University of Southampton

SAMARIUM DIIODIDE MEDIATED CASCADE RADICAL CYCLISATIONS OF METHYLENECYCLOPROPANE DERIVATIVES: SYNTHESIS OF BICYCLO-[3.2.1]-OCTANES

By Alexandre Christian Claude Saint-Dizier

Doctor of Philosophy

FACULTY OF SCIENCE

DEPARTMENT OF CHEMISTRY

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It's all part of the learning process...

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

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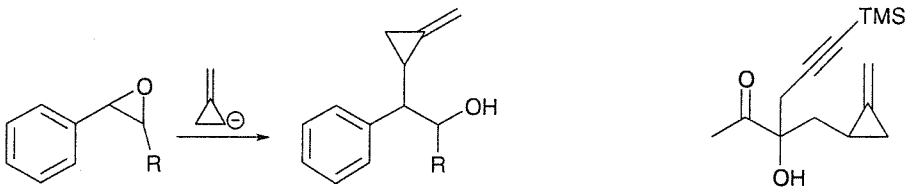
This thesis is concerned with the synthesis of methylenecyclopropane derivatives and their cascade radical cyclisations mediated by samarium diiodide to access bicyclo-octane polycyclic systems.

Chapter 2 describes the nucleophilic addition of lithiated methylenecyclopropane to epoxides and studies towards synthesis of keto-alcohol derivatives of methylenecyclopropane such as **189**.

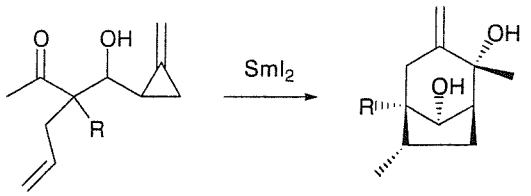


230: R=H
233: R=Me

231: R=H
234: R=Me

189

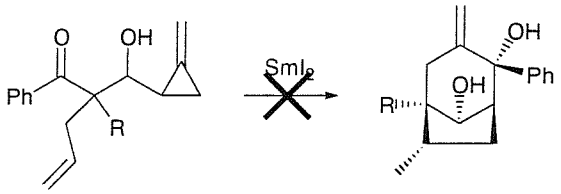
Chapter 3 details the of samarium diiodide mediated cascade cyclisation of methylenecyclopropyl methyl ketones **285** and **327**. Bicyclic compounds **305** and **348** were obtained in reasonable to good yields and good diastereoselectivity. The cyclisations of these precursors were found to be stereoselective due to chelation control with the samarium species.



285: R=H
327: R=Allyl

305: R=H
348: R=Allyl

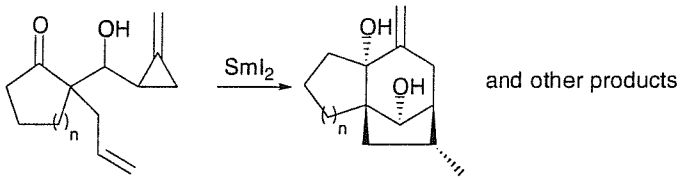
Chapter 4 concentrates on the synthesis of phenyl ketone derivatives of methylenecyclopropane **351** and **352** and their cyclisations, which failed to give bicyclo-octanes **353** and **354**.



351: R=H
352: R=Allyl

353: R=H
354: R=Allyl

Chapter 5 presents the synthesis and samarium diiodide mediated radical cyclisations of cyclic ketone derivatives of methylenecyclopropane **400** towards tricyclic compounds **401**.



400 n= 1 or 2 **401**

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ACKNOWLEDGEMENTS

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Finally, a few words for my parents: "merci du fond du coeur pour m'avoir permis de faire cette thèse, pour le soutien moral et matériel. Papa, j'en serais quand même arrivé là si j'étais allé au camp scout ... "

ABBREVIATIONS

AIBN	2,2'-azobisisobutyronitrile
app.	apparent
aq.	aqueous
br s	broad singlet
d	doublet
DCM	dichloromethane
de	diastereomeric excess
DEPT	distortionless enhancement by polarisation transfer
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethylsulfoxide
EWG	electron withdrawing group
HMPA	hexamethylphosphoramide
hv	irradiation
IR	infrared spectroscopy
J	coupling constant
m-CPBA	*meta*-chloroperbenzoic acid
m	multiplet
MCP	methylenecyclopropane
MeCN	acetonitrile
MS	mass spectrometry
n	normal
NBS	N-bromo succinimide
NMR	nuclear magnetic resonance spectroscopy
nOe	nuclear Overhauser enhancement
o	*ortho*
p	*para*
petrol	petroleum ether, boiling point in the range 40-60°C
ppm	part per million

p-TsOH	*para*-toluene sulfonic acid
q	quartet
R_f	retention factor
rt	room temperature
SmI_2	samarium (II) iodide
t	*tert*
t	triplet
TEA	triethylamine
THF	tetrahydrofuran
TMS	trimethylsilyl

CHAPTER 1: INTRODUCTION

1.1) FREE RADICALS

1.1.1) Definition

Free radicals, species with one unpaired electron, are very reactive and readily interact with different types of compounds to form new bonds, an ability that has been used extensively in organic synthesis. The investigation of the chemistry and characteristics of radicals dates back to the begining of the last century with pioneering work from Gomberg[1], who studied the formation and reactions of the trimethylphenyl radical. Following Gomberg's work, studies on a wide range of radical systems were performed to build the basic foundation of the knowledge of radicals. This has led to their extensive use in modern synthetic chemistry.

1.1.2) Radical Formation and Basic Reactions

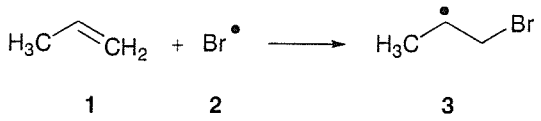
i- Radical formation:

There are three main methods of generating radicals that can be used in organic synthesis:

-Homolytic cleavage of a covalent bond: photolysis, radiolysis, pyrolysis or thermolysis may result in the formation of two radicals.

-Oxido-reduction reactions involving single electron exchange in metals: a metal may be oxidised or reduced to produce a radical.[2] This method includes redox couples such as Fe^{2+}/Fe^{3+}, Cu^{+}/Cu^{2+} and Sm^{2+}/Sm^{3+}.

-Use of a radical to generate another radical. A good example of this method is the anti-Markovnikov addition of bromine to alkenes. (**Scheme 1.1**)

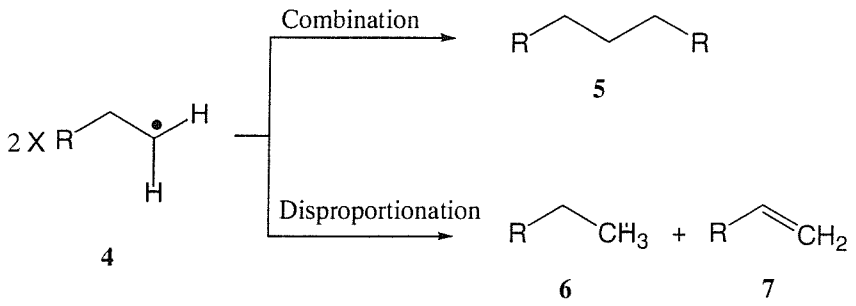


Scheme 1.1

ii- Basic reactions:

Radicals may be involved in a range of reactions. They can react in a number of ways including taking part in a chain reaction mechanism.[2] Two types of radical interactions are distinguishable, reactions between radicals and reactions between a radical species and a non-radical compound:

-Two types of reactions between radicals can be described: combination and disproportionation. (**Scheme 1.2**)



Scheme 1.2

Combination leads to the formation of a σ-bond and a single molecule, disproportionation proceeds with H atom abstraction and leads to two fragment molecules, a saturated one, **6**, and an unsaturated one, **7**. These reactions are very fast but they are not the most useful to organic chemists as the radical character is destroyed, the process in not very selective and the low concentration of radicals may lead to side reactions. However, some radical-radical processes may be used in specific cases.

-Reactions between radical and non-radical species are easier to control and are the basis of most radical processes, displaying two main advantages:

i) A new radical is formed as the result of the reaction, hence a chain reaction mechanism is established controlling the overall process.

ii) The selectivity of the reaction can be influenced by the type of substituent on the radical and the nature of the non-radical species.

Restrictions apply to reactions between radicals and non-radical species. The selectivity of the radicals must be different from each other and the radicals must react with the non-radicals faster than the rate at which they recombine. Radicals are often used in synthesis for their ability to trigger and participate in chain reaction mechanisms.[3] **(Fig. 1.1)**

INITIATION

$$A\text{-}B \rightarrow A^{\bullet} + B^{\bullet} \qquad (1)$$

PROPAGATION

$$A^{\bullet} + H\text{-}R \rightarrow A\text{-}H + R^{\bullet} \qquad (2)$$

$$A^{\bullet} + R\text{-}HC{=}CH\text{-}R \rightarrow R\text{-}C(A)\text{-}C^{\bullet}\text{-}R \qquad (3)$$

$$A^{\bullet} \rightarrow D + R^{\bullet} \qquad (4)$$

$$R_3C\text{-}CH_2^{\bullet} \rightarrow R_2C^{\bullet}\text{-}CH_2R \qquad (5)$$

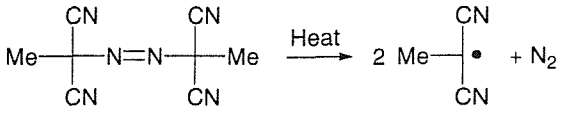
TERMINATION

$$A^{\bullet} + B^{\bullet} \rightarrow A\text{-}B \qquad (6)$$

$$A^{\bullet} + B^{\bullet} \rightarrow A + B' \qquad (7)$$

Figure 1.1

The initiation step *(1)* may occur spontaneously but may also require the use of a non-stoichiometric amount of initiator and can be triggered by heating or irradiation. The choice of such a chemical depends on the conditions needed for the reaction. A very commonly used radical initiator is azobisisobutyronitrile (AIBN) **8**. **(Scheme 1.3)**



8 **9**

Scheme 1.3

There are four possible propagation steps, in which the radical character is preserved:

-Atom abstraction *(2)*; an atom, generally hydrogen, is transferred from one molecule to another.

-Addition or cyclisation *(3)*; the radical species reacts with a non radical moiety either intramolecularly or in a different molecule, leading to the formation of a new radical.

-Decomposition *(4)*; a neutral species and a new radical are obtained from the breakdown of the initial molecule.

-Rearrangement *(5)*; internal reorganisation allows transformation of one radical species into another.

Finally termination can occur in two ways, by combination of two radicals *(6)* yielding a neutral molecule or by disproportionation *(7)*. In both cases, the radical character is lost.

1.1.3) Uses in Organic Synthesis

The specific characteristics, behaviour and reactions of radical species make them a useful alternative to the more classical polar or ionic processes. Curran[4] has stated some profitable differences:

i. Highly reactive carbon-centred radicals react under mild neutral conditions.

ii. Radical processes often proceed with high levels of chemo-, regio- and stereoselectivity. The advantage over ionic reactions is often increased in complex molecules, where ionic reactions encounter problems in reactivity and chemoselectivity.

iii. Carbon-centred radicals do not react spontaneously with OH or NH groups so protection of these groups is unnecessary.

iv. Carbon-centred radicals are not subject to β-elimination of OR or NR_2.

1.1.4) Example of Radical Reactions

The scope of organic reactions involving radicals is very wide, publications about new uses of radicals regularly appear and many reference books are available to cover the theoretical aspect of radical reactions.[2,5] Radicals are used in academic research as well as in industry, notably for the synthesis of pharmaceuticals or for large scale polymerisation.

i- Halide reduction

One example is the tributyltin hydride method for the reduction of an organic halide by $^{n}Bu_3SnH$ (**Fig. 1.2**). AIBN is usually associated with tin hydride to trigger the radical sequence.

INITIATION

$Bu_3SnH \rightarrow Bu_3Sn^{\bullet}$

PROPAGATION

$Bu_3Sn^{\bullet} + R\text{-}X \rightarrow R^{\bullet} + Bu_3SnX$	*Step1*
$R^{\bullet} \rightarrow R^{2\bullet}$ (addition or cyclisation)	*Step 2*
$R^{2\bullet} + Bu_3SnH \rightarrow Bu_3Sn^{\bullet} + R^2\text{-}H$	*Step 3*
$R^{\bullet} + Bu_3SnH \rightarrow Bu_3Sn^{\bullet} + R\text{-}H$	*Step 4*

TERMINATION

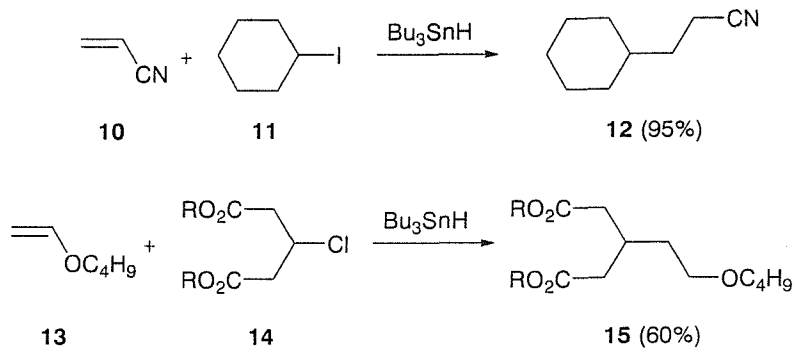
$R^{\bullet}$ and $R^{2\bullet} \rightarrow$ non- radical products	*Step 5*

Figure 1.2

ii- Intermolecular radical reactions

Apart from initiation of radical processes, polymerisation is probably the type of reaction that uses intermolecular radical reactions to the largest extent. These again proceed *via* chain reaction mechanisms.

Synthetically useful intermolecular processes are also well-known, Giese and co-workers reported efficient intermolecular radical reactions.[6] (**Scheme 1.4**)



Scheme 1.4

A number of radicals are simultaneously present in either reaction, therefore it is important to be able to have some control over the reaction to avoid unwanted products. Choosing suitable substituents on the alkene allows the selectivity to be influenced so that the reaction is tuned to favour certain interactions.[7] Alkyl radicals incorporating electron-donating groups behave like nucleophiles and will react faster with electron deficient alkenes whereas radicals with electron-withdrawing substituents will react faster with electron rich alkenes.

1.2) INTRAMOLECULAR RADICAL REACTIONS

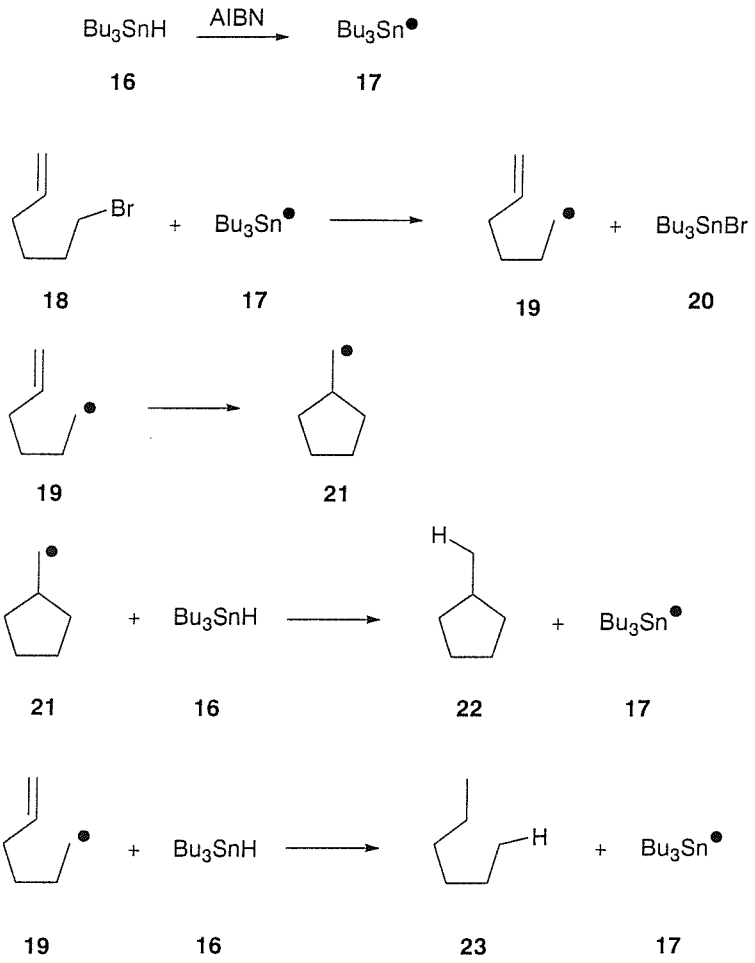
Intramolecular radical reactions are usually known as radical cyclisations. Such processes are of prime importance in organic synthesis as they allow cyclic/polycyclic compounds to be made from linear or cyclic ones. Amongst all processes involving radicals, they are the type we are mostly interested in.

1.2.1) Concept of Radical Cyclisation

Intramolecular radical reactions can be of particular value, especially in natural product synthesis.[4] These reactions exhibit interesting regioselectivities and stereoselectivities and can be carried out with a variety of functional groups as radical traps such as carbon-carbon, carbon-oxygen or carbon-nitrogen multiple bonds. Intramolecular radical cyclisations are usually more successful than their intermolecular counterparts where the competing rate of reaction and reduction are an important factor.

The principles and basics of radical cyclisations have been extensively studied allowing some prediction of the outcome of the reactions.[8,9,10]

The most widely used method to conduct free radical reactions utilises tri-^{n}butyltin hydride. Walling studied the importance of the radical concentration on the product distribution, as illustrated by the cyclisation of 5-hexenyl radical.[10] (**Scheme 1.5**)



Scheme 1.5

The distribution of the products **22** and **23** has been shown to depend on the concentration of the radical species.[10] When a high concentration (5M) of tin hydride is used, the main product is hexane **23**, the reduced compound. Alternatively, at low concentration (< 0.05M), cyclisation prevails and methylcyclopentane **22** is the major product. To achieve such low concentration of tin hydride during the reaction, *in situ* generation from a catalytic amount of tin halide and use of a strong reducing agent is one of the solutions.[11] The other possibility is to proceed *via* slow addition of the tin hydride.

Radical cyclisations are unsuitable to construct 3- and unsubstituted 4-membered rings. The rate constants of cyclisation for propenyl and butenyl radicals have been measured and it was found that the rate of opening is much faster than the rate of closure. [12] **(Fig. 1.3)**

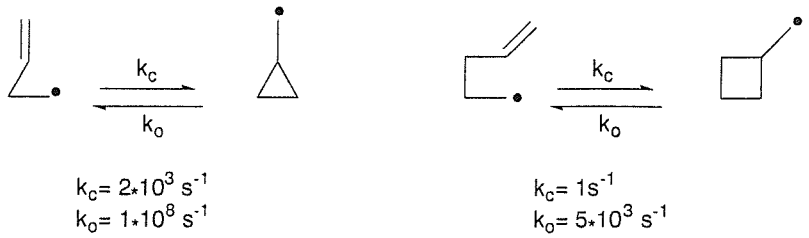
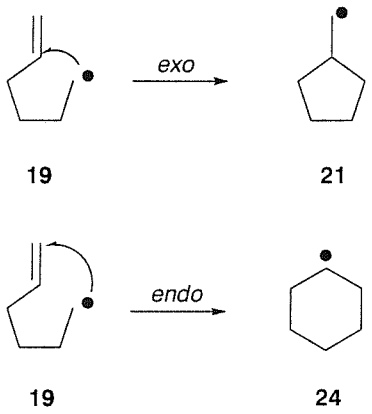


Figure 1.3

1.2.2) Regioselectivity of Cyclisation Processes

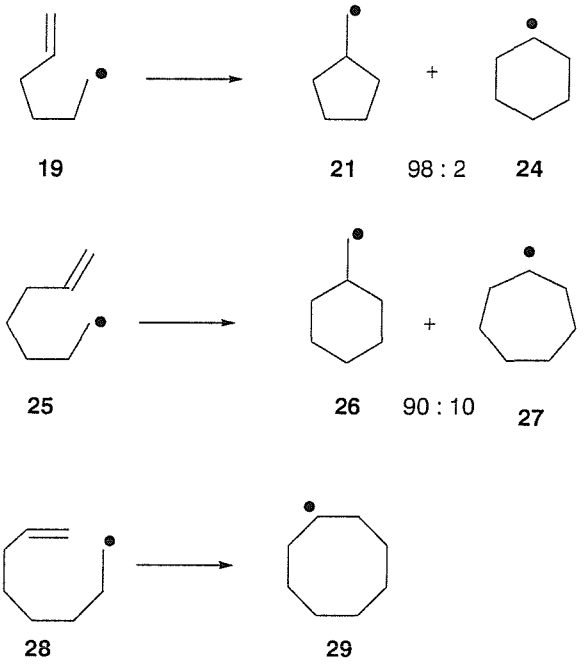
Two competing cyclisation pathways are available to radical **19**, they are named *exo* and *endo* cyclisation, as stated in Baldwin's guidelines.[13] **(Scheme 1.6)**



Scheme 1.6

Following Baldwin's guidelines of cyclisation, the 5-*exo* cyclisation of 5-hexenyl radical is favoured, yielding cyclopentyl methyl radical **21**.

Beckwith has studied the relative rates of cyclisation of 5-hexenyl, 6-heptenyl and 7-octenyl radicals in order to explain the regioselectivity.[14] **(Scheme 1.7)** He used theoretical calculations to show the reason for the outcome of these cyclisation.



Scheme 1.7

Despite the resulting primary radicals **21** and **26** being less stable than the secondary radical resulting from the *endo* process, *exo* products are formed preferentially in the case of hexenyl **19** and heptenyl radical **25**. Beckwith argued that the overall difference in entropy between the two modes of cyclisation is too small to dictate the proceeding of the reaction.[14]

One of the arguments presented is that the 1,6 transition state is destabilised by steric interaction between the pseudo-axial protons at C_2 and C_6. (**Fig. 1.5**)

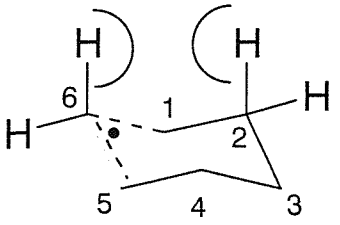


Figure 1.4

A stereoelectronic approach confirms the argument, stating that 5-*exo* cyclisation is favoured by achieving more efficient orbital overlap. Essentially, the strain engendered to obtain the most favourable transition state is much greater for the *endo* cyclisation. The

three reactive centres have to be situated at the vertices of a slightly obtuse triangle lying within a plane orthogonal to the nodal plane of the π-system.[15] **(Fig. 1.5)**

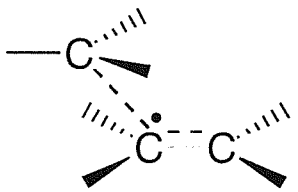
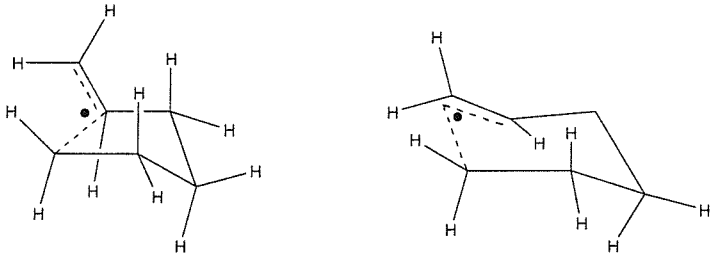


Figure 1.5

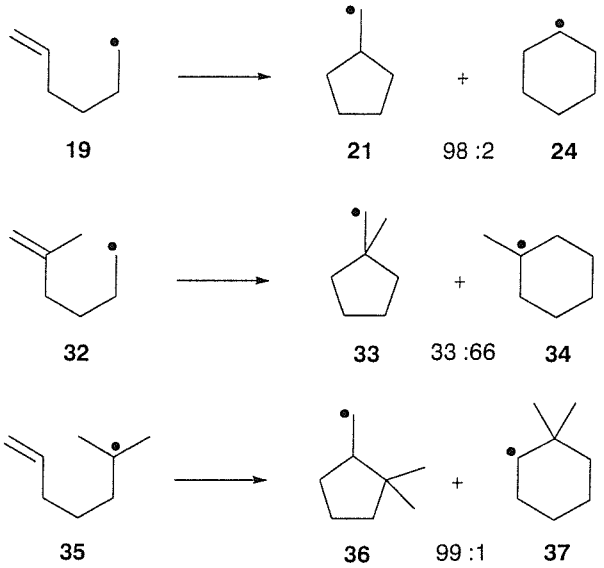
Molecular modelling showed that the most stable conformer for both the *endo* and *exo* ring closure proceeds *via* distorted chair-like transition states. Calculations revealed that the 5-*exo* process is less energy demanding than the 6-*endo* by 2.8 kcal.mol^{-1} (1.7 kcal.mol^{-1} obtained experimentally).[12] **(Fig. 1.6)**



30 5-hexenyl, *exo* **31** 5-hexenyl, *endo*

Figure 1.6

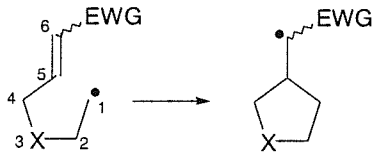
Although substitution at the radical centre has little influence on the cyclisation, introducing substituents on the double bond can help alter the *exo*:*endo* product ratio. **(Scheme 1.8)**



Scheme 1.8

Radical **32** leads preferentially to the *endo* product, **34**, and this is thought to occur for steric reasons.

The presence of electron withdrawing groups helps to accelerate cyclisation as does a heteroatom, if in the 3- position.[9] However, any substitution at the 2- or 4- position has little if any beneficial effect. **(Fig. 1.7)**

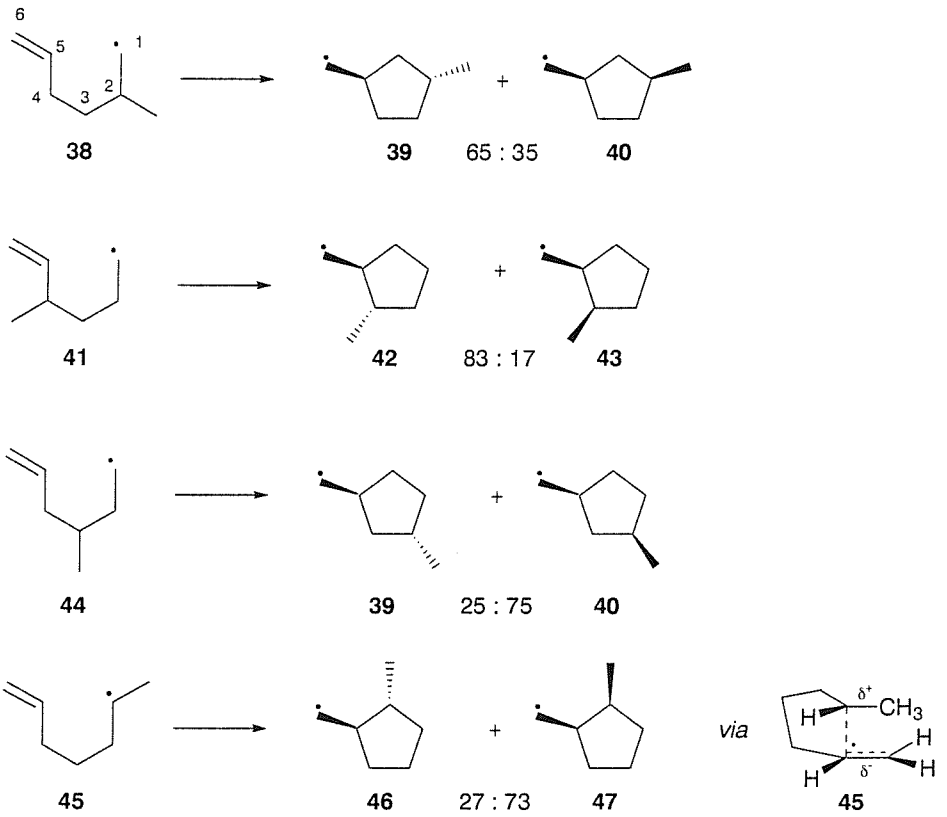


X= O or N

Figure 1.7

1.2.3) Stereoselectivity of Cyclisation Processes

The stereochemical selectivity of radical cyclisation reactions has been studied and a set of guidelines was established by Beckwith.[16] Radical mediated 1,5-ring closures afford mainly the *cis* disubstituted product when R groups are present at the 1- or 3- position. Alternatively, substitution at the 2- or 4- position give predominantly *trans* compounds. **(Scheme 1.9)**



Scheme 1.9

The rules result from considering a chair-like transition state where the most favoured conformation is with the substituent in a pseudo equatorial position.[17] (**Fig. 1.8**)

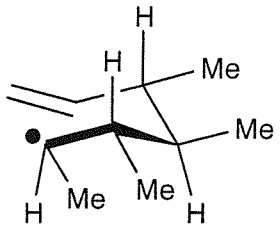
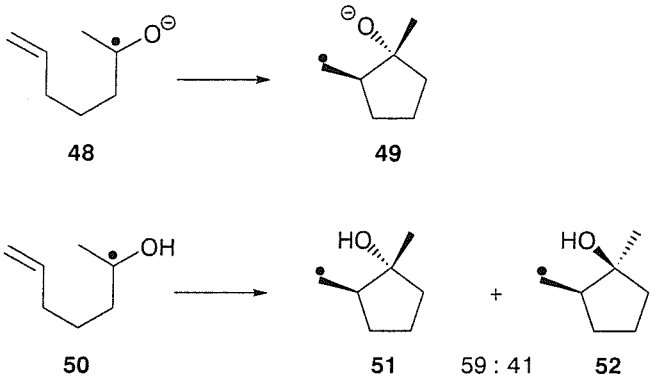


Figure 1.8

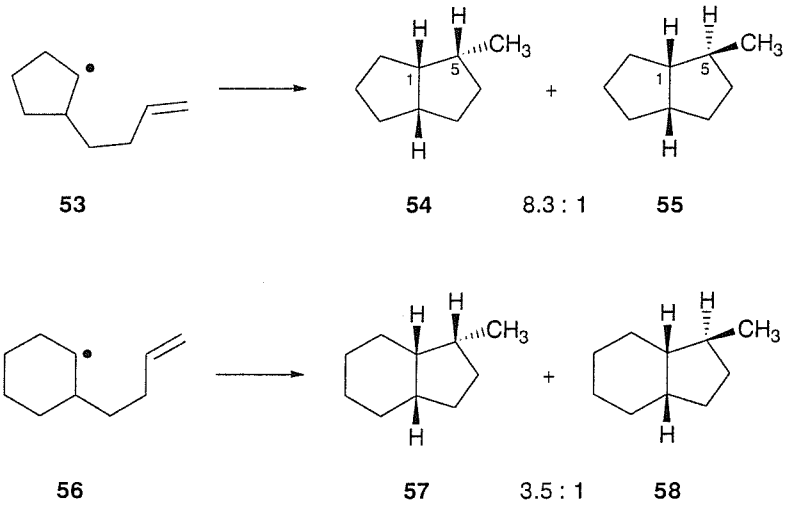
The formation of **47** preferentially over **46** in the cyclisation of **45** does not result from these rules straight away. A possible explanation for this phenomenon resides in the fact that an electrostatic interaction in a dipolar transition state can account for the preferred *cis*- cyclisation.[18] Similar electronic arguments also explain why radical ion **48** only gives **49** upon cyclisation. The cyclisation proceeds *via* a chair-like transition and electronic repulsion between the π-system and the charged oxygen is thought to favour the formation

of **49**. In the case of the protonated counterpart such interaction is not present and **50** leads to the formation of both possible isomers **51** and **52**. (**Scheme 1.10**)



Scheme 1.10

When cyclic radicals are subjected to cyclisation, the resulting product exhibits 1,2-*cis* fused stereochemistry at the ring junction.[18, 19] (**Scheme 1.11**)



Scheme 1.11

Curran argued that 1,5-*cis* cyclisation is preferred over 1,5-*trans* cyclisation because the best orbital overlap is achieved when the radical adopts a chair-like transition state.[20] Houk undertook theoretical calculations to show that the chair-like conformation is less energy demanding than the boat-like conformer by about 0.5 kcal.mol^{-1}. (**Fig. 1.9**)

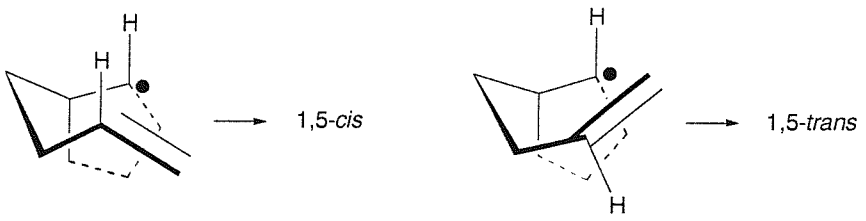


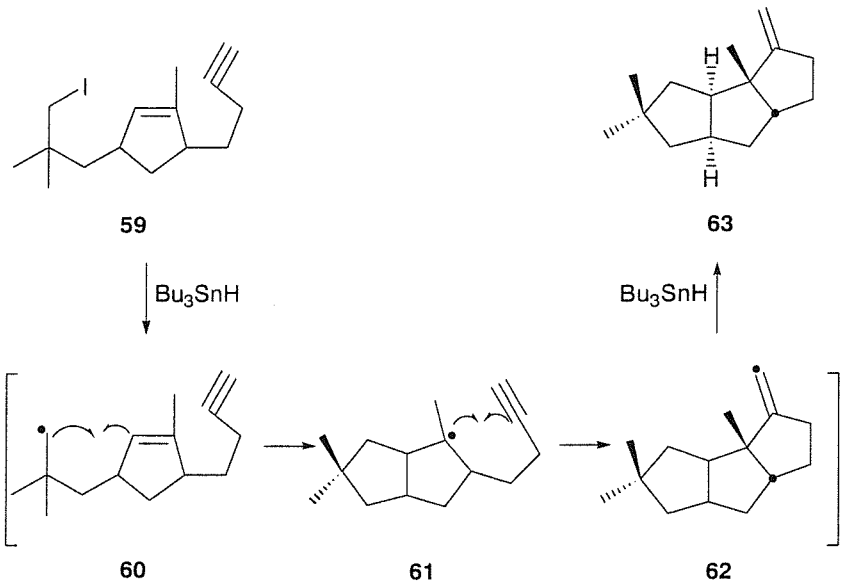
Figure 1.9

Evidence to support that the 1,5-*trans* product arises from the radical adopting a boat-like transition state was provided by RajanBabu.[17]

When a substrate is set up to undergo more than one radical cyclisation in one single process, the reaction is called cascade, tandem or domino radical cyclisation.

1.2.4) Example of Cascade Radical Cyclisation

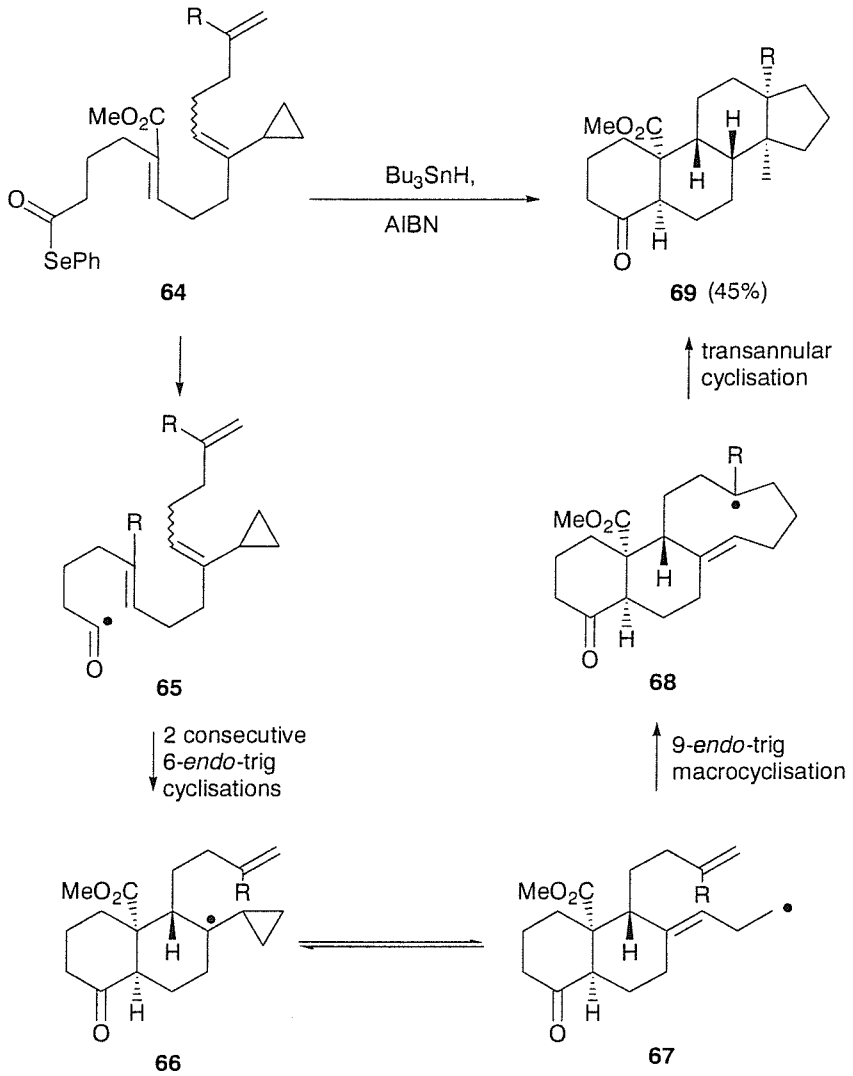
Cascade radical cyclisations have provided efficient routes to complex polycyclic natural products.[21] For example, intramolecular addition of carbon centred radicals to substituted carbon-carbon, carbon-oxygen, and carbon-nitrogen multiple bonds can all be performed with high efficiency as illustrated by Curran in his synthesis of (±)hirsutene **63**.[20] **(Scheme 1.12)**



Scheme 1.12

Radical **60** was obtained by treating iodide **59** with tributyltin hydride and AIBN, and then underwent two successive 5-*exo* cyclisations to give radical **62** which was quenched to lead to (±)hirsutene **63**.

Cascade processes allow the rapid construction of polycyclic systems. Very elaborate and high order cascade radical sequences have been developed and can allow access to complex polycyclic system such as steroid skeletons.[22] **(Scheme 1.13)**



Scheme 1.13

Acyl radical **65** was generated by treating acylselenide **64** with Bu_3SnH. Radical **65** undergoes two consecutive 6-*endo* cyclisations, resulting in bicyclic radical **66**. Opening of the cyclopropane ring can occur and **66** is in equilibrium with primary radical **67** which

undergoes a 9-*endo* cyclisation to form macrocyclic compound **68**. Radical **68** cyclises onto the remaining double bond and quenching of the radical provides steroid **69** in 45% yield. The sequence illustrates the versatility and efficiency of cascades radical processes.

1.3) SAMARIUM (II) IODIDE

1.3.1) Introduction

The examples presented so far all involve the use of tributyltin hydride but a number of other methods exist to initiate radical reactions.[9, 23] An alternative method involves samarium diiodide (SmI_2).

Samarium (II) iodide was introduced as a powerful and polyvalent reducing agent by Kagan and co-workers who reported a method for *in situ* generation.[24] SmI_2 has developed into a remarkable and widely used reagent for a large number of reactions thanks to the work of numerous researchers including Molander,[25] Curran,[26] Kagan,[27] Inanaga[28] and many others.[29]

1.3.2) Synthesis of Samarium Iodide

Samarium diiodide is easily obtained in moderate concentration (0.1 M) in solvents like MeCN or THF.[30] (**Fig. 1.10**) Other methods exist[25,31,32] but the reaction of diiodoethane with samarium metal proves fast, reliable and efficient.

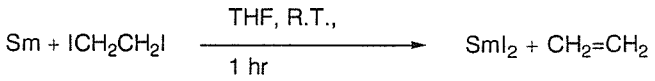


Figure 1.10

Reaction of samarium metal and diiodoethane in THF provides SmI_2 as a dark blue solution. Additionally, when hexamethylphosphoramide (HMPA) is added to SmI_2 in THF (the THF/HMPA system has been shown to increase the reducing potential of SmI_2),[30] the solution turns deep purple. An advantage of samarium (II) iodide is that Sm^{III} salts are

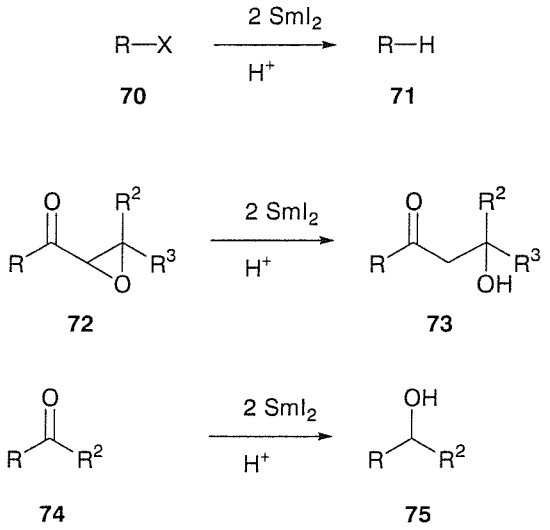
yellow-greenish allowing easy visualisation of the quality of the reagent as well as the reaction proceeding.

1.3.3) Samarium (II) iodide in Organic Synthesis

Samarium (II) iodide can be applied to a multitude of important synthetic transformations, which generally proceed with high levels of regio- and chemoselectivity. A number of reviews have covered the scope of reactions involving samarium (II) iodide[33,26,29a,34,30,35,36] and they can be divided in several categories.

i- Functional group reductions

Samarium (II) iodide can be used to reduce halides and leaving groups,[26] conjugated double bonds, epoxides,[37] sulfoxides,[24] and carbonyl groups.[38] α,β-Epoxy ketones can be reduced to keto alcohols.[39] (**Scheme 1.14**)



Scheme 1.14

ii- Reductive coupling of halides with π-bonds

Such reductions are equivalents to Grignard or Barbier-type reactions[34] and can be inter- or intramolecular.[26] (**Fig. 1.11**)

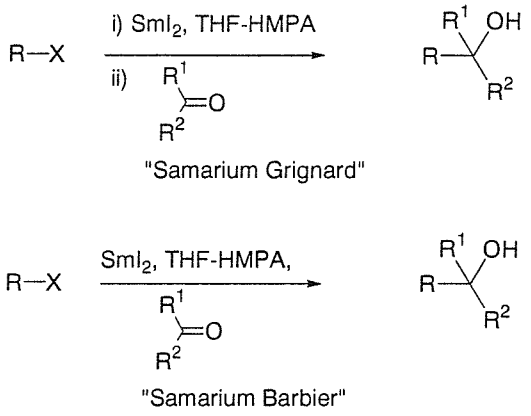


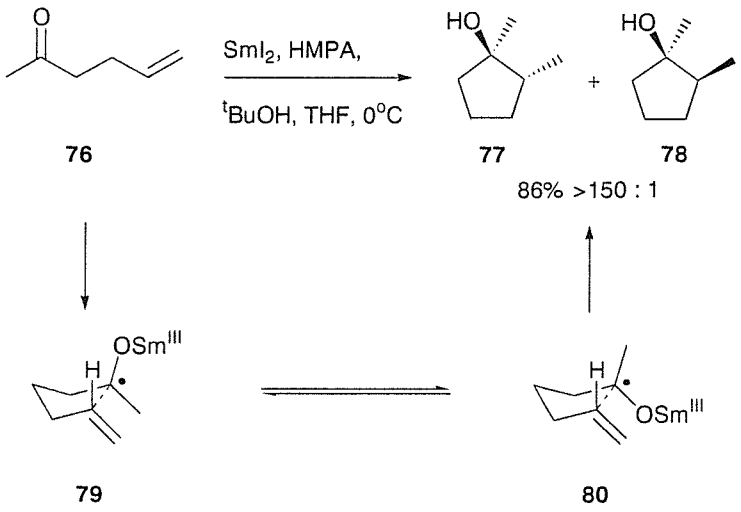
Figure 1.11

iii- Reductive coupling of two π-bonds

Such processes include pinacol couplings[27] and especially reductive couplings of carbonyls with alkenes, this is the type of reaction we are most interested in.

SmI_2 has the ability to reduce aldehydes or ketones to radicals which in turn can cyclise onto carefully placed radical traps (i.e. alkenes or alkynes). Extensive work has been carried out on SmI_2 mediated radical cyclisation,[26,40,41,42] including significant contributions by Molander.[29,43]

Molander reported the cyclisation of ketone **76** with SmI_2. The resulting alcohols **77** and **78** were isolated in 86% yield with a >150:1 diastereoselectivity in favour of *trans*-alcohol **77**.[44b] **(Scheme 1.15)**

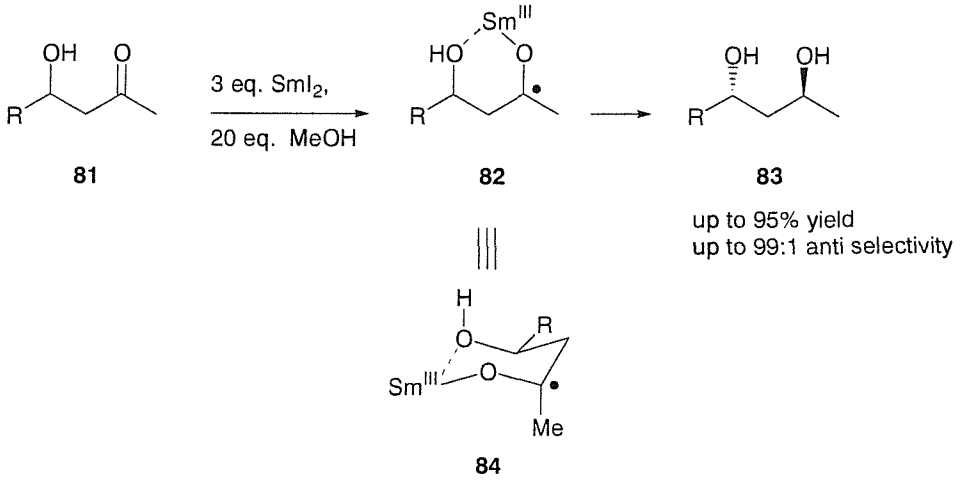


Scheme 1.15

The cyclisation proceeds *via* a chair-like transition state similar to 5-hexenyl radical and there are two possible conformations that the radical can adopt: **79** and **80**. However, electronic repulsion between the π-system and the oxygen lone pair is thought to favour **79** leading to the *trans*-alcohol **77** almost exclusively.

1.3.4) Samarium (II) Iodide and Diastereoselectivity

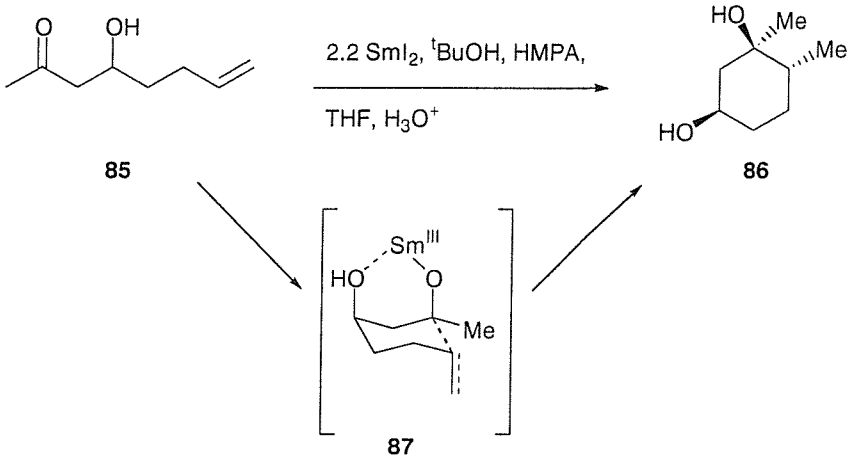
Another important and interesting characteristic of samarium diiodide is the influence it can have on the diastereoselectivity of the reactions. Recently, Keck[29b] reported a stereoselective reduction of α,β-hydroxy ketones to 1,3-*anti* diols. (**Scheme 1.16**)



Scheme 1.16

The reaction proceeds *via* generation of ketyl radical **82** which is then further reduced and quenched by a proton source. The stereoselectivity is accounted for by samarium co-ordination to both oxygens in a 6-membered ring transition state. The methyl group of the intermediate radical **84** is in the axial position and to proceed to the final product it reacts with another equivalent of SmI_2 leading to an organosamarium species where the bulky Osm^{III} group has to go equatorial. (*vide infra*, **Scheme1.19**)

The stereochemical outcome of samarium (II) iodide mediated radical cyclisation was previously discussed by Molander in his study of 5-*exo* and 6-*exo* cyclisations.[43c] (**Scheme 1.17**)

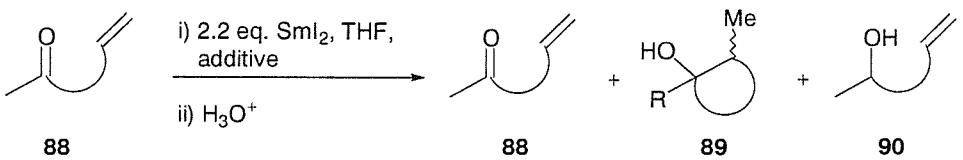


Scheme 1.17

The chelation of samarium on both oxygen atoms forces them to go axial in the transition state **87**, resulting in a *syn* relationship between both alcohols in the final product **86**.

1.3.5) Influence of Reaction Conditions

Molander conducted an in-depth study of the radical cyclisation of cyclic and acyclic olefinic ketones in order to established the optimised conditions for yield and diastereoselectivity.[43c] It was reported that additives such as HMPA or DMPU have a positive impact on the cyclisation of unactivated olefins. Molander was concerned with the influence of the additive and its concentration over the outcome of the cyclisation of such ketones. (**Scheme 1.18**)

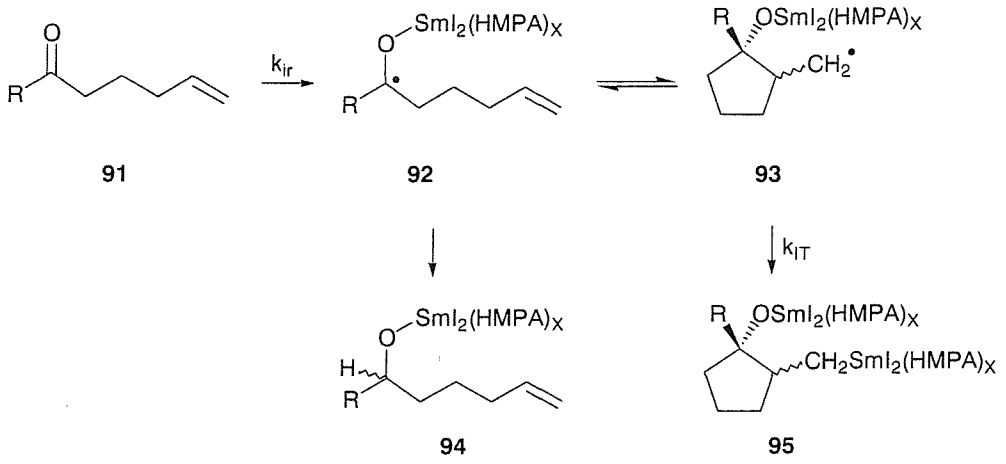


Scheme 1.18

Molander undertook the reactions in the absence of additives, with DMPU (8 eq.) or with HMPA (2eq., 4eq. and 8eq.) It was found that DMPU improved the rate of reaction, yields and diastereoselectivity compared with reaction without additives. However a certain amount of the alcohol and starting material was isolated when DMPU was used. Moving to

HMPA, the reaction times, yields and diastereoselectivity was improved, compared with reactions without additives but was also superior to DMPU. Moreover, the quantities of starting material recovered and reduced compound had fallen significantly. The best results were obtained with eight equivalents of HMPA and a larger excess did not give any improvements.

The exact role of HMPA is still not fully understood but it is believed that it complexes with samarium (II), making hydrogen transfer to **94** less feasible and therefore favouring the formation of cyclic compound **93**. (**Scheme 1.19**)

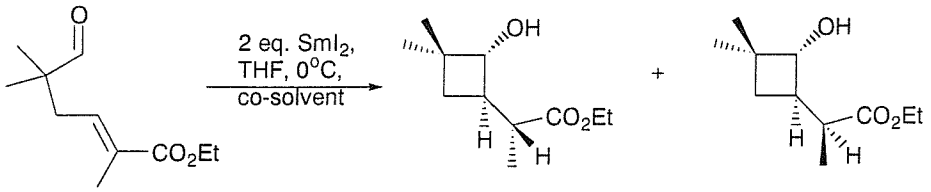


Scheme 1.19

The increased cyclisation relative to H abstraction is attributed to the complexation of HMPA, rather than THF, with Sm(II). Molander argues that in the THF/Sm(II) complex, formed in the absence of HMPA, THF provides a source of hydrogen for abstraction, favouring the formation of **94**. Another approach is to consider the cyclisation of **92** to **93** to be reversible and that HMPA would increase the rate of radical reduction (**93** to **95**).

The improved diastereoselectivity in the presence of HMPA may be attributed to the increased destabilisation of the minor transition state by the bulky HMPA/Sm(II) complex.

The main drawback to using HMPA is its high toxicity but Procter has studied potential alternatives in a series of 4-*exo*-trig cyclisations of unsaturated aldehydes.[44] (**Scheme 1.20**)



96 97 98

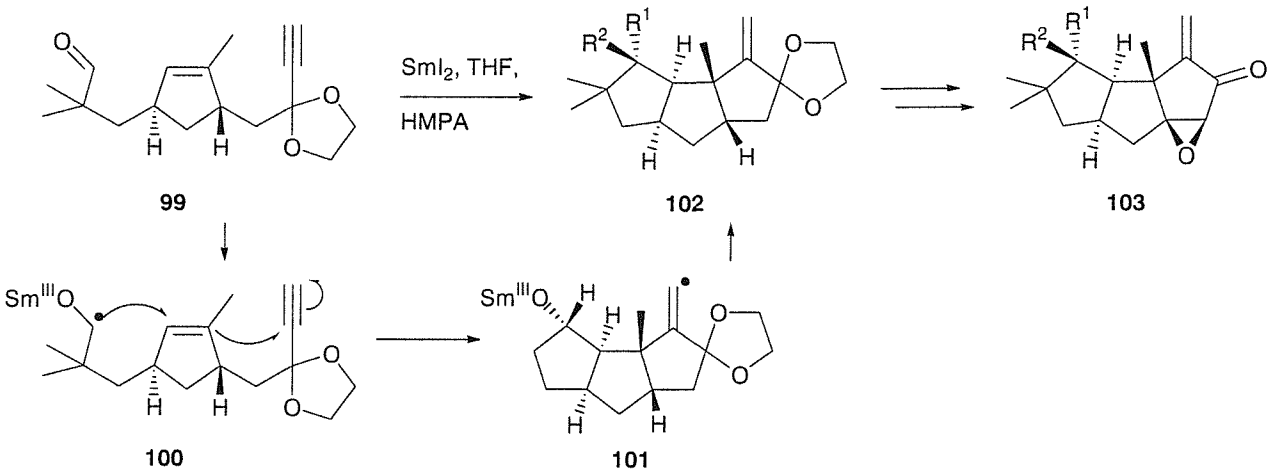
Co-solvent	Time (min)	97 : 98	Yield
H_2O	<1	4.5 : 1	44
MeOH	5	4 : 1	66
MeOH/HMPA	<1	4 : 1	35
EtOH	85	1 : 1	84
^{t}BuOH	540	1 : 2	53

Scheme 1.20

The additives used were probed for their capacity at improving the reducing potential of SmI_2 as well as being proton sources. Methanol (in a 1:4 ratio in THF) proved to be the most effective additive overall and was successfully used, being even more efficient than HMPA in that particular case (35% isolated yield of the products). MeOH has since been used in other examples of cyclisations.[45]

1.3.6) Application of Samarium (II) Iodide to Natural Products

Samarium diiodide has been successfully used in natural product syntheses by Curran.[46] (**Scheme 1.21**)



99 100 101 102 103

Scheme 1.21

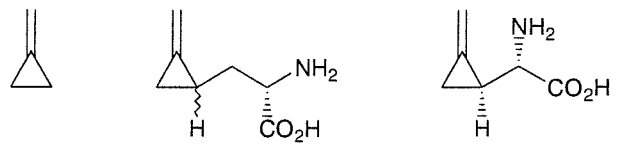
The success of total syntheses using samarium diiodide again shows the versatility and powerfulness of the method.

1.4) METHYLENECYCLOPROPANE

1.4.1) Biological and Physical Characteristics

Methylenecyclopropane **104** is a commercially available volatile olefin (Bp. 8-11°C) it is stable at ambient temperature and pressure and can be stored for years without decomposition.

