University of Southampton

Lewis Acid Mediated Cyclisation of Methylenecyclopropane Derivatives

By

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Doctor of Philosophy

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Abstract

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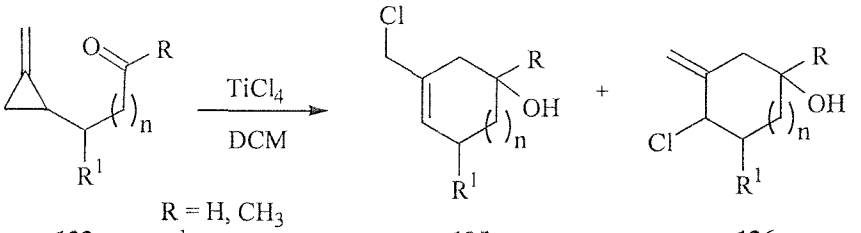
This thesis is concerned with the synthesis, and cyclisation of compounds containing a methylenecyclopropane moiety. Special interest is given to Lewis acid mediated cyclisation of methylenecyclopropyl ketones and ketals, which proceed with high yields of highly functionalised carbocycles.

Chapter 1 discussed the synthesis and the cyclisation of methylenecyclopropyl ketones and aldehydes **122**, which gave cyclised compounds **125** and **126**.



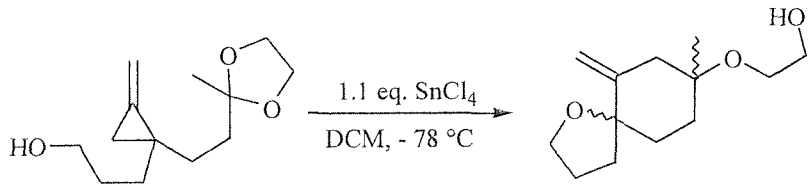
R = H, CH_3
R^1 = H, OH, Bn, OMe

122 **125** **126**

In addition, a rapid method for the preparation of precursors for the Lewis acid mediated cyclisation of methylenecyclopropane derivatives was developed with addition of methylenecyclopropyl cuprate to conjugated ketones.

Chapter 2 focused on the cascade process of 1,2-disubstituted methylenecyclopropanes with first cyclisation induced by Lewis acid to give an allyl cation intermediate which can be trapped in a cycloaddition reaction.

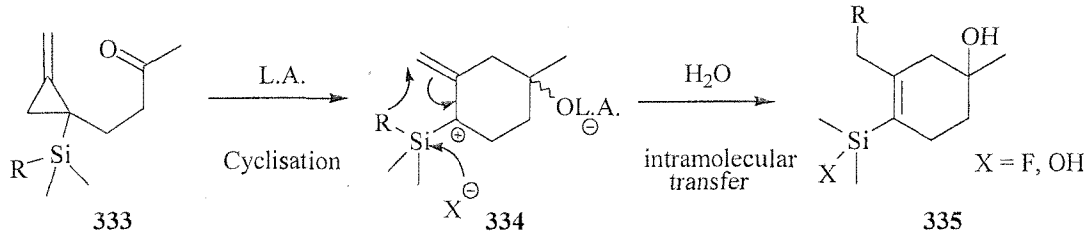
Chapter 3 also discussed the cyclisation of 1,1-disubstituted methylenecyclopropane derivatives mediated by Lewis acid, especially the synthesis of spirocycle **293** obtained as a 2 : 1 mixture of diastereoisomers.



285 **293**
2 : 1
50%

Chapter 4 discussed the effect of a silyl group on the cyclisation reaction. Ketone **300** gave, under treatment with Lewis acid, cyclised compounds **303** and **304** in very good yields, due to presumably the ability of silicon to stabilised β-carbocation intermediate **301**.

Chapter 5 is concerned with the development of a cascade process in which the silicon atom is used to transfer allyl and phenyl groups to the substrate.



333 **334** **335**

Compounds, such as **354** and **385** were obtained in reasonable yields with high diastereoselectivity.

Finally Chapter 6 is concerned with an attempt, which failed, to synthesise the natural product norketoagarofuran **396**.

CONTENTS

Chapter 2

Cyclisation Study of 1,2-Disubstituted Methylenecyclopropane Derivatives

Chapter 3

Cyclisation Study of 1,1-Disubstituted Methylenecyclopropane Derivatives

Chapter 4

Lewis Acid Mediated Cyclisation of Methylenecyclopropyl Ketones: Effect of a Silyl Group on the Cyclisation

Chapter 5

Lewis Acid Mediated Cascade Reaction of Methylenecyclopropyl Ketones

Chapter 6

Towards the synthesis of Norketoagarofuran

Experimental

PREFACE

The research described in this thesis was carried out under the supervision of Prof. Jeremy D. Kilburn at the University of Southampton between October 1997 and September 2000. No part of this thesis has been previously submitted at this or any other University.

ACKNOWLEDGEMENTS

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

I am indebted to SmithKline Beecham for providing the financial support of the project and especially Mr John Kitteringham for his help and advice throughout the research, and his assistance and availability during my time in Harlow. John, thank you for coming to see Austin Powers, which is probably still running at the back of the course...

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I must thank Joan Street for all the help with NMR experiments, Dr. John Langley for the mass spectra analysis and Dr. Thomas Gelbrich for the X-ray crystallography work.

A special thank to John and Faye for proof reading this thesis and for their constructive advice and to all the past and present member of the Kilburn group.

Finally, I would like to thank my wife and my two sons, without whom life would not be the same, for their help and support during these years. Je n'ai qu'une chose a vous dire : merci du fond du cœur.

ABBREVIATIONS

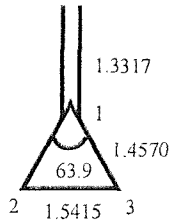
Ac	acetyl
aq.	aqueous
Ar	aryl
Bn	benzyl
bp.	boiling point
Bu	butyl
BuLi	n-butyllithium
^{t}Bu	*tert*-butyl
cat.	catalytic amount
CI	chemical ionisation
DBU	1,8-diazabicyclo[5.4.0]undec-ene
DCM	dichloromethane
DHP	3,4-dihydro-*2H*-pyran
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformaldehyde
DMPU	*N,N'*-dimethyl-*N,N'*-propylene urea
DMSO	dimethyl sulphoxide
EDC	1,2-dichloroethane
EI	electron impact
eq.	equivalent
Et	ethyl
HMPA	hexamethylphosphoramide
hv	light
L	ligand
LDA	lithium diisopropylamine
liq.	liquid
lit.	literature
M	metal
maj	major

m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeO	methoxy
min	minor
mp.	melting point
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
petrol	petroleum ether, bp. 40-60 °C
Ph	phenyl
p-TsOH	*para*-toluenesulfonic acid
py	pyridine
q	quartet
r. t.	room temperature
s	singlet
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
Th	thexyl (1,1,2-trimethylpropyl)
THF	tetrahydrofuran
THP	tetrahydropyran
T. L. C.	thin layer chromatography
TMS	trimethylsilyl

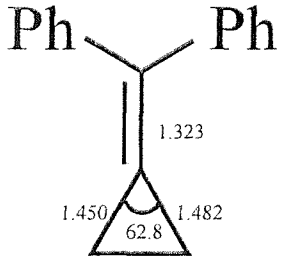
INTRODUCTION

I-General Information on Methylenecyclopropanes

Methylenecyclopropane **1** is a highly strained molecule due to the exocyclic double bond, which imposes steric strain in the cyclopropyl ring. The structure of methylenecyclopropane **1** has been determined by microwave spectroscopy[1] and shows that the strain in the molecule is reflected by an increase in the C2-C3 bond length and the C2-C1-C3 bond angle compared with cyclopropane.



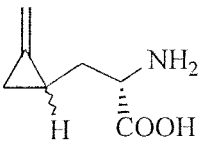
1



2

In addition, the structure of 1-(diphenylmethylene)-cyclopropane **2** has been established by X-ray analysis[2] and similar observations can be made. The increase in the bond length and the bond angle indicate clearly that the exocyclic double bond is responsible for the steric strain and substituents at the terminus alkene carbon have very little effect.

Despite its strain, methylenecyclopropane **1** can be stored for months in a cylinder at room temperature and a perception of its stability can be gained from it incorporation in natural products such as the amino acids hypoglycine A[3] **3**, isolated from the unripe fruit of the Ackee tree *Blighia sapida* and methylenecyclopropylglycine **4** isolated from the kernel of litchi fruits.



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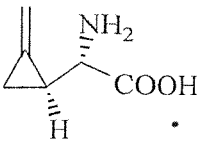
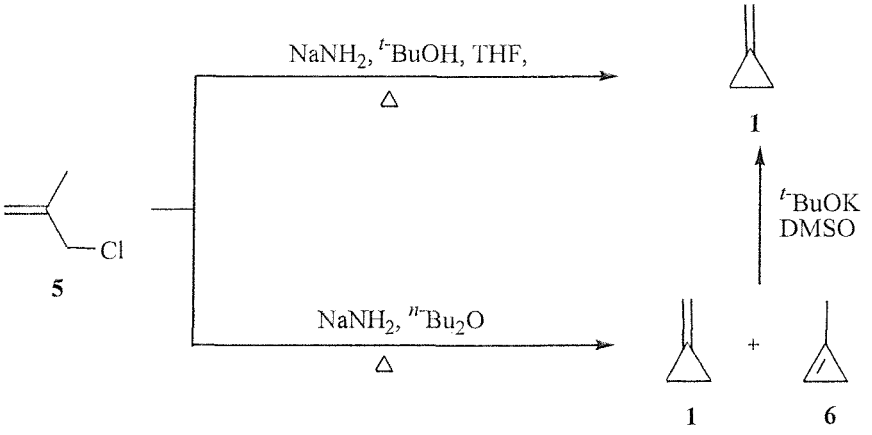


4

Both amino acids exhibit powerful biological activities : hypoglycine A **3** is responsible for Jamaican vomiting sickness and methylenecyclopropylglycine **4** causes hypoglycaemia in mice and rats.

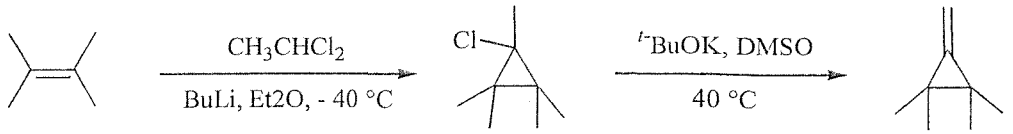
II-Synthesis of Methylenecyclopropane

Many synthesis for methylenecyclopropanes[4] have been developed, however, the ones described in this section are among the most commonly used. Methylenecyclopropane **1** is a readily available molecule prepared from methallyl chloride **5**.[5] The reaction can be carried out in one or two steps. The first method uses a mixture of $NaNH_2$ and t-BuOH to which is added **5**. However, this method requires a tricky purification. The second method produces a mixture of methylenecyclopropane **1** and methylcyclopropene **6**, but the latter can be isomerised under equilibrating conditions to give **1** only (**Scheme 1**).



Scheme 1

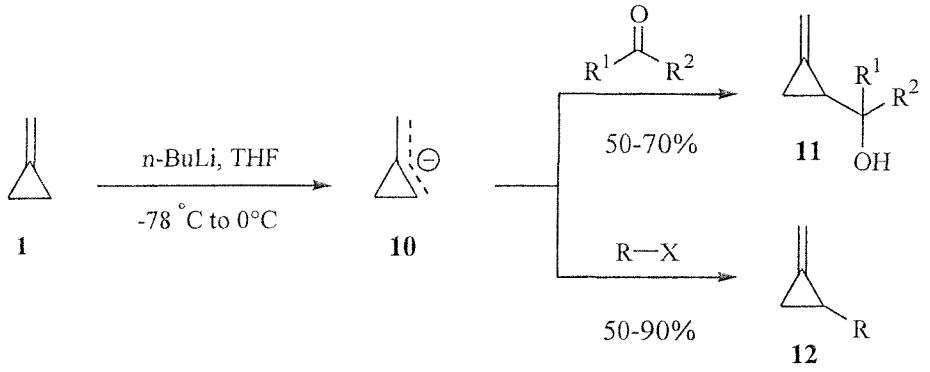
The best method for synthesising substituted methylenecyclopropane is the addition of methylchlorocarbene to a suitably functionalised alkene **7** to give a chloro cyclopropane such as **8**, followed by dehalogenation to give substituted methylenecyclopropane **9** (**Scheme 2**).[6]



7 8 9

Scheme 2

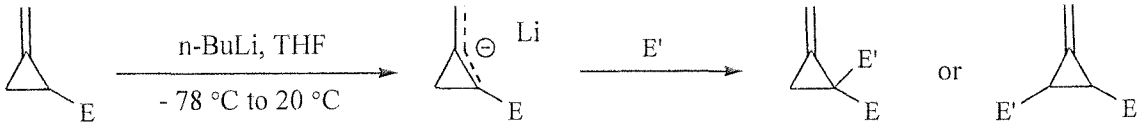
An alternative strategy for the preparation of substituted methylenecyclopropanes is to alkylate the methylenecyclopropyl anion **10** (**Scheme 3**). Indeed, methylenecyclopropane **1** can be deprotonated using a strong base such as BuLi to give allyl anion **10** which can be trapped with electrophiles such as ketones,[7] aldehydes[8] and alkyl halides[8,9].



1 **10** **11** **12**

Scheme 3

Disubstituted methylenecyclopropanes can be also obtained using this method. However, if the first electrophile is a silyl group, 1,1-disubstituted methylenecyclopropanes **15** will be obtained[8a] and if the first electrophile is an alkyl group, 1,2-disubstituted methylenecyclopropanes **16** will be formed (**Scheme 4**).[9,10]

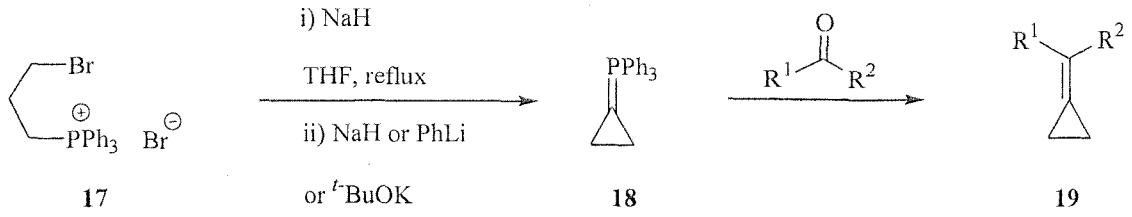


13 **14** **15** **16**

Scheme 4

The Wittig olefination has been extensively used for the synthesis of diversely functionalised methylene- and alkylidenecyclopropanes. The most commonly used method employs 3-bromotriphenylphosphonium bromide **17** as the precursor for the preparation of

the ylide **18**. Then, reaction with ketones or aldehydes produced the alkylidenecyclopropane **19** (**Scheme 5**).[11]

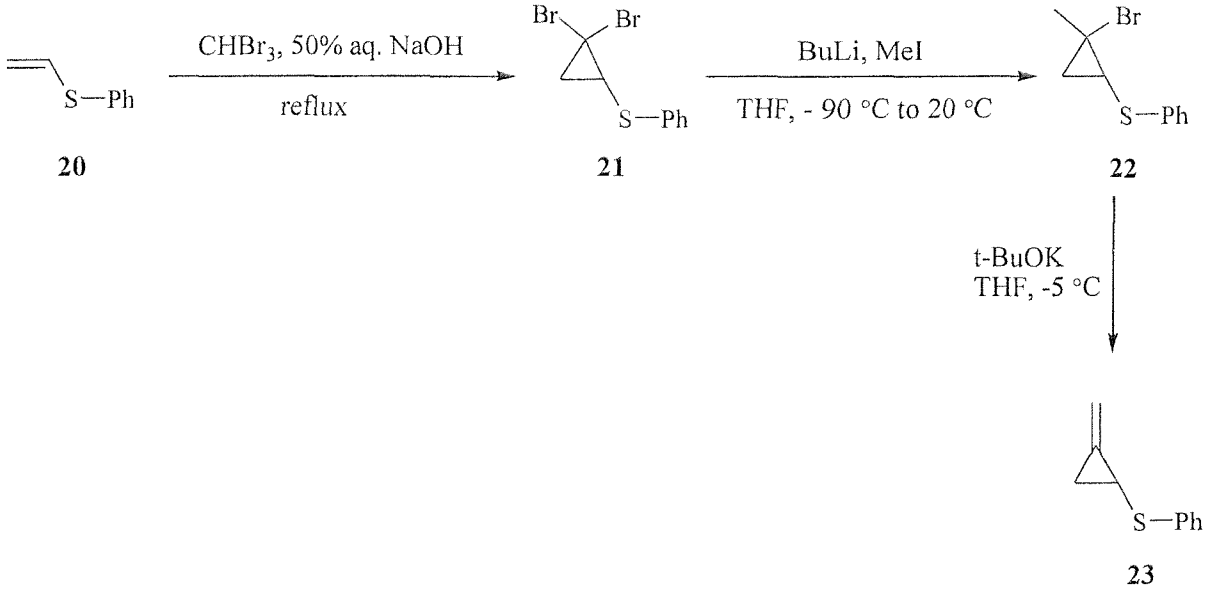


17 **18** **19**

Scheme 5

However, enolisable aldehydes cannot survive the reaction conditions. A great improvement in the yields of the reaction has been found by using 10 mol % of an additive phase-transfer catalyst, tris[2-(2-methoxyethoxy)ethyl]-amine (TDA-1).[12]

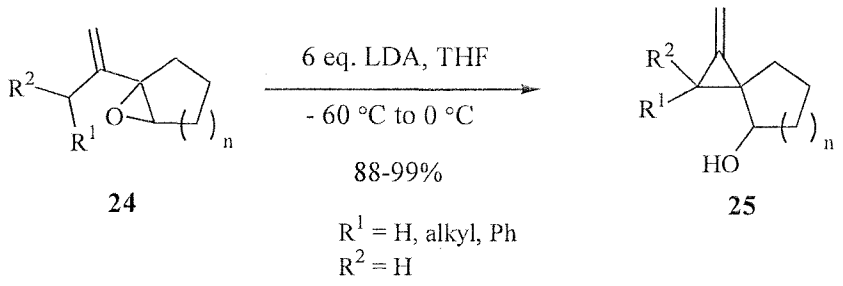
Methylene(thiophenyl)cyclopropane **23** can be obtain using bromoform and aqueous NaOH (**Scheme 6**).[13] Addition of BuLi to a mixture of MeI and dibromocyclopropyl ring **21** obtained generates bromomethylcyclopropane **22** which eliminates HBr under treatment with t-BuOK to give **23**.



