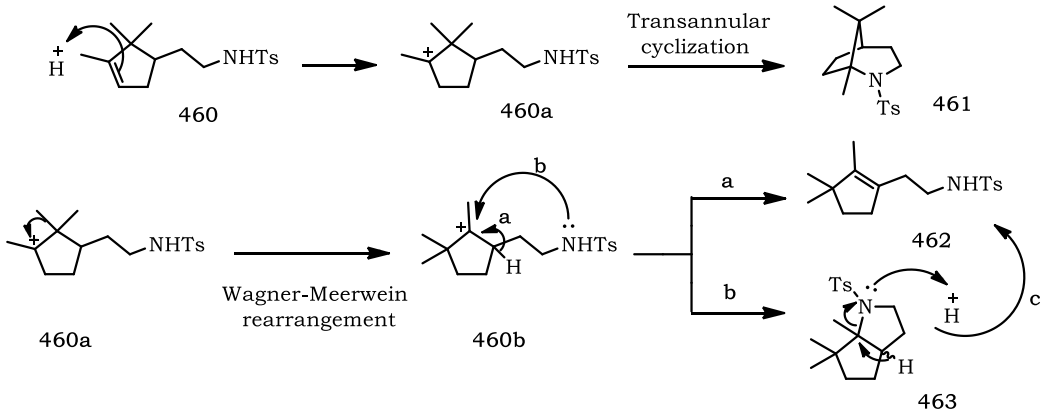
Scheme 3.38

After the reaction of amine **459** with tosyl chloride in the presence of triethylamine during the chromatography purification the sulfonamide **460** was separateed. 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 rearrenged sulfonamide **462**, which would have resulted in the Wagner-Meerwein rearrangement. The azabicyclo[3.2.1]octane **461** was separated by simple cristalization; the ^{13}C NMR spectrum showed a quaternary carbon next to nitrogen (NCq) at δ_C 53.7 ppm and four CH_2 carbons at δ_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 ^1H 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**).



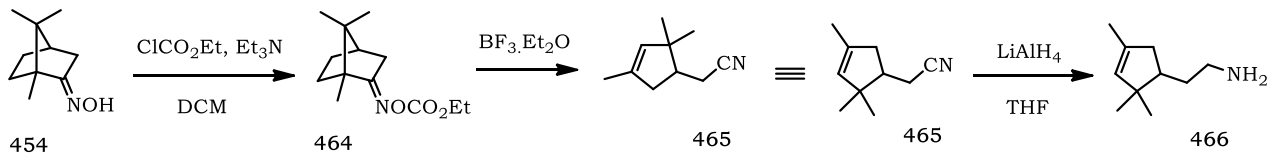
Scheme 3.39

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**).



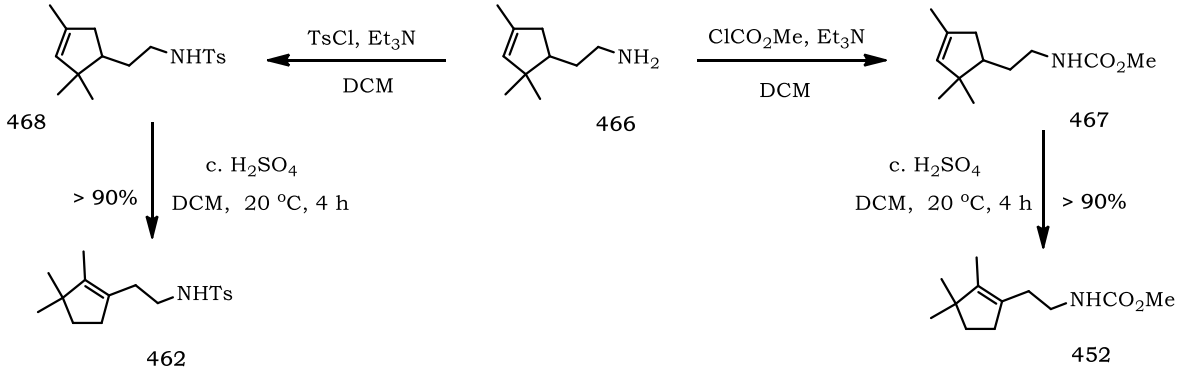
Scheme 3.40

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

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

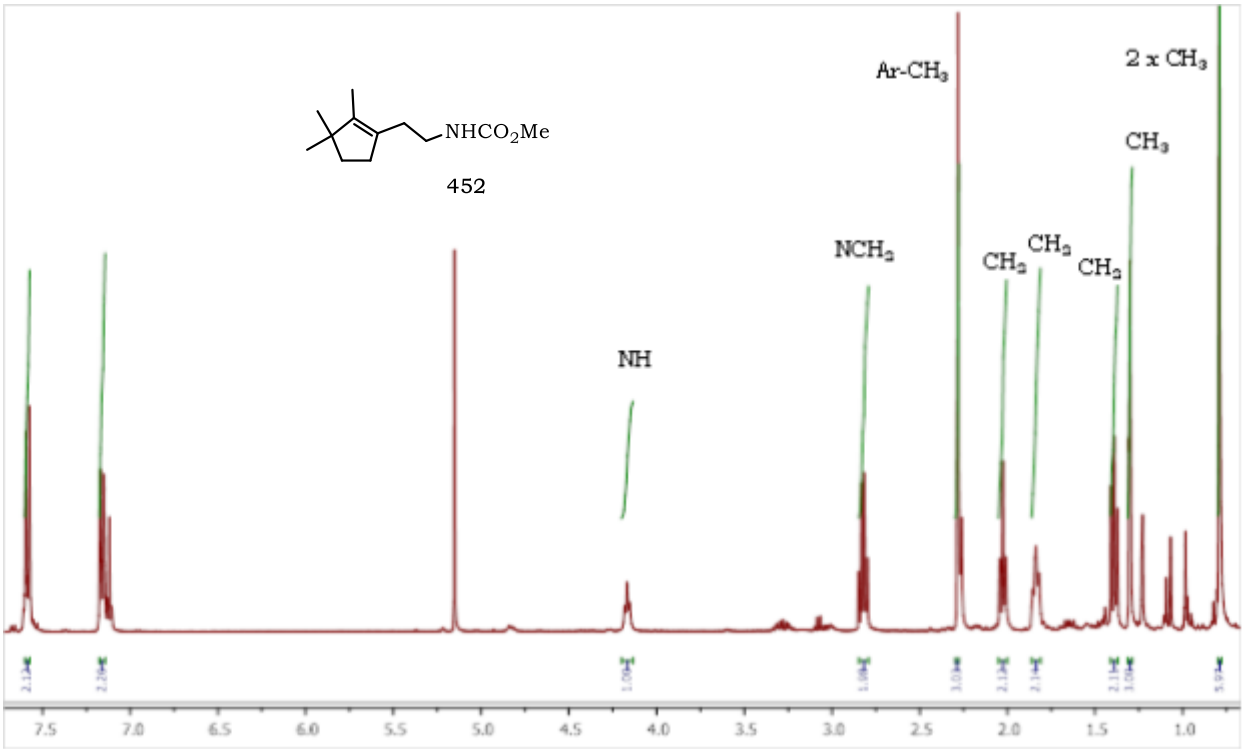
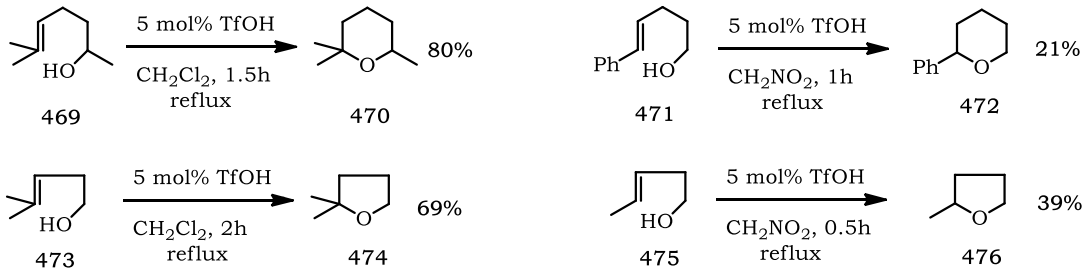


Fig 3.5 ^{1}H NMR spectrum of the Wagner-Meerwein sulfonamide **462**.

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

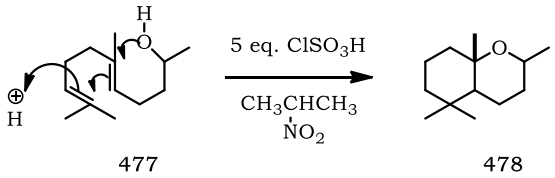
3.5 Acid-catalysed Hydroalkoxylation Cyclisations

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]



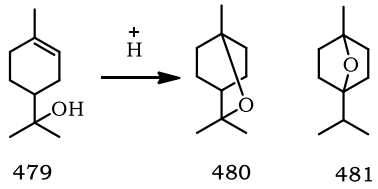
Scheme 3.43

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 tetrahydropyrans 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**).[33]



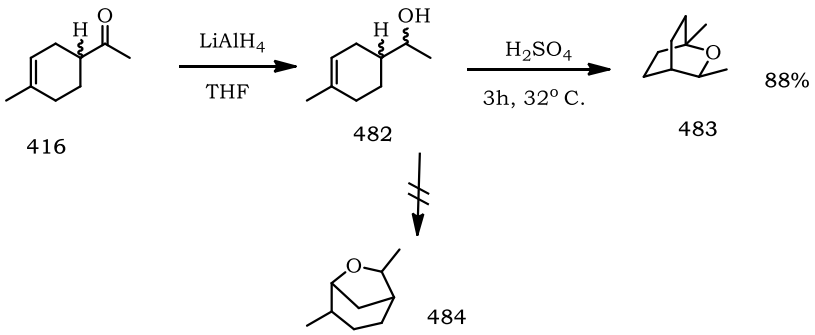
Scheme 3.44

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. [34] 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 $H_3PW_{12}O_{40}$ (PW), as homogeneous and solid acid catalysts for the isomerization of α-terpineol **479** to cineoles **480** and **481** (**Scheme 3.45**).[35]



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 sterically 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 ^{o}C. In the ^{1}H NMR spectrum, the proton next to oxygen at δ_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 δ_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 ^{o}C (**Scheme 3.46**).

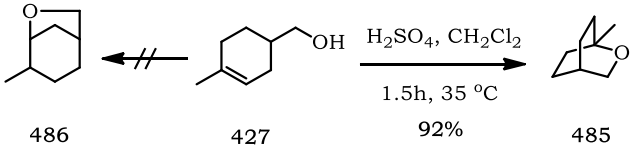


Scheme 3.46

The presence of the (4-methylcyclohex-3-enyl)methanol **427** in our chemical list was worthy to try the cyclisation rection. When the alcohol **427** was heated with a catalytic amount of sulfuric acid for 1.5 hours at 35 ^{o}C, it gave oxabicyclo-octane **485** in an excellent yield of 92%. Infrared data showed the absence of the alcohol functional group. The ^{1}H 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.

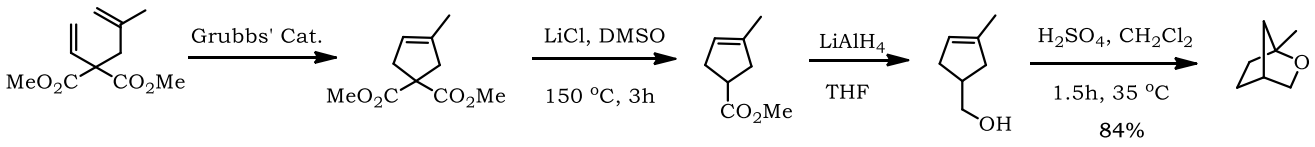
As the rearrangement was in our minds during the whole time, there was no evidence of formation of the alternative secondary carbocation product **486**, which would have resulted in this less hindered product (**Scheme 3.47**).



486 427 485

Scheme 3.47

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 δ_C 78.2 (OCq) ppm, one CH carbon at δ_C 38.4 ppm, four CH_2 carbons at δ_C 76.6 (OCH_2), 42.2, 36.1 and 28.8 ppm and one methyl carbon at 26.9 ppm **(Scheme 3.48)**.



487 488 489 490 491

Scheme 3.48

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.

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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 H_2O and urea NH_2CONH_2 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. Tetrahydropyrans (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)**.

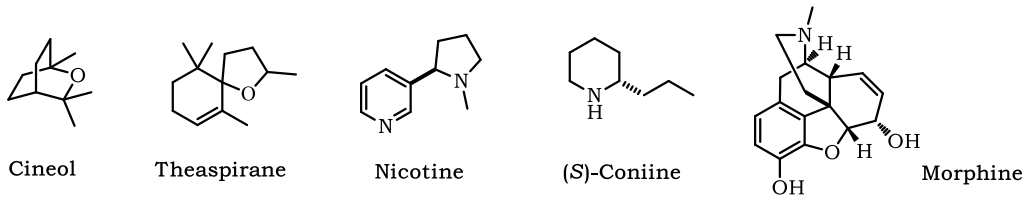
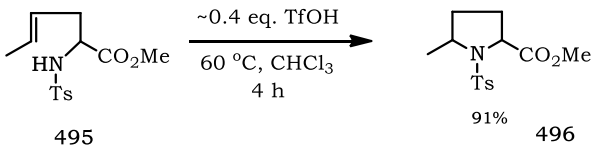


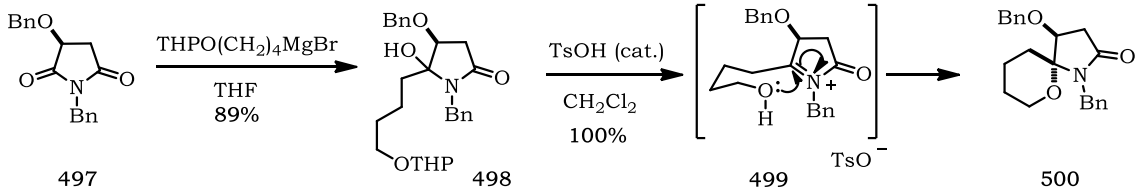
Fig. 4.1

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 CF_3SO_3H (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 ^oC to give pyrrolidine **496** in an excellent yield of 91% **(Scheme 4.1)**.[1]



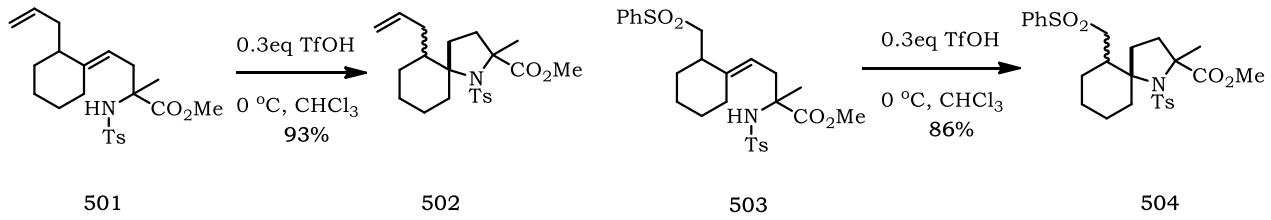
Scheme 4.1

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 °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]



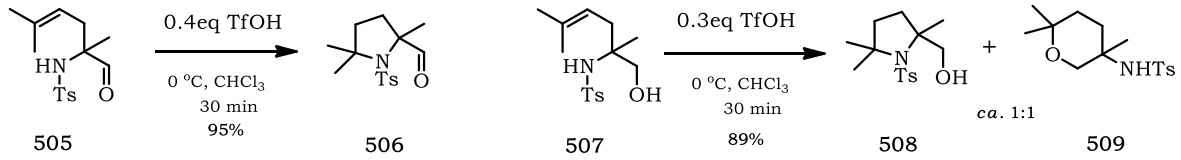
Scheme 4.2

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]



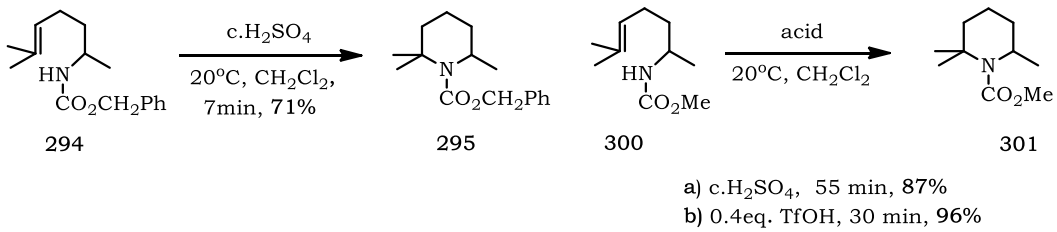
Scheme 4.3

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 precusor **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

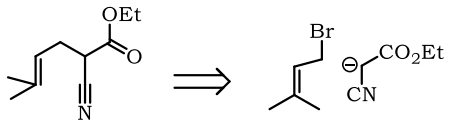
To incorporate alcohol groups in a controlled way was clearly a challenge, to this methodology, however, as almost all protecting groups for these are acid-sensitive. To mask the useful hydroxyl group, we expected benzyl ether (OBn) and *para*-methoxylbenzyl ether (OPMB) unlikely to survive in such acidic conditions. Trimethylsilyl ether $OSi(CH_3)_3$ 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 benzyloxycarbonyl CO_2CH_2Ph survives in acidic condition at 20 °C (see p. 57 and 59) and CO_2Me 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

Preparation the cyclisation precursors

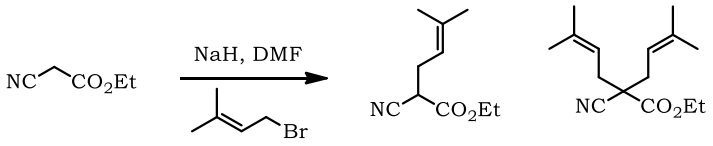
Cyanoester derivatives **511** can be prepared from cyanoacetate **510** and allylic halides in reasonably good yields (55%).[3] The prenyl bromide used was not completely pure, due to its sensitive nature; this could result in lower yield. In the case of using pure alkyl halide the yield was much better (74%) (**Fig. 4.2**).



511 252 510

Fig. 4.2

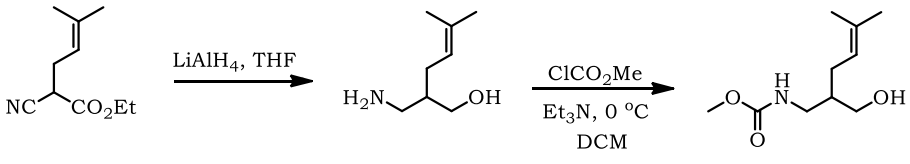
In all cases there was also formed double alkylated product **512** (*ca.* 20%), which was used in future to synthesise *spiro*-products (**Scheme 4.6**). The two product were separated by using column chromatography.



510 511 512

Scheme 4.6

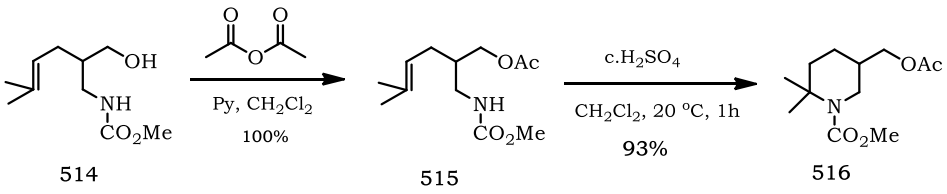
Prenyl cyanoacetate **511** was reduced by lithium aluminium hydride to γ-amino alcohol **513**. By selective addition of CO_2Me to the more nucleophilic nitrogen over oxygen, unsaturated amino-alcohol **514** was synthesized. Now the reactant was ready to test both the protected alcohol stability to 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**).



511 513 514

Scheme 4.7

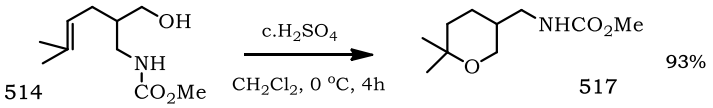
In the event, when the alcohol group was blocked as the corresponding acetate **515**, then only the piperidine **516** was formed after one hour of reaction at room temperature with a catalytic amount of sulfuric acid in an excellent yield of 93%. The products did not require any chromatographic purification as the reaction proceeded very cleanly. Infrared spectroscopy showed the absence of NH absorption and the presence of two carbonyl groups at υ/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 δ_H 5.02 ppm and NH proton at δ_H 4.94 ppm and the appearance of two ABX systems. Four methyls could be seen clearly; methoxy methyl at δ_H 3.55 ppm, methyl acetyl at δ_H 1.91 ppm and two methyls on quaternary carbons at δ_H 1.35 and 1.23 ppm. The ^{13}C NMR spectrum showed a quaternary carbon next to a nitrogen atom at δ_C 54.8 ppm and four CH_2 carbons, one next to oxygen at δ_C 66.4 ppm and three on the piperidine ring at δ_C 43.1 (NCH_2), 36.2 and 21.3 ppm (**Scheme 4.8, Table 4.1 and Fig 4.3**).



Scheme 4.8

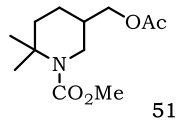
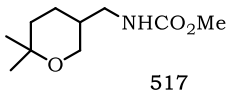
However, we were very much excited to know what would happen when we attempt to cyclise the free amino-alcohol **514**, especially as this had not been tried before in the literature. It was clear that cyclisation had occurred after four hours of reaction at ice temperature with a catalytic amount of sulfuric acid in excellent yield (93%), as the olefinic =CH at 5.02 ppm had disappeared. Surprisingly, the NH proton at δ_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 δ_C 71.3 ppm and four $\underline{C}H_2$ carbons one next to an oxygen at 64.3 ppm, one next to nitrogen at δ_C 43.1, and two others at 35.1 and 23.7 ppm (**Scheme 4.9, Table 4.1)**.

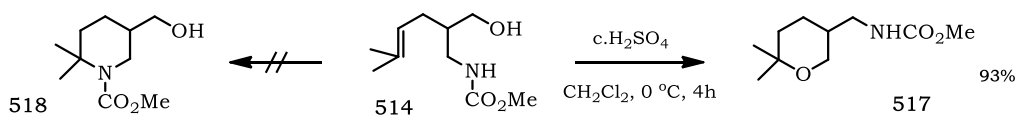


Scheme 4.9

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

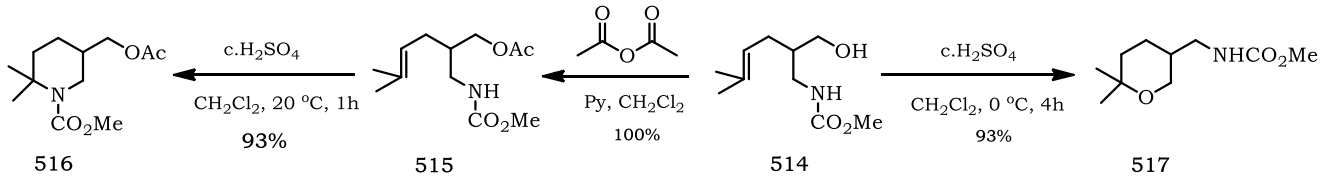
^{13}C NMR ppm / Structure	Cq	CH	CH_2	CH_3
 516	Ac-C=O : 171.0 C=O : 156.9 NCq : 54.8	CH : 33.8	OCH_2 : 66.4 NCH_2 : 43.1 36.2 and 21.3	OCH_3 : 51.9 Ac-CH_3 : 27.9 24.5 and 20.8
 517	C=O : 157.2 OCq : 71.3	CH : 36.2	OCH_2 : 64.3 NCH_2 : 43.1 35.1 and 23.7	OCH_3 : 52.1 29.2 and 23.3

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

The reactions are remarkably clean: the NMR spectra shown below were obtained from *crude* products.



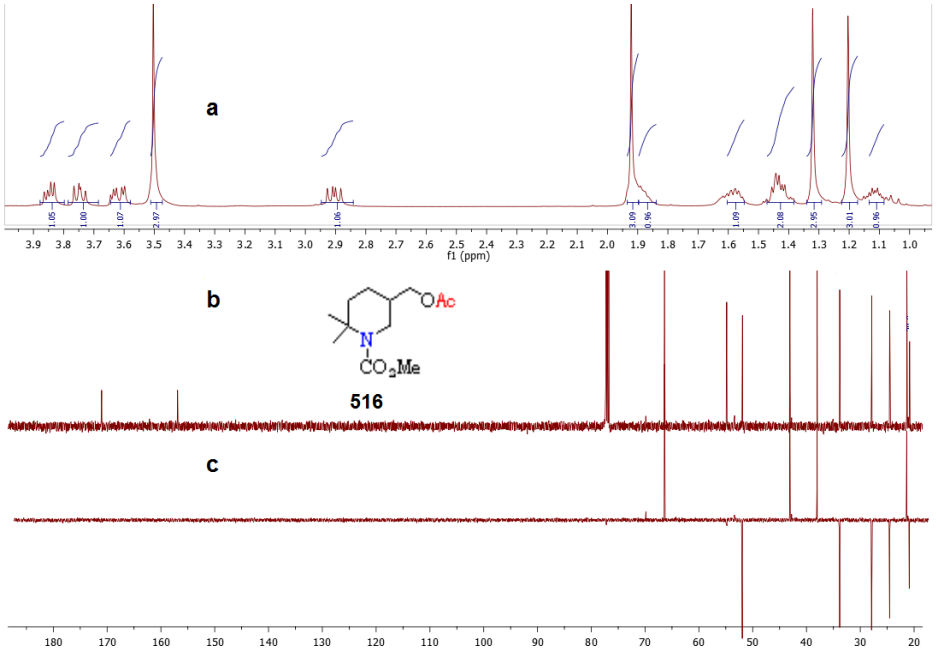


Fig 4.3 ^{1}H and ^{13}C NMR spectra of piperidine **516**:

a) proton, b) decoupled ^{13}C, c) DEPT CH_2 positive; CH, CH_3 negative.

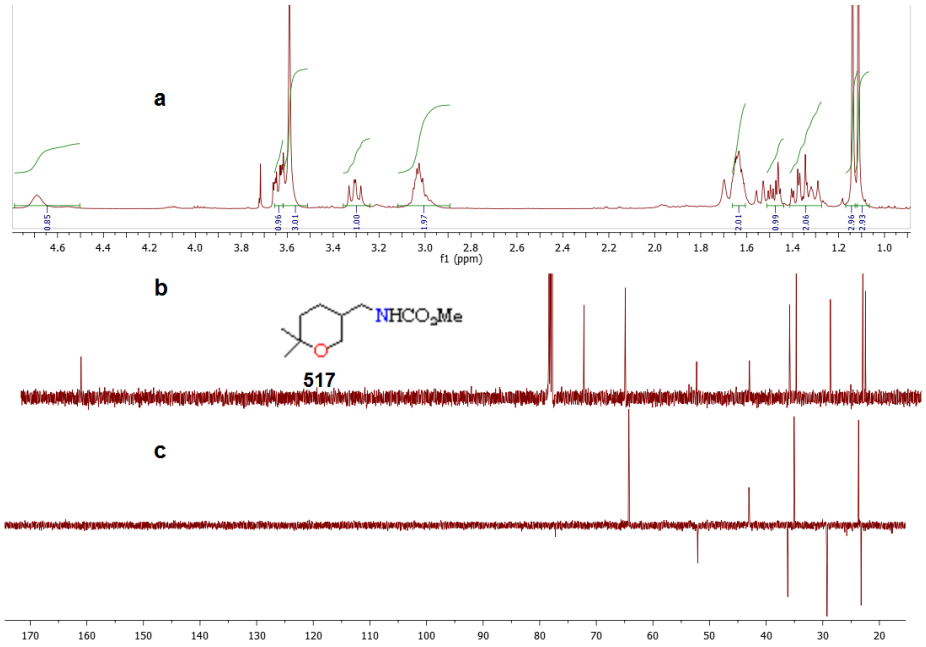
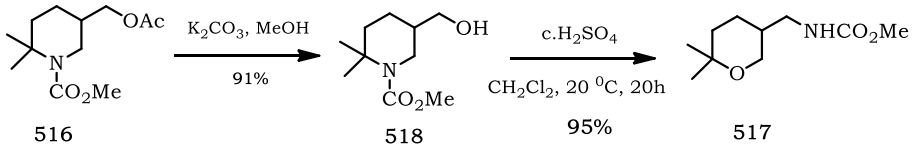


Fig 4.4 ^{1}H and ^{13}C NMR spectra of tetrahydropyran **517**:

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!



516 518 517

Scheme 4.11

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 δ_H 1.91 ppm had disappeared and a new hydroxyl proton was visible also at δ_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 δ_C 55.1 ppm and four CH_2 carbons, one next to oxygen at δ_C 65.2 ppm and three on the piperidine ring one next to a nitrogen atom at δ_C 42.7 (NCH_2) and two others at 38.0 and 20.8 ppm. Three methyls could be seen clearly; methoxy methyl at δ_C 51.9 ppm and two other methyls on quaternary carbons at δ_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.**

^{13}C NMR ppm	OCH_2 65.2	NCH_2 42.7	CH_2 38.0	CH 36.8	CH_2 20.8
^{1}H NMR ppm	3.46 (dd) 3.42–3.38 (m)	3.62 (dd) 3.12 (dd)	1.58–1.43 (m)	1.85–1.79 (m)	1.22–1.07 (m) 1.71–1.59 (m)

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 δ_H 3.46 and 3.42 – 3.38 ppm) whose resonance is the carbon next to oxygen at δ_C 65.2 ppm. The cross peak between the carbon (6-C) next to nitrogen at δ_C 42.7 ppm resonates the two protons whose appearance is as doublets of doublets at δ_H 3.62 and 3.12 ppm. The cross peak between the methine proton is the carbon (5-C) at δ_C 36.8 ppm. We expect the cross peak between the carbon (3-C) at δ_C 38.0 ppm is the two protons whose resonsnce is the multiplet at δ_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 δ_H 1.22 – 1.07 and 1.71 – 1.59 ppm) is the carbon (4-C) at δ_C 20.8 ppm (**Table 4.2** and **Fig 4.5**).

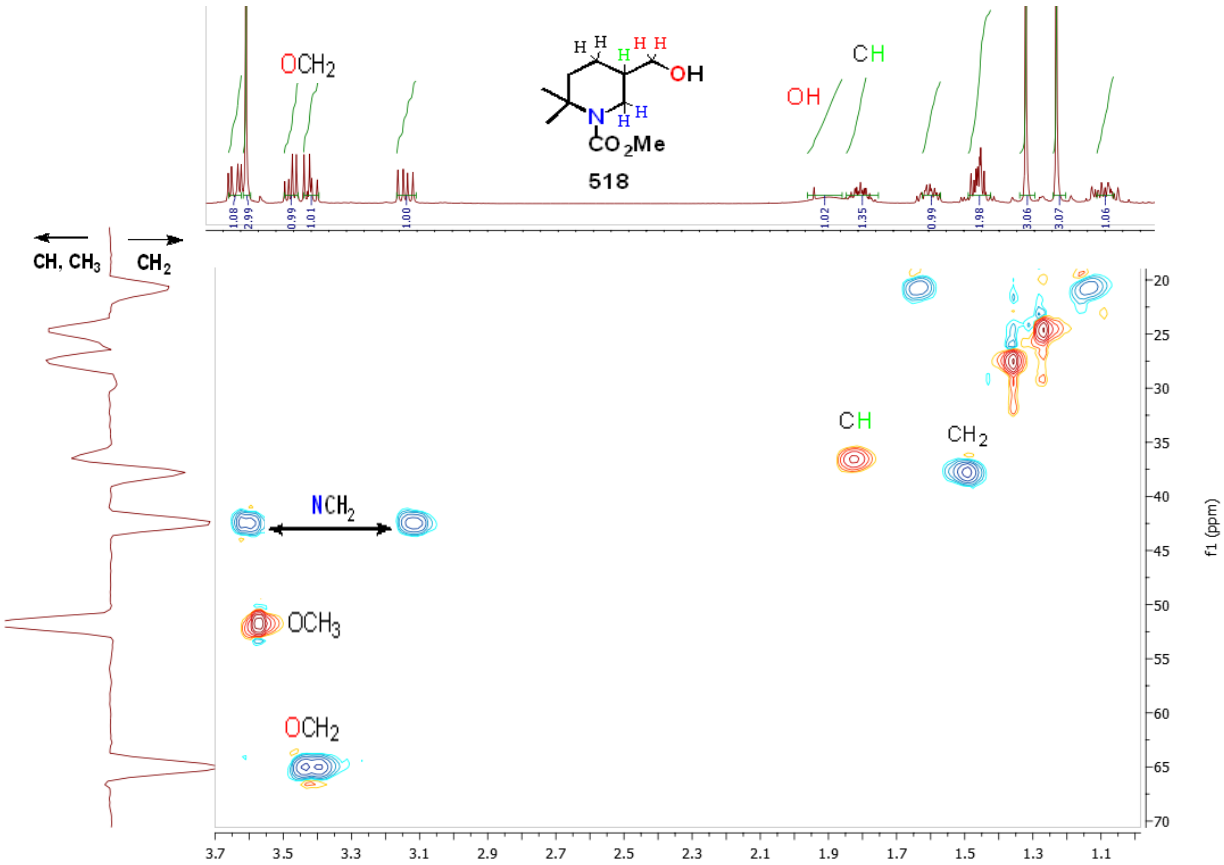


Fig 4.5 ^{1}H ^{13}C COSY analysis of piperidine **518**

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 δ_H 1.85 – 1.79 ppm, the methine proton at the carbon (5-C), is coupled not only to the 6-CH_2N at (δ_H 3.62 and 3.12 ppm protons) and CH_2O protons in the left at (δ_H 3.46 and 3.42 – 3.38 ppm), but also to the 4-CH_2 protons. Now we can confirm the multiplet at δ_H 1.58 – 1.43 ppm is the two protons whose carbon is the carbon (3-C) at δ_C 38.0 ppm.

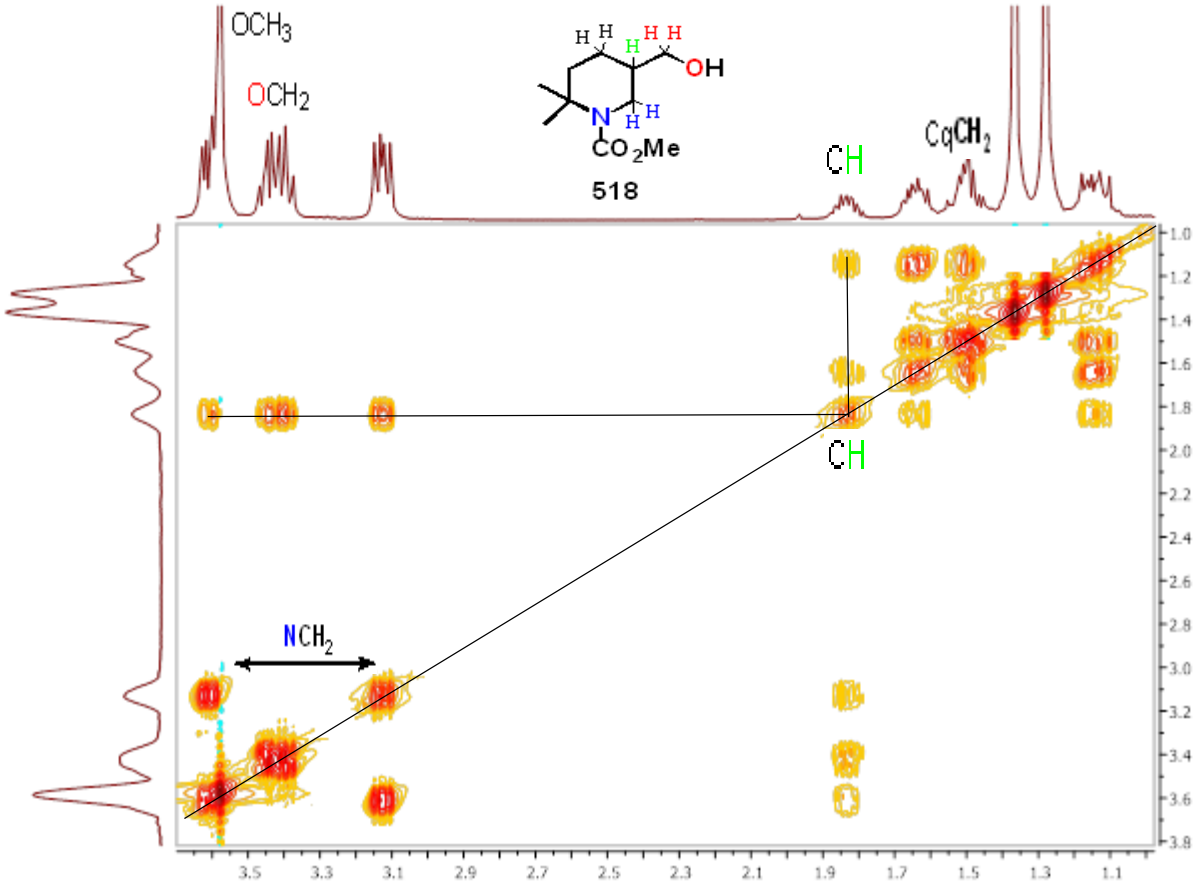
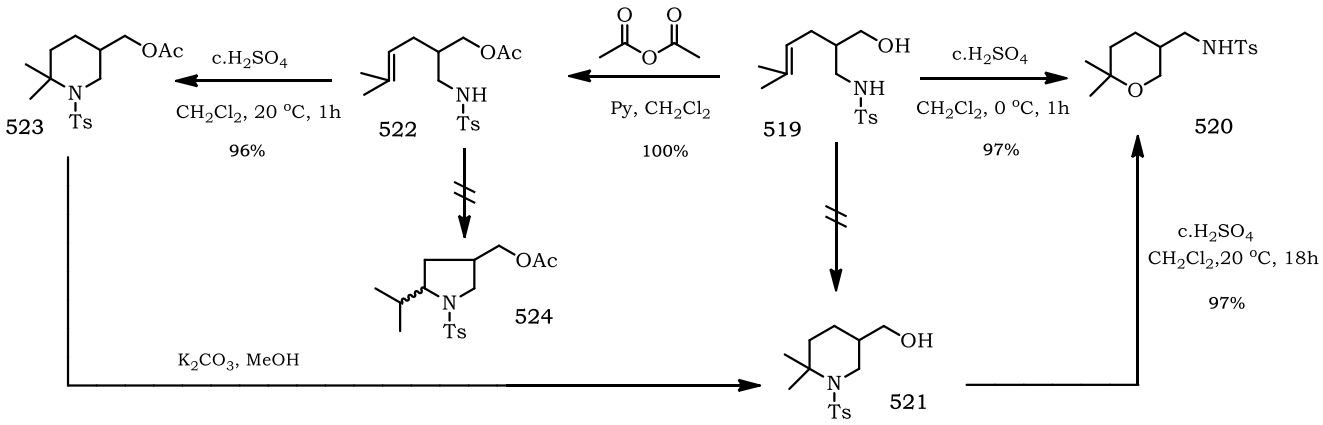


Fig 4.6 ^{1}H ^{1}H COSY analysis of piperidine **518**

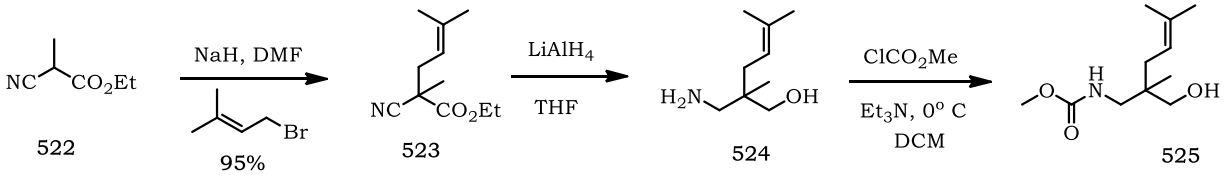
While the initial piperidine protected alcohol **516** had a formula of $C_{12}H_{21}NO_4$, the piperidine methanol **518** showed m/z = 201.1365 for the formula $C_{10}H_{19}NO_3$ $[M]^+$. This was confirmed by high resolution measurements and so confirmed the piperidine methanol **518**. Also, infrared spectroscopy showed the presence of hydroxyl group absorption at υ/cm^{-1} 3416 and the presence of the carbamate group at υ/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 ^{o}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 ^{1}H NMR spectum. 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 ^{1}H and ^{13}C NMR spectra. In ^{1}H 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 ^{13}C NMR showed a quaternary carbon next to the nitrogen atom at δ_C 57.8 ppm and four $\underline{C}H_2$ carbons one next to oxygen at δ_C 65.9 ppm and three on the piperidine ring at δ_C 45.4 (NCH_2), 39.8 and 23.2 ppm. Morever, 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**).



