UNIVERSITY OF SOUTHAMPTON

SAMARIUM DIIODIDE MEDIATED CASCADE RADICAL CYCLISATIONS OF METHYLENECYCLOPROPANE DERIVATIVES

By

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Doctor of Philosophy

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Abstract

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This thesis is concerned with the synthesis, and radical cyclisations of methylenecyclopropane derivatives. Special interest is given to developing samarium diiodide mediated cascade radical cyclisations to create polycyclic systems.

Chapter 2 describes the synthesis of cyclopentanone (**160** and **171**) and cyclohexanone cyclisation precursors (**184** and **185**), and the investigations into their cascade cyclisation to produce bicyclic diols **162** and **186**. The cyclisations of these precursors were found to be stereoselective due to chelation control with the samarium(III) ion.
Chapter 3 describes the samarium diiodide mediated cascade cyclisation of methylenecyclopropyl cyclohexanone adducts with a pendant alkene or alkyne. The cascade reactions were found to proceed with high yields and diastereoselectivity, which was dependent on the presence of co-solvent HMPA or MeOH.
Chapter 4 reports the investigations into the synthesis of natural product dihydrotournefortiolide **154** *via* a key radical cyclisation step using samarium diiodide. Cyclisations precursors **270** and **271** were synthesised from ethyl acetoacetate and preliminary studies into the cyclisations of such adducts were investigated.
Chapter 5 outlines the samarium diiodide mediated radical cyclisations of simple α,β-unsaturated ketones as model studies towards the natural product dihydrotournefortiolide **154**.

Nothing happens unless first a dream.
Carl Salsberg

Contents

Preface

The research described in this thesis was carried out under the supervision of Prof. Jeremy Kilburn at the University of Southampton between October 1998 and October 2001. No part of this thesis has been previously submitted at this or any other University.

Acknowledgements

I would like to thank Prof. Jeremy Kilburn for his encouragement and supervision during the course of this research.

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I must thank Mrs Joan Street and Mr Neil Wells for all their help with NMR experiments, Dr. John Langley and Miss Julie Herniman for their constant help with obtaining mass spectra, and Dr Mark Light for the X-ray crystallography work.

A special thanks to Mell Tyte, Lee Patient and especially Neil Wells for taking the time to proof read this thesis and for their constructive advice.

I would like to take this opportunity to thanks all my friends for their constant support and friendship; Fay Thomas for having the same name as me and confusing everyone we meet; Mell Tyte for the chats, alcohol and "cheese" support, (I am still not convinced it is me that is the bad influence!); Niggle Swain for being Niggle and Sara Chunn for putting up with him; Emma Shepherd for the long talks, shopping trips and massive car park bills; Alex Saint-Dizier for always being Dizzy and unconventional; Lee for making my last year in the lab. not quite so scary and for the endless games of pool (One day I will win a game!); Jon "if you didn't have a boyfriend I'd do you" Underwood for his amazing pole-dancing skills; Neil Wells for all the sober support, cinema trips and arm aching darts games; Richard "computerman" Fitzmaurice for his wonderful knowledge of EndNote (you really should get out more); Chlöe and the rats for endless sleepless nights and early morning wake up calls, and also the Kilburn group members past and present who made doing a PhD more fun than I ever imagined it could be.

I would also like to thank my mum, dad and brother Lee for their full support and for always keeping faith in me.

Last but not least I would like to say "Thanks to John", for getting me through the good and the bad times of my PhD and putting up with me for all this time.

Abbreviations

Ac	acetyl
AIBN	2,2'-Azobisisobutyronitrile
APCI	atmospheric pressure chemical ionisation
aq.	aqueous
br s	broad singlet
BuLi	butyl lithium
cat.	catalytic
CI	chemical ionisation
COD	cyclooctadiene
d	doublet
dba	dibenzylideneacetone
DCM	dichloromethane
de	diastereomeric excess
DEPT	distortionless enhancement by polarisation transfer
DIBAL-H	diisobutylaluminium hydride
DMA	*N*,*N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N*-dimethyl-*N*,*N*-propylene urea
DMSO	dimethylsulfoxide
ether	diethyl ether
eq.	equivalent
h	hour
HMPA	hexamethylphosphoramide
i	*iso*
IR	Infrared spectroscopy
J	coupling constant
LUMO	lowest unoccupied molecular orbital
m	multiplet
MCP	methylenecyclopropane
min	minute
n	normal

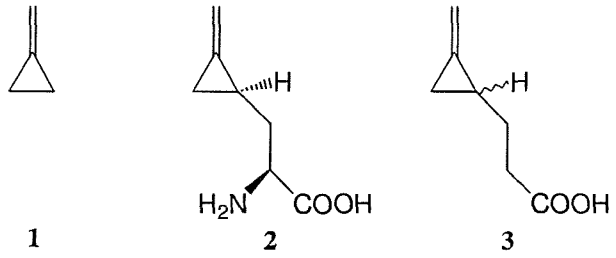
NBS	*N*-bromosuccinimide
nmr	nuclear magnetic resonance
nOe	nuclear Overhauser enhancement
p	*para*
PCC	pyridinium chlorochromate
petrol	petroleum ether b.p. 40-60°C
q	quartet
R_f	retention factor
RT	room temperature
SOMO	singly occupied molecular orbital
t	*tert*
t	triplet
TEA	triethylamine
THF	tetrahydrofuran
THP	tetrahydropyran
TMS	trimethylsilyl

CHAPTER 1

INTRODUCTION

1. METHYLENECYCLOPROPANE

1.1 BIOLOGICAL BACKGROUND



1 2 3

Figure 1

The methylenecyclopropane moiety **1** can be found in natural products such as Hypoglycin A **2**, which is an unnatural amino acid isolated from the arillus and seeds of unripe ackee (*Blighia sapida*). When ripe the ackee fruit is part of the Jamaican diet but ingestion of Hypoglycin A from unripe fruit has been mistakenly attributed as the cause of Jamaican vomiting sickness.[1] The actual cause is methylenecyclopropaneacetic acid **3**, which results from metabolic degradation of hypoglycin A.[2]

1.2 CHEMICAL BACKGROUND

Methylenecyclopropane derivatives have been used in synthetic transformations over the past 15 years and were chosen for their surprising stability accompanied with a high level of ring strain. The structure of methylenecyclopropane **1** has been determined by microwave spectroscopy.[3] The C(2) - C(3) bond length and the C(2) - C(1) - C(3) bond angle are larger compared with those of cyclopropane **4** due to steric strain imposed on the ring by the exocyclic double bond **(Figure 2)**. Indeed upon hydrogenation of the double bond 13.0 kcal/mol of strain energy is released.[3]

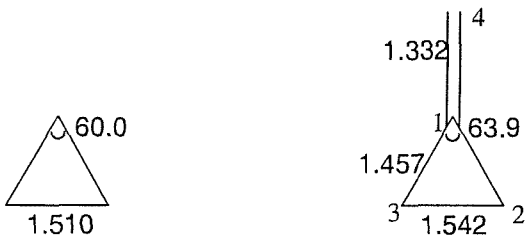
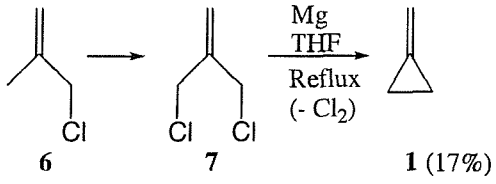


Figure 2

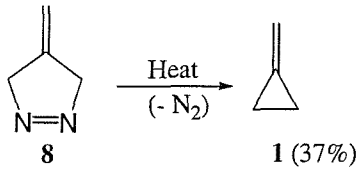
1.3 SYNTHESIS OF METHYLENECYCLOPROPANE AND SUBSTITUTED METHYLENECYCLOPROPANES.

Methylenecyclopropane (MCP) **1** is a volatile olefin with a boiling point of 11°C that can be stored in ampules. It is commercially available (Fluka) but methylenecyclopropane can be synthesised in a number of ways.
Dichloropropene **7**, prepared by chlorination of methallyl chloride **6**, can be dechlorinated with magnesium to give MCP **(Scheme 1)**.[4]



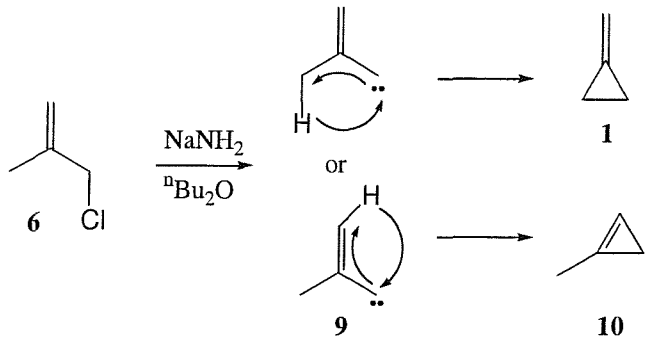
Scheme 1

Heating of pyrazoline **8** also produces methylenecyclopropane **1**, but this time the driving force is the loss of nitrogen **(Scheme 2)**.[5]



Scheme 2

However, methylenecyclopropane has been best prepared by the treatment of methallyl chloride **6** with base to afford an allyl carbene **9**, which in turn yields a mixture of methylenecyclopropane **1** and methylcyclopropene **10 (Scheme 3)**.[6]

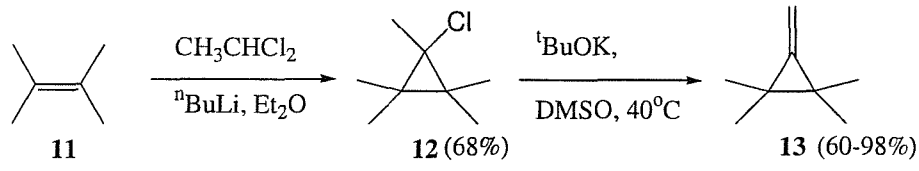


Scheme 3

Methylcyclopropene **10** can be converted into methylenecyclopropane **1** using ^{t}BuOK/^{t}BuOH.

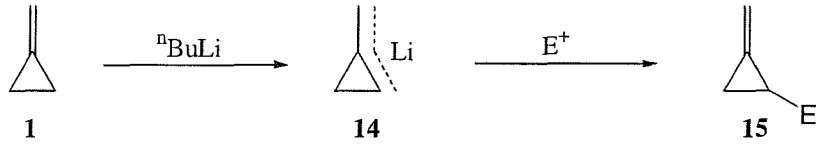
There are two main methods to prepare substituted methylenecyclopropanes:

1) by the addition of methyl chlorocarbene to a suitably functionalised alkene to give a cyclopropyl compound such as **12**, followed by dehydrohalogenation **(Scheme 4)**.[7]



Scheme 4

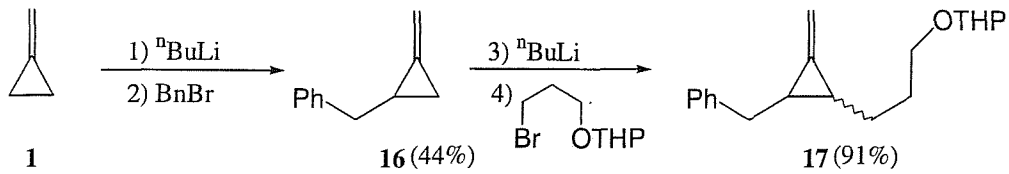
2) by deprotonation and alkylation of the methylenecyclopropane ring **(Scheme 5)**.[8,9]



Scheme 5

Methylenecyclopropane **1** can be deprotonated with ^{n}BuLi and reacted with a variety of electrophiles such as trimethylsilylchloride, alkylbromides and carbonyl compounds.[8,9]

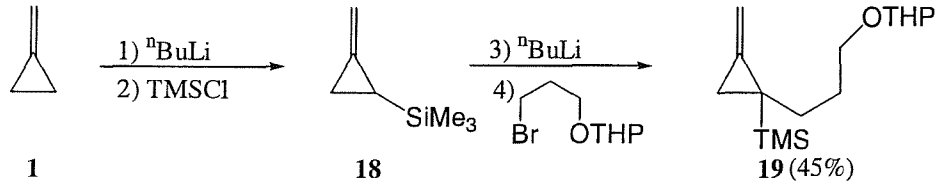
Sequential deprotonation and alkylation of MCP proceeds regioselectively to give 1,2-disubstituted methylenecyclopropanes, such as **17 (Scheme 6)**.[10]



1 **16** (44%) **17** (91%)

Scheme 6

However, the presence of Si directs the second deprotonation onto the silicon-bearing carbon to give a 1,1-disubstituted product, such as **19 (Scheme 7)**.[8,11]

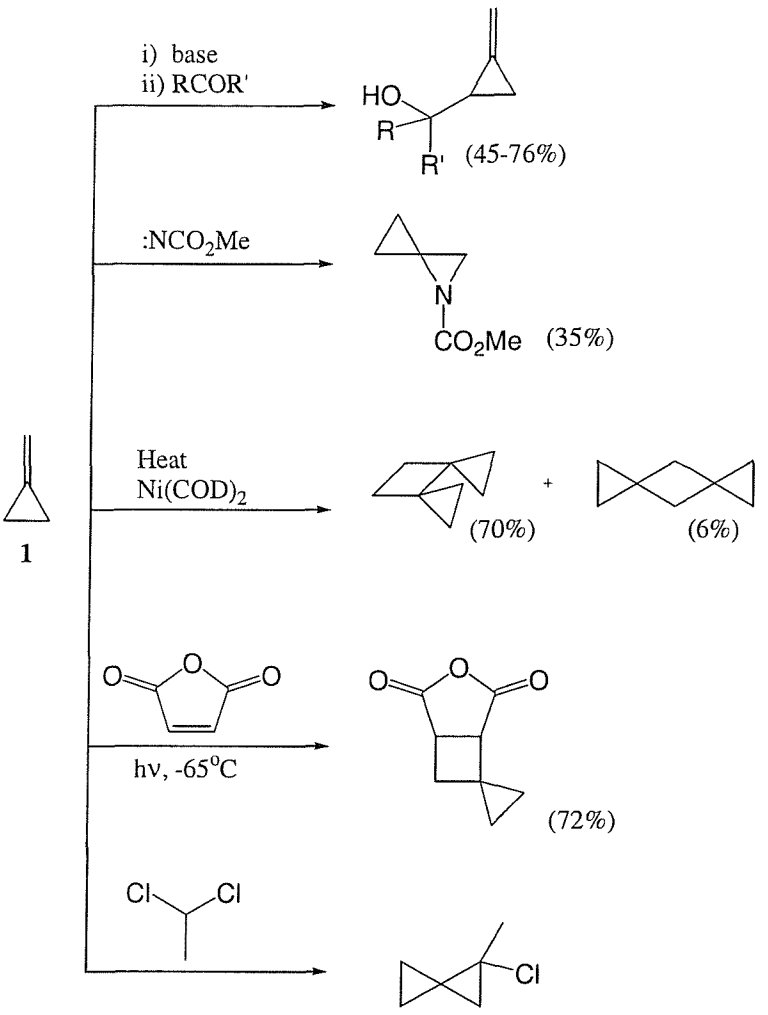


1 **18** **19** (45%)

Scheme 7

1.4 REACTIONS OF METHYLENECYCLOPROPANES

Methylenecyclopropane, due to its inherent ring strain, has been the subject of many mechanistic investigations. Its derivatives have served as key intermediates in synthetic sequences[8,9] and it has a broad chemistry of its own **(Scheme 8)**.[8,9,12-14] They are unlike three membered heterocycles which have a tendency to react *via* open chain 1,3 dipolar intermediates. Reactive methylenecyclopropane derivatives have been used in numerous reactions and due to the alkene moiety can undergo electrophilic additions, carbene additions and Diels-Alder reactions, leaving the cyclopropane ring intact in the products **(Scheme 8)**.[8,9,12-14]



Scheme 8

[3+2] CYCLOADDITIONS

Significant interest lies in the synthesis of five membered rings *via* cycloaddition reactions. Methylenecyclopropane can undergo transition metal catalysed [3 + 2] cycloadditions with alkenes to form five membered rings by the cleavage of either the distal or proximal bond of the cyclopropyl ring **(Figure 3)**.

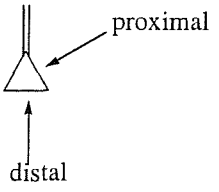
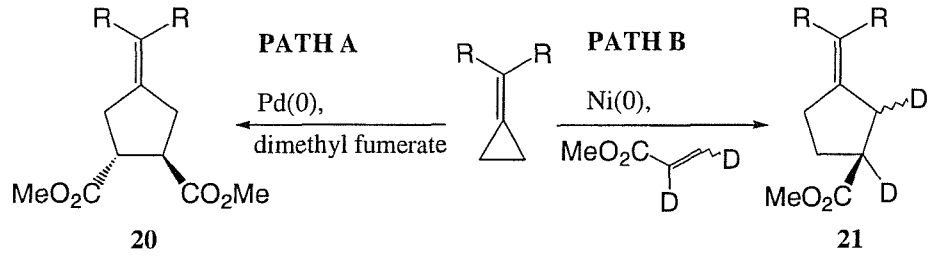


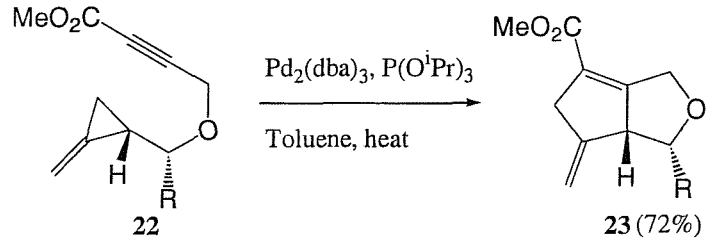
Figure 3

The nickel or palladium catalysed reactions between methylenecyclopropane and an alkene or alkyne have received considerable attention **(Scheme 9)**.[12] Palladium or nickel catalysts facilitate this cycloaddition process equally although the regiochemical outcome of the reactions is highly dependent on the nature of the metal and it is associated ligands. Nickel catalysts, particularly in the absence of phosphine ligands, favour formation of products derived from cleavage of the proximal bond of the cyclopropane (path B), whereas palladium catalysts yield cycloadducts derived from distal bond cleavage (path A) **(Scheme 9)**.[12]



Scheme 9

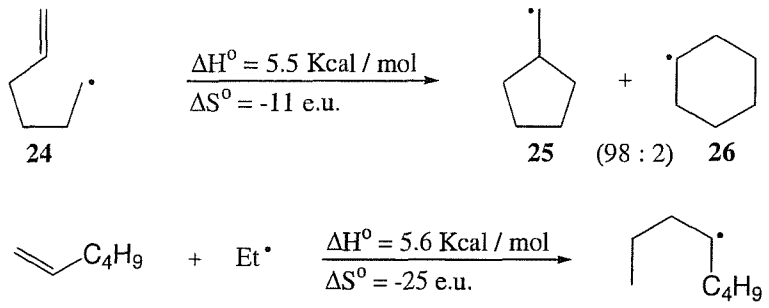
Intramolecular [3+2] cycloadditions can also occur **(Scheme 10)**.[15]



Scheme 10

1.5 INTRAMOLECULAR RADICAL CYCLISATIONS

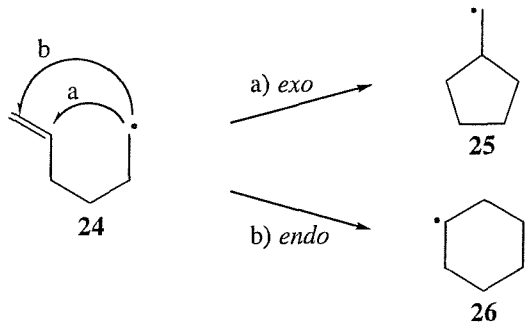
Intramolecular cyclisation reactions have found much use in natural product synthesis, especially for the formation of five membered rings.[16] The efficiency of the intramolecular cyclisation is the result of less negative activation entropies compared with those of the intermolecular analogues **(Scheme 11)**.[17]



Scheme 11

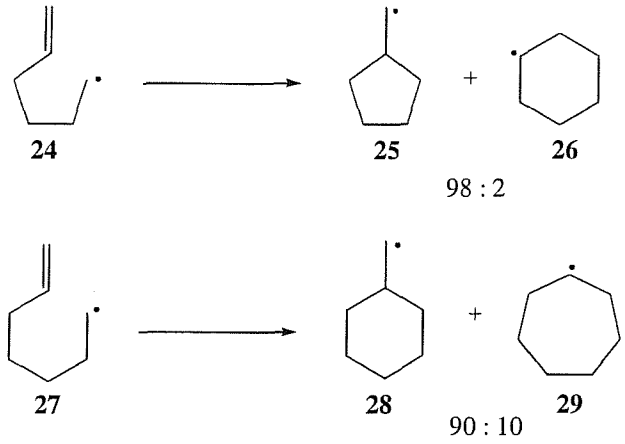
REGIOSELECTIVITY

For intramolecular cyclisations the radicals can cyclise in two possible ways, *exo* or *endo* **(Scheme 12)**. Baldwin has defined a system to classify types of cyclisation and has suggested guidelines for which cyclisations will be favoured.[18]



Scheme 12

5-Hexenyl **24** and 6-heptenyl **27** radicals both cyclise in the *exo* manner, in accordance with Baldwin's rules, to give the less thermodynamically favoured primary radicals **25** and **28 (Scheme 13)**.



Scheme 13

Beckwith has explained the observed regioselectivities using stereoelectronic arguments.[19] The addition of an alkyl radical to an olefin proceeds *via* an unsymmetrical transition state in which three atoms involved in bond breaking and bond formation are at the corners of an obtuse triangle orthogonal to the nodal plane of the π system **30 (Figure 4)**. The overriding frontier molecular orbital interaction in this transition state is that between the radical SOMO and the alkene LUMO (π^*) **31**. Therefore, transition states **32** and **33** are favoured for the cyclisations **(Figure 4)**. The synthesis of 6-membered rings *via* cyclisation of 6-heptenyl radicals is synthetically less useful than the synthesis of 5-membered rings since the rate of cyclisation is twenty times slower. The decrease in rate leads to an increase in the amount of reduced uncyclised product and to competition by 1,5-allylic hydrogen abstraction.[20,21]

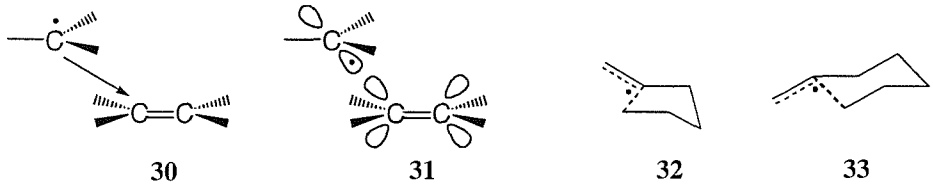
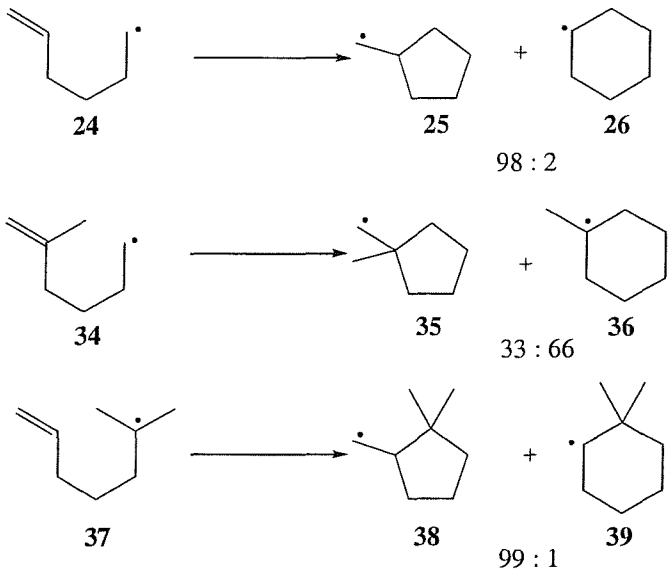


Figure 4

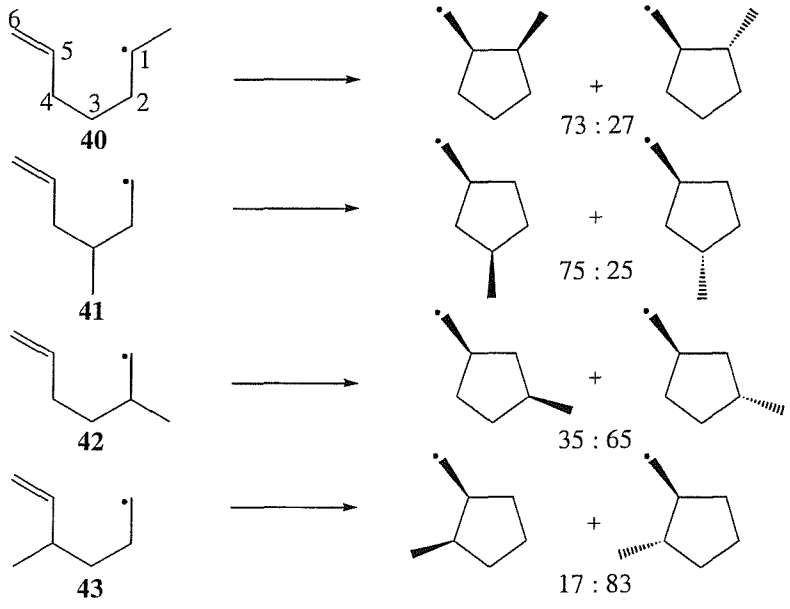
The regiochemistry of cyclisations can be affected by substitution on the alkene,[19] probably due to steric influence, but substituents at the radical centre have only small effects **(Scheme 14)**.



Scheme 14

STEREOSELECTIVITY

Beckwith has defined a set of guidelines governing ring closure of substituted hexenyl radicals,[22] which explains the observation that 1- or 3- substituted 5-hexenyl radicals give preferentially *cis* products, and that 2- and 4- substituted radicals give predominantly *trans* products **(Scheme 15)**.



Scheme 15

In Beckwith's model the early transition state resembles a cyclohexane ring and prefers a chair-like structure to a boat-like structure, and the substituents preferentially adopt pseudo-equatorial positions **(Figure 5)**.[23]

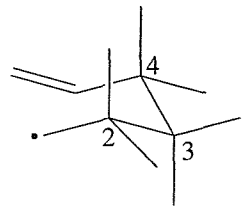
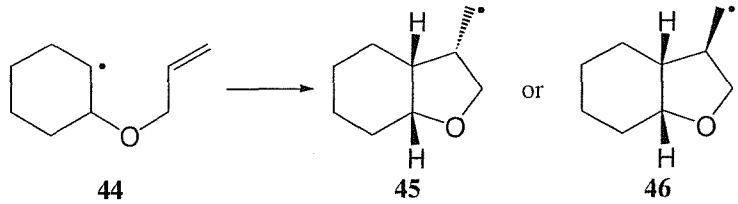


Figure 5

However, this effect does not satisfactorily account for the results observed for the cyclisation of 1-substituted radicals and it is thought that additional stereoelectronic factors may be important in this case.[24]

1.6 INTRAMOLECULAR RADICAL CYCLISATIONS TO FORM BICYCLIC PRODUCTS

Model studies by Beckwith[25-29] and RajanBabu[30] with cyclohexenyl radicals show that intramolecular 5-*exo* cyclisations onto an alkene moiety result in *cis* fused products as well as a new methyl chiral centre **(Scheme 16)**. Assuming that the reaction goes through a chair-like transition state, then if the allyloxy group is equatorial the major product will be the *cis*-fused *syn* product **45**. However, if the allyloxy group is held axially then the *cis*-fused *anti* product **46** is the major product.



44 **45** **46**

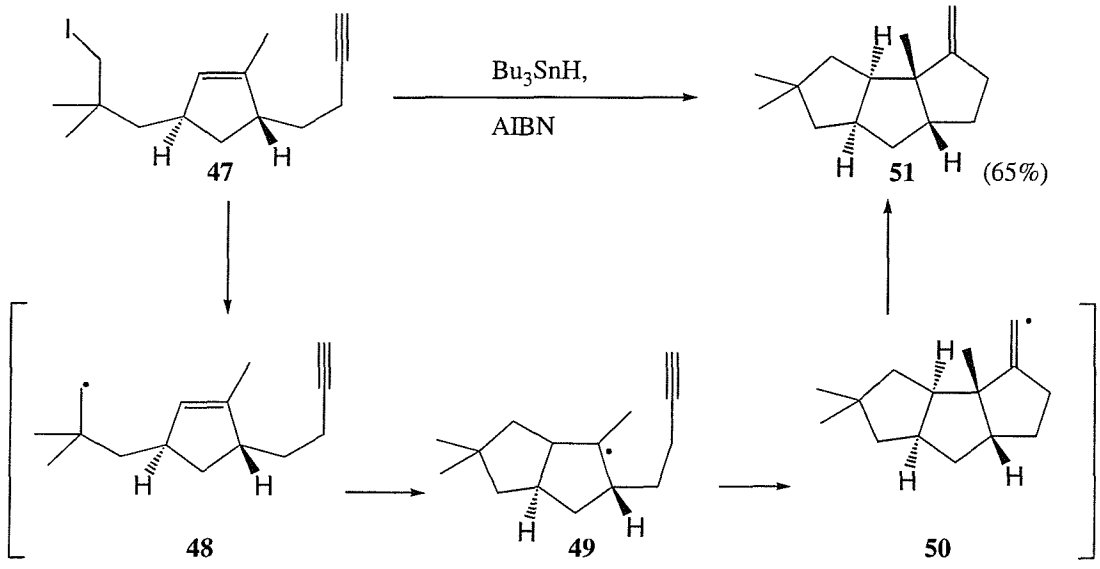
Scheme 16

1.7 TANDEM RADICAL CYCLISATIONS

Tandem and cascade radical cyclisation reactions are of interest because they allow the rapid construction of several C-C bonds in a single reaction step and are therefore more efficient than step-wise synthesis. Consequently, they can provide elegant routes to complex polycyclic compounds and natural products.[31-35]

There are many radical cyclisations in the literature, for example:

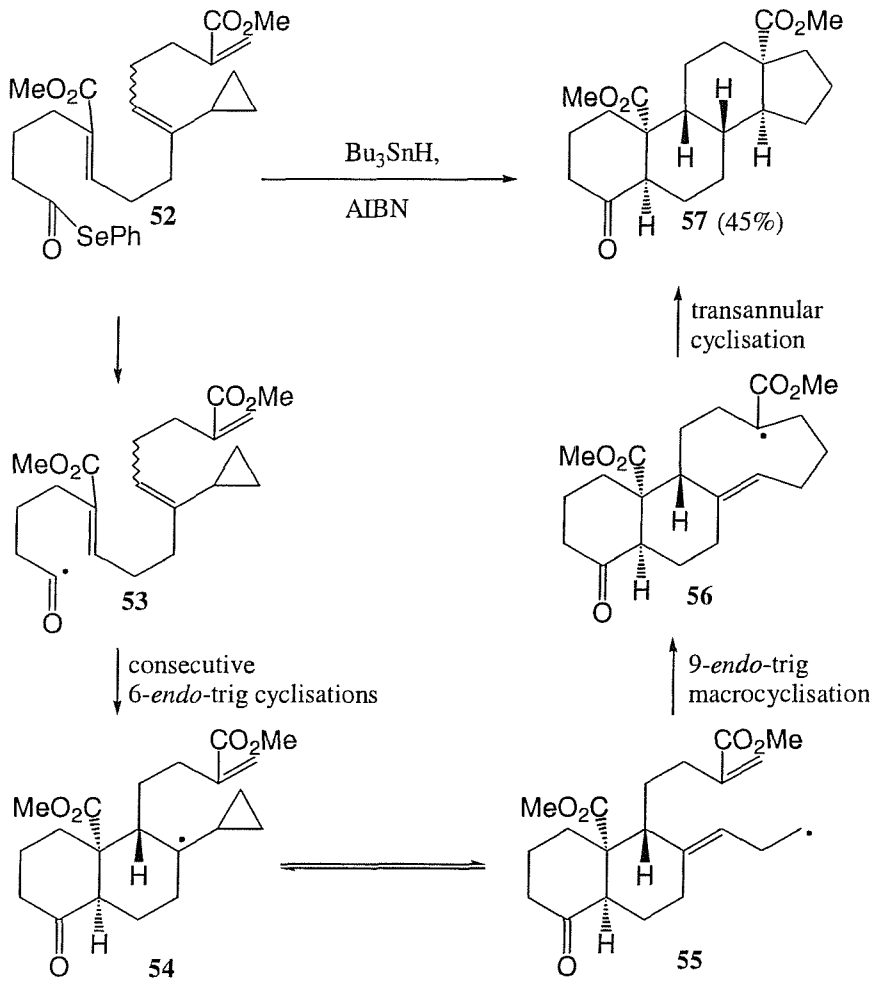
1) Tandem cyclisation to produce (±)-hirsutene **51 (Scheme 17)**.[36]



Scheme 17

Tributyltin hydride is used to generate radical **48** which undergoes a 5-*exo* cyclisation onto the alkene followed by a further 5-*exo* cyclisation onto the alkyne to yield hirsutene **51**.[36] Although tertiary radical **49** is relatively stable the second 5-*exo* cyclisation is driven by the formation of a σ- bond with the loss of a π-bond and is therefore energetically favoured.

2) Cascade cyclisation to produce a steroid ring construction **(Scheme 18)**.[37]

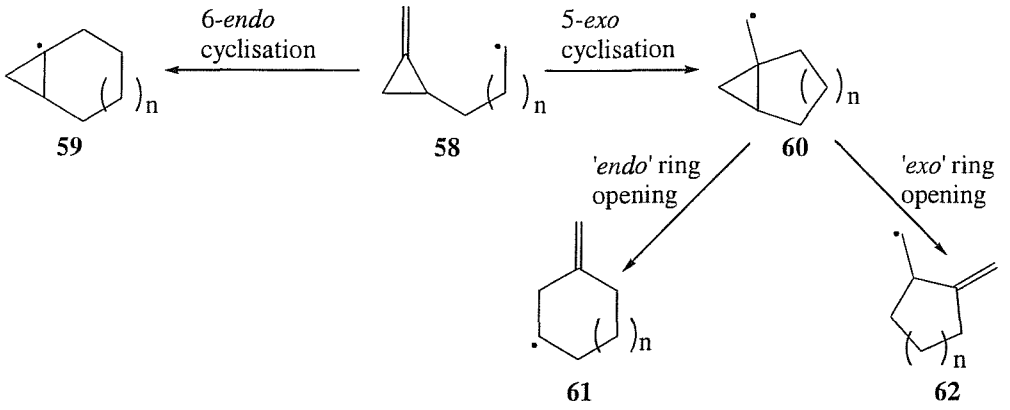


Scheme 18

Radical **53** is generated from the acylselenide **52** and undergoes a sequence of 6-*endo*-trig cyclisations to produce tertiary radical **54** which is in equilibrium with primary radical **55**. **55** undergoes a 9-*endo*-trig cyclisation and transannulation to produce the steroid-like structure **57**.[37]

1.8 RADICAL CYCLISATIONS OF METHYLENECYCLOPROPANE DERIVATIVES

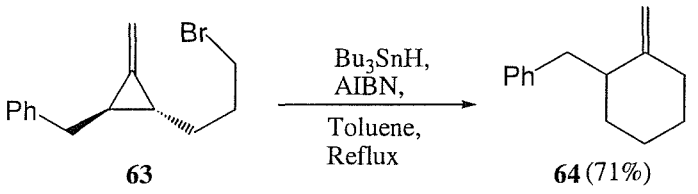
Radical cyclisations of methylenecyclopropyl substituted alkyl radicals have been utilised in an effort to develop new and efficient approaches to larger ring systems. The methylenecyclopropane unit was used as a radical trap, which provides a number of possible pathways that the radical cyclisation can follow **(Scheme 19)**.[38]



Scheme 19

Initial *endo* cyclisation of **58** might be favoured, due to less steric hinderance encountered on such a pathway, which would lead to a relatively stable cyclopropyl radical **59**. Alternatively, *exo* cyclisation of **58** would lead to an intermediate cyclopropyl methyl radical **60**, which would be expected to open rapidly, to give either ring expanded methylenecycloalkyl radical **61**, *via* '*endo*' ring opening, or cycloalkylmethyl radical **62**, *via* '*exo*' ring opening. Kinetically there is no clear preference for either ring opening, however '*exo*' ring opening would give a thermodynamically less favourable primary radical. Such cyclopropyl '*exo*' ring openings are often reversible and consequently result in the thermodynamically favoured product **61**.[39]

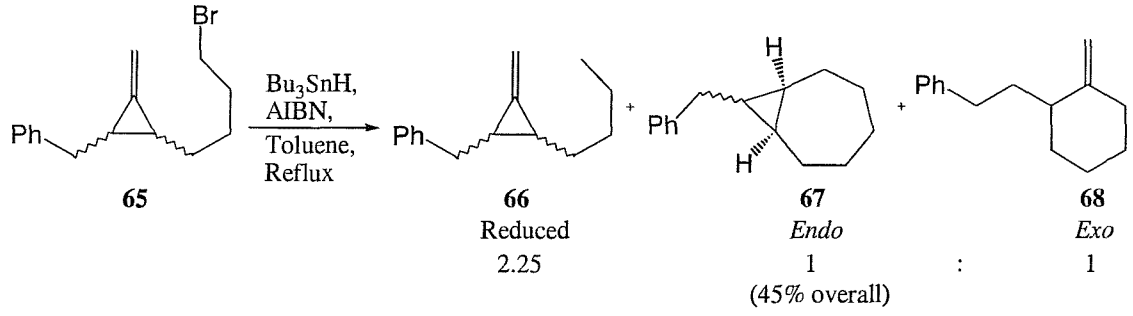
Investigations by Destabel have shown that (methylenecyclopropyl)propyl radical generated from, for example, **63** cleanly gave methylenecyclohexane **64** which resulted from a 5-*exo* cyclisation, followed by the '*endo*' ring opening of the intermediate cyclopropylmethyl radical (**Scheme 20**).[10,11,38]



Scheme 20

It was therefore concluded that (methylenecyclopropyl)propyl radicals can be expected to cyclise exclusively in 5-*exo* fashion, followed by '*endo*' ring opening to give the ring expanded methylenecyclohexane product.

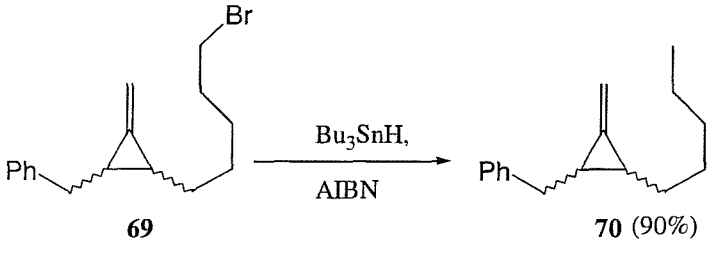
(Methylenecyclopropyl)butyl radical generated from bromides such as **65**, gave a mixture of products resulting from *exo* and *endo* cyclisation and also from straightforward reduction (**Scheme 21**).[10,11,38]



65 → **66** Reduced 2.25 : **67** *Endo* 1 (45% overall) : **68** *Exo* 1

Scheme 21

Cyclisation of (methylenecyclopropyl)pentyl radical derived from, for example, **69** simply gave the reduced, uncyclised product (**Scheme 22**).[10,11,38]

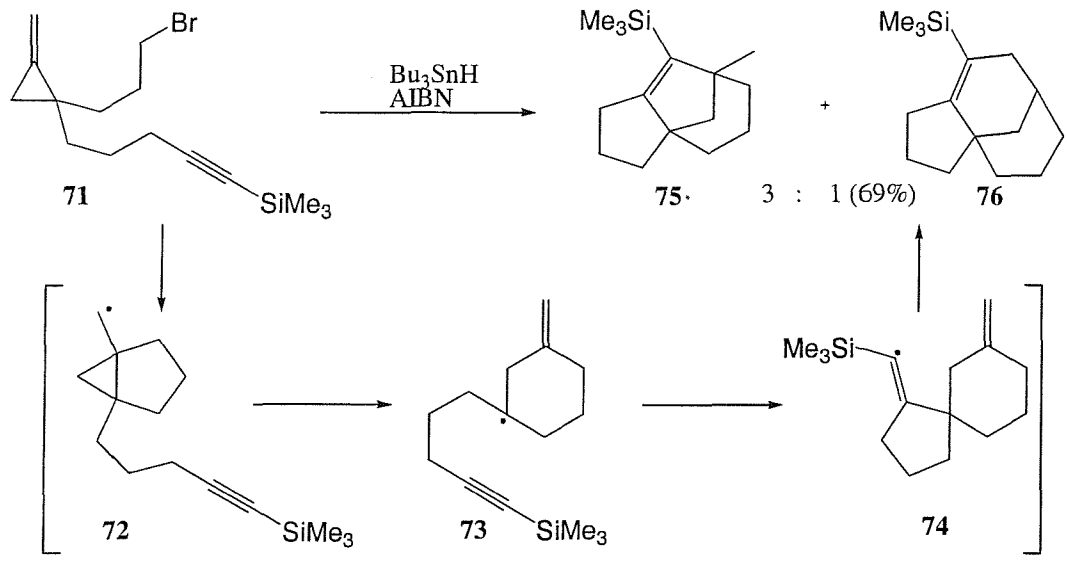


69 → **70** (90%)

Scheme 22

1.9 TANDEM RADICAL CYCLISATIONS OF METHYLENECYCLOPROPANE DERIVATIVES

Continuing the investigations with radical cyclisations of methylenecyclopropane derivatives, Santagostino showed that cyclisation of **71** ultimately led to the tricyclic compounds **75** and **76** *via* the spirocyclic vinyl radical **74** (**Scheme 23**).[40,41] Radical **72** generated from bromide **71**, cyclises onto methylenecyclopropane and then opens to give methylenecyclohexane radical **73**. Intramolecular cyclisation of radical **73** onto the alkyne moiety affords the reactive vinyl radical **74**, which can further cyclise onto the methylenecyclohexane with the observed 3:1 regioselectivity.[40,41] Several other examples of tandem cyclisations involving methylenecyclopropane derivatives have also been described.[42,43]



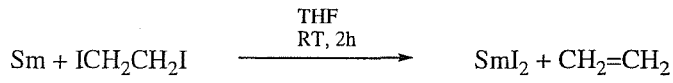
Scheme 23

A major disadvantage of these previous syntheses is that they use tributyltin hydride, which is very toxic, and difficulties can occur in the removal of tin residues.

2. SAMARIUM(II) IODIDE

Radical reactions in the past have traditionally concentrated on the tin hydride method to generate radicals from alkyl halides. However, a number of alternative methods exist,[44,45] one of which utilises samarium diiodide. SmI_2 has made a significant contribution to synthetic methodology during the last twenty years, and became of general interest and importance during 1980, when Kagan and co-workers developed a convenient '*in situ*' synthesis.[46] Since then, SmI_2 has rapidly become an established reagent through the work of Kagan,[46,47] Curran,[48] Inanaga,[49] Molander,[50] and many others.

SmI_2 is unusual because it is a powerful, yet selective, one-electron reducing agent that can be prepared in moderate concentration (0.1M) in THF. Samarium powder reacts smoothly with 1,2-diiodoethane in THF to give samarium diiodide **(Scheme 24)**.[46]



Scheme 24

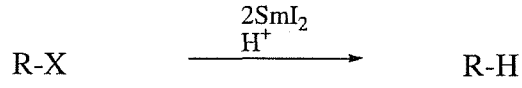
Solutions of samarium diiodide are deeply coloured *e.g.* blue in THF, purple in HMPA-THF, deep green in MeOH-THF; additionally Sm^{3+} salts are light yellow or orange and this allows the progress of the reaction to be followed by simply watching

the colour change. Samarium diiodide reactions proceed slowly in THF, but are greatly accelerated by the presence of a co-solvent, such as HMPA or MeOH. Samarium diiodide ligated to HMPA is a very powerful reductant; it is well established that electron-donating ligands will increase the reduction potentials of low valent metals. Samarium diiodide can have many ligands, so it is probably ligated to several HMPA molecules, thus increasing the reaction rate of the samarium-mediated reactions.[48]

Samarium diiodide mediated transformations can be split into three main groups:

1) **Functional Group Reductions**

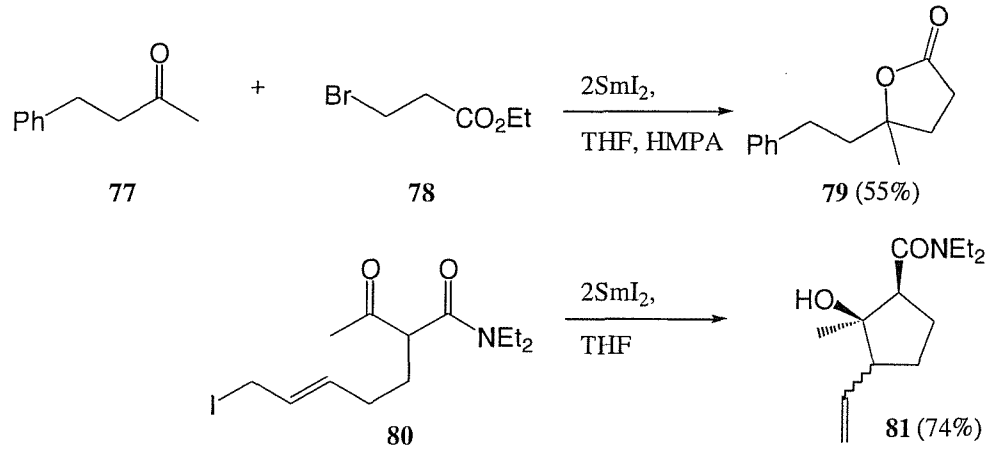
Functional group reductions include the reduction of sulfoxides and sulfones, epoxides, halides (and related leaving groups), conjugated double bonds and carbonyl groups (**Scheme 25**).[48]



Scheme 25

2) **Reductive Coupling of Halides with π-Bonds**

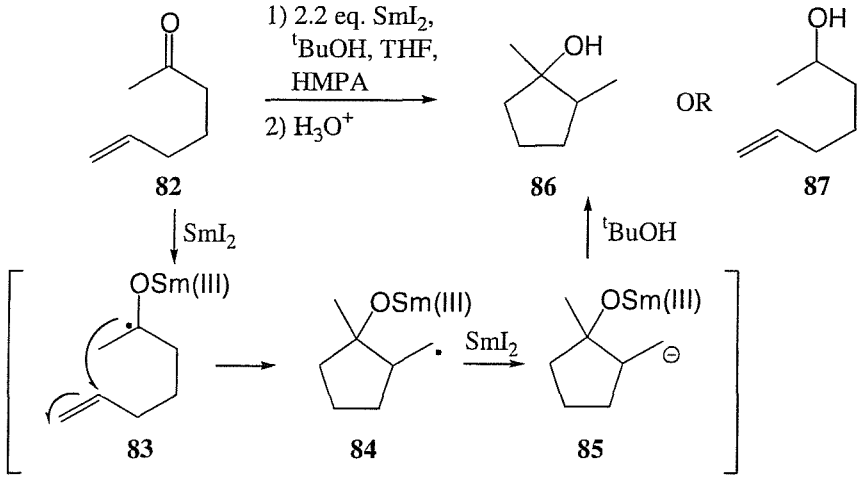
These transformations show similarities to the addition of organolithium or Grignard reagents to carbonyls, however Molander[51] and Inanaga[52] have demonstrated that samarium diiodide can mediate transformations, which are not readily conducted by standard Grignard-type procedures (**Scheme 26**).



Scheme 26

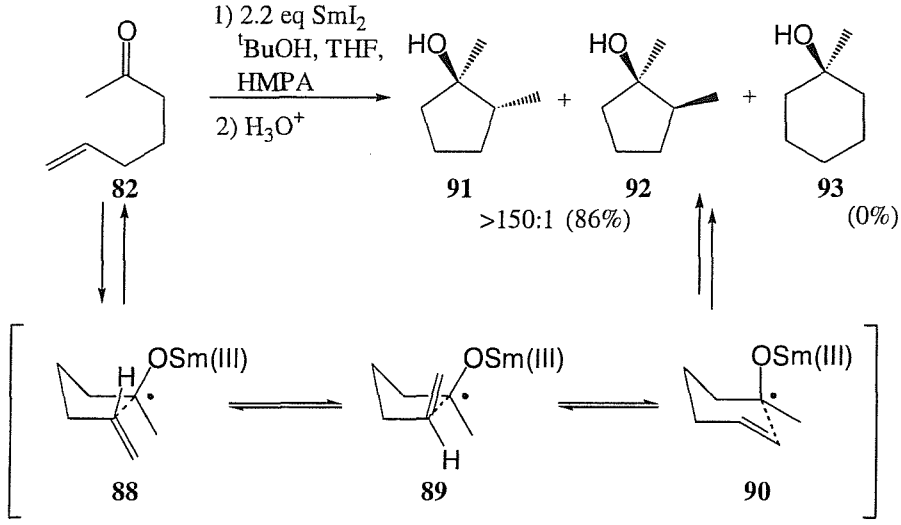
3) **Reductive Coupling of two π-bonds**

Includes pinacol couplings and reductive couplings of carbonyls with both conjugated and isolated alkenes.[48] Detailed studies by Molander investigated the intramolecular cyclisations of ketyl radicals onto unactivated alkenes (**Scheme 27**).[53] Ketone **82** was reduced to ketyl radical **83** using a solution of samarium diiodide in THF with HMPA and ^{t}BuOH. Ketyl radical **83** undergoes a cyclisation onto the unactivated alkene to give primary radical **84**, which is further reduced by another equivalent of samarium diiodide to yield anion **85**. Protonation from ^{t}BuOH furnishes the alcohol **86**. However, if the cyclisation was not favoured, ketyl radical **83** could be reduced to its corresponding anion, followed by quenching to yield alcohol **87**. Thus, for a cyclisation to happen it must occur before the ketyl radical is further reduced.



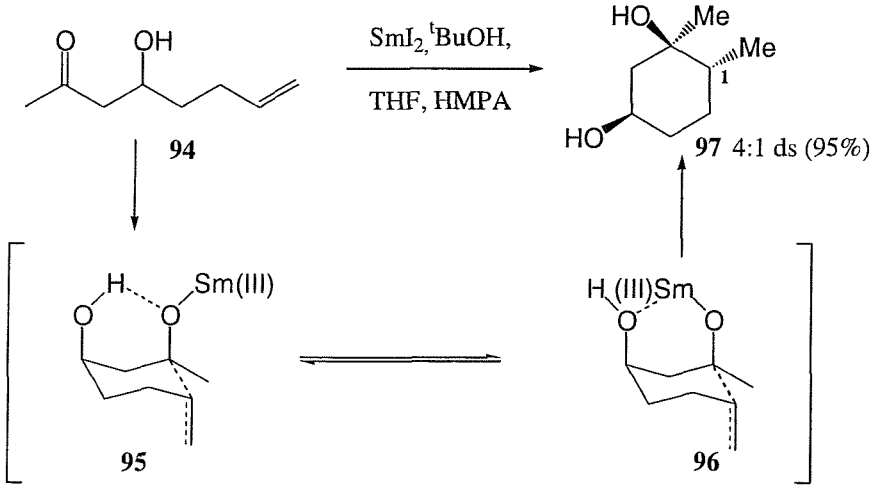
Scheme 27

Ketyl radical **83** could cyclise in a 5-*exo* or a 6-*endo* manner as before (**Scheme 12**). However, the 6-*endo* cyclisation is not favoured and no cyclohexyl product was observed due to the poor orbital overlap in the 6-*endo* transition state **90** (**Scheme 28**). The 5-*exo* cyclisation gave cyclopentyl products **91** and **92** in an overall yield of 86% and a >150:1 diastereomeric ratio. Major isomer **91** was obtained through transition state **88**, which has the π-system and the ketyl oxygen *gauche* to each other allowing the cyclisation to occur smoothly. However, when the π-system and the ketyl oxygen are eclipsed **89** electronic repulsions occur[24] and the cyclisation is disfavoured and therefore only a small amount of isomer **92** was observed.



Scheme 28

Chelation with the Sm(III) ion can also play a major role in the stereochemical outcome of a cyclisation reaction. Intramolecular H-bonding **95** or chelation with the Sm(III) ion **96** allow both alcohols to end up on the same side of the cyclohexane ring to afford *cis* diol **97** in 95% yield (and 4:1 ds with the methyl group at C1 down) **(Scheme 29)**.[53]

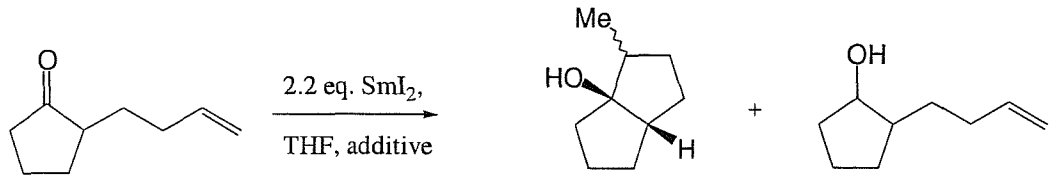


Scheme 29

The stereochemistry of the major diastereomeric diol **97** was established using single crystal X-ray analysis.[53] In the absence of HMPA, only reduction of the ketone is observed with no cyclisation.

2.1 SOLVENT EFFECTS

The diastereoselectivity of a samarium diiodide cyclisation reaction can be influenced by the additive/co-solvent used. Molander has conducted in-depth studies on a range of ketones, such as **98**, to observe the effect that the additives HMPA and DMPU have on the reductive radical cyclisation **(Table 1)**.[54]

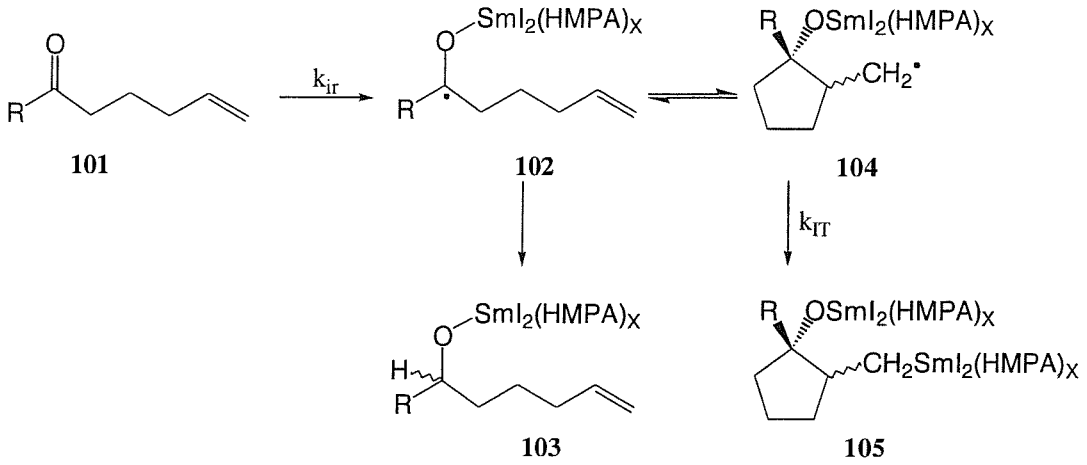


98 **99** **100**

Reaction conditions	**99**	de%	**100**	**98**
HMPA (8 equiv.)	100	>99	0	0
HMPA (4 equiv.)	100	>99	0	0
HMPA (2 equiv.)	98	96	2	0
No additive	62	92	5	33
DMPU (8 equiv.)	62	94	2	36

Table 1 The effects of the additives HMPA and DMPU on the reductive radical cyclisation of ketone 98.

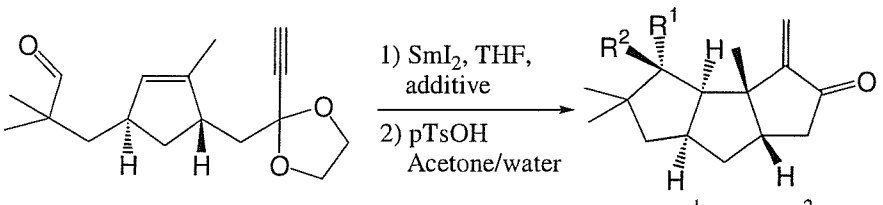
In general, the results from Molander's work indicate that with increasing concentration of HMPA the rate of hydrogen abstraction of **102** to give **103** decreases relative to that of cyclisation of **102** to give **104 (Scheme 30)**.[54] Molander suggests in the absence of HMPA, THF complexes with Sm(II) and is present when the samarium ion coordinates to the carbonyl before the reduction. The THF is then available as a hydrogen donor for the conversion of **102** to give **103** and hence as the cyclisation rate decreases for different substrates the amount of **103** increases. As HMPA is added to the reaction mixture it complexes with Sm(II) and displaces THF from the Sm(II) coordination sphere. Therefore HMPA is effectively shielding the reacting carbonyl centre from hydrogen atom donors allowing the cyclisation to occur. In this process the relative rate of hydrogen abstraction of **102** to give **103** decreases with respect to the rate of cyclisation.[54]



Scheme 30

An increase in diastereoselectivity was also observed with increasing HMPA concentration, which could be due to the bulky HMPA ligands destabilising the transition state that leads to the minor diastereomeric carbocycles. The transition state has the alkene moiety nearly eclipsed with the ketyl oxygen.[54]

Replacement of HMPA with DMPU gave lower yields of cyclised products and also a small decrease in stereoselectivity.[54] This small decrease in stereoselectivity with DMPU was also seen in Curran's synthesis of (±)-hypnophilin (**Scheme 31**).[55] Aldehyde **106** was cyclised with samarium diiodide in the presence of HMPA or DMPU. Tricyclic alcohol **107** was obtained exclusively in 57% yield with HMPA, when DMPU was used alcohol **107** was obtained in slightly better yield but another diastereoisomer **108** was also present in 6% yield.[55]



106

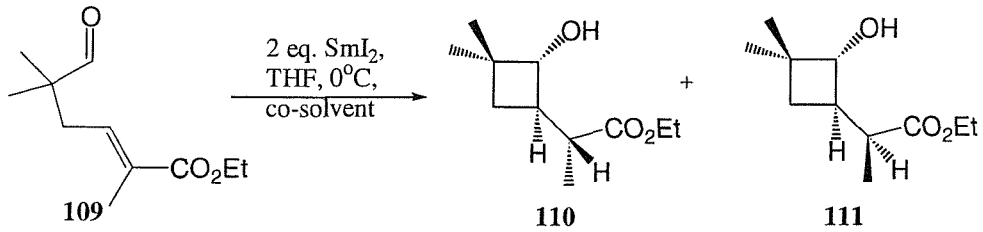
107: R^1 = OH, R^2 = H
108: R^1 = H, R^2 = OH

Additive	107	108
HMPA	57	0
DMPU	60	6

Scheme 31

HMPA is extremely toxic and so work by Procter investigated using alcohol co-solvents instead in the cyclisation of **109** (**Table 2**).[56] The alcohol is not only a proton source but it also increases the reducing potential of samarium diiodide. Cyclisations using EtOH and ^{t}BuOH were slow and did not give good stereoselectivity. Using

water as co-solvent gave the highest stereoselectivity but only a 44 % yield of cyclobutane. In the presence of MeOH as co-solvent high stereoselectivity was observed and a good yield (66%). However, when HMPA was added this yield decreased to 35%.[56]



109 110 111

Co-solvent	Additive	Time / min	110 : 111	Yield
H_2O		<1	4.5 : 1	44
MeOH		5	4 : 1	66
MeOH	HMPA	<1	4 : 1	35
EtOH		85	1 : 1	84
^{t}BuOH		540	1 : 2	53

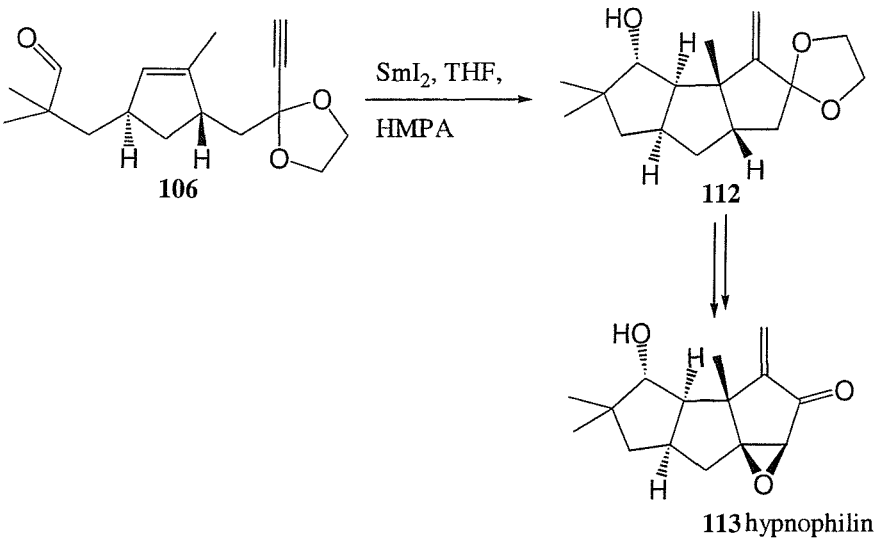
Table 2 Samarium diiodide cyclisations of 109 using alcohols as co-solvent

The optimal conditions proved to be MeOH:THF (1:4), which gave a high stereoselectivity and good yield.[56]

2.2 TANDEM RADICAL REACTIONS USING SAMARIUM DIIODIDE

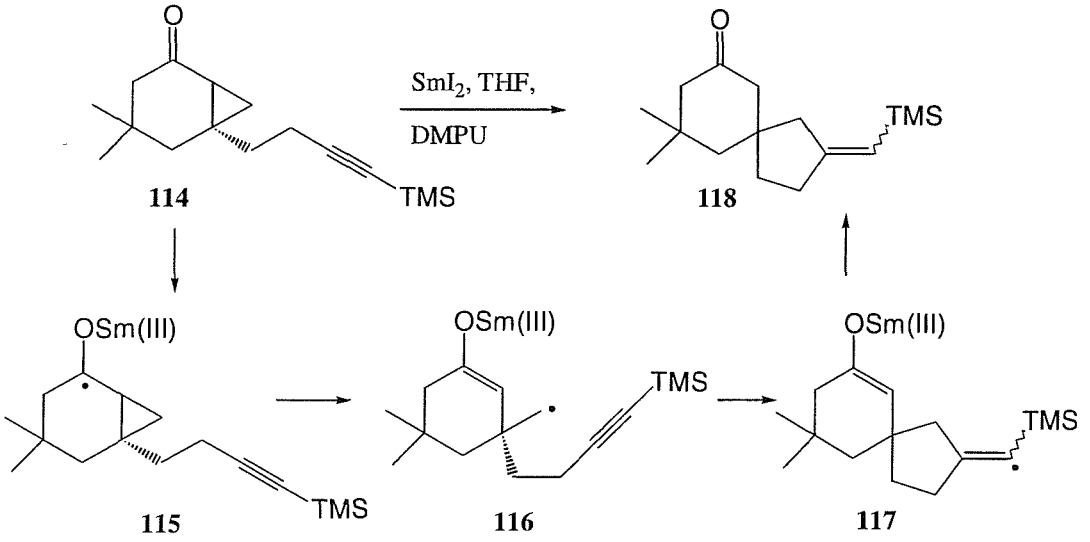
Tandem reactions are possible due to the ability of samarium diiodide to promote both one and two electron processes,[55] which can happen in any combination or order. We are interested in the radical-radical sequential processes,[57,58] of which there are few examples in the literature.[55,59,60] In order to work efficiently each radical cyclisation step must compete with reduction of the radical species to an anion, which would terminate the tandem sequence. One prominent example is the synthesis of (±)-hypnophilin **113** by Curran (**Scheme 32**).[55]

Aldehyde **106** is reduced to a ketyl radical by samarium diiodide, which initially undergoes a 5-*exo*-trig cyclisation, followed by a 5-*exo*-dig cyclisation to give **112**.



Scheme 32

Another example is Motherwell's synthesis of spirocycle cyclohexanone **118**, which was formed in 79% yield when ketone **114** was treated with samarium diiodide and after fragmentation of the cyclopropane **(Scheme 33)**.



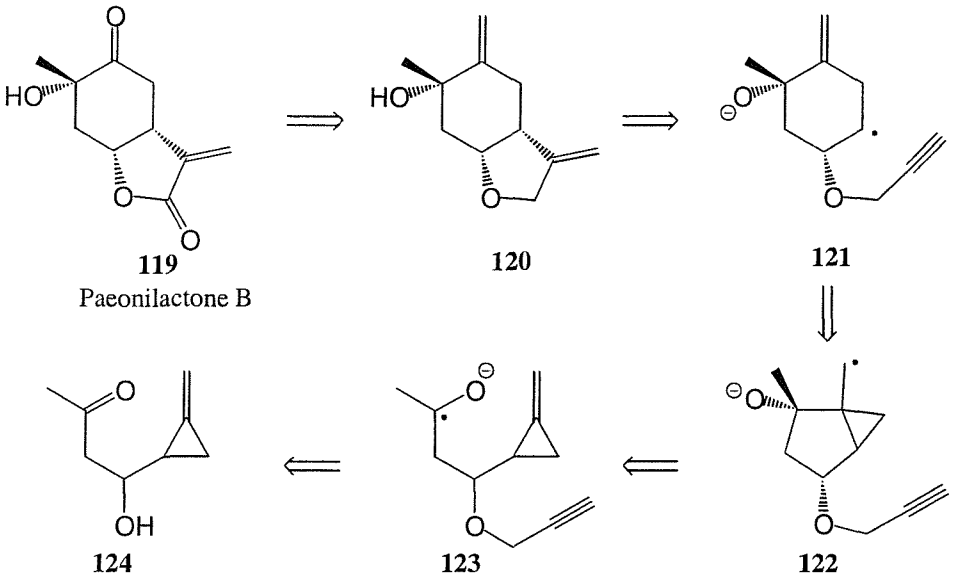
Scheme 33

2.3 DISCONNECTION OF PAEONILACTONE B

Previous work within the group considered cyclisations of alkyl radicals onto the methylenecyclopropane moiety.[10,11,38,40,41,43,61] The main direction of the work was to extend the methodology using ketyl radicals in the total synthesis of a natural product.[62] Cascade radical cyclisations were employed to show that a reasonably

complex natural product could be made in a short number of steps, and to demonstrate control of regio- and stereoselectivity in the key cyclisation step.[62]

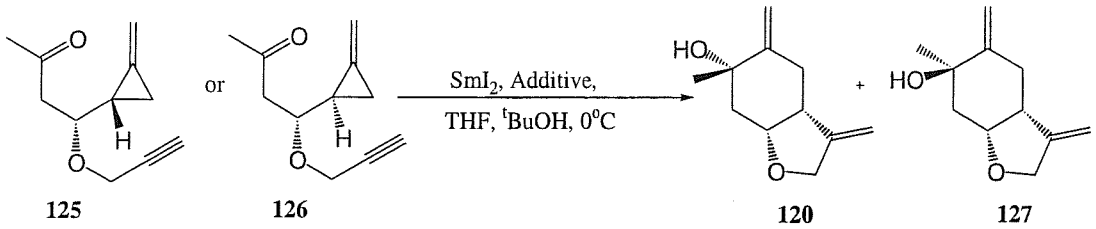
A retrosynthetic analysis of paeonilactone B **119 (Scheme 34)** suggested that the *cis*-fused bicyclic methylenecyclohexane **120** could be prepared by a 5-*exo* cyclisation of methylenecyclohexyl radical **121** onto a pendant alkyne, and **121** could, in turn arise from cyclisation of ketyl radical **123** onto the methylenecyclopropane unit with subsequent '*endo*' ring opening.[62]



Scheme 34

2.4 CYCLISATION STUDIES TOWARDS PAEONILACTONE B

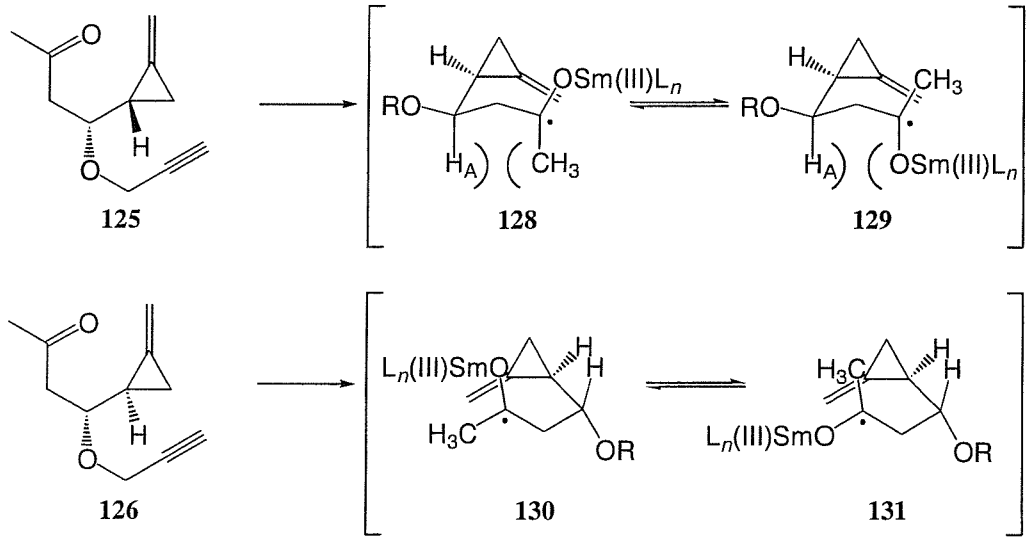
Ketones **125** and **126** were synthesised and obtained as a separable mixture of diastereoisomers.[63] Treatment of ketone **125** with SmI_2 and HMPA gave the desired bicyclic product as a mixture of **120** and **127**, in a 10 : 1 ratio and 63% yield. The same mixture of bicyclic products was obtained when DMPU was used as an alternative to HMPA but in a lower yield and in a 1.5 : 1 ratio **(Scheme 35)**.[63] However, treatment of ketone **126** with either additive gave the bicyclic product **127** in a good isolated yield and only a trace of the other diastereoisomer **120 (Scheme 35)**.



Starting material	Additive	Yield (%)	120 : 127
125	HMPA	63	10 : 1
126	HMPA	79	<1 : 30
125	DMPU	40	1.5 : 1
126	DMPU	62	<1 : 30

Scheme 35

The relative stereochemistry of the product is effectively determined in the first step and it seems likely that this proceeds through a chair-like transition state allowing the prop-2-ynyl ether substituent to adopt a pseudo-equatorial position **(Scheme 36)**.[62]

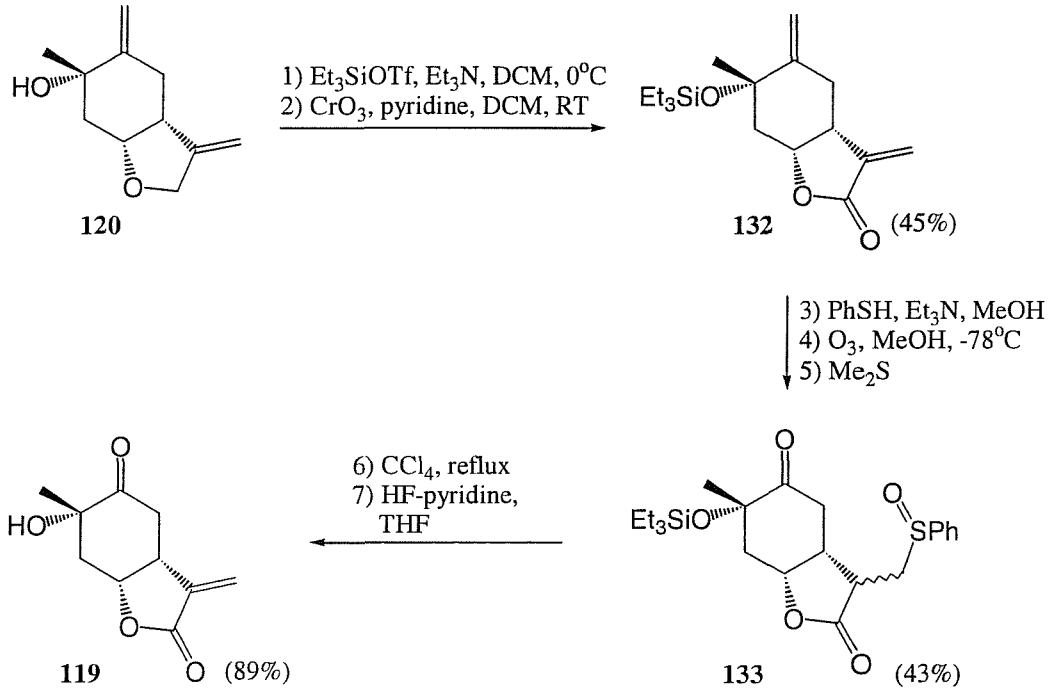


Scheme 36

Due to the bond angles of the methylenecyclopropyl group, the alkene moiety appears to be staggered between the oxygen of the ketyl radical and the methyl group. When HMPA is used as a co-solvent the $OSm^{III}(HMPA)_n$ group is very bulky and so it adopts a pseudo-equatorial position **128** to avoid a 1,3-diaxial interaction with H_A, **129**. Therefore, the product has the tertiary alcohol and the ether oxygen *cis* to each other in the bicyclic product **120**. Replacement of HMPA with DMPU reduces the steric bulk of the $OSm^{III}L_n$ group, leading to a lower selectivity for conformer **128**. When neither HMPA nor DMPU are present then the ketyl methyl becomes sterically dominant, which leads to a reversal in selectivity. However, the other diastereoisomer **126** is not

likely to proceed *via* a chair-like transition state, since the prop-2-ynyl ether substituent would be forced into a severely hindered axial orientation, so the first step of the cyclisation may well go through a boat-like transition state. In the boat-like transition state the alkene appears to be eclipsed with either the methyl group **130** or the oxygen of the ketyl radical **131**. The preferred conformer is now **130** as it alleviates the electronic repulsion between the ketyl oxygen functionality and the alkene π^* and so the product observed has the tertiary alcohol on the opposite side of the cyclohexane ring to the ether oxygen **127**. This preference is unaffected by replacing HMPA with DMPU.[62]

A short series of functional group transformations permitted elaboration of **120** to give paeonilactone B **119 (Scheme 37)**.[62]

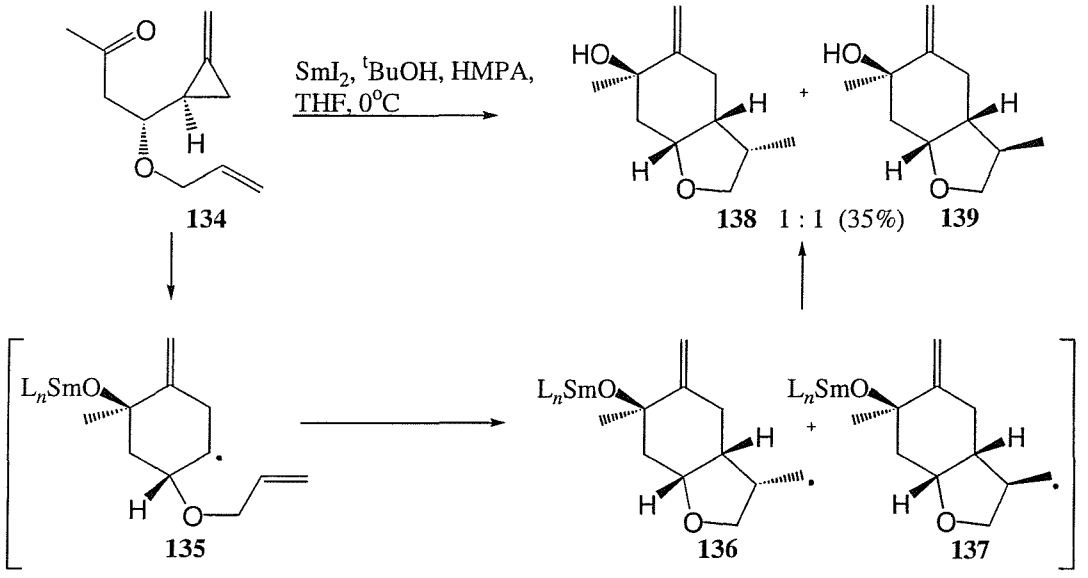


Scheme 37

2.5 CYCLISATION STUDIES TOWARDS PAEONILACTONE A

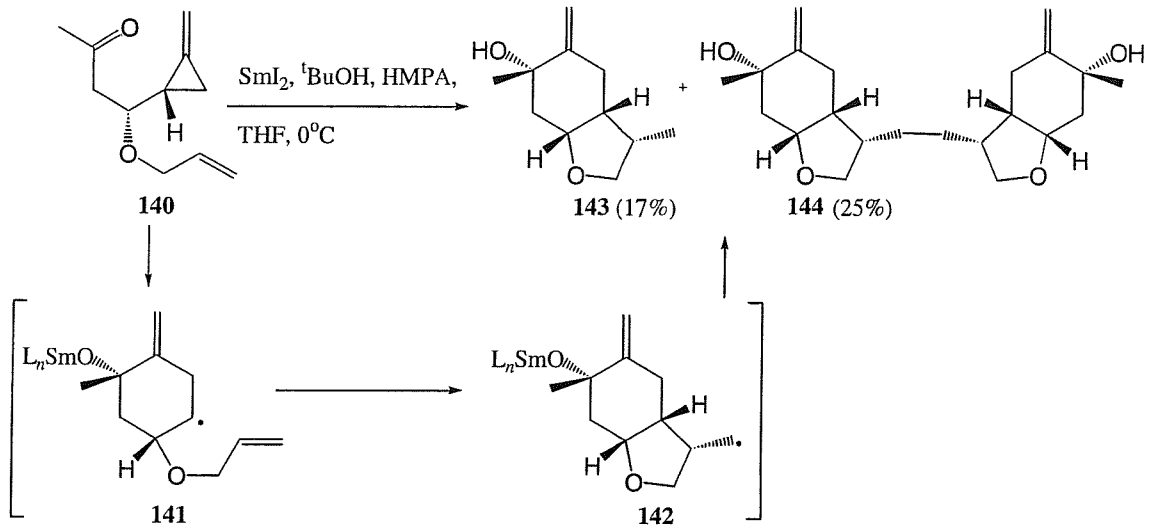
Having successfully completed the total synthesis of paeonilactone B, work was directed towards the synthesis of paeonilactone A, which involved the formation of a new stereocentre.[62] Allyl ether **134** was synthesised and treated with SmI_2 in the presence of HMPA. A 1:1 mixture of diastereoisomers **138** and **139** were obtained in a

35% yield. If the cyclisation of the allyl ether **134** occurred *via* a boat-like transition state, analogous to the propargyl ether **126** (*vide infra*), then the methylenecyclohexyl radical **135** would be formed essentially as a single diastereoisomer. The radical could then cyclise further to give the mixture of diastereoisomers **136** and **137**. The only difference between these diastereoisomers is the stereochemistry at the new methyl group **(Scheme 38)**.[62]



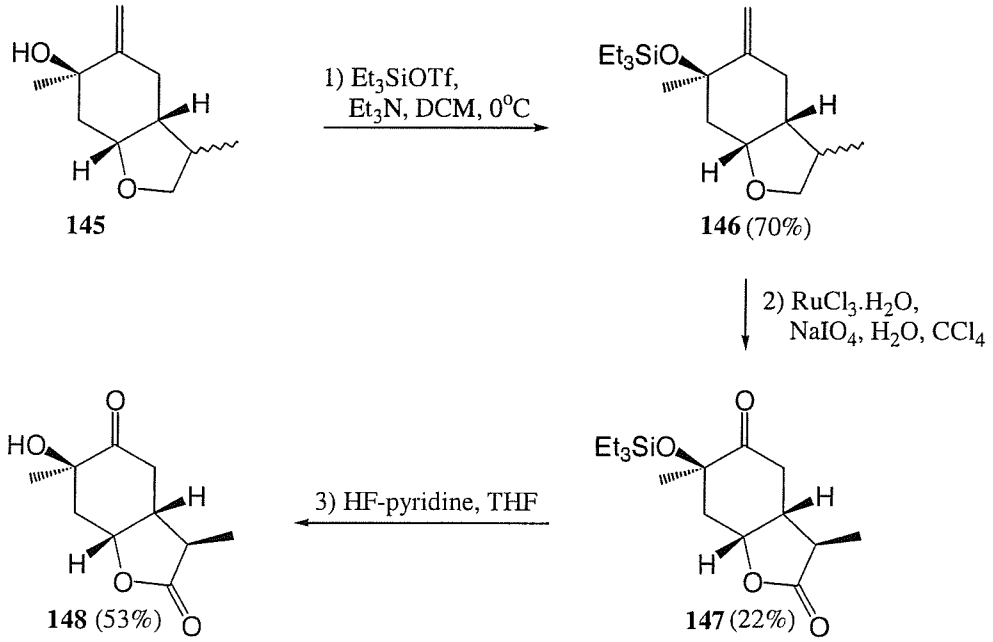
Scheme 38

The stereochemical outcome of the cyclisation can be readily explained by Beckwith[25-29] and RajanBabu's[30] earlier studies discussed in the introduction **(Scheme 16)**. Cyclisation of the other allyl ether isomer **140** using the same conditions gave a single diastereoisomer **143** in a poor yield of 17%. However, the dimeric product **144** was also found in a 25% yield, which had the same stereochemistry as the diastereoisomer **143 (Scheme 39)**.[64]



Scheme 39

The ketyl radical is formed, which cyclises *via* a chair-like transition state, as for the propargyl ether **125**, to give methylenecyclohexyl radical **141**. Radical **141** then undergoes a further cyclisation onto the alkene moiety to give isomer **143** exclusively. Although the cyclisations of the allyl ethers failed to give the correct stereochemistry for paeonilactone A itself, it proved possible to make 6-*epi* paeonilactone A **148** **(Scheme 40)**.[62]

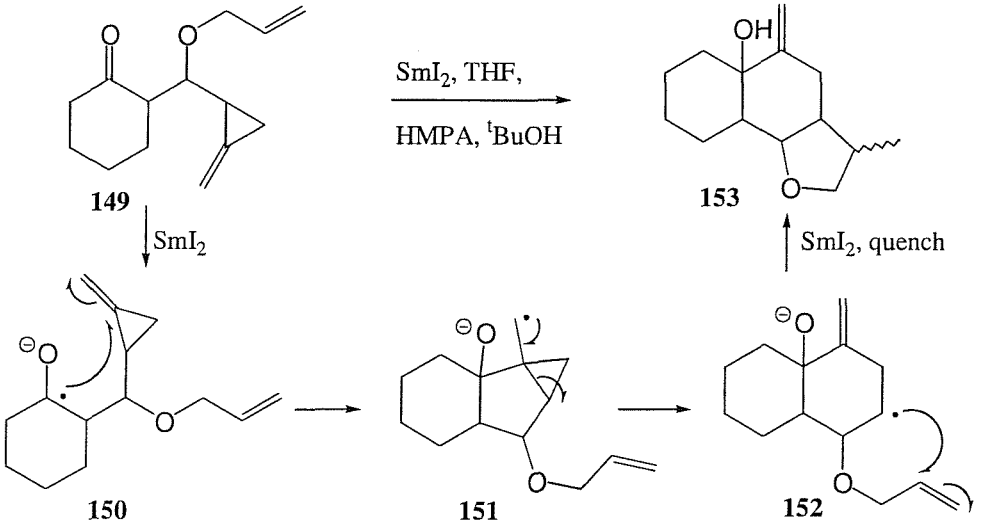


Scheme 40

To conclude, short and efficient routes to the total synthesis of natural products paeonilactone B and 6-*epi* paeonilactone A were realised, using a stereoselective cascade radical cyclisation as the key step.[62]

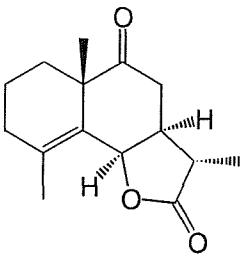
3. PROGRAM OF WORK

Previous work within the group has established basic guidelines for the cyclisation of radicals onto the methylenecyclopropane moiety.[10,11,38,40,41,43,61] Further research had incorporated these cyclisations into a range of tandem cyclisations to yield polycyclic systems.[63] The established methodology was then used to show its synthetic usefulness by total synthesis of the bicyclic natural products paeonilactone B and 6-*epi* paeonilactone A.[62] The main objective of this project was to extend this methodology to develop cascades for efficient syntheses of tricyclic compounds such as tricycle **153 (Scheme 41)**. Tricycle **153** could arise from a cyclisation reaction, using samarium diiodide, of allyl ether **149**. On treatment with samarium diiodide, allyl ether **149** could be reduced to ketyl radical **150**, which could undergo a 5-*exo* cyclisation onto the MCP moiety, followed by an '*endo*' ring opening to yield secondary radical **152**. Further 5-*exo* cyclisation followed by another equivalent of samarium diiodide could give an anion which could be quenched with a proton source to yield tricycle **153 (Scheme 41)**.



Scheme 41

Once the methodology has been developed fully work could be directed towards total synthesis of complex natural products, such as dihydrotournefortiolide **154 (Figure 6)**.[65]



9-oxo-11β, 13-dihydrotournefortiolide

154

Figure 6

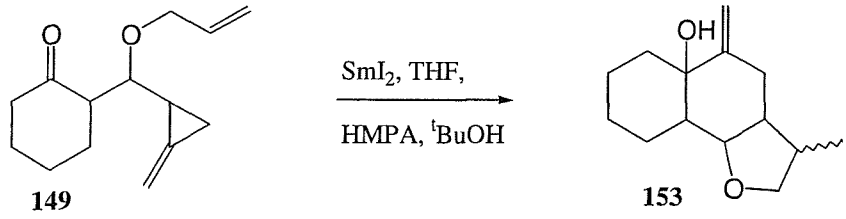
Whether such a synthesis of the tricycles would prove to be diastereoselective and provide the correct relative stereochemistry of the methyl group required for the natural product remained to be investigated by experiment.

CHAPTER 2

MODEL STUDIES

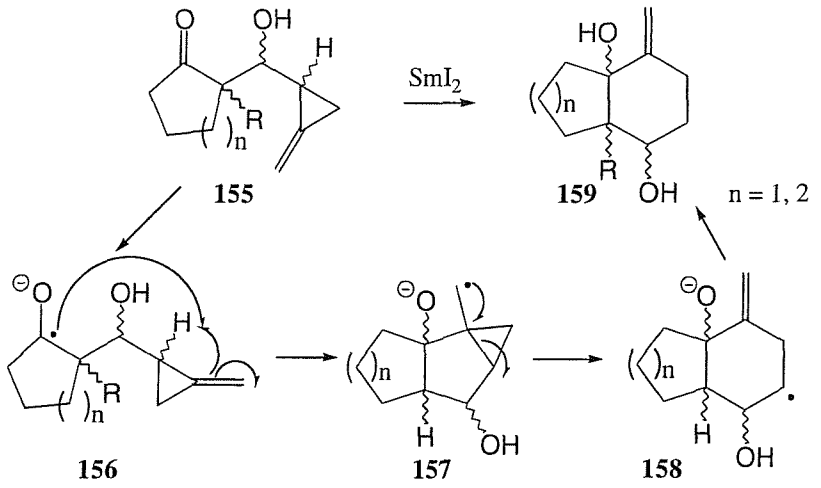
1. INTRODUCTION

The aim of this research was to extend the methodology developed with methylenecyclopropane cyclisations for efficient syntheses of tricyclic compounds, for example **153 (Scheme 42)**.



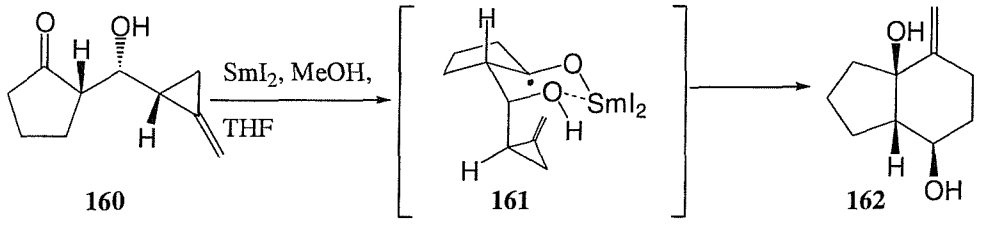
Scheme 42

To understand the cyclisations for such complex systems, model studies with alcohols **155**, which were expected to lead to bicyclic compounds **159** were first investigated. The ketyl radical could now be generated from a cyclic ketone instead of a methyl ketone, as in the case of paeonilactone B. Thus, we were interested in preparing ketone **155**, which on treatment with samarium diiodide it was hoped would lead to bicyclic product **159 (Scheme 43)**. Ketone **155** could be reduced to ketyl radical **156** using samarium diiodide and undergo a 5-*exo* cyclisation onto the MCP moiety to give primary radical **157**. '*Endo*' ring opening, followed by further reduction of the radical to an anion and quench with a proton source could give bicycle **159**.



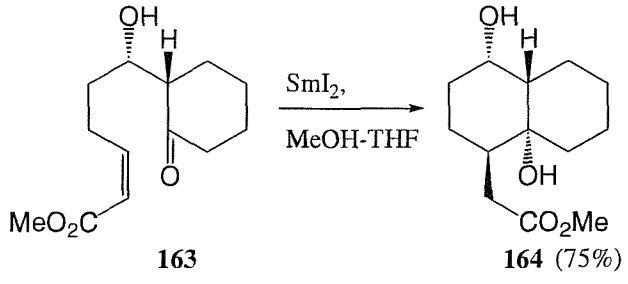
Scheme 43

It was envisaged that the cyclisation reaction could occur with control of stereochemistry from chelation of the alcohol and ketyl radical to the samarium ion **161** to furnish diol **162** with the two alcohol groups on the same side of the ring system **(Scheme 44)**.



Scheme 44

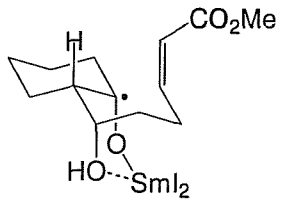
Previous work by Matsuda studied the samarium diiodide induced ketone-olefin coupling of cyclohexanone derivatives, such as **163 (Scheme 45)**.[66] Bicyclic product **164** was obtained with good stereochemical control.



Scheme 45

The proposed transition state of the ketyl radical suggests that the cyclisation occurs under chelation control. After an initial single-electron reduction of the ketone by

samarium diiodide, chelation of the β-hydroxy group with the samarium bound to the ketyl radical gives the 6 membered ring ketyl intermediate **165 (Figure 7)**. The oxygens are held *cis* to each other and are both therefore on the same side of the bicyclic product **164** after the cyclisation.[66]

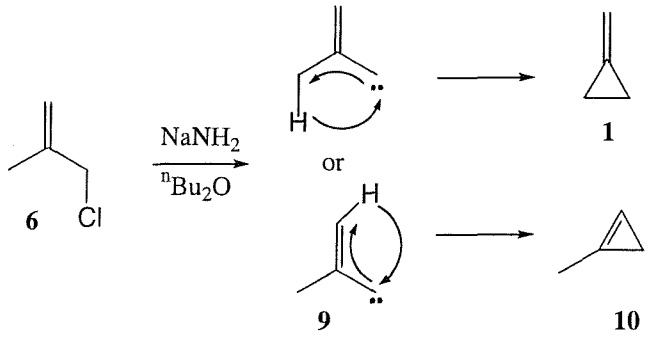


165

Figure 7

2. SYNTHESIS OF CYCLOPENTANONE PRECURSORS

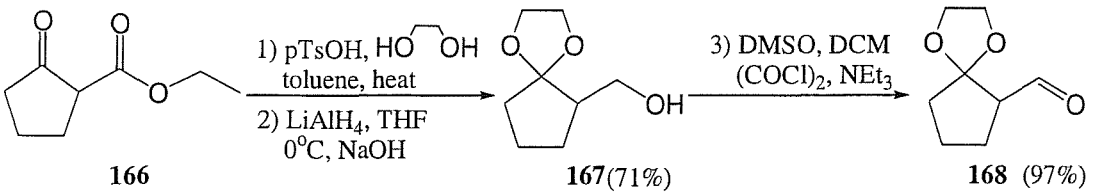
Methylenecyclopropane **1** was prepared by treating readily available methallyl chloride **6** with sodium amide to give an allyl carbene, leading to a mixture of isomers **10** and **1** (1:5.5 ratio of methylcyclopropene **10** : methylenecyclopropane **1**) **(Scheme 3)**.[67]



Scheme 3

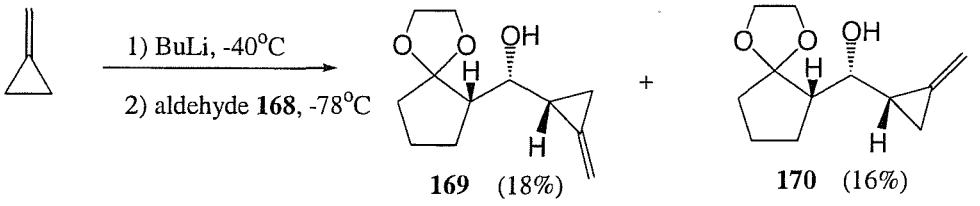
Methylcyclopropene **10** was converted into methylenecyclopropane **1** using ^{t}BuOK/^{t}BuOH.

Ketoester **166** was protected using ethylene glycol[68] and then reduced using excess lithium aluminium hydride[69] to produce alcohol **167** in good yield (71%) **(Scheme 46)**.



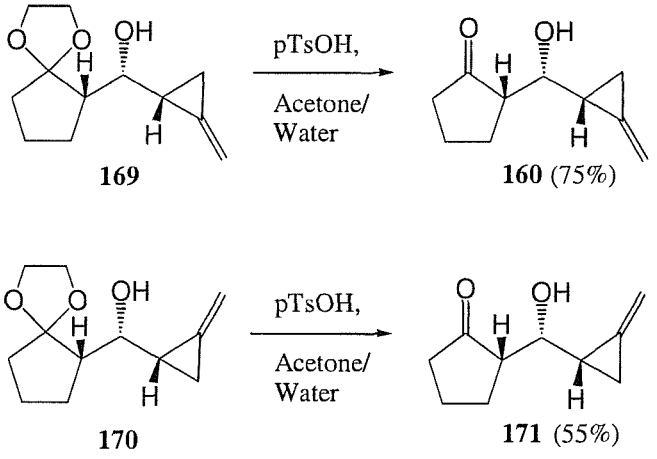
Scheme 46

A Swern oxidation[70] converted alcohol **167** to aldehyde **168** in excellent yield (97%) **(Scheme 46)**. Methylenecyclopropane was reacted with ^{n}BuLi to produce a methylenecyclopropane anion, which added to the aldehyde to give diastereoisomers **169** and **170** in adequate yield (18%, 16% respectively) **(Scheme 47)**.



Scheme 47

The mixture of diastereoisomers **169** and **170** were separated using flash column chromatography. The two diastereoisomers were deprotected separately using toluene sulfonic acid and wet acetone to yield the desired products **160** and **171** in yields of 75% and 55% respectively **(Scheme 48)**.



Scheme 48

X-ray crystallographic studies of the two alcohol isomers **160** and **171** showed that the relative stereochemistry of the alcohol and the cyclopentane proton are the same, and only differs at the methylenecyclopropane ring **(Figure 8 and Figure 9)**.

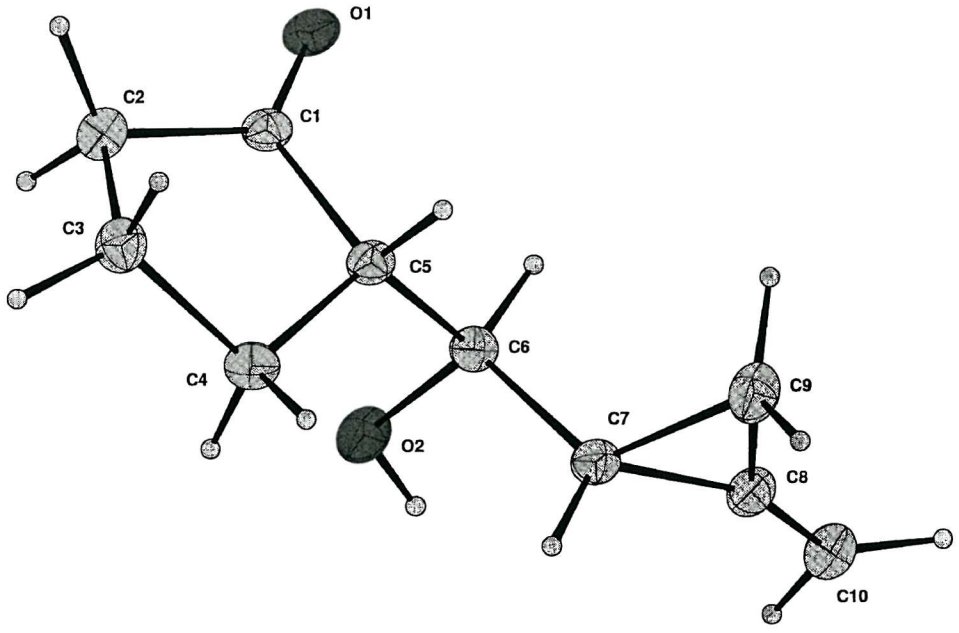


Figure 8 Isomer 160

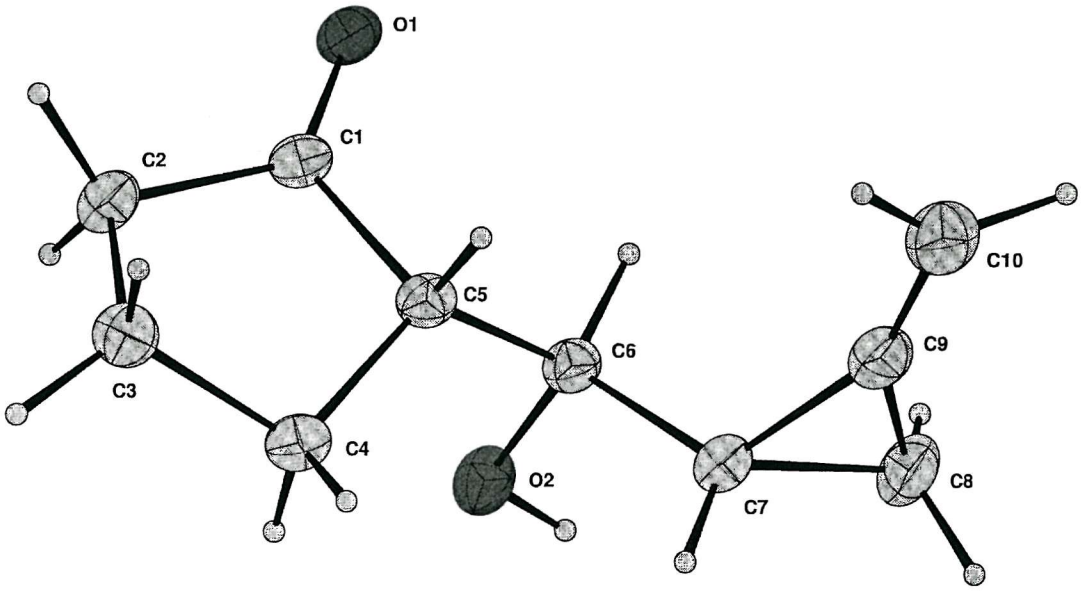


Figure 9 Isomer 171

The generation of diastereoisomers **160** and **171** provided the cyclisation precursors in an acceptable overall yield.

3. PREPARATION OF SAMARIUM DIIODIDE

Initially preparation of samarium diiodide was attempted by reaction of samarium metal with diiodomethane according to Molander's method **(Scheme 49)**.[53]

$$Sm + ICH_2I \xrightarrow{THF,\ 2h} SmI_2 + :CH_2$$

Scheme 49

The reaction was attempted on several occasions, however, despite the rigorously dry and degassed conditions employed the formation of samarium diiodide could not be achieved.

Therefore, samarium diiodide was generated using Curran's conditions **(Scheme 50)**.[55]

$$Sm + ICH_2CH_2I \xrightarrow{THF,\ 1.5h} SmI_2 + CH_2{=}CH_2$$

Scheme 50

The addition of diiodoethane to samarium powder proved successful and generated a blue solution of the desired samarium(II) iodide for use in the cyclisation of the precursors.

4. CYCLISATION OF PRECURSORS

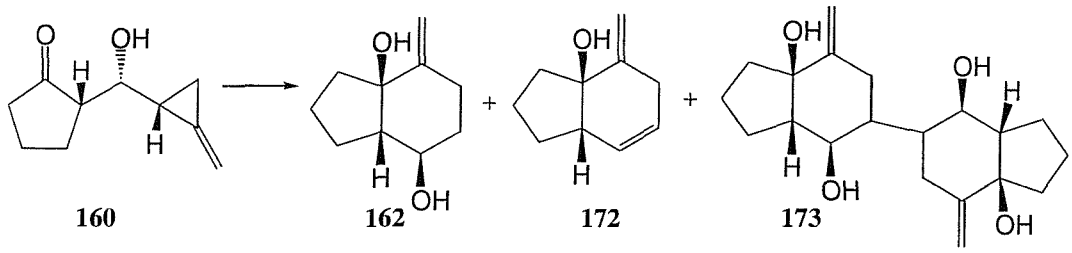
With both diastereoisomers **160** and **171** in hand, the SmI_2 cyclisations were attempted using three general sets of conditions.[53,55,71]

1) Molander's method whereby HMPA was added to a solution of SmI_2 followed by the addition of the substrate and ^tBuOH over 90 min.[53]

2) The reverse addition method by Curran where the solution of samarium diiodide was added to a solution of the substrate, ^tBuOH and HMPA in THF over 5min.[55]

3) A procedure by Procter was employed, whereby MeOH was added to the samarium diiodide solution as a co-solvent (MeOH/THF 1:4 mixture).[71]

Having determined the general methods for achieving cyclisation, we sought to investigate them further in order to optimise conditions (**Table 3**).



160 **162** **172** **173**

Reaction Conditions	**160**	**162**	**172**	**173**	**Overall yield**
Add SmI_2 to substrate, HMPA, THF, ^tBuOH.					
-78°C, HMPA, ^{t}BuOH	-	10%	-	-	10%
Add substrate to SmI_2, HMPA or MeOH in THF.					
0°C, HMPA, ^{t}BuOH	-	10%	30%	15%	55%
0°C, HMPA	-	12%	26%	12%	50%
-78°C, HMPA, ^{t}BuOH	-	18%	-	12%	30%
-78°C, HMPA	-	13%	4%	10%	27%
RT, HMPA, ^{t}BuOH	30%	9%	25%	6%	-
0°C, MeOH	-	47%	5%	-	52%
-78°C, MeOH	-	67%	-	-	67%

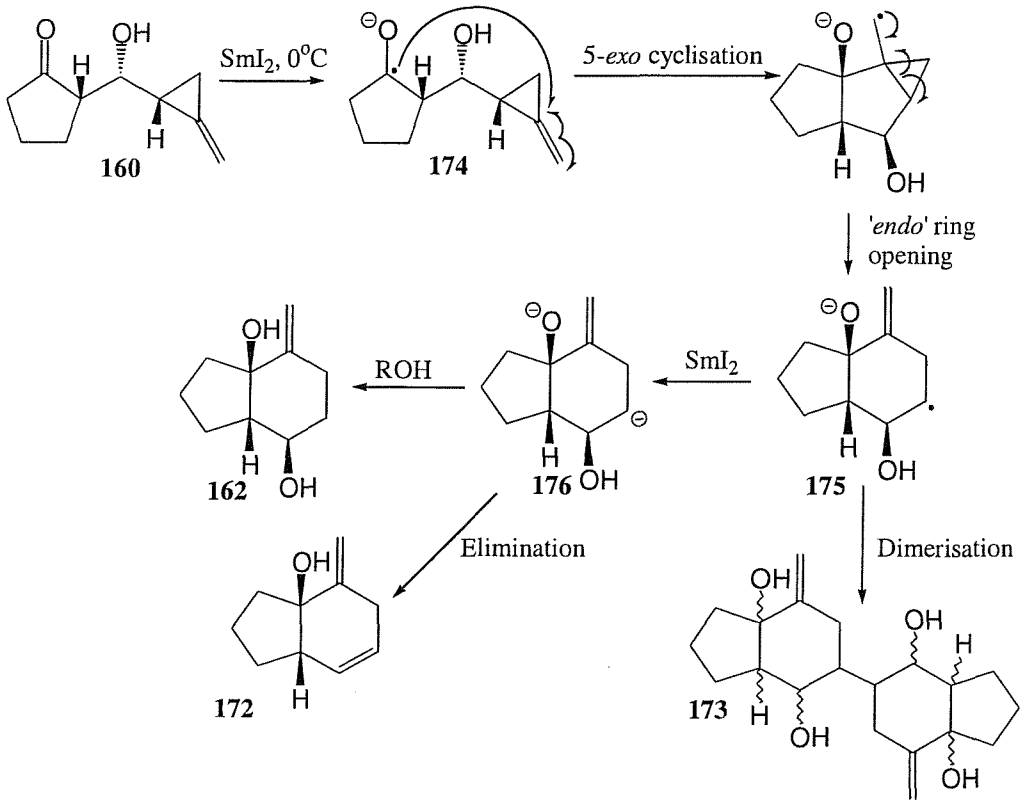
Table 3 Cyclisations of cyclopentanone 160

At higher temperatures all three products were observed with HMPA as co-solvent, but at lower temperatures the yield of the eliminated product **172** was reduced significantly and the yield of diol **162** slightly increased. The reaction yields were largely unaffected by the presence of ^{t}BuOH. However, using a MeOH/THF (1:4) mixture as

solvent, as described by Procter,[71] at -78°C, gave a clean reaction to diol **162** in 67% yield.

4.1 REACTION MECHANISM

Using the information gathered from these studies, a mechanism for the cyclisation can be proposed **(Scheme 51)**.



Scheme 51

Ketone **160** is reduced to ketyl radical **174** by SmI_2, which undergoes a 5-*exo* cyclisation, followed by an '*endo*' ring opening to yield cyclohexane radical **175**. Dimerisation can occur at this point to yield dimer **173**, which is surprising, given the high concentration of samarium diiodide in the reaction but is precedented by previous work from within the group.[64] A further equivalent of SmI_2 then reduces radical **175** to produce an anion intermediate, which can be protonated with ^tBuOH or MeOH to produce the desired diol **162** or eliminate to give product **172**. Compound **172** also provided evidence for the chelation control of the stereochemistry **(Figure 10)**.

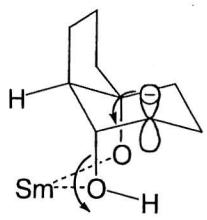


Figure 10 Intermediate 176

The axial position of the alcohol group of anion intermediate **176** holds it antiperiplanar to the anion of the intermediate and therefore facilitates elimination of the alcohol group; this would not be possible if the alcohol was equatorial.

4.2 PROOF OF STEREOCHEMISTRY

The stereochemistry of cyclised products **162** and **173** has been proven by crystal structure **(Figure 11 and Figure 12)** which showed the bicyclic product **162** was *cis* fused. The two alcohol groups also ended up *cis* to each other, which suggests chelation control by the samarium metal fixes both alcohol groups below the plane of the ring **(Figure 10)**.

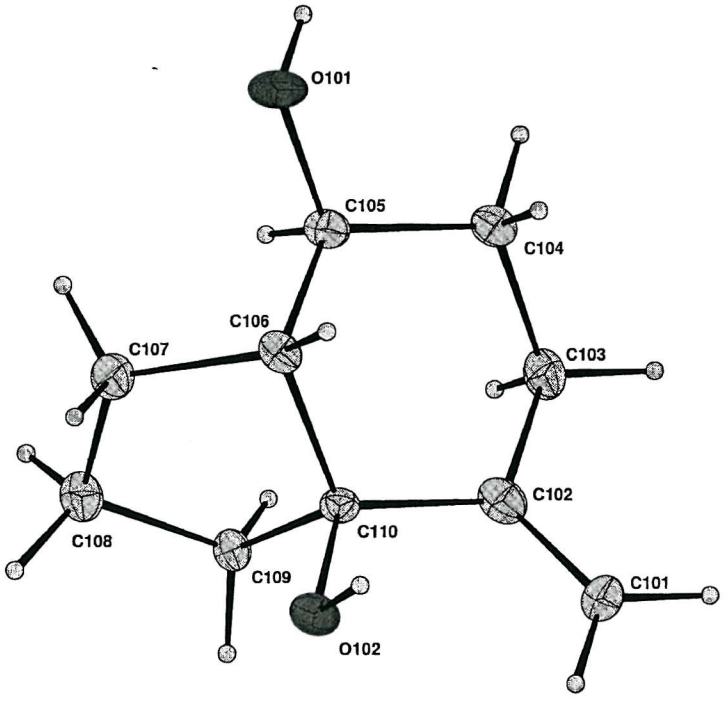


Figure 11 Diol 162

An inseparable mixture of isomers were observed for dimer **173**, however a crystal structure was obtained from a single crystal of one of the isomers showing the stereochemistry to be *cis* fused as for the monomer **162 (Figure 12)**.

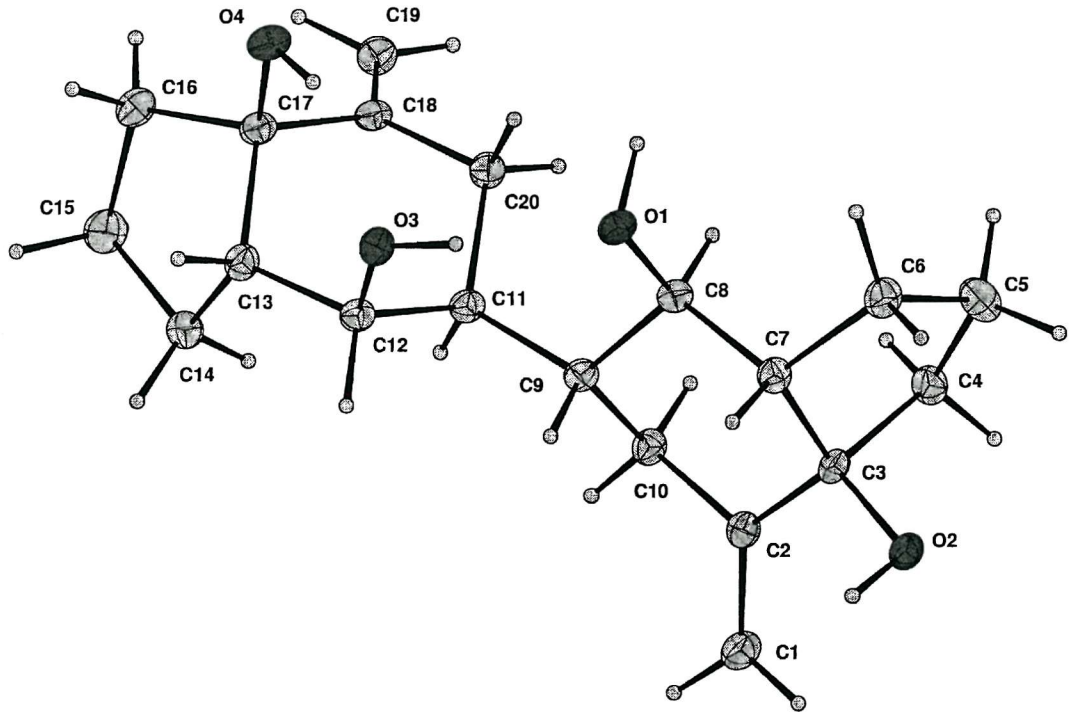
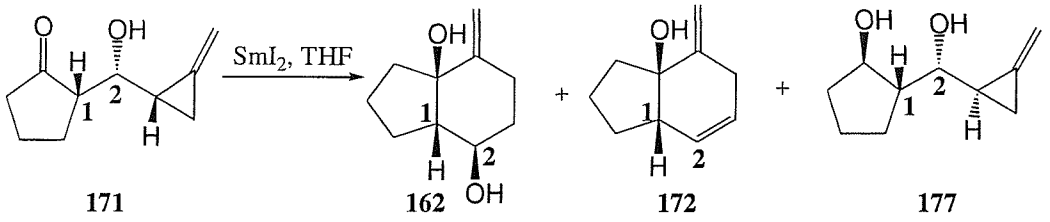


Figure 12 Dimer 173

It was assumed that the bicyclic product **172** was also *cis* fused as indicated by literature precedent for the closure of cycloalkyl radicals onto tethered alkenes[26-29] and since it is presumably derived from the same pathway that produces the *cis* fused products **162** and **173**.

The cyclisation was repeated using the other isomer **171** (**Table 4**).

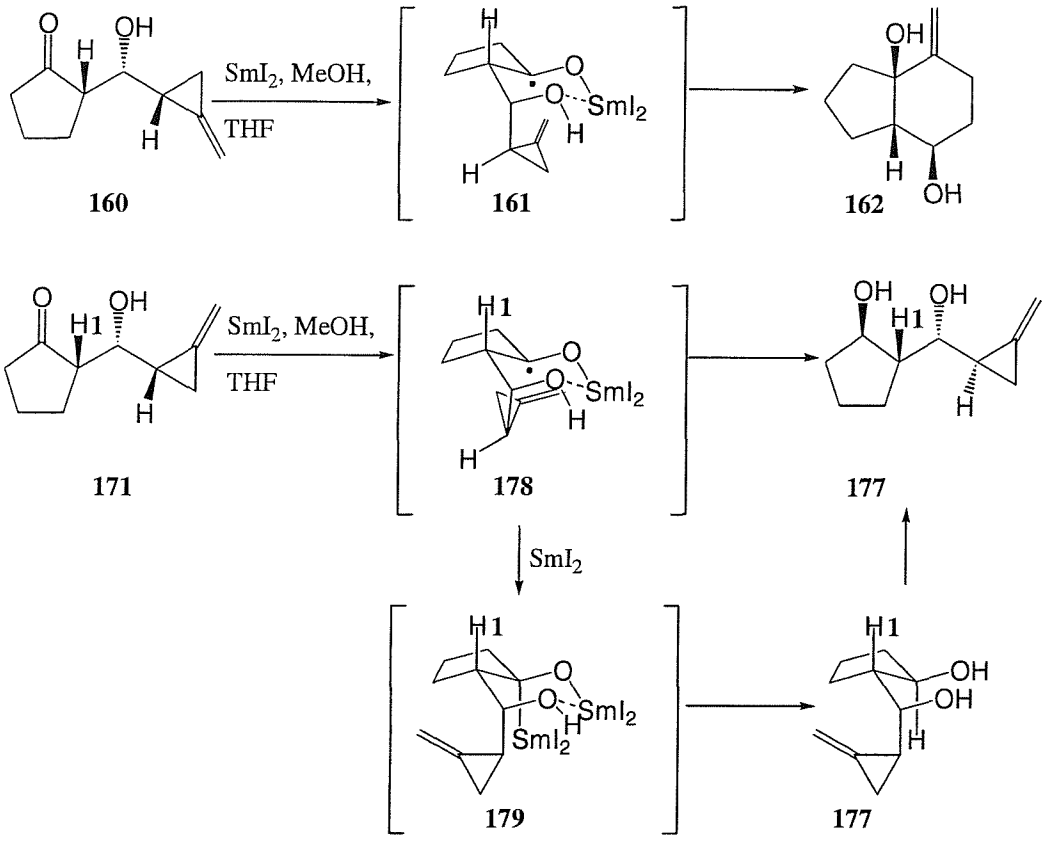


171 162 172 177

Reaction Conditions	171	162	172	177	Overall yield
-78°C, HMPA, ^{t}BuOH	-	51%	14%	-	65%
-40°C, HMPA, ^{t}BuOH	30%	20%	15%	18%	-
0°C, HMPA, ^{t}BuOH	-	10%	30%	-	40%
0°C, MeOH	-	35%	-	40%	75%
-78°C, MeOH	-	41%	-	32%	73%

Table 4 Cyclisations of cyclopentanone 171

The bicyclic compounds **162** and **172** were again observed with the same stereochemistry as previously, which is not surprising as we can assume the compounds are *cis* fused due to literature precedent[26-29] and the stereochemistry at C1 and C2 in the starting material remains the same after cyclisation (**Table 4**).
Ketone **171** does not undergo dimerisation upon treatment with samarium diiodide but instead was reduced to the alcohol **177** prior to cyclisation. This has been attributed to a less favourable cyclisation conformation (**Scheme 52**). Assuming the cyclisation of isomer **160** goes through a chair like transition state **161** with the samarium bound ketyl oxygen in an equatorial position, then the cyclisation occurs smoothly as the alkene moiety is positioned *gauche* to the ketyl C-O bond. However, ketone **171** has the alkene group eclipsed with the ketyl C-O bond in the transition state **178** and so due to electronic repulsions the cyclisation is not favoured (as shown in the introduction (**Scheme 28**)) and consequently the radical is reduced to the anion **179** and quenched with a proton to give the observed diol **177**. Presumably in order to maintain the chelated intermediate the protonation of **178** must occur from the axial direction.

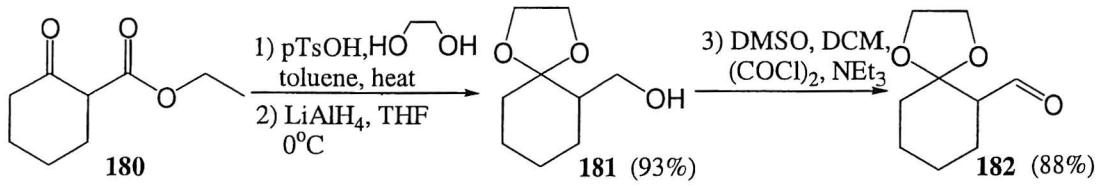


Scheme 52

The stereochemistry for reduced compound **177** can be explained by looking at transition state **178**, which shows the new alcohol group on the same side of the cyclopentane ring as H1. Keck has also reported that the samarium diiodide mediated reduction of β-hydroxy ketones can be highly diastereoselective.[72]

5. SYNTHESIS OF CYCLOHEXANONE PRECURSORS

Having successfully synthesised and investigated the cyclisation of the cyclopentanone precursors, work was directed towards the cyclohexanone series. The synthetic route to the cyclohexanone cyclisation precursors was identical to that previously illustrated for the cyclopentanone series. Ethylene glycol was used to protect ketoester **180**[68] which was then reduced to alcohol **181** using lithium aluminium hydride[69] in excellent yield (93%) **(Scheme 53)**. A Swern[70] oxidation was used to convert alcohol **181** to aldehyde **182** in good yield (88%) **(Scheme 53)**.



Scheme 53

Aldehyde **182** proved unstable so it was purified and used quickly. To that effect methylenecyclopropane was treated with ^{n}BuLi at -40°C to yield the methylenecyclopropane anion and aldehyde **182** was added to give alkylated product **183** as a mixture of two diastereoisomers. Once again it proved possible to separate the diastereoisomers by careful flash column chromatography **(Scheme 54)**. The major isomer **183a** was a solid and a crystal structure was obtained **(Figure 13)**. The stereochemistry of the minor isomer **183b** was not determined but could be inferred from the stereochemistry of the cyclisation products (*vide infra*) and also from comparison to the cyclopentane series *i.e.* only the stereochemistry at the methylenecyclopropane ring differs in the two diastereoisomers.

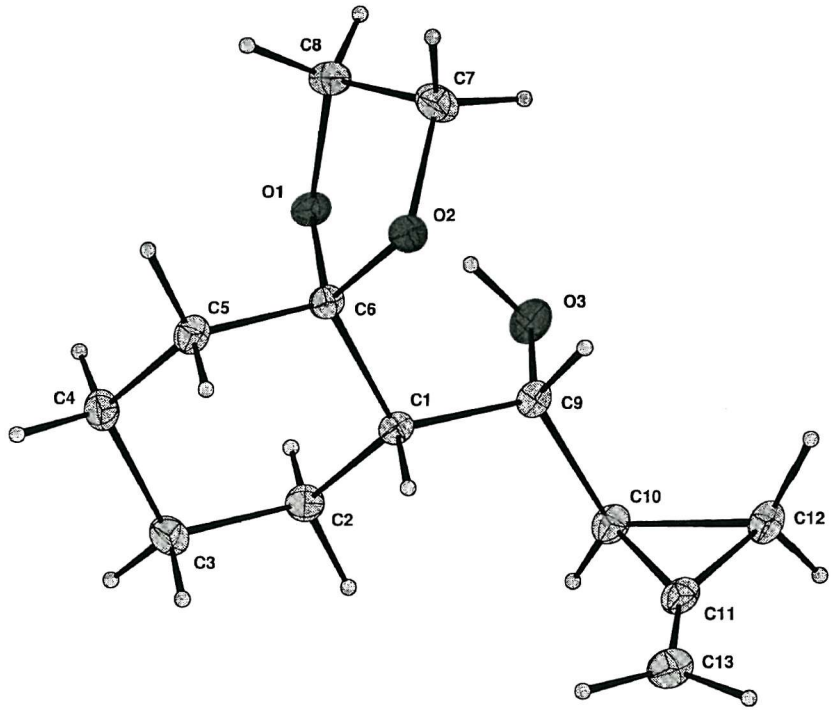
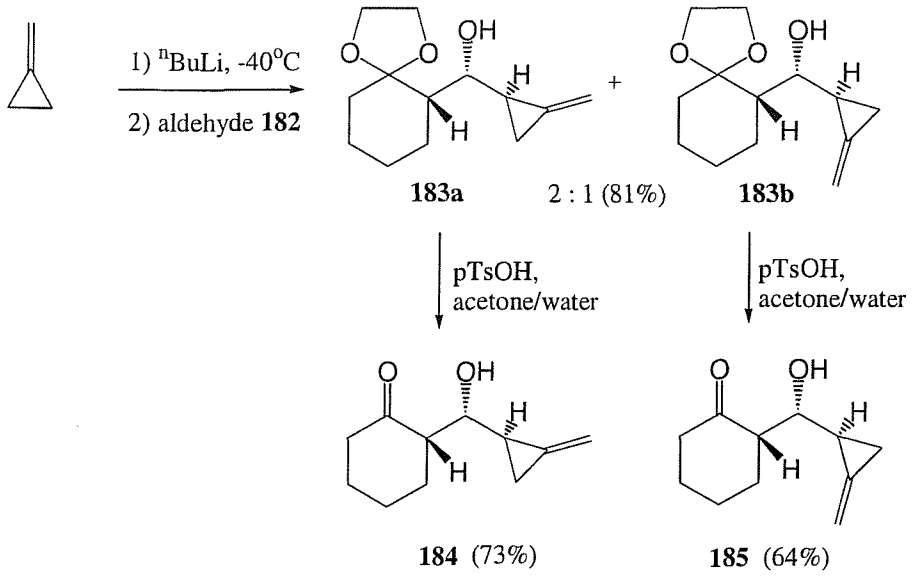


Figure 13 Isomer 183a

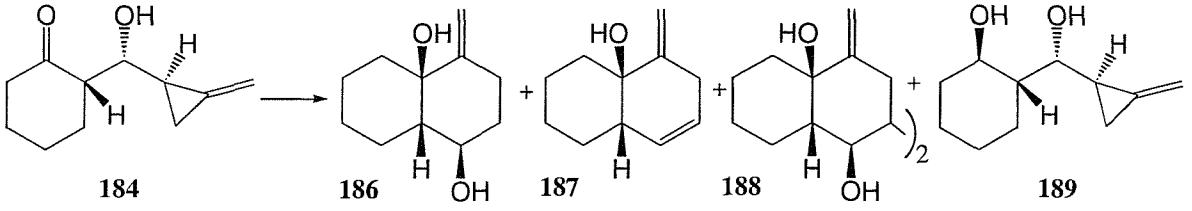
Ketals **183a** and **183b** were deprotected separately to produce the ketones **184** and **185** respectively **(Scheme 54)**.



Scheme 54

6. CYCLISATION OF PRECURSORS

The cyclisation of the cyclohexanone precursor **184** was investigated using different procedures and reaction conditions **(Table 5)**.



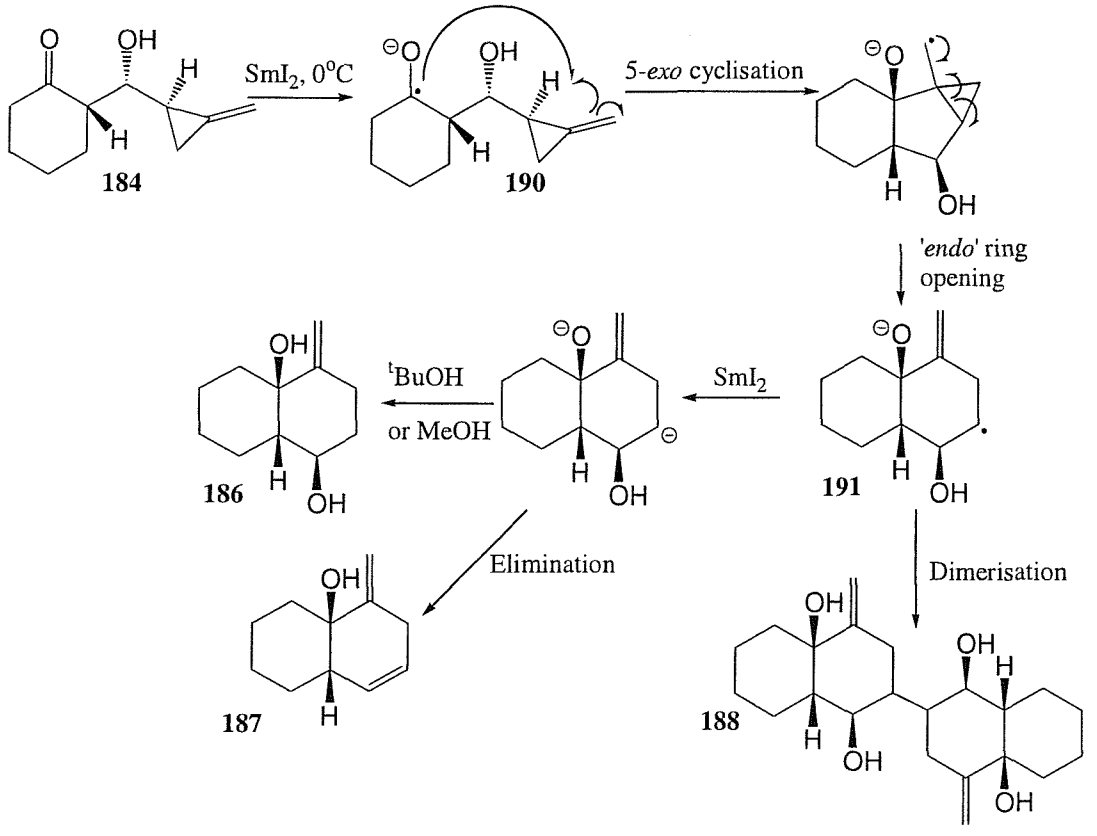
Reaction Conditions	184	186	187	188	189	Overall yield of cyclised products
Add substrate to SmI_2, HMPA/MeOH in THF.						
0°C, HMPA, ^{t}BuOH	-	9%	14%	20%	-	43%
-78°C, HMPA, ^{t}BuOH	-	10%	15%	15%	-	40%
-78°C, THF	-	-	5%	-	47%	5%
0°C, MeOH	-	19%	28%	-	-	47%
-78°C, MeOH	-	62%	35%	-	-	97%
-78°C, 2MeOH	-	63%	-	-	-	63%

Table 5 Cyclisation of cyclohexanone 184

When HMPA was used as co-solvent a mixture of cyclised products was obtained and these results were largely unaffected by changing the temperature. Without any co-solvent the major product was the reduced diol **189**. However, using MeOH as a co-solvent gave a much cleaner reaction and higher yields of cyclised products.

6.1 REACTION MECHANISM

The results were analogous to the cyclopentanone series and the mechanism proposed earlier **(Scheme 55)**. 5-*exo* cyclisation of ketyl radical **190** onto the methylenecyclopropane moiety followed by '*endo*' ring opening gives **191**. Further reduction of radical **191** gives the corresponding anion, which is then quenched with a proton from ^{t}BuOH or MeOH to afford diol **186**, or by elimination of water to give alcohol **187**. Again, it was found that dimerisation of radical **191** occurred to furnish dimer **188**.



Scheme 55

6.2 PROOF OF STEREOCHEMISTRY

The stereochemistry of the elimination product **187** was established using X-ray crystallography, which shows a *cis* fused ring system **(Figure 14)**. It was deduced that bicyclic product **186** was *cis* fused from extensive nmr studies. These studies proved problematic as broad peaks were observed as a result of ring flipping, that would not occur had the ring fusion been *trans*. The stereochemistry at C1 and C2 is defined from the starting material. The stereochemical outcome of the reaction presumably arises, again from chelation control to furnish both alcohols on the same side of the ring system (as with the cyclopentanone precursors). The dimer is assumed to have the identical stereochemistry as the bicyclic diol **186** as it is presumably derived from the dimerisation of two cyclohexyl radicals **191 (Scheme 55)**. Further support for this stereochemistry came from the studies in the cyclopentanone series **(Figure 12)** that reacted in an analogous fashion.

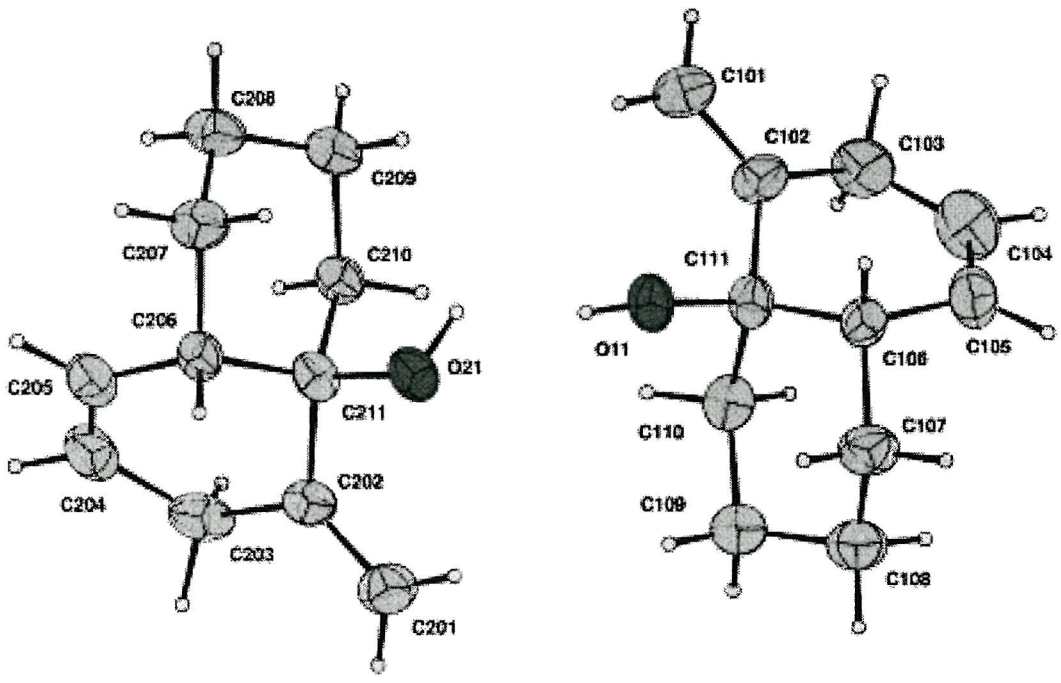
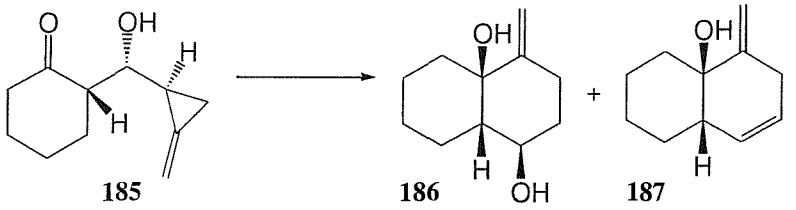


Figure 14 Elimination product 187

The best methods of cyclisation were repeated using the other isomer **185** as substrate **(Table 6)**.