20 **21** **22** **23**

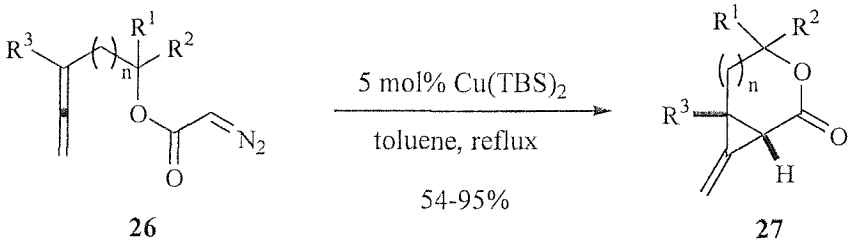
Scheme 6

Spirocyclic methylenecyclopropanes can be prepared from nucleophilic addition to epoxides.[14] Addition of excess LDA to epoxide **24** gave spirocyclic methylenecyclopropane **25** in good to excellent yields (**Scheme 7**). However, tetrasubstituted spirocyclic methylenecyclopropane could not be obtained, demonstrating the limitation of this method.



Scheme 7

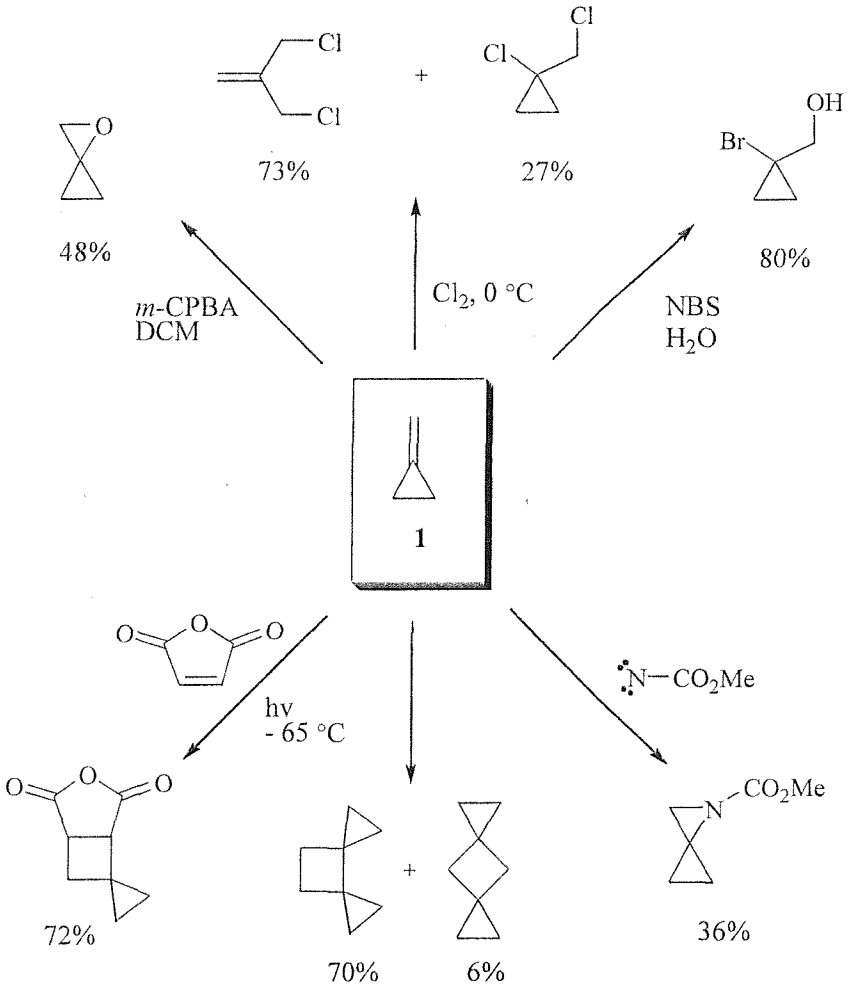
Finally, Lautens reported recently the synthesis of fused cyclic methylenecyclopropanes using intramolecular cyclopropanation of allenic diazoacetates.[15] Addition of allene **26** to a suspension of 5 mol% bis-(*N-tert*-butylsalicylaldiminato) copper(II) as catalyst in toluene gave 1,2-disubstituted methylenecyclopropanes **27** (**Scheme 8**).



Scheme 8

III-Use of Methylenecyclopropane in Organic Chemistry

Methylenecyclopropanes undergo reactions characteristic of reactive olefins such as electrophilic additions, radical additions, additions of carbenes and nitrenes and various other types of cycloadditions (**Scheme 9**).[1b,4]

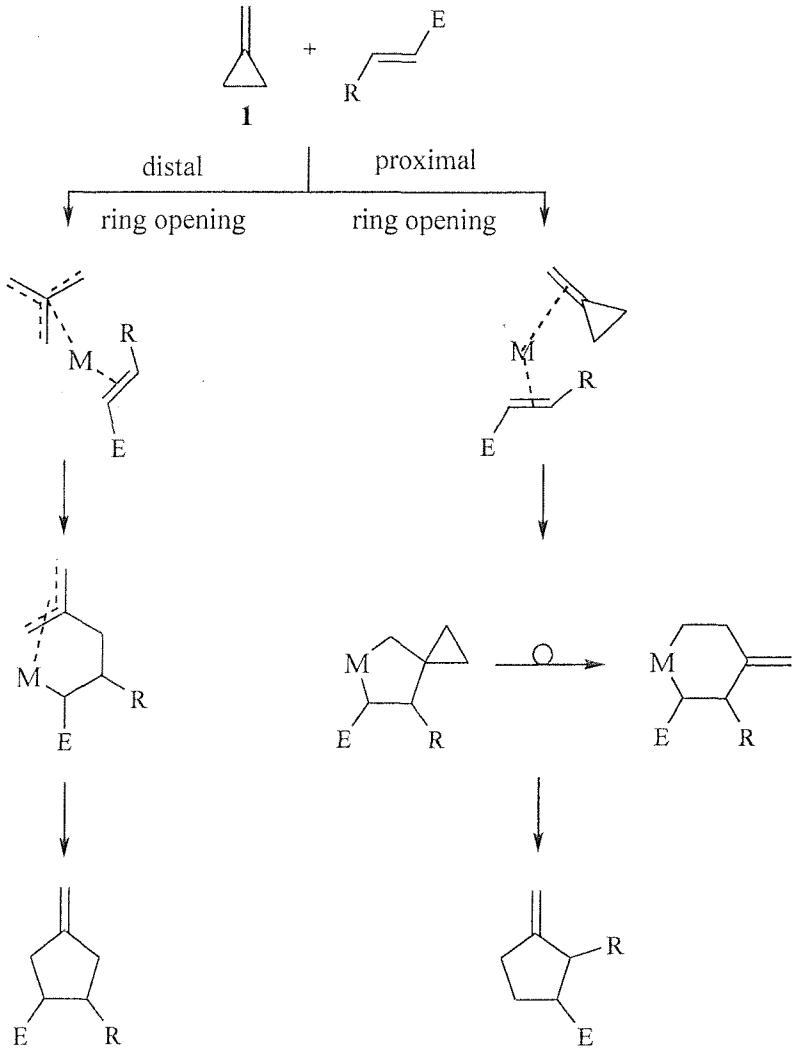


Scheme 9

1-Cycloaddition Catalysed by Transition Metal

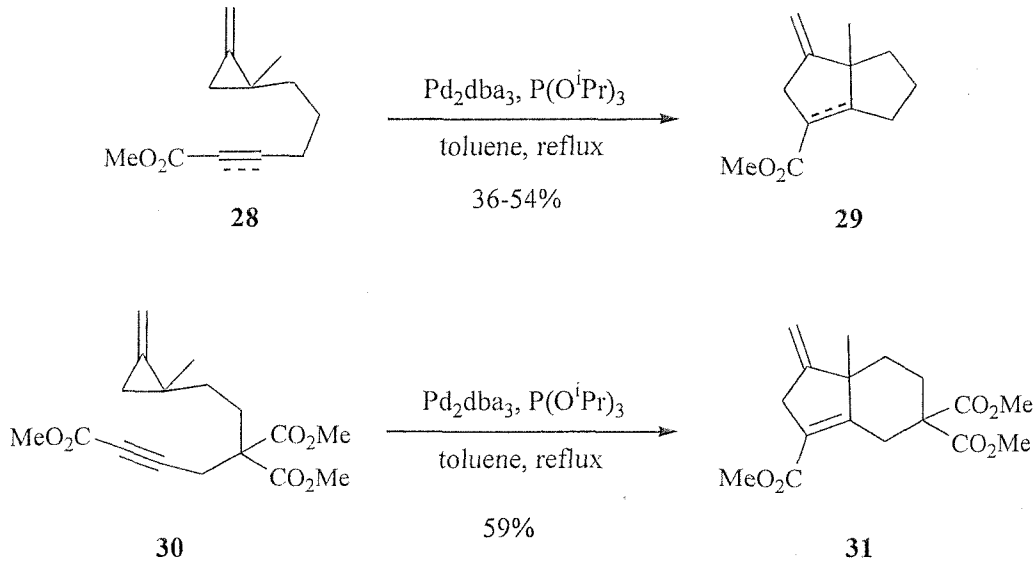
Thermally induced [4+2] cycloaddition of methylenecyclopropanes occur at high temperature. However, the use of transition metal catalysts allows the [3+2] cycloaddition reaction to proceed at moderate temperatures and this process has been extensively studied as it allows the formation of carbocycles especially 5-membered rings.[16] The cyclopropyl ring can react either by ring opening of the proximal (C_1-C_3) or the distal (C_2-C_3) bond, which opens is metal catalyst dependent, Ni(0) can either open the distal or proximal bond, whereas Pd(0) opens the distal bond exclusively. Whilst the mechanism for the distal bond cleavage is relatively straightforward, the mechanism for the proximal ring opening proceeds first by an oxidative coupling of the two alkenes with Ni(0) catalyst, followed by a cyclopropylmethyl/3-

butenyl rearrangement. Reductive elimination of the catalyst gives the cyclic product (**Scheme 10**).



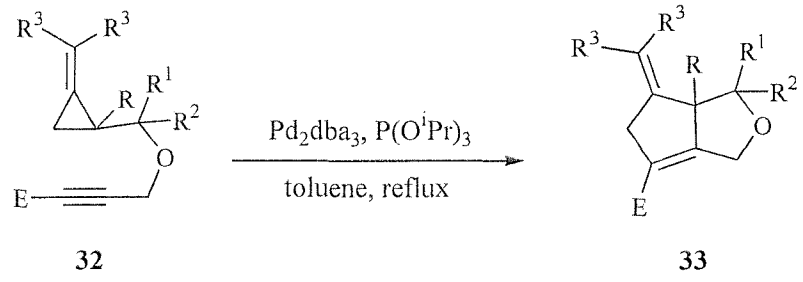
Scheme 10

However, a problem of dimerisation in these processes encouraged Motherwell[17] to investigate the intramolecular cycloaddition of methylenecyclopropane derivatives. Intramolecular [3+2] cycloaddition of precursors such as **28** and **30**, catalysed by the *in situ* prepared Pd(0), gave bicycles **29** and **31** in reasonable yields (**Scheme 11**).



Scheme 11

Lautens[18] carried out a detailed study on the effect of substituents at different positions on the cycloaddition process. Methylenecyclopropane derivative **32** was cyclised, using the *in situ* prepared Pd(0), to give bicycle **33** (**Scheme 12**).

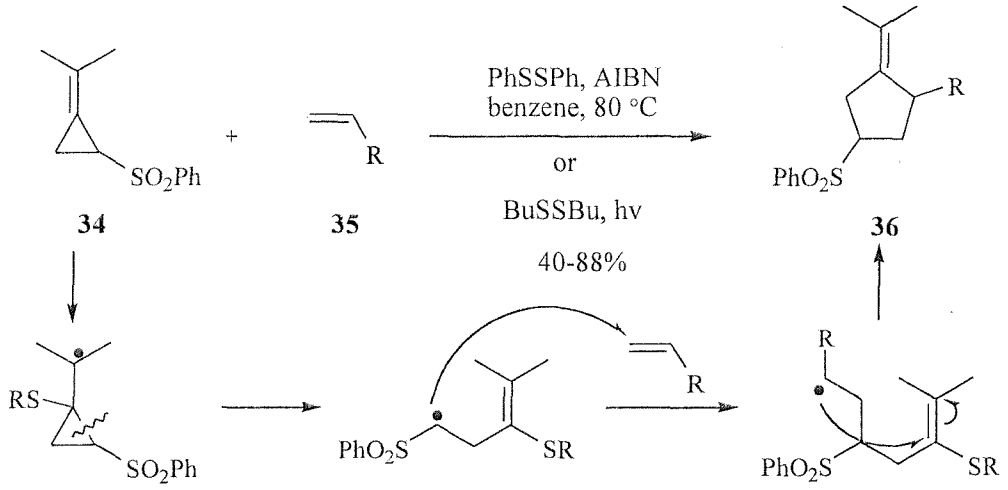


Scheme 12

Depending on substituents, cyclisation occurred in either modest to excellent yields or none of the expected cyclised products were observed. Substituents on the carbinol carbon (R^1 and R^2) had very little effect on the reaction, as well as substituent on the terminus methylene (R^3). Substituents at the sp^3 carbon of the cyclopropyl ring have a marked effect on the success of the cycloaddition. For example, good yields were obtained when R = H or MeO but a mixture of products was obtained with R = Me. More significant is the effect of substituents at the alkyne position: electron withdrawing groups favoured the reaction and silyl substitution led to capricious reactions. The choice of catalyst was also shown to be crucial for the cycloaddition reaction.

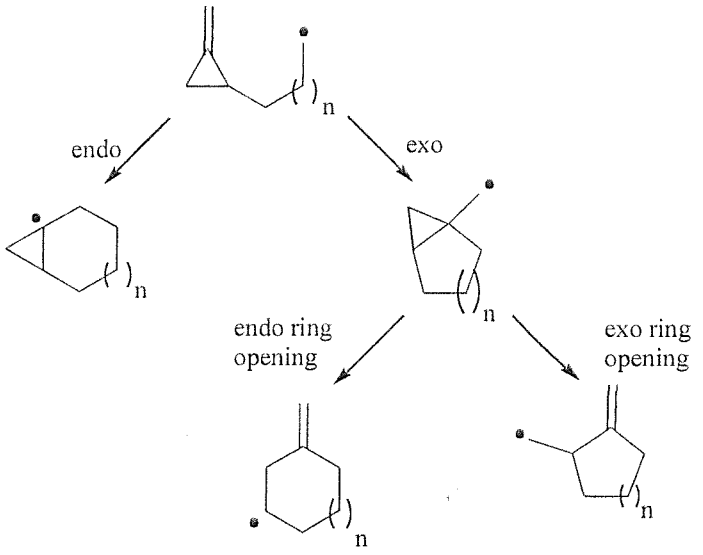
2-Radical Addition onto Methylenecyclopropanes

The use of radical chemistry in organic synthesis has become increasingly important over the last decade[19] especially for the formation of C-C bonds as reactions proceed under mild conditions and often exhibit a high level of chemo-, regio- and stereoselectivity. Singleton and Church studied the effect of adding sulfur radicals onto methylenecyclopropane.[20] When (phenylsulfonyl)-methylenecyclopropane **34** was treated with thiyl radicals in the presence of an electron rich or electron poor alkene **35**, a [3+2] annulation reaction occurred to give methylenecyclopentane **36** (**Scheme 13**).



Scheme 13

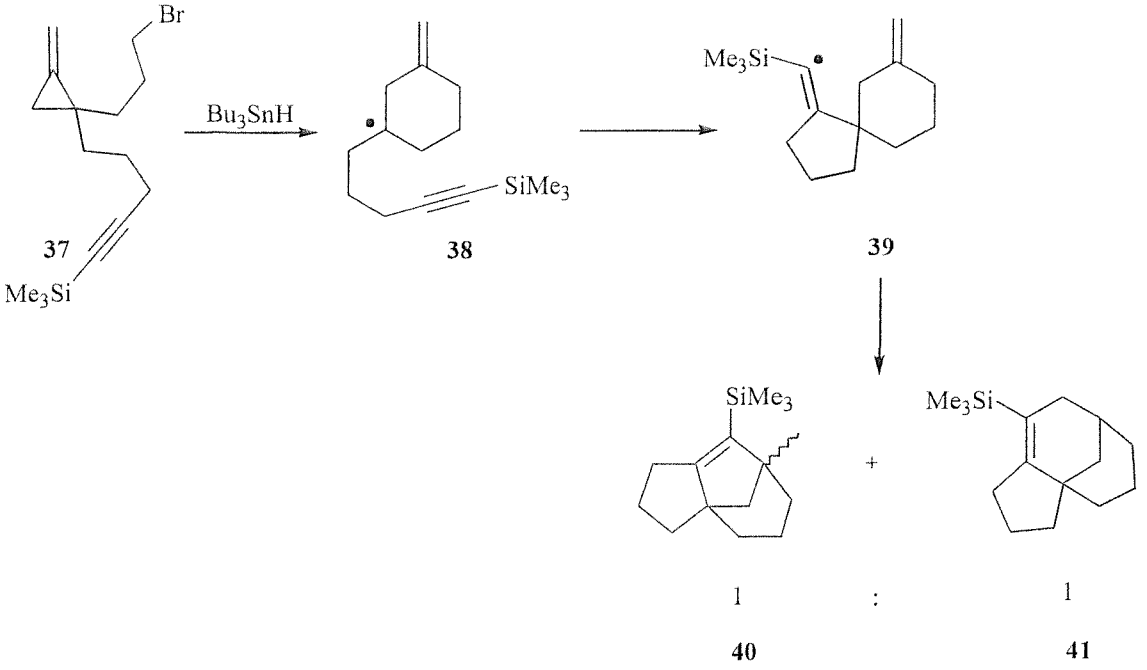
Work by Kilburn and Destabel[9,21] established general rules for the radical cyclisation of methylenecyclopropane derivatives (**Scheme 14**). Initial *endo*-cyclisation would be favoured, due to less steric hindrance encountered in such a pathway, and leads to a relatively stable cyclopropyl radical. Alternatively, *exo*-cyclisation would lead to an intermediate cyclopropylmethyl radical, which was expected to open rapidly, to give either the ring expanded methylenecycloalkyl radical or the cycloalkylmethyl radical.