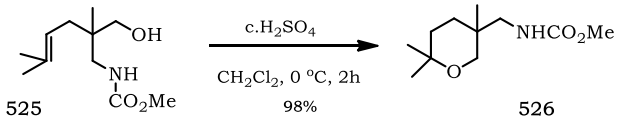
Scheme 4.12

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**).



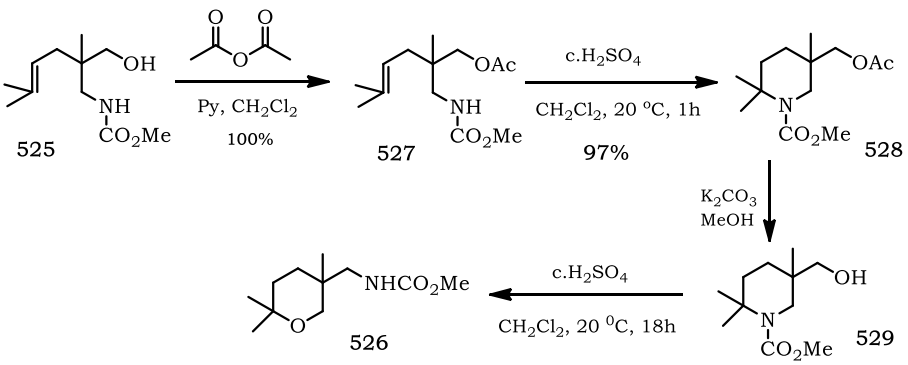
Scheme 4.13

When the free amino-alcohol **514** was exposure to a catalytic amount of concentrated sulfuric acid for two hours at 0 ^{o}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 =CH at δ_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 δ_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 δ_C 71.3 ppm and four $\underline{C}H_2$ carbons one next to oxygen at δ_C 68.5 ppm, one next to nitrogen at 47.3 and two on the ring at 32.1and 27.1 ppm (**Scheme 4.14**).



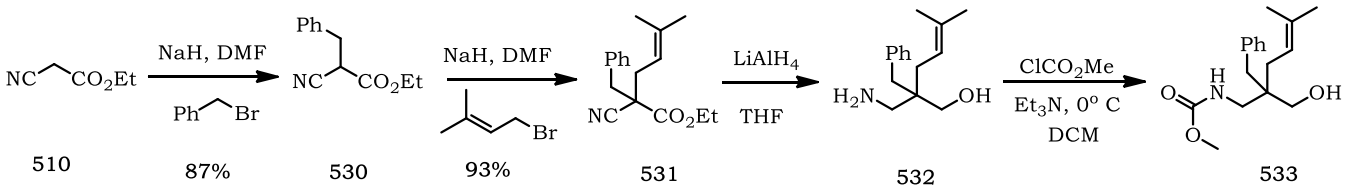
Scheme 4.14

In the event, when the alcohol group was blocked as the corresponding acetate **527**, then only the piperidine **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 υ/cm^{-1} 1699. Both ^{1}H and ^{13}C NMR spectra support the successful synthesis of piperidine **528**; starting material **527** had clearly disappeared. Most obvious was the disappearance of the olefinic =CH at δ_H 5.07 ppm and NH proton at δ_H 4.91 ppm, with the appearance of two AB systems one next to oxygen at δ_H 3.75 and another next to nitrogen at 3.31 (d, *J* = 13.9 Hz, 1H, $NC\underline{H}_AH_B$) and 2.96 (d, *J* = 13.9 Hz, 1H, $NCH_A\underline{H}_B$). Five methyls could be seen clearly; methoxy methyl at δ_H 3.54 ppm, methyl acetyl at δ_H 1.99 ppm and two methyls on quaternary carbon at δ_H 1.33 and 1.30 ppm and tinaly a singlet at δ_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 δ_C 171.1 and 157.0 ppm, one next to the nitrogen atom at δ_C 55.0 ppm and anther quaternary at the 5-position of the ring at 34.4 ppm. Four CH_2 carbons were present, one next to oxygen at δ_C 70.2 ppm and three on the piperidine ring at δ_C 47.6 (NCH_2), 36.4 and 28.1 ppm. When the acetate was hydrolysed in piperidine **528**, the resulting alcohol **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 **529** was treated with acid, it rearranged to the initial tetrahydropyran **526** after 18 h at room temperature (**Scheme 4.15**).



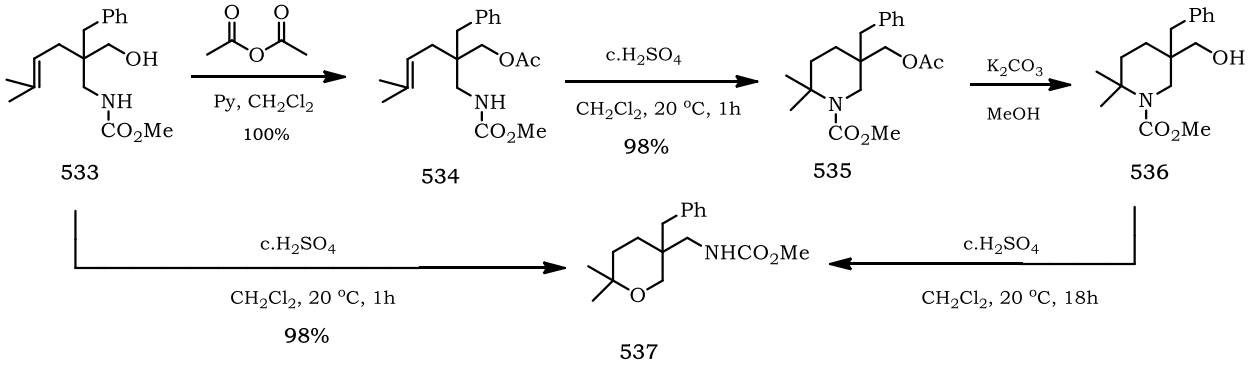
Scheme 4.15

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**).



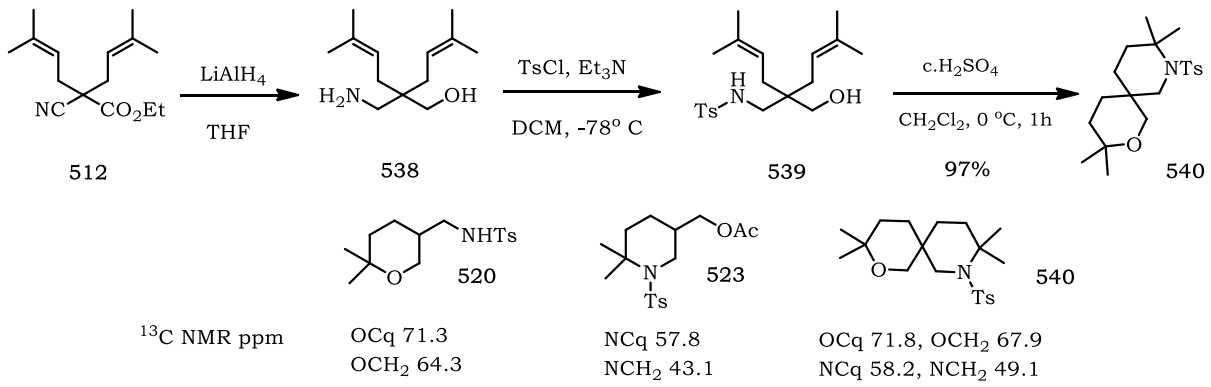
Scheme 4.16

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 δ_H 5.19 ppm and NH proton at δ_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 δ_C 55.3 ppm and four CH_2 carbons one next to oxygen at δ_C 67.3 ppm and three on the piperidine ring at δ_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**).



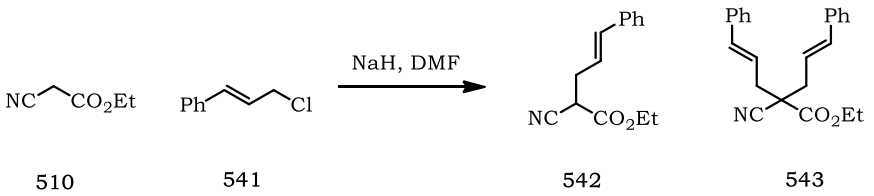
Scheme 4.17

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 $\underline{C}H_2$ 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).**



Scheme 4.18

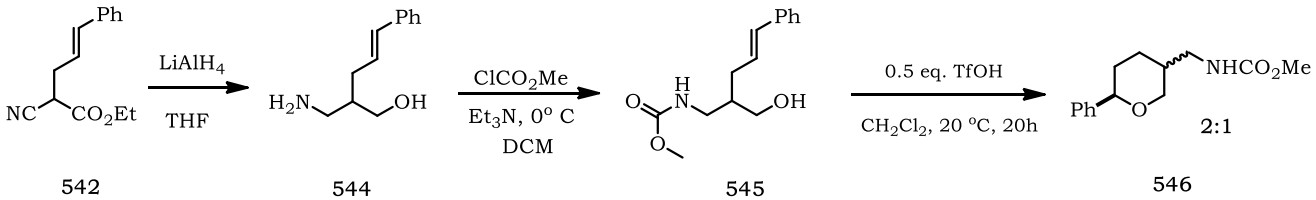
The generality of the new rearrangement was next tested by using substituent such as cinnamyl. Cinnamyl cyanoacetate **542** was synthesized by reaction of ethyl cyanoacetate **510** in the presence of sodium hydride with cinnamyl chloride **541** in DMF. The double alkylated product **543** was present. The two products were separated by using column chromatography (**Scheme 4.19**).



510 541 542 543

Scheme 4.19

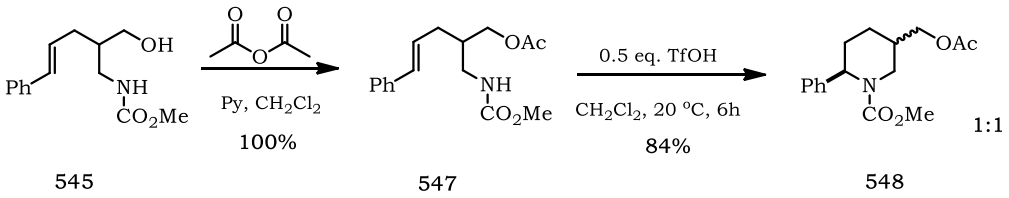
Cinnamyl cyanoacetate **542** was then converted into the amino-alcohol **544** by a standard lithium aluminium hydride redaction. Finally, carbamate was added by using methyl chloroformate in the presence of triethylamine at ice temperature; all of these reactions proceeded in good yields. The cyclisation 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 diasteroisomers, 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)**.



542 544 545 546

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 diasteroisomers. 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**).

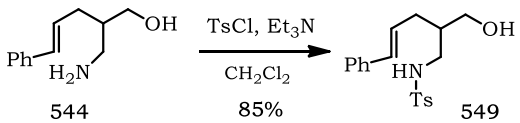


545 547 548

Scheme 4.21

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.

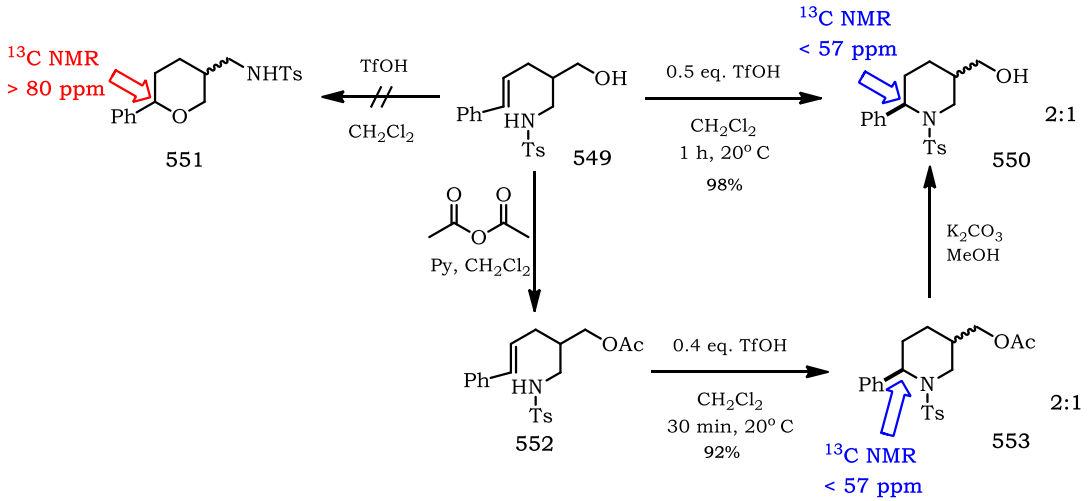
We found in Chapter 2 (p.50), the steric hindrance was the key reason behind the tosyl and nosyl substituted piperidine rearrangements to pyrrolidines as the tosyl and nosyl groups are bulky groups. To study the effect of sufonamide on this new *N*- to *O*-rearrangement, sulfonamide **549** was synthesized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



544 549

Scheme 4.22

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 diasteroisomers. The ^{1}H NMR spectrum showed no starting material was present by the disappearance of the olefinic protons at δ_H 5.87 and 5.58 and the NH proton at δ_H 4.70 ppm with the increasing in the complexity of the spectrum. Two new low field resonances were visible at δ_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 δ_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 δ_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 δ_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-pheny 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

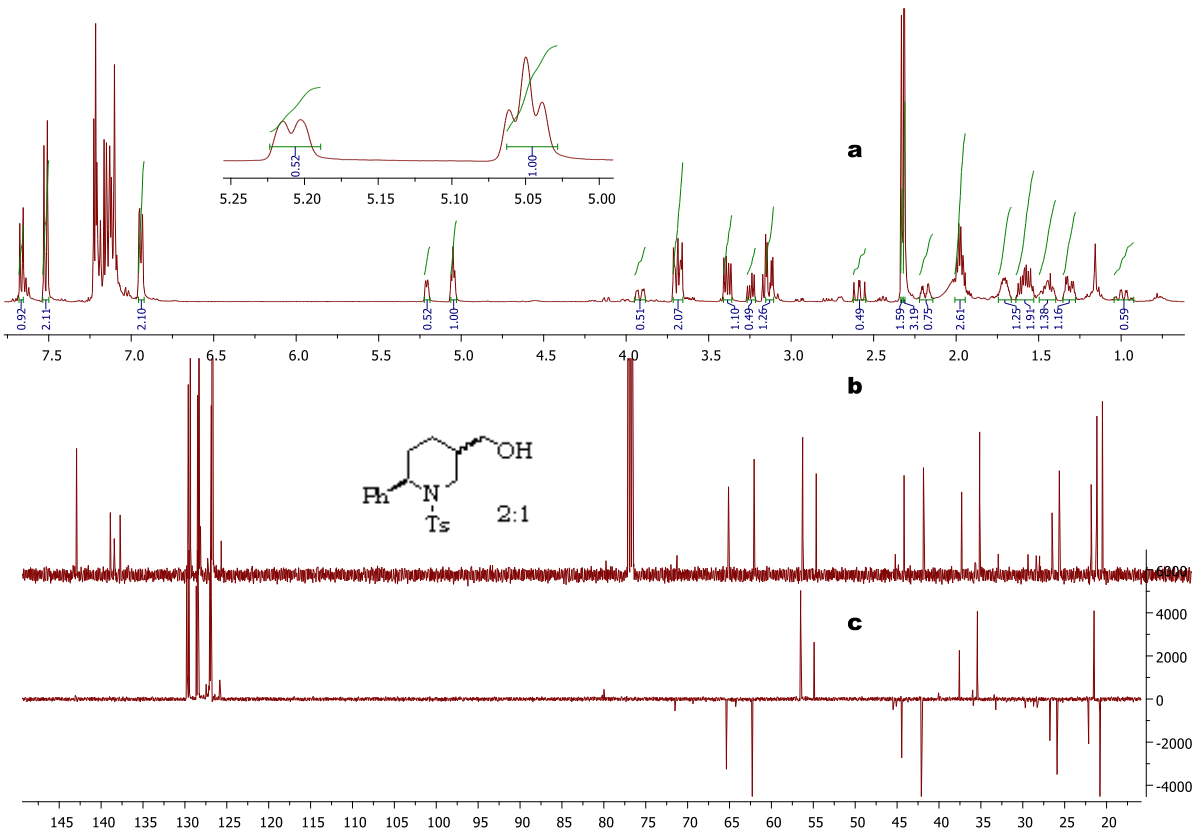
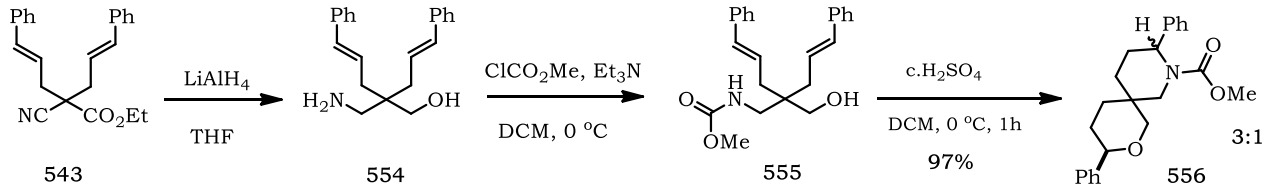


Fig 4.7 ^{1}H and ^{13}C NMR spectra of (6-phenyl-1-tosylpiperidin-3-yl)methanol **550**

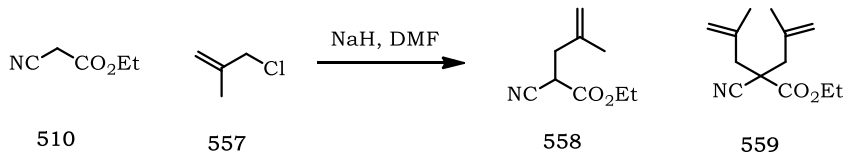
a) proton, b) decoupled ^{13}C, c) DEPT CH, CH_3 positive; CH_2 negative.

The double cinnamyl product **543** was reduced by lithium aluminium hydride to amino-alcohol **554,** then selective addition of CO_2Me 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 ^{o}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

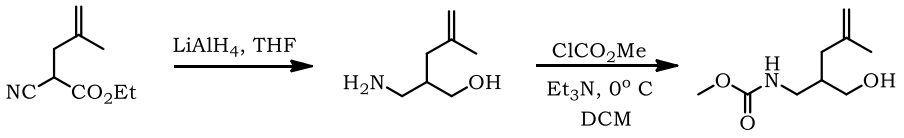
Following these successful results, a logical extension of this methodology was its application to some pyrrolidines and tetrahydrofurans syntheses and the pattern of this rearrangement. Therefore, the cyclisation precursor was prepared from the reaction of 3-chloro-2-methylprop-1-ene **557** with ethyl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



510 557 558 559

Scheme 4.25

The cyanoacetate **558** was reduced by lithium aluminium hydride to γ-amino alcohol **560**. By selective addition of CO_2Me to nitrogen over oxygen unsaturated amino-alcohol **561** was synthesized. (**Scheme 4.26**).

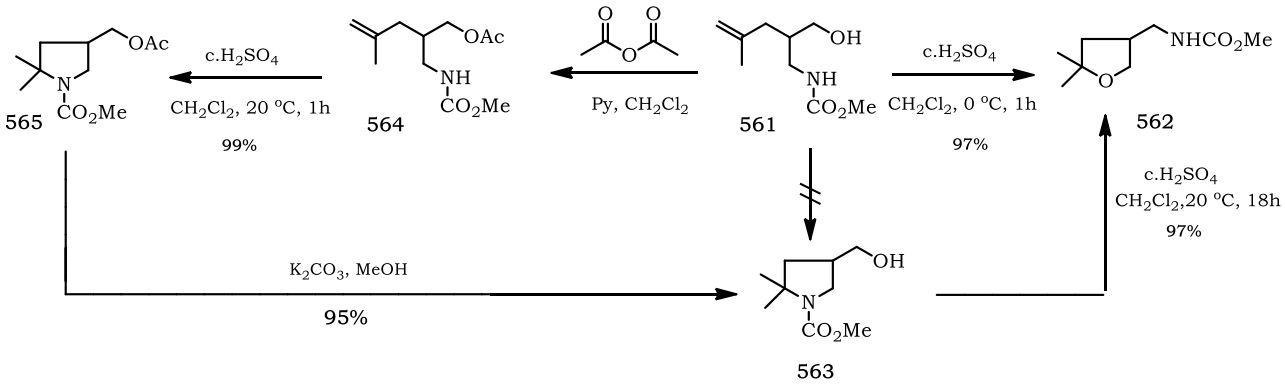


558 560 561

Scheme 4.26

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}H NMR, There was no trace of starting material **561:** both olefinic protons $=CH_2$ at δ_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}H NMR spectrum and there were three sharp methyl singlets related to methyl carbamate at δ_H 3.60 ppm and two methyl groups on quaternary carbon at δ_H 1.23 and 1.12 ppm. The ^{13}C NMR showed a quaternary carbon next to the oxygen atom at δ_C 80.9 ppm and three $\underline{C}H_2$ carbons one next to oxygen at δ_C 69.9 ppm, one next to nitrogen at δ_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 δ_H 4.92 ppm and olefinic protons $=CH_2$ at δ_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 δ_C 60.9 ppm and three $\underline{C}H_2$ carbons one next to oxygen at δ_C 65.8 ppm and two on the pyrrolidine ring at δ_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

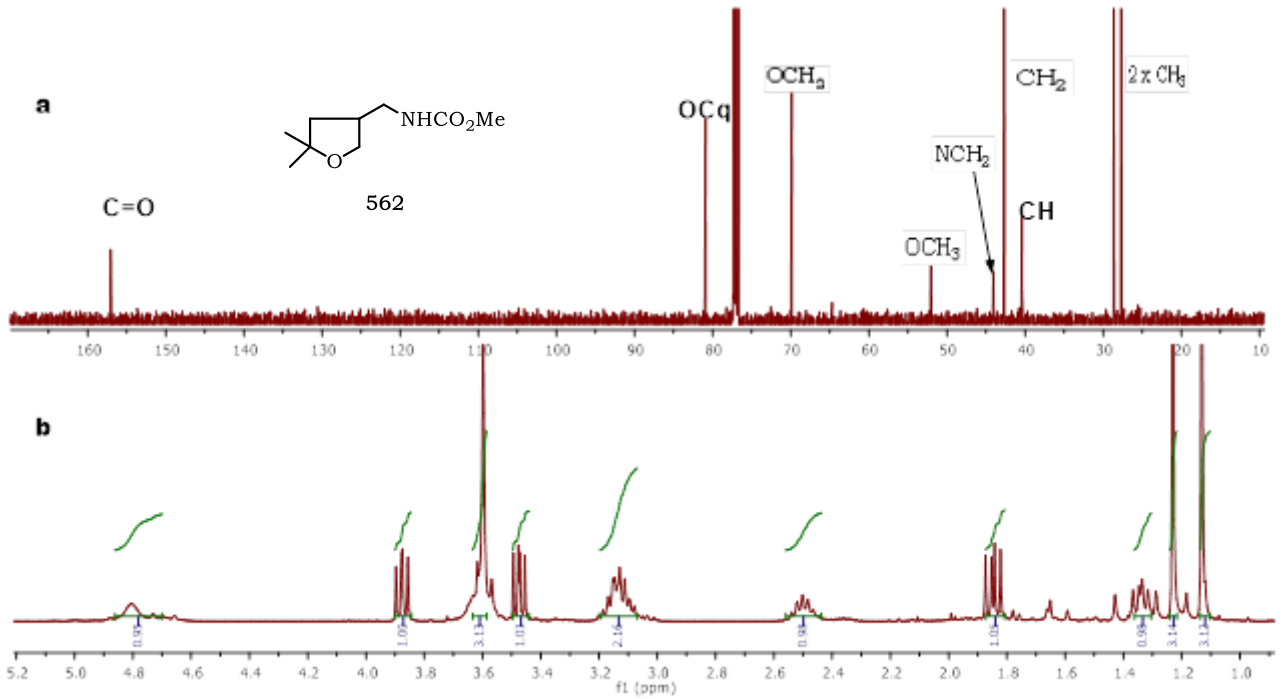
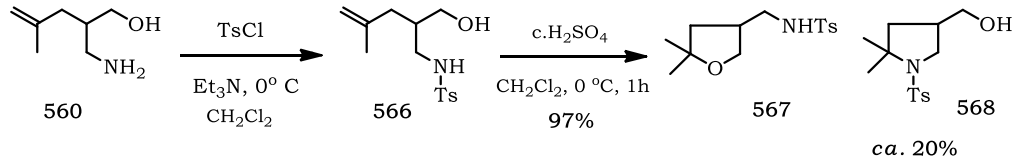


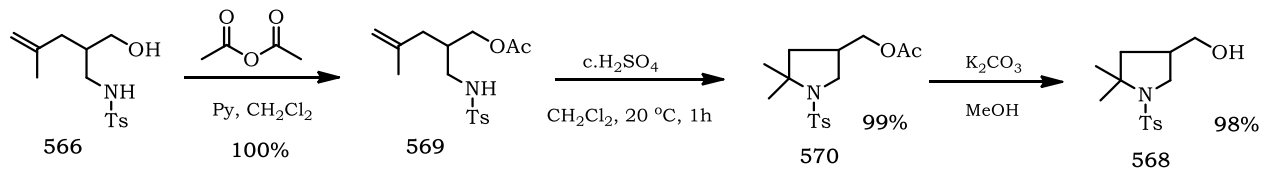
Fig 4.8 ^{1}H and ^{13}C NMR spectra of tetrahydrofuran **562** a) decoupled ^{13}C, b) proton.

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 ^{o}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 ^{1}H NMR resonances corresponding to the tosyl group. There was no trace of any starting material **566** as the olefinic protons at δ_H 4.76 and 4.67 ppm had disappeared. There were two methyl singlets related to methyl tosyl *ca*. 2.34 ppm in ^{1}H NMR spectrum. The key quaternary carbon (OCq) at δ_C 81.0 ppm related to tetrahydrofuran **567** and another small quaternary carbon (NCq) at δ_C 65.0 ppm referred to pyrrolidine **568** (**Scheme 4.28**).



Scheme 4.28

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 ^{1}H and ^{13}C NMR spectra. In ^{1}H NMR, all NH proton at δ_H 4.95 ppm and olifinic protons =CH_2 at δ_H 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 ^{13}C NMR showed a quaternary carbon next to the nitrogen atom at δ_C 65.5 ppm and three $\underline{C}H_2$ carbons one next to oxygen at δ_C 64.4 ppm and two on the pyrrolidine ring at δ_C 51.8 (NCH_2) and 45.6 ppm. One CH carbon at 38.0 ppm (**Fig 4.9** and **Scheme 4.29**).



Scheme 4.29

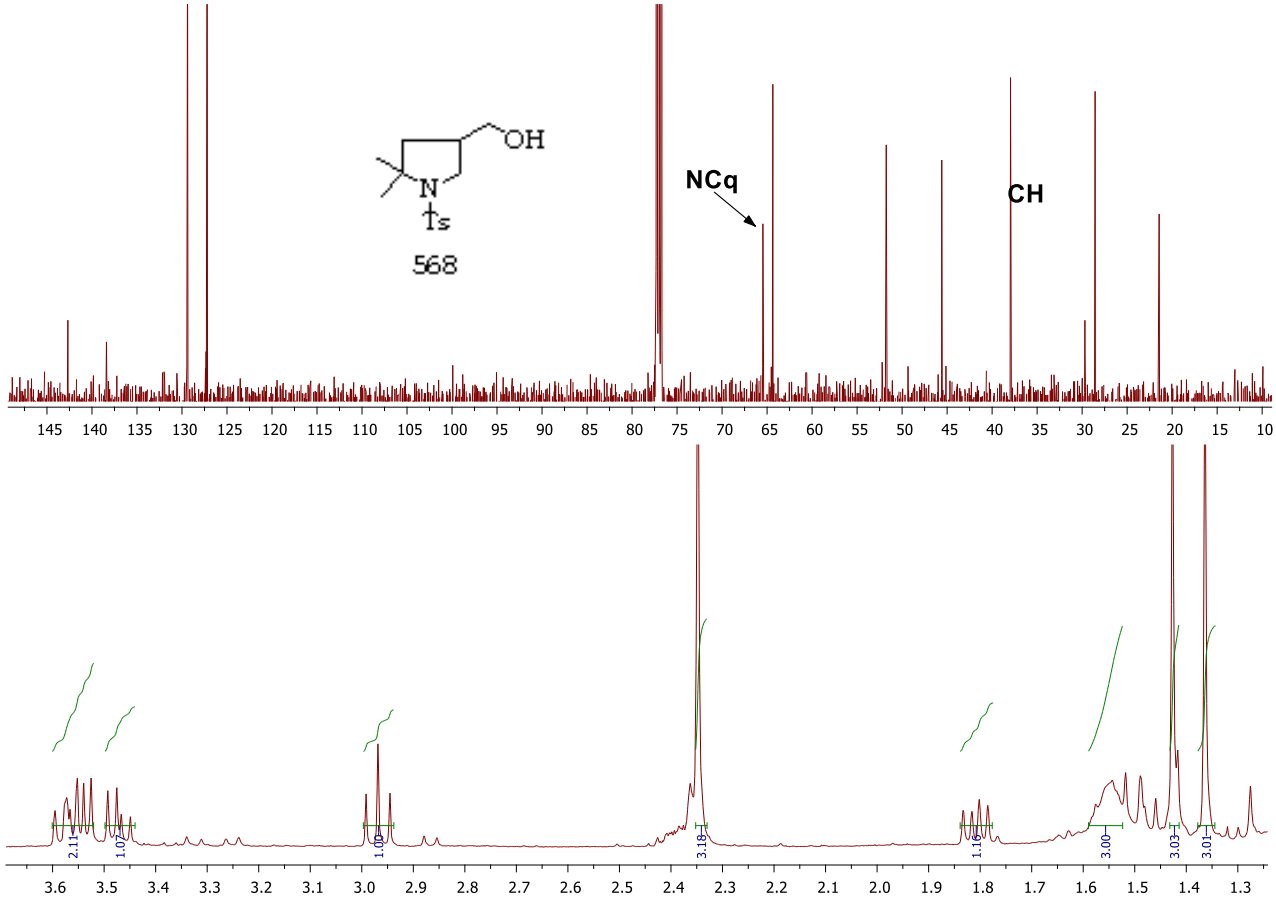
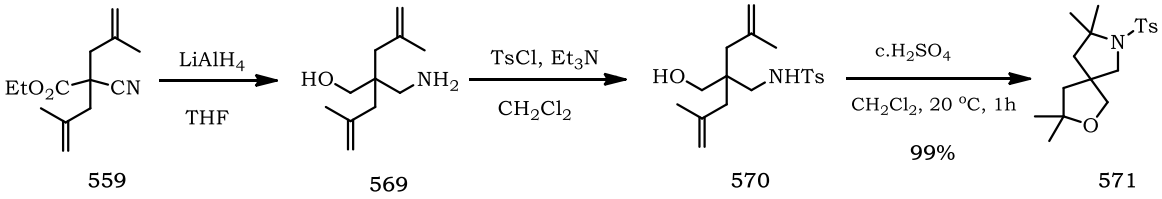


Fig 4.9 ^{1}H and decoupled ^{13}C NMR spectra of pyrrolidine methanol **568.**

Spirocyclic Frameworks

Spirocyclic framework structures have a well-defined three-dimensional spatial arrangement that exhibit specificity of action with biological receptors and enzymes.[5] 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 oxa-azaspiro[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 $\underline{C}H_2$ 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, 21.5ppm (**Fig 4.10, Scheme 4.30 and Table 4.3**).



Scheme 4.30

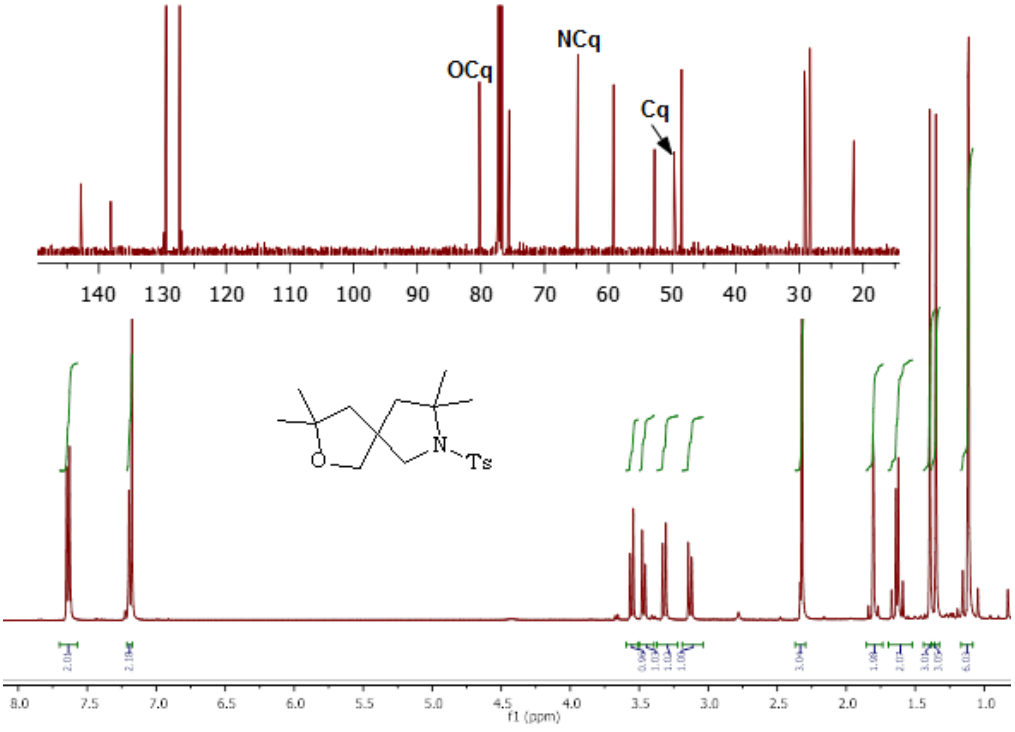
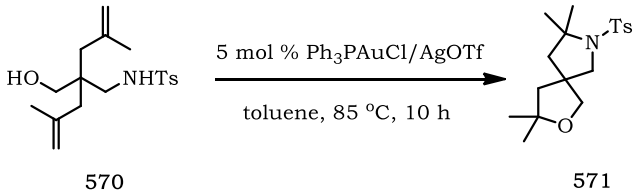


Fig 4.10 ^{1}H and decoupled ^{13}C NMR spectra of oxa-azaspiro[4.4]nonane **568**

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 intrarmolecular hydroamination/hydroalkoxylation of olefin **570** to give oxa-azaspiro **571** after ten hours of reaction with a catalytic amount of $Ph_3PAuOTf$ (generated by mixing equal equivalents of Ph_3PAuCl and AgOTf) at 85 ^{o}C in toluene (**Scheme 4.31** and **Table 4.3**).



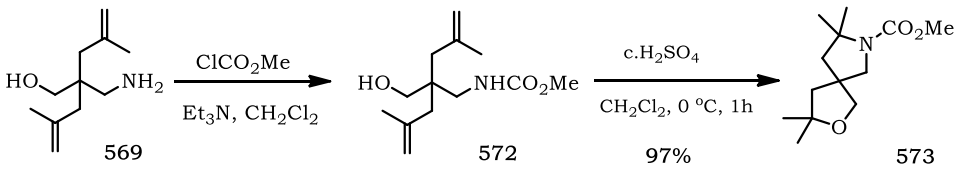
570 571

Scheme 4.31

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

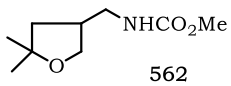
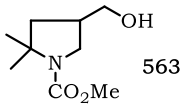
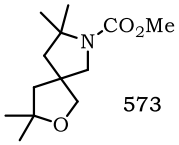
^{13}C ppm	Cq	CH	OCH_2	NCH_2	CH_2	CH_3
Chuan He	142.9 and 137.9 OCq : 80.2 NCq : 64.7 *spiro* Cq : 49.4	129.4 (2 x CH) 127.3 (2 x CH)	75.4	59.1	52.5 48.5	29.1, 29.1, 29.0, 28.3, 21.5
D. W. Knight	142.8 and 138.1 OCq : 80.2 NCq : 64.8 *spiro* Cq : 49.7	129.4 (2 x CH) 127.3 (2 x 2H)	75.6	59.2	52.7 48.5	29.2, 29.1, 29.0, 28.3, 21.5

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 δ_C 79.9 ppm, a quaternary carbon next to the nitrogen at δ_C 60.3 and *spiro*-quaternary carbon at 48.2 ppm. Four $\underline{C}H_2$ carbons one next to oxygen at δ_C 75.8 ppm, one next to nitrogen at δ_C 58.2 ppm and two on the rings at δ_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**.



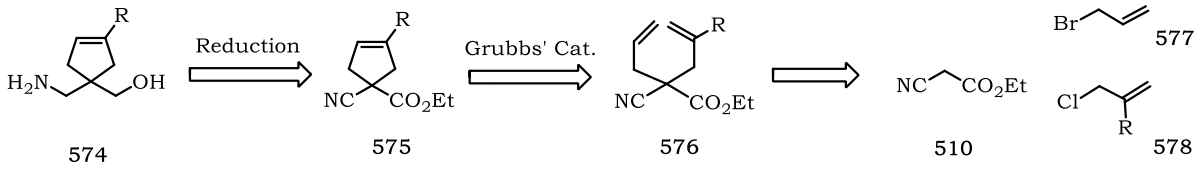
Scheme 4.32

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

^{13}C NMR ppm / Structure	Cq	CH_2	CH_3
 562	C=O : 157.2 OCq : 80.9	OCH_2 : 69.9 NCH_2 : 44.1 42.7	OCH_3 : 52.8 28.7 and 27.7
 563	C=O : 157.5 NCq : 60.9	OCH_2 : 64.8 NCH_2 : 50.5 29.8	OCH_3 : 51.8 25.6 (2 x CH_3)
 573	C=O : 153.8 OCq : 79.9 NCq : 60.3 *spiro*-Cq : 48.2	OCH_2 : 75.8 NCH_2 : 58.2 50.7 and 50.0	OCH_3 : 51.8 29.4, 28.8, 27.2 and 26.8

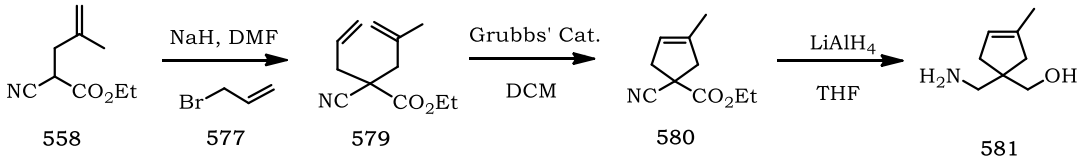
Transannular Cyclisations

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[7] 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

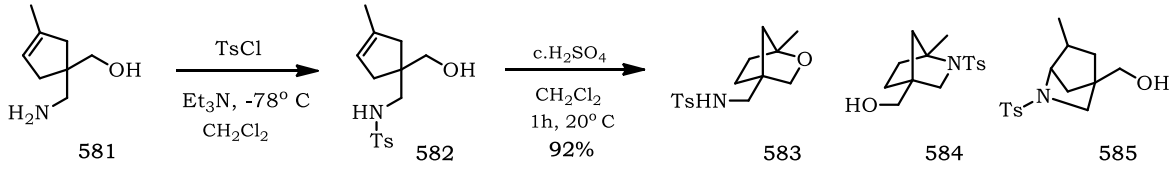
It was decided to first focus on a simplified model, with the transannular precursor simplified to a methyl group. Synthesising this methyl model **558** was achieved as before (**Scheme 4.25**), followed a second allylation by allyl bromide **577** in the presence of sodium hydride to give substituted 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 compatable 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

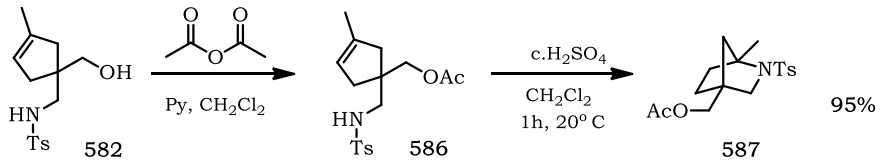
Sulfonamide **582** was prepared by selective addition of tosyl to nitrogen over oxygen in a similar way as described before. When sulfonamide **582** was subjected to a catalytic amount of sulfuric acid in dry dichloromethane, the starting material disappeared after just one hour of reaction at

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 δ_H 5.06 ppm had disappeared. The resonances corresponding to the tosyl group about δ_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 δ_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**).



