I learnt what not to do, and that is always something.

Sir Arthur Wellesley, Duke of Wellington.

UNIVERSITY OF SOUTHAMPTON

Synthesis of Cycloheptanes Using Radical Cyclisations of Methylenecyclopropane Derivatives

by

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Doctor of Philosophy

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ABSTRACT

FACULTY OF SCIENCE

CHEMISTRY

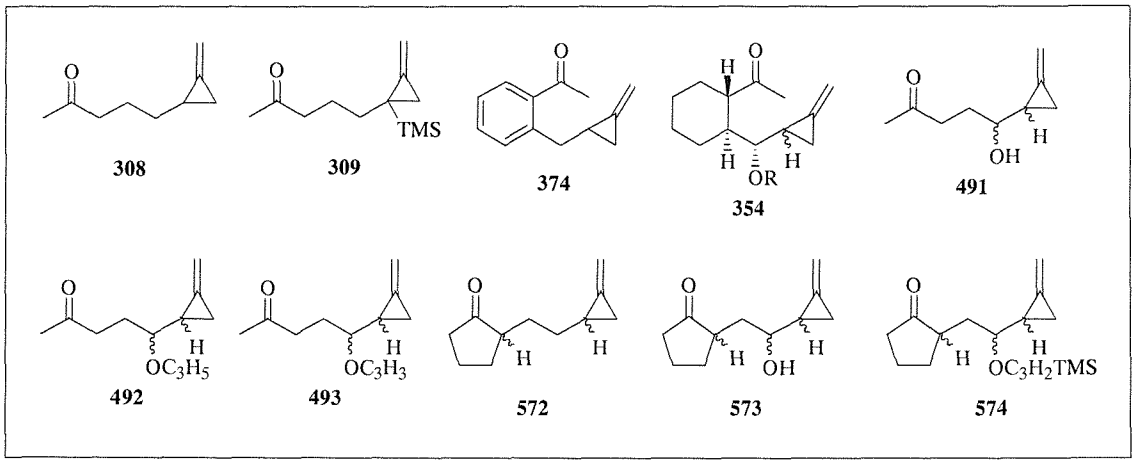
Doctor of Philosophy

SYNTHESIS OF CYCLOHEPTANES USING RADICAL CYCLISATIONS OF METHYLENECYCLOPROPANE DERIVATIVES

By Jonathan James Underwood

This thesis is concerned with the synthesis and radical cyclisations of compounds containing a methylenecyclopropane moiety. The focus of the work is to use a samarium (II) iodide-mediated radical cyclisation to prepare cycloheptanes.

Chapter two describes the synthesis of basic precursors (**308** and **309**) to explore the potential for the desired transformation and also the optimum conditions required. Chapter three reports the synthesis and cyclisation of precursors with an aromatic backbone (**374**) or a cyclohexyl backbone (**354**) and either an alcohol or allyl ether moiety; *trans* decalins were produced in moderate yields. Chapter four details the synthesis and cyclisation of open-chain precursors that have either an alcohol (**491**), allyl ether (**492**) or propargyl ether (**493**) functionality present; many different bicyclic products were isolated. Chapter five outlines the synthesis and cyclisation of a series of cyclopentanone (**572**, **573** and **574**) precursors leading to bicyclic and tricyclic products.



Contents

Preface

The research described in this thesis was carried under the supervision of Professor Jeremy Kilburn at the University of Southampton between October 1999 and December 2002. No part of this thesis has been previously submitted at this or any other university.

Acknowledgments

I would like to thank Professor Jeremy Kilburn for his supervision, encouragement, patience, tolerance of my sense of humour and some interesting discussions during the course of this project.

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Thanks to Mrs. Joan Street and Dr. Neil Wells for some excellent NMR experiments (sorry about the chair!). Thanks also to Dr. John Langley and Julie Herniman for a large amount of Mass Spectrometry analysis. Thanks to Dr. Simon Coles, Dr. Mark Light and Dr. Pete Horton for their work on obtaining X-ray crystal structures.

I would also like to thank Merck, Sharp & Dohme and the EPSRC for funding over the three years.

Thanks to Jeremy, Lee Patient and Neil Wells for taking the time to proof-read my work. Also thanks to Richard Fitzmaurice for help with the computer-side of production.

I would like to thank the many people who have made the three years enjoyable and bearable. Tobias Braxmeier for some fine Deutsche humour; Graham "fire" Kyne for buying the drinks and revealing the wrong way to use a sleeping bag; Guillaume LN Peron for showing me how to be a cowboy; Emma Shepherd for encouragement, support and very happy times; Alex Saint-Dizier for "invovling" the "strarting point"; David Douheret for not being very French; Faye Dr Watson for help and late night Tom Jones sessions; Lee "Frak" Patient for loads: excellent music, great humour, trivial pursuit quizes (how can you answer more questions correctly and still lose?), having many different surnames, urgh-huh-huh (tourrettes); Anawat Ajavakom for providing new gambling opportunities with his time-keeping; Richard "Seba" Fitzmaurice for interesting numbers and club-dancing (fructiciously); Neil Wells for humour, help, lifts and taking so many jokes; Geoff Head for being a great mate; Ben "Timmy" Sutton for taking the point. Thanks to members of the Kilburn group past and present: Mariangela, Rosella, Sara, Jenny, Kim, Andrew, Nittaya, Lene, Max, Tom, Suvi, Sandra, Andrea, Sarah, Pla, Pasquale. Simmons-Smith – duh!

Thanks to Mark and Moe for some great times and plenty of cigarettes.

Finally thanks to my family Dave, Jean and Tim for understanding, encouragement and support.

Remember, mixing sodium and water produces an exothermic reaction!

Abbreviations

AIBN	azobisisobutyronitrile
Ar	Argon
aq.	aqueous
bp.	Boiling point
^{n}Bu	n-butyl
^{t}Bu	*tert*-butyl
CI	chemical ionisation
COSY	correlation spectroscopy
Δ	reflux
DCM	dichloromethane
DIBAL	diisobutylaluminium hyrdide
DMF	dimethyl formamide
DMSO	dimethylsulphoxide
DMPU	*N,N'*-dimethyl-*N,N'*-propylene urea
EI	electron impact
Et	ethyl
eq.	equivalent
FT-IR	Fourier transform infrared
GOESY	gradient nuclear Overhauser spectroscopy
HMBC	heteronuclear multi-bond connectivity
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum correlation
hv	light
maj.	major
MCPBA	*meta*-chloroperbenzoic acid
Me	methyl

min.	minor
mp.	melting point
NCS	N-chloro succinnimide
NMR	nuclear magent resonance
Ph	phenyl
ppm	parts per million
R_f	retention factor
RT	room temperature
SmI_2	samarium (II) iodide
THF	tetrahydrofuran
TLC	thin layer chromatography
TMANO	trimethylamine N-oxide
TMS	trimethylsilyl
Ts	tosyl

Chapter One

1 Introduction

1.1 Radical Chemistry

Radical chemistry has a long history dating back to the early 1900s with Gomberg's investigation of the formation and reactions of the triphenylmethyl radical[1]. The nature of radicals, their formation, structure, and reactivity are now very well documented and there are many excellent papers, reviews and books on the subject[2-14]. Radical chemistry has become such a useful synthetic tool that the synthesis of natural products and their key intermediates *via* a radical reaction is now commonplace[6, 7, 10].

1.1.1 Types of Radical Reaction

Radicals are species with at least one unpaired electron. The generation and fate of the radical depend on many factors but most radical reactions involve one or more of the following steps (Figure 1) in which A, B and C represent atoms or groups[2, 9].

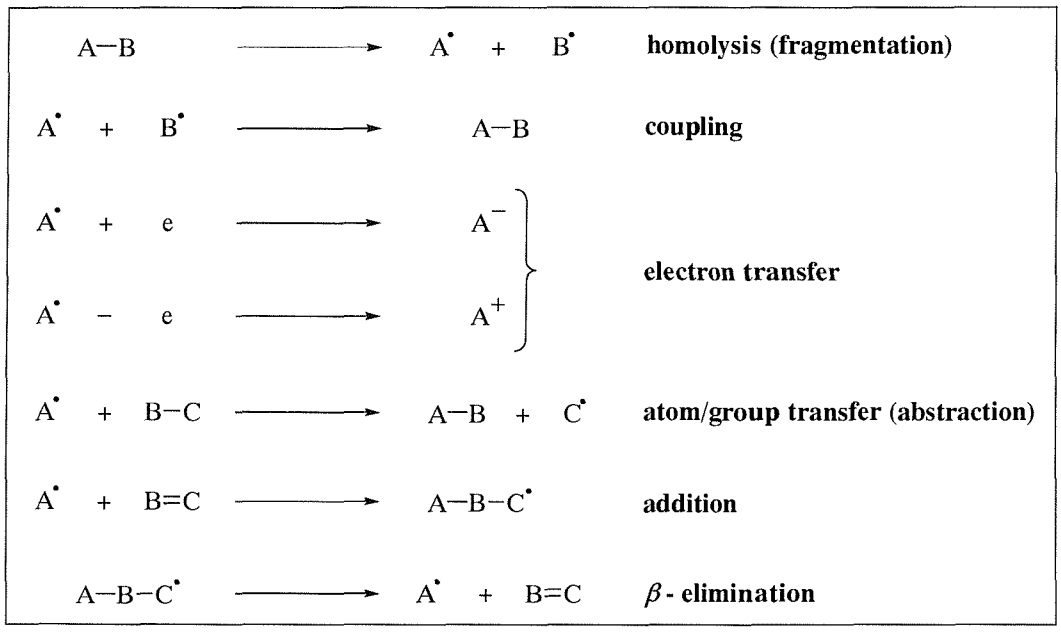


Figure 1. Elementary radical mechanisms.

The number of potential radical reactions may initially suggest that they react in an indiscriminate way, but this is not the case[3]. Radical species have a well-defined character and, as such, generally react in a predictable fashion.

There are many advantages of radical reactions over ionic reactions[3, 10]. Carbanions and carbocations are not simple entities: they have associated counterions (making them much more bulky) which can lead to problematic solvation or aggregation phenomena. Neutral radicals tend to bypass solvation problems, and, because radicals are small, reactive species they can perform the desired transformation in highly hindered situations.

Radical reactions can be carried out under mild neutral conditions without compromising the chemo-, regio- or stereoselectivity. Indeed, a given radical reaction may be carried out successfully over a wide range of solvents and molecules of varying polarity with a greater degree of confidence of success than with their ionic counterparts.

Carbon radicals are inert toward alcoholic or amino functionalities. As a consequence, radical reactions often do not need to be dry and the protection of alcohols, amines and similar moieties is seldom necessary. Carbocations have problems due to their electrophilic nature; and the basicity of nucleophilic carbanions can present a problem especially in cases where there is the possibility to epimerize a susceptible centre such as those α to carbonyls.

1.1.2 The Character of Radicals

The stability, character and reactivity of the radical species depend mainly on two factors: the atom which is carrying the unpaired electron and the atoms or groups that are bonded to the radical bearing atom. Thus, radicals can be described as electrophilic or nucleophilic and show hard or soft behaviour.[3]

1.1.2.1 The Stability of Radicals

Many factors affect the stability of a radical[15]. Hyperconjugation with neighbouring groups gives rise to the trend below (Figure 2).

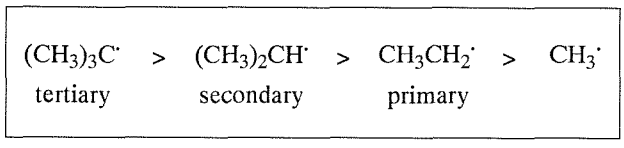


Figure 2. Order of stability of radicals.

A simple model proposes that the 2p orbital containing the radical interacts with the σ and σ* orbitals of the alkyl groups adjacent to the radical centre (Figure 3). The overall effect is an energetically favourable one, thus the more adjacent groups present that can interact through hyperconjugation, the more stable the radical. An explanation of greater depth is more complicated and involves the radical SOMO interaction with the π-type orbitals of the adjacent carbon causing a lowering in energy of the orbitals[4].

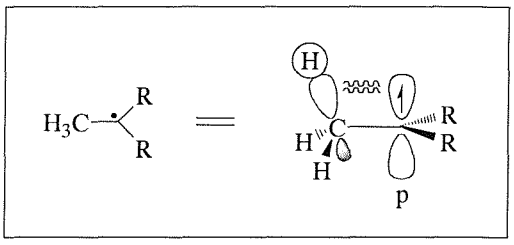


Figure 3. Hyperconjugation stabilization effects.

Like cations and anions, delocalization into the π system of multiple bonds and aromatic systems also greatly increases the stability of the radical through resonance. The hybridization of the radical also has an effect on stability. A π type radical, where the electron is in a pure p orbital, is more stable than a σ type radical, where the orbital has more s character. It follows that increasing the p character of an orbital increases the stability of the radical.

Finally, the orbital interactions due to synergistic (captodative) effects stabilize the radical by increasing the favourable interactions with both the electron-donating and electron-accepting groups.

1.1.2.2 Electrophilic and Nucleophilic Characteristics

The chemoselectivity of radical reactions can be explained by examining the electronic structure of the radicals involved[2-4]. Since it is believed that radical reactions have early transition states[6], it is possible to use a frontier molecular orbital theory approach[4]. It is clear the frontier orbital of the radical is a SOMO which can interact with the HOMO or LUMO of the other reactant molecule (Figure 4)[4].

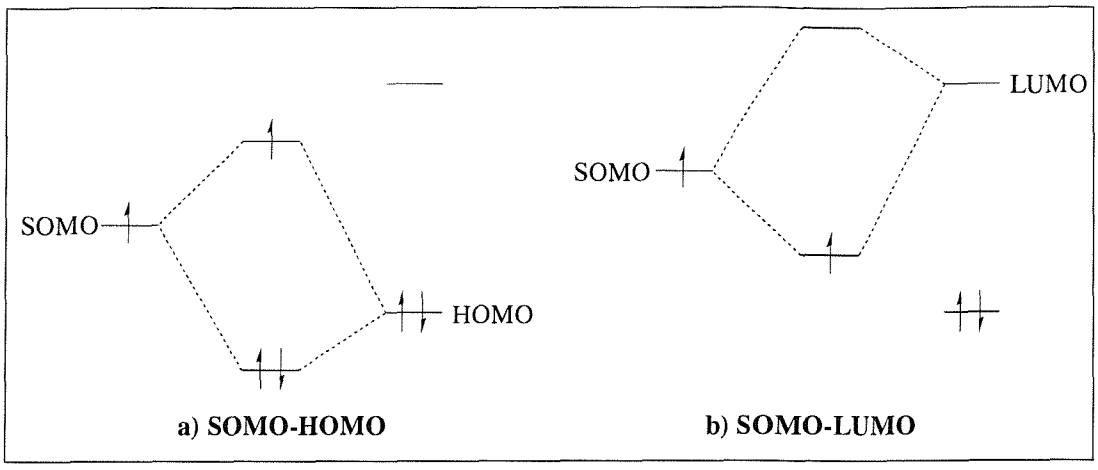
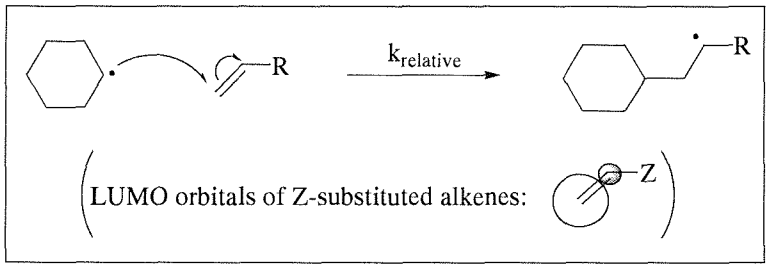


Figure 4. Interactions of the radical SOMO with the a) HOMO and b) LUMO of a reactant molecule.

It can be seen that both types of interaction lead to a drop in energy. Radicals with a low-energy SOMO will react quickly with molecules with a high-energy HOMO (nucleophiles); conversely radicals with a high-energy SOMO will react quickly with molecules with a low-energy LUMO (electrophiles). In general, radicals that have a low-energy SOMO show electrophilic properties, and radicals that have a high-energy SOMO show nucleophilic properties[4]. This can be illustrated by considering the addition of two radicals to differently substituted alkenes. Simple alkyl radicals are nucleophilic (high SOMO) and will preferentially react with the LUMO of the alkene. The LUMO of the alkene is lowered in energy if an electron withdrawing group (Z) is added, thereby increasing the orbital interaction leading to a faster rate of reaction (Figure 5)[8].

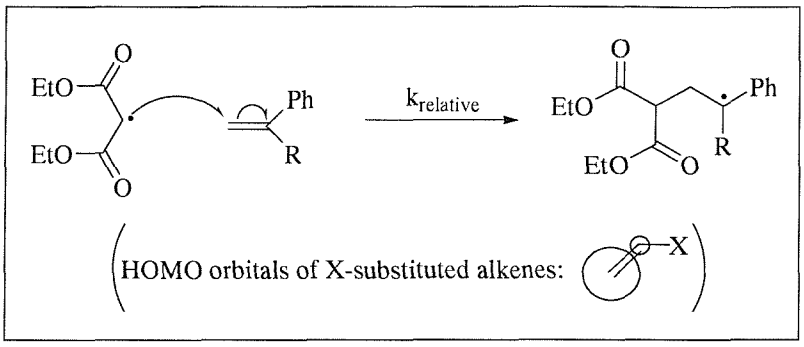


R	C_4H_9	H	Cl	Ph	CO_2CH_3	$COCH_3$	CN	CHO
$k_{relative}$	0.004	0.015[a]	0.12	1.0	6.7	13	24	34

a) extrapolated from the Hammett relationship

Figure 5. Relative rates of addition of C_6H_{11}· to substituted alkenes.

Radicals with electron withdrawing substituents are electrophilic (low SOMO) and will preferentially react with the HOMO of the alkene. Electron donating groups (X) raise the energy of the HOMO of the alkene, again increasing the orbital interaction leading to a faster rate of reaction (Figure 6)[16].



R	$CO_2C_2H_5$	OCH_3	Ph	CH_3	$N(CH_3)_2$
$k_{relative}$	1.0	2.7	3.5	3.7	23

Figure 6. Relative rates of addition of $(EtO_2C)_2CH^{\cdot}$ to substituted alkenes.

1.1.2.3 Hard and Soft Characteristics

Consideration of the preferred reactions of radicals within group 16 (VI) demonstrates the hard/soft variations[3]. Alkoxy radicals are electrophilic and favoured reactions are hydrogen atom abstraction and β-elimination (Figure 7).

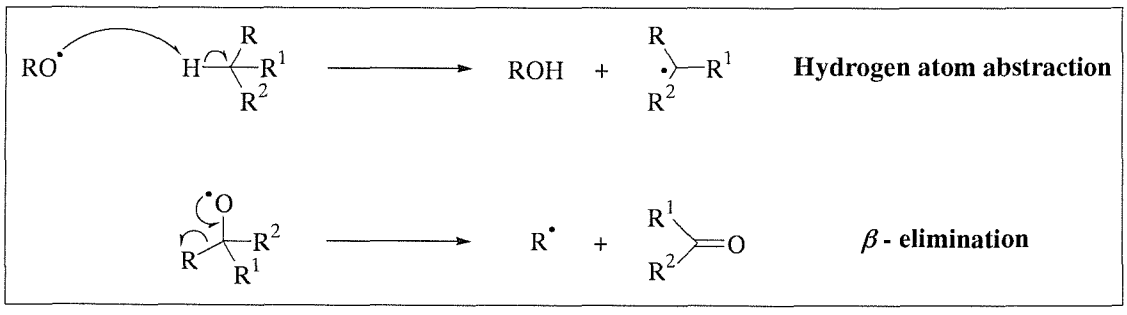


Figure 7. Favoured alkoxy radical processes.

The favourable nature of these processes can be explained by examining the bond strengths involved (Table 1)[17]. Formation of a strong O-H bond from a weaker C-H bond is a thermodynamically favoured process. The π C=O bond formed by β-elimination is comparable in strength to the σ C-C bond. Alkoxy radicals tend not to add to C-C

multiple bonds and the reverse β-elimination of the alkoxy radical is also a slow, disfavoured process[2, 3].

C–H	410	C–O	350	C–C	350
O–H	460	C=O	740	C=C	610
S–H	340	C–S	260	C≡C	840

Table 1. Approximate bond strengths ($kJmol^{-1}$)

Thiyl radicals are larger than alkoxy radicals and hence softer. They are less inclined towards the abstraction of hydrogen atoms. Addition to C-C double bonds and the reverse β-elimination reaction is a much more favoured process than for alkoxy radicals (Figure 8).[3]

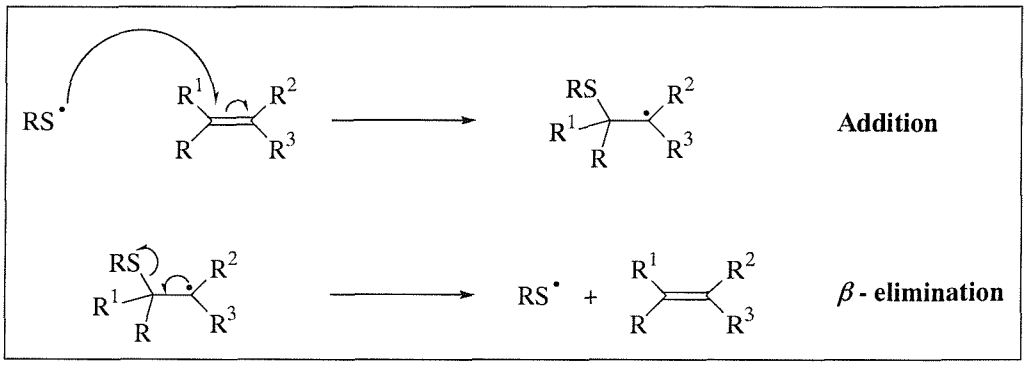


Figure 8. Favoured thiyl radical processes.

1.1.3 Radical Cyclisations

One of the most important radical reactions is an intramolecular radical addition – the radical cyclisation reaction. The real power behind this type of reaction is the potential for high degrees of regio- and stereo-selectivity. There is also the opportunity to form multiple ring systems in one step from precursors already containing a ring system or from completely acyclic precursors.[13] This allows the construction of natural product skeletons. [6, 7, 10]

1.1.3.1 Regio-selectivity

By considering the geometry of nucleophilic, cationic and radical attack on tetrahedral, trigonal and digonal centres, Baldwin has compiled guidelines for ring closure[18]. These rules apply well in general to radical cyclisations. Cyclisations can follow either an *exo* mode or an *endo* mode of addition (Figure 9)[18].

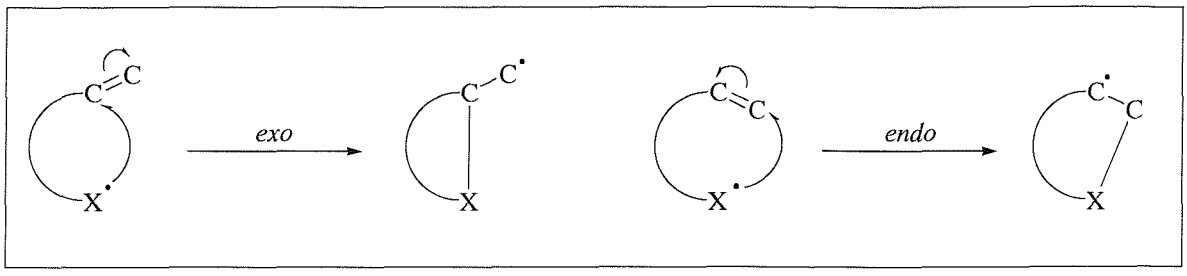


Figure 9. *Exo* and *endo* modes of cyclisation.

Although the *exo* mode leads to a less stable primary radical (see section 1.1.2.1), for small ring sizes it tends to be the preferred route as exemplified by the intramolecular cyclisation of the hex-5-enyl **1** and hept-6-enyl **4** radicals (Figure 10).[19-21]

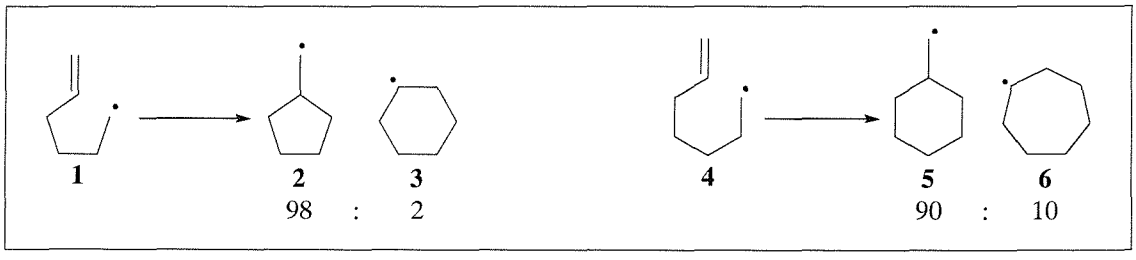


Figure 10. Yields of simple cyclisations.

The kinetic product (**2** and **5**) is clearly the dominant product. When a radical attacks a double bond it does so in an unsymmetrical fashion (Figure 11)[8, 22, 23]. The angle of attack (~109°) maximizes the orbital overlap and this leads to the regio-selectivity observed in the hexenyl and heptenyl cyclisations[21].

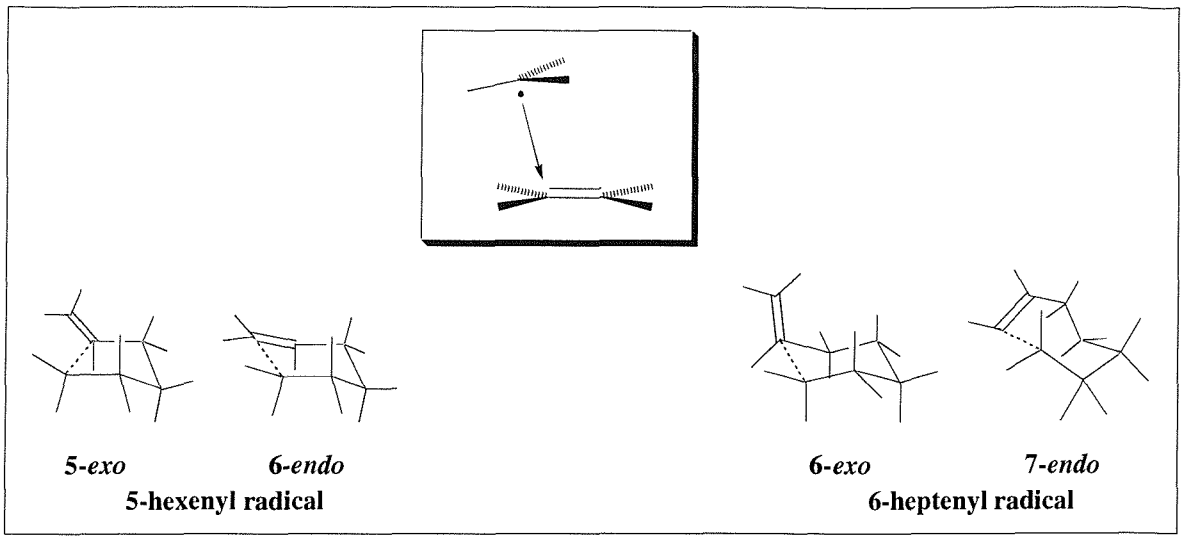


Figure 11. The approach of a radical adding to an alkene and the transition states for 5-hexenyl and 6-heptenyl radicals.

There have been many studies on rates of reaction and yield of products from the intramolecular addition of simple alkyl radicals to alkenes (Table 2)[15].

The *endo* cyclisations of **7** and **10** leading to 4- and 5- membered rings **9** and **12** simply do not occur as the required transition state geometry is unfavourable. The *exo* cyclisations do occur for **7** and **10**, but the formation of the strained ring system means that the rate of ring-opening is faster than ring-closing. The energy of ring-strain must be greater than the net energy gained from the formation of a carbon-carbon bond.

For **13** and **16**, the reverse reaction is usually not observed as there is no ring strain involved and this process is very slow. The geometry of the transition state indicates that there is better orbital overlap for the *exo* modes and this is reflected in the relative rates.

Finally, **19** shows little preference for either mode, but the rates of cyclisation are relatively slow and other faster side-reactions may become more involved in cyclisations of this type.

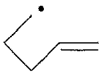
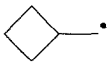
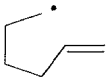
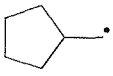
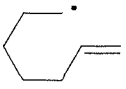
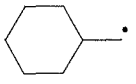
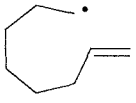
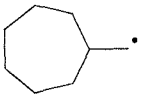
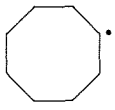
Alkene	*Exo* product	*Endo* product	k_{exo}	k_{endo}	k_{exo}/k_{endo}	k_{-exo}
 7	 8	 9	1.8×10^4	not observed	-	2.0×10^8
 10	 11	 12	1.0	not observed	-	4.7×10^3
 13	 14	 15	2.3×10^5	4.1×10^3	58	-
 16	 17	 18	5.4×10^3	7.5×10^2	6	-
 19	 20	 21	<70	1.2×10^2	<0.6	-

Table 2. Cyclisation and opening of alkyl radicals (k in s^{-1} at 25°C).

1.1.3.2 The Effect of Substituents on Rate

Substitution along the chain can greatly affect the rate of cyclisations and promote formation of either the *exo* or *endo* product (Table 3)[15, 21, 24]. Addition of methyl groups at the 1-position of the 5-hexenyl radical stabilize the radical and lead to an increase in the rate of both *exo* and *endo* cyclisations (**22** & **23**). Placing the methyl group on the alkene has a marked effect: in **24** the *endo* mode is hindered and its rate drops; in **25**, however, the *exo* mode is now hindered and the *endo* route has a better rate of cyclisation. The gem-dimethyl analogue **26** increases the rates due to the Thorpe-Ingold effect[25]. The incorporation of heteroatoms into the chain can also dramatically alter the rates of cyclisation as evinced by **27**. The geometry of the transition state is altered by the carbon-oxygen bond angles and lengths.

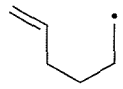
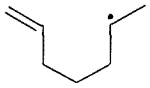
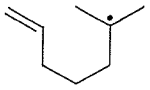
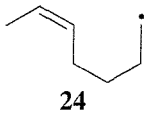
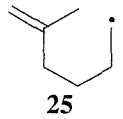
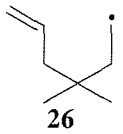
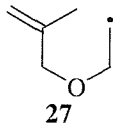
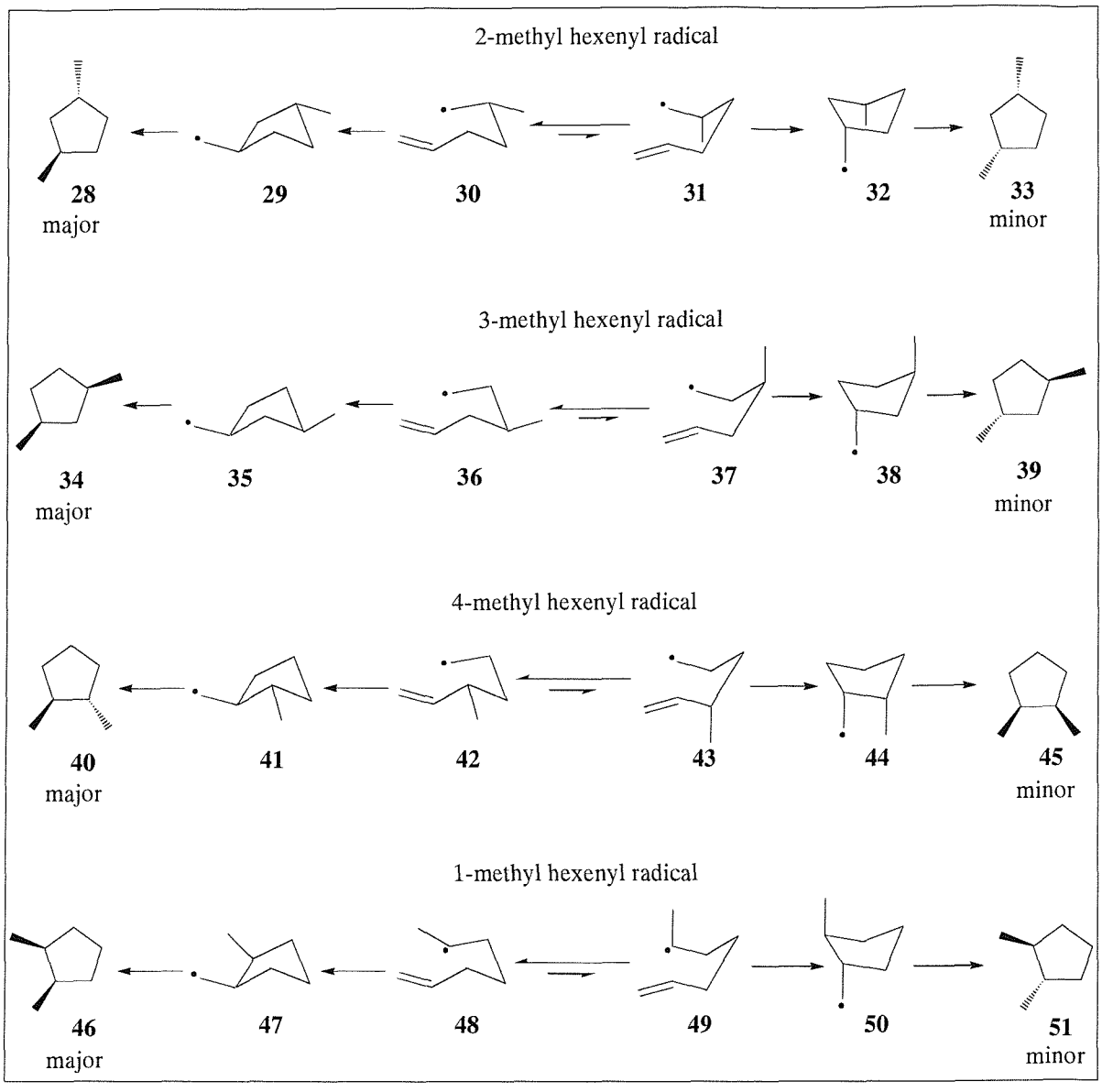
Alkene	k_{exo}	k_{endo}	k_{exo}/k_{endo}
 **13**	1	0.017	58
 **22**	1.4	0.02	70
 **23**	1.4	0.02	70
 **24**	1.0	<0.01	>100
 **25**	0.022	0.04	0.55
 **26**	22	<0.4	>51
 **27**	24	0.27	85

Table 3. Effect of methyl substituents on relative rate (at 65°C).

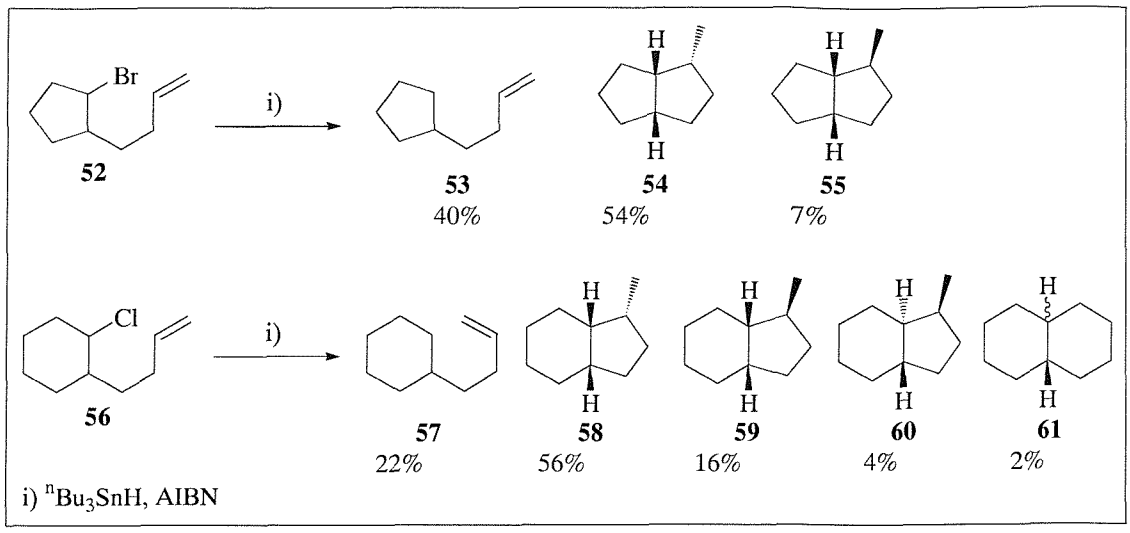
1.1.3.3 Stereo-selectivity of Cyclisations

The products from substituted hexenyl radical cyclisations have a preference for *cis* or *trans* products (Scheme 1)[3]. By considering the transition state of the 2-, 3- and 4-methyl substituted hexenyl radicals it is clear that the transition state that places the methyl group in a pseudo-equatorial position is favoured (**30** to **29**; **36** to **35**; **42** to **41**) [26]. For the 1-methyl hexenyl radical the preference for the *cis* product **46** may be due to stereoelectronic or steric reasons[27]. Thus, 2- and 4- substituted hexenyl radicals tend to give the *trans* product as the major component (**28** and **40**) and 1- and 3- substituted hexenyl radicals will tend to give the *cis* product (**34** and **46**) as the major component.



Scheme 1. 1-, 2-, 3- and 4- methyl hexenyl radical transition states.

Studies on the formation of bicyclic products have shown *cis*-fused geometry is preferred in systems such as those below (Scheme 2). The bicyclic products **54** and **55** from the cyclopentyl precursor **52** are exclusively *cis*[28], whereas the cyclohexyl analogue **56** has a very small amount of *trans* bicyclic product **60** formed as well as the *cis*-fused bicycles **58** and **59** [20].



Scheme 2. Radical cyclisations forming *cis*-fused bicycles.

By examining the transition states[29], it is clear that the *cis*-products arise from the energetically favourable chair-like transition states **62** and **63** (Figure 12). The preference for **54** over **55**, and **58** over **59** arises from the fact that transition state **62** can achieve effective orbital overlap of the radical SOMO and the alkene π orbitals with less strain than transition state **63**.

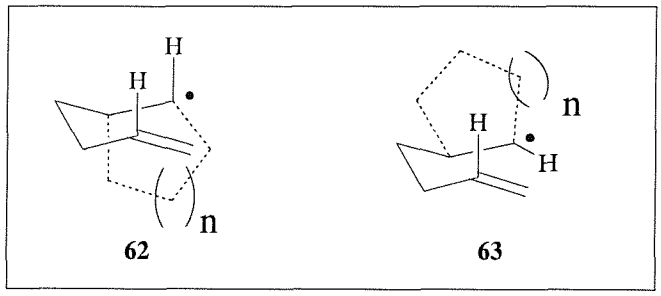


Figure 12. Chair-like transition states.

1.1.4 Radical Chain Reactions[2, 3, 5-7]

1.1.4.1 The Usefulness of Chain Processes

The coupling of two radicals is not the most synthetically useful reaction.[2]

- Equivalent amounts of radical initiator must be used.
- Diffusion controlled rates give rise to poor selectivity.

- Necessary low concentrations of radicals mean that potential reactions with solvent are hard to prevent.

Far more useful is the reaction between a radical and a non-radical.

- Another radical is produced and there is potential for the use of non-stoichiometric quantities of initiator and chain carriers.

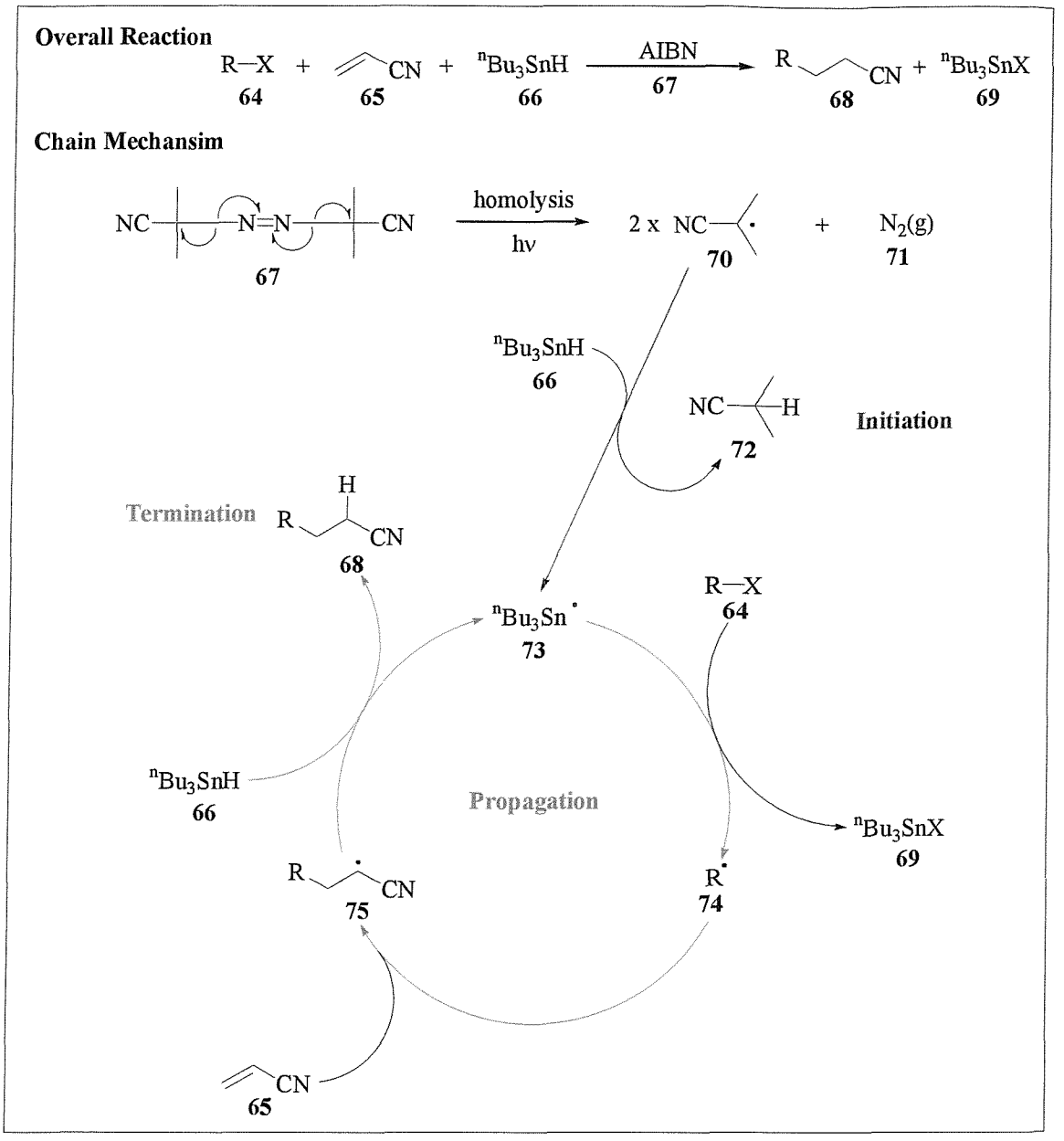
- The rates of reaction are often not diffusion controlled, hence selectivity can be influenced.

- The concentrations of the non-radical reactant are easily controlled, removing undesired side-reactions.

The reaction of a radical and a non-radical allows a chain process to develop if two conditions are met.[2] Firstly, the chemoselectivities of radicals involved in the chain must be different. Secondly, the reaction between radical and non-radical must be faster than the radical-radical coupling reaction. If these two requirements are met then the chain mechanism will work correctly.

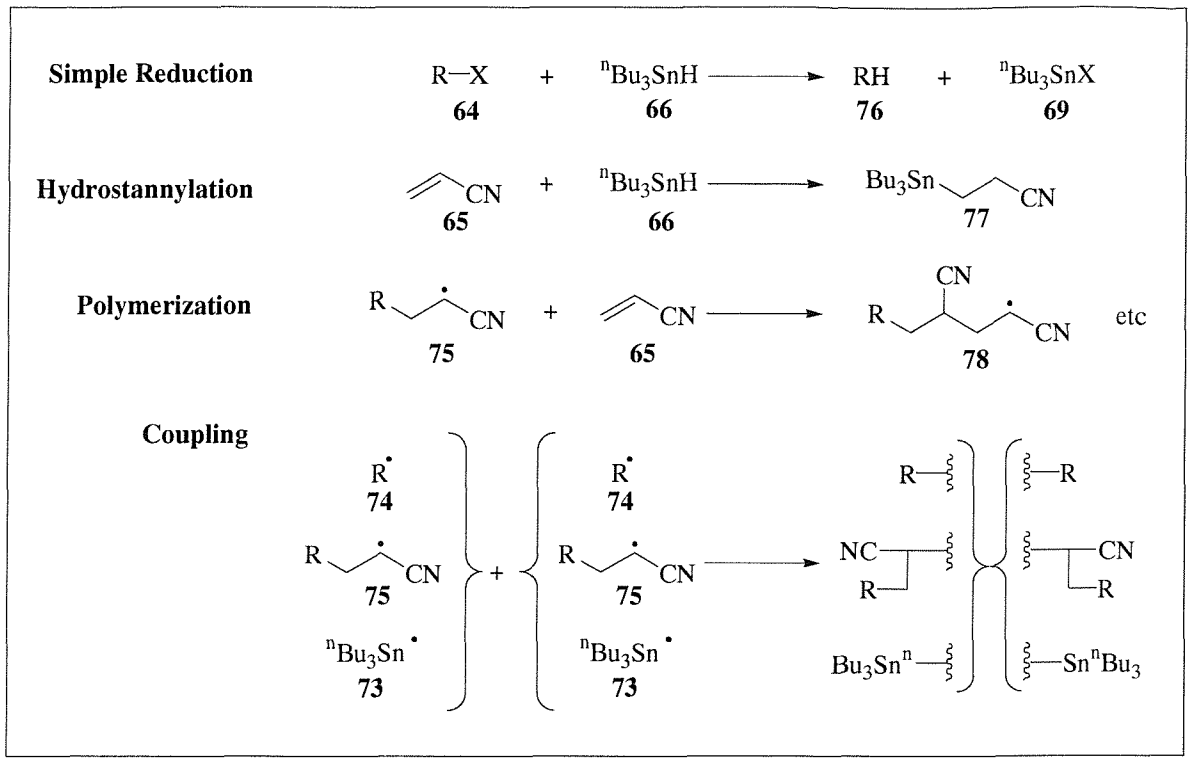
1.1.4.2 A Basic Chain Reaction Example

There are several stages to a chain mechanism: initiation, propagation, and termination. These are illustrated by the reaction on an alkyl halide **64** with acrylonitrile **65** mediated by tributyl tin hydride **66** (Scheme 3) [2, 3]. For the cycle to begin tributyl tin radical **73** must be generated. This is achieved by use of an initiator. AIBN **67** decomposes to form radical **70** which reacts with tin hydride **66**. The cycle can now begin: the tin radical **73** abstracts the halide atom from alkyl halide **64**; the alkyl radical **74** adds to acrylonitrile **65**; the addition product then abstracts a hydrogen atom from tin hydride **66** to yield the desired product **68** and the tin radical **73** essential for the cycle to begin again. It must be noted that theoretically this process can continue *ad infinitum* with only one tin radical **73** present so long as there are supplies of alkyl halide **64**, acrylonitrile **65**, and tin hydride **66**. In practice this is not the case, as not all collisions are reactive and other processes can terminate the chain[3].



Scheme 3. Basic radical chain mechanism.

There are also numerous side reactions that can occur (Scheme 4). If any one of these undesirables is allowed to occur in any large capacity, the chain process fails and the yield of desired addition products will be poor. Careful choice of reaction conditions should prevent these side reactions from occurring[3]. Ultimately, though, termination must occur when feed-stocks of reagents run out, and so one or more of the radical destroying reactions will be involved in this.



Scheme 4. Undesired reactions that compete with the chain mechanism.

It is essential to ensure that the alkyl radical **74** reacts with acrylonitrile **65** and not tin hydride **66**. These reactions occur at similar rates and so a low concentration of tin hydride **66** is normally employed. This can be achieved by a slow addition of tin hydride **66** over the course of the reaction to halide **64** and a large excess of acrylonitrile **65**. However, now there is the chance of the polymerization reaction occurring. Perhaps perversely, the potentially problematic extremely fast reaction between tin hydride **66** and radicals in general is the answer to avoiding polymerization. The tin hydride **66** / radical **75** reaction is 10000 times faster than the reaction of radical **75** with acrylonitrile **65**. This leads to an optimum ratio of 100-fold excess of acrylonitrile relative to tin hydride **66**. [2, 3]

There are other methods for reducing the tin hydride concentration.[6] Use of polymer-bound tin hydrides has been reported[30-32]. Generation of tin hydride **66** *in situ* by the reduction of catalytic tributyltin chloride with a normal reducing agent such as sodium borohydride or sodium cyanoborohydride is also possible[33-37]. This method is only of value where the reactants are compatible with the reducing agent.

The above protocols prevent the simple reduction, polymerization and coupling reactions. The hydrostannylation reaction can still occur if the reaction of alkyl halide **64** and tin radical **73** is not always successful. This happens because the alkyl-halide bond is too

strong, as can be the case with chlorides. The solution is to use a weaker bonded alkyl-halide reagent such as the bromide, or even better the iodide. Employment of iodides ensures that the iodostannane product **69** dominates over hydrostannylation, and also that enough alkyl radicals **74** are produced to carry on the chain. [3]

There are many conditions that can be varied to bring about successful chain reactions: initiator; radical precursor; chain carrier; solvent; and temperature.[3, 5, 7] The rates of reactions in the initiation, propagation and termination determine the optimum reaction conditions.

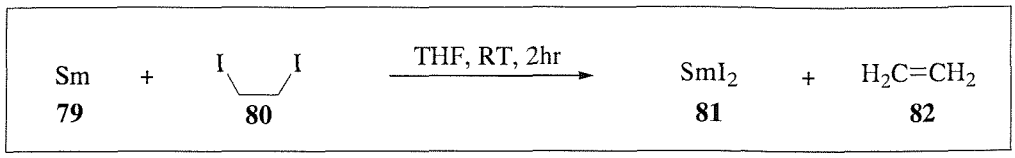
1.1.5 Non-chain Radical Reactions with Samarium (II) Iodide[38]

Radical chain reactions have many attractive features, but non-chain reaction methods also offer a number of synthetically useful qualities. Samarium iodide has been found to be an extremely useful powerful, yet selective, one-electron reducing agent[39]. There are many publications that give an indication of the widespread use of the reagent[38-44].

1.1.5.1 Preparation of Samarium (II) Iodide

Samarium (II) iodide is commercially available (Aldrich Chemical Co.) but can be prepared readily in the laboratory following a method similar to Kagan's[38] introduced in 1980 (Scheme 5). The reaction of samarium metal **79** with diiodoethane **80** produces samarium iodide **81**. A useful driving force in this reaction is the evolution of ethene gas **82**. Samarium iodide can be prepared at concentrations of around 0.1M in various solvents such as THF, MeCN, THP and water[40]. However, samarium iodide reacts rapidly with oxygen, hence its exclusion from the reaction is essential.

The colouration of samarium compounds is a useful indicator allowing the progress of the reaction to be monitored. Samarium (II) iodide in THF is deep Prussian blue whereas Sm^{3+} salts are yellow. Additives such as water; low molecular weight alcohols; HMPA; and DMPU may be used to increase the reduction potential of the samarium (II) iodide[45]. Addition of HMPA to SmI_2-THF turns the solution deep purple and, contrastingly, addition of MeOH changes the solution deep emerald green.



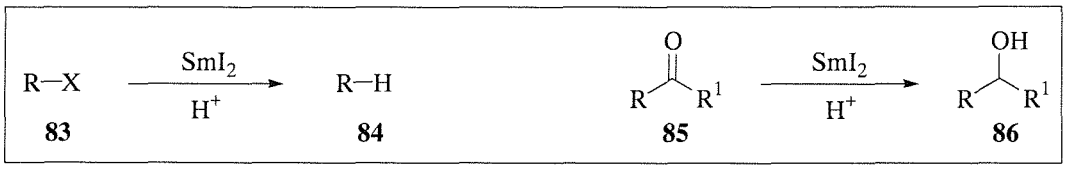
Scheme 5. Preparation of SmI_2.

1.1.5.2 Basic Reactions Using Samarium (II) Iodide

Samarium (II) iodide is a one-electron reductant and hence usually two equivalents must be used. The first equivalent generates the radical and the second is used to reduce the radical (usually after some transformation) to an anion when it is then quenched by abstracting a hydrogen, *e.g.* from ^{t}BuOH. It can be used in chain-reaction processes but the scope is limited[43]. Other types of reaction are more useful and this means that stoichiometric quantities must be used but the potential for sequenced radical/polar crossover reactions is then available[43, 44].

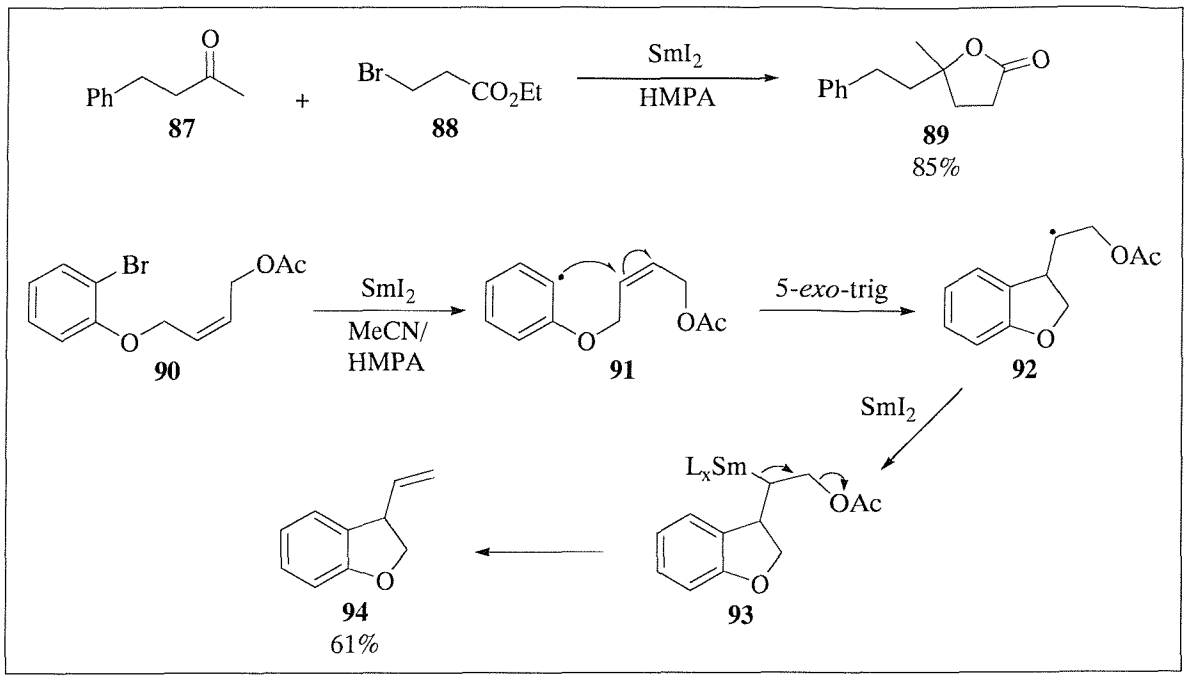
There are three main classes of transformation:

i) Functional group reduction (Scheme 6). A wide range of functional groups can be reduced including sulphoxides and sulphones[46, 47]; epoxides[48]; halides **83** and related leaving groups[38] [39, 49]; conjugated double bonds[38]; and carbonyls **85** [39, 50].



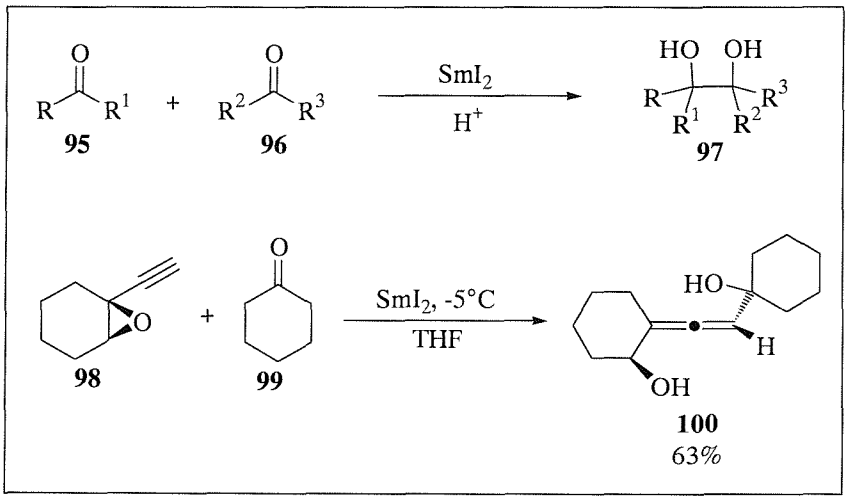
Scheme 6. Functional group reduction with SmI_2.

ii) Reductive coupling of halides with π-bonds (Scheme 7). These reactions have found use as alternatives to Grignard or Barbier-type reactions[39, 43] as with the reaction between **87**and **88**. The cyclisation of **90** is an example of a radical/anion crossover reaction[51]. Following the 5-*exo*-trig cyclisation, a second reduction forms the anion **93** (shown here as a formal bond) that allows elimination of the acetate group forming bicycle **94**.



Scheme 7. Reductive coupling of halides with π-bonds.

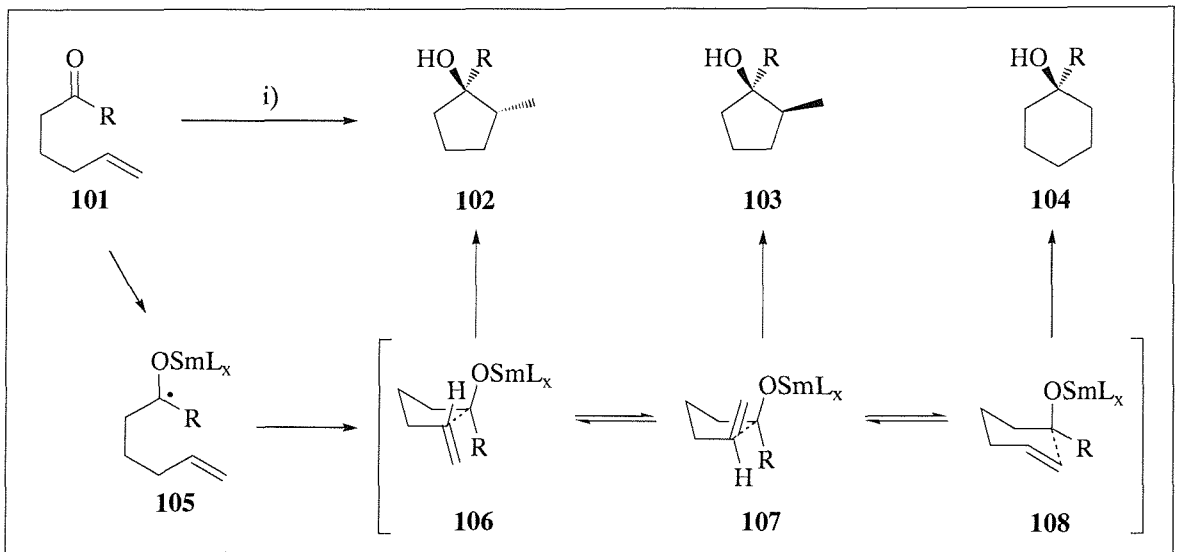
iii) Reductive coupling of two π-bonds (Scheme 8). Pinacol couplings (**95** with **96**) [39, 50] and coupling of carbonyls with conjugated or isolated alkenes and alkynes are possible (**98** with **99**) [39, 52]. In the example below, a ketyl radical is generated from cyclohexanone **99** [53]. This attacks the terminal end of the alkyne **98** resulting in allene **100** formation by opening of the epoxide.



Scheme 8. Reductive coupling of two π-bonds with SmI_2.

1.1.5.3 Stereoselective Influence of Samarium (II) Iodide

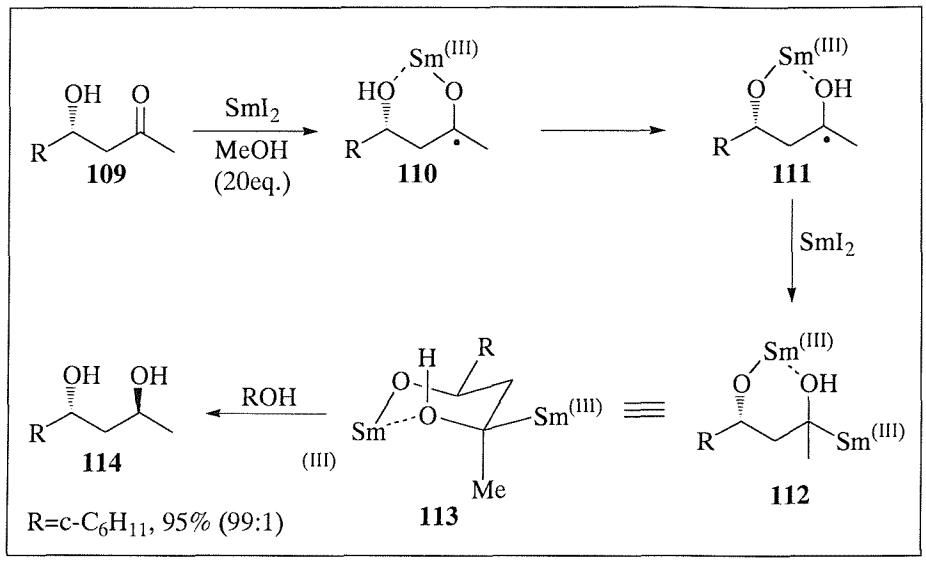
The alkyl radical models proposed by Beckwith[26, 27] (see section 1.1.3.3), place the two large methyl groups *cis* to provide the major product from the cyclisation of 1-methyl hexenyl radicals. Studies by Molander[54] on cyclisations of simple ketyl radical analogues **101** give interesting results (Scheme 9). The alkene was placed preferentially *trans* to the bulky oxygen-samarium moiety, even with R groups as large as tertiary butyl **101c**. Following a chair-like transition state **106**, the alkene eclipses the R group to place the newly-formed methyl group *trans* to the oxygen-samarium. The repulsion of the π system of the alkene and the ketyl oxygen is likely to be electronic but steric factors may also be involved[54]. As the size of the R group increases the steric demand between the alkene and R group is reduced by placing the alkene *cis* to the ketyl oxygen. With isopropyl **101b** and tertiary butyl **101c** a minor 6-*endo*-trig product **104b** and **104c** is observed. This may be due to the relief of steric repulsion overcoming the poor orbital overlap required in the transition state.



Substrate	R	% Yield 102 + 103 (ratio 102 : 103)	% Yield 104
101a	Me	86 (>150:1)	-
101b	^{i}Pr	85 (23:1)	3
101c	^{t}Bu	78 (3:1)	4

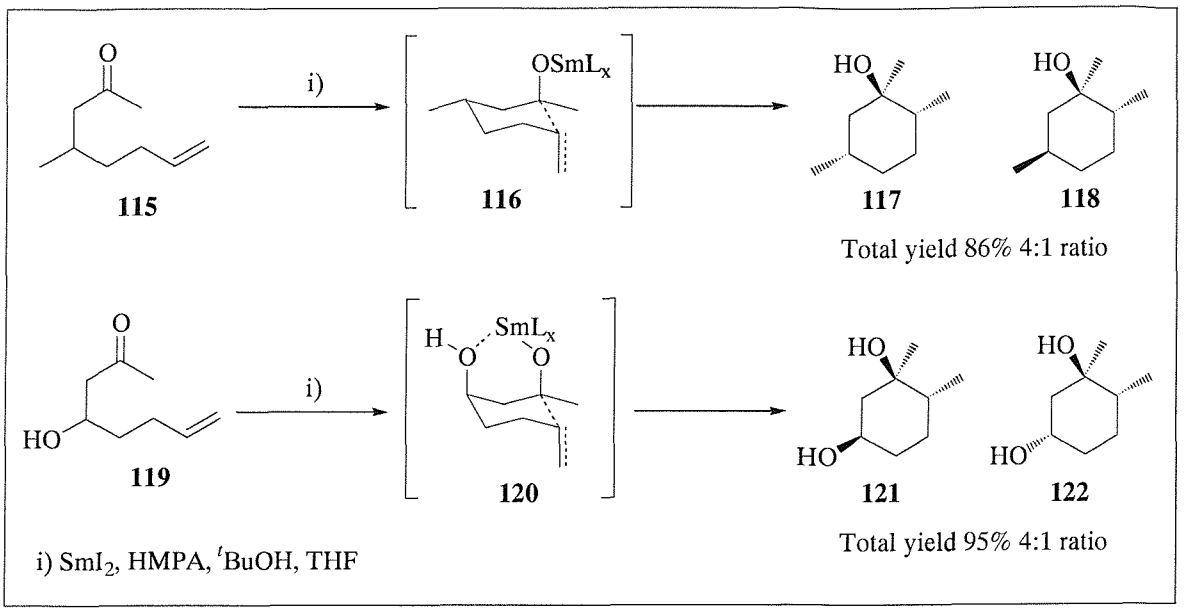
Scheme 9. Transition states showing the preference for the *trans* methyl-alcohol product.

The chelating ability of samarium has proved to be very useful in influencing the diastereoselectivities obtained from radical reactions. Keck[55] has suggested the mechanism below that demonstrates the chelation control in the stereoselective reduction of β-hydroxy ketones such as **109** (Scheme 10). The larger samarium group prefers to be equatorial forcing the methyl group into an axial position **113**.



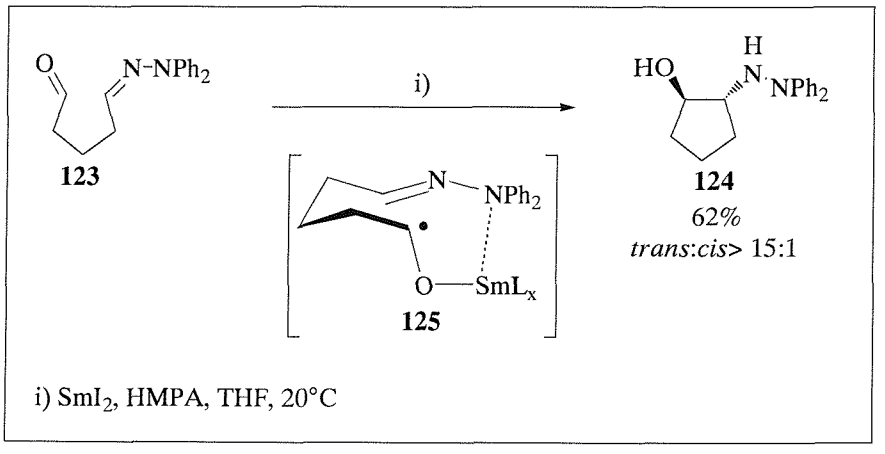
Scheme 10. Stereoselective reduction of β-hydroxy ketones.

The chelation control is also marked in cyclisation reactions. Studies by Molander[54] showed a reversal of diastereoselectivity of cyclisation products when substituting a methyl group with an alcohol (Scheme 11). Molander has suggested the preference for **117** comes from a chair-like transition state **116** placing the methyl substituent in an equatorial position; the minor isomer arises from a boat-like or alternative transition state. Alcohol analogue **119** gives the reverse stereoselectivity to methyl precursor **115**, presumably due to chelation in transition state **120**.



Scheme 11. Reversal of diastereoselectivity due to chelation.

In the cyclisation of carbonyl-hydrazones **123**, Fallis[56, 57] found that *trans* stereochemistry was also observed. This was explained by a nine-membered ring template **125** that placed the large hydrazone in a pseudo-equatorial orientation and ketyl oxygen in an axial position to avoid gauche interactions *en route* to the product **124** (Scheme 12).



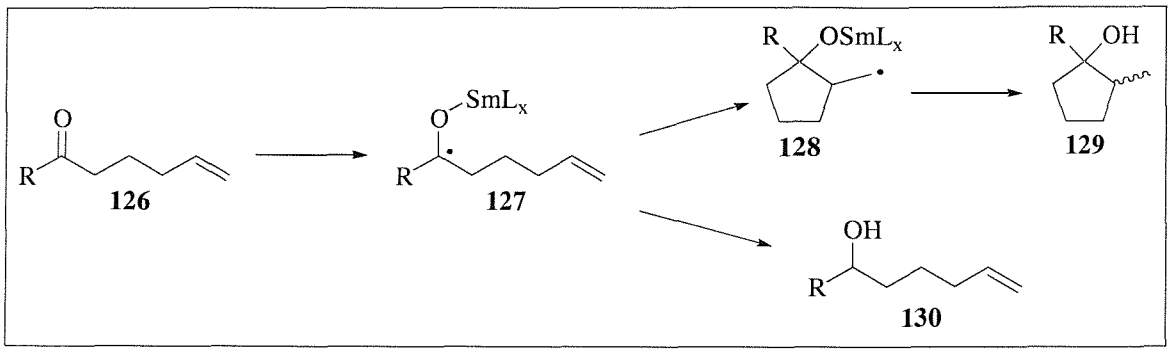
Scheme 12. Nine-membered ring chelation control leading to *trans* stereochemistry.

1.1.5.4 Influence of Additives/Co-solvents

The outcome of SmI_2 reactions can be markedly altered by the addition of additives and co-solvents[43]. Studies by Flowers[45] have revealed that DMPU produces the maximum

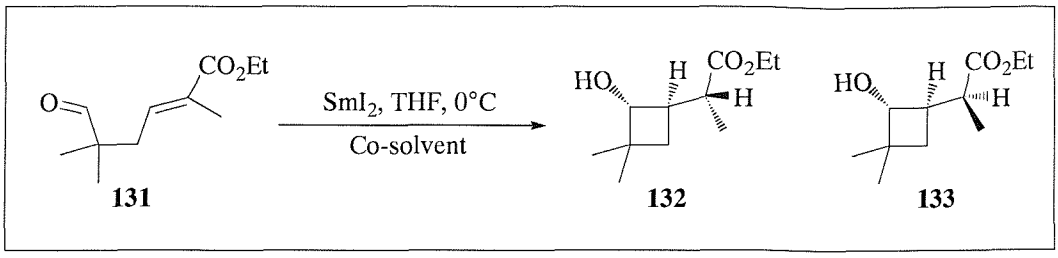
increase in the redox potential for Sm^{3+}/Sm^{2+} in THF. However, the concentration of DMPU required causes precipitation of the complex. HMPA was found to have optimal enhancement with only 4 ligating molecules: increase from -1.33V to -2.05V. This is consistent with studies which show that in solution $Sm(HMPA)_4I_2$ is monomeric and active[58].

Detailed studies by Molander[54, 59-61] revealed reduced reaction times, improved yields and diastereoselectivity when moving from DMPU to HMPA in the ketyl/alkene cyclisation reactions (Scheme 13). The amount of simple reduction product **130** was reduced as more HMPA was used. Molander suggested that THF coordinated to the samarium centre provides a source of hydrogen to be abstracted. HMPA displaces THF molecules and removes a source of hydrogen prolonging the lifetime of the ketyl radical allowing cyclisation to occur in greater yields. The improved diastereoselectivity may be attributed to the bulky nature of the HMPA ligand, thus favouring one transition state over another.



Scheme 13. Cyclisation studies on the effect of HMPA and DMPU.

The toxicity of HMPA has directed research towards alternatives that offer similar improvements to the dynamics of the reactions. The use of methanol by Procter[62] demonstrates its potential (Scheme 14). Good yields and high diastereoselectivity were obtained in the cyclisation of aldehyde **131** when methanol was used in a 1:4 ratio to THF.

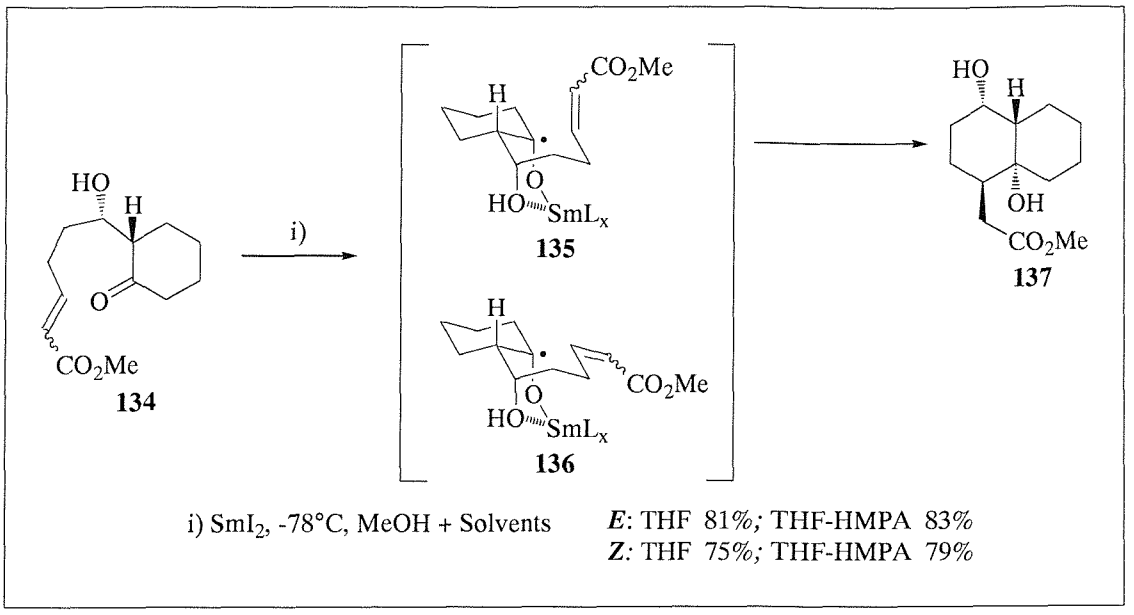


131 **132** **133**

Co-solvent	Time (min.)	132 : 133	Yield %
H_2O	<1	4.5 : 1	44
MeOH	5	4 : 1	66
MeOH/HMPA	<1	4 : 1	35
EtOH	85	1 : 1	84

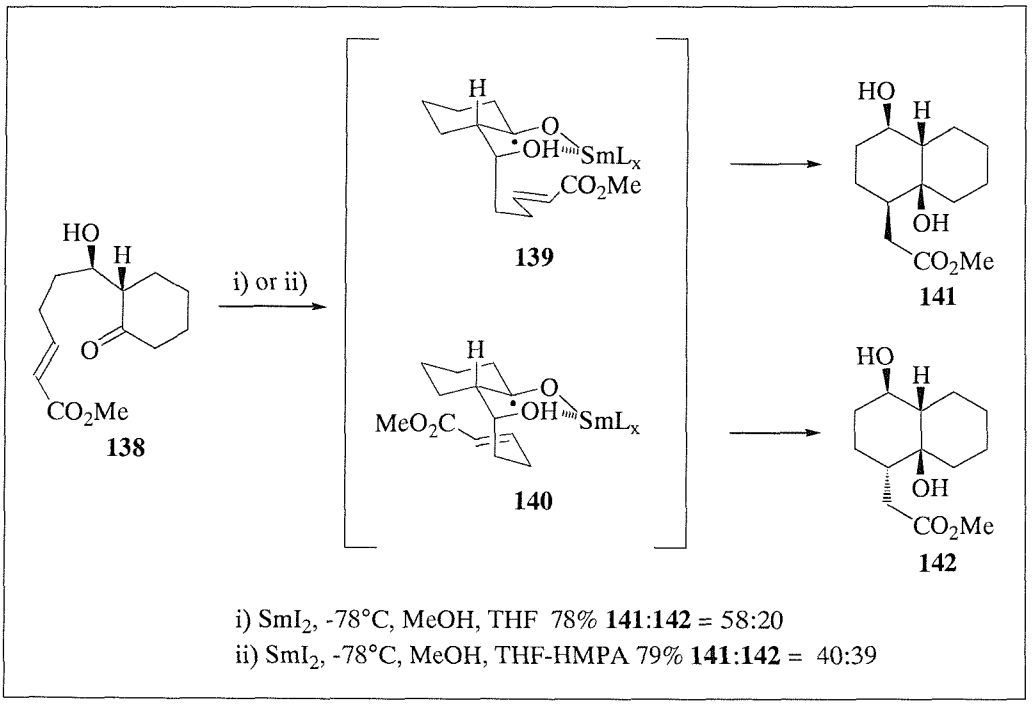
Scheme 14. Alternatives to HMPA as additives.

The formation of *trans* and *cis* decalins using methanol and methanol/HMPA mixtures was investigated by Matsuda[63]. With precursor **134**, the β hydroxyl group chelates to samarium forcing the formation of *trans* decalins *via* potential transition states **135** and **136** (Scheme 15). With both *E* and *Z* precursors the sole product was **137** arising from transition state **135** which places the alkene in an axial position. This *trans* arrangement of the ketyl oxygen and the alkene minimizes electrostatic repulsions. Addition of HMPA increased the yields slightly and would also be expected to destabilize transition state **136** since the developing radical centre is nearly eclipsed with the ketyl oxygen.



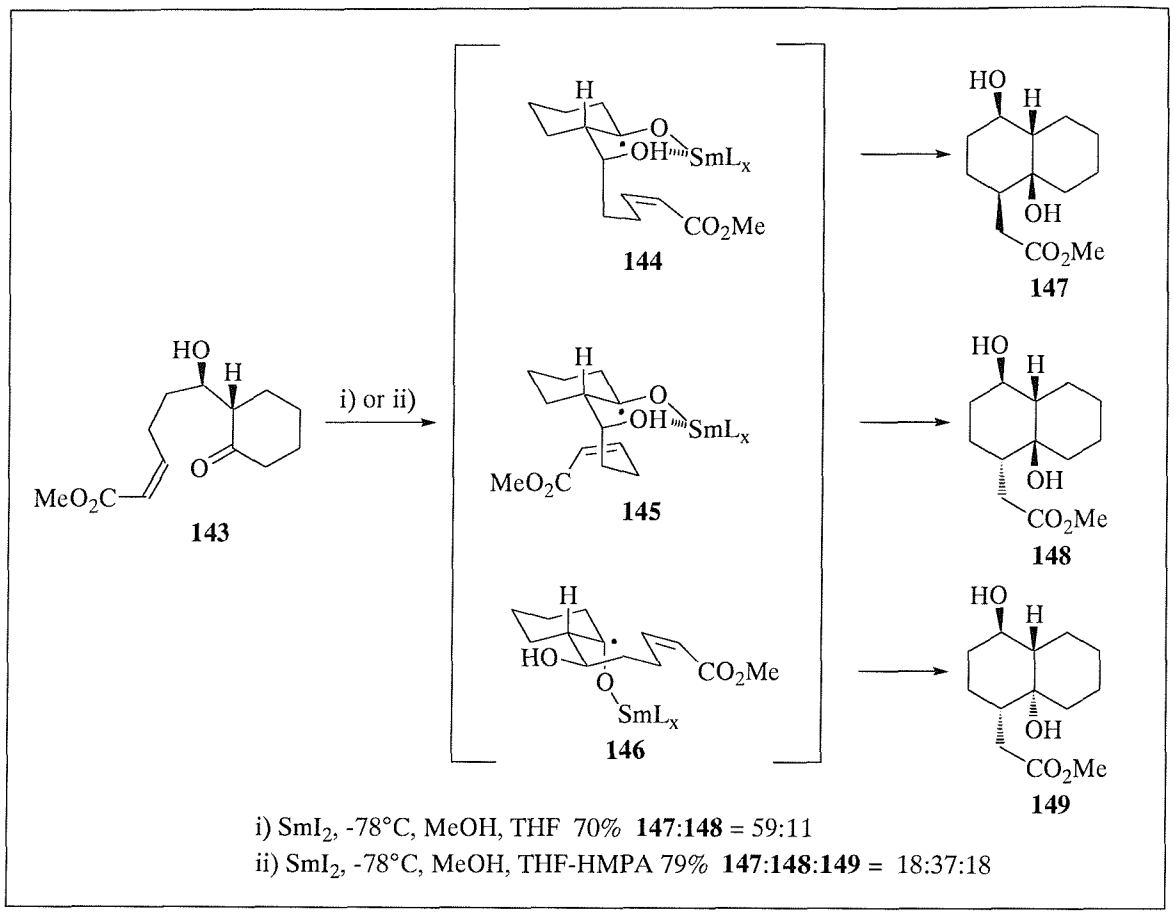
Scheme 15. Formation of *trans* decalins.

E-Precursor **138** was expected to produce *cis* decalins and the result from (i) reflects steric factors (Scheme 16). The non-bonded repulsion between the ester and the cyclohexanone ring in **140** outweighs the electrostatic interaction, hence **141** is more favourable than **142**. Addition of HMPA in (ii) destabilized transition state **139** (*vide supra*) and this is reflected in the changed yields of products.



Scheme 16. Formation of *cis* decalins I.

The analogous *Z*-precursor **143** gave similar results (Scheme 17). Transition state **144** is favoured over **145** in (i), but when HMPA was used in (ii), not only was the effect to destabilize **144** it also allowed the formation of *trans* decalin **149** *via* a non-chelated transition state **146**.

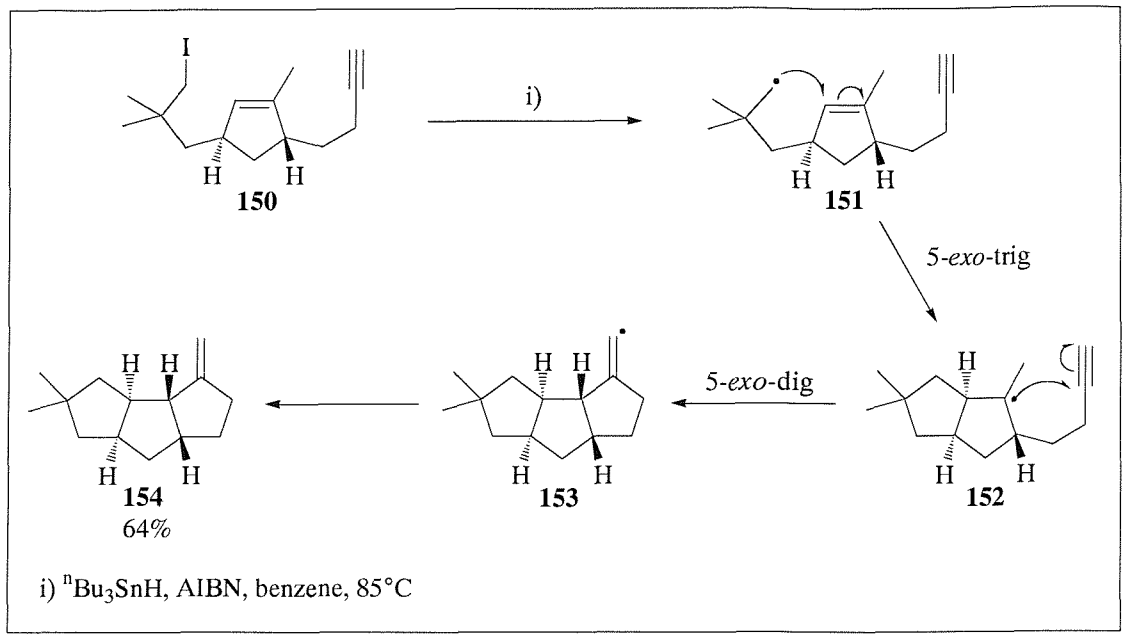


Scheme 17. Formation of *cis* decalins II.

1.1.6 Tandem and Cascade Radical Reactions

Tandem and cascade processes are those that form polycycles in one synthetic operation. Natural products can be directly made using tandem methodology as demonstrated by Curran[64] in the preparation of hirsutene **154** (Scheme 18). In this reaction, iodide **150** is treated with tributyl tin radical to produce primary radical **151**. This radical undergoes a 5-*exo*-trig cyclisation to afford tertiary radical **152** which then performs a 5-*exo*-dig

cyclisation to give vinyl radical **153**. Finally **153** then abstracts a hydrogen from tributyl tin hydride to furnish hirsutene **154** in a 64% yield.

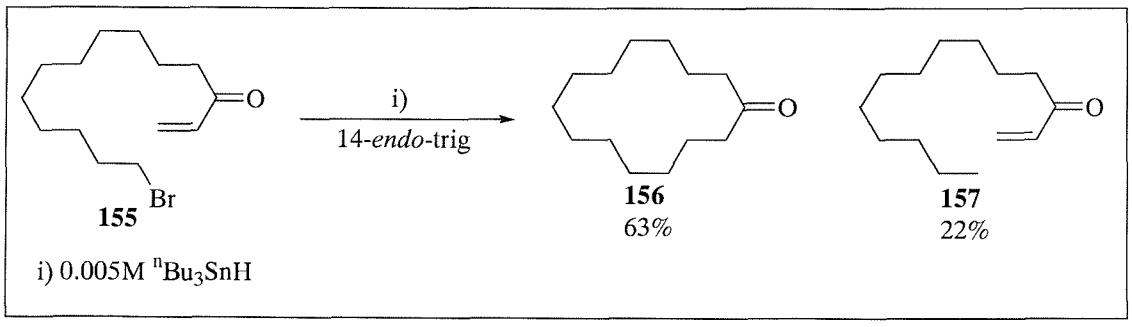


Scheme 18. Tandem cyclisation preparation of hirsutene.

1.1.7 Medium Ring and Macrocycle Formation

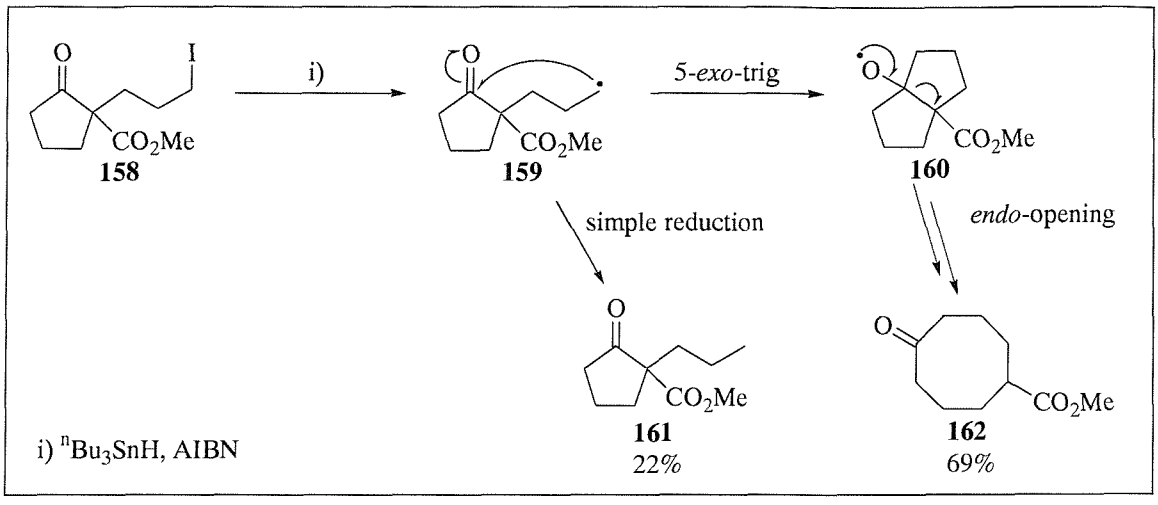
Medium-ring sizes and macrocycles are more difficult to prepare than cyclopentanes and cyclohexanes because the rates of cyclisation are slower. Nevertheless, there are many successful cyclisations and versatile strategies that can be employed[3, 6, 10, 12, 14].

It is best to apply intermolecular considerations when approaching macrocyclisations[6]. A simple yet effective example from Porter[65] shows that good yields can be obtained (Scheme 19).



Scheme 19. 14-*endo*-trig radical macrocyclisation.

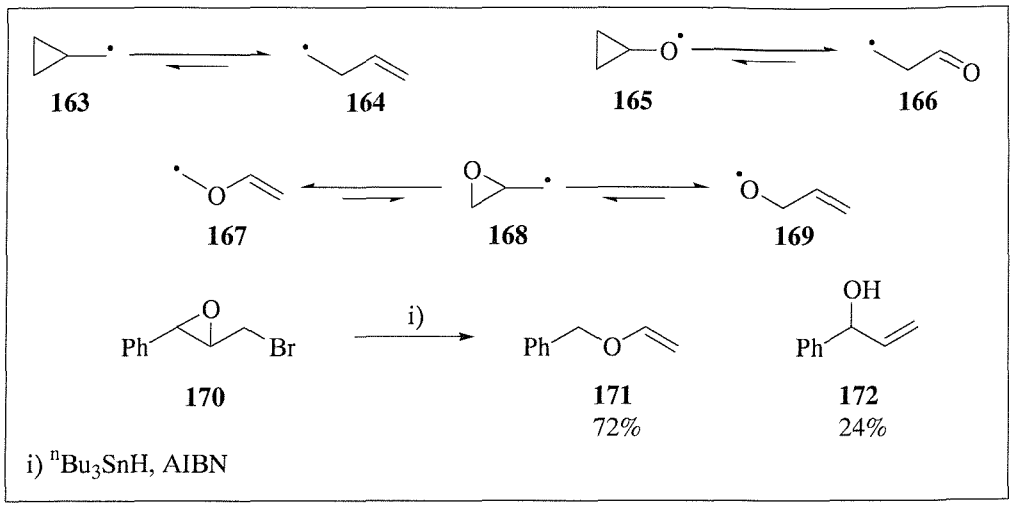
Another approach is to use existing cyclic structures and expand them by cleaving an internal bond. In this example, radical **159** attacks the carbonyl and, due to the favourable process of β-elimination (*vide supra*) and stabilizing effect of the ester, breaks the internal bond to form cyclooctanone **162** as the major product (Scheme 20). This strategy can be applied using different chain lengths to create larger or smaller rings following fragmentation[12, 14].



Scheme 20. Cyclisation followed by ring expansion.

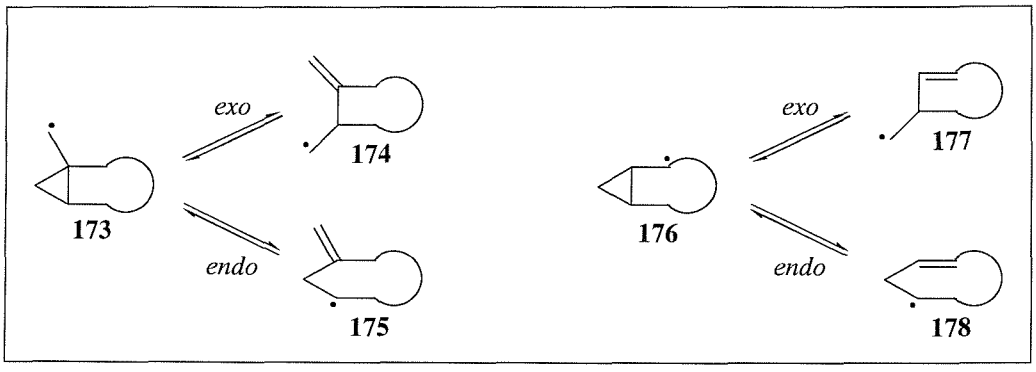
1.1.8 Radicals α to 3-Membered Rings

Radicals that are generated α to 3-membered rings are the key intermediates in many radical strategies[12, 14]. The ring-opening of these radicals is fast and has many useful synthetic applications. In the case of the radical α to an epoxide **168**, the preference is to break the slightly weaker C-O bond (to give **169**) unless there are substituents that stabilize the radical formed by breaking the C-C bond. This is exemplified by the products from the epoxide opening of **170** (Scheme 21)[3, 66, 67].



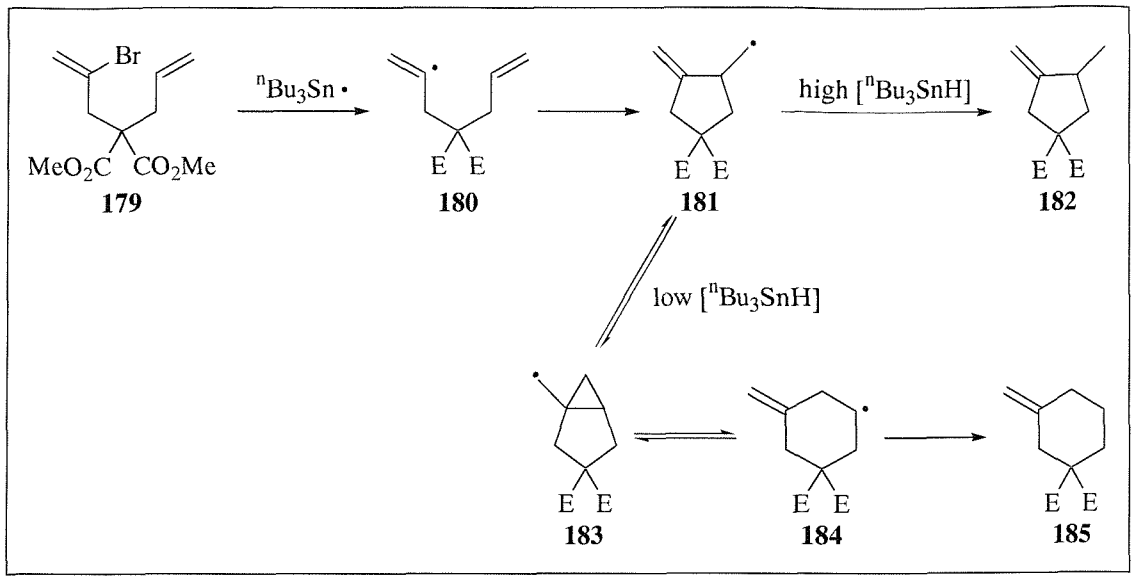
Scheme 21. Ring-opening of 3-membered rings.

When the 3-membered ring is part of a larger cyclic system, the ring-opening can follow either an *exo* or *endo* mode (Scheme 22). There are many factors[12, 68] that affect which mode is followed including stereoelectronics, ring-strain of transition states and the nature of the cyclic products formed.



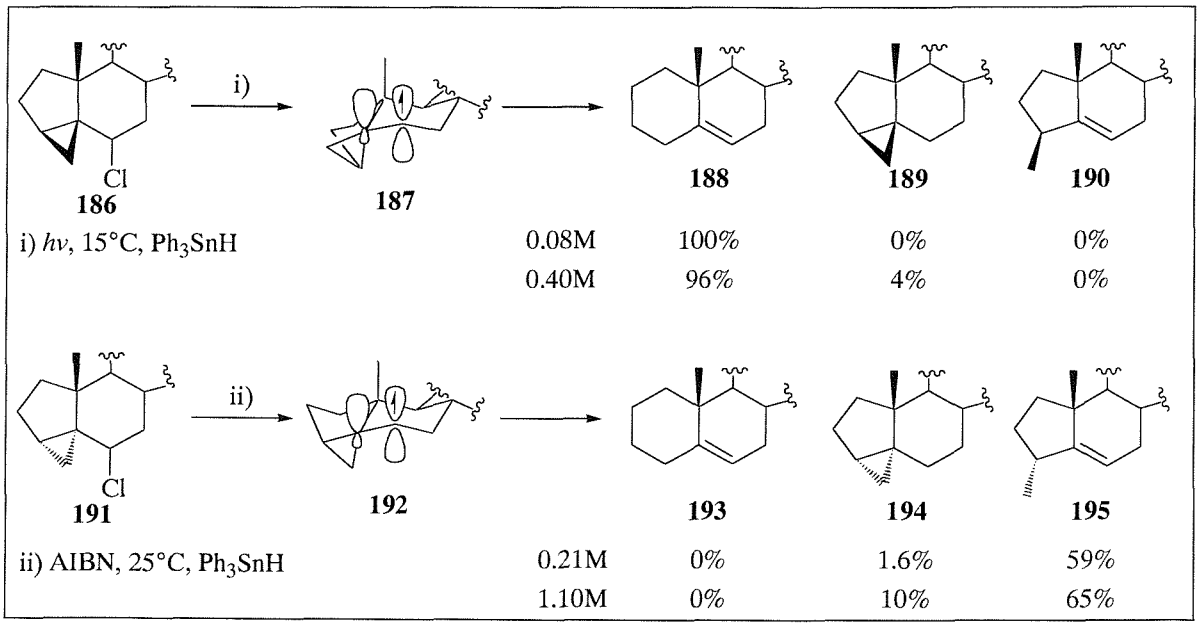
Scheme 22. *Exo* and *endo* modes for ring-opening of 3-membered rings.

This is illustrated well by two examples. Firstly, in the cyclisation reaction of vinyl bromide **179**, altering the concentrations of tributyltin hydride affects the yields of cyclopentyl **182** and cyclohexyl **185** products (Scheme 23)[69]. At high concentrations the primary radical **181** abstracts the hydrogen quickly and there is little time for the 3-*exo*-trig attack onto the alkene. But at low concentrations of tributyltin hydride, the cyclisation to form cyclopropylcarbinyl radical **183** can occur. The primary radical can then open the cyclopropane ring in an *endo* fashion to form secondary radical **184**, leading to methylenecyclohexane **185** on abstraction of hydride.



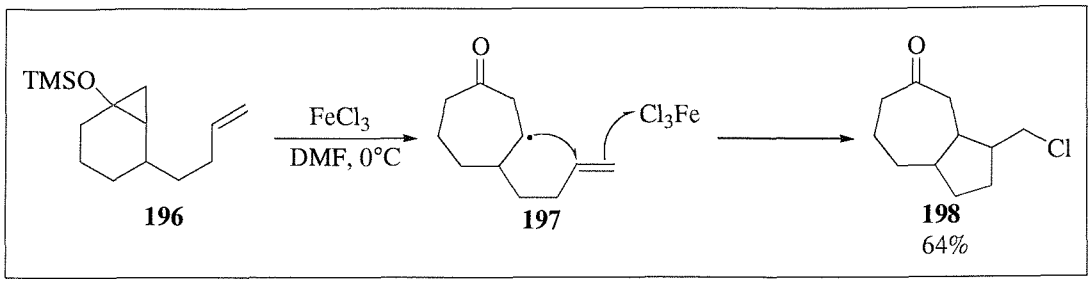
Scheme 23. Effects of concentration on outcome of vinyl radical cyclisation.