Scheme 14

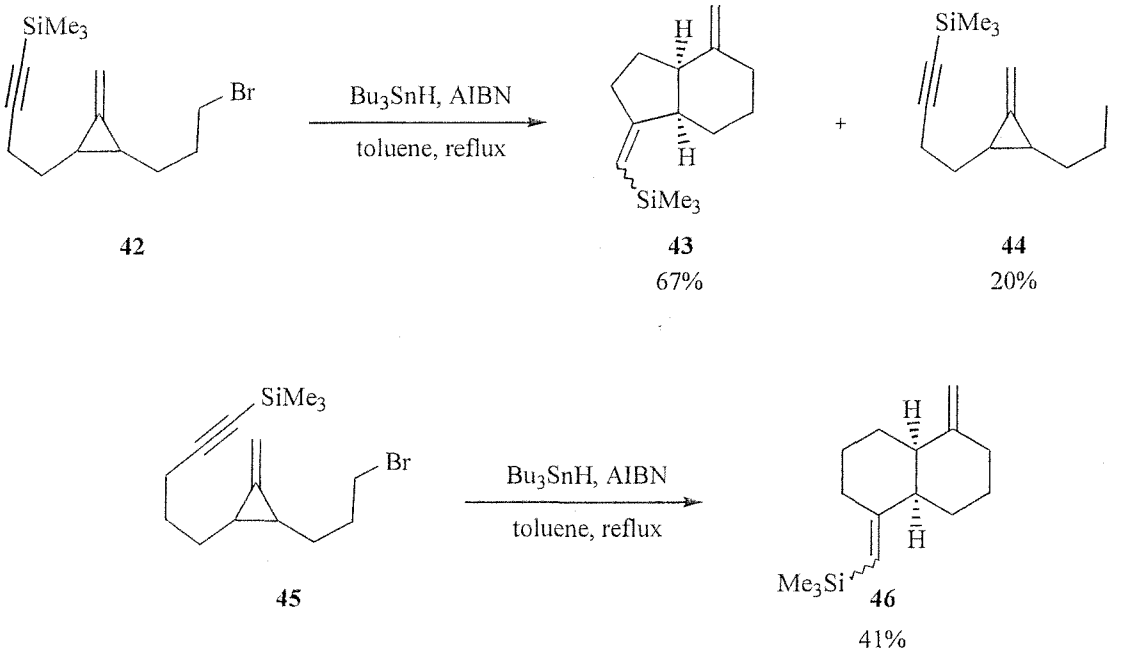
It was found that methylenecyclopropyl propyl radicals cyclised exclusively in a 5-*exo* fashion, followed by *endo* ring opening of the resultant cyclopropylmethyl radical, whereas methylenecyclopropyl butyl radicals gave a mixture of *exo* and *endo* products.

Santagostino[22] extended the radical cyclisations to polycyclic compounds through a cascade process (**Scheme 15**). The formation of tricycles **40** and **41** was unexpected, but is readily understood. Formation of **39** was expected, but the radical **39** underwent a further cyclisation to give **40** and **41** in a 1 : 1 ratio.



Scheme 15

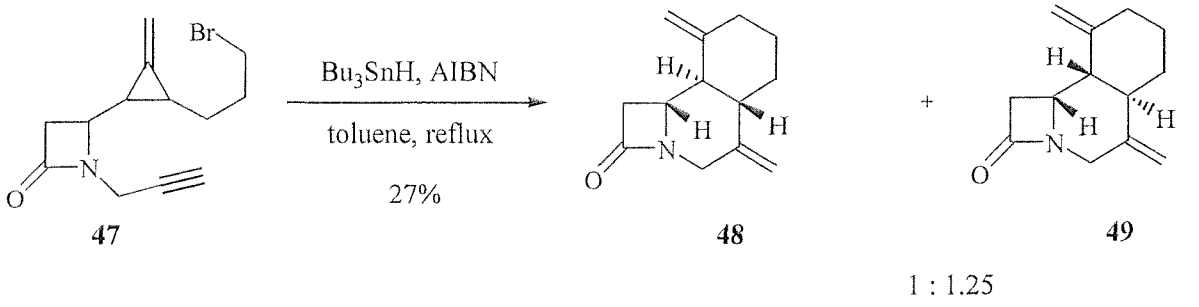
Further tandem methodology was carried out by Pike[10,23] in order to develop a new route for the preparation of 6,5- (**43**) and 6,6- (**46**) bicyclic compounds (**Scheme 16**).



Scheme 16

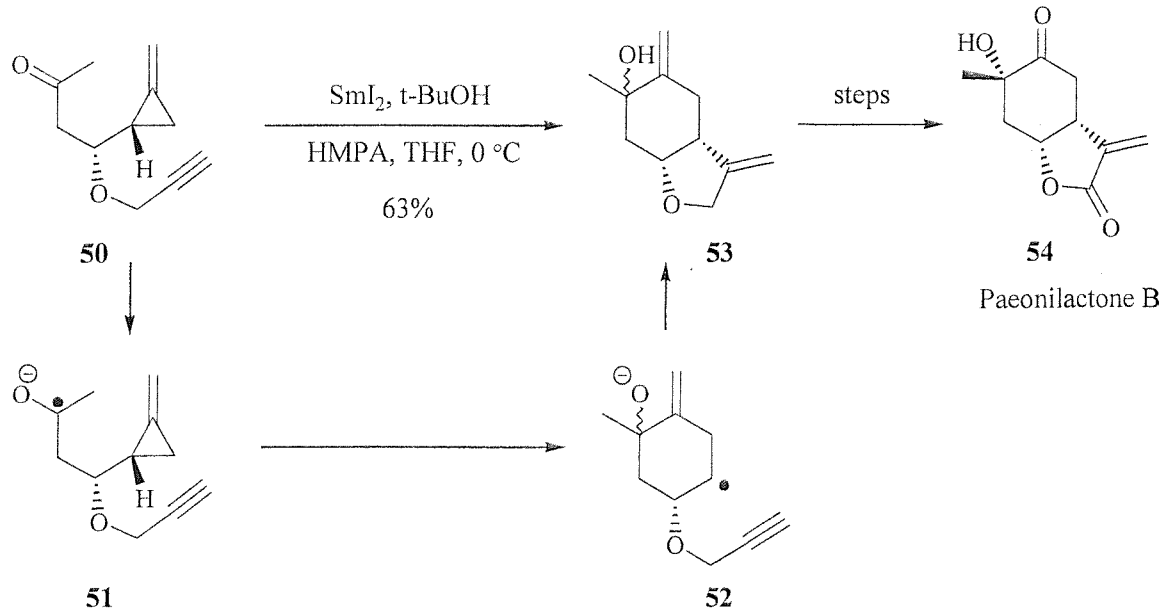
Treatment of **42** with Bu_3SnH gave **43** in 67% yield, with 20% of the reduced starting material **44**. Reaction of **45** with Bu_3SnH, using a syringe pump, gave the bicyclic compound **46** in 41% as the only isolated product. In both cases, the fused structure was assigned to have cis stereochemistry based on literature precedent.[24]

Work by Penfold[25] used methylenecyclopropanes for the preparation of tribactams (**Scheme 17**). Addition of tin hydride to azetidinone **47** gave an alkenyl radical which added onto methylenecyclopropane to give tribactams **48** and **49** as a 1 : 1.25 mixture of diastereoisomers.



Scheme 17

Boffey utilised SmI_2 to generate ketyl radical which then added onto methylenecyclopropane.[26] This methodology was applied for the synthesis of the natural product Paeonilactone B **54** (**Scheme 18**).

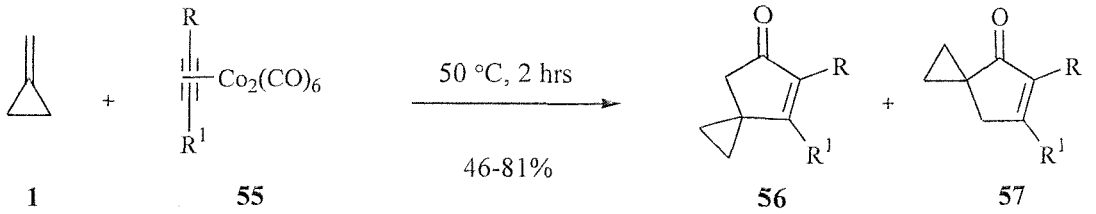


Scheme 18

Addition of ketone **50** to SmI_2 generated ketyl radical anion **51** which cyclised in a 5-*exo* fashion to give, after *endo* ring opening, cyclohexyl radical **52** which underwent a further cyclisation to give **53**. Paeonilactone B **54** was then obtained after a few functional groups transformations.

3-Methylenecyclopropane and Pauson-Khand Reactions

Reaction of a dicobalthexacarbonyl complex of an alkyne with an alkene, leading to the formation of cyclopentenones, proceeds especially easily with strained alkenes. The strained nature of methylenecyclopropane **1** encouraged Smit[27] to study the intermolecular Pauson-Khand reaction of **1** with various alkynes. Cyclopentenones **56** and **57** were obtained in reasonable to excellent yield (**Scheme 19**).

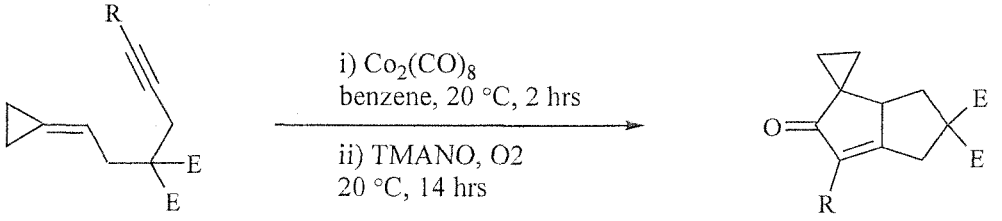


1 **55** **56** **57**

Scheme 19

However, the conventional conditions of reaction (heating the reaction in hydrocarbon solvents for several hours) were unsuccessful and cyclopentenones **56** and **57** were obtained in poor yields. The Pauson-Khand reaction occurred smoothly when the reaction was carried out under dry-state adsorption, by removing solvent and suspending the reagents on chromatography adsorbents, such as SiO_2 or Al_2O_3.

The intramolecular version of the reaction was investigated by de Meijere[28] with substituents grafted onto the terminal alkene. For example, [2+2+1] cycloaddition of precursor **58** gave bicycle **59** in good yields (**Scheme 20**).

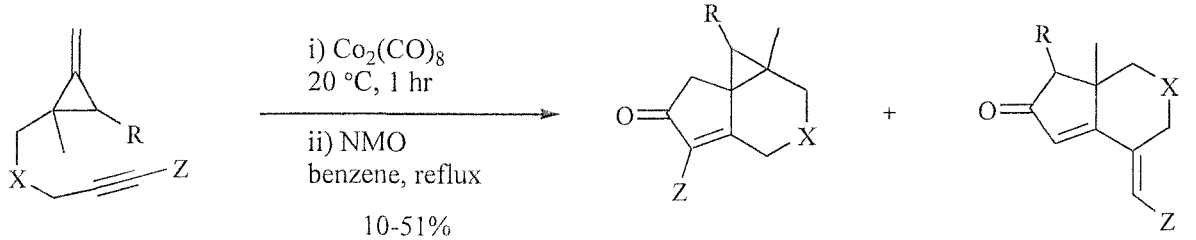


58 R = H, TMS
E = H, CO_2Me

59

Scheme 20

Motherwell[29] has also studied the intramolecular Pauson-Khand reaction with methylenecyclopropane and found, for example, that derivative **60** gave a mixture of products **61** and **62** (**Scheme 21**).



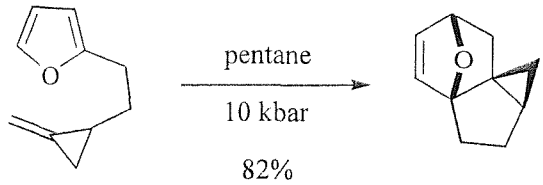
60 R = H, Et
Z = H, TMS
X = O, CH_2

61 **62**

Scheme 21

4-Diels-Alder Cycloaddition

The Diels-Alder reaction is a very efficient and economic way to construct complex molecules, and work by de Meijere[30] showed that methylenecyclopropane can undergo intramolecular cycloaddition with furan under high pressure to give complex molecules such as **64** (**Scheme 22**). Treatment of **63** with $LiClO_4$ or with a Lewis acid led exclusively to polymerisation. However, when the substrate was exposed to high pressure the cycloaddition took place smoothly and good yields of cycloadducts such as **64** were obtained.

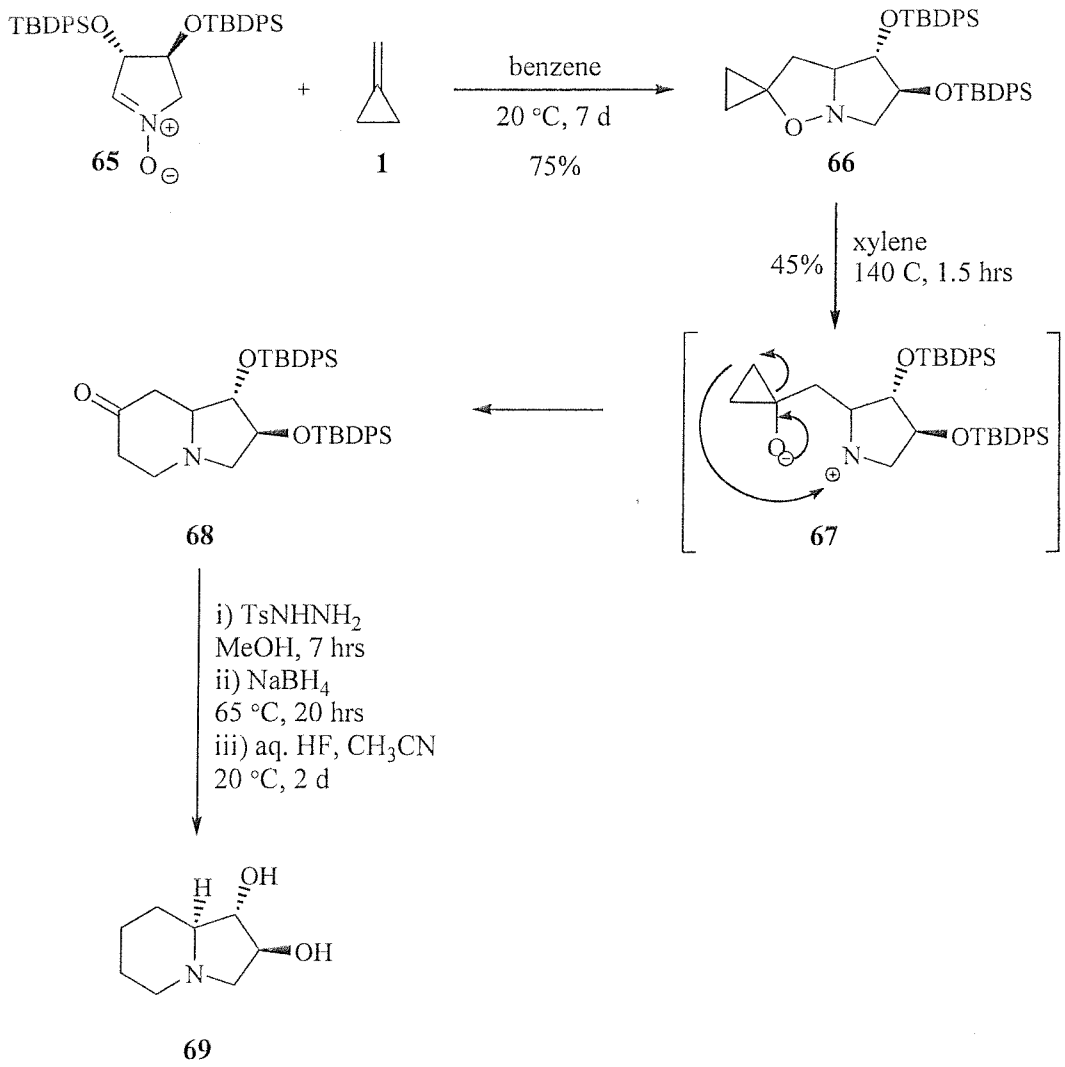


63 **64**

Scheme 22

5-Cycloaddition of Methylenecyclopropane with Nitrones

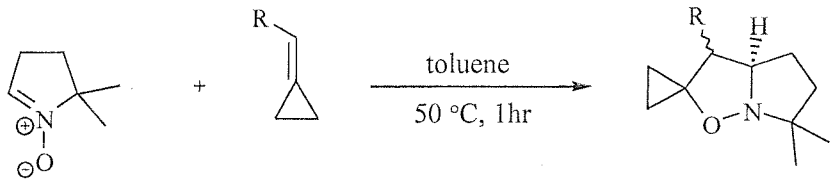
The thermal rearrangement of spirocyclopropane isoxazolidines revealed a practical and versatile method for synthesis of indolizidine skeletons. The substrate can be easily obtained from 1,3-dipolar cycloaddition of nitrones and methylenecyclopropane. Brandi[31] demonstrated the efficiency of this method through the synthesis of natural products such as Lentiginosine **69** (**Scheme 23**).



Scheme 23

Reaction between methylenecyclopropane **1** and nitrone **65** gave spirocyclopropane **66** which underwent rearrangement under heating in xylene to give indolizidine **67**. Reduction followed by deprotection afforded Lentiginosine **69**. Similar results were obtained by Guarna.[32]

Langlois[33] also used nitrones with methylenecyclopropanes substituted with electron withdrawing groups on the terminus alkene to carry out cycloadditions (**Scheme 24**). The electron withdrawing group accelerated the reaction and cycloadduct **72** was obtained in an hour (whereas reaction of **65** with **1** had taken 7 days) and in good yields.



70 **71** R = CN, 87% R = CO_2Me, 63% **72**

Scheme 24

IV-Use of Lewis Acid in Organic Chemistry

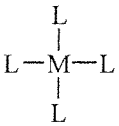
Lewis acids are electron deficient and are therefore capable of accepting an electron pair and are commonly used today to catalyse a range of reactions.