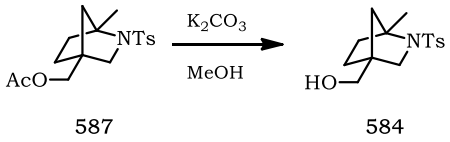
Scheme 4.35

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 δ_H 5.09 and NH proton at δ_H 4.99 ppm had disappeared to confirm the complete reaction. The ^{13}C NMR showed a quaternary carbon next to the nitrogen at δ_C 70.8 ppm, another quaternary carbon at δ_C 46.8 ppm and five $\underline{C}H_2$ carbons, one next to oxygen at δ_C 65.5 ppm, one next to nitrogen (NCH_2) at δ_C 58.5 ppm. Clearly, three $\underline{C}H_2$ carbons could be seen; one between two quaternaries at δ_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**).



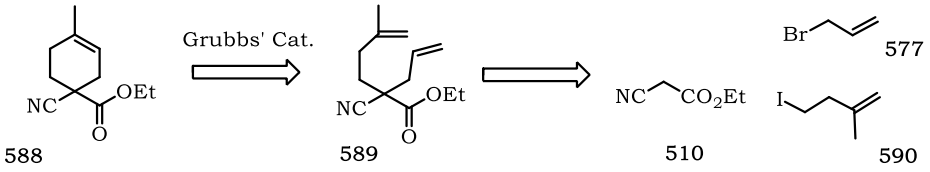
Scheme 4.36

A pure authentic sample of pyrrolidine **584 (Scheme 4.35**) was synthsized after the alcohol group was deprotected. The ^{1}H NMR showed a new ABX system reflexed the coupling between OCH_2 protons with hydroxyl group at δ_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 δ_C 70.9 ppm, another quaternary carbon at δ_C 49.2 ppm. The $\underline{C}H_2$ carbon next to oxygen was at δ_C 64.4 ppm, which showed no big difference comparing with $\underline{C}H_2$ carbon next to oxygen in protecting alcohol **587** at δ_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**)**.**



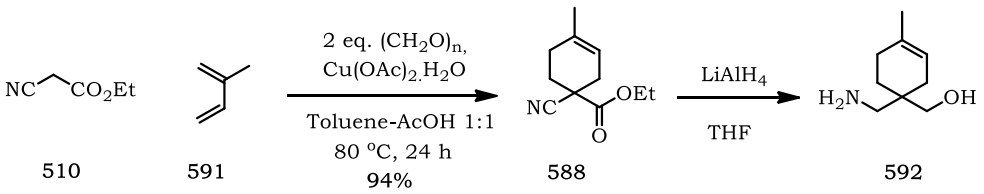
Scheme 4.37

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**).



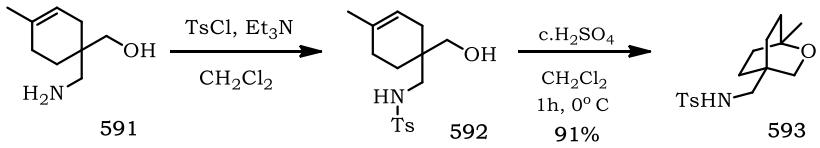
Scheme 4.38

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.[8] 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 ^{o}C in toluene-acetic acid 1:1 gave methyl cyanocyclohexene carboxylate **588** in excellent yield 94% (**Scheme 4.39**).[9]



Scheme 4.39

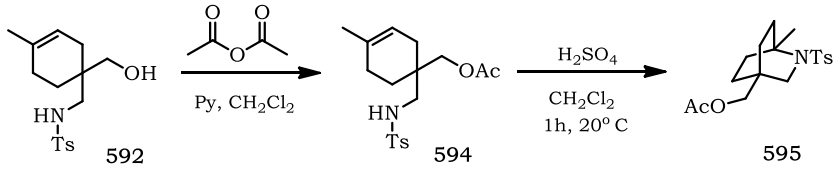
Sulfonamide **591** was prepared after selective addition of tosyl to nitrogen over oxygen. The cineol framework **592** could be formed from in excellent yield (91%) after just one hour of reaction with concentrated sulfuric acid at ice temperature. In ^{1}H NMR spectrum, the NH proton was still visible and there were two sharp methyl singlets related to methyl tosyl at δ_H 2.25 ppm and one methyl group on quaternary carbon at δ_H 0.90 ppm. The ^{13}C NMR showed two quaternary carbons; one next to the oxygen atom (OCq) at δ_C 69.1 ppm and another at 32.4 ppm. Six $\underline{C}H_2$ carbons one next to oxygen at δ_C 71.7 ppm one next to nitrogen at δ_C 49.4 ppm, four on the rings, which showed a plane of symmetry at δ_C 32.1 (2 x CH_2), 28.0 (2 x CH_2) ppm (**Scheme 4.40**).



Scheme 4.40

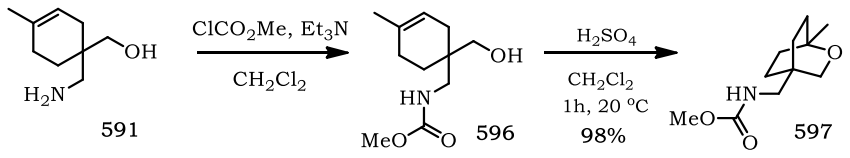
When the alcohol group was protected as the corresponding acetate **594**, then only the azabicyclo-octane **595** was formed at room temperature, which was distinguished by its ^{1}H and ^{13}C NMR

spectra. In ^{1}H NMR, both olefinic proton (=CH) at δ_H 5.14 ppm and NH proton at δ_H 4.98 ppm had disappeared to confirm complete reaction. Three methyl signals could be seen clearly; aryl methyl at δ_H 2.36 ppm, methyl acetyl at δ_H 2.01 ppm and one methyl on quaternary carbon at δ_H 1.27 ppm. The stability of acetate was confirmed by infrared spectroscopy, which showed an absorption band at υ/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 δ_C 55.2 ppm and another at 34.0 ppm. Six $\underline{C}H_2$ carbons one next to oxygen at δ_C 69.4 ppm, one next to nitrogen at δ_C 53.8 and four the rings at δ_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 quantitive yield (98%) after just one hour of reaction with concentrated sulfuric acid at room temperature. In ^{1}H NMR spectum the NH proton was still visible and there were two sharp methyl singlets related to methyl carbamate at δ_H 3.61 ppm and one methyl group on quaternary carbon at δ_H 1.02 ppm (**Fig 4.9**). The ^{13}C NMR showed three quaternary carbons; a carbonyl carbon at δ_C 157.2 ppm, one next to the oxygen atom (OCq) at δ_C 68.9 ppm and another at 33.0 ppm. Six $\underline{C}H_2$ carbons one next to oxygen at δ_C 71.7 ppm one next to nitrogen at δ_C 47.1 ppm, four on the rings, which showed a plane of symmetry at δ_C 32.1 (2 x CH_2), 27.8 (2 x CH_2) ppm. Two methyl carbamate (OCH_3) was at δ_C 52.1 ppm and one methyl carbon on quaternary carbon at δ_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 δ_H 3.71 – 3.49 ppm) whose resonance is the carbon next to oxygen at δ_C 71.7 ppm. The cross peak between the carbon next to nitrogen at δ_C 47.1 ppm resonates the two protons whose appearance is as doublets at δ_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 δ_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 δ_C 32.1 (2 x CH_2) and 27.8 (2 x CH_2) ppm (**Fig 4.11**).

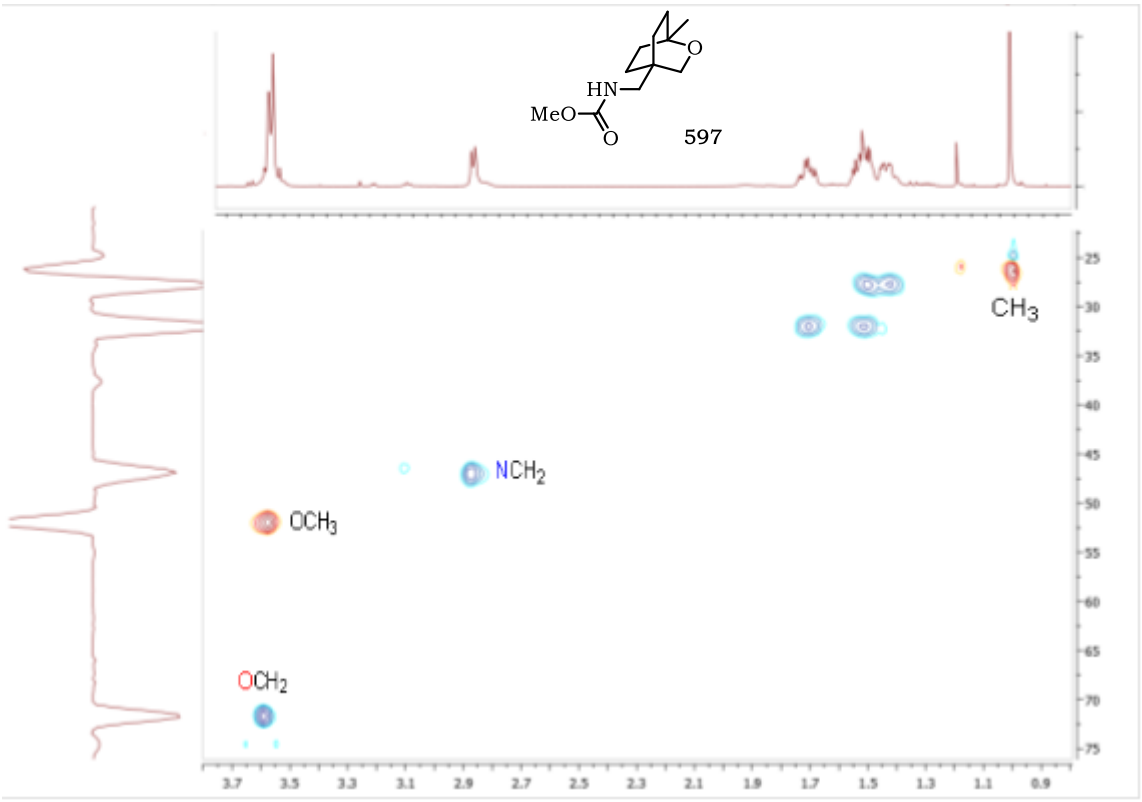
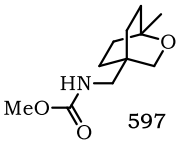


Fig 4.11 ^{1}H ^{13}C COSY analysis oxabicyclo-octane **597.**

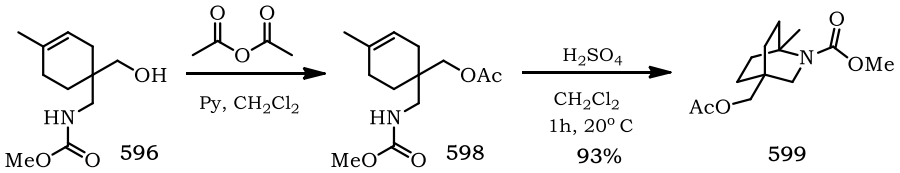
The oxabicyclo-octane **597** was very pure and crystallized by itself and the structure was confirmed by X-ray crystallography **(Fig 3.12).**



597

Fig 3.12 The X-ray structure of oxabicyclo-octane **597.** Full crystallographic data is included in the **Appendix 8**.

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 δ_H 3.55 ppm, methyl acetyl at δ_H 1.97 ppm and one methyl on quaternary carbon at δ_H 1.42 ppm. (**Scheme 4.43**)**.**



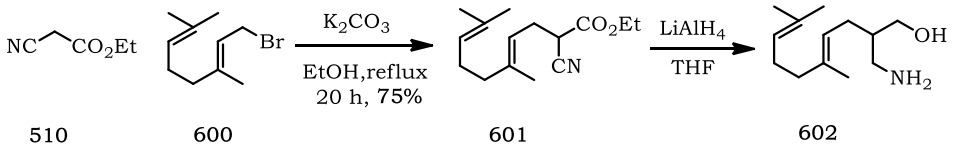
Scheme 4.43

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

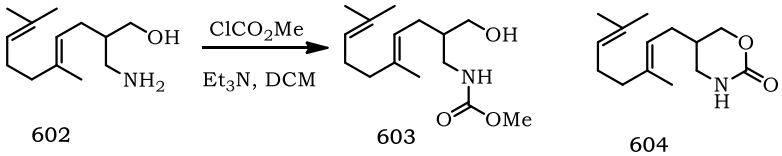
As hydroquinolines were studied before in Chapter 3, it was decided to see if such methodology would be extended to the formation of six membered rings by using cascade cyclisations.

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)**.



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 δ_H 5.08 ppm and two olefinic protons at δ_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 δ_C 70.2 ppm, one next to nitrogen atom at δ_C 45.3 ppm and three CH_2 carbons next to double bonds at δ_C 39.7, 27.3 and 26.5 ppm **(Scheme 4.45)**.



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**).

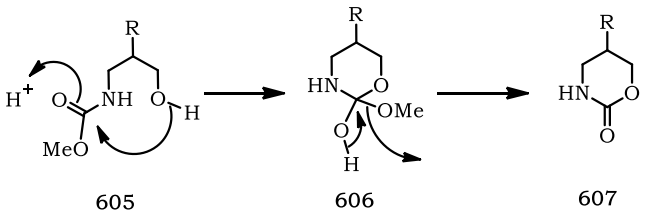
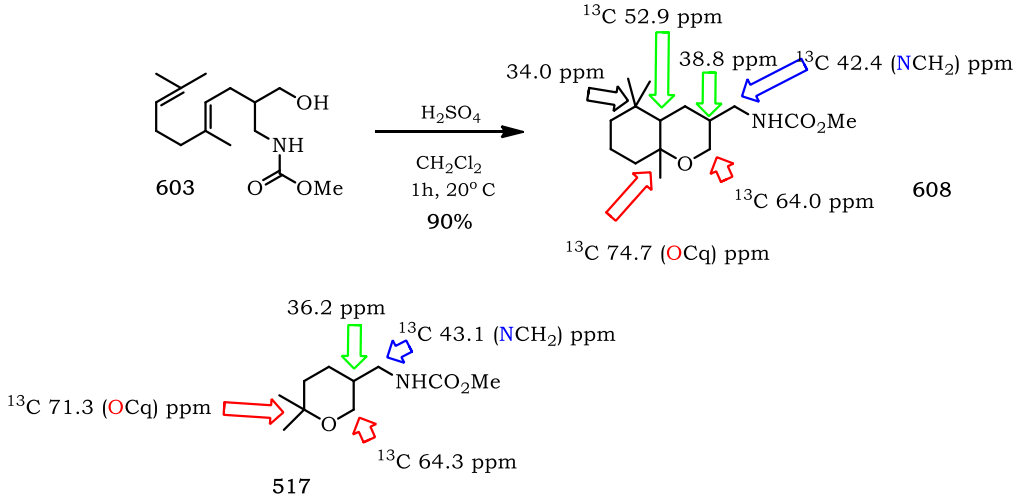


Fig 3.13

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 synthsized 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 δ_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 δ_C 157.2 (C=O), 74.7 (OCq), and 34.0 ppm, six CH_2 signals δ_C 64.0 (OCH_2), 42.4 (NCH_2), 41.5, 40.0, 23.6 and 21.1 ppm and two CH carbons at δ_C 52.9 and 38.8 ppm **(Scheme 4.46)**.



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 dowon. 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.

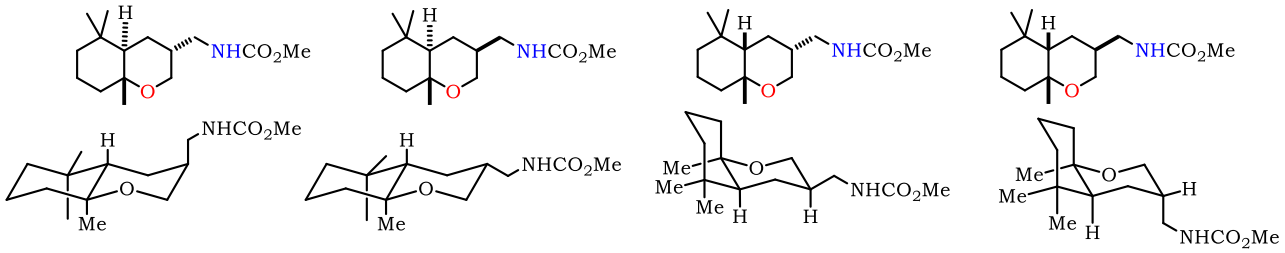
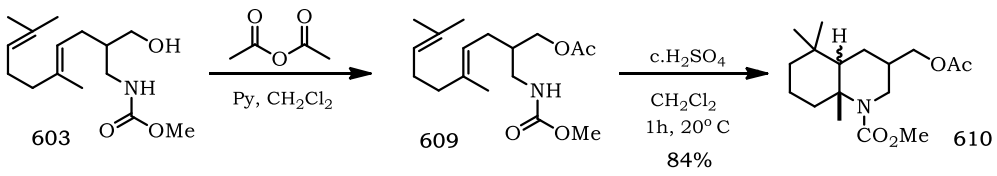


Fig 3.14

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 δ_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 δ_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 δ_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 δ_C 66.8 (OCH_2), 44.3 (NCH_2), 41.2, 38.5, 32.8 and 22.9 ppm (**Scheme 4.47**).

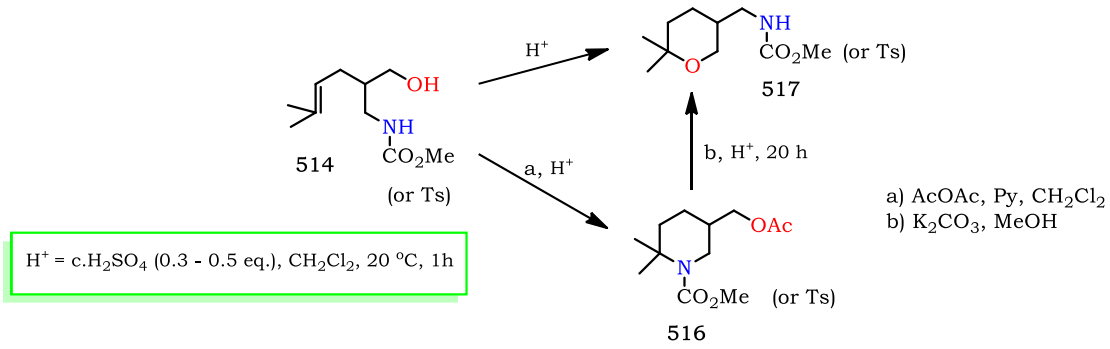


Scheme 4.47

Thus, octahydro-chromene and perhydroquinoline skeletons were synthsized directly from the corresponding geranyl amino-alcohols in excellent yields after only one hour of reaction with catalytic amounts of sulfuric acid.

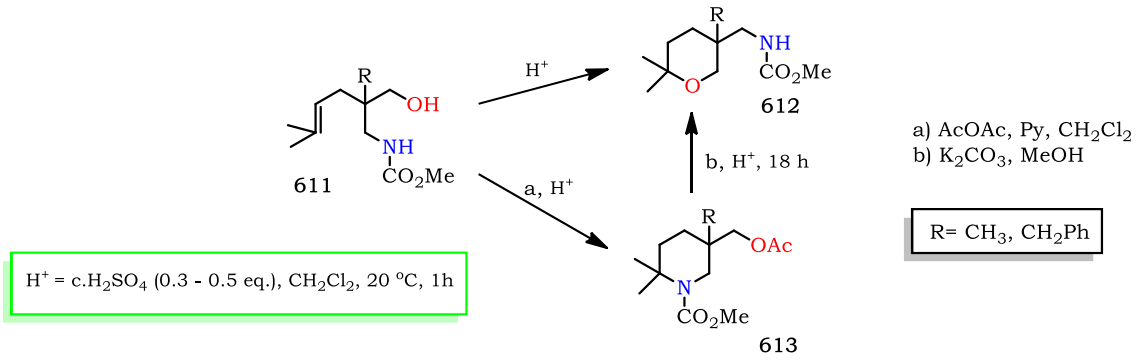
Conclusions:

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.



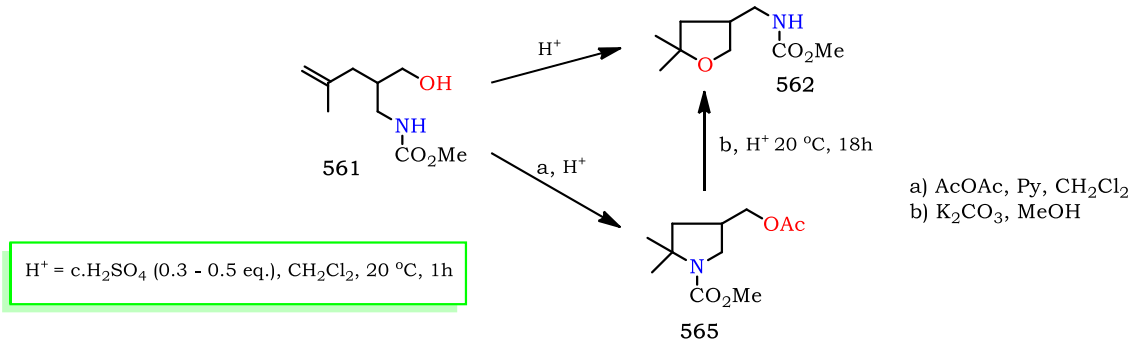
Scheme 4.48

The inclusion of additional substituents (R = CH_3 and CH_2Ph) has no obvious affect on the reactions (**Scheme 4.49**).



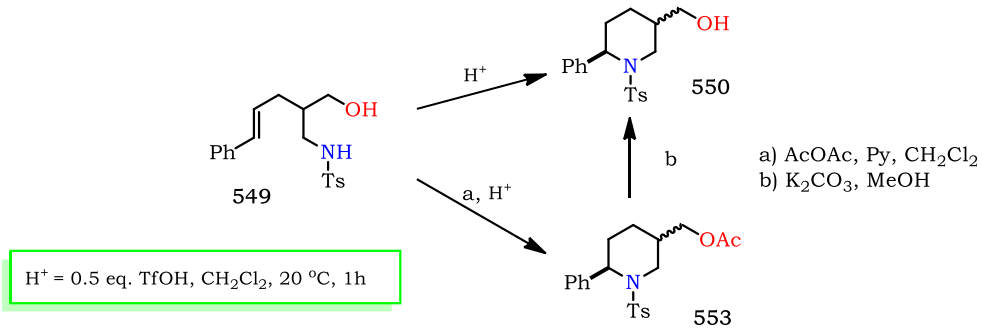
Scheme 4.49

Exactly the same occurred with the corresponding five-membered rings (**Scheme 4.50**).



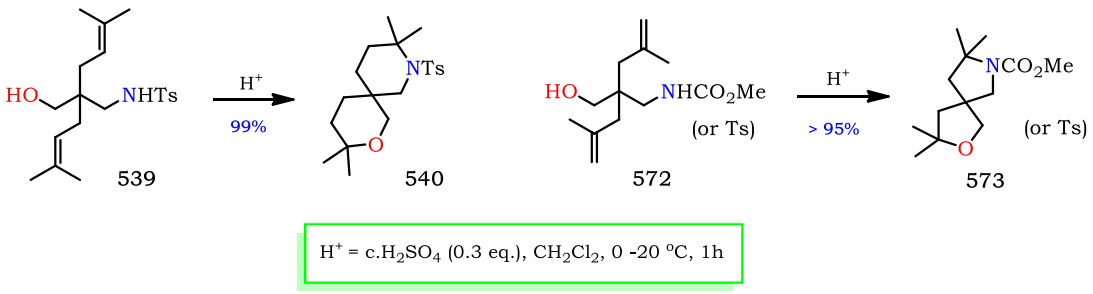
Scheme 4.50

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**).



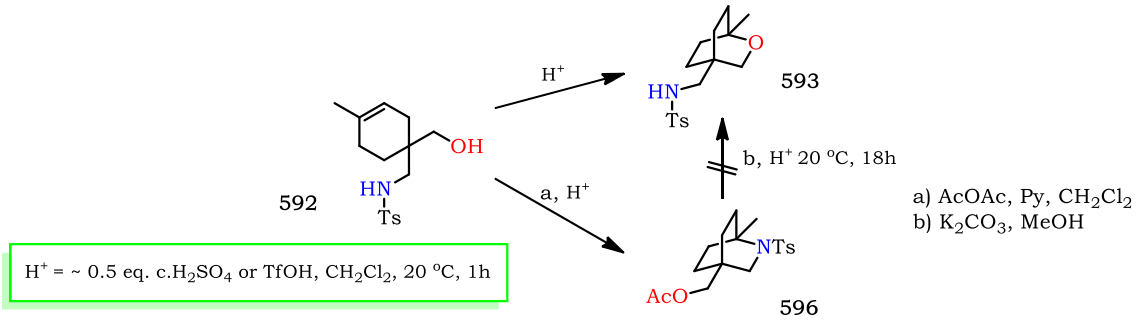
Scheme 4.51

The synthesis of *spiro*-compounds was achieved by double acid-catalysed cyclization reactions (**Scheme 4.52**).



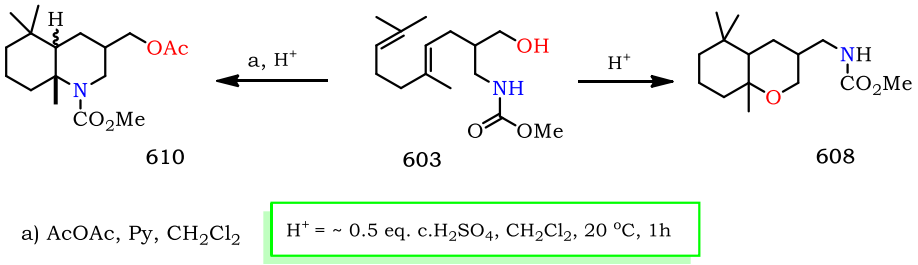
Scheme 4.52

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 4.53

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*- → *O*-rearrangement gave mixed results and were not clean.

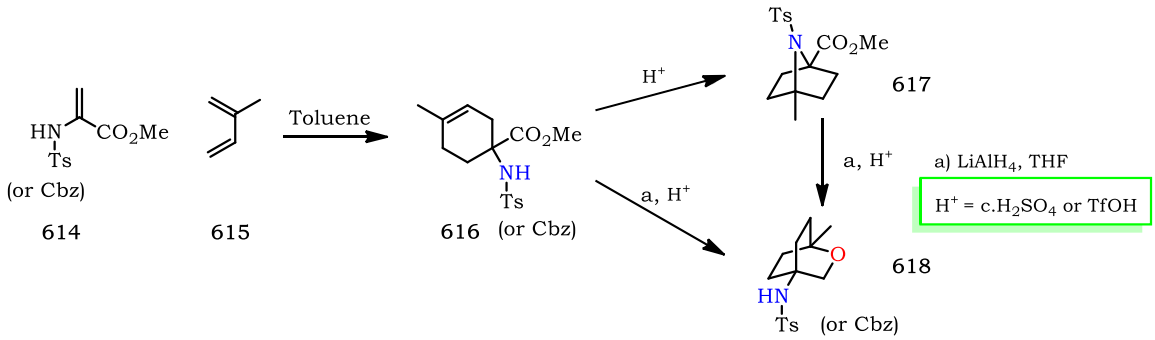


Scheme 4.54

Future work:

1- Amino acid derivatives:

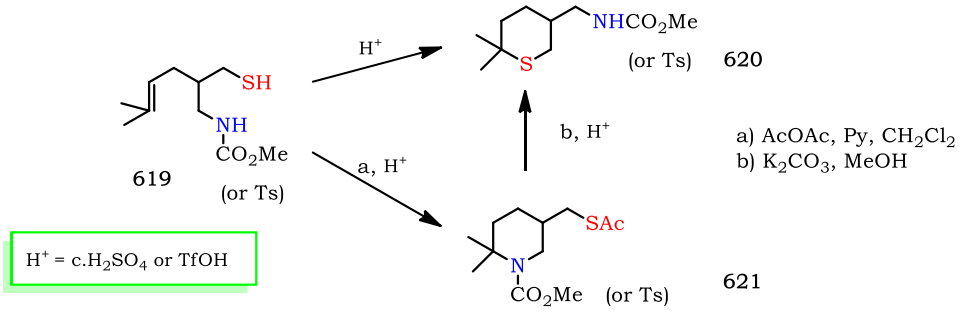
The cyclohexenes **616** derived from dehydroalanine **614** by Diles-Alder cyclisation should cyclise to give the proline homologues **617** which may well undergo subsequent rearrangement to the *O*-heterocycles **618**, following reduction (**Scheme 4.55**). The incorporation of more substituents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



Scheme 4.55

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

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

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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}).

^1H NMR spectra (δ_H) were recorded using an Avance Bruker DPX 400 (400 MHz). ^{13}C NMR spectra (δ_H) were recorded using an Avance Bruker DPX 400 (500 MHz), with ^{13}C NMR spectra (δ_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 Protiction by Ts, Ns, CO_2Me 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 H_2SO_4.

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.

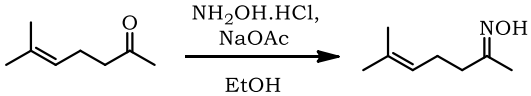
General Procedure C: Reductions of oximes or cyanoacetates to the corresponding amines or amino-alcohols using lithium aluminium hydride; typical method.

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[5]



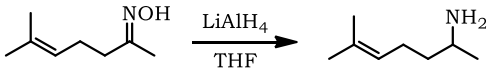
233 234

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 ^{o}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:[5] δ_H 9.75 – 8.00 (*br*. s, NOH), 5.30–5.00 (m, 1H, =CH), 2.24 – 2.10 (m, 4H, 2 × CH_2), 1.91 (2 x s, 3H, *E:Z* isomers 3:1 ratio, CH_3),* 1.70 (s, 3H, CH_3), 1.63 (s, 3H, CH_3). δ_C 158.7 (Cq), 132.7 (Cq), 122.8 (CH), 35.8 (CH_2), 25.7 (CH_3), 25.0 (CH_2), 17.6 (CH_3), 13.5 (CH_3).

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

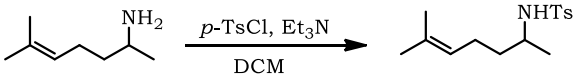
6-Methylhept-5-en-2-amine 235[6]



234 235

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:[6] δ_H 5.10 – 5.00 (m, 1H, =CH), 2.85 (*app*. sext, 1H, *J* = *ca*. 6.5 Hz, NCH), 2.10 – 1.89 (m, 2H, CH_2), 1.60 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.40 – 1.20 (m, 2H, CH_2), 0.95 (d, 3H, *J* = 6.3 Hz, CH_3). δ_C 133.2 (Cq), 124.2 (CH), 46.6 (NCH), 35.9 (CH_2), 25.7 (CH_2), 25.0 (CH_3), 21.0 (CH_3), 17.7 (CH_3).

***N*-(6-Methylhept-5-en-2-yl)-4-methyl benzenesulfonamide 236**[7]

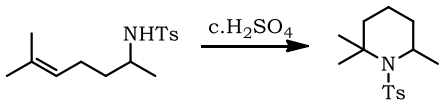


235 236

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 Et_3N (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:[7] δ_H 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, $ArCH_3$), 1.92 – 1.86 (m, 2H, CH_2), 1.51 (s, 3H,

CH_3), 1.45 (d, *J* = 1.3 Hz, 3H, CH_3), 1.30 (dt, *J* = 7.7, 6.5 Hz, 2H, CH_2), 0.97 (d, *J* = 6.5 Hz, 3H, CH_3). δ_C 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 (CH_2), 26.6 ($ArCH_3$), 24.2 (CH_2), 21.7 (CH_3), 21.4 (CH_3), 17.5 (CH_3). IR (neat) υ/cm^{-1}: 3282, 2970, 2924, 1599, 1303, 1150. HRMS (EI) *m/z* calculated for $C_{15}H_{23}NO_2S$ $[M]^+$ = 281.1450; found: 281.1443.

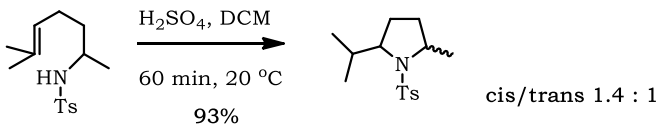
1-Toluenesulfonyl-2,2,6-trimethylpiperidine 237



236 237

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. δ_H 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, $ArCH_3$), 1.84 – 1.75 (m, 2H), 1.70 – 1.65 (m, 1H), 1.53 (s, 3H, CH_3), 1.32 (d, *J* = 6.9 Hz, 3H, CH_3), 1.45 – 1.35 (m, 3H, CH_2 and CH), 1.07 (s, 3H, CH_3). δ_C 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 (CH_2), 30.9 ($ArCH_3$), 30.2 (CH_2), 29.6 (CH_3), 22.6 (CH_3), 22.6 (CH_3), 15.3 (CH_2). IR (neat) υ/cm^{-1}: 2936, 2873, 1599, 1465, 1321, 1158, 1141, 1095. HRMS (EI) *m/z* calculated for $C_{15}H_{23}NO_2S$ $[M]^+$ = 281.1450; found: 281.1453.

(*Cis* and *trans*)-2-Isopropyl-5-methyl-1-tosylpyrrolidine 239

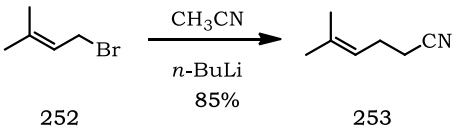


236 239

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 ºC 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).

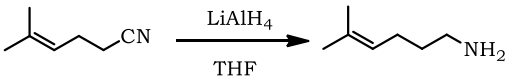
5-Methyl-4-hexenenitrile 253[9]



252 253

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



253 254

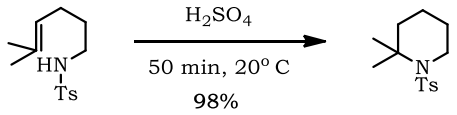
By general procedure C, 5-methyl-4-hexene nitrile **253** (1.90 g, 17 mmol, 1.0 eq.) was reduced using lithium aluminium hydride (0.76 g, 20 mmol, 1.1eq.) to give the *amine* **254** (1.57 g, 83%) as a clear oil, which was used directly in the next step. All data obtained were in accordance with those previously reported in the literature:[8] δ_H 5.04 – 5.10 (m, 1H, =CH), 2.69 – 2.44 (m, 2H, CH_2N), 1.90 – 2.08 (m, 2H, CH_2), 1.63 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 1.21 – 1.10 (m, 2H, CH_2). δ_C 132.2 (Cq), 122.9 (=CH), 42.8 (CH_2N), 30.3 (CH_2), 25.6 (CH_2), 17.8 (CH_3), 17.6 (CH_3).

***N*-(5-Methylhex-4-en-1-yl)-4-methyl benzenesulfonamide 249**[10]

254 249

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 Et_3N (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, CH_2N), 2.36 (s, 3H, $ArCH_3$), 1.95 – 1.79 (m, 2H, CH_2), 1.58 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.41 (p, *J* = 7.2 Hz, 2H, CH_2). 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 (CH_2N), 29.6 (CH_2), 25.6 ($ArCH_3$), 25.0 (CH_2), 21.5 (CH_3), 17.6 (CH_3). IR (neat) υ/cm^{-1}: 3287, 2928, 2257, 1599, 1323, 1157, 1094, 907, 814. HRMS (EI) *m/z* calculated for $C_{14}H_{21}NO_2S$ $[M]^+$ = 267.1293; found: 267.1287.

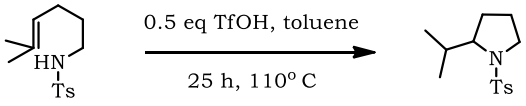
2,2-Dimethyl-1-tosylpiperidine 250[8]



249 250

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] δ_H 7.64 – 7.53 (m, 2H), 7.23 – 7.10 (m, 2H), 3.40 (t, *J* = 6.0 Hz, 2H, CH_2N), 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). δ_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_2N), 41.3 (CH_2), 26.2 ($ArCH_3$), 26.2 (CH_2), 21.4 (2 x CH_3), 20.5 (CH_2). IR (neat) υ/cm^{-1}: 2930, 2866, 1599, 1454, 1157, 1319, 1139, 943, 814, 673. HRMS (EI) *m/z* calculated for $C_{14}H_{21}NO_2S$ $[M]^+$ = 267.1293; found: 267.1287.

2-Isopropyl-1-tosylpyrrolidine 251

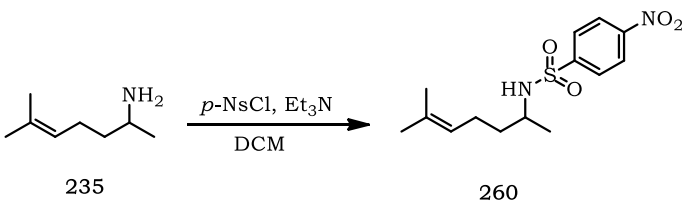


249 251

The sulfonamide **249** (0.14 g, 0.5 mmol) was dissolved in dry toluene (10 ml) and to this triflic acid (76 mg, 46 µl, 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] δ_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, NCH_2), 2.24 (s, 3H, $ArCH_3$), 2.16 – 2.15 (m, 1H, CH), 1.85 (p, *J* = 6.9 Hz, 2H, CH_2), 1.65 – 1.54 (m, 2H, CH_2), 0.85 (d, *J* = 6.0 Hz, 3H, CH_3), 0.81 (d, *J* = 6.8 Hz, 3H, CH_3).

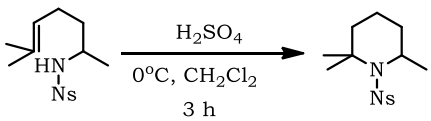
***N*-(6-Methylhept-5-en-2-yl)-4-nitrobenzenesulfonamide 260**



235 260

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 Et_3N (0.8 ml, 4.0 mmol, 1.2 eq.) to give the *nosyl* derivative **260** (0.50 g, 50%). as a clear oil. δ_H 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). δ_C 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 (CH_2), 25.6 (CH_3), 24.2 (CH_2), 21.7 (CH_3), 17.6 (CH_3). IR (neat) υ/cm^{-1}: 3295, 2967, 2922, 2855, 1607, 1530, 1350, 1306, 1160, 1092. HRMS (EI) *m/z* calculated for $C_{14}H_{20}N_2O_4S$ $[M]^+$ = 312.1144; found: 312.1138.