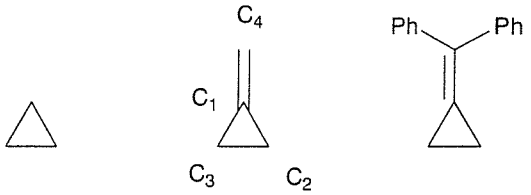
A measure of the stability of methylenecyclopropane can be appreciated by its presence in some naturally occurring molecules such as hypoglycin A **105** and methylenecyclopropylglycine **106** both displaying powerful biological activity.[47] (**Fig. 1.12**). Hypoglycine A can be isolated from the seeds of unripe fruit of ackee tree (*Blighia sapida*) and is responsible for the Jamaican vomiting sickness.[48] Methylenecylopropylglycine is found in the kernels of litchi fruits and causes hypoglycaemia in rats and mice.[49]



104 **105** **106**

Figure 1.12

The structure of methylenecyclopropane has been determined by microwave spectroscopy.[50] The ring is even more strained than cyclopropane due to the exocyclic double bond, which reduces both bond lengths and angles within the cycle. (**Fig. 1.13**)



107 **104** **108**

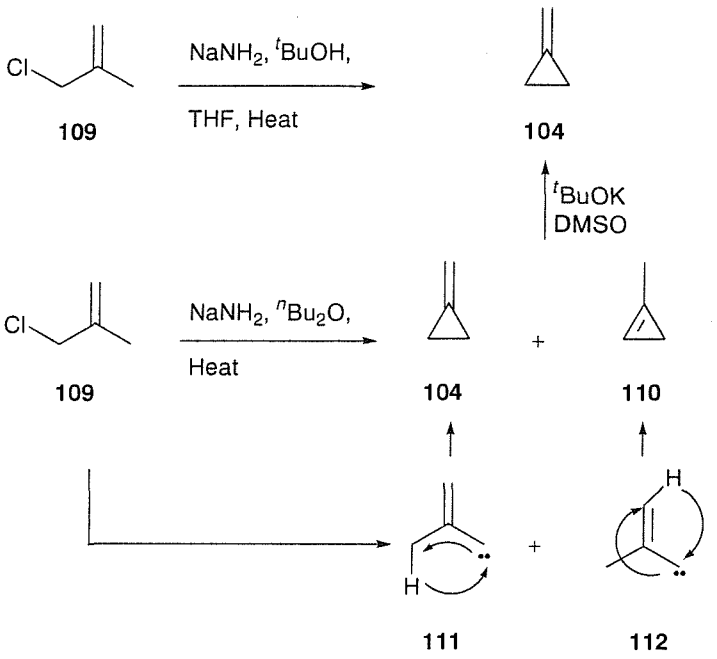
	Angle C_3-C_1-C_2	Bond Length (Å) C_1-C_2	C_1-C_3	C_2C_3	C_1-C_4
Cyclopropane **107**:	60.0	1.510			
Methylencyclopropane **104**:	63.9	1.457	1.457	1.457	1.332
1-(diphenylmethylene) **108**: -cyclopropane	62.8	1.482	1.450	1.528	1.323

Figure 1.13

Upon hydrogenation of this double bond 13.0 kcal.mol^{-1} of strain energy is released confirming the importance of the exocyclic double bond in the overall strain.[50b]

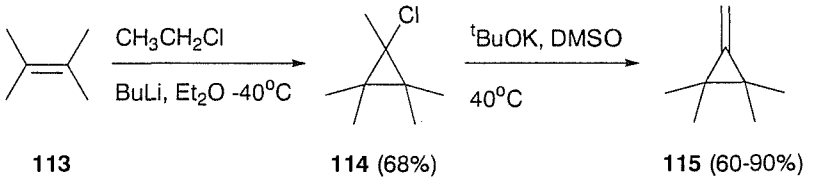
1.4.2) Synthesis of Methylenecyclopropanes

Although there have been numerous methods for the synthesis of substituted methylenecyclopropanes,[46,51,52] there are fewer reports which account for the formation of the substance itself.[53,54] Methylenecyclopropane **104** is a readily available molecule prepared from methallyl chloride **109**.[55] The reaction can be carried out in one or two steps. The first method requires **109** to be added to a mixture of $NaNH_2$ and ^tBuOH but the purification is difficult. The second method yields a mixture of methylenecyclopropane **104** and methylcyclopropene **110**, but the latter can be isomerised to **104** exclusively. (**Scheme 1.22**)



Scheme 1.22

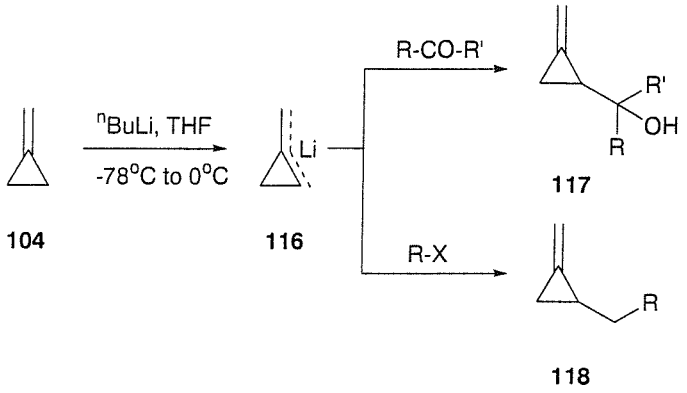
A useful alternative strategy for the synthesis of methylenecyclopropane derivatives is to add a methyl chlorocarbene to a suitably functionalised alkene **113** to give a chloro cyclopropyl **114**, this can be followed by dehydrohalogenation to give compound **115**.[56] **(Scheme 1.23)**



Scheme 1.23

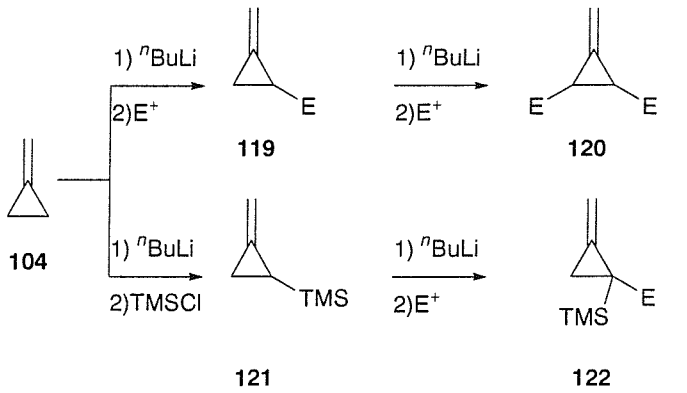
Other methods do exist,[47] but those shown above and in particular the use of methallyl chlorides and sodium amide, seem to be the most convenient and successful.

Methylenecyclopropane **104** can then be deprotonated using ^{n}BuLi to produce the anion **116**, which can be quenched by aldehydes,[57] ketones[58] and alkyl halides[59] to produce a wide variety of substrates. **(Scheme 1.24)**



Scheme 1.24

Disubstituted methylenecyclopropanes can also be obtained using this method. 1,2-Disubstituted methylenecyclopropanes will be formed by two successive deprotonations then alkylation sequences. However, if the first electrophile is a silyl group, 1,1-disubstituted methylenecyclopropanes **122** will be the exclusive product.[60] (**Scheme 1.25**)



Scheme 1.25

1.4.3) Methylenecyclopropanes in Organic Synthesis

Over the last two decades the chemistry of methylenecyclopropane derivatives has been reviewed showing its utility in a number of synthetic transformations.[61,62,62b] Numerous examples exist allowing access to medium sized ring systems have been described.[50b,63]

i- Reactions of the double bond

The double bond of methylenecyclopropane is very reactive. It can take part in a wide range of reactions such as transition metal catalysed reactions, characteristic reactions of olefins, cycloadditions[50b] and can act as a radical trap.[54] **(Fig 1.14)**

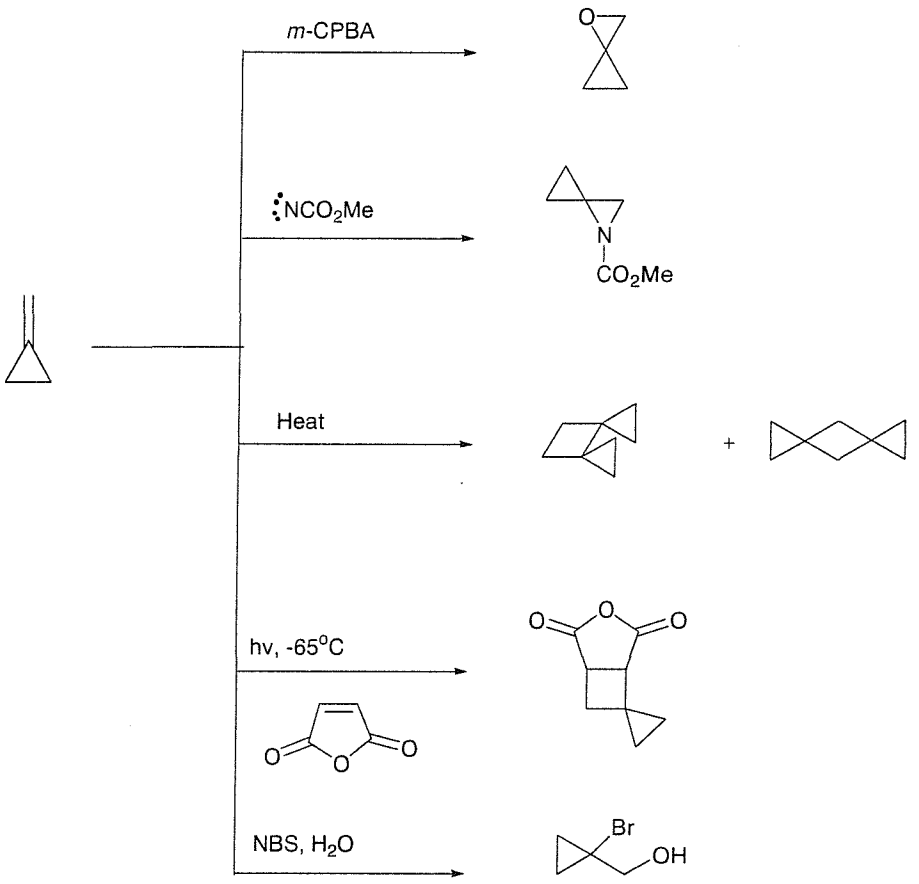
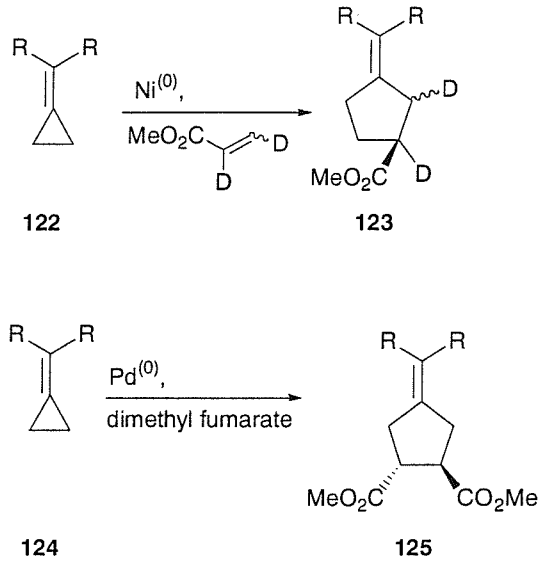


Figure 1.14

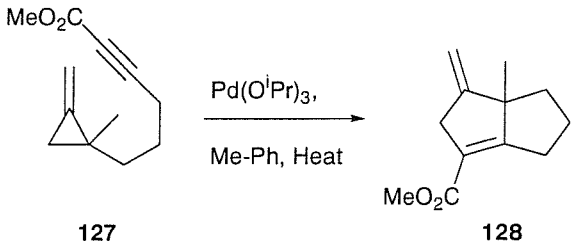
ii- Cycloaddition catalysed by transition metals

[3+2] Cycloadditions take place in the presence of transition metal catalysts and the reactions proceed at moderate temperatures. Such processes have been extensively studied as they allow easy formation of 5-membered rings.[62b,64] The cyclopropyl ring can react in two ways: ring opening of the proximal (C_1-C_2 or C_1-C_3) or the distal (C_2-C_3) bond. Opening of either of these bonds can be targeted selectively depending on the metal catalyst: nickel catalysts have the capacity to open the proximal bond, particularly in the absence of phosphine ligands, whereas palladium opens the distal bond exclusively. **(Scheme 1.26)**



Scheme 1.26

Such reactions also occur intramolecularly.[65] **(Scheme 1.27)**



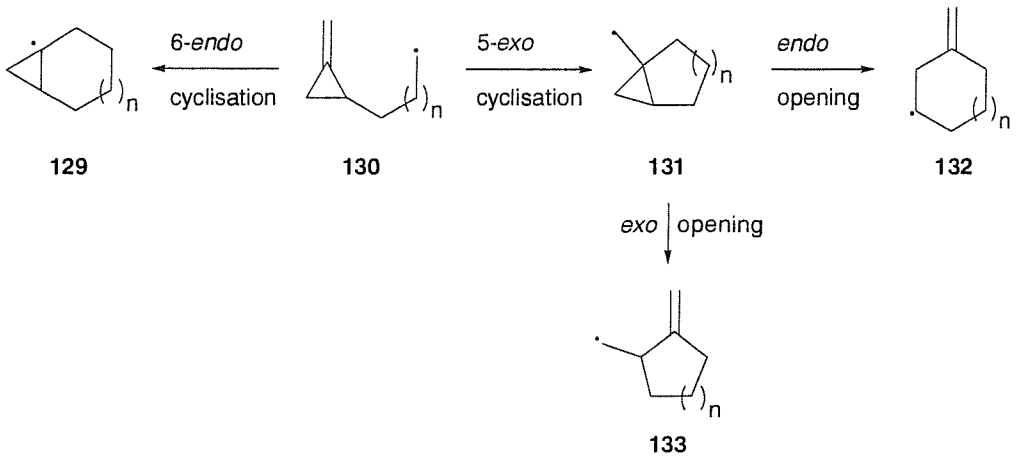
Scheme 1.27

The scope of reactions that involve methylenecyclopropanes is very wide and includes the Pauson-Khand reaction,[66] Diels-Alder cycloadditions,[67] or Lewis acid catalysed cyclisations.[68] It is not possible to give a comprehensive coverage within this introduction and the rest of the section will focus on radical cyclisations of methylenecyclopropane derivatives.

1.4.4) Radical Cyclisation of Methylenecyclopropane Derivatives

i- Introduction

Initial work by Kilburn and co-workers has established the basic methodology of intramolecular radical cyclisations of methylenecyclopropane derivatives. **(Scheme 1.28)**

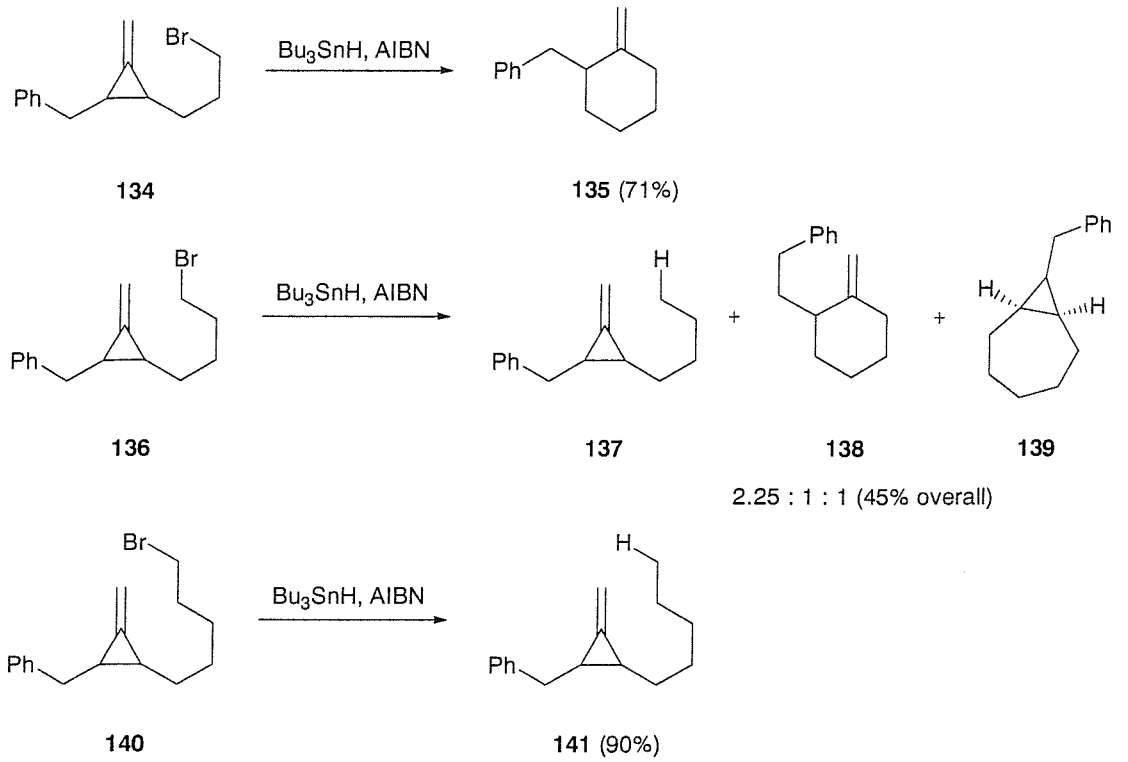


Scheme 1.28

Radical **130** can cyclise in a 6-*endo* fashion leading to radical **129** or undergo a 5-*exo* cyclisation to give **131**. Subsequently, opening of the cyclopropyl ring can occur, again in two different ways: *endo* opening leads to radical **132** while *exo* opening results in radical **133**. Work by Kilburn and Destabel focused on the influence of the alkyl chain length on the distribution of the possible products.[69]

ii- Cyclisation of methylenecyclopropylalkyl radicals

Methylenecyclopropyl-propyl, -butyl and -pentyl radicals were generated from bromides **134**, **136** and **138** respectively. (**Scheme 1.29**) Cyclisation studies showed that the product formed and hence the reaction pathway, varies with the alkyl chain length. Methylenecyclopropylpropyl radical exclusively undergoes a 5-*exo* cyclisation followed by *endo* opening of the cyclopropyl ring to afford cyclohexyl product **135**. When an additional methylene group is incorporated and bromide **136** is reduced to the methylenecyclopropylbutyl radical, a number of products are formed. The radical can be reduced to **137**, it can also cyclise in a 6-*exo* fashion followed by *endo* opening yielding **138** or cyclise in a 7-*endo* fashion to give **139**. The overall process is much less selective and efficient with 45% overall yield. Only the reduced product **141** could be isolated from the attempted cyclisation of bromide **140**.

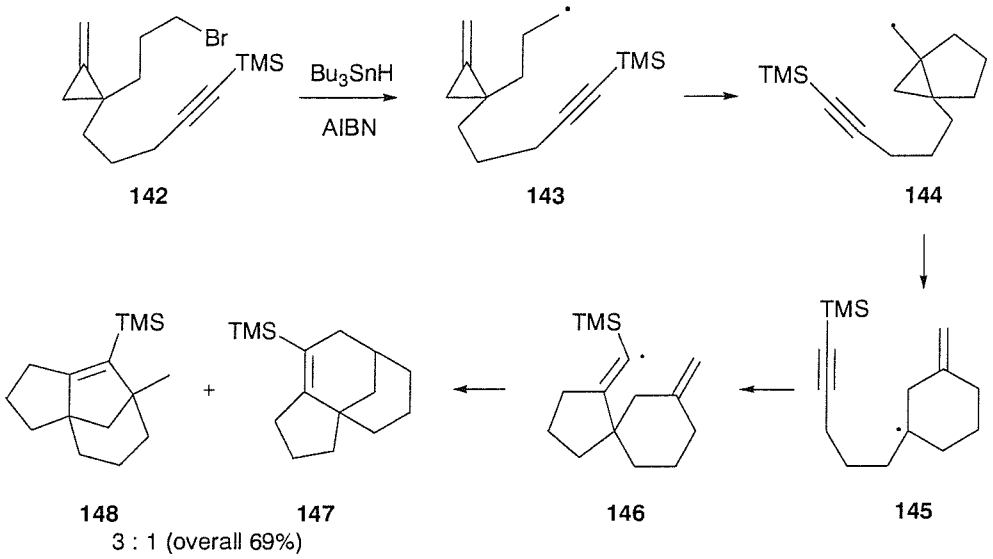


Scheme 1.29

From this work, it was concluded that methylenecyclopropyl propyl radicals cyclise exclusively and efficiently in a 5-*exo* fashion, followed by *endo* ring opening of the resultant cyclopropylmethyl radical, proving an effective method to access 6-membered rings.

iii- Cascade radical cyclisation of methylenecyclopropane derivatives

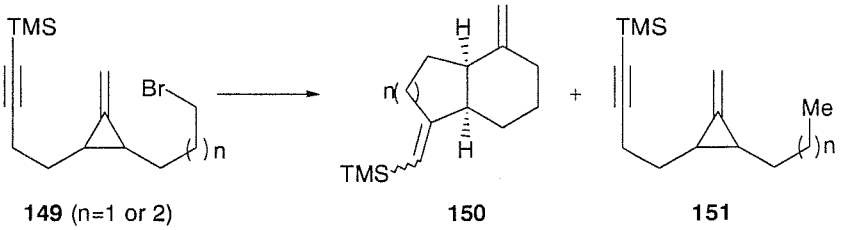
Work by Kilburn and Santagostino investigated whether the methylene-cyclohexyl radical such as **145** could be trapped using an additional alkyne moiety tethered to the methylenecyclopropane to produce spirocyclic systems.[70] (**Scheme 1.30**).



Scheme 1.30

Radical **143**, generated from the bromide **142**, underwent a 5-*exo* cyclisation followed by *endo* ring opening to give the intermediate methylenecyclohexyl radical **145**. The alkyne moiety then trapped the intermediate through a further 5-*exo* radical cyclisation to give **146**. Although the cascade was expected to stop at this point, vinyl radical **146** was sufficiently reactive to undergo further 5-*exo* and 6-*endo* cyclisation onto the cyclohexyl double bond to form tricyclic products **147** and **148** in 69% overall yield. Note that the use of the bulky TMS group ensured that radical **145** would undergo a 5-*exo* attack.

Kilburn and Pike produced 6,5- and 6,6-bicyclic systems and carried out further investigation of this methodology, directed towards the synthesis of coronafacic acid.[71] **(Scheme 1.31)**



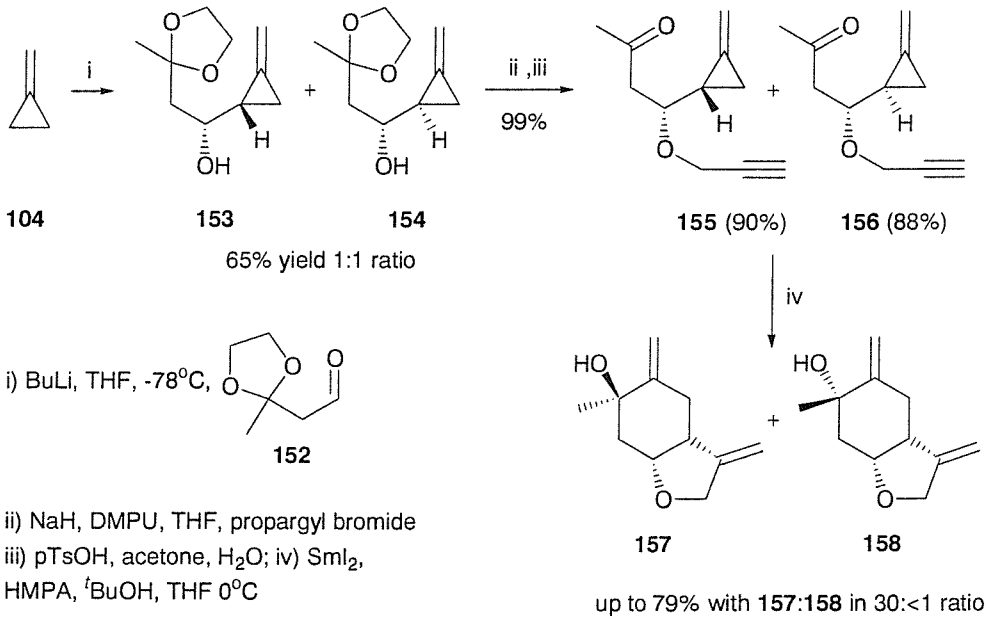
	150	**151**
n=1	67%	20%
n=2	40%	18%

Scheme 1.31

Once formed from the corresponding bromide **149**, 1,2-disubsituted methylenecyclopropyl radical underwent the usual sequence of 5-*exo* cyclisation followed by *endo* opening of the cyclopropyl ring. Subsequently, a 5-*exo* cyclisation allowed the formation of bicyclic skeleton **150** in reasonable to good yields. Alongside the cyclisation adduct, reduction product **151** was also formed.

1.4.5) Samarium (II) Iodide Mediated Cascade Radical Cyclisations

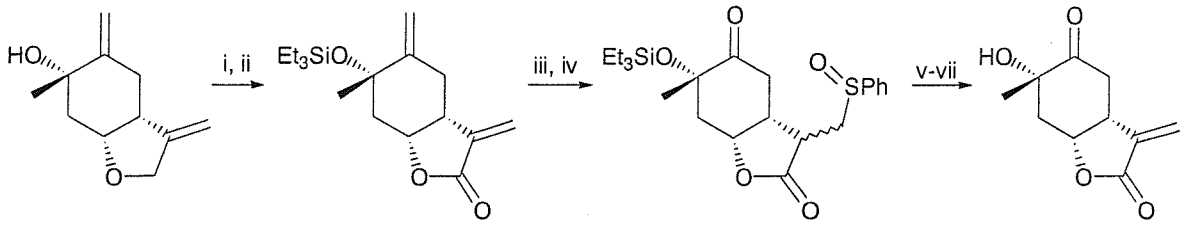
An application of samarium diiodide radical cyclisation involving methylenecyclopropanes is shown by the work undertaken by Kilburn and Boffey in the total synthesis of Paeonilactone B **161.**[72] **(Scheme 1.32 and 1.33)**



Scheme 1.32

Ketals **153** and **154** were obtained in overall 65% yield as a 1:1 mixture of isomers by reaction of aldehyde **152** with lithiated methylenecyclopropane. After propargylation of the alcohol moieties and deprotection to ketones **155** and **156**, a cyclisation study was undertaken for both isomers. The most promising result for the complete synthesis was the cyclisation of **156** with SmI_2, HMPA and ^tBuOH at 0°C, yielding **158** in 79% and high diastereoselectivity.

Bicyclic compound **158** underwent some functional group manipulations to obtain the target molecule. (**Scheme 1.33**)



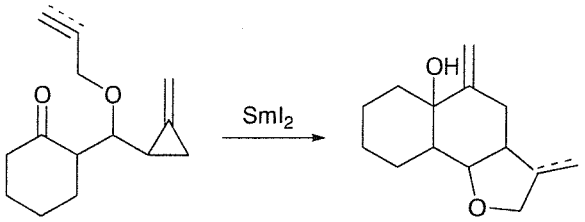
158 **159** (45%) **160** (43%) **161** (43%)

Reagents and conditions:
i) Et_3SiOTf, CH_2Cl_2, 0°C; ii) CrO_3, py, CH_2Ci_2, room T; iii) PhSH, Et_3N, MeOH
iv) O_3, MeOH v) Me_2S; vi) CCl_4, reflux vii) HF, py, THF

Scheme 1.33

Building on the promising success of the cyclisation, Kilburn and Watson reported samarium (II) iodide mediated radical cyclisation of methylenecyclopropane applied to the synthesis of the eudesmane tricyclic framework.[45]

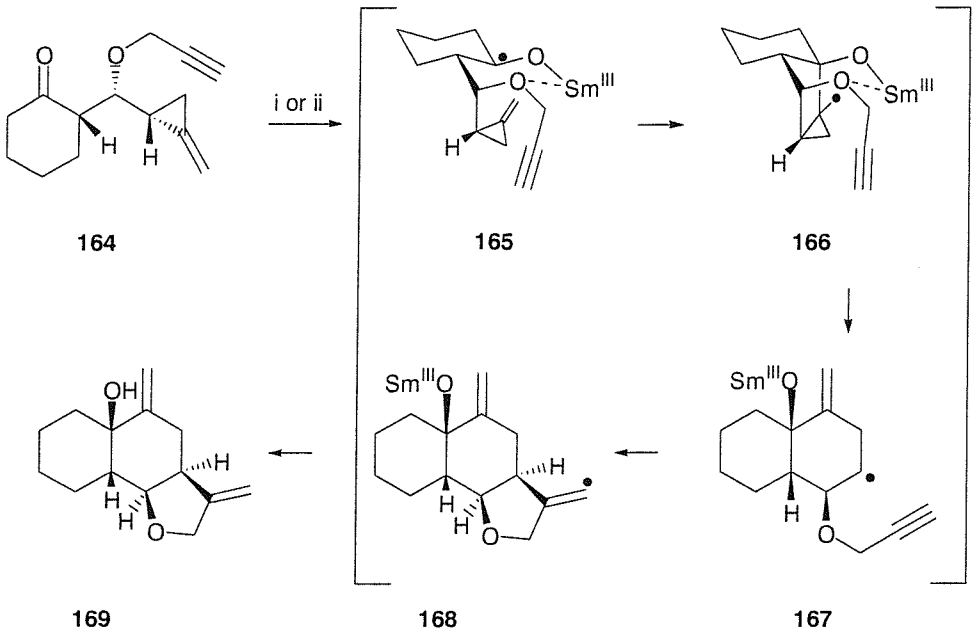
Both propargyl and allylether ketone derivatives of methylenecyclopropane were synthesised and subjected to cyclisation using SmI_2. (**Scheme 1.34**)



162 **163**

Scheme 1.34

Two isomers of propargyl ether **164** and **170** were obtained and used in the cyclisation studies. When isomer **164** was cyclised, tricyclic product **169** was obtained in good yield as a single diastereoisomer. (**Scheme 1.35**)



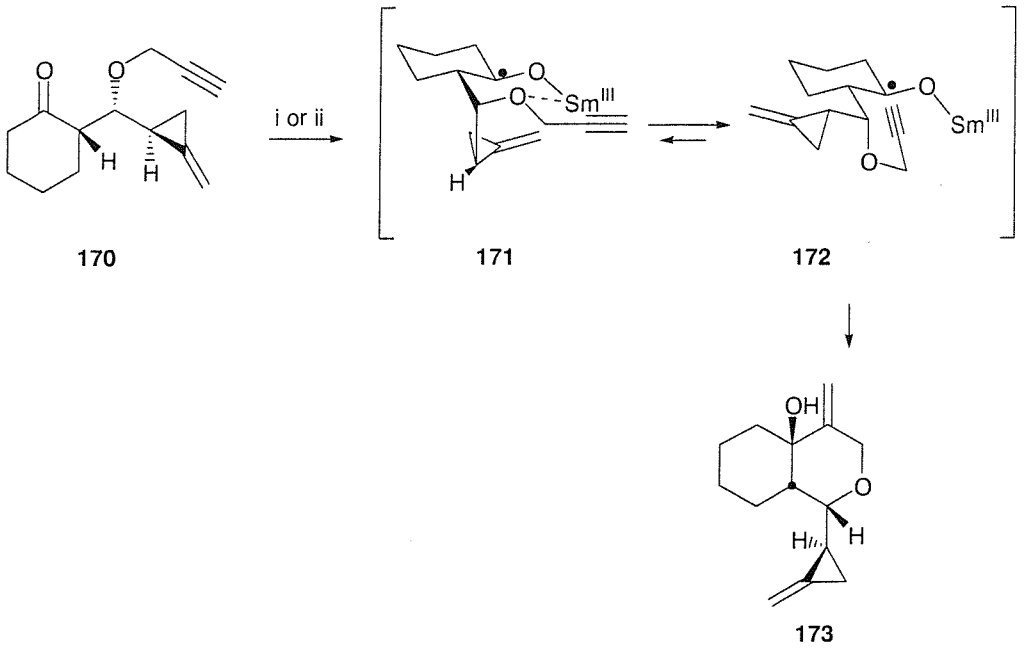
164 165 166 167 168 169

Conditions: i) SmI_2, ^tBuOH, HMPA, THF, -78°C (50% yield); ii) SmI_2, MeOH, THF, -78°C (60% yield)

Scheme 1.35

The presence of the propargyl group reduces the effectiveness of the chelation but radical **165** still adopts a chair-like transition state to give product **169**.

Cyclisation of the second isomer **170**, however, does not proceed similarly. Instead, radical **171** flips to the more favoured conformation **172** where the π-system of methylenecyclopropane is no longer eclipsed with the ketyl radical, losing the chelation. Thus the radical cyclises onto the propargyl moiety, leading to bicycle **173**. (**Scheme 1.36**)



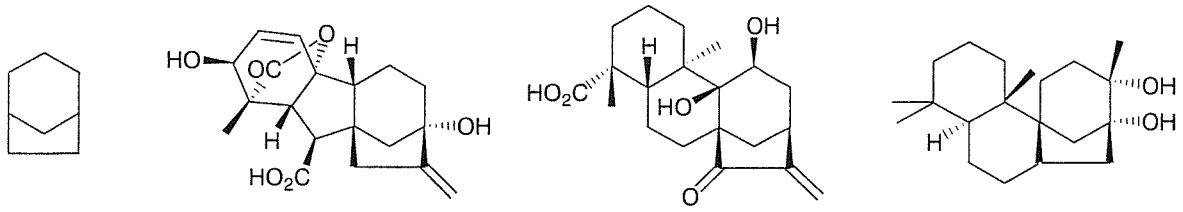
Conditions: i) SmI_2, ^tBuOH, HMPA, THF, -78°C (74% yield); ii) SmI_2, MeOH, THF, -78°C (75% yield)

Scheme 1.36

Similar results were obtained upon cyclisation of allyl ether precursors.

1.5) PROGRAMME OF WORK

The starting point of the project was to attempt the synthesis of bicylo-[3.2.1]-octanes. This system can be found in a number of higher order polycyclic skeletons of natural products.[73] **(Fig. 1.15)**



Bicyclo[3.2.1]octane

Gibberellic Acid

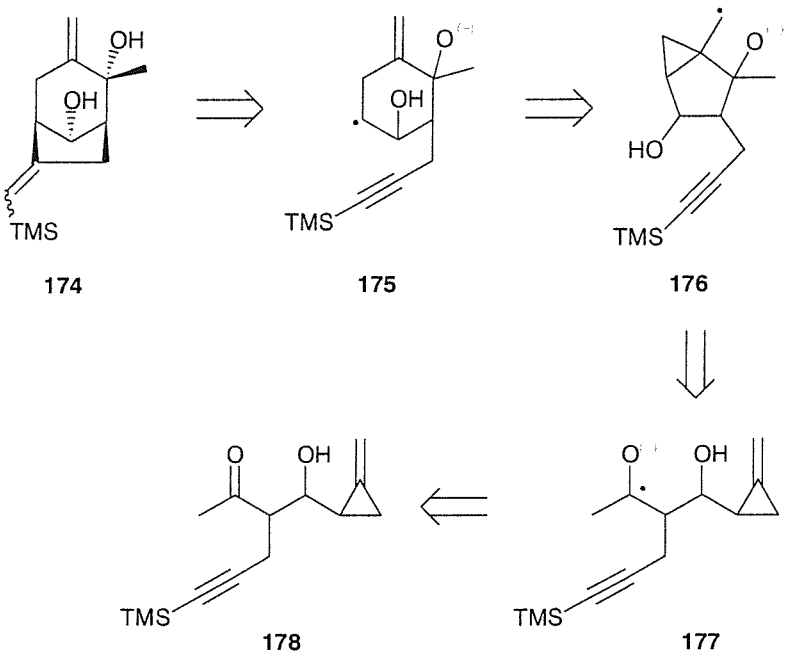
Adenostemmoic acid
Kaurenoid family

13$^{\alpha}$,14$^{\alpha}$-Stemodandiol

Figure 1.15

Gibberellins and kaurenoids are families of more than one hundred highly functionalised diterpenoids found in most plants. They act as growth factors but some members have been shown to have other biological activities. Kaurenoids also have an important role in the biology of plants. Some work on partial synthesis and manipulation between gibberellins has been undertaken but very few total syntheses have been reported.[73,74]

We wanted to investigate the possibility of synthesising the bicyclo octane unit *via* samarium diiodide mediated cascade radical cyclisations of methylenecyclopropane derivatives. Functionalised bicyclo-[3.2.1]-octane **174** can be disconnected to ketone derivatives of methylenecyclopropane **178**. Using samarium (II) iodide as the radical initiator should allow some control over the stereochemical outcome of the process. (**Scheme 1.37**)

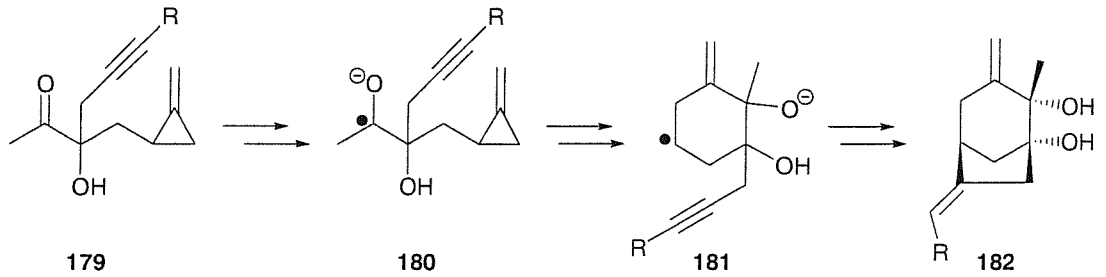


Scheme 1.37

The high functionalisation of the products was seen as an advantage if the route could be pursued towards total synthesis.

Stemodandiol (**Fig. 1.15**) is another example of natural product containing the bicyclo-octane skeleton.[75] Besides, the bicyclo-octane fragment **174** contains two alcohols

in a *syn* configuration, which we expected to achieve through samarium co-ordination. **(Scheme 1.38)**



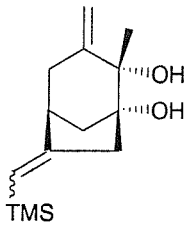
Scheme 1.38

The work focused on the synthesis of bicyclo-octanes of increasing complexity and resemblance to the family of natural products.

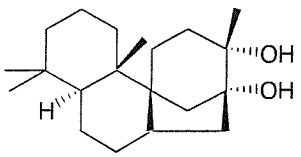
CHAPTER 2: EPOXIDE OPENING WITH METHYLENECYCLOPROPANE, AN APPROACH TO BICYCLO-[3.2.1]-OCTANES

2.1) INTRODUCTION

One of our aims was to look at the synthesis of **183**, a bicyclo[3.2.1]octane containing a *syn*-1,2-diol. Such a system is of interest as it can be found in the natural product 13^{α},14^{α}-stemodandiol.[76] **(Scheme 2.1)**.



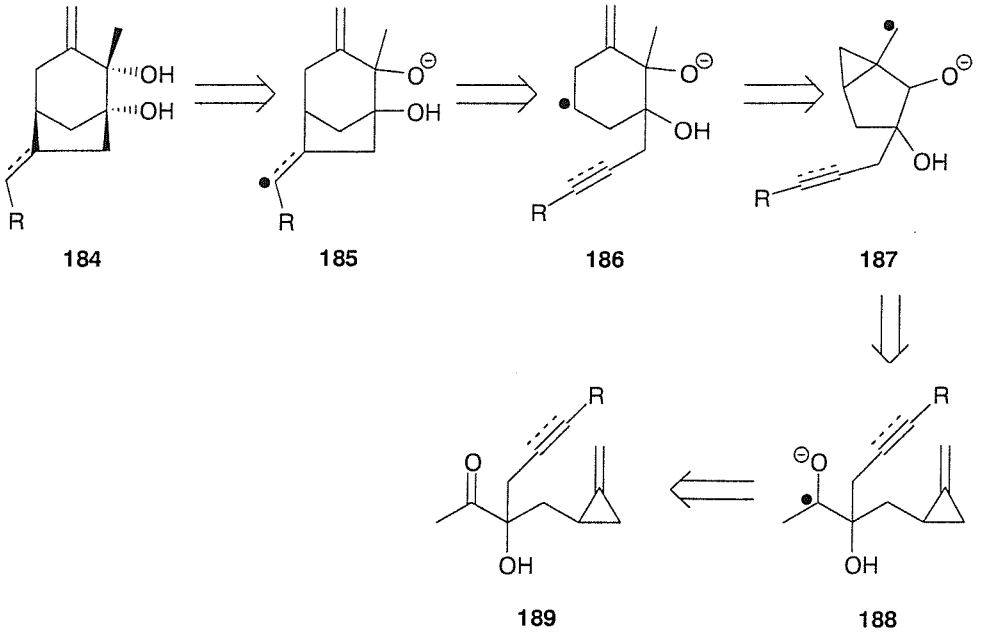
183



13^{α},14^{α}-Stemodandiol

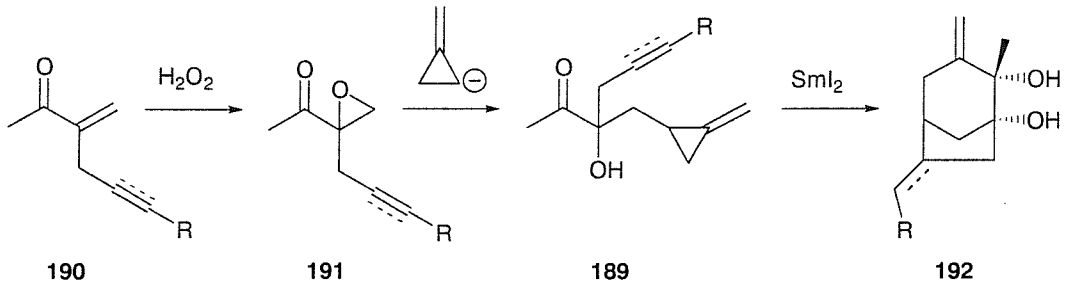
Scheme 2.1

Compound **183** was targeted because it could be disconnected back to a methylenecyclopropane derivative and the use of samarium diiodide as the radical initiator would also allow the *syn*-stereochemistry between the two alcohol groups to be obtained. **(Scheme 2.2)**



Scheme 2.2

1,2-Keto alcohol **189**, the starting material for the cyclisation process, could arise from the regioselective attack of a nucleophilic methylenecyclopropane onto a 1,2-ketoepoxide. (**Scheme 2.3**)

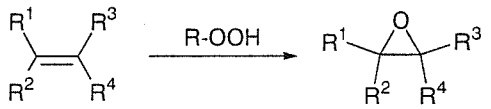


Scheme 2.3

Work was therefore directed towards the study of the reactions of methylenecyclopropane nucleophiles with epoxides as a route to precursor **189**.

2.2) *SYNTHESIS OF EPOXIDES*

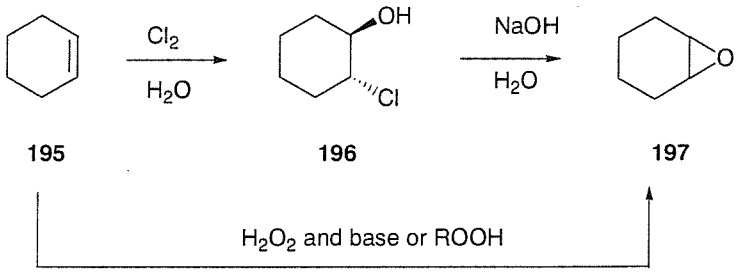
Epoxides are strained 3-membered ring heterocycles which can be synthesised in a number of ways. The most widely used method of epoxidation is the reaction of alkenes with peroxides.[80] **(Scheme 2.4)**



193 **194**

Scheme 2.4

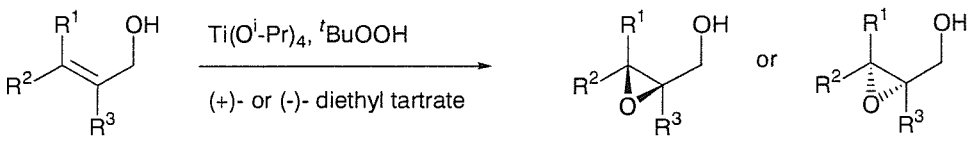
The peroxide oxidant can be hydrogen peroxide (R= H), an alkyl group (R= ^{t}Butyl) or an aryl group such as in 4-chloroperbenzoic acid (*m*-CPBA).
Other precursors include halohydrins[77] or allylic alcohols.[78] **(Scheme 2.5)**



195 **196** **197**

Scheme 2.5

In 1980, Sharpless and co-workers reported the first method of asymmetric synthesis of epoxides.[80] **(Scheme 2.6)**



198 **199** **200**

70-90% yield; 90% ee minimum

Scheme 2.6

Treatment of an allylic alcohol with ^{t}BuOOH, a titanium complex, titanium tetraisopropoxide, and the chiral diethyl tartrate was used to induce asymmetry. The method is now known as the Sharpless asymmetric epoxidation.

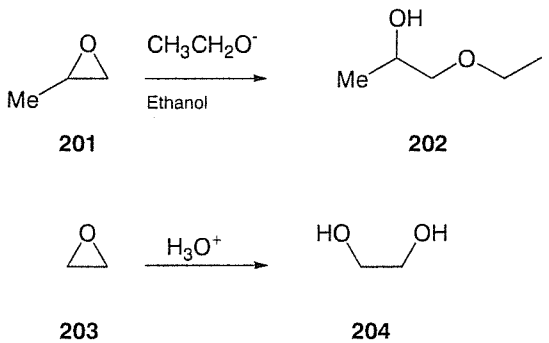
Since then, numerous routes to asymmetric epoxides have been investigated and new methodology has been devised. Regular updates are available in the literature.[79]

2.3) REACTIONS OF EPOXIDES

Reactions of epoxides with nucleophiles occur under mild conditions due to ring strain and result in ring opening and the generation of an alcohol. Over the years epoxides have developed into useful intermediates in organic synthesis and a lot of attention has focused on the regio- and stereo-selectivity of epoxide opening reactions.

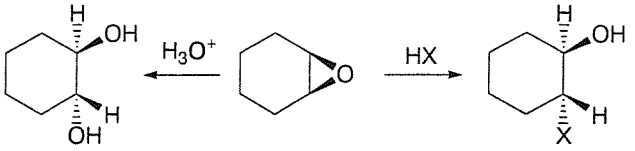
2.3.1) Attack by Nucleophilic Anions

A wide number of nucleophiles can be used to cleave epoxides and the product and regioselectivity depend on a number of factors such as the nature of the nucleophile or the epoxide itself.[80] **(Scheme 2.7)**



Scheme 2.7

Treatment of epoxides with acids or halogen hydrides result in *trans*-diols or *trans*-halohydrins *via* a S_N2 mechanism.[80] **(Scheme 2.8)**



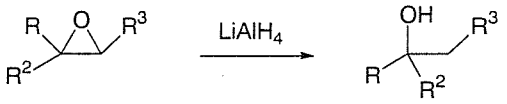
206 205 207

Scheme 2.8

Attack under S_N2 conditions usually occurs at the less substituted end of more complex epoxides whereas acid catalysed opening under S_N1 conditions proceeds *via* the most stable cation.

2.3.2) Reduction of Epoxides

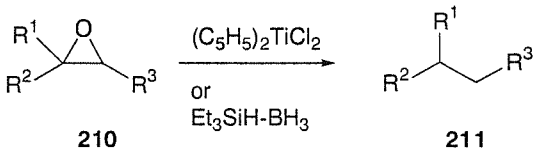
Epoxides can be reduced to the alcohol, by reaction with reagents such as $LiAlH_4$ forming higher order alcohols preferentially.[80] (**Scheme 2.9**)



208 209

Scheme 2.9

Epoxides can be fully reduced by titanocene dichloride[81] or by triethylsilane-boron complex,[82] leading to alkanes. (**Scheme 2.10**)

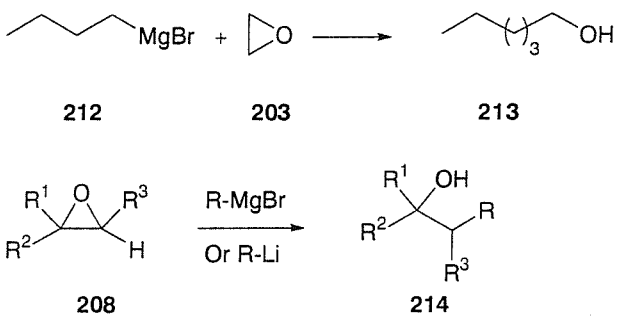


210 211

Scheme 2.10

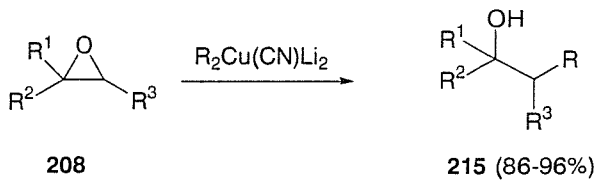
2.3.3) Epoxide Opening with Organometallic Reagents

Alkyl lithiums are widely used to open epoxides, attacking at the least hindered end.[80] (**Scheme 2.11**) Grignard reagents also add to unsubstituted epoxides to yield alcohols in a S_N2 fashion. Reaction occurs at the least hindered carbon of substituted epoxides.



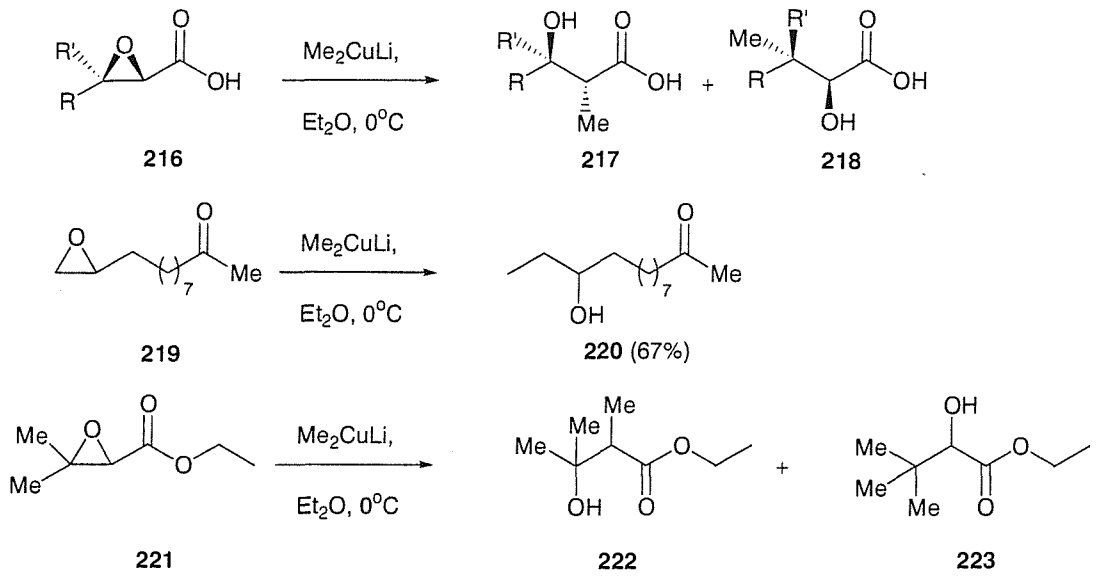
Scheme 2.11

High yields can also be achieved by using organocopper reagents to open epoxides. Lipshutz reported that higher order mixed organocuprates react with polysubstituted epoxides in good to excellent yield.[83] (**Scheme 2.12**)



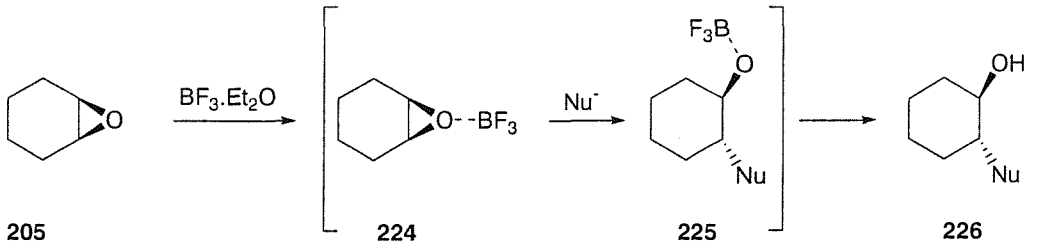
Scheme 2.12

Moreover, organocuprates have the advantage over lithium alkyls as they will not react with other functional groups present in the substrate such as carboxylic acids, ester or ketones. (**Scheme 2.13**) Sharpless showed that reactions of 2,3-epoxy acids with methyl cuprates lead to 1,3- and 2,3-hydroxy carboxylic acids.[84] The regiochemistry of the opening depends on the substrate. Work by Johnson presented the reactions of epoxy-ketones under the same conditions, allowing the formation of keto-alcohols.[85] Epoxy esters can also be opened by reaction with alkyl cuprates, leading to both regioisomers of the hydroxy ester product.[86]



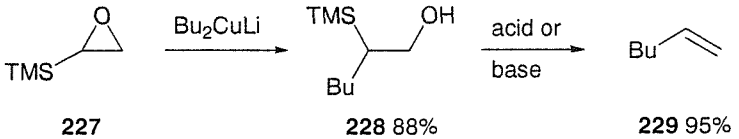
Scheme 2.13

To overcome the problem of the thermal instability of organocopper reagents but also to enhance the reactivity of some epoxides, Alexakis studied the effect of the Lewis acid BF_3 on the opening of epoxides with organocuprates.[87] The addition of a stoichiometric amount of $BF_3.Et_2O$ to the reaction greatly improved the yield of the opening of the poorly reactive cyclohexene oxide. **(Scheme 2.14)**



Scheme 2.14

α,β-Epoxysilanes react with organocuprates specifically to give β-hydroxysilanes in excellent yields, moreover, as shown by Hudrlik, these compounds can be readily converted to alkenes by elimination.[88] **(Scheme 2.15)**



Scheme 2.15

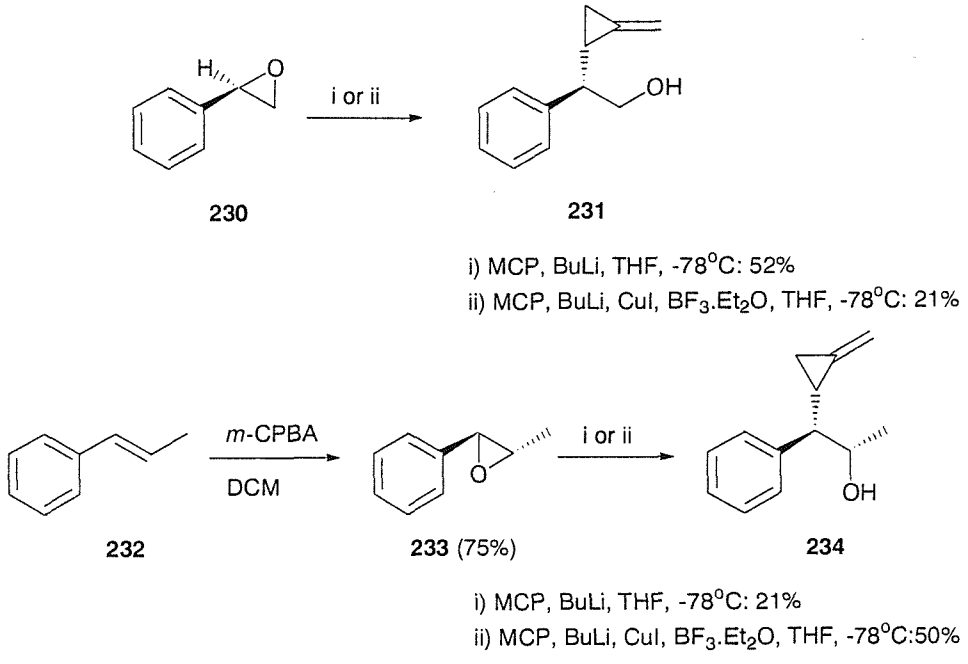
Work therefore began by investigating the opening of epoxides with methylenecyclopropane lithium and methylenecyclopropyl cuprate.

2.4) Opening Of Epoxides With Methylenecyclopropanes

2.4.1) Opening of simple epoxides

The first stage of our work looked at phenyl epoxides and their behaviour upon reaction with nucleophilic methylenecyclopropanes. (**Scheme 2.16**)

Reaction of styrene oxide **230** with both lithiated methylenecyclopropane and methylenecyclopropyl cuprate gave primary alcohol **231** *via* opening of the epoxide next to the aromatic ring.[89] Lithiated methylenecyclopropane gave a better yield than the cuprate, which would only react in the presence of a Lewis acid, here $BF_3.Et_2O$.



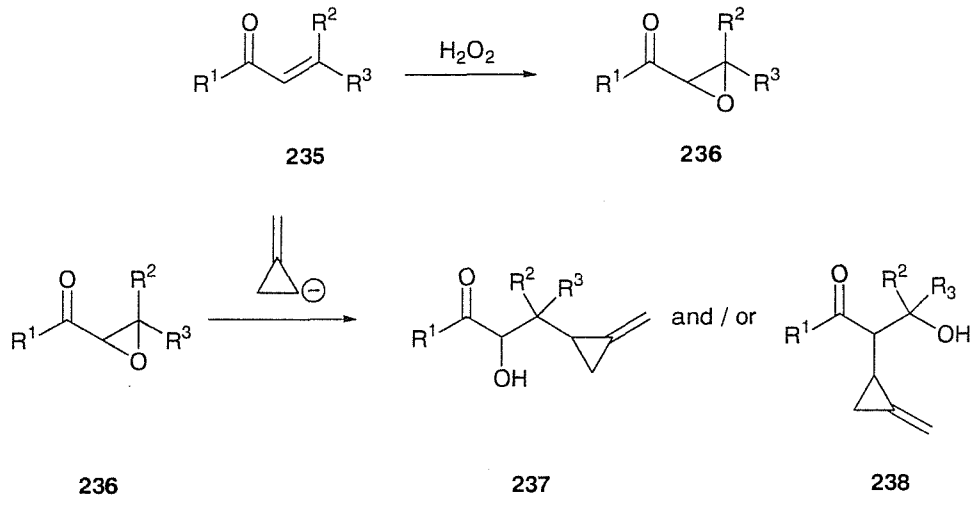
Scheme 2.16

Reaction of 2-methyl-3-phenyloxirane **233**, synthesised from *trans*-β-stirene **232** in good yield, again led to reaction α- to the benzene ring. Both reactions resulted in the formation of two separable isomers of **234** in a 2:1 ratio. Reaction with methylenecyclopropyl cuprate gave the best result.

Having shown that methylenecyclopropanes can be used in epoxide opening reaction, work was then extended to consider keto-epoxide in an effort to prepare compounds such as the cyclisation precursor **189**.

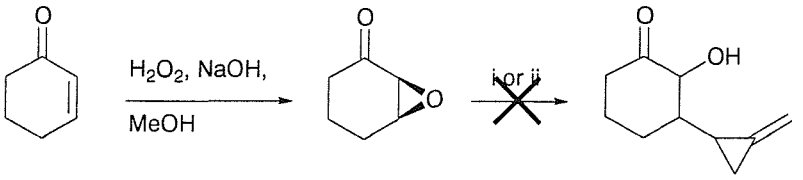
2.4.2) Synthesis and opening of keto-epoxides

Keto-epoxides are easily accessed by oxidation of 1,2-unsaturated ketones with hydrogen peroxide.[90] Two test compounds were synthesised anticipating that their reaction with a nucleophilic methylenecyclopropane would result in the formation of a keto-alcohol. **(Scheme 2.17)**

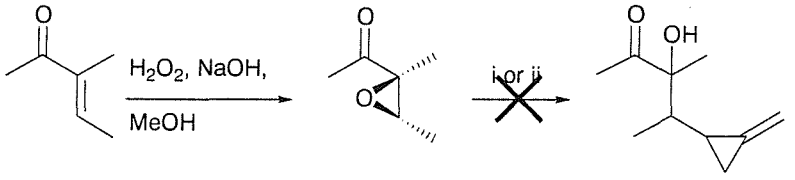


Scheme 2.17

Two keto-epoxides were synthesised by treatment of cyclohexenone **239** and 3-methyl-3-penten-2-one **242** with alkaline hydrogen peroxide in 91% and 83% yield respectively. **(Scheme 2.18)**



239 **240** (91%) **241**



242 **243** (83%) **244**

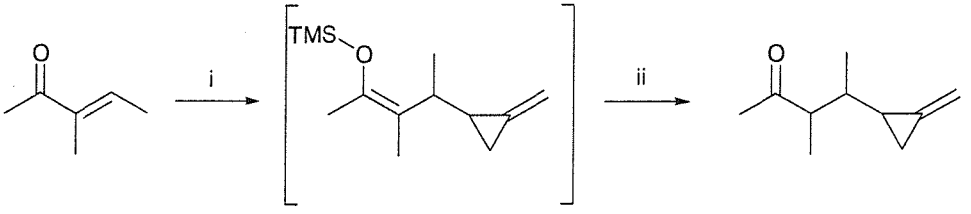
i) MCP, ^{n}BuLi; ii) MCP, ^{n}BuLi, CuI, $BF_3.Et_2O$

Scheme 2.18

Unfortunately no product could be isolated from the treatment of **240** and **243** with either lithiated methylenecyclopropane or methylenecyclopropyl cuprate which so far is unexplained. Referring to the literature, all reported examples of opening of keto-epoxides with nucleophiles yielded the 1,3-regioisomer (Cf. **238**).[91]

2.4.3) Methylenecyclopropyl cuprate reaction with Michael acceptors

Previous work in the group studied the addition of methylenecyclopropyl cuprates to 1,2-unsaturated ketones in a Michael type reaction.[89] **(Scheme 2.19)** The cuprate of methylenecyclopropane attacks Michael acceptors **242** in a 1,4 fashion and the resulting enolate anion can then be trapped with TMSCl. On acidic work-up, silyl enol ether **245** is cleaved to restore ketone **246**. The versatility of the method was demonstrated by the successful use of a number of Michael acceptors.

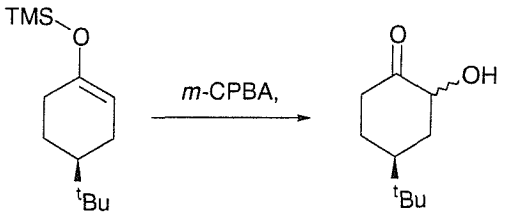


242 **245** **246**

I) MCP, ^{n}BuLi, CuI, Me_3SiCl, THF, -78°C; ii) 1M HCl

Scheme 2.19

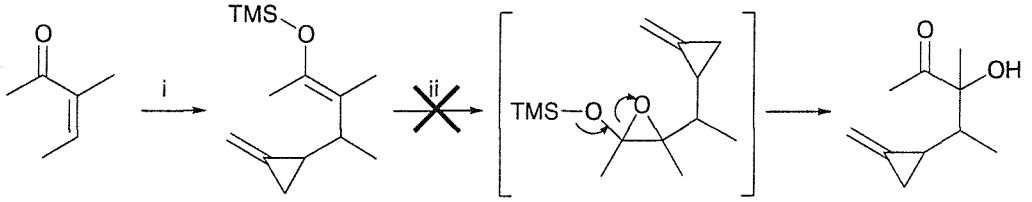
Cain reported the conversion of silyl enol ethers to 1,2-keto-alcohols in the presence of *m*-CPBA.[92] **(Scheme 2.20)**



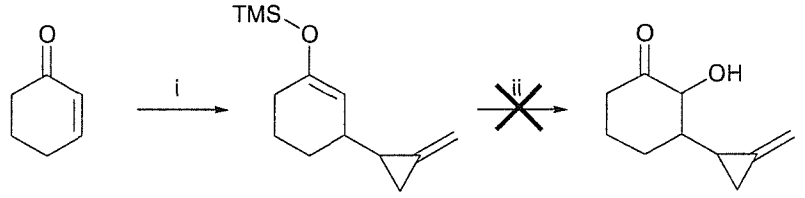
247 **248**

Scheme 2.20

We therefore wanted to combine these two methods to try to obtain 1,2-keto alcohols similar to the designed precursor **189. (Scheme 2.21)**



242 **249** **250** **251**



239 **252** **253**

i) MCP, ^{n}BuLi, CuI, THF, -78°C; ii) *m*-CPBA, DCM, 0°C

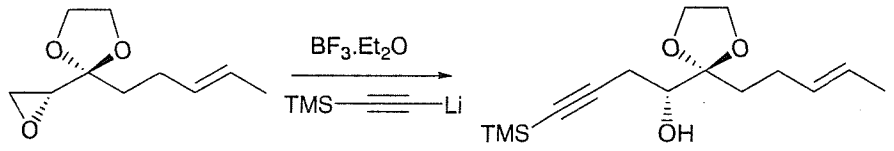
Scheme 2.21

The chemistry was again attempted using ketones **242** and **239**. In both cases, silyl enol ethers **249** and **252** could not be isolated as decomposition occurred during chromatography. Reaction of the crude mixture was not successful either and no meaningful product could be isolated from either of the reactions. It is possible that competition for oxidation between the double bond of methylenecyclopropane and the enol

or double oxidation could be the cause of the problem as oxidation of the double bond of methylenecyclopropane derivatives has been reported.[93]

2.4.4) Opening of epoxides of protected ketones

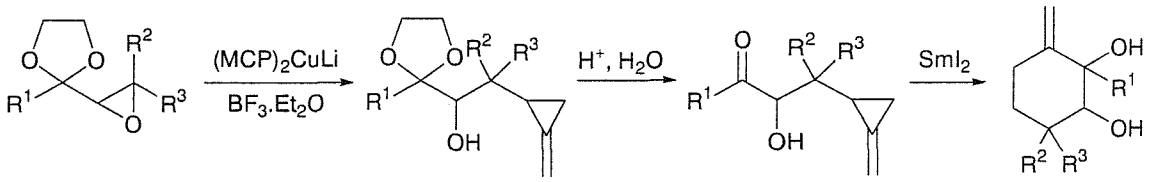
Shair reported the regiospecific opening of an epoxide substituted with a ketone, protected under the form of a ketal as part of their total synthesis of phomoidride B.[94] (**Scheme 2.22**) Therefore attention was turned back to keto-epoxides.



254 **255** (85%)

Scheme 2.22

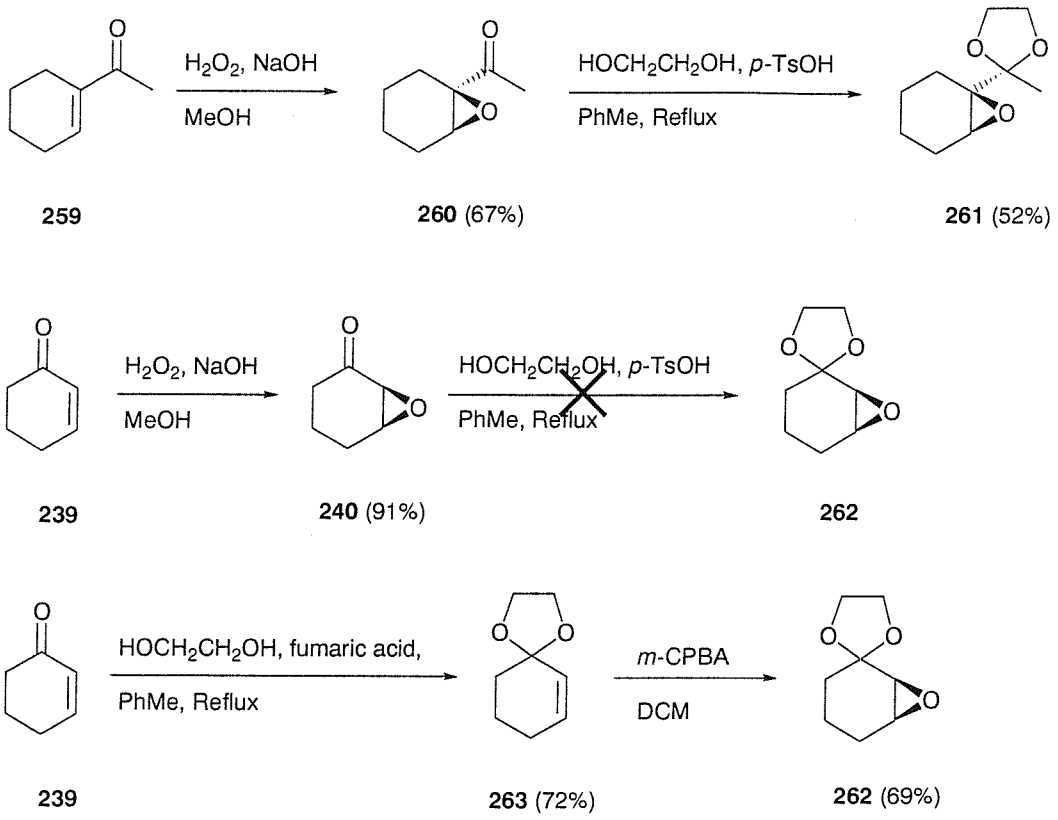
Reaction of compound **256** with a cuprate or lithiated MCP was anticipated to give the right regioselectivity and that, after deprotection of the ketone, cyclisation studies could be undertaken. (**Scheme 2.23**)



256 **257** **237** **258**

Scheme 2.23

We wanted to study the opening of several epoxides before attempting to obtain **189**, the precursor to the cyclisation. (**Scheme 2.24**)

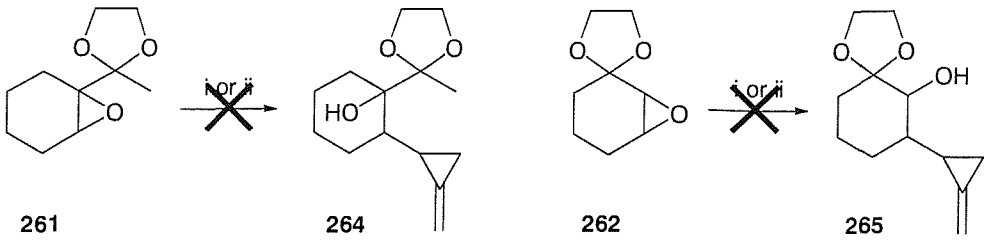


Scheme 2.24

Acetyl cyclohexene **259** could easily be converted to the corresponding epoxide **260** by reaction with hydrogen peroxide in methanol under basic conditions in good yield. Protection of the ketone to the ketal afforded compound **261** in average yield.

Attempts at the protection of cyclohexanone epoxide **240** proved unsuccessful but the protected cyclohexanone epoxide **262** could be obtained in 72% by *m*-CPBA epoxidation of the cyclohexene ketal **263**. Protection of cyclohexenone **239** was undertaken with fumaric acid to avoid migration of the double bond as observed when *p*-toluene sulphonic acid is used.[95]

Unfortunately treatment of the epoxy ketals with methylenecyclopropane nucleophiles was unsuccessful for both compounds. (**Scheme 2.25**)



261 264 262 265

i) MPC, ^{n}BuLi; ii) MCP, ^{n}BuLi, CuI, $BF_3.EtO_2$

Scheme 2.25

When **261** or **262** where treated with lithiated MCP, decomposition occurred and no product could be isolated. Reaction with the milder methylenecyclopropyl cuprate and $BF_3.Et_2O$, no reaction occurred and the starting material was recovered.

2.5) CONCLUSION

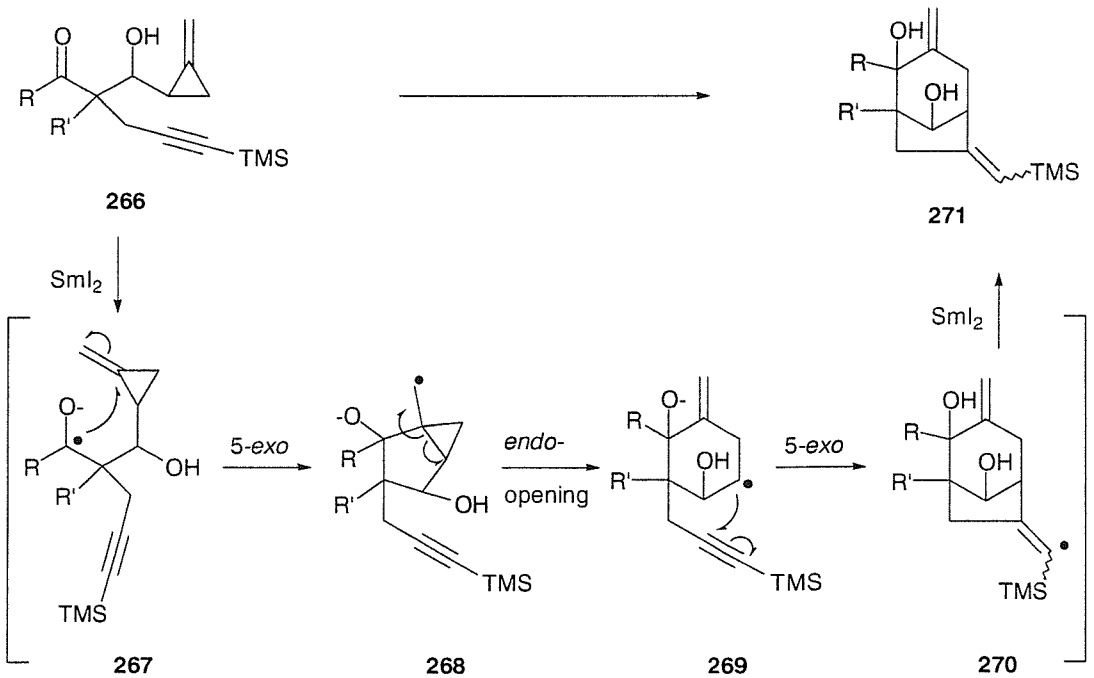
Opening some epoxides with both lithiated MCP and methylenecyclopropyl cuprate proved successful. Unfortunately, precursor **189** or any related compounds could not be obtained by reaction of keto-epoxides, protected keto-epoxides or by oxidation of silyl enol ethers. Synthesising bicyclo-octane **183** and therefore any extension of the methodology toward the synthesis of the natural product stemodandiol or its polycyclic skeleton was abandoned.

CHAPTER 3: CYCLISATIONS OF METHYL KETONES – SYNTHESIS OF BICYCLO-[3.2.1]-OCTANES

3.1) INTRODUCTION

3.1.1) Another Approach to Bicyclo-Octanes

Another focus point in the project was to look at bicyclo-octane systems related to those found in the two families of natural products gibberellins and kaurenoids. (**Scheme 3.1**) Once again, it was anticipated that compounds such as **271** could be formed by the treatment of a ketone containing methylenecyclopropane derivative with samarium diiodide.

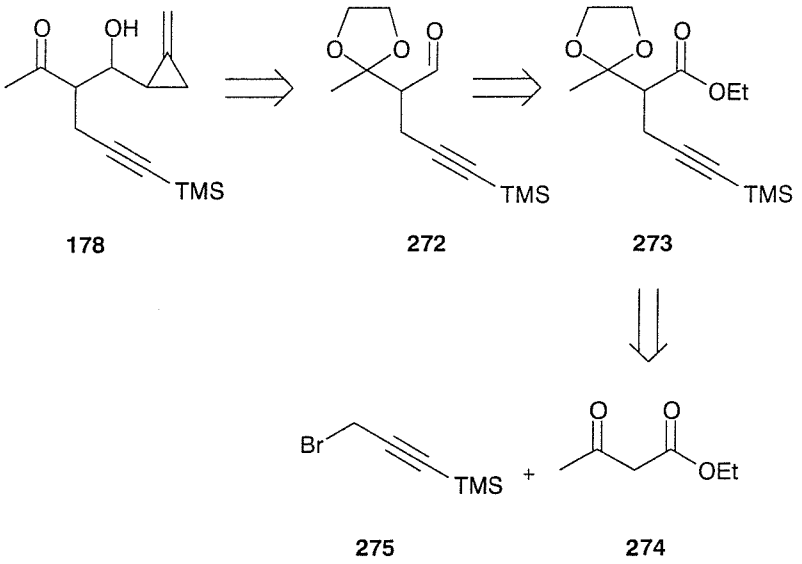


Scheme 3.1

It was anticipated that samarium (II) iodide would reduce ketone **266** to the ketyl radical **267** which would then undergo a 5-*exo* cyclisation onto the cyclic end of the methylenecyclopropane double bond forming **268**. The cyclopropane ring would then open in an *endo* fashion leading to cyclohexanyl radical **269**. A final 5-*exo* cyclisation onto the propargylic moiety would give **270**, which could be further reduced to give cyclic product **271.**

3.1.2) Retrosynthesis of the Precursor

The first precursor considered was **178**, where R=Me and R'=H (in **266**). The strategy was to start from readily available ethyl acetoacetate and propargyl bromide **275**. **(Scheme 3.2)**

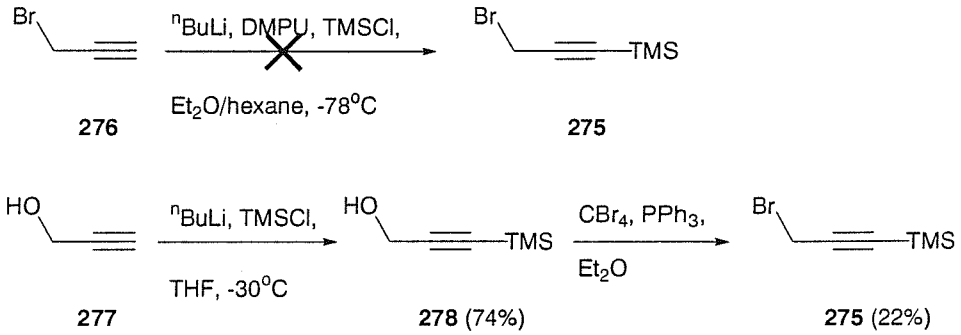


Scheme 3.2

3.2) SYNTHESIS OF THE PROPARGYL CYCLISATION PRECURSOR

The preparation of trimethylsilyl propargyl bromide **275** by direct reaction of propargyl bromide **276** with ^{n}BuLi, DMPU, TMSCl in ether/hexane as reported by Holmes was attempted but was not successful.[96] Bromide **275** was prepared following a different method by Holmes.[96] **(Scheme 3.3)** Propargyl alcohol **278** was deprotonated using two

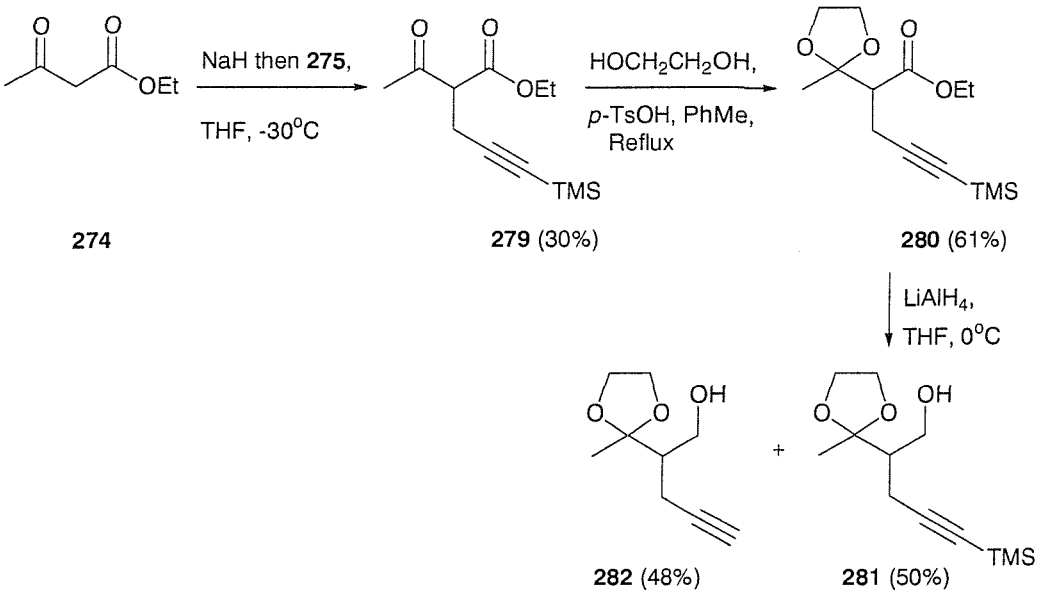
equivalents of ^{n}BuLi and the dianion was trapped with TMSCl. After acidic aqueous work-up, alcohol **278** was obtained in 74% yield when carried out on small quantities of material. Scaling up of the process resulted in a significant drop in yield with only about 30% isolated alcohol.



Scheme 3.3

A number of methods were tried for the conversion of **278** to bromide **275**. Product could only be isolated in 21% yield when alcohol **278** was treated with bromine and triphenylphosphine as carried out by Holmes.[96] Tribromophosphine and pyridine in refluxing ether[98] afforded bromide **275** in 28% yield. However, upon treatment with triphenylphosphine and carbon tetrabromide,[97] **275** was obtained in 78% yield. Unfortunately, this yield was difficult to reproduce and both small and larger scale reactions typically gave bromide **275** in about 20-25% yield but the straight forward procedure made it the easiest route.

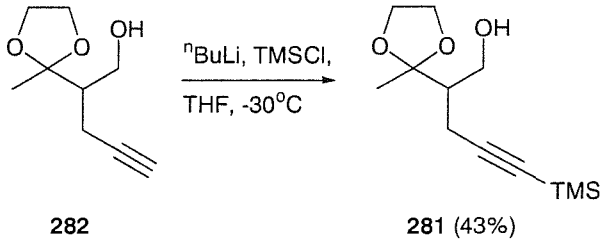
Ethyl acetoacetate **274** was treated by NaH followed by bromide **275** to give keto ester **279** in only 30% yield. (**Scheme 3.4**) Ketone **279** was protected to the ketal by reaction with ethylene glycol and *p*-TsOH in refluxing toluene, affording **280** in 61% yield. Reaction of **280** with $LiAlH_4$ led to the formation of the expected alcohol **281** but in a disappointing 50% yield, along with the undesired desilylated alcohol **282** in 48% yield.



Scheme 3.4

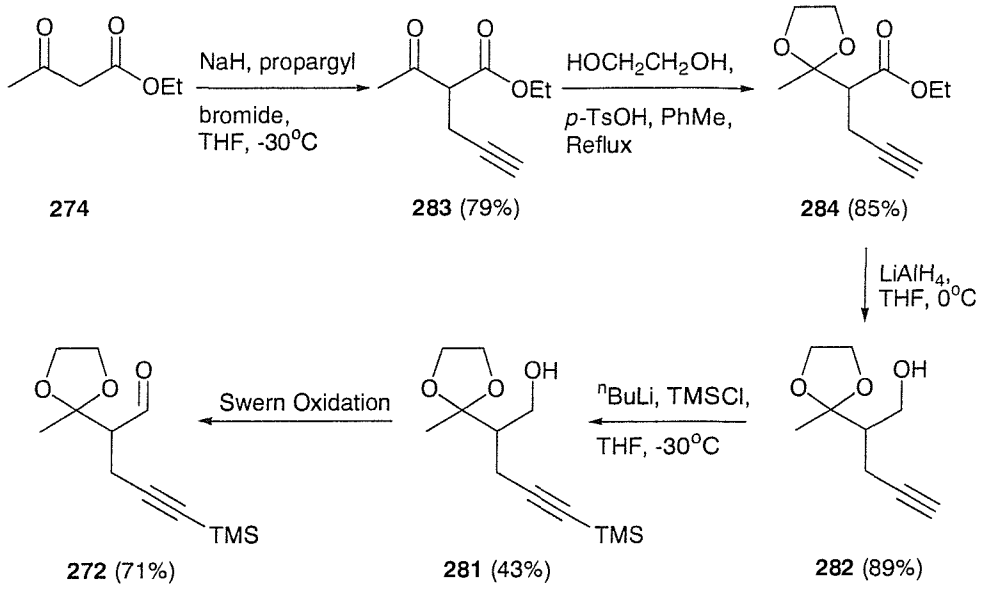
The overall result was disappointing as the five steps leading to alcohol **281** gave a yield of 2.7% when carried out on a small scale. We had to think of a way of improving either the yields or the overall route.

Trying to re-attach the TMS group on compound **282** to obtain the originally desired alcohol **281** was attempted. **(Scheme 3.5)**



Scheme 3.5

Alcohol **282** was treated with two equivalents of ^{n}BuLi, TMSCl and acidic work-up gave **281** in 43% yield. It was therefore decided to alkylate ethyl acetoacetate with propargyl bromide and to incorporate the TMS group at the alcohol stage which would reduce the route by one step and would hopefully help improve the yields. **(Scheme 3.6)**



Scheme 3.6

Ethyl acetoacetate **274** was deprotonated with NaH followed by quenching of the anion with propargyl bromide to give keto ester **283** in 79% yield. Ketone **283** was protected by reaction with ethylene glycol and *p*-TsOH in refluxing toluene, affording **284** in 85% yield. Reaction of **284** with $LiAlH_4$[98] gave the expected alcohol **282** in 89% yield. The TMS group was introduced upon treatment with ^{n}BuLi and TMSCl in 43% yield and alcohol **281** was converted to aldehyde **272** by Swern oxidation[99] in 71% yield. Unfortunately, aldehyde **272** was unstable and began to decompose during ^{13}C NMR analysis. Reacting **272** crude with lithiated methylenecyclopropane did not lead to any meaningful product.

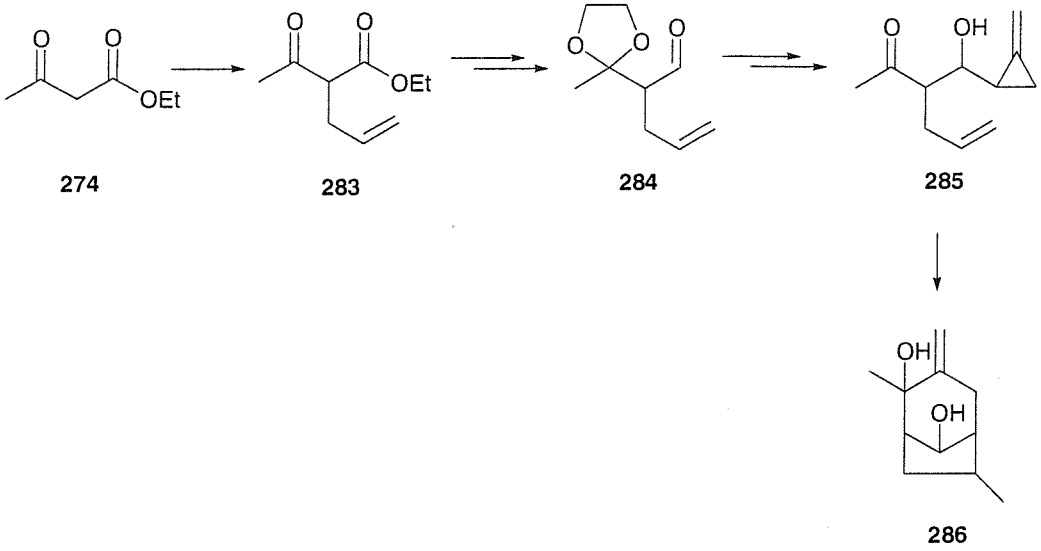
The new approach to alcohol **281** proved to be more successful but cyclisation precursor **178** could not be obtained and this route was abandoned.

3.3) Synthesis Of A Modified Precursor

3.3.1) Synthetic Route to the Cyclisation Precursor

It was decided that a modified precursor would be used, avoiding the presence of a -C≡C-TMS group as it might be the cause of the problems encountered. In order to retain

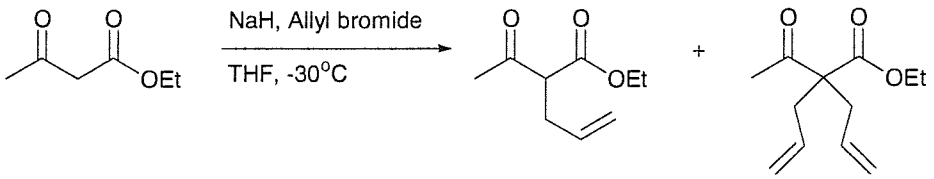
the unsaturation necessary for the last cyclisation step, an allyl group would be used instead of the silyl substituted propargylic moiety. The use of an allyl group would lead to a less functionalised bicyclic product and would introduce an additional stereocentre instead of a TMS substituted double bond. (**Scheme 3.7**)



274 **283** **284** **285** **286**

Scheme 3.7

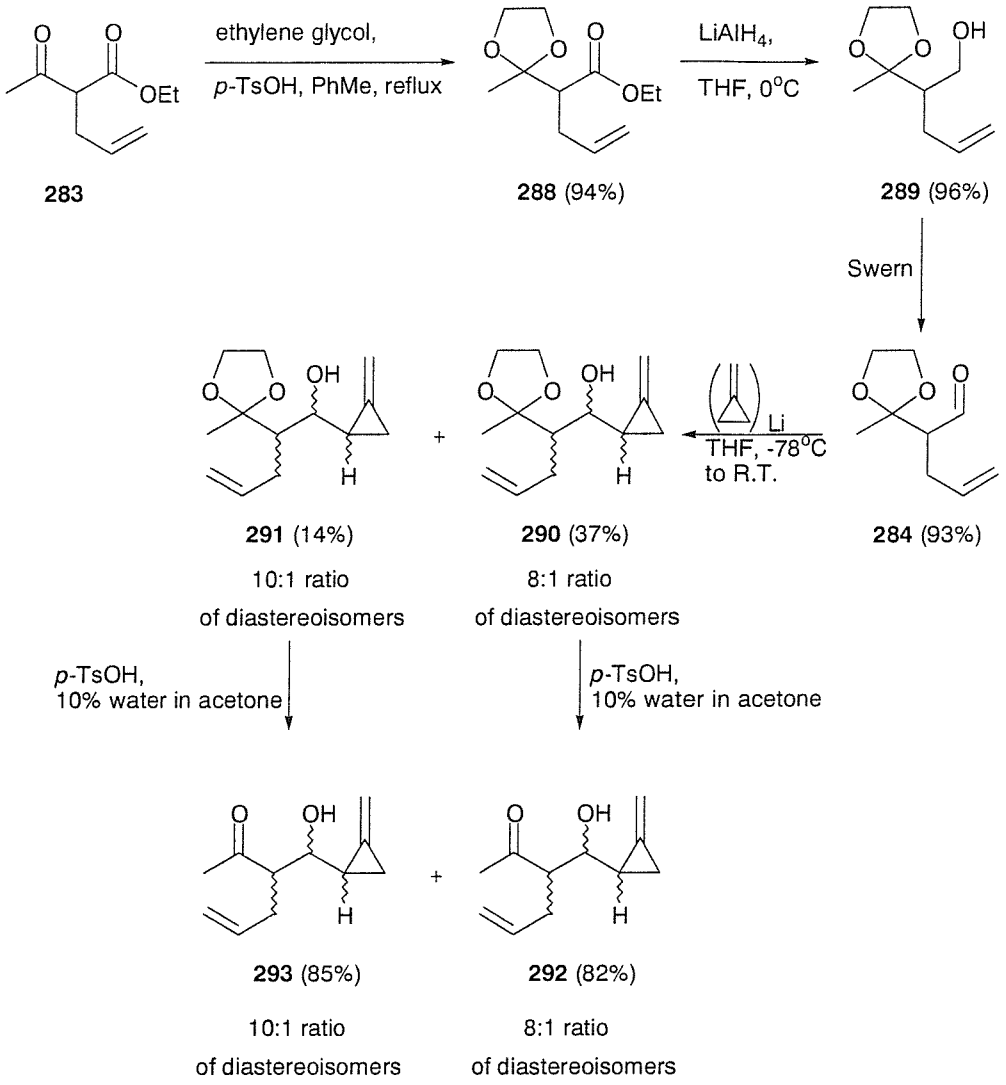
Ethyl acetoacetate **274** was deprotonated and the anion was quenched with allyl bromide to form the alkylated ethyl ester **283** in good yield (77%). (**Scheme 3.8**) A small quantity of the di-allylated compound **287** could also be isolated from the reaction.



274 **283** (77%) **287** (11%)

Scheme 3.8

Protection of ketone **283** upon treatment with *p*-toluene sulfonic acid and ethylene glycol gave ketal ester **288** in 94% yield. The ester was reduced to alcohol **289** by reaction with lithium aluminium hydride (96% yield) and oxidised to aldehyde **284** in 93% yield *via* Swern oxidation. (**Scheme 3.9**)

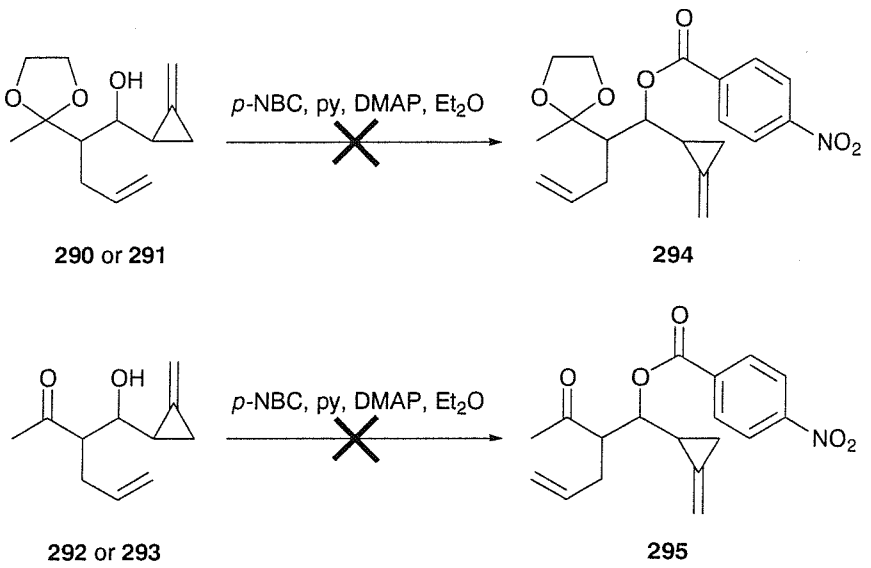


Scheme 3.9

The aldehyde was reacted with lithiated MCP[100] and gave four diastereoisomers of the protected precursor. The mixture of isomers could be separated to give two sets of two inseparable isomers. Ketone **290** in 37% yield as a 8:1 ratio of isomers whereas **291** was obtained in14% yield as a 10:1 ratio of isomers. Each set could then be deprotected with *p*-toluene sulfonic acid and 10% water in acetone, to give precursors **292** in 82% yield and **293** in 85% yield.

3.3.2) Stereochemistry of the Precursors

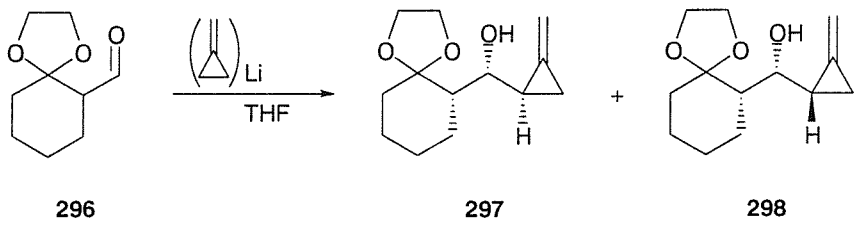
In order to rationalise the outcome of the subsequent cyclisations we wanted to investigate the stereochemistry of the precursors. Both **292** and **293** were isolated as oils so it was decided to attempt the synthesis of potentially crystalline derivatives. (**Scheme 3.10**)



Scheme 3.10

Thus both ketal alcohols **290** or **291** and ketone alcohols **292** or **293** were reacted with *p*-nitrobenzoyl chloride but no product could be isolated.

Referring to similar reactions (nucleophilic additions to ketal aldehydes) in the literature it was found that the stereochemistry of the few related compounds encountered was never established as this was not useful in the synthetic routes presented. However previous work in the group offers an example of such alkylations.[45] **(Scheme 3.11)**

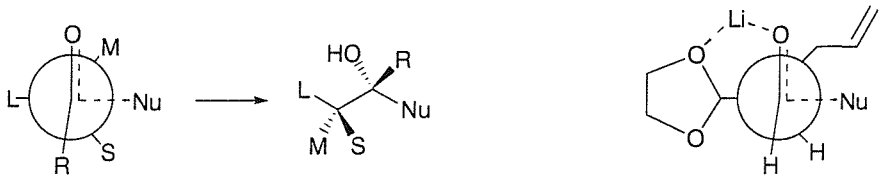


Scheme 3.11

Thus addition of lithiated methylenecyclopropane to aldehyde **296** gave alcohols **297** and **298**. The stereochemistry of **297** and **298** was established by X-ray crystallography.

To try and rationalise the outcome of the alkylation it is possible to consider the Felkin-Ahn model for the prediction of diastereoselectivity.[64] According to the model, the

reaction should proceed *via* a reactant-like transition state where the nucleophile attack is dictated by the arrangement of the substituents on the carbon α to the carbonyl group. (**Fig. 3.1**)

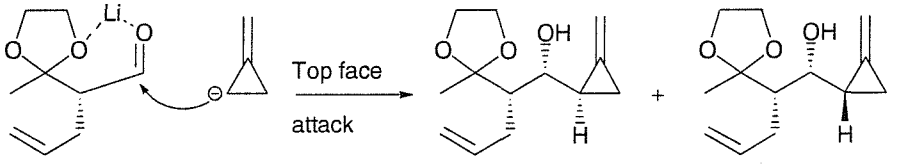


L: largest substituent,
M: medium sized substituent,
S: smallest substituent.

284
L: acetal,
M: allyl,
S: H,
R: H.

Figure 3.1

In the case of addition to ketaldehyde **284** the largest group would be the acetal and the smallest the hydrogen atom. Such arrangement of the transition state may also be favoured as chelation of lithium between the carbonyl oxygen and one of the oxygen from the acetal could occur. The transition state would lead to two isomers of the resulting alcohol (**299** and **300**) where the only difference between them is the configuration at the cyclopropyl ring. (**Scheme 3.12**)



284 **104** **299** **300**

Scheme 3.12

We presume that the minor isomers arose from reaction *via* a different transition state.

In practice, the stereochemistry of the subsequent cyclised products confirms that of the precursors. Effectively, the relative stereochemistry at the allyl and hydroxy groups was established from the cyclised product (*vide infra*) and remains unchanged in the cyclisation process.

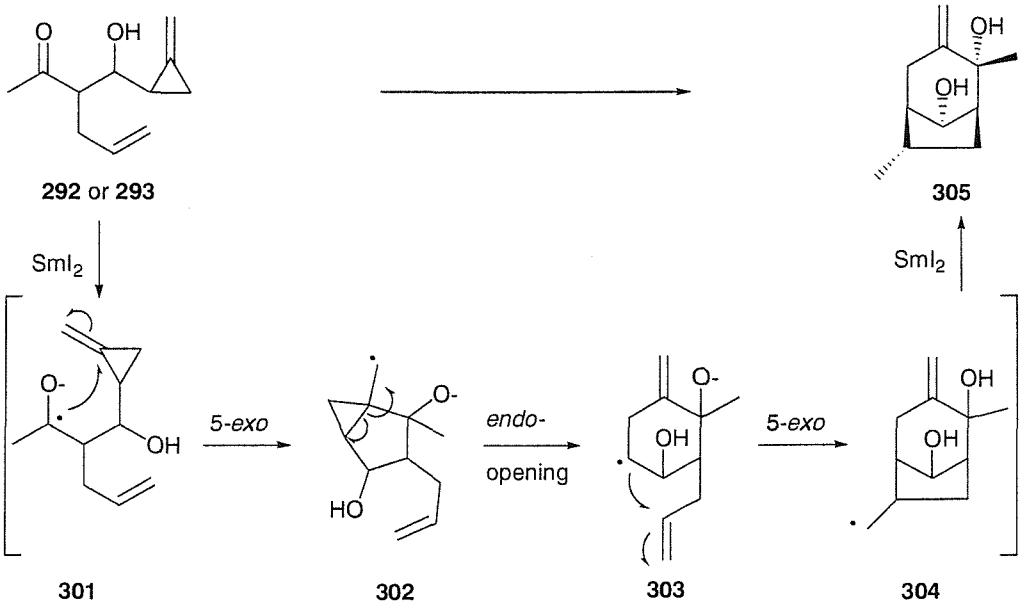
3.4) CYCLISATION STUDIES

3.4.1) Cyclisation Conditions

Both **292** and **293** were subjected to a series of cyclisations under a number of reaction conditions, varying temperature and additives. The reactions were undertaken by slowly adding a solution of the ketone and ^{t}BuOH in THF to a SmI_2/HMPA mixture in THF or by adding the ketone in THF to a solution of SmI_2 and MeOH in THF (normal addition).[101,45] Alternatively, a solution of SmI_2 and HMPA -or MeOH- was added *via* cannula to a solution of the ketone -and ^{t}BuOH if required- in THF The temperature was also varied, with reactions attempted at 0^{o}C and -78^{o}C. In all cases two equivalents of SmI_2 were used, the first equivalent initiating the cascade and the second one being thought to reduce the final radical to an anion that will be quenched with a proton found in the reaction medium.

3.4.2) Cyclisation Mechanism

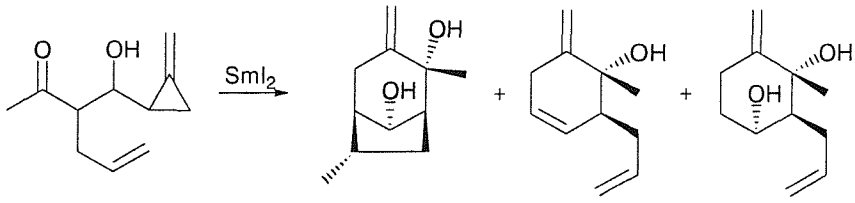
As described previously, ketyl radical **301** was expected to undergo successively a 5-*exo* cyclisation, *endo* opening of the cyclopropane ring and an additional 5-*exo* cyclisation leading ultimately to the formation the final product **305**. **(Scheme 3.13)**



Scheme 3.13

3.4.3) Cyclisation results

Cyclisations were undertaken using a number of conditions. Both ketone precursors **292** and **293** afforded bicycle **305** in modest to good yield with best results obtained with HMPA/^{t}BuOH at 0°C. (**Table 3.1**) Alongside the cyclised product, two by-products were isolated. (**Scheme 3.14**)



292 or 293 305 306 307

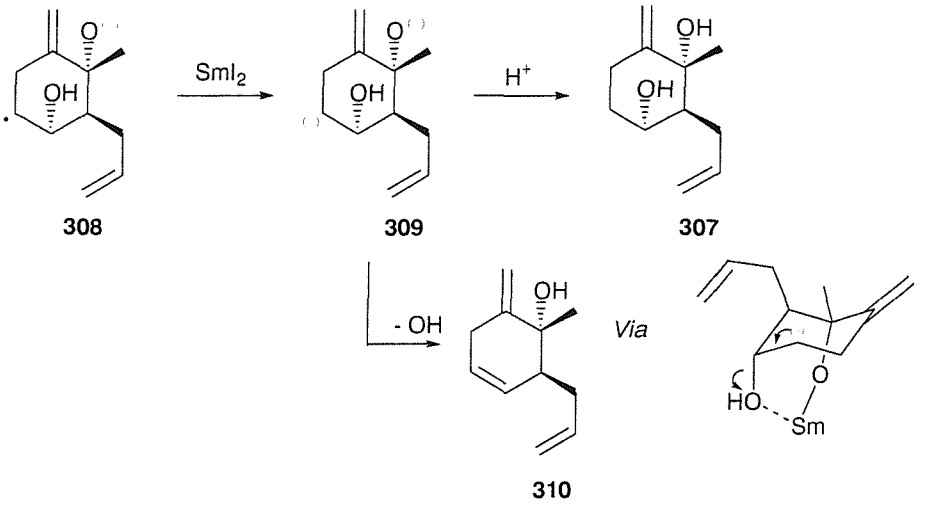
Scheme 3.14

Isomer	Conditions	292/293	306	307	305	TOTAL
292	MeOH, 0°C	5	5	4	**67**	81
292	MeOH, -78°C	9	-	9	51	69
292	HMPA, ^{t}BuOH, 0°C	4	-	-	50	55
292	HMPA, ^{t}BuOH, -78°C	-	6	-	48	54
293	MeOH, 0°C	6	-	-	65	71
293	MeOH, 0°C	-	10	-	60	70
293	HMPA, ^{t}BuOH, 0°C	6	-	-	**71**	77
293	HMPA, ^{t}BuOH, -78°C	60	-	8	19	87

Table 3.1

Bicycle **305** was always isolated as a mixture of two isomers in a 9:1 ratio. The two isomers are thought to arise from the orientation of the methyl group from the C_{10} bridgehead carbon.

The formation of **306** and **307**, both isolated as single diastereoisomers, confirmed the proposed mechanism as they presumably arise from a premature reduction of radical **303**. The resulting ions can either be quenched, forming **307**, or proceed to **310** *via* elimination of the antiperiplanar hydroxyl group. (**Scheme 3.15**)



Scheme 3.15

3.4.4) Stereochemistry of the Cyclised Product

i- Observed stereochemistry

The major isomer of the fully cyclised product **305** could be isolated as a crystalline solid and its relative stereochemistry was established unambiguously by X-ray diffraction. **(Fig. 3.2)**

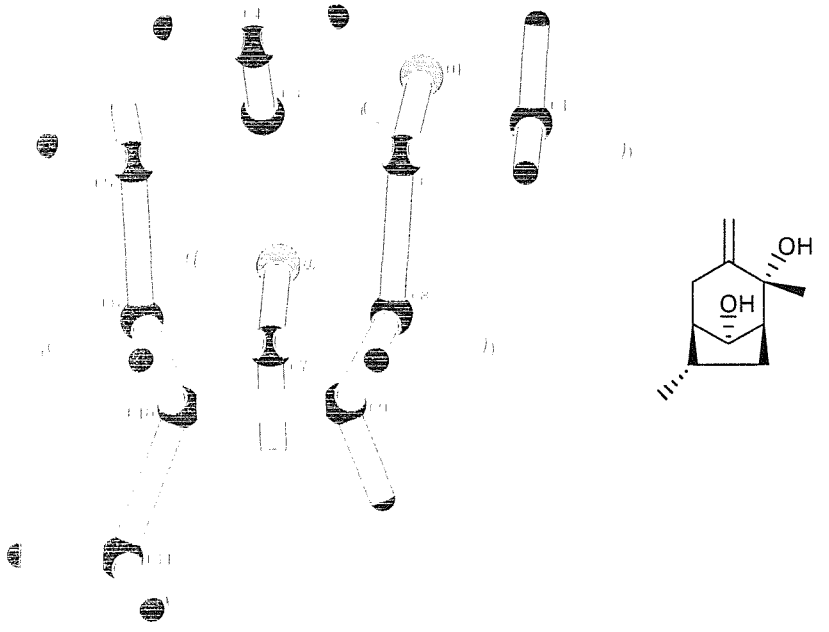


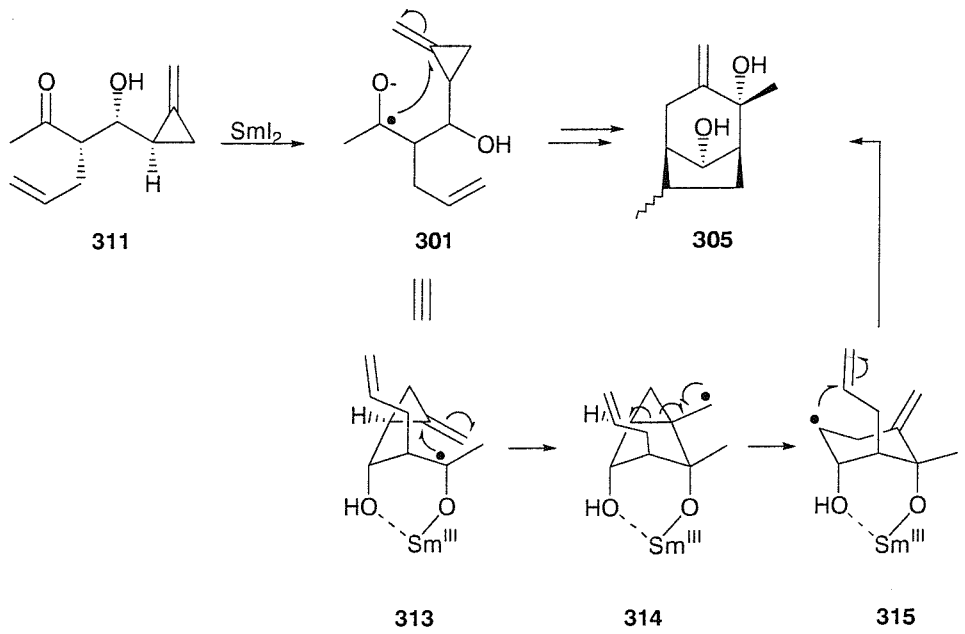
Figure 3.2

ii- Origin of stereochemistry

One of the reasons for the use of samarium diiodide as the radical initiator was to take advantage of its ability to influence the conformation of the substrate by chelation making the synthesis stereoselective.

a) Cyclisation of **311**

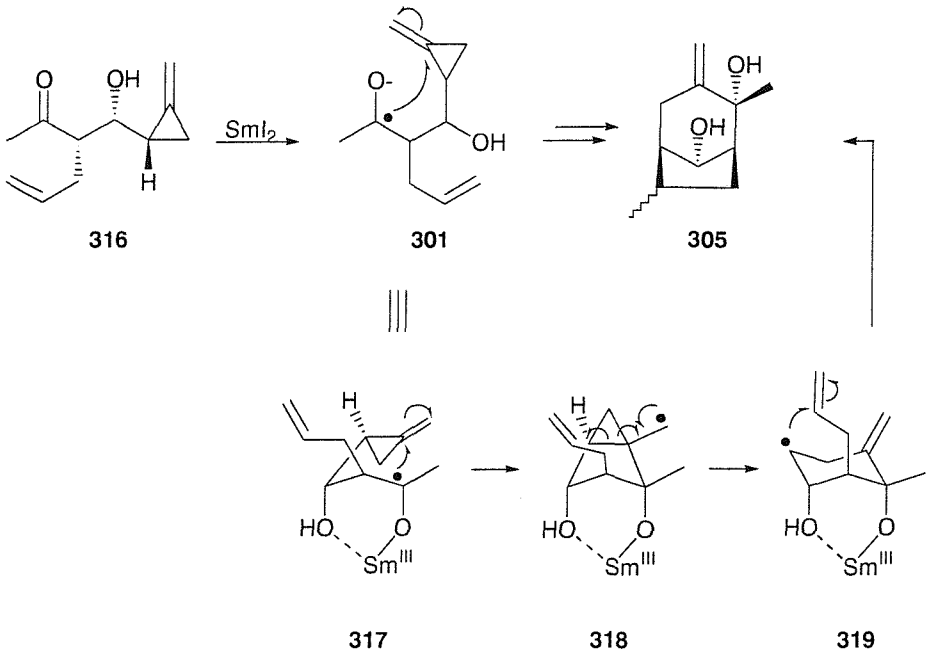
The cyclisation presumably proceeds *via* a chair-like transition state with the samarium species chelated to both oxygen atoms (**313**), placing them axial. The initial cyclisation onto the MCP double bond leads to radical **314** which, after opening of the cyclopropane ring, undergoes a final cyclisation onto the allylic double bond. In the case of **311** the allyl group should also be axial in the chair-like intermediate. This therefore leads to the cyclised product with the hydroxy groups *syn* to each other and *anti* to the bridge-head. (**Scheme 3.16**)



Scheme 3.16

b) Cyclisation of **316**

The only difference is the stereochemistry at the cyclopropyl centre. However, this should not have any effect on the cyclisation and after generation of radical **301**, the process should follow a similar path to that of **311**, leading to the same cyclic product **305**. (**Scheme 3.17**)



Scheme 3.17

3.4.5) Conclusion

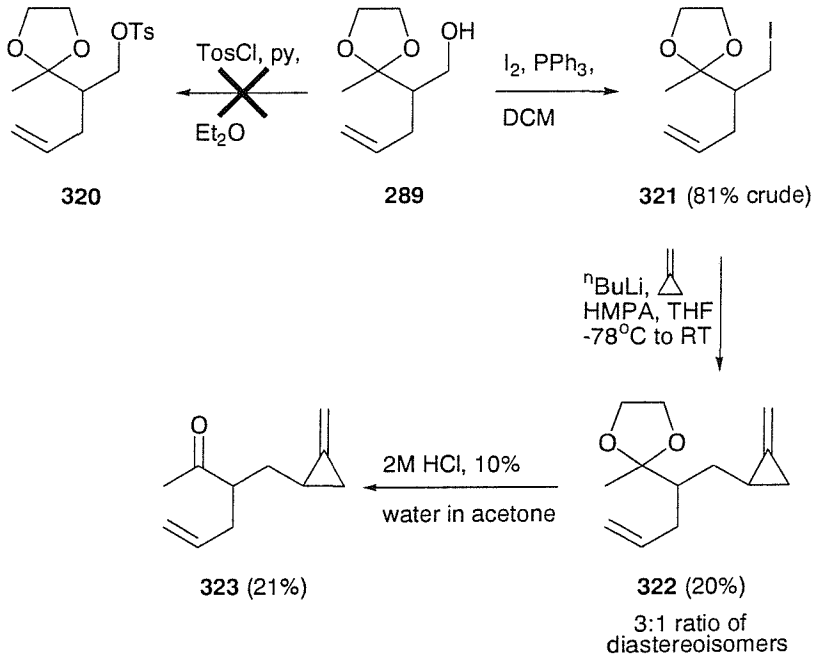
Cyclisations of both precursor afforded the desired bicyclo-octane in average to good yield. The stereochemistry of the cyclised product could be established by X-ray crystallography and the presence of a number of by-products helped to confirm the cyclisation mechanism.

3.5) STUDIES ON THE DEHYDROXYLATED PRECURSOR

It was established that the stereochemistry of the cyclised product arises from chelation of the samarium species. The influence of the chelation in the overall process was yet to be fully understood. It was therefore decided to compare the results obtained with a closely related precursor where chelation would not be present.

3.5.1) Synthesis of the Precursor

The dehydroxylated precursor **323** was synthesised from alcohol **289**. (**Scheme 3.18**) It was hoped that conversion of the hydroxyl group of **289** into a leaving group then reaction with lithiated methylenecyclopropane would easily give protected precursor **322**.



Scheme 3.18

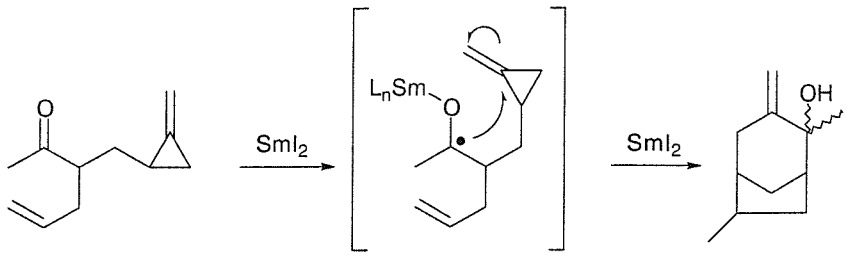
Tosylation of alcohol **289** in the presence of pyridine did not afford compound **320** as the compound was not stable towards chromatographic conditions. Reaction of the crude **320** with MCP anion was unsuccessful. Alcohol **289** could be converted to iodide **321**. The iodide was also unstable and had to be reacted with lithiated methylenecyclopropane in the presence of HMPA without purification to give ketal **322** in 20% yield. Compound **322** was deprotected to ketone **323** with 2M HCl in wet acetone (21%).

These reactions were undertaken on a small scale and due to time constraints, the synthesis of more alcohol **289** could not be undertaken. Not all of the intermediates in this synthesis have been fully characterised.

3.5.2) Cyclisation

i- Theoretical result

Without the influence of chelation, the stereochemical outcome of the cyclisation was uncertain. (**Scheme 3.19**)



323 324 325

Scheme 3.19

ii- Cyclisation

Cyclisation of precursor **323** was attempted under the optimum conditions established for it hydroxylated counterpart **293**, i.e. HMPA, ^{t}BuOH, 0^{o}C. Unfortunately, the cyclisation gave a complex mixture and no identifiable product.

3.5.3) Conclusion

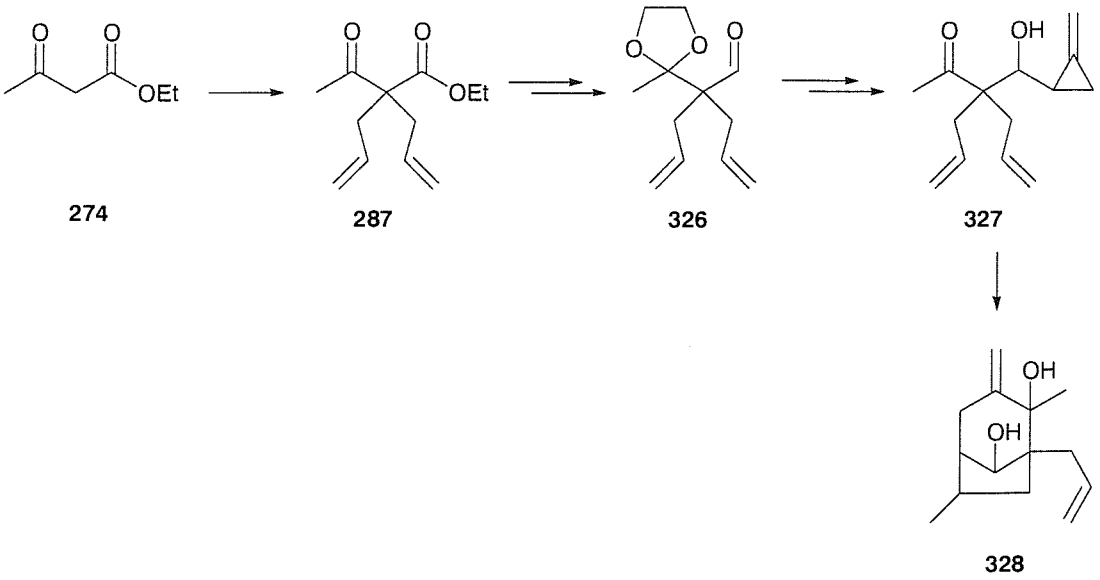
The cyclisation of compound **323**, where no chelation is possible, did not afford any identifiable product and it can be assumed that the chelation plays an important role in the overall process.

3.6) SYNTHESIS OF A MORE FUNCTIONALISED BICYLO-[3.2.1]-OCTANE

3.6.1) Design of the Precursor

In an effort to build on the promising results obtained in the previous series of cyclisations we wanted to study the cyclisations of more complex compounds. Keeping in

mind the possibility of accessing quadricyclic systems, we considered compound **327**, the di-allylated version of precursor **285**. **(Scheme 3.20)**



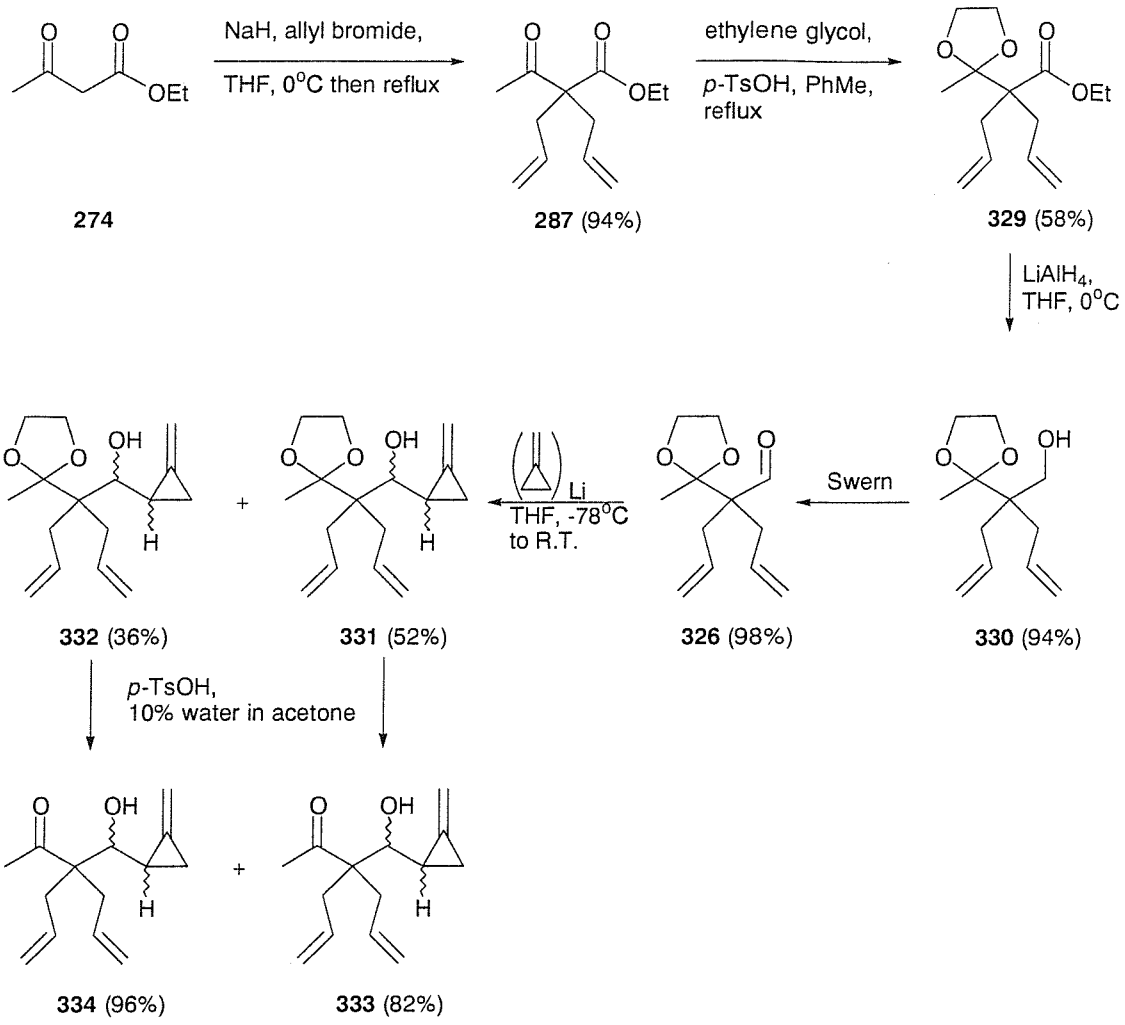
274 287 326 327 328

Scheme 3.20

The synthesis of the precursor followed the same strategy as before.

3.6.2) Synthesis of the Precursor

The di-allylated keto-ester **287**, could be easily obtained from ethyl acetoactetate by using two equivalents of base and allyl bromide, resulting in the formation of the product in 86% yield. The reaction was improved when the mixture was heated to reflux for 18 hours, giving **287** in excellent yield (94%). **(Scheme 3.21)** Protection of the ketone gave ketal **329** in 58% yield. Reduction of the ester group to give alcohol **330** and oxidation to aldehyde **326** both proceeded in excellent yield (94% and 98% respectively). The aldehyde was added to methylenecyclopropane previously deprotonated with ^{n}BuLi to lead to **331** in 52% yield and **332** in 36% yield, both isolated as single diastereoisomers. Deprotection of **331** afforded **333** in a good 84% yield while **334** was obtained from **332** in 96% yield.



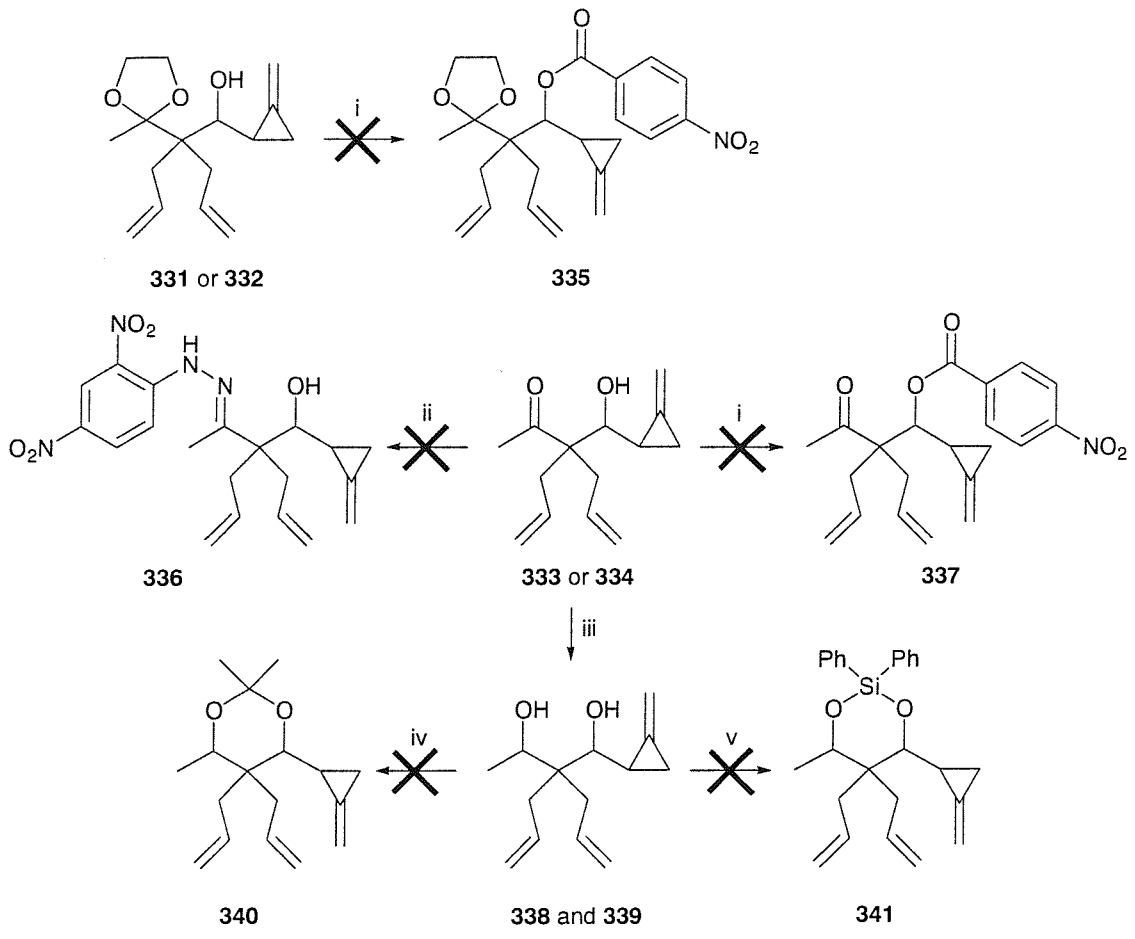
Scheme 3.21

3.6.3) Stereochemistry of the Precursors

As before the relative stereochemistry of the two diastereoisomeric alcohols **333** and **334** could not be obtained although the synthesis of a number of potentially crystalline derivatives was attempted.

The same types of derivatives as for the previous precursor were considered. Reaction of neither ketones **333** and **334** nor ketals **331** and **332** with *p*-nitro benzoyl chloride, in the presence of pyridine, afforded the expected nitrobenzoyl ester. Conversion of the ketone into hydrazone **335** following a method by Enholm,[102] was attempted but no product could be isolated. (**Scheme 3.22**)

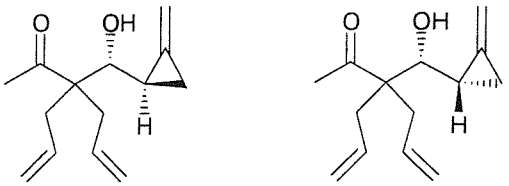
Reduction of **333** and **334** with tetramethylammonium triacetoxyborohydride, according to a method by Evans[103], did not show any stereoselectivity. Then, the ketones were reduced with $LiAlH_4$ to give diols **338** and **339**. The reactions to form acetal **340** or silylether[104] **341** also proved unsuccessful.



Conditions and reagents:
i) *p*-NBC, py, Et_2O; ii) 2,4-DNPH, AcOH, MeOH; iii) $LiAlH_4$, Et_2O;
iv) DMP, *p*-TsOH, molecular sieves; v) DCDPS, TEA, Et_2O

Scheme 3.22

By comparison with the mono-allyl precursor, the two possible stereochemical conformations the precursor can adopt is easily rationalised. Attack of methylenecyclopropyl anion onto aldehyde **326** will lead to two isomers differing in stereochemistry only at the cyclopropyl ring. (**Fig. 3.3**)

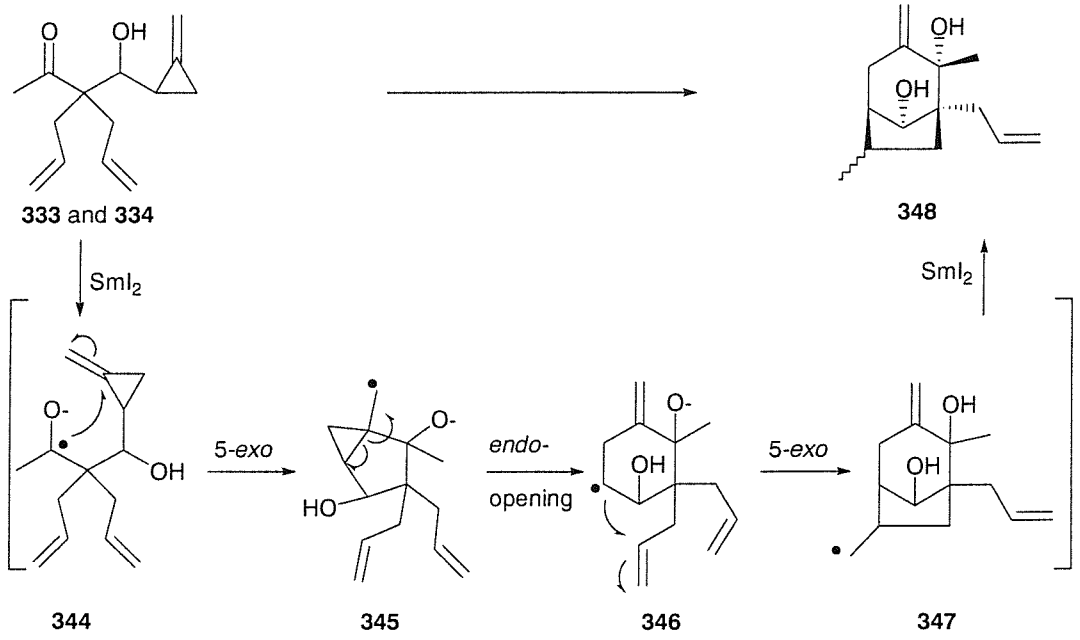


342 343

Figure 3.3

3.6.4) Cyclisation studies

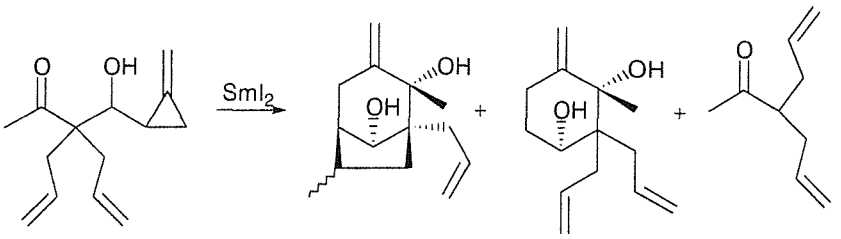
We expected the cyclisation to follow a similar pathway to that of the mono-allyl precursor resulting in the formation of a more functionalised bicyclic system. (**Scheme 3.23**)



Scheme 3.23

3.6.5) Cyclisation results

As with the mono-allyl precursor, cyclisations of **333** and **334** led to a number of by-products. (**Scheme 3.24**)



333 and 334 348 349 350

Scheme 3.24

3.6.6) Cyclisation of 333

With precursor **333**, the yields of the different products varied with the different conditions used. Using the conditions described previously bicyclic compound **348** could only be isolated in up to 43%. We therefore decided to try yet again different conditions to try and improve the yield of bicyclic product. It was decided to try cyclisation in the absence of ^{t}BuOH but cyclised product **348** could only be obtained in 28 % yield (*entry 5*). Using four equivalents of SmI_2 proved more successful as the expected product **348** was isolated in 53% yield. (*entry 6*) (**Table 3.2**)

Entry	Conditions	333	349	350	348	TOTAL
1	2eq. SmI_2, MeOH, $0^{o}C$	22	-	15	24	61
2	2eq. SmI_2, MeOH, $-78^{o}C$	37	-	12	33	82
3	2eq. SmI_2, HMPA, ^{t}BuOH, $0^{o}C$	15	10	7	25	57
4	2eq. SmI_2, HMPA, ^{t}BuOH, $-78^{o}C$	12	-	7	43	62
5	2eq. SmI_2, HMPA, $0^{o}C$	5	7	-	28	40
6	4eq. SmI_2, HMPA, ^{t}BuOH, $-78^{o}C$	2	8	-	**53**	63

Table 3.2

3.6.7) Cyclisation of 334

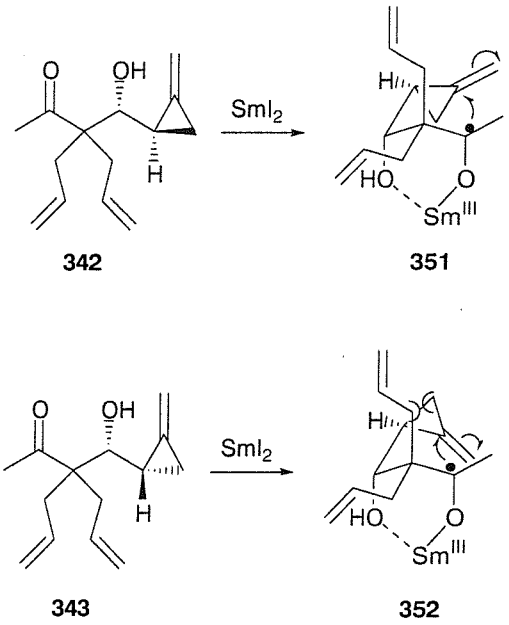
Isomer **334** was subjected to cyclisation under the same initial sets of conditions. (**Table 3.3**, *entry 1* to *4*) Again the desired cyclised product **348** was obtained in all cases but in lower yields. SmI_2/HMPA/^{t}BuOH at 0°C gave **348** in 28% yield. (*entry 3*) However, when four equivalents of SmI_2 were used instead of two (*entry 5*) the yield of cyclised product did not improve (26%).

Entry	Conditions	334	333	349	350	348	TOTAL
1	2eq. SmI_2, MeOH, 0°C	10	20	7	30	25	92
2	2eq. SmI_2, MeOH, -78°C	9	13	6	34	19	81
3	2eq. SmI_2, HMPA, ^{t}BuOH, 0°C	15	5	12	18	**28**	78
4	2eq. SmI_2, HMPA, ^{t}BuOH, -78°C	12	14	-	10	22	58
5	4eq. SmI_2, HMPA, ^{t}BuOH, -78°C	12	5	-	-	26	43

Table 3.3

Both isomers of the cyclisation precursor afforded **348** in average yield. As previously observed, **348** was always isolated as a mixture of 2 isomers in a 6:1 ratio. Again, the two isomers are thought to arise from the orientation of the methyl group at the C_{10} bridge-head.

Looking at the cyclisation transition states for both **333** and **334** may help understand why one isomer is more successful in giving the cyclic product then the other. Some steric clash occurs between the cyclopropyl ring and the axial allyl CH_2 in the case of radical **352** which may make this conformation less favourable to cyclisation. (**Scheme 3.25**)

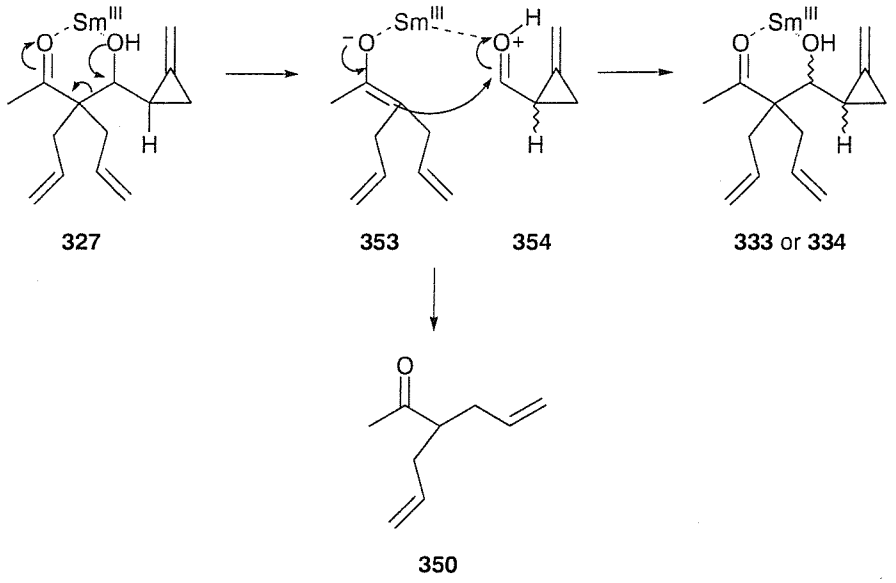


Scheme 3.25

However, such an event is probably not significant enough to explain the difference in the yield of cyclisation.

3.6.8) Retro-Aldol Side Reaction and the Origin of Ketone 350

In all the cyclisations of **334 (Table 3.3)** a significant quantity of the isomer **333** was isolated. This phenomenon is thought to arise from a retro-aldol-aldol reaction process. Retro-aldol reactions are known to be catalysed by Lewis acids and lanthanides in the oxidation state III have some degree of Lewis acid character. It is therefore possible to assume that Sm^{III}, a by-product of the cyclisation process, would act as a Lewis acid and hence could catalyse a retro-aldol reaction of the precursor leading to **353**. Recombination of **353** and aldehyde **354** would lead to keto-alcohols **333** or **334**. **(Scheme 3.26)**



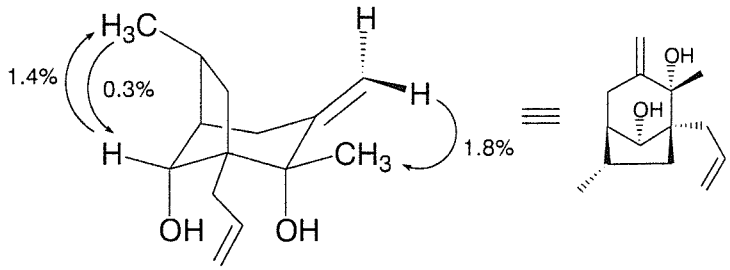
Scheme 3.26

The formation of **333** in the cyclisation of **334** suggests that **333** is the more stable isomer. Ketone **350** was also formed in the cyclisations of **333** but none of **334** was formed, reinforcing this theory.

3.6.9) Stereochemistry of the cyclised product

i- Observed stereochemistry

The cyclised product **348** was isolated as an oil but n.O.e. studies allowed structural information to be gained. (**Fig. 3.4**)



Important n.O.e. signals

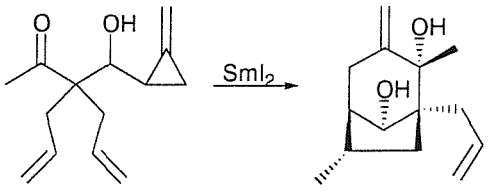
Figure 3.4

By analogy with the previous precursor, it can be assumed that both hydroxy groups would be held axial by virtue of chelation. Additionally, n.O.e. signal between the methylene CH_2 and the β-methyl group agrees with this assumption. Reciprocal interaction

between the hydrogen next to the other alcohol and the methyl group on the bridge-head suggests that the methyl group adopted a similar conformation to that of bicycle **312**, i. e. away from the double bond. The stereochemistry can therefore be assumed to be the expected one, the presence of a second allyl group not interfering with the stereochemical outcome of the reaction.

ii- Origin of the stereochemistry

Based on the previous work, we expected to obtain a stereochemistry similar to that of **312** because of the chelation between the samarium species and both oxygen atoms. **(Scheme 3.27)**



333 and **334** **348**

Scheme 3.27

3.7) CONCLUSION

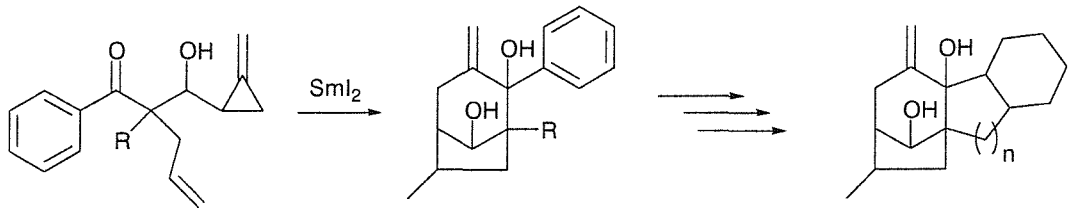
We have shown that carefully designed ketones containing derivatives of methylenecyclopropanes do form functionalised bicyclo-[3.2.1]-octanes in average to good yields when treated with samarium (II) iodide. The advantage of samarium diiodide is twofold: initiating a cascade radical sequence from a ketone starting material leaves an alcohol functionality at the end of the process. Samarium (II) iodide also influences the stereochemistry of the product by chelation, making the cyclisation diastereoselective.

CHAPTER 4: CYCLISATIONS OF PHENYL KETONES

4.1) INTRODUCTION

Having established that bicyclo-[3.2.1]-octanes can be easily accessed *via* samarium (II) iodide mediated cascade radical cyclisation of methylenecyclopropane derivatives, we wished to extend the methodology to more complex substrates. Moreover, since one of the aims of the project was the attempted synthesis of polycyclic systems related to natural products of the gibberellins and kaurenoids families, we ensured that the design of the new precursors could help us toward this goal.

Phenyl-ketone based precursors and their cyclisations were targeted. (**Scheme 4.1**)



351: R=H
352: R= allyl

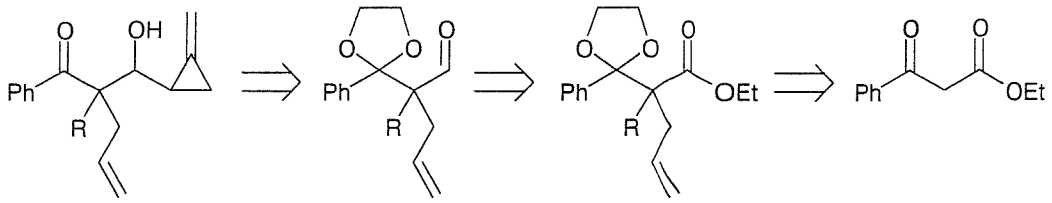
353: R=H
354: R= allyl

355
n=1,2

Scheme 4.1

Cyclisation of **351** or **352** would lead to **353** or **354** respectively. The presence of the phenyl moiety and the pendant allyl group (when R= allyl) should allow manipulation towards the construction of the quadricyclic systems.

Following a similar strategy as for the previous precursors, compound **356** can be disconnected to the commercially available benzoyl acetoacetate **359**. (**Scheme 4.2**)



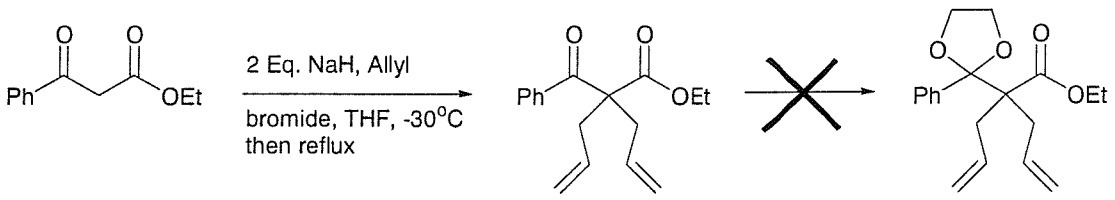
356 357 358 359

Scheme 4.2

4.2) STUDIES ON THE DI-ALLYL PRECURSOR

4.2.1) Synthesis of the Precursor

Initially, the synthesis of precursor **352** was considered. Benzoyl acetoacetate **359** was deprotonated with two equivalents of sodium hydride and was quenched with allyl bromide. Heating to reflux allowed us to isolate keto-ester **360** in 98% yield without any mono-allyl by product. (**Scheme 4.3**)



359 360 (98%) 361

Scheme 4.3

Protection of the ketone to ketal **361** proved problematic. The standard ethylene glycol/*p*-TsOH/PhMe/reflux conditions[105] did not yield any desired product and the starting material was fully recovered. A number of other procedures were attempted but all met with little success, leading to either recovery of starting material or decomposition of the substrate. (**Table 4.1**)

Entry	Conditions	Result
1	Ethylene glycol, *p*-TsOH, Xylene, reflux	Starting Material Recovered
2	Ethylene glycol, fumaric acid, Toluene, reflux	Starting Material Recovered
3	Neopentyl glycol, *p*-TsOH, Toluene, reflux	Decomposition
4	Neopentyl glycol, *p*-TsOH, Xylene, reflux	Decomposition
5	Neopentyl glycol, TMSCl, Toluene, RT	Decomposition
6	TMSOTf, 1,2-bis-(TMSoxy)ethane, DCM, -78^{O}C[106]	Starting Material Recovered
7	Ethane dithiol, BF_3Et_2O, DCM, 0^{O}C	Starting Material Recovered

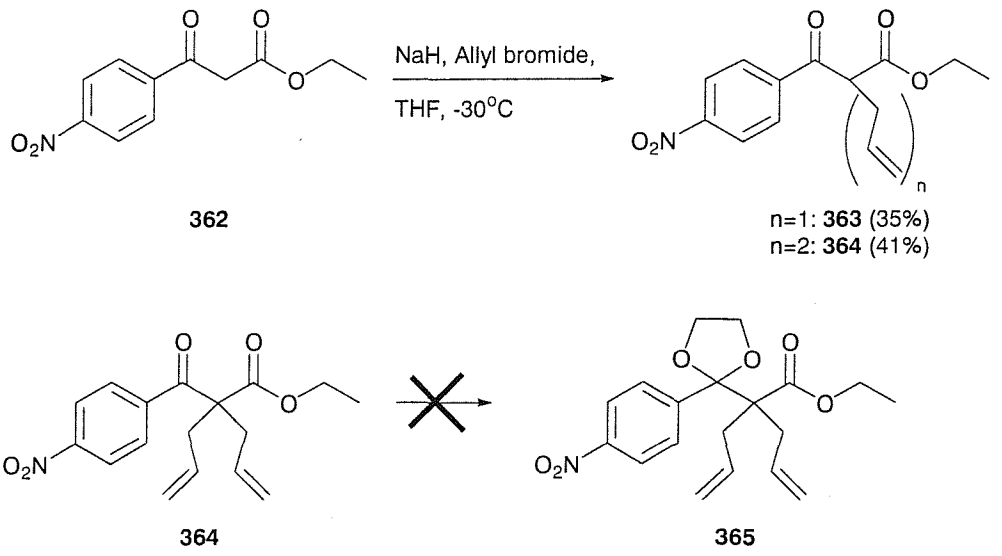
Table 4.1

The failure of this protection is probably explained as the result of two additive factors: the benzene ring increases the electron density around the ketone moiety rendering it less reactive towards nucleophilic attack. Also, steric bulk of the ring which, added to the two allyl groups, could make the ketone less available to react.

In order to try to overcome this problem, we anticipated that adding an electron withdrawing group at the *para* position could have an influence on the electron density around the ketone, making the protection easier. Thus, we chose to try the protection with a *para*-nitro group on the benzene ring.

4.2.2) Synthesis of the *para*-Nitro Substituted Keto-ester

Ethyl-4-nitrobenzoyl acetate **362** was deprotonated with sodium hydride and addition of allyl bromide allowed the formation of **364** and **363** in 35% and 41% yield respectively. **(Scheme 4.4)**



Scheme 4.4

The di-allyl adduct **364** then had to be converted to ketal **365**. (**Scheme 4.4**) Unfortunately, the protection was unsuccessful under a number of different conditions. (**Table 4.2**)

Entry	Conditions	Result
1	Ethylene glycol, *p*-TsOH, Toluene, reflux	Starting Material Recovered
2	Ethylene glycol, *p*-TsOH, Xylene, reflux	Decomposition
3	Neopentyl glycol, *p*-TsOH, Toluene, reflux	Decomposition
4	Neopentyl glycol, *p*-TsOH, Xylene, reflux	Decomposition
5	TMSOTf, 1,2-bis-(TMS-oxy)ethane, DCM, -78°C	Starting Material Recovered

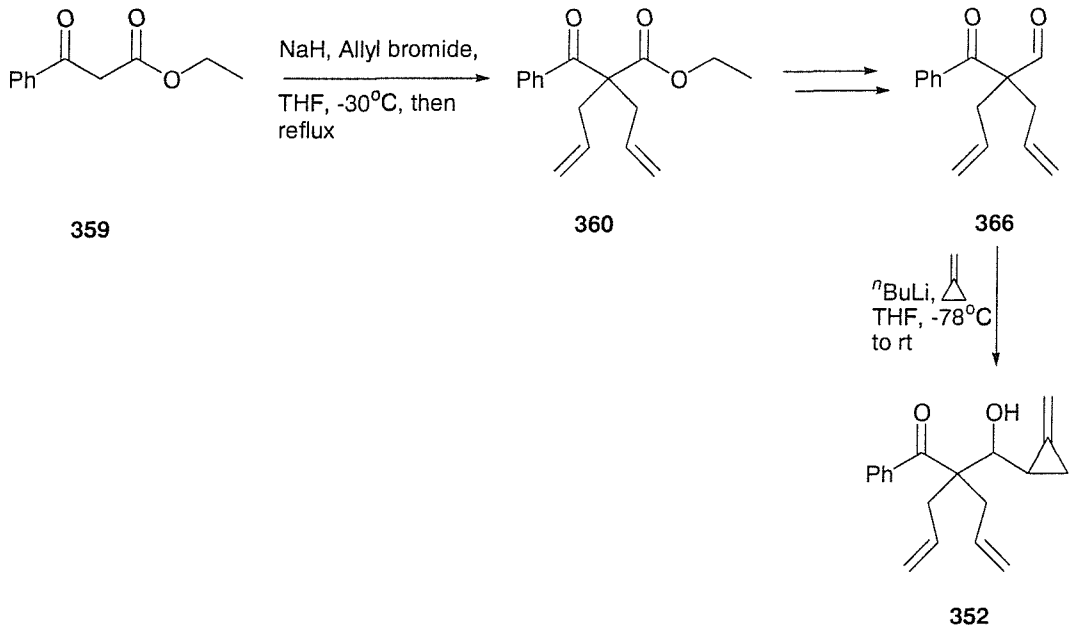
Table 4.2

These results suggest that steric hindrance is the main factor stopping the protection reaction from progressing. Next it was decided to investigate whether a protecting group for the ketone in **360** was in fact at all necessary.

4.2.3) Synthesis of the Precursor Without Using a Protecting Group

i- Strategy

Considering the overall route, it was decided to attempt the synthesis of **352** without utilising any ketone protecting group. We anticipated that, having easily synthesised di-allyl compound **360**, direct reduction to the diol and subsequent oxidation would lead to keto-aldehyde **366**. (**Scheme 4.5**)

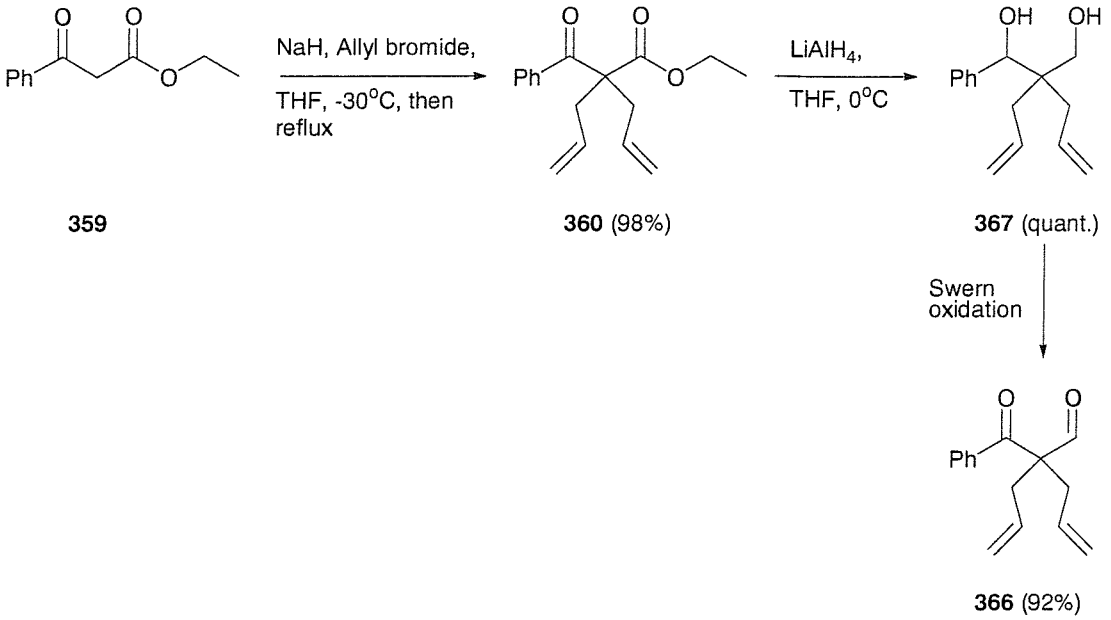


Scheme 4.5

It was also hoped that addition of keto-aldehyde **366** to lithiated MCP would lead to precursor **352** by reacting preferentially with the aldehyde carbonyl rather than the ketone.

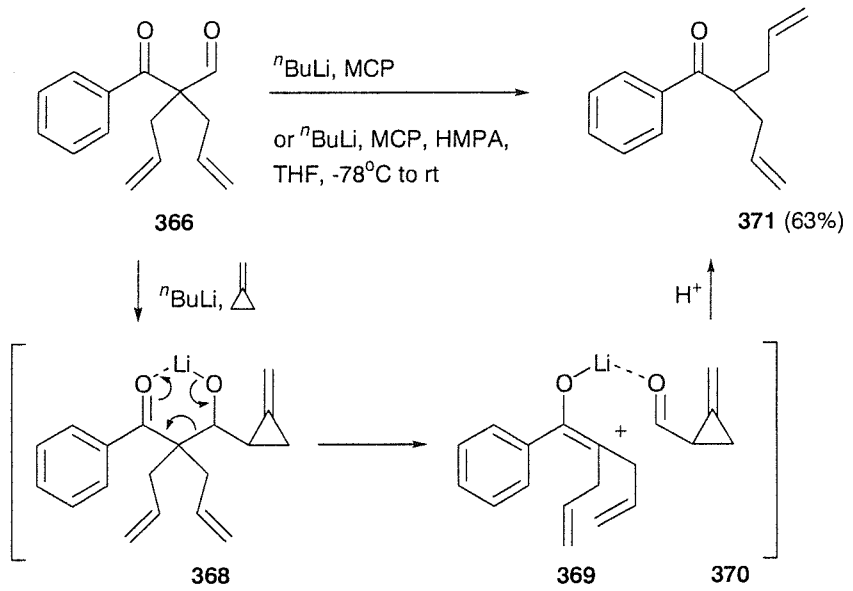
ii- Synthesis of the precursor

Keto ester **360** was obtained in very good yield (98%) by treatment with NaH followed by allyl bromide. (**Scheme 4.6**) Reduction to diol **367** with $LiAlH_4$ proceeded in quantitative yield and Swern oxidation afforded keto-aldehyde **366** in 92% yield.



Scheme 4.6

When keto-aldehyde **366** was added to a solution of either lithiated methylenecyclopropane or lithiated methylenecyclopropane and HMPA, the only isolated product was ketone **371** in 63% yield. (**Scheme 4.7**)



Scheme 4.7

Ketone **371** is the result of a retro aldol reaction occurring once the MCP anion has attacked the aldehyde. The reaction might occur because **368** is stabilised by co-ordination with lithium. Aldehyde **370** was not isolated probably because of its high volatility.

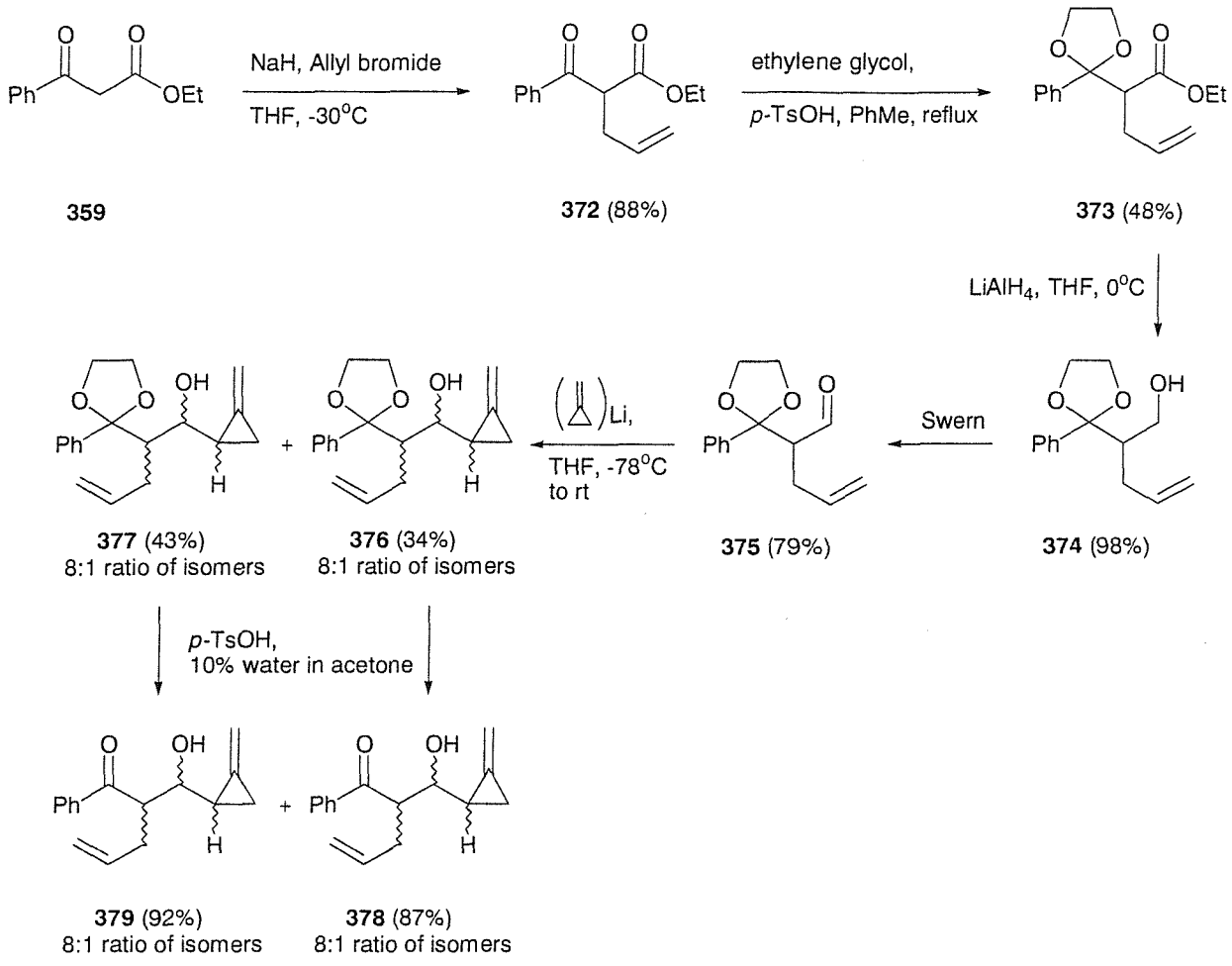
4.2.4) Conclusion

Di-allyl precursor **352** could not be obtained. A protecting group was required to prevent the retro-aldol reaction but it could not be put in place mainly due to steric reasons. Keen to investigate the cyclisation of phenyl ketones, we turned our attention to **351**, the mono-allyl version of the precursor, hoping that the protection of the ketone would proceed as the steric hindrance would be less.

4.3) STUDIES ON THE MONO-ALLYL PRECURSOR

4.3.1) Synthesis of the Precursor

Benzoyl acetoacetate **359** was deprotonated with sodium hydride and addition of allyl bromide allowed the formation of keto-ester **372** in 88% yield. **(Scheme 4.8)** Protection of the ketone to ketal **373** proceeded in a disappointing 48% yield. The low yield may again be due to steric hindrance and the influence of the benzene ring. Protected keto-ester **373** was reduced to the corresponding alcohol in excellent yield (98%) and **374** was then converted to aldehyde **375** in 79% yield by Swern oxidation. Addition of aldehyde **375** to methylenecyclopropane anion gave **376** and **377** in 34% and 43% yield respectively both as a 8:1 ratio of diastereoisomers.

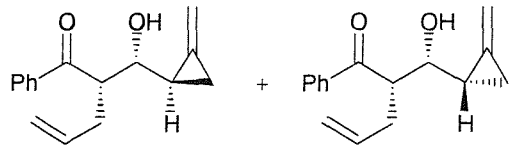


Scheme 4.8

Both **376** and **377** were isolated as mixtures of 2 isomers in about 8:1 ratio. They could then be deprotected by reaction with *p*-TsOH in wet acetone. Compound **378** was isolated in 87% yield and **379** in 92% yield again as mixtures of diastereosiomers.

4.3.2) Stereochemistry of the Precursor

Compounds **376, 377, 378** and **379** were isolated as oils and no information about their relative stereochemistry could be obtained. However, by analogy with the previous precursors (*vide infra*) it can be suggested that in both cases the major isomers have the allyl group and the alcohol *syn* to each other. (**Fig. 4.1**)



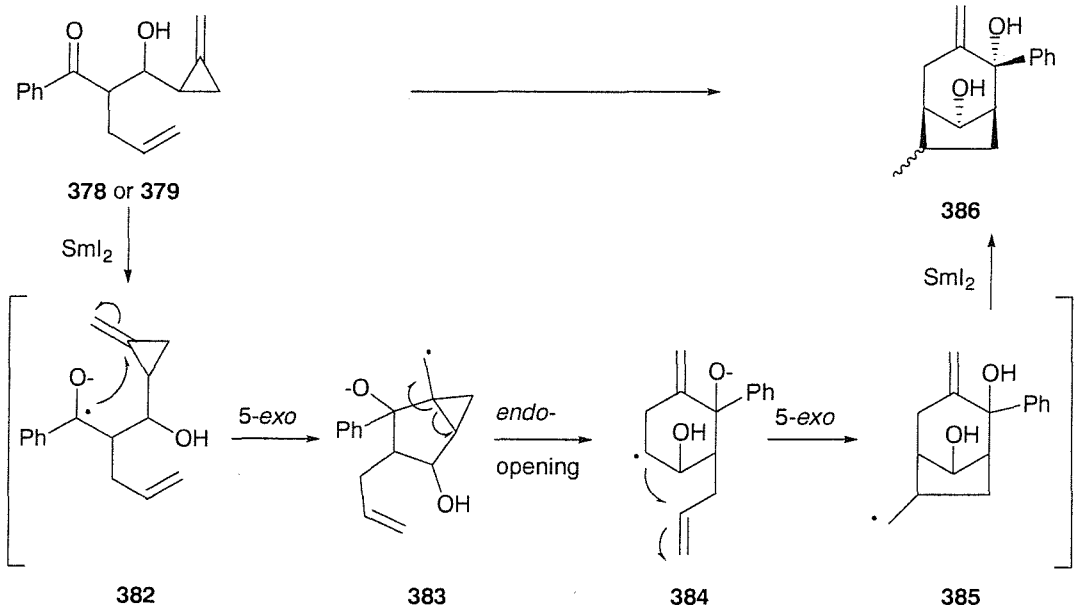
Probable major isomer of **380** | Probable major isomer of **381**

Figure 4.1

4.3.3) Cyclisations Of The Precursor

i- Expected result

It was anticipated that, similarly to the previous studies, ketone **351** would produce ketyl radical **382**. The radical would then undergo a 5-*exo* cyclisation onto the cyclic end of the double bond of methylenecyclopropane. The cyclopropane ring of **383** would open in an *endo* fashion to yield cyclohexyl radical **384**. Trapping of the radical by the pendant allyl group would lead to **385** which would be further reduced and quenched to the final cyclic product **386**. **(Scheme 4.9)**

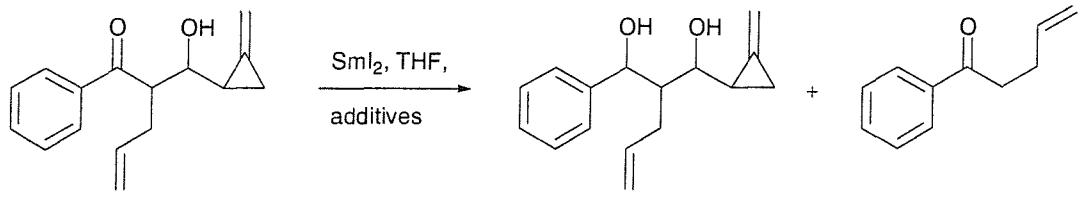


Scheme 4.9

Chelation of the samarium species should ensure that the stereochemistry observed is consistent with the previous studies (*vide infra*).

ii- Cyclisation results

When both **378** and **379** where subjected to reaction with SmI_2 under all previously used sets of conditions, none of the expected product was isolated. Instead, only the reduced product **387** (as a 4:1 ratio of diastereoisomers in both cases) and the retro-aldol product **388** were isolated. (**Scheme 4.10**)



378 or **379** **387** **388**

Scheme 4.10

Isomer	Addition Mode	Conditions	378/379	387	388	TOTAL
378	*Normal*	MeOH, 0°C	6	23	70	99
378	*Normal*	MeOH, -78°C	-	28	69	97
378	*Normal*	HMPA, ^{t}BuOH, 0°C	14	17	48	79
378	*Normal*	HMPA, ^{t}BuOH, -78°C	4	33	58	95
378	*Reverse*	MeOH, 0°C	-	83	12	95
379	*Normal*	MeOH, 0°C	-	26	40	66
379	*Normal*	MeOH, -78°C	3	26	49	78
379	*Normal*	HMPA, ^{t}BuOH, 0°C	-	37	52	89
379	*Normal*	HMPA, ^{t}BuOH, -78°C	-	40	36	76
379	*Reverse*	MeOH, 0°C	-	40	-	40
379	*Reverse*	HMPA, ^{t}BuOH, 0°C	-	17	-	17

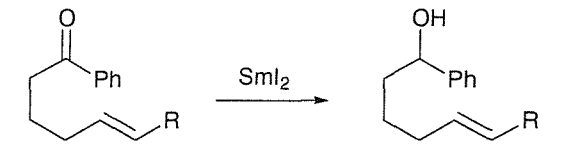
Table 4.3

To try to avoid complete reduction of the ketone to alcohol **387**, we undertook the cyclisation in a "reverse addition" fashion where a solution of SmI_2 is added *via* canula to the precursor in THF. Using this procedure, the precursor should never be in the presence of an excess of samarium (II) and should have time to cyclise before being reduced.

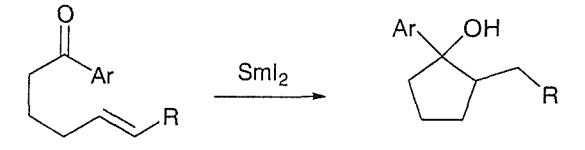
Unfortunately, reverse addition did not prove any more successful and only diol **387** and retro-aldol **388** could be isolated. The retro aldol adduct was thought to be formed by

the same mechanism as explained previously (**Scheme 3.24**) while the presence of the reduced diol can be rationalised by considering the influence of the adjacent benzene ring. Radical **382** is deactivated by the neighbouring aromatic ring and the opportunity for delocalisation could also be the source of the problem as the delocalised radical also has the possibility of being reduced.

Very little work is reported on the samarium (II) iodide mediated cyclisation of phenyl ketones. One of the few examples is the work of Molander[107] which shows that only reduction occurs for such compounds. However, substitution of the benzene ring allows cyclisation to occur. (**Scheme 4.11**)



389 **390**

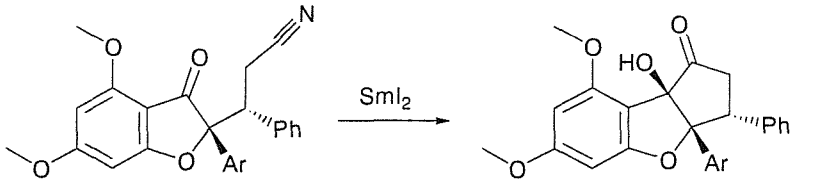


391 **392** 43%

Ar= 2,4-dimethoxybenzene

Scheme 4.11

Cyclisation of other polysubstituted phenyl ketones have also been reported to proceed when the radical trap is a cyanide moiety.[108] (**Scheme 4.12**)

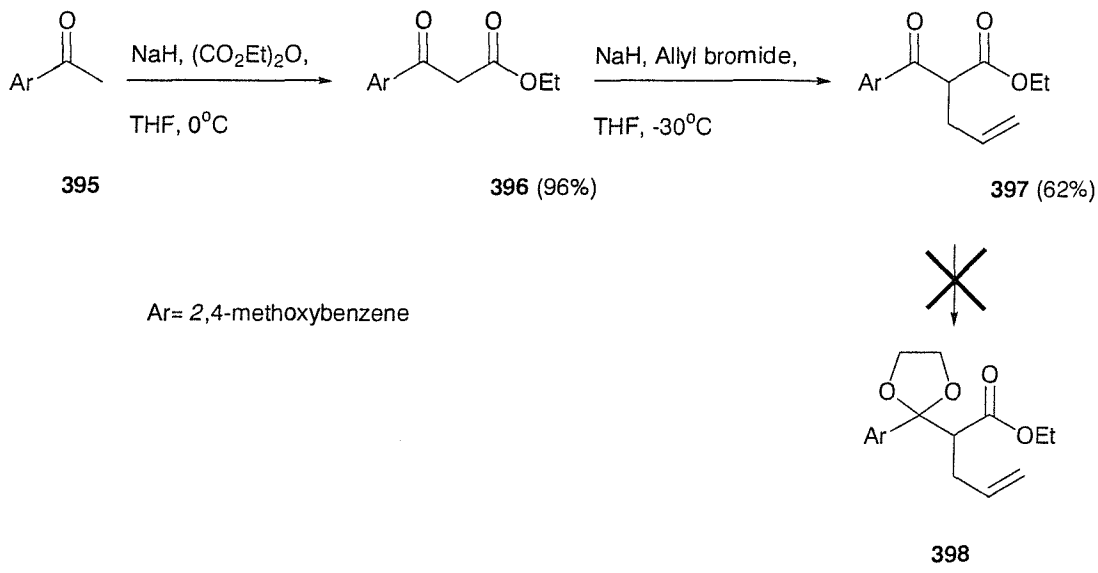


393 **394**

Ar= *p*-methoxybenzene

Scheme 4.12

We therefore wanted to modify the precursor by including methoxy groups in the *ortho* and *para* position, hoping that the cascade would happen successfully (**Scheme 4.13**)



Scheme 4.13

2,3-Dimethoxy acetophenone **395** was converted to keto-ester **396** according to a procedure by Farid[109] in 96% yield upon treatment with sodium hydride and diethyl carbonate. Deprotonation of **396** followed by exposure to allyl bromide afforded **397** in 62% yield. Unfortunately the ketone moiety of **397** could not be protected to **398** by any of the previously attempted protection methods. The protection is thought to have failed for two reasons: the *o*-methoxy group and the allyl group provoked steric hindrance around the carbonyl and both electron donating methoxy groups made the ketone even more electron rich, preventing a nucleophilic attack. We therefore decided not to pursue this route any further but to investigate other ways of introducing the remaining cyclic parts of the natural product skeletons.

4.4) CONCLUSION

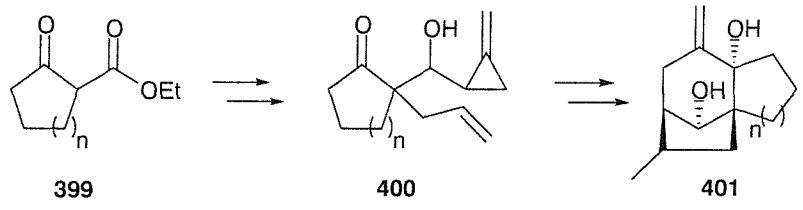
Steric and electronic factors in the protection step to compound **361** of our approach prevented the synthesis of the di-allyl precursors. However, precursor **351** was successfully obtained and was submitted to a number of cyclisation reactions. We have been able to

establish that, in accordance to the literature, phenyl ketones are quickly reduced to alcohols in the presence of samarium diiodide. We have also observed that another type of 1,3-ketoalcohol readily undergoes retro aldol-reaction catalysed by samarium species.

CHAPTER 5: CYCLISATIONS OF CYCLIC KETONES TOWARDS TRICYCLIC SYSTEMS

5.1) INTRODUCTION

The next approach consisted of incorporating a cyclic framework in the cyclisation precursor in order to access tricyclic systems directly. (**Scheme 5.1**)



399 **400** **401**

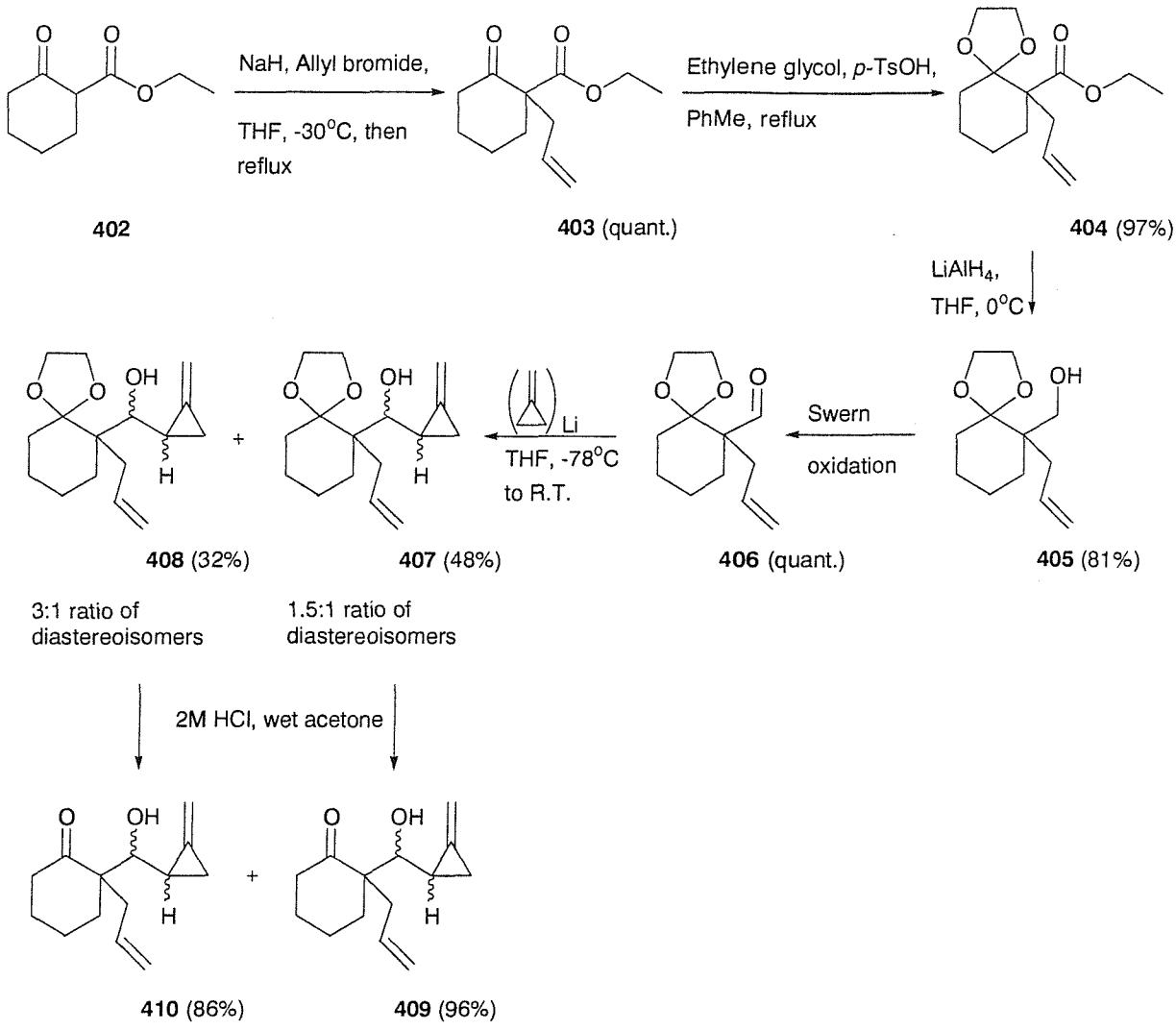
Scheme 5.1

Cyclopentyl (n=1) and the cyclohexyl (n=2) keto-esters **399** are commercially available and were used as the starting materials in the synthesis of the precursors.

5.2) STUDY OF THE CYCLOHEXYL PRECURSOR

5.2.1) Synthesis of the Precursor

Reaction of ethyl cyclohexanone carboxylate **402** with NaH followed by allyl bromide gave **403** in quantitative yield. Protection of the ketone to ketal **404** proceeded in 97% yield. (**Scheme 5.2**)



Scheme 5.2

Reduction of **404** with lithium aluminium hydride gave alcohol **405** in good yield (81%). Compound **405** was oxidised to aldehyde **406** in quantitative yield *via* Swern oxidation. Addition of **406** to lithiated MCP led to two separable mixtures of two isomers **407** (48% yield) and **408** (32% yield). Deprotection of **407**and **408** upon treatment with 2M HCl in wet acetone allowed precursors **409** and **410** to be isolated in 96% and 86% yield respectively as mixtures of 2 isomers in a 1.5:1 and 3:1 ratio respectively.

5.2.2) Stereochemistry of the precursors

The major isomer of **410** was isolated as a crystalline solid and its stereochemistry was unambiguously established by X-ray crystallography. (**Fig. 5.1**)

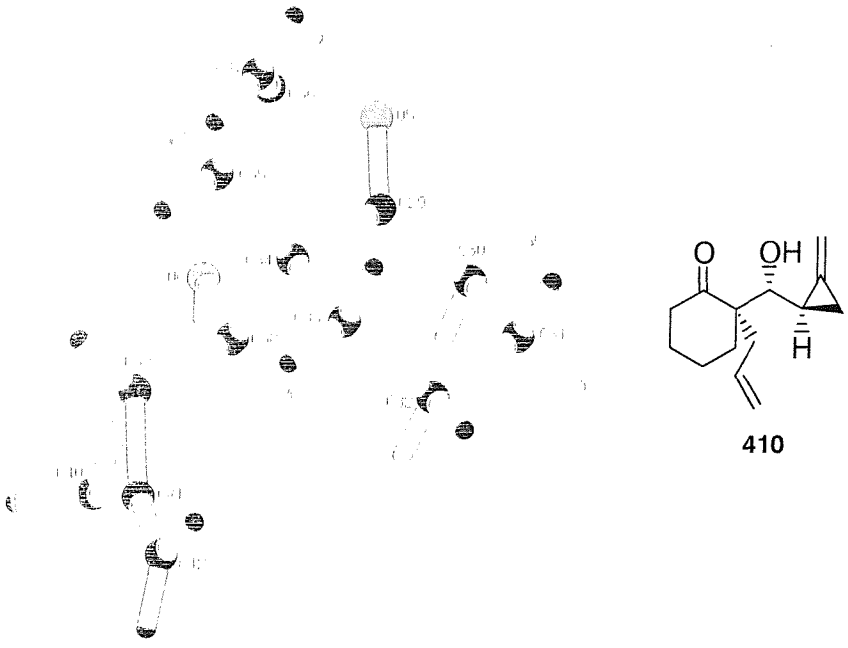


Figure 5.1

By comparison with previous studies it may be that the major isomer of **409** has the opposite relative stereochemistry at the cyclopropyl ring. However this is not certain, particularly in view of the fact that all four possible diastereoisomers have been obtained in significant quantity.

5.3) Cyclisation Of The Cyclohexyl Precursor

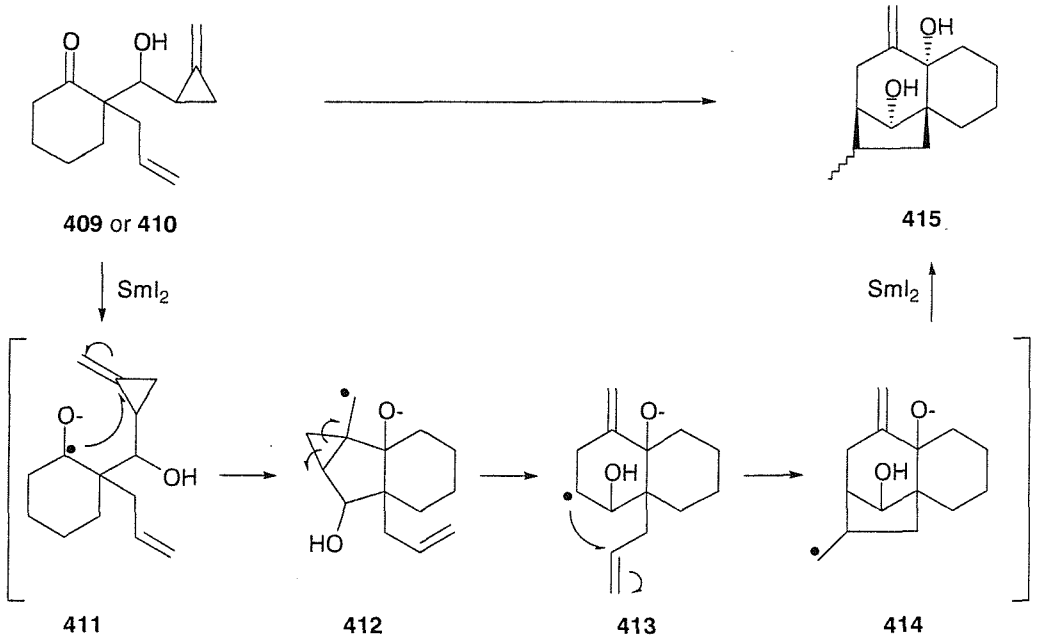
The usual conditions (2 equivalents of SmI_2, MeOH or HMPA/^{t}BuOH, 0°C or -78°C) were used in the cyclisation studies of the precursor. Temperature and co-solvent were varied as well as the mode of addition.

5.3.1) Expected Results

i- Outcome of the radical sequence

On treatment with SmI_2, the precursor should be reduced to ketyl radical **411** which it was hoped would undergo the usual sequence of 5-*exo* cyclisation, *endo* opening of the cyclopropyl ring and another 5-*exo* cyclisation should result in the formation of tricycle **415**. (**Scheme 5.3**) The stereochemistry of the precursor would have a crucial importance on the likelihood of the sequence occurring.

Chelation of the samarium species with both oxygen atoms should again dictate the stereochemistry of the process leading to both hydroxy groups being on the same face of the cyclohexane ring.



Scheme 5.3

Since all four possible diastereoisomers were present in reasonable amount in the two mixtures, it is appropriate to consider the possible cyclisation pathway for each of them.

ii- Nature of the precursors

The stereochemistry of the major isomer of **410** was established but all four diastereoisomers are present. For the purpose of this discussion, they have been labelled **A** to **D**. **(Fig.5.2)**

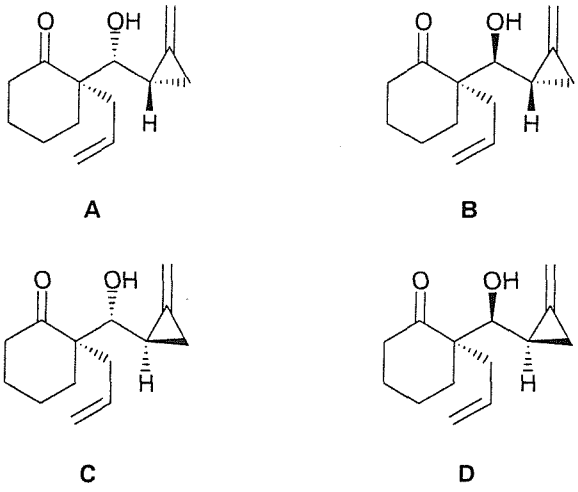
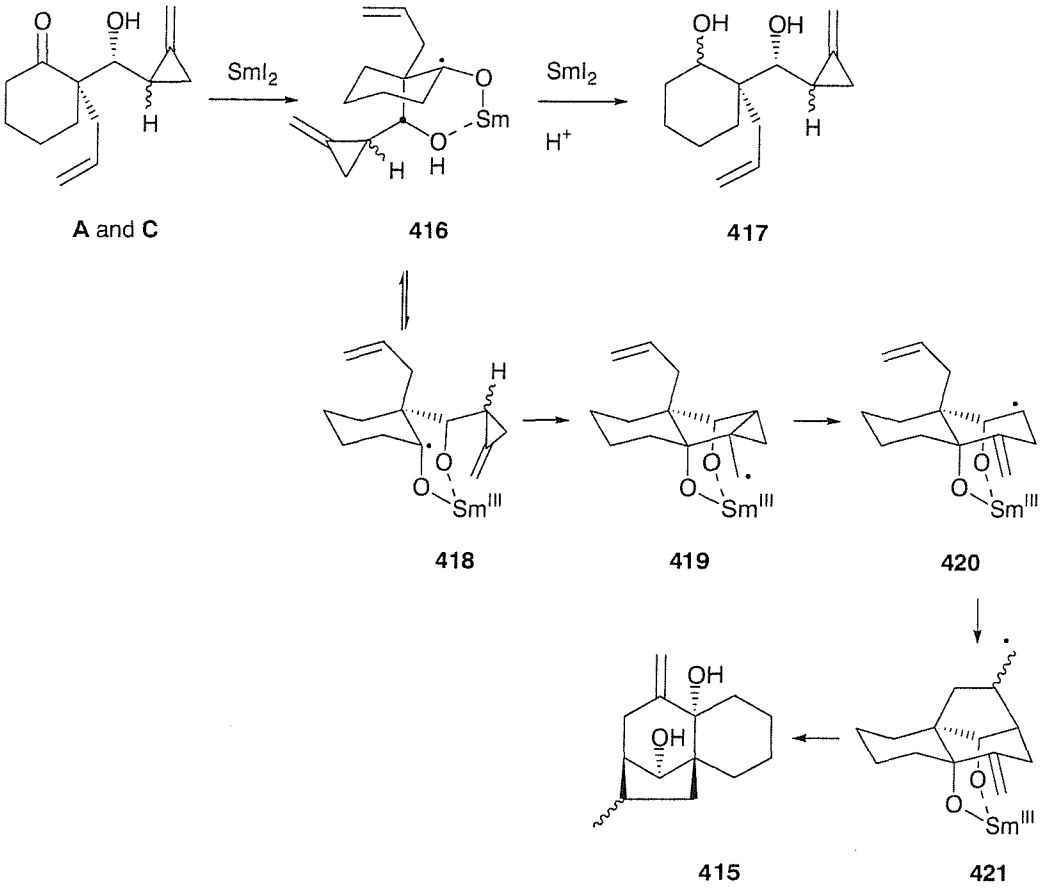


Figure 5.2

The relative stereochemistry between the allyl and hydroxy groups is the main factor affecting the outcome of the cyclisation, we can therefore consider **A** and **C** together.

iii- Precursors A and C

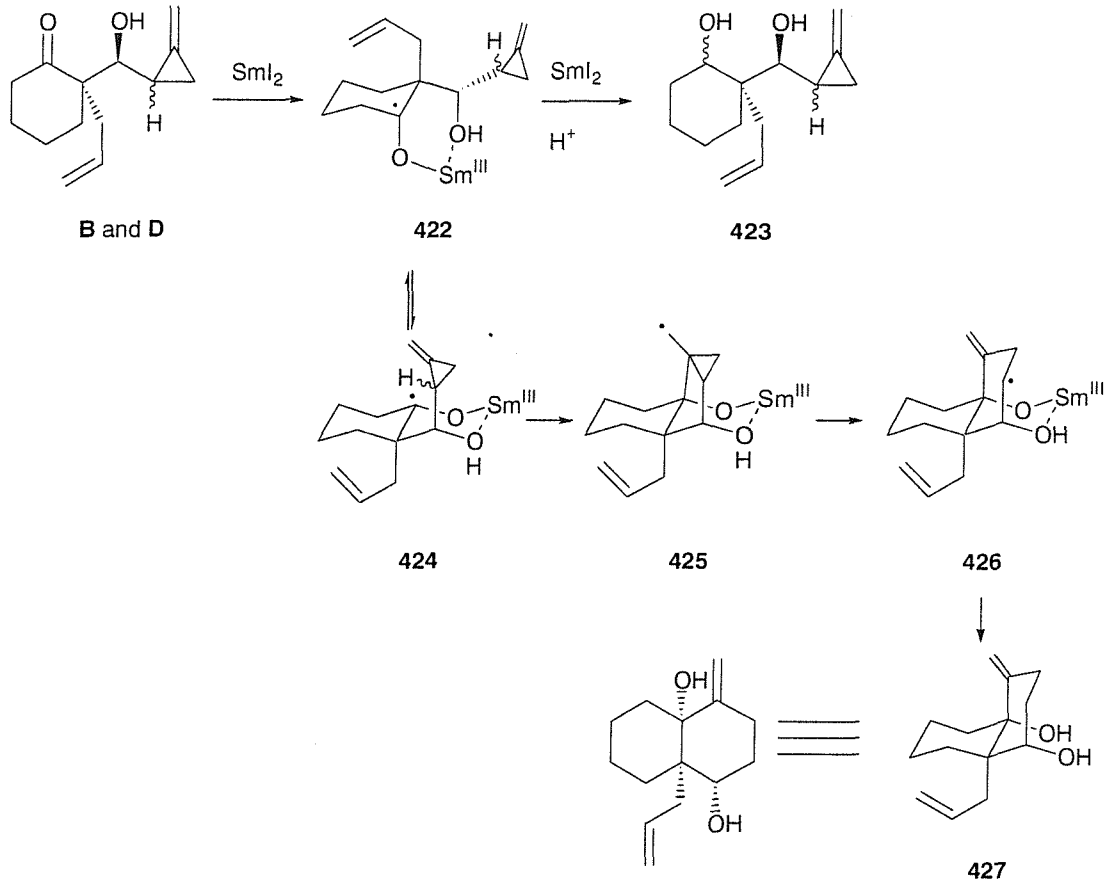
Isomers **A** and **C** were expected to cyclise to the tricycle. Formation of the ketyl radical and chelation would allow the O-Sm group to adopt an equatorial **416** or axial **418** orientation. In conformer **416**, the chelation exerted by the samarium species between both oxygens should prevent the first cyclisation from occurring. In the absence of a possible moiety to react with, the radical should end up being reduced, leading to diol **417** as the only product. However if the initial radical adopts the other conformation **418**, the cyclisation can proceed to give intermediate **420** with the allyl group suitably oriented for a further cyclisation and the tricyclic compound **415** could be formed. **(Scheme 5.4)**



Scheme 5.4

iv- Precursors B and D

Alternatively, isomers **B** and **D** were not expected to cyclise to the tricycle. Radical **422**, where the O-Sm group is held axial, does not provide a suitable configuration for the cyclisation to occur. However, partial cyclisation can happen if the initial intermediate is **424**. In this case, cyclisation onto the methylenecyclopropane double bond results in radical **425** and opening of the ring gives decalin **426**. At this point, the allylic double bond is not accessible to the radical centre and reduction, followed by quenching of the resulting ion should lead to bicyclic compound **427**. (**Scheme 5.5**)



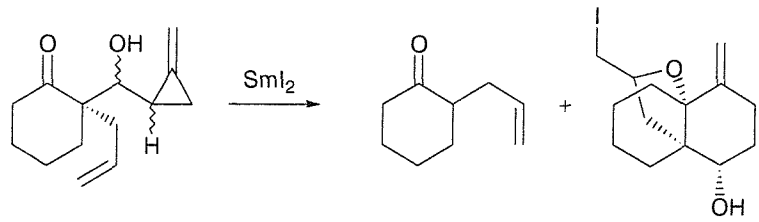
Scheme 5.5

5.3.2) Cyclisation of precursor 409

Ketone **409** was submitted to reactions with SmI_2/HMPA/^{t}BuOH and SmI_2/MeOH using "normal" and "reverse" addition procedure.

i- Cyclisation Results

Upon treatment with SmI_2, precursor **409** did not afford the expected tricyclic compound. (**Scheme 5.6**) Instead, retro-aldol product **428**, and tricyclic compound **429** were isolated.



409 428 429

Scheme 5.6

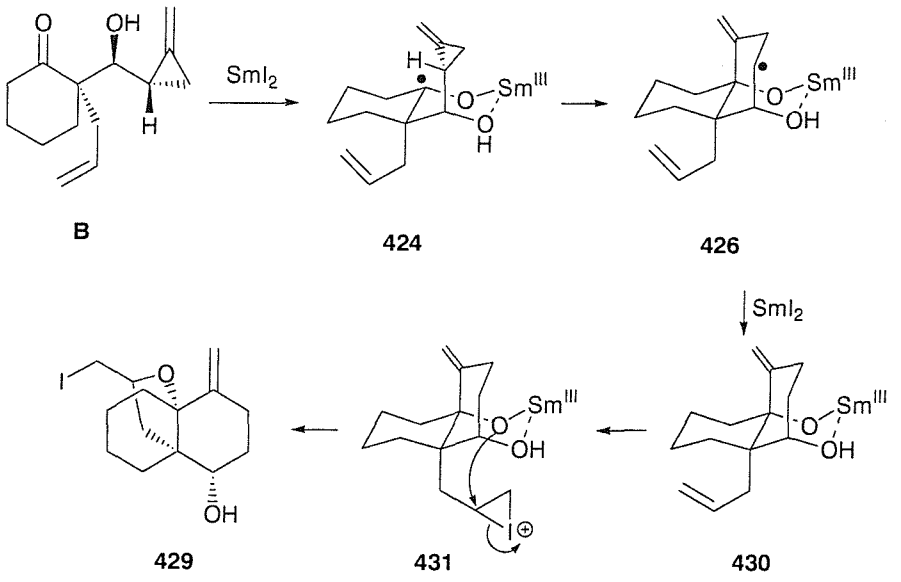
Ketone **428** was isolated in up to 73% yield (entry 5) and arose from a samarium (III) mediated retro-aldol reaction as discussed previously. (**Table 5.1**) Most surprisingly, tricyclic iodide **429** was isolated in 23% yield as a single diastereoisomer, from the cyclisation undertaken with methanol as solvent (entry 1, 2 and 5).

Entry	Conditions	428	429	TOTAL
1	MeOH, 0°C	34	23	57
2	MeOH, -78°C	42	23	65
3	HMPA, ^{t}BuOH, 0°C	64	-	64
4	HMPA, ^{t}BuOH, -78°C	44	-	44
5	MeOH, -78°C Reverse addition	73	11	84

Table 5.1

ii- Formation of 429

The origin of tricycle **429** can be understood when considering the intermediate **426**. (**Scheme 5.7**) Once the first cyclisation and the ring opening has occurred and radical **426** is formed, there may be an interaction between the allyl double bond and some iodine present in the reaction medium to generate iodide intermediate **431**. Then the oxygen could attack **431** to give iodide **429**.



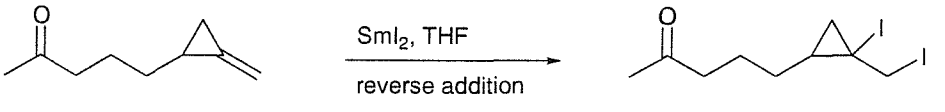
B 424 426 430 431 429

Scheme 5.7

The stereochemistry of **429** is therefore likely to be as shown, however it cannot be ruled out that its formation may have arisen from another isomer *via* a non-chelation pathway.

iii- Evidence for the identity of 429

The information obtained from mass spectrometry revealed the presence of iodine in the molecule. The interference of iodide with unsaturations during SmI_2 mediated cyclisations has been encountered before in the group.[110] **(Scheme 5.8)**



432

433
SmI_2, MeOH, -78°C: 45%
SmI_2, HMPA, -78°C: 21%

Scheme 5.8

The NMR data also confirmed the identity of **429**. **(Fig. 5.3)**

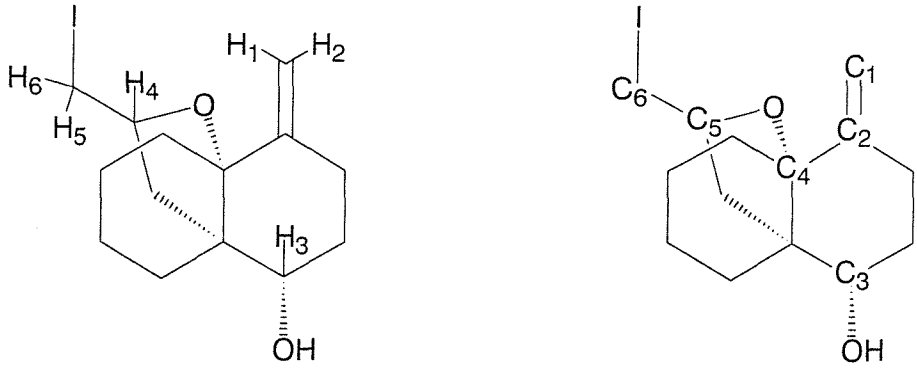


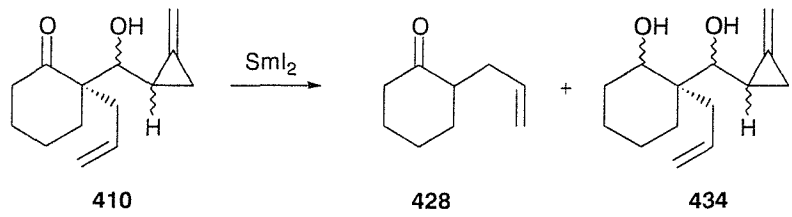
Figure 5.3

The chemical shift for C_1 and C_2 was in agrement with those found in previous related cyclisation products. The downfield chemical shift of H_5 and H_6 (δ 3.39 and 3.13 ppm) as well as the highfield position of C_6 (12.2 ppm) were consistent with a neighbouring iodine. Additionally, three carbons (one of which was quaternary) were found in the region characteristic for O-C chemical shifts, (^{1}H-^{1}H and ^{1}H-^{13}C correlations helped assign them as C_3, C_4 and C_5). The position of H_4 was concordant with a hydrogen atom attached to an oxygen bearing carbon and its splitting revealed the presence of two neighbouring CH_2's.

5.3.3) Cyclisation of precursor 410

i- Cyclisation Results

Ketone **410** was reacted with SmI_2/HMPA/^{t}BuOH and SmI_2/MeOH using "normal" and "reverse" addition procedure. Unfortunately, precursor **410** did not afford the desired tricycle and instead, retro-aldol product **428** and reduced compound **434** were isolated. **(Scheme 5.9)**



Scheme 5.9

The retro aldol product, ketone **428** was isolated in most cases in up to 78% yield (entry 3). (**Table 5.2**) The reduced compound **434** (2:1 ratio of isomers) was also formed in up to 27% yield. Undertaking the reaction by reverse addition did not change the outcome as the same products were the only product isolated.

Entry	Conditions	410	428	434	TOTAL
1	MeOH, $0^{o}C$	10	60	27	97
2	MeOH, $-78^{o}C$	14	61	22	97
3	HMPA, $^{t}BuOH$, $0^{o}C$	-	78	-	78
4	HMPA, $^{t}BuOH$, $-78^{o}C$	-	18	24	42
5	MeOH, $-78^{o}C$ Reverse addition	16	18	23	57

Table 5.2

5.3.4) Conclusion

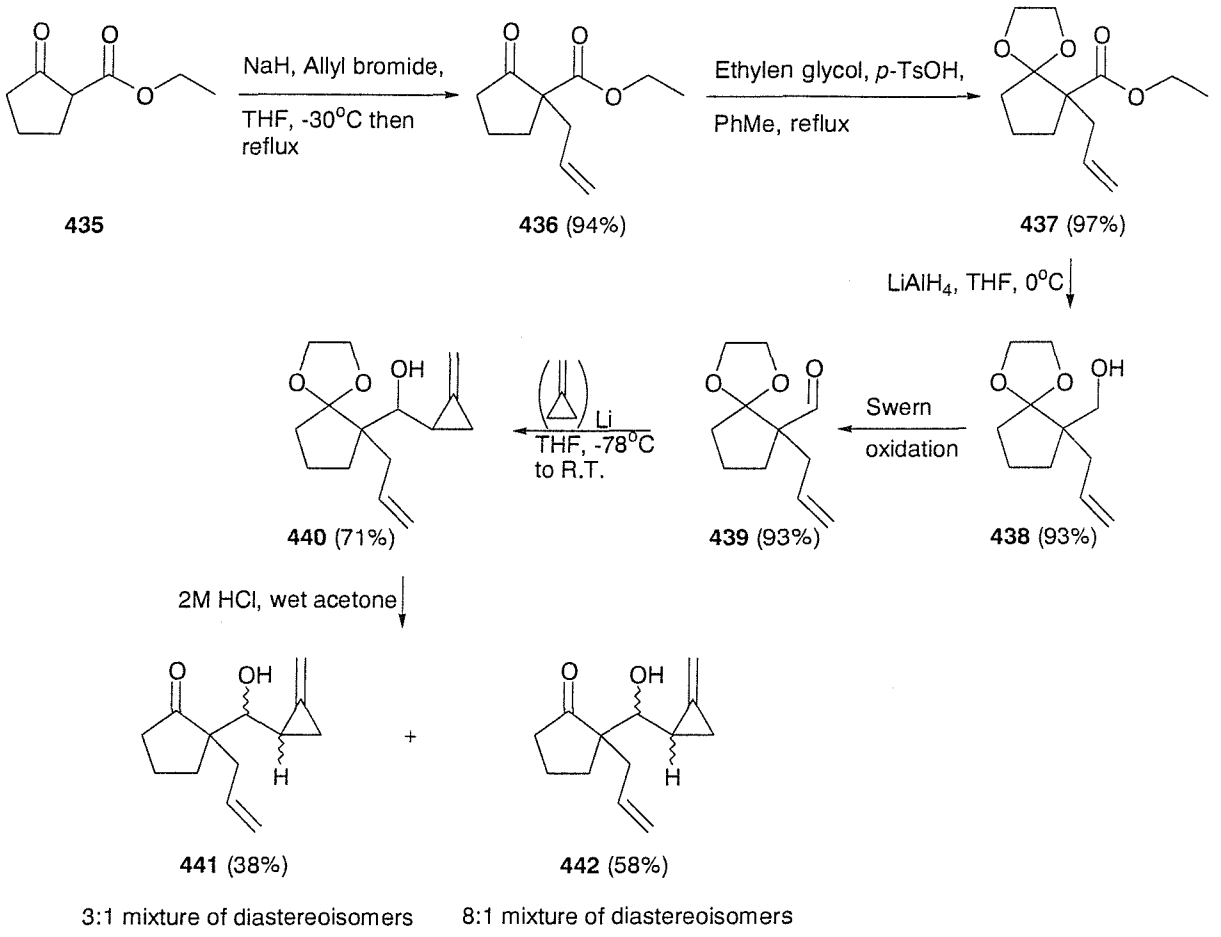
Unfortunately, none of the desired tricycles could be isolated from the attempted cyclisations of ketones **409** and **410**. Instead, the reduced compound **434** and **428** arising from a samarium (III) mediated retro aldol reaction were the major products obtained.

5.4) Study of The Cyclopentyl Precursor

5.4.1) Synthesis of the Precursor

Following a similar strategy, ethyl cyclopentanone carboxylate **435** was deprotonated with NaH and addition of allyl bromide afforded **436** in 94% yield. Protection of the ketone to ketal **437** proceeded in 97% yield. Ketal **437** was then reduced to alcohol

438 with lithium aluminium hydride in very good yield (93%). Alcohol **438** was subsequently oxidised to aldehyde **439** in 93% yield, *via* Swern oxidation. Addition of **439** to lithiated MCP led to **440** as a mixture of isomers, in 71% yield. **(Scheme 5.10)**



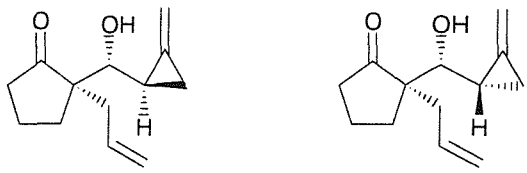
Scheme 5.10

The protected precursor **440** was used crude in the deprotection step and two mixtures of two isomers, ketones **441** and **442** were formed. **441** was obtained in 38% as a 3:1 ratio of isomers whereas **442** could be isolated in 58% yield as an 8:1 ratio of isomers.

5.4.2) Stereochemistry of the Precursors

Both precursors were isolated as oils and their stereochemistry could not be established. By comparison with earlier results, the stereochemistry of the major isomers

are likely to be **443** and **444** but the exact stereochemistry of either isomer of **441** and **442** remains unknown. **(Fig 5.4)**



443 444

Figure 5.4

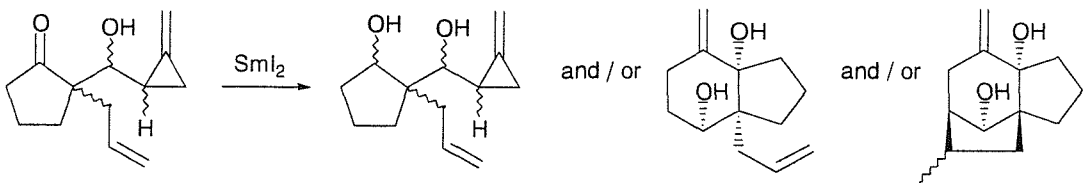
Both precursors were used in the cyclisation studies.

5.5) Cyclisation Of The Cyclopentyl Precursor

Due to time constraints, there was not enough time to apply all the conditions previously used in the cyclisation the precursors. Instead, one trial cyclisation was attempted on each precursor, using SmI_2 and methanol at 0°C.

5.5.1) Expected Results

Both cyclopentyl ketone precursors **441** and **442** should behave in a similar fashion to the cyclohexyl precursors **408** and **409**. It can be therefore be anticipated that the cyclisation sequence may occur, or it may stop before the last step, or the reduced compound might be the only product. Once again, the ratio of isomers in **441** means that the minor isomer may have a significant role. **(Scheme 5.11)**

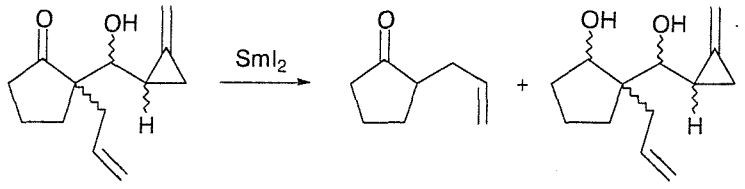


441 or 442 445 446 447

Scheme 5.11

5.5.2) Cyclisation of Precursor 441

From the predicted stereochemistry, **441** could cyclise to the tricycle. Unfortunately, precursor **441** afforded retro-aldol product **448** and reduced compound **449**. (**Scheme 5.12**)



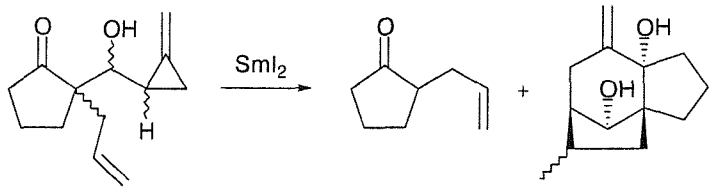
441 **448** (22%) **449** (36%)

Scheme 5.12

From the cyclisation of precursor **441**, ketone **448** was isolated in 22% yield, arising from a samarium (III) mediated retro-aldol reaction as discussed previously. The reduced compound **449** was formed in 36% yield (2:1 ratio of isomers). Starting material **441** was recovered in 23% yield.

5.5.3) Cyclisation of Precursor 442

When **442** was subjected to the cyclisation conditions, ketone **448** was isolated in 52% yield, alongside tricyclic compound **447**, which was obtained in 16% yield as a single diastereoisomer. (**Scheme 5.13**)

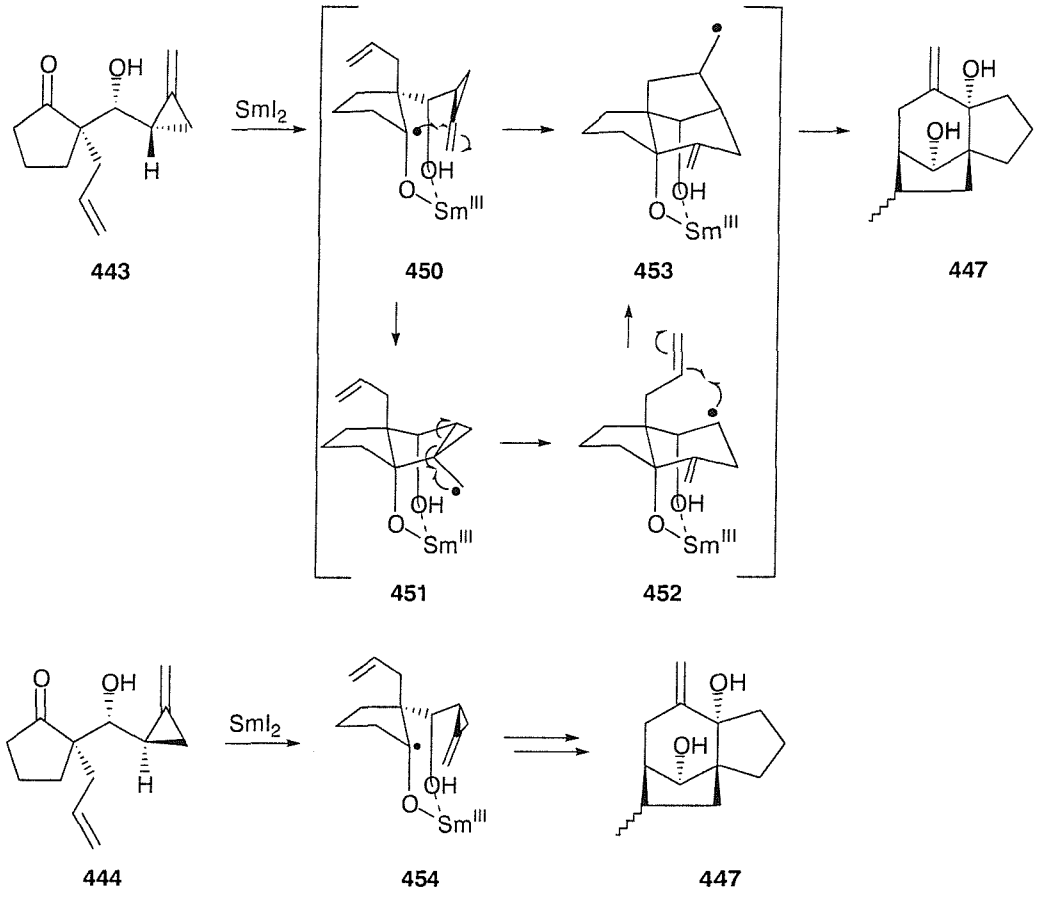


442 **448** (52%) **447** (16%)

Scheme 5.13

ii- Formation of 447

As discussed for the cyclohexyl precursors, one the isomers of **442** could cyclise providing it has the relative stereochemistry shown in **443** or **444**. If the initial radical is **450** where the O-Sm group is held axial in a pseudo chair-like transition state the sequence of cyclisation could occur, leading to tricycle **447**.(**Scheme 5.14**)



Scheme 5.14

iii- Evidence for the identity of 447

The cyclised product was obtained as an oil and its stereochemistry remains unknown. However, from the previous study and the proposed mechanism it was assumed that both hydroxy groups would be *syn* and on the opposite side to the bridge-head.

Mass spectrometry could not be of any help as the molecular weight of the tricyclic compound is similar to that of the reduced diol **449**. NMR spectrometry gave important clues to confirm that the cyclisation product was indeed the desired one. All the signals

characteristic of methylenecyclopropane had disappeared as well as those for the allyl group. Signals similar to those found for the double bond CH_2 of the previously obtained cyclic product were present. There were also two signals corresponding to oxygen-bearing carbons, one of which was quaternary. Unfortunately, n.O.e. studies proved inconclusive and no additional information could be obtained

It can however be said we are confident the product isolated from the cyclisation of ketone **442** is tricyclic compound **447**.

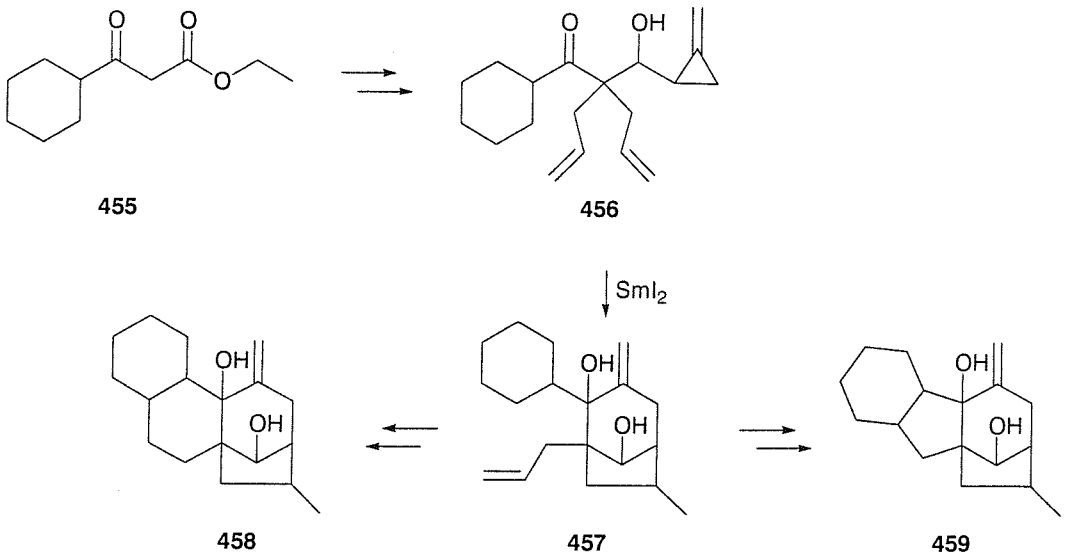
5.6) Conclusion and Future Work

Cyclisations of cyclohexyl ketone derivatives of methylenecyclopropanes proved ineffective to access tricyclic compounds related to kaurenoids because the radical initially formed was reduced before it could cyclise. The formation of iodotricycle **429** shows that cyclisation does occur but only for the isomer with the wrong stereochemistry to proceed to the desired tricycle.

The trial cyclisations of precursor **441** resulted only in the reduced compound, diol **449**, and retro-aldol ketone **448**. When precursor **442** was treated with samarium diiodide, tricycle **447** and ketone **448** were isolated in low yield. Unfortunately only one cyclisation could be undertaken and it is not possible to say whether other conditions would have given better results.

No explanation can be given to account for the successful cyclisation of the 5-membered ring precursor when the corresponding 6-membered ring failed to give any tricyclic compound.

Future work may wish to further the investigation of the cyclopentyl precursors and if successful, consider the introduction of the remaining ring to access the natural product skeleton. An alternative to get to the quadricyclic system would be to investigate the cyclisation of precursors related to **352** where a cyclohexane would replace the benzene ring. (**Scheme 5.15**)



Scheme 5.15

CHAPTER 6: EXPERIMENTAL SECTION

6.1) GENERAL EXPERIMENTAL

Solvents and reagents were purified according to the procedures outlined in Perin and Armarego, *"Purification of Laboratory Chemicals"*, when required.[111]

Reactions requiring anhydrous conditions were conducted in flame-dried or oven-dried apparatus under inert atmosphere.

Flash column chromatography was performed according to the procedure described by Still,[112] using Sorbsil C60, 40-60 mesh silica.

Solvents were all commercial grade and used without further purification unless otherwise stated. THF was distilled from benzophenone ketal, DCM was distilled from calcium hydride, and petrol was distilled and the fraction boiling between 40°C and 60°C was used throughout.

6.2) INSTRUMENTATION

Proton nmr spectra were all obtained at 300 MHz on a Bruker AC 300 spectrometer, and at 400 MHz on a Bruker DPX400 spectrometer. Peak positions are quoted in ppm relative to the residual chloroform signal (δ= 7.27 ppm), using the following abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad singlet (br s).

Carbon-13 NMR spectra at 75 MHz were obtained on a Bruker AC 300 and at 100 MHz were obtained on a Bruker DPX400 spectrometer. The multiplicities of the signals are indicated in parentheses, using the following abbreviations: quaternary carbon, tertiary (1), secondary (2) and primary (3), and in some cases were elucidated using the distortionless enhancement by phase transfer (DEPT) spectral editing technique with second pulse at 135°.

IR spectra were recorded on a Bio-Rad Golden Gate ATR FT-IR spectrometer.

Mass spectroscopy data was obtained on a ThermoQuest TraceMS gas chromatography mass spectrometer configured for open access operation.

X-ray diffraction data was obtained from an *Enraf Nonius KappaCCD* diffractometer, the structure determined by direct methods using the program *SHELXS97*[113] and refined using *SHELXL97*.[114]

Compounds were named using the program ACD/Name version 2.51 from Advanced Chemistry Development Inc.

6.3) EXPERIMENTAL FOR CHAPTER TWO

General Procedure for the opening of epoxides with MCP:

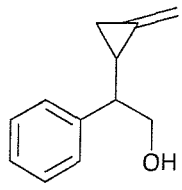
Method A: lithiated methylenecyclopropane:

^{n}BuLi (2.5M in hexanes, 1.2 eq.) was added to a solution of MCP (1.2 eq.) in THF at -40°C under argon. The solution was warmed to 0°C over 30 min and stirred for 30 min. It was then allowed to reach room temperature over 30 minutes and kept at room temperature for 15 minutes. The reaction mixture was then cooled to -78°C. Epoxide (1 eq.) in THF was slowly added and the mixture was allowed to reach rt. The reaction was quenched with aq. NH_4Cl. The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*.

Method B: methylenecyclopropyl cuprate:

^{n}BuLi (2.5M in hexanes, 4 eq.) was added to a solution of MCP (4 eq.) in THF at -40°C under argon. The solution was warmed to 0°C over 30 min and stirred for 30 min. It was then allowed to reach room temperature over 30 minutes and kept at room temperature for 15 minutes. The reaction mixture was then cooled to -40°C and rapidly cannulated into a suspension of CuI (2 eq.) in THF at -40°C under argon. The resulting solution was stirred at -40° for 30 min and cooled to -78°C. Epoxide (1 eq.) and $BF_3.Et_2O$ (2 eq.) in THF were slowly added and the mixture was allowed to reach room temperature. The reaction was quenched with aqueous NH_4Cl. The aqueous layer was extracted with ether (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*.

(±)-2-(2-Methylidenecyclopropyl)-2-phenylethan-1-ol 231:



Using method A and styrene oxide (1.26 mL, 11 mmol). After column chromatography (Et_2O in Pet Ether 0-30%), **231** was obtained as a colourless oil, 940 mg (52% yield).

Using method B and styrene oxide (0.2 mL, 1.78 mmol). After column chromatography (Et_2O in petrol, 0-30%), alcohol **231** was obtained as a colourless oil, 65 mg (21% yield).

Rf= 0.13 (10% EtOAc in petrol)

δ_H (300 MHz, $CDCl_3$): 7.49-7.22 (5H, m, aromatics), 5.56 (1H, d, *J* 2 Hz, C=CH_AH$_B$), 5.47 (1H, d, *J* 2 Hz, C=CH$_A$$H_B$), 3.97-3.88 (2H, m C$H_2$OH), 2.33 (1H, dt, *J* 7, 10 Hz, CHPh), 1.76 (1H, m, cyclopropyl CH_AH$_B$), 1.53 (1H, br s, OH), 1.32 (1H, tt, *J* 2, 7 Hz, cyclopropyl CH), 0.88 (1H, m, cyclopropyl CH$_A$$H_B$).

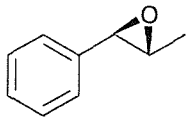
δ_C (75 MHz, $CDCl_3$): 141.71, 135.75, 128.84 (1 ×2), 128.06 (1 ×2), 127.12 (1), 103.90 (2), 67.36 (1), 52.23 (1), 18.03 (1), 9.01 (2).

ν_{max}: 3338, 3064, 3029, 2983, 2909, 1492, 1452, 1061, 1024, 883, 756.

m/z(CI): 175 (M+H, 100), 157 (64), 105 (62).

HRMS (CI): found: 157.1094 ([M+H-H_2O]$^+$), requires: 157.1087.

(±)-(2R, 3R)-2-Methyl-3-phenyloxirane 233:



(E)-Methylstyrene (2.2 mL, 17 mmol) in DCM (20 mL) was added to a slurry of *m*-CPBA (4.38 g, 25.5 mmol) in DCM (30 mL). The mixture was stirred for 18 hours. The reaction was washed with aq. sodium sulphite, aq. $NaHCO_3$ and brine. The aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layers were dried ($MgSO_4$)

and concentrated *in vacuo*. The crude was purified by column chromatography (Et_2O in petrol, 0-5%) to give epoxide **233** as a colourless oil (1.69 g, 75% yield)

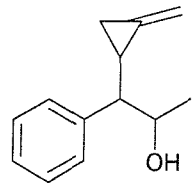
Rf= 0.61 (10% EtOAc in petrol)

δ_H (300 MHz, $CDCl_3$): 7.54-7.22 (5H, m, aromatic H), 3.62 (1H, d, *J* 2 Hz, PhCH), 3.06 (1H, dq, *J* 2, 5 Hz, C*H*CH_3), 1.48 (3H, d, *J* 5 Hz, CH_3)

δ_C (75 MHz, $CDCl_3$): 137.92, 128.60 (1 ×2), 128.20 (1 ×2), 125.72 (1), 59.69 (1), 59.20 (1), 18.08 (3).

All data agreed with those reported by Dickinson[115].

(±)-1-(2-Methylenecyclopropyl)-1-phenyl-2-propanol 234:



Using method A and 2-methyl-3-phenyloxirane **233** (0.71 g, 5 mmol). After column chromatography (Et_2O in petrol, 0-30%), two isomers of alcohol **234** were obtained as colourless oils, 67 mg (7% yield) and 139 mg (14% yield).

Using method B and **233** (0.5 g, 3.73 mmol). After column chromatography (Et_2O in petrol, 0-30%), two isomers of alcohol **234** were obtained as colourless oils, 57 mg (15% yield) and 132 mg (35% yield).

Data for the first isomer:

Rf= 0.24 (10% EtOAc in petrol)

δ_H (300 MHz, $CDCl_3$): 7.47-7.16 (5H, m, aromatic H), 5.56 (1H, s with fine splitting, C=C$H_A$$H_B$), 5.49 (1H, s with fine splitting, C=C$H_A$$H_B$), 4.12 (1H, m C*H*OH), 2.06 (1H, dd, *J* 7, 13 Hz, CHPh), 1.88 (1H, m, cyclopropyl C$H_A$$H_B$), 1.64 (1H, br s, OH), 1.35 (3H, d, *J* 7 Hz, CH_3), 1.21 (1H, m, cyclopropyl C$H_A$$H_B$), 0.70 (1H, m, cyclopropyl CH).

δ_C (75 MHz, $CDCl_3$): 141.72, 136.83, 128.73 (1 ×2), 128.54 (1 ×2), 127.06 (1), 103.38 (2), 71.86 (1), 57.75 (1), 21.41 (3), 18.39 (1), 8.57 (2).

ν_{max}: 3427, 3061, 3028, 2971, 2929, 1493, 1452, 1118, 1075, 889, 751.

m/z(CI): 189 (M+H, 62), 171 (24), 145 (100).

HRMS (EI): found: 204.1514 ($M+NH_4$), requires: 204.1358.

Data for the second isomer:

Rf= 0.22 (10% EtOAc in petrol)

δ_H (300 MHz, $CDCl_3$): 7.42-7.18 (5H, m, aromatic H), 5.30 (1H, s with fine splitting, C=CH_AH$_B$), 5.02 (1H, s with fine splitting, C=CH$_A$$H_B$), 4.18 (1H, m C*H*OH), 2.12 (1H, dd, *J* 9, 12 Hz, CHPh), 1.85 (1H, m, cyclopropyl CH_AH$_B$), 1.56 (1H, br s, OH), 1.42-1.32 (4H, m, CH_3, and, cyclopropyl CH$_A$$H_B$), 0.92 (1H, m, cyclopropyl CH).

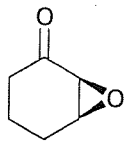
δ_C (75 MHz, $CDCl_3$): 141.47, 134.29, 128.83 (1 ×2), 128.59 (1 ×2), 127.32 (1), 103.78 (2), 71.65 (1), 57.49 (1), 21.40 (3), 17.96 (1), 10.68 (2).

ν_{max}: 3428, 3061, 3031, 2970, 2926, 1492, 1452, 1123, 1076, 891, 747.

m/z(CI): 189 (M+H, 62), 171 (24), 145 (100).

HRMS (EI): found: 204.1514 ($M+NH_4$), requires: 204.1358.

(±)-(1aS, 5aS)-Perhydro-1-benzoxiren-2-one 240:



Following a method by House[116].

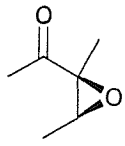
Hydrogen peroxide (30% wt., 3.4 g, 30 mmol) was added to a solution of cyclohexenone (1 g, 10 mmol) in methanol (10 mL) at 20°C. 6M NaOH (0.83 mL, 5 mmol) was added dropwise, keeping the temperature of the solution between 15°C and 25°C and the reaction was allowed to stir for 3 hours. The solution was poured into water (10 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (Et_2O in petrol, 0-10%) to give epoxy-ketone **240** as a colourless oil (1.06g, 91% yield)

Rf= 0.5 (20% EtOAc in petrol)

δ_H (300 MHz, $CDCl_3$): 3.58 (1H, s with fine splitting, COCH), 3.18 (1H, d, *J* 4 Hz, OCHCH$_2$), 2.52 (1H, app. dt, *J* 4, 17 Hz, CH_AH$_B$CO), 2.25 (1H, m, CH$_A$$H_B$CO), 2.12-1.85 (3H, m, CH_2 and CH_AH$_B$), 1.65 (1H, m, CH$_A$$H_B$)

δ_C (75 MHz, $CDCl_3$): 206.69, 56.58 (1), 55.76 (1), 37.02 (2), 23.48 (2), 17.61 (2).
All data agreed with those reported by Jung[117].

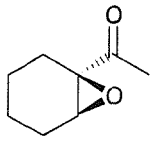
(±)-1-[(2S, 3S)-2,3-dimethyloxiran-2-yl]-1-ethanone 243:



Following a method by House[116].

Hydrogen peroxide (30% wt., 8.5 mL, 75 mmol) was added to a solution of 3-methyl-3-penten-2-one (2.5 g, 25 mmol) in methanol at 20°C. 6M NaOH (6 mL, 37.5 mmol) was added dropwise, keeping the temperature of the solution between 15°C and 25°C and the reaction was allowed to stir for 3 hours. The solution was poured into water (10 mL) and extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (Et_2O in petrol, 0-10%) to give epoxy-ketone **243** as a colourless oil (2.40 g, 83% yield)
Rf= 0.61 (20% EtOAc in petrol)
δ_H (300 MHz, $CDCl_3$): 3.17 (1H, q, *J* 5 Hz, $CHCH_3$), 2.03 (3H, s, CH_3CO), 1.41 (3H, s, CH_3C), 1.35 (3H, d, *J* 5 Hz, CH_3CH).
δ_C (75 MHz, $CDCl_3$): 209.16, 66.19, 56.85 (1), 23.50 (3), 13.88 (3), 12.33 (3).
All data agreed with those reported by Reed[118].

(±)-1-[(1aR, 5aS)-Perhydro-1-benzoxiren-1-yl]-1-ethanone 260:



Following a method by Reed[118].

Hydrogen peroxide (30% wt., 2.54 g, 22.5 mmol) was added to a solution of 1-acetyl cyclohex-1-ene (1 mL, 7.5 mmol) in methanol (10 mL) at 20°C. 6M NaOH (0.6 mL, 3.75 mmol) was added dropwise, keeping the temperature between 15°C and 25°C and the

reaction was allowed to stir for 3 hours. The solution was poured into water (10 mL) and extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (Et_2O in petrol, 0-10%) to give epoxy-ketone **260** as a colourless oil (0.740g, 67% yield)

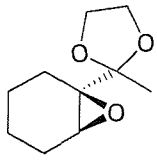
Rf= 0.49 (15% EtOAc in petrol)

δ_H (300 MHz, $CDCl_3$): 3.22 (1H, d, *J* 3 Hz, CHOC), 2.50 (1H, app. dt, *J* 6, 15 Hz cyclic CH_AH_BCCO), 2.09-1.98 (4H, m, cyclic CH_AH_BCCO and CH_3), 1.83 (1H, m, cyclic CH_AH_B), 1.65 (1H, m, cyclic CH_AH_B), 1.47-1.23 (4H, m, cyclic $(CH_2)_2$)

δ_C (75 MHz, $CDCl_3$): 208.67, 63.22, 57.15 (1), 24.49 (2), 23.47 (3), 22.26 (2), 19.52 (2), 19.00 (2).

All data agreed with those reported by Reed[118].

(±)-(1aS, 5aS)-1a-(2-Methyl-1,3-dioxolan-2-yl)perhydro-1-benzoxirene 261:



1-perhydro-1-benzoxiren-1-ylethan-1-one **260** (1.6 g, 11.41 mmol), *p*-toluene sulfonic acid (217 mg, 1.14 mmol) and ethylene glycol (5 mL) were refluxed in toluene (30 mL) for 20 hours, using a Dean-Stark apparatus. The reaction mixture was concentrated *in vacuo*. Diethyl ether (30 mL) was added, the solution was washed with aq. $NaHCO_3$ (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (Ether in petrol 0-25%) to give ketal **261** as a colourless oil (1.10 g, 52% yield).

R_f= 0.37 (20% EtOAc in petrol).

δ_H (300 MHz, $CDCl_3$): 3.98-3.87 (4H, m, OCH_2CH_2O), 3.19 (1H, d, *J* 2 Hz, CHOC), 2.02-1.70 (4H, m, cyclic $(CH_2)_2$), 1.52-1.09 (5H, m, cyclic CH_2 and CH_3), 0.84 (2H, m, cyclic CH_2)

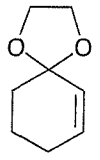
δ_C (75 MHz, $CDCl_3$): 108.61, 65.98 (2), 65.56 (2), 62.56, 55.19 (1), 24.58 (2), 24.33 (2), 21.79 (2), 20.37 (2), 19.50 (3).

ν_{max}: 2988, 2936, 2891, 1446, 1437, 1374, 1182, 1146, 1112, 1040, 950, 873.

m/z(CI): 185 ($[M+H]^+$, 48), 167 ($[M+H-H_2O]^+$, 12), 87 (100).

HRMS (CI): requires: 185.1178 ($[M+H]^+$), found: 185.1177.

1,4-Dioxaspiro[4.5]dec-6-ene 263:



Following a method by Jommi[119]

Cyclohexenone (2.5 mL, 25.8 mmol), fumaric acid (300 mg, 2.58 mmol) and ethylene glycol (15 mL, excess) were refluxed in toluene (30 mL) for 20 hours, using a Dean-Stark apparatus. The reaction mixture was concentrated *in vacuo*. Diethyl ether (30 mL) was added, the solution was washed with aq. $NaHCO_3$ (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (5% triethylamine, Et_2O in petrol, 0-25%) to give ketal **263** as a colourless oil (2.61 g, 72% yield).

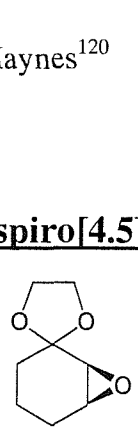
R_f= 0.80 (20% EtOAc in petrol).

δ_H (300 MHz, $CDCl_3$): 5.72 (1H, m, CC*H*=CH), 5.62 (1H, m, C=C*H*CH_2), 4.06-3.93 (4H, m, OCH_2CH_2O), 2.31-2.22 (4H, m, cyclic $(CH_2)_2$), 1.82-1.74 (2H, m, cyclic CH_2)

δ_C (75 MHz, $CDCl_3$): 126.67 (1), 124.44 (1), 107.87, 64.55 (2 ×2), 35.86 (2), 31.12 (2), 24.73 (2).

All data agreed with those reported by Haynes[120]

(±)-(6S, 7S)-6,7-Epoxy-1,4-dioxaspiro[4.5]decane 262:



Following a method by Klumpp[121]

1,4-dioxaspiro[4.5]dec-6-ene **263** (210 mg, 1.50 mmol) in DCM (5 mL) was added to a slurry of *m*-CPBA (443 mg, 1.80 mmol) in DCM (10 mL) The mixture was stirred for

18 hours. The reaction was washed with aq. sodium sulphite, aq. $NaHCO_3$ and brine. The aqueous layer was extracted with DCM (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was purified by column chromatography (Ether in petrol, 0-20%) to give epoxide **262** as a colourless oil (160 mg, 69% yield).

Rf= 0.37 (10% EtOAc in petrol)

δ_H (300 MHz, $CDCl_3$): 3.93-3.84 (4H, m, OCH_2CH_2O), 3.21-3.13 (2H, m, 2× CHOC), 2.22-2.11 (1H, m, cyclic CH_AH_B), 2.10-1.99 (3H, m, cyclic CH_AH_B and cyclic CH_2), 1.63 (1H, app. dt, *J* 6, 8 Hz, CH_AH_BC), 1.42 (1H, m, CH_AH_BC).

δ_C (75 MHz, $CDCl_3$): 106.71, 64.59 (2), 64.16 (2), 52.09 (1), 51.35 (1), 34.76 (2), 27.37 (2), 22.69 (2).

All data agreed with those reported by Klumpp.[121]

6.4) EXPERIMENTAL FOR CHAPTER THREE

Methylenecyclopropane 104:

Following a modified method by Binger.[122]

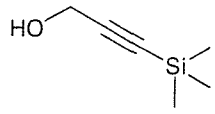
Methallyl chloride (280 ml, 2.84 mol) was added dropwise, over 9 hours to a rapidly stirred suspension of sodium amide (139 g, 3.56 mol) in dry ^{n}dibutyl ether (400 ml) at 130-140°C under a slow stream of nitrogen. In a reaction flask fitted with a cold finger (-40°C) and 3 subsequent traps, the first at room temperature, the two subsequent traps at -78°C. The reaction mixture was refluxed for a further 10 h. Acetone was removed from the cold finger and replaced with warm water (c.a. 40°C) Products were collected in the second trap as a mixture of unreacted methallyl chloride, methylcyclopropene **110**, methylenecyclopropane **104** and ammonia as a by-product. The ammonia layer was allowed to evaporate and the resulting mixture was added to a solution of ^{t}BuOH (10 g, 0.13 mol) and DMSO (25 ml), at 0°C under a flow of nitrogen, ^{t}BuOK (8 g, 0.07 mol) in DMSO (25 ml) was added over 3 h. The mixture was allowed to warm to 45 °C over 14 h under a cold finger condenser at -60 °C. The cold finger was allowed to warm to 35 °C over 6 h. The product was collected in traps at -78 °C to give **104** (60 mL, 49%)

δ_H (300 MHz, $CDCl_3$): 5.42 (2H, quintet, *J* 2 Hz, C=CH_2), 1.08 (4H, t, *J* 2 Hz, cyclopropyl $(CH_2)_2$),

δ_C (75 MHz, $CDCl_3$): 130.7, 102.9 (2), 2.5 (2 ×2).

Data agreed with that previously reported by Binger[122].

3-(1,1,1-Trimethylsilyl)prop-2-yn-1-ol 278:



Based on a method by Denmark.[123]

^{n}Butyl lithium (2.5 M in hexanes, 14 mL, 0.033 mol) was added dropwise to a stirred solution of propargyl alcohol (0.087 mL, 0.015 mol) in THF (70 mL) at -30°C under nitrogen. The solution was allowed to warm to 0°C over 10 minutes, then stirred at 0°C for 1 hour. Trimethylsilyl chloride (15 mL, 0.032 mol) was added and the mixture was allowed to warm to room temperature overnight. The reaction was quenched with hydrochloric acid (3 M, 20 mL). The aqueous layer was extracted with Et_2O (3×10 mL), washed with brine and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo.* The crude mixture was purified by column chromatography (EtOAc in petrol, 0-30%) to yield the product **278** as a colourless oil (4.57 g, 76% yield).

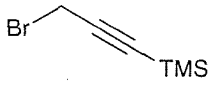
R_f= 0.46 (30% EtOAc in petrol)

δ_H (300 MHz, $CDCl_3$): 4.28 (2H, br s, CH_2OH), 1.75 (1H,br s, OH), 0.20 (9H, br s, $(CH_3)_3Si$),

δ_C (75 MHz, CDCl3): 103.7, 90.7, 51.7 (2), -0.2 (3).

Data agreed with that previously reported by Denmark.[123]

3-Bromo-1-trimethylsillyl-1-propyne 275:



1) Based on a first method by Holmes. [124]

Triphenylphosphine (1.5 g, 4.67 mmol) was added to a stirred solution of Br_2 (290 μL, 5.6 mmol) in DCM (20 mL) until the solution went cloudy. The reacting medium was kept under nitrogen and 3-trimethylsilyl-2-propyn-1-ol **278** (600 mg, 4.67 mmol in DCM, 5 mL) was added dropwise to the solution and the reaction was stirred overnight at room temperature. The reaction mixture was washed with H_2O (10 mL) and the aqueous layer was extracted with DCM (3×10 mL). The combined organic layers were concentrated *in*

vacuo and the crude reaction mixture purified by column chromatography (Et_2O in petrol, 0-30%). To give bromide **275** as a colourless oil (0.243g, 21%)

2) Based on a method by Hooz.[125]

Triphenylphosphine was added to a solution of alcohol **278** (1.00 g, 15.38 mmol.) and carbon tetrabromide (5.1 g, 15.4mmol) in Et_2O (20 mL). An exothermic reaction took place and the initially cloudy solution went yellowish. The reaction was allowed to stir for 3 hours. The solution was then filtered and the solid washed with Et_2O (50 mL). The crude reaction mixture was purified by column chromatography (Et_2O in petrol, 0-10%) to give bromide **275** as a colourless oil (0.323g, 22%)

3) Based on a second method by Holmes.[124]

Alcohol **278** (1.5g, 12 mmol) was dissolved in pyridine (0.13 mL) and dry Et_2O (25 mL). Phosphorus tribromide (0.5 mL, 12 mmol) in ether (15 mL) was added to the solution and refluxed for 3 hours. The mixture was poured onto ice and the aqueous layer extracted (3×25 mL). The combined organic layers were washed with H_2O, aq. $NaHCO_3$ and aq. NH_4Cl solution, dried over $MgSO_4$ and concentrated *in vacuo*. the crude reaction mixture was purified by column chromatography (Et_2O in petrol, 0-10%) to give bromide **275** as a colourless oil (0.652g, 28%)

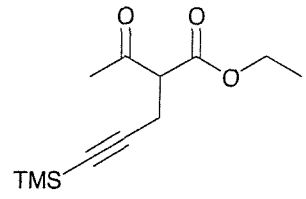
R_f= 0.89 (20% EtOAc in petrol)

δ_H (300 MHz, $CDCl_3$): 3.80 (2H, br s, CH_2-Br), 0.10 (9H, br s, $(CH_3)_3Si$),

δ_C (75 MHz, CDCl3): 100.1, 92.4, 14.8(2), -0.2 (3 ×3).

Data agreed with that previously reported by Holmes.[124]

(±)-2-Acetyl-5- trimethylsilyl-4-pentynoate 279:



Ethyl acetoacetate (0.68 g, 5 mmol) was added to suspension of NaH (60% in oil 209 mg, 5 mmol) in THF (10 mL) at 0°C under nitrogen. The solution was allowed to stir for 10 min. 3-Bromo-1-trimethylsillyl-1-propyne **275** (1.0 g, 5 mmol) was added and the reaction was left to warm to room temperature over 4 hours. The reaction mixture was quenched with NH_4Cl (sat.) and the aqueous layer extracted with Et_2O (3×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography (Et_2O in petrol, 0-50%), to give keto-ester **279** as a colourless oil (0.380 g, 30% yield)

R_f= 0.7 (20% EtOAC in petrol)

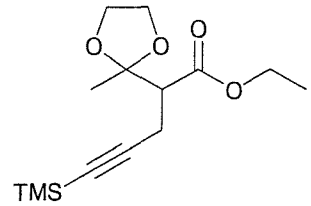
δ_H (300 MHz, $CDCl_3$): 4.22 (2H, q, *J* 7 Hz, OCH_2), 3.68 (1H, t, *J* 8 Hz, COCHCO), 2.73 (2H, d, *J* 8Hz $COCH_2C{\equiv}C$), 2.17 (3H, s, CH_3CO), 1.28 (3H, t, OCH_2CH_3, *J* 7 Hz), 0.15 (9H, br s, $(CH_3)_3Si$).

δ_C (75 MHz, CDCl3): 201.44, 168.27, 102.78, 87.01, 61.78 (2), 58.44 (1), 29.79 (3), 18.97 (2), 14.18 (3), -0.01 (3 ×3).

ν_{max}: 2961, 2179, 1742, 1719, 1249, 1031, 839, 759.

Data agreed with those reported by Shostakovskii.[126]

(±)-Ethyl-2-(2-methyl-1,3-dioxolan-2-yl)-5-trimethylsilyl-4-pentynoate 280:



Ethyl-2-acetyl-5-trimethylsilyl-4-pentynoate **279** (0.46 g, 1.9 mmol), *p*-toluene sulfonic acid (3.8 mg, 0.02 mmol) and ethylene glycol (260 mg, 4.18 mmol) were refluxed

in toluene (10 mL) overnight, using a Dean-Spark apparatus. The reaction mixture was concentrated *in vacuo*. Et_2O (50 mL) was added, the solution was washed with aq. $NaHCO_3$ (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (EtOAc in petrol 0-20%) giving ketal **280** as a colourless oil (0.332 g, 61% yield).

R_f= 0.35 (20% EtOAc in petrol).

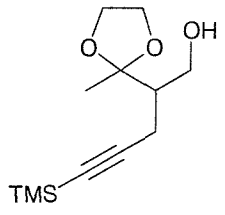
δ_H (300 MHz, $CDCl_3$): 4.20 (2H, m, OCH_2), 4.02-3.83 (4H, m, OCH_2CH_2O), 2.80 (1H, dd, *J* 11, 4 Hz, $CCHCH_2$), 2.58 (1H, dd, *J* 11, 17 Hz, $CH_AH_BC{\equiv}C$), 2.30 (1H, dd, *J* 17, 4 Hz $CH_AH_BC{\equiv}C$), 2.05 (3H, s, CH_3CO), 1.2 (3H,t , *J* 7 Hz, OCH_2CH_3) 0.05 (9H, s, $(CH_3)_3Si$).

δ_C (75 MHz, CDCl3): 171.39, 108.87, 104.09, 86.03, 65.14 (2), 65.01 (2), 60.89 (2), 53.80 (1), 21.88 (3), 19.18 (2), 14.47 (3), 0.13 (3 ×3).

ν_{max}: 2962, 2889, 2179, 1736, 1723, 1371, 1250, 1045, 843.

m/z(CI): 285 ($[M+H]^+$, 10), 87 (100).

(±)-Ethyl-2-(2-methyl-1,3-Dioxolan-2-yl)-5-trimethylsilyl-4-pentyn-1-ol 281:



Based on a method by Albizati.[98]

Ketone protected ester **280** (400 mg, 1.41 mmol) was added slowly to a stirred suspension of $LiAlH_4$ (161 mg, 4.23 mmol) in THF (10 mL) at 0°C under nitrogen. The solution was allowed to stir and reach room temperature over 2 hours. The reaction was quenched after 3 hours by adding 4M NaOH dropwise until the residual solid had turned completely white. The mixture was then filtered and washed thoroughly with ether (250 mL). The combined organic layers were concentrated *in vacuo*. The crude compound was purified by column chromatography (EtOAc in petrol, 0-40%) to give alcohol **281** as a colourless oil (170 mg, 50% yield).

R_f= 0.29 (20% EtOAc in petrol).

δ_H (300 MHz, $CDCl_3$): 4.04-3.90 (4H, m, OCH_2CH_2O), 3.89 (1H, dd, *J* 4, 11 Hz, CH_AH_BOH), 3.80 (1H, dd, *J* 7, 11 Hz, CH_AH_BOH), 2.78 (1H, br s, OH),2.53 (1H, dd, *J* 17, 10 Hz, $CH_AH_BC{\equiv}C$), 2.22 (1H, dd, *J* 17, 4 Hz, $CH_AH_BC{\equiv}C$), 2.07 (1H, m, $CHCH_2OH$), 1.15 (3H, s, CH_3), 0.05 (9H, s, $(CH_3)_3Si$).

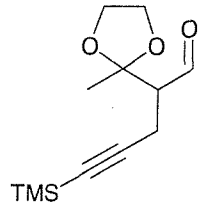
δ_C (75 MHz, $CDCl_3$): 111.43, 105.17, 86.03, 64.54 (2 ×2), 62.49 (2), 47.32 (1), 21.00 (3), 17.93 (2), 0.00 (3 ×3).

ν_{max}: 3428, 2958, 2889, 2174, 1380, 1248, 1044, 838, 759.

m/z(CI): 243 ($[M+H]^+$, 27), 181 (16), 87 (100).

HRMS (EI): requires 242.9728 ($M^{+\bullet}$) found: 242.9756.

(±)-2-(2-Methyl-1,3-dioxolan-2-yl)-5-(1,1,1-trimethylsilyl)pent-4-ynal 272:



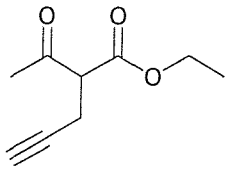
Based on a method by Swern.[99]

Oxalyl chloride (0.57 g, 4.45 mmol) in DCM (20 mL) was cooled to -78°C and stirred. DMSO (0.58 g, 9.28 mmol) in DCM (5 mL) was added dropwise keeping the temperature between -50°C and -60°C. The reaction mixture was stirred for 2 minutes. Alcohol **281** (900 mg, 3.71 mmol) was added dropwise over 5 minutes at -78°C and stirred for 15 minutes. Triethylamine (1.88 g, 18.58 mmol) was added and the reaction was allowed to reach room temperature over 2 hours. The reaction was quenched with water. The aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude compound was purified by column chromatography (EtOAc in petrol, 0-10%) to give aldehyde **272** as a colourless oil (632 mg, 71% yield).

R_f= 0.39 (10% EtOAc in petrol).

δ_H (300 MHz, $CDCl_3$): 9.74 (1H, d, *J* 2 Hz, CHO), 4.05-3.93 (4H, m, OCH_2CH_2O), 2.85 (1H, ddd, *J* 2, 5, 9 Hz, $CHCHO$), 2.72 (1H, dd, *J* 9, 17 Hz, $CH_AH_BC{\equiv}C$), 2.52 (1H, dd, *J* 5, 17 Hz, $CH_AH_BC{\equiv}C$), 1.30 (3H, s, CH_3CO), 0.10 (9H, s, $(CH_3)_3Si$).

(±)-Ethyl-2-acetyl-4-pentynoate 283:



Based on a method published by Chadha.[127]

Ethyl acetoacetate (3.20 mL, 0.025 mol) was added to a stirred solution of NaH (60% in oil, 0.800 g, 0.020 mol) in THF (30 mL) at 0°C under nitrogen and stirred for 30 minutes. Propargyl bromide (2.25 mL, 0.020 mol) was added dropwise at 0 °C, the solution was stirred and allowed to warm to room temperature overnight. The reaction was quenched with NH_4Cl (aq) and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (EtOAc in petrol, 0-10%) to give keto-ester **283** as a colourless oil (3.32 g, 79% yield).

R_f= 0.75 (30% EtOAc in petrol).

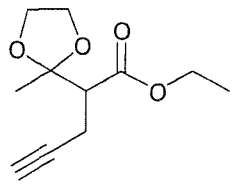
δ_H (300 MHz, $CDCl_3$): 4.19 (2H, q, *J* 7 Hz, OCH_2CH_3), 2.93 (1H, t, *J* 8 Hz, COCHCO), 2.77-2.69 (2H, m, $CH_2C{\equiv}CH$), 2.28 (3H, s, CH_3CO), 2.02 (1H, t, *J* 3 Hz, C≡CH), 1.38 (3H, t, *J* 7 Hz, OCH_2CH_3).

δ_C (75 MHz, $CDCl_3$): 201.21, 168.17, 80.49 (1), 69.86, 61.94 (2), 58.30 (1), 29.68 (3), 17.47 (2), 14.12 (3).

ν_{max}: 3278, 2985, 2033, 1739, 1716, 1362, 1227, 1149, 1037, 1018, 855.

Data agreed with those reported by Reynolds.[128]

(±)-Ethyl-2-(2-methyl-1,3-dioxolan-2-yl) acetyl-4-pentynoate 284:



Ethyl-2-acetyl-4-pentynoate **283** (1.0 g, 5.95 mmol), *p*-toluene sulfonic acid (33 mg, 0.18 mmol) and ethylene glycol (0.923 g, 14.9 mmol) were refluxed in toluene (30 mL) overnight, using a Dean-Stark apparatus. The reaction mixture was concentrated *in vacuo*.

Et_2O (30 mL) was added, the solution was washed with aq. $NaHCO_3$ (30 mL), the aqueous layer was extracted (Et_2O, 3×30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (EtOAc in petrol, 0-20%) to give ketal **284** as a colourless oil (15.59 g, 94% yield).

R_f= 0.34 (20% EtOAc in petrol).

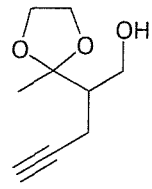
δ_H (300 MHz, $CDCl_3$): 4.22 (2H, q, *J* 7 Hz, OCH_2CH_3), 4.05-3.90, (4H, m, OCH_2CH_2O), 2.92 (1H, dd, *J* 3, 11 Hz, $CHCH_2C{\equiv}C$), 2.68 (1H, ddd, *J* 3, 11, 17 Hz, $CH_ACH_BC{\equiv}C$), 2.48 (1H, dt, *J* 17, 3 Hz, $CH_AH_BC{\equiv}C$), 1.95 (1H, t, *J* 3 Hz, C≡CH), 1.38 (3H, s, CH_3CO), 1.29 (3H, t, *J* 7 Hz, OCH_2CH_3).

δ_C (75 MHz, $CDCl_3$): 171.30, 108.80, 81.62, 69.61(1), 65.13 (2), 65.00 (2), 61.03 (2), 53.66 (1), 21.94 (3), 17.66 (2), 14.39 (3).

ν_{max}: 2982, 2960, 2896, 2177, 1733, 1372, 1248, 1044, 838.

m/z(CI): 213 ($[M+H]^+$, 23), 181 (16), 87 (100).

(±)-2-(2-Methyl-1,3-dioxolan-2-yl)acetyl-4-pentyn-1-ol 282:



Based on a method published by Albizati.[98]

Ester **284** (1.05 g, 4.95 mmol) was slowly added to a stirred suspension of $LiAlH_4$ (563 mg, 14.85 mmol) in THF (30 mL) at 0°C under nitrogen. The reaction mixture was allowed to stir and reach room temperature over 2 hours. The reaction was quenched after 2.5 hours by carefully adding 4M NaOH until the residual solid had turned completely white. The mixture was then filtered and washed thoroughly with ether (200 mL) and concentrated *in vacuo* to give alcohol **282** as a colourless oil (0.735 g, 96% yield) which was used without further purification.

R_f= 0.23 (10% EtOAc in petrol).

δ_H (300 MHz, $CDCl_3$): 4.00-3.90 (4H, m, OCH_2CH_2O), 3.92-3.73 (2H, m, CH_2OH), 2.75 (1H, br s, OH), 2.47 (1H, app. dt, *J* 3, 16 Hz, $CH_AH_BC{\equiv}CH$), 2.21, (1H, ddd, *J* 2, 10, 16 Hz, $CHCH_2OH$), 2.04 (1H, m, $CH_AH_BC{\equiv}CH$), 1.98 (1H, t, *J* 3 Hz, C≡CH), 1.28 (3H, s, CH_3).

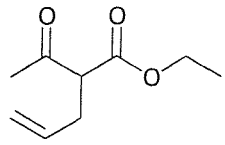
δ_C (75 MHz, $CDCl_3$): 111.52, 82.73, 69.64 (1), 64.72 (2 ×2), 62.20 (2), 47.40 (1), 21.33 (3), 16.46 (2).

ν_{max}: 3451, 3289, 2984, 2941, 2886, 2173, 2115, 1379, 1211, 1151, 1039, 948, 864.

m/z(CI): 171 ($[M+H]^+$, 11), 87 (100).

HRMS (EI): requires 170.0943 ($M^{+\bullet}$), found 171.1015.

(±)-Ethyl-2-acetyl-4-pentenoate 283:



Based on a method published by Chadha.[127]

Ethyl acetoacetate (13.02 g, 0.10 mmol) was added to a stirred solution of NaH (60% in oil, 4.0g, 0.10 mmol) in THF (200 mL) at -30°C under nitrogen and stirred for 30 minutes. Allyl Bromide (12.1g, 0.10 mmol) was then added dropwise at -30°C. The solution was stirred and allowed to warm to room temperature overnight. The reaction was quenched with NH_4Cl (aq) and the aqueous layer was extracted (Et_2O, 3 × 60 mL) .The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (EtOAc in petrol, 0-20%) to give keto-ester **283** as a colourless oil (13.22 g 77% yield).

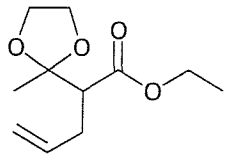
R_f= 0.54 (20% EtOAc in petrol).

δ_H (300 MHz, $CDCl_3$): 5.73 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.12-5.00 (1H, m, CH=CH_AH_B), 4.17 (2H, q, *J* 7 Hz, OC$H_2$$CH_3$), 3.52 (1H, t, *J* 7 Hz, COCHCO), 2.57 (2H, t, *J* 7 Hz, CH_2C=C), 2.18 (3H, s, CH_3CO), 1.25 (3H, t, *J* 7 Hz, OCH_2CH_3).

δ_C (75 MHz, $CDCl_3$): 202.62, 169.36, 134.34 (1), 117.58 (2), 61.56 (2), 59.35 (1), 32.29 (2), 29.25 (3), 14.23 (3).

Data agreed with those reported by Chadha.[127]

(±)-Ethyl-2-(2-methyl-1,3-Dioxolan-2-yl)acetyl-4-pentenoate 288:



Ethyl-2-acetyl-4-pentenoate **283** (13.2g, 77.5 mmol), *p*-toluene sulfonic acid (150mg, 0.78 mmol) and ethylene glycol (10.58g, 170.5 mmol) were refluxed in toluene (125 mL) overnight, using a Dean-Spark apparatus. The reaction mixture was concentrated *in vacuo*. Diethyl ether (100 mL) was added, the solution was washed with aq. $NaHCO_3$ (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (EtOAc in petrol 0-10%) to give ketal **288** as a colourless oil (15.59 g, 94% yield).

R_f= 0.44 (20% EtOAc in petrol).

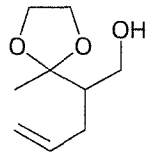
δ_H (300 MHz, $CDCl_3$): 5.81-5.65 (1H, m, $CH=CH_2$,), 5.07 (1H, dd, *J* 1, 17 Hz, $CH=CH_AH_B$), 4.98 (1H, dd, *J* 1, 10 Hz, $C=CH_AH_B$), 4.11 (2H, q, *J* 7 Hz, OCH_2CH_3), 4.02-3.94 (4H, m, OCH_2CH_2O), 2.75 (1H, dd, *J* 4, 11 Hz, COCHCO), 2.45-2.31 (2H, m, $CH_2C=C$), 1.45 (3H, s, CH_3CO), 1.26 (3H, t, *J* 7 Hz, OCH_2CH_3).

δ_C (75 MHz, CDCl3): 172.19, 135.49 (1), 116.70 (2), 109.54, 65.00 (2), 64.93 (2), 60.61 (2), 54.01 (1), 32.54 (2), 21.80 (3), 14.42 (3).

ν_{max}: 2982, 2889, 1731, 1373, 1186, 1037, 877.

Data agreed with those reported by Chadha.[127]

(±)-2-(2-methyl-1,3-dioxolan-2-yl)acetyl-4-penten-1-ol 289:



Based on a method published by Albizati.[98]

Ester **288** (1.0 g, 4.66 mmol) was slowly added to a stirred suspension of $LiAlH_4$ (531 mg, 14 mmol) in THF (40 mL) at 0°C under nitrogen. The solution was allowed to stir and reach room temperature over 2 hours. The reaction was quenched after 3 hours by

adding 4M NaOH dropwise until the residual solid had turned completely white. The adding 4M NaOH until the residue had turned white. The mixture was then filtered and washed thoroughly with ether (100 mL) and concentrated *in vacuo*. The crude compound did not need any purification, giving alcohol **289** as a colourless oil (747 mg, 93% yield).

R_f= 0.39 (30% EtOAc in petrol).

δ_H (300 MHz, $CDCl_3$): 5.87-5.72 (1H, m, CH=CH_2,), 5.09-4.99 (2H, m, CH=CH_2), 4.08-3.96 (4H, m, OCH_2CH_2O), 3.69 (1H, dd, *J* 3, 12 Hz, CH_AH_BOH), 3.63 (1H, dd, *J* 7, 12 Hz, CH_AH_BOH), 2.83, (1H, br s, OH), 2.34 (1H, dt, *J* 2, 6 Hz, CH_AH_BCH=CH_2), 2.32 (1H, dt, *J* 2, 6 Hz, CH_AH_BCH=CH_2), 1.90 (1H, m, $CHCH_2OH$) 1.37 (3H, s, CH_3CO).

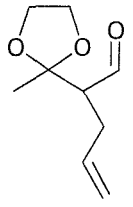
δ_C (75 MHz, CDCl3): 137.43 (1), 116.97 (2), 113.08, 65.19 (2), 65.00 (2), 62.88 (2), 48.29 (1), 32.19 (2), 21.47 (3).

ν_{max}: 3457, 3078, 2981, 2887, 1379, 1210, 1156, 1036, 948, 912, 863.

m/z(CI): 190 ($[M+NH_4]^+$, 4), 173 ($[M+H]^+$, 71), 143 ($[M+H-H_2O]^+$, 100)

HRMS (CI): requires 173.1178 ($[M+H]^+$), found 173.1182.

(±)-2-(2-Methyl-1,3-dioxolan-2-yl) acetyl-4-pentenal 284:



Based on a method by Swern.[99]

Oxalyl chloride (5.75 mL, 66 mmol) in DCM (200 mL) was cooled to -78°C and stirred in a flask fitted with a drying tube. DMSO (9.8 mL, 0.138 mol) in DCM (20 mL) was added dropwise keeping the temperature between -50 and -60°C. The reaction mixture was stirred for 2 minutes. Alcohol **289** (9.47 g, 55 mmol) was added dropwise over 5 minutes at -78°C and stirred for 15 minutes. Triethylamine (38 mL, 0.275 mol) was added and the reaction was allowed to reach room temperature over 2 hours. The reaction was quenched with water (75 mL). The aqueous layer was extracted with DCM (3 × 70 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude compound was purified by column chromatography (Et_2O in petrol, 0-10%) to give aldehyde **284** as a colourless oil (8.73 g, 93% yield).

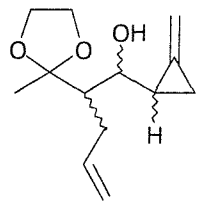
R_f= 0.64 (20% EtOAc in petrol).

δ_H (300 MHz, $CDCl_3$): 9.70 (1H, d, *J* 3 Hz, CHO), 5.75 (1H, ddt, *J* 17, 10, 7 Hz, *CH*=CH_2), 5.11-4.98 (2H, m, CH=*CH*$_2$), 4.05-3.97 (4H, m, OCH_2CH_2O), 2.68 (1H, dt, *J* 10, 3 Hz, *CH*CHO), 2.55 (1H, m, $CH_AH_BCH{=}CH_2$), 2.48 (1H, m, $CH_AH_BCH{=}CH_2$), 1.35 (3H, s, CH_3CO).

δ_C (75 MHz, $CDCl_3$): 202.81 (1), 135.54 (1), 116.80 (2), 109.56, 65.02 (2), 64.88 (2), 59.85 (1), 29.28 (3), 22.94 (2).

ν_{max} (cm^{-1}): 2984, 2889, 1723, 1381, 1210, 1157, 1040, 948, 916, 872.

(±)-2-(2-Methyl-1,3-dioxolan-2-yl)-1-(2-methylenecyclopropane)-4-penten -1-ol 290 and 291:



^{n}BuLi (2.53M in hexanes, 2.35 mL, 8.9 mmol) was added to a stirred solution of methylenecyclopropane (0.55 mL, 8.1 mmol) in THF (20 mL) at -78°C under argon. The solution was warmed to 0°C over 1 hour and stirred for 30 minutes. It was then allowed to reach room temperature over 30 minutes and stirred for 15 minutes. The reaction mixture was then cooled to -78°C. aldehyde **284** (0.400 g, 5.4 mmol), cooled to -78°C was added to the mixture and the solution was allowed to reach room temperature overnight. The reaction was quenched with aq. NH_4Cl (50 mL). The aqueous layer was extracted with ether (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude compound was purified by column chromatography (EtOAc in petrol, 0-40%) to give the alcohol as one major diastereoisomers **290** (448 mg, 37% yield) contaminated with a minor diastereoisomer (ratio 10:1) and a second major diastereoisomer**291** (170 mg, 14% yield) also contaminated with a minor diastereoisomer (ratio 13:1).

Data for the major isomer of **290**:

R_f= 0.70 (35% EtOAc in petrol).

δ_H (300 MHz, $CDCl_3$): 5.95 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.57 (1H, s, C=CH_AH_B), 5.44 (1H, s with fine splitting, C=CH_AH_B), 5.07 (1H, dd, *J* 1, 17 Hz, CH=CH_AH_B), 4.96 (1H, dd, *J* 1, 10 Hz, CH=CH_AH_B), 4.09-3.88 (4H, m, OCH_2CH_2O), 3.52 (1H, d with fine splitting, *J* 7 Hz, C*H*OH), 2.78 (1H, d, *J* 3 Hz, OH), 2.53 (1H, dt, *J* 1, 10 Hz, CH_AH_BC=C), 2.47 (1H, dt, *J* 1, 7 Hz, CH_AH_BCH=CH_2), 2.02 (1H, m, C*H*CH_2CH=CH_2), 1.30 (3H, s, CH_3), 1.22 (1H, m, cyclopropyl CH), 0.8 (2H, m, cyclopropyl CH_2).

δ_C (75 MHz, $CDCl_3$): 139.54 (1), 134.47, 114.96 (2), 112.54, 103.83 (2), 74.21 (1), 64.70 (2), 64.26 (2), 50.56 (1), 29.16 (2), 22.45 (3), 19.97 (1), 7.44 (2).

ν_{max}: 3516, 3069, 2984, 2881, 2672, 2337, 1372, 1203, 1039, 951, 906.

m/z(CI): 143 ([M-C_4H_5CHO+H]$^+$, 16), 87 (100).

Data for the major isomer of **291**:

R_f= 0.56 (35% EtOAc in petrol).

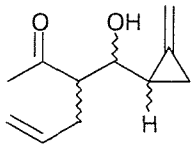
δ_H (300 MHz, $CDCl_3$): 5.96 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.43 (2H, br s, C=CH_2), 5.06 (1H, d, *J* 17 Hz, CH=CH_AH_B), 4.98 (1H, d, *J* 10 Hz, CH=CH_AH_B), 4.08-3.97 (4H, m, OCH_2CH_2O), 3.43 (1H, d with fine splitting, *J* 7 Hz, C*H*OH), 3.03 (1H, br s, OH), 2.50 (1H, dt, *J* 1, 10 Hz, CH_AH_BCH=CH_2), 2.33 (1H, m, CH_AH_BCH=CH_2), 1.96 (1H, m, C*H*CH_2), 1.48-1.39 (2H, m, cyclopropyl CH_2),1.35 (3H, s, CH_3), 1.10 (H, m, cyclopropyl CH).

δ_C (75 MHz, $CDCl_3$): 139.56 (1), 133.15, 114.95 (2), 112.46, 104.06 (2), 74.41 (1), 64.73 (2), 64.16 (2), 51.29 (1), 28.70 (2), 22.57 (3), 20.35 (1), 9.57 (2).

ν_{max}: 3514, 3071, 2978, 2886, 2668, 2333, 1371, 1206, 1034, 949, 908.

m/z(CI): 143 ([M-C_4H_5CHO+H]$^+$, 16), 87 (100).

(±)-3[Hydroxy-2-(methylenecyclopropane) methyl] 5 hexen-2-one 292 and 293:



Ketal **290** (300 mg, 1.34 mmol) and *p*-toluene sulfonic acid (catalytic amount) were stirred in a solution of 10% water in acetone (30 mL) for 48 hours. The reaction mixture

was concentrated *in vacuo*. Et_2O (20 mL) was added, the solution was washed with aq. $NaHCO_3$ (30 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (EtOAc in petrol, 0-20%) to give ketone **292** as a colourless oil (196 mg, overall 82% yield) as a ratio of diastereoisomer (10:1).

R_f= 0.54 (20% EtOAc in petrol).

Data for the major diastereoisomer:

δ_H (300 MHz, $CDCl_3$): 5.78 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.54 (1H, d, *J* 2 Hz, C=C$H_A$$H_B$), 5.47 (1H, d, *J* 2 Hz, C=C$H_A$$H_B$), 5.07-4.86 (2H, m, CH=CH_2), 3.40 (1H, t, *J* 7 Hz, C*H*OH), 2.88, (1H, m, COCH) 2.52-2.39 (1H, m, C$H_A$$H_B$CH=$CH_2$), 2.33-2.19 (1H, m, C$H_A$$H_B$CH=$CH_2$), 2.02 (3H, s, CH_3), 1.72 (1H, m, cyclopropyl CH), 1.32 (1H, m, cyclopropyl C$H_A$$H_B$), 0.97 (1H, m, cyclopropyl C$H_A$$H_B$).

δ_C (75 MHz, $CDCl_3$): 211.62, 135.80 (1), 132.54, 117.16 (2), 104.87 (2), 74.45 (1), 57.82 (1), 32.20 (2), 32.16 (3), 19.50 (1), 8.34 (2).

ν_{max}: 3432, 3075, 2980, 2916, 2363, 1703, 1418, 1357, 1039, 899, 749.

m/z (CI): 198 ($[M+NH_4]^+$, 24), 163 ($[M+H-H_2O]^+$, 78), 35 (100).

HRMS (EI): requires 180.1150($M^{+\bullet}$), found 180.1146.

Ketal **291** (200 mg, 0.9 mmol) and *p*-toluene sulfonic acid (catalytic amount) were stirred in a solution of 10% water in acetone (50 mL) for 18 hours. The reaction mixture was concentrated *in vacuo*. Et_2O (20 mL) was added, the solution was washed with aq. $NaHCO_3$ (30 mL). The aqueous layer was extracted with Et_2O (3×30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (EtOAc in petrol, 10%) to give ketone **293** as a colourless oil (138 mg, overall 85% yield) as a ratio of diastereoisomer (10:1).

R_f= 0.69 (35% EtOAc in petrol).

Data for the major diastereoisomer:

δ_H (300 MHz, $CDCl_3$): 5.81 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.43 (2H, dd, *J* 2, 17 Hz, C=CH_2), 5.11-4.98 (2H, m, CH=CH_2), 3.35 (1H, dd, *J* 5, 8 Hz, C*H*OH), 2.87, (1H, m, C*H*CH_2CH=CH_2) 2.54-2.38 (2H, m, CH_2CH=CH_2), 2.22 (3H, s, CH_3), 1.71 (1H, m, cyclopropyl CH), 1.34 (1H, m, cyclopropyl C$H_A$$H_B$), 0.97 (1H, m, cyclopropyl C$H_A$$H_B$).

δ_C (75 MHz, $CDCl_3$): 211.91, 135.99 (1), 132.06, 117.12 (2), 105.08 (2), 74.27 (1), 57.51 (1), 31.90 (2), 31.69 (3), 19.99 (1), 8.30 (2).

ν_{max}: 3432, 3075, 2980, 2916, 2363, 1703, 1641, 1418, 1357, 1039, 899, 749.

m/z (CI): 198 ($[M+NH_4]^+$, 24), 163 ($[M+H-H_2O]^+$, 78), 35 (100).

$C_{11}H_{16}O_2$, calculated: C, 73.30; H, 8.95; O, 17.75; found C, 72.93; H, 9.06; O, 18.01.

General Method For The Synthesis Of Samarium Diiodide Solution

Following a modified version of methods by Molander[129] and Curran[130].

Excess I_2 was removed from ICH_2CH_2I by extraction with DCM and $Na_2S_2O_3$. The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. THF (10 mL) was added to Samarium metal (2.5 equivalent relative to the ketone) in a previously thoroughly dried flask and stirred at room temperature under a flow of argon, then diiodoethane (4 eq.) was added. When blue, the solution was allowed to stir for 2 hours.

Using HMPA:

HMPA (10 eq.) was added and the solution turned purple.

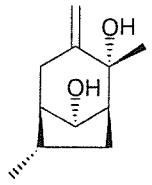
Using methanol:

Methanol (2 mL) was added and the solution turned deep dark green.

Normal addition proceeds by adding the precursor (and ^{t}BuOH -2 eq.- if required) in THF *via* syringe pump over 90 min if using HMPA or 30 min if using MeOH.

Reverse addition consists of adding the solution of SmI_2 in THF at the appropriate temperature to a solution of the ketone (and ^{t}BuOH if required) in THF *via* cannula.

(±)-(1*S*,2*R*,5*R*,6*S*,8*R*)-2,6-Dimethyl-3-methylidenebicyclo[3.2.1]octane-2,8-diol 305:



The solution was cooled to the appropriate temperature and **292** or **293** (100 mg, 0.55 mmol) and ^{t}BuOH (81 mg, 1.1 mmol) in THF (10 mL) were added *via* normal

addition. The reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched with aq. citric acid (1 g in 20 mL H_2O) and extracted with a 1:1 ratio solution of ethyl acetate and hexane (3 × 25 mL). The combined organic layers were washed with brine then water, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (EtOAc in petrol, 0-20%) to give bicycle **305** as a yellowish crystalline solid.

Data for the major isomer formed:

m.p.= 43-45°C

R_f= 0.22 (20% EtOAc in petrol).

δ_H (300 MHz, $CDCl_3$): 4.92 (1H, s with fine splitting, C=CH_AH$_B$), 4.80 (1H, s with fine splitting, C=CH$_A$$H_B$), 4.15, (1H, t, *J* 6 Hz, C*H*OH), 2.94 (1H, dd with fine splitting, *J* 14, 2 Hz, CH_AH$_B$C=CH$_2$), 2.03 (1H, dt, *J* 1, 6 Hz, C*H*COH), 1.91 (1H, dd, *J* 4, 14 Hz, CH$_A$$H_B$C=CH$_2$), 1.73 (1H, m, C*H*CHCH$_3$), 1.69 (1H, m, C*H*CH$_3$), 1.40 (1H, dd, *J* 10, 14 Hz, CH_AH$_B$CHCH$_3$), 1.27 (3H, s, CH_3COH), (1H, ddd, *J* 5, 7, 14 Hz, CH$_A$$H_B$CHCH$_3$), 0.90 (1H, d, *J* 7 Hz, CH_3CH).

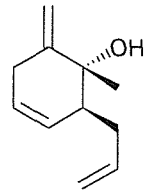
δ_C (75 MHz, $CDCl_3$): 149.31, 110.88 (2), 77.22, 75.04 (1), 48.66 (1), 45.91 (1), 33.54 (2), 32.34(2), 31.50(1), 25.55 (3), 22.98(3).

ν_{max}: 3269, 2924, 2868, 1438, 1369, 1119, 1088, 958, 898.

m/z(EI): 164 ([M-H_2O]$^{+\bullet}$, 33), 121 (38), 107 (64), 81 (100).

HRMS (EI): requires 182.1307 ($M^{+\bullet}$), found 182.1303.

(±)-(1*R*,2*S*)-2-Allyl-1-methyl-6-methylidenecyclohex-3-en-1-ol 306:



R_f= 0.44 (20% EtOAc in petrol).

δ_H (300 MHz, $CDCl_3$): 5.83 (1H, m, C*H*=CH$_2$), 5.64 (1H, m, CH$_2$C*H*=CH), 5.53 (1H, m, CH$_2$CH=C*H*), 5.14-4.81 (4H, m, CH=CH_2 and C=CH_2), 2.94 (1H, br. s, OH), 2.52 (1H, m, CH_AH$_B$CH=C), 2.25 (1H, m, CH$_A$$H_B$CH=C), 2.18-1.87 (2H, m, CH$_2$=CCH_2), 1.84 (1H, m, CH$_3$CC*H*), 1.26 (3H, s, CH$_3$).

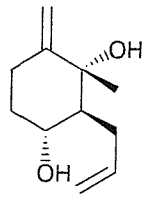
δ_C (75 MHz, $CDCl_3$): 148.91 , 137.87 (1), 129.99 (1), 124.86 (1), 116.07 (2), 106.74 (2), 74.66, 47.99 (1), 36.00 (2), 34.12 (2), 27.21 (3).

ν_{max}: 3461, 3075, 3027, 2954, 2922, 2853, 1459, 1083, 893.

m/z(EI): 182 ($[M+NH_4]^{+\bullet}$, 10), 164 ($M^{+\bullet}$, 10), 146 ($[M-H_2O]^{+\bullet}$, 60), 91 (100).

HRMS (EI): requires 164.1201 ($M^{+\bullet}$), found 164.1200.

(±)-(1*R*,2*S*,3*R*)-2-Allyl-1-methyl-6-methylidenecyclohexane-1,3-diol 307:



R_f= 0.92 (20% EtOAc in petrol).

δ_H (300 MHz, $CDCl_3$): 5.92 (1H, m, C*H*=CH_2), 5.29-5.02 (2H, m, CH=C*H*$_2$), 4.99-4.77 (2H, m, C=CH_2), 4.11 (1H, m, C*H*OH), 3.10 (1H br s, CHO*H*), 2.32 (1H, m, C*H*CHOH), 2.58-2.41 (2H, m, C*H*$_2$CH=CH_2), 2.16 (1H, m, C*H*$_A$H$_B$C=CH_2), 2.02 (1H, m, CH$_A$*H*$_B$C=CH_2), 1.61 (1H, m, C*H*$_A$H$_B$CHOH), 1.52 (1H, m, CH$_A$*H*$_B$CHOH), 1.40 (3H, s, CH_3).

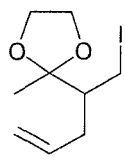
δ_C (75 MHz, $CDCl_3$): 152.89, 137.84 (1), 116.38 (2), 107.69 (2), 75.50, 74.31 (1), 49.12 (1), 34.82 (2), 30.34 (2), 26.93 (2), 22.74 (3).

ν_{max}: 3311, 3077, 2927, 1440, 1117, 902.

m/z(EI): 164 ($[M-H_2O]^{+\bullet}$, 5), 146 ($[M-2H_2O]^{+\bullet}$, 35), 91 (100).

HRMS (EI): requires 164.1201 ($[M-H_2O]^{+\bullet}$), found 164.1206.

(±)-2-(1-(Iodomethyl)but-3-enyl)-2-methyl-1,3-dioxolane 321:

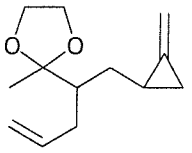


Based on a method by Allberg.[131]

Triphenylphosphine (685 mg, 2.63 mmol) and iodine (663 mg, 2.63 mmol) were added to a solution of alcohol **289** (200 mg, 1.74 mmol) in a 3:1 mixture of MeCN:Et_2O (12 mL) and the reaction was left to stir for 1 hour. The mixture was diluted with Et_2O (15 mL) and washed with aq. $Na_2S_2O_3$ (10 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The compound was too unstable to undertake NMR analysis and the crude mixture was used directly in the next step.

R_f= 0.86 (10% EtOAc in petrol).

(±)-2-Methyl-2-(1-((2-methylidenecyclopropyl)methyl)but-3-enyl)-1,3-dioxolane 322:



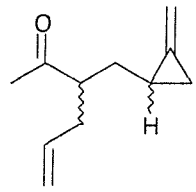
^{n}BuLi (2.40M in hexanes, 3 mL, 8.52 mmol) was added to a stirred solution of methylenecyclopropane (4.25 mL, 8.52 mmol) in THF (15 mL) at -78°C under argon. The solution was warmed to 0°C over 1 hour and stirred for 30 minutes. It was then allowed to reach room temperature over 30 minutes and stirred for 15 minutes. The reaction mixture was then cooled to -78°C. Iodide **321** (800 mg, 2.84 mmol), cooled to -78°C was added to the mixture and the solution was allowed to reach room temperature overnight. The reaction was quenched with aq. NH_4Cl (50 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude compound was purified by column chromatography (Et_2O in petrol, 0-5%) to give ketal **322** (120 mg, 20% yield) as a yellowish oil.

R_f= 0.85 (10% EtOAc in petrol).

δ_H (400 MHz, $CDCl_3$): 5.81 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.32 (1H, s, C=C$H_A$$H_B$), 5.26 (1H, s, C=C$H_A$$H_B$), 4.96 (1H, d, *J* 17 Hz, CH=C$H_A$$H_B$), 4.90 (1H, d, *J* 10 Hz, CH=C$H_A$$H_B$), 3.89-3.83 (4H, m, OCH_2CH_2O), 2.31 (1H, m, C$H_A$$H_B$CH=$CH_2$), 2.05 (1H, quintet, *J* 7Hz, C*H*CH_2CH=CH_2), 1.76 (1H, m, C$H_A$$H_B$CH=$CH_2$), 1.52- 1.41 (2H, m, CHCH_2CH), 1.29 (1H, m, cyclopropyl CH), 1.20 (3H, s, CH_3), 1.13 (1H, t, *J* 9 Hz, cyclopropyl C$H_A$$H_B$), 0.70 (1H, m, cyclopropyl C$H_A$$H_B$).

δ_C (100 MHz, $CDCl_3$): 138.66 (1), 138.05, 115.63 (2), 112.50, 102.82(2), 64.87 (2), 64.84 (2), 46.87 (1), 35.15 (2), 33.87 (2), 21.45 (3), 15.35 (1), 9.95 (2).

(±)-3-((2-Methylidenecyclopropyl)methyl)hex-5-en-2-one 323:



Ketal **322** (120 mg, 0.58 mmol) and 2M HCl (0.5 mL, 0.58 mmol) were stirred in a solution of 10% water in acetone (5 mL) for 48 hours. Et_2O (20 mL) was added, the solution was washed with aq. $NaHCO_3$ (30 mL). The aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (neat petrol) to give ketone **323** as a colourless oil contaminated with a small amount of unknown compound (20 mg, 21% yield).

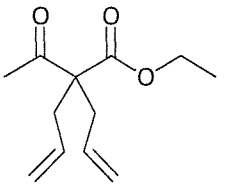
R_f= 0.87 (10% EtOAc in petrol).

δ_H (300 MHz, $CDCl_3$): 5.71 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.44-5.34 (2H, m, C=CH_2), 5.10-4.98 (2H, m, CH=C*H*$_2$), 2.18 (3H, s, CH_3), 1.83-1.61 (2H, m, C*H*$_2$CH=CH_2), 1.49-1.20 (4H, m, C*H*$CH_2CH=CH_2$, $CHCH_2CH$ and cyclopropyl CH), 1.15 (1H, m, cyclopropyl CH_AH_B), 0.77 (1H, m, cyclopropyl CH_AH_B).

δ_C (75 MHz, $CDCl_3$): 212. 27, 135.55 (1), 125.92, 117.07 (2), 103.53 (2), 52.74 (1), 35.75 (2), 34.81 (2), 22.77 (3), 13.73 (1), 9.99 (2).

m/z (CI): 165 ($[M+H]^+$, 9), 149 ($[M+H-H_2O]^+$, 17), 43 (100).

Ethyl 2-acetyl-2-allyl-4-pentenoate 287:



Based on a method published by Chadha.[127]

Ethyl acetoacetate (5 g, 0.038 mol) was added to a stirred solution of NaH (60% in oil, 1.94 g, 0.081 mol) in THF (100 mL) at 0°C under nitrogen and stirred for 30 minutes. Allyl Bromide (8.76 g, 0.081 mol) was then added dropwise at 0°C, the solution was stirred and allowed to warm to room temperature overnight. The reaction was quenched with NH_4Cl (aq) and the aqueous layer was extracted with Et_2O (3×50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (EtOAc in petrol, 0-5%) to give keto-ester **287** as a colourless oil (6.87 g, 86% yield).

R_f= 0.66 (10% EtOAc in petrol).

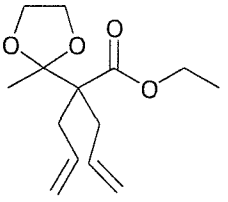
δ_H (300 MHz, $CDCl_3$): 5.88 (2H, ddt, *J* 7, 10, 17 Hz, C*H*=CH_2), 4.99-5.05 (4H, m, CH=CH_2), 4.18 (2H, q, *J* 7 Hz, OC$H_2$$CH_3$), 2.69-2.52 (4H, m, C$H_2$CH=$CH_2$), 2.09, (3H, s, CH_3CO) 1.21 (3H, t, *J* 7 Hz, OCH_2CH_3).

δ_C (75 MHz, $CDCl_3$): 204.16, 171.59, 132.30 (1 ×2), 119.31 (2 ×2), 63.34, 61.53 (2), 36.06 (2 ×2), 27.05 (3), 14.24 (3).

ν_{max}: 2982, 1739, 1711, 1441, 1357, 1278, 1207, 1139, 918, 855.

Data agreed with those reported by Zhang.[132]

Ethyl 2-allyl-2-(2-methyl-1,3-dioxolan-2-yl)-4-pentenoate 329:



Ethyl 2-acetyl-2-allyl-4-pentenoate **287** (6.17 g, 30 mmol), *p*-toluene sulfonic acid (57 mg, 0.30 mmol) and ethylene glycol (4.10 g, 66 mmol) were refluxed in toluene (60

mL) overnight, using a Dean-Stark apparatus. The reaction mixture was concentrated *in vacuo*. Et_2O (100 mL) was added, the solution was washed with aq.$NaHCO_3$ (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (Et_2O in petrol, 0-20%) to give ketal **329** as a colourless oil (3.18 g, 42% yield).

R_f= 0.46 (10% EtOAc in petrol).

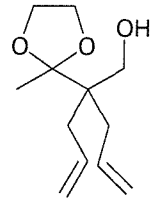
δ_H (300 MHz, $CDCl_3$): 5.88 (2H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.07 (2H, dd, *J* 1, 17 Hz, CH=C$H_A$$H_B$), 4.98 (2H, dd, *J* 1, 10 Hz, CH=C$H_A$$H_B$), 4.18 (2H, q, *J* 7 Hz, OC$H_2$$CH_3$), 4.05-3.96 (4H, m, OCH_2CH_2O), 2.56 (4H, m, CH_2CH=CH_2), 1.45 (3H, s, CH_3CO), 1.26 (3H, t, *J* 7 Hz, OCH_2CH_3).

δ_C (75 MHz, CDCl3): 173.32, 135.29 (1 ×2), 117.25 (2 ×2), 111.72, 64.93 (2 ×2), 60.83 (2), 57.51, 36.09 (2 ×2), 21.66 (3), 14.32 (3).

ν_{max}: 2981, 1722, 1445, 1219, 1097, 912, 734.

m/z(CI): 255.1 ($[M+H]^+$, 80), 211.1 (10), 169.1 (6), 123.0 (4), 87.0 (100).

2-allyl-2-(2-methyl-1,3-dioxolan-2-yl)-4-penten-1-ol 4:



Based on a method published by Albizati.[98]

Ester **329** (5.40 g, 21 mmol) was slowly added to a stirred suspension of $LiAlH_4$ (2.42 g, 63 mmol) in THF (100 mL) at 0°C under nitrogen. The solution was allowed to stir and warm to room temperature over 2 hours. The reaction was quenched after 3 hours by adding 4M NaOH dropwise until the residual solid had turned completely white. The mixture was then filtered and washed thoroughly with ether (100 mL) and concentrated *in vacuo*. The crude compound did not need any purification, giving alcohol **330** as a colourless oil (4.06 g, 91% yield).

R_f= 0.51 (10% EtOAc in petrol).

δ_H (300 MHz, $CDCl_3$): 5.93 (2H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.15-5.04 (4H, m, CH=CH_2), 4.02-3.90 (4H, m, OCH_2CH_2O), 3.52(2H, d, *J* 6 Hz, CH_2OH), 3.17 (1H, t, *J* 6 Hz, OH), 2.20 (4H, m, CH_2CH=CH_2), 1.43 (3H, s, CH_3CO).

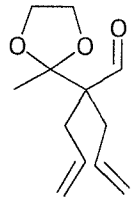
δ_C (75 MHz, CDCl3): 135.12 (1 ×2), 117.43 (2 ×2), 114.80, 66.09 (2), 64.52 (2 ×2), 47.99, 34.97 (2 ×2), 20.13 (3).

ν_{max}: 3524, 2896, 1414, 1380, 1246, 1135.

m/z(CI): 213.1 ($[M+H]^+$, 80), 183.1 (94), 156.1 (10), 139.0 (40), 87.0 (100).

HRMS (EI): requires 212.1412($M^{+\bullet}$), found 121.1414.

2-allyl-2-(2-methyl-1,3-dioxolan-2-yl)-4-pentenal 326:



Based on a method by Swern.[99]

Oxalyl chloride (0.50 mL, 5.7 mmol) in DCM (20 mL) was cooled to -78°C and stirred in a flask fitted with a drying tube. DMSO (0.84 mL, 12 mol) in DCM (10 mL) was added dropwise keeping the temperature between -50 and -60°C. The reaction mixture was stirred for 2 minutes. Alcohol **330** (1 g, 4.71 mmol) was added dropwise over 5 minutes at -78°C and stirred for 15 minutes. Triethylamine (3.28 mL, 23.6 mmol) was added and the reaction was allowed to reach room temperature over 2 hours. The reaction was quenched with water. The aqueous layer was extracted with DCM (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude compound was purified by column chromatography (EtOAc in petrol, 0-10%) to give aldehyde **326** as a colourless oil (0.94 g, 95% yield).

R_f= 0.67 (20% EtOAc in petrol).

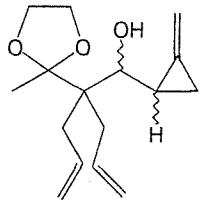
δ_H (300 MHz, $CDCl_3$): 9.60 (1H, s, CHO), 5.79 (2H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.13-4.99 (4H, m, CH=CH_2), 4.04-3.90 (4H, m, OCH_2CH_2O), 2.48 (4H, d, *J* 7 Hz, CH_2CH=CH_2), 1.26 (3H, s, CH_3).

δ_C (75 MHz, $CDCl_3$): 205.06 (1), 135.88 (1 ×2), 117.94 (2 ×2), 111.89, 64.84 (2 ×2), 59.62, 33.49 (2 ×2), 21.53 (1).

ν_{max}: 2984, 2889, 2740, 2723, 2641. 1381, 1210, 1040, 871.

m/z(CI): 228.1 ($[M+NH_4]^+$, 2),183.1 ($[M-CO+H]^+$, 4), 124.0 (6), 87.0 (100).

(±)-2-allyl-2-(2-methyl-1,3-dioxolan-2-yl)-1-(2-methylenecyclopropyl)-4-penten-1-ol 331 and 332:



^{n}BuLi (2.53M in hexanes, 8 mL, 21 mmol) was added to a stirred solution of methylenecyclopropane (1.3 mL, 22 mmol) in THF (20 mL) at -78°C under argon. The solution was warmed to 0°C over 1 hour and stirred for 30 minutes. It was then allowed to reach room temperature over 30 minutes and stirred for 15 minutes. The reaction mixture was then cooled to -78°C. Aldehyde **326** (2.70 g, 12.8 mmol), cooled to -78°C was added to the mixture and the solution was allowed to reach room temperature overnight. The reaction was quenched with aq. NH_4Cl (50 mL). The aqueous layer was extracted with ether (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude compound was purified by column chromatography (Et_2O in petrol, 0-20%) to give the alcohol as a first isomers **331** (1.475 g, 52% yield) and a second isomer **332** (1.231 g, 36% yield).

Data for **331**:

R_f= 0.62 (20% EtOAc in petrol).

δ_H (300 MHz, $CDCl_3$): 6.05 (2H ddt, *J* 17, 10, 7 Hz C*H*=CH_2), 5.58 (1H, s, C=CH_AH_B), 5.47 (1H, s, C=CH_AH_B), 5.15-4.98 (4H, m, CH=CH_2), 4.10-3.92 (4H, m OCH_2CH_2O), 3.23 (1H, dd, *J* 9, 4 Hz, C*H*OH), 2.56-2.43 (2H, m, CH_2CH=CH_2), 2.41-2.29 (2H, m, CH_2CH=CH_2), 1.89 (1H, m, cyclopropyl CH), 1.48 (3H, s, CH_3), 1.33 (1H, m, cyclopropyl CH_AH_B), 1.08 (1H, m, cyclopropyl CH_AH_B).

δ_C (75 MHz, $CDCl_3$): 136.84 (1), 136.28 (1), 134.48, 116.77 (2), 116.69 (2), 115.04, 104.61 (2), 78.14 (1), 64.42 (2), 64.19 (2), 51.37, 36.76 (2), 34.03 (2), 21.34 (3), 19.43(1), 8.01 (2).

ν_{max}: 3515, 3073, 2980, 2881, 1376, 1202, 1037, 908.

m/z(CI): 265 ($[M+H]^+$, 3), 249 ($[M+H-H_2O]^+$, 5), 183 (54), 35 (100).

HRMS (CI): requires 265.1504, ($[M+H]^+$), found 265.1452.

Data for **332**:

R_f= 0.56 (20% EtOAc in petrol).

δ_H (300 MHz, $CDCl_3$): 6.04 (2H ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.51-5.42 (2H, m, C=CH_2), 5.14-5.00 (4H, m, CH=C*H*$_2$), 4.07-3.95 (4H, m OCH_2CH_2O), 3.77 (1H, d, *J* 4 Hz, OH), 3.16 (1H, dd, *J* 9, 4 Hz, C*H*OH), 2.59-2.25 (4H, m, C*H*$_2$CH=CH_2), 1.82 (1H, m, cyclopropyl CH), 1.42 (3H, s, CH_3), 1.38 (1H, m, cyclopropyl C*H*$_A$H$_B$), 1.10 (1H, m, cyclopropyl CH$_A$*H*$_B$).

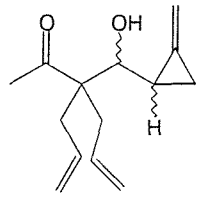
δ_C (75 MHz, $CDCl_3$): 136.60 (1), 136.01 (1), 134.81, 116.88 (2), 116.81 (2), 114.98, 104.61 (2), 78.26 (1), 64.35 (2), 64.14 (2), 51.38, 36.70 (2), 34.12 (2), 21.00 (3), 19.34(1), 8.30 (2).

ν_{max}: 3515, 3073, 2980, 2881, 1376, 1202, 1037, 908.

m/z(CI): 265 ($[M+H]^+$, 3), 249 ($[M+H-H_2O]^+$, 5), 183 (54), 35 (100).

HRMS (CI): requires 265.1504, ($[M+H]^+$), found 265.1452.

(±)-3-Allyl-3-[hydroxy (2-methylenecyclopropyl)methyl]-5-hexen-2-one 333 and 334:



Ketal **331** (500 mg, 1.89 mmol) and *p*-toluene sulfonic acid (catalytic amount) were stirred in a solution of 10% water in acetone (20 mL) for 48 hours. The reaction mixture was concentrated *in vacuo*. Et_2O (20 mL) was added, the solution was washed with aq. $NaHCO_3$ (30 mL). The aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (EtOAc in petrol, 0-20%) to give ketone **333** as a colourless oil (417 mg, overall 82% yield).

R_f = 0.48 (20% EtOAc in petrol).

δ_H (300 MHz, $CDCl_3$): 5.85 (1H, m, C*H*=CH_2), 5.81-5.65 (1H, m, C*H*=CH_2C), 5.52 (1H, d, *J* 2 Hz, C=CH_2), 5.45 (1H, d, *J* 2 Hz, C=CH_2), 5.17-5.08 (4H, m, CH=C*H*$_2$), 3.45 (1H, t, *J* 7

Hz, C*H*OH), 2.72-2.46, (4H, m, C*H*$_2$CH=CH$_2$), 2.33 (1H, d, *J* 7 Hz, OH), 2.24 (3H, s, CH$_3$), 1.77 (1H, m, cyclopropyl CH), 1.37 (1H, m, cyclopropyl C*H*$_A$H$_B$), 1.10 (1H, m, cyclopropyl CH$_A$*H*$_B$).

δ_C (75 MHz, $CDCl_3$): 214.18, 134.64 (1), 133.45 (1), 132.12, 118.95 (2), 118.43 (2), 105.25 (2), 76.75 (1), 59.46, 37.48 (2), 36.30 (2), 28.86 (3), 17.58 (1), 9.15 (2).

ν_{max}: 3438, 3068, 2984, 2914, 1707, 1417, 1357, 1041, 903, 732.

m/z(CI): 139 ([M+H-C_4H_5CO]$^+$), 97 (100).

HRMS (CI): requires 221.1542 ([M+H]$^+$), found 221.1535.

Ketal **332** (200 mg, 0.75 mmol) and *p*-toluene sulfonic acid (catalytic amount) were stirred in a solution of 10% water in acetone (20 mL) for 48 hours. The reaction mixture was concentrated *in vacuo*. Et_2O (20 mL) was added, the solution was washed with aq. $NaHCO_3$ (30 mL). The aqueous layer was extracted with Et_2O (3×30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (EtOAc in petrol, 0-10%) to give ketone **334** as a colourless oil (155 mg, overall 96% yield).

R_f = 0.42 (20% EtOAc in petrol).

δ_H (300 MHz, $CDCl_3$): 5.99-5.82 (1H, m, C*H*=CH$_2$), 5.80-5.64 (1H, m, C*H*=CH$_2$), 5.49 (1H, d, *J* 2 Hz, C=C*H*$_A$H$_B$), 5.39 (1H, d, *J* 2 Hz, C=CH$_A$*H*$_B$), 5.13-5.02 (4H, m, CH=*CH*$_2$), 3.34 (1H, dd, *J* 9, 6 Hz, C*H*OH), 2.63-2.59, (4H, m, C*H*$_2$CH=CH$_2$), 2.22 (3H, s, CH$_3$), 1.73 (1H, m, cyclopropyl CH), 1.35 (1H, m, cyclopropyl C*H*$_A$H$_B$), 1.03 (1H, m, cyclopropyl CH$_A$*H*$_B$).

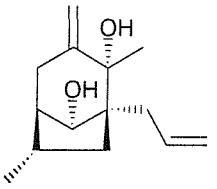
δ_C (75 MHz, $CDCl_3$): 213.94, 135.00 (1), 133.49 (1), 132.90, 118.86 (2), 118.37 (2), 105.45 (2), 76.75 (1), 59.31, 37.72 (2), 36.46 (2), 28.47 (3), 18.07 (1), 7.79 (2).

ν_{max}: 3430, 3073, 2977, 2920, 1683, 1435, 1355, 1041, 915.

m/z(CI): 139 ([M+H-C_4H_5CO]$^+$), 97 (100).

HRMS (CI): requires 221.1542 ([M+H]$^+$), found 221.1535.

(±)-(1*S*,2*S*,5*R*,6*S*,8*R*)-1-Allyl-2,6-dimethyl-3-methylidenebicyclo[3.2.1] octane-2,8-diol 348:



The solution was cooled to the appropriate temperature and ketone **333** or **334** (100 mg, 0.55 mmol) in THF (10 mL) was used in the cyclisation. The crude mixture was washed with aqueous citric acid (1 g in 20 mL H_2O) and extracted with a 1:1 ratio solution of EtOAc and hexane (3 × 25 mL). The combined organic layers were washed with brine then water, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (EtOAc in petrol, 0-20%) to give bicycle **348** as a colourless oil.

Data for the major isomer:

R_f= 0.22 (20% EtOAc in petrol).

δ_H (400 MHz, $CDCl_3$): 6.00 (1H, m, CH=CH_2), 5.18-5.08 (2H, m, CH=CH_2), 5.02 (1H, s with fine splitting, C=CH_AH_B), 4.85 (1H, s with fine splitting, C=CH_AH_B), 3.95 (1H, d, *J* 6 Hz $CHOH$), 3.50 (1H, br s, OH), 3.00 (1H, dd, *J* 4 Hz, 14, cyclohexyl CH_AH_B), 2.64 (1H, dd, *J* 7, 14 Hz, CH_AH_BCH=CH_2), 2.13 (1H, dd, *J* 4, 14 Hz, cyclohexyl CH_AH_B), 2.00 (1H, dd, *J* 7, 14 Hz, CH_AH_BCH=CH_2), 1.83 (1H, m, $CHCHOH$), 1.63 (1H, m, $CHCH_3$) 1.44 (1H, dd, *J* 4, 14, $CH_AH_BCHCH_3$), 1.30 (3H, s, CH_3), 0.98-0.87 (4H, m, CH_3CH and $CH_AH_BCHCH_3$).

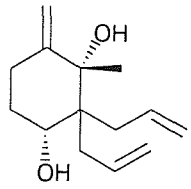
δ_C (100 MHz, $CDCl_3$): 150.17, 135.65 (1), 118.04 (2), 111.11 (2), 79.62, 75.90 (1), 49.56, 46.19 (1), 36.35 (2), 34.97 (2), 33.28 (2), 30.57 (1), 22.74 (3), 20.88 (3).

ν_{max}: 3236, 3081, 2951, 2928, 2869, 1441, 1109, 902.

m/z(CI): 205 ($[M+H-H_2O]^+$, 100.

HRMS (EI): requires 222.1620 ($M^{+\bullet}$), found 222.1611.

(±)-(1*S*,3*R*)-2,2-Diallyl-1-methyl-6-methylidenecyclohexane-1,3-diol 349:



R_f= 0.22 (20% EtOAc in petrol).

δ_H (300 MHz, $CDCl_3$): 6.01 (2H, m, C*H*=CH_2), 5.18-5.08 (4H, m, CH=C*H*$_2$), 5.02 (1H, s with fine splitting, C=C*H*$_A$H$_B$), 4.85 (1H, s with fine splitting, C=CH$_A$*H*$_B$), 3.98 (1H, d, *J* 5 Hz, CHO*H*), 3.00 (1H, dd, *J* 5, 14 Hz, C*H*OH), 2.64 (2H, dd, *J* 7, 14 Hz, C*H*$_A$H$_B$CH=CH_2), 2.13 (1H, dd, *J* 4, 14 Hz, CH$_A$*H*$_B$C=CH_2), 2.00 (2H, dd, *J* 7, 14, CH$_A$*H*$_B$CH=CH_2), 1.83 (1H, m, C*H*$_A$H$_B$CHOH), 1.68 (1H, m, CH$_A$*H*$_B$CHOH), 1.44 (2H, dd, *J* 10, 14 Hz, CH_2C=CH_2), 1.29 (1H, s, CH_3).

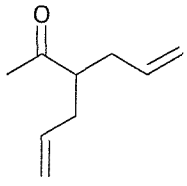
δ_C (75 MHz, $CDCl_3$): 150.09, 135.51 (1 ×2), 117.89 (2 ×2), 110.28 (2), 79.62, 75.89 (1), 49.50, 36.33 (2), 34.95 (2), 33.28 (2), 30.57 (2), 22.74 (3).

ν_{max}: 3311, 3077, 2927, 1440, 1117, 902.

m/z(EI): 222 ($M^{+\bullet}$, 20), 207 (100).

HRMS (EI): requires 204.1514 ([M-H_2O]$^{+\bullet}$), found 204.1507.

3-Allyl-5-hexen-2-one 350:



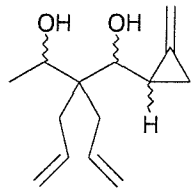
R_f= 0.86 (20% EtOAc in petrol).

δ_H (300 MHz, $CDCl_3$): 5.72 (2H, m, C*H*=CH_2), 5.08-4.92 (4H, m, CH=CH_2), 2.64 (1H, m, COCH), 2.35 (2H, m, C*H*$_2$CH=CH_2) 2.28 (2H, m, C*H*$_2$CH=CH_2), 2.14 (3H, s, CH_3).

δ_C (75 MHz, $CDCl_3$): 212.34, 135.41 (1 ×2), 118.53 (2 ×2), 55.75 (1), 36.26 (2 ×2), 28.17 (3).

Data agreed with those reported by Yoshio.[133]

(±)-2,2-Diallyl-1-(2-methylenecyclopropyl)-1,3-butanediol 338 and 339:



Using method by Albizati.[98]

Ketone **333** or **334** (50 mg, 0.23 mmol) was slowly added to a stirred suspension of $LiAlH_4$ (22 mg, 0.58 mmol) in THF (10 mL) at -30°C under nitrogen. The solution was allowed to stir and reach room temperature over 2 hours. The reaction was quenched after 3 hours by adding 4M NaOH dropwise until the residual solid had turned completely white. The mixture was then filtered and washed thoroughly with Et_2O (100 mL) and concentrated *in vacuo*. The crude mixture was purified by column chromatography (EtOAc in petrol, 0-20%) to give diols **338** or **339** as colourless oils (27 mg, 53% yield). The products isolated were mixtures of the 2 possible isomers, both in a 1:1 ratio.

Using method by Evans.[134]

A solution of **333** or **334** (50 mg, 0.23 mmol) in MeCN was added to a solution of tetramethylammonium triacetoxy borohydride in 1:1 MeCN:acetic acid (2mL) at -40°C under argon. The mixture was stirred a 0°C for 20 hours and at room temperature for a further 12 hours. The reaction was poured into a slurry of ice and aq. sat. Na_2CO_3 then basified with 2M NaOH. The aqueous layer was extracted with DCM (3 × 10 mL) and EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (EtOAc in petrol, 0-10%) to give **338** or **339** as a colourless oil (12 mg, 23% yield). The products isolated were mixtures of the 2 possible isomers, both in c.a. 1:1 ratio.

Data for **338** product of the reduction of **333**:

R_f= 0.36 (20% EtOAc in petrol).

δ_H (300 MHz, $CDCl_3$): 6.19-5.81 (2H, m, C*H*=CH_2), 5.61-5.49 (2H, m, C=CH_2), 5.22-4.96 (4H, m, CH=CH_2), 4.02 (1H, m, CH_3CHOH), 3.44 (1H, t, *J* 8 Hz, C*H*OH), 2.78-2.62 (2H, br s, OH), 2.58-2.07, (4H, m, CH_2CH=CH_2), 1.83 (1H, m, CH cyclopropyl), 1.44-1.09 (4H, m, cyclopropyl CH_AH$_B$ and CH_3), 1.17-1.02 (1H, m, cyclopropyl CH$_A$$H_B$).

Data for **339** product of the reduction of **334**:

R_f= 0.36 (20% EtOAc in petrol).

δ_H (300 MHz, $CDCl_3$): 6.19-5.75 (2H, m, C*H*=CH_2), 5.55-5.38 (2H, m, C=CH_2), 5.20-4.95 (4H, m, CH=C*H*$_2$), 4.02 (1H, m, CH_3C*H*OH), 3.44 (1H, t, *J* 8 Hz, C*H*OH), 3.07-2.98 (2H, br s, OH), 2.58-2.22, (3H, m, C*H*$_2$CH=CH_2 and C*H*$_A$$H_B$CH=$CH_2$), 2.00 (1H, m, C*H*$_A$$H_B$CH=$CH_2$) 1.73 (1H, m, cyclopropyl CH), 1.44-1.16 (4H, m, cyclopropyl C*H*$_A$$H_B$ and CH_3), 1.09 (1H, m, cyclopropyl CH_A*H*$_B$).

δ_C (75 MHz, $CDCl_3$): 136.65 (1), 135.18(1), 133.57, 117.94 (2), 117.72 (2), 105.21 (2), 79.95 (1), 73.00 (1), 47.02, 38.34 (2), 35.22 (2), 19.59 (1), 18.48 (3), 7.78 (2).

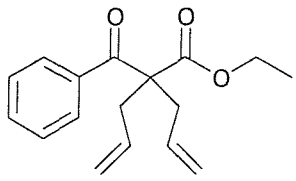
ν_{max}: 3308, 3074, 2978, 2920, 1438, 1016, 1000, 911, 891.

m/z(CI): 223 ($[M+H]^+$, 2), 187 ($[M+H-H_2O]^+$, 8), 91 (100).

HRMS (CI): requires 205.1592 ($[M+H]^+$), found 205.1584.

6.5) *Experimental For Chapter Four*

Ethyl 2-allyl-2-benzoylpent-4-enoate 360:



Based on a method published by Chadha.[127]

Ethyl benzoylacetate (5.50 mL, 0.03 mol) was added to a stirred solution of NaH (60% in oil, 3 g, 0.075 mol) in THF (60 mL) at 0°C under nitrogen and stirred for 30 minutes. Allyl Bromide (10.4 mL, 0.09 mol) was added dropwise at 0 °C. The solution was heated to reflux and stirred for 36 hours. The reaction was quenched with NH_4Cl (aq) and the aqueous layer was extracted (Et_2O, 3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (Et_2O in petrol, 0-10%) to give keto-ester **360** as a colourless oil (7.98 g, 98% yield).

R_f= 0.63 (15% EtOAc in petrol)

δ_H (300 MHz, $CDCl_3$): 7.88-7.82 (2H, m, 2× aromatic H), 7.54 (1H, t, *J* 7 Hz, aromatic H), 7.43 (2H, t, *J* 7 Hz, 2× aromatic H), 5.58 (2H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.11-4.87 (4H, m, CH=CH_2), 4.14 (2H, q, *J* 7 Hz, OCH_2), 2.82 (4H, d, *J* 7 Hz, 2 × CH_2CH=CH_2), 1.09 (3H, t, *J* 7 Hz, CH_3).

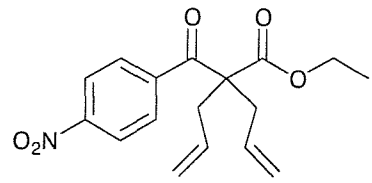
δ_C (75 MHz, $CDCl_3$): 196.32, 172.79, 136.03, 132.92 (1), 132.07 (1 ×2), 128.67 (1 ×2), 128.57 (1 ×2), 119.55 (2 ×2), 61.27 (2), 60.62, 37.29 (2 ×2), 14.04 (3).

ν_{max}: 3077, 2980, 1732, 1680, 1640, 1446, 1280, 1215, 1136, 993, 917.

m/z(CI): 273 ($[M+H]^+$, 11), 227 (3), 185 (4), 105 (100).

HRMS (EI): requires 272.1412 ($M^{+\bullet}$), found 272.1414.

Ethyl 2-allyl-2-(4-nitrobenzoyl)pent-4-enoate 364:



Based on a method published by Chadha.[127]

Ethyl 4-nitrobenzoylacetoacetate (2 g, 8.43 mmol) was added to a stirred solution of NaH (60% in oil, 0.71 g, 17.7 mmol) in THF (30 mL) at 0°C under nitrogen and stirred for 30 minutes. Allyl Bromide (1.82 mL, 21.08 mmol) was added dropwise at 0°C. The solution was heated to reflux and stirred for 36 hours. The reaction was quenched with NH_4Cl (aq) and the aqueous layer extracted (Et_2O, 3×50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (EtOAc in petrol, 0-10%) to give keto-ester **364** as a yellow crystalline solid (930 mg, 35% yield).

R_f= 0.68 (20% EtOAc in petrol)

m.p.= 62-64°C

δ_H (300 MHz, $CDCl_3$): 8.29 (2H, d, *J* 9 Hz, 2× aromatic H), 7.98 (2H, d, *J* 9 Hz, 2× aromatic H), 5.58 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.11 (2H, d, *J* 9 Hz, CH=C*H*$_2$), 5.03 (1H, dd, *J* 1, 9 Hz, CH=C*H*$_2$), 4.18 (2H, q, *J* 7 Hz, OCH_2), 2.90-2.73 (4H, m, 2× C*H*$_2$CH=CH_2), 1.12 (3H, t, *J* 7 Hz, CH_3).

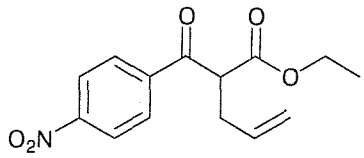
δ_C (75 MHz, $CDCl_3$): 195.12, 172.08, 150.26, 140.88, 131.41 (1 ×2), 129.55 (1×2), 123.88 (1 ×2), 120.11 (2 ×2), 61.99 (2), 61.14, 37.23 (2 ×2), 14.10 (3).

ν_{max}: 3080, 2979, 2863, 1735, 1689, 1604, 1526, 1349, 1280, 1201, 920, 853.

m/z(CI): 318 ($[M+H]^+$, 8), 288 (11), 150 (48), 120 (100).

$C_{17}H_{19}NO_5$, calculated: C: 64.34; H: 6.03; N: 4.41; O: 25.22; found C: 64.36; H: 6.06; N: 4.44; O: 25.14.

(±)-Ethyl 2-(4-nitrobenzoyl)pent-4-enoate 363:



Keto-ester **363** was isolated as a yellow crystalline solid 1.1g (41% yield).

R_f= 0.49 (20% EtOAc in petrol)

m.p.= 56-58°C

δ_H (300 MHz, $CDCl_3$): 8.33 (2H, d, *J* 9 Hz, 2× aromatic H), 8.15 (2H, d, *J* 9 Hz, 2× aromatic H), 5.80 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.21-5.02 (2H, m, CH=CH_2), 4.13 (2H, m, OCH_2), 3.52 (1H, t, *J* 7 Hz, COCHCO), 2.78 (2H, t, *J* 7 Hz, CH_2CH=CH_2), 1.27 (3H, t, *J* 7 Hz, CH_3).

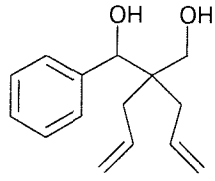
δ_C (75 MHz, $CDCl_3$): 193.33, 168.80, 150.86, 140.85, 134.02 (1), 129.77 (1 ×2), 124.11 (1 ×2), 118.15 (2), 62.02 (2), 54.58, 32.86 (2), 14.16.

ν_{max}: 3116, 3081, 2982, 1734, 1696, 1526, 1345, 1236, 1045, 920, 852.

m/z(CI): 278 ($[M+H]^+$, 19), 248 (15), 150 (100), 120 (98).

$C_{14}H_{15}NO_5$, calculated: C: 60.64; H: 5.45; N: 5.05; O: 28.86; found C: 60.71; H: 5.73; N: 4.82; O: 28.74.

(±)-2,2-Diallyl-1-phenylpropane-1,3-diol 367:



Based on a method published by Albizati.[98]

Keto-ester **360** (500 mg, 1.84 mmol) was added slowly to a stirred suspension of $LiAlH_4$ (174 mg, 4.6 mmol) in THF (20 mL) at 0°C under nitrogen. The solution was allowed to stir and reach room temperature over 2 hours. The reaction was quenched after 3 hours by adding 4M NaOH dropwise until the residual solid had turned completely white. The mixture was then filtered and washed thoroughly with ether (250 mL). The combined organic layers were concentrated *in vacuo*. The crude compound was purified by column

chromatography (EtOAc in petrol, 0-20%) to give diol **367** as a colourless oil (426 mg, 100% yield).

R_f= 0.3 (20% EtOAc in petrol)

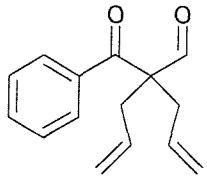
δ_H (300 MHz, $CDCl_3$): 7.35-7.26 (5H, m, 5× aromatic H), 6.08-5.65 (2H, m, 2 × CH=CH_2), 5.25-4.96 (3H, m, CH=CH_2 and CH=CH_AH$_B$), 4.78 (1H, m, CH=CH$_A$$H_B$), 3.77-3.45 (3H, m, C$H_2$OH and CHOH), 2.66 (2H, br s, $(OH)_2$), 2.48 (1H, dd *J* 7, 14 Hz, CH_AH$_B$CH=CH_2), 4.53 (1H, dd *J* 7, 14 Hz, CH$_A$$H_B$CH=$CH_2$), 2.03-1.79 (2H, m, C$H_2$CH=$CH_2$).

δ_C (75 MHz, $CDCl_3$): 141.09, 134.38 (1), 134.26 (1), 128.16 (1 ×2), 127.92 (1 ×3), 118.57 (2), 118.46 (2), 80.14 (1), 67.27 (2), 44.47, 36.24 (2), 35.90 (2).

ν_{max}: 3309, 3074, 2922, 2873, 1638, 1441, 1051, 1016, 912.

m/z(CI): 197 ($[M-H_2O+H]^+$, 76), 75 (100).

2-Allyl-2-benzoylpent-4-enal 366:



Based on a method published by Swern.[99]

Oxalyl chloride (1.13 mL, 13 mmol) in DCM (20 mL) was cooled to -78°C and stirred. DMSO (1.53 mL, 21.5 mmol) in DCM (5 mL) was added dropwise keeping the temperature between -50°C and -60°C. The reaction mixture was stirred for 2 minutes. Alcohol **367** (1 g, 4.3 mmol) was added dropwise over 5 minutes at -78°C and stirred for 15 minutes. Triethylamine (4.8 mL, 34.4 mmol) was added and the reaction was allowed to reach room temperature over 2 hours. The reaction was quenched with water. The aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude compound was purified by column chromatography (EtOAc in petrol, 0-5%) to give keto-aldehyde **366** as a colourless oil (910 mg, 92% yield).

R_f= 0.72 (20% EtOAc in petrol)

δ_H (300 MHz, $CDCl_3$): 9.83 (1H, s, CHO), 7.79-7.71 (2H, m, 2× aromatic H), 7.56 (1H, t, *J* 7 Hz, aromatic H), 7.45 (2H, t, *J* 7 Hz, 2× aromatic H), 5.61 (2H, ddt, *J* 17, 10, 7 Hz, 2 ×

C*H*=CH_2), 5.14-5.02 (3H, m, CH=C*H*$_2$ and C=C$H_A$$H_B$), 4.97 (1H, m, C=C$H_A$*H*$_B$), 2.86-2.79 (4H, m, 2× C*H*$_2$CH=CH_2).

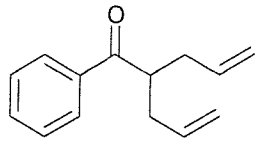
δ_C (75 MHz, $CDCl_3$): 200.96 (1), 198.09, 137.02, 133.19 (1), 131.51 (1 ×2), 128.92 (1 ×2), 128.84 (1 ×2), 119.99 (2 ×2), 66.54, 36.06 (2 ×2)

ν_{max}: 3078, 2977, 2918, 2829, 1722, 1672, 1639, 1446, 1270, 1215, 991, 785.

m/z(CI): 246 ($[M+NH_4]^+$, 7), 229 ($[M+H]^+$, 100), 201 ($[M-CO+H]^+$, 51).

HRMS (EI): requires 200.1201 ($[M-CO]^{+\bullet}$), found 200.1202.

2-Allyl-1-phenylpent-4-en-1-one 371:



^{n}BuLi (1.45M in hexanes, 0.8 mL, 1.12 mmol) was added to a stirred solution of methylenecyclopropane (0.08 mL, 1.12 mmol) in THF (10 mL) at -78°C under argon. The solution was warmed to 0°C over 1 hour and stirred for 30 minutes. It was then allowed to reach room temperature over 30 minutes and stirredfor 15 minutes. The reaction mixture was then cooled to -78°C. Aldehyde **366** (150 mg, 1.09 mmol), cooled to -78°C was added to the mixture and the solution was allowed to reach room temperature overnight. The reaction was quenched with aqueous NH_4Cl (10 mL). The aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude compound was purified by column chromatography (Et_2O in petrol, 0-5%) to give ketone **371** (95 mg, 63% yield).

R_f= 0.85 (20% EtOAc in petrol)

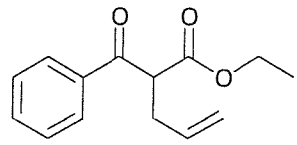
δ_H (300 MHz, $CDCl_3$): 7.98-7.86 (2H, m, 2× aromatic H), 7.58 (1H, m, aromatic H), 7.48 (2H, t, *J* 7 Hz, 2× aromatic H), 5.75 (2H, ddt, *J* 17, 10, 7 Hz, 2× C*H*=CH_2), 5.03 (1H, d, *J* 1 Hz, CH=C$H_A$$H_B$), 5.03-4.96 (3H, m, CH=CH_A*H*$_B$ and CH=C*H*$_2$), 3.60 (1H, quintet, *J* 7 Hz, CHCO), 2.54 (2H, dt, *J* 7, 14 Hz, C*H*$_2$CH=CH_2), 2.31 (2H, dt, *J* 7, 14 Hz, C*H*$_2$CH=CH_2).

δ_C (75 MHz, $CDCl_3$): 202.93, 137.23, 135.58 (1, ×2), 133.15 (1), 128.82 (1 ×2), 128.43 (1 ×2), 117.15 (2 ×2), 45.73 (1), 35.98 (2 ×2).

ν_{max}: 3077, 2978, 2912, 1679, 1446, 1365, 1239, 1206, 993, 913.

Data agreed with those reported by Calo.[135]

(±)-Ethyl 2-benzoylpent-4-enoate 372:



Based on a method published by Chadha.[126]

Ethyl benzoylacetate (13 mL, 75 mmol) was added to a stirred solution of NaH (60% in oil, 3.3 g, 82.5 mmol) in THF (100 mL) at 0°C under nitrogen and stirred for 30 minutes. Allyl Bromide (9.75 mL, 0.112 mol) was added dropwise at 0 °C and the solution was allowed to reach room temperature overnight. The reaction was quenched with NH_4Cl (aq) and the aqueous layer was extracted (Et_2O, 3×50 mL) .The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (Et_2O in petrol, 0-10%) to give keto-ester **372** as a colourless oil (15.34 g, 88% yield).

R_f= 0.68 (20% EtOAc in petrol)

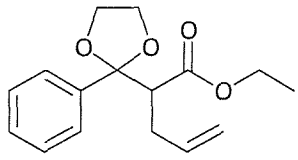
δ_H (300 MHz, $CDCl_3$): 8.00 (2H, d, *J* 9 Hz, 2× aromatic H), 7.57 (1H, m, aromatic H), 7.52-7.44 (2H, m, 2× aromatic H), 5.82 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.12 (1H, dd *J* 1, 15 Hz, CH=C$H_A$$H_B$), 5.00 (1H, dd, *J* 1, 7 Hz, CH=C$H_A$$H_B$), 4.41 (1H, t, *J* 7 Hz, $CHCO_2Et$), 4.18 (2H, d, *J* 7 Hz, OCH_2), 2.76 (2H, m, CH_2CH=CH_2), 1.17 (3H, t, *J* 7 Hz, CH_3).

δ_C (75 MHz, $CDCl_3$): 194.65, 169.54, 136.32, 134.65 (1), 133.70 (1), 128.89 (1 ×2), 128.77 (1 ×2), 117.57 (2), 61.60 (2), 54.07 (1), 33.15 (2), 14.16 (3).

ν_{max}: 3070, 2981, 1734, 1687, 1447, 1369, 1233, 1177, 1155, 1026, 916.

All data agreed with those reported by Queignec.[136]

(±)-Ethyl 2-(2-phenyl-1,3-dioxolan-2-yl)pent-4-enoate 373:



Ethyl 2-benzoylpent-4-enoate **372** (5 g, 22 mmol), *p*-toluene sulfonic acid (418 mg, 2.2 mmol) and ethylene glycol (6.82 g, 0.11 mol) were refluxed in toluene (80 mL) overnight, using a Dean-Stark apparatus. The reaction mixture was concentrated *in vacuo*. Et_2O (50 mL) was added, the solution was washed with aq. $NaHCO_3$ (30 mL), the aqueous layer was extracted (Et_2O, 3×50 mL). The organic layers were recombined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (Et_2O in petrol, 0-20%) to give ketal **373** as a colourless oil (2.91 g, 48% yield).

R_f= 0.76 (20% EtOAc in petrol)

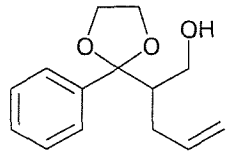
δ_H (300 MHz, $CDCl_3$): 7.48-7.26 (5H, m, 5× aromatic H), 5.68 (1H, m, C*H*=CH_2), 5.04 (1H, dd, *J* 1, 17 Hz, CH=CH_AH$_B$), 4.96 (1H, d, *J* 10 Hz, CH=CH$_A$*H*$_B$), 4.13-3.85 (4H, m, OCH_2CH_2O), 3.83-3.75 (2H, m, OCH_2), 3.06 (1H, dd, *J* 3, 12 Hz, $CHCO_2Et$), 2.57 (1H, m, CH_AH$_B$CH=CH_2), 2.33 (1H, m, CH$_A$*H*$_B$CH=CH_2), 1.08 (3H, t, *J*, 7 Hz, CH_3).

δ_C (75 MHz, $CDCl_3$): 171.39, 140.77, 135.36 (1), 128.45 (1), 128.14 (1 ×2), 126.42 (1 ×2), 116.82 (2), 109.33, 65.21 (2), 64.76 (2), 60.48 (2), 55.28 (1), 31.51 (2), 14.24 (3).

ν_{max}: 304, 2980, 1734, 1446, 1371, 1341, 1228, 1154, 1045, 916, 774, 751.

m/z(CI): 277 ($[M+H]^+$), 149 (100).

(±)-2-(2-Phenyl-1,3-dioxolan-2-yl)pent-4-en-1-ol 374:



Based on a method published by Albizati.[98]

Keto-ester **373** (1.45 g, 5.23 mmol) was added slowly to a stirred suspension of $LiAlH_4$ (400 mg, 10.46 mmol) in THF (20 mL) at 0°C under nitrogen. The solution was

allowed to stir and reach room temperature over 2 hours The reaction was quenched after 3 hours by adding 4M NaOH dropwise until the residual solid had turned completely white. The mixture was then filtered and washed thoroughly with ether (150 mL). The combined organic layers were concentrated *in vacuo*. The crude compound was purified by column chromatography (EtOAc in petrol, 0-20%) to give alcohol **374** as a colourless oil (1.20 g, 98% yield).

R_f= 0.32 (20% EtOAc in petrol)

δ_H (300 MHz, $CDCl_3$): 7.53-7.34 (5H, m, aromatic H), 5.71 (1H, m, C*H*=CH_2), 5.04-4.96 (2H, m, CH=C*H*$_2$), 4.07 (2H, m, C*H*$_2$OH), 3.75-3.64 (4H, m, OCH_2CH_2O), 2.48, (1H, br s, OH), 2.25-2.14 (2H, m, C*H*$_2$CH=CH_2), 1.95 (1H, m, C*H*CH=CH_2).

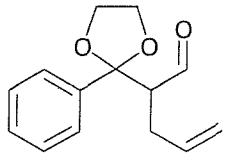
δ_C (75 MHz, $CDCl_3$): 140.30, 136.65 (1), 128.27 (1), 128.16 (1 ×2), 126.32 (1 ×2), 116.45 (2), 112.71, 64.50 (2), 64.07 (2), 61.36 (2), 48.37 (1), 30.64 (2).

ν_{max}: 3434, 3071, 236, 2889, 1446, 1175, 1028, 912, 773, 757.

m/z(CI): 235 ($[M+H]^+$, 7), 217 ($[M-H_2O+H]^+$, 5), 149 (100).

HRMS (EI): requires 234.1256 ($M^{+\bullet}$), found 234.1251.

(±)-2-(2-Phenyl-1,3-dioxolan-2-yl)pent-4-enal 375:



Based on a method published by Swern.[99]

Oxalyl chloride (0.425 mL, 4.9 mmol) in DCM (5 mL) was cooled to -78°C and stirred. DMSO (0.720 mL, 10.15 mmol) in DCM (5 mL) was added dropwise keeping the temperature between -50°C and -60°C. The reaction mixture was stirred for 2 minutes. Alcohol **374** (950 mg, 4.06 mmol) was added dropwise over 5 minutes at -78°C and stirred for 15 minutes. Triethylamine (2.85 mL, 20.3 mmol) was added and the reaction was allowed to reach room temperature over 2 hours. The reaction was quenched with water (20 mL). The aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude compound was purified by column chromatography (EtOAc in petrol, 0-5%) to give aldehyde **375** as a colourless oil (740 mg, 79% yield).

R_f= 0.77 (20% EtOAc in petrol)

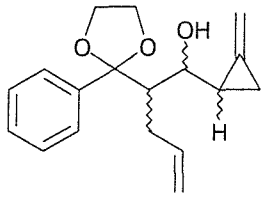
δ_H (300 MHz, $CDCl_3$): 9.70 (1H, d, *J*, 4 Hz, CHO), 7.48-7.33 (5H, m, 5× aromatic H), 5.63 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.00-4.92 (2H, m, CH=CH_2), 4.10-4.01 (2H, m, OCH_2), 3.89-3.72 (2H, m, OCH_2), 2.90 (1H, dt, *J* 4, 10 Hz, C*H*CHO), 2.50 (1H, m, C$H_A$$H_B$CH=$CH_2$), 2.24 (1H, m, $CH_A$$H_B$CH=$CH_2$).

δ_C (75 MHz, $CDCl_3$): 202.25 (1), 140.11, 135.17 (1), 128.76 (1), 128.52 (1 ×2), 126.26 (1 ×2), 116.88 (2), 110.10, 64.96 (2), 64.58 (2), 59.74 (1), 29.30 (2).

ν_{max}: 3070, 2978, 2893, 1724, 1447, 1218, 1176, 1047, 1024, 916, 773.

m/z(CI): 233 ($[M+H]^+$, 1), 205 ($[M-CO+H]^+$, 3), 149 (100).

(±)-1-(2-Methylidenecyclopropyl)-2-(2-phenyl-1,3-dioxolan-2-yl)pent-4-en-1-ol 376 and 377:



^{n}BuLi (2.4M in hexanes, 2.42 mL, 4.53 mmol) was added to a stirred solution of methylenecyclopropane (0.40 mL, 4.53 mmol) in THF (20 mL) at -78°C under argon. The solution was warmed to 0°C over 1 hour and stirred for 30 minutes. It was then allowed to reach room temperature over 30 minutes and stirred for 15 minutes. The reaction mixture was then cooled to -78°C. Aldehyde **375** (0.700 g, 3.02 mmol) in THF (5mL) was cooled to -78°C and added to the mixture and the solution was allowed to reach room temperature overnight. The reaction was quenched with aq. NH_4Cl (50 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude compound was purified by column chromatography (EtOAc in petrol, 0-40%) to give the alcohol as one major diastereoisomers **376** (371 mg, 43% yield) contaminated with a minor diastereoisomer (ratio 8:1) and a second major diastereoisomer **377** (293 mg, 34% yield) also contaminated with a minor diastereoisomer (ratio 8:1).

Data for the major isomer of **376**:

R_f= 0.72 (20% EtOAc in petrol)

δ_H (300 MHz, $CDCl_3$): 8.01-7.96 (2H, m, 2× aromatic H), 7.58 (1H, t, *J* 7 Hz, aromatic H), 7.54-7.49 (2H, t, *J* 7 Hz, 2× aromatic H), 5.79 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.50 (1H, d, *J* 2 Hz, C=C$H_A$$H_B$), 5.42 (1H, s, C=$CH_A$$H_B$), 5.02 (1H, dd, *J* 1, 17 Hz, CH=C$H_A$$H_B$), 4.95 (1H, d, *J* 17 Hz, CH=$CH_A$$H_B$), 4.08-3.97 (4H, m, OCH_2CH_2O), 3.54 (1H, t, *J*, 7 Hz, C*H*OH), 2.70-2.64 (2H, m, CH_2CH=CH_2), 2.11 (1H, m, C*H*CH_2CH=CH_2), 1.70 (1H, m, cyclopropyl CH), 1.19 (1H, dt, *J* 2, 9 Hz, cyclopropyl C$H_A$$H_B$), 1.00 (1H, m, cyclopropyl $CH_A$$H_B$).

δ_C (75 MHz, $CDCl_3$): 140.77, 139.27 (1), 134.51, 128.28 (1 ×2), 128.24 (1), 126.27 (1 ×2), 114.54 (2), 112.82, 103.61 (2), 74.04 (1), 64.60 (2), 64.47 (2), 50.82 (1), 28.18 (2), 19.52 (1), 7.27 (2).

ν_{max}: 3533, 3067, 2958, 2893, 1446, 1314, 1178, 1024, 905, 889, 773, 753.

m/z(CI): 204 ($[M\text{-}COC_4H_5]^{+\bullet}$, 4), 149 (100)

Data for the major isomer of **377**:

R_f= 0.59 (20% EtOAc in petrol)

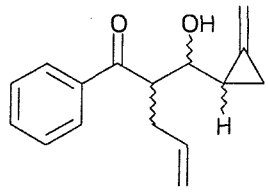
δ_H (300 MHz, $CDCl_3$): 8.04-7.99 (2H, m, 2× aromatic H), 7.71 (1H, t with fine splitting, *J* 7 Hz, aromatic H), 7.50 (2H, t, *J* 7 Hz, 2× aromatic H), 5.81 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.43 (2H, dd, *J* 2, 15 Hz, C=CH_2), 5.08 (1H, dd, *J* 1, 17 Hz, CH=C$H_A$$H_B$), 4.95 (1H, d with fine splitting, *J* 10 Hz, CH=$CH_A$$H_B$), 4.09-3.88 (4H, m, OCH_2CH_2O), 3.50 (1H, dd, *J*, 4, 8 Hz, C*H*OH), 2.68-2.57 (3H, m, CH_2CH=CH_2 and OH), 2.02 (1H, m, C*H*CH_2CH=CH_2), 1.80 (1H, m, cyclopropyl CH), 1.35 (1H, tt, *J* 2, 7 Hz, cyclopropyl C$H_A$$H_B$), 1.10 (1H, m, cyclopropyl $CH_A$$H_B$).

δ_C (75 MHz, $CDCl_3$): 140.72, 140.02 (1), 134.48, 128.48 (1 ×2), 127.99 (1), 126.28 (1 ×2), 114.12 (2), 113.20, 104.08 (2), 74.33 (1), 64.72 (2), 64.51 (2), 50.69 (1), 28.27 (2), 19.45 (1), 8.13 (2).

ν_{max}: 3557, 3070, 2975, 2893, 1638, 1446, 1314, 1178, 1024, 904, 774, 758.

m/z(CI): 204 ($[M\text{-}COC_4H_5]^{+\bullet}$, 4), 149 (100)

(±)-2-(Hydroxy(2-methylidenecyclopropyl)methyl)-1-phenylpent-4-en-1-one 378 and 379:



Following a method by Crimmins[137]

Ketal **376** (290 mg, 1.02 mmol) and 1M HCl (0.5 mL, 1.02 mmol) were stirred in wet acetone (5 mL) for 3 days. The reaction was quenched with aq. $NaHCO_3$. The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude compound was purified by column chromatography (Et_2O in petrol, 0-15%) to give ketone **378** as a colourless oil (214 mg, 87% yield, 8:1 ratio of isomers).

R_f= 0.72 (20% EtOAc in petrol)

δ_H (400 MHz, $CDCl_3$): 8.00-7.96 (2H, m, 2× aromatic H), 7.58 (1H, t, *J* 7 Hz, aromatic H), 7.48 (2H, t, *J* 7 Hz, 2× aromatic H), 5.79 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.50 (1H, d, *J* 2 Hz, C=C$H_A$$H_B$), 5.42 (1H, s, C=C$H_A$$H_B$), 5.02 (1H, dd, *J* 1, 17 Hz, CH=C$H_A$$H_B$), 4.95 (1H, d, *J* 17 Hz, CH=C$H_A$$H_B$), 3.82 (1H, dt, *J*, 5, 8 Hz, COCH), 3.54 (1H, t, *J*, 7 Hz, C*H*OH), 2.70-2.64 (2H, m, CH_2CH=CH_2), 1.70 (1H, m, cyclopropyl CH), 1.19 (1H, dt, *J* 2, 9 Hz, cyclopropyl C$H_A$$H_B$), 1.00 (1H, m, cyclopropyl C$H_A$$H_B$).

δ_C (100 MHz, $CDCl_3$): 203.44, 138.17, 136.05 (1), 133.67 (1), 133.16, 129.09 (1 ×2), 128.87 (1 ×2), 117.36 (2), 104.96 (2), 75.33 (1), 51.94 (1), 33.41 (2), 20.24 (2), 9.25 (1).

ν_{max}: 3434, 3070, 2977, 1674, 1446, 1357, 1237, 1023, 892, 792, 770.

m/z(CI): 161 ($[M\text{-}COC_4H_5+H]^+$, 100).

HRMS (EI): requires 242.1307 ($M^{+\bullet}$), found 242.1299.

Ketal **377** (320 mg, 1.12 mmol) and 1M HCl (0.56 mL, 0.112 mmol) were stirred in wet acetone (5 mL) for 3 days. The reaction was quenched with aq. $NaHCO_3$. The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude compound was purified by column chromatography (Et_2O in petrol, 0-15%) to give ketone **379** as a colourless oil (246 mg, 92% yield, 8:1 ratio of isomers).

R_f= 0.58 (20% EtOAc in petrol)

δ_H (300 MHz, $CDCl_3$): 8.02-7.96 (2H, m, 2× aromatic H), 7.71 (1H, t with fine splitting, *J* 7 Hz, aromatic H), 7.50 (2H, t, *J* 7 Hz, 2× aromatic H), 5.81 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.43 (2H, dd, *J* 2, 15 Hz, C=CH_2), 5.08 (1H, dd, *J* 1, 17 Hz, CH=C$H_A$$H_B$), 4.95 (1H, d with fine splitting, *J* 11 Hz, CH=C$H_A$$H_B$), 3.82 (1H, m, COCH), 3.50 (1H, dd, *J*, 4, 8 Hz, C*H*OH), 2.68-2.57 (3H, m, CH_2CH=CH_2 and OH), 1.80 (1H, m, cyclopropyl CH), 1.35 (1H, tt, *J* 2, 7 Hz, cyclopropyl C$H_A$$H_B$), 1.10 (1H, m, cyclopropyl C$H_A$$H_B$).

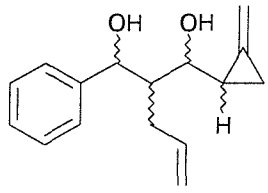
δ_C (75 MHz, $CDCl_3$): 203.47, 137.31, 135.99 (1), 133.61 (1), 132.31, 128.89 (1 ×2), 128.72 (1 ×2), 117.09 (2), 104.94 (2), 74.65 (1), 51.07 (1), 32.31 (2), 20.18 (1), 8.51 (2).

ν_{max}: 3451, 3070, 2977, 1673, 1446, 1237, 1021, 893, 796, 759.

m/z(CI): 161 ([M-COC_4H_5+H]$^+$, 100).

HRMS (EI): requires 242.1307 ($M^{+\bullet}$), found 242.1299.

(±)-2-Allyl-1-(2-methylidenecyclopropyl)-3-phenylpropane-1,3-diol 387:



From the cyclisation of **378** isolated as a 3:1 ratio of isomers:

R_f= 0.38 (20% EtOAc in petrol)

δ_H (300 MHz, $CDCl_3$): 7.44-7.21 (5H, m, 5× aromatic H), 5.73 (1H, m, C*H*=CH_2), 5.58 (1H, m, C=C$H_A$$CH_B$), 5.46 (1H, m, C=C$H_ACH_B$), 5.14-4.92 (2H, m, CH=CH_2,), 3.48-3.37 (2H, m, 2× C*H*OH), 3.04 (1H, br s, OH), 2.52 (2H, m, CH_2CH=CH_2), 2.07 (1H, m, C*H*CHOH) 1.88 (1H, m, cyclopropyl CH), 1.30 (1H, m, cyclopropyl C$H_A$$H_B$), 0.98 (1H, m, cyclopropyl C$H_A$$H_B$).

δ_C (75 MHz, $CDCl_3$): 143.23, 139.36 (1), 133.70, 128.43 (1 ×2), 127.35 (1), 126.00 (1 ×2), 115.38 (2), 104.38 (2), 78.58 (1), 76.95 (1), 49.96 (1), 27.48 (2), 20.37 (1), 7.98 (2).

ν_{max}: 3329, 3068, 2903, 1450, 1197, 1021, 906, 893, 763, 736.

m/z(CI): 227 ([M-H_2O+H]$^+$, 7). 161 (24), 139 (26), 105 (100).

HRMS (EI): requires 226.1358 ([M-H_2O]$^{+\bullet}$), found 226.1349.

From the cyclisation of **379** isolated as a 3:1 ratio of isomers:

R_f= 0.38 (20% EtOAc in petrol)

δ_H (300 MHz, $CDCl_3$): 7.42-7.26 (5H, m, 5× aromatic H), 5.74 (1H, m, C*H*=CH_2), 5.51-5.34 (2H, m, C=CH_2), 5.03-4.82 (2H, m, C=CH_2), 3.38-3.47 (2H, m, 2× C*H*OH), 3.11 (1H, br s, OH), 2.53-2.27 (2H, m, CH_2CH=CH_2), 1.9 (1H, m, C*H*CHOH), 1.87 (1H, m, cyclopropyl CH), 1.38 (1H, m, cyclopropyl CH_AH_B), 1.06 (1H, m, cyclopropyl CH_AH_B).

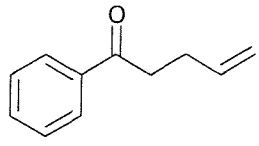
δ_C (75 MHz, $CDCl_3$): 143.06, 139.46 (1), 132.53, 128.41 (1 ×2), 127.32 (1), 125.94 (1 ×2), 115.37 (2), 104.55 (2), 79.01 (1), 77.19 (1), 50.51 (1), 27.06 (2), 20.94 (1), 9.12 (2).

ν_{max}: 3334, 3068, 2904, 1446, 1192, 1023, 908, 890, 757, 729.

m/z(CI): 227 ($[M-H_2O+H]^+$, 7). 161 (24), 139 (26), 105 (100).

HRMS (EI): requires 226.1358 ($[M-H_2O]^{+\bullet}$), found 226.1349.

1-Phenylpent-4-en-1-one 388:



R_f= 0.87 (20% EtOAc in petrol)

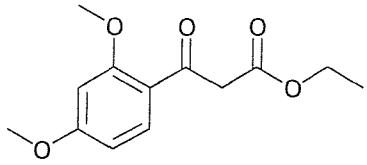
δ_H (300 MHz, $CDCl_3$): 8.02-7.93 (2H, m, 2× aromatic H), 7.56 (1H, t, *J* 7 Hz, aromatic H), 7.48 (2H, t, *J* 7 Hz, 2× aromatic H), 5.93 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.08 (1H, dd, *J* 1, 17 Hz, CH=C$H_A$$H_B$), 5.03 (1H, dd, *J* 1, 10 Hz, CH=CH_AH_B), 3.10 (2H, t, *J* 7 Hz, CH_2CO), 2.52 (2H, q, *J* 7 Hz, CH_2CH=CH_2).

δ_C (75 MHz, $CDCl_3$): 199.63, 137.46 (1), 137.07, 133.19 (1), 128.76 (1 ×2), 128.19 (1 ×2), 115.46 (2), 37.90 (2), 28.30 (2).

ν_{max}: 3067, 2920, 1684, 1597, 1448, 1360, 1206, 999, 970, 912, 743.

Data agreed with those reported by Thomas.[138]

Ethyl 3-(2,4-dimethoxyphenyl)-3-oxopropanoate 396:



Following a modified method by McPherson.[139]

2',4'-Dimethoxyacetophenone (1 g, 5.55 mmol) was added to a stirred solution of NaH (60% in oil, 222 mg, 5.55 mmol) in THF (30 mL) at 0°C under nitrogen and stirred for 30 minutes. Diethyl carbonate (1.35 mL, 11.1 mmol) was added dropwise at 0 °C. The solution was heated to reflux and stirred for 36 hours. The reaction was quenched with NH_4Cl (aq) and the aqueous layer was extracted (Et_2O, 3×50 mL) .The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (Et_2O in petrol, 0-30%) to give keto-ester **396** as a colourless oil (1.34 g, 96% yield).

R_f= 0.20 (20% EtOAc in petrol)

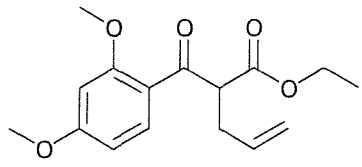
δ_H (400 MHz, $CDCl_3$): 7.95 (1H, d, *J* 9 Hz, aromatic H), 6.57 (1H, dd, *J* 2, 9 Hz, aromatic H), 6.44 (1H, d, *J* 2 Hz, aromatic H), 4.19 (2H, q, *J* 7 Hz, OCH_2), 3.93 (2H, s, $COCH_2CO$), 3.89-3.83, (6H, s, $(OCH_3)_2$), 1.25 (3H, t, *J* 7 Hz).

δ_C (100 MHz, $CDCl_3$): 191.37, 168.72, 165.41, 161.26, 133.44 (1), 119.64, 105.76 (1), 98.23 (1), 60.99 (2), 55.75 (3), 55.44 (3), 50.79 (2), 14.32 (3).

ν_{max}: 3086, 2987, 2943, 2841, 1734, 1660, 1596, 1572, 1459, 1419, 1324, 1267, 1206, 1126, 1021, 831.

Data agreed with those reported by McPherson.[139]

(±)-Ethyl 2-(2,4-dimethoxybenzoyl)pent-4-enoate 397:



Based on a method published by Chadha.[127]

Ethyl 3-(2,4-dimethoxyphenyl)-3-oxopropanoate **396** (0.5 g, 1.98 mmol) was added to a stirred solution of NaH (60% in oil, 0.82 g, 1.98 mmol) in THF (10 mL) at 0°C under nitrogen and stirred for 30 minutes. Allyl Bromide (0.43 mL, 4.95 mmol) was added dropwise at 0°C. The solution was allowed to reach room temperature overnight. The reaction was quenched with aq. NH_4Cl and the aqueous layer was extracted (Et_2O, 3×50 mL) .The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (EtOAc in petrol 0-30%) to give keto-ester **397** as a colourless oil (359 mg, 62% yield).

R_f= 12 (20% EtOAc in petrol)

δ_H (400 MHz, $CDCl_3$): 7.88 (1H, d, *J* 9 Hz, aromatic H), 6.56 (1H, dd, *J* 2, 9 Hz, aromatic H), 6.44 57 (1H, d, *J* 2 Hz, aromatic H), 5.86 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.08 (1H, dd, *J* 2, 17 Hz, C$H_A$$H_B$=$CH_2$), 4.92 (1H, d, *J* 10 Hz, CH_AH_B=CH_2), 4.15 (2H, q, *J* 7 Hz, OCH_2), 3.89-3.80, (7H, s, 2×OCH_3 and COCHCO), 2.74-2.65 (2H, m, CH_2CH=CH_2) 1.20 (3H, t, *J* 7 Hz).

δ_C (100 MHz, $CDCl_3$): 194.29, 170.85, 165.32, 160.93, 136.09 (1), 133.89 (1), 120.41, 116.90 (2), 105.99 (1), 98.59 (1), 61.19 (2), 58.36 (1), 55.97 (3), 55.61 (3), 33.35 (2), 14.54 (3).

ν_{max}: 3076, 2978, 2841, 1734, 1656, 1599, 1577, 1459, 1252, 1212, 119, 1025, 915, 834.

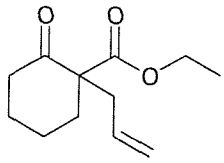
m/z(CI): 293 ($[M+H]^+$, 73), 221 ($[M-CO_2Et+H]^+$, 22), 181 ($[M-CO_2Et-allyl+H]^+$, 13), 35 (100).

HRMS (EI): requires 292.1311 ($M^{+\bullet}$), found 292.1311.

$C_{16}H_{20}O_5$, calculated: C: 65.74; H: 6.90; O: 27.36; found C: 65.82; H: 6.94; O: 27.24.

6.6) *EXPERIMENTAL FOR CHAPTER FIVE*

(±)-Ethyl 1-allyl-2-oxocyclohexane-1-carboxylate 403:



Based on a method published by Chadha.[127]

Ethyl 2-oxocyclohexane-1-carboxylate (12 g, 70 mmol) was added to a stirred solution of NaH (60% in oil, 2.8 g, 70 mmol) in THF (120 mL) at 0°C under nitrogen and stirred for 30 minutes. Allyl Bromide (7.6 mL, 87.5 mmol) was added dropwise at 0°C. The solution was heated to reflux and stirred for 36 hours. The reaction was quenched with aq. NH_4Cl and the aqueous layer was extracted with Et_2O (3×50 mL) .The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (Et_2O in petrol, 0-15%) to give keto-ester **403** as a colourless oil (14.72 g, 100% yield).

R_f= 0.43 (20% EtOAc in petrol)

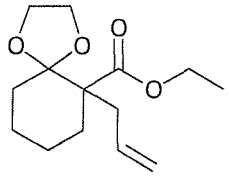
δ_H (400 MHz, $CDCl_3$): 5.86 (1H, m, C*H*=CH_2), 4.98-4.87 (2H, m, CH=CH_2), 4.09 (2H, q, *J* 7 Hz, OCH_2), 2.52 (1H, dd, *J* 7, 12 Hz, C$H_A$$H_B$CH=$CH_2$), 2.42-2.31 (3H, m, CH_2C and C$H_A$$H_B$CO), 2.24 (1H, dd, *J* 7, 12 Hz, $CH_A$$H_B$CH=$CH_2$), 1.91 (1H, m, $CH_A$$H_B$CO), 1.71-1.47 (3H, m, C$H_2$$CH_2$CO and C$H_A$$H_B$$(CH_2)_2$CO), 1.38 (1H, m, $CH_A$$H_B$$(CH_2)_2$CO), 1.16 (3H, t, *J* 7 Hz, CH_3).

δ_C (100 MHz, $CDCl_3$): 207.84, 171.85, 133.74 (1), 118.60 (2), 61.58 (2), 61.25, 41.50 (2), 39.69 (2), 36.15 (2), 27.90 (2), 22.85 (2), 11.79 (3).

ν_{max}: 3077, 2939, 2866, 1710, 1438, 1198, 915.

Data agreed with those reported by Koga.[140]

(±)-Ethyl 6-allyl-1,4-dioxaspiro[4.5]decane-6-carboxylate 404:



Ethyl 1-allyl-2-oxocyclohexane-1-carboxylate **403** (14 g, 66.6 mmol), *p*-toluene sulfonic acid (2.5 g, 13.32 mmol) and excess ethylene glycol were refluxed in toluene (100 mL) overnight, using a Dean-Stark apparatus. The reaction mixture was concentrated *in vacuo*. Et_2O (80 mL) was added, the solution was washed with aq. $NaHCO_3$ (50 mL), the aqueous layer was extracted with Et_2O (3×50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (Et_2O in petrol, 0-20%) to give ketal **404** as a colourless oil (16.48 g, 97% yield).

R_f= 0.45 (20% EtOAc in petrol)

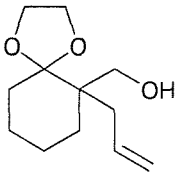
δ_H (400 MHz, $CDCl_3$): 5.64 (1H, m, CH=CH_2), 5.08-4.97 (2H, m, CH=CH_2), 3.96-3.88 (2H, m, OCH_2), 4.19-4.10 (4H, m OCH_2CH_2O), 2.81 (1H, dd, *J* 6, 14 Hz, CH_AH_BCH=CH_2), 2.34 (1H, dd, *J* 8, 14 Hz, CH_AH_BCH=CH_2), 2.01 (1H, ddd, *J* 4, 9, 14 Hz, cyclohexyl CH_AH_B), 1.76-1.34 (7H, m, cyclohexyl CH_AH_B and cyclohexyl $(CH_2)_3$), 1.26 (3H, t, *J* 7 Hz, OCH_2CH_3).

δ_C (100 MHz, $CDCl_3$): 173.56, 134.21 (1), 117.51 (2), 110.82, 64.89 (2), 64.62 (2), 60.37 (2), 54.47, 36.12 (2), 32.19 (2), 30.16 (2), 23.17 (2), 20.79 (2), 14.30 (3)

ν_{max}: 3076, 2977, 2937, 2866, 1722, 1444, 1288, 1212, 1045, 958.

Data agreed with those reported by Koga.[140]

(±)-(6-Allyl-1,4-dioxaspiro[4.5]dec-6-yl)-methanol 405:



Based on a method published by Albizati.[98]

Ketal-ester **404** (4.24 g, 16.67 mmol) was slowly added to a stirred suspension of $LiAlH_4$ (1.26 g, 33.34 mmol) in THF (50 mL) at 0°C under nitrogen. The solution was allowed to stir and reach room temperature over 2 hours. The reaction was quenched after 3 hours by adding 4M NaOH dropwise until the residual solid had turned completely white. The mixture was then filtered and washed thoroughly with Et_2O (250 mL). The combined organic layers were concentrated *in vacuo*. The crude compound was purified by column chromatography (Et_2O in petrol, 0-20%) to give alcohol **405** as a colourless oil (2.87 g, 81% yield).

R_f= 0.47 (20% EtOAc in petrol)

δ_H (300 MHz, $CDCl_3$): 5.87 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.10-4.99 (2H, m, CH=C*H*$_2$), 4.08-3.97 (4H, m, OCH_2CH_2O), 3.80 (1H, d, *J* 12 Hz, C*H*$_A$H$_B$OH), 3.42 (1H, d, *J* 12 Hz, CH$_A$*H*$_B$OH), 2.79 (1H, br s, OH), 2.44 (1H, dd, *J* 7, 13 Hz, C*H*$_A$H$_B$CH=CH_2), 2.23 (1H, dd, *J* 8, 13 Hz, CH$_A$*H*$_B$CH=CH_2), 1.77-1.42 (8H, m, cyclohexyl $(CH_2)_4$).

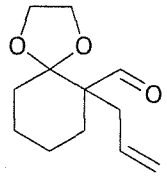
δ_C (75 MHz, $CDCl_3$): 134.52 (1), 117.96 (2), 113.87, 65.39 (2), 64.74 (2), 64.31 (2), 44.68, 34.42 (2), 30.41 (2), 29.76 (2), 23.46 (2), 20.34 (2).

ν_{max}: 3535, 3072, 2932, 2886, 2865, 1446, 1172, 1085, 1022, 948, 911.

m/z(EI): 212 ($M^{+\bullet}$, 7), 99 (100).

HRMS (EI): requires 212.1412 ($M^{+\bullet}$), found 212.1414.

(±)-6-Allyl-1,4-dioxaspiro[4.5]decane-6-carbaldehyde 406:



Based on a method published by Swern.[99]

Oxalyl chloride (1.36 mL, 15.55 mmol) in DCM (10 mL) was cooled to -78°C and stirred. DMSO (2.29 mL, 32.38 mmol) in DCM (5 mL) was added dropwise keeping the temperature between -50°C and -60°C. The reaction mixture was stirred for 2 minutes. Alcohol **405** (2.75 g, 12.95 mmol) in DCM (15 mL) was added dropwise over 5 minutes at -78°C and stirred for 15 minutes. Triethylamine (9.03 mL, 64.75 mmol) was added and the reaction was allowed to reach room temperature overnight. The reaction was quenched with

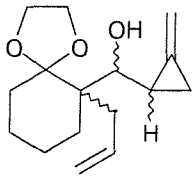
water (50 mL). The aqueous layer was extracted with DCM (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude compound **406** was obtained as a colourless oil (2.72 g, 100% yield) and used directly in the next step.