The best known use of Lewis acids are :

- catalysts in Diels-Alder reactions.[34]
- catalysts for Friedel-Crafts reactions.[35]
- catalysts for coupling reactions.[36]
- catalysts for reactions with carbonyl groups. [37]

1-Basic principles of Lewis acids

Reaction of carbonyl compounds with a neutral Lewis acid generates a negatively charged metal complex called an ate complex.[37] The level of acidity comes from the central atom M.



Acidity is diminished when two electron pairs are required. There is a smaller energy gain upon receipt of the first pair, and there is an accumulation of negative charge on M if two pairs are received. Consequently, the result is that group III metal Lewis acids are more acidic than transition metal Lewis acids :

$$BF_3 > AlCl_3 > FeCl_3 > TiCl_4$$

In addition, the acidity of M will decrease within any group with increasing atomic volume owing to the weaker attraction between nuclear charge and incoming electron pairs. This leads to this order (Fajan rules)[38] :

$$BX_3 > AlX_3 > GaX_3 > InX_3$$

and

$$TiX_4 > ZrX_4$$

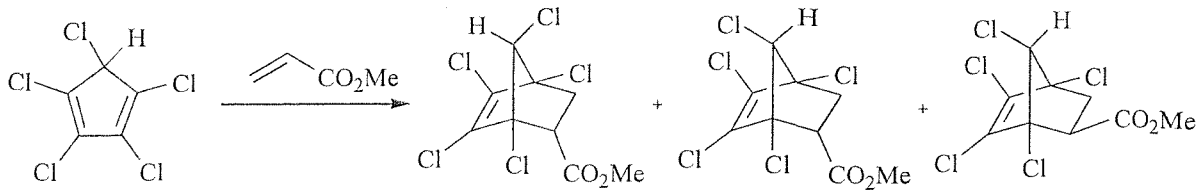
In general, the energies of different atomic orbitals lie closer with increasing atomic number, because orbital contractions arising from the electronegativity of the nucleus tend to decrease with increasing atomic number. This allows more effective overlap of hybridised orbitals. The availability of d orbitals will become easier and more effective the heavier the element. Taking all of these points together gives an acidic series :

$$B > Al > Ga > In > Fe > Ti > Zr$$

There are no acidic properties when M = C and when M = Si, only weak acidic properties are observed. Finally, the formation of a Lewis acid-Lewis base complex is allowed according to the HSAB theory, which allows the formation of a complex between hard acid and hard base or between soft acid and soft base. Indeed, if a big difference exists between the hardness or softness of the Lewis acid and the Lewis base, no reaction will occur.

2-Lewis Acids in Organic Synthesis

The relative strength of a Lewis acid is important to many major classes of organic reactions utilised in synthesis. Lewis acids are used in connection with several important C-C bond forming reactions. This includes Friedel-Crafts type reactions[35] and Diels-Alder reactions,[34] as well as other pericyclic reactions. Changing the Lewis acid can have dramatic effects on the rate of reactions and the products distribution in both the Diels-Alder and Friedel Crafts reactions[35b], and no real predictive rules exist for these reactions. Williamson[39] showed the influence of Lewis acid on selectivity in the reaction of pentachlorocyclopentadiene **73** and methyl acrylate (**Scheme 25**, **Table 1**).



73 **74** **75** **76**

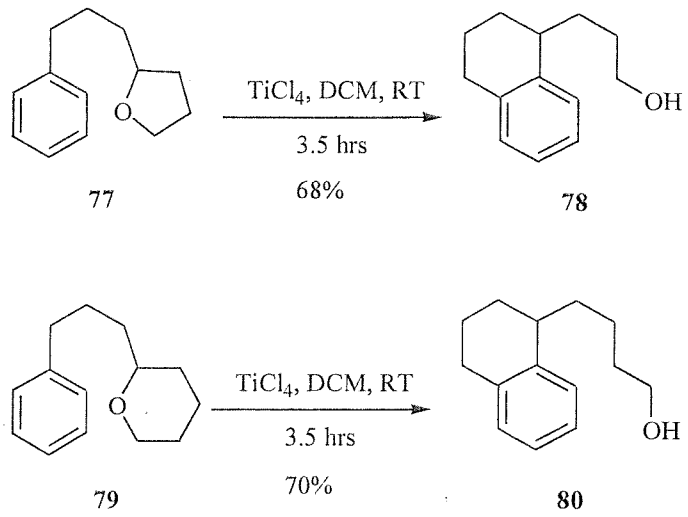
Scheme 25

L.A	Time (h)	Yield (%)	**74**	**75**	**76**
None	6	60	53	37	10
BF_3	4.5	60	53	39	8
$TiCl_4$	3	85	64	33	3
$AlCl_3$	0.75	97	69	29	2

Table 1

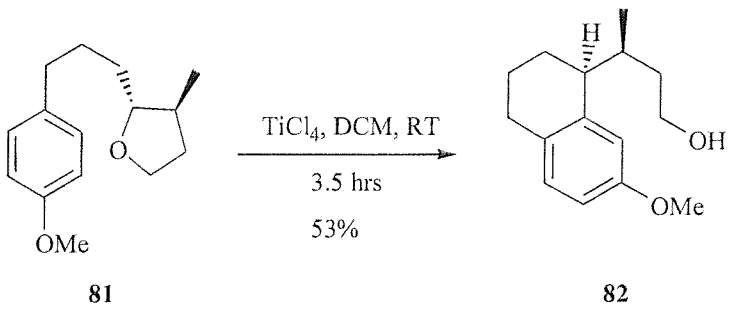
The Lewis acid can also be so reactive that the resulting product is unstable under the reaction conditions. For these reasons, Lewis acids possessing a wide range of acidic strengths in various reactions are required in synthesis. Aluminium chloride ($AlCl_3$) is a very reactive and unselective catalyst, reacting with virtually all functional groups which have Lewis base properties.[34e,40] Zinc chloride ($ZnCl_2$) is a mild and selective catalyst in reactions where halides or alcohols are required to react selectively with an olefin double bond.[35b,41] Tin tetrachloride ($SnCl_4$) is a very mild catalyst which can be used for acylation of reactive aromatic nuclei such as thiophene. Catalysis of reactions involving thiophene with $AlCl_3$ is too vigorous, and extensive decomposition accompanies the process.[35b,42] $TiCl_4$ has also been applied to Friedel Crafts reactions of active aromatics[35b,43] which cannot tolerate vigorous reaction conditions, as with furan derivatives for example.[35b,44]

Harrowven[45] obtained tetralins from tetrahydrofuran and tetrahydropyran tethered aromatics in good yields with excellent stereocontrol. Treatment of **77** and **79** with $TiCl_4$ in DCM at room temperature led to tetralins **78** and **80** in 68% and 70% yields respectively (**Scheme 26**).



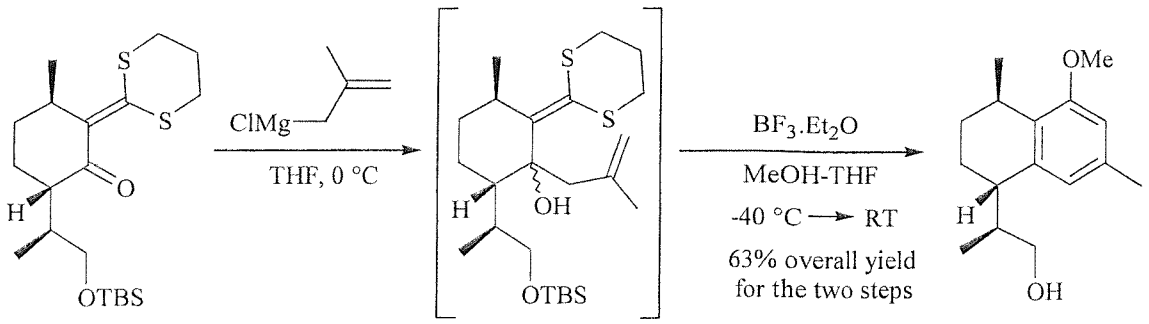
Scheme 26

In both cases, when $TiCl_4$ was replaced by $AlCl_3$, decomposition of the substrate was observed. Cyclisation of the *trans*-disubstituted tetrahydrofuran **81** gave tetralin **82** as a single diastereoisomer (**Scheme 27**).



Scheme 27

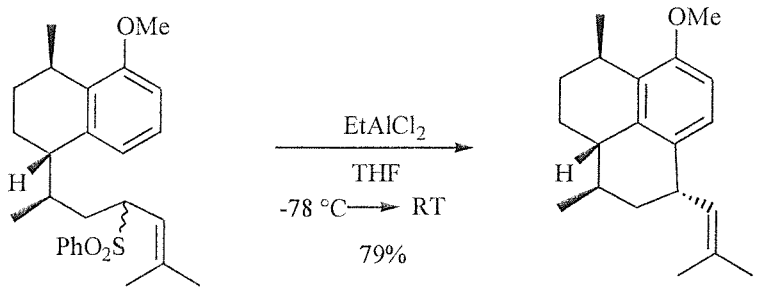
Kocienski[46] used Dieter methodology to obtain aromatic ring **85** (**Scheme 28**). Treatment of allyl ketone **83** with methallylmagnesium chloride afforded **84**, which upon addition of $BF_3.Et_2O$ gave **85** in a 63% overall yield for the two steps.



83 **84** **85**

Scheme 28

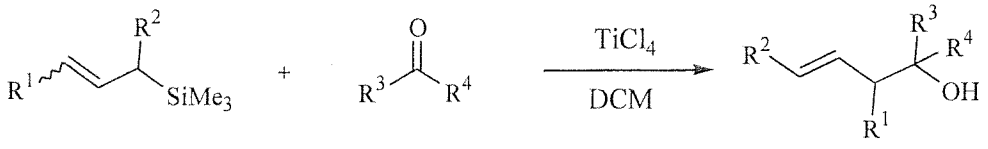
He also used $EtAlCl_2$ in THF to cyclise sulfone **86** into pseudopterosin precursor **87** (**Scheme 29**).



86 **87**

Scheme 29

One of the best known Lewis acid activated reactions, is the Hosomi-Sakurai[47] reaction of allyl silanes with carbonyl compounds. When $TiCl_4$ was added to carbonyl **89**, followed by the addition of allyl silane **88**, allyl alcohol **90** was obtained in very good yield (**Scheme 30**). The reaction can be carried out with a wide range of aliphatic and aromatic groups either on the allyl silane or on the carbonyl with no dramatic effect on the reaction. Furthermore, this process works with either ketones or aldehydes.

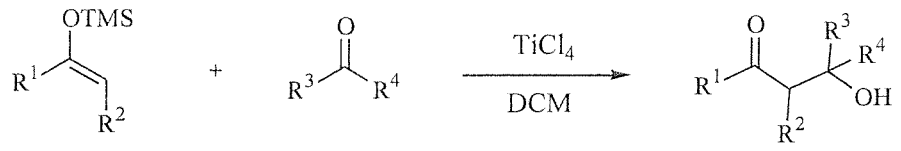


88 **89** 40-100% **90**

R^1, R^2, R^3, R^4 = H, alkyl, aryl

Scheme 30

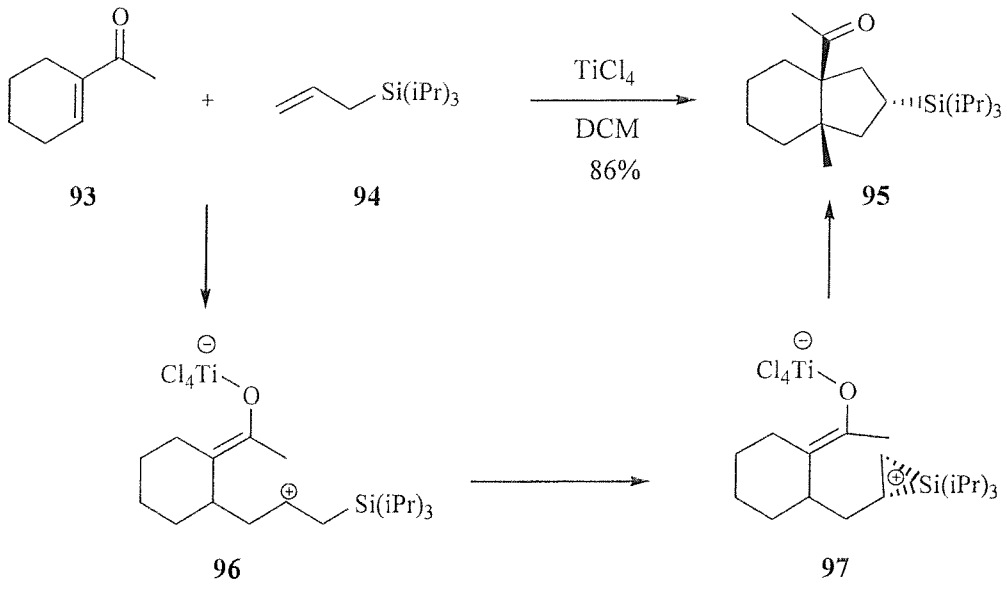
A modification was introduced by Mukaiyama[48] with the aldol type reaction of silyl enol ethers with carbonyl compounds (**Scheme 31**). Addition of $TiCl_4$ to silyl enol ether **91** in the presence of carbonyl **89** gave the aldol adduct **92** in good yield.



91 **89** **92**

Scheme 31

An elegant new annulation reaction induced by Lewis acid was reported by Knolker[49] and other groups.[50] Addition of $TiCl_4$ to a mixture of conjugated ketone **93** and allyl silane **94** gave the annulated bicycle **95** in a good 86% yield (**Scheme 32**).



93 **94** **95**

96 **97**

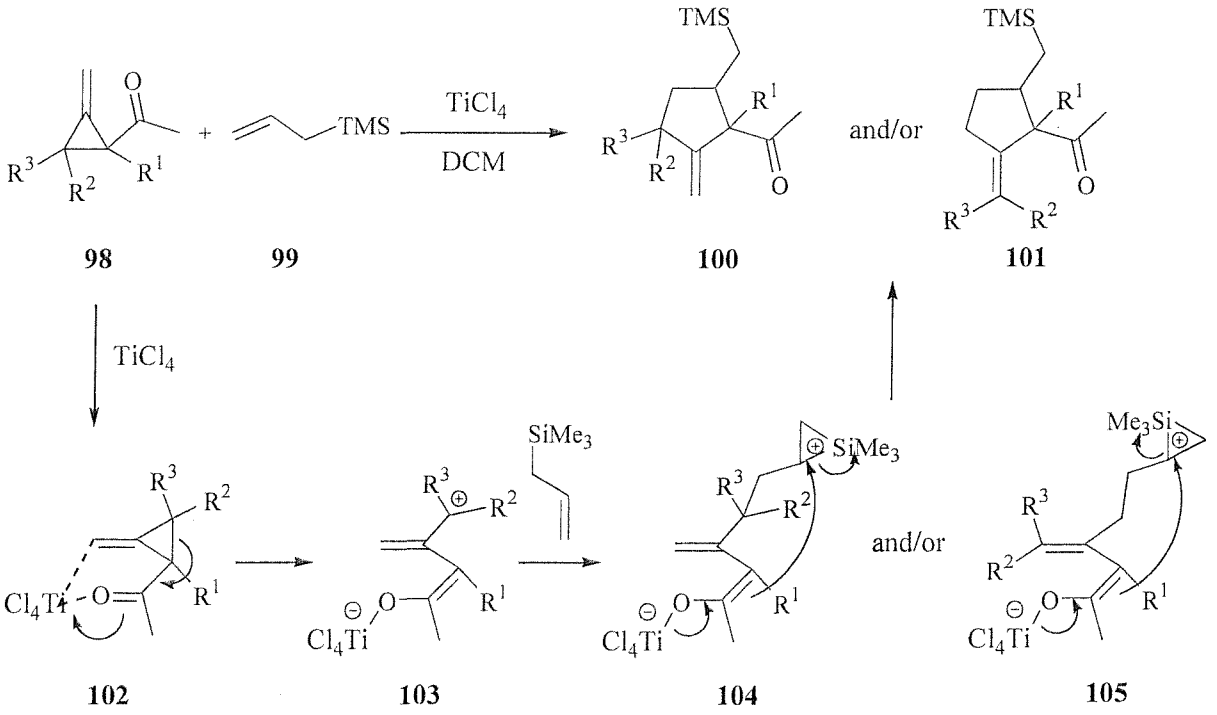
Scheme 32

The reaction is thought to proceed by addition of the allyl silane to give intermediate **96**, which rearranges to the siliranium cation **97**. Subsequent addition of the titanium enolate at the siliranium ion **97** gives the annulated product **95**.

Many other reactions induced by Lewis acid exist and those discussed above are a personal selection that illustrates the scope of chemistry mediated by these reagents.[32,51]

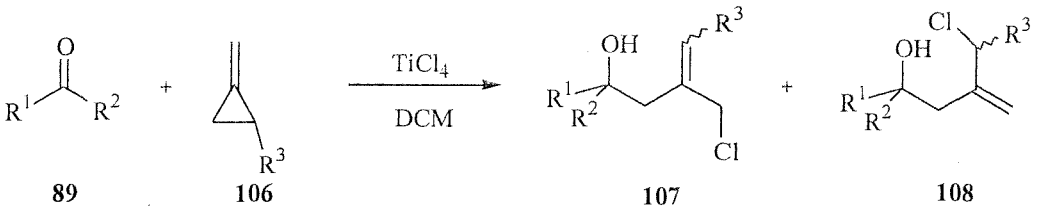
3-Methylenecyclopropane and Lewis Acid

Very little work has been carried out concerning the reaction of methylenecyclopropanes in combination with Lewis acid. Work by Monti[52] showed that Lewis acids can catalyse [3+2] cycloadditions between methylenecyclopropane derivatives such as **98** and allyl silane **99** to give methylenecyclopentane **100** and/or **101** (**Scheme 33**). The mechanism of this reaction is assumed to go through the allyl cation intermediate **103** due to chelation between $TiCl_4$, the exocyclic double bond and the carbonyl. Addition of the allyl silane generates the siliranium cations intermediates **104** and/or **105** (as proposed by Knolker[48]) which is then quenched by the titanium enolate to give the annulated products **100** and/or **101**.



Scheme 33

Hosomi[53] has shown that it is possible to couple methylenecyclopropane derivatives with carbonyl compounds (**Scheme 34**).