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



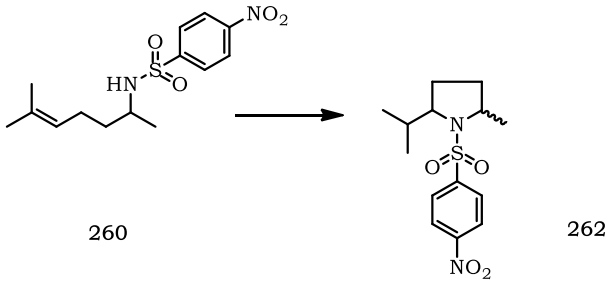
260 261

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. δ_H 8.13 (d, *J* = 8.0 Hz,

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, CH_3), 1.32 (d, *J* = 7.0 Hz, 3H, CH_3), 1.26 – 1.14 (m, 1H), 1.07 (s, 3H, CH_3). δ_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 (CH_2), 30.9 (CH_3), 30.6 (CH_2), 29.0 (CH_3), 23.6 (CH_3), 15.3 (CH_2).

IR (neat) υ/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.

(*Cis* and *trans*)- 2-Isopropyl-5-methyl-1-(4-nitrophenylsulfonyl)pyrrolidine 262

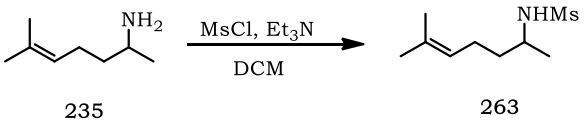


260 262

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 ^oC to give the *pyrrolidine* **262** (137 mg, 94%) (*cis:trans* 2:1 ratio) as a colourless oil. *Cis*-2-isopropyl-5-methylpyrrolidine: δ_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, CH_3), 0.81 (d, *J* = 4.9 Hz, 3H, CH_3), 0.47 (d, *J* = 6.9 Hz, 3H, CH_3). δ_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 (CH_2), 29.7 (CH), 23.4 (CH_2), 21.2 (CH_3), 19.8 (CH_3), 15.3 (CH_3).

Trans-2- isopropyl-5-methylpyrrolidine: δ_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, CH_3), 0.79 (dd, *J* = 6.8, 5.0 Hz, 1H), 0.92 (d, *J* = 6.9 Hz, 3H, CH_3), 0.86 (d, *J* = 6.7 Hz, 3H, CH_3). δ_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 (CH_2), 31.4 (CH), 25.4 (CH_2), 21.2 (CH_3), 20.0 (CH_3), 15.3 (CH_3).

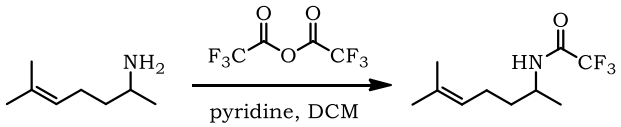
***N*-(6-Methylhept-5-en-2-yl)methanesulfonamide 263**[12]



235 263

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 Et_3N (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:[8] δ_H 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-CH_3), 2.23 – 1.91 (m, 2H, CH_2), 1.87 – 1.69 (m, 2H, CH_2), 1.67 (d, *J* = 1.5 Hz, 3H, CH_3), 1.64 (s, 3H, CH_3), 1.41 (d, *J* = 6.2 Hz, 3H, CH_3).

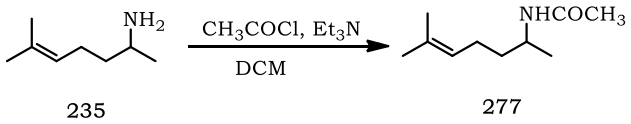
***N*-(6-Methylhept-5-en-2-yl)-2,2,2-trifluoroacetamide 272**



235 272

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%). δ_H 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, CH_2), 1.60 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.50 – 1.45 (m, 2H, CH_2), 1.14 (d, *J* = 6.7 Hz, 3H, CH_3). δ_C 156.6 (q, *J* = 36.6 Hz, Cq), 132.8 (Cq), 123.0 (=CH), 115.9 (q, *J* = 288.0 Hz, CF_3), 46.3 (NCH), 35.9 (CH_2), 25.6 (CH_3), 24.4 (CH_2), 20.1 (CH_3), 17.5 (CH_3). IR (neat) υ/cm^{-1}: 3293, 2978, 2924, 1699, 1557, 1182, 723. HRMS (EI) *m/z* calculated for $C_{10}H_{16}F_3NO$ $[M]^+$ = 223.1184; found: 223.1179.

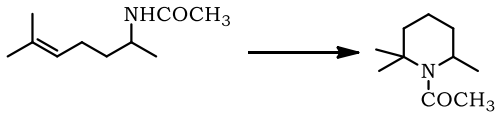
***N*-(6-Methylhept-5-en-2-yl)acetamide 277**



235 277

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_3N (0.6 ml, 5.5 mmol) to give the *acetamide* **277** as a clear oil (0.5 g, 63%). δ_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). δ_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) υ/cm^{-1}: 3269, 2969, 2928, 1722, 1640, 1549, 1441, 1373, 1284. HRMS (EI) *m/z* calculated for $C_{10}H_{19}NO$ $[M]^+$ = 169.1467; found: 169.1463.

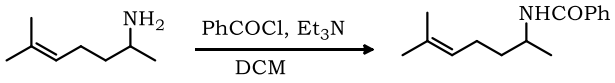
1-Acetyl-2,2,6-trimethylpiperidine 278



277 278

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%). δ_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). δ_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) υ/cm^{-1}: 3293, 2964, 2934, 2870, 1672, 1549, 1448, 1373, 1259, 1161, 1089, 1012, 910, 796, 731. HRMS (EI) *m/z* calculated for $C_{10}H_{19}NO$ $[M]^+$ = 169.1467; found: 169.1466.

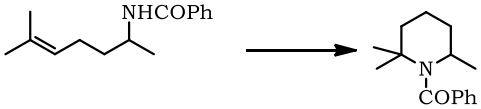
***N*-(6-Methylhept-5-en-2-yl)benzamide 285**



235 285

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 Et_3N (0.6 ml, 5.5 mmol, 1.1 eq.) to give the *benzamide* **285** (0.83 g, 72%) as a clear oil. δ_H 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, CH_2), 1.60 (d, *J* = 1.4 Hz, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.48 - 1.52 (m, 2H, CH_2), 1.16 (d, *J* = 6.5 Hz, 3H, CH_3). δ_C 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 (CH_2), 25.7 (CH_3), 24.70 (CH_2), 21.0 (CH_3), 17.7 (CH_3). IR (neat) υ/cm^{-1}: 3320, 2967, 2931, 1716, 1640, 1578, 1541, 1491, 1450, 1276, 1161, 910, 723. HRMS (APCI) *m/z* calculated for $C_{15}H_{22}NO$ $[M+H]^+$ = 232.1701; found: 232.1712.

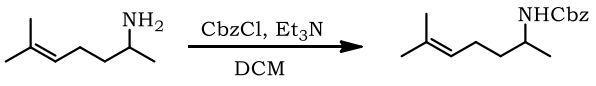
1-Benzoyl-2,2,6-trimethylpiperidine 286



285 286

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%). δ_H 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 CH_2), 1.39 – 1.33 (m, 2H, CH_2), 1.16 (d, 3H, *J* = 6.5 Hz, CH_3), 1.12 (s, 3H, CH_3), 1.11 (s, 3H, CH_3). δ_C 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 (CH_2), 29.4 (Ac-CH_3), 25.7 (CH_3), 24.7 (CH_2) 21.0 (2 x CH_3), 20.7 (CH_2). IR (neat) υ/cm^{-1}: 3302, 2963, 2930, 1717, 1603, 1578, 1537, 1491, 1271, 1160, 910, 731. HRMS (APCI) *m/z* calculated for $C_{15}H_{22}NO$ $[M+H]^+$ = 232.1701; found: 232.1701.

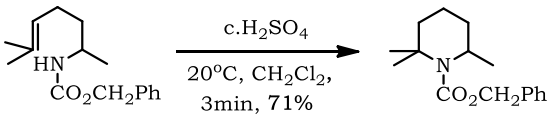
Benzyl *N*-(6-methylhept-5-en-2-yl)carbamate 294



235 294

By general procedure A, benzyl chloroformate (0.95 g, 5.5 mmol, 1.1 eq.) was added to the amine **235** (0.60 g, 5.0 mmol, 1.0 eq.) and Et_3N (0.6 ml, 5.5 mmol, 1.1 eq.) to give the *Z-carbamate* **294** as a clear oil (0.90 g, 70%). δ_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_2), 1.64 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 1.42 – 1.28 (m, 2H, CH_2), 1.05 (d, *J* = 7.1, 3H, CH_3). δ_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 (O<u>C</u>H_2Ph), 48.3 (NCH), 39.2 (CH_2), 29.7 (CH_3), 28.3 (CH_2), 27.8 (CH_3), 21.9 (CH_3). IR (neat) υ/cm^{-1}: 2967, 2936, 1696, 1456, 1329, 1290, 1148, 1062, 773, 696. HRMS (EI) *m/z* calculated for $C_{16}H_{23}NO_2$ $[M]^+$ = 261.1729; found: 261.1730.

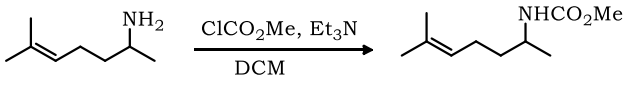
Benzyl 2,2,6-trimethylpiperidine-1-carboxylate 295



294 295

By general procedure B, to carbamate **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 *piperidine* **295** as a colourless oil (92 mg, 71%). δ_H 7.32 – 7.27 (m, 4H), 7.25 – 7.20 (m, 1H), 5.07 (d, *J* = 12.5, 1H, OCH_AH_B), 5.02 (d, *J* = 12.5, 1H, OCH_AH_B), 4.35 – 4.25 (m, 1H, NCH), 1.76 – 1.54 (m, 3H), 1.50 – 1.47 (m, 2H, CH_2), 1.41 (s, 3H, CH_3), 1.40 – 1.37 (m, 1H), 1.32 (s, 3H, CH_3), 1.13 (d, *J* = 6.9 Hz, 3H, CH_3). δ_C 156.1 (Cq), 137.2 (Cq), 128.5 (2 x CH), 127.8 (2 x CH), 127.7 (CH), 66.4 (OCH_2), 54.4 (Cq, 2-C), 48.3 (NCH, 6-CH), 39.2 (CH_2), 29.8 (CH_3), 28.3 (CH_2), 27.8 (CH_3), 21.9 (CH_3), 14.7 (CH_2). IR (neat) υ/cm^{-1}: 2967, 2935, 1695, 1496, 1456, 1329, 1300, 1148, 1063, 1049, 1028, 696. HRMS (APCI) *m/z* calculated for $C_{16}H_{23}NO_2$ $[M]^+$ = 261.1729; found: 261.1732.

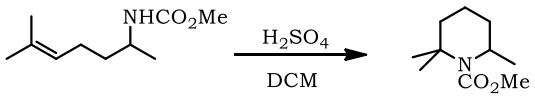
Methyl 6-methylhept-5-en-2-ylcarbamate 300



235 300

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_3N (2.5 ml, 22 mmol) to give the *carbamate* **300** as a clear oil (0.61 g, 38%). δ_H 5.05 - 4.95 (m, 1H, =CH), 4.75 (*br*. s, 1H, NH), 3.50 – 3.60 (m, 1H, NCH), 3.59 (s, 3H, OCH_3), 1.94 (*app*. q, 2H, *J* = 7.5 Hz, CH_2), 1.61 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.42 – 1.30 (m, 2H, CH_2), 1.06 (d, 3H, *J* = 6.0 Hz, CH_3). δ_C 156.3 (C=O), 131.8 (Cq), 123.5 (=CH), 51.6 (OCH_3), 46.7 (NCH), 36.9 (CH_2), 25.4 (CH_3), 24.4 (CH_2), 21.0 (CH_3), 17.4 (CH_3). IR (neat) υ/cm^{-1}: 3374, 2967, 2915, 1723, 1527, 1441, 1234, 885. HRMS (EI) *m/z* calculated for $C_{10}H_{19}NO_2$ $[M]^+$ = 185.1416; found: 185.1414.

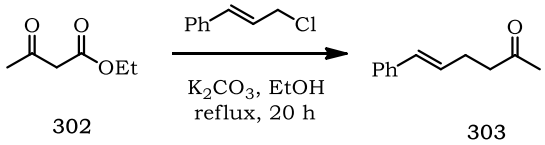
Methyl 2,2,6-trimethylpiperidine-1-carboxylate 301



300 301

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. δ_H 4.24 – 4.17 (m 1H, NCH), 3.55 (s, 3H, OCH_3), 1.71 – 1.60 (m, 4H, 2 × CH_2), 1.55 – 1.45 (m, 2H, CH_2), 1.42 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.10 (d, 3H, *J* = 6.9 Hz, CH_3). δ_C 156.8 (C=O), 54.1 (Cq, 2-C), 51.6 (CH_3O), 48.1 (NCH, 6-CH), 39.0 (CH_2), 29.5 (CH_3), 28.2 (CH_2), 27.7 (CH_3), 21.8 (CH_3), 14.6 (CH_2). IR (neat) υ/cm^{-1}: 2949, 2872, 1701, 1438, 1342, 1332, 1303, 1288, 1148, 1192. HRMS (APCI) *m/z* calculated for $C_{10}H_{20}NO_2$ $[M+H]^+$ = 186.1494; found: 186.1493.

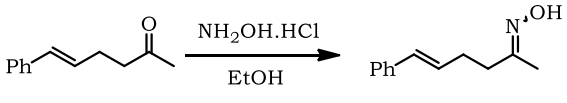
6-Phenylhex-5-en-2-one 303[13]



302 303

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:[13] 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).

6-Phenylhex-5-en-2-one oxime 304[14]

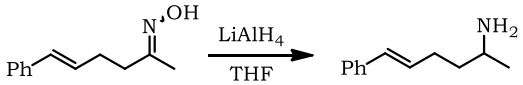


303 304

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 ºC 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] δ_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_3, major isomer), 1.79 (s, 1H, CH_3, minor isomer). δ_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_2), 41.8 (CH_2), 38.2 (CH_3).

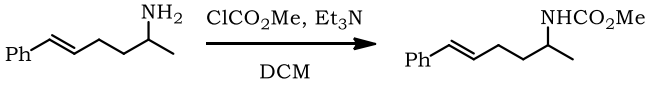
6-Phenylhex-5-en-2-amine 305[15]



304 305

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] δ_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_2), 1.42 (td, *J* = 7.9, 6.4 Hz, 2H, CH_2), 1.01 (d, *J* = 6.3 Hz, 3H, CH_3).

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

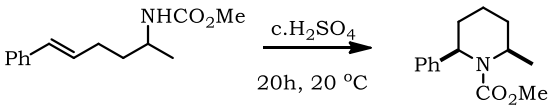


305 306

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_3N (1.25 ml, 11 mmol, 1.2 eq.) to give the *carbamate* **306** as a clear oil (0.72 g, 48%). δ_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, OCH_3), 2.19 (td, *J* = 8.5, 5.4 Hz, 2H, CH_2), 1.53 (td, *J* = 8.5, 4.2 Hz, 2H, CH_2), 1.10 (d, *J* = 6.5 Hz, 3H, CH_3). δ_C 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 (OCH_3), 46.9 (NCH), 36.9 (CH_2), 29.5 (CH_2), 21.3 (CH_3). IR (neat) υ/cm^{-1}: 3323, 2934, 1696, 1520, 1449, 1248, 1192, 1072, 909, 723, 694. HRMS (EI) *m/z* calculated for $C_{14}H_{19}NO_2$ $[M]^+$ = 233.1416; found: 233.1414.

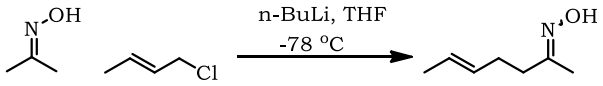
Methyl *cis*-2-methyl-6-phenylpiperidine-1-carboxylate 307



306 307

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%). δ_H 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, OCH_3), 2.37 (dd, *J* = 11.5, 2.0 Hz, 1H), 1.83 – 1.61 (m, 3H, CH_2 and CH), 1.52 – 1.45 (m, 1H), 1.46 – 1.39 (m, 1H), 0.75 (d, *J* = 7.1 Hz, 3H, CH_3). δ_C 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 (OCH_3), 46.9 (NCH, 2-CH), 30.5 (CH_2), 27.0 (CH_2), 20.5 (CH_3), 15.0 (CH_2). IR (neat) υ/cm^{-1}: 2934, 2859, 1693, 1531, 1445, 1361, 1330, 1248, 1094, 1068, 1028. HRMS (EI) *m/z* calculated for $C_{14}H_{19}NO_2$ $[M]^+$ = 233.1416; found: 233.1413.

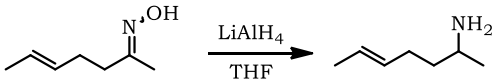
(*E*)-Hept-5-en-2-one oxime 310



308 309 310

To a solution of 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: δ_H 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, CH_2), 2.21 – 1.95 (m, 2H, CH_2), 1.75 (s, 1H, CH_3, minor isomer), 1.74 (s, 2H, CH_3, major isomer), 1.54 (d, *J* = 6.2, 3H, 7-CH_3). δ_C 158.5 (Cq), 130.0 (=CH), 125.7 (=CH), 28.5 (CH_2), 28.3 (CH_2), 20.0 (CH_3, isomers), 19.9 (CH_3, isomers), 17.8 (CH_3). IR (neat) υ/cm^{-1}: 3246, 2920, 2885, 1663, 1441, 1370, 1330. HRMS (EI) *m/z* calculated for $C_7H_{13}NO$ $[M]^+$ = 127.0997; found: 127.0998.

Hept-5-en-2-amine 311[16]

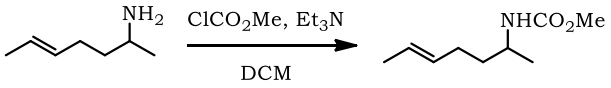


310 311

Using general procedure C, the foregoing oxime **310** (1.01g, 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] δ_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). δ_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).

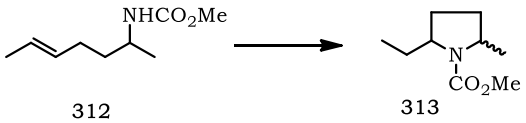
Methyl hept-5-en-2-ylcarbamate 312



311 312

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_3N (0.62 ml, 5.5 mmol, 1.1 eq.) to give the *carbamate* **312** as a clear oil (0.57 g, 72%). δ_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). δ_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) υ/cm^{-1}: 3327, 2966, 2931, 1695, 1531, 1450, 1352, 1250, 1192, 1078, 964, 777. HRMS (EI) *m/z* calculated for $C_9H_{17}NO_2$ $[M]^+$ = 171.1259; found: 171.1258.

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



312 313

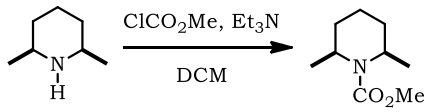
To a stirred solution of the carbamate **312** (171 mg, 1.0 mmol) in dry dichloromethane (10 ml) under nitrogen, cooled in an ice-water bath, was added triflic acid (76 mg, 46 µl, 0.5 mmol, 0.5 eq). The resulting mixture stirred was stirred at 40 °C for 3.5 hours to give the *pyrrolidines* **313**

(*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: δ_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). δ_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: δ 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). δ_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) υ/cm^{-1}: 2967, 2935, 1690, 1533, 1454, 1379, 1250, 1163, 1097, 1040, 912, 775, 731, 638. HRMS (EI) *m/z* calculated for $C_9H_{17}NO_2$ $[M]^+$ = 171.1259; found: 171.1262.

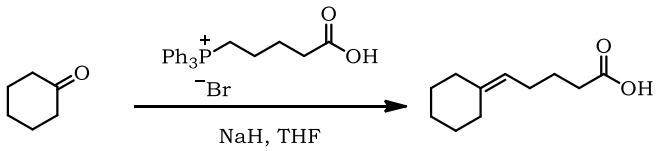
Methyl *cis*-2,6-dimethylpiperidine-1-carboxylate 316[17]



315 316

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_3N (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:[17] δ_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). δ_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) υ/cm^{-1}: 2969, 2937, 1691, 1441, 1400, 1344, 1311, 1275, 1255, 1192, 775. HRMS (EI) *m/z* calculated for $C_9H_{17}NO_2$ $[M]^+$ = 171.1259; found: 171.1258.

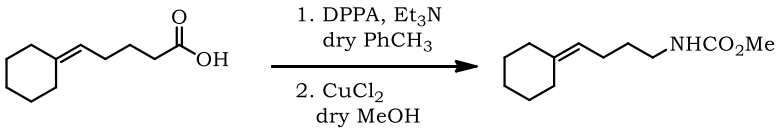
5-Cyclohexylidenepentanoic acid 318[18]



317 318

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:[19] δ_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). δ_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[20]

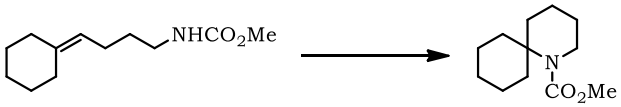


318 319

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 *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.· δ_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). δ_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) υ/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.

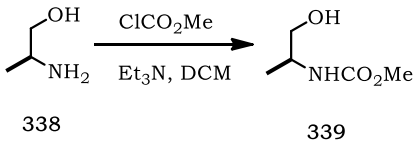
Methyl 1-aza*spiro*[5.5]undecane-1-carboxylate 320



319 320

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. δ_H 3.50 (s, 3H, OCH_3), 3.47 (*app*. t, *J* = 6.0, 2H, CH_2N), 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). δ_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) υ/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.

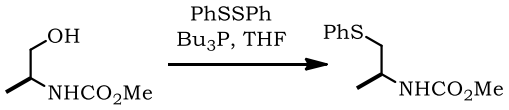
(*S*)-Methyl *N*-(1-hydroxypropan-2-yl)carbamate 339



338 339

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_3N (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. δ_H 5.41 – 5.17 (m, 1H, NH), 3.85 – 3.69 (m, 1H), 3.63 (s, 3H, OCH_3), 3.60 – 3.53 (m, 1H), 3.47 (dd, *J* = 10.6, 5.1 Hz, 2H, OCH_2), 1.12 (d, *J* = 6.6 Hz, 3H). δ_C 157.3 (C=O), 65.7 (OCH_2), 51.5 (OCH_3), 48.8 (NCH), 16.6 (CH_3). IR (neat) υ/cm^{-1}: 3393, 3311, 2972, 2942, 1712, 1532, 1454, 1260, 1190, 1193, 1097, 1074, 1053, 993, 779. HRMS (EI) *m/z* calculated for $C_5H_{11}NO_3$ $[M]^+$ = 133.0739; found: 133.0738.

(*S*)-(+)-Methyl *N*-(1-(phenylthio)propan-2-yl)carbamate 340[21]

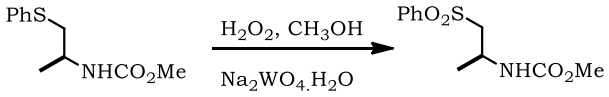


339 340

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: $[\alpha]^{20}_D$ +20.0 (*c* 1.0 g/100 ml, CH_3OH); δ_H 7.23 (d, *J* = 7.6 Hz, 2H), 7.14 (t, *J* = 7.6 Hz, 2H), 7.02 (t, *J* = 7.6 Hz, 1H), 4.78 – 4.59 (m, 1H, NH), 3.80 – 3.69 (m, 1H, NCH), 3.48 (s, 3H, OCH_3), 3.01 (dd, *J* = 14.1, 6.1 Hz, 1H, PhSH_AH_B), 2.81 (dd, *J* = 14.1,

6.0 Hz, 1H, PhSCH$_A$*H*$_B$), 1.09 (d, *J* = 6.6 Hz, 3H, CH$_3$). δ_C 156.1 (C=O), 135.9 (Cq), 129.3 (2 x CH), 128.8 (2 x CH), 126.1 (CH), 51.9 (OCH$_3$), 46.5 (NCH), 40.2 (PhS<u>C</u>H$_2$), 19.8 (CH$_3$). IR (neat) υ/cm^{-1}: 3312, 2971, 1710, 1583, 1514, 1481, 1452, 1439, 1348, 1327, 1242, 1192, 1053, 1024, 779, 737. HRMS (EI) *m/z* calculated for $C_{11}H_{15}NO_2S$ $[M]^+$ = 225.0824; found: 225.0825.

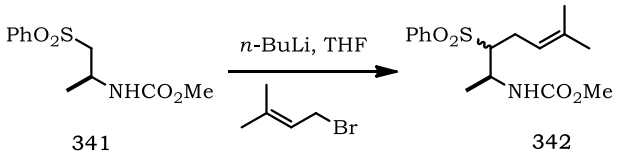
(*S*)-(-)-Methyl *N*-(1-(phenylsulfonyl)propan-2-yl)carbamate 341



340 341

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: $[\alpha]^{20}_D$ -8.89 (*c* 0.9 g/100 ml, CH$_3$OH); δ_H 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, OCH$_3$), 3.42 (dd, *J* = 14.3, 5.5 Hz, 1H, PhSO$_2$C*H*$_A$H$_B$), 3.15 (dd, *J* = 14.3, 5.5 Hz, 1H, PhSO$_2$CH$_A$*H*$_B$), 1.31 (d, *J* = 6.8 Hz, 3H, CH$_3$). δ_C 155.8 (C=O), 139.9 (Cq), 133.8 (CH), 129.4 (2 x CH), 127.9 (2 x CH), 52.0 (OCH$_3$), 43.6 (NCH), 24.3 (PhSO$_2$<u>C</u>H$_2$), 20.5 (CH$_3$). IR (neat) υ/cm^{-1}: 3362, 2976, 1699, 1528, 1447, 1304, 1254, 1178, 1101, 1084, 1053, 779, 737. HRMS (EI) *m/z* calculated for $C_{11}H_{15}NO_4S$ $[M]^+$ = 257.0722; found: 257.0727.

Methyl (*2S, 3RS*)-(6-methyl-3-(phenylsulfonyl)hept-5-en-2-yl)carbamate 342[22]



341 342

A solution of the phenyl sulfone **341** (1.30 g, 5 mmol, 1.0 eq.) in dry tetrahydrofuran (10 ml) at -78 ^{o}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.

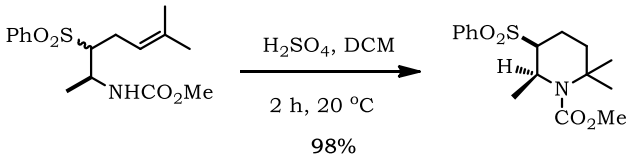
The major isomer showed: δ_H 7.95 – 7.82 (m, 2H), 7.67 – 7.60 (m, 1H), 7.60 – 7.46 (m, 2H), 5.37 (d, *J* = 8.6 Hz, 1H, NH), 4.81 – 4.92 (m, 1H, =CH), 4.36 – 4.2 (m, 1H, NCH), 3.60 (s, 3H, OCH_3), 3.30 (dt, *J* = 7.9, 6.4 Hz, 1H, $PhSO_2\underline{C}H$), 2.52 – 2.23 (m, 2H, CH_2), 1.54 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.37 (d, *J* = 7.0 Hz, 3H). δ_C 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 (OCH_3) , 46.2 ($PhSO_2\underline{C}H$), 25.6 (CH_3), 24.2 (CH_2), 17.8 (CH_3), 17.6 (CH_3).

The minor isomer showed: δ_H 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, OCH_3), 3.21 (dt, *J* = 7.9, 6.4 Hz, 1H, $PhSO_2CH$), 2.52 – 2.23 (m, 2H, CH_2), 1.67 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.37 (d, *J* = 7.0 Hz, 3H). δ_C 156.0 (C=O), 136.0 (Cq), 133.7 (CH), 129.2 (2 x

CH), 128.3 (2 x CH), 118.3 (=CH), 68.4 (NCH), 52.0 (OCH_3), 47.0 ($PhSO_2\underline{C}H$), 26.1 (CH_2), 25.6 (CH_3), 17.8 (CH_3), 17.6 (CH_3).

The whole sample showed IR (neat) υ/cm^{-1}: 3370, 2972, 1715, 1512, 1447, 1302, 1248, 1178, 1101, 1084, 1070, 914, 727. HRMS (APCI) *m/z* calculated for $C_{16}H_{24}NO_4S$ $[M+H]^+$ = 326.1426; found: 326.1428.

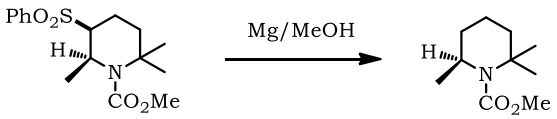
(6S)-(-)-Methyl-2,2,6-trimethyl-5-(phenylsulfonyl)piperidine-1-carboxylate 343



342 343

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: $[\alpha]^{20}_D$ -23.33 (*c* 0.6 g/100 ml, CH_3OH); δ_H 7.67 (d, *J* = 7.8 Hz, 2H), 7.44 (t, *J* = 8.6, 1.3 Hz, 1H), 7.40 – 7.22 (m, 2H), 4.59 (qd, *J* = 6.9, 4.4 Hz, 1H, 6-H), 3.43 (s, 3H, OCH_3), 3.18 (ddd, *J* = 10.8, 7.7, 4.4 Hz, 1H, $PhSO_2C\underline{H}$), 2.02 (dddd, *J* = 13.8, 11.2, 7.5, 4.1 Hz, 1H), 1.93 – 1.83 (m, 1H), 1.35 – 1.28 (m, 2H), 1.24 (d, *J* = 6.9 Hz, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.10 (s, 3H, CH_3). δ_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 (OCH_3), 47.2 ($PhSO_2\underline{C}H$), 36.0 (CH_2), 29.1 (CH_3), 27.3 (CH_3), 18.9 (CH_3), 15.9 (CH_2). IR (neat) υ/cm^{-1}: 2964, 1697, 1514, 1446, 1338, 1305, 1084, 1070, 727, 690. HRMS (EI) *m/z* calculated for $C_{16}H_{23}NO_4S$ $[M]^+$ = 325.1348; found: 325.1336.

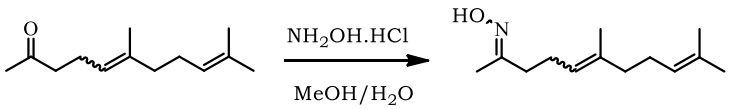
(S)-Methyl 2,2,6-trimethylpiperidine-1-carboxylate 344[23]



343 344

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).

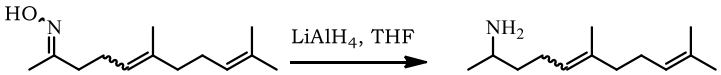
(*E/Z*)-6,10-Dimethylundeca-5,9-dien-2-one oxime 381



380 **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 ^{o}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. δ_H (selected resonances) 5.10– 4.90 (m, 2H, =CH), 2.14 – 2.21 (m, 6H, 3× 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 δ_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 δ_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]

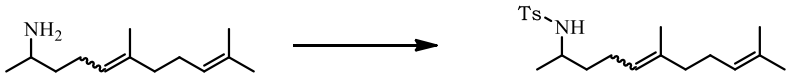
6,10-Dimethylundeca-5,9-dien-2-amine 382



381 382

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. δ_H 5.10 - 4.96 (m, 2H, 2 × =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).[24] 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**

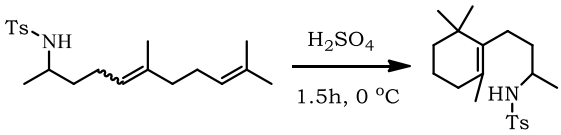


382 383

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_3N (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). δ_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: δ_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: δ_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) υ/cm^{-1}: 3296, 2969, 2930, 1599, 1321, 1158, 1091, 814, 661. HRMS (EI) *m/z* calculated for $C_{20}H_{31}NO_2S$ $[M]^+$ = 349.2076; found: 349.2078.

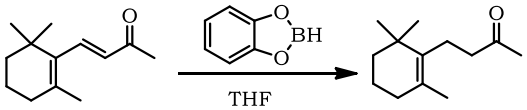
4-Methyl-*N*-(4-(2,6,6-trimethylcyclohex-1-en-1-yl)butan-2-yl)benzenesulfonamide 384



383 384

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 ^{o}C to give *the sulfonamide* **384** as a colourless oil (190 mg, 95%). δ_H 7.52 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 2H), 4.71 (d, *J* = 8.4 Hz, 1H, 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 Hz, 3H, CH_3), 0.79 (s, 3H, CH_3), 0.78 (s, 3H, CH_3). δ_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) υ/cm^{-1}: 3296, 2969, 29306, 1599, 1321, 1158, 1091, 814, 661. HRMS (EI) *m/z* calculated for $C_{20}H_{31}NO_2S$ $[M]^+$ = 349.2076; found: 349. 2076.

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

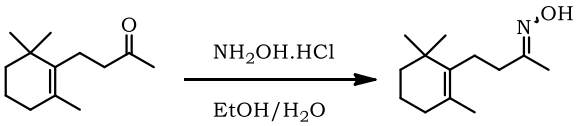


386 387

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 *β*-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:[25] δ_H 2.45 (*app*. dt, *J* = 8.2, 7.5 Hz, 1H), 2.23 – 2.13 (m, 1H), 2.10 (s, 3H, CH_3), 1.87 – 1.76 (m, 4H, 2 x CH_2), 1.52 (s, 3H, CH_3), 1.37 – 1.28 (m, 4H, 2 x CH_2), 0.88 (s, 6H, 2 x CH_3).

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

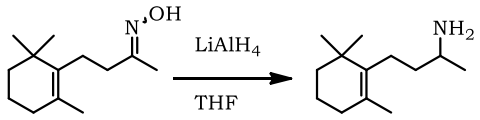


387 388

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 ^oC 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: δ_H 2.22 – 2.13 (m, 2H, CH_2), 2.12 – 2.03 (m, 2H, CH_2), 1.87 (s, 2H, isomer), 1.82 (s, 1H, isomer), 1.53 – 1.50 (m, 2H, CH_2), 1.37 – 1.26 (m, 2H, CH_2), 0.89 (s, 6H, 2 x CH_3). Major isomer δ_C 157.2 (Cq), 136.7 (Cq), 133.5 (Cq), 40.7 (CH_2), 39.8 (CH_2), 34.9 (Cq), 32.7 (CH_2), 28.5 (2 x CH_3), 25.4 (CH_2), 23.3 (CH_3), 19.7 (CH_3), 19.5 (CH_2). Minor isomer δ_C 39.9 (CH_2), 32.8 (CH_2), 28.4 (CH_3), 19.8 (CH_2); only four distinct peaks.

The whole sample showed IR (neat) υ/cm^{-1}: 3366, 2955, 2928, 2903, 1512, 1470, 1445, 1362, 1260, 1096. HRMS (EI) *m/z* calculated for $C_{13}H_{23}NO$ $[M]^+$ = 209.1780; found: 209.1783.

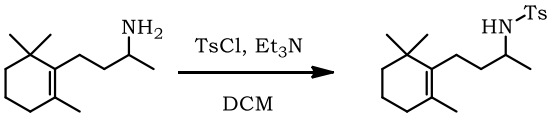
4-(2,6,6-Trimethylcyclohex-1-en-1-yl)butan-2-amine 389[26]



388 389

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. δ_H 2.81 (m, 1H, NCH), 1.99 – 1.84 (m, 4H, 2 x CH_2), 1.53 (s, 3H, CH_3), 1.50 – 1.44 (m, 2H, CH_2), 1.37 – 1.30 (m, 4H, 2 x CH_2), 1.02 (d, J = 6.3 Hz, 3H, CH_3), 0.91 (s, 6H, 2 x CH_3). δ_C 137.1 (Cq), 126.7 (Cq), 47.9 (NCH), 40.7 (CH_2), 39.9 (CH_2), 34.9 (Cq), 32.7 (CH_2), 28.5 (2 x CH_3), 25.4 (CH_2), 23.3 (CH_3), 19.7 (CH_3), 19.5 (CH_2). IR (neat) υ/cm^{-1}: 3264, 2963, 2926, 2866, 1458, 1375, 908. HRMS (APCI) *m/z* calculated for $C_{13}H_{26}N$ $[M+H]^+$ = 196.2065; found: 196.2058.

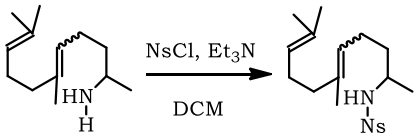
4-Methyl-*N*-(4-(2,6,6-trimethylcyclohex-1-en-1-yl)butan-2-yl)benzenesulfonamide 384



389 384b

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 Et_3N (0.6 ml, 5.5 mmol) to give the *sulfonamide* **384** (1.50 g, 84%) as a thick, clear oil, which showed ^1H and ^{13}C 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**



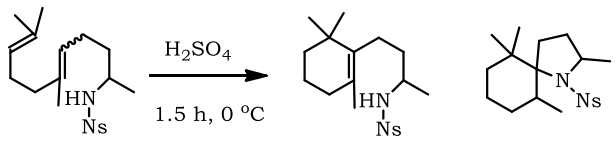
382 390

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_3N (0.6 ml, 5.5 mmol) to give the *sulfonamide* **390** (1.00 g, 54%) as yellow oil (2:1 mixture of isomers). δ_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: δ_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: δ_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) υ/cm^{-1}: 3281, 2968, 2928, 2858, 1530, 1433, 1306, 1092, 852, 750, 687. HRMS (EI) *m/z* calculated for $C_{19}H_{28}N_2O_4S$ $[M]^+$ = 380.1770; found: 380. 1763.

4-Nitro-*N*-(4-(2,6,6-trimethylcyclohex-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



390 391 392

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

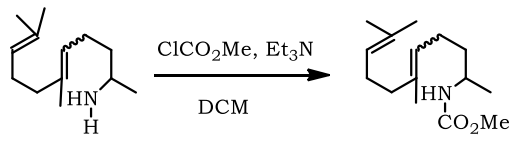
0 °C to give the *sulfonamide* **391** and *Spiro*-pyrrolidine **392** (total 218 mg, 93%) as a colourless oil.

Sulfonamide **391** δ_H 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 CH_2), 1.48 – 1.40 (m, 2H, CH_2), 1.46 (s, 3H, CH_3), 1.40 - 1.33 (m, 4H, 2 x CH_2), 1.10 (d, *J* = 6.6 Hz, 3H, CH_3), 0.88 (s, 3H, CH_3), 0.86 (s, 3H, CH_3). δ_C 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 (CH_2), 37.9 (CH_2), 34.9 (Cq), 32.6 (CH_2), 28.5 (CH_3), 24.8 (CH_2), 21.7 (CH_3), 19.7 (CH_2), 19.3 (2 x CH_3).

Spiro-pyrrolidine **392**: δ_H 3.54 – 3.43 (m, 1H, NCH), 1.10 (d, *J* = 5.7 Hz, 3H, CH_3), 0.81 (d, *J* = 5.5 Hz, 3H, CH_3); only 3 distinct peaks. δ_C 67.8 (NCq), 51.9 (NCH), 37.0 (CH_2), 35.9 (Cq), 36.0 (CH_2); only 5 distinct peaks.

The whole sample showed IR (neat) υ/cm^{-1}: 3281, 2922, 1705, 1532, 1456, 1354, 1165, 1091, 914, 855, 737. HRMS (EI) *m/z* calculated for $C_{19}H_{28}N_2O_4S$ $[M]^+$ = 211. 1572; found: 211. 1576.

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



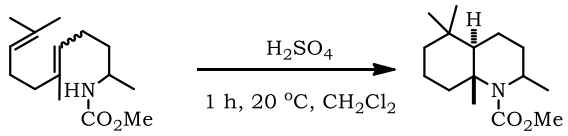
382 393

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 Et_3N (2.5 ml, 22 mmol, 1.2 eq.) to give the *carbamate* **393** as a clear oil (0.71 g, 28%). δ_H 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 (OCH_3), 2.00 – 1.85 (m, 6H, 3 x CH_2), 1.60 (s, 3H, CH_3), 1.50 (s, 6H, 2 x CH_3), 1.42 – 1.30 (m, 2H, CH_2), 1.06 (d, 3H, *J* = 6.7 Hz, CH_3). δ_C 156.4 (CO_2), 135.7 (Cq), 131.5 (Cq), 124.3 (=CH), 123.5 (=CH), 51.8 (OCH_3), 47.0 (NCH), 39.6 (CH_2), 31.9 (CH_2), 26.7 (CH_2), 25.6 (CH_3), 24.4 (CH_2), 23.3 (CH_3), 17.6 (CH_3), 15.9 (CH_3).