Secondly, the opening of cyclopropylcarbinyl radicals **186** and **191** leads to different products[70, 71]. The stereoelectronics of the systems determine the outcome of the ring-opening. In **187** the orbital overlap is achieved with the bond that will break in the *endo* fashion. In the other example **192**, orbital overlap is best with the bond that will break in the *exo* fashion. [12] In each case, the bond that breaks, then, is axially disposed relative to the cyclohexyl radical.



Scheme 24. Two different cyclopropylcarbinyl radical ring-openings.

Medium-sized rings are accessible using this type of methodology, and Booker-Milburn[72] has employed it successfully in the preparation of 7,5 bicyclic product **198** (Scheme 25). An alkoxy radical is generated by treatment with iron (III) chloride. The cyclopropyl ring is opened in an *endo* fashion to give **197** and then a 5-*exo*-trig cyclisation followed by chlorine abstraction gives **198** in a good yield.



Scheme 25. Radical *endo*-opening of cyclopropane ring.

1.2 Methylenecyclopropane

1.2.1 General Properties

Methylenecyclopropane **200** is a highly strained molecule. The extra strain imposed by the exocyclic double bond on the molecule can be shown by comparison of the methylenecyclopropane bond angles and lengths to those of already strained cyclopropane **199** (Figure 13)[73, 74].

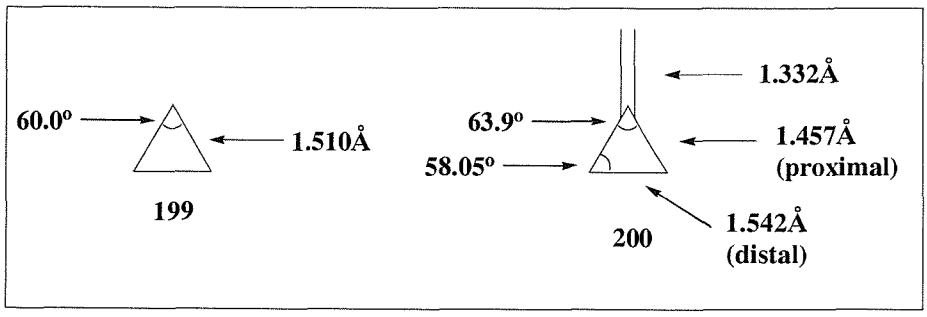


Figure 13. Comparison of cyclopropane to methylenecyclopropane.

The strain energy relieved upon hydrogenation of the double bond also gives a good indication of the reactivity of the molecule (Figure 14)[75].

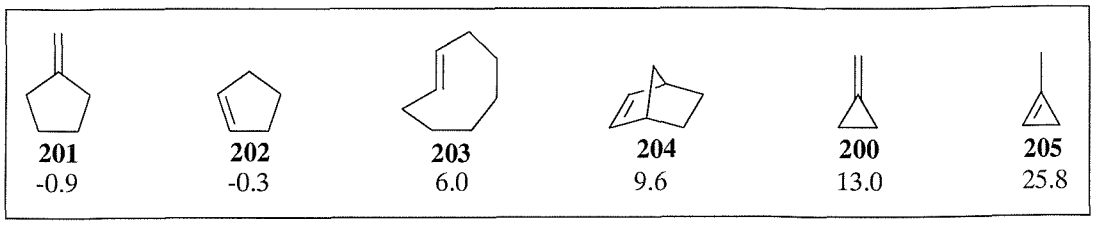


Figure 14. Strain relieved upon hydrogenation of alkenes (kcal mol^{-1}).

Despite its inherent strain, methylenecyclopropane is stable and can be stored in a sealed container (B.p. 11°C) for years without decomposition [76]. A considerable amount of interest has been taken in the synthesis and reactions of methylenecyclopropane and its derivatives because the reactivity of compounds of its type is difficult to attain without compromising stability of the molecule[76, 77].

1.2.2 Biology

Methylenecyclopropane derivatives do occur naturally. Hypoglycin A[78, 79] **206** has been isolated from the unripe fruit of the ackee tree *Blighia sapida*, and methylenecyclopropylglycine[80] **207** is found in the kernels of litchi fruits. The isomers of methylenecyclopropane derivative synadenol[81] **208** have shown some promise as an anti-viral drug due to their activity against viruses such as hepatitis B, Epstein-Barr and HIV(Figure 15).

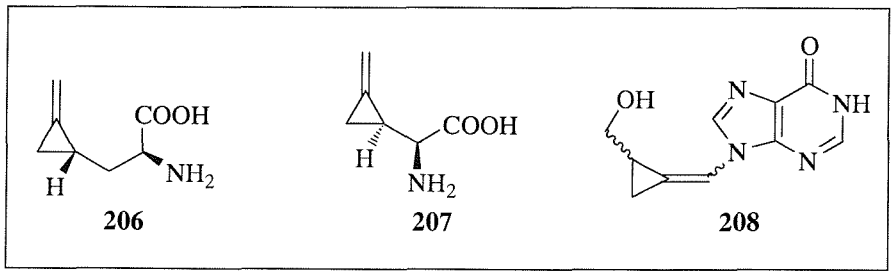
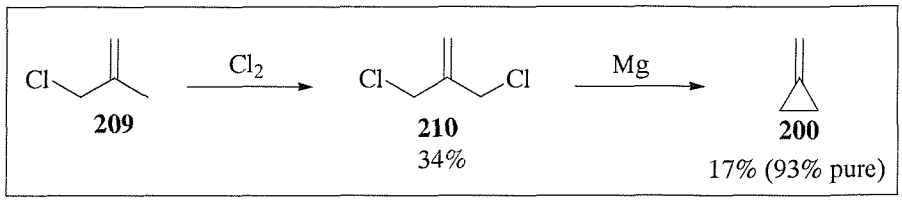


Figure 15. Naturally occurring methylenecyclopropanes and potential anti-HIV drug synadenol.

1.2.3 Chemistry

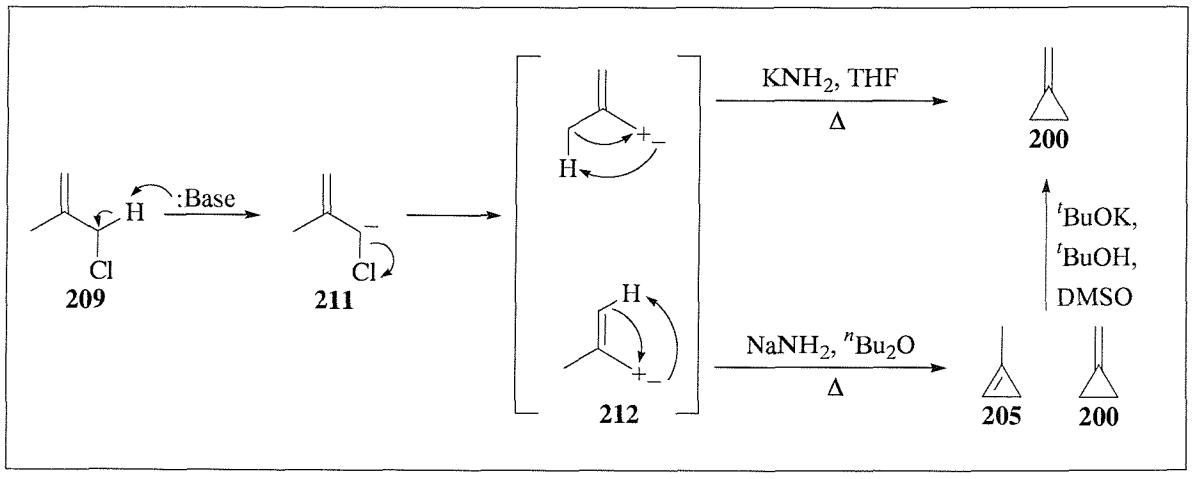
1.2.3.1 Preparation

There now exist numerous ways to prepare methylenecyclopropane and its derivatives and an excellent review by Brandi and Goti[76] outlines the various approaches taken. The first synthesis of the parent compound was reported by Gragson[82] in 1953. The synthesis involved preparation of 3-chloro-(2-chloromethyl)-1-propene **210** from 2-methyallyl chloride **209**. The dichloride **210** was then treated with magnesium metal to afford methylenecyclopropane **200** in a 17% yield (Scheme 26).



Scheme 26. Early synthesis of methylenecyclopropane.

A higher yielding synthesis of methylenecyclopropane was introduced by Binger[83] and used a carbene insertion reaction with 2-methyallyl chloride **209** (Scheme 27).

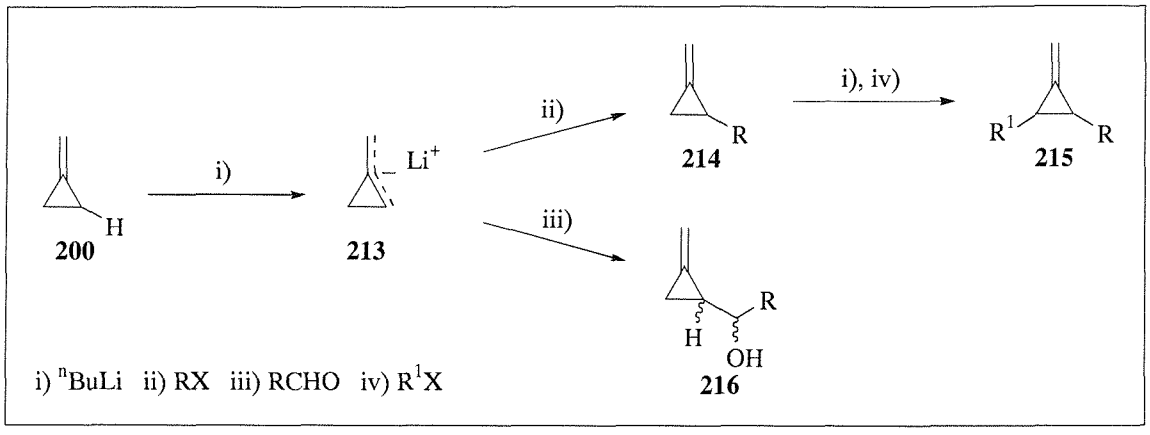


Scheme 27. Binger's synthesis of methylenecyclopropane.

A base is used to deprotonate 2-methylallyl chloride **209**. The chloride is then ejected to form carbene **212**. This carbene can insert into either CH bond; the choice is affected by the base and solvent. When potassium amide is used in THF, a 96% yield of methylenecyclopropane is isolated. However, when sodium amide is used in dibutylether,

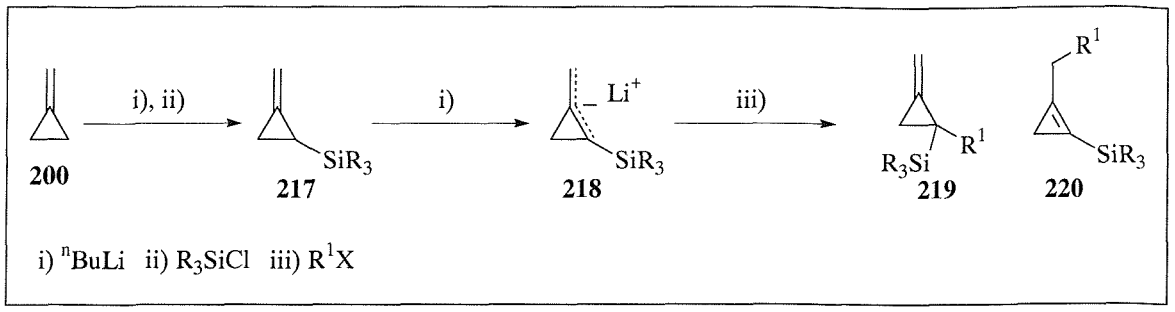
a mixture of methylenecyclopropane **200** and methylcyclopropene **205** is isolated in 99% yield. The methylcyclopropene **205** is formed by carbene insertion into the vinyl CH bond. The ratio of products varies but the cause is not known. Fortunately methylcyclopropene **205** can be easily isomerised to methylenecyclopropane **200** using potassium ^{t}butoxide in ^{t}butanol and DMSO. Recently, Binger[84] has reported modifications to the original procedure that avoid metal-amide base solubility and off-gas problems.

Introducing functionalisation on the cyclopropane ring is possible.[85, 86] Treatment of methylenecyclopropane **200** with ^{n}BuLi affords the allylic anion **213**. Anion **213** can then be quenched with a suitable electrophile to give **214** or **216**. This process can be repeated and 1,2 di-substituted products **215** can be prepared (Scheme 28).



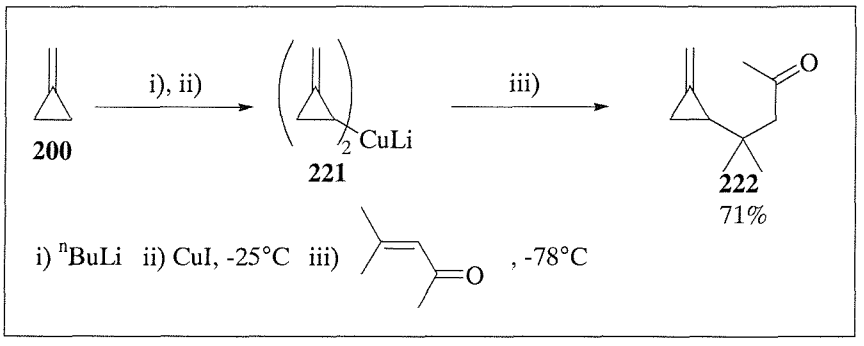
Scheme 28. Functionalisation of methylenecyclopropane I.

If anion **213** is quenched with trimethylsilylchloride, subsequent deprotonation takes place at the original site of substitution (**218**) leading to 1,1 disubstituted products **219**[86]. This is due to the stabilizing effect of the silicon. However, reaction of the second anion with a carbonyl or use of a larger silicon group can give rise to products **220** from the reaction through the double bond (Scheme 29).



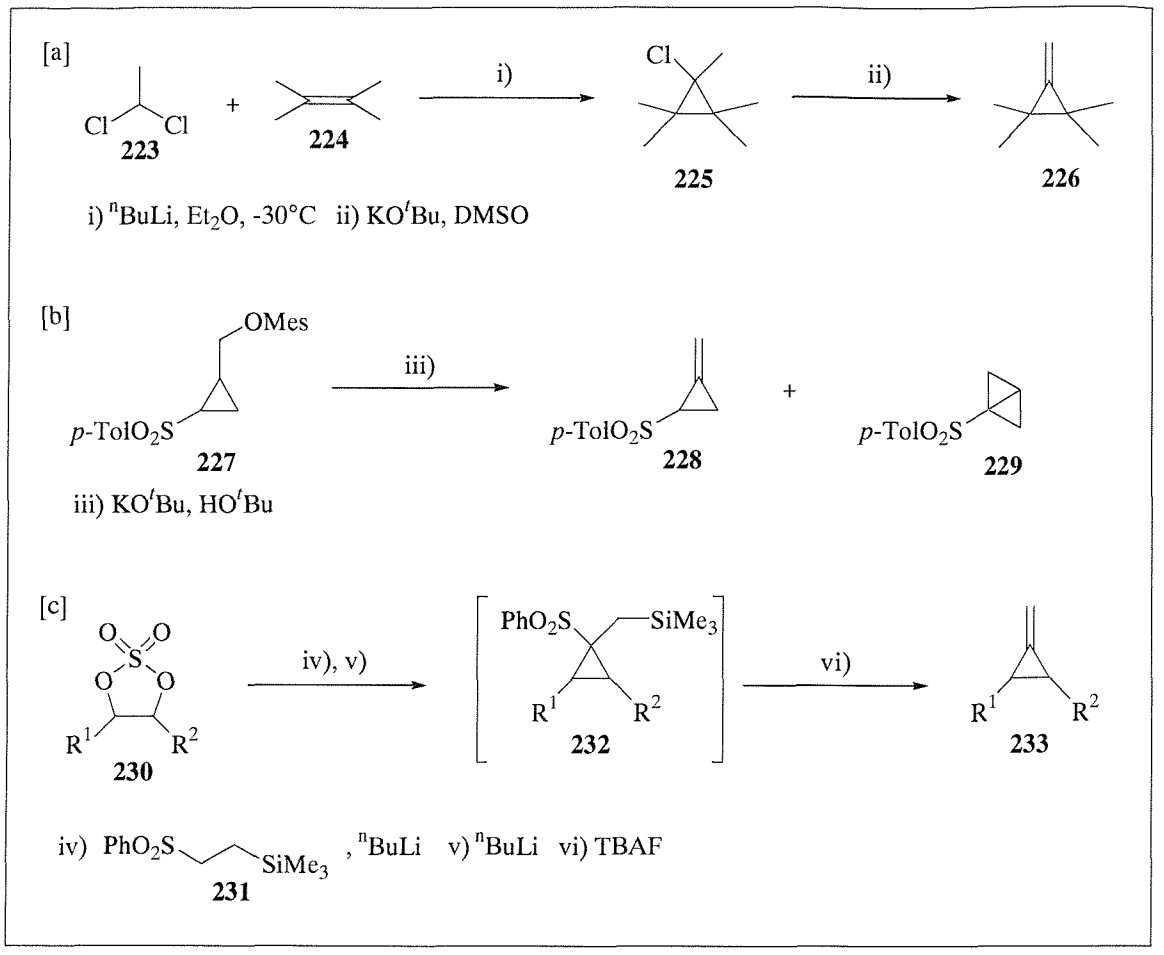
Scheme 29. Functionalisation of methylenecyclopropane II.

The cuprate **221** from methylenecyclopropyl lithium also can be prepared and used in normal cuprate reactions (Scheme 30)[87].



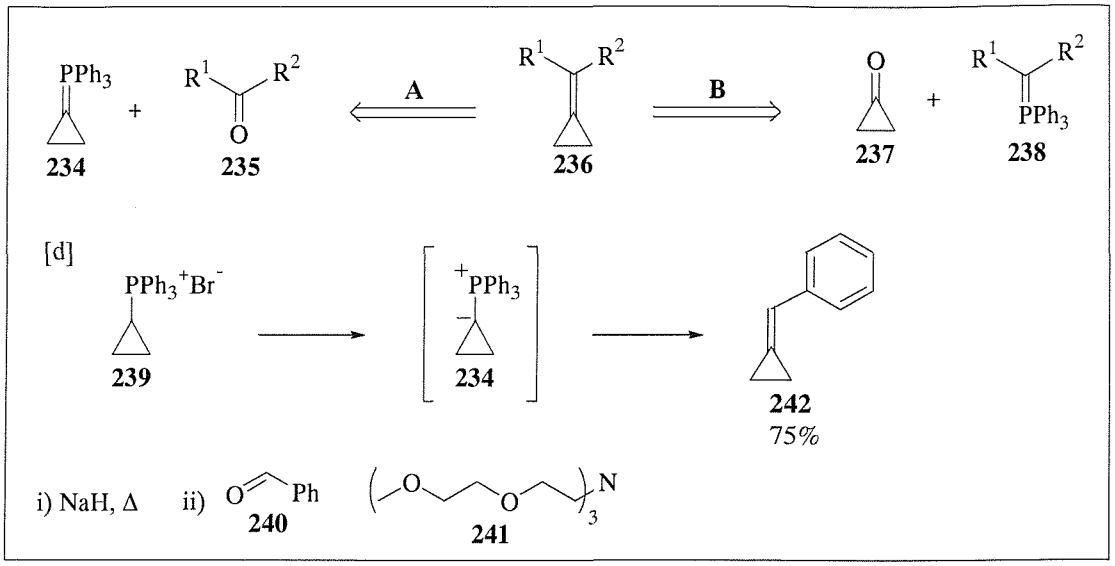
Scheme 30. Methylenecyclopropyl cuprate reactions.

An indication of the variety of other methods for preparation of methylenecyclopropanes is given below. The first is elimination of groups from preformed cyclopropanes (Scheme 31). The position of the leaving group can vary and there is scope in the reacting groups possible. In [a][88], a carbene is formed by treatment of 1,1 dichloroethane **223** with a strong base. The carbene reacts with an alkene **224** and final elimination of HCl from **225** affords the multi-substituted methylenecyclopropane **226**. In [b][89], 1,2 elimination of the mesylate to give **228** is preferential to 1,3 elimination giving **229**, which is a much more strained product. In [c][90], the intermediate **232** is formed by a double-nucleophilic displacement of a sulphate group with compound **231**. Attack of the silyl group with fluoride effects an elimination to give **233**.



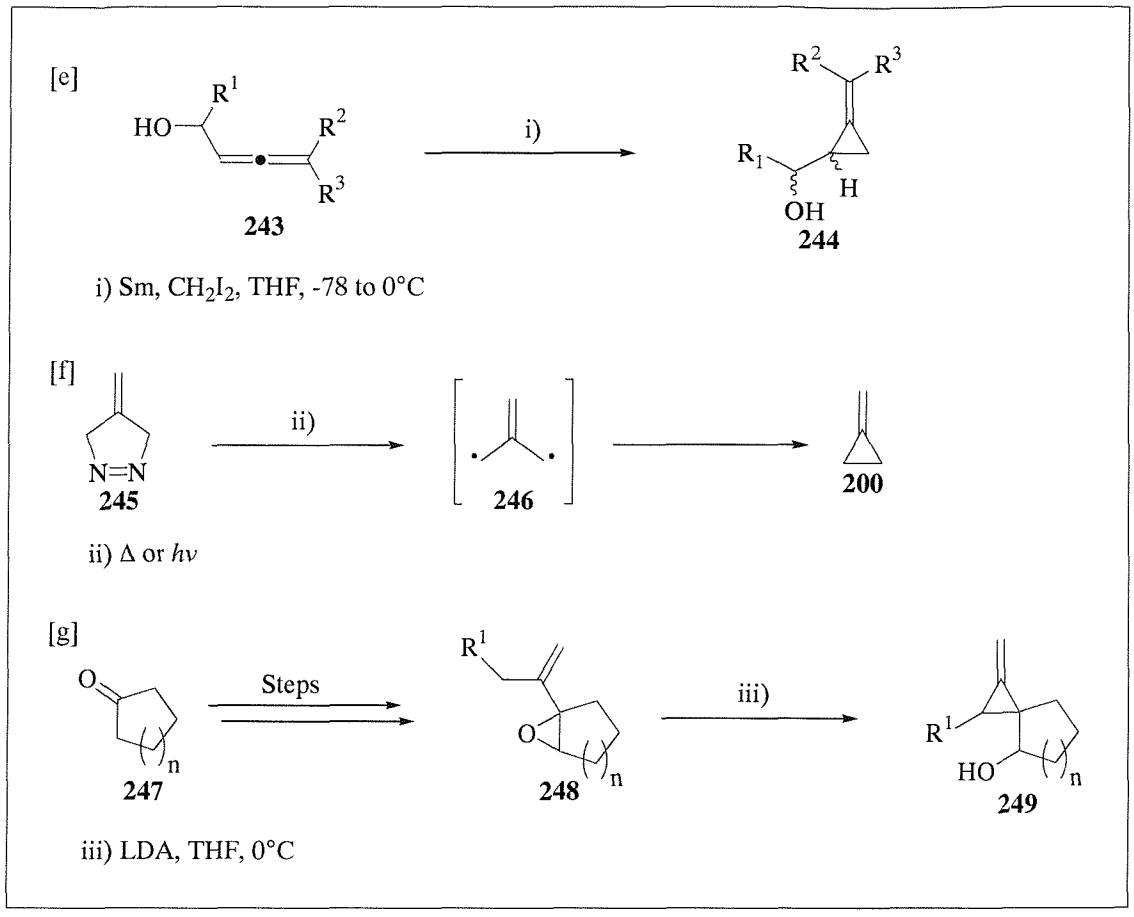
Scheme 31. Preparation of methylenecyclopropanes from pre-formed cyclopropanes.

Wittig-type reactions are also possible, and retrosynthetic analysis provides two possible routes (Scheme 32). The most widely used has been route **A** employing the cyclopropylidene phosphorane intermediate **234**. This is largely because of the unavailability of cyclopropanones **237** and the unreactive nature of its synthetic equivalents (*e.g.* hemi-acetals). There are many examples of the generation and use of the phosphorane **234**, but a simple reaction, [d], uses commercially available triphenylphosphonium bromide **239** and sodium hydride, coupling with benzaldehyde **240** [91]. The complete formation of phosphorane **234** takes a little time and the Wittig-reaction may take some time depending on the nature of the carbonyl species. TDA-1 **241** is used to help solvate counter-ions, thereby increasing reactivity and decreasing reactions times.



Scheme 32. Wittig-type preparations of methylenecyclopropanes.

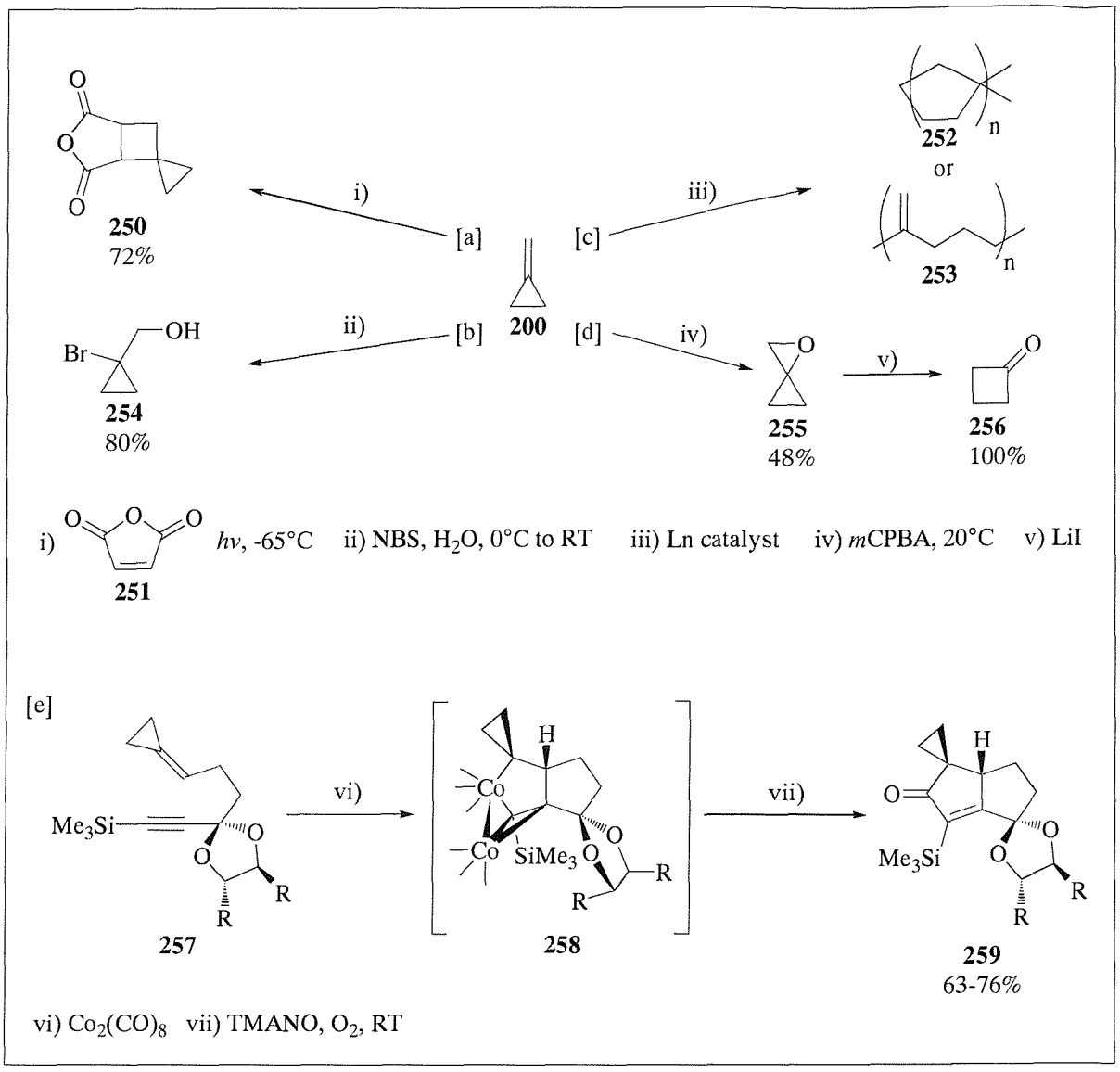
The final general method is formation of the cyclopropane with the alkene moiety in place (Scheme 33). In [e], the cyclopropanation of an α-allenic alcohol **243** can be performed with high regio- and stereo-selectivities[92, 93]. In [f], elimination of nitrogen gas from pyrazolines **245** can be achieved by irradiation[94, 95] or thermolysis[96]. The reaction proceeds *via* di-radical intermediate **246** and this can lead to isomeric products when substitution patterns allow.[76] In [g], spiro-methylenecyclopropanes **249** are prepared with various ring sizes (n = 1, 2, 3, 7).[97, 98] Precursor **248** is prepared from the relevant ketone **247**. The epoxide **248** is then treated with LDA to cyclise to give spiro-methylenecyclopropane **249**.



Scheme 33. Preparation of methylenecyclopropanes forming the cyclopropane.

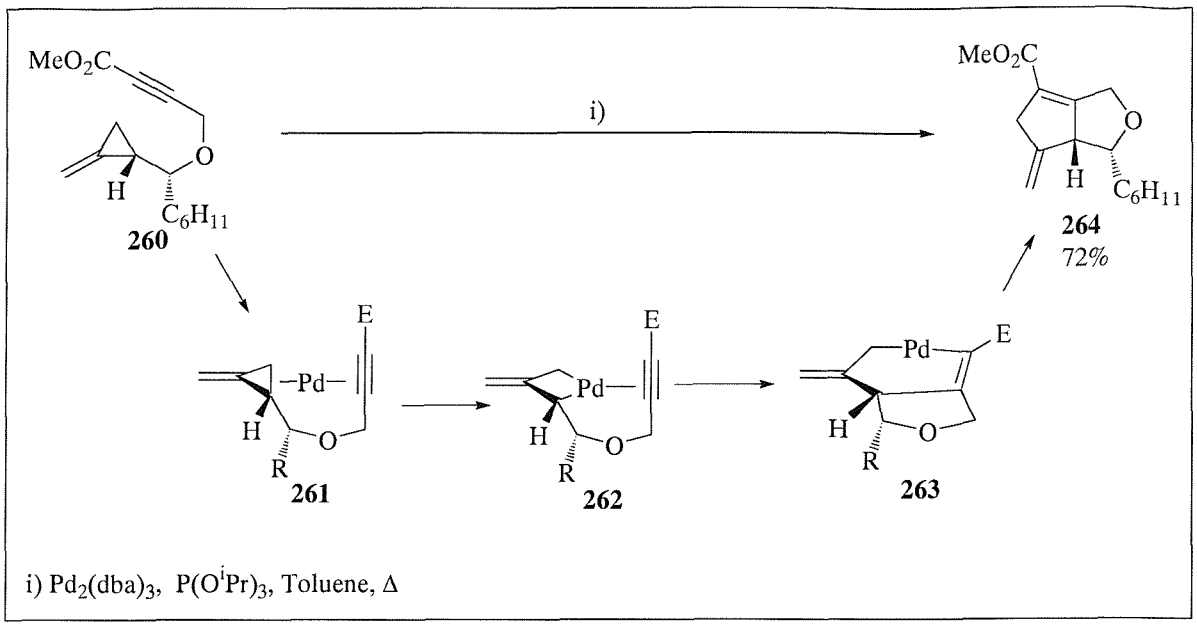
1.2.3.2 Reactions of Methylenecyclopropanes

Studies on the reactivity of methylenecyclopropane began when it could be reliably synthesized[82, 99]. Nowadays, reactions are known involving the double-bond and cyclopropane unit including ring-opening of both proximal and distal bonds of the cyclopropane and complexation.[77] Representative reactions with the double bond are [a] [2+2] cycloaddition[100]; [b] Markownikov addition[101]; [c] polymerization[102]; [d] epoxidation[103, 104]; [e] Pauson-Khand[105].



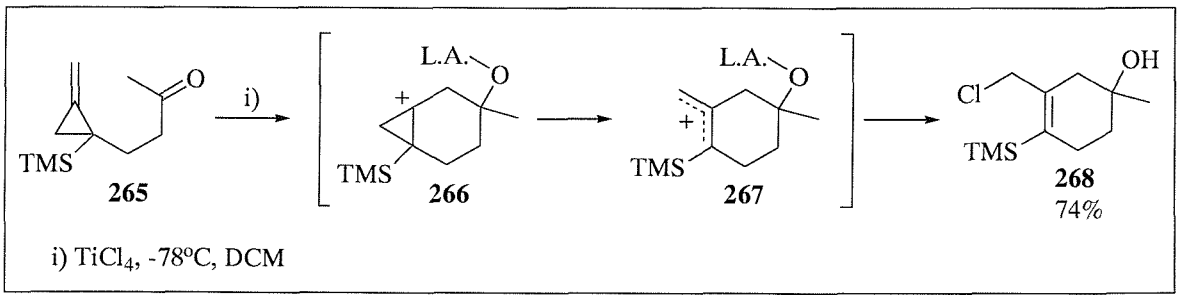
Scheme 34. Reactions using the alkene of methylenecyclopropane.

High yielding 5,5 bicyclic product **264**, from the palladium catalysed [3+2] cycloaddition, shows the potential for ring-opening of the cyclopropane by insertion into the distal bond (Scheme 35)[106].



Scheme 35. [3+2] Cycloaddition with methylenecyclopropane.

Finally, Lewis-acids can be used to effect the ring-opening of the cyclopropane ring. The TMS-substituted methylenecyclopropane group of ketone **265** acts like an allyl silane when **265** is treated with $TiCl_4$. The alkene attacks the activated carbonyl to form a cyclopropyl cation intermediate **266** stabilized by the silyl group. The ring then opens to form allyl cation **267**, which is then quenched with a chloride to form cyclohexene **268** (Scheme 36).

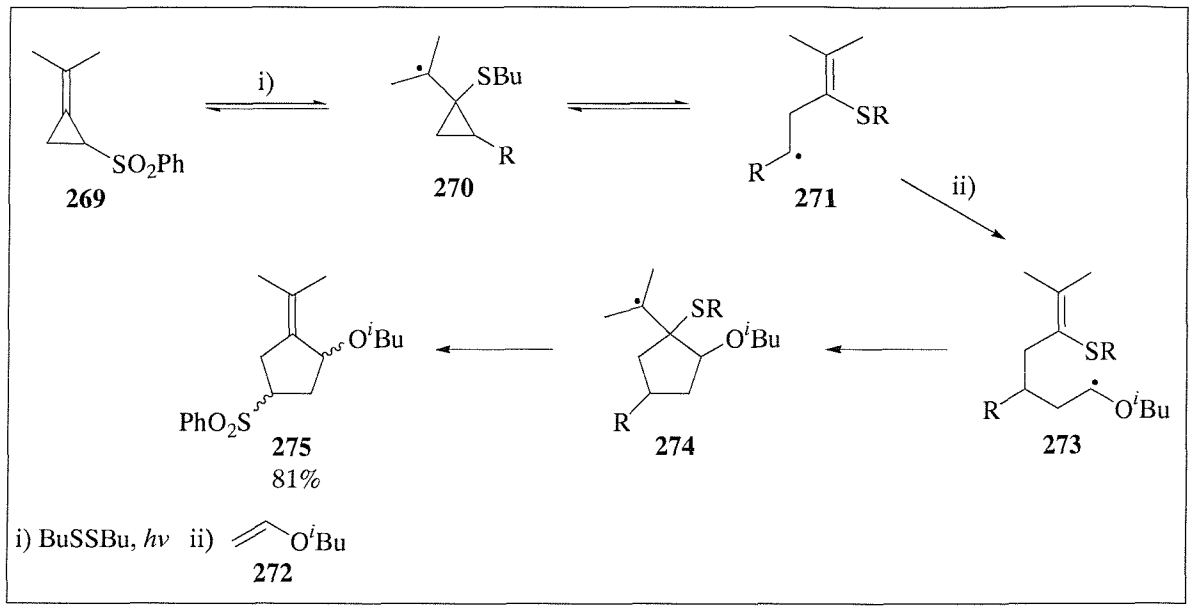


Scheme 36. Lewis-acid cyclisation of methylenecyclopropane derivative.

1.2.3.3 Radical Reactions of Methylenecyclopropane Derivatives

The structure of methylenecyclopropane makes it very useful for radical reactions. The strained double bond is activated towards radical attack and, depending on the regio-selectivity, cyclopropyl carbinyl radical intermediates may be formed. In the work of

Singleton[107], intermolecular reactions involved additions of a thiyl radical to the double bond of **269**. This led to the ring-opening of the cyclopropane unit to give **271**, followed by attack onto a suitable alkene **272**. The ring then re-closed forming a cyclopentyl carbinyl radical **274** that ejected the thiyl radical to give alkylidenecyclopentane **275** in high yield (Scheme 37).

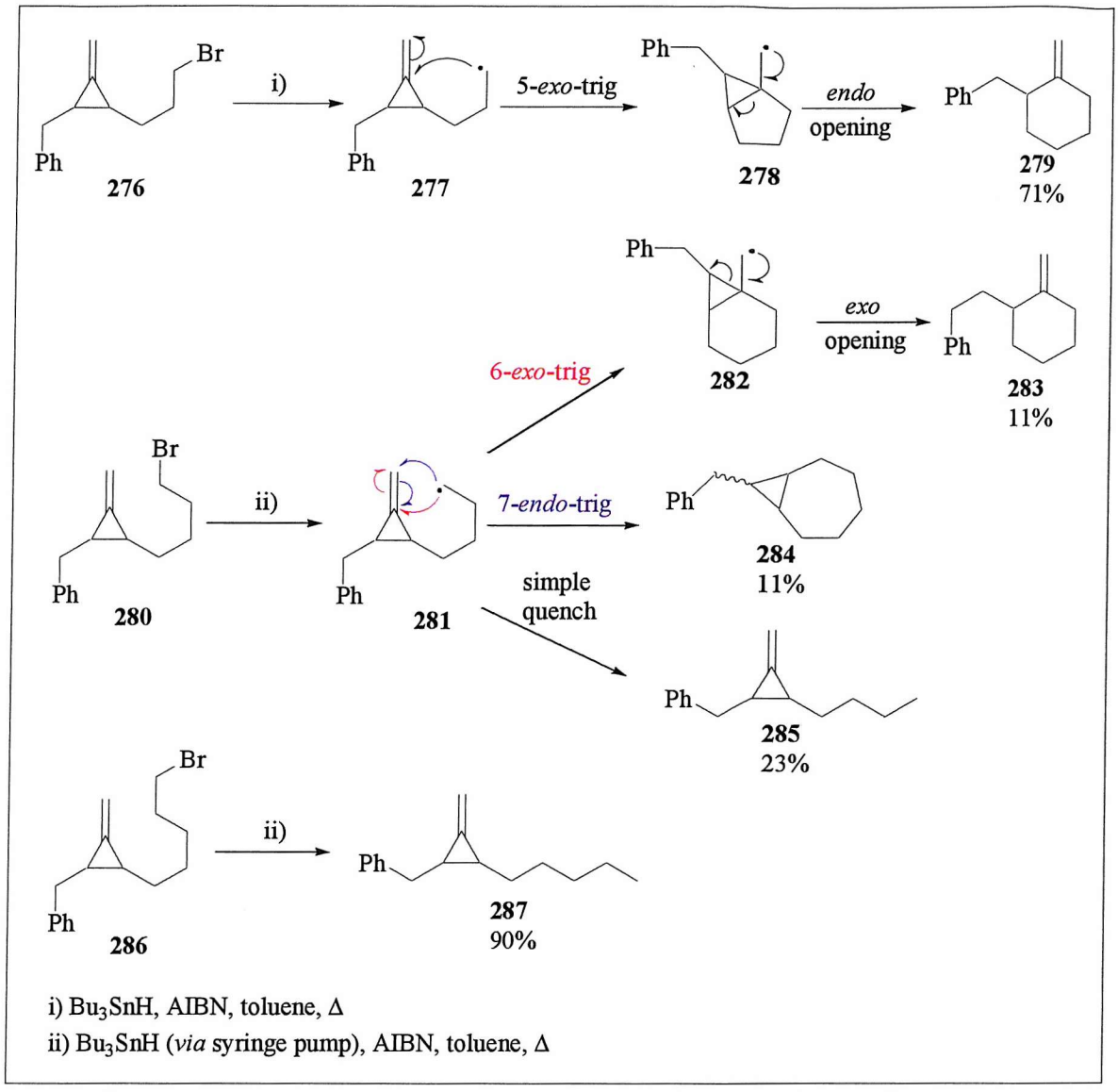


Scheme 37. Intermolecular radical reactions with methylenecyclopropane.

Work in the Kilburn[108-119] group has explored intramolecular radical cyclisations with methylenecyclopropane derivatives.

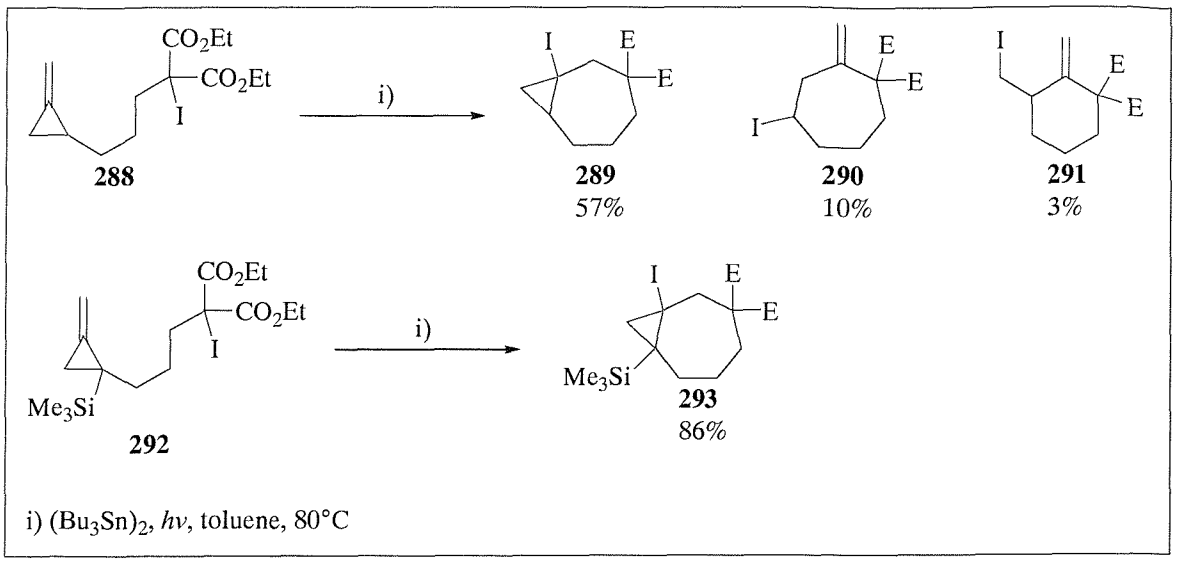
Early work by Destabel[112] showed that intramolecular radical additions were possible and a range of products were isolated. Cyclisation of bromide **276** began with a 5-*exo*-trig cyclisation followed by *endo* ring-opening to give methylenecyclohexane **279** as the sole product in high yield (Scheme 38).

Extending the chain by one CH_2 unit completely altered the reaction profile. The simple reduction product **285** was obtained in highest yield but also two cyclised products: **283** arising from the 6-*exo*-trig cyclisation followed by *exo* ring-opening; and 7-*endo*-trig product **284**. The cyclisation rates were clearly slower for the longer chain bromide **286**. Increasing the chain length by another CH_2 unit to attempt 7-*exo*- or 8-*endo*-trig attack on the methylenecyclopropane gave only simple reduction product **287**.



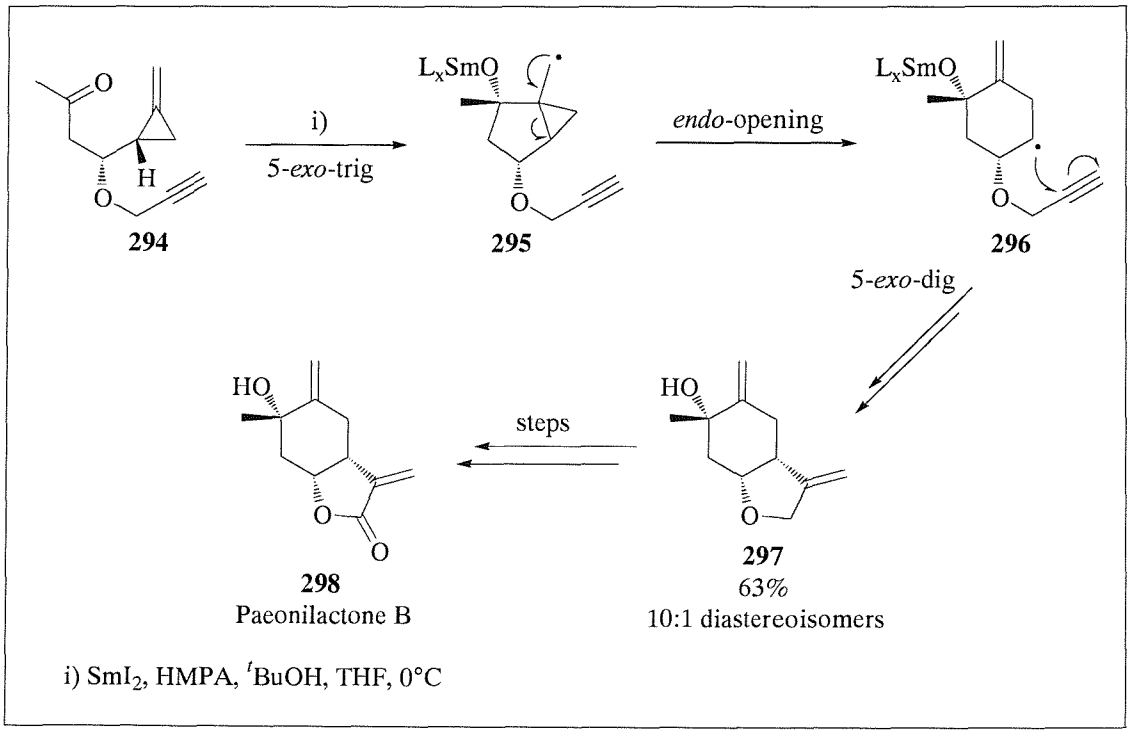
Scheme 37. Intramolecular radical cyclisations with methylenecyclopropanes.

Further investigation with malonate radical cyclisations[113] gave improved yields of cyclised products. Irradiation of iodide **288** with hexabutylditin gave 7-*endo*-trig product **289** in good yield with small amounts of 6-*exo*-trig products **290** and **291**. Interestingly, the *endo* ring-opening product **290** was favoured over the *exo*-opened product **291** (Scheme 38).



Scheme 39. Intramolecular malonate radical cyclisations with methylenecyclopropanes.

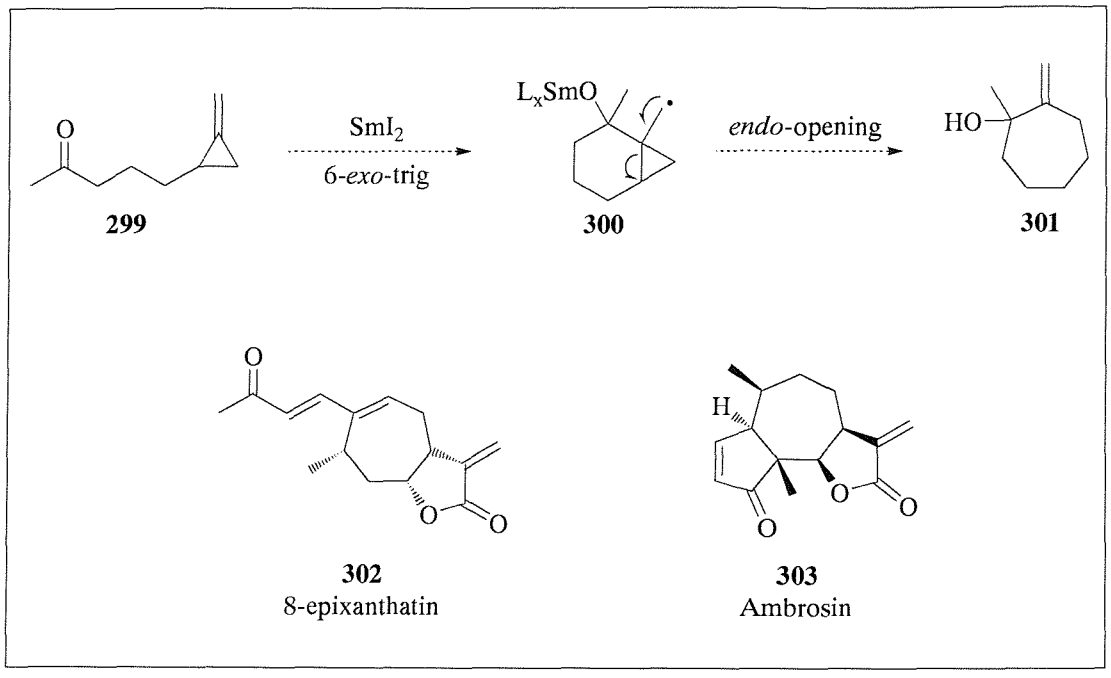
Use of samarium iodide was explored by Boffey[108-110] and this resulted in the synthesis of Paeonilactone B **298**. Ketone **294** was treated with samarium iodide with HMPA/^{t}BuOH as co-solvent. This resulted in a 5-*exo*-trig cyclisation followed by *endo*-opening to give **296**. A 5-*exo*-dig cyclisation followed affording **297** in good yield and high diastereoselectivity. By further manipulation Paeonilactone B **298** was prepared (Scheme 40).



Scheme 40. Preparation of Paeonilactone B from a methylenecyclopropane derivative.

1.3 Scheme of Work

The aim of the project was to explore further the synthesis of cycloheptanes **301** from methylenecyclopropane derivatives such as **299**. The radical initiator focused on was samarium iodide as this had offered high diastereoselectivity in previous work (*vide supra*). Investigation of substituent effects and cascade potential was also to be investigated with a view towards natural product skeletons. A wide range of natural products have a cycloheptane unit incorporated into their skeleton, such as xanthanolides (*e.g.* **302**[120, 121]) and pseudoguaianolides (*e.g.* Ambrosin **303**[122, 123]) (Scheme 41).



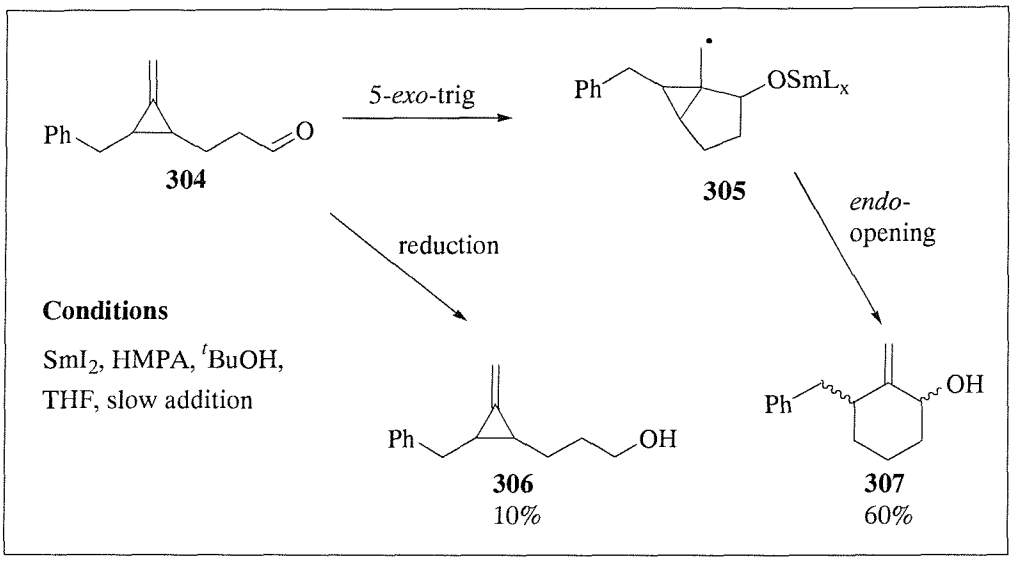
Scheme 41. Key cyclisation and potential natural product targets.

Chapter Two

2 Simple Precursors

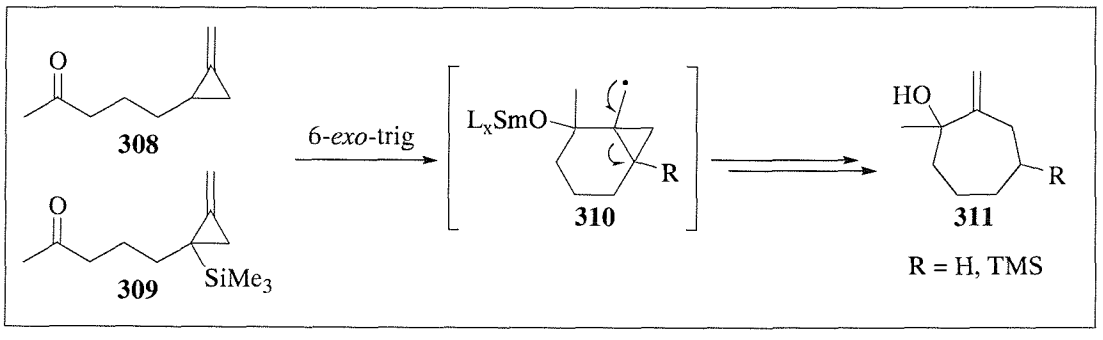
2.1 Aims

The aim of the project was to synthesize cycloheptanes using methylenecyclopropane derivatives. Cyclisation reactions of carbonyls such as **304** mediated by samarium iodide had shown that the ketyl radical formed attacks methylenecyclopropane selectively in an *exo* fashion. Cyclopropylcarbinyl radical **305** then *endo* ring-opened to afford methylenecyclohexanes such as **307** (Scheme 42)[124].



Scheme 42. 5-*exo*-trig cyclisation leading to cyclohexane product.

To explore the feasibility of the desired cyclisation, two simple precursors **308** and **309** were targeted that would possibly give cycloheptanes such as **311** (Scheme 43).

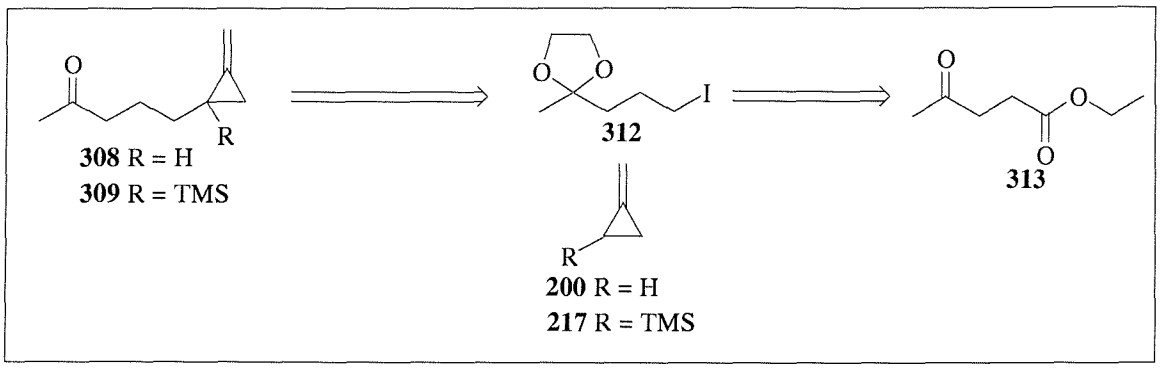


Scheme 43. Targeted precursors and desired cyclisation.

Silicon groups are known to stabilize radicals in the α position[125], hence the TMS group was included to explore whether it would promote the desired cyclisation. In previous work by Destabel[113], the effect of including the TMS group was to promote the 7-*endo*-trig cyclisation onto methylenecyclopropane (see chapter 1 section 1.2.3.3). This system used an iodo-malonate as the precursor with initiation of the reaction was by *hv* irradiation of hexabutylditin at 80°C in toluene. However, this is quite different from a ketone precursor initiated with SmI_2 at 0 or -78°C in THF and so it was necessary to investigate whether the TMS group would enhance the desired cyclisation under these different conditions.

2.2 Synthesis of Precursors

The retrosynthetic analysis of both precursors led to common intermediate iodide **312** (Scheme 44).

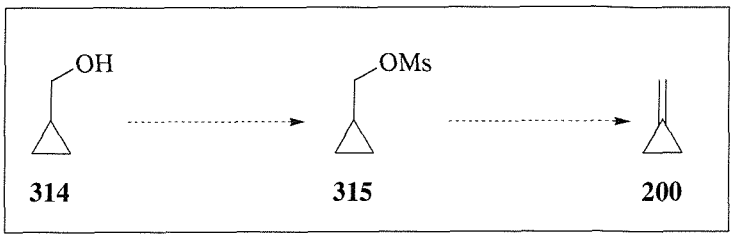


Scheme 44. Retrosynthetic analysis of simple precursors.

Methylenecyclopropane **200** was prepared following the method of Binger[83] (see chapter 1 section 1.2.3.1). The reaction conditions required that the equipment was dry; the reaction at reflux (143°C); and to ensure the minimal loss of unreacted starting materials, a -78°C cold finger was placed directly above the reaction vessel before the exhaust pipe. The process was lengthy, requiring constant supervision over 12 hours and therefore labour intensive.

A different route to methylenecyclopropane **200** was proposed that might reduce the workload whilst keeping the cost of production down. The formation of the alkene by elimination of a functional group from preformed substituted cyclopropanes is known[88-90]

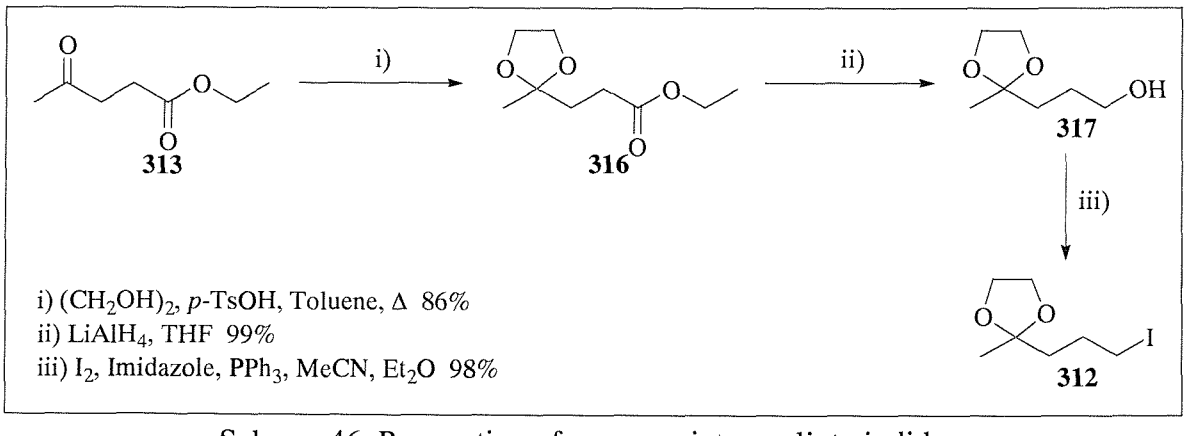
(see chapter 1 section 1.2.3.1), and so a similar approach was attempted. Cyclopropylmethanol **314** is commercially available. The conversion to the mesylate **315** was attempted but this was not trivial and the crude material had to be used for the elimination with ^{t}BuOK and ^{t}BuOH (Scheme 45).



Scheme 45. Proposed alternative preparation of methylenecyclopropane.

The procedure required a large quantity of base. Even on a moderate scale the gelatinous nature of the base/solvent mixture proved very difficult to handle. It was felt that rectifying these problems would ultimately not prove to be cost effective and so the original procedure remained the production method of choice.

The preparation of the precursors started from ethyl levulinate **313** (Scheme 46). Protection of the ketone using ethylene glycol and catalytic *p*-TsOH was achieved on a large scale in high yields. Reduction of the ester functionality of **316** with $LiAlH_4$ was performed quantitatively affording alcohol **317**. The common iodide **312** intermediate was prepared in 98% yield using a quick and very satisfactory method reported by Motherwell[126].

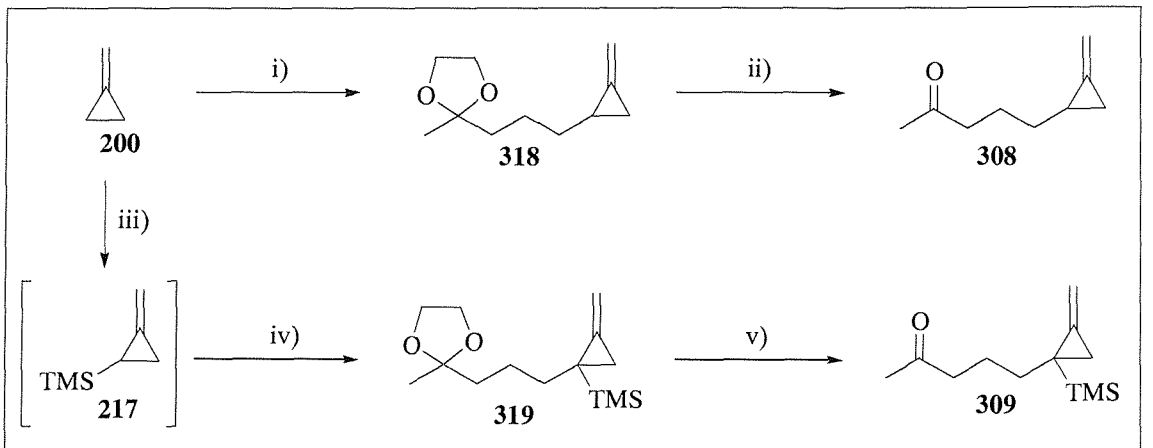


Scheme 46. Preparation of common intermediate iodide.

Substituting iodide **312** with different methylenecyclopropyl moieties followed similar procedures (Scheme 47). Treatment of methylenecyclopropane **200** with ^{n}BuLi deprotonated at the allylic position. Direct displacement of iodine with this methylenecyclopropyl anion afforded ketal **318** in a high yield. HMPA was used to coordinate lithium counter-ions and produce a more naked, and hence reactive, anion. Indeed, addition of HMPA to the methylenecyclopropyl anion deepened the colour of the solution from light orange to red/brown.

To prepare the TMS-substituted analogue **319**, the methylenecyclopropyl anion was treated with TMSCl. TMS-methylenecyclopropane **217** is difficult to isolate due to its volatility, and so was used directly without purification. Addition of a further aliquot of ^{n}BuLi to the reaction mixture deprotonated at the allylic position α to the silicon[86]. Displacement of the iodide **312** with this anion did not require the addition of HMPA as good yields were obtained without it.

The final step in the synthesis required deprotection of the ketal group. This was a straight-forward procedure using *p*-TsOH in acetone/water. Excellent yields of both ketones **308** and **309** were isolated.



i) ^{n}BuLi, HMPA, iodide **312**, -78°C to RT, THF 74%. ii) *p*-TsOH, acetone, water 90%
iii) ^{n}BuLi, TMSCl, -78°C to RT, THF. iv) ^{n}BuLi, iodide **312**, -78°C to RT, THF 77%
v) *p*-TsOH, acetone, water 97%

Scheme 47. Final steps in the preparation of the simple precursors.

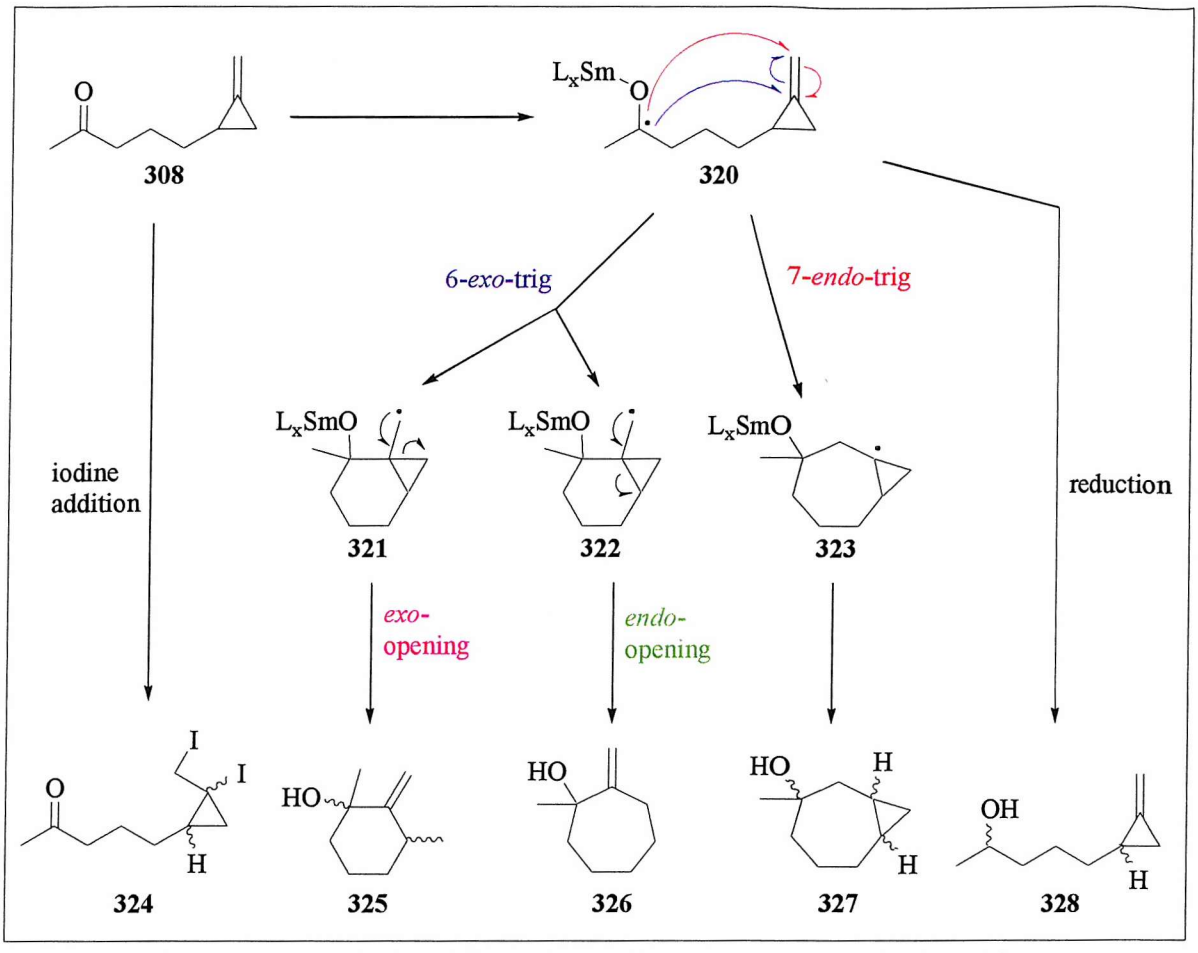
2.3 Cyclisation Studies

2.3.1 Variety of Conditions

Previous work[124] in the research group had shown that HMPA and ^{t}BuOH were the most useful additives for effecting successful cyclisations with samarium iodide. Recent work by Procter[62] (see chapter 1 section 1.1.5.4) had also shown that methanol was a potential alternative additive to the toxic HMPA. Therefore two different additives in THF were tested. The effect of temperature on the reaction was also a simple factor that could be varied and so the cyclisations were carried out at -78 and 0°C. The final consideration was the effective concentration of the reactant. Addition of the precursors *via* syringe pump to the samarium iodide solution ("normal addition") resulted in a high concentration of radical mediator relative to the precursor. A low concentration of radical mediator was achieved by addition of the samarium iodide to the precursors *via* cannula needle ("reverse addition").

2.3.2 Cyclisation Studies on Unsubstituted Ketone

A variety of products were isolated from the cyclisation studies with **308** (Scheme 48). Diiodide **324** was formed by the addition of iodine to the methylenecyclopropane alkene. Methylenecyclohexane **325** arises from an initial 6-*exo*-trig cyclisation of **320** onto methylenecyclopropane followed by *exo*-opening of the cyclopropylcarbinyl radical **321**. Methylenecycloheptane **326** is formed by a 6-*exo*-trig cyclisation of **320** onto methylenecyclopropane followed by *endo*-opening of the cyclopropylcarbinyl radical **322**. Bicyclo[5.1.0]octane **327** arises from an initial 7-*endo*-trig cyclisation onto methylenecyclopropane. Secondary alcohol **328** is formed by reduction of the ketyl radical **320** by samarium iodide to the corresponding anion followed by hydrogen atom abstraction from the solvent.



Scheme 47. Products isolated from the cyclisation of the unsubstituted ketone.

Examination of the results leads to some conclusions (Table 4). High concentrations of samarium iodide (**entries 1**, **2**, **3**) generally reduce the ketone to the corresponding alcohol **328** without cyclisation. Two diastereoisomers are possible for **328** but no selectivity for one over the other was observed. Evidence for cyclisation was observed in **entry 1** but the products were only isolated in trace yields. Although full characterisation proved impossible, strong evidence for the formation of a mixture of methylenecyclohexane **325**; methylenecycloheptane **326**; and iodine addition product **324** was observed in the NMR spectrum. Temperature and additive appeared to make little difference to the outcome of the cyclisations using the normal addition procedure.

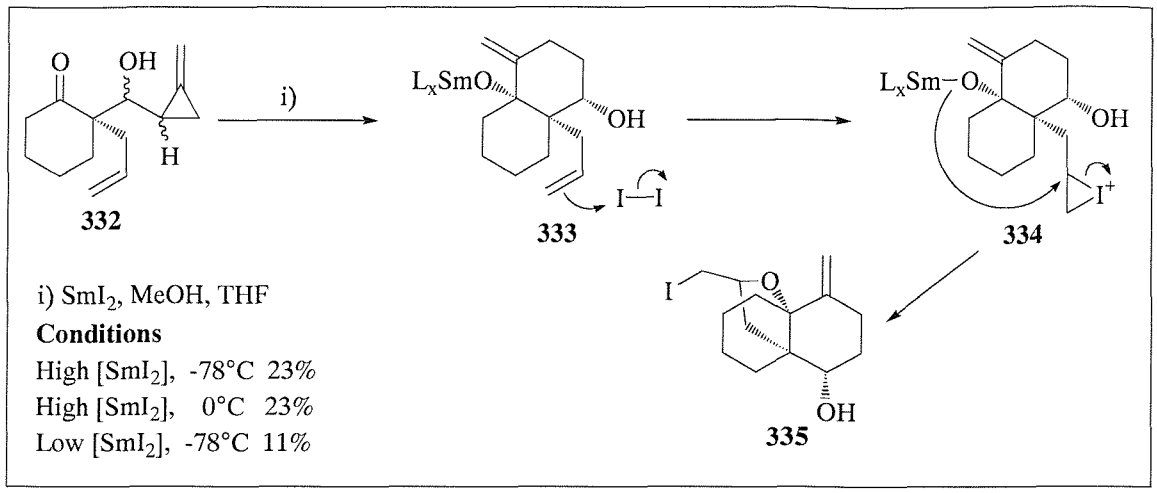
Entry	Mode	Additive	Temp. (°C)	RSM	324	325	326	327	328
1	Normal	MeOH	-78	4	5				84
2	Normal	MeOH	0	-					74
3	Normal	HMPA/ ^{t}BuOH	-78	16					34
4	Reverse	MeOH	-78	20	35 (5:1 isomers)				
5	Reverse	HMPA/ ^{t}BuOH	-78	26	7 (4:1 isomers)		4		
6	Reverse	HMPA/ ^{t}BuOH	0	38			15	8	2

Table 4. Cyclisation results for ketone **308** (yields in %).

However, using the low concentration techniques afforded very different results. Use of the HMPA/^{t}BuOH additive mixture led to formation of cyclisation products **326** and **327** in low yields (**entry 6**). At 0°C, the cyclisation favours the 6-*exo* over the 7-*endo* pathway. No methylenecyclohexane **325** was observed and the initial 6-*exo*-trig gave rise solely to the ring enlarged product **326**.

At a lower temperature with HMPA/^{t}BuOH (**entry 5**), the only products isolated were methylenecycloheptane **326** and di-iodide **324** (4 to 1 ratio of diastereoisomers). Switching to methanol at the lower temperature (**entry 4**) formed a large amount of the di-iodide **324** in a 5 to 1 ratio of diastereoisomers. It was not possible to determine which diastereoisomer was the major product, but in both cases the same isomer was dominant. The occurrence of this addition product is likely to be due to residual iodine in the reaction mixture. Saint-Dizier[127] found several instances of the formation of **335** when using methanol as an additive (Scheme 49). The proposed mechanism adds iodine to a double

bond in cyclisation product **333**. The ketyl oxygen of **334** then attacks in a 5-*exo*-fashion to form novel tricycle **335**.



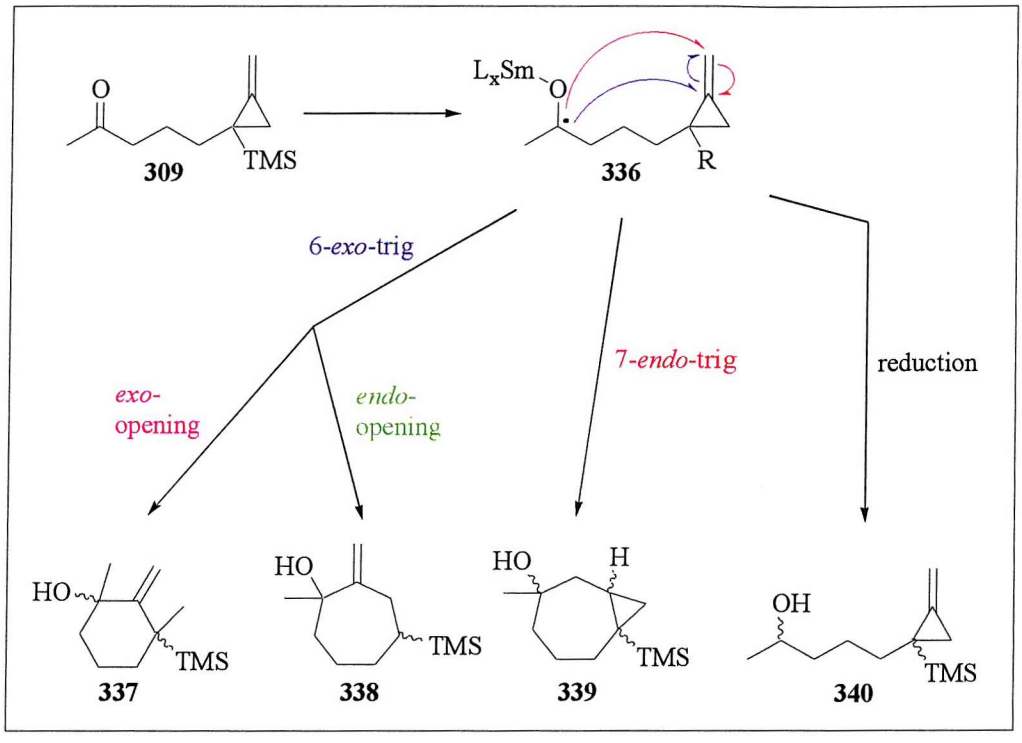
Scheme 49. Previous observation of free iodine presence in cyclisation reactions.

For the cyclisations of **308**, methanol did not promote the desired cyclisation, whereas HMPA did and this could be due to several reasons. The reduction potential of the samarium iodide might not be increased enough with methanol to allow cyclisation to occur; HMPA is known to increase the reduction potential substantially[45]. Alternatively, when methanol is co-ordinated to the samarium metal centre, the ketyl radical may abstract a hydrogen (*i.e.* quench) from the co-ordinated solvent faster than it can cyclise onto the methylenecyclopropane; when HMPA is co-ordinated to the samarium metal centre the abstraction of a hydrogen does not occur so readily and so the cyclisation reaction can take place before quenching. Certainly a low concentration of SmI_2 is still necessary with HMPA. By keeping the concentration of SmI_2 to substrate low, ketyl **320** has more time to undergo the desired cyclisation before reduction to the anion occurs. This is similar to the necessary low concentration of $^nBu_3SnH$ for a good chain reaction cycle to build up seen in the addition of an alkyl halide to acrylonitrile (see chapter 1 section 1.1.4.2).

There is no marked preference for *exo* over *endo* attack in this system. The cyclopropyl ring might be expected to hinder the *exo* mode. Ketyl radicals are nucleophilic[4] and will prefer to react with the LUMO of the acceptor alkene. The cyclopropyl ring could also promote *exo* attack by acting as an electron-donating substituent to the double-bond.

2.3.2 Cyclisation Studies on TMS-substituted Ketone

Cyclisation studies on the TMS analogue **309** also gave a variety of products (Scheme 49). Methylenecyclohexane **337** and methylenecycloheptane **338** are formed from an initial 6-*exo*-trig cyclisation of ketyl radical **336** onto methylenecyclopropane followed by *exo* or *endo* ring-opening respectively. Bicyclo[5.1.0]octane **339** arises from an initial 7-*endo*-trig cyclisation of ketyl radical **336** onto methylenecyclopropane. Secondary alcohol **340** is formed by reduction of ketyl radical **336** to the anion followed by hydrogen atom abstraction from the solvent.



Scheme 49. Products isolated from the cyclisation of TMS-substituted ketone.

The results are in stark contrast to the unsubstituted analogue **308** and a pattern of reactivity is more clearly discernible (Table 5). When methanol is used as the additive (**entries 1, 2, 5**) simple reduction product **340** is the only product from the ketyl radical **336**. The simple reduction product **340** was isolated as a mixture of diastereoisomers, but neither isomer was dominant. No product from the addition of iodine to the double bond was isolated.

Use of HMPA/^{t}BuOH promoted the cyclisations (**entries 3**, **4**, **6**, 7), although some simple reduction product **340** was isolated. However, the major cyclisation product was always the bicycle **339** from the 7-*endo*-trig mode of attack. In two cases (**entries 3** and 7), products **337** and **338** from initial 6-*exo*-trig cyclisation were observed but in very low yields and full characterisation was not possible.

Entry	Mode	Additive	Temp. (°C)	RSM	337	338	339	340
1	Normal	MeOH	-78	40				21
2	Normal	MeOH	0	46				20
3	Normal	HMPA/ ^{t}BuOH	-78	-	1	2	69	14
4	Normal	HMPA/ ^{t}BuOH	0	-			48	4
5	Reverse	MeOH	0	57				13
6	Reverse	HMPA/ ^{t}BuOH	-78	-			41	8
7	Reverse	HMPA/ ^{t}BuOH	0	-	2	3	57	11

Table 5. Cyclisation results for TMS-substituted ketone (yields in %).

The TMS group has clearly had a significant effect on the cyclisation. Ketyl radical **336** cyclises, even at high concentrations of samarium iodide, but only with the presence of HMPA. From an FMO point of view, the silyl substituent might be expected to promote *exo* cyclisation. From a steric approach, the effect of the TMS group may be to distort the transition state for cyclisation so that the 7-*endo* mode is favoured over the 6-*exo* path.

However, ketone **309** does not contain a simple allyl silane functionality and the influence from the cyclopropyl ring is difficult to ascertain but certainly important. Research by Wilt[24, 128] has shown that silicon has an interesting effect on radical reactions. The position of silicon in the alkyl chain was varied and it was found that in the β position radical **344** cyclised by the *endo* mode exclusively (Figure 16).

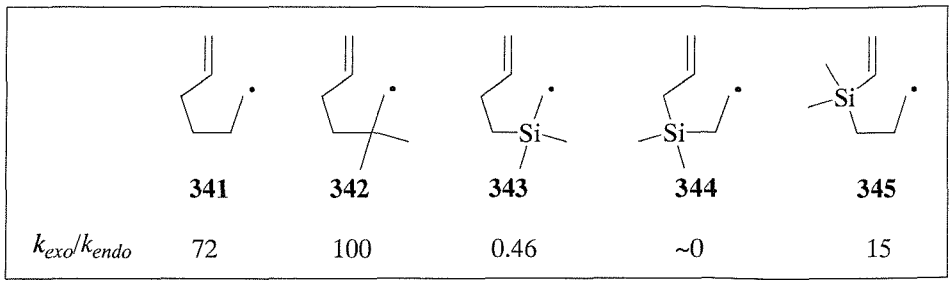
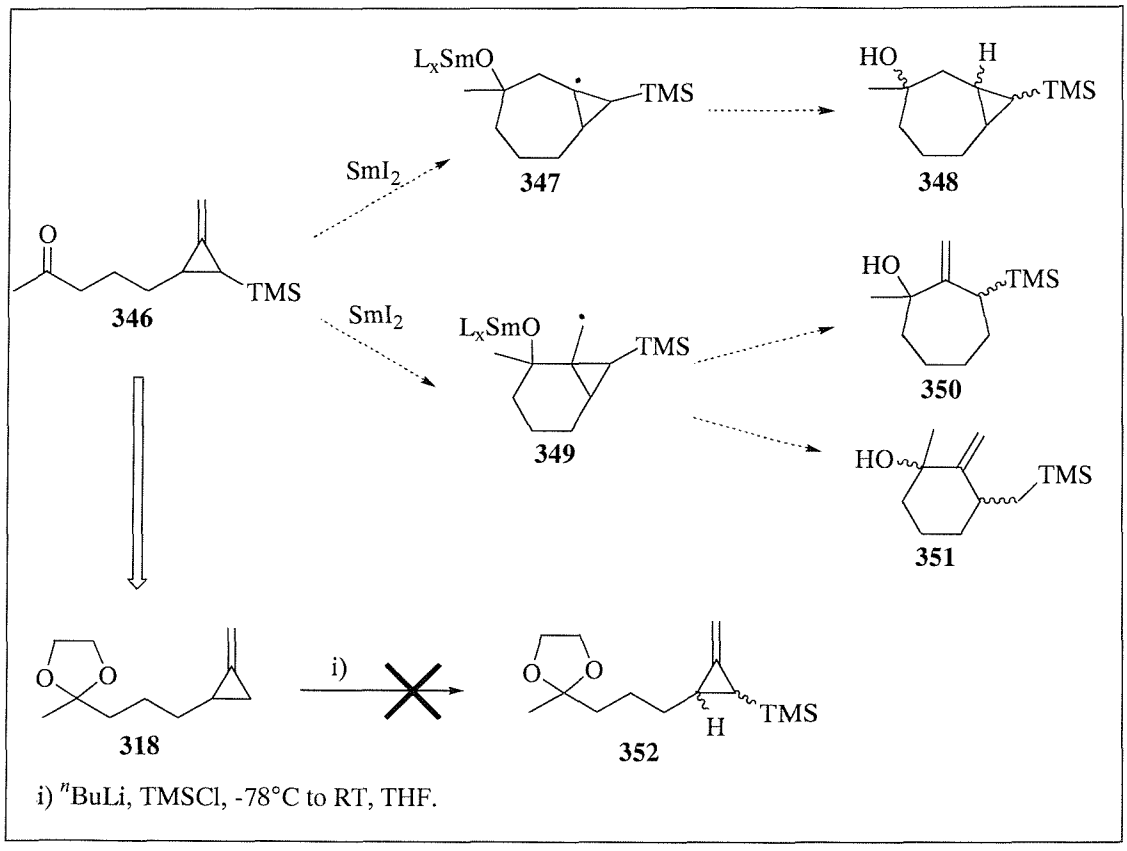


Figure 16. Rates of cyclisation and the effect of silicon substitution.

However, in this case the silicon is part of the ring formed and the length of carbon-silicon bonds will have an effect on the transition state; no direct comparisons can be made with ketone **309**.

A simple analogue **346** was targeted to explore the nature of the effect of the TMS group (Scheme 51). Cyclisation studies using this analogue would hopefully allow more definite conclusions to be made about the steric or electronic effects of the silyl appendage.



Scheme 51. Potential cyclisation products of 1,2-TMS substituted analogue and the failed preparation.

The TMS group has to be introduced after the addition of the methylenecyclopropane unit to the carbon backbone (see section 1.2.3.1, chapter1). Thus, the synthesis of the precursor was attempted from intermediate **318**. Unfortunately, attempts to prepare this analogue from **318** were unsuccessful. Both ^{n}BuLi and ^{s}BuLi were used as the base but no desired product **352** could be identified (a mixture of *cis* and *trans* isomers would be expected). It is likely that side-reactions occur and inhibit the desired reaction. The synthesis of 1,2 TMS precursor **346** was therefore abandoned.

2.4 Conclusions

The inclusion of a TMS group did not have the desired effect of promoting the formation of the methylenecycloheptane **338**. With either precursor **308** or **309**, methanol was found to be an unsatisfactory additive, and promising quantities of cyclic products were only formed with HMPA. The rate of cyclisation is slow compared to reduction with unsubstituted methylenecyclopropanes and hence a low concentration of samarium iodide must be used. The rate of reaction at -78°C proved prohibitively slow. Hence, the "best" conditions were low concentration of samarium iodide using HMPA additive at 0°C.

Chapter Three

3 Cyclic Precursors

3.1 Aims

The results of the cyclisations from the simple precursor **308** suggested that the there was a small preference for *exo* over *endo* cyclisation but both were obtained in low yields. To build on these results and further explore the potential of the reaction, three new precursors **353**, **354** and **355** were targeted whose structures were hoped would favour cyclisation (Figure 17). It was hoped that restricting bond movement would hold the reactive centres in closer proximity and promote the cyclisation reaction and also favour the *exo* mode. The inclusion of an alcohol or ether functionality would also allow exploration of the co-ordination effects and the possibility to prepare tricycles if a suitable radical trap (allyl or propargyl group) were used as the ether functionality.

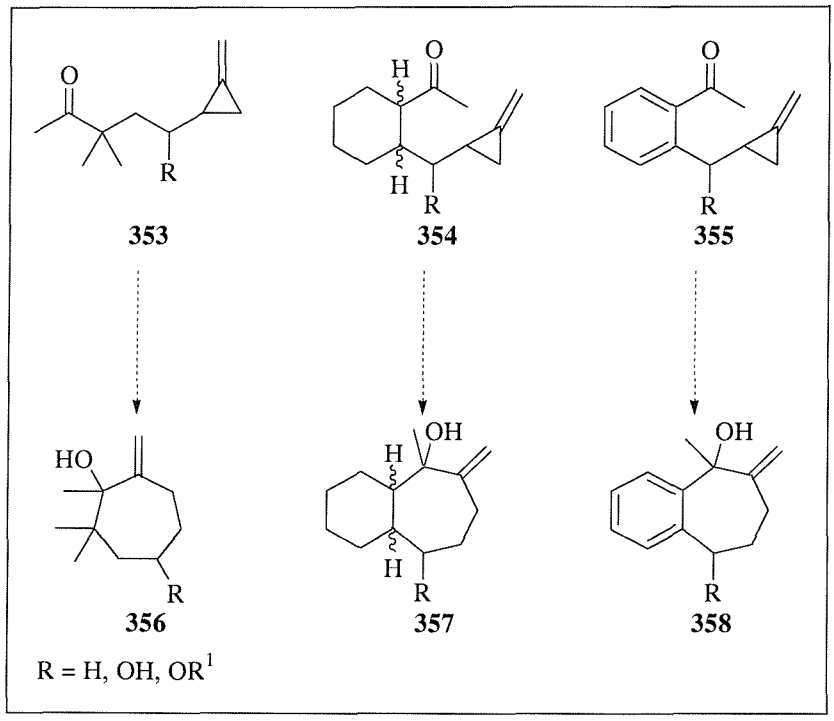
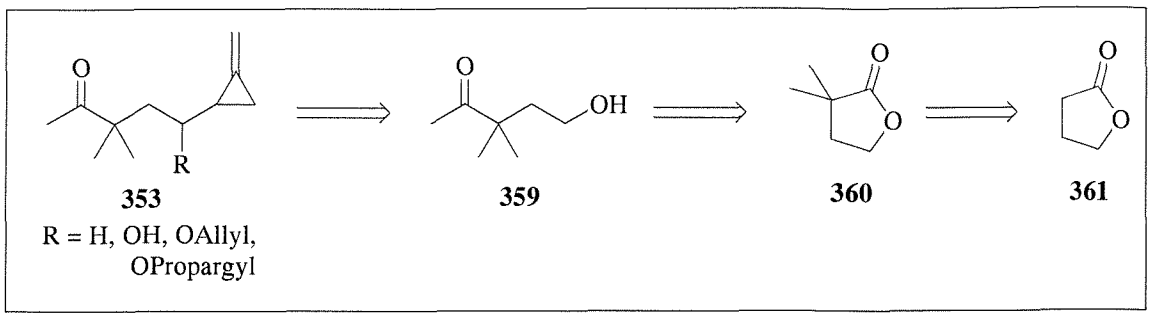


Figure 17. Constrained target precursors.

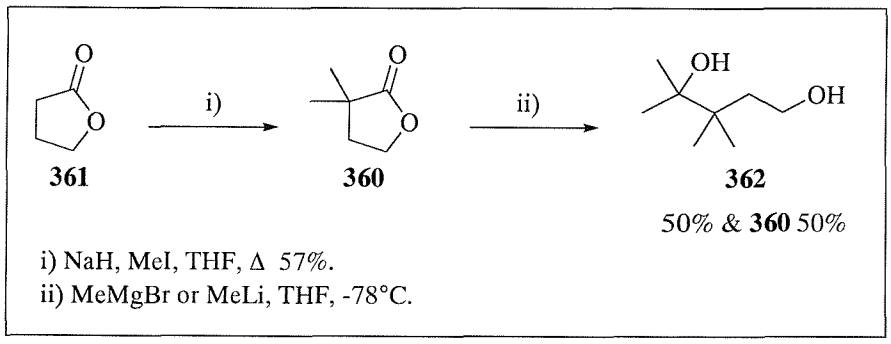
3.2 Gem-dimethyl Precursor

The retrosynthetic analysis of **353** led to lactone **360** (Scheme 52). Once intermediate **361** had been prepared, the synthesis of the precursor would use the same synthetic transformations as used for the simple precursor (see chapter 2).



Scheme 52. Retrosynthsis of gem dimethyl precursor.

The preparation of lactone **360** was facile and a good 57% yield of the dimethylated product was obtained. However, opening lactone **360** with the methyl anion in the desired fashion was not possible (Scheme 53). The type of reagent and temperature were varied, but ultimately only a statistical mixture of tertiary alcohol **362** and starting material was obtained. This approach was not working and literature searches failed to provide an alternative retrosynthetic analysis. Further work in this area was halted and effort was now focussed on the two cyclic precursors **354** and **355**. It was felt that they offered more attractive cyclisation products, and afford direction toward natural product skeletons.

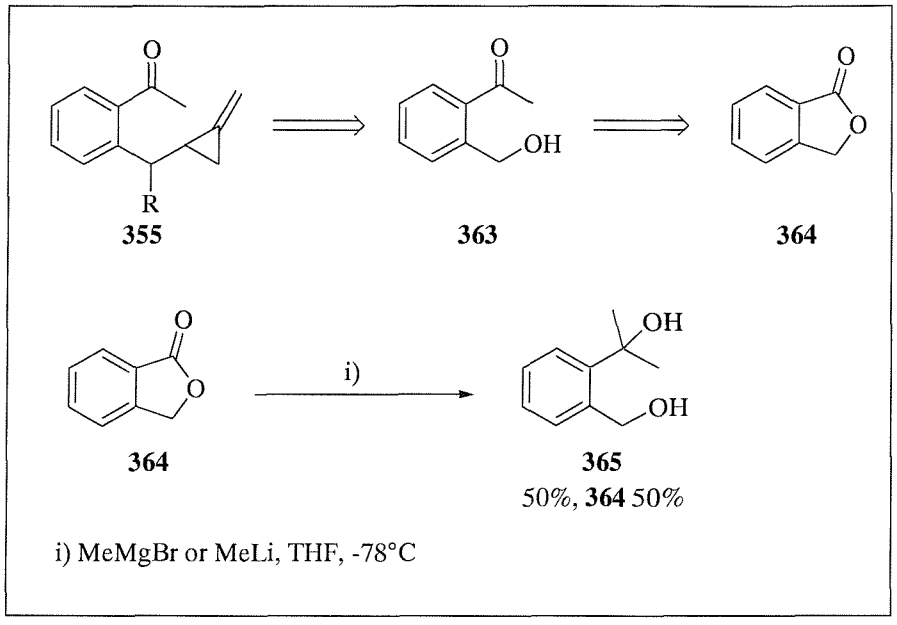


Scheme 53. Failed synthesis of required intermediates.

3.3 Aromatic Target

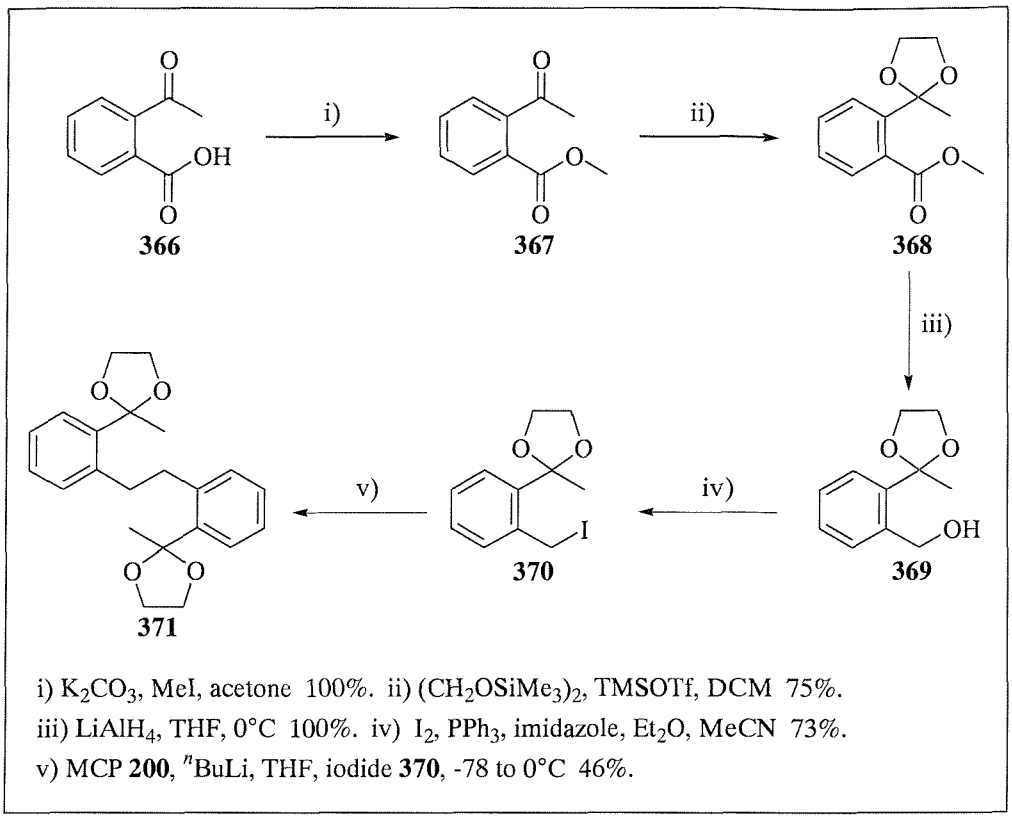
3.3.1 Synthesis of Aromatic Precursor

The initial approach was based on the route to the gem dimethyl precursor **353** (Scheme 54). Lactone **364** was commercially available but attempted addition of MeMgBr and MeLi was found to be unreliable for the same reasons as in the case of the gem dimethyl precursor **360**. Again, only tertiary alcohol **365** and starting material were recovered from the attempted ring-opening reaction.



Scheme 54. Retrosynthesis and failed first step towards the aromatic precursor.

A new approach to the aromatic target required similar intermediates to the initial route (Scheme 55). Acetyl benzoic acid **366** is commercially available and is structurally similar to intermediate **364** by possessing a carboxylic acid instead of a primary alcohol. The first step was to protect the ketone to allow manipulation of the acid. Attempts to protect the ketone with ethylene glycol failed, most likely due to interactions with the acid. This was overcome by converting the acid group into methyl ester **367** in quantitative yield with mild base and methyl iodide. Protection with ethylene glycol again failed, but Noyori's procedure[129] with 1,2 bis-trimethylsilyloxyethane and trimethylsilyl triflate gave ketal **368** in a very good 75% yield. Reduction of ester **368** to the corresponding alcohol **369** was quantitative.

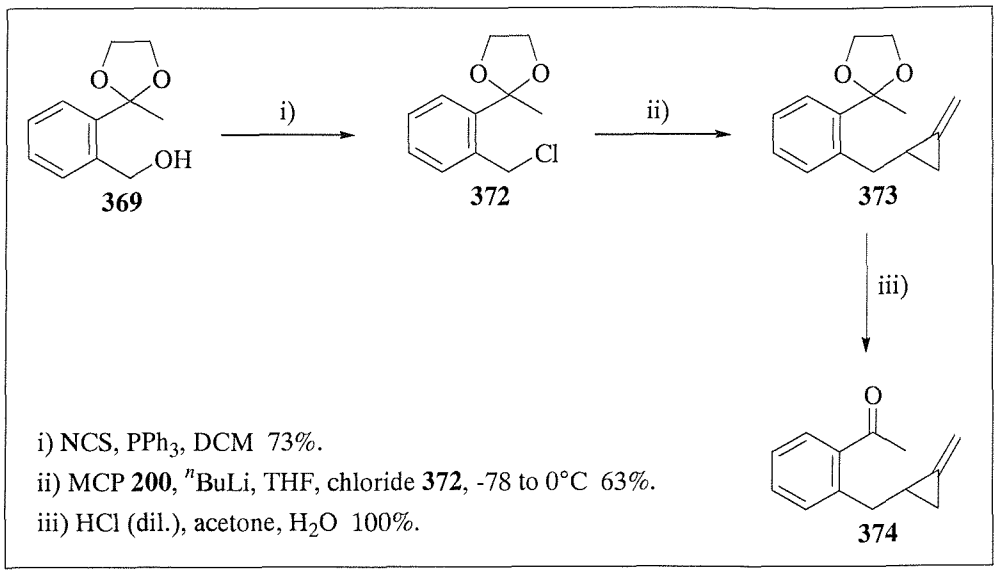


i) K_2CO_3, MeI, acetone 100%. ii) $(CH_2OSiMe_3)_2$, TMSOTf, DCM 75%.
iii) $LiAlH_4$, THF, 0°C 100%. iv) I_2, PPh_3, imidazole, Et_2O, MeCN 73%.
v) MCP **200**, ^{n}BuLi, THF, iodide **370**, -78 to 0°C 46%.

Scheme 55. Early steps in the synthesis of the aromatic precursor.

An iodide was chosen as the leaving group for the nucleophilic substitution reaction. The synthesis was standard (very good 73% yield) but the stability of compound **370** was poor. A sample in $CDCl_3$ had already started to decompose in the time taken to obtain a ^{13}C NMR spectrum. Iodide **370** was used quickly in the next reaction after purification to try to avoid contaminants from its decomposition. All attempts to displace the iodide with methylenecyclopropyl anion failed. A white solid was isolated in 46% yield and found to be the dimerised product **371**. Lithiation of the iodide **370** with lithiated methylenecyclopropane must be faster than the desired displacement.

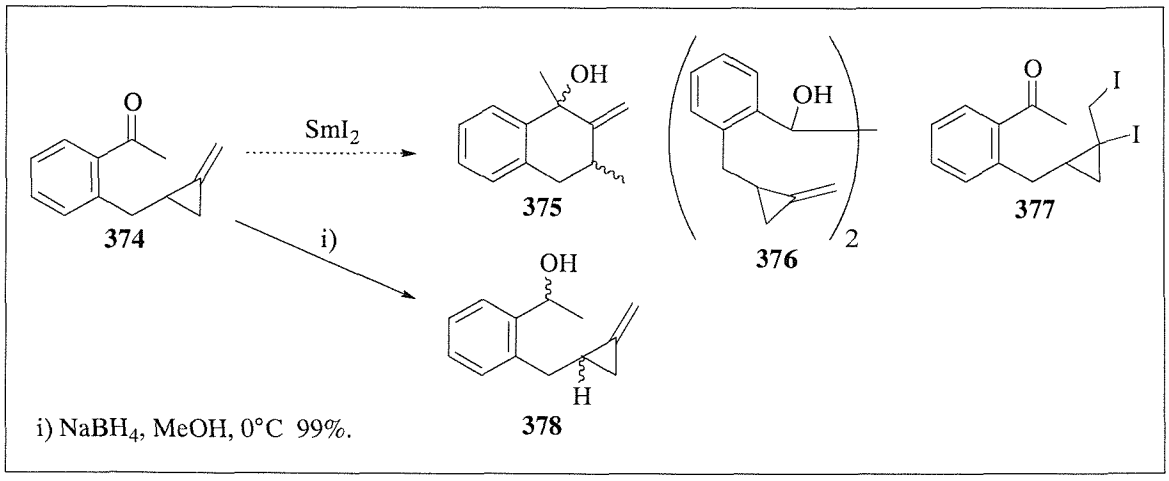
Changing the leaving-group to a mesylate did not avoid these reactivity problems and furthermore this analogue was awkward to handle. Conversion of alcohol **369** to the chloride **372** proved to be a very suitable change (Scheme 56). The chlorination with NCS proceeded in a high 73% yield, and now the displacement reaction was successful furnishing the desired ketal **373** in a good 63% yield. Finally, deprotection of the ketal was quantitative affording precursor **374** in an overall 34% yield from acetyl benzoic acid **366**.



Scheme 56. Final steps to prepare the aromatic precursor.

3.3.2 Cyclisation Studies on the Aromatic Precursor

Cyclisation studies on the aromatic precursor were disappointing. Initially the "best" conditions from simple precursor **308** (normal addition, HMPA, ^{t}BuOH, 0°C) were employed but ultimately all of the original eight conditions were tried. In general, the purification of the reactions was far from trivial and the only product that could unambiguously be identified was the simple reduction product **378** (Scheme 57). This was proved by reducing the starting ketone **374** with sodium borohydride and comparing spectra as the product from the radical reaction contained other inseparable unknown materials. There was some evidence for products **375**, **376** and **377** but these structures could not be proved as again there were other inseparable unknown materials.



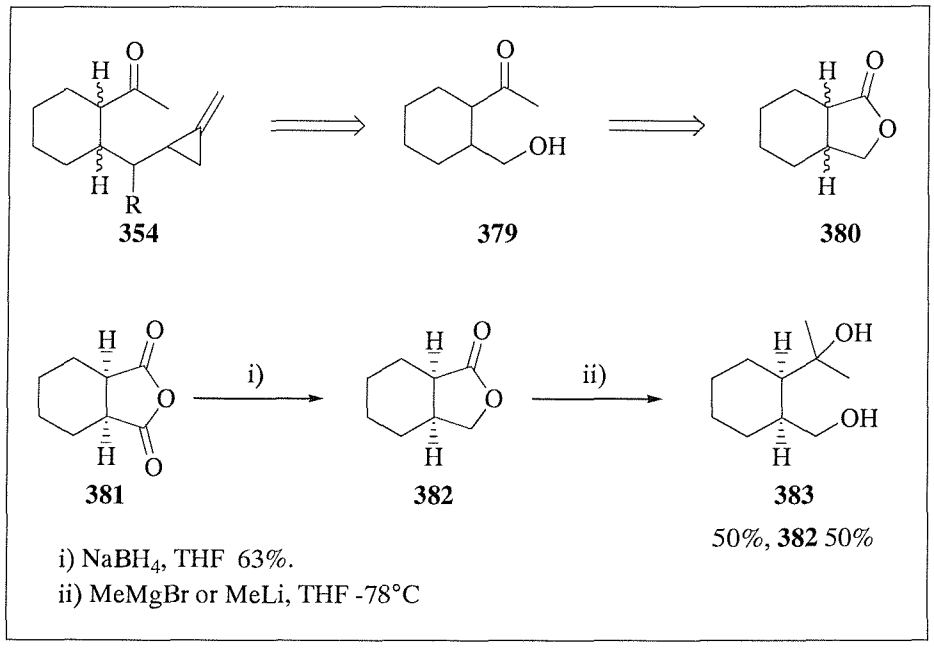
Scheme 57. Attempted cyclisation of the aromatic precursor.

The relative stability of the benzylic ketyl radical may suppresses any cyclisation pathways. With this in mind further studies on aromatic systems were deemed to be unlikely to give clean cyclised products and work in this area was stopped.

3.4 Cyclohexyl Precursors

3.4.1 Initial Route

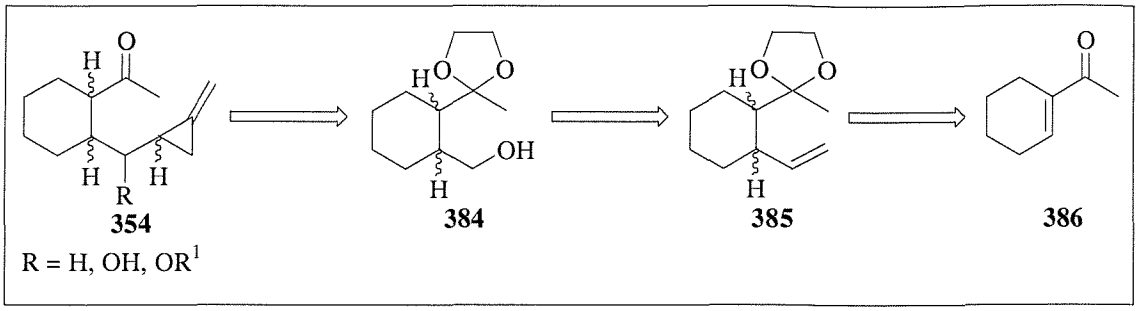
The initial approach was based on the route to the gem dimethyl precursor **353** (Scheme 58). Theoretically both *cis* and *trans* isomers of cyclohexyl precursor **354** could be prepared and allow exploration of the effects of the different geometries. Lactone **382** was prepared in a good 63% yield from anhydride **381** by reduction with sodium borohydride. Again, this route was quickly found to be unsuitable for the same reasons observed before. Only tertiary alcohol **383** and starting material were recovered from the attempted ring-opening reaction.



Scheme 58. Retrosynthesis and unsuccessful first step towards the cyclohexyl precursor.

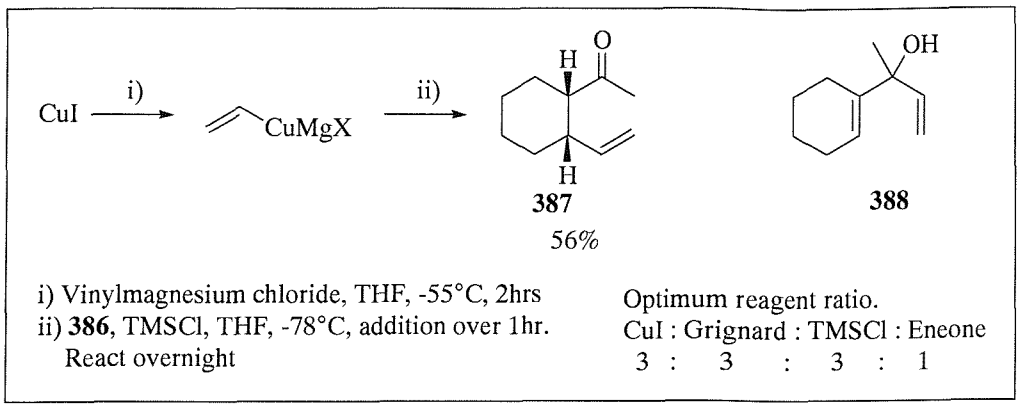
3.4.2 Second Route

Ideally, a new route would also allow access to both *cis* and *trans* isomers and another retrosynthetic analysis appeared to offer this possibility (Scheme 59).



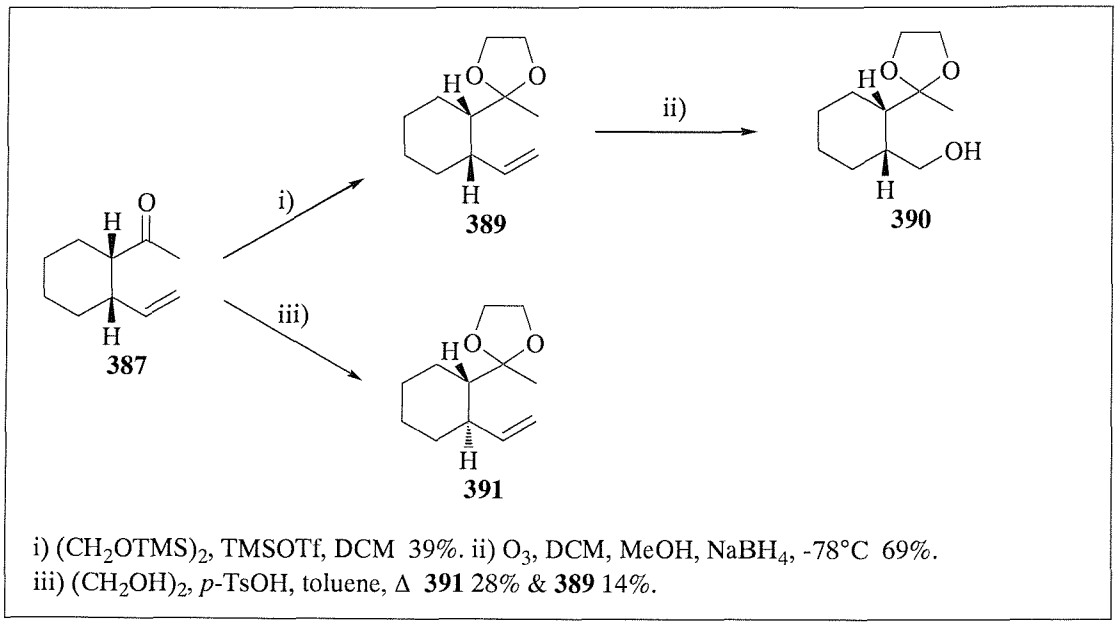
Scheme 59. Alternative retrosynthetic analysis of cyclohexyl precursors.

The synthesis required addition of a vinyl group to acetylcyclohexene **386** (Scheme 60). A cuprate was chosen as it was hoped that this would allow exclusive preparation of the 1,4-addition product **387**[130]. Vinyl lithium was no longer commercially available, and so vinyl magnesium bromide was chosen as the source of the vinyl group. After much investigation, suitable conditions were found that allowed preparation on a medium scale whilst avoiding the 1,2-addition by-product **388**. It was found that the stoichiometry of the reagents was important: an equimolar amount of copper and Grignard reagent had to be used to ensure formation of the correct cuprate. To obtain a good yield, an excess of reactants had to be used. The temperature was also very important: if the formation of the cuprate took place at too low a temperature, then 1,2-product **388** was observed; if it was too high then no reaction occurred and presumably the organo-copper reagent had decomposed. TMSCl was important in promoting the 1,4 attack of the nucleophile. Finally, the reaction had to be kept at the correct temperature for long enough for the reaction to go to completion and quenched whilst cold. Addition of the Grignard reagent on its own to enone **386** at 0°C gave both 1,2- **388** and 1,4-addition **387** products. Using the optimum conditions, ketone **387** was prepared in a good 56% yield and isolated solely as the *cis* product.



Scheme 60. Best conditions for 1,4-addition product.

Protection of ketone **387** fortuitously allowed access to both *cis* **389** and *trans* **391** ketal isomers (Scheme 61). The Noyori protocol[129] retained the stereochemistry to afford the *cis* ketal **389** in a moderate 39% yield. When ethylene glycol and *p*-TsOH in refluxing toluene were used to protect the ketone, both *cis* **389** (14%) and *trans* **391** (28%) products were isolated.



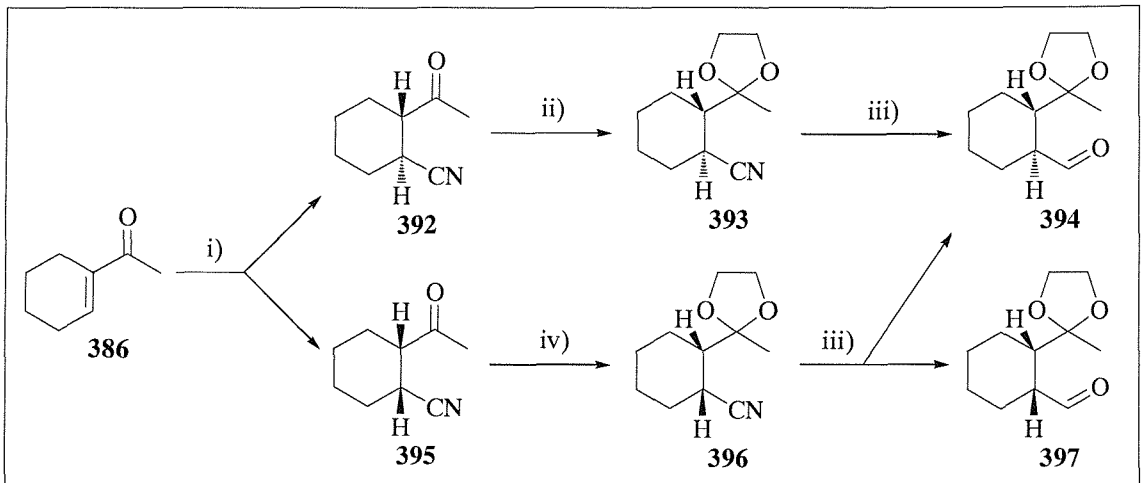
Scheme 61. Accessing both *cis* and *trans* intermediates.

Treatment of *cis* alkene **389** with ozone and destruction of the ozonide intermediate with sodium borohydride afforded alcohol **390** in a good 69% yield. It seemed highly likely that this route would be suitable to complete the syntheses of the desired precursors. However, the route was developed whilst on industrial placement. When the synthesis

was attempted on return to the university laboratories the first step of addition of the vinyl group could not be achieved. All the reagents were varied, but the transformation proved elusive. Insufficient quantities of intermediate material had been made to allow adequate exploration of the final steps of the synthesis and unfortunately this approach had to be abandoned. The reasons for its failure are unknown.

3.4.3 Third route

The next approach started again from acetylcyclohexene **386** following similar lines to the "vinyl route". It was hoped that addition of a cyanide would also allow access to both *trans* and *cis* precursors (Scheme 62). Indeed, both *cis* and *trans* products **395** and **392** were produced from the first step. Using established methodology[131], a consistent yield of products on large scale was possible (**392** 41%, **395** 28%). The ketones had to be protected using Noyori's procedure[129] as isomerisation occurred using the alternative ethylene glycol method. Excellent yields of both *cis* (97%) and *trans* (89%) ketals **396** and **393** were obtained.



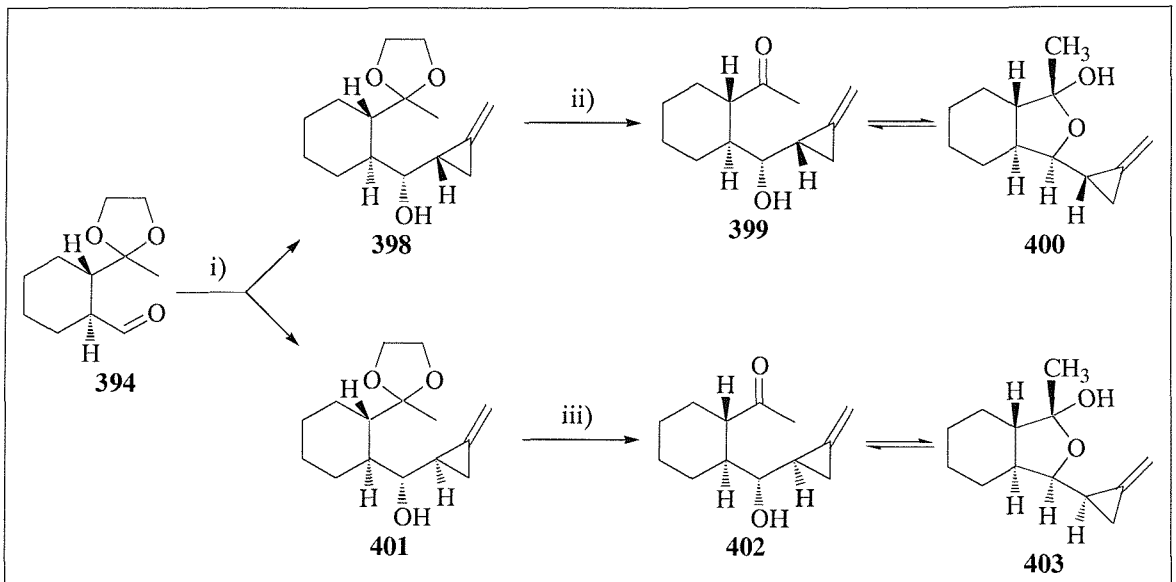
i) KCN, NH_4Cl, H_2O, DMF, 80°C **392** 41% & **395** 28%.
ii) $(CH_2OTMS)_2$, TMSOTf, DCM, -40°C to RT 99%.
iii)a) DIBAL-H, -20°C, hexane; b) 25%AcOH, THF, MeOH, $NaOCH_3$, RT 96% (**394** from **393**).
iv) $(CH_2OTMS)_2$, TMSOTf, DCM, -40°C to RT 97%.

Scheme 62. Early steps in cyanide addition route.

Reduction of the cyanide group using DIBAL-H and hydrolysis of the resulting imine with buffered mild acid afforded *trans* aldehyde **394** in an excellent 96% yield (Scheme 62).

Attempts to use the same procedure with *cis* cyanide **396** all resulted in some isomerisation giving a mixture of *cis* and *trans* aldehydes **397** and **394** which could not be separated. Numerous attempts to minimise the isomerisation were ineffective and ultimately the *cis* analogues were discarded as possible precursors using this route.

Preparation of the alcohol and ether precursors required addition of methylenecyclopropyl anion to aldehyde **394** (Scheme 63)[85]. Four isomers of the alcohol were produced in a very good overall 73% yield. They were isolated as two pairs of isomers in a 9:1 ratio (37%) and in a 15:1 ratio (36%) containing the major isomers **398** and **401** respectively. Proof of the relative stereochemistry of major isomers **398** and **401** in each mixture respectively came from the crystal structures of the deprotection products **400** and **403**. The ketal mixtures **398** and **401** were deprotected with mild acid to give the keto-alcohols in very good 65% (**399**) and 82% (**402**) yields. Fortunately, both keto-alcohols formed large crystalline solids in their bicyclic lactol tautomeric forms **400** and **403**. However, in solution both lactol and keto-alcohol forms existed and the matter was complicated further by the presence of other possible lactol forms. This meant that complete NMR assignment was impossible.



i) MCP **200**, ^{n}BuLi, THF, aldehyde **394**, -78 to 0°C **398** 37% (9:1) & **401** 36% (15:1).
ii) HCl (dil.), acetone, H_2O 65%.
iii) HCl (dil.), acetone, H_2O 82%.

Scheme 63. Final preparation of the keto-alcohol precursors.

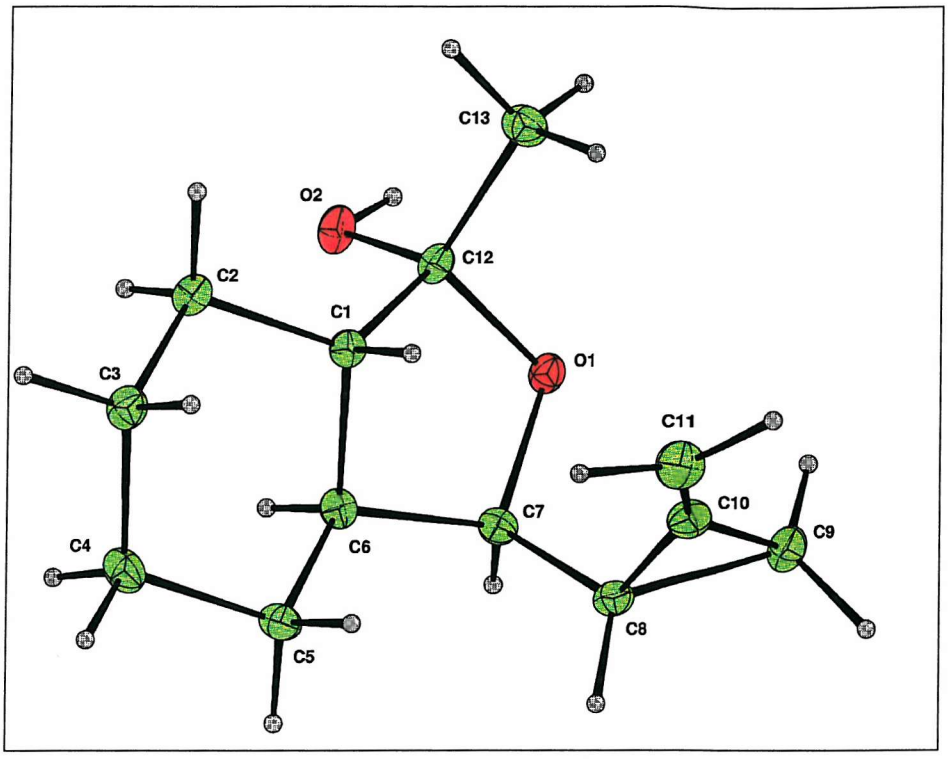


Figure 18. X-ray crystal structure of lactol **400**.

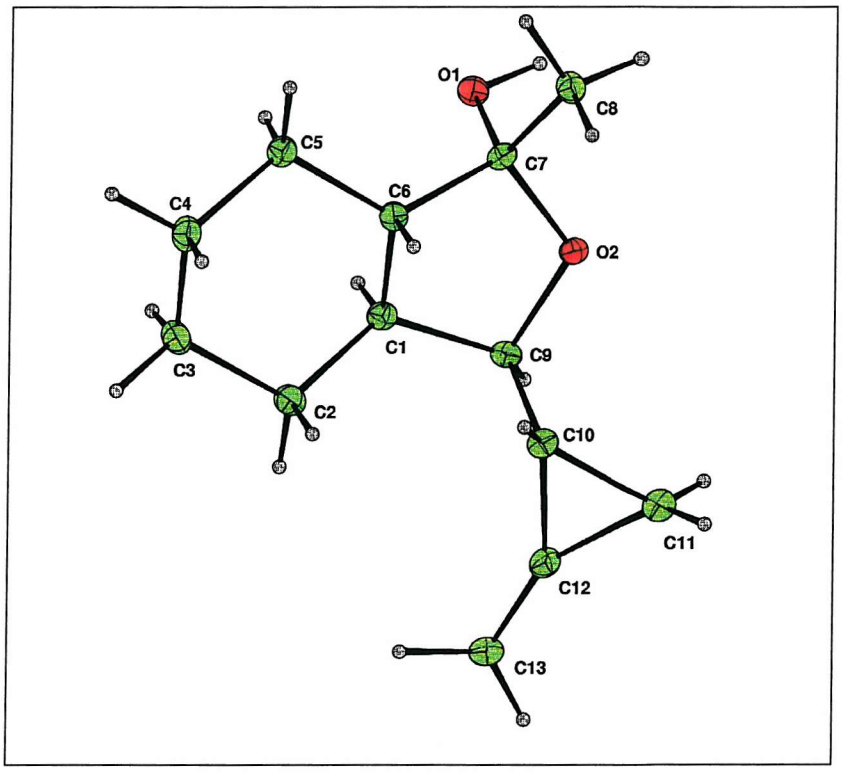
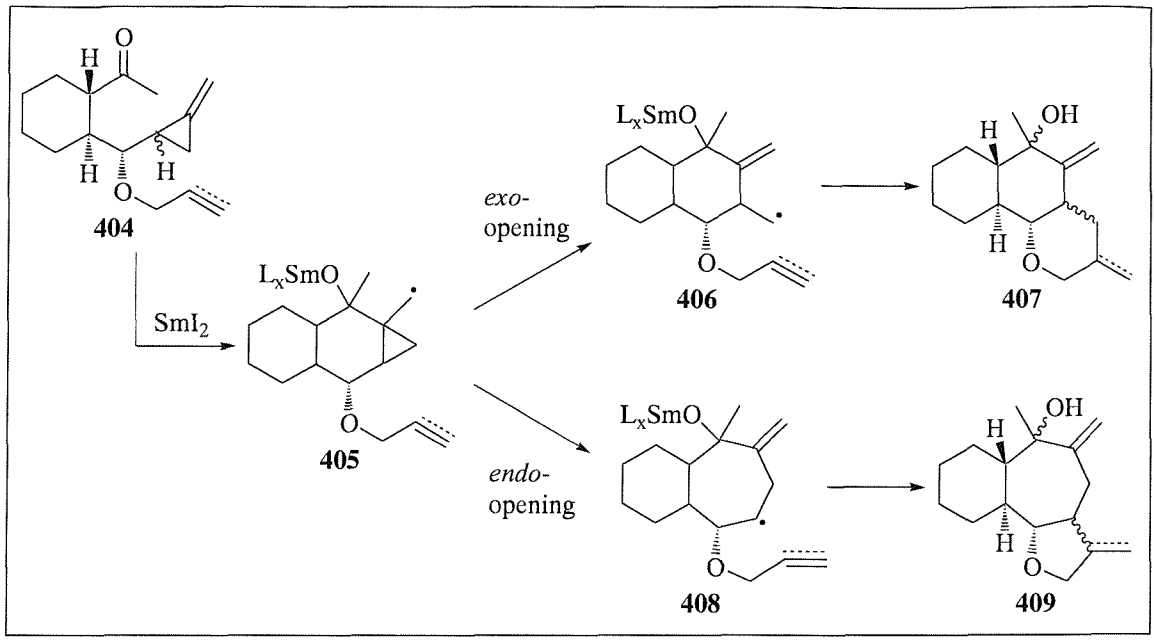


Figure 19. X-ray crystal structure of lactol **403**.

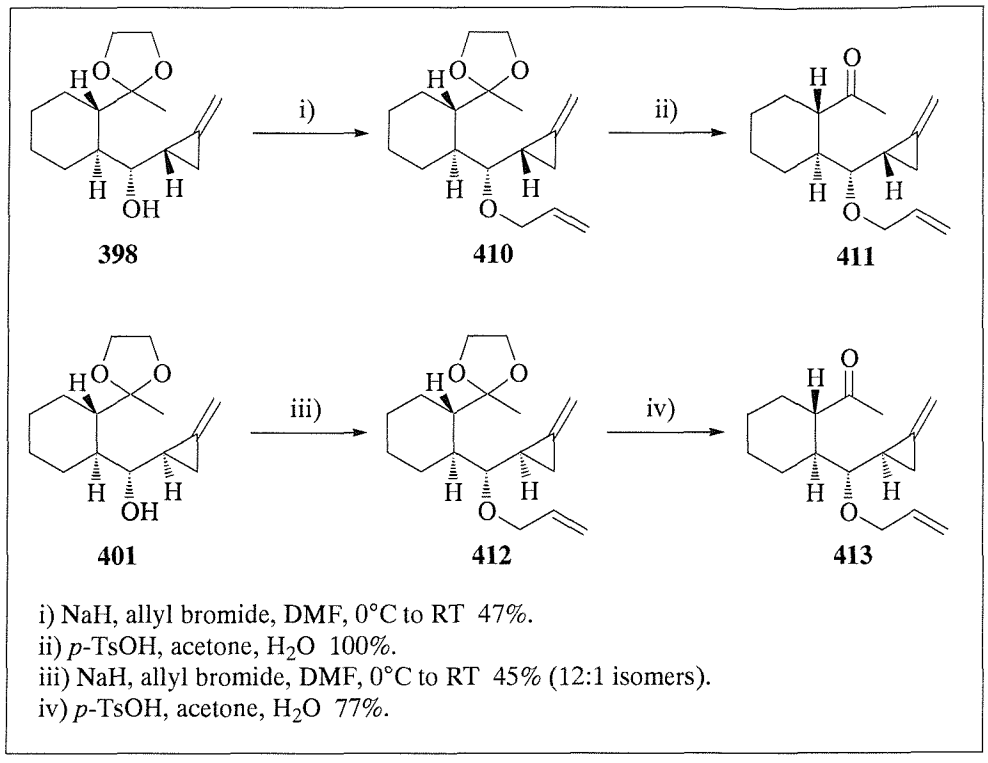
It was hoped that the cyclisation of the methylenecyclopropyl ketones such as **399** and **402** would proceed by a 6-*exo*-trig pathway followed by ring-opening of the cyclopropane.

Thus, it was anticipated that radicals **406** or **408** produced from cyclopropyl ring-opening could be trapped with an allyl or propargyl group and form a tricyclic structure such as **407** or **409** (Scheme 64).



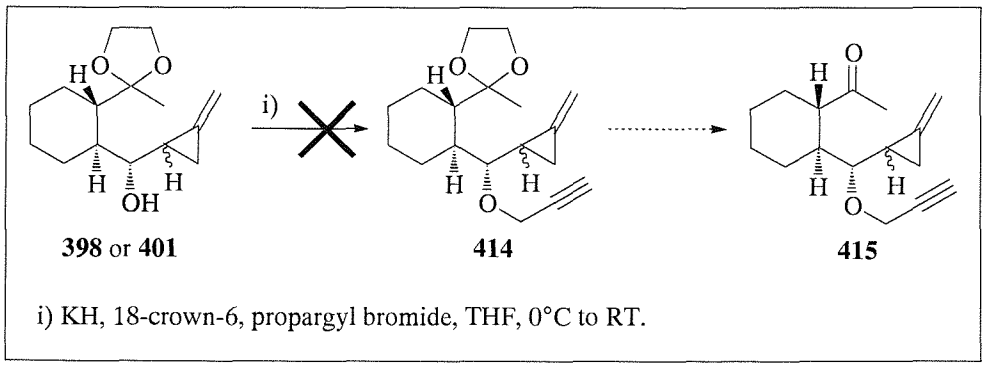
Scheme 64. Potential tricycles from cascade radical cyclisation.

Thus, the allyl ethers were prepared from the ketal-alcohols **398** and **401** (Scheme 65). Allylation of alcohol **398** gave a single isomer of the product **410** in 47% yield. Alcohol **401** gave **412** as two isomers in a 12:1 ratio in 45% yield. Deprotection of the ketals **410** and **412** afforded the desired allyl ether ketones **411** (quantitative) and **413** (77%) effectively as single isomers in very good yields.



Scheme 65. Preparation of allyl ether precursors.

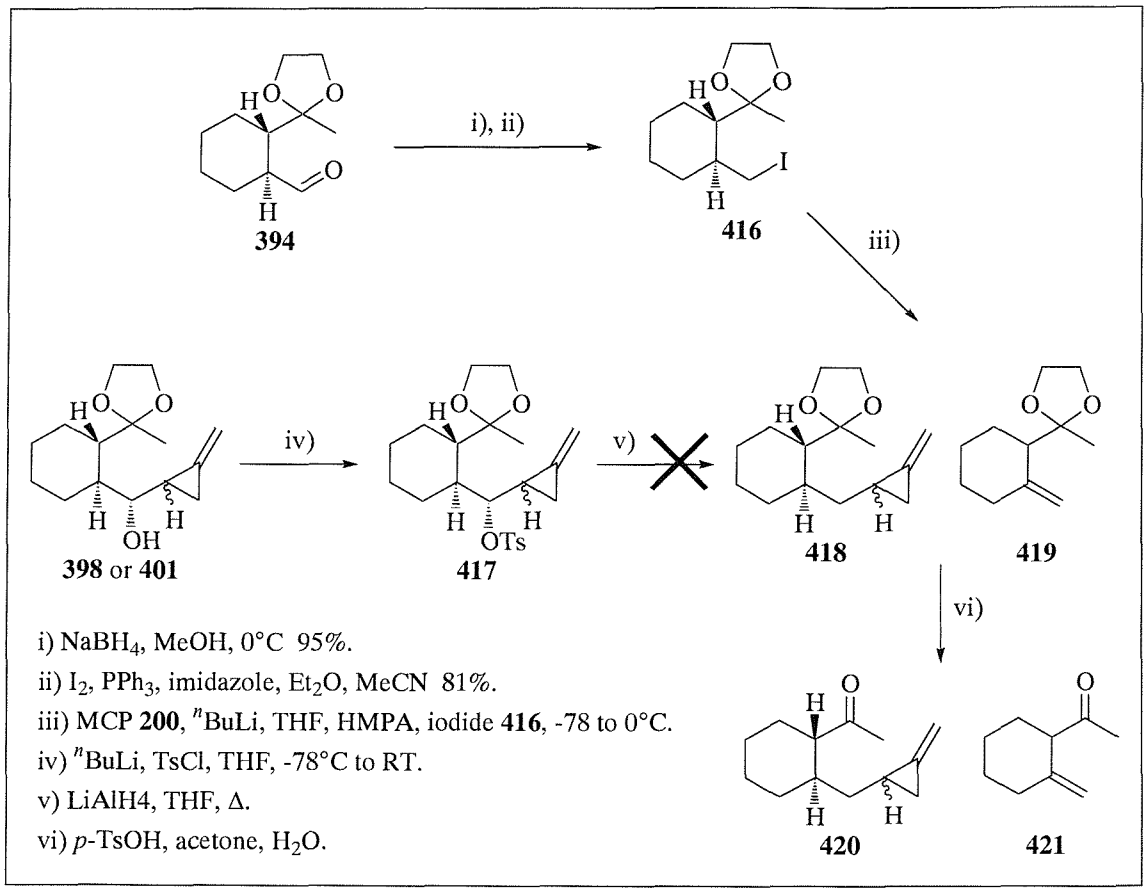
Attempts to prepare the analogous propargyl ethers **414** were unsuccessful using potassium hydride, 18-crown-6, and propargyl bromide (Scheme 66). The alcohol group is quite congested and the low yields from the allylation reactions demonstrate its hindered location. Propargylations are generally harder to effect than allylations and unfortunately the preparation of the propargyl ethers had to be abandoned.



Scheme 66. Failed preparation of the propargyl precursors.

The final precursor to be prepared was the unsubstituted ketone **420** (Scheme 67). Aldehyde **394** was reduced to alcohol in an excellent 95% yield. Iodide **416** was prepared

using familiar conditions and was isolated in a very high 81% yield. Nucleophilic substitution with the methylenecyclopropyl anion proved problematic. Without HMPA the reaction was poor, but with HMPA, an inseparable mixture of two alkene products likely to be **418** and **419** was isolated. Some displacement had occurred but also some elimination of HI. Changing to a softer methylenecyclopropyl cuprate did not improve the reaction and the only product isolated was believed to be the deprotected ketone from iodide **416**. Using the analogous chloride gave no reaction. Deprotection of the inseparable ketal mixture **418** and **419** afforded another inseparable mixture of postulated ketones **420** and **421** in a poor yield. An alternative route required preparation of the tosylate **417** from the ketal alcohol **398** or **401**. This step was also problematic and although various different bases (NEt_3, NaH, ^nBuLi)[132, 133] were used, tosylate **417** could not be isolated. A crude reaction mixture was refluxed with $LiAlH_4$ in THF, but this did not produce the desired ketal **418**. Attempts to synthesise precursor **420** had to be halted.



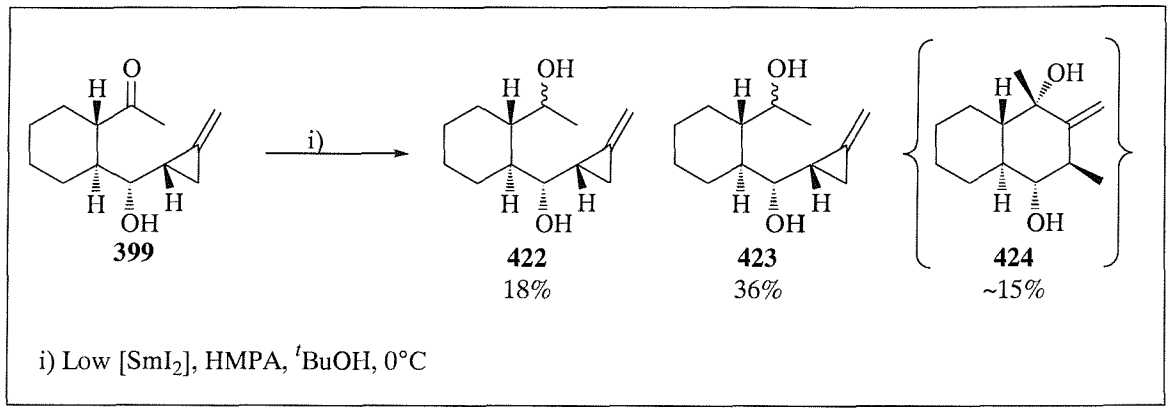
Scheme 67. Attempts to synthesise the unsubstituted cyclohexyl precursor.

3.5 Cyclisation Studies on Cyclohexyl Precursors

3.5.1 Cyclisation of Keto-alcohols

The cyclisation studies of the keto-alcohol precursors **399** and **402** were investigated. Reactions with methanol were unsuccessful, but reactions using the "best" conditions from the simple precursor **308** (reverse addition, HMPA, ^{t}BuOH, 0°C) gave interesting results.

Ketone **399** afforded two simple reduction products **422** (18%) and **423** (36%) which were confirmed by sodium borohydride reduction of the starting ketone **399** (Scheme 68). From the same cyclisation reaction, an inseparable mixture of apparently 3 cyclised products (~46%) was isolated. One of these products (approximately one third of the mixture) was a crystalline material and an X-ray structure was obtained which revealed that the crystalline product was *trans*-decalin **424**.



Scheme 68. Cyclisation products from keto-alcohol **399**.

The cyclisation of the other ketone **402** gave slightly different results. Again, simple reduction products **425** (7%) and **426** (36%) were obtained confirmed by sodium borohydride reduction of the starting ketone **402** (Scheme 69). Mixed with the less polar diol **426** was a crystalline product and X-ray analysis gave the same *trans*-decalin **424** as obtained from the cyclisation of the other ketone **45**. Finally a small amount of the 7-*endo* product **427** was isolated in a 5% yield.

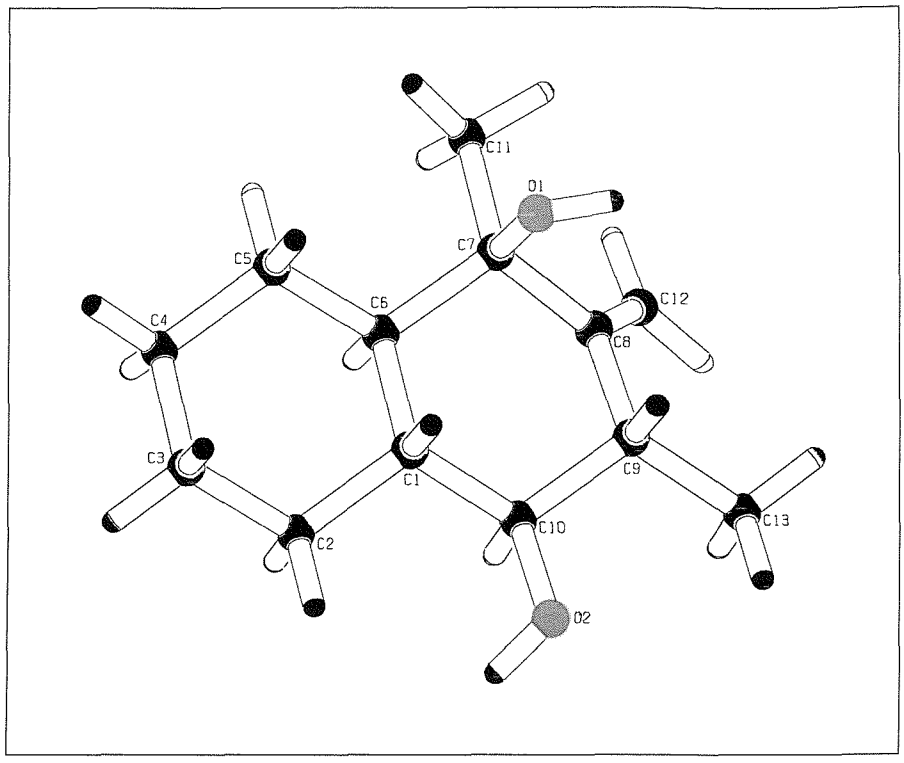
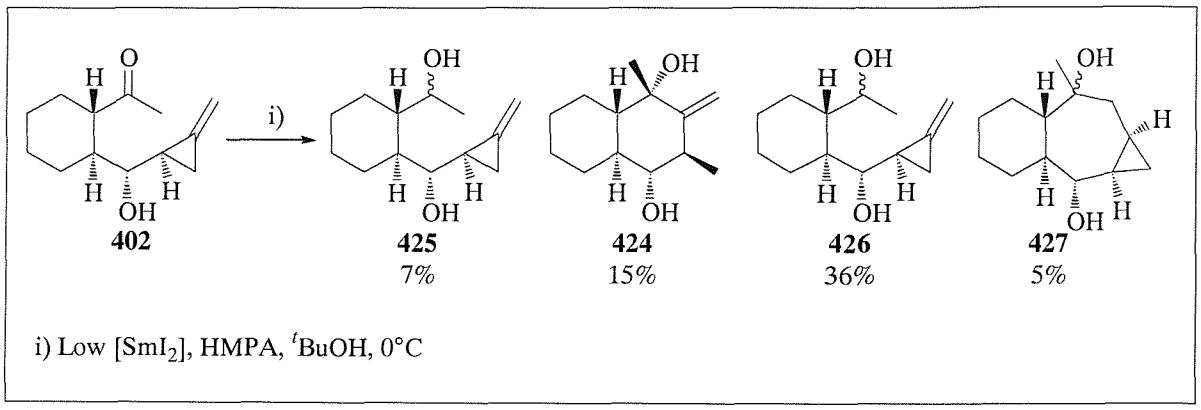


Figure 20. X-ray crystal structure of *trans*-decalin from the cyclisation of **399**.



Scheme 69. Cyclisation products from keto-alcohol **402**.

It is important to note that in decalin **424** both of the oxygens are on the same side of the ring indicating chelation to the metal centre. The two likely modes of chelation are **429** and **430**. By examining a model of these intermediates it becomes apparent that to cyclise the intermediate must adopt the right hand structure **430** (Figure 21). This shows why *trans* decalin **424** displays the stereochemistry derived from the ketone placing the methyl group of the ketone equatorially and the oxygen ketyl axially.

Both keto-alcohols **399** and **402** with different stereochemistry gave the same bicyclic product **424**. In the case of **399**, at least two other unidentified products were isolated

mixed with **424**. It is possible that these are other bicyclic products and are isomers of *trans* decalin **424** or 6,7 bicycles.

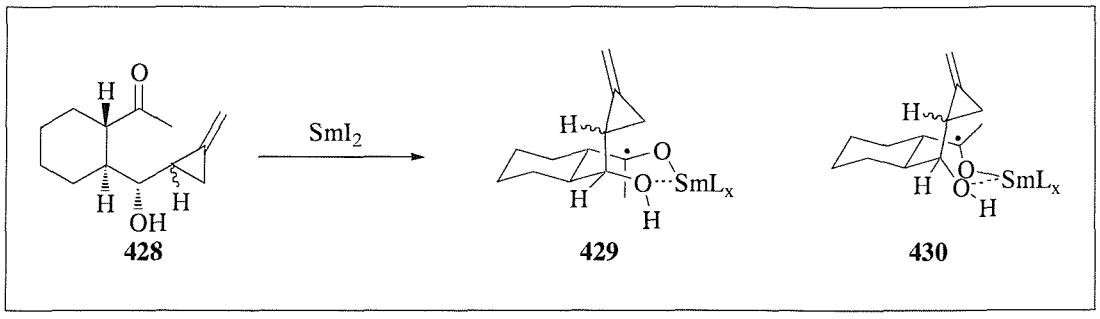
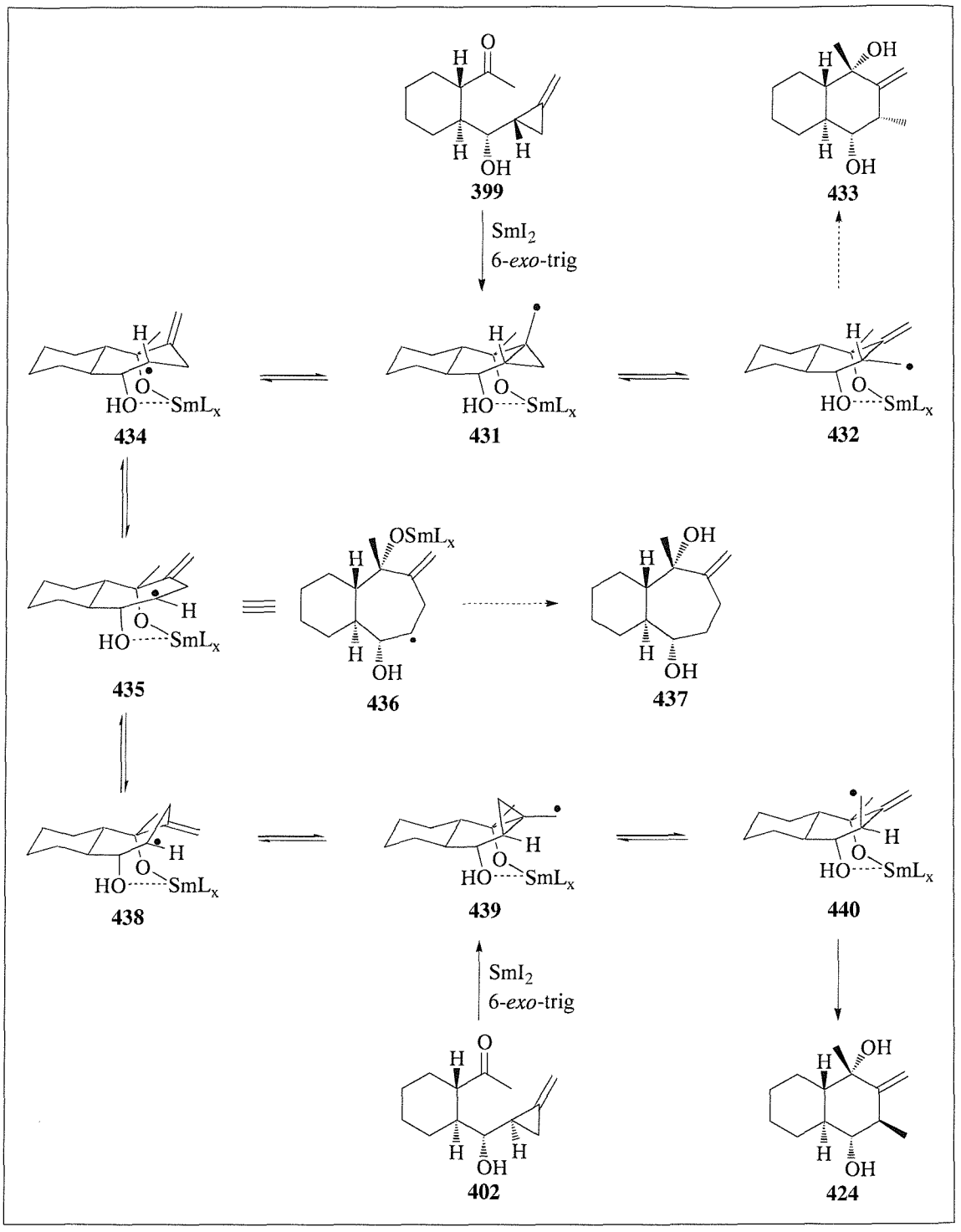


Figure 21. Chelation of the oxygens to the samarium metal centre.

It is not clear why ketone **399** does not solely give *trans* decalin **433** (Scheme 70). There may be a steric clash in **432** due to interactions of the methyl radical and the chelated samarium and its ligands. Whatever the reasons are, the cyclopropylcarbinyl radical **431** must undergo *endo* cyclopropyl ring-opening to form the 6,7 bicyclic intermediate **434**. This then twists and re-closes to form 6,6 cyclopropylcarbinyl radical **439** that is formed directly from the other ketone **402**. The *exo* ring-opening of this system, subsequent reduction and quenching gives the crystalline product **424** isolated from both cyclisations. Again, the reasons for **402** leading only to *trans* decalin **424** are not clear, but examining the necessary transition state **440** shows that the methyl radical is unlikely to interact with the chelated samarium and its ligands.

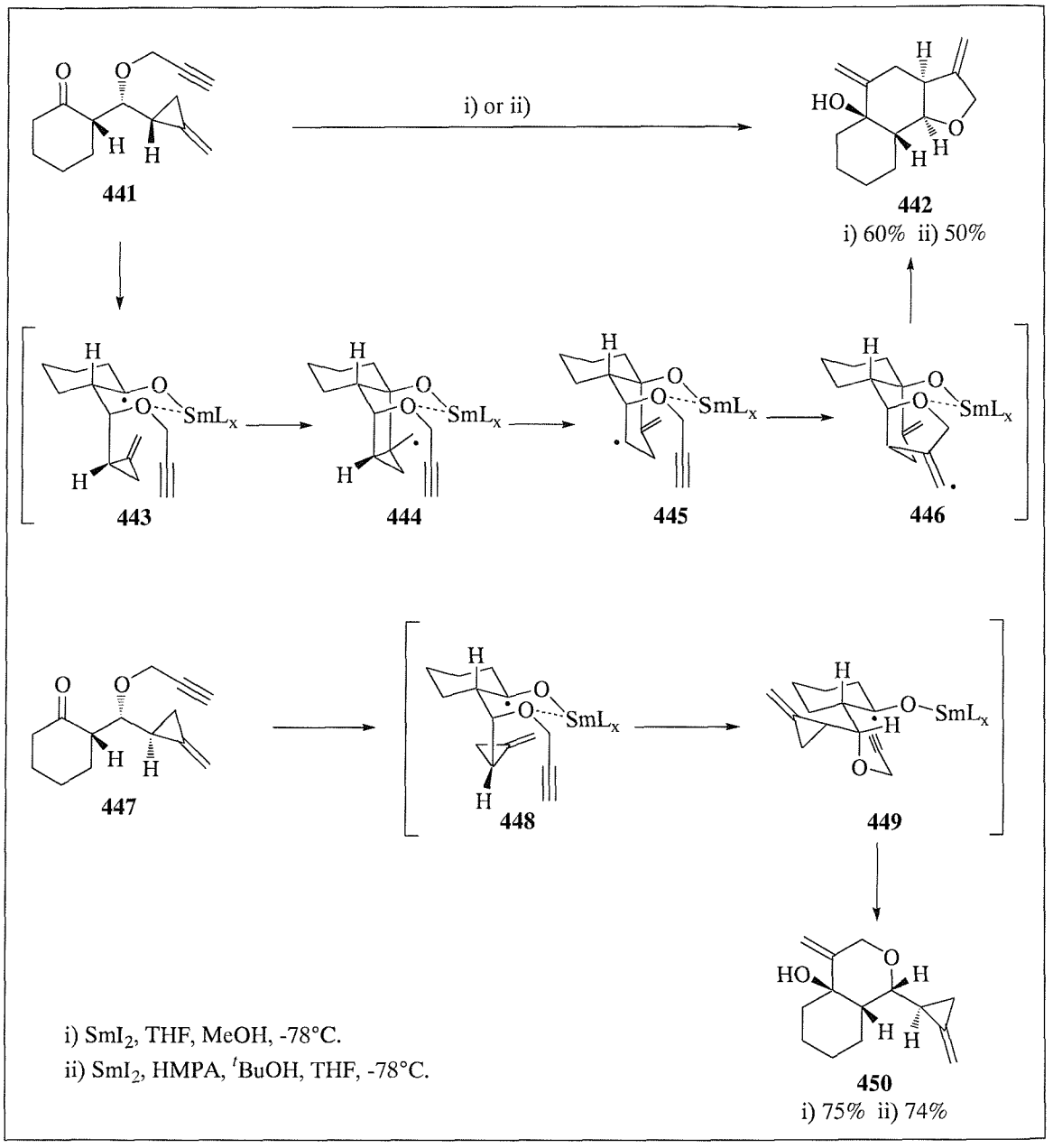
Another approach is that the cyclopropylcarbinyl radical **431** opens but the step is not energetically favourable due to poor orbital overlap and the preferable ring-opening is *via* the *endo* mode. The *exo* opening of cyclopropylcarbinyl radical **439** may be more favourable due to better orbital overlap. The preference for *trans* decalin product **424** over the potential 6,7 bicycle **437** is not unexpected as *trans* decalins are very stable systems and given the reversible nature of the cyclisation reaction the more thermodynamically stable product would be anticipated.



Scheme 70. Mechanism for formation of the *trans* decalin from two different ketones.

These sorts of chelated transition states have already been discussed (see section 1.1.5.4, chapter 1). Previous work by Watson[119] and Saint-Dizier[116] has demonstrated the effect of chelation on cyclisations with methylenecyclopropanes (Scheme 71) and (Scheme 72). For analogues **441** and **447** markedly different outcomes are obtained due to the stereochemistry of the methylenecyclopropane[119]. The desired tricycle **442** is obtained in

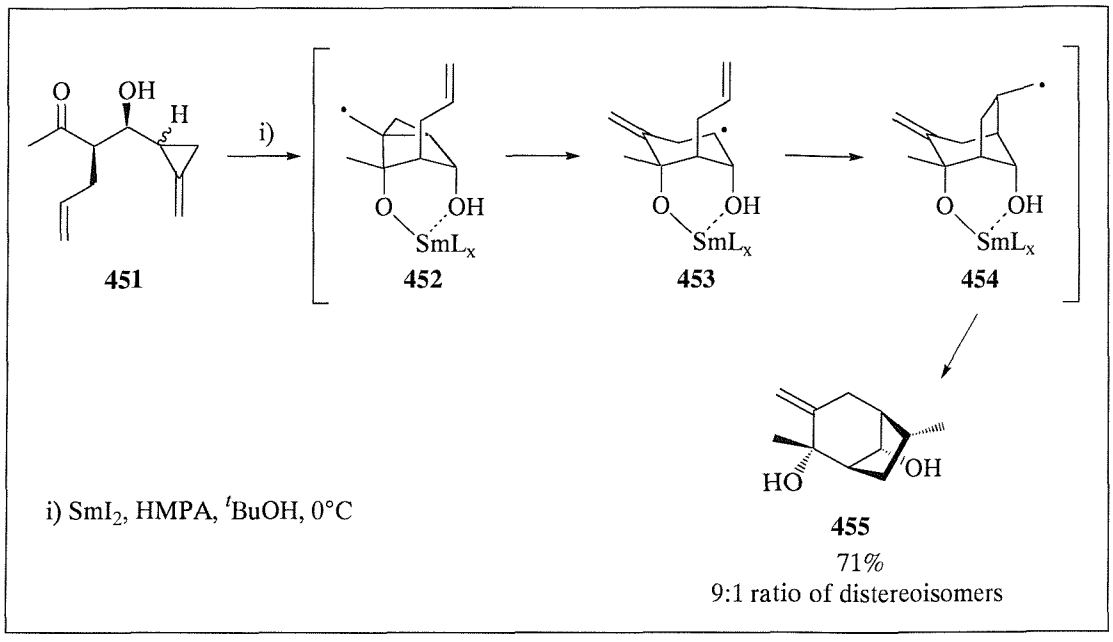
good yields from **441**, but with **447** the forming radical centre would eclipse the ketyl oxygen and hence this transition state **448** does not lead to any desired tricyclic products. Instead the chelation is broken to form **449** and the 6,6 bicycle **450** is isolated as the major product.



Scheme 71. Different cyclisation products from isomers differing at the methylenecyclopropyl position.

For simpler methylenecyclopropane systems the chelation is very important[116]. Bridged bicycle **455** was formed from transition states **452**, **453** and **454** under chelation control in

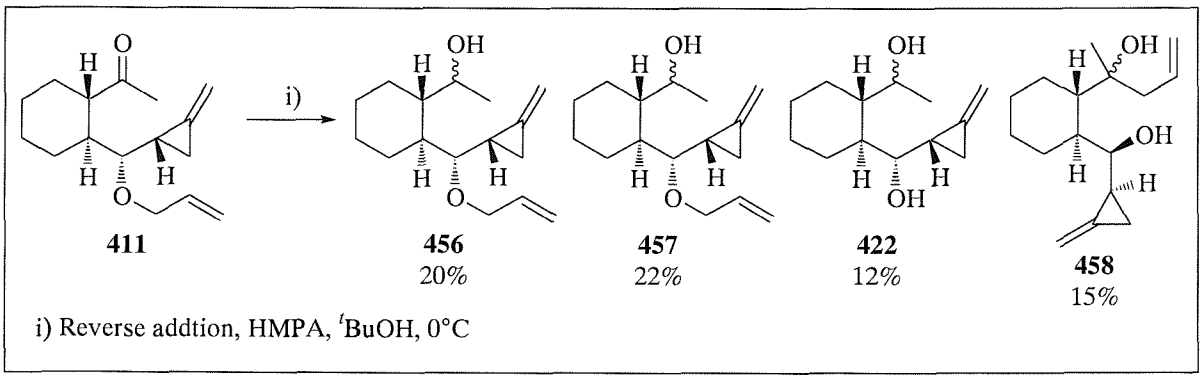
a high diastereomeric ratio. The removal of the hydroxyl group resulted in poor cyclisation reactions from which no discernable cyclic products could be isolated.



Scheme 72. Chelation control during cyclisation giving a high diastereomeric ratio in the cyclic product.

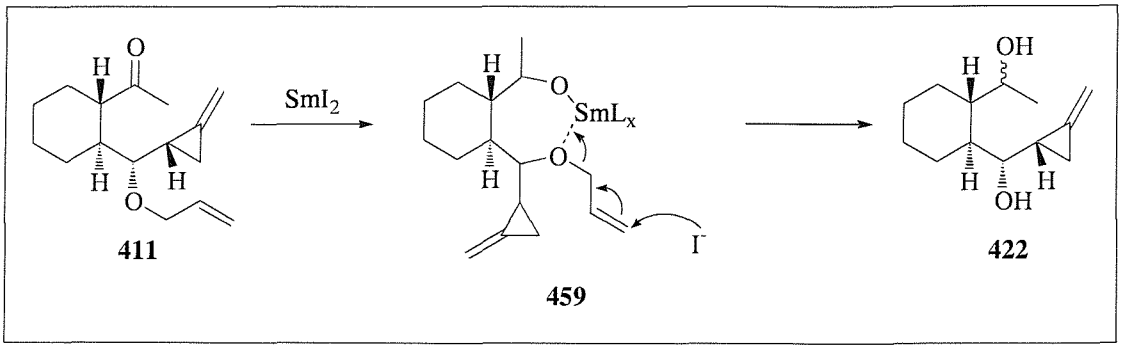
3.5.2 Cyclisation of Keto-allyl Ethers

The studies were carried using the "best" conditions: reverse addition, HMPA, ^{t}BuOH, 0°C. Ketone **411** gave simple reduction products **456** (20%) and **457** (22%) confirmed by sodium borohydride reduction of the starting ketone **411** (Scheme 73). Two other products were isolated: the (less polar) diol **422** (12%) observed from the cyclisation of keto-alcohol **399**; and tertiary alcohol **458** (15%). No products from an initial 6-*exo*- or 7-*endo*-trig cyclisation onto methylenecyclopropane were observed.



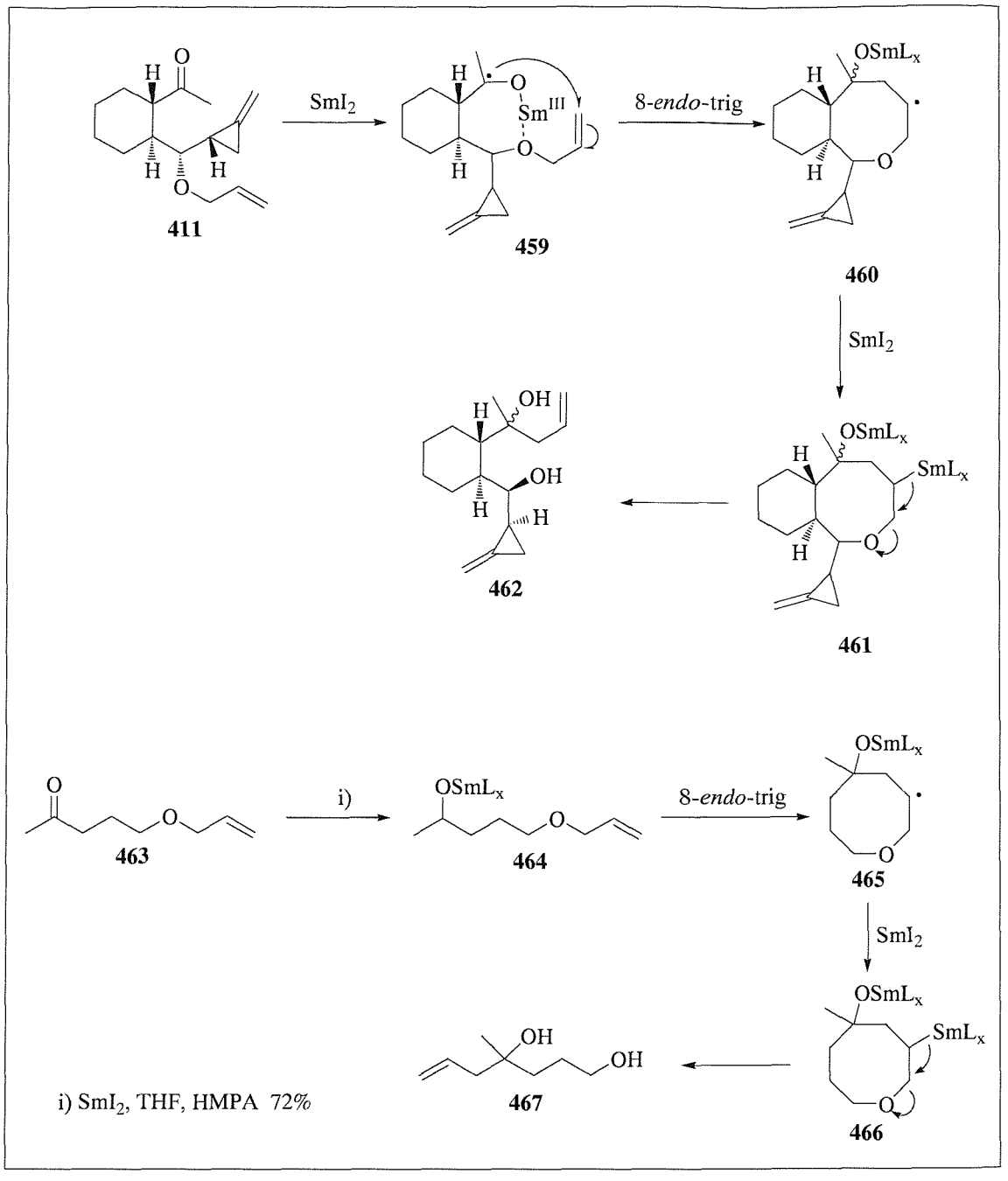
Scheme 73. Cyclisation products from allyl ether precursor **411**.

De-allylation of allyl ethers with Lewis-acids and a nucleophile is known[134]. $SmCl_3$ has been shown to catalyze electrochemical cleavage of allyl ethers[135]. The chelation of the samarium metal centre to both oxygens could promote the de-allylation with some residual iodide (Scheme 74). This could happen either before or after the reduction of the ketone, but it is more likely that the de-allylation occurs after reduction of the ketyl radical to the anion. If the de-allylation occurred before the ketyl radical was reduced, then the chance of some cyclisation onto methylenecyclopropane arises. No evidence was obtained for any other products from the cyclisation of alcohol precursor **399**. However, the conformation that intermediate **459** adopts may not allow successful cyclisation and the reduction step may be faster than the necessary re-organisation steps. The exact mechanism remains unknown.



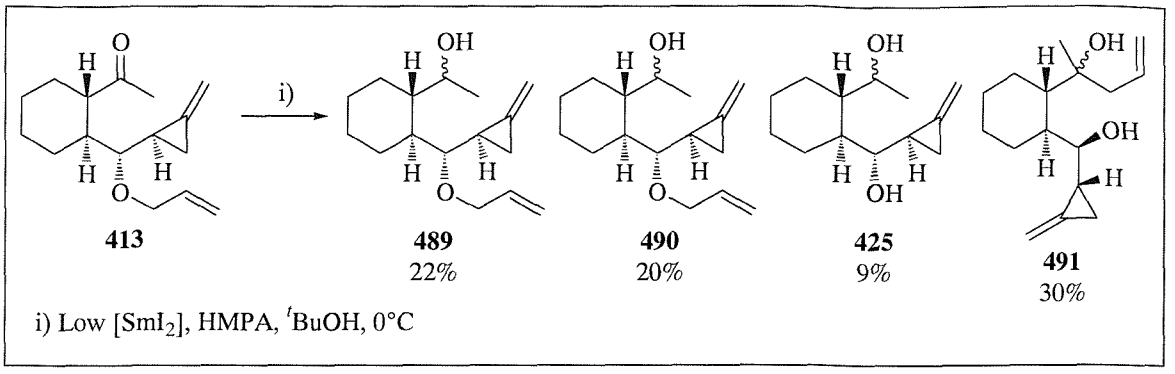
Scheme 74. Possible mechanism for the de-allylation process.

The transfer of the allyl group occurs *via* a radical-anion crossover process. It requires an initial 8-*endo*-trig cyclisation to form eight-membered ring intermediate **460**. After the reduction of the secondary radical to the anion **461**, the transfer can be completed. It is possible that the process takes place whilst the two oxygens are chelated to the samarium metal centre. However, the stereochemistry of the tertiary alcohol was not determined. In the absence of all of the relative stereochemistries, evidence for any transition state (with both oxygens chelated or otherwise) has no firm basis and so structures have not been suggested. This transfer process is known from work by Molander[59]. Allyl ether **463** was treated with samarium iodide and HMPA. After an 8-*endo*-trig cyclisation followed by fragmentation, tertiary alcohol **467** was isolated in very high 72% yield.



Scheme 75. Mechanism for the formation of the unexpected products **462**.

Cyclisation studies on the other allyl ether precursor **413** gave similar results (Scheme 76). Simple reduction alcohols **489** (22%) and **490** (20%), both confirmed by sodium borohydride reduction of starting ketone **413**; de-allylated diol product **425** (9%); and allylic group transfer product **491** (30%) were isolated. Again, no products from an initial 6-*exo*- or 7-*endo*-trig cyclisation onto methylenecyclopropane were observed.



Scheme 76. Cyclisation products from allyl ether precursor **413**.

Clearly the presence of the allyl group must hinder the transition state that allowed the formation of the *trans* decalin bicycle **424**. The lack of evidence for cyclisation onto methylenecyclopropane in both allyl ether cases may also suggest that some coordination to the free alcohol by the samarium metal centre may be necessary in this type of constrained system.

3.6 Conclusions

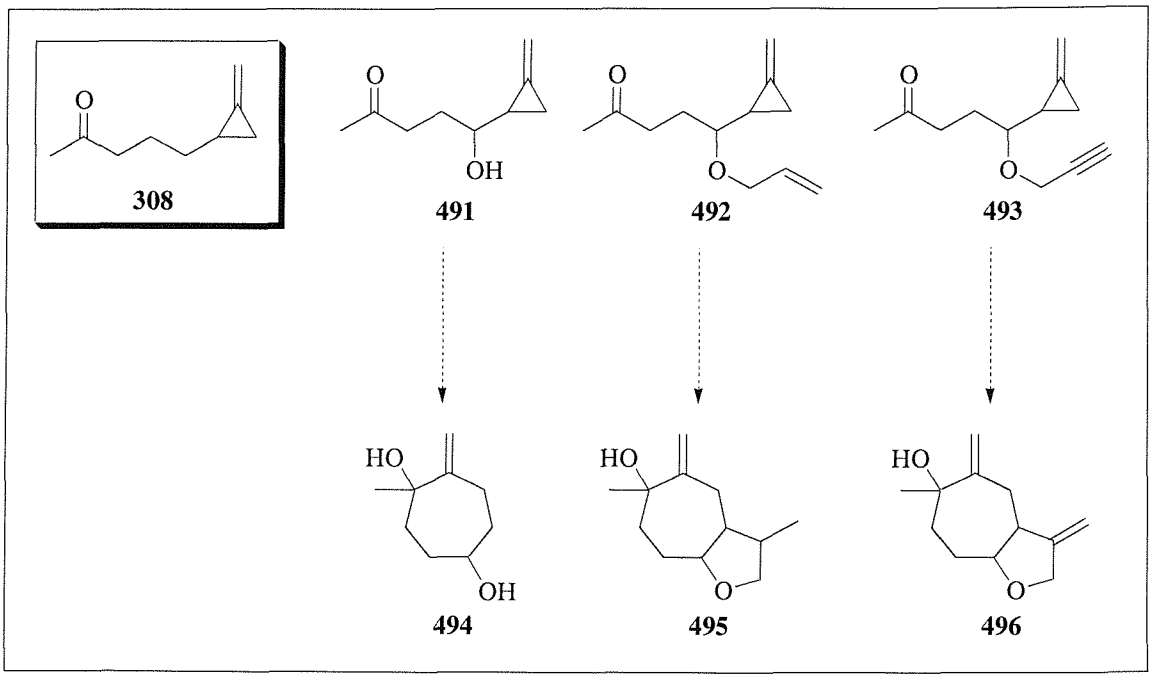
Synthesis of precursors that incorporated a gem dimethyl functionality was not possible and so cyclisation studies could not be investigated. The aromatic series proved unproductive in increasing the yield of cyclised products. The cyclohexyl precursors gave good overall yields but the desired bi- and tri-cyclic products were not obtained. Without the possibility to explore cyclisations of the non-OH containing precursor **420**; the propargyl ether analogues **415**; or any of the analogous *cis* series, the full picture cannot be gained. Ultimately, constraining the system by restricting the free movement of the carbon-chain backbone did not produced the desired results. However, the evidence for chelation of the alcohol/allyl functionalities to the ketyl-bound samarium is strong. The influence of the ability to chelate in a 7-membered ring for these systems is important.

Chapter Four

4 Acyclic Precursors

4.1 Aims

The constraints imposed by the benzene and cyclohexyl rings did not have the desired effect. However, the inclusion of an alcohol or ether moiety did appear to affect the outcome of the cyclisation reaction by chelating to the samarium metal centre. New precursors were targeted that would allow the effects of alcohol or ether functionalities to be probed (Scheme 77). These new precursors **491**, **492** and **493** were based on the original simple precursor **308**. The allyl and propargyl analogues **492** and **493** would theoretically afford bicyclic products **495** and **496** following attack on methylenecyclopropane *via* 6-*exo*-trig mode; *endo* ring-opening; and finally trapping the radical with the allyl or propargyl group.

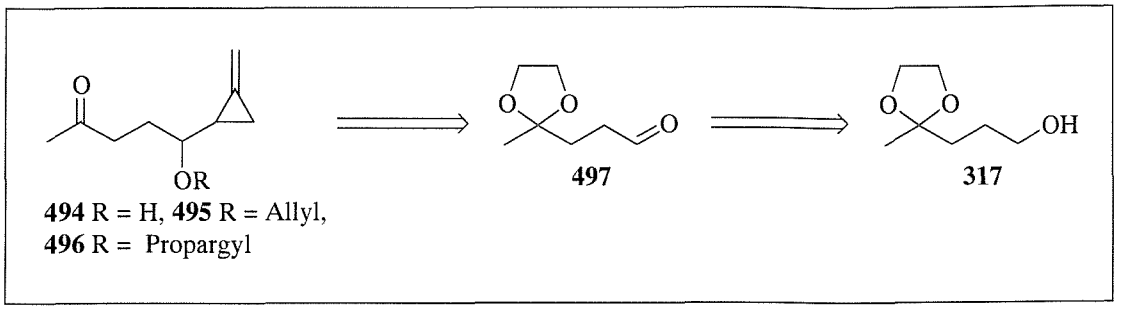


Scheme 77. Precursors allowing probing of the effects of alcohol and ethers.

4.2 Synthesis of Precursors

Retrosynthetic analysis for all three led back to alcohol **317** used in the synthesis of the simple precursors **308** and **309** in Chapter 2. All three targets could be prepared from the

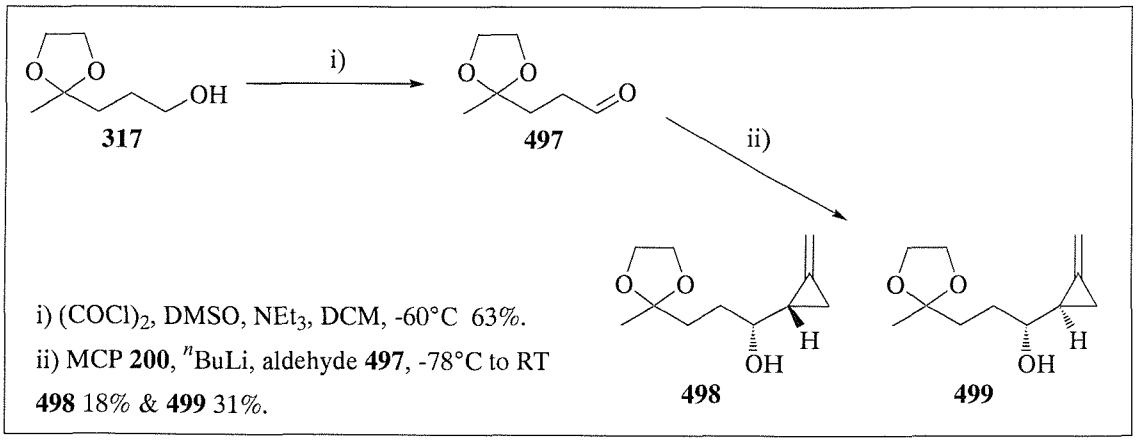
product of addition of methylenecyclopropyl anion to aldehyde **497** derived from alcohol **317** (Scheme 78).



Scheme 78. Retrosynthetic analysis of alcohol and ether precursors.

4.2.1 Preparation of Alcohol Precursors

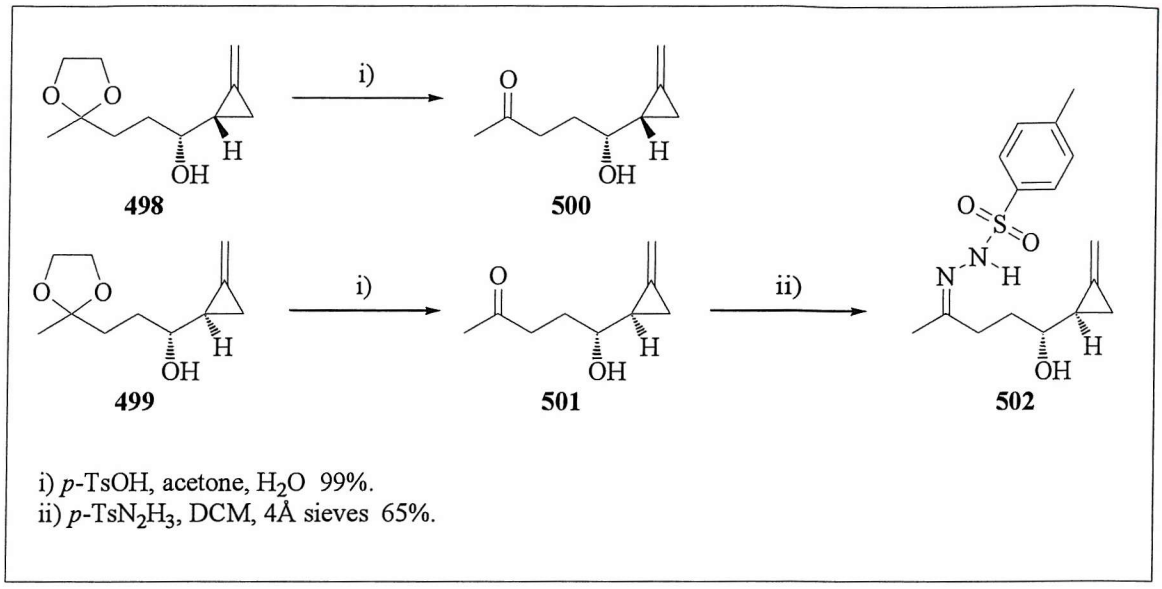
The synthesis began with the Swern oxidation[136] of alcohol **317** (Scheme 79). Aldehyde **497** was isolated in a good 63% yield. The addition of methylenecyclopropyl anion to aldehyde **497** afforded two alcohols **498** (18%) and **499** (31%) that were separable by column chromatography. The yields were lower than expected but acceptable nonetheless. It is possible that the methylenecyclopropyl anion could abstract the hydrogen α to the carbonyl and aldol reaction side products could be generated[85].



Scheme 79. Preparation of key alcohol intermediates **9** and **10**.

The more polar product was the *syn* alcohol proved by derivatisation of the keto-alcohol from the deprotection of the ketal **499**. Both alcohols were deprotected using *p*-TsOH to afford precursors **500** (99%) and **501** (99%) in near quantitative yields (Scheme 80). Ketone **501** was reacted with *p*-tosyl hydrazine. The hydrazone product **502** was

fortunately crystalline allowing determination of the relative stereochemistry of keto-alcohols **500** and **501** and any related structures (Figure 22).



Scheme 76. Preparation of keto-alcohol cyclisation precursors and derivatisation to form crystalline hydrazone.

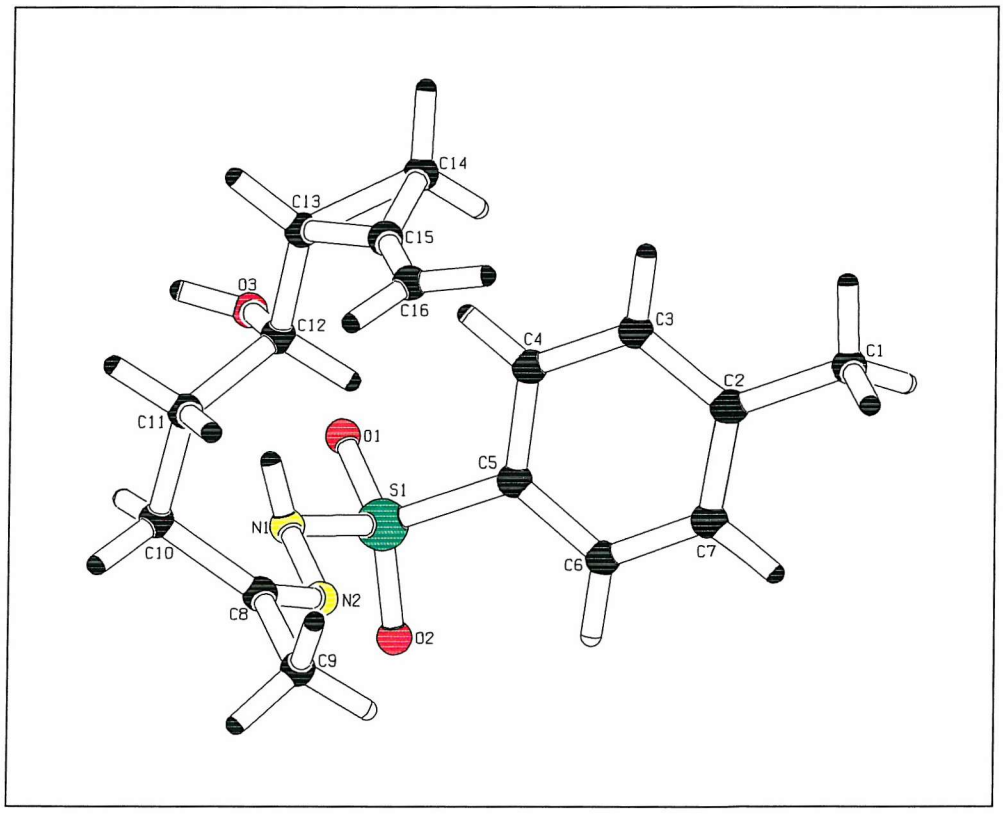
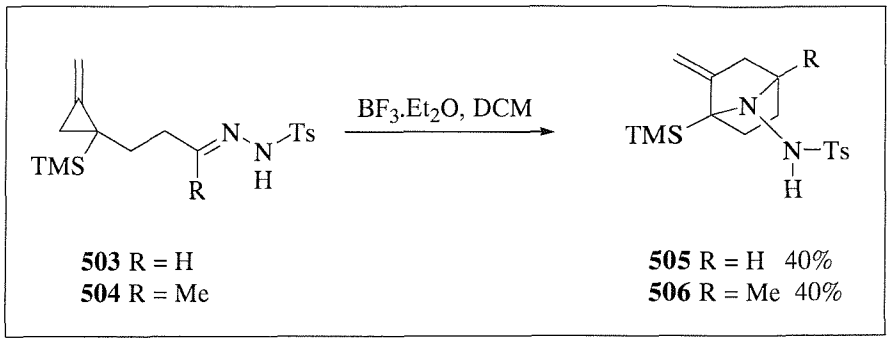


Figure 22. X-ray crystal structure of hydrazone product **502**.

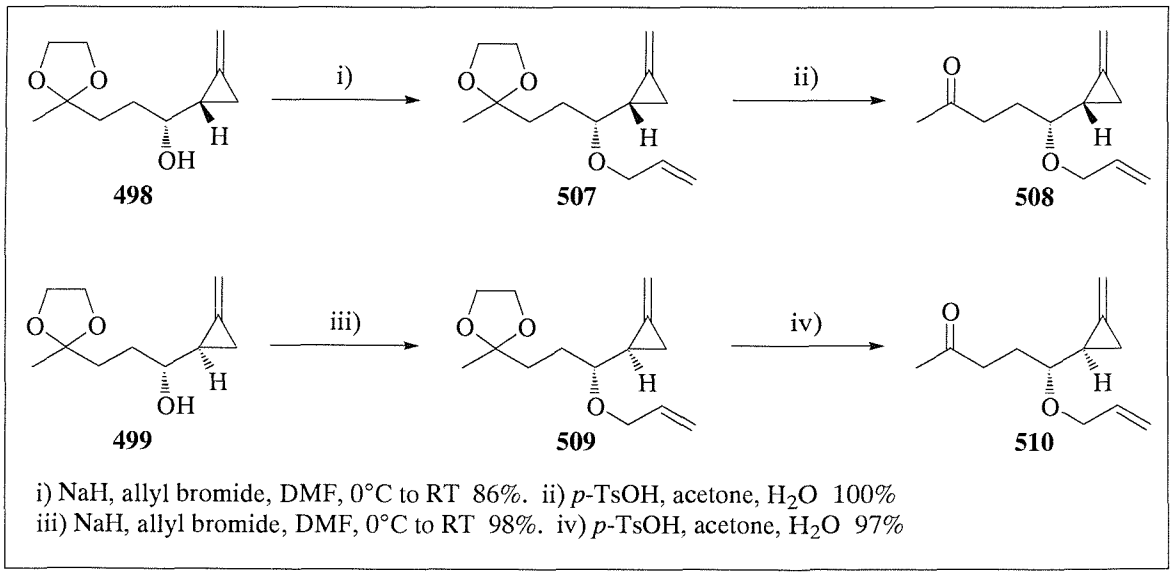
The hydrazide was slow to dissolve in $CDCl_3$ and mild heating used to obtain a solution with which to obtain NMR data caused decomposition. Cyclisation reactions with hydrazides and methylenecyclopropanes using Lewis acids have been carried out by Patient[137] (Scheme 81). It is possible that the acidic chloroform and the mild heating brought about a cyclisation or some other unwanted reaction.



Scheme 81. Cyclisation of methylenecyclopropanes onto hydrazones with Lewis acids.

4.2.2 Preparation of Allyl Ether Precursors

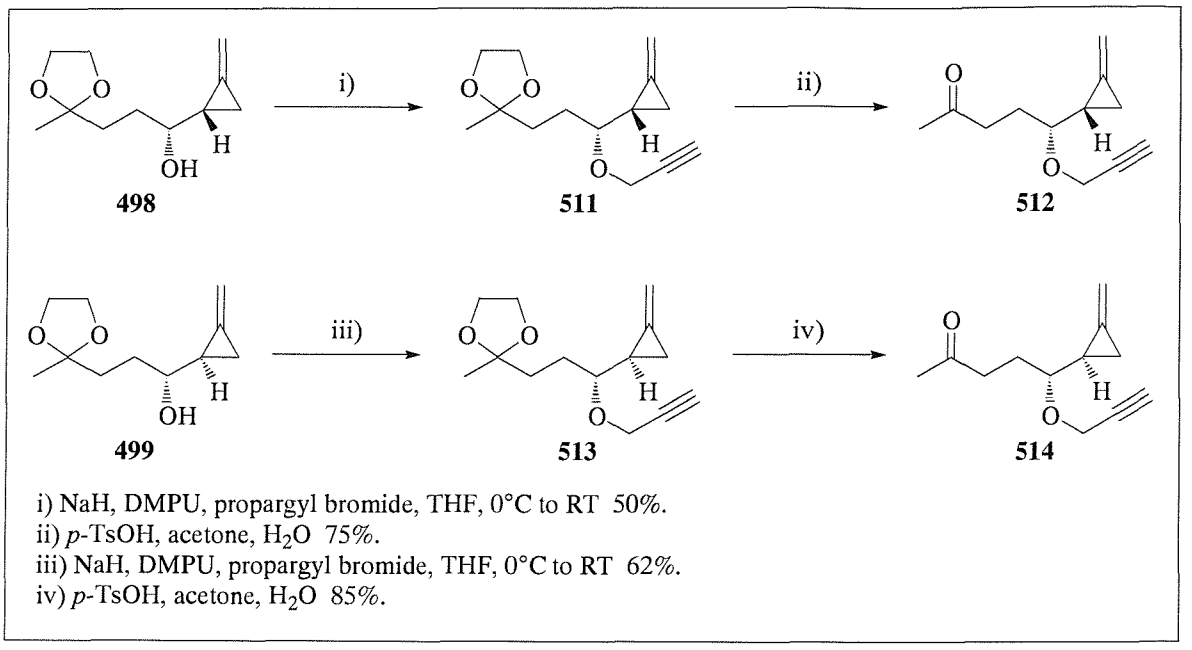
The preparation of the allyl precursors was uncomplicated (Scheme 82). Treatment of each alcohol with sodium hydride and allyl bromide fructiciously evolved the allyl ethers in excellent yields. The deprotection was standard and quantitative or near quantitative yields of the precursors **508** and **510** were obtained.



Scheme 82. Synthesis of allyl ether precursors.

4.2.3 Preparation of Propargyl Ether Precursors

The first step in the preparation of the propargyl precursors was problematic and poor results were obtained with potassium hydride, 18-crown-6 and propargyl bromide. An acceptable reaction[124] using sodium hydride, DMPU and propargyl bromide was used successfully but this was not an ideal method (Scheme 83). The reaction was clean giving only the desired propargyl ethers **511** and **513** and recovered starting materials **498** and **499**. The amount of alcohol converted seemed to depend on the quality of the DMPU. Fresh distillation was therefore necessary to avoid moisture problems and the maximum absolute yield of propargyl ether was 50% and 62%.



i) NaH, DMPU, propargyl bromide, THF, 0°C to RT 50%.
ii) *p*-TsOH, acetone, H_2O 75%.
iii) NaH, DMPU, propargyl bromide, THF, 0°C to RT 62%.
iv) *p*-TsOH, acetone, H_2O 85%.

Scheme 83. Preparation of propargyl ether precursors.

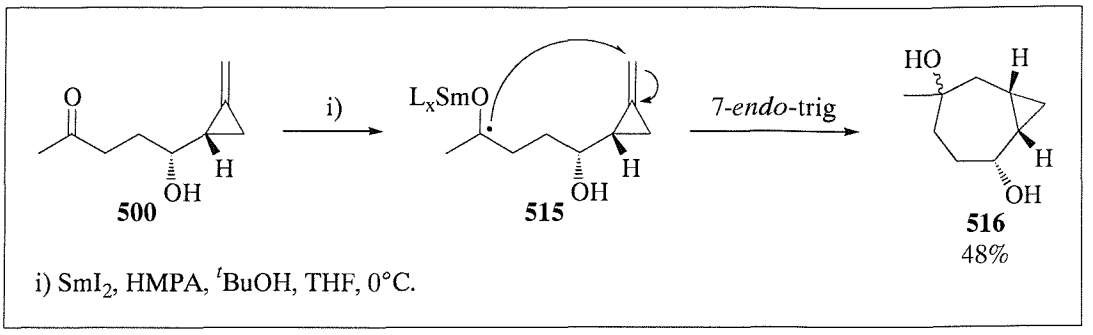
Nevertheless, sufficient quantities of ketals **511** and **513** were collected to allow progress in the synthesis. The deprotections proceeded well and the cyclisation precursors were isolated in very good 75% and 85% yields for **512** and **514** respectively.

4.3 Cyclisation Studies

4.3.1 Cyclisation of Keto-alcohol Precursors

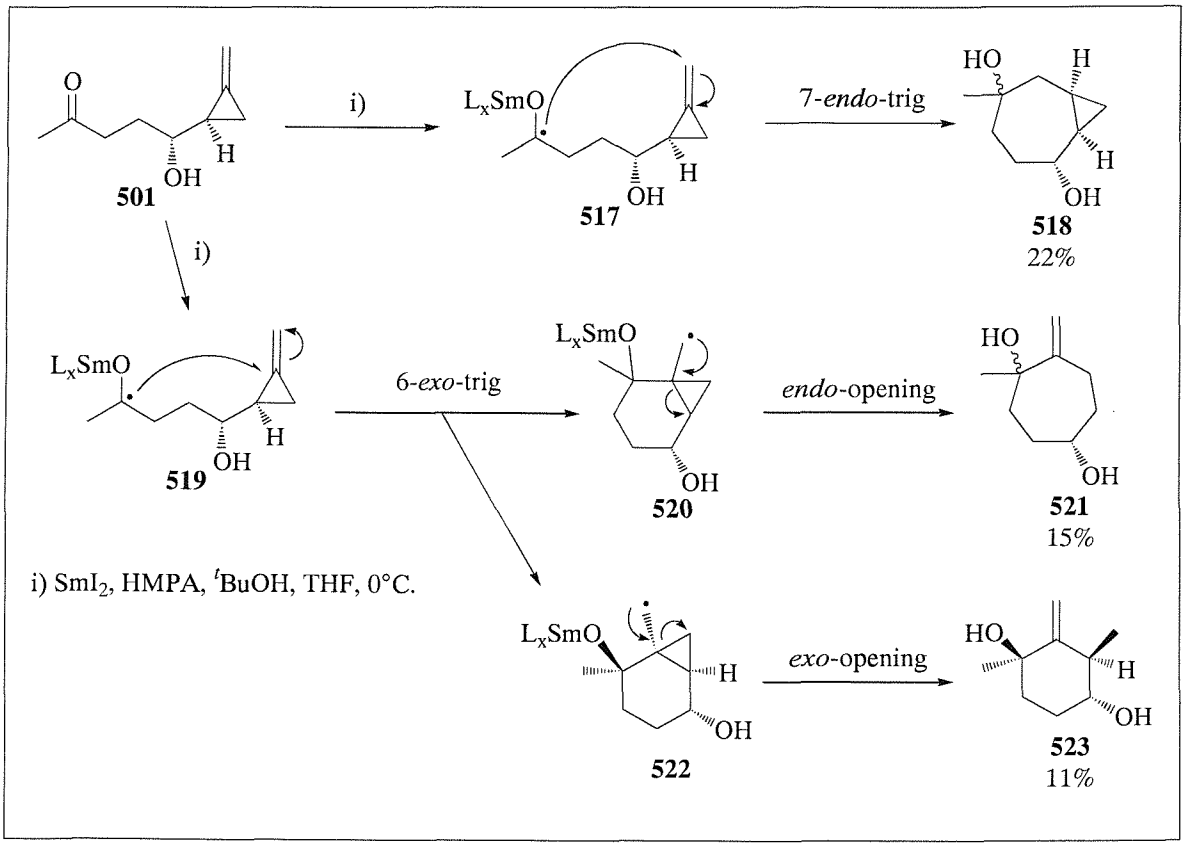
Cyclisation studies on the alcohol precursors were carried out using the "best" conditions of reverse addition, HMPA, ^{t}BuOH, THF, 0°C. The two ketones gave very different

results. Ketone **500** gave 7-*endo*-trig bicycle **516** as the sole product in 48% yield (Scheme 84). The relative stereochemistry of the cyclopropyl ring to the secondary alcohol was determined from the starting material (unless 1,5 H-abstraction occurs to scramble the stereochemistry), but the stereochemistry of the tertiary alcohol could not be determined.



Scheme 84. Cyclisation of *anti* keto-alcohol.

However, ketone **501** gave a more complex mixture of cyclisation products (Scheme 85).



Scheme 85. Cyclisation of *syn* keto-alcohol.

The total yield was the same as for the other precursor **500**, but now products **521** and **523** formed by an initial 6-*exo*-trig cyclisation were isolated as well as the 7-*endo*-trig bicycle **518**.

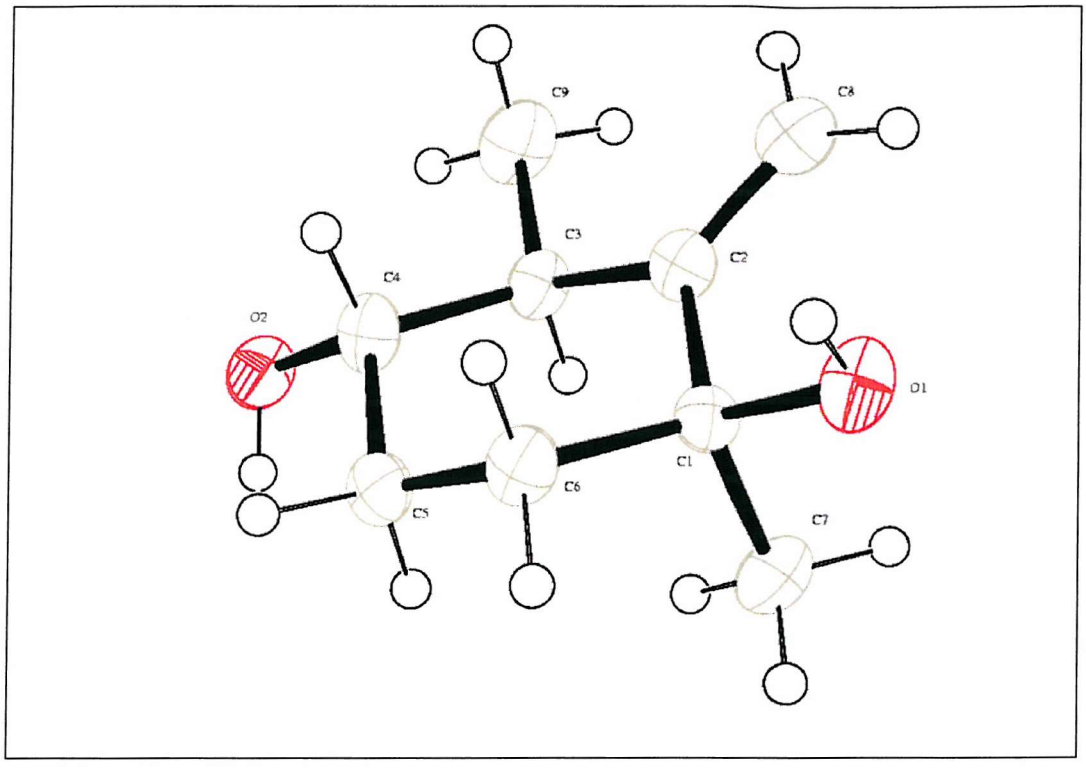
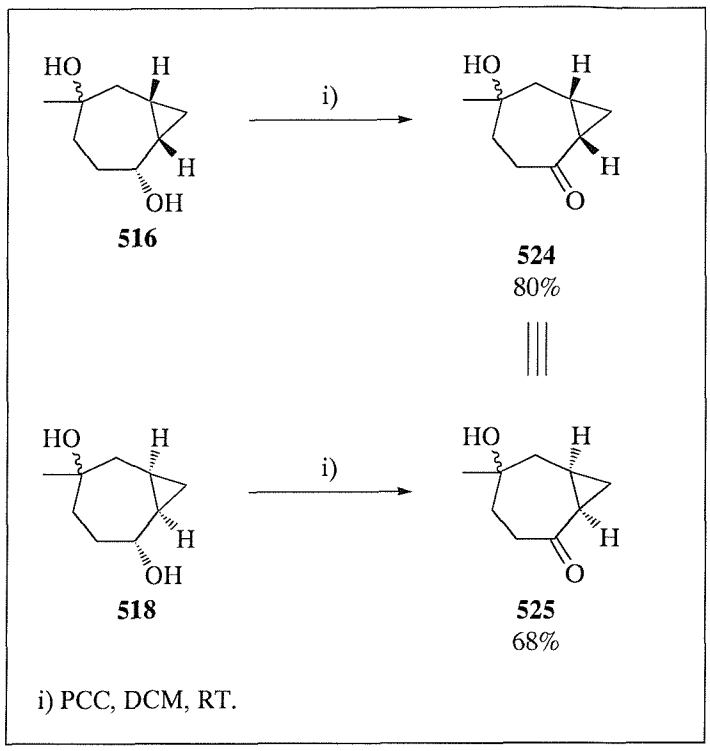


Figure 23. X-ray crystal structure of methylecyclohexane cyclisation product **523**.

Again, barring scrambling due to 1,5 H-abstraction, the relative stereochemistry of the cyclopropane ring and secondary alcohol in **518** must still arise from the starting material but the tertiary alcohol's stereochemistry could not be determined. Both 7-*endo*-trig products **516** and **518** were oxidized separately to afford the relevant ketone **524** and **525** in good yields (Scheme 81). Both precursors gave ketone products with identical ^{1}H and ^{13}C NMR spectra. Therefore their relative stereochemistry in the ketone must be the same, *i.e.* the position of the tertiary alcohol relative to the cyclopropane ring in the cyclisation products **516** and **518** is the same. Attempts to form crystalline hydrazone products from **524/525** failed and so the relative stereochemistry remains unknown.



Scheme 86. Oxidation of 7,3 bicycles.

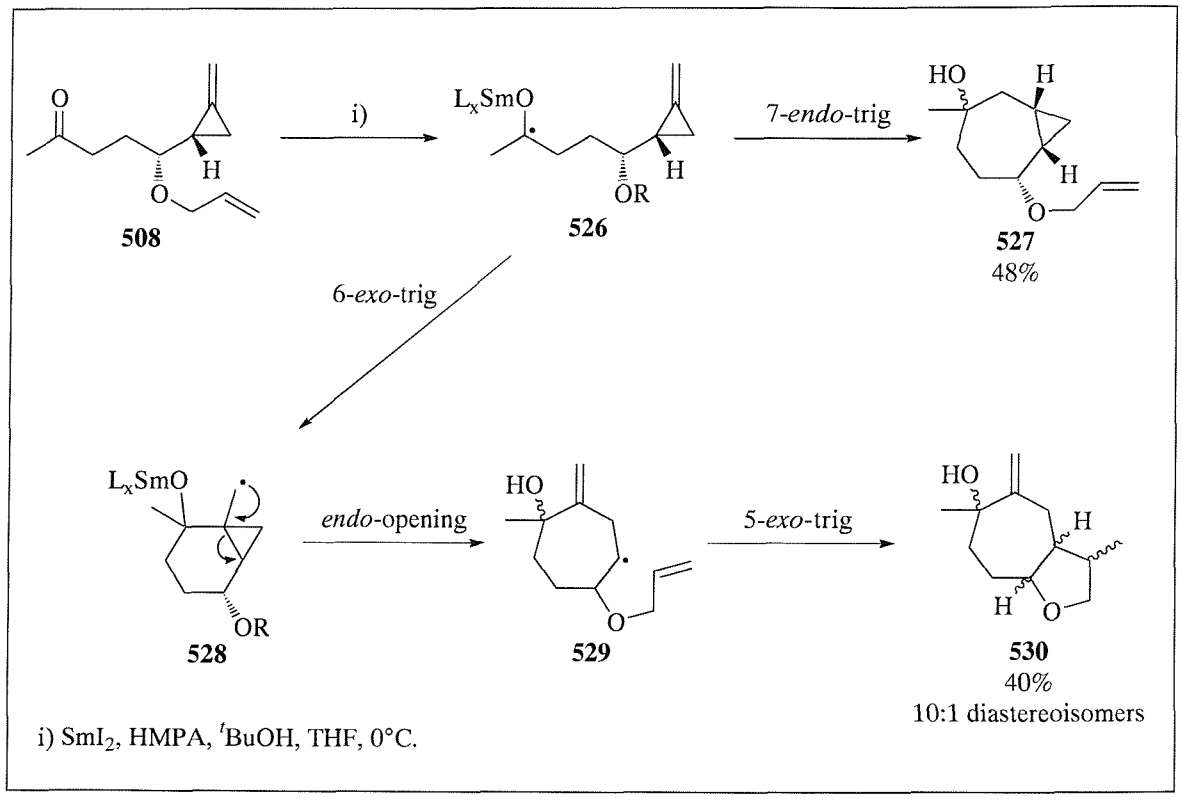
The desired methylenecycloheptane **521** was isolated from the cyclisation of **501**. Attempts to determine the stereochemistry of this product failed. Fortunately the other product from an initial 6-*exo*-trig cyclisation, methylenecyclohexane **523**, was isolated as a crystalline solid. The X-ray structure revealed that both alcohols are equatorial and *trans* to each other on the cyclohexane ring. Therefore, both oxygen atoms could not have been co-ordinated to the samarium metal centre during the cyclisation and ring-opening process.

The inclusion of the alcohol moieties onto the simple precursor **308** has dramatically altered the results of the cyclisation reaction (see section 2.3, chapter 2). No starting material was recovered, nor was any simple reduction product and the overall yields were improved. The stereochemistry complicates the picture with both isomers behaving differently, but in each case the 7-*endo*-trig was the major product. The difference in stereochemistry is very important. Precursor **500** gives exclusively the 7-*endo*-trig product, whereas the preference for 7-*endo* over 6-*exo* products is less defined from precursor **501**. The effects of chelation to samarium by both oxygen atoms, if any occurs, are unclear and there is insufficient evidence to make specific conclusions on how this may alter the transition states for cyclisations.

4.3.2 Cyclisation of Keto-allyl Ether Precursors

Cyclisation studies on the allyl ether precursors were carried out using the "best" conditions of reverse addition, HMPA, ^{t}BuOH, THF, 0°C.

Precursor **508** gave two products in an excellent overall 88% yield (and starting material recovered in 6% yield) (Scheme 87). 7-*endo*-trig product **527** was the major product isolated in 48% yield, but pleasingly the desired 7,5 bicycle **530** was isolated in 40% yield as a 10:1 mixture of diastereoisomers. The stereochemistry of either of the products could not be fully determined. However, the relative stereochemistry of cyclopropyl ring and allyl ether in **527** is most likely to be identical to the precursor. The 7,5 bicycle **530** could be either *cis* or *trans* fused at the ring junctions (although later work strongly suggests that it is *cis* fused, see section 5.3.3, chapter 5). It is unclear what the difference between the diastereoisomers is. The orientation of either methyl group is the most likely difference.



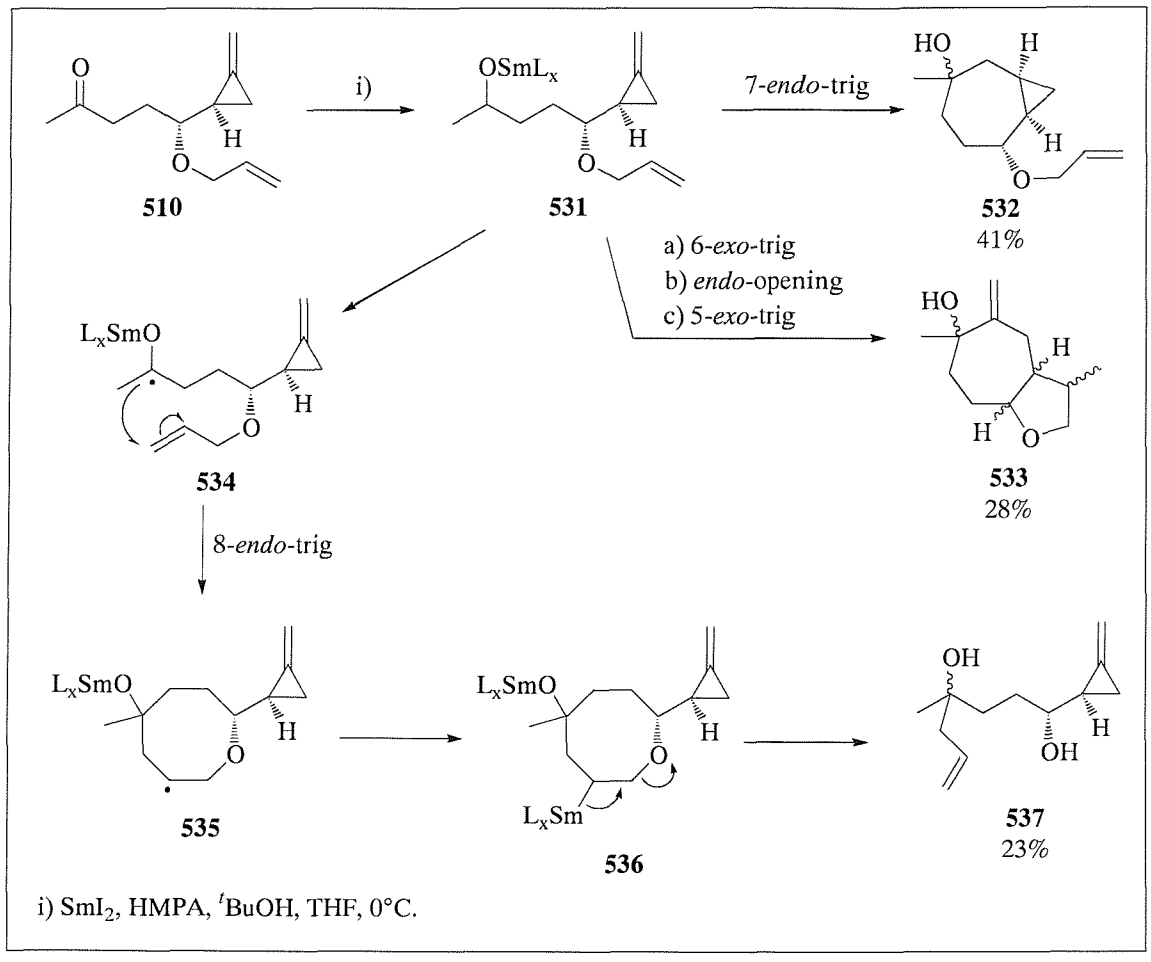
Scheme 87. Cyclisation of *anti* allyl ether.

The *syn* precursor **510** afforded a slightly different product profile (Scheme 88). The overall yield was again an excellent 92% (with starting material recovered in 3% yield). An inseparable mixture of 7,3- and 7,5- bicycles **532** and **533** was isolated giving 41% and 28% yields respectively. Comparison of the mixture to the spectrum of the individual 7,5

bicycle **530** prepared from *anti* precursor isomer **508** revealed that the two bicycles **530** and **533** were not the same isomer.

No methylenecyclohexane products were found but a new tertiary alcohol **537** was isolated in a 23% yield. This product presumably arises from an 8-*endo*-trig cyclisation onto the allyl ether, followed by elimination (see chapter 3 section 3.4.3.2).

Moving from the alcohol functionality in precursors **500** and **501** to an allyl ether has had a marked difference. Now the *anti* precursor **508** gives both 7-*endo* and 6-*exo* products **527** and **530**. The *syn* precursor **510** does not appear to favour 6-*exo* cyclisation onto the methylenecyclopropane: the major product being the 7,3 bicycle **532**; the yields of 6-*exo* **533** and 8-*endo* **537** products are fairly similar.

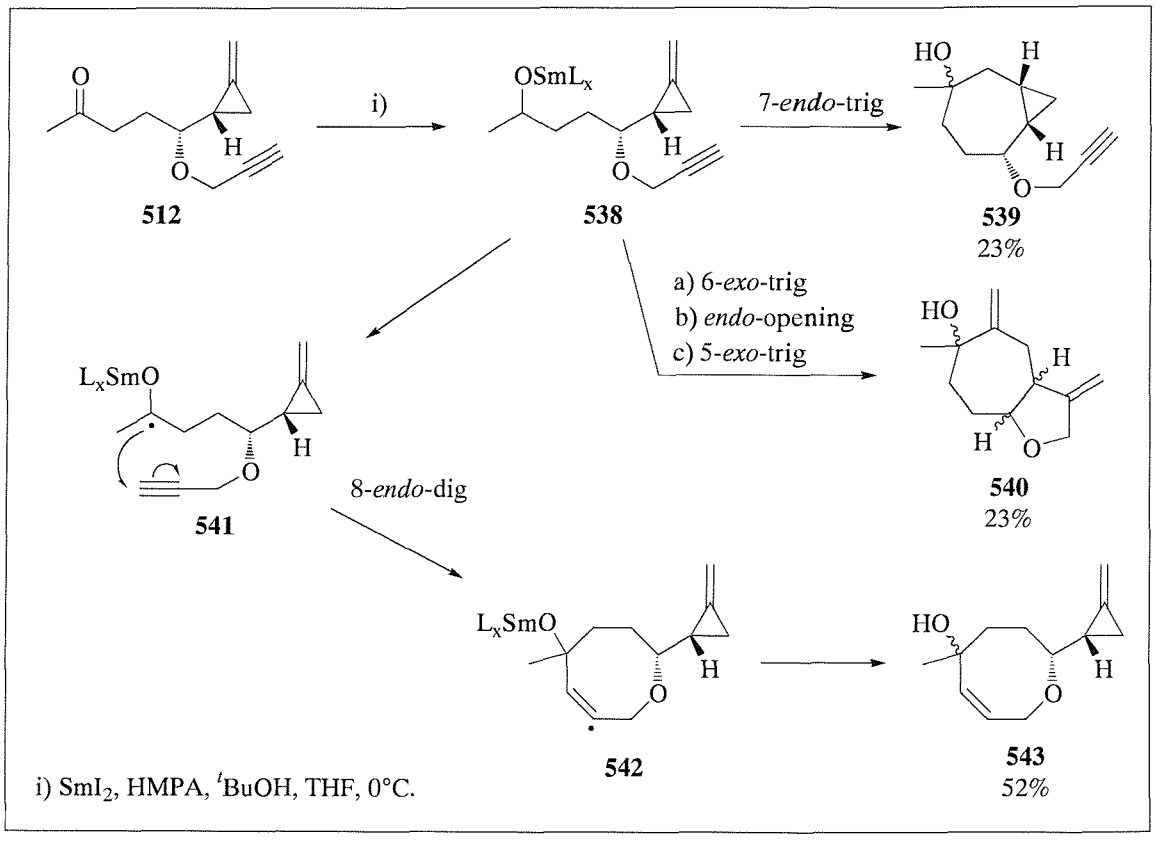


Scheme 88. Cyclisation of *syn* allyl ether.

4.3.3 Cyclisation of Keto-propargyl Ether Precursors

Cyclisation studies on the propargyl ether precursors were carried out using the "best" conditions of reverse addition, HMPA, ^{t}BuOH, THF, 0°C.

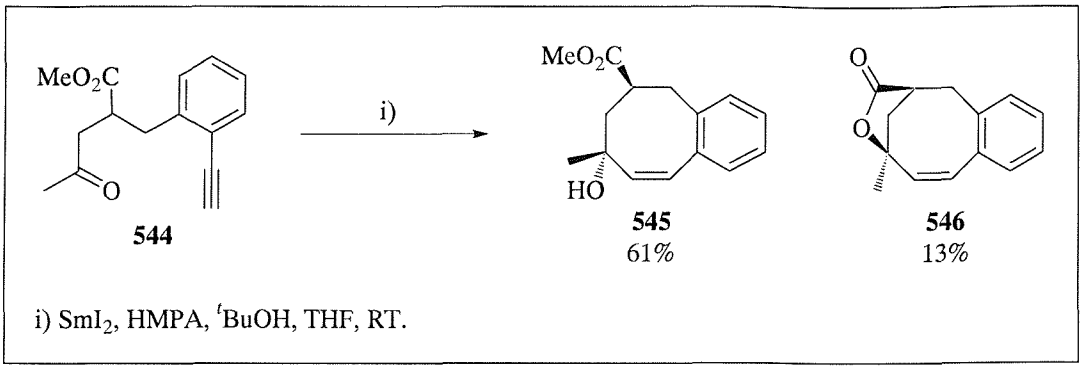
Precursor **512** gave three products in a near quantitative conversion (95%) of the starting material (recovered 2% yield) (Scheme 89). However, the nature of the products was unexpected. The 7,3 bicycle **539** and 7,5 bicycle **540** from 7-*endo*-trig and 6-*exo*-trig cyclisations onto methylenecyclopropane were obtained as an inseparable mixture, with a 23% yield for each component. (The structures were assigned based on comparisons with the products from the cyclisations of precursors **508**, **510** and **514**.) The highest yielding product was oxocine **543** isolated in 52% yield. The stereochemistries of the products unfortunately could not be determined.



Scheme 89. Cyclisation of *anti* propargyl ether.

Oxocine **543** must have arisen from an 8-*endo*-dig cyclisation onto the terminal end of the propargyl group. The transference of the propargyl group does not occur because vinyl radical intermediate **542** is highly reactive and abstracts a hydrogen atom from the solvent

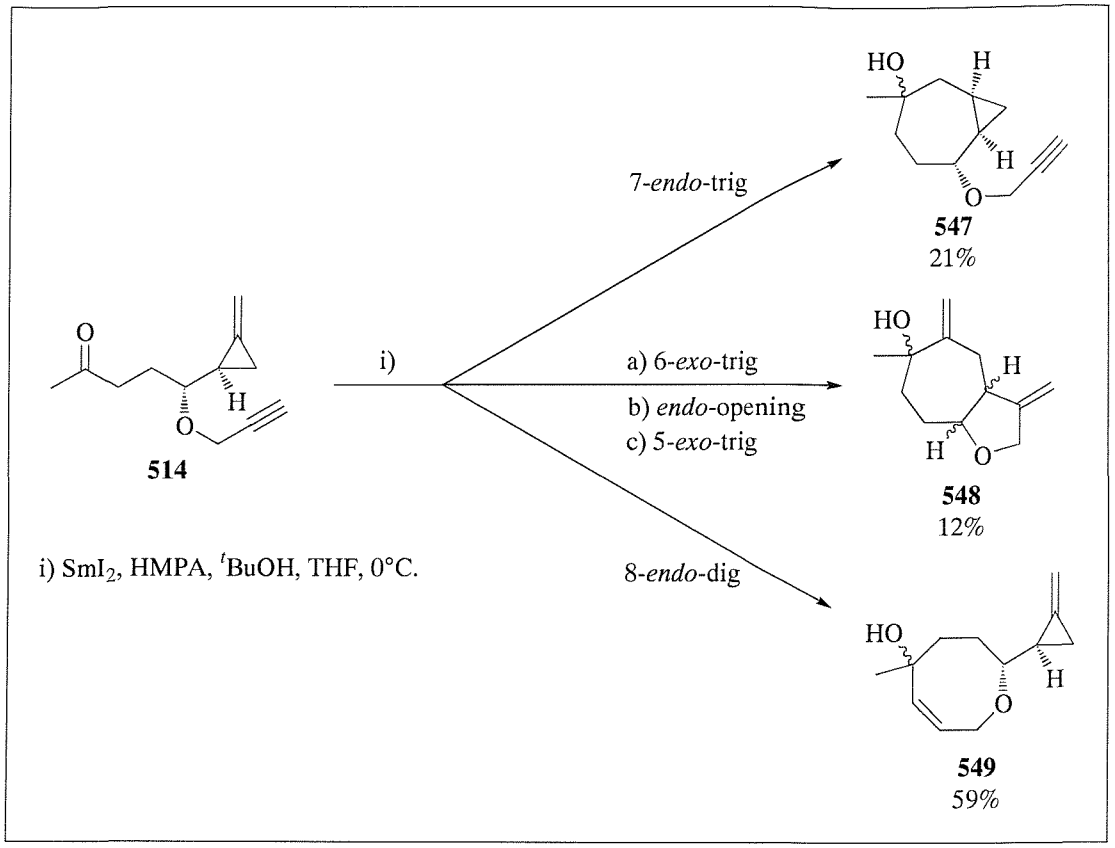
faster than the reduction to the corresponding anion[39]. This sort of 8-*endo*-dig process has precedence as shown by the work of Reissig[138, 139] (Scheme 90).



Scheme 90. 8-*endo*-dig radical cyclisation mediated by samarium iodide.

Syn propargyl precursor **514** gave similar results to **512** (Scheme 91). The 7,3 bicycle **547** was isolated in 21% yield; the 7,5 bicycle **548** was obtained in 12% yield; the oxocine product **549** was the major product isolated in a 59% yield. The combined yield was an excellent 92%.

As previously, unfortunately the stereochemistries of the products could not be determined. Changing from an allyl to a propargyl ether has considerably altered the product profile. The transition states for both precursors must be very favourable for the 8-*endo*-dig cyclisation. The relative yields of 7,3 and 7,5 bicycles appears to be fairly consistent with the allyl ethers: the *anti* ether precursor gives fairly even mixtures of the 6-*exo* and 7-*endo* bicycles; whereas the *syn* precursor favours formation of the 7-*endo* bicycle.

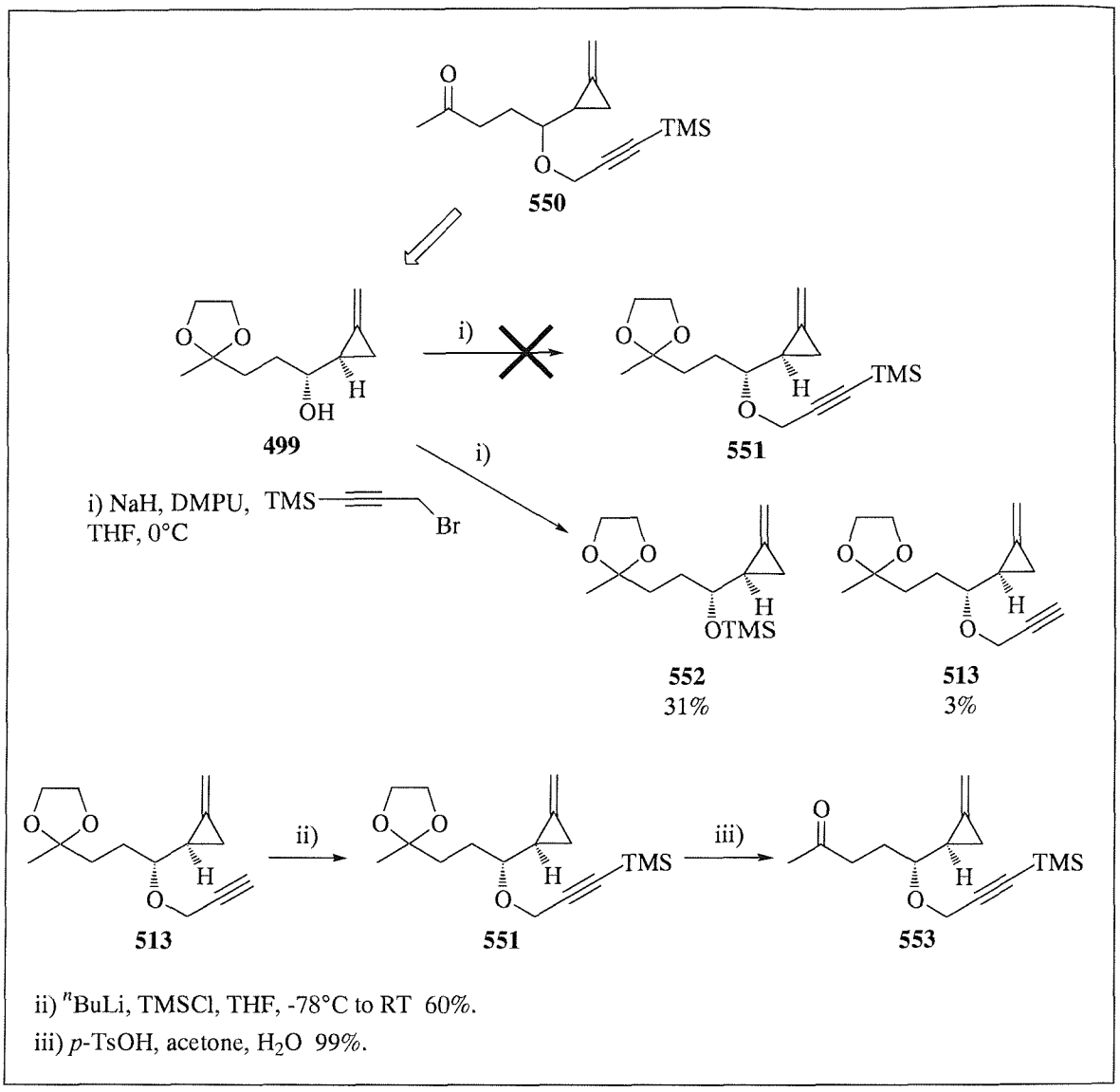


Scheme 91. Cyclisation of *syn* propargyl ether.

4.3.4 Synthesis and Cyclisation of TMS Analogue

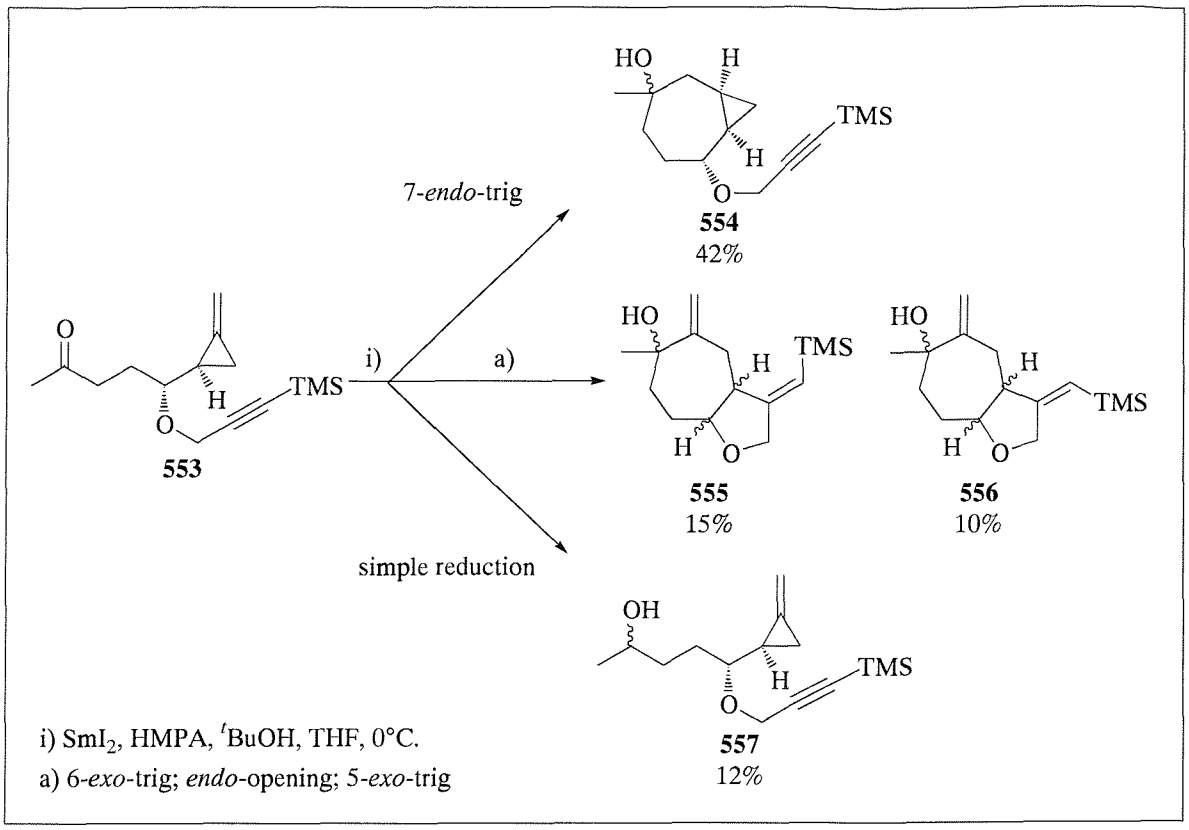
The formation of the oxocine products **543** and **549** occurred *via* an 8-*endo*-trig process. To investigate the possibility of avoiding this undesirable product, another cyclisation precursor **550** was targeted (Scheme 92). Attempts to prepare the TMS-propargyl ether directly by reaction of alcohol **499** with TMS-propargyl bromide did not give the desired intermediate **551**. Instead, the major product isolated was the silyl ether **552** in 31% yield and a very small amount of propargyl ether **513** (3%).

An alternative route involved substitution of the TMS group directly onto the preformed propargyl ether. An initial attempt gave an inseparable 1:1 mixture of ketal **551** and ketone **553** in 30% yield. This was attributed to an unnecessary use of an excess of TMSCl. A subsequent attempt using near equivalent molar quantities of TMSCl, ^{n}BuLi, and alkyne **513** (1.05 : 0.95 : 1.00) gave a much improved yield of **551**: 60% product with 30% recovered starting material. The subsequent deprotection of ketal **551** to give precursor **553** went in a near quantitative yield of 99%.



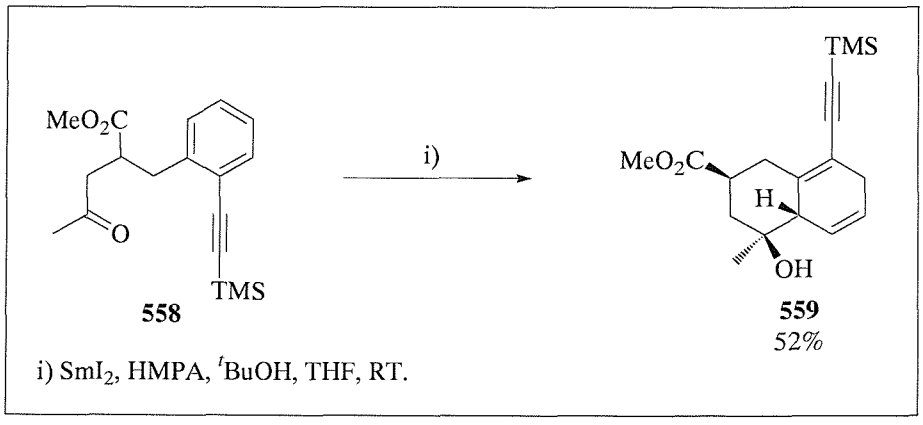
Scheme 92. Synthesis of TMS-propargyl ether.

The cyclisation of the ketone **553** was carried out using reverse addition, HMPA, ^{t}BuOH, THF, 0°C. No oxocine-type products were isolated so the inclusion of the TMS group had successfully blocked the 8-*endo*-dig mode of cyclisation (Scheme 93). Three products were the 7,3 bicycle **554** from the 7-*endo*-trig cyclisation (42%); an inseparable mixture of the two 7,5 bicycles **555** and **556** from the desired 6-*exo*-trig cyclisation (15% *E*; 10% *Z*); and an inseparable mixture of diastereoisomers of the simple reduction product **557** (12%). Thus, although the overall yield (79%) was slightly lower than the non-TMS propargyl analogue **514**, the relative amounts of 7-*endo* and 6-*exo* products had remained the same. The appearance of simple reduction product **557** suggests that the rate of cyclisation is slower than for the other ether analogues. The increase in bulkiness of the propargyl group may slightly destabilize the transition states of the cyclisations.



Scheme 93. Cyclisation of TMS-propargyl ether.

The blocking of the 8-*endo*-dig pathway by adding the TMS group was also observed by Reissig[138, 139] (Scheme 94). Instead of **558** cyclising to give 8-*endo* products as with the previous analogue **544** (Scheme 90), this route is blocked by the bulky TMS group and the ketyl radical attacks the benzene ring instead forming bicycle **559** in a good 52% yield.



Scheme 94. Blocking the 8-*endo*-dig route.

The ratio of *E* and *Z* isomers **555** and **556** was determined by GOESY NMR experiments. In the major isomer an interaction between the allylic ring junction hydrogen and the TMS group, together with no interaction to the sole vinyl hydrogen, suggested that this was the *E* form **555**. In the minor isomer, no interaction between the allylic ring junction hydrogen and the TMS group was found, but an interaction with the single vinyl hydrogen was observed suggesting that this was the *Z* form **556**.

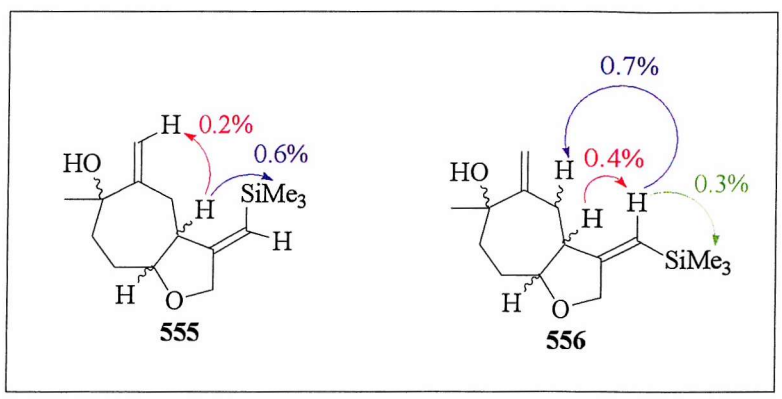
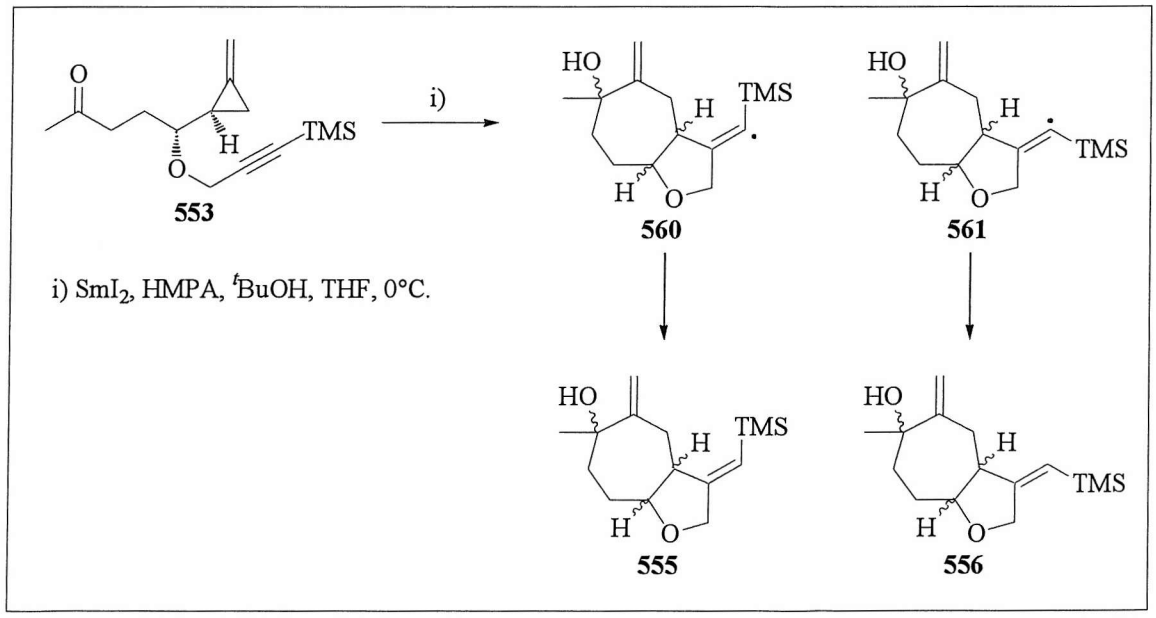


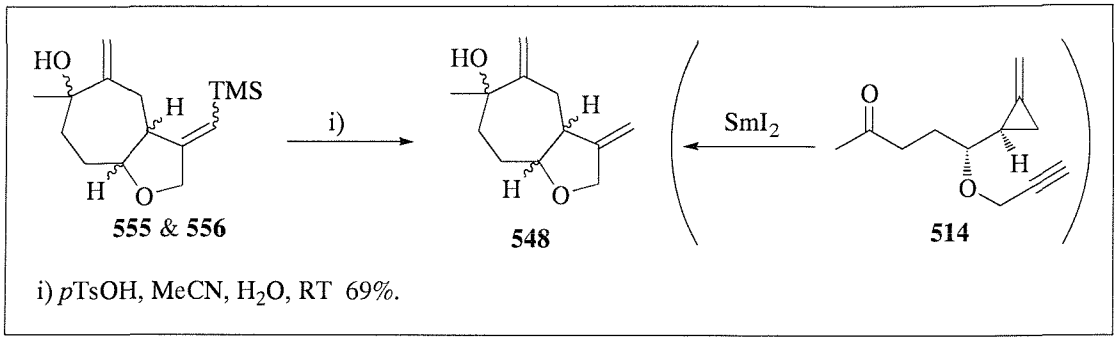
Figure 24. Important NOE's from the mixture of 7,5 bicycles.

The slight preference for the formation of the *E* over the *Z* isomer may arise from the possible geometries of the vinyl radical formed from the 5-*exo*-trig cyclisation (Scheme 89). Steric hindrance imposed by the ring systems in **561** could hinder the approach of solvent molecules and reduce the formation of isomer **556**.



Scheme 89. Transitions states for the formation of 7,5 bicycles.

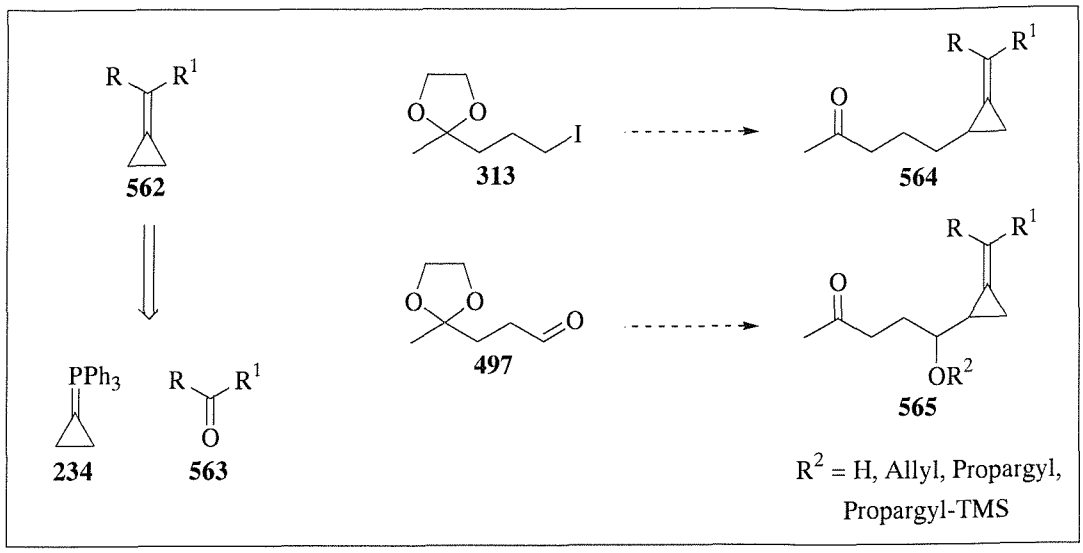
Definite confirmation of the formation of the mixture of the two 7,5 bicycles **555** and **556** could be demonstrated by the removal of the TMS group. The investigations of de-silylating other similar products (see section 5.3.3 chapter 5) had shown that *p*-TsOH was an appropriate reagent and this transformation was carried out (Scheme 96). The product was obtained in a 69% yield and identical to the 7,5 bicycle **548** from the cyclisation of the non-TMS propargyl ether **514**.



Scheme 96. Proto-desilylation of TMS analogues.

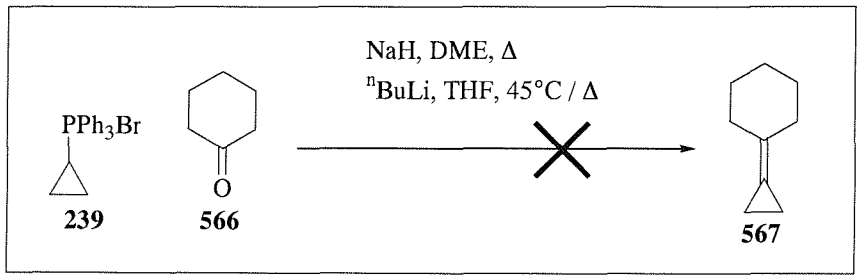
4.4 Attempts to Block the *Endo* Cyclisation Mode

The inclusion of the alcohol and ether moieties had improved the overall cyclisation yields and it was also possible to block cyclisations onto the ether functionality. However, the major product from these new modifications was the undesired 7-*endo*-trig bicyclic system. A blocking group on the free end of the alkene of methylenecyclopropane should have the effect of reducing or even cancelling out the prospect of 7-*endo*-trig cyclisations. Simple methylenecyclopropane analogues **562** (see chapter 1 section 1231) were targeted with a view to substituting this group onto a carbon backbone (Scheme 97) to prepare many precursors such as **564** or **565**.



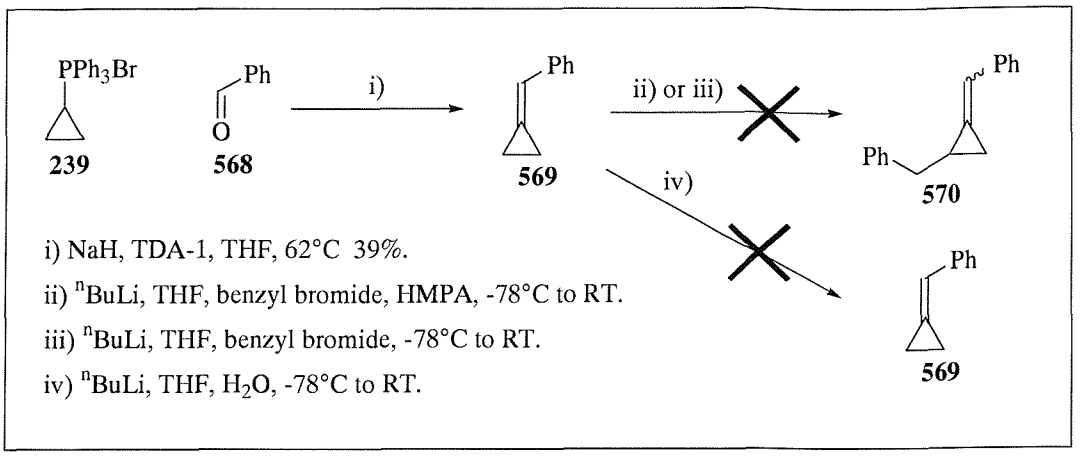
Scheme 97. Inclusion of groups to block 7-*endo*-trig cyclisation pathway.

The synthesis of two differently substituted methylenecyclopropanes was attempted. Initially, incorporation of a cyclohexane group using cyclohexanone **566** was envisaged as this would avoid *E/Z* isomer problems. Different methods[140, 141] using various bases were tried but these were all unsuccessful and the desired product **567** was not isolated (Scheme 98).



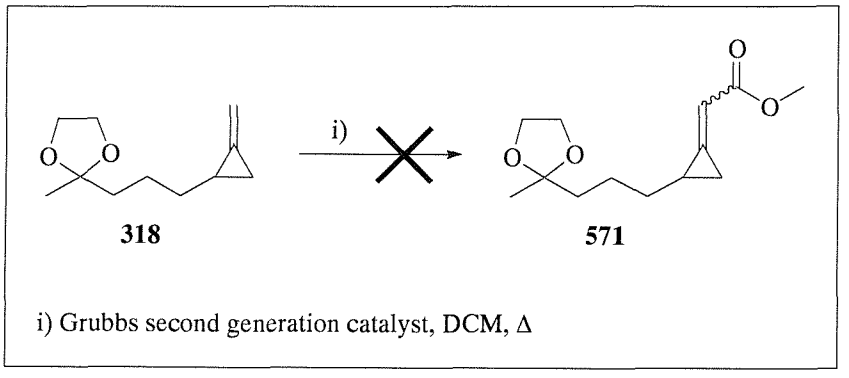
Scheme 98. Unsuccessful attemtps to prepare cyclopropylidenecyclohexane

The reasons for the failure of these literature reported methods was unknown. There may have been problems with the base and deprotonation α to the carbonyl of cyclohexanone **566**. A new precursor **569** was targeted (Scheme 99). The synthesis of this intermediate was relatively successful yielding the desired product in 39% yield. Attempts to form the anion **572** and react it with a benzyl bromide as a model electrophile were unsuccessful. Methylenecyclopropane analogue **569** was then deprotonated and quenched with water to test the stability of **569** to the reaction conditions. This reaction did not give back starting material and thus the route was abandoned as it appeared to cause degradation of **569**.



Scheme 99. Attempts to prepare phenylmethylenecyclopropane analogues.

Another approach was to use metathesis to functionalise the methylenecyclopropane once already attached to the backbone of the precursor. There was no precedent for this type of reaction but a successful procedure for other systems was employed[142, 143]. Unfortunately the trial reaction using the Grubbs second generation catalyst and methylacrylate showed no promise (Scheme 100).



Scheme 100. Attempt at metathesis with a methylenecyclopropane derivative.

Further investigation in the attempts to synthesize precursors that might block the 7-*endo*-trig cyclisation onto methylenecyclopropane were halted as the potential of obtaining large enough quantities of good quality precursors was low.

4.5 Conclusions

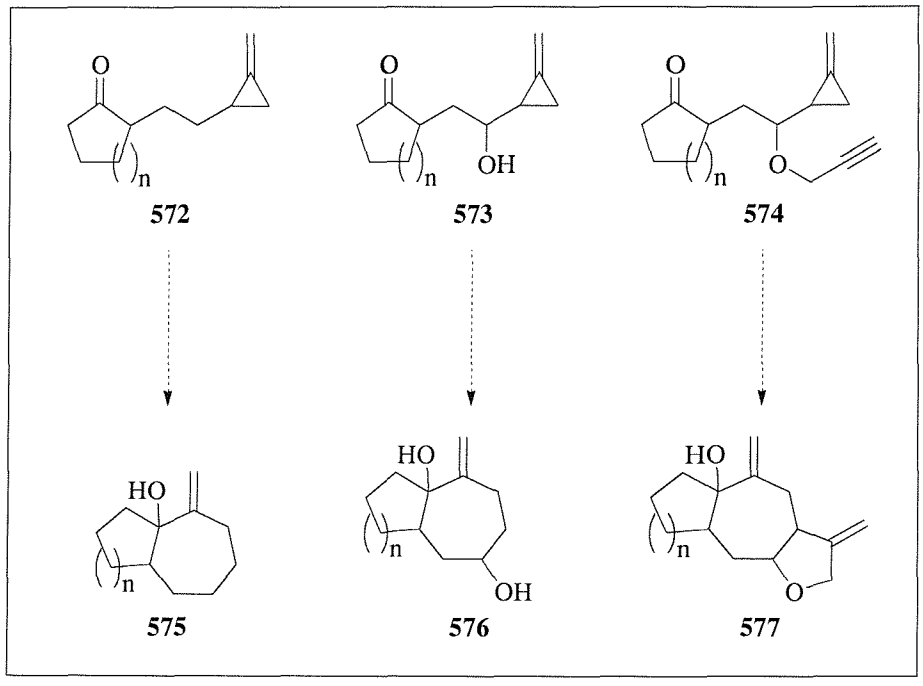
The functionalisation of the basic backbone had dramatic effects on the cyclisation of the precursors by both improving yields and altering the product profile. The inclusion of the oxygen-containing functionalities appeared to allow some chance of chelation but its effect of it could not be fully determined. The cascade potential had been shown to work and access to polycycles was possible in good yields.

Chapter Five

5 Cyclopentanone Precursors

5.1 Aims

The previous work on the project had shown the importance of the nature of the precursor. All of the precursors had a simple methyl ketone as the source of the ketyl radical. Previous work by Watson had shown that successful cyclisations onto methylenecyclopropanes was possible with cyclic ketone precursors[119] (see section 3.4.3.1 chapter 3). The influence of a cyclic ketone on the 6-*exo*-trig cyclisation was unknown and precursors of this type offered the potential to form tricycles in one synthetic operation (Scheme 101).

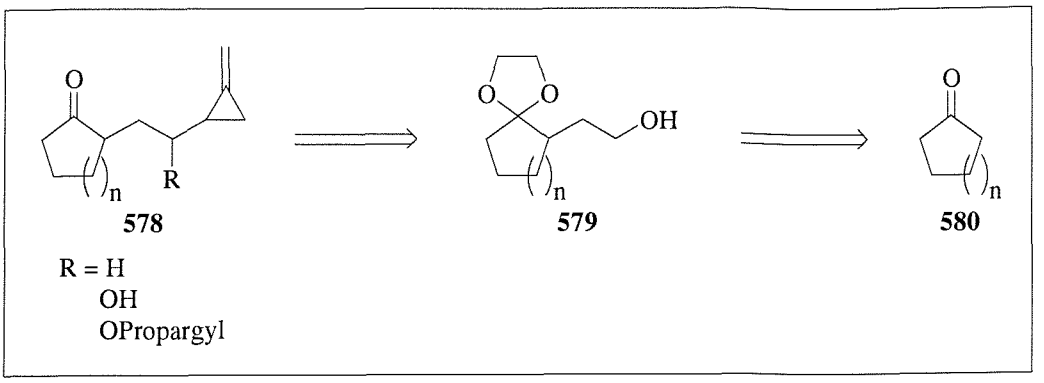


Scheme 101. Potential bi- and tricyclic products.

5.2 Synthesis of Precursors

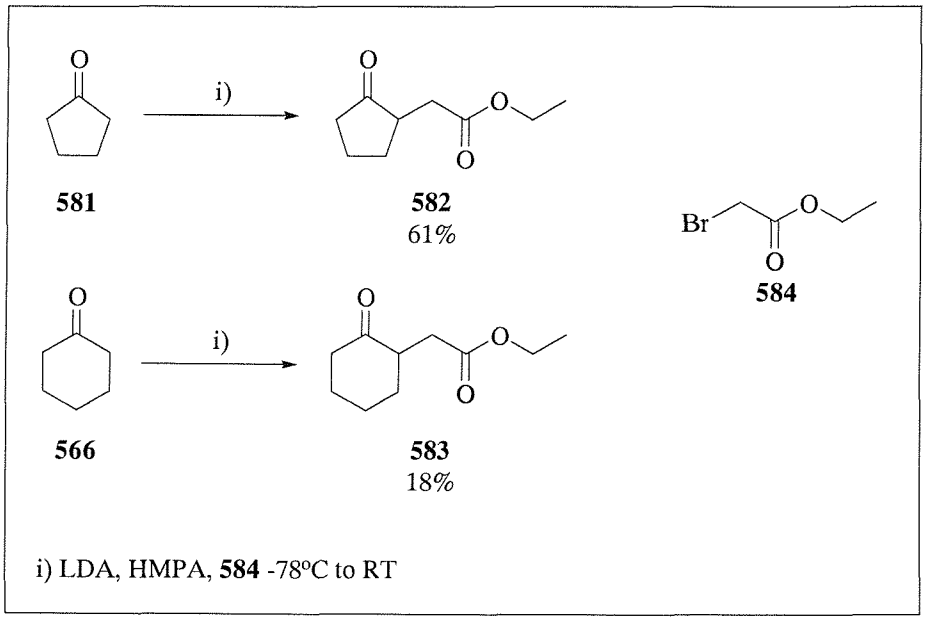
5.2.1 Basic Precursor

The retrosynthesis of the precursors lead back to cycloalkanones **580** (Scheme 102). Alcohol **579** was a common intermediate allowing conversion to the iodide or aldehyde followed by addition to the methylenecyclopropane anion.



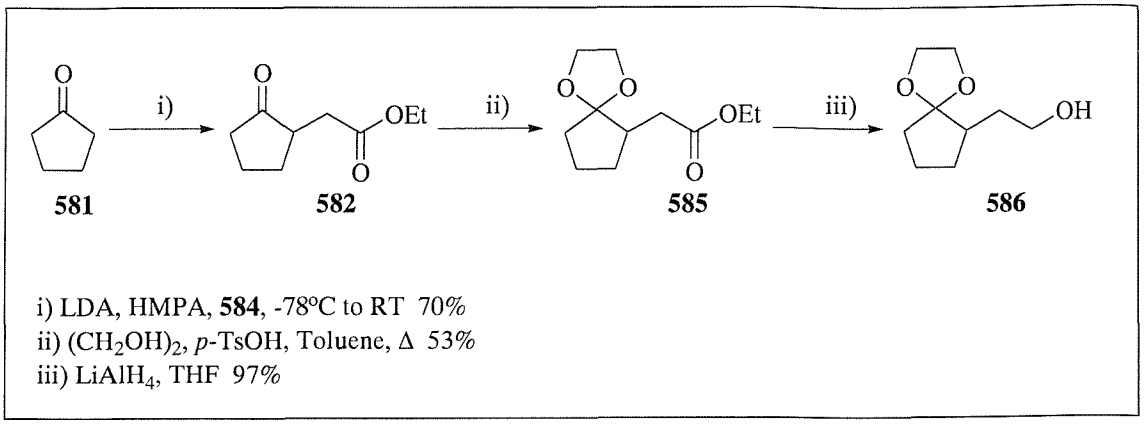
Scheme 102. Retrosynthesis of cyclisation precursors.

The size of the cyclic ketone could be readily varied but initial work was focused on cyclopentanone **581** and cyclohexanone **566**. Following established methodology[144], the synthesis of the esters was explored (Scheme 103). Cyclopentanone gave much cleaner and higher yielding results than the cyclohexanone analogue on a test scale reaction (**582** 61% compared to **583** 18%), and thus efforts were concentrated on the cyclopentanone series of precursors.



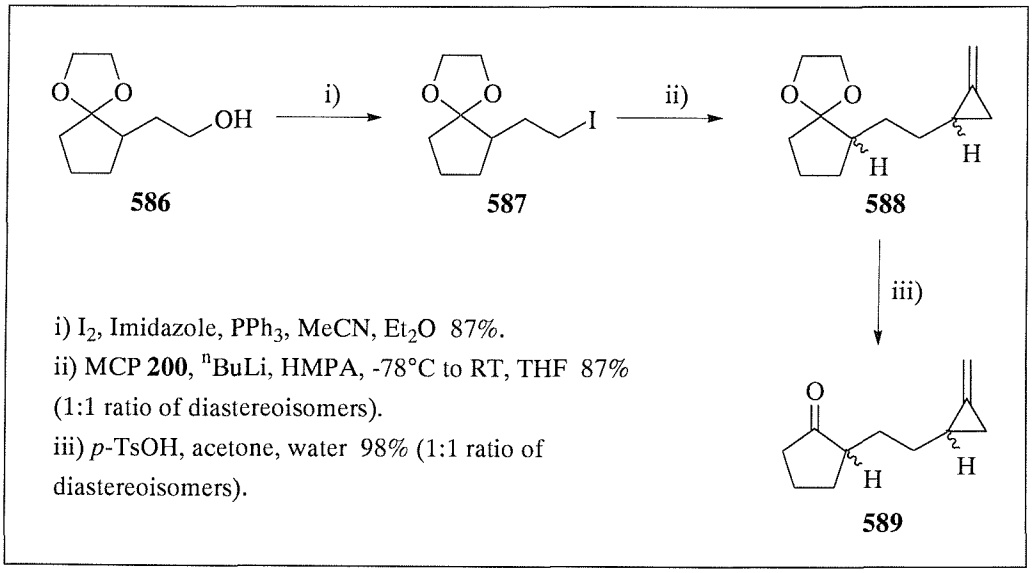
Scheme 103. Determining the cycloalkanone to be used in the cyclisation precursor.

Thus, ester **582** was prepared on large scale in a 70% yield. The ketone moiety of **582** was protected using the standard ethylene glycol protocol in an acceptable 53% yield (Scheme 104). The ester functionality of **585** was reduced to the corresponding alcohol **586** that served as a common intermediate for the cyclisation precursors.



Scheme 104. Preparation of the common intermediate alcohol.

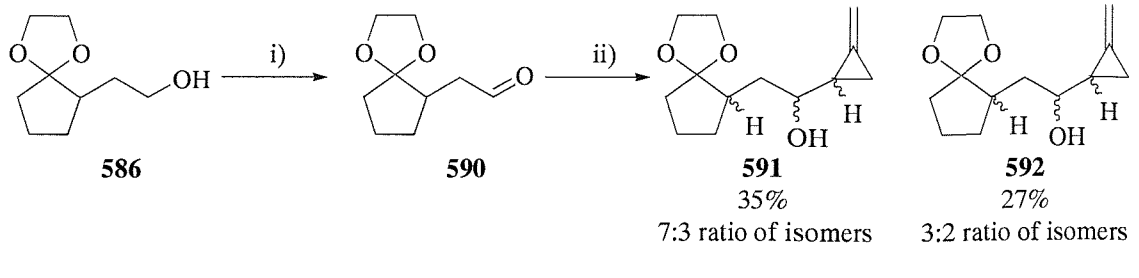
The final steps in the preparation of the basic cyclopentanone precursor were standard (Scheme 105). Alcohol **586** was converted to iodide **587** using the familiar protocol[126] in a very high 87% yield. Alkylation of the methylenecyclopropane anion with iodide **587** proceeded in an excellent 87% yield affording an inseparable mixture of diastereoisomers of **588** in a 1:1 ratio. Deprotection of ketal **588** afforded ketone **589** in a near quantitative 98% yield, again as an inseparable mixture of diastereoisomers in a 1:1 ratio.



Scheme 105. Final steps in the preparation of basic precursor.

5.2.2 Keto-alcohol and Ether Precursors

Common intermediate alcohol **586** was converted to aldehyde **590** using the Swern oxidation[136] in a good 69% yield (Scheme 106). The addition of aldehyde **590** to the methylenecyclopropane anion gave a complex set of products.



586 **590** **591** 35% 7:3 ratio of isomers **592** 27% 3:2 ratio of isomers

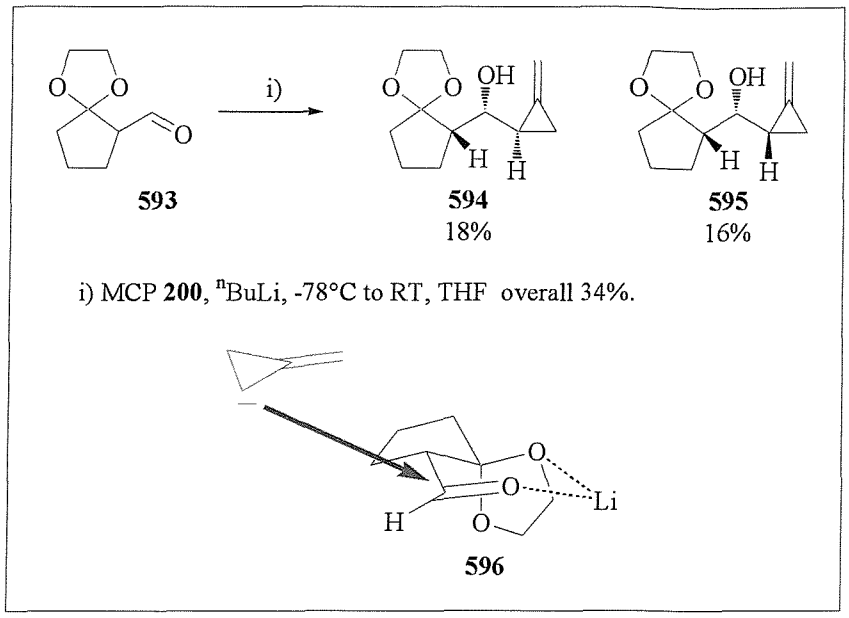
i) $(COCl)_2$, DMSO, NEt_3, DCM, -60°C 69%.

ii) MCP **200**, ^{n}BuLi, -78°C to RT, THF overall 62%.

Scheme 106. Towards keto-alcohol and ether precursors.

Two pairs of inseparable isomers were isolated: the less polar **591** in a higher 35% yield in a 7:3 ratio; and the more polar **592** in a lower 27% yield in a 3:2 ratio. It had been hoped that the number of isomers produced would be two. In the synthesis of the shorter chain analogues by Watson[145] from **593**, only two isomers **594** and **595** were isolated from the similar transformation (Scheme 107). However, with these shorter chain analogues, there must be a well defined 6-membered ring chelate between the aldehyde, ketal oxygen and lithium ion **596**. Therefore, the stereochemistry at the cyclopentyl ring junction is fixed.

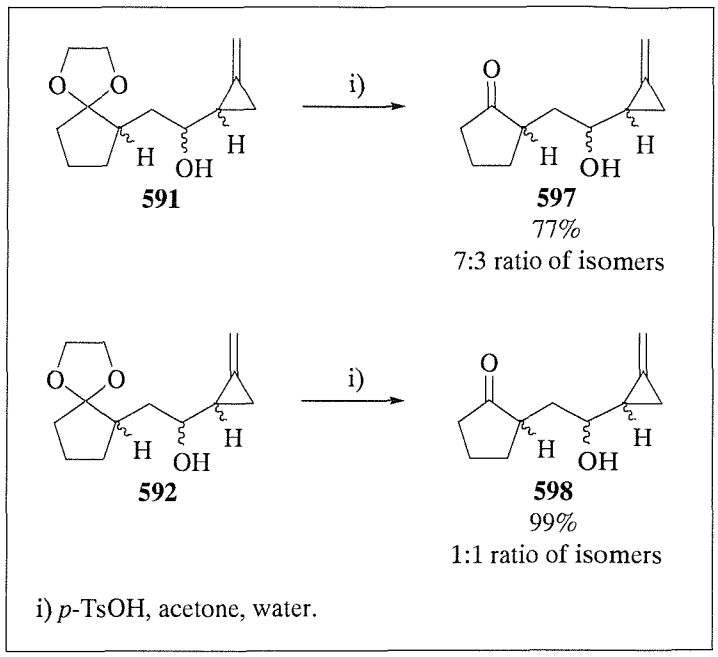
The imposed steric hindrance of the ring systems on the approaching large nucleophile suggests that the attack is only from above as shown in **596**. Thus, the only variable is which face of the methylenecyclopropyl anion attacks. By considering the relative yields of the two isomers **594** and **595**, there appears to be no discernable preference for this facial selectivity.



Scheme 100. Shorter chain analogue leading to two isomers.

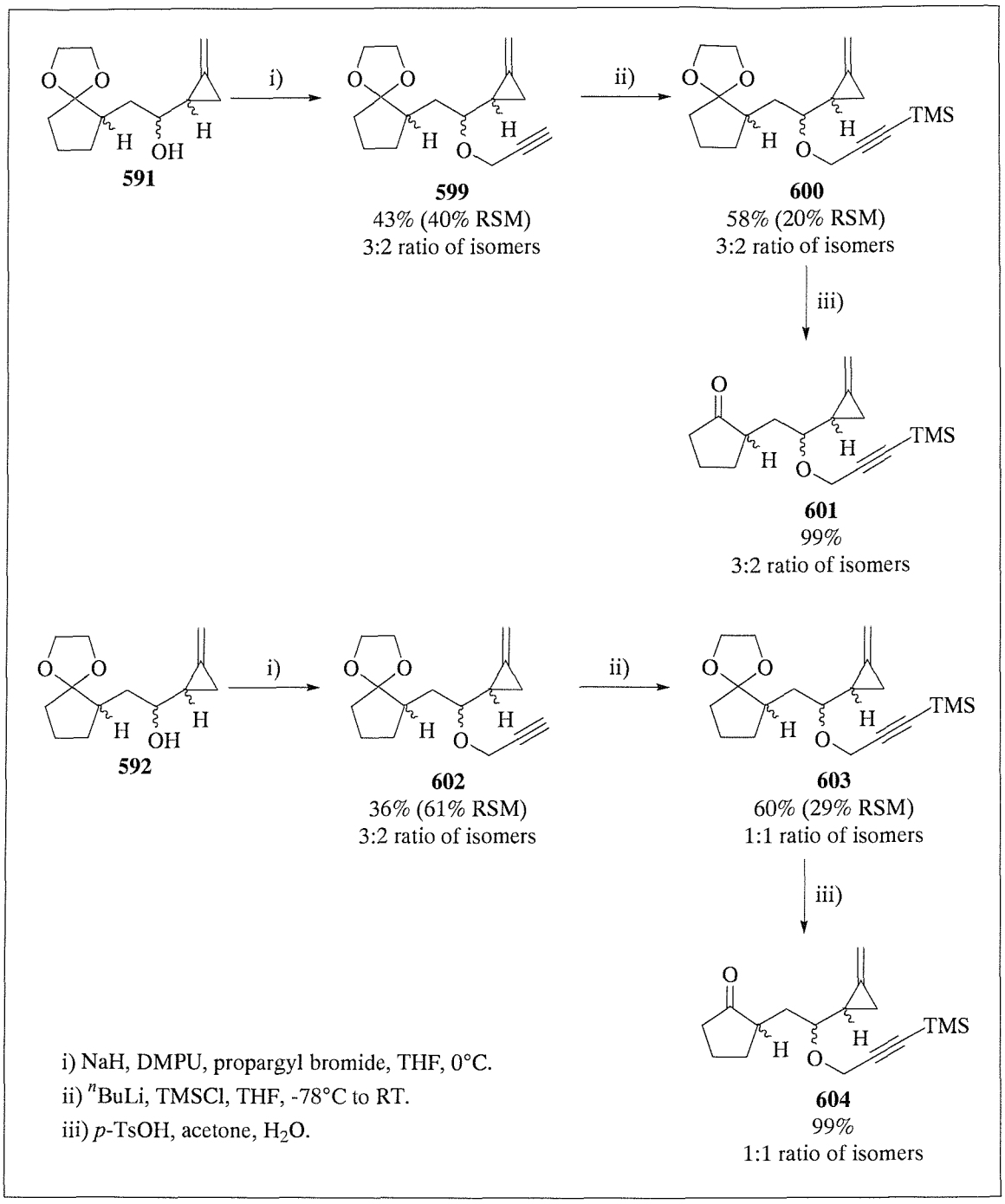
In the longer chain system the chelate is less likely to form as there is now a 7-membered ring required. It is also possible that if a chelate did form, the transition states might not have enough difference between them to affect the outcome of the nucleophilic attack. Although there are major and minor products isolated, all four possible isomers are produced. The nature of these isomers is discussed in section 5.2.3 (*vide infra*).

The preparation of the keto-alcohol precursors **597** and **598** was completed by deprotecting the ketals **591** and **592** using standard conditions (Scheme 101). The less polar ketal mixture **591** afforded an inseparable mixture of ketones **597** in a high 77% yield in a 7:3 ratio of isomers. The more polar ketal mixture **592** afforded an inseparable mixture of ketones **598** in near quantitative 99% yield in a 1:1 ratio of isomers.



Scheme 108. Preparation of keto-alcohol cyclisation precursors.

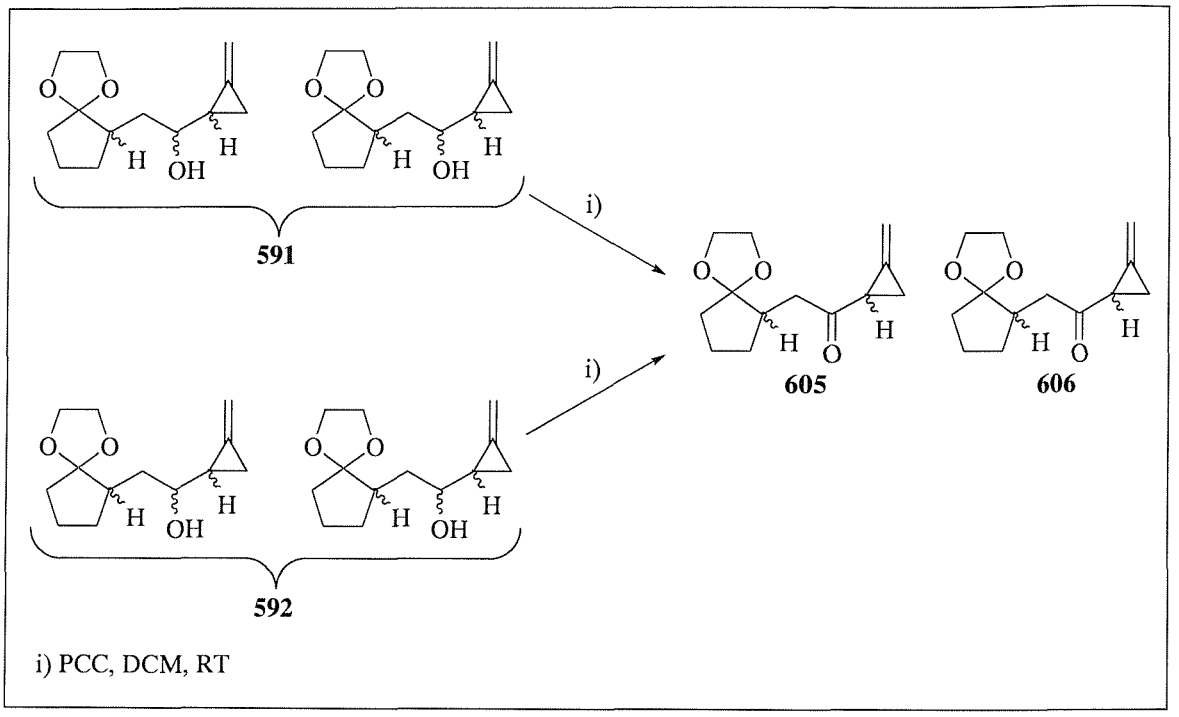
The results from chapter 4 (see section 4.3.4) had shown that it was necessary to use TMS-substituted propargyl ethers to avoid undesired 8-*endo*-dig cyclisation. Therefore, the radical trap chosen was a TMS-propargyl ether and the cyclisation of the simpler propargyl ether was not investigated. The synthesis followed the successful route developed for the acyclic analogues (Scheme 109). Complete conversion to the propargyl ether, **599** or **602**, was still problematic as large amounts of unreacted starting material were recovered (40% and 61% respectively). Sufficient quantities of the propargyl ethers **599** and **602** were obtained to allow the substitution of the terminal hydrogen for the TMS group. The TMS-propargyl ethers **600** and **603** were obtained in good yields of 58% and 60% respectively. The final deprotection step went in quantitative yields for both pairs of isomers **601** and **604**. The ratio of isomers had altered slightly due to recovery of the products from the synthetic steps.



Scheme 109. Synthesis of TMS-propargyl ether precursors.

5.2.3 Stereochemistry of the Keto-alcohols and Related Analogues

The nature of the pairs of isomers was investigated as this would greatly aid conclusions drawn from the cyclisation studies. The two pairs of ketal-alcohols **591** and **592** obtained from the reaction of methylenecyclopropane anion with aldehyde **590** were separately oxidised to the corresponding ketone (Scheme 110). Both pairs gave an identical, inseparable mixture of ketones **605** and **606**. Therefore, both pairs had to contain isomers that differed in stereochemistry at either the methylenecyclopropane or the cyclopentane position.

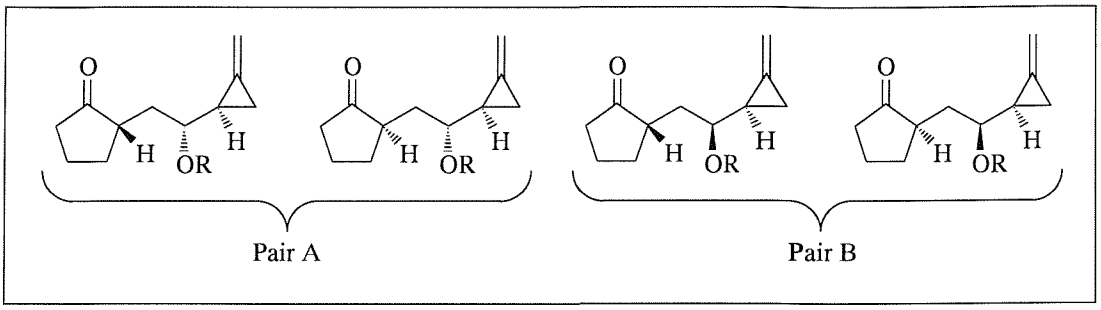


Scheme 110. Oxidation of mixed alcohols to give mixed ketones.

The exact nature of the mixtures was still unanswered. To determine whether the difference was at the cyclopentane or the methylenecyclopropane, a simple NMR experiment was designed. The less polar cyclisation precursors **597** and **601** were dissolved separately in $CDCl_3$ and ^1H and ^{13}C NMR spectra recorded. A catalytic amount of DBU was dissolved in $CDCl_3$ and added to the precursor solution. The change in ^1H and ^{13}C spectra was monitored over time. Only the original two starting materials were present in the subsequent spectra but the ratio of components had changed. This was evinced by the change in the ^1H spectra of the C*H*OR peaks and the change in the ^{13}C spectra of the *C*HC=O and *C*HOR peaks. Therefore, the difference between the two isomers was at the cyclopentane junction. The relative stereochemistry between

alcohol/ether and methylenecyclopropane must be the same for both of the isomers in each pair, but different between the pairs. Unfortunately, attempts to obtain a crystal structure of any precursor or derivative failed.

As such, the exact isomer pairing could not be determined, only that each pair must be either one of pair A or pair B shown below (Scheme 111).



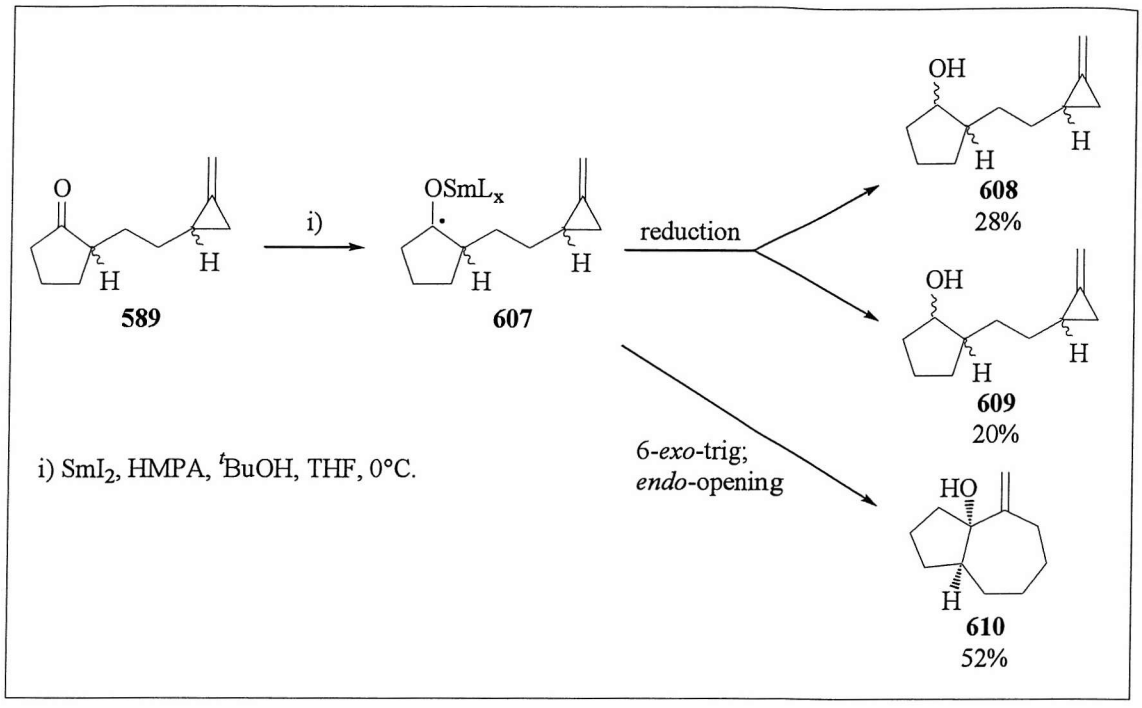
Scheme 111. Nature of the pairing of alcohol and ether precursors.

5.3 Cyclisation Studies

5.3.1 Basic Precursor

Cyclisation studies on the basic precursor were carried out using the conditions of reverse addition, HMPA, ^{t}BuOH, THF, 0°C.

As the starting material **589** for the cyclisation was an inseparable mixture of diastereoisomers (1:1 ratio) and so complicated results were expected. However, only three products were isolated from the cyclisation in an excellent quantitative yield (Scheme 112). The 5,7 bicycle **610** was isolated as a crystalline solid in good 52% yield. The other two products were simple reduction products **608** (28%) and **609** (20%).



Scheme 105. Cyclisation of basic precursor.

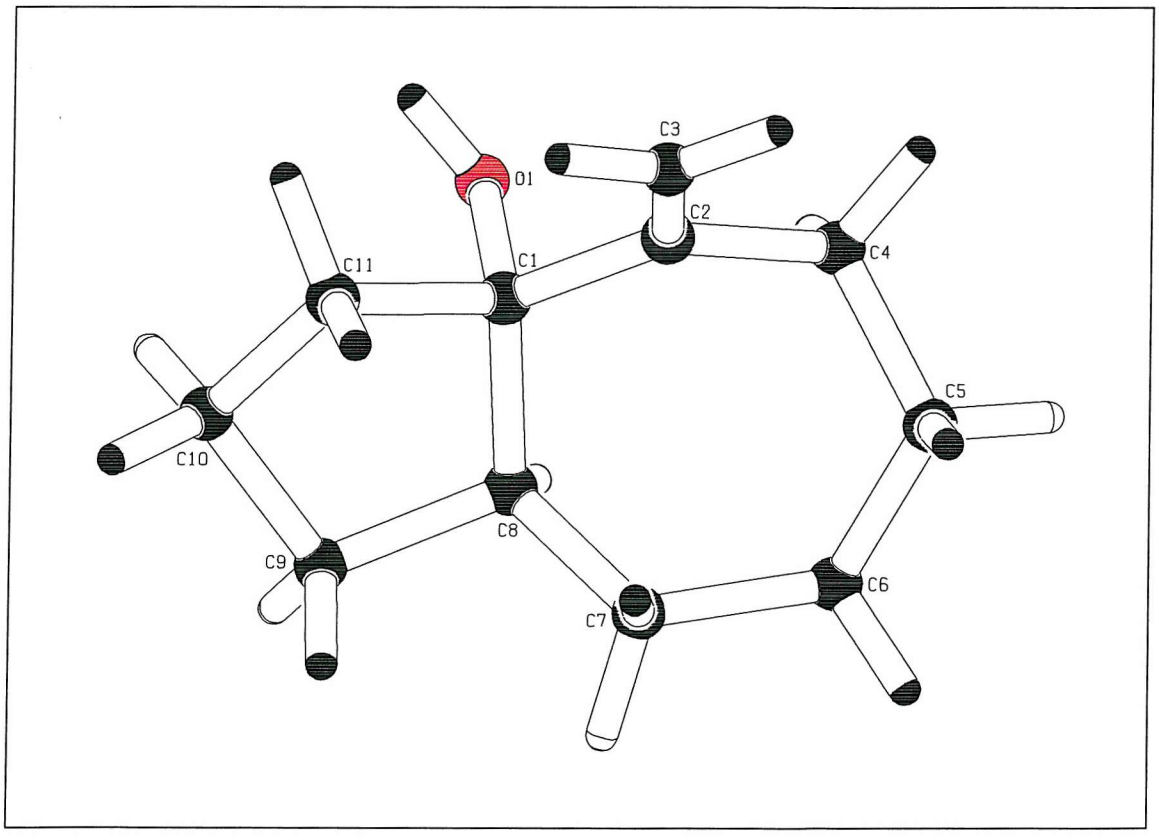
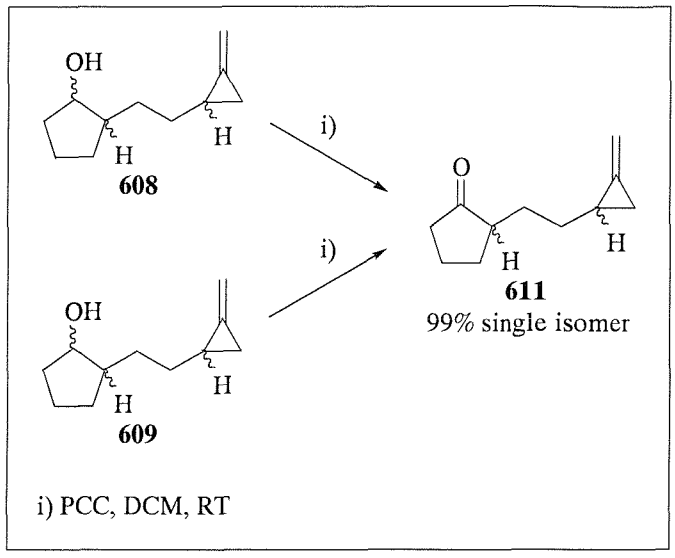


Figure 25. Crystal structure of 5,7 bicycle from cyclisation of basic precursor.

The two simple reduction alcohols **608** and **609** were oxidized with PCC to afford the same ketone product in quantitative yield in both cases (Scheme 113). Therefore, only one isomer had cyclised to give the 5,7 bicyclic compound **610**. The other isomer had simply been reduced. Attempts to prepare a crystalline product from the single isomer ketone **611** with tosyl-hydrazine were unsuccessful. Thus the stereochemistry of this ketone could not be determined.



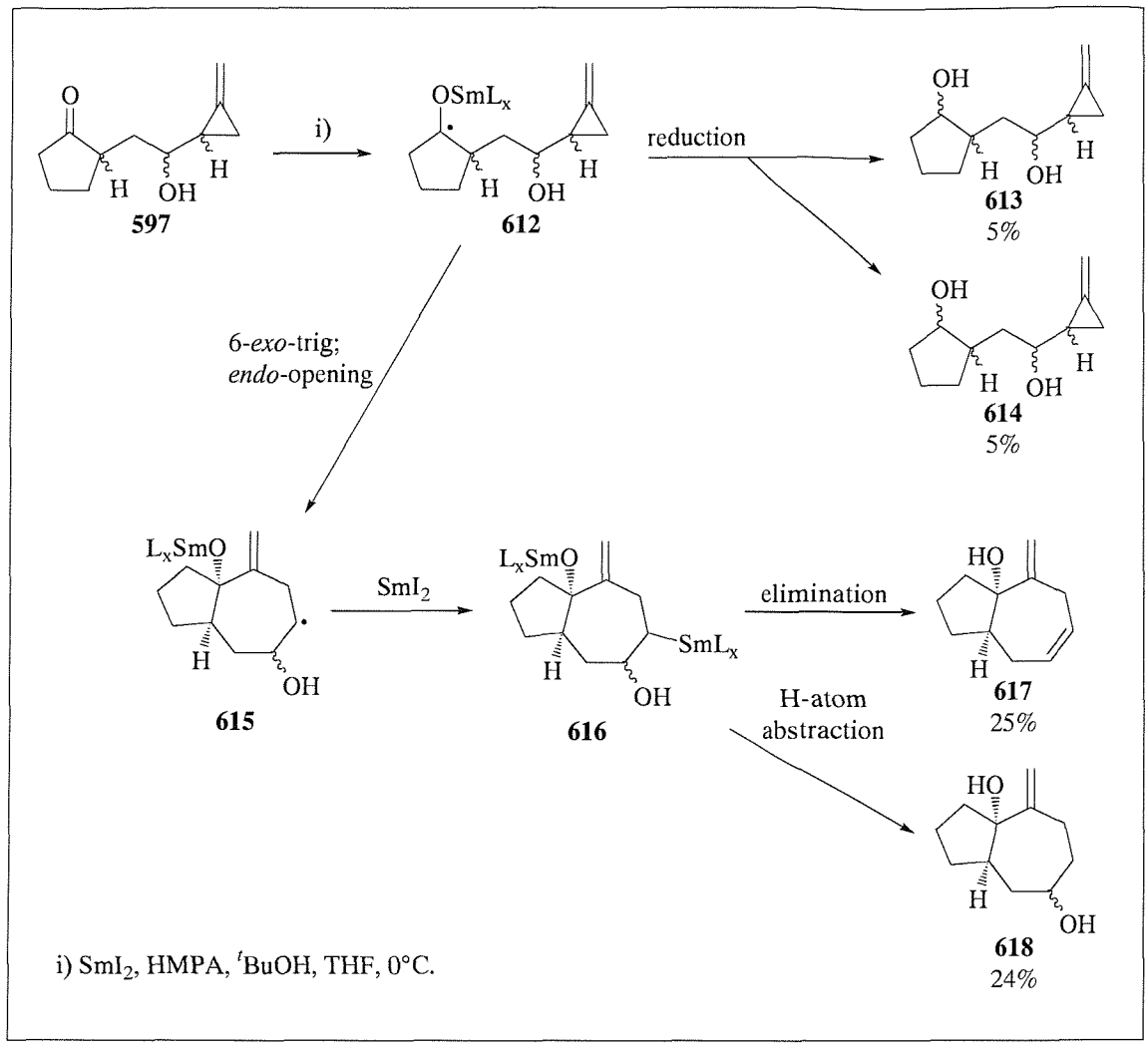
Scheme 113. Oxidation of simple reduction alcohols to identical ketone.

The X-ray structure of the crystalline solid **610** revealed that the ring junction was *cis*-fused (Figure 25). The stereocentre of the methylenecyclopropane is destroyed in the cyclisation because the *endo* ring-opening affords a radical at that position. Therefore, determination of which isomer cyclised and which did not cyclise could not be confirmed.

5.3.2 Keto-alcohol Precursors

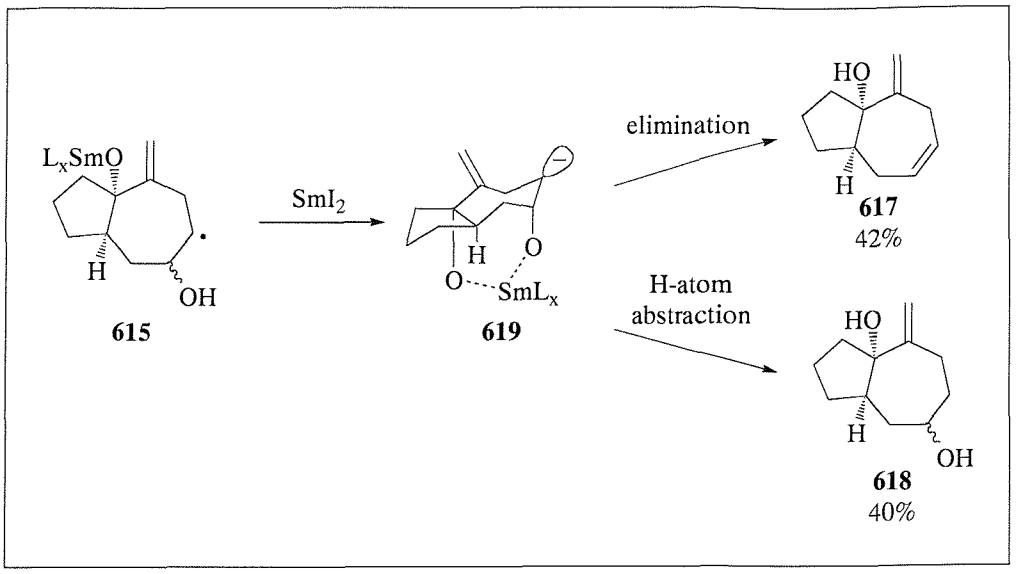
Cyclisation studies on the keto-alcohol precursors **597** and **598** were carried out using the conditions of reverse addition, HMPA, ^{t}BuOH, THF, 0°C.

Starting material **597** for the cyclisation was a 7:3 ratio mixture of isomers and gave four products from the cyclisation reaction (Scheme 114). The overall yield of these products was 59% (with 40% recovered starting material).



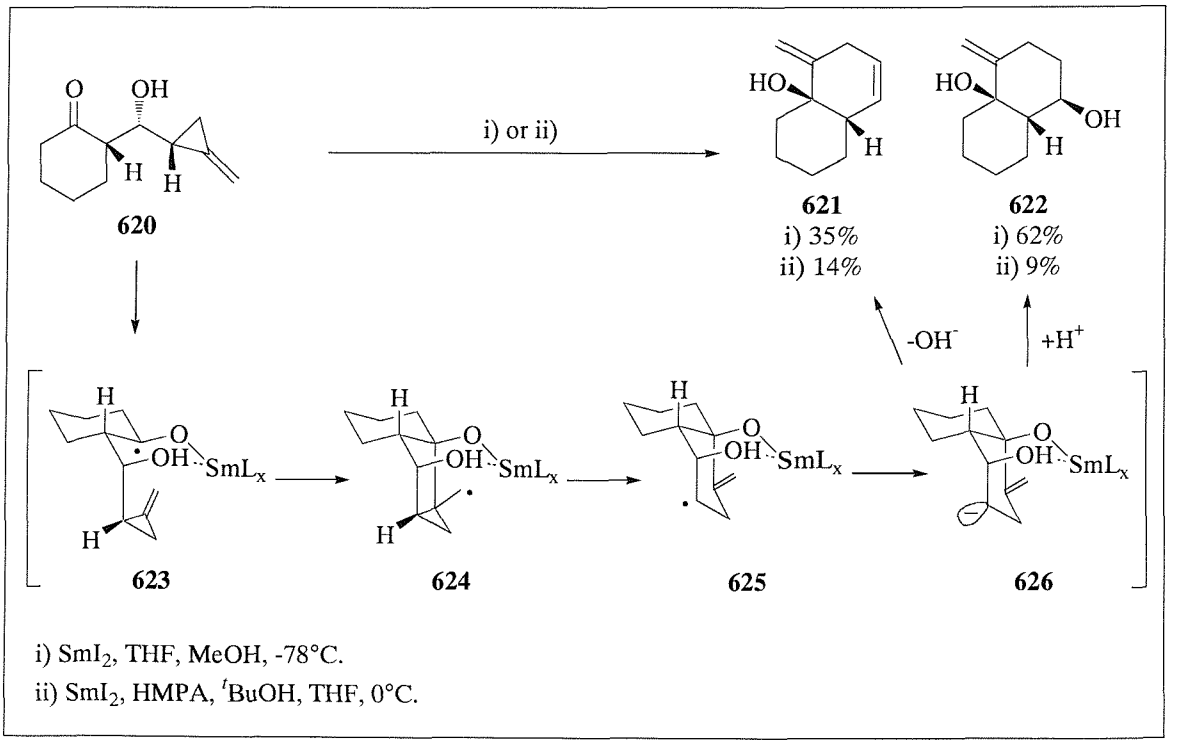
Scheme 114. Cyclisation of keto-alcohol **597**.

The incomplete reaction of the starting material makes definite conclusions impossible. The cyclic materials **617** and **618** could arise either from both isomers or from only the major isomer. The 5,7 bicycle **610** from the basic precursor **589** had a *cis*-fused ring junction and it is very likely that the cyclic products isolated from this cyclisation are also *cis*-fused. The origin of diene **617** is from elimination of the alcohol from intermediate **619**. This may occur *via* the transition state shown below (Scheme 115).



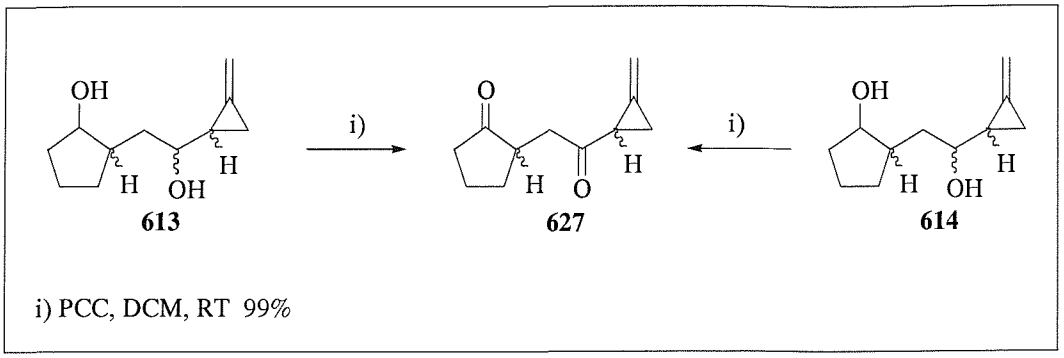
Scheme 115. Possible transition states leading to 5,7 bicycles.

The appearance of both types of product has been observed before in cyclisation studies from within the group (Scheme 116)[119].



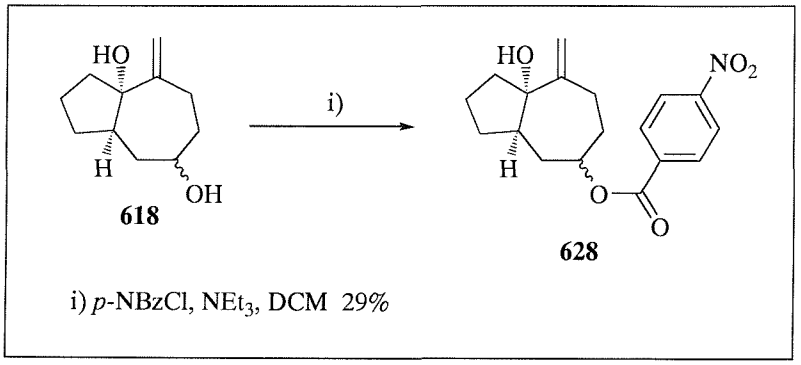
Scheme 116. Diol and diene products from realated cyclisations.

The simple reduction diols **613** and **614** were oxidized with PCC to yield an identical diketone **627** (Scheme 117). Therefore, both simple reduction products came from the same isomer, although the stereochemistry of that isomer is unknown.



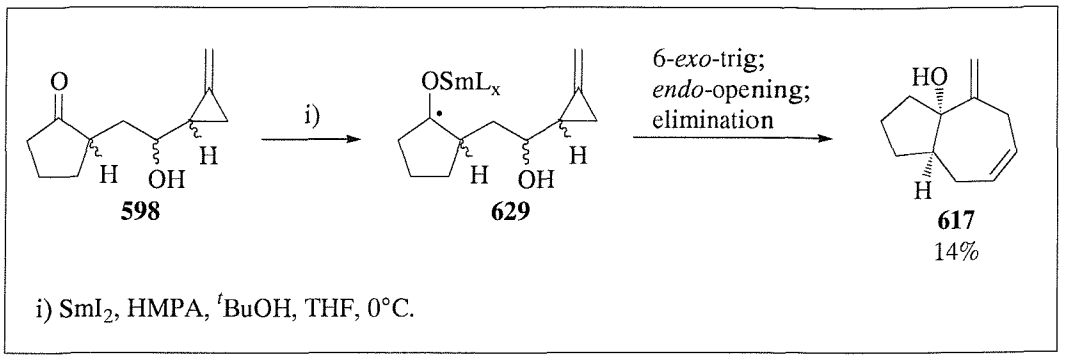
Scheme 117. Oxidation of diols to identical diketone.

5,7 bicyclic diol **618** was treated with *p*-nitrobenzoyl chloride but product **628** was not crystalline and so the stereochemistry could not be determined (Scheme 118).



Scheme 118. Attempt to prepare crystalline derivative.

The cyclisation of the other pair of isomers **598** was less successful. Although identical conditions were used the only identifiable product was the elimination diene **617** isolated in 14% yield and identical to the diene isolated from the cyclisation of the first pair of isomers. Despite attempts to purify the remainder of the reaction products no other discernable structures could be assigned.



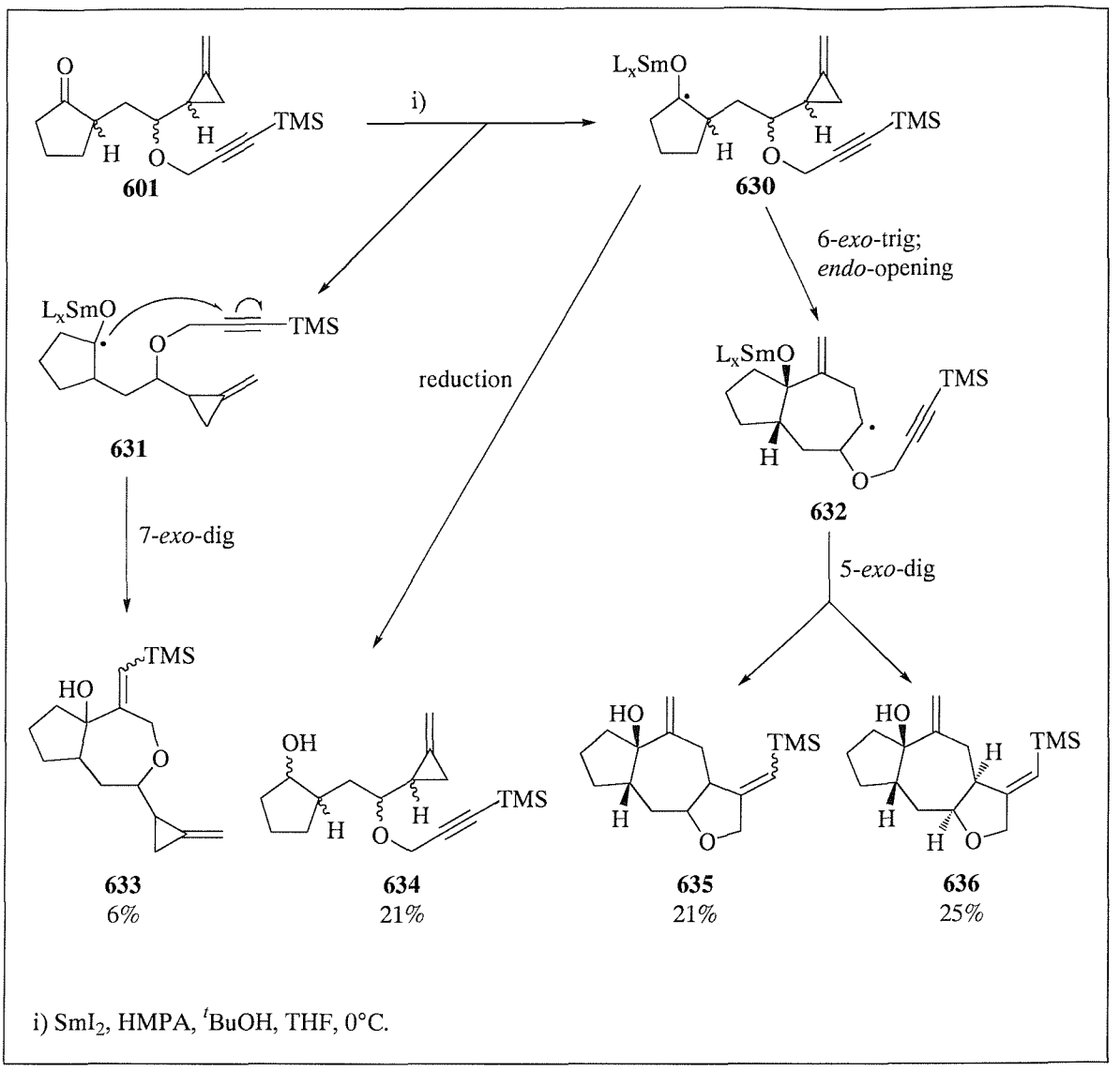
Scheme 119. Cyclisation of keto-alcohol **598**.

5.3.3 TMS-propargyl Ether Precursors

Cyclisation studies on the TMS-propargyl ether precursors **601** and **604** were carried out using the conditions of reverse addition, HMPA, ^{t}BuOH, THF, 0°C.

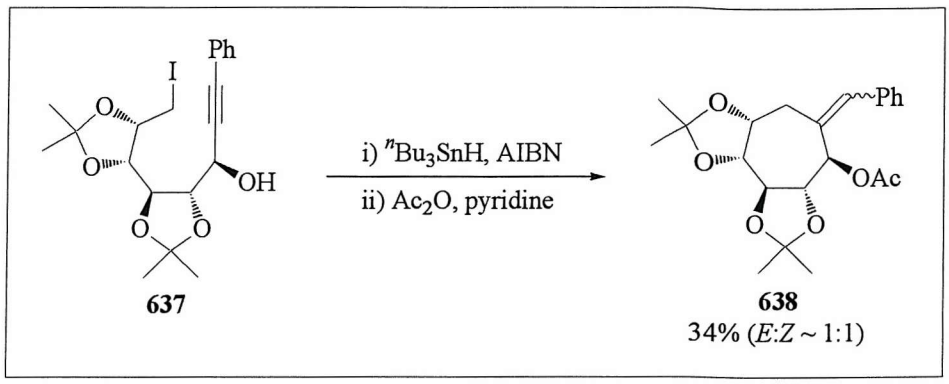
Starting material **601** for the cyclisation was a 3:2 ratio mixture of isomers. The cyclisation of **601** afforded four products from the cyclisation reaction (Scheme 120). The overall yield of these products was a high 73% (with 18% recovered starting material).

The assignment of structures to the four products was not trivial. Tricycle **636** eventually formed crystals and X-ray data was obtained confirming assignments made by NMR (Figure 26). This very pleasing result confirmed the structure beyond doubt and provided solid evidence for the *cis*-fusion at both ring junctions.



Scheme 120. Cyclisation products from TMS-propargyl ether **601**.

The unusual product **633** from the 7-*exo*-dig cyclisation onto the TMS-propargyl ether is based on data that indicated changes to the TMS-propargyl ether group whilst the methylenecyclopropane remained intact. This cyclic product is highly unlikely to be the 8-*endo*-dig product due to the hindrance from the TMS group. The 7-*exo*-dig radical cyclisation is unusual but there are reports of this type of cyclisation[146] (Scheme 121).



Scheme 113. Literature example of 7-*exo*-dig cyclisation.

The other tricycle **635** is assumed to have the *Z* geometry for the vinyl silane but was isolated together with the simple reduction product **634** (21% yield for each component). Comparisons between the crystalline tricycle **636** and the mixture provided good evidence for the other tricycle **635**. The simple reduction product **634** is based on evidence that both TMS-propargyl ether and methylenecyclopropane groups remained intact.

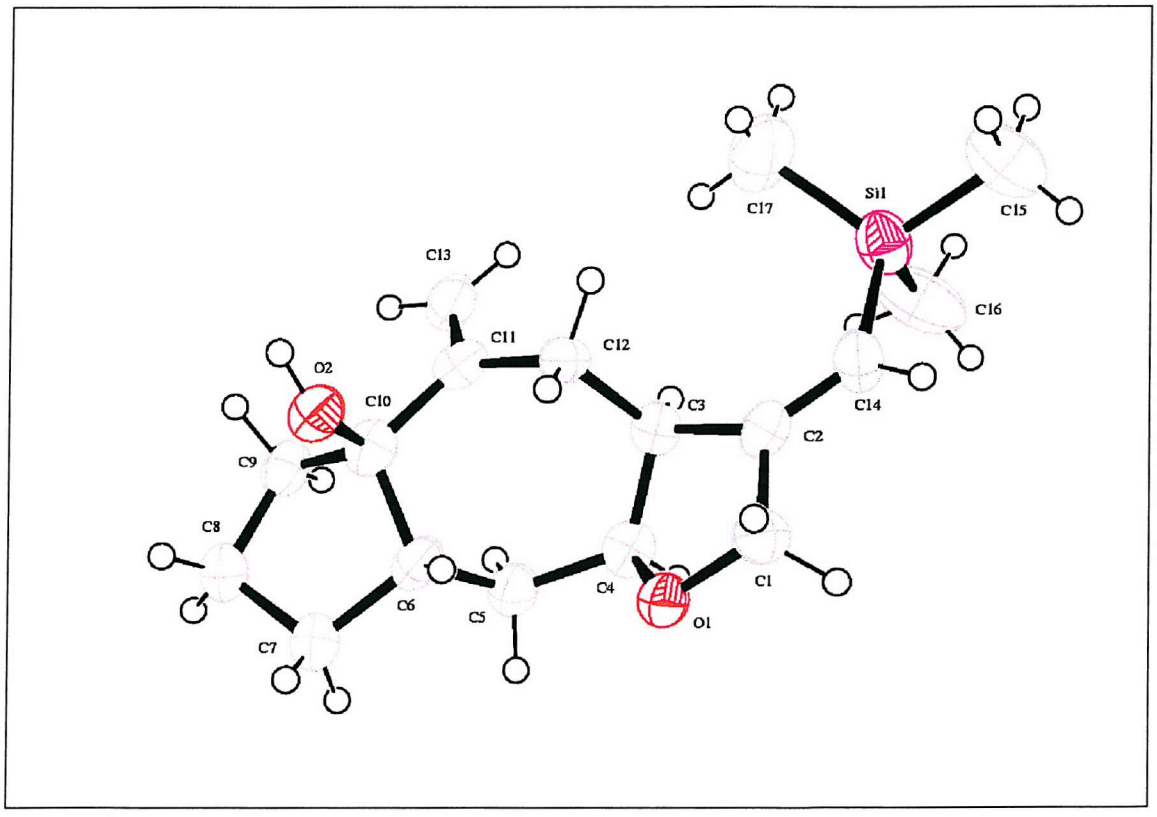
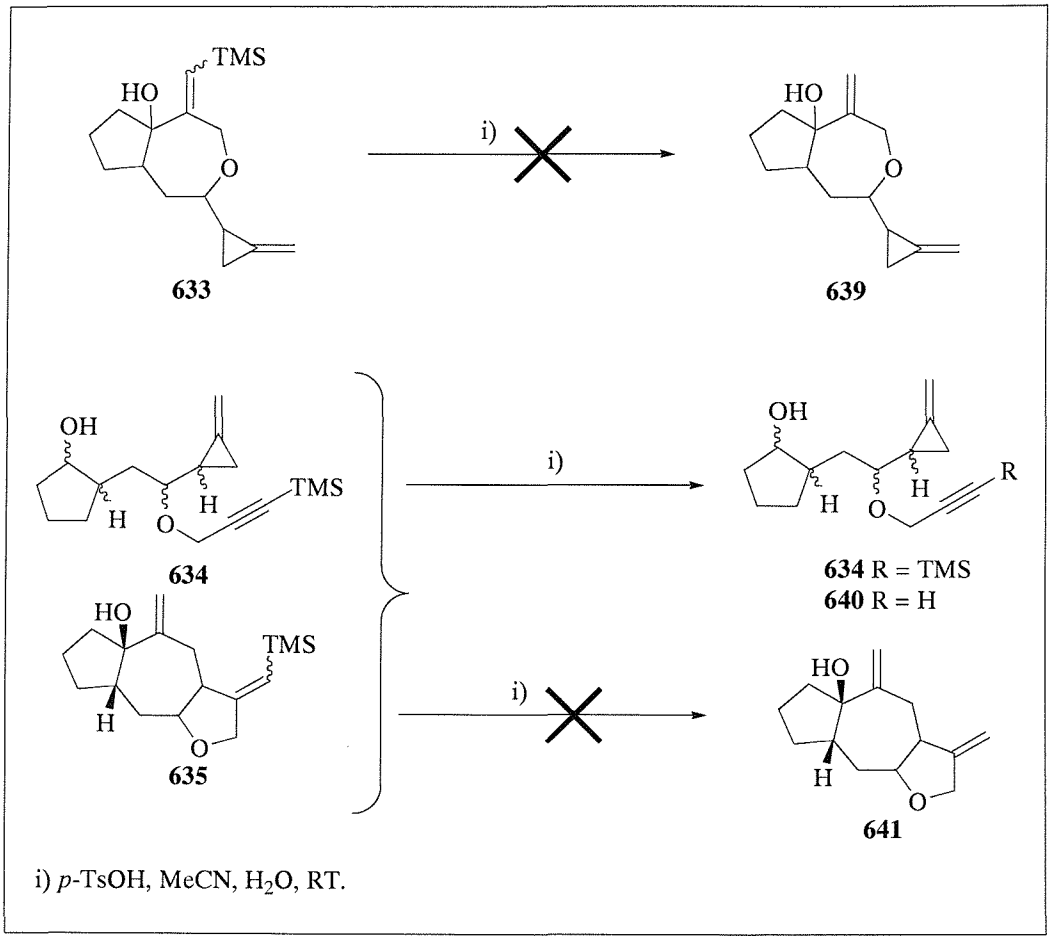


Figure 26. X-ray crystal structure of 5,7,5 tricyclic cyclisation product.

To obtain more conclusive evidence, derivatisation of the mixture of **634** and **635** in the form of proto-desilylation was attempted. Trial reactions with phenyl sulphinic acid or *p*-TsOH suggested that the *p*-TsOH was a better reagent as it gave cleaner results. The proto-desilylation was carried out separately on the 7-*exo*-dig product **633** and the mixture of products **634** and **635** (Scheme 122). The 7-*exo*-dig product **633** did not give any identifiable products (*e.g.* **639**) that any conclusions could be drawn from.

The mixture of products **634** and **635** afforded a single product which appeared to be related to the simple reduction product **634** (Scheme 122). The product was difficult to purify and hence absolute assignment was not possible. Even so, the NMR data strongly suggested the simple reduction alcohols **634** or **640**. The limited amount of material and propensity for propargyl groups to fragment made mass spectrometry difficult and only evidence for the backbone was obtained. No evidence for a de-silylated tricycle **641** was found.



Scheme 122. Proto-desilylation reactions.

Using identical conditions, cyclisation studies on the other mixture of precursors **604** were disappointing. No identifiable products were obtained despite repeated attempts at purification. This result seemed to be in accordance with the related keto-alcohol precursor **598**. The reasons for the complexity of the products are not known.

5.4 Conclusions

The change from an acyclic ketone to a cyclic ketone as the precursor for cyclisations has had a marked effect. Throughout, no 7-*endo*-trig cyclisations onto the methylenecyclopropane have been observed. It would appear that if the stereochemistry is suitable, that isomer will cyclise predominantly to give the desired cycloheptane product. In direct comparison to the simple precursor **308** (see chapter 2), this is a remarkable result as 7-*endo* and reduction products were isolated for the simpler system.

Inclusion of an alcohol moiety with a cyclic ketone would also appear to further encourage the desired cycloheptane formation. Although the experiments were complicated by multiple isomers, good yields of bicyclic products were obtained.

Conversion of the alcohol to a TMS-propargyl ether moiety gave a further complicated outcome on cyclisation. Nonetheless, successful cyclisation to obtain 5,7,5 tricycles did occur, although there are some undesired side reactions.

5.5 Project Conclusions

The synthesis of cycloheptanes using an initial 6-*exo*-trig cyclisation onto methylenecyclopropane has not been a trivial investigation. Very basic open-chain precursors did not give high yields of the desired cycloheptane, and also 7-*endo*-trig products were isolated (chapter 2). "Best" conditions were found for the cyclisation reaction.

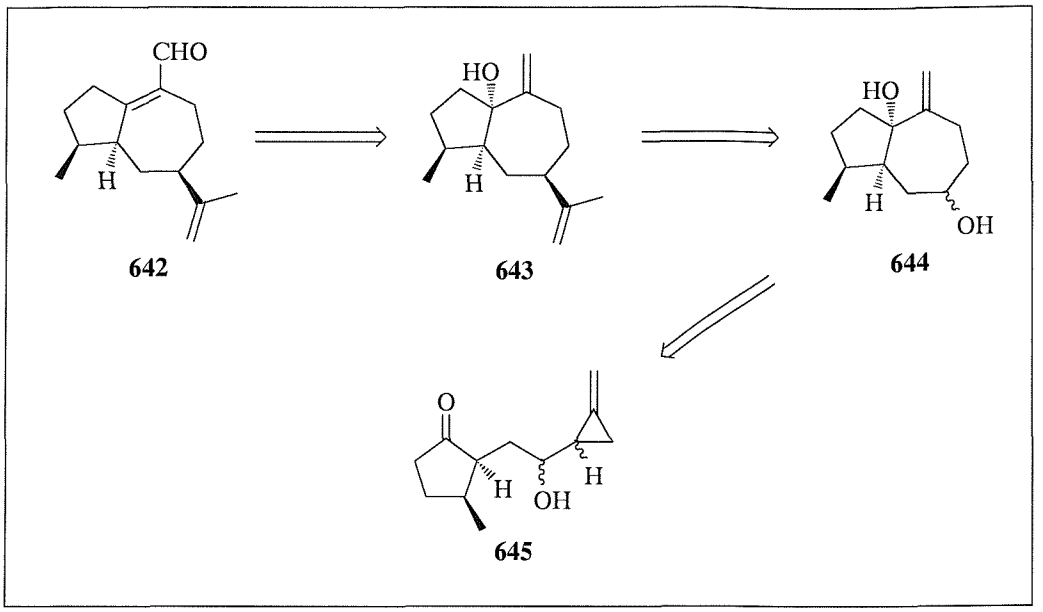
Inclusion of an alcohol functionality on this backbone greatly increased overall yields but the major product was never the desired cycloheptane (chapter 4). 7-*endo*-trig bicycles were persistent products, and when tandem processes were attempted problems with other

cyclisation paths (8-*endo*) became apparent, although a solution to this problem was found.

Attempts to affect the outcome of the cyclisation by locking the backbone also did have the desired effect (chapter 3). Studies were hampered initially by the tricky synthesis of the precursors in the cyclohexane series. When the cyclisations were attempted none of the products contained the desired cycloheptane. Although 6-*exo*-trig cyclisation did occur, the only identifiable product was a *trans*-decalin. Locking the backbone with an aromatic system was investigated but the cyclisation reactions were fruitless.

Using a carbocyclic ketone introduced unforeseen complications with inseparable mixtures of isomers of the various precursors (chapter 5). This was particularly apparent with the alcohol and ether precursors. The desired cycloheptane products were isolated on several occasions. The alcohol/ether precursors gave a more complicated product profile, but bi- and tri-cyclic products were obtained. The apparent complete suppression of the 7-*endo*-trig path was achieved.

Further investigation into the effects of precursor stereochemistry would possibly shed some light on the geometry of the cyclisation transition states. Ultimately, this approach to cycloheptanes and natural products containing cycloheptanes would appear to be very limited in scope as it is likely that major stereochemical control in the precursors would be necessary. However, using the methodology developed, a synthesis of guaia-1(10),11-diene-15-al **642**[147, 148], or related natural product, from a suitable cyclopentyl analogue **645** could be envisaged (Scheme 123). If the cyclisation were successful, the synthesis would require substitution of the secondary alcohol in **644** for an isopropene unit. The conversion of tertiary alcohol **643** to the α,β unsaturated aldehyde with PCC is known[147, 148]. **642** is reported[147] to have a woody-floral aroma and is present in the highly valued Kanankoh oriental incense.



Scheme 123. Potential synthesis of guaia-1(10),11-diene-15-al using the established methodology.

Chapter Six

6 Experimental

6.1 General

Reactions requiring anhydrous conditions were conducted in oven-dried or flame-dried glassware. Reagents used were of commercial grade and, where necessary, purified prior to use following the procedures outlined by Perrin and Armarego[149]. Solvents were distilled prior to use: THF distilled from sodium and benzophenone under argon; DCM distilled from calcium hydride; PE distilled from calcium hydride using the fraction boiling between 40 and 60°C.

TLC was performed on aluminium backed sheets coated with silica gel (0.25mm) which contained the fluorescent indicator UV_{254}. Flash column chromatography was carried out using Sorbsil C60 40-60 mesh silica, broadly following the methods reported by Still[150, 151].

6.1.1 Instrumentation

^{1}H NMR spectra were obtained on Bruker AC300 or DPX 400 spectrometers at 300 or 400 MHz respectively at RT unless otherwise indicated. Peak positions are quoted in ppm relative to the residual solvent peak for the deuterated solvent. The following abbreviations are used for 1H spectra: broad (br.), singlet (s), doublet (d), triplet (t) quartet (q), quintet (quin).

^{13}C NMR spectra were obtained on Bruker AC300 or DPX 400 spectrometers at 75.5 or 100 MHz respectively at RT. Peak positions are quoted in ppm relative to the residual solvent peak for the deuterated solvent. The multiplicities of the signals were determined using DEPT experiments, and are indicated using the following notation in parentheses: primary (3), secondary (2), tertiary (1), quaternary (0).

Where relevant, the following correlation spectroscopic techniques were used to help assignment of NMR peaks: COSY, HMQC, HMBC.

Infrared spectra were obtained on a Bio-Rad Golden Gate ATR FT-IR spectrometer. The nature of the peaks is indicated using the following notation in parentheses: broad (br.), strong (s), medium (m), weak (w).

Melting points were measured in open capillary tubes using a Gallenkamp Electrothermal Melting Point Apparatus and are uncorrected.

Low resolution EI and CI mass spectra were obtained on a ThermoQuest TraceMS gas chromatography mass spectrometer. High resolution EI and CI mass spectra were obtained on a VG 70-SE Normal geometry double focusing mass spectrometer. High resolution electrospray mass spectra were obtained on a Bruker Apex III FT-ICR mass spectrometer.

X-ray diffraction data was obtained from an Enraf Nonius KappaCCD diffractometer. The structure was determined by direct methods using the program SHELXS97[151] and refined using SHELXL97[152].

6.1.2 Compound Reporting

In general, all data is reported as for a single compound or isomer. However, where two different isomers or compounds are inseparable the data is reported for each single isomer or compound as much as possible. In some cases it is possible to report the data for each compound separately; in other cases this is not possible and an indication as to which compound the data refers to is added. Where minor isomer or compound signals are obscured by major isomer or compound signals, discernable signals are reported. Two carbon signals that have coincidental chemical shifts are marked by an asterisk (*). In some cases an inseparable impurity was isolated with the cyclisation product. This is believed to come from stabilising agents in the elution solvent and is not reported with the data.

6.2 Experimental details

6.2.1 Preparation and Use of SmI_2 for Cyclisation Reactions

Following modified methods of Curran[153] and Molander[54], excess iodine was removed from di-iodoethane using DCM and $Na_2S_2O_3$. The DCM layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give a crystalline white powder.

All solvents and additives were distilled and degassed with Ar.

A typical size reaction used 0.080g of ketone. Samarium metal (4-8 equivalents to ketone) was placed in flame-dried glassware under a flow of Ar. Degassed, dry THF (30mL) was added, followed by di-iodoethane (2.5-5 equivalents to ketone). The mixture was stirred at RT for 2 hours under a flow of Ar and the resulting deep Prussian blue solution used directly. If necessary, THF was added to bring the volume to approximately 30mL.

Additives:

HMPA (4 equivalents to di-iodoethane), turned SmI_2 solution deep purple; ^{t}BuOH (2 equivalents to ketone) was used with HMPA. Methanol[154] (2.5mL), turned SmI_2 solution deep emerald green upon cooling below 0°C.

Method A: Addition of substrate to SmI_2.

The required additive was added to the SmI_2 solution and then cooled to the required temperature. The ketone was added in THF (5mL), with ^{t}BuOH when required, to the SmI_2 solution over 90 minutes (HMPA) or 45 minutes (methanol) *via* syringe pump.

Method B: Addition of SmI_2 to substrate.

The ketone was dissolved in THF (30mL) and added to flame-dried glassware under Ar. Methanol or HMPA with ^{t}BuOH was added to the ketone solution and the mixture cooled to the required temperature. The SmI_2 solution was cooled to the required temperature and, whilst both flasks were kept under a flow of Ar, the SmI_2 solution was transferred *via* cannula at a slow rate (~ 1 drop per second) to the ketone-additive mixture. As the drops of SmI_2 were added, the relevant colour change was observed which then dissipated upon stirring.

The reaction was allowed to proceed at the required temperature and when completed quenched with citric acid (1.0g) in brine (20mL). The reaction mixture was extracted with ether (100mL) and EA (100mL), the organic phases combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification was achieved by column chromatography using the eluant specified.

6.2.2 Experimental for Chapter 2

Methylenecyclopropane 200

200

Using a modified method of Binger[83], methallyl chloride **209** (280mL, 2.84mol) was added drop-wise over 9 hours to a rapidly stirred suspension of sodium amide (139g, 3.56mol) in dry *n*-butyl ether (400mL) at 130°C under a slow stream of nitrogen. The reaction was allowed to stir for a further 20 hours using a cold-finger condenser at -40°C. Cold traps at -78°C were employed to collect products. The cold-finger condenser was allowed to warm to RT and then heated to 40°C. A biphasic mixture was isolated in the cold trap. The upper layer was ammonia and was allowed to boil off to give a mixture of methylenecyclopropane and methylcyclopropene (100mL, 52%, 3:1 ratio).

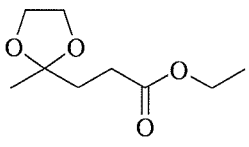
A suspension of potassium *t*butoxide (3.32g, 0.030mol) in DMSO (40mL) was added slowly to a solution of *t*-butanol (3.29g, 0.044mol), DMSO (60mL) and the C_4H_6 mixture (100mL, 1.48mol in total of which 25mL, 0.37mol of methylcyclopropene) at 0°C under a slow stream of nitrogen. The reaction mixture was left to react for 3 hours using a cold-finger condenser at -60°C. The reaction was then allowed to warm to room temperature and stirred for 16 hours. The reaction was then warmed to 45°C, with the cold-finger warmed to 45°C for 4 hours and the product was collected in a cold trap at -78°C to yield pure methylenecyclopropane (100ml, 52% overall). Data agrees with Binger[83].

^{1}H NMR (300MHz, $CDCl_3$) **δ**: 5.42 (2H, br.s, $=CH_2$), 1.08 (4H, br.s, cyclopropyl CH_2CH_2)

^{13}C NMR (75MHz, $CDCl_3$) **δ**: 131.3 (0), 103.4 (2), 3.0 (2)*

* = 2 carbons.

Ethyl 3-(2-methyl-1,3-dioxolan-2-yl)propanoate 316



316

Following the method of Kelly[155], ethylene glycol (28.0g, 0.451mol), ethyl levulinate **313** (28.0g, 0.194mol) and *p*-TsOH (0.350g, 0.002mol) were refluxed together in toluene (210mL) for 36 hours using Dean-Stark apparatus to remove water. The reaction was cooled and concentrated *in vacuo*. Ether (150mL) was added and the organic phase

washed with $NaHCO_3$ (50mL) and with brine (50mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The yellow crude oil was purified by distillation (b.p. 55–56 °C, 0.1mmHg) to yield ketal **316** as a colourless oil (31.5g, 86%). Data agrees with Trivedi[156].

R_f: 0.8 (30% EA/PE)

FT-IR ν_{max}: 2982 (s), 2884 (s), 1735 (s), 1446 (m), 1375 (s), 1180 (s), 1048 (s)

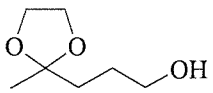
^{1}H NMR (300MHz, $CDCl_3$) **δ**: 4.12 (2H, q, *J* = 7Hz, OCH_2CH_3), 3.93 (4H, s, OCH_2CH_2O), 2.38 (2H, t, *J* = 8Hz, CH_2CO_2Et), 2.02 (2H, t, *J* = 8Hz, $CH_2CH_2CO_2Et$), 1.32 (3H, s, CH_3), 1.25 (3H, t, *J* = 7Hz, OCH_2CH_3)

^{13}C NMR (75MHz, $CDCl_3$) **δ**: 174.0 (0), 109.5 (0), 65.1 (2)*, 60.7 (2), 34.3 (2), 29.4 (2), 24.3 (3), 14.6 (3)

* = 2 carbons

LRMS (CI) m/z: 189 $(M+H)^+$ [100%].

3-(2-Methyl-1,3-dioxolan-2-yl)propan-1-ol 317



317

Following the method Albizati[157], ethyl-3-(2-methyl-1,3-dioxolan-2-yl)propanoate **316** (3.70g, 19.7mmol) in THF (10mL) was added drop-wise to a suspension of $LiAlH_4$ (1.12g, 29.5mmol) in THF (50mL) at 0°C and stirred for 1 hour. Ether (40mL) was added and the solution stirred for 5 minutes. NaOH (4M, 10mL) was added drop-wise slowly until a heavy white ppt was observed. The mixture was filtered, washed with ether (100mL) and concentrated *in vacuo* to give alcohol **317** as a colourless oil (2.84g, 99%). Data agrees with Liu[158].

R_f: 0.1 (30% EA/PE)

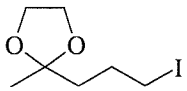
FT-IR ν_{max}: 3416 (br.s), 2981 (m), 2953 (s), 2879 (s), 1448 (m), 1378 (s), 1220 (m), 1066 (s)

^{1}H NMR (300MHz, $CDCl_3$) **δ**: 3.98 – 3.91 (4H, m, OCH_2CH_2O), 3.62 (2H, q, *J* = 5Hz, CH_2OH), 2.45 (1H, t, *J* = 5Hz, OH), 1.78 – 1.63 (4H, m, $CH_2CH_2CH_2OH$), 1.32 (3H, s, CH_3)

^{13}C NMR (75MHz, $CDCl_3$) **δ**: 110.3 (0), 65.0 (2)*, 63.2 (2), 36.1 (2), 27.5 (2), 24.0 (3)

* = 2 carbons.

2-(3-Iodopropyl)-2-methyl-1,3-dioxolane 312



312

Following the method Motherwell[126], triphenylphosphine (6.73g, 25.7mmol), imidazole (1.98g, 29.1mmol) and finally iodine (6.95g, 27.4mmol) were added to a stirred solution of 3-(2-methyl-1,3-dioxolan-2-yl)propan-1-ol **317** (2.50g, 17.1mmol) in ether (75mL) and acetonitrile (25mL). The solution was stirred for 15 minutes. The resulting red-brown solution was diluted with ether (120mL), washed with $Na_2S_2O_3$ (120mL) and then water (60mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was triturated with PE, filtered, concentrated *in vacuo* and purified by column chromatography (0 to 10% EA/PE) to yield iodide **312** as a very pale yellow oil (4.30g, 98%). Data agrees with Ahlberg[159].

R_f: 0.7 (30% EA/PE)

FT-IR ν_{max}: 2983 (m), 2956 (m), 2881 (m), 1438 (m), 1377 (s), 1235 (s), 1044 (s)

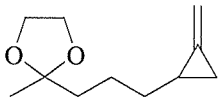
^{1}H NMR (300MHz, $CDCl_3$) δ: 3.95 – 3.92 (4H, m, OCH_2CH_2O), 3.21 (2H, t, J = 7Hz, CH_2I), 2.00 – 1.89 (2H, m, CH_2), 1.77 – 1.71 (2H, m, CH_2), 1.32 (3H, s, CH_3)

^{13}C NMR (75MHz, $CDCl_3$) δ: 109.7 (0), 65.1 (2)*, 40.2 (2), 28.6 (2), 24.4 (3), 7.4 (2)

* = 2 carbons

LRMS (CI) m/z: 257 $(M+H)^+$ [35%], 129 [100%].

2-Methyl-2-[3-(2methylenecyclopropyl)propyl]-1,3-dioxolane 318



5

^{n}BuLi (13.9mL, 2.33M in hexanes, 32.3mmol) was added to methylenecyclopropane **200** (3.0mL, 43.1mmol) in THF (90mL) at -60°C and allowed to warm to 0°C over 45 minutes. The reaction was left for 45 minutes at 0°C, then cooled to -60°C and HMPA (9.4mL, 53.9mmol) was added, immediately followed by the drop-wise addition of 2-(3-iodopropyl)-2-methyl-1,3-dioxolane **312** (6.90g, 26.9mmol). The reaction was allowed to warm to RT overnight. It was then quenched with NH_4Cl (120mL) and extracted with ether (3 x 150mL). The combined organic phases were washed with brine (200mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (0 to 10% ether/PE) to give ketal **318** as a colourless oil (3.65g, 74%). Data agrees with Peron[160].

R_f: 0.7 (30% Ether/PE)

FT-IR ν_{max}: 3064 (m), 3039 (m), 2980 (s), 2942 (s), 2874 (s), 1460 (m), 1375 (s), 1218 (s), 1138 (m), 1067 (s)

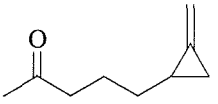
^{1}H NMR (300MHz, $CDCl_3$) **δ**: 5.36 (1H, s with fine splitting, $=CH_AH_B$), 5.30 (1H, s with fine splitting, $=CH_AH_B$), 3.93 – 3.88 (4H, m, OCH_2CH_2O), 1.67 – 1.55 (2H, m, CH_2), 1.54 – 1.41 (2H, m, CH_2), 1.40 – 1.30 (3H, m, CH_2, cyclopropyl CH), 1.29 (3H, s, CH_3), 1.18 (1H, m, cyclopropyl CH_CH_D), 0.69 (1H, m, cyclopropyl CH_CH_D)

^{13}C NMR (75MHz, $CDCl_3$) **δ**: 137.2 (0), 110.4 (0), 102.8 (2), 64.9 (2)*, 39.2 (2), 33.5 (2), 24.2 (2), 24.0 (3), 15.9 (1), 9.7 (2)

* = 2 carbons

LRMS (CI) m/z: 183 $(M + H)^+$ [16%], 121 [100%].

5-(2-Methylenecyclopropyl)pentan-2-one 308



308

2-Methyl-2-[3-(2-methylenecyclopropyl)propyl]-1,3-dioxolane **318** (3.62g, 20mmol) was stirred with *p*-TsOH (3.80g, 20mmol) in a mixture of acetone (270mL) and water (30mL) under Ar for 48 hours. The mixture was concentrated *in vacuo* and ether (100mL) added. The mixture was washed with $NaHCO_3$ (100mL) and the aqueous phase extracted with ether (100mL) and then DCM (100mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. This gave ketone **308** as a colourless oil (2.47g, 90%). Data agrees with Peron[160].

R_f: 0.6 (30% Ether/PE)

FT-IR ν_{max}: 3067 (w), 2975 (m), 2935 (m), 2856 (w), 1713 (s), 1443 (w), 1360 (m), 1261 (m), 1163 (m), 1098 (w)

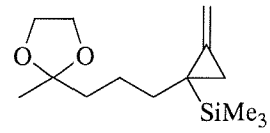
^{1}H NMR (400MHz, $CDCl_3$) **δ**: 5.40 (1H, s with fine splitting, $=CH_AH_B$), 5.35 (1H, s with fine splitting, $=CH_AH_B$), 2.47 (2H, t, J = 7Hz, $COCH_2$), 2.15 (3H, s, CH_3), 1.74 – 1.65 (2H, m, $COCH_2CH_2$), 1.41 – 1.31 (3H, m, $COCH_2CH_2CH_2$, cyclopropyl CH), 1.23 (1H, m, cyclopropyl CH_CH_D), 0.74 (1H, m, cyclopropyl CH_CH_D)

^{13}C NMR (100MHz, $CDCl_3$) **δ**: 209.3 (0), 137.0 (0), 103.1 (2), 43.7 (2), 32.9 (2), 30.2 (3), 24.0 (2), 15.8 (1), 9.8 (2)

LRMS (CI) m/z: 156 $(M + H_2O)^+$ [100%], 139 $(M+H)^+$ [69%]

HRMS (EI) m/z: $C_8H_{11}O$ $(M-CH_3)^+$ requires 123.08099, found 123.08106 [100%].

Trimethyl{1-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]-2-methylenecyclopropyl}silane 319



319

^{n}BuLi (8.6mL, 2.29M in hexanes, 19.6mmol) was added to methylenecyclopropane **200** (1.3mL, 22.0mmol) in THF (30mL) at -40°C and allowed to warm to 0°C over 30 minutes. The reaction was left for 1 hour at 0°C, then cooled to -55°C and freshly distilled TMSCl (2.35mL, 18.5mmol) was added to the orange solution which became colourless. The solution was warmed to 0°C over 30 minutes. The reaction was left for 30 minutes at 0°C, then cooled to -60°C. ^{n}BuLi (8.6mL, 2.29M in hexanes, 19.6mmol) was added and the reaction warmed to 0°C over 30 minutes. The reaction was left for 30 minutes at 0°C, then cooled to -78°C, followed by the drop-wise addition of 2-(3-iodopropyl)-2-methyl-1,3-dioxolane **313** (4.70g, 18.4mmol). A yellow ppt was formed upon complete addition. The reaction was allowed to warm to RT overnight. It was then quenched with NH_4Cl (80mL) and extracted with ether (3 x 80mL). The organic phase was washed with brine (120mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (0 to 1% EA/PE) to give ketal **319** as a pale yellow oil (3.60g, 77%). Data agrees with Peron[160].

R_f: 0.4 (10% EA/PE)

FT-IR ν_{max}: 3065 (m), 2952 (s), 2879 (s), 1461 (m), 1376 (s), 1249 (s), 1220 (s), 1117 (s), 1070 (s)

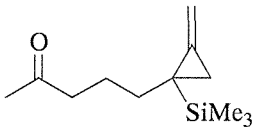
^{1}H NMR (300MHz, $CDCl_3$) δ: 5.24 (1H, s, $=CH_AH_B$), 5.20 (1H, s, $=CH_AH_B$), 3.96 – 3.88 (4H, m, OCH_2CH_2O), 1.62 – 1.36 (6H, m, $CH_2CH_2CH_2$), 1.31 (3H, s, CH_3), 1.04 (1H, d, J = 7Hz, cyclopropyl CH_CH_D), 0.82 (1H, d, J = 7Hz, cyclopropyl CH_CH_D), -0.02 (9H, s, $Si(CH_3)_3$)

^{13}C NMR (75MHz, $CDCl_3$) δ: 140.3 (0), 110.4 (0), 100.4 (2), 65.0 (2)*, 39.8 (2), 36.1 (2), 24.1 (3), 23.2 (2), 14.3 (0), 12.7 (2), -2.2 (3)

* = 2 carbons

LRMS (CI) m/z: 255 $(M+H)^+$ [2%], 73 $(SiMe_3)^+$ [100%].

5-[2-Methylene-1-(1,1,1-trimethylsilyl) cyclopropyl]-2-pentanone 309



309

Trimethyl{1-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]-2-methylenecyclopropyl}silane **319** (1.16g, 4.5mmol) was stirred with *p*-TsOH (0.87g, 4.5mmol) in a mixture of acetone (90mL) and water (10mL) under Ar for 48 hours. The mixture was concentrated *in vacuo* and ether (50mL) added. The mixture was washed with $NaHCO_3$ (50mL) and the aqueous phase extracted with ether (2 x 50mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give ketone **309** as a colourless oil (0.933g, 97%). Data agrees with Peron[160].

R_f: 0.6 (30% Ether/PE)

FT-IR ν_{max}: 3066 (w), 2954 (m), 2891 (m), 2846 (w), 1716 (s), 1408 (w), 1359 (m), 1249 (s), 1163 (m), 1114 (w)

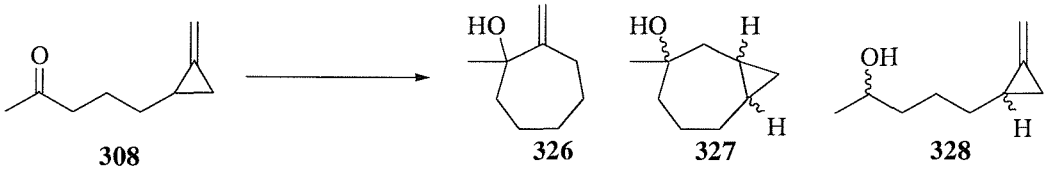
^{1}H NMR (400MHz, $CDCl_3$) δ: 5.26 (1H, br.s, $=CH_AH_B$), 5.19 (1H, m, $=CH_AH_B$), 2.38 (2H, t, J = 7Hz, $COCH_2$), 2.12 (3H, s, CH_3CO), 1.67 – 1.43 (3H, m, $COCH_2CH_2CH_CH_D$), 1.35 (1H, ddd, J = 5, 11, 16Hz, $COCH_2CH_2CH_CH_D$), 1.06 (1H, dt, J = 2, 7Hz, cyclopropyl CH_EH_F), 0.81 (1H, dt, J = 2, 7Hz, cyclopropyl CH_EH_F), 0.00 (9H, s, $Si(CH_3)_3$)

^{13}C NMR (100MHz, $CDCl_3$) δ: 209.1 (0), 140.1 (0), 100.7 (2), 44.3 (2), 35.5 (2), 30.2 (3), 23.0 (2), 14.2 (0), 12.9 (2), -2.2 (3)

LRMS (CI) m/z: 211 $(M+H)^+$ [2%], 73 $(SiMe_3)^+$ [100%]

HRMS (EI) m/z: $C_{12}H_{22}OSi$ $(M)^+$ requires 210.14399, found 210.14439 [5%]; $C_{11}H_{19}OSi$ $(M-CH_3)^+$ requires 195.12052, found 195.12128 [100%].

Cyclisation of 5-(2-methylenecyclopropyl)pentan-2-one 308



308 **326** **327** **328**

Following method B at 0°C, samarium (0.544g, 3.58mmol); di-iodoethane (0.612g, 2.16mmol); ketone **308** (0.130g, 0.94mmol); HMPA (1.26mL, 7.25mmol); ^{t}BuOH (0.2mL, 2.07mmol) were used. Column chromatography (0 to 50% ether/PE) afforded 1-methyl-2-methylenecycloheptanol **326** (0.020g, 24%) as a colourless oil; and an

inseparable mixture of 3-methylbicyclo[5.1.0]octan-3-ol (0.010g, 12%) **327** and 5-(2-methylenecyclopropyl)pentan-2-ol **328** (0.002g, 2%). Yields based on RSM [0.049g].

1-Methyl-2-methylenecycloheptanol 326

R_f: 0.3 (50% Ether/PE)

FT-IR ν_{max}: 3402 (br.m), 2923 (s), 2854 (m), 1636 (m), 1444 (m), 1365 (m), 1173 (m), 1025 (m), 897 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.19 (1H, s with fine splitting, =CH_AH$_B$), 4.89 (1H, s with fine splitting, =CH$_A$$H_B$), 2.36 (1H, ddd, J = 3, 7, 13Hz, CH_CH$_D$), 1.99 (1H, m, CH$_C$$H_D$), 1.88 – 1.78 (2H, m, C$H_EH_F$, C$H_GH_H$), 1.76 – 1.66 (3H, m, CH$_E$$H_F$, C$H_IH_J$, OH), 1.59 – 1.51 (1H, m, CH_KH$_L$), 1.44 – 1.32 (3H, m, CH$_G$$H_H$, CH$_I$$H_J$, CH$_K$$H_L$), 1.32 (3H, s, CH_3)

^{13}C NMR (100MHz, $CDCl_3$) δ: 159.1 (0), 110.8 (2), 76.1 (0), 42.9 (2), 34.0 (2), 32.2 (2), 31.0 (3), 30.9 (2), 23.9 (2)

LRMS (EI) m/z: 140 $(M)^+$ [4%], 122 $(M\text{-}H_2O)^+$ [20%], 42 [100%]

HRMS (EI) m/z: $C_9H_{16}O$ $(M)^+$ requires 140.12012, found 140.12004 [29%].

3-Methylbicyclo[5.1.0]octan-3-ol 327

R_f: 0.2 (50% Ether/PE)

FT-IR ν_{max}: 3407 (m), 2909 (s), 2853 (m), 1459 (m), 1370 (m), 1173 (m), 1075 (m), 920 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 2.25 – 2.17 (2H, m, CH_AH$_B$, CH_CH$_D$), 1.84 (1H, m, CH_EH$_F$), 1.62 (1H, m, CH_GH$_H$), 1.41 – 1.15 (4H, m, CH$_A$$H_B$, CH$_C$$H_D$, CH$_E$$H_F$, CH$_G$$H_H$), 1.21 (3H, s, CH_3), 0.98 – 0.75 (3H, m, cyclopropyl CH, cyclopropyl CH_2), 0.10 (1H, m, cyclopropyl CH)

^{13}C NMR (100MHz, $CDCl_3$) δ: 73.5 (0), 45.7 (2), 42.9 (2), 32.2 (3), 31.1 (2), 24.6 (2), 17.1 (1), 16.1 (2), 9.9 (1)

LRMS (EI) m/z: 140 $(M)^+$ [4%], 122 $(M\text{-}H_2O)^+$ [10%], 42 [100%]

HRMS (EI) m/z: $C_9H_{16}O$ $(M)^+$ requires 140.12012, found 140.12037 [9%].

Cyclisation of 5-(2-methylenecyclopropyl)pentan-2-one 308

308 **328**

Following method A at -78°C, samarium (0.435g, 2.90mmol); di-iodoethane (0.510g, 1.81mmol); ketone **308** (0.100g, 0.72mmol); methanol (2.5mL) were used. Column chromatography (0 to 20% ether/PE) afforded as a mixture of diastereoisomers 5-(2-methylenecyclopropyl)pentan-2-ol **328** (1:1 ratio, 0.085g, 92% based on RSM [0.009g]) as a colourless oil.

5-(2-Methylenecyclopropyl)pentan-2-ol 328

R_f: 0.2 (50% Ether/PE)

FT-IR ν_{max}: 3343 (br. m), 2968 (m), 2923 (s), 2854 (m), 1459 (m), 1370 (m), 1306 (m), 1128 (m), 1015 (m), 936 (m), 882 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.40 (1H, m, =CH_AH$_B$), 5.34 (1H, m, =CH$_A$$H_B$), 3.82 (1H, sextet, J = 6Hz, CH(OH)), 1.58 – 1.33 (8H, m, $CH_2CH_2CH_2$, OH, cyclopropyl CH), 1.22 (1H, m, cyclopropyl CH_CH$_D$), 1.21 (3H, d, J = 6Hz, CH_3), 0.73 (1H, m, cyclopropyl CH$_C$$H_D$)

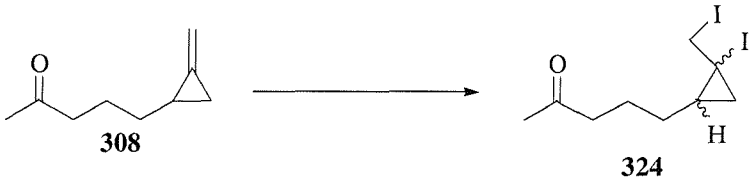
^{13}C NMR (100MHz, $CDCl_3$) δ: 137.4 (0)*, 102.9 (2)*, 68.53 & 68.51 (1), 39.39 & 39.37 (2), 33.47 & 33.45 (2), 26.01 & 25.97 (2), 23.9 (3)*, 16.1 (1)*, 9.8 (2)*

* = 2 carbons

LRMS (CI) m/z: 141 $(M+H)^+$ [100%]

HRMS (EI) m/z: $C_8H_{13}O$ $(M-CH_3)^+$ requires 125.09664 found 125.09644 [10%].

Cyclisation of 5-(2-methylenecyclopropyl)pentan-2-one 308



308 **324**

Following method B at -78°C, samarium (0.544g, 3.58mmol); di-iodoethane (0.612g, 2.16mmol); ketone **308** (0.100g, 0.72mmol); methanol (2.5mL) were used. Column chromatography (0 to 50% ether/PE) afforded 5-[2-iodo-2-(iodomethyl)cyclopropyl]pentan-2-one **324** as a mixture of diastereoisomers (5:1 ratio, 0.100g, 42% based on RSM [0.020g]) as a yellow oil.

5-[2-Iodo-2-(iodomethyl)cyclopropyl]pentan-2-one 324

Major isomer

R_f: 0.3 (50% Ether/PE)

FT-IR ν_{max}: 3063 (w), 2989 (m), 2935 (s), 2855 (m), 1712 (s), 1437 (m), 1413 (m), 1355 (m), 1255 (m), 1225 (m), 1173 (s), 1034 (m), 930 (w), 862 (w), 721 (w)

^{1}H NMR (400MHz, $CDCl_3$) δ: 3.74 (1H, d, *J* = 11Hz, CH_AH_BI), 3.58 (1H, d, *J* = 11Hz, CH_AH_BI), 2.52 (2H, t, *J* = 7Hz, $COCH_2$), 2.17 (3H, s, CH_3), 1.85 – 1.67 (2H, m, $CH_3COCH_2CH_2$), 1.59 (1H, m, $COCH_2CH_2CH_CH_D$), 1.44 (1H, m, $COCH_2CH_2CH_CH_D$), 1.26 (1H, dd, *J* = 6.5, 10Hz, cyclopropyl CH_EH_F), 1.12 (1H, t, *J* = 6.5Hz, cyclopropyl CH_EH_F), 0.27 (1H, dtd, *J* = 6.5, 7, 10Hz, cyclopropyl CH)

^{13}C NMR (100MHz, $CDCl_3$) δ: 209.0 (0), 43.6 (2), 37.0 (2), 30.3 (3), 29.7 (1), 29.1 (2), 26.8 (2), 23.1 (2), 19.0 (0)

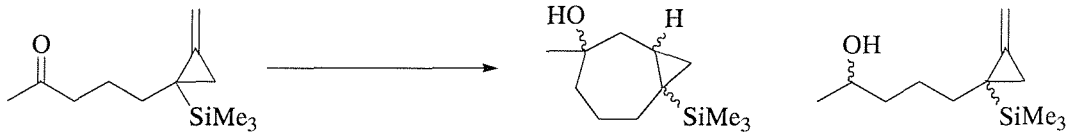
LRMS (CI) m/z: 410 $(M+ H_2O)^+$ [70%], 392 $(M)^+$ [1%]

Minor isomer (assignment based on following data)

^{1}H NMR (400MHz, $CDCl_3$) δ: 3.69 (1H, d, *J* = 11Hz, CH_AH_BI), 3.48 (1H, d, *J* = 11Hz, CH_AH_BI), 2.49 (2H, t, *J* = 7Hz, $COCH_2$), 2.15 (3H, s, CH_3), 0.60 (1H, t, *J* = 6.5Hz, cyclopropyl CH_CH_D)

^{13}C NMR (100MHz, $CDCl_3$) δ: 208.6 (0), 43.3 (2), 34.9 (1), 30.4 (3), 28.1 (2), 27.7 (2), 23.5 (2), 21.4 (2), 10.4 (0).

Cyclisation of 5-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-pentanone 309



309 **339** **340**

Following method A at -78°C, samarium (0.357g, 2.38mmol); di-iodoethane (0.402g, 1.43mmol); ketone **309** (0.100g, 0.48mmol); HMPA (0.83mL, 4.75mmol); ^{t}BuOH (0.09mL, 0.94mmol) were used. Column chromatography (0 to 50% ether/PE) afforded 3-methyl-7-(1,1,1-trimethylsilyl)bicyclo[5.1.0]octan-3-ol **339** (0.069g, 69%) as a colourless oil; and as a mixture of diastereoisomers 5-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-pentanol **340** (1:1 ratio, 0.014g, 14%) as a colourless oil.

3-Methyl-7-(1,1,1-trimethylsilyl)bicyclo[5.1.0]octan-3-ol 339

R_f: 0.5 (50% Ether/PE)

FT-IR ν_{max}: 3438 (br.w), 2952 (m), 2914 (m), 2848 (w), 1462 (m), 1372 (m), 1246 (s), 830 (s)

^{1}H NMR (400MHz, $CDCl_3$) **δ**: 2.29 (1H, ddd, *J* = 2, 6, 14Hz, C(OH)CH_AH$_B$CH), 2.22 (1H, tdd, *J* = 2, 7, 14Hz, C(OH)CH_CH$_D$CH$_2$), 1.94 (1H, br.s, OH), 1.81 (1H, m, C(OH)CH$_2$CH$_2$CH_EH$_F$), 1.66 (1H, m, CH$_2$CH_GH$_H$CH$_2$), 1.57 (1H, m, CH$_2$CH$_G$$H_HCH_2$), 1.41 (1H, dd, *J* = 10, 14Hz, C(OH)CH$_A$$H_B$CH), 1.33 (1H, ddd, *J* = 4, 12, 14Hz, C(OH)CH$_2$CH$_2$CH$_E$$H_F$), 1.21 (3H, s, CH_3), 0.97 (1H, ddd, *J* = 2, 11, 14Hz, C(OH)CH$_C$$H_DCH_2$), 0.83 (1H, m, cyclopropyl CH), 0.73 (1H, dd, *J* = 4, 8Hz, cyclopropyl CH_IH$_J$), 0.21 (1H, t, *J* = 4Hz, cyclopropyl CH$_I$$H_J$), 0.00 (9H, s, Si(CH$_3$)$_3$)

^{13}C NMR (100MHz, $CDCl_3$) **δ**: 73.2 (0), 45.6 (2), 43.6 (2), 33.4 (2), 31.9 (3), 24.1 (2), 21.9 (2), 14.6 (1), 12.0 (0), -2.0 (3)

LRMS (CI) m/z: 213 $(M+H)^+$ [15%], 90 [100%]

HRMS (EI) m/z: $C_{12}H_{24}OSi$ $(M)^+$ requires 212.15964, found 212.15988 [85%].

Cyclisation of 5-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-pentanone 309

309 **340**

Following method A at 0°C, samarium (0.357g, 2.38mmol); di-iodoethane (0.402g, 1.43mmol); ketone **309** (0.100g, 0.48mmol); methanol (2.5mL) were used. Column chromatography (0 to 50% ether/PE) afforded a mixture of diastereoisomers of 5-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-pentanol **340** (1:1 ratio, 0.020g, 37% based on RSM [0.046g]) as a colourless oil.

5-[2-Methylene-1-(1,1,1-trimethylsilyl) cyclopropyl]-2-pentanol 340

R_f: 0.3 (50% Ether/PE)

FT-IR ν_{max}: 3325 (br.m), 2960 (m), 2932 (m), 2892 (m), 2835 (m), 1372 (m), 1247 (s), 1119 (m), 1044 (m)

^{1}H NMR (400MHz, $CDCl_3$) **δ**: 5.26 (1H, s with fine splitting, =CH_AH$_B$), 5.20 (1H, s with fine splitting, =CH$_A$$H_B$), 3.78 (1H, sextet, *J* = 6Hz, C*H*(OH)), 1.57 – 1.29 (7H, m, CH$_2$CH$_2$CH$_2$, OH), 1.18 (3H, d, *J* = 6Hz, CH$_3$CO), 1.05 (1H, td, *J* = 2, 7Hz, cyclopropyl CH_CH$_D$), 0.81 (1H, td, *J* = 2, 7Hz, cyclopropyl CH$_C$$H_D$), -0.01 (9H, s, Si(CH$_3$)$_3$)

^{13}C NMR (100MHz, $CDCl_3$) **δ**: 140.4 & 140.3 (0), 100.5 (2)*, 68.4 (1)*, 40.04 & 40.02 (2), 35.9 (2)*, 24.81 & 24.76 (2), 23.9 (3)*, 14.4 (0)*, 12.8 (2)*, -2.2 (3)*

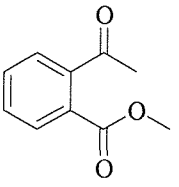
* = 2 carbons

LRMS (CI) m/z: 213 $(M+H)^+$ [4%], 35 [100%]

HRMS (EI) m/z: $C_{11}H_{21}OSi$ $(M-CH_3)^+$ requires 197.13617, found 197.13592 [100%].

6.2.3 Experimental for Chapter 3

Methyl 2-acetylbenzoate 367



367

Following the method of Newman[161], 2-acetylbenzoic acid **366** (25.0g, 0.152mol) was dissolved in acetone (600mL). Potassium carbonate (31.6g, 0.228mol) was added followed by methyl iodide (14.2mL, 0.228mol). The reaction mixture was refluxed for 18 hours. The mixture was then filtered and concentrated *in vacuo*. The residue was dissolved in DCM (200mL) and washed with water (200mL), dried ($MgSO_4$) and concentrated *in vacuo*. This afforded ester **367** as a pale yellow oil (27.1g, 100%). Data agrees with Newman[161].

R_f: 0.3 (40% Ether/PE)

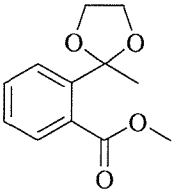
FT-IR ν_{max}: 3067 (w), 3001 (w), 2958 (w), 1720 (s), 1698 (s), 1691 (s), 1597 (w), 1574 (m), 1432 (m), 1266 (s), 1065 (m)

^{1}H NMR (360MHz, $CDCl_3$) δ: 7.86 (1H, dd, *J* = 1, 7Hz, aryl CH), 7.57 (1H, dt, *J* = 1, 7Hz, aryl CH), 7.50 (1H, dt, *J* = 1, 7Hz, aryl CH), 7.42 (1H, dd, *J* = 1, 7Hz, aryl CH), 3.90 (3H, s, CO_2CH_3), 2.54 (3H, s, $COCH_3$)

^{13}C NMR (90MHz, $CDCl_3$) δ: 203.2 (0), 167.8 (0), 143.1 (0), 132.4 (1), 130.5 (1), 130.1 (1), 129.3 (0), 126.9 (1), 52.9 (3), 30.3 (3)

LRMS (CI) m/z: 179 $(M+H)^+$ [100%].

Methyl 2-(2-methyl-1,3-dioxolan-2-yl)benzoate 368



368

Following the method of Noyori[129], methyl 2-acetylbenzoate **367** (10.5g, 58.9mmol) was dissolved in DCM (150mL). 1,2-Bis(trimethylsilyloxy)ethane (24g, 118mmol) was added and the reaction mixture cooled to -78°C under nitrogen. Trimethylsilyl trifluoromethanesulfonate (0.11mL, 0.59mmol) was added and the reaction was allowed to warm to RT slowly overnight. A further aliquot of trimethylsilyl

trifluoromethanesulfonate was added and the reaction allowed to proceed for a further 8 hours. $NaHCO_3$ (10mL) was added and the DCM layer washed with brine (100mL). The organic layer was collected, dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (0 to 30% ether/PE). Ketal **368** was isolated as a white solid (9.93g, 75%).

R_f: 0.3 (30% Ether/PE)

M.p.: 57 – 61°C

FT-IR ν_{max}: 2986 (w), 2953 (w), 2892 (w), 1725 (s), 1419 (s), 1250 (s), 1027 (s)

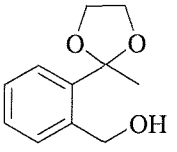
^{1}H NMR (400MHz, $CDCl_3$) δ: 7.55 (1H, d, *J* = 7Hz, aryl CH), 7.41 (1H, ddd, *J* = 2, 6, 8Hz, aryl CH), 7.34 – 7.31 (2H, m, aryl CH, aryl CH), 4.00 – 3.93 (2H, m, CH_2), 3.89 (3H, s, CO_2CH_3), 3.64 – 3.59 (2H, m, CH_2), 1.80 (3H, s, CH_3)

^{13}C NMR (100MHz, $CDCl_3$) δ: 171.7 (0), 141.7 (0), 132.4 (0), 130.4 (1), 128.3 (1), 127.8 (1), 127.0 (1), 109.2 (0), 64.6 (2)*, 52.7 (3), 27.7 (3)

* = 2 carbons

LRMS (CI) m/z: 223 $(M+H)^+$ [100%].

[2-(2-Methyl-1,3-dioxolan-2-yl)phenyl]methanol 369



369

Following the method Albizati[157], lithium aluminium hydride (3.75g, 98.9mmol) was dissolved in THF (100mL) and cooled to 0°C. Methyl 2-(2-methyl-1,3-dioxolan-2-yl)benzoate **368** (15.7g, 70.6mmol) was added dropwise in THF (20mL). The reaction was stirred overnight. Ether (80mL) was added and then NaOH (4M, 15mL) was added slowly drop-wise until a white ppt formed. The reaction mixture was filtered and washed with EA (120mL). The organic layer was concentrated *in vacuo* affording alcohol **369** as a colourless oil (13.7g, 100%).

R_f: 0.1 (60% Ether/PE)

FT-IR ν_{max}: 3393 (br.w), 2987 (w), 2937 (w), 2886 (w), 1374 (m), 1190 (s), 1028 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 7.58 (1H, m, aryl CH), 7.40 (1H, m, aryl CH), 7.35 – 7.27 (2H, m, aryl CH), 4.76 (2H, s, CH_2OH), 4.11 – 4.07 (2H, m, OCH_2CH_2O), 3.87 – 3.82 (2H, m, OCH_2CH_2O), 3.05 (1H, br.s, OH), 1.74 (3H, s, CH_3)

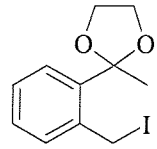
^{13}C NMR (100MHz, $CDCl_3$) δ: 141.4 (0), 138.5 (0), 131.3 (1), 129.0 (1), 128.2 (1), 126.5 (1), 110.2 (0), 64.8 (2)*, 64.6 (2), 28.0 (3)

* = 2 carbons

LRMS (CI) m/z: 194 $(M)^+$ [4%], 179 $(M\text{-}CH_3)^+$ [100%].

HRMS (EI) m/z: $C_{11}H_{14}O_3$ $(M)^+$ requires 194.09429, found 194.09488 [3%]

2-[2-(Iodomethyl)phenyl]-2-methyl-1,3-dioxolane 370



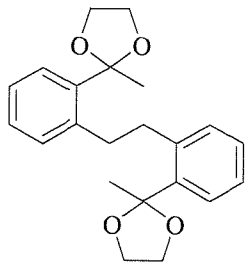
18

Following the method of Motherwell[126], triphenylphosphine (0.203g, 0.77mmol), imidazole (0.060g, 0.88mmol) and finally iodine (0.209g, 0.82mmol) were added to a stirred solution of [2-(2-methyl-1,3-dioxolan-2-yl)phenyl]methanol **369** (0.300g, 1.54mmol) in ether (6mL) and acetonitrile (2mL). The solution was stirred for 20 minutes. The resulting red-brown solution was diluted with ether (10mL), washed with $Na_2S_2O_3$ (10mL) and then water (5mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (isocratic 10% ether/hexane) to yield iodide **370** as a yellow oil (0.115g, 73%). The product is unstable and decomposes rapidly and therefore complete characterisation was not possible. Iodide **370** was used directly in the next reaction.

R_f: 0.5 (20% Ether/hexane)

^{1}H NMR (400MHz, CD_3OD) δ: 7.47 – 7.42 (2H, m, aryl CH, aryl CH), 7.24 – 7.18 (2H, m, aryl CH, aryl CH), 4.87 (2H, s, CH_2I), 4.03 – 3.99 (2H, m, OCH_2CH_2O), 3.76 – 3.73 (2H, m, OCH_2CH_2O), 1.65 (3H, s, CH_3).

2-Methyl-2-{2-[2-(2-methyl-1,3-dioxolan-2-yl)phenylethyl]phenyl}-1,3-dioxolane 371



371

^{n}BuLi (1.0mL, 1.6M in hexanes, 1.6mmol) was added to methylenecyclopropane **200** (1.8mL, 1M in THF 1.8mmol) in THF (5mL) at -50°C under nitrogen and allowed to warm to 0°C over 30 minutes. The reaction was left for 45 minutes at 0°C, then cooled to -60°C and HMPA (0.5mL, 3.0mmol) was added, immediately followed by the drop-wise addition of 2-[2-(iodomethyl)phenyl]-2-methyl-1,3-dioxolane **370** (0.316g, 1.0mmol) in THF (2mL). The reaction was allowed to come to RT overnight. It was then quenched with NH_4Cl (5mL) and extracted with EA (15mL). The organic phase was washed with brine (5mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (0 to 90% DCM/PE) to give ketal-dimer **371** as a white solid (0.085g, 46%).

R_f: 0.5 (90% DCM/PE)

M.p.: 174 – 176°C

FT-IR ν_{max}: 3063 (w), 2988 (m), 2935 (w), 2890 (w), 2349 (w), 1480 (w), 1371 (m), 1194 (s), 1039 (s), 1033 (s)

^{1}H NMR (400MHz, $CDCl_3$) **δ**: 7.58 (2H, dd, *J* = 1, 7Hz, aryl CH), 7.42 (2H, dd, *J* = 1, 7Hz, aryl CH), 7.28 (2H, dt, *J* = 1, 7Hz, aryl CH), 7.18 (2H, dt, *J* = 1, 7Hz, aryl CH), 4.10 – 4.05 (4H, m, OCH_2CH_2O), 3.84 – 3.79 (4H, m, OCH_2CH_2O), 3.13 (4H, s, $(C_6H_4)CH_2CH_2(C_6H_4)$), 1.73 (6H, s, CH_3)

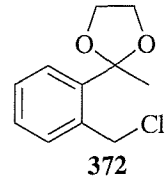
^{13}C NMR (100MHz, $CDCl_3$) **δ**: 140.8 (0)*, 140.7 (0)*, 131.7 (1)*, 128.5 (1)*, 126.5 (1)*, 126.0 (1)*, 110.0 (0)*, 64.7 (2)$^{\#}$, 36.6 (2)*, 28.1 (3)*

* = 2 carbons, $^{\#}$ = 4 carbons

LRMS (CI) m/z: 355 $(M+H)^+$ [43%], 73 [100%]

Elemental Analysis: $C_{22}H_{26}O_4$ requires **C:** 74.55%, **H:** 7.39%; found **C:** 74.31%, **H:** 7.32%.

2-[2-(Chloromethyl)phenyl]-2-methyl-1,3-dioxolane 372



372

Following the method of Ohfune[162], [2-(2-methyl-1,3-dioxolan-2-yl)phenyl]methanol **369** (0.300g, 1.54mmol) was dissolved in DCM (25mL). The mixture was cooled to 0°C and then triphenylphosphine (0.810g, 3.08mmol) was added followed by *N*-chlorosuccinimide (0.309g, 2.32mmol). The reaction was stirred for 1 hour and allowed

to warm to RT slowly. The reaction was then concentrated *in vacuo*. The crude material was purified by column chromatography (0 to 10% ether/PE). Chloride **372** was obtained as a pale yellow oil (0.242g, 74%).

R_f: 0.3 (10% Ether/PE)

FT-IR ν_{max}: 2987 (w), 2937 (w), 2887 (w), 1378 (m), 1202 (s), 1027 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 7.59 (1H, dd, *J* = 1, 7Hz, aryl CH), 7.48 (1H, dd, *J* = 1, 7Hz, aryl CH), 7.31 (2H, dt, *J* = 2, 7Hz, aryl CH, aryl CH), 4.96 (2H, s, CH_2Cl), 4.08 – 4.04 (2H, m, OCH_2CH_2O), 3.80 – 3.76 (2H, m, OCH_2CH_2O), 1.74 (3H, s, CH_3)

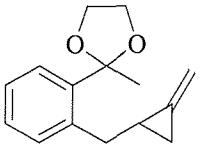
^{13}C NMR (100MHz, $CDCl_3$) δ: 141.4 (0), 135.5 (0), 132.5 (1), 129.0 (1), 128.7 (1), 126.9 (1), 109.4 (0), 64.7 (2)*, 44.5 (2), 28.2 (3)

* = 2 carbons

LRMS (CI) m/z: 213 $(M+H)^+$ [100%]

HRMS (EI) m/z: $C_{11}H_{13}O_2{}^{35}Cl$ $(M)^+$ requires 212.06041, found 212.06064 [3%]; $C_{10}H_{10}O_2{}^{35}Cl$ $(M-CH_3)^+$ requires 197.03693, found 137.03632 [100%].

2-Methyl-2-{2-[(2-methylenecyclopropyl)methyl]phenyl}-1,3-dioxolane 373



373

^{n}BuLi (6.7mL, 2.4M in hexanes, 16.1mmol) was added to methylenecyclopropane **200** (3.0mL, 42.9mmol) in THF (40mL) at -50°C under Ar and allowed to warm to 0°C over 30 minutes. The reaction was left for 45 minutes at 0°C, then cooled to -60°C and HMPA (3.7mL, 21.4mmol) was added, immediately followed by the drop-wise addition of 2-[2-(chloromethyl)phenyl]-2-methyl-1,3-dioxolane **372** (2.28g, 10.7mmol) in THF (4mL). The reaction was allowed to warm to RT overnight. It was then quenched with NH_4Cl (10mL) and extracted with EA (40mL). The combined organic phase was washed with brine (20mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (0 to 90% DCM/PE) to give ketal **373** as a colourless oil (1.56g, 63%).

R_f: 0.5 (90% DCM/PE)

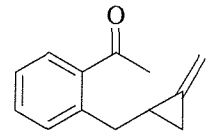
FT-IR ν_{max}: 3070 (w), 2986 (w), 2883 (w), 1477 (w), 1373 (m), 1235 (m), 1186 (m), 1033 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 7.58 (1H, d, *J* = 8Hz, aryl CH), 7.44 (1H, d, *J* = 8Hz, aryl CH), 7.28 (1H, t, *J* = 8Hz, aryl CH), 7.20 (1H, t, *J* = 8Hz, aryl CH), 5.48 (1H, s, $=CH_AH_B$), 5.43 (1H, s, $=CH_AH_B$), 4.07 – 4.01 (2H, m, OCH_2CH_2O), 3.79 – 3.74 (2H, m, OCH_2CH_2O), 3.04 (1H, dd, *J* = 7, 15Hz, $(C_6H_4)CH_CH_D$), 2.84 (1H, dd, *J* = 7, 15Hz, $(C_6H_4)CH_CH_D$), 1.75 (1H, m, cyclopropyl CH), 1.70 (3H, s, CH_3), 1.35 (1H, t, *J* = 9Hz, cyclopropyl CH_EH_F), 0.97 (1H, m, cyclopropyl CH_EH_F)

^{13}C NMR (100MHz, $CDCl_3$) δ: 140.7 (0), 139.6 (0), 137.2 (0), 130.8 (1), 128.4 (1), 126.4 (1), 126.2 (1), 109.8 (0), 103.6 (2), 64.6 (2), 64.5 (2), 36.4 (2), 27.9 (3), 17.0 (1), 10.3 (2)

LRMS (EI) m/z: 231 $(M+H)^+$ [100%].

1-{2-[(2-Methylenecyclopropyl)methyl]phenyl}ethanone 374



374

2-methyl-2-{2-[(2-methylenecyclopropyl)methyl]phenyl}-1,3-dioxolane **373** (1.50g, 6.50mmol) was dissolved in acetone (85mL) and water (10mL). Hydrochloric acid 2M (5mL, 10.0mmol) was added. The reaction was stirred overnight. $NaHCO_3$ (10mL) was added and the reaction mixture concentrated *in vacuo*. The aqueous layer was extracted with EA (100mL). The organic layer was washed with brine (50mL), dried ($MgSO_4$) and concentrated *in vacuo*. Ketone **374** was isolated as a yellow oil (1.20g, 100%).

R_f: 0.6 (50% Ether/PE)

FT-IR ν_{max}: 3068 (w), 2987 (w), 2915 (w), 2848 (w), 2349 (w), 1680 (s), 1593 (w), 1574 (w), 1483 (w), 1349 (m), 1248 (s)

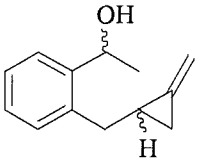
^{1}H NMR (400MHz, $CDCl_3$) δ: 7.68 (1H, d, *J* = 8Hz, aryl CH), 7.48 – 7.38 (2H, m, aryl CH, aryl CH), 7.31 (1H, t with fine splitting, *J* = 8Hz, aryl CH), 5.38 (2H, s, $=CH_2$), 3.06 (1H, dd, *J* = 7, 15Hz, $(C_6H_4)CH_AH_B$), 2.85 (1H, dd, *J* = 7, 15Hz, $(C_6H_4)CH_AH_B$), 2.60 (3H, s, CH_3), 1.79 (1H, m, cyclopropyl CH), 1.29 (1H, t, *J* = 9Hz, cyclopropyl CH_CH_D), 0.89 (1H, m, cyclopropyl CH_CH_D)

^{13}C NMR (100MHz, $CDCl_3$) δ: 202.4 (0), 141.7 (0), 138.2 (0), 136.7 (0), 131.8 (1), 131.3 (1), 129.5 (1), 126.4 (1), 103.6 (2), 37.2 (2), 30.3 (3), 16.6 (1), 9.9 (2)

LRMS (CI) m/z: 187 $(M+H)^+$ [100%]

HRMS (EI) m/z: $C_{13}H_{14}O$ $(M)^+$ requires 186.10447, found 186.10367 [41%].

1-{2-[(2-Methylenecyclopropyl)methyl]phenyl}ethanol 378



23

1-{2-[(2-methylenecyclopropyl)methyl]phenyl}ethanone **374** (0.060g, 0.32mmol) was dissolved in methanol (5mL) and cooled to 0°C. Sodium borohydride (0.122g, 3.2mmol) was added and the reaction stirred at RT for 24 hours. Acetone (10mL) was added and the reaction mixture was then concentrated *in vacuo*. The residue was partitioned between EA (10mL) and water (5mL). The organic layer was washed with brine (5mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford alcohol **378** as a colourless oil as a mixture of diastereoisomers (1:1 ratio, 0.060g, 99%).

R_f: 0.2 (30% Ether/PE)

FT-IR ν_{max}: 3347 (br.m), 3066 (m), 2973 (s), 2926 (m), 2869 (m), 1488 (m), 1452 (m), 1369 (m), 1276 (m), 1073 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 7.68 (1H, m, aryl CH), 7.34 – 7.25 (3H, m, aryl CH, aryl CH, aryl CH), 5.46 (1H, m, $=CH_AH_B$), 5.43 (1H, br.s, $=CH_AH_B$), 5.18 (1H, dq, J = 2, 7Hz, CH(OH)), 2.89 – 2.67 (2H, m, $(C_6H_4)CH_2$), 2.04 (1H, br.s, OH), 1.71 (1H, m, cyclopropyl CH), 1.49 (3H, d, J = 7Hz, CH_3), 1.35 (1H, tq, J = 2, 9Hz, cyclopropyl CH_CH_D), 0.91 (1H, m, cyclopropyl CH_CH_D)

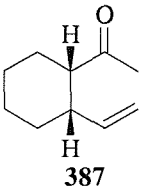
^{13}C NMR (100MHz, $CDCl_3$) δ: 143.8 (0)*, 137.8 & 137.6 (0), 136.4 & 136.3 (0), 129.5 & 129.4 (1), 127.7 & 127.6 (1), 127.0 (1)*, 125.2 (1)*, 103.85 & 103.82 (2), 66.53 & 66.47 (1), 35.3 & 35.1 (2), 24.9 & 24.8 (3), 16.4 & 16.3 (1), 10.1 & 9.8 (2)

* = 2 carbons

LRMS (CI) m/z: 189 $(M+H)^+$ [100%]

HRMS (EI) m/z: $C_{12}H_{13}O$ $(M-CH_3)^+$ requires 173.09664, found 173.09718 [41%].

1-[(1S,2S)-2-Vinylcyclohexyl]ethanone 387



387

Copper (I) iodide (13.8g, 72.5mmol) was dissolved in THF (120mL) and cooled to -60°C under a flow of nitrogen. Vinyl magnesium chloride (42.0mL, 1.73M in THF, 72.5mmol)

was dissolved in THF (50mL) and added drop-wise to the CuI slurry keeping the temperature below -55°C. The reaction was stirred at -55°C for 2 hours. TMSCl (9.2mL, 72.5mmol) was added to 1-acetylcyclohexene **386** (3.00g, 24.2mmol) in THF (120mL). This mixture was cooled to -78°C before transfer *via* cannula, under a flow of nitrogen, to the cuprate mixture over 1 hour. The reaction was kept at -78°C for 4 hours and then allowed to warm to RT slowly overnight. The reaction was quenched with NH_4Cl (150mL) and filtered through celite. The mixture was extracted with EA (300mL) and the organic layer then washed with brine (150mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (isocratic 100% DCM) to afford ketone **387** as a yellow oil (2.05g, 56%). All data agrees with House[163].

R_f: 0.4 (20% Ether/PE)

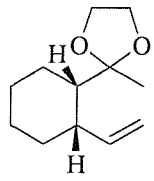
FT-IR ν_{max}: 2932 (m), 2857 (w), 1708 (s), 1450 (w), 1351 (w), 1172 (w), 915 (w)

^{1}H NMR (360MHz, $CDCl_3$, 330K) **δ**: 5.93 (1H, ddd, *J* = 8, 10.5, 17Hz, C*H*=CH_2), 5.08 – 5.00 (2H, m, CH=CH_2), 2.75 (1H, qd, *J* = 4, 8Hz, C*H*(CH=CH_2)), 2.58 (1H, td, *J* = 4, 9Hz, C*H*$COCH_3$), 2.09 (3H, s, CH_3), 1.91 – 1.33 (8H, m, $CH_2CH_2CH_2CH_2$)

^{13}C NMR (90MHz, $CDCl_3$) **δ**: 211.2 (0), 138.4 (1), 116.1 (2), 54.3 (1), 41.5 (1), 32.0 (2), 29.1 (3), 25.1 (2), 23.8 (2), 22.0 (2)

LRMS (CI) m/z: 153 $(M+H)^+$ [100%].

2-Methyl-2-[(1S,2S)-2-vinylcyclohexyl]-1,3-dioxolane 389



389

Following the method of Noyori[129], 1-[(1S,2S)-2-vinylcyclohexyl]ethanone **387** (0.100g, 0.657mmol) was dissolved in DCM (5mL). 1,2-Bis(trimethylsilyloxy)ethane (0.407g, 1.97mmol) was added and the reaction mixture cooled to -78°C under nitrogen. Trimethylsilyl-trifluoromethanesulfonate (0.001mL, 0.006mmol) was added and the reaction was allowed to warm to RT slowly overnight. $NaHCO_3$ (1mL) was added and the DCM layer washed with brine (2mL). The organic layer was collected and concentrated *in vacuo*. The crude material was purified by column chromatography (isocratic 5% ether/PE) to afford ketal **389** as a yellow oil (0.05g, 39%). Data agrees with House[163].

R_f: 0.4 (100% DCM)

FT-IR ν_{max}: 2974 (m), 2921 (s), 2874 (m), 2850 (m), 1632 (m), 1451 (m), 1375 (m), 1304 (m), 1214 (m), 1143 (m), 1076 (m), 1034 (m), 902 (m)

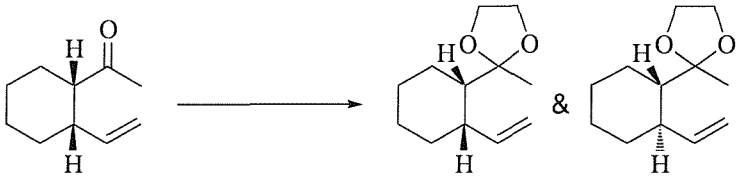
^{1}H NMR (400MHz, CD_3OD) δ: 6.29 (1H, dt with fine splitting, J = 9, 17Hz, C*H*=CH_2), 5.03 (1H, dd with fine splitting, J = 2, 17Hz, CH=CH_AH$_B$), 4.99 (1H, dd, J = 2, 9Hz, CH=CH$_A$*H$_B$*), 3.97 – 3.87 (4H, m, OCH_2CH_2O), 2.71 (1H, m, C*H*CH=CH_2), 1.89 – 1.29 (9H, m, C*H*$_2$C*H*$_2$C*H*$_2$C*H*$_2$C*H*C($O_2C_2H_4$)), 1.24 (3H, s, CH_3)

^{13}C NMR (100MHz, CD_3OD) δ: 142.2 (1), 115.2 (2), 113.5 (0), 66.8 (2), 65.9 (2), 51.6 (1), 41.7 (1), 36.9 (2), 28.7 (2), 24.3 (2), 23.4 (3), 23.0 (2)

LRMS (CI) m/z: 197 $(M+H)^+$ [14%], 87 [100%]

HRMS (EI) m/z: $C_{12}H_{20}O_2$ $(M)^+$ requires 196.14633, found 196.14619 [4%].

2-Methyl-2-(2-vinylcyclohexyl)-1,3-dioxolane 389 & 391



1-[(1S,2S)-2-Vinylcyclohexyl]ethanone **387** (1.687g, 11mmol) was dissolved in toluene (20mL). Ethylene glycol (1.376g, 22mmol) and *p*-TsOH (0.021g, 0.1mmol) were added and the mixture refluxed for 72 hours using Dean-Stark apparatus to remove water. $NaHCO_3$ (5mL) was added and the mixture extracted with EA (20mL). The organic layers were washed with brine (10mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (isocratic 80% DCM/hexane) gave the *cis* ketal **389** as a yellow oil (0.303g, 14%) and the *trans* ketal **391** as a yellow oil (0.623g, 29%). Data agrees with House[163].

2-Methyl-2-[(1S,2R)-2-vinylcyclohexyl]-1,3-dioxolane 391

R_f: 0.3 (DCM)

FT-IR ν_{max}: 2976 (m), 2924 (s), 2876 (m), 2854 (m), 1637 (w), 1449 (m), 1376 (m), 1148 (m), 1080 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.86 (1H, td with fine splitting, J = 10, 17Hz, C*H*=CH_2), 4.87 (1H, dd, J = 2, 17Hz, CH=CH_AH$_B$), 4.83 (1H, dd, J = 10, 17Hz, CH=CH$_A$*H$_B$*), 3.96 (1H, m, OC*H$_C$*H$_D$CH$_2$O), 3.90 – 3.82 (3H, m, OCH$_C$*H$_D$*C*H*$_2$O), 2.01 – 1.89 (2H, m, C*H$_E$*H$_F$CH(C($O_2C_2H_4$)), C*H*(CH=CH_2)), 1.81 – 1.68 (2H, m, CH_2), 1.62 (1H, m, C*H$_G$*H$_H$),

1.46 (1H, dt, J = 3, 12Hz, C*H*(C($O_2C_2H_4$))), 1.26 (3H, s, CH_3), 1.26 – 1.15 (3H, m, CH_2, CH_G*H*$_H$), 1.07 (1H, dq, J = 3, 12Hz, CH_E*H*$_F$CH(C($O_2C_2H_4$)))

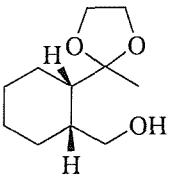
^{13}C NMR (100MHz, $CDCl_3$) δ: 145.9 (1), 112.2 (0), 110.7 (2), 64.9 (2), 63.9 (2), 50.5 (1), 45.8 (1), 35.4 (2), 28.4 (2), 26.5 (2)*, 21.1 (3)

* = 2 carbons

LRMS (CI) m/z: 197 $(M+H)^+$ [49%], 87 [100%]

HRMS (EI) m/z: $C_{12}H_{21}O_2$ $(M+H)^+$ requires 197.15416, found 197.15403 [90%].

[(1R,2S)-2-(2-Methyl-1,3-dioxolan-2-yl)cyclohexyl]methanol 390



390

2-Methyl-2-[(1S,2S)-2-vinylcyclohexyl]-1,3-dioxolane **389** (0.300g, 1.53mmol) was dissolved in methanol (25mL) and DCM (25mL). The mixture was cooled to -78°C and then degassed with nitrogen for 10 minutes. Oxygen was then bubbled through the reaction for 5 minutes and then ozone was bubbled through until a permanent blue colour was observed. The reaction was stirred for 5 minutes before oxygen was bubbled through until the blue colour disappeared. Finally nitrogen was used to degas the reaction and bubbled through for 10 minutes. Sodium borohydride (0.578g, 15.3mmol) was added and the reaction stirred for a further 10 minutes at -78°C before warming to RT. After 30 minutes at RT, acetone (5mL) was added and the reaction mixture was concentrated *in vacuo*. The crude material was partitioned between EA (25mL) and water (10mL). The organic phase was washed with brine (10mL), dried ($MgSO_4$) and then concentrated *in vacuo*. This afforded alcohol **390** as a colourless oil (0.210g, 69%).

R_f: 0.3 (60% Ether/PE)

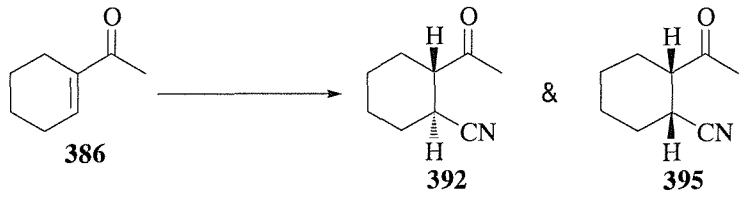
FT-IR ν_{max}: 3446 (br.m), 2983 (m), 2917 (s), 2874 (s), 2850 (s), 1451 (m), 1375 (s), 1224 (m), 1162 (s), 1105 (s), 1034 (s), 949 (m), 850 (m)

^{1}H NMR (400MHz, $(CD_3)_2SO$) δ: 4.10 (1H, br.s, OH), 3.89 (1H, m, OC*H*$_A$H$_B$CH$_2$O), 3.82 – 3.74 (3H, m, OCH$_A$*H*$_B$C*H*$_2$O), 3.60 (1H, br.d, J = 11Hz, C*H*$_C$H$_D$OH), 3.40 (1H, dt, J = 5, 11Hz, CH$_C$*H*$_D$OH), 2.02 (1H, m, C*H*$_E$H$_F$), 1.93 (1H, m, C*H*CH$_2$OH), 1.73 – 1.66 (2H, m, C*H*C($O_2C_2H_4$), C*H*$_G$H$_H$), 1.50 (1H, m, C*H*$_I$H$_J$), 1.39 – 1.32 (2H, m, CH_2), 1.21 (3H, s, CH_3), 1.20 – 1.10 (3H, m, CH$_E$*H*$_F$, CH$_G$*H*$_H$, CH$_I$*H*$_J$)

^{13}C NMR (100MHz, $(CD_3)_2SO$) δ: 110.7 (0), 65.0 (2), 63.4 (2), 57.3 (2), 48.1 (1), 36.6 (1), 26.7 (2), 26.0 (2), 22.4 (3), 21.0 (2), 20.0 (2)

HRMS (EI) m/z: $C_{11}H_{20}O_3$ $(M)^+$ requires 200.14124, found 200.14111 [1%].

2-Acetylcyclohexanecarbonitrile 392 & 395



386 **392** **395**

Following the procedure of Valenta[131], potassium cyanide (11.5g, 177mmol) and ammonium chloride (7.30g, 137mmol) were dissolved in water (120mL) and added to 1-acetylcyclohexene **386** (10.0g, 81mmol) in DMF (400mL). The mixture was heated to 80°C for 16 hours. The reaction was allowed to cool to RT and water (1000mL) was added. The mixture was extracted with EA (1000mL) and the organic layer concentrated *in vacuo*. The residual mixture was partitioned between EA (600mL) and water (300mL). The organic phase was washed with brine (300mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (isocratic 40% ether/PE) to yield the *trans* ketal **392** as a pale yellow oil (4.954g, 41%) and the *cis* ketal **395** as a white solid (3.429, 28%). Data for both isomers agrees with Jackson[164].

(1S,2S)-2-Acetylcyclohexanecarbonitrile 392

R_f: 0.5 (80% Ether/PE)

FT-IR ν_{max}: 2937 (m), 2858 (m), 2237 (w), 1714 (s), 1447 (m), 1363 (m), 1166 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 2.77 (1H, dt, J = 4, 10Hz, CH(CN)), 2.69 (1H, dt, J = 4, 10Hz, CHCOCH$_3$), 2.24 (3H, s, CH_3), 2.13 (1H, m, CH_AH_BCH(CN)), 2.06 (1H, m, CH_CH_DCHCO), 1.83 – 1.71 (2H, m, CH_2), 1.59 (1H, m, CH_CH_DCHCO), 1.45 – 1.20 (3H, m, CH_2, CH_AH_BCH(CN))

^{13}C NMR (100MHz, $CDCl_3$) δ: 208.3 (0), 121.9 (0), 53.1 (1), 29.09 (1), 29.05 (3), 28.8 (2), 28.3 (2), 24.8 (2), 24.4 (2)

LRMS (CI) m/z: 169 $(M+NH_4)^+$ [100%], 152 $(M+H)^+$ [25%]

HRMS (EI) m/z: $C_9H_{13}NO$ $(M)^+$ requires 151.09971, found 151.09965 [45%].

(1R,2S)-2-Acetylcyclohexanecarbonitrile 395

R_f: 0.3 (20% Ether/PE)

FT-IR ν_{max}: 2937 (m), 2863 (m), 2237 (w), 1709 (s), 1447 (m), 1364 (m), 1176 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 3.22 (1H, d, J = 4 Hz, CHCOCH$_3$), 2.43 (1H, dt, J = 4, 12Hz, CH(C≡N)), 2.21 (3H, s, CH_3), 2.19 – 2.11 (2H, br.dd, J = 3, 14Hz, CH_AH_BCHCO, CH_CH_D),

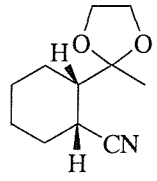
1.89 (1H, br.dt, J = 3, 13Hz, CH_EH_F), 1.79 – 1.52 (4H, m, CH_EH_F CH_AH_BCHCO, CH_2CHC≡N), 1.37 (1H, m, CH_CH_D)

^{13}C NMR (100MHz, $CDCl_3$) δ: 207.4 (0), 120.5 (0), 52.2 (1), 29.2 (1), 28.9 (2), 28.0 (3), 25.54 (2), 25.46 (2), 22.2 (2)

LRMS (CI) m/z: 169 $(M+NH_4)^+$ [92%], 152 $(M+H)^+$ [26%]

HRMS (EI) m/z: $C_9H_{13}NO$ $(M)^+$ requires 151.09971, found 151.09917 [43%]

(1R,2S)-2-(2-Methyl-1,3-dioxolan-2-yl)cyclohexanecarbonitrile 396



396

Following the method of Noyori[129], (1R,2S)-2-acetylcyclohexanecarbonitrile **395** (0.763g, 5.05mmol) was dissolved in DCM (15mL). 1,2-Bis(trimethylsilyloxy)ethane (2.2ml, 8.83mmol) was added and the reaction mixture cooled to -78°C under nitrogen. Trimethylsilyl trifluoromethanesulfonate (0.02mL, 0.110mmol) was added and the reaction was allowed to warm to RT overnight. $NaHCO_3$ (1mL) was added and the DCM layer then washed with brine (5mL). The organic layers were collected and concentrated *in vacuo*. The crude material was purified by column chromatography (0 to 60% ether/PE). Ketal **396** was isolated as a colourless oil (0.960g, 97%).

R_f: 0.5 (60% Ether/PE)

FT-IR ν_{max}: 2983 (w), 2938 (s), 2891 (m), 2864 (m), 2235 (w), 1450 (m), 1219 (m), 1039 (s), 869 (m)

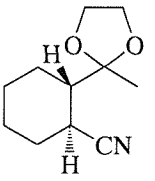
^{1}H NMR (400MHz, $CDCl_3$) δ: 4.08 – 3.94 (4H, m, OCH_2CH_2O), 3.20 (1H, s with fine splitting, CH(C≡N)), 2.06 (1H, m, CH_AH_BCH(C≡N)), 1.92 – 1.80 (2H, m, CH_CH_D, CH_EH_F), 1.74 – 1.58 (4H, m, CH(C($O_2C_2H_4$)), CH_2, CH_CH_D), 1.52 (1H, tt, J = 5, 13Hz, CH_AH_BCH(C≡N)), 1.34 (3H, s, CH_3), 1.27 (1H, m, CH_EH_F)

^{13}C NMR (100MHz, $CDCl_3$) δ: 121.7 (0), 110.2 (0), 65.2 (2), 64.9 (2), 48.4 (1), 30.4 (2), 27.9 (1), 26.1 (2), 24.6 (2), 22.4 (2), 22.2 (3)

LRMS (CI) m/z: 87 [100%], 196 $(M+H)^+$ [64%]

HRMS (EI) m/z: $C_{10}H_{14}NO_2$ $(M-CH_3)^+$ requires 180.10245, found 180.10222 [68%].

(1S,2S)-2-(2-Methyl-1,3-dioxolan-2-yl)cyclohexanecarbonitrile 393



393

Following the method of Noyori[129], (1S,2S)-2-acetylcyclohexanecarbonitrile **392** (5.00g, 33mmol) was dissolved in dry DCM (100mL). 1,2-Bis(trimethylsilyloxy)ethane (12.2mL, 50mmol) was added and the reaction mixture cooled to -40°C under Ar. Trimethylsilyltrifluoromethanesulfonate (0.06mL, 0.30mmol) was added and the reaction was allowed to warm to RT slowly overnight. $NaHCO_3$ (5mL) was added and the reaction mixture extracted with DCM (100mL). The organic layers were washed with brine (100mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (isocratic 50% ether/PE). Ketal **393** was isolated as a pale yellow oil (6.37g, 99%).

R_f: 0.5 (70% Ether/PE)

FT-IR ν_{max}: 2937 (s), 2891 (m), 2862 (m), 2235 (w), 1449 (m), 1379 (m), 1306 (m), 1217 (m), 1162 (s), 1101 (m), 1035 (s)

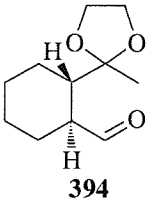
^{1}H NMR (400MHz, $CDCl_3$) δ: 4.09 – 3.95 (4H, m, OCH_2CH_2O), 2.42 (1H, dt, J = 3, 12Hz, CH(C≡N)), 2.19 (1H, m, $CH_AH_BCH(C{\equiv}N)$), 1.96 (1H, m, CH_CH_D), 1.88 (1H, dt, J = 3, 12Hz, $CH(C(O_2C_2H_4))$), 1.84 – 1.74 (2H, m, CH_2), 1.61 (1H, dq, J = 4, 13Hz, $CH_AH_BCH(C{\equiv}N)$), 1.32 (3H, s, CH_3), 1.30 – 1.07 (3H, m, CH_2, CH_CH_D)

^{13}C NMR (100MHz, $CDCl_3$) δ: 123.3 (0), 110.7 (0), 65.4 (2), 64.4 (2), 47.7 (1), 31.7 (2), 29.1 (1), 27.3 (2), 25.40 (2), 25.36 (2), 22.0 (3)

LRMS (CI) m/z: 196 $(M+H)^+$ [46%], 87 [100%]

HRMS (EI) m/z: $C_{10}H_{14}NO_2$ $(M-CH_3)^+$ requires 180.10245, found 180.10206 [99%].

(1S,2S)-2-(2-Methyl-1,3-dioxolan-2-yl)cyclohexanecarbaldehyde 394



394

Following the method of Boeckman[165], (1S,2S)-2-(2-methyl-1,3-dioxolan-2-yl)cyclohexanecarbonitrile **393** (4.70g, 24.0mmol) was dissolved in hexane (180mL) and cooled to-40°C. DIBAL-H (34mL, 1.0M solution in hexane, 34.0mmol) was added and the reaction stirred between -20 and -10°C for 2 hours. Dry MeOH (15mL) was added followed by brine (45mL). The mixture was stirred for 20 minutes. $MgSO_4$ was added until granules formed. The solid was filtered and washed with ether (200mL). The filtrate was then concentrated *in vacuo*. The residue was treated with 100mL of {(1:1:1) MeOH : THF : 25%AcOH in which sodium acetate (~7g) had been dissolved} and stirred for 30 minutes. The mixture was diluted with ether (100mL) and washed with $NaHCO_3$ (250mL) and brine (100mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Aldehyde **394** was isolated as a pale yellow oil (4.59g, 96%).

R_f: 0.4 (50% Ether/PE)

FT-IR ν_{max}: 2982 (w), 2930 (m), 2856 (m), 2810 (w), 2715 (w), 1716 (s), 1448 (m), 1376 (m), 1162 (m), 1030 (s)

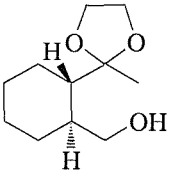
^{1}H NMR (400MHz, $CDCl_3$) **δ**: 9.28 (1H, d, *J* = 5.5Hz, CHO), 3.95 – 3.79 (3H, m, $OCH_AH_BCH_2O$), 3.72 (1H, m, $OCH_AH_BCH_2O$), 2.08 (1H, m, CH(CHO)), 2.00 – 1.85 (2H, m, CH_CH_D, CH($C(O_2C_2H_4)$)), 1.84 – 1.74 (2H, m, CH_EH_F, CH_GH_H), 1.62 (1H, m, CH_IH_JCH(CHO)), 1.36 – 1.16 (4H, m, CH_CH_D, CH_EH_F, CH_GH_H, CH_IH_JCH(CHO)), 1.27 (3H, s, CH_3)

^{13}C NMR (100MHz, $CDCl_3$) **δ**: 202.6 (1), 111.3 (0), 65.3 (2), 63.7 (2), 51.1 (1), 47.1 (1), 26.73 (2), 26.69 (2), 25.8 (2), 24.8 (2), 22.2 (3)

LRMS (CI) m/z: 199 $(M+H)^+$ [100%]

HRMS (EI) m/z: $C_{10}H_{15}O_3$ $(M-CH_3)^+$ requires 183.10212, found 183.10223 [57%].

[(1S,2S)-2-(2-Methyl-1,3-dioxolan-2-yl)cyclohexyl]methanol



(1S,2S)-2-(2-methyl-1,3-dioxolan-2-yl)cyclohexanecarbaldehyde **394** (5.90g, 30.0mmol) was dissolved in methanol (150mL) and cooled to -60°C. Sodium borohydride (3.40g, 89.0mmol) was added and the reaction allowed to warm to RT over 2 hours. Acetone (20mL) was added and the reaction mixture was then concentrated *in vacuo*. The residue was partitioned between ether (200mL) and water (100mL). The aqueous phase was

extracted with EA (100mL). The organic layers were combined and washed with brine (100mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the alcohol as a pale yellow oil (5.69g, 95%).

R_f: 0.3 (60% Ether/PE)

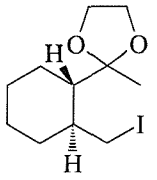
FT-IR ν_{max}: 3436 (br.w), 2983 (w), 2920, (m), 2882 (m), 2854 (m), 1449 (m), 1379 (m), 1157 (s), 1032 (s), 950 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 4.03 – 3.91 (4H, m, OCH_2CH_2O), 3.70 (1H, ddd, J = 3, 7.5, 12Hz, CH_AH_BOH), 3.43 (1H, ddd, J = 4, 7.5, 12Hz, CH_AH_BOH), 3.27 (1H, t, J = 7.5Hz, OH), 2.01 (1H, m, CH_CH_D), 1.79 – 1.72 (2H, m, CH_EH_F, CH_GH_H), 1.63 (1H, m, CH_IH_J), 1.48 – 1.35 (2H, m, CH, CH), 1.30 (3H, s, CH_3), 1.30 – 1.17 (3H, m, CH_EH_F, CH_GH_H, CH_IH_J), 1.05 (1H, dq, J = 3, 12Hz, CH_CH_D)

^{13}C NMR (100MHz, $CDCl_3$) δ: 112.8 (0), 67.8 (2), 64.9 (2), 63.9 (2), 49.1 (1), 42.8 (1), 31.5 (2), 29.3 (2), 26.9 (2), 26.6 (2), 19.6 (3)

HRMS (EI) m/z: $C_{10}H_{17}O_3$ $(M-CH_3)^+$ requires 185. 11777, found 185.11794 [17%].

2-[(1S,2S)-2- (Iodomethyl)cyclohexyl]-2-methyl-1,3-dioxolane 416



416

Following the method of Motherwell[126], triphenylphosphine (1.55g, 5.90mmol), imidazole (0.460g, 6.70mmol) and finally iodine (1.60g, 6.30mmol) were added to a stirred solution of [(1S,2S)-2-(2-methyl-1,3-dioxolan-2-yl)cyclohexyl]methanol (0.790g, 3.90mmol) in ether (45mL) and acetonitrile (15mL). The solution was stirred for 15 minutes. The resulting red-brown solution was diluted in ether (60mL), washed with $Na_2S_2O_3$ (60mL) and then water (60mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (isocratic 20% ether/PE) to yield iodide **416** as a pale yellow oil (0.995g, 81%).

R_f: 0.5 (30% Ether/PE)

FT-IR ν_{max}: 2983 (w), 2924, (s), 2881 (m), 2854 (m), 1448 (w), 1379 (m), 1240 (m), 1118 (m), 1036 (m), 949 (m), 855 (m)

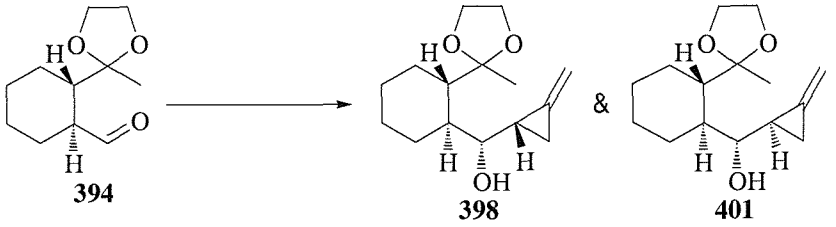
^{1}H NMR (400MHz, $CDCl_3$) δ: 4.01 – 3.96 (2H, m, OCH_2CH_2O), 3.91 – 3.85 (2H, m, OCH_2CH_2O), 3.63 (1H, dd, J = 3, 10 Hz, CH_AH_BI), 3.43 (1H, dd, J = 6, 10 Hz, CH_AH_BI), 1.98 (1H, m, CH_CH_D), 1.88 (1H, m, CH_EH_F), 1.79 – 1.70 (2H, m, CH_GH_H, CH_IH_J), 1.40

(1H, m, $CH(C(O_2C_2H_4))$), 1.32 – 1.02 (5H, m, $CH(CH_2I)$, CH_CH_D, CH_EH_F, CH_GH_H, CH_IH_J), 1.25 (3H, s, CH_3)

^{13}C NMR (100MHz, $CDCl_3$) δ: 112.1 (0), 65.4 (2), 64.0 (2), 48.9 (1), 40.5 (1), 35.0 (2), 28.7 (2), 26.45 (2), 26.40 (2), 20.0 (3), 19.1 (2)

LRMS (CI) m/z: 311 $(M+H)^+$ [62%], 183 $(M+H\text{-}HI)^+$ [100%].

[2-(2-Methyl-1,3-dioxolan-2-yl)cyclohexyl](2-methylenecyclopropyl)methanol 398 & 401



^{n}BuLi (0.32mL, 2.4M in hexanes, 0.76mmol) was added to methylenecyclopropane **200** (0.5mL, 2M solution in THF, 1.0mmol) in THF (2mL) at -50°C under Ar and allowed to warm to 0°C over 30 minutes. The reaction was left for 45 minutes at 0°C, then cooled to -60°C before addition of (1S,2S)-2-(2-methyl-1,3-dioxolan-2-yl)cyclohexanecarbaldehyde **394** (0.1g, 0.5mmol) in THF (1mL). The reaction was allowed to warm to RT overnight. It was then quenched with NH_4Cl (2mL) and extracted with EA (10mL). The organic phase was washed with brine (5mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (isocratic 20% ether/PE) to give a two pairs of a mixture of isomers of the ketal: the less polar **398** as a colourless oil (9:1 ratio of isomers, 0.047g, 37%); the more polar **401** as a colourless oil (15:1 ratio of isomers, 0.045g, 36%).

(R)-[(1S,2S)-2-(Methyl-1,3-dioxolan-2-yl)cyclohexyl][(1S)-2-methylenecyclopropyl]-methanol 398

Major isomer.

R_f: 0.5 (60% Ether/PE)

FT-IR ν_{max}: 3530 (br.w), 2988 (m), 2926, (s), 2886 (m), 2856 (m), 1451 (w), 1380 (m), 1162 (s), 1100 (s), 1033 (m), 987 (m), 885(m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.54 (1H, s, $=CH_AH_B$), 5.43 (1H, s, $=CH_AH_B$), 4.00 – 3.86 (4H, m, OCH_2CH_2O), 3.59 (1H, m, $CH(OH)$), 2.83 (1H, d, J = 5Hz, OH), 2.07 (1H, br.d with fine splitting, J = 12.5Hz, $CH_CH_DCH(C(O_2C_2H_4))$), 2.00 (1H, br.d, J = 12Hz, $CH_2CH_EH_FCH(CH(OH))$), 1.86 – 1.70 (2H, m, CH_GH_H, CH_IH_J), 1.66 (1H, m, cyclopropyl CH), 1.59 (1H, m, $CH(C(O_2C_2H_4))$), 1.45 (1H, m, $CH_2CH_2CH(CH(OH))$), 1.32 (1H, m,

$CH_2CH_E\mathit{H_F}CH(CH(OH)))$, 1.28 – 1.17 (3H, m, cyclopropyl $C\mathit{H_K}H_L$, $CH_G\mathit{H_H}$, $CH_I\mathit{H_J}$), 1.23 (3H, s, CH_3), 1.08 (1H, dq, J = 4, 12.5Hz, $CH_C\mathit{H_D}CH(C(O_2C_2H_4)))$, 0.89 (1H, m, cyclopropyl $CH_K\mathit{H_L}$)

^{13}C NMR (100MHz, $CDCl_3$) δ: 135.2 (0), 112.6 (0), 103.8 (2), 74.2 (1), 65.0 (2), 63.7 (2), 47.9 (1), 45.3 (1), 29.5 (2), 27.0 (2), 26.7 (2), 26.0 (2), 19.3 (1), 18.8 (3), 7.3 (2)

HRMS (EI) m/z: $C_{14}H_{21}O_3$ $(M\text{-}CH_3)^+$ requires 237.14907, found 237.14944 [28%]

Minor isomer (assignment based on following data)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.50 (2H, br.s, $=CH_2$), 3.72 (1H, td, J = 5, 7Hz, $C\mathit{H}OH$), 2.58 (1H, d, J = 7Hz, OH), 1.34 (3H, s, CH_3)

^{13}C NMR (100MHz, $CDCl_3$) δ: 134.3 (0), 112.8 (0), 105.0 (2), 64.9 (2), 63.8 (2), 48.6 (1), 46.8 (1), 29.2 (2), 27.8 (2), 26.3 (2), 20.0 (3), 19.1 (1), 7.8 (2)

(R)-[(1S,2S)-2-(Methyl-1,3-dioxolan-2-yl)cyclohexyl][(1R)-2-methylenecyclopropyl]-methanol 401

Major isomer.

R_f: 0.4 (60% Ether/PE)

FT-IR ν_{max}: 3510 (br.w), 2986 (m), 2928, (s), 2886 (m), 2857 (m), 1451 (w), 1381 (m), 1162 (s), 1100 (s), 1035 (m), 991 (m), 885 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.40 (2H, br.s with fine splitting, $=CH_2$), 3.99 – 3.86 (4H, m, OCH_2CH_2O), 3.36 (1H, m, $C\mathit{H}(OH)$), 2.98 (1H, d, J = 5Hz, OH), 2.06 (1H, m, $C\mathit{H_A}H_B$), 2.00 (1H, m, $C\mathit{H_C}H_D$), 1.83 (1H, m, $C\mathit{H_E}H_F$), 1.80 – 1.71 (2H, m, $C\mathit{H_G}H_H$, cyclopropyl CH), 1.57 (1H, m, $C\mathit{H}(C(O_2C_2H_4)))$, 1.42 – 1.33 (3H, m, $CH_2CH_2C\mathit{H}CH(OH)$, cyclopropyl $C\mathit{H_I}H_J$, $C\mathit{H_C}H_D$), 1.29 – 1.21 (2H, m, $CH_E\mathit{H_F}$, $CH_G\mathit{H_H}$), 1.20 (3H, s, CH_3), 1.12 – 1.02 (2H, m, $CH_A\mathit{H_B}$, cyclopropyl $CH_I\mathit{H_J}$)

^{13}C NMR (100MHz, $CDCl_3$) δ: 134.2 (0), 112.6 (0), 103.9 (2), 75.6 (1), 65.0 (2), 63.7 (2), 48.1 (1), 45.8 (1), 29.5 (2), 27.0 (2), 26.7 (2), 26.1 (2), 19.3 (1), 19.1 (3), 9.9 (2)

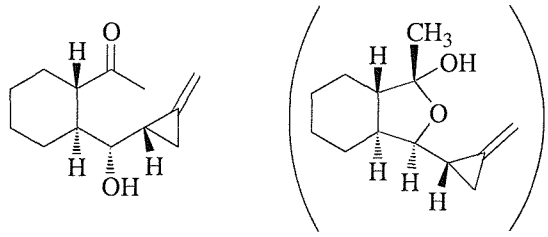
HRMS (EI) m/z: $C_{14}H_{21}O_3$ $(M\text{-}CH_3)^+$ requires 237.14907, found 237.14852 [42%]

Minor isomer (assignment based on following data)

^{1}H NMR (400MHz, $CDCl_3$) δ: 3.75 (1H, d, J = 5 Hz, OH), 3.19 (1H, td, J = 5, 8 Hz, $C\mathit{H}OH$), 1.38 (3H, s, CH_3),

^{13}C NMR (100MHz, $CDCl_3$) δ: 64.9 (2), 63.9 (2),49.4 (1), 46.5 (1), 29.7 (2), 29.1 (2), 26.3 (2), 21.4 (1), 20.1 (3), 8.2 (2)

1-((1S,2S)-2-{(R)-Hydroxy[(1S)-2-methylenecyclopropyl]methyl}cyclohexyl)ethanone 399



399 **400**

(R)-[(1S,2S)-2-(methyl-1,3-dioxolan-2-yl)cyclohexyl][(1S)-2-methylenecyclopropyl]-methanol **398** (0.100g, 0.400mmol) was dissolved in acetone (5mL) and water (0.5mL). HCl (0.3mL, 2M, 0.6mmol) was added and the reaction was stirred overnight. $NaHCO_3$ (1mL) was added and the reaction concentrated *in vacuo*. The aqueous layer was extracted with EA (10mL). The organic layer was washed with brine (5mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification was by column chromatography (25 to 40% ether/PE) affording colourless crystals of the lactol form **400** (0.054g, 65%). The NMR spectra are complicated by the fact that the compound exists in both keto-alcohol and cyclic lactol forms in solution (approximate 2:1 ratio ketone to lactol). The data reported for the NMR spectra are for the keto-alcohol form.

R_f: 0.4 (60% Ether/PE)

M.p.: 80 – 84°C

FT-IR ν_{max}: 3343 (m), 2981 (m), 2938 (s), 2923 (s), 2898 (m), 2860 (m), 1704 (w), 1452 (m), 1375 (s), 1250 (m), 1142 (s), 1100 (s), 1083 (s)

^{1}H NMR (400MHz, $CDCl_3$) **δ**: 5.50 – 5.45 (2H, m, $=CH_2$), 3.12 (1H, m, CH(OH)), 2.68 (1H, m, CHCO), 2.17 (3H, s, CH_3), 1.99 – 1.20 (11H, m, $(CH_2)_4CH$(CH(OH)), cyclopropyl CH, cyclopropyl CH_AH_B), 0.95 (1H, m, cyclopropyl CH_AH_B),

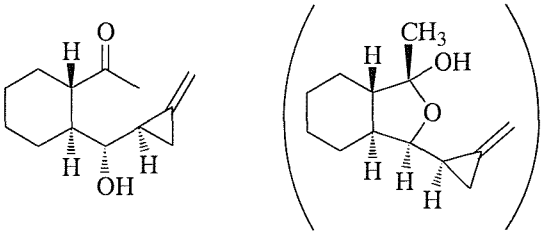
^{13}C NMR (100MHz, $CDCl_3$) **δ**: 213.9 (0), 133.9 (0), 104.9 (2), 75.4 (1), 53.2 (1), 44.1 (1), 30.3 (2), 30.0 (3), 26.1 (2), 26.0 (2), 24.7 (2), 19.6 (1), 7.8 (2)

LRMS (CI) m/z: 191 $(M+H-H_2O)^+$ [100%]

Elemental Analysis: $C_{13}H_{20}O_2$ requires **C:** 74.96%, **H:** 9.68%; found **C:** 74.89%, **H:** 9.49%

X-ray: see appendix.

1-((1S,2S)-2-{(R)-Hydroxy[(1R)-2-ethylenecyclopropyl]methyl}cyclohexyl)ethanone 402



402 **403**

(R)-[(1S,2S)-2-(methyl-1,3-dioxolan-2-yl)cyclohexyl][(1R)-2-methylenecyclopropyl]-methanol **401** (0.100g, 0.400mmol) was dissolved in acetone (5mL) and water (0.5mL). HCl (0.3mL, 2M, 0.6mmol) was added and the reaction was stirred overnight. $NaHCO_3$ (1mL) was added and the reaction concentrated *in vacuo*. The aqueous layer was extracted with EA. The organic layers were washed with brine (5mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification was by column chromatography (35 to 40% ether/PE) affording colourless crystals of the lactol form **403** (0.068g, 82%). The NMR spectra are complicated by the fact that the compound exists in both keto-alcohol and cyclic lactol forms in solution (approximate 2:1 ratio ketone to lactol). The data reported for the NMR spectra are for the keto-alcohol form. It is, however, impossible to assign the four cyclohexyl CH_2 ^{13}C NMR signals with certainty.

R_f: 0.4 (60% Ether/PE)

M.p.: 74 – 78°C

FT-IR ν_{max}: 3344 (m), 2977 (m), 2920, (s), 2856 (m), 1704 (w), 1444 (m), 1375 (m), 1245 (m), 1189 (s), 1081 (s)

^{1}H NMR (400MHz, $CDCl_3$) **δ**: 5.45 (2H, m, $=CH_2$), 3.03 (1H, d with fine splitting, J = 8Hz, C*H*(OH)), 2.64 (1H, m, CHCO), 2.16 (3H, s, CH_3), 1.95 – 0.96 (12H, m, $CH_2CH_2CH_2CH_2CH$(CH(OH)C*H*(CH_2))

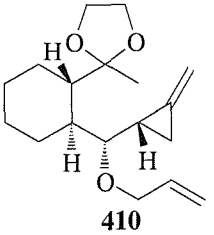
^{13}C NMR (100MHz, $CDCl_3$) **δ**: 214.1 (0), 132.6 (0), 105.0 (2), 75.9 (1), 53.8 (1), 44.6 (1), 29.2 (3), 19.8 (1), 8.5 (2)

LRMS (CI) m/z: 191 $(M+H-H_2O)^+$ [100%]

Elemental Analysis: $C_{13}H_{20}O_2$ requires **C:** 74.96%, **H:** 9.68%; found **C:** 74.80%, **H:** 9.57%

X-ray: see appendix.

2-((1S,2S)-2-{(R)-(Allyloxy)[(1S)-2-methylenecyclopropyl]methyl}cyclohexyl)-2-methyl-1,3-dioxolane 410



410

Following a modified method of Grubbs[166], sodium hydride (0.127g, 60% dispersion in mineral oil, 3.17mmol) was suspended in DMF (10mL) and cooled to 0°C. (R)-[(1S,2S)-2-(methyl-1,3-dioxolan-2-yl)cyclohexyl][(1S)-2-methylenecyclopropyl]methanol **398** (0.400g, 1.59mmol) in DMF (10mL) was added to the mixture. The reaction was stirred for 1 hour at 0°C. The yellow solution was allowed to warm to RT for 15 minutes and then cooled to 0°C. Allyl bromide (0.27mL, 3.17mmol) in DMF (1mL) was added. The reaction was stirred overnight before quenching with water (5mL). The aqueous layer was extracted with DCM (20mL). The organic phase was then washed with brine (10mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification was by column chromatography (0 to 60% ether/PE) affording ketal **410** a colourless oil (0.220g, 53% based on RSM [0.040g]).

R_f: 0.7 (60% Ether/PE)

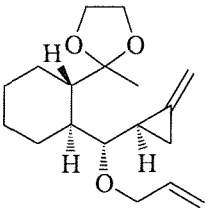
FT-IR ν_{max}: 2988 (m), 2932, (s), 2856 (m), 1646 (w), 1451 (w), 1380 (m), 1166 (s), 1102 (s), 1043 (m)

^{1}H NMR (400MHz, $CDCl_3$) **δ**: 5.99 (1H, br.tdd, J = 5, 10, 17Hz, $OCH_2CH{=}CH_2$), 5.45 (2H, br.s, $C{=}CH_2$), 5.31 (1H, br.d with fine splitting, J = 17Hz, $OCH_2CH{=}CH_AH_B$), 5.11 (1H, br.d with fine splitting, J = 10Hz, $OCH_2CH{=}CH_AH_B$), 4.30 (1H, dd, J = 5, 13Hz, $OCH_CH_DCH{=}CH_2$), 3.92 – 3.79 (5H, m, OCH_2CH_2O, $OCH_CH_DCH{=}CH_2$), 3.30 (1H, br.d, J = 9 Hz, $CH(OC_3H_5)$), 2.04 – 1.95 (2H, m, CH_EH_F, CH_GH_H), 1.84 – 1.71 (3H, m, CH_IH_J, CH_KH_L, $CH(C(O_2C_2H_4))$), 1.66 (1H, m, cyclopropyl CH), 1.54 – 1.37 (2H, m, CH_EH_F, $CH(CH(OC_3H_5))$), 1.29 – 1.15 (3H, m, CH_IH_J, CH_KH_L, cyclopropyl CH_MH_N), 1.22 (3H, s, CH_3), 1.03 (1H, dq, J = 3.5, 12.5Hz, CH_GH_H), 0.68 (1H, m, cyclopropyl CH_MH_N)

^{13}C NMR (100MHz, $CDCl_3$) **δ**: 136.7 (1), 136.4 (0), 115.1 (2), 112.3 (0), 104.2 (2), 82.6 (1), 70.3 (2), 64.7 (2), 63.7 (2), 44.6 (1), 44.0 (1), 29.2 (2), 27.0 (2), 26.6 (2), 25.5 (2), 20.2 (3), 18.5 (1), 6.5 (2)

LRMS (CI) m/z: 235 $(M+H-HOC_3H_5)^+$ [46%], 87 [100%].

2-((1S,2S)-2-{(R)-(Allyloxy)[(1R)-2-methylenecyclopropyl]methyl}cyclohexyl)-2-methyl-1,3-dioxolane 412



412

Following a modified method of Grubbs[166], sodium hydride (0.158g, 60% dispersion in mineral oil, 3.96mmol) was suspended in DMF (10mL) and cooled to 0°C. (R)-[(1S,2S)-2-(methyl-1,3-dioxolan-2-yl)cyclohexyl][(1R)-2-methylenecyclopropyl]methanol **401** (0.400g, 1.59mmol) in DMF (5mL) was added to the mixture. The reaction was stirred for 1 hour at 0°C. The yellow solution was allowed to warm to RT for 15 minutes and then cooled to 0°C. Allyl bromide (0.34mL, 3.96mmol) in DMF (5mL) was added. The reaction was stirred overnight before quenching with water (5mL). The aqueous layer was extracted with DCM (20mL). The organic phase was then washed with brine (10mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification was by column chromatography (isocratic 20% ether/PE) affording ketal **412** as a mixture of isomers as a colourless oil (12:1 ratio of isomers, 0.208g, 54% based on RSM [0.066g]).

Major isomer

R_f: 0.7 (60% Ether/PE)

FT-IR ν_{max}: 2987 (m), 2931, (s), 2856 (m), 1646 (w), 1452 (w), 1381 (m), 1167 (s), 1103 (s), 1083 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.99 (1H, br.tdd, J = 5, 10, 17Hz, $OCH_2CH{=}CH_2$), 5.45 – 5.40 (2H, m, $C{=}CH_2$), 5.29 (1H, br.d with fine splitting, J = 17Hz, $OCH_2CH{=}CH_AH_B$), 5.11 (1H, br.d with fine splitting, J = 10Hz, $OCH_2CH{=}CH_AH_B$), 4.38 (1H, dd, J = 5, 13Hz, $OCH_CH_DCH{=}CH_2$), 3.97 – 3.79 (5H, m, OCH_2CH_2O, $OCH_CH_DCH{=}CH_2$), 3.37 (1H, d, J = 8Hz, $CH(OC_3H_5)$), 2.02 – 1.95 (2H, m, CH_EH_F, CH_GH_H), 1.81 – 1.71 (3H, m, CH_IH_J, CH_KH_L, $CH(C(O_2C_2H_4))$), 1.67 (1H, m, cyclopropyl CH), 1.49 – 1.38 (3H, m, cyclopropyl CH_MH_N, CH_GH_H, $CH_2CH_2CHCH(OC_3H_5)$), 1.28 – 1.16 (2H, m, CH_IH_J, CH_KH_L), 1.20 (3H, s, CH_3), 1.11 (1H, m, cyclopropyl CH_MH_N), 1.02 (1H, dq, J = 3.5, 12.5Hz, CH_EH_F)

^{13}C NMR (100MHz, $CDCl_3$) δ: 136.9 (1), 132.5 (0), 115.1 (2), 112.5 (0), 104.5 (2), 82.8 (1), 70.6 (2), 64.6 (2), 63.7 (2), 45.2 (1), 44.4 (1), 29.2 (2), 27.0 (2), 26.6 (2), 25.8 (2), 20.0 (3), 18.3 (1), 11.6 (2)

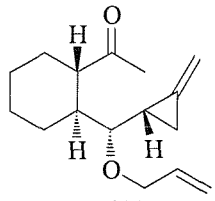
LRMS (CI) m/z: 235 $(M+H-HOC_3H_5)^+$ [42%], 87 [100%].

Minor isomer (assignment based on following data)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.90 (1H, br.tdd, *J* = 5, 10, 17Hz, $OCH_2CH{=}CH_2$), 4.10 (1H, dd, *J* = 5, 13Hz, $OCH_AH_BCH{=}CH_2$), 4.00 (1H, dd, *J* = 5, 13Hz, $OCH_AH_BCH{=}CH_2$), 1.29 (3H, s, CH_3)

^{13}C NMR (100MHz, $CDCl_3$) δ: 136.4 (1), 116.3 (2), 112.7 (0), 103.9 (2), 79.5 (1), 71.1 (2), 64.5 (2), 64.0 (2), 46.3 (1), 45.6 (1), 28.9 (2), 26.9 (2), 26.5 (2), 26.3 (2), 20.3 (3), 17.3 (1)

1-((1S,2S)-2-{(R)-(Allyloxy)[(1S)-2-methylenecyclopropyl]methyl}cyclohexyl)-ethanone 411



411

2-((1S,2S)-2-{(R)-(allyloxy)[(1S)-2-methylenecyclopropyl]methyl}cyclohexyl)-2-methyl-1,3-dioxolane **410** (0.200g, 0.700mmol) was dissolved in acetone (20mL) and water (5mL). *p*-TsOH (0.001g, 0.007mmol) was added and the reaction was stirred overnight. $NaHCO_3$ (1mL) was added and the reaction concentrated *in vacuo*. The aqueous layer was extracted with EA (20mL). The organic layer was washed with brine (10mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification was by column chromatography (isocratic 10% ether/PE) affording ketone **411** as a colourless oil (0.169g, 100%).

R_f: 0.5 (30% Ether/PE)

FT-IR ν_{max}: 2990 (w), 2930, (m), 2855 (m), 1707 (s), 1647 (w), 1450 (m), 1360 (m), 1168 (m), 1079 (m), 885 (m)

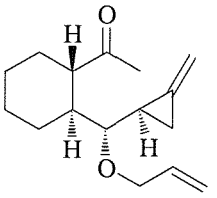
^{1}H NMR (400MHz, $CDCl_3$) δ: 5.90 (1H, br.tdd, *J* = 5, 10, 17Hz, $OCH_2CH{=}CH_2$), 5.45 – 5.40 (2H, m, $C{=}CH_2$), 5.27 (1H, br.d with fine splitting, *J* = 17Hz, $OCH_2CH{=}CH_AH_B$), 5.14 (1H, br.d with fine splitting, *J* = 10Hz, $OCH_2CH{=}CH_AH_B$), 4.20 (1H, br.dd, *J* = 5, 13Hz, $OCH_CH_DCH{=}CH_2$), 3.75 (1H, br.dd, *J* = 5, 13Hz, $OCH_CH_DCH{=}CH_2$), 2.74 (1H, m, $CHCOCH_3$), 2.58 (1H, dd, *J* = 2.5, 9Hz, $CH(OC_3H_5)$), 2.11 (3H, s, CH_3), 2.01 – 1.85 (3H, m, $CH_2CH_2CH(CH(OC_3H_5))$, CH_EH_F, CH_GH_H), 1.84 – 1.76 (2H, m, CH_IH_J, CH_KH_L), 1.64 – 1.56 (1H, m, cyclopropyl CH), 1.46 – 1.35 (1H, m, CH_EH_F), 1.31 – 1.20 (4H, m, CH_GH_H, CH_IH_J, CH_KH_L, cyclopropyl CH_MH_N), 0.84 – 0.78 (1H, m, cyclopropyl CH_MH_N)

^{13}C NMR (100MHz, $CDCl_3$) δ: 213.6 (0), 135.7 (1), 135.6 (0), 116.5 (2), 104.4 (2), 83.0 (1), 70.4 (2), 53.0 (1), 43.3 (1), 30.4 (3), 30.3 (2), 26.24 (2), 26.21 (2), 24.9 (2), 17.7 (1), 6.7 (2)

LRMS (CI) m/z: 249 $(M+H)^+$ [4%], 191 $(M+H\text{-}HOC_3H_5)^+$ [100%]

HRMS (EI) m/z: $C_{15}H_{21}O_2$ $(M\text{-}CH_3)^+$ requires 233.15416, found 233.15430 [100%].

1-((1S,2S)-2-{(R)-(Allyloxy)[(1R)-2-methylenecyclopropyl]methyl}cyclohexyl)-ethanone 413



413

2-((1S,2S)-2-{(R)-(allyloxy)[(1R)-2-methylenecyclopropyl]methyl}cyclohexyl)-2-methyl-1,3-dioxolane **412** (0.200g, 0.700mmol) was dissolved in acetone (20mL) and water (5mL). *p*-TsOH (0.002g, 0.014mol) was added and the reaction was stirred for 3 days. $NaHCO_3$ (1mL) was added and the reaction concentrated *in vacuo*. The aqueous layer was extracted with EA (20mL). The organic layer was washed with brine (10mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification was by column chromatography (isocratic 5% ether/PE) affording ketal **413** as a colourless oil (0.130g, 77%).

R_f: 0.5 (30% Ether/PE)

FT-IR ν_{max}: 2990 (w), 2929, (m), 2855 (m), 1707 (s), 1647 (w), 1450 (m), 1351 (m), 1168 (m), 1080 (m), 889 (m)

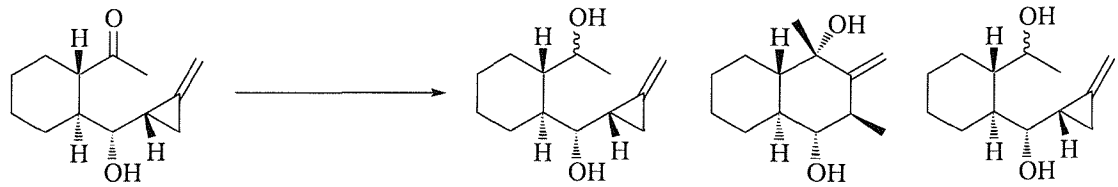
^{1}H NMR (400MHz, $CDCl_3$) δ: 5.89 (1H, br.tdd, J = 5, 10, 17Hz, $OCH_2CH{=}CH_2$), 5.47 – 5.43 (2H, m, $C{=}CH_2$), 5.26 (1H, br.d with fine splitting, J = 17Hz, $OCH_2CH{=}CH_AH_B$), 5.14 (1H, br.d with fine splitting, J = 10Hz, $OCH_2CH{=}CH_AH_B$), 4.20 (1H, br.dd with fine splitting, J = 5, 13Hz, $OCH_CH_DCH{=}CH_2$), 3.85 (1H, br.dd with fine splitting, J = 5, 13Hz, $OCH_CH_DCH{=}CH_2$), 2.74 – 2.66 (2H, m, $CH(OC_3H_5)$, $CHCOCH_3$), 2.12 (3H, s, CH_3), 1.93 – 1.75 (5H, m, $CH_2CH_2CH(CH(OC_3H_5))$, CH_EH_F, CH_GH_H, CH_IH_J, CH_KH_L), 1.61 (1H, m, cyclopropyl CH), 1.41 (1H, m, cyclopropyl CH_MH_N), 1.35 – 1.22 (4H, m, CH_EH_F, CH_GH_H, CH_IH_J, CH_KH_L), 1.02 (1H, m, cyclopropyl CH_MH_N)

^{13}C NMR (100MHz, $CDCl_3$) δ: 213.4 (0), 135.7 (1), 131.6 (0), 116.6 (2), 105.2 (2), 82.8 (1), 70.8 (2), 53.1 (1), 44.1 (1), 30.2 (2), 29.8 (3), 26.3 (2), 26.1 (2), 25.5 (2), 17.7 (1), 10.7 (2)

LRMS (CI) m/z: 249 $(M+H)^+$ [4%], 191 $(M+H\text{-}HOC_3H_5)^+$ [100%]

HRMS (EI) m/z: $C_{15}H_{21}O_2$ $(M\text{-}CH_3)^+$ requires 233.15416, found 233.15388 [89%].

Cyclisation of 1-((1S,2S)-2-{(R)-hydroxy[(1S)-2-methylenecyclopropyl]methyl}-cyclohexyl)ethanone 399



Following method B at 0°C, samarium (0.231g, 1.50mmol); di-iodoethane (0.217g, 0.77mmol); ketone **399** (0.040g, 0.19mmol); HMPA (0.34mL, 1.90mmol); ^{t}BuOH (0.04mL, 0.38mmol) were used. Column chromatography (0 to 60% ether/PE) afforded less polar 1-((1S,2S)-2-{(R)-hydroxy[(1S)-2-methylenecyclopropyl]methyl}cyclohexyl)-ethanol **422** (0.008g, 18%) as a colourless oil; a colourless crystalline solid containing several inseparable unknown products but also (1S,3R,4R,4aS,8aS)-1,3-dimethyl-2-methylenedecahydronaphthalene-1,4-diol **424** (total inseparable product mass 0.019g, (1S,3R,4R,4aS,8aS)-1,3-dimethyl-2-methylenedecahydronaphthalene-1,4-diol approximately 0.006g, 15%); and more polar 1-((1S,2S)-2-{(R)-hydroxy[(1S)-2-methylenecyclopropyl]methyl}cyclohexyl)ethanol **423** (0.015g, 36%) as a colourless oil.

1-((1S,2S)-2-{(R)-hydroxy[(1S)-2-methylenecyclopropyl]methyl}cyclohexyl)ethanol 422

R_f: 0.5 (Ether)

FT-IR ν_{max}: 3327 (br.m), 2973 (m), 2922 (s), 2854 (s), 1448 (m), 1375 (m), 1239 (m), 1117 (m), 1075 (m), 982 (s)

^{1}H NMR (400MHz, $CDCl_3$) **δ**: 5.52 (1H, s with fine splitting, $=CH_AH_B$), 5.45 (1H, s, $=CH_AH_B$), 4.08 (1H, m, $CH(OH)CH_3$), 3.46 (1H, d, J = 7 Hz, $CH(CH(OH)CH)$), 2.63 (1H, br.s, $CH(OH)CH_3$), 2.34 (1H, br.s, $CH(CH(OH)CH)$), 1.84 – 1.61 (6H, m, cyclopropyl CH, $CH(CH(OH)CH)$, CH_CH_D, CH_EH_F, CH_GH_H, CH_IH_J), 1.55 (1H, tt, J = 3, 11Hz, $CH(CH(OH)CH_3)$), 1.32 – 1.19 (4H, m, cyclopropyl CH_KH_L, CH_CH_D, CH_EH_F, CH_GH_H), 1.16 (3H, d, J = 7 Hz, CH_3), 1.14 (1H, m, CH_IH_J), 0.96 (1H, m, cyclopropyl CH_KH_L)

^{13}C NMR (100MHz, $CDCl_3$) **δ**: 134.2 (0), 104.5 (2), 76.4 (1), 69.2 (1), 44.8 (1), 43.9 (1), 27.8 (2), 27.1 (2), 26.8 (2), 26.7 (2), 19.5 (1), 18.7 (3), 8.2 (2)

LRMS (CI) m/z: 193 $(M+H\text{-}H_2O)^+$ [44%], 109 [100%]

HRMS (CI) m/z: $C_{13}H_{26}NO_2$ $(M+NH_4)^+$ requires 228.19635, found 228.19606 [9%]; $C_{13}H_{24}NO$ $(M+NH_4-H_2O)^+$ requires 210.18579, found 210.18570 [28%]; $C_{13}H_{21}O$ $(M+H-H_2O)^+$ requires 193.15924, found 193.15881 [100%].

1-((1S,2S)-2-{(R)-hydroxy[(1S)-2-methylenecyclopropyl]methyl}cyclohexyl)ethanol 423

R_f: 0.3 (Ether)

FT-IR ν_{max}: 3351 (br.m), 2972 (m), 2925 (s), 2854 (s), 1448 (m), 1377 (m), 1260 (m), 1112 (m), 1079 (m), 983 (m)

^{1}H NMR (400MHz, $CDCl_3$) **δ**: 5.53 (1H, s, $=CH_AH_B$), 5.48 (1H, s, $=CH_AH_B$), 4.02 (1H, quin., J = 6.5Hz, $CH(OH)CH_3$), 3.44 (1H, d with fine splitting, J = 7Hz, $CH(CH(OH)CH)$), 2.09 (1H, br.s, $CH(OH)CH_3$), 1.94 (1H, br.s, $CH(CH(OH)CH)$), 1.91 – 1.71 (5H, m, cyclopropyl CH, CH_CH_D, CH_EH_F, CH_GH_H, CH_IH_J), 1.60 (1H, m, $CH(CH(OH)CH_3)$), 1.38 (1H, m, $CH(CH(OH)CH)$), 1.32 – 1.21 (4H, m, cyclopropyl CH_KH_L, CH_CH_D, CH_EH_F, CH_GH_H), 1.13 (3H, d, J = 6.5Hz, CH_3), 1.02 (1H, qd, J = 3, 12Hz, CH_IH_J), 0.93 (1H, m, cyclopropyl CH_KH_L)

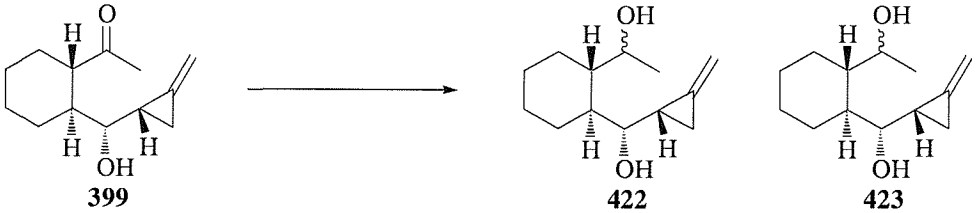
^{13}C NMR (100MHz, $CDCl_3$) **δ**: 134.2 (0), 104.7 (2), 74.8 (1), 69.2 (1), 46.5 (1), 45.6 (1), 26.7 (2)*, 26.4 (2)*, 19.5 (1), 19.4 (3), 7.8 (2)

* = 2 carbons

LRMS (CI) m/z: 193 $(M+H-H_2O)^+$ [26%], 81 [100%]

HRMS (CI) m/z: $C_{13}H_{26}NO_2$ $(M+NH_4)^+$ requires 228.19635, found 228.19472 [5%]; $C_{13}H_{24}NO$ $(M+NH_4-H_2O)^+$ requires 210.18579, found 210.18611 [20%]; $C_{13}H_{21}O$ $(M+H-H_2O)^+$ requires 193.15924, found 193.15917 [100%].

Reduction of 1-((1S,2S)-2-{(R)-hydroxy[(1S)-2-methylenecyclopropyl]methyl}-cyclohexyl)ethanone 399

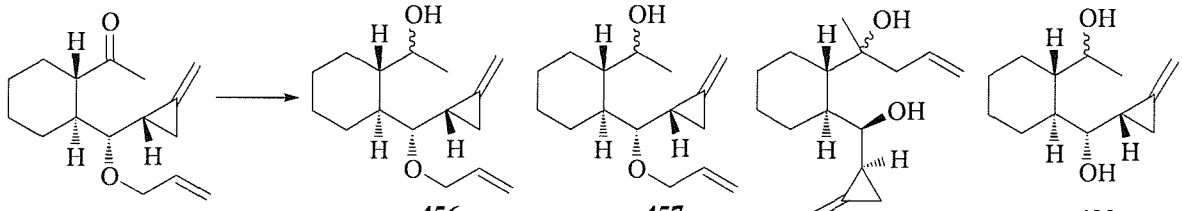


399 **422** **423**

1-((1S,2S)-2-{(R)-hydroxy[(1S)-2-methylenecyclopropyl]methyl}-cyclohexyl)ethanone **399** (0.057g, 0.27mmol) was dissolved in methanol (10mL) and cooled to 0°C. Sodium borohydride (0.031g, 0.82mmol) was added and the reaction allowed to warm to RT over 24 hours. Acetone (5mL) was added and the reaction mixture was then concentrated *in*

vacuo. The residue was partitioned between ether (10mL) and water (1mL). The aqueous phase was extracted with EA (10mL). The organic layers were combined and washed with brine (5mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford alcohol **422** as a colourless oil (0.047g, 82%) and alcohol **423** as a colourless oil (0.010g, 18%). Al data agrees with those from the cyclisation of 1-((1S,2S)-2-{(R)-hydroxy[(1S)-2-methylenecyclopropyl]methyl}-cyclohexyl)ethanone **399**.

Cyclisation of 1-((1S,2S)-2-{(R)-(allyloxy)[(1S)-2-methylenecyclopropyl]methyl}-cyclohexyl)ethanone 411



411 **456** **457** **458** **422**

Following method **B** at 0°C, Sm (0.462g, 3.07mmol); di-iodoethane (0.434g, 1.54mmol); ketone **411** (0.040g, 0.16mmol); HMPA (0.8mL, 4.61mmol); ^{t}BuOH (0.09mL, 0.96mmol) were used. Column chromatography (0 to 40% ether/PE) afforded less polar 1-((1S,2S)-2-{(R)-(allyloxy)[(1S)-2-methylenecyclopropyl]methyl}cyclohexyl)ethanol **456** (0.008g, 20%) as a colourless oil; more polar 1-((1S,2S)-2-{(R)-(allyloxy)[(1S)-2-methylenecyclopropyl]methyl}cyclohexyl)ethanol **457** as a colourless oil contaminated with an inseparable impurity (approximate weight of alcohol 0.009g, 22%); 2-((1S,2S)-2-{(R)-hydroxy[(1S)-2-methylenecyclopropyl]methyl}cyclohexyl)pent-4-en-2-ol **458** (0.006g, 15%) as a colourless oil with a minor inseparable impurity; and more polar 1-((1S,2S)-2-{(R)-hydroxy[(1S)-2-methylenecyclopropyl]methyl}cyclohexyl)ethanol **422** (0.004g, 12%) as a colourless oil.

1-((1S,2S)-2-{(R)-(allyloxy)[(1S)-2-methylenecyclopropyl]methyl}cyclohexyl)ethanol 456

R_f: 0.4 (40% Ether/PE)

FT-IR ν_{max}: 3423 (br.w), 3071 (w), 2972 (m), 2930 (s), 2855 (m), 1646 (w), 1449 (w), 1371 (w), 1164 (m), 1076 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.92 (1H, br.tdd, J = 5.5, 10, 17Hz, $OCH_2CH{=}CH_2$), 5.50 – 5.46 (2H, m, $C{=}CH_2$), 5.28 (1H, br.d with fine splitting, J = 17Hz, $OCH_2CH{=}CH_AH_B$),

5.16 (1H, br.d with fine splitting, J = 10Hz, $OCH_2CH{=}CH_A\mathit{H_B}$), 4.28 (1H, br.dd with fine splitting, J = 5.5, 13Hz, $OC\mathit{H_C}H_DCH{=}CH_2$), 4.09 (1H, m, $C\mathit{H}$(OH)), 3.90 (1H, br.dd with fine splitting, J = 5.5, 13Hz, $OCH_C\mathit{H_D}CH{=}CH_2$), 2.93 (1H, dd, J = 2, 9Hz, $C\mathit{H}(OC_3H_5)$), 2.43 (1H, br.s, OH), 1.82 – 1.73 (5H, m, $C\mathit{H_E}H_F$, CH_2, CH_2), 1.72 – 1.65 (2H, m, cyclopropyl CH, $CH_2CH_2C\mathit{H}(CH(OC_3H_5))$), 1.56 (1H, m, $C\mathit{H}(CH(OH)CH_3)$), 1.41 (1H, m, $CH_E\mathit{H_F}$), 1.33 (1H, tt, J = 2, 9Hz, cyclopropyl $C\mathit{H_G}H_H$), 1.28 – 1.18 (2H, m, CH_2), 1.15 (3H, d, J = 6.5Hz, CH_3), 0.86 (1H, m, cyclopropyl $CH_G\mathit{H_H}$)

^{13}C NMR (100MHz, $CDCl_3$) **δ**: 135.5 (1), 134.8 (0), 116.8 (2), 104.8 (2), 85.2 (1), 70.7 (2), 68.0 (1), 45.0 (1), 44.2 (1), 29.2 (2), 27.1 (2), 26.7 (2), 25.8 (2), 19.9 (3), 16.9 (1), 7.6 (2)

LRMS (CI) m/z: 251 $(M+H)^+$ [8%], 175 $(M+H\text{-}HOC_3H_5\text{-}H_2O)^+$ [100%]

HRMS (EI) m/z: $C_{16}H_{26}O_2$ $(M)^+$ requires 250.19328, found 250.19229 [33%].

1-((1S,2S)-2-{(R)-(allyloxy)[(1S)-2-methylenecyclopropyl]methyl}cyclohexyl)ethanol 457

Assignment based on following data.

R_f: 0.3 (40% Ether/PE)

FT-IR ν_{max}: 3418 (br.w), 3078 (w), 2966 (m), 2924 (s), 2854 (m), 1631 (w), 1449 (m), 1376 (w), 1120 (m), 1080 (m), 1018 (m)

^{1}H NMR (400MHz, $CDCl_3$) **δ**: 5.94 (1H, tdd, J = 5, 10, 17Hz, $OCH_2C\mathit{H}{=}CH_2$), 5.47 (2H, s, $C{=}CH_2$), 5.29 (1H, br.d with fine splitting, J = 17Hz, $OCH_2CH{=}C\mathit{H_A}H_B$), 5.16 (1H, br.d with fine splitting, J = 10Hz, $OCH_2CH{=}CH_A\mathit{H_B}$), 4.26 (1H, br.dd, J = 5, 13Hz, $OC\mathit{H_C}H_DCH{=}CH_2$), 4.01 – 3.84 (2H, m, $C\mathit{H}$(OH), $OCH_C\mathit{H_D}CH{=}CH_2$), 2.81 (1H, d with fine splitting, J = 9Hz, $C\mathit{H}(OC_3H_5)$), 1.08 (3H, d, J = 6.5Hz, CH_3), 0.75 (1H, m, cyclopropyl $C\mathit{H_E}H_F$)

^{13}C NMR (100MHz, $CDCl_3$) **δ**: 135.6 (1), 135.3 (0), 116.6 (2), 104.6 (2), 83.4 (1), 70.4 (2), 68.8 (1), 18.6 (3), 7.1 (2)

LRMS (CI) m/z: 251 $(M+H)^+$ [4%], 193 $(M+H\text{-}HOC_3H_5)$ [89%], 123 [100%]

HRMS (EI) m/z: $C_{16}H_{26}O_2$ $(M)^+$ requires 250.19328, found 250.19331 [63%].

2-((1S,2S)-2-{(R)-Hydroxy[(1S)-2-methylenecyclopropyl]methyl}cyclohexyl)pent-4-en-2-ol 458

R_f: 0.2 (40% Ether/PE)

FT-IR ν_{max}: 3328 (br.w), 2926, (s), 2855 (m), 1639 (w), 1448 (m), 1376 (w), 1098 (m), 1019 (m), 907 (m), 860 (w)

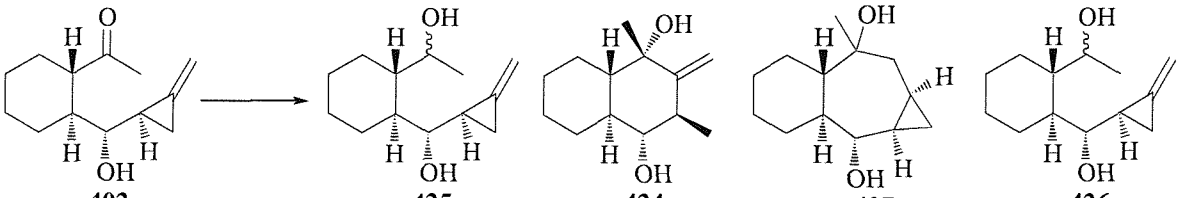
^{1}H NMR (400MHz, $CDCl_3$) δ: 5.98 – 5.86 (1H, tdd, J = 7.5, 10, 17Hz CH_2CH=CH_2), 5.53 (1H, s, C=C$H_A$$H_B$), 5.44 (1H, s, C=C$H_A$$H_B$), 5.18 (1H, d, J = 10Hz, CH_2CH=C$H_C$$H_D$), 5.11 (1H, d, J = 17Hz, CH_2CH=C$H_C$$H_D$), 3.76 (1H, d, C$H$(OH)), 2.36 (1H, dd, J = 7.5, 14Hz, C$H_E$$H_F$CH=$CH_2$), 2.18 (1H, dd, J = 7.5, 14Hz, C$H_E$$H_F$CH=$CH_2$), 2.00 (1H, m, C$H_G$$H_H$), 1.85 – 1.70 (4H, m, cyclopropyl CH, C$H_I$$H_J$, C$H_K$$H_L$, C$H_M$$H_N$), 1.69 – 1.52 (2H, m, C$HCH$(CH(OH))), 1.44 (3H, s, CH_3), 1.41 – 1.20 (5H, m, cyclopropyl C$H_O$$H_P$, C$H_G$$H_H$, C$H_I$$H_J$, C$H_K$$H_L$, C$H_M$$H_N$), 0.94 (1H, m, cyclopropyl C$H_O$$H_P$)

^{13}C NMR (100MHz, $CDCl_3$) δ: 135.1 (0), 134.4 (1), 119.5 (2), 104.0 (2), 75.9 (0), 75.5 (1), 50.0 (1), 45.2 (1), 40.2 (2), 30.7 (3), 29.9 (2), 29.4 (2), 27.4 (2), 27.0 (2), 18.9 (1), 7.7 (2)

LRMS (CI) m/z: 251 $(M+H)^+$ [17%], 233 $(M+H-H_2O)^+$ [98%], 149 [100%]

HRMS (EI) m/z: $C_{16}H_{26}O_2$ $(M)^+$ requires 250.19328, found 250.19277 [100%].

Cyclisation of 1-((1S,2S)-2-{(R)-hydroxy[(1R)-2-ethylenecyclopropyl]methyl}-cyclohexyl)ethanone 402



Following method **B** at 0°C, samarium (0.462g, 3.07mmol); di-iodoethane (0.434g, 1.54mmol); ketone **402** (0.040g, 0.19mmol); HMPA (0.8mL, 4.61mmol); ^{t}BuOH (0.08mL, 0.77mmol) were used. Column chromatography (0 to 90% ether/PE) afforded an inseparable mixture of less polar 1-((1S,2S)-2-{(R)-hydroxy[(1R)-2-methylenecyclopropyl]methyl}cyclohexyl)ethanol **425** (0.003g, 7%) and (1S,3R,4R,4aS,8aS)-1,3-dimethyl-2-methylenedecahydronaphthalene-1,4-diol **424** (0.006g, 15%) as colourless crystals; (2S,2aS,6aS)-7-methyldodecahydrobenzo[a]-cycloprop[d][7]annulene-2,7-diol **427** (0.002g, 5%) as a colourless oil with a minor inseparable impurity; and more polar 1-((1S,2S)-2-{(R)-hydroxy[(1R)-2-methylenecyclopropyl]methyl}cyclohexyl)ethanol **426** (0.015g, 36%) as a colourless oil.

1-((1S,2S)-2-{(R)-hydroxy[(1R)-2-methylenecyclopropyl]methyl}cyclohexyl)ethanol 425

R_f: 0.2 (75% Ether/PE)

FT-IR ν_{max}: 3309 (br.m), 2974 (m), 2923 (s), 2854 (s), 1448 (m), 1375 (m), 1240 (m), 1126 (m), 1094 (m), 1044 (m), 885 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.43 (1H, s with fine splitting, $=CH_AH_B$), 5.41 (1H, s with fine splitting, $=CH_AH_B$), 4.06 (1H, br.d, J = 7 Hz, $CH(OH)CH_3$), 3.34 (1H, d, J = 9 Hz, $CH(CH(OH)CH)$), 2.46 (1H, br.s, $CH(CH(OH)CH)$), 2.41 (1H, br.s, $CH(OH)CH_3$), 1.85 – 1.67 (5H, m, cyclopropyl CH, CH_CH_D, CH_EH_F, CH_GH_H, CH_IH_J), 1.65 – 1.53 (2H, m, $CH(CH(OH)CH_3)$, $CH(CH(OH)CH)$), 1.39 – 1.19 (4H, m, cyclopropyl CH_KH_L, CH_CH_D, CH_EH_F, CH_GH_H), 1.16 (3H, d, J = 7 Hz, CH_3), 1.13 (1H, m, CH_IH_J), 1.02 (1H, m, cyclopropyl CH_KH_L)

^{13}C NMR (100MHz, $CDCl_3$) δ: 133.4 (0), 104.8 (2), 77.0 (1), 69.9 (1), 45.0 (1), 44.0 (1), 27.7 (2), 27.6 (2), 26.8 (2), 26.7 (2), 19.6 (1), 19.2 (3), 9.0 (2)

LRMS (CI) m/z: 193 $(M+H-H_2O)^+$ [20%], 67 [100%]

HRMS (CI) m/z: $C_{13}H_{26}NO_2$ $(M+NH_4)^+$ requires 228.19635, found 228.19786 [3%]; $C_{13}H_{24}NO$ $(M+NH_4-H_2O)^+$ requires 210.18579, found 210.18618 [23%]; $C_{13}H_{21}O$ $(M+H-H_2O)^+$ requires 193.15924, found 193.15906 [100%].

(1S,3R,4R,4aS,8aS)-1,3-Dimethyl-2-methylenedecahydronaphthalene-1,4-diol 424

R_f: 0.2 (60% Ether/PE)

FT-IR ν_{max}: 3316 (br.s), 2931 (s), 2853 (m), 1642 (w), 1445 (m), 1368 (m), 1251 (m), 1120 (m), 1095 (m), 1023 (s), 903 (s), 891 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.03 (1H, s, $=CH_AH_B$), 4.83 (1H, s with fine splitting, $=CH_AH_B$), 2.76 – 2.59 (2H, m, $CH(OH)CH(CH_3)$), 2.24 (1H, m, CH_CH_D), 1.91 – 1.68 (3H, m, CH_EH_F, CH_GH_H, CH_IH_J), 1.56 (1H, m, $CH(CH(OH)CH(CH_3))$), 1.39 (3H, s, $C(CH_3)$), 1.31 – 1.20 (3H, m, CH_EH_F, CH_GH_H, CH_IH_J), 1.17 (3H, d, J = 6.5Hz, $CH(CH_3)$), 0.97 (1H, m, $C(OH)CH$)0.86 (1H, m, CH_CH_D)

^{13}C NMR (100MHz, $CDCl_3$) δ: 155.8 (0), 106.8 (2), 81.5 (1), 73.5 (0), 49.9 (1), 44.6 (1), 40.5 (1), 30.5 (2), 26.8 (2), 26.2 (2), 26.0 (2), 24.9 (3), 14.8 (3)

LRMS (CI) m/z: 210 $(M+NH_4-H_2O)^+$ [11%], 193 $(M+H-H_2O)^+$ [100%]

HRMS (EI) m/z: $C_{13}H_{22}O_2$ $(M)^+$ requires 210.16198, found 210.16214 [20%]

X-ray: see appendix.

(2S,2aS,6aS)-7-Methyldodecahydrobenzo[a]cycloprop[d][7]annulene-2,7-diol 427

R_f: 0.3 (Ether)

FT-IR ν_{max}: 3386 (br.m), 2922 (s), 2854 (m), 1448 (m), 1038 (m), 1012 (m), 983 (m), 927 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 2.94 (1H, dd, J = 8, 10Hz, C*H*OH), 2.25 – 2.17 (2H, m, C(OH)CH_AH$_B$, CH_CH$_D$), 1.90 (1H, m, CH_EH$_F$), 1.75 – 1.68 (2H, m, CH_GH$_H$, CH_IH$_J$), 1.59 (1H, dtd, J = 4, 10, 12Hz, $CH_2CH_2CHCHOH$), 1.49 (2H, br.s, OH, OH), 1.20 – 1.05 (4H, m, C(OH)CH$_A$*H$_B$*, CH$_E$*H$_F$*, CH$_G$*H$_H$*, CH$_I$*H$_J$*), 1.16 (3H, s, CH_3), 0.96 – 0.86 (2H, m, cyclopropyl CHCH), 0.85 – 0.79 (3H, m, CH$_C$*H$_D$*, CH_2CHCOH, cyclopropyl CH_KH$_L$), 0.26 (1H, q, J = 4.5Hz, cyclopropyl CH$_K$*H$_L$*)

^{13}C NMR (100MHz, $CDCl_3$) δ: 77.9 (0), 75.0 (1), 53.1 (1), 46.5 (1), 44.5 (2), 30.8 (3), 29.6 (2), 28.2 (2), 27.2 (2), 26.5 (2), 23.8 (1), 14.4 (2), 8.6 (1)

LRMS (CI) m/z: 193 $(M+H-H_2O)^+$ [60%], 175 $(M+H-H_2O-H_2O)^+$ [100%].

1-((1S,2S)-2-{(R)-hydroxy[(1R)-2-methylenecyclopropyl]methyl}cyclohexyl)ethanol 426

R_f: 0.1 (75% Ether/PE)

FT-IR ν_{max}: 3338 (br.m), 2972 (m), 2927 (s), 2855 (s), 1448 (m), 1376 (m), 1260 (m), 1160 (m), 1081(s), 985 (m), 886 (m)

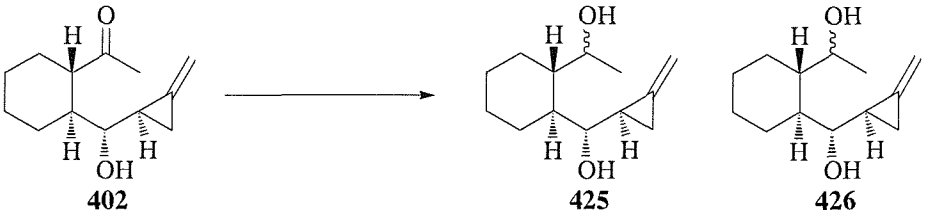
^{1}H NMR (400MHz, $CDCl_3$) δ: 5.43 (1H, s with fine splitting, =CH_AH$_B$), 5.40 (1H, s with fine splitting, =CH$_A$*H$_B$*), 3.97 (1H, quin., J = 7 Hz, C*H*(OH)CH_3), 3.28 (1H, dd, J = 2, 8 Hz, CH(C*H*(OH)CH)), 2.10 (2H, br.s, OH, OH), 1.93 – 1.73 (5H, m, cyclopropyl CH, CH_CH$_D$, CH_EH$_F$, CH_GH$_H$, CH_IH$_J$), 1.58 (1H, m, C*H*(CH(OH)CH_3)), 1.42 – 1.30 (3H, m, cyclopropyl CH_KH$_L$, CH$_C$*H$_D$*, CH$_E$*H$_F$*), 1.29 – 1.22 (2H, m, C*H*(CH(OH)CH), CH$_G$*H$_H$*), 1.12 (3H, d, J = 7 Hz, CH_3), 1.06 – 0.98 (2H, m, cyclopropyl CH$_K$*H$_L$*, CH$_I$*H$_J$*)

^{13}C NMR (100MHz, $CDCl_3$) δ: 133.3 (0), 104.6 (2), 75.7 (1), 69.6 (1), 47.1 (1), 45.7 (1), 26.9 (2), 26.6 (2), 26.5 (2), 26.3 (2), 20.1 (1), 19.9 (3), 9.3 (2)

LRMS (CI) m/z: 193 $(M+H-H_2O)^+$ [25%], 109 [100%]

HRMS (CI) m/z: $C_{13}H_{24}NO$ $(M+NH_4-H_2O)^+$ requires 210.18579, found 210.18644 [19%]; $C_{13}H_{21}O$ $(M+H-H_2O)^+$ requires 193.15924, found 193.15906 [100%].

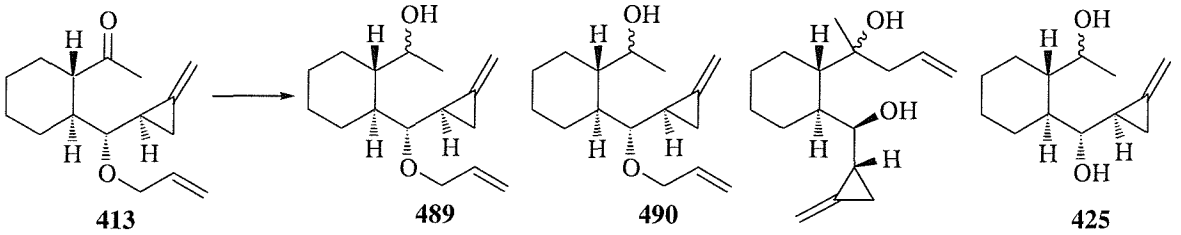
Reduction of 1-((1S,2S)-2-{(R)-hydroxy[(1R)-2-ethylenecyclopropyl]methyl}-cyclohexyl)ethanone 402



402 **425** **426**

1-((1S,2S)-2-{(R)-hydroxy[(1R)-2-ethylenecyclopropyl]methyl}-cyclohexyl)ethanone **402** (0.018g, 0.09mmol) was dissolved in methanol (10mL) and cooled to 0°C. Sodium borohydride (0.010g, 0.26mmol) was added and the reaction allowed to warm to RT over 24 hours. Acetone (5mL) was added and the reaction mixture was then concentrated *in vacuo*. The residue was partitioned between ether (10mL) and water (1mL). The aqueous phase was extracted with EA (10mL). The organic layers were combined and washed with brine (5mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford alcohol **425** as a colourless oil (0.012g, 67%) and alcohol **426** as a colourless oil (0.006g, 33%). All data agrees with those from the cyclisation of 1-((1S,2S)-2-{(R)-hydroxy[(1R)-2-ethylenecyclopropyl]methyl}-cyclohexyl)ethanone **402**.

Cyclisation of 1-((1S,2S)-2-{(R)-(allyloxy)[(1R)-2-methylenecyclopropyl]methyl}-cyclohexyl)ethanone 413



413 **489** **490** **491** **425**

Following method **B** at 0°C, Sm (0.291g, 1.93mmol); di-iodoethane (0.272g, 0.97mmol); ketone **413** (0.040g, 0.16mmol); HMPA (0.5mL, 2.90mmol); ^{t}BuOH (0.06mL, 0.64mmol) were used. Column chromatography (0 to 50% ether/PE) afforded less polar 1-((1S,2S)-2-{(R)-(allyloxy)[(1R)-2-methylenecyclopropyl]methyl}cyclohexyl)ethanol **489** (0.009g, 22%) as a colourless oil; more polar 1-((1S,2S)-2-{(R)-(allyloxy)[(1R)-2-methylenecyclopropyl]methyl}cyclohexyl)ethanol **490** with a minor inseparable impurity (0.008g, 20%) as a colourless oil; 2-((1S,2S)-2-{(R)-hydroxy[(1R)-2-methylenecyclopropyl]methyl}cyclohexyl)pent-4-en-2-ol **491** (0.012g, 30%) as a colourless oil; and less polar 1-((1S,2S)-2-{(R)-hydroxy[(1R)-2-methylenecyclopropyl]methyl}-cyclohexyl)ethanol **425** (0.003g, 9%) as a colourless oil.

1-((1S,2S)-2-{(R)-(allyloxy)[(1R)-2-methylenecyclopropyl]methyl}cyclohexyl)ethanol 489

R_f: 0.5 (50% Ether/PE)

FT-IR ν_{max}: 3438 (br.w), 3071 (w), 2972 (m), 2930 (s), 2854 (m), 1647 (w), 1449 (m), 1370 (m), 1261 (m), 1164 (m), 1077 (s), 1042 (s), 916 (m), 888 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.92 (1H, tdd, *J* = 5, 10, 17Hz, $OCH_2CH{=}CH_2$), 5.48 (1H, s with fine splitting, $C{=}CH_AH_B$), 5.44 (1H, s with fine splitting, $C{=}CH_AH_B$), 5.28 (1H, d with fine splitting, *J* = 17Hz, $OCH_2CH{=}CH_CH_D$), 5.17 (1H, d, *J* = 10Hz, $OCH_2CH{=}CH_CH_D$), 4.32 (1H, dd, *J* = 5, 13Hz, $OCH_EH_FCH{=}CH_2$), 4.06 (1H, m, CH(OH)), 3.98 (1H, dd, *J* = 5, 13Hz, $OCH_EH_FCH{=}CH_2$), 3.01 (1H, dd, *J* = 2, 9Hz, $CH(OC_3H_5)$), 2.46 (1H, br.s, OH), 1.80 – 1.60 (6H, m, CH_GH_H, CH_IH_J, CH_KH_L, CH_MH_N, cyclopropyl CH, $CH_2CH_2CH(CH(OC_3H_5))$), 1.55 (1H, m, $CH(CH(OH)CH_3)$), 1.48 – 1.29 (3H, m, cyclopropyl CH_OH_P, CH_GH_H, CH_IH_J), 1.29 – 1.15 (2H, m, CH_KH_L, CH_MH_N), 1.15 (3H, d, *J* = 7Hz, CH_3), 1.08 (1H, m, cyclopropyl CH_OH_P)

^{13}C NMR (100MHz, $CDCl_3$) δ: 135.6 (1), 132.1 (0), 116.9 (2), 105.5 (2), 84.7 (1), 70.9 (2), 68.4 (1), 45.0 (1), 44.0 (1), 28.6 (2), 27.0 (2), 26.6 (2), 26.1 (2), 19.6 (3), 17.4 (1), 10.8 (2)

LRMS (CI) m/z: 251 $(M+H)^+$ [14%], 193 $(M+H\text{-}HOC_3H_5)$ [80%], 81 [100%]

HRMS (EI) m/z: $C_{16}H_{26}O_2$ $(M)^+$ requires 250.19328, found 250.19430 [68%].

1-((1S,2S)-2-{(R)-(allyloxy)[(1R)-2-methylenecyclopropyl]methyl}cyclohexyl)ethanol 490

R_f: 0.5 (50% Ether/PE)

FT-IR ν_{max}: 3407 (br.w), 3069 (w), 2964 (m), 2926 (s), 2854 (m), 1647 (w), 1449 (m), 1376 (m), 1260 (m), 1081 (s), 1052 (s), 914 (m), 888 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.92 (1H, tdd, *J* = 5.5, 10.5, 17Hz, $OCH_2CH{=}CH_2$), 5.46 (1H, s with fine splitting, $C{=}CH_AH_B$), 5.41 (1H, s with fine splitting, $C{=}CH_AH_B$), 5.30 (1H, d with fine splitting, *J* = 17Hz, $OCH_2CH{=}CH_CH_D$), 5.16 (1H, d with fine splitting, *J* = 10.5Hz, $OCH_2CH{=}CH_CH_D$), 4.31 (1H, br.dd, *J* = 5.5, 13Hz, $OCH_EH_FCH{=}CH_2$), 4.02 – 3.85 (2H, m, CH(OH), $OCH_EH_FCH{=}CH_2$), 2.88 (1H, dd, *J* = 2, 9Hz, $CH(OC_3H_5)$), 2.16 (1H, br.s, OH), 1.89 – 1.61 (5H, m, CH_GH_H, CH_IH_J, CH_KH_L, CH_MH_N, cyclopropyl CH,), 1.50 – 1.19 (6H, m, $CH(CH(OH)CH_3)$, $CH_2CH_2CH(CH(OC_3H_5))$, cyclopropyl CH_OH_P,

CH_GH_H, CH_IH_J, CH_KH_L), 1.09 – 0.92 (2H, m, CH_MH_N, cyclopropyl CH_OH_P), 1.16 (3H, d, J = 6.5Hz, CH_3)

^{13}C NMR (100MHz, $CDCl_3$) δ: 135.6 (1), 132.0 (0), 116.7 (2), 105.1 (2), 83.1 (1), 70.5 (2), 68.9 (1), 46.0 (1), 45.5 (1), 27.4 (2), 27.0 (2), 26.4 (2), 26.0 (2), 18.5 (3), 17.8 (1), 11.1 (2)

LRMS (CI) m/z: 251 $(M+H)^+$ [8%], 193 $(M+H-HOC_3H_5)$ [48%], 41 [100%]

HRMS (EI) m/z: $C_{16}H_{26}O_2$ $(M)^+$ requires 250.19328, found 250.19311 [55%].

2-((1S,2S)-2-{(R)-Hydroxy[(1R)-2-methylenecyclopropyl]methyl}cyclohexyl)pent-4-en-2-ol 491

R_f: 0.2 (50% Ether/PE)

FT-IR ν_{max}: 3297 (br.m), 3072 (w), 2975 (m), 2926, (s), 2874 (m), 2855 (m), 1639 (w), 1449 (m), 1377 (w), 1300 (w), 1250 (w), 1126 (w), 1020 (m), 908 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.89 (1H, m, CH_2CH=CH_2), 5.44 – 5.39 (2H, m, C=CH_2), 5.19 (1H, d with fine splitting, J = 10Hz, CH_2CH=CH_AH_B), 5.08 (1H, d with fine splitting, J = 17Hz, CH_2CH=CH_AH_B), 3.56 (1H, m, CH(OH)), 3.35 (1H, d, J = 4Hz, CH(OH)), 2.31 (1H, dd, J = 8, 14Hz, CH_CH_DCH=CH_2), 2.15 (1H, dd, J = 7, 14Hz, CH_CH_DCH=CH_2), 2.03 (1H, m, CH_EH_F), 1.87 – 1.75 (5H, m, cyclopropyl CH, CH_GH_H, CH_IH_J, CH_KH_L, COH), 1.61 – 1.51 (2H, m, $CHCH$(CH(OH))), 1.38 (1H, m, cyclopropyl CH_MH_N), 1.31 – 1.16 (3H, m, CH_EH_F, CH_GH_H, CH_IH_J), 1.19 (3H, s, CH_3), 1.09 – 0.99 (2H, m, cyclopropyl CH_MH_N, CH_KH_L)

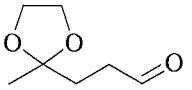
^{13}C NMR (100MHz, $CDCl_3$) δ: 134.20 (1), 134.16 (0), 119.9 (2), 104.1 (2), 76.5 (1), 76.0 (0), 49.9 (1), 45.6 (1), 39.9 (2), 29.8 (2), 29.5 (3), 27.4 (2), 27.1 (2), 27.0 (2), 19.5 (1), 10.0 (2)

LRMS (CI) m/z: 233 $(M+H-H_2O)^+$ [24%], 43 [100%]

HRMS (EI) m/z: $C_{16}H_{26}O_2$ $(M)^+$ requires 250.19328, found 250.19252 [66%].

6.2.4 Experimental for Chapter 4

3-(2-Methyl-1,3-dioxolan-2-yl)propanal 497



497

Following the method of Swern[136], oxalyl chloride (7.1mL, 81mmol) was dissolved in DCM (120mL). The mixture was cooled to -78°C before addition of DMSO (11.5mL, 163mmol) in DCM (40mL). After 5 minutes, 3-(2-methyl-1,3-dioxolan-2-yl)propan-1-ol **317** (9.9g, 68mmol) in DCM (60mL) was added keeping the temperature below -60°C. After 30 minutes at -60°C, NEt_3 (47.2mL, 339mmol) was added. The reaction was stirred for 45 minutes before warming to RT over 2 hours. Water (100mL) was added to the white ppt which then disappeared. The organic phase was separated, and the aqueous phase extracted with DCM (3 x 100mL). The combined organics were washed with brine (100mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification was by column chromatography (0 to 50% ether/PE) affording aldehyde **497** as a colourless oil (6.17g, 63%). Data agrees with Pak[167].

R_f: 0.3 (50% Ether/PE)

FT-IR ν_{max}: 2984 (m), 2938, (m), 2889 (m), 1722 (s), 1378 (m), 1222 (m), 1147 (m), 1057 (m)

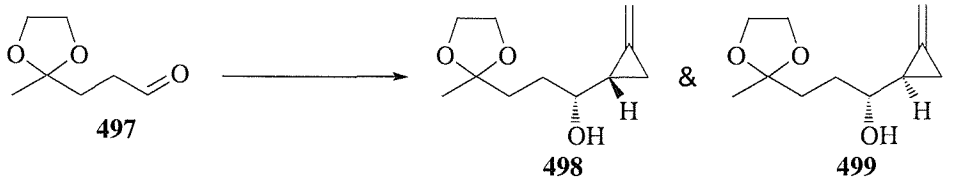
^{1}H NMR (400MHz, $CDCl_3$) **δ**: 9.72 (1H, t, *J* = 2Hz, CHO), 3.97 – 3.87 (4H, m, OCH_2CH_2O), 2.47 (2H, dt, *J* = 2, 7Hz, CH_2CH_2CHO), 2.07 (2H, t, *J* = 7Hz, CH_2CH_2CHO), 1.33 (3H, s, CH_3)

^{13}C NMR (100MHz, $CDCl_3$) **δ**: 202.4 (1), 109.5 (0), 65.1 (2)*, 38.8 (2), 32.2 (2), 24.5 (3)

* = 2 carbons

LRMS (CI) m/z: 145 $(M+H)^+$ [100%].

3-(2-Methyl-1,3-dioxolan-2-yl)-1-(2-methylenecyclopropyl)propan-1-ol 498 & 499



497 **498** **499**

^{n}BuLi (29.3mL, 2.17M in hexanes, 63.5mmol) was added to methylenecyclopropane **200** (5.7mL, 84.6mmol) in THF (80mL) at -60°C under Ar and allowed to warm to 0°C over 30 minutes. The reaction was left for 45 minutes at 0°C, then cooled to -60°C before

addition of 3-(2-methyl-1,3-dioxolan-2-yl)propanal **54** (6.10g, 42.3mmol) in THF (30mL). The reaction was allowed to warm to RT overnight. It was then quenched with NH_4Cl (100mL) and extracted with EA (2 x 100mL). The combined organic phases were washed with brine (100mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (0 to 75% ether/PE) to give the ketals as colourless oils (anti **498**: 1.47g, 18%; syn **499**: 2.59g, 31%).

Anti: (1R)-3-(2-methyl-1,3-dioxolan-2-yl)-1-[(1S)-2-methylenecyclopropyl]propan-1-ol 498

R_f: 0.2 (75% Ether/PE)

FT-IR ν_{max}: 3433 (br.m), 2982 (m), 2933, (m), 2880 (m), 1377 (m), 1220 (m), 1133 (m), 1065 (s)

^{1}H NMR (400MHz, $CDCl_3$) **δ**: 5.53 (1H, s with fine splitting, $=CH_AH_B$), 5.46 (1H, s, $=CH_AH_B$), 3.97 – 3.94 (4H, m, OCH_2CH_2O), 3.25 (1H, m, $CH(OH)$), 1.97 (1H, d, J = 5Hz, OH), 1.92 – 1.73 (3H, m, CH_2, CH_CH_D), 1.72 – 1.59 (2H, m, cyclopropyl CH, CH_CH_D), 1.35 (3H, s, CH_3), 1.28 (1H, tt, J = 3, 9Hz, cyclopropyl CH_EH_F), 1.00 (1H, m, cyclopropyl CH_EH_F)

^{13}C NMR (100MHz, $CDCl_3$) **δ**: 133.6 (0), 110.4 (0), 104.4 (2), 74.6 (1), 65.1 (2), 65.0 (2), 35.7 (2), 31.7 (2), 24.2 (3), 22.1 (1), 7.8 (2)

LRMS (CI) m/z: 199 $(M+H)^+$ [4%], 181 $(M+H-H_2O)^+$ [46%], 137 [100%]

HRMS (EI) m/z: $C_{11}H_{18}O_3$ $(M)^+$ requires 198.12559, found 198.12464 [1%]; $C_{10}H_{15}O_3$ $(M-CH_3)^+$ requires 183.10212, found 183.10257 [100%].

Syn: (1R)-3-(2-methyl-1,3-dioxolan-2-yl)-1-[(1R)-2-methylenecyclopropyl]propan-1-ol 499

R_f: 0.2 (75% Ether/PE)

FT-IR ν_{max}: 3435 (br.m), 2982 (m), 2934, (m), 2880 (m), 1377 (m), 1220 (m), 1127 (m), 1065 (s)

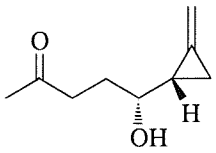
^{1}H NMR (400MHz, $CDCl_3$) **δ**: 5.43 (2H, s with fine splitting, $=CH_2$), 3.99 – 3.93 (4H, m, OCH_2CH_2O), 3.17 (1H, m, $CH(OH)$), 2.20 (1H, d, J = 3Hz, OH), 1.88 – 1.79 (2H, m, $CH_2CH_2CH(OH)$), 1.76 – 1.68 (2H, m, $CH_2CH_2CH(OH)$), 1.61 (1H, m, cyclopropyl CH), 1.34 (3H, s, CH_3), 1.30 (1H, tt, J = 2, 9Hz, cyclopropyl CH_AH_B), 1.04 (1H, m, cyclopropyl CH_AH_B)

^{13}C NMR (100MHz, $CDCl_3$) δ: 133.3 (0), 110.4 (0), 104.5 (2), 74.6 (1), 65.1 (2), 65.0 (2), 35.5 (2), 31.8 (2), 24.2 (3), 22.8 (1), 8.2 (2)

LRMS (CI) m/z: 199 $(M+H)^+$ [4%], 181 $(M+H-H_2O)^+$ [66%], 87 [100%]

HRMS (EI) m/z: $C_{11}H_{18}O_3$ $(M)^+$ requires 198.12559, found 198.12368 [0.5%]; $C_{10}H_{15}O_3$ $(M-CH_3)^+$ requires 183.10212, found 183.10276 [100%].

(5R)-5-Hydroxy-5-[(1S)-2-methylenecyclopropyl]pentan-2-one 500



500

(1R)-3-(2-methyl-1,3-dioxolan-2-yl)-1-[(1S)-2-methylenecyclopropyl]propan-1-ol **498** (0.400g, 2.02mmol) was dissolved in acetone (25mL) and water (5mL). *p*-TsOH (0.010g, 0.053mmol) was added. The reaction was stirred overnight. $NaHCO_3$ (10mL) was added and the reaction concentrated *in vacuo*. The aqueous layer was extracted with EA (50mL). The organic layers were washed with brine (25mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification was by column chromatography (0 to 75% ether/PE) affording ketone **500** as a colourless oil (0.312g, 99%) with a minor impurity.

R_f: 0.2 (75% Ether/PE)

FT-IR ν_{max}: 3418 (br.m), 2985 (m), 2927, (m), 1710 (s), 1409 (m), 1363 (m), 1165 (m), 1082 (m)

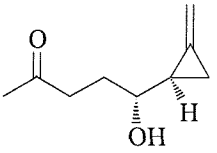
^{1}H NMR (400MHz, $CDCl_3$) δ: 5.52 (1H, s with fine splitting, $=CH_AH_B$), 5.45 (1H, s with fine splitting, $=CH_AH_B$), 3.25 (1H, m, CH(OH)), 2.64 (2H, dt, J = 4, 7Hz, $COCH_2$), 2.17 (3H, s, CH_3), 1.96 (1H, m, $COCH_2CH_CH_D$), 1.80 (1H, m, $COCH_2CH_CH_D$), 1.75 (1H, d, J = 5Hz, OH), 1.62 (1H, m, cyclopropyl CH), 1.28 (1H, tt, J = 2, 9Hz, cyclopropyl CH_EH_F), 0.99 (1H, m, cyclopropyl CH_EH_F)

^{13}C NMR (100MHz, $CDCl_3$) δ: 209.6 (0), 133.3 (0), 104.5 (2), 73.9 (1), 40.3 (2), 30.9 (2), 30.4 (3), 22.1 (1), 7.7 (2)

LRMS (CI) m/z: 154 $(M+NH_4-H_2O)^+$ [12%], 137 $(M+H-H_2O)^+$ [34%], 43 [100%]

HRMS (EI) m/z: $C_9H_{13}O$ $(M+H-H_2O)^+$ requires 137.09664, found 137.09667 [25%].

(5R)-5-Hydroxy-5-[(1R)-2-methylenecyclopropyl]pentan-2-one 501



501

(1R)-3-(2-methyl-1,3-dioxolan-2-yl)-1-[(1R)-2-methylenecyclopropyl]propan-1-ol **499** (0.600g, 3.03mmol) was dissolved in acetone (40mL) and water (10mL). *p*-TsOH (0.010g, 0.053mmol) was added. The reaction was stirred overnight. $NaHCO_3$ (10mL) was added and the reaction concentrated *in vacuo*. The aqueous layer was extracted with EA (50mL). The organic layers were washed with brine (25mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification was by column chromatography (0 to 75% ether/PE) affording ketone **501** as a colourless oil (0.464g, 99%) with a minor impurity.

R_f: 0.2 (75% Ether/PE)

FT-IR ν_{max}: 3423 (br.m), 2987 (m), 2927, (m), 1711 (s), 1409 (m), 1363 (m), 1166 (m), 1083 (m)

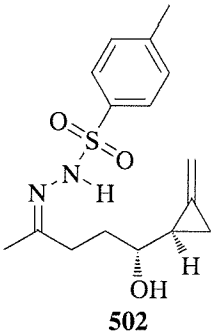
^{1}H NMR (400MHz, $CDCl_3$) δ: 5.45 – 5.42 (2H, m, $=CH_2$), 3.18 (1H, m, CH(OH)), 2.69 – 2.60 (2H, m, $COCH_2$), 2.18 (3H, s, CH_3), 1.98 (1H, d, J = 5Hz, OH), 1.92 – 1.84 (2H, m, $COCH_2CH_2$), 1.61 (1H, m, cyclopropyl CH), 1.30 (1H, tt, J = 2, 9Hz, cyclopropyl CH_AH_B), 1.03 (1H, m, cyclopropyl CH_AH_B)

^{13}C NMR (100MHz, $CDCl_3$) δ: 209.7 (0), 132.8 (0), 104.7 (2), 73.9 (1), 40.4 (2), 31.0 (2), 30.4 (3), 22.7 (1), 8.1 (2)

LRMS (CI) m/z: 154 $(M+NH_4-H_2O)^+$ [8%], 49 [100%]

HRMS (EI) m/z: $C_9H_{13}O$ $(M+H-H_2O)^+$ requires 137.09664, found 137.09655 [100%].

***N*'1-(*Z*,4*R*)-4-hydroxy-1-methyl-4-[(1*R*)-2-methylenecyclopropyl]butylidene-4-methyl-1-benzenesulfonohydrazide 502**



502

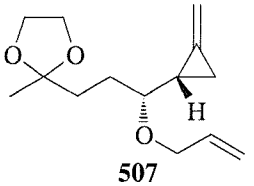
(5R)-5-Hydroxy-5-[(1R)-2-methylenecyclopropyl]pentan-2-one **501** (0.100g, 0.65mmol) was dissolved in DCM (10mL) and *p*-tosyl hydrazine (0.109g, 0.65mmol) was added.

Highly activated 4A molecular sieves were added and the reaction stirred gently for 90 minutes. Water (1mL) was added and the aqueous layer extracted with DCM. The combined organic phases were washed with $NaHCO_3$ (2mL), dried ($MgSO_4$) and concentrated *in vacuo*. Colourless crystals of hydrazone **502** were isolated (0.136g, 65%). Addition of $CDCl_3$ caused decomposition of hydrazone **502** and data other than retention factor (TLC) and X-ray analysis were unable to be obtained.

R_f: 0.1 (75% Ether/PE)

X-ray: see appendix.

2-{(3R)-3-(Allyloxy)-3-[(1S)-2-methylenecyclopropyl]propyl}-2-methyl-1,3-dioxolane 507



507

Following a modified method of Grubbs[166], sodium hydride (0.121g, 60% dispersion in mineral oil, 3.03mmol) was suspended in DMF (10mL) and cooled to 0°C. (1R)-3-(2-methyl-1,3-dioxolan-2-yl)-1-[(1S)-2-methylenecyclopropyl]propan-1-ol **498** (0.400g, 2.02mmol) was dissolved in DMF (5mL) and added drop-wise to the mixture. The reaction was stirred for 30 minutes at 0°C. Allyl bromide (0.26mL, 3.03mmol) in DMF (5mL) was added. The reaction was allowed to warm to RT and then quenched with water (10mL) and the aqueous layer was extracted with EA (50mL). The organic phase was then washed with brine (20mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification was by column chromatography (0 to 30% ether/PE) affording ketal **507** as a colourless oil (0.413g, 86%).

R_f: 0.5 (30% Ether/PE)

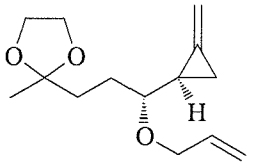
FT-IR ν_{max}: 2982 (m), 2932, (m), 2875 (m), 1376 (m), 1220 (m), 1133 (m), 1067 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.93 (1H, tdd, J = 5, 10, 17Hz, $OCH_2CH{=}CH_2$), 5.47 (1H, s with fine splitting, $C{=}CH_AH_B$), 5.45 (1H, s with fine splitting, $C{=}CH_AH_B$), 5.27 (1H, dd, J = 2, 17Hz, $OCH_2CH{=}CH_CH_D$), 5.15 (1H, dd, J = 2, 10Hz, $OCH_2CH{=}CH_CH_D$), 4.21 (1H, dd, J = 5, 13Hz, $OCH_EH_FCH{=}CH_2$), 3.97 – 3.90 (5H, m, $OCH_EH_FCH{=}CH_2$, OCH_2CH_2O), 2.84 (1H, m, $CH(OC_3H_5)$), 1.91 (1H, m, $CH_GH_HCH_2CH(OC_3H_5)$), 1.79 – 1.69 (3H, m, $CH_GH_HCH_2CH(OC_3H_5)$), 1.55 (1H, m, cyclopropyl CH), 1.34 (3H, s, CH_3), 1.28 (1H, tt, J = 2, 9Hz, cyclopropyl CH_IH_J), 0.85 (1H, m, cyclopropyl CH_IH_J)

^{13}C NMR (100MHz, $CDCl_3$) δ: 135.8 (1), 134.7 (0), 116.7 (2), 110.5 (0), 104.5 (2), 82.0 (1), 70.3 (2), 65.05 (2), 65.01 (2), 35.5 (2), 30.0 (2), 24.2 (3), 20.4 (1), 7.2 (2)

LRMS (CI) m/z: 239 $(M+H)^+$ [10%], 181 $(M-OC_3H_5)^+$ [100%].

2-{(3R)-3-(Allyloxy)-3-[(1R)-2-methylenecyclopropyl]propyl}-2-methyl-1,3-dioxolane 509



509

Following a modified method of Grubbs[166], sodium hydride (0.121g, 60% dispersion in mineral oil, 3.03mmol) was suspended in DMF (10mL) and cooled to 0°C. (1R)-3-(2-methyl-1,3-dioxolan-2-yl)-1-[(1R)-2-methylenecyclopropyl]propan-1-ol **499** (0.400g, 2.02mmol) was dissolved in DMF (5mL) and added drop-wise to the mixture. The reaction was stirred for 30 minutes at 0°C. Allyl bromide (0.26mL, 3.03mmol) in DMF (5mL) was added. The reaction was allowed to warm to RT and then quenched with water (10mL) and the aqueous layer was extracted with EA (50mL). The organic phase was then washed with brine (20mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification was by column chromatography (0 to 30% ether/PE) affording ketal **509** as a colourless oil (0.469g, 98%).

R_f: 0.5 (30% Ether/PE)

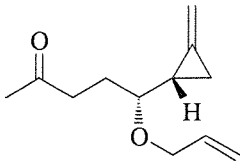
FT-IR ν_{max}: 2982 (m), 2933, (m), 2875 (m), 1376 (m), 1219 (m), 1132 (m), 1068 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.92 (1H, tdd, J = 6, 10.5, 17Hz, OCH_2CH=CH_2), 5.46 – 4.40 (2H, m, C=CH_2), 5.27 (1H, dd, J = 1, 17Hz, OCH_2CH=CH_AH_B), 5.15 (1H, dd, J = 1, 10.5Hz, OCH_2CH=CH_AH_B), 4.20 (1H, dd, J = 6, 13Hz, OCH_CH_DCH=CH_2), 4.02 (1H, dd, J = 6, 13Hz, OCH_CH_DCH=CH_2), 3.97 – 3.92 (4H, m, OCH_2CH_2O), 2.87 (1H, m, $CH(OC_3H_5)$), 1.86 (1H, m, $CH_EH_FCH_2CH(OC_3H_5)$), 1.76 – 1.69 (3H, m, $CH_EH_FCH_2CH(OC_3H_5)$), 1.55 (1H, m, cyclopropyl CH), 1.39 (1H, tt, J = 2, 9Hz, cyclopropyl CH_GH_H), 1.34 (3H, s, CH_3), 1.07 (1H, m, cyclopropyl CH_GH_H)

^{13}C NMR (100MHz, $CDCl_3$) δ: 135.9 (1), 132.6 (0), 116.8 (2), 110.5 (0), 104.7 (2), 81.6 (1), 70.4 (2), 65.05 (2), 64.99 (2), 35.0 (2), 30.1 (2), 24.2 (3), 20.3 (1), 9.9 (2)

LRMS (CI) m/z: 239 $(M+H)^+$ [8%], 181 $(M-OC_3H_5)^+$ [100%].

(5R)-5-(Allyloxy)-5-[(1S)-2-methylenecyclopropyl]pentan-2-one 508



508

2-{(3R)-3-(allyloxy)-3-[(1S)-2-methylenecyclopropyl]propyl}-2-methyl-1,3-dioxolane **507** (0.400g, 1.69mmol) was dissolved in acetone (25mL) and water (5mL). *p*-TsOH (0.010g, 0.053mmol) was added. The reaction was stirred for 72 hours. $NaHCO_3$ (10mL) was added and the reaction concentrated *in vacuo*. The aqueous layer was extracted with EA (30mL). The organic layer was washed with brine (15mL), dried ($MgSO_4$) and concentrated *in vacuo*. Ketone **508** was isolated as a colourless oil (0.327g, 100%).

R_f: 0.5 (30% Ether/PE)

FT-IR ν_{max}: 3071 (w), 2990 (w), 2928, (w), 2862 (w), 1716 (s), 1409 (w), 1360 (m), 1135 (m), 1087 (s)

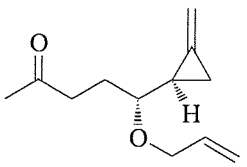
^{1}H NMR (400MHz, $CDCl_3$) **δ**: 5.92 (1H, tdd, J = 5.5, 10.5, 17Hz, $OCH_2CH{=}CH_2$), 5.49 – 5.43 (2H, m, $C{=}CH_2$), 5.27 (1H, qd, J = 1.5, 17Hz, $OCH_2CH{=}CH_AH_B$), 5.16 (1H, br.dd, J = 1, 10.5Hz, $OCH_2CH{=}CH_AH_B$), 4.22 (1H, tdd, J = 1.5, 5.5, 13Hz, $OCH_CH_DCH{=}CH_2$), 3.89 (1H, tdd, J = 1.5, 5.5, 13Hz, $OCH_CH_DCH{=}CH_2$), 2.83 (1H, dt, J = 4, 9Hz, $CH(OC_3H_5)$), 2.68 – 2.51 (2H, m, CH_3COCH_2), 2.16 (3H, s, CH_3), 2.00 (1H, m, $CH_EH_FCH(OC_3H_5)$), 1.85 (1H, m, $CH_EH_ECH(OC_3H_5)$), 1.53 (1H, m, cyclopropyl CH), 1.28 (1H, tt, J = 2, 9Hz, cyclopropyl CH_GH_H), 0.85 (1H, m, cyclopropyl CH_GH_H)

^{13}C NMR (100MHz, $CDCl_3$) **δ**: 209.2 (0), 135.5 (1), 134.5 (0), 116.9 (2), 104.6 (2), 81.2 (1), 70.3 (2), 40.2 (2), 30.4 (3), 29.3 (2), 20.1 (1), 7.0 (2)

LRMS (CI) m/z: 195 $(M+H)^+$ [16%], 137 $(M-OC_3H_5)^+$ [100%]

HRMS (CI) m/z: $C_{12}H_{19}O_2$ $(M+H)^+$ requires 195.13850, found 195.13819 [70%].

(5R)-5-(Allyloxy)-5-[(1R)-2-methylenecyclopropyl]pentan-2-one 510



510

2-{(3R)-3-(allyloxy)-3-[(1R)-2-methylenecyclopropyl]propyl}-2-methyl-1,3-dioxolane **509** (0.455g, 1.91mmol) was dissolved in acetone (25mL) and water (5mL). *p*-TsOH (0.010g, 0.053mmol) was added. The reaction was stirred for 72 hours. $NaHCO_3$ (10mL)

was added and the reaction concentrated *in vacuo*. The aqueous layer was extracted with EA (30mL). The organic layer was washed with brine (15mL), dried ($MgSO_4$) and concentrated *in vacuo*. Ketone **510** was isolated as a colourless oil (0.360g, 97%).

R_f: 0.5 (30% Ether/PE)

FT-IR ν_{max}: 3072 (w), 2989 (w), 2926, (w), 2859 (w), 1716 (s), 1421 (w), 1358 (m), 1133 (m), 1084 (s)

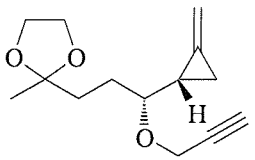
^{1}H NMR (400MHz, $CDCl_3$) δ: 5.91 (1H, br.tdd, J = 5.5, 10.5, 17Hz, OCH_2CH=CH_2), 5.47 – 5.42 (2H, m, C=CH_2), 5.26 (1H, br.d, J = 17Hz, OCH_2CH=CH_AH_B), 5.16 (1H, br.d, J = 10.5Hz, OCH_2CH=CH_AH_B), 4.22 (1H, dd with fine splitting, J = 5.5, 13Hz, OCH_CH_DCH=CH_2), 3.97 (1H, dd with fine splitting, J = 5.5, 13Hz, OCH_CH_DCH=CH_2), 2.86 (1H, m, $CH(OC_3H_5)$), 2.67 – 2.49 (2H, m, CH_3COCH_2), 2.15 (3H, s, CH_3), 1.92 – 1.83 (2H, m, $CH_2CH(OC_3H_5)$), 1.53 (1H, m, cyclopropyl CH), 1.41 (1H, t, J = 9Hz, cyclopropyl CH_EH_F), 1.07 (1H, m, cyclopropyl CH_EH_F)

^{13}C NMR (100MHz, $CDCl_3$) δ: 209.2 (0), 135.6 (1), 132.0 (0), 117.0 (2), 104.9 (2), 80.8 (1), 70.4 (2), 40.0 (2), 30.3 (3), 29.7 (2), 20.0 (1), 10.1 (2)

LRMS (CI) m/z: 195 $(M+H)^+$ [12%], 137 $(M-OC_3H_5)^+$ [100%]

HRMS (CI) m/z: $C_{12}H_{19}O_2$ $(M+H)^+$ requires 195.13850, found 195.13821 [100%].

2-Methyl-2-[(3R)-3-[(1S)-2-methylenecyclopropyl]-3-(prop-2-ynyloxy)propyl]-1,3-dioxolane 511



511

Following the method of Boffey[124], sodium hydride (0.202g, 60% dispersion in mineral oil, 5.04mmol) was suspended in THF (15mL) and cooled to 0°C. (1R)-3-(2-methyl-1,3-dioxolan-2-yl)-1-[(1S)-2-methylenecyclopropyl]propan-1-ol **498** (0.400g, 1.59mmol) was dissolved in THF (5mL) and added drop-wise to the mixture. The reaction was stirred for 20 minutes allowing to warm to RT. DMPU (0.61mL, 5.04mmol) was added and the reaction stirred for 10 minutes. Propargyl bromide (1.14g, 80% in toluene, 7.67mmol) in THF (5mL) was added. The reaction was stirred overnight. Although TLC did not show completion the reaction was quenched with NH_4Cl (20mL). The aqueous layer was extracted with EA (70mL). The organic phase was then washed with brine (30mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification was by column chromatography (0 to

50% ether/PE) affording ketal **511** as a colourless oil (0.240g, 91% based on RSM [0.178g]).

R_f: 0.5 (50% Ether/PE)

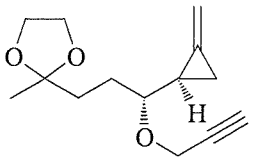
FT-IR ν_{max}: 3292 (w), 2981 (m), 2931, (m), 2878 (m), 2115 (w), 1376 (m), 1220 (m), 1134 (m), 1066 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.49 (1H, d, *J* = 2Hz, $=CH_AH_B$), 5.47 (1H, d, *J* = 2Hz, $=CH_AH_B$), 4.32 (1H, dd, *J* = 2, 16Hz, $OCH_CH_DC{\equiv}CH$), 4.20 (1H, dd, *J* = 2, 16Hz, $OCH_CH_DC{\equiv}CH$), 3.97 – 3.92 (4H, m, OCH_2CH_2O), 3.01 (1H, m, $CH(OC_3H_3)$), 2.38 (1H, t, *J* = 2Hz, $OCH_2C{\equiv}CH$), 1.90 (1H, m, $CH_EH_FCH_2CH(OC_3H_3)$), 1.82 – 1.68 (3H, m, $CH_EH_FCH_2CH(OC_3H_3)$), 1.53 (1H, m, cyclopropyl CH), 1.34 (3H, s, CH_3), 1.29 (1H, tt, *J* = 2, 9Hz, cyclopropyl CH_GH_H), 0.87 (1H, m, cyclopropyl CH_GH_H)

^{13}C NMR (100MHz, $CDCl_3$) δ: 134.1 (0), 110.4 (0), 104.8 (2), 81.6 (1), 80.9 (0), 74.2 (1), 65.1 (2), 65.0 (2), 56.4 (2), 35.3 (2), 29.8 (2), 24.2 (3), 19.8 (1), 7.2 (2)

LRMS (CI) m/z: 237 $(M+H)^+$ [4%], 181 $(M-OC_3H_3)^+$ [44%], 87 [100%].

2-Methyl-2-[(3R)-3-[(1R)-2-methylenecyclopropyl]-3-(prop-2-ynyloxy)propyl]-1,3-dioxolane 513



513

Following the method of Boffey[124], sodium hydride (0.202g, 60% dispersion in mineral oil, 5.04mmol) was suspended in THF (15mL) and cooled to 0°C. (1R)-3-(2-methyl-1,3-dioxolan-2-yl)-1-[(1R)-2-methylenecyclopropyl]propan-1-ol **499** (0.400g, 1.59mmol) was dissolved in THF (5mL) and added drop-wise to the mixture. The reaction was stirred for 20 minutes allowing to warm to RT. DMPU (0.61mL, 5.04mmol) was added and the reaction stirred for 10 minutes. Propargyl bromide (1.14g, 80% in toluene, 7.67mmol) in THF (5mL) was added. The reaction was stirred overnight. Although TLC did not show completion the reaction was quenched with NH_4Cl (20mL). The aqueous layer was extracted with EA (70mL). The organic phase was then washed with brine (30mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification was by column chromatography (0 to 50% ether/PE) affording ketal **513** as a colourless oil (0.163g, 99% based on RSM [0.262g]).

R_f: 0.5 (50% Ether/PE)

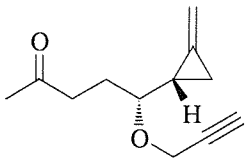
FT-IR ν_{max}: 3070 (w), 2981 (m), 2959, (m), 2878 (m), 2114 (w), 1376 (m), 1220 (m), 1131 (m), 1068 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.47 – 5.44 (2H, m, $=CH_2$), 4.35 (1H, dd, J = 2, 16Hz, $OCH_AH_BC{\equiv}CH$), 4.29 (1H, dd, J = 2, 16Hz, $OCH_AH_BC{\equiv}CH$), 3.98 – 3.90 (4H, m, OCH_2CH_2O), 3.08 (1H, m, $CH(OC_3H_3)$), 2.39 (1H, t, J = 2Hz, $OCH_2C{\equiv}CH$), 1.86 (1H, m, $CH_CH_DCH_2CH(OC_3H_3)$), 1.76 – 1.69 (3H, m, $CH_CH_DCH_2CH(OC_3H_3)$), 1.52 (1H, m, cyclopropyl CH), 1.41 (1H, tt, J = 2, 9Hz, cyclopropyl CH_EH_F), 1.34 (3H, s, CH_3), 1.17 (1H, m, cyclopropyl CH_EH_F)

^{13}C NMR (100MHz, $CDCl_3$) δ: 131.9 (0), 110.4 (0), 105.0 (2), 80.7 (1), 80.6 (0), 74.4 (1), 65.1 (2), 65.0 (2), 56.3 (2), 34.9 (2), 29.9 (2), 24.2 (3), 19.6 (1), 9.9 (2)

LRMS (CI) m/z: 237 $(M+H)^+$ [4%], 181 $(M-OC_3H_3)^+$ [54%], 87 [100%].

(5R)-5-[(1S)-2-Methylenecyclopropyl]-5-(prop-2-ynyloxy)pentan-2-one 512



512

2-methyl-2-[(3R)-3-[(1S)-2-methylenecyclopropyl]-3-(prop-2-ynyloxy)propyl]-1,3-dioxolane **511** (0.374g, 1.58mmol) was dissolved in acetone (25mL) and water (5mL). *p*-TsOH (0.010g, 0.053mmol) was added. The reaction was stirred for 48 hours. $NaHCO_3$ (10mL) was added and the reaction concentrated *in vacuo*. The aqueous layer was extracted with EA (50mL). The organic layer was washed with brine (25mL), dried ($MgSO_4$) and concentrated *in vacuo*. Ketone **512** was isolated as a colourless oil (0.227g, 75%).

R_f: 0.3 (50% Ether/PE)

FT-IR ν_{max}: 3291 (w), 2926 (w), 2961, (w), 2115 (w), 1712 (m), 1438 (w), 1358 (m), 1166 (m), 1079 (s)

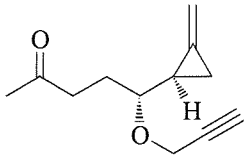
^{1}H NMR (400MHz, $CDCl_3$) δ: 5.49 – 5.47 (2H, m, $=CH_2$), 4.33 (1H, dd, J = 2, 16Hz, $OCH_AH_BC{\equiv}CH$), 4.18 (1H, dd, J = 2, 16 Hz, $OCH_AH_BC{\equiv}CH$), 2.98 (1H, dt, J = 3, 9Hz, $CH(OC_3H_3)$), 2.70 – 2.53 (2H, m, CH_3COCH_2), 2.39 (1H, t, J = 2 Hz, $OCH_2C{\equiv}CH$), 2.16 (3H, s, CH_3), 2.02 (1H, m, $CH_CH_DCH(OC_3H_3)$), 1.82 (1H, dtd, J = 6, 9, 17Hz, $CH_CH_DCH(OC_3H_3)$), 1.51 (1H, m, cyclopropyl CH), 1.30 (1H, tt, J = 2, 9Hz, cyclopropyl CH_EH_F), 0.88 (1H, m, cyclopropyl CH_EH_F)

^{13}C NMR (100MHz, $CDCl_3$) δ: 209.1 (0), 134.0 (0), 104.9 (2), 80.7 (1), 80.7 (0), 74.3 (1), 56.5 (2), 39.9 (2), 30.5 (3), 29.1 (2), 19.7 (1), 7.0 (2)

LRMS (CI) m/z: 193 $(M+H)^+$ [18%], 137 [100%]

HRMS (CI) m/z: $C_{12}H_{17}O_2$ $(M+H)^+$ requires 193.12285, found 193.12273 [78%].

(5R)-5-[(1R)-2-Methylenecyclopropyl]-5-(prop-2-ynyloxy)pentan-2-one 514



514

2-methyl-2-[(3R)-3-[(1R)-2-methylenecyclopropyl]-3-(prop-2-ynyloxy)propyl]-1,3-dioxolane **513** (0.525g, 2.22mmol) was dissolved in acetone (25mL) and water (5mL). *p*-TsOH (0.010g, 0.053mmol) was added. The reaction was stirred for 48 hours. $NaHCO_3$ (10mL) was added and the reaction concentrated *in vacuo*. The aqueous layer was extracted with EA (50mL). The organic layer was washed with brine (25mL), dried ($MgSO_4$) and concentrated *in vacuo*. Ketone **514** was isolated as a colourless oil (0.365g, 85%).

R_f: 0.4 (50% Ether/PE)

FT-IR ν_{max}: 3292 (w), 2975 (w), 2930, (w), 2862 (w), 2114(w), 1712 (m), 1438 (w), 1357 (m), 1259 (w), 1166 (m), 1076 (s)

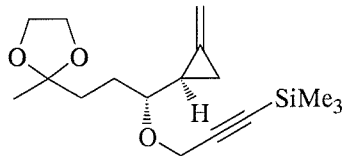
^{1}H NMR (400MHz, $CDCl_3$) δ: 5.49 – 5.45 (2H, m, $=CH_2$), 4.31 (2H, d, J = 2Hz, $OCH_2C{\equiv}CH$), 3.07 (1H, dt, J = 4, 8Hz, $CH(OC_3H_3)$), 2.64 (1H, ddd, J = 6, 8, 17Hz, $CH_3COCH_AH_B$), 2.55 (1H, ddd, J = 6, 8, 17Hz, $CH_3COCH_AH_B$), 2.40 (1H, t, J = 2Hz, $OCH_2C{\equiv}CH$), 2.16 (3H, s, CH_3), 1.97 – 1.80 (2H, m, $CH_2CH(OC_3H_3)$), 1.49 (1H, m, cyclopropyl CH), 1.42 (1H, tt, J = 2, 8Hz, cyclopropyl CH_CH_D), 1.17 (1H, m, cyclopropyl CH_CH_D)

^{13}C NMR (100MHz, $CDCl_3$) δ: 209.1 (0), 131.3 (0), 105.2 (2), 80.5 (0), 79.8 (1), 74.5 (1), 56.3 (2), 39.8 (2), 30.4 (3), 29.4 (2), 19.2 (1), 10.0 (2)

LRMS (CI) m/z: 193 $(M+H)^+$ [12%], 137 [100%]

HRMS (CI) m/z: $C_{12}H_{17}O_2$ $(M+H)^+$ requires 193.12285, found 193.12321 [49%].

(1R)-3-(2-Methyl-1,3-dioxolan-2-yl)-1-[(1R)-2-methylenecyclopropyl]propyl[3-(1,1,1-trimethylsilyl)-2-propynyl]ether 551



551

Following the method of Lautens[168], 2-methyl-2-[(3R)-3-[(1R)-2-methylenecyclopropyl]-3-(prop-2-ynyloxy)propyl]-1,3-dioxolane **513** (0.450g, 1.91mmol) in THF (30mL) was cooled to -78°C. ^{n}BuLi (0.75mL, 2.4M in hexanes, 1.81mmol) was added slowly and the mixture then stirred for 1 hour at -78°C. TMSCl (0.25mL, 2.00mmol) was added slowly and the reaction stirred for 1 hour at -78°C before warming to RT overnight. Water (10mL) was added and the reaction extracted with EA (30mL). The organic phase was washed with brine (20mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (0 to 50% ether/PE) affording ketal **551** as a colourless oil (0.354g, 87% based on RSM [0.139g]).

R_f: 0.5 (50% Ether/PE)

FT-IR ν_{max}: 3070 (w), 2981 (m), 2959, (m), 2878 (m), 2114 (w), 1446 (w), 1376 (m), 1252 (s), 1131 (m), 1070 (s), 990 (m), 844 (s)

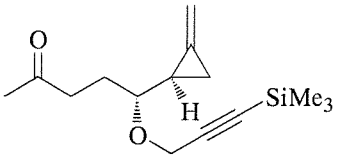
^{1}H NMR (400MHz, $CDCl_3$) **δ**: 5.47 – 5.42 (2H, m, $=CH_2$), 4.32 (1H, d, J = 16 Hz, $OCH_AH_BC{\equiv}CSiMe_3$), 4.28 (1H, d, J = 16 Hz, $OCH_AH_BC{\equiv}CSiMe_3$), 3.99 – 3.90 (4H, m, $O(CH_2)_2O$), 3.06 (1H, m, $CHOC_3H_2SiMe_3$), 1.86 (1H, m, $CH_CH_DCH_2CHOC_3H_2SiMe_3$), 1.76 – 1.67 (3H, m, $CH_CH_DCH_2CHOC_3H_2SiMe_3$), 1.52 (1H, m, cyclopropyl CH), 1.39 (1H, tt, J = 2, 9Hz, cyclopropyl CH_EH_F), 1.34 (3H, s, CH_3), 1.17 (1H, m, cyclopropyl CH_EH_F), 0.17 (9H, s, $Si(CH_3)_3$)

^{13}C NMR (100MHz, $CDCl_3$) **δ**: 132.2 (0), 110.4 (0), 104.8 (2), 102.8 (0), 91.2 (0), 80.8 (1), 65.1 (2), 65.0 (2), 57.3 (2), 35.0 (2), 29.9 (2), 24.3 (3), 19.8 (1), 9.9 (2), 0.2 (3)

LRMS (CI) m/z: 309 $(M+H)^+$ [2%], 181 $(M-OC_3H_3SiMe_3)^+$ [100%]

HRMS (ES) m/z: $C_{17}H_{28}O_3SiNa$ $(M+Na)^+$ requires 331.16999, found 331.17062 [55%].

(5R)-5-[(1R)-2-Methylenecyclopropyl]-5-{[3-(1,1,1-trimethylsilyl)-2-propynyl]oxy}pentan-2-one 553



553

(1R)-3-(2-methyl-1,3-dioxolan-2-yl)-1-[(1R)-2-methylenecyclopropyl]propyl[3-(1,1,1-trimethylsilyl)-2-propynyl]ether **551** (0.222g, 0.72mmol) was dissolved in acetone (10mL) and water (2mL). *p*-TsOH (cat.) was added. The reaction was stirred for 48 hours. $NaHCO_3$ (2mL) was added and the reaction concentrated *in vacuo*. The aqueous layer was extracted with EA (20mL). The organic layer was washed with brine (10mL), dried ($MgSO_4$) and concentrated *in vacuo*. Ketone **553** was obtained as a colourless oil (0.188g, 99%).

R_f: 0.5 (50% Ether/PE)

FT-IR ν_{max}: 2958 (w), 2927, (w), 2895 (w), 2859 (w), 2173 (w), 1713 (m), 1404 (w), 1359 (m), 1250 (m), 1163 (m), 1073 (s), 991 (s), 834 (s)

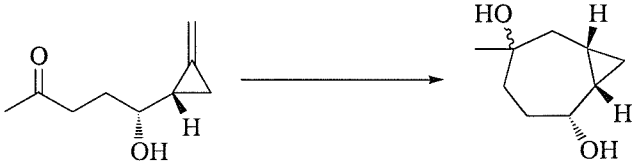
^{1}H NMR (400MHz, $CDCl_3$) **δ**: 5.48 – 5.44 (2H, m, $=CH_2$), 4.29 (2H, s, $OCH_2C{\equiv}CSiMe_3$), 3.05 (1H, dt, J = 4, 8 Hz, $CH(OC_3H_2SiMe_3)$), 2.65 (1H, ddd, J = 6, 8, 17 Hz, $CH_3COCH_AH_B$), 2.53 (1H, ddd, J = 6.5, 8.5, 17 Hz, $CH_3COCH_AH_B$), 2.16 (3H, s, CH_3), 1.96 – 1.80 (2H, m, $CH_2CH(OC_3H_2SiMe_3)$), 1.49 (1H, m, cyclopropyl CH), 1.40 (1H, tt, J = 2, 8 Hz, cyclopropyl CH_CH_D), 1.17 (1H, m, cyclopropyl CH_CH_D), 0.17 (9H, s, $Si(CH_3)_3$)

^{13}C NMR (100MHz, $CDCl_3$) **δ**: 209.0 (0), 131.5 (0), 105.1 (2), 102.5 (0), 91.4 (0), 79.9 (1), 57.3 (2), 39.9 (2), 30.5 (3), 29.4 (2), 19.4 (1), 10.0 (2), 0.2 (3)

LRMS (CI) m/z: 265 $(M+H)^+$ [4%], 137 $(M-OC_3H_3SiMe_3)^+$ [100%]

HRMS (ES) m/z: $C_{15}H_{24}O_2SiNa$ $(M+Na)^+$ requires 287.14378, found 287.14366 [8%].

Cyclisation of (5R)-5-hydroxy-5-[(1S)-2-methylenecyclopropyl]pentan-2-one 500



500 **516**

Following method B at 0°C, samarium (0.680g, 4.50mmol); di-iodoethane (0.910g, 3.20mmol); ketone **500** (0.100g, 0.65mmol); HMPA (1.7mL, 9.70mmol); ^{t}BuOH (0.2mL, 1.70mmol) were used. Column chromatography (0 to 90% ether/PE) afforded (1S,2R,7S)-5-methylbicyclo[5.1.0]octane-2,5-diol **516** as a white solid (0.049g, 48%).

R_f: 0.3 (Ether)

M.p.: 67 – 69°C

FT-IR ν_{max}: 3374 (br.m), 2998 (w), 2964 (m), 2908 (m), 2873 (m), 1438 (m), 1372 (m), 1286 (m), 1233 (m), 1208 (m), 1158 (m), 1101 (s), 1010 (s), 991 (s), 956 (s), 919 (s)

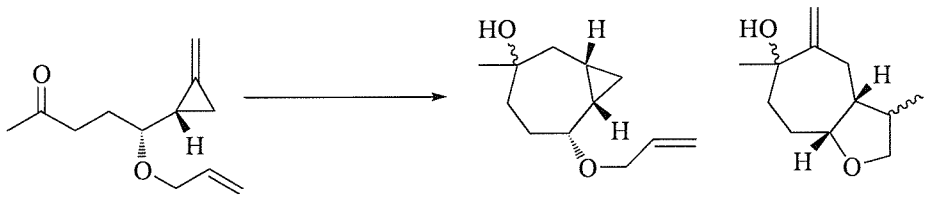
^{1}H NMR (400MHz, $CDCl_3$) δ: 4.42 (1H, m, C*H*OH), 2.15 (1H, ddd, *J* = 3, 7, 14Hz, $C(CH_3)CH_AH_BCH$), 1.91 – 1.74 (3H, m, CH_2CH_2CHOH, $CH_CH_DCH_2CHOH$), 1.54 (1H, m, $CH_CH_DCH_2CHOH$), 1.38 (1H, dd, *J* = 10, 14Hz, $C(CH_3)CH_AH_BCH$), 1.21 (3H, s, CH_3), 1.08 (1H, m, CHOHC*H*), 0.89 (1H, m, $C(CH_3)CH_2CH$), 0.68 (1H, dt, *J* = 4.5, 9Hz, cyclopropyl CH_EH_F), 0.50 (1H, q, *J* = 5Hz, cyclopropyl CH_EH_F)

^{13}C NMR (100MHz, $CDCl_3$) δ: 73.6 (0), 66.7 (1), 42.3 (2), 37.5 (2), 32.4 (3), 30.1 (2), 21.9 (1), 10.6 (1), 9.9 (2)

LRMS (CI) m/z: 156 $(M+NH_4-H_2O)^+$ [10%], 139 $(M+H-H_2O)^+$ [56%], 121 $(M+H-H_2O-H_2O)^+$ [100%]

HRMS (EI) m/z: $C_9H_{14}O$ $(M-H_2O)^+$ requires 138.10447, found 138.10437 [12%].

Cyclisation of (5R)-5-(allyloxy)-5-[(1S)-2-methylenecyclopropyl]pentan-2-one 508



508 **527** **530**

Following method B at 0°C, samarium (0.542g, 3.60mmol); di-iodoethane (0.725g, 2.60mmol); ketone **508** (0.100g, 0.51mmol); HMPA (1.34mL, 7.70mmol); ^{t}BuOH (0.15mL, 1.50mmol) were used. Column chromatography (0 to 75% ether/PE) afforded (1S,6R,7S)-6-(allyloxy)-3-methylbicyclo[5.1.0]octan-3-ol **527** (0.049g, 52%) as a colourless oil; and an inseparable mixture of diastereoisomers of (3aR,8aR)-3,6-dimethyl-5-methyleneoctahydro-2H-cyclohepta[b]furan-6-ol **530** (10:1 ratio, 0.040g, 42%) as a colourless oil. Yields based on RSM [0.006g].

(1S,6R,7S)-6-(Allyloxy)-3-methylbicyclo[5.1.0]octan-3-ol 527

R_f: 0.4 (75% Ether/PE)

FT-IR ν_{max}: 3410 (br.w), 2999 (w), 2964 (m), 2911 (m), 2862 (m), 1647 (w), 1459 (m), 1370 (m), 1274 (m), 1207 (m), 1099 (s), 1060 (s), 991 (s), 918 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.89 (1H, tdd, *J* = 5, 10, 17Hz, $OCH_2CH=CH_2$), 5.27 (1H, qd, *J* = 2, 17Hz, $OCH_2CH=CH_AH_B$), 5.16 (1H, dd, *J* = 2, 10 Hz, $OCH_2CH=CH_AH_B$), 3.99

– 3.93 (3H, m, $OCH_2CH{=}CH_2$, $CH(OC_3H_5)$), 2.14 (1H, ddd, J = 2, 6, 14Hz, $C(OH)CH_CH_DCH$), 1.95 – 1.67 (3H, m, $CH_EH_FCH_2CH(OC_3H_5)$), 1.53 (1H, m, $CH_EH_FCH_2CH(OC_3H_5)$), 1.40 (1H, dd, J = 11, 14Hz, $C(OH)CH_CH_DCH$), 1.22 (3H, s, CH_3), 1.01 (1H, m, $CH(OC_3H_5)CH$), 0.84 (1H, m, $C(OH)CH_2CH$), 0.72 (1H, dt, J = 4, 9Hz, cyclopropyl CH_GH_H), 0.54 (1H, br.q, J = 4Hz, cyclopropyl CH_GH_H)

^{13}C NMR (100MHz, $CDCl_3$) δ: 135.6 (1), 115.9 (2), 73.7 (1), 73.7 (0), 70.0 (2), 42.5 (2), 38.0 (2), 32.3 (3), 28.4 (2), 20.1 (1), 10.7 (1), 10.3 (2)

LRMS (CI) m/z: 197 $(M+H)^+$ [12%], 121 $(M+H-H_2O-HOC_3H_5)^+$ [100%]

HRMS (EI) m/z: $C_{11}H_{17}O_2$ $(M-CH_3)^+$ requires 181.12285, found 181.12298 [7%]; $C_{12}H_{18}O$ $(M-H_2O)^+$ requires 178.13577, found 178.13594 [34%].

(3aR,8aR)-3,6-Dimethyl-5-methyleneoctahydro-2H-cyclohepta[b]furan-6-ol 530

R_f: 0.3 (75% Ether/PE)

FT-IR ν_{max}: 3411 (br.m), 2955 (m), 2926 (m), 2870 (m), 1638 (w), 1458 (m), 1368 (m), 1237 (m), 1194 (m), 1089 (m), 1065 (s), 1034 (s), 900 (s)

Major isomer

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.12 (1H, s, $=CH_AH_B$), 4.83 (1H, s, $=CH_AH_B$), 4.02 – 3.94 (2H, m, $CHOCH_CH_D$), 3.22 (1H, dd, J = 8, 10Hz, OCH_CH_D), 2.46 (1H, dd, J = 9, 13.5Hz, allylic CH_EH_F), 2.20 (1H, dd, J = 4, 13.5Hz, allylic CH_EH_F), 1.98 (1H, m, $CHCH_3$), 1.88 – 1.79 (3H, m, $CHCHCH_3$, $CH_GH_HCH_IH_JCH$), 1.61 (1H, m, $CH_2CH_IH_JCH$), 1.48 (1H, m, $CH_GH_HCH_2CH$), 1.38 (3H, s, CH_3), 1.01 (3H, d, J = 7Hz, $CHCH_3$)

^{13}C NMR (100MHz, $CDCl_3$) δ: 153.1 (0), 111.8 (2), 82.7 (1), 74.7 (0), 74.5 (2), 50.6 (1), 38.8 (1), 38.2 (2), 31.5 (2), 29.6 (3), 27.3 (2), 15.3 (3)

LRMS (CI) m/z: 197 $(M+H)^+$ [21%], 179 $(M+H-H_2O)^+$ [100%]

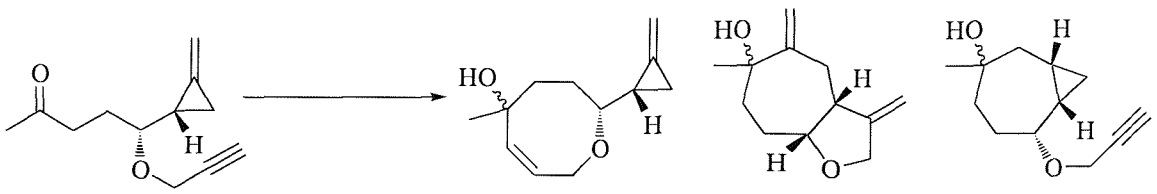
HRMS (EI) m/z: $C_{12}H_{20}O_2$ $(M)^+$ requires 196.14633, found 196.14625 [66%]; $C_{11}H_{17}O_2$ $(M-CH_3)^+$ requires 181.12285, found 181.12336 [48%]; $C_{12}H_{18}O$ $(M-H_2O)^+$ requires 178.13577, found 178.13584 [100%]

Minor isomer (assignment based on following data)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.09 (1H, s, $=CH_AH_B$), 4.90 (1H, s, $=CH_AH_B$), 4.09 (1H, dd, J = 6, 8Hz, $CHOCH_CH_D$), 3.49 (1H, m, OCH_CH_D), 0.96 (3H, d, J = 7Hz, $CHCH_3$)

^{13}C NMR (100MHz, $CDCl_3$) δ: 156.7 (0), 112.0 (2), 82.5 (1), 75.6 (2), 49.7 (1), 15.2 (3).

Cyclisation of (5R)-5-[(1S)-2-methylenecyclopropyl]-5-(prop-2-ynyloxy)pentan-2-one 512



512 **543** **540** **539**

Following method B at 0°C, samarium (0.438g, 2.91mmol); di-iodoethane (0.586g, 2.08mmol); ketone **512** (0.080g, 0.42mmol); HMPA (1.10mL, 6.24mmol); ^{t}BuOH (0.13mL, 1.25mmol) were used. Column chromatography (0 to 75% ether/PE) afforded (2R)-5-methyl-2-[(1S)-2-methylenecyclopropyl]-3,4,5,8-tetrahydro-2H-oxocin-5-ol **543** (0.041g, 52%) as a colourless oil; and an inseparable mixture of (3aR,8aR)-6-methyl-3,5-bis(methylene)octahydro-2H-cyclohepta[b]furan-6-ol **540** (0.018g, 23%) and (1S,6R,7S)-3-methyl-6-(prop-2-ynyloxy)bicyclo[5.1.0]octan-3-ol **539** (0.018g, 23%) as a colourless oil. Yields based on RSM [0.002g].

(2R)-5-Methyl-2-[(1S)-2-methylenecyclopropyl]-3,4,5,8-tetrahydro-2H-oxocin-5-ol 543

R_f: 0.4 (75% Ether/PE)

FT-IR ν_{max}: 3435 (br.m), 3010 (w), 2972 (m), 2917 (m), 2852 (m), 1444 (m), 1413 (m), 1386 (m), 1361 (m), 1273 (m), 1159 (m), 1086 (s), 1060 (m), 1026 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.71 (1H, td, J = 2, 13Hz, C*H*=CH), 5.54 (1H, s with fine splitting, =CH_AH$_B$), 5.42 (1H, br.s, =CH$_A$$H_B$), 5.40 (1H, ddd, J = 2, 4, 13Hz, CH=C*H*), 4.47 (1H, td, J = 2, 18Hz, CH_CH$_D$O), 4.01 (1H, ddd, J = 2, 4, 18Hz, CH$_C$$H_D$O), 3.05 (1H, m, C*H*(OCH$_2$)), 1.96 – 1.87 (3H, m, CH_EH$_F$CH_2CH(OCH$_2$)), 1.76 (1H, m, cyclopropyl CH), 1.65 (1H, m, CH$_E$$H_FCH_2$CH(OCH$_2$)), 1.37 (3H, s, CH$_3$), 1.30 (1H, tt, J = 2, 9Hz, cyclopropyl CH_GH$_H$), 0.89 (1H, m, cyclopropyl CH$_G$$H_H$)

^{13}C NMR (100MHz, $CDCl_3$) δ: 138.2 (1), 133.6 (0), 127.7 (1), 104.5 (2), 83.4 (1), 69.5 (0), 69.0 (2), 39.0 (2), 32.9 (3), 29.9 (2), 20.2 (1), 8.0 (2)

LRMS (CI) m/z: 195 $(M+H)^+$ [10%], 177 $(M+H-H_2O)^+$ [100%]

HRMS (EI) m/z: $C_{11}H_{15}O_2$ $(M-CH_3)^+$ requires 179.10720, found 179.10675 [49%]; $C_{12}H_{17}O$ $(M+H-H_2O)^+$ requires 177.12794, found 177.12743 [100%].

(3aR,8aR)-6-Methyl-3,5-bis(methylene)octahydro-2H-cyclohepta[b]furan-6-ol 540 & (1S,6R,7S)-3-methyl-6-(prop-2-ynyloxy)bicyclo[5.1.0]octan-3-ol 539

R_f: 0.3 (75% Ether/PE)

FT-IR ν_{max}: 3419 (br.m), 3308 (m), 3075 (w), 2966 (m), 2929 (m), 2915 (m), 2857 (m), 1664 (w), 1639 (w), 1459 (m), 1442 (m), 1371 (m), 1276 (m), 1208 (m), 1099 (s), 1063 (s), 921 (m)

7, 5 bicycle 73

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.09 (1H, s, C(OH)C=C$H_A$$H_B$), 4.98 (2H, m, CHC=C$H_2$), 4.93 (1H, s, C(OH)C=C$H_A$$H_B$), 4.39 (1H, br.d, J = 13Hz, OC$H_C$$H_D$), 4.25 (1H, br.d, J = 13Hz, OC$H_C$$H_D$), 4.06 (1H, m, C$HOCH_2$), 2.73 (1H, m, C$H_2CH$C=C$H_2$), 2.59 (1H, dd, J = 11, 13Hz, C$H_G$$H_H$CHC=C$H_2$), 2.23 (1H, dd, J = 5, 13Hz, C$H_G$$H_H$CHC=C$H_2$), 2.07 – 1.50 (4H, m, C(OH)CH_2CH_2CH), 1.42 (3H, s, CH_3)

^{13}C NMR (100MHz, $CDCl_3$) δ: 152.9 (0), 152.8 (0), 112.3 (2), 104.6 (2), 82.5 (1), 74.2 *or* 73.6 (0), 70.8 (2), 48.6 (1), 37.2 (2), 33.8 (2), 32.3 or 28.9 (3), 26.3 (2)

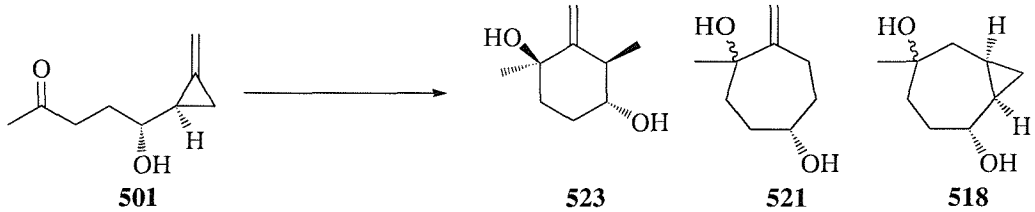
7, 3 bicycle 74

^{1}H NMR (400MHz, $CDCl_3$) δ: 4.16 – 4.10 (3H, m, CH(OCH_2C≡CH)), 2.37 (1H, t, J = 2Hz, C≡CH), 2.13 (1H, ddd, J = 2.5, 6, 14Hz, C(OH)C$H_A$$H_B$), 2.02 – 1.45 (4H, m, C(OH)CH_2CH_2CH), 1.33 (1H, dd, J = 11, 14Hz, C(OH)C$H_A$$H_B$), 1.20 (3H, s, CH_3), 1.01 (1H, m, $CH_2CH_2CH(OC_3H_3)$CH), 0.86 (1H, m, C(OH)CH_2CH), 0.74 (1H, dt, J = 5, 9Hz, cyclopropyl C$H_C$$H_D$), 0.49 (1H, q, J = 5Hz, cyclopropyl C$H_C$$H_D$)

^{13}C NMR (100MHz, $CDCl_3$) δ: 80.8 (0), 74.2 or 73.6 (0), 73.8 (1), 73.7 (1), 56.5 (2), 42.5 (2), 38.0 (2), 32.3 *or* 28.9 (3), 28.3 (2), 19.5 (1), 10.8 (2), 10.5 (1)

LRMS (CI) m/z: 195 $(M+H)^+$ [13%], 177 $(M+H-H_2O)^+$ [100%].

Cyclisation of (5R)-5-hydroxy-5-[(1R)-2-methylenecyclopropyl]pentan-2-one 501



501 **523** **521** **518**

Following method B at 0°C, samarium (0.680g, 4.50mmol); di-iodoethane (0.910g, 3.20mmol); ketone **501** (0.100g, 0.65mmol); HMPA (1.7mL, 9.70mmol); ^{t}BuOH (0.2mL, 1.70mmol) were used. Column chromatography (0 to 90% ether/PE) afforded (1R,3R,4R)-1,3-dimethyl-2-methylenecyclohexane-1,4-diol **523** (0.011g, 11%) as colourless crystals; (4S)-1-methyl-7-methylenecycloheptane-1,4-diol **521** (0.015g, 15%)

as a colourless oil; and (1R,2R,7R)-5-methylbicyclo[5.1.0]octane-2,5-diol **518** (0.022g, 22%) as a white solid.

(1R,3R,4R)-1,3-Dimethyl-2-methylenecyclohexane-1,4-diol 523

R_f: 0.4 (Ether)

M.p.: 101 – 105°C

FT-IR ν_{max}: 3351 (br.s), 2966 (m), 2934 (s), 2880 (m), 1458 (m), 1369 (m), 1261 (w), 1207 (w), 1149 (s), 1115 (m), 1074 (m), 1034 (s), 966 (m), 906 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.22 (1H, s, $=CH_AH_B$), 4.86 (1H, s, $=CH_AH_B$), 3.18 (1H, m, $CHOH$),2.19 (1H, m, $CHCH_3$), 2.02 (1H, qd, J = 4, 13Hz, $CH_2CH_CH_DCHOH$), 1.88 (1H, td, J = 4, 13Hz, $CH_EH_FCH_2CHOH$), 1.61 (1H, m, $CH_2CH_CH_DCHOH$), 1.57 (2H, br.s, OH, OH), 1.46 (1H, m, $CH_EH_FCH_2CHOH$), 1.40 (3H, s, $CH_3C(OH)$), 1.21 (3H, d, J = 7Hz, $CHCH_3$)

^{13}C NMR (100MHz, $CDCl_3$) δ: 156.0 (0), 105.6 (2), 76.6 (1), 73.7 (0), 43.0 (1), 39.6 (2), 32.5 (2), 27.4 (3), 15.0 (3)

LRMS (CI) m/z: 156 $(M+NH_4-H_2O)^+$ [25%], 139 $(M+H-H_2O)^+$ [100%], 121 $(M+H-H_2O-H_2O)^+$ [61%]

HRMS (EI) m/z: $C_9H_{16}O_2$ $(M)^+$ requires 156.11503, found 156.11531 [8%]

X-ray: see appendix.

(4S)-1-Methyl-7-methylenecycloheptane-1,4-diol 521

R_f: 0.2 (Ether)

FT-IR ν_{max}: 3350 (br.s), 2966 (m), 2930 (s), 2868 (m), 1640 (w), 1440 (m), 1368 (m), 1285 (m), 1246 (w), 1208 (m), 1168 (w), 1095 (m), 1043 (s), 957 (m), 936 (m), 900 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.21 (1H, s, $=CH_AH_B$), 4.95 (1H, s, $=CH_AH_B$), 4.02 (1H, m, $CH(OH)$), 2.33 – 2.15 (3H, m, CH_2, CH_CH_D), 1.88 – 1.52 (5H, m, CH_2, CH_2, CH_CH_D), 1.36 (3H, s, CH_3)

^{13}C NMR (100MHz, $CDCl_3$) δ: 158.1 (0), 111.3 (2), 75.8 (0), 69.6 (1), 40.1 (2), 34.6 (2), 31.1 (2), 30.9 (3), 28.6 (2)

LRMS (CI) m/z: 156 $(M+NH_4-H_2O)^+$ [19%], 139 $(M+H-H_2O)^+$ [100%], 121 $(M+H-H_2O-H_2O)^+$ [62%]

HRMS (EI) m/z: $C_9H_{14}O$ $(M-H_2O)^+$ requires 138.10447, found 138.10432 [27%].

(1R,2R,7R)-5-methylbicyclo[5.1.0]octane-2,5-diol 518

R_f: 0.1 (Ether)

M.p.: 84 – 87°C

FT-IR ν_{max}: 3374 (br.s), 2962 (m), 2925 (s), 1442 (m), 1373 (m), 1262 (m), 1204 (m), 1163 (m), 1091 (m), 1029 (s), 926 (m), 908 (m)

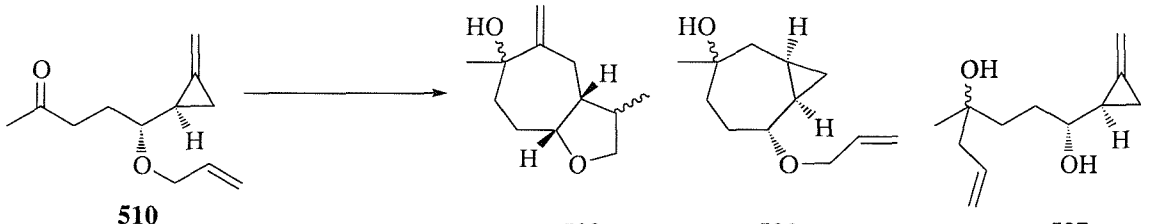
^{1}H NMR (400MHz, $CDCl_3$) δ: 3.28 (1H, m, C*H*OH), 2.26 (1H, m, $C(CH_3)CH_AH_BCH$), 2.03 (1H, m, $CH_2CH_CH_DCHOH$), 1.90 – 1.69 (4H, m, $CH_EH_FCH_CH_DCHOH$, C(OH)), 1.41 (1H, m, $CH_EH_FCH_2CHOH$), 1.21 (3H, s, CH_3), 1.09 – 0.85 (4H, m, $C(CH_3)CH_AH_BCHCH$, cyclopropyl CH_GH_H), 0.33 (1H, q, J = 4Hz, cyclopropyl CH_GH_H)

^{13}C NMR (100MHz, $CDCl_3$) δ: 76.3 (1), 72.2 (0), 43.1 (2), 41.3 (2), 32.1 (2), 32.4 (3), 24.1 (1), 15.1 (2), 8.7 (1)

LRMS (CI) m/z: 121 $(M+H-H_2O-H_2O)^+$ [100%], 139 $(M+H-H_2O)^+$ [73%], 156 $(M+NH_4-H_2O)^+$ [13%]

HRMS (EI) m/z: $C_9H_{14}O$ $(M-H_2O)^+$ requires 138.10447, found 138.10449 [34%].

Cyclisation of (5R)-5-(allyloxy)-5-[(1R)-2-methylenecyclopropyl]pentan-2-one 510



510 **533** **532** **537**

Following method B at 0°C, samarium (0.542g, 3.60mmol); di-iodoethane (0.725g, 2.60mmol); ketone **510** (0.100g, 0.51mmol); HMPA (1.34mL, 7.70mmol); ^{t}BuOH (0.15mL, 1.50mmol) were used. Column chromatography (0 to 75% ether/PE) afforded an inseparable mixture of (3aR,8aR)-3,6-dimethyl-5-methyleneoctahydro-2H-cyclohepta[b]furan-6-ol **533** (0.028g, 29%) and (1S,6R,7S)-6-(allyloxy)-3-methylbicyclo[5.1.0]octan-3-ol **532** (0.041g, 42%) as a colourless oil; and (1R)-4-methyl-1-[(1R)-2-methylenecyclopropyl]hept-6-ene-1,4-diol **537** (0.023g, 23%) as a pale yellow oil with a minor impurity. Yields based on RSM [0.003g].

(3aR,8aR)-3,6-Dimethyl-5-methyleneoctahydro-2H-cyclohepta[b]furan-6-ol 533 & (1R,6R,7R)-6-(allyloxy)-3-methylbicyclo[5.1.0]octan-3-ol 532

Assignment based on following data, some peaks are ambiguous and are not attributed to either component.

R_f: 0.3 (75% Ether/PE)

FT-IR ν_{max}: 3431 (br.m), 3061 (w), 2958 (m), 2926 (m), 2869 (m), 1639 (w), 1458 (m), 1442 (m), 1370 (m), 1262 (m), 1207 (m), 1173 (m), 1089 (s), 1059 (s), 1044 (s), 904 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.94 (1H, tdd, *J* = 5.5, 11, 17Hz, [OCH_2CH=CH_2 **532**]), 5.28 (1H, dd, *J* = 1.5, 17Hz, [OCH_2CH=CH_AH_B **532**]), 5.17 (1H, s, [=CH_CH_D **533**]), 5.16 (1H, m, [OCH_2CH=CH_AH_B **532**]), 4.83 (1H, s, [=CH_CH_D **533**]), 4.21 (1H, dd, *J* = 5.5, 13Hz, [OCH_EH_FCH=CH_2 **532**]), 4.04 – 3.94 (3H, m, [OCH_EH_FCH=CH_2 **532**], [$CH(OCH_CH_HCH(CH_3))$ **533**]), 3.21 (1H, t, *J* = 8Hz, [$OCH_GH_HCH(CH_3)$ **533**]), 2.93 (1H, dd, *J* = 8.5, 9Hz, [$CH(OC_3H_5)$ **532**]), 2.33 (1H, dd, *J* = 4.5, 13Hz, CH_IH_J), 2.25 (1H, ddd, *J* = 2, 5, 14Hz, [$C(OH)CH_KH_LCH$) **532**]), 2.05 – 1.67 (9H, m, CH_2, CH_2, CH_IH_J, CH_MH_N, CH_OH_P, [$CH_2CH(CH(CH_3))$ **533**]), 1.48 – 1.36 (2H, m, CH_MH_N, CH_OH_P), 1.35 (3H, s, CH_3), 1.20 (3H, s, CH_3), 1.06 – 0.83 (4H, m, [$C(OH)CH_KH_LCHCH_QH_RCH$) **532**]), 1.04 (3H, d, *J* = 6.5Hz, [$CH(CH_3)$ **533**]), 0.29 (1H, q, *J* = 4.5Hz, [$C(OH)CH_2CHCH_QH_RCH$) **532**])

^{13}C NMR (100MHz, $CDCl_3$) δ: 154.7 (0) **533**, 135.6 (1) **532**, 117.0 (2) **532**, 110.2 (2) **533**, 82.3 (1) **532**, 81.1 (1) **533**, 75.5 (0), 74.2 (2) **533**, 71.9 (0), 69.6 (2) **532**, 51.8 (1) **533**, 43.1 (2) **533**, 41.5 (2), 40.8 (1) **533**, 37.3 (2), 34.4 (2), 32.3 (3), 31.9 (2), 29.1 (3), 26.8 (2), 21.6 (1) **532**, 17.1 (3) **533**, 15.8 (2) **532**, 7.6 (1) **532**

LRMS (CI) m/z: 197 $(M+H)^+$ [8%], 179 $(M+H-H_2O)^+$ [100%], 121 $(M+H-H_2O-HOC_3H_5)^+$ [13%].

(1R)-4-methyl-1-[(1R)-2-methylenecyclopropyl]hept-6-ene-1,4-diol 537

R_f: 0.1 (75% Ether/PE)

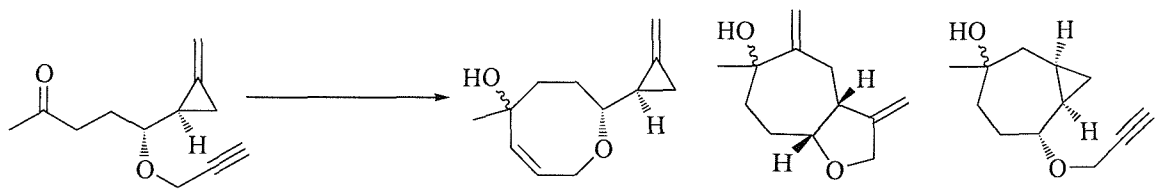
FT-IR ν_{max}: 3367 (br.s), 3074 (w), 2974 (s), 2932 (s), 2870 (m), 1745 (w), 1721 (w), 1668 (w), 1640 (m), 1458 (m), 1438 (m), 1375 (m), 1248 (m), 1126 (m), 1071 (m), 1023 (m), 912 (s), 888 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.88 (1H, m, CH=CH_2), 5.43 (2H, br.s, C=CH_2), 5.18 – 5.10 (2H, m, CH=CH_2), 3.17 (1H, m, CH(OH)), 2.30 – 2.24 (2H, m, CH_2CH=CH_2), 1.73 – 1.60 (5H, m, $CH_2CH_2CH(OH)CH$), 1.31 (1H, tt, *J* = 2, 9Hz, cyclopropyl CH_AH_B), 1.21 (3H, s, CH_3), 1.04 (1H, m, cyclopropyl CH_AH_B)

^{13}C NMR (100MHz, $CDCl_3$) δ: 134.3 (1), 133.2 (0), 119.1 (2), 104.6 (2), 75.1 (1), 72.3 (0), 47.2 (2), 38.1 (2), 31.6 (2), 27.0 (3), 22.8 (1), 8.1 (2)

LRMS (CI) m/z: 179 $(M+H-H_2O)^+$ [90%], 161 $(M+H-H_2O-H_2O)^+$ [69%], 137 [100%]

Cyclisation of (5R)-5-[(1R)-2-methylenecyclopropyl]-5-(prop-2-ynyloxy)pentan-2-one 514



514 **549** **548** **547**

Following method B at 0°C, samarium (0.620g, 4.16mmol); di-iodoethane (0.821g, 2.91mmol); ketone **514** (0.080g, 0.42mmol); HMPA (1.52mL, 8.74mmol); ^{t}BuOH (0.13mL, 1.25mmol) were used. Column chromatography (0 to 75% ether/PE) afforded (2R)-5-methyl-2-[(1R)-2-methylenecyclopropyl]-3,4,5,8-tetrahydro-2H-oxocin-5-ol **549** (0.048g, 59%) as a colourless oil; (3aR,8aR)-6-methyl-3,5-bis(methylene)octahydro-2H-cyclohepta[b]furan-6-ol **548** (0.010g, 12%) as a colourless oil; and (1R,6R,7R)-3-methyl-6-(prop-2-ynyloxy)bicyclo[5.1.0]octan-3-ol **547** (0.017g, 21%) as a colourless oil.

(2R)-5-methyl-2-[(1R)-2-methylenecyclopropyl]-3,4,5,8-tetrahydro-2H-oxocin-5-ol 549

R_f: 0.4 (75% Ether/PE)

FT-IR ν_{max}: 3427 (br.s), 3006 (m), 2969 (s), 2912 (s), 2846 (m), 1644 (w), 1446 (m), 1408 (m), 1384 (m), 1361 (m), 1271 (m), 1125 (m), 1082 (s), 1020 (s), 921 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.71 (1H, td, J = 2, 13Hz, C*H*=CH), 5.49 – 5.40 (3H, m, =CH_2, CH=C*H*), 4.51 (1H, td, J = 2, 18Hz, CH_CH_DO), 3.95 (1H, td with fine splitting, J = 2, 18Hz, CH_C*H*$_D$O), 3.09 (1H, m, C*H*OCH_2), 2.04 – 1.79 (4H, m, $CH_EH_FCH_2CHOCH_2$, cyclopropyl CH), 1.67 (1H, m, CH_E*H*$_F$$CH_2CHOCH_2$), 1.39 (1H, m, cyclopropyl CH_GH_H), 1.38 (3H, s, CH_3), 1.11 (1H, m, cyclopropyl CH_G*H*$_H$)

^{13}C NMR (100MHz, $CDCl_3$) δ: 137.2 (1), 132.9 (0), 128.7 (1), 104.3 (2), 83.3 (1), 69.73 (2), 69.67 (0), 38.4 (2), 32.7 (3), 30.3 (2), 19.8 (1), 8.8 (2)

LRMS (CI) m/z: 195 $(M+H)^+$ [15%], 177 $(M+H-H_2O)^+$ [100%]

HRMS (EI) m/z: $C_{12}H_{17}O$ $(M-OH)^+$ requires 177.12794, found 177.12761 [100%].

(3aR,8aR)-6-methyl-3,5-bis(methylene)octahydro-2H-cyclohepta[b]furan-6-ol 548

R_f: 0.3 (75% Ether/PE)

FT-IR ν_{max}: 3446 (br.w), 2954 (s), 2917 (s), 2847 (s), 1660 (w), 1640 (w), 1456 (m), 1367 (m), 1369 (m), 1228 (w), 1153 (w), 1067 (m), 1044 (m), 883 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.27 (1H, s, C(OH)C=CH_AH$_B$), 5.03 (1H, m, CH(C=CH_CH$_D$)), 4.98 (1H, s, C(OH)C=CH$_A$$H_B$), 4.95 (1H, m, CH(C=CH$_C$$H_D$)), 4.45 (1H, br.d, J = 13Hz, OCH_EH$_F$), 4.22 (1H, br.d, J = 13Hz, OCH$_E$$H_F$), 3.99 (1H, dt, J = 3, 6Hz, CH(OCH$_2$)), 2.59 (1H, m, CH$_2$CH(C=CH$_2$)), 2.24 (1H, dd, J = 5, 13Hz, CH_GH$_H$CH(C=CH$_2$)), 2.20 – 2.10 (2H, m, CH$_G$$H_H$CH(C=CH$_2$), C$H_IH_JCH_2$CH(OCH$_2$)), 1.91 (1H, m, CH$_2CH_LH_K$CH(OCH$_2$)), 1.81 (1H, m, CH$_2CH_L$$H_K$CH(OCH$_2$)), 1.60 (1H, br.s, OH), 1.49 (1H, m, CH$_I$$H_JCH_2$CH(OCH$_2$)), 1.32 (3H, s, CH$_3$)

^{13}C NMR (100MHz, $CDCl_3$) δ: 154.6 (0), 153.5 (0), 110.9 (2), 104.8 (2), 80.9 (1), 76.0 (0), 70.5 (2), 50.3 (1), 36.5 (2), 34.8 (2), 30.3 (3), 25.7 (2)

LRMS (CI) m/z: 195 $(M+H)^+$ [6%], 177 $(M+H-H_2O)^+$ [100%]

HRMS (EI) m/z: $C_{12}H_{16}O_2$ $(M-H_2O)^+$ requires 176.12012, found 176.12028 [33%].

(1R,6R,7R)-3-Methyl-6-(prop-2-ynyloxy)bicyclo[5.1.0]octan-3-ol 547

R_f: 0.2 (75% Ether/PE)

FT-IR ν_{max}: 3432 (br.m), 3304 (m), 2959 (s), 2921 (s), 2847 (m), 1460 (m), 1438 (m), 1370 (m), 1261 (m), 1167 (m), 1060 (s), 1039 (m), 921 (m)

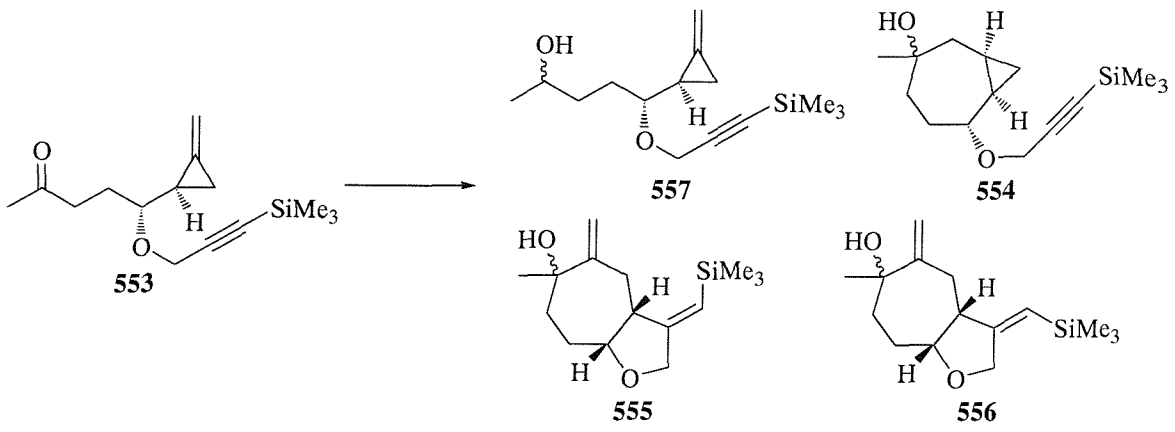
^{1}H NMR (400MHz, $CDCl_3$) δ: 4.31 (1H, dd, J = 2, 16Hz, OCH_AH$_B$C≡CH), 4.28 (1H, dd, J = 2, 16Hz, OCH$_A$$H_B$C≡CH), 3.15 (1H, m, C$HOC_3H_3$), 2.40 (1H, t, J = 2Hz, OCH$_2$C≡CH), 2.26 (1H, m, C(OH)CH_CH$_D$CH), 2.02 (1H, m, CH$_2$CH_EH$_F$CHOC$_3$H$_3$), 1.84 – 1.75 (2H, m, CH_GH$_H$CH$_E$$H_F$CHOC$_3H_3$), 1.64 (1H, br.s, OH), 1.44 (1H, m, CH$_G$$H_HCH_2$CHOC$_3H_3$), 1.22 (3H, s, CH$_3$), 1.09 – 0.98 (2H, m, C(OH)CH$_C$$H_D$CH, cyclopropyl C$H_IH_J$), 0.94 – 0.85 (2H, m, cyclopropyl CHCH), 0.39 (1H, q, J = 5Hz, cyclopropyl CH$_I$$H_J$)

^{13}C NMR (100MHz, $CDCl_3$) δ: 81.5 (1), 80.6 (0), 74.2 (1), 71.9 (0), 55.6 (2), 43.0 (2), 41.4 (2), 32.3 (3), 31.8 (2), 20.8 (1), 15.6 (2), 7.5 (1)

LRMS (CI) m/z: 195 $(M+H)^+$ [6%], 177 $(M+H-H_2O)^+$ [20%], 121 $(M+H-H_2O-HOC_3H_3)^+$ [100%]

HRMS (ES) m/z: $C_{24}H_{36}O_4Na$ $(2M+Na)^+$ requires 411.25113, found 411.25130 [100%].

Cyclisation of (5R)-5-[(1R)-2-methylenecyclopropyl]-5-{[3-(1,1,1-trimethylsilyl)-2-propynyl]oxy}pentan-2-one 553



Following method **B** at 0°C, samarium (0.435g, 3.00mmol); di-iodoethane (0.597g, 2.10mmol); ketone **553** (0.040g, 0.30mmol); HMPA (1.11mL, 6.40mmol); ^{t}BuOH (0.09mL, 0.91mmol) were used. Column chromatography (0 to 50% ether/PE) afforded (5R)-5-[(1R)-2-methylenecyclopropyl]-5-{[3-(1,1,1-trimethylsilyl)-2-propynyl]oxy}-pentan-2-ol **557** as an inseparable mixture of diastereoisomers (1:1 ratio, 0.005g, 12%) as a pale yellow oil with a minor inseparable impurity; an inseparable mixture of (3aR,8aR)-6-methyl-5-methylene-3-[(*E*)-1-(1,1,1-trimethylsilyl)methylidene]octahydro-2H-cyclohepta-[b]furan-6-ol **555** and (3aR,8aR)-6-methyl-5-methylene-3-[(*Z*)-1-(1,1,1-trimethylsilyl)-methylidene]octahydro-2H-cyclohepta[b]furan-6-ol **556** as a pale yellow oil (3:2 *E*:*Z* ratio, 0.010g, 25%); and (1R,6R,7R)-3-methyl-6-{[3-(1,1,1-trimethylsilyl)-2-propynyl]oxy}-bicyclo[5.1.0]octan-3-ol (0.017g, 42%) **554** as a pale yellow oil.

(5R)-5-[(1R)-2-Methylenecyclopropyl]-5-{[3-(1,1,1-trimethylsilyl)-2-propynyl]oxy}-pentan-2-ol 557

R_f: 0.3 (50% Ether/PE)

FT-IR ν_{max}: 3400 (br.w), 2960 (m), 2929 (m), 2852 (w), 2173 (w), 1447 (w), 1373 (w), 1250 (m), 1077 (m), 992 (m), 845 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.47 – 5.42 (2H, br.s with fine splitting, $=CH_2$), 4.33 (2H, s with fine splitting, $OCH_2C{\equiv}CSiMe_3$), 3.83 (1H, m, CH_3CHOH), 3.09 (1H, dt, J = 4, 8 Hz, $CHOC_3H_2SiMe_3$), 1.80 – 1.51 (5H, m, CH_2CH_2, cyclopropyl CH), 1.42 (1H, tt, J = 2, 9Hz, cyclopropyl CH_AH_B), 1.21 (3H, d, J = 6Hz, CH_3CHOH), 1.19 (1H, m, cyclopropyl CH_AH_B), 0.18 (9H, s, $Si(CH_3)_3$)

^{13}C NMR (100MHz, $CDCl_3$) δ: 131.9 (0)*, 104.9 (2)*, 102.5 (0)*, 91.6 (0)*, 80.9 & 80.8 (1), 68.34 & 68.30 (1), 57.2 (2)*, 35.6 & 35.4 (2), 31.9 & 31.8 (2), 24.0 & 23.9 (3), 19.53 & 19.50 (1), 10.1 (2)*, 0.2 (3)*

* = 2 carbons

LRMS (CI) m/z: 267 $(M+H)^+$ [9%], 139 $(M+H\text{-}HOC_3H_3SiMe_3)^+$ [100%]

HRMS (ES) m/z: $C_{15}H_{26}O_2SiNa$ $(M+Na)^+$ requires 289.15943, found 289.15937 [100%].

(3aR,8aR)-6-Methyl-5-methylene-3-[(*E*)-1-(1,1,1-trimethylsilyl)methylidene] octahydro-2H-cyclohepta[b]furan-6-ol 555 & (3aR,8aR)-6-Methyl-5-methylene-3-[(*Z*)-1-(1,1,1-trimethylsilyl)methylidene]octahydro-2H-cyclohepta[b]furan-6-ol 556

R_f: 0.2 (50% Ether/PE)

FT-IR ν_{max}: 3450 (br.w), 2954 (m), 2852 (w), 1636 (w), 1433 (w), 1366 (w), 1250 (m), 1046 (m), 841 (s)

Major isomer (*E*) 85

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.31 (2H, br.s, $=CH_AH_B$, $=CHSiMe_3$), 5.05 (1H, s, $=CH_AH_B$), 4.47 (1H, m, OCH_CH_D), 4.18 (1H, dd, J = 2, 13.5Hz, OCH_CH_D), 3.97 (1H, m, $CHOCH_2$), 2.61 (1H, td, J = 4.5, 10Hz, $CH_2CHC{=}CHSiMe_3$), 2.31 – 2.10 (3H, m, $CH_2CHC{=}CHSiMe_3$, $CH_EH_FCH_2CHOCH_2$), 1.94 (1H, m, $CH_2CH_GH_HCHOCH_2$), 1.79 (1H, m, $CH_2CH_GH_HCHOCH_2$), 1.60 (1H, br.s, OH), 1.48 (1H, m, $CH_EH_FCH_2CHOCH_2$), 1.30 (3H, s, CH_3), 0.18 (9H, s, $Si(CH_3)_3$)

^{13}C NMR (100MHz, $CDCl_3$) δ: 161.6 (0), 155.3 (0), 118.4 (1), 111.2 (2), 80.5 (1), 76.1 (0), 72.7 (2), 50.4 (1), 35.6 (2), 33.4 (2), 30.7 (3), 25.5 (2), 0.5 (3)

Minor isomer (*Z*) 86

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.52 (1H, m, $=CHSiMe_3$), 5.25 (1H, s, $=CH_AH_B$), 4.96 (1H, s, $=CH_AH_B$), 4.47 (1H, m, OCH_CH_D), 4.21 (1H, dd, J = 2, 13.5Hz, OCH_CH_D), 3.97 (1H, m, $CHOCH_2$), 2.51 (1H, td, J = 5, 10.5Hz, $CH_2CHC{=}CHSiMe_3$), 2.31 – 2.10 (3H, m, $CH_2CHC{=}CHSiMe_3$, $CH_EH_FCH_2CHOCH_2$), 1.94 (1H, m, $CH_2CH_GH_HCHOCH_2$), 1.79 (1H, m, $CH_2CH_GH_HCHOCH_2$), 1.60 (1H, br.s, OH), 1.48 (1H, m, $CH_EH_FCH_2CHOCH_2$), 1.31 (3H, s, CH_3), 0.09 (9H, s, $Si(CH_3)_3$)

^{13}C NMR (100MHz, $CDCl_3$) δ: 162.0 (0), 154.8 (0), 119.1 (1), 110.8 (2), 79.9 (1), 75.9 (0), 70.1 (2), 53.5 (1), 36.7 (2), 34.7 (2), 30.4 (3), 25.6 (2), -0.2 (3)

LRMS (CI) m/z: 267 $(M+H)^+$ [10%], 249 $(M+H\text{-}H_2O)^+$ [100%]

HRMS (ES) m/z: $C_{15}H_{26}O_2SiNa$ $(M+Na)^+$ requires 289.15943, found 289.15962 [100%].

(1R,6R,7R)-3-Methyl-6-{[3-(1,1,1-trimethylsilyl)-2-propynyl]oxy}bicyclo[5.1.0]octan-3-ol 554

R_f: 0.2 (50% Ether/PE)

FT-IR ν_{max}: 3427 (br.w), 2960 (m), 2929 (m), 2173 (w), 1663 (w), 1443 (m), 1351 (w), 1250 (s), 1061 (s), 988 (s)

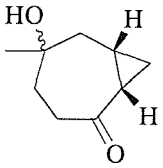
^{1}H NMR (400MHz, $CDCl_3$) δ: 4.32 (1H, d, *J* = 16Hz, $OCH_AH_BC{\equiv}CSiMe_3$), 4.25 (1H, d, *J* = 16Hz, $OCH_AH_BC{\equiv}CSiMe_3$), 3.12 (1H, m, $CHOC_3H_2SiMe_3$), 2.26 (1H, m, $C(OH)CH_CH_DCH$), 2.01 (1H, m, $CH_2CH_EH_FCHOC_3H_2SiMe_3$), 1.85 – 1.74 (2H, m, $CH_GH_HCH_EH_FCHOC_3H_2SiMe_3$), 1.62 (1H, br.s, OH), 1.43 (1H, m, $CH_GH_HCH_2CHOC_3H_2SiMe_3$), 1.22 (3H, s, CH_3), 1.06 – 0.97 (2H, m, $C(OH)CH_CH_DCH$, cyclopropyl CH_IH_J), 0.94 – 0.86 (2H, m, cyclopropyl CHCH), 0.37 (1H, q, J = 5Hz, cyclopropyl CH_IH_J), 0.18 (9H, s, $Si(CH_3)_3$)

^{13}C NMR (100MHz, $CDCl_3$) δ: 102.5 (0), 91.2 (0), 81.7 (1), 71.9 (0), 56.6 (2), 43.1 (2), 41.4 (2), 32.3 (3), 31.7 (2), 20.9 (1), 15.7 (2), 7.6 (1), 0.2 (3)

LRMS (CI) m/z: 267 $(M+H)^+$ [18%], 249 $(M+H-H_2O)^+$ [25%], 121 $(M+H-H_2O-HOC_3H_2SiMe_3)^+$ [100%]

HRMS (ES) m/z: $C_{30}H_{52}O_4Si_2Na$ $(2M+Na)^+$ requires 555.32963, found 555.33030 [100%].

5-hydroxy-5-methylbicyclo[5.1.0]octan-2-one 524/525



524/525

(1S,2R,7S)-5-Methylbicyclo[5.1.0]octane-2,5-diol **516** (0.010g, 0.06mmol) was dissolved in DCM (1.5mL). PCC (0.021g, 0.10mmol) was added and the reaction stirred overnight. The reaction mixture was filtered through celite and concentrated *in vacuo*. The crude material was purified by column chromatography (0 to 90% ether/PE) to afford ketone **524/525** as a colourless oil (0.008g, 80%).

R_f: 0.4 (Ether)

FT-IR ν_{max}: 3412 (br.m), 2964 (m), 2922 (m), 2852 (w), 1690 (s), 1443 (m), 1366 (m), 1254 (m), 1146 (m), 1100 (m), 1050 (m), 1015 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 2.82 (1H, ddd, *J* = 4, 9, 13Hz, $CH_AH_BCH_2$), 2.34-2.24 (2H, m, $C(OH)CH_CH_DCH$, $CH_2CH_EH_F$), 2.06-1.96 (2H, m, COCH, $CH_AH_BCH_2$), 1.63-

1.52 (2H, m, OH, $CH_2CH_E\mathit{H_F}$), 1.32 (1H, m, $C(OH)CH_2C\mathit{H}$), 1.25 (3H, s, CH_3), 1.03 (1H, dt, J = 5.5, 7.5Hz, cyclopropyl $C\mathit{H_G}H_H$), 0.91 (1H, dd, J = 11, 15Hz, $C(OH)CH_C\mathit{H_D}CH$), 0.80 (1H, q, J = 5.5Hz, cyclopropyl $CH_G\mathit{H_H}$)

^{13}C NMR (100MHz, $CDCl_3$) δ: 210.1 (0), 72.4 (0), 42.4 (2), 39.1 (2), 38.7 (2), 31.4 (3), 28.6 (1), 12.6 (2), 10.8 (1)

LRMS (CI) m/z: 155 $(M+H)^+$ [94%], 137 $(M+H-H_2O)^+$ [100%]

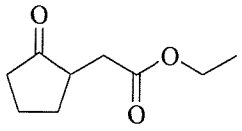
HRMS (EI) m/z: $C_9H_{14}O_2$ $(M)^+$ requires 154.09938, found 154.09932 [29%].

5-hydroxy-5-methylbicyclo[5.1.0]octan-2-one 524/525

(1R,2R,7R)-5-methylbicyclo[5.1.0]octane-2,5-diol **518** (0.006g, 0.04mmol) was dissolved in DCM (1.5mL). PCC (0.012g, 0.06mmol) was added and the reaction stirred overnight. The reaction mixture was filtered through celite and concentrated *in vacuo*. The crude material was purified by column chromatography (0 to 90% ether/PE) to afford ketone **524/525** as a colourless oil (0.004g, 68%). All data was identical to the product from the analagous oxidation of (1S,2R,7S)-5-methylbicyclo[5.1.0]octane-2,5-diol **516**.

6.2.5 Experimental for Chapter 5

Ethyl (2-oxocyclopentyl)acetate 582



582

Following the method of Molander[144], di-isopropylamine (25.0mL, 0.178mol) was dissolved in THF (100mL) and cooled to -78°C. ^{n}BuLi (56.9mL, 2.3M in hexane, 0.131mmol) was added slowly and the reaction mixture allowed to warm to 0°C over approximately 1 hour. This freshly made LDA mixture was cooled to -78°C. Cyclopentanone **581** (10.0g, 0.119mol) in THF (40mL) was added slowly to the LDA solution. The reaction was stirred for 30 minutes at -78°C before addition of HMPA (24.8mL, 0.143mol) followed by ethyl bromoacetate (14.5mL, 0.131mol) in THF (60mL). The reaction was stirred for 1 hour at -78°C and then allowed to warm to RT slowly overnight. The mixture was then quenched with NH_4Cl (100mL) and extracted with EA (150mL) and ether (150mL) sequentially. The combined organic phases were washed with brine (150mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (isocratic 20% ether/PE) to give ketone **582** as a yellow oil (7.13g, 70%). Data agrees with Molander[144].

R_f: 0.2 (40% Ether/PE)

FT-IR ν_{max}: 2971 (w), 2879 (w), 1733 (s), 1447 (w), 1374 (w), 1262 (m), 1185 (m), 1154 (m), 1034 (w), 922 (w)

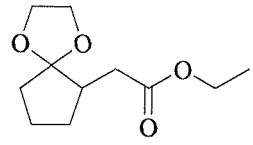
^{1}H NMR (400MHz, $CDCl_3$) δ: 4.13 (2H, q, J = 7Hz, OCH_2CH_3), 2.72 (1H, m, CH_AH_B), 2.47 – 2.25 (4H, m, CH, CH_AH_B, CH_CH_D, CH_EH_F), 2.17 (1H, m, CH_CH_D), 2.05 (1H, m, CH_GH_H), 1.81 (1H, m, CH_GH_H), 1.62 (1H, dq, J = 6.5, 11.5Hz, CH_EH_F), 1.25 (3H, t, J = 7Hz, OCH_2CH_3)

^{13}C NMR (100MHz, $CDCl_3$) δ: 219.5 (0), 172.5 (0), 61.0 (2), 46.0 (1), 37.8 (2), 34.4 (2), 29.7 (2), 21.0 (2), 14.6 (3)

LRMS (CI) m/z: 171 $(M+H)^+$ [100%]

HRMS (EI) m/z: $C_9H_{14}O_3$ $(M)^+$ requires 170.09429, found 170.09452 [61%].

Ethyl 1,4-dioxaspiro[4.4]non-6-ylacetate 585



585

Following the method of Kelly[155], ethylene glycol (12.7g, 0.204mol), ethyl (2-oxocyclopentyl)acetate **582** (7.00g, 0.0411mol) and *p*-TsOH (0.080g, 0.400mmol) were refluxed together in toluene (70mL) for 36 hours using Dean-Stark apparatus to remove water. The reaction was cooled and concentrated *in vacuo*. EA (150mL) was added and the organic phase washed with $NaHCO_3$ (20mL) and brine (50mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The crude oil was purified by column chromatography (isocratic 20% ether/PE) to yield ketal **585** as a pale yellow oil (4.673g, 53%). Data agrees with Lee-Ruff[169].

R_f: 0.4 (50% Ether/PE)

FT-IR ν_{max}: 2964 (m), 2875 (w), 1733 (s), 1374 (w), 1289 (w), 1154 (m), 1030 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 4.13 (2H, q, *J* = 7Hz, OCH_2CH_3), 3.95 – 3.83 (4H, m, OCH_2CH_2O), 2.51 – 2.37 (2H, m, CH_AH_B, CH), 2.22 (1H, dd, *J* = 8, 14Hz, CH_AH_B), 2.00 (1H, m, CH_CH_D), 1.80 – 1.62 (4H, m, CH_2, CH_2), 1.41 (1H, m, CH_CH_D), 1.25 (3H, t, *J* = 7Hz, OCH_2CH_3)

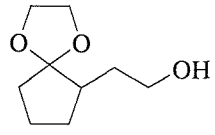
^{13}C NMR (100MHz, $CDCl_3$) δ: 173.7 (0), 118.1 (0), 65.0 (2)*, 60.6 (2), 42.9 (1), 35.5 (2), 35.0 (2), 29.8 (2), 20.9 (2), 14.6 (3)

* = 2 carbons

LRMS (CI) m/z: 215 $(M+H)^+$ [100%]

HRMS (EI) m/z: $C_{11}H_{18}O_4$ $(M)^+$ requires 214.12051, found 214.12017 [51%].

2-(1,4-Dioxaspiro[4.4]non-6-yl)ethanol 586



586

Following the method Albizati[157], ethyl 1,4-dioxaspiro[4.4]non-6-ylacetate **585** (4.60g, 21.5mmol) in THF (10mL) was added drop-wise to a suspension of $LiAlH_4$ (1.06g, 27.9mmol) in THF (40mL) at 0°C and stirred for 1 hour. The reaction was allowed to warm to RT for 1 hour and then cooled to 0°C. Ether (40mL) was added and the solution stirred for 5 minutes. NaOH (4M) was added drop-wise very slowly until a heavy white

ppt was observed. The mixture was filtered, washed with EA (75mL) and concentrated *in vacuo* to give alcohol **586** as a pale yellow oil (3.59g, 97%). Data agrees with Coward[170].

R_f: 0.1 (50% Ether/PE)

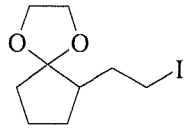
FT-IR ν_{max}: 3404 (br.m), 2949 (s), 2879 (s), 1440 (w), 1320 (m), 1200 (m), 1154 (m), 1102 (m), 1034 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 3.96 – 3.85 (4H, m, OCH_2CH_2O), 3.70 (1H, m, CH_AH_BOH), 3.62 (1H, m, CH_AH_BOH), 2.12 – 2.01 (2H, m, CH, OH), 1.91 (1H, dtd, J = 4, 8, 12Hz, $CH_CH_DCH(CH_2CH_2OH)$), 1.85 – 1.60 (5H, m, CH_2, CH_2, $CH_EH_FCH_2OH$), 1.56 (1H, m, $CH_EH_FCH_2OH$), 1.41 (1H, m, $CH_CH_DCH(CH_2CH_2OH)$),

^{13}C NMR (100MHz, $CDCl_3$) δ: 118.3 (0), 64.75 (2), 64.69 (2), 62.3 (2), 43.6 (1), 35.7 (2), 32.1 (2), 30.1 (2), 21.0 (2)

HRMS (EI) m/z: $C_9H_{16}O_3$ $(M)^+$ requires 172.10994 found 172.11020 [100%].

6-(2-Iodoethyl)-1,4-dioxaspiro[4.4]nonane 587



587

Following the method of Motherwell[126], triphenylphosphine (1.60g, 6.10mmol), imidazole (0.470g, 6.91mmol) and finally iodine (1.65g, 6.50mmol) were added to a stirred solution of 2-(1,4-dioxaspiro[4.4]non-6-yl)ethanol **586** (0.700g, 17.1mmol) in ether (45mL) and acetonitrile (15mL) at 0°C. The solution was stirred for 5 minutes. The resulting red-brown solution was diluted with ether (30mL), washed with $Na_2S_2O_3$ (45mL) and then water (30mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (isocratic 10% ether/PE) to yield iodide **587** as a very pale yellow oil (0.993g, 87%).

R_f: 0.4 (30% Ether/PE)

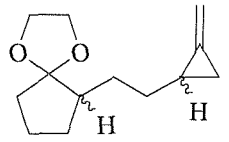
FT-IR ν_{max}: 2953 (s), 2875 (m), 1432 (w), 1316 (w), 1139 (m), 1046 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 3.95 – 3.86 (4H, m, OCH_2CH_2O), 3.27 (1H, m, CH_AH_BI), 3.15 (1H, m, CH_AH_BI), 2.14 – 2.00 (2H, m, $CHCH_CH_DCH_2I$), 1.93 (1H, dtd, J = 4, 8, 12Hz, $CH_EH_FCH(CH_2CH_2I)$), 1.84 – 1.59 (5H, m, CH_2, CH_2, $CH_CH_DCH_2I$), 1.32 (1H, m, $CH_EH_ECH(CH_2CH_2I)$),

^{13}C NMR (100MHz, $CDCl_3$) δ: 118.2 (0), 64.9 (2), 64.8 (2), 47.2 (1), 36.0 (2), 34.0 (2), 29.1 (2), 21.0 (2), 6.1 (2)

LRMS (CI) m/z: 283 $(M+H)^+$ [100%].

6-[2-(2-Methylenecyclopropyl)ethyl]-1,4-dioxaspiro[4.4]nonane 588



588

^{n}BuLi (1.7mL, 2.3M in hexanes, 3.83mmol) was added to methylenecyclopropane **200** (0.5mL, 6.38mmol) in THF (10mL) at -60°C and allowed to warm to 0°C over 45 minutes. The reaction was left for 45 minutes at 0°C, then cooled to -60°C and HMPA (1.1mL, 6.38mmol) was added, immediately followed by the drop-wise addition of 6-(2-iodoethyl)-1,4-dioxaspiro[4.4]nonane **587** (0.900g, 3.19mmol). The reaction was allowed to warm to RT overnight. It was then quenched with NH_4Cl (5mL) and extracted with ether (20mL). The organic phase was washed with brine (10mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (10% ether/PE) to give ketal **588** as a mixture of isomers as a colourless oil (1:1 ratio, 0.580g, 87%).

R_f: 0.5 (30% Ether/PE)

FT-IR ν_{max}: 2953 (s), 2875 (s), 1455 (w), 1316 (m), 1200 (m), 1154 (m), 1112 (s), 1034 (s), 949 (m), 884 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.40 (1H, m, $=CH_AH_B$), 5.33 (1H, br.s, $=CH_AH_B$), 3.97 – 3.85 (4H, m, OCH_2CH_2O), 1.96 – 1.85 (2H, m, $C(O_2C_2H_4)CH$, CH_CH_D), 1.79 – 1.55 (5H, m, CH_2, CH_2, CH_CH_D), 1.42 – 1.26 (5H, m, CH_2, CH_2, cyclopropyl CH), 1.21 (1H, m, cyclopropyl CH_EH_F), 0.72 (1H, m, cyclopropyl CH_EH_F)

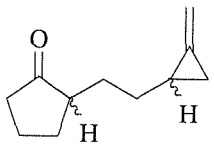
^{13}C NMR (100MHz, $CDCl_3$) δ: 137.7 & 137.5 (0), 118.7 (0)*, 102.7 (2)*, 65.0 (2)*, 64.9 (2)*, 46.3 & 46.1 (1), 36.2 & 36.1 (2), 32.3 & 32.1 (2), 29.9 & 29.8 (2), 29.2 & 29.0 (2), 21.1 & 21.0 (2), 16.4 (1)*, 9.9 & 9.7 (2)

* = 2 carbons

LRMS (CI) m/z: 209 $(M+H)^+$ [40%]

HRMS (EI) m/z: $C_{13}H_{20}O_2$ $(M)^+$ requires 208.14633, found 208.14662 [62%].

2-[2-(2-Methylenecyclopropyl)ethyl]cyclopentanone 589



589

6-[2-(2-methylenecyclopropyl)ethyl]-1,4-dioxaspiro[4.4]nonane **588** (0.100g, 0.48mmol) was stirred with *p*-TsOH (0.01g, 0.05mmol) in a mixture of acetone (4mL) and water (1mL) under Ar for 48 hours. The mixture was concentrated *in vacuo* and ether (10mL) added. The mixture was washed with $NaHCO_3$ (1mL) and extracted with EA (5mL) and ether (5mL). The organic phases were combined, dried ($MgSO_4$) and concentrated *in vacuo*. This gave ketone **589** as a mixture of isomers as a colourless oil (1:1 ratio, 0.077g, 98%).

R_f: 0.4 (20% Ether/PE)

FT-IR ν_{max}: 2964 (m), 2935 (m), 2846 (m), 1733 (s), 1455 (m), 1405 (m), 1277 (w), 1154 (m), 884 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.39 (1H, m, $=CH_AH_B$), 5.34 (1H, br.s, $=CH_AH_B$), 2.35 – 1.85 (6H, m, COCH, CH_2, CH_2, CH_CH_D), 1.78 (1H, m, CH_CH_D), 1.57 – 1.32 (5H, m, CH_2, CH_2, cyclopropyl CH), 1.23 (1H, m, cyclopropyl CH_EH_F), 0.74 (1H, m, cyclopropyl CH_EH_F)

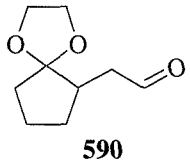
^{13}C NMR (100MHz, $CDCl_3$) δ: 221.7 (0)*, 137.1 & 136.9 (0), 103.0 (2)*, 49.2 & 49.1 (1), 38.55 & 38.52 (2), 31.5 & 31.4 (2), 30.1 & 29.8 (2), 30.0 (2)*, 21.1 (2)*, 15.9 (1)*, 9.9 & 9.7 (2)

* = 2 carbons

LRMS (CI) m/z: 165 $(M+H)^+$ [100%]

HRMS (EI) m/z: $C_{11}H_{16}O$ $(M)^+$ requires 164.12012, found 164.11976 [7%].

1,4-Dioxaspiro[4.4]non-6-ylacetaldehyde 590



590

Following the method of Swern[136], oxalyl chloride (3.1mL, 35mmol) was dissolved in DCM (50mL). The mixture was cooled to -78°C before addition of DMSO (5.0mL, 70mmol) in DCM (15mL). After 5 minutes, 2-(1,4-dioxaspiro[4.4]non-6-yl)ethanol **586** (5.0g, 29mmol) in DCM (30mL) was added keeping the temperature below -60°C. After

15 minutes at -60°C, NEt_3 (20.2mL, 145mmol) was added. The reaction was stirred for 45 minutes before warming to RT over 2 hours. Water (75mL) was added to the white ppt which then disappeared. The organic phase was separated, and the aqueous phase extracted with DCM (100mL). The combined organic phases were washed with brine (100mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification was by column chromatography (isocratic 30% ether/PE) affording aldehyde **590** a pale yellow oil (3.45g, 69%).

R_f: 0.3 (50% Ether/PE)

FT-IR ν_{max}: 2960 (m), 2879 (m), 2723 (w), 1721 (s), 1405 (w), 1324 (w), 1200 (m), 1154 (m), 1104 (m), 1030 (m), 949 (m), 838 (w)

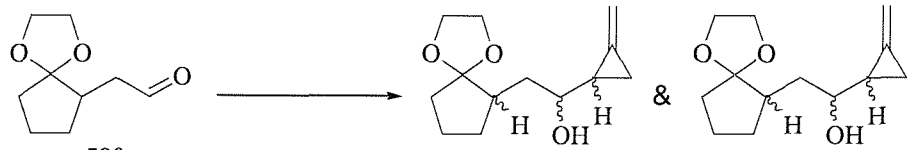
^{1}H NMR (400MHz, $CDCl_3$) δ: 9.76 (1H, t, *J* = 2Hz, CHO), 3.91 – 3.82 (4H, m, OCH_2CH_2O), 2.58 (1H, ddd, *J* = 2, 7, 16Hz, CH_AH_BCHO), 2.49 (1H, m, $CH(CH_2CHO)$), 2.33 (1H, ddd, *J* = 2, 7, 16Hz, CH_AH_BCHO), 2.00 (1H, dtd, *J* = 4.5, 7.5, 12Hz, $CH_CH_DCH(CH_2CHO)$), 1.80 – 1.64 (4H, m, CH_2, CH_2), 1.41 (1H, dtd, *J* = 8, 9, 12Hz, $CH_CH_DCH(CH_2CHO)$)

^{13}C NMR (100MHz, $CDCl_3$) δ: 202.7 (1), 118.0 (0), 65.0 (2), 64.9 (2), 44.2 (2), 41.3 (1), 35.4 (2), 29.7 (2), 21.2 (2)

LRMS (CI) m/z: 171 $(M+H)^+$ [100%]

HRMS (EI) m/z: $C_9H_{14}O_3$ $(M)^+$ requires 170.09429 found 170.09443 [34%].

2-(1,4-Dioxaspiro[4.4]non-6-yl)-1-(2-methylenecyclopropyl)ethanol 591 & 592



590 **591** **592**

^{n}BuLi (3.7mL, 2.3M in hexanes, 8.5mmol) was added to methylenecyclopropane **200** (1.0mL, 13.6mmol) in THF (12mL) at -60°C under Ar and allowed to warm to 0°C over 30 minutes. The reaction was left for 45 minutes at 0°C, then cooled to -60°C before addition of 1,4-dioxaspiro[4.4]non-6-ylacetaldehyde **590** (1.16g, 6.82mmol) in THF (3mL). The reaction was allowed to warm to RT overnight. It was then quenched with NH_4Cl (20mL) and extracted with EA (2 x 75mL). The combined organic phases were washed with brine (50mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (0 to 70% ether/PE) to give the ketals as two

pairs of mixtures of isomers: the less polar **591** as a colourless oil (7:3 isomer ratio, 0.538g, 35%); the more polar **592** as a colourless oil (3:2 isomer ratio, 0.419g, 27%).

2-(1,4-Dioxaspiro[4.4]non-6-yl)-1-(2-methylenecyclopropyl)ethanol 591

R_f: 0.3 (70% Ether/PE)

FT-IR ν_{max}: 3444 (br.m), 2953 (s), 2875 (s), 1432 (w), 1316 (m), 1200 (m), 1092 (s), 1034 (s), 949 (s), 892 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.54 (1H, br.s, =CH_AH$_B$), 5.44 (1H, br.s, =CH$_A$$H_B$), 3.98 – 3.85 (4H, m, OCH_2CH_2O), 3.35 (0.7H, m, CH(OH) maj.), 3.25 (0.3H, m, CH(OH) min.), 2.23 (1H, m, $CH_2CH(CH_2)$), 1.97 – 1.84 (2H, m, CH_CH$_D$, CH_EH$_F$), 1.80 – 1.55 (6H, m, CH_2, CH_2, CH$_E$$H_F$, cyclopropyl CH), 1.44 (1H, m, CH$_C$$H_D$), 1.27 (1H, m, cyclopropyl CH_GH$_H$), 0.99 (1H, m, cyclopropyl CH$_G$$H_H$)

^{13}C NMR (100MHz, $CDCl_3$)

Major isomer δ: 133.8 (0), 118.5 (0), 104.3 (2), 73.1 (1), 64.72 (2), 64.67 (2), 42.7 (1), 36.6 (2), 35.8 (2), 30.5 (2), 22.2 (1), 21.1 (2), 7.8 (2)

Minor isomer δ: 134.0 (0), 118.3 (0), 104.3 (2), 73.7 (1), 64.9 (2), 64.7 (2), 43.5 (1), 36.4 (2), 35.6 (2), 30.2 (2), 22.6 (1), 20.8 (2), 7.7 (2)

LRMS (CI) m/z: 225 $(M+H)^+$ [13%], 163 [100%]

HRMS (ES) m/z: $C_{13}H_{20}O_3Na$ $(M+Na)^+$ requires 247.13047 found 247.13028 [81%].

2-(1,4-Dioxaspiro[4.4]non-6-yl)-1-(2-methylenecyclopropyl)ethanol 592

R_f: 0.2 (70% Ether/PE)

FT-IR ν_{max}: 3427 (br.m), 2949 (s), 2875 (s), 1432 (w), 1320 (m), 1200 (m), 1112 (s), 1030 (s), 949 (s), 892 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.45 – 5.39 (2H, m, $=CH_2$), 3.98 – 3.86 (4H, m, OCH_2CH_2O), 3.25 (0.4H, m, CH(OH) min.), 3.17 (0.6H, m, CH(OH) maj.), 2.44 (0.6H, d, J = 3Hz, OH maj.), 2.31 (0.4H, d, J = 4Hz, OH min.), 2.20 (1H, m, $CH_2CH(CH_2)$), 1.93 (1H, m, CH_AH$_B$CH(CH_2CH(OH))), 1.87 – 1.49 (7H, m, CH_2, CH_2, CH_2, cyclopropyl CH), 1.41 (1H, m, CH$_A$$H_B$CH($CH_2$CH(OH))), 1.29 (1H, tt, J = 2, 9Hz, cyclopropyl CH_CH$_D$), 1.04 (1H, m, cyclopropyl CH$_C$$H_D$)

^{13}C NMR (100MHz, $CDCl_3$)

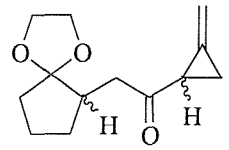
Major isomer δ: 133.5 (0), 118.3 (0), 104.2 (2), 73.9 (1), 64.87 (2), 64.71 (2), 43.7 (1), 36.7 (2), 35.6 (2), 30.3 (2), 23.1 (1), 20.8 (2), 8.2 (2)

Minor isomer δ: 133.5 (0), 118.4 (0), 104.4 (2), 73.1 (1), 64.75 (2), 64.66 (2), 42.6 (1), 36.4 (2), 35.9 (2), 30.4 (2), 22.9 (1), 21.1 (2), 8.1 (2)

LRMS (CI) m/z: 225 $(M+H)^+$ [15%], 163 [100%]

HRMS (ES) m/z: $C_{13}H_{20}O_3Na$ $(M+Na)^+$ requires 247.13047 found 247.13034 [46%].

2-(1,4-dioxaspiro[4.4]non-6-yl)-1-(2-methylenecyclopropyl)ethanone 605/606



605/606

2-(1,4-Dioxaspiro[4.4]non-6-yl)-1-(2-methylenecyclopropyl)ethanol **592** (0.030g, 0.13mmol) was dissolved in DCM (5mL). PCC (0.043g, 0.20mmol) was added and the reaction stirred overnight. The reaction mixture was filtered through celite and concentrated *in vacuo*. The crude material was purified by column chromatography (0 to 50% ether/PE) to afford ketone **605/606** as an inseparable pair of diastereoisomers as a colourless oil (1:1 ratio, 0.015g, 50%).

R_f: 0.4 (50% Ether/PE)

FT-IR ν_{max}: 2960 (m), 2875 (m), 1696 (s), 1324 (m), 1200 (m), 1146 (m), 1104 (s), 1023 (m), 949 (m), 892 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.47 (1H, m, $=CH_AH_B$), 5.43 (1H, m, $=CH_AH_B$), 3.94 – 3.79 (4H, m, OCH_2CH_2O), 2.68 – 2.45 (3H, m, $CH_2CH(CH_2)$, cyclopropyl CH, CH_CH_D), 2.31 (1H, m, CH_CH_D), 2.00 (1H, m, CH_EH_F), 1.86 (1H, m, cyclopropyl CH_CH_H), 1.79 – 1.60 (5H, m, CH_2, CH_2, cyclopropyl CH_GH_H), 1.31 (1H, m, CH_EH_F),

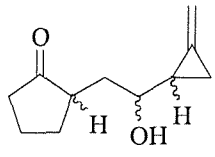
^{13}C NMR (100MHz, $CDCl_3$) δ: 207.5 & 207.4 (0), 132.30 & 132.27 (0), 118.3 (0)*, 104.34 & 104.25 (2), 64.9 (2)#, 42.0 & 41.8 (1), 41.9 & 41.7 (2), 35.5 & 35.4 (2), 30.00 & 29.95 (2), 27.2 & 27.1 (1), 21.1 & 21.0 (2), 12.5 (2)*

* = 2 carbons; # = 2 x 2 carbons

LRMS (CI) m/z: 223 $(M+H)^+$ [75%], 99 [100%]

HRMS (EI) m/z: $C_{13}H_{18}O_3$ $(M)^+$ requires 222.12559 found 222.12640 [62%].

2-[2-Hydroxy-2-(2-methylenecyclopropyl)ethyl]cyclopentanone 597



597

2-(1,4-Dioxaspiro[4.4]non-6-yl)-1-(2-methylenecyclopropyl)ethanol **591** (0.200g, 0.89mmol) was dissolved in acetone (4mL) and water (1mL). *p*-TsOH (0.017g, 0.09mmol) was added. The reaction was stirred for 72 hours. $NaHCO_3$ (2mL) was added and the reaction concentrated *in vacuo*. The aqueous layer was extracted with EA (10mL). The organic layer was washed with brine (3mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude was purified by column chromatography (isocratic 50% ether/PE) to afford ketone **597** as a mixture of isomers as a colourless oil (7:3 ratio, 0.155g, 77%) with a minor inseparable impurity.

R_f: 0.3 (70% Ether/PE)

FT-IR ν_{max}: 3439 (br.m), 2972 (m), 2879 (m), 1729 (s), 1405 (m) 1154 (m), 1019 (m), 892 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.53 (1H, m, $=CH_AH_B$), 5.45 (1H, br.s, $=CH_AH_B$), 3.48 (0.7H, m, CH(OH) maj.), 3.38 (0.3H, m, CH(OH) min.), 2.47 (0.3H, d, J = 5.5Hz, OH min.), 2.39 – 2.23 (3H, m, COCH, CH_CH_D, CH_EH_F), 2.16 (1H, m, CH_CH_D), 2.09 – 1.98 (2H, m, CH_GH_H, CH_IH_J), 1.92 (0.7H, d, J = 6Hz, OH maj.), 1.82 (1H, m, CH_GH_H), 1.71 – 1.58 (3H, m, cyclopropyl CH, CH_EH_F, CH_IH_J), 1.27 (1H, m, cyclopropyl CH_KH_L), 1.01 (1H, m, cyclopropyl CH_KH_L)

^{13}C NMR (100MHz, $CDCl_3$)

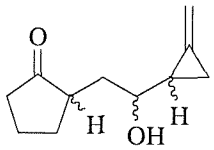
Major isomer δ: 222.3 (0), 133.3 (0), 104.63 (2), 72.7 (1), 46.9 (1), 38.2 (2), 37.0 (2), 30.7 (2), 22.0 (1), 21.4 (2), 7.6 (2)

Minor isomer δ: 222.9 (0), 133.5 (0), 104.58 (2), 72.9 (1), 47.7 (1), 38.4 (2), 37.2 (2), 30.8 (2), 22.4 (1), 21.3 (2), 7.5 (2)

LRMS (CI) m/z: 181 $(M+H)^+$ [5%], 163 $(M+H-H_2O)^+$ [20%], 43 [100%]

HRMS (EI) m/z: $C_{11}H_{14}O$ $(M-H_2O)^+$ requires 162.10447 found 162.10454 [15%].

2-[2-Hydroxy-2-(2-methylenecyclopropyl)ethyl]cyclopentanone 598



598

2-(1,4-Dioxaspiro[4.4]non-6-yl)-1-(2-methylenecyclopropyl)ethanol **592** (0.250g, 1.11mmol) was dissolved in acetone (4mL) and water (1mL). *p*-TsOH (0.017g, 0.09mmol) was added. The reaction was stirred for 72 hours. $NaHCO_3$ (2mL) was added and the reaction concentrated *in vacuo*. The aqueous layer was extracted with EA (10mL).

The organic layer was washed with brine (3mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude was purified by column chromatography (isocratic 50% ether/PE) to afford ketone **598** as a mixture of isomers as a colourless oil (1:1 ratio, 0.199g, 99%) with a minor inseparable impurity.

R_f: 0.2 (70% Ether/PE)

FT-IR ν_{max}: 3417 (br.m), 2964 (m), 2875 (m), 1733 (s), 1405 (m) 1158 (m), 1023 (m), 895 (m)

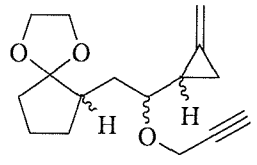
^{1}H NMR (400MHz, $CDCl_3$) **δ**: 5.46 – 5.17 (2H, m, $=CH_2$), 3.38 (0.5H, m, $CH(OH_X)$), 3.23 (0.5H, m, $CH(OH_Y)$), 2.91 (0.5H, d, J = 3.5Hz, OH_Y), 2.39 – 2.23 (3H, m, COCH, CH_CH_D, CH_EH_F), 2.22 (0.5H, d, J = 5Hz, OH_X), 2.15 (1H, m, CH_CH_D), 2.09 – 1.93 (2H, m, CH_GH_H, CH_IH_J), 1.82 (1H, m, CH_GH_H), 1.75 – 1.54 (3H, m, cyclopropyl CH, CH_EH_F, CH_IH_J), 1.32 (1H, m, cyclopropyl CH_KH_L), 1.07 (1H, m, cyclopropyl CH_KH_L)

^{13}C NMR (100MHz, $CDCl_3$) **δ**: 223.2 & 222.5 (0), 133.2 & 133.0 (0), 104.6 & 104.4 (2), 73.7 & 72.9 (1), 48.1 & 46.7 (1), 38.4 & 38.3 (2), 37.6 & 37.0 (2), 30.9 & 30.8 (2), 23.0 & 22.6 (1), 21.4 & 21.3 (2), 8.4 & 8.2 (2)

LRMS (CI) m/z: 181 $(M+H)^+$ [4%], 43 [100%]

HRMS (EI) m/z: $C_{11}H_{14}O$ $(M-H_2O)^+$ requires 162.10447 found 162.10482 [17%].

6-[2-(2-Methylenecyclopropyl)-2-(prop-2-ynyloxy)ethyl]-1,4-dioxaspiro[4.4]nonane 599



599

Following the method of Boffey[124], sodium hydride (0.290g, 60% dispersion in mineral oil, 7.20mmol) was suspended in THF (30mL) and cooled to 0°C. 2-(1,4-Dioxaspiro[4.4]non-6-yl)-1-(2-methylenecyclopropyl)ethanol **591** (0.650g, 2.90mmol) was dissolved in THF (10mL) and added drop-wise to the mixture. The reaction was stirred for 20 minutes allowing to warm to RT. DMPU (0.9mL, 7.20mmol) was added and the reaction stirred for 10 minutes. Propargyl bromide (2.16g, 80% in toluene, 14.5mmol) in THF (10mL) was added. The reaction was stirred overnight. Although TLC did not show completion the reaction was quenched with NH_4Cl (20mL). The aqueous layer was extracted with EA (100mL). The organic phase was then washed with brine (40mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification was by column

chromatography (isocratic 40% ether/PE) affording ketal **599** as a mixture of isomers as a colourless oil (3:2 ratio, 0.254g, 80% based on RSM [0.378g]).

R_f: 0.4 (50% Ether/PE)

FT-IR ν_{max}: 3300 (w), 2953 (s), 2875 (s), 2362 (w), 1440 (w), 1320 (m), 1084 (s), 1030 (m), 949 (s), 892 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.51 – 5.45 (2H, m, $=CH_2$), 4.36 – 4.16 (2H, m, $OCH_2C{\equiv}CH$), 3.97 – 3.84 (4H, m, OCH_2CH_2O), 3.35 (0.4H, dt, *J* = 5, 8.5Hz, $CH(OC_3H_3)$ *min.*), 3.25 (0.6H, dt, *J* = 3.5, 10Hz, $CH(OC_3H_3)$ *maj.*), 2.38 (0.4H, t, *J* = 2.5Hz, $OCH_2C{\equiv}CH$ *min.*), 2.36 (0.6H, t, *J* = 2.5Hz, $OCH_2C{\equiv}CH$ *maj.*), 2.26 (0.6H, m, $CH_2CH(CH_2)$ *maj.*), 2.18 (0.4H, m, $CH_2CH(CH_2)$ *min.*), 1.97 (1H, m, $CH_CH_DCH(CH_2CH(OC_3H_3))$), 1.90 – 1.48 (7H, m, CH_2, CH_2, CH_2, cyclopropyl CH), 1.41 (0.4H, m, $CH_CH_DCH(CH_2CH(OC_3H_3))$ *min.*), 1.33 – 1.23 (1.6H, m, $CH_CH_DCH(CH_2CH(OC_3H_3))$ *maj.*, cyclopropyl CH_GH_H), 0.88 (0.4H, m, cyclopropyl CH_GH_H *min.*), 0.83 (0.6H, m, cyclopropyl CH_GH_H *maj.*)

^{13}C NMR (100MHz, $CDCl_3$)

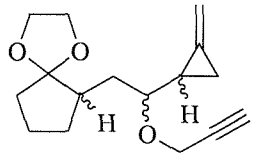
Major isomer δ: 134.5 (0), 118.7 (0), 104.68 (2), 81.0 (0), 79.8 (1), 74.0 (1), 65.0 (2), 64.9 (2), 56.2 (2), 42.3 (1), 36.1 (2), 34.8 (2), 29.6 (2), 21.0 (2), 20.4 (1), 7.1 (2)

Minor isomer δ: 134.1 (0), 118.8 (0), 104.71 (2), 81.3 (1), 81.0 (0), 74.0 (1), 64.8 (2)*, 56.5 (2), 43.0 (1), 35.9 (2), 35.2 (2), 30.9 (2), 21.1 (2), 20.3 (1), 7.3 (2)

* = 2 carbons

HRMS (EI) m/z: $C_{13}H_{19}O_3$ $(M\text{-}C_3H_3)^+$ requires 223.13342 found 223.13422 [100%].

6-[2-(2-Methylenecyclopropyl)-2-(prop-2-ynyloxy)ethyl]-1,4-dioxaspiro[4.4]nonane 602



602

Following the method of Boffey[124], sodium hydride (0.136g, 60% dispersion in mineral oil, 3.40mmol) was suspended in THF (15mL) and cooled to 0°C. 2-(1,4-Dioxaspiro[4.4]non-6-yl)-1-(2-methylenecyclopropyl)ethanol **592** (0.380g, 1.70mmol) was dissolved in THF (5mL) and added drop-wise to the mixture. The reaction was stirred for 20 minutes allowing to warm to RT. DMPU (0.4mL, 3.40mmol) was added and the reaction stirred for 10 minutes. Propargyl bromide (1.01g, 80% in toluene, 6.8mmol) in

THF (5mL) was added. The reaction was stirred overnight. Although TLC did not show completion the reaction was quenched with NH_4Cl (10mL). The aqueous layer was extracted with EA (60mL). The organic phase was then washed with brine (30mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification was by column chromatography (isocratic 40% ether/PE) affording ketal **602** as a mixture of isomers as a colourless oil (3:2 ratio, 0.159g, 92% based on RSM [0.233g]).

R_f: 0.5 (50% Ether/PE)

FT-IR ν_{max}: 3299 (w), 2953 (m), 2875 (m), 2359 (w), 1447 (w), 1324 (m), 1204 (m), 1077 (s), 1034 (m), 888 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.48 (0.4H, m, $=CH_AH_B$ *min.*), 5.46 – 5.42 (1.6H, m, $=CH_AH_B$ *min.*, $=CH_2$ *maj.*), 4.42 – 4.26 (2H, m, $OCH_2C{\equiv}CH$), 3.98 – 3.84 (4H, m, OCH_2CH_2O), 3.11 (1H, m, $CH(OC_3H_3)$), 2.39 (1H, m, $OCH_2C{\equiv}CH$), 2.24 (0.6H, m, $CH_2CH(CH_2)$ *maj.*), 2.18 (0.4H, m, $CH_2CH(CH_2)$ *min.*), 1.96 (1H, m, $CH_CH_DCH(CH_2CH(OC_3H_3))$), 1.87 – 1.58 (4H, m, CH_2, CH_2), 1.54 – 1.35 (4H, m, CH_2, cyclopropyl CH, cyclopropyl CH_GH_H), 1.29 (1H, m, $CH_CH_DCH(CH_2CH(OC_3H_3))$), 1.18 (1H, m, cyclopropyl CH_GH_H)

^{13}C NMR (100MHz, $CDCl_3$)

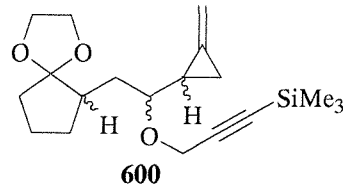
Major isomer δ: 132.3 (0), 118.7 (0), 104.84 (2), 80.8 (0), 78.8 (1), 74.3 (1), 64.95 (2)*, 56.1 (2), 42.3 (1), 36.0 (2), 35.2 (2), 29.6 (2), 21.04 (2), 19.9 (1), 10.0 (2)

Minor isomer δ: 131.8 (0), 118.8 (0), 104.80 (2), 80.9 (0), 80.3 (1), 74.2 (1), 64.95 (2), 64.88 (2), 56.4 (2), 42.6 (1), 35.9 (2), 34.8 (2), 30.8 (2), 21.01 (2), 20.3 (1), 9.7 (2)

* = 2 carbons

HRMS (EI) m/z: $C_{13}H_{19}O_3$ $(M\text{-}C_3H_3)^+$ requires 223.13342 found 223.13336 [100%].

{3-[2-(1,4-Dioxaspiro[4.4]non-6-yl)-1-(2-methylenecyclopropyl)ethoxy]-1-propynyl}(trimethyl)silane 600



600

Following the method of Lautens[168], 6-[2-(2-methylenecyclopropyl)-2-(prop-2-ynyloxy)ethyl]-1,4-dioxaspiro[4.4]nonane **599** (0.426g, 1.62mmol) in THF (30mL) was cooled to -78°C. ^{n}BuLi (0.71mL, 2.3M in hexanes, 1.62mmol) was added slowly and the mixture then stirred for 1 hour at -78°C. TMSCl (0.21mL, 1.62mmol) was added slowly

and the reaction stirred for 1 hour at -78°C before warming to RT overnight. Water (10mL) was added and the reaction extracted with EA (40mL). The organic phase was washed with brine (20mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (0 to 50% ether/PE) affording ketal **600** as a mixture of isomers as a colourless oil (3:2 ratio, 0.315g, 73% based on RSM [0.086g]).

R_f: 0.5 (50% Ether/PE)

FT-IR ν_{max}: 2960 (m), 2879 (m), 1347 (w), 1250 (m), 1085 (m), 1030 (m), 992 (m), 949 (m), 845 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.51 (0.6H, m, $=CH_AH_B$ *maj.*), 5.48 (0.4H, m, $=CH_AH_B$ *min.*), 5.45 (1H, m, $=CH_AH_B$), 4.35 – 4.15 (2H, m, $OCH_2C{\equiv}CSiMe_3$), 3.96 – 3.85 (4H, m, OCH_2CH_2O), 3.05 (0.6H, m, $CH(OC_3H_2SiMe_3)$ *maj.*), 2.99 (0.4H, m, $CH(OC_3H_2SiMe_3)$ *min.*), 2.27 (0.6H, m, $CH_2CH(CH_2)$ *min.*), 2.17 (0.4H, m, $CH_2CH(CH_2)$ *maj.*), 1.99 (1H, m, $CH_CH_DCH(CH_2CH(OC_3H_2SiMe_3))$), 1.91 – 1.48 (7H, m, CH_2, CH_2, CH_2, cyclopropyl CH), 1.42 (0.6H, m, $CH_CH_DCH(CH_2CH(OC_3H_2SiMe_3))$ *maj.*), 1.32 – 1.23 (1.4H, m, $CH_CH_DCH(CH_2CH(OC_3H_2SiMe_3))$ *min.*, cyclopropyl CH_GH_H), 0.88 (0.6H, m, cyclopropyl CH_GH_H *maj.*), 0.83 (0.4H, m, cyclopropyl CH_GH_H *min.*), 0.17 (9H, s, $Si(CH_3)_3$)

^{13}C NMR (100MHz, $CDCl_3$)

Major isomer δ: 134.0 (0), 118.8 (0), 104.69 (2), 103.0 (0), 90.8 (0), 81.4 (1), 65.0 (2), 64.9 (2), 57.5 (2), 43.2 (1), 35.8 (2), 35.1 (2), 30.8 (2), 21.1 (2), 20.4 (1), 7.4 (2), 0.2 (3)

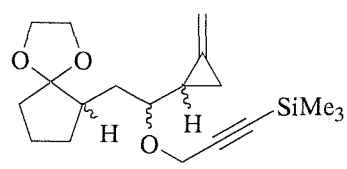
Minor isomer δ: 134.5 (0), 118.7 (0), 104.65 (2), 103.0 (0), 90.8 (0), 79.7 (1), 64.8 (2)*, 57.1 (2), 42.3 (1), 36.2 (2), 34.7 (2), 29.6 (2), 21.0 (2), 20.5 (1), 7.1 (2), 0.2 (3)

* = 2 carbons

LRMS (CI) m/z: 207 $(M+H-HOC_3H_3SiMe_3)^+$ [100%]

HRMS (EI) m/z: $C_{19}H_{30}O_3Si$ $(M)^+$ requires 334.19642 found 334.19694 [14%]; $C_{18}H_{27}O_3Si$ $(M-CH_3)^+$ requires 319.17295 found 319.17300 [41%].