89 **106** **107** **108**

Scheme 34

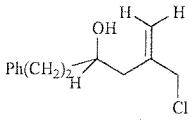
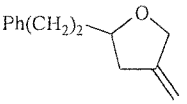
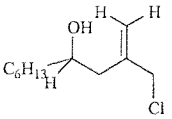
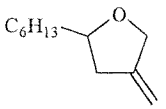
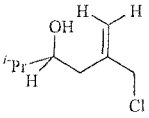
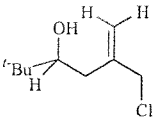
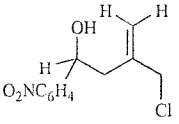
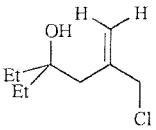
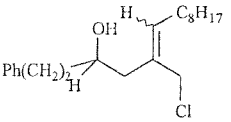
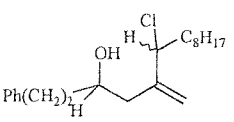
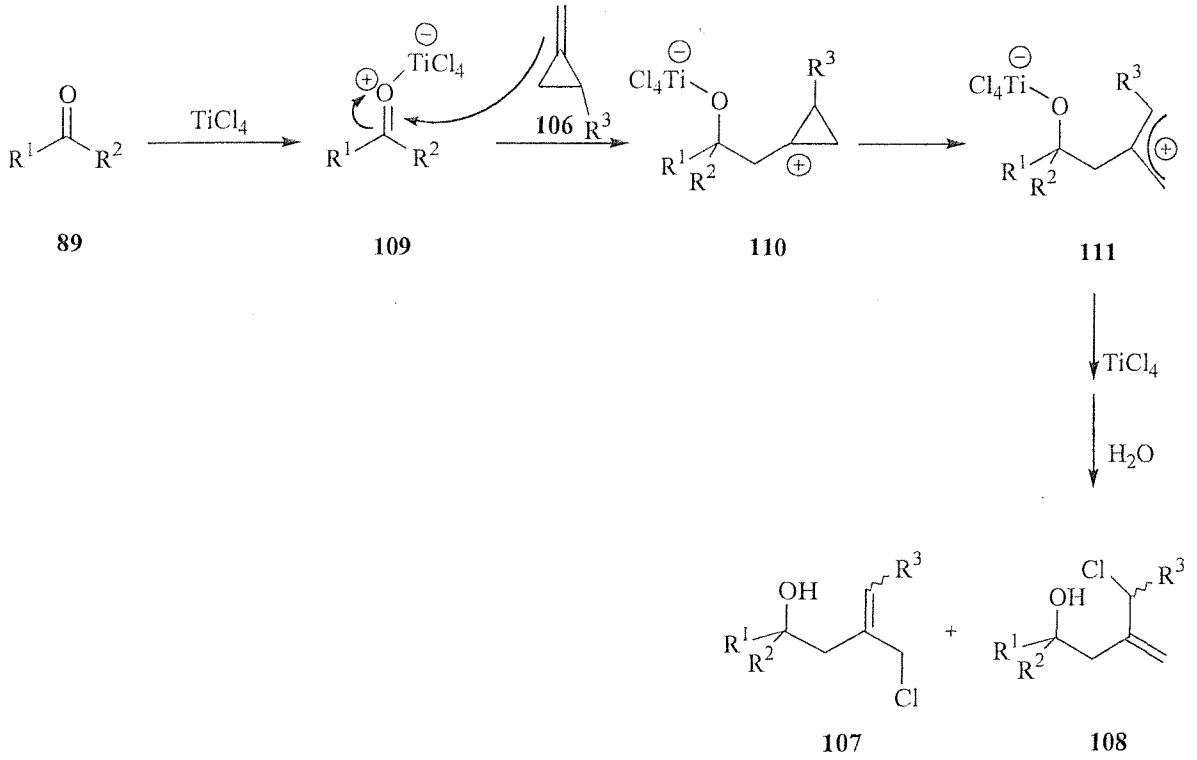
R^1	R^2	R^3	Conditions	Products 107	Products 108	Yield (%)
$Ph(CH_2)_2$	H	H	-78°C, 2 h			72
C_6H_{13}	H	H	-78°C, 2 h			73
^{i}Pr	H	H	-40°C, 2.5 h			75
^{t}Bu	H	H	0°C, 24 h			49
p-$O_2NC_6H_4$	H	H	- 78°C, 2h to RT, 2h			20
Et	Et	H	0°C, 14 h			5
$Ph(CH_2)_2$	H	C_8H_{17}	-78°C, 2 h			18

Table 2

Hosomi tried different Lewis acids and $TiCl_4$ gave the best results. When R^1 is a saturated alkyl group and R^2 = H, the allylated products were obtained in decent yields (49% to 73% yield). For unsaturated ketones and aromatic aldehydes with substituted

methylenecyclopropanes, the reaction did not work very well, even at room temperature. In addition, a similar tendency was observed in the allylation of ketones (**Table 2**).

A possible mechanism for this allylation was proposed by Hosomi (**Scheme 35**). The first step is coordination of the carbonyl group to $TiCl_4$ to form the complex **109**. Nucleophilic addition of **106** gives the cyclopropyl cation **110** which isomerises to the π-allyl cation intermediate **111**. Trapping of the allyl cation **111** by a chlorine anion gives the homoallylalcohols **107** and **108**.



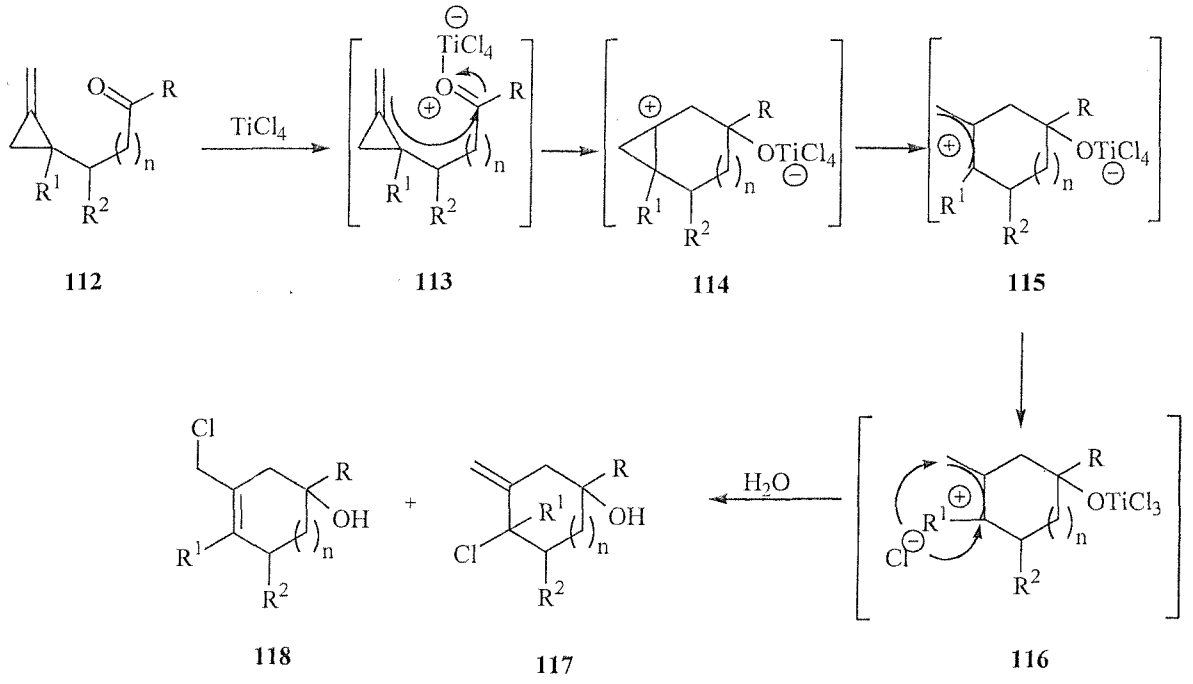
89 109 110 111 107 108

Scheme 35

These few examples clearly demonstrate that a good knowledge of the relative acid strength of a Lewis acid is essential for understanding many important reactions in synthesis. Moreover, the Lewis acid chosen for a particular reaction must not react with other functional groups in the reacting partners.

V-Program of Work

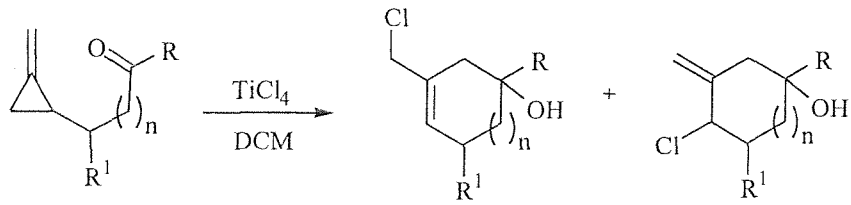
Following Hosomi's results from the intermolecular addition of methylenecyclopropanes onto an activated carbonyl, the aim of this project was to investigate the intramolecular version of this process (**Scheme 36**). Thus, Lewis acid activation of the carbonyl **112** followed by intramolecular nucleophilic attack by the double bond should lead to **114** and thus **115** and, by Hosomi's mechanism to **117** and **118**. Hosomi reported that ketones were insensitive to this nucleophilic attack, but we assumed that in an intramolecular reaction, the reaction might still work.



112 **113** **114** **115** **116** **117** **118**

Scheme 36

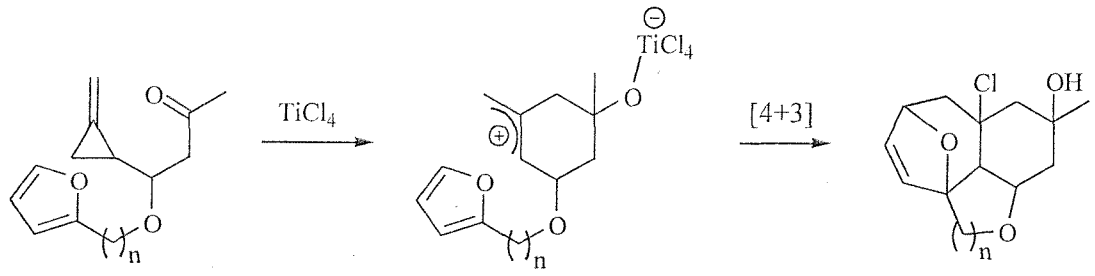
Cyclisation of methylenecyclopropyl ketones and aldehydes **119** will be investigated first. It was anticipated that **119** would give cyclised compounds **120** and **121** (**Scheme 37**).



119 R = H, CH_3; R^1 = H, OH, Bn, OMe **120** **121**

Scheme 37

The mechanism involves a π-allyl cation, so if the intramolecular cyclisation occurs, the reaction to polycyclic compounds could be extended by using a [3+4] intramolecular cycloaddition as a second step (**Scheme 38**).



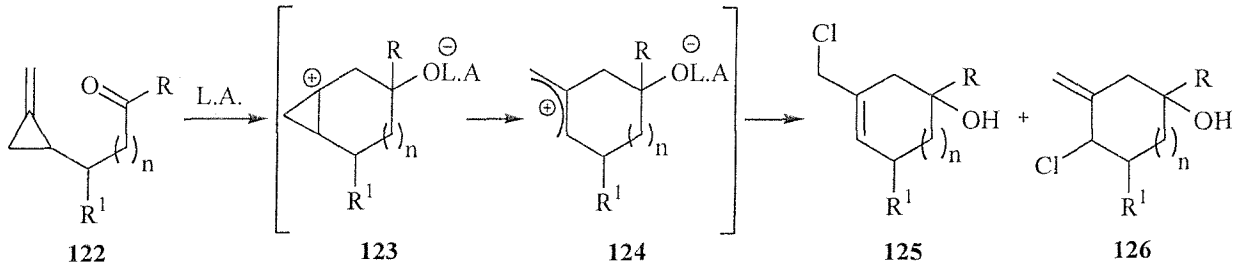
Scheme 38

The cascade process with first cyclisation to give the allyl cation intermediate which can be trapped in a cycloaddition reaction will be investigated.

CHAPTER ONE

Cyclisation Study of Methylenecyclopropyl Ketones and Aldehyde

The aim of the research was to study the scope and limitations of the intramolecular version of the Lewis acid mediated cyclisation of methylenecyclopropane derivatives, the intermolecular version of which had been investigated previously by Hosomi.[52] It was anticipated that activation of aldehyde or ketone **122**, with a suitable Lewis acid, such as $TiCl_4$, should allow intramolecular nucleophilic attack of the double bond of the methylenecyclopropyl unit leading to cyclopropyl cation **123**, which, following Hosomi's mechanism, should open to give π-allyl cation intermediate **124**, which in turn, can be quenched by a chloride anion to give cyclohexene **125** or methylenecyclohexane **126** (**Scheme 39**).



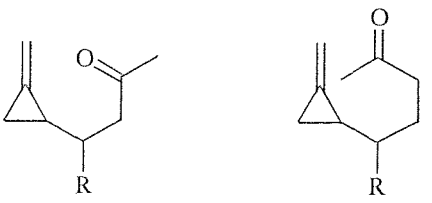
122 **123** **124** **125** **126**

R = H, CH_3

R^1 = H, OH, MeO or BnO

Scheme 39

Ketones **127** and **128** were chosen as the model compounds for this study.

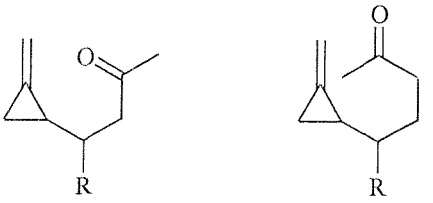


127 **128**

R = H, OH, MeO or OBn

I-Cyclisation Study of Methylenecyclopropyl Ketyl Alcohol and Keto-ether Derivatives

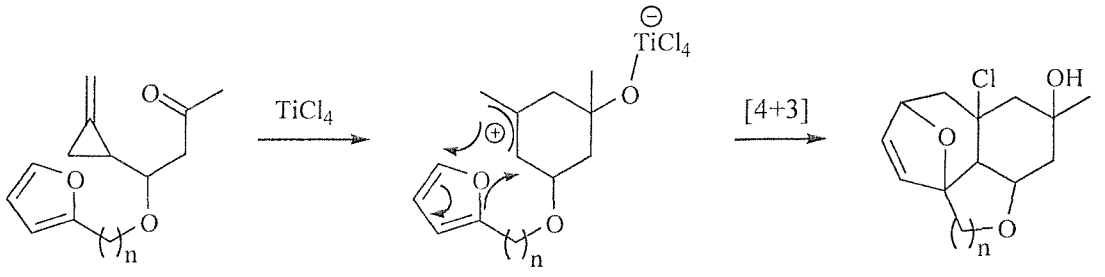
Ketones **127** and **128** were chosen for the initial cyclisation study, as they could be functionalised very easily by etherification with several suitable groups, in order to produce polycyclic compounds under cyclisation conditions.



127 **128**

R = OH, OBn or OMe

Indeed, ketones such as **129** would give polycyclic compound **131** after trapping of the allyl cation intermediate **130** in a [4 + 3] cycloaddition (**Scheme 40**).



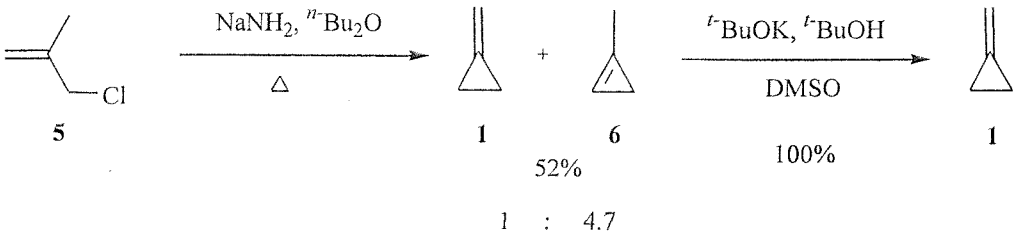
129 **130** **131**

Scheme 40

1-Synthesis of Methylenecyclopropane

Several synthesis of methylenecyclopropane **1** exist, but previous studies[8b,9,10] showed that the method of Binger[1b] was the most convenient and successful.

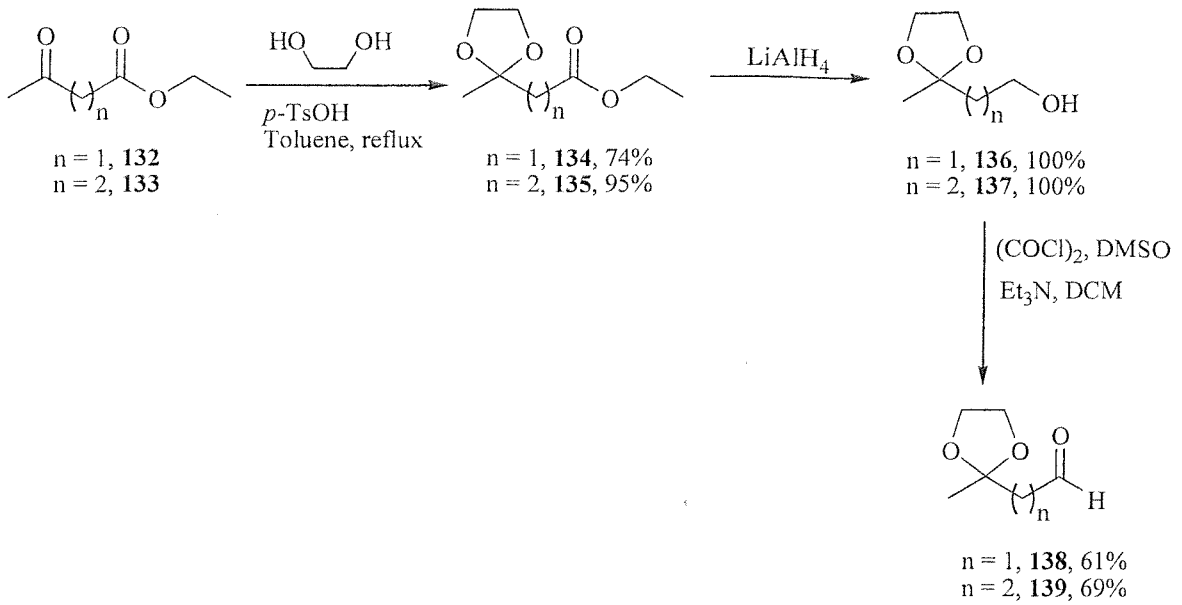
Reaction of commercially available methallyl chloride **5** with sodium amide, in hot *n*-butyl ether, produced a mixture of two carbenes adducts, methylenecyclopropane **1** and methylcyclopropene **6**, as well as an immiscible layer of ammonia. All products are gaseous at ambient temperature, so they were trapped in vessels at - 78 °C. The ammonia was then evaporated from the reaction mixture. Although, the reaction favoured the carbene addition to give the by-product methyl cyclopropene **6**, isomerisation with potassium *tert*-butoxide in *tert*-butanol and DMSO gave pure methylenecyclopropane **1** (**Scheme 41**).