Z-isomer: δ_C 131.6 (Cq), 124.4 (=CH), 32.1 (CH_2), 24.5 (CH_2)- only four distinct peaks.

IR (neat) υ/cm^{-1}: 3333, 2970, 2931, 1695, 1531, 1450, 1375, 1252, 1078, 777. HRMS (EI) *m/z* calculated for $C_{15}H_{27}NO_2$ $[M]^+$ = 253. 2042; found: 253. 2036.

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

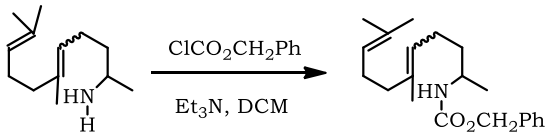


393 394

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_H 4.08 – 3.99 (m, 1H, NCH), 3.61 (dd, *J* = 9.7, 4.1 Hz, 1H), 3.56 (s, 3H, OCH_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_3), 1.20 (d, *J* = 6.5, 3H, CH_3), 1.18 – 1.01 (m, 1H), 0.82 (s, 6H, 2 x CH_3), 0.73 (dd, *J* = 8.9, 5.1 Hz, 1H). δ_C 156.1 (Cq), 59.6 (Cq), 51.7 (OCH_3), 48.6 (CH), 46.5 (CH), 41.7 (CH_2), 39.4 (CH_2), 34.1 (Cq), 31.8 (CH_3) 25.0 (CH_2), 21.6 (CH_3), 20.6 (CH_3), 19.9 (CH_2), 19.7(CH_3), 14.4 (CH_2). The *minor diastereoisomer* could be characterized by δ_C 53.6 (Cq), 37.1 (CH_2), 36.4 (CH_2), 38.3 (CH_3), 36.9 (CH_3), 19.9 (CH_2), 13.6 (CH_3).

The whole sample showed IR (neat) υ/cm^{-1}: 2937, 1701, 1693, 1512, 1344, 1244, 1087, 987, 775. HRMS (EI) *m/z* calculated for $C_{15}H_{27}NO_2$ $[M]^+$ = 253. 2042; found: 253. 2042.

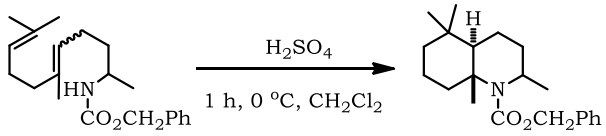
Benzyl (6,10-dimethylundeca-5,9-dien-2-yl)carbamate 395



382 395

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 Et_3N (0.6 ml, 5.5 mmol) to give the *Z-carbamate* **395** as a clear oil (0.88 g, 52%). δ_H 7.30 – 7.19 (m, 5H), 5.02 - 4.91 (m, 4H, 2 x =CH, OCH_2), 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 CH_2), 1.60 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.42 – 1.29 (m, 2H, CH_2), 1.07 (d, *J* = 5.1 Hz, 3H, CH_3). δ_C 154.5 (CO_2), 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 (OCH_2), 46.9 (NCH), 39.6 (CH_2), 37.5 (CH_2), 26.6 (CH_2), 25.6 (CH_3), 24.2 (CH_2), 21.2 (CH_3), 17.6 (CH_3), 15.8 (CH_3). IR (neat) υ/cm^{-1}: 3337, 2969, 2920, 1696, 1526, 1452, 1244, 1060, 1028, 735, 698. HRMS (EI) *m/z* calculated for $C_{21}H_{31}NO_2$ $[M]^+$ = 329. 2355; found: 329. 2347.

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

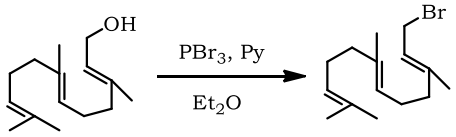


395 396

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. δ_H 7.29 – 7.18 (m, 4H), 7.24 – 7.21 (m, 1H), 4.99 – 4.94 (d, *J* = 12.7 Hz, 1H, OCH_AH_B), 4.90 (d, *J* = 12.7 Hz, 1H, OCH_AH_B), 4.08 – 4.00 (m, 1H, NCH), 3.09 (dtd, *J* = 13.1, 3.5, 1.6 Hz, 1H), 1.89 – 1.77 (m, 2H, CH_2), 1.67 (ddd, *J* = 10.6, 7.7, 4.6 Hz, 2H, CH_2), 1.42 (d, *J* = 5.8 Hz, 2H, CH_2), 1.40

– 1.31 (m, 2H, CH_2), 1.22 (s, 3H, CH_3), 1.16 (d, *J* = 6.9 Hz, 3H, CH_3), 1.04 – 0.96 (m, 1H), 0.84 – 0.77 (m, 1H), 0.75 (s, 6H, 2 x CH_3). δ_C 156.2 (Cq), 136.7 (Cq), 128.5 (CH), 128.4 (2 x CH), 127.9 (2 x CH), 66.1 (OCH_2), 59.9 (Cq), 48.7 (NCH), 41.8 (CH_2), 39.4 (CH_2), 34.2 (Cq), 33.0 (CH_3) 23.1 (CH_2), 21.0 (CH_3), 19.6 (CH_3), 19.9 (CH_2), 19.7(CH_3), 14.8 (CH_2). IR (neat) υ/cm^{-1}: 2872, 2855, 1694, 1552, 1393, 912, 731. HRMS (EI) *m/z* calculated for $C_{21}H_{31}NO_2$ $[M]^+$ = 329.2355; found: 329.2348.

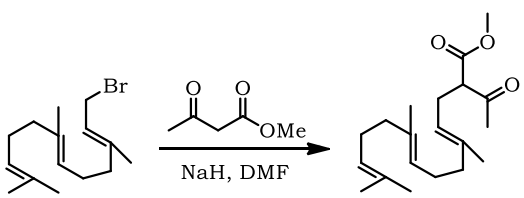
(2*E*,6*E*)-1-Bromo-3,7,11-trimethyldodeca-2,6,10-triene 398[27]



397 398

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] δ_H 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, CH_2Br), 2.30 – 1.97 (m, 8H, 4 x CH_2), 1.77 (s, 3H, CH_3), 1.66 (s, 6H, 2 x CH_3), 1.59 (d, *J* = 3.8 Hz, 3H, CH_3).

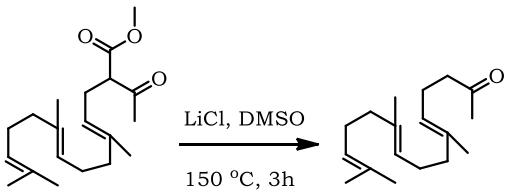
(4*E*,8*E*)-Methyl 2-acetyl-5,9,13-trimethyltetradeca-4,8,12-trienoate 399[28]



398 399

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] δ_H 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).

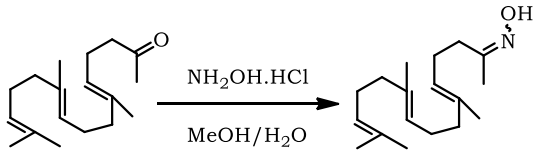
(5*E*,9*E*)-6,10,14-Trimethylpentadeca-5,9,13-trien-2-one 400[29]



399 400

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] δ_H 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, CH_2), 2.05 (s, 3H, CH_3), 2.01 – 1.93 (m, 4H, 2 x CH_2), 1.93 – 1.84 (m, 4H, 2 x CH_2), 1.61 (s, 6H, 2 x CH_3), 1.53 (s, 6H, 2 x CH_3). δ_C 158.3 (C=O), 136.3 (Cq), 135.3 (Cq), 131.3 (Cq), 124.9 (=CH), 124.0 (=CH), 122.5 (=CH), 39.63 (CH_2), 36.2 (CH_2), 29.8 (CH_2), 26.61 (CH_2), 24.9 (CH_3), 24.7 (CH_2), 24.8 (CH_2), 23.4 (CH_3), 17.7 (CH_3), 16.1 (CH_3), 13.3 (CH_3).

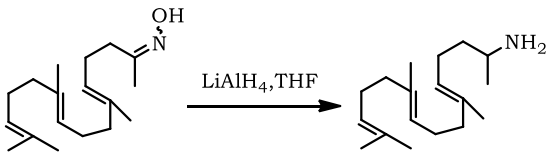
(5*E*,9*E*)-6,10,14-Trimethylpentadeca-5,9,13-trien-2-one oxime 401[30]



400 401

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 ^{o}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: δ_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).

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

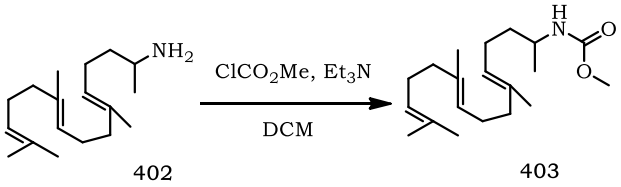


401 402

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

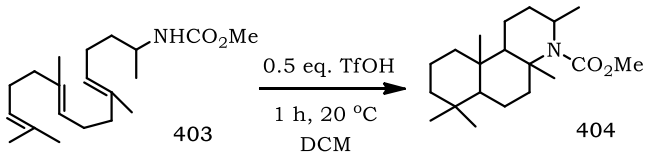
concentrated to give the *amine* **402** (1.20 g, 67%) as a yellow oil which was used directly in the next step. δ_H 5.10 - 4.96 (m, 3H, 3 × =CH), 2.88 – 2.80 (m, NCH), 2.00 – 1.85 (m, 10H, 5 x CH_2), 1.6 (s, 6H, 2 x CH_3), 1.55 (s, 6H, 2 x CH_3), 1.35 - 1.28 (m, 2H, CH_2), 1.01 (d, 3H, *J* = 4.4 Hz, CH_3). 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 CH_2), 31.9 (CH_2), 26.7 (CH_2), 25.6 (CH_3), 24.4 (2 x CH_2), 23.3 (2 x CH_3), 17.7 (CH_3), 15.9 (CH_3). IR (neat) υ/cm^{-1}: 3462, 2971, 2936, 1740, 1705, 1445, 1244, 1084, 1049, 912. HRMS (AP) *m/z* calculated for $C_{18}H_{34}N$ $[M+H]^+$ = 264.2691; found: 264.2696.

Methyl ((5*E*,9*E*)-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 Et_3N (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, OCH_3), 2.16 - 1.98 (m, 10H, 5 x CH_2), 1.70 (s, 6H, 2 x CH_3), 1.62 (s, 6H, 2 x CH_3), 1.50 - 1.41 (m, 2H, CH_2), 1.15 (d, *J* = 6.4 Hz, 3H, CH_3). 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 (OCH_3), 47.0 (NCH), 39.7 (2 x CH_2), 31.9 (CH_2), 26.7 (CH_2), 25.6 (CH_3), 24.4 (2 x CH_2), 23.3 (2 x CH_3), 17.7 (CH_3), 15.9 (CH_3). IR (neat) υ/cm^{-1}: 3323, 2965, 2926, 1700, 1532, 1451, 1377, 1248, 1078. HRMS (EI) *m/z* calculated for $C_{20}H_{35}NO_2$ $[M]^+$ = 321.2668; found: 321.2674.

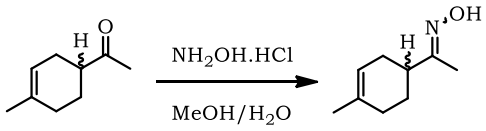
Methyl 3,4a,7,7,10a-pentamethyldodecahydrobenzo[f]quinoline-4(4aH)-carboxylate 404



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. δ_H (whole sample) 4.39 – 1.34 (s, m, 1H, NCH), 3.56 (s, 3H, OCH_3), 1.72 – 1.63 (m, 2H, CH_2), 1.47– 1.52 (m, 4H, 2 x CH_2), 1.36 – 1.23 (m, 4H, 2 x CH_2), 1.19 – 1.10 (m, 6H, 3 x CH_2), 0.87 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.85 (s, 3H, CH_3), 0.84 (d, J = 6.8 Hz, 3H, CH_3), 0.79 (s, 3H, CH_3).

The whole sample showed IR (neat) υ/cm^{-1}: 2934, 2872, 1701, 1528, 1452, 1252, 1084, 908, 722. HRMS (EI) *m/z* calculated for $C_{20}H_{35}NO_2$ $[M]^+$ = 321.2668; found: 321.2666.

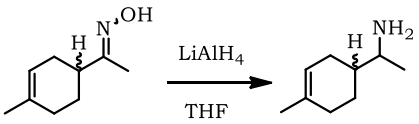
1-(4-Methylcyclohex-3-en-1-yl)ethanone oxime 417[31]



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] δ_H 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 CH_2), 1.76 – 1.65 (m, 1H), 1.62 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.36 – 1.25 (m, 1H).

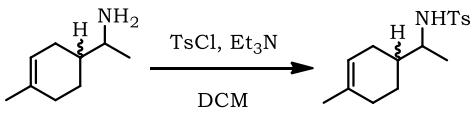
1-(4-Methylcyclohex-3-en-1-yl)ethanamine 418



417 418

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* - δ_H 5.28 (t, *J* = 10.0 Hz, H, =CH), 2.75 – 2.66 (m, 1H, NCH), 1.94 – 1.86 (m, 4H, 2 x CH_2), 1.66 (s, 3H, CH_3), 1.33 – 1.36 (m, 2H, CH_2), 1.37 (dddt, *J* = 8.9, 8.4, 6.8, 5.7 Hz, 1H), 1.02 (d, *J* = 7.2, 3H). δ_C 134.0 (Cq), 120.0 (=CH), 51.0 (NCH), 40.8 (CH), 30.4 (CH_2), 27.7 (CH_2), 25.4 (CH_2), 23.4 (CH_3), 20.3 (CH_3). *Diastereoisomer B* - δ_H 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. δ_C 120.6 (=CH), 41.0 (CH), 28.0 (CH_2); only 3 distinct peaks. IR (neat) υ/cm^{-1}: 3279, 2887, 2855, 1659, 1437, 1377, 1153, 951. HRMS (ES) *m/z* calculated for $C_9H_{18}N$ $[M+H]^+$ = 140.1439; found: 140.1440.

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

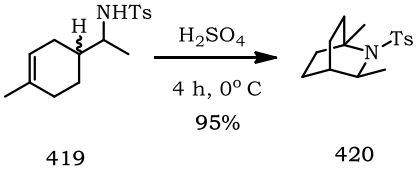


418 419

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 Et_3N (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* - δ_H 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, $ArCH_3$), 2.01 - 1.82 (m, 4H, 2 x CH_2), 1.53 (s, 3H, CH_3), 1.40 (dd, *J* = 7.0, 4.2 Hz, 1H), 1.28 – 0.98 (m, 1H), 0.89 (d, *J* = 6.7 Hz, 3H). δ_C 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 (CH_2), 27.8 (CH_2), 25.2 (CH_2), 23.3 (CH_3), 21.4 (CH_3), 18.8 (CH_3). *Diastereoisomer B:* δ_H 0.88 (d, *J* = 6.7 Hz, 3H) - only 1 distinct peak. δ_C 133.9 (Cq), 53.7 (NCH), 39.5 (CH), 29.9 (CH_2), 27.5 (CH_2), 25.0 (CH_2) - 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 $C_{16}H_{24}NO_2S$ $[M+H]^+$ = 294.1528; found: 294.1514.

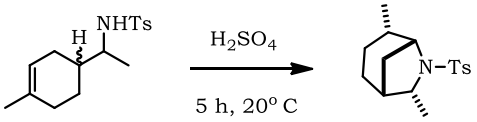
1,3-Dimethyl-2-tosyl-2-azabicyclo[2.2.2]octane 420



419 420

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. δ_H 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 CH_3), 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, CH_3), 1.19 (s, 3H, CH_3). δ_C 142.5 (Cq), 140.9 (Cq), 129.5 (2 x CH), 127.0 (2 x CH), 57.0 (NCH), 55.2 (Cq), 36.7 (CH_2), 31.5 (CH), 30.1 (CH_2), 26.4 (CH_2), 26.3 (CH_3), 22.2 (CH_3), 21.4 (CH_3), 19.2 (CH_2). IR (neat) υ/cm^{-1}: 2930, 1597, 1456, 1329, 1311, 1076, 1160, 1078, 980, 878, 739. HRMS (EI) *m/z* calculated for $C_{16}H_{23}NO_2S$ $[M]^+$ = 293.1450; found: 293.1448.

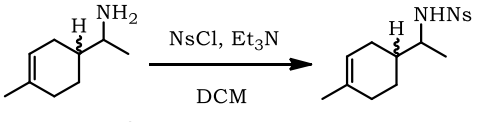
(1R,4S,5R,7R)-4,7-Dimethyl-6-tosyl-6-azabicyclo[3.2.1]octane 421



419 421

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. δ_H 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, $ArCH_3$), 2.13 (*app*. s, 1H), 1.98 (*app*. s, 1H), 1.82 (d, *J* = 4.0 Hz, 1H), 1.41 – 1.37 (m, 2H, CH_2), 1.31 – 1.26 (m, 1H), 1.21 (d, *J* = 6.8 Hz, 3H, CH_3), 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, CH_3), 0.71 (dd, *J* = 6.8, 3.9 Hz, 1H). δ_C 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 (CH_2), 26.3 (CH_3), 21.5 (CH_2), 21.0 (CH_3), 20.5 (CH_3), 19.2 (CH_2). IR (neat) υ/cm^{-1}: 2957, 2930, 1458, 1333, 1155, 1091, 812. HRMS (ES) *m/z* calculated for $C_{16}H_{24}NO_2S$ $[M+H]^+$ = 294.1528; found: 294.1524.

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



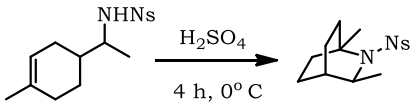
418 422

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 Et_3N (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* δ_H 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 CH_2), 1.50 (s, 3H, CH_3), 1.29 – 1.12 (m, 2H, CH_2), 0.99 (d, *J* = 6.7 Hz, 3H, CH_3). δ_C 149.9 (Cq),

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 (CH_2), 27.9 (CH_2), 27.5 (s), 25.3 (CH_2), 23.3 (CH_3), 19.2 (CH_3). *Diastereoisomer B:* δ_H 0.90 (d, *J* = 6.7 Hz, 3H) - only 1 distinct peak. δ_C 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 (CH_2), 27.5 (CH_2), 25.1 (CH_2), 23.3 (CH_3), 19.1 (CH_3).

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 $C_{15}H_{19}N_2O_4S$ $[M+H]^+$ = 323.1066; found: 323.1077.

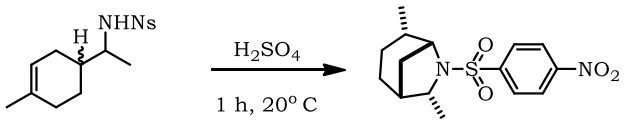
1,3-Dimethyl-2-(4-nitrophenylsulfonyl)-2-azabicyclo[2.2.2]octane 423



422 423

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. δ_H 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, CH_3), 1.32 – 1.16 (m, 2H, CH_2), 1.14 (s, 3H, CH_3). δ_C 150.0 (Cq), 140.9 (Cq), 128.5 (2 x CH), 124.1 (2 x CH), 57.0 (NCH), 56.1 (Cq), 36.2 (CH_2), 31.8 (CH), 30.6 (CH_2), 26.4 (CH_3), 26.3 (CH_2), 21.4 (CH_3), 19.4 (CH_2). IR (neat) υ/cm^{-1}: 2938, 1525, 1338, 1302, 1161, 1085, 983, 910, 855. HRMS (EI) *m/z* calculated for $C_{15}H_{20}N_2O_4S$ $[M]^+$ = 324.1144; found: 324.1146.

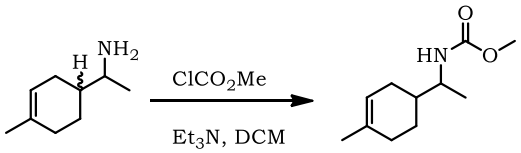
(1R,4S,5R,7R)-4,7-Dimethyl-6-((4-nitrophenyl)sulfonyl)-6-azabicyclo[3.2.1]octane 424



422 424

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 ºC to give the *[3.2.1]-azabicyclo-octane* **424** (132 mg, 93%) as yellowish crystals m.p. 174 – 177 °C. δ_H 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, CH_2), 1.41 (d, *J* = 6.6 Hz, 3H, CH_3), 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, CH_3). δ_C 150.0 (Cq), 140.9 (Cq), 129.0 (2 x CH), 124.1 (2 x CH), 65.3 (NCH), 60.6 (NCH), 38.9 (CH), 37.4 (CH_2), 36.8 (CH), 27.6 (CH_2), 25.0 (CH_2), 19.4 (CH_3), 15.6 (CH_3). IR (neat) υ/cm^{-1}: 2934, 1525, 1348, 1306, 1157, 1090, 855. HRMS (EI) *m/z* calculated for $C_{15}H_{20}N_2O_4S$ $[M]^+$ = 324.1144; found: 324.1142.

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

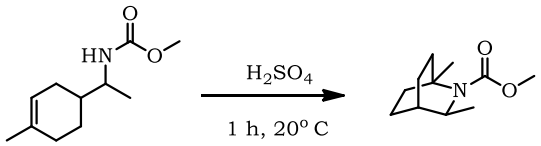


418 425

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 Et_3N (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* δ_H 5.27 (*br*. s, 1H, =CH), 5.09 – 4.84 (m, 1H, NH), 3.35 – 3.29 (m, 1H, NCH), 3.25 (s, 3H, OCH_3), 2.06 – 1.80 (m, 4H, 2 x CH_2), 1.79 – 1.60 (m, 1H), 1.53 – 1.42 (m, 1H), 1.31 – 1.08 (m, 4H, 2 x CH_2), 1.08 (d, *J* = 6.7 Hz, 3H, CH_3). δ_C 156.7 (*Cq*), 133.9 (*Cq*), 120.0 (=CH), 51.6 (OCH_3), 50.7

(NCH), 39.4 (CH), 30.1 (CH_2), 28.2 (CH_2), 25.6 (CH_2), 23.3 (CH_3), 18.5 (CH_3). *Diastereoisomer B* δ_H 1.00 (d, *J* = 6.7 Hz, 3H, CH_3) - only 1 distinct peak. δ_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) υ/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.

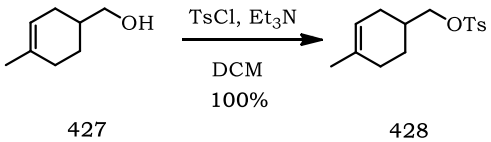
Methyl 1,3-dimethyl-2-azabicyclo[2.2.2]octane-2-carboxylate 426



425 426

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. δ_H 4.51 - 4.44 (m, 1H, NCH), 3.49 (s, 3H, OCH_3), 1.72 (dd, *J* = 8.3, 4.0 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 Hz, 3H, CH_3). δ_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) υ/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-Methylcyclohex-3-en-1-yl)methyl methanesulfonate 428

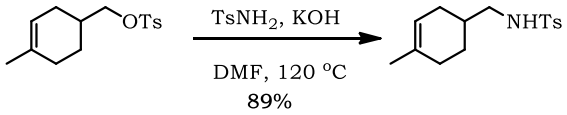


427 428

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_2O (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).

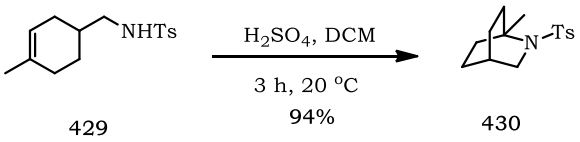
4-Methyl-N-(4-methylcyclohex-3-en-1-ylmethyl)benzenesulfonamide 429



428 429

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 (EI) *m/z* calculated for $C_{15}H_{21}NO_2S$ $[M]^+$ = 279.1293; found: 279.1293.

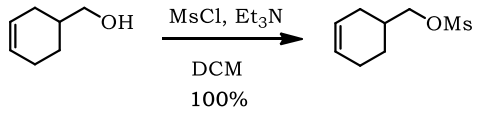
1-Methyl-2-tosyl-2-azabicyclo[2.2.2]octane 430



429 430

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. δ_H 7.71 – 7.58 (m, 2H), 7.20 (d, *J* = 7.1 Hz, 2H), 3.52 (d, *J* = 2.5 Hz, 2H, NCH_2), 2.35 (s, 3H, $ArCH_3$), 1.83 (dd, *J* = 5.9, 3.0 Hz, 1H, CH), 1.70 – 1.60 (m, 2H, CH_2), 1.53 – 1.40 (m, 4H, 2 x CH_2), 1.34 – 1.25 (m, 2H, CH_2), 1.23 (s, 3H, CH_3). δ_C 142.1 (Cq), 140.3 (Cq), 129.4 (2 x CH), 127.0 (2 x CH), 54.6 (Cq), 52.7 (CH_2N), 34.7 (2 x CH_2), 26.4 (CH_3), 25.9 (CH), 24.6 (2 x CH_2), 21.5 (CH_3). IR (neat) υ/cm^{-1}: 2920, 1454, 1329, 1158, 1094, 816. HRMS (EI) *m/z* calculated for $C_{15}H_{21}NO_2S$ $[M]^+$ = 279.1293; found: 279.1292.

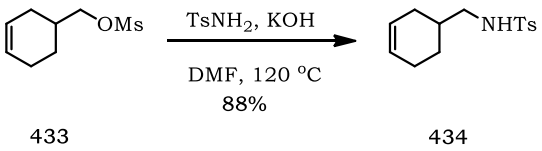
Cyclohex-3-en-1-ylmethyl methanesulfonate 433



432 433

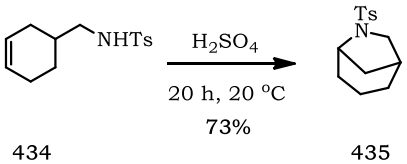
To a stirred solution of the alcohol **432** (1.12 g, 10.0 mmol) in pyridine (10 ml), methanesulfonyl chloride (1.14 g, 10 mmol) was added dropwise. After 2 h the reaction mixture was diluted with water (10 ml), acidified to pH 4 with HCl (5%) and extracted with dichloromethane (3 × 15 ml). The combined 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. δ_H 5.71 – 5.46 (m, 2H, 2 x =CH), 4.04 (d, *J* = 6.6 Hz, 2H, OCH_2), 2.95 (s, 3H, Ms-CH_3), 2.04 – 1.98 (m, 4H, 2 x CH_2), 1.81 – 1.70 (m, 2H, CH_2), 1.41 – 1.23 (m, 1H, CH). δ_C 127.1 (=CH), 125.0 (=CH), 74.0 (OCH_2), 37.0 (CH), 33.3 (Ms-CH_3), 27.5 (CH_2), 25.2 (CH_2), 24.0 (CH_2).

***N*-(Cyclohex-3-en-1-ylmethyl)-4-methylbenzenesulfonamide 434**



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. δ_H 7.78 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 5.63 – 5.58 (m, 2H, NCH_2), 5.18 (*br.* s, 1H, NH), 2.83 (t, *J* = 6.2 Hz, 2H, CH_2), 2.43 (s, 3H, $ArCH_3$), 2.15 – 2.10 (m, 1H, CH), 2.10 – 1.89 (m, 2H, CH_2), 1.83 – 1.50 (m, 3H, CH and CH_2), 1.33 – 1.03 (m, 1H, CH). δ_C 143.3 (Cq), 137.1 (Cq), 129.7 (2 x CH), 127.0 (2 x CH), 125.4 (2 CH), 48.5 (NCH_2), 33.7 (CH), 29.1 (CH_2), 26.0 (CH_2), 24.3 (CH_2), 21.4 (CH_3). IR (neat) υ/cm^{-1}: 3281, 2916, 1431, 1306, 1094, 814. HRMS (EI) *m/z* calculated for $C_{14}H_{19}NO_2S$ $[M]^+$ = 265.1137; found: 265.1135.

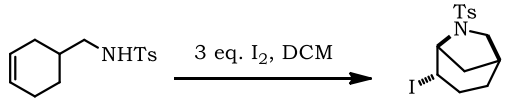
6-Tosyl-6-azabicyclo[3.2.1]octane 435



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. δ_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, NC*H*$_A$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). δ_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) υ/cm^{-1}: 2934, 1454, 1331, 1158, 1091, 814. HRMS (EI) *m/z* calculated for $C_{14}H_{19}NO_2S$ $[M]^+$ = 265.1137; found: 265.1138.

(1S,4S,5S)-4-Iodo-6-tosyl-6-azabicyclo[3.2.1]octane 437[32]

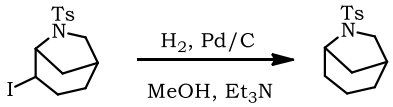


434 436

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 ^{o}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 × 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 °C; δ_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, NC*H*$_A$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). δ_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 (CH_2), 31.0 (CH), 29.6 (CH_2), 26.1 (CH_2), 21.5 ($ArCH_3$). IR (neat) υ/cm^{-1}: 2945, 1597, 1445, 1342, 1159, 1024, 980, 903, 814, 667. HRMS (EI) *m/z* calculated for $C_{14}H_{18}INO_2S$ $[M]^+$ = 391.0103; found: 391. 0093.

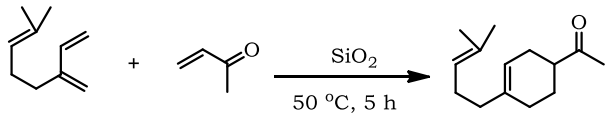
6-Tosyl-6-azabicyclo[3.2.1]octane 435



436 435

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).

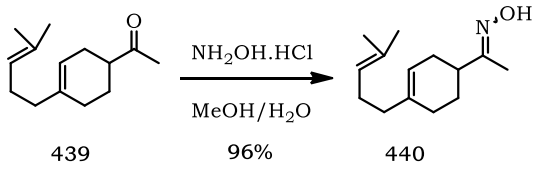
1-(4-(4-Methylpent-3-en-1-yl)cyclohex-3-en-1-yl)ethanone 439[33]



437 438 439

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:[33] δ_H 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, $COCH_3$), 1.91 – 1.78 (m, 8H, 4 x CH_2), 1.21 – 1.25 (m, 2H, CH_2), 1.51 (s, 3H, CH_3), 1.43 (s, 3H, CH_3).

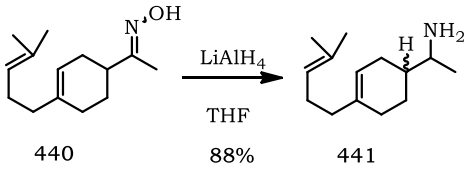
(*E*)-1-(4-(4-Methylpent-3-en-1-yl)cyclohex-3-en-1-yl)ethanone oxime 440[33]



439 96% 440

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 ^{o}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. δ_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_2), 1.91 – 1.85 (m, 2H, CH_2), 1.81 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.53 (s, 3H, CH_3).

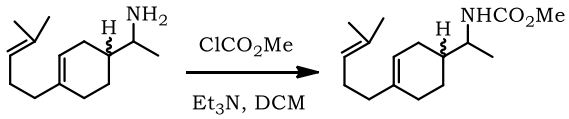
1-(4-(4-Methylpent-3-en-1-yl)cyclohex-3-en-1-yl)ethanamine 441[33]



440 88% 441

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* δ_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_2), 1.90 (dt, *J* = 14.5, 8.9 Hz, 2H, CH_2), 1.68 (dd, *J* = 10.6, 5.7, Hz, 2H, CH_2), 1.61 (s, 3H, CH_3), 1.53 (s, 3H, CH_3) 1.38 – 1.22 (m, 4H, 2 x CH_2), 1.22 – 1.08 (m, 1H, CH), 0.98 (d, *J* = 3.2 Hz, 3H, CH_3). *Diastereoisomer B* δ_H 2.66 – 2.56 (m, 1H, NCH), 1.00 – 0.99 (m, 1H, CH), 1.01 (d, *J* = 3.2 Hz, 3H, CH_3) - only 3 distinct peaks.

Methyl (1-(4-(4-methylpent-3-en-1-yl)cyclohex-3-en-1-yl)ethyl)carbamate 442

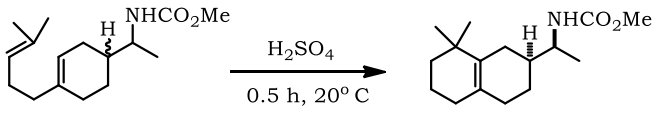


441 82% 442

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 Et_3N (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* δ_H 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, OCH_3), 2.05 – 1.94 (m, 3H, CH and CH_2), 1.93 – 1.84 (m, 3H, CH and CH_2), 1.67 (dd, *J* = 21.6, 8.2 Hz, 2H, CH_2), 1.60 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.27 – 1.09 (m, 1H, CH), 1.08 – 1.05 (d, *J* = 4.1 Hz, 3H, CH_3). δ_C 156.6 (CO_2), 137.6 (Cq), 131.3 (Cq), 124.3 (=CH), 119.6 (=CH), 53.4 (OCH_3), 50.8 (NCH), 39.6 (CH), 37.7 (CH_2), 28.6 (CH_2), 28.4 (CH_2), 27.6 (CH_2), 25.6 (CH_3), 24.8 (CH_2), 17.6 (CH_3).

Diastereoisomer B δ_H 1.04 (d, *J* = 4.1 Hz, 3H, CH_3) only 1 distinct peak. δ_C 137.8 (Cq), 120.0 (=CH), 120.6 (=CH), 120.5 (=CH), 51.8 (OCH_3), 50.7 (NCH), 39.5 (CH), 37.5 (CH_2), 28.2 (CH_2) - only 9 distinct peaks.

Methyl ((*S*)-1-((*S*)-8,8-dimethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-2-yl)ethyl)carbamate 443

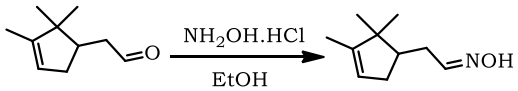


442 90% 443

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; δ_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). δ_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).

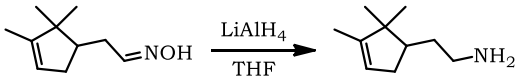
2-(2,2,3-Trimethylcyclopent-3-en-1-yl)acetaldehyde oxime 448



447 448

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 ^oC 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: δ_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 (dddd, *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). δ_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).

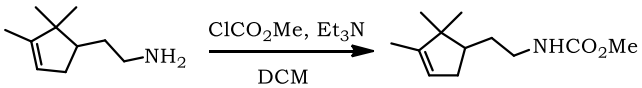
2-(2,2,3-Trimethylcyclopent-3-en-1-yl)ethanamine 449



448 449

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**.

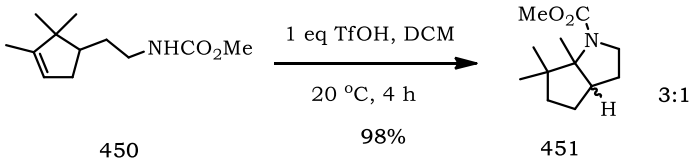
Methyl (2-(2,2,3-trimethylcyclopent-3-en-1-yl)ethyl)carbamate 450



449 450

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_3N (1 ml, 8.8 mmol) at 0 ºC. The mixture was then stirred for 1 h at room temperature to give the *carbamate* **450** (1.39 g, 91%) as a colourless oil. δ_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). δ_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) υ/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



450 451

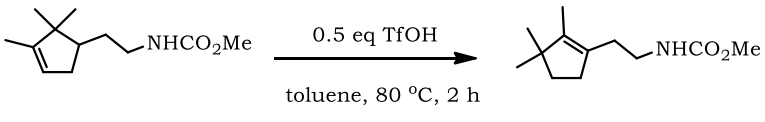
To a stirred solution of the carbamate **450** (211 mg, 1 mmol) in dry diclromethane (10 ml) under nitrogen, cooled in an ice-water bath, was added triflic acid (150 mg, 1 mmol). The resulting mixture stirred was stirred at 20 °C for 4 hours to give the *bicycle* 451 (207 mg, 98%) as a colourless oil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

major product : δ_H 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). δ_C 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).

M*inor product :* δ_H 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). δ_C 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) υ/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.

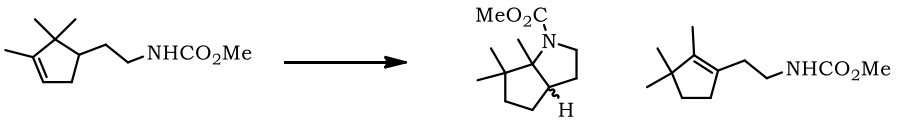
Methyl (2-(2,3,3-trimethylcyclopent-1-en-1-yl)ethyl)carbamate 452



450 452

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%)

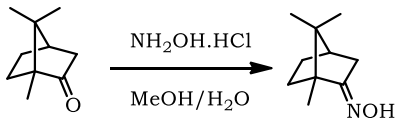
as a colourless oil. δ_H 4.56 (s, 1H, NH), 3.57 (s, 3H, OCH_3), 3.17 – 3.12 (m, 2H, NCH_2), 2.19 – 2.2 (m, 4H, 2 x CH_2), 1.54 (t, *J* = 3.8 Hz, 2H, CH_2), 1.43 (s, 3H, CH_3), 0.89 (s, 6H, 2 x CH_3). δ_C 157.0 (C=O), 142.1 (Cq), 129.8 (Cq), 51.9 (OCH_3), 46.9 (Cq), 49.3 (NCH_2), 38.8 (CH_2), 32.3 (CH_2), 29.2 (CH_2), 26.4 (3 x CH_3).



450 451 452

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^o 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.

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



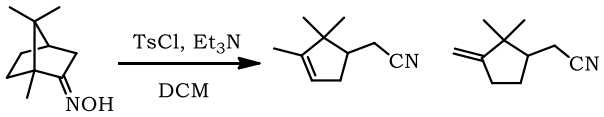
453 454

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 ^{o}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:[34] δ_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). δ_C 169.6 (C=N, Cq), 51.8

(Cq), 48.3 (Cq), 43.8 (CH), 33.1 (CH_2), 32.7 (CH_2), 27.3 (CH_2), 19.8 (CH_3), 18.5 (CH_3), 11.1 (CH_3). IR (neat) υ/cm^{-1}: 3298, 2959, 2876, 1740, 1448, 907. HRMS (EI) *m/z* calculated for $C_{10}H_{17}NO$ $[M]^+$ = 167.1310; found: 167. 1311.

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

2-(2,2-Dimethyl-3-methylenecyclopentyl)acetonitrile 457[35]



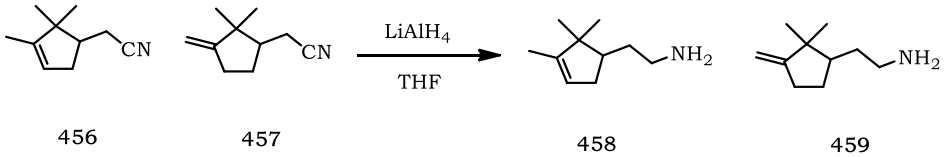
454 456 457

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** δ_H 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, CH_3), 1.06 (s, 3H, CH_3), 0.84 (s, 3H, CH_3). δ_C 147.4 (Cq), 121.1 (=CH), 119.3 (CN), 47.5 (Cq), 46.2 (CH), 37.0 (CH_2), 22.9 (CH_3), 19.8 (CH_3), 17.9 (CH_2), 12.4 (CH_3).

nitriles **457** (<5%) δ_H 4.91 (d, *J* = 12.2 Hz, 1H, $=CH_A$), 4.85 – 4.76 (m, 1H, $=CH_B$), 0.98 (s, 3H, CH_3), 0.89 (s, 3H, CH_3). δ_C 161.2 (=Cq), 104.1 ($=CH_2$), 118.3 (CN), 46.5 (Cq), 45.2 (CH), 38.7 (CH_2), 28.8 (CH_2), 21.8 (CH_2), 19.7 (CH_3), 12.0 (CH_3).

2-(2,2,3-Trimethylcyclopent-3-en-1-yl)ethanamine 458 and

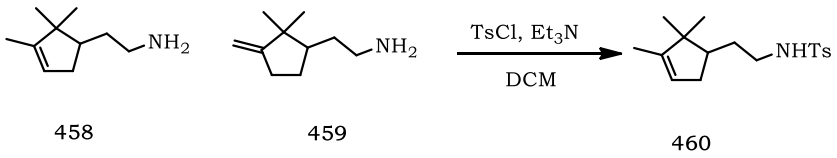
2-(2,2-dimethyl-3-methylenecyclopentyl)ethanamine 259



456 457 458 459

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:[37] 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



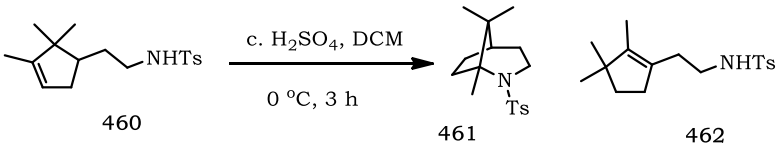
458 459 460

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:[36] 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 (NCH_2), 35.5 (CH_2), 30.3 (CH_2), 25.8 (CH_3), 21.4 (CH_3), 19.8 (CH_3), 12.5 (CH_3).

IR (neat) υ/cm^{-1}: 3277, 2955, 2930, 2866, 1435, 1323, 1092, 910, 813. HRMS (EI) *m/z* calculated for $C_{17}H_{25}NO_2S$ $[M]^+$ = 307.1606; found: 307.1603.

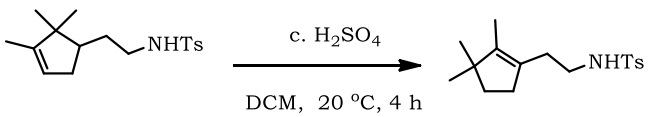
6,6,6a-Trimethyl-1-tosyloctahydrocyclopenta[b]pyrrole 457



460 461 462

By general procedure B, to the sulfonamide **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 *sulfonamide* **462** as a mixture 1:1 with *azabicyclo-octane* **457** (86 mg, 46%), wich separated after crystallization in dichloromethane/hexanes as colourless crystals m.p. 124 – 126 °C. δ_H 7.68 – 7.64 (d, *J* = 7.9 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 2H), 3.19 – 3.03 (m, 2H, NCH_2), 2.44 (dt, *J* = 14.8, 5.7 Hz, 1H), 2.36 (s, 3H, Ar-CH_3), 2.18 – 2.06 (m, 2H, CH_2), 1.94 – 1.83 (m, 4H, 2 x CH_2), 1.32 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 0.87 (s, 3H, CH_3). δ_C 143.4 (Cq), 139.2 (Cq), 129.8 (2 x CH), 127.1 (2 x CH), 53.7 (NCq), 39.2 (NCH_2), 33.3 (CH_2), 27.3 (CH_2), 27.0 (CH_2), 21.5 (CH_3), 19.7 (CH_3), 17.3 (CH_3), 15.3 (CH_3). IR (neat) υ/cm^{-1}: 2951, 2926, 1655, 1329, 1094, 910. HRMS (EI) *m/z* calculated for $C_{17}H_{25}NO_2S$ $[M]^+$ = 307.1606; found: 307.1599.

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

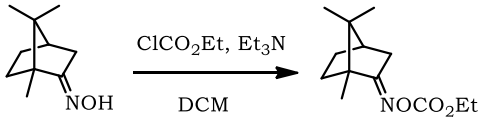


460 462

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. δ_H 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).

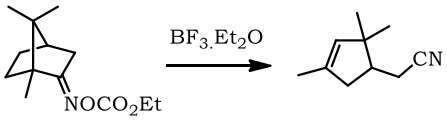
(1*S*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one O-ethoxycarbonyl oxime 464[38]



454 464

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. δ_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). δ_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) υ/cm^{-1}: 2961, 2876, 1770, 1447, 1361, 997, 984.

2-(2,2,4-Trimethylcyclopent-3-en-1-yl)acetonitrile 465[38]

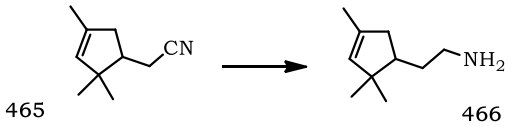


464 465

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:[38] δ_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). δ_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) υ/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.

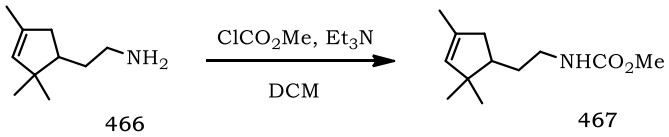
2-(2,2,4-Trimethylcyclopent-3-en-1-yl)ethanamine 466



465 466

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. δ_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). δ_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) υ/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.

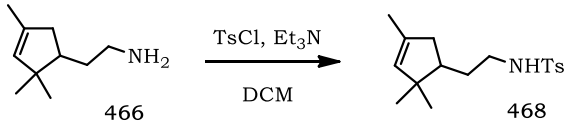
Methyl (2-(2,2,4-trimethylcyclopent-3-en-1-yl)ethyl)carbamate 467



466 467

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 Et_3N (1 ml, 8.8 mmol) at 0 ^oC. The mixture was then stirred for 1 h at room temperature to give the *carbamate* **467** (1.12 g, 88%) as a colourless oil. δ_H 5.15 (s, 1H,=CH), 4.71 (*br*. s, 1H, NH), 3.60 (s, 3H, OCH_3), 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, CH_3), 1.44 – 1.31 (m, 1H, CH), 0.89 (s, 3H, CH_3), 0.67 (s, 3H, CH_3). δ_C 157.1 (C=O), 148.5 (Cq), 121.5 (=CH), 51.9 (OCH_3), 47.7 (Cq), 46.8 (CH), 40.6 (NCH_2), 35.4 (CH_2), 30.5 (CH_2), 25.7 (CH_3), 19.7 (CH_3), 12.5 (CH_3). HRMS (EI) *m/z* calculated for $C_{12}H_{21}NO_2$ $[M]^+$ = 211.1572; found: 211. 1571.

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

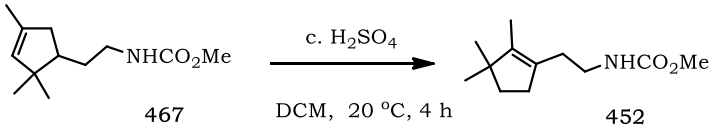


466 468

By general procedure A, tosyl chloride (1.96 g, 10 mmol) was added to the amine **466** (1.00 g, 6.5 mmol) and Et_3N (1.5 ml, 12.1 mmol) at 0 ^oC. The mixture was then stirred for 1 h at room temperature to give the *sulfonamide* **468** (1.80 g, 90%) as a colourless oil. δ_H 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-CH_3), 2.13 – 2.05 (m, 1H, CH), 1.70 – 1.58 (m, 3H, CH and CH_2), 1.49 (s, 3H, CH_3), 1.31 (dddd, *J* = 12.4, 10.2, 8.1, 4.6 Hz, 1H, CH), 0.82 (s, 3H, CH_3), 0.59 (s, 3H, CH_3). δ_C 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 (NCH_2), 35.1 (CH_2), 30.1 (CH_2), 25.6 (CH_3), 21.5 (CH_3), 19.6

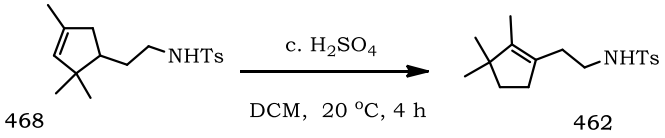
(CH_3), 12.5 (CH_3). IR (neat) υ/cm^{-1}: 3279, 2963, 1699, 1448, 1327, 1094, 815. HRMS (ES) *m/z* calculated for $C_{17}H_{24}NO_2S$ $[M]^+$ = 306.1528; found: 306.1527.

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



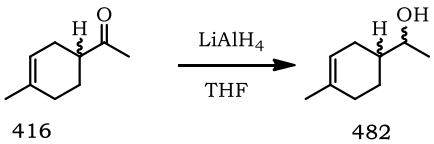
To a stirred solution of the carbamate **467** (211 mg, 1 mmol) in dry dicloromethane (10 ml) under nitrogen, cooled in an ice-water bath, was added sulfuric acid (3 drops). The resulting mixture stirred was stirred at 20 °C for 4 hours to give the *carbamate* **452** (200 mg, 95%) as a colourless oil.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



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.

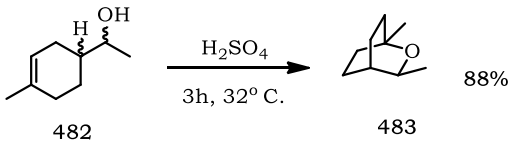
1-(4-Methylcyclohex-3-en-1-yl)ethanol 482[39]



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* δ_H 5.37 – 5.22 (m, 1H, =CH), 3.64 – 3.55 (m, 1H, CH), 2.12 – 1.98 (m, 1H,

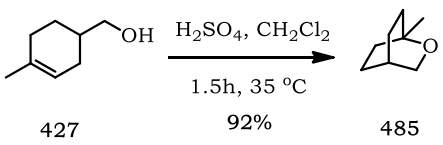
CH), 1.99 – 1.86 (m, 3H, CH and CH_2), 1.71 (*app*. d, *J* = 14.8 Hz, 1H, CH), 1.58 (s, 3H, CH_3), 1.47 – 1.38 (m, 1H, CH), 1.12 (d, *J* = 7.1 Hz, 3H, CH_3). δ_C 134.0 (Cq), 120.2 (=CH), 71.7 (OCH), 41.1 (CH), 30.8 (CH_2), 28.0 (CH_2), 25.4 (CH_2), 23.4 (CH_3), 20.8 (CH_3). *Diastereoisomer B* δ_H 3.54 – 3.49 (m, 1H, CH) - only 1 distinct peak. δ_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) υ/cm^{-1}: 3351, 2916, 1448, 1375, 1072, 1017, 912. HRMS (EI) *m/z* calculated for $C_9H_{14}O$ $[M]^+$ = 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 ºC to give the *oxabicyclo-octane* **483** (135 mg, 88%) as a pale yellow oil. δ_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). δ_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) υ/cm^{-1}: 2986, 2912, 2888, 1713, 1458, 1373, 1209, 1055, 957. HRMS (EI) *m/z* calculated for $C_9H_{16}O$ $[M]^+$ = 140.1201; found: 140.1206.

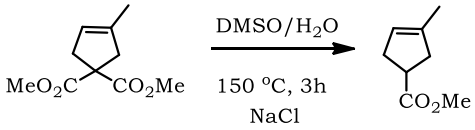
1-Methyl-2-oxabicyclo[2.2.2]octane 485



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%). δ_H 3.81 (*app*. dd, *J* = 2.9, 1.5 Hz, 2H, CH_2), 1.70 (dd, *J* = 1.1, 1.1 Hz, 4H, 2 x CH_2), 1.56 (br. s, 2H, CH_2), 1.54 – 1.45 (m, 2H, CH_2), 1.15 (d, *J* = 8.2 Hz, 1H), 0.96 (s, 3H, CH_3). δ_C 70.1 (OCH_2), 68.1 (Cq), 32.9 (2 x CH_2), 27.1 (CH_3), 24.9 (CH), 24.8 (2 x CH_2). IR (neat) υ/cm^{-1}: 2924, 2864, 1377, 1262, 1093, 910. HRMS (EI) *m/z* calculated for $C_8H_{14}O$ $[M]^+$ = 126.1045; found: 126.1044.

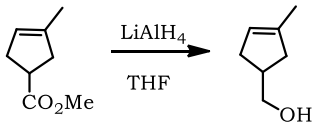
Methyl 3-methylcyclopent-3-enecarboxylate 489



488 489

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. δ_H 5.20 – 5.11 (m, 1H, =CH), 3.61 (s, 3H, OCH_3), 3.15 – 3.00 (m, 1H, CH), 2.59 – 2.48 (m, 3H, CH and CH_2), 2.47 – 2.35 (m, 1H, CH), 1.63 (s, 3H, CH_3). δ_C 176.6 (Cq, CO_2), 138.6 (Cq), 122.4 (=CH), 51.6 (OCH_3), 42.2 (CH), 40.2 (CH_2), 36.4 (CH_2), 16.1 (CH_3). All data obtained were in accordance with those previously reported in the literature.[40]

(3-Methylcyclopent-3-en-1-yl)methanol 490[38]

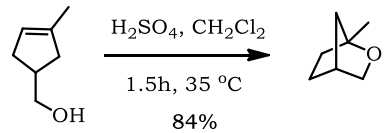


489 490

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. δ_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). δ_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



490 491

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%). δ_H 3.70 (d, *J* = 6.7 Hz, 1H, OC*H*$_A$CH$_B$), 3.49 (d, *J* = 6.7 Hz, 1H, OCH$_A$C*H*$_B$), 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). δ_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[41]

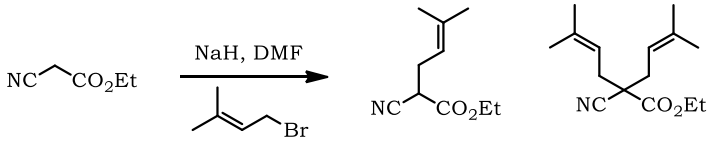
To sodium hydride (60% dispersion in mineral oil, 0.80 g, 20 mmol, 1.0 eq.) was added dry DMF (20 ml) under nitrogen and the suspension then cooled to 0 °C. To the suspension was slowly added ethyl cyanoacetate (6.80 g, 60 mmol, 3.0 eq.) in DMF (10 ml). After 15 min, an alkyl halide (20 mmol, 1.0 eq.) were added dropwise *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[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[43] and

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



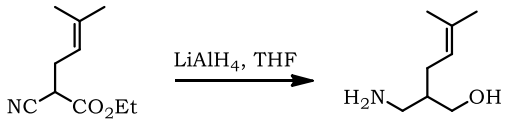
510 511 512

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).

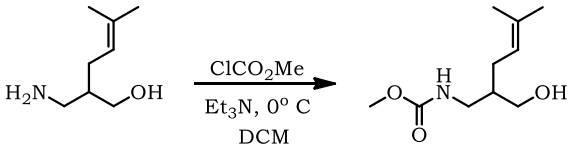
2-(Aminomethyl)-5-methylhex-4-en-1-ol 513



511 513

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_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_3), 1.10 (s, 3H, CH_3). δ_C 132.7 (Cq), 121.8 (=CH), 67.6 (OCH_2), 46.2 (NCH_2), 41.9 (CH), 27.7 (CH_2), 25.4 (CH_3), 17.5 (CH_3). IR (neat) υ/cm^{-1}: 3323, 2967, 2913, 2856, 1451, 1377, 1038, 910. HRMS (EI) *m/z* calculated for $C_8H_{17}NO$ $[M]^+$ = 143.1310; found: 143.1310.

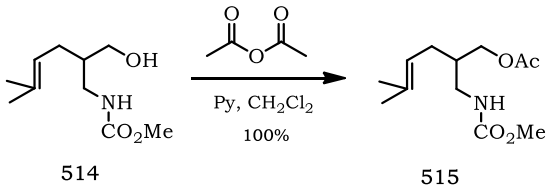
Methyl 2-(hydroxymethyl)-5-methylhex-4-en-1-ylcarbamate 514



513 514

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_3N (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_H 5.19 (*br*. s, 1H, NH), 5.16 – 5.04 (m, 1H, =CH), 3.68 (s, 3H, OCH_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_3), 1.63 (s, 3H, CH_3). δ_C 158.3 (C=O), 133.2 (Cq), 121.7 (=CH), 62.9 (CH_2OH), 52.2 (OCH_3), 41.9 (CH), 41.6 (NCH_2), 27.5 (CH_2), 25.6 (CH_3), 17.6 (CH_3). IR (neat) υ/cm^{-1}: 3343, 2934, 1700, 1526, 1449, 1256, 1194, 1034, 910. HRMS (EI) *m/z* calculated for $C_{10}H_{17}NO_2$ $[M]^+$ = 183.1269; found: 183.1258.

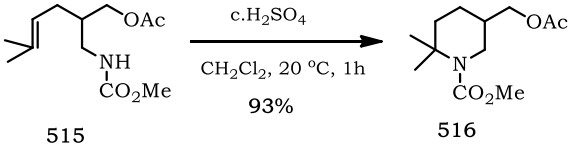
2-(Methoxycarbonylaminomethyl)-5-methylhex-4-en-1-yl acetate 515



514 515

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. δ_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). δ_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).

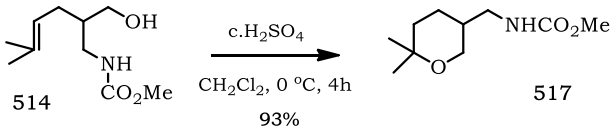
Methyl 5-(acetoxymethyl)-2,2-dimethylpiperidine-1-carboxylate 516



515 516

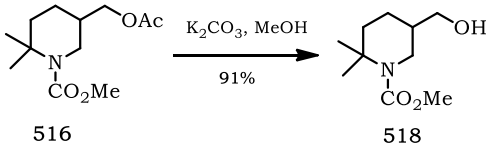
By general procedure B, to the protected amino-alcohol **515** (243 mg, 1.0 mmol) in dry dichloromethane (10 ml) concentrated sulfuric acid (3 drops) was added and the resulting mixture stirred for 1 h at 20 °C to give the *piperidine* **516** (225 mg, 93%) as a colourless oil. δ_H 3.85 (dd, *J* = 11.0, 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). δ_C 171.0 (Ac-C=O), 156.9 (C=O), 66.4 (OCH_2), 54.8 (NCq), 51.9 (OCH_3), 43.1 (CH_2N), 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%). δ_H 4.60 (*app*. *br*. s, NH, 1H), 3.66 (dd, *J* = 3.9, 1.9 Hz, 1H), 3.65 (s, 3H, OCH_3), 3.62 (dd, *J* = 4.1, 1.9 Hz, 1H), 3.09 - 2.92 (m, 2H, CH_2N), 1.91 (m, 1H), 1.70 - 1.60 (m, 2H) 1.43 - 1.29 (m, 2H), 1.16 (s, 3H, CH_3), 1.12 (s, 3H, CH_3). δ_C 157.2 (C=O), 71.3 (OCq), 64.3 (OCH_2), 52.1 (OCH_3), 43.1 (CH_2N), 36.2 (CH), 35.1 (CH_2), 29.2 (CH_3), 23.7 (CH_2), 23.3 (CH_3). IR (neat) υ/cm^{-1}: 3329, 2970, 2930, 1701, 1533, 1452, 1247, 1084, 1009. HRMS (EI) *m/z* calculated for $C_{10}H_{19}NO_3$ $[M]^+$ = 201.1365; found: 201.1370.

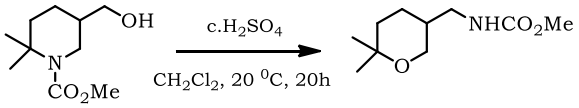
Methyl 2,2-dimethyl-5-(hydroxymethyl)piperidine-1-carboxylate 518



To a solution of the acetoxymethyl 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. δ_H 3.62 (dd, *J* = 13.7, 4.6 Hz, 1H), 3.58 (s, 3H, OCH_3), 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, CH_2), 1.39 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.22 – 1.07 (m, 1H, CH). δ_C 157.2

(C=O), 65.2 (OCH_2), 55.1 (NCq), 51.9 (OCH_3), 42.7 (CH_2N), 38.0 (CH_2), 36.8 (CH), 27.6 (CH_3), 24.8 (CH_3), 20.8 (CH_2). IR (neat) υ/cm^{-1}: 3416, 2947, 2930, 1684, 1539, 1440, 1381, 1157, 1022. HRMS (EI) *m/z* calculated for $C_{10}H_{19}NO_3$ $[M]^+$ = 201.1365; found: 201.1368.

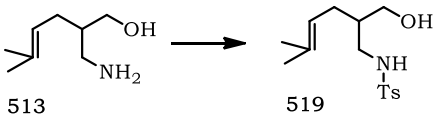
Methyl (6,6-dimethyltetrahydro-2H-pyran-3-yl)methylcarbamate 517



518 517

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 ^oC 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**.

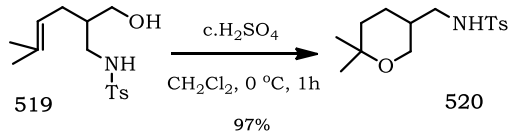
***N*-(2-(Hydroxymethyl)-5-methylhex-4-en-1-yl)-4-methylbenzenesulfonamide 519**



513 519

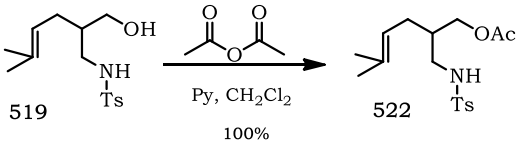
By general procedure A, tosyl chloride (553 mg, 3.0 mmol) was added to the amino-alcohol **513** (0.41 g, 2.9 mmol) and Et_3N (0.5 ml, 4.4 mmol) at -78 ^oC. The mixture was then stirred for 1 h as it warmed to room temperature to give the *sulfonamide* **519** (0.60 g, 70%) as a colourless oil. δ_H 7.71 – 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, $ArCH_3$), 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, CH_3), 1.49 (s, 3H, CH_3). δ_C 143.1 (Cq), 136.4 (Cq), 133.7 (Cq), 129.5 (2 x CH), 126.8 (2 x CH), 120.9 (CH), 64.2 (OCH_2), 44.9 (NCH_2), 40.6 (CH), 27.2 (CH_2), 25.5 ($ArCH_3$), 21.3 (CH_3), 17.6 (CH_3).

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



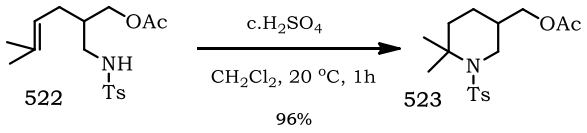
By general procedure B, to the *N*-tosyl alcohol **519** (100 mg, 0.3 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for 1 h at 0 °C to give the *tetrahydropyran* **520** (97 mg, 97%) as a colourless oil. δ_H 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). δ_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) υ/cm^{-1}: 3220, 2974, 2930, 1454, 1325, 1090, 912. HRMS (EI+) *m/z* calculated for $C_{15}H_{23}NO_3NaS$ $[M+Na]^+$ = 320.1296; found: 320.1285.

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



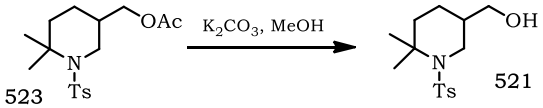
By procedure E, the alcohol **519** (297 mg, 1.0 mmol) was converted into the corresponding *acetate* **522** (339 mg, 100%), a colourless oil. δ_H 7.72 – 7.62 (m, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 4.98 – 4.87 (m, 1H, =CH), 4.79 (t, *J* = 6.1 Hz, 1H, NH), 4.01 (dd, *J* = 11.4, 4.3 Hz, 1H), 3.90 – 3.75 (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). δ_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) υ/cm^{-1}: 3285, 2969, 1732, 1599, 1447, 1327, 1240, 1092, 1033, 910. HRMS (EI) *m/z* calculated for $C_{17}H_{25}NNaO_4S$ $[M+Na]^+$ = 362.1402; found: 362.1400.

Methyl 5-(acetoxymethyl)-2,2-dimethylpiperidine-1-carboxylate 523



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^{o} C to give the *piperidine* **523** as a colourless oil (269 mg, 96%). δ_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, $ArCH_3$), 1.91 (s, 3H, $COCH_3$), 1.90 – 1.77 (m, 1H), 1.51 (ddd, *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_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 (NCq), 45.4 (NCH_2), 39.8 (CH_2), 35.7 (CH), 28.7 ($ArCH_3$), 23.2 (CH_2), 23.0 (Ac-CH_3), 21.4 (CH_3), 20.8 (CH_3). IR (neat) υ/cm^{-1}: 2928, 1737, 1454, 1321, 1228, 1089, 910. HRMS (ES) *m/z* calculated for $C_{17}H_{26}NO_4S$ $[M+H]^+$ = 340.1583; found: 340.1585.

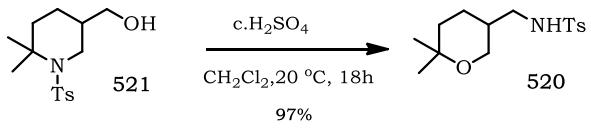
6,6-Dimethyl-1-tosylpiperidine-3-methanol 521



To a solution of acetoxymethyl 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_H δ 7.65 – 7.59 (m, 2H), 7.19 (d, *J* = 7.8 Hz, 2H), 3.81 (ddd, *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, $ArCH_3$), 2.01 (*br*. s, 1H, OH), 1.84 – 1.70 (m, 1H), 1.59 (dq, *J* =

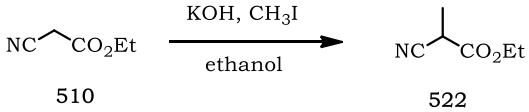
13.3, 4.3 Hz, 1H), 1.51 – 1.35 (m, 2H), 1.30 (s, 3H, CH_3), 1.23 (ddd, *J* = 10.2, 8.0, 4.4 Hz, 1H), 1.12 (s, 3H, CH_3). δ_C 142.5 (Cq), 139.6 (Cq), 129.2 (2 x CH), 126.7 (2 x CH), 64.3 (OCH_2), 57.7 (NCq), 45.2 (NCH_2), 39.5 (CH_2), 38.4 (CH), 28.2 (CH_3), 23.3 (CH_3), 22.5 (CH_2), 21.2 (CH_3). IR (neat) υ/cm^{-1}: 3489, 2926, 1454, 1317, 1089, 1016, 914. HRMS (EI) *m/z* calculated for $C_{15}H_{23}NO_3S$ $[M]^+$ = 297.1399; found: 297.1388.

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



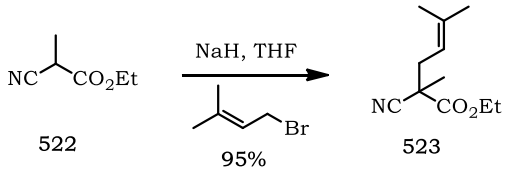
By general procedure B, to the alcohol **521** (103 mg, 0.35 mmol) in dry dichloromethane (10 ml) concentrated sulfuric acid (12 mg, 0.12 mmol) was added and the resulting mixture stirred for 18 h at 20 °C to give the *tetrahydropyran* **520** (98 mg, 97%) as a colourless oil, which exhibited spectroscopic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

Ethyl 2-cyanopropanoate 522



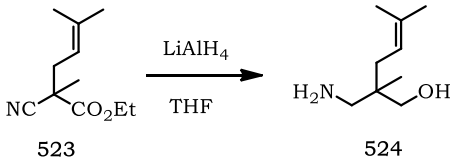
By typical procedure C, to potasium hydroxide (1.12 g, 20 mmol, 1.0 eq.) in ethanol (20 ml) under nitrogen at 0 °C was slowly added ethyl cyanoacetate **510** (2.27 g, 20 mmol, 1.0 eq.). After 15 min, methyl iodide (2.84 g, 20 mmol, 1.0 eq.) was added to give the *cyanopropanoate* **522** (2.14 g, 84%) as colourless oil. All data obtained were in accordance with those previously reported in the literature:[44] δ_H 4.28 (q, *J* = 7.1 Hz, 2H, OCH_2), 3.56 (q, *J* = 7.4 Hz, 1H, CH), 1.63 (d, *J* = 7.4 Hz, 3H, CH_3), 1.34 (t, *J* = 7.1 Hz, 3H, CH_3). δ_C166.5 (CO_2), 117.3 (CN), 62.8 (OCH_2), 31.5 (CH), 15.3 (CH_3), 13.9 (CH_3).

Methyl 2-cyano-2,5-dimethylhex-4-enoate 523



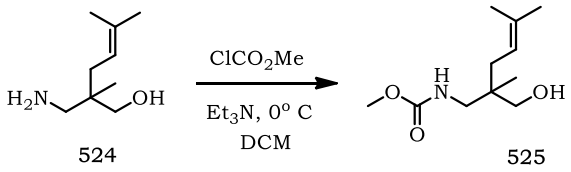
By typical procedure D, to sodium hydride (60% dispersion in mineral oil, 0.40 g, 10 mmol, 1.0 eq.) in dry tetrahydrofuran (20 ml) under nitrogen at 0 °C was slowly added methyl cyanoacetate **522** (1.10 g, 10 mmol, 1.0 eq.) in dry tetrahydrofuran (10 ml). After 15 min, prenyl bromide (1.50 g, 10 mmol, 1.0 eq.) was added to give the *cyanoacetate* **523** (1.71 g, 95%) as a colourless oil. δ_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_A), 2.42 (dd, *J* = 14.2, 7.6 Hz, 1H, 3-H_B), 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). δ_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) υ/cm^{-1}: 2986, 2247, 1786, 1717, 1452, 1381, 1236, 1190, 1122, 1111, 1016, 914. HRMS (EI) *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



Following generasl 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. δ_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_AH_B), 2.63 (d, *J* = 12.5 Hz, 1H, NCH_AH_B), 2.57 – 2.52 (*br*. s, 3H, NH_2, OH), 1.99 (dd, *J* = 14.4, 8.0 Hz, 1H, =CCH_AH_B), 1.90 (dd, *J* = 14.4, 7.4 Hz, 1H, =CCH_AH_B), 1.65 (d, *J* = 0.7 Hz, 3H, CH_3), 1.53 (s, 3H, CH_3), 0.75 (s, 3H, CH_3). δ_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).

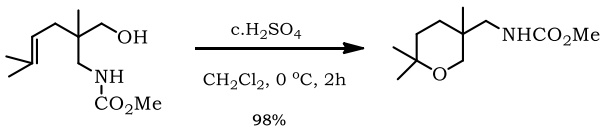
Methyl (2-(hydroxymethyl)-2,5-dimethylhex-4-en-1-yl)carbamate 525



524 525

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_3N (1.25 ml, 11 mmol, 1.3 eq.) to give the *N-protected amino-alcohol* **525** (1.54 g, 90%) as a colourless oil. δ_H 5.29 (*br*. s, 1H, NH), 5.15 – 5.10 (m, 1H, =CH), 3.66 (s, 3H, OCH_3), 3.23 (dd, *J* = 11.7, 7.0 Hz, 1H), 3.21 (dd, *J* = 11.7, 7.0 Hz, 1H), 3.07 (dd, *J* = 14.3, 6.7 Hz, 1H), 2.99 (dd, *J* = 14.3, 6.7 Hz, 1H), 1.91 (d, *J* = 7.7 Hz, 2H, CH_2), 1.70 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 0.79 (s, 3H, CH_3). δ_C 158.6 (C=O), 134.1 (Cq), 119.2 (=CH), 67.1 (CH_2OH), 52.4 (OCH_3), 46.4 (NCH_2), 40.3 (Cq), 33.3 (CH_2), 26.0 (CH_3), 19.2 (CH_3), 17.8 (CH_3). IR (neat) υ/cm^{-1}: 3331, 2964, 2928, 1696, 1527, 1454, 1194, 1141, 777, 731. HRMS (EI) *m/z* calculated for $C_{11}H_{19}NO_2$ $[M-H_2O]^+$ = 197.1416; found: 197.1422.

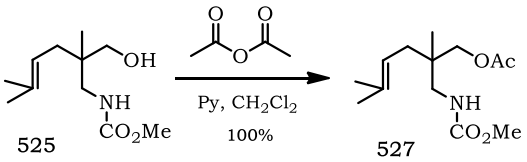
Methyl (3,6,6-trimethyltetrahydro-2H-pyran-3-ylmethyl)carbamate 526



525 526

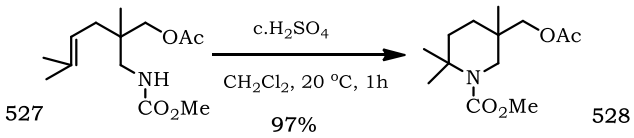
By general procedure B, to the *N*-protected amino-alcohol **525** (160 mg, 0.74 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for 2 h at 0 °C to give the *tetrahydropyran* **526** as a colourless oil (156 mg, 98%). δ_H 4.73 (*br*. s, NH, 1H), 3.60 (s, 3H, OCH_3), 3.33 – 3.24 (m, 2H), 3.22 (dd, *J* = 11.9, 4.8 Hz, 1H), 2.98 (dd, *J* = 13.8, 6.1 Hz, 1H), 1.55 – 1.41 (m, 2H), 1.41 – 1.26 (m, 2H), 1.13 (s, 6H, 2 x CH_3), 0.80 (s, 3H, CH_3). δ_C 157.5 (C=O), 71.3 (OCq), 68.5 (OCH_2), 52.1 (OCH_3), 47.3 (CH_2N), 33.7 (Cq), 32.1 (CH_2), 29.1 (CH_2), 27.1 (CH_3), 25.4 (CH_3), 21.3 (CH_3). IR (neat) υ/cm^{-1}: 3354, 2931, 1705, 1537, 1452, 1367, 1074, 1011, 916, 829. HRMS (EI) *m/z* calculated for $C_{11}H_{21}NO_3$ $[M]^+$ = 215.1521; found: 215.1518.

2-(Methoxycarbonylaminomethyl)-2,5-dimethylhex-4-en-1-yl acetate 527



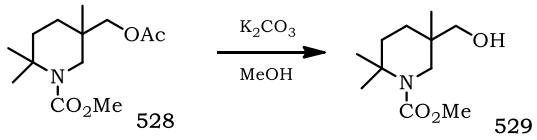
By general procedure E, the alcohol **525** (180 mg, 0.8 mmol) was reacted with acetic anhydride (0.1 ml, 1.1 mmol) to give the *protected alcohol* **527** (215 mg, 100%) as a colourless oil. δ_H 5.07 (t, *J* = 7.8 Hz, 1H, =CH), 4.91 (*br*. s, 1H, NH), 3.82 (d, *J* = 11.2 Hz, 1H), 3.75 – 3.70 (m, 1H), 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) υ/cm^{-1}: 3360, 2968, 1699, 1531, 1456, 1369, 1240, 1037, 910, 777.

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



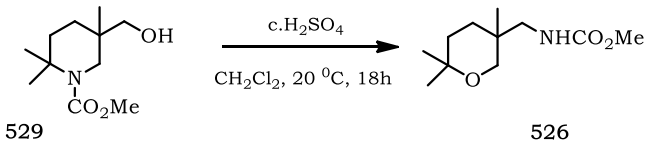
By general procedure B, to the protected amino-alcohol **527** (190 mg, 0.74 mmol) in dry dichloromethane (10 ml) concentrated sulfuric acid (2 drops) was added and the resulting mixture stirred for 1 h at 20 °C to give the *piperidine* **528** (184 mg, 97%) as a colourless oil. δ_H 3.75 (*app*. d, *J* = 1.9 Hz, 2H, OCH_2), 3.54 (s, 3H, OCH_3), 3.31 (d, *J* = 13.9 Hz, 1H, NCH_AH_B), 2.96 (d, *J* = 13.9 Hz, 1H, NCH_AH_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). δ_C 171.1 (Me-C=O), 157.0 (CO_2), 70.2 (OCH_2), 55.0 (NCq), 51.9 (OCH_3), 47.6 (CH_2N), 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) υ/cm^{-1}: 2962, 1742, 1699, 1526, 1442, 1379, 1138, 1035, 910, 775. HRMS (ES) *m/z* calculated for $C_{13}H_{23}NO_4Na$ $[M+Na]^+$ = 280.1525; found: 280.1534.

Methyl 5-(hydroxymethyl)-2,2,5-trimethylpiperidine-1-carboxylate 529



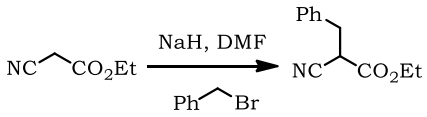
To a solution of acetoxymethyl piperidine **528** (150 mg, 0.6 mmol) in undried methanol (5 ml) was added potassium carbonate (200 mg, 1.45 mmol). The reaction was stirred for 24 h at room temperature. The solvent was removed and the residue was diluted with water (5 ml) and extracted with dichloromethane (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, OCH_3), 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, CH_3), 1.32 (*app*. t, *J* = 3.3 Hz, 1H), 1.29 (s, 3H, CH_3), 1.20 (ddd, *J* = 14.0, 6.6, 4.0 Hz, 1H), 0.87 (s, 3H, CH_3). δ_C 157.7 (C=O), 69.4 (OCH_2), 55.1 (NCq), 52.0 (OCH_3), 47.2 (CH_2N), 36.5 (CH_2), 36.1 (Cq), 27.9 (CH_2), 26.1 (CH_3), 25.9 (CH_3), 22.5 (CH_2). IR (neat) υ/cm^{-1}: 3447, 2932, 2870, 1682, 1440, 1364, 1275, 1190, 1154, 1049. HRMS (EI) *m/z* calculated for $C_{11}H_{21}NO_3$ $[M]^+$ = 215.1521; found: 215.1521.

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



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 ^{o}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

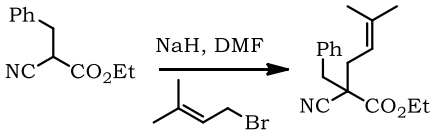


510 87% 530

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:[45] δ_H 7.44 – 7.24 (m, 5H), 4.25 (q, *J* = 7.1 Hz, 2H, OCH_2), 3.75 (dd, *J* = 8.4, 5.8 Hz, 1H), 3.30 (dd, *J* = 13.8, 5.8 Hz, 1H, PhC$\underline{H}_A$H$_B$), 3.21 (dd, *J* = 13.8, 8.4 Hz, 1H, PhCH$_A$$\underline{H}_B$), 1.29 (t, *J* = 7.1 Hz, 3H, CH_3). δ_C 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 (OCH_2), 39.6 (CH), 35.8 (CH_2), 13.9 (CH_3).

IR (neat) υ/cm^{-1}: 3032, 2988, 2251, 1720, 1456, 1260, 1198, 1030. HRMS (APCI) *m/z* calculated for $C_{12}H_{14}NO_2$ $[M+H]^+$ = 204.1025; found: 204.1019.

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

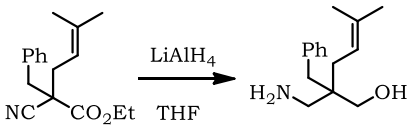


530 93% 531

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. δ_H 7.44 – 7.09 (m, 5H), 5.15 (*br*. t, *J* = 7.5 Hz, 1H, =CH), 4.05 (q, *J* = 7.1 Hz, 2H, OCH_2), 3.12 (d, *J* = 13.5 Hz, PhC$\underline{H}_A$H$_B$), 3.00 (d, *J* = 13.5 Hz,

PhCH$_A$$\underline{H}_B$), 2.65 (dd, *J* = 14.1, 7.7 Hz, 1H, =CHC$\underline{H}_A$H$_B$), 2.49 (dd, *J* = 14.1, 7.3 Hz, 1H, =CHCH$_A$$\underline{H}_B$), 1.68 (s, 3H, CH$_3$), 1.59 (s, 3H, CH$_3$), 1.07 (t, *J* = 7.1 Hz, 3H, CH$_3$). δ_C 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.

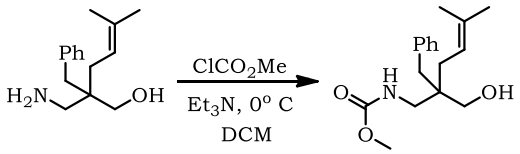
2-(Aminomethyl)-2-benzyl-5-methylhex-4-en-1-ol 532



531 532

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_AH$_B$), 1.83 (dd, *J* = 13.7, 5.8 Hz, 1H, =CCH$_A$$H_B$), 1.68 (d, *J* = 1.0 Hz, 3H, CH$_3$), 1.53 (s, 3H, CH$_3$). δ_C 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.

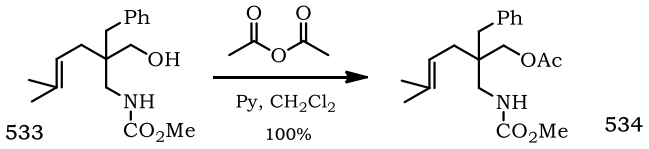
Methyl (2-(hydroxymethyl)-2,5-dimethylhex-4-en-1-yl)carbamate 533



532 533

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_3N (1.25 ml, 11 mmol, 1.3 eq.) to give the *N-protected amino-alcohol* **533** (1.65 g, 71%) as a colourless oil. δ_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). δ_C 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_2OH), 52.5 (CH_3O), 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) υ/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.

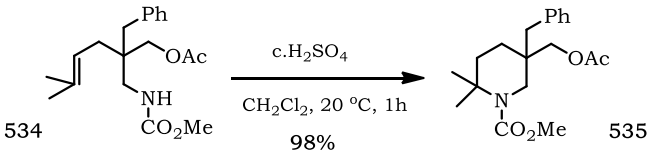
2-Acetyloxymethyl-2-benzyl-1-methoxycarbonylamino-5-methylhex-4-ene 534



533 534

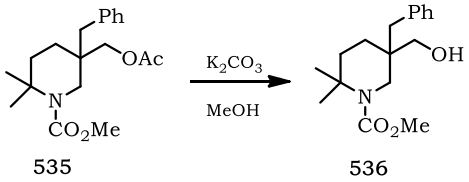
By procedure E, but for 16 h, the alcohol **533** (180 mg, 0.8 mmol) was converted into the corresponding *acetate* **534** (215 mg, 100%), a colourless oil. δ_H 7.26 – 7.12 (m, 4H), 7.06 (d, *J* = 7.0 Hz, 1H), 5.19 (*br*. t, *J* = 7.0 Hz, 1H, =CH), 4.78 (*br*. s, 1H, NH), 3.83 (d, *J* = 11.3 Hz, 1H, CH_AH_BOAc), 3.73 (d, *J* = 11.3 Hz, 1H, CH_AH_BOAc), 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). δ_C 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-(acetoxymethyl)-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. δ_H 7.37 – 6.67 (m, 5H), 3.76 (d, J = 11.1 Hz, 1H, CH_AH$_B$OAc), 3.65 (d, J = 11.1 Hz, 1H, CH$_A$$H_B$OAc), 3.56 (s, 3H, OCH$_3$), 3.28 (d, J = 14.1 Hz, 1H, NCH_AH$_B$), 3.18 (d, J = 14.1 Hz, 1H, NCH$_A$$H_B$), 2.64 (d, J = 13.4 Hz, 1H, PhCH_AH$_B$), 2.52 (d, J = 13.4 Hz, 1H, PhCH$_A$$H_B$), 2.03 (s, 3H, Ac-CH$_3$), 1.44 – 1.38 (m, 2H), 1.31 (s, 6H, 2 x CH$_3$), 1.18 – 1.11 (m, 2H, CH$_2$). δ_C 171.1 (Ac-CO), 157.1 (CO$_2$), 137.0 (Cq), 132.2 (CH), 130.4 (2 x CH), 128.1 (2 x CH), 67.3 (OCH$_2$), 55.3 (NCq), 52.1 (OCH$_3$), 46.4 (CH$_2$N), 41.2 (CH$_2$), 38.2 (CH$_2$), 36.3 (Cq), 26.0 (CH$_3$), 25.7 (CH$_3$), 25.7 (CH$_2$), 20.9 (CH$_3$).

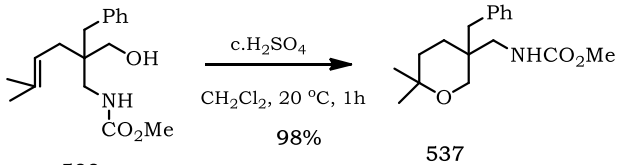
Methyl 5-benzyl-2,2-dimethyl-5-hydroxymethylpiperidine-1-carboxylate 536



To a solution of the acetoxymethyl 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. δ_H 7.34 – 6.71 (m, 5H), 3.59 (s, 3H, OCH$_3$), 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, CH_2), 1.37 (t, *J* = 4.2 Hz, 2H, CH_2), 1.30 (s, 3H, CH_3), 1.27 (s, 3H, CH_3). δ_C 157.6 (Cq, CO_2), 147.6 (Cq), 130.5 (2 x CH), 127.9 (2 x CH), 126.1 (CH), 66.4 (OCH_2), 55.3 (NCq), 52.4 (OCH_3), 47.0 (CH_2N), 40.4 (CH_2), 39.1 (Cq), 26.3 (CH_2), 26.1 (CH_3), 25.9 (CH_3), 22.5 (CH_2).

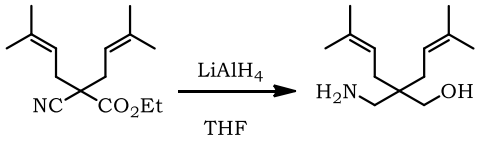
3-Benzyl-6,6-dimethyl-3-(methoxycarbonylaminomethyl)-tetrahydo-2H-pyran 537



533 537

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%). δ_H 7.27 – 7.09 (m, 4H), 7.05 (d, *J* = 7.1 Hz, 1H), 4.55 (*br*. s, NH, 1H), 3.56 (s, 3H, OCH_3), 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, CH_3), 1.09 (s, 3H, CH_3). δ_C 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 (OCH_2), 52.1 (OCH_3), 44.8 (CH_2N), 40.5 (CH_2), 37.0 (Cq), 31.9 (CH_2), 27.0 (CH_3), 26.7 (CH_2), 25.4 (CH_3). IR (neat) υ/cm^{-1}: 3335, 2931, 1705, 1520, 1452, 1244, 1074, 1030, 1074, 909. HRMS (EI) *m/z* calculated for $C_{17}H_{25}NO_3$ $[M]^+$ = 291.1834; found: 291.1830.

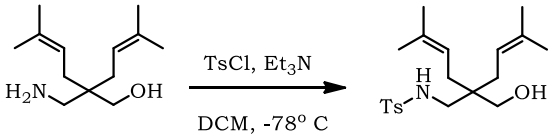
2-(Aminomethyl)-5-methyl-2-(3-methylbut-2-en-1-yl)hex-4-en-1-ol 538



512 538

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. δ_H 5.08 (t, *J* = 7.3 Hz, 2H, 2 x =CH), 3.51 (s, 2H, OCH_2), 3.72 (s, 2H, NCH_2), 2.68 – 2.53 (*br*. s, 3H OH and NH_2), 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 CH_3), 1.54 (s, 6H, 2 x CH_3). δ_C 133.7 (2 x Cq), 119.6 (2 x =CH), 70.9 (OCH_2), 49.3 (NCH_2), 41.8 (Cq), 30.9 (2 x CH_2), 26.1 (2 x CH_3), 17.8 (2 x CH_3). IR (neat) υ/cm^{-1}: 3308, 2972, 2916, 2859, 1452, 1379, 1049. HRMS (APCI) *m/z* calculated for $C_{13}H_{26}NO$ $[M+H]^+$ = 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

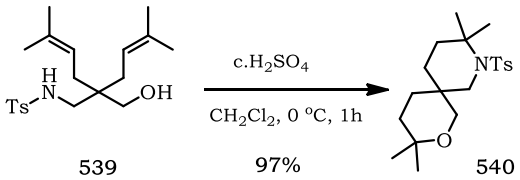


538 539

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 Et_3N (0.5 ml, 4.4 mmol) at -78 ^oC. 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. δ_H 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, OCH_2), 3.72 (d, *J* = 6.4, 2H, NCH_2), 2.40 (s, 3H, $ArCH_3$), 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 CH_3), 1.52 (s, 6H, 2 x CH_3). δ_C 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 (OCH_2), 47.6

(NCH_2), 42.3 (Cq), 30.1 (2 x CH_2), 25.8 ($ArCH_3$), 21.2 (2 x CH_3), 17.6 (2 x CH_3). IR (neat) υ/cm^{-1}: 3506, 3295, 2982, 2924, 1452, 1331, 1092, 912. HRMS (ES) *m/z* calculated for $C_{20}H_{30}NO_3S$ $[M-H]^+$ = 364.1946; found: 364.1933.

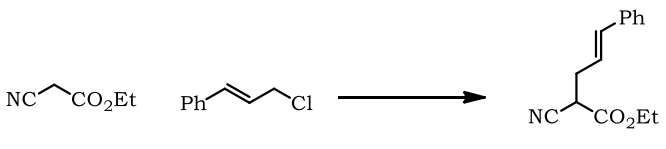
3,3,9,9-Tetramethyl-8-tosyl-2-oxa-8-azaspiro[5.5]undecane 540



539 97% 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%). δ_H 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-CH_3), 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 CH_2), 1.34 (dt, *J* = 5.8, 4.6 Hz, 1H, CH), 1.29 (s, 3H, CH_3), 1.28 – 1.21 (m, 1H, CH), 1.12 (m, 6H, 2 x CH_3), 1.08 (s, 3H, CH_3), 0.73 – 0.81 (m, 2H, CH_2). δ_C 142.7 (Cq), 139.8 (Cq), 129.4 (2 x CH), 127.3 (2 x CH), 71.8 (OCq), 67.9 (OCH_2), 58.2 (NCq), 49.1 (NCH_2), 37.9 (CH_2), 32.9 (Cq), 31.7 (CH_2), 28.5 (CH_2), 28.1 (CH_2), 27.3 ($ArCH_3$), 24.9 (2 x CH_3), 22.6 (2 x CH_3). IR (neat) υ/cm^{-1}: 2972, 2930, 2861, 1454, 1327, 1221, 1150, 1090, 906, 729. HRMS (EI) *m/z* calculated for $C_{20}H_{31}NO_3S$ $[M]^+$ = 365.2025; found: 365.2022.

Methyl (*E*)-2-cyano-5-phenylpent-4-enoate 542[46]

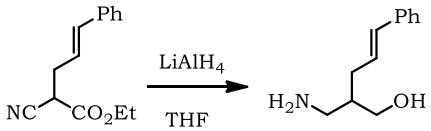


510 541 542

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. δ_H 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, OCH_2), 3.54 (dd, *J* = 7.1, 6.3 Hz, 1H), 2.77 (dd, *J* = 7.1, 4.3 Hz, 2H, CH_2), 1.23 (t, *J* = 6.9 Hz, 3H, CH_3). δ_C 165.5 (CO), 135.8 (Cq), 135.0 (=CH), 128.6 (2 x =CH), 126.5 (2 x =CH), 116.2 (CN), 62.9 (OCH_2), 37.9 (CH), 33.3 (CH_2), 14.1 (CH_3). IR (neat) υ/cm^{-1}: 2984, 2251, 1741, 1449, 1256, 1200, 1026, 966. HRMS (EI) *m/z* calculated for $C_{14}H_{15}NO_2$ $[M]^+$ = 229.1103; found: 229.1108.

(*E*)-2-(Aminomethyl)-5-phenylpent-4-en-1-ol 544

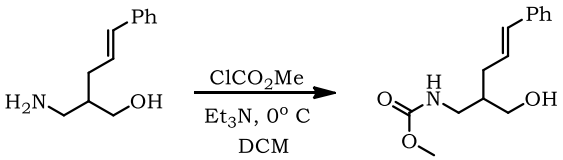


542 544

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. δ_H 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_ACH_B), 3.22 – 3.20 (dt, *J* = 4.5, 2.0 Hz, 2H, NCH_2), 3.13 (dd, *J* = 8.4, 5.7 Hz, 1H, OCH_ACH_B), 2.57 – 2.53 (m, 1H), 2.23 (dd, *J* = 12.3, 8.7 Hz, 2H, CH_2), 1.94 (*br*. s, 3H, OH and NH_2). δ_C 136.7 (Cq), 128.5 (=CH), 127.9 (2 x =CH), 127.9 (=CH), 127.1 (=CH), 126.0 (2 x =CH), 68.6 (OCH_2), 44.5 (NCH_2), 42.4 (CH), 33.4 (CH_2).

IR (neat) υ/cm^{-1}: 3356, 3254, 2922, 1597, 1448, 1028, 964. HRMS (EI) *m/z* calculated for $C_{12}H_{17}NO$ $[M]^+$ = 291.1310; found: 291.1309.

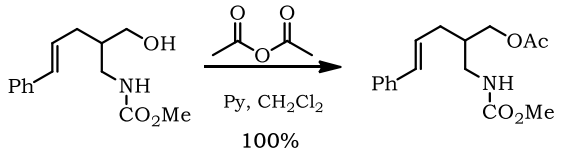
Methyl (2-(hydroxymethyl)-4-methylpent-4-en-1-yl)carbamate 545



544 545

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 Et_3N (2.5 ml, 22 mmol) to give the *N-protected amino-alcohol* **545** (1.20 g, 71%) as a colourless oil. δ_H 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, OCH_3), 3.42 (dd, *J* = 11.3, 6.5 Hz, 1H, OCH_ACH_B), 3.30 – 3.25 (m, 1H, OCH_ACH_B), 3.18 – 3.11 (m, 2H, NCH_2), 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). δ_C 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 (OCH_2), 52.4 (OCH_3), 41.6 (CH), 41.5 (NCH_2), 32.7 (CH_2). IR (neat) υ/cm^{-1}: 3343, 2928, 1696, 1523, 1449, 1255, 1192, 1028, 966. HRMS (EI) *m/z* calculated for $C_{14}H_{17}NO_2$ $[M\text{-}H_2O]^+$ = 231.1259; found: 231.1250.

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

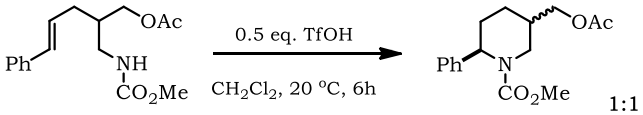


545 547

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. δ_H 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, OCH_ACH_B), 3.98 – 3.96 (m, 1H, OCH_ACH_B), 3.59 (s, 3H, OCH_3), 3.21 – 3.16 (m, 1H, NCH_ACH_B), 3.08 (dd, *J* = 14.0, 6.6 Hz, 1H, NCH_ACH_B), 2.20 (dd, *J* = 6.7, 5.0 Hz, 2H, CH_2), 2.01 (s, 3H, $COCH_3$), 1.67 – 1.60 (m,

1H, CH). δ_C 171.1 (Ac-CO), 157.2 (C=O), 137.2 (Cq), 134.9 (=CH), 128.7 (2 x =CH), 127.7 (=CH), 126.2 (2 x =CH), 127.2 (=CH), 64.7 (OCH_2), 52.1 (OCH_3), 42.0 (NCH_2), 38.8 (CH), 32.8 (CH_2), 20.9 (Ac-CH_3). IR (neat) υ/cm^{-1}: 3349, 2949, 1705, 1524, 1449, 1368, 1192, 1030, 968. HRMS (EI) *m/z* calculated for $C_{16}H_{21}NO_4$ $[M]^+$ = 291.1471; found: 291.1471.

Methyl 5-(acetoxymethyl)-2-phenylpiperidine-1-carboxylate 548



547 548

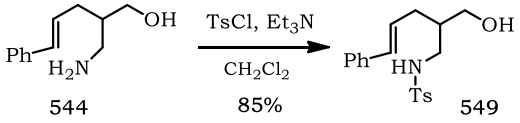
The protected amino-alcohol **547** (267 mg, 0.92 mmol) under nitrogen was dissolved in dichloromethane (10 ml) and to this triflic acid (76 mg, 46 µl, 0.5 mmol) was added. The resulting mixture stirred for 6 h at 20 °C. The reaction was allowed to cool and was then quenched with saturated aqueous potassium 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:* δ_H 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, OCH_3), 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-CH_3), 1.93 – 1.83 (m, 2H, CH_2), 1.81 – 1.75 (m, 1H, CH), 1.48 – 1.40 (m, 1H, CH). δ_C 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 (OCH_2), 52.9 (NCH), 52.1 (OCH_3), 42.1 (NCH_2), 32.5 (CH), 28.5 (CH_2), 23.9 (CH_2), 20.9 (Ac-CH_3).

The second *isomer:* δ_H 4.88 (br. s, 1H), 3.90 (dd, *J* = 11.3, 6.2 Hz, 11H), 3.66 (m, 3H, OCH_3), 1.96 (s, 3H, Ac-CH_3) only 4 distinct peaks. δ_C 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 (OCH_2), 52.1 (NCH), 52.1 (OCH_3), 43.0 (NCH_2), 38.2 (CH), 28.5 (CH_2), 20.9 (Ac-CH_3), 23.8 (CH_2).

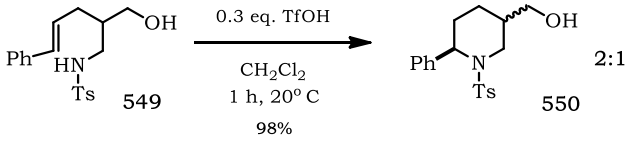
The whole sample showed : IR (neat) υ/cm^{-1}: 2945, 2860, 1728, 1699, 1529, 1447, 1190, 1034, 912, 735. HRMS (EI) *m/z* calculated for $C_{16}H_{21}NO_4$ $[M]^+$ = 291.1471; found: 291.1479.

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



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_3N (0.5 ml, 4.4 mmol) at -78 ºC. 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. δ_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, OC*H*$_A$CH$_B$), 3.15 – 3.08 (m, 1H, OCH$_A$C*H*$_B$), 2.63 – 2.56 (m, 1H, NC*H*$_A$CH$_B$), 2.51 – 2.43 (m, 1H, OCH$_A$C*H*$_B$), 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). δ_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), 64.0 (OCH_2), 44.6 (NCH_2), 40.6 (CH), 32.4 (CH_2), 21.5 ($ArCH_3$). IR (neat) υ/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



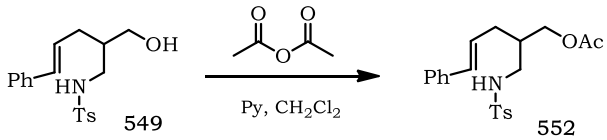
To a stirred solution of the sulfonamide **549** (173 mg, 0.5 mmol) in dry dichloromethane (10 ml) under nitrogen, cooled in an ice-water bath, was added triflic acid (38 mg, 23 µl, 0.25 mmol). The resulting solution was stirred at 20 °C for 1 h to give the *piperidine* **550** (170 mg, 98%) as a colourless oil and as a 2:1 ratio of stereoisomers, which were not separated.

Major isomer: δ_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). δ_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: δ_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). δ_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) υ/cm^{-1}: 3530, 2926, 2859, 1452, 1334, 1329, 1155, 1090, 907. HRMS (EI) *m/z* calculated for $C_{19}H_{23}NO_3S$ $[M]^+$ = 345.1399; found: 345.1396.

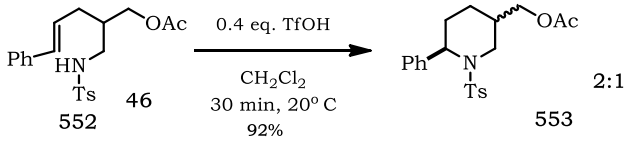
(*E*)-2-((4-Methylphenylsulfonamido)methyl)-5-phenylpent-4-en-1-yl acetate 552



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. δ_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). δ_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_2), 43.8 (NCH_2), 38.5 (CH), 32.5 (CH_2), 21.5 (Ar-CH_3), 21.0 (Ac-CH_3). IR (neat) υ/cm^{-1}: 3298, 2958, 1740, 1599, 1327, 1238, 1096, 970. HRMS (E) *m/z* calculated for $C_{21}H_{25}NO_4SNa$ $[M+Na]^+$ = 410.1402; found: 410.1392.

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



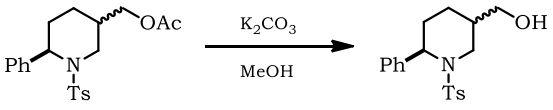
To a stirred solution of the protected amino-alcohol **552** (388 mg, 1.0 mmol) in dry dichloromethane (10 ml) under nitrogen, cooled in an ice-water bath, was added triflic acid (61 mg, 37 µl, 0.5 mmol). The resulting mixture stirred was stirred at 20 °C for 30 min to give the *piperidine* **553** (358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

Major isomer : δ_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_3), 2.24 – 2.18 (m, 1H), 2.00 (s, 3H, Ar-CH_3), 1.96 – 192 (m, 2H, CH_2), 1.66 – 1.50 (m, 2H, CH_2). δ_C 170.7 (C=O), 143.2 (Cq), 139.2 (Cq), 137.5 (Cq), 129.8 (CH), 129.7 (2 x CH), 129.5 (CH), 128.7 (CH), 128.5 (CH), 127.0 (CH), 126.8 (CH), 126.8 (CH), 64.6 (OCH_2), 56.9 (NCH), 43.2 (NCH_2), 32.6 (CH), 26.3 (CH_2), 21.5 (Ar-CH_3), 21.1 (CH_2), 20.9 (Ac-CH_3).

Minor isomer δ_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_3), 2.25 – 2.17 (m, 1H, CH), 1.57 – 1.49 (m, 2H, CH_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). δ_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_2), 54.7 (NCH), 44.3 (NCH_2), 34.5 (CH), 26.5 (CH_2), 22.2 (CH_2), 21.5 (Ar-

CH_3), 20.7 (Ac-CH_3). The whole sample showed IR (neat) υ/cm^{-1}: 2928, 1738, 1452, 1334 1236, 1159, 1092, 907. HRMS (EI) *m/z* calculated for $C_{21}H_{25}NO_4S$ $[M]^+$ = 387.1504; found: 387.1487.

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



553 550

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

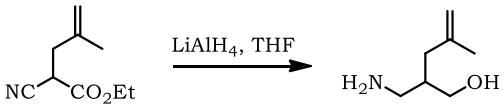
510 557 558 559

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: δ_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). δ_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) υ/cm^{-1}: 2984, 2251, 1722, 1457, 1370, 1260, 1202, 1022, 902. HRMS (ES) *m/z* calculated for $C_9H_{12}NO_2$ $[M\text{-}H]^+$ = 166.0868; found: 166.0868.

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

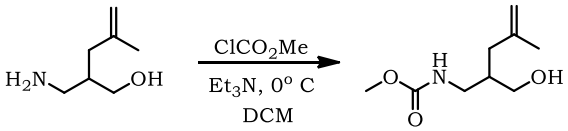
2-(Aminomethyl)-4-methylpent-4-en-1-ol 560



558 560

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 amino-alcohol* **560** (1.19 g, 92%) as a clear oil, which was used directly in the next step. δ_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_AH_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). δ_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).

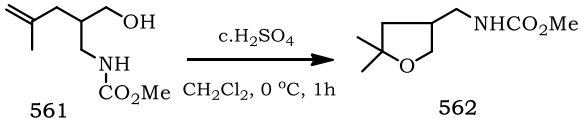
Methyl (2-(hydroxymethyl)-4-methylpent-4-en-1-yl)carbamate 561



560 561

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 Et_3N (2.5 ml, 22 mmol) to give the *N-protected amino-alcohol* **561** (1.20 g, 71%) as a colourless oil. δ_H 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, OCH_3), 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, CH_3). δ_C 158.4 (C=O), 143.3 (Cq), 112.4 ($=CH_2$), 62.9 (CH_2OH), 52.3 (OCH_3), 41.2 (NCH_2), 38.9 (CH), 37.5 (CH_2), 22.1 (CH_3). IR (neat) υ/cm^{-1}: 3329, 2928, 1695, 1525, 1444, 1377, 1257, 1194, 1033, 891. HRMS (ES) *m/z* calculated for $C_9H_{18}NO_3$ $[M+H]^+$ = 188.1287; found: 188.1281.

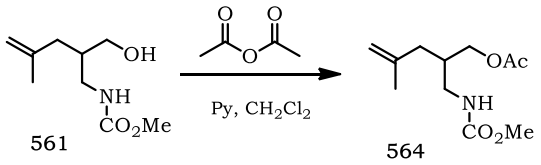
Methyl ((5,5-dimethyltetrahydrofuran-3-yl)methyl)carbamate 562



561 562

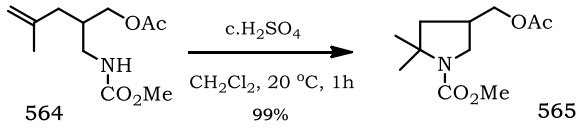
By general procedure B, to the *N*-protected amino-alcohol **561** (116 mg, 0.62 mmol) in dry dichloromethane (10 ml) under nitrogen concentrated sulfuric acid (25 mg, 0.25 mmol) was added and the resulting mixture stirred for 1 h at 0 °C to give the *tetrahydrofuran* **562** as a colourless oil (112 mg, 97%). δ_H 4.80 (*br*. s, NH, 1H), 3.88 (dd, *J* = 8.8, 7.3 Hz, 1H), 3.60 (s, 3H, OCH_3), 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, CH_3), 1.12 (s, 3H, CH_3). δ_C 157.2 (C=O), 80.9 (OCq), 69.9 (OCH_2), 52.8 (OCH_3), 44.1 (CH_2N), 42.7 (CH_2), 40.4 (CH), 28.7 (CH_3), 27.7 (CH_3). IR (neat) υ/cm^{-1}: 3327, 2969, 2932, 1701, 1537, 1449, 1368, 1192, 1146, 775. HRMS (ES) *m/z* calculated for $C_9H_{18}NO_3$ $[M+H]^+$ = 188.1287; found: 188.1283.

2-((Methoxycarbonylamino)methyl)-4-methylpent-4-en-1-yl acetate 564



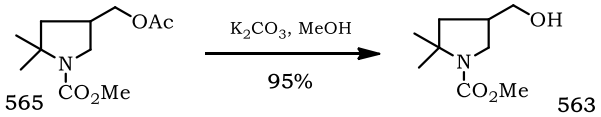
By general procedure E, the alcohol **561** (187 mg, 1.0 mmol) was converted into the *acetate* **564** (229 mg, 100%), a colourless oil. δ_H 4.92 (*br*. s, 1H, NH), 4.75 (*app*. s, 1H, $=CH_A$), 4.67 (*app*. s, 1H, $=CH_B$), 4.09 (dd, *J* = 11.3, 3.5 Hz, 1H), 3.87 (dd, *J* = 11.3, 5.5 Hz, 1H), 3.59 (s, 3H, OCH_3), 3.25 – 3.17 (m, 1H), 3.02 – 2.94 (m, 1H), 2.01 (s, 3H, Ac-CH_3), 1.99 – 1.93 (m, 2H, CH_2), 1.67 (s, 3H, CH_3). δ_C 172.2 (Ac-CO), 157.7 (C=O), 133.9 (Cq), 112.9 ($=CH_2$), 64.8 (OCH_2), 52.1 (OCH_3), 42.2 (NCH_2), 37.9 (CH_2), 36.1 (CH), 22.1 (Ac-CH_3), 20.8 (CH_3).

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



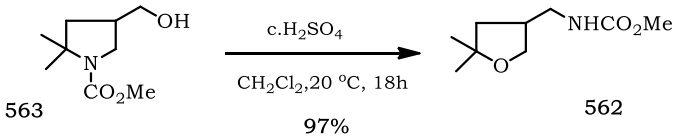
By general procedure B, to the protected amino-alcohol **564** (200 mg, 0.9 mmol) in dry dichloromethane (10 ml) concentrated sulfuric acid (2 drops) was added and the resulting mixture stirred for 1 h at 20 °C to give the *pyrrolidine* **565** (197 mg, 99%) as a colourless oil. δ_H 4.02 (dd, *J* = 10.9, 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, OCH_3), 2.99 (t, *J* = 10.4 Hz, 1H), 2.51 – 2.36 (m, 1H), 1.97 (s, 3H, Ac-CH_3), 1.87 – 1.76 (m, 1H), 1.50 (dt, *J* = 24.1, 12.1 Hz, 1H), 1.41 (s, 3H, CH_3), 1.25 (d, *J* = 15.7 Hz, 3H, CH_3). δ_C 170.8 (Ac-CO), 154.4 (Cq, CO), 65.8 (OCH_2), 60.9 (NCq), 51.6 (OCH_3), 50.6 (CH_2N), 44.7 (CH_2), 34.6 (CH), 27.3 (Ac-CH_3), 25.5 (CH_3), 20.8 (CH_3). IR (neat) υ/cm^{-1}: 2961, 1743, 1699, 1445, 1233, 1190, 1111, 1084, 1033. HRMS (EI) *m/z* calculated for $C_{13}H_{23}NO_2$ $[M]^+$ = 229.1314; found: 229.1316.

Methyl 2,2-dimethyl-4-(hydroxymethyl)pyrrolidine-1-carboxylate 563



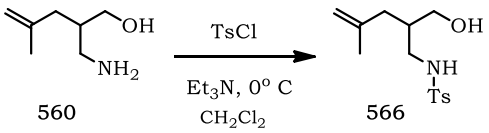
To a solution of the acetoxymethyl pyrrolidine **565** (170 mg, 0.74 mmol) in undried methanol (5 ml) was added potassium carbonate (200 mg, 1.5 mmol). The reaction was stirred for 18 h at room temperature. The solvent was removed and the residue was diluted with water (5 ml) extracted with dichloromethane (3 x 5 ml). The combined organic layers were dried and concentrated to give the *pyrrolidine* **563** (131 mg, 95%) as a colourless oil. δ_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). δ_C 64.8 (OCH_2), 60.9 (NCq), 51.8 (OCH_3), 50.5 (CH_2N), 37.6 (CH), 29.8 (CH_2), 25.6 (2 x CH_3).

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^o 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**.

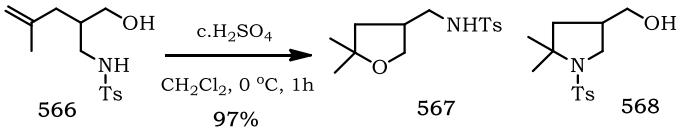
***N*-(2-(Hydroxymethyl)-4-methylpent-4-en-1-yl)-4-methylbenzenesulfonamide 566**



560 566

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_3N (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. δ_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, OC*H*$_A$CH$_B$), 3.52 (d, *J* = 11.0 Hz, 1H, OCH$_A$C*H*$_B$), 3.05 (dd, *J* = 11.7, 3.8 Hz, 1H, NC*H*$_A$CH$_B$), 2.88 (dd, *J* = 11.7, 3.8 Hz, 1H, NCH$_A$C*H*$_B$), 2.44 (s, 3H, ArCH$_3$), 1.93 – 1.88 (m, 3H, CH and CH$_2$), 1.65 (s, 3H, CH$_3$). δ_C 143.4 (Cq), 142.8 (Cq), 137.0 (Cq), 129.8 (CH), 129.7 (CH), 127.0 (CH), 112.6 (=CH$_2$), 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) υ/cm^{-1}: 3520, 3281, 2922, 1599, 1445, 1319, 1092, 893. HRMS (APCI) *m/z* calculated for $C_{14}H_{22}NO_3S$ $[M+H]^+$ = 284.1320; found: 284.1316.

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



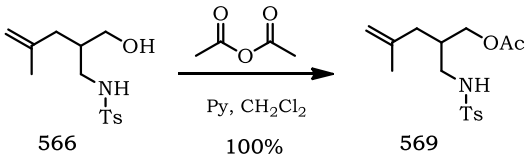
566 567 568

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 :** δ_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,

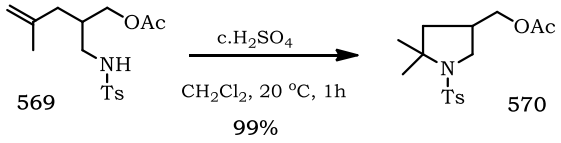
NCH_2), 2.48 – 2.39 (m, 1H), 2.34 (s, 3H, $ArCH_3$), 1.82 – 1.71 (m, 2H, CH_2), 1.13 (s, 3H, CH_3), 1.05 (s, 3H, CH_3). δ_C 14.5 (Cq), 136.9 (Cq), 129.8 (2 x CH), 127.2 (2 x CH), 81.0 (OCq), 69.7 (OCH_2), 46.3 (NCH_2), 42.7 (CH_2), 40.0 (CH), 29.2 ($ArCH_3$), 27.6 (CH_3), 21.5 (CH_3). IR (neat) υ/cm^{-1}: 3266, 2971, 2930, 2868, 1599, 1456, 1329, 1091, 910. HRMS (APCI) *m/z* calculated for $C_{14}H_{22}NO_3S$ $[M+H]^+$ = 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. δ_H 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, $ArCH_3$), 1.96 (s, 3H, $AcCH_3$), 1.59 (s, 3H, CH_3). δ_C 171.1 (C=O), 143.4 (Cq), 142.1 (Cq), 129.7 (2 x CH), 127.1 (2 x CH), 113.1 ($=CH_2$), 64.5 (OCH_2), 44.1 (NCH_2), 37.6 (CH_2), 35.9 (CH), 22.0 (Ar-CH_3), 22.5 (Ac-CH_3), 20.7 (CH_3). 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 $C_{16}H_{24}NO_4S$ $[M+H]^+$ = 326.1426; found: 326.1425.

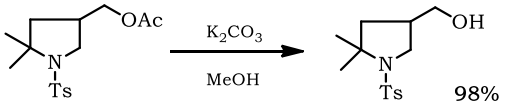
(5,5-Dimethyl-1-tosylpyrrolidin-3-yl)methyl acetate 570



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%). δ_H 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). δ_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) υ/cm^{-1}: 29681, 2928, 2870, 1740, 1456, 1369, 1332, 1230, 1090, 1034, 912. HRMS (ES) *m/z* calculated for $C_{16}H_{24}NO_4S$ $[M+H]^+$ = 326.1426; found: 326.1426.

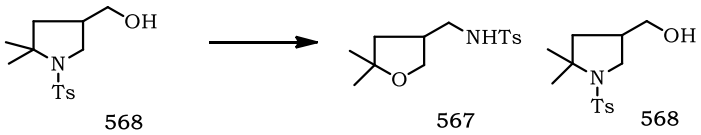
(5,5-Dimethyl-1-tosylpyrrolidin-3-yl)methanol 569



570 568

To a solution of acetoxymethyl 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. δ_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). δ_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) υ/cm^{-1}: 3513, 2924, 1330, 1261, 1091, 941. HRMS (EI) *m/z* calculated for $C_{14}H_{21}NO_3S$ $[M]^+$ = 283.1242; found: 283.1236.

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

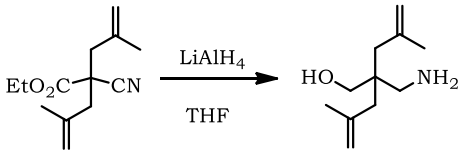


568 567 568

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^{o} 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 trahydrofuran 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)**.**

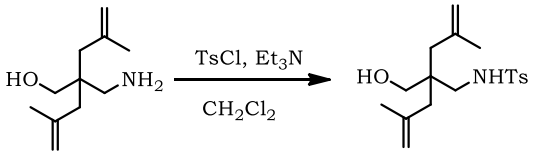
2-(Aminomethyl)-4-methyl-2-(2-methylallyl)pent-4-en-1-ol 569[47]



559 569

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. δ_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, 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, 2H, 2 x CH_A), 2.12 (d, *J* = 13.6, 2H, 2 x CH_B), 1.55 (s, 6H, 2 x CH_3). δ_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).

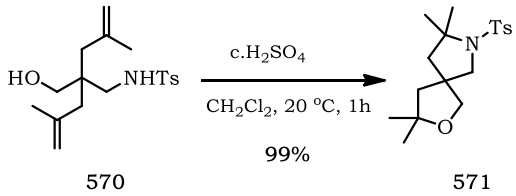
***N*-(2-(Hydroxymethyl)-4-methyl-2-(2-methylallyl)pent-4-en-1-yl)-4-ethylbenzenesulfonamide 570**[47]



569 570

By general procedure A, tosyl chloride (191 mg, 1 mmol) was added to the amino-alcohol **569** (156 mg, 0.85 mmol) and Et_3N (0.2 ml) at -78 ^oC. 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. δ_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). δ_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).

3,3,8,8-Tetramethyl-7-tosyl-2-oxa-7-azaspiro[4.4]nonane 571[47]

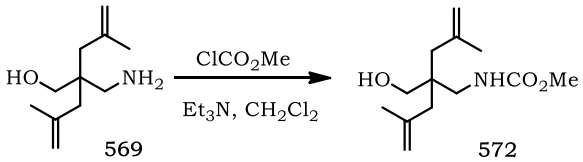


570 571

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 ^oC to give the *oxa-azaspiro* **571** as a colourless oil (114 mg, 99%). δ_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). δ_C 142.8

(Cq), 138.1 (Cq), 129.4 (2 x CH), 127.3 (2 x CH), 80.2 (OCq), 75.6 (OCH_2), 64.8 (NCq), 59.2 (NCH_2), 52.7 (CH_2), 49.7 (Cq), 48.5 (CH_2), 29.2 (CH_3), 29.1 (CH_3), 29.0 (CH_3), 28.3 (CH_3), 21.5 ($ArCH_3$). IR (neat) υ/cm^{-1}: 2971, 2930, 2868, 1599, 1451, 1334, 1090, 1007, 814, 677. HRMS (EI) *m/z* calculated for $C_{18}H_{27}NO_3S$ $[M]^+$ = 337.1712; found: 337.1710.

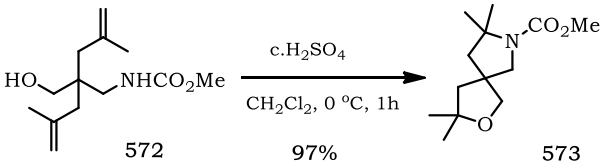
Methyl (2-(hydroxymethyl)-4-methyl-2-(2-methylallyl)pent-4-en-1-yl)carbamate 572



569 572

By general procedure A, methyl chloroformate (0.1 ml, 1.2 mmol) was added to the amino-alcohol **569** (183 mg, 1 mmol) and Et_3N (2.5 ml, 22 mmol) to give the *N-protected amino-alcohol* **572** (231 mg, 96%) as a colourless oil. δ_H 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, OCH_3), 3.51 (*br*. s, 1H, OH), 3.41 (d, *J* = 6.8 Hz, 2H, OCH_2), 2.27 (d, *J* = 6.4 Hz, 2H, NCH_2), 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 CH_3). δ_C 158.5 (C=O), 143.1 (2 x Cq), 115.3 (2 x CH_2), 65.4 (OCH_2), 45.9 (NCH_2), 43.7 (Cq), 41.3 (2 x CH_2), 25.4 (2 x CH_3). IR (neat) υ/cm^{-1}: 3345, 2970, 2948, 1705, 1520, 1450, 1244, 1046, 907. HRMS (EI) *m/z* calculated for $C_{13}H_{23}NO_2$ $[M]^+$ = 241.1678; found: 241.1677.

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

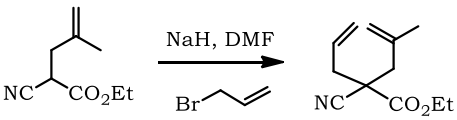


572 97% 573

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%). δ_H

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). δ_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.

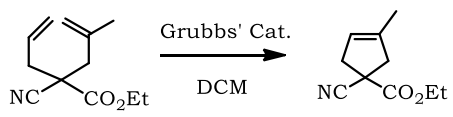
Ethyl 2-allyl-2-cyano-4-methylpent-4-enoate 579



558 577 579

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. δ_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). δ_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) υ/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.

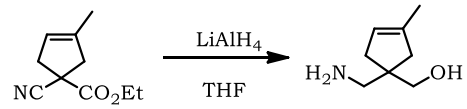
Ethyl 1-cyano-3-methylcyclopent-3-enecarboxylate 580



579 580

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 *cyanopentene* **580** (0.66 g, 100%) as a colourless oil. δ_H 5.82 – 5.69 (m, 1H, =CH), 4.20 (q, *J* = 6.7 Hz, 2H, OCH_2), 2.98 (d, *J* = 9.4 Hz, 2H, CH_2), 2.60 (d, *J* = 8.7 Hz, 1H), 2.46 (d, *J* = 8.7 Hz, 1H), 1.68 (s, 3H, CH_3), 1.32 (t, *J* = 6.7 Hz, 3H, OCH_3). δ_C 169.3 (C=O, Cq), 137.4 (Cq), 121.3 (CN, Cq), 120.9 (=CH), 62.9 (OCH_2), 47.3 (CH_2), 46.2 (Cq), 44.0 (CH_2), 15.8 (CH_3), 13.9 (CH_3).

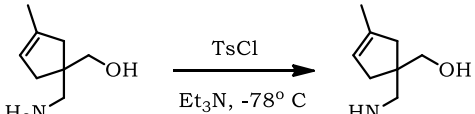
(1-(Aminomethyl)-3-methylcyclopent-3-en-1-yl)methanol 581



580 581

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. δ_H 4.99 (s, 1H, =CH), 3.42 (s, 2H, OCH_2), 2.71 (s, 2H, NCH_2), 2.49 – 2.30 (br. s, 3H, OH and NH_2), 1.99 (d, *J* = 11.7 Hz, 2H, CH_2), 1.80 (s, 2H, CH_2), 1.48 (s, 2H, CH_3). δ_C 138.3 (Cq), 122.3 (=CH), 68.0 (OCH_2), 51.7 (NCH_2), 47.2 (Cq), 43.8 (CH_2), 39.7 (CH_2), 16.7 (CH_3).

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



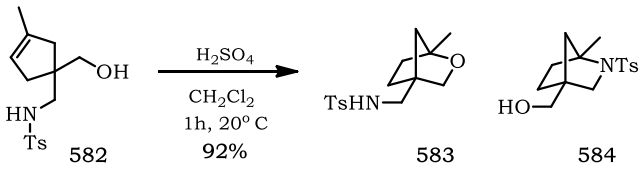
581 582

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 Et_3N (0.5 ml, 4.4 mmol) at -78 ^oC. 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_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_2), 2.89 (dd, *J* = 6.3 Hz, 2H, NCH_2), 2.54 – 2.41 (*br*. s, 1H, OH), 2.36 (s, 3H, Ar-CH_3), 2.11 – 1.99 (m, 2H, CH_2), 1.93 (m, 2H, CH_2), 1.56 (s, 3H, CH_3). δ_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_2), 49.4 (NCH_2), 47.5 (Cq), 43.7 (CH_2), 39.6 (CH_2), 21.5 (CH_3), 16.5 (CH_3).

4-Methyl-*N*-((1-methyl-2-oxabicyclo[2.2.1]heptan-4-yl)methyl)benzenesulfonamide 583 and

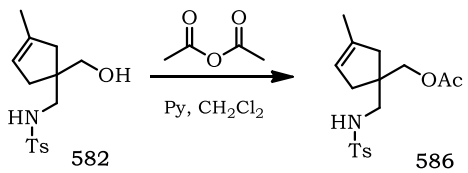
1-Methyl-2-tosyl-2-azabicyclo[2.2.1]heptan-4-yl)methanol 584 and



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_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_2), 2.48 (d, *J* = 6.9 Hz, NCH_2), 2.25 (s, 3H, Ar-CH_3), 1.58 (dd, *J* = 9.8, 4.0 Hz, 2H, CH_2), 1.41 – 1.20 (m, 6H, 3 x CH_2), 0.90 (s, 3H, CH_3). δ_C 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).

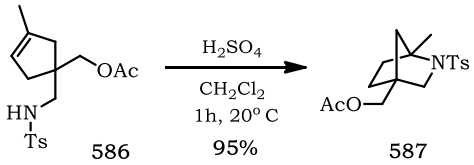
*The structure of *azabicyclo* **584** was confirmed by different way (p. 264).

(3-Methyl-1-((4-methylphenylsulfonamido)methyl)cyclopent-3-en-1-yl)methyl acetate 586



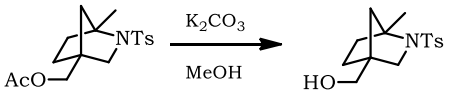
By general procedure E, but with a reaction time of 19 h, the alcohol **582** (295 mg, 1.0 mmol) was converted into the *acetate* **586** (337 mg, 100%), a colourless oil. δ_H 7.65 (t, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 5.09 (s, 1H, =CH), 4.99 (t, *J* = 6.8 Hz, 1H, NH), 3.93 (d, *J* = 4.9 Hz, 1H, OC*H*$_A$CH$_B$), 3.89 (d, *J* = 4.9 Hz, 1H, OCH$_A$C*H*$_B$), 2.78 (d, *J* = 6.8 Hz, 2H, NCH_2), 2.36 (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, CH_3). δ_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), 43.9 (CH_2), 39.8 (CH_2), 22.1 (CH_3), 21.5 (CH_3), 20.8 (CH_3). IR (neat) υ/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 ºC to give the *azabicycloheptane* **587** as a colourless oil (287 mg, 95%). δ_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, NC*H*$_A$CH$_B$), 3.27 (d, *J* = 2.3 Hz, 1H, NCH$_A$C*H*$_B$), 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), 1.33 (d, *J* = 0.8 Hz, 1H, CH). δ_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) υ/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.

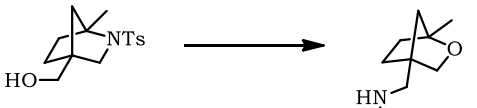
(1-Methyl-2-tosyl-2-azabicyclo[2.2.1]heptan-4-yl)methanol 584



587 584

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. δ_H 7.65 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 3.62 (s, 2H, NCH_2), 3.35 (dd, *J* = 8.5, 3.2 Hz, 1H, OCH_ACH_B), 3.27 (dd, *J* = 8.5, 1.4 Hz, 1H, OCH_ACH_B), 2.35 (s, 3H, Ar-CH_3), 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, CH_3), 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). δ_C 142.9 (Cq), 138.9 (Cq), 129.5 (2 x CH), 127.1 (2 x CH), 70.9 (NCq), 64.4 (OCH_2), 58.6 (NCH_2), 49.2 (Cq), 48.6 (CH_2), 36.1 (CH_2), 31.6 (CH_2), 21.5 (CH_3), 19.5 (CH_3). IR (neat) υ/cm^{-1}: 3510, 2932, 2872, 1333, 1288, 1012, 814. HRMS (EI) *m/z* calculated for $C_{15}H_{21}NO_3S$ $[M]^+$ = 295.1242; found: 295.1239.

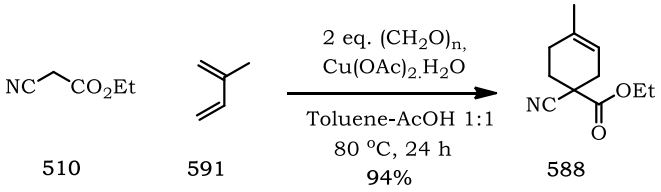
4-methyl-N-((1-methyl-2-oxabicyclo[2.2.1]heptan-4-yl)methyl)benzenesulfonamide 583



584 583

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).

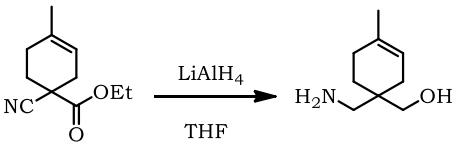
Ethyl 1-cyano-4-methylcyclohex-3-enecarboxylate 588[48]



510 591 588

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 ^{O}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:[48] δ_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). δ_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).

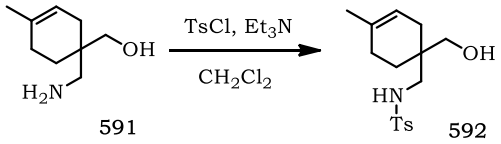
(1-(Aminomethyl)-4-methylcyclohex-3-en-1-yl)methanol 592[48]



588 592

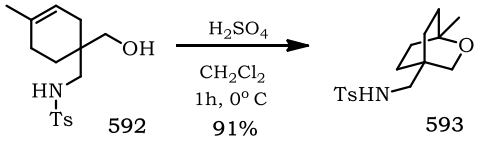
Following general procedure C, the cyanoacetate **588** (3.50 g, 18.1 mmol) was reduced using lithium aluminium hydride (1.52 g, 40 mmol) to give the *amino-alcohol* **592** (2.50 g, 89 %) as a yellowish oil, which was used directly in the next step. δ_H 5.21 (d, *J* = 1.5 Hz, 1H, =CH), 3.48 (s, 2H, 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). δ_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 Et_3N (1 ml, 8.8 mmol) at -78 ^oC. The mixture was then stirred for 1 h without additional cooling to give the *sulfonamide* **592** (1.76 g, 74%) as a colourless oil. δ_H 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, OCH_2), 2.83 (d, *J* = 13.0 Hz, 1H), 2.73 (d, *J* = 13.0 Hz, 1H), 2.36 (s, 3H, Ar-CH_3), 1.94 – 1.83 (m, 2H, CH_2), 1.69 – 1.60 (m, 2H, CH_2), 1.54 (s, 3H, CH_3), 1.50 – 1.35 (m, 2H, CH_2). δ_C 142.6 (Cq), 136.6 (Cq), 133.5 (Cq), 129.7 (2 x CH), 127.0 (2 x CH), 118.0 (CH), 67.7 (OCH_2), 48.1 (NCH_2), 36.6 (Cq), 30.7 (CH_2), 26.9 (CH_2), 26,3 (CH_2), 23.3 (CH_3), 21.5 (CH_3). IR (neat) υ/cm^{-1}: 3505, 3295, 2926, 1452, 1327, 1094, 814. HRMS (EI) *m/z* calculated for $C_{16}H_{24}NO_3S$ $[M+H]^+$ = 310.1477; found: 310.1465.

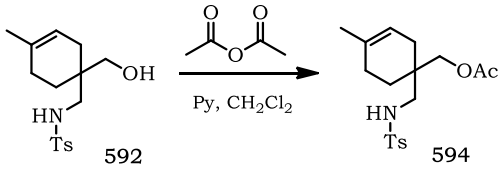
4-Methyl-*N*-((1-methyl-2-oxabicyclo[2.2.2]octan-4-yl)methyl)benzenesulfonamide 693



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 ^oC to give the *oxabicyclo-octane* **593** as a colourless oil (124 mg, 91%). δ_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_2), 2.48 (d, *J* = 6.8 Hz, NCH_2), 2.25 (s, 3H, Ar-CH_3), 1.58 (dd, *J* = 9.8, 4.0 Hz, 2H, CH_2), 1.41 – 1.20 (m, 6H, 3 x CH_2), 0.90 (s, 3H, CH_3). δ_C 143.5 (Cq), 136.9 (Cq), 129.8 (2 x CH), 127.0

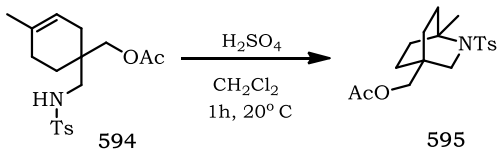
(2 x CH), 71.7 (OCH_2), 69.1 (OCq), 49.4 (NCH_2), 32.4 (Cq), 32.1 (2 x CH_2), 28.0 (2 x CH_2), 26.3 (CH_3), 21.5 (CH_3). IR (neat) υ/cm^{-1}: 3283, 2924, 2862, 1452, 1321, 1094, 814. HRMS (EI) *m/z* calculated for $C_{16}H_{24}NO_3S$ $[M+H]^+$ = 310.1477; found: 310.1471.

(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. δ_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_ACH_B), 3.78 (d, *J* = 11.4 Hz, 1H, OCH_ACH_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). δ_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) υ/cm^{-1}: 3286, 2934, 1732, 1327, 1236, 1092, 1036, 910. HRMS (ES) *m/z* calculated for $C_{18}H_{25}NNaO_4S$ $[M+Na]^+$ = 374.1402; found: 374.1399.

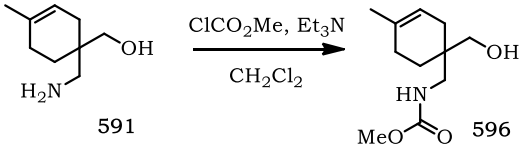
(1-Methyl-2-tosyl-2-azabicyclo[2.2.2]octan-4-yl)methyl acetate 595



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 ºC to give the *azabicyclo-octane* **595** as a colourless oil (306 mg, 94%). δ_H

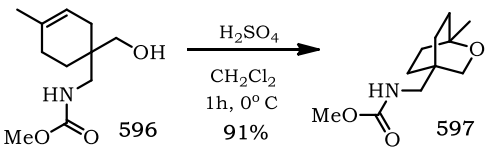
7.67 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 3.73 (s, 2H, OCH_2), 3.43 (s, 2H, NCH_2), 2.36 (s, 3H, Ar-CH_3), 2.01 (s, 3H, Ac-CH_3), 1.73 (s, 2H, CH_2), 1.60 (d, *J* = 9.5 Hz, 2H), 1.51 (s, 2H, CH_2), 1.44 – 1.34 (m, 2H, CH_2), 1.27 (s, 3H, CH_3). δ_C 171.5 (C=O) 143.4 (Cq), 139.2 (Cq), 129.5 (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) υ/cm^{-1}: 2940, 2870, 1740, 1458, 1331, 1235, 1092, 1040, 1010, 980. HRMS (EI) *m/z* calculated for $C_{18}H_{25}NO_4S$ $[M]^+$ = 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_3N (1 ml, 8.8 mmol) at 0 ^oC. The mixture was then stirred for 1 h at room temperature to give the *carbamate* **596** (1.26 g, 71%) as a colourless oil. δ_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). δ_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).

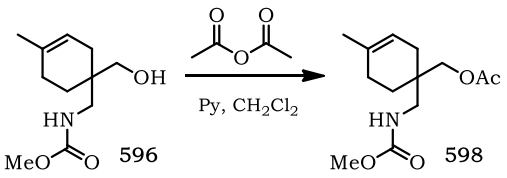
Methyl (1-methyl-2-oxabicyclo[2.2.2]octan-4-yl)methyl)carbamate 597



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 ^oC to give the *oxabicyclo-octane* **597** (104 mg, 98%)

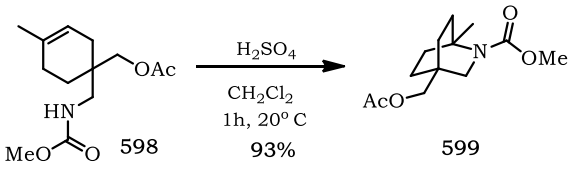
as sharp, colourless crystals, m.p. 92 – 94 °C. δ_H 4.65 (*br*. s, 1H, NH), 3.71 – 3.49 (m, 2H, OCH_2), 3.61 (s, 3H, OCH_3), 2.89 (d, *J* = 6.5 Hz, 2H, NCH_2), 1.79 – 1.67 (m, 2H, CH_2), 1.57 – 1.40 (m, 6H, 3 x CH_2), 1.02 (s, 3H, CH_3). δ_C 157.2 (C=O, Cq), 71.7 (OCH_2), 68.9 (OCq), 52.1 (OCH_3), 47.1 (NCH_2), 33.0 (Cq), 32.1 (2 x CH_2), 27.8 (2 x CH_2), 26.3 (CH_3). IR (neat) υ/cm^{-1}: 3335, 2930, 2862, 1722, 1694, 1545, 1447, 1192, 1117, 1047, 997. HRMS (EI) *m/z* calculated for $C_{11}H_{19}NO_3$ $[M]^+$ = 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_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_2), 3.59 (s, 3H, OCH_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_3), 1.88 (d, *J* = 1.5 Hz, 2H, CH_2), 1.76 – 1.72 (m, 2H, CH_2), 1.58 (s, 3H, CH_3), 1.48 – 1.39 (m, 2H, CH_2). δ_C 166.3 (C=O, Cq), 133.3 (Cq), 118.0 (CH), 67.5 (OCH_2), 52.1 (OCH_3), 45.6 (NCH_2), 36.9 (Cq), 30.7 (CH_2), 27.0 (CH_2), 26.4 (CH_2), 23.3 (CH_3), 22.1 (CH_3).

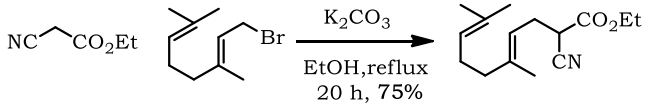
Methyl 4-(acetoxymethyl)-1-methyl-2-azabicyclo[2.2.2]octane-2-carboxylate 599



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^{o} C to give the *azabicyclo* **599** (204 mg, 93%) as a colourless oil. δ_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). δ_C 157.2 (C=O, Cq), 71.7 (OCH_2), 68.9 (NCq), 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) υ/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.

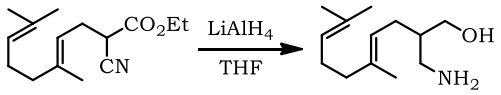
(*E*)-Ethyl 2-cyano-5,9-dimethyldeca-4,8-dienoate 601[49]



510 600 601

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. δ_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). δ_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

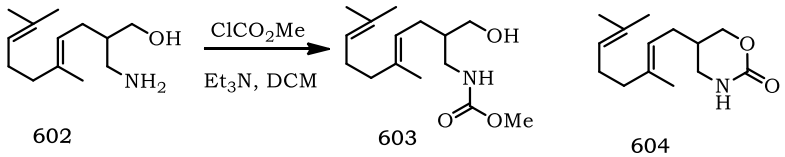


601 602

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% aquous 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 NH_2), 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 CH_2), 1.85 – 1.82 (m, 2H, CH_2), 1.61 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 1.51 (s, 3H, CH_3). δ_C 136.7 (Cq), 131.4 (Cq), 124.3 (=CH), 121.9 (=CH), 62.9 (OCH_2), 46.0 (NCH_2), 41.8 (CH), 39.8 (CH_2), 27.8 (CH_2), 26.7 (CH_2), 25.7 (CH_3), 16.3 (CH_3). IR (neat) υ/cm^{-1}: 3370, 2967, 2918, 2853, 1648, 1443, 1375, 1150, 1105, 908. HRMS (EI) *m/z* calculated for $C_{13}H_{25}NO$ $[M]^+$ = 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



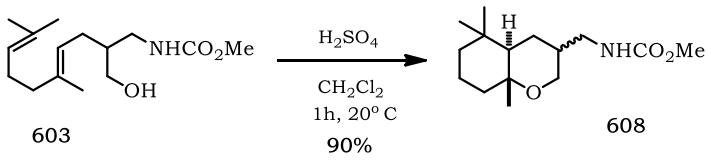
602 603 604

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 Et_3N (0.5 ml, 4.4 mmol) at 0 ^oC. 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 CH_2), 1.68 (s, 3H, CH_3), 1.61 (s, 6H, 2 x CH_3). δ_C 158.4 (C=O, Cq), 138.6 (Cq), 137.0 (Cq), 131.5 (Cq), 124.2 (=CH), 121.8 (=CH), 62.9 (OCH_2), 52.3 (OCH_3), 44.9 (NCH_2), 42.0 (CH), 27.5 (CH_2), 27.3 (CH_2), 26.6 (CH_2), 25.7 (CH_3), 17.7 (CH_3), 16.0 (CH_3).

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 CH_2 and CH), 1.98 – 1.88 (m, 2H, CH_2), 1.61 (s, 3H, CH_3), 1.53 (s, 6H, 2 x CH_3). δ_C 154.4 (C=O, Cq), 139.6 (Cq), 137.0 (Cq), 124.2 (=CH), 119.7 (=CH), 70.2 (OCH_2), 45.3 (NCH_2), 39.7 (CH_2), 31.7 (CH), 27.3 (CH_2), 26.5 (CH_2), 25.7 (CH_3), 17.7 (CH_3), 16.1 (CH_3).

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



603 608

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 ^oC to give the *trimethyloctahydro chromen* **608** (122 mg, 90%) as a colourless oil and an inseparable 2:1 mixture of diastereoisomers.

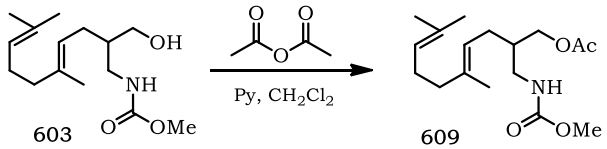
The major diastereoisomer showed: δ_H 8.91 (s, 1H, NH), 3.59 (s, 3H, OCH_3), 3.28 (dd, *J* = 12.4, 9.8 Hz, 2H, CH_2), 2.97 (d, *J* = 7.0 Hz, 2H, CH_2), 1.76 (ddd, *J* = 11.6, 8.2, 4.1 Hz, 1H, CH), 1.61 – 1.55 (m, 1H, CH), 1.49 (ddd, *J* = 7.4, 6.1, 2.4 Hz, 1H, CH), 1.33 – 1.25 (m, 6H), 1.12 (s, 3H,

CH_3), 0.76 (s, 3H, CH_3), 0.65 (s, 3H, CH_3). δ_C 157.2 (Cq), 74.7 (OCq), 64.0 (OCH_2), 52.9 (CH), 52.0 (OCH_3), 42.4 (NCH_2), 41.5 (CH_2), 40.0 (CH_2), 38.8 (CH), 34.0 (Cq), 31.9 (CH_3) 23.6 (CH_2), 21.3 (CH_3), 21.1 (CH_2), 19.2 (CH_3).

The minor diastereoisomer could be characterized by: δ_H 4.87 (s, 1H, NH), 3.79 (dd, *J* = 12.4, 3.2 Hz, 2H, CH_2), 3.42 (d, *J* = 12.5 Hz, 1H, CH), 1.90 (d, *J* = 6.5 Hz, 1H, CH), 1.19 (s, 3H, CH_3), 0.77 (s, 3H, CH_3), 0.67 (s, 3H, CH_3). δ_C 75.4 (OCq), 61.4 (OCH_2), 43.7 (CH), 52.1 (OCH_3), 40.2 (CH_2), 33.2 (Cq), 30.6 (CH_3), 20.7 (CH_3), 18.7 (CH_3).

The whole sample showed IR (neat) υ/cm^{-1}: 3327, 2930, 2866, 1701, 1533, 1458, 1375, 1256, 1090, 777. HRMS (APCI) *m/z* calculated for $C_{15}H_{27}NO_3Na$ $[M+Na]^+$ = 292.1889; found: 292.1877.

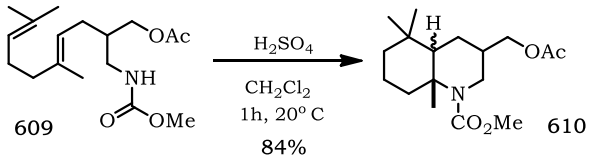
(*E*)-2-(((Methoxycarbonyl)amino)methyl)-5,9-dimethyldeca-4,8-dien-1-yl acetate 609



603 609

By general procedure E, the alcohol **603** (269 mg, 1.0 mmol) was converted into the *acetate* **609** (302 mg, 97%), a colourless oil. δ_H 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, OCH_3), 3.18 (dd, *J* = 12.1, 6.0 Hz, 1H, CH), 3.10 – 3.00 (m, 1H, CH), 2.00 (s, 3H, Ac-CH_3), 1.98 – 1.89 (m, 6H, 3 x CH_2), 1.85 – 1.81 (m, 1H, CH), 1.61 (s, 3H, CH_3), 1.53 (s, 6H, 2 x CH_3). δ_C 154.4 (C=O, Cq), 137.1 (Cq), 136.9 (Cq), 133.5 (Cq), 126.2 (=CH), 122.3 (=CH), 66.8 (OCH_2), 53.2 (OCH_3), 44.3 (NCH_2), 42.6 (CH), 27.6 (CH_2), 27.0 (CH_2), 26.2 (CH_2), 26.0 (CH_3), 19.8 (CH_3), 17.7 (CH_3), 16.1 (CH_3).

Methyl 3-(acetoxymethyl)-5,5,8a-trimethyloctahydroquinoline-1(2H)-carboxylate 610



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: δ_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). δ_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: δ_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 (dddd, *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). δ_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).

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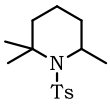
Appendices

Appendices

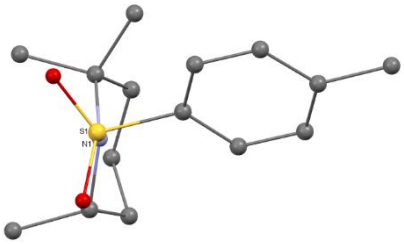
Appendix 1

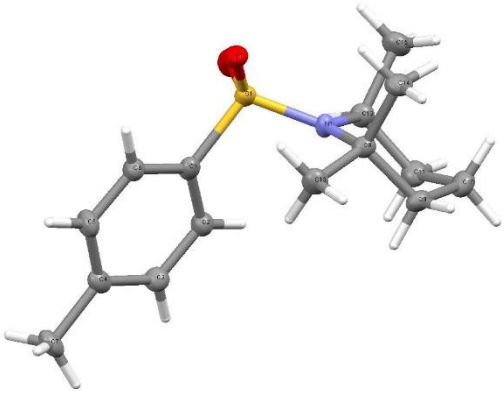
1-Toluenesulfonyl-2,2,6-trimethylpiperidine 237

m.p. 82 – 83°C



237





CCDC 797890

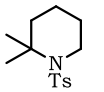
Table 2. Crystal data and structure refinement for CCDC 797890.

Identification code	CCDC 797890	
Empirical formula	C15 H23 N O2 S	
Formula weight	281.40	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 6.3290(3) Å	α = 93.562(2)°.
	b = 11.4162(5) Å	β = 91.070(3)°.
	c = 20.4228(8) Å	γ = 96.162(2)°.
Volume	1463.77(11) Å3	
Z	4	
Density (calculated)	1.277 Mg/m3	
Absorption coefficient	0.220 mm-1	
F(000)	608	
Crystal size	0.50 x 0.10 x 0.06 mm3	
Theta range for data collection	1.80 to 27.58°.	
Index ranges	-8<=h<=8, -13<=k<=14, -24<=l<=26	
Reflections collected	9269	
Independent reflections	6609 [R(int) = 0.0452]	
Completeness to theta = 27.58°	97.4 %	
Max. and min. transmission	0.9869 and 0.8981	
Refinement method	Full-matrix least-squares on F2	
Data / restraints / parameters	6609 / 0 / 351	
Goodness-of-fit on F2	1.035	
Final R indices [I>2sigma(I)]	R1 = 0.1073, wR2 = 0.2578	
R indices (all data)	R1 = 0.1557, wR2 = 0.2870	
Largest diff. peak and hole	1.101 and -0.493 e.Å-3	

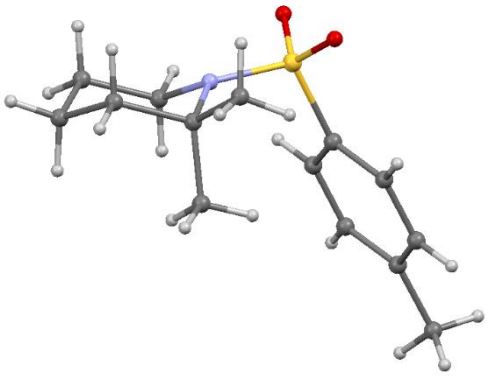
Appendix 2

2,2-Dimethyl-1-tosylpiperidine 250

m.p. 66 – 67 °C



250



CCDC 1021610

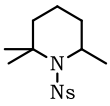
Table 1. Crystal data and structure refinement for CCDC 1021610.

Identification code	CCDC 1021610	
Empirical formula	C14 H21 N O2 S	
Formula weight	267.38	
Temperature	170(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 8.1099(2) Å	α = 90°.
	b = 11.2069(2) Å	β = 92.522(2)°.
	c = 15.4545(3) Å	γ = 90°.
Volume	1403.25(5) Å3	
Z	4	
Density (calculated)	1.266 Mg/m3	
Absorption coefficient	2.002 mm-1	
F(000)	576	
Crystal size	0.279 x 0.214 x 0.024 mm3	
Theta range for data collection	4.876 to 73.966°.	
Index ranges	-10<=h<=7, -10<=k<=13, -19<=l<=19	
Reflections collected	5574	
Independent reflections	2752 [R(int) = 0.0157]	
Completeness to theta = 67.684°	99.8 %	
Absorption correction	Gaussian	
Max. and min. transmission	0.990 and 0.921	
Refinement method	Full-matrix least-squares on F2	
Data / restraints / parameters	2752 / 0 / 166	
Goodness-of-fit on F2	1.046	
Final R indices [I>2sigma(I)]	R1 = 0.0327, wR2 = 0.0887	
R indices (all data)	R1 = 0.0374, wR2 = 0.0926	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.296 and -0.296 e.Å-3	

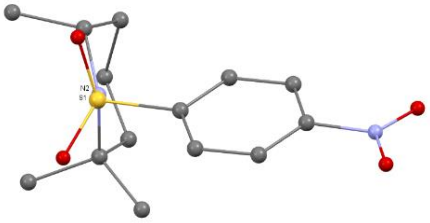
Appendix 3

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

m.p. 124 – 127 °C



261



CCDC 797889

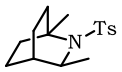
Table 1. Crystal data and structure refinement for CCDC 797889.

Identification code	CCDC 797889	
Empirical formula	C14 H20 N2 O4 S	
Formula weight	312.38	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/a	
Unit cell dimensions	a = 6.2943(18) Å	α = 90°.
	b = 19.982(7) Å	β = 96.79(2)°.
	c = 11.764(3) Å	γ = 90°.
Volume	1469.2(8) Å3	
Z	4	
Density (calculated)	1.412 Mg/m3	
Absorption coefficient	0.238 mm-1	
F(000)	664	
Crystal size	0.30 x 0.04 x 0.02 mm3	
Theta range for data collection	3.42 to 20.92°.	
Index ranges	-6<=h<=6, -18<=k<=20, -11<=l<=11	
Reflections collected	2647	
Independent reflections	1534 [R(int) = 0.0947]	
Completeness to theta = 20.92°	98.1 %	
Max. and min. transmission	0.9953 and 0.9320	
Refinement method	Full-matrix least-squares on F2	
Data / restraints / parameters	1534 / 0 / 193	
Goodness-of-fit on F2	1.164	
Final R indices [I>2sigma(I)]	R1 = 0.0865, wR2 = 0.1593	
R indices (all data)	R1 = 0.1428, wR2 = 0.1816	
Largest diff. peak and hole	0.264 and -0.304 e.Å-3	

Appendix 4

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

m.p. 112 – 114 °C



420

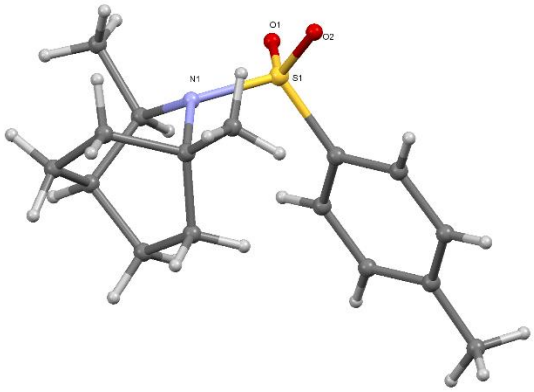


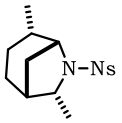
Table 4. Crystal data and structure refinement for dwk1016.

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

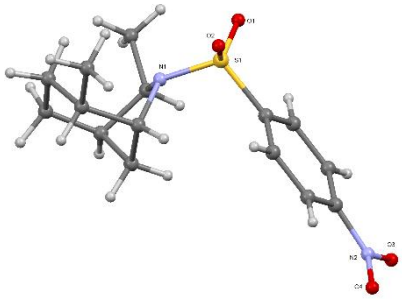
Appendix 5

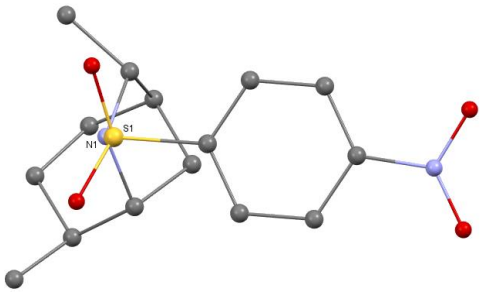
4,7-Dimethyl-6-((4-nitrophenyl)sulfonyl)-6-azabicyclo[3.2.1]octane 242

m.p. 174 – 177 °C



424





CCDC 1021607

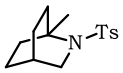
Table 1. Crystal data and structure refinement for CCDC 1021607.

Identification code	CCDC 1021607	
Empirical formula	C15 H20 N2 O4 S	
Formula weight	324.39	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 6.2309(10) Å	α = 90°.
	b = 10.869(3) Å	β = 102.250(18)°.
	c = 11.970(3) Å	γ = 90°.
Volume	792.2(3) Å3	
Z	2	
Density (calculated)	1.360 Mg/m3	
Absorption coefficient	0.224 mm-1	
F(000)	344	
Crystal size	0.500 x 0.040 x 0.010 mm3	
Theta range for data collection	1.741 to 20.796°.	
Independent reflections	1642	
Completeness to theta = 25.242°	58.1 %	
Refinement method	Full-matrix-block least-squares on F2	
Data / restraints / parameters	1642 / 104 / 181	
Goodness-of-fit on F2	1.240	
Final R indices [I>2sigma(I)]	R1 = 0.1183, wR2 = 0.2744	
R indices (all data)	R1 = 0.2021, wR2 = 0.3613	
Absolute structure parameter	0.5(6)	
Largest diff. peak and hole	1.044 and -0.576 e.Å-3	

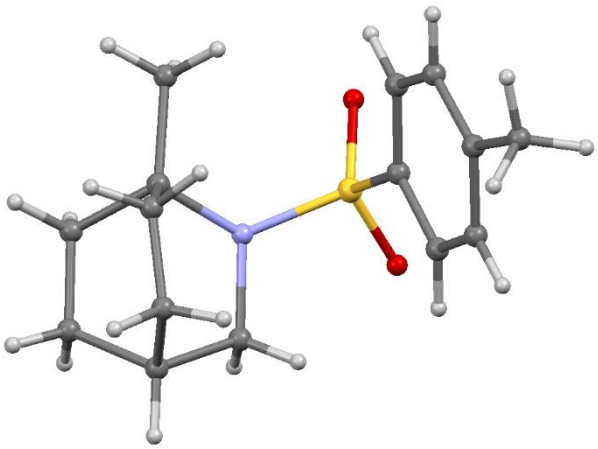
Appendix 6

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

m.p. 135 – 138 °C



430



CCDC 1061506

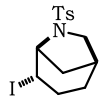
Table 1. Crystal data and structure refinement for exp_769.

Identification code	CCDC 1061506	
Empirical formula	C15 H21 N O2 S	
Formula weight	279.39	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P n a 21	
Unit cell dimensions	a = 7.6489(4) Å	α = 90°.
	b = 16.1308(7) Å	β = 90°.
	c = 11.3067(6) Å	γ = 90°.
Volume	1395.05(12) Å3	
Z	4	
Density (calculated)	1.330 Mg/m3	
Absorption coefficient	0.230 mm-1	
F(000)	600	
Crystal size	0.200 x 0.101 x 0.055 mm3	
Theta range for data collection	3.455 to 29.574°.	
Index ranges	-10<=h<=7, -15<=k<=22, -15<=l<=9	
Reflections collected	4434	
Independent reflections	2636 [R(int) = 0.0426]	
Completeness to theta = 25.242°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.71986	
Refinement method	Full-matrix least-squares on F2	
Data / restraints / parameters	2636 / 425 / 257	
Goodness-of-fit on F2	1.089	
Final R indices [I>2sigma(I)]	R1 = 0.0567, wR2 = 0.1293	
R indices (all data)	R1 = 0.0745, wR2 = 0.1410	
Absolute structure parameter	0.6(3)	
Largest diff. peak and hole	0.460 and -0.328 e.Å-3	

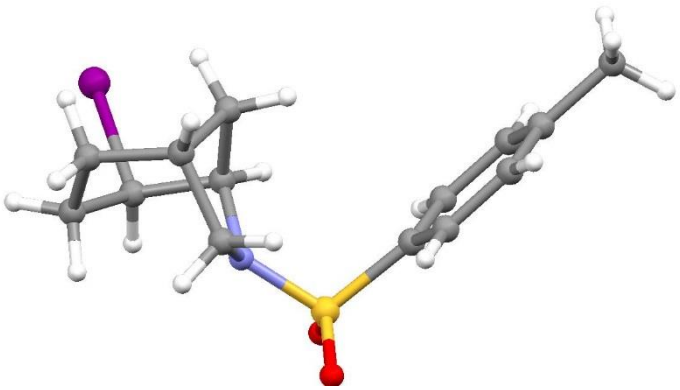
Appendix 7

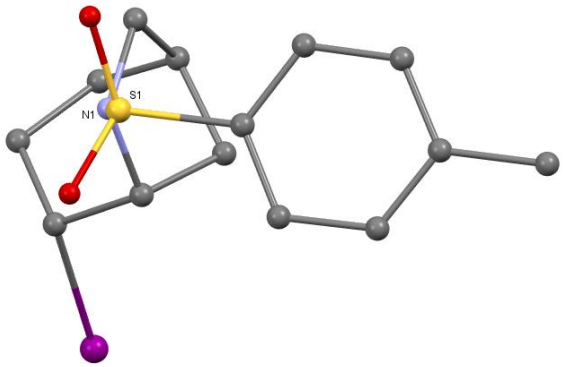
4-Iodo-6-tosyl-6-azabicyclo[3.2.1]octane 436

m.p. 116 – 118 °C



436





CCDC 1021608

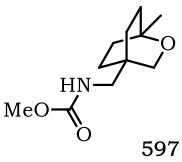
Table 1. Crystal data and structure refinement for CCDC 1021608

Identification code	CCDC 1021608	
Empirical formula	C14 H18 I N O2 S	
Formula weight	391.25	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 7.2761(2) Å	α = 69.202(2)°.
	b = 9.8338(3) Å	β = 80.029(2)°.
	c = 11.1700(3) Å	γ = 80.879(2)°.
Volume	731.77(4) Å3	
Z	2	
Density (calculated)	1.776 Mg/m3	
Absorption coefficient	2.328 mm-1	
F(000)	388	
Crystal size	0.150 x 0.100 x 0.100 mm3	
Theta range for data collection	2.228 to 27.867°.	
Index ranges	-9<=h<=9, -10<=k<=12, -14<=l<=13	
Reflections collected	4991	
Independent reflections	3447 [R(int) = 0.0259]	
Completeness to theta = 25.242°	99.1 %	
Refinement method	Full-matrix least-squares on F2	
Data / restraints / parameters	3447 / 0 / 174	
Goodness-of-fit on F2	1.119	
Final R indices [I>2sigma(I)]	R1 = 0.0385, wR2 = 0.0891	
R indices (all data)	R1 = 0.0419, wR2 = 0.0921	
Extinction coefficient	0.054(3)	
Largest diff. peak and hole	1.563 and -1.267 e.Å-3	

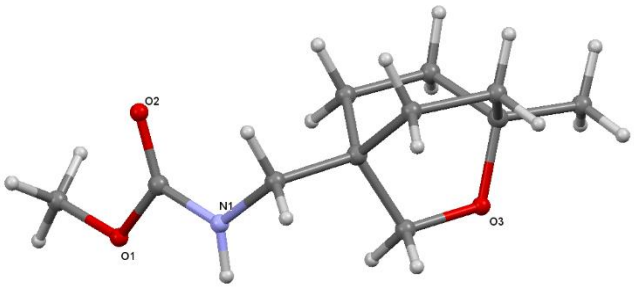
Appendix 8

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

m.p. 92 – 94 °C



597



CCDC 1021609

Table 1. Crystal data and structure refinement for CCDC 1021609.

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