{3-[2-(1,4-Dioxaspiro[4.4]non-6-yl)-1-(2-methylenecyclopropyl)ethoxy]-1-propynyl}(trimethyl)silane 603



603

Following the method of Lautens[168], 6-[2-(2-methylenecyclopropyl)-2-(prop-2-ynyloxy)ethyl]-1,4-dioxaspiro[4.4]nonane **602** (0.210g, 0.80mmol) in THF (15mL) was cooled to -78°C. ^{n}BuLi (0.35mL, 2.3M in hexanes, 0.80mmol) was added slowly and the mixture then stirred for 1 hour at -78°C. TMSCl (0.10mL, 0.80mmol) was added slowly and the reaction stirred for 1 hour at -78°C before warming to RT overnight. Water (5mL) was added and the reaction extracted with EA (30mL). The organic phase was washed with brine (15mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (0 to 50% ether/PE) affording ketal **603** as a mixture of isomers as a colourless oil (1:1 ratio, 0.161g, 85% based on RSM [0.061g]).

R_f: 0.5 (50% Ether/PE)

FT-IR ν_{max}: 2960 (m), 2875 (m), 1443 (w), 1347 (w), 1324 (w), 1250 (m), 1077 (m), 1030 (m), 988 (m), 891 (m), 841 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.47 (0.5H, m, =CH_AH$_B$), 5.45 – 5.41 (1.5H, m, =CH$_A$$H_B$, =$CH_2$), 4.41 – 4.25 (2H, m, OCH_2C≡CSiMe$_3$), 3.97 – 3.85 (4H, m, OCH_2CH_2O), 3.10 (1H, m, CH($OC_3H_2SiMe_3$)), 2.24 (0.5H, m, $CH_2CH(CH_2)$), 2.15 (0.5H, m, $CH_2CH(CH_2)$), 1.97 (1H, m, CH_CH$_D$CH($CH_2CH(OC_3H_2SiMe_3)$)), 1.86 – 1.58 (4H, m, CH_2, CH_2), 1.54 – 1.23 (5H, m, CH_2, cyclopropyl CH, cyclopropyl CH_GH$_H$, CH$_C$$H_D$CH($CH_2CH(OC_3H_2SiMe_3)$)), 1.18 (1H, m, cyclopropyl CH$_G$$H_H$), 0.17 (9H, s, $Si(CH_3)_3$)

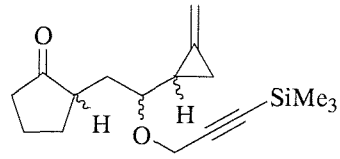
^{13}C NMR (100MHz, $CDCl_3$) δ: 132.6 & 131.9 (0), 118.8 & 118.7 (0), 104.75 & 104.68 (2), 103.0 & 102.9 (0), 91.2 & 91.1 (0), 80.4 & 78.7 (1), 65.0 (2)*, 64.9 (2)*, 57.3 & 57.0 (2), 42.8 & 42.3 (1), 36.1 & 35.9 (2), 35.2 & 34.8 (2), 30.6 & 29.6 (2), 21.02 & 20.98 (2), 20.5 & 20.0 (1), 10.1 & 9.7 (2), 0.2 (3)

* = 2 carbons

LRMS (CI) m/z: 207 $(M+H-HOC_3H_3SiMe_3)^+$ [100%]

HRMS (EI) m/z: $C_{19}H_{30}O_3Si$ $(M)^+$ requires 334.19642 found 334.19538 [17%]; $C_{18}H_{27}O_3Si$ $(M-CH_3)^+$ requires 319.17295 found 319.17397 [45%].

2-(2-(2-Methylenecyclopropyl)-2-{[3-(1,1,1-trimethylsilyl)-2-propynyl]oxy}ethyl)-1-cyclopentanone 601



601

{3-[2-(1,4-Dioxaspiro[4.4]non-6-yl)-1-(2-methylenecyclopropyl)ethoxy]-1-propynyl}-(trimethyl)silane **600** (0.300g, 0.90mmol) was dissolved in acetone (15mL) and water (5mL). *p*-TsOH (0.010g, 0.05mmol) was added. The reaction was stirred for 48 hours. $NaHCO_3$ (4mL) was added and the reaction concentrated *in vacuo*. The aqueous layer was extracted with EA (20mL). The organic layer was washed with brine (6mL), dried ($MgSO_4$) and concentrated *in vacuo*. Ketone **601** was isolated as a mixture of isomers as a colourless oil (3:2 ratio, 0.260g, 99%).

R_f: 0.5 (40% Ether/PE)

FT-IR ν_{max}: 2960 (m), 2875 (w), 1741 (m), 1405 (w), 1347 (w), 1250 (m), 1154 (m), 1077 (m), 992 (m), 838 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.54 – 5.45 (2H, m, $=CH_2$), 4.37 – 4.15 (2H, m, $OCH_2C{\equiv}CSiMe_3$), 3.22 (0.6H, dt, J = 3.5, 9Hz, $CH(OC_3H_2SiMe_3)$ *maj.*), 3.06 (0.4H, m, $CH(OC_3H_2SiMe_3)$ *min.*), 2.46 – 1.97 (6H, m, CH_2, CH_2, CH_AH_B, COCH), 1.86 – 1.42 (4H, m, CH_2, CH_AH_B, cyclopropyl CH), 1.28 (1H, br.t, J = 7Hz, cyclopropyl CH_CH_D), 0.89 (0.6H, m, cyclopropyl CH_CH_D *maj.*), 0.82 (0.4H, m, cyclopropyl CH_CH_D *min.*), 0.17 (9H, s, $Si(CH_3)_3$)

^{13}C NMR (100MHz, $CDCl_3$)

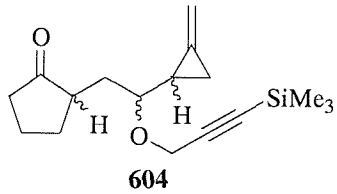
major isomer δ: 221.5 (0), 133.9 (0), 104.9 (2), 102.7 (0), 91.1 (0), 80.4 (1), 57.4 (2), 46.8 (1), 38.2 (2), 35.3 (2), 30.7 (2), 21.3 (2), 20.0 (1), 7.1 (2), 0.2 (3)

minor isomer δ: 221.7 (0), 134.0 (0), 104.9 (2), 102.8 (0), 91.1 (0), 79.0 (1), 57.0 (2), 46.4 (1), 38.4 (2), 35.1 (2), 30.3 (2), 21.0 (2), 19.9 (1), 7.0 (2), 0.2 (3)

LRMS (CI) m/z: 291 $(M+H)^+$ [5%], 163 $(M+H-HOC_3H_3SiMe_3)^+$ [100%]

HRMS (EI) m/z: $C_{16}H_{23}O_2Si$ $(M-CH_3)^+$ requires 275.14673 found 275.14808 [100%].

2-(2-(2-Methylenecyclopropyl)-2-{[3-(1,1,1-trimethylsilyl)-2-propynyl]oxy}ethyl)-1-cyclopentanone 604



604

{3-[2-(1,4-dioxaspiro[4.4]non-6-yl)-1-(2-methylenecyclopropyl)ethoxy]-1-propynyl}-(trimethyl)silane **603** (0.150g, 0.45mmol) was dissolved in acetone (7mL) and water (2mL). *p*-TsOH (0.005g, 0.03mmol) was added. The reaction was stirred for 48 hours. $NaHCO_3$ (2mL) was added and the reaction concentrated *in vacuo*. The aqueous layer

was extracted with EA (15mL). The organic layer was washed with brine (5mL), dried ($MgSO_4$) and concentrated *in vacuo*. Ketone **604** was isolated as a mixture of isomers as a colourless oil (1:1 ratio, 0.130g, 99%).

R_f: 0.5 (40% Ether/PE)

FT-IR ν_{max}: 2960 (m), 2868 (w), 1741 (m), 1405 (w), 1347 (w), 1250 (m), 1154 (m), 1070 (m), 988 (m), 841 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.48 – 5.42 (2H, m, $=CH_2$), 4.42 – 4.28 (2H, m, $OCH_2C{\equiv}CSiMe_3$), 3.26 (0.5H, dt, J = 3.5, 9Hz, $CH(OC_3H_2SiMe_3)$), 3.12 (0.5H, m, $CH(OC_3H_2SiMe_3)$), 2.44 – 1.96 (5H, m, CH_2, CH_AH_B, CH_CH_D, COCH), 1.85 – 1.33 (6H, m, CH_2, CH_AH_B, CH_CH_D, cyclopropyl CH, cyclopropyl CH_EH_F), 1.19 (1H, m, cyclopropyl CH_EH_F), 0.17 (9H, s, $Si(CH_3)_3$)

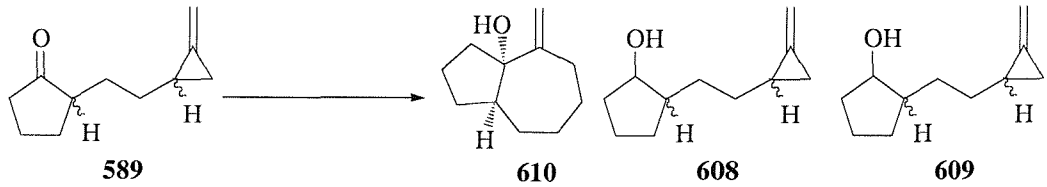
^{13}C NMR (100MHz, $CDCl_3$) δ: 221.7 & 221.3 (0), 131.7 & 131.4 (0), 105.1 & 105.0 (2), 102.6 & 102.5 (0), 91.5 (0)*, 79.2 & 78.0 (1), 57.1 & 56.9 (2), 46.6 & 46.4 (1), 38.4 & 38.2 (2), 35.8 & 35.4 (2), 30.5 & 30.2 (2), 21.3 & 21.0 (2), 19.7 & 19.4 (1), 10.2 & 10.0 (2), 0.2 (3)*

* = 2 carbons

LRMS (CI) m/z: 291 $(M+H)^+$ [4%], 163 $(M+H\text{-}HOC_3H_3SiMe_3)^+$ [100%]

HRMS (EI) m/z: $C_{16}H_{23}O_2Si$ $(M\text{-}CH_3)^+$ requires 275.14673 found 275.14729 [74%].

Cyclisation of 2-[2-(2-Methylenecyclopropyl)ethyl]cyclopentanone 589



589 **610** **608** **609**

Following method B at 0°C, samarium (0.732g, 4.87mmol); di-iodoethane (0.961g, 3.41mmol); ketone **589** (0.080g, 0.49mmol); HMPA (1.80mL, 10.2mmol); ^{t}BuOH (0.15mL, 1.46mmol) were used. Column chromatography (0 to 40% ether/PE) afforded (3aS,8aS)-4-methyleneoctahydroazulen-3a(1H)-ol **610** as a white solid (0.042g, 52%); 2-[2-(2-methylenecyclopropyl)ethyl]cyclopentanol **608** as a colourless oil (0.023g, 28%); and 2-[2-(2-methylenecyclopropyl)ethyl]cyclopentanol **609** as a colourless oil (0.017, 20%).

(3aS,8aS)-4-methyleneoctahydroazulen-3a(1H)-ol 610

R_f: 0.4 (40% Ether/PE)

M.p.: 51 – 54°C

FT-IR ν_{max}: 3352 (br.m), 2918 (s), 2852 (m), 1636 (w), 1443 (m), 1378 (m), 1320 (m), 1185 (m), 1085 (m), 1023 (m), 965 (m), 895 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.03 (1H, s, $=CH_AH_B$), 4.88 (1H, s with fine splitting, $=CH_AH_B$), 2.39 – 2.14 (3H, m, CH_2, CH_CH_D), 1.97 – 1.62 (7H, m, CH_2, CH_2, CH, CH_EH_F, CH_GH_H), 1.52 – 1.09 (5H, m, CH_2, CH_CH_D, CH_EH_F, CH_GH_H)

^{13}C NMR (100MHz, $CDCl_3$) δ: 155.7 (0), 111.7 (2), 86.6 (0), 51.1 (1), 38.4 (2), 35.2 (2), 34.5 (2), 34.0 (2), 32.8 (2), 30.4 (2), 23.6 (2)

LRMS (CI) m/z: 149 $(M+H-H_2O)^+$ [100%]

HRMS (EI) m/z: $C_{11}H_{17}$ $(M-OH)^+$ requires 149.13303, found 149.13234 [5%]; $C_{11}H_{16}$ $(M-H_2O)^+$ requires 148.12520, found 148.12434 [6%]

X-ray : see appendix.

2-[2-(2-methylenecyclopropyl)ethyl]cyclopentanol 608

R_f: 0.3 (40% Ether/PE)

FT-IR ν_{max}: 3369 (br.m), 2960 (s), 2929 (s), 2856 (m), 1445 (m), 1298 (w), 1154 (w), 1119 (w), 988 (m), 884 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.40 (1H, s with fine splitting, $=CH_AH_B$), 5.34 (1H, s, $=CH_AH_B$), 4.15 (1H, m, $CH(OH)$), 1.88 – 1.13 (13H, m, $CH_2CH_2CH_2CH(CH_2CH_2)$, cyclopropyl CH, cyclopropyl CH_CH_D), 0.75 (1H, m, cyclopropyl CH_CH_D)

^{13}C NMR (100MHz, $CDCl_3$) δ: 137.5 (0), 102.8 (2), 75.2 (1), 45.8 (1), 35.3 (2), 32.5 (2), 29.3 (2), 29.2 (2), 22.2 (2), 16.4 (1), 9.8 (2)

LRMS (CI) m/z: 167 $(M+H)^+$ [53%], 149 $(M+H-H_2O)^+$ [100%]

HRMS (EI) m/z: $C_{11}H_{18}O$ $(M)^+$ requires 166.13577, found 166.13667 [38%].

2-[2-(2-methylenecyclopropyl)ethyl]cyclopentanol 609

R_f: 0.3 (40% Ether/PE)

FT-IR ν_{max}: 3335 (br.m), 2953 (s), 2922 (s), 2852 (m), 1445 (m), 1378 (w), 1262 (w), 1077 (w), 1023 (w), 884 (m)

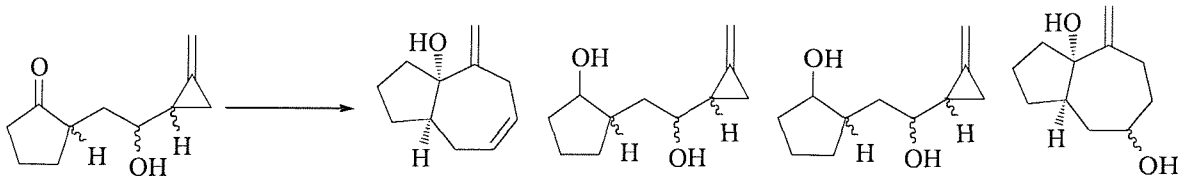
^{1}H NMR (400MHz, $CDCl_3$) δ: 5.41 (1H, br.s, $=CH_AH_B$), 5.34 (1H, br.s, $=CH_AH_B$), 3.83 (1H, q, J = 5.5Hz, $CH(OH)$), 1.97 – 1.12 (13H, m, $CH_2CH_2CH_2CH(CH_2CH_2)$, cyclopropyl CH, cyclopropyl CH_CH_D), 0.74 (1H, m, cyclopropyl CH_CH_D)

^{13}C NMR (100MHz, $CDCl_3$) δ: 137.5 (0), 102.8 (2), 79.7 (1), 48.4 (1), 35.1 (2), 34.0 (2), 32.2 (2), 30.4 (2), 22.2 (2), 16.2 (1), 9.8 (2)

LRMS (CI) m/z: 167 $(M+H)^+$ [54%], 149 $(M+H-H_2O)^+$ [100%]

HRMS (EI) m/z: $C_{11}H_{17}$ $(M-OH)^+$ requires 149.13303, found 149.13419 [7%].

Cyclisation of 2-[2-Hydroxy-2-(2-methylenecyclopropyl)ethyl]cyclopentanone 597



597 **617** **613** **614** **618**

Following method B at 0°C, samarium (0.667g, 4.44mmol); di-iodoethane (0.876g, 3.11mmol); ketone **597** (0.080g, 0.44mmol); HMPA (1.62mL, 9.32mmol); ^{t}BuOH (0.13mL, 1.33mmol) were used. Column chromatography (0 to 90% ether/PE) afforded (3aS,8aR)-4-methylene-2,3,4,5,8,8a-hexahydroazulen-3a(1H)-ol **617** as a white waxy solid (0.018g, 25%); 2-[2-hydroxy-2-(2-methylenecyclopropyl)ethyl]cyclopentanol **613** as a yellow oil (0.004g, 5%) with minor inseparable impurities; 2-[2-hydroxy-2-(2-methylenecyclopropyl)ethyl]cyclopentanol **614** as a yellow oil (0.004g, 5%) with minor inseparable impurities; and (3aS,8aR)-4-methyleneoctahydroazulene-3a,7(1H)-diol **618** as a colourless oil (0.019g, 24%) with minor inseparable impurities. RSM [0.032g].

(3aS,8aR)-4-methylene-2,3,4,5,8,8a-hexahydroazulen-3a(1H)-ol 617

R_f: 0.6 (90% Ether/PE)

FT-IR ν_{max}: 3369 (br.m), 3014 (m), 2960 (s), 2918 (s), 2867 (m), 1644 (w), 1440 (m), 1216 (w), 1088 (w), 1042 (m), 969 (m), 899 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.62 – 5.58 (2H, m, CH=CH), 5.07 (1H, s with fine splitting, $=CH_AH_B$), 4.93 (1H, br.s, $=CH_AH_B$), 3.29 (1H, br.d, J = 17Hz, $CH=CHCH_CH_DC=CH_2$), 2.78 (1H, br.d, J = 17Hz, $CH=CHCH_CH_DC=CH_2$), 2.23 – 1.67 (8H, m, $CH(CH_2CH=CH)$, CH_2, CH_2, CH_EH_F), 1.30 (1H, m, CH_EH_F)

^{13}C NMR (100MHz, $CDCl_3$) δ: 151.4 (0), 129.3 (1), 128.8 (1), 111.6 (2), 86.5 (0), 51.0 (1), 37.5 (2), 35.9 (2), 32.7 (2), 32.6 (2), 23.1 (2)

LRMS (CI) m/z: 147 $(M+H-H_2O)^+$ [100%]

HRMS (EI) m/z: $C_{11}H_{16}O$ $(M)^+$ requires 164.12012, found 164.12023 [10%].

2-[2-hydroxy-2-(2-methylenecyclopropyl)ethyl]cyclopentanol 613

R_f: 0.3 (90% Ether/PE)

FT-IR ν_{max}: 3373 (br.m), 2960 (s), 2933 (s), 2868 (m), 1459 (w), 1262 (w), 1131 (m), 1019 (m), 892 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.53 (1H, s with fine splitting, $=CH_AH_B$), 5.46 (1H, br.s, $=CH_AH_B$), 4.26 (1H, m, cyclopentyl CH(OH)), 3.37 (1H, dt, J = 4, 7Hz, $CH(CH_2CH(OH))$), 2.08 – 1.22 (11H, m, $CH_2CH_2CH_2CH(CH_2)$, cyclopropyl CH, cyclopropyl CH_CH_D), 0.99 (1H, m, cyclopropyl CH_CH_D)

^{13}C NMR (100MHz, $CDCl_3$) δ: 133.9 (0), 104.4 (2), 74.6 (1), 74.3 (1), 42.3 (1), 35.8 (2), 35.2 (2), 30.1 (2), 22.4 (2), 21.6 (1), 8.0 (2)

LRMS (CI) m/z: 165 $(M+H-H_2O)^+$ [100%], 147 $(M+H-H_2O-H_2O)^+$ [71%]

2-[2-hydroxy-2-(2-methylenecyclopropyl)ethyl]cyclopentanol 614

R_f: 0.2 (90% Ether/PE)

FT-IR ν_{max}: 3354 (br.m), 2960 (s), 2929 (s), 2868 (m), 1447 (w), 1262 (w), 1069 (m), 1019 (m), 892 (m)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.54 (1H, br.s, $=CH_AH_B$), 5.45 (1H, s with fine splitting, $=CH_AH_B$), 3.84 (1H, q, J = 7Hz, cyclopentyl CH(OH)), 3.42 (1H, m, $CH(CH_2CH(OH))$), 2.06 – 1.18 (11H, m, $CH_2CH_2CH_2CH(CH_2)$, cyclopropyl CH, cyclopropyl CH_CH_D), 0.98 (1H, m, cyclopropyl CH_CH_D)

^{13}C NMR (100MHz, $CDCl_3$) δ: 133.9 (0), 104.4 (2), 79.4 (1), 74.1 (1), 44.5 (1), 40.7 (2), 34.9 (2), 31.8 (2), 22.1 (2), 21.6 (1), 8.1 (2)

LRMS (CI) m/z: 165 $(M+H-H_2O)^+$ [29%], 147 $(M+H-H_2O-H_2O)^+$ [34%], 44 [100%]

(3aS,8aR)-4-methyleneoctahydroazulene-3a,7(1H)-diol 618

R_f: 0.1 (90% Ether/PE)

FT-IR ν_{max}: 3354 (br.m), 2929 (s), 2868 (m), 1455 (m), 1262 (m), 1077 (m), 1030 (m), 953 (m), 895 (s)

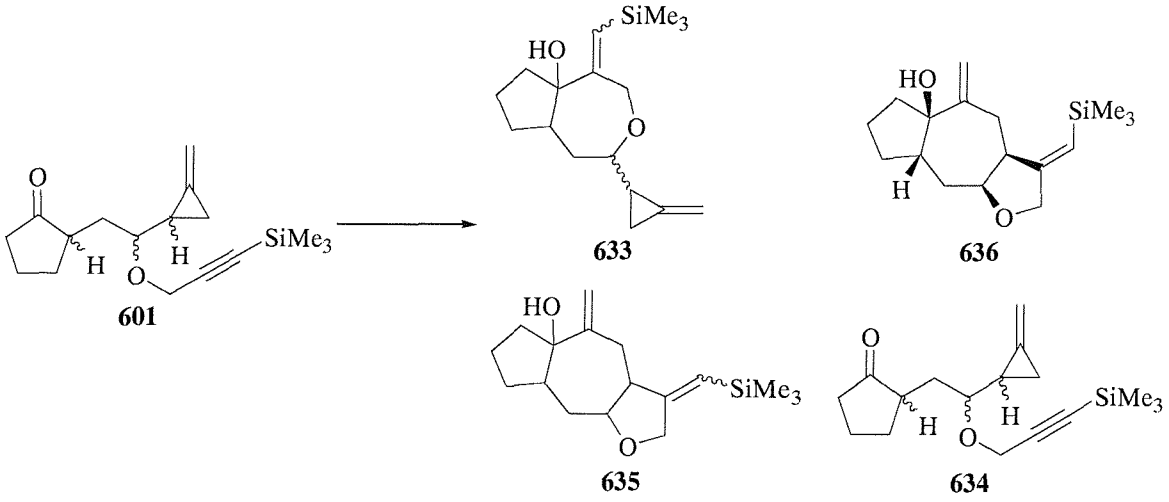
^{1}H NMR (400MHz, $CDCl_3$) δ: 5.01 (1H, s, $=CH_AH_B$), 4.92 (1H, s, $=CH_AH_B$), 4.05 (1H, m, CH(OH)), 2.65 (1H, m, CH_CH_D), 2.37 (1H, m, CH), 2.15 – 2.07 (2H, m, CH_CH_D, CH_EH_F), 2.00 – 1.66 (6H, m, CH_2, CH_2, CH_GH_H, CH_IH_J), 1.60 (1H, m, CH_GH_H), 1.42 (1H, m, CH_IH_J), 1.21 (1H, m, CH_EH_F)

^{13}C NMR (100MHz, $CDCl_3$) δ: 154.5 (0), 111.8 (2), 86.2 (0), 68.6 (1), 43.7 (1), 40.3 (2), 39.7 (2), 38.7 (2), 34.2 (2), 28.1 (2), 23.4 (2)

LRMS (CI) m/z: 165 $(M+H-H_2O)^+$ [82%], 147 $(M+H-H_2O-H_2O)^+$ [100%]

HRMS (EI) m/z: $C_{11}H_{18}O_2$ $(M)^+$ requires 182.13068, found 182.13085 [10%]; $C_{11}H_{16}O$ $(M-H_2O)^+$ requires 164.12012, found 164.11894 [100%]

Cyclisation of 2-(2-(2-Methylenecyclopropyl)-2-{[3-(1,1,1-trimethylsilyl)-2-propynyl]oxy}ethyl)-1-cyclopentanone 601



Following method B at 0°C, samarium (0.518g, 3.44mmol); di-iodoethane (0.679g, 2.41mmol); ketone **601** (0.100g, 0.34mmol); HMPA (1.30mL, 7.23mmol); ^{t}BuOH (0.10mL, 1.03mmol) were used. Column chromatography (0 to 40% ether/PE) afforded 2-(2-methylenecyclopropyl)-5-[1-(1,1,1-trimethylsilyl)methylidene]perhydro-cyclopenta[*d*]oxepin-5a-ol **633** as a yellow oil (0.006g, 6%) with inseparable impurities; an inseparable mixture of 5-methylene-3-[1-(1,1,1-trimethylsilyl)methylidene]-perhydroazuleno[5,6-*b*]furan-5a-ol **635** and 2-(2-(2-methylenecyclopropyl)-2-[3-(1,1,1-trimethylsilyl)-2-propynyl]oxyethyl)-1-cyclopentanol **634** as a yellow oil (0.042g, 42%) with minor inseparable impurities; and 5-methylene-3-[(*Z*)-1-(1,1,1-trimethylsilyl)methylidene]-perhydroazuleno[5,6-*b*]furan-5a-ol **636** as a crystalline solid (0.025g, 25%) with minor inseparable impurities.

2-(2-methylenecyclopropyl)-5-[1-(1,1,1-trimethylsilyl)methylidene]-perhydrocyclopenta[*d*]oxepin-5a-ol 633

R_f: 0.4 (40% Ether/PE)

FT-IR ν_{max}: 3462 (br.w), 2953 (s), 2926 (m), 2860 (m), 1602 (w), 1447 (m), 1351 (w), 1250 (s), 1081 (s), 1023 (m), 838 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.55 (1H, br.s, $=CH_AH_B$), 5.47 – 5.42 (2H, m, $=CH_AH_B$, $=CHSiMe_3$), 4.71 (1H, dd, J = 2, 15.5Hz, CH_CH_DO), 4.28 (1H, d, J = 15.5Hz, CH_CH_DO),

3.23 (1H, m, $CHOCH_2$), 2.27 (1H, m, CH_2CHCH_2), 2.12 – 1.09 (10H, m, $CH_2CH_2CH_2CH(CH_2CH(CH))$ cyclopropyl CH_EH_F), 0.92 (1H, m, cyclopropyl CH_EH_F), 0.13 (9H, s, $Si(CH_3)_3$)

^{13}C NMR (100MHz, $CDCl_3$) δ: 160.0 (0), 134.1 (0), 120.6 (1), 104.5 (2), 86.7 (0), 81.0 (1), 70.9 (2), 49.4 (1), 37.6 (2), 35.9 (2), 34.0 (2), 24.3 (2), 20.4 (1), 7.7 (2), 0.3 (3)

LRMS (CI) m/z: 275 $(M+H-H_2O)^+$ [23%] , 73 $(SiMe_3)^+$ [100%]

HRMS (EI) m/z: $C_{17}H_{28}O_2Si$ $(M)^+$ requires 292.18586, found 292.18679 [39%].

5-methylene-3-[1-(1,1,1-trimethylsilyl)methylidene]perhydroazuleno[5,6-*b*]-furan-5a-ol 635 & 2-(2-(2-methylenecyclopropyl)-2-[3-(1,1,1-trimethylsilyl)-2-propynyl]oxyethyl)-1-cyclopentanol 634

Assigned based on following data.

R_f: 0.3 (40% Ether/PE)

FT-IR ν_{max}: 3412 (br.w), 2953 (m), 2864 (m), 2173 (w), 1636 (m), 1447 (m), 1347 (m), 1250 (m), 1061 (m), 1015 (m), 842 (s), 800 (s)

5,7,5

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.54 – 5.45 (1H, m, $=CHSiMe_3$), 5.10 (1H, s, $=CH_AH_B$), 4.97 (1H, s, $=CH_AH_B$), 4.49 (1H, br.d, J = 14Hz, OCH_CH_D), 4.25 – 4.16 (2H, m, OCH_CH_D), 3.87 (1H, m, $CH(OCH_2)$), 2.54 – 1.20 (12H, m, $[C(OH)CH_2CH_2CH_2CH(CH_2CH(CH(CH_2))))$, 0.17 – 0.06 (9H, m, $Si(CH_3)_3$)

LRMS (CI) m/z: 275 $(M+H-H_2O)^+$ [100%]

red

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.54 – 5.45 (2H, m, $=CH_2$), 4.35 (1H, d, J = 16Hz, $OCH_EH_FC{\equiv}CSiMe_3$), 4.25 – 4.16 (2H, m, $OCH_EH_FC{\equiv}CSiMe_3$), 3.80 (1H, q, J = 6.5Hz, $CH(OH)$), 3.17 (1H, m, $CH(OC_3H_2SiMe_3)$), 2.54 – 1.20 (11H, m, $CH(OH)CH_2CH_2CH_2CH(CH_2CH(CH(CH_GH_H))))$, 0.83 (1H, m, cyclopropyl CH_GH_H), 0.17 – 0.06 (9H, m, $Si(CH_3)_3$)

LRMS (CI) m/z: 275 $(M+H-H_2O)^+$ [3%], 165 $(M+H-HOC_3H_3SiMe_3)^+$ [52%], 90 [100%]

^{13}C NMR (100MHz, $CDCl_3$) δ: 162.2 (0), 151.4 (0), 134.1 (0), 118.7 (1), 112.5 (2), 104.8 (2), 102.4 (0), 91.6 (0), 86.6 (0), 81.1 (1), 79.3 (1)*, 69.8 (2), 57.4 (2), 54.1 (1), 44.7 (1), 41.0 (1), 39.0 (2), 36.6 (2), 36.4 (2), 36.1 (2), 34.5 (2), 33.1 (2), 31.9 (2), 22.9 (2), 22.0 (2), 19.3 (1), 7.1 (2), two from 1.4 or 0.2 or -0.2 (3)

5-methylene-3-[(*Z*)-1-(1,1,1-trimethylsilyl)methylidene]perhydroazuleno[5,6-*b*]furan-5a-ol 636

R_f: 0.2 (40% Ether/PE)

FT-IR ν_{max}: 3416 (br.w), 2953 (m), 2856 (m), 1644 (m), 1455 (w), 1386 (w), 1316 (w), 1250 (m), 1169 (w), 1115 (m), 1058 (m), 863 (m), 837 (s)

^{1}H NMR (400MHz, $CDCl_3$) δ: 5.30 (1H, s, =C*H*SiMe$_3$), 5.13 (1H, s, =CH_AH$_B$), 5.02 (1H, s, =CH$_A$$H_B$), 4.50 (1H, d, J = 14Hz, OCH_CH$_D$), 4.17 (1H, d with fine splitting, J = 14Hz, OCH$_C$$H_D$), 3.90 (1H, m, C*H*(OCH$_2$)), 2.63 – 2.43 (3H, m, CH$_2$C*H*CH$_2$, CH_EH$_F$C*H*(C=CHSiMe$_3$)), 2.30 (1H, m, CH_GH$_H$), 2.14 (1H, dd, J = 4, 12.5Hz, CH$_E$$H_F$CH(C=CHSiMe$_3$)), 1.96 – 1.68 (5H, m, CH$_2$, CH$_2$, CH_IH$_J$), 1.54 (1H, m, CH$_I$$H_J$), 1.28 (1H, m, CH$_G$$H_H$), 0.18 (9H, s, Si(CH$_3$)$_3$)

^{13}C NMR (100MHz, $CDCl_3$) δ: 161.5 (0), 151.9 (0), 118.0 (1), 112.5 (2), 86.8 (1), 80.5 (2), 72.5 (0), 50.5 (1), 40.6 (1), 37.1 (2), 36.1 (2), 35.1 (2), 33.3 (2), 23.1 (2), 0.5 (3)

LRMS (CI) m/z: 275 $(M+H-H_2O)^+$ [100%]

HRMS (EI) m/z: $C_{17}H_{28}O_2Si$ $(M)^+$ requires 292.18586, found 292.18573 [34%]; $C_{17}H_{26}OSi$ $(M-H_2O)^+$ requires 274.17529, found 274.17607 [66%].

X-ray : see appendix.

Chapter Seven

7 References

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Appendix

X-ray data for compound **400**

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Table 1. Crystal data and structure refinement.

Identification code	**01SOT171**	
Empirical formula	$C_{13}H_{20}O_2$	
Formula weight	208.29	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 8.1393(3) Å	
	b = 11.0009(4) Å	β = 104.450(2)°
	c = 13.2527(6) Å	
Volume	1149.10(8) Å^3	
Z	4	
Density (calculated)	1.204 Mg / m^3	
Absorption coefficient	0.079 mm^{-1}	
F(000)	456	
Crystal	Colourless Plate	
Crystal size	0.3 x 0.2 x 0.04 mm^3	
θ range for data collection	3.17 – 25.03°	
Index ranges	$-9 \le h \le 9$, $-13 \le k \le 13$, $-15 \le l \le 15$	
Reflections collected	8084	
Independent reflections	2022 [R_{int} = 0.0718]	
Completeness to θ = 25.03°	99.5 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2022 / 0 / 217	
Goodness-of-fit on F^2	1.028	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0378, $wR2$ = 0.0883	
R indices (all data)	$R1$ = 0.0553, $wR2$ = 0.0969	
Extinction coefficient	0.016(3)	
Largest diff. peak and hole	0.229 and -0.235 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. **A51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) **A46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were located from the difference map and fully refined.

X-ray data for compound **400**

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [Å$^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U_{eq}	*S.o.f.*
C1	7069(2)	10310(1)	2563(1)	18(1)	1
C2	6400(2)	10955(1)	3392(1)	22(1)	1
C3	7310(2)	10440(1)	4458(1)	24(1)	1
C4	7171(2)	9059(1)	4510(1)	27(1)	1
C5	7771(2)	8416(1)	3643(1)	23(1)	1
C6	6817(2)	8935(1)	2604(1)	20(1)	1
C7	7250(2)	8515(1)	1600(1)	19(1)	1
C8	9080(2)	8152(1)	1714(1)	21(1)	1
C9	9948(2)	8400(2)	826(1)	26(1)	1
C10	10475(2)	9028(1)	1828(1)	22(1)	1
C11	11526(2)	9794(2)	2418(1)	28(1)	1
C12	6324(2)	10583(1)	1420(1)	20(1)	1
C13	6994(2)	11700(1)	994(1)	27(1)	1
O1	6835(1)	9542(1)	898(1)	20(1)	1
O2	4548(1)	10608(1)	1233(1)	24(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–C12	1.515(2)	C7–C8	1.5133(19)
C1–C2	1.518(2)	C8–C10	1.467(2)
C1–C6	1.5292(19)	C8–C9	1.541(2)
C2–C3	1.531(2)	C9–C10	1.464(2)
C3–C4	1.526(2)	C10–C11	1.311(2)
C4–C5	1.530(2)	C12–O2	1.4048(17)
C5–C6	1.514(2)	C12–O1	1.4513(17)
C6–C7	1.530(2)	C12–C13	1.510(2)
C7–O1	1.4480(17)		
C12–C1–C2	120.30(11)	C10–C8–C9	58.17(10)
C12–C1–C6	101.98(11)	C7–C8–C9	120.30(13)
C2–C1–C6	111.16(12)	C10–C9–C8	58.41(10)
C1–C2–C3	108.44(12)	C11–C10–C9	147.57(15)
C4–C3–C2	112.73(13)	C11–C10–C8	148.91(15)
C3–C4–C5	112.63(12)	C9–C10–C8	63.42(10)
C6–C5–C4	108.76(12)	O2–C12–O1	109.62(11)
C5–C6–C1	111.25(12)	O2–C12–C13	111.75(12)
C5–C6–C7	119.98(12)	O1–C12–C13	106.96(12)
C1–C6–C7	101.88(11)	O2–C12–C1	108.50(11)
O1–C7–C8	109.64(11)	O1–C12–C1	103.24(10)
O1–C7–C6	104.78(11)	C13–C12–C1	116.31(12)
C8–C7–C6	115.28(12)	C7–O1–C12	111.02(10)
C10–C8–C7	123.64(13)		

X-ray data for compound **400**

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	14(1)	20(1)	19(1)	0(1)	2(1)	0(1)
C2	21(1)	23(1)	22(1)	−3(1)	5(1)	2(1)
C3	27(1)	26(1)	18(1)	−3(1)	5(1)	2(1)
C4	32(1)	30(1)	18(1)	3(1)	7(1)	−1(1)
C5	28(1)	19(1)	21(1)	2(1)	6(1)	−1(1)
C6	18(1)	22(1)	19(1)	−1(1)	4(1)	−4(1)
C7	20(1)	18(1)	19(1)	0(1)	3(1)	−2(1)
C8	23(1)	18(1)	21(1)	1(1)	4(1)	4(1)
C9	23(1)	31(1)	25(1)	−2(1)	8(1)	5(1)
C10	19(1)	24(1)	23(1)	3(1)	5(1)	6(1)
C11	21(1)	32(1)	29(1)	−1(1)	5(1)	−1(1)
C12	16(1)	22(1)	20(1)	−2(1)	4(1)	3(1)
C13	32(1)	27(1)	23(1)	4(1)	6(1)	1(1)
O1	21(1)	24(1)	16(1)	0(1)	4(1)	4(1)
O2	17(1)	37(1)	18(1)	−1(1)	2(1)	6(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	x	y	z	U_{eq}	*S.o.f.*
H01	4130(20)	10617(17)	546(18)	44(5)	1
H1	8300(18)	10463(11)	2719(11)	11(3)	1
H2A	6560(18)	11843(14)	3373(12)	25(4)	1
H2B	5200(20)	10830(14)	3275(11)	22(4)	1
H3A	8530(20)	10656(13)	4605(12)	26(4)	1
H3B	6878(19)	10843(15)	5017(13)	29(4)	1
H4A	7820(20)	8769(15)	5204(14)	32(4)	1
H4B	5970(20)	8836(15)	4431(13)	31(4)	1
H5A	8990(20)	8572(13)	3731(11)	18(4)	1
H5B	7590(18)	7541(16)	3669(12)	30(4)	1
H6	5609(19)	8779(13)	2530(11)	17(4)	1
H7	6521(17)	7835(13)	1288(11)	16(3)	1
H8	9390(17)	7413(15)	2088(12)	20(4)	1
H9A	9260(20)	8855(14)	237(13)	25(4)	1
H9B	10680(20)	7741(15)	645(13)	34(4)	1
H11A	12400(30)	10199(17)	2153(15)	47(5)	1
H11B	11460(20)	9953(16)	3165(15)	37(4)	1
H13A	8260(20)	11659(14)	1125(13)	31(4)	1
H13B	6700(20)	12442(17)	1362(14)	39(5)	1
H13C	6499(19)	11764(15)	239(14)	30(4)	1

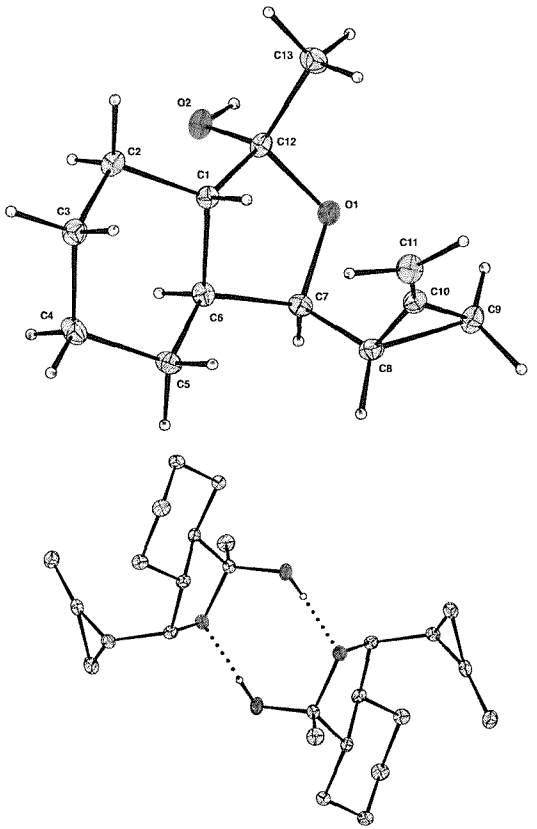
Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*HA)
O2–H01···O1^{i}	0.89(2)	1.89(2)	2.7727(15)	173.7(18)

X-ray data for compound **400**

Symmetry transformations used to generate equivalent atoms:

(i) −x+1,−y+2,−z



X-ray data for compound **403**

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Table 1. Crystal data and structure refinement.

Identification code	01sot183	
Empirical formula	$C_{13}H_{20}O_2$	
Formula weight	208.29	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.0079(2) Å	α = 77.6060(10)°
	b = 9.6889(2) Å	β = 79.0170(10)°
	c = 14.5251(4) Å	γ = 75.928(2)°
Volume	1188.13(5) Å^3	
Z	4	
Density (calculated)	1.164 Mg / m^3	
Absorption coefficient	0.076 mm^{-1}	
F(000)	456	
Crystal	Colourless plate	
Crystal size	0.10 × 0.10 × 0.03 mm^3	
θ range for data collection	2.94 – 25.03°	
Index ranges	$-10 \le h \le 10$, $-11 \le k \le 11$, $-17 \le l \le 17$	
Reflections collected	14115	
Independent reflections	4112 [R_{int} = 0.0452]	
Completeness to θ = 25.03°	97.8 %	
Max. and min. transmission	0.9977 and 0.9924	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4112 / 0 / 432	
Goodness-of-fit on F^2	1.022	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0379, $wR2$ = 0.0909	
R indices (all data)	$R1$ = 0.0542, $wR2$ = 0.0995	
Extinction coefficient	0.020(4)	
Largest diff. peak and hole	0.213 and –0.173 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. **A51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) **A46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were located from the difference map and fully refined.

X-ray data for compound **403**

Relative chirality: S = C1 C6 C9 C20 C23 , R = C7 C10 C14 C19 C22

X-ray data for compound **403**

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
O2	3882(1)	1159(1)	704(1)	23(1)	1
O1	4944(1)	−1282(1)	1219(1)	22(1)	1
C6	2978(2)	52(2)	2226(1)	19(1)	1
C1	4013(2)	1033(2)	2325(1)	21(1)	1
C7	3557(2)	−226(1)	1214(1)	19(1)	1
C10	2821(2)	3384(2)	1300(1)	24(1)	1
C5	2987(2)	−1209(2)	3058(1)	23(1)	1
C8	2434(2)	−585(2)	695(1)	24(1)	1
C9	4069(2)	2034(2)	1355(1)	21(1)	1
C3	3433(2)	424(2)	4090(1)	28(1)	1
C13	3636(2)	5454(2)	1917(1)	29(1)	1
C12	3215(2)	4734(2)	1380(1)	26(1)	1
C4	2467(2)	−621(2)	3992(1)	27(1)	1
C2	3470(2)	1664(2)	3234(1)	25(1)	1
C11	2984(2)	4599(2)	434(1)	33(1)	1
O4	6644(1)	4298(1)	4189(1)	26(1)	1
O3	5732(1)	6656(1)	4496(1)	29(1)	1
C22	7099(2)	4238(2)	3178(1)	22(1)	1
C19	8166(2)	6014(2)	3557(1)	20(1)	1
C14	7506(2)	5704(2)	2750(1)	21(1)	1
C23	8378(2)	2933(2)	3061(1)	22(1)	1
C18	8413(2)	7550(2)	3364(1)	24(1)	1
C17	9479(2)	7786(2)	2414(1)	26(1)	1
C20	7045(2)	5531(2)	4425(1)	23(1)	1
C15	8583(2)	5896(2)	1808(1)	25(1)	1
C25	8406(2)	2100(2)	2320(1)	27(1)	1
C16	8874(2)	7434(2)	1595(1)	29(1)	1
C24	7960(2)	1438(2)	3307(1)	29(1)	1
C26	8620(2)	2033(2)	1415(1)	40(1)	1
C21	7681(2)	5007(2)	5357(1)	33(1)	1

Table 3. Bond lengths [Å] and angles [°].

O2–C9	1.4545(16)	C3–C2	1.534(2)
O2–C7	1.4552(16)	C13–C12	1.309(2)
O1–C7	1.4090(16)	C12–C11	1.466(2)
C6–C7	1.5211(19)	O4–C20	1.4526(17)
C6–C5	1.5231(19)	O4–C22	1.4574(17)
C6–C1	1.5272(19)	O3–C20	1.4048(17)
C1–C2	1.520(2)	C22–C23	1.5045(19)
C1–C9	1.529(2)	C22–C14	1.525(2)
C7–C8	1.5119(19)	C19–C18	1.5173(19)
C10–C12	1.469(2)	C19–C20	1.5228(19)
C10–C9	1.502(2)	C19–C14	1.5242(19)
C10–C11	1.539(2)	C14–C15	1.5226(19)
C5–C4	1.531(2)	C23–C25	1.471(2)
C3–C4	1.529(2)	C23–C24	1.536(2)

X-ray data for compound **403**

C18–C17	1.532(2)	C15–C16	1.532(2)
C17–C16	1.530(2)	C25–C26	1.305(2)
C20–C21	1.508(2)	C25–C24	1.463(2)
C9–O2–C7	111.29(9)	C20–O4–C22	111.22(10)
C7–C6–C5	120.18(12)	O4–C22–C23	109.09(11)
C7–C6–C1	101.87(11)	O4–C22–C14	103.73(10)
C5–C6–C1	110.92(11)	C23–C22–C14	116.22(11)
C2–C1–C6	111.49(12)	C18–C19–C20	119.20(12)
C2–C1–C9	120.07(12)	C18–C19–C14	111.74(12)
C6–C1–C9	102.13(11)	C20–C19–C14	101.91(11)
O1–C7–O2	109.59(10)	C15–C14–C19	111.56(11)
O1–C7–C8	111.58(11)	C15–C14–C22	120.28(12)
O2–C7–C8	106.36(11)	C19–C14–C22	101.82(11)
O1–C7–C6	108.48(11)	C25–C23–C22	119.27(12)
O2–C7–C6	102.89(10)	C25–C23–C24	58.16(10)
C8–C7–C6	117.40(12)	C22–C23–C24	118.22(12)
C12–C10–C9	118.07(13)	C19–C18–C17	108.49(12)
C12–C10–C11	58.28(10)	C16–C17–C18	112.53(12)
C9–C10–C11	118.26(13)	O3–C20–O4	110.00(11)
C6–C5–C4	109.19(12)	O3–C20–C21	111.64(12)
O2–C9–C10	109.02(11)	O4–C20–C21	106.66(12)
O2–C9–C1	104.24(10)	O3–C20–C19	108.00(11)
C10–C9–C1	114.83(12)	O4–C20–C19	103.48(10)
C4–C3–C2	112.36(13)	C21–C20–C19	116.64(12)
C13–C12–C11	149.11(15)	C14–C15–C16	108.59(12)
C13–C12–C10	147.23(14)	C26–C25–C24	148.64(16)
C11–C12–C10	63.26(10)	C26–C25–C23	148.15(16)
C3–C4–C5	112.38(12)	C24–C25–C23	63.15(10)
C1–C2–C3	108.98(12)	C17–C16–C15	112.25(12)
C12–C11–C10	58.46(10)	C25–C24–C23	58.69(10)

Table 4. Anisotropic displacement parameters [$Å^2$× 10^3]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O2	31(1)	17(1)	19(1)	−4(1)	0(1)	−7(1)
O1	22(1)	21(1)	22(1)	−6(1)	−1(1)	0(1)
C6	18(1)	20(1)	19(1)	−4(1)	−2(1)	−2(1)
C1	19(1)	19(1)	24(1)	−5(1)	−5(1)	−1(1)
C7	18(1)	15(1)	22(1)	−2(1)	0(1)	−3(1)
C10	26(1)	20(1)	25(1)	−3(1)	−5(1)	−3(1)
C5	25(1)	23(1)	22(1)	−2(1)	−4(1)	−7(1)
C8	25(1)	26(1)	20(1)	−5(1)	−2(1)	−7(1)
C9	21(1)	20(1)	23(1)	−7(1)	−1(1)	−5(1)
C3	34(1)	30(1)	21(1)	−8(1)	−6(1)	−2(1)
C13	36(1)	20(1)	30(1)	−6(1)	−5(1)	−2(1)
C12	32(1)	19(1)	24(1)	−2(1)	−4(1)	0(1)
C4	30(1)	28(1)	20(1)	−2(1)	−2(1)	−4(1)
C2	26(1)	24(1)	25(1)	−7(1)	−7(1)	−2(1)

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C11	49(1)	24(1)	26(1)	−2(1)	−11(1)	−4(1)
O4	29(1)	23(1)	24(1)	−7(1)	6(1)	−11(1)
O3	26(1)	22(1)	30(1)	−5(1)	8(1)	−2(1)
C22	19(1)	25(1)	23(1)	−6(1)	−2(1)	−5(1)
C19	20(1)	19(1)	21(1)	−5(1)	−2(1)	−3(1)
C14	18(1)	21(1)	24(1)	−4(1)	−2(1)	−3(1)
C23	20(1)	22(1)	25(1)	−6(1)	−2(1)	−6(1)
C18	25(1)	22(1)	26(1)	−6(1)	0(1)	−5(1)
C17	22(1)	22(1)	31(1)	−3(1)	2(1)	−7(1)
C20	24(1)	19(1)	24(1)	−6(1)	2(1)	−4(1)
C15	25(1)	29(1)	20(1)	−6(1)	−1(1)	−6(1)
C25	25(1)	23(1)	33(1)	−9(1)	−8(1)	2(1)
C16	26(1)	30(1)	25(1)	1(1)	2(1)	−6(1)
C24	29(1)	23(1)	35(1)	−6(1)	−3(1)	−6(1)
C26	48(1)	35(1)	35(1)	−14(1)	−15(1)	9(1)
C21	40(1)	34(1)	23(1)	−3(1)	−2(1)	−8(1)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2$ × 10^3].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H4A	1362(19)	−98(17)	4022(11)	28(4)	1
H17B	9642(17)	8781(18)	2254(11)	27(4)	1
H2B	2408(18)	2286(16)	3206(10)	24(4)	1
H19	9180(17)	5340(15)	3604(10)	18(3)	1
H14	6509(17)	6405(15)	2680(10)	20(4)	1
H6	1929(17)	615(15)	2217(9)	15(3)	1
H15B	9581(19)	5180(17)	1858(11)	30(4)	1
H13A	3933(18)	6379(18)	1664(11)	31(4)	1
H11A	3870(20)	4404(18)	−45(13)	41(5)	1
H17A	10528(19)	7135(17)	2468(11)	28(4)	1
H22	6168(16)	4096(14)	2937(10)	17(3)	1
H23	9371(18)	2970(16)	3211(11)	25(4)	1
H8C	2165(18)	−1524(18)	1015(11)	33(4)	1
H3A	4511(19)	−124(17)	4137(11)	33(4)	1
H18B	7410(19)	8230(17)	3335(11)	28(4)	1
H9	5107(17)	2283(15)	1126(10)	20(4)	1
H8B	1478(19)	178(17)	682(10)	28(4)	1
H10	1735(19)	3240(16)	1552(11)	29(4)	1
H1	5039(17)	419(15)	2370(10)	18(3)	1
H16B	7876(19)	8120(18)	1482(11)	33(4)	1
H24B	6900(20)	1395(16)	3532(11)	32(4)	1
H18A	8894(17)	7749(15)	3888(11)	26(4)	1
H145	8146(16)	5678(16)	1283(11)	25(4)	1
H8A	2890(18)	−663(16)	50(12)	29(4)	1
H13B	3648(18)	5066(18)	2619(13)	36(4)	1
H2A	4157(18)	2309(16)	3323(11)	29(4)	1
H5B	2284(17)	−1830(16)	2998(10)	26(4)	1
H3B	3018(17)	828(16)	4685(11)	27(4)	1
H16A	9615(19)	7545(17)	1011(12)	32(4)	1
H4B	2514(18)	−1424(18)	4546(12)	32(4)	1
H5A	4047(19)	−1805(17)	3040(11)	29(4)	1

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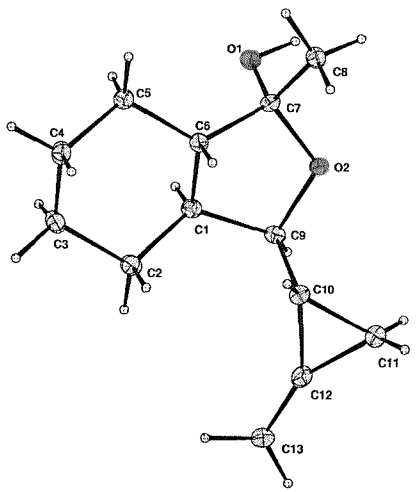
H11B	2030(20)	5120(20)	204(13)	44(5)	1	
H21B				6860(20)		4630(19)
				5866(13)		46(5) 1
H1B	5340(20)	−1350(20)	601(15)	51(5)	1	
H21A	8630(20)	4248(18)	5282(11)	32(4)	1	
H26B	8480(20)	1170(20)	1180(13)	54(5)	1	
H21C	7950(20)	5830(20)	5561(12)	42(5)	1	
H26A	8970(20)	2810(20)	935(13)	40(5)	1	
H24A	8686(19)	604(19)	3618(12)	36(4)	1	
H3C	5000(20)	6350(20)	4982(16)	63(6)	1	

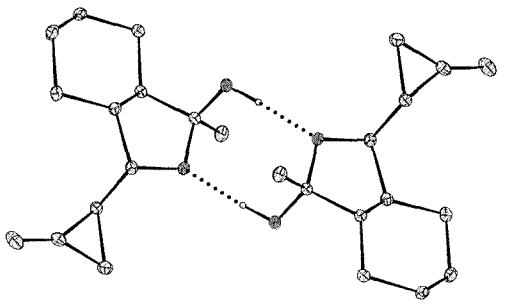
Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*HA)
O1–H1B···O2^{i}	0.91(2)	1.88(2)	2.7798(13)	170.7(17)
O3–H3C···O4^{ii}	0.92(2)	1.87(2)	2.7799(14)	170.8(18)

Symmetry transformations used to generate equivalent atoms:
(i) −x+1,−y,−z (ii) −x+1,−y+1,−z+1



X-ray data for compound **403**



X-ray data for compound **424**

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Table 1. Crystal data and structure refinement.

Identification code	**01sot194**	
Empirical formula	$C_{13}H_{22}O_2$	
Formula weight	210.31	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*C2/c*	
Unit cell dimensions	a = 15.9901(5) Å	α = 90°
	b = 12.0579(5) Å	β = 105.651(4)°
	c = 12.9800(5) Å	γ = 90°
Volume	2409.84(16) Å^3	
Z	8	
Density (calculated)	1.159 Mg / m^3	
Absorption coefficient	0.076 mm^{-1}	
F(000)	928	
Crystal	Needle; colourless	
Crystal size	0.30 x 0.04 x 0.04 mm^3	
θ range for data collection	3.38 – 27.46°	
Index ranges	$-20 \le h \le 20$, $-15 \le k \le 15$, $-13 \le l \le 14$	
Reflections collected	11430	
Independent reflections	2514 [R_{int} = 0.0591]	
Completeness to θ = 27.46°	91.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9970 and 0.9776	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2514 / 0 / 141	
Goodness-of-fit on F^2	1.020	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0543, $wR2$ = 0.1249	
R indices (all data)	$R1$ = 0.1037, $wR2$ = 0.1471	
Extinction coefficient	0.0032(11)	
Largest diff. peak and hole	0.238 and –0.416 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) **A46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Further information: http://www.soton.ac.uk/~xservice/strat.htm

Special details:

Chirality: C1 = R, C6 = R, C7 = R, C9 = S, C10 = S.

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [Å$^2 \times 10^3$] and site occupancy factors.

X-ray data for compound **424**

U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	1080(1)	3972(1)	−91(1)	21(1)	1
C2	1660(1)	4300(2)	−803(2)	26(1)	1
C3	2410(1)	5041(2)	−223(2)	31(1)	1
C4	2931(1)	4517(2)	811(2)	30(1)	1
C5	2355(1)	4185(2)	1523(2)	29(1)	1
C6	1619(1)	3414(1)	935(1)	21(1)	1
C7	1043(1)	2994(1)	1639(2)	23(1)	1
C8	351(1)	2239(1)	952(1)	22(1)	1
C9	−237(1)	2820(2)	−1(1)	24(1)	1
C10	321(1)	3263(2)	−703(1)	22(1)	1
C11	1578(1)	2438(2)	2654(2)	35(1)	1
C12	293(1)	1170(2)	1147(2)	31(1)	1
C13	−985(1)	2124(2)	−650(2)	35(1)	1
O1	629(1)	3939(1)	1970(1)	37(1)	1
O2	−226(1)	3880(1)	−1573(1)	42(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–C10	1.521(2)
C1–C2	1.529(2)
C1–C6	1.534(2)
C1–H1	1.0000
C2–C3	1.522(3)
C2–H2A	0.9900
C2–H2B	0.9900
C3–C4	1.514(3)
C3–H3A	0.9900
C3–H3B	0.9900
C4–C5	1.524(3)
C4–H4A	0.9900
C4–H4B	0.9900
C5–C6	1.531(2)
C5–H5A	0.9900
C5–H5B	0.9900
C6–C7	1.547(2)
C6–H6	1.0000
C7–O1	1.441(2)
C7–C11	1.519(3)
C7–C8	1.522(3)
C8–C12	1.322(3)
C8–C9	1.509(2)
C9–C13	1.517(3)
C9–C10	1.533(2)
C9–H9	1.0000
C10–O2	1.436(2)
C10–H10	1.0000
C11–H11A	0.9800
C11–H11B	0.9800
C11–H11C	0.9800

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C12–H12A	0.9500
C12–H12B	0.9500
C13–H13A	0.9800
C13–H13B	0.9800
C13–H13C	0.9800
O1–H1A	0.8400
O2–H2	0.8400
C10–C1–C2	111.04(14)
C10–C1–C6	112.94(14)
C2–C1–C6	110.34(14)
C10–C1–H1	107.4
C2–C1–H1	107.4
C6–C1–H1	107.4
C3–C2–C1	112.23(15)
C3–C2–H2A	109.2
C1–C2–H2A	109.2
C3–C2–H2B	109.2
C1–C2–H2B	109.2
H2A–C2–H2B	107.9
C4–C3–C2	111.42(15)
C4–C3–H3A	109.3
C2–C3–H3A	109.3
C4–C3–H3B	109.3
C2–C3–H3B	109.3
H3A–C3–H3B	108.0
C3–C4–C5	111.65(16)
C3–C4–H4A	109.3
C5–C4–H4A	109.3
C3–C4–H4B	109.3
C5–C4–H4B	109.3
H4A–C4–H4B	108.0
C4–C5–C6	111.49(15)
C4–C5–H5A	109.3
C6–C5–H5A	109.3
C4–C5–H5B	109.3
C6–C5–H5B	109.3
H5A–C5–H5B	108.0
C5–C6–C1	110.05(14)
C5–C6–C7	113.87(14)
C1–C6–C7	111.80(14)
C5–C6–H6	106.9
C1–C6–H6	106.9
C7–C6–H6	106.9
O1–C7–C11	106.68(15)
O1–C7–C8	109.12(15)
C11–C7–C8	113.24(15)
O1–C7–C6	108.12(14)
C11–C7–C6	111.78(15)
C8–C7–C6	107.76(14)
C12–C8–C9	123.32(17)

X-ray data for compound **424**

C12–C8–C7	123.26(17)
C9–C8–C7	113.37(15)
C8–C9–C13	114.96(15)
C8–C9–C10	108.41(15)
C13–C9–C10	111.15(15)
C8–C9–H9	107.3
C13–C9–H9	107.3
C10–C9–H9	107.3
O2–C10–C1	110.53(14)
O2–C10–C9	108.65(14)
C1–C10–C9	113.33(14)
O2–C10–H10	108.1
C1–C10–H10	108.1
C9–C10–H10	108.1
C7–C11–H11A	109.5
C7–C11–H11B	109.5
H11A–C11–H11B	109.5
C7–C11–H11C	109.5
H11A–C11–H11C	109.5
H11B–C11–H11C	109.5
C8–C12–H12A	120.0
C8–C12–H12B	120.0
H12A–C12–H12B	120.0
C9–C13–H13A	109.5
C9–C13–H13B	109.5
H13A–C13–H13B	109.5
C9–C13–H13C	109.5
H13A–C13–H13C	109.5
H13B–C13–H13C	109.5
C7–O1–H1A	109.5
C10–O2–H2	109.5

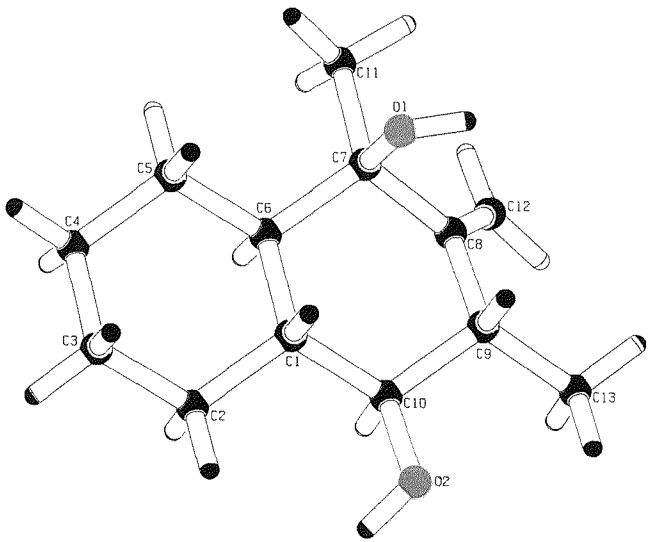
Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	22(1)	17(1)	26(1)	2(1)	8(1)	2(1)
C2	26(1)	28(1)	26(1)	5(1)	9(1)	0(1)
C3	31(1)	28(1)	38(1)	2(1)	15(1)	−5(1)
C4	23(1)	31(1)	36(1)	−6(1)	10(1)	−7(1)
C5	25(1)	34(1)	28(1)	−5(1)	7(1)	−5(1)
C6	19(1)	20(1)	23(1)	−2(1)	7(1)	0(1)
C7	24(1)	24(1)	24(1)	−2(1)	8(1)	0(1)
C8	25(1)	22(1)	21(1)	−1(1)	11(1)	1(1)
C9	21(1)	22(1)	29(1)	1(1)	7(1)	−2(1)
C10	21(1)	23(1)	21(1)	5(1)	3(1)	3(1)
C11	36(1)	45(1)	22(1)	5(1)	5(1)	−5(1)
C12	39(1)	26(1)	29(1)	2(1)	9(1)	−4(1)

X-ray data for compound **424**

C13	28(1)	39(1)	35(1)	4(1)	2(1)	−10(1)
O1	30(1)	37(1)	51(1)	−22(1)	23(1)	−8(1)
O2	24(1)	53(1)	41(1)	28(1)	−3(1)	−4(1)



X-ray data for compound **502**

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Table 1. Crystal data and structure refinement.

Identification code	**02sot041**	
Empirical formula	$C_{16}H_{22}N_2O_3S$	
Formula weight	322.42	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P*–1	
Unit cell dimensions	a = 8.4521(2) Å	α = 94.629(2)°
	b = 8.5199(2) Å	β = 91.170(2)°
	c = 11.5427(3) Å	γ = 96.0610(10)°
Volume	823.51(3) Å^3	
Z	2	
Density (calculated)	1.300 Mg / m^3	
Absorption coefficient	0.210 mm^{-1}	
F(000)	344	
Crystal	Block; colourless	
Crystal size	0.24 × 0.24 × 0.20 mm^3	
θ range for data collection	2.96 – 27.49°	
Index ranges	$-10 \le h \le 10$, $-11 \le k \le 11$, $-14 \le l \le 14$	
Reflections collected	10641	
Independent reflections	3602 [R_{int} = 0.0387]	
Completeness to θ = 27.49°	95.5 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9591 and 0.9512	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3602 / 0 / 207	
Goodness-of-fit on F^2	1.030	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0397, $wR2$ = 0.0993	
R indices (all data)	$R1$ = 0.0467, $wR2$ = 0.1050	
Extinction coefficient	0.019(4)	
Largest diff. peak and hole	0.556 and –0.406 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. **A51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) **A46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Further information: http://www.soton.ac.uk/~xservice/strat.htm

Special details:

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*

X-ray data for compound **502**

C1	2399(2)	9246(2)	9767(2)	33(1)	1
C2	2000(2)	10728(2)	10438(2)	23(1)	1
C3	1824(2)	10783(2)	11643(2)	24(1)	1
C4	1535(2)	12170(2)	12273(1)	22(1)	1
C5	1399(2)	13520(2)	11687(1)	18(1)	1
C6	1498(2)	13479(2)	10487(1)	20(1)	1
C7	1805(2)	12085(2)	9877(1)	23(1)	1
C8	–3263(2)	14446(2)	12364(1)	19(1)	1
C9	–4463(2)	14042(2)	11388(1)	24(1)	1
C10	–3836(2)	14379(2)	13584(1)	20(1)	1
C11	–4047(2)	12686(2)	13970(1)	22(1)	1
C12	–2535(2)	11846(2)	13898(1)	23(1)	1
C13	–2797(2)	10213(2)	14299(2)	29(1)	1
C14	–1767(2)	8951(2)	13806(2)	37(1)	1
C15	–3439(2)	8925(2)	13432(2)	31(1)	1
C16	–4640(2)	8333(2)	12753(2)	35(1)	1
N1	–676(1)	15157(2)	12980(1)	19(1)	1
N2	–1824(1)	14808(2)	12061(1)	19(1)	1
O1	2126(1)	15441(1)	13529(1)	24(1)	1
O2	1295(1)	16554(1)	11727(1)	25(1)	1
O3	–1219(1)	12778(1)	14517(1)	23(1)	1
S1	1131(1)	15310(1)	12487(1)	18(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–C2	1.500(2)
C2–C7	1.393(2)
C2–C3	1.399(2)
C3–C4	1.384(2)
C4–C5	1.394(2)
C5–C6	1.388(2)
C5–S1	1.7559(16)
C6–C7	1.383(2)
C8–N2	1.2849(19)
C8–C9	1.495(2)
C8–C10	1.502(2)
C10–C11	1.537(2)
C11–C12	1.529(2)
C12–O3	1.4376(19)
C12–C13	1.497(2)
C13–C15	1.474(2)
C13–C14	1.536(3)
C14–C15	1.466(3)
C15–C16	1.303(3)
N1–N2	1.4150(17)
N1–S1	1.6367(13)
O1–S1	1.4435(11)
O2–S1	1.4264(11)
C7–C2–C3	118.45(15)
C7–C2–C1	120.75(15)
C3–C2–C1	120.79(15)

X-ray data for compound **502**

C4–C3–C2	120.95(15)
C3–C4–C5	118.99(15)
C6–C5–C4	121.19(15)
C6–C5–S1	119.48(12)
C4–C5–S1	119.32(12)
C7–C6–C5	118.76(14)
C6–C7–C2	121.56(15)
N2–C8–C9	115.55(14)
N2–C8–C10	126.64(14)
C9–C8–C10	117.81(13)
C8–C10–C11	112.82(13)
C12–C11–C10	113.92(13)
O3–C12–C13	111.67(13)
O3–C12–C11	111.40(13)
C13–C12–C11	111.79(14)
C15–C13–C12	117.20(15)
C15–C13–C14	58.25(12)
C12–C13–C14	118.83(16)
C15–C14–C13	58.77(12)
C16–C15–C14	150.09(19)
C16–C15–C13	146.59(18)
C14–C15–C13	62.97(13)
N2–N1–S1	111.20(10)
C8–N2–N1	115.90(13)
O2–S1–O1	119.06(7)
O2–S1–N1	109.06(7)
O1–S1–N1	103.43(7)
O2–S1–C5	108.66(7)
O1–S1–C5	108.15(7)
N1–S1–C5	107.97(7)

Symmetry transformations used to generate equivalent atoms:

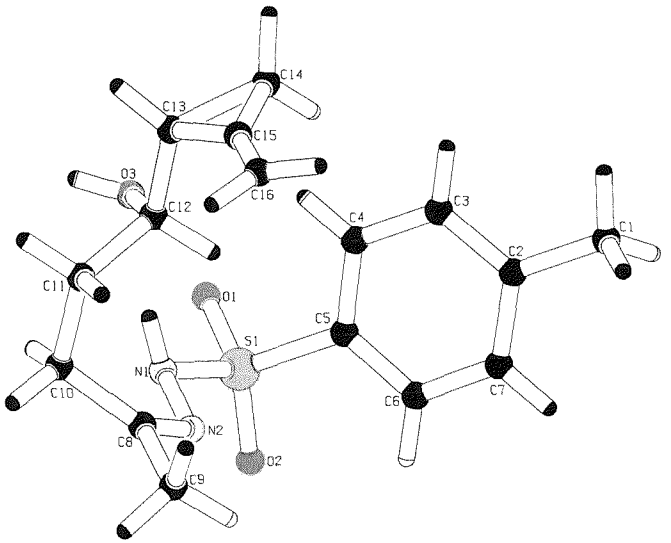
Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	34(1)	26(1)	38(1)	−4(1)	9(1)	3(1)
C2	17(1)	24(1)	27(1)	−1(1)	3(1)	0(1)
C3	23(1)	22(1)	28(1)	5(1)	3(1)	4(1)
C4	21(1)	27(1)	20(1)	4(1)	2(1)	2(1)
C5	12(1)	21(1)	21(1)	2(1)	0(1)	0(1)
C6	15(1)	25(1)	20(1)	4(1)	0(1)	1(1)
C7	20(1)	29(1)	20(1)	1(1)	2(1)	0(1)
C8	16(1)	16(1)	24(1)	2(1)	0(1)	4(1)
C9	16(1)	29(1)	28(1)	4(1)	−4(1)	1(1)
C10	16(1)	20(1)	24(1)	2(1)	3(1)	4(1)
C11	21(1)	22(1)	24(1)	4(1)	1(1)	1(1)
C12	24(1)	21(1)	24(1)	1(1)	−3(1)	3(1)
C13	36(1)	26(1)	27(1)	5(1)	2(1)	6(1)

X-ray data for compound **502**

C14	36(1)	24(1)	51(1)	1(1)	−2(1)	10(1)
C15	34(1)	19(1)	39(1)	2(1)	6(1)	4(1)
C16	36(1)	25(1)	42(1)	0(1)	2(1)	0(1)
N1	14(1)	24(1)	18(1)	2(1)	−1(1)	2(1)
N2	16(1)	21(1)	19(1)	2(1)	−3(1)	2(1)
O1	16(1)	32(1)	23(1)	−5(1)	−4(1)	1(1)
O2	25(1)	21(1)	31(1)	5(1)	3(1)	−2(1)
O3	23(1)	24(1)	21(1)	−1(1)	−2(1)	4(1)
S1	13(1)	21(1)	20(1)	−1(1)	0(1)	0(1)

X-ray data for compound **502**



X-ray data for compound **523**

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Table 1. Crystal data and structure refinement.

Identification code	**02sot062**	
Empirical formula	$C_9H_{16}O_2$	
Formula weight	156.22	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*Cc*	
Unit cell dimensions	a = 8.3316(6) Å	α = 90°
	b = 12.8619(6) Å	β = 94.024(7)°
	c = 8.2215(5) Å	γ = 90°
Volume	878.85(9) Å^3	
Z	4	
Density (calculated)	1.181 Mg / m^3	
Absorption coefficient	0.081 mm^{-1}	
F(000)	344	
Crystal	Needle; Colourless	
Crystal size	0.15 x 0.01 x 0.005 mm^3	
θ range for data collection	2.92 – 25.02°	
Index ranges	$-9 \le h \le 9$, $-15 \le k \le 15$, $-9 \le l \le 9$	
Reflections collected	6168	
Independent reflections	1473 [R_{int} = 0.1355]	
Completeness to θ = 25.02°	99.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9996 and 0.9879	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1473 / 2 / 104	
Goodness-of-fit on F^2	1.035	
Final R indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0727, *wR2* = 0.1456	
R indices (all data)	*R1* = 0.1501, *wR2* = 0.1824	
Absolute structure parameter	−1(4)	
Largest diff. peak and hole	0.280 and −0.242 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. **A51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) **A46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details:

All hydrogen atoms are fixed.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

X-ray data for compound **523**

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
O2	–210(5)	3993(3)	9288(4)	34(1)	1
O1	4408(5)	874(3)	10783(4)	34(1)	1
C1	3191(7)	1527(5)	9987(6)	25(2)	1
C4	1038(7)	3376(5)	10088(6)	31(2)	1
C5	424(7)	2285(5)	10301(7)	30(2)	1
C6	1723(7)	1559(5)	11015(6)	31(2)	1
C3	2530(7)	3407(5)	9095(6)	28(2)	1
C2	3798(8)	2624(5)	9726(6)	28(2)	1
C8	5339(8)	2845(5)	9996(7)	35(2)	1
C9	3143(8)	4514(5)	8979(8)	44(2)	1
C7	2762(7)	1001(4)	8351(6)	35(1)	1

Table 3. Bond lengths [Å] and angles [°].

O2–C4	1.432(6)	O2–C4–C5	109.2(5)
O2–H2	0.8400	O2–C4–C3	109.3(5)
O1–C1	1.438(7)	C5–C4–C3	112.4(5)
O1–H1	0.8400	O2–C4–H4	108.6
C1–C2	1.519(8)	C5–C4–H4	108.6
C1–C7	1.526(7)	C3–C4–H4	108.6
C1–C6	1.535(8)	C4–C5–C6	112.3(5)
C4–C5	1.508(8)	C4–C5–H5A	109.2
C4–C3	1.534(8)	C6–C5–H5A	109.2
C4–H4	1.0000	C4–C5–H5B	109.2
C5–C6	1.516(8)	C6–C5–H5B	109.2
C5–H5A	0.9900	H5A–C5–H5B	107.9
C5–H5B	0.9900	C5–C6–C1	112.2(5)
C6–H6A	0.9900	C5–C6–H6A	109.2
C6–H6B	0.9900	C1–C6–H6A	109.2
C3–C9	1.518(8)	C5–C6–H6B	109.2
C3–C2	1.524(8)	C1–C6–H6B	109.2
C3–H3	1.0000	H6A–C6–H6B	107.9
C2–C8	1.318(9)	C9–C3–C2	114.3(5)
C8–H8A	0.9500	C9–C3–C4	110.3(5)
C8–H8B	0.9500	C2–C3–C4	111.7(5)
C9–H9A	0.9800	C9–C3–H3	106.7
C9–H9B	0.9800	C2–C3–H3	106.7
C9–H9C	0.9800	C4–C3–H3	106.7
C7–H7A	0.9800	C8–C2–C1	120.4(6)
C7–H7B	0.9800	C8–C2–C3	124.0(6)
C7–H7C	0.9800	C1–C2–C3	115.6(5)
		C2–C8–H8A	120.0
C4–O2–H2	109.5	C2–C8–H8B	120.0
C1–O1–H1	109.5	H8A–C8–H8B	120.0
O1–C1–C2	112.1(5)	C3–C9–H9A	109.5
O1–C1–C7	104.8(5)	C3–C9–H9B	109.5
C2–C1–C7	110.3(5)	H9A–C9–H9B	109.5
O1–C1–C6	109.2(4)	C3–C9–H9C	109.5
C2–C1–C6	109.8(5)	H9A–C9–H9C	109.5
C7–C1–C6	110.5(5)	H9B–C9–H9C	109.5

X-ray data for compound **523**

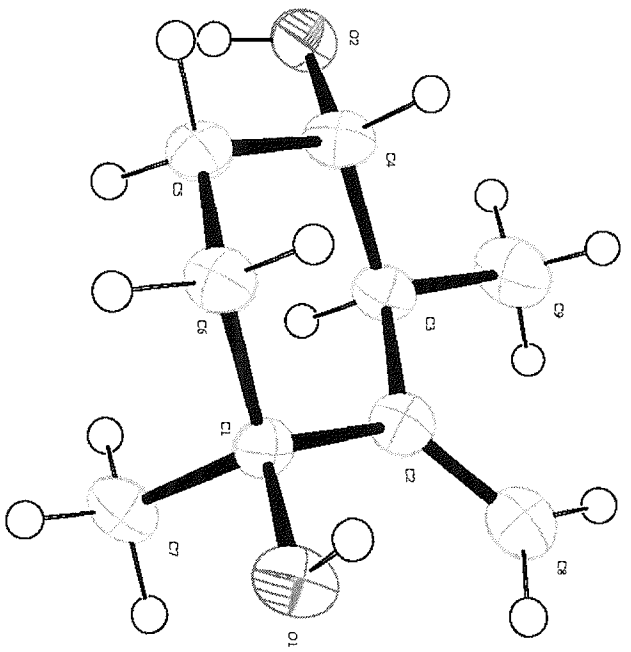
C1–C7–H7A	109.5	C1–C7–H7C	109.5
C1–C7–H7B	109.5	H7A–C7–H7C	109.5
H7A–C7–H7B	109.5	H7B–C7–H7C	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O2	36(3)	36(3)	30(2)	–2(2)	–2(2)	8(2)
O1	42(3)	37(3)	23(2)	3(2)	3(2)	12(2)
C1	24(4)	30(4)	19(3)	1(2)	–3(3)	3(3)
C4	35(4)	31(4)	27(4)	7(3)	10(3)	5(3)
C5	32(4)	33(4)	26(4)	2(3)	13(3)	–4(3)
C6	36(4)	27(4)	30(4)	4(3)	10(3)	0(3)
C3	32(4)	27(4)	25(3)	4(3)	0(3)	8(3)
C2	33(4)	32(4)	20(3)	3(3)	6(3)	0(3)
C8	43(4)	33(3)	30(3)	1(3)	7(3)	–1(3)
C9	58(4)	26(4)	49(4)	9(3)	14(3)	1(3)
C7	44(4)	32(3)	30(3)	–5(3)	4(3)	5(3)

X-ray data for compound **523**



X-ray data for compound **610**

University of Southampton · Department of Chemistry

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Table 1. Crystal data and structure refinement.

Identification code	**02sot116**	
Empirical formula	$C_{11}H_{18}O$	
Formula weight	166.25	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Tetragonal	
Space group	*I*–4	
Unit cell dimensions	a = 15.9792(6) Å	α = 90°
	b = 15.9792(6) Å	β = 90°
	c = 7.8963(7) Å	γ = 90°
Volume	2016.2(2) Å^3	
Z	8	
Density (calculated)	1.095 Mg / m^3	
Absorption coefficient	0.068 mm^{-1}	
F(000)	736	
Crystal	Block; colourless	
Crystal size	0.20 × 0.08 × 0.06 mm^3	
θ range for data collection	3.85 – 27.45°	
Index ranges	$-18 \le h \le 19$, $-17 \le k \le 20$, $-9 \le l \le 10$	
Reflections collected	6056	
Independent reflections	2254 [R_{int} = 0.0676]	
Completeness to θ = 27.45°	99.6 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9960 and 0.9866	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2254 / 0 / 111	
Goodness-of-fit on F^2	1.324	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.1220, $wR2$ = 0.3407	
R indices (all data)	$R1$ = 0.1746, $wR2$ = 0.3773	
Absolute structure parameter	6(5)	
Extinction coefficient	0.000(7)	
Largest diff. peak and hole	0.524 and –0.250 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details:

X-ray data for compound **610**

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	1915(3)	429(3)	1179(9)	72(2)	1
C2	2414(3)	969(4)	36(10)	78(2)	1
C3	2524(4)	1778(4)	315(12)	94(2)	1
C4	2763(4)	579(5)	−1501(8)	86(2)	1
C5	3637(4)	216(6)	−1198(13)	110(3)	1
C6	3680(5)	−528(6)	−21(11)	106(2)	1
C7	3291(3)	−400(4)	1753(9)	80(2)	1
C8	2361(3)	−392(3)	1758(9)	77(2)	1
C9	2047(5)	−541(5)	3606(12)	114(3)	1
C10	1366(6)	118(5)	3941(14)	120(3)	1
C11	1611(5)	831(4)	2851(8)	84(2)	1
O1	1186(2)	150(2)	155(8)	94(2)	1

Table 3. Bond lengths [Å] and angles [°].

C1–C2	1.481(8)
C1–O1	1.487(7)
C1–C11	1.546(9)
C1–C8	1.562(7)
C2–C3	1.323(9)
C2–C4	1.474(10)
C3–H3A	0.9500
C3–H3B	0.9500
C4–C5	1.532(10)
C4–H4A	0.9900
C4–H4B	0.9900
C5–C6	1.510(11)
C5–H5A	0.9900
C5–H5B	0.9900
C6–C7	1.546(11)
C6–H6A	0.9900
C6–H6B	0.9900
C7–C8	1.486(7)
C7–H7A	0.9900
C7–H7B	0.9900
C8–C9	1.562(11)
C8–H8	1.0000
C9–C10	1.536(9)
C9–H9A	0.9900
C9–H9B	0.9900
C10–C11	1.480(10)
C10–H10A	0.9900
C10–H10B	0.9900
C11–H11A	0.9900
C11–H11B	0.9900

X-ray data for compound **610**

O1–H1	0.8400
C2–C1–O1	105.3(5)
C2–C1–C11	116.6(5)
O1–C1–C11	110.1(5)
C2–C1–C8	115.0(5)
O1–C1–C8	105.3(4)
C11–C1–C8	104.0(5)
C3–C2–C4	120.0(6)
C3–C2–C1	122.6(7)
C4–C2–C1	117.4(5)
C2–C3–H3A	120.0
C2–C3–H3B	120.0
H3A–C3–H3B	120.0
C2–C4–C5	112.1(6)
C2–C4–H4A	109.1
C5–C4–H4A	109.1
C2–C4–H4B	109.2
C5–C4–H4B	109.2
H4A–C4–H4B	107.9
C6–C5–C4	115.9(6)
C6–C5–H5A	108.3
C4–C5–H5A	108.3
C6–C5–H5B	108.3
C4–C5–H5B	108.3
H5A–C5–H5B	107.4
C5–C6–C7	115.7(6)
C5–C6–H6A	108.4
C7–C6–H6A	108.4
C5–C6–H6B	108.3
C7–C6–H6B	108.3
H6A–C6–H6B	107.4
C8–C7–C6	114.0(6)
C8–C7–H7A	108.8
C6–C7–H7A	108.7
C8–C7–H7B	108.8
C6–C7–H7B	108.7
H7A–C7–H7B	107.7
C7–C8–C9	108.8(6)
C7–C8–C1	117.5(4)
C9–C8–C1	104.7(5)
C7–C8–H8	108.5
C9–C8–H8	108.5
C1–C8–H8	108.5
C10–C9–C8	106.5(6)
C10–C9–H9A	110.4
C8–C9–H9A	110.4
C10–C9–H9B	110.5
C8–C9–H9B	110.4
H9A–C9–H9B	108.6
C11–C10–C9	103.9(6)

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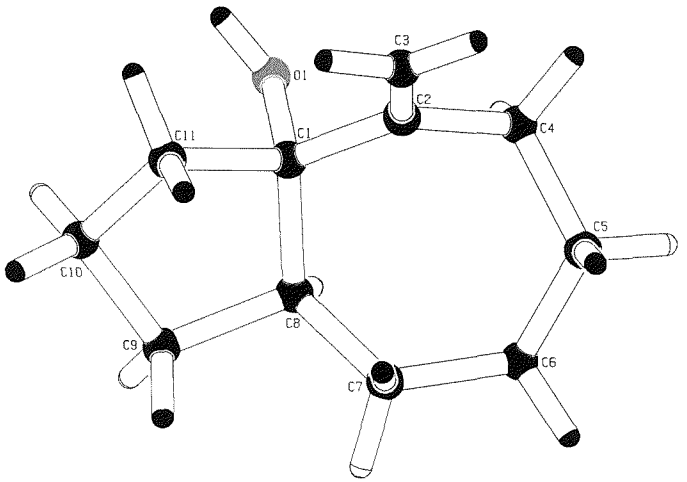
C11–C10–H10A	111.1
C9–C10–H10A	111.1
C11–C10–H10B	110.9
C9–C10–H10B	110.9
H10A–C10–H10B	109.0
C10–C11–C1	105.1(5)
C10–C11–H11A	110.8
C1–C11–H11A	110.8
C10–C11–H11B	110.6
C1–C11–H11B	110.7
H11A–C11–H11B	108.8
C1–O1–H1	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	46(2)	46(2)	122(5)	4(3)	−6(3)	−5(2)
C2	54(3)	81(3)	100(4)	24(4)	−10(3)	−8(2)
C3	73(3)	60(3)	149(7)	26(4)	−30(4)	−18(3)
C4	73(3)	110(5)	74(4)	28(3)	8(3)	−5(3)
C5	79(4)	132(6)	118(6)	21(5)	23(4)	13(4)
C6	98(5)	117(5)	104(5)	22(5)	35(4)	32(4)
C7	65(3)	65(3)	109(5)	11(3)	−16(3)	3(2)
C8	65(3)	41(2)	124(5)	5(3)	10(3)	2(2)
C9	123(6)	89(4)	131(6)	58(5)	61(5)	41(4)
C10	115(6)	101(5)	145(7)	26(5)	71(5)	36(4)
C11	109(5)	60(3)	83(4)	8(3)	18(3)	27(3)
O1	44(2)	43(2)	196(5)	−7(2)	−32(3)	−5(1)

X-ray data for compound **610**



X-ray data for compound **636**

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Table 1. Crystal data and structure refinement.

Identification code	**02sot146**	
Empirical formula	$C_{17}H_{28}O_2Si$	
Formula weight	292.48	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 6.8522(14) Å	α = 90°
	b = 17.611(4) Å	β = 90°
	c = 7.0718(14) Å	γ = 90°
Volume	853.4(3) Å^3	
Z	2	
Density (calculated)	1.138 Mg / m^3	
Absorption coefficient	0.138 mm^{-1}	
$F(000)$	320	
Crystal	Block; Colourless	
Crystal size	0.18 × 0.16 × 0.10 mm^3	
θ range for data collection	2.97 – 28.12°	
Index ranges	$-9 \le h \le 8$, $-22 \le k \le 23$, $-9 \le l \le 9$	
Reflections collected	8552	
Independent reflections	3732 [R_{int} = 0.1321]	
Completeness to θ = 28.12°	94.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9864 and 0.9756	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3732 / 1 / 186	
Goodness-of-fit on F^2	1.016	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0858, $wR2$ = 0.1512	
R indices (all data)	$R1$ = 0.1813, $wR2$ = 0.1834	
Absolute structure parameter	-0.1(3)	
Largest diff. peak and hole	0.273 and -0.281 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. **A51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) **A46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details:

All hydrogen atoms were fixed.
The absolute structure could not be accurately determined.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors.

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U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U_{eq}	*S.o.f.*
C1	-167(9)	6217(3)	-535(8)	45(1)	1
C2	-1(9)	6960(3)	514(7)	42(1)	1
C3	-1753(9)	6985(3)	1829(7)	39(1)	1
C4	-3215(9)	6513(3)	775(8)	43(1)	1
C5	-4924(9)	6132(3)	1756(7)	48(2)	1
C6	-4487(10)	5561(3)	3319(7)	45(2)	1
C7	-6261(11)	5031(4)	3706(8)	61(2)	1
C8	-7054(10)	5215(3)	5664(8)	53(2)	1
C9	-6157(8)	5994(3)	6125(8)	45(1)	1
C10	-4153(8)	5944(3)	5226(8)	43(1)	1
C11	-3030(9)	6683(3)	5063(7)	43(1)	1
C12	-1259(8)	6675(3)	3798(7)	41(1)	1
C13	-3597(11)	7316(3)	5960(7)	51(2)	1
C14	1361(9)	7475(3)	175(8)	49(2)	1
C15	4212(10)	8737(4)	585(12)	78(2)	1
C16	45(12)	9095(4)	-200(14)	92(3)	1
C17	1233(14)	8541(5)	3671(10)	96(3)	1
O1	-2048(6)	5914(2)	-104(5)	42(1)	1
O2	-2962(6)	5408(2)	6224(5)	44(1)	1
Si1	1683(3)	8461(1)	1115(3)	53(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–O1	1.428(7)	C9–H9A	0.9900
C1–C2	1.507(7)	C9–H9B	0.9900
C1–H1A	0.9900	C10–O2	1.434(7)
C1–H1B	0.9900	C10–C11	1.517(8)
C2–C14	1.323(8)	C11–C13	1.340(8)
C2–C3	1.520(8)	C11–C12	1.508(8)
C3–C4	1.500(7)	C12–H12A	0.9900
C3–C12	1.533(7)	C12–H12B	0.9900
C3–H3	1.0000	C13–H13A	0.9500
C4–O1	1.463(6)	C13–H13B	0.9500
C4–C5	1.518(8)	C14–Si1	1.872(6)
C4–H4	1.0000	C14–H14	0.9500
C5–C6	1.524(7)	C15–Si1	1.839(7)
C5–H5A	0.9900	C15–H15A	0.9800
C5–H5B	0.9900	C15–H15B	0.9800
C6–C10	1.525(7)	C15–H15C	0.9800
C6–C7	1.557(8)	C16–Si1	1.836(8)
C6–H6	1.0000	C16–H16A	0.9800
C7–C8	1.522(8)	C16–H16B	0.9800
C7–H7A	0.9900	C16–H16C	0.9800
C7–H7B	0.9900	C17–Si1	1.839(7)
C8–C9	1.537(8)	C17–H17A	0.9800
C8–H8A	0.9900	C17–H17B	0.9800
C8–H8B	0.9900	C17–H17C	0.9800
C9–C10	1.516(8)	O2–H2	0.8400

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O1–C1–C2	106.7(4)	C8–C9–H9B	111.2
O1–C1–H1A	110.4	H9A–C9–H9B	109.1
C2–C1–H1A	110.4	O2–C10–C9	110.3(4)
O1–C1–H1B	110.4	O2–C10–C11	108.3(5)
C2–C1–H1B	110.4	C9–C10–C11	116.2(5)
H1A–C1–H1B	108.6	O2–C10–C6	103.3(4)
C14–C2–C1	124.0(5)	C9–C10–C6	105.1(5)
C14–C2–C3	130.4(5)	C11–C10–C6	112.8(5)
C1–C2–C3	105.5(5)	C13–C11–C12	121.5(5)
C4–C3–C2	102.0(4)	C13–C11–C10	122.1(6)
C4–C3–C12	113.7(4)	C12–C11–C10	116.4(5)
C2–C3–C12	111.8(5)	C11–C12–C3	111.0(4)
C4–C3–H3	109.7	C11–C12–H12A	109.4
C2–C3–H3	109.7	C3–C12–H12A	109.4
C12–C3–H3	109.7	C11–C12–H12B	109.4
O1–C4–C3	104.2(4)	C3–C12–H12B	109.4
O1–C4–C5	107.3(4)	H12A–C12–H12B	108.0
C3–C4–C5	122.2(5)	C11–C13–H13A	120.0
O1–C4–H4	107.4	C11–C13–H13B	120.0
C3–C4–H4	107.4	H13A–C13–H13B	120.0
C5–C4–H4	107.4	C2–C14–Si1	130.9(5)
C4–C5–C6	118.1(5)	C2–C14–H14	114.6
C4–C5–H5A	107.8	Si1–C14–H14	114.6
C6–C5–H5A	107.8	Si1–C15–H15A	109.5
C4–C5–H5B	107.8	Si1–C15–H15B	109.5
C6–C5–H5B	107.8	H15A–C15–H15B	109.5
H5A–C5–H5B	107.1	Si1–C15–H15C	109.5
C5–C6–C10	112.3(5)	H15A–C15–H15C	109.5
C5–C6–C7	111.7(5)	H15B–C15–H15C	109.5
C10–C6–C7	103.1(4)	Si1–C16–H16A	109.5
C5–C6–H6	109.9	Si1–C16–H16B	109.5
C10–C6–H6	109.9	H16A–C16–H16B	109.5
C7–C6–H6	109.9	Si1–C16–H16C	109.5
C8–C7–C6	108.1(5)	H16A–C16–H16C	109.5
C8–C7–H7A	110.1	H16B–C16–H16C	109.5
C6–C7–H7A	110.1	Si1–C17–H17A	109.5
C8–C7–H7B	110.1	Si1–C17–H17B	109.5
C6–C7–H7B	110.1	H17A–C17–H17B	109.5
H7A–C7–H7B	108.4	Si1–C17–H17C	109.5
C7–C8–C9	103.9(5)	H17A–C17–H17C	109.5
C7–C8–H8A	111.0	H17B–C17–H17C	109.5
C9–C8–H8A	111.0	C1–O1–C4	108.3(4)
C7–C8–H8B	111.0	C10–O2–H2	109.5
C9–C8–H8B	111.0	C16–Si1–C17	110.4(5)
H8A–C8–H8B	109.0	C16–Si1–C15	108.2(4)
C10–C9–C8	102.8(5)	C17–Si1–C15	109.8(4)
C10–C9–H9A	111.2	C16–Si1–C14	108.2(3)
C8–C9–H9A	111.2	C17–Si1–C14	113.6(3)
C10–C9–H9B	111.2	C15–Si1–C14	106.5(3)

X-ray data for compound **636**

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

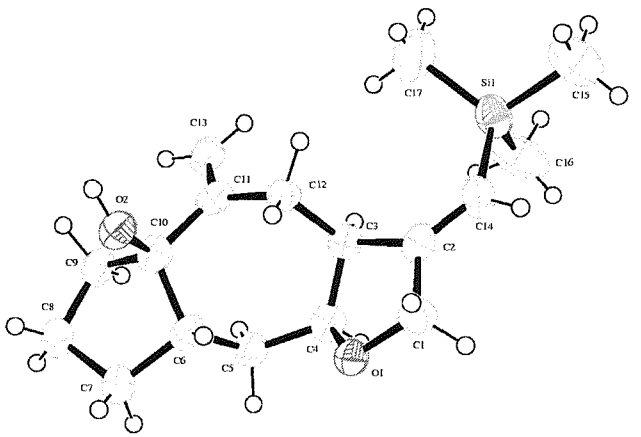
Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	36(4)	50(3)	47(3)	−7(3)	0(3)	3(3)
C2	48(4)	45(3)	34(3)	5(3)	2(3)	8(3)
C3	41(4)	35(3)	41(3)	1(2)	3(3)	5(3)
C4	40(4)	45(3)	43(3)	2(3)	1(3)	9(3)
C5	43(4)	62(4)	38(3)	−1(3)	3(3)	−6(3)
C6	57(4)	50(3)	29(3)	0(3)	1(3)	2(3)
C7	75(5)	64(4)	43(4)	0(3)	10(3)	−24(4)
C8	55(4)	61(4)	43(3)	6(3)	8(3)	−12(3)
C9	47(4)	52(3)	36(3)	9(3)	−1(3)	6(3)
C10	39(4)	48(3)	42(3)	5(3)	−2(3)	8(3)
C11	51(4)	47(3)	32(3)	−3(3)	−3(3)	4(3)
C12	46(4)	41(3)	37(3)	0(3)	−7(3)	−8(3)
C13	73(5)	44(3)	37(3)	2(3)	3(3)	−1(3)
C14	54(4)	43(3)	50(3)	3(3)	14(3)	−2(3)
C15	62(5)	51(4)	123(7)	−6(4)	−2(5)	1(3)
C16	76(6)	42(4)	156(8)	−8(5)	−24(5)	−2(4)
C17	158(8)	64(4)	65(5)	−18(4)	30(5)	−24(5)
O1	40(2)	48(2)	39(2)	−2(2)	5(2)	−2(2)
O2	52(3)	43(2)	37(2)	0(2)	0(2)	4(2)
Si1	54(1)	40(1)	64(1)	1(1)	11(1)	−1(1)

X-ray data for compound **636**

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1A	−35	6301	−1914	53	1
H1B	870	5862	−123	53	1
H3	−2238	7519	1939	47	1
H4	−3757	6835	−265	51	1
H5A	−5708	5870	778	57	1
H5B	−5757	6536	2301	57	1
H6	−3319	5251	2970	54	1
H7A	−7284	5113	2740	73	1
H7B	−5846	4493	3650	73	1
H8A	−6641	4828	6597	64	1
H8B	−8497	5242	5650	64	1
H9A	−6934	6411	5565	54	1
H9B	−6060	6072	7508	54	1
H12A	−766	6149	3681	50	1
H12B	−215	6988	4371	50	1
H13A	−2878	7773	5805	61	1
H13B	−4718	7308	6750	61	1
H14	2340	7318	−693	59	1
H15A	4479	8652	−760	117	1
H15B	5110	8431	1348	117	1
H15C	4396	9276	883	117	1
H16A	−1288	9039	281	137	1
H16B	77	8962	−1545	137	1
H16C	474	9621	−37	137	1
H17A	1456	9066	4075	143	1
H17B	2123	8203	4354	143	1
H17C	−119	8397	3945	143	1
H2	−2844	5546	7356	66	1

X-ray data for compound **636**



Man will occasionally stumble over the truth, but usually manages to pick himself up, walk over or around it, and carry on.

Sir Winston Churchill.