Scheme 41

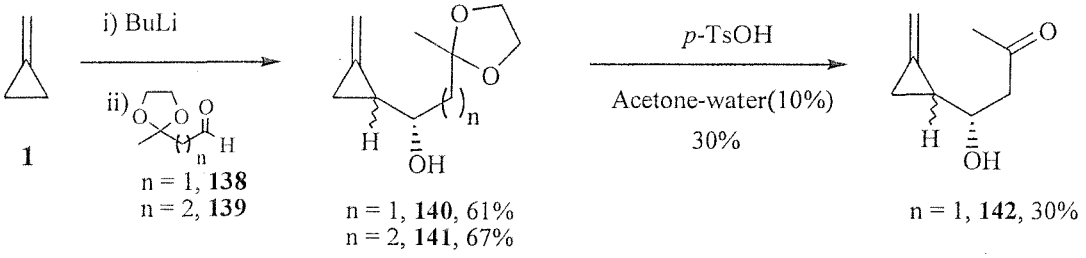
2-Preparation of Precursors

A method for the preparation of ketone **142**, as described by Boffey[8b], was applied to the preparation of ketones **127** and **128**. Protection of keto esters **132** and **133**, with ethylene glycol in the presence of catalytic amount of *p*-TsOH gave ketals **134** and **135** in 74% and 95% yield respectively. Quantitative reduction to alcohols **136** and **137** and subsequent Swern oxidation afforded aldehydes **138** and **139** in 61% and 69% yield respectively (**Scheme 42**).



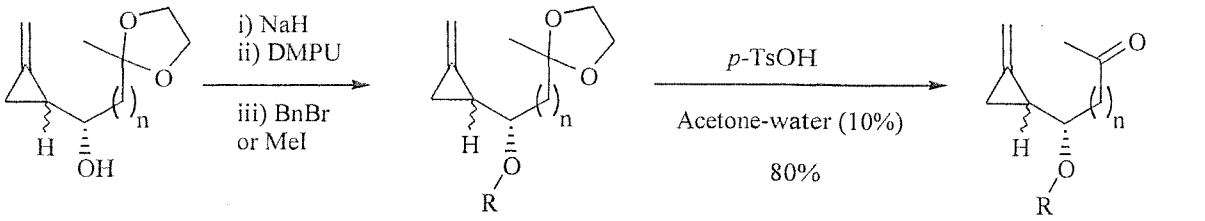
Scheme 42

Aldehydes **138** and **139** were respectively added to a solution of lithiated methylenecyclopropane to give alcohols **140** and **141**, as a 1 : 1 mixture of separable diastereoisomers (**Scheme 43**). The stereochemistry of both isomers of alcohol **140** had been determined previously by X-ray diffraction of the *p*-nitrobenzoate derivative, as *syn* and *anti* products.[8b] Deprotection of ketal **140**, using *p*-TsOH in wet acetone, gave ketone **142**, as an inseparable 1 : 1 mixture of diastereoisomers.



Scheme 43

Alcohols **140** and **141** were easily alkylated, using NaH and benzyl bromide or methyl iodide, to give benzyl ether **143**, as a 1 : 1 mixture of diastereoisomers, or methyl ether **144**, as a 1 : 1 mixture of diastereoisomers, in 91% and 95% yield respectively. Deprotection of the ketone function of **143** and **144** gave keto ether **145**, as a 1 : 1 mixture of diastereoisomers, and keto ether **146**, as a 1 : 1 mixture of diastereoisomers, in 80% and 65% yield respectively (**Scheme 44**).



n = 1, **140**
n = 2, **141**

n = 1, R = Bn, **143**, 91%
n = 2, R = Me, **144**, 95%

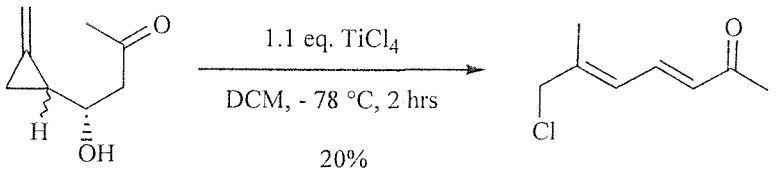
n = 1, R = Bn, **145**, 80%
n = 2, R = Me, **146**, 65%

Scheme 44

3-Cyclisation Study

Cyclisation Study of Methylenecyclopropyl Ketones

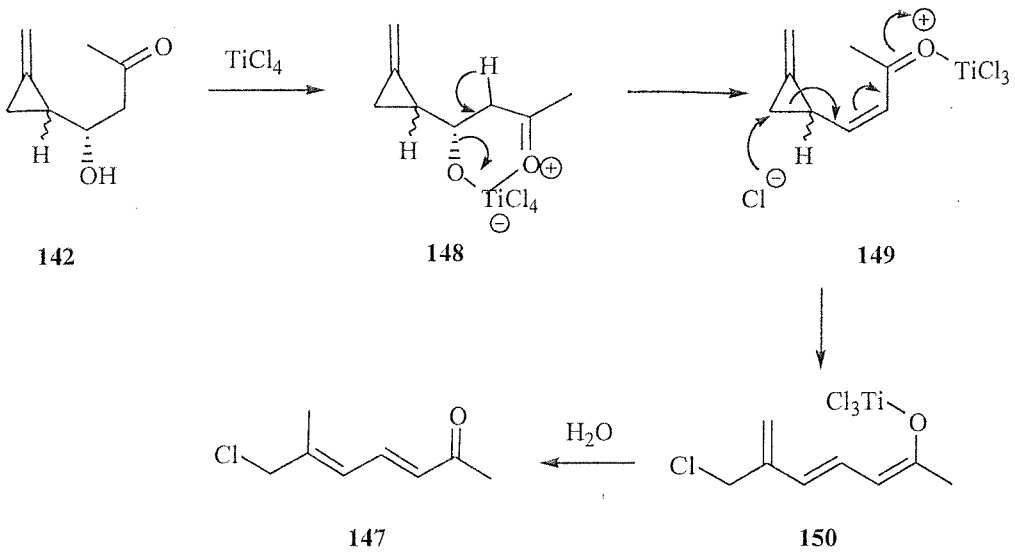
Cyclisation of ketone **142** was investigated first. When 1.1 eq. $TiCl_4$ was added to ketone **142**, a complex mixture of compounds was obtained, where none of the wanted cyclohexyl products were observed and only dieneone **147** could be isolated in 20% yield (**Scheme 45**).



142 **147**

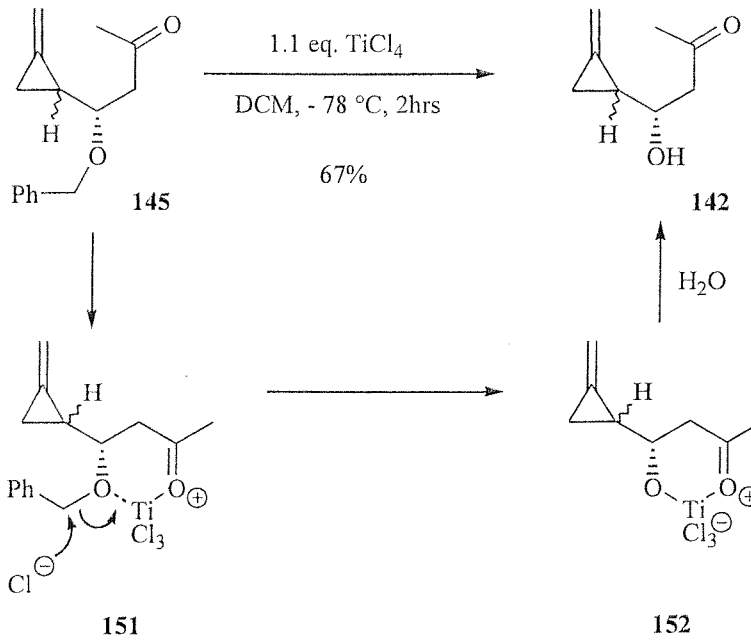
Scheme 45

The formation of dieneone **147** is presumably due to the relative acidity of the hydrogen atoms bearing the carbonyl function, which promotes dehydration, favoured by the formation of chelate **148**, to give intermediate **149**. A chloride anion can then attack the cyclopropyl ring to give **150** which is hydrolysed to **147** (**Scheme 46**).



Scheme 46

Benzyl ether **145** was anticipated to overcome this problem of dehydroxylation-chelation. However, when $TiCl_4$ was added to the mixture of *syn* and *anti* isomer of ketone **145**, debenzylation occurred to give ketone **142** (**Scheme 47**). Jung *et al.* reported a similar reaction, where ketals were deprotected under Lewis acid condition, such as TMSI.[54]

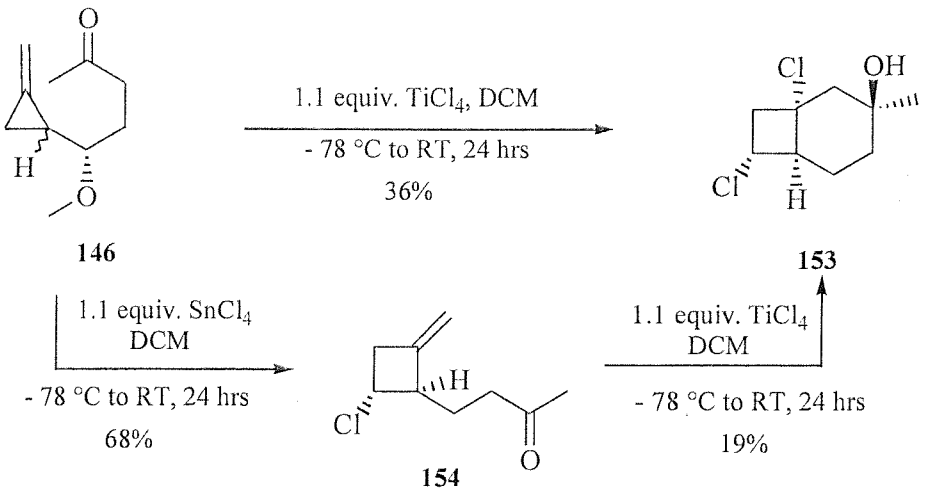


Scheme 47

Following the mechanism proposed by Jung, a chlorine anion can attack the chelate intermediate **151** to give intermediate **152**, which is hydrolysed to give ketone **142**.

In addition, $BF_3.Et_2O$, as a monodentate Lewis acid, was also investigated. In this case chelation control should be avoided. Unfortunately, analysis of the ^1H NMR of the crude reaction mixture showed only the presence of the ring opened compound and the debenzylated ketone **142**.

It was then assumed that ketone **146** would also overcome the problem of dehydroxylation. However, treatment of the mixture of diastereoisomers of ketone **146** with 1.1 eq. $TiCl_4$ gave bicyclic dichloride **153**, as a single diastereoisomer, in 36% yield. Moreover, addition of 1.1 eq. $SnCl_4$ gave methylenecyclobutyl ketone **154**, as a single diastereoisomer, in a good 68% yield. When $TiCl_4$ was added to methylenecyclobutyl ketone **154**, bicyclic dichloride **153**, as a single diastereoisomer, was again obtained (**Scheme 48**).



Scheme 48

The stereochemistry of **153** was determined by X-ray diffraction (**Figure 1**).[55]

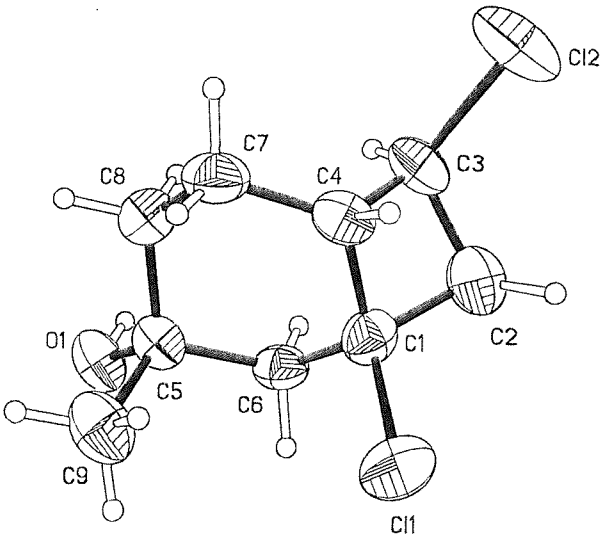
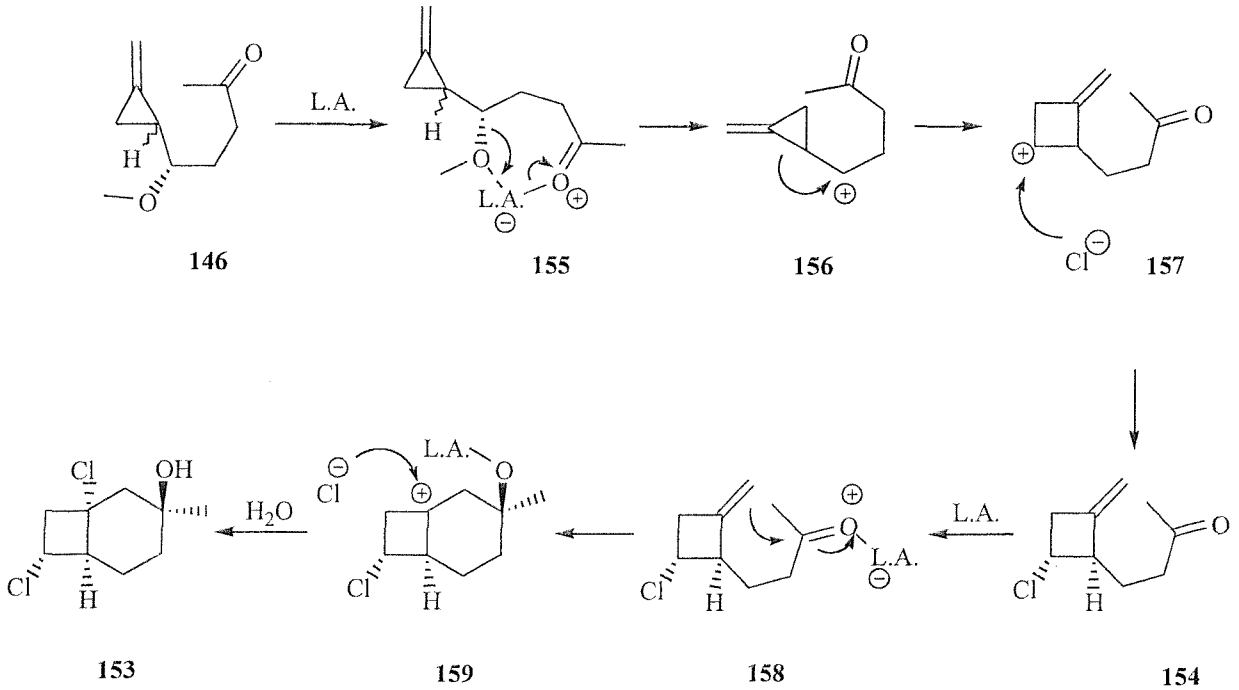


Figure 1: Crystal structure of **153**

For full details of the X-ray crystallographic data, see appendix A.

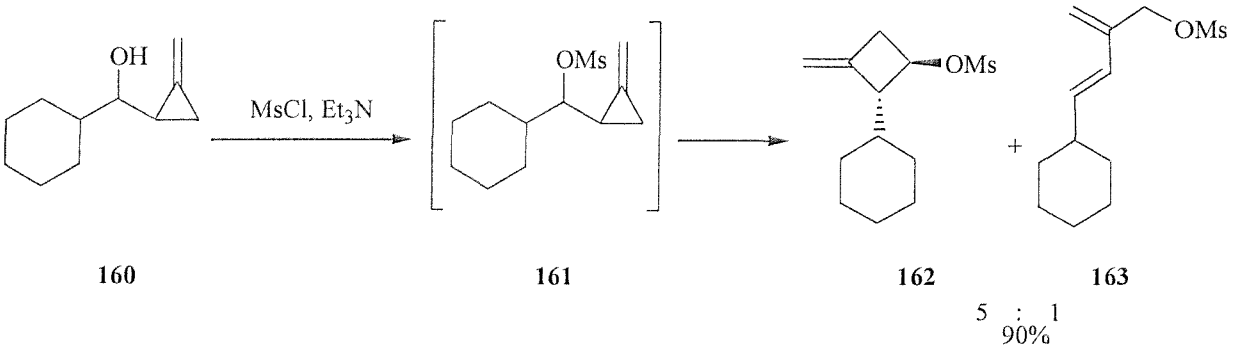
As methylenecyclobutyl ketone **154** gave bicyclic dichloride **153** upon treatment with $TiCl_4$, its formation may be part of the mechanism involved in the formation of **153** (**Scheme 49**).



Scheme 49

Activation of ketone **146** with Lewis acid would give intermediate **155** promoting a ring enlargement[56] to give methylenecyclobutyl cation **157**. Methylenecyclobutyl cation **157** is presumably quenched by a chloride anion, to give methylenecyclobutyl ketone **154**. When $SnCl_4$ is used, the reaction gave only methylenecyclobutyl ketone **154**, whereas, with $TiCl_4$, **154** underwent a further cyclisation. However, in contrast to the corresponding cyclopropyl cation formed in Hosomi's mechanism, the cyclobutyl cation **159** did not open, presumably because its ring is less strained than the cyclopropyl ring and the trapping of the cation, by a chlorine anion, is faster than the ring opening.

Baldwin *et al.*[56] has reported an analogous rearrangement of methylenecyclopropane to methylenecyclobutane (**Scheme 50**).