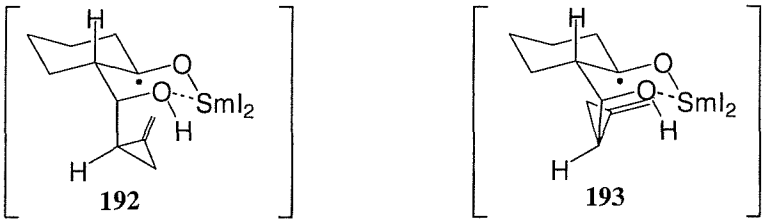


185 186 187

Reaction Conditions	185	186	187	Overall yield of cyclised products
0°C, MeOH	-	44%	17%	61%
-78°C, MeOH	-	50%	12%	62%
0°C, HMPA, ^{t}BuOH	20%	7%	4%	11%
-78°C, HMPA, ^{t}BuOH	26%	9%	5%	14%

Table 6 Cyclisation of cyclohexanone 185

Cyclisation of isomer **185** gave similar results to those obtained with **184** with MeOH as a co-solvent. However, a poor reaction was observed with HMPA as a co-solvent. The overall yields of cyclised products were lower for the minor isomer **185** than for the major isomer **184**, which could be attributed to the transition states of the cyclisations (**Scheme 56**). Cyclisation of isomer **184** proceeds *via* transition state **192**, which has the ketyl C-O bond *gauche* to the alkene group.



192 193

Scheme 56

However, isomer **185** undergoes cyclisation *via* transition state **193**, which has the alkene bond eclipsing the ketyl C-O bond which disfavours cyclisation due to electronic repulsion and hence the yields for the cyclisation are lower.

7. CONCLUSIONS

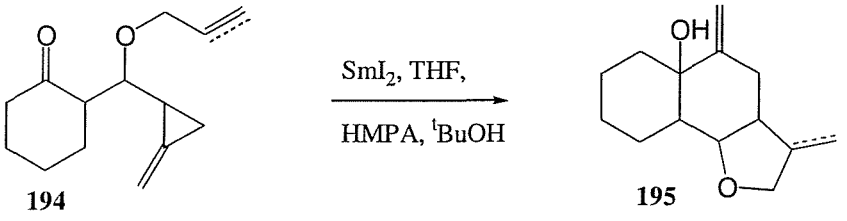
The aims of the model studies using the cyclopentanone and cyclohexanone alcohols were to see if the key cyclisation step using samarium diiodide would work and also to observe the levels of stereocontrol that could be achieved. We observed that the stereochemistry of the alcohols was controlled by chelation of the samarium bound to the ketyl oxygen with the oxygen of the alcohol. Additionally, a number of methods were attempted for the cyclisation step and it was found that using HMPA as a co-solvent gave lower yields and a mixture of cyclised compounds. However, when MeOH was used as a co-solvent the yields were increased and the desired *cis* diol was obtained as the major product.

CHAPTER 3

CASCADE CYCLISATIONS LEADING TO TRICYCLIC PRODUCTS

1. INTRODUCTION

Studies with the cyclopentanone and cyclohexanone derivatives **(Chapter 2)**, showed that the samarium diiodide mediated cyclisation could successfully be used to produce bicyclic compounds, with chelation control. The next direction of the research was to extend this methodology to radical cascade cyclisations to obtain tricyclic products, such as **195**, from propargyl or allyl ethers **194 (Scheme 57)**.

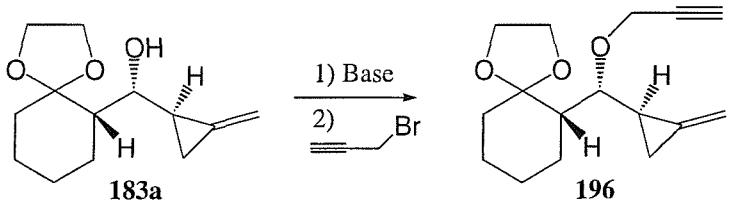


194 **195**

Scheme 57

2. SYNTHESIS OF PROPARGYL ETHER PRECURSORS

The two propargyl ether diastereoisomers **196** and **197** were prepared from the alcohols **183a** and **183b**, described in chapter 2. Alcohol **183a** was treated with base and then propargyl bromide to afford propargyl ether **196.** However, this proved troublesome and many methods were employed before the transformation was optimised **(Table 7)**.[73,74]

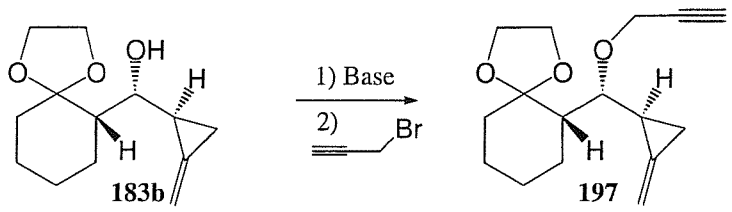


183a **196**

Reagents and conditions	Starting material 183a	Propargyl ether 196
1) NaH, DMPU, THF 2) Propargyl bromide	100%	-
1) NaH, THF, reflux, 90 min 2) NBu_4I, propargyl bromide, RT	100%	-
1) NaH, THF, reflux, 90 min 2) NBu_4I, propargyl bromide, reflux	100%	-
1) NaH, DMF, 0°C 2) Propargyl bromide	60%	25%
1) NaH, DMF, 0°C 2) Propargyl bromide, NBu_4I	Decomposition	
1) KH, cat. 18-crown-6, THF 2) Propargyl bromide	50%	38%
1) KH, stoich. 18-crown-6, THF 2) Propargyl bromide	10%	79%

Table 7 Different methods of propargylation of alcohol 183a

Using sodium hydride as the base proved consistently unsuccessful with THF as a solvent, even at higher temperatures and only starting material was ever observed. Tetrabutylammonium iodide[75] was added as a phase transfer catalyst but no product was formed even when the reaction was heated to reflux.[74] However, when THF was replaced with DMF, propargyl ether **196** was produced in a low yield (25%). Therefore, potassium hydride accompanied with 18-crown-6 was employed in place of sodium hydride.[73] Catalytic amounts of 18-crown-6 led to an increase in the yield of propargyl ether, however the yield was increased further on using stoichiometric amounts of 18-crown-6 to a good 79%. With the results from the first isomer in hand, the most successful reaction conditions were applied to the other isomer. **(Table 8)**

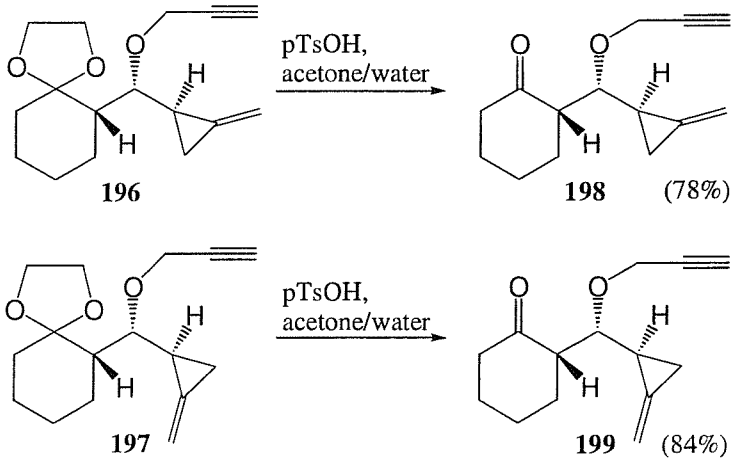


Reagents and conditions	Starting material 183b	Propargyl ether 197
1) NaH, DMF, 0°C 2) Propargyl bromide	100%	-
1) KH, cat. 18-crown-6, THF 2) Propargyl bromide	25%	72%

Table 8 Different methods of propargylation of alcohol 183b

The best method for the second isomer proved to be potassium hydride with a catalytic amount of 18-crown-6, followed by propargyl bromide to produce propargyl ether **197** in 72% yield.[73] In this case use of stoichiometric 18-crown-6 did not give a further improvement of yield.

Propargyl ethers **196** and **197** were deprotected using toluene sulfonic acid and wet acetone to yield ketones **198** and **199** in yields of 78% and 84% respectively **(Scheme 58)**.



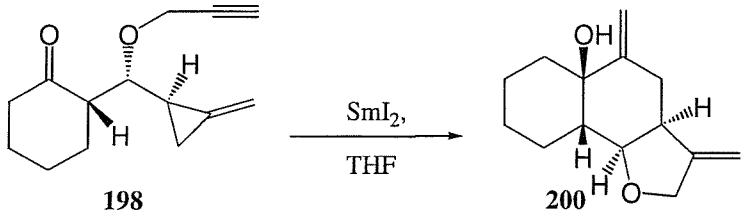
Scheme 58

3. CYCLISATION OF PROPARGYL ETHER PRECURSORS

3.1 PROPARGYL ETHER ISOMER 198

Chelation of the samarium(III) ion to the ketone and alcohol was important in the cyclisations of alcohols **184** and **185**. As a consequence of adding the propargyl group to the alcohol this chelation would be weakened and thus the chelation effect can be investigated.

Cyclisations with isomer **198** were attempted using either MeOH or HMPA as co-solvent (**Table 9**).[53,71]



198 **200**

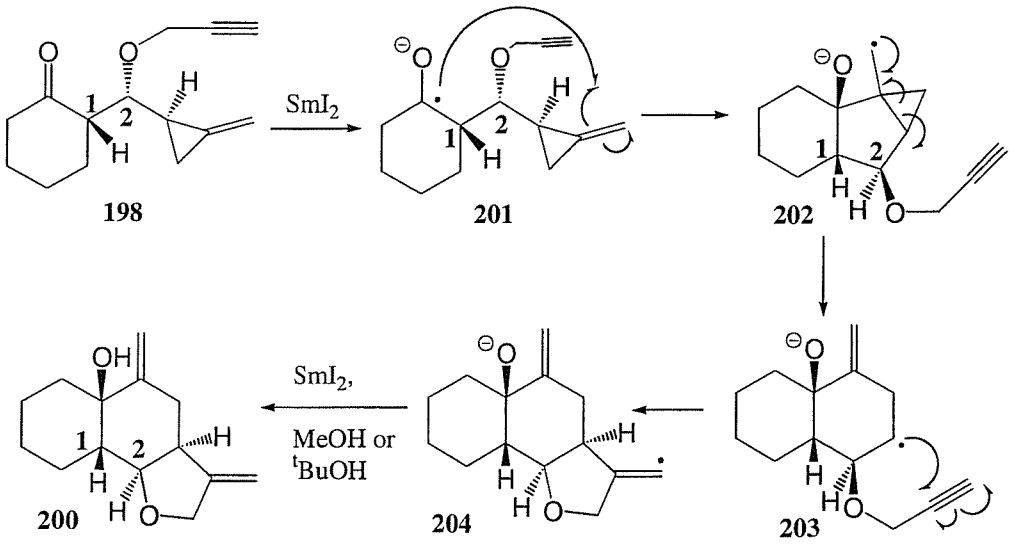
Reagents and conditions	198	Tricycle 200
SmI_2, THF, MeOH, 0°C	-	60%
SmI_2, THF, MeOH, -78°C	-	60%
SmI_2, THF, HMPA, ^tBuOH, 0°C	-	45%
SmI_2, THF, HMPA, ^tBuOH, -78°C	-	50%

Table 9 Cyclisations of propargyl ether 198

Cyclisation of propargyl ether **198** using samarium diiodide with ^tBuOH/HMPA in THF at –78°C gave the tricyclic ether **200** in 50% yield and pleasingly as a single diastereoisomer. An improved yield of 60% was obtained using a MeOH/THF (1:4) solvent system, although change of reaction temperature did not appear to alter the yield.

3.2 REACTION MECHANISM

Samarium diiodide reduces ketone **198** to ketyl radical **201** (**Scheme 59**), which undergoes a 5-*exo* cyclisation, followed by an '*endo*' ring opening to produce radical **203**. The reaction then undergoes a further 5-*exo* cyclisation onto the alkyne moiety.



Scheme 59

An extra equivalent of SmI_2 may be used to reduce the radical to produce an anion intermediate, which can be protonated with ^{t}BuOH or MeOH to produce the *cis* fused cyclic ether **200**.

3.3 PROOF OF STEREOCHEMISTRY

The stereochemistry of tricycle **200** can be deduced by considering the coupling constants from the ^{1}H nmr spectrum (**Figure 15**). H1 couples to H2 and H3 giving a triplet with coupling constant of 4 Hz, which implies H1 is equatorial. The stereochemistry at C1 and C2 is derived from the starting material so H1 and H3 are *trans* to one another and are therefore both equatorial as in **206**, which is consistent with the observed coupling constant of 4 Hz. The signal for H2 in the ^{1}H nmr is a ddd (J = 4, 7 and 11 Hz), which implies that it is axial, as in **206**, and is consistent with the expectation that cyclisation of radical intermediate **203** would give a *cis* fused tetrahydrofuran ring.

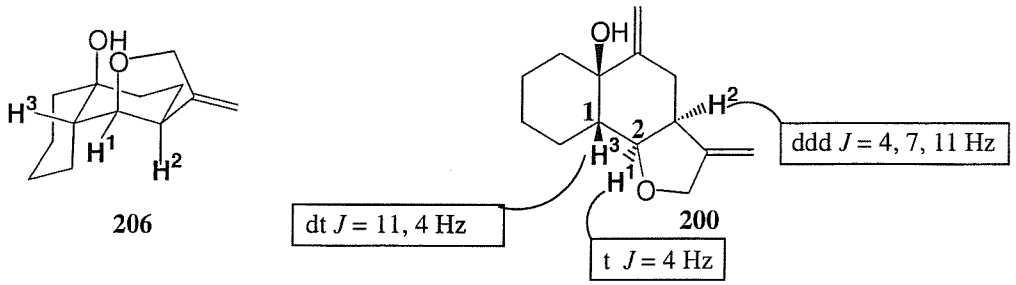
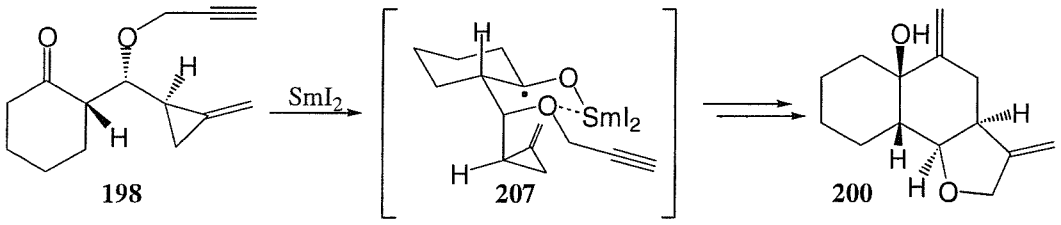


Figure 15

3.4 EXPLANATION OF STEREOCHEMISTRY

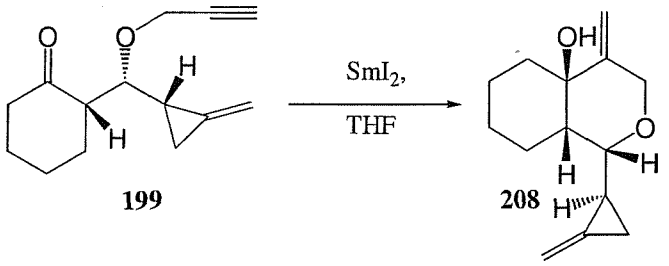
The stereochemistry observed can be explained by chelation of the ketyl radical and the propargyl ether by the samarium. Although chelation of the propargyl ether to the ketyl-bound samarium is not as effective as that of the free alcohol **(Chapter 2)**, the preferred conformation of the ketyl radical derived from **198** can still be expected to place substituents on the starting cyclohexyl ring in an equatorial orientation as in **207 (Scheme 60)**. Therefore, the cyclopropyl alkene bond can be placed *gauche* to the C-O bond and the cyclisation onto the methylenecyclopropane can occur with ease leading to tricycle **200** with the observed stereochemistry.



Scheme 60

3.5 PROPARGYL ETHER ISOMER 199

Similar reaction conditions were attempted on the other propargyl ether isomer **199 (Table 10)**.



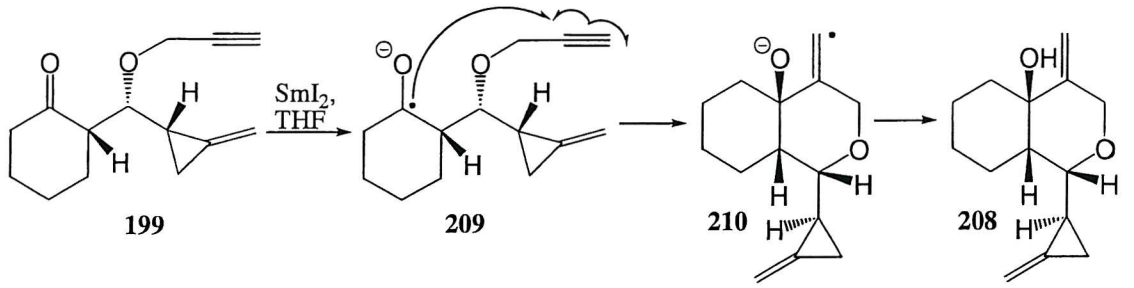
Reagents and conditions	199	Bicycle 208
SmI_2, THF, MeOH, 0°C	-	74%
SmI_2, THF, MeOH, -78°C	24%	51%
SmI_2, THF, HMPA, ^tBuOH, 0°C	-	70%
SmI_2, THF, HMPA, ^tBuOH, -78°C	-	75%
SmI_2, THF, HMPA, 0°C	-	60%
SmI_2, THF, DMPU, ^tBuOH, 0°C	40%	20%

Table 10 Cyclisation of propargyl ether 199

The cyclisations for the isomer **199** all gave bicycle **208** in yields of up to 75% and no tricyclic products were observed.

3.6 REACTION MECHANISM

Ketone **199** does not undergo a 5-*exo* cyclisation onto the methylenecyclopropane moiety but instead the reaction goes *via* a 6-*exo* cyclisation onto the alkyne group to give methylenecyclopropane derivative **208 (Scheme 61)**.



Scheme 61

3.7 PROOF OF STEREOCHEMISTRY

The stereochemistry of bicycle **208** has been proven using X-ray crystallography, and shows a *cis* fused ring system with the methylenecyclopropane group still intact **(Figure 16)**.

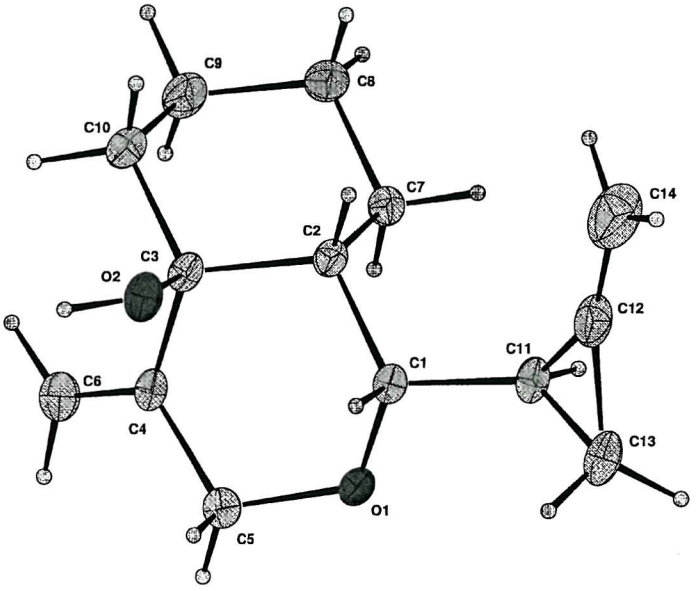
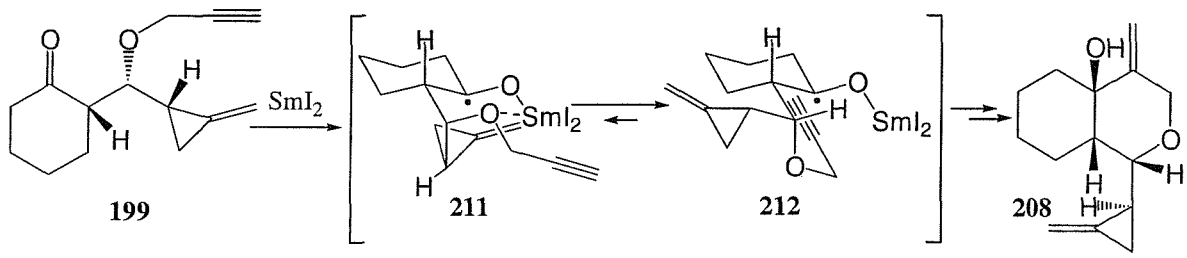


Figure 16 Bicycle 208

3.8 EXPLANATION OF STEREOCHEMISTRY

The stereochemistry, and the way in which the cyclisation occurs, can again be explained by looking at the ketyl radical intermediate and the role played by chelation as was demonstrated by the model studies and invoked for the cyclisation of **185**

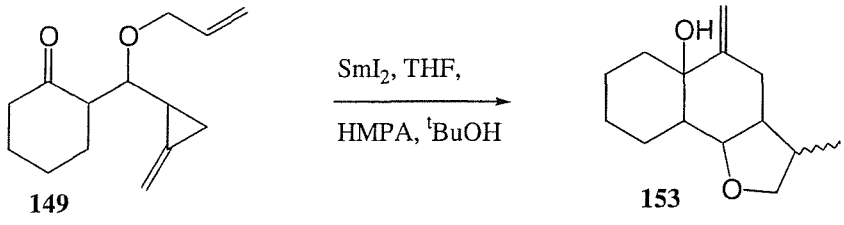
(**Chapter 2**). Presumably, in the case of propargyl ether **199** the analogous transition state leads to the cyclopropyl alkene bond being eclipsed with the ketyl C-O bond **211**, which is disfavoured as a result of electronic repulsion (**Scheme 62**). Instead the cyclisation proceeds *via* intermediate **212**, although this does require breaking the weak chelate to the propargyl ether.



Scheme 62

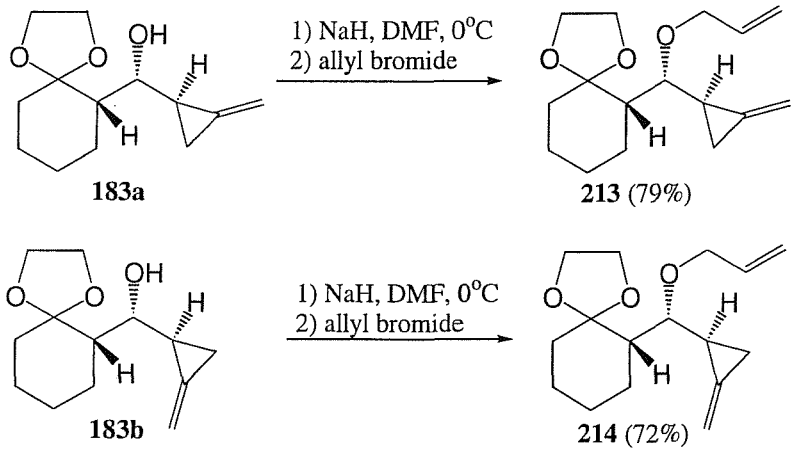
4. SYNTHESIS OF ALLYL ETHER PRECURSORS

Having successfully synthesised a tricyclic framework using the propargyl ethers, work was directed towards the synthesis of the same tricyclic framework containing an additional chiral centre. Allyl ethers **149** could hopefully be cyclised using samarium diiodide to make tricycles, such as **153** with the new stereocentre at the methyl group.



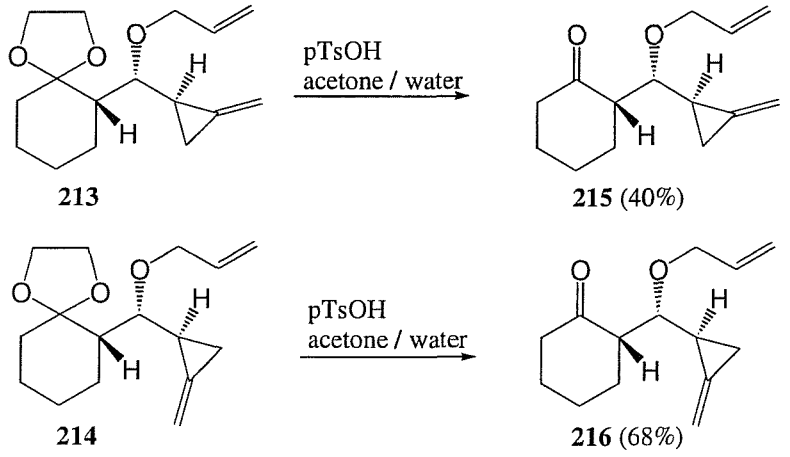
Scheme 63

Alcohols **183a** and **183b** were treated separately with NaH, followed by allyl bromide to give allyl ethers **213** and **214** in good yields (79% and 72%) (**Scheme 64**). Potassium hydride with 18-crown-6 was also attempted but as the yields were not significantly improved the milder sodium hydride method was used.



Scheme 64

Isomers **213** and **214** were deprotected separately using toluene sulfonic acid and wet acetone to yield ketones **215** and **216** in moderate yields of 40% and 68% respectively **(Scheme 65)**.

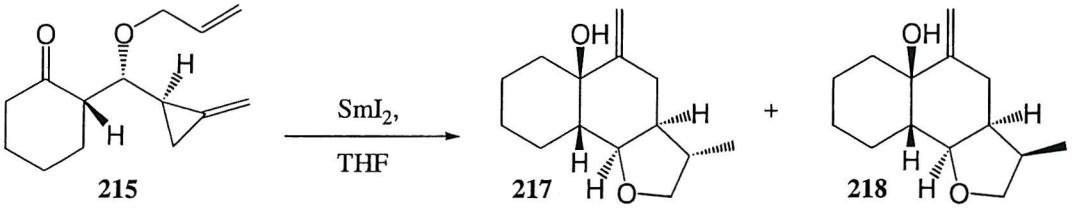


Scheme 65

5. CYCLISATION OF ALLYL ETHER PRECURSORS

5.1 ALLYL ETHER ISOMER 215

Cyclisations were attempted on isomer **215** and the stereochemistry of the new chiral centre investigated **(Table 11).**



Reaction conditions	217	218
SmI_2, MeOH, THF, -78°C	70%	20%
SmI_2, HMPA, THF, ^tBuOH, -78°C	5%	50%

Table 11 Cyclisation of allyl ether isomer 215

The cyclisation of allyl ether **215** yielded two different diastereoisomers **217** and **218**. The only difference between these two products was the stereochemistry at the new methyl group. The results were interesting because using MeOH as co-solvent for the cyclisation afforded one major diastereoisomer **217** but when employing HMPA the other diastereoisomer **218** was dominant. The mechanism for the reaction was analogous to that for the cyclisation of propargyl ether **198 (Scheme 59)**.

5.2 PROOF OF STEREOCHEMISTRY

The stereochemistry of isomer **217** has been proven by X-ray crystallography, which shows the *anti*-methyl substituent **(Figure 17)**.

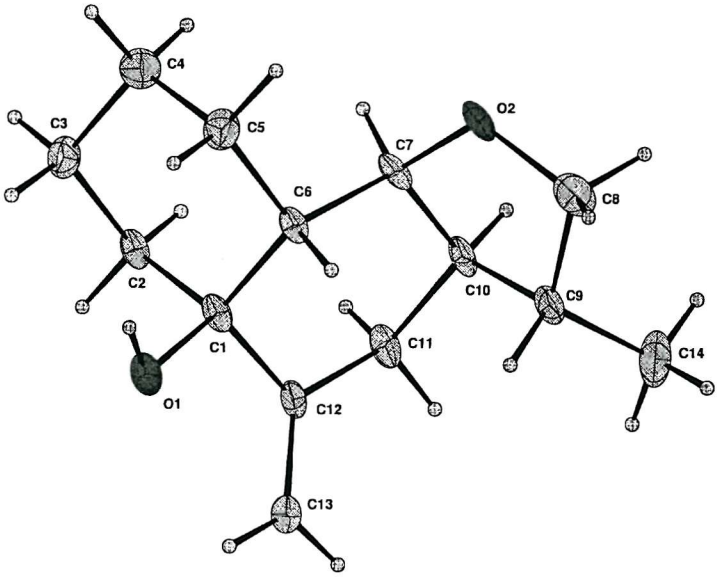


Figure 17 Tricycle 217

The stereochemistry of isomer **218** can be inferred from the following considerations. Cyclisation of propargyl ether **198** gave the tricyclic product as a single isomer. Since the cyclisation of allyl ether **215** presumably follows the same mechanism *via* intermediate **220** (as a single isomer) the two diastereoisomers formed must differ at the new chiral centre produced in the final cyclisation. The stereochemistry of both isomers has been defined by nOe studies **(Figure 18)**, which support the above assumption. The stereochemistry at C1 and C2 is derived from the starting allyl ether **215**. Irradiation of H1 of isomer **217** (stereochemistry confirmed by X-ray crystallography) gave a 0.7% enhancement of the methyl group and *vice-versa.* Irradiation of the methyl group also gave a 0.8% enhancement with H2, which suggested that the methyl group, H1 and H2 were all on the same side of the ring (as seen from the crystal structure).

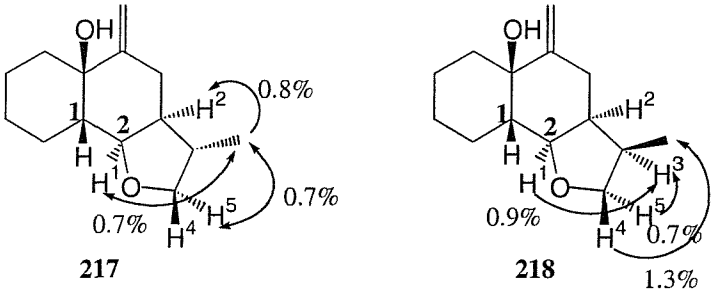
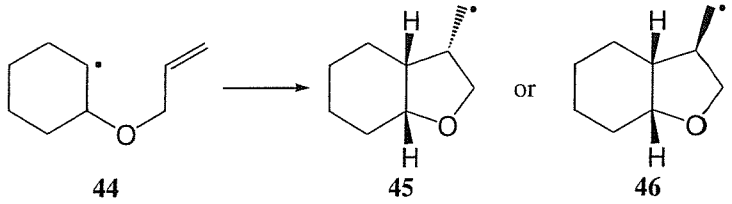


Figure 18 Important nOe cross peaks

However, irradiation of H1 in isomer **218** gave a 0.9% enhancement with H3 and none with the methyl group. Further nOe's from H4 to the methyl and H5 to H3 confirm that H1, H3 and H5 are all on the same side of the tetrahydrofuran ring.

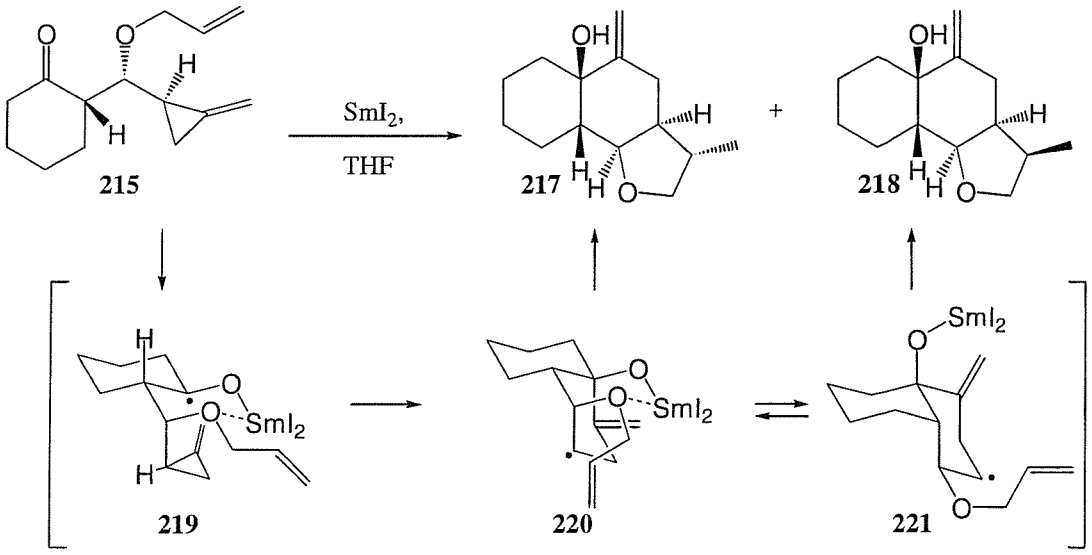
5.3 STEREOSELECTIVITY

The unexpected reversal of stereoselectivity can be understood with reference to Beckwith[25-29] and RajanBabu's[30] detailed studies of the cyclisation of cyclohexyl radicals onto pendant allyloxy groups **(Scheme 16)**, which demonstrated that if the cyclisation goes through a chair-like transition state, then if the allyloxy group is equatorial to the cyclohexyl ring the new stereocentre will be the *cis*-fused *syn* product **45**. However, if the allyloxy group is held axially then the *cis*-fused *anti* product **46** is observed.



Scheme 16

Assuming that allyl ether **215** cyclises *via* a weakly chelated intermediate **219**, then the resulting cyclohexyl radical intermediate **220** will have the allyloxy substituent in an *axial* position, which should cyclise to give the *anti*-methyl substituent **217** according to Beckwith/RajanBabu (**Scheme 66**).[25-30] Flipping the conformation of **220** breaks the weak chelation of the allyl ether oxygen to the samarium metal. This may be favoured in the presence of HMPA and gives **221** with the allyloxy substituent in an equatorial position, which should cyclise to give the *syn*-methyl substituent **218**.

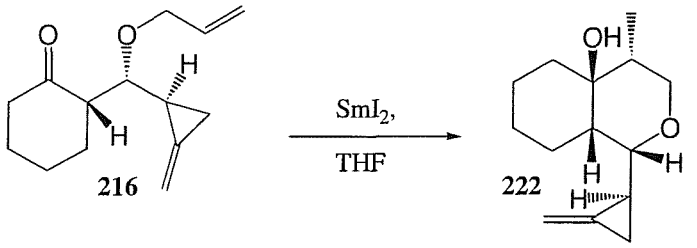


Scheme 66

5.4 ALLYL ETHER ISOMER 216

Cyclisations using samarium diiodide were attempted on allyl ether **216** (**Table 12**). Cyclisation of allyl ether isomer **216** gave the bicyclic ether **222**, which was obtained *via* a 6-*exo* cyclisation onto the allyl ether instead of the cyclopropyl alkene

bond as was observed for propargyl ether **199**. Bicyclic product **222** was formed in very good yields of up to 73%.

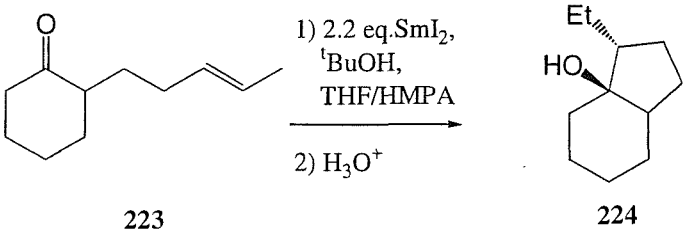


Reaction conditions	222
SmI_2, MeOH, THF, 0°C	72%
SmI_2, MeOH, THF, -78°C	73%
SmI_2, HMPA, THF, ^tBuOH, 0°C	70%
SmI_2, HMPA, THF, ^tBuOH, -78°C	70%

Table 12 Cyclisations of allyl ether isomer 216

5.5 STEREOCHEMISTRY

The stereochemistry of bicycle **222** can be established by comparison with bicycle **208** produced from cyclisation of propargyl ether **199**. Both cyclisations follow the same mechanism and have the same stereochemistry in their starting materials. The only difference is bicycle **222** has a new stereocentre at the methyl group. The stereochemistry at the methyl group can be assumed to be *trans* to the alcohol group by reference to the cyclisation of **223** described by Molander (**Scheme 67**).[53] Molander's work showed that the stereochemistry at the new ethyl group in the product **224** was *trans* to the alcohol as would be expected for cyclisations mediated by samarium diiodide, which proceed with the alkene avoiding electronic repulsion from the ketyl radical oxygen.[53]



Scheme 67

6. CONCLUSIONS

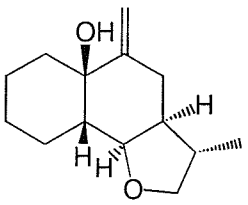
Initially a tricyclic skeleton was obtained in good yield after cyclisation of propargyl ether **198**, which showed the radical cascade reaction was successful. However, the isomeric propargyl ether **199** only gave a bicyclic product with the methylenecyclopropane still intact. An analogous bicyclic compound was also produced from the same isomer of the allyl ethers **216**. However, samarium diiodide mediated cyclisation of allyl ether **215** gave a very interesting result and under suitable solvent conditions, a stereoselective route to tricyclic ethers was obtained. Thus, using the MeOH/THF (1:4) solvent system gave one tricyclic isomer as the major product, but if HMPA was substituted for MeOH then the stereochemistry at the new methyl chiral centre was reversed.

CHAPTER 4

TOWARDS A NATURAL PRODUCT - DIHYDROTOURNEFORTIOLIDE

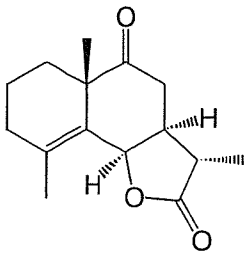
1. INTRODUCTION

With the methodology and stereochemistry firmly established[76] work was directed towards the synthesis of a complex natural product. Tricyclic skeleton **217**, produced from cyclisation of allyl ether **215** with samarium diiodide and MeOH/THF in good yield, has the correct stereochemistry for natural product dihydrotournefortiolide to be a possible target.[65,77] A number of tricyclic natural products have been isolated[78,79]. For example 9-oxo-11β, 13-dihydrotournefortiolide **154**[65,77] and stoebenolide **225 (Figure 19)**,[78] both of which are members of the eudesmane family.



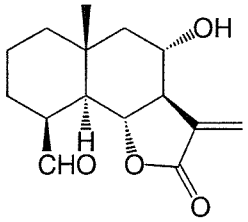
Tricyclic skeleton

217



9-oxo-11β, 13-dihydrotournefortiolide

154

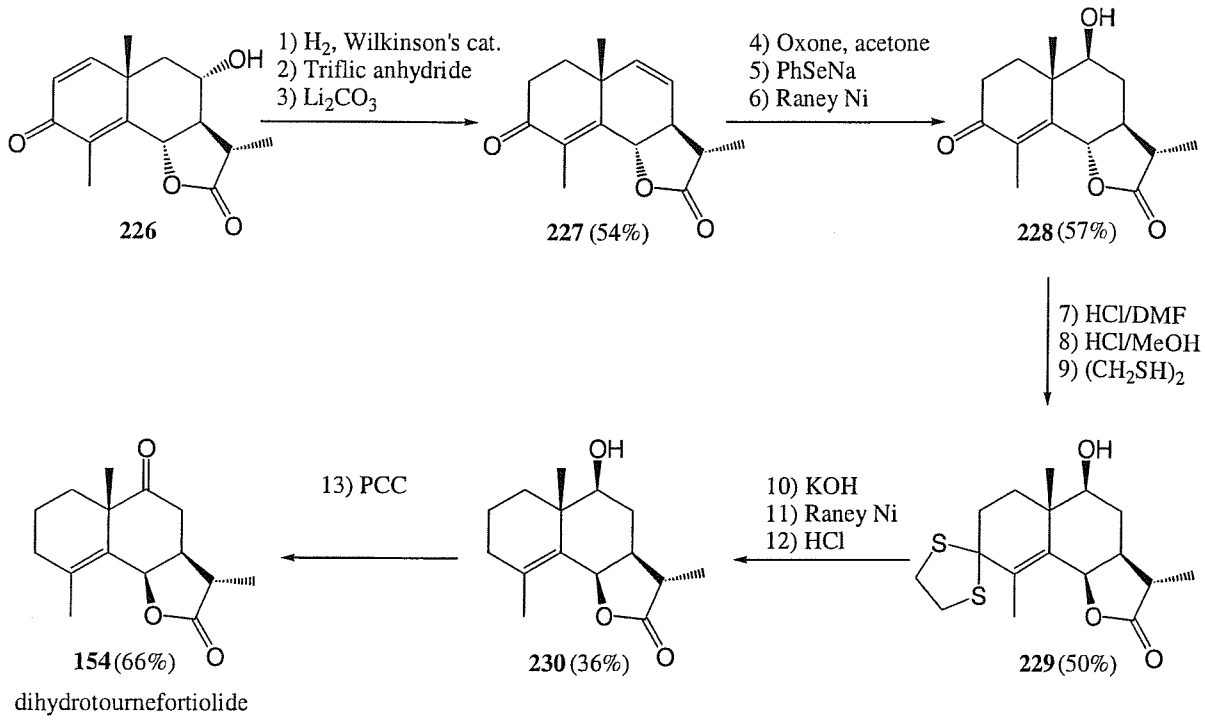


Stoebenolide

225

Figure 19

Dihydrotournefortiolide **154** was first isolated from *Artemisia tournefortiana*, one of the Spanish species of the genus *Artemisia* (Fam. Compositae, tribe Anthemideae). A previous synthesis of dihydrotournefortiolide **154** has been described by Pedro, starting from artemusin **226 (Scheme 68)**.[65,80,81]

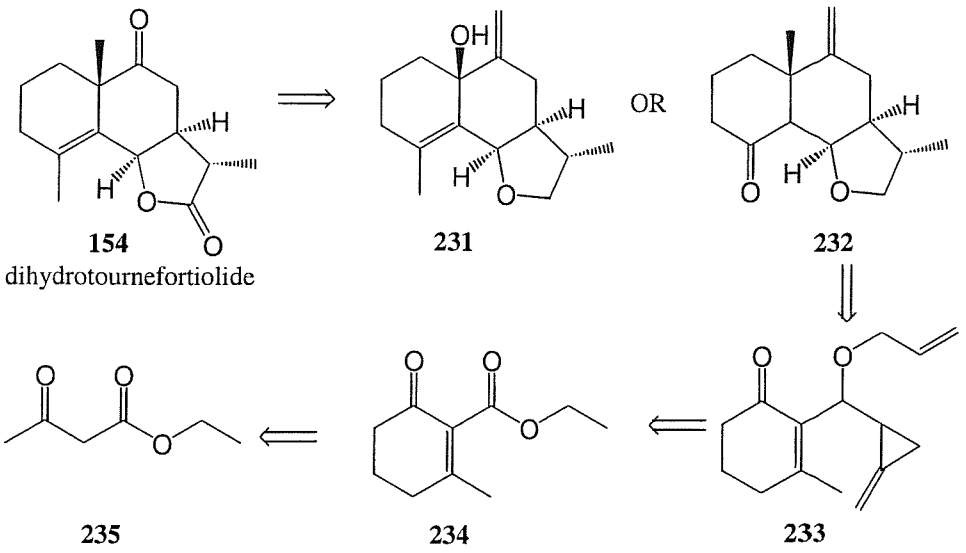


Scheme 68

1,2 Hydrogenation was carried out using Wilkinson's catalyst, followed by dehydration to give tricycle **227**. Oxone was used for epoxidation of the double bond. The epoxide was opened using PhSeNa and the phenylselenium group was removed using Raney Ni giving alcohol **228**. Epimerisation of the lactone[82] followed by protection of the ketone using ethanedithiol produced thioketal **229**. Removal of the thioketal[83] afforded alcohol **230**, which was finally oxidised using PCC[84] to afford the natural product dihydrotournefortiolide **154**.[65]

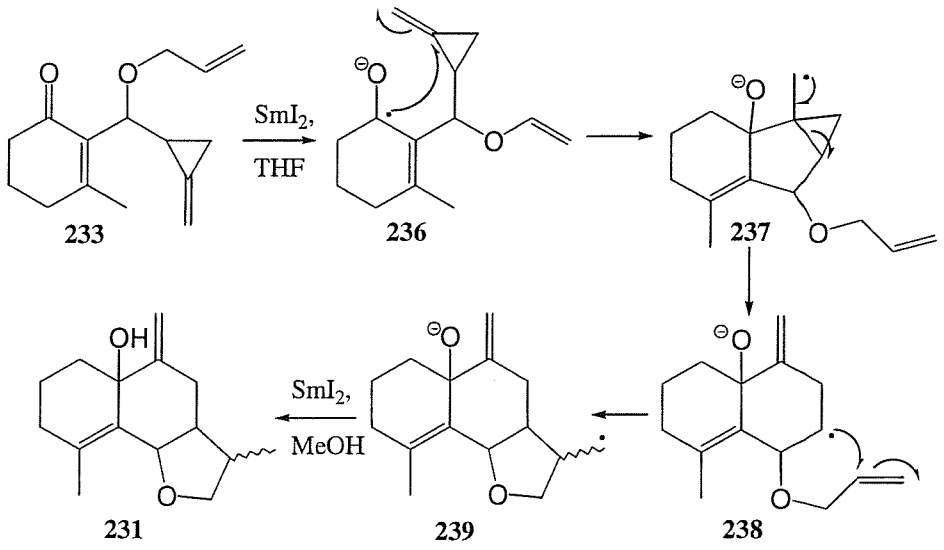
2. DISCONNECTION OF DIHYDROTOURNEFORTIOLIDE

A retrosynthetic analysis of dihydrotournefortiolide **154** suggested that it might be obtained from precursor **233** by one of two possible cyclisation modes leading to tricycle **231** or **232 (Scheme 69)**.



Scheme 69

The cyclisation of the α,β-unsaturated ketone **233** could happen by one of two pathways **(Scheme 70 and Scheme 71)**.

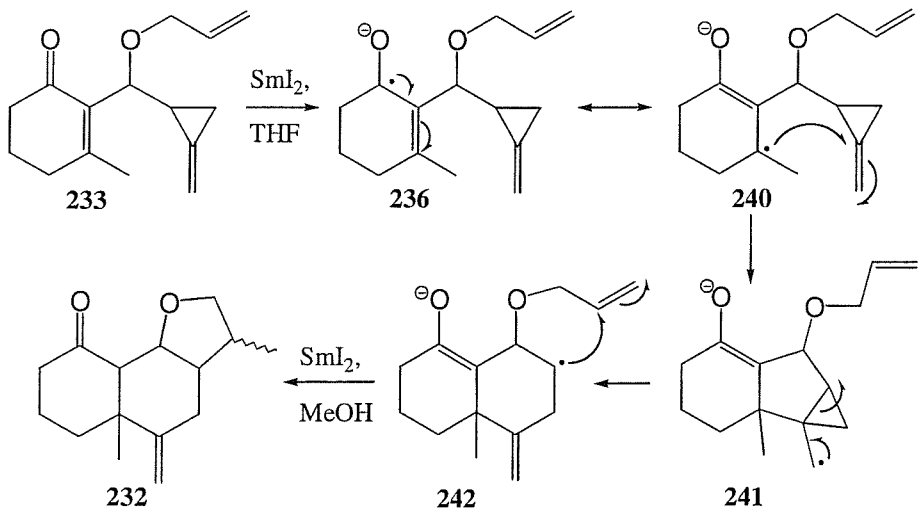


Scheme 70

Ketyl radical **236** could be produced from reduction of ketone **233** with samarium diiodide, which could undergo a 5-*exo* cyclisation, followed by an '*endo*' ring opening to produce radical **238**. This radical could undergo a further 5-*exo* cyclisation, followed by reduction of the radical to an anion that may be quenched by protonation from methanol to afford tricycle **231 (Scheme 70).**

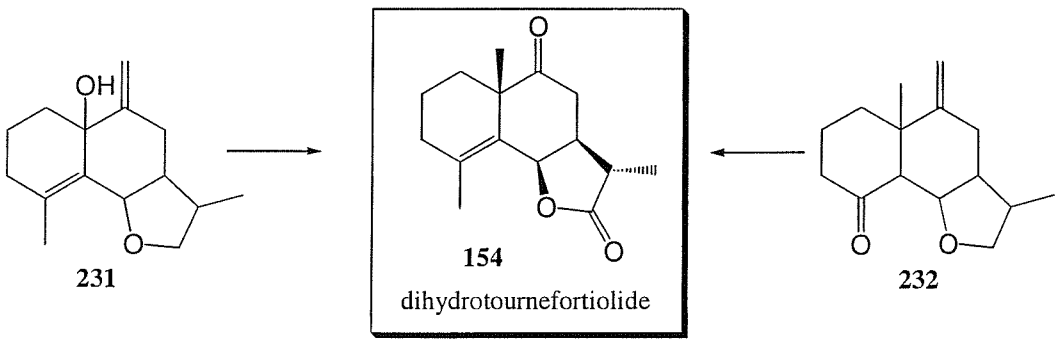
However, the ketyl radical can also be delocalised to give radical **240 (Scheme 71)**. From the β-position **240** could undergo a 5-*exo* cyclisation onto the methylenecyclopropane moiety, followed by an '*endo*' ring opening to give cyclohexyl

radical **242**. A 5-*exo* cyclisation followed by further reduction of the radical to an anion, which could be quenched by protonation from methanol would furnish tricyclic compound **232**.



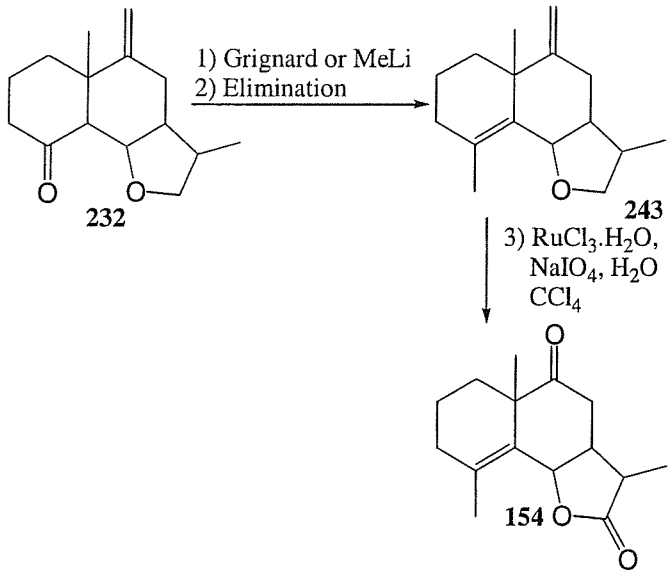
Scheme 71

Either method would give a suitable building block to make the natural product, as tricycle **231** has the double bond and methyl group in place but contains a tertiary alcohol **(Scheme 72)**, whereas tricycle **232** has the other methyl group in place and a ketone which could be readily converted to the required alkene.



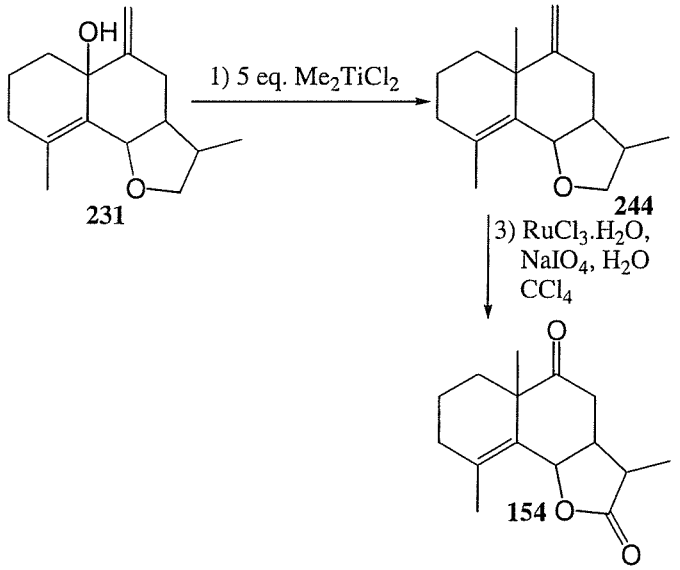
Scheme 72

If the cyclisation gave tricycle **232** then a short series of functional group manipulations could give the natural product **(Scheme 73)**.[85,86]



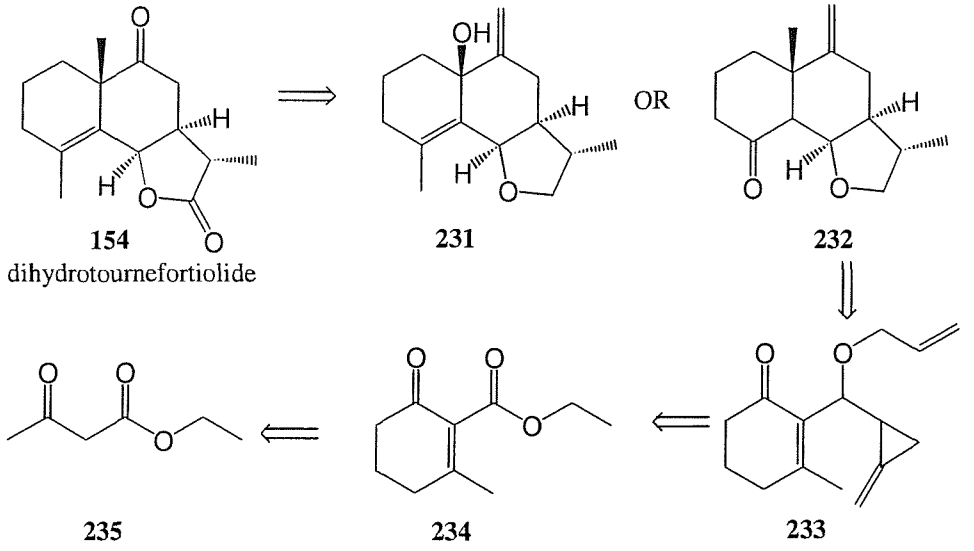
Scheme 73

However, if tricycle **231** was produced then the following steps might produce the natural product **(Scheme 74)**.[85-88]



Scheme 74

Allyl ether **233** could be prepared from ketoester **234**, which in turn could be made from ethyl acetoacetate **235 (Scheme 69)**

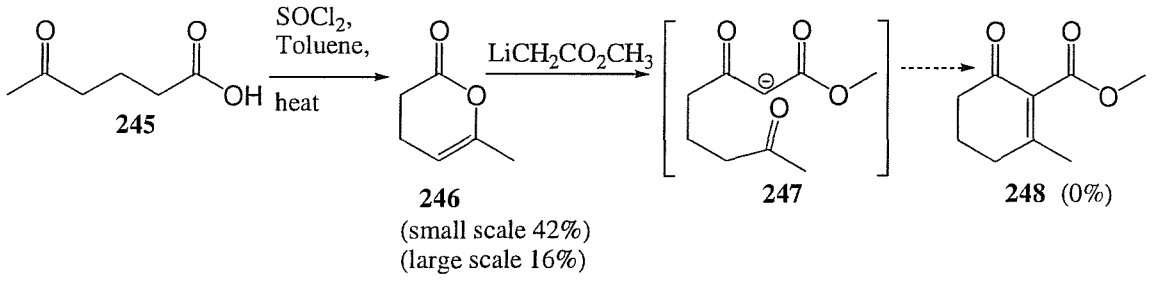


Scheme 69

3. SYNTHESIS OF CYCLISATION PRECURSORS

3.1 INITIAL STUDIES

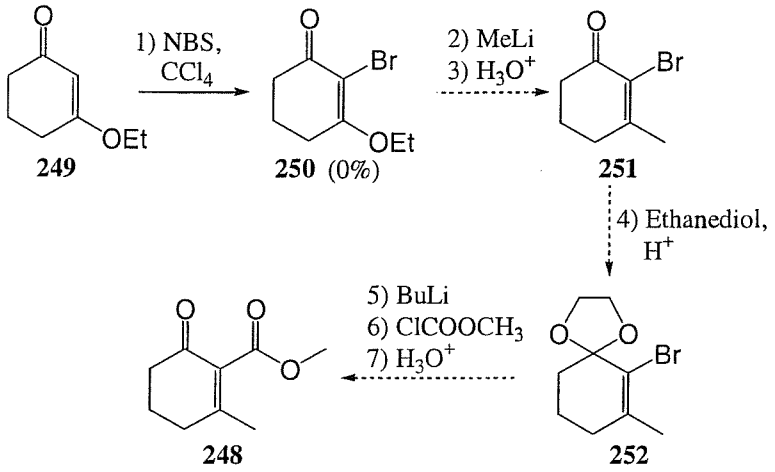
Work began with an attempt to synthesise the ketone precursor **233** using a method described by Paquette.[89] Ketoacid **245** was treated with thionyl chloride and refluxed in toluene to produce lactone **246** in poor yield, particularly on a large scale (small scale 42%, large scale 16%) **(Scheme 75)**.



Scheme 75

Unfortunately, the subsequent reaction with the enolate of methyl acetate did not give the desired product **248**, and as a consequence this method was abandoned. A new route was attempted as also described by Paquette,[89] which relies on introduction of a bromide followed by transmetallation and ethoxycarbonylation.

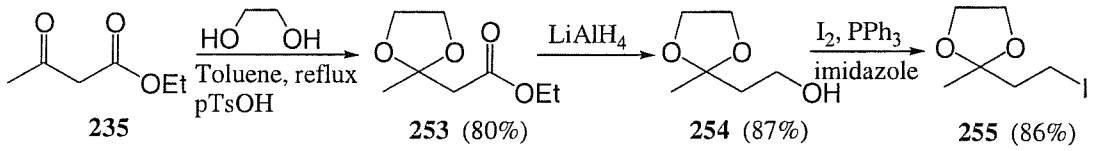
Thus, ketone **249** was reacted with NBS in carbon tetrachloride in an attempt to prepare bromide **250** according to Paquette's method **(Scheme 76)**.[89]



Scheme 76

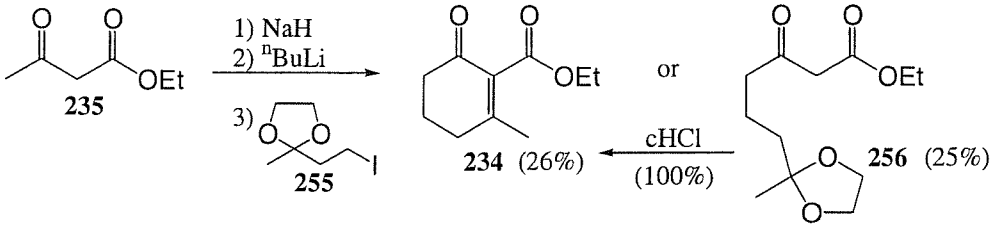
The reaction was attempted several times but without success and so another method was tried.

Ethyl acetoacetate **235** was protected using ethanediol[90] and then reduced to alcohol **254** using lithium aluminium hydride[69] in good yield (87%). Alcohol **254** was converted to the iodide **255** in yields of up to 86% using iodine, PPh_3 and imidazole **(Scheme 77)**.[91]



Scheme 77

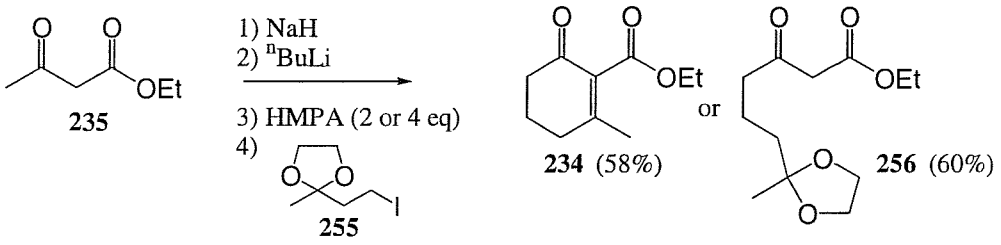
The dianion of ethyl acetoacetate was prepared, using sodium hydride and butyl lithium,[92] and reacted with iodide **255 (Scheme 78)**. When concentrated acid was used in the work up, cyclised product **234** was produced in poor yield (26%), whereas when weak acid was added the uncyclised product **256** was produced in equally poor yield (25%).



Scheme 78

The conversion of **256** to **234** was attempted using the literature method by Funk employing Lewis acid $TiCl_4$,[93] but this gave a mixture of products and a low yield. It was found that the uncyclised product **256** could be readily converted into **234** using concentrated HCl in quantitative yield.

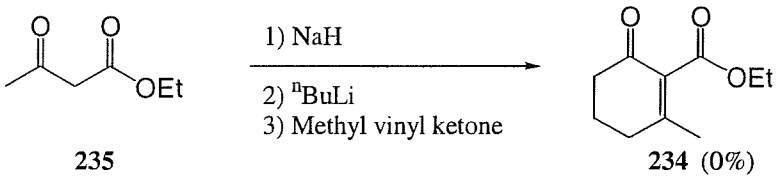
In an attempt to increase the poor yield of the cyclisation, HMPA was added, in order to make the dianion more reactive **(Scheme 79)**.[94]



Scheme 79

The reaction was attempted initially with 4 equivalents of HMPA,[94] and subsequently repeated with 2 equivalents of HMPA. As there was no detriment to the yield it was deemed preferable to use the minimum amount of HMPA necessary due to its toxicity. With a concentrated acid work up cyclised product **234** was obtained in a gratifyingly improved yield (58%). With a weak acid work up the uncyclised product **256** was produced, again in a better yield (60%).

Due to the success of the synthesis of cyclised compound **234** a one-step process was attempted. Ethyl acetoacetate **235** was treated first with sodium hydride followed by butyl lithium to give the dianion,[92] which was subsequently reacted with methyl vinyl ketone **(Scheme 80)**.

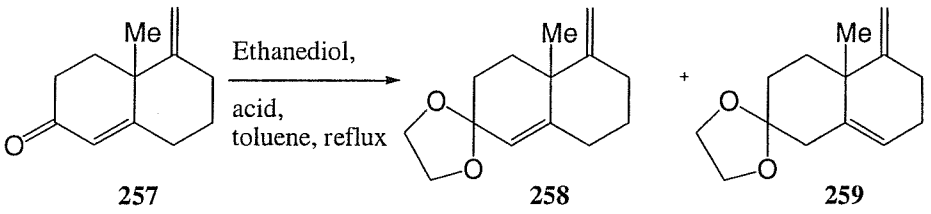


Scheme 80

Unfortunately, cyclised product **234** was never observed after repeated attempts and as a viable route existed the reaction was abandoned.

3.2 TOWARDS CYCLISATION PRECURSORS

Protection of α,β-unsaturated ketones using ethanediol has been studied by De Leeuw.[95] These investigations showed the effect different acids had on the reaction **(Scheme 81)**. Ethanediol and pTsOH gave the double bond out of conjugation **259** in 100% yield, however ethanediol and fumaric acid gave 100% of **258** with the double bond retained in its original position.

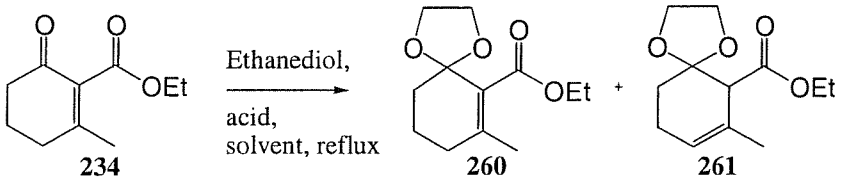


257 **258** **259**

pTsOH	0%	100%
Fumaric acid	100%	0%
phthalic acid	70%	30%
oxalic acid	80%	20%

Scheme 81

Ketoester **234** was protected using ethanediol and acid: when pTsOH was used only product **261** was produced with the double bond out of conjugation (48% and 50% starting material **234**) as expected, whereas when fumaric acid was used a 3:1 mixture of **260**:**261** was observed (36% and 14% respectively) **(Scheme 82)**. The products were easily separated by column chromatography.



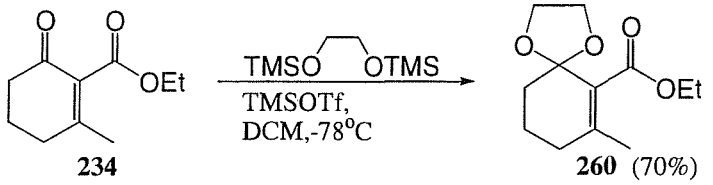
234 **260** **261**

pTsOH	toluene	0%	48%
Fumaric acid	toluene	36%	14%
pTsOH	benzene	27%	0%
pTsOH	xylene	0%	35%

Scheme 82

The protection was also attempted using different solvents to enable the reaction temperature to be changed, for example benzene and xylene. However the reactions were not as clean and the yields were lower than observed with toluene **(Scheme 82)**.

The protecting group was also introduced using a method by Noyori,[96] which gave the α,β-unsaturated product in good yield (70%) **(Scheme 83)**.

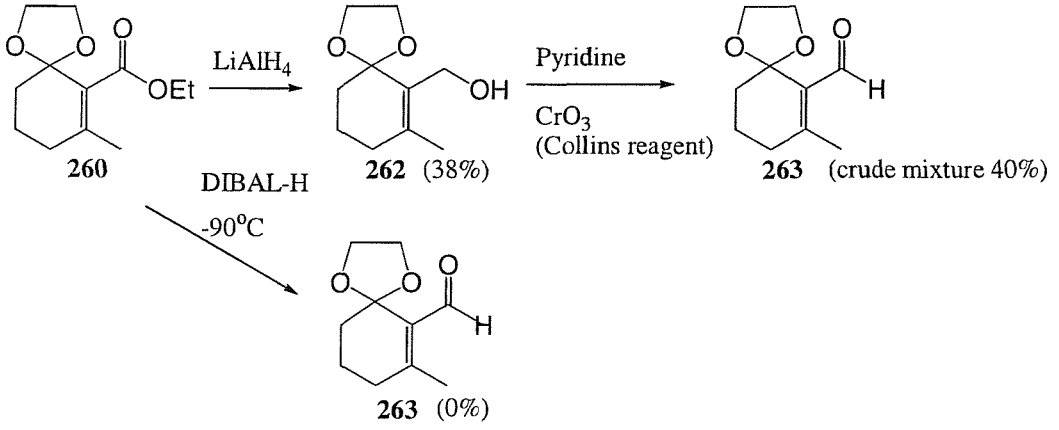


234 **260** (70%)

Scheme 83

Neopentyl glycol was also used as a protecting group instead of ethanediol but only starting material and a mixture of inseparable compounds were observed.

Conjugated ester **260** was reduced using lithium aluminium hydride[68] in very poor yield (38%) followed by oxidation using Collins reagent.[97] Unfortunately a crude yield of only 40% was observed, consisting of a mixture of three inseparable compounds **(Scheme 84)**.

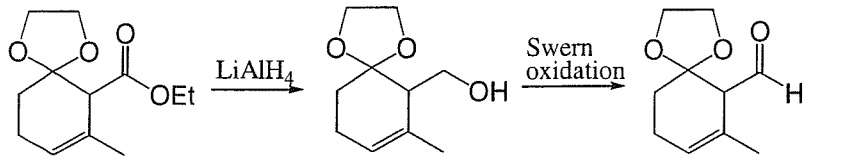


260 **262** (38%) **263** (crude mixture 40%)

263 (0%)

Scheme 84

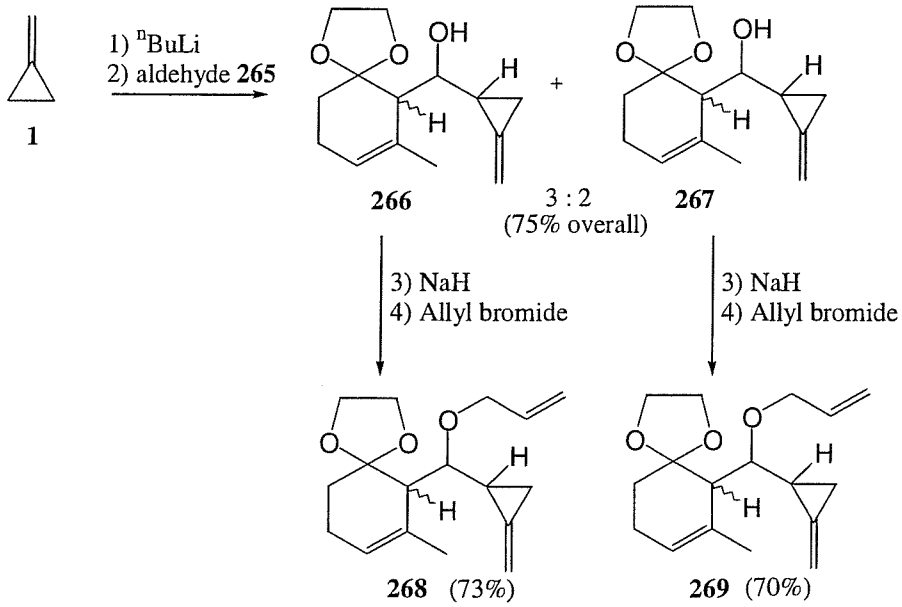
A different method of synthesising aldehyde **263** was adopted. Ester **260** was treated with DIBAL-H,[98] but again no aldehyde was produced so a new route was needed. On protection of ketoester **234** with ethanediol and pTsOH the double bond moved "out-of-conjugation", therefore upon deprotection it was hoped it would move back. Following this premise work began using the "out-of-conjugation" protected ester **261.** Ester **261** was reduced using lithium aluminium hydride[68] to give alcohol **264** in good yield (84%). A Swern oxidation[70] was used to convert alcohol **264** to aldehyde **265** in excellent yield (98%) **(Scheme 85)**. Oxidation of alcohol **264** was also attempted using Collins reagent[97] but only a low yielding mixture was produced.



261 **264** (84%) **265** (98%)

Scheme 85

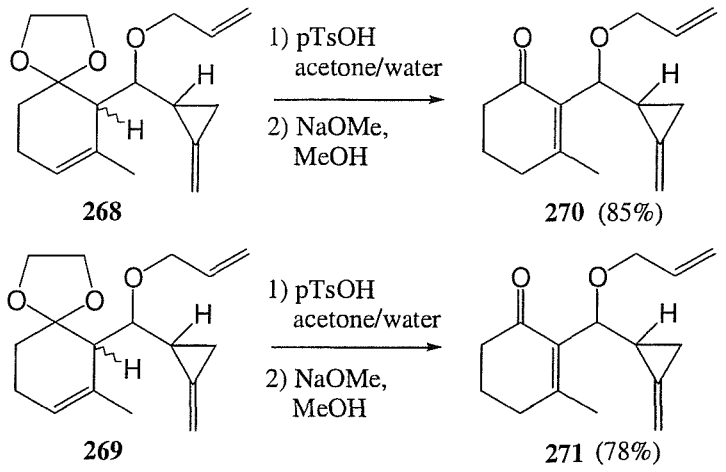
Methylenecyclopropane **1** was reacted with ^{n}BuLi to produce a methylenecyclopropane anion, which reacted with aldehyde **265** to give diastereoisomers **266** and **267** in good yield (3:2 respectively 75% overall) **(Scheme 86)**. However, it proved very difficult to purify the diastereoisomers **266** and **267** after separation so the compounds were used crude in the following reactions. Alcohols **266** and **267** were treated separately with NaH, then allyl bromide to afford allyl ethers **268** and **269**.



1 **266** **267** **268** (73%) **269** (70%)

Scheme 86

Unfortunately, after deprotection using pTsOH and wet acetone the double bond did not move back into conjugation. The reaction was forced using sodium methoxide in methanol to give α,β-unsaturated cyclisation precursors **270** and **271** in up to 85% and 78% yields respectively **(Scheme 87)**.



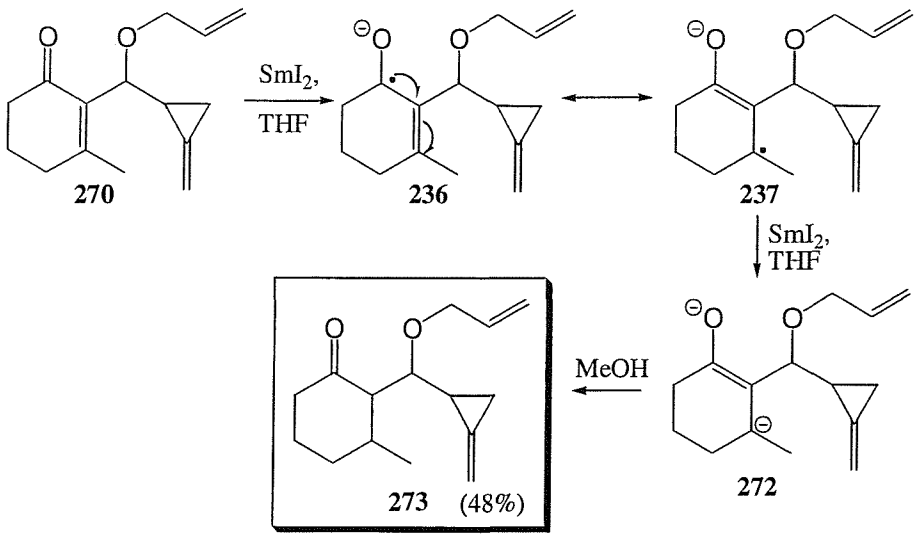
Scheme 87

However, the overall yield for the synthesis from ethyl acetoacetate **235** was very low (~8.5% for **270** and ~7.5% for **271** over 9 steps) and so only small amounts of cyclisation precursor were produced. The stereochemistries have not been assigned due to the lack of material.

4. CYCLISATION OF NATURAL PRODUCT PRECURSORS

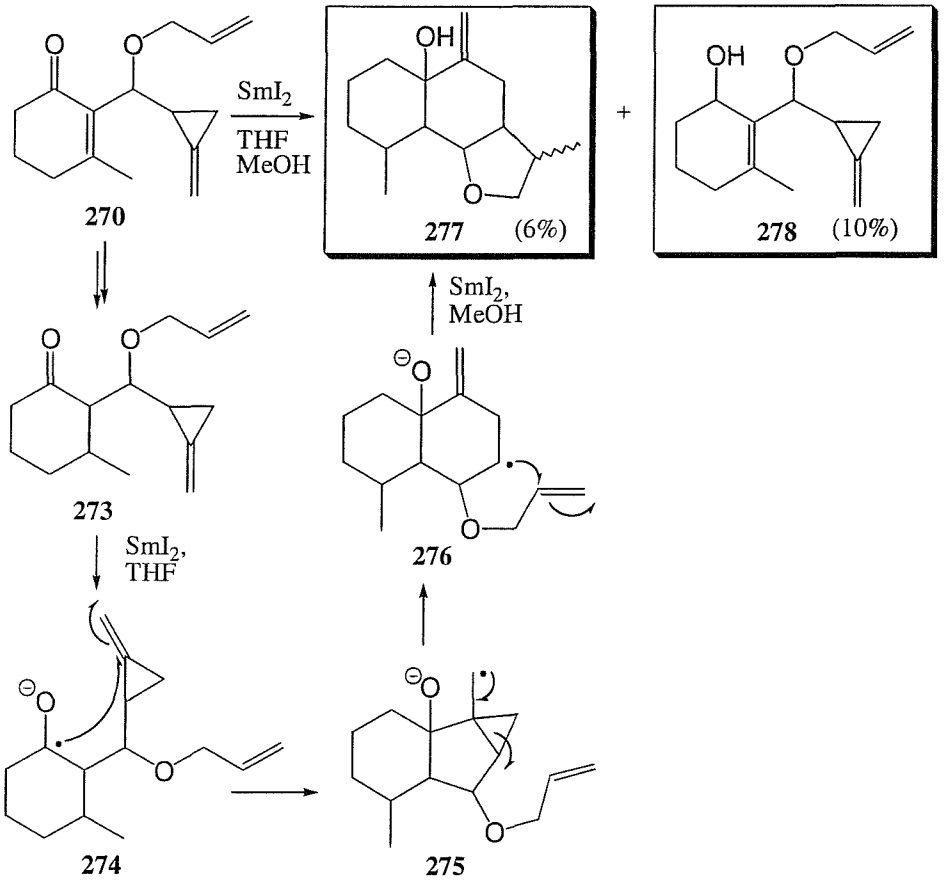
4.1 CYCLISATION OF PRECURSOR 270

Using the best conditions established from the model studies **(Chapter 3)**,[76] α,β-unsaturated ketone **270** was added to samarium diiodide in MeOH/THF (1:4) as solvent. Unfortunately no tricyclic compounds were observed, the only product being the starting material with the double bond reduced **273 (Scheme 88)**. Presumably precursor **270** is reduced to ketyl radical **236** with samarium diiodide leading to **237**. A further equivalent of samarium diiodide reduces radical **237** to anion **272**, which can be quenched by protonation from methanol to furnish ketone **273** in 48% yield.



Scheme 88

A possible reason for the failure of the reaction was the high concentration of samarium diiodide in the reaction mixture, as the substrate was added to the solution of SmI_2. To overcome this problem the reaction was attempted using the reverse addition of samarium diiodide. When the SmI_2 was added dropwise to the substrate a different result was observed **(Scheme 89)**.



Scheme 89

Ketone **273** was presumably produced as before, followed by reduction of the ketone to ketyl radical **274**, which underwent a 5-*exo* cyclisation and an '*endo*' ring opening to give cyclohexyl radical **276 (Scheme 89)**. A 5-*exo* cyclisation onto the alkene moiety gave a tricyclic radical, which was reduced further to the anion followed by protonation from methanol to yield tricycle **277** in poor yield (6%). The stereochemistry of **279** can be inferred by comparison with the tricyclic compounds described in chapter 3. Assuming *cis* fusion on both the cyclisations, H2 would therefore be *cis* to H1 and the alcohol group would be *cis* to H3 **(Figure 20)**. Comparison with the tricycles **217** and **218** described in chapter 3 would give the methyl group on the furan ring *cis* to H2. NMR studies on **279** revealed that H1 couples to H3 with a coupling constant of 3 Hz and to H2 with a coupling constant of 5 Hz **(Figure 20)**, which implies H1 is equatorial **279 (Figure 20)**. A coupling constant of 3 Hz between H1 and H3 implies H3 would be equatorial, which gives a *trans* relationship between H1 and H3. A coupling constant of 11 Hz suggests axial coupling of H3 to H4, which would put H3 *trans* to H4 and *cis* to the methyl group on the cyclohexane ring.

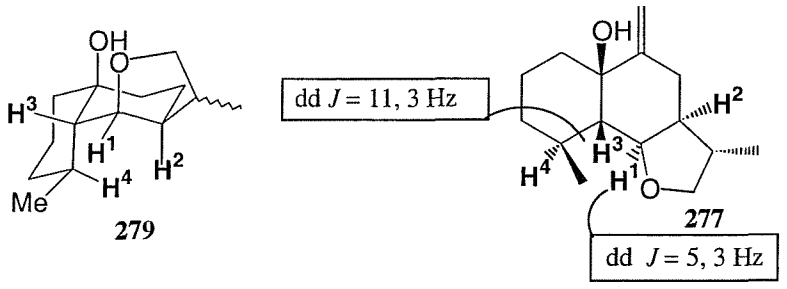


Figure 20

Reduced starting material was also observed in a 10% yield **(Scheme 89)**. Precursor **270** was reduced to the ketyl radical **236**, which was reduced with an extra equivalent of samarium diiodide and quenched to yield alcohol **278**.

The stereochemistry of alcohol **278** can be assumed to be the 1,3 *anti* compound *i.e.* the stereochemistry at the alcohol will be opposite to that of the allyl ether (as explained in the model studies in chapter 2).

The reverse addition cyclisation was attempted on the other precursor isomer **271**, unfortunately the reaction was not as clean and no products could be isolated from the reaction mixture.

5. CONCLUSIONS

The synthesis of the cyclisation precursors proved problematic due to the migration of the double bond in and out of conjugation. A few of the synthetic steps also caused problems due to erratic yields. However, upon cyclisation of precursor **270** a number of different compounds were produced. Unfortunately none of them were the desired tricyclic products, so work was directed towards cyclisations of simpler α,β-unsaturated ketones to try and develop optimised conditions for the cyclisation and to see whether it would prove possible to obtain the tricyclic compounds for the natural product synthesis.

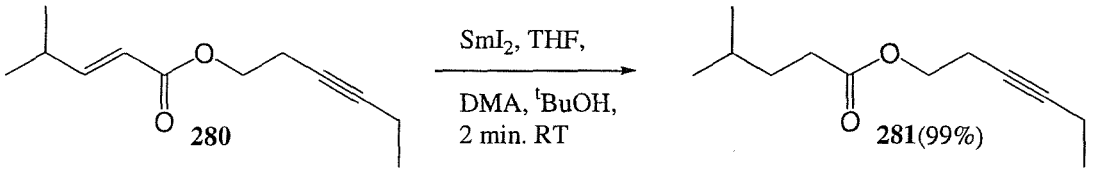
CHAPTER 5

MODEL STUDIES TOWARDS NATURAL PRODUCT

1. INTRODUCTION

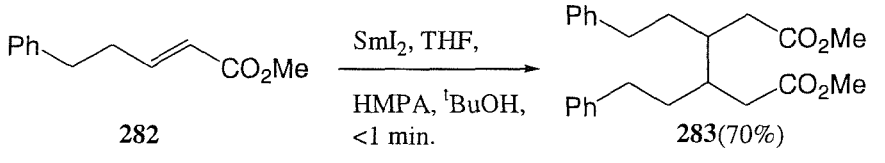
A number of problems arose whilst attempting to synthesise the natural product dihydrotournefortiolide. As a consequence bringing through enough compound to investigate the cyclisation in detail proved very difficult **(Chapter 4)**. Investigations were therefore directed towards model studies of samarium diiodide mediated cyclisations of simpler α,β-unsaturated carbonyl compounds.

α,β-Unsaturated esters can behave in many different ways under treatment with samarium diiodide depending on the additives used. For example, under optimised conditions, various substituted α,β-unsaturated esters can be rapidly and selectively reduced without affecting co-existing isolated double or triple bonds **(Scheme 90)**.[99]



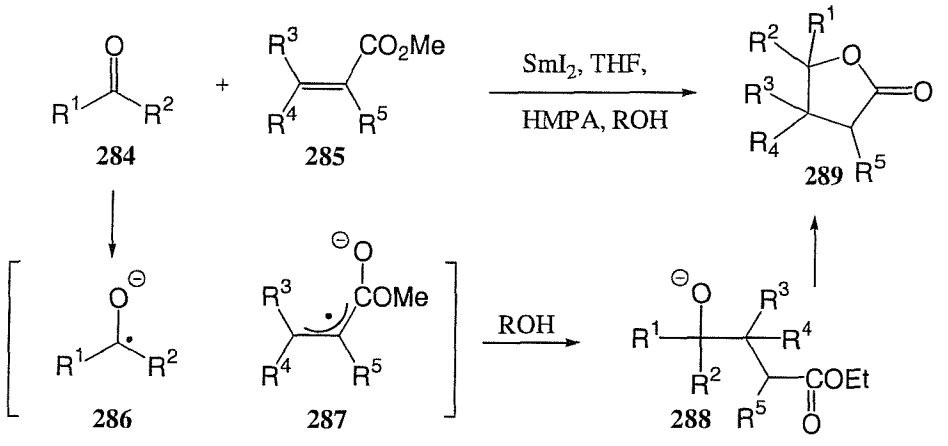
Scheme 90

For example, α,β-unsaturated ester **280** was treated with SmI_2-DMA-^{t}BuOH in THF to give ester **281** in very good yield. However, if the additive DMA was replaced with HMPA then an intermolecular dimerisation occurred at the β position of the α,β-unsaturated esters **(Scheme 91)**.[100,101]



Scheme 91

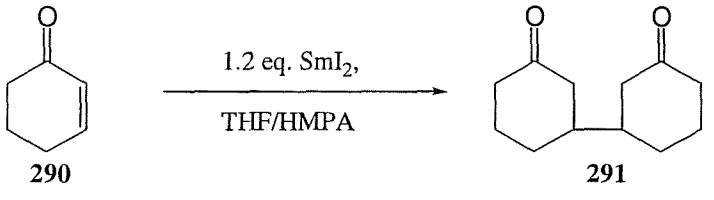
Work by Inanaga[49] has demonstrated the samarium diiodide induced reductive cross-coupling of carbonyl compounds with α,β-unsaturated esters. The reaction was greatly accelerated by the addition of HMPA **(Scheme 92)**.



Scheme 92

A mechanism was postulated by Fukuzawa[102] that involved reduction of ketone **284** to ketyl radical **286** with subsequent coupling to an allylic radical **287** generated by a one-electron transfer from samarium diiodide to the α,β-unsaturated ester **285** **(Scheme 92)**. A proton from an alcohol was then incorporated into the α-carbon of the ester group followed by cyclisation to provide γ-lactone **289**.

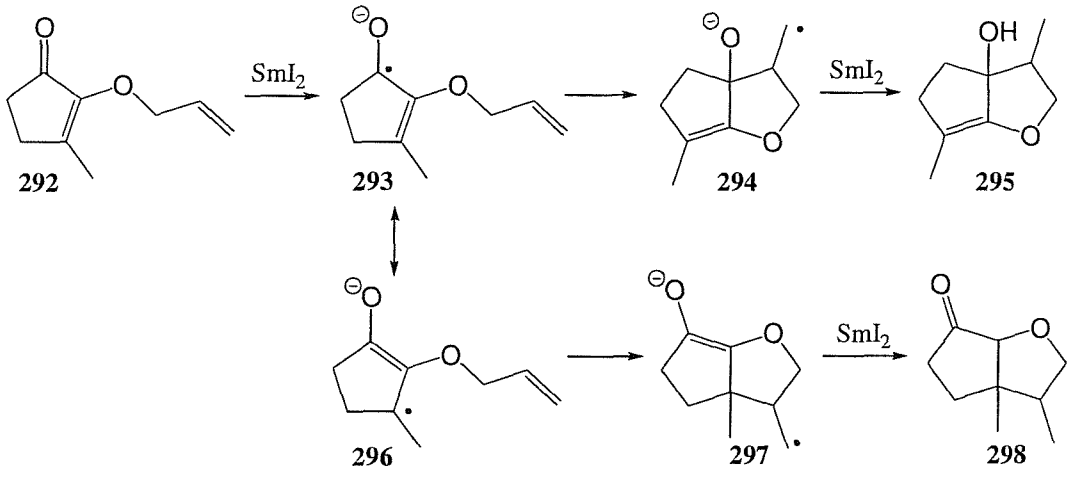
Simple α,β-unsaturated ketones such as cyclohexenone **290** have been reported in the literature to undergo dimerisation upon treatment with samarium diiodide in THF with HMPA to give dimer **291 (Scheme 93)**.[103]



Scheme 93

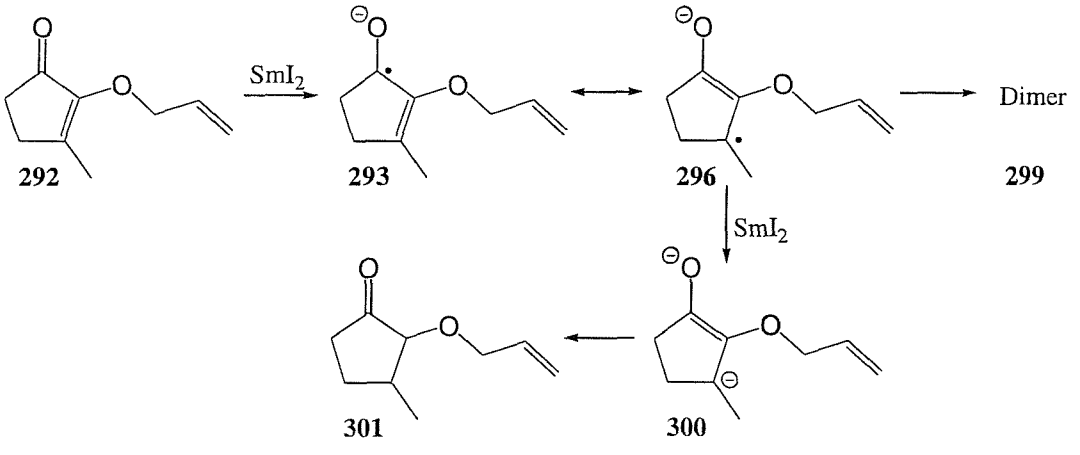
2. INVESTIGATIONS INTO THE INTRODUCTION OF A COMPETITIVE CYCLISATION

The main direction of this work was to investigate cyclisations of a simple α,β-unsaturated ketone **292** with a pendant alkene, which could in principle undergo a 5-*exo* cyclisation upon treatment with samarium diiodide *via* **293** or **296** to give either **295** or **298** respectively **(Scheme 94)**.



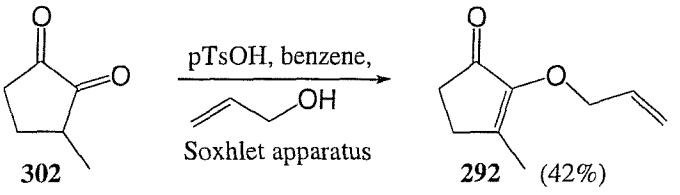
Scheme 94

Alternatively treatment of **292** with samarium diiodide might simply lead to reduced products or dimers **(Scheme 95)**.



Scheme 95

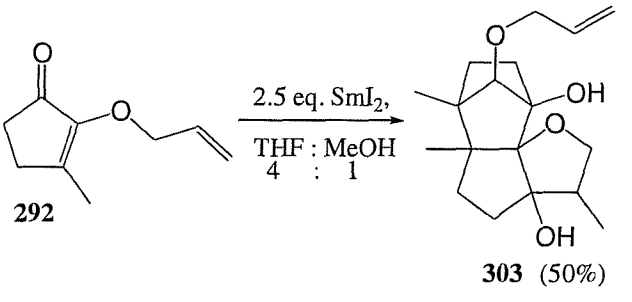
Work began by synthesising the cyclisation precursor **292**.[104]



Scheme 96

Diketone **302** was refluxed in benzene with allyl alcohol and toluene sulfonic acid using Soxhlet apparatus to yield α,β-unsaturated ketone **292** in 42% after distillation.[104] When the same reaction was attempted using toluene as solvent, a mixture of isomers was observed.

Initially precursor **292** was treated with 2.5 equivalents of samarium diiodide in THF with MeOH as a co-solvent **(Scheme 97)**. A single product was obtained in 50% yield which, proved to be the unexpected tetracycle **303**.



Scheme 97

The structure of tetracycle **303** was determined by extensive nmr studies and X-ray crystallography **(Figure 21)**.

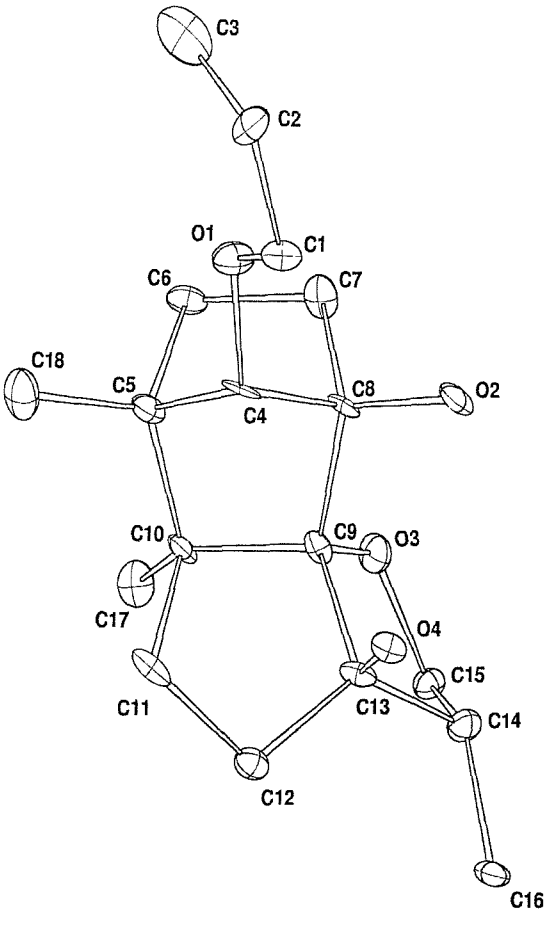
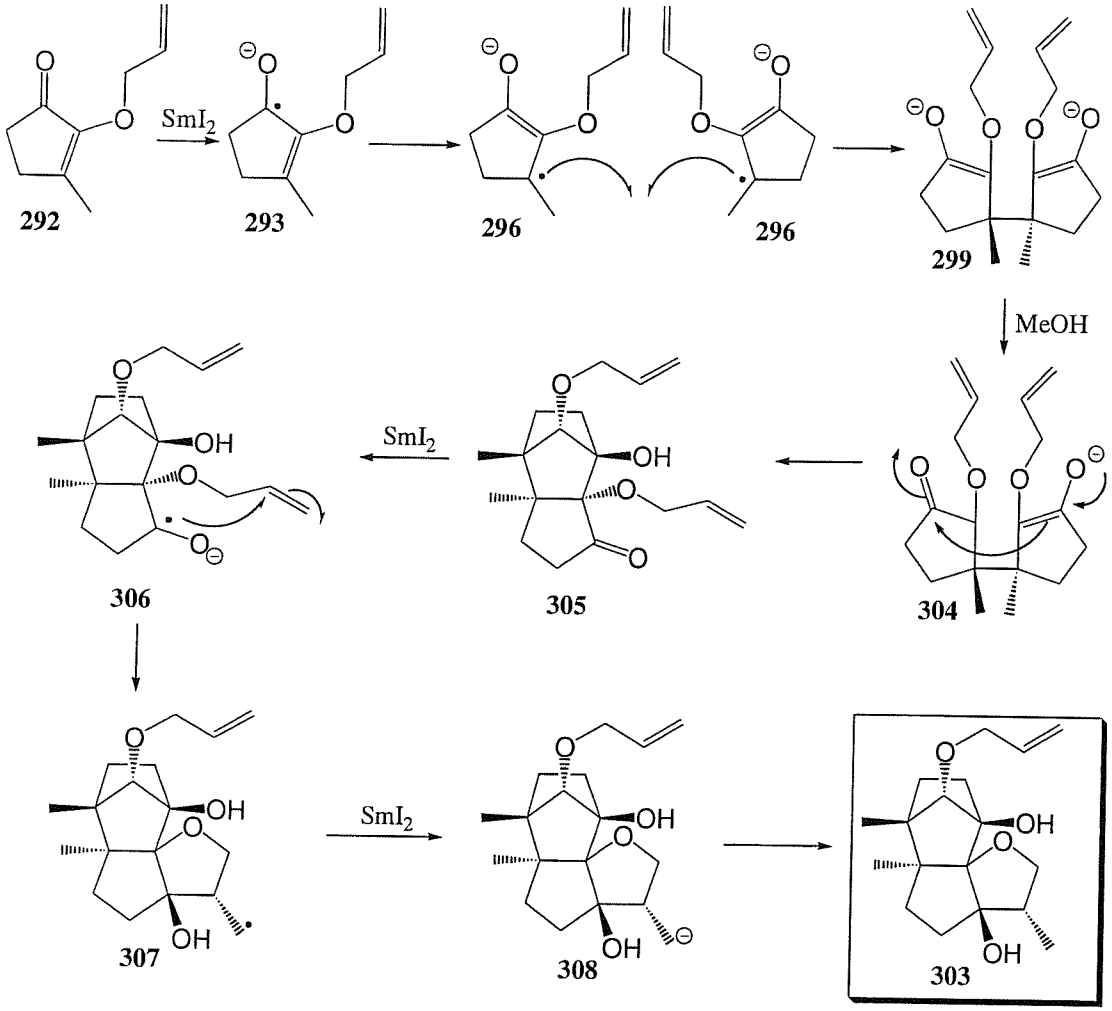


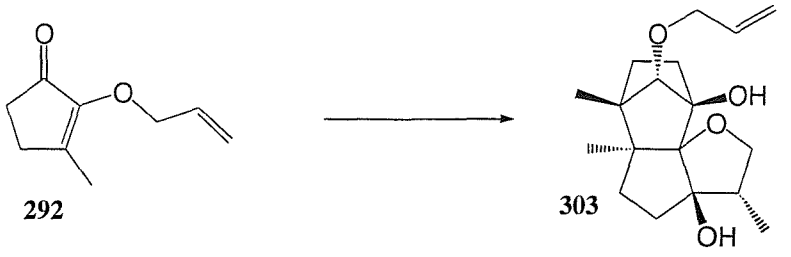
Figure 21 Tetracycle 303

The proposed mechanism for the formation of **303** begins with formation of **293** which dimerises *via* **296** to give **299** with the two methyl groups *trans* to each other. Alternatively a single radical **296** could add (Michael addition) to enone **292**. Protonation of one of the enolates with methanol, followed by an intramolecular aldol condensation gives *cis* fused cyclised product **305**. Ketone **305** is reduced to ketyl radical **306** by an additional equivalent of samarium diiodide and now undergoes a 5-*exo* cyclisation onto the alkene moiety to produce primary radical **307**. Samarium diiodide reduces radical **307** to anion **308**, which is quenched by a proton source to furnish tetracycle **303 (Scheme 98)**.



Scheme 98

Different methods and conditions were applied to precursor **292** in an attempt to alter the reaction pathway and obtain the desired bicyclic compounds **295** or **298** (**Table 13**).



292 303

Reaction Conditions	292	303
Add substrate to SmI_2 and co-solvent in THF.		
1) 2.5 eq. SmI_2, MeOH, THF, -78°C		50%
2) 2.5 eq. SmI_2, MeOH, THF, 0°C		20%
3) 2.5 eq. SmI_2, HMPA, ^{t}BuOH, THF, -78°C	Decomposed	
4) 4 eq. SmI_2, MeOH, THF, -78°C		67%
5) 4 eq. SmI_2, HMPA, ^{t}BuOH, THF, -78°C	Decomposed	
6) 4 eq. SmI_2, ^{t}BuOH, THF, -78°C	Decomposed	
7) 4 eq. SmI_2, MeOH, THF, -78°C, addition of substrate over 6 hours.		60%
8) 4 eq. SmI_2, MeOH, THF, -78°C, addition of substrate over 1 minute.		62%
9) 4 eq. SmI_2, THF, -78°C	Decomposed	
Add SmI_2 to substrate, co-solvent, THF, ROH.		
10) 4 eq. SmI_2, MeOH, THF, -78°C	24%	46%
11) 4 eq. SmI_2, HMPA, ^{t}BuOH, THF, -78°C	Decomposed	
12) 4 eq. SmI_2, THF, -78°C	Decomposed	
13) 4 eq. SmI_2, 4 eq. MeOH, THF, 0°C	26%	42%

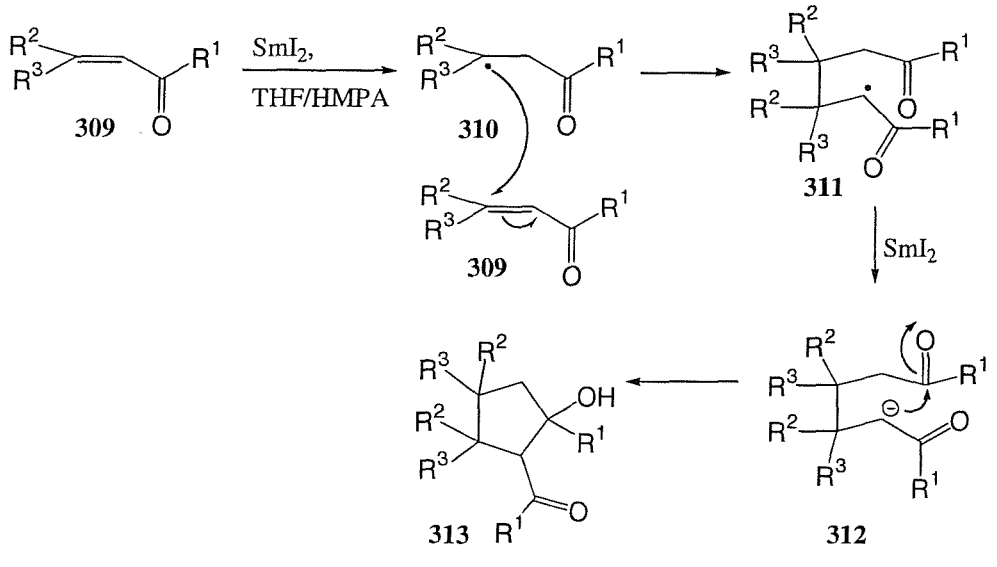
Table 13 Cyclisation of α,β-unsaturated ketone 292

When HMPA was used as co-solvent no tetracycle was produced and a mixture of inseparable and unidentifiable products was obtained **(Entries 3, 5 and 11)**. The same result was observed using ^{t}BuOH as a proton source without HMPA, and also in the absence of any co-solvents **(Entry 6 and 9)**. When MeOH was used as co-solvent tetracycle **303** was obtained. On normal addition with 2.5 equivalents of samarium diiodide the reaction proceeded better at lower temperatures **(Entry 1)**. Increasing to 4 equivalents of samarium diiodide gave slightly higher yields **(Entry 4)**.

Slow addition of the substrate to samarium diiodide should have reduced the concentration of substrate in the reaction mixture potentially allowing the radical more time to cyclise. However, the rate of addition of the substrate to the samarium diiodide had minimal effect on the overall yield of the tetracycle **303 (Entries 7 and 8)**. Slow addition of samarium diiodide to the precursor (reverse addition) would lower the concentration of samarium diiodide in the reaction mixture, which might also allow the radical to cyclise before it could dimerise with another radical. However, upon reverse addition the reaction appeared to be slower and never went to completion but again led to tetracycle **303** as the only product **(Entries 10 and 13)**. Increasing the concentration of MeOH in the reverse addition reaction also seemed to have no impact on the overall yield **(Entry 13)**.

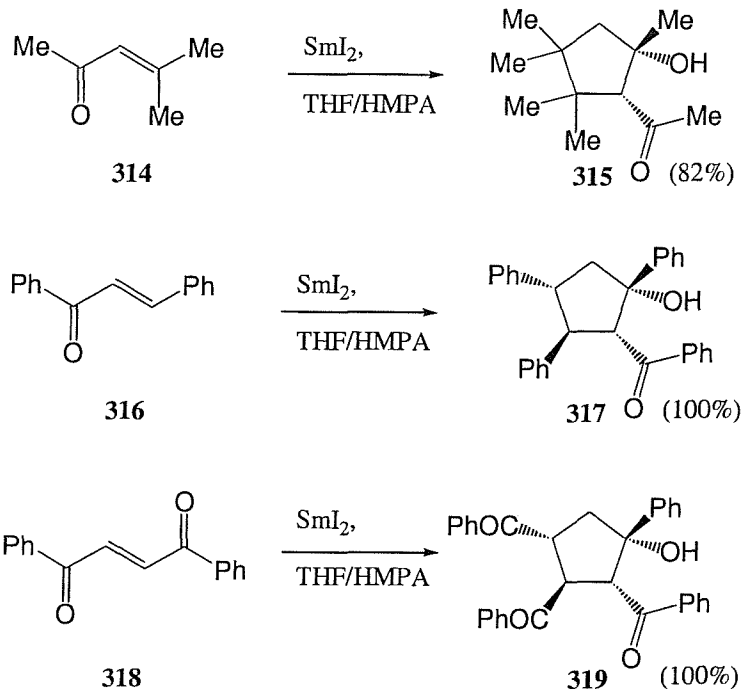
Thus under all conditions tried tetracycle **303** was the only product ever obtained, but the conditions could be optimised to obtain a 67% yield of tetracycle **303 (Entry 4)**.

Further investigation of the literature showed that Cabrera[103] had reported a related cyclodimerisation of α,β-unsaturated ketones. Thus treatment of ketone **309** with samarium diiodide, HMPA in THF led to cyclopentanol **313**. Cabrera proposed that ketone **309** was reduced using SmI_2-HMPA in THF to produce radical **310**, which adds to another α,β-unsaturated ketone to yield diketone radical **311**. The radical was reduced by an additional equivalent of samarium diiodide to give anion **312**, which could undergo an intramolecular aldol condensation to yield β-hydroxy ketone **313 (Scheme 99)**.[103]



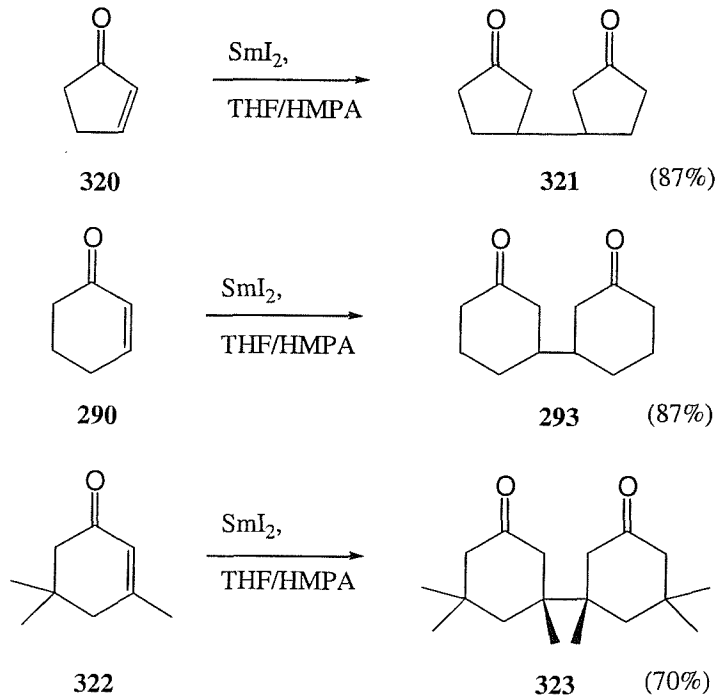
Scheme 99

Cabrera reported several examples of acyclic α,β-unsaturated ketones which undergo this cyclodimerisation reaction **(Scheme 100)**.[103,105,106]



Scheme 100

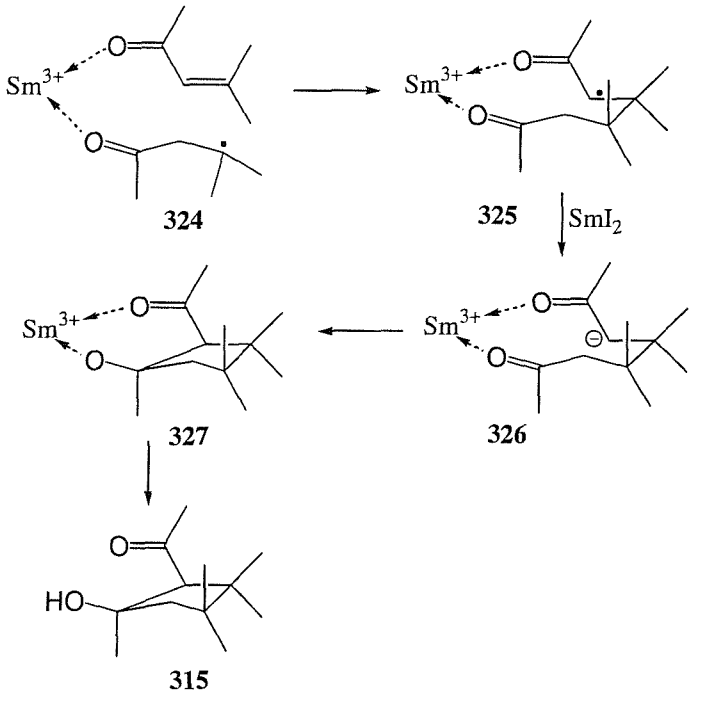
Cabrera's work also considered simple cyclic α,β-unsaturated ketones, however for these substrates only simple dimerisation was observed **(Scheme 101)**.[103]



Scheme 101

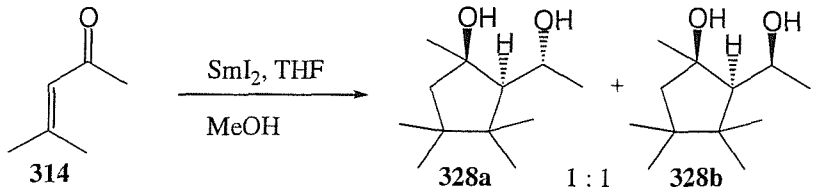
Interestingly dimerisation of **322** was reported to give dimer **323** with the two methyls *cis*, which is in contrast to the dimerisation of **292** which gave the methyls *trans* **299**.

The stereochemistry of cyclic product **315** was proven by nOe studies to show that only one diastereoisomer was formed. Cabrera proposed that the stereochemistry observed arose from chelation control between the samarium ion and the two ketone groups **(Scheme 102)**.[103]



Scheme 102

In Cabrera's study the cyclodimerisation required the use of samarium diiodide in THF with HMPA, but the absence of any proton source. If an alcohol was present only reduction of the double bond was observed.[103] However, with the cyclisation of **292**, methanol is present but a cyclodimerisation reaction does occur. The cyclisation of ketone **314** was therefore attempted using our optimised conditions, which gave diol **328 (Scheme 103)**.



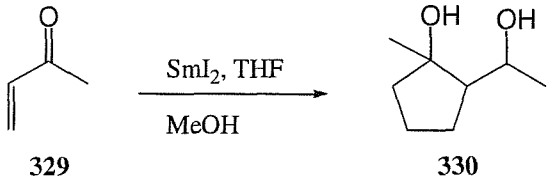
Temp.	Yield
-78°C	88%
0°C	81%

Scheme 103

The reactions gave a 1:1 mixture of diastereoisomers of diol **328** in very good overall yields. Changing the temperature from -78°C to 0°C made no real difference to the yields.

The stereochemistry of diastereoisomers **328a** and **328b** has not been determined unambiguously, however the reaction mechanism may be the same as in Cabrera's work **(Scheme 102)**, which should give ketone **315**. A further equivalent of samarium diiodide present in the reaction would reduce ketone **315** to a ketyl radical, which could be reduced further to the anion and quenched with a proton source. If this process is not stereoselective then two diastereoisomers would be observed. However, it cannot be ruled out that the reaction mechanism does not follow Cabrera's work and two diastereoisomers of the intermediate ketone are produced, which can then be reduced stereoselectively (as demonstrated in work by Keck[72]) to obtain only two diastereoisomeric products.

The reaction was repeated using methyl vinyl ketone **329** with the intention of obtaining diol **330**, however no identifiable products could be obtained **(Scheme 104)**.

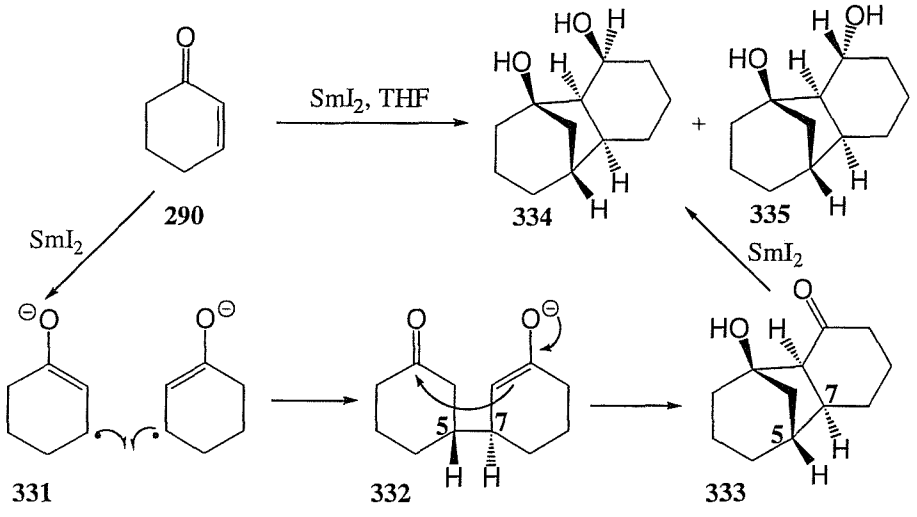


Scheme 104

3. CYCLISATIONS OF SIMPLE CYCLIC α,β-UNSATURATED KETONES

Cyclisations were also attempted with cyclic α,β-unsaturated ketones cyclopentenone **320** and cyclohexenone **290** which Cabrera reported did not cyclodimerise using his conditions **(Scheme 101)**.

Initially, work began by cyclising cyclohexenone **290**.**(Table 14)**.



Reaction conditions	334	335	Overall yield
4 eq. SmI_2, THF, MeOH, -78°C	47%	21%	68%
4 eq. SmI_2, THF, MeOH, 0°C	54%	25%	79%
3 eq. SmI_2, THF, MeOH, -78°C	45%	22%	67%

Table 14 Cyclisations of cyclohexanone 290

The results observed differ from the literature precedent.[103] Two diastereoisomers **334** and **335** were produced from the cyclisation of cyclohexanone **290**. The stereochemistry of tricycle **334** was proven using X-ray crystallography **(Figure 22)**, which is in agreement with the stereochemistry of tetracycle **303**. The tricycle is *cis* fused and the protons at C7 and C5 are *trans* as before with **303**, (and in contrast to the reported dimerisation of **322**).

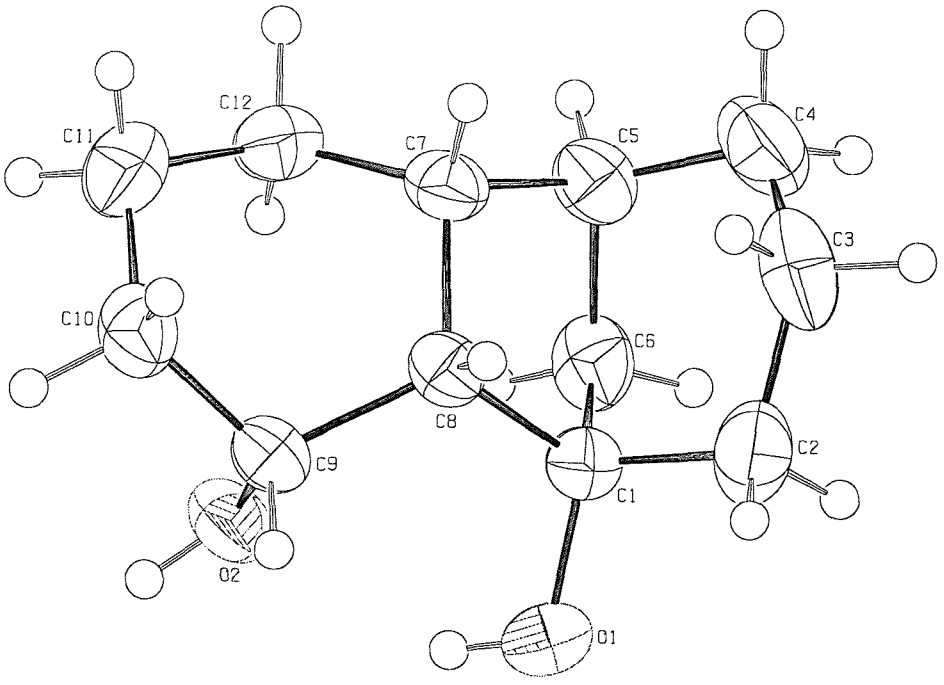


Figure 22 Tricycle 334

It is assumed that the stereochemistry of the two diastereoisomeric products **334** and **335** only differs at the secondary alcohol, which is consistent with the coupling constants at that centre **(Figure 23)**. The ^{1}H nmr spectrum for **334** shows H1 as a broad singlet, which implies very small coupling constants that are consistent with equatorial couplings as in **336**. For diastereoisomer **335**, however H4 is a doublet triplet ($J = 5$, 12 Hz), implying two axial couplings, consistent with the alcohol being in the equatorial position **337**.

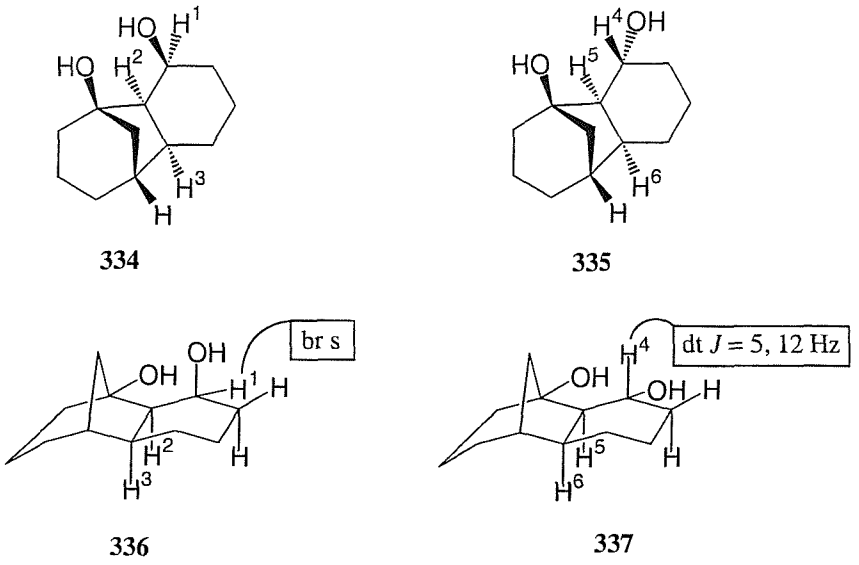
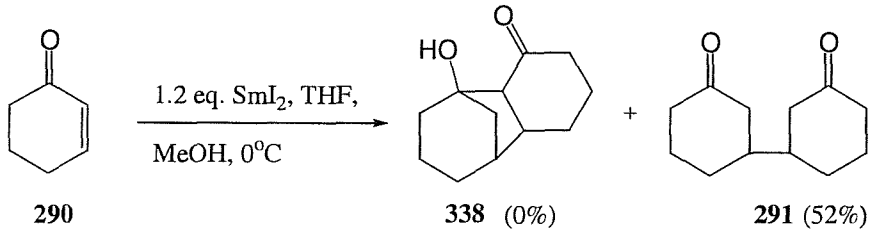


Figure 23

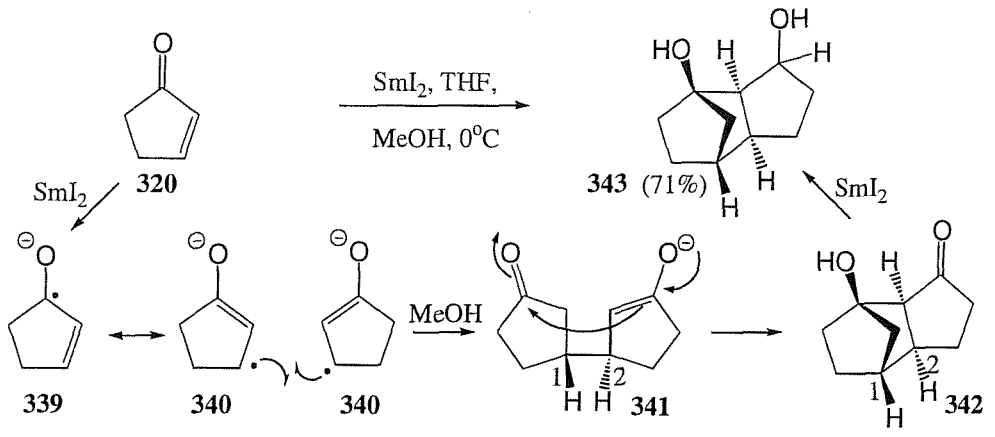
An attempt was made to isolate intermediate ketone **338** using fewer equivalents of samarium diiodide to prevent the final reduction **(Scheme 105)**.



Scheme 105

However, when treated with only 1.2 eq. of samarium diiodide in MeOH and THF at -78°C, the dimer **291** was formed exclusively.

When cyclopentenone **320** was treated with 4 equivalents of samarium diiodide in THF with MeOH at 0°C, tricycle **343** was formed in a 71% yield and as a single diastereoisomer **(Scheme 106)**.



Scheme 106

The reaction was repeated at -78°C and the same tricycle was produced with a reduced yield of 45%.

It was not possible to assign the stereochemistry of **343** unambiguously. The initial dimerisation gives intermediate **341** presumably with the two protons at C1 and C2 *trans* given that this was clearly found for cyclisation of **290** and **292 (Scheme 106)**. However, unlike the cyclisation of cyclohexenone **290**, cyclisation of cyclopentenone **320** gave the tricycle **343** as a single diastereoisomer, implying that the reduction of the ketone intermediate **342** must be stereoselective. Coupling constants for H1 do not help in the assignment of this centre and thus far we have been unable to determine the stereochemistry **(Figure 24)**.

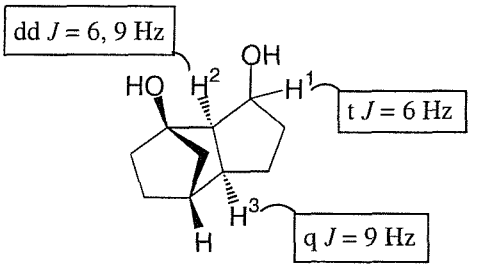
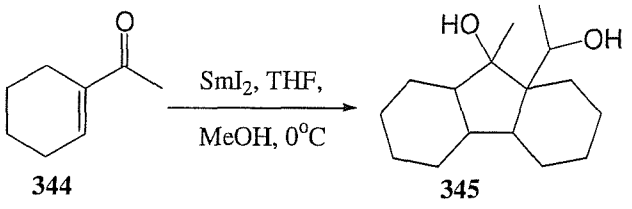


Figure 24

The cyclisation of α,β-unsaturated ketone **344** was also attempted but no product **345** was observed **(Scheme 107)**.



344 345

Scheme 107

4. CONCLUSIONS

The samarium diiodide mediated radical cascade cyclisations of simple α,β-unsaturated ketone **292** using MeOH/THF co-solvents provided a surprising but efficient route to tetracycle **303**. Whilst this result was frustrating from the standpoint of synthesising dihydrotournefortiolide **154** by cyclisation of **270**, it does offer an unforeseen route into new chemistry. Commercially available α,β-unsaturated compounds were also cyclised using these optimised conditions and showed some interesting divergence from existing literature that may merit further study. From these model studies we can conclude that it is unlikely the natural product dihydrotournefortiolide **154** could have been synthesised by cyclisation of **270**.

CHAPTER 6

EXPERIMENTAL

GENERAL EXPERIMENTAL

Whenever possible solvents and reagents were purified according to the procedures outlined in Perin and Armarego, *"Purification of Laboratory Chemicals"*, Pergamon Press, 3rd Edition (1989).[107]

All reactions requiring anhydrous conditions were conducted in flame-dried or oven-dried apparatus under a static, inert atmosphere.

Flash column chromatography was performed according to the procedure outlined by Still,[108] using Sorbsil C60, 40-60 mesh silica.

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

Methylenecyclopropane was handled using the experimental methods as described by Binger and Thomas.[8,9]

INSTRUMENTAL

Proton nmr spectra were all obtained at 300 MHz on a Bruker AC 300 spectrometer, and at 400 MHz on a Bruker DPX400 spectrometer. Peak positions are quoted against the δ scale relative to the residual chloroform signal (δ 7.27) or to an internal standard of tetramethylsilane (δ 0.00), using the following abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad singlet (br s).

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

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

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

X-ray diffraction data was obtained from an *Enraf Nonius KappaCCD* diffractometer, the structure determined by direct methods using the program *SHELXS97*[109] and refined using *SHELXL97*.[110]

EXPERIMENTAL FOR CHAPTER 2

1

Methylenecyclopropane 1

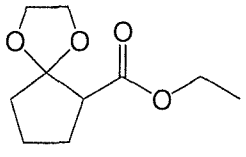
Using a modification of the method of Binger,[67] methallyl chloride **6** (280 mL, 2.84 mol) was added dropwise over 9 h to a rapidly stirred suspension of sodium amide (139 g, 3.56 mol) in dry n-dibutyl ether (400 mL) at 110-130 °C under a slow stream of nitrogen. The reaction mixture was refluxed for a further 12 h using a cold finger condenser at –40 °C. Acetone was removed from the cold finger condenser and replaced with warm water (30 - 40 °C). The products were condensed in cold traps (*ca.* –78 °C). The top layer was ammonia, which was allowed to boil away. The bottom layer (120 mL, 96 g, 1.778 mol, 63%) contained methylenecyclopropane **1** and methylcyclopropene **10** in a ratio of 5.5:1.

The mixture was added to a solution of ^{t}BuOH (1.32 g, 0.018 mol) and DMSO (40 mL), at 0 °C under a flow of nitrogen, and ^{t}BuOK (1.33 g, 0.012 mol) in DMSO (20 mL) was added. The reaction mixture was left for 3 h at –60 °C, allowed to warm to 10 °C over 2 h and then to room temperature overnight. The cold finger was warmed to 45 °C over 4 h. The methylenecyclopropane **1** (120 mL, 96 g, 1.778 mol, 100%) was trapped in vessels at –78 °C;

δ_H (300 MHz, $CDCl_3$): 5.43 (2H, br s, $=CH_2$), 1.09 (4H, br s, 2 x CH_2);

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

All data agrees with that previously reported by Binger.[111]



166

Ethyl 1,4-dioxaspiro[4.4]nonane-6-carboxylate 166

Following the method of Albizati,[68] ethyl cyclopentanone-2-carboxylate (23.2 mL, 0.160 mol), ethylene glycol (20.2 mL, 0.362 mmol) and pTsOH (353.4 mg, 1.860 mmol) were refluxed in toluene (150 mL) overnight, collecting water using Dean-Stark

apparatus. The reaction mixture was concentrated *in vacuo*, Et_2O (300 mL) was added and washed with aq. $NaHCO_3$ (2 x 50 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give ester **166** (27.8 g, 0.139 mol, 87%) as a yellow oil, $R_f = 0.41$ (30% EtOAc-petrol);

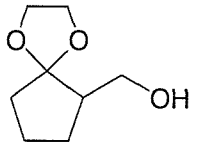
ν_{max} (cm^{-1}): 2975, 2879, 1731, 1372, 1212, 1083, 1037;

δ_H (300 MHz, $CDCl_3$): 4.20-4.05 (2H, m, OCH_2CH_3), 4.05-3.80 (4H, m, $O(CH_2)_2O$), 2.63 (1H, dd, $J = 8$, 5 Hz, CH), 2.20-1.60 (6H, m, $CH(CH_2)_3$), 1.25 (3H, t, $J = 7$ Hz, CH_3);

δ_C (75 MHz, $CDCl_3$): 172.5, 118.5, 65.3 (2), 64.6 (2), 60.5 (2), 52.4 (1), 36.9 (2), 27.0 (2), 22.2 (2), 14.4 (3);

$^m/z$ (CI+): 201 $[M + H]^+$ (100%);

All data agrees with that previously reported by Paulsen.[112]



167

1,4-dioxaspiro[4.4]non-6-ylmethanol 167

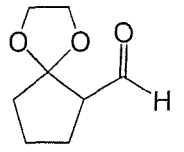
Following the method of Ferris,[69] ethyl 1,4-dioxaspiro[4.4]nonane-6-carboxylate **166** (15.0 g, 0.075 mol) in THF (30 mL) was added dropwise to a suspension of $LiAlH_4$ (8.54 g, 0.225 mol) in THF (80 mL) at 0 °C. The reaction was allowed to warm to room temperature over 1 h, and left to stir overnight. Et_2O (150 mL) was added to the reaction mixture and NaOH (4M) was added until a white precipitate persisted. The reaction mixture was filtered, the residue washed with Et_2O (3 x 50 mL), and the combined organic layers were concentrated *in vacuo*. The crude product was purified using flash column chromatography, eluting with petrol and gradually increasing the polarity to 50% EtOAc-petrol to give alcohol **167** (8.42 g, 0.053 mol, 71%) as a colourless oil, $R_f = 0.60$ (75% EtOAc-petrol);

ν_{max} (cm^{-1}): 3380, 2950, 2873, 1460, 1091;

δ_H (300 MHz, $CDCl_3$): 3.95-3.80 (4H, m, $O(CH_2)_2O$), 3.57-3.54 (2H, m, CH_2OH), 2.80 (1H, s, OH), 2.05 (1H, m, $CHCH_2OH$), 1.85-1.45 (6H, m, $(CH_2)_3$);

δ_C (75 MHz, $CDCl_3$): 119.1, 64.7 (2), 64.2 (2), 62.6 (2), 47.2 (1), 35.8 (2), 25.9 (2), 21.5 (2);

All data agrees with that previously reported by Paulsen.[112]



168

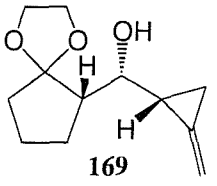
1,4-dioxa-spiro[4.4]nonane-6-carbaldehyde 168

Following the method of Swern,[70] oxalyl chloride (2.65 mL, 0.030 mol) in DCM (100 mL) was cooled to –70 °C and stirred vigorously. DMSO (4.49 mL, 0.063 mol) in DCM (10 mL) was added at < -50 °C and the reaction was stirred for 2 min. 1,4-dioxaspiro[4.4]non-6-ylmethanol **167** (4.00 g, 0.025 mol) in DCM (10 mL) was added over 5 min at < -50 °C and the reaction was stirred for a further 15 min. TEA (17.8 mL, 0.127 mol) was added at < -50 °C and the reaction mixture was warmed to room temperature. Water (100 mL) was added and the reaction mixture was washed with DCM (5 x 50 mL). The combined organic layers were concentrated *in vacuo* to yield aldehyde **168** (3.80 g, 0.024 mol, 97%) as a colourless oil, $R_f = 0.58$ (30% EtOAc-petrol);

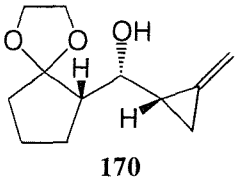
δ_H (300 MHz, $CDCl_3$): 9.59 (1H, d, J = 3 Hz, CHO), 3.97-3.81 (4H, m, $O(CH_2)_2O$), 2.78 (1H, dt, J = 3, 8 Hz, C*H*CHO), 2.03 (1H, m, CH_AH_BCHCHO), 1.85-1.60 (5H, m, CH_AH_BCHCHO and $(CH_2)_2$);

δ_C (75 MHz, $CDCl_3$): 201.5 (1), 118.6, 64.9 (2), 64.7 (2), 58.2 (1), 37.0 (2), 24.0 (2), 22.2 (2);

Aldehyde **168** was difficult to purify and was used directly in the next reaction.



169



170

rac-(S)(6R)-1,4-dioxaspiro[4.4]non-6-yl[(1R)-2-methylenecyclopropyl]methanol 169 and rac-(S)(6R)-1,4-dioxaspiro[4.4]non-6-yl[(1S)-2-methylenecyclopropyl]methanol 170

^{n}BuLi (2.22 M, 16 mL, 0.04 mol) was added to methylenecyclopropane **1** (2.7 mL, 0.04 mol) in THF (20 mL) at –40 °C. The reaction temperature was allowed to rise to 0 °C over 30 min and held at 0 °C for a further 30 min. The reaction was

allowed to warm to room temperature for 15 min before cooling to –78 °C. 1,4-dioxa-spiro[4.4]nonane-6-carbaldehyde **168** (3.7 g, 0.02 mol) in THF (10 mL) at –78 °C was added *via* cannula to the methylenecyclopropane anion. The reaction mixture was allowed to warm to room temperature overnight, quenched with aq. NH_4Cl, extracted with ether (5 x 10 mL) and the organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified using flash column chromatography, eluting with petrol and gradually increasing polarity to 30% Et_2O-petrol to yield the (S, R, R) isomer **169** (901 mg, 4.29 mmol, 18%) and the (S, R, S) isomer **170** (820 mg, 3.90 mmol, 16%), both as yellow oils.

Data for diastereoisomer **169** R_f = 0.44 (50% Et_2O-petrol);

ν_{max} (cm^{-1}): 3445, 2960, 2875, 892;

δ_H (300 MHz, $CDCl_3$): 5.50 (1H, s with fine splitting, =CH_AH$_B$), 5.37 (1H, s, =CH$_A$$H_B$), 3.96-3.80 (4H, m, O($CH_2$)$_2$O), 3.39 (1H, dd, *J* = 9, 2 Hz, C*H*OH), 3.14 (1H, br s, OH), 2.23 (1H, td, *J* = 9, 2 Hz, (CH_2)$_3$C*H*), 2.00-1.55 (7H, m, cyclopropyl C*H*, (CH_2)$_3$CH), 1.18 (1H, tt, *J* = 9, 2 Hz, cyclopropyl CH), 0.90 (1H, m, cyclopropyl CH);

δ_C (75 MHz, $CDCl_3$): 134.3, 118.9, 103.7 (2), 72.3 (1), 64.4 (2), 64.4 (2), 50.3 (1), 36.8 (2), 22.3 (2), 21.7 (2), 19.9 (1), 7.1 (2);

^{m}/z (CI+): 193 $[M - OH]^+$ (100%), 211 $[M + H]^+$ (2%);

HRMS $C_{12}H_{17}O_2$ $[M - OH]^+$ requires 193.1229, found 193.1232.

Data for diastereoisomer **170** R_f = 0.34 (50% Et_2O-petrol);

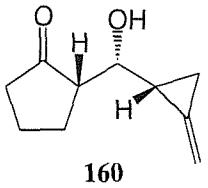
ν_{max} (cm^{-1}): 3447, 2960, 2879, 886;

δ_H (300 MHz, $CDCl_3$): 5.40-5.30 (2H, br s with fine splitting, =CH_2), 3.95-3.80 (4H, m, O(CH_2)$_2$O), 3.31 (1H, dd, *J* = 9, 2 Hz, C*H*OH), 3.22 (1H, br s, OH), 2.15 (1H, td, *J* = 9, 2 Hz, (CH_2)$_3$C*H*), 2.05-1.55 (7H, m, cyclopropyl C*H*, (CH_2)$_3$CH), 1.30 (1H, tt, *J* = 9, 2 Hz, cyclopropyl CH), 1.07 (1H, m, cyclopropyl CH);

δ_C (75 MHz, $CDCl_3$): 133.1, 118.9, 103.9 (2), 72.5 (1), 64.4 (2), 64.4 (2), 51.0 (1), 36.9 (2), 22.3 (2), 21.7 (2), 20.2 (1), 9.1 (2);

^{m}/z (CI+): 193 $[M - OH]^+$ (40%);

HRMS $C_{12}H_{19}O_3$ $[M + H]^+$ requires 211.1334, found 211.1341.



160

rac-(2S)-2-{(R)-1-hydroxy-1-[(1R)-2-methylenecyclopropyl]methyl}cyclopentan-1-one 160

rac-(S)(6R)-1,4-dioxaspiro[4.4]non-6-yl[(1R)-2-methylenecyclopropyl] methanol **169** (840 mg, 4.00 mmol) in acetone/water (100 mL/10 mL) was stirred with pTsOH (914 mg, 4.80 mmol) for 3 days. The reaction mixture was concentrated *in vacuo* and diluted with Et_2O (50 mL). The solution was washed with aq. $NaHCO_3$ (50 mL) and the aqueous layer extracted with Et_2O (3 x 50 mL). Organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified using flash column chromatography, eluting with 10% Et_2O-petrol and gradually increasing the polarity to 35% Et_2O-petrol to yield deprotected ketone **160** (500 mg, 3.01 mmol, 75%) as a white solid, $R_f = 0.51$ (70% Et_2O-petrol);

Melting point: 73-75 °C (Recrystallised from hot EtOAc);

ν_{max} (cm^{-1}): 3436, 3080, 2990, 2960, 2873, 1715;

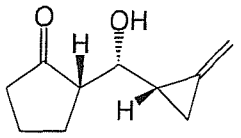
δ_H (300 MHz, $CDCl_3$): 5.52 (1H, d with fine splitting, J = 2 Hz, =CH_AH$_B$), 5.39 (1H, d, J = 2 Hz, =CH$_A$$H_B$), 3.68 (1H, dd, J = 9, 2 Hz, C*H*OH), 2.45-1.90 (6H, m, $(CH_2)_3$), 1.75 (1H, m, CHCO), 1.68 (1H, m, cyclopropyl CH), 1.21 (1H, tt, J = 9, 2 Hz, cyclopropyl CH), 0.91 (1H, m, cyclopropyl CH);

δ_C (75 MHz, $CDCl_3$): 220.8, 133.0, 104.6 (2), 72.6 (1), 54.2 (1), 39.2 (2), 23.6 (2), 20.9 (2), 19.8 (1), 7.6 (2);

^{m}/z (CI+): 149 $[M - OH]^+$ (100%);

Microanalysis: Found C, 72.20; H, 8.48. $C_{10}H_{14}O_2$ requires C, 72.26; H, 8.49%;

Stereochemistry was confirmed by X-ray crystallography.



171

rac-(2S)-2-{(R)-1-hydroxy-1-[(1S)-2-methylenecyclopropyl]methyl}cyclopentan-1-one 171

rac-(S)(6R)-1,4-dioxaspiro[4.4]non-6-yl[(1S)-2-methylenecyclopropyl] methanol **170** (763 mg, 3.63 mmol) in acetone/water (100 mL/10 mL) was stirred with pTsOH (830 mg, 4.36 mmol) for 3 days. The reaction mixture was concentrated *in vacuo* and diluted with Et_2O (50 mL). The solution was washed with aq. $NaHCO_3$ (50 mL) and the aqueous layer extracted with Et_2O (3 x 50 mL). Organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified using column chromatography, eluting with 10% Et_2O-petrol and gradually increasing the polarity to 35% Et_2O-petrol to yield deprotected ketone **171** (330 mg, 1.99 mmol, 55%) as a white solid, R_f = 0.50 (70% Et_2O-petrol);

Melting point: 65-67°C (Recrystallised from hot EtOAc);

ν_{max} (cm^{-1}): 3411, 3180, 3075, 2965, 2883, 1712;

δ_H (300 MHz, $CDCl_3$): 5.40 (1H, d, J = 2 Hz, =CH_AH$_B$), 5.35 (1H, d, J = 2 Hz, =CH$_A$$H_B$), 3.61 (1H, dd, J = 9, 3 Hz, C*H*OH), 2.40-2.05 (6H, m, $(CH_2)_3$), 1.80 (1H, m, CHCO), 1.65 (1H, m, cyclopropyl CH), 1.35 (1H, tt, J = 9, 2 Hz, cyclopropyl CH), 1.10 (1H, m, cyclopropyl CH);

δ_C (75 MHz, $CDCl_3$): 221.0, 132.4, 104.6 (2), 72.7 (1), 54.6 (1), 39.1 (2), 23.6 (2), 20.9 (2), 20.3 (1), 8.5 (2);

^{m}/z (CI+): 149 $[M - OH]^+$ (100%);

Microanalysis: Found C, 72.25; H, 8.57. $C_{10}H_{14}O_2$ requires C, 72.26; H, 8.49%;

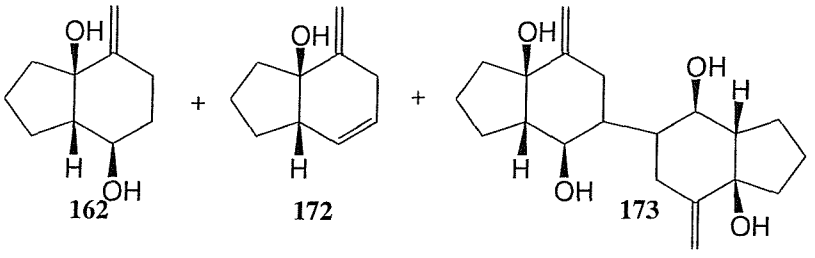
Stereochemistry was confirmed by X-ray crystallography.

General Method for the Preparation of SmI_2 solution:

Using a modification of the method of Molander,[53] samarium metal (452.9 mg, 3.01 mmol) was weighed out and transferred to flame dried glassware under an Ar atmosphere. The metal was flame dried and degassed THF (20 mL) was added followed by freshly purified ICH_2CH_2I (509.4 mg, 1.81 mmol).[55] The mixture was

stirred at room temperature for 2 h and the resulting deep blue solution was used directly to effect the following reductive cyclisation reaction.

Typical procedure:



rac-(3aR, 7S, 7aR)-4-methyleneperhydro-3a,7-indenediol 162, rac-(3aR, 7S)-4-methylene-2,3,3a,4,5,7a-hexahydro-1*H*-3a-indenol 172 and rac-di(3aR, 7S, 7aR)-4-methyleneperhydro-3a,7-indenediol 173.

Following the procedure by Molander,[53] HMPA (1.05 mL, 6.02 mmol) was added to SmI_2 (0.15 M solution in THF, 10 mL, 1.50 mmol) to give a purple solution. The solution was cooled to 0 °C, rac-(2S)-2-{(R)-1-hydroxy-1-[(1R)-2-methylenecyclopropyl]methyl}cyclopentan-1-one **160** (100 mg, 0.60 mmol) and ^{t}BuOH (89 mg, 1.20 mmol) in THF (10 mL) were added over 90 min and the reaction mixture was allowed to warm to room temperature. The crude mixture was then washed with aq. citric acid (1g in 20 mL water) and extracted with 1:1 EtOAc-petrol (5 x 25 mL). The combined organic phase was washed with brine (25 mL), water (25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography eluting with petrol and gradually increasing the polarity to neat EtOAc to give alcohols **162** (10 mg, 0.06 mmol, 10%), **172** (30 mg, 0.20 mmol, 30%) and **173** (15 mg, 0.05 mmol, 15%).

Data for **162** obtained as colourless crystals, R_f= 0.30 (60% EtOAc-petrol);
Melting point = 119-121°C (Recrystallised from hot EtOAc);
ν_{max} (cm^{-1}): 3306, 2923, 2850, 1454, 1034;
δ_H (400 MHz, $CDCl_3$): 5.11 (1H, s with fine splitting, =CH_AH$_B$), 4.90 (1H, s with fine splitting, =CH$_A$$H_B$), 3.43 (1H, ddd, J = 10, 8, 4 Hz, C*H*OH), 2.49 (1H, dt, J = 15, 5 Hz, =CCH_AH$_B$) 2.20-1.40 (10H, m, =CCH$_A$$H_B$, C$H_2$CHOH, (C$H_2$)$_3$, C*H*CHOH);
δ_C (100 MHz, $CDCl_3$): 150.5, 108.7 (2), 83.3, 72.0 (1), 58.1 (1), 37.3 (2), 35.1 (2), 29.9 (2), 26.7 (2), 21.3 (2);

$^{m}/z$ (CI+): 151 $[M - OH]^+$ (30%), 133 $[M - OH - H_2O]^+$ (100%);

HRMS $C_{10}H_{15}O$ $[M - OH]^+$ requires 151.1123, found 151.1129;

Stereochemistry was confirmed by X-ray crystallography.

Data for **172** obtained as a yellowish oil, $R_f = 0.81$ (60% EtOAc-petrol);

ν_{max} (cm^{-1}): 3397, 3075, 2946, 2870, 1714, 1017;

δ_H (400 MHz, $CDCl_3$): 5.56 (1H, m, =CH), 5.39 (1H, dq, J = 10, 2 Hz, =CH), 5.10 (1H, s, $=CH_AH_B$), 4.91 (1H, s with fine splitting, $=CH_AH_B$), 2.95 (1H, m, $=CCH_AH_B$), 2.46 (1H, br s, $=CCH_AH_B$), 2.30-1.40 (7H, m, CH, $(CH_2)_3$);

δ_C (100 MHz, $CDCl_3$): 147.5, 130.2 (1), 123.3 (1), 105.5 (2), 81.8, 50.3 (1), 36.2 (2), 32.2 (2), 29.5 (2), 21.2 (2)

LRMS could not be obtained for this compound.

Data for **173** obtained as yellow crystals within a yellow oil, $R_f = 0.11$ (60% EtOAc-petrol);

ν_{max} (cm^{-1}): 3339, 2948, 2880, 1461, 1038;

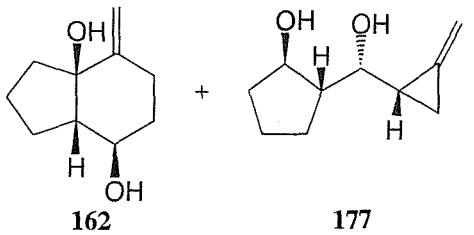
δ_H (400 MHz, $CDCl_3$): 5.15 (1H, s with fine splitting, $=CH_AH_B$), 5.00 (2H, s, 2 x $=CH_AH_B$), 4.87 (1H, s, $=CH_AH_B$), 3.90 (1H, br s, OH), 3.12 (1H, t, J = 10 Hz, CHOH), 2.76 (1H, t, J = 13 Hz, CHOH) 2.42-1.20 (20H, m, 2 x $=CCH_2$, 2 x $(CH_2)_3$, 2 x CHCHOH, 2 x $CHCH_2C=$);

δ_C (100 MHz, $CDCl_3$): 149.6, 146.2, 109.1 (2), 107.1 (2), 82.0, 79.7, 72.1 (1), 69.8 (1), 57.9 (1), 50.8 (1), 47.1 (1), 43.3 (1), 37.2 (2), 36.0 (2), 34.2 (2), 26.4 (2), 26.0 (2), 23.3 (2), 20.2 (2), 18.8 (2);

$^{m}/z$ (APCI+): 333 $[M + H]^+$ (100%);

HRMS could not be obtained for this compound;

Stereochemistry was confirmed by X-ray crystallography.



162 **177**

rac-(3aR, 7S, 7aR)-4-methyleneperhydro-3a,7-indenediol 162 and rac-(1R, 2S)-2{(R)-1-hydroxy-1-[(1S)-2-methylenecyclopropyl]methyl}cyclopentan-1-ol 177

Following the method of Procter,[71] to SmI_2 (0.15 M solution in THF, 10 mL, 1.50 mmol) and MeOH (3 mL) at 0°C under Ar, was added rac-(2S)-2{(R)-1-hydroxy-1-[(1S)-2-methylenecyclopropyl]methyl}cyclopentan-1-one **171** (100 mg, 0.60 mmol) in THF (5 mL) over 45 min. The reaction mixture was stirred for 2 h at 0 °C before the addition of brine (3 mL) and citric acid (128 mg, 0.61 mmol). The aqueous layer was then extracted with EtOAc (5 x 10 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography, eluting with petrol and gradually increasing the polarity to neat EtOAc to give diols **162** (35 mg, 0.21 mmol, 35%) and **177** (40mg, 0.24 mmol, 40%);

Data for compound **177** was obtained as a viscous oil, $R_f = 0.53$ (55% EtOAc-petrol);

ν_{max} (cm^{-1}): 3311, 2954, 2874, 1431, 1013;

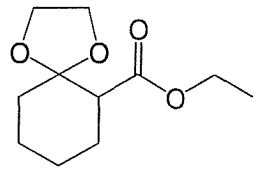
δ_H (300 MHz, $CDCl_3$): 5.43-5.38 (2H, m, $=CH_2$), 4.31 (1H, m, CH_2CHOH), 3.48 (1H, dd, $J = 9$, 2 Hz, $CHOH$), 3.25 (2H, br s, 2 x OH), 2.00-1.50 (8H, m, $(CH_2)_3$, $CHCHOH$, cyclopropyl CH), 1.32 (1H, tt, $J = 9$, 2 Hz, cyclopropyl CH), 1.10 (1H, m, cyclopropyl CH);

δ_C (75 MHz, $CDCl_3$): 133.1, 104.1 (2), 76.6 (1), 75.1 (1), 49.5 (1), 35.6 (2), 22.2 (2), 22.1 (2), 21.5 (1), 8.8 (2);

$^m/z$ (CI+): 151 $[M - OH]^+$ (70%), 133 $[M - OH - H_2O]^+$ (100%);

HRMS $C_{10}H_{15}O$ $[M - OH]^+$ requires 151.1123, found 151.1129.

All data for compound **162** agrees with that reported above.



180

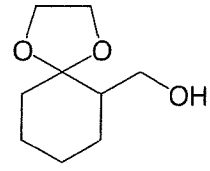
Ethyl 1,4-dioxaspiro[4.5]decane-6-carboxylate 180

Following the method of Albizati,[68] ethyl 2-cyclohexanone carboxylate (23.5 mL, 0.147 mol), ethylene glycol (18.5 mL, 0.332 mmol) and pTsOH (324.4 mg, 1.705 mmol) were refluxed in toluene (150 mL) overnight, collecting water using Dean-Stark apparatus. The reaction mixture was concentrated *in vacuo*, diluted with Et_2O (200 mL) and washed with aq. $NaHCO_3$ (2 x 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give ketal **180** (30.4 g, 0.142 mol, 97%) as slightly yellow oil, $R_f = 0.4$ (30% EtOAc-petrol);

δH (300 MHz, $CDCl_3$): 4.15 (2H, q, J = 7 Hz, OCH_2CH_3), 4.00-3.85 (4H, m, $O(CH_2)_2O$), 2.63 (1H, dd, J = 8, 5 Hz, CH), 2.10-1.25 (8H, m, $(CH_2)_4$), 1.28 (3H, t, J = 7 Hz, CH_3);

δC (75 MHz, $CDCl_3$): 172.5, 108.8, 65.0 (2), 64.7 (2), 60.4 (2), 50.1 (1), 34.8 (2), 27.4 (2), 23.5 (2), 23.1 (2), 14.4 (3);

All data agrees with that previously reported by Albizati.[68]



181

1,4-Dioxaspiro[4.5]dec-6-yl methanol 181

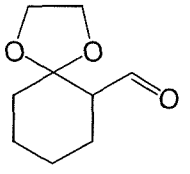
Following the method of Ferris,[69] ethyl 1,4-dioxaspiro[4.5]decane-6-carboxylate **180** (15.0 g, 0.070 mol) in THF (10 mL) was added dropwise to a suspension of $LiAlH_4$ (7.50 g, 0.197 mol) in THF (100 mL) at 0 °C and allowed to warm to room temperature over 30 min, the reaction mixture was left to stir overnight. Et_2O (140 mL) was added to the reaction mixture and NaOH (4M, *ca.* 15mL) was added until white precipitate was formed. The reaction mixture was filtered and the residue washed with Et_2O (3 x 50 mL) and the combined organic layers were concentrated *in vacuo* to give alcohol **181** (11.2 g, 0.065 mol, 93%) as a colourless oil, $R_f = 0.38$ (60% EtOAc-petrol);

ν_{max} (cm^{-1}): 3424, 2937, 1447, 1089;

δ_H (300 MHz, $CDCl_3$): 3.95 (4H, br s, $O(CH_2)O$), 3.68 (1H, m, CH_AH_BOH), 3.45 (1H, m, CH_AH_BOH), 2.85 (1H, s with fine splitting, OH), 1.87-1.15 (9H, m, $(CH_2)_4CH$);

δ_C (75 MHz, $CDCl_3$): 111.5, 64.4 (2), 64.1 (2), 63.3 (2), 45.7 (1), 34.1 (2), 27.0 (2), 24.3 (2), 23.5 (2);

All data agrees with that previously reported by Albizati.[68]



182

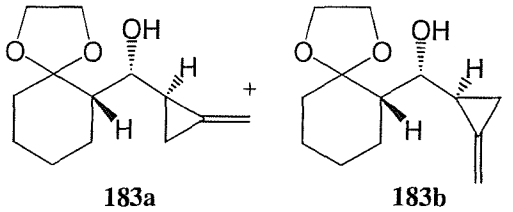
1,4-Dioxaspiro[4.5]decane-6-carbaldehyde 182

Following the method of Swern,[70] oxalyl chloride (4.43 mL, 0.035 mol) in DCM (100 mL) was cooled to –70 °C and stirred vigorously. DMSO (5.14 mL, 0.073 mol) in DCM (10 mL) was added at < –50 °C and the reaction mixture was stirred for 2 min. 1,4-Dioxaspiro[4.5]dec-6-yl methanol **181** (5 g, 0.029 mol) in DCM (10 mL) was added over 5 min at < –50 °C and the reaction was stirred for a further 15 min. TEA (20.4 mL, 0.145 mol) was added at < –50 °C and the reaction mixture was allowed to reach room temperature. Water (150 mL) was added to the reaction mixture, washed with DCM (4 x 50 mL) and combined organic layers were concentrated *in vacuo*. The crude product was purified using flash column chromatography, eluting with petrol and gradually increasing the polarity to 30% EtOAc-petrol to give aldehyde **182** (2.3 g, 0.014 mol, 47%) as a colourless oil, R_f = 0.53 (30% EtOAc-petrol);

δ_H (300 MHz, $CDCl_3$): 9.76 (1H, d, J = 1 Hz, CHO), 4.00-3.83 (4H, m, $O(CH_2)_2O$), 2.45 (1H, ddd, J = 10, 5, 1 Hz, C*H*CHO), 1.90-1.15 (8H, m, $(CH_2)_4$);

δ_C (75 MHz, $CDCl_3$): 203.6 (1), 109.3, 64.9 (2), 64.7 (2), 56.1 (1), 34.7 (2), 24.4 (2), 23.5 (2), 23.4 (2);

All data agrees with that previously reported by Huet.[113]



183a **183b**

rac-(S)(6R)-1,4-Dioxaspiro[4.5]dec-6-yl[(1R)-2-methylidenecyclopropyl]methanol 183a and rac-(S)(6R)-1,4-Dioxaspiro[4.5]dec-6-yl[(1S)-2-methylidenecyclopropyl] methanol 183b

^{n}BuLi (2.53 M, 7.67 mL, 0.019 mol) was added to a solution of methylenecyclopropane (1.49 mL, 0.022 mol) in THF (20 mL) at –40 °C. The temperature was allowed to warm to 0 °C over 30 min and held at 0 °C for a further 30 min. The reaction was allowed to reach room temperature for 15 min before cooling to -78 °C. 1,4-Dioxaspiro[4.5]decane-6-carbaldehyde **182** (2.2 g, 0.013 mol) in THF (10 mL) at –78 °C was added *via* cannula to the methylenecyclopropane anion. The reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched with aq. NH_4Cl, extracted with Et_2O (5 x 50 mL) and the organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified using flash column chromatography, eluting with petrol and slowly increasing polarity to 10% Et_2O-petrol to yield alcohol **183a** (1.50 g, 6.696 mmol, 54%) as a white solid and as a single diastereoisomer and alcohol **183b** (750 mg, 3.348 mmol, 27%) as a colourless oil;

Data for diastereoisomer **183a** R_f = 0.63 (30% EtOAc-petrol);

Melting point: 43-45°C (Recrystallised from hot EtOAc);

ν_{max} (cm^{-1}): 3503, 2988, 2935, 2889, 2857, 1160, 921;

δ_H (300 MHz, $CDCl_3$): 5.58 (1H, br s, =CH_AH$_B$), 5.44 (1H, s, =CH$_A$$H_B$), 4.12-3.88 (4H, m, O($CH_2$)$_2$O), 3.57 (1H, d, J = 9Hz, C*H*OH), 3.25 (1H, br s, OH), 2.01-1.18 (11H, m, (CH_2)$_4$C*H*, 2 x cyclopropyl C*H*), 0.90 (1H, m, cyclopropyl CH);

δ_C (75 MHz, $CDCl_3$): 134.8, 111.8, 103.7 (2), 72.9 (1), 64.7 (2), 64.0 (2), 47.6 (1), 34.7 (2), 25.2 (2), 23.6 (2), 22.6 (2), 18.8 (1), 7.3 (2);

^{m}/z (CI+): 225 $[M + H]^+$ (5%), 207 $[M - OH]^+$ (100%);

Microanalysis: Found C, 69.37; H, 9.12. $C_{13}H_{20}O_3$ requires C, 69.61; H, 8.99%;

Stereochemistry was confirmed by X-ray crystallography.

Data for diastereoisomer **183b** R_f = 0.48 (30% EtOAc-petrol);

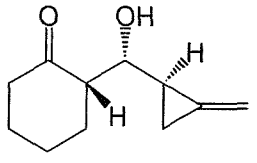
ν_{max} (cm^{-1}): 3515, 3065, 2935, 2889, 1163, 921;

δ_H (300 MHz, $CDCl_3$): 5.40 (2H, s with fine splittings, $=CH_2$), 4.05-3.84 (4H, m, $O(CH_2)_2O$), 3.53 (1H, d, J = 9Hz, C*H*OH), 3.27 (1H, br s, OH), 2.00-1.18 (11H, m, $(CH_2)_4CH$, 2 x cyclopropyl C*H*), 1.08 (1H, m, cyclopropyl CH);

δ_C (75 MHz, $CDCl_3$): 133.0, 111.8, 104.0 (2), 72.5 (1), 64.7 (2), 63.9 (2), 48.4 (1), 34.6 (2), 25.2 (2), 23.7 (2), 22.7 (2), 19.3 (1), 9.2 (2);

$^m/z$ (CI+): 207 $[M - OH]^+$ (100%);

HRMS: $C_{13}H_{19}O_2$ $[M - OH]^+$ requires 207.1385, found 207.1394.



184

rac-(2S)-2-{(R)-1-hydroxy-1-[(1R)-2-methylenecyclopropyl]methyl}-1-cyclohexanone 184

rac-(S)(6R)-1,4-Dioxaspiro[4.5]dec-6-yl[(1R)-2-methylidenecyclopropyl] methanol **183a** (850 mg, 3.80 mmol) in acetone/water (150 mL/15 mL) was stirred with pTsOH (866 mg, 4.55 mmol) overnight. The reaction mixture was concentrated *in vacuo*. Et_2O (50 mL) was added and washed with aq. $NaHCO_3$ (50 mL). The aqueous layer was washed with Et_2O (3 x 50 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified using flash column chromatography eluting with petrol and gradually increasing the polarity to 30% EtOAc-petrol to yield ketone **184** (501.8 mg, 2.79 mmol, 73%) as a viscous oil.

R_f = 0.68 (30% EtOAc-petrol);

ν_{max} (cm^{-1}): 3448, 2990, 2945, 2875, 1696;

δ_H (300 MHz, $CDCl_3$): 5.43 (1H, d, J = 1 Hz, $=CH_AH_B$), 5.30 (1H, d, J = 1 Hz, $=CH_AH_B$), 3.50 (1H, dd, J = 8, 3 Hz, C*H*OH), 2.45-1.48 (10H, m, $(CH_2)_4CH$, cyclopropyl C*H*), 1.15 (1H, tt, J = 9, 2 Hz, cyclopropyl CH), 0.80 (1H, m, cyclopropyl CH);

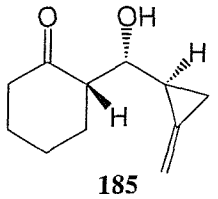
δ_C (75MHz, $CDCl_3$): 214.3, 133.4, 104.3 (2), 72.4 (1), 55.5 (1), 42.7(2), 27.7(2), 27.5(2), 25.0 (2), 18.1 (1), 7.5 (2);

$^m/z$ (CI+): 163 $[M - OH]^+$ (100%);

HRMS: $C_{11}H_{16}O_2$ $[M]^+$ requires 180.1150, found 180.1156;

$C_{11}H_{15}O$ [M - OH]$^+$ requires 163.1123, found 163.1128;

Stereochemistry was confirmed by X-ray crystallography.



185

rac-(2S)-2-{(R)-1-hydroxy-1-[(1S)-2-methylenecyclopropyl]methyl}-1-cyclohexanone 185

rac-(S)(6R)-1,4-Dioxaspiro[4.5]dec-6-yl[(1S)-2-methylidenecyclopropyl] methanol **183b** (390 mg, 1.74 mmol) in acetone/water (75 mL/7.5 mL) was stirred with pTsOH (397 mg, 2.09 mmol) overnight. The reaction mixture was concentrated *in vacuo*. Et_2O (50 mL) was added and washed with aq. $NaHCO_3$ (50 mL). The aqueous layer was washed with Et_2O (3 x 30 mL). Organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified using flash column chromatography eluting with petrol, and gradually increasing the polarity to 30% EtOAc-petrol to yield ketone **185** (200.7 mg, 1.12 mmol, 64%) as a colourless oil. R_f = 0.70 (50% EtOAc-petrol);

ν_{max} (cm^{-1}): 3441, 3071, 2933, 2864, 1701;

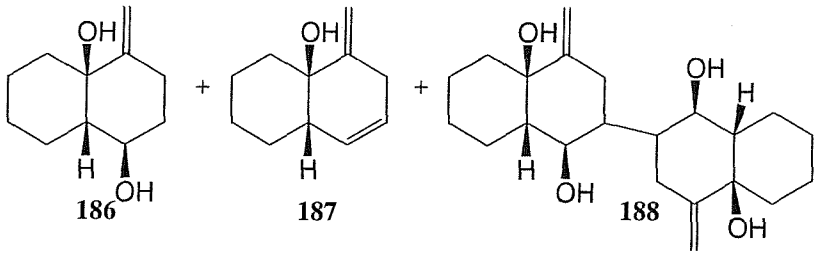
δ_H (400 MHz, $CDCl_3$): 5.43 (1H, s with fine splitting, =C*H*$_A$H$_B$), 5.37 (1H, s with fine splitting, =CH$_A$*H*$_B$), 3.50 (1H, dd, *J* = 9, 3 Hz, C*H*OH), 2.90 (1H, d, *J* = 3 Hz, OH), 2.60-1.62 (10H, m, (C*H*$_2$)$_4$C*H*, cyclopropyl C*H*), 1.39 (1H, tt, *J* = 9, 2 Hz, cyclopropyl CH), 1.12 (1H, m, cyclopropyl CH);

δ_C (100 MHz, $CDCl_3$): 214.7, 133.3, 104.6 (2), 73.2 (1), 56.0 (1), 42.9 (2), 28.0 (2), 27.7 (2), 25.2 (2), 19.0 (1), 9.2 (2);

^{m}/z (CI+): 163 [M - OH]$^+$ (100%);

HRMS: $C_{11}H_{16}O_2$ [M]$^+$ requires 180.1150, found 180.1157;

$C_{11}H_{15}O$ [M - OH]$^+$ requires 163.1123, found 163.1124.



rac-(1R, 4aS, 8aR)-4-methyleneperhydro-1,4a-napthalenediol 186, rac-(4aS, 8aR)-5-methylene-1,2,3,4,4a,5,6,8a-octahydro-4a-napthalenol 187 and dimer 188

Following the procedure by Molander,[53] HMPA (0.77 mL, 6.02 mmol) was added to the SmI_2 (0.11 M solution in THF, 10 mL, 1.10 mmol) to give a purple solution. The solution was cooled to 0 °C, rac-(2S)-2-{(R)-1-hydroxy-1-[(1R)-2-methylenecyclopropyl]methyl}-1-cyclohexanone **184** (80 mg, 0.44 mmol), ^{t}BuOH (66 mg, 0.88 mmol) in THF (10 mL) was added over 90 min and the reaction mixture was allowed to warm to room temperature. The crude mixture was washed with aq. citric acid (1g in 20 mL water) and extracted with 1:1 EtOAc-petrol (5 x 25 mL). The combined organic phase was washed with brine (25 mL), water (25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography eluting with petrol, and gradually increasing the polarity to neat EtOAc to give alcohols **187** (7 mg, 0.04 mmol, 9%), **186** (10 mg, 0.62 mmol, 14%) and **188** (32 mg, 0.09 mmol, 20%);

Data for **187** obtained as a single crystal in a viscous colourless oil, $R_f = 0.85$ (55% EtOAc-petrol);

ν_{max} (cm^{-1}): 3432, 2930, 1687, 1014;

δ_H (300 MHz, $CDCl_3$): 5.64 (1H, dq, J = 10, 3 Hz, =CH), 5.41 (1H, dq, J = 10, 2 Hz, =CH), 5.09 (1H, s with fine splitting, $=CH_AH_B$), 4.85 (1H, s with fine splitting, $=CH_AH_B$), 2.96 (2H, br s, $=CCH_2$), 2.28 (1H, br s, OH), 2.00-1.25 (9H, m, CH, $(CH_2)_4$);

δ_C (75 MHz, $CDCl_3$): 147.6, 131.0 (1), 124.3 (1), 107.3 (2), 75.2, 58.1 (1), 36.3 (2), 34.2 (2), 28.5 (2), 24.4 (2), 23.6 (2);

$^m/z$ (CI+): 147 $[M - OH]^+$ (100%);

HRMS could not be obtained on this compound.

Stereochemistry was confirmed by X-ray crystallography.

Data for **186** obtained as a yellow oil, R_f = 0.41 (55% EtOAc-petrol);

ν_{max} (cm^{-1}): 3349, 2929, 2858, 1647, 1446, 1060, 989, 940, 901;

δ_H (400 MHz, $CDCl_3$ at 323 K): 4.92 (1H, s with fine splittings, =CH_AH$_B$), 4.87 (1H, s with fine splittings, =CH$_A$$H_B$), 3.76 (1H, q, J = 5 Hz, C*H*OH), 3.03 (1H, br s, OH), 2.62 (1H, ddd, J = 14, 11, 5 Hz, =CCH_AH$_B$), 2,46 (1H, br s, OH), 2.06 (1H, dt, J = 14, 5 Hz, =CCH$_A$$H_B$), 1.99 (1H, m, C$H_AH_B$), 1.78 (1H, dddd, J = 14, 11, 5, 4 Hz, CH_AH$_B$CHOH), 1.73-1.20 (9H, m, CH$_A$$H_B$CHOH, C*H*OH, CH$_A$$H_B$, (C$H_2$)$_3$);

δ_C (100 MHz, $CDCl_3$ at 323 K): 149.7, 109.4 (2), 75.0, 71.7 (1), 50.4 (1), 36.4 (2), 32.1 (2), 28.0 (2), 26.0 (2), 24.4 (2), 23.4 (2);

^{m}/z (CI+): 182 $[M]^+$ (20%), 165 $[M - OH]^+$ (45%), 147 $[M - OH - H_2O]^+$ (100%);

HRMS: $C_{11}H_{18}O_2$ $[M]^+$ requires 182.1307, found 182.1311.

Data for **188** obtained as colourless oil, R_f = 0.12 (55% EtOAc-petrol)

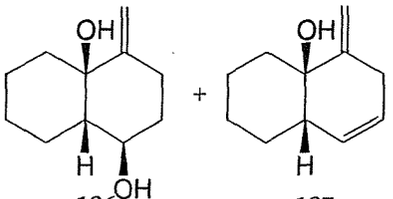
ν_{max} (cm^{-1}): 3341, 2949, 2888, 1458, 1031;

δ_H (300 MHz, $CDCl_3$): 5.13 (2H, br s, 2 x =CH_AH$_B$), 4.79 (2H, br s, 2 x =CH$_A$$H_B$), 4.01 (2H, t, J = 10 Hz, 2 x C*H*OH), 2.34-0.90 (24H, br m, 2 x =CCH_2, 2 x (CH_2)$_4$, 2 x C*H*CHOH, 2 x C*H*CH$_2$C=);

δ_C (100 MHz, $CDCl_3$): 153.4, 106.0 (2), 73.3, 69.5 (1), 51.2 (1), 46.5 (1), 33.1 (2), 32.7 (2), 29.2 (2), 21.1 (2), 19.4 (2);

^{m}/z (APCI+): 363 $[M + H]^+$ (100%);

HRMS could not be obtained for this compound.



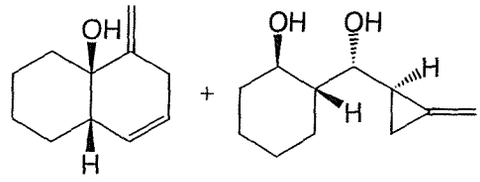
186 **187**

rac-(1R, 4aS, 8aR)-4-methyleneperhydro-1,4a-napthalenediol 186, rac-(4aS, 8aR)-5-methylene-1,2,3,4,4a,5,6,8a-octahydro-4a-napthalenol 187

Following the method by Procter,[71] to a solution of SmI_2 (0.11 M solution in THF, 10 mL, 1.10 mmol) and MeOH (2 mL) at -78°C under Ar, was added rac-(2S)-2-{(R)-1-hydroxy-1-[(1S)-2-methylenecyclopropyl]methyl}-1-cyclohexanone **185** (80 mg, 0.44 mmol) in THF (5 mL). The reaction mixture was stirred for 2 h at 0°C before the addition of brine (3 mL) and citric acid (128 mg, 0.61 mmol). The aqueous layer was then extracted with EtOAc (5 x 10 mL), the combined organic extracts were dried

over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography eluting with petrol, and gradually increasing the polarity to neat EtOAc to give alcohols **186** (61 mg, 0.33 mmol, 76%) and **187** (9 mg, 0.05 mmol, 12%);

All data for **186** and **187** agrees with that previously reported above.



187 **189**

rac-(4aS, 8aR)-5-methylene-1,2,3,4,4a,5,6,8a-octahydro-4a-napthalenol 187 and rac-(1R, 2S)-2-{(R)-1-hydroxy-1-[(1S)-2-methylenecyclopropyl] methyl}cyclohexan-1-ol 189

To a solution of SmI_2 (0.11 M solution in THF, 10 mL, 1.10 mmol) at -78°C under Ar, was added rac-(2S)-2-{(R)-1-hydroxy-1-[(1R)-2-methylenecyclopropyl]methyl}-1-cyclohexanone **184** (80 mg, 0.44 mmol) in THF (5 mL). The reaction mixture was stirred for 2 h at 0°C before the addition of brine (3 mL) and citric acid (128 mg, 0.61 mmol). The aqueous layer was then extracted with EtOAc (5 x 10 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography eluting with petrol, and gradually increasing the polarity to neat EtOAc to give alcohols **187** (4 mg, 0.022 mmol, 5%) and **189** (38 mg, 0.207 mmol, 47%);

Data for **189** obtained as colourless oil, $R_f = 0.32$ (30% EtOAc-petrol);

ν_{max} (cm^{-1}): 3327, 2989, 2928, 2857, 1450;

δ_H (400 MHz, $CDCl_3$): 5.38 (1H, br s, $=CH_AH_B$), 5.32 (1H, br s, $=CH_AH_B$), 3.72 (1H, dt, J = 4, 10 Hz, CH_2CHOH), 3.23 (1H, dd, J = 3, 9 Hz, $CHCHOH$), 3.21 (1H, br s, OH), 2.85 (1H, br s, OH), 1.94 (1H, m, $CHCHOH$), 1.75-1.53 (5H, m, $(CH_2)_2$, cyclopropyl CH), 1.29 (1H, tt, J = 9, 2 Hz, cyclopropyl CH), 1.25-1.10 (4H, m, $(CH_2)_2$), 0.80 (1H, m, cyclopropyl CH);

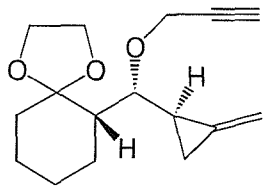
δ_C (100MHz, $CDCl_3$): 133.3, 105.2 (2), 77.8 (1), 72.5 (1), 49.7 (1), 36.2 (2), 27.1 (2), 26.0 (2), 25.0 (2), 19.1 (1), 8.1 (2);

$^m/z$ (CI+): 182 $[M]^+$ (22%), 165 $[M - OH]^+$ (100%);

HRMS: $C_{11}H_{18}O_2$ $[M]^+$ requires 182.1307, found 182.1311.

All data for **187** agrees with that previously reported above.

EXPERIMENTAL FOR CHAPTER 3



196

rac-(S)-1-[(6R)-1,4-dioxaspiro[4.5]dec-6-yl]-1-[(1R)-2-methylenecyclopropyl]methyl (2-propynyl)ether 196

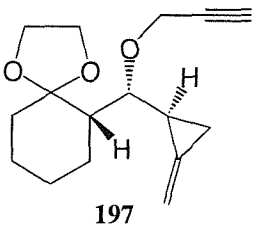
Following a modified procedure by Lautens,[73] potassium hydride (35% dispersion in oil, 1.53 g, 0.013 mol) was weighed in a flame dried round bottom flask and washed with petrol (3 x 10 mL). The remaining petrol was taken off by vacuum. Dry THF (20 mL) was added and the solution was cooled to 0°C. rac-(S)(6R)-1,4-Dioxaspiro[4.5]dec-6-yl[(1R)-2-methylidenecyclopropyl]methanol **183a** (2 g, 8.93 mmol) in THF (5 mL) with 18-crown-6 (236 mg, 0.89 mmol) were added slowly at 0°C. The reaction mixture was stirred at 0°C for 60 min prior to the addition of propargyl bromide (80% dispersion in oil, 1.7 mL, 0.02 mol). The reaction mixture was allowed to reach room temperature and stirred for two days. The reaction mixture was quenched by the addition of water and extracted with DCM (5 x 25 mL). The combined DCM layers were washed with water (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified using flash column chromatography eluting with petrol and gradually increasing the polarity to 35% EtOAc-petrol to yield propargyl ether **196** (900 mg, 3.43 mmol, 38%) as a pale yellow oil, $R_f = 0.74$ (20% EtOAc-petrol);

ν_{max} (cm^{-1}): 3397, 3290, 2931, 2862, 2192, 1085, 1057, 927, 889;

δ_H (400 MHz, $CDCl_3$): 5.40 (2H, s with fine splittings, $=CH_2$), 4.21 (2H, dq, $J = 2$, 16 Hz, OCH_2C), 4.00-3.81 (4H, m, $O(CH_2)_2O$), 3.28 (1H, dd, $J = 1$, 9 Hz, $CHOCH_2$), 2.27 (1H, t, $J = 2$ Hz, CCH), 1.90-1.30 (9H, m, $(CH_2)_3$, cyclopropyl CH, CH_AH_B, $CHCHOCH_2$), 1.27 (1H, dt, $J = 4$, 13 Hz, CH_AH_B), 1.18 (1H, m, cyclopropyl CH), 0.78 (1H, m, cyclopropyl CH);

δ_C (100 MHz, $CDCl_3$): 132.1, 110.7, 104.5 (2), 81.4, 78.3 (1), 74.3 (1), 64.9 (2), 64.8 (2), 56.4 (2), 49.5 (1), 35.8 (2), 25.7 (2), 24.3 (2), 24.2 (2), 19.6 (1), 7.1 (2);

$^m/z$ (CI+): 207 $[M - HOCH_2CCH]^+$ (97%).



197

rac-(S)-1-[(6R)-1,4-dioxaspiro[4.5]dec-6-yl]-1-[(1S)-2-methylenecyclopropyl]methyl (2-propynyl)ether 197

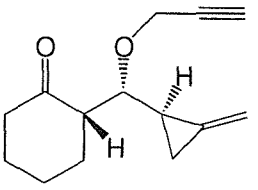
Following a modified procedure by Lautens,[73] potassium hydride (35% dispersion in oil, 1.15 g, 0.01 mol) was weighed in a flame dried round bottom flask and washed with petrol (3 x 10 mL). The remaining petrol was taken off by vacuum. Dry THF (20 mL) was added and the solution was cooled at 0°C. rac-(S)(6R)-1,4-Dioxaspiro[4.5]dec-6-yl[(1S)-2-methylidenecyclopropyl]methanol **183b** (1.5 g, 6.70 mmol) in THF (5 mL) with 18-crown-6 (177 mg, 0.67 mmol) were added slowly at 0°C. The reaction mixture was stirred at 0°C for 60 min prior to the addition of propargyl bromide (80% dispersion in oil, 1.3 mL, 0.01 mol). The reaction mixture was allowed to reach room temperature and stirred for two days. The reaction was quenched by the addition of water and extracted with DCM (5 x 25 mL). The combined DCM layers were washed with water (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified using flash column chromatography eluting with petrol and gradually increasing the polarity to 35% EtOAc-petrol to yield propargyl ether **197** (1.26 g, 4.82 mmol, 72%) as a pale yellow oil, $R_f = 0.61$ (20% EtOAc-petrol);

ν_{max} (cm^{-1}): 3425, 3267, 2934, 2864, 1083, 926, 893;

δ_H (400 MHz, $CDCl_3$): 5.35 (2H, s with fine splittings, $=CH_2$), 4.30 (2H, dq, $J = 2$, 16 Hz, OCH_2C), 4.00-3.80 (4H, m, $O(CH_2)O$), 3.45 (1H, dd, $J = 1$, 9 Hz, $CHOCH_2$), 2.30 (1H, t, $J = 2$ Hz, CCH), 1.84-1.41 (9H, m, $(CH_2)_3$, cyclopropyl CH, CH_AH_B, $CHCHOCH_2$), 1.36 (1H, tt, $J = 2$, 9 Hz, cyclopropyl CH), 1.27 (1H, dt, $J = 5$, 13 Hz, CH_AH_B), 1.19 (1H, m, cyclopropyl CH);

δ_C (100 MHz, $CDCl_3$): 131.9, 110.3, 104.7 (2), 81.0, 77.4 (1), 74.3 (1), 64.8 (2), 64.7 (2), 56.3 (2), 49.9 (1), 36.1 (2), 25.7 (2), 24.2 (2), 24.2 (2), 18.7 (1), 10.6 (2);

$^m/z$ (CI+): 207 [M – $HOCH_2CCH]^+$ (100%).



198

rac-(2S)-2-[(R)-1-[(1R)-2-methylenecyclopropyl]-1-(2-propynyloxy)methyl] cyclohexan-1-one 198

rac-(S)-1-[(6R)-1,4-dioxaspiro[4.5]dec-6-yl]-1-[(1R)-2-methylenecyclopropyl]methyl (2-propynyl)ether **196** (600 mg, 2.29 mmol) in acetone/water (50 mL/5 mL) was stirred with pTsOH (523 mg, 2.75 mmol) for 3 days. The reaction mixture was concentrated *in vacuo* and diluted with Et_2O (50 mL). The solution was washed with aq. $NaHCO_3$ (50 mL) and the aqueous layer extracted with Et_2O (5 x 50 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified using flash column chromatography eluting with petrol and gradually increasing the polarity to 50% EtOAc-petrol to yield deprotected ketone **198** (389 mg, 1.79 mmol, 78%) as a colourless oil, $R_f = 0.73$ (20% EtOAc-petrol);

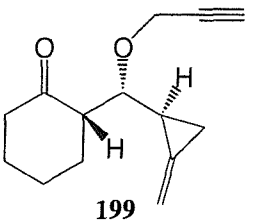
ν_{max} (cm^{-1}): 3272, 3079, 2937, 2861, 2173, 1707, 1077, 894;

δ_H (400 MHz, $CDCl_3$): 5.52 (1H, d, J = 2 Hz, $=CH_AH_B$), 5.48 (1H, d, J = 2 Hz, $=CH_AH_B$), 4.28 (2H, dq, J = 2, 16 Hz, OCH_2C), 3.58 (1H, dd, J = 4, 9 Hz, $CHOCH_2$), 2.56-1.60 (11H, m, CC*H*, $(CH_2)_4$ cyclopropyl C*H*, $CHCHOCH_2$), 1.27 (1H, tt, J = 2, 9 Hz, cyclopropyl CH), 0.87 (1H, m, cyclopropyl CH);

δ_C (100 MHz, $CDCl_3$): 211.2, 134.1, 105.0 (2), 80.8, 78.8 (1), 74.2 (1), 57.4 (2), 55.4 (1), 42.5 (2), 27.7 (2), 27.3 (2), 24.8 (2), 18.1 (1), 7.2 (2);

$^m/z$ (CI+): 219 $[M + H]^+$ (12%), 163 $[M - HOCH_2CCH]^+$ (100%);

HRMS: $C_{14}H_{19}O_2$ $[M + H]^+$ requires 219.1385, found 219.1386.



199

rac-(2S)-2-[(R)-1-[(1S)-2-methylenecyclopropyl]-1-(2-propynyloxy)methyl] cyclohexan-1-one 199

rac-(S)-1-[(6R)-1,4-dioxaspiro[4.5]dec-6-yl]-1-[(1S)-2-methylenecyclopropyl]methyl (2-propynyl)ether **197** (1.00 g, 3.82 mmol) in acetone/water (75 mL/7.5 mL) was stirred with pTsOH (870 mg, 4.58 mmol) for 3 days. The reaction mixture was concentrated *in vacuo* and diluted with Et_2O (50 mL). The solution was washed with aq. $NaHCO_3$ (50 mL) and the aqueous layer extracted with Et_2O (5 x 50 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified using flash column chromatography eluting with petrol and gradually increasing the polarity to 50% EtOAc-petrol to yield ketone **199** (700 mg, 3.21 mmol, 84%) as a colourless oil, R_f = 0.61 (20% EtOAc-petrol);

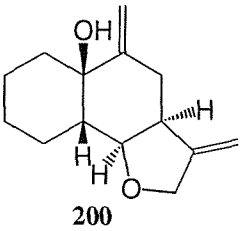
ν_{max} (cm^{-1}): 3283, 2940, 2864, 1708, 1075, 899;

δ_H (400 MHz, $CDCl_3$): 5.22 (1H, br s, $=CH_AH_B$), 5.16 (1H, br s, $=CH_AH_B$), 4.12 (2H, d, J = 2 Hz, OCH_2C), 3.44 (1H, dd, J = 4, 8 Hz, $CHOCH_2$), 2.50-1.39 (11H, m, CCH, $(CH_2)_4$ cyclopropyl CH, $CHCHOCH_2$), 1.21 (1H, tt, J = 2, 9 Hz, cyclopropyl CH), 1.03 (1H, m, cyclopropyl CH);

δ_C (100 MHz, $CDCl_3$): 210.5, 131.1, 104.8 (2), 80.3, 77.7 (1), 73.8 (1), 57.1 (2), 55.4 (1), 41.8 (2), 26.6 (2), 26.5 (2), 23.9 (2), 17.4 (1), 9.5 (2);

m/z (CI+): 219 $[M + H]^+$ (12%), 163 $[M - HOCH_2CCH]^+$ (100%);

HRMS: $C_{14}H_{19}O_2$ $[M + H]^+$ requires 219.1385, found 219.1380.



200

rac-(3aR, 5aS, 9aR, 9bR)-5-dimethyleneperhydronaptho[1,2-b]furan-5a-ol 200

Following the procedure by Molander,[53] HMPA (0.64 mL, 3.67 mmol) was added to the SmI_2 (0.09 M solution in THF, 10 mL, 0.93 mmol) to give a purple

solution. The solution was cooled to -78°C, rac-(2S)-2-[(R)-1-[(1R)-2-methylenecyclopropyl]-1-(2-propynyloxy)methyl] cyclohexan-1-one **198** (80 mg, 0.37 mmol), ^{t}BuOH (54 mg, 0.73 mmol) in THF (10 mL) was added over 90 min and the reaction mixture was allowed to warm to room temperature. The crude mixture was washed with aq. citric acid (1 g in 20 mL water) and extracted with 1:1 EtOAc-petrol (5 x 25 mL). The combined organic phase was washed with brine (25 mL), and water (25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography eluting with petrol and gradually increasing the polarity to neat EtOAc to give tricycle **200** (41 mg, 0.185 mmol, 50%) as a colourless oil, R_f = 0.59 (20% EtOAc-petrol);

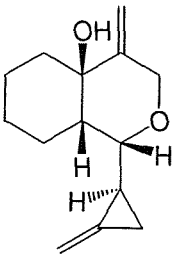
ν_{max} (cm^{-1}): 3457, 3074, 2932, 2860, 1448, 1047, 997, 940, 901, 738;

δ_H (400 MHz, $CDCl_3$): 4.95 (1H, br s, cyclohexene =CH_AH$_B$), 4.93-4.90 (2H, m, cyclohexene =CH$_A$$H_B$, furan =C$H_AH_B$), 4.80 (1H, br s, furan =CH$_A$$H_B$), 4.47 (1H, d, *J* = 13 Hz, OCH_AH$_B$), 4.19 (1H, dt, *J* = 13, 2 Hz, OCH$_A$$H_B$) 3.81 (1H, t, *J* = 4 Hz, C*H*OCH$_2$), 2.61 (1H, ddd, *J* = 4, 7, 11 Hz, CHC=), 2.49 (1H, dd, *J* = 11, 15 Hz, =CCH_AH$_B$), 2.19 (1H, dd, *J* = 7, 15 Hz, =CCH$_A$$H_B$), 2.07 (1H, br s, OH), 1.92 (1H, dt, *J* = 11, 4 Hz, C*H*CHOCH$_2$), 1.68-1.05 (8H, m, $(CH_2)_4$);

δ_C (100 MHz, $CDCl_3$): 151.7, 146.9, 111.5 (2), 104.5 (2), 84.2 (1), 73.0, 70.0 (2), 45.5 (1), 42.7 (1), 35.7 (2), 33.6 (2), 27.1 (2), 25.6 (2), 23.6 (2);

^{m}/z (CI+): 203 $[M - OH]^+$ (100%);

HRMS: $C_{14}H_{24}NO_2$ $[M + NH_4]^+$ requires 238.1807, found 238.1811.



208

rac-(1R, 4aS, 8aR)-4-methylene-1-[(1S)-2-methylenecyclopropyl]perhydro-4a-isochromenol 208

Following the procedure by Procter,[71] to a solution of SmI_2 (0.09 M solution in THF, 10 mL, 0.93 mmol) and MeOH (2 mL) at 0°C under Ar, was added rac-(2S)-2-[(R)-1-[(1S)-2-methylenecyclopropyl]-1-(2-propynyloxy)methyl] cyclohexan-1-one **199** (80 mg, 0.37 mmol) in THF (5 mL) over 45 min. The reaction mixture was stirred

for 2 h at 0°C before the addition of brine (3 mL) and citric acid (128 mg, 0.61 mmol). The aqueous layer was extracted with DCM (5 x 10 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography eluting with petrol and gradually increasing the polarity to EtOAc to give bicycle **208** (60 mg, 0.27 mmol, 74%) as a white solid, $R_f = 0.33$ (20% EtOAc-petrol);

Melting point: 84-86°C (Recrystallised from hot EtOAc);

ν_{max} (cm^{-1}): 3413, 3074, 2935, 2862, 1448, 1044, 997, 951, 908;

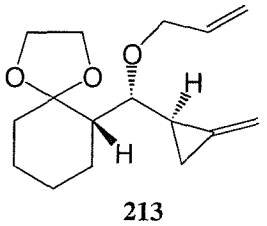
δ_H (400 MHz, $CDCl_3$): 5.35 (1H, d, $J = 2$ Hz, methylenecyclopropyl $=CH_AH_B$), 5.33 (1H, d, $J = 2$ Hz, methylenecyclopropyl $=CH_AH_B$), 5.00 (2H, s, cyclohexene $=CH_2$), 4.33 (1H, d, $J = 13$ Hz, $=CCH_AH_BO$), 4.01 (1H, d, $J = 13$ Hz, $=CCH_AH_BO$) 3.46 (1H, dd, $J = 2, 9$ Hz, $CHOCH_2$), 2.19 (1H, m, OH) 1.85-1.16 (11H, m, $(CH_2)_4$, 2 x cyclopropyl CH, CHCHOH), 1.03 (1H, m, cyclopropyl CH);

δ_C (100 MHz, $CDCl_3$): 144.5, 132.5, 111.7 (2), 104.6 (2), 79.0 (1), 72.5, 70.7 (2), 49.0 (1), 37.9 (2), 26.4 (2), 24.6 (2), 22.9 (2), 17.8 (1), 10.1 (2);

$^m/z$ (CI+): 203 $[M - OH]^+$ (63%);

Microanalysis: Found C, 76.32; H, 9.10. $C_{14}H_{20}O_2$ requires C, 76.33; H, 9.15%;

Stereochemistry was confirmed by X-ray crystallography.



213

rac-(6S)-6-{(R)-1-(allyloxy)-1-[(1R)-2-methylenecyclopropyl]methyl}-1,4-dioxaspiro[4.5]decane 213

To a suspension of NaH (0.4 g, 0.01 mol, 60% dispersion in oil) in DMF (20 mL) under argon, was added rac-(S)(6R)-1,4-Dioxaspiro[4.5]dec-6-yl[(1R)-2-methylidenecyclopropyl]methanol **183a** (1.5 g, 6.70 mmol) in DMF (10 mL) at 0°C. The reaction was stirred at room temperature for 1 h. Allyl bromide (0.93 mL, 0.01 mol) was added at 0°C and the reaction was stirred at room temperature overnight. Water was added and extracted with DCM (4 x 25 mL). The DCM layers were washed with water (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography eluting with

petrol and gradually increasing the polarity to 30% EtOAc-petrol to give allyl ether **213** (1.4 g, 5.30 mmol, 79%) as a yellow oil, $R_f = 0.76$ (20% EtOAc-petrol);

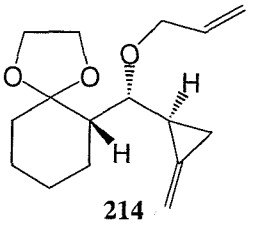
ν_{max} (cm^{-1}): 3436, 3071, 2928, 2869, 1128, 1025, 882;

δ_H (400 MHz, $CDCl_3$): 5.84 (1H, ddt, J = 17, 10, 5 Hz, =CH), 5.38 (1H, br s, methylenecyclopropyl =CH_AH$_B$), 5.36 (1H, br s, methylenecyclopropyl =CH$_A$$H_B$), 5.19 (1H, dq, J = 17, 2 Hz, allyl =CH_AH$_B$), 5.02 (1H, dq, J = 10, 2 Hz, allyl =CH$_A$$H_B$), 4.13 (1H, ddt, J = 13, 5, 2 Hz, OCH_AH$_B$), 3.93-3.76 (5H, m, OCH$_A$$H_B$, O(C$H_2$)$_2$O), 3.01 (1H, dd, J = 9, 1 Hz, CHOCH$_2$), 1.84-1.41 (8H, m, (CH_2)$_3$, cyclopropyl CH, CHCHOCH$_2$), 1.31-1.17 (2H, m, CH$_2$), 1.14 (1H, tt, J = 9, 2 Hz , cyclopropyl CH), 0.73 (1H, m, cyclopropyl CH);

δ_C (100 MHz, $CDCl_3$): 135.4, 135.3 (1), 115.9 (2), 109.6, 103.2 (2), 78.3 (1), 70.1 (2), 63.9 (2), 63.8 (2), 48.4 (1), 34.7 (2), 24.6 (2), 23.7 (2), 23.3 (2), 19.8 (1), 6.5 (2);

$^m/z$ (CI+): 265 $[M + H]^+$ (10%), 207 $[M- CH_2=CHCH_2O]^+$ (100%);

HRMS: $C_{16}H_{24}O_3$ $[M]^+$ requires 264.1725, found 264.1722.



214

rac-(6S)-6-{(R)-1-(allyloxy)-1-[(1S)-2-methylenecyclopropyl]methyl}-1,4-dioxaspiro[4.5]decane 214

To a suspension of NaH (0.27 g, 6.7 mmol, 60% dispersion in oil) in DMF (15 mL) under argon, was added rac-(S)(6R)-1,4-Dioxaspiro[4.5]dec-6-yl[(1S)-2-methylidenecyclopropyl]methanol **183b** (1.00 g, 4.46 mmol) in DMF (10 mL) at 0°C. The reaction was stirred at room temperature for 1 h. Allyl bromide (0.67 mL, 7.14 mmol) was added at 0°C and the reaction was stirred at room temperature overnight. Water was added and extracted with DCM (4 x 25 mL). The DCM layers were washed with water (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography eluting with petrol and gradually increasing the polarity to 30% EtOAc-petrol to give allyl ether **214** (848 mg, 4.46 mmol, 72%) as a yellow oil, $R_f = 0.77$ (20% EtOAc-petrol);

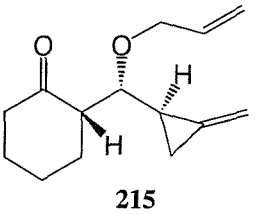
ν_{max} (cm^{-1}): 3434, 3063, 2931, 2865, 1131, 1035, 893;

δ_H (400 MHz, $CDCl_3$): 5.85 (1H, ddt, J = 17, 10, 5 Hz, =CH), 5.34 (2H, br s, methylenecyclopropyl $=CH_2$), 5.19 (1H, dq, J = 17, 2 Hz, allyl $=CH_AH_B$), 5.04 (1H, dq, J = 10, 2 Hz, allyl $=CH_AH_B$), 4.16 (1H, ddt, J = 13, 5, 2 Hz, OCH_AH_B), 3.97-3.78 (5H, m, OCH_AH_B, $O(CH_2)_2O$), 3.19 (1H, dd, J = 9, 1 Hz, $CHOCH_2$), 1.84-1.43 (8H, m, $(CH_2)_3$, cyclopropyl CH, $CHCHOCH_2$), 1.37-1.14 (3H, m, CH_2, cyclopropyl CH), 1.04 (1H, m, cyclopropyl CH);

δ_C (100 MHz, $CDCl_3$): 136.3(1), 136.2, 116.2 (2), 110.6, 104.4 (2), 79.6 (1), 71.5 (2), 64.8 (2), 64.7 (2), 49.7 (1), 35.5 (2), 25.3 (2), 24.5 (2), 24.5 (2), 19.7 (1), 10.5 (2);

$^m/z$ (CI+): 265 $[M + H]^+$ (8%), 207 $[M- CH_2=CHCH_2O]^+$ (100%);

HRMS: $C_{16}H_{24}O_3$ $[M - H]^+$ requires 263.1647, found 263.1645.



215

rac-(2S)-2-{(R)-1-(allyloxy)-1-[(1R)-2-methylenecyclopropyl]methyl}cyclohexan-1-one 215

rac-(6S)-6-{(R)-1-(allyloxy)-1-[(1R)-2-methylenecyclopropyl]methyl}-1,4-dioxaspiro[4.5]decane **213** (1.20 g, 4.55 mmol) in acetone/water (170 mL/17 mL) was stirred with pTsOH (1.04 g, 5.45 mmol) overnight. The reaction mixture was concentrated *in vacuo* and diluted with Et_2O (50 mL). The solution was washed with aq. $NaHCO_3$ (50 mL) and the aqueous layer extracted with Et_2O (5 x 50 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified using flash column chromatography eluting with petrol and gradually increasing the polarity to 25% EtOAc-petrol to yield ketone **215** (400 mg, 1.82 mmol, 40%) as a colourless oil, R_f = 0.79 (20% EtOAc-petrol);

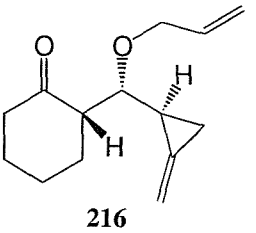
ν_{max} (cm^{-1}): 3067, 2940, 2858, 1699, 1066, 889;

δ_H (400 MHz, $CDCl_3$): 5.90 (1H, ddt, J = 17, 10, 5 Hz, $CH_2=CH$), 5.45 (2H, br s, methylenecyclopropyl $=CH_2$), 5.25 (1H, dq, J = 17, 2 Hz, allyl $=CH_AH_B$), 5.14 (1H, dq, J = 10, 2 Hz, allyl $=CH_AH_B$), 4.21 (1H, ddt, J = 13, 5, 1 Hz, OCH_AH_B), 3.99 (1H, ddt, J = 13, 5, 2 Hz, OCH_AH_B), 3.46 (1H, dd, J = 4, 9 Hz, $CHOCH_2$), 2.60-1.60 (10H, m, $(CH_2)_4$, cyclopropyl CH, $CHCHOCH_2$), 1.25 (1H, tt, J = 9, 2 Hz, cyclopropyl CH), 0.85 (1H, m, cyclopropyl CH);

δ_C (100 MHz, $CDCl_3$): 211.4, 135.5 (1), 134.4, 116.3 (2), 104.5 (2), 78.6 (1), 71.0 (2), 55.2 (1), 42.2 (2), 27.2 (2), 27.0 (2), 24.6 (2), 18.3 (1), 6.9 (2);

$^m/z$ (CI+): 221 $[M + H]^+$ (12%), 163 $[M - CH_2{=}CHCH_2OH]^+$ (100%);

HRMS could not be obtained on this compound.



216

rac-(2S)-2-{(R)-1-(allyloxy)-1-[(1S)-2-methylenecyclopropyl]methyl}cyclohexan-1-one 216

rac-(6S)-6-{(R)-1-(allyloxy)-1-[(1S)-2-methylenecyclopropyl]methyl}-1,4-dioxaspiro[4.5]decane **214** (700 mg, 2.65 mmol) in acetone/water (100 mL/10 mL) was stirred with pTsOH (605 mg, 3.18 mmol) overnight. The reaction mixture was concentrated *in vacuo* and diluted with Et_2O (50 mL). The solution was washed with aq. $NaHCO_3$ (50 mL) and the aqueous layer extracted with Et_2O (5 x 50 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified using flash column chromatography eluting with petrol and gradually increasing the polarity to 20% EtOAc-petrol to yield ketone **216** (396 mg, 1.82 mmol, 68%) as a colourless oil, $R_f = 0.83$ (20% EtOAc-petrol);

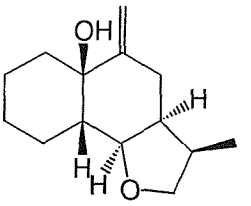
ν_{max} (cm^{-1}): 3067, 2947, 2857, 1705, 1070, 889;

δ_H (400 MHz, $CDCl_3$): 5.85 (1H, ddt, J = 17, 10, 5 Hz, $CH_2{=}CH$), 5.42 (1H, d, J = 2 Hz, methylenecyclopropyl $=CH_AH_B$), 5.35 (1H, d, J = 2 Hz, methylenecyclopropyl $=CH_AH_B$), 5.25 (1H, dq, J = 17, 2 Hz, allyl $=CH_AH_B$), 5.13 (1H, dq, J = 17, 2 Hz, allyl $=CH_AH_B$), 4.23 (1H, ddt, J = 13, 5, 1 Hz, OCH_AH_B), 4.08 (1H, ddt, J = 13, 5, 1 Hz, OCH_AH_B), 3.52 (1H, dd, J = 8, 4 Hz, $CHOCH_2$), 2.50-1.55 (10H, m, $(CH_2)_4$, cyclopropyl CH, $CHCHOCH_2$), 1.42 (1H, tt, J = 9, 2 Hz, cyclopropyl CH), 1.10 (1H, m, cyclopropyl CH);

δ_C (100 MHz, $CDCl_3$): 211.1, 135.7 (1), 131.8, 116.4 (2), 104.7 (2), 78.3 (1), 71.4 (2), 55.9 (1), 42.1 (2), 26.9 (2), 26.8 (2), 24.3 (2), 18.3 (1), 9.8 (2);

$^m/z$ (CI+): 221 $[M + H]^+$ (2%), 163 $[M - CH_2{=}CHCH_2OH]^+$ (100%);

HRMS, $C_{14}H_{20}O_2$ $[M]^+$ requires 220.1463 found 220.1465.



218

rac-(3R, 3aR, 5aS, 9aR, 9bR)-3-methyl-5-methyleneperhydronaptho[1,2-b]furan-5a-ol 218

Following the procedure by Molander,[53] HMPA (0.41 mL, 2.27 mmol) was added to the SmI_2 (0.12 M solution in THF, 5 mL, 0.58 mmol) to give a purple solution. The solution was cooled to –78 °C, rac-(2S)-2-{(R)-1-(allyloxy)-1-[(1R)-2-methylenecyclopropyl]methyl}cyclohexan-1-one **215** (50 mg, 0.23 mmol) and ^{t}BuOH (33.7 mg, 0.45 mmol) in THF (5 mL) were added over 90 min and the reaction mixture was allowed to warm to room temperature. The crude mixture was washed with aq. citric acid (1g in 20 mL water) and extracted with 1:1 EtOAc-petrol (5 x 10 mL). The combined organic phase was washed with brine (10 mL), and water (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography eluting with petrol and gradually increasing the polarity to neat EtOAc to give tricycle **218** (25 mg, 0.12 mmol, 50%) as a colourless oil, R_f = 0.58 (20% EtOAc-petrol);

ν_{max} (cm^{-1}): 3472, 3079, 2921, 2854, 1445, 1037, 1004, 941, 898;

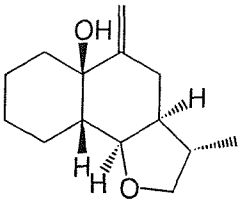
δ_H (400 MHz, $CDCl_3$): 5.00 (1H, br s, =CH_AH$_B$), 4.89 (1H, br s, =CH$_A$$H_B$), 3.90 (1H, t, J = 8 Hz, OCH_AH$_B$), 3.75 (1H, br s, CHOCH$_2$), 3.50 (1H, dd, J = 8, 10 Hz, OCH$_A$$H_B$), 2.50-1.20 (13H, m, (C$H_2$)$_4$, C$HCH_3$, C$HCOH, CH$CHO, =CC$H_2$), 0.94 (3H, d, J = 7 Hz, CH$_3$);

δ_C (100 MHz, $CDCl_3$): 147.0, 111.9 (2), 86.1 (1), 73.2 (2), 72.0, 46.1 (1), 39.7 (1), 38.0 (1), 36.1 (2), 33.6 (2), 28.3 (2), 26.7 (2), 24.1 (2), 12.2 (3);

^{m}/z (CI+): 223 $[M + H]^+$, (17%), 205 $[M - OH]^+$ (100%);

HRMS, $C_{14}H_{22}O_2$ $[M]^+$ requires 222.1620 found 222.1617;

nOe studies were used to determine stereochemistry.



217

rac-(3S, 3aR, 5aS, 9aR, 9bR)-3-methyl-5-methyleneperhydronaptho[1,2-b]furan-5a-ol 2l

Following the procedure by Procter,[71] to a solution of SmI_2 (0.12 M solution in THF, 5 mL, 0.58 mmol) and MeOH (1.5 mL) at 0°C under Ar, was added rac-(2S)-2-{(R)-1-(allyloxy)-1-[(1S)-2-methylenecyclopropyl]methyl}cyclohexan-1-one **215** (50 mg, 0.23 mmol) in THF (5 mL) over 45 min. The reaction mixture was stirred for 2 h at 0°C before the addition of brine (3 mL) and citric acid (128 mg, 0.61 mmol). The aqueous layer was extracted with DCM (5 x 10 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography eluting with petrol and gradually increasing the polarity to EtOAc to give tricycle **217** (35 mg, 0.16 mmol, 70%) as a white solid, R_f = 0.41 (20% EtOAc-petrol);

Melting point: 76-78°C (Recrystallised from hot EtOAc);

ν_{max} (cm^{-1}): 3405, 3084, 2916, 2854, 1440, 1061, 1004, 924, 898;

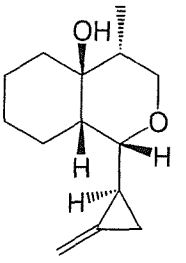
δ_H (400 MHz, $CDCl_3$): 4.92 (1H, br s, $=CH_AH_B$), 4.88 (1H, br s, $=CH_AH_B$), 4.10 (1H, dd, J = 9, 8 Hz, OCH_AH_B), 3.86 (1H, t, J = 4 Hz, $CHOCH_2$), 3.27 (1H, ddd, J = 9, 5, 1 Hz, OCH_AH_B), 2.30 (1H, dd, J = 14.5, 9 Hz, $=CCH_AH_B$), 2.21 (1H, dd, J = 14.5, 6.5 Hz, $=CCH_AH_B$), 2.00 (1H, m, $CHCH_3$), 1.86 (1H, ddd, J = 9, 5, 4 Hz, CHCOH), 1.78 (1H, m, CHCHOH), 1.65-1.10 (8H, m, $(CH_2)_4$), 0.95 (3H, d, J = 7 Hz, CH_3);

δ_C (100 MHz, $CDCl_3$): 148.4, 110.8 (2), 81.6 (1), 74.0 (2), 73.2, 45.6 (1), 44.3 (1), 38.8 (1), 35.5 (2), 33.5 (2), 26.6 (2), 24.9 (2), 23.4 (2), 19.0 (3);

$^m/z$ (CI+): 205 $[M - OH]^+$ (100%);

Microanalysis: Found C, 75.59; H, 10.05: $C_{14}H_{22}O_2$ requires C, 75.63; H, 9.97%;

X-ray crystallography and nOe studies were used to determine stereochemistry.



222

rac-(1R, 4aS, 4aS, 8aR)-4-methyl-1-[(1S)-2-methylidenecyclopropyl]perhydro-4a-isochromenol 222

Following the procedure by Molander,[53] HMPA (0.64 mL, 3.67 mmol) was added to the SmI_2 (0.09 M solution in THF, 10 mL, 0.93 mmol) to give a purple solution. The solution was cooled to -78°C, rac-(2S)-2-{(R)-1-(allyloxy)-1-[(1S)-2-methylenecyclopropyl]methyl}cyclohexan-1-one **216** (80 mg, 0.37 mmol) and ^{t}BuOH (54 mg, 0.73 mmol) in THF (10 mL) were added over 90 min and the reaction mixture was allowed to warm to room temperature. The crude mixture was washed with aq. citric acid (1g in 20 mL water) and extracted with 1:1 EtOAc-petrol (5 x 25 mL). The combined organic phase was washed with brine (25 mL), water (25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography eluting with petrol and gradually increasing the polarity to neat EtOAc to give bicycle **222** (61 mg, 0.28 mmol, 75%) as a colourless viscous oil,

R_f = 0.33 (20% EtOAc-petrol);

ν_{max} (cm^{-1}): 3456, 3074, 2924, 2859, 1449, 1054, 985, 940, 877;

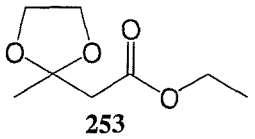
δ_H (400 MHz, $CDCl_3$): 5.34 (2H, s with fine splittings, methylenecyclopropyl $=CH_2$), 3.65 (1H, dd, J = 11, 5 Hz, OCH_AH_B), 3.45 (1H, t, J = 11 Hz, OCH_AH_B), 3.34 (1H, dd, J = 9, 2 Hz, $CHOCH_2$), 2.23-1.00 (12H, m, $CHCH_3$, $(CH_2)_4$, 3 x cyclopropyl CH), 0.75 (3H, d, J = 6 Hz, CH_3);

δ_C (100 MHz, $CDCl_3$): 132.5, 104.2 (2), 78.7 (1), 71.7, 70.2 (2), 48.2 (1), 37.7 (2), 30.3 (1), 25.8 (2), 23.1 (2), 22.7 (2), 17.7 (1), 9.9 (2), 8.7 (3);

$^{m}/z$ (CI+): 205 $[M - OH]^+$ (100%);

HRMS: $C_{14}H_{21}O$ $[M - OH]^+$ requires 205.1592 found 205.1600.

EXPERIMENTAL FOR CHAPTER 4



253

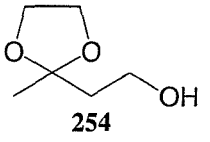
Ethyl-2-(2-methyl-dioxolanyl)-acetate 253

Following the method of Kelly,[90] ethylene glycol (25.7 mL, 0.46 mol), ethyl acetoacetate **235** (30.0 mL, 0.23 mol) and pTsOH (0.44 g, 2.30 mmol) were refluxed together in toluene (200 mL) for 20 hours using Dean Stark apparatus to remove water. The reaction mixture was cooled and concentrated *in vacuo*. Et_2O (100 mL) was added and washed with aq. $NaHCO_3$ (2 x 50 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil which was distilled (88-92 °C/10 mm Hg ; lit.[90] bp. 99.5-101 °C/17-18 mm Hg) to give ketal **253** (32 g, 0.184 mol, 80%) as a colourless oil;

δ_H (300 MHz, $CDCl_3$): 4.15 (2H, q, J = 7 Hz, OCH_2CH_3), 3.89 (4H, s, $O(CH_2)_2O$), 2.60 (2H, s, CH_2COOEt), 1.45 (3H, s, CCH_3) and 1.28 (3H, t, J = 7 Hz, OCH_2CH_3);

δ_C (75 MHz, $CDCl_3$): 169.5, 107.6, 64.8 (2), 60.5 (2), 44.2 (2), 24.5 (3), 14.2 (3);

All data agrees with that reported by Kelly.[90]



254

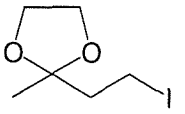
2-(2-Methyl-dioxolanyl)-hydroxyethyl 254

Following the method of Albizati,[68] ethyl-2-(2-methyl-dioxolanyl)-acetate **253** (15 g, 86.0 mmol) was added dropwise to a suspension of $LiAlH_4$ (6.5 g, 0.17 mol) in THF (100 mL) at 0 °C and stirred overnight. Et_2O (150 mL) was added and the solution was stirred at 0 °C for 5 minutes. NaOH (4 M) was added carefully to the mixture until a white heavy precipitate persisted. The mixture was filtered and washed with Et_2O (100 mL) and concentrated *in vacuo* to give alcohol **254** (10.0 g, 0.076 mol, 87%) as a colourless oil R_f = 0.33 (50% Et_2O -petrol);

δ_H (300 MHz, $CDCl_3$): 3.97 (4H, s, $O(CH_2)_2O$), 3.76 (2H, t, J = 5 Hz, CH_2OH), 2.80 (1H, br s, OH), 1.95 (2H, t, J = 5 Hz, CH_2CH_2OH) and 1.36 (3H, s, CH_3);

δ_C (75 MHz, $CDCl_3$): 110.5, 64.6 (2), 59.0 (2), 40.4 (2), 24.0 (3);

All data agrees with data reported by Albizati.[68]



255

2-(2-Methyl-dioxolanyl)-iodoethane 255

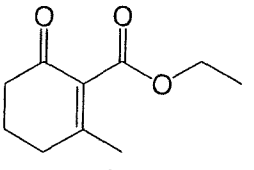
Following the method of Motherwell,[91] triphenylphosphine (10.4 g, 0.04 mol), imidazole (3.1 g, 45.0 mmol) and finally iodine (10.8 g, 40.0 mmol) were added to a stirred solution of 2-(2-methyl-dioxolanyl)-hydroxyethyl **254** (3.5 g, 30.0 mmol) in Et_2O (60 mL) and acetonitrile (20 mL). The solution was stirred for 30 minutes. The resulting red solution was diluted in Et_2O (100 mL), washed with aq. $Na_2S_2O_3$ (5 x 50 mL), water (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with petrol (5 x 20 mL), filtered, concentrated *in vacuo*. The crude mixture was purified using flash column chromatography eluting with petrol and gradually increasing the polarity to EtOAc to give iodide **255** (6.22 g, 0.026 mol, 86%) as a light brown oil $R_f = 0.58$ (50% Et_2O-petrol);

δ_H (300 MHz, $CDCl_3$): 3.99-3.87 (4H, m, $O(CH_2)_2O$), 3.15 (2H, t, $J = 8$ Hz, CH_2I), 2.29 (2H, t, $J = 8$ Hz, CH_2CH_2I) and 1.30 (3H, s, CH_3);

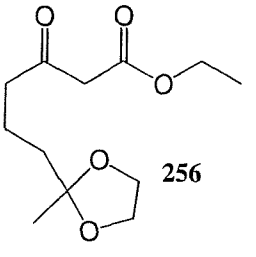
δ_C (75 MHz, $CDCl_3$): 109.9, 65.0 (2), 44.4 (2), 23.9 (3), -2.12 (2);

$^m/z$ (CI+): 243 $[M + H]^+$ (25%);

All data agrees with data reported by Trost.[114]



234



256

Ethyl 2- methyl-6-oxocyclohex-1-ene-1-carboxylate 3d and ethyl 6-(2-methyl-1,3-dioxaolan-2-yl)-3-oxohexanoate 3e.

Following the method of DeMilo,[94] to a stirred suspension of sodium hydride (0.91 g, 0.023 mol) in THF (100 mL) at 0°C and under an argon atmosphere, was added dropwise ethyl acetoacetate **235** (2.7 g, 0.021 mol). After stirring for 30 min, nBuLi (9.5 mL) was added and the resulting solution stirred for an additional 30 min at 0°C. Following the addition of HMPA (7.22 mL) and stirring for 15 min 2-(2-methyl-

dioxolanyl)-iodoethane **255** (5 g, 0.021 mol) was added and the mixture was stirred overnight at room temperature. The reaction mixture was split into two (a and b).

a) The reaction was quenched by the addition of sat. $NH_4Cl_{(aq)}$ and stirred for 5 min. The mixture was extracted with Et_2O. The Et_2O layer was washed with water (3 x 50 mL) and brine (2 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography eluting with petrol and gradually increasing the polarity to EtOAc to give ketal **256** (2.29 g, 0.013 mol, 60%) as a slightly yellow oil, $R_f = 0.39$ (30% EtOAc-petrol);

ν_{max} (cm^{-1}): 2983, 2882, 1738, 1707, 1046, 731;

δ_H (400 MHz, $CDCl_3$): 4.03 (2H, q, $J = 7$ Hz, CH_2CH_3), 3.80-3.74 (4H, m, $O(CH_2)_2O$), 3.24 (2H, s, $COCH_2CO$), 2.41 (2H, t, $J = 6$ Hz, CH_2CH_2CO), 1.50 (4H, m, $(CH_2)_2$), 1.15 (3H, s, CCH_3), 1.12 (3H, t, $J = 7$ Hz, CH_2CH_3);

δ_C (100 MHz, $CDCl_3$): 171.4, 167.6, 110.1, 65.0 (2), 61.7 (2), 49.7 (2), 43.2 (2), 38.4 (2), 24.2 (3), 18.4 (2), 14.5 (3);

All data agrees with that previously reported by Funk.[93]

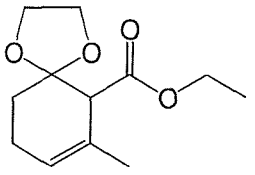
b) The reaction was quenched by the careful addition of concentrated HCl and stirred for 15 min. The mixture was extracted with Et_2O. The Et_2O layer was washed with water (3 x 50 mL) and brine (2 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography eluting with petrol and gradually increasing the polarity to EtOAc to give cyclohexenone **234** (2.18 g, 0.012 mol, 58%) as a colourless oil, $R_f = 0.35$ (30% EtOAc-petrol);

ν_{max} (cm^{-1}): 2978, 2927, 2876, 1722, 1672, 1372, 736;

δ_H (400 MHz, $CDCl_3$): 4.30 (2H, q, $J = 7$ Hz, CH_2CH_3), 2.50-2.35 (4H, m, CH_2CH_2), 2.06-1.97 (2H, m, CH_2CO), 1.90 (3H, s, CCH_3), 1.33 (3H, t, $J = 7$ Hz, CH_2CH_3);

δ_C (100 MHz, $CDCl_3$): 195.2, 167.0, 160.2, 133.4, 61.4 (2), 37.0 (2), 31.7 (2), 22.3 (3), 21.8 (2), 14.3 (3);

All data agrees with that previously reported by Funk.[93]



261

Ethyl 7-methyl-1, 4-dioxaspiro[4.5]dec-7-ene-6-carboxylate 261

Following a modified procedure of Kelly,[90] ethyl 2- methyl-6-oxocyclohex-1-ene-1-carboxylate **234** (1 g, 5.49 mmol), ethylene glycol (0.61 mL, 0.011 mol) and pTsOH (105 mg, 0.055 mmol) were refluxed in toluene (25 mL) overnight, collecting water using Dean-Stark apparatus. The reaction mixture was concentrated *in vacuo* and diluted with Et_2O (50 mL). The solution was washed with aq. $NaHCO_3$ (3 x 50 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified using flash column chromatography eluting with 20% Et_2O - petrol and gradually increasing polarity to 50% Et_2O-petrol to yield ketal **261** (596 mg, 2.64 mmol, 48%) as a colourless oil. $R_f = 0.81$ (30% EtOAc-petrol);

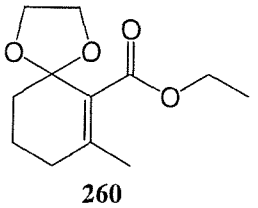
ν_{max} (cm^{-1}): 2988, 2887, 1733, 1138, 746;

δ_H (400 MHz, $CDCl_3$): 5.60 (1H, br s, =CH), 4.22 (2H, q, J = 7 Hz, CH_2CH_3), 4.05-3.96 (4H, m, $O(CH_2)_2O$), 3.05 (1H, s, COCH), 2.31-2.30 (2H, m, $CHCH_2$), 1.70 (3H, s, CCH_3), 1.61-1.60 (2H, m, CH_2), 1.31 (3H, t, J = 7 Hz, CH_2CH_3);

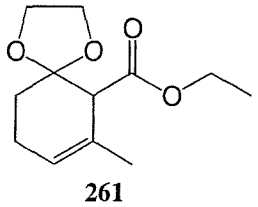
δ_C (100 MHz, $CDCl_3$): 171.5, 129.7, 124.5 (1), 108.6, 65.2 (2), 64.8 (2), 61.2 (2), 55.9 (1), 28.1 (2), 24.1 (2), 22.5 (3), 14.6 (3);

$^m/z$ (Cl+): 227 $[M + H]^+$ (100%);

HRMS, $C_{12}H_{18}O_4$ requires 226.1205, found 226.1206.



260



261

Ethyl 7-methyl-1, 4-dioxaspiro[4.5]dec-6-ene-6-carboxylate 260 and ethyl 7-methyl-1, 4-dioxaspiro[4.5]dec-7-ene-6-carboxylate 261

Following a modified procedure of De Waard,[95] ethyl 2- methyl-6-oxocyclohex-1-ene-1-carboxylate **234** (8.7 g, 0.048 mol), ethylene glycol (122 mL) and fumaric acid (461 mg, 0.40 mmol) were refluxed in toluene (75 mL) overnight, collecting water using Dean-Stark apparatus. The reaction mixture was concentrated

in vacuo and diluted with Et_2O (100 mL). The solution was washed with aq. $NaHCO_3$ (3 x 100 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified using column chromatography eluting with 20% Et_2O -petrol and gradually increasing polarity to 50% Et_2O-petrol to yield ketal **260** (3.9 g, 0.017 mol, 36%) as a colourless oil and ketal **261** (1.5g, 0.007 mol, 14%) as a colourless oil.

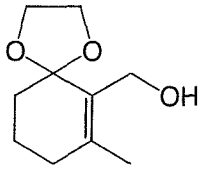
Data for product **260**, $R_f = 0.67$ (30% EtOAc-petrol);

ν_{max} (cm^{-1}): 2988, 2948, 2866, 1728, 1661, 1072, 741;

δ_H (400 MHz, $CDCl_3$): 4.29 (2H, q, $J = 7$ Hz, CH_2CH_3), 4.13-3.97 (4H, m, $O(CH_2)_2O$), 2.14 (2H, t, $J = 6$ Hz, CCH_2), 1.92-1.76 (4H, m, CH_2CH_2), 1.86 (3H, s, CCH_3), 1.36 (3H, t, $J = 7$ Hz, CH_2CH_3);

δ_C (100 MHz, $CDCl_3$): 168.5, 145.3, 129.0, 107.2, 65.6 (2), 60.8 (2), 34.1 (2), 31.7 (2), 21.5 (3), 20.0 (2), 14.7 (3);

All data for product **261** agrees with that reported above.



262

(7-methyl-1, 4-dioxaspiro[4.5]dec-6-en-6-yl)methanol 262

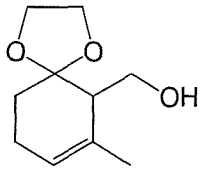
Following a modified method of Ferris,[69] ethyl 7-methyl-1, 4-dioxaspiro[4.5]dec-6-ene-6-carboxylate **260** (3.90 g, 0.017 mol) in THF (10 mL) was added dropwise to a suspension of $LiAlH_4$ (1.31 g, 0.035 mol) in THF (50 mL) at 0°C and allowed to warm to room temperature over 1 h, and the reaction mixture was left to stir overnight. Et_2O (50 mL) was added to the reaction mixture and NaOH (4 M) was added until only white precipitate was formed. The reaction mixture was filtered and the residue was washed with Et_2O and the combined organic layers were concentrated *in vacuo*. The crude material was purified using flash column chromatography eluting with petrol and gradually increasing the polarity to 50% EtOAc-petrol to give alcohol **262** (1.20 g, 6.52 mmol, 38%) as a colourless oil, $R_f = 0.24$ (40% EtOAc-petrol);

ν_{max} (cm^{-1}): 3461, 2937, 2876, 2821, 1667, 1051, 731;

δ_H (300 MHz, $CDCl_3$): 4.10 (2H, m, CH_2OH), 3.95-3.88 (4H, m, $O(CH_2)_2O$), 2.23 (1H, br s, OH), 1.93 (2H, t, J = 6 Hz, $=CCH_2$), 1.70 (3H, s, CH_3), 1.63-1.53 (4H, m, CH_2CH_2);

δ_C (75 MHz, $CDCl_3$): 142.2, 130.4, 109.6, 65.1 (2), 58.2 (2), 33.3 (2), 32.3 (2), 20.5 (2), 19.8 (3);

$^m/z$ (CI+): 141 $[M + H - CH_2CH_2O]^+$ (100%).



264

(7-methyl-1, 4-dioxaspiro[4.5]dec-7-en-6-yl)methanol 264

Following a modified method of Ferris,[69] ethyl 7-methyl-1, 4-dioxaspiro[4.5]dec-7-ene-6-carboxylate **261** (1.5 g, 0.007 mol) in THF (5 mL) was added dropwise to a suspension of $LiAlH_4$ (0.51 g, 0.013 mol) in THF (25 mL) at 0°C and allowed to warm to room temperature over 1 h, and was left to stir overnight. Et_2O (25 mL) was added to the reaction mixture and NaOH (4 M) was added until a white precipitate was formed. The reaction mixture was filtered and the residue was washed with Et_2O and the combined organic layers were concentrated *in vacuo*. The crude material was purified using column chromatography eluting with petrol and gradually increasing the polarity to 50% EtOAc-petrol to give alcohol **264** (1.08 g, 0.006 mol, 84%) as a colourless oil, R_f = 0.30 (40% EtOAc-petrol);

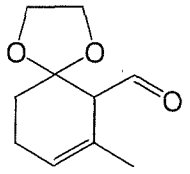
ν_{max} (cm^{-1}): 3522, 2958, 2882, 1667, 1107, 741;

δ_H (400 MHz, $CDCl_3$): 5.40 (1H, s, C=CH), 4.00-3.90 (4H, m, $O(CH_2)_2O$), 3.74 (1H, dd, J = 3, 12 Hz, CH_AH_BOH), 3.57 (1H, dd, J = 8, 12 Hz, CH_ACH_BOH), 3.20 (1H, br s, OH), 2.21 (1H, br d, J = 8 Hz, CHCO), 2.13-2.05 (2H, m, $CHCH_2$), 1.80 (1H, dt, J = 13, 8 Hz, CCH_AH_B), 1.68 (3H, s, Me), 1.55 (1H, m, CCH_AH_B);

δ_C (100 MHz, $CDCl_3$): 131.8, 123.7 (1), 111.9, 65.1 (2), 64.6 (2), 62.9 (2), 50.4 (1), 27.7 (2), 24.3 (2), 22.3 (3);

$^m/z$ (CI+): 185 $[M + H]^+$ (100%);

HRMS: $C_{10}H_{16}O_3$ $[M]^+$ requires 184.1099, found 184.1109.



265

7-methyl-1, 4-dioxaspiro[4.5]dec-7-ene-6-carbaldehyde 265

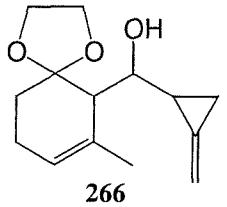
Following the method of Swern,[70] oxalyl chloride (56 µl, 0.650 mmol) in DCM (5 mL) was cooled to -70°C and stirred vigorously. DMSO (96 µl, 1.360 mmol) in DCM (1 mL) was added at < -50°C and the reaction was stirred for 2 min. (7-Methyl-1, 4-dioxaspiro[4.5]dec-7-en-6-yl)methanol **264** (100 mg, 0.543 mmol) in DCM (1 mL) was added over 5 min at < -50°C and the reaction was stirred for a further 15 min. TEA (0.380 mL, 2.72 mmol) was added at < -50°C and the reaction mixture was warmed to room temperature. Water (30 mL) was added and the reaction mixture was washed with DCM (5 x 5 mL) and combined organic layers were concentrated *in vacuo*. The crude material was purified using flash column chromatography, (prewashed with 1% TEA in DCM), eluting with petrol and gradually increasing polarity to 30 % EtOAc-petrol to yield aldehyde **265** (97 mg, 0.53 mmol, 98%) as a colourless oil, $R_f = 0.83$ (30% EtOAc-petrol);

ν_{max} (cm^{-1}): 2958, 2902, 1717, 1672, 1026, 736;

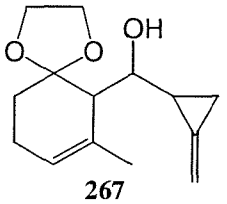
δ_H (300 MHz, $CDCl_3$): 9.47 (1H, d, $J = 4$ Hz, CHO), 5.75 (1H, s with fine splitting, C=CH), 4.03-3.96 (4H, m, $O(CH_2)_2O$), 2.95 (1H, br s, C*H*CHO), 2.34-2.24 (2H, m, $=CCH_2$), 1.92-1.83 (2H, m, CCH_2), 1.65 (3H, br s, CH_3);

δ_C (75 MHz, $CDCl_3$): 198.7 (1), 127.4, 125.6 (1), 107.6, 65.4 (2), 64.9 (2), 62.1 (1), 29.6 (2), 24.2 (2), 22.1 (3);

The aldehyde was unstable and was used directly into the next reaction.



266



267

(7-methyl-1,4 –dioxaspiro[4.5] dec-7-en-6-yl)(2-methylidenecyclopropyl) methanol 266 and 267

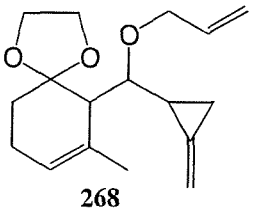
^{n}BuLi (2.24 M, 4.8 mL, 0.011 mol) was added to methylenecyclopropane **1** (4.8 mL, 0.011 mol) in THF (10 mL) at –40 °C. The reaction was allowed to rise to 0

°C over 30 min and held at 0 °C for a further 30 min. The reaction was allowed to reach room temperature for 15 min before cooling to –78 °C. 7-Methyl-1, 4-dioxaspiro[4.5]dec-7-ene-6-carbaldehyde **265** (1.9 g, 0.01 mol) in THF (5 mL) at –78 °C was added *via* cannula to the methylenecyclopropane anion. The reaction mixture was allowed to warm to room temperature overnight, quenched with aq. NH_4Cl, extracted with Et_2O (5 x 10 mL) and the organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was separated using flash column chromatography, eluting with petrol and gradually increasing polarity to 30% Et_2O-petrol to yield isomer **266** (1.06 g, 4.50 mmol, 45%) and isomer **267** (708 mg, 3.00 mmol, 30%), both as light yellow oils.

Data for diastereoisomer **266** R_f = 0.49 (30% EtOAc-petrol);

Data for diastereoisomer **267** R_f = 0.33 (30% EtOAc-petrol);

Neither diastereoisomer could be obtained free of impurities by flash column chromatography and so were used directly in the next reaction



268

6-[(allyloxy)(2-methylidenecyclopropyl)methyl]-7-methyl-1,4-dioxaspiro[4.5]dec-7-ene 268

To a suspension of sodium hydride (64.8 mg, 1.62 mmol, 60% dispersion in oil) in DMF (2.5 mL) under argon, was added (7-methyl-1,4 –dioxaspiro[4.5] dec-7-en-6-yl)(2-methylidenecyclopropyl) methanol **266** (255 mg, 1.08 mmol) in DMF (1 mL) at 0°C. The reaction was stirred at room temperature for 1 h. A yellow solution occurred. Allyl bromide (0.15 mL, 1.73 mmol) was added at 0°C and the reaction was stirred at room temperature overnight. Water was added and extracted with DCM (4 x 5 mL). The combined DCM layers were washed with water (3 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography eluting with petrol and gradually increasing the polarity to 30% EtOAc-petrol to give ketal **268** (217 mg, 0.788 mmol, 73%) as a yellow oil, R_f = 0.89 (30% EtOAc-petrol);

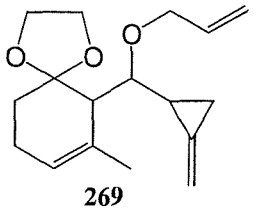
ν_{max} (cm^{-1}): 3020, 2924, 2894, 1439, 1084, 993, 916;

δ_H (300 MHz, $CDCl_3$): 5.91 (1H, ddt, J = 17, 10, 5 Hz, CH_2=C*H*), 5.59 (1H, br s, =CH), 5.45 (2H, s with fine splittings, methylenecyclopropyl =CH_2), 5.25 (1H, dq, J = 17, 2 Hz, allyl =C$H_A$$H_B$), 5.11 (1H, dq, J = 10, 2 Hz, allyl =$CH_A$$H_B$), 4.28 (1H, ddt, J = 13, 5, 2 Hz, OC$H_A$$H_B$), 4.00-3.91 (5H, m, O($CH_2$)$_2$O, $OCH_A$$H_B$), 3.13 (1H, dd, J = 9, 2 Hz, CHO), 2.40-1.52 (6H, m, cyclopropyl C*H*, (CH_2)$_2$, C*H*CHOCH_2), 1.89 (3H, br s, CH_3), 1.30 (1H, tt, J = 9, 2 Hz, cyclopropyl CH), 0.89 (1H, m, cyclopropyl CH);

δ_C (75 MHz, $CDCl_3$): 136.0, 135.6 (1), 131.6, 123.6 (1), 115.9 (2), 110.3, 104.0 (2), 80.8 (1), 70.3 (2), 64.6 (2), 64.3 (2), 53.1 (1), 27.7 (2), 25.0 (3), 24.4 (2), 21.2 (1), 7.0 (2);

^{m}/z (CI+): 277 $[M + H]^+$ (34%), 219 $[M - CH_2=CHCH_2O]^+$ (72%);

HRMS: $C_{17}H_{24}O_3$ $[M]^+$ requires 276.1725, found 276.1721.



269

6-[(allyloxy)(2-methylidenecyclopropyl)methyl]-7-methyl-1,4-dioxaspiro[4.5]dec-7-ene 269

To a suspension of sodium hydride (68.6 mg, 1.72 mmol, 60% dispersion in oil) in DMF (2.5 mL) under argon, was added (7-methyl-1,4 –dioxaspiro[4.5] dec-7-en-6-yl)(2-methylidenecyclopropyl) methanol **267** (270 mg, 1.14 mmol) in DMF (1 mL) at 0°C. The reaction was stirred at room temperature for 1 h. A yellow solution occurred. Allyl bromide (0.16 mL, 1.83 mmol) was added at 0°C and the reaction was stirred at room temperature overnight. Water was added and extracted with DCM (4 x 5 mL), DCM layers were washed with water (3 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography eluting with petrol and gradually increasing the polarity to 30% EtOAc-petrol to give ketal **269** (220 mg, 0.798 mmol, 70%) as a yellow oil, R_f = 0.85 (30% EtOAc-petrol);

ν_{max} (cm^{-1}): 3023, 2924, 2896, 1444, 1089, 926;

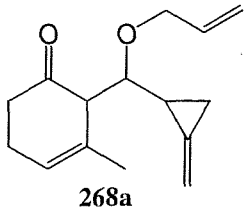
δ_H (300 MHz, $CDCl_3$): 5.92 (1H, ddt, J = 17, 10, 5 Hz, CH_2=C*H*), 5.61 (1H, br s, =CH), 5.48 (2H, q, J = 2 Hz, methylenecyclopropyl =CH_2), 5.25 (1H, dq, J = 17, 2 Hz, allyl =C$H_A$$H_B$), 5.12 (1H, dq, J = 10, 2 Hz, allyl =$CH_A$$H_B$), 4.33 (1H, ddt, J = 13, 5, 2

Hz, OCH_AH$_B$), 4.05 (1H, ddt, J = 13, 5, 2 Hz, OCH$_A$$H_B$), 3.98-3.88 (4H, m, O(CH$_2$)$_2$O), 3.26 (1H, dd, J = 9, 1 Hz, CHOCH$_2$), 2.24-1.55 (6H, m, cyclopropyl CH, (CH_2)$_2$, CHCHOCH$_2$), 1.89 (3H, br s, CH$_3$), 1.50 (1H, tt, J = 9, 2 Hz, cyclopropyl CH), 1.10 (1H, m, cyclopropyl CH);

δ_C (75 MHz, CDCl$_3$): 135.7 (1), 132.2, 131.1, 124.2 (1), 116.1 (2), 110.2, 104.7 (2), 80.8 (1), 70.7 (2), 64.5 (2), 64.2 (2), 53.1 (1), 28.1 (2), 25.0 (3), 24.3 (2), 20.3 (1), 12.0 (2);

^{m}/z (CI+): 277 [M + H]$^+$ (20%), 219 [M - CH$_2$=CHCH$_2$O]$^+$ (100%);

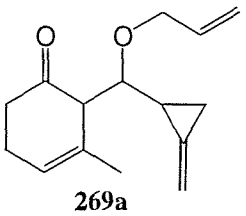
HRMS could not be obtained on this compound.



268a

2-[(allyloxy)(2-methylidenecyclopropyl)methyl]-3-methylcyclohex-3-en-1-one 268a

6-[(Allyloxy)(2-methylidenecyclopropyl)methyl]-7-methyl-1,4-dioxaspiro[4.5]dec-7-ene **268** (80 mg, 0.29 mmol) in acetone/water (10 mL/1 mL) was stirred with pTsOH (66.2 mg, 0.35 mmol) overnight. The reaction mixture was concentrated *in vacuo* and diluted with Et$_2$O (10 mL). The solution was washed with aq. NaHCO$_3$ (10 mL) and the aqueous layer extracted with Et$_2$O (5 x 10 mL). Organic layers were combined, dried over MgSO$_4$ and concentrated *in vacuo*. The crude material was purified using flash column chromatography eluting with petrol and gradually increasing the polarity to 25% EtOAc-petrol to yield ketone **268a** (70 mg, 0.30 mmol, 104% crude) as a colourless oil, R$_f$ = 0.89 (30% EtOAc-petrol);

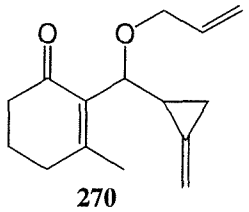


269a

2-[(allyloxy)(2-methylidenecyclopropyl)methyl]-3-methylcyclohex-3-en-1-one 269a

6-[(Allyloxy)(2-methylidenecyclopropyl)methyl]-7-methyl-1,4-dioxaspiro[4.5]dec-7-ene **269** (65 mg, 0.24 mmol) in acetone/water (10 mL/1 mL) was stirred with pTsOH (53.8 mg, 0.29 mmol) overnight. The reaction mixture was concentrated *in vacuo* and diluted with Et_2O (10 mL). The solution was washed with aq. $NaHCO_3$ (10 mL) and the aqueous layer extracted with Et_2O (5 x 10 mL). Organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified using column chromatography eluting with petrol and gradually increasing the polarity to 25% EtOAc-petrol to yield deprotected ketone **269a** (60 mg, 0.259 mmol, 108% crude) as a colourless oil, $R_f = 0.85$ (30% EtOAc-petrol);

Allyl ethers **268a** and **269a** were used directly into the next reaction without further purification.



270

2-[(allyloxy)(2-methylidenecyclopropyl)methyl]-3-methylcyclohex-2-en-1-one 270

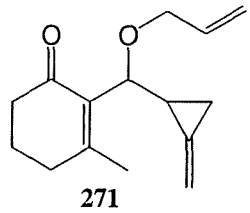
2-[(Allyloxy)(2-methylidenecyclopropyl)methyl]-3-methylcyclohex-3-en-1-one **268a** (70 mg, 0.30 mmol) in MeOH (0.5 mL) was added to NaOMe (0.7 mg in 1 mL MeOH) at 0°C and stirred for 30 min. The reaction mixture was allowed to warm to room temperature over 30 min, quenched with aq. NH_4Cl, extracted with Et_2O (5 x 2 mL) and the organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified using flash column chromatography eluting with petrol and gradually increasing the polarity to 15% EtOAc-petrol to yield allyl ether **270** (59 mg, 0.255 mmol, 85%) as a colourless oil, $R_f = 0.79$ (30% EtOAc-petrol); ν_{max} (cm^{-1}): 3071, 2992, 2924, 2869, 1656, 1626, 1074, 986, 912, 879;

δ_H (400 MHz, $CDCl_3$): 5.82 (1H, ddt, *J* = 17, 10, 5 Hz, CH_2=C*H*), 5.43 (1H, m, methylenecyclopropane =C$H_A$$H_B$), 5.35 (1H, s with fine splittings, methylenecyclopropane =$CH_A$$H_B$), 5.16 (1H, dq, *J* = 17, 2 Hz, allyl =C$H_A$$H_B$), 5.05 (1H, dq, *J* = 10, 2 Hz, allyl =$CH_A$$H_B$), 4.24 (1H, d, *J* = 9 Hz, C*H*OCH_2), 3.88 (1H, ddt, *J* = 13, 5, 2 Hz, OC$H_A$$H_B$), 3.80 (1H, ddt, *J* = 13, 5, 2 Hz, $OCH_A$$H_B$), 2.32 (4H, t, *J* = 6 Hz, $(CH_2)_2$), 2.11 (3H, s, CH_3), 1.89 (2H, quintet, *J* = 6 Hz, CH_2), 1.80 (1H, m, cyclopropyl CH), 1.06 (1H, tt, *J* = 9, 2 Hz, cyclopropyl CH), 0.89 (1H, m, cyclopropyl CH);

δ_C (75 MHz, $CDCl_3$): 197.4, 158.3, 134.2 (1), 133.5, 133.5, 115.4 (2), 103.0 (2), 75.1 (1), 68.8 (2), 36.8 (2), 33.0 (2), 21.2 (2), 20.7 (3), 18.4 (1), 5.8 (2);

^{m}/z (CI+): 175 [M - CH_2=$CHCH_2O$]$^+$ (100%);

HRMS could not be obtained for this compound.



271

2-[(allyloxy)(2-methylidenecyclopropyl)methyl]-3-methylcyclohex-2-en-1-one 271

2-[(Allyloxy)(2-methylidenecyclopropyl)methyl]-3-methylcyclohex-3-en-1-one **269a** (60 mg, 0.26 mmol) in MeOH (0.5 mL) was added to NaOMe (0.6 mg in 1 mL MeOH) at 0°C and stirred for 30 min. The reaction mixture was allowed to warm to room temperature over 30 min, quenched with aq. NH_4Cl, extracted with Et_2O (5 x 2 mL) and the organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified using flash column chromatography eluting with petrol and gradually increasing the polarity to 15% EtOAc-petrol to yield allyl ether **271** (47 mg, 0.203 mmol, 78%) as a colourless oil, R_f = 0.72 (30% EtOAc-petrol);

ν_{max} (cm^{-1}): 3076, 2918, 2854, 1651, 1617, 1069, 985, 916, 872;

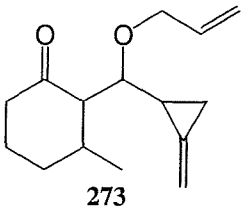
δ_H (400 MHz, $CDCl_3$): 5.82 (1H, ddt, *J* = 17, 10, 5 Hz, CH_2=C*H*), 5.26 (1H, br s, methylenecyclopropane =C$H_A$$H_B$), 5.16 (1H, dq, *J* = 17, 2 Hz, allyl =C$H_A$$H_B$), 5.10 (1H, s with fine splittings, methylenecyclopropane =$CH_A$$H_B$), 5.06 (1H, dq, *J* = 10, 2 Hz, allyl =$CH_A$$H_B$), 4.19 (1H, d, *J* = 8 Hz, C*H*OCH_2), 3.83 (2H, br dt, *J* = 6, 2 Hz, $CHOCH_2$), 2.32 (4H, t, *J* = 6 Hz, $COCH_2$, CCH_2), 2.10 (3H, s, CH_3), 1.92 (1H, m,

cyclopropyl CH), 1.89 (2H, quintet, J = 6 Hz, CH_2), 1.06 (1H, tt, J = 9, 2 Hz, cyclopropyl CH), 0.89 (1H, m, cyclopropyl CH);

δ_C (75 MHz, $CDCl_3$): 196.8, 158.4, 134.2 (1), 133.4, 131.2, 115.7 (2), 103.0 (2), 74.9 (1), 68.7 (2), 37.0 (2), 32.9 (2), 21.3 (2), 20.7 (3), 18.5 (1), 9.0 (2);

$^m/z$ (CI+): 233 $[M + H]^+$ (5%), 175 $[M - CH_2{=}CHCH_2O]^+$ (100%);

HRMS: $C_{15}H_{21}O_2$ requires 233.1542 found 233.1543.



273

2-[(allyloxy)(2-methylidenecyclopropyl)methyl]-3-methylcyclohexan-1-one 273

Following the procedure by Procter,[71] to a solution of SmI_2 (0.10 M solution in THF, 5 mL, 0.48 mmol) and MeOH (1.5 mL) at 0°C under Ar, was added 2-[(allyloxy)(2-methylidenecyclopropyl)methyl]-3-methylcyclohex-2-en-1-one **270** (45 mg, 0.19 mmol) in THF (5 mL) over 45 min. The reaction mixture was stirred for 2 h at 0°C before the addition of brine (3 mL) and citric acid (64 mg, 0.30 mmol). The aqueous layer was extracted with DCM (5 x 5 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography eluting with petrol and gradually increasing the polarity to EtOAc to give allyl ether **273** (21 mg, 0.09 mmol, 48%) as a colourless oil, R_f = 0.83 (30% EtOAc-petrol);

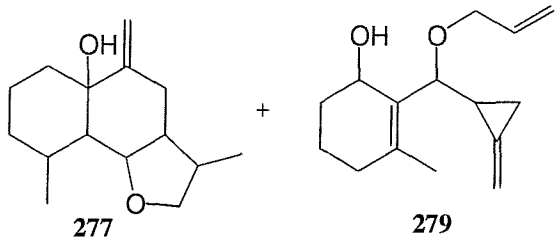
ν_{max} (cm^{-1}): 3068, 2945, 2856, 1700, 1070, 885;

δ_H (400 MHz, $CDCl_3$): 5.82 (1H, ddt, J = 17, 10, 5 Hz, $CH_2{=}CH$), 5.43-5.39 (2H, m, methylenecyclopropane $=CH_2$), 5.19 (1H, dq, J = 17, 2 Hz, allyl $=CH_AH_B$), 5.07 (1H, dq, J = 10, 2 Hz, allyl $=CH_AH_B$), 4.20 (1H, ddt, J = 13, 5, 2 Hz, OCH_AH_B), 3.84 (1H, ddt, J = 13, 5, 2 Hz, OCH_AH_B), 3.21 (1H, dd, J = 9, 4 Hz, $CHOCH_2$), 2.35-2.20 (4H, m, $(CH_2)_2$), 1.92-1.28 (5H, m, CH_2, $CHCH_3$, CHCHO, cyclopropyl CH), 1.24 (1H, tt, J = 9, 2 Hz, cyclopropyl CH), 1.01 (3H, d, J = 6 Hz, CH_3), 0.85 (1H, m, cyclopropyl CH);

δ_C (75 MHz, $CDCl_3$): 174.4, 135.2 (1), 134.2, 116.6 (2), 104.6 (2), 80.7 (1), 70.2 (2), 61.6 (1), 41.5 (2), 34.7 (1), 31.5 (2), 23.8 (2), 20.7 (3), 18.2 (1), 7.1 (2);

$^m/z$ (CI+): 235 $[M + H]^+$ (7%);

HRMS: $C_{15}H_{21}O_2$ $[M - H]^+$ requires 233.1541, found 233.1538.



277 279

3,9-dimethyl-5-methyleneperhydronaphtho[1,2-b]furan-5a-ol 278 and 2-[(allyloxy)(2-methylenecyclopropyl)methyl]-3-methyl-2-cyclohexen-1-ol 279

To a solution of 2-[(allyloxy)(2-methylidenecyclopropyl)methyl]-3-methylcyclohex-2-en-1-one **270** (20 mg, 0.086 mmol) in THF (4 mL) and MeOH (1 mL) at -78°C under argon was added a solution of samarium diiodide (0.05 M solution in THF, 5 mL, 0.22 mmol) *via* cannula over 45 min. The reaction mixture was stirred for 2 h and allowed to warm to room temperature. Brine (3 mL) and citric acid (64 mg, 0.30 mmol) were added. The aqueous layer was then extracted with DCM (5 x 5 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography eluting with petrol and gradually increasing the polarity to EtOAc to give tricycle **277** (1.2 mg, 0.005 mmol, 6%) as a colourless oil and alcohol **279** (2 mg, 0.009 mmol, 10%) as a slightly yellow oil;

Data for tricycle **277**, $R_f = 0.81$ (30% EtOAc-petrol);

ν_{max} (cm^{-1}): 3486, 3094, 2924, 2864, 1651, 1370, 1097;

δ_H (400 MHz, $CDCl_3$, resolution enhanced): 4.90 (1H, br s, $=CH_AH_B$), 4.81 (1H, br s, $=CH_AH_B$), 4.24 (1H, dd, J = 9, 7 Hz, OCH_AH_B), 4.20 (1H, dd, J = 5, 3 Hz, CHO), 3.30 (1H, dd, J = 9, 5 Hz, OCH_AH_B), 2.37 (1H, dd, J = 14, 10 Hz, $=CCH_AH_B$), 2.24 (1H, dd, J = 14, 7 Hz, $=CCH_AH_B$), 2.17-1.20 (9H, m, $CHCH_3$, $CHCH_3$, $CHCHCH_3$, $(CH_2)_3$), 1.15 (1H, dd, J = 11, 3 Hz, $CHCHOCH_2$), 1.06 (3H, d, J = 7 Hz, CH_3), 1.02 (3H, d, J = 7 Hz, CH_3);

$^m/_z$ (CI+): 219 $[M - OH]^+$ (100%);

Data for alcohol **279** $R_f = 0.58$ (30% EtOAc-petrol);

ν_{max} (cm^{-1}): 3422, 3094, 2933, 2864, 1646, 1069, 955;

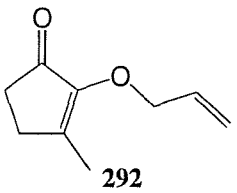
δ_H (400 MHz, $CDCl_3$, resolution enhanced): 5.90 (1H, dddd, J = 17, 11, 6, 5 Hz, $CH_2=CH$), 5.56 (1H, m, methylenecyclopropane $=CH_AH_B$), 5.43 (1H, m, methylenecyclopropane $=CH_AH_B$), 5.26 (1H, ddt, J = 17, 2, 2 Hz, allyl $=CH_AH_B$), 5.15

(1H, ddt, J = 10, 2, 2 Hz, allyl =CH_AH_B), 4.35 (1H, br s, C*H*OH), 3.96 (1H, ddt, J = 13, 5, 2 Hz, OCH_AH$_B$), 3.88 (1H, ddt, J = 13, 6, 2 Hz, OCH$_A$$H_B$), 3.85 (1H, d, J = 8 Hz, C*H*OCH$_2$), 2.10-1.96 (3H, m, CH_2, cyclopropyl C*H*), 1.88-1.77 (2H, m, CH$_2$), 1.69 (3H, s, CH$_3$), 1.68-1.58 (2H, m, CH$_2$), 1.26 (1H, tt, J = 9, 2 Hz, cyclopropyl CH), 0.97 (1H, m, cyclopropyl CH);

δ_C (100 MHz, $CDCl_3$): 135.7 (1), 134.9, 132.4, 116.9 (2), 104.1 (2), 80.2 (1), 77.6, 69.7 (2), 65.1 (1), 32.8 (2), 31.7 (2), 20.7 (3), 20.0 (1), 18.0 (2), 7.6 (2);

$^m/z$ (CI+): 217 [M - OH]$^+$ (8%), 177 [M - CH_2=$CHCH_2O$]$^+$ (38%), 159 [M - H_2O - CH_2=$CHCH_2O$]$^+$ (100%).

EXPERIMENTAL FOR CHAPTER 5



292

2-(allyloxy)-3-methylcyclopent-2-en-1-one 292.

Following a modified procedure by Pirrung,[104] dione **302** (5 g, 0.044 mol), allyl alcohol (3.11 g, 0.054 mol) and pTsOH (424 mg, 0.002 mol) were refluxed in benzene (125 mL) overnight, removing water using molecular sieves in the Soxhlet apparatus. The reaction mixture was cooled and quenched with NaOH (1 M) and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was distilled (82-84°C/10 mm Hg) to give ether **292**, (2.8 g, 0.018 mol, 42%) as a yellow oil, $R_f = 0.63$ (30% EtOAc-petrol);

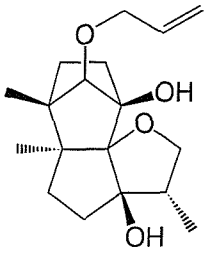
ν_{max} (cm^{-1}): 3076, 2978, 2918, 2864, 1691, 1631, 1390, 990, 926;

δ_H (400 MHz, $CDCl_3$): 5.97 (1H, ddt, J = 17, 10, 6 Hz, =CH), 5.32 (1H, dq, J = 17, 2 Hz, $=CH_AH_B$), 5.21 (1H, dq, J = 10, 1 Hz, $=CH_AH_B$), 4.70 (2H, dt, J = 6, 1 Hz, OCH_2), 2.48-2.44 (2H, m, CH_2), 2.40-2.36 (2H, m, CH_2), 2.02 (3H, s, CH_3);

δ_C (100 MHz, $CDCl_3$): 208.2, 155.9, 152.0, 134.5 (1), 118.1 (2), 71.2 (2), 33.3 (2), 27.6 (2), 15.3 (3);

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

All data agrees with that previously reported by Ponaras.[115]



303

rac-(1R, 5R, 6S, 9R, 10R)-13-(allyloxy)-5,9,10-trimethyl-3-oxatetracyclo [8.2.1.$0^{2,6}$.$0^{2,9}$]tridecane-1,6-diol 303

Following the procedure by Procter,[71] to a solution of SmI_2 (0.26 M solution in THF, 10 mL, 2.62 mmol) and MeOH (2 mL) at -78°C under Ar, was added 2-(allyloxy)-3-methylcyclopent-2-en-1-one **292** (100 mg, 0.658 mmol) in THF (5 mL)

over 45 min. The reaction mixture was then stirred for 2 h at 0°C before the addition of brine (3 mL) and citric acid (128 mg, 0.61 mmol). The aqueous layer was then extracted with DCM (5 x 10 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography eluting with petrol and gradually increasing the polarity to EtOAc to give diol **303** (67 mg, 0.218 mmol, 67%) as a white solid, $R_f = 0.56$ (30% EtOAc-petrol);

Melting point: 116-118°C (Recrystallised from EtOAc-petrol);

ν_{max} (cm^{-1}): 3362, 3052, 2953, 2869, 1464, 1266, 1099, 936;

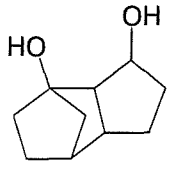
δ_H (400 MHz, $CDCl_3$): 5.86 (1H, ddt, J = 17, 11, 5 Hz, =CH), 5.24 (1H, dq, J = 17, 2 Hz, =CH_AH$_B$), 5.10 (1H, dq, J = 10, 2 Hz, =CH$_A$$H_B$), 4.14 (2H, dt, J = 17, 2 Hz, OCH_2), 3.89 (1H, dd, J = 9, 7 Hz, OCH_AH$_B$CHCH$_3$), 3.82 (1H, s, CHOCH$_2$), 3.11 (1H, dd, J = 11, 9 Hz, OCH$_A$$H_B$CHCH$_3$), 2.10 (1H, m, C$HCH_3$), 1.94 (1H, m, C$^1H_AH_B$), 1.83 (1H, dt, J = 7, 13 Hz, C^2H_AH$_B$), 1.60-1.27 (6H, m, C^{1}H$_A$$H_B$, C^{2}H$_A$$H_B$, ($CH_2$)$_2$), 0.87 (3H, d, J = 7 Hz, CH_3), 0.82 (3H, s, CH_3), 0.71 (3H, s, CH_3);

δ_C (100 MHz, $CDCl_3$): 136.1 (1), 116.8 (2), 94.5, 93.4, 87.5, 84.8 (1), 72.5 (2), 72.2 (2), 52.5, 47.2, 45.1 (1), 37.0 (2), 30.1 (2), 29.0 (2), 27.6 (2), 15.0 (3), 14.5 (3), 9.2 (3);

$^m/_z$ (CI+): 309 $[M + H]^+$ (18%), 291 $[M - OH]^+$ (62%), 233 $[M - CH_2{=}CHCH_2O]^+$ (100%);

Microanalysis: Found C, 69.96; H, 9.38. $C_{18}H_{28}O_4$ requires C, 70.10; H, 9.15%;

Stereochemistry was confirmed by X-ray crystallography.



343

Tricyclo[5.2.1.0^{2,6}]decane-1,3-diol 343

Following the procedure by Procter,[71] to a solution of SmI_2 (0.5 M solution in THF, 10 mL, 4.88 mmol) and MeOH (2 mL) at 0°C under Ar, was added cyclopentenone **320** (100 mg, 1.218 mmol) in THF (5 mL) over 45 min. The reaction mixture was stirred for 2 h at 0°C before the addition of brine (3 mL) and citric acid (128 mg, 0.61 mmol). The aqueous layer was then extracted with DCM (5 x 10 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*.

The crude reaction mixture was purified by flash column chromatography eluting with petrol and gradually increasing the polarity to EtOAc to give diol **343** (72 mg, 0.423 mmol, 71%) as a colourless oil, $R_f = 0.25$ (30% EtOAc-petrol);

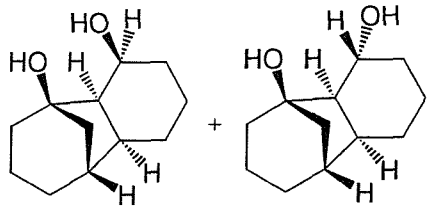
ν_{max} (cm^{-1}): 3328, 2943, 2864, 1459, 1306, 1109;

δ_H (400 MHz, $CDCl_3$): 4.50 (1H, t, $J = 5$ Hz, C*H*OH), 3.32 (1H, s, OH), 2.62 (1H, s, OH), 2.01 (1H, q, $J = 9$ Hz, C*H*CHCOH), 1.92 (1H, dd, $J = 6, 9$ Hz, C*H*COH), 1.87 (1H, dq, $J = 9, 2$ Hz, CH_AH_B), 1.86-1.19 (9H, m, 3 x C*H*, 3 x CH_2), 1.16 (1H, dq, $J = 9$, 2 Hz, CH_AH_B);

δ_C (100 MHz, $CDCl_3$): 85.0, 76.5 (1), 52.8 (1), 50.4 (1), 40.2 (2), 37.0 (1), 36.8 (2), 36.2 (2), 29.8 (2), 29.7 (2);

$^m/z$ (CI+ at T = 150K): 169 $[M + H]^+$ (2%);

HRMS: $C_{10}H_{15}O_2$ $[M-H]^+$ requires 167.1072 found 167.1078, $C_{10}H_{15}O$ $[M - OH]^+$ requires 151.1122 found 151.1123.



334 **335**

rac-(1S, 2S, 3R, 7R, 8R)Tricyclo[6.3.1.$0^{2,7}$]dodecane-1,3-diol 334 and rac-(1S, 2S, 3S, 7R, 8R)Tricyclo[6.3.1.$0^{2,7}$]dodecane-1,3-diol 335.

Following the procedure by Procter,[71] to a solution of SmI_2 (0.5 M solution in THF, 10 mL, 4.17 mmol) and MeOH (2 mL) at 0°C under Ar, was added cyclohexenone **290** (100 mg, 1.042 mmol) in THF (5 mL) over 45 min. The reaction mixture was stirred for 2 h at 0°C before the addition of brine (3 mL) and citric acid (128 mg, 0.61 mmol). The aqueous layer was then extracted with DCM (5 x 10 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography eluting with petrol and gradually increasing the polarity to EtOAc to give diol **334** (55 mg, 0.281 mmol, 54%) as a white solid and diol **335** (26 mg, 0.133 mmol, 25%) as a pale yellow solid,

Data for tricycle **334** $R_f = 0.36$ (30% EtOAc-petrol);

Melting point: 101-103°C (Recrystallised from EtOAc-petrol);

ν_{max} (cm^{-1}): 3362, 2924, 2859, 1454, 1331, 1109;

δ_H (400 MHz, $CDCl_3$): 4.10 (1H, br s, C*H*OH), 2.68 (1H, d, *J* = 13 Hz, CHO*H*), 2.13 (1H, m, OH), 1.76-1.17 (16H, m, 6 x CH_2, 3 x C*H*, CH_AH$_B$), 1.12 (1H, d, *J* = 10 Hz, CH$_A$*H*$_B$);

δ_C (100 MHz, $CDCl_3$): 83.2, 69.4 (1), 49.2 (1), 45.5 (2), 43.2 (1), 42.7 (2), 41.9 (1), 32.8 (2), 28.1 (2), 26.6 (2), 22.3 (2), 19.2 (2);

$^m/z$ (CI+): 179 $[M - OH]^+$ (100%);

Microanalysis: Found C, 73.39; H, 10.39. $C_{12}H_{20}O_2$ requires C, 73.43; H, 10.27%;

Stereochemistry was confirmed by X-ray crystallography.

Data for tricycle **335** R_f = 0.19 (30% EtOAc-petrol);

Melting point: 110-112°C (Recrystallised from EtOAc-petrol);

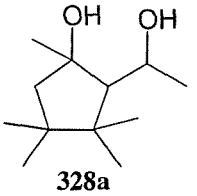
ν_{max} (cm^{-1}): 3343, 2943, 2869, 1464, 1356, 1133;

δ_H (400 MHz, $CDCl_3$): 3.98 (1H, dt, *J* = 5, 12 Hz, C*H*OH), 3.50 (1H, s, CHO*H*), 2.45 (1H, s, OH), 1.96-1.15 (17H, m, 7 x CH_2, 3 x C*H*);

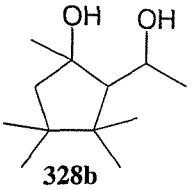
δ_C (100 MHz, $CDCl_3$): 82.0, 67.5 (1), 52.0 (1), 42.7 (1), 42.3 (2), 42.2 (2), 41.0 (1), 31.0 (2), 28.1 (2), 25.3 (2), 20.5 (2), 19.8 (2);

$^m/z$ (CI+): 197 $[M + H]^+$ (48%), 179 $[M - OH]^+$ (100%);

Microanalysis: Found C, 73.11; H, 10.39. $C_{12}H_{20}O_2$ requires C, 73.43; H, 10.27%.



328a



328b

2-(1-hydroxyethyl)-1,3,3,4,4-pentamethyl-1-cyclopentanols 328a and 328b

Following the procedure by Procter,[71] to a solution of SmI_2 (0.41 M solution in THF, 10 mL, 4.08 mmol) and MeOH (2 mL) at 0°C under Ar, was added **314** (100 mg, 1.020 mmol) in THF (5 mL) over 45 min. The reaction mixture was stirred for 2 h at 0°C before the addition of brine (3 mL) and citric acid (128 mg, 0.61 mmol). The aqueous layer was then extracted with DCM (5 x 10 mL), and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography eluting with petrol and

gradually increasing the polarity to EtOAc to give product **328a** (46mg, 0.230 mmol, 45%) as a colourless oil and product **328b** (44mg, 0.220 mmol, 43%)

Data for compound **328a,** R_f = 0.29 (30% EtOAc-petrol);

ν_{max} (cm^{-1}): 3313, 2698, 2943, 2874, 1365, 1168, 936, 887;

δ_H (400 MHz, $CDCl_3$): 4.08 (1H, quintet, *J* = 6 Hz, C*H*OH), 2.68 (1H, br s, OH), 2.50 (1H, br s, OH), 1.92 (1H, d, *J* = 14 Hz, C*H*CHOH), 1.58 (1H, d, *J* = 3 Hz, CH_AH_B), 1.55 (1H, d, *J* = 3 Hz, CH_AH_B), 1.42 (3H, s, CH_3COH), 1.26 (3H, d, *J* = 6Hz, CH_3CHOH), 0.84 (3H, s, CH_3), 0.82 (3H, s, CH_3), 0.79 (3H, s, CH_3), 0.77 (3H, s, CH_3);

δ_C (100 MHz, $CDCl_3$): 78.8, 67.5 (1), 62.3 (1), 56.3 (2), 44.7, 42.3, 34.3 (3), 25.2 (3), 23.7 (3), 23.3 (3), 22.8 (3), 19.4 (3);

$^m/z$ (CI+ at T = 150K): 183 $[M - OH]^+$ (10%);

HRMS: $C_{12}H_{25}O_2$ $[M + H]^+$ requires 201.1855 found 201.1859.

Data for compound **328b,** R_f = 0.25 (30% EtOAc-petrol);

ν_{max} (cm^{-1}):3333, 2963, 2864, 1370, 1158, 941, 862;

δ_H (400 MHz, $CDCl_3$): 4.26 (1H, dq, *J* = 1, 6 Hz, C*H*OH), 1.91 (1H, d, *J* = 14 Hz, CH_AH_B), 1.66 (1H, d, *J* = 14 Hz, CH_AH_B), 1.52 (1H, d, *J* = 6 Hz, C*H*CHOH), 1.32 (3H, s, CH_3COH), 1.30 (3H, br s, CH_3CHOH), 1.08 (3H, s, CH_3), 0.92 (3H, s, CH_3), 0.79 (3H, s, CH_3), 0.78 (3H, s, CH_3);

δ_C (100 MHz, $CDCl_3$): 79.7, 68.2 (1), 61.4 (1), 58.5 (2), 46.9, 42.7, 32.6 (3), 26.1 (3), 25.3 (3), 24.0 (3), 23.5 (3), 21.4 (3);

$^m/z$ (CI+ at T = 150K): 183 $[M - OH]^+$ (45%);

HRMS: $C_{12}H_{25}O_2$ $[M + H]^+$ requires 201.1855 found 201.1843.

REFERENCES

1 M. Lai and L. Liu, *J. Am. Chem. Soc.*, **1991**, *57*, 6344.

2 S. Ramaswamy, K. Prasad and O. Repic, *J. Org. Chem.*, **1992**, *6344*,

3 P. Binger and H. M. Buchi, *Top. Curr. Chem.*, **1987**, *135*, 77.

4 J. T. Gragson, K. W. Greenlee, J. M. Derfer and C. E. Boord, *J. Am. Chem. Soc.*, **1953**, *75*, 3344.

5 M. H. Chang and R. J. Crawford, *Can. J. Chem.*, **1981**, *59*, 2556.

6 J. R. Salaun, J. M. Conia and J. Champion, *Organic Syntheses*, **1977**, *57*, 36.

7 S. Arora and P. Binger, *Synthesis*, **1974**, 801.

8 E. Sternberg and P. Binger, *Tetrahedron Lett.*, **1985**, *26*, 301.

9 E. Thomas, *Tetrahedron Lett.*, **1983**, *24*, 1467.

10 C. Destabel, J. D. Kilburn and J. Knight, *Tetrahedron*, **1994**, *50*, 11267.

11 C. Destabel, J. D. Kilburn and J. Knight, *Tetrahedron Lett.*, **1993**, *34*, 3151.

12 R. T. Lewis, W. B. Motherwell, M. Shipman, A. M. Z. Slawin and D. J. Williams, *Tetrahedron*, **1995**, *51*, 3289.

13 P. Binger, *Angew. Chem., Int. Ed. Engl.*, **1972**, *11*, 433.

14 D. Aue, R. Lorens and G. Helwig, *J. Org. Chem.*, **1979**, *44*, 1202.

15 M. Lautens, Y. Ren and P. H. M. Delanghe, *J. Am. Chem. Soc.*, **1994**, *116*, 8821.

16 D. P. Curran, C. P. Jasperse and T. L. Felvig, *Chem. Rev.*, **1991**, *91*, 1237.

17 B. Giese, *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon Press, **1986**,

18 J. E. Baldwin, *J. Chem. Soc. Chem. Commun.*, **1976**, 734.

19 A. L. Beckwith and C. H. Schiesser, *Tetrahedron*, **1985**, *41*, 3925.

20 P. J. Parsons, D.C. Lathbury and I. Pinto, *J. Chem. Soc. Chem. Commun.*, **1988**, 81.

21 P. J. Parsons, A. D. Borthwick and S. Caddick, *Tetrahedron*, **1992**, *48*, 10655.

22 A. L. Beckwith, C. J. Easton and A. K. Serelis, *J. Chem. Soc. Chem. Commun.*, **1980**, 482.

23 A. J. Beckwith, *Chem. Soc. Rev.*, **1993**, *22*, 143.

24 A. J. Beckwith, I. Blair and G. Phillipou, *J. Am. Chem. Soc.*, **1975**, *96*, 1613.

25 A. J. Beckwith and D. M. Page, *Tetrahedron*, **1999**, *55*, 3246.

26 A. J. Beckwith, *Tetrahedron*, **1981**, 3073.

27 A. J. Beckwith, G. Phillipou and A. K. Serelis, *Tetrahedron Lett.*, **1981**, *22*, 2811.

28 A. J. Beckwith, C. H. Schiesser, A. Wallner and D. H. Roberts, *Tetrahedron Lett.*, **1985**, *26*, 3349.

29 S. Wolff and W. C. Agosta, *J. Chem. Res. Synop.*, **1981**, 78.

30 T. V. RajanBabu, *Acc. Chem. Res.*, **1991**, *24*, 139.

31 D. P. Curran and S. C. Kuo, *J. Am. Chem. Soc.*, **1986**, *108*, 1106.

32 D. P. Curran, S. -B. Ko and H. Josien, *Angew. Chem., Int. Ed. Engl.*, **1995**, *34*, 3683.

33 M. Malacria, *Chem. Rev.*, **1996**, *96*, 289.

34 M. Malacria, M. R. Elliot and A. -L. Dhimane, *J. Am. Chem. Soc.*, **1997**, *119*, 3427.

35 T. Takahashi, S. Tomida, Y. Sakamoto and H. Yamada, *J. Org. Chem.*, **1997**, *62*, 1913.

36 D. P. Curran and D. M. Rakiewics, *Tetrahedron*, **1985**, *41*, 3943.

37 G. Pattenden, S. Handa and W. -S. Li, *J. Chem. Soc. Chem. Commun.*, **1998**, 312.

38 C. Destabel and J. D. Kilburn, *J. Chem. Soc. Chem. Commun.*, **1992**, 596.

39 W. B. Motherwell, R. A. Batey, P. Grice, J. D. Harling and H. S. Rzepa, *J. Chem. Soc. Chem. Commun.*, **1992**, 942.

40 M. Santagostino and J. D. Kilburn, *Tetrahedron Lett.*, **1994**, *35*, 8863.

41 M. Santagostino and J. D. Kilburn, *Tetrahedron Lett.*, **1995**, *36*, 1365.

42 D. J. Penfold, K. Pike, A. Genge, M. Anson, J. Kitteringham and J. D. Kilburn, *Tetrahedron Lett.*, **2000**, *41*, 10347.

43 K. G. Pike, C. Destabel, M. Anson and J. D. Kilburn, *Tetrahedron Lett.*, **1998**, *39*, 5877.

44 D. P. Curran, *Synthesis*, **1988**, 417.

45 D. P. Curran, *Synthesis*, **1988**, 489.

46 H. B. Kagan, J. L. Namy and P. Girard, *J. Am. Chem. Soc.*, **1980**, *102*, 2693.

47 H. B. Kagan, J. L. Namy and J. Souppe, *Tetrahedron Lett.*, **1983**, *24*, 765.

48 D. P. Curran, T. L. Felvig, C. P. Jasperse and M. J. Totleben, *SynLett.*, **1992**,

49 J. Inanaga, K. Otsubo and M. Yamaguchi, *Tetrahedron Lett.*, **1986**, *27*, 5763.

50 G. A. Molander in *Organic Reactions,* ed. L. A. Paquette, J. Wiley & Sons Inc., New York, **1994**, vol. 46, p. 211.

51 G. A. Molander, J. B. Etter and P. W. Zinke, *J. Am. Chem. Soc.*, **1987**, *109*, 453.

52 J. Inanaga, K. Ishikawa and M. Yamaguchi, *Chem. Lett.*, **1987**, 1485.

53 G. A. Molander and J. A. McKie, *J. Org. Chem.*, **1995**, *60*, 872.

54 G. A. Molander and J. A. McKie, *J. Org. Chem.*, **1992**, *57*, 3132.

55 D. P. Curran, T. L. Fevig and R. L. Elliot, *J. Am. Chem. Soc.*, **1988**, *110*, 5064.

56 D. J. Procter, D. Johnston, C. F. McCusker and K. Muir, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 681.

57 G. A. Molander and C. R. Harris, *Chem. Rev.*, **1996**, *96*, 307.

58 G. A. Molander and C. R. Harris, *Tetrahedron*, **1998**, *54*, 3321.

59 W. B. Motherwell and R. A. Batey, *Tetrahedron Lett.*, **1991**, *32*, 6649.

60 W. B. Motherwell, R. A. Batey and J. D. Harling, *Tetrahedron*, **1996**, *52*, 11421.

61 C. Destabel, J. Knight and J. D. Kilburn, *Tetrahedron*, **1994**, *38*, 11289.

62 R. J. Boffey, W. G. Whittingham and J. D. Kilburn, *J. Chem. Soc., Perkin Trans. 1*, **2001**, 487.

63 R. J. Boffey, M. Santagostino, J. D. Kilburn and W. G. Whittingham, *J. Chem. Soc. Chem. Commun.*, **1998**, 1875.

64 R. J. Boffey, W. G. Whittingham and J. D. Kilburn, *Tetrahedron Lett.*, **1999**, *40*, 5625.

65 V. Bargues, G. Blay, B. Garcia, C. L. Garcia and J. R. Pedro, *Tetrahedron*, **1995**, 5609.

66 M. Kito, T. Sakai, K. Yamada, F. Matsuda and H. Shirahama, *SynLett.*, **1993**, 158.

67 R. Köster, S. Arora and P. Binger, *Angew. Chem., Int. Ed. Engl.*, **1969**, *8*, 205.

68 K. F. Albizati, S. R. Hitchcock, F. Perron and V. A. Martin, *Synthesis*, **1990**, 1059.

69 J. P. Ferris and R. W. Trimmer, *J. Org. Chem.*, **1976**, *41*, 13.

70 D. Swern, A. J. Mancuso and S.-L. Huang, *J. Org. Chem.*, **1978**, *43*, 2480.

71 D. Johnston, C. M. McCusker and D. J. Procter, *Tetrahedron Lett.*, **1999**, *40*, 4913.

72 G. E. Keck, C. A. Wager, T. Sell and T. T. Wager, *J. Org. Chem.*, **1999**, *64*, 2172.

73 M. Lautens and Y. Ren, *J. Am. Chem. Soc.*, **1996**, *118*, 9597.

74 P. Rochet, J. -M. Vatèle and J. Goré, *Synthesis*, **1994**, *8*, 795.

75 J. March, *Advanced Organic Chemistry*, 4th ed., Wiley, New York, **1992**, 364.

76 F. C. Watson and J. D. Kilburn, *Tetrahedron Lett.*, **2000**, *41*, 10341.

77 J. F. Sanz and J. A. Marco, *Liebigs. Ann. Chem.*, **1990**, 541.

78 A. F. Barrero, J. E. Oltra and M. Àlvarez, *Tetrahedron Lett.*, **1998**, *39*, 1401.

79 L. Cardona, B. Garcia, M. C. Muñoz, F. I. Navarro and J. R. Pedro, *Recueil*, **1997**, 527.

80 G. Blay, L. Cardona, B. Garcia and J. R. Pedro, *J. Org. Chem.*, **1993**, *58*, 7204.

81 G. Blay, L. Cardona, B. Garcia and J. R. Pedro, *Tetrahedron Lett.*, **1992**, *33*, 5253.

82 E. Piers and K. F. Cheng, *Can. J. Chem.*, **1968**, *46*, 377.

83 A. E. Greene, J. C. Muller and G. Ourisson, *J. Org. Chem.*, **1974**, *39*, 2.

84 E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, **1975**, 2647.

85 K. B. Sharpless, P. H. J. Carlsen, T. Katsuki and V. S. Martin, *J. Org. Chem.*, **1981**, *46*, 3936.

86 K. Mori and H. Mori, *Tetrahedron*, **1985**, *41*, 5487.

87 M. T. Reetz, J. Westermann and S. -H. Kyung, *Chem. Ber.*, **1985**, *118*, 1050.

88 M. T. Reetz, B. Wenderoth, R. Peter, R. Steinbach and J. Westermann, *J. Chem. Soc. Chem. Commun.*, **1980**, 1202.

89 Belmont and L. A. Paquette, *J. Org. Chem.*, **1985**, *50*, 4102.

90 T. R. Kelly, L. Ananthsubramanian, K. Borah, J. W. Gillard, R. N. Goerner, P. F. King, W. G. Trang and J. Vaya, *Tetrahedron*, **1984**, *40*, 4569.

91 H. Corlay, R. T. Lewis, W. B. Motherwell and M. Shipman, *Tetrahedron*, **1995**, *51*, 3303.

92 S. N. Huckin and L. Weiler, *Can. J. Chem.*, **1974**, *52*, 2159.

93 R. L. Funk, J. F. Fitzgerald, T. A. Olmstead, K. S. Para and J. A. Wos, *J. Am. Chem. Soc.*, **1993**, *115*, 8849.

94 C. J. Lee and A. B. DeMilo, *Synth. Comm.*, **1996**, *26*, 153.

95 J. W. De Leeuw, E. R. De Waard, T. Beetz and H. O. Huisman, *Recueil*, **1973**, *92*, 1047.

96 R. Noyori, T. Tsunoda and M. Suzuki, *Tetrahedron Lett.*, **1980**, *21*, 1357.

97 R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **1970**, *35*, 4000.

98 D. Romo, R. M. Rzasa, H. A. Shea, K. Park, J. M. Langenham, L. Sun, A. Akhiezer and J. O. Liu, *J. Am. Chem. Soc.*, **1998**, *47*, 12237.

99 J. Inanaga, S. Sakai, Y. Handa, M. Yamaguchi and Y. Yokoyama, *Chem. Lett.*, **1991**, 2117.

100 J. Inanaga, Y. Handa, T. Tabuchi, K. Otsubo, M. Yamaguchi and T. Hanamoto, *Tetrahedron Lett.*, **1991**, *32*, 6557.

101 Y. Fujita, S. Fukusumi and J. Otera, *Tetrahedron Lett.*, **1997**, *38*, 2121.

102 S. Fukuzawa, A. Nakanishi, T. Fujinami and S. Sakai, *J. Chem. Soc., Perkin Trans. 1*, **1988**, 1669.

103 A. Cabrera, R. Le Lagadec, P. Sharma, J. L. Arias, R. A. Toscano, L. Velasco, T. Gaviño, C. Alvarez and M. Salmón, *J. Chem. Soc., Perkin Trans. 1*, **1998**, 3609.

104 M. C. Pirrung, V. K. Chang and C. V. DeAmicis, *J. Am. Chem. Soc.*, **1989**, *111*, 5824.

105 L. Zhou and Y. Zhang, *Synth. Comm.*, **2000**, *30*, 597.

106 A. Cabrera, N. Roasa, C. Alvarez, P. Sharma, A. Toscano, M. Salmón and J. L. Arias, *Polyhedron*, **1996**, *15*, 2971.

107 D. D. Perin and W. L. F. Armarego, *Purification of Laboratory Chemicals*, 3rd ed., Pergamon Press, **1989**,

108 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, **1978**, *43*, 2923.

109 G. M. Sheldrick, *Acta Cryst.*, **1990**, 467.

110 G. M. Sheldrick, University of Gottingen, Germany, PhD Thesis, **1997**.

111 R. Köster, S. Arora and P. Binger, *Liebigs. Ann. Chem.*, **1973**, 1219.

112 H. Paulsen and U. Maab, *Chem. Ber.*, **1981**, *114*, 346.

113 F. Huet, *Synthesis*, **1985**, 496.

114 B. M. Trost and R. A. Kunz, *J. Am. Chem. Soc.*, **1975**, *97*, 7152.

115 A. A. Ponaras, *J. Org. Chem.*, **1983**, *48*, 3866.

Appendix

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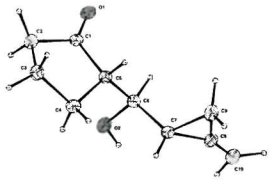
EPSRC National Crystallography Service



160

Table 1. Crystal data and structure refinement.

Identification code	**99SOT010**
Empirical formula	$C_{10}H_{14}O_2$
Formula weight	166.21
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 14.6687(13) Å
	b = 5.2792(4) Å β = 100.41(4)°
	c = 11.8019(17) Å
Volume	898.89(17) Å^3
Z	4
Density (calculated)	1.228 Mg / m^3
Absorption coefficient	0.084 mm^{-1}
$F(000)$	360
Crystal	Colourless Plate
Crystal size	0.40 × 0.20 × 0.02 mm^3
θ range for data collection	2.82 – 24.70°
Index ranges	$-17 \le h \le 17$, $-6 \le k \le 6$, $-13 \le l \le 13$
Reflections collected	11893
Independent reflections	1523 [R_{int} = 0.0957]
Completeness to θ = 24.70°	99.3 %
Max. and min. transmission	0.9983 and 0.9672
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1523 / 0 / 165
Goodness-of-fit on F^2	1.006
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0447, $wR2$ = 0.0972
R indices (all data)	$R1$ = 0.0793, $wR2$ = 0.1126
Largest diff. peak and hole	0.167 and -0.216 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (*Z.* Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. **A51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) **A46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were located from the difference map and fully refined.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U_{eq}	$S.o.f.$
O1	2551(1)	2186(3)	3376(1)	34(1)	1
O2	2967(1)	1163(3)	719(1)	36(1)	1
C1	3068(1)	475(3)	3200(2)	26(1)	1
C2	4028(2)	13(4)	3873(2)	33(1)	1
C3	4276(2)	−2640(4)	3524(2)	34(1)	1
C4	3754(2)	−2899(4)	2280(2)	31(1)	1
C5	2835(1)	−1537(4)	2279(2)	26(1)	1
C6	2332(2)	−475(3)	1145(2)	28(1)	1
C7	1967(2)	−2491(4)	288(2)	30(1)	1
C8	1118(1)	−2080(4)	−568(2)	32(1)	1
C9	1061(2)	−3860(5)	369(2)	38(1)	1
C10	694(2)	−829(4)	−1468(2)	40(1)	1

Table 3. Bond lengths [Å] and angles [°].

O1–C1	1.221(2)	C5–C6	1.514(3)
O2–C6	1.428(2)	C6–C7	1.499(3)
C1–C2	1.506(3)	C7–C8	1.472(3)
C1–C5	1.515(3)	C7–C9	1.531(3)
C2–C3	1.523(3)	C8–C10	1.308(3)
C3–C4	1.534(3)	C8–C9	1.465(3)
C4–C5	1.528(3)		
O1–C1–C2	125.51(18)	C8–C7–C6	120.86(18)
O1–C1–C5	124.99(18)	C8–C7–C9	58.37(14)
C2–C1–C5	109.49(16)	C6–C7–C9	120.07(19)
C1–C2–C3	104.65(17)	C10–C8–C9	148.5(2)
C2–C3–C4	103.81(17)	C10–C8–C7	148.3(2)
C5–C4–C3	104.31(17)	C9–C8–C7	62.85(14)
C6–C5–C1	112.69(16)	C8–C9–C7	58.78(14)
C6–C5–C4	117.65(17)		
C1–C5–C4	104.14(16)		
O2–C6–C7	111.61(16)		
O2–C6–C5	106.91(16)		
C7–C6–C5	113.01(16)		

Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	40(1)	35(1)	27(1)	−6(1)	6(1)	6(1)
O2	44(1)	38(1)	26(1)	6(1)	3(1)	−11(1)
C1	31(1)	27(1)	21(1)	2(1)	8(1)	−2(1)
C2	33(1)	37(1)	29(1)	−3(1)	2(1)	−2(1)
C3	31(2)	36(1)	34(1)	1(1)	2(1)	4(1)
C4	36(1)	30(1)	29(1)	2(1)	9(1)	3(1)
C5	30(1)	26(1)	23(1)	1(1)	6(1)	−3(1)
C6	29(1)	30(1)	26(1)	−1(1)	7(1)	1(1)
C7	29(1)	34(1)	27(1)	−5(1)	5(1)	3(1)
C8	32(1)	34(1)	28(1)	−6(1)	1(1)	1(1)
C9	38(1)	39(1)	36(1)	0(1)	1(1)	−8(1)
C10	36(2)	49(2)	31(1)	−2(1)	0(1)	−2(1)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [Å^2 × 10^3].

Atom	x	y	z	U_{eq}	*S.o.f.*
H2A	4071(14)	320(40)	4683(19)	43(6)	1
H2B	4431(15)	1300(40)	3631(17)	38(6)	1
H3A	4951(16)	−2890(30)	3600(17)	34(6)	1
H3B	4049(14)	−3880(30)	4008(17)	36(6)	1
H4A	3660(13)	−4730(40)	2037(16)	33(5)	1
H4B	4057(15)	−1990(40)	1738(19)	43(6)	1
H5	2432(14)	−2670(40)	2550(18)	32(5)	1
H6	1794(13)	510(30)	1305(14)	25(5)	1
H7	2415(15)	−3500(40)	71(18)	37(6)	1
H9B	1007(14)	−5700(40)	195(17)	45(6)	1
H9A	752(15)	−3340(40)	982(19)	39(6)	1
H10B	1033(16)	430(40)	−1877(19)	50(6)	1
H10A	62(18)	−1090(40)	−1770(20)	55(7)	1
H2O	2776(17)	1460(40)	10(20)	57(8)	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
O2–H2O···O1^{i}	0.85(3)	2.03(3)	2.858(2)	166(2)

Symmetry transformations used to generate equivalent atoms:
(i) x,−y+1/2,z−1/2

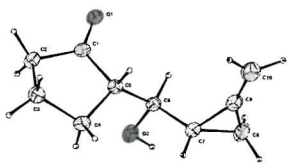


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Table 1. Crystal data and structure refinement.

Identification code	**99SOT005**
Empirical formula	$C_{10}H_{14}O_2$
Formula weight	166.21
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 14.584(2) Å
	b = 5.2345(6) Å β = 92.550(6)°
	c = 11.950(3) Å
Volume	911.4(3) Å^3
Z	4
Density (calculated)	1.211 Mg / m^3
Absorption coefficient	0.083 mm^{-1}
F(000)	360
Crystal	Colourless Needle
Crystal size	0.02 x 0.05 x 0.1 mm^3
θ range for data collection	3.41 – 24.71°
Index ranges	$-17 \le h \le 17$, $-6 \le k \le 6$, $-14 \le l \le 14$
Reflections collected	12224
Independent reflections	1546 [R_{int} = 0.1281]
Completeness to θ = 24.71°	99.7 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1546 / 0 / 165
Goodness-of-fit on F^2	0.969
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0506, $wR2$ = 0.1051
R indices (all data)	$R1$ = 0.1175, $wR2$ = 0.1307
Largest diff. peak and hole	0.172 and −0.169 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. **A51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) **A46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were located from the difference map and fully refined.

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
O1	7569(1)	2126(3)	3842(1)	47(1)	1
O2	8075(1)	1157(3)	1064(2)	49(1)	1
C1	8088(2)	432(5)	3561(2)	38(1)	1
C2	9031(2)	−70(6)	4071(3)	45(1)	1
C3	9272(2)	−2718(6)	3663(3)	47(1)	1
C4	8777(2)	−2901(6)	2504(2)	42(1)	1
C5	7872(2)	−1500(5)	2643(2)	37(1)	1
C6	7397(2)	−316(5)	1611(2)	38(1)	1
C7	6967(2)	−2278(5)	837(2)	44(1)	1
C8	6177(2)	−1392(8)	36(3)	59(1)	1
C9	6013(2)	−3040(5)	993(2)	52(1)	1
C10	5437(3)	−4256(7)	1612(3)	67(1)	1

Table 3. Bond lengths [Å] and angles [°].

O1–C1	1.222(3)	C5–C6	1.520(3)
O2–C6	1.434(3)	C6–C7	1.500(3)
C1–C2	1.502(4)	C7–C9	1.468(4)
C1–C5	1.515(3)	C7–C8	1.537(4)
C2–C3	1.516(4)	C8–C9	1.460(4)
C3–C4	1.536(4)	C9–C10	1.308(4)
C4–C5	1.526(4)		
O1–C1–C2	125.6(2)	O2–C6–C5	106.9(2)
O1–C1–C5	124.9(2)	C7–C6–C5	112.6(2)
C2–C1–C5	109.5(2)	C9–C7–C6	118.8(2)
C1–C2–C3	104.5(2)	C9–C7–C8	58.1(2)
C2–C3–C4	103.9(2)	C6–C7–C8	117.3(3)
C5–C4–C3	104.2(2)	C9–C8–C7	58.6(2)
C1–C5–C6	112.8(2)	C10–C9–C8	149.5(4)
C1–C5–C4	104.3(2)	C10–C9–C7	147.1(3)
C6–C5–C4	118.2(2)	C8–C9–C7	63.3(2)
O2–C6–C7	111.5(2)		

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	53(1)	51(1)	36(1)	−5(1)	0(1)	6(1)
O2	53(1)	55(1)	38(1)	8(1)	−4(1)	−10(1)
C1	47(2)	38(2)	31(2)	2(1)	6(1)	0(1)
C2	52(2)	45(2)	37(2)	−7(1)	−4(2)	1(2)
C3	47(2)	48(2)	45(2)	3(1)	2(2)	2(2)
C4	49(2)	40(2)	37(2)	0(1)	6(2)	−1(1)
C5	40(2)	38(2)	33(2)	1(1)	6(1)	−4(1)
C6	40(2)	42(2)	32(2)	−1(1)	4(1)	−4(1)
C7	45(2)	52(2)	35(2)	−8(1)	−1(1)	−2(2)
C8	61(2)	76(3)	38(2)	−3(2)	−9(2)	−10(2)
C9	53(2)	59(2)	43(2)	−13(2)	2(2)	−10(2)
C10	68(3)	73(2)	62(3)	−13(2)	8(2)	−23(2)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H2A	9421(19)	1270(50)	3780(20)	55(8)	1
H2B	9069(17)	260(40)	4860(20)	48(8)	1
H3A	9051(17)	−3910(40)	4160(20)	41(7)	1
H3B	9940(20)	−2920(40)	3630(20)	46(8)	1
H4A	9106(17)	−1960(40)	1960(20)	45(8)	1
H4B	8701(16)	−4740(50)	2280(19)	45(7)	1
H5	7475(17)	−2650(50)	2970(20)	38(7)	1
H6	6876(15)	880(40)	1854(16)	28(6)	1
H7	7373(19)	−3620(50)	620(20)	53(8)	1
H8A	6140(19)	−2080(50)	−670(30)	60(9)	1
H8B	5990(20)	450(70)	40(20)	77(11)	1
H10A	4790(20)	−4230(50)	1430(20)	67(10)	1
H10B	5680(20)	−5150(60)	2260(30)	80(12)	1
H2O	7840(20)	1640(60)	440(30)	88(13)	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···A)	∠(*D*HA)
O2–H2O···O1^{i}	0.85(4)	2.04(4)	2.870(3)	168(3)

Symmetry transformations used to generate equivalent atoms:
(i) x,−y+1/2,z−1/2

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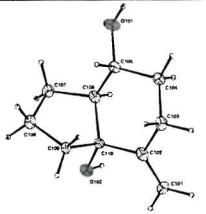

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Table 1. Crystal data and structure refinement.

Identification code	**99SOT020**
Empirical formula	$C_{10}H_{16}O_2$
Formula weight	168.23
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C2
Unit cell dimensions	a = 23.3173(9) Å
	b = 8.2296(4) Å β = 119.149(2)°
	c = 21.4400(8) Å
Volume	3593.1(3) Å^3
Z	16
Density (calculated)	1.244 Mg / m^3
Absorption coefficient	0.085 mm^{-1}
F(000)	1472
Crystal	Colourless plate
Crystal size	0.30 × 0.20 × 0.05 mm^3
θ range for data collection	3.06 – 25.03°
Index ranges	$-26 \le h \le 27$, $-9 \le k \le 9$, $-25 \le l \le 25$
Reflections collected	11371
Independent reflections	5667 [R_{int} = 0.0453]
Completeness to θ = 25.03°	99.6 %
Max. and min. transmission	0.9958 and 0.9751
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5667 / 1 / 690
Goodness-of-fit on F^2	1.010
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0454, $wR2$ = 0.0841
R indices (all data)	$R1$ = 0.0758, $wR2$ = 0.0947
Extinction coefficient	0.0020(2)
Largest diff. peak and hole	0.161 and –0.171 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U_{eq}	*S.o.f.*
O101	1508(1)	14239(4)	–651(1)	35(1)	1
O102	2758(1)	18101(4)	1224(1)	28(1)	1
C101	1709(2)	20211(7)	525(2)	36(1)	1
C102	1595(2)	18614(6)	441(2)	31(1)	1
C103	930(2)	17941(7)	–76(2)	35(1)	1
C104	989(2)	16750(6)	–587(2)	33(1)	1
C105	1453(2)	15391(6)	–173(2)	27(1)	1
C106	2138(2)	16010(6)	339(2)	25(1)	1
C107	2565(2)	14693(6)	870(2)	31(1)	1
C108	2463(2)	14879(7)	1525(2)	34(1)	1
C109	2040(2)	16387(6)	1394(2)	24(1)	1
C110	2122(2)	17360(5)	833(2)	21(1)	1
O201	2031(1)	21618(4)	2693(1)	35(1)	1
O202	–226(1)	23216(4)	1720(1)	27(1)	1
C201	–491(2)	19962(8)	1824(2)	36(1)	1
C202	22(2)	20334(6)	1736(2)	27(1)	1
C203	499(2)	19045(7)	1771(2)	32(1)	1
C204	1202(2)	19509(6)	2334(2)	32(1)	1
C205	1377(2)	21152(6)	2170(2)	25(1)	1
C206	913(2)	22479(5)	2151(2)	20(1)	1
C207	992(2)	24071(6)	1828(2)	28(1)	1
C208	591(2)	23814(7)	1014(2)	35(1)	1
C209	116(2)	22414(6)	898(2)	26(1)	1
C210	187(1)	22042(6)	1634(2)	21(1)	1
O301	–2086(1)	24879(4)	2413(1)	35(1)	1
O302	113(1)	23093(4)	3162(1)	27(1)	1
C301	471(2)	26303(8)	3171(2)	38(1)	1
C302	–48(2)	26003(6)	3248(2)	25(1)	1
C303	–515(2)	27295(7)	3217(2)	32(1)	1
C304	–1221(2)	26875(7)	2681(2)	35(1)	1
C305	–1404(2)	25258(6)	2870(2)	25(1)	1
C306	–965(2)	23887(5)	2861(2)	22(1)	1
C307	–1052(2)	22330(6)	3179(2)	28(1)	1
C308	–625(2)	22566(6)	3993(2)	32(1)	1

C309	−129(2)	23929(6)	4095(2)	29(1)	1
C310	−230(1)	24294(6)	3341(2)	22(1)	1
O401	3658(1)	27144(5)	5718(1)	45(1)	1
O402	2255(1)	23230(4)	3946(1)	31(1)	1
C401	3329(2)	21156(7)	4508(2)	40(1)	1
C402	3433(2)	22719(6)	4580(2)	25(1)	1
C403	4104(2)	23436(7)	5045(2)	39(1)	1
C404	4092(2)	24645(7)	5579(2)	39(1)	1
C405	3608(2)	25990(6)	5198(2)	26(1)	1
C406	2912(2)	25333(6)	4739(2)	24(1)	1
C407	2449(2)	26617(7)	4226(2)	39(1)	1
C408	2484(2)	26430(7)	3535(2)	39(1)	1
C409	2908(2)	24932(6)	3633(2)	26(1)	1
C410	2892(2)	23979(6)	4231(2)	24(1)	1

Table 3. Bond lengths [Å] and angles [°].

O101–C105	1.447(5)	O301–C305	1.438(4)
O102–C110	1.436(4)	O302–C310	1.438(5)
C101–C102	1.335(7)	C301–C302	1.322(5)
C102–C103	1.506(6)	C302–C303	1.500(6)
C102–C110	1.509(6)	C302–C310	1.511(6)
C103–C104	1.526(6)	C303–C304	1.520(5)
C104–C105	1.507(6)	C304–C305	1.512(7)
C105–C106	1.519(5)	C305–C306	1.530(6)
C106–C107	1.535(6)	C306–C307	1.511(6)
C106–C110	1.547(6)	C306–C310	1.546(4)
C107–C108	1.543(5)	C307–C308	1.543(5)
C108–C109	1.524(7)	C308–C309	1.548(6)
C109–C110	1.535(5)	C309–C310	1.544(5)
O201–C205	1.436(4)	O401–C405	1.426(5)
O202–C210	1.436(5)	O402–C410	1.440(4)
C201–C202	1.332(5)	C401–C402	1.304(7)
C202–C210	1.502(6)	C402–C403	1.505(6)
C202–C203	1.512(6)	C402–C410	1.520(6)
C203–C204	1.538(5)	C403–C404	1.527(7)
C204–C205	1.502(7)	C404–C405	1.506(6)
C205–C206	1.524(5)	C405–C406	1.530(5)
C206–C207	1.534(6)	C406–C407	1.528(6)
C206–C210	1.549(4)	C406–C410	1.542(6)
C207–C208	1.542(5)	C407–C408	1.531(6)
C208–C209	1.532(6)	C408–C409	1.530(7)
C209–C210	1.536(5)	C409–C410	1.520(5)

C101–C102–C103	121.8(4)	C104–C105–C106	112.1(4)
C101–C102–C110	122.9(4)	C105–C106–C107	111.9(4)
C103–C102–C110	115.3(4)	C105–C106–C110	111.6(3)
C102–C103–C104	110.0(3)	C107–C106–C110	102.9(3)
C105–C104–C103	110.1(3)	C106–C107–C108	105.8(3)
O101–C105–C104	110.7(3)	C109–C108–C107	106.7(3)
O101–C105–C106	107.9(3)	C108–C109–C110	104.6(3)

O102–C110–C102	111.4(4)	C402–C403–C404	111.1(3)
O102–C110–C109	104.6(3)	C405–C404–C403	110.7(3)
C102–C110–C109	114.5(3)	O401–C405–C404	108.1(3)
O102–C110–C106	110.1(3)	O401–C405–C406	113.2(3)
C102–C110–C106	113.2(3)	C404–C405–C406	111.7(4)
C109–C110–C106	102.4(3)	C407–C406–C405	112.0(4)
C201–C202–C210	123.2(4)	C407–C406–C410	102.9(3)
C201–C202–C203	121.3(5)	C405–C406–C410	111.5(3)
C210–C202–C203	115.4(3)	C406–C407–C408	106.0(4)
C202–C203–C204	110.1(4)	C409–C408–C407	106.5(3)
C205–C204–C203	110.3(3)	C410–C409–C408	104.5(3)
O201–C205–C204	111.3(3)	O402–C410–C402	110.8(4)
O201–C205–C206	107.4(3)	O402–C410–C409	107.9(3)
C204–C205–C206	112.4(3)	C402–C410–C409	114.3(3)
C205–C206–C207	112.6(3)	O402–C410–C406	106.2(3)
C205–C206–C210	111.5(3)	C402–C410–C406	114.4(3)
C207–C206–C210	101.8(3)	C409–C410–C406	102.6(4)
C206–C207–C208	104.7(4)		
C209–C208–C207	106.2(3)		
C208–C209–C210	106.0(3)		
O202–C210–C202	112.1(3)		
O202–C210–C209	104.7(3)		
C202–C210–C209	115.4(3)		
O202–C210–C206	108.6(3)		
C202–C210–C206	112.4(3)		
C209–C210–C206	102.9(3)		
C301–C302–C303	123.4(5)		
C301–C302–C310	121.7(4)		
C303–C302–C310	114.8(3)		
C302–C303–C304	111.6(4)		
C305–C304–C303	110.0(4)		
O301–C305–C304	111.8(3)		
O301–C305–C306	110.9(3)		
C304–C305–C306	111.5(3)		
C307–C306–C305	112.5(3)		
C307–C306–C310	103.4(3)		
C305–C306–C310	111.3(3)		
C306–C307–C308	104.4(3)		
C307–C308–C309	106.1(3)		
C310–C309–C308	105.6(3)		
O302–C310–C302	112.0(3)		
O302–C310–C309	108.9(3)		
C302–C310–C309	114.3(3)		
O302–C310–C306	104.7(3)		
C302–C310–C306	113.9(3)		
C309–C310–C306	102.1(3)		
C401–C402–C403	122.6(4)		
C401–C402–C410	123.5(4)		
C403–C402–C410	113.8(4)		

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O101	25(1)	46(2)	32(1)	−17(1)	13(1)	−8(1)
O102	22(1)	35(2)	26(1)	−3(1)	10(1)	−7(1)
C101	47(3)	23(4)	32(2)	1(2)	16(2)	2(2)
C102	28(2)	41(4)	25(2)	1(2)	13(2)	1(2)
C103	26(2)	35(4)	35(2)	4(2)	7(2)	7(2)
C104	25(2)	33(3)	27(2)	−4(2)	2(2)	0(2)
C105	26(2)	31(3)	23(2)	−4(2)	11(2)	0(2)
C106	19(2)	33(3)	22(2)	1(2)	10(1)	−1(2)
C107	24(2)	30(3)	32(2)	−1(2)	8(2)	2(2)
C108	39(2)	30(3)	30(2)	7(2)	15(2)	1(2)
C109	29(2)	24(3)	21(2)	4(2)	12(2)	1(2)
C110	18(2)	21(3)	20(2)	−3(2)	7(1)	−2(2)
O201	18(1)	48(2)	30(1)	−11(1)	6(1)	2(1)
O202	22(1)	38(2)	22(1)	1(1)	10(1)	7(1)
C201	30(2)	48(4)	29(2)	−4(2)	13(2)	−9(2)
C202	26(2)	33(3)	17(2)	−4(2)	7(2)	−6(2)
C203	30(2)	26(3)	29(2)	−1(2)	6(2)	−7(2)
C204	25(2)	33(4)	29(2)	2(2)	7(2)	8(2)
C205	21(2)	36(3)	18(2)	−5(2)	9(1)	−5(2)
C206	21(2)	20(3)	20(2)	0(2)	10(1)	1(2)
C207	24(2)	26(3)	30(2)	2(2)	11(2)	−2(2)
C208	43(2)	39(4)	28(2)	2(2)	20(2)	−5(2)
C209	22(2)	30(3)	21(2)	4(2)	8(2)	1(2)
C210	19(2)	27(3)	18(2)	1(2)	10(1)	5(2)
O301	18(1)	53(2)	28(1)	−15(1)	7(1)	−3(1)
O302	22(1)	33(2)	24(1)	4(1)	9(1)	10(1)
C301	40(2)	40(4)	32(2)	−7(2)	18(2)	−18(2)
C302	20(2)	32(3)	13(2)	−1(2)	1(1)	−6(2)
C303	31(2)	25(3)	33(2)	−1(2)	10(2)	5(2)
C304	34(2)	26(3)	34(2)	1(2)	8(2)	5(2)
C305	16(2)	34(3)	20(2)	−4(2)	4(1)	5(2)
C306	17(2)	30(3)	18(2)	−3(2)	7(1)	−1(2)
C307	31(2)	27(3)	29(2)	−1(2)	16(2)	−5(2)
C308	35(2)	34(4)	30(2)	6(2)	17(2)	−5(2)
C309	29(2)	40(4)	19(2)	1(2)	11(2)	2(2)
C310	18(2)	27(3)	24(2)	−2(2)	11(1)	3(2)
O401	27(1)	67(3)	44(2)	−32(2)	19(1)	−10(1)
O402	25(1)	39(2)	30(1)	−11(1)	14(1)	−13(1)
C401	40(2)	30(4)	42(2)	4(2)	15(2)	5(2)
C402	30(2)	17(3)	23(2)	3(2)	10(2)	4(2)
C403	28(2)	28(4)	44(2)	−3(2)	4(2)	11(2)
C404	31(2)	34(3)	32(2)	0(2)	1(2)	2(2)
C405	22(2)	30(3)	26(2)	−10(2)	12(2)	−5(2)
C406	26(2)	27(3)	26(2)	−3(2)	16(2)	−3(2)
C407	31(2)	41(4)	38(2)	−8(2)	12(2)	7(2)
C408	36(2)	36(4)	34(2)	8(2)	8(2)	8(2)
C409	25(2)	30(3)	22(2)	0(2)	11(2)	−5(2)
C410	17(2)	32(3)	21(2)	1(2)	9(1)	−4(2)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	x	y	z	U_{eq}	*S.o.f.*
H1A	1330(20)	21020(80)	270(20)	68(15)	1
H1B	2130(20)	20650(70)	880(20)	57(13)	1
H1C	−560(20)	18780(90)	1930(30)	110(20)	1
H1D	−764(15)	20720(50)	1814(17)	28(11)	1
H1E	543(14)	27500(50)	3095(14)	17(9)	1
H1F	791(18)	25250(70)	3210(20)	74(16)	1
H1G	3690(19)	20420(70)	4777(19)	45(12)	1
H1H	2860(17)	20660(60)	4215(18)	34(10)	1
H3A	629(18)	18850(60)	−360(20)	58(13)	1
H3B	735(15)	17350(60)	200(17)	40(11)	1
H3C	428(15)	18910(60)	1273(18)	38(10)	1
H3D	393(16)	17910(70)	1911(18)	39(12)	1
H3E	−472(13)	27380(50)	3725(16)	17(8)	1
H3F	−371(15)	28340(60)	3134(18)	29(11)	1
H3G	4250(18)	24060(70)	4710(20)	70(14)	1
H3H	4409(17)	22480(60)	5257(19)	49(12)	1
H4A	1205(17)	17300(60)	−854(19)	55(12)	1
H4B	548(15)	16250(60)	−960(16)	40(10)	1
H4C	1254(14)	19440(60)	2794(16)	26(9)	1
H4D	1534(19)	18710(70)	2346(19)	59(14)	1
H4E	−1273(14)	26720(60)	2173(16)	31(9)	1
H4F	−1476(16)	27710(60)	2659(17)	30(11)	1
H4G	3969(16)	24020(60)	5905(17)	44(11)	1
H4H	4536(17)	25080(60)	5909(17)	49(12)	1
H5A	1278(14)	14650(50)	93(15)	21(9)	1
H5B	1363(12)	21130(50)	1701(15)	16(8)	1
H5C	−1344(11)	25410(40)	3354(13)	2(7)	1
H5D	3750(14)	26490(50)	4842(16)	26(10)	1
H6A	2336(13)	16550(50)	49(16)	30(9)	1
H6B	984(10)	22600(40)	2671(12)	1(7)	1
H6C	−1071(14)	23730(50)	2367(17)	38(10)	1
H6D	2753(12)	24920(50)	5036(15)	23(9)	1
H7A	2435(16)	13640(60)	659(16)	32(10)	1
H7B	3040(16)	14860(50)	1042(15)	36(10)	1
H7C	1467(13)	24250(40)	1961(13)	9(8)	1
H7D	867(18)	25060(60)	2027(19)	42(12)	1
H7E	−866(17)	21430(60)	3026(19)	33(11)	1
H7F	−1555(17)	22090(60)	2997(18)	53(13)	1
H7G	1984(14)	26340(40)	4163(15)	28(8)	1
H7H	2580(20)	27830(80)	4450(20)	79(16)	1
H8A	2236(17)	13930(60)	1566(18)	46(13)	1
H8C	355(18)	24920(70)	781(19)	43(12)	1

H8D	898(16)	23650(60)	797(18)	55(12)	1
H8E	-920(13)	23010(50)	4192(14)	24(8)	1
H8F	-361(17)	21540(70)	4256(18)	38(12)	1
H8G	2034(16)	26100(50)	3121(18)	43(11)	1
H8H	2639(19)	27400(70)	3440(20)	59(15)	1
H9A	2195(13)	16950(50)	1826(16)	18(8)	1
H9B	1548(15)	16150(60)	1181(16)	34(10)	1
H9B	2884(17)	14870(50)	1948(18)	47(11)	1
H9C	-364(14)	22830(50)	554(14)	23(9)	1
H9D	237(16)	21420(70)	720(17)	30(11)	1
H9E	330(15)	23820(50)	4416(15)	25(9)	1
H9F	-219(16)	24990(70)	4308(18)	35(11)	1
H9G	3368(15)	25250(50)	3788(15)	27(9)	1
H9H	2740(15)	24210(60)	3177(18)	44(11)	1
H10A	1090(16)	13830(40)	-954(16)	42(10)	1
H10B	2320(20)	21050(70)	2600(30)	108(19)	1
H10C	-2115(14)	24470(50)	2034(16)	30(10)	1
H10D	3300(20)	27410(70)	5680(20)	98(19)	1
H11A	2910(20)	18540(60)	910(20)	93(16)	1
H11B	-112(18)	23160(60)	2177(18)	78(15)	1
H11C	518(17)	22890(50)	3535(18)	56(11)	1
H11D	2169(18)	22670(50)	3530(20)	66(14)	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
O101–H10A···O202^{i}	0.93(3)	1.95(3)	2.868(3)	170(3)
O102–H11A···O101^{ii}	0.96(5)	1.80(5)	2.714(3)	157(4)
O201–H10B···O301^{iii}	0.92(4)	1.89(5)	2.801(3)	179(5)
O202–H11B···O302	0.88(3)	1.91(3)	2.796(2)	178(4)
O301–H10C···O102^{iv}	0.85(3)	1.97(3)	2.805(4)	168(3)
O302–H11C···O401^{v}	0.91(3)	1.91(4)	2.808(3)	172(4)
O401–H10D···O402^{vi}	0.84(5)	1.94(5)	2.710(4)	154(4)
O402–H11D···O201	0.93(4)	1.88(4)	2.807(4)	177(4)

Symmetry transformations used to generate equivalent atoms:
(i) -x,y-1,-z (ii) -x+1/2,y+1/2,-z (iii) x+1/2,y-1/2,z
(iv) x-1/2,y+1/2,z (v) -x+1/2,y-1/2,-z+1 (vi) -x+1/2,y+1/2,-z+1

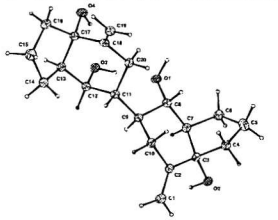

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Table 1. Crystal data and structure refinement.

Identification code	**99SOT023**	
Empirical formula	$C_{20}H_{30}O_4$	
Formula weight	334.44	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 10.4223(4) Å	
	b = 11.0202(5) Å	β = 100.005(5)°
	c = 15.8724(6) Å	
Volume	1795.31(13) Å^3	
Z	4	
Density (calculated)	1.237 Mg / m^3	
Absorption coefficient	0.084 mm^{-1}	
F(000)	728	
Crystal	Colourless Block	
Crystal size	0.15 x 0.15 x 0.15 mm^3	
θ range for data collection	2.99 – 25.02°	
Index ranges	$-12 \le h \le 12$, $-13 \le k \le 11$, $-18 \le l \le 18$	
Reflections collected	5501	
Independent reflections	3167 [R_{int} = 0.0363]	
Completeness to θ = 25.02°	94.5 %	
Absorption correction	Empirical, SORTAV	
Max. and min. transmission	0.9875 and 0.9875	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3167 / 0 / 338	
Goodness-of-fit on F^2	0.980	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0417, $wR2$ = 0.0904	
R indices (all data)	$R1$ = 0.0717, $wR2$ = 0.1022	
Extinction coefficient	0.0074(14)	
Largest diff. peak and hole	0.189 and -0.178 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were located from the difference map and fully refined.

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
O1	2169(1)	4759(1)	-636(1)	29(1)	1
O2	-1626(1)	2274(1)	-1393(1)	28(1)	1
O3	2992(1)	5768(1)	874(1)	27(1)	1
O4	5695(1)	5695(1)	1381(1)	31(1)	1
C1	-1211(2)	1535(2)	309(1)	34(1)	1
C2	-193(2)	1856(2)	-36(1)	25(1)	1
C3	-302(2)	2195(2)	-967(1)	23(1)	1
C4	336(2)	1304(2)	-1508(1)	30(1)	1
C5	507(2)	2028(2)	-2303(1)	40(1)	1
C6	474(2)	3377(2)	-2055(1)	34(1)	1
C7	390(2)	3395(2)	-1098(1)	25(1)	1
C8	1721(2)	3540(2)	-521(1)	25(1)	1
C9	1653(2)	3302(2)	419(1)	24(1)	1
C10	1146(2)	2002(2)	490(1)	27(1)	1
C11	2909(2)	3554(2)	1077(1)	24(1)	1
C12	2906(2)	4804(2)	1488(1)	25(1)	1
C13	4046(2)	5000(2)	2210(1)	26(1)	1
C14	4103(2)	4246(2)	3026(1)	32(1)	1
C15	5543(2)	4258(2)	3453(1)	41(1)	1
C16	6293(2)	4842(2)	2806(1)	33(1)	1
C17	5381(2)	4751(2)	1950(1)	26(1)	1
C18	5374(2)	3542(2)	1482(1)	26(1)	1
C19	6325(2)	2736(2)	1642(1)	32(1)	1
C20	4215(2)	3343(2)	769(1)	27(1)	1

Table 3. Bond lengths [Å] and angles [°].

O1–C8	1.444(2)	C9–C11	1.552(2)
O2–C3	1.4302(19)	C18–C19	1.322(3)
O3–C12	1.455(2)	C18–C20	1.520(2)
O4–C17	1.452(2)	C18–C17	1.525(3)
C9–C8	1.529(2)	C11–C12	1.524(2)
C9–C10	1.537(2)	C11–C20	1.542(2)
C12–C13	1.516(2)	C8–C7	1.532(2)
C13–C14	1.532(3)	C2–C1	1.324(2)
C13–C17	1.543(2)	C6–C7	1.537(2)
C10–C2	1.505(2)	C6–C5	1.539(3)
C3–C2	1.509(2)	C16–C15	1.536(3)
C3–C4	1.532(2)	C4–C5	1.529(3)
C3–C7	1.538(2)	C14–C15	1.536(3)
C17–C16	1.520(2)		
C8–C9–C10	107.80(14)	C13–C14–C15	105.01(15)
C8–C9–C11	116.73(13)	C16–C15–C14	106.31(16)
C10–C9–C11	112.22(14)	C4–C5–C6	106.43(16)
C19–C18–C20	121.26(18)		
C19–C18–C17	123.55(17)		
C20–C18–C17	115.09(14)		
C12–C11–C20	109.85(14)		
C12–C11–C9	112.69(14)		
C20–C11–C9	116.57(14)		
O3–C12–C13	105.69(13)		
O3–C12–C11	111.61(13)		
C13–C12–C11	113.09(14)		
C12–C13–C14	118.13(15)		
C12–C13–C17	113.46(14)		
C14–C13–C17	103.07(14)		
C2–C10–C9	110.89(15)		
C18–C20–C11	111.89(14)		
O2–C3–C2	112.34(13)		
O2–C3–C4	104.56(14)		
C2–C3–C4	115.12(15)		
O2–C3–C7	108.67(13)		
C2–C3–C7	112.87(14)		
C4–C3–C7	102.47(14)		
O4–C17–C16	109.58(14)		
O4–C17–C18	107.82(13)		
C16–C17–C18	116.24(16)		
O4–C17–C13	110.49(14)		
C16–C17–C13	101.69(14)		
C18–C17–C13	110.91(14)		
O1–C8–C9	110.67(14)		
O1–C8–C7	107.46(14)		
C9–C8–C7	112.00(13)		
C1–C2–C10	122.17(17)		
C1–C2–C3	122.78(16)		
C10–C2–C3	114.89(14)		
C7–C6–C5	105.82(15)		
C8–C7–C6	112.98(14)		
C8–C7–C3	113.92(14)		
C6–C7–C3	103.40(14)		
C17–C16–C15	104.95(15)		
C5–C4–C3	104.59(16)		

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	25(1)	29(1)	31(1)	4(1)	4(1)	-5(1)
O2	22(1)	32(1)	30(1)	-4(1)	-1(1)	0(1)
O3	26(1)	26(1)	27(1)	2(1)	0(1)	2(1)
O4	25(1)	32(1)	37(1)	7(1)	5(1)	-2(1)
C1	27(1)	42(1)	32(1)	3(1)	0(1)	-5(1)
C2	27(1)	22(1)	27(1)	-1(1)	3(1)	0(1)
C3	19(1)	24(1)	25(1)	-2(1)	-1(1)	-1(1)
C4	28(1)	33(1)	29(1)	-4(1)	3(1)	4(1)
C5	40(1)	49(2)	31(1)	-1(1)	8(1)	10(1)
C6	33(1)	43(1)	25(1)	3(1)	0(1)	-5(1)
C7	24(1)	27(1)	24(1)	1(1)	1(1)	2(1)
C8	22(1)	26(1)	27(1)	1(1)	5(1)	0(1)
C9	19(1)	26(1)	25(1)	1(1)	2(1)	3(1)
C10	28(1)	28(1)	24(1)	2(1)	2(1)	-2(1)
C11	21(1)	28(1)	24(1)	3(1)	3(1)	0(1)
C12	21(1)	27(1)	27(1)	0(1)	4(1)	1(1)
C13	24(1)	26(1)	28(1)	-2(1)	2(1)	1(1)
C14	29(1)	41(1)	26(1)	-1(1)	4(1)	-2(1)
C15	33(1)	56(2)	30(1)	5(1)	-2(1)	1(1)
C16	23(1)	39(1)	34(1)	0(1)	-2(1)	1(1)
C17	22(1)	31(1)	27(1)	2(1)	4(1)	-2(1)
C18	19(1)	31(1)	27(1)	4(1)	5(1)	-1(1)
C19	28(1)	32(1)	34(1)	1(1)	4(1)	3(1)
C20	24(1)	28(1)	28(1)	-2(1)	3(1)	3(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	x	y	z	U_{eq}	$S.o.f.$
H1	-2020(20)	2870(20)	-1121(14)	60(7)	1
H1A	-2062(18)	1475(16)	-18(11)	31(5)	1
H1B	-1122(17)	1365(17)	959(13)	42(5)	1
H1C	2910(20)	4680(20)	-898(15)	78(8)	1
H3	2640(20)	5510(20)	354(14)	60(7)	1
H4A	-244(19)	585(19)	-1649(12)	39(5)	1
H4B	1190(18)	1005(17)	-1149(11)	38(5)	1
H4C	4940(20)	5900(20)	1040(14)	63(7)	1
H5A	-220(20)	1850(20)	-2788(14)	59(7)	1
H5B	1330(20)	1850(20)	-2482(14)	61(6)	1
H6A	-337(19)	3769(18)	-2415(12)	44(6)	1
H6B	1256(19)	3843(19)	-2166(11)	45(6)	1
H7	-140(15)	4090(16)	-944(10)	21(4)	1
H8	2371(15)	2943(16)	-696(10)	23(4)	1
H9	986(16)	3836(16)	567(10)	22(4)	1
H10A	1119(16)	1814(16)	1086(12)	30(5)	1
H10B	1812(17)	1393(17)	289(11)	38(5)	1
H11	2900(14)	2990(16)	1566(11)	22(4)	1
H12	2043(15)	4898(14)	1693(9)	16(4)	1
H13	4059(16)	5861(17)	2374(10)	27(5)	1
H14A	3523(18)	4598(19)	3381(12)	45(6)	1
H14B	3805(18)	3420(20)	2896(12)	43(6)	1
H15A	5870(20)	3450(20)	3619(14)	59(7)	1
H15B	5670(20)	4740(20)	3990(15)	69(7)	1
H16A	7159(18)	4463(17)	2826(11)	34(5)	1
H16B	6434(18)	5730(20)	2930(12)	49(6)	1
H19A	6309(15)	1995(17)	1306(11)	24(5)	1
H19B	7122(18)	2887(18)	2125(12)	40(5)	1
H20A	4237(16)	2481(18)	534(11)	34(5)	1
H20B	4276(16)	3916(17)	273(11)	30(5)	1

Table 6. Hydrogen bonds [Å and °].

D–H···A	$d(D$–H)	d(H···A)	$d(D$···$A)$	$\angle(D$H$A)$
O2–H1···O3^{i}	0.92(2)	1.89(2)	2.7864(18)	164(2)
O1–H1C···O4^{ii}	0.94(3)	1.81(3)	2.7425(16)	173(2)
O4–H4C···O3	0.90(2)	2.01(2)	2.7936(17)	145(2)
O3–H3···O1	0.89(2)	1.77(2)	2.6455(17)	169(2)

Symmetry transformations used to generate equivalent atoms:
(i) -x,-y+1,-z (ii) -x+1,-y+1,-z

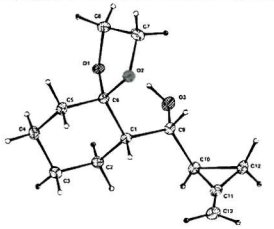

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Table 1. Crystal data and structure refinement.

Identification code	**00SOT059**	
Empirical formula	$C_{13}H_{20}O_3$	
Formula weight	224.29	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.0208(16) Å	α = 79.19(3)°
	b = 8.6714(17) Å	β = 69.41(3)°
	c = 9.761(2) Å	γ = 69.97(3)°
Volume	595.3(2) Å^3	
Z	2	
Density (calculated)	1.251 Mg / m^3	
Absorption coefficient	0.087 mm^{-1}	
F(000)	244	
Crystal	Colourless Block	
Crystal size	0.45 × 0.15 × 0.13 mm^3	
θ range for data collection	3.02 – 27.50°	
Index ranges	$-10 \le h \le 10$, $-11 \le k \le 11$, $-12 \le l \le 12$	
Reflections collected	6467	
Independent reflections	2709 [R_{int} = 0.0490]	
Completeness to θ = 27.50°	98.4 %	
Max. and min. transmission	0.9892 and 0.9618	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2709 / 0 / 146	
Goodness-of-fit on F^2	1.051	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0431, $wR2$ = 0.1119	
R indices (all data)	$R1$ = 0.0544, $wR2$ = 0.1208	
Largest diff. peak and hole	0.236 and –0.243 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. **A51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) **A46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U_{eq}	*S.o.f.*
O1	2868(1)	4056(1)	6345(1)	24(1)	1
O2	482(1)	4097(1)	8501(1)	25(1)	1
O3	723(1)	6991(1)	5355(1)	33(1)	1
C1	1537(2)	6539(1)	7644(1)	20(1)	1
C2	3286(2)	7107(2)	6948(1)	26(1)	1
C3	4669(2)	6359(2)	7816(2)	31(1)	1
C4	5199(2)	4488(2)	7965(1)	27(1)	1
C5	3470(2)	3907(1)	8652(1)	24(1)	1
C6	2090(2)	4651(1)	7789(1)	20(1)	1
C7	323(2)	3153(2)	7538(2)	33(1)	1
C8	2264(2)	2646(2)	6460(2)	31(1)	1
C9	39(2)	7324(1)	6872(1)	23(1)	1
C10	–712(2)	9166(1)	6923(1)	25(1)	1
C11	–2157(2)	9879(1)	8243(1)	26(1)	1
C12	–2749(2)	10040(2)	6949(1)	30(1)	1
C13	–2604(2)	10111(2)	9628(1)	32(1)	1

Table 3. Bond lengths [Å] and angles [°].

O1–C8	1.4350(15)	C3–C4	1.5225(18)
O1–C6	1.4414(14)	C4–C5	1.5241(17)
O2–C7	1.4192(15)	C5–C6	1.5204(16)
O2–C6	1.4306(14)	C7–C8	1.5084(19)
O3–C9	1.4338(14)	C9–C10	1.5061(16)
C1–C2	1.5330(16)	C10–C11	1.4636(18)
C1–C6	1.5354(16)	C10–C12	1.5414(17)
C1–C9	1.5361(16)	C11–C13	1.3069(18)
C2–C3	1.5264(18)	C11–C12	1.4672(17)
C8–O1–C6	106.05(9)	C2–C1–C9	113.95(9)
C7–O2–C6	108.99(9)	C6–C1–C9	112.57(9)
C2–C1–C6	110.01(9)	C3–C2–C1	111.33(10)

C4–C3–C2	111.28(10)
C3–C4–C5	111.06(10)
C6–C5–C4	111.26(10)
O2–C6–O1	105.73(9)
O2–C6–C5	108.83(9)
O1–C6–C5	110.64(9)
O2–C6–C1	110.82(9)
O1–C6–C1	109.09(9)
C5–C6–C1	111.58(9)
O2–C7–C8	103.67(10)
O1–C8–C7	101.77(10)
O3–C9–C10	106.95(10)
O3–C9–C1	112.40(9)
C10–C9–C1	112.70(10)
C11–C10–C9	119.54(10)
C11–C10–C12	58.38(8)
C9–C10–C12	118.99(11)
C13–C11–C10	147.73(12)
C13–C11–C12	148.69(12)
C10–C11–C12	63.46(8)
C11–C12–C10	58.16(8)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	24(1)	23(1)	23(1)	−7(1)	−1(1)	−8(1)
O2	22(1)	25(1)	26(1)	−2(1)	−1(1)	−11(1)
O3	39(1)	31(1)	24(1)	−5(1)	−13(1)	0(1)
C1	21(1)	18(1)	20(1)	−2(1)	−4(1)	−5(1)
C2	26(1)	21(1)	31(1)	2(1)	−9(1)	−11(1)
C3	28(1)	30(1)	40(1)	−1(1)	−14(1)	−13(1)
C4	21(1)	28(1)	33(1)	−1(1)	−9(1)	−7(1)
C5	23(1)	21(1)	25(1)	1(1)	−7(1)	−5(1)
C6	18(1)	20(1)	20(1)	−3(1)	−2(1)	−7(1)
C7	30(1)	38(1)	38(1)	−7(1)	−9(1)	−17(1)
C8	31(1)	27(1)	37(1)	−10(1)	−10(1)	−9(1)
C9	22(1)	21(1)	22(1)	−1(1)	−6(1)	−4(1)
C10	24(1)	21(1)	26(1)	2(1)	−6(1)	−6(1)
C11	24(1)	17(1)	32(1)	0(1)	−6(1)	−6(1)
C12	27(1)	23(1)	34(1)	0(1)	−11(1)	−2(1)
C13	35(1)	26(1)	34(1)	−4(1)	−6(1)	−10(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	x	y	z	U_{eq}	*S.o.f.*
H3	1454	6028	5258	49	1
H1	965	6903	8665	24	1
H2A	3895	6778	5928	31	1
H2B	2920	8322	6913	31	1
H3A	5808	6703	7312	37	1
H3B	4105	6779	8805	37	1
H4A	6032	4042	8584	33	1
H4B	5889	4061	6984	33	1
H5A	3847	2692	8678	29	1
H5B	2859	4226	9675	29	1
H7A	−598	3821	7033	40	1
H7B	−55	2178	8076	40	1
H8A	3075	1644	6842	37	1
H8B	2237	2451	5501	37	1
H9	−1022	6854	7378	27	1
H10	200	9791	6380	30	1
H12A	−3032	11139	6416	35	1
H12B	−3515	9351	6956	35	1
H13A	−1691	9677	10123	39	1
H13B	−3842	10713	10141	39	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)

O3–H3···O1	0.84	2.04	2.7603(15)	143.0

Symmetry transformations used to generate equivalent atoms:

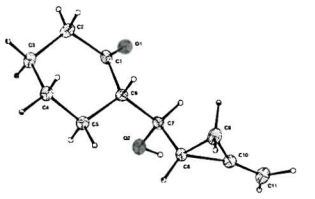

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Table 1. Crystal data and structure refinement.

Identification code	**99SOT004**	
Empirical formula	$C_{11}H_{16}O_2$	
Formula weight	180.24	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 9.5173(7) Å	
	b = 5.9583(3) Å	β = 102.567(3)°
	c = 18.1327(15) Å	
Volume	1003.62(12) Å^3	
Z	4	
Density (calculated)	1.193 Mg / m^3	
Absorption coefficient	0.080 mm^{-1}	
F(000)	392	
Crystal	Colourless Needle	
Crystal size	0.20 × 0.05 × 0.02 mm^3	
θ range for data collection	3.61 – 24.71°	
Index ranges	$-11 \le h \le 11$, $-7 \le k \le 7$, $-21 \le l \le 21$	
Reflections collected	7671	
Independent reflections	1652 [R_{int} = 0.1225]	
Completeness to θ = 24.71°	97.1 %	
Max. and min. transmission	0.9984 and 0.9841	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1652 / 0 / 183	
Goodness-of-fit on F^2	0.967	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0533, $wR2$ = 0.1057	
R indices (all data)	$R1$ = 0.1230, $wR2$ = 0.1311	
Extinction coefficient	0.012(4)	
Largest diff. peak and hole	0.176 and –0.215 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (*Z.* Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. **A51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) **A46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).
Special details: All hydrogen atoms were located from the difference map and fully refined.

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
O1	6451(2)	3354(3)	10070(1)	33(1)	1
O2	4837(2)	−327(3)	9078(1)	33(1)	1
C1	6357(3)	4077(4)	9427(2)	28(1)	1
C2	7488(4)	5633(5)	9255(2)	34(1)	1
C3	7937(3)	4993(6)	8524(2)	33(1)	1
C4	6633(3)	4787(5)	7880(2)	35(1)	1
C5	5609(3)	3006(5)	8053(2)	32(1)	1
C6	5096(3)	3541(5)	8784(2)	25(1)	1
C7	4096(3)	1772(5)	8998(2)	26(1)	1
C8	2676(3)	1563(5)	8436(2)	28(1)	1
C9	1517(3)	3393(6)	8412(2)	36(1)	1
C10	1365(3)	1162(5)	8728(2)	30(1)	1
C11	649(4)	−174(6)	9084(2)	38(1)	1

Table 3. Bond lengths [Å] and angles [°].

O1–C1	1.228(3)	C5–C6	1.542(4)
O2–C7	1.428(3)	C6–C7	1.526(4)
C1–C2	1.505(4)	C7–C8	1.511(4)
C1–C6	1.515(4)	C8–C10	1.476(4)
C2–C3	1.527(4)	C8–C9	1.545(4)
C3–C4	1.513(4)	C9–C10	1.467(4)
C4–C5	1.519(4)	C10–C11	1.306(4)
O1–C1–C2	120.4(3)	O2–C7–C6	108.0(2)
O1–C1–C6	122.7(2)	C8–C7–C6	113.6(2)
C2–C1–C6	116.9(3)	C10–C8–C7	118.3(2)
C1–C2–C3	112.0(3)	C10–C8–C9	58.03(18)
C4–C3–C2	110.7(3)	C7–C8–C9	119.3(3)
C3–C4–C5	110.7(3)	C10–C9–C8	58.65(18)
C4–C5–C6	111.7(2)	C11–C10–C9	148.4(3)
C1–C6–C7	112.5(2)	C11–C10–C8	147.9(3)
C1–C6–C5	111.1(2)	C9–C10–C8	63.3(2)
C7–C6–C5	114.1(2)		
O2–C7–C8	110.2(2)		

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	32(1)	36(1)	31(1)	0(1)	6(1)	−2(1)
O2	31(1)	28(1)	43(1)	6(1)	12(1)	4(1)
C1	26(2)	26(2)	35(2)	1(1)	11(2)	5(1)
C2	29(2)	35(2)	35(2)	1(1)	3(2)	−7(2)
C3	27(2)	37(2)	38(2)	4(1)	12(2)	−4(2)
C4	35(2)	39(2)	32(2)	−1(2)	14(2)	−6(2)
C5	30(2)	37(2)	30(2)	−4(1)	9(2)	−5(2)
C6	24(2)	20(2)	29(2)	0(1)	6(1)	2(1)
C7	26(2)	28(2)	26(2)	−3(1)	9(1)	3(1)
C8	24(2)	34(2)	28(2)	−5(1)	10(1)	−2(1)
C9	26(2)	41(2)	39(2)	8(2)	3(2)	2(1)
C10	24(2)	36(2)	29(2)	−4(1)	3(1)	−2(1)
C11	29(2)	40(2)	44(2)	7(2)	6(2)	0(2)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	4450(40)	−1260(60)	9360(20)	75(13)	1
H2A	7060(30)	7180(50)	9187(15)	37(8)	1
H2B	8290(30)	5710(40)	9699(18)	45(9)	1
H3A	8470(30)	3540(50)	8599(15)	37(8)	1
H3B	8550(30)	6180(40)	8407(13)	19(7)	1
H4A	6160(30)	6290(50)	7783(15)	33(8)	1
H4B	6930(30)	4440(40)	7397(15)	25(7)	1
H5A	4710(30)	2850(40)	7633(16)	41(8)	1
H5B	6120(30)	1440(40)	8145(15)	37(8)	1
H6	4620(20)	4980(40)	8721(13)	17(6)	1
H7	3880(20)	2210(30)	9469(13)	8(6)	1
H8	2740(30)	880(40)	7954(15)	27(7)	1
H9A	1800(30)	4660(50)	8786(17)	45(9)	1
H9B	920(30)	3820(40)	7916(17)	42(8)	1
H11A	−230(30)	320(40)	9216(15)	42(8)	1
H11B	970(30)	−1610(50)	9250(15)	38(9)	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
O2–H1···O1^{i}	0.89(4)	1.93(4)	2.822(3)	177(4)

Symmetry transformations used to generate equivalent atoms:
(i) −x+1,−y,−z+2

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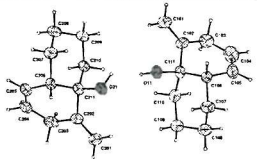

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Table 1. Crystal data and structure refinement.

Identification code	99SOT024
Empirical formula	$C_{11}H_{16}O$
Formula weight	164.24
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	*C2/c*
Unit cell dimensions	a = 23.812(5) Å
	b = 9.449(2) Å β = 113.41(3)°
	c = 18.724(4) Å
Volume	3866.3(14) Å^3
Z	16
Density (calculated)	1.129 Mg / m^3
Absorption coefficient	0.070 mm^{-1}
F(000)	1440
Crystal	Colourless Block
Crystal size	0.10 × 0.08 × 0.05 mm^3
θ range for data collection	3.06 – 22.22°
Index ranges	$-25 \le h \le 25$, $-10 \le k \le 10$, $-19 \le l \le 19$
Reflections collected	8070
Independent reflections	2420 [R_{int} = 0.0781]
Completeness to θ = 22.22°	99.1 %
Max. and min. transmission	0.9965 and 0.9930
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2420 / 0 / 220
Goodness-of-fit on F^2	0.979
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0924, *wR2* = 0.2556
R indices (all data)	*R1* = 0.1674, *wR2* = 0.3170
Extinction coefficient	0.006(2)
Largest diff. peak and hole	0.425 and –0.204 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. **A51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) **A46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C101	6310(4)	4248(8)	1771(4)	123(2)	1
C102	6407(3)	2912(7)	1680(4)	102(2)	1
C103	6876(4)	2392(9)	1389(5)	137(3)	1
C104	7180(5)	1161(13)	1761(7)	180(4)	1
C105	7017(4)	397(9)	2276(5)	135(3)	1
C106	6474(3)	820(6)	2480(4)	91(2)	1
C107	6161(4)	–492(7)	2618(5)	131(3)	1
C108	5855(4)	–1351(7)	1890(5)	136(3)	1
C109	5389(3)	–455(7)	1259(5)	123(2)	1
C110	5682(3)	879(6)	1096(4)	101(2)	1
C111	6044(3)	1732(6)	1850(3)	86(2)	1
O11	5615(2)	2323(4)	2119(2)	100(1)	1
C201	3736(3)	1108(8)	427(5)	124(2)	1
C202	3626(3)	2449(7)	274(4)	95(2)	1
C203	3120(4)	2989(9)	–478(4)	124(3)	1
C204	2820(3)	4296(10)	–328(6)	131(3)	1
C205	3012(3)	5005(8)	318(5)	108(2)	1
C206	3541(3)	4573(6)	997(4)	86(2)	1
C207	3882(3)	5879(7)	1476(4)	113(2)	1
C208	4193(3)	6719(7)	1061(4)	116(2)	1
C209	4654(3)	5795(7)	899(4)	101(2)	1
C210	4344(3)	4490(6)	418(3)	85(2)	1
C211	3988(3)	3663(6)	809(3)	83(2)	1
O21	4414(2)	3069(5)	1507(2)	104(1)	1

Table 3. Bond lengths [Å] and angles [°].

C101–C102	1.307(8)	C108–C109	1.518(9)
C102–C103	1.505(9)	C109–C110	1.530(8)
C102–C111	1.520(8)	C110–C111	1.555(8)
C103–C104	1.401(12)	C111–O11	1.420(6)
C104–C105	1.379(11)	C201–C202	1.302(8)
C105–C106	1.539(10)	C202–C203	1.533(9)
C106–C111	1.491(7)	C202–C211	1.541(8)
C106–C107	1.520(8)	C203–C204	1.507(10)
C107–C108	1.502(9)	C204–C205	1.297(10)

C205–C206	1.449(9)	C208–C209	1.524(8)
C206–C211	1.514(7)	C209–C210	1.533(7)
C206–C207	1.552(8)	C210–C211	1.536(7)
C207–C208	1.497(8)	C211–O21	1.413(6)

C101–C102–C103	123.9(6)
C101–C102–C111	122.5(6)
C103–C102–C111	113.7(5)
C104–C103–C102	113.8(6)
C105–C104–C103	123.2(8)
C104–C105–C106	122.4(7)
C111–C106–C107	112.1(5)
C111–C106–C105	109.6(5)
C107–C106–C105	110.4(6)
C108–C107–C106	112.4(6)
C107–C108–C109	110.2(6)
C108–C109–C110	111.3(6)
C109–C110–C111	112.2(5)
O11–C111–C106	108.2(4)
O11–C111–C102	109.5(5)
C106–C111–C102	108.7(5)
O11–C111–C110	108.0(5)
C106–C111–C110	112.1(5)
C102–C111–C110	110.2(5)
C201–C202–C203	122.8(6)
C201–C202–C211	124.8(7)
C203–C202–C211	112.4(5)
C204–C203–C202	111.1(6)
C205–C204–C203	125.4(7)
C204–C205–C206	122.3(7)
C205–C206–C211	113.7(5)
C205–C206–C207	110.9(6)
C211–C206–C207	109.4(5)
C208–C207–C206	112.0(5)
C207–C208–C209	110.1(6)
C208–C209–C210	111.2(5)
C209–C210–C211	111.0(4)
O21–C211–C206	108.9(4)
O21–C211–C210	108.2(4)
C206–C211–C210	113.2(5)
O21–C211–C202	108.4(5)
C206–C211–C202	108.2(5)
C210–C211–C202	109.9(4)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C101	151(6)	100(5)	128(6)	15(4)	66(5)	−13(4)
C102	125(5)	84(4)	128(5)	6(4)	83(5)	−4(4)
C103	145(7)	144(6)	168(7)	12(6)	111(6)	−14(5)
C104	149(8)	201(10)	249(12)	8(9)	143(9)	1(8)
C105	97(5)	142(6)	143(7)	−13(5)	23(5)	23(5)
C106	89(4)	87(3)	97(4)	20(3)	36(4)	6(3)
C107	136(6)	109(5)	135(6)	29(5)	39(5)	−20(5)
C108	130(6)	110(5)	148(7)	7(5)	34(6)	−23(5)
C109	112(5)	105(5)	147(7)	5(5)	45(5)	−8(4)
C110	108(5)	109(4)	89(5)	4(4)	44(4)	12(4)
C111	83(4)	99(4)	94(4)	7(4)	53(4)	15(3)
O11	87(3)	122(3)	110(3)	10(2)	60(3)	17(2)
C201	129(6)	102(5)	157(7)	−20(5)	74(5)	−12(4)
C202	97(4)	96(5)	101(5)	−14(4)	49(4)	−18(4)
C203	128(6)	134(6)	83(5)	−8(4)	14(5)	−50(5)
C204	84(5)	146(7)	134(8)	45(6)	13(5)	−8(5)
C205	78(5)	127(5)	116(6)	5(5)	34(5)	−5(4)
C206	80(4)	97(4)	97(4)	2(3)	51(4)	3(3)
C207	126(5)	110(4)	121(5)	−25(4)	68(5)	−19(4)
C208	116(5)	117(5)	141(6)	−48(4)	78(5)	−37(4)
C209	96(4)	117(5)	100(5)	−15(4)	48(4)	−27(4)
C210	80(4)	99(4)	85(4)	−4(3)	43(3)	−6(3)
C211	73(3)	110(4)	64(4)	5(3)	24(3)	−4(3)
O21	80(3)	130(3)	86(3)	10(2)	17(2)	−1(2)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	x	y	z	U_{eq}	*S.o.f.*
H10G	6542	4956	1651	148	1
H10H	6007	4511	1957	148	1
H10C	6670	2206	823	164	1
H10D	7181	3149	1464	164	1
H104	7516	837	1653	216	1
H105	7248	−421	2514	162	1
H106	6636	1384	2972	109	1
H10E	6468	−1086	3020	157	1
H10F	5851	−200	2818	157	1
H10I	5649	−2179	2004	163	1
H10J	6167	−1704	1708	163	1
H10A	5057	−181	1423	148	1
H10B	5205	−1019	776	148	1
H11A	5359	1489	727	121	1
H11B	5964	607	847	121	1

H11	5312	2632	1739	150	1
H20I	3497	418	64	148	1
H20J	4054	819	900	148	1
H20E	3296	3210	−863	148	1
H20F	2808	2240	−700	148	1
H204	2460	4627	−741	157	1
H205	2798	5838	346	130	1
H206	3390	4002	1334	104	1
H20C	3586	6493	1580	136	1
H20D	4191	5558	1984	136	1
H20G	4406	7539	1385	139	1
H20H	3885	7083	565	139	1
H20A	4978	5489	1398	122	1
H20B	4849	6354	613	122	1
H21A	4658	3867	362	102	1
H21B	4060	4790	−108	102	1
H21	4760	3431	1613	156	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
O11–H11···O21	0.84	2.05	2.718(6)	136.4
O21–H21···O11	0.84	2.15	2.718(6)	125.2

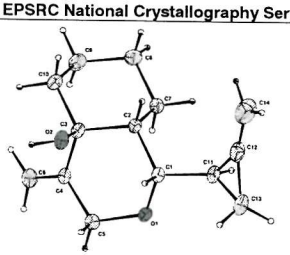

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Table 1. Crystal data and structure refinement.

Identification code	**00sot057**
Empirical formula	$C_{14}H_{20}O_2$
Formula weight	220.30
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 11.7383(3) Å
	b = 10.1001(2) Å β = 92.982(9)°
	c = 21.5543(7) Å
Volume	2551.97(12) Å^3
Z	8
Density (calculated)	1.147 Mg / m^3
Absorption coefficient	0.075 mm^{-1}
F(000)	960
Crystal	Colourless Plate
Crystal size	0.12 × 0.10 × 0.05 mm^3
θ range for data collection	3.21 – 25.09°
Index ranges	$-14 \le h \le 13$, $-12 \le k \le 12$, $-24 \le l \le 25$
Reflections collected	13700
Independent reflections	4402 [R_{int} = 0.0673]
Completeness to θ = 25.09°	97.1 %
Max. and min. transmission	0.9963 and 0.9911
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4402 / 0 / 354
Goodness-of-fit on F^2	0.860
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0526, $wR2$ = 0.1101
R indices (all data)	$R1$ = 0.1370, $wR2$ = 0.1306
Extinction coefficient	0.0039(9)
Largest diff. peak and hole	0.269 and −0.139 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (*Z.* Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. **A51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) **A46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).
Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
O1	5550(1)	3983(1)	1473(1)	51(1)	1
O2	6657(1)	5145(2)	2883(1)	61(1)	1
C1	6512(2)	3425(2)	1826(1)	44(1)	1
C2	7434(2)	4466(2)	1946(1)	45(1)	1
C3	6960(2)	5651(2)	2295(1)	48(1)	1
C4	5864(2)	6123(2)	1965(1)	46(1)	1
C5	5040(2)	5036(2)	1805(1)	58(1)	1
C6	5576(3)	7364(3)	1856(1)	67(1)	1
C7	8000(2)	4896(2)	1363(1)	55(1)	1
C8	8916(2)	5927(2)	1489(2)	74(1)	1
C9	8445(3)	7117(3)	1813(2)	82(1)	1
C11	6889(2)	2240(2)	1481(1)	54(1)	1
C10	7871(2)	6704(2)	2397(1)	68(1)	1
C12	7550(3)	1225(2)	1805(1)	77(1)	1
C13	6405(3)	880(3)	1608(2)	73(1)	1
C14	8503(4)	920(4)	2096(2)	156(2)	1
O1'	6636(1)	9539(1)	171(1)	54(1)	1
O2'	6251(1)	7864(1)	−1239(1)	51(1)	1
C1'	7148(2)	9858(2)	−392(1)	45(1)	1
C2'	7823(2)	8678(2)	−615(1)	42(1)	1
C3'	7032(2)	7486(2)	−729(1)	41(1)	1
C4'	6335(2)	7265(2)	−173(1)	43(1)	1
C5'	5823(2)	8499(2)	81(1)	56(1)	1
C6'	6107(2)	6106(3)	67(2)	59(1)	1
C7'	8836(2)	8316(2)	−176(1)	54(1)	1
C8'	9493(2)	7137(2)	−394(2)	66(1)	1
C9'	8727(2)	5946(2)	−487(1)	63(1)	1
C10'	7715(2)	6283(2)	−928(1)	56(1)	1
C11'	7854(2)	11084(2)	−277(1)	54(1)	1
C12'	8053(3)	11962(3)	−780(2)	72(1)	1
C13'	7302(3)	12446(2)	−337(2)	71(1)	1
C14'	8521(5)	12113(6)	−1301(2)	139(2)	1

Table 3. Bond lengths [Å] and angles [°].

O1–C5	1.430(2)	O1'–C5'	1.426(2)
O1–C1	1.444(2)	O2'–C3'	1.445(2)
O2–C3	1.430(3)	C1'–C11'	1.503(3)
C1–C11	1.488(3)	C1'–C2'	1.523(3)
C1–C2	1.521(3)	C2'–C7'	1.526(3)
C2–C7	1.516(3)	C2'–C3'	1.532(3)
C2–C3	1.532(3)	C3'–C4'	1.504(3)
C3–C4	1.514(3)	C3'–C10'	1.529(3)
C3–C10	1.517(3)	C4'–C6'	1.312(3)
C4–C6	1.316(3)	C4'–C5'	1.499(3)
C4–C5	1.492(3)	C7'–C8'	1.506(3)
C7–C8	1.512(3)	C8'–C9'	1.510(3)
C8–C9	1.508(3)	C9'–C10'	1.521(3)
C9–C10	1.517(4)	C11'–C12'	1.428(4)
C11–C12	1.444(3)	C11'–C13'	1.523(3)
C11–C13	1.516(4)	C12'–C14'	1.284(4)
C12–C14	1.290(4)	C12'–C13'	1.419(4)
C12–C13	1.432(4)		
O1'–C1'	1.419(3)		
C5–O1–C1	111.24(17)	O1'–C1'–C11'	107.54(18)
O1–C1–C11	107.19(17)	O1'–C1'–C2'	110.05(17)
O1–C1–C2	110.47(16)	C11'–C1'–C2'	113.93(18)
C11–C1–C2	114.45(19)	C1'–C2'–C7'	113.12(18)
C7–C2–C1	113.27(18)	C1'–C2'–C3'	110.18(17)
C7–C2–C3	111.65(17)	C7'–C2'–C3'	110.96(16)
C1–C2–C3	110.51(18)	O2'–C3'–C4'	107.19(16)
O2–C3–C4	106.54(18)	O2'–C3'–C10'	108.55(17)
O2–C3–C10	109.12(19)	C4'–C3'–C10'	114.84(18)
C4–C3–C10	114.99(19)	O2'–C3'–C2'	105.66(15)
O2–C3–C2	105.60(17)	C4'–C3'–C2'	109.83(18)
C4–C3–C2	109.73(18)	C10'–C3'–C2'	110.31(18)
C10–C3–C2	110.4(2)	C6'–C4'–C5'	120.3(3)
C6–C4–C5	120.2(2)	C6'–C4'–C3'	125.2(2)
C6–C4–C3	126.0(2)	C5'–C4'–C3'	114.33(18)
C5–C4–C3	113.63(18)	O1'–C5'–C4'	112.59(18)
O1–C5–C4	112.35(19)	C8'–C7'–C2'	113.0(2)
C8–C7–C2	112.7(2)	C7'–C8'–C9'	111.1(2)
C9–C8–C7	110.9(2)	C8'–C9'–C10'	110.2(2)
C8–C9–C10	110.7(2)	C9'–C10'–C3'	114.02(19)
C12–C11–C1	119.7(2)	C12'–C11'–C1'	119.8(2)
C12–C11–C13	57.78(17)	C12'–C11'–C13'	57.38(19)
C1–C11–C13	121.0(3)	C1'–C11'–C13'	120.1(2)
C3–C10–C9	114.3(2)	C14'–C12'–C13'	148.8(4)
C14–C12–C13	149.6(3)	C14'–C12'–C11'	146.2(4)
C14–C12–C11	146.6(3)	C13'–C12'–C11'	64.7(2)
C13–C12–C11	63.64(19)	C12'–C13'–C11'	57.96(19)
C12–C13–C11	58.58(18)		
C1'–O1'–C5'	111.15(17)		

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	54(1)	47(1)	53(1)	−9(1)	−5(1)	−3(1)
O2	87(1)	56(1)	40(1)	−2(1)	4(1)	3(1)
C1	55(2)	39(1)	40(2)	−1(1)	3(1)	0(1)
C2	51(2)	42(1)	42(2)	−3(1)	−3(1)	1(1)
C3	59(2)	44(1)	40(2)	−3(1)	3(1)	−7(1)
C4	61(2)	38(1)	40(2)	−4(1)	7(1)	−1(1)
C5	55(2)	53(1)	66(2)	−7(1)	2(2)	3(1)
C6	81(2)	52(2)	68(2)	−1(2)	6(2)	7(2)
C7	54(2)	56(1)	56(2)	−10(1)	10(2)	−3(1)
C8	62(2)	76(2)	84(2)	−12(2)	16(2)	−16(2)
C9	79(2)	66(2)	102(3)	−17(2)	23(2)	−29(2)
C11	75(2)	45(1)	44(2)	−8(1)	12(1)	−4(1)
C10	66(2)	60(2)	77(2)	−20(2)	4(2)	−13(1)
C12	97(3)	57(2)	77(2)	−17(1)	−19(2)	22(2)
C13	108(3)	41(2)	70(2)	−8(2)	5(2)	−4(2)
C14	158(4)	97(3)	203(5)	−50(3)	−83(4)	49(3)
O1'	60(1)	48(1)	55(1)	−8(1)	10(1)	−6(1)
O2'	56(1)	47(1)	50(1)	8(1)	−12(1)	−11(1)
C1'	40(1)	43(1)	51(2)	−2(1)	−2(1)	−2(1)
C2'	40(1)	39(1)	46(2)	0(1)	2(1)	−4(1)
C3'	40(1)	39(1)	42(2)	2(1)	−4(1)	−1(1)
C4'	37(1)	42(1)	49(2)	5(1)	−8(1)	−4(1)
C5'	51(2)	54(1)	64(2)	3(1)	9(2)	−5(1)
C6'	61(2)	53(2)	64(2)	8(2)	0(2)	−6(1)
C7'	45(2)	45(1)	71(2)	−6(1)	−10(1)	−2(1)
C8'	47(2)	60(2)	90(2)	−4(1)	−4(2)	5(1)
C9'	59(2)	48(1)	80(2)	−10(1)	−3(2)	12(1)
C10'	62(2)	46(1)	59(2)	−5(1)	−3(2)	1(1)
C11'	49(2)	38(1)	72(2)	−5(1)	−9(1)	−5(1)
C12'	81(2)	65(2)	71(2)	−3(2)	7(2)	−40(2)
C13'	71(2)	40(2)	100(3)	2(2)	−1(2)	−5(1)
C14'	178(4)	139(4)	103(4)	−18(3)	35(3)	−99(4)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	x	y	z	U_{eq}	$S.o.f.$
H2	6361	5734	3081	150(17)	1
H1	6251	3130	2228	38(6)	1
H2	8027	4063	2222	49(6)	1
H5A	4747	4686	2184	51(7)	1
H5B	4402	5392	1554	59(7)	1
H7A	8335	4128	1173	58(7)	1

H7B	7425	5252	1070	66(7)	1
H8A	9534	5546	1747	59(7)	1
H8B	9222	6202	1100	88(10)	1
H9A	7896	7566	1534	81(10)	1
H9B	9059	7731	1920	92(9)	1
H11	7085	2402	1051	57(7)	1
H10A	8449	6376	2696	80(9)	1
H10B	7528	7480	2576	66(7)	1
H14A	8586	101	2291	220(20)	1
H14B	9106	1518	2111	139(16)	1
H2'	5784	7271	−1306	72(9)	1
H1'	6542	10061	−707	39(6)	1
H2'	8125	8921	−1015	39(6)	1
H5'1	5210	8798	−204	46(6)	1
H5'2	5498	8297	474	68(8)	1
H7'1	9346	9070	−135	53(6)	1
H7'2	8563	8126	232	55(7)	1
H8'1	10104	6930	−89	63(7)	1
H8'2	9833	7352	−782	62(8)	1
H9'1	8457	5665	−90	73(9)	1
H9'2	9154	5221	−657	76(8)	1
H10C	7210	5523	−959	68(7)	1
H10D	7990	6449	−1337	56(7)	1
H11'	8480	11004	40	41(6)	1
H14C	8352	12855	−1544	158(19)	1
H14D	9028	11480	−1435	170(20)	1
H6D	6368(16)	5310(20)	−100(9)	45(6)	1
H6B	6080(20)	8070(20)	1966(12)	80(9)	1
H6C	5658(19)	6080(20)	422(11)	57(8)	1
H13B	6240(20)	300(20)	1281(13)	78(9)	1
H6A	4860(20)	7540(20)	1660(12)	67(8)	1
H13C	6430(30)	12470(30)	−442(15)	117(11)	1
H13C	7620(20)	13110(30)	−40(13)	96(9)	1
H13A	5830(20)	840(20)	1929(14)	81(10)	1

Table 6. Hydrogen bonds [Å and °].

D–H···A	$d(D$–H)	d(H···A)	$d(D$···$A)$	$\angle(D$H$A)$
O2–H2···O2^{ii}	0.82	2.05	2.820(2)	156.7
O2'–H2'···O1^{ii}	0.82	2.03	2.845(2)	171.5

Symmetry transformations used to generate equivalent atoms:
(i) x,−y+3/2,z+1/2 (ii) −x+1,−y+1,−z

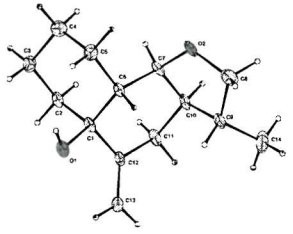

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Table 1. Crystal data and structure refinement.

Identification code	**00SOT135**	
Empirical formula	$C_{14}H_{22}O_2$	
Formula weight	222.32	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 11.8071(4) Å	α = 101.9669(17)°
	b = 13.1670(7) Å	β = 108.241(2)°
	c = 17.5307(10) Å	γ = 91.136(5)°
Volume	2521.6(2) Å^3	
Z	8	
Density (calculated)	1.171 Mg / m^3	
Absorption coefficient	0.076 mm^{-1}	
F(000)	976	
Crystal	Colourless Block	
Crystal size	0.30 × 0.20 × 0.10 mm^3	
θ range for data collection	3.14 – 23.25°	
Index ranges	$-12 \le h \le 12$, $-14 \le k \le 14$, $-19 \le l \le 19$	
Reflections collected	20596	
Independent reflections	6863 [R_{int} = 0.1897]	
Completeness to θ = 23.25°	94.6 %	
Max. and min. transmission	0.9924 and 0.9775	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6863 / 0 / 582	
Goodness-of-fit on F^2	0.912	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0985, $wR2$ = 0.2297	
R indices (all data)	$R1$ = 0.1663, $wR2$ = 0.2902	
Extinction coefficient	0.023(4)	
Largest diff. peak and hole	0.488 and –0.571 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. **A51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) **A46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U_{eq}	*S.o.f.*
C1	1658(4)	6140(3)	3082(3)	24(1)	1
C2	3011(4)	6243(4)	3264(3)	29(1)	1
C3	3382(4)	5749(4)	2539(3)	36(1)	1
C4	2789(5)	6200(4)	1796(3)	42(2)	1
C5	1422(4)	6078(4)	1579(3)	36(1)	1
C6	1005(4)	6533(3)	2300(3)	25(1)	1
C7	1095(4)	7741(3)	2459(3)	28(1)	1
C8	–758(5)	8382(5)	2070(4)	51(2)	1
C9	–480(4)	8263(4)	2965(4)	37(1)	1
C10	868(4)	8300(4)	3229(3)	31(1)	1
C11	1491(4)	7864(4)	3992(3)	33(1)	1
C12	1291(4)	6683(4)	3789(3)	27(1)	1
C13	802(5)	6197(4)	4218(4)	43(2)	1
C14	–977(5)	9067(5)	3485(5)	68(2)	1
C15	–1920(4)	8220(3)	–1053(3)	22(1)	1
C16	–1173(4)	7871(3)	–284(3)	28(1)	1
C17	–1583(4)	6760(4)	–293(4)	39(1)	1
C18	–2912(4)	6656(4)	–394(4)	40(1)	1
C19	–3682(4)	6992(3)	–1159(3)	32(1)	1
C20	–3259(4)	8098(3)	–1166(3)	20(1)	1
C21	–3626(4)	8901(3)	–531(3)	24(1)	1
C22	–5192(4)	9735(4)	–1245(3)	36(1)	1
C23	–4028(4)	10335(3)	–1157(3)	31(1)	1
C24	–3141(4)	10022(3)	–421(3)	24(1)	1
C25	–1814(4)	10138(3)	–356(3)	28(1)	1
C26	–1558(4)	9356(3)	–1024(3)	24(1)	1
C27	–1100(4)	9632(4)	–1551(3)	35(1)	1
C28	–4108(5)	11509(4)	–1030(4)	59(2)	1
C29	–6559(4)	13017(3)	4007(3)	25(1)	1
C30	–6639(4)	13638(4)	4820(3)	34(1)	1
C31	–7904(5)	13590(4)	4849(4)	43(2)	1
C32	–8426(5)	12459(4)	4689(4)	47(2)	1
C33	–8363(4)	11829(4)	3866(3)	37(1)	1

C34	−7105(4)	11881(3)	3817(3)	25(1)	1
C35	−6313(4)	11209(3)	4354(3)	27(1)	1
C36	−6056(5)	9727(4)	3467(4)	40(2)	1
C37	−5061(4)	10550(4)	3572(3)	30(1)	1
C38	−5006(4)	11277(3)	4375(3)	24(1)	1
C39	−4466(4)	12399(4)	4539(3)	32(1)	1
C40	−5266(4)	13033(3)	4001(3)	27(1)	1
C41	−4842(5)	13602(4)	3596(4)	43(2)	1
C42	−3878(5)	10093(4)	3565(4)	45(2)	1
C43	−8454(4)	16597(3)	8281(3)	25(1)	1
C44	−7903(4)	17737(4)	8529(3)	33(1)	1
C45	−8348(5)	18289(4)	7827(4)	43(2)	1
C46	−8117(5)	17722(4)	7056(4)	46(2)	1
C47	−8667(4)	16592(4)	6796(3)	37(1)	1
C48	−8246(4)	16014(3)	7491(3)	24(1)	1
C49	−6956(4)	15726(3)	7612(3)	25(1)	1
C50	−7153(5)	13960(4)	7098(4)	37(1)	1
C51	−6952(4)	14112(4)	8007(3)	30(1)	1
C52	−6426(4)	15250(3)	8349(3)	23(1)	1
C53	−6652(4)	15816(4)	9127(3)	30(1)	1
C54	−7949(4)	16047(4)	8981(3)	26(1)	1
C55	−8595(5)	15771(4)	9413(4)	41(2)	1
C56	−6149(5)	13351(4)	8405(4)	43(2)	1
O1	1266(3)	5039(2)	2886(2)	31(1)	1
O2	184(3)	8025(3)	1791(2)	40(1)	1
O3	−1756(3)	7556(2)	−1760(2)	30(1)	1
O4	−4906(3)	8922(2)	−810(2)	35(1)	1
O5	−7263(3)	13520(2)	3386(2)	30(1)	1
O6	−6715(3)	10122(2)	4003(2)	35(1)	1
O7	−9713(3)	16669(2)	8126(2)	32(1)	1
O8	−6906(3)	14947(2)	6927(2)	32(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–O1	1.450(5)	C11–C12	1.518(6)
C1–C12	1.488(7)	C12–C13	1.328(7)
C1–C2	1.525(6)	C15–O3	1.430(5)
C1–C6	1.547(7)	C15–C16	1.529(7)
C2–C3	1.499(7)	C15–C20	1.531(6)
C3–C4	1.519(7)	C15–C26	1.533(6)
C4–C5	1.535(7)	C16–C17	1.528(6)
C5–C6	1.511(7)	C17–C18	1.523(7)
C6–C7	1.552(6)	C18–C19	1.523(7)
C7–O2	1.441(6)	C19–C20	1.534(6)
C7–C10	1.503(7)	C20–C21	1.542(6)
C8–O2	1.401(6)	C21–O4	1.437(5)
C8–C9	1.542(8)	C21–C24	1.525(6)
C9–C14	1.502(7)	C22–O4	1.426(6)
C9–C10	1.509(6)	C22–C23	1.519(6)
C10–C11	1.542(7)	C23–C24	1.523(7)
C23–C28	1.525(7)	C40–C41	1.321(7)
C24–C25	1.537(6)	C43–O7	1.434(5)
C25–C26	1.502(6)	C43–C54	1.521(7)
C26–C27	1.313(6)	C43–C48	1.532(6)
C29–O5	1.437(5)	C43–C44	1.542(6)
C29–C30	1.521(7)	C44–C45	1.517(7)
C29–C40	1.530(6)	C45–C46	1.509(8)
C29–C34	1.544(6)	C46–C47	1.529(7)
C30–C31	1.511(7)	C47–C48	1.528(7)
C31–C32	1.536(7)	C48–C49	1.538(6)
C32–C33	1.533(7)	C49–O8	1.425(5)
C33–C34	1.515(6)	C49–C52	1.515(7)
C34–C35	1.540(6)	C50–O8	1.437(6)
C35–O6	1.441(5)	C50–C51	1.505(7)
C35–C38	1.532(6)	C51–C56	1.518(7)
C36–O6	1.425(6)	C51–C52	1.532(6)
C36–C37	1.524(6)	C52–C53	1.517(7)
C37–C38	1.510(7)	C53–C54	1.520(6)
C37–C42	1.534(6)	C54–C55	1.324(7)
C38–C39	1.531(6)		
C39–C40	1.510(7)		

O1–C1–C12	109.3(4)	O3–C15–C20	106.6(3)
O1–C1–C2	107.7(3)	C16–C15–C20	111.3(4)
C12–C1–C2	112.8(4)	O3–C15–C26	109.5(4)
O1–C1–C6	105.4(3)	C16–C15–C26	111.8(4)
C12–C1–C6	110.3(4)	C20–C15–C26	108.9(3)
C2–C1–C6	111.0(4)	C17–C16–C15	111.7(4)
C3–C2–C1	113.1(4)	C18–C17–C16	110.8(4)
C2–C3–C4	111.3(4)	C19–C18–C17	112.5(4)
C3–C4–C5	110.2(4)	C18–C19–C20	111.1(4)
C6–C5–C4	113.0(4)	C15–C20–C19	112.3(4)
C5–C6–C1	112.7(4)	C15–C20–C21	113.3(3)
C5–C6–C7	110.4(4)	C19–C20–C21	109.7(4)
C1–C6–C7	112.4(4)	O4–C21–C24	104.4(3)
O2–C7–C10	105.3(4)	O4–C21–C20	109.3(4)
O2–C7–C6	107.8(4)	C24–C21–C20	114.3(4)
C10–C7–C6	115.9(4)	O4–C22–C23	108.1(4)
O2–C8–C9	108.4(4)	C22–C23–C24	102.6(4)
C14–C9–C10	115.4(5)	C22–C23–C28	113.1(4)
C14–C9–C8	114.0(5)	C24–C23–C28	113.1(4)
C10–C9–C8	100.3(4)	C23–C24–C21	101.4(4)
C7–C10–C9	102.9(4)	C23–C24–C25	116.2(4)
C7–C10–C11	113.7(4)	C21–C24–C25	113.7(4)
C9–C10–C11	116.7(4)	C26–C25–C24	111.3(4)
C12–C11–C10	110.9(4)	C27–C26–C25	122.4(4)
C13–C12–C1	124.1(4)	C27–C26–C15	123.3(4)
C13–C12–C11	120.7(5)	C25–C26–C15	114.2(4)
C1–C12–C11	115.3(4)	O5–C29–C30	105.6(4)
O3–C15–C16	108.5(3)	O5–C29–C40	109.7(4)

C30–C29–C40	111.5(4)	C55–C54–C53	122.8(5)
O5–C29–C34	108.6(4)	C55–C54–C43	122.8(4)
C30–C29–C34	111.3(4)	C53–C54–C43	114.4(4)
C40–C29–C34	110.0(4)	C8–O2–C7	108.8(4)
C31–C30–C29	112.1(4)	C22–O4–C21	108.4(3)
C30–C31–C32	111.4(4)	C36–O6–C35	108.0(3)
C33–C32–C31	110.4(4)	C49–O8–C50	106.4(3)
C34–C33–C32	112.3(4)		
C33–C34–C35	110.9(4)		
C33–C34–C29	111.8(4)		
C35–C34–C29	113.4(4)		
O6–C35–C38	103.5(3)		
O6–C35–C34	109.7(4)		
C38–C35–C34	113.7(4)		
O6–C36–C37	108.9(4)		
C38–C37–C36	101.9(4)		
C38–C37–C42	114.7(4)		
C36–C37–C42	113.2(4)		
C37–C38–C39	117.6(4)		
C37–C38–C35	102.7(4)		
C39–C38–C35	113.1(4)		
C40–C39–C38	112.6(4)		
C41–C40–C39	121.3(5)		
C41–C40–C29	123.3(5)		
C39–C40–C29	115.3(4)		
O7–C43–C54	110.3(4)		
O7–C43–C48	109.2(4)		
C54–C43–C48	110.9(4)		
O7–C43–C44	104.9(3)		
C54–C43–C44	110.5(4)		
C48–C43–C44	110.9(4)		
C45–C44–C43	111.5(4)		
C46–C45–C44	112.1(4)		
C45–C46–C47	111.0(5)		
C48–C47–C46	112.2(4)		
C47–C48–C43	111.9(4)		
C47–C48–C49	111.1(4)		
C43–C48–C49	114.2(4)		
O8–C49–C52	104.2(3)		
O8–C49–C48	110.7(4)		
C52–C49–C48	114.3(4)		
O8–C50–C51	108.7(4)		
C50–C51–C56	113.6(4)		
C50–C51–C52	103.0(4)		
C56–C51–C52	113.2(4)		
C49–C52–C53	114.0(4)		
C49–C52–C51	101.9(4)		
C53–C52–C51	116.5(4)		
C52–C53–C54	112.9(4)		

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	24(3)	11(2)	31(3)	3(2)	0(2)	−2(2)
C2	34(3)	16(3)	36(3)	7(2)	8(3)	5(2)
C3	28(3)	37(3)	45(4)	12(3)	12(3)	9(2)
C4	49(3)	45(4)	34(4)	11(3)	15(3)	9(3)
C5	38(3)	37(3)	31(3)	6(3)	11(3)	10(2)
C6	28(3)	16(3)	30(3)	7(2)	5(2)	4(2)
C7	33(3)	15(3)	35(3)	12(2)	4(2)	0(2)
C8	38(3)	53(4)	73(5)	38(4)	16(3)	7(3)
C9	32(3)	24(3)	63(4)	24(3)	20(3)	9(2)
C10	36(3)	13(3)	43(4)	11(3)	9(3)	7(2)
C11	42(3)	18(3)	35(3)	5(3)	7(3)	8(2)
C12	26(3)	22(3)	33(3)	11(2)	7(2)	11(2)
C13	57(4)	36(3)	55(4)	22(3)	36(3)	27(3)
C14	58(4)	50(4)	115(7)	32(4)	46(4)	32(3)
C15	24(3)	13(2)	29(3)	4(2)	8(2)	5(2)
C16	34(3)	17(3)	34(3)	9(2)	11(2)	4(2)
C17	39(3)	27(3)	48(4)	18(3)	7(3)	6(2)
C18	46(3)	19(3)	57(4)	22(3)	12(3)	4(2)
C19	31(3)	13(3)	48(4)	5(3)	8(3)	−1(2)
C20	22(2)	17(3)	26(3)	8(2)	11(2)	4(2)
C21	20(3)	23(3)	28(3)	7(2)	7(2)	3(2)
C22	33(3)	39(3)	40(4)	13(3)	15(3)	11(2)
C23	35(3)	19(3)	40(4)	10(3)	11(3)	12(2)
C24	27(3)	14(2)	31(3)	2(2)	10(2)	5(2)
C25	26(3)	15(3)	44(4)	8(2)	13(2)	1(2)
C26	20(2)	24(3)	28(3)	6(2)	6(2)	0(2)
C27	31(3)	39(3)	46(4)	22(3)	19(3)	9(2)
C28	59(4)	30(3)	80(5)	20(3)	4(4)	14(3)
C29	37(3)	19(3)	20(3)	11(2)	3(2)	9(2)
C30	47(3)	28(3)	30(3)	10(3)	12(3)	8(2)
C31	64(4)	34(3)	37(4)	8(3)	23(3)	20(3)
C32	41(3)	54(4)	64(5)	26(3)	32(3)	20(3)
C33	37(3)	33(3)	50(4)	16(3)	20(3)	13(2)
C34	24(3)	26(3)	28(3)	15(2)	5(2)	5(2)
C35	35(3)	23(3)	25(3)	13(2)	7(2)	6(2)
C36	52(3)	27(3)	52(4)	17(3)	26(3)	12(2)
C37	31(3)	24(3)	38(4)	16(3)	10(2)	6(2)
C38	26(3)	26(3)	26(3)	21(2)	4(2)	7(2)
C39	30(3)	31(3)	33(3)	16(3)	3(2)	0(2)
C40	35(3)	20(3)	27(3)	6(2)	10(2)	1(2)
C41	40(3)	42(3)	55(4)	26(3)	17(3)	3(2)
C42	49(3)	47(4)	59(4)	27(3)	32(3)	23(3)
C43	15(2)	19(3)	37(3)	2(2)	7(2)	3(2)
C44	28(3)	19(3)	47(4)	−1(3)	11(3)	2(2)
C45	36(3)	14(3)	73(5)	11(3)	8(3)	4(2)
C46	53(4)	27(3)	67(5)	32(3)	17(3)	10(2)

C47	36(3)	33(3)	45(4)	19(3)	13(3)	8(2)
C48	22(3)	21(3)	28(3)	8(2)	5(2)	2(2)
C49	28(3)	17(3)	35(3)	11(2)	15(2)	3(2)
C50	48(3)	19(3)	53(4)	11(3)	26(3)	8(2)
C51	30(3)	24(3)	43(4)	12(3)	17(3)	6(2)
C52	15(2)	21(3)	36(3)	11(2)	10(2)	3(2)
C53	22(3)	30(3)	40(4)	16(3)	9(2)	4(2)
C54	30(3)	24(3)	22(3)	−1(2)	9(2)	3(2)
C55	45(3)	38(3)	48(4)	12(3)	25(3)	8(2)
C56	41(3)	30(3)	72(5)	28(3)	27(3)	17(2)
O1	36(2)	12(2)	40(2)	0(2)	9(2)	0(1)
O2	40(2)	34(2)	53(3)	31(2)	12(2)	14(2)
O3	34(2)	23(2)	29(2)	−3(2)	10(2)	5(1)
O4	26(2)	32(2)	56(3)	13(2)	23(2)	9(1)
O5	44(2)	20(2)	27(2)	10(2)	9(2)	14(2)
O6	37(2)	18(2)	59(3)	21(2)	20(2)	6(1)
O7	22(2)	18(2)	51(3)	0(2)	9(2)	4(1)
O8	43(2)	18(2)	48(3)	10(2)	30(2)	6(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H2A	3303	6992	3436	35	1
H2B	3395	5915	3729	35	1
H3A	3160	4988	2397	43	1
H3B	4263	5863	2688	43	1
H4A	3017	5835	1319	50	1
H4B	3070	6948	1918	50	1
H5A	1056	6425	1123	43	1
H5B	1139	5327	1383	43	1
H6	137	6289	2137	30	1
H7	1901	8001	2466	34	1
H8A	−1519	7970	1715	61	1
H8B	−840	9122	2046	61	1
H9	−809	7554	2958	44	1
H10	1188	9046	3349	37	1
H11A	2360	8079	4186	40	1
H11B	1170	8156	4441	40	1
H13A	667	5459	4079	52	1
H13B	587	6589	4663	52	1
H14A	−1854	8982	3267	101	1
H14B	−689	9766	3474	101	1
H14C	−712	8978	4054	101	1
H16A	−321	7908	−252	33	1
H16B	−1241	8351	212	33	1
H17A	−1431	6268	−753	46	1
H17B	−1117	6576	229	46	1
H18A	−3164	5921	−430	48	1
H18B	−3045	7089	99	48	1
H19A	−4527	6970	−1171	39	1
H19B	−3642	6500	−1658	39	1
H20	−3698	8222	−1723	24	1
H21	−3366	8699	14	28	1
H22A	−5704	10207	−1014	43	1
H22B	−5633	9436	−1834	43	1
H23	−3794	10076	−1659	37	1
H24	−3236	10449	94	29	1
H25A	−1602	10851	−398	34	1
H25B	−1312	10039	189	34	1
H27A	−917	10349	−1517	42	1
H27B	−950	9115	−1965	42	1
H28A	−4686	11664	−1522	89	1
H28B	−3319	11858	−936	89	1
H28C	−4369	11760	−551	89	1
H30A	−6114	13361	5277	41	1
H30B	−6345	14375	4899	41	1
H31A	−8414	13933	4428	52	1
H31B	−7909	13975	5396	52	1
H32A	−7970	12137	5141	56	1
H32B	−9270	12450	4677	56	1
H33A	−8648	11092	3793	44	1
H33B	−8903	12100	3410	44	1
H34	−7170	11564	3233	31	1
H35	−6351	11404	4927	33	1
H36A	−6594	9555	2888	48	1
H36B	−5708	9083	3602	48	1
H37	−5326	10931	3118	36	1
H38	−4530	10962	4834	29	1
H39A	−4319	12739	5125	38	1
H39B	−3684	12388	4441	38	1
H41A	−4019	13619	3640	51	1
H41B	−5361	13996	3260	51	1
H42A	−3279	10656	3626	68	1
H42B	−4006	9590	3042	68	1
H42C	−3595	9742	4022	68	1
H44A	−8112	18113	9010	40	1
H44B	−7020	17749	8694	40	1
H45A	−9219	18346	7705	52	1
H45B	−7943	19004	7999	52	1
H46A	−7243	17734	7158	56	1
H46B	−8465	18083	6605	56	1
H47A	−9550	16583	6621	44	1
H47B	−8446	16225	6317	44	1
H48	−8764	15340	7305	28	1
H49	−6434	16362	7667	30	1
H50A	−6617	13454	6932	45	1
H50B	−7991	13682	6781	45	1
H51	−7744	14038	8094	36	1
H52	−5540	15269	8463	28	1

H53A	−6133	16480	9354	35	1
H53B	−6427	15385	9543	35	1
H55A	−8249	15412	9836	49	1
H55B	−9403	15931	9300	49	1
H56A	−6057	13491	8994	64	1
H56B	−5362	13434	8337	64	1
H56C	−6510	12637	8142	64	1
H1	1161	4787	2385	46	1
H3	−2281	7047	−1941	45	1
H5	−7350	13147	2917	45	1
H7A	−10094	16118	7803	48	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
O1–H1···O7^{i}	0.84	2.37	2.776(4)	110.7
O5–H5···O3^{ii}	0.84	1.98	2.770(5)	155.7
O7–H7A···O1^{i}	0.84	1.95	2.776(4)	167.8

Symmetry transformations used to generate equivalent atoms:
(i) −x−1,−y+2,−z+1 (ii) −x−1,−y+2,−z

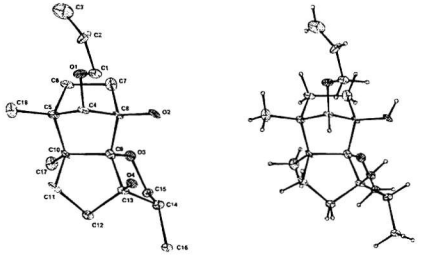

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Table 1. Crystal data and structure refinement.

Identification code	**01SOT074**	
Empirical formula	$C_{18}H_{28}O_4$	
Formula weight	308.40	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P*–1	
Unit cell dimensions	a = 9.6537(19) Å	α = 94.77(3)°
	b = 10.664(2) Å	β = 97.10(3)°
	c = 15.994(3) Å	γ = 90.01(3)°
Volume	1628.2(6) Å^3	
Z	4	
Density (calculated)	1.258 Mg / m^3	
Absorption coefficient	0.087 mm^{-1}	
F(000)	672	
Crystal	Colourless plate	
Crystal size	0.15 × 0.10 × 0.01 mm^3	
θ range for data collection	3.08 – 23.26°	
Index ranges	$-10 \le h \le 10$, $-11 \le k \le 11$, $-17 \le l \le 17$	
Reflections collected	9719	
Independent reflections	3783 [R_{int} = 0.1274]	
Completeness to θ = 23.26°	81.0 %	
Max. and min. transmission	0.9991 and 0.9871	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3783 / 24 / 402	
Goodness-of-fit on F^2	1.229	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.1287, *wR2* = 0.3349	
R indices (all data)	*R1* = 0.2082, *wR2* = 0.3785	
Extinction coefficient	0.023(8)	

Largest diff. peak and hole	0.898 and –0.386 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (*Z.* Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. **A51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	–3027(9)	1473(9)	3445(6)	26(3)	1
C2	–3724(11)	1051(11)	4153(6)	40(3)	1
C3	–3140(13)	384(12)	4731(9)	66(4)	1
C4	–818(9)	1541(9)	2930(6)	22(2)	1
C5	751(9)	1459(9)	3245(6)	24(3)	1
C6	938(10)	31(8)	3160(6)	26(3)	1
C7	–69(10)	–457(9)	2371(6)	26(3)	1
C8	–715(9)	756(9)	2085(6)	20(2)	1
C9	391(9)	1510(9)	1689(6)	19(2)	1
C10	1394(9)	2003(9)	2499(6)	22(3)	1
C11	1191(10)	3473(9)	2495(7)	29(3)	1
C12	879(10)	3708(9)	1579(6)	23(3)	1
C13	–125(10)	2657(9)	1200(6)	22(3)	1
C14	–70(10)	2208(9)	270(6)	24(3)	1
C15	1154(9)	1314(9)	358(6)	21(2)	1
C16	69(10)	3246(9)	–321(6)	26(3)	1
C17	2892(9)	1715(10)	2423(6)	33(3)	1
C18	1263(10)	2062(10)	4127(6)	37(3)	1
O1	–1625(6)	975(6)	3486(4)	30(2)	1
O2	–2004(6)	608(6)	1539(4)	26(2)	1
O3	1008(6)	669(6)	1099(4)	25(2)	1
O4	–1508(6)	3091(6)	1354(4)	22(2)	1
C19	9405(10)	6440(11)	3477(7)	36(3)	1
C20	10355(10)	5870(11)	4142(7)	38(3)	1
C21	11419(16)	6407(15)	4633(9)	87(5)	1
C22	6989(9)	6538(10)	2944(6)	26(3)	1
C23	5542(10)	6438(9)	3283(6)	22(2)	1
C24	5352(10)	4976(9)	3188(6)	29(3)	1
C25	6034(10)	4546(9)	2388(6)	25(3)	1
C26	6574(9)	5749(9)	2103(6)	21(3)	1
C27	5307(9)	6500(9)	1723(6)	19(2)	1
C28	4631(10)	7021(9)	2515(6)	26(3)	1
C29	4827(10)	8500(9)	2523(6)	25(3)	1
C30	4760(9)	8716(9)	1602(6)	20(2)	1
C31	5653(10)	7631(9)	1214(6)	21(2)	1
C32	5196(10)	7218(8)	310(6)	22(3)	1
C33	3995(9)	6320(10)	370(6)	26(3)	1
C34	4808(10)	8232(9)	–305(6)	27(3)	1
C35	3083(9)	6713(10)	2489(7)	34(3)	1
C36	5409(11)	7039(10)	4144(6)	36(3)	1
O5	8050(7)	5944(6)	3497(4)	31(2)	1
O6	7608(6)	5616(6)	1540(4)	26(2)	1
O7	4426(6)	5679(6)	1114(4)	28(2)	1
O8	7044(6)	8074(6)	1368(4)	25(2)	1

Table 3. Bond lengths [Å] and angles [°].

C1–O1	1.450(10)	C19–C20	1.486(14)
C1–C2	1.485(13)	C20–C21	1.313(17)
C2–C3	1.289(16)	C22–O5	1.449(11)
C4–O1	1.422(10)	C22–C26	1.535(14)
C4–C5	1.541(12)	C22–C23	1.566(13)
C4–C8	1.543(13)	C23–C36	1.491(13)
C5–C18	1.525(13)	C23–C24	1.563(13)
C5–C6	1.530(13)	C23–C28	1.590(13)
C5–C10	1.563(13)	C24–C25	1.547(13)
C6–C7	1.548(13)	C25–C26	1.511(12)
C7–C8	1.517(13)	C26–O6	1.424(10)
C8–O2	1.430(11)	C26–C27	1.550(13)
C8–C9	1.562(13)	C27–O7	1.446(11)
C9–O3	1.431(10)	C27–C28	1.558(13)
C9–C13	1.556(12)	C27–C31	1.568(12)
C9–C10	1.572(13)	C28–C35	1.525(13)
C10–C17	1.496(12)	C28–C29	1.588(14)
C10–C11	1.581(13)	C29–C30	1.503(12)
C11–C12	1.501(13)	C30–C31	1.574(12)
C12–C13	1.518(13)	C31–O8	1.409(11)
C13–O4	1.456(10)	C31–C32	1.489(12)
C13–C14	1.531(13)	C32–C33	1.521(12)
C14–C15	1.519(12)	C32–C34	1.536(12)
C14–C16	1.531(12)	C33–O7	1.439(11)
C15–O3	1.440(10)		
C19–O5	1.415(11)		
O1–C1–C2	109.8(8)	C4–C5–C10	100.5(7)
C3–C2–C1	124.6(11)	C5–C6–C7	105.6(7)
O1–C4–C5	110.4(8)	C8–C7–C6	101.6(7)
O1–C4–C8	114.8(8)	O2–C8–C7	115.2(8)
C5–C4–C8	94.5(7)	O2–C8–C4	114.4(7)
C18–C5–C6	113.2(8)	C7–C8–C4	102.6(7)
C18–C5–C4	117.7(8)	O2–C8–C9	111.9(7)
C6–C5–C4	100.2(8)	C7–C8–C9	109.1(8)
C18–C5–C10	115.9(8)	C4–C8–C9	102.5(7)
C6–C5–C10	107.5(8)	O3–C9–C13	106.1(7)

O3–C9–C8	108.3(7)	C25–C24–C23	104.4(7)
C13–C9–C8	117.7(7)	C26–C25–C24	104.3(8)
O3–C9–C10	115.3(7)	O6–C26–C25	116.3(8)
C13–C9–C10	108.5(7)	O6–C26–C22	116.5(7)
C8–C9–C10	101.3(7)	C25–C26–C22	102.4(8)
C17–C10–C5	117.0(8)	O6–C26–C27	111.1(7)
C17–C10–C9	112.5(8)	C25–C26–C27	108.2(7)
C5–C10–C9	104.3(7)	C22–C26–C27	100.9(7)
C17–C10–C11	108.5(8)	O7–C27–C26	109.3(7)
C5–C10–C11	112.0(8)	O7–C27–C28	115.6(7)
C9–C10–C11	101.4(7)	C26–C27–C28	103.4(7)
C12–C11–C10	105.1(8)	O7–C27–C31	104.1(7)
C11–C12–C13	104.7(8)	C26–C27–C31	116.1(7)
O4–C13–C12	105.8(7)	C28–C27–C31	108.7(7)
O4–C13–C14	112.2(7)	C35–C28–C27	115.1(8)
C12–C13–C14	116.9(8)	C35–C28–C29	109.1(8)
O4–C13–C9	114.2(7)	C27–C28–C29	103.4(7)
C12–C13–C9	103.6(8)	C35–C28–C23	111.7(8)
C14–C13–C9	104.2(7)	C27–C28–C23	104.2(7)
C15–C14–C13	100.3(7)	C29–C28–C23	113.1(8)
C15–C14–C16	115.0(8)	C30–C29–C28	103.5(8)
C13–C14–C16	115.6(8)	C29–C30–C31	105.0(7)
O3–C15–C14	105.6(7)	O8–C31–C32	113.5(8)
C4–O1–C1	112.1(7)	O8–C31–C27	115.5(7)
C9–O3–C15	108.5(7)	C32–C31–C27	105.6(7)
O5–C19–C20	107.4(9)	O8–C31–C30	105.3(7)
C21–C20–C19	127.7(13)	C32–C31–C30	114.8(7)
O5–C22–C26	112.8(8)	C27–C31–C30	101.9(7)
O5–C22–C23	109.7(7)	C31–C32–C33	102.3(7)
C26–C22–C23	96.2(7)	C31–C32–C34	118.3(8)
C36–C23–C24	114.5(8)	C33–C32–C34	113.2(8)
C36–C23–C22	117.7(8)	O7–C33–C32	104.6(7)
C24–C23–C22	99.3(8)	C19–O5–C22	112.9(7)
C36–C23–C28	116.5(8)	C33–O7–C27	109.9(7)
C24–C23–C28	109.2(8)		
C22–C23–C28	97.1(7)		

Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	24(6)	23(7)	34(7)	6(5)	11(5)	1(5)
C2	37(7)	64(9)	23(7)	23(6)	6(5)	5(6)
C3	49(9)	60(10)	93(12)	15(8)	24(8)	–3(8)
C4	24(5)	13(5)	30(5)	5(4)	10(4)	–4(4)
C5	14(5)	27(7)	33(7)	12(5)	0(4)	–5(5)
C6	25(6)	13(7)	42(7)	9(5)	10(5)	2(5)
C7	26(6)	19(7)	32(7)	–5(5)	5(5)	10(5)
C8	21(6)	10(6)	30(6)	2(5)	4(4)	–8(5)
C9	20(6)	11(6)	24(6)	–5(4)	2(4)	2(5)
C10	17(5)	14(6)	33(6)	4(4)	–6(4)	–10(4)
C11	20(6)	15(7)	53(8)	–3(5)	8(5)	–9(5)
C12	22(6)	17(7)	30(7)	6(5)	4(4)	1(5)
C13	24(6)	15(6)	29(6)	5(5)	10(4)	–4(5)
C14	25(6)	21(7)	27(6)	9(5)	4(4)	5(5)
C15	20(6)	24(7)	21(6)	8(5)	3(4)	0(5)
C16	29(6)	23(7)	27(6)	8(5)	6(5)	–8(5)
C17	28(6)	35(7)	35(7)	–1(5)	1(5)	3(5)
C18	32(6)	38(8)	36(7)	–8(6)	–2(5)	2(6)
O1	27(4)	31(5)	36(5)	14(3)	12(3)	1(4)
O2	18(4)	17(4)	41(5)	5(3)	0(3)	–9(3)
O3	29(4)	21(4)	25(4)	–2(3)	8(3)	0(3)
O4	18(4)	17(4)	30(4)	3(3)	5(3)	0(3)
C19	17(6)	43(8)	47(8)	7(6)	3(5)	–7(6)
C20	19(6)	45(8)	45(8)	–2(6)	–6(5)	2(6)
C21	97(13)	95(13)	70(12)	14(10)	9(10)	14(11)
C22	6(5)	36(7)	37(7)	12(5)	6(4)	1(5)
C23	26(6)	13(7)	23(6)	–2(5)	–6(4)	–4(5)
C24	27(6)	26(8)	33(7)	6(5)	2(5)	–6(5)
C25	29(6)	5(6)	42(7)	10(5)	5(5)	–3(5)
C26	14(5)	21(7)	31(7)	8(5)	7(4)	–4(5)
C27	26(5)	7(5)	23(5)	–1(4)	4(4)	–8(4)
C28	21(6)	16(7)	40(7)	2(5)	0(5)	2(5)
C29	22(6)	35(8)	19(6)	–9(5)	10(4)	6(5)
C30	10(5)	9(6)	40(7)	2(5)	2(4)	–4(4)
C31	21(5)	11(5)	30(6)	6(4)	–4(4)	–8(4)
C32	23(6)	6(6)	36(7)	4(5)	3(4)	–5(5)
C33	17(6)	32(7)	30(7)	2(5)	7(4)	–3(5)
C34	26(6)	35(7)	21(6)	5(5)	5(4)	8(5)
C35	21(6)	27(7)	51(8)	–3(5)	0(5)	4(5)
C36	38(7)	32(7)	38(7)	4(6)	8(5)	–9(6)
O5	30(4)	26(5)	38(5)	14(3)	–3(3)	–1(4)
O6	23(4)	22(4)	34(4)	5(3)	9(3)	4(3)
O7	33(4)	23(4)	25(4)	4(3)	–5(3)	–4(4)
O8	21(4)	18(4)	36(5)	2(3)	5(3)	–4(3)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [Å^2 × 10^3].

Atom	x	y	z	U_{eq}	$S.o.f.$
H1A	–3570	1175	2899	31	1
H1B	–2987	2404	3483	31	1
H2	–4666	1290	4181	48	1
H3A	–2198	128	4723	79	1
H3B	–3650	148	5165	79	1
H4	–1110	2425	2842	26	1
H6A	697	–344	3670	31	1
H6B	1914	–182	3083	31	1
H7A	442	–889	1932	31	1

H7B	−784	−1038	2520	31	1
H11A	407	3750	2808	35	1
H11B	2049	3930	2757	35	1
H12A	1742	3675	1302	27	1
H12B	443	4540	1515	27	1
H14	−936	1706	58	28	1
H15A	1123	708	−148	25	1
H15B	2050	1786	429	25	1
H16A	−759	3779	−336	39	1
H16B	152	2865	−891	39	1
H16C	903	3758	−113	39	1
H17A	3173	2101	1934	50	1
H17B	3009	802	2347	50	1
H17C	3475	2053	2937	50	1
H18A	803	1654	4547	55	1
H18B	1041	2960	4157	55	1
H18C	2276	1961	4244	55	1
H2	−2302	−133	1532	38	1
H4A	−2089	2500	1222	32	1
H19A	9407	7367	3589	43	1
H19B	9714	6229	2915	43	1
H20	10171	5016	4221	45	1
H21A	11654	7261	4583	105	1
H21B	11953	5943	5038	105	1
H22	7242	7424	2862	31	1
H24A	5826	4597	3690	34	1
H24B	4350	4738	3115	34	1
H25A	6806	3957	2522	30	1
H25B	5339	4127	1945	30	1
H29A	4072	8953	2784	30	1
H29B	5739	8781	2836	30	1
H30A	5158	9550	1531	23	1
H30B	3783	8668	1326	23	1
H32	5966	6710	93	26	1
H33A	3122	6788	428	31	1
H33B	3843	5716	−138	31	1
H34A	4535	7828	−874	41	1
H34B	5615	8788	−311	41	1
H34C	4028	8726	−121	41	1
H35A	2748	7076	3009	50	1
H35B	2948	5798	2440	50	1
H35C	2559	7067	2000	50	1
H36A	5547	7950	4152	53	1
H36B	6117	6697	4555	53	1
H36C	4477	6863	4292	53	1
H6	7943	4889	1548	39	1
H8	7581	7501	1219	38	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
O2–H2···O8^{i}	0.84	2.00	2.835(9)	172.8
O4–H4A···O2	0.84	2.12	2.737(9)	130.2
O6–H6···O4^{ii}	0.84	2.00	2.828(8)	168.8
O8–H8···O6	0.84	2.11	2.707(9)	127.3

Symmetry transformations used to generate equivalent atoms:
(i) x−1,y−1,z (ii) x+1,y,z

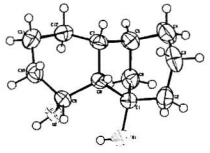

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Table 1. Crystal data and structure refinement.

Identification code	**01sot117**	
Empirical formula	$C_{12}H_{20}O_2$	
Formula weight	196.28	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 12.081(2) Å	α = 90°
	b = 8.9358(18) Å	β = 113.24(3)°
	c = 11.019(2) Å	γ = 90°
Volume	1093.0(4) Å^3	
Z	4	
Density (calculated)	1.193 Mg / m^3	
Absorption coefficient	0.079 mm^{-1}	
F(000)	432	
Crystal	Plate; colourless	
Crystal size	0.18 × 0.14 × 0.02 mm^3	
θ range for data collection	2.93 – 27.49°	
Index ranges	$-14 \le h \le 15$, $-11 \le k \le 11$, $-14 \le l \le 13$	
Reflections collected	8144	
Independent reflections	2485 [R_{int} = 0.0778]	
Completeness to θ = 27.49°	98.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9984 and 0.9859	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2485 / 0 / 130	
Goodness-of-fit on F^2	0.974	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0525, $wR2$ = 0.1076	
R indices (all data)	$R1$ = 0.1316, $wR2$ = 0.1325	
Extinction coefficient	0.026(6)	
Largest diff. peak and hole	0.156 and –0.173 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Further information: http://www.soton.ac.uk/~xservice/strat.htm

Special details:

Chirality: C1 = S, C5 = S, C7 = R, C8 = S, C9 = R.

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	6680(2)	4534(2)	9341(2)	43(1)	1
C2	6665(2)	5860(2)	10196(2)	62(1)	1
C3	7757(2)	5835(2)	11504(2)	68(1)	1
C4	8918(2)	5476(2)	11342(2)	68(1)	1
C5	8761(2)	4199(2)	10373(2)	51(1)	1
C6	7803(2)	4622(2)	9043(2)	50(1)	1
C7	8225(2)	2776(2)	10706(2)	42(1)	1
C8	6847(1)	3046(2)	10112(2)	37(1)	1
C9	6114(2)	1721(2)	9316(2)	40(1)	1
C10	6596(2)	268(2)	10035(2)	52(1)	1
C11	7916(2)	−19(2)	10299(2)	62(1)	1
C12	8572(2)	1381(2)	10143(2)	51(1)	1
O1	5589(1)	4594(1)	8184(1)	67(1)	1
O2	6124(1)	1723(1)	8014(1)	49(1)	1

Table 3. *Bond lengths [Å] and angles [°].*

C1–O1	1.429(2)
C1–C6	1.518(3)
C1–C2	1.518(2)
C1–C8	1.548(2)
C2–C3	1.523(3)
C2–H2A	0.9700
C2–H2B	0.9700
C3–C4	1.516(3)
C3–H3A	0.9700
C3–H3B	0.9700
C4–C5	1.523(3)
C4–H4A	0.9700
C4–H4B	0.9700
C5–C6	1.514(3)
C5–C7	1.537(2)
C5–H5	0.9800
C6–H6A	0.9700
C6–H6B	0.9700
C7–C12	1.523(2)
C7–C8	1.549(2)
C7–H7	0.9800
C8–C9	1.530(2)
C8–H8	0.9800
C9–O2	1.439(2)
C9–C10	1.513(2)
C9–H9	0.9800
C10–C11	1.526(3)
C10–H10A	0.9700
C10–H10B	0.9700

C11–C12	1.526(2)
C11–H11A	0.9700
C11–H11B	0.9700
C12–H12A	0.9700
C12–H12B	0.9700
O1–H1	0.8200
O2–H2	0.8200
O1–C1–C6	113.14(16)
O1–C1–C2	106.95(14)
C6–C1–C2	108.90(15)
O1–C1–C8	113.37(13)
C6–C1–C8	103.29(13)
C2–C1–C8	111.19(15)
C1–C2–C3	110.93(15)
C1–C2–H2A	109.5
C3–C2–H2A	109.5
C1–C2–H2B	109.5
C3–C2–H2B	109.5
H2A–C2–H2B	108.0
C4–C3–C2	112.81(17)
C4–C3–H3A	109.0
C2–C3–H3A	109.0
C4–C3–H3B	109.0
C2–C3–H3B	109.0
H3A–C3–H3B	107.8
C3–C4–C5	112.12(16)
C3–C4–H4A	109.2
C5–C4–H4A	109.2
C3–C4–H4B	109.2
C5–C4–H4B	109.2
H4A–C4–H4B	107.9
C6–C5–C4	109.13(16)
C6–C5–C7	101.80(14)
C4–C5–C7	113.55(16)
C6–C5–H5	110.7
C4–C5–H5	110.7
C7–C5–H5	110.7
C5–C6–C1	100.66(15)
C5–C6–H6A	111.6
C1–C6–H6A	111.6
C5–C6–H6B	111.6
C1–C6–H6B	111.6
H6A–C6–H6B	109.4
C12–C7–C5	111.73(15)
C12–C7–C8	112.19(13)
C5–C7–C8	104.73(14)
C12–C7–H7	109.4
C5–C7–H7	109.4
C8–C7–H7	109.4

C9–C8–C1	115.44(14)
C9–C8–C7	113.86(13)
C1–C8–C7	104.54(12)
C9–C8–H8	107.5
C1–C8–H8	107.5
C7–C8–H8	107.5
O2–C9–C10	111.68(13)
O2–C9–C8	109.86(13)
C10–C9–C8	110.34(14)
O2–C9–H9	108.3
C10–C9–H9	108.3
C8–C9–H9	108.3
C9–C10–C11	113.67(14)
C9–C10–H10A	108.8
C11–C10–H10A	108.8
C9–C10–H10B	108.8
C11–C10–H10B	108.8
H10A–C10–H10B	107.7
C10–C11–C12	112.99(15)
C10–C11–H11A	109.0
C12–C11–H11A	109.0
C10–C11–H11B	109.0
C12–C11–H11B	109.0
H11A–C11–H11B	107.8
C7–C12–C11	112.74(15)
C7–C12–H12A	109.0
C11–C12–H12A	109.0
C7–C12–H12B	109.0
C11–C12–H12B	109.0
H12A–C12–H12B	107.8
C1–O1–H1	109.5
C9–O2–H2	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	40(1)	39(1)	42(1)	2(1)	8(1)	0(1)
C2	64(1)	41(1)	84(2)	−7(1)	34(1)	−2(1)
C3	90(2)	52(1)	67(2)	−23(1)	35(1)	−22(1)
C4	63(2)	62(2)	67(2)	−10(1)	12(1)	−23(1)
C5	40(1)	51(1)	59(1)	−2(1)	17(1)	−9(1)
C6	61(1)	43(1)	50(1)	6(1)	25(1)	−9(1)
C7	37(1)	47(1)	33(1)	4(1)	5(1)	−4(1)
C8	37(1)	41(1)	33(1)	−1(1)	14(1)	−4(1)
C9	35(1)	44(1)	39(1)	−3(1)	14(1)	−7(1)
C10	59(1)	41(1)	52(1)	2(1)	20(1)	−10(1)
C11	63(2)	45(1)	72(2)	9(1)	21(1)	6(1)
C12	39(1)	51(1)	57(1)	5(1)	12(1)	6(1)
O1	55(1)	51(1)	66(1)	6(1)	−7(1)	11(1)
O2	51(1)	51(1)	37(1)	−6(1)	9(1)	−10(1)

Elementary my dear Watson

Sherlock Holmes