UNIVERSITY OF SOUTHAMPTON

Samarium Diiodide Mediated Radical Cyclisations of α, β-Unsaturated Carbonyl Compounds.

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Doctor of Philosophy

FACULTY OF ENGINEERING, SCIENCE & MATHEMATICS
SCHOOL OF CHEMISTRY

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ABSTRACT

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This thesis is concerned with the synthesis, and samarium diiodide mediated radical cyclisations of α,β-unsaturated carbonyl compounds. Particular interest is directed at the development of a range of cyclic α,β-unsaturated carbonyl systems which have been designed as mechanistic probes to elucidate the nature of the key dimerisation step in the cascade sequence towards polycyclic products.

Chapter 1 presents an overview of radical chemistry, including history and key principles. A discussion on samarium diiodide chemistry is also provided, which focuses on key mechanistic aspects and the reactivity of α,β-unsaturated carbonyl compounds with the reagent. A programme of work is also discussed.

Chapter 2 describes the design and synthesis of a range of cyclic α,β-unsaturated carbonyl systems, and their uses as mechanistic probes for testing the intermediacy of radical species **253** and **254** and anionic species **255**.

Chapter 3 depicts the development of a variety of acyclic α,β-unsaturated carbonyl systems, and their reactivity upon exposure to samarium diiodide.

Dedicated to my Great Grandmother
Elsie Adelaide Lloyd
1904-1997

Contents

Preface

The research described in this thesis was carried out under the supervision of Professor Jeremy Kilburn at the University of Southampton between October 2004 and November 2007. No part of this thesis has been previously submitted at this or any other University.

Acknowledgements

First and foremost I would like to thank Professor Jeremy Kilburn for his continual support and advice during my time with the group. I would also like to thank my advisor Dr Bruno Linclau for his help and taking such a big interest in this project.

I would like to take this opportunity to thank Joan Street and Dr Neil Wells for the NMR service. Thank you to Dr John Langley and Julie Herniman for the excellent mass spectrometry service and for providing me with help and advice whenever I needed it. A big thank you goes out to Dr Mark Light and Graham Tizzard for the crystal structures. I must also thank Karl Hagon and his team of workers for providing a great service from stores. Thank you to the glass blowers for continually fixing my never ending list of breakages, without you I don't think I would have been able to do half as much research.

A huge thank you to Allison, Sarah, Luke, Francesca, Jon, Suad, Sara, Oscar, Jean-Mathieu and the many other past and present members of the Kilburn Empire, you all made the tough times easier to bear, and the good times even better. In particular, a big thanks to Allison, Sarah, and Jon for welcoming me into the group when I first started and taking the time to show me the ropes. Also, a big warm hearted thank you to my main man in the lab Luke aka MC P, one day we'll make it big, MC P and DJ SmI on the decks of effect....'put your hands up, it's a robbery!' I am also indebted to my special team of proof readers; Allison, Sarah, Sally and Jeremy. I must also say a special thank you to Jason for his important contribution to the work in chapter three.

I wish to dedicate a paragraph to a group of people who I'm lucky enough to have met during my time at Southampton, and thank them all for everything they have done for me; Will, Iain, Louise, Helen and Paul I will never forget the great times we all had during the last few years.

I also want to express my gratitude to my family for all their constant love and support; Mum, Helen, Dad, Ita, Deborah and William, thank you so much for everything you've done, you know how much I appreciate it.

Finally I would like to say a big thank you to Allison; I truly appreciate the encouragement and support you have given to me over the last three years – thank you.

Abbreviations

Ac	acetyl
AIBN	2, 2'-azobisisobutyronitrile
aq.	aqueous
ax	axial
Boc	*tert*-butyloxycarbonyl
br	broad
BT	benzotriazole
Bu	butyl
°C	degrees centigrade
Cbz	carboxybenzyl
CI	chemical ionisation
d	doublet
DBU	1, 8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DEPT	distortionless enhancement by polarisation transfer
DHP	3, 4 –dihydro-2*H*-pyran
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DMPU	1, 3-dimethyl-3, 4, 5, 6-tetrahydro-2(1*H*)-pyrimidinone
DMA	*N*, *N*-dimethylacetamide
DMAP	dimethylaminopyridine
DMF	*N*, *N*-dimethylformamide
EI	electron ionisation
eq	equatorial
equiv.	equivalent(s)
ES	electrospray
Et	ethyl
ether	diethyl ether
EWG	electron withdrawing group
FMO	frontier molecular orbital
h	hour(s)
HMPA	Hexamethylphosphoramide

HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectroscopy
Hz	Hertz
i	iso
IR	infrared spectroscopy
ISBR	intramolecular samarium Barbier reaction
J	coupling constant
LRMS	low resolution mass spectroscopy
LUMO	lowest unoccupied molecular orbital
M	molar
$[M]^+$	positive molecular ion
m	multiplet, medium
m	*meta*
m-CPBA	*meta*-chloroperoxybenzoic acid
Mpt	melting point
NMR	nuclear magnetic resonance
p	*para*
PCC	pyridinium chlorochromate
petrol	petroleum ether, boiling point in the range 40-60 °C
PG	protecting group
Ph	phenyl
PhH	benzene
ppm	parts per million
ppt	precipitate
Pr	propyl
p-TsOH	*para*-toluene sulfonic acid
q	quartet
qn	quintet
rac	racemic
R_f	retention factor
RT	room temperature
s	singlet, strong
SBR	samarium Barbier reaction
sext	sextet

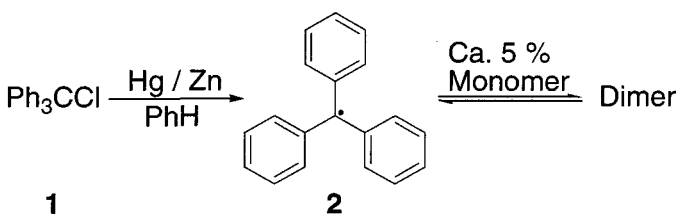
SGR	samarium Grignard reaction
SET	single electron transfer
SOMO	singly occupied molecular orbital
t	triplet
t	*tertiary*
TBAF	tetrabutyl ammonium fluoride
TBS	*tert*-butyldimethylsilyl
Tf	triflate, trifluoromethanesulfonyl
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	toluenesulfonic, toluenesulfonyl
UV	ultraviolet
w	weak

Chapter 1 Introduction

1.1 Free Radicals

1.1.1 History and Background

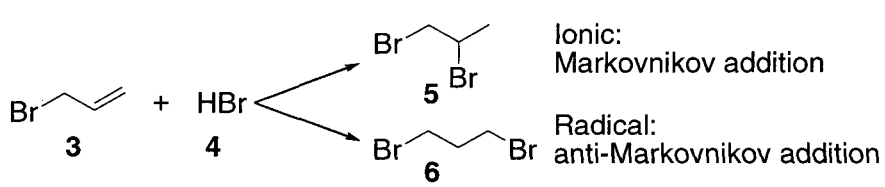
Free radicals can be defined as species with at least one unpaired electron. They are often extremely reactive and react with a wide variety of compounds to form new strong bonds at the expense of weaker ones. Investigations into the chemistry of radicals date back over one hundred years to when Gomberg first declared that he had identified the first trivalent carbon species **2** (**Scheme 1**).[1]



Scheme 1

The scientific community initially reacted with scepticism and disbelief, as it had only been recently accepted that carbon was universally tetravalent. However, Gomberg was indeed correct, and many other examples of triarylmethyl radicals soon followed. Despite this key discovery, it was over thirty years before radicals were considered as key intermediates in a solution state.[2]

Organic synthesis with radicals began with Hey and Waters with their work on the phenylation of aryl compounds by benzoyl peroxide as a radical reaction.[3, 4] Almost at the same time across the Atlantic, Kharasch was investigating the reactivity of HBr **4** with alkenes.[5] Kharasch recognised that the anti-Markovnikov addition of HBr **4** to alkenes was due not to the conventional ionic process, but to a radical chain process (**Scheme 2**).



Scheme 2

The Second World War proved to be a major spark in the development of radical chemistry. Japan's occupation of South East Asia led to a shortage of latex in America, and so it fell upon the shoulders of chemists to develop substitutes for natural rubber. Mayo, Walling and Lewis developed the rules of polymerisation and copolymerisation of vinyl compounds during this period, and their work in demonstrating the electrophilic and nucleophilic nature of radicals forms the basis of explaining the differences in the selectivity and reactivity of radicals.[6, 7]

During the 1960's and 1970's pioneering work from the likes of Ingold[8, 9] and Beckwith[10] gave deeper insights into the structure, formation and reactivity of radical species. Most importantly they determined absolute rate constants for many of the most important radical processes in solution. This knowledge would allow the organic chemist to master the course of radical reactions; thus began the development of new synthetic methods using radical chemistry.

Over the course of the 1970's several important synthetic methods using radical reactions were developed; including Barton's deoxygenation reaction,[11] Bunnet's radical substitution of aromatic compounds,[12] Beckwith[13-15] and Julia's[16, 17] work on intramolecular radical reactions and Giese's advances on intermolecular radical reactions.[18, 19]

The improved understanding of radical reactivity, selectivity and stability acquired over this period allowed radicals to now be exploited by chemists as a synthetic tool in natural product synthesis from around 1980 onwards.[20-22] The continual development in this field has made radical chemistry one of the most important tools in organic synthesis for the formation of carbon-carbon bonds, and as such it is now routinely considered in the strategic planning of complex targets.[22]

1.1.2 Generation and Fate of Radicals

1.1.2.1 Generation of Radicals[2, 23]

The first step in any radical reaction is to form a radical which is capable of initiating a chain reaction. There are a number of ways to do this:

i) Homolysis – through a variety of methods including thermolysis, photolysis and radiolysis (ionising radiation in the form of X or γ rays or α or β particles).

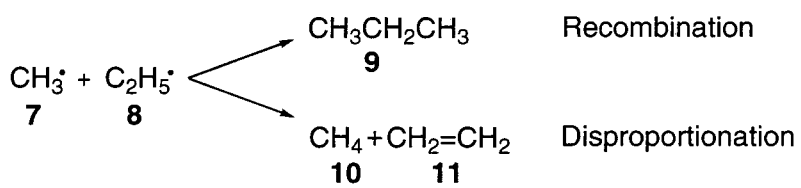
ii) Electron transfer – involving redox reactions carried out by means of a metal salt or electrochemically. Examples include Na / Na^+ (Birch reduction), Sm^{2+} / Sm^{3+} (SmI_2 mediated reduction).

iii) Transformation of one radical into another – these are characteristic of chain mechanisms that occur during a radical process **(Section 1.1.2.2)**.

1.1.2.2 Fate of Radicals[2, 23]

Radical reactions can be divided into two major categories: radical-radical reactions (i) and radical – non-radical reactions (ii).

i) The reaction between two radical species is in most cases a very fast process, and is considered very important due to the role they play in forming non-radical products. There are two types of radical-radical reaction: recombination and disproportionation **(Scheme 3)**.



Scheme 3

Recombination reactions may also be referred to as coupling reactions or dimerisation (if the two radical species are identical); in any case a single non-radical product is obtained. Disproportionation involves the transfer of a β hydrogen atom from one radical species to another, giving rise to two products, a saturated and unsaturated species. Although these processes are extremely fast they are not necessarily the most synthetically useful to organic chemists because the radical character is destroyed and side reactions due to concentration effects can occur.

ii) In contrast, reactions between radicals and non-radicals are more advantageous and easier to control. In this case the radical character is retained during the reaction, selectivities can be controlled by substituent effects and the concentration of the non-radicals can easily be monitored. To be successful at employing radical – non-radical reactions two main conditions must be obeyed: the selectivities of each of the radicals in the system must differ from each other and the reaction between radicals and non-radicals must be faster than the radical-radical processes. This can best be demonstrated by a simple chain reaction between an alkyl halide **18**, alkene **13** and tributyltin hydride **(15, Figure 1)**.

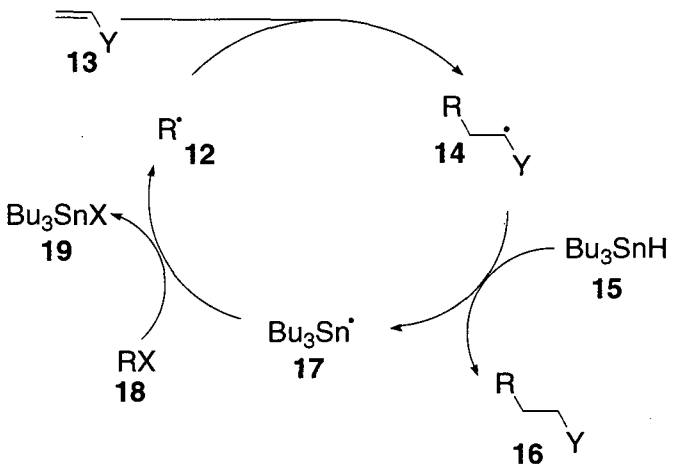


Figure 1: Radical chain mechanism mediated by Bu_3SnH **15**.

For the chain reaction to be successful alkyl radical **12** must react with the alkene adduct **13**. Trapping of the resultant radical **14** with tributyltin hydride **15** generates the coupled product **16** and tributyltin radical **17** which reacts further with alkyl halide **18** to restart the cycle. It is evident that general reactivities of the radical species play an important role. If for example radical species **12** possessed the same selectivity as radical **14** then one could envisage alkene polymerisation and simple reduction of the alkyl halide occurring. This problem can be prevented by choosing suitable substituents on either the alkyl halide **18** or alkene **13** to alter the electronic character of each species **(Section 1.1.3)**. Radical processes can be represented by the 'radical chain mechanism' **(Figure 2)**.[24]

INITIATION

$$A\text{-}B \longrightarrow A\bullet + B\bullet \quad (1)$$

PROPAGATION

$$A\bullet + R\text{-}R' \longrightarrow AR' + R\bullet \quad (2a)$$

$$A\bullet + R\text{-}R' \longrightarrow AR + R'\bullet \quad (2b)$$

$$A\bullet + RCH{=}CHR \longrightarrow RCH(A)\text{-}CHR\bullet \quad (3)$$

$$ARB\bullet \longrightarrow RAB\bullet \quad (4)$$

$$ARB\bullet \longrightarrow AR + B\bullet \quad (5)$$

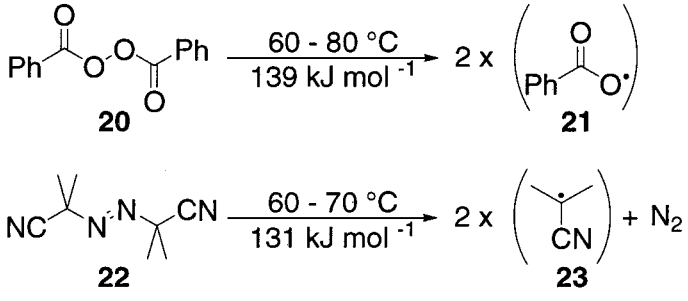
TERMINATION

$$A\bullet + B\bullet \longrightarrow AB \quad (6)$$

$$A\bullet + B\bullet \longrightarrow A + B' \quad (7)$$

Figure 2: Radical Chain Mechanism.

Initiation[2, 23, 25] The most important way of making radicals is by homolysis. Temperatures over 200 °C will homolyse most bonds, but in some instances temperatures not much above ambient temperatures will cause homolysis of weaker bonds. Light is an alternative energy source for the homolysis of bonds. Red light (650 nm) has associated with it 167 kJ mol^{-1}, blue light (475 nm) 293 kJ mol^{-1} and ultraviolet (200 nm) 586 kJ mol^{-1}, which is enough to decompose most organic compounds.[25] Most important to chemists are those compounds which have weak σ bonds and are able to generate radicals that can be used in reactions; these are often called initiators. Below are shown two examples,[25] dibenzoyl peroxide **20** and azo*iso*butyronitrile (AIBN) **22**, and their associated active radical intermediates (**Scheme 4**).



Scheme 4

Propagation There are five key elementary steps involved in the radical chain mechanism:[24]

(2a) Atom abstraction: if R' is a monovalent atom such as hydrogen or a halide it is transferred from one species to another.

(2b) Substitution: if R' is a multivalent atom such as an ether it will undergo a substitution reaction.

(3) Addition / cyclisation: the radical reacts inter or intramolecularly with a non-radical species such as a double bond to form a new σ bond and a new radical intermediate.

(4) Rearrangement: the radical species undergoes reorganisation to form a new radical species e.g. rearrangement of the cyclopropyl radical into its open chain form.

(5) Decomposition / fragmentation: this is the reverse process of addition and involves the breakdown of a radical species to form a non-radical product and a radical intermediate.

Termination As previously discussed this process involves the recombination of two radical species (6) to give a non-radical product. Alternatively the radical may disproportionate (7) to give a saturated and unsaturated product.[2, 23]

1.1.3 Substituent Influence on the Reactivity of Radicals

The formation of C-C bonds by the addition of radicals to alkenes is an important reaction in organic synthesis. The relative rates of addition are determined on the one hand by substituents attached to the radical species and on the other by the substituents on the alkene. The addition of alkyl radicals to alkenes is exothermic since a σ bond is formed and a π bond is broken, thus, according to Hammond's postulate the transition state should lie very early in the reaction coordinate.[26] This being the case one can describe the reactivity of radicals with alkenes in terms of frontier molecular orbital (FMO) theory.[27, 28]

FMO theory states that the energy differences between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of the reacting species is decisive in determining the relative rates of reaction. In the case of a radical it is the interaction between its singly occupied molecular orbital (SOMO) and the HOMO and LUMO of the alkene which are important. The nature of the SOMO is dependent upon the substituents directly attached to the radical centre. Electron donating groups such as ethers will stabilise the radical system, while at the same time making the radical more nucleophilic in character by raising the energy of the SOMO. In contrast whilst electron withdrawing groups such as ketones or nitriles also stabilise the radical system, they make the radical more electrophilic in character by lowering the energy of the SOMO.[27, 28]

This is important in determining the nature of the interaction between the SOMO and the frontier orbitals of the alkene. Nucleophilic radicals with a high energy SOMO, interact most efficiently with the LUMO of an alkene (**Figure 3**). Electron withdrawing groups incorporated into the alkene lower the energy of the LUMO, thus the SOMO-LUMO energy difference is reduced and the reaction rate is increased.[27, 28]

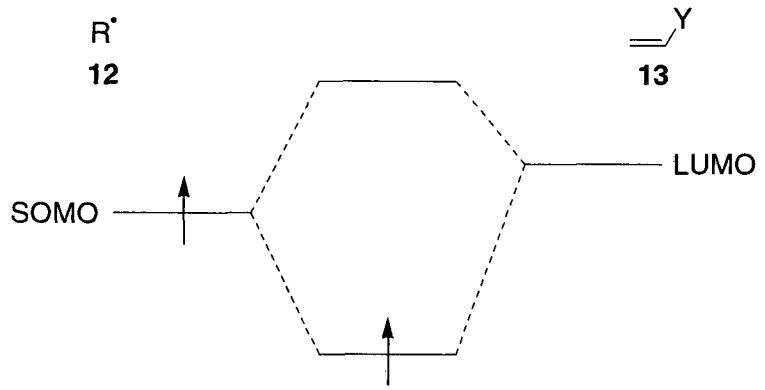


Figure 3: Interaction between a radical SOMO and LUMO of an alkene.

In contrast electrophilic radicals with a low energy SOMO interact favourably with the HOMO of an alkene. The interaction is enhanced when the alkene is substituted with electron donating substituents which raise the energy of the HOMO thus reducing the SOMO-HOMO energy gap (**Figure 4**).[27, 28]

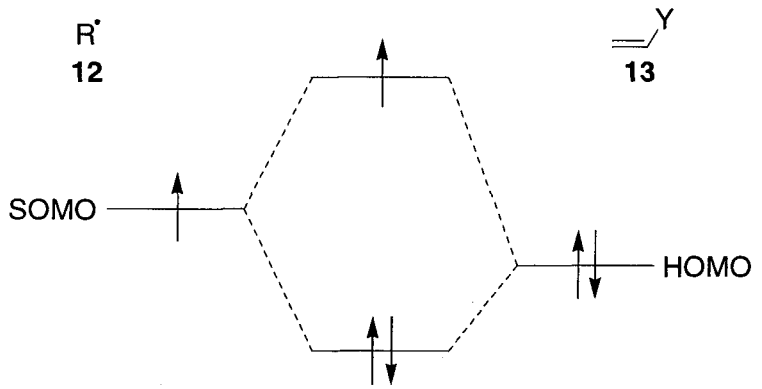
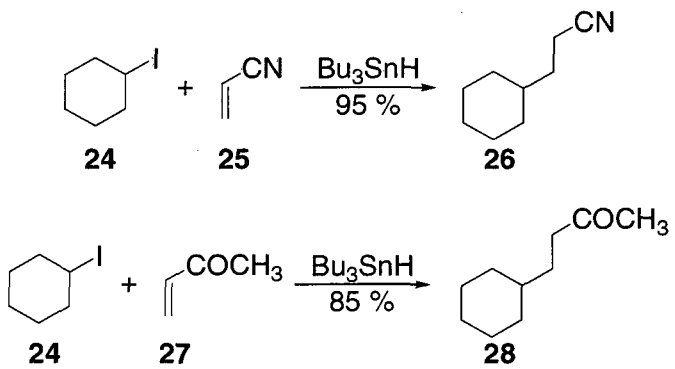


Figure 4: Interaction between a radical SOMO and HOMO of an alkene.

1.1.4 Intermolecular Radical Reactions

Unlike the entropically favoured intramolecular cyclisations, intermolecular additions are somewhat more difficult to conduct. At any one time during the reaction several radical species exist in solution, thus it is important to ensure a level of control to prevent unwanted side reactions from occurring. The intermolecular addition of a nucleophilic alkyl radical to an unactivated alkene is not practical; however the problem can easily be remedied if the alkene is modified by incorporating an electron withdrawing substituent.

Giese has shown that product yields can be maximised by careful design of the reaction conditions taking into accounts the rate of competing reactions. Some examples are shown (**Scheme 5**). [29]



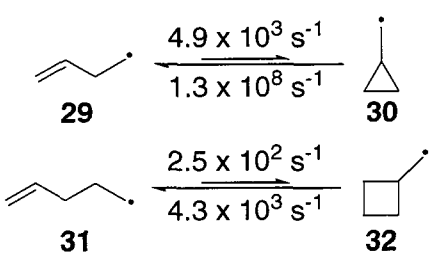
Scheme 5

1.1.5 Intramolecular Radical Reactions

Intramolecular radical additions, also known as radical cyclisations, are an important facet of organic synthesis. Since their first inception into natural product synthesis in the early 1980's their use in this area has grown substantially due to their importance in forming cyclic / polycyclic products from simple starting materials.

1.1.5.1 Three and Four Membered Rings

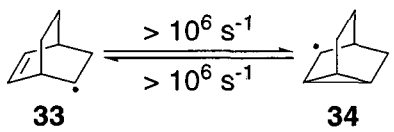
Radical reactions involving small rings are in principal reversible with the relative strengths of bonds broken and relative stability of the radicals playing a role in the position of equilibrium. The formation of three and four membered rings by radical cyclisation is a very fast process, however, the ring opening of species **30** and **32** to the more stable ring opened species **29** and **31** is faster still (**Scheme 6**).[8]



Scheme 6

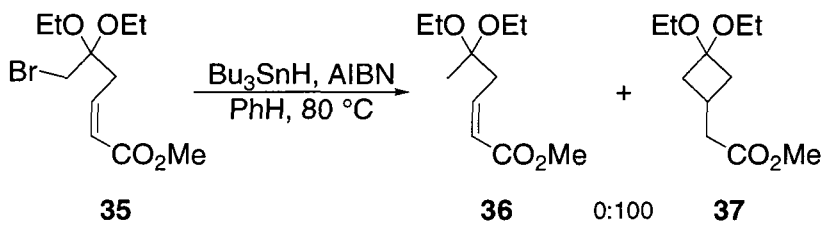
As a result radical cyclisations were generally considered unsuitable for construction of three and four membered rings. However, when a large proportion of ring strain is

already present such as in the norbornenyl radical **33** a three membered ring can be formed (**Scheme 7**).[30]



Scheme 7

Similarly, for the synthesis of cyclobutanes, only certain conditions can favour ring formation. Jung has reported the presence of geminal substitution that favours ring formation over ring opened product (**Scheme 8**).[31, 32]

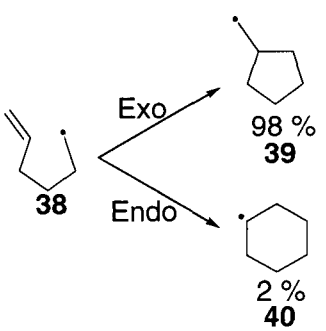


Scheme 8

1.1.5.2 Five Membered Rings and Upwards

Since it was first reported by Lamb,[33] the radical cyclisation of the hex-5-enyl radical **38** (**Scheme 9**) attracted widespread interest across the organo-physical community. Its use as a mechanistic probe and radical clock has proved invaluable to many organic chemists who are interested in designing experimental conditions to meet their synthetic needs.[34]

Regioselectivity There are two possible modes of intramolecular cyclisation of the 5-hexenyl radical **38** (**Scheme 9**).

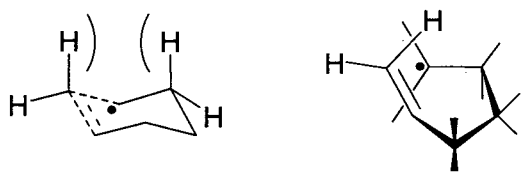


Scheme 9

Following Baldwin's guidelines,[35] ring closure by a 5-*exo-trig* pathway to yield cyclopentylmethyl radical **39** is more favourable than the corresponding 6-*endo-trig* pathway to give cyclohexyl radical **40**.

This is an interesting result because according to thermochemical predictions the primary cyclopentylmethyl radical **39** is thermodynamically less stable than the secondary radical **40**, yet it is the primary radical which is preferentially formed.[36]

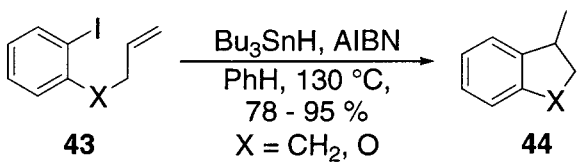
An explanation brought forward by Julia is that unfavourable interactions between the pseudo axial proton at C-2 and the *syn* proton at C-6 will destabilise the 6-*endo* transition state **41** (**Figure 5**).[17]



41 **42**

Figure 5: Transition states proposed by Julia.[17]

In contrast the 5-*exo* transition state **42** does not exhibit any unfavourable interactions. Further studies by Beckwith[15] proved that C-2 to C-6 non bonded interactions in the 6-*endo* transition state **41** are indeed present, however the magnitude to which they destabilise the transition state is extremely small. The conclusion is supported by the observation that alkenylaryl radicals in which there is no pseudo-axial C-2 proton in the transition state, undergo 1, 5 cyclisation in a highly regiospecific manner (**Scheme 10**).[14, 37]

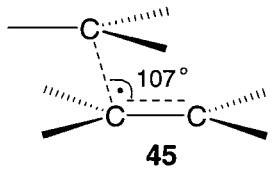


43 **44**

Scheme 10

A widely accepted hypothesis is the stereo-electronic approach to radical ring closing reactions.[36, 38] First developed by Beckwith, this theory dictates that radical cyclisation is governed by the interaction of a partially filled p orbital of the radical with a π^* orbital of the alkene. Consequently the required disposition of the reactive centres to ensure maximum orbital overlap is of great importance. Beckwith proposed that the

transition state **45** consisted of three reactive centres situated at the vertices of a slightly obtuse triangle lying within a plane orthogonal to the nodal plane of the π system **(Figure 6)**.[36, 38] Theoretical studies confirm the structure of the transition state to be correct.[39]

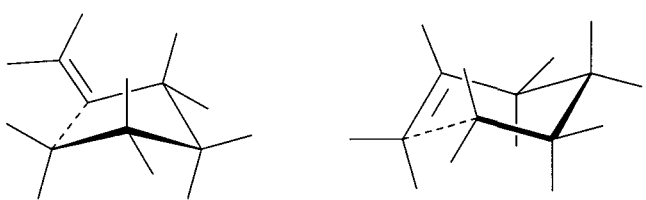


45

Figure 6: Transition state of the three reactive centres.

The ring strain engendered in accommodating the three reactive centres is greater in a 6-*endo* system than it is for a 5-*exo* system. The difference in ring strain outweighs those steric and thermochemical factors influencing ring formation.

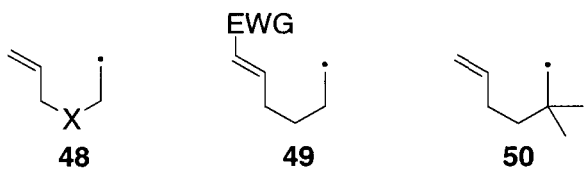
The formulation of the stereoelectronic hypothesis has led to the transition structures for the ring closure of alkenyl radicals to be developed. Initial work by Beckwith, followed by Houk gave rise to transition state models where both the 5-*exo* **46** and 6-*endo* **47** transition states occupy a distorted chair conformation **(Figure 7)**.[36, 40, 41]



46 **47**

Figure 7: Transition states for 5-*exo* **46** and 6-*endo* **47** cyclisations.

There are numerous factors that affect the radical cyclisation of the 5-hexenyl radicals. Those which increase the rate of cyclisation are shown below **(Figure 8)**.



48 **49** **50**

Figure 8: Factors enhancing the rate of ring closure.

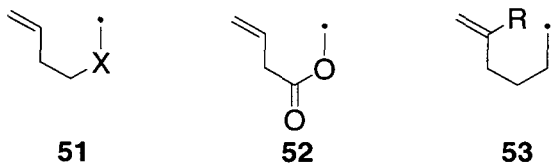
i) Nitrogen or oxygen atoms at the C-3 position of **48** enhance the 1,5 / 1,6 cyclisation ratio. The narrower bond angle between C-N-C and C-O-C compared with C-C-C, plus the shorter bond lengths (C-N 1.47 Å, C-O 1.41 Å compared with C-C 1.51

Å) bring the reactive centres in closer proximity and reduce the overall strain energy of the system.[42]

ii) Electron withdrawing groups attached to the alkene **49** lower the LUMO of the alkene and dramatically enhance the rate of cyclisation.[27, 28]

iii) Significant rate enhancements are noted when a *gem*-dimethyl group is incorporated into the 5-hexenyl backbone **50**. This type of rate enhancement can be attributed to the 'Thorpe-Ingold' effect.[15]

Conversely there are also factors which decrease cyclisation rates **(Figure 9)**.



51 **52** **53**

Figure 9: Factors retarding the rate of ring closure.

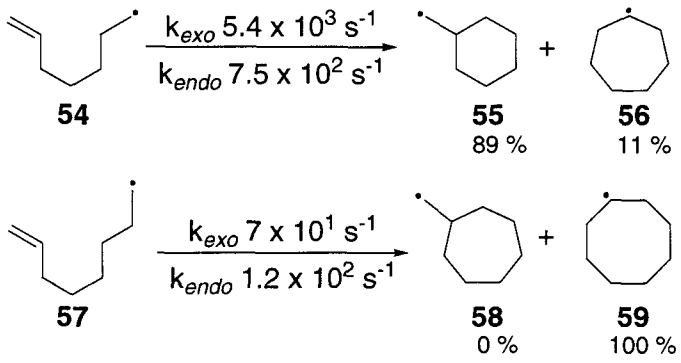
i) An oxygen or nitrogen atom at C-2 of the 5-hexenyl backbone **51** can retard the rates of cyclisation. The delocalisation of the unpaired electron with adjacent oxygen lone pairs can help stabilise the radical. A consequence of this is the restricted rotation about the C-O bond which is required to obtain maximum orbital overlap with the alkene in the chair-like transition state.[42]

ii) Incorporation of functional groups which severely restrict bond rotation will adversely affect radical cyclisation of 5-hexenyl radicals **52**. For example in **52**, the restricted rotation about the CO-O bond gives rise to unfavourable conformational effects.[42]

iii) The presence of an R group on the C-5 position of the 5-hexenyl chain **53** reduces the rate of the 5-*exo* cyclisation, and enhances the 6-*endo* pathway.[15, 36] This can be explained simply in terms of the anti-Markovnikov addition of radicals to unsymmetrical alkenes as originally observed by Kharsch.[5] Radical attack is not a reflection of the relative stabilities of the resultant products, but due to the sterics at each carbon centre.

Stereoelectronic factors can be used to explain the outcome of larger ring systems such as the 6-heptenyl radical **54** and 7-octenyl radical **57** systems. Both systems transition

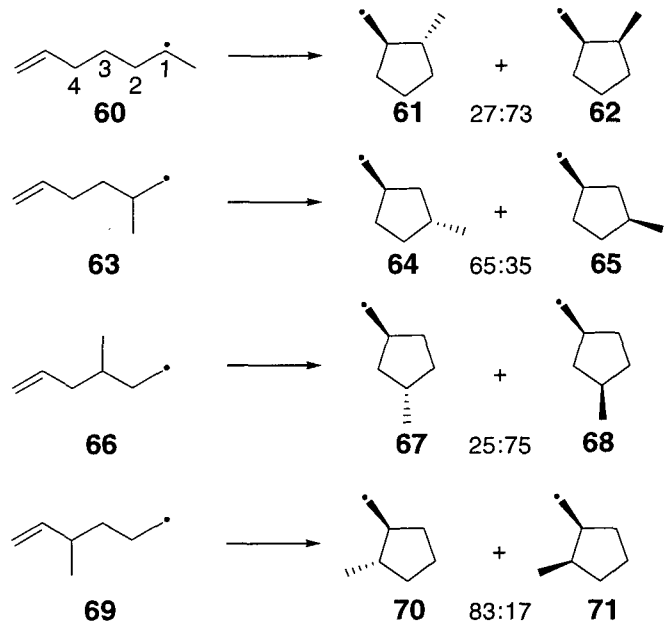
states resemble that of a distorted chair configuration which gives rise to *exo* product **55** and *endo* product **59** respectively **(Scheme 11)**.[40]



Scheme 11

The significant loss in selectivity of *exo* products is due to the increase in chain length. In a larger system the *endo* preference increases since the system is able to accommodate the preferred radical attack angle of 107 ° **(Figure 6)**.[41]

Stereoselectivity Beckwith outlined some simple guidelines for ring closure of substituted 5-hexenyl radicals.[36, 40] Beckwith states that for 1 and 3 substituted radicals the *cis* product predominates, while 2 and 4 substituted radicals give mainly *trans* products **(Scheme 12)**.[28]



Scheme 12

Beckwith rationalised these observations by hypothesising that the large R groups occupy the pseudo-equatorial positions in a chair like transition state **72 (Figure 10)**

giving rise to the major product **73**. His subsequent force field calculations have proven this to be correct.[36, 40]

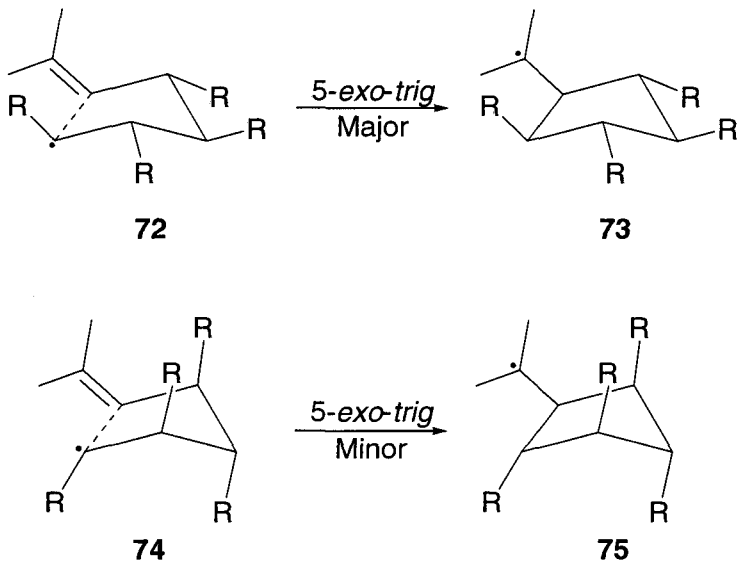


Figure 10: Chair transition states for major and minor products.

Further evidence for the chair like transition state proposed by Beckwith has been provided by Houk using modified force field calculations.[41] Interestingly, Houk's model predicts that the minor components of the reaction arise from the R substituents occupying an equatorial position in a boat like transition state **76 (Figure 11)** rather than the axial positions in a chair like transition state **74 (Figure 10)**.

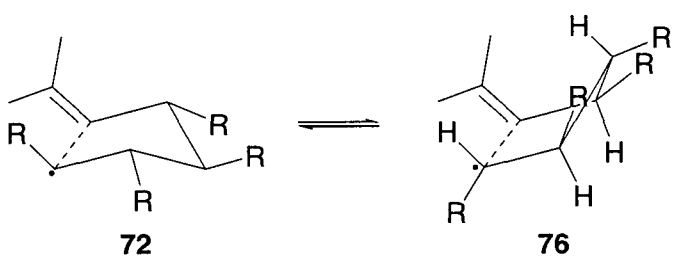
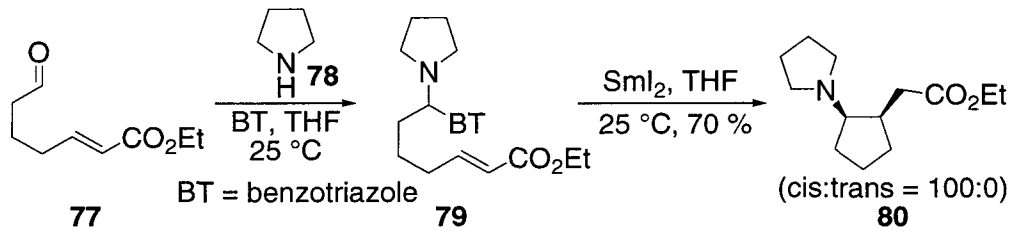


Figure 11: Alternative boat like transition state **76**.

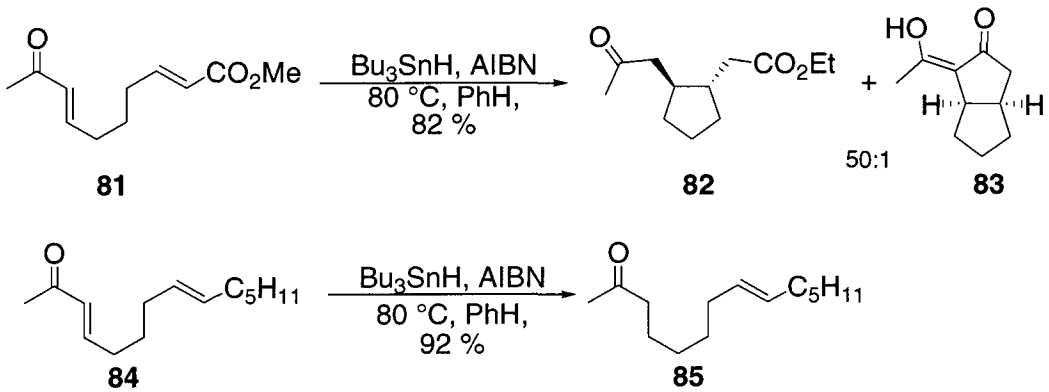
Calculations reveal that the energy increase from the chair **72** to boat **76** transition state is only 0.5 Kcal / mol for the substituted 5-hexenyl system (**Figure 11**); this is in contrast with cyclohexane where the energy increase between its conformers is 6.5 Kcal / mol. Crucially the energy of the boat like transition state **76** is lower than that of the axially substituted transition state **74**, making it the most stable of the two transition states.

The preferential formation of a *cis* fused product from a C-1 substituted 5-hexenyl radical is thought to arise from favourable stereoelectronic interactions between the partially filled p orbital of the radical and the π^* of the alkene. This factor considerably outweighs the non bonded repulsive forces between C-6 and C-1. However, an important note is that if the substituent becomes too bulky e.g. *t*-butyl, then steric factors take precedence and the *trans* product predominates. An example which is consistent with the predictions is shown (**Scheme 13**).[43]



Scheme 13

In contrast Enholm observes higher percentages of *trans* 1, 2-disubstituted cyclopentanes (**Scheme 14**).[44] Resonance stabilisation of the resultant radical intermediate possibly permits a level of reversibility and thus allows the kinetic *syn* product to equilibrate to the more stable *anti* thermodynamic product **82**.



Scheme 14

A further interesting observation is the lack of radical cyclisation of precursor **84** and the simple reduction to **85**. This is a nice example demonstrating the importance of substituents on the alkene, and how they can influence reactivity.

1.1.6 Radical Reactions in Natural Product Synthesis

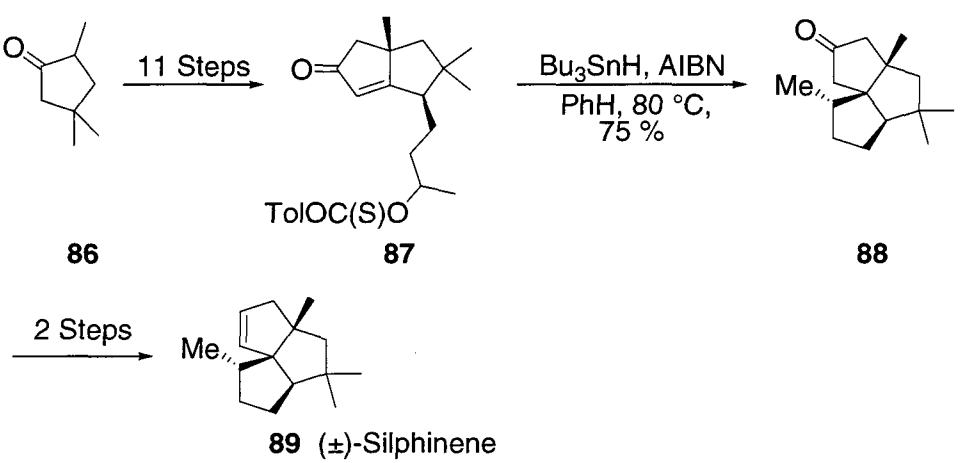
There are several synthetic advantages of radical reactions over their ionic counterparts including:[22]

i) Radical reactions typically proceed under mild conditions and exhibit a high level of chemio, regio and stereoselectivity.

ii) Radicals tend not to be cluttered with solvent spheres or counterions making them useful for the synthesis of crowded bonds.

iii) Radicals are inert towards OH and NH groups, thus the protection of alcohols and amines is often unnecessary.

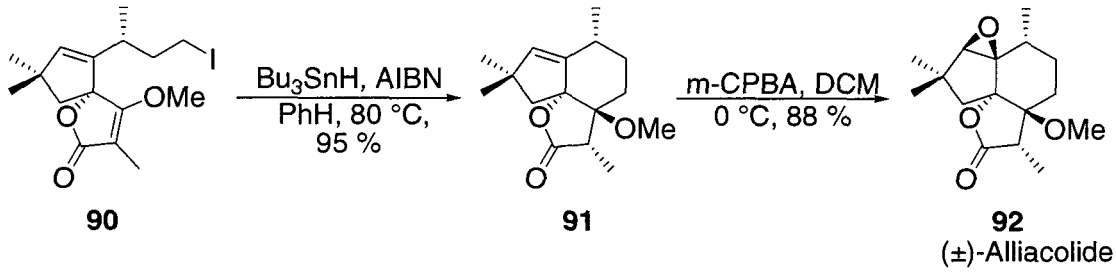
Radical cyclisations are most often used in the construction of five membered rings due to their superior rates of cyclisation. They also command a high degree of regioselectivity and stereoselectivity. A 5-*exo* cyclisation is central to Nagarajan's synthesis of siliphinene **89 (Scheme 15)**, an example that also demonstrates the ability of radicals to form crowded quaternary centres.[45]



Scheme 15

Although radical cyclisations to six membered rings are not as favourable as that of five membered rings, they are still important in synthesis. The main problems of larger ring formation are competing reactions such as radical reduction and 1,5-hydrogen atom abstraction. They can also exhibit reduced regio and stereoselectivities. By designing a radical precursor that is able to influence the selectivity of radical attack, one can lead to

improved cyclisation reactions. This is exemplified in Pattenden's synthesis of alliacolide **92 (Scheme 16)**.[46]

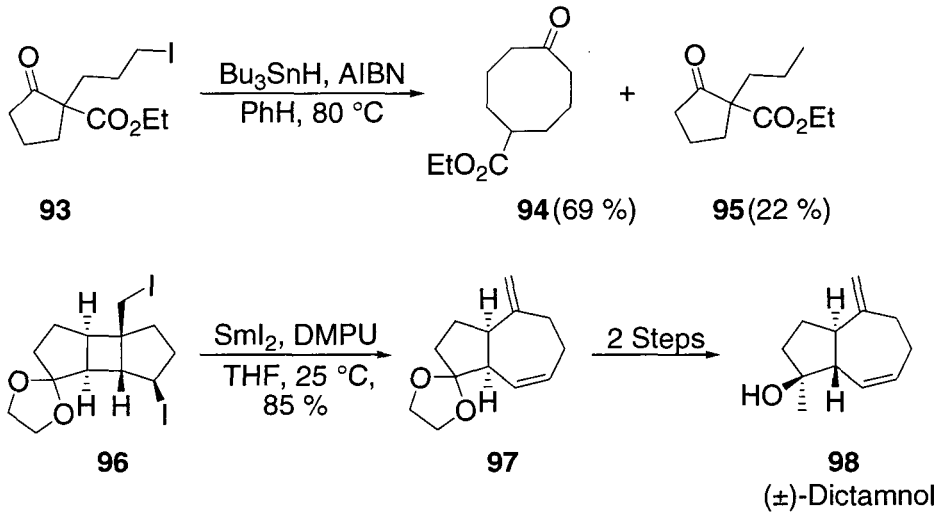


90 **91** **92** (±)-Alliacolide

Scheme 16

Lactone activation of the double bond promotes 6-*exo* cyclisation even at a sterically congested carbon to form the neopentyl quaternary centre.

A useful method of making larger ring systems is *via* ring expansion utilising fragmentation of radical species such as oxy radicals and cyclobutylcarbinyl radicals **(Scheme 17)**.[47-49]

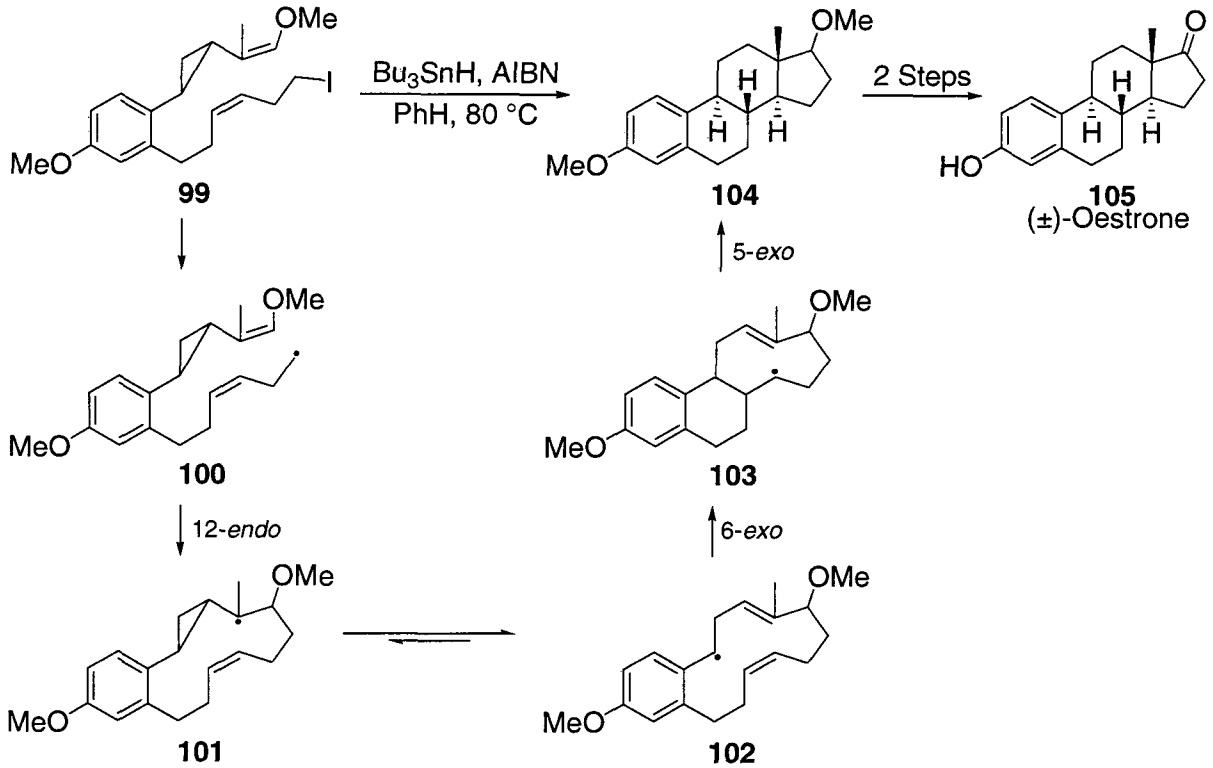


93 **94** (69 %) **95** (22 %)

96 **97** **98** (±)-Dictamnol

Scheme 17

Reactions involving two or more radical cyclisation sequences are known as radical cascade reactions. They provide an efficient route to making polycyclic structures and as such there are many examples of their uses in the literature.[20-22, 50, 51] A prime example is the recent total synthesis of oestrone **105** which utilises a radical cascade involving tandem 12-*endo*, 6-*exo* and 5-*exo* cyclisations, as well as cyclopropyl methyl to but-2-enyl radical equilibration to construct the tetracyclic framework **104 (Scheme 18)**.[52]



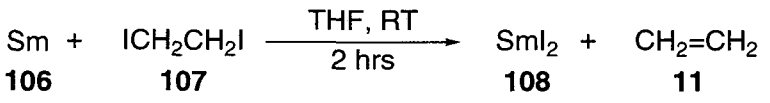
Scheme 18

1.2 Samarium Diiodide

1.2.1 History and Background

Since the first reliable preparation of SmI_2 was published in 1980 by Kagan,[53] this very versatile reagent has become one of the most widely used in synthetic chemistry. Kagan's pioneering work established a facile synthesis of SmI_2, and gave a comprehensive overview of the types of reductive processes the reagent can carry out. Subsequent research into the synthetic utility of SmI_2 by the likes of Molander,[54-63] Inanaga[64, 65] and Curran,[66] have ensured SmI_2 has become an important reagent in organic synthesis.

SmI_2 can be prepared as a solution in THF *via* several reported routes, including reacting Sm metal with iodomethane[63] or 1, 2-diiodoethane **107**.[53] Whilst they still tend to be the two most popular methods, SmI_2 can also be prepared directly by the reaction of Sm metal **106** with iodine.[67] Kagan was the first to report the preparation of SmI_2 by use of Sm metal **106** with 1, 2-diiodoethane **107 (Scheme 19)**.



Scheme 19

The reaction is carried out under an inert atmosphere and anhydrous conditions. Typically SmI_2 is made as a 0.1 M solution in THF and is characterised by a distinct deep blue colouration. With the addition of additives such as HMPA (purple), MeOH (dark green) and Et_3N / H_2O (black) the solution will change colour accordingly. An advantage of the Sm (II) / Sm (III) system is that the Sm (III) salts are a distinct yellow solid, thus allowing easy visualisation of the quality of the reagent.

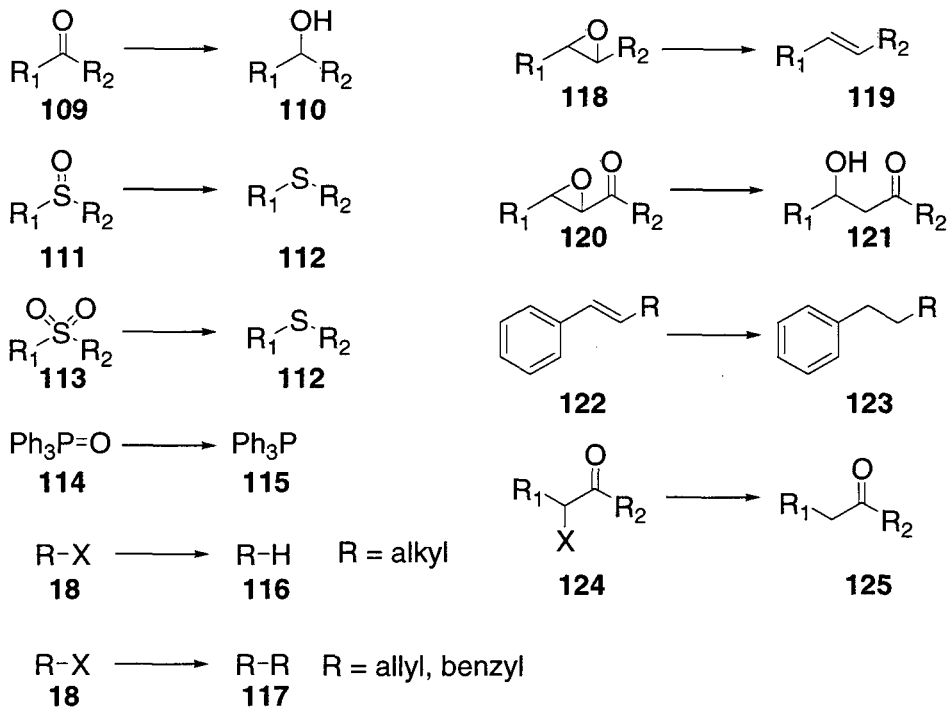
SmI_2 is an extremely versatile reagent; as well as being able to carry out radical processes and anionic processes with ease, it can reduce various functionalities in a highly chemoselective (of the order RX (X = halide) > RCHO > RC(O)R' > RCO_2R' (1, 4 - reduction of α, β unsaturated esters only) > conjugated C=C) and stereoselective manner. Adding to the appeal of SmI_2 is the fact that the reactivity and or selectivity can be modified by the addition of various catalysts, co-solvents or additives to the reaction mixture, thus allowing organic chemists to fine tune the conditions to suit their synthetic requirements.[58, 67]

1.2.2 Types of Reaction Mediated by Samarium Diiodide

SmI_2 can mediate a vast array of reactions, a substantial number of which were reported in Kagan's pioneering paper.[53] Reactions involving SmI_2 fall into four main categories.

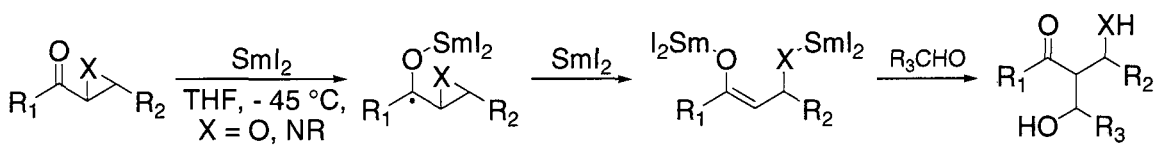
1.2.2.1 Functional Group Reduction

Much of the early work with SmI_2 focussed upon its ability to reduce a wide variety of functional groups.[68] These transformations include the reduction of aldehydes and ketones **109**,[53, 68] sulfoxides **111**,[53, 68, 69] sulfones **113**,[69] phosphine oxides **114**,[69] halides **18**,[53, 68] epoxides **118** and **120**,[53, 56, 61, 65, 68] conjugated double bonds **122**[53, 68] and α-X-carbonyls **124**[57, 64] **(Scheme 20)**.



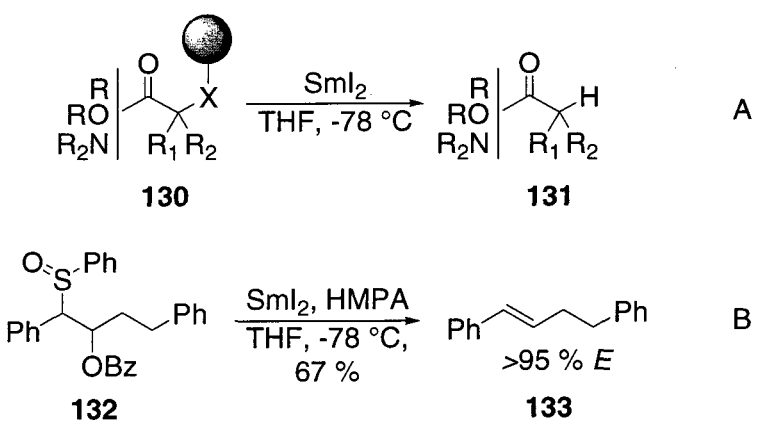
Scheme 20

In some instances, the reduction of a functional group to generate an organolanthanide species has been subsequently used in C-C bond forming reactions such as the samarium aldol[70, 71] (**Scheme 21**) and samarium Reformatsky reaction.[53, 72]



Scheme 21

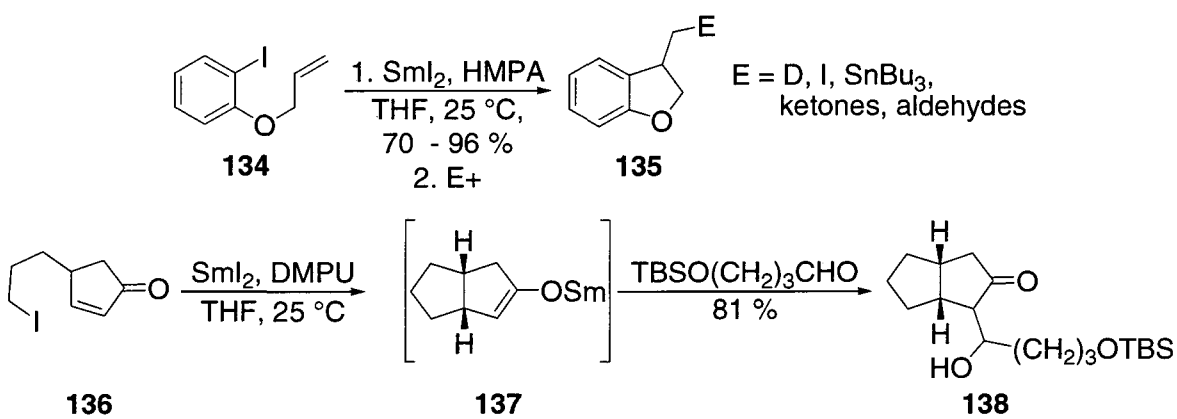
Recent applications of functional group reduction include the development of new traceless linkers in solid phase synthesis[73] (**A, Scheme 22**) and modifications of the Julia-Lythgoe olefination (**B, Scheme 22**).[74]



Scheme 22

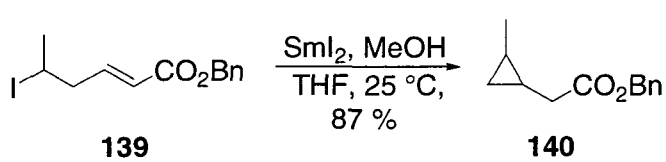
1.2.2.2 Radical to Alkene Addition Reactions

SmI_2 mediated radical cyclisations offer a useful alternative to the more traditional methods such as Bu_3SnH and mercuric hydride. A significant advantage of SmI_2 over these methods is its ability to further reduce carbon centred radicals to carbanions, which allow further anionic mediated C-C bond formations to ensue after the radical process is complete.[75] Curran amongst others has demonstrated the utility of these reactions **(Scheme 23)**.[76-78]



Scheme 23

Conjugate addition reactions with α, β-unsaturated carbonyl compounds have become a useful extension to the methodology.[67] They are especially useful in providing simple routes to cyclopropyl structures which are known to be thermodynamically unfavourable **(Scheme 24)**.[79]



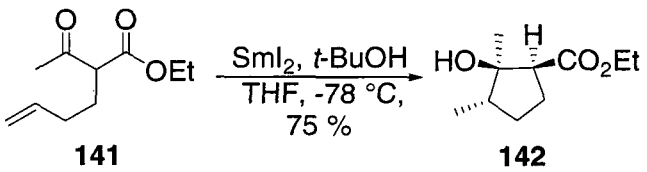
Scheme 24

Although the equilibrium lies towards the ring opened product, it is believed that the overall displacement of the reaction towards radical cyclisation is caused by the single electron reduction of the cyclopropyl radical to the corresponding enolate, thus halting ring opening.

1.2.2.3 Reductive Coupling of Two π Bonds

These types of transformations typically include pinacol couplings[53, 60, 80] and reductive couplings between carbonyls and alkenes.

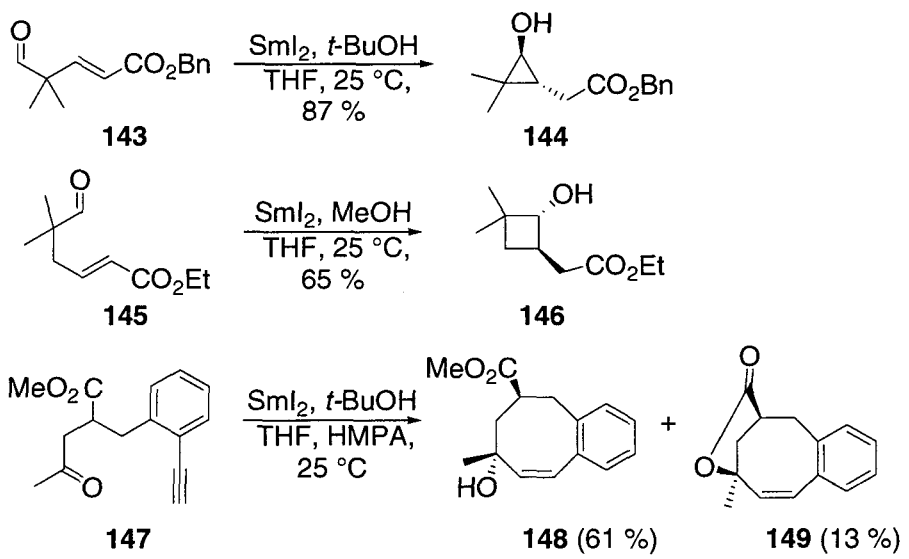
Intramolecular ketyl radical to alkene reactions were first reported by Molander for a range of substrates giving rise to five membered rings (**Scheme 25**).[60] Molander found that these cyclisations were facile, and generally gave rise to good diastereoselectivities rationalised by a chair like transition state (**Section 1.2.3**).[63]



141 **142**

Scheme 25

Rings of various sizes can be obtained *via* this methodology; three and four membered rings have been reported as well as larger systems such as eight membered rings (**Scheme 26**).[81-85]



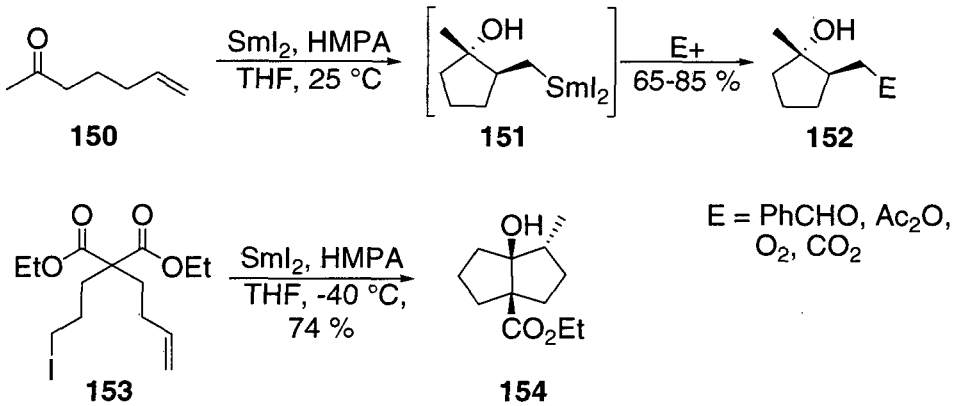
143 **144**

145 **146**

147 **148** (61 %) **149** (13 %)

Scheme 26

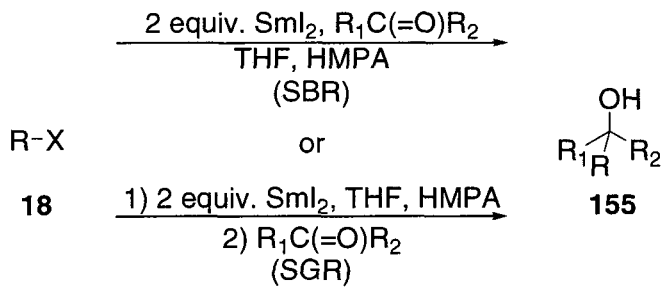
Tandem radical cyclisation and nucleophilic addition has also been reported, once again illustrating the unique ability of SmI_2 to conduct radical and anionic processes in the same reaction vessel (**Scheme 27**).[62, 75, 86]



Scheme 27

1.2.2.4 Reductive Coupling of Halides with C=O Bonds

The SmI_2 promoted alkylation of carbonyl compounds with organic halides, also known as the samarium Barbier-Grignard reaction, was initially reported by Kagan.[53, 87] His initial work focussed upon the intermolecular samarium-Barbier reaction (SBR), and was later developed by Molander into an intramolecular process (ISBR).[54] Some years later Curran introduced a procedure called the 'samarium Grignard' reaction (SGR).[76] There is a distinct difference between Barbier and Grignard procedures (**Scheme 28**).



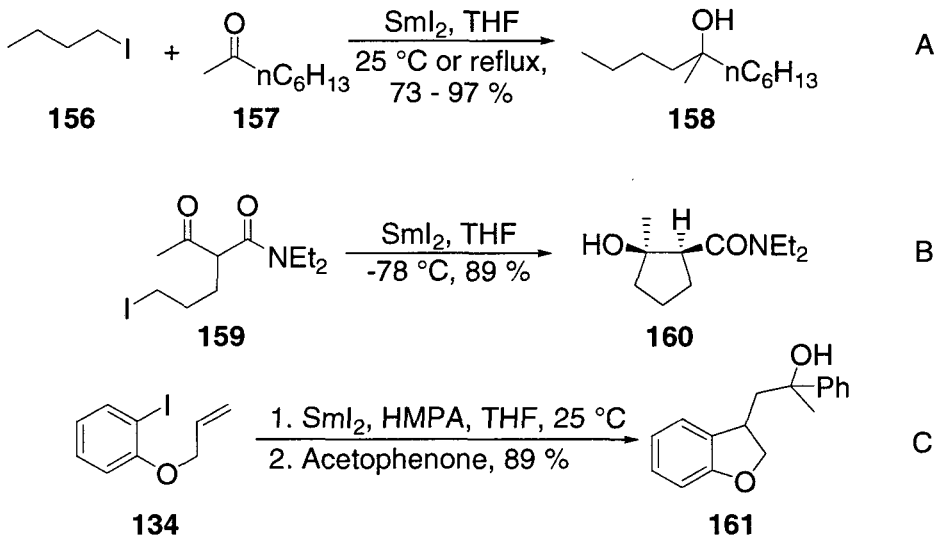
Scheme 28

The SBR involves a single pot procedure in which the halide, carbonyl compound and SmI_2 are mixed together all at once. In contrast, the SGR involves a stepwise procedure in which the halide and SmI_2 are combined together first, then the carbonyl compound is added some time later. SmI_2 promoted reactions function well under both sets of conditions, each have their own advantages depending on the circumstances:[88]

SBR conditions must be used when the halide (i) is prone to dimerisation (allyl or benzyl halides), (ii) can decompose by α-elimination (e.g. benzyloxymethyl chloride) and (iii) can react with itself intramolecularly (halogeno-carbonyl compounds).

SGR conditions are best used when the carbonyl compound (i) is prone to pinacol coupling and (ii) have a tendency to be reduced faster by SmI_2 than the halide.

Some examples are shown, ranging from the relatively simple intermolecular additions reported by Kagan (**A, Scheme 29**),[89] to the intramolecular cyclisations pioneered by Molander (**B, Scheme 29**) finally leading to Curran's SGR processes (**C, Scheme 29**).[90]

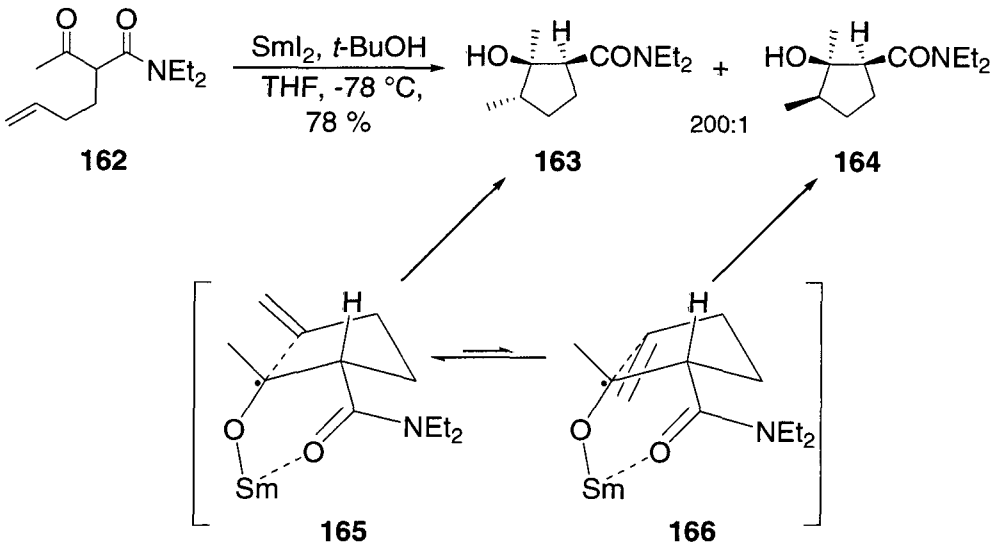


Scheme 29

1.2.3 Diastereoselectivity in Samarium Diiodide Mediated Reactions

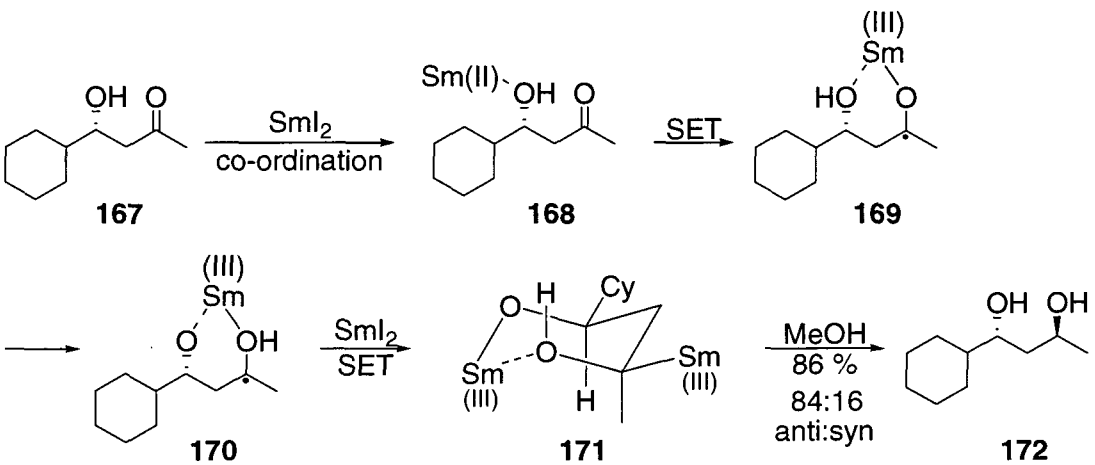
An interesting property of SmI_2 is its ability to facilitate stereoselective processes. The Sm (II) and Sm (III) centres are able to chelate to one or several heteroatoms in a molecule, and subsequently give rise to favourable transition states.

A good example of this selectivity can be demonstrated by the highly stereoselective radical cyclisations of β-keto esters and β-keto amides (**Scheme 30**).[60, 91, 92] The samarium centre acts as a template, and serves to co-ordinate to the ketyl oxygen and amide side chain locking the conformation into a chair-like transition state. A possible conformational change regarding the orientation of the olefin moiety (**165** or **166**) can be considered, however the equilibrium lies significantly towards the transition state **165** which minimises the electronic repulsion between the ketyl oxygen and alkene π-system.[36]



Scheme 30

Recent examples published by Keck exploit the chelation control of SmI_2 to reduce β-hydroxy ketones to *anti*-1,3-diols in a highly stereoselective manner.[93] The selectivity is attributed to the formation of a chelated Sm (III) complex in which the samarium carbanion occupies the equatorial position of a chair transition state (**171, Scheme 31**).



Scheme 31

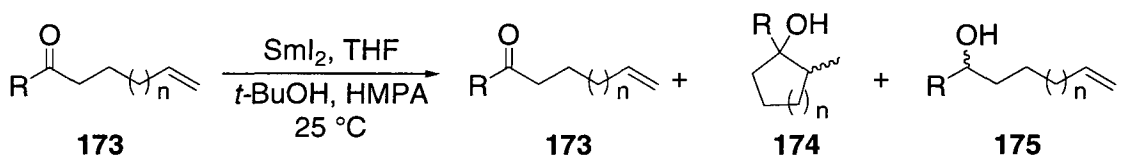
Keck has recently demonstrated that replacing the β-hydroxy component with a β-alkoxy substituent such as OMe and OEt does not affect the selectivity of the reaction, although if larger groups such as OBn are used then the reaction is hindered and selectivity decreases.[94]

1.2.4 Solvent Effects on Samarium Diiodide Chemistry

Solvents play a crucial role in influencing SmI_2 chemistry. In some instances the reaction rates can be enhanced, while in others improved diastereoselectivities can be observed.

The beneficial effects of HMPA were first noted by Inanaga in the late 1980's.[95] He found that the addition of HMPA (~ 5 % of the SmI_2-THF solution) significantly enhanced the reduction of organic halides to the corresponding alkanes. A similar rate enhancement was observed for Barbier reactions - in the presence of HMPA the reaction proceeded at room temperature (rather than reflux as reported by Kagan) and were complete in less than one minute.[96]

Subsequent electrochemical studies on the influence of HMPA in SmI_2 mediated reactions have concluded that four equivalents of HMPA with respect to SmI_2 are the optimal conditions.[68, 97, 98] Molander has carried out a detailed study on the effects of HMPA (zero, two, four, eight equivalents) on ketyl-olefin couplings. It is clear from his findings that not only does the amount of HMPA greatly influence the rate of reaction but also the product distribution **(Scheme 32)**.[62]



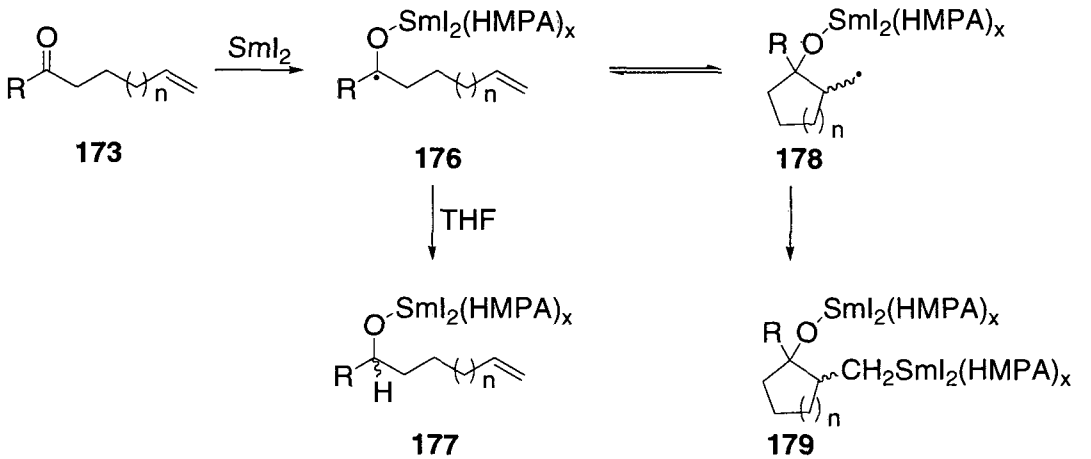
173 **173** **174** **175**

Scheme 32

Decreasing the amount of HMPA from eight to zero equivalents drastically affects the outcome of the reaction. Using eight and four equivalents of HMPA, result in > 87 % formation of **174** with a small quantity (< 13 %) of reduced product **175**. Decreasing the equivalents further (two and zero equiv.) gives rise to significantly more reduced product **175** (55-96 %) and in some instances recovered starting material **173** (up to 36 %).