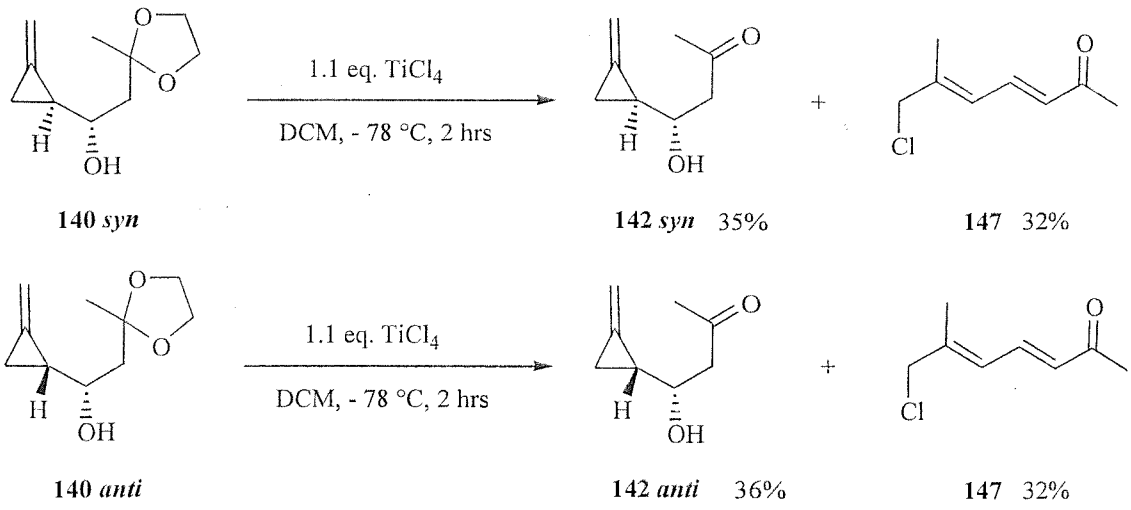
160 **161** **162** **163**

5 : 1
90%

Scheme 50

Cyclisation Study of Methylenecyclopropyl Ketals

Cyclisation of ketals was also studied as the ketal unit could be activated by a Lewis acid. Ketal **140** was initially investigated. However, addition of $TiCl_4$ on each separated *syn* and *anti* isomer of **140**, resulted in deprotection of the ketal function to give the *syn* and *anti* isomer of ketone **142** in 35% and 36% yield respectively. Dieneone **147** was also isolated in 32% yield (**Scheme 51**).

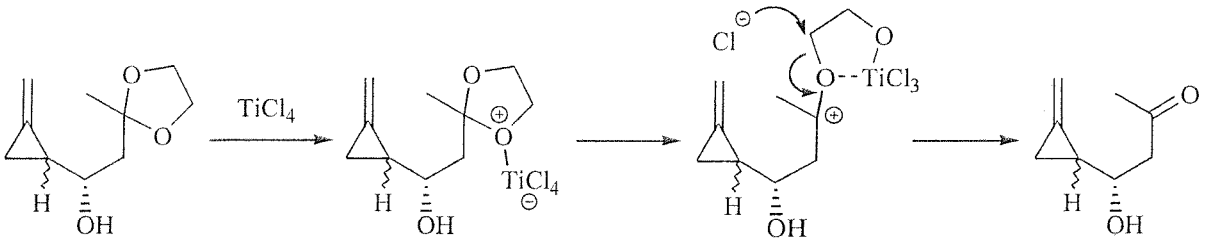


140 ***syn*** **142** ***syn*** 35% **147** 32%

140 ***anti*** **142** ***anti*** 36% **147** 32%

Scheme 51

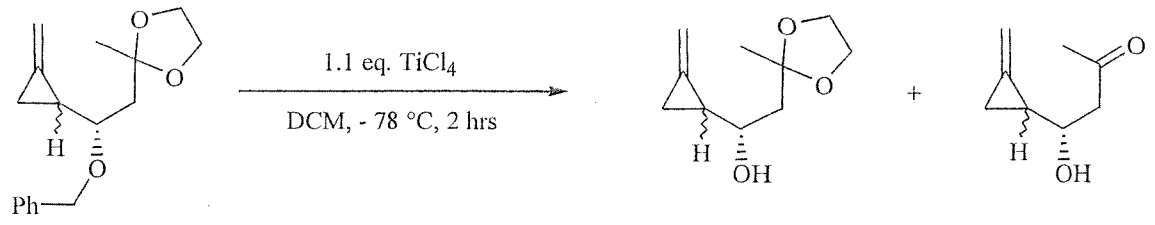
Deprotection of ketal **140** can be explained following the mechanism proposed by Jung *et al.*[54] (**Scheme 52**). Activation of ketal **140** with $TiCl_4$ gave intermediate **164**, which open to cation **165**. A chlorine anion can then attack the alkoxy side chain to give ketone **142**. Dieneone **147** is presumably obtained from ketone **142** following the mechanism proposed in **Scheme 46**.



140 **164** **165** **142**

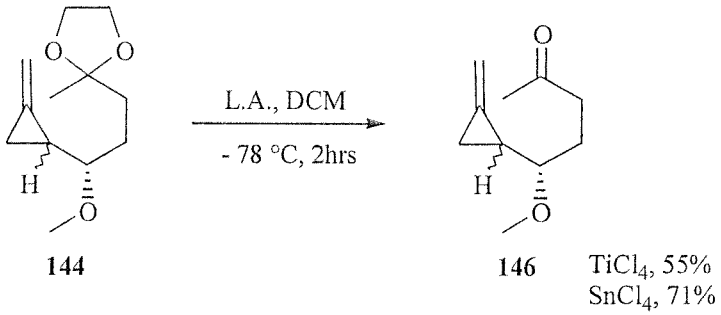
Scheme 52

Cyclisation of benzyl ether **143** was also investigated. Treatment of the mixture of *syn* and *anti* isomers of ketal **143** with $TiCl_4$ gave debenzylated ketal **140**, as a 1 : 1 mixture of separable diastereoisomers, in 21% yield and debenzylated deprotected ketone **142**, as a 1 : 1 mixture of inseparable diastereoisomers, in 37% yield (**Scheme 53**).



Scheme 53

Finally, cyclisation of ketal **144** was studied, in order to obtained seven membered ring systems. Addition of 2 eq. of either $TiCl_4$ or $SnCl_4$ to the mixture of diastereoisomers of ketal **144** gave ketone **146**, as a 1 : 1 mixture of inseparable diastereoisomers, in 55% and 71% yield respectively (**Scheme 54**). If the reaction had been left longer, presumably methylenecyclobutane **154** would have been obtained with $SnCl_4$ and bicycle **153** would have been also obtained with $TiCl_4$. The mechanism of the deprotection of ketal **144** is the same as for deprotection of ketal **140** (**Scheme 52**).



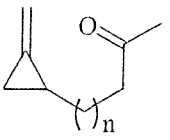
Scheme 54

Summary

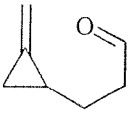
Cyclisation of precursors **127** and **128** was not successful, presumably due to chelation between the ketone and the alkoxy functions. Alternative cyclisation precursors were therefore investigated.

II-Cyclisation Study of Methylenecyclopropyl Ketones and Aldehyde

Methylenecyclopropane derivatives **166-169** were chosen as simple cyclisation precursors.



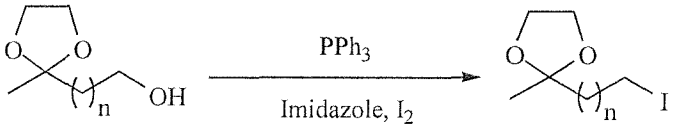
n = 1, **166**
n = 2, **167**
n = 3, **168**



169

1-Preparation of Precursors

Ketones **166** and **167** were prepared, starting from alcohols **136** and **137**. Conversion of the alcohol function to iodide was easily achieved, using triphenylphosphine, imidazole and iodine to give iodide **170** and **171** in 91% and 98% yield respectively (**Scheme 55**).

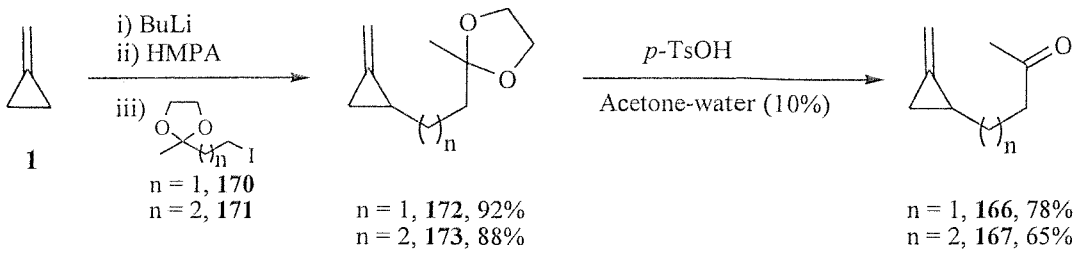


n = 1, **136**
n = 2, **137**

n = 1, **170**, 91%
n = 2, **171**, 98%

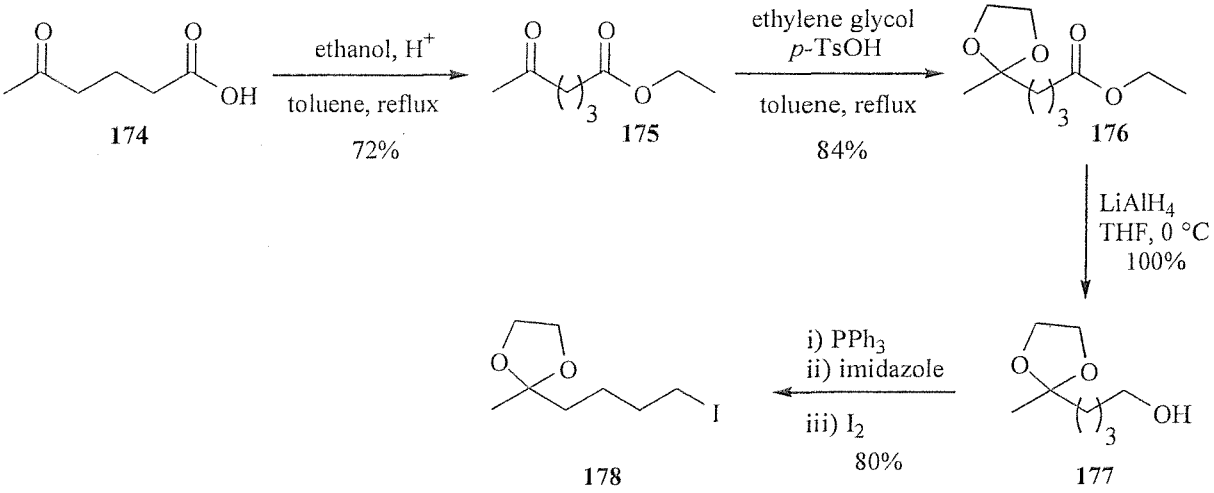
Scheme 55

Alkylation of lithiated methylenecyclopropane with iodide **170** and **171**, in the presence of HMPA, gave ketals **172** and **173** in 92% and 88% yield respectively (**Scheme 56**). When HMPA was not used, none of the alkylated product was obtained. Deprotection of ketals **172** and **173** afforded ketones **166** and **167**.



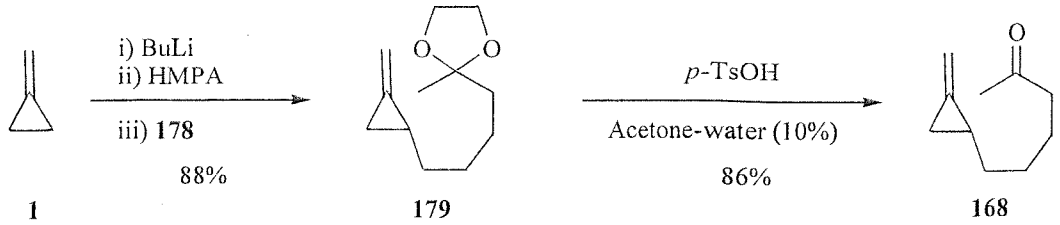
Scheme 56

Ketone **168** was prepared following the same method, but starting from 4-acetylbutyric acid **174** (**Scheme 57**). Esterification of 4-acetylbutyric acid **174** with ethanol in the presence of acid afforded ethyl ester **175** in 72% yield. Protection of ketoester **175** with ethylene glycol and *p*-toluenesulfonic acid gave ketal **176** in 84% yield. Quantitative reduction of **176** gave alcohol **177** which was easily converted to the corresponding iodide **178** in 80% yield, using triphenylphosphine, imidazole and iodine.



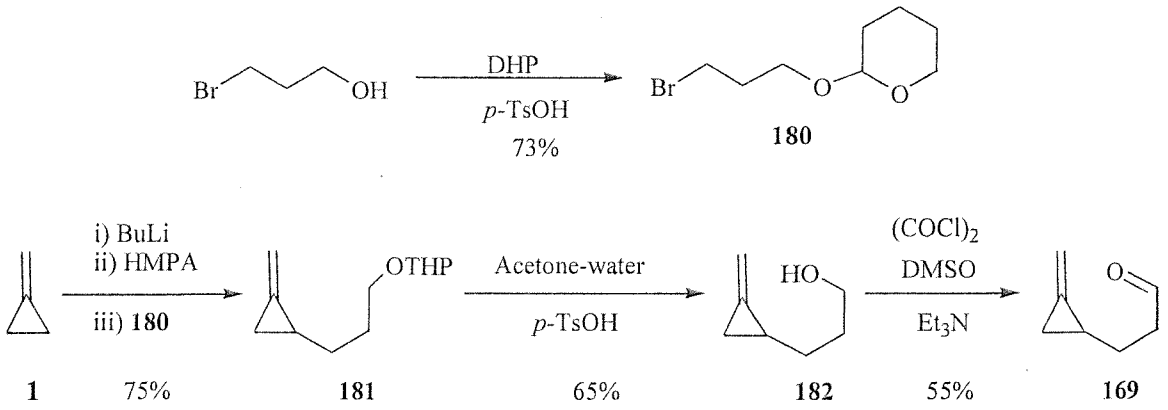
Scheme 57

Methylenecyclopropane **1** was then deprotonated, with BuLi, and alkylated with iodide **178**, in the presence of HMPA, to give ketal **179** in 88% yield, which gave ketone **168** after deprotection of its ketal function (**Scheme 58**).



Scheme 58

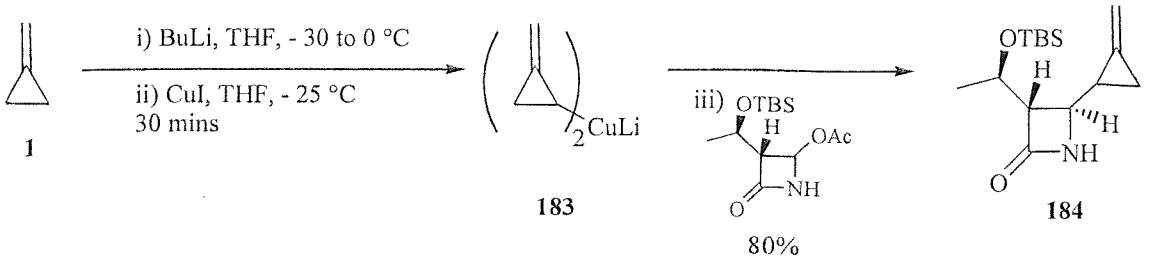
Aldehyde **169** was prepared in 4 steps, starting from 3-bromopropanol. THP protection of 3-bromopropanol gave bromide **180** in 73% yield. Alkylation of lithiated methylenecyclopropane with bromide **180** in the presence of HMPA, gave methylenecyclopropyl ether **181** in 75% yield and THP deprotection gave alcohol **182**. Alcohol **182** had previously been synthesised by Destabel and her method was followed.[9] Swern oxidation afforded aldehyde **169** in only 55% yield, due to the volatility of the aldehyde (**Scheme 59**).



Scheme 59

2-Addition of Methylenecyclopropylcuprate to Conjugated Ketones

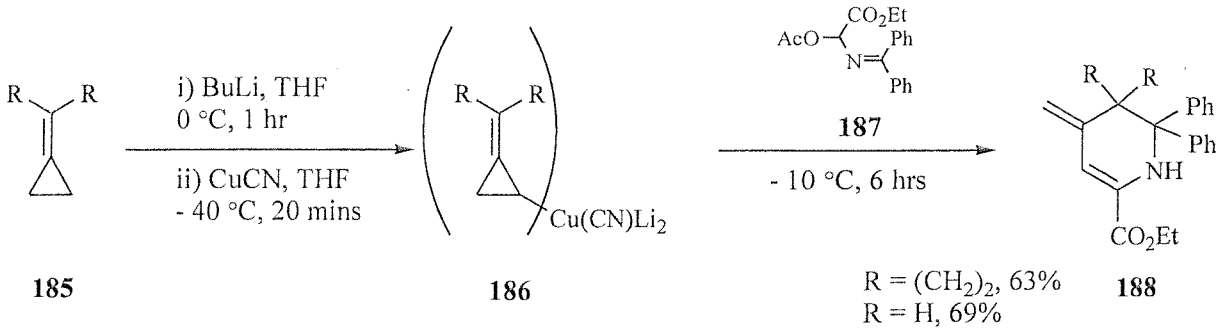
As the preparation of ketones such as **166** required several steps, a faster process had to be developed if we wanted to have a rapid access to more substrates. Earlier, in our group, Pike[10] and Penfold[25] developed a method for the preparation of methylenecyclopropylcuprate. These organocuprates were used in the synthesis of β-lactam compounds (**Scheme 60**).



Scheme 60

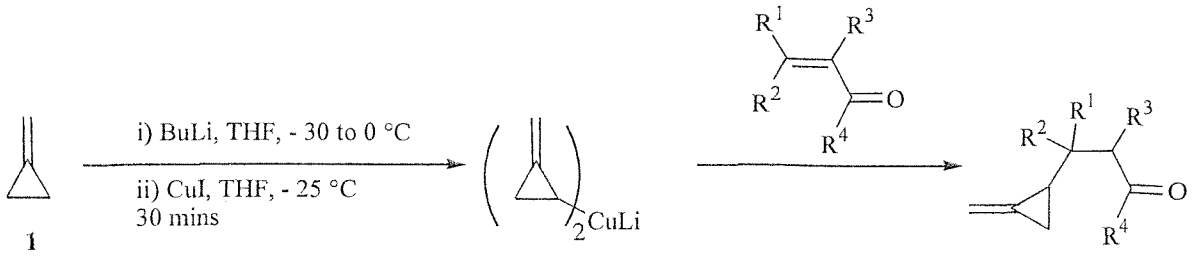
Following the method used by Hanessian[57] for the coupling of an allylcuprate to azetidinone, methylenecyclopropane was deprotonated with BuLi and then added to a suspension of copper(I) iodide in THF to give organocuprate **183**. Addition of the azetidinone gave an excellent yield of alkylated product **184**. To our knowledge, this was the first example of such a cuprate.