R_f= 0.74 (20% EtOAc in petrol)

ν_{max}: 3072, 2933, 2865, 1719, 1604, 1446, 1173, 1085, 1040, 948, 913, 878.

m/z(CI): 211 ($[M+H]^+$, 47), 182 ($[M+H-CO]^+$, 18), 99 (100)

(±)-(6-Allyl-1,4-dioxaspiro[4.5]dec-6-yl)-(2-methylidenecyclopropyl)-methanol 407 and 408:



^{n}BuLi (2.4M in hexanes, 13.4 mL, 32.1 mmol) was added to a stirred solution of methylenecyclopropane (2.2 mL, 32.1 mmol) in THF (100 mL) at -78°C under argon. The solution was warmed to 0°C over 1 hour and stirred for 30 minutes. It was then allowed to reach room temperature over 30 minutes and stirred for 15 minutes. The reaction mixture was then cooled to -78°C. Aldehyde **406** (4.5 g, 21.4 mmol) in THF (25mL) was cooled to -78°C and added to the mixture and the solution was allowed to reach room temperature overnight. The reaction was quenched with aq. NH_4Cl (50 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude compound was purified by column chromatography (Et_2O in petrol, 0-20%) to give the alcohol as one major diastereoisomer **407** (2.71 g, 48% yield) contaminated with a minor diastereoisomer (ratio 1.5:1) and a second major diastereoisomer **408** (1.81 g, 32% yield) also contaminated with a minor diastereoisomer (ratio 3:1).

Data for the major isomer of **407**:

R_f= 0.63 (20% EtOAc in petrol)

δ_H (400 MHz, $CDCl_3$): 6.12 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.62 (1H, s, C=C$H_A$$H_B$), 5.47 (1H, s, C=C$H_A$$H_B$), 5.11 (1H, d, *J* 17 Hz, CH=C$H_A$$H_B$), 5.03 (1H, d, *J* 10 Hz, CH=C$H_A$$H_B$), 4.07-3.97 (4H, m, OCH_2CH_2O), 3.74 (1H, s, OH), 3.63 (1H, d, *J* 8 Hz,

C*H*OH), 2.66 (1H, dd, *J* 8, 15 Hz, CH_AH$_B$CH=CH$_2$), 2.46 (1H, dd, *J* 7, 15 Hz, CH$_A$$H_B$CH=CH$_2$), 1.89-1.77 (2H, m, cyclopropyl CH and cyclohexyl CH_AH$_B$) 1.74-1.45 (6H, m, cyclohexyl (CH$_2$)$_3$), 1.32 (1H, m, cyclopropyl CH_AH$_B$), 1.23 (1H, m, cyclohexyl CH$_A$$H_B$), 1.08 (1H, m, cyclopropyl CH$_A$$H_B$).

δ_C (100 MHz, $CDCl_3$): 136.42 (1), 133.39, 115.85 (2), 113.86, 103.79 (2), 76.51 (1), 64.25 (2), 63.85 (2), 47.67, 33.35 (2), 30.65 (2), 29.71 (2), 22.91 (2), 20.45 (2), 17.02 (1), 8.97 (2).

ν_{max}: 3505, 3071, 2974, 2935, 2866, 1449, 1172, 1117, 1083, 1016, 948, 883.

m/z(CI): 265 ([M+H]$^+$, 7), 247 ([M+H-H_2O]$^+$, 21), 183 (100).

HRMS (EI): requires 264.1725 ($M^{+\bullet}$), found 264.1714.

Data for the major isomer of **408**:

R_f= 0.51 (20% EtOAc in petrol)

δ_H (400 MHz, $CDCl_3$): 6.07 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH$_2$), 5.43 (1H, s, C=CH_AH$_B$), 5.32 (1H, s, C=CH$_A$$H_B$), 5.13-4.97 (2H, m, CH=CH$_2$), 4.06-3.91 (4H, m, OCH$_2$CH$_2$O), 3.51 (1H, d, *J* 10 Hz, C*H*OH), 2.63 (1H, dd, *J* 8, 15 Hz, CH_AH$_B$CH=CH$_2$), 2.43 (1H, dd, *J* 7, 15 Hz, CH$_A$$H_B$CH=CH$_2$), 1.94 (1H, m, cyclopropyl CH), 1.76-1.40 (8H, m, cyclohexyl (CH$_2$)$_4$), 1.31 (1H, m, cyclopropyl CH_A), 1.06 (1H, m, cyclopropyl CH$_A$$H_B$).

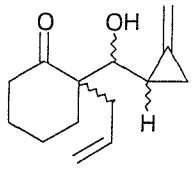
δ_C (100 MHz, $CDCl_3$): 136.53 (1), 134.18, 116.05 (2), 114.08, 104.32 (2), 77.37 (1), 64.50 (2), 63.37 (2), 47.30, 33.50 (2), 30.79 (2), 29.99 (2), 23.04 (2), 20.59 (2), 18.33 (1), 7.80 (2).

ν_{max}: 3497, 3070, 2934, 2866, 1450, 1172, 1172, 1083, 1016, 948, 884.

m/z(CI): 265 ([M+H]$^+$, 7), 247 ([M+H-H_2O]$^+$, 21), 183 (100).

HRMS (EI): requires 264.1725 ($M^{+\bullet}$), found 264.1714.

(±)-2-Allyl-2-(hydroxy(2-methylidenecyclopropyl)methyl)-cyclohexan-1-one 409 and 410:



Following a method by Crimmins[137]

Ketal **407** (500 mg, 1.89 mmol) and 1M HCl (0.95 mL, 1.89 mmol) were stirred in wet acetone (10 mL) for 3 days. The reaction was quenched with aq. $NaHCO_3$. The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude compound was purified by column chromatography (Et_2O in petrol, 0-10%) to give ketone **409** as a colourless oil (399 mg, 96% yield, 1.5:1 ratio of isomers).

R_f= 0.60 (20% EtOAc in petrol)

Data for the major isomer:

δ_H (400 MHz, $CDCl_3$): 5.86 (1H, m, C*H*=CH_2), 5.58-5.51 (2H, m, C=CH_2), 5.15-5.02 (2H, m, CH=C*H*$_2$), 3.70 (1H, d, *J* 6 Hz, C*H*OH), 2.64 (1H, dd, *J* 7, 14 Hz, C*H*$_A$H$_B$CH=CH_2), 2.52-2.27 (3H, m, CH_AH_BCH=CH_2 and cyclohexyl CH_2), 1.98- 1.69 (7H, m, cyclohexyl $(CH_2)_3$ and cyclopropyl CH), 1.32 (1H, m, cyclopropyl C*H*$_A$H$_B$), 1.10 (1H, m, cyclopropyl CH_AH_B).

δ_C (100 MHz, $CDCl_3$): 215.52, 134.58 (1), 132.65, 118.00 (2), 105.30 (2), 76.08 (1), 56.81, 40.26 (2), 37.01 (2), 33.18 (2), 26.66 (2), 21.08 (2), 17.29 (1), 8.54 (2).

ν_{max}: 3449, 3072, 2937, 2865, 1691, 1452, 1438, 1312, 1218, 1124, 1020, 904, 890.

m/z(CI): 156 ($[M\text{-}C_4H_5CO+NH_4]^+$, 48), 139 ($[M\text{-}C_4H_5CO+H]^+$, 100).

Ketal **408** (400 mg, 1.51 mmol) and 1M HCl (0.75 mL, 1.51 mmol) were stirred in wet acetone (10 mL) for 3 days. The reaction was quenched with aq. $NaHCO_3$. The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude compound was purified by column chromatography (Et_2O in petrol, 0-15%) to give ketone **410** as a yellowish crystalline solid (286 mg, 86% yield, 3:1 ratio of isomers).

R_f= 0.55 (20% EtOAc in petrol)

m.p.= 50-52°C

Data for the major isomer:

δ_H (400 MHz, $CDCl_3$): 5.95 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.45 (1H, d, *J* 2Hz, C=C$H_A$$H_B$), 5.35 (1H, d, *J* 2Hz, C=C$H_A$$H_B$), 5.16-5.04 (2H, m, CH=CH_2), 3.35 (1H, d, *J* 9 Hz, C*H*OH), 2.88 (1H, br s, OH), 2.65 (1H, dd, *J* 7, 14 Hz, C$H_A$$H_B$CH=$CH_2$), 2.48 (1H, dd, *J* 8, 14 Hz, $CH_A$$H_B$CH=$CH_2$), 2.46-2.34 (2H, m, cyclohexyl CH_2), 1.98-1.85 (2H, m, cyclohexyl CH_2), 1.83-1.71 (5H, m, cyclohexyl $(CH_2)_2$ and cyclopropyl CH), 1.35 (1H, tt, *J* 2, 7 Hz, cyclopropyl C$H_A$$H_B$), 1.10 (1H, m, cyclopropyl $CH_A$$H_B$).

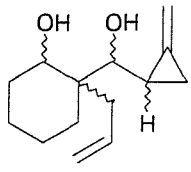
δ_C (100 MHz, $CDCl_3$): 216.66, 135.01 (1), 133.69, 117.95 (2), 104.80 (2), 77.94 (1), 56.36, 40.21 (2), 36.57 (2), 34.14 (2), 26.79 (2), 21.03 (2), 17.94 (1), 7.61 (2).

ν_{max}: 3449, 3072, 2937, 2865, 1691, 1452, 1438, 1312, 1218, 1124, 1020, 904, 890.

m/z(CI): 156 ($[M-C_4H_5CO+NH_4]^+$, 48), 139 ($[M-C_4H_5CO+H]^+$, 100).

$C_{14}H_{20}O_2$, calculated: C, 76.33; H, 9.15; O, 14.52; found C, 76.00; H, 9.17; O, 14.83.

(±)-2-Allyl-2-(hydroxy(2-methylidenecyclopropyl)methyl)-cyclohexan-1-ol 434:



From the cyclisation of **409** isolated as a 2:1 ratio of isomers:

Data for the major isomer:

R_f= 0.24 (20% EtOAc in petrol)

δ_H (300 MHz, $CDCl_3$): 5.80 (1H, m, C*H*=CH_2), 5.46 (1H, s, C=C$H_A$$H_B$), 5.37 (1H, s, C=$CH_A$$H_B$), 5.23-5.02 (2H, m, CH=CH_2), 4.10 (1H, dd, *J* 4, 11 Hz, cyclohexyl C*H*OH), 3.74 (1H, d, *J* 9 Hz, C*H*OH), 3.05 (1H, dd, *J* 9, 17 Hz, C$H_A$$H_B$CH=$CH_2$), 2.87-2.62 (4H, m, $CH_A$$H_B$CH=$CH_2$, cyclohexyl C$H_A$$H_B$ and cyclohexyl CH_2), 2.41-2.29 (1H, m, cyclohexyl $CH_A$$H_B$), 1.96-1.69 (3H, m, cyclohexyl CH_2 and cyclohexyl C$H_A$$H_B$), 1.65-1.22 (4H, m, cyclohexyl CH_2 and cyclopropyl CH_2), 0.99 (1H, m, cyclopropyl CH).

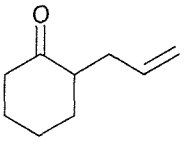
δ_C (75 MHz, $CDCl_3$): 137.26, 134.56 (1), 118.23 (2), 105.12 (2), 85.87 (1), 73.72 (2), 40.43, 29.77 (2 ×2), 29.13 (2), 24.38 (2), 18.48 (1), 7.04 (2).

ν_{max}: 3293, 3073, 2976, 2934, 2862, 1451, 1443, 1351, 1119, 1068, 1007, 901, 883.

m/z(CI): 223 ($[M+H]^+$, 3), 205 ($[M+H-H_2O]^+$, 10), 187 ($[M+H-2H_2O]^+$, 27), 35 (100).

HRMS (CI): requires 205.1592 ($[M+H-H_2O]^+$), found 205.1586.

2-Allylcyclohexan-1-one 428:



R_f= 0.74 (20% EtOAc in petrol)

δ_H (300 MHz, $CDCl_3$): 5.78 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.08-4.93 (2H, m, CH=CH_2), 2.54 (1H, m, C$H_A$$H_B$CH=$CH_2$), 2.41-2.28 (3H, m, CH_AH_BCH=CH_2 and cyclohexyl CH_2), 2.19-1.92 (3H, m, cyclohexyl CH_2 and cyclohexyl CH), 1.90-1.82 (2H, m, cyclohexyl CH_2), 1.44-1.25 (2H, m, cyclohexyl CH_2).

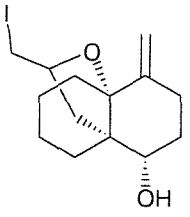
δ_C (75 MHz, $CDCl_3$): 212.69, 136.57 (1), 116.32 (2), 50.35 (1), 42.15 (2), 33.85 (2), 33.47 (2), 28.04 (2), 25.05 (2).

ν_{max}: 3076, 2934, 2861, 1711, 1448, 1250, 1199, 1032, 912, 844.

m/z(CI): 139 ($[M+H]^+$, 20), 39 (100).

Data agreed with those reported by Thomas.[138]

Iodo-tricycle 429 obtained from the cyclisation of 409:



R_f= 0.34 (20% EtOAc in petrol)

δ_H (300 MHz, $CDCl_3$): 5.23 (1H, s, C=C$H_A$$H_B$), 4.85 (1H, s, C=$CH_AH_B$), 4.39 (1H, dtt, *J* 15, 9, 6 Hz, C*H*CH_2I), 3.92 (1H, dd, *J* 5, 11 Hz, C*H*OH), 3.39 (1H, dd, *J* 6, 9 Hz, C$H_A$$H_B$I), 3.13 (1H, t, *J* 11 Hz, CH_AH_BI), 2.24 (1H, m, C$H_A$$H_B$C=$CH_2$), 2.08 (1H, m, CH_AH_BC=CH_2), 1.95 (1H, m, cyclohexyl C$H_A$$H_B$), 1.86 (1H, m, C$H_A$$H_B$CHOH), 1.81 (1H, dd, *J* 7, 12 Hz,

cyclopentyl C*H*$_A$H$_B$), 1.64 (1H, dd, *J* 7, 16 Hz, cyclopentyl CH$_A$*H*$_B$), 1.57 (1H, m, CH$_A$*H*$_B$CHOH), 1.53-1.40 (4H, m, cyclohexyl (CH$_2$)$_2$), 1.39-1.16 (3H, m, cyclohexyl C*H*$_A$H$_B$ and cyclohexyl CH$_2$).

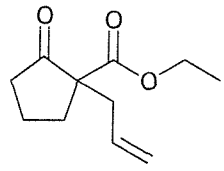
δ_C (100 MHz, $CDCl_3$): 152.46, 110.40 (2), 86.11, 78.27 (1), 69.60 (1), 50.29, 39.47 (2), 33.85 (2), 31.42 (2), 30.93 (2), 29.41 (2), 21.89 (2), 21.41(2), 12.02 (2).

ν_{max}: 3387,3073, 2932, 2866, 2360, 1638, 1447, 1065, 941, 906.

m/z(Cl): 349 ([M+H]$^+$, 12), 221 (89), 147 (87), 91 (100).

HRMS (EI): requires 348.0586 ($M^{+\bullet}$), found 348.0584.

(±)-Ethyl 1-allyl-2-oxocyclopentane-1-carboxylate 436:



Based on a method published by Chadha.[127]

Ethyl 2-oxocyclopentane-1-carboxylate (7.5 mL, 48.86 mmol) was added to a stirred solution of NaH (60% in oil, 2.3 g, 57.43 mmol) in THF (120 mL) at 0°C under nitrogen and stirred for 30 minutes. Allyl Bromide (5.2 mL, 61.08 mmol) was added dropwise at 0°C. The solution was heated to reflux and stirred for 36 hours. The reaction was quenched with aq. NH_4Cl and the aqueous layer was extracted with Et_2O (3×50 mL) .The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (Et_2O in petrol, 0-20%) to give keto-ester **436** as a colourless oil (8.82 g, 94% yield).

R_f= 0.68 (20% EtOAc in petrol)

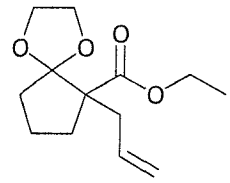
δ_H (300 MHz, $CDCl_3$): 5.70 (1H, m, C*H*=CH$_2$), 5.12 (1H, d, *J* 5 Hz, CH=C*H*$_A$H$_B$), 5.08 (1H, s, CH=CH$_A$*H*$_B$), 4.16 (2H, q, *J* 7 Hz, OCH$_2$), 2.67 (1H, dd, *J* 7, 14 Hz, C*H*$_A$H$_B$CH=CH$_2$), 2.45-2.33 (3H, m, CH$_A$*H*$_B$CH=CH$_2$ and cyclopentyl CH$_2$), 2.24 (1H, m, cyclopentyl C*H*$_A$H$_B$), 2.09-1.84 (3H, m, cyclopentyl CH$_2$ and cyclopentyl CH$_A$*H*$_B$), 1.25 (3H, t, *J* 7 Hz, CH$_3$).

δ_C (75 MHz, $CDCl_3$): 214.84, 171.50, 133.18 (1), 119.23 (2), 61.61 (2), 60.07, 38.25 (2), 37.99 (2), 32.28 (2), 19.67 (2), 14.25 (3).

ν_{max}: 3078, 2978, 1749, 1719, 1447, 1405, 1281, 1222, 1154, 1132, 1028, 1005, 921, 860.

Data agreed with those reported by Hwu.[141]

(±)-Ethyl 6-allyl-1,4-dioxaspiro[4.4]nonane-6-carboxylate 437:



Ethyl 1-allyl-2-oxocyclopentane-1-carboxylate **436** (8.5 g, 43.31 mmol), *p*-toluene sulfonic acid (1.65 g, 8.66 mmol) and excess ethylene glycol were refluxed in toluene (100 mL) overnight, using a Dean-Stark apparatus. The reaction mixture was concentrated *in vacuo*. Et_2O (60 mL) was added, the solution was washed with aq. $NaHCO_3$ (50 mL), the aqueous layer was extracted with Et_2O (3×50 mL). The organic layers were recombined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (Et_2O in petrol, 0-20%) to give ketal **437** as a colourless oil (10.10 g, 97% yield).

R_f= 0.63 (% EtOAc in petrol)

δ_H (400 MHz, $CDCl_3$): 5.67 (1H, m, CH=CH_2), 5.15-4.93 (2H, m, CH=CH_2), 4.18 (2H, q, *J* 7 Hz, OCH_2), 4.07-3.93 (3H, m OCH_2CH_2O and $OCH_2CH_AH_BO$), 3.87 (1H, m, $OCH_2CH_AH_BO$), 2.87 (1H, dd, *J* 6, 14 Hz, CH_AH_BCH=CH_2), 2.42 (1H, m, cyclopentyl CH_AH_B), 2.15 (1H, dd, *J* 8, 14 Hz, CH_AH_BCH=CH_2), 1.92-1.82 (2H, m, cyclopentyl CH_2), 1.80-1.62 (3H, m, cyclopentyl CH_2 and CH_AH_B), 1.29 (3H, t, *J* 7 Hz, OCH_2CH_3).

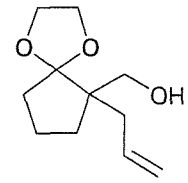
δ_C (100 MHz, $CDCl_3$): 173.83, 134.69 (1),119.17, 118.22 (2), 65.90 (2), 65.14 (2), 60.74 (2), 58.69, 38.38 (2), 36.52 (2), 31.10 (2), 19.68 (2), 14.64 (3).

ν_{max}: 3076, 2976, 2881, 1726, 1438, 1313, 1218, 1033, 949, 916, 828.

m/z(Cl): 241 ($[M+H]^+$, 42), 195 ($[M+H\text{-}OMe]^+$, 73), 167 (43), 99 (100).

HRMS (EI): requires 240.1362 ($M^{+\bullet}$), found 240.1354.

(±)-(6-Allyl-1,4-dioxaspiro[4.4]non-6-yl)-methanol 438:



Based on a method published by Albizati.[98]

Ketal-ester **437** (8 g, 33.3 mmol) was added slowly to a stirred suspension of $LiAlH_4$ (2.53 g, 66.6 mmol) in THF (120 mL) at 0°C under nitrogen. The solution was allowed to stir and reach room temperature over 2 hours. The reaction was quenched after 3 hours by adding 4M NaOH dropwise until the residual solid had turned completely white. The mixture was then filtered and washed thoroughly with Et_2O (150 mL). The combined organic layers were concentrated *in vacuo*. The crude compound was purified by column chromatography (Et_2O in petrol, 0-30%) to give alcohol **438** as a colourless oil (6.07 g, 93% yield).

R_f= 0.47 (20% EtOAc in petrol)

δ_H (300 MHz, $CDCl_3$): 5.82 (1H, m, C*H*=CH_2), 5.15-5.02 (2H, m, CH=C*H*$_2$), 4.03-3.89 (4H, m, OCH_2CH_2O), 3.62 (1H, d, *J* 12 Hz, C*H*$_A$H$_B$OH), 3.45 (1H, d, *J* 12 Hz, CH$_A$*H*$_B$OH), 2.76 (1H, br s, OH), 2.32 (1H, dd, *J* 7, 14 Hz, C*H*$_A$H$_B$CH=CH_2), 2.13 (1H, dd, *J* 8, 14 Hz, CH$_A$*H*$_B$CH=CH_2), 1.95-1.72 (3H, m, cyclopentyl C*H*$_A$H$_B$ and CH_2), 1.69-1.59 (3H, m, cyclopentyl CH$_A$*H*$_B$ and CH_2).

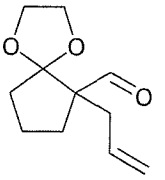
δ_C (75 MHz, $CDCl_3$): 135.46 (1), 120.44, 117.57 (2), 65.82 (1), 64.77 (2), 64.43 (2), 49.65, 35.48 (2), 34.55 (2), 30.38 (2), 19.05 (2).

ν_{max}: 3495, 3073, 2953, 2879, 1637, 1438, 1331, 1211, 1131, 1033, 913, 822.

m/z(CI): 199 ($[M+H]^+$, 21), 169 ($[M+H-H_2O]^+$, 23), 99 (100).

HRMS (EI): requires 198.1256 ($M^{+\bullet}$), found 198.1259.

(±)-6-Allyl-1,4-dioxaspiro[4.4]nonane-6-carbaldehyde 439:



Based on a method published by Swern.[99]

Oxalyl chloride (1.58 mL, 18.16 mmol) in DCM (10 mL) was cooled to -78°C and stirred. DMSO (2.69 mL, 37.83 mmol) in DCM (5 mL) was added dropwise keeping the temperature between -50°C and -60°C. The reaction mixture was stirred for 2 minutes. Alcohol **438** (3 g, 15.13 mmol) in DCM (15 mL) was added dropwise over 5 minutes at -78°C and stirred for 15 minutes. Triethylamine (10.54 mL, 75.65 mmol) was added and the reaction was allowed to reach room temperature overnight. The reaction was quenched with water. The aqueous layer was extracted with DCM (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude compound was purified by column chromatography (Et_2O in petrol, 0-10%) to give aldehyde **439** as a colourless oil (2.76 g, 93% yield).

R_f= 0.74 (20% EtOAc in petrol)

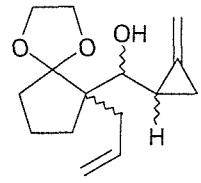
δ_H (400 MHz, $CDCl_3$): 9.62 (1H, s, CHO), 5.62 (1H, ddt, *J* 17, 10, 7 Hz, CH=CH_2), 5.13-5.03 (2H, m, CH=CH_2), 4.03-3.85 (4H, m, OCH_2CH_2O), 2.71 (1H, dd, *J* 7, 14 Hz, CH_AH_BCH=CH_2), 2.13 (1H, dd, *J* 8, 14 Hz, CH_AH_BCH=CH_2), 1.86-1.60 (6H, m, cyclopentyl $(CH_2)_3$).

δ_C (100 MHz, $CDCl_3$): 204.13, 134.14 (1), 119.37, 118.42 (2), 65.36 (2), 65.24 (2), 60.96, 36.02 (2), 35.20 (2), 28.36 (2), 19.80 (2).

ν_{max}: 3071, 2947, 2885, 1708, 1639, 1313, 1166, 1072, 1032, 921, 886, 827.

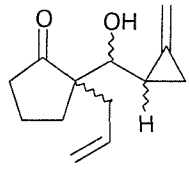
m/z(CI): 197 ($[M+H]^+$, 24), 139 ($[M+H-OCH_2CH_2O]^+$, 5), 99 (100).

(±)-(6-Allyl-1,4-dioxaspiro[4.4]non-6-yl)(2-methylidenecyclopropyl)-methanol 440:



^{n}BuLi (2.4M in hexanes, 13.4 mL, 32.1 mmol) was added to a stirred solution of methylenecyclopropane (2.2 mL, 32.1 mmol) in THF (100 mL) at -78°C under argon. The solution was warmed to 0°C over 1 hour and stirred for 30 minutes. It was then allowed to reach room temperature over 30 minutes and stirred for 15 minutes. The reaction mixture was then cooled to -78°C. Aldehyde **439** (4.5 g, 21.4 mmol) in THF (25mL) was cooled to -78°C and added to the mixture and the solution was allowed to reach room temperature overnight. The reaction was quenched with aq. NH_4Cl (50 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude compound was used directly in the next step.

(±)-2-Allyl-2-(hydroxy(2-methylidenecyclopropyl)methyl)-cyclopentan-1-one 441 and 442:



Following a method by Crimmins.[137]

Ketal **440** (600 mg, 2.40 mmol) and 1M HCl (1.2 mL, 2.40 mmol) were stirred in wet acetone (10 mL) for 3 days. The reaction was quenched with aq. $NaHCO_3$. The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude compound was purified by column chromatography (Et_2O in petrol, 0-10%) to give the ketone as one major diastereoisomer **441** (188 mg, 38% yield) contaminated with a minor diastereoisomer (ratio 3:1) and a second major diastereoisomer **442** (287 mg, 58% yield) also contaminated with a minor diastereoisomer (ratio 8:1).

Data for the major isomer of **441**:

R_f= 0.40 (20% EtOAc in petrol)

δ_H (400 MHz, $CDCl_3$): 5.67 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.47 (1H, d, *J* 2 Hz, C=C$H_A$$H_B$), 5.41 (1H, d, *J* 2 Hz, C=C$H_A$$H_B$), 5.07-4.99 (2H, m, CH=CH_2), 3.22 (1H, d, *J* 8 Hz, C*H*OH), 2.44 (1H, dd, *J* 7, 14 Hz, C$H_A$$H_B$CH=$CH_2$), 2.31-2.08 (3H, m, cyclopentyl CH_2 and $CH_A$$H_B$CH=$CH_2$), 1.97-1.75 (4H, m, cyclopentyl $(CH_2)_2$), 1.70 (1H, m, cyclopropyl CH), 1.24 (1H, m, cyclopropyl C$H_A$$H_B$), 0.97 (1H, m, cyclopropyl $CH_A$$H_B$).

δ_C (100 MHz, $CDCl_3$)*: 134.37 (1), 132.90, 119.01 (2), 105.10 (2), 77.90 (1), 56.66, 40.06(2), 38.62 (2), 30.71 (2), 19.71 (2), 18.05 (2), 9.21 (1).

ν_{max}: 3441, 3074, 2961, 2879, 1720, 1638, 1404, 1271, 1163, 999, 885.

m/z(CI): 125 ([M-C_4H_5CO+NH_4]$^+$, 63), 96 (25), 35 (100).

HRMS (EI): requires 206.1307 ($M^{+\bullet}$) found 206.1314.

Data for the major isomer of **442**:

R_f= 0.30 (20% EtOAc in petrol)

δ_H (400 MHz, $CDCl_3$): 5.60 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.31 (1H, d, *J* 2 Hz, C=C$H_A$$H_B$), 5.23 (1H, d, *J* 2 Hz, C=C$H_A$$H_B$), 5.01-4.89 (2H, m, CH=CH_2), 2.97 (1H, d, *J* 9 Hz, C*H*OH), 2.65 (1H, br s, OH), 2.42 (1H, dd, *J* 7, 14 Hz, C$H_A$$H_B$CH=$CH_2$), 2.22-2.10 (4H, m, cyclopentyl CH_2, cyclopentyl C$H_A$$H_B$ and $CH_A$$H_B$CH=$CH_2$), 2.02-1.64 (4H, m, cyclopentyl CH_2, cyclopentyl C$H_A$$H_B$ and cyclopropyl CH), 1.19 (1H, m, cyclopropyl C$H_A$$H_B$), 0.91 (1H, m, cyclopropyl $CH_A$$H_B$).

δ_C (100 MHz, $CDCl_3$)*: 134.42 (1), 132.97, 119.06 (2), 105.39 (2), 77.87 (1), 55.92, 39.83 (2), 37.63 (2), 31.31 (2), 19.64 (2), 18.73 (2), 8.03 (1).

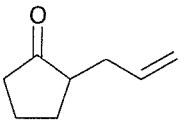
ν_{max}: 3441, 30.74, 2961, 2879, 1720, 1638, 1404, 1271, 1163, 999, 885.

m/z(CI): 125 ([M-C_4H_5CO+NH_4]$^+$, 63), 96 (25), 35 (100).

$C_{15}H_{22}O_2$, calculated: C, 75.69; H, 8.79; O, 15.52; found C, 75.68; H, 8.94; O, 15.38.

(*): The signal for the quaternary carbonyl carbon could not be observed at 300 and 400 MHz (512 scans) nor at 400 MHz with extended scans (1024 scans).

2-Allylcyclopentan-1-one 448:



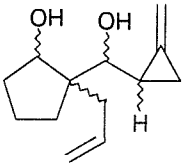
R_f= 0.78 (20% EtOAc in petrol)

δ_H (300 MHz, $CDCl_3$): 5.77 (1H, ddt, *J* 17, 10, 7 Hz, C*H*=CH_2), 5.11-4.99 (2H, m, CH=CH_2), 2.52 (1H, m, C$H_A$$H_B$CH=$CH_2$), 2.33 (1H, m, $CH_A$$H_B$CH=$CH_2$), 2.25-1.96 (4H, m, cyclohexyl CH_2 and cyclohexyl C$H_A$$H_B$ and COCH), 1.79 (1H, m, cyclohexyl C$H_A$$H_B$), 1.62-1.54 (2H, m, cyclohexyl CH_2).

δ_C (75 MHz, $CDCl_3$): 221.12, 136.09 (1), 116.58 (2), 48.78 (1), 38.37 (2), 34.05 (2), 29.14 (2), 20.82 (2).

All data agreed with those reported by Hiaro[142]

(±)-2-Allyl-2-(hydroxy(2-methylidenecyclopropyl)methyl)-cyclopentan-1-ol 449:



From the cyclisation of **441** isolated as a 2:1 ratio of isomers:

R_f= 0.2 (20% EtOAc in petrol)

δ_H (300 MHz, $CDCl_3$): 6.13 (1H, m, C*H*=CH_2), 5.60-5.47 (2H, m, C=CH_2), 5.21-5.03 (2H, m, CH=CH_2), 4.16 (1H, t, *J* 8 Hz, cyclopentyl C*H*OH), 3.16 (1H, d, *J* 7 Hz, C*H*OH), 2.45 (1H, dd, *J* 7, 14 Hz, C$H_A$$H_B$CH=$CH_2$), 2.38-2.25 (1H, m, $CH_A$$H_B$CH=$CH_2$), 1.93-1.22 (8H, m, cyclopentyl $(CH_2)_2$ and cyclopropyl CH_2), 1.03 (1H, m, cyclopropyl CH).

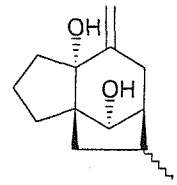
δ_C (75 MHz, $CDCl_3$): 137.21 (1), 135.64, 117.10 (2), 104.86 (2), 83.09 (1), 81.05 (1), 46.72, 33.18 (2), 31.77 (2), 21.70 (2), 19.64 (2), 18.82 (1), 8.57 (2),

ν_{max}: 3372, 3072, 2954, 2874, 1637, 1438, 1079, 1020, 910, 889.

m/z(EI): 208 ($M^{+\bullet}$, 9), 190 ($[M-H_2O]^{+\bullet}$, 24), 41 (100).

HRMS (EI): requires 190.1358 ($[M-H_2O+H]^+$), found 190.1357.

(±)-(1*R*,5*R*,8*S*,9*R*,11*S*)-9-Methyl-6-methylidenetricyclo[6.2.1.$0^{1,5}$] undecane-5,11-diol 447:



From the cyclisation of **442**:

R_f= 0.20 (20% EtOAc in petrol)

δ_H (300 MHz, $CDCl_3$): 5.34 (1H, s, C=C*H*$_A$H$_B$), 4.91 (1H, s, C=CH$_A$*H*$_B$), 3.64 (1H, s, C*H*OH), 2.29 (1H, dd, *J* 2, 15 Hz, CH_2=CC*H*$_A$H$_B$), 2.21 (1H, dd, *J* 4, 15 Hz, CH_2=CCH$_A$*H*$_B$), 1.82-1.65 (9H, m, C*H*CHOH, C*H*CH_3, C*H*$_A$H$_B$CHCH_3 and cyclopentyl $(CH_2)_3$), 1.31 (1H, m, CH$_A$*H*$_B$CHCH_3), 1.03 (3H, d, *J* 6 Hz, CH_3).

δ_C (75 MHz, $CDCl_3$): 150.19, 133.73 (2), 84.27, 81.03 (1), 63.66, 48.74 (1), 38.65 (2), 37.66 (2), 34.78 (2), 34.47 (1), 26.55 (2), 23.80 (3), 21.00 (2).

ν_{max}: 3463, 2926, 2870, 1726, 1598, 1458, 1266, 1212, 1026, 997, 904, 734.

m/z(EI): 208 ($M^{+\bullet}$, 9), 191 ([M-H_2O+H]$^+$, 100), 173 ([M-2H_2O+H]$^+$, 59).

HRMS (EI): requires 208.1467 ($M^{+\bullet}$), found 208.1463.

APPENDIX A

X-Ray Crystal Structure Data for 305

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) A**46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Table 1. Crystal data and structure refinement.

Identification code	**00sot130**	
Empirical formula	$C_{11}H_{18}O_2$	
Formula weight	182.25	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 6.8216(14) Å	α = 90°
	b = 18.934(4) Å	β = 107.76(3)°
	c = 8.1610(16) Å	γ = 90°
Volume	1003.9(3) Å^3	
Z	4	
Density (calculated)	1.206 Mg / m^3	
Absorption coefficient	0.081 mm^{-1}	
F(000)	400	
Crystal	Needle; colourless	
Crystal size	0.40 × 0.05 × 0.05 mm^3	
θ range for data collection	3.32 – 27.50°	
Index ranges	$-8 \le h \le 8$, $-23 \le k \le 24$, $-9 \le l \le 10$	
Reflections collected	7926	
Independent reflections	2262 [R_{int} = 0.0584]	
Completeness to θ = 27.50°	97.8 %	
Absorption correction	Semi–empirical from equivalents	

Max. and min. transmission	0.9960 and 0.9684
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2262 / 0 / 123
Goodness-of-fit on F^2	0.991
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0461, $wR2$ = 0.1031
R indices (all data)	$R1$ = 0.0903, $wR2$ = 0.1225
Extinction coefficient	0.011(4)
Largest diff. peak and hole	0.258 and -0.204 e Å^{-3}

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.*
C1	9978(2)	956(1)	11015(2)	35(1)	1
C2	8479(2)	1397(1)	9650(2)	26(1)	1
C3	6694(2)	1693(1)	10178(2)	27(1)	1
C4	6481(2)	1612(1)	11724(2)	36(1)	1
C5	5074(2)	2056(1)	8740(2)	30(1)	1
C6	4411(2)	1589(1)	7132(2)	28(1)	1
C7	6261(2)	1441(1)	6509(2)	27(1)	1
C8	7577(2)	978(1)	7964(2)	26(1)	1
C9	5944(2)	441(1)	8111(2)	31(1)	1
C10	3852(2)	841(1)	7559(2)	30(1)	1
C11	2270(2)	486(1)	6052(2)	44(1)	1
O1	9715(1)	1975(1)	9332(1)	32(1)	1
O2	7341(2)	2046(1)	6192(1)	32(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–C2	1.513(2)
C2–O1	1.4523(17)
C2–C3	1.517(2)
C2–C8	1.544(2)
C3–C4	1.322(2)
C3–C5	1.510(2)
C5–C6	1.531(2)
C6–C7	1.523(2)
C6–C10	1.534(2)
C7–O2	1.4277(17)
C7–C8	1.527(2)
C8–C9	1.540(2)
C9–C10	1.556(2)
C10–C11	1.523(2)
O1–C2–C1	104.41(11)

O1–C2–C3	109.41(12)
C1–C2–C3	114.51(12)
O1–C2–C8	108.87(11)
C1–C2–C8	111.64(13)
C3–C2–C8	107.85(11)
C4–C3–C5	121.79(14)
C4–C3–C2	124.03(14)
C5–C3–C2	114.06(12)
C3–C5–C6	111.02(13)
C7–C6–C5	109.51(11)
C7–C6–C10	101.22(12)
C5–C6–C10	111.52(12)
O2–C7–C6	116.03(13)
O2–C7–C8	112.82(11)
C6–C7–C8	101.33(12)
C7–C8–C9	99.91(11)
C7–C8–C2	112.22(12)
C9–C8–C2	111.78(12)
C8–C9–C10	106.09(12)
C11–C10–C6	112.84(13)
C11–C10–C9	112.37(13)
C6–C10–C9	104.20(11)

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	33(1)	39(1)	32(1)	4(1)	7(1)	8(1)
C2	26(1)	26(1)	26(1)	3(1)	8(1)	0(1)
C3	31(1)	23(1)	27(1)	−5(1)	10(1)	1(1)
C4	40(1)	39(1)	30(1)	−3(1)	13(1)	3(1)
C5	29(1)	31(1)	32(1)	3(1)	11(1)	7(1)
C6	24(1)	33(1)	25(1)	3(1)	6(1)	2(1)
C7	27(1)	31(1)	24(1)	0(1)	9(1)	−5(1)
C8	28(1)	26(1)	27(1)	0(1)	12(1)	3(1)
C9	37(1)	26(1)	31(1)	−2(1)	13(1)	−2(1)
C10	30(1)	34(1)	28(1)	1(1)	11(1)	−6(1)
C11	40(1)	51(1)	38(1)	−1(1)	9(1)	−16(1)
O1	28(1)	35(1)	30(1)	4(1)	5(1)	−5(1)
O2	28(1)	35(1)	33(1)	10(1)	9(1)	−3(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.*
H1A	11082	787	10578	53	1
H1B	9253	551	11306	53	1
H1C	10568	1244	12046	53	1
H4A	5283	1784	11953	43	1
H4B	7526	1382	12605	43	1

H5A	5628	2507	8458	36	1
H5B	3862	2163	9123	36	1
H6	3260	1810	6207	33	1
H7	5799	1152	5434	33	1
H8	8694	739	7614	31	1
H9A	6260	268	9309	37	1
H9B	5902	32	7346	37	1
H10	3297	864	8559	36	1
H11A	979	753	5755	65	1
H11B	2022	3	6373	65	1
H11C	2790	473	5058	65	1
H1	9133	2150	8359	48	1
H2	6493	2363	5725	48	1

APPENDIX B

X-Ray Crystal Structure Data for 410

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) A**46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Table 1. Crystal data and structure refinement.

Identification code	**01sot129**	
Empirical formula	$C_{14}H_{20}O_2$	
Formula weight	220.30	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P*–1	
Unit cell dimensions	a = 12.0395(2) Å	α = 109.0460(10)°
	b = 14.1768(2) Å	β = 114.8230(10)°
	c = 14.2627(3) Å	γ = 101.4950(10)°
Volume	1921.38(6) Å^3	
Z	6	
Density (calculated)	1.142 Mg / m^3	
Absorption coefficient	0.074 mm^{-1}	
F(000)	720	
Crystal	Block; colourless	
Crystal size	0.36 × 0.28 × 0.26 mm^3	
θ range for data collection	2.94 – 27.50°	
Index ranges	$-15 \le h \le 15$, $-18 \le k \le 18$, $-18 \le l \le 18$	
Reflections collected	31170	
Independent reflections	8708 [R_{int} = 0.0608]	
Completeness to θ = 27.50°	98.5 %	
Absorption correction	Semi–empirical from equivalents	

Max. and min. transmission	0.9809 and 0.9737
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8708 / 0 / 437
Goodness-of-fit on F^2	1.026
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0433, $wR2$ = 0.1091
R indices (all data)	$R1$ = 0.0585, $wR2$ = 0.1181
Extinction coefficient	0.0009(19)
Largest diff. peak and hole	0.307 and –0.195 e Å^{-3}

Special details:

3 Molecules in the asymmetric unit.

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	9700(1)	5075(1)	3385(1)	30(1)	1
C2	8434(1)	5105(1)	3342(1)	35(1)	1
C3	8669(1)	6228(1)	4190(1)	35(1)	1
C4	9292(1)	7101(1)	3957(1)	32(1)	1
C5	10594(1)	7077(1)	4047(1)	30(1)	1
C6	10465(1)	5965(1)	3245(1)	28(1)	1
C7	11856(1)	5977(1)	3531(1)	33(1)	1
C8	12785(1)	6190(1)	4748(1)	39(1)	1
C9	13946(1)	7012(1)	5482(1)	49(1)	1
C10	9605(1)	5694(1)	1942(1)	27(1)	1
C11	10229(1)	6380(1)	1542(1)	31(1)	1
C12	9284(1)	6425(1)	430(1)	35(1)	1
C13	10022(1)	7377(1)	1573(1)	35(1)	1
C14	10305(2)	8400(1)	2174(1)	53(1)	1
C15	4306(1)	6243(1)	645(1)	30(1)	1
C16	5082(1)	6801(1)	246(1)	35(1)	1
C17	6578(1)	7310(1)	1146(1)	35(1)	1
C18	6861(1)	8080(1)	2330(1)	32(1)	1
C19	6112(1)	7481(1)	2736(1)	30(1)	1
C20	4591(1)	6908(1)	1875(1)	28(1)	1
C21	3951(1)	6181(1)	2263(1)	32(1)	1
C22	4454(1)	5309(1)	2366(1)	38(1)	1
C23	4991(2)	5206(1)	3319(1)	47(1)	1
C24	3972(1)	7764(1)	1788(1)	27(1)	1
C25	4106(1)	8515(1)	2901(1)	30(1)	1
C26	3914(1)	9574(1)	2961(1)	36(1)	1
C27	5211(1)	9585(1)	3682(1)	33(1)	1
C28	6478(1)	10166(1)	4467(1)	43(1)	1
O1	10088(1)	4375(1)	3533(1)	37(1)	1
O2	9326(1)	4575(1)	1288(1)	34(1)	1
O3	3498(1)	5312(1)	22(1)	37(1)	1
O4	2593(1)	7162(1)	890(1)	32(1)	1
C29	3007(1)	8838(1)	–693(1)	29(1)	1

C30	3203(1)	8250(1)	−1667(1)	34(1)	1
C31	3107(1)	8826(1)	−2424(1)	36(1)	1
C32	1801(1)	8979(1)	−2878(1)	33(1)	1
C33	1659(1)	9616(1)	−1868(1)	31(1)	1
C34	1768(1)	9112(1)	−1039(1)	28(1)	1
C35	1819(1)	9899(1)	42(1)	31(1)	1
C36	3018(1)	10955(1)	807(1)	36(1)	1
C37	2992(2)	11911(1)	918(1)	41(1)	1
C38	574(1)	8006(1)	−1682(1)	28(1)	1
C39	−762(1)	8072(1)	−2008(1)	33(1)	1
C40	−2004(1)	7020(1)	−2960(1)	39(1)	1
C41	−1671(1)	7954(1)	−3162(1)	40(1)	1
C42	−1999(2)	8371(1)	−3882(2)	60(1)	1
O5	3791(1)	9072(1)	311(1)	36(1)	1
O6	879(1)	7510(1)	−925(1)	35(1)	1

Table 3. Bond lengths [Å] and angles [°].

		C15–O3	1.2147(15)
C1–O1	1.2187(15)	C15–C16	1.5058(18)
C1–C2	1.5090(17)	C15–C20	1.5389(16)
C1–C6	1.5286(17)	C16–C17	1.5326(18)
C2–C3	1.5340(18)	C16–H16A	0.9900
C2–H2A	0.9900	C16–H16B	0.9900
C2–H2B	0.9900	C17–C18	1.5251(18)
C3–C4	1.5205(19)	C17–H17A	0.9900
C3–H3A	0.9900	C17–H17B	0.9900
C3–H3B	0.9900	C18–C19	1.5251(18)
C4–C5	1.5258(16)	C18–H18A	0.9900
C4–H4A	0.9900	C18–H18B	0.9900
C4–H4B	0.9900	C19–C20	1.5455(16)
C5–C6	1.5467(16)	C19–H19A	0.9900
C5–H5A	0.9900	C19–H19B	0.9900
C5–H5B	0.9900	C20–C21	1.5409(17)
C6–C7	1.5439(16)	C20–C24	1.5579(16)
C6–C10	1.5600(16)	C21–C22	1.5042(17)
C7–C8	1.4998(18)	C21–H21A	0.9900
C7–H7A	0.9900	C21–H21B	0.9900
C7–H7B	0.9900	C22–C23	1.310(2)
C8–C9	1.317(2)	C22–H22	0.9500
C8–H8	0.9500	C23–H23A	0.9500
C9–H9A	0.9500	C23–H23B	0.9500
C9–H9B	0.9500	C24–O4	1.4358(13)
C10–O2	1.4352(14)	C24–C25	1.5140(16)
C10–C11	1.5053(17)	C24–H24	1.0000
C10–H10	1.0000	C25–C27	1.4697(17)
C11–C13	1.4730(18)	C25–C26	1.5446(17)
C11–C12	1.5479(17)	C25–H25	1.0000
C11–H11	1.0000	C26–C27	1.4592(18)
C12–C13	1.4625(18)	C26–H26A	0.9900
C12–H12A	0.9900	C26–H26B	0.9900
C12–H12B	0.9900	C27–C28	1.3117(19)
C13–C14	1.3044(19)	C28–H28A	0.9500
C14–H14A	0.9500	C28–H28B	0.9500
C14–H14B	0.9500	O2–H2	0.8400

O4–H4	0.8400
C29–O5	1.2175(15)
C29–C30	1.5088(17)
C29–C34	1.5353(16)
C30–C31	1.5352(19)
C30–H30A	0.9900
C30–H30B	0.9900
C31–C32	1.5196(18)
C31–H31A	0.9900
C31–H31B	0.9900
C32–C33	1.5299(17)
C32–H32A	0.9900
C32–H32B	0.9900
C33–C34	1.5429(17)
C33–H33A	0.9900
C33–H33B	0.9900
C34–C35	1.5488(16)
C34–C38	1.5570(16)
C35–C36	1.5050(17)
C35–H35A	0.9900
C35–H35B	0.9900
C36–C37	1.3197(19)
C36–H36	0.9500
C37–H37A	0.9500
C37–H37B	0.9500
C38–O6	1.4348(15)
C38–C39	1.5081(17)
C38–H38	1.0000
C39–C41	1.4720(18)
C39–C40	1.5453(17)
C39–H39	1.0000
C40–C41	1.459(2)
C40–H40A	0.9900
C40–H40B	0.9900
C41–C42	1.308(2)
C42–H42A	0.9500
C42–H42B	0.9500
O6–H6	0.8400

O1–C1–C2	121.05(12)
O1–C1–C6	122.25(11)
C2–C1–C6	116.70(10)
C1–C2–C3	111.26(10)
C1–C2–H2A	109.4
C3–C2–H2A	109.4
C1–C2–H2B	109.4
C3–C2–H2B	109.4
H2A–C2–H2B	108.0
C4–C3–C2	110.47(10)
C4–C3–H3A	109.6
C2–C3–H3A	109.6
C4–C3–H3B	109.6
C2–C3–H3B	109.6
H3A–C3–H3B	108.1
C3–C4–C5	110.99(10)
C3–C4–H4A	109.4
C5–C4–H4A	109.4
C3–C4–H4B	109.4
C5–C4–H4B	109.4
H4A–C4–H4B	108.0
C4–C5–C6	114.24(10)
C4–C5–H5A	108.7
C6–C5–H5A	108.7
C4–C5–H5B	108.7
C6–C5–H5B	108.7
H5A–C5–H5B	107.6
C1–C6–C7	111.70(10)
C1–C6–C5	109.20(10)
C7–C6–C5	110.11(9)
C1–C6–C10	105.49(9)
C7–C6–C10	109.96(9)
C5–C6–C10	110.29(9)
C8–C7–C6	116.15(10)
C8–C7–H7A	108.3
C6–C7–H7A	108.2
C8–C7–H7B	108.2
C6–C7–H7B	108.3
H7A–C7–H7B	107.4
C9–C8–C7	124.41(15)
C9–C8–H8	117.8
C7–C8–H8	117.8
C8–C9–H9A	120.0
C8–C9–H9B	120.0
H9A–C9–H9B	120.0
O2–C10–C11	110.20(9)
O2–C10–C6	105.28(9)
C11–C10–C6	115.82(10)
O2–C10–H10	108.4
C11–C10–H10	108.4
C6–C10–H10	108.4
C13–C11–C10	121.95(10)
C13–C11–C12	57.85(8)
C10–C11–C12	117.22(10)
C13–C11–H11	115.7
C10–C11–H11	115.7
C12–C11–H11	115.7
C13–C12–C11	58.51(8)
C13–C12–H12A	117.9
C11–C12–H12A	117.9
C13–C12–H12B	117.9
C11–C12–H12B	117.9
H12A–C12–H12B	115.1
C14–C13–C12	147.36(13)
C14–C13–C11	148.97(13)
C12–C13–C11	63.64(9)
C13–C14–H14A	120.0
C13–C14–H14B	120.0
H14A–C14–H14B	120.0
O3–C15–C16	121.24(11)
O3–C15–C20	121.93(11)
C16–C15–C20	116.83(10)
C15–C16–C17	111.18(10)
C15–C16–H16A	109.4

C17–C16–H16A	109.4	C25–C26–H26B	117.9
C15–C16–H16B	109.4	H26A–C26–H26B	115.1
C17–C16–H16B	109.4	C28–C27–C26	147.21(13)
H16A–C16–H16B	108.0	C28–C27–C25	149.13(13)
C18–C17–C16	110.33(10)	C26–C27–C25	63.65(9)
C18–C17–H17A	109.6	C27–C28–H28A	120.0
C16–C17–H17A	109.6	C27–C28–H28B	120.0
C18–C17–H17B	109.6	H28A–C28–H28B	120.0
C16–C17–H17B	109.6	C10–O2–H2	109.5
H17A–C17–H17B	108.1	C24–O4–H4	109.5
C19–C18–C17	110.51(10)	O5–C29–C30	121.22(11)
C19–C18–H18A	109.5	O5–C29–C34	122.24(11)
C17–C18–H18A	109.5	C30–C29–C34	116.54(10)
C19–C18–H18B	109.5	C29–C30–C31	111.50(10)
C17–C18–H18B	109.5	C29–C30–H30A	109.3
H18A–C18–H18B	108.1	C31–C30–H30A	109.3
C18–C19–C20	114.24(10)	C29–C30–H30B	109.3
C18–C19–H19A	108.7	C31–C30–H30B	109.3
C20–C19–H19A	108.7	H30A–C30–H30B	108.0
C18–C19–H19B	108.7	C32–C31–C30	110.65(10)
C20–C19–H19B	108.7	C32–C31–H31A	109.5
H19A–C19–H19B	107.6	C30–C31–H31A	109.5
C15–C20–C21	111.23(10)	C32–C31–H31B	109.5
C15–C20–C19	109.18(9)	C30–C31–H31B	109.5
C21–C20–C19	110.40(10)	H31A–C31–H31B	108.1
C15–C20–C24	105.42(9)	C31–C32–C33	110.55(10)
C21–C20–C24	110.42(9)	C31–C32–H32A	109.5
C19–C20–C24	110.07(9)	C33–C32–H32A	109.5
C22–C21–C20	115.65(10)	C31–C32–H32B	109.5
C22–C21–H21A	108.4	C33–C32–H32B	109.5
C20–C21–H21A	108.4	H32A–C32–H32B	108.1
C22–C21–H21B	108.4	C32–C33–C34	114.47(10)
C20–C21–H21B	108.4	C32–C33–H33A	108.6
H21A–C21–H21B	107.4	C34–C33–H33A	108.6
C23–C22–C21	124.68(13)	C32–C33–H33B	108.6
C23–C22–H22	117.7	C34–C33–H33B	108.6
C21–C22–H22	117.7	H33A–C33–H33B	107.6
C22–C23–H23A	120.0	C29–C34–C33	109.20(10)
C22–C23–H23B	120.0	C29–C34–C35	111.49(9)
H23A–C23–H23B	120.0	C33–C34–C35	110.23(9)
O4–C24–C25	110.18(9)	C29–C34–C38	105.10(9)
O4–C24–C20	106.08(9)	C33–C34–C38	110.47(10)
C25–C24–C20	115.48(10)	C35–C34–C38	110.25(10)
O4–C24–H24	108.3	C36–C35–C34	115.07(10)
C25–C24–H24	108.3	C36–C35–H35A	108.5
C20–C24–H24	108.3	C34–C35–H35A	108.5
C27–C25–C24	120.58(11)	C36–C35–H35B	108.5
C27–C25–C26	57.84(8)	C34–C35–H35B	108.5
C24–C25–C26	116.38(10)	H35A–C35–H35B	107.5
C27–C25–H25	116.4	C37–C36–C35	124.81(13)
C24–C25–H25	116.4	C37–C36–H36	117.6
C26–C25–H25	116.4	C35–C36–H36	117.6
C27–C26–C25	58.51(8)	C36–C37–H37A	120.0
C27–C26–H26A	117.9	C36–C37–H37B	120.0
C25–C26–H26A	117.9	H37A–C37–H37B	120.0
C27–C26–H26B	117.9	O6–C38–C39	109.72(10)

O6–C38–C34	106.50(9)	C40–C39–H39	115.8
C39–C38–C34	115.36(10)	C41–C40–C39	58.60(9)
O6–C38–H38	108.4	C41–C40–H40A	117.9
C39–C38–H38	108.4	C39–C40–H40A	117.9
C34–C38–H38	108.4	C41–C40–H40B	117.9
C41–C39–C38	122.01(11)	C39–C40–H40B	117.9
C41–C39–C40	57.76(9)	H40A–C40–H40B	115.1
C38–C39–C40	116.84(10)	C42–C41–C40	147.08(14)
C41–C39–H39	115.8	C42–C41–C39	149.26(14)
C38–C39–H39	115.8		
C40–C41–C39	63.64(9)		
C41–C42–H42A	120.0		
C41–C42–H42B	120.0		
H42A–C42–H42B	120.0		
C38–O6–H6	109.5		

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)	27(1)	22(1)	7(1)	12(1)	10(1)
C2	33(1)	34(1)	34(1)	16(1)	18(1)	10(1)
C3	34(1)	41(1)	34(1)	17(1)	20(1)	18(1)
C4	34(1)	32(1)	28(1)	11(1)	14(1)	16(1)
C5	29(1)	27(1)	26(1)	8(1)	11(1)	9(1)
C6	27(1)	26(1)	25(1)	8(1)	12(1)	10(1)
C7	31(1)	35(1)	31(1)	13(1)	16(1)	14(1)
C8	36(1)	45(1)	34(1)	16(1)	17(1)	21(1)
C9	39(1)	52(1)	37(1)	11(1)	10(1)	21(1)
C10	28(1)	24(1)	25(1)	8(1)	12(1)	9(1)
C11	30(1)	32(1)	30(1)	14(1)	16(1)	12(1)
C12	37(1)	37(1)	33(1)	18(1)	19(1)	14(1)
C13	30(1)	34(1)	39(1)	19(1)	16(1)	10(1)
C14	56(1)	33(1)	49(1)	18(1)	13(1)	14(1)
C15	28(1)	29(1)	30(1)	12(1)	14(1)	14(1)
C16	41(1)	34(1)	32(1)	14(1)	22(1)	17(1)
C17	38(1)	34(1)	45(1)	20(1)	27(1)	16(1)
C18	28(1)	30(1)	36(1)	15(1)	15(1)	10(1)
C19	29(1)	30(1)	30(1)	14(1)	13(1)	12(1)
C20	28(1)	25(1)	28(1)	11(1)	14(1)	9(1)
C21	33(1)	31(1)	35(1)	16(1)	20(1)	12(1)
C22	39(1)	32(1)	48(1)	21(1)	26(1)	15(1)
C23	48(1)	43(1)	58(1)	31(1)	26(1)	20(1)
C24	26(1)	25(1)	26(1)	10(1)	12(1)	8(1)
C25	31(1)	28(1)	29(1)	11(1)	16(1)	11(1)
C26	40(1)	31(1)	34(1)	11(1)	19(1)	16(1)
C27	39(1)	29(1)	27(1)	9(1)	17(1)	11(1)
C28	40(1)	33(1)	36(1)	7(1)	13(1)	7(1)
O1	46(1)	31(1)	35(1)	15(1)	21(1)	18(1)
O2	40(1)	25(1)	25(1)	7(1)	11(1)	12(1)
O3	34(1)	30(1)	35(1)	7(1)	15(1)	9(1)
O4	27(1)	28(1)	29(1)	10(1)	8(1)	10(1)
C29	29(1)	24(1)	32(1)	13(1)	15(1)	7(1)
C30	32(1)	33(1)	36(1)	12(1)	18(1)	15(1)

C31	35(1)	38(1)	30(1)	10(1)	19(1)	11(1)
C32	36(1)	29(1)	26(1)	10(1)	16(1)	9(1)
C33	35(1)	25(1)	30(1)	12(1)	17(1)	11(1)
C34	30(1)	25(1)	26(1)	10(1)	14(1)	10(1)
C35	35(1)	28(1)	28(1)	10(1)	17(1)	11(1)
C36	37(1)	32(1)	30(1)	6(1)	18(1)	9(1)
C37	50(1)	31(1)	37(1)	9(1)	26(1)	9(1)
C38	30(1)	26(1)	27(1)	11(1)	14(1)	11(1)
C39	30(1)	29(1)	31(1)	8(1)	16(1)	11(1)
C40	30(1)	34(1)	38(1)	8(1)	14(1)	8(1)
C41	32(1)	35(1)	37(1)	9(1)	11(1)	15(1)
C42	54(1)	48(1)	48(1)	22(1)	5(1)	18(1)
O5	34(1)	35(1)	32(1)	15(1)	13(1)	12(1)
O6	38(1)	26(1)	31(1)	13(1)	13(1)	7(1)

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...It's not quite what we expected, but it's an interesting result anyway.