Although the exact role of HMPA is not clear, Molander has put forward two plausible explanations **(Scheme 33)**. In the absence (or low concentrations) of HMPA, THF complexes with Sm (II) and is subsequently present when the samarium ion coordinates to the carbonyl. The THF is ideally placed to act as hydrogen donor in the conversion

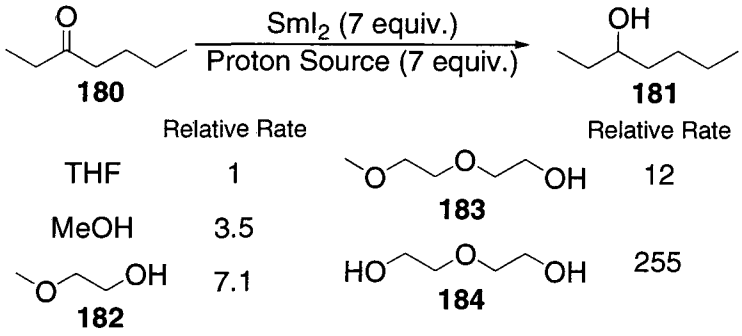
of **176** to **177**. In contrast, HMPA preferentially complexes with the Sm (II) at high concentration, displacing the THF. The HMPA effectively shields the resultant ketyl radical from THF preventing hydrogen atom abstraction- resulting in a more persistent radical. In this case the rate of hydrogen abstraction decreases (**176** to **177**) and favours cyclisation (**176** to **178**) with increasing concentration of HMPA.



Scheme 33

A second explanation considers the cyclisation of **176** to **178** being reversible. If this is so, then an increase in HMPA concentration would favour alkyl radical reduction (**178** to **179**), thus removing **178** from the system shifting the equilibrium in favour of cyclised products.[62]

HMPA however is carcinogenic, and so other solvents and additives are commonly used including proton donor species. These, like HMPA, have a significant role to play in the product distribution and stereochemical outcome of SmI_2 reactions.[82, 93] Typically they include alcohols (of which MeOH and *t*-BuOH are most commonly employed) and H_2O. Use of such solvent systems date back to Kagan's seminal work in which he reports positive effects on the rate of reaction.[53] A recent study by Flowers has shown that water has the highest affinity for SmI_2 than any other simple alcohol - 'simple' implying alcohols with a single heteroatom.[99] Research by Hilmersson has shown that polydentate alcohols (i.e. diols or ethereal alcohols) are far better at promoting SmI_2 mediated processes than mono alcohols (**Scheme 34**).[100]



Scheme 34

Hilmersson has also recently discovered the use of a SmI_2 / water / tertiary amine system as a useful alternative to HMPA.[101-104] In most instances the system is comparable, if not superior to the SmI_2 / HMPA system.

1.2.5 Catalytic Samarium Diiodide Mediated Processes

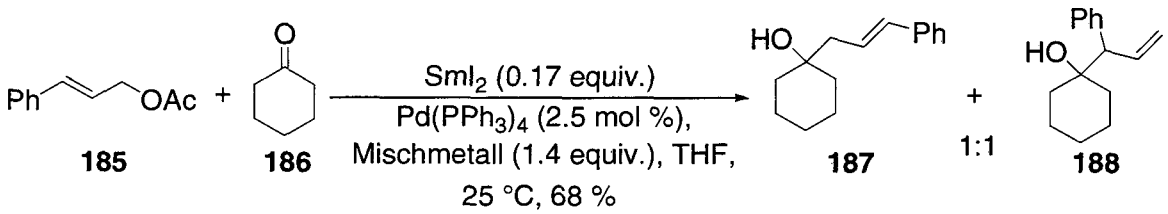
Although one of the most popular reagents used in synthetic chemistry, SmI_2 suffers from one major drawback, due to a high molecular weight (404 $gmol^{-1}$), and the use of stoichiometric quantities, SmI_2 can be considered a relatively expensive reagent.

To address this problem, attempts have been made to run reactions in the presence of catalytic Sm (II) which is then regenerated *in situ* by a catalytic cycle. In 1996, Endo demonstrated a novel SmI_2 catalysed pinacol coupling of carbonyl compounds, by using Mg as the co-reductant.[105] The reactions were successfully run in the presence of 10 mol % SmI_2. Several recent publications also make use of Mg as the co-reductant in pinacol and Reformatsky reactions.[72, 106]

In 1997, Corey demonstrated another SmI_2 catalysed process in which he used Zn amalgam for the generation of γ-lactones from the annulation of ketones and acrylic esters, the deoxygenation of styrene oxide to styrene and the cyclisation of iodo-olefins.[107] Although successful his method required the use of TMSOTf which in itself is an expensive reagent.

More recently a new co-reductant has come to light - mischmetall. Mischmetall is an alloy of various light lanthanide elements, and has the main advantages of being cheap, unreactive to organic substrates, usable in a wide variety of SmI_2 mediated processes and efficient at reducing Sm (III) to Sm (II).[108] Namy has illustrated a wide variety of

uses for mischmetall; it has been used in SBR, SGR, pinacol and Reformatsky reactions.[108, 109] Recently still, a mischmetall / $[SmI_2/Pd^0_{cat}]_{cat}$ system has been shown to effectively mediate the allylation of ketones with a variety of allylic esters (**Scheme 35**).[110]



Scheme 35

SmI_2 can also be used in reactions to generate a Sm (III) species, which is then capable of catalysing a transformation.[111] An example is the Tishchenko reduction of β-hydroxy ketones to 1, 3-*anti* diols, in which 15 mol % of SmI_2 is converted to an active Sm (III) species which then catalyses the reduction accordingly.

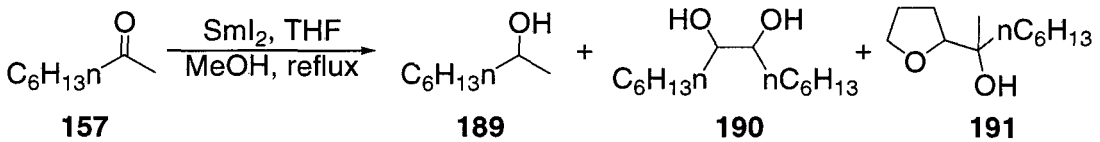
1.2.6 Mechanistic Considerations

A report dedicated to addressing the mechanism of SmI_2 reactions was published by Kagan in 1981.[87] Therein he describes the mode of action of organic halide reduction, carbonyl group reduction and condensation between ketones and organic halides (SBR).

With regard to the reduction of organic halides Kagan dismisses a mechanism involving an organosamarium intermediate in favour of a radical process in which the radical intermediates abstract a hydrogen atom from the solvent (THF). In support of this view he reports that when reduction of halides were followed by a D_2O quench no deuterated products were isolated, furthermore when ketones were added no coupled products were observed leading to the conclusion that organosamarium intermediates were not involved.

The reduction of ketones by SmI_2 gave rise to the corresponding alcohols in good yields, and Kagan proposed that the mechanism proceeds *via* a ketyl radical intermediate. In accord with this mechanism Kagan reports that upon reduction of 2-octanone **157**, as well as the expected alcohol product **189**, trace amounts of pinacolisation **190** and 'solvent adduct' products **191** were isolated (**Scheme 36**)

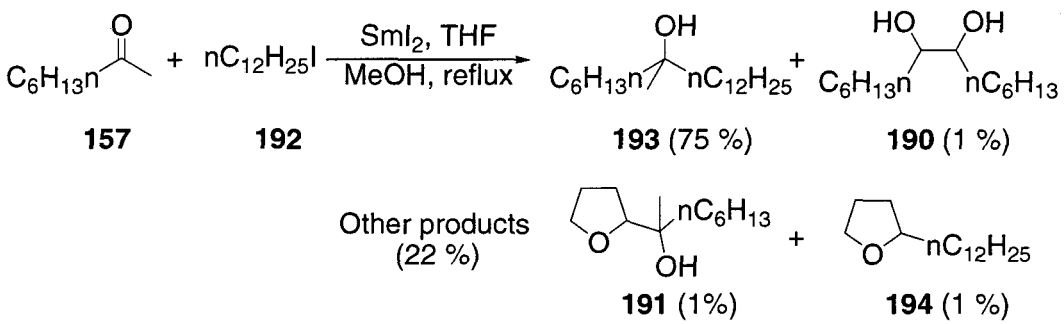
indicative of ketyl intermediates. In a subsequent paper Kagan reports the successful pinacolisation of numerous aldehydes and ketones using a SmI_2 / THF system in which no alcohol additive is used.[80]



157 **189** **190** **191**

Scheme 36

Kagan then turned his attention to the coupling between organic halides and ketones. In order to determine the exact nature of the transformation a thorough examination of the reaction products was undertaken in the reaction between 2-octanone **157** and 1-iodododecane **192 (Scheme 37)**.



157 **192** **193** (75 %) **190** (1 %)

191 (1%) **194** (1 %)

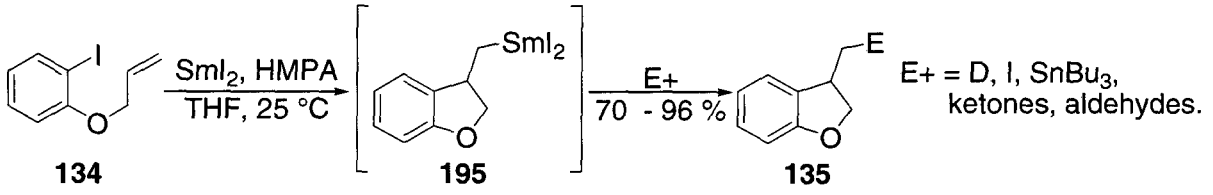
Scheme 37

As well as expected tertiary alcohol product **193**, trace amounts of pinacolised product **190** and 'solvent adduct' products **191** were once again detected. In addition a 'solvent adduct' product **194** arising from coupling between dodecane radicals and THF radicals was also found. This result clearly indicated the presence of radicals and ketyl radicals in solution, and coupled with his observations for the reduction of organic halides and carbonyl compounds, appears to suggest that organosamarium species are not involved in Barbier type reactions.

Kagan tentatively concluded that a radical to ketyl coupling could be a plausible mechanism. Although, he falls short of declaring it the only possible process at work due to some evidence of anionic chemistry, which he puts down to transient anions rather than stable organosamarium species.

The view that organosamarium species were not viable intermediates was soon altered in light of work carried out by Curran.[76] In a study on aryl radical cyclisations mediated

by SmI_2, Curran found that by performing a deuterium quench after cyclisation resulted in 90 % deuterium incorporation into the final product. Further quenching investigations with a multitude of electrophiles gave rise to highly functionalised products **135 (Scheme 38)**.[66, 90]



134 **195** **135**

Scheme 38

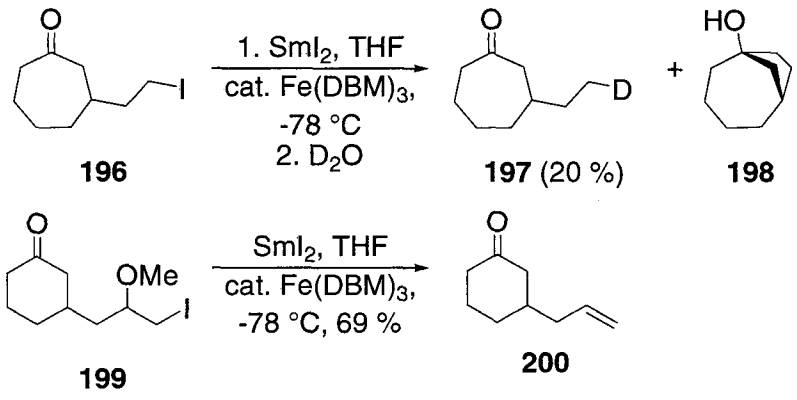
If the anionic species were indeed transient as Kagan pointed out, then they would be instantaneously protonated before the electrophile was even added. In a report by Molander from 1987 he describes a reaction in which deuterium trapping was successful with MeOD;[60] however, the MeOD was added at the beginning of the reaction as a proton source not as a quench, making it difficult to conclude whether the deuterium incorporation was from transient anions or an organosamarium species. What is clear from Curran's studies is that because the electrophiles were added after the cyclisation, then any transient anions would have been already quenched by the solvent system. Thus, the formation of coupled products must be down to long lived stable organosamarium intermediates of the type **195 (Scheme 38)** .[66]

In agreement with Curran's work, Molander also published a paper describing similar *in situ* electrophilic quenches subsequent to SmI_2 mediated ketyl-olefin radical cyclisations.[92]

It is clear then that under SGR conditions organosamarium intermediates play a pivotal role in product formation. Curran then set about determining whether or not such intermediates were present in SBR conditions by using a stereochemical probe. The idea was to react an alkylsamarium species with a prochiral ketone under SBR and SGR conditions. If the mechanisms were the same then the same degree of asymmetric induction should be observed. In over a dozen systems the level of induction was always the same ratio (within experimental error) thus providing strong evidence that SBR conditions operate using the same organosamarium intermediates.[66, 112]

Although SGR and SBR conditions are now generally considered to proceed *via* organosamarium intermediates, a question mark still remains over the exact nature of

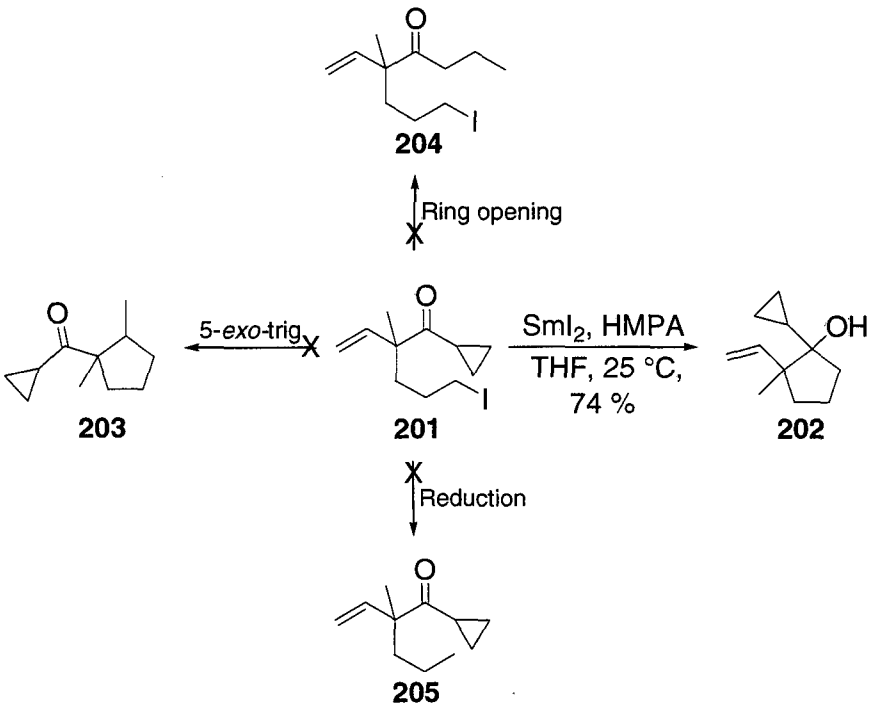
the intermediates involved in the intramolecular samarium Barbier reaction (ISBR).[68, 88] Molander has provided the strongest evidence yet that ISBR's proceed *via* organosamarium intermediates (**Scheme 39**).[113]



Scheme 39

Reaction of cycloheptanone derivative **196** with SmI_2 at low temperature, followed by a rapid D_2O quench provided deuterated product **197**, along with an unspecified amount of recovered **196** and cyclised product **198**. Moreover, when **199** was treated with SmI_2, there was no evidence of a cyclised bridgehead product, only alkene **200** as a result of β-elimination. Molander states that these results provide irrefutable evidence that an organosamarium species can exist in a SmI_2 promoted intramolecular Barbier process.[113]

However, Curran has provided somewhat conflicting evidence.[112] In his report he describes a variety of systems in which he attempts to probe for certain intermediates under the ISBR conditions. His most interesting results were obtained with substrate **201 (Scheme 40)**.



Scheme 40

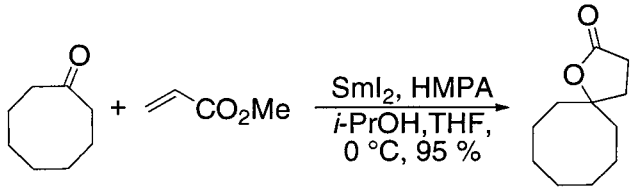
Substrate **201** was designed to probe for several intermediates: (i) If a carbon radical is present then 5-*exo-trig* cyclisation (analogous to the 5-hexenyl radical **38**) to **203** would be expected. (ii) If the reaction proceeds *via* a ketyl radical one would expect favourable cyclopropyl ring opening to occur to give **204**. (iii) Finally, if the intermediate is an organosamarium species, then a proton source such as MeOH and H_2O would be expected to yield **205**.

Remarkably under numerous conditions (varying HMPA concentrations, SmI_2 concentration and the use of 10 equiv. of MeOH or H_2O in some cases) consistently gave rise to cyclised product **202** with no detectable side products (**203**, **204** and **205**). With regard to the organosamarium species this result is most unfortunate, since such species would expect to be quenched by the addition of a proton source, however in this instance they are not.

The main conclusions that can be drawn from these conflicting results is that even subtle changes in the nature of the reaction (SBR versus SGR, or inter versus intra) must play some part in influencing the nature of the C-C bond forming process. Additionally, the reaction conditions and the structure of the substrate itself have the potential to dramatically impact the nature of the mechanism.

1.2.7 α, β-Unsaturated Carbonyl Compounds and Samarium Diiodide

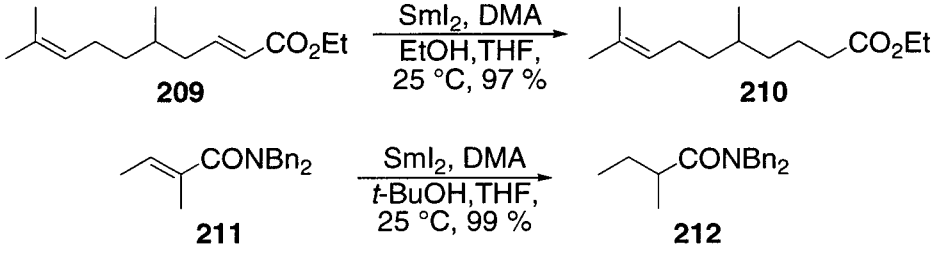
Among its many uses SmI_2 can be used in the treatment of various α, β-unsaturated carbonyl compounds. In 1986 Inanaga demonstrated a two component synthesis of γ-lactones arising from cross coupling of aldehydes and ketones with α, β-unsaturated esters (**Scheme 41**).[114]



206 **207** **208**

Scheme 41

In a subsequent publication Inanaga shows that in the absence of aldehydes and ketones, α, β-unsaturated esters can be effectively reduced to the corresponding saturated esters using a SmI_2, *N*, *N*-dimethylacetamide (DMA) / alcohol and THF system (**Scheme 42**).[115] The reaction is extremely efficient - it takes under two minutes to go to completion.

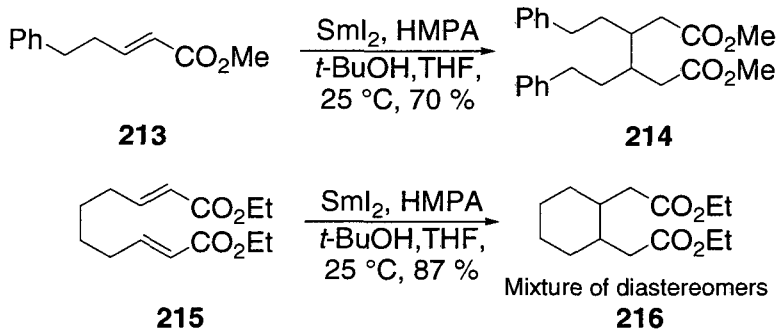


209 **210**

211 **212**

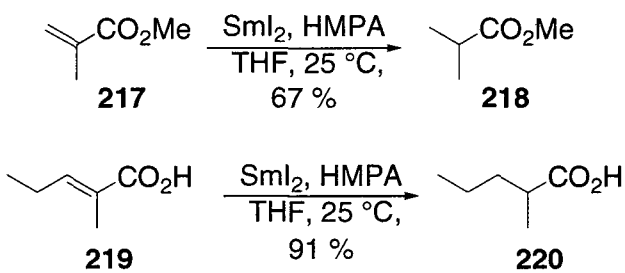
Scheme 42

Noteworthy, is that the unconjugated alkene in ester **209** is not reduced during the course of the reaction and the methodology can be extended to α, β-unsaturated amides **211** also. Interestingly, when HMPA was used as the additive instead of DMA, only hydrodimerised products were observed (**Scheme 43**).[115, 116]



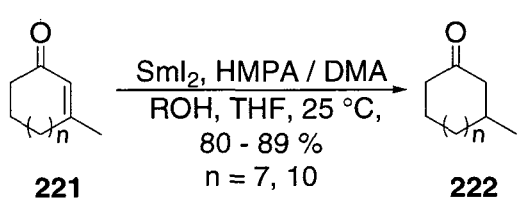
Scheme 43

In contrast, work by Cabrera illustrates that HMPA is in fact an excellent promoter of 1, 4 reduction of α, β-unsaturated esters, amides and acids, giving good to excellent yields (**Scheme 44**).[117] In order to observe behaviour different from Inanaga's results Cabrera found that it is essential that proton sources such as alcohols are not used.



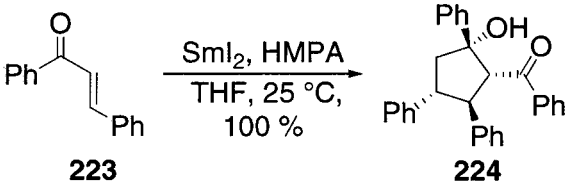
Scheme 44

With regard to α, β-unsaturated ketones, solvent effects have been shown to also have a dramatic effect on the reaction course. Otera found that in the presence of alcohols (*t*-BuOH or MeOH) and an additive (HMPA or DMA), enones were exclusively reduced 1, 4-fashion, with no other products isolated (**Scheme 45**).[118]



Scheme 45

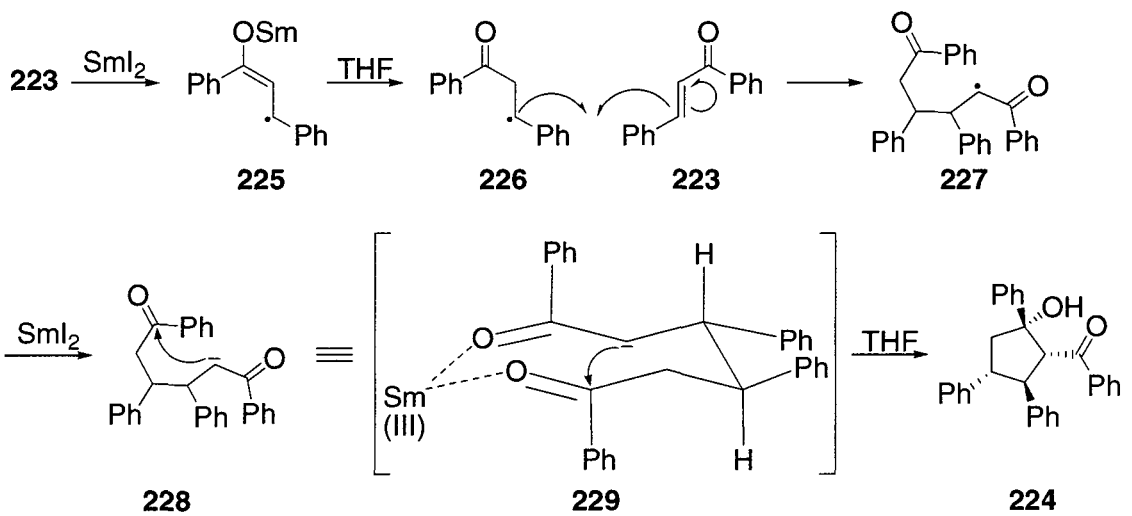
Cabrera has reported that in the presence of HMPA, without a proton source, α, β-unsaturated ketones are not selectively 1, 4-reduced, but undergo cyclo or hydrodimerisation depending on the nature of the substrate.[119] Thus, acyclic ketones have been shown to cyclodimerise in a SmI_2 / HMPA / THF system to give cyclopentanol structures (**Scheme 46**).



223 **224**

Scheme 46

Cabrera proposes a mechanism for the transformation of acyclic ketones into their subsequent cyclopentanol products (**Scheme 47**), which involves THF acting as the proton donor species and radical intermediate **226** adding Michael fashion to another equivalent of enone **223**.[120]

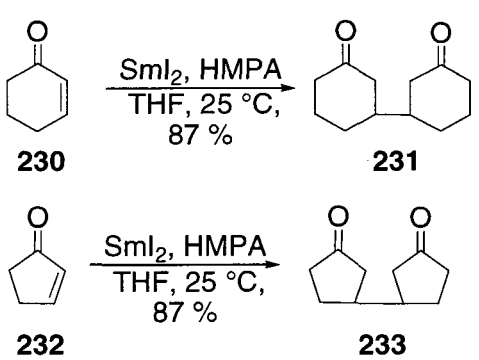


225 **226** **223** **227**

228 **229** **224**

Scheme 47

Further reduction by SmI_2 to **228** and subsequent aldol cyclisation gives **224**, the stereochemistry of which is governed by a chair like transition state **229**, accommodating both ketone oxygens chelating to a Sm (III) species. Contrary to these results, cyclic α, β-unsaturated ketones gave rise to hydrodimerised products (**Scheme 48**).[120, 121] The stereochemistry of these products was not specified.

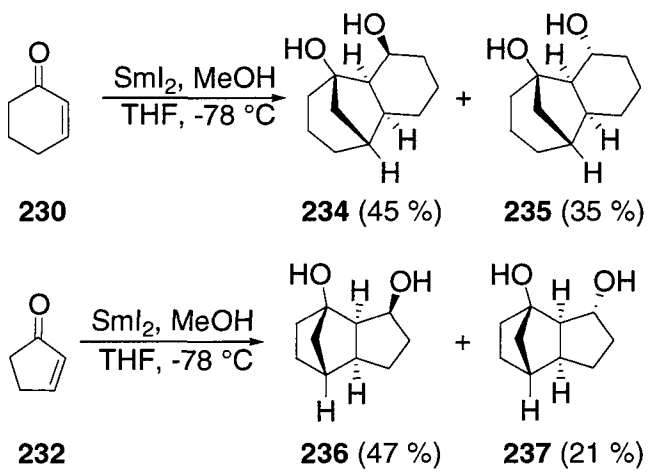


230 **231**

232 **233**

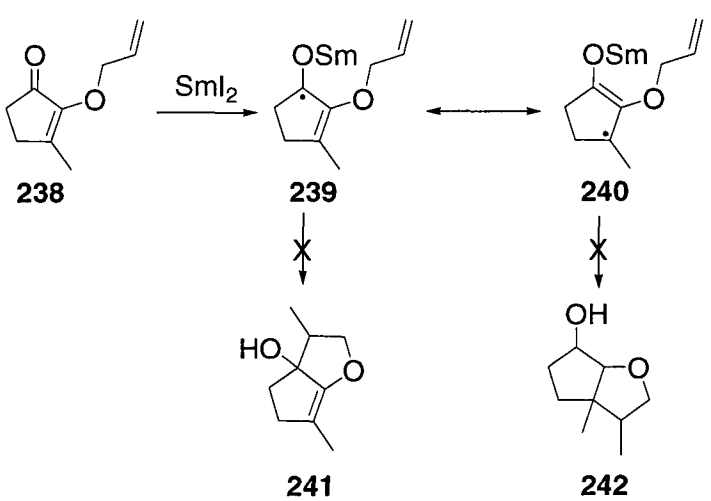
Scheme 48

Recently, in a publication by Kilburn, he reports that cyclic α, β-unsaturated ketones do undergo cyclodimerisation in good yields (**Scheme 49**).[122] This is in stark contrast to Cabrera's results in which no cyclodimerisation was observed.[120, 121] The significant difference between the two sets of results is down to the conditions employed in the reaction. Whereas Cabrera uses HMPA as an additive with no proton source, Kilburn's conditions utilise a MeOH / THF (4:1) system without using HMPA.[123, 124] This is yet another prime example of solvent effects in SmI_2 mediated chemistry.



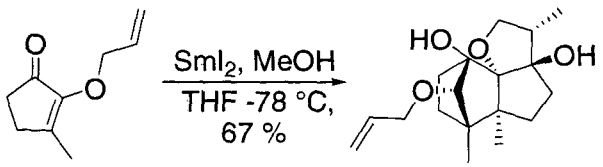
Scheme 49

Cabrera's mechanism proposed that radical intermediate **226** couples with an equivalent of enone **223** (**Scheme 47**). Kilburn suggested therefore that it might be possible to trap the first formed radical with a suitably tethered alkene to provide a novel radical cyclisation pathway (**Scheme 50**). However using ketone **238** as the starting material, products **241** and **242** were not isolated.



Scheme 50

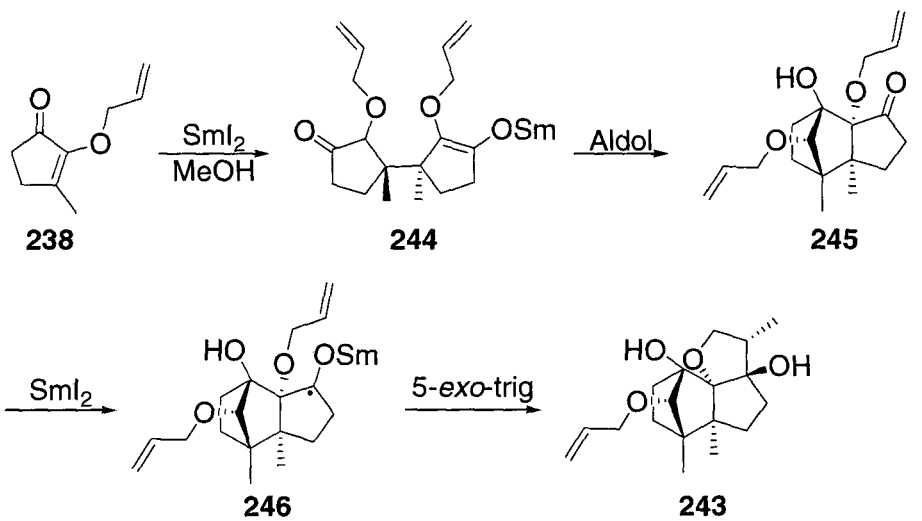
When **238** was treated with SmI_2 using the SmI_2 / MeOH / THF (4:1) system a new compound **243** was formed (**Scheme 51**) in good yield and as a single diastereoisomer.[122]



238 **243**

Scheme 51

Tetracycle **243** appears to be the result of an initial dimerisation followed by an intramolecular aldol condensation. The resulting ketone **245** can then be further reduced to a ketyl **246** which then undergoes a subsequent 5-*exo-trig* cyclisation onto the pendant alkene moiety (**Scheme 52**).



238 **244** **245**

246 **243**

Scheme 52

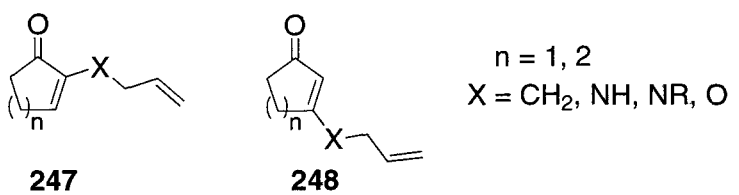
A possible explanation put forward is that the radical cyclisation onto the alkene moiety may be reversible and thermodynamically unfavourable. Alternatively, it was suggested that a complex may exist in which the ketyl oxygen, allyl ether and allylic radical coordinate to a samarium centre and are rendered unreactive towards radical cyclisation. It is then possible that a single electron transfer from SmI_2 to the allylic radical could form an anionic organosamarium intermediate which is unreactive towards cyclisation onto the pendant alkene. Such a species could however react intermolecularly in a Michael fashion to another equivalent of enone **238**. Subsequent aldol, SmI_2 reduction and 5-*exo-trig* cyclisation gives rise to tetracycle **243**.

1.3 Programme of Work

The starting point of this research stems from work previously carried out within the group on cyclic enones in which substrates **230**, **232** and **238** were shown to cyclodimerise utilising a SmI_2 / MeOH / THF system.[122] The interesting reactivity of cyclopentenone derivative **238** which gave rise to complex tetracyclic product **243** **(Scheme 51)** raised questions as to why the anticipated intramolecular 5-*exo-trig* radical cyclisation did not occur.

The main objectives of this research were to investigate the nature of the cyclodimerisation mechanism in more detail, while at the same time extending the methodology to various other types of cyclic enone species

Initial work focussed on the synthesis and SmI_2 studies of substrates of the type **247** and **248 (Figure 12)**, which like cyclopentenone derivative **238** were expected to undergo intramolecular 5-*exo-trig* cyclisation, but could, as already proven give rise to intermolecular products.[122]



247 **248**

Figure 12: Initial substrates targeted.

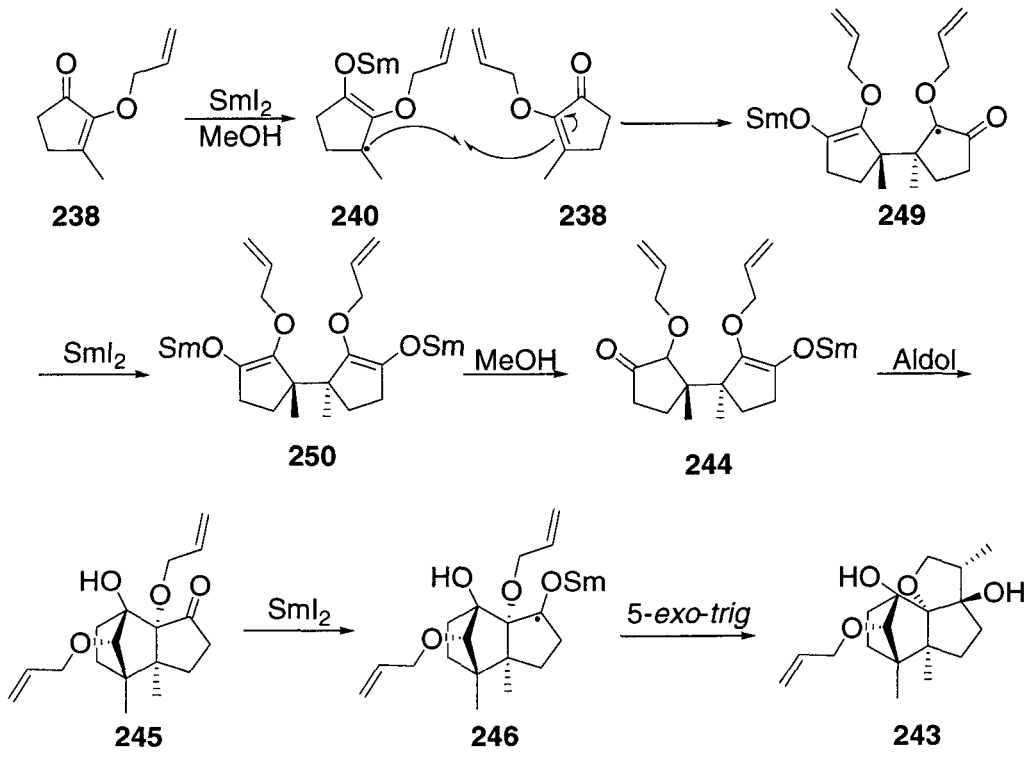
Throughout the course of this project a multitude of different precursors were developed in order to conduct a thorough investigation into the reaction process. Thus, over the course of the research many other substrates were synthesised and studied that have not been shown in this section. The synthesis and SmI_2 investigations of these and substrates of the type **247** and **248** will be fully discussed in the following chapters.

Chapter 2 Cyclic Substrates

2.1 Preamble

2.1.1 Mechanistic Considerations

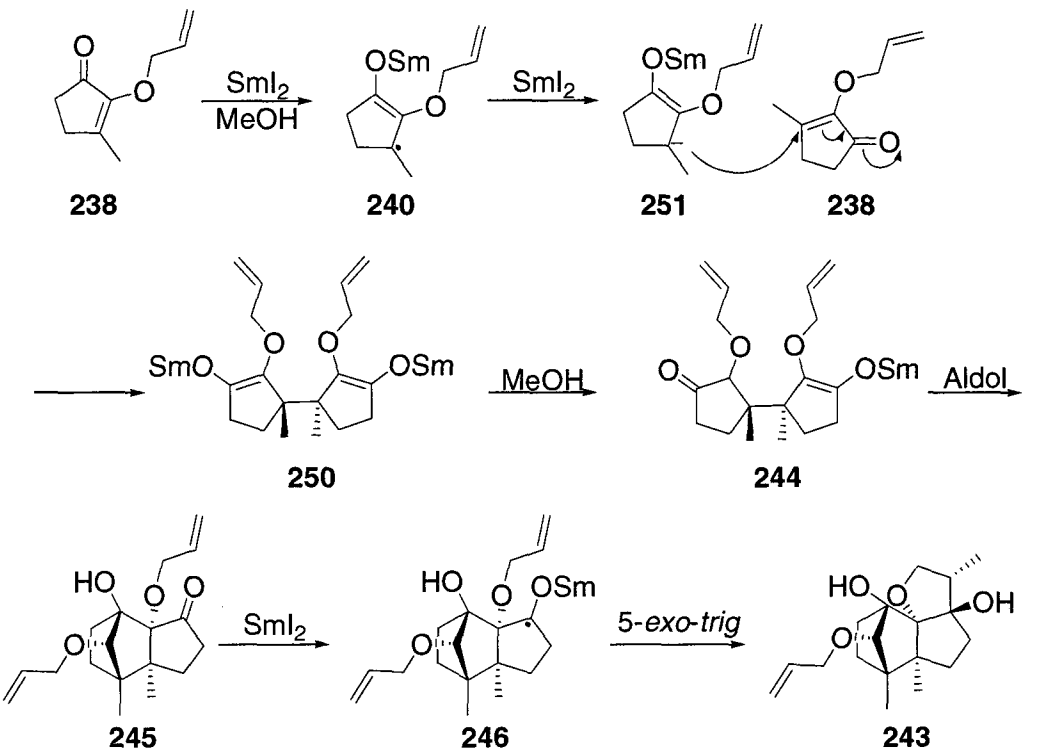
As previously discussed (**Section 1.2.7**), the two major aims of this research were to develop a clearer understanding of the cyclodimerisation mechanism and at the same time extend the methodology to other types of cyclic enone systems. In order to do this, plausible mechanisms by which the transformation of **238** to **243** could occur were considered, and in doing so focus was directed upon particular intermediates to investigate. Therefore, three main mechanisms were considered – a radical based mechanism (**Scheme 53**), an anionic based mechanism (**Scheme 54**) and a radical-radical coupling mechanism (**Scheme 56**).



Scheme 53

It may seem a little surprising that a radical based mechanism was still being considered even though there was no evidence of intramolecular trapping of radical intermediate **240** (**Scheme 50**), however, it was not fully discounted at this stage. Initial radical

dimerisation (reminiscent of Cabrera's mechanism[120] (**Scheme 47**)) between radical **240** and enone **238** would initiate the sequence and subsequently be followed by SmI_2 radical reduction, intramolecular aldol, SmI_2 ketone reduction and finally *5-exo-trig* cyclisation to give **243**.

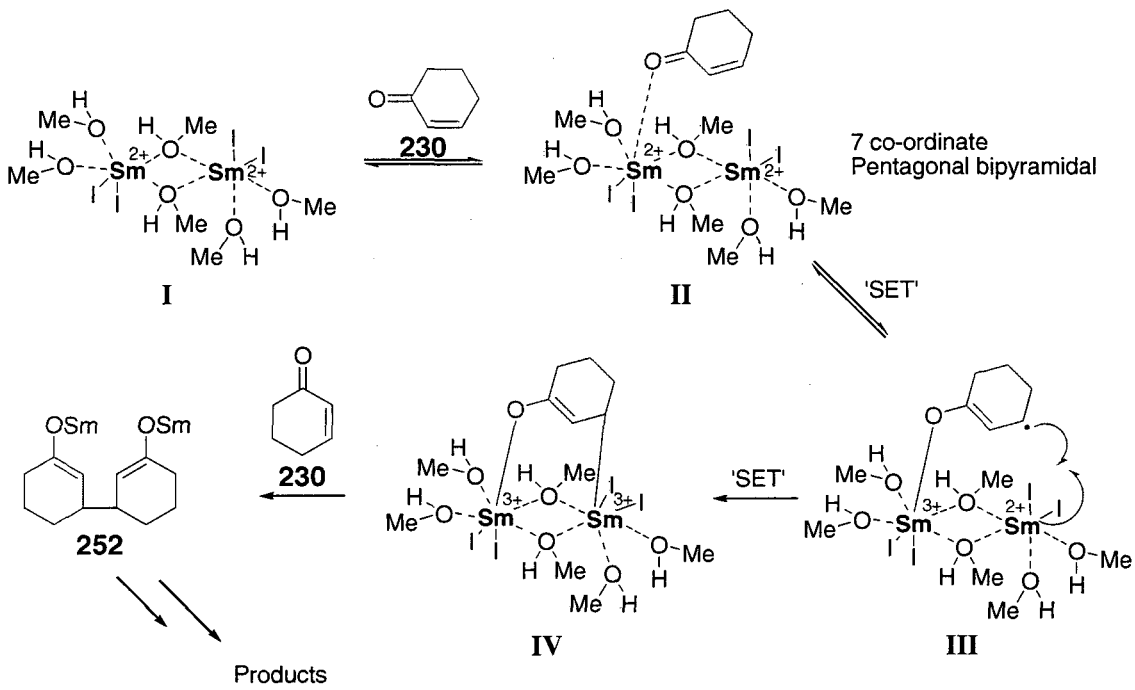


Scheme 54

In a similar vein an alternative anionic based mechanism was also considered (**Scheme 54**). In this instance the initial steps involve SmI_2 reduction of the enone **238** to give radical **240**, ensuing reduction of the radical by a further equivalent of SmI_2 gives anion **251** which then dimerises in a Michael fashion with enone **238**. The remainder of the mechanism follows the same course as before.

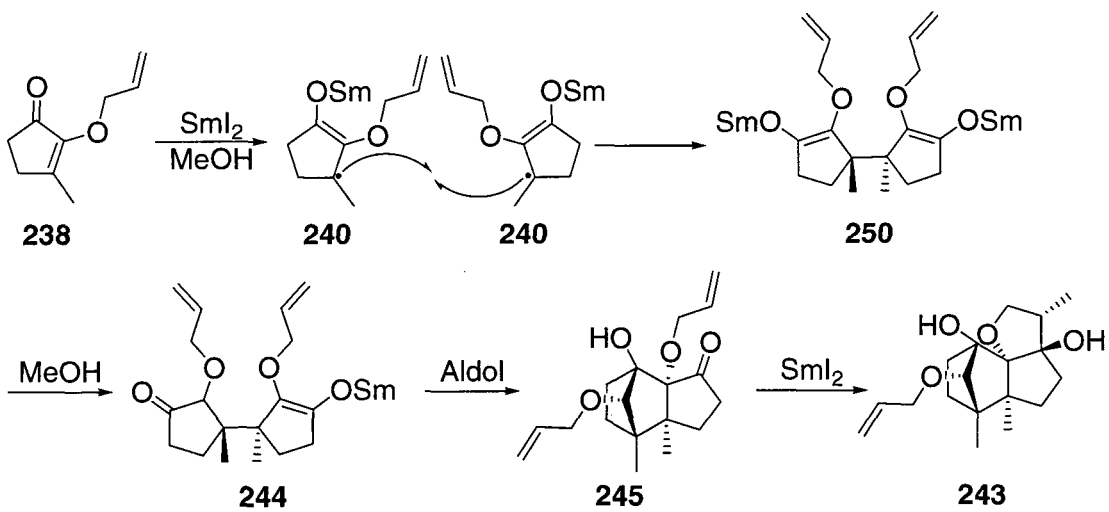
There is good evidence to suggest that an anionic species such as **251** could be a viable intermediate. The well documented reduction of aldehydes and ketones[53, 57, 68, 87, 93, 94] has been shown to occur *via* a dianionic species in which the two anions sit adjacent to one another. More recently it has been suggested that a dimeric samarium species may exist in solution which is able to facilitate such a two electron process in an extremely efficient manner.[101, 103] Consequently, under suitable conditions a samarium species **I** may exist in solution which serves to stabilise such an anionic intermediate (**Scheme 55**). Initial chelation **II** and subsequent reduction of the enone to radical species **III**,

could, due to the proximity to which a further molecule of SmI_2 is situated, undergo a rapid SET to generate anionic species **IV**, which is then stabilised *via* chelation to a Sm (III) species. The anionic species can then undergo Michael addition onto a further equivalent of enone **230**.



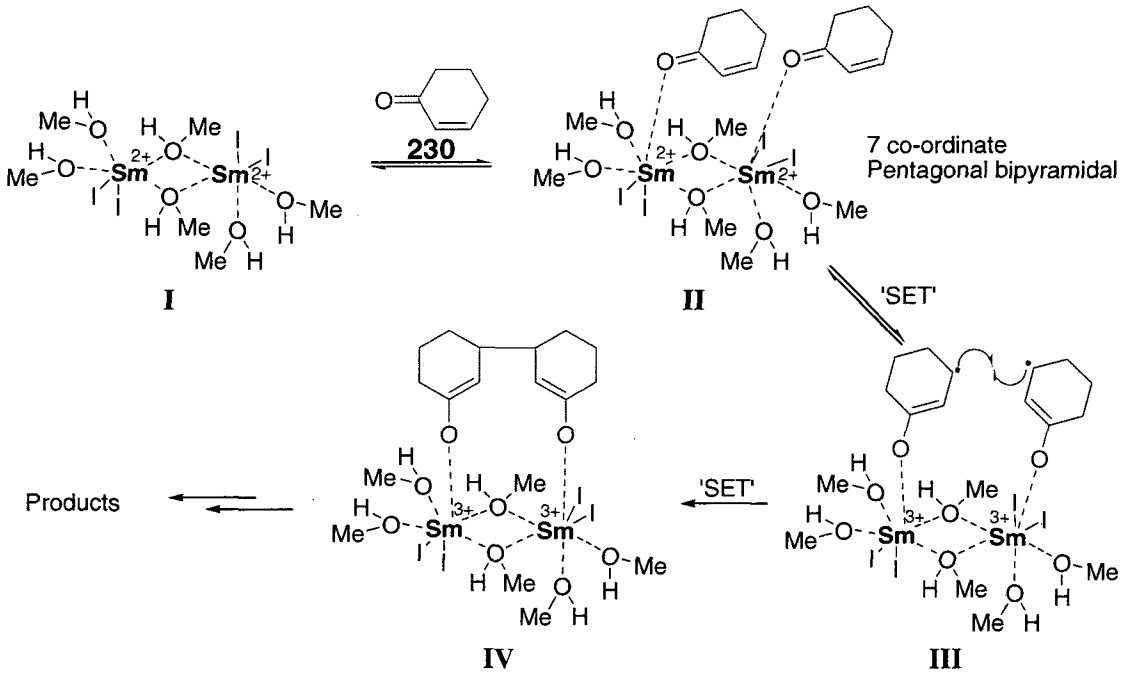
Scheme 55

The third mechanism considered was a radical-radical coupling mechanism (**Scheme 56**), in which the enone is reduced to radical intermediate **240** which then dimerises.



Scheme 56

If an oligomeric samarium species does exist this could serve to favour an intermolecular radical coupling by fixing the two β reacting centres into close proximity to one another **(III, Scheme 57)**, thus disfavouring the expected intramolecular cyclisation pathway.



Scheme 57

Based upon these three proposed mechanisms, three main types of intermediate were targeted for probing studies **(Figure 13)**: β-radical Intermediate **253** (analogous to **240**), radical dimer **254** (analogous to **249**) and β-anion **255** (analogous to **251**).

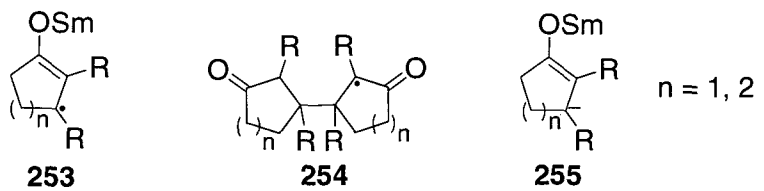
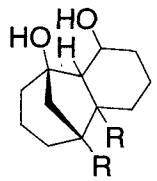


Figure 13: Intermediates targeted for probing studies.

Evidence of intermediates of the type **253** would provide support for the radical Michael addition **(Scheme 53)** and radical-radical mechanism **(Scheme 56)**. Evidence for intermediates of the type **254** would point towards the radical Michael addition mechanism **(Scheme 53)** only, whereas evidence of **255** would point towards the anionic based mechanism **(Scheme 54)**. Therefore a variety of substrates were designed, synthesised and studied in order to probe the intermediacy of **253**, **254** and **255**, and give a greater insight into the exact nature of the dimerisation mechanism.

2.1.2 Stereochemical Evaluation

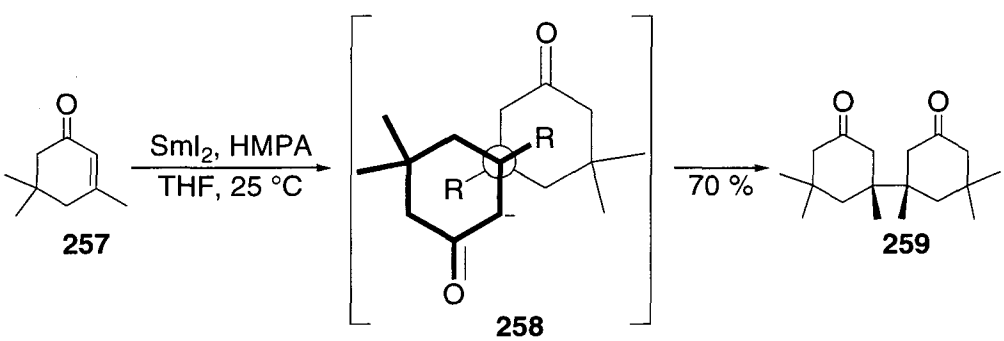
Throughout the course of this research a number of compounds were synthesised with the general tricyclic structure **256 (Figure 14)**.



256

Figure 14: General tricyclic structure **256**.

Interestingly, as already discussed **(Section 1.2.7)**, Cabrera[120] does not observe any cyclodimerised products through reaction of his cyclic substrates. The reason for this, as Cabrera outlines, is exemplified in the reaction with isophorone **257** in which the sterically hindered cyclohexyl rings cannot occupy a suitable position for carbanion attack onto the carbonyl **(Scheme 58)**.



257 **258** **259**

Scheme 58

Isophorone **257** could be considered a unique case due to the bulky nature of the cyclohexyl ring; however, further studies by Cabrera on less sterically demanding cyclohexenone **230** and cyclopentenone **232 (Scheme 48)** species also did not give rise to cyclodimerised products. It seems reasonable to assume therefore that similar conformations to the one shown **258 (Scheme 58)** may also exist for less hindered cyclic substrates such as **230** and **232** using Cabrera's particular HMPA conditions.

In contrast, we propose a system in which both oxygen atoms are brought into close proximity to one another through chelation with a Sm^{3+} species, bringing the cyclohexyl rings into a suitable position for subsequent carbanion attack (cyclodimerisation).

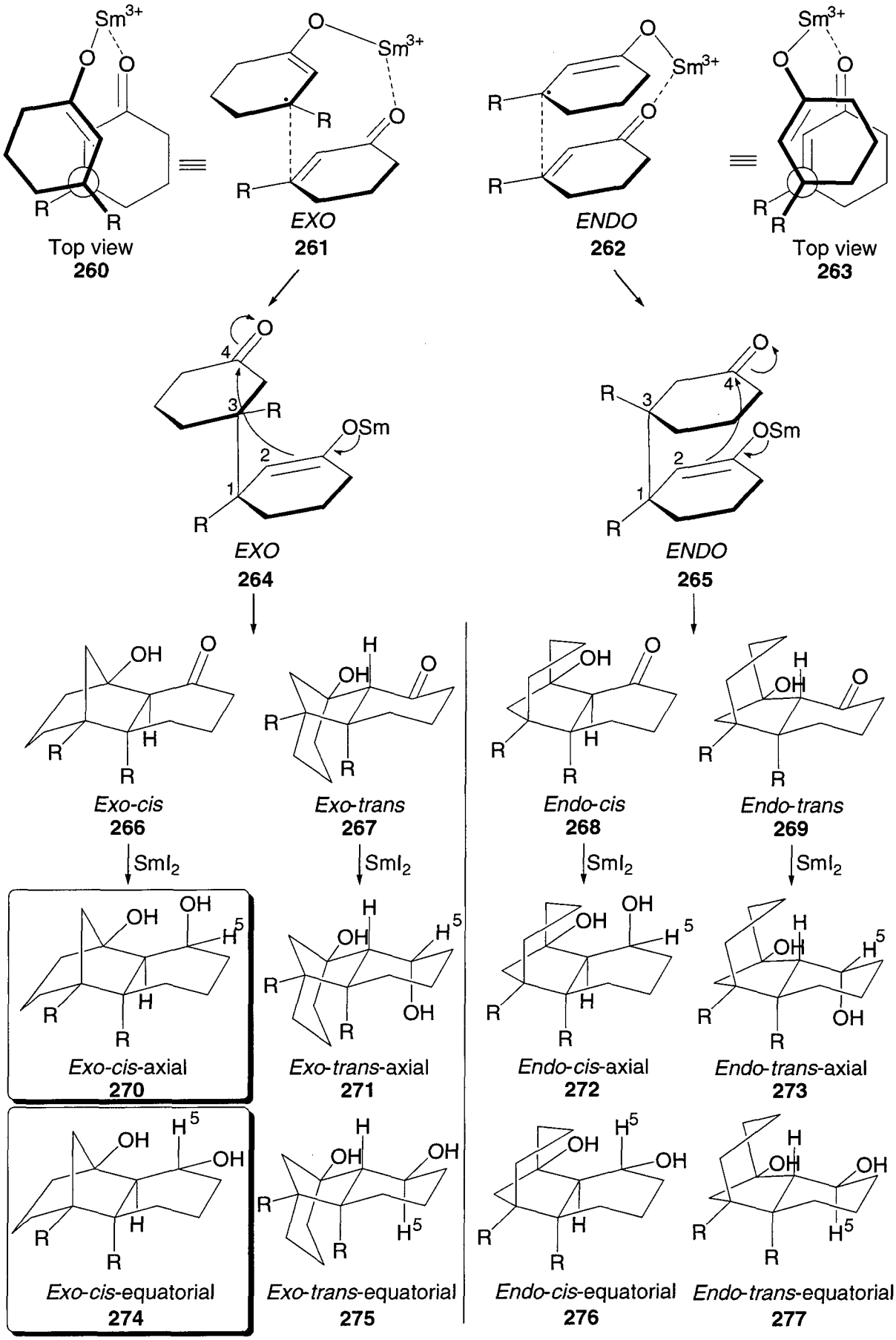
In order to delineate the most probable diastereoisomers that may arise throughout the course of the SmI_2 mediated reactions, different modes of dimerisation were considered: an *exo* or *endo* mode of dimerisation (**261** and **262, Scheme 59**). An important aspect also considered was that rotation about the forming C-C bond could lead to a number of conformations; however, the conformations shown (**260** and **263**) are probably the most stable due to chelation control from a samarium species fixing the ketyl oxygen and enone oxygen in close proximity to one another. For clarity, a monomeric samarium species is shown, however it is reasonable to assume that an oligomeric samarium species (**I, Scheme 55**) may play an important role in fixing the conformation.

Thus, it seems probable that during the aldol condensation (**264** and **265**), continual co-ordination between the ketone, Sm^{3+} and enolate ensures that the cyclohexanone is held in a pseudo axial orientation on the enone ring system. Consequently, enolate attack from the top face onto the bottom face of the cyclohexyl ketone ensures that the resulting alcohol at C4 and the R group at C3 are *cis* with respect to one another, and the ring juncture at C1 and C2 is also *cis* (**266** and **268**).

Importantly, although these arguments imply a *cis* ring juncture will predominate, they cannot rule out that a small proportion of **267** and **269** with a *trans* ring junction could occur. Finally, SmI_2 mediated reduction of the ketones **266**, **267**, **268** and **269** to the axial or equatorial alcohols **270** - **277** completes the process (**Scheme 59**).

Scheme 59 shows two important structures **264** and **265** resulting from attack of the radical species in an *exo* or *endo* fashion onto the enone. *Exo* conformation **261** can be considered the major route of attack as it minimises any steric interactions with the enone. In contrast, *endo* conformation **262** in which both rings are largely eclipsed, gives rise to large amounts of steric repulsion, making it the minor route of attack.

Thus, based on these arguments, the two expected dominant diastereoisomers would be *exo-cis*-axial **270** and *exo-cis*-equatorial **274** (as highlighted in **Scheme 59**) whilst *exo-trans*-axial **271** and *exo-trans*-equatorial **275** would make up a minor proportion. Following a similar pattern *endo-cis*-axial **272** and *endo-cis*-equatorial **276** would occur in even smaller quantities, whilst *endo-trans*-axial **273** or *endo-trans*-equatorial **277** would be most disfavoured of all.


Top view
260
EXO
261
ENDO
262
Top view
263
EXO
264
ENDO
265
Exo-cis
266
Exo-trans
267
Endo-cis
268
Endo-trans
269
SmI2
Exo-cis-axial
270
Exo-trans-axial
271
Endo-cis-axial
272
Endo-trans-axial
273
Exo-cis-equatorial
274
Exo-trans-equatorial
275
Endo-cis-equatorial
276
Endo-trans-equatorial
277

Scheme 59

The assignments, *exo* or *endo* refers to the mode of attack, and axial or equatorial to the position of the OH group. In order to determine the exact position of the OH group i.e. axial or equatorial, the characteristic axial and equatorial coupling constants observed for H5 were utilised.

For *exo-cis*-axial **270**, *exo-trans*-axial **271**, *endo-cis*-axial **272** and *endo-trans*-axial **273** structures, one would expect to observe two eq-ax couplings and a single eq-eq coupling. This was most commonly represented by a broad singlet in the ^{1}H NMR due to the small coupling constants typical of equatorial couplings. Conversely, for *exo-cis*-equatorial **274**, *exo-trans*-equatorial **275**, *endo-cis*-equatorial **276** and *endo-trans*-equatorial **277** structures, one would expect two ax-ax couplings and a single ax-eq coupling. This was most commonly represented by a td or ddd in the ^{1}H NMR with coupling constants in the range of 9-12 Hz typical of ax-ax couplings.

For clarity, the structures can be drawn in an alternative manner (**Figure 15**).

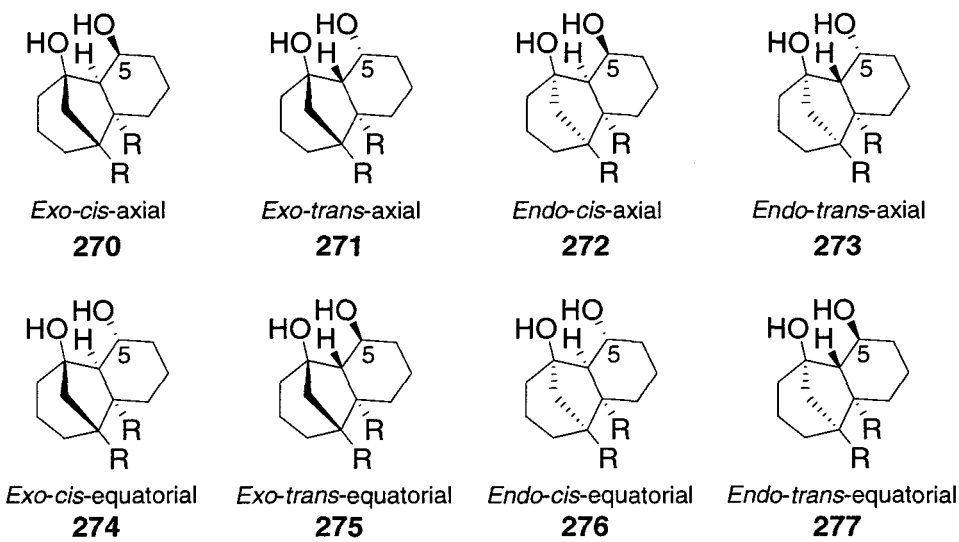
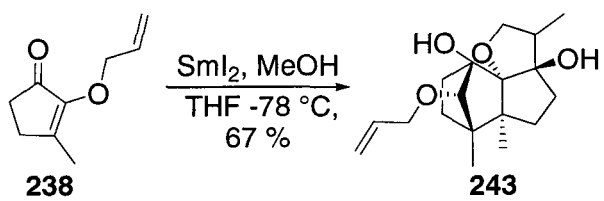


Figure 15: The eight proposed diastereoisomers.

Previous work from within the group gives strong support in favour of the proposed major *exo-cis* diastereoisomers **270** and **274** [122] (**Scheme 51**).



Scheme 51

The only product isolated from reaction of **238** with SmI_2 was the *exo-cis* isomer **243**, x-ray data confirmed the structure.[122] It was confidently assumed then, that any compounds of the type **256 (Figure 14)** isolated were in the form of the *exo-cis* isomers **270** or **274**. In certain circumstances in which more than two isomers have been isolated, it has been assumed that they are either *exo-trans* (**271** or **275**) or *endo-cis* in nature (**272** or **276**).

To summarise, eight possible diastereoisomers that can arise for the tricyclic structures have been proposed **(Scheme 59)**. Furthermore, of the eight isomers, it has been determined that the *exo-cis* isomers are the most likely products to be obtained due to chelation control and steric grounds in the intermediates **(Scheme 59)**. The process of determining the axial or equatorial nature of the OH group at C5 has also been discussed.

2.2 Preparation of Samarium Diiodide

Throughout the course of this project SmI_2 (0.1 M) was prepared using Curran's procedure of mixing Sm metal and 1, 2-diiodoethane together in oxygen and moisture free THF under an atmosphere of argon.[125] A deep blue solution with no visible evidence of a yellow solid was observed after one to two hours of vigorous stirring, indicative of good quality SmI_2. Distilled and de-gassed MeOH was then added in one portion (THF / MeOH, 4:1) resulting in a purple solution of SmI_2 which was subsequently cooled to – 78 °C before addition of the substrates.[122]

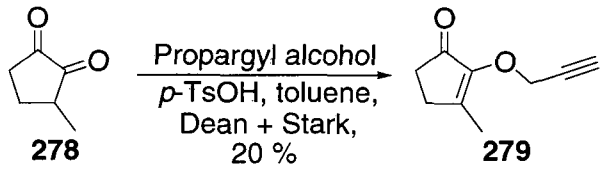
2.3 α-Substituted Substrates

Building upon the interesting result obtained with α-substituted allyloxy enone **238**,[122] a variety of other α-substituted analogues were investigated. Substrates of this type were expected to probe the intermediacy of radical intermediate **253 (Figure 13)**.

2.3.1 Synthesis

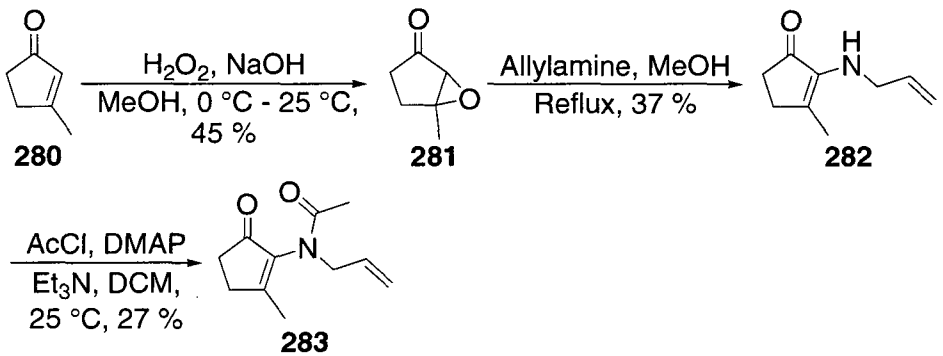
A variety of α-substituted substrates were synthesised incorporating ether, amine and amide functionalities into the side chain. Propargylic ether **279** was synthesised from

commercially available 3-methylcyclopentane-1, 2-dione **278** using Pirrung's protocol[126] **(Scheme 60)**.



Scheme 60

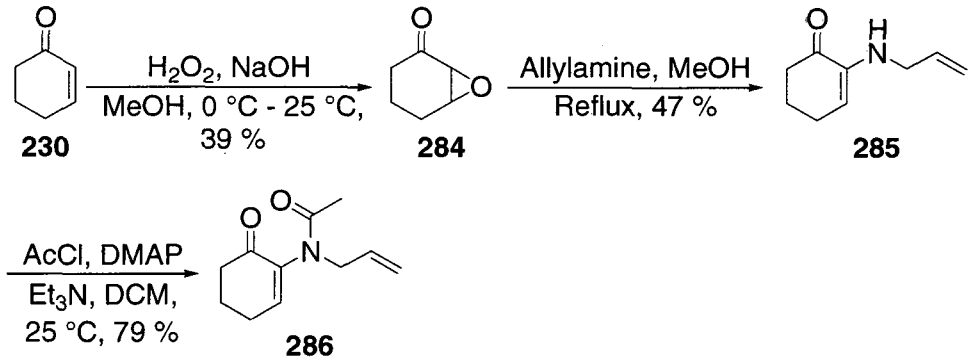
Acetamide **283** was synthesised in three steps from commercially available 3-methyl-2-cyclopentenone **280 (Scheme 61)**. Nucleophilic epoxidation[127] with hydrogen peroxide gave **281**, which, following treatment with allylamine[128] afforded unstable amine **282**.



Scheme 61

Amine **282** proved difficult to isolate in any appreciable amounts; upon purification by column chromatography, clear degradation of **282** was observed and only very small quantities could be isolated. Furthermore, when isolated, if left open to the atmosphere **282** degraded over the course of one to two hours. The purification problem was resolved when a small amount (2-3 %) of Et_3N was used in the initial eluent making up the column. Upon isolation, **282** was immediately stored under argon and directly acylated to yield the more stable acetamide **283**.

Amine **285** and acetamide **286** were next targeted **(Scheme 62)**. The synthesis follows the same course as precursor **283**, and thus, the same isolation issues with amine **285** were faced. Interestingly, although unstable, **285** did not degrade as quickly as **282** (if stored under argon it could last up to 24 hours), and so this allowed SmI_2 studies to be conducted and its reactivity directly compared with amide counterpart **286**.

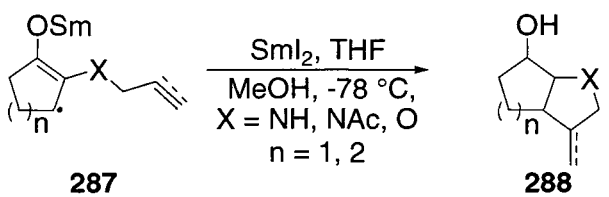


230 **284** **285** **286**

Scheme 62

2.3.2 Samarium Diiodide Studies

The construction of fused rings by the hexenyl radical cyclisation is well documented and understood.[36, 129-133] Thus, the α-substituted precursors were expected to undergo 5-*exo-trig* cyclisation, leading to bicyclo-octane compounds of the type **288 (Scheme 63)**. It was also conceivable, that these types of substrates could also react intermolecularly as demonstrated by allyloxy enone **238 (Scheme 51)**.[122]

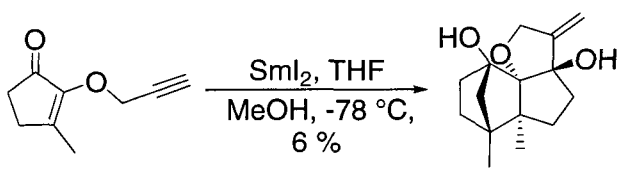


287 **288**

Scheme 63

2.3.2.1 Propargylic Ether 279

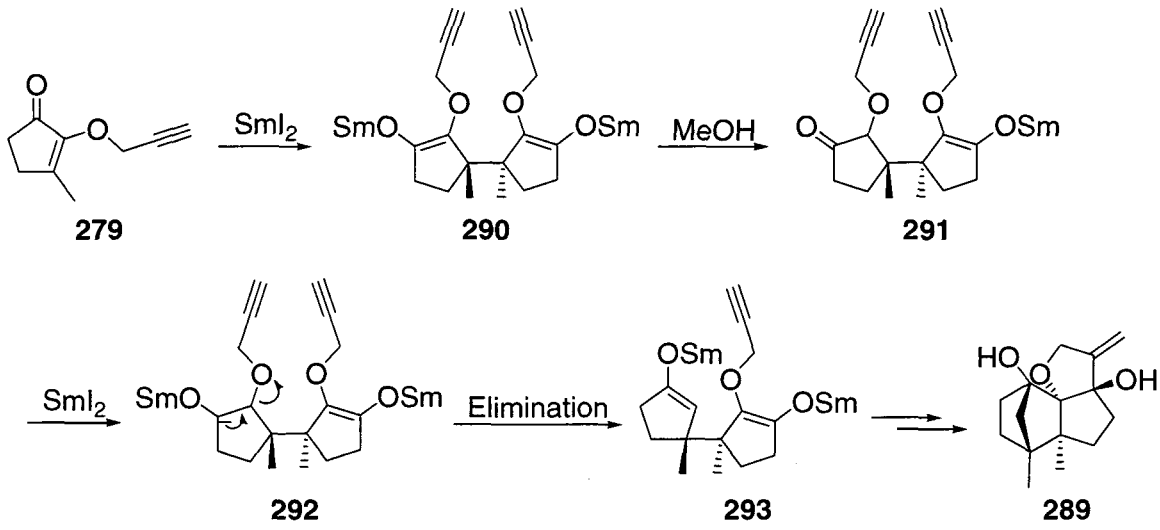
Propargylic ether **279** was treated with SmI_2 and afforded tetracycle **289** as a single diastereoisomer **(Scheme 64)**. The reaction, although low yielding, gave only one other product which unfortunately could not be identified (5 % yield by mass), in addition a small quantity of starting material **279** was also recovered.



279 **289**

Scheme 64

At first glance this result appeared analogous to that of the allyloxy precursor **238** **(Scheme 51)**, however, analysis revealed that there was no longer an ether moiety attached to the bridgehead. Molander[56, 57] has reported similar β-eliminations of OR substituents from saturated ketones, and so a mechanism by which this process could occur in these unsaturated systems is proposed **(Scheme 65)**.

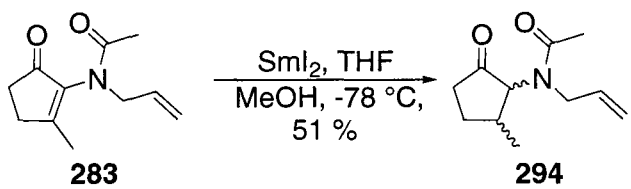


Scheme 65

Dimerisation of **279** to the di-enolate **290** and subsequent protonation with MeOH gives ketone **291** which is subject to rapid reduction to the corresponding anion **292**. The instability of the di-anion species **292** is quickly dissipated upon β-elimination of propargyl alcohol leading to enolate species **293**. The mechanism from this point then follows the same course as outlined in **Section 2.1**. The formation of product **289** does not help to determine the nature of the dimerisation process.

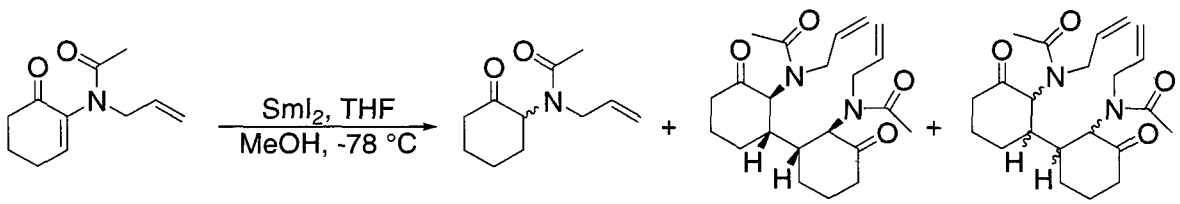
2.3.2.2 Cyclopentyl Acetamide 283 and Cyclohexyl Acetamide 286

Upon treatment with SmI_2, acetamide **283** gave the unexpected 1, 4-reduced product **294** as the only product **(Scheme 66)**. Unlike previous precursors **238**[122] and **279**, acetamide **283** does not follow the same reaction course.



Scheme 66

As a direct comparison with cyclopentyl acetamide **283**, cyclohexyl acetamide **286** was also studied. Treatment with SmI_2 afforded dimers **296** and **297** along with a small quantity of 1, 4-reduced compound **295** (**Scheme 67**). X-ray data subsequently confirmed the stereochemistry of dimer **296** (**Figure 16**).



286 **295** (9 %) **296** (43 %) **297** (28 %)

Scheme 67

In contrast with cyclopentyl acetamide **283** in which 1, 4-reduction predominated, cyclohexyl acetamide **286** gave rise to hydrodimers **296** and **297** as the major products. The stereochemistry of hydrodimer **296** is *meso* and is reminiscent of Cabrera's work in which isophorone **257** generated *meso* dimer **259** (**Scheme 58**). Thus, in a similar fashion to isophorone **257**, acetamide **286** may not cyclodimerise due to the bulky α-substituents stopping the cyclohexyl rings from taking up the required position for anionic attack onto the carbonyl moiety (cyclodimerisation). The dimerisation of acetamide **286** might therefore proceed *via* a similar conformation **258** to the one shown for isophorone **257** (**Scheme 58**).

The difference in reactivity between cyclopentyl acetamide **283** and cyclohexyl acetamide **286** is difficult to interpret, however a possible explanation can be ascribed to steric factors. In the case of cyclopentyl acetamide **283**, due to the presence of the bulky α substituent, the reacting β centres are unable to move into close enough proximity to one another to allow dimerisation. Therefore 1, 4-reduction is faster than dimerisation in this instance.

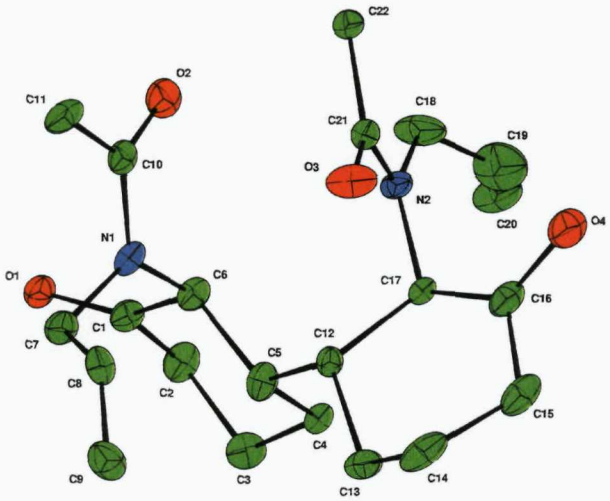
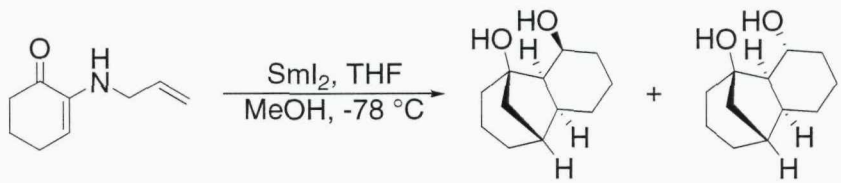


Figure 16: Crystal structure of dimer **296**.

2.3.2.3 Amine 285

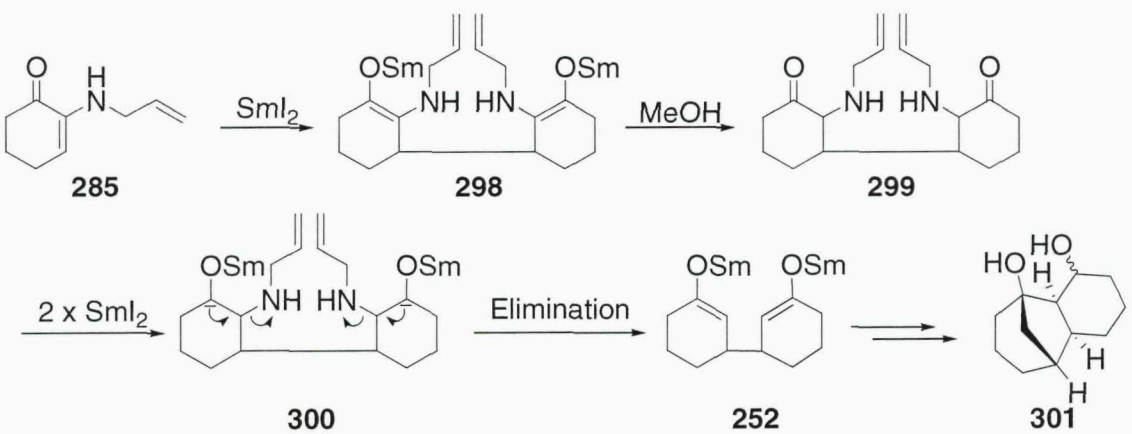
Exposure of **285** to SmI_2 gave cyclodimerised products **234** and **235**, in which both amine substituents had been eliminated (**Scheme 68**).



285 **234** (30 %) **235** (7 %)

Scheme 68

Many examples of β-eliminations mediated by SmI_2 have been described,[56, 57, 64, 73] however, to the best of our knowledge β-elimination of an amine component from an enone has not been reported. A mechanism by which this process could occur is shown (**Scheme 69**).



285 **298** **299** **300** **252** **301**

Scheme 69

Initial dimerisation of amine **285** to the di-enolate **298**, followed by protonation with MeOH gives di-ketone **329**. Subsequent reduction to the anionic intermediate **300** is then followed by a double elimination of the amine side chains. The resultant di-enolate **252** is then converted into tricycle **301** *via* the mechanism previously discussed in **Section 2.1**.

The difference in reactivity of acetamide **286** (dimerisation) and amine **285** (elimination) is difficult to interpret, since theoretically one would expect the amide side chain to undergo β elimination more readily in comparison to the amine **285** counterpart. However, this was not the case, and unfortunately the observed reactivity cannot be explained.

The crystal structure of **234** confirmed the *exo-cis*-axial stereochemistry (**Figure 17**).

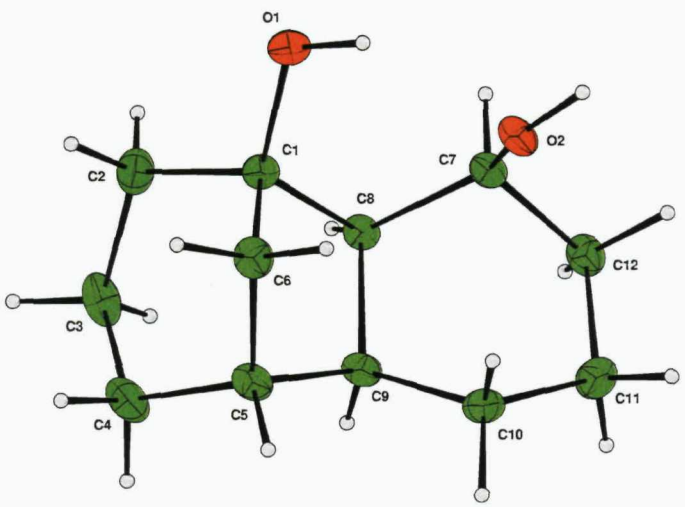


Figure 17: Crystal structure of cyclodimer **234**.

2.3.3 Conclusion

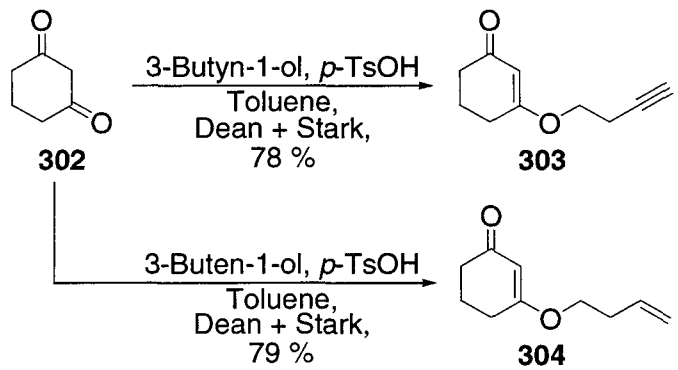
None of the investigated α-substituted precursors underwent radical cyclisation to generate bicyclo-octane type compounds **288**. As a result, these studies gave no evidence for the intermediacy of radical species **253** (**Figure 13**) and therefore no evidence for either of the radical dimerisation mechanisms (**Schemes 53** and **56**). In a similar fashion to previous work,[122] these results point towards a possible anionic dimerisation pathway (**Scheme 54**).

2.4 β-Substituted Substrates

Another objective was to synthesise a range of β-substituted precursors, and study their reactivity upon treatment with SmI_2. Precursors of this type were designed to probe the intermediacy of radical **253** (**Figure 13**).

2.4.1 Synthesis

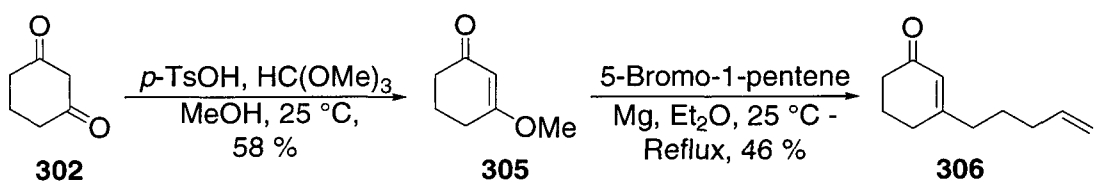
Synthesis of ether **303** was straightforwardly achieved in one step from commercially available 1, 3-cyclohexandione **302**[134] (**Scheme 70**).



Scheme 70

Similarly, ether **304** was also synthesised from 1, 3-cyclohexandione **302**[135] in a straightforward manner (**Scheme 70**).

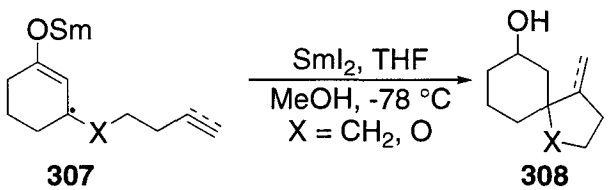
Synthesis of an all carbon β-chain substituent **306** was successfully accomplished *via* a two step procedure starting from 1, 3-cyclohexandione **302**. Conversion into enol ether **305**[136] followed by condensation with the Grignard reagent derived from 5-bromo-1-pentene[137] furnished the desired substrate **306** in moderate yield (**Scheme 71**).



Scheme 71

2.4.2 Samarium Diiodide Studies

In a similar vein to α-substituted enones **(Section 2.3)**, β-substituted precursors were expected to trap initial radical intermediate **307**, *via* a 5-*exo-trig* cyclisation to give rise to spirocyclic compounds **308 (Scheme 72)**.



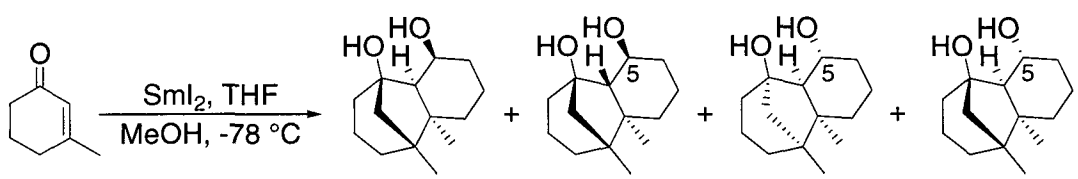
307 **308**

Scheme 72

Previous α-substituted precursors had failed to give any intramolecular cyclised products; however, by introducing substituents at the β-radical centre, the course of the reaction was expected to change. If the reaction did proceed *via* a radical mechanism, then by adding a level of steric bulk around the reacting β centre, one would expect dimerisation to become disfavoured and consequently promote intramolecular cyclisation.

2.4.2.1 3-Methyl-2-cyclohexenone 309

Commercially available 3-methyl-2-cyclohexenone **309** was studied in order to ascertain the types of products that could be obtained without the presence of an intramolecular radical trap. In a similar vein to 2-cyclohexen-1-one **230** and 2-cyclopenten-1-one **232 (Scheme 49)**, cyclodimerised type products were expected to form. Indeed, upon treatment with SmI_2 3-methyl-2-cyclohexenone **309** gave four diastereomeric cyclodimers **310**, **311**, **312** and **313** in good overall yield **(Scheme 73)**.



309 **310** (35 %) **311** (12 %) **312** (6 %) **313** (30 %)

Scheme 73

Based on the model predictions **(Section 2.1.2)** the diastereoisomers shown would be expected. Major cyclodimer **310** exists as the *exo-cis*-axial isomer, the stereochemistry

has been confirmed by x-ray (**Figure 18**). The other major product isolated is *exo-cis*-equatorial isomer **313**; the equatorial nature of the OH has been confirmed by ^{1}H NMR (H5 = td, J = 11.5, 4.3 Hz). *Exo-trans*-equatorial **311** and *endo-cis*-equatorial **312** were isolated as an inseparable 1.5:1 mixture of diastereoisomers, and once again the equatorial nature of the OH in each case was confirmed by ^{1}H NMR (H5, ddd, J = 11.7, 9.3, 5.0 Hz and H5, ddd J = 12.8, 9.5, 3.1 Hz).

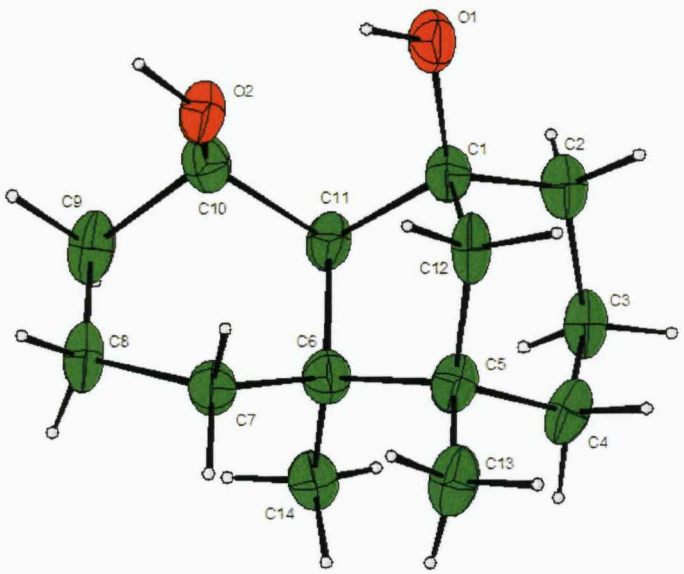
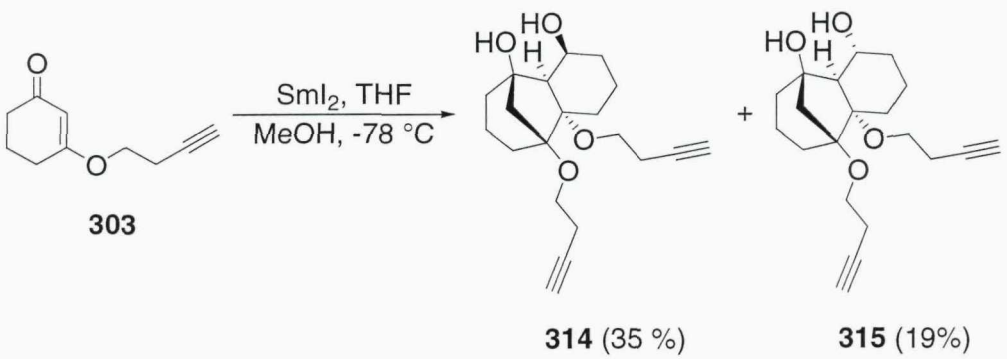


Figure 18: Crystal structure of cyclodimer **310**.

2.4.2.2 Ethers 303 and 304

Upon treatment with SmI_2, ether **303** gave two tricyclic compounds, *exo-cis*-axial isomer **314**, and *exo-cis*-equatorial isomer **315** (**Scheme 74**). There was no evidence of spirocyclic product **308**.



303

314 (35 %) **315** (19%)

Scheme 74

Confirmation of the stereochemistry of **315** was provided by x-ray crystal structure **(Figure 19)**.

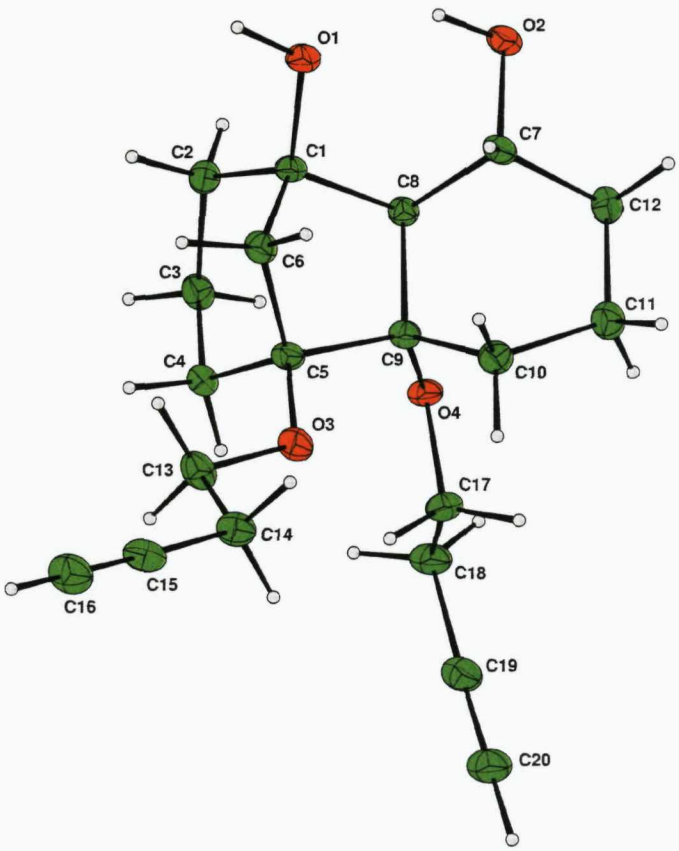
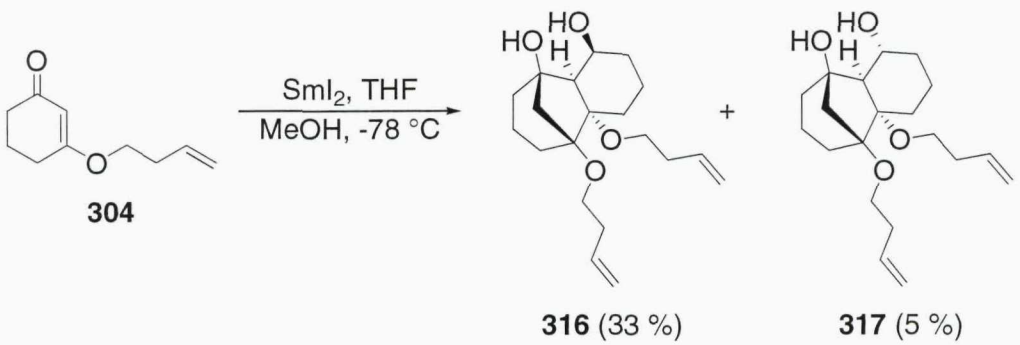


Figure 19: Crystal structure of cyclodimer **315**.

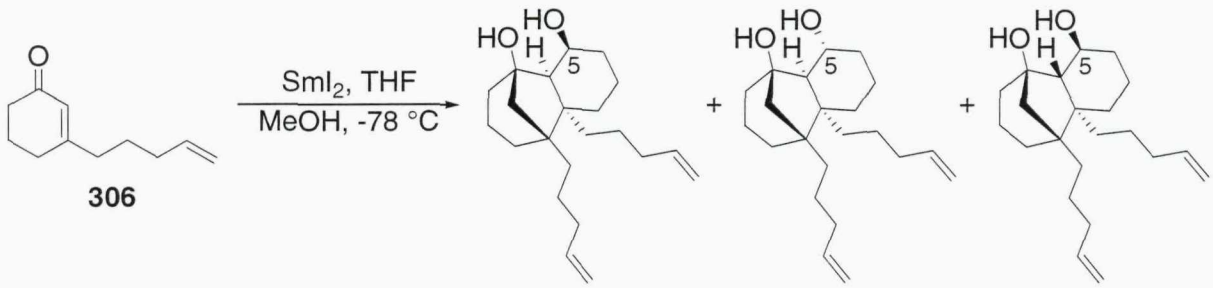
In a similar fashion, ether **304** also gave two tricyclic products upon exposure to SmI_2, giving *exo-cis*-axial isomer **316** and *exo-cis*-equatorial isomer **317** as the only detectable products **(Scheme 75)**.



Scheme 75

2.4.2.3 Substrate 306

A SmI_2 study of substrate **306** was then conducted (**Scheme 76**). Continuing the trend, tricyclic products **318**, **319** and **320** were obtained in a good overall yield.



306

318 (17 %) **319** (33 %) **320** (23 %)

Scheme 76

The stereochemistry of *exo-cis*-equatorial isomer **319** was confirmed by x-ray (**Figure 20**). The differentiation between *exo-cis*-axial isomer **318** and its diastereomeric counterpart **320** was based upon the coupling patterns observed for H5 in the ^{1}H NMR; (H5 **318** = br s, H5 **320** = td J = 12.0, 4.5 Hz). The absolute stereochemistry of tricycle **320** was difficult to assign with complete certainty, but it is likely to exist as the *exo-trans*-equatorial diastereoisomer.

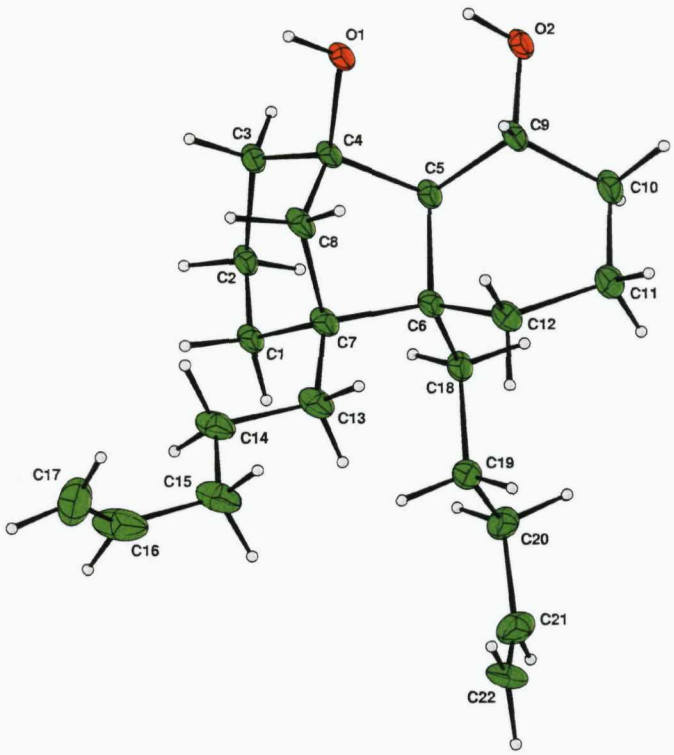


Figure 20: Crystal structure of cyclodimer **319**.

2.4.3 Conclusions so Far

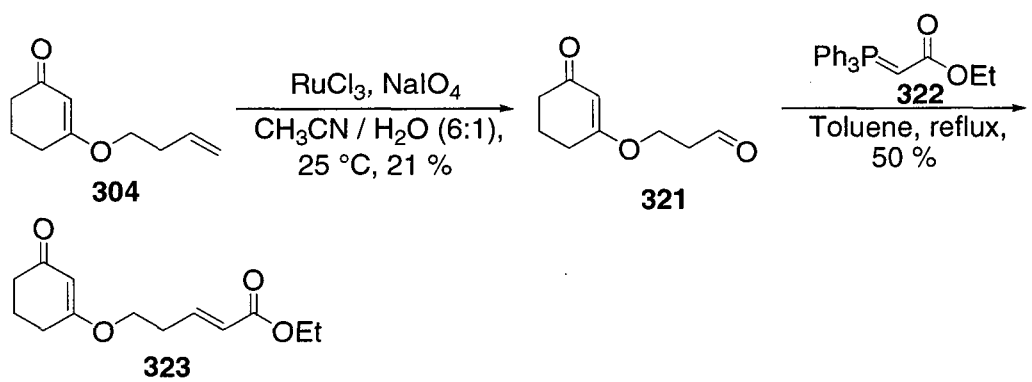
At this point of the research, the results appeared to point towards the anionic mechanism outlined in **Scheme 54**. This conclusion was drawn because in none of the studies carried out so far had any intramolecular radical cyclised products been isolated. If the reactive intermediate of the type **253 (Figure 13)** was anionic, then one would not expect to observe any intramolecular cyclisation, however an intermolecular Michael addition to a further equivalent of enone was entirely feasible. In order to examine this hypothesis the precursors were modified in such a way that would allow the anionic intermediate **255 (Figure 13)** to be probed.

2.5 Activated β-Substituted Substrates

The next stage was to synthesise and study a range of activated β-substituted substrates, that would probe the intermediacy of anionic species **255 (Figure 13)**. In order to do this the tethered alkenes were functionalised with electron withdrawing groups to set up a possible intramolecular Michael addition.

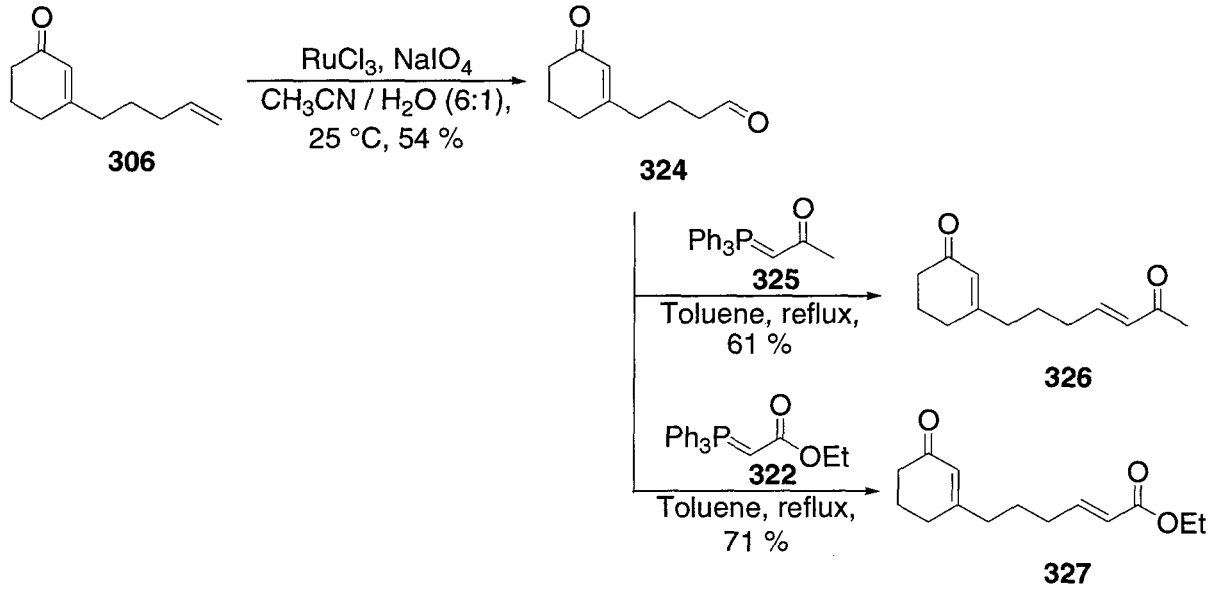
2.5.1 Synthesis

A common starting point for each of the activated β-substrates was their analogous non-activated counterparts **304** and **306**. Thus, ruthenium catalysed oxidative cleavage[138] of olefin **304** to unstable aldehyde **321**, followed by Wittig olefination with commercially available phophorane **322** gave activated substrate **323 (Scheme 77)**. The low yield of the oxidation step can be attributed in some part to the instability of the product aldehyde, but more importantly to the enone also being prone to oxidative cleavage.[138]



Scheme 77

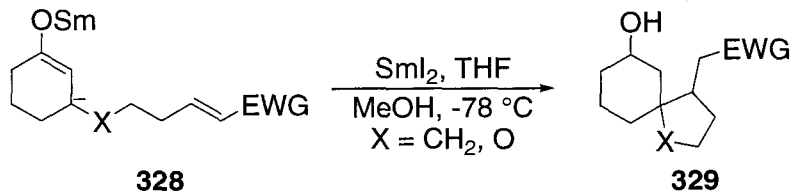
Conversion of **306** to activated substrates **326** and **327** was effected along parallel lines to those utilised for the synthesis of **323**. Oxidation[138] of **306** gave aldehyde **324** which was then converted into **326** and **327** *via* Wittig olefination with previously prepared keto-phosphorane **325**[139, 140] and commercially available phosphorane **322** (**Scheme 78**).



Scheme 78

2.5.2 Samarium Diiodide Studies

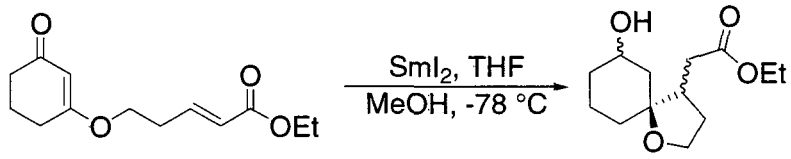
If the reaction mechanism proceeded *via* an anionic intermediate (**255**, **Figure 13**), it was rationalised that spirocycle formation by way of an intramolecular Michael addition would occur (**Scheme 79**).



Scheme 79

2.5.2.1 Activated Alkoxy 323

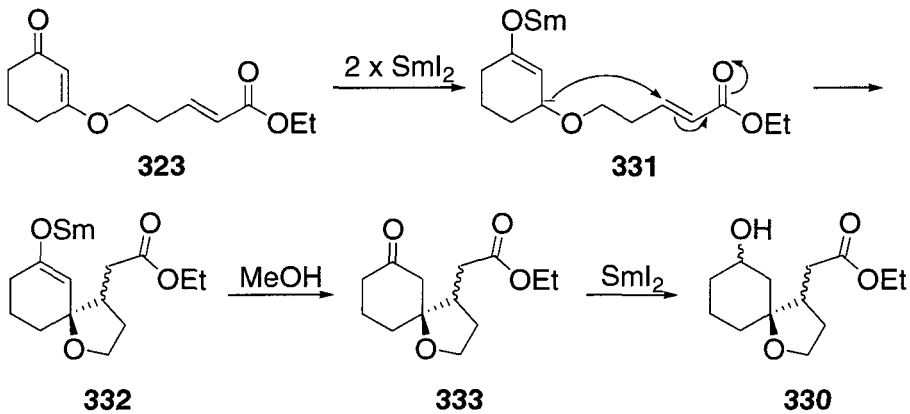
Studies began with activated alkoxy **323**, which upon treatment with SmI_2 gave spirocycles **330a** and **330b** in good yield. **330a** and **330b** were isolated as two major diastereoisomers which were inseparable from two minor diastereoisomers (**Scheme 80**).



323 **330a** (23 %) **330b** (48 %)

Scheme 80

This result was pleasing as it gave significant evidence in support of the proposed anionic dimerisation mechanism (**Scheme 54**). A mechanism for the formation of spirocycles **330a** and **330b** is shown (**Scheme 81**).



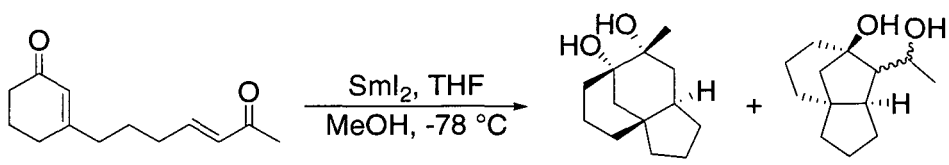
323 **331** **332** **333** **330**

Scheme 81

Double reduction of enone **323** by SmI_2 gives di-anion **331** which then undergoes conjugate addition onto the pendant α, β-unsaturated ester. The resultant samarium enolate **332** is then quenched with MeOH leading to ketone **333** which is subsequently reduced to the alcohol furnishing spirocycle **330**.

2.5.2.2 Activated Di-Ketone 326

The reaction of substrate **326** with SmI_2 gave three spirocyclic products **334**, **335a** and **335b** in an overall moderate yield (**Scheme 82**).



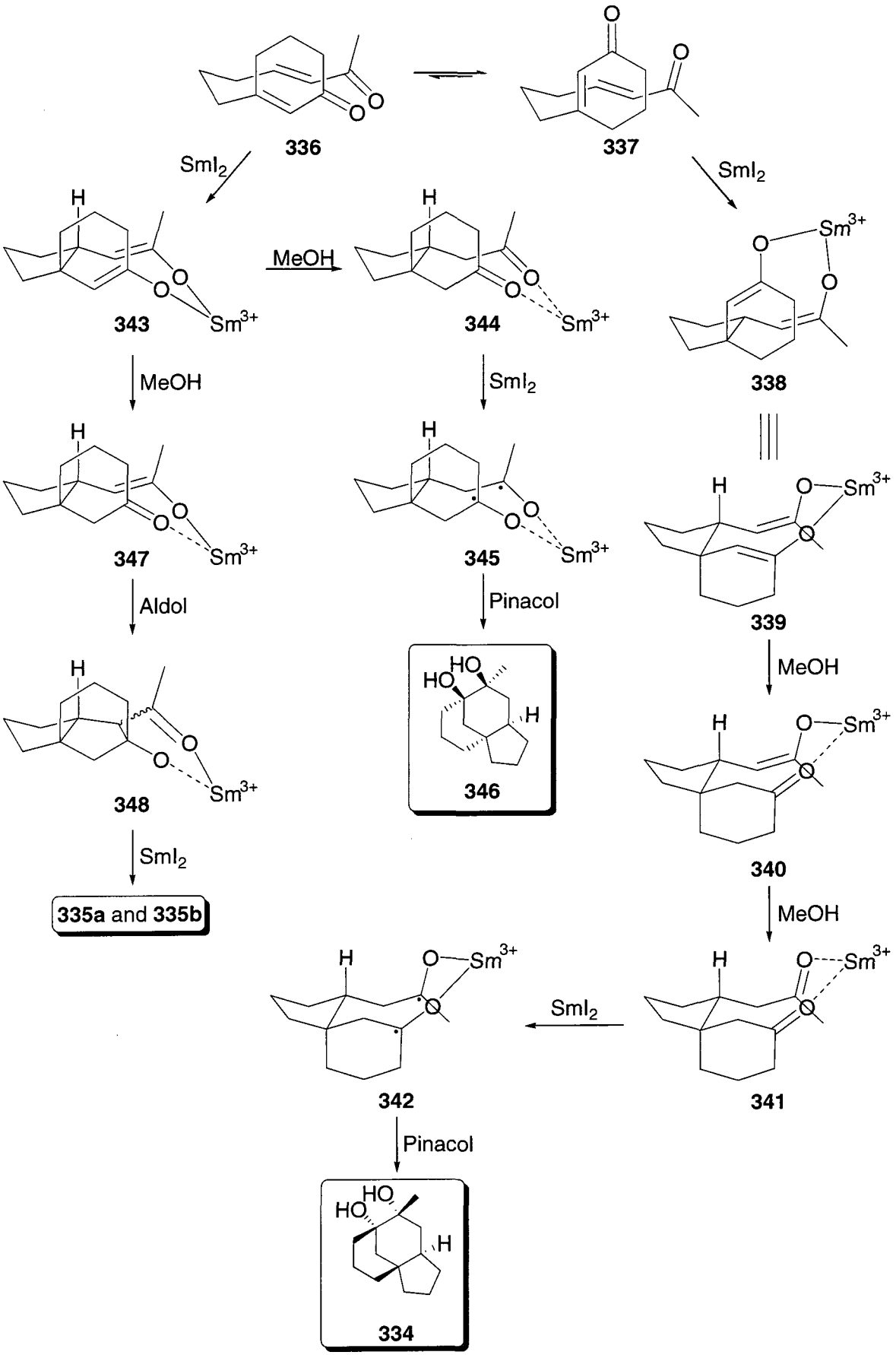
326 **334** (18 %) **335a** (16 %) **335b** (9 %)

Scheme 82

Spirocycles **334** and **335** are the result of an intramolecular cyclisation followed by a subsequent pinacol coupling or aldol condensation. Although no x-ray data has been obtained the stereochemistry can be rationalised to a certain degree, based upon the intermediates outlined below (**Scheme 83**). These intermediates are modelled on an acyclic di-ketone **407** system in which each of the pinacol and aldol diastereoisomers have been confirmed by x-ray (**Section 3.2**).

Di-ketone **326** can occupy a chair like configuration in which the alkene moieties lie in a *cis* **336** or *trans* **337** orientation. By virtue of electronic repulsion between the olefins and ketones, the arrangement which reduces these electronic interactions will be the most favoured, thus conformation **337** in which an olefin moiety is held in a pseudo-axial orientation will be preferred. **337** subsequently gives rise to cyclic intermediate **339** with a *trans* ring juncture and is protonated by MeOH to give enolate **340** which does not undergo aldol condensation and is instead protonated by a further equivalent of MeOH leading to di-ketone **341**. Upon reduction to di-ketyl species **342** pinacolisation occurs to furnish pinacol product **334**. In addition to this, pinacol product **346** may also arise from the minor aldol pathway.

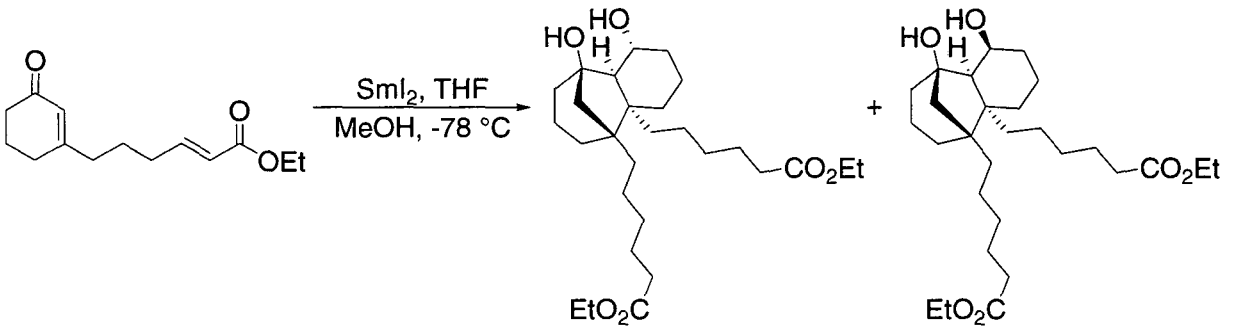
In contrast, minor conformation **336** leads to the minor pathway and aldol products **335a** and **335b**. The key difference is the *cis* ring juncture, which enables the samarium enolate and carbonyl moiety to lie in close proximity to one another, and thus favour aldol condensation **347**.


336
337
SmI2
SmI2
MeOH
343
344
338
MeOH
SmI2
347
345
339
Aldol
Pinacol
MeOH
348
346
340
SmI2
MeOH
335a and 335b
342
341
SmI2
Pinacol
334

Scheme 83

2.5.2.3 Activated Keto-Ester 327

The final activated substrate studied was keto-ester **327**, which upon treatment with SmI_2 gave the unexpected *exo-cis*-equatorial cyclodimer **349** and cyclodimer **350** **(Scheme 84)**.



327 **349** (14 %) **350** (25 %)

Scheme 84

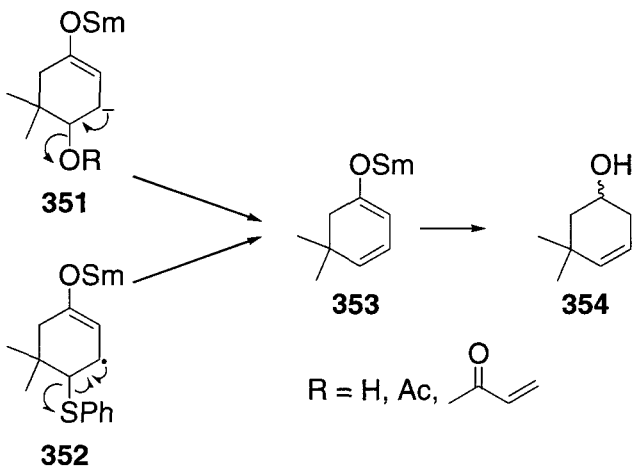
The stereochemistry for cyclodimer **350** has not been fully resolved due the H5 signal in the ^1H NMR being masked by the two ester quartets. Therefore, it was difficult to conclusively assign **350** as the *exo-cis*-axial isomer; however, based on the model predictions **(Scheme 59, Section 2.1.2)**, the *exo-cis*-axial diastereoisomer would be expected. A third product was also isolated (10 %), however it was not possible to identify its structure.

2.5.3 Conclusions

The change in reactivity between alkoxy **323**, di-ketone **326** and keto-ester **327** was intriguing. The results obtained with keto-ester **323** and di-ketone **326** gave encouraging evidence for an anionic pathway **(Scheme 54)**, however the drastic change in selectivity observed with keto-ester **327** was concerning. If the reaction proceeded *via* an anionic pathway then spirocyclic products were expected to be obtained in all instances; however, because this was not the case, further evidence was required in order to conclusively assign one mechanism over another.

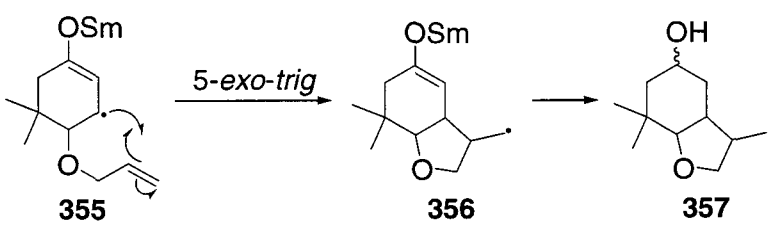
2.6 γ-Substituted Substrates

A range of γ-substituted substrates were synthesised which would probe the intermediacy of radical species **253** and anionic species **255** (**Figure 13**). In order to specifically probe for the anionic intermediate, several precursors were designed in which β-elimination of a suitable leaving group would occur in the presence of an anion **351** (**Scheme 85**). Likewise, to probe for radical intermediate **352** a substrate incorporating a good radical leaving group to set up a radical based β-elimination sequence was also designed (**Scheme 85**).



Scheme 85

A further radical based probe investigated was allyl ether **364** (**Scheme 89**); in a similar fashion to α and β-substituted enones, it was envisaged that a 5-*exo-trig* cyclisation in the presence of radical intermediate **355** could occur (**Scheme 86**).

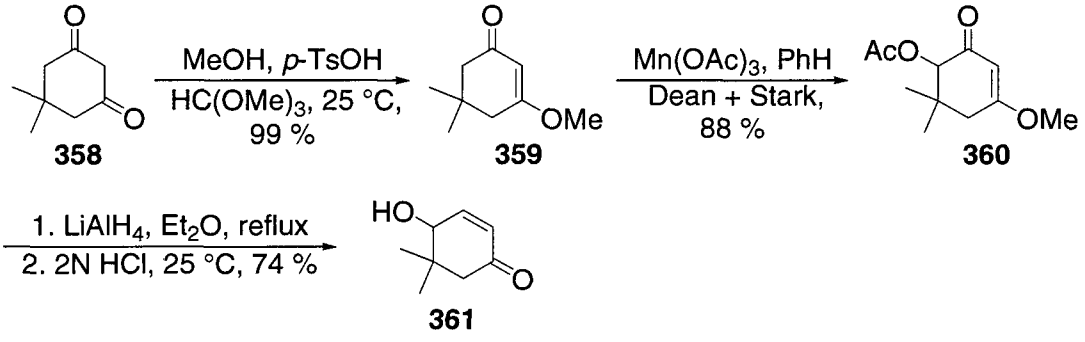


Scheme 86

2.6.1 Synthesis

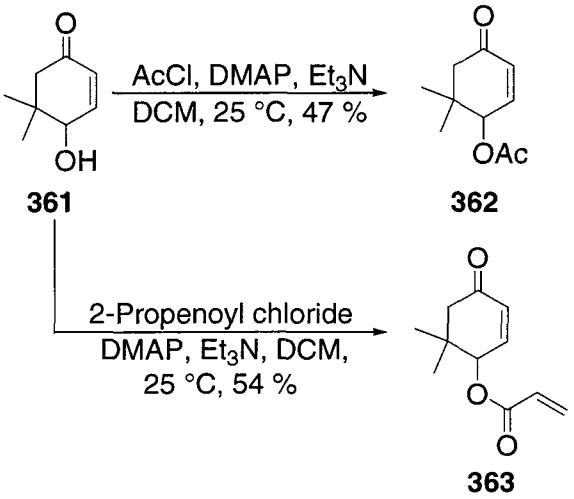
In order to synthesise a range of γ-substituted substrates, attention was focussed on the synthesis of 4-hydroxy enone **361**.[141, 142] 4-Hydroxy enone **361** provides a common

starting point for all target precursors, as well as being a useful substrate to study in itself. Commercially available dimedone **358** was converted into the enol ether **359**, and subsequently subjected to $Mn(OAc)_3$ mediated oxidation to furnish 6-acetoxy enone **360**.[141, 142] Final $LiAlH_4$ reduction gave the desired 4-hydroxy enone **361** in good overall yield (**Scheme 87**).[141, 142]



Scheme 87

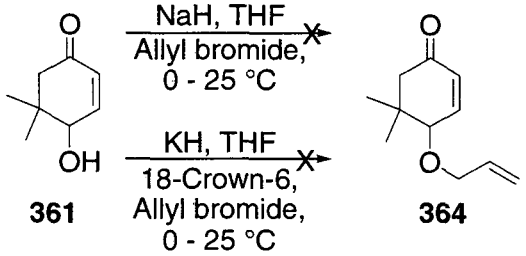
With 4-hydroxy enone **361** now in hand, simple acylation with acetyl chloride and 2-propenoyl chloride gave γ-substituted substrates **362** and **363** respectively (**Scheme 88**). All three substrates **361**, **362** and **363** are useful probes into the intermediacy of anionic species **351** (**Scheme 85**).



Scheme 88

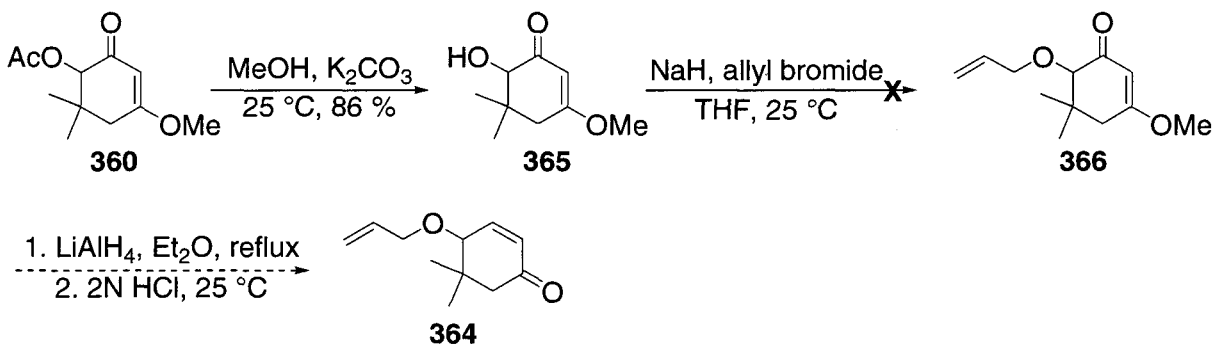
Syntheses of γ-substituted substrates that could probe the intermediacy of radical **253** (**Figure 13**) were also conducted. It was assumed that allyl substrate **364** could straightforwardly be prepared *via* alkylation of 4-hydroxy enone **361** (**Scheme 89**). Unfortunately however, none of the desired precursor **364** was obtained; instead the reaction gave multiple unidentifiable products in both sets of conditions employed. It

was concluded that the main problem was due to the acidic α protons adjacent to the ketone. Reaction conditions utilising Ag_2O[143, 144] and NaOH[145] were also used to no avail.



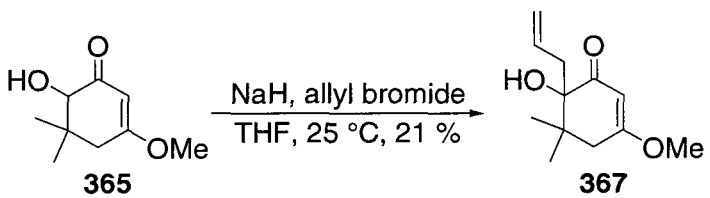
Scheme 89

Therefore, an alternative approach that minimised the number of acidic carbonyl protons, and gave an improved chance of alkylation on the alcohol was investigated. Thus, transesterification[146] of 6-acetoxy enone **360** gave 6-hydroxy enone **365**, which has only a single acidic α proton, and in addition is sterically hindered by the hydroxyl group (**Scheme 90**).



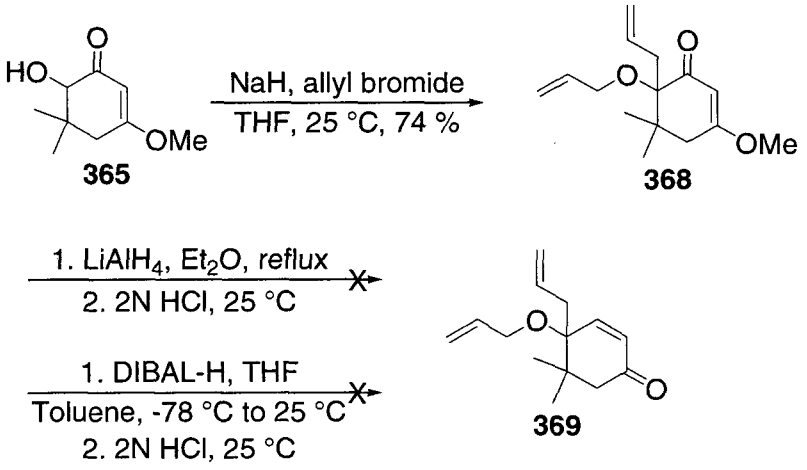
Scheme 90

However, exposure of **365** to NaH and allylbromide[147] did not give the desired allyl ether **366**, instead the C alkylated adduct **367** was obtained as the only product (**Scheme 91**).



Scheme 91

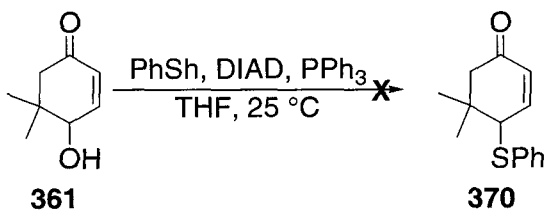
In order to obtain the required allyl ether moiety, a double alkylation on alcohol **365** was performed. Thus, treatment of **365** with three equivalents of NaH and allyl bromide gave the di-alkylated product **368** in good yield **(Scheme 92)**.



Scheme 92

Subsequent reduction with $LiAlH_4$ and acid catalysed hydrolysis[141, 142, 148] to give **369** proved fruitless. Alternative reduction methods were utilised including DIBAL-H and $NaBH_4$, however, in all instances the reaction degrades. Due to the inability to synthesise allyl precursors **364** and **369**, SmI_2 studies using these particular types of radical probe were not conducted.

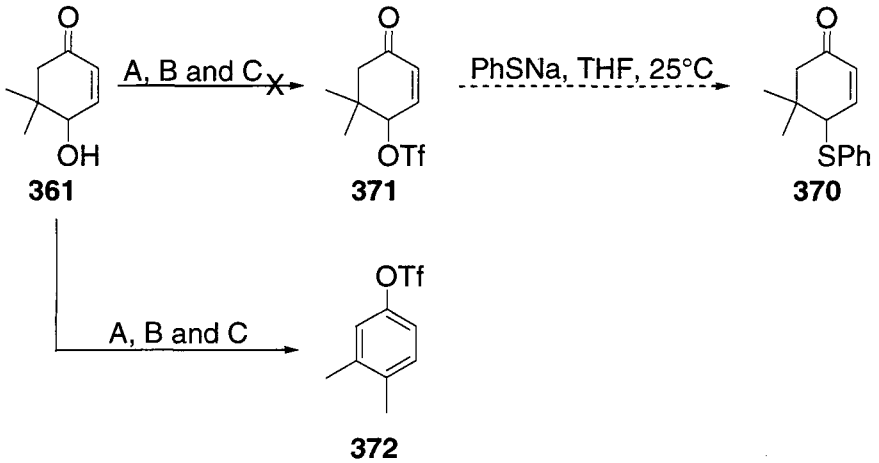
Another radical probe targeted was thioether **370**, the synthesis of which proved slightly more challenging than initially expected. In the first instance, a single step synthesis of thioether **370** *via* Mitsunobu reaction between 4-hydroxy enone **361** and thiophenol was attempted **(Scheme 93)**. However, this was unsuccessful and instead of isolating the desired product **370**, recovered starting materials were obtained.



Scheme 93

The next strategy involved converting the alcohol into a good leaving group, followed by an S_N2 reaction with sodium thiophenolate. Conversion into the triflate **371**[149]

however proved unsuccessful, and in all instances 3, 4-dimethylphenyl trifluoromethane sulfonate **372**[150] was obtained as the major product (**Scheme 94** and **Table 1**).

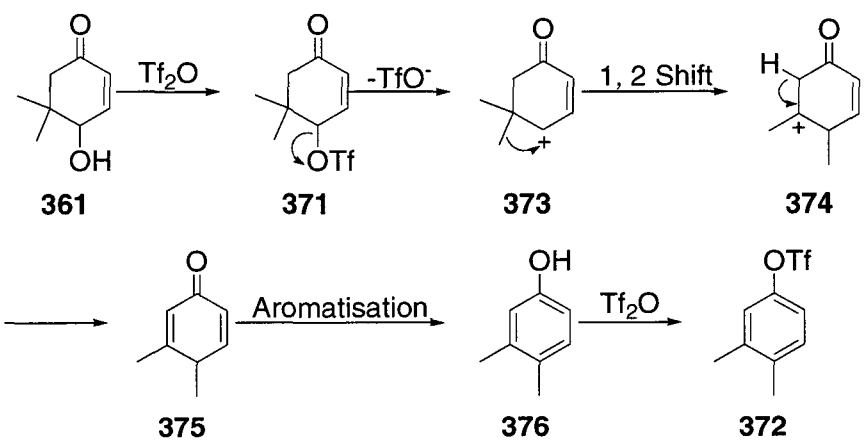


Scheme 94

Conditions	Method
A[149]	**361** and pyridine in DCM at 0 °C *then* Tf_2O added dropwise, warmed to 25 °C
B	**361** and pyridine in DCM – 15 °C *then* Tf_2O added dropwise, warmed to 25 °C
C[151]	Tf_2O in DCM at – 30 °C *then* **361** and pyridine added in DCM, kept at – 30 °C

Table 1

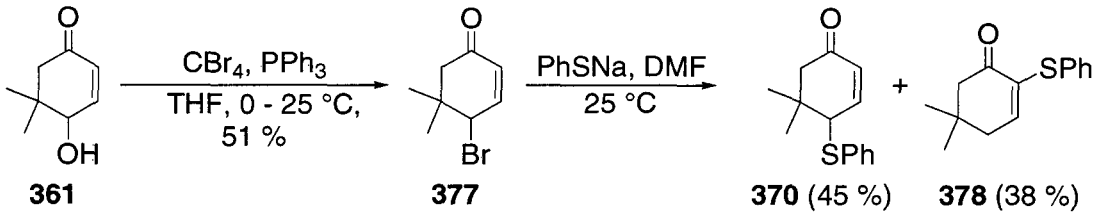
Using the conditions outlined in A,[149] B and C[151] none of the desired triflate **371** was obtained, instead aromatic triflate **372** was isolated in a 44 % yield – the result of a 1, 2 methyl migration, aromatisation and triflation of the resultant phenol (**Scheme 95**).



Scheme 95

Pursuing a similar line, an alternative leaving group was utilised. Thus, treatment of 4-hydroxy enone **361** with CBr_4[152] gave bromide **377** in moderate yield and subsequent

reaction with sodium thiophenolate in DMF gave the desired 4-substituted thioether **370** as well as a significant proportion of the 2-substituted adduct **378 (Scheme 96)**.



361 **377** **370** (45 %) **378** (38 %)

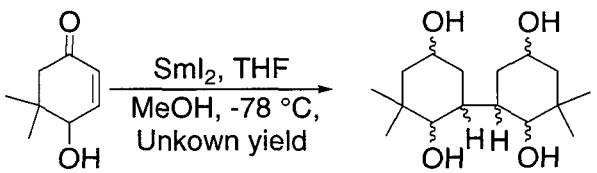
Scheme 96

Substrate **377** can be thought of as an allylic bromide species, thus, 2-substituted adduct **378** presumably arises *via* an S_N2' type reaction displacing the bromide. Re-conjugation of the double bond with the carbonyl provides the more stable enone product **378**.

2.6.2 Samarium Diiodide Studies

2.6.2.1 4-Hydroxy Enone 361

As outlined in **Scheme 85**, if 4-hydroxy enone **361** underwent *β*-elimination upon exposure to SmI_2, this would provide convincing evidence that an anionic pathway exists. However, upon treatment with SmI_2 4-hydroxy enone **361** failed to undergo *β*-elimination, instead dimerising to generate a complex diastereomeric mixture of tetraols **379 (Scheme 97)**.



361 **379**

Scheme 97

It has not been possible to determine the exact number of diastereoisomers that have been made due to the complexity of the diastereomeric mixtures isolated, however based upon LRMS (^{m}/z 309 $[M + Na]^+$, 596 $[2M + Na]^+$) and limited ^{13}C data **(Figure 21)** it was possible to conclude that a dimeric species had been obtained. A distinct lack of alkene resonances, coupled with two discrete CHOH regions in the ^{13}C NMR gave good evidence to suggest that *β*-elimination had not occurred.

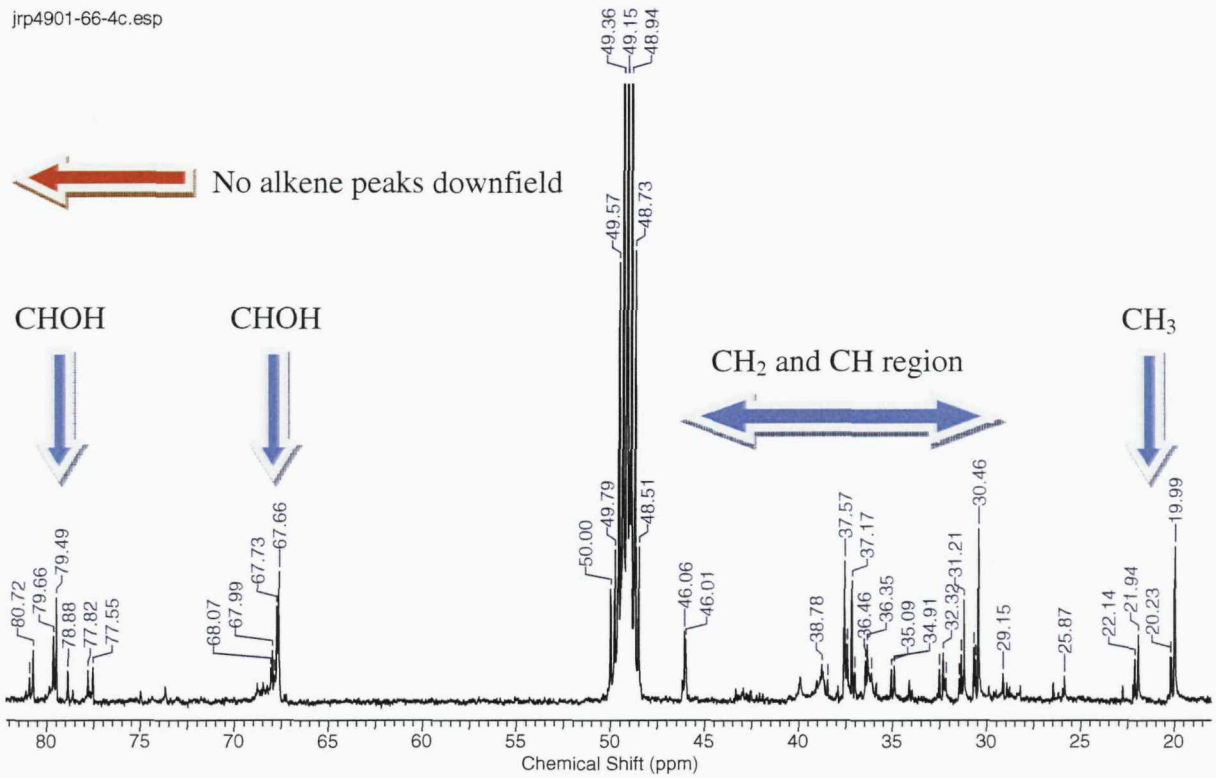
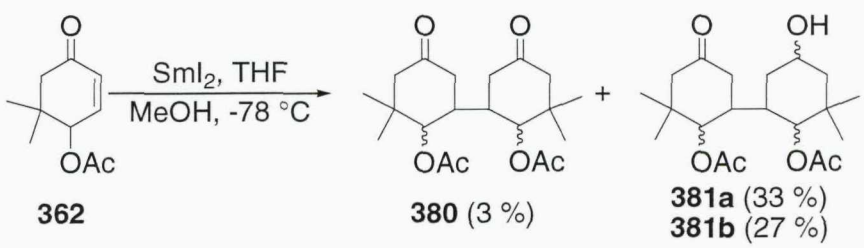


Figure 21: NMR data for **379** with key peaks indicated.

A further complication arose during the isolation of tetraol diastereoisomers **379** – a mass balance of 150 % was obtained, and as such this is why a yield has not been reported for the reaction. Tetraols **379** are extremely polar molecules, exhibiting R_f's in the region of 0.1 – 0.2 in a 10 % MeOH / DCM solvent system. Consequently even upon careful column chromatography they co-eluted with baseline inorganic material giving rise to the observed erroneous mass balances.

2.6.2.2 4-Acetoxy enone 362

Subjection of 4-acetoxy enone **362** to SmI_2 gave dimerised products **380**, **381a** and **381b** (**Scheme 98**). In contrast with 4-hydroxy enone **361**, a clean single diastereoisomer **380** was isolated which allowed confident assignment of its structure.



362 **380** (3 %) **381a** (33 %) **381b** (27 %)

Scheme 98

Dimer **380** gave clean unambiguous NMR data **(Figure 22)** which was then used as a guide in assigning the complex mixtures of dimers **381a** and **381b**.

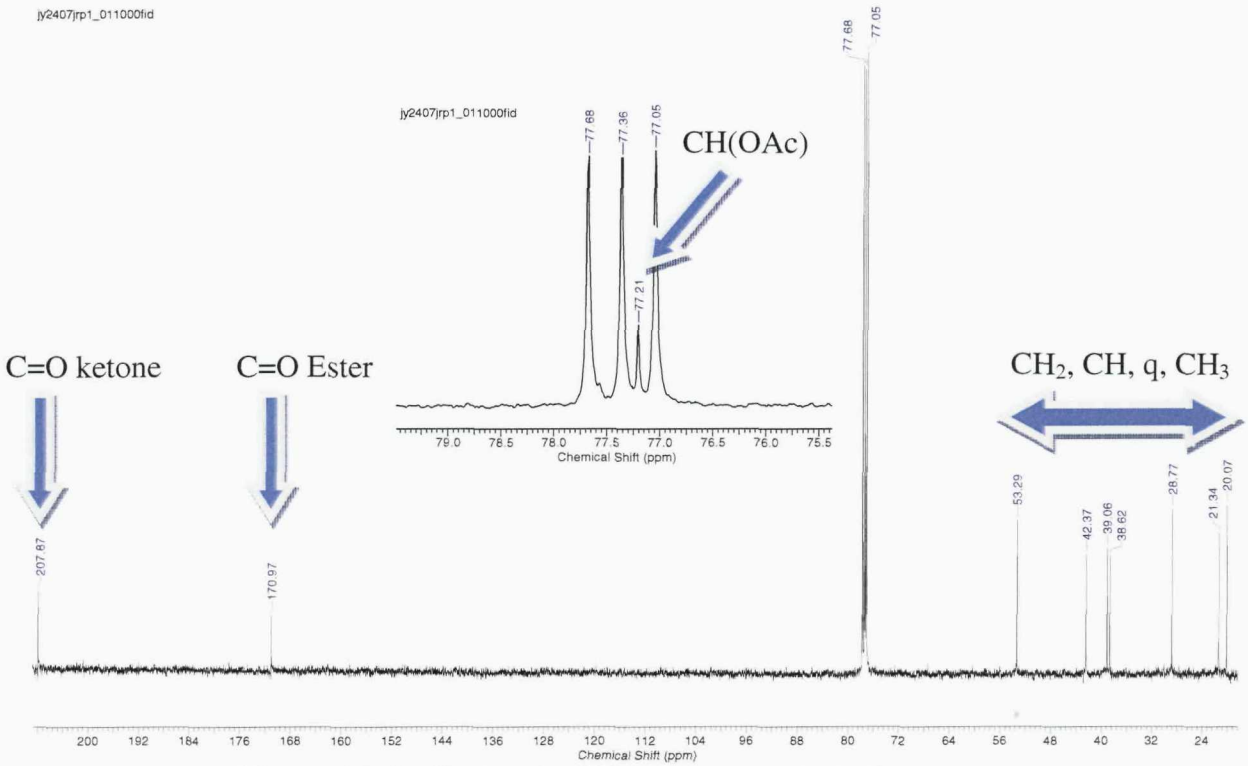


Figure 22: NMR data for **380** with key peaks indicated.

Dimeric species **381a** and **381b** were isolated as inseparable mixtures of diastereoisomers, but due to the complexity of the NMR data it has not been possible to determine the exact number of isomers present. Although the ^{13}C NMR was complicated several characteristic peaks were picked out that enabled the structure to be cautiously assigned **(Figure 23)**. The ^{13}C NMR clearly indicated the presence of ketone and CHOAc functionalities in the structure. This, coupled with LRMS data ($^{m}/z$ 391 [M + Na]$^{+}$, 760 [2M + Na]$^{+}$) led to the structures of **381a** and **381b** to be tentatively assigned as shown above **(Scheme 98)**.

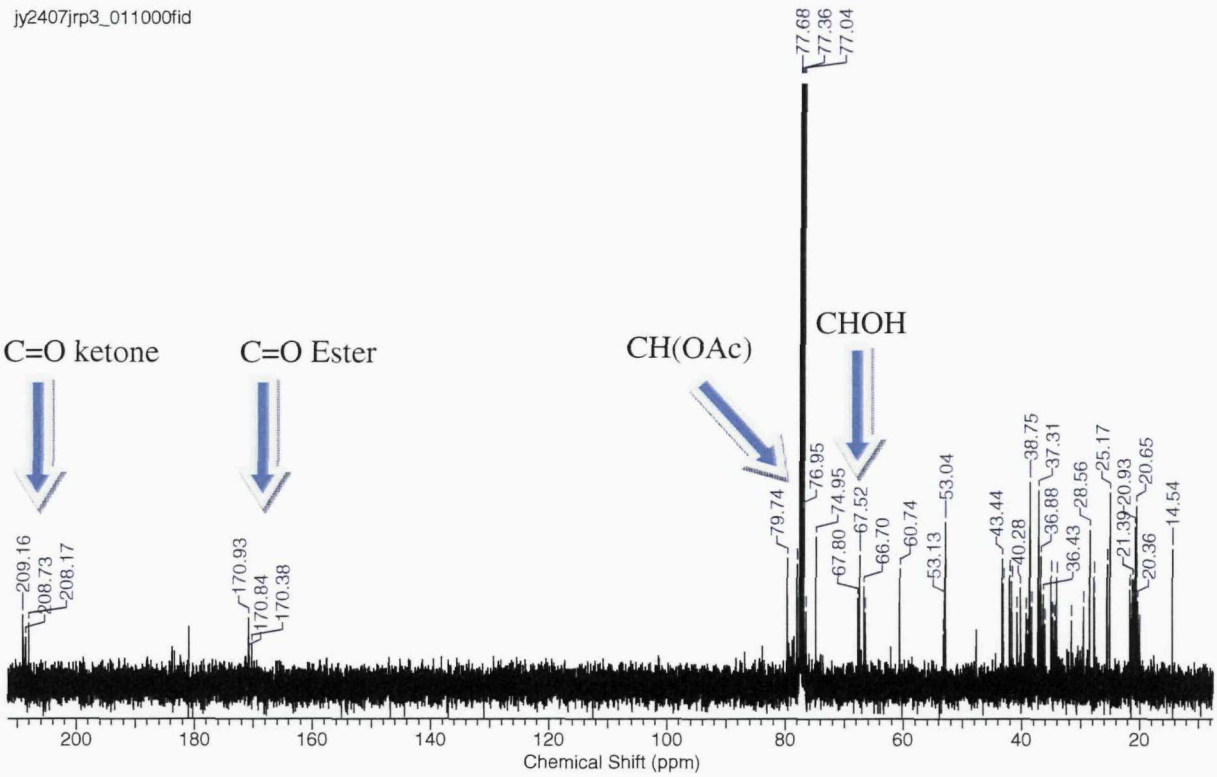
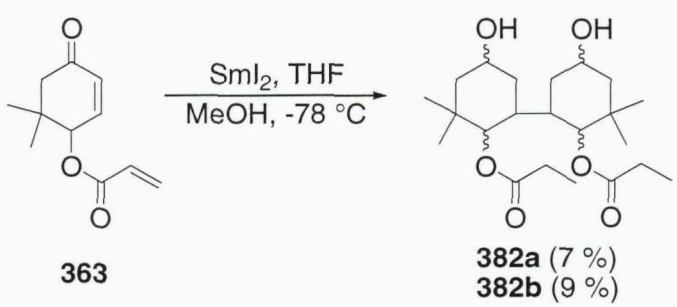


Figure 23: NMR data for **381a** with key peaks indicated.

An important conclusion that was drawn from this result was that β elimination had not occurred in this particular system.

2.6.2.3 Ester Substituted Enone 363

The final substrate for investigating the intermediacy of anionic species **255** (**Figure 13**) was ester substituted enone **363**; which, upon exposure to SmI_2 underwent dimerisation to provide **382a** and **382b** (**Scheme 99**). A number of other dimeric products were also isolated as complex mixtures of diastereoisomers.



363

382a (7 %)
382b (9 %)

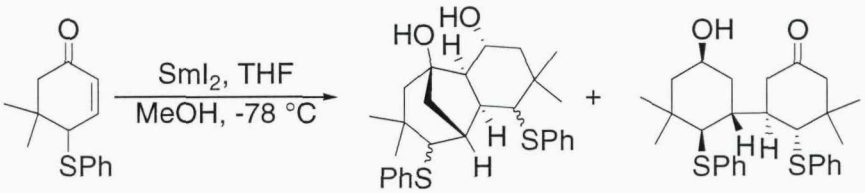
Scheme 99

Once more, as observed with 4-hydroxy **361** and 4-acetoxy enones **362**, there was no evidence that β-elimination had occurred.

2.6.2.4 Thioether 370

Thioether **370** was designed to probe the intermediacy of radical species **253** (**Figure 13**), and was expected to undergo β-elimination in the presence of such a radical intermediate. Thus, based upon the results with anion probing γ-substituted precursors **361**, **362** and **363** in which no β-elimination was observed, it was predicted that thioether **370** would give rise to radical based β-elimination products of the type **354** (**Scheme 85**).

However, this was not the case. Subsequent treatment of **370** with SmI_2 yielded a complex mixture of products including *exo-cis*-equatorial tricycle **383** and dimer **384** (**Scheme 100**) in which rather surprisingly no β-elimination had occurred.



370 **383** (23 %) **384** (11 %)

Scheme 100

The stereochemistry of **384** has been confirmed by x-ray crystallography (**Figure 24**).

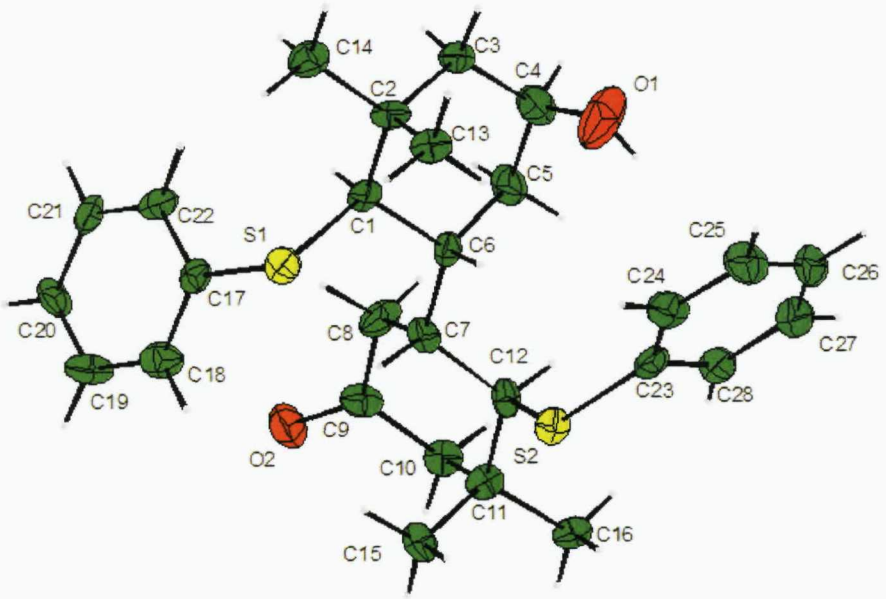


Figure 24: Crystal structure of dimer **384**.

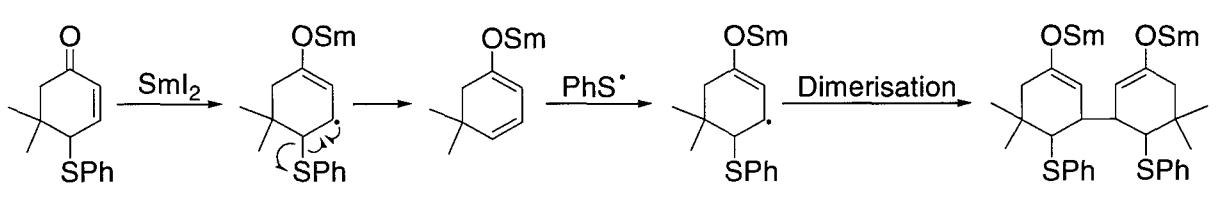
If the reaction does proceeds *via* radical intermediate **352 (Scheme 85)**, then it may be possible that radical dimerisation is faster than β-elimination. Thus, slow addition of thioether **370** to a solution of SmI_2 should suppress dimerisation by maintaining a low concentration of radical species **352** and favour β-elimination. However, the outcome of the reaction was unaffected by the rate of addition of **370** to SmI_2 (addition over 80 minutes gave tricycle **383** in 22 % yield, and dimer **384** in 10 % yield).

2.6.3 Conclusion

The results obtained with anionic probes **361**, **362** and **363** distinctly pointed towards a radical based pathway. This evidence is based upon the fact that in all three cases only dimeric compounds with no evidence of β-elimination were obtained, leading us to conclude that anionic species **255 (Figure 13)** is not an intermediate.

In order to investigate this further, radical probe **370** was developed, which based upon the results with **361**, **362** and **363** that discount the anionic mechanism, was fully expected to undergo a radical based β-elimination. Remarkably however, this did not occur, instead giving tricyclic product **383** and dimeric species **384**.

A possible explanation regarding the thioether **370** result may be that the expected radical β-elimination may be a reversible process. The thiophenol radical may undergo radical addition back onto the first formed double bond **353** thus regenerating radical species **352** which can then dimerise **(Scheme 101)**. Although, if this is the case it is still surprising that no β-eliminated products were isolated using either of the conditions employed.



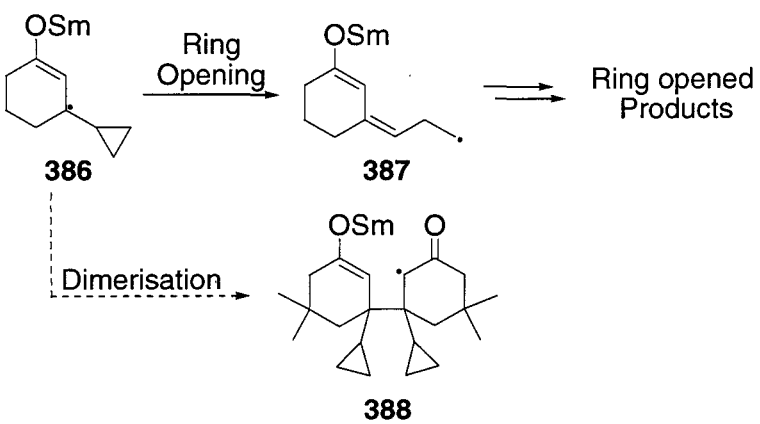
370 **352** **353** **352** **385**

Scheme 101

In conclusion the results obtained thus far, give strong evidence to suggest that a radical pathway exists – this was proven indirectly *via* anionic probes **361**, **362** and **363**. However, due to the ambiguous nature of the result obtained with thioether precursor **370**, in order to fully support the radical based mechanisms **(Scheme 53** or **56)** further direct evidence was required.

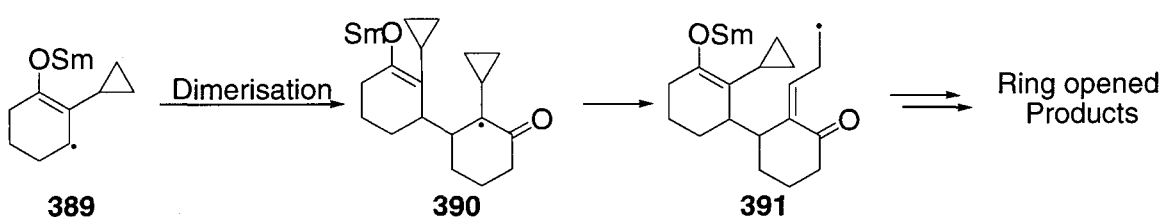
2.7 Cyclopropyl Substrates

Studies subsequently moved on to cyclopropyl based substrates **392** and **397** (**Schemes 104** and **105**). Cyclopropanes have been used for many years as radical clocks to determine rates of reactions, and have also been utilised as mechanistic probes.[8, 9, 153] It was hoped that the extremely rapid nature of the radical ring opening process would compete with the apparently efficient dimerisation that has been encountered throughout these studies, and provide conclusive evidence for radical based intermediate **386** (**Scheme 102**).



Scheme 102

In addition a cyclopropyl based substrate that would probe the intermediacy of radical species **390** post dimerisation was also designed (**Scheme 103**). This substrate would specifically probe for a radical based dimerisation process, and if successful provide strong evidence in favour of the radical Michael addition pathway (**Scheme 53**).

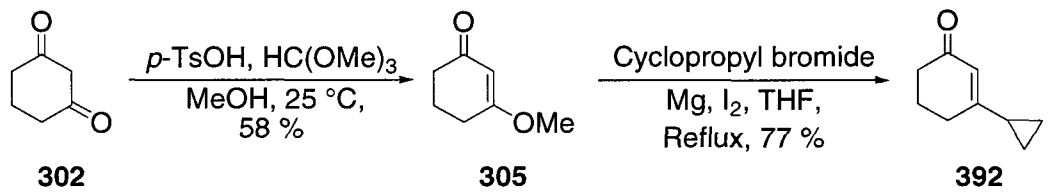


Scheme 103

Clearly there are a large possible number of ring opened products that could arise from both substrates, a consequence of which may be that extremely complicated mixtures of products would be handled. Although a disadvantage, this would provide crucial evidence in itself that a radical pathway exists.

2.7.1 Synthesis

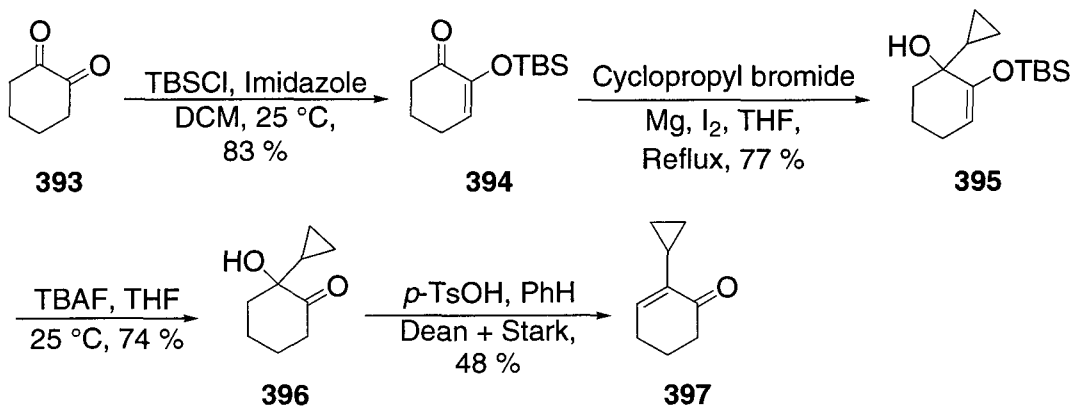
Synthesis of cyclopropyl substrate **392** followed a parallel course to that of β-substrate **306** (**Scheme 71**). Conversion of 1, 3-cyclohexandione **302** into enol ether **305**[136] followed by condensation with the Grignard reagent[137, 154] derived from cyclopropyl bromide gave β-cyclopropyl precursor **392** in a good overall yield (**Scheme 104**).



302 **305** **392**

Scheme 104

Cyclopropyl substrate **397** was synthesised in four steps beginning with mono protection of 1, 2-cyclohexandione **393** with TBSCl[155] to give silyl enol ether **394**. Subsequent Grignard condensation with cyclopropyl bromide[154] followed by TBAF deprotection[155] gave cyclopropyl adduct **396**, which upon dehydration at elevated temperature[156] gave the desired α-cyclopropyl substrate **397** in moderate yield (**Scheme 105**).



393 **394** **395**

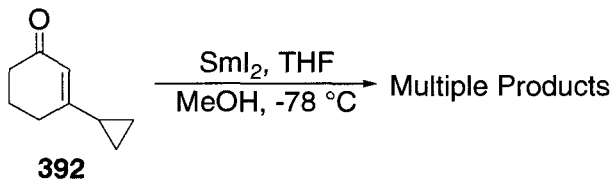
396 **397**

Scheme 105

2.7.2 Samarium Diiodide Studies

2.7.2.1 β-Cyclopropyl Substrate 392

Treatment of **392** with SmI_2 yielded an extremely complicated mixture of products **(Scheme 106)**. By analysis with TLC at least ten (if not more) products were produced throughout the course of this reaction, and as a consequence purification was not attempted.



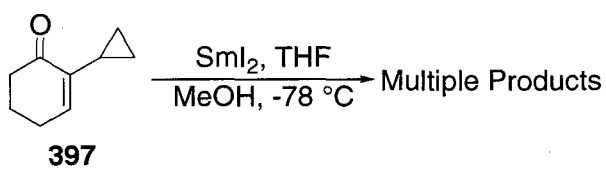
392

Scheme 106

Analysis by NMR was not conclusive; however, this result when compared to the analogous β-substituted methyl substrate **309 (Scheme 73)** in which only four cyclodimerised products were obtained, gave good evidence to suggest that the formation of multiple products is reflective of radical intermediate **386 (Scheme 102)** and numerous radical pathways.

2.7.2.2 α-Cyclopropyl Substrate 397

In comparison with previously studied α-substituted precursors **(Section 2.3)**, in which well defined products were isolated, cyclopropyl substrate **397** yielded a multitude of products **(Scheme 107)**.



397

Scheme 107

Attempted purification served only to provide a complicated mixture of products which could not be fully assigned. ^{13}C data provided good evidence for ring opened type products: alkene peaks at 120 to 130 ppm, coupled with an extremely complicated CH and CH_2 region, signified that ring opening had taken place. Further resonances at > 10 ppm indicated that a cyclopropyl moiety was still present, however this was to be

expected when probing intermediate **390** **(Scheme 103)**, since only one of the cyclopropyl rings will undergo ring opening post dimerisation **(Scheme 103)**.

In order for ring opening to have occurred, a radical based Michael addition must have ensued, thus providing the strongest evidence yet that the dimerisation mechanism proceeds *via* a radical based Michael addition pathway **(Scheme 53)**.

2.7.3 Conclusion

Cyclopropyl substrates **392** and **397** were designed to confirm the intermediacy of radical species **253** and **254** **(Figure 13)**. Subsequent treatment with SmI_2 gave rise to a complicated array of products in both instances, which can only be the result of multiple radical based pathways. The result obtained with β-cyclopropyl precursor **392** provides good evidence for radical intermediate **386** **(Scheme 102)**, but does not conclusively prove that a radical based intermolecular Michael addition has occurred. In contrast, the result obtained with α-substituted substrate **397** provides strong evidence to suggest that radical-radical coupling **(Scheme 56)** does not occur, and instead infers that the radical based Michael addition is the dimerisation mechanism at large **(Scheme 53)**.

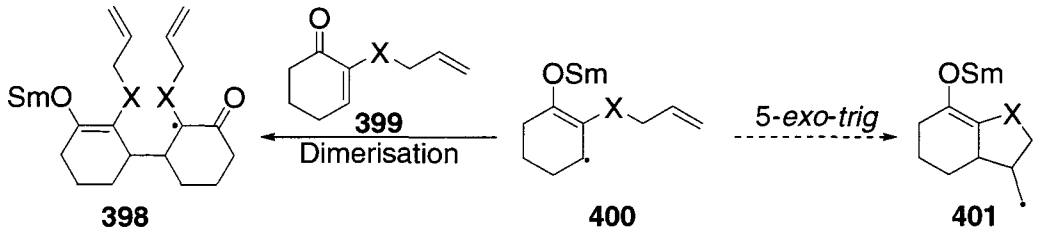
Although the result with thioether **370** still raises question marks over the radical based dimerisation, the results obtained with cyclopropyl substrates **392** and **397**, coupled with evidence provided by γ-substituted enones **361**, **362** and **363** which discount the anionic pathway, provides convincing evidence for the intermediacy of radical species **253** and **254** **(Figure 13)**, and for the existence of a radical based Michael addition dimerisation mechanism **(Scheme 53)**.

2.8 Final Discussion

Having collected a considerable amount of evidence to support the radical based Michael addition mechanism **(Scheme 53)**, the observed reactivity for the α-substituted, β-substituted and activated β- substituted substrates can now be explained.

For α-substituted and β-substituted substrates there is a relatively simple explanation. It is well documented that substituents about the radical centre can influence the rate and course of radical reactions.[27, 28] Radical species of the type **400** can be considered nucleophilic in character, due to the electron donating character of the alkyl groups to

which it is attached, and also the allylic double bond (**Scheme 108**). These influences all combine to increases the energy of the radical SOMO making it electron rich and thus more nucleophilic in character. As a consequence, radical **400** does not cyclise with the tethered electron rich alkene, and instead prefers to react with the more electrophilic enone in an intermolecular fashion (**Scheme 108**).



Scheme 108

Similarly the β-substituted substrates can also be considered nucleophilic in character. Additional substitution about the radical centre with an alkyl or ether chain will have the effect of enhancing the nucleophilicity of radical species **307** (**Figure 25**), thus a similar reaction pathway is observed.

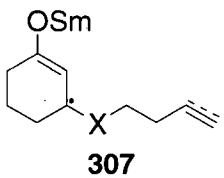


Figure 25: β-substituted radical intermediate **307**.

The observed reactivity of activated β-substituted substrates **323**, **326** and **327** can now be discussed in greater detail. The results are summarised below (**Figure 26**); substrates **323** and **326** underwent intramolecular cyclisation to generate spirocyclic type products, whereas **327** cyclodimerised to generate the characteristic tricyclic framework.

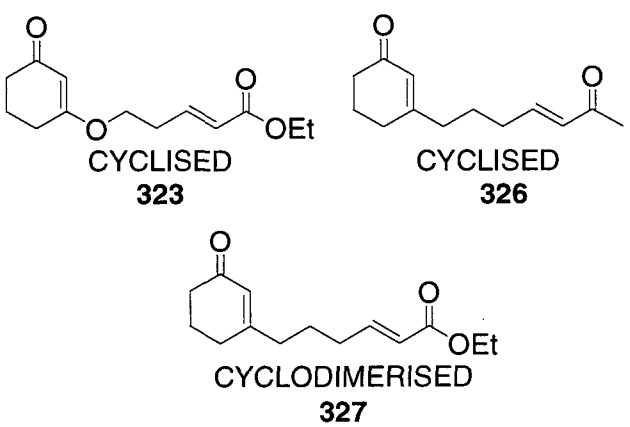
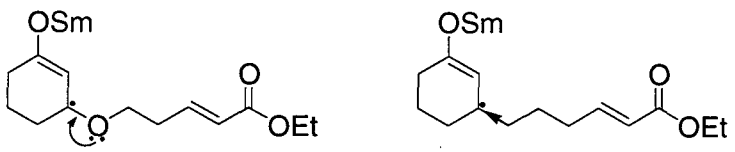


Figure 26: Summary of results obtained with **323**, **326** and **327**.

Giese and others[27, 28] have demonstrated that in changing from alkyl to ether substituents, one is able to enhance the rate of addition of a radical species to a suitably activated alkene. In comparison with alkyl substituents, ether substituents exhibit a stronger electron releasing effect by virtue of the lone pairs of electrons (**Figure 27**), which has the effect of raising the energy of the SOMO, thus giving a more reactive and nucleophilic radical species.

As a result, ether radical **402** will be more nucleophilic in character than alkyl radical **403** and consequently more reactive towards electron deficient alkenes. The comparatively slower cyclisation of alkyl radical **403** onto the pendant alkene may allow a competing pathway to intercept the radical; this competing pathway must be the intermolecular process.



402 **403**

Figure 27: Alkoxy **402** and alkyl **403** radical intermediates.

α, β-Unsaturated ketones are more electron deficient than α, β-unsaturated esters, thus a less nucleophilic alkyl radical, such as **403**, will prefer to react with an α, β-unsaturated ketone. This, coupled with the relatively persistent nature of the radical **403**, can serve to favour the intermolecular addition to the unsaturated ketone over the expected intramolecular addition to the unsaturated ester.

In the case of di-ketone **326 (Scheme 82)**, in which both alkenes in the system are highly electrophilic, the alkyl radical intermediate can react intramolecularly or intermolecularly - as expected, the intramolecular process is favoured.

Although the difference in reactivity between keto-ester **323 (Scheme 80)** and keto-ester **327 (Scheme 84)** has been explained in terms of radical and inter *versus* intramolecular arguments, it is important to point out that the nature of the reactive species in solution is not known. A dimeric samarium species (**Scheme 55**) or samarium cluster may exist in which radical intermediate **403** may be held in close proximity to another molecule of α, β-unsaturated ketone, which favours an intermolecular process. Consequently, relative nucleophilicity and electrophilicity may not play such an important role.

In conclusion, these mechanistic studies have provided convincing evidence in support of a radical based Michael addition mechanism (**Scheme 53**). In addition, through utilising the SmI_2 / MeOH / THF system, we have been able to efficiently construct from simple achiral molecules an array of complex poly-cyclic products in reactions involving the formation of up to three carbon-carbon bonds and five chiral centres.

Chapter 3 Acyclic Substrates

3.1 Introduction

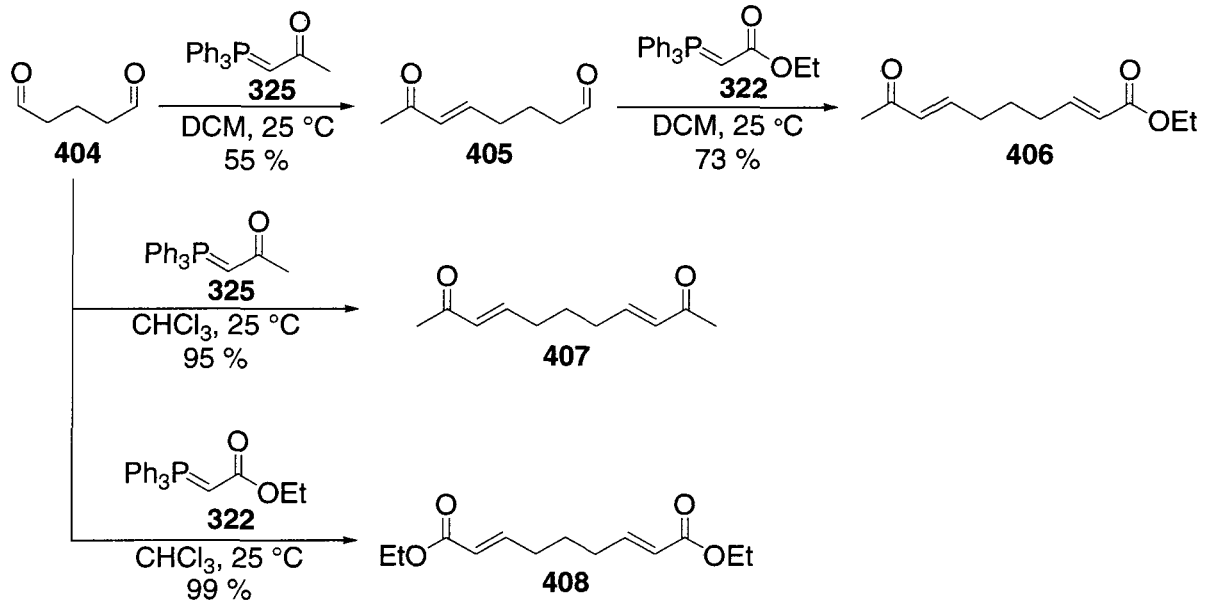
Studies with cyclic enone derivatives (**Chapter 2**) showed that the SmI_2 / MeOH / THF system could successfully be used to produce a range of complex polycyclic products. The next stage of the research therefore was to extend this methodology to other types of α, β-unsaturated systems. These systems were acyclic in nature, and ranged from simple all carbon examples, through to more complex systems incorporating heteroatoms or substituents. In this chapter the synthesis of these substrates and their reaction when treated with SmI_2 will be discussed in detail.

3.2 Simple Acyclic Substrates

3.2.1 Synthesis

Syntheses of keto-ester **406**,[157] di-ketone **407**[44] and di-ester **408**[158] were successfully achieved starting from commercially available glutaraldehyde **404** (**Scheme 109**).[44] Keto-ester **406** was synthesised in two steps *via* mono-ketone adduct **405**, which was prepared by the very slow addition of methyl ketone phosphorane **325** to a dilute and large excess of glutaraldehyde **404**. Subsequent Wittig olefination with commercially available (carbethoxymethylene)triphenylphosphorane **322** furnished the desired activated diene **406**.[44]

Preparation of di-ketone **407** and di-ester **408** was straightforwardly accomplished by a one step Wittig olefination with the appropriate ylids in high yields (**Scheme 109**).



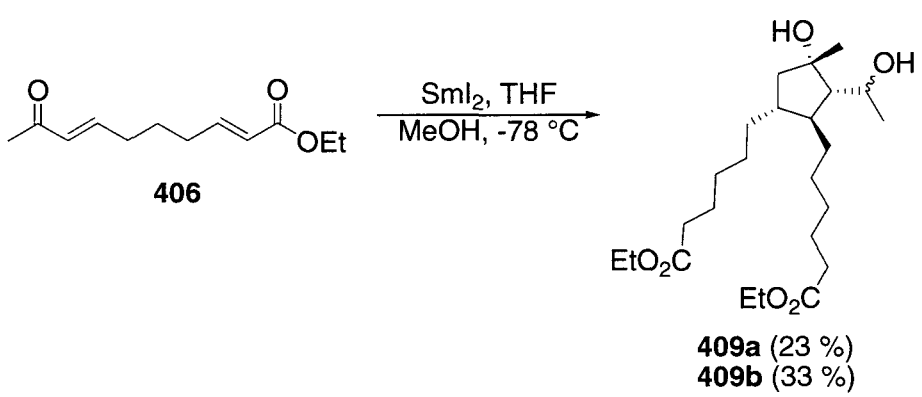
Scheme 109

3.2.2 Samarium Diiodide Studies

Having carried out SmI_2 studies on the analogous cyclic precursors, a set of similar results were expected be obtained with acyclic substrates **406**, **407** and **408**. Keto-ester **406** was expected to undergo cyclodimerisation and di-ketone **407** expected to undergo intramolecular cyclisation. Di-ester **408** in a similar fashion to di-ketone **407** was expected to undergo radical cyclisation.

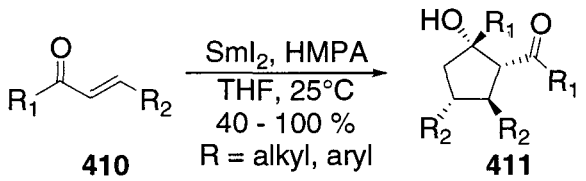
3.2.2.1 Keto-Ester 406

Studies began with keto-ester **406**, which upon exposure to SmI_2 gave the expected cyclodimerised products **409a** and **409b** (**Scheme 110**). **409a** and **409b** were isolated as two major diastereoisomers, of which **409a** was inseparable from a minor diasteroisomer.



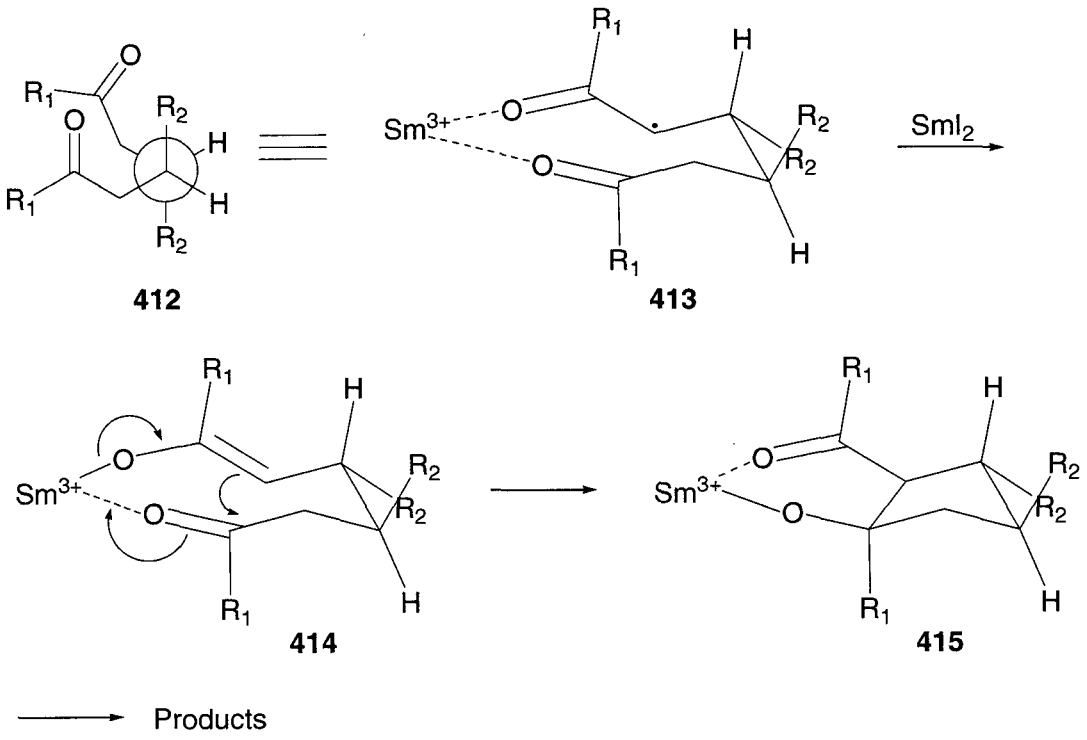
Scheme 110

Although the stereochemistry of the products has not been deduced with certainty, the stereochemical assignments of the major diastereoisomers are based upon previous results reported by Cabrera.[120] In his studies Cabrera reports the cyclodimerisation of a variety of α, β-unsaturated ketone species **410**, which in all instances provide cyclopentanol products **411** with the observed stereochemistry (**Scheme 111**).



Scheme 111

The observed selectivity is based upon the types of conformations that can undergo ring closure to generate the cyclopentanol structure (**Scheme 112**). The conformation shown **412** will be favoured since the steric interactions between the R_2 groups are minimised, thus giving rise to their *trans* geometry.[120]



Scheme 112

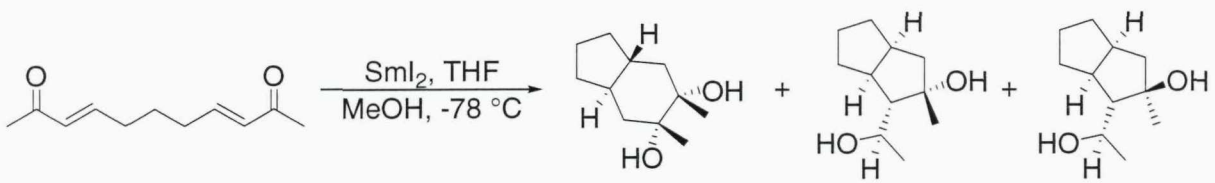
Subsequent chelation by a Sm^{3+} species holds the conformation in such a way so as to ensure both oxygen moieties occupy the same face of the cyclopentyl ring **414**.[120] The

two major diastereoisomers **409a** and **409b** obtained presumably differ only in the stereochemistry of the resultant secondary alcohol.

According to these results, it is apparent that the reaction prefers to proceed *via* an intermolecular pathway – much like the results obtained with cyclic keto-ester **327** (**Scheme 84**). Thus, slow addition of acyclic keto-ester **406** to a solution of SmI_2 should, by maintaining a low concentration of ketone, reduce dimerisation in favour of intramolecular cyclisation. However, slow addition of **406** to SmI_2 did not alter the result significantly (addition over 80 minutes gave diastereoisomers **409a** in 13 % yield and **409b** in 30 % yield).

3.2.2.2 Di-Ketone 407

Treatment of di-ketone **407** with SmI_2 gave rise to the expected intramolecular products in a good overall yield (**Scheme 113**).



407 **416** (53 %) **417** (12 %) **418** (6 %)

Scheme 113

The stereochemistry of pinacol derived product **416** (**Figure 28**) and aldol derived products **417** and **418** were confirmed by x-ray crystallography (**Figure 29**).

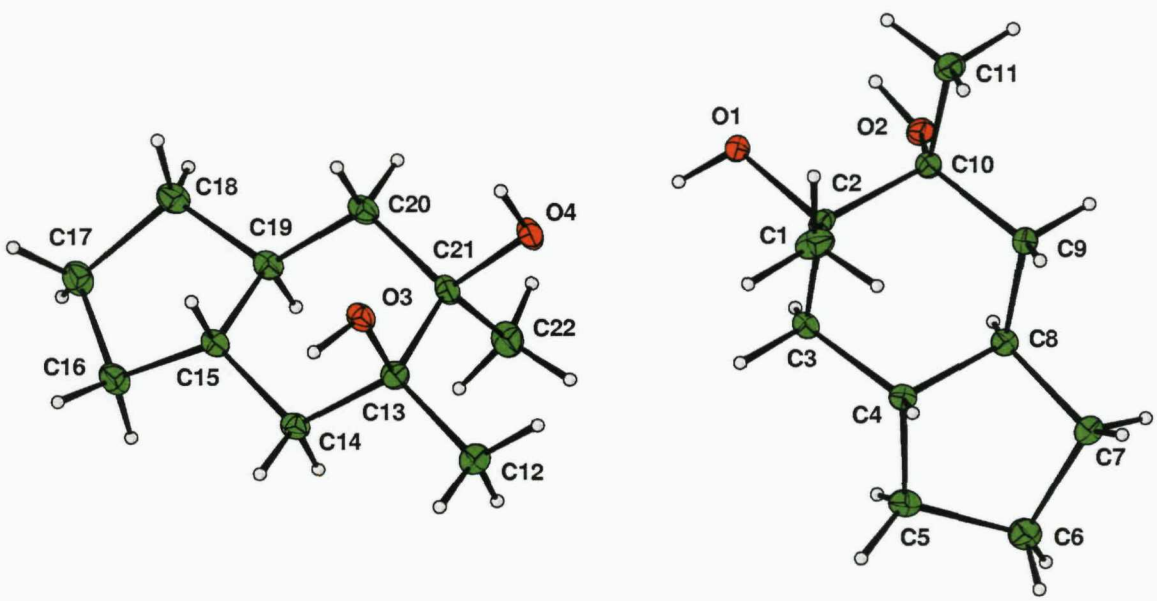


Figure 28: Crystal structure of pinacol product **416**.

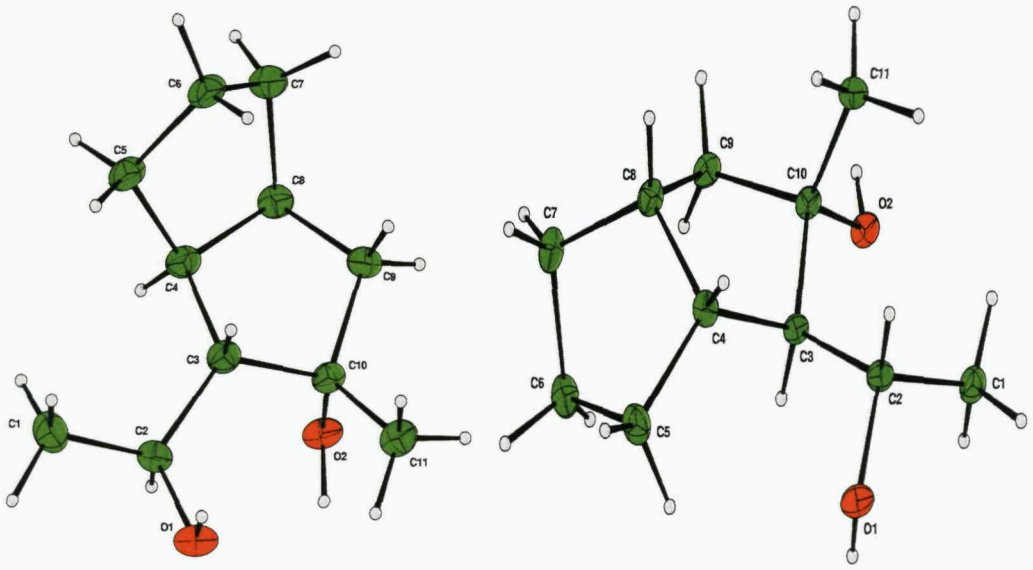
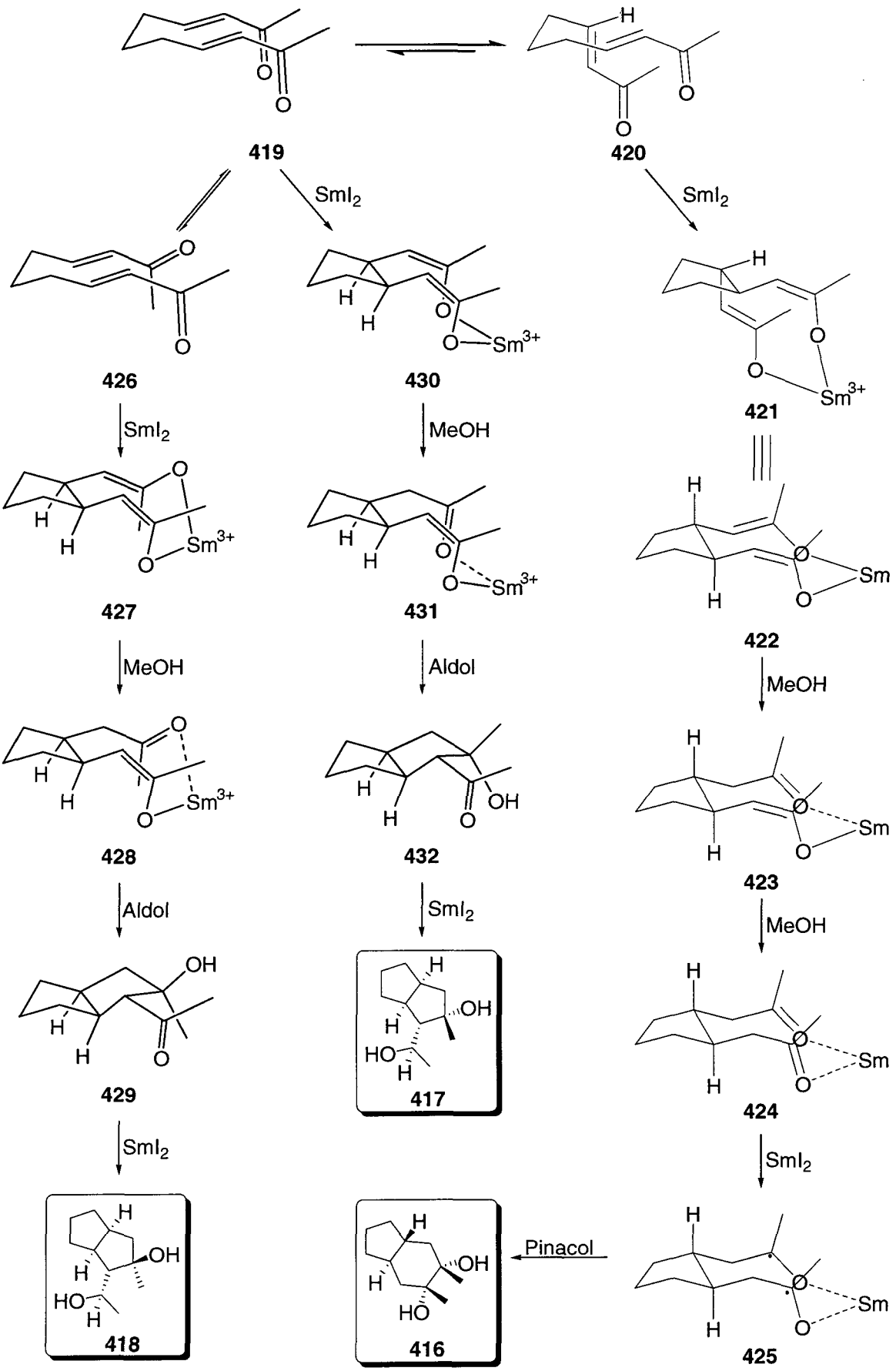


Figure 29: Crystal structures of aldol products **417** and **418**.

Product **416** is the result of an intramolecular 5-*exo-trig* cyclisation, and subsequent pinacolisation, whereas products **417** and **418** arise from a 5-*exo-trig* cyclisation then aldol condensation. The observed selectivity for the pinacol product is best explained by considering the intermediates in **Scheme 114**.

The di-ketone chain will occupy an arrangement which minimises electronic repulsion between the olefin and carbonyl groups, thus, conformation **420** in which a single olefin moiety is held in a pseudo axial orientation will be favoured over the alternative **419**. As a consequence upon cyclisation of species **420** a *trans* ring juncture will be formed **422**. Subsequent protonation with MeOH yields species **423**, which does not undergo aldol condensation as it would lead to a highly strained bicyclo-3.3.0-octane intermediate and is therefore protonated by a further equivalent of MeOH. Further reduction of di-ketone **424** gives rise to di-ketyl radical adduct **425** which then undergoes pinacolisation to give **416**.

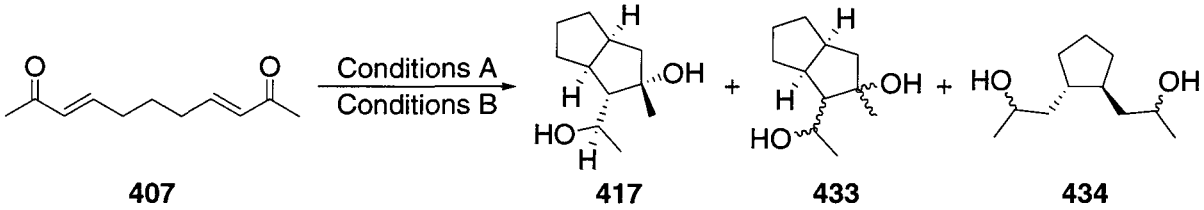
In contrast, the minor pathway which results from initial conformation **419** gives rise to the aldol products **417** and **418**. By looking at structures **428** and **431** one can see the proximity to which the samarium enolates are held to the carbonyl moieties, consequently it appears that aldol condensation is faster than protonation in these instances.


419
420
SmI2
SmI2
426
430
421
SmI2
MeOH
427
431
422
MeOH
Aldol
MeOH
428
432
423
Aldol
SmI2
MeOH
429
417
424
SmI2
SmI2
Pinacol
418
416
425

Scheme 114

α, β-Unsaturated carbonyl compounds and their reactivity with SmI_2 have been extensively studied by Inanaga,[114-116] Otera,[118] Cabrera[117, 119-121] and Kilburn.[122] Inanaga from his studies with α, β-unsaturated esters and amides found that solvent additives (HMPA or DMPU) play a crucial role in determining the rate, and more importantly the course the reactions will take. In addition to this, Otera,[118] Cabrera[117, 119-121] and Kilburn[122] conducted studies on α, β-unsaturated ketones, in which it became apparent that solvent effects play a pivotal role in determining the reactivity of these types of systems (please see **Section 1.2.7** for a detailed discussion).

Thus, based upon the significant effect that solvents appear to have on such α, β-unsaturated carbonyl systems a brief solvent study was conducted using di-ketone **407** (**Scheme 115** and **Table 2**). The first study made use of the well documented HMPA / THF solvent system[62, 95-98] and the second involved the more recent Et_3N / H_2O / THF solvent system pioneered by Hilmersson.[101-104]



407 **417** **433** **434**

Scheme 115

Conditions	Products
A: SmI_2, HMPA, THF, – 78 °C	**417**: Single isomer **433a** and **433b**: Single isomers **434**: Mixture of isomers
B: SmI_2, Et_3N, H_2O, THF, – 78 °C	**433**: Complex mixture of isomers **434**: Mixture of isomers

Table 2

The important conclusion that can be drawn from these results is that different solvent systems clearly have a dramatic effect on the reactivity of di-ketone **407**. In contrast with the conditions (MeOH / THF (4:1)) previously utilised **(Scheme 113)** in which pinacol adduct **416** was the major product, aldol products **417** and **418** as well as cyclic diol **434** now predominate.

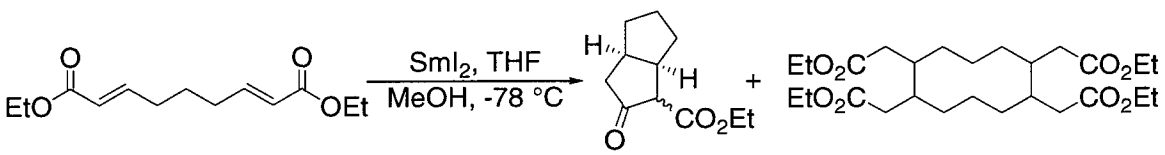
The reason for the difference in reactivity is down to the nature of the reactive samarium species in solution. The reducing power of SmI_2 in THF is sensitive to the

presence of co-solvents, many of which increase the oxidation potential of SmI_2 thus making it a stronger reducing agent. [103] HMPA and Et_3N / H_2O significantly enhance the reductive power of SmI_2 to a greater extent than MeOH / THF, a consequence of which being that any radical species present will be reduced to the corresponding anionic species more efficiently. This enhancement in reductive power of SmI_2 accounts for the observed change in reactivity of di-ketone **407**.

Using the MeOH / THF solvent system, ketyl radical **425 (Scheme 114)** is able to undergo radical coupling to generate pinacol product **416**, however in HMPA and Et_3N / H_2O radical intermediate **425** may rapidly undergo reduction to a di-anionic species which can no longer undergo pinacol coupling and therefore leads to the observed cyclic diol products **434 (Scheme 115)**, which presumably take up a *trans* geometry reflective of pinacol product **416 (Scheme 113)**.

3.2.2.3 Di-Ester 408

Treatment of di-ester **408** with SmI_2 gave β-keto ester **435** and cyclodecane derivative **436** which was isolated as an inseparable 4:1 mixture with an unidentified side product **(Scheme 116)**.

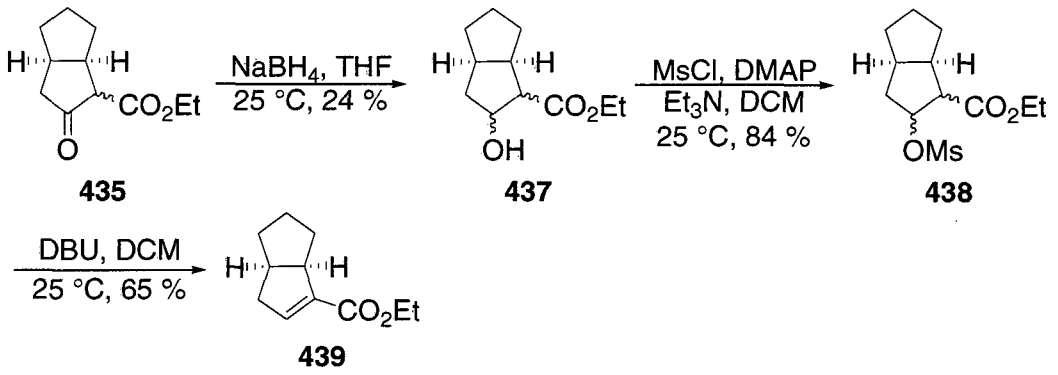


408 **435** (35 %) **436** (38 %)

Scheme 116

Unlike di-ketone **407 (Scheme 113)**, in which only products from intramolecular reaction were obtained, di-ester **408** gave rise to an approximate 1:1 mixture of inter and intra molecular products.

The data obtained for β-keto ester **435** was extremely complex; therefore in order to clarify its structure derivatisation studies were performed **(Scheme 117)**. Reduction using $NaBH_4$ gave β-hydroxy ester **437** as a single isomer, which upon treatment with methane sulfonyl chloride gave the corresponding mesylate **438**. Final elimination mediated by DBU gave α, β-unsaturated ester **439** in good yield.



Scheme 117

The simplification of NMR data in progressing from β-keto ester **435** to β-hydroxy ester **437** confirmed its structure, and subsequent derivatisation to mesylate **438** and α, β-unsaturated ester **439** gave further verification.

β-keto ester **435** is expected to have a *cis* ring juncture, this is based on the fact that an intramolecular cyclisation followed by a Dieckmann condensation took place – analogous to the cyclisation / aldol sequence observed for di-ketone **407 (Scheme 114)** in which the aldol condensation occurred due to the *cis* ring fusion.

3.2.3 Conclusion

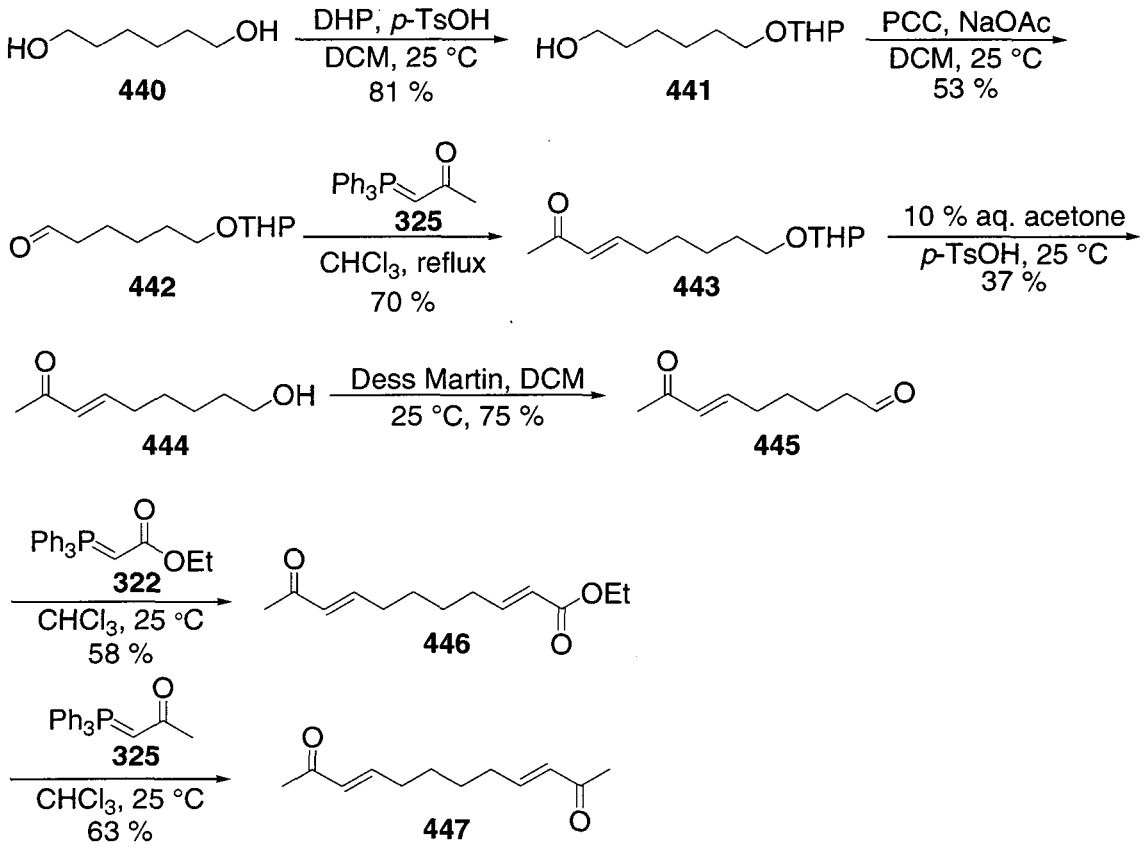
The methodology was extended from cyclic substrates to a range of analogous acyclic substrates with success. It was pleasing to find that the results with acyclic keto-ester **406** and di-ketone **407** were analogous to that of the cyclic substrates, and with the exception of di-ester **408** the outcome of these reactions were successfully predicted. With regard to the solvent study undertaken on di-ketone **407**, it is apparent that a MeOH / THF solvent system is required in order to obtain clean diastereomeric mixtures of pinacol product **416** and aldol products **417** and **418**.

3.3 Long Chain Substrates

The scope of the methodology was successfully applied to a set of acyclic substrates as outlined above. The following section details investigations into the effect of increasing the chain length between the reactive olefin centres by the addition of an extra methylene component.

3.3.1 Synthesis

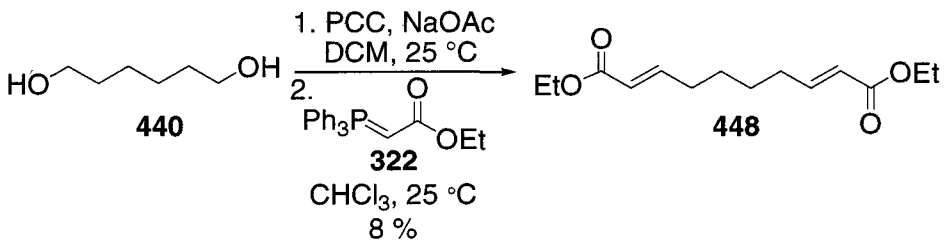
The syntheses of keto-ester **446**[157] di-ketone **447**[159] began with the mono protection of 1, 6 hexanediol **440** as the THP ether **441 (Scheme 118).**[160] Attempted oxidation to the corresponding aldehyde **442** utilising a TEMPO, NaOCl, $NaHCO_3$ system[160] and TEMPO, TCICA, $NaHCO_3$ system[161] failed to give any of the required product, instead in each case a complex mixture of products were obtained.



Scheme 118

Subsequent treatment of **441** with PCC[162] gave aldehyde **442**[160] in moderate yield which was subjected to Wittig olefination with previously prepared methyl ketone phosphorane **325**.[139, 140] The resulting THP-enone **443** was deprotected using aqueous acetone and acid to give alcohol **444** which upon exposure to Dess Martin periodinane[163] gave aldehyde **445** in good yield. Final Wittig olefination with (carbethoxymethylene)triphenylphosphorane **322** and methyl ketone phosphorane **325** furnished the required keto-ester **446**[157] and di-ketone **447**[159] respectively, in moderate yields.

Synthesis of di-ester **448** was successfully achieved over the course of two steps **(Scheme 119)**. In an attempt to shorten the synthesis, a double oxidation of 1, 6-hexanediol **440** to the corresponding di-aldehyde, followed directly by Wittig olefination to the desired di-ester species **448** was proposed. Thus, treatment of 1, 6-hexanediol **440** with PCC[162] followed by immediate reaction with (carbethoxymethylene) triphenylphosphorane **322** after workup, gave the target di-ester **448**[164] in overall 8 % yield **(Scheme 119)**.



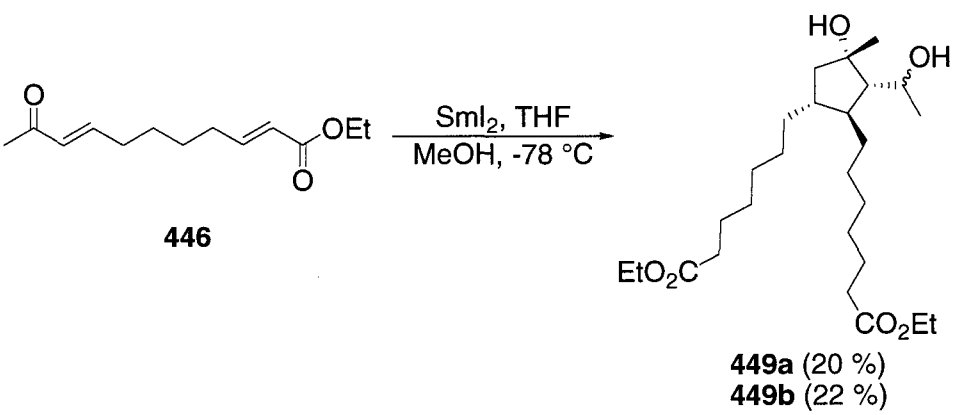
Scheme 119

3.3.2 Samarium Diiodide Studies

Based upon the previous results obtained with simple acyclic substrates **(Section 3.2)**, longer chain systems **446**, **447** and **448** were expected to follow a similar reaction course. Thus, keto-ester **446** was expected to undergo cyclodimerisation, di-ketone **447** to undergo intramolecular cyclisation and di-ester **448** to react to give a mixture of intra and intermolecular products.

3.3.2.1 Keto-Ester 446

Treatment of keto-ester **446** with SmI_2 gave rise to two diastereomeric cyclopentanol compounds **449a** and **449b** with no evidence of any other products **(Scheme 120)**.

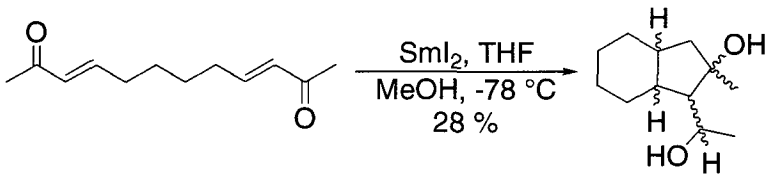


Scheme 120

It is assumed that the products have the stereochemistry shown, with the difference between the two diastereoisomers arising from the orientation of the secondary alcohol.

3.3.2.2 Di-Ketone 447

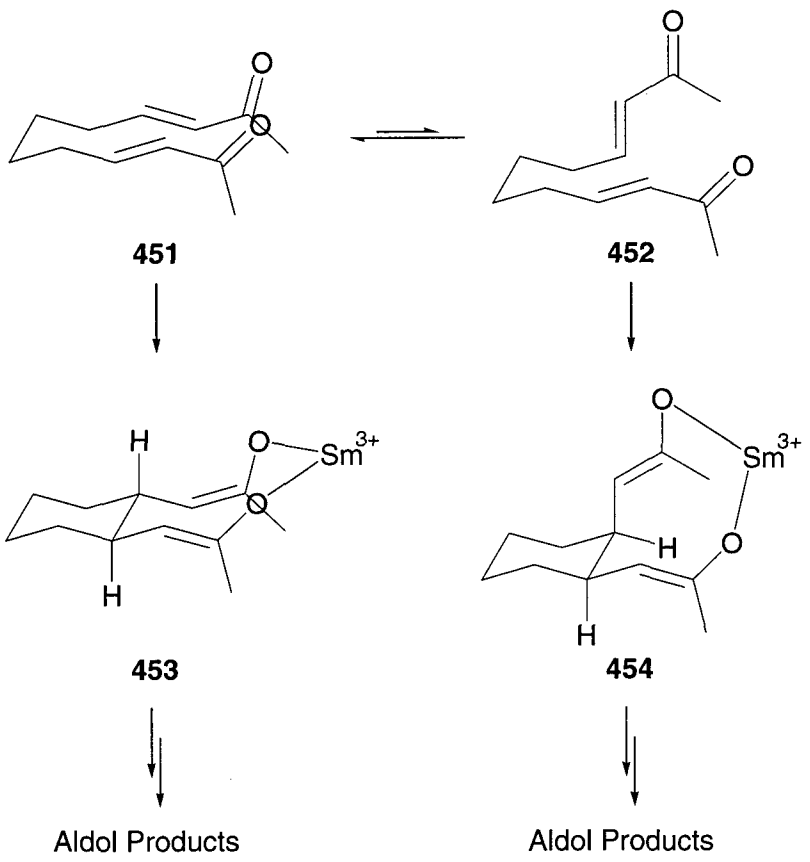
Upon exposure of di-ketone **447** to SmI_2, intramolecular aldol product **450** was obtained **(Scheme 121)**, and isolated as an inseparable 2:1 mixture of diastereoisomers. No other products were isolated from the reaction mixture.



447 **450**

Scheme 121

The stereochemistry has not been determined, but in a similar fashion to previously discussed di-ketone **407 (Scheme 113)**, in which the ring juncture stereochemistry was assigned based upon the conformational nature of the reactive intermediates **(Scheme 114)**, the same can be applied here **(Scheme 122)**.

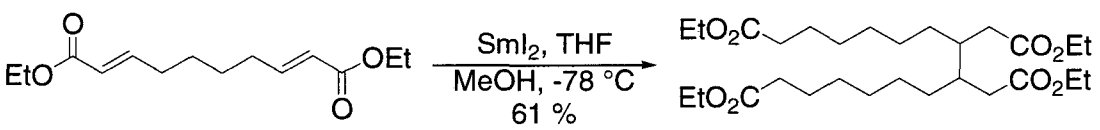


Scheme 122

In contrast with di-ketone **407** in which electronic repulsion between the olefin and carbonyl moieties played a critical role in determining the preferred conformation **(Scheme 114)**, they do not have such an important role to play with longer chain di-ketone **447**. As shown in conformation **451 (Scheme 122)**, the additional carbon spacer has the effect of staggering the functionalities, thus reducing the level of electronic repulsion. As a consequence, steric factors may play a more important role in determining the most stable conformation, and in comparison with conformation **452** in which one of the olefin moieties is held in an axial orientation, conformation **451** may be the most stable based on steric grounds. As a result, aldol products with a *trans* ring juncture are most likely to predominate.

3.3.2.3 Di-Ester 448

The final study of longer chain substrates involved di-ester **448**, which, when treated with SmI_2 gave dimeric species **455** as a single isomer **(Scheme 123)**.



448 **455**

Scheme 123

In contrast to di-ester **408** in which a mixture of inter and intramolecular products were isolated **(Scheme 116)**, longer chain substrate **448** yielded only a single intermolecular product **455**.

Considering di-ester **408**, an extremely efficient 5-*exo-trig* cyclisation is competing with a rapid intermolecular process – which is reflected in the approximate 1:1 product distribution between inter and intramolecular products **(Scheme 116)**. However, in the case of longer chain di-ester **448**, the comparatively slow 6-*exo-trig* cyclisation is apparently unable to compete with the faster dimerisation process, thus resulting in the formation of the observed intermolecular product **455** only.

3.3.3 Conclusion

The SmI_2 / MeOH / THF system was successfully applied to longer chain acyclic substrates **446**, **447** and **448**. In the case of keto-ester **446** and di-ketone **447** the

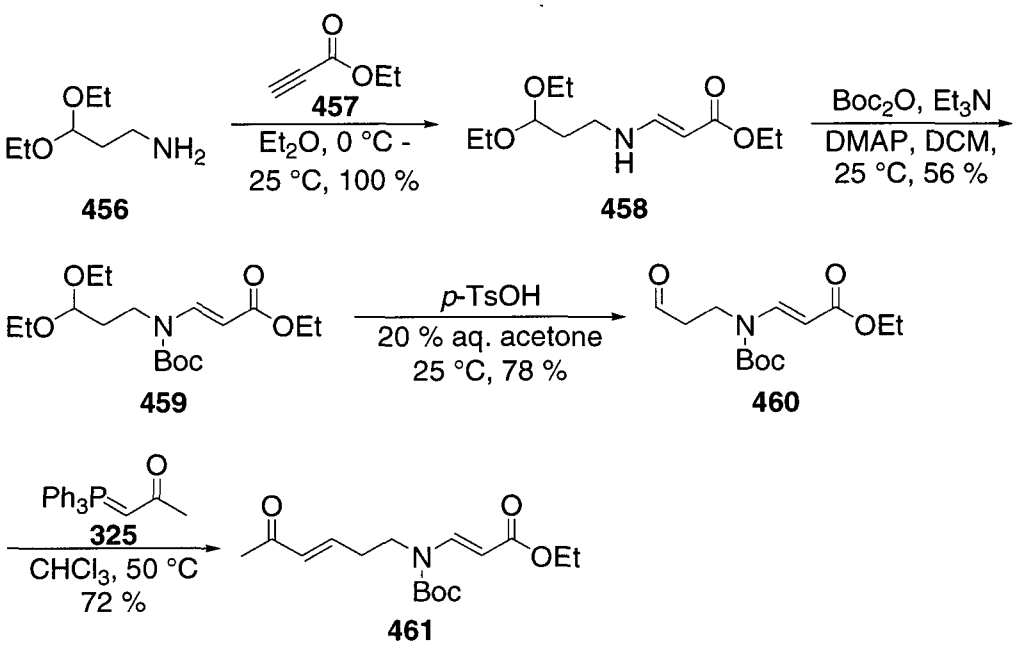
predicted cyclodimerised and intramolecular products were obtained respectively. Di-ester **448** was expected to give rise to a mixture of intra and intermolecular type products; however dimeric species **455** was formed as the only product and as a single diastereoisomer.

3.4 Functionalised Acyclic Substrates

Having successfully extended the methodology to a range of simple acyclic enones and long chain enones, studies shifted to more complex substrates. The following section outlines the syntheses and SmI_2 studies of two substrates incorporating nitrogen into the chain, plus an additional substrate featuring mono-substitution about the chain.

3.4.1 Synthesis

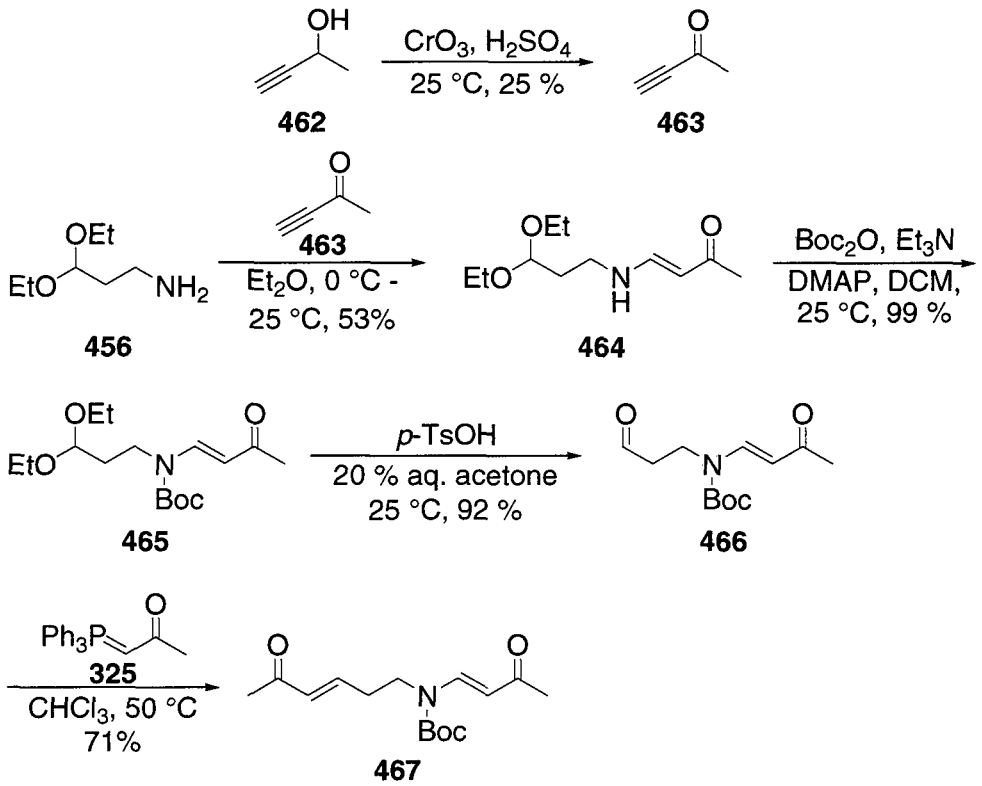
Syntheses of the two *N*-heteroatom incorporated substrates **461** and **467** were carried out in a similar fashion **(Schemes 124 and 125)**.



Scheme 124

Coupling between 1-amino-3, 3-diethoxy propane **456** and ethyl propiolate **457** gave amine **458**[165, 166] which when treated with Boc anhydride yielded carbamate **459** in moderate yield.[165] Acid catalysed deprotection to aldehyde **460**[165] and subsequent Wittig olefination with methyl ketone phosphorane **325** furnished the desired keto-ester

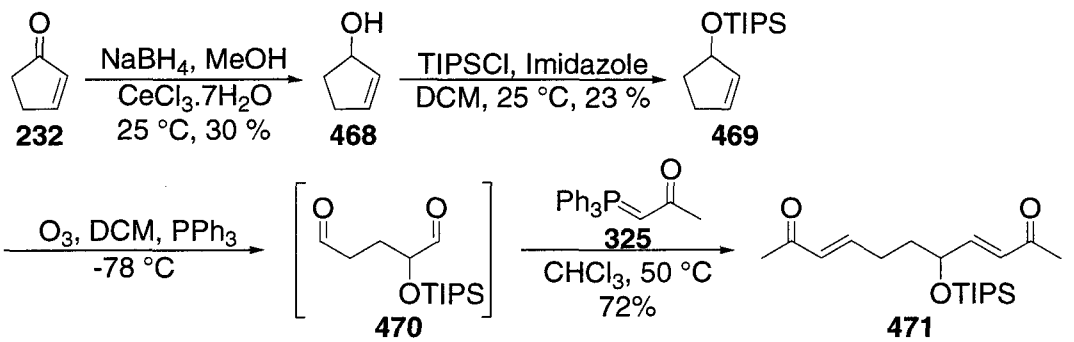
461 in good yield. Synthesis of di-ketone **467** (**Scheme 125**) was effected along parallel lines to those utilised for keto-ester **461**.



Scheme 125

Synthesis of 3-butyn-2-one **463** was achieved *via* Jones oxidation of 3-butyn-2-ol **462**.[167] Subsequent coupling[165, 168, 169] with 1-amino-3, 3-diethoxy propane **456** gave amine **464** which when subjected to Boc anhydride protection[165] gave carbamate **465** in excellent yield. Acid catalysed deprotection[165] to aldehyde **466** and Wittig olefination with methyl ketone phosphorane **325** furnished di-ketone **467** in good yield.

Substituted substrate **471**,[159] was synthesised in three steps starting from commercially available 2-cyclopenten-1-one **232** (**Scheme 126**). Luche reduction to 2-cyclopenten-1-ol **468**[170] followed by treatment with TIPSCl furnished silyl ether **469**.[171] The next reaction was key to the synthesis, and involved an *in situ* ozonolysis / Wittig olefination developed by Montgomery[159] which would provide the target substrate **471** in a single step. Thus, ozonolysis of the silane **469** and subsequent reaction with methyl ketone phosphorane **325** gratifyingly gave the desired substituted substrate **471** in good yield.



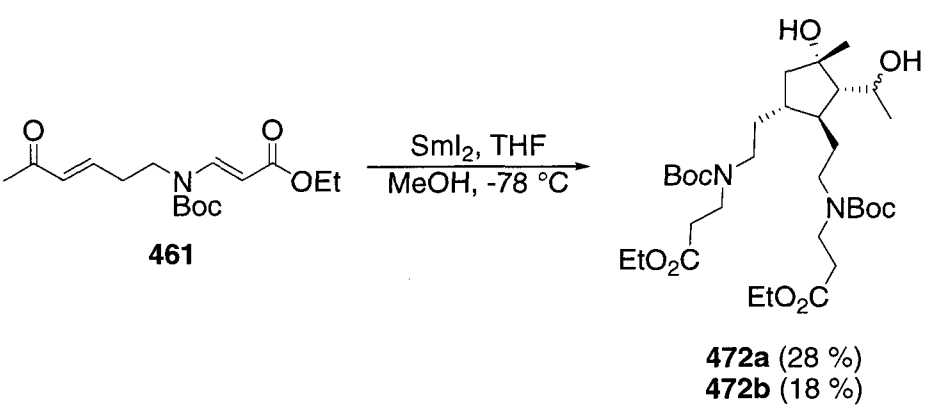
Scheme 126

3.4.2 Samarium Diiodide Studies

Based upon the results obtained with simple acyclic substrates **406** and **407** (**Section 3.2**), functionalised substrates **461**, **467** and **471** were expected to react in an analogous fashion to give rise to cyclodimerised and intramolecular pinacol or aldol products.

3.4.2.1 Keto-Ester 461

Treatment of keto-ester **461** with SmI_2 gave a mixture of products, including two major components tentatively assigned as cyclodimers **472a** and **472b** (**Scheme 127**).



Scheme 127

Due to the relatively poor NMR data obtained, caused by the presence of the two Boc groups, it was difficult to fully assign the structures. However based upon LRMS ($^{m}/z$ 653 $[M + Na]^+$) and several key characteristic peaks in the ^{13}C NMR (**Figure 30**) structures **472a** and **472b** have been tentatively assigned.

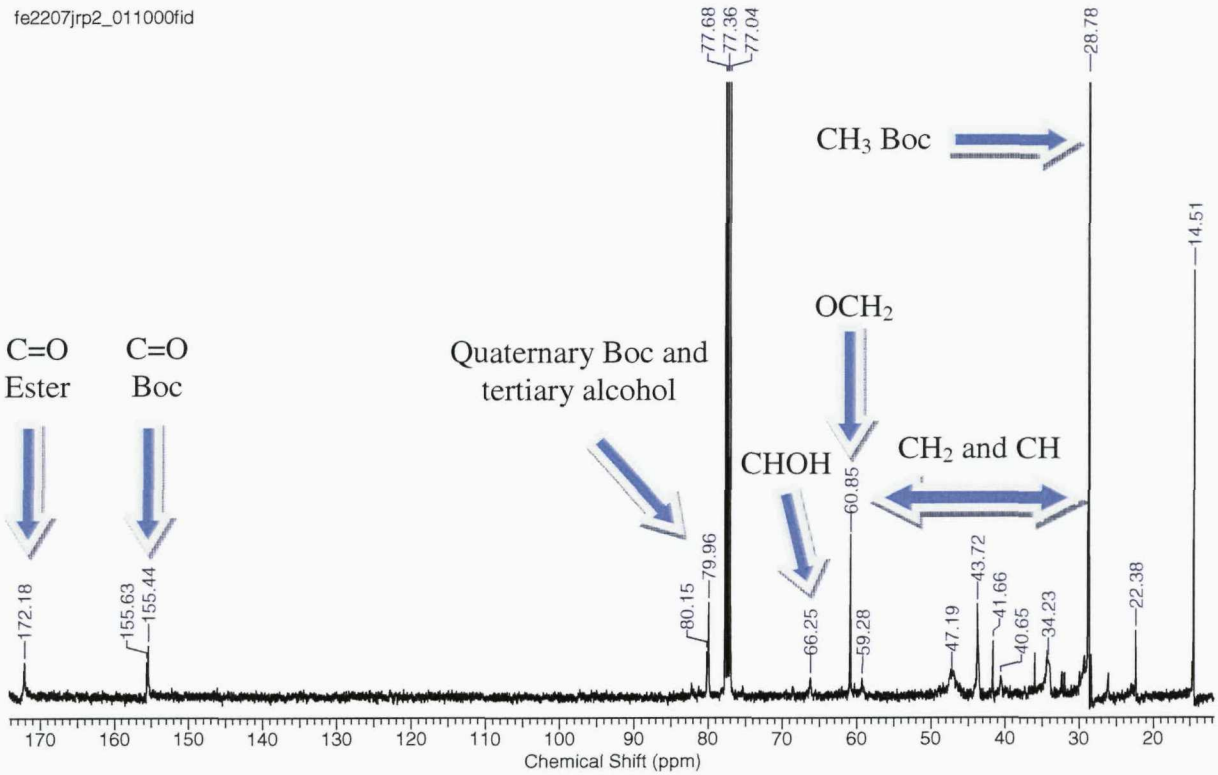
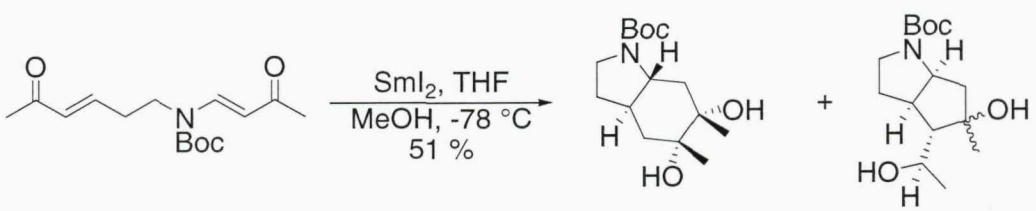


Figure 30: NMR data for **472a** with key peaks indicated.

In an attempt to obtain improved NMR data, **472a** and **472b** were treated with TFA to remove the problematic Boc groups; however, upon reaction complex mixtures of decomposition products were obtained.

3.4.2.2 Di-Ketone 467

In a further study of these types of substrates, exposure of di-ketone **467** to SmI_2 gave heterocyclic products **473** and **474 (Scheme 128)**.



467 **473** **474**

Scheme 128

Once again, relatively poor NMR data proved problematic in terms of assigning the structures definitively; however in a similar vein to keto-ester **461**, the structural assignments were based upon the limited data obtained.

The major component isolated from the reaction contained a mixture of pinacol **473** and aldol **474** products, the cautious structural assignments of which are based upon LRMS (^{m}/z 593 $[2M + Na]^{+}$) and limited ^{13}C data **(Figure 31)**.

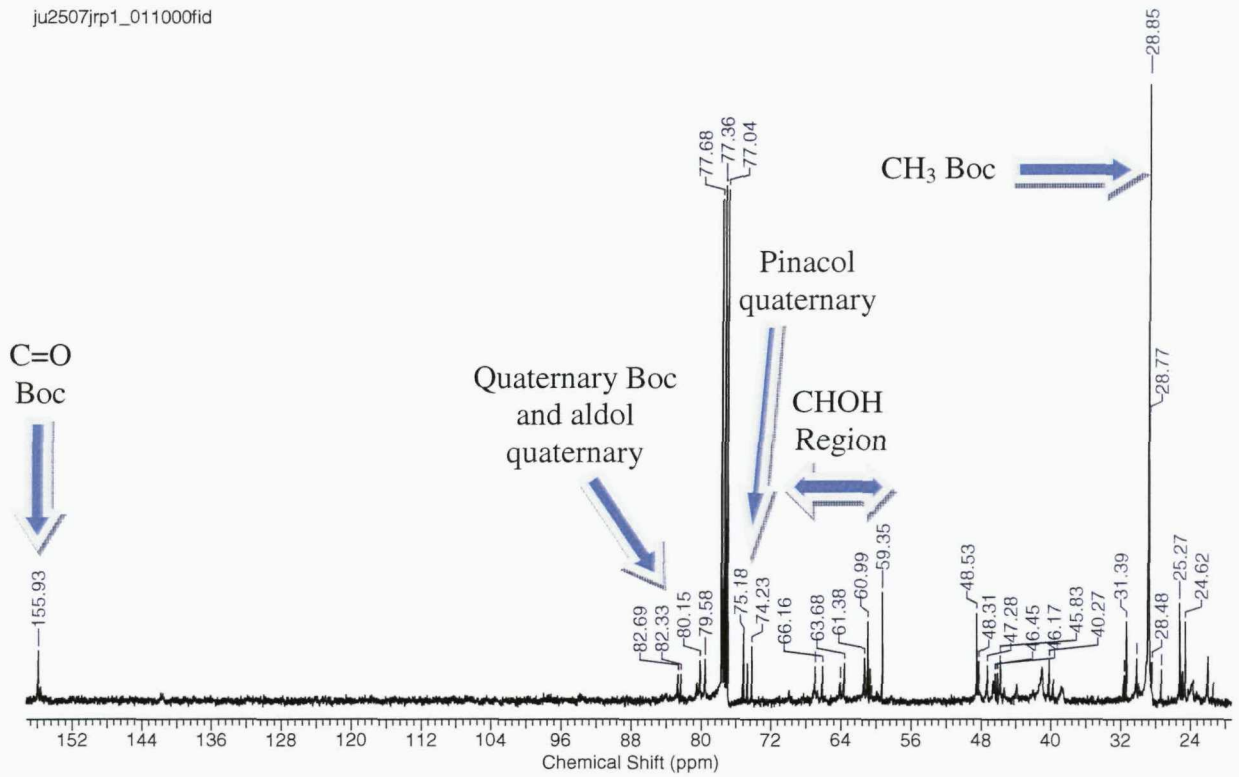
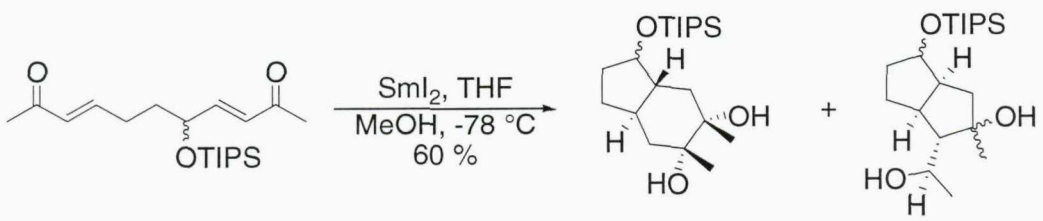


Figure 31: NMR data for mixture of **473** and **474** with key peaks indicated.

There is evidence for quaternary environments from both aldol (80-85 ppm) and pinacol products (75 ppm) including characteristic CHOH signals. This, coupled with LRMS data provides reasonable evidence in support of structures **473** and **474 (Scheme 128)**. The stereochemical assignments are based upon the precedence set by di-ketone **407 (Scheme 113)**.

3.4.2.3 Substituted Di-Ketone 471

Substituted di-ketone **471** gave a mixture of intramolecular pinacol **475** and aldol **476** products upon treatment with SmI_2 **(Scheme 129)**.



471 **475** **476**

Scheme 129

The reaction appeared to proceed in an analogous fashion to that of simple di-ketone **407 (Scheme 113)** giving rise to the expected intramolecular bi-cyclic products. Due to the additional chiral group in the molecule, an added level of complexity was imparted, and consequently product mixtures isolated appeared complex by ^{13}C NMR **(Figure 32)**.

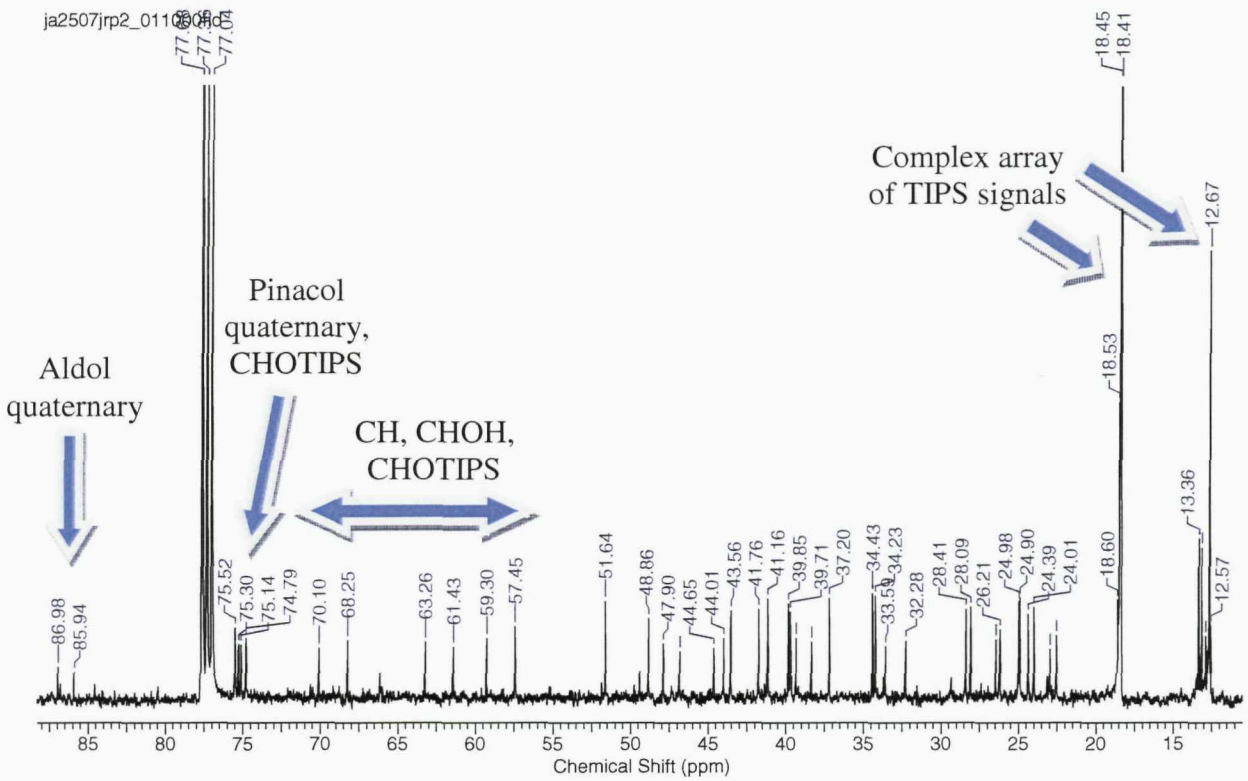


Figure 32: NMR data for mixture of **475** and **476** with key peaks indicated.

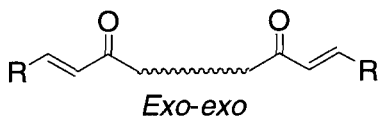
The above ^{13}C NMR **(Figure 32)** is indicative of pinacol **475** and aldol **476** products; the key peaks of which have been highlighted. Further product mixtures were also isolated, each exhibiting a similar NMR to the one shown above.

3.4.3 Conclusion

The SmI_2 / MeOH / THF system was applied to more complex enones **461**, **467** and **471** with moderate success. Substrates **461** and **467** gave the expected cyclodimerised and intramolecular products which were tentatively assigned using LRMS and limited NMR data. Similarly, substituted di-ketone **471** gave the expected intramolecular pinacol and aldol products, which could only be isolated as complex mixtures.

3.5 *Exo-Exo* Substrates

The following section discusses a set of substrates which are labelled '*exo-exo*'. The key difference being the side to which the carbon-carbon double bond is situated with respect to the carbonyl group has changed **(Figure 33)**. The term '*exo-exo*' has been coined because the positions of the double bonds are *exo* with respect to the main body of the chain.



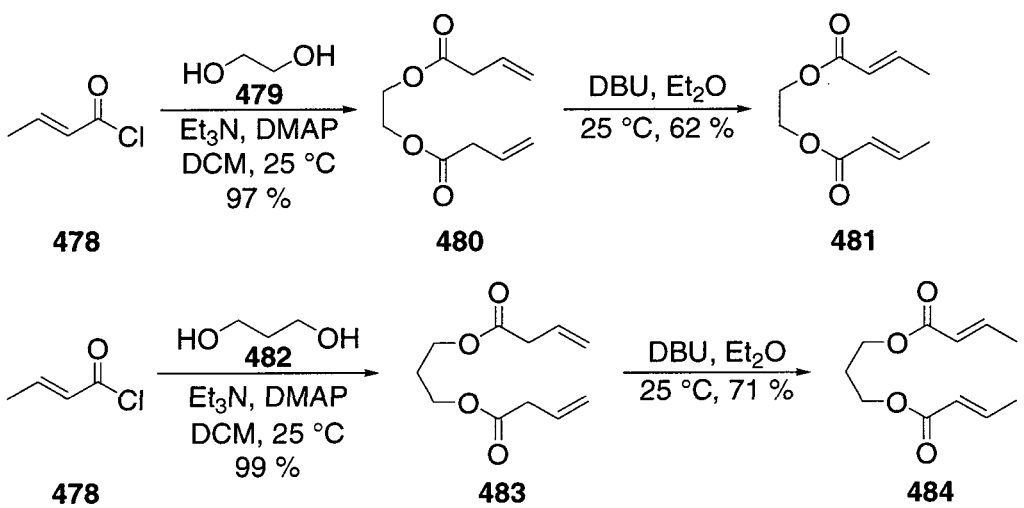
Exo-exo

477

Figure 33: An *exo-exo* type precursor **477**.

3.5.1 Synthesis

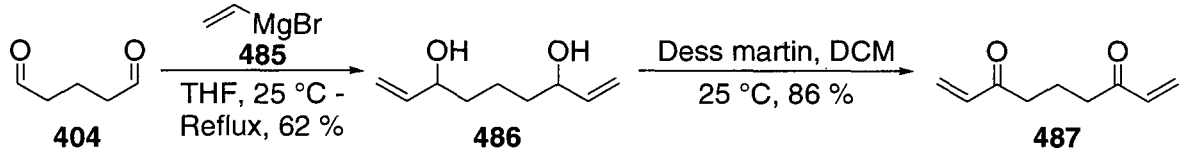
Syntheses of *exo-exo* di-esters **481** and **484** were successfully accomplished in two steps **(Scheme 130)**.



Scheme 130

Treatment of crotonyl chloride **478** with ethylene glycol **479** and propane 1, 3-diol **482** gave non conjugated systems **480** and **483** respectively. Subsequent treatment with DBU[172] gave rise to the desired conjugated di-ester products **481** and **484** in a good overall yield.

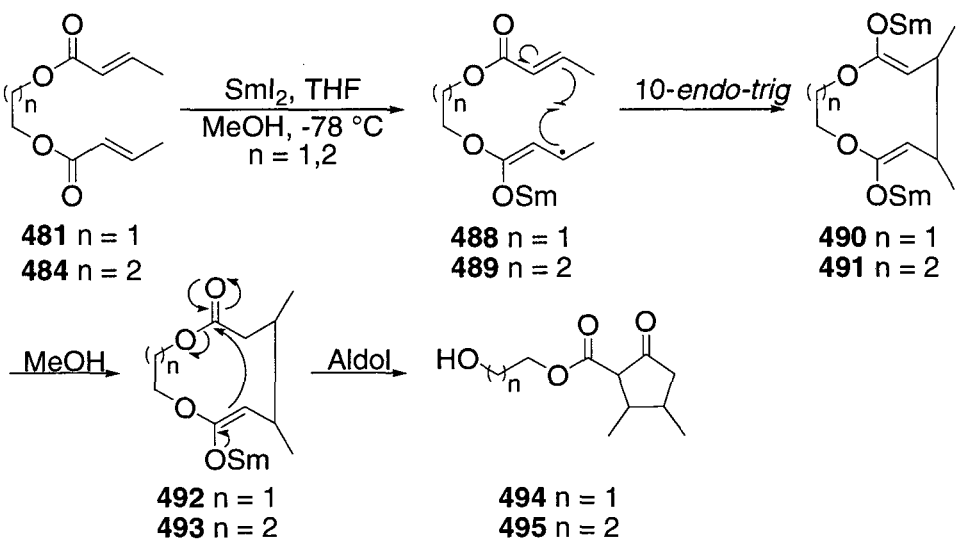
Synthesis of the third and final *exo-exo* substrate **487** was accomplished in two steps. Grignard reaction of commercially available glutaraldehyde **404** and vinyl magnesium bromide **485** furnished vinyl diol **486**[173] which was oxidised to the corresponding di-ketone **487**[173] using Dess Martin periodinane[163] **(Scheme 131)**.



Scheme 131

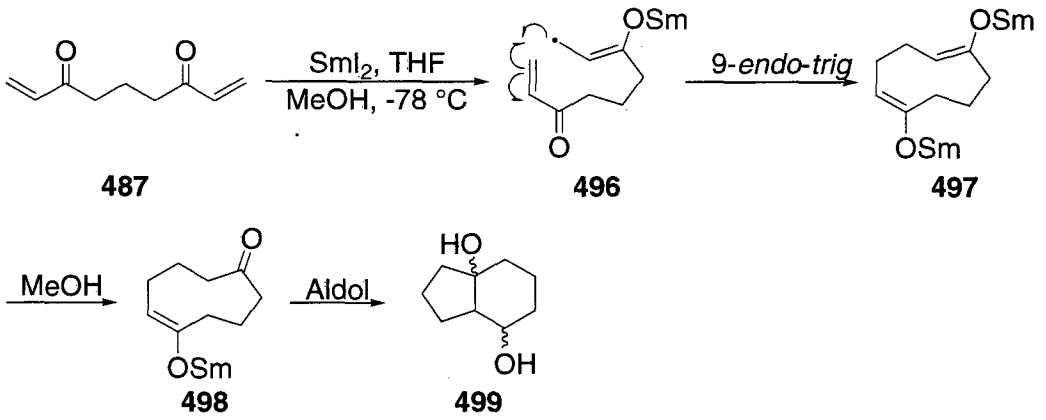
3.5.2 Samarium Diiodide Studies

The previous studies with di-esters **408** and **448** yielded a range of intermolecular and intramolecular type products, which were preferentially formed depending on the nature of the ring closing process (5-*exo-trig* or 6-*exo-trig*). A significant shift towards intermolecular products was observed when long chain di-ketone **448** was studied, thus, *exo-exo* di-ester precursors **481** and **484** were expected to react intermolecularly to give dimeric products. The alternative 10-*endo-trig* intramolecular pathway which could lead to functionalised cyclopentanones was also considered **(Scheme 132)**.



Scheme132

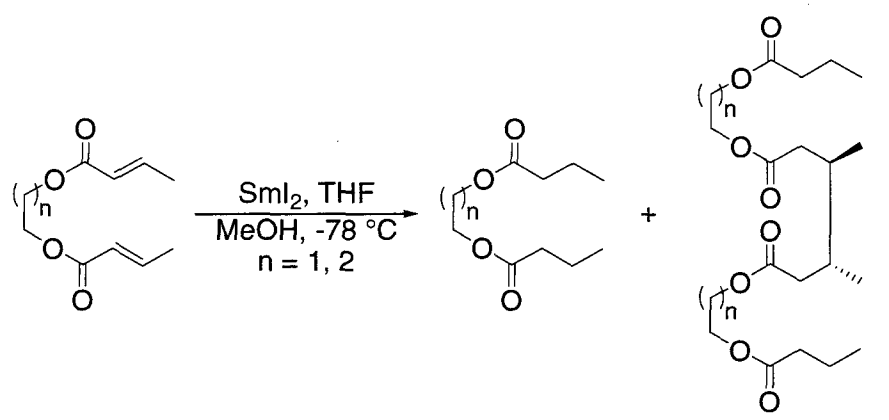
Analogous to diketones **407** and **447**, di-ketone **487** was expected to react in an intramolecular fashion to generate bicyclo-nonane derivative **499 (Scheme 133)**.



Scheme 133

3.5.2.1 *Exo-Exo* Di-Esters 481 and 484

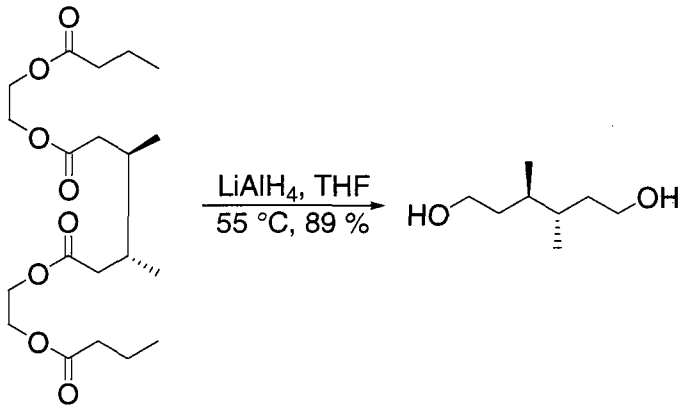
Treatment of di-esters **481** and **484** with SmI_2 gave 1, 4-reduced products **500** and **501** and the expected dimeric species **502** and **503 (Scheme 134)**.



Scheme 134

In both instances the major products were the 1, 4-reduced products **500** and **501**. One explanation for the observed results may be that dimerisation is reversible and entropically unfavourable. Alternatively, upon reaction with SmI_2 the unsaturated esters may form a complex in which the four oxygen atoms chelate to the samarium centre rendering it unreactive towards radical dimerisation. This complex could then undergo reduction to generate an organosamarium species which is unable to dimerise but can lead to the reduced products **500** and **501**.

In order to elucidate the stereochemistry dimeric species **502** was reduced to the corresponding known *trans*-diol **504** in excellent yield **(Scheme 135)**.[174]

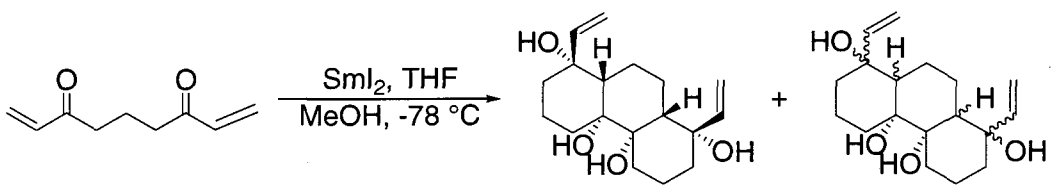


502 **504**

Scheme 135

3.5.2.2 *Exo-Exo* Di-Ketone 487

Upon exposure to SmI_2 di-ketone **487** yielded a complex diastereomeric mixture of tricycles **505** and **506a-e (Scheme 136)**.



487 **505** (5 %) **506a-e** (35 %)

Scheme 136

The stereochemistry of **505** was confirmed by x-ray crystallography **(Figure 34)**.

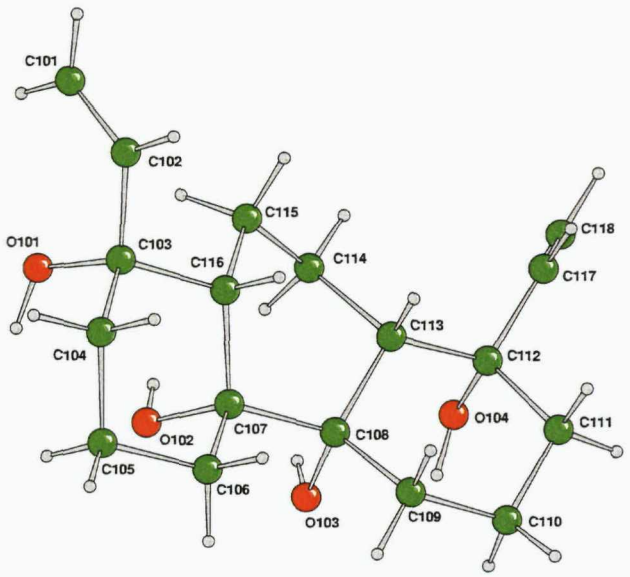
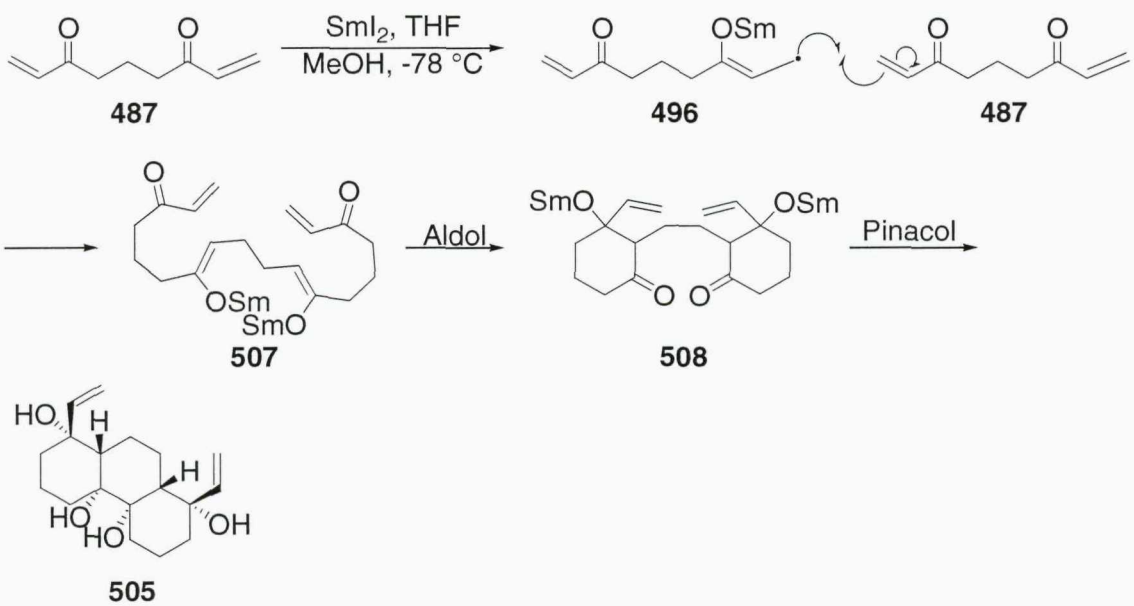


Figure 34: Crystal structure of tricycle **505**.

In addition to tricycle **505**, a number of other isomers **506a-e** were also obtained and isolated as inseparable mixtures (mixture one, 2:1 mixture of isomers **506a** and **506b**; mixture two, 5:2:1 mixture of isomers **506c-e**). Further isomeric mixtures of tricyclic products were also isolated in a 25 % yield, giving a total yield of 65 %.

This result was unexpected, as it was anticipated that an intramolecular pathway would predominate (**Scheme 133**). Di-ketone **487** clearly underwent a dimerisation sequence to provide the observed tricyclic products **505** and **506a-e** (**Scheme 137**).



Scheme 137

Reduction of di-ketone **487** generates radical intermediate **496** which subsequently couples to a further equivalent of di-ketone **487**. The resultant di-samarium enolate **507** will then undergo intramolecular aldol condensation onto the pendant ketones to give intermediate **508** in which two of the three cyclohexyl rings have been constructed. The final pinacol coupling stage furnishes the observed tricyclic products **505** and **506a-e**.

In order for the intramolecular pathway to have taken place, a 9-*endo-trig* cyclisation would have had to have occurred **(Scheme 133)**. In contrast to the previously studied di-ketones **407** and **447** in which the faster 5-*exo-trig* and 6-*exo-trig* cyclisations were able to compete favourably with the dimerisation process, the slower 9-*endo-trig* cyclisation was clearly unable compete with the rapid dimerisation sequence and as a result the observed dimerised products **505** and **506a-e** were formed.

3.5.3 Conclusion

The methodology was successfully extended to a set of *exo-exo* substrates. Di-esters **481** and **484** gave predominantly 1, 4-reduced products, with a small quantity of the expected dimerised components. This was in contrast to the previously studied di-esters **408** and **448** in which both dimerised and intramolecular products were obtained. Studies with di-ketone **487** led to intermolecular tricyclic products, which was in stark contrast with previously studied di-ketones **407** and **447** which yielded intramolecular pinacol and aldol products.

3.6 Final Discussion

Several investigations were carried out on acyclic precursors utilising the SmI_2 / MeOH / THF methodology. Studies on simple substrates **406** and **407** and long chain precursors **446** and **447** gave results analogous to the corresponding cyclic systems providing evidence that the methodology can be extended to acyclic precursors. It was interesting to note the difference in reactivity between simple di-ester **408** and long chain di-ester **448**, which showed a significant shift towards dimerisation products upon elongation of the chain.

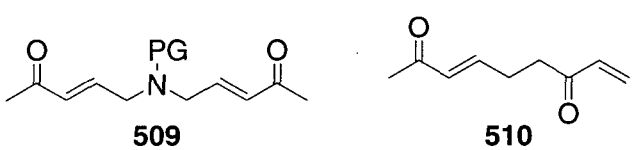
The studies carried out on *N*-substituted substrates **461** and **467** and substituted di-ketone **471** gave some evidence to suggest that the methodology had been successfully

applied to more complex systems; poor quality analytical data however proving the stumbling block in these instances.

A final set of investigations were carried out on *exo-exo* substrates **481**, **484** and **487** with reasonable success. Of particular interest was the result with di-ketone **487**, in which a set of highly functionalised tricyclic structures **505** and **506a-e** were formed. Although a considerably powerful reaction (four new carbon-carbon bonds and six chiral centres generated) the reaction was not diastereoselective, and produced a complicated mixture of products.

There is reasonable scope with which the acyclic research could be taken forward and improved upon, particularly with regard to *N*-substituted substrates **461** and **467** in which a range of apparent heterocyclic products were obtained. The major difficulty was the protecting Boc group, which made data analysis particularly difficult, and which upon deprotection with TFA led to decomposed mixtures. A possible improvement may be to incorporate an alternative protecting group, for example Cbz, which could be removed by mild hydrogenation conditions.

Future work may also wish to consider the synthesis of an alternative *N*-substituted substrate **509** **(Figure 35)** which may provide an additional pathway into further interesting heterocyclic products when treated with SmI_2.[175] In addition, further studies may also wish to be conducted on *exo-endo* type substrates **510** **(Figure 35)**, which may provide further interesting reaction pathways.



509 **510**

Figure 35: *N*-substituted substrate **509** and *exo-endo* substrate **510**.

Chapter 4 Experimental

4.1 General Experimental

Reactions requiring anhydrous conditions were conducted in oven-dried or flame-dried glassware under an atmosphere of argon. All anhydrous solvents were prepared by refluxing with an appropriate drying agent and purified by distillation according to the procedures outlined in Perin and Armarego, *"Purification of Laboratory Chemicals"*.[176] THF and Et_2O were refluxed from sodium and benzophenone under argon until a persistent purple colour was maintained. DCM, Et_3N and pyridine were refluxed from CaH_2. The distilled solvents were taken using the usual syringe techniques. Solvents were of commercial grade and were used without further purification unless otherwise stated. All chemicals were attained from commercial suppliers without further purification unless otherwise stated.

Thin layer chromatography was performed on aluminium backed sheets coated with silica gel (0.25 mm) containing the fluorescent indicator UV_{254}. The plates were visualised under UV lamp at 254 nm and / or using $KMnO_4$ or ninhydrin stains. Flash column chromatography was performed according to the procedure described by Still,[177] on Sorbil C_{60}, 35 - 70 mesh silica.

4.2 Instrumentation

Infrared spectra were obtained on a Thermo Nicolet 380 FT - IR spectrometer. Absorptions are given in wavenumbers (cm^{-1}). The relative intensity of the peaks are indicated in parentheses using the following abbreviations; strong (s), medium (m) and weak (w). All samples were run either as neat solids or as oils. Melting points were determined in open capillary tubes using a Gallenkamp Electrothermal melting point apparatus and are uncorrected.

^1H NMR spectra were recorded at 300 MHz on a Bruker AC 300 spectrometer or 400 MHz on a Bruker DPX 400 spectrometer using the deuterated solvent as the lock and the residual protons as internal standard. Peak positions are quoted against the δ scale relative to the residual solvent signal, using the following abbreviations;

singlet (s), doublet (d), triplet (t), quartet (q), quintet (qn), sextet (sext), multiplet (m) and broad (br). ^{13}C NMR (proton decoupled) spectra were obtained at 75.5 MHz on a Bruker AC 300 or at 100 MHz on a Bruker DPX 400 spectrometer. The multiplicities of the signals are indicated in parentheses, using the following abbreviations: quaternary carbon (0), tertiary (1), secondary (2) and primary (3). In some cases the signals were elucidated using the distortionless enhancement by phase transfer (DEPT) spectral editing technique with second pulse at 135°. Coupling constants, *J*, are measured in Hertz (Hz).

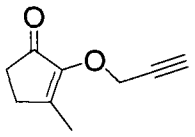
Low resolution ES^+ mass spectra were obtained on a Micromass Platform II with a quadrupole mass analyser. High resolution ES^+ mass spectra were obtained on a Bruker Apex III FT - ICR mass spectrometer, or on a Micromass Q - Tof 1 mass spectrometer. EI and CI mass spectra were obtained on a ThermoQuest TraceMS gas chromatography mass spectrometer configured for open access operation. M/z signals are reported in atomic mass units followed in parentheses by the ion found and peak intensity. Microanalyses were performed by MEDAC Ltd., Surrey.

X - Ray diffraction data was obtained on an Enraf Nonius KappaCCD diffractometer, and the structures were determined by direct methods using the program SHELXS97 and refined using SHELXL97.

Compounds were named using the program ACD Labs version 10.0 from Advanced Chemistry Development Inc. or ChemDraw version 8.0 from CambridgeSoft.

4.3 Experimental For Chapter Two

3-Methyl-2-(prop-2-yn-1-yloxy)cyclopent-2-en-1-one 279



279

$C_9H_{10}O_2$

Mw: 150.17 $gmol^{-1}$

Following the reported procedure by Pirrung,[126] commercially available 3-methylcyclopentanedione **278** (2.5 g, 22.3 mmol) was dissolved in toluene (60 mL) and propargyl alcohol (3.89 mL, 66.9 mmol) followed by *p*-toluenesulfonic acid monohydrate (212 mg, 1.10 mmol, 5 mol %) was added in one portion. The orange mixture was refluxed in a Dean and Stark apparatus and allowed to stir for 20 h. The dark brown reaction mixture was allowed to cool to RT, before being washed with saturated $NaHCO_3$ aqueous solution (2 x 30 mL), and brine (2 x 25 mL) respectively. The organic extracts were dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave a deep red oil which was purified by flash column chromatography, eluting with 5 % EtOAc / petrol to 40 % EtOAc / petrol, to give alkyne **279** as a yellow oil (650 mg, 4.33 mmol, 20 %), R_f = 0.44 (40 % EtOAc / petrol);

IR ν_{max} (film): 3276 (m), 2921 (m), 2361 (w), 1697 (s), 1645 (s), 1094 (s) cm^{-1}.

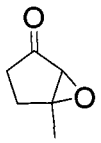
^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.85 (2H, d, *J* = 2.4 Hz, OCH_2), 2.50 - 2.45 (2H, m, $C(O)CH_2$), 2.43 (1H, t, *J* = 2.4 Hz, CH_2CCH), 2.39 - 2.35 (2H, m, CH_2), 2.02 (3H, s, CH_3) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.9 (0), 157.6 (0), 150.4 (0), 79.4 (1), 75.0 (0), 57.4 (2), 32.9 (2), 27.3 (2), 15.0 (3) ppm.

LRMS (EI): $^m/z$ (relative intensity), 150 $[M]^+$ (34 %).

HRMS (EI): $[M]^+$ $C_9H_{10}O_2$ requires $^m/z$ 150.06808, found $^m/z$ 150.06845.

5-Methyl-6-oxabicyclo[3.1.0]hexan-2-one 281



281

$C_6H_8O_2$

Mw: 112.13 $gmol^{-1}$

Following the reported procedure by House,[127] 3-methyl-2-cyclopentenone **280** (10 mL, 100 mmol) was dissolved in MeOH (73 mL) and hydrogen peroxide (35 % aq. solution, 26.3 mL, 300 mmol) added in one portion. The solution was cooled to 0 °C and 6M NaOH aqueous solution (8 mL, 50.0 mmol) was then added drop-wise over a period of 45 minutes ensuring the temperature of the reaction did not rise above 2 °C. The reaction was allowed to stir at RT for 1 h, before being poured onto water (50 mL), and DCM (5 x 100 mL) used to extract the product. The combined organic extracts were washed with brine (2 x 60 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave a colourless oil which was purified by flash column chromatography, eluting with 10 % EtOAc / petrol, to give epoxide **281** (5.00 g, 44.6 mmol, 45 %) as a colourless oil, $R_f = 0.37$ (40 % EtOAc / petrol);

IR ν_{max} (film): 2935 (w), 2360 (m), 2341 (m), 1743 (s), 1448 (m), 1404 (m) cm^{-1}.

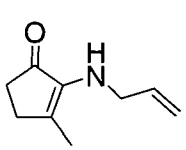
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.13 (1H, s, **CHO**), 2.42 - 2.24 (2H, m, **CH_2**), 2.12 - 1.88 (2H, m, **CH_2**), 1.57 (3H, s, **CH_3**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.1 (0), 61.2 (1), 53.7 (0), 33.2 (2), 28.1 (2), 18.2 (3) ppm.

LRMS (EI): $^m/z$ (relative intensity), 112 $[M]^+$ (58 %).

HRMS (EI): $[M]^+$ $C_6H_8O_2$ requires $^m/z$ 112.05243, found $^m/z$ 112.05109.

3-Methyl-2-(prop-2-en-1-ylamino)cyclopent-2-en-1-one 282



282

$C_9H_{13}NO$

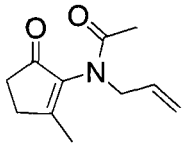
Mw: 151.21 $gmol^{-1}$

Following the reported procedure by Pete,[128] previously prepared epoxide **281** (2.00 g, 17.8 mmol) was dissolved in MeOH (40 mL) and allylamine (1.60 mL, 21.4 mmol) added in one portion. The colourless mixture was heated to reflux and allowed to stir for 16 h. Upon allowing the reaction mixture to cool to RT, the solvent was removed *in vacuo* to give a brown oil. The crude material was purified by flash column chromatography, eluting with 1 % EtOAc / petrol gradually increasing the polarity to 10 % EtOAc / petrol to give pure enamine **282** (1.00 g, 6.61 mmol, 37 %) as a yellow oil, R_f = 0.2 (10 % EtOAc / petrol);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.85 (1H, ddt, *J* = 17.3, 10.6, 5.3 Hz, C**H**=CH_2), 5.16 (1H, dd, *J* = 17.3, 1.5 Hz, CH=C**H**$_{trans}$H), 5.09 (1H, dd, *J* = 10.3, 1.3 Hz, CH=CH**H**$_{cis}$), 3.79 (2H, d, *J* = 3.9 Hz, NCH_2), 2.41 - 2.34 (4H, m, 2 x CH_2), 2.05 (3H, s, CH_3) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.9 (0), 142.0 (0), 140.4 (0), 136.8 (1), 115.9 (2), 47.9 (2), 33.1 (2), 30.1 (2), 16.9 (3) ppm.
LRMS (ES+): m/z (relative intensity), 152 $[M + H]^+$ (10 %), 174 $[M + Na]^+$ (100 %).

Degrades over the course of several h; used immediately in the following reaction.

***N*-(2-Methyl-5-oxocyclopent-1-en-1-yl)-*N*-prop-2-en-1-ylacetamide 283**



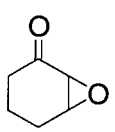
283
$C_{11}H_{15}NO_2$
Mw: 193.24 $gmol^{-1}$

Enamine **282** (1.00 g, 6.61 mmol) was dissolved in freshly distilled DCM (40 mL) and to the brown solution added DMAP (74.0 mg, 0.606 mmol, 10 mol %) and Et_3N (1 mL, 7.17 mmol) consecutively. The reaction mixture was cooled to 0 °C and acetyl chloride (0.520 mL, 7.31 mmol) added dropwise over a period of 25 minutes, before allowing the reaction mixture to warm to RT and stir for 48 h. Saturated $NaHCO_3$ aqueous solution (10 mL) was added in one portion and allowed to stir for 5 minutes before separating the phases, and washing the aqueous layer with DCM (2 x 20 mL). The combined organic phases were washed with brine (30 mL) and dried over magnesium sulfate. Removal of the solvent *in vacuo* gave a brown oil, which was purified by flash column chromatography eluting with neat DCM increasing the polarity to 1% MeOH /

DCM to give pure amide **283** (350 mg, 1.81 mmol, 27 %) as a pale orange oil, $R_f = 0.49$ (10 % MeOH / DCM);

IR ν_{max} (film): 2922 (w), 1704 (s), 1660 (s), 1638 (s), 1433 (m), 1379 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.72 (1H, ddt, J = 17.0 10.3, 6.5 Hz, **CH**=CH_2), 5.09 - 5.03 (2H, m, CH=**CH_2**), 4.21 (1H, dd, J = 14.5, 6.3 Hz, N**CH_AH_B**), 3.98 (1H, dd, J = 14.8, 7.0 Hz, N**CH_AH_B**), 2.64 - 2.62 (2H, m, **CH_2**), 2.47 - 2.45 (2H, m, **CH_2**), 2.05 (3H, s, C(O)**CH_3**), 1.82 (3H, s, **CH_3**) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.2 (0), 172.4 (0), 170.3 (0), 141.1 (0), 133.5 (1), 118.5 (2), 49.6 (2), 33.4 (2), 29.8 (2), 21.9 (3), 17.4 (3) ppm.
LRMS (ES+): ^{m}/z (relative intensity), 194 $[M + H]^+$ (75 %), 216 $(M + Na]^+$ (100 %).
HRMS (ES+): $[M + Na]^+$ $C_{11}H_{15}NO_2Na$ requires ^{m}/z 216.0995, found ^{m}/z 216.0998.

7-Oxabicyclo[4.1.0]heptan-2-one 284



284
$C_6H_8O_2$
Mw: 112.13 $gmol^{-1}$

Following the reported procedure by House,[127] 2-cyclohexen-1-one **230** (25.0 mL, 260 mmol) was dissolved in MeOH (180 mL) and hydrogen peroxide (35 % aq. solution, 68.0 mL, 770 mmol) added in one portion. The solution was cooled to 0 °C and 6M NaOH aqueous solution (22 mL, 130 mmol) was then added drop-wise over a period of 45 minutes ensuring the temperature of the reaction did not rise to above 0 °C. The reaction was allowed to stir at 10 °C for 1 h, before being poured onto water (100 mL), and Et_2O (5 x 100 mL) used to extract the product. The combined organic extracts were washed with brine (2 x 60 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave a colourless oil which was purified by flash column chromatography, eluting with 10 % EtOAc / petrol gradually increasing the polarity to 100 % EtOAc to give epoxide **284** (11.3 g, 101 mmol, 39 %) as a colourless oil, $R_f = 0.33$ (30 % EtOAc / petrol);

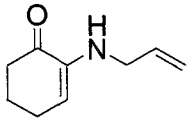
IR ν_{max} (film): 2938 (m), 2880 (w), 1707 (s), 1405 (w) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.55 (1H, br s, CHO**CH**), 3.20 (1H, d, J = 4.0 Hz, **CH**OCH), 2.56 - 1.60 (6H, m, 3 x **CH_2**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.2 (0), 56.2 (1), 55.4 (1), 36.7 (2), 23.2 (2), 17.3 (2) ppm.

LRMS (EI+): ^{m}/z (relative intensity), 112 $[M]^+$ (53 %).

HRMS (EI+): $[M]^+$ $C_6H_8O_2$ requires ^{m}/z 112.05243, found ^{m}/z 112.05269.

2-(Prop-2-en-1-ylamino)cyclohex-2-en-1-one 285



285

$C_9H_{13}NO$

Mw: 151.21 $gmol^{-1}$

Following the reported procedure by Pete,[128] epoxide **284**, (2.00 g, 17.8 mmol) was dissolved in MeOH (40 mL) and allylamine (2 mL, 26.7 mmol) added in one portion. The resultant yellow mixture was heated to reflux and allowed to stir for 16 h. Upon allowing the reaction mixture to cool to RT, the solvent was removed *in vacuo* to give a dark red oil. The crude material was purified by flash column chromatography, eluting with 10 % EtOAc / petrol increasing the polarity to 30 % EtOAc / petrol to give unstable enamine **285** (1.25 g, 8.27 mmol, 47 %) as a yellow oil, R_f = 0.5 (50 % EtOAc / petrol);

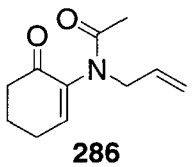
^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.85 (1H, ddt, *J* = 17.2, 10.2, 4.8 Hz, C**H**=CH_2), 5.45 (1H, t, *J* = 4.6 Hz, C(NH)=C**H**), 5.19 (1H, dq, *J* = 17.2, 1.5 Hz, CH=CH**H**), 5.11 (1H, dq, *J* = 10.3, 1.5 Hz, CH=CH**H**), 4.30 (1H, br s, N**H**), 3.50 (2H, d, *J* = 5.5 Hz, NHC$\mathbf{H_2}$), 2.50 - 2.41 (2H, m, C$\mathbf{H_2}$), 2.38 - 2.31 (2H, m, C$\mathbf{H_2}$), 1.90 (2H, qn, *J* = 5.6 Hz, $CH_2C\mathbf{H_2}CH_2$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.1 (0), 140.6 (0), 135.3 (1), 116.3 (1), 112.0 (2), 46.1 (2), 38.2 (2), 24.9 (2), 23.8 (2) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 152 $[M + H]^+$ (100 %), 174 $[M + Na]^+$ (25 %).

Enamine **285** degrades over the course of several h; used immediately in the following reaction.

_N_-(6-Oxocyclohex-1-en-1-yl)-_N_-prop-2-en-1-ylacetamide 286



286

$C_{11}H_{15}NO_2$
Mw: 193.24 $gmol^{-1}$

Enamine **285** (1.20 g, 7.94 mmol) was dissolved in freshly distilled DCM (40 mL) and to the orange solution added DMAP (90.0 mg, 0.80 mmol, 10 mol %) and Et_3N (1.2 mL, 8.70 mmol) consecutively. The reaction mixture was cooled to 0 °C and acetyl chloride (0.62 mL, 8.72 mmol) added dropwise over a period of 20 minutes, before allowing the reaction mixture to warm to RT and stir for 24 h. Saturated $NaHCO_3$ aqueous solution (10 mL) was added in one portion and allowed to stir for 5 minutes before separating the organic phase, washing with brine (30 mL) and drying over magnesium sulfate. Removal of the solvent *in vacuo* gave a brown oil, which was purified by flash column chromatography eluting with neat DCM increasing the polarity to 1 % MeOH / DCM to give pure amide **286** (1.20 g, 6.21 mmol, 79 %) as a pale orange oil, $R_f = 0.48$ (10 % MeOH / DCM);

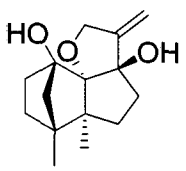
IR ν_{max} (film): 2927 (w), 1680 (s), 1656 (s), 1626 (s), 1385 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.85 (1H, t, J = 7.0 Hz, NC=C**H**), 5.71 (1H, ddt, J = 16.8, 10.0, 6.4 Hz, CH_2C**H**=CH_2), 5.10 - 5.0 (2H, m, CH=C**H$_2$**), 4.38 (1H, br s, NCH_AH_B), 3.65 (1H, br s, NCH_AH_B), 2.51 (4H, t, J = 7.0 Hz, 2 x **CH$_2$**), 2.04 (2H, qn, J = 6.6 Hz, $CH_2CH_2CH_2$), 1.83 (3H, s, **CH$_3$**) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.0 (0), 170.2 (0), 148.7 (1), 139.9 (0), 133.6 (1), 117.8 (2), 50.3 (2), 38.4 (2), 25.9 (2), 22.5 (2), 21.8 (3) ppm.
LRMS (ES+): ^{m}/z (relative intensity), 216 $[M + Na]^+$ (100 %).
HRMS (ES+): $[M + Na]^+$ $C_{11}H_{15}NO_2Na$ requires ^{m}/z 216.09949, found ^{m}/z 216.09918.

General Method for the Preparation of SmI_2 (0.1 M) Solution:

Following the reported procedure by Curran,[125] to flame dried glassware under an atmosphere of argon was added samarium metal, degassed and distilled THF and freshly purified 1,2-diiodoethane. The resultant mixture was vigorously stirred at 25 °C for 2 h, over which time the reaction turned from green with a yellow precipitate to a

deep blue solution of SmI_2. The reagent was used directly in the following reductive cyclisation reactions.

***rac* - (1*R*, 6*R*, 9*S*, 10*R*)-9, 10-Dimethyl-5-methylidene-3-oxatetracyclo[8.2.1.$0^{2,6}$.$0^{2,9}$] tridecane-1,6-diol 289**



289

$C_{15}H_{22}O_3$

Mw: 250.33 $gmol^{-1}$

Following the reported procedure by Kilburn,[122] MeOH (7 mL) was added to a stirring solution of SmI_2 in THF (0.1 M, 27 mL) and the resultant purple mixture cooled to – 78 °C, where upon the reaction turned a dark green. Alkyne **279** (100 mg, 0.665 mmol) as a solution in THF (5 mL) was then added drop-wise over a period of 20 minutes and the reaction allowed to stir at – 78 °C for a further 2 h. Brine (20 mL), followed by citric acid (168 mg, 0.800 mmol) was then added and allowed to stir for a further 15 minutes. Brine (10 mL) was then added and the products extracted with EtOAc (4 x 50 mL), before the combined organic extracts were washed with brine once again (25 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave a yellow oil which was purified by flash column chromatography, eluting with 10 % EtOAc / petrol to 40 % EtOAc / petrol to give tetracycle **289** (5.00 mg, 0.0399 mmol, 6 %) as a yellow oil, R_f = 0.16 (40 % EtOAc / petrol);

IR ν_{max} (film): 3447 (br), 2951 (m), 2870 (m), 1735 (s) cm^{-1}.

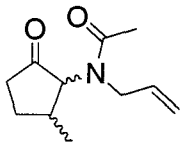
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.27 (1H, t, *J* = 2.3 Hz, C=CH**H**), 5.09 (1H, t, *J* = 2.2 Hz, C=C**H**H), 4.80 (1H, dt, *J* = 13.3, 2.6 Hz, OC**H$_A$**H$_B$), 4.46 (1H, dt, *J* = 13.3, 2.0 Hz, OCH$_A$**H$_B$**), 2.30 (1H, m, C**H$_A$**H$_B$), 2.16 (1H, m, CH$_A$**H$_B$**), 1.95 - 1.60 (5H, m, 2 x C**H$_2$** and C**H$_A$**H$_B$), 1.49 (1H, td, *J* = 13.0, 4.3 Hz, C**H$_A$**H$_B$), 1.35 (1H, m, CH$_A$**H$_B$**), 1.25 (2H, br s, 2 x O**H**), 1.10 (1H, m, CH$_A$**H$_B$**), 0.87 (3H, s, C**H$_3$**), 0.75 (3H, s, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.7 (0), 104.3 (2), 98.4 (0), 84.0 (0), 80.8 (0), 69.9 (2), 51.3 (0), 47.7 (2), 43.4 (0), 31.6 (2), 30.4 (2), 29.3 (2), 28.1 (2), 20.8 (3), 15.5 (3) ppm.

LRMS (ES+): $^{m}/z$ (relative intensity), 273 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{15}H_{22}O_3Na$ requires $^{m}/z$ 273.1461, found $^{m}/z$ 273.1465.

***N*-(2-Methyl-5-oxocyclopentyl)-*N*-prop-2-en-1-ylacetamide 294**



294

$C_{11}H_{17}NO_2$

Mw: 195.26 $gmol^{-1}$

Following the reported procedure by Kilburn,[122] MeOH (10 mL) was added to a stirring solution of SmI_2 in THF (0.1 M, 41 mL) and the resultant purple mixture cooled to – 78 °C, where upon the reaction turned dark green. Amide **283** (200 mg, 1.03 mmol) as a solution in THF (5 mL) was then added drop-wise over a period of 10 minutes and the reaction allowed to stir at – 78 °C for a further 2 h. Brine (30 mL), followed by citric acid (259 mg, 1.23 mmol) was then added and allowed to stir for a further 20 minutes. EtOAc (70 mL) was added to the stirring solution and allowed to stir for 10 minutes, after which the reaction mixture was allowed to settle and the organic phase decanted off. This process was then repeated (4 x 70 mL EtOAc). The aqueous phase was transferred to a separating funnel and further extracted with EtOAc (2 x 70 mL), before the combined organic extracts were washed with brine (2 x 50 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave a yellow oil which was purified by flash column chromatography, eluting with neat DCM gradually increasing the polarity to 5 % MeOH / DCM to give acetamide **294** (99.0 mg, 0.507 mmol, 51 %) as a yellow oil, $R_f = 0.41$ (10 % MeOH / DCM);

IR ν_{max} (film): 3420 (br), 2635 (m), 2896 (w), 1719 (s), 1635 (s), 1411 (m) cm^{-1}.

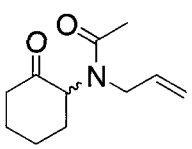
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.80 (1H, m, C**H**=CH_2), 5.36 (1H, br d, J = 17.0 Hz, CH=C**H**$_{trans}$H), 5.21 (1H, dd, J = 10.3, 1.24 Hz, CH=CH**H**$_{cis}$), 4.00 (1H, dd, J = 17.1, 5.3 Hz, NC**H**$_A$H$_B$), 3.75 (1H, dd, J = 17.3, 5.3 Hz, NCH$_A$**H**$_B$), 3.39 (1H, m, NC**H**C(O)), 2.57 - 2.36 (3H, m, C**H**$_2$, C**H**$_A$H$_B$), 2.27 (1H, m, CH$_A$**H**$_B$), 2.07 (3H, s, C(O)C**H**$_3$), 1.35 (1H, m, C**H**), 1.11 (3H, d, J = 6.3 Hz, C**H**$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 213.6 (0), 170.7 (0), 133.6 (1), 118.0 (2), 71.7 (1), 53.7 (2), 36.6 (2), 34.9 (1), 28.1 (2), 21.8 (3), 19.2 (3) ppm.

LRMS (ES+): $^{m}/z$ (relative intensity), 196 $[M + H]^+$ (15 %), 218 $[M + Na]^+$ (100 %), 413 $[2M + Na]^+$ (50 %).

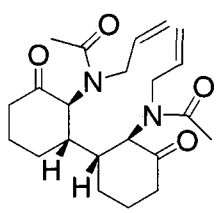
HRMS (ES+): $[M + H]^+ C_{11}H_{18}NO_2$ requires $^{m}/z$ 196.1332, found $^{m}/z$ 196.1330.

***N*-(2-Oxocyclohexyl)-*N*-prop-2-en-1-ylacetamide 295, *rac* - *N*-[(1*S*, 6*S*)-2-oxo-6-[(1*R*, 2*R*)-3-oxo-2-[*N*-(prop-2-en-1-yl)acetamido]cyclohexyl]cyclohexyl]-*N*-(prop-2-en-1-yl)acetamide 296 and *rac* - *N*-[(6*S*)-2-oxo-6-[(1*R*)-3-oxo-2-[*N*-(prop-2-en-1-yl)acetamido]cyclohexyl] cyclohexyl]-*N*-(prop-2-en-1-yl)acetamide 297**



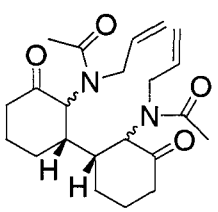
295

$C_{11}H_{17}NO_2$
Mw: 195.26 $gmol^{-1}$



296

$C_{22}H_{32}N_2O_4$
Mw: 388.5 $gmol^{-1}$



297

$C_{22}H_{32}N_2O_4$
Mw: 388.5 $gmol^{-1}$

Following the reported procedure by Kilburn,[122] MeOH (13 mL) was added to a stirring solution of SmI_2 in THF (0.1 M, 52 mL) and the resultant purple mixture cooled to – 78 °C, where upon the reaction turned dark green. Amide **286** (250 mg, 1.29 mmol) as a solution in THF (10 mL) was then added dropwise over a period of 15 minutes and the reaction allowed to stir at – 78 °C for a further 2 h. Brine (20 mL), followed by citric acid (325 mg, 1.54 mmol) was then added and allowed to stir for a further 15 minutes. The products were extracted with EtOAc (6 x 50 mL), before the combined organic extracts were washed with brine once again (40 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave a pale yellow oil which was purified by flash column chromatography, eluting with neat DCM gradually increasing the polarity to 6 % MeOH / DCM to give the 1,4 reduced product **295** (23.0 mg, 0.118 mmol, 9 %) as a yellow oil, R_f = 0.36 (10 % MeOH / DCM), dimer **296** (108 mg, 0.556 mmol, 43 %) as a yellow solid, R_f = 0.3 (10 % MeOH / DCM) and dimer **297** (71 mg, 0.366 mmol, 28 %) as a yellow oil, R_f = 0.19 (10 % MeOH / DCM);

Data for 1,4 reduced product **295**:

IR ν_{max} (film): 3403 (br), 2930 (m), 2860 (w), 1718 (s), 1627 (s), 1417 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.85 - 5.77 (1H, m, $CH_2CH{=}CH_2$), 5.19 - 5.15 (2H, m, $CH{=}CH_2$), 5.10 - 5.00 (1H, m, C(O)CHN), 4.07 (1H, ddt, *J* = 18.3, 5.0, 1.8 Hz,

NCH_AH_B), 3.70 (1H, ddt, J = 18.3, 4.5, 2.0 Hz, NCH_AH_B), 2.54 - 2.45 (2H, m, CH_2), 2.10 (3H, s, CH_3), 1.98 - 1.91 (2H, m, CH_2), 1.79 - 1.70 (4H, m, 2 x CH_2) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.8 (0), 172.1 (0), 135.3 (1), 116.7 (2), 63.0 (1), 49.6 (2), 41.7 (2), 31.9 (2), 26.6 (2), 25.0 (2), 22.0 (3) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 196 $[M + H]^+$ (100 %).

HRMS (ES+): $[M + H]^+$ $C_{11}H_{18}NO_2$ requires ^{m}/z 196.1332, found ^{m}/z 196.1333.

Data for dimer **296**:

Mpt: 105-107 °C, recrystallised from DCM / petrol.

IR ν_{max} (solid): 3546 (br), 2929 (w), 2860 (w), 1716 (s), 1629 (s), 1413 (m) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6, 80 °C): δ = 6.10 - 5.91 (2H, m, 2 x $NCH_2CH=CH_2$), 5.30 - 5.15 (4H, m, 2 x $NCH_2CH=CH_2$), 4.32 (1H, br d, J = 11.4 Hz, NCH_AH_B), 4.01 (1H, ddt, J = 17.2 Hz, 5.8, 1.9 Hz, NCH_AH_B), 3.88 - 3.74 (4H, m, 2 x C(O)CHN, 2 x NCH_AH_B), 2.42 - 2.35 (4H, m, 2 x CH_2), 1.99 (3H, s, CH_3), 1.99 (3H, s, CH_3), 1.95 - 1.30 (10H, m, 4 x CH_2 and 2 x CH) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.7 (0), 173.2 (0), 135.1 (1), 117.6 (2), 66.5 (1), 43.3 (1), 52.0 (2), 41.2 (2), 25.1 (2), 23.8 (2), 22.7 (3) ppm.

LRMS: ^{m}/z (relative intensity), 411 $[M + Na]^+$ (100 %), 800 $[2M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{22}H_{32}N_2O_4Na$ requires ^{m}/z 411.2254, found ^{m}/z 411.2253.

X-ray: Please see appendix.

Data for dimer **297**:

IR ν_{max} (film): 3501 (br), 2933 (w), 2856 (w), 1716 (s), 1630 (s), 1414 (m) cm^{-1}.

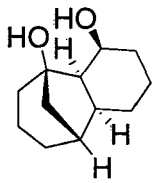
^{1}H NMR (400 MHz, DMSO-d_6, 80 °C): δ = 5.98 (2H, ddt, J = 16.4, 10.6, 6.1 Hz, 2 x $NCH_2CH=CH_2$), 5.31 (2H, br d, J = 17.2 Hz, 2 x $NCH_2CH=CH_{\textit{trans}}H$), 5.19 (2H, br d, J = 9.1 Hz, 2 x $NCH_2CH=CHH_{\textit{cis}}$), 4.15 - 9.96 (2H, m, 2 x C(O)CHN) 3.86 (4H, apparent qd, J = 16.9, 5.8 Hz, 2 x NCH_2), 2.50 - 2.39 (4H, m, 2 x CH_2), 2.00 (6H, s, 2 x CH_3), 1.99 - 1.90 (6H, m, 3 x CH_2), 1.62 - 1.48 (4H, m, CH_2, 2 x CH) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.5 (0), 173.3 (0), 135.0 (1), 134.5 (1), 118.3 (2), 117.7 (2), 66.6 (1), 66.3 (1), 53.7 (2), 41.1 (2), 25.1 (2), 23.8 (2), 22.7 (3) ppm. Not all peaks are resolved.

LRMS (ES+): ^{m}/z (relative intensity), 411 $[M + Na]^+$ (65 %), 800 $[2M + Na]^+$ (100 %).

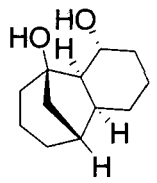
HRMS (ES+): $[M + Na]^+$ $C_{22}H_{32}N_2O_4Na$ requires ^{m}/z 411.2254, found ^{m}/z 411.2252.

***rac* - (1*R*, 2*R*, 3*S*, 7*S*, 8*R*)-Tricyclo[6.3.1.0^{2,7}]dodecane-1,3-diol 234 and *rac* - (1*R*, 2*R*, 3*R*, 7*S*, 8*R*) -tricyclo[6.3.1.0^{2,7}]dodecane-1,3-diol 235**



234

$C_{12}H_{20}O_2$
Mw: 196.29 gmol^{-1}



235

$C_{12}H_{20}O_2$
Mw: 196.29 gmol^{-1}

Following the reported procedure by Kilburn,[122] MeOH (14 mL) was added to a stirring solution of SmI_2 in THF (0.1 M, 58 mL) and the resultant purple mixture cooled to – 78 °C, where upon the reaction turned a dark green. Enamine **285** (220 mg, 1.45 mmol) as a solution in THF (5 mL) was then added drop-wise over a period of 10 minutes and the reaction allowed to stir at – 78 °C for a further 90 minutes. Brine (30 mL), followed by citric acid (378 mg, 1.80 mmol) was then added and allowed to stir for a further 20 minutes. EtOAc (50 mL) was added to the stirring solution and allowed to stir vigorously for 10 minutes, after which the reaction mixture was allowed to settle and the organic phase decanted off. This process was repeated a further three times (3 x 50 mL EtOAc). The aqueous phase was transferred to a separating funnel and further extracted with EtOAc (2 x 50 mL), before the combined organic extracts were washed with brine (2 x 50 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave a yellow oil which was purified by flash column chromatography, eluting with 10 % EtOAc / petrol increasing the polarity to 25 % EtOAc / petrol to give tricycle **234** (44.0 mg, 0.448 mmol, 30 %) as a pale brown solid, R_f = 0.34 (40 % EtOAc / petrol) and tricycle **235** (9.00 mg, 0.0917 mmol, 7 %) as a pale brown solid, R_f = 0.17 (40 % EtOAc / Petrol);

Data for tricycle **234**:

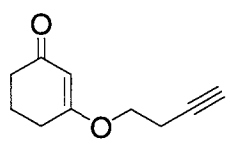
Mpt: 100-102 °C, recrystallised from Et_2O / petrol, (lit 101-103 °C, EtOAc / petrol).[122]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.18 (br s, 1H, C**H**OH), 2.51 (1H, br s, O**H**), 2.21 (1H, br s, O**H**), 1.81 - 1.10 (17H, m, 7 x C**H$_2$**, 3 x C**H**) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 81.7 (0), 67.9 (1), 47.8 (1), 44.0 (2), 41.7 (1), 41.2 (2), 40.4 (1), 31.3 (2), 26.6 (2), 25.1 (2), 20.8 (2), 17.7 (2) ppm.
X-ray: Please see appendix.

Data for tricycle **235**:

Mpt: 108-110 °C, recrystallised from Et_2O / petrol, (lit 110-112 °C, EtOAc / petrol).[122]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.97 (ddd, 1H, *J* = 15.5, 10.3, 5.0 Hz, C**H**OH), 2.31 (2H, br s, 2 x O**H**), 2.00 - 1.15 (17H, m, 7 x C**H$_2$**, 3 x C**H**) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 82.0 (0), 67.5 (1), 52.0 (1), 42.7 (1), 42.3 (2), 42.2 (2), 40.9 (1), 31.0 (2), 28.1 (2), 25.3 (2), 20.5 (2), 19.8 (2) ppm.

Data is consistent with that reported by Kilburn.[122]

3-(But-3-yn-1-yloxy)cyclohex-2-en-1-one 303



303
$C_{10}H_{12}O_2$
Mw: 164.2 gmol^{-1}

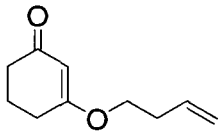
Following the reported procedure by Middleton,[134] 1,3-cyclohexandione **302** (1.00 g, 8.93 mmol) and 3-butyn-1-ol (2.00 mL, 26.8 mmol) were dissolved in toluene (25 mL) and a catalytic quantity of *p*-toluenesulfonic acid monohydrate (25 mg) added in one portion. The reaction was refluxed for 16 h, using a Dean and Stark apparatus to remove the water. The crude reaction mixture was poured onto water (20 mL) and EtOAc (30 mL) was then added. The organic extracts were washed with saturated $NaHCO_3$ aqueous solution (20 mL), brine (20 mL) and dried over magnesium sulfate, before the solvent was removed under a reduced pressure to give a brown oil. The crude material was purified by flash column chromatography, eluting with 20 % EtOAc / petrol gradually increasing the polarity to 40 % EtOAc / petrol, to give alkyne **303** (1.20 g, 7.31 mmol, 82 %) as a pale yellow crystalline solid, R_f = 0.12 (40 % EtOAc / petrol);

Mpt: 60 - 62 °C, recrystallised from EtOAc, (lit. 47-49 °C, Et_2O / petrol).[134]
^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.35 (1H, s, C(O)C**H**=C), 3.90 (2H, t, *J* = 7.0 Hz, O**CH$_2$**), 2.65 (2H, td, *J* = 7.0, 2.9 Hz, OCH$_2$**CH$_2$**), 2.40 (2H, t, *J* = 5.8 Hz, C(O)**CH$_2$**), 2.35 (2H, t, *J* = 5.8 Hz, CHC**CH$_2$**), 2.03 (1H, t, *J* = 2.6 Hz, CH$_2$C**CH**), 1.97 (2H, qn, *J* = 6.2 Hz, CH$_2$**CH$_2$**CH$_2$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.9 (0), 177.58 (0), 103.4 (1), 79.9, 70.6 (1), 66.4 (2), 37.0 (2), 29.1 (2), 21.5 (2), 19.3 (2) ppm.

Data is consistent with that reported by Middleton.[134]

3-(But-3-en-1-yloxy)cyclohex-2-en-1-one 304



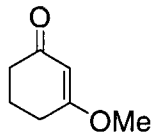
304

$C_{10}H_{14}O_2$
Mw: 166.22 $gmol^{-1}$

Following the reported procedure by Matlin,[135] 1,3-cyclohexandione **302** (3.00 g, 26.7 mmol) and 3-buten-1-ol (6.90 mL, 80.2 mmol) were dissolved in toluene (25 mL), and a catalytic quantity of *p*-toluenesulfonic acid monohydrate (250 mg, 5 mol %) added in one portion. The reaction was refluxed for 5 h, using a Dean and Stark apparatus to remove the water. The crude reaction mixture was poured onto water (20 mL) and the phases separated. The organic layer was washed with saturated $NaHCO_3$ aqueous solution(2 x 25 mL), brine (30 mL) and then finally dried over magnesium sulfate, before the solvent was removed under a reduced pressure to give an orange oil. The crude material was purified by flash column chromatography, eluting with neat DCM gradually increasing the polarity to 3 % MeOH / DCM, to give alkene **304** (3.51 g, 21.1 mmol, 79 %) as a pale yellow oil, R_f = 0.19 (40 % EtOAc / petrol);

IR ν_{max} (film): 2646 (w), 2884 (2884), 1647 (s), 1597 (s), 1434 (w) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.80 (1H, ddt, *J* = 17.0, 10.2, 6.8 Hz, C**H**=CH_2), 5.34 (1H, s, C(O)C**H**=C), 5.16 - 5.10 (2H, m, CH=C**H$_2$**), 3.87 (2H, t, *J* = 6.8 Hz, O**CH$_2$**), 2.46 (2H, qt, *J* = 6.8, 1.3 Hz, OCH_2**CH$_2$**), 2.39 (2H, t, *J* = 6.4 Hz, **CH$_2$**), 2.33 (2H, t, *J* = 6.5 Hz, **CH$_2$**), 1.96 (2H, qn, *J* = 6.4 Hz, CH_2**CH$_2$**CH_2) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.6 (0), 177.7 (0), 133.6 (1), 117.5 (2), 102.8 (1), 67.5 (2), 36.8 (2), 32.8 (2), 29.0 (2), 21.2 (2) ppm.
LRMS (ES+): ^{m}/z (relative intensity), 167 $[M + H]^+$ (50 %), 189 $[M + Na]^+$ (30 %).
HRMS (ES+): $[M + Na]^+$ $C_{10}H_{14}O_2Na$ requires ^{m}/z 189.0886, found ^{m}/z 189.0884.

3-Methoxycyclohex-2-en-1-one 305



305

$C_7H_{10}O_2$

Mw: 126.15 $gmol^{-1}$

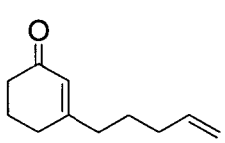
Following the reported procedure by Takahashi,[136] commercially available 1, 3-cyclohexendione **302** (5.00 g, 44.6 mmol) was dissolved in MeOH (50 mL) and to the stirring solution added trimethylorthoformate (4.9 mL, 44.6 mmol) in one portion. *p*-Toluenesulfonic acid monohydrate (25.0 mg) was then added, and the resultant orange solution allowed to stir at RT for 48 h. The mixture was concentrated *in vacuo* and water (25 mL) added, before the product was extracted with DCM (3 x 60 mL). The combined organic extracts were washed with brine (50 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave a yellow oil which was purified by flash column chromatography, eluting with 20 % EtOAc / petrol to give enone **305** (3.20 g, 25.4 mmol, 58 %) as a yellow oil, R_f= 0.3 (50 % EtOAc / petrol);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.34 (1H, s, C(O)C**H**=C), 3.66 (3H, s, O**CH$_3$**), 2.67 (2H, t, *J* = 6.2 Hz, C(O)C**H$_2$**), 2.31 (2H, t, *J* = 6.2 Hz, C(OCH$_3$)C**H$_2$**), 1.95 (2H, m, $CH_2CH_2CH_2$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.6 (0), 178.7 (0), 102.3 (1), 55.6 (3), 36.7 (2), 28.8 (2), 21.2 (2) ppm.

Data is consistent with that reported by Takahashi.[136]

3-Pent-4-en-1-ylcyclohex-2-en-1-one 306



306

$C_{11}H_{16}O$

Mw: 164.24 $gmol^{-1}$

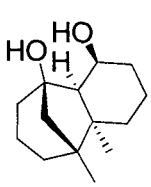
Following the reported procedure by Mattay,[137] to flame dried glassware was added freshly distilled Et_2O (20 mL) and magnesium turnings (1.35 g, 56.0 mmol), followed

by 5-bromo-1-pentene (5.20 mL, 44.0 mmol) as a solution in Et_2O (20 mL) added over a period of 20 minutes at RT. The resultant mixture was allowed to stir for a further 15 minutes at RT after which time a turbid solution had formed. The solution was cooled to 0 °C and to it added 3-methoxycyclohex-2-en-1-one **305** (5.00 g, 40.0 mmol) dropwise, which, after complete addition was refluxed for 2 h. Upon cooling the reaction mixture to RT, the solution was acidified using 1M HCl aqueous solution and allowed to stir for 30 minutes before being diluted with water (100 mL). The product was extracted with Et_2O (2 x 100 mL) and the combined organic extracts washed with brine (50 mL) and dried over magnesium sulfate. Removal of the solvent *in vacuo* gave the crude product as a yellow oil which was purified by flash column chromatography, eluting with 10 % EtOAc / petrol to give the olefin **306** (2.96 g, 18.0 mmol, 46 %) as a yellow oil, $R_f = 0.67$ (40 % EtOAc / petrol);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.87 (1H, br s, C(O)C**H**=C) 5.77 (1H, m, C**H**=CH_2), 5.04 - 4.96 (2H, m, CH=C**H$_2$**), 2.35 (2H, t, *J* = 6.2 Hz, C(O)C**H$_2$**), 2.30 - 2.18 (4H, m, 2 x C**H$_2$**), 2.10 - 1.95 (4H, m, 2 x C**H$_2$**), 1.61 (2H, qn, *J* = 7.3 Hz, CH_2C**H$_2$**CH_2) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.8 (0), 166.1 (0), 137.8 (1), 125.8 (1), 115.3 (2), 37.3 (2 x 2), 33.2 (2), 29.7 (2), 26.1 (2), 22.7 (2) ppm.

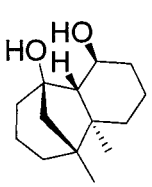
Data is consistent with that reported by Mattay.[137]

***rac* - (1*R*, 2*R*, 3*S*, 7*R*, 8*R*)-7, 8-dimethyltricyclo[6.3.1.0^{2,7}]dodecane-1, 3-diol 310, *rac* - (1*R*, 2*S*, 3*S*, 7*R*, 8*R*)-7, 8-dimethyltricyclo[6.3.1.0^{2,7}]dodecane-1, 3-diol 311, *rac* - (1*S*, 2*R*, 3*R*, 7*R*, 8*S*)-7, 8-dimethyltricyclo[6.3.1.0^{2,7}]dodecane-1, 3-diol 312 and *rac* - (1*R*, 2*R*, 3*R*, 7*R*, 8*R*)-7, 8-dimethyltricyclo[6.3.1.0^{2,7}]dodecane-1, 3-diol 313**



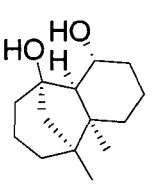
310

$C_{14}H_{24}O_2$
Mw: 224.34 gmol^{-1}



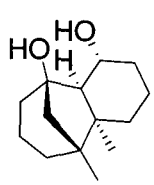
311

$C_{14}H_{24}O_2$
Mw: 224.34 gmol^{-1}



312

$C_{14}H_{24}O_2$
Mw: 224.34 gmol^{-1}



313

$C_{14}H_{24}O_2$
Mw: 224.34 gmol^{-1}

Following the reported procedure by Kilburn,[122] MeOH (19 mL) was added to a stirring solution of SmI_2 in THF (0.1 M, 76 mL) and the resultant purple mixture cooled to – 78 °C, where upon the reaction turned dark green. 3-Methyl-2-cyclohexenone **309** (200 mg, 1.82 mmol) as a solution in THF (5 mL) was then added drop-wise over a

period of 10 minutes and the reaction allowed to stir at – 78 °C for a further 2 h. Brine (30 mL), followed by citric acid (457 mg, 2.17 mmol) was then added and allowed to stir for 10 minutes. EtOAc (80 mL) was added to the stirring solution and allowed to stir vigorously for 5 minutes, after which the reaction mixture was allowed to settle and the organic phase decanted off. This process was then repeated (3 x 80 mL EtOAc). The aqueous phase was transferred to a separating funnel and further extracted with EtOAc (2 x 80 mL), before the combined organic extracts were washed with brine (2 x 30 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave the crude product as a yellow oil which upon purification by flash column chromatography, eluting with 5 % EtOAc / petrol gradually increasing the polarity to 25 % EtOAc / petrol, gave diol **310** (71.0 mg, 0.633 mmol, 35 %) as a white solid, $R_f = 0.33$ (40 % EtOAc / petrol), diol mixture **311** and **312** (36.0 mg, 0.321 mmol, 18 %) as a pale yellow oil, $R_f = 0.25$ (40 % EtOAc / petrol) and diol **313** (61.0 mg, 0.544 mmol, 30 %) as a pale yellow solid, $R_f = 0.17$ (40 % EtOAc / petrol);

Data for **310**:

Mpt: 148 - 150 °C, recrystallised from EtOAc.

IR ν_{max} (film): 3240 (br), 2975 (w), 2928 (s), 2893 (s), 1461 (s), 1429 (s), 1334 (s) cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.14 (1H, br s, **CH**OH), 3.33 (1H, br s, O**H**), 2.93 (1H, br s, O**H**), 2.19 (1H, dt, *J* = 10.7, 2.5 Hz, CH_AH_B), 1.79 - 1.47 (11H, m, 2 x CH_2, 3 x CH_AH_B, $CH_A\mathbf{H_B}$, **CH**), 1.16 - 1.08 (3H, m, 3 x $CH_A\mathbf{H_B}$), 0.92 (3H, s, CH_3), 0.77 (3H, s, CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 80.5 (0), 69.1 (1), 54.8 (1), 51.7 (2), 43.9 (2 x 0), 41.0 (2), 36.5 (2), 28.6 (2), 25.7 (2), 21.0 (3), 20.9 (2), 19.4 (3), 15.8 (2) ppm.

LRMS (ES+): $^m/z$ (relative intensity), 247 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{14}H_{24}O_2Na$ requires $^m/z$ 247.1669, found 247.1667.

Microanalysis: $C_{14}H_{24}O_2$ requires C, 74.95; H, 10.78. Found C, 75.12; H, 10.81 %.

X-ray: Please see appendix.

Data for **311** and **312** - isolated as an inseparable 1.7:1 mixture of diastereoisomers. Major and minor peaks reported in ^{1}H and ^{13}C NMR where possible:

IR ν_{max} (film): 3493 (br), 3308 (br), 2956 (m), 2926 (s), 2858 (m), 1448 (m), 1342 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.17 (1H, ddd, *J* = 11.7, 9.3, 5.0 Hz, **CH**OH major), 3.90 (1H, ddd, *J* = 12.8, 9.5, 3.1 Hz, **CH**OH minor), 3.12 (1H, br s, **OH** minor), 2.78 (1H, br s, **OH** major), 2.59 (1H, br s, **OH** major), 2.50 (1H, br s, **OH** minor), 2.24 (1H, m, CH_AH_B major), 2.11 (1H, d, *J* = 9.3 Hz, **CH** major), 2.01 (1H, dt, *J* = 10.7, 2.4 Hz, CH_AH_B minor), 1.84 - 1.09 (27H, m, 6 x CH_2, CH_ACH_B major and 6 x CH_2, CH_AH_B, **CH** minor), 1.04 (3H, s, CH_3 major), 0.96 (3H, s, CH_3 minor), 0.86 (3H, s, CH_3 major), 0.72 (3H, s, CH_3 minor) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 80.5 (0, major), 79.6 (0, minor), 71.8 (1, major), 68.8 (1, minor), 59.9 (1, minor), 57.7 (1, major), 52.4 (2, major), 49.9 (2, minor), 45.6 (0, minor), 44.5 (0, minor), 44.4 (0, major), 42.1 (0, major), 41.6 (2, minor), 37.9 (2, major), 36.5 (2, minor), 35.2 (2, major), 31.9 (2, major), 30.7 (3, major), 28.6 (2, major), 27.5 (2, minor), 26.7 (2, minor), 23.4 (3, major), 21.2 (3, minor), 21.0 (2, major), 20.4 (2, minor), 20.0 (2, major), 19.3 (3, minor), 17.4 (2, minor) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 247 $[M + Na]^+$ (100%).

HRMS (ES+): $[M + Na]^+$ $C_{14}H_{24}O_2Na$ requires ^{m}/z 247.1669, found 247.1667.

Data for **313**:

Mpt: 151 - 153 °C, recrystallised from EtOAc.

IR ν_{max} (film): 3489 (br), 3312 (br), 2931 (s), 2859 (s), 1459 (m), 1326 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.07 (1H, td, *J* = 11.5, 4.3 Hz, **CH**OH), 2.21 (1H, br s, **OH**), 2.00 - 1.93 (2H, m, 2 x CH_AH_B), 1.85 (1H, m, CH_AH_B), 1.75 - 1.67 (4H, m, CH_2, CH_AH_B, CH_AH_B), 1.57 - 1.50 (2H, m, 2 x CH_AH_B), 1.43 (1H, d, *J* = 10.7 Hz, **CH**), 1.30 (1H, m, CH_AH_B), 1.21 - 1.10 (3H, 3 x CH_AH_B), 1.05 (3H, s, CH_3), 1.00 (1H, m, CH_AH_B), 0.84 (3H, s, CH_3) ppm.

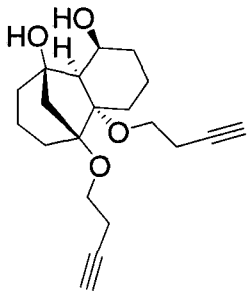
^{13}C NMR (100 MHz, $CDCl_3$): δ = 79.3 (0), 68.5 (1), 64.1 (1), 50.6 (2), 45.0 (0), 43.7 (0), 36.2 (2), 35.1 (2), 29.5 (3), 29.3 (2), 23.7 (2), 22.9 (3), 20.2 (2), 17.7 (2) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 247 $[M + Na]^+$ (70 %), 471 $[2M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{14}H_{24}O_2Na$ requires ^{m}/z 247.1669, found 247.1666.

Microanalysis: $C_{14}H_{24}O_2$ requires C, 74.95; H, 10.78. Found C, 74.62; H, 10.82 %.

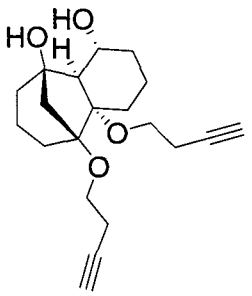
***rac* - (1*R*, 2*R*, 3*S*, 7*S*, 8*S*)-7,8-bis(but-3-yn-1-yloxy)tricyclo[6.3.1.0^{2,7}]dodecane-1, 3-diol 314 and *rac* - (1*R*, 2*R*, 3*R*, 7*S*, 8*S*)-7, 8-bis(but-3-yn-1-yloxy) tricyclo[6.3.1.0^{2,7}]dodecane-1,3-diol 315**



314

$C_{20}H_{28}O_4$

Mw: 332.43 gmol^{-1}



315

$C_{20}H_{28}O_4$

Mw: 332.43 gmol^{-1}

Following the reported procedure by Kilburn,[122] MeOH (6 mL) was added to a stirring solution of SmI_2 in THF (0.1 M, 24 mL) and the resultant purple mixture cooled to – 78 °C, where upon the solution turned dark green. Alkyne **303** (100 mg, 0.610 mmol) as a solution in THF (5 mL) was then added dropwise over a period of 20 minutes and the reaction allowed to stir at – 78 °C for a further 2 h. Brine (5 mL), followed by citric acid (153 mg, 0.729 mmol) was then added and allowed to stir for 20 minutes. Water (20 mL) was added and the products extracted with EtOAc (3 x 50 mL), before the combined organic extracts were washed with brine (40 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave a pale yellow oil which was purified by flash column chromatography, eluting with 5 % EtOAc / petrol increasing the polarity to neat EtOAc to give **314** (35.0 mg, 0.211 mmol, 35 %) as a pale yellow oil, R_f = 0.39 (60 % EtOAc / petrol) and **315** (19.0 mg, 0.114 mmol, 19 %) as a white solid, R_f = 0.31 (60 % EtOAc / petrol);

Data for tricycle **314**:

IR ν_{max} (film): 3294 (br), 2929 (m), 2876 (m), 1707 (m), 1084 (s) cm^{-1}.

^{1}H NMR (300MHz, $CDCl_3$): δ = 4.21 (1H, br s, C**H**OH), 3.72 (1H, q, *J* = 7.3 Hz, OCH_AH_B), 3.57 (1H, *J* = 7.0 Hz, $OCH_A\mathbf{H_B}$), 3.56 (1H, q, *J* = 7.0 Hz, OCH_AH_B), 3.40 (1H, q, *J* = 7.0 Hz, $OCH_A\mathbf{H_B}$), 2.80 (2H, br s, CHO**H**), 2.55 - 2.30 (4H, m, 2 x OCH_2CH_2), 2.25 - 1.40 (17H, m, 7 x CH_2, 3 x C**H**) ppm.

^{13}C NMR (75MHz, $CDCl_3$): δ = 86.0 (0), 85.1 (0), 82.4 (0), 82.2 (0), 77.4 (0), 69.8 (1), 69.4 (1), 67.3 (1), 62.8 (2), 62.6 (2), 55.8 (1), 48.7 (2), 40.4 (2), 34.4 (2), 25.6 (2), 21.1 (2), 20.7 (2), 20.6 (2), 18.8 (2), 13.9 (2) ppm.

LRMS (ES+): $^{m}/z$ (relative intensity), 355 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{20}H_{28}O_4Na$ requires $^{m}/z$ 355.1880, found $^{m}/z$ 355.1877.

Data for tricycle **315**:

Mpt: 119-121 °C, recrystallised from DCM / petrol.

IR ν_{max} (solid): 3286 (br), 2941 (m), 2870 (m), 2116 (w), 1079 (s), 1056 (s) cm^{-1}.

^{1}H NMR (300MHz, $CDCl_3$): δ = 3.95 (1H, ddd, *J* = 12.3, 9.9, 4.2 Hz, **CH**OH), 3.70 (1H, q, *J* = 7.3 Hz, OCH_AH_B), 3.61 - 3.48 (2H, m, $OCH_A\mathbf{H_B}$, OCH_AH_B) 3.37 (1H, q, *J* = 7.0 Hz, $OCH_A\mathbf{H_B}$), 2.45 (2H, br s, 2 x **OH**), 2.43 - 2.34 (4H, m, 2 x OCH_2CH_2), 2.20 - 1.20 (17H, m, 7 x CH_2, 3 x **CH**) ppm.

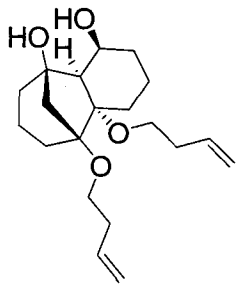
^{13}C NMR (75 MHz, $CDCl_3$): δ = 87.8 (0), 85.4 (0), 82.2 (0), 82.1 (0), 76.8 (0), 69.3 (1), 69.2 (1), 67.9 (1), 62.5 (2), 62.4 (2), 60.3 (1), 46.7 (2), 41.9 (2), 30.8 (2), 27.3 (2), 21.1 (2), 20.7 (2), 20.6 (2), 18.5 (2), 16.0 (2) ppm.

LRMS (ES+): $^{m}/z$ (relative intensity), 355 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{20}H_{28}O_4Na$ requires $^{m}/z$ 355.1880, found $^{m}/z$ 355.1877.

X-ray: Please see appendix.

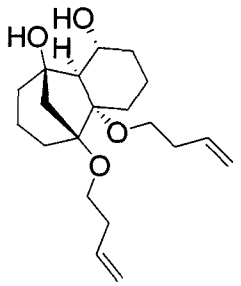
***rac* - (1*R*, 2*R*, 3*S*, 7*S*, 8*S*)-7, 8-Bis(but-3-en-1-yloxy)tricyclo[6.3.1.0^{2,7}]dodecane-1,3-diol 316 and *rac* - (1*R*, 2*R*, 3*R*, 7*S*, 8*S*)-7, 8-bis(but-3-en-1-yloxy)tricycle [6.3.1.0^{2,7}]dodecane-1,3-diol 317**



316

$C_{20}H_{32}O_4$

Mw: 336.47 $gmol^{-1}$



317

$C_{20}H_{32}O_4$

Mw: 336.47 $gmol^{-1}$

Following the reported procedure by Kilburn,[122] MeOH (15 mL) was added to a stirring solution of SmI_2 in THF (0.1 M, 60 mL) and the resultant purple mixture cooled to – 78 °C, where upon the reaction turned dark green. Olefin **304** (250 mg, 1.50 mmol) as a solution in THF (5 mL) was then added drop-wise over a period of 10 minutes and the reaction allowed to stir at – 78 °C for a further 1 h. Brine (30 mL), followed by citric acid (380 mg, 1.81 mmol) was then added and allowed to stir for 10 minutes. EtOAc

(70 mL) was then added to the stirring solution and allowed to stir vigorously for 10 minutes, after which the reaction mixture was allowed to settle and the organic phase decanted off. This process was repeated a further five times (5 x 70 mL EtOAc). The remaining aqueous residue was transferred to a separating funnel and re-extracted with a further quantity of EtOAc (80 mL), before the combined organic extracts were washed with brine (2 x 50 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave a yellow oil which was purified by flash column chromatography, eluting with 10 % EtOAc / petrol increasing the polarity to 50 % EtOAc / petrol to give tricycle **316** (84.0 mg, 0.499 mmol, 33 %) as a yellow oil, $R_f = 0.29$ (40 % EtOAc / petrol) and tricycle **317** (13.0 mg, 0.0773 mmol, 5 %) as a yellow oil, $R_f = 0.23$ (40 % EtOAc / petrol);

Data for tricycle **316**:

IR ν_{max} (film): 3326 (br), 2936 (m), 2875 (m), 1650 (m) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.83 (1H, ddt, *J* = 17.1, 8.5, 6.8 Hz, $CH_2CH{=}CH_2$), 5.81 (1H, ddt, *J* = 17.1, 8.8, 6.8 Hz, $CH_2CH{=}CH_2$), 5.07 - 4.96 (4H, m, 2 x $CH{=}CH_2$), 4.22 (1H, td, *J* = 4.8, 1.8 Hz, CHOH), 3.58 (1H, m, OCH_AH_B), 3.51 - 3.44 (2H, m, OCH_2), 3.27 (1H, m, OCH_AH_B), 2.50 (1H, br s, OH), 2.25 - 2.15 (5H, m, 2 x CH_2 + CH), 2.11 - 1.98 (3H, m, CH_2, CH_AH_B), 1.76 - 1.45 (11H, m, 5 x CH_2, CH_AH_B) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.4 (1), 136.4 (1), 116.1 (2), 116.1 (2), 85.6 (0), 84.7 (0), 79.2 (0), 67.4 (1), 63.8 (2), 63.4 (2), 56.0 (1), 48.8 (2), 40.5 (2), 35.5 (2), 35.2 (2), 31.0 (2), 25.6 (2), 20.6 (2), 18.7 (2), 14.0 (2) ppm.
LRMS (ES+): $^m/z$ (relative intensity), 359 $[M + Na]^+$ (100 %).
HRMS (ES+): $[M + Na]^+$ $C_{20}H_{32}O_4Na$ requires $^m/z$ 359.2193, found $^m/z$ 359.2189.

Data for tricycle **317**:

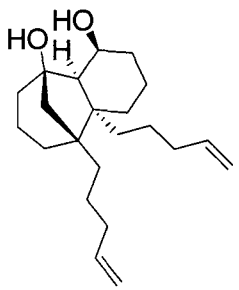
IR ν_{max} (film): 3328 (br), 2930 (m), 2869 (m), 1660 (m) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.83 (1H, ddt, *J* = 17.0, 10.3, 6.8 Hz, $CH_2CH{=}CH_2$), 5.79 (1H, ddt, *J* = 17.0, 10.3, 6.8 Hz, $CH_2CH{=}CH_2$), 5.08 - 4.97 (4H, m, 2 x $CH{=}CH_2$), 3.93 (1H, ddd, *J* = 14.0, 9.8, 4.2 Hz, CHOH), 3.54 (1H, dt, *J* = 8.8, 6.8 Hz, OCH_AH_B), 3.50 (1H, dt, *J* = 8.5, 6.5 Hz OCH_AH_B), 3.45 (1H, dt, *J* = 8.8, 6.8 Hz, OCH_AH_B), 3.26 (1H, dt, *J* = 8.5, 6.5 Hz, OCH_AH_B), 2.65 (1H, br s, OH), 2.27 - 2.19 (4H, m, 2 x CH_2), 2.12 - 2.01 (3H, m, CH_2, CH), 1.85 - 1.46 (12H, m, 6 x CH_2) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.3 (1), 136.3 (1), 116.3 (2), 116.2 (2), 87.5 (0), 85.1 (0), 76.8 (0), 67.0 (1), 63.4 (2), 63.4 (2), 60.5 (1), 46.8 (2), 42.0 (2), 35.4 (2), 35.2 (2), 30.7 (2), 27.4 (2), 20.7 (2), 18.4 (2), 16.1 (2) ppm.

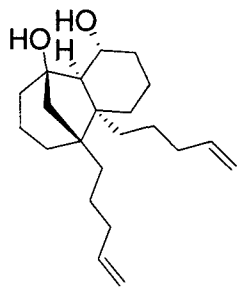
LRMS (ES+): ^{m}/z (relative intensity), 359 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{20}H_{32}O_4Na$ requires ^{m}/z 359.2193, found ^{m}/z 359.2190.

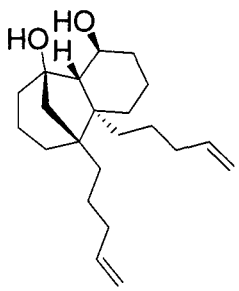
***rac* - (1*R*, 2*R*, 3*S*, 7*R*, 8*R*)-7,8-Bis(pent-4-en-1-yl)tricyclo[6.3.1.0^{2,7}]dodecane-1,3-diol 318, *rac* - (1*R*, 2*R*, 3*R*, 7*R*, 8*R*)-7,8-bis(pent-4-en-1-yl)tricyclo[6.3.1.0^{2,7}] dodecane-1,3-diol 319 and *rac* - (1*R*, 2*R*, 3*R*)-7,8-bis(pent-4-en-1-yl)tricycle [6.3.1.0^{2,7}]dodecane-1,3-diol 320**



318
$C_{22}H_{36}O_2$
Mw: 332.52 gmol^{-1}



319
$C_{22}H_{36}O_2$
Mw: 332.52 gmol^{-1}



320
$C_{22}H_{36}O_2$
Mw: 332.52 gmol^{-1}

Following the reported procedure by Kilburn,[122] MeOH (15 mL) was added to a stirring solution of SmI_2 in THF (0.1 M, 61 mL) and the resultant purple mixture cooled to – 78 °C, where upon the reaction turned dark green. Olefin **306** (250 mg, 1.52 mmol) as a solution in THF (10 mL) was then added drop-wise over a period of 20 minutes and the reaction allowed to stir at – 78 °C for a further 2 h. Brine (20 mL), followed by citric acid (380 mg, 1.81 mmol) was then added and allowed to stir for a further 60 minutes. Brine (20 mL) was then added and the products extracted with EtOAc (5 x 50 mL), before the combined organic extracts were washed with brine once again (40 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave a yellow oil which was purified by flash column chromatography, eluting with 10 % EtOAc / petrol increasing the polarity to 30 % EtOAc / petrol to give tricycle **318** (43.0 mg, 0.259 mmol, 17 %) as a yellow oil, R_f = 0.39 (50 % EtOAc / petrol), tricycle **319** (81.0 mg, 0.487 mmol, 33 %) as a white crystalline solid, R_f = 0.33 (50 % EtOAc / petrol) and tricycle **320** (54.0 mg, 0.325 mmol, 23 %) as a yellow oil, R_f = 0.21 (50 % EtOAc / petrol);

Data for tricycle **318**:

IR ν_{max} (film): 3336 (br), 2930 (s), 2896 (s), 2859 (s), 1640 (m), 1468 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.85 - 5.73 (2H, m, 2 x CH_2**C**H=CH_2), 5.01 - 4.91 (4H, m, 2 x CH=**C**H_2), 4.21 (1H, br s, **C**HOH), 3.10 (2H, br s, 2 x O**H**), 2.10 - 1.94 (4H, m, 2 x **C**H_2), 1.85 - 1.30 (19H, m, 9 x **C**H_2 and **C**H), 1.29 - 1.18 (4H, m, 2 x **C**H_2) ppm.

^{13}C NMR (100 MHz, DMSO-d_6, 80 °C): δ = 139.3 (1), 139.2 (1), 115.0 (2), 114.8 (2), 78.9 (0), 68.7 (1), 55.5 (1), 50.1 (0), 48.4 (2), 47.3 (0), 41.2 (2), 35.4 (2), 35.0 (2), 34.9 (2), 34.7 (2), 31.8 (2), 26.6 (2), 25.7 (2), 25.3 (2), 24.9 (2), 20.9 (2), 17.5 (2) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 355 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{22}H_{36}O_2Na$ requires ^{m}/z 355.2607, found ^{m}/z 355.2610.

Data for tricycle **319**:

Mpt: 114-115 °C, recrystallised from DCM / petrol.

IR ν_{max} (solid): 3332 (br), 2930 (s), 1639 (w), 1468 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.78 (1H, ddt, *J* = 17.0, 10.3, 6.8 Hz, CH_2**C**H=CH_2), 5.77 (1H, ddt, 17.0, 10.3, 6.5 Hz, CH_2**C**H=CH_2), 5.08 - 4.97 (4H, m, 2 x CH=**C**H_2), 3.94 (1H, td, *J* = 13.0, 4.0 Hz, **C**HOH), 2.63 (2H, s, 2 x O**H**), 2.10 - 1.65 (8H, m, 4 x **C**H_2), 1.60 - 1.15 (19H, m, 9 x **C**H_2 and **C**H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.3 (1), 139.1 (1), 115.1 (2), 114.7 (2), 79.3 (0), 68.4 (1), 61.0 (1), 50.0 (0), 48.1 (2), 47.9 (0), 41.7 (2), 36.2 (2), 35.3 (2), 35.1 (2), 34.8 (2), 31.3 (2), 26.4 (2), 25.7 (2), 25.4 (2), 22.6 (2), 20.8 (2), 17.1 (2) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 355 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{22}H_{36}O_2Na$ requires ^{m}/z 355.2607, found ^{m}/z 355.2612.

X-ray: Please see appendix.

Data for tricycle **320**:

IR ν_{max} (film): 3333 (br), 2931 (s), 2872 (s), 1640 (w), 1468 (m) cm^{-1}.

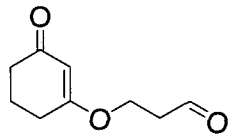
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.83 - 4.92 (2H, m, 2 x CH_2**C**H=CH_2), 5.03 - 4.92 (4H, m, 2 x CH=**C**H_2), 4.09 (1H, td, *J* = 12.0, 4.5 Hz, **C**HOH), 2.15 (2H, br s, 2 x O**H**), 2.10 - 1.95 (6H, m, 3 x **C**H_2), 1.88 - 1.15 (21H, m, 10 x **C**H_2 and **C**H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.2 (1), 139.0 (1), 115.1 (2), 114.8 (2), 79.0 (0), 68.4 (1), 63.1 (1), 49.5 (2), 49.3 (0), 47.5 (0), 42.1 (2), 36.8 (2), 35.2 (2 x 2), 35.1 (2), 32.4 (2), 29.6 (2), 26.0 (2), 25.3 (2), 22.7 (2), 20.0 (2), 18.5 (2) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 355 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{22}H_{36}O_2Na$ requires $^m/z$ 355.2607, found $^m/z$ 355.2614.

3-[(3-Oxocyclohex-1-en-1-yl)oxy]propanal 321



321

$C_9H_{12}O_3$

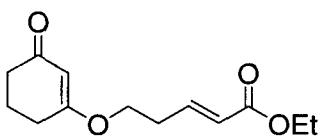
Mw: 168.19 $gmol^{-1}$

Following the reported procedure by Yang,[138] to a stirring solution of alkene **304** (1.69 g, 10.1 mmol) and $RuCl_3$ (74.0 mg, 0.0350 mmol, 3.5 mol %) in CH_3CN / H_2O (10 mL, 6:1), was added $NaIO_4$ (4.32 g, 20.2 mmol) over a period of 5 minutes. An exotherm was observed, and the black solution was stirred at RT for 4 h. Saturated $Na_2S_2O_3$ aqueous solution (100 mL) was added to the reaction mixture and the solution then transferred to a separating funnel and the product extracted with EtOAc (3 x 80 mL). The combined organic extracts were washed with brine (80 mL) and dried over magnesium sulfate before removal of the solvent *in vacuo* gave a brown oil (1.00 g). Approximately 35 % of this material was the aldehyde from analysis with ^1H NMR. Aldehyde **321** (350 mg, 2.08 mmol, 21 %);

^1H NMR (300 MHz, $CDCl_3$): δ = 9.79 (1H, t, *J* = 1.3 Hz, C**H**O), 5.37 (1H, s, C(O)C**H**=C), 4.16 (2H, t, *J* = 6.1 Hz, OC**H**$_2$), 2.87 (2H, td, *J* = 5.9, 1.3 Hz, OCH_2CH_2CHO), 2.39 - 2.31 (4H, m, 2 x C**H**$_2$), 2.00 - 1.92 (2H, m, C**H**$_2$) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.2 (0), 199.1 (1), 177.8 (0), 103.4 (1), 62.1 (2), 42.7 (2), 37.0 (2), 29.1 (2), 21.4 (2) ppm.

Unstable aldehyde **321** was taken as crude into the next reaction.

Ethyl (2*E*)-5-[(3-oxocyclohex-1-en-1-yl)oxy]pent-2-enoate 323



323

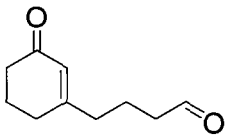
$C_{13}H_{18}O_4$

Mw: 238.28 $gmol^{-1}$

To a stirring solution of aldehyde **321** (818 mg, 4.86 mmol) in toluene (50 mL), was added (carbethoxymethylene) triphenylphosphorane **322** (2.03 g, 5.84 mmol) in one portion. The brown solution was brought heated at 60 °C overnight. The solvent was removed *in vacuo* to give a brown oil / solid. Purification by flash column chromatography eluting with 10 % EtOAc / petrol gradually increasing the polarity to 25 % EtOAc / petrol gave olefin **323** (584 mg, 2.45 mmol, 50 %) as a yellow oil, $R_f = 0.3$ (50 % EtOAc / petrol);

IR ν_{max} (film): 3412 (w), 2896 (w), 2860 (w), 1716 (s), 1659 (w), 1598 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.91 (1H, dt, *J* = 15.7, 7.0 Hz, CH_2CH=CH), 5.90 (1H, dt, *J* = 15.7, 1.4 Hz, C(O)C**H**=CH chain), 5.32 (1H, s, C(O)C**H**=C ring system), 4.18 (2H, q, *J* = 7.1 Hz, O**CH$_2$** ester), 3.92 (2H, t, *J* = 6.4 Hz, O**CH$_2$**), 2.62 (2H, qd, *J* = 6.2, 1.5 Hz, OCH_2**CH$_2$**), 2.39 (2H, t, *J* = 6.4 Hz, **CH$_2$**), 2.33 (2H, t, *J* = 6.1 Hz, **CH$_2$**), 1.96 (2H, qn, *J* = 6.4 Hz, **CH$_2$**), 1.28 (3H, t, *J* = 7.1 Hz, OCH_2**CH$_3$**) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.6 (0), 177.4 (0), 166.1 (0), 143.5 (1), 123.9 (1), 103.0 (1), 66.24 (2), 60.4 (2), 36.7 (2), 31.2 (2), 28.9 (2), 21.2 (2), 14.2 (3) ppm.
LRMS (ES+): ^{m}/z (relative intensity), 261 $[M + Na]^+$ (100 %).
HRMS (ES+): $[M + Na]^+$ $C_{13}H_{18}O_4Na$ requires ^{m}/z 261.1097, found ^{m}/z 261.1097.

4-(3-Oxocyclohex-1-en-1-yl)butanal 324



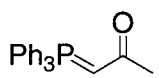
324
$C_{10}H_{14}O_2$
Mw: 166.12 $gmol^{-1}$

Following the reported procedure by Yang,[138] to a stirring solution of alkene **306** (1.00 g, 6.09 mmol) and $RuCl_3$ (48.0 mg, 0.231 mmol, 3.5 mol %) in CH_3CN / H_2O (30 mL, 6:1), was added $NaIO_4$ (2.9 g, 13.4 mmol) over a period of 5 minutes. An exotherm was observed, and the black solution was stirred at RT for 4 h. Saturated $Na_2S_2O_3$ aqueous solution (10 mL) was added to the reaction mixture and then transferred to a separating funnel, before the product was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (30 mL) and dried over magnesium sulfate before removal of the solvent *in vacuo* gave a yellow oil. Purification by flash column chromatography eluting with 10 % EtOAc / petrol

increasing the polarity to 40 % EtOAc / petrol gave the aldehyde **324** (606 mg, 3.65 mmol, 54 %) as a colourless oil, $R_f = 0.1$ (50 % EtOAc / petrol);

IR ν_{max} (film): 2942 (m), 2872 (w), 2823 (w), 1718 (s), 1660 (s), 1622 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.77 (1H, t, *J* = 1.3 Hz, **CHO**), 5.86 (1H, t, *J* = 1.3 Hz, C(O)C**H**=C), 2.49 (2H, td, *J* = 7.1, 1.3 Hz, **CH$_2$**CHO), 2.35 (2H, t, *J* = 6.4 Hz, C(O)C**H$_2$**), 2.30 - 2.21 (4H, m, 2 x **CH$_2$**), 2.03 - 1.94 (2H, m, **CH$_2$**), 1.84 (2H, qn, *J* = 7.1 Hz, $CH_2CH_2CH_2$) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.6 (1), 199.9 (0), 165.2 (0), 126.4 (1), 43.4 (2), 37.6 (2), 37.4 (2), 29.9 (2), 22.8 (2), 19.5 (2) ppm.
LRMS (ES+): ^{m}/z (relative intensity), 167 $[M + H]^+$ (38 %), 189 $[M + Na]^+$ (100 %).
HRMS (ES+): $[M + H]^+$ $C_{10}H_{15}O_2$ requires ^{m}/z 167.10637, found ^{m}/z 167.10720.

1-(Triphenylphosphoranylidene)acetone 325



325
$C_{21}H_{19}OP$
Mw: 318.35 $gmol^{-1}$

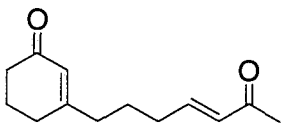
Following the reported procedures by Ramirez[140] and Font,[139] triphenylphosphine (44.7 g, 0.140 mol) and chloroacetone (11.2 mL, 0.140 mol) were dissolved in $CHCl_3$ (120 mL) and the mixture refluxed. After 4 h the reaction was allowed to cool, and the yellow solution poured into Et_2O (700 mL) where upon a white solid instantly precipitated. The solid was collected by filtration, and a further quantity of Et_2O (1 L) was needed to trituate the gum that had been left at the bottom of the beaker. The Wittig salt (50.0 g, 0.125 mol) was subsequently dissolved in H_2O (1.6 L) and treated with 1M NaOH aqueous solution (~ 150 mL) until the pH reached 7 - 8. At this point the solution was left stirring for 30 minutes, and the white solid formed collected by filtration and washed with H_2O (1 L) until the pH of the filtrate was neutral. The wet solid was dried over P_2O_5 under vacuum for 36 h to give the phosphorane **325** (37.0 g, 0.120 mol, 83 %) as a white powder;

Mpt: 200 - 201 °C, recrystallised from EtOAc, (lit: 206 - 208 °C).[139]
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68 - 7.42 (15H, m, 15 x Ph**H**), 3.77 (1H, br d, *J* = 20.7 Hz, P=C**H**C(O)), 2.09 (3H, s, **CH$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.2 (0), 133.4 (5 x 1, d, J_{CP} = 9.9 Hz), 132.3 (1), 129.2 (5 x 1, d, J_{CP} = 12.1 Hz), 128.0 (3 x 0, d, J_{CP} = 90.6 Hz) 52.7 (5 x 1, d, J_{CP} = 108.5 Hz), 28.8 (3, d, J_{CP} = 15.4 Hz) ppm.

Data is consistent with that reported by Font[139] and Kuroda.[178]

3-[(4*E*)-6-Oxohept-4-en-1-yl]cyclohex-2-en-1-one 326



326

$C_{13}H_{18}O_2$

Mw: 206.28 $gmol^{-1}$

1-(Triphenylphosphoranylidene) acetone **325** (1.87 g, 5.87 mmol) was added to a stirring solution of aldehyde **324** (650 mg, 3.91 mmol) in toluene (40 mL) and the resultant yellow solution reluxed for 16 h. The solvent was removed *in vacuo* to leave the crude material as a white solid. Purification by flash column chromatography eluting with 10 % EtOAc / petrol, gradually increasing the polarity to 50 % EtOAc / petrol gave unsaturated ketone **326** (490 mg, 2.38 mmol, 61 %) as a yellow oil, R_f = 0.24 (50 % EtOAc / petrol);

IR ν_{max} (film): 2931 (m), 2868 (w), 1696 (s), 1664 (s), 1624 (s) cm^{-1}.

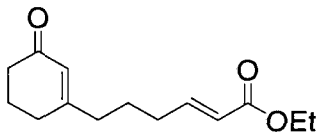
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.76 (1H, dt, *J* = 15.8, 6.8 Hz, C(O)CH=C**H**), 6.08 (1H, dt, *J* = 16.1, 1.5 Hz, C(O)C**H**=CH), 5.86 (1H, s, C(O)C**H**=C), 2.35 (2H, t, *J* = 6.2 Hz, C(O)C**H$_2$**), 2.27 - 2.22 (9H, m, C**H$_3$**, 3 x C**H$_2$**), 1.98 (2H, qn, *J* = 6.3 Hz, $CH_2CH_2CH_2$ ring), 1.69 (2H, qn, *J* = 7.8 Hz, $CH_2CH_2CH_2$ chain) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.9 (0), 198.6 (0), 165.4 (0), 147.0 (1), 132.1 (1), 126.3 (1), 37.6 (2), 37.6 (2), 32.1 (2), 30.0 (2), 27.4 (3), 25.6 (2), 23.0 (2) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 207 $[M + H]^+$ (85 %), 229 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{13}H_{18}O_2Na$ requires ^{m}/z 229.1199, found ^{m}/z 229.1197.

Ethyl (2*E*)-6-(3-oxocyclohex-1-en-1-yl)hex-2-enoate 327



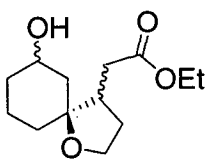
327

$C_{14}H_{20}O_3$
Mw: 236.31 $gmol^{-1}$

To a stirring solution of aldehyde **324** (600 mg, 3.61 mmol) in toluene (30 mL), was added (carbethoxymethylene) triphenylphosphorane **322** (1.91 g, 5.48 mmol) in one portion. The brown solution was refluxed and allowed to stir for 3 h. The solvent was removed *in vacuo* to give a yellow oil / solid. Purification by flash column chromatography eluting with 10% EtOAc / petrol gradually increasing the polarity to 25 % EtOAc / petrol gave alkene **327** (606 mg, 2.56 mmol, 71 %) as a colourless oil, R_f = 0.57 (50 % EtOAc / petrol);

IR ν_{max} (film): 2979 (w), 2935 (m), 1714 (s), 1665 (s), 1625 (m) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (1H, dt, *J* = 15.8, 6.8 Hz, EtOC(O)CH=C**H**), 5.85 (1H, t, *J* = 1.2 Hz, C(O)C**H**=C), 5.80 (1H, dt, *J* = 15.8, 1.5 Hz, EtOC(O)C**H**=CH), 4.16 (2H, q, *J* = 7.0 Hz, OC**H$_2$**CH$_3$), 2.34 (2H, t, *J* = 6.5 Hz, C(O)C**H$_2$**), 2.28 - 2.19 (6H, m, 3 x C**H$_2$**), 1.97 (2H, qn, *J* = 6.2 Hz, CH$_2$C**H$_2$**CH$_2$ cyclohexyl ring), 1.66 (2H, qn, *J* = 7.5 Hz, CH$_2$C**H$_2$**CH$_2$ alkyl chain), 1.27 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H$_3$**) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.9 (0), 166.8 (0), 165.5 (0), 148.1 (1), 126.3 (1), 122.5 (1), 60.6 (2), 37.6 (2), 37.5 (2), 31.8 (2), 30.0 (2), 25.5 (2), 23.0 (2), 14.6 (3) ppm.
LRMS (ES+): ^{m}/z (relative intensity), 237 $[M + H]^+$ (65 %), 259 $[M + Na]^+$ (100 %).
HRMS (ES+): $[M + Na]^+$ $C_{14}H_{20}O_3Na$ requires ^{m}/z 259.1305, found ^{m}/z 259.1303.

Ethyl (7-hydroxy-1-oxaspiro[4.5]dec-4-yl)acetates 330a and 330b



330a
330b

$C_{13}H_{22}O_4$
Mw: 242.31 $gmol^{-1}$

Following the reported procedure by Kilburn,[122] MeOH (12 mL) was added to a stirring solution of SmI_2 in THF (0.1 M, 47 mL) and the resultant purple mixture cooled to

– 78 °C, where upon the colour changed to a dark green. Olefin **323** (282 mg, 1.18 mmol) as a solution in THF (5 mL) was then added dropwise over a period of 15 minutes and the reaction allowed to stir at – 78 °C for a further 90 minutes. Brine (30 mL), followed by citric acid (302 mg, 1.44 mmol) was then added and allowed to stir for 20 minutes. Brine (30 mL) was added and the products extracted with EtOAc (4 x 60 mL), before the combined organic extracts were washed with brine (2 x 30 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave a yellow oil which was purified by flash column chromatography, eluting with 10 % EtOAc / petrol gradually increasing the polarity to 35 % EtOAc / petrol to give bicycle **330a** (66.0 mg, 0.272 mmol, 23 %) as a yellow oil, R_f = 0.27 (40 % EtOAc / petrol) and bicycle **330b** (139 mg, 0.574 mmol, 48 %) as a yellow oil, R_f = 0.14 (40 % EtOAc / petrol);

Data for bicycle **330a**:

IR ν_{max} (film): 3501 (br), 2935 (m), 1731 (s), 1446 (m), 1413 (m) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.13 (2H, q, *J* = 7.3 Hz, OCH_2 ester), 4.01 (1H, br s, CHOH), 3.89 - 3.78 (2H, m, OCH_2 ring), 2.35 (1H, m, CH_AH_B), 2.25 - 2.14 (2H, m, CH_AH_B, CH), 2.00 - 1.70 (3H, m, 3 x CH_AH_B), 1.60 - 1.28 (4H, m, 2 x CH_AH_B, 2 x CH_AH_B), 1.38 - 1.30 (1H, m, CH_AH_B), 1.25 (3H, t, *J* = 7.3 Hz, OCH_2CH_3), 1.13 (2H, td, *J* = 13.0, 3.7 Hz, 2 x CH_AH_B) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8 (0), 84.0 (0), 67.9 (1), 65.5 (2), 61.0 (2), 45.4 (1), 40.9 (2), 35.3 (2), 33.1 (2), 31.3 (2), 30.8 (2), 16.3 (2), 14.5 (3) ppm.
LRMS (ES+): ^{m}/z (relative intensity), 265 $[M+Na]^+$ (100 %).
HRMS (ES+): $[M + Na]^+ C_{13}H_{22}O_4Na$ requires ^{m}/z 265.1410, found ^{m}/z 265.1410.

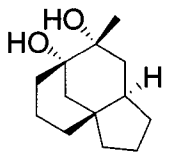
Data for bicycle **330b**:

IR ν_{max} (film): 3412 (br), 2935 (m), 1731 (s), 1442 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.13 (2H, q, *J* = 7.0 Hz, OCH_2 ester), 3.84 (1H, m, CHOH), 3.82 - 3.72 (2H, m, OCH_2 ring), 2.37 (1H, m, CH_AH_B), 2.27 - 2.16 (3H, m, 2 x CH_AH_B, CH), 1.97 (1H, m, CH_AH_B), 1.86 (1H, tqn, *J* = 12.5, 2.2 Hz, CH_AH_B), 1.65 - 1.50 (3H, m, CH_2, CH_AH_B), 1.40 (1H, m, CH_AH_B), 1.33 (1H, t, *J* = 12.6 Hz, CH_AH_B), 1.25 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 1.03 - 0.95 (2H, m, 2 x CH_ACH_B) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0 (0), 84.0 (0), 68.5 (1), 65.1 (2), 60.9 (2), 45.4 (2), 45.2 (1), 35.5 (2 x 2), 31.8 (2), 29.9 (2), 20.1 (2), 14.6 (3) ppm.

LRMS (ES+): $^{m}/z$ (relative intensity), 265 $[M+Na]^+$ (100 %).

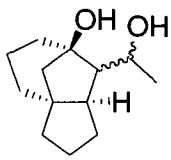
HRMS (ES+): $[M + Na]^+ C_{13}H_{22}O_4Na$ requires $^{m}/z$ 265.1410, found $^{m}/z$ 265.1411.

***rac* - (1*R*, 7*S*, 8*R*)-7-Methyltricyclo[6.3.1.0^{1,5}]dodecane-7,8-diol 334 and *rac* - (1*R*, 7*R*)-6-(1-hydroxyethyl)tricyclo[5.3.1.0^{1,5}]undecan-7-ol 335a and 335b**



334

$C_{13}H_{22}O_2$
Mw: 210.31 gmol^{-1}



335a
335b

$C_{13}H_{22}O_2$
Mw: 210.31 gmol^{-1}

Following the reported procedure by Kilburn,[122] MeOH (12 mL) was added to a stirring solution of SmI_2 in THF (0.1 M, 49 mL) and the resultant purple mixture cooled to – 78 °C, where upon the reaction turned dark green. Di-ketone **326** (250 mg, 1.21 mmol) as a solution in THF (5 mL) was then added drop-wise over a period of 10 minutes and the reaction allowed to stir at – 78 °C for a further 2 h. Brine (40 mL), followed by citric acid (305 mg, 1.45 mmol) was then added and allowed to stir for 30 minutes. EtOAc (80 mL) was added to the stirring solution and allowed to stir vigorously for 5 minutes, after which the reaction mixture was allowed to settle and the organic phase decanted off. This process was then repeated (3 x 80 mL EtOAc). The aqueous phase was transferred to a separating funnel and further extracted with EtOAc (2 x 60 mL), before the combined organic extracts were washed with brine (2 x 40 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave the crude product as a yellow oil which upon purification by flash column chromatography, eluting with 10 % EtOAc / petrol gradually increasing the polarity to 50 % EtOAc / petrol gave diol **334** (46.0 mg, 0.218 mmol, 18 %) as a yellow oil, $R_f = 0.51$ (40 % EtOAc / petrol), diol **335a** (41.0 mg, 0.195 mmol, 16 %) as a yellow oil, $R_f = 0.46$ (40 % EtOAc / petrol) and diol **335b** (24.0 mg, 0.114 mmol, 9 %) as a yellow oil, $R_f = 0.16$ (40 % EtOAc / petrol);

Data for diol **334**:

IR ν_{max} (film): 3383 (br), 2926 (s), 2857 (s), 1456 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (1H, br s, O**H**), 2.08 (1H, br s, O**H**), 1.85 - 1.81 (3H, m, 2 x C**H$_A$**H$_B$ and C**H**), 1.76 - 1.59 (9H, m, 2 x CH$_A$CH$_B$, CH$_A$C**H$_B$** and 3 x C**H$_2$**),

1.52 - 1.44 (2H, m, 2 x CH_ACH_B), 1.34 - 1.25 (3H, m, CH_ACH_B, CH_2), 1.19 (3H, s, CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 75.7 (0), 75.1 (0), 46.8 (2), 45.7 (0), 44.3 (1), 40.8 (2), 40.0 (2), 35.7 (2), 30.4 (2), 27.6 (2), 24.4 (3), 22.4 (2), 21.2 (2) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 233 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{13}H_{22}O_2Na$ requires ^{m}/z 233.1512, found ^{m}/z 233.1509.

Data for diol **335a**:

IR ν_{max} (film): 3379 (br), 2986 (m), 2845 (m), 1456 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.07 (1H, m, CHOH), 3.00 (1H, br s, OH), 2.80 (1H, br s, OH), 2.05 (1H, apparent d, J = 7.5 Hz, CH), 1.99 - 1.92 (1H, m, CH_ACH_B), 1.97 (1H, apparent d, J = 7.3 Hz, CH), 1.79 (1H, m, CH_AH_B), 1.67 - 1.57 (5H, m, 2 x CH_2, CH_ACH_B), 1.56 - 1.52 (2H, m, CH_ACH_B, CH_AH_B), 1.50 (3H, brs, CH_3), 1.37 - 1.15 (5H, m, CH_2, 3 x CH_ACH_B) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 81.8 (0), 72.4 (1), 56.4 (1), 51.7 (0), 49.7 (2), 47.9 (1), 41.9 (2), 38.4 (2), 33.2 (2), 32.8 (2), 27.3 (3), 25.7 (2), 22.5 (2) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 233 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{13}H_{22}O_2Na$ requires ^{m}/z 233.1512, found ^{m}/z 233.1506.

Data for diol **335b**:

IR ν_{max} (film): 3391 (br), 2936 (s), 2867 (s), 1456 (m) cm^{-1}.

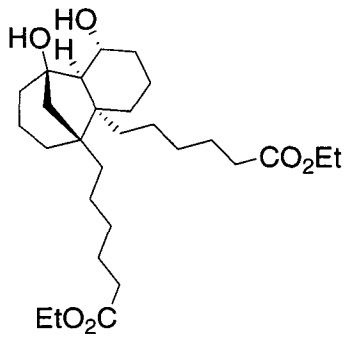
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.00 (1H, qd, J = 6.0, 3.8 Hz, CHOH), 1.90 (1H, br s, CH_AH_B), 1.88 (1H, t, J = 7.0 Hz, CH), 1.78 - 1.51 (4H, m, CH_2, CH_AH_B and CH), 1.41 - 1.33 (4H, m, CH_2 and 2 x CH_ACH_B), 1.32 - 1.23 (9H, m, 3 x CH_2 and CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 80.8 (0), 68.2 (1), 63.7 (1), 50.5 (0), 48.5 (1), 48.4 (2), 43.1 (2), 34.9 (2), 32.1 (2), 30.2 (2), 25.3 (2), 25.1 (3), 18.0 (2) ppm.

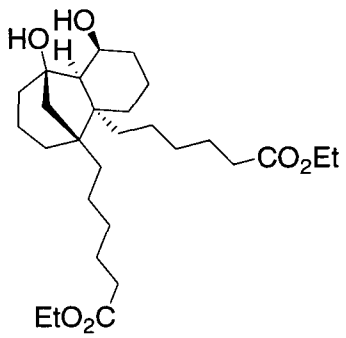
LRMS (ES+): ^{m}/z (relative intensity), 233 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{13}H_{22}O_2Na$ requires ^{m}/z 233.1512, found ^{m}/z 233.1514.

***rac* -Ethyl 6-[(1*R*, 2*R*, 3*R*, 7*R*, 8*R*)-1-(6-ethoxy-6-oxohexyl)-6, 8-dihydroxytricyclo [6.3.1.0^{2,7}] dodecan-2-yl]hexanoate 349 and *rac* - ethyl 6-[(1*R*, 2*R*, 3*S*, 7*R*, 8*R*)-1-(6-ethoxy-6-oxohexyl)-6, 8-dihydroxytricyclo [6.3.1.0^{2,7}] dodecan-2-yl]hexanoate 350**



349
$C_{28}H_{48}O_6$
Mw: 480.68 gmol^{-1}



350
$C_{28}H_{48}O_6$
Mw: 480.68 gmol^{-1}

Following the reported procedure by Kilburn,[122] MeOH (13 mL) was added to a stirring solution of SmI_2 in THF (0.1 M, 51 mL) and the resultant purple mixture cooled to – 78 °C, where upon the reaction turned dark green. Alkene **327** (300 mg, 1.29 mmol) as a solution in THF (5 mL) was then added drop-wise over a period of 10 minutes and the reaction allowed to stir at – 78 °C for a further 2 h. Brine (40 mL), followed by citric acid (320 mg, 1.57 mmol) was then added and allowed to stir for 20 minutes. EtOAc (80 mL) was added to the stirring solution and allowed to stir vigorously for 5 minutes, after which the reaction mixture was allowed to settle and the organic phase decanted off. This process was then repeated (5 x 80 mL EtOAc). The aqueous phase was transferred to a separating funnel and further extracted with EtOAc (80 mL), before the combined organic extracts were washed with brine (2 x 50 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave the crude products as a yellow oil which upon purification by flash column chromatography, eluting with 30 % EtOAc / petrol gave diol **349** (43.0 mg, 0.179 mmol, 14 %) as a yellow oil, R_f = 0.28 (50 % EtOAc / petrol) and diol **350** (75.0 mg, 0.312 mmol, 25 %) as a yellow oil, R_f = 0.19 (50 % EtOAc / petrol);

Data for diol **349**:

IR ν_{max} (film): 3420 (br), 2933 (s), 2862 (m), 1732 (s), 1466 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.12 (2H, q, *J* = 7.0 Hz, OC**H**$_2$), 4.11 (2H, q, *J* = 7.0 Hz, OC**H**$_2$), 3.92 (1H, td, *J* = 10.0, 4.0 Hz, C**H**OH), 2.61 (2H, br s, 2 x O**H**), 2.27 (4H, apparent q, *J* = 7.3 Hz, 2 x C**H**$_2$CO$_2$Et), 1.88 - 1.52 (10H, m, 3 x C**H**$_2$ and 4 x

CH_AH_B), 1.46 - 0.81 (21H, m, 8 x CH_2, 4 x CH_AH_B and CH), 1.24 (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.23 (3H, t, J = 7.0 Hz, OCH_2CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2 (0), 174.1 (0), 79.2 (0), 68.3 (1), 60.9 (1), 60.5 (2 x 2), 49.8 (2), 48.0 (0), 47.8 (0), 41.7 (2), 36.5 (2), 35.3 (2), 34.7 (2), 34.6 (2 x 2), 31.3 (2), 30.9 (2), 30.7 (2), 26.0 (2), 25.8 (2), 25.3 (2), 25.2 (2), 22.6 (2), 20.8 (2), 17.2 (2), 14.6 (2 x 3) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 503 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{28}H_{48}O_6Na$ requires ^{m}/z 503.3343, found ^{m}/z 503.3349.

Data for diol **350**:

IR ν_{max} (film): 3407 (br), 2933 (s), 2862 (m), 1732 (s), 1466 (w) cm^{-1}.

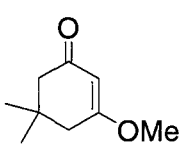
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.12 (2H, q, J = 7.3 Hz, OCH_2), 4.11 (2H q, J = 7.3 Hz, OCH_2). 4.08 (1H, m, CHOH), 2.31 (2H, br s, 2 x OH), 2.28 (4H, apparent q, J = 7.5 Hz, 2 x CH_2CO_2Et), 1.97 (1H, m, CH_AH_B), 1.85 - 1.79 (2H, m, 2 x CH_AH_B), 1.69 - 1.49 (13H, m, 4 x CH_2, 3 x CH_AH_B, CH_AH_B, CH), 1.40 - 1.12 (15H, m, 5 x CH_2, 5 x CH_AH_B), 1.24 (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.23 (3H, t, J = 7.0 Hz, OCH_2CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1 (2 x 0), 79.0 (0), 68.3 (1), 62.9 (1), 60.5 (2), 60.4 (2), 49.5 (2), 49.3 (0), 47.4 (0), 42.5 (2), 37.1 (2), 35.2 (2), 34.7 (2), 34.6 (2), 32.4 (2), 30.8 (2), 30.6 (2), 29.6 (2), 26.3 (2), 25.6 (2), 25.3 (2 x 2), 22.8 (2), 20.0 (2), 18.5 (2), 14.6 (2 x 3) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 503 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{28}H_{48}O_6Na$ requires ^{m}/z 503.3343, found ^{m}/z 503.3339.

3-Methoxy-5,5-dimethylcyclohex-2-en-1-one 359



359

$C_9H_{14}O_2$

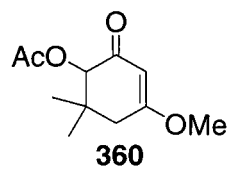
Mw: 154.21 $gmol^{-1}$

Following the reported procedure by Takahashi,[136] commercially available dimedone **358** (10.0 g, 71.4 mmol) was dissolved in MeOH (125 mL) and to the stirring solution added trimethylorthoformate (8.59 mL, 78.5 mmol) in one portion. *p*-Toluenesulfonic acid monohydrate (50.0 mg, 0.263 mmol) was then added, and the resultant yellow

solution allowed to stir at RT for 30 h. The mixture was concentrated *in vacuo* and water (50 mL) added, before the product was extracted with DCM (3 x 80 mL). The combined organic extracts were washed with brine (50 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave a yellow oil which was purified by flash column chromatography, eluting with 40 % EtOAc / petrol to give enone **359** (10.8 g, 70.0 mmol, 99 %) as a yellow oil, $R_f = 0.45$ (70 % EtOAc / petrol);

IR ν_{max} (film): 2958 (m), 2360 (m), 2341 (m), 1651 (s), 1604 (s), 1372 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.36 (1H, s, C(O)C**H**=C), 3.69 (3H, s, OC**H$_3$**), 2.26 (2H, s, C**H$_2$**), 2.20 (2H, s, C**H$_2$**), 1.06 (6H, s, 2 x C**H$_3$**) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.8 (0), 177.3 (0), 101.5 (1), 56.0 (3), 51.1 (2), 43.0 (2), 32.8 (0), 28.6 (2 x 3) ppm.
LRMS (ES+): $^m/z$ (relative intensity), 155 $[M + H]^+$ (100 %), 177 $[M + Na]^+$ (20 %).
HRMS (EI): $[M]^+$ $C_9H_{14}O_2$ requires $^m/z$ 154.09938, found $^m/z$ 154.09889.

4-Methoxy-6, 6-dimethyl-2-oxocyclohex-3-en-1-yl acetate 360



360

$C_{11}H_{16}O_4$
Mw: 212.24 $gmol^{-1}$

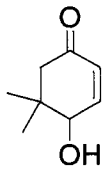
Following the reported procedures by Demir,[141, 142] a solution of enone **359** (2.00 g, 12.9 mmol), $Mn(OAc)_3.2H_2O$ (13.9 g, 51.8 mmol) and benzene (80 mL) was heated at relux in a Dean and Stark apparatus for 48 h. The reaction mixture was allowed to cool to RT, filtered through a pad of celite and the black residue washed with EtOAc (~ 100 mL). Removal of the solvent *in vacuo* gave a black oil which was purified by flash column chromatography, eluting with 20 % EtOAc / petrol increasing the polarity to 30 % EtOAc / petrol), to furnish the acetate **360** (2.39 g, 11.3 mmol, 88 %) as a pale yellow oil. $R_f = 0.47$ (70 % EtOAc / petrol);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.37 (1H, d, *J* = 1.6 Hz, C(O)C**H**=C), 5.19 (1H, s, C**H**OAc), 3.68 (3H, s, OC**H$_3$**), 2.62 (1H, d, *J* = 17.6 Hz, C**H$_A$H$_B$**), 2.30 (1H, d, *J* = 17.6 Hz, CH$_A$C**H$_B$**), 2.19 (3H, s, C(O)C**H$_3$**), 1.09 (3H, s, C**H$_3$**), 1.02 (3H, s, C**H$_3$**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.8 (0), 175.5 (0), 170.9 (0), 100.4 (1), 80.2 (1), 56.4 (3), 43.3 (2), 36.8 (0), 27.4 (3), 21.0 (3), 20.4 (3) ppm.

Data is consistent with that reported by Demir.[141, 142]

4-Hydroxy-5,5-dimethylcyclohex-2-en-1-one 361



361

$C_8H_{12}O_2$

Mw: 140.18 $gmol^{-1}$

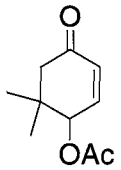
Following the reported procedures by Demir,[141, 142] to a suspension of $LiAlH_4$ (2.14 g, 56.3 mmol) and freshly distilled Et_2O (250 mL) was added acetate **360** (2.39 g, 11.3 mmol) as a solution in Et_2O (10 mL) dropwise. The reaction mixture was reluxed for 2 h before being cooled to 0 °C and 2M HCl aqueous solution (250 mL) added slowly. The bi-phasic mixture was stirred vigorously for a further 2 h and the layers then separated. The aqueous layer was re-extracted with EtOAc (50 mL), and the combined organic extracts washed with saturated $NaHCO_3$ aqueous solution (2 x 50 mL) and brine (2 x 50 mL), before being dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave a colourless oil which upon purification by flash column chromatography, eluting with 20 % EtOAc / petrol gradually increasing the polarity to 50 % EtOAc / petrol, gave hydroxyl **361** (1.17 g, 8.35 mmol, 74 %) as a colourless oil, R_f = 0.39 (70 % EtOAc / petrol);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.77 (1H, dd, *J* = 10.3, 2.6 Hz, C(O)CH=C**H**), 5.98 (1H, ddd, 10.2, 1.1, 0.9 Hz, C(O)C**H**=CH), 4.30 (1H, d, *J* = 2.4 Hz, C**H**OH), 2.34 (1H, dd, *J* = 16.3, 1.1 Hz, C(O)C$\mathbf{H_A}$$CH_B$), 2.29 (1H, dd, *J* = 16.3, 0.5 Hz, C(O)CH_AC$\mathbf{H_B}$), 2.17 (1H, br s, O**H**), 1.12 (3H, s, C$\mathbf{H_3}$), 0.98 (3H, s, C$\mathbf{H_3}$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.4 (0), 151.1 (1), 129.3 (1), 74.8 (1), 50.6 (2), 40.0 (0), 27.7 (3), 20.1 (3) ppm.

Data is consistent with that reported by Demir.[141, 142]

6, 6-Dimethyl-4-oxocyclohex-2-en-1-yl acetate 362



362

$C_{10}H_{14}O_3$
Mw: 182.22 $gmol^{-1}$

To a stirring solution of alcohol **361** (1.00 g, 7.13 mmol), Et_3N (2.29 mL, 16.5 mmol) and DMAP (87 mg, 0.71 mmol) in DCM (30 mL), was added acetyl chloride (1.00 mL, 14.3 mmol) dropwise. The resultant yellow solution was allowed to stir for 21 h at RT. At this point the reaction was diluted with saturated $NaHCO_3$ aqueous solution (10 mL), and the layers separated. The organic phase was washed with brine (10 mL) before being dried over magnesium sulfate. Removal of the solvent *in vacuo* gave a yellow oil which upon purification by flash column chromatography, eluting with 10 % EtOAc / petrol increasing the polarity to 15 % EtOAc / petrol, gave the product **362** (610 mg, 3.35 mmol, 47 %) as a colourless oil, $R_f = 0.63$ (50 % EtOAc / petrol);

IR ν_{max} (film): 2967 (w), 1739 (s), 1683 (s), 1369 (s), 1226 (s) cm^{-1}.

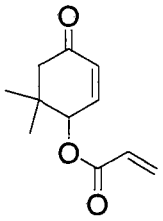
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.65 (1H, dd, J = 10.2, 2.9 Hz, C(O)CH=C**H**), 6.04 (1H, ddd, J = 10.2, 2.0, 0.9 Hz, C(O)C**H**=CH), 5.43 (1H, dd, J = 2.8, 2.0 Hz, C**H**OAc), 2.40 (1H, dd, J = 16.3, 0.9 Hz, C(O)C**H$_A$**H$_B$), 2.35 (1H, d, J = 16.3 Hz, C(O)CH$_A$**H$_B$**), 2.13 (3H, s, C(O)C**H$_3$**), 1.06 (3H, s, C**H$_3$**), 1.02 (3H, s, C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.5 (0), 170.9 (0), 146.5 (1), 130.5 (1), 75.3 (1), 50.4 (2), 38.6 (0), 27.5 (3), 21.7 (3), 21.2 (3) ppm.

LRMS (EI): ^{m}/z (relative intensity), 182 $[M]^+$ (20 %), 140 $[M - C_2H_2O]^+$ (70 %), 122 $[M - C_2H_4O_2]^+$ (70 %).

HRMS (EI): $[M]^+$ $C_{10}H_{14}O_3$ requires ^{m}/z 182.09429, found ^{m}/z 182.09295.

6, 6-Dimethyl-4-oxocyclohex-2-en-1-yl prop-2-enoate 363



363

$C_{11}H_{14}O_3$
Mw: 194.23 $gmol^{-1}$

Alcohol **361** (500 mg, 3.57 mmol) was dissolved in freshly distilled DCM (12 mL) and to the yellow solution added DMAP (44.0 mg, 0.360 mmol, 10 mol %) and Et_3N (2.00 mL, 14.3 mmol) consecutively. The reaction mixture was cooled to 0 °C and 2-propenoyl chloride (0.870 mL, 10.7 mmol) added dropwise over a period of 5 minutes, before allowing the reaction mixture to warm to RT and stir for 16 h. Saturated $NaHCO_3$ aqueous solution (10 mL) was added in one portion and the layers separated. The aqueous phase was back extracted with DCM (2 x 15 mL) and the combined organic phase, washed with brine (30 mL) and dried over magnesium sulfate. Removal of the solvent *in vacuo* gave a yellow oil, which was purified by flash column chromatography eluting with 5 % EtOAc / petrol increasing the polarity to 10 % EtOAc / petrol, giving ester **363** (374 mg, 1.93 mmol, 54 %) as a colourless oil, R_f = 0.36 (20 % EtOAc / petrol);

IR ν_{max} (film): 2698 (m), 1723 (s), 1683 (s), 1633 (m), 1472 (w), 1405 (s), 1390 (m) cm^{-1}.

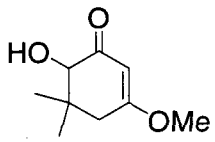
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.69 (1H, dd, *J* = 10.2, 2.8 Hz, C(O)CH=C**H**), 6.49 (1H, dd, *J* = 17.3, 1.4 Hz, OC(O)CH=C**H**$_{trans}$H$_{cis}$), 6.19 (1H, dd, *J* = 17.3, 10.4 Hz, OC(O)C**H**=CH_2), 6.07 (1H, ddd, *J* = 10.3, 2.0, 0.8 Hz, C(O)C**H**=CH), 5.93 (1H, dd, *J* = 10.5, 1.4 Hz, OC(O)CH=CH$_{trans}$**H**$_{cis}$), 5.53 (1H, br dd, *J* = 2.6, 2.0 Hz, C**H**OC(O)), 2.42 (1H, dd, *J* = 16.3, 0.7 Hz, C(O)C**H**$_A$H$_B$), 2.39 (1H, d, *J* = 16.3 Hz, C(O)CH$_A$**H**$_B$), 1.08 (3H, s, CH_3), 1.06 (3H, s, CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.5 (0), 165.9 (0), 146.4 (1), 132.2 (2), 130.5 (1), 128.2 (1), 75.4 (1), 50.5 (2), 38.8 (0), 27.5 (3), 21.7 (3) ppm.

LRMS (EI): ^{m}/z (relative intensity), 194 $[M]^+$ (30 %), 138 $[M - C_3H_4O]^+$ (70 %), 122 $[M - C_3H_4O_2]^+$ (90 %).

HRMS (EI): $[M]^+$ $C_{11}H_{14}O_3$ requires ^{m}/z 194.09429, found ^{m}/z 194.0943.

6-Hydroxy-3-methoxy-5, 5-dimethylcyclohex-2-en-1-one 365



365

$C_9H_{14}O_3$
Mw: 170.21 $gmol^{-1}$

Following the reported procedure by Watt,[146] acetate ester **360** (1.06 g, 5.00 mmol) was dissolved in MeOH (50 mL) and K_2CO_3 (691 mg, 5.00 mmol) added portion-wise over a period of 2 minutes. The resultant yellow solution was left to stir at RT for 6 h, after which time the reaction was complete. The reaction was diluted with EtOAc (50 mL) then subsequently washed with 1M HCl aqueous solution (20 mL), brine (30 mL) and finally dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave a yellow oil, which upon purification by flash column chromatography, eluting with 10 % EtOAc / petrol, gave the β-hydroxyl ketone **365** (754 mg, 4.42 mmol, 86 %) as a white solid, $R_f = 0.47$ (10 % EtOAc / petrol);

Mpt: 60 - 61 °C, recrystallised from EtOAc.

IR ν_{max} (solid): 3434 (s), 2960 (m), 2933 (m), 1647 (s), 1598 (s), 1433 (m), 1365 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.41 (1H, d, J = 1.3 Hz, C(O)C**H**=C), 3.87 (1H, s, C**H**OH), 3.81 (1H, br s, O**H**), 3.70 (3H, s, OC**H$_3$**), 2.55 (1H, dd, J = 17.6, 1.3 Hz, C**H$_A$**H$_B$), 2.26 (1H, d, J = 17.6 Hz, CH$_A$**H$_B$**), 1.20 (3H, s, C**H$_3$**), 0.86 (3H, s, C**H$_3$**) ppm.

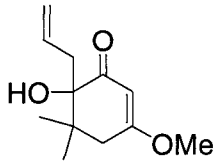
^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.0 (0), 177.3 (0), 98.7 (1), 79.4 (1), 56.4 (3), 43.3 (2), 38.6 (0), 27.9 (3), 18.6 (3) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 193 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+ C_9H_{14}O_3Na$ requires ^{m}/z 193.0835, found ^{m}/z 193.0834.

Microanalysis: $C_9H_{14}O_3$ requires C, 63.51; H, 8.29. Found C, 62.74; H, 8.17 %.

6-Hydroxy-3-methoxy-5, 5-dimethyl-6-prop-2-en-1-ylcyclohex-2-en-1-one 367



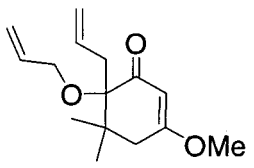
367

$C_{12}H_{18}O_3$
Mw: 210.27 $gmol^{-1}$

Alcohol **365** (100 mg, 0.587 mmol) was dissolved in THF (2 mL) and added dropwise to a stirring solution of NaH, 60 % dispersion in mineral oil (23.5 mg, 0.587 mmol) in THF (2 mL) at 0 °C. The resultant yellow solution was allowed to warm to RT and stir for 2 h. At this point allyl iodide (80.0 μL, 0.881 mmol) as a solution in THF (2 mL) was added, and the pale yellow solution stirred at RT for a further 23 h. The reaction was quenched with saturated NH_4Cl aqueous solution (5 mL) followed by EtOAc (5 mL), and the layers separated. The aqueous layer was back extracted with EtOAc (3 x 20 mL) and the combined organic extracts washed with brine (20 mL) and finally dried over magnesium sulfate. Removal of the solvent *in vacuo* gave a yellow oil, which upon purification by flash column chromatography, eluting with 5 % EtOAc / petrol increasing the polarity to 10 % EtOAc / petrol, gave alcohol **367** (26.0 mg, 0.123 mmol, 21 %) as a yellow oil, $R_f = 0.54$ (40 % EtOAc / petrol);

IR ν_{max} (film): 3455 (br), 2956 (m), 1653 (s), 1604 (s), 1450 (m), 1364 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.64 (1H, dddd, *J* = 16.9, 10.2, 7.7, 6.8 Hz, CH_2=C**H**CH_2), 5.35 (1H, d, *J* = 1.8 Hz, C(O)C**H**=C), 5.03 - 4.96 (2H, m, **CH_2**=CH), 3.80 (1H, br s, **OH**), 3.70 (3H, s, O**CH_3**), 2.60 (1H, br d, *J* = 18.3 Hz, **CH_AH_B**), 2.47 (1H, ddt, *J* = 13.6, 6.8, 1.1 Hz, CH_2=CHC**H_AH_B**), 2.31 (1H, dd, *J* = 13.6, 7.7 Hz, CH_2=CHCH_A**H_B**), 2.22 (1H, br d, *J* = 18.3 Hz, CH_A**H_B**), 1.14 (3H, s, **CH_3**), 0.95 (3H, s, **CH_3**) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.4 (0), 176.2 (0), 133.2 (1), 118.4 (2), 98.5 (1), 80.1 (0), 56.4 (3), 42.9 (2), 39.3 (0), 39.2 (2), 23.6 (3), 23.3 (3) ppm.
LRMS (ES+): ^{m}/z (relative intensity), 233 $[M + Na]^+$ (100 %), 443 $[2M + Na]^+$ (25 %).
HRMS (ES+): $[M + Na]^+$ $C_{12}H_{18}O_3$ requires ^{m}/z 233.1148, found ^{m}/z 233.1146.

3-Methoxy-5, 5-dimethyl-6-prop-2-en-1-yl-6-(prop-2-en-1-yloxy)cyclohex-2-en-1-one 368



368
$C_{15}H_{22}O_3$
Mw: 250.33 $gmol^{-1}$

To a stirring suspension of NaH, 60 % dispersion in mineral oil (365 mg, 9.11 mmol) in THF (20 mL) was added alcohol **365** (776 mg, 4.56 mmol) as a solution in THF

(10 mL) at 45 °C. The resultant orange suspension was allowed to stir at this temperature for 75 minutes before allyl bromide (1.18 mL, 13.7 mmol) was then added dropwise. The reaction was left to stir at 45 °C for a further 3 h, and NaH, 60 % dispersion in mineral oil (273 mg, 6.83 mmol) was added in one portion and the orange mixture allowed to stir for a further 45 minutes. Allyl bromide (1.18 mL, 13.7 mmol) was then added and the reaction mixture left to stir for 19 h. The orange reaction was diluted with H_2O (15 mL) and EtOAc (15 mL), and the layers separated. The aqueous layer was back extracted with EtOAc (4 x 40 mL) and the combined organic extracts washed with brine (2 x 30 mL) before being dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave a yellow oil which upon purification by flash column chromatography, eluting with 5 % EtOAc / petrol, gave the product **368** (847 mg, 3.38 mmol, 74 %) as a pale yellow oil, $R_f = 0.6$ (30 % EtOAc / petrol);

IR ν_{max} (film): 2990 (w), 2960 (m), 1646 (s), 1611 (s), 1437 (m), 1382 (s), 1365 (m) cm^{-1}.

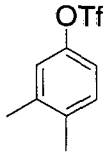
^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.96 (1H, dddd, *J* = 17.5, 10.3, 7.6, 6.1 Hz, CH_2=C**H**CH_2), 5.81 (1H, dddd, *J* = 17.3, 10.3, 7.0, 4.9 Hz, CH_2=C**H**CH_2O), 5.26 (1H, d, *J* = 1.5 Hz, C(O)C**H**=C), 5.23 (1H, apparent dq, *J* = 17.3, 1.8 Hz, C**H**$_{trans}$$H_{cis}$=CH), 5.12 - 5.03 (2H, m, C**H**$_{trans}$$H_{cis}$=CH, CH_{trans}**H**$_{cis}$=CH), 4.99 (1H, apparent dq, *J* = 10.3, 1.7 Hz, CH_{trans}**H**$_{cis}$), 3.98 (1H, dd, *J* = 13.0, 4.9 Hz, CH_2=CHC**H**$_A$$H_B$O), 3.72 (1H, m, CH_2=CHCH_A**H**$_B$O), 3.67 (3H, s, OC**H**$_3$), 3.02 (1H, dd, *J* = 16.2, 5.9 Hz, CH_2=CHC**H**$_A$$H_B$), 2.93 (1H, br d, *J* = 17.6 Hz, C**H**$_A$$H_B$), 2.39 (1H, dd, *J* = 16.2, 7.7 Hz, CH_2=CHCH_A**H**$_B$), 1.85 (1H, br d, *J* = 17.6 Hz, CH_A**H**$_B$), 1.18 (3H, s, C**H**$_3$), 1.00 (3H, s, C**H**$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.1 (0), 176.7 (0), 136.2 (1), 135.6 (1), 116.0 (2), 115.2 (2), 99.1 (1), 82.7 (0), 65.4 (2), 55.9 (3), 42.5 (2), 41.0 (0), 31.8 (2), 25.1 (3), 24.2 (3) ppm.

LRMS (ES+) ^{m}/z (relative intensity), 273 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{15}H_{22}O_3Na$ requires ^{m}/z 273.1461, found ^{m}/z 273.1455.

3, 4-Dimethylphenyl trifluoromethanesulfonate 372



372

$C_9H_9F_3O_3S$

Mw: 254.23 $gmol^{-1}$

Following the reported procedure by Takeuchi,[149] alcohol **361** (280 mg, 2.00 mmol) was dissolved in DCM (10 mL) and pyridine (0.340 mL, 4.20 mmol) added in one portion. To the stirring solution was then added trifluorosulfonic anhydrdide (0.500 mL, 3 mmol) at 0 °C, dropwise over a period of 10 minutes. The pale brown solution was stirred at 25 °C for 2 h, after which time it was diluted with H_2O (10 mL) and DCM (10 mL). The layers were separated and the organic phase washed with H_2O (2 x 10 mL), 2M HCl aqueous solution (10 mL), H_2O (10 mL) and finally brine (10 mL) before being dried over magnesium sulfate. The solvent was removed under a reduced pressure to give a brown oil, which upon purification by flash column chromatography, eluting with 2 % EtOAc / petrol, gave triflate **372** (226 mg, 0.889 mmol, 44 %) as a colourless oil, $R_f = 0.78$ (40 % EtOAc / petrol);

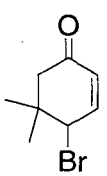
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19 (1H, d, *J* = 8.2 Hz, Ph**H**), 7.05 (1H, d, *J* = 2.5 Hz, Ph**H**), 7.01 (1H, dd, *J* = 8.2, 2.6 Hz, Ph**H**), 2.29 (3H, s, **CH_3**), 2.27 (3H, s, **CH_3**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.0 (0), 139.5 (0), 137.5 (0), 131.3 (1), 122.4 (1), 119.2 (0, q, J_{CF} = 320.7 Hz), 118.6 (1), 20.3 (3), 19.6 (3) ppm.

^{19}F NMR (300 MHz, $CDCl_3$): δ = – 73.0 ppm.

Data is consistent with that reported by Toy.[150]

4-Bromo-5, 5-dimethylcyclohex-2-en-1-one 377



377

$C_8H_{11}BrO$

Mw: 203.08 $gmol^{-1}$

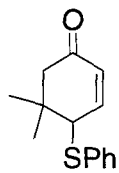
Following the reported procedure by Diederichsen,[152] alcohol **361** (1.75 g, 12.5 mmol), CBr_4 (6.21 g, 18.7 mmol), PPh_3 (4.91 g, 18.8 mmol) and THF (80 mL) were combined and the resultant white suspension stirred at RT for 46 h. The solvent was removed under a reduced pressure to give a white solid, which upon purification by flash column chromatography, eluting with 5 % EtOAc / petrol increasing the polarity to 10 % EtOAc / petrol, gave the unstable bromide **377** (1.30 g, 6.40 mmol, 51 %) as a colourless oil, $R_f = 0.43$ (20 % EtOAc / petrol);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96 (1H, dd, *J* = 9.9, 4.6 Hz, C(O)CH=C**H**), 5.93 (1H, dt, *J* = 9.9, 0.8 Hz, C(O)C**H**=CH), 4.61 (1H, d, *J* = 4.6 Hz, C**H**Br), 2.63 (1H, d, *J* = 16.3 Hz, C(O)C$\mathbf{H_A}$H$_B$), 2.28 (1H, d, *J* = 16.3 Hz, C(O)CH$_A$**H$_B$**), 1.23 (3H, s, **C**$\mathbf{H_3}$), 1.18 (3H, s, **C**$\mathbf{H_3}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.5 (0), 146.8 (1), 128.1 (1), 57.2 (1), 48.8 (2), 38.4 (0), 28.4 (3), 26.6 (3) ppm.

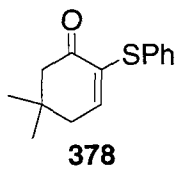
LRMS (EI): ^{m}/z (relative intensity), 202 $[C_8H_{11}{}^{79}BrO]^+$ (20 %), 123 [M - ^{79}Br] (100 %).

5, 5-Dimethyl-4-(phenylsulfanyl)cyclohex-2-en-1-one 370 and 5, 5-dimethyl-2-(phenylsulfanyl) cyclohex-2-en-1-one 378



370

$C_{14}H_{16}OS$
Mw: 232.34 gmol^{-1}



378

$C_{14}H_{16}OS$
Mw: 232.34 gmol^{-1}

To a stirring solution of bromide **377** (1.30 g, 6.40 mmol) in dry DMF (15 mL) was added 90 % sodiumthiophenolate (987 mg, 6.73 mmol) as a solution in dry DMF (10 mL) over a period of 10 minutes. The resultant purple reaction mixture was stirred at RT for 30 minutes before being quenched with H_2O (10 mL) and Et_2O (15 mL). The layers were separated and the aqueous layer back extracted with Et_2O (4 x 40 mL), before the combined organic phases were washed with H_2O (2 x 20 mL), brine (40 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave an orange oil, which upon purification by flash column chromatography, eluting with 2 % EtOAc / petrol, gave 4-substituted enone **370** (670 mg, 2.88 mmol, 45 %) as a

yellow oil, R_f = 0.30 (5 % EtOAc / petrol) and 2-substituted enone **378** (563 mg, 2.42 mmol, 38 %) as an orange oil, R_f = 0.35 (5 % EtOAc / petrol);

Data for 4-substituted enone **370**:

IR ν_{max} (film): 2963 (m), 2869 (w), 1673 (s), 1582 (m), 1469 (m), 1438 (m) 1388 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 - 7.46 (2H, m, 2 x Ph**H**), 7.36 - 7.28 (3H, m, 3 x Ph**H**), 6.85 (1H, dd, *J* = 10.0, 4.0 Hz, C(O)CH=C**H**), 5.97 (1H, dd, *J* = 10.0, 1.6 Hz, C(O)C**H**=CH), 3.78 (1H, dd, *J* = 3.9, 1.5 Hz, C**H**SPh), 2.53 (1H, d, *J* = 16.2 Hz, C(O)C$\mathbf{H_A}$$H_B$), 2.29 (1H, 16.2 Hz, C(O)C$H_A$$\mathbf{H_B}$), 1.23 (3H, s, $\mathbf{CH_3}$), 1.15 (3H, s, $\mathbf{CH_3}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.1 (0), 148.6 (1), 135.0 (0), 132.8 (2 x 1), 129.6 (2 x 1), 128.0 (1), 127.9 (1), 56.8 (1), 50.7 (2), 38.6 (0), 28.8 (3), 25.5 (3) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 255 $[M + Na]^+$ (33 %).

HRMS (ES+): $[M + Na]^+$ $C_{14}H_{16}OSNa$ requires ^{m}/z 255.0814, found ^{m}/z 255.0812.

Data for 2-substituted enone **378**:

IR ν_{max} (film): 2952 (m), 2930 (m), 2899 (m), 1668 (s), 1593 (s), 1471 (s), 1440 (s) cm^{-1}.

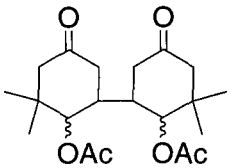
^{1} H NMR (300 MHz, $CDCl_3$): δ = 7.45 - 7.30 (5H, m, 5 x Ph**H**), 6.40 (1H, t, *J* = 4.5 Hz, C(O)C=C**H**CH_2), 2.41 (2H, s, C(O)C$\mathbf{H_2}$), 2.27 (2H, d, *J* = 4.5 Hz, C=CHC$\mathbf{H_2}$), 1.05 (6H, s, 2 x $\mathbf{CH_3}$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.6 (0), 143.8 (1), 136.6 (0), 133.8 (2 x 1), 132.6 (0), 129.7 (2 x 1), 128.4 (1), 52.4 (2), 41.5 (2), 34.5 (0), 28.5 (2 x 3) ppm.

LRMS (ES+): ^{m}/z (relative intensity) 255 $[M + Na]^+$ (100 %), 487 $[2M + Na]^+$ (80 %).

HRMS (ES+): $[M + Na]^+$ $C_{14}H_{16}OSNa$ requires ^{m}/z 255.0814, found ^{m}/z 255.0813.

6-[2-(Acetyloxy)-3, 3-dimethyl-5-oxocyclohexyl]-2, 2-dimethyl-4-oxocyclohexyl acetate 380



380

$C_{20}H_{30}O_6$

Mw: 366.45 $gmol^{-1}$

Following the reported procedure by Kilburn,[122] MeOH (17 mL) was added to a stirring solution of SmI_2 in THF (0.1 M, 69 mL) and the resultant purple mixture cooled to – 78 °C, where upon the reaction turned dark green. Acetate ester **362** (300 mg, 1.65 mmol) as a solution in THF (5 mL) was then added drop-wise over a period of 10 minutes and the reaction allowed to stir at – 78 °C for a further 2 h. Brine (35 mL), followed by citric acid (415 mg, 1.98 mmol) was then added and allowed to stir for 10 minutes. EtOAc (80 mL) was added to the stirring solution and allowed to stir vigorously for 5 minutes, after which the reaction mixture was allowed to settle and the organic phase decanted off. This process was then repeated (4 x 80 mL EtOAc). The aqueous phase was transferred to a separating funnel and further extracted with EtOAc (2 x 70 mL), before the combined organic extracts were washed with brine (2 x 30 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave the crude product as a yellow oil which upon purification by flash column chromatography, eluting with 5 % EtOAc / petrol gradually increasing the polarity to 25 % EtOAc / petrol, gave dimer **380** (9.00 mg, 0.0493 mmol, 3 %) as a yellow oil, R_f = 0.67 (70 % EtOAc / petrol);

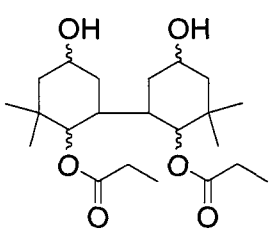
IR ν_{max} (film): 3435 (br), 2963 (m), 1725 (s), 1460 (m), 1371 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.06 (2H, d, *J* = 11.3 Hz, 2 x C**H**OAc), 2.45 - 2.24 (6H, m, 2 x C$\mathbf{H_2}$, 2 x C$\mathbf{H_A}$H$_B$), 2.20 (6H, s, 2 x C(O)C$\mathbf{H_3}$), 2.18 - 2.12 (4H, m, 2 x CH$_A$C$\mathbf{H_B}$, 2 x C**H**), 0.94 (6H, s, 2 x C$\mathbf{H_3}$), 0.86 (6H, s, 2 x C$\mathbf{H_3}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.9 (0), 171.0 (0), 77.2 (1), 53.3 (2), 42.4 (2), 39.1 (0), 38.6 (1), 28.8 (3), 21.3 (3), 20.1 (3) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 389 $[M + Na]^+$ (100 %).

4-Hydroxy-6-[5-hydroxy-3, 3-dimethyl-2-(propanoyloxy)cyclohexyl]-2, 2 dimethyl cyclohexyl propanoate 382a and 382b



382a
382b

$C_{22}H_{38}O_6$
Mw: 398.53 $gmol^{-1}$

Following the reported procedure by Kilburn,[122] MeOH (11 mL) was added to a stirring solution of SmI_2 in THF (0.1 M, 43 mL) and the resultant purple mixture cooled to – 78 °C, where upon the reaction turned dark green. Acrylate **363** (200 mg, 1.03 mmol) as a solution in THF (5 mL) was then added drop-wise over a period of 10 minutes and the reaction allowed to stir at – 78 °C for a further 2 h. Brine (30 mL), followed by citric acid (260 mg, 1.24 mmol) was then added and allowed to stir for 10 minutes. EtOAc (70 mL) was added to the stirring solution and allowed to stir vigorously for 10 minutes, after which the reaction mixture was allowed to settle and the organic phase decanted off. This process was then repeated (3 x 70 mL EtOAc). The aqueous phase was transferred to a separating funnel and further extracted with EtOAc (2 x 70 mL), before the combined organic extracts were washed with brine (2 x 30 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave the crude product as a yellow oil which upon purification by flash column chromatography, eluting with 5 % EtOAc / petrol gradually increasing the polarity to 30 % EtOAc / petrol, gave the dimer **382a** (14.0 mg, 0.0702 mmol, 7 %) as a yellow oil, R_f = 0.26 (40 % EtOAc / petrol) and dimer **382b** (19.0 mg, 0.0954 mmol, 9 %) as a yellow oil, R_f = 0.22 (40 % EtOAc / petrol);

Data for dimer **382a**:

IR ν_{max} (film): 3365 (br), 2965 (m), 2945 (m), 2882 (m), 1714 (s), 1465 (s), 1371 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.69 (1H, d, *J* = 11.3 Hz, **CH**OC(O)), 4.61 (1H, d, *J* = 11.4 Hz, **CH**OC(O)), 4.11 - 4.08 (2H, m, 2 x **CH**OH), 2.43 - 2.34 (4H, m, 2 x $\mathbf{CH_2}$), 2.06 - 1.94 (2H, m, **CH**, $\mathbf{CH_AH_B}$), 1.79 - 1.59 (3H, m, **CH**, 2 x $\mathbf{CH_AH_B}$), 1.38 - 1.27 (3H, m, 3 x $\mathbf{CH_AH_B}$), 1.22 - 1.12 (9H,m, 2 x $CH_2\mathbf{CH_3}$, $\mathbf{CH_3}$), 1.01 - 0.97 (2H, m, $\mathbf{CH_2}$), 0.94 (3H, s, $\mathbf{CH_3}$), 0.89 (3H, s, $\mathbf{CH_3}$), 0.83 (3H, s, $\mathbf{CH_3}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.7 (0), 174.7 (0), 79.1 (1), 78.3 (1), 66.7 (1), 66.7 (1), 47.9 (2), 44.5 (2), 36.4 (0), 36.2 (0), 34.9 (2), 34.6 (1), 33.3 (2), 30.6 (3), 30.3 (1), 29.7 (3), 26.3 (2 x 2), 22.6 (3), 20.7 (3), 10.2 (3), 9.8 (3) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 421 $[M + Na]^+$ (90 %), 820 $[2M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{22}H_{38}O_6Na$ requires ^{m}/z 421.2561, found ^{m}/z 421.2560.

Data for dimer **382b**:

IR ν_{max} (film): 3391 (br), 2964 (m), 2937 (m), 2881 (m), 1712 (s), 1463 (s), 1368 (s) cm^{-1}.

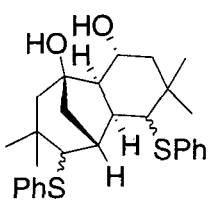
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.69 (1H, d, *J* = 11.4 Hz, CHOC(O)), 4.64 (1H, d, *J* = 11.5 Hz, CHOC(O)), 4.12 (1H, m, CHOH), 3.81 (1H, m, CHOH), 2.48 - 2.39 (4H, m, 2 x CH_2), 2.22 (1H, td, *J* = 13.3, 2.5 Hz, CH), 1.88 (1H, m, CH), 1.77 - 1.70 (2H, m, 2 x CH_AH_B), 1.64 (1H, dt, *J* = 14.9, 2.5 Hz, CH_AH_B), 1.54 (1H, m, CH_AH_B), 1.43 (1H, dd, *J* = 14.9, 3.3 Hz, CH_AH_B), 1.22 - 1.15 (9H, m, 2 x CH_2CH_3, CH_2, CH_AH_B), 1.07 (3H, s, CH_3), 0.87 (3H, s, CH_3), 0.83 (3H, s, CH_3), 0.78 (3H, s, CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.7 (0), 174.5 (0), 80.3 (1), 79.2 (1), 67.0 (1), 67.0 (1), 48.3 (2), 45.4 (2), 38.2 (2), 37.1 (0), 37.0 (1), 36.8 (0), 36.4 (2), 33.2 (1), 30.9 (3), 30.0 (3), 28.3 (2), 28.3 (2), 22.2 (3), 20.2 (3), 9.9 (3), 9.8 (3) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 421 $[M + Na]^+$ (100 %), 820 $[2M + Na]^+$ (75 %).

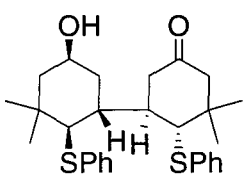
HRMS (ES+): $[M + Na]^+$ $C_{22}H_{38}O_6Na$ requires ^{m}/z 421.2561, found ^{m}/z 421.2559.

***rac* - (1*S*, 2*R*, 3*R*, 7*R*, 8*R*)-5, 5, 10, 10-tetramethyl-6, 9-bis (phenylsulfanyl)tricycle [6.3.1.0^{2,7}]dodecane-1, 3-diol 383 and *rac* - (4*R*, 5*R*)-5-[(1*R*, 2*R*, 5*S*)-5-hydroxy-3, 3-dimethyl-2-(phenylsulfanyl)cyclohexyl]-3,3-dimethyl-4-(phenylsulfanyl) cyclohexan -1-one 384**



383

$C_{28}H_{36}O_2S_2$
Mw: 468.71 $gmol^{-1}$



384

$C_{28}H_{36}O_2S_2$
Mw: 468.71 $gmol^{-1}$

Following the reported procedure by Kilburn,[122] MeOH (9 mL) was added to a stirring solution of SmI_2 in THF (0.1 M, 36 mL) and the resultant purple mixture cooled to – 78 °C, where upon the reaction turned dark green. Olefin **370** (200 mg, 0.861 mmol) as a solution in THF (5 mL) was then added drop-wise over a period of 10 minutes and the reaction allowed to stir at – 78 °C for a further 2 h. Brine (30 mL), followed by citric acid (217 mg, 1.03 mmol) was then added and allowed to stir for 10 minutes. EtOAc (50 mL) was added to the stirring solution and allowed to stir vigorously for 5 minutes, after which the reaction mixture was allowed to settle and the organic phase

decanted off. This process was then repeated (4 x 50 mL EtOAc). The aqueous phase was transferred to a separating funnel and further extracted with EtOAc (3 x 70 mL), before the combined organic extracts were washed with brine (2 x 30 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave the crude product as a yellow oil which upon purification by flash column chromatography, eluting with 5 % EtOAc / petrol gradually increasing the polarity to 30 % EtOAc / petrol, gave the dimer **383** (46.0 mg, 0.196 mmol, 23 %) as a yellow solid, R_f = 0.54 (60 % EtOAc / petrol) and dimer **384** (23.0 mg, 0.0982 mmol, 11 %) as a yellow oil, R_f = 0.43 (60 % EtOAc / petrol);

383 isolated as a 2:1 mixture of diastereoisomers. Only major diastereoisomer peaks reported in ^{1}H NMR for clarity. Both sets of diastereoisomer peaks reported in ^{13}C NMR where possible.

Mpt: 227 - 229 °C, recrystallised from EtOAc.

IR ν_{max} (film): 3323 (br), 2954 (m), 2930 (m), 2862 (m), 1582 (m), 1478 (m), 1437 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (1H, m, PhH), 7.36 - 7.30 (3H, m, 3 x PhH), 7.13 - 7.08 (4H, m, 4 x PhH), 6.99 - 6.95 (2H, m, 2 x PhH), 4.00 (1H, ddd, *J* = 11.9, 10.3, 5.0 Hz, CHOH), 3.82 (1H, br s, OH), 3.40 (1H, d, *J* = 2.8 Hz, CHSPh), 2.74 (2H, m, CHSPh, CH), 2.38 (1H, br s, OH), 2.29 (1H, m, CH), 1.98 - 1.87 (3H, m, 2 x CH_ACH_B, CH), 1.79 - 1.71 (3H, m, CH_2, CH_ACH_B), 1.36 (1H, m, CH_AH_B), 1.35 (3H, s, CH_3), 1.21 (3H, s, CH_3), 1.09 (3H, s, CH_3), 1.07 (3H, s, CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.9 (0, minor), 138.8 (0, major), 136.3 (0, major), [131.5, 130.3, 130.1, 129.5, 129.1, 126.8, 126.2] (1, major and minor), 81.6 (0, major), 66.5 (1, minor), 65.9 (1, major), 63.8 (1, minor), 60.7 (1, major), 59.5 (1, major), 54.7 (2, major), 52.2 (1, major), 46.8 (1, major), 46.3 (2, major), 46.0 (2, minor), 45.8 (1, major), 36.6 (major), 36.2 (major), 36.0 (3, minor), 35.6 (2, major), 34.7 (2, minor), 34.5 (3, major), 34.4 (3, major), 33.4 (3, minor), 31.9 (3, major), 27.4 (3, major), 24.6 (3, minor), 24.2 (3, minor) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 491 $[M + Na]^+$ (90 %), 960 $[2M + Na]^+$ (60 %).

HRMS (ES+): $[M + Na]^+$ $C_{28}H_{36}O_2S_2Na$ requires ^{m}/z 491.2049, found ^{m}/z 491.2051.

Data for dimer **384**:

Mpt: 198 - 200 °C, recrystallised from EtOAc.

IR ν_{max} (film): 3402 (br), 2927 (m), 1712 (s), 1580 (m), 1479 (s), 1438 (s), 1364 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 - 7.54 (2H, m, 2 x Ph**H**), 7.44 - 7.42 (2H, m, 2 x Ph**H**), 7.35 - 7.27 (4H, m, 4 x Ph**H**), 7.25 - 7.18 (2H, m, 2 x Ph**H**), 3.86 (1H, apparent dt, *J* = 5.7, 2.9 Hz, C**H**OH), 3.29 (1H, dddd, *J* = 17.2, 12.2, 4.5, 1.9 Hz, C**H**), 3.17 (1H, d, *J* = 12.1 Hz, C**H**SPh), 3.15 (1H, m, C**H**), 2.67 (1H, d, *J* = 11.9 Hz, C**H**SPh), 2.29 (1H, d, *J* = 13.8 Hz, CH_AH_B), 2.17 (1H, dd, *J* = 13.8, 2.4 Hz, $CH_A\mathbf{H_B}$), 1.83 (1H, t, *J* = 3.2 Hz, CH_AH_B), 1.73 (1H, m, CH_AH_B), 1.55 (1H, m, $CH_A\mathbf{H_B}$), 1.40 (3H, s, CH_3), 1.29 (1H, m, $CH_A\mathbf{H_B}$), 1.26 (3H, s, CH_3), 1.24 (1H, m, CH_AH_B), 1.22 (3H, s, CH_3), 1.17 (1H, m, $CH_A\mathbf{H_B}$), 1.00 (3H, s, CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.7 (0), 138.6 (0), 138.4 (0), 131.8 (2 x 1), 130.9 (2 x 1), 129.7 (2 x 1), 129.6 (2 x 1), 127.2 (1), 126.9 (1), 66.5 (1), 65.2 (1), 61.8 (1), 55.7 (2), 46.1 (2), 42.4 (1), 41.1 (2), 40.3 (0), 36.8 (0), 36.0 (1), 34.5 (2), 33.5 (3), 31.9 (3), 24.3 (3), 22.4 (3) ppm.

LRMS: (ES+): ^{m}/z (relative intensity), 491 $[M + Na]^+$ (40 %).

HRMS (ES+): $[M + Na]^+$ $C_{28}H_{36}O_2S_2Na$ requires ^{m}/z 491.2049, found ^{m}/z 491.2040.

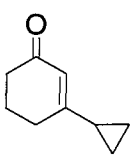
X-ray: Please see appendix.

Slow addition method:

On the same scale as above, addition of olefin **370** over 80 minutes gave the dimer **383** (45.0 mg, 0.192 mmol, 22 %) as a yellow oil, R_f = 0.54 (60 % EtOAc / petrol) and dimer **384** (20.0 mg, 0.0853 mmol, 10 %) as a yellow oil, R_f = 0.43 (60 % EtOAc / petrol);

Data for both **383** and **384** is consistent with the normal addition experiment above.

3-Cyclopropylcyclohex-2-en-1-one 392



392

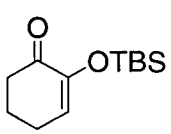
$C_9H_{12}O$

Mw: 136.19 $gmol^{-1}$

Following the reported procedure by Mattay,[137] to a stirring solution of magnesium turnings (849 mg, 34.9 mmol), THF (25 mL) and a single iodine crystal was added neat cyclopropyl bromide (1.70 mL, 20.6 mmol) dropwise so as to maintain a gentle reflux. The resultant turbid grey solution was warmed to 50 °C and stirred for 1 h, after which time it was then allowed to cool to RT. Previously prepared ketone **305** (2.00 g, 15.9 mmol) was then added as a solution in THF (10 mL) over a period of 5 minutes. After complete addition the reaction was heated to reflux and allowed to stir for 2 h before being cooled to 0 °C and 2M HCl aqueous solution (40 mL) added. The reaction was allowed to warm to RT and stir for a further 2 h. The layers were separated and the aqueous layer re-extracted with EtOAc (40 mL). The combined organic extracts were washed with water (30 mL), brine (30 mL) and finally dried over magnesium sulfate. Removal of the solvent *in vacuo* gave a the crude product as a yellow oil which was purified by flash column chromatography, eluting with 10 % EtOAc / petrol to give cyclopropyl enone **392** (1.66 g, 12.2 mmol, 77 %) as a pale yellow oil, R_f = 0.25 (40 % EtOAc / petrol);

IR ν_{max} (film): 3011 (w), 2946 (m), 2860 (w), 1654 (s), 1617 (s), 1603 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.84 (1H, s, C(O)C**H**=C), 2.34 (2H, t, *J* = 6.2 Hz, C(O)C**H$_2$**), 2.13 (2H, t, *J* = 6.4 Hz, C**H$_2$**C=CH), 1.95 (2H, qn, *J* = 6.1 Hz, $CH_2CH_2CH_2$), 1.54 (1H, tt, *J* = 8.2, 5.1 Hz, C**H** cyclopropyl), 0.94 - 0.88 (2H, m, C**H$_2$** cyclopropyl), 0.78 - 0.72 (2H, m, C**H$_2$** cyclopropyl) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.5 (0), 168.9 (0), 123.5 (1), 37.8 (2), 27.3 (2), 22.9 (2), 18.2 (1), 8.5 (2 x 2) ppm.
LRMS (ES+): ^{m}/z (relative intensity), 137 $[M + H]^+$ (60 %), 159 $[M + Na]^+$ (60 %).
HRMS (EI): $[M]^+$ $C_9H_{12}O$ requires ^{m}/z 136.08882, found ^{m}/z 136.08892.

2-[(*tert*-Butyldimethylsilyl)oxy]cyclohex-2-en-1-one 394



394
$C_{12}H_{22}O_2Si$
Mw: 226.39 $gmol^{-1}$

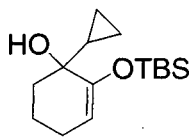
Following the reported procedure by Rodriguez,[155] to a stirring solution of 1, 2-cyclohexandione **393** (5.00 g, 44.6 mmol) and DCM (125 mL) was added

imidazole (6.07 g, 89.1 mmol) and TBDMSCl (7.70 g, 51.1 mmol). The resultant yellow solution was allowed to stir for 46 h at RT. At this point the reaction was quenched by the addition of brine (150 mL), and the two phases separated. The organic layer was dried over magnesium sulfate and the solvent removed under a reduced pressure to give a pale yellow oil. Purification by flash column chromatography, eluting with 1 % EtOAc / petrol increasing the polarity to 2 % EtOAc/ petrol, gave the product **394** as a pale yellow oil (8.40 g, 37.1 mmol, 83 %), R_f = 0.38 (10 % EtOAc / petrol);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.15 (1H, t, *J* = 4.8 Hz, TBSOC=C**H**), 2.46 (2H, t, *J* = 6.6 Hz, C(O)C$\mathbf{H_2}$), 2.37 (2H, q, *J* = 6.0 Hz, CH_2CH_2CH), 1.96 (2H, qn, *J* = 6.3 Hz, $CH_2CH_2CH_2$), 0.93 (9H, s, C(CH_3)$_3$), 0.13 (6H, s, 2 x CH_3) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.9 (0), 148.5 (0), 127.9 (1), 39.1 (2), 26.0 (3 x 3), 25.2 (2), 23.5 (2), 18.8 (0), -4.3 (2 x 3) ppm.

Data is consistent with that reported by Rodriguez.[155]

2-[(*tert*-Butyldimethylsilyl)oxy]-1-cyclopropylcyclohex-2-en-1-ol 395



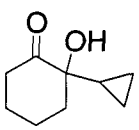
395
$C_{15}H_{28}O_2Si$
Mw: 268.47 gmol^{-1}

Following the reported procedure by Coombs,[154] to a mixture of Mg turnings (1.20 g, 48.7 mmol), THF (25 mL) and an iodine crystal, was added bromocyclopropane (2.30 mL, 28.8 mmol) at such a rate so as to maintain a gentle reflux of the reaction mixture. After complete addition the pale brown solution was stirred at 50 °C for 1 h, before being cooled to RT and the silyl protected ketone **394** (5.00 g, 22.1 mmol) as a solution in THF (10 mL) added dropwise over 5 minutes. The reaction was left to stir for 90 minutes at RT and was then heated, and stirred at reflux for a further 2 h. The reaction was cooled to 0 °C and saturated NH_4Cl aqueous solution (50 mL) added before the phases were separated and the remaining aqueous layer re-extracted with EtOAc (3 x 40 mL). The combined organic extracts were washed with brine (40 mL) and dried over magnesium sulfate, before the solvent was removed *in vacuo* to leave a yellow oil, which upon purification by flash column chromatography, eluting with 0.5

% EtOAc / petrol increasing the polarity to 1 % EtOAc / petrol, gave the cyclopropanated product **395** (4.56 g, 16.9 mmol, 77 %) as a colourless oil, R_f = 0.45 (10 % EtOAc / petrol);

IR ν_{max} (film): 3486 (br), 2930 (m), 2857 (m), 1661 (w), 1472 (w) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.79 (1H, t, *J* = 4.0 Hz, TBSOC=C**H**), 2.11 (1H, m, CH_AH_B), 2.05 (1H, m, CH_AH_B), 1.78 - 1.67 (4H, m, 2 x CH_2), 0.94 (9H, s, $C(CH_3)_3$), 0.55 - 0.42 (2H, m, CH_2), 0.38 - 0.22 (3H, m, C**H** + CH_2), 0.19 (3H, s, CH_3), 0.18 (3H, s, CH_3) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.9 (0), 103.4 (1), 70.8 (0), 36.7 (2), 26.2 (3 x 3), 24.7 (2), 20.1 (1), 19.9 (2), 18.5 (0), 2.7 (2), -0.4 (2), -4.1 (3), -4.1 (3) ppm.
LRMS (ES+): ^{m}/z (relative intensity), 291 $[M + Na]^+$ (100 %).
HRMS (ES+): $[M + Na]^+$ $C_{15}H_{28}O_2SiNa$ requires ^{m}/z 291.1751, found ^{m}/z 291.1749.

2-Cyclopropyl-2-hydroxycyclohexanone 396



396
$C_9H_{14}O_2$
Mw: 154.21 $gmol^{-1}$

Following the reported procedure by Rodriguez,[155] to a solution of cyclopropyl silyl protected ketone **395** (4.50 g, 16.8 mmol) dissolved in THF (80 mL) at RT was added TBAF (1 M in THF, 20 mL, 20.1 mmol) in one portion. The resultant solution was allowed to stir for 8 h at RT, before the reaction was then poured into brine (40 mL) and the phases separated. The remaining aqueous layer was extracted with EtOAc (50 mL) and the combined organic extracts dried over magnesium sulfate before removal of the solvent under a reduced pressure gave a brown oil. Purification by flash column chromatography, eluting with 5 % EtOAc / petrol gave the product **396** (1.91 g, 12.4 mmol, 74 %) as a pale yellow oil, R_f = 0.41 (20 % EtOAc / petrol);

IR ν_{max} (film): 3475 (br), 2938 (m), 2859 (m), 2361 (w), 1708 (s), 1445 (m) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.55 (1H, br s, O**H**), 2.74 (1H, td, *J* = 14.1, 6.3 Hz, CH_AH_B), 2.51 (1H, dqn, *J* = 14.0, 2.0 Hz, CH_AH_B), 2.27 (1H, apparent dq, *J* = 13.0, 3.0 Hz, CH_AH_B), 2.14 (1H, m, CH_AH_B), 1.94 - 1.80 (2H, m, CH_2), 1.72 - 1.60 (2H, m,

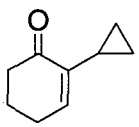
CH_2), 1.28 (1H, m, CH_AH_B), 0.60 (1H, m, CH_AH_B), 0.41 - 0.26 (3H, m, CH_2, CH cyclopropyl) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 214.3 (0), 75.9 (0), 41.2 (2), 38.0 (2), 28.0 (2), 22.8 (2), 16.3 (1), 0.6 (2), 0.1 (2) ppm.

LRMS (EI): ^{m}/z (relative intensity), 154 $[M]^+$ (50 %).

HRMS (EI): $[M]^+$ $C_9H_{14}O_2$ requires ^{m}/z 154.09938, found ^{m}/z 154.09996.

2-Cyclopropylcyclohex-2-en-1-one 397



397

$C_9H_{12}O$

Mw: 136.19 gmol^{-1}

Following the reported procedure by Pattenden,[156] cyclopropyl alcohol **396** (1.00 g, 6.48 mmol), benzene (80 mL) and *p*-toluenesulfonic acid monohydrate (185 mg, 0.970 mmol) were combine and reluxed using a Dean and Stark apparatus for 4 days. The reaction was allowed to cool to RT and the reaction poured into saturated $NaHCO_3$ aqueous solution (50 mL). The layers were separated and the organic layer washed with brine (40 mL) and dried over magnesium sulfate, before removal of the solvent *in vacuo* gave the crude product as a brown oil. Purification by flash column chromatography, eluting with neat petrol increasing the polarity to 5 % EtOAc / petrol gave the desired alkene **397** (420 mg, 3.08 mmol, 48 %) as a pale yellow oil, R_f = 0.35 (20 % EtOAc / petrol);

IR ν_{max} (film): 3002 (w), 2939 (m), 2869 (w), 1654 (s), 1617 (s), 1603 (s), 1454 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.42 (1H, t, *J* = 4.2 Hz, C(O)C=CH), 2.41 (2H, t, *J* = 6.9 Hz, C(O)CH_2), 2.34 - 2.28 (2H, m, C=CHCH_2), 1.94 (2H, qn, *J* = 6.6 Hz, $CH_2CH_2CH_2$), 1.83 - 1.65 (1H, m, CH cyclopropyl), 0.72 (2H, dq, *J* = 6.6, 4.2 Hz, CH_2 cyclopropyl), 0.39 - 0.34 (2H, m, CH_2 cyclopropyl) ppm.

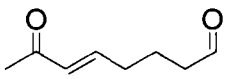
^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.8 (0), 141.2 (1), 39.0 (2), 26.1 (2), 23.3 (2), 9.8 (1), 6.6 (2 x 2) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 137 $[M + H]^+$ (100 %).

HRMS (EI): $[M]^+$ $C_9H_{12}O$ requires ^{m}/z 136.08882, found ^{m}/z 136.08747.

4.4 Experimental For Chapter Three

(5*E*)-7-Oxooct-5-enal 405



405

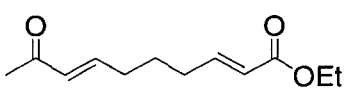
$C_8H_{12}O_2$
Mw: 140.18 $gmol^{-1}$

Following the reported procedures by Enholm[44] and Richards,[179] to a two necked RB flask were added glutaraldehyde **404** (50 % in water, 60 mL, 0.330 mol) and DCM (50 mL). 1-(Triphenylphosphoranylidene) acetone **325** (15.0 g, 47.1 mmol) as a solution in DCM (100 mL) was then added to the aldehyde solution *via* dropping funnel over a period of 4 h. After complete addition the reaction was allowed to stir at RT overnight, before being transferred to a separating funnel and the two phases separated. The organic layer was washed with 0.2M HCl aqueous solution (5 x 150 mL) and brine (100 mL) then finally dried over magnesium sulfate. Removal of the solvent *in vacuo* gave a white solid which was purified by flash column chromatography, eluting with 2 % EtOAc / petrol gradually increasing the polarity to 20 % EtOAc / petrol , to give aldehyde **405** (3.60 g, 25.7 mmol, 55 %) as a colourless oil, R_f = 0.32 (50 % EtOAc / petrol);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.76 (1H, m, C**H**O), 6.75 (1H, dt, *J* = 15.8, 6.8 Hz, C(O)CH=C**H**), 6.08 (1H, dt, *J* = 15.8, 1.2 Hz, C(O)C**H**=CH), 2.53 - 2.46 (2H, m, **CH_2**), 2.28 - 2.23 (5H, m, **CH_3**, **CH_2**), 1.80 (2H, qn, *J* = 7.3 Hz, CH_2**CH_2**CH_2) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.8 (1), 198.7 (0), 146.9 (1), 132.2 (1), 43.3 (2), 31.8 (2), 27.3 (3), 20.6 (2) ppm.

Data is consistent with that reported by Enholm.[44]

Ethyl (2*E*, 7*E*)-9-oxodeca-2,7-dienoate 406



406

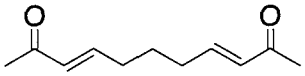
$C_{12}H_{18}O_3$
Mw: 210.27 $gmol^{-1}$

Following the reported procedure by Enholm,[44] to a solution of aldehyde **405** (1.09 g, 7.80 mmol) in DCM (30 mL) was added (carbethoxymethylene)triphenylphosphorane **322** (2.72 g, 7.80 mmol) as a solution in DCM (10 mL). The pale yellow reaction was allowed to stir at RT for 70 h. Removal of the solvent *in vacuo* gave a white residue, which upon purification by flash column chromatography, eluting with 10 % EtOAc / petrol increasing the polarity to 20 % EtOAc / petrol, gave keto-ester **406** (1.21 g, 5.75 mmol, 73 %) as a colourless oil, $R_f = 0.53$ (50 % EtOAc / petrol);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (1H, dt, *J* = 16.0, 7.0 Hz, C(O)CH=C**H**), 6.75 (1H, dt, *J* = 16.0, 7.0 Hz, C(O)CH=C**H**), 6.08 (1H, dt, *J* = 16.1, 1.5 Hz, C(O)C**H**=CH), 5.83 (1H, dt, *J* = 15.6, 1.5 Hz, C(O)C**H**=CH), 4.18 (2H, q, *J* = 7.3 Hz, O**CH$_2$**), 2.22 (7H, m, 2 x **CH$_2$**, **CH$_3$**), 1.64 (2H, qn, *J* = 8.1 Hz, CH_2**CH$_2$**CH_2), 1.27 (3H, t, *J* = 7.3 Hz, OCH_2**CH$_3$**) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.7 (0), 166.8 (0), 148.2 (1), 147.4 (1), 132.0 (1), 122.4 (1), 60.6 (2), 32.0 (2), 31.8 (2), 27.3 (3), 26.7 (2), 14.6 (3) ppm.

Data is consistent with that reported by Pandey.[157]

(3*E*, 8*E*)-Undeca-3,8-diene-2, 10-dione 407



407

$C_{11}H_{16}O_2$
Mw: 180.24 $gmol^{-1}$

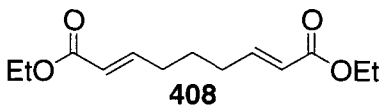
Glutaraldehyde **404** (5.42 mL, 29.9 mmol) was dissolved in $CHCl_3$ (40 mL) and previously prepared 1-(triphenylphosphoranylidene)acetone **325** (20.0 g, 62.8 mmol) added in one portion. The reaction was allowed to stir at RT for 48 h before the solvent was removed under a reduced pressure to leave the crude residue. A short filtration through a pad of silica to remove the majority of triphenylphosphine oxide, followed by purification by flash column chromatography, eluting with 10 % EtOAc / petrol increasing the polarity to 20 % EtOAc / petrol, gave the di-ketone **407** (5.13 g, 28.5 mmol, 95 %) as a colourless oil, $R_f = 0.23$ (40 % EtOAc / petrol);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.75 (2H, dt, *J* = 15.9, 6.8 Hz, 2 x C(O)CH=C**H**), 6.06 (2H, dt, *J* = 15.9, 1.3 Hz, 2 x C(O)C**H**=CH), 2.29 - 2.01 (10H, m, 2 x **CH$_2$** + 2 x **CH$_3$**), 1.65 (2H, qn, *J* = 2.0 Hz, CH_2**CH$_2$**CH_2) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.6 (0), 147.1 (1), 132.1 (1), 32.0 (2), 27.3 (3), 26.7 (2) ppm.

Data is consistent with that reported by Enholm.[44]

Diethyl (2*E*, 7*E*)-nona-2, 7-dienedioate 408



408

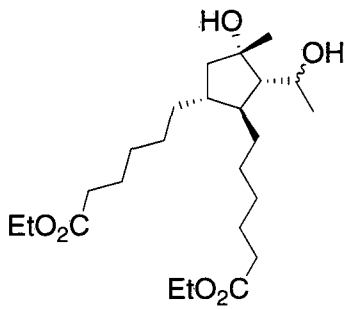
$C_{13}H_{20}O_4$
Mw: 240.3 $gmol^{-1}$

Glutaraldehyde **404** (1.50 mL, 8.29 mmol), (carbethoxymethylene)triphenyl phosphorane **322** (6.35 g, 18.2 mmol) and $CHCl_3$ (20 mL) were combined and allowed to stir at RT for 16 h. At this point the solvent was removed *in vacuo* to leave the crude residue, which was filtered through a short pad of silica to remove the majority of the triphenylphosphine oxide. Purification of the remaining material by flash column chromatography, eluting with 5% EtOAc / petrol increasing the polarity to 10 % EtOAc / petrol gave the di-ester **408** (1.98 g, 8.24 mmol, 99 %) as a colourless oil, R_f = 0.58 (40 % EtOAc / petrol);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.92 (2H, dt, *J* = 15.5, 7.1 Hz, 2 x C(O)CH=C**H**), 5.81 (2H, dt, *J* = 15.7, 1.5 Hz, 2 x C(O)C**H**=CH), 4.17 (4H, q, *J* = 7.1 Hz, 2 x O**CH$_2$**), 2.23 (4H, q, *J* = 7.3 Hz, 2 x **CH$_2$**), 1.63 (2H, qn, *J* = 7.3 Hz, CH_2**CH$_2$**CH_2), 1.28 (6H, t, *J* = 7.1 Hz, 2 x OCH_2**CH$_3$**) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8 (0), 148.3 (1), 122.4 (1), 60.5 (2), 31.7 (2), 27.0 (2), 14.6 (3) ppm.

Data is consistent with that reported by Davies.[158]

Ethyl 6-[2-(6-ethoxy-6-oxohexyl)-4-hydroxy-3-(1-hydroxyethyl)-4-methylcyclopentyl] hexanoate 409a and 409b



409a
409b
$C_{24}H_{44}O_6$
Mw: 428.6 $gmol^{-1}$

Following the reported procedure by Kilburn,[122] MeOH (19 mL) was added to a stirring solution of SmI_2 in THF (0.1 M, 76 mL) and the resultant purple mixture cooled to – 78 °C, where upon the colour changed to a dark green. Keto-ester **406** (400 mg, 1.90 mmol) as a solution in THF (5 mL) was then added drop-wise over a period of 10 minutes and the reaction was allowed to stir at – 78 °C for a further 1 h 45 minutes. Brine (40 mL), followed by citric acid (479 mg, 2.28 mmol) was then added and allowed to stir for 1 hour. EtOAc (70 mL) was added to the stirring solution and allowed to stir vigorously for 10 minutes, after which the reaction mixture was allowed to settle and the organic phase decanted off. This process was then repeated (4 x 70 mL EtOAc). The aqueous phase was transferred to a separating funnel and further extracted with EtOAc (2 x 80 mL), before the combined organic extracts were washed with brine (2 x 60 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave a yellow oil which was purified by flash column chromatography, eluting with 5 % EtOAc / petrol increasing the polarity to 40 % EtOAc / petrol to give diester **409a** (95.0 mg, 0.443 mmol, 23 %), $R_f = 0.26$ (40 % EtOAc / petrol) and **409b** (135 mg, 0.630 mmol 33 %), $R_f = 0.13$ (40 % EtOAc / petrol) as yellow oils;

Data for diester **409a**:

IR ν_{max} (film): 3442 (br), 2931 (s), 2857 (m), 1732 (s), 1462 (m), 1418 (m) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.21 (1H, m, **CH**OH), 4.12 (4H, q, J = 7.0 Hz, 2 x OCH_2CH_3), 2.58 (2H, br s, 2 x **OH**), 2.27 (4H, t, J = 7.6 Hz, 2 x C(O)CH_2), 1.90 - 1.80 (2H, m, **CH**, CH_AH_B), 1.61 - 1.52 (4H, m, 2 x CH_2), 1.51 - 1.39 (4H, m, CH_2, **CH**, CH_AH_B), 1.35 - 1.15 (23H, m, 5 x CH_2, **CH**, 4 x CH_3) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.1 (2 x 0), 82.0 (0), 67.0 (1), 60.5 (2 x 2), 58.8 (1), 48.0 (2), 43.6 (1), 42.5 (1), 36.7 (2), 36.3 (2), 34.7 (2 x 2), 30.0 (2), 29.9 (3), 29.7 (2), 28.6 (2), 27.2 (2), 25.3 (2 x 2), 22.1 (3), 14.6 (2 x 3) ppm.
LRMS (ES+): ^{m}/z (relative intensity), 451 $[M + Na]^+$ (100 %).
HRMS (ES+): $[M + Na]^+$ $C_{24}H_{44}O_6Na$ requires ^{m}/z 451.3030, found ^{m}/z 451.3025.

Data for diester **409b**:

IR ν_{max} (film): 3428 (br), 2931 (s), 2857 (m), 1732 (s), 1462 (m), 1418 (m) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.12 (4H, q, *J* = 7.0 Hz, 2 x OCH_2CH_3), 3.84 (1H, dq, *J* = 9.1, 6.2 Hz, CHOH), 2.27 (4H, t, *J* = 7.5 Hz, 2 x $C(O)CH_2$), 1.85 (1H, m, CH), 1.76 (1H, dd, *J* = 11.8, 6.2 Hz, CH_AH_B), 1.65 - 1.51 (5H, m, 2 x CH_2 and CH), 1.49 - 1.40 (2H, m, CH_AH_B, CH), 1.35 - 1.20 (18H, m, 6 x CH_2, 2 x CH_3), 1.25 (6H, t, *J* = 7.1 Hz, OCH_2CH_3) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2 (0), 174.1 (0), 79.1 (0), 70.4 (1), 61.4 (1), 60.5 (2 x 2), 47.5 (2), 41.4 (1), 38.9 (1), 34.7 (2 x 2), 31.5 (2), 30.7 (2), 30.0 (2), 29.8 (2), 29.2 (2), 28.8 (2), 25.3 (2), 25.3 (2), 24.5 (3), 23.9 (3), 14.6 (2 x 3) ppm.
LRMS (ES+): ^{m}/z (relative intensity), 451 $[M + Na]^+$ (100 %).
HRMS (ES+): $[M + Na]^+$ $C_{24}H_{44}O_6Na$ requires ^{m}/z 451.3030, found ^{m}/z 451.3022.

Slow addition method:

Addition of Keto-ester **406** (300 mg, 1.43 mmol) as a solution in THF (6 mL) over 80 minutes gave diester **409a** (40.0 mg, 0.187 mmol, 13 %), R_f = 0.26 (40 % EtOAc / petrol) and **409b** (90.0 mg, 0.419 mmol 30 %), R_f = 0.13 (40 % EtOAc / petrol) as yellow oils;

409a isolated as a 3:1 mixture of diastereoisomers. Only major diastereoisomer peaks reported in ^{1}H NMR for clarity. Both sets of diastereoisomer peaks reported in ^{13}C NMR where possible.

IR ν_{max} (film): 3442 (br), 2931 (s), 2857 (m), 1732 (s), 1462 (m), 1418 (m) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.21 (1H, m, CHOH), 4.12 (4H, q, *J* = 7.0 Hz, 2 x OCH_2CH_3), 2.58 (2H, br s, 2 x OH), 2.27 (4H, t, *J* = 7.6 Hz, 2 x $C(O)CH_2$), 1.90 - 1.80 (2H, m, CH, CH_AH_B), 1.61 - 1.52 (4H, m, 2 x CH_2), 1.51 - 1.39 (4H, m, CH_2, CH, CH_AH_B), 1.35 - 1.15 (23H, m, 5 x CH_2, CH, 4 x CH_3) ppm.

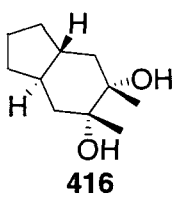
^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2 (2 x 0, minor), 174.1 (2 x 0, major), 81.8 (0, major), 81.1 (0, minor), 70.3 (1, minor), 67.0 (1, major), 60.5 (2 x 2, minor and major), 59.7 (1, minor), 58.8 (1, major), 48.5 (2, minor), 47.9 (1, minor), 47.9 (2, major), 43.6 (1, major), 42.5 (1, major), 42.1 (1, minor), 36.7 (2, major), 36.3 (2, major), 35.8 (2, minor), 34.6 (2 x 2, minor and major), 32.2 (3, minor), 30.0 (2, major), 29.8 (3, major), 29.7 (2, major), 28.5 (2, major), 28.4 (2, minor), 27.2 (2, major), 25.3 (2 x 2, minor and major), 22.6 (3, minor), 22.0 (3, major), 14.5 (2 x 3, minor and major) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 451 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{24}H_{44}O_6Na$ requires ^{m}/z 451.3030, found ^{m}/z 451.3025.

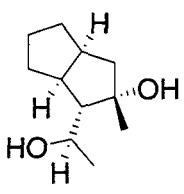
Data for diester **409b** is consistent with the normal addition method above.

***rac* - (3a*S*, 5*R*, 6*S*, 7a*S*)-5,6-Dimethyloctahydro-1*H*-indene-5,6-diol 416, *rac* - (1*S*, 2*S*, 3a*S*, 6a*S*)-1-[(1*R*)-1-Hydroxyethyl]-2-methyloctahydropentalen-2-ol 417 and *rac* - (1*R*, 2*S*, 3a*R*, 6a*R*)-1-[(1*S*)-1-Hydroxyethyl]-2-methyloctahydropentalen-2-ol 418**



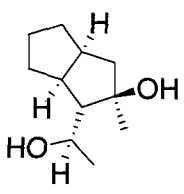
416

$C_{11}H_{20}O_2$
Mw: 184.28 $gmol^{-1}$



417

$C_{11}H_{20}O_2$
Mw: 184.28 $gmol^{-1}$



418

$C_{11}H_{20}O_2$
Mw: 184.28 $gmol^{-1}$

Following the reported procedure by Kilburn,[122] MeOH (19 mL) was added to a stirring solution of SmI_2 in THF (0.1 M, 78 mL) and the resultant purple mixture cooled to – 78 °C, where upon the reaction turned dark green. Di-ketone **407** (350 mg, 1.94 mmol) as a solution in THF (5 mL) was then added drop-wise over a period of 10 minutes, after which the reaction was allowed to stir at – 78 °C for a further 2 h. Brine (40 mL), followed by citric acid (489 mg, 2.33 mmol) was then added and allowed to stir for 20 minutes. EtOAc (80 mL) was added to the stirring solution and allowed to stir vigorously for 10 minutes, after which the reaction mixture was allowed to settle and the organic phase decanted off. This process was then repeated five times (5 x 80 mL EtOAc). The aqueous phase was transferred to a separating funnel andwas further extracted with EtOAc (80 mL), before the combined organic extracts were

washed with brine (2 x 50 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave the crude products as a yellow oil which upon purification by flash column chromatography, eluting with 10 % EtOAc / petrol gradually increasing the polarity to 20 % EtOAc / petrol gave diol **416** (190 mg, 1.03 mmol, 53 %) as a white crystalline solid, R_f = 0.36 (40 % EtOAc / petrol), diol **417** (43 mg, 0.233 mmol, 12 %) as a pale yellow solid, R_f = 0.22 (40 % EtOAc / petrol) and diol **418** (21 mg, 0.113 mmol, 6 %) as a yellow solid, R_f = 0.17 (40 % EtOAc / petrol);

Data for diol **416**:

Mpt: 42 - 44 °C, recrystallised from EtOAc / petrol.
IR ν_{max} (solid): 3279 (br), 2650 (s), 2926 (s), 2860 (m), 1449 (m) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.10 (2H, br s, 2 x **OH**), 1.88 (1H, dd, *J* = 13.8, 3.8 Hz, CH_AH_B), 1.72 - 1.54 (6H, m, 3 x CH_2), 1.27 - 1.23 (2H, m, **CH** and $CH_A\mathbf{H_B}$), 1.21 (3H, s, CH_3), 1.19 (3H, s, CH_3), 1.17 - 1.03 (3H, m, **CH**, CH_2) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 75.6 (0), 75.1 (0), 44.3 (1), 43.1 (2), 41.6 (1), 41.4 (2), 30.8 (2), 30.3 (2), 24.9 (3), 24.4 (3), 22.9 (2) ppm.
LRMS (ES+): ^{m}/z (relative intensity), 207 $[M + Na]^+$ (60 %).
HRMS (ES+): $[M + Na]^+$ $C_{11}H_{20}O_2Na$ requires ^{m}/z 207.1356, found ^{m}/z 207.1355.
Microanalysis: $C_{11}H_{20}O_2$ requires C, 71.70; H, 10.94. Found C, 72.34; H, 11.14 %.
X-ray: Please see appendix.

Data for diol **417**:

Mpt: 111 - 113 °C, recrystallised from EtOAc / petrol.
IR ν_{max} (solid): 3279 (br), 2950 (s), 2926 (s), 2860 (m), 1446 (m) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.99 (1H, qn, *J* = 6.6 Hz, **CH**OH), 2.64 (1H, m, **CH**), 2.35 (1H, qd, *J* = 8.5, 3.2 Hz, **CH**), 2.15 (2H, br s, 2 x **OH**), 1.87 (2H, dd, *J* = 13.6, 8.3 Hz, CH_2), 1.60 - 1.53 (4H, m, 2 x CH_2), 1.45 (3H, s, CH_3), 1.32 (3H, d, *J* = 6.3 Hz, $CHCH_3$), 1.25 - 1.20 (3H, m, **CH** and CH_2) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 84.1 (0), 70.6 (1), 62.0 (1), 50.7 (2), 47.7 (1), 41.0 (1), 34.0 (2), 33.1 (2), 29.1 (3), 25.6 (2), 24.0 (3) ppm.
LRMS (EI): ^{m}/z (relative intensity), 166 $[M - H_2O]^+$ (14 %).
HRMS (EI): $[C_{11}H_{18}O]^+$ $C_{11}H_{18}O$ requires ^{m}/z 166.13577, found ^{m}/z 166.13559.
Microanalysis: $C_{11}H_{20}O_2$ requires C, 71.70; H, 10.94. Found C, 71.07; H, 10.91 %.

X-ray: Please see appendix.

Data for diol **418**:

Mpt: 93 - 95 °C, recrystallised from EtOAc / petrol.

IR ν_{max} (solid): 3364 (br), 2937 (s), 2861 (s), 2359 (m), 1446 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88 (1H, qn, *J* = 6.6 Hz, **CH**OH) 2.37 - 2.26 (2H, m, 2 x **CH**) 1.88 (1H, dd, *J* =12.0, 8.3 Hz, CH_AH_B) 1.63 - 1.51 (4H, m, 2 x CH_2) 1.43 - 1.35 (4H, m, CH_AH_B, **CH**, CH_2) 1.32 (3 H, d, *J* = 6.3 Hz, CH_3CH) 1.20 (3 H, s, CH_3) ppm.

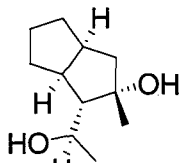
^{13}C NMR (100 MHz, $CDCl_3$): δ = 80.8 (0), 69.6 (1), 62.4 (1), 50.4 (2), 44.3 (1), 39.1 (1), 34.8 (2), 33.3 (2), 25.8 (2), 23.5 (3), 23.3 (3) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 207 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{11}H_{20}O_2Na$ requires ^{m}/z 207.1356, found ^{m}/z 207.1355.

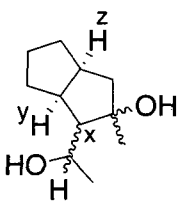
X-ray: Please see appendix.

***rac* - (1*S*, 2*S*, 3a*S*, 6a*S*)-1-[(1*R*)-1-Hydroxyethyl]-2-methyloctahydropentalen-2-ol 417, *rac* - 1-(1-hydroxyethyl)-2-methyloctahydropentalen-2-ols 433a + 433b and *rac* - 1, 1'-(1*S*, 2*S*)-cyclopentane-1, 2-diyldipropan-2-ol 434**



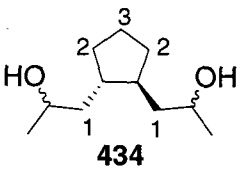
417

$C_{11}H_{20}O_2$
Mw: 184.28 $gmol^{-1}$



433a
433b

$C_{11}H_{20}O_2$
Mw: 184.28 $gmol^{-1}$



434

$C_{11}H_{22}O_2$
Mw: 186.29 $gmol^{-1}$

Following the reported procedure by Molander,[62] HMPA (3.30 mL, 19.2 mmol) was added in one portion to a stirring solution of SmI_2 (0.1 M, 84 mL). The resultant deep purple solution was cooled to – 78 °C where upon the colour remained deep purple. Di-ketone **407** (350 mg, 1.94 mmol) as a solution in THF (6 mL) was added drop-wise over 10 minutes and the reaction allowed to stir at – 78 °C for a further 2 h. 1M HCl aqueous solution (30 mL) was added to the reaction mixture and allowed to stir for 10 minutes to dissolve the inorganic salts. A 50:50 mixture of EtOAc and ether (60 mL) was then added and the reaction allowed to stir vigorously for 5 minutes, after which the phases were allowed to settle and the organic layer decanted off. This process

was then repeated a further three times (3 x 60 mL, 50:50 EtOAc / Et_2O). The remaining aqueous residue was transferred to a separating funnel and further extracted with a 50:50 mixture of EtOAc and ether (60 mL). The combined organic extracts were washed with water (2 x 50 mL) and brine (2 x 60 mL) before being dried over magnesium sulfate. Removal of the solvent *in vacuo* gave the crude products as an orange oil. Purification by flash column chromatography, eluting with 10 % EtOAc / petrol gradually increasing the polarity to 50 % EtOAc / petrol gave diol **417** (16.0 mg, 0.0868 mmol, 5 %) as a white solid, $R_f = 0.29$ (50 % EtOAc / petrol), diol **433a** (31.0 mg, 0.168 mmol, 9 %) as a yellow oil, $R_f = 0.42$ (50 % EtOAc / petrol), diol **433b** (16.0 mg, 0.0868 mmol, 5 %) as a yellow oil, $R_f = 0.37$ (50 % EtOAc / petrol) , and diol **434** (68.0 mg, 0.365 mmol, 20 %) as a yellow oil, $R_f = 0.24$ (50 % EtOAc / petrol);

Data for diol **417** - as reported above.

Data for diol **433a**:

IR ν_{max} (film): 3333 (br), 2944 (m), 2862 (m), 1452 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.29 (1H, qd, *J* = 6.6, 1.5 Hz, C**H**OH), 2.84 (1H, qd, *J* = 9.0, 3.2 Hz, C$\mathbf{H}^y$), 2.66 (1H, m, C$\mathbf{H}^z$), 2.15 (2H, br s, 2 x O**H**), 1.84 (1H, dd, *J* = 13.3, 8.0 Hz, C$\mathbf{H}_A$H$_B$), 1.76 - 1.47 (4H, m, 2 x C$\mathbf{H}_2$), 1.38 - 1.33 (2H, m, C$\mathbf{H}_2$), 1.31 (3H, s, C$\mathbf{H}_3$), 1.20 (3H, d, *J* = 6.5 Hz, CH(OH)C$\mathbf{H}_3$), 1.18 - 1.14 (2H, m, CH$_A$C$\mathbf{H}_B$ and C$\mathbf{H}^x$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 85.1 (0), 66.1 (1), 60.1 (1), 49.6 (2), 41.3 (1), 40.6 (1), 35.1 (2), 32.9 (2), 26.2 (3), 26.1 (2), 22.9 (3) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 207 $[M + Na]^+$ (40 %).

HRMS (ES+): $[M + Na]^+$ $C_{11}H_{20}O_2Na$ requires ^{m}/z 207.1356, found ^{m}/z 207.1355.

Data for diol **433b**:

IR ν_{max} (film): 3360 (br), 2943 (m), 2863 (w), 2374 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (1H, qd, *J* = 6.2, 2.5 Hz, C**H**OH), 2.85 (1H, br s, O**H**), 2.67 (1H, br s, O**H**), 2.33 (1H, m, C$\mathbf{H}^y$), 1.88 (2H, dd, *J* = 11.8, 8.0 Hz, CH$_A$CH$_B$ and C$\mathbf{H}^z$), 1.67 - 1.52 (4H, m, 2 x CH$_A$CH$_B$ and C$\mathbf{H}_2$), 1.42 - 1.35 (4H, m, 3 x CH$_A$C$\mathbf{H}_B$ and C$\mathbf{H}^x$), 1.27 (3H, s, C$\mathbf{H}_3$), 1.23 (3H, d, *J* = 6.0 Hz, CH(OH)C$\mathbf{H}_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 81.6 (0), 71.0 (1), 61.8 (1), 48.4 (2), 43.8 (1), 39.6 (1), 33.9 (2), 33.3 (2), 25.6 (2), 23.6 (3), 22.9 (3) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 207 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{11}H_{20}O_2Na$ requires $^m/z$ 207.1356, found $^m/z$ 207.1355.

Data for diol **434** - isolated as an inseparable mixture of diastereoisomers:

IR ν_{max} (film): 3356 (br), 2961 (m), 2929 (m), 2863 (m), 1373 (m) cm^{-1}.

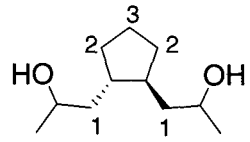
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.92 - 3.80 (2H, m, 2 x **CH**OH), 2.07 (2H, br s, 2 x **OH**), 1.93 - 1.78 (2H, m, 2 x $CH_ACH_B^2$), 1.66 - 1.51 (6H, m, 2 x **CH**, CH_2^3 and 2 x $CH_ACH_B^1$), 1.27 - 1.23 (4H, m, 2 x $CH_ACH_B^1$ and 2 x $CH_ACH_B^2$), 1.21 - 1.17 (6H, m, 2 x CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = [68.0, 67.7, 67.6, 67.5] (1), [45.3, 45.2, 45.1] (2), [43.2, 43.1, 42.7, 42.5] (1), [32.9, 32.8, 32.7] (2), [25.0, 24.9] (3), [24.3, 24.2, 24.1] (2), [23.9, 23.8] (3) ppm.

LRMS (ES+): $^m/z$ (relative intensity), 209 $[M + Na]^+$ (60 %).

HRMS (ES+): $[M + Na]^+$ $C_{11}H_{22}O_2Na$ requires $^m/z$ 209.1512, found $^m/z$ 209.1512.

1, 1'-Cyclopentane-1, 2-diyldipropan-2-ol 434



$C_{11}H_{22}O_2$
Mw: 186.29 $gmol^{-1}$

Following the reported procedure by Dahlen,[101] oxygen free Et_3N (2.20 mL, 15.5 mmol) and H_2O (0.400 mL, 23.3 mmol) were added to a stirring solution of SmI_2 (0.1 M, 78 mL). The colour of the reaction changed from dark blue to dark purple / black. The reaction was cooled to – 78 °C and di-ketone **407** (350 mg, 1.94 mmol) was added as a solution in THF (5 mL) over a period of 10 minutes. Once addition was complete the reaction was stirred for 2 h at – 78 °C, and it was noted that during this time the reaction turned grey with a white precipitate. 1M HCl aqueous solution (30 mL) was added to the reaction mixture and allowed to stir for 20 minutes to dissolve the inorganic salts. A 50:50 mixture of EtOAc and ether (60 mL) was then added and the reaction stirred vigorously for 5 minutes, after which time the phases allowed to settle and the organic layer decanted off. This process was then repeated a further three times (3 x 60 mL, 50:50 EtOAc / Et_2O). The remaining aqueous residue was transferred to a separating funnel and was further extracted using a 50:50 mixture of EtOAc and ether (80 mL). The combined organic extracts were washed with water (2 x 50 mL) then brine (2 x

60 mL) before being dried over magnesium sulfate. Removal of the solvent *in vacuo* gave a yellow oil / solid. Purification by flash column chromatography, eluting with 10 % EtOAc / petrol gradually increasing the polarity to 55 % EtOAc / petrol gave the diastereomeric mixture of diol **434** (48.0 mg, 0.258 mmol, 13 %) as a pale yellow oil, $R_f = 0.14$ (50 % EtOAc / petrol);

Data for diol **434** - isolated as an inseparable mixture of diastereoisomers:

Mpt: 98 - 100 °C, recrystallised from EtOAc.

IR ν_{max} (solid): 3305 (br), 2958 (s), 2916 (s), 2859 (s), 1454 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.90 - 3.79 (2H, m, 2 x CHOH), 1.92 - 1.77 (2H, m, 2 x $CH_AH_B{}^2$), 1.65 - 1.50 (6H, m, 2 x CH_2CHCH_2 and 2 x $CH_AH_B{}^1$ + $CH_2{}^3$), 1.42 - 1.26 (4H, m, 2 x $CH_AH_B{}^1$ and 2 x $CH_ACH_B{}^2$), 1.21 - 1.16 (6H, m, 2 x CH_3) ppm.

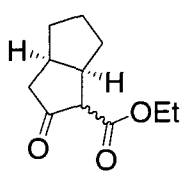
^{13}C NMR (100 MHz, $CDCl_3$): δ = [67.8, 67.5, 67.4] (1), [45.4, 45.1] (2), [43.1, 43.0, 42.7, 42.4] (1), [32.9, 32.7, 32.6, 32.5] (2), [25.0, 24.9] (3), [24.3, 24.2, 24.0] (2), [23.9, 23.8,] (3) ppm.

LRMS (ES+): $^m/z$ (relative intensity), 209 $[M + Na]^+$ (20 %).

HRMS (ES+): $[M + Na]^+$ $C_{11}H_{22}O_2Na$ requires $^m/z$ 209.1512, found $^m/z$ 209.1511.

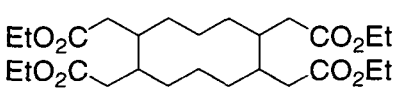
Microanalysis: $C_{11}H_{22}O_2$ requires C, 70.92; H, 11.90. Found C, 70.80; H, 11.94 %.

***rac* - Ethyl (3a*R*, 6a*R*)-2-oxooctahydropentalene-1-carboxylate 435 and *rac* - ethyl 2-[2, 6,7-tris(2-ethoxy-2-oxoethyl)cyclodecyl]acetate 436**



435

$C_{11}H_{16}O_3$
Mw: 196.24 $gmol^{-1}$



436

$C_{26}H_{44}O_8$
Mw: 484.62 $gmol^{-1}$

Following the reported procedure by Kilburn,[122] MeOH (17 mL) was added to a stirring solution of SmI_2 in THF (0.1 M, 69 mL) and the resultant purple mixture cooled to – 78 °C, where upon the reaction turned dark green. Di-ester **408** (384 mg, 1.60 mmol) as a solution in THF (5 mL) was then added drop-wise over a period of 10 minutes, after which the reaction was allowed to stir at – 78 °C for a further 2 h. Brine (30 mL), followed by citric acid (403 mg, 1.92 mmol) was then added and allowed to stir for 30 minutes. EtOAc (80 mL) was added to the stirring solution and allowed to stir

vigorously for 5 minutes, after which the reaction mixture was allowed to settle and the organic phase decanted off. This process was then repeated (3 x 80 mL EtOAc). The aqueous phase was transferred to a separating funnel and was further extracted with EtOAc (2 x 70 mL), before the combined organic extracts were washed with brine (2 x 30 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave the crude product as a yellow oil which upon purification by flash column chromatography, eluting with 2 % EtOAc / petrol gradually increasing the polarity to 10 % EtOAc / petrol gave β-keto ester **435** (110 mg, 0.561 mmol, 35 %) as a colourless oil, R_f = 0.61 (20 % EtOAc / petrol) and dimer **436** (147 mg, 0.607 mmol, 38 %) as a colourless oil, R_f = 0.50 (20 % EtOAc / petrol);

Data for β-keto ester **435** - exists as 2 main tautomers, all peaks reported:

IR ν_{max} (film): 2953 (m), 2865 (m), 1722 (s), 1656 (s), 1448 (m), 1407 (m) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.38 (1H, br s, O**H**), 4.18 (2H, q, J = 7.2 Hz, OC**H$_2$**), 4.15 (2H, q, J = 7.2 Hz, OC**H$_2$**), 3.18 (1H, m, C**H**), 2.97 (1H, dd, J = 7.5, 4.3 Hz, C**H**), 2.92 (1H, dd, J = 15.1, 1.0 Hz, C**H**), 2.73 (2H, dd, J = 18.5, 9.9 Hz, 2 x C**H$_A$**CH$_B$), 2.62 - 2.51 (2H, m, 2 x C**H**), 2.17 - 2.08 (2H, m, 2 x CH$_A$C**H$_B$**), 1.92 (1H, m, C**H$_A$**CH$_B$) 1.73 - 1.58 (4H, m, 2 x C**H$_2$**), 1.50 - 1.40 (5H, m, 2 x C**H$_2$**, CH$_A$C**H$_B$**), 1.31 - 1.26 (2H, m, C**H$_2$**), 1.23 (3H, t, J = 7.2 Hz, OCH$_2$C**H$_3$**), 1.21 (3H, t, J = 7.2 Hz, OCH$_2$C**H$_3$**) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 213.3 (0), 175.4 (0), 170.5 (0), 169.9 (0), 104.3 (0), 61.7 (2), 61.4 (1), 60.1 (2), 45.5 (1), 45.0 (1), 44.9 (2), 40.2 (2), 38.5 (1), 36.6 (1), 35.5 (2), 33.6 92), 33.2 (2), 32.9 (2), 25.7 (2), 25.6 (2), 14.7 (3), 14.5 (3) ppm.
LRMS (ES+): ^{m}/z (relative intensity), 197 $[M + H]^+$ (55 %), 219 $[M + Na]^+$ (100 %).

Dimer **436** isolated as an inseparable 4:1 mixture with an unkown side product. Side product peaks are reported in the ^{13}C NMR only (labelled as minor):

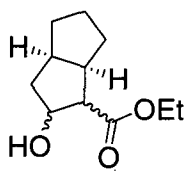
IR ν_{max} (film): 2954 (m), 2869 (w), 1729 (s), 1447 (w), 1371 (m) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.10 (8H, q, J = 7.2 Hz, 4 x OC**H$_2$**), 2.46 (2H, dd, J = 15.1, 4.4 Hz, 2 x C(O)C**H$_A$**CH$_B$), 2.43 - 2.38 (2H, m, 2 x C**H**), 2.32 (2H, dd, J = 14.8, 5.7 Hz, 2 x C(O)C**H$_A$**CH$_B$), 2.18 (2H, dd, J = 15.2, 8.7 Hz, 2 x C(O)CH$_A$C**H$_B$**), 2.11 (2H, dd, J = 14.8, 9.0 Hz, 2 x C(O)CH$_A$C**H$_B$**), 1.95 - 1.86 (6H, m, 2 x C**H$_2$**, 2 x C**H**), 1.64 - 1.54 (4H, m, 2 x C**H$_2$**), 1.38 - 1.28 (4H, m, 2 x C**H$_2$**), 1.24 (12H, t, J = 7.2 Hz, 4 x OCH$_2$C**H$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1 (0, minor), 173.5 (0, major), 173.4 (0, major), 60.6 (2, major), 60.5 (2, minor), 60.5 (2, major), 42.2 (1, major), 39.6 (2, major), 39.1 (1, major), 35.6 (2, major), 34.6 (2, minor), 32.5 (2, major), 30.7 (2, major), 29.3 (2, minor), 29.2 (2, minor), 25.2 (2, minor), 23.7 (2, major), 22.5 (2, minor), 14.6 (2 x 3, major) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 507 $[M+ Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{26}H_{44}O_8Na$ requires ^{m}/z 507.2928, found ^{m}/z 507.2924.

***rac* - Ethyl (3a*R*, 6a*R*)-2-hydroxyoctahydropentalene-1-carboxylate 437**



437

$C_{11}H_{18}O_3$

Mw: 198.26 $gmol^{-1}$

β-Keto ester **435** (95.0 mg, 0.484 mmol) was dissolved in wet THF (8 mL) and $NaBH_4$ (20 mg, 0.533 mmol) added in one portion. The reaction was allowed to stir at RT for 5 h after which it was quenched by adding 1M HCl aqueous solution (5 mL) and transferred to a separating funnel. The product was extracted with EtOAc (2 x 20 mL) and the combined organic extracts washed with brine (15 mL) before being dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave the crude product as a yellow oil which was purified by flash column chromatography, eluting with 10 % EtOAc / petrol to give the β-hydroxy ester **437** (23.0 mg, 0.116 mmol, 24 %) as a colourless oil, R_f = 0.31 (40 % EtOAc / petrol);

IR ν_{max} (film): 3430 (br), 2941 (s), 2863 (m), 1728 (s), 1709 (s), 1448 (m) cm^{-1}.

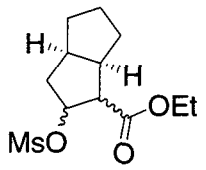
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.19 (1H, m, **CH**OH), 4.18 (2H, q, *J* = 7.2 Hz, OCH_2), 2.51 (1H, m, **CH**), 2.39 (1H, m, **CH**), 2.26 - 2.17 (2H, m, C(O)**CH**, CH_ACH_B), 1.61 - 1.57 (4H, m, CH_2, 2 x CH_ACH_B), 1.42 (1H, m, CH_AH_B), 1.27 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.22 - 1.15 (2H, m, 2 x CH_ACH_B) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.4 (0), 77.0 (1), 60.9 (2), 58.6 (1), 44.4 (1), 40.9 (2), 38.4 (1), 33.6 (2), 33.1 (2), 24.9 (2), 14.6 (3) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 199 $[M + H]^+$ (10 %), 221 $[M + Na]^+$ (60 %).

HRMS (ES+): $[M + Na]^+$ $C_{11}H_{18}O_3Na$ requires ^{m}/z 221.1148, found ^{m}/z 221.1143.

***rac* - Ethyl (3a*R*, 6a*R*)-2-[(methylsulfonyl)oxy]octahydropentalene-1-carboxylate 438**



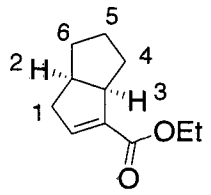
438

$C_{12}H_{20}O_5S$
Mw: 276.35 $gmol^{-1}$

Methanesulfonyl chloride (0.0539 mL, 0.696 mmol) was added dropwise to a stirring solution of β-hydroxy ester **437** (23.0 mg, 0.116 mmol), Et_3N (0.190 mL, 1.39 mmol), DMAP (1.50 mg, 0.0116 mmol, 10 mol %) and DCM (5 mL). The resultant yellow solution was allowed to stir at RT for 16 h before 1M HCl aqueous solution (10 mL) and DCM (20 mL) were added and the layers separated. The organic extracts were washed with brine (10 mL), dried over magnesium sulfate and the solvent removed *in vacuo* to leave the crude product as a yellow oil. Purification by flash column chromatography, eluting with 10 % EtOAc / petrol increasing the polarity to 15 % EtOAc / petrol gave the mesylate **438** (27.0 mg, 0.0980 mmol, 84 %) as a pale yellow oil, $R_f = 0.50$ (40 % EtOAc / petrol);

IR ν_{max} (film): 2943 (w), 2862 (w), 1725 (s), 1355 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.99 (1H, m, **CH**OMs), 4.19 (1H, q, J = 7.2 Hz, OCH_AH_B), 4.18 (1H, q, J = 7.2 Hz, $OCH_A\mathbf{H_B}$), 3.01 (3H, s, $S(O)_2\mathbf{CH_3}$), 2.54 - 2.46 (4H, m, 3 x **CH**, $\mathbf{CH_A}H_B$), 1.71 - 1.59 (5H, m, 2 x $\mathbf{CH_2}$, $\mathbf{CH_A}H_B$), 1.50 - 1.46 (2H, m, 2 x $CH_A\mathbf{CH_B}$), 1.27 (3H, t, J = 7.2 Hz, $OCH_2\mathbf{CH_3}$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7 (0), 83.0 (1), 61.3 (2), 55.7 (1), 44.8 (1), 39.1 (2), 38.8 (1), 38.2 (3), 33.5 (2), 33.0 (2), 24.8 (2), 14.6 (3) ppm.
LRMS (ES+): ^{m}/z (relative intensity), 299 $[M + Na]^+$ (91 %), 575 $[2M + Na]^+$ (100 %).
HRMS (ES+): $[M + Na]^+$ $C_{12}H_{20}O_5SNa$ requires ^{m}/z 299.0924, found ^{m}/z 299.0919.

***rac* - Ethyl (3a*R*, 6a*R*)-3, 3a, 4, 5, 6, 6a-hexahydropentalene-1-carboxylate 439**



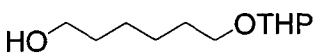
439

$C_{11}H_{16}O_2$
Mw: 180.24 $gmol^{-1}$

A solution of mesylate **438** (26.0 mg, 0.0941 mmol) and DBU (0.110 mL, 0.736 mmol) in DCM (6 mL) was stirred for 16 h, before the solvent was removed under a reduced pressure to give the crude product as a colourless oil / solid. Purification by flash column chromatography eluting with 10 % EtOAc / petrol gave the unsaturated ester **439** (11.0 mg, 0.0610 mmol, 65 %) as a colourless oil, R_f = 0.72 (40 % EtOAc / petrol);

IR ν_{max} (film): 2939 (m), 2863 (w), 1712 (s), 1630 (w), 1448 (m) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.64 (1H, br s, C**H**=C), 4.19 (1H, dq, *J* = 10.8, 7.0 Hz, OC$\mathbf{H_A}$CH$_B$CH$_3$), 4.17 (1H, dq, *J* = 10.8, 7.0 Hz, OCH$_A$C$\mathbf{H_B}$CH$_3$), 3.35 (1H, m, C$\mathbf{H}^2$), 2.82 - 2.69 (2H, m, C$\mathbf{H}^3$ and C$\mathbf{H_A}$H$_B{}^1$), 2.14 (1H, dt, *J* = 15.8, 3.0 Hz, CH$_A\mathbf{H_B}{}^1$), 1.87 - 1.72 (2H, m, C$\mathbf{H_A}$H$_B{}^4$ and C$\mathbf{H_A}$H$_B{}^6$), 1.61 (1H, m, CH$\mathbf{H_B}{}^6$), 1.52 - 1.44 (2H, m, C$\mathbf{H_2}{}^5$), 1.35 (1H, m, CH$\mathbf{H_B}{}^4$), 1.29 (3H, t, *J* = 7.0 Hz, OCH$_2\mathbf{CH_3}$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7 (0), 143.0 (1), 139.4 (0), 60.3 (2), 49.8 (1), 41.3 (1), 40.9 (2), 35.8 (2), 32.7 (2), 25.8 (2), 14.7 (3) ppm.
LRMS (ES+): ^{m}/z (relative intensity), 181 $[M + H]^+$ (80 %), 203 $[M + Na]^+$ (100 %).
HRMS (EI): $[M]^+$ $C_{11}H_{16}O_2$ requires ^{m}/z 180.11503, found ^{m}/z 180.11522.

6-(Tetrahydro-2*H*-pyran-2-yloxy)hexan-1-ol 441



441

$C_{11}H_{22}O_3$
Mw: 202.29 $gmol^{-1}$

Following the reported procedure by Hayashi,[160] to a DCM (100 mL) solution of DHP (10.5 g, 125 mmol) and 1, 6-hexanediol **440** (60.0 g, 508 mmol) was added *p*-toluenesulfonic acid monohydrate (0.960 g, 5.05 mmol) in one portion at 0 °C. The resultant pale yellow reaction mixture was stirred at RT for 18 h after which time the reaction was complete. Saturated $NaHCO_3$ aqueous solution (100 mL) was added to the

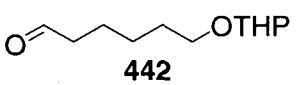
reaction mixture and the organic materials extracted with EtOAc (3 x 100 mL), washed with brine (100 mL) and dried over magnesium sulfate. Removal of the solvent *in vacuo* gave a colourless oil which upon purification by flash column chromatography, eluting with 20 % EtOAc / petrol increasing the polarity to 40 % EtOAc / petrol, gave mono protected product **441** (20.5 g, 101 mmol, 81 %) as a colourless oil, R_f = 0.5 (70 % EtOAc / petrol);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.57 (1H, m, CH_2CHOCH_2), 3.86 (1H, m, OCH_AH_B), 3.74 (1H, dt, *J* = 9.5, 6.8 Hz, OCH_AH_B), 3.63 (2H, t, *J* = 6.6 Hz, OCH_2), 3.49 (1H, m, OCH_AH_B), 3.39 (1H, dt, *J* = 9.7, 6.6 Hz, OCH_AH_B), 1.82 (1H, m, CH_AH_B), 1.73 (1H, m, CH_AH_B), 1.65 - 1.45 (8H, m, 3 x CH_2, 2 x CH_ACH_B), 1.42 - 1.37 (4H, m, 2 x CH_2) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 99.3 (1), 67.9 (2), 63.2 (2), 62.7 (2), 33.1 (2), 31.1 (2), 30.0 (2), 26.4 (2), 25.9 (2), 25.8 (2), 20.1 (2), ppm.

Data is consistent with that reported by Hayashi.[160]

6-(Tetrahydro-2*H*-pyran-2-yloxy)hexanal 442



442

$C_{11}H_{20}O_3$

Mw: 200.27 $gmol^{-1}$

Following the reported procedure by Corey,[162] to a stirring slurry off PCC (145 g, 676 mmol) and NaOAc (4.06 g, 49.5 mmol) in DCM (470 mL) was added mono protected alcohol **441** (19.6 g, 96.7 mmol) as a solution in DCM (30 mL) slowly. The resultant black suspension was left to stir at RT for 2 h after which time the reaction was complete. The supernatant was decanted from the reaction vessel, and the remaining black gum triturated with Et_2O / petrol (1:1, 4 x 200 mL) where it became a granular solid. The organics were filtered through a pad of silica to leave a colourless green solution which upon removal of the solvent *in vacuo* gave a pale green oil. Purification by flash column chromatography, eluting with neat DCM, gave the aldehyde **442** (10.2 g, 50.9 mmol, 53 %) as a colourless oil, R_f = 0.87 (50 % EtOAc / petrol);

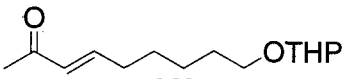
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.73 (1H, t, *J* = 1.74 Hz, CHO), 4.54 (1H, m, CH_2CHOCH_2), 3.82 (1H, m, OCH_AH_B), 3.71 (1H, dt, *J* = 9.7, 6.6 Hz, OCH_AH_B), 3.46

(1H, m, OCH_AH_B), 3.36 (1H, dt, J = 9.7, 6.4 Hz, OCH_AH_B), 2.41 (2H, td, J = 7.3, 1.7 Hz, $CHOCH_2$), 1.85 - 1.34 (12H, m, 6 x CH_2) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.8 (1), 99.2 (1), 67.5 (2), 62.6 (2), 44.1 (2), 31.1 (2), 29.8 (2), 26.2 (2), 25.8 (2), 22.2 (2), 20.0 (2) ppm.

Data is consistent with that reported by Hayashi.[160]

(3*E*)-9-(Tetrahydro-2*H*-pyran-2-yloxy)non-3-en-2-one 443



443

$C_{14}H_{24}O_3$

Mw: 240.34 gmol^{-1}

1-(Triphenylphosphoranylidene)acetone **325** (32.4 g, 101 mmol) was added to a stirring solution of 6-(tetrahydro-pyran-2-yloxy)-hexanal **442** (10.2 g, 50.9 mmol) in $CHCl_3$ (100 mL) and the resultant pale yellow solution reluxed for 16 h. The solvent was removed *in vacuo* to leave the crude material as a white solid. Purification by flash column chromatography, eluting with 20 % EtOAc / petrol gave ketone **443** (8.58 g, 35.7 mmol, 70 %) as a yellow oil, R_f = 0.58 (20 % EtOAc / petrol);

IR ν_{max} (film): 2936 (m), 2861 (m), 1716 (m), 1698 (m), 1674 (s), 1626 (m), 1356 (m) cm^{-1}.

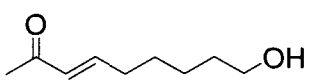
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.79 (1H, dt, J = 15.9, 6.9 Hz, C(O)CH=C**H**), (1H, dt, J = 15.9, 1.5 Hz, C(O)C**H**=CH), 4.55 (1H, t, J = 4.3 Hz, CH_2CHO), 3.85 (1H, m, OCH_AH_B), 3.73 (1H, dt, J = 9.6, 6.7 Hz, OCH_AH_B), 3.48 (1H, m, OCH_AH_B), 3.38 (1H, dt, J = 9.6, 6.5 Hz, OCH_AH_B), 2.22 (3H, s, CH_3), 1.83 - 1.36 (14H, m, 7 x CH_2) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.9 (0), 148.6 (1), 131.7 (1), 99.3 (1), 67.7 (2), 62.8 (2), 32.7 (2), 31.1 (2), 29.8 (2), 28.3 (2), 21.2 (3), 26.2 (2), 25.8 (2), 20.1 (2) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 263 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{14}H_{24}O_3Na$ requires ^{m}/z 263.1618, found ^{m}/z 263.1618.

(3*E*)-9-Hydroxynon-3-en-2-one 444



444

$C_9H_{16}O_2$

Mw: 156.22 gmol^{-1}

To a stirring solution of THP protected alcohol **443** (8.59 g, 35.7 mmol) and 10 % v/v aqueous acetone (150 mL), was added *p*-toluenesulfonic acid monohydrate (6.79 g, 35.7 mmol) portion-wise over 5 minutes. The pale yellow solution was stirred at RT for 4 days after which time the reaction was complete. Saturated $NaHCO_3$ aqueous solution (50 mL) was added and the organic materials extracted with Et_2O (4 x 150 mL). The combined organic extracts were washed with brine and dried over magnesium sulfate, before removal of the solvent under a reduced pressure gave a pale yellow oil. Purification by flash column chromatography, eluting with 10 % EtOAc / petrol, increasing the polarity to 40 % EtOAc / petrol, gave alcohol **444** (2.08 g, 13.3 mmol, 37 %) as a colourless oil, $R_f = 0.16$ (50 % EtOAc / petrol);

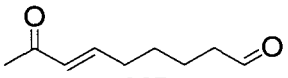
IR ν_{max} (film): 3463 (br), 2927 (m), 2857 (w), 1712 (s), 1674 (m), 1429 (w), 1358 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.78 (1H, dt, *J* = 15.9, 6.9 Hz, C(O)CH=C**H**), 6.06 (1H, dt, *J* = 15.9, 1.5 Hz, C(O)C**H**=CH), 3.61 (2H, t, *J* = 6.5 Hz, O**CH$_2$**), 2.25 - 2.19 (2H, m, **CH$_2$**), 2.21 (3H, s, **CH$_3$**), 1.82 (1H, br s, **OH**), 1.59 - 1.45 (4H, m, 2 x **CH$_2$**), 1.41 - 1.36 (2H, m, **CH$_2$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.1 (0), 148.6 (1), 131.7 (1), 62.9 (2), 32.7 (2), 32.7 (2), 28.2 (2), 27.1 (3), 25.7 (2) ppm.

LRMS (ES+): m/z (relative intensity), 179 $[M + Na]^+$ (100 %).

(6*E*)-8-Oxonon-6-enal 445



445

$C_9H_{14}O_2$

Mw: 154.21 $gmol^{-1}$

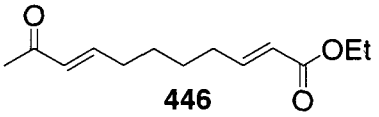
Following the reported procedure by Dess,[163] alcohol **444** (2.00 g, 12.8 mmol) was dissolved in DCM (20 mL) and added to a stirring solution of Dess - Martin periodinane (6.19 g, 14.6 mmol) in DCM (50 mL) in one portion. The resultant white suspension was allowed to stir at RT for 3 h after which time the reaction was complete. The reaction was quenched with saturated $Na_2S_2O_3$ aqueous solution (30 mL) and saturated $NaHCO_3$ aqueous solution (10 mL). The layers were separated and the aqueous phases back extracted with DCM (2 x 50 mL), before the combined organic extracts were washed with brine (50 mL) and dried over magnesium sulfate. Removal of the solvent

under a reduced pressure gave a yellow oil, which upon purification by flash column chromatography, eluting with 20 % EtOAc / petrol, gave the unstable aldehyde **445** (1.69 g, 11.0 mmol, 75 %) as a colourless oil, $R_f = 0.74$ (50 % EtOAc / petrol);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.75 (1H, t, *J* = 1.6 Hz, **CHO**), 6.76 (1H, dt, *J* = 15.9, 6.9 Hz, C(O)CH=**CH**), 6.08 (1H, dt, *J* = 15.9, 1.5 Hz, C(O)**CH**=CH), 2.45 (1H, td, *J* = 7.0, 1.6 Hz, $\mathbf{CH_AH_B}$CHO), 2.25 (1H, td, *J* = 7.1, 1.6 Hz, $CH_A\mathbf{H_B}$CHO), 2.21 (3H, s, $\mathbf{CH_3}$), 1.70 - 1.44 (6H, m, 3 x $\mathbf{CH_2}$) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.3 (1), 198.8 (0), 147.6 (1), 131.9 (1), 43.8 (2), 32.4 (2), 27.8 (2), 27.2 (3), 21.8 (2) ppm.

The unstable aldehyde **445** was used immediately in the following Wittig olefinations.

Ethyl (2*E*, 8*E*)-10-oxo-undeca-2, 8-dienoate 446



446

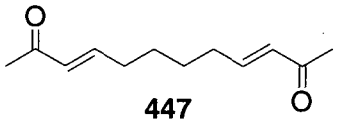
$C_{13}H_{20}O_3$
Mw: 224.3 $gmol^{-1}$

Following the reported procedure by Enholm,[44] to a solution of aldehyde **445** (844 mg, 5.47 mmol) in $CHCl_3$ (50 mL) was added (carboxymethylene) triphenylphosphorane **322** (3.82 g, 10.9 mmol) as a solution in $CHCl_3$ (20 mL). The pale yellow reaction was allowed to stir at RT for 72 h. Removal of the solvent *in vacuo* gave a white residue, which upon purification by flash column chromatography, eluting with 10 % EtOAc / petrol increasing the polarity to 30 % EtOAc / petrol, gave keto - ester **446** (701 mg, 3.1 mmol, 58 %) as a colourless oil, $R_f = 0.49$ (50 % EtOAc / petrol);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.93 (1H, dt, *J* = 15.6, 7.0 Hz, C(O)CH=**CH**), 6.77 (1H, dt, *J* = 15.9, 6.9 Hz, C(O)CH=**CH**), 6.08 (1H, dt, *J* = 15.9, 1.6 Hz, C(O)**CH**=CH), 5.83 (1H, dt, *J* = 15.6, 1.6 Hz, C(O)**CH**=CH), 4.18 (2H, q, *J* = 7.1 Hz, $O\mathbf{CH_2}CH_3$), 2.26 - 2.17 (4H, m, 2 x $\mathbf{CH_2}$), 2.23 (3H, s, $\mathbf{CH_3}$), 1.52 - 1.47 (4H, m, 2 x $\mathbf{CH_2}$), 1.27 (3H, t, *J* = 7.1 Hz, $OCH_2\mathbf{CH_3}$) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.8 (0), 166.9 (0), 148.8 (1), 147.9 (1), 131.8 (1), 122.1 (1), 60.5 (2), 32.5 (2), 32.2 (2), 27.9 (2 x 2), 27.2 (3), 14.6 (3) ppm.

Data is consistent with that reported by Pandey.[157]

(3*E*, 9*E*)-Dodeca-3, 9-diene-2, 11-dione 447



447

$C_{12}H_{18}O_2$
Mw: 194.27 $gmol^{-1}$

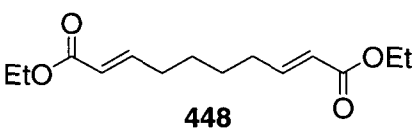
Following the reported procedure by Enholm,[44] to a solution of aldehyde **445** (844 mg, 5.47 mmol) in $CHCl_3$ (50 mL) was added 1-(triphenylphosphoranylidene)acetone **325** (3.82 g, 10.9 mmol) as a solution in $CHCl_3$ (20 mL). The pale yellow reaction was allowed to stir at RT for 24 h. Removal of the solvent *in vacuo* gave a white residue, which upon purification by flash column chromatography, eluting with 10 % EtOAc / petrol increasing the polarity to 40 % EtOAc / petrol, gave di - ketone **447** (673 mg, 3.46 mmol, 63 %) as a colourless oil, $R_f = 0.34$ (50 % EtOAc / petrol);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.73 (2H, dt, *J* = 15.9, 6.9 Hz, 2 x C(O)CH=CH), 6.04 (2H, dt, *J* = 15.9, 1.5 Hz, 2 x C(O)CH=CH), 2.23 - 2.16 (4H, m, 2 x CH_2), 2.18 (6H, s, 2 x CH_3), 1.49 - 1.44 (4H, m, 2 x CH_2) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.7 (0), 147.8 (1), 131.7 (1), 32.3 (2), 27.8 (2), 27.1 (3) ppm.

Data is consistent with that reported by Montgomery.[159]

Diethyl (2*E*, 8*E*)-deca-2, 8-dienedioate 448



448

$C_{14}H_{22}O_4$
Mw: 254.32 $gmol^{-1}$

Following the reported procedure by Corey,[162] to a solution of Hexane-1,6-diol **440** (3.00 g, 25.4 mmol) in DCM (150 mL), was added NaOAc (2.08 g, 25.4 mmol), celite (~ 50 mL) and PCC (27.4 g, 127 mmol). The resultant black mixture was allowed to stir at RT for 18 h after which time the reaction was complete. The black suspension was filtered through a pad of celite and the black residue washed thoroughly with Et_2O (3 x 100 mL). Removal of the solvent *in vacuo* gave a yellow oil (1.89 g) which was dissolved in $CHCl_3$ (125 mL) and (carboxymethylene) triphenylphosphorane **322** (17.3 g, 49.5 mmol) added in one portion. The resulting yellow solution was stirred at

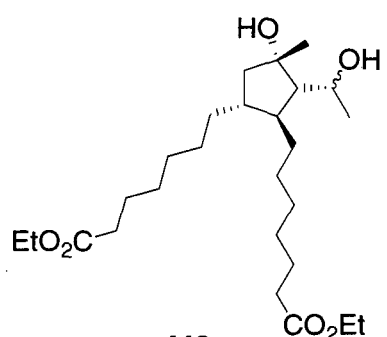
RT for 3 days after which time the solvent was removed under a reduced pressure to give a pink solid. Purification by flash column chromatography, eluting with 20 % EtOAc / petrol gave di - ester **448** (499 mg, 1.96 mmol, 8 %);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.91 (2H, dt, *J* = 15.6, 7.0 Hz, 2 x C(O)CH=C**H**), 5.80 (2H, dt, *J* = 15.6, 1.6 Hz, 2 x C(O)C**H**=CH), 4.16 (4H, q, *J* = 7.1 Hz, O**CH_2**CH_3), 2.22 - 2.15 (4H, m, 2 x **CH_2**), 1.49 - 1.44 (4H, m, 2 x **CH_2**), 1.26 (6H, t, *J* = 7.1 Hz, 2 x OCH_2**CH_3**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8 (0), 148.8 (1), 122.0 (1), 60.4 (2), 32.1 (2), 27.8 (2), 14.5 (3) ppm.

Data is consistent with that reported by Hong.[164]

Ethyl-[2-(7-ethoxy-7-oxoheptyl)-4-hydroxy-3-(1-hydroxyethyl)-4-methyl cyclopentyl] heptanoate 449a and 449b



449a
449b

$C_{26}H_{48}O_6$
Mw: 456.66 gmol^{-1}

Following the reported procedure by Kilburn,[122] MeOH (14 mL) was added to a stirring solution of SmI_2 in THF (0.1 M, 56 mL) and the resultant purple mixture cooled to – 78 °C, where upon the reaction turned dark green. Keto-ester **446** (295 mg, 1.32 mmol) as a solution in THF (5 mL) was then added drop-wise over a period of 10 minutes and the reaction allowed to stir at – 78 °C for a further 2 h. Brine (25 mL), followed by citric acid (331 mg, 1.58 mmol) was then added and allowed to stir for 10 minutes. EtOAc (80 mL) was added to the stirring solution and allowed to stir vigorously for 5 minutes, after which the reaction mixture was allowed to settle and the organic phase decanted off. This process was then repeated (4 x 80 mL EtOAc). The aqueous phase was transferred to a separating funnel and further extracted with EtOAc (2 x 80 mL), before the combined organic extracts were washed with brine (2 x 30 mL)

and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave the crude product as a yellow oil which upon purification by flash column chromatography, eluting with 7 % EtOAc / petrol gradually increasing the polarity to 40 % EtOAc / petrol, gave dimer **449a** (58.0 mg, 0.254 mmol, 20 %) as a yellow oil, $R_f = 0.35$ (35 % EtOAc / petrol) and dimer **449b** (65.0 mg, 0.285 mmol, 22 %) as a yellow oil, $R_f = 0.2$ (35 % EtOAc / petrol);

449a isolated as an approximate 2:1 diastereomeric mixture with dimer **449b**, only the peaks corresponding to **449a** are reported for clarity.

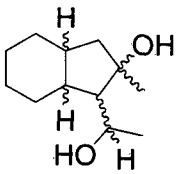
IR ν_{max} (film): 3436 (br), 2930 (m), 2856 (m), 1732 (s), 1463 (m), 1372 (m) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.22 (1H, m, **CH**OH), 4.13 (4H, q, *J* = 7.2 Hz, 2 x O**CH$_2$**CH$_3$), 2.29 (2H, t, *J* = 7.3 Hz, **CH$_2$**CO$_2$Et), 2.28 (2H, t, *J* = 7.3 Hz, **CH$_2$**CO$_2$Et), 1.92 - 1.81 (2H, m, **CH**, **CH$_A$H$_B$**), 1.67 - 1.58 (4H, m, 2 x **CH$_2$**), 1.54 - 1.42 (2H, m, **CH**, **CH$_A$H$_B$**), 1.36 - 1.18 (23H, m, 8 x **CH$_2$**, 2 x **CH$_3$**, **CH**), 1.25 (6H, t, *J* = 7.2 Hz, 2 x O**CH$_2$CH$_3$**) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2 (2 x 0), 82.0 (0), 67.0 (1), 60.5 (2 x 2), 58.8 (1), 48.1 (2), 43.7 (1), 42.5 (1), 36.8 (2), 36.5 (2), 34.7 (2 x 2), 30.2 (2), 30.0 (3), 29.8 (2), 29.5 (2), 29.5 (2), 28.7 (2), 27.4 (2), 25.4 (2), 25.3 (2), 22.1 (3), 14.6 (2 x 3) ppm.
LRMS (ES+): ^{m}/z (relative intensity), 479 $[M + Na]^+$ (100 %), 935 $[2M + Na]^+$ (40 %).
HRMS (ES+): $[M + Na]^+$ $C_{26}H_{48}O_6Na$ requires ^{m}/z 479.3343, found ^{m}/z 479.3342.

Data for dimer **449b**:

IR ν_{max} (film): 3448 (br), 2930 (m), 2856 (m), 1732 (s), 1463 (m), 1372 (m) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.12 (4H, q, *J* = 7.2 Hz, 2 x O**CH$_2$**CH$_3$), 3.85 (1H, dq, *J* = 9.2, 6.2 Hz, **CH**OH), 2.27 (4H, t, *J* = 7.4 Hz, 2 x **CH$_2$**CO$_2$Et), 1.88 (1H, m, **CH**), 1.74 (1H, dd, *J* = 11.7, 6.2 Hz, **CH$_A$H$_B$**), 1.62 - 1.55 (5H, m, 2 x **CH$_2$**, **CH**), 1.52 - 1.44 (3H, m, CH$_A$**CH$_B$**, **CH**, **CH$_A$H$_B$**), 1.35 - 1.20 (18H, m, 7 x **CH$_2$**, CH$_A$**CH$_B$**, **CH$_3$**CHOH), 1.33 (3H, s, **CH$_3$**), 1.24 (6H, t, *J* = 7.2 Hz, 2 x O**CH$_2$CH$_3$**) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2 (2 x 0), 79.7 (0), 70.4 (1), 61.4 (1), 60.5 (2 x 2), 47.6 (2), 41.5 (1), 38.9 (1), 34.7 (2 x 2), 31.6 (2), 30.9 (2), 30.2 (2), 29.9 (2), 29.5 (2), 29.4 (2), 29.4 (2), 29.0 (2), 25.3 (2 x 2), 24.5 (3), 23.9 (3), 14.6 (2 x 3) ppm.
LRMS (ES+): ^{m}/z (relative intensity), 479 $[M + Na]^+$ (100 %), 935 $[2M + Na]^+$ (10 %).

HRMS (ES+): $[M + Na]^+$ $C_{26}H_{48}O_6Na$ requires $^m/z$ 479.3343, found $^m/z$ 479.3338.

***rac* - (3a*R*, 7a*S*)-1-(1-Hydroxyethyl)-2-methyloctahydro-1*H*-inden-2-ol 450**



450

$C_{12}H_{22}O_2$

Mw: 198.3 $gmol^{-1}$

Following the reported procedure by Kilburn,[122] MeOH (15 mL) was added to a stirring solution of SmI_2 in THF (0.1 M, 61 mL) and the resultant purple mixture cooled to – 78 °C, where upon the reaction turned dark green. Di-ketone **447** (279 mg, 1.44 mmol) as a solution in THF (5 mL) was then added drop-wise over a period of 10 minutes and the reaction allowed to stir at – 78 °C for a further 2 h. Brine (40 mL), followed by citric acid (362 mg, 1.72 mmol) was then added and allowed to stir for 10 minutes. EtOAc (70 mL) was added to the stirring solution and allowed to stir vigorously for 5 minutes, after which the reaction mixture was allowed to settle and the organic phase decanted off. This process was then repeated (4 x 80 mL EtOAc). The aqueous phase was transferred to a separating funnel and further extracted with EtOAc (2 x 80 mL), before the combined organic extracts were washed with brine (2 x 30 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave the crude product as a yellow oil which upon purification by flash column chromatography, eluting with 10 % EtOAc / petrol gradually increasing the polarity to 20 % EtOAc / petrol, gave diol **450** (78.0 mg, 0.393 mmol, 28 %) as a yellow oil, $R_f = 0.63$ (50 % EtOAc / petrol);

450 isolated as a 2:1 mixture of diastereoisomers. Only major diastereoisomer peaks reported in ^1H NMR for clarity. Both sets of diastereoisomer peaks reported in ^{13}C NMR where possible.

IR ν_{max} (film): 3338 (br), 2920 (m), 2851 (m), 1446 (m), 1372 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.20 (1H, qd, J = 6.9, 1.6 Hz, **CH**OH), 2.67 (2H, br s, 2 x O**H**), 2.08 (1H, m, CH_AH_B), 1.91 (1H, dd, J = 12.5, 6.1 Hz, CH_AH_B), 1.85 - 1.80 (2H, m, CH_2), 1.76 - 1.70 (4H, m, 2 x CH_2), 1.67 - 1.53 (2H, m, 2 x **CH**), 1.40 - 1.36

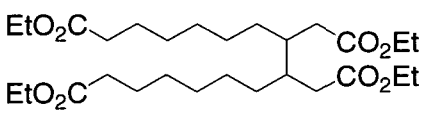
(2H, m, 2 x CH_AH_B), 1.30 (3H, s, CH_3), 1.28 (3H, d, J = 6.8 Hz, CH_3CHOH), 1.21 (1H, m, CH) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 80.6 (0, minor), 80.2 (0, major), 69.5 (1, minor), 66.7 (1, major), 60.7 (1, minor), 60.0 (1, major), 50.5 (2, minor), 49.9 (2, major), 48.5 (1, minor), 44.6 (1, major), 44.0 (1, minor), 43.5 (1, major), 33.8 (3, minor), 33.2 (2, major), 32.0 (2, major), 31.9 (2, minor), 31.8 (2, minor), 31.3 (3, major), 27.1 (2 x 2, minor) 26.7 (2 x 2, major), 23.4 (3, minor), 22.7 (3, major) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 221 $[M + Na]^+$ (100 %), 419 $[2M + Na]^+$ (25 %).

HRMS (ES+): $[M + Na]^+$ $C_{12}H_{22}O_2Na$ requires ^{m}/z 221.1512, found ^{m}/z 221.1510.

1, 16-Diethyl 8, 9-bis(2-ethoxy-2-oxoethyl)hexadecanedioate 455



455

$C_{28}H_{50}O_8$

Mw: 514.69 gmol^{-1}

Following the reported procedure by Kilburn,[122] MeOH (7 mL) was added to a stirring solution of SmI_2 in THF (0.1 M, 29 mL) and the resultant purple mixture cooled to – 78 °C, where upon the reaction turned dark green. Di-ester **448** (174 mg, 0.68 mmol) as a solution in THF (5 mL) was then added drop-wise over a period of 10 minutes and the reaction allowed to stir at – 78 °C for a further 2 h. Brine (50 mL), followed by citric acid (172 mg, 0.819 mmol) was then added and allowed to stir for 10 minutes. EtOAc (50 mL) was added to the stirring solution and allowed to stir vigorously for 5 minutes, after which the reaction mixture was allowed to settle and the organic phase decanted off. This process was then repeated (4 x 50 mL EtOAc). The aqueous phase was transferred to a separating funnel and further extracted with EtOAc (2 x 60 mL), before the combined organic extracts were washed with brine (2 x 25 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave the crude product as a yellow oil which upon purification by flash column chromatography, eluting with 10 % EtOAc / petrol, gave dimer **455** (107 mg, 0.416 mmol, 61 %) as a yellow oil, R_f = 0.64 (25 % EtOAc / petrol);

IR ν_{max} (film): 2926 (m), 2855 (m), 1731 (s), 1450 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.12 (8H, q, J = 7.2 Hz, 4 x OCH_2CH_3), 2.48 (2H, dd, J = 14.8, 3.8 Hz, 2 x $C(O)CH_AH_BCH$), 2.27 (4H, t, J = 7.5 Hz, 2 x $C(O)CH_2$), 2.10

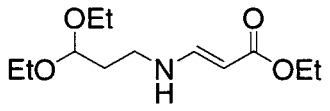
(2H, dd, J = 14.8, 8.3 Hz, 2 x C(O)CH$_A$**H$_B$**CH), 1.76 - 1.72 (4H, m, 2 x **CH$_2$**), 1.69 - 1.65 (2H, m, 2 x **CH$_A$**H$_B$CH), 1.64 - 1.59 (6H, 2 x **CH$_2$**, 2 x **CH**), 1.34 - 1.27 (10H, m, 4 x **CH$_2$**, 2 x CH$_A$**H$_B$**CH), 1.24 (12H, t, J = 7.2 Hz, 4 x OCH$_2$**CH$_3$**) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ = 174.1 (0), 173.4 (0), 60.5 (2), 60.5 (2), 39.6 (2), 39.4 (1), 34.7 (2), 32.7 (2), 29.4 (2 x 2), 26.1 (2), 25.3 (2), 14.6 (2 x 3) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 537 [M + Na]$^+$ (40%).

HRMS (ES+): [M + Na]$^+$ $C_{28}H_{50}O_8Na$ requires ^{m}/z 537.3398, found ^{m}/z 537.3395.

Ethyl (2*E*)-3-[(3, 3-diethoxypropyl)amino]prop-2-enoate 458



458

$C_{12}H_{23}NO_4$

Mw: 245.32 gmol^{-1}

Following the reported procedure by Macdonald,[166] ethyl propiolate **457** (0.690 mL, 6.79 mmol) in Et$_2$O (10 mL) was added dropwise to a stirring solution of 1-amino-3,3-diethoxy propane **456** (1 g, 6.79 mmol) in Et$_2$O (10 mL). The reaction was allowed to stir at RT for 16 h after which the reaction was complete. Removal of the solvent *in vacuo* gave the product **458** (1.69 g, 6.79 mmol, 100 %) as a colourless oil, R$_f$ = 0.46 (50 % EtOAc / petrol);

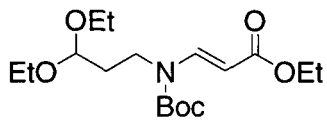
Mixture of *E* and *Z* isomers:

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.83 (1H, br s, N**H**, *Z* isomer), 7.48 (1H, dd, J = 13.2, 8.0 Hz, NHC**H**=CH, *E* isomer), 6.59 (1H, dd, J = 13.2, 8.0 Hz, NHC**H**=CH, *Z* isomer), 4.99 (1H, brs, N**H**, *E* isomer), 4.70 (1H, d, J = 13.4 Hz, NHCH=C**H**, *E* isomer), 4.55 (2H, t, J = 5.7 Hz, 2 x C**H**(OEt)$_2$, *E* and *Z* isomer), 4.44 (1H, d, J = 7.9 Hz, NHCH=C**H**, *Z* isomer), 4.11 (4H, q, J = 7.3 Hz, C(O)OC**H$_2$**, *Z* isomer and C(O)OC**H$_2$**, *E* isomer), 3.69 - 3.59 (4H, m, CH$_3$C**H$_2$**O *E* isomer and CH$_3$C**H$_2$**O *Z* isomer), 3.52 (2H, q, J = 7.1 Hz, CH$_3$C**H$_2$**O, *Z* isomer), 3.51 (2H, q, J = 7.1 Hz, CH$_3$C**H$_2$**O, *E* isomer), 3.26 (2H, q, J = 6.6 Hz, NHC**H$_2$**, *Z* isomer), 3.14 (2H, q, J = 6.2 Hz, NHC**H$_2$**, *E* isomer), 1.89 - 1.80 (4H, m, NCH$_2$C**H$_2$**, *Z* isomer and NCH$_2$C**H$_2$**, *E* isomer), 1.25 (6H, t, J = 7.1 Hz, C(O)OCH$_2$C**H$_3$** *Z* isomer and C(O)OCH$_2$C**H$_3$** *E* isomer), 1.20 (12 H, t, J = 7.1 Hz, 2 x C**H$_3$**CH$_2$O, *Z* isomer and 2 x C**H$_3$**CH$_2$O *E* isomer) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1 (0, *Z*), 170.0 (0, *E*), 152.5 (1, *E* and *Z*), 102.4 (1, *E*), 101.1 (1, *Z*), 85.9 (1, *E*), 82.3 (1, *Z*), 62.4 (2, *E*), 61.9 (2, *Z*), 59.2 (2, *E*), 58.9 (2, *Z*), 44.9 (2, *E* and *Z*), 35.5 (2, *E* and *Z*), 15.6 (3, *Z*), 14.9 (3, *E*) ppm.

Data is consistent with that reported by Ajavakom.[165]

Ethyl (2*E*)-3-{[(tert-butoxy)carbonyl](3,3-diethoxypropyl)amino}prop-2-enoate 459



459

$C_{17}H_{31}NO_6$

Mw: 345.43 $gmol^{-1}$

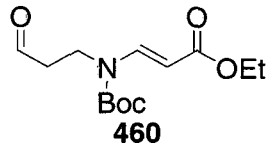
Enamine **458** (1.69 g, 6.89 mmol), Et_3N (1.45 mL, 10.3 mmol), DMAP (169 mg, 1.39 mmol) and DCM (10 mL) were combined, and Boc_2O (1.60 mL, 6.89 mmol) as a solution in DCM (10 mL) was added dropwise at 0 °C. The reaction was allowed to warm to RT and left to stir for 16 h after which time the reaction was complete. The reaction mixture was washed with 1M HCl aqueous solution (2 x 30 mL) followed by H_2O (25 mL) and the aqueous phases re-extracted with DCM (2 x 50 mL). The combined organic extracts were dried over magnesium sulfate, before removal of the solvent under a reduced pressure gave the crude product as a pale yellow oil. Purification by flash column chromatography, eluting with 10 % EtOAc / petrol, gave the Boc protected product **459** (1.35 g, 3.91 mmol, 56 %) as a colourless oil, R_f = 0.49 (30 % EtOAc / petrol);

^{1} H NMR (300 MHz, $CDCl_3$): δ = 8.17 (1H, d, *J* = 14.1 Hz, NHC**H**=CH), 5.23 (1H, d, *J* = 14.1 Hz, NHCH=C**H**), 4.50 (1H, t, *J* = 5.5 Hz, C**H**$(OEt)_2$), 4.19 (2H, q, *J* = 7.1 Hz, C(O)OC**H**$_2$$CH_3$), 3.70 - 3.57 (4H, m, 2 x CH_3C**H**$_2$O), 3.53 - 3.43 (2H, m, NC**H**$_2$), 1.88 (2H, m, NCH_2C**H**$_2$), 1.52 (9H, s, $C(CH_3)_3$), 1.27 (3H, t, *J* = 7.1 Hz, C(O)OCH_2C**H**$_3$), 1.21 (6H, t, *J* = 7.1 Hz, 2 x C**H**$_3$$CH_2$O) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.3 (0), 152.3 (0), 142.9 (1), 101.2 (1), 97.5 (1), 83.3 (0), 61.9 (2 x 2), 60.2 (2), 40.7 (2), 31.5 (2), 28.4 (3 x 3), 15.6 (2 x 3), 14.7 (3) ppm.

Data is consistent with that reported by Ajavakom.[165]

Ethyl (2*E*)-3-[(*tert*-butoxycarbonyl)(3-oxopropyl)amino]prop-2-enoate 460



460

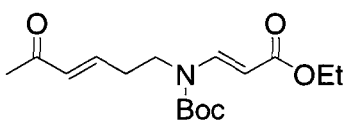
$C_{13}H_{21}NO_5$
Mw: 271.31 $gmol^{-1}$

Carbamate **459** (1.30 g, 3.76 mmol) and *p*-toluenesulfonic acid monohydrate (931 mg, 4.89 mmol) were stirred in a 20 % v/v aqueous acetone solution (300 mL) at RT for 3 days. Upon completion the reaction was diluted with Et_2O (100 mL) and washed with saturated $NaHCO_3$ aqueous solution (2 x 50 mL). The aqueous layer was extracted with EtOAc (2 x 60 mL) and the combined organic extracts dried over magnesium sulfate. Removal of the solvent *in vacuo* gave a pale yellow oil which upon purification by flash column chromatography, eluting with 10 % EtOAc / petrol, gave the aldehyde **460** (761 mg, 2.80 mmol, 78 %) as a colourless oil, $R_f = 0.31$ (30 % EtOAc / petrol);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.80 (1H, t, *J* = 1.2 Hz, C**H**O), 8.14 (1H, d, *J* = 14.3 Hz, NC**H**=CH), 5.13 (1H, d, *J* = 14.3 Hz, NCH=C**H**), 4.18 (2H, q, *J* = 7.3 Hz, O**CH$_2$**CH$_3$), 3.87 (2H, t, *J* = 7.3 Hz, N**CH$_2$**), 2.72 (2H, td, *J* = 7.6, 1.3 Hz, CHOC**H$_2$**), 1.52 (9H, s, C(**CH$_3$**)$_3$), 1.28 (3H, t, *J* = 7.3 Hz, OCH$_2$**CH$_3$**) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.7 (1), 167.8 (0), 152.1 (0), 142.3 (1), 97.7 (1), 84.0 (0), 60.4 (2), 41.5 (2), 38.2 (2), 28.4 (3 x 3), 14.7 (3) ppm.

Data is consistent with that reported by Ajavakom.[165]

Ethyl (2*E*)-3-{(*tert*-butoxycarbonyl)[(3*E*)-5-oxohex-3-en-1-yl]amino}prop-2-enoate 461



461

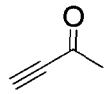
$C_{16}H_{25}NO_5$
Mw: 311.37 $gmol^{-1}$

Aldehyde **460** (750 mg, 2.76 mmol) and 1-(triphenylphosphoranylidene)acetone **325** (1.14 g, 3.59 mmol) were dissolved in $CHCl_3$ (30 mL) and stirred at 50 °C for 24 h where upon the reaction was complete. The solvent was removed *in vacuo* to give a white solid which upon purification by flash column chromatography, eluting with 5 %

EtOAc / petrol gradually increasing the polarity to 20 % EtOAc / petrol, gave the keto-ester **461** (623 mg, 2.00 mmol, 72 %) as a colourless oil, $R_f = 0.46$ (50 % EtOAc / petrol);

IR ν_{max} (film): 2976 (w), 1724 (s), 1694 (s), 1622 (s), 1458 (w), 1383 (m) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (1H, d, *J* = 14.3 Hz, NC**H**=CH), 6.72 (1H, dt, *J* = 15.9, 7.3 Hz, C(O)CH=C**H**), 6.07 (1H, d, *J* = 15.9 Hz, C(O)C**H**=CH), 5.13 (1H, d, *J* = 14.3 Hz, NCH=C**H**), 4.18 (2H, q, *J* = 7.1 Hz, O**CH$_2$**CH$_3$), 3.70 (2H, t, *J* = 7.1 Hz. N**CH$_2$**), 2.48 (2H, apparent qd, *J* = 7.5, 1.3 Hz, NCH$_2$**CH$_2$**), 2.22 (3H, s, **CH$_3$**C(O)), 1.50 (9H, s, C(**CH$_3$**)$_3$), 1.28 (3H, t, *J* = 7.1 Hz, OCH$_2$**CH$_3$**) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.3 (0), 167.9 (0), 152.2 (0), 143.5 (1), 142.4 (1), 133.4 (1), 97.7 (1), 83.8 (0), 60.4 (2), 42.9 (2), 30.2 (2), 28.3 (3 x 3), 27.3 (3), 14.7 (3) ppm.
LRMS (ES+): ^{m}/z (relative intensity), 312 $[M + H]^+$ (20 %), 334 $[M + Na]^+$ (65 %).
HRMS (ES+): $[M + Na]^+$ $C_{16}H_{25}NO_5Na$ ^{m}/z requires 334.1625, found ^{m}/z 334.1630.

But-3-yn-2-one 463



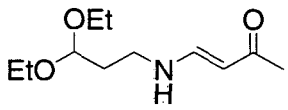
463
C_4H_4O
Mw: 68.07 $gmol^{-1}$

Following the reported procedure by Rawal,[167] a solution of CrO_3 (3.99 g. 39.9 mmol) in H_2SO_4 / H_2O (14.4 mL / 72 mL) was added slowly over 30 minutes to a stirring solution of 3-butyn-2-ol **462** (2.20 mL, 28.5 mmol) in H_2SO_4 / H_2O (21.6 mL / 72 mL) at 0 °C. The resultant black mixture was stirred between 2 - 10 °C for 7 h before DCM (120 mL) was added in one portion. The two phases were separated and the organic phase washed with saturated $NaHCO_3$ aqueous solution (40 mL), followed by water (40 mL) and finally dried over magnesium sulfate. The solvent was removed extremely slowly *in vacuo* over an ice cold water bath to give the volatile ketone **463** (700 mg, 10.2 mmol, 25 %) as a pale yellow oil;

IR ν_{max} (film): 3256 (m), 2094 (s), 1711 (m), 1682 (s), 1391 (m) cm^{-1}.

The ketone **463** was used directly in the following reaction.

(3*E*)-4-[(3, 3-Diethoxypropyl)amino]but-3-en-2-one 464



464

$C_{11}H_{21}NO_3$
Mw: 215.29 $gmol^{-1}$

Following the reported procedures by Winkler,[168, 169] but-3-yn-2-one **463** (700 mg, 10.2 mmol) in DCM (25 mL) was added dropwise to a stirring solution of 1-amino-3,3-diethoxy propane **456** (1.51 g, 10.2 mmol) in DCM (10 mL). The reaction was allowed to stir at RT for 24 h after which time the reaction was complete. Removal of the solvent *in vacuo* gave enamine **464** (1.16 g, 5.39 mmol, 53 %) as a yellow oil, $R_f = 0.14$ (40 % EtOAc / petrol);

Mixture of *E* and *Z* isomers:

IR ν_{max} (film): 3274 (br), 2974 (m), 2930 (m), 2873 (m), 1638 (s), 1559 (s), 1486 (m) cm^{-1}.

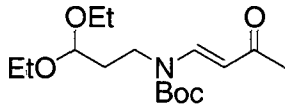
^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.76 (1H, br s, N**H**, *Z* isomer), 7.47 (1H, dd, *J* = 13.8, 8.1 Hz, NHC**H**=CH, *E* isomer), 6.61 (1H, dd, *J* = 12.7, 7.3 Hz, NHC**H**=CH, *Z* isomer), 5.38 (1H, br s, N**H**, *Z* isomer), 5.22 (1H, d, *J* = 13.3 Hz, NHCH=C**H**, *E* isomer), 4.96 (1H, d, *J* = 7.3 Hz, NHCH=C**H**, *Z* isomer), 4.58 (1H, t, *J* = 5.7 Hz, C**H**$(OEt)_2$, *Z* isomer), 4.53 (1H, t, *J* = 5.6 Hz, C**H**$(OEt)_2$, *E* isomer), 3.69 - 3.58 (4H, m, 2 x $OCH_AH_BCH_3$, *E* and *Z* isomers), 3.53 - 3.43 (4H, m, 2 x $OCH_A\mathbf{H_B}CH_3$, *E* and *Z* isomers), 3.27 (2H, q, *J* = 6.8 Hz, NC**H$_2$**, *Z* isomer), 2.77 (2H, t, *J* = 6.8 Hz, NC**H$_2$**, *E* isomer), 2.08 (3H, s, C**H$_3$**, *E* isomer), 2.02 (3H, s, C**H$_3$**, *Z* isomer), 1.85 (2H, q, *J* = 6.7 Hz, $NCH_2\mathbf{CH_2}$, *Z* isomer), 1.76 (2H, q, *J* = 6.7 Hz, $NCH_2\mathbf{CH_2}$, *E* isomer), 1.19 (3H, t, *J* = 7.0 Hz, $OCH_2\mathbf{CH_3}$, *Z* isomer), 7.19 (3H, t, *J* = 7.0 Hz, $OCH_2\mathbf{CH_3}$, *E* isomer) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.6 (0, *E* and *Z*), 152.7 (1, *E* and *Z*), 102.2 (1, *E*), 101.0 (1, *Z*), 94.0 (1, *E* and *Z*), 62.0 (2 x 2, *Z*), 61.6 (2 x 2, *E*), 45.3 (2, *Z*), 38.5 (2, *E*), 38.0 (2, *E*), 35.3 (2, *Z*), 29.3 (3, *E* and *Z*), 15.6 (2 x 3, *E* and *Z*) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 238 $[M + Na]^+$ (100 %), 453 $[2M + Na]^+$ (70 %).

HRMS (ES+): $[M + Na]^+$ $C_{11}H_{21}NO_3Na$ requires ^{m}/z 238.1414, found ^{m}/z 238.1412.

tert-Butyl _N_-(3, 3-diethoxypropyl)-_N_-[(1_E_)-3-oxobut-1-en-1-yl]carbamate 465



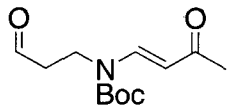
465

$C_{16}H_{29}NO_5$
Mw: 315.41 $gmol^{-1}$

Enamine **464** (1.32 g, 6.13 mmol), Et_3N (1.50 mL, 11.1 mmol), DMAP (150 mg, 1.23 mmol) and DCM (70 mL) were combined, and Boc_2O (2 g, 9.16 mmol) as a solution in DCM (10 mL) was added dropwise at 0 °C. The reaction was allowed to warm to RT and left to stir for 16 h after which time the reaction was found to be incomplete. Further Boc_2O (1.34 g, 6.13 mmol) and Et_3N (0.86 mL, 6.13 mmol) were added and the mixture stirred for 42 h until completion. The reaction mixture was washed with 1M HCl aqueous solution (2 x 30 mL) followed by H_2O (30 mL) and the aqueous phases re-extracted with DCM (3 x 50 mL). The combined organic extracts were dried over magnesium sulfate, before removal of the solvent under a reduced pressure gave the crude product as a pale yellow oil. Purification by flash column chromatography, eluting with 5 % EtOAc / petrol increasing the polarity to 20 % EtOAc / petrol, gave the Boc protected product **465** (1.92 g, 6.09 mmol, 99 %) as a colourless oil, R_f = 0.30 (30 % EtOAc / petrol);

IR ν_{max} (film): 2971 (m), 2926 (w), 1723 (s), 1621 (s), 1588 (s), 1369 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (1H, d, *J* = 14.6 Hz, NC**H**=CH), 5.62 (1H, d, *J* = 14.6 Hz, NCH=C**H**), 4.50 (1H, t, *J* = 5.5 Hz, C**H**$(OEt)_2$), 3.66 (1H, q, *J* = 7.0 Hz, OC**H**$_A$H$_B$), 3.64 (1H, q, *J* = 7.0 Hz, OC**H**$_A$H$_B$), 3.63 - 3.5 (2H, m, NC**H**$_2$), 3.50 (1H, q, *J* = 7.0 Hz, OCH$_A$**H**$_B$), 3.47 (1H, q, *J* = 7.0 Hz, OCH$_A$**H**$_B$), 2.22 (3H, s, C(O)C**H**$_3$), 1.86 (2H, ddd, *J* = 9.0, 7.5, 5.4 Hz, NCH$_2$C**H**$_2$), 1.52 (9H, s, C(C**H**$_3$)$_3$), 1.20 (6H, t, *J* = 7.0 Hz, 2 x OCH$_2$C**H**$_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.7 (0), 152.5 (0), 142.8 (1), 108.3 (1), 101.1 (1), 83.7 (0), 61.9 (2 x 2), 40.8 (2), 31.5 (2), 28.4 (3 x 3), 27.6 (3), 15.6 (2 x 3) ppm.
LRMS (ES+): ^{m}/z (relative intensity), 338 $[M + Na]^+$ (100 %), 654 $[2M + Na]^+$ (42 %).
HRMS (ES+): $[M + Na]^+$ $C_{16}H_{29}NO_5Na$ requires ^{m}/z 338.1938, found ^{m}/z 338.1933.

***tert*-Butyl [(1*E*)-3-oxobut-1-en-1-yl](3-oxopropyl)carbamate 466**



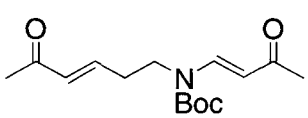
466

$C_{12}H_{19}NO_4$
Mw: 241.28 $gmol^{-1}$

Carbamate **465** (1.92 g, 6.09 mmol) and *p*-toluenesulfonic acid monohydrate (1.39 g, 7.30 mmol) were stirred in a 20 % v/v aqueous acetone solution (500 mL) at RT for 30 h. The reaction was incomplete so further *p*-toluenesulfonic acid monohydrate (471 mg, 2.48 mmol) was added. The reaction was stirred for a further 35 h and, upon completion was diluted with Et_2O (100 mL) and washed with saturated $NaHCO_3$ aqueous solution (100 mL). The aqueous layer was extracted with Et_2O (3 x 80 mL) and the combined organic extracts dried over magnesium sulfate. Removal of the solvent *in vacuo* gave a pale yellow oil which upon purification by flash column chromatography, eluting with 10 % EtOAc / petrol gradually increasing the polarity to 40 % EtOAc / petrol, gave the product **466** (1.33 g, 5.51 mmol, 92 %) as a colourless oil, $R_f = 0.13$ (30 % EtOAc / petrol);

IR ν_{max} (film): 2979 (m), 1717 (s), 1682 (s), 1620 (s), 1588 (s), 1369 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.79 (1H, t, *J* = 1.3 Hz, **CHO**), 8.08 (1H, d, *J* = 14.6 Hz, NC**H**=CH), 5.52 (1H, d, *J* = 14.6 Hz, NCH=C**H**), 3.88 (2H, t, *J* = 7.1 Hz, NC**H$_2$**), 2.72 (2H, td, *J* = 7.2, 1.3 Hz, $NCH_2C\mathbf{H_2}$), 2.22 (3H, s, C(O)C**H$_3$**), 1.52 (9H, s, $C(C\mathbf{H_3})_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.6 (1), 197.4 (0), 152.1 (0), 142.1 (1), 108.3 (1), 84.3 (0), 41.5 (2), 38.3 (2), 28.4 (3), 28.3 (3 x 3) ppm.
LRMS (ES+): ^{m}/z (relative intensity), 264 $[M + Na]^+$ (57 %), 505 $[2M + Na]^+$ (100 %).
HRMS (ES+): $[M + Na]^+$ $C_{12}H_{19}NO_4Na$ requires ^{m}/z 264.1206, found ^{m}/z 264.1209.

***tert*-Butyl [(1*E*)-3-oxobut-1-en-1-yl][(3*E*)-5-oxohex-3-en-1-yl]carbamate 467**



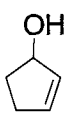
467

$C_{15}H_{23}NO_4$
Mw: 281.35 $gmol^{-1}$

Aldehyde **466** (1.33 g, 5.51 mmol) and 1-(triphenylphosphoranylidene)acetone **325** (2.28 g, 7.16 mmol) were dissolved in $CHCl_3$ (60 mL) and stirred at 65 °C for 22 h after which time the reaction was found to be complete. The solvent was removed *in vacuo* to give a yellow solid which upon purification by flash column chromatography, eluting with 10 % EtOAc / petrol gradually increasing the polarity to 40 % EtOAc / petrol, gave the product **467** (1.09 g, 3.87 mmol, 71 %) as a colourless oil, R_f = 0.24 (50 % EtOAc / petrol);

IR ν_{max} (film): 2975 (w), 1720 (s), 1674 (s), 1620 (s), 1586 (s), 1367 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (1H, d, *J* = 14.6 Hz, NC**H**=CH), 6.74 (1H, dt, *J* = 15.9, 6.7 Hz, C(O)CH=C**H**), 6.10 (1H, d, *J* = 15.9 Hz, C(O)C**H**=CH), 5.50 (1H, d, *J* = 14.6 Hz, NCH=C**H**), 3.70 (2H, t, *J* = 7.0 Hz, N**CH$_2$**), 2.48 (2H, q, *J* = 7.0 Hz, NC**H$_2$**CH$_2$), 2.24 (3H, s, **CH$_3$**), 2.22 (3H, s, **CH$_3$**), 1.51 (9H, s, C(**CH$_3$**)$_3$) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.2 (0), 197.5 (0), 152.2 (0), 143.2 (1), 142.4 (1), 133.4 (1), 108.5 (1), 84.2 (0), 43.0 (2), 30.3 (2), 28.3 (3 x 3), 27.4 (2 x 3) ppm.
LRMS (ES+): ^{m}/z (relative intensity), 282 $[M + H]^+$ (91 %), 304 $[M + Na]^+$ (95 %).
HRMS (ES+): $[M + Na]^+$ $C_{15}H_{23}NO_4Na$ requires ^{m}/z 304.1519, found ^{m}/z 304.1513.

Cyclopent-2-en-1-ol 468



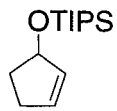
468
C_5H_8O
Mw: 84.12 $gmol^{-1}$

Following the reported procedure by Luche,[170] 2-cyclopenten-1-one **232** (7.00 mL, 83.5 mmol), $CeCl_3.7H_2O$ (31.1 g, 83.5 mmol) and MeOH (200 mL) were combined, and $NaBH_4$ (3.16 g, 83.5 mmol) added portion-wise over a period of 20 minutes. Vigorous evolution of gas was observed. The reaction was left to stir at RT for 2 h after which the pH was adjusted to 7 using 1M HCl aqueous solution. Water (50 mL) was added and the product extracted using Et_2O (4 x 80 mL), and the combined organic extracts washed with brine (2 x 30 mL) and dried over magnesium sulfate. Removal of the solvent *in vacuo* gave pure product **468** (2.09 g, 24.9 mmol, 30 %) as a pale yellow oil, R_f = 0.5 (40 % EtOAc / petrol);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.96 (1H, m, CH(OH)C**H**=CH), 5.83 (1H, m, CH(OH)CH=C**H**), 4.86 (1H, m, C**H**OH), 2.49 (1H, m, CH_ACH_B), 2.31 - 2.18 (2H, m, CH_2), 1.68 (1H, m, CH_ACH_B), 1.61 (1H, br s, O**H**) ppm.
^{13}CNMR (75 MHz, $CDCl_3$): δ = 135.5 (1), 133.6 (1), 77.9 (1), 33.6 (2), 31.3 (2) ppm.

Data is consistent with that reported by Carreira.[180]

(Cyclopent-2-enyloxy)triisopropylsilane 469



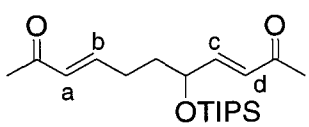
469
$C_{14}H_{28}OSi$
Mw: 240.46 $gmol^{-1}$

Following the reported procedure by Bunnelle,[171] alcohol **468** (2.09 g, 24.9 mmol), imidazole (3.38 g, 49.7 mmol), TIPSCl (6.42 mL, 30.0 mmol) and DCM (25 mL) were allowed to stir at RT for 16 h, at which point the reaction was complete. The reaction mixture was quenched with 5 % H_2SO_4 aqueous solution (20 mL) and saturated $NaHCO_3$ aqueous solution (25 mL) and the layers separated. The organic layer was dried over magnesium sulfate before removal of the solvent under a reduced pressure gave the product **469** (1.40 g, 5.82 mmol, 23 %) as a colourless oil, R_f = 0.75 (40 % EtOAc / petrol);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.89 (1H, m, CH(OTIPS)C**H**=CH), 5.76 (1H, m, CH(OTIPS)CH=C**H**), 4.99 (1H, m, C**H**(OTIPS)), 2.49 (1H, m, CH_ACH_B), 2.27 - 2.18 (2H, m, CH_2), 1.70 (1H, m, CH_ACH_B), 1.08 (21H, s, Si(C**H**$(CH_3)_2)_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.5 (1), 133.7 (1), 78.4 (1), 34.3 (2), 31.4 (2), 18.4 (6 x 3), 12.6 (3 x 1) ppm.

Data is consistent with that reported by Bunnelle.[171]

(3*E*, 8*E*)-5-[Tris(propan-2-yl)silyl]oxyundeca-3, 8-diene-2, 10-dione 471



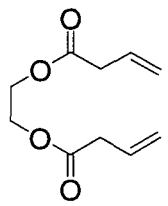
471
$C_{20}H_{36}O_3Si$
Mw: 352.58 $gmol^{-1}$

Following the reported procedure by Montgomery,[159] silane **469** (1.40 g, 5.82 mmol) was dissolved in DCM (150 mL) then cooled to – 78 °C before O_3 was bubbled through the reaction mixture until a blue colour became apparent. The reaction was purged with O_2 to disperse any remaining O_3 and PPh_3 (3.06 g, 11.7 mmol) was then added and allowed to stir at 25 °C for 1 h. 1-(Triphenylphosphoranylidene)acetone **325** (4.60 g, 14.6 mmol) was then added in one portion and the reaction refluxed for 60 h. Removal of the solvent under a reduced pressure gave a white solid which was purified by flash column chromatography eluting with 5 % EtOAc / petrol increasing the polarity to 20 % EtOAc / petrol, to give product **471** (1.47 g, 4.17 mmol, 72 %) as a colourless oil, R_f = 0.40 (40 % EtOAc / petrol);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.78 (1H, dt, *J* = 15.9, 6.8 Hz, CH=C**H$_b$**), 6.70 (1H, dd, *J* = 15.9, 5.4 Hz, CH=C**H$_c$**), 6.24 (1H, dd, *J* = 15.9, 1.3 Hz, C**H$_d$**=CH), 6.07 (1H, dt, *J* = 15.9, 1.5 Hz, C**H$_a$**=CH), 4.56 (1H, dt, *J* = 5.3, 1.1 Hz, C**H**OTIPS), 2.38 - 2.15 (2H, m, C**H$_2$**), 2.27 (3H, s, C(O)C**H$_3$**), 2.23 (3H, s, C(O)C**H$_3$**), 1.84 - 1.76 (2H, m, C**H$_2$**), 1.06 (21H, s, Si(C**H**(C**H$_3$**)$_2$)$_3$) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.5 (2 x 0), 149.1 (1), 147.6 (1), 131.8 (1), 130.1 (1), 71.5 (1), 36.1 (2), 27.7 (2 x 3), 27.3 (2), 18.4 (6 x 3), 12.7 (3 x 1) ppm.

Data is consistent with that reported by Montgomery.[159]

Ethane-1, 2-diyl bisbut-3-enoate 480



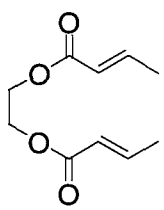
480
$C_{10}H_{14}O_4$
Mw: 198.22 gmol^{-1}

Ethylene glycol **479** (0.900 mL, 16.1 mmol), Et_3N (5.62 mL, 40.3 mmol) and DCM (30 mL) were combined and cooled to 0 °C, before *trans* crotonyl chloride **478** (3.86 mL, 40.3 mmol) was added dropwise over 5 minutes. The resultant suspension was left to stir at RT for 16 h. The reaction was quenched with saturated NH_4Cl aqueous solution (20 mL) and the layers separated. The aqueous layer was back extracted with DCM (2 x 30 mL) and the combined organic extracts washed with brine

(20 mL) and dried over over magnesium sulfate before removal of the solvent *in vacuo* gave a yellow oil. Purification by flash column chromatography, eluting with 5 % EtOAc / petrol increasing the polarity to 10 % EtOAc / petrol, gave the non-conjugated di-ester **480** (3.18 g, 16.0 mmol, 97 %) as a pale yellow oil, $R_f = 0.36$ (20 % EtOAc / petrol);

IR ν_{max} (film): 2959 (w), 1735 (s), 1643 (w), 1426 (w), 1372 (m) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.90 (2H, ddt, J = 16.8, 9.8, 7.0 Hz, 2 x C**H**=CH_2), 5.20 - 5.15 (4H, m, 2 x CH=C**H$_2$**), 4.30 (4H, s, 2 x O**CH$_2$**), 3.11 (4H, dt, J = 7.0, 1.3 Hz, 2 x C(O)**CH$_2$**) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6 (0), 130.3 (1), 119.1 (2), 62.6 (2), 39.2 (2) ppm.
LRMS (ES+): ^{m}/z (relative intensity), 221 $[M + Na]^+$ (100 %).
HRMS (ES+): $[M + Na]^+ C_{10}H_{14}O_4Na$ requires ^{m}/z 221.0784, found ^{m}/z 221.0784.

Ethane-1, 2-diyl (2*E*, 2'*E*)bis-but-2-enoate 481



481
$C_{10}H_{14}O_4$
Mw: 198.22 $gmol^{-1}$

Following the reported procedure by Chiu,[172] non-conjugated ethyl precursor **480** (3.29 g, 16.6 mmol), DBU (0.250 mL, 10 mol %) and Et_2O (25 mL) were combined and stirred at RT for 24 h. NMR analysis of the reaction showed there to be a small amount of product formation. The reaction was then allowed to continue stirring for a further 4 days after which time it was quenched with H_2O (20 mL) and brine (20 mL) and the phases separated. The organic layer was dried over magnesium sulfate before removal of the solvent *in vacuo* gave a brown oil, which upon purification by flash column chromatography, eluting with 10 % EtOAc / petrol gave conjugated ester **481** (2.01 g, 10.1 mmol, 62 %) as a yellow oil, $R_f = 0.54$ (30 % EtOAc / petrol);

IR ν_{max} (film): 2952 (w), 1716 (s), 1656 (s), 1444 (m), 1376 (w) cm^{-1}.

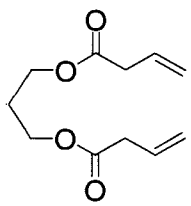
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.99 (2H, dq, *J* = 15.4, 6.8 Hz, 2 x C(O)CH=C**H**), 5.85 (2H, dq, *J* = 15.5, 1.7 Hz, 2 x C(O)C**H**=CH), 4.34 (4H, s, 2 x O**C**$\mathbf{H_2}$), 1.87 (6H, dd, *J* = 6.9, 1.8 Hz, 2 x $\mathbf{CH_3}$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5 (0), 145.7 (1), 122.6 (1), 62.3 (2), 18.3 (3) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 199 $[M + H]^+$ (10 %), 221 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{10}H_{14}O_4Na$ requires ^{m}/z 221.0744, found ^{m}/z 221.0780.

Propane-1, 3-diyl bisbut-3-enoate 483



483

$C_{11}H_{16}O_4$

Mw: 212.24 $gmol^{-1}$

1,3- Propanediol **482** (0.950 mL, 13.1 mmol), Et_3N (4.58 mL, 32.9 mmol) and DCM (30 mL) were combined and cooled to 0 °C, before *trans* crotonyl chloride **478** (3.15 mL, 32.9mmol) was added dropwise over 5 minutes. The resultant suspension was left to stir at RT for 16 h. The reaction was quenched with saturated NH_4Cl aqueous solution (20 mL) and the layers separated. The aqueous layer was back extracted with DCM (2 x 30 mL) and the combined organic extracts washed with brine (20 mL) and dried over over magnesium sulfate before removal of the solvent *in vacuo* gave a yellow oil. Purification by flash column chromatography, eluting with 5 % EtOAc / petrol increasing the polarity to 10 % EtOAc / petrol, gave the non-conjugated di-ester **483** (2.75 g, 12.9 mmol, 99 %) as a pale yellow oil, R_f = 0.38 (20 % EtOAc / petrol);

IR ν_{max} (film): 2968 (w), 1732 (s), 1643 (w), 1425 (w), 1405 (w) cm^{-1}.

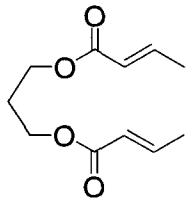
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.90 (2H, ddt, *J* = 17.6, 9.8, 7.0 Hz, 2 x C**H**=CH_2), 5.18 - 5.14 (4H, m, 2 x CH=C$\mathbf{H_2}$), 4.17 (4H, t, *J* = 6.3 Hz, 2 x O**C**$\mathbf{H_2}$), 3.09 (4H, dt, *J* = 7.0, 1.2 Hz, 2 x C(O)C$\mathbf{H_2}$), 1.98 (2H, qn, *J* = 6.3 Hz, $\mathbf{CH_2}$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7 (0), 130.4 (1), 119.0 (2), 61.6 (2), 39.4 (2), 28.3 (2) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 235 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{11}H_{16}O_4Na$ requires ^{m}/z 235.0941, found ^{m}/z 235.0938.

Propane-1, 3-diyl (2*E*, 2'*E*)bis-but-2-enoate 484



484

$C_{11}H_{16}O_4$

Mw: 212.24 $gmol^{-1}$

Following the reported procedure by Chiu,[172] non-conjugated propyl precursor **483** (2.71 g, 12.8 mmol), DBU (0.19 mL, 1.28 mmol) and Et_2O (25 mL) were combined and stirred at RT for 24 h. NMR analysis of the reaction showed there to be a small amount of product formation. The reaction was then allowed to continue stirring for a further 4 days after which time it was quenched with H_2O (20 mL) and brine (20 mL) and the phases separated. The organic layer was dried over magnesium sulfate, before removal of the solvent *in vacuo* gave a brown oil which upon purification by flash column chromatography, eluting with 10 % EtOAc / petrol gave conjugated ester **484** (1.93 g, 9.09 mmol, 71 %) as a yellow oil, $R_f = 0.54$ (30 % EtOAc / petrol);

IR ν_{max} (film): 2971 (w), 1714 (s), 1658 (s), 1444 (m) cm^{-1}.

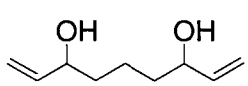
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.96 (2H, dq, *J* = 15.5, 6.9 Hz, 2 x C(O)CH=C**H**), 5.82 (2H, dq, *J* = 15.5, 1.7 Hz, 2 x C(O)C**H**=CH), 4.21 (4H, t, *J* = 6.4 Hz, 2 x O**CH$_2$**), 2.01 (2H, qn, *J* = 6.4 Hz, **CH$_2$**), 1.86 (6H, dd, *J* = 7.0, 1.7 Hz, 2 x **CH$_3$**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7 (0), 145.2 (1), 122.8 (1), 61.1 (2), 28.4 (2), 18.3 (3) ppm.

LRMS (ES+): ^{m}/z (relative intensity), 213 $[M + H]^+$ (10 %), 235 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{11}H_{16}O_4Na$ requires ^{m}/z 235.0941, found ^{m}/z 235.0943.

Nona-1,8-diene-3,7-diol 486



486

$C_9H_{16}O_2$

Mw: 156.22 $gmol^{-1}$

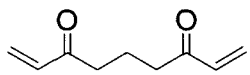
Following the reported procedure by Christoffers,[173] glutaraldehyde **404** (4.20 g, 41.9 mmol) was dissolved in THF (30 mL) and vinylmagnesium bromide **485** (1M in

THF, 126 mL, 126 mmol) added dropwise over 10 minutes. The reaction mixture turned to a pale yellow colour and began to reflux gently. After complete addition the reaction was refluxed for 2 h and the reaction quenched using saturated NH_4Cl aqueous solution (40 mL) and Et_2O (50 mL) added to aid separation of the layers. The aqueous layer was back extracted with Et_2O (4 x 40 mL) and the combined ethereal extracts washed with brine (40 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave a pale yellow oil, which upon purification by flash column chromatography, eluting with 30 % EtOAc / petrol increasing the polarity to 40 % EtOAc / petrol, gave diol **486** (4.09 g, 26.2 mmol, 62 %) as a colourless oil, $R_f = 0.23$ (60 % EtOAc / petrol);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.86 (2H, ddd, J = 17.0, 10.4, 6.2 Hz, 2 x C**H**=CH_2), 5.20 (2H, dt, J = 17.2, 1.3 Hz, 2 x C**H**$_{trans}$H$_{cis}$=CH), 5.10 (2H, dt, J = 10.2, 1.5 Hz, 2 x CH$_{trans}$**H**$_{cis}$=CH), 4.14 - 4.06 (2H, m, 2 x C**H**OH), 1.86 (2H, br s, 2 x O**H**), 1.57 - 1.40 (6H, m, 3 x C**H**$_2$) ppm.
^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.5 (1), 115.0 (2), 114.9 (2) 73.4 (1), 73.3 (1), 37.1 (2), 37.1 (2), 21.5 (2), 21.4 (2) ppm.

Data is consistent with that reported by Christoffers.[173]

Nona-1, 8-diene-3, 7-dione 487



487

$C_9H_{12}O_2$
Mw: 152.19 gmol^{-1}

Following the reported procedure by Dess,[163] diol **486** (1.00 g, 6.40 mmol) was dissolved in DCM (16 mL) and added in one portion to a stirring solution of Dess Martin periodinane (5.73 g, 13.5 mmol) in DCM (50 mL). A white suspension formed over the next 5 minutes and was allowed to stir at RT for 30 minutes in total. The reaction mixture was diluted with saturated $Na_2S_2O_3$ and $NaHCO_3$ aqueous solution (2:1, 40 mL) and the resultant bi-phasic mixture stirred for 5 minutes. The layers were separated and the aqueous layer re-extracted with DCM (2 x 40 mL). The combined organic extracts were washed with brine (30 mL) and dried over magnesium sulfate before removal of the solvent under a reduced pressure gave the crude product as a pale yellow oil. Purification by flash column chromatography, eluting with 10 % EtOAc /

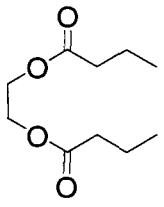
petrol gradually increasing the polarity to 20 % EtOAc / petrol, gave enone **487** (835 mg, 5.49 mmol, 86 %) as a colourless oil, R_f = 0.56 (40 % EtOAc / petrol);

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.35 (2H, dd, *J* = 17.6, 10.1 Hz, 2 x C**H**=CH_2), 6.21 (2H, dd, *J* = 17.6, 1.5 Hz, 2 x $CH_{trans}H_{cis}$=CH), 5.82 (2H, dd, 10.2, 1.6 Hz, 2 x $CH_{trans}H_{cis}$=CH), 2.65 (4H, t, *J* = 7.1 Hz, 2 x CH_2C(O)), 1.95 (2H, qn, *J* = 7.0 Hz, $CH_2CH_2CH_2$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.6 (0), 136.8 (1), 128.6 (2), 38.7 (2), 18.3 (2) ppm.

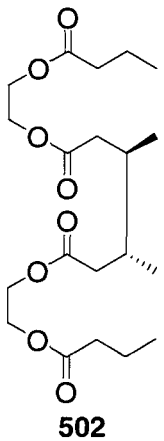
Data is consistent with that reported by Christoffers.[173]

Ethane-1, 2-diyl dibutanoate 500 and *rac* - 1, 6-bis[2-(butanoyloxy)ethyl] (3*R*, 4*R*)-3, 4-dimethylhexanedioate 502



500

$C_{10}H_{18}O_4$
Mw: 202.25 $gmol^{-1}$



502

$C_{20}H_{34}O_8$
Mw: 402.48 $gmol^{-1}$

Following the reported procedure by Kilburn,[122] MeOH (16 mL) was added to a stirring solution of SmI_2 in THF (0.1 M, 64 mL) and the resultant purple mixture cooled to – 78 °C, where upon the reaction turned dark green. Di-ester **481** (300 mg, 1.51 mmol) as a solution in THF (5 mL) was then added drop-wise over a period of 10 minutes and the reaction allowed to stir at – 78 °C for a further 2 h. Brine (30 mL), followed by citric acid (378 mg, 1.80 mmol) was then added and allowed to stir for 10 minutes. EtOAc (80 mL) was added to the stirring solution and allowed to stir vigorously for 10 minutes, after which the reaction mixture was allowed to settle and the organic phase decanted off. This process was then repeated (4 x 70 mL EtOAc). The aqueous phase was transferred to a separating funnel and further extracted with EtOAc (2 x 70 mL), before the combined organic extracts were washed with brine (2 x 30 mL) and dried

over magnesium sulfate. Removal of the solvent under a reduced pressure gave the crude product as a yellow oil which upon purification by flash column chromatography, eluting with 5 % EtOAc / petrol gradually increasing the polarity to 12 % EtOAc / petrol, gave the 1, 4 reduced product **500** (125 mg, 0.618 mmol, 41 %) as a yellow oil, R_f = 0.61 (40 % EtOAc / petrol) and dimer **502** (62 mg, 0.308 mmol, 21 %) as a yellow oil, R_f = 0.53 (40 % EtOAc / petrol);

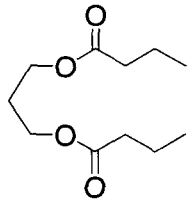
Data for **500**:

IR ν_{max} (film): 2965 (m), 2933 (m), 2869 (w), 1735 (s), 1376 (m) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.27 (4H, s, 2 x OCH_2), 2.30 (4H, t, *J* = 7.4 Hz, $C(O)CH_2$), 1.66 (4H, sext, *J* = 7.4 Hz, 2 x $C(O)CH_2CH_2CH_3$), 0.95 (6H, t, *J* = 7.3 Hz, 2 x CH_3) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7 (0), 62.3 (2), 36.4 (2), 18.7 (2), 13.9 (3) ppm.
LRMS (ES+): m/z (relative intensity), 225 $[M + Na]^+$ (100 %).
HRMS (ES+): $[M + Na]^+$ $C_{10}H_{18}O_4Na$ requires m/z 225.1097, found m/z 225.1095.

Data for dimer **502**:

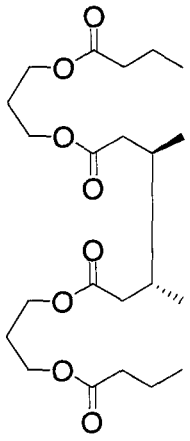
IR ν_{max} (film): 2964 (m), 2937 (m), 2877 (w), 1735 (s), cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.27 (8H, s, 4 x OCH_2), 2.37 (2H, dd, *J* = 14.8, 4.9 Hz, 2 x $C(O)CH_AH_BCHCH_3$), 2.30 (4H, t, *J* = 7.4 Hz, 2 x $C(O)CH_2CH_2CH_3$), 2.16 (2H, dd, *J* = 14.8, 8.8 Hz, 2 x $C(O)CH_ACH_BCHCH_3$), 2.09 - 2.00 (2H, m, 2 x CH_2CHCH_3), 1.66 (4H, sext, *J* = 7.4 Hz, 2 x $CH_2CH_2CH_3$), 0.95 (6H, t, *J* = 7.4 Hz, 2 x CH_2CH_3), 0.89 (6H, d, *J* = 6.5 Hz, 2 x $CHCH_3$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7 (0), 173.0 (0), 62.5 (2), 62.3 (2), 39.6 (2), 36.3 (2), 34.4 (1), 18.7 (2), 15.2 (3), 14.0 (3) ppm.
LRMS (ES+): m/z (relative intensity), 403 $[M + H]^+$ (5 %), 425 $[M + Na]^+$ (100 %).
HRMS (ES+): $[M + Na]^+$ $C_{20}H_{34}O_8Na$ requires m/z 425.2146, found m/z 425.2140.

Propane-1, 3-diyl dibutanoate 501 and *rac* - 1, 6-bis[3-(butanoyloxy)propyl] (3*R*, 4*R*)-3, 4-dimethylhexanedioate 503



501

$C_{11}H_{20}O_4$
Mw: 216.27 $gmol^{-1}$



503

$C_{22}H_{38}O_8$
Mw: 430.53 $gmol^{-1}$

Following the reported procedure by Kilburn,[122] MeOH (15 mL) was added to a stirring solution of SmI_2 in THF (0.1 M, 59 mL) and the resultant purple mixture cooled to – 78 °C, where upon the reaction turned dark green. Di-ester **484** (300 mg, 1.41 mmol) as a solution in THF (5 mL) was then added drop-wise over a period of 10 minutes and the reaction allowed to stir at – 78 °C for a further 2 h. Brine (30 mL), followed by citric acid (355 mg, 1.69 mmol) was then added and allowed to stir for 10 minutes. EtOAc (80 mL) was added to the stirring solution and allowed to stir vigorously for 10 minutes, after which the reaction mixture was allowed to settle and the organic phase decanted off. This process was then repeated (3 x 80 mL EtOAc). The aqueous phase was transferred to a separating funnel and further extracted with EtOAc (2 x 80 mL), before the combined organic extracts were washed with brine (2 x 30 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave the crude product as a yellow oil which upon purification by flash column chromatography, eluting with 5 % EtOAc / petrol gradually increasing the polarity to 20 % EtOAc / petrol, gave the 1, 4 reduced product **501** (112 mg, 0.518 mmol, 37 %) as a yellow oil, R_f = 0.69 (40 % EtOAc / petrol) and dimer **503** (50 mg, 0.232 mmol, 16 %) as a yellow oil, R_f = 0.58 (40 % EtOAc / petrol);

Data for **501**:

IR ν_{max} (film): 2965 (m), 2877 (w), 1732 (s), 1459 (m), 1383 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.14 (4H, t, *J* = 6.4 Hz, 2 x OCH_2), 2.28 (4H, t, *J* = 7.4 Hz, 2 x $C(O)CH_2$), 1.96 (2H, qn, *J* = 6.4 Hz, $OCH_2CH_2CH_2O$), 1.65 (4H, sext, *J* = 7.4 Hz, 2 x $C(O)CH_2CH_2CH_3$), 0.94 (6H, t, *J* = 7.4 Hz, 2 x CH_2CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9 (0), 61.1 (2), 36.5 (2), 28.4 (2), 18.8 (2), 14.0 (3) ppm.

LRMS (ES+): $^m/z$ (relative intensity), 239 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{11}H_{20}O_4Na$ requires $^m/z$ 239.1254, found $^m/z$ 239.1250.

Data for dimer **503**:

IR ν_{max} (film): 2965 (m), 2881 (m), 1735 (s), 1458 (m) cm^{-1}.

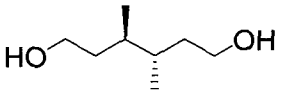
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.15 (4H, t, *J* = 6.4 Hz, 2 x OCH_2), 4.14 (4H, t, *J* = 6.4 Hz, 2 x OCH_2), 2.34 (2H, dd, *J* = 14.7, 4.9 Hz, 2 x $C(O)CH_AH_BCHCH_3$), 2.28 (4H, t, *J* = 7.4 Hz, 2 x $C(O)CH_2CH_2CH_3$), 2.14 (2H, dd, *J* = 14.7, 8.8 Hz, 2 x $C(O)CH_AH_BCHCH_3$), 2.06 - 2.00 (2H, m, 2 x CH_2CHCH_3), 1.96 (4H, qn, *J* = 6.4 Hz, 2 x $OCH_2CH_2CH_2O$), 1.65 (4H, sext, *J* = 7.4 Hz, 2 x $CH_2CH_2CH_3$), 0.94 (6H, t, *J* = 7.4 Hz, 2 x CH_2CH_3), 0.88 (6H, d, *J* = 6.5 Hz, 2 x $CHCH_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9 (0), 173.2 (0), 61.3 (2), 61.1 (2), 39.7 (2), 36.5 (2), 34.4 (1), 28.4 (2), 18.8 (2), 15.2 (3), 14.0 (3) ppm.

LRMS (ES+): $^m/z$ (relative intensity), 453 $[M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{22}H_{38}O_8Na$ requires $^m/z$ 453.2459, found $^m/z$ 453.2448.

***rac* - (3*R*, 4*S*)-3, 4-dimethylhexane-1,6-diol 504**



504

$C_8H_{18}O_2$

Mw: 146.23 $gmol^{-1}$

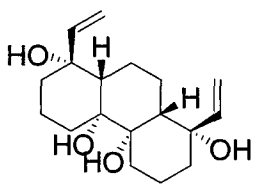
To a stirring solution of dimer **502** (62 mg, 0.154 mmol) and THF (3 mL), was added $LiAlH_4$ (70.0 mg, 1.85 mmol) in one portion. Slight effervescence was observed before heating the reaction to 55 °C and stirring for 3 h. Et_2O (20 mL) and H_2O (5 mL) were added to the reaction and the layers separated. The aqueous layer was back extracted with Et_2O (2 x 20 mL), and the combined organic phases washed with brine (15 mL) before being dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave a pale pink oil, which upon purification by flash column chromatography

eluting with 20 % EtOAc / petrol, gave the diol **504** (20.0 mg, 0.139 mmol, 89 %) as a colourless oil, R_f = 0.18 (50 % EtOAc / petrol);

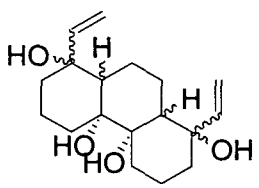
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.70 (2H, dt, *J* = 10.5, 6.8 Hz, 2 x OCH_AH_B), 3.64 (2H, dt, *J* = 10.5, 6.8 Hz, 2 x OCH_AH_B), 1.99 (2H, br s, 2 x **OH**), 1.67 - 1.55 (4H, m, 2 x CH_2), 1.47 - 1.38 (2H, m, 2 x CH_2CHCH_3), 0.81 (6H, d, *J* = 6.7 Hz, 2 x CH_3) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 61.5 (2), 37.8 (2), 33.0 (1), 14.7 (3) ppm.

Data is consistent with that reported by Zheng.[174]

***rac* - (1*R*, 4a*R*, 4b*S*, 8*S*, 8a*R*, 10a*S*)-1, 8-Diethenyldodecahydrophenanthrene-1, 4a, 4b, 8-tetrol 505, 1, 8-diethenyldodecahydrophenanthrene-1, 4a, 4b, 8-tetrols 506a and 506b and 1, 8-diethenyldodecahydrophenanthrene-1, 4a, 4b, 8-tetrols 506c-e**



505
$C_{18}H_{28}O_4$
Mw: 308.41 $gmol^{-1}$



506a-e
$C_{18}H_{28}O_4$
Mw: 308.41 $gmol^{-1}$

Following the reported procedure by Kilburn,[122] MeOH (21 mL) was added to a stirring solution of SmI_2 in THF (0.1 M, 83 mL) and the resultant purple mixture cooled to – 78 °C, where upon the reaction turned dark green. Di-ketone **487** (300 mg, 1.97 mmol) as a solution in THF (5 mL) was then added drop-wise over a period of 10 minutes and the reaction allowed to stir at – 78 °C for a further 2 h. Brine (40 mL), followed by citric acid (504 mg, 2.40 mmol) was then added and allowed to stir for 10 minutes. EtOAc (80 mL) was added to the stirring solution and allowed to stir vigorously for 5 minutes, after which the reaction mixture was allowed to settle and the organic phase decanted off. This process was then repeated (4 x 80 mL EtOAc). The aqueous phase was transferred to a separating funnel and further extracted with EtOAc (2 x 80 mL), before the combined organic extracts were washed with brine (2 x 30 mL) and dried over magnesium sulfate. Removal of the solvent under a reduced pressure gave the crude product as a yellow oil which upon purification by flash column chromatography, eluting with 10 % EtOAc / petrol gradually increasing the polarity to 25 % EtOAc / petrol, gave tetraol **505** (14.0 mg, 0.0908 mmol, 5 %) as a white crystalline solid, R_f = 0.31 (40 % EtOAc / petrol), mixture of tetraols **506a** and **506b**

(46.0 mg, 0.298 mmol, 15 %) as a yellow solid, R_f = 0.22 (40 % EtOAc / petrol) and mixture of tetraols **506c-e** (60.0 mg, 0.389 mmol, 20 %) as a yellow oil, R_f = 0.11 (40 % EtOAc / petrol);

Data for tetraol **505**:

IR ν_{max} (film): 3361 (br), 1945 (s), 2873 (s), 1455 (m), 1395 (m) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.71 (2H, dd, *J* = 17.3, 10.8 Hz, 2 x C**H**=CH_2), 5.24 (2H, dd, *J* = 17.3, 1.2 Hz, 2 x CH=C**H**$_{trans}$H$_{cis}$), 5.14 (2H, br s, 2 x O**H**), 5.07 (2H, dd, *J* = 10.8, 1.2 Hz, 2 x CH=CH$_{trans}$**H**$_{cis}$), 3.66 (2H, br s, 2 x O**H**), 2.05 (1H, dt, *J* = 13.9, 3.8 Hz, C**H**$_A$H$_B$), 1.99 (1H, dt, *J* = 13.7, 3.8 Hz, C**H**$_A$H$_B$), 1.83 - 1.80 (2H, m, 2 x C**H**$_A$H$_B$), 1.72 - 1.59 (6H, m, 4 x C**H**$_A$H$_B$, 2 x CH$_A$**H**$_B$), 1.51 - 1.41 (4H, m, 4 x CH$_A$**H**$_B$), 1.36 - 1.25 (4H, m, 2 x C**H**, 2 x CH$_A$**H**$_B$) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.5 (1), 112.7 (2), 76.7 (0), 75.2 (0), 43.1 (1), 39.2 (2), 34.5 (2), 18.2 (2), 17.9 (2), ppm.
LRMS (ES+): ^{m}/z (relative intensity), 331 $[M + Na]^+$ (100 %), 639 $[2M + Na]^+$ (70 %).
HRMS (ES+): $[M + Na]^+$ $C_{18}H_{28}O_4Na$ requires ^{m}/z 331.1880, found ^{m}/z 331.1876.
X-ray: Please see appendix.

506a and **506b** isolated as a 2:1 mixture of diastereoisomers. Both sets of diastereoisomer peaks reported in ^{1}H and ^{13}C NMR where possible.

IR ν_{max} (film): 3356 (br), 2945 (s), 2878 (m), 1450 (m), 1396 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.56 (2H, dd, *J* = 17.6, 10.9 Hz, 2 x C**H**=CH_2 minor), 5.71 (1H, dd, *J* = 17.2, 10.8 Hz, C**H**=CH_2 major), 5.71 (1H, dd, *J* = 17.2, 10.8 Hz, C**H**=CH_2 major), 5.25 (2H, dd, *J* = 17.6, 1.5 Hz, 2 x CH=C**H**$_{trans}$H$_{cis}$ minor), 5.24 (1H, dd, *J* = 17.3, 1.3 Hz, CH=C**H**$_{trans}$H$_{cis}$ major), 5.22 (1H, dd, *J* = 17.3, 1.2 Hz, CH=C**H**$_{trans}$H$_{cis}$ major), 5.12 - 5.05 (4H, m, 2 x CH=CH$_{trans}$**H**$_{cis}$ minor, 2 x CH=CH$_{trans}$**H**$_{cis}$ major), 4.74 (2H, br s, 2 x O**H**), 3.61 (2H, br s, 2 x O**H**), 3.59 (2H, br s, 2 x O**H**), 2.85 (2H, br s, 2 x O**H**), 2.04 - 1.26 (36 H, 8 x C**H$_2$**, 2 x C**H** minor and 8 x C**H$_2$**, 2 x C**H** major) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.5 (1, major), 143.1 (1, minor), 112.7 (2, major), 112.6 (2, major), 112.3 (2, minor), 76.9 (0), 76.7 (0), 75.7 (0), 75.7 (0), 75.2 (0), 75.0 (0), 49.0 (1), 43.1 (1), 42.5 (1), 40.9 (2), 39.2 (2), 39.1 (2), 34.7 (2), 34.5 (2), 20.3 (2), 18.2 (2), 18.2 (2), 18.1 (2), 17.9 (2), 16.9 (2) ppm.
LRMS (ES+): ^{m}/z (relative intensity), 331 $[M + Na]^+$ (60 %), 639 $[2M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{18}H_{28}O_4Na$ requires $^m/z$ 331.1880, found $^m/z$ 331.1875.

506c, **506d** and **506e** isolated as a 5:1.6:1 mixture of diastereoisomers. All three sets of diastereoisomer peaks reported in ^1H and ^{13}C NMR where possible.

Mpt: 95 - 97 °C, recrystallised from EtOAc.

IR ν_{max} (film): 3353 (br), 2941 (m), 2862 (w), 1395 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.49 (2H, dd, *J* =17.7, 10.8 Hz, 2 x C**H**=CH_2, d), 5.92 (2H, dd, *J* = 17.4, 10.8 Hz, 2 x C**H**=CH_2, e), 5.74 (1H, dd, *J* = 17.3, 10.8 Hz, C**H**=CH_2, c), 5.70 (1H, dd, *J* = 17.3, 10.8 Hz, C**H**=CH_2, c), 5.38 (2H, dd, *J* = 17.7, 0.9 Hz, 2 x CH=C**H**$_{trans}$H$_{cis}$, d), 5.24 (2H, dd, *J* = 17.3, 1.3 Hz, 2 x CH=C**H**$_{trans}$H$_{cis}$, c), 5.24 - 5.18 (2H, m, 2 x CH=C**H**$_{trans}$H$_{cis}$, e), 5.16 (2H, dd, *J* = 10.8, 0.9 Hz, 2 x CH=CH$_{trans}$**H**$_{cis}$, d), 5.08 (2H, dd, *J* = 10.8, 1.3 Hz, 2 x CH=CH$_{trans}$**H**$_{cis}$, c), 5.06 - 5.03 (2H, m, 2 x CH=CH$_{trans}$**H**$_{cis}$, e), 3.95 (1H, br s, O**H**), 3.60 (1H, br s, O**H**), 3.53 (1H, br s, O**H**), 3.51 (1H, br s, O**H**), 3.34 (1H, br s, O**H**), 2.33 (1H, br s, O**H**), 2.14 - 1.19 (54H, m, 8 x CH_2, 2 x C**H**, isomer c; 8 x CH_2, 2 x C**H**, isomer d; 8 x CH_2, 2 x C**H**, isomer e) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = [147.2, 144.9, 144.8, 144.5] (1), [113.7, 112.8, 112.7] (2), [78.0, 76.7, 76.6, 76.0, 75.6, 75.2] (0), [49.2, 46.4, 45.4, 44.9, 43.1] (1), [39.8, 39.7, 39.2, 34.5, 32.3, 31.1, 30.8, 27.3, 26.7, 25.4, 23.4, 20.9, 20.8, 19.5, 18.2, 17.9, 17.2, 17.1, 14.5] (2) ppm.

LRMS (ES+): $^m/z$ (relative intensity), 331 $[M + Na]^+$ (40 %), 639 $[2M + Na]^+$ (100 %).

HRMS (ES+): $[M + Na]^+$ $C_{18}H_{28}O_4Na$ requires $^m/z$ 331.1880, found $^m/z$ 331.1876.

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