However, recently de Meijere[58] reported the use of higher order cuprates in the alkylation of glycine derivatives. When the higher order methylenecyclopropylcuprate **186** was formed by addition of the lithiated methylenecyclopropane to a suspension of CuCN at - 40 °C followed by addition of glycine acetate derivative **187**, he observed an unusual ring opening of the cyclopropyl ring to give methylenetetrahydropyridine **188** (**Scheme 61**).



Scheme 61

As organocuprates are excellent soft nucleophiles for the addition to Michael acceptors.[37,59] It was anticipated that addition of α,β-unsaturated ketones to the Gilman reagent methylenecyclopropyl cuprate **183** would give [1,4] Michael addition. In this way the precursors for the Lewis acid cyclisation study could be obtained in one step (**Scheme 62**).



1 **183** **189**

Scheme 62

Different enones were used and the results are shown in **Table 3**.

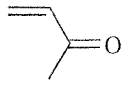
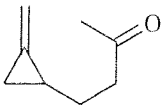
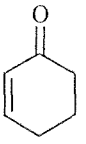
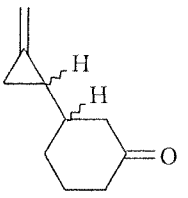
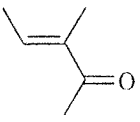
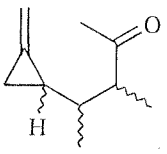
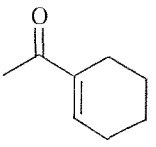
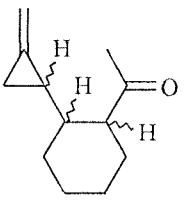
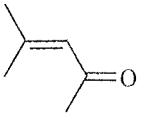
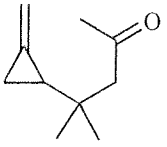
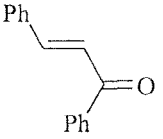
Substrate	Product	Yield	Substrate	Product	Yield
 **190**	 **166**	79%	 **195**	 **196**	95%
 **191**	 **192**	59%	 **197**	 **198**	76%
 **193**	 **194**	71%	 **199**	-	-

Table 3

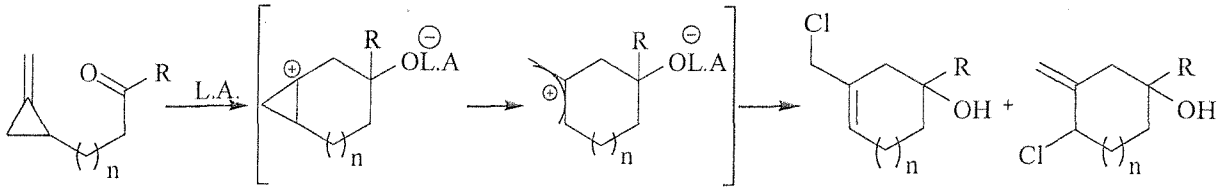
However, the use of TMSCl was required in all cases. The role of the TMSCl was first to activate the enones and second to trap the enolate formed after addition, in order to prevent the formation of side products as previously demonstrated by Taylor[60] and Matsuzawa *et al.*[61]

Methyl vinyl ketone gave in one step precursor **166** in 79% yield. The reaction also proved to work with hindered enones such as **191** and **196**, which gave ketones **192** as a 3 : 3 : 2 : 1 mixture of inseparable diastereoisomers and ketone **194** in 59% and 71% yields respectively. Cyclic ketones worked well too. Cyclohexenone **195** gave a 1 : 1 mixture of inseparable diastereoisomers **196** in an excellent 95% yield and enone **197** gave ketone **198** as a 5 : 5 : 3 : 2 mixture of inseparable diastereoisomers in 76% yield. Unfortunately the reaction of chalcone **199** with methylenecyclopropyl cuprate **183** failed to give any expected product.

α,β-unsaturated esters were also tried. Methyl acrylate and methyl crotonate gave polymeric material and methyl cinamate gave a complex mixture of products. Michael addition onto acrylonitrile was also attempted, but failed to give any of the expected product. Polymerisation was observed instead.

3-Cyclisation Study

Ketones **166**, **167** and **168** and aldehyde **169** were expected to give six, seven and eight membered systems respectively, upon treatment with a suitable Lewis acid, such as $TiCl_4$ (**Scheme 63**). Activation of ketone or aldehyde **200** with $TiCl_4$, should allow intramolecular nucleophilic attack of the double bond of the methylenecyclopropyl moiety leading to cyclopropyl cation **201**. This should open to give π-allyl cation intermediate **202**, which in turn, would be quenched by a chloride anion to give cyclised products **203** and **204**.



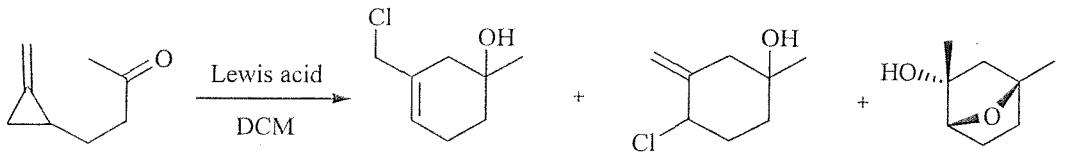
200 **201** **202** **203** **204**

R = H, CH_3

Scheme 63

Cyclisation Study of Methylenecyclopropyl Ketones and Aldehyde

Lewis acid mediated cyclisation of ketone **166** was first attempted with a range of Lewis acids (**Scheme 64**, **Table 4**).



166 **205** **206** **207**

Scheme 64

Lewis acid	Temp required (°C)	Time (h)	Yield (%) 205	206	207
BF_3,Et_2O	- 78 to 15	24	0	0[1]	0
$BF_3(AcOH)_2$	- 78 to 15	24	0	0[1]	0
$ZnBr_2$	- 78 to 15	24	0	0[2]	0
$SnCl_4$	- 40	4	6	0	0
HCl	- 78 to 15	24	0	0[2]	0
Et_2AlCl	- 78 to 15	24	0	0[2]	0
$EtAlCl_2$	- 78 to 15	24	0	0[2]	0
$TiCl_4$	- 78	2	10	0	0
$TiCl_4$	- 40	1.5	50	0	9
$TiCl_4$	0	1	30	0	25

[1] a mixture impossible to separate was obtained.

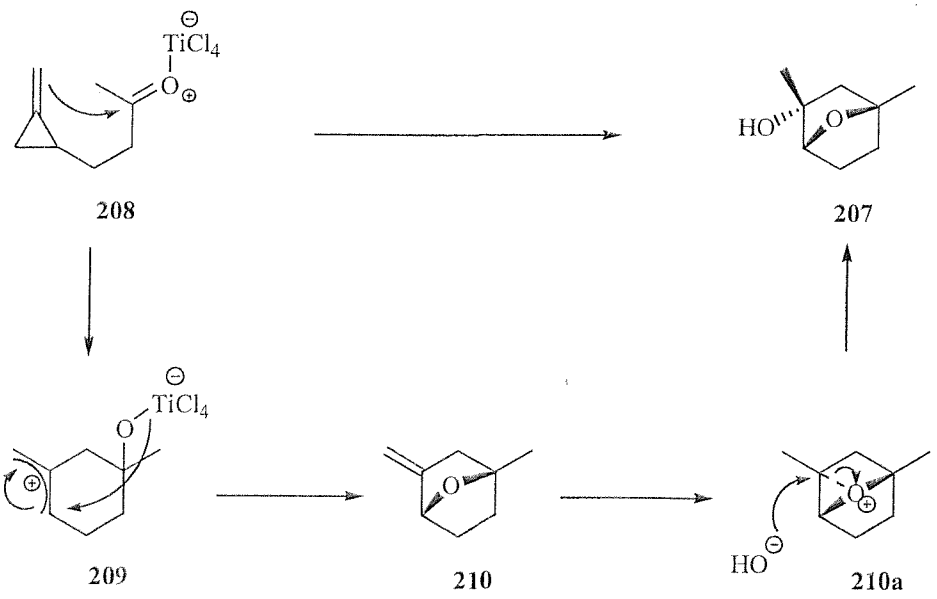
[2] only starting material was recovered.

Table 4

Only $TiCl_4$ gave a reasonable yield of cyclohexene **205**. No methylenecyclohexane **206** was ever obtained. With $SnCl_4$, at - 78 °C, a low yield (6%) of cyclohexene **205** was obtained, whereas treatment of ketone **166** with $BF_3.Et_2O$ and $BF_3(AcOH)_2$ only ever gave a complex mixture of products, and no reaction was observed with $ZnBr_2$, HCl, Et_2AlCl or $EtAlCl_2$ (**Table 4**).

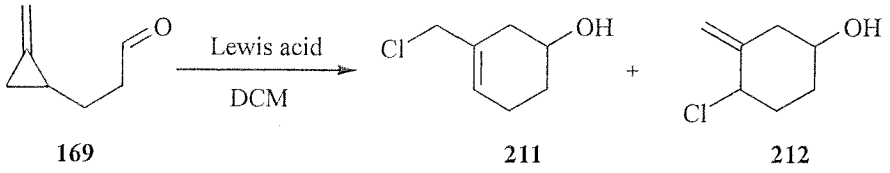
The best yield of **205** was obtained by conducting the reaction at - 40 °C. At higher temperatures, an increasing amount of byproduct **207**, as a single diastereoisomer, was formed, presumably by intramolecular trapping of the intermediate allyl cation **209** by the alkoxide. Subsequent hydration of the double bond assisted by the ether bridge, which may formed intermediate **210a** before hydroxide quenching, gave **207** (**Scheme 65**). However, all attempts to prove the stereochemistry of **207** failed and the stereochemistry is tentatively assigned based on the proposed mechanism. One clue for the proposed assignment of the

stereochemistry of **207** is the broad peak observed for the tertiary alcohol at 3.24 ppm on the ^{1}H NMR.



Scheme 65

A similar range of Lewis acids was investigated for the cyclisation of aldehyde **169** (**Scheme 66**).



Scheme 66

Lewis acids	Temp required (°C)	Time (h)	Yield (%) 211	212
BF_3, Et_2O	- 78 to 15	24	0	0[1]
$ZnCl_2$	- 78 to 15	24	0	0[2]
$SnCl_4$	- 78	3	7	0
$TiCl_4$	- 78	2	22.5	0
$TiCl_4$	- 40	1	39	0
$TiCl_4$	0	1	50	0
$TiCl_4$	15	0.5	21	0

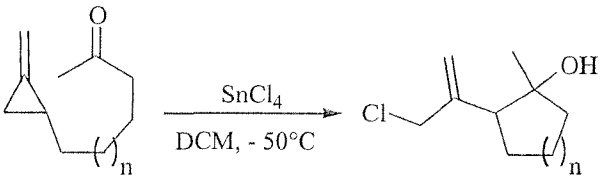
[1] a mixture impossible to separate was obtained.

[2] only starting material was recovered.

Table 5

In common with Hosomi, we found that $TiCl_4$ worked best for aldehyde **169**, giving a 50% yield of cyclohexene **211** as the only isolated product when the reaction was conducted at 0 °C. Lower yields of **211** were obtained at either higher or lower temperatures. With $SnCl_4$, at - 78 °C, a low yield (7%) of cyclohexene **211** was obtained, whereas treatment of aldehyde **169** with $BF_3.Et_2O$ only ever gave a complex mixture of products, and no reaction was observed using $ZnCl_2$ (**Table 5**).

Cyclisation of ketones **167** and **168** was best carried out with $SnCl_4$, but now gave cyclopentanol **213** in 43% yield and cyclohexanol **214** in 40%, as single diastereoisomers (**Scheme 67**). Using $BF_3.Et_2O$ or $TiCl_4$, a complex mixture of inseparable products was obtained and there was no reaction with HCl, Et_2AlCl or $EtAlCl_2$. However, all attempts to determine the stereochemistry of **213** and **214** were unsuccessful.

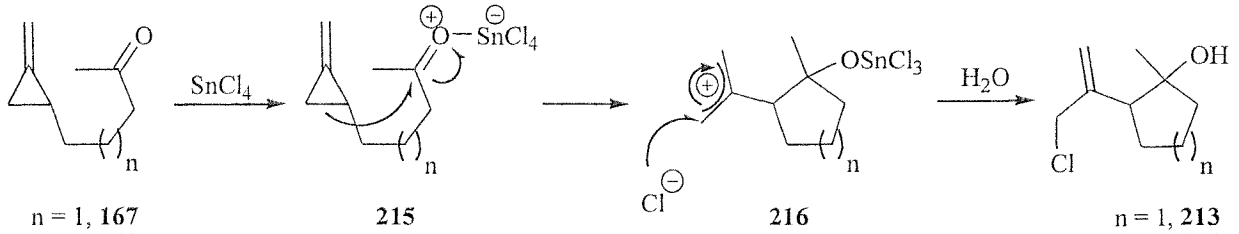


n = 1, **167**
n = 2, **168**

n = 1, **213**, 43%
n = 2, **214**, 40%

Scheme 67

Cyclopentanol **213** and cyclohexanol **214** are presumably obtained by nucleophilic attack of the distal σ-bond of the cyclopropyl ring of intermediate **215** to give π-allyl cation **216**, which can be then trapped by a chlorine anion to give **213** and **214** after hydrolysis (**Scheme 68**). This pathway is favoured, over Hosomi's mechanism, probably because of favourable overlapping of the σ orbitals of the cyclopropyl ring with the π^* orbital of the carbonyl.



n = 1, **167**
n = 2, **168**

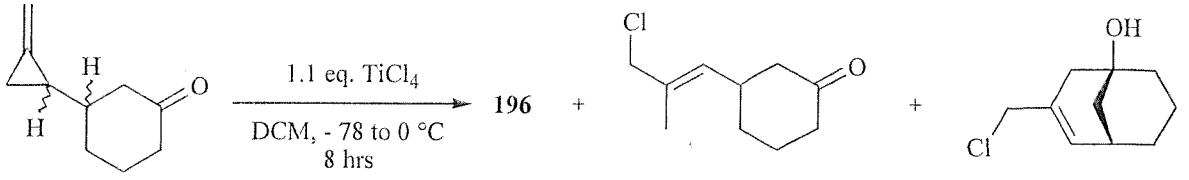
215

216

n = 1, **213**
n = 2, **214**

Scheme 68

Attention was turned to precursors obtained from the cuprate addition. Regarding the previous results, it was decided to attempt the cyclisation only with $TiCl_4$. Cyclisation of ketone **196** was initially investigated and gave upon treatment with $TiCl_4$ three products (**Scheme 69**). The first isolated compound was the starting ketone **196** as a single diastereoisomer in 43% yield followed by *trans* alkene **217** in 15% yield and finally the expected cyclised product **218** in 35% yield.

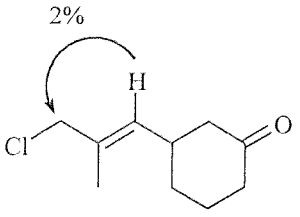


196 **217** **218**

43% 15% 35%

Scheme 69

The stereochemistry of trans alkene **217** was suggested by nOe experiment. Irradiation of the alkene H gave a 2% enhancement of the proton of CH_2Cl and no enhancement in the signal of the methyl group (**Figure 2**).



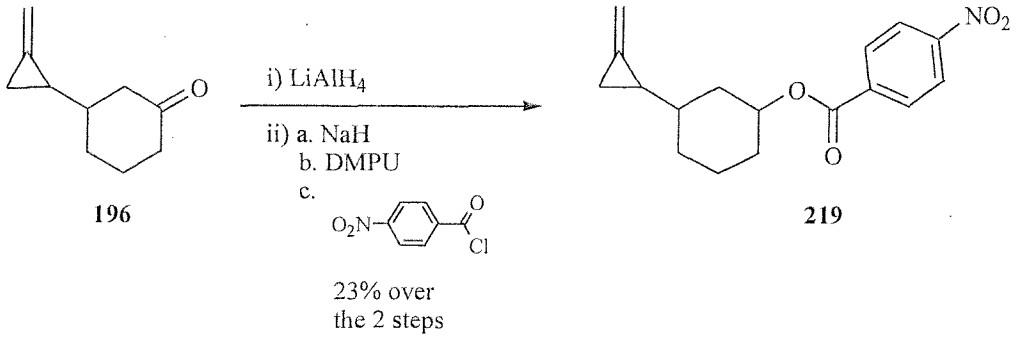
217

Figure 2: nOe cross peak

The recovery of the starting ketone **196** in 43%, as a single diastereoisomer, indicated that only one isomer is cyclising. Investigation of models does not give any obvious clue as to the stereochemistry of the isomer which reacts.

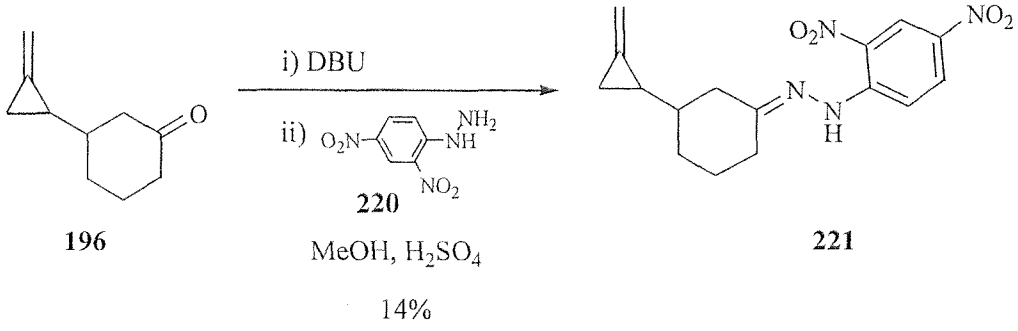
In order to elucidate the stereochemistry of the unreacted ketone **196**, a *p*-nitrobenzoate derivative was prepared (**Scheme 70**). Reduction of ketone **196** with $LiAlH_4$ to alcohol, followed by alkylation with *p*-nitrobenzoyl chloride, using NaH and DMPU, gave the expected p-nitrobenzoyl ester **219** in 23% yield, as a single diastereoisomer. However, all

attempts to obtain good quality single crystals, for X-ray diffraction, failed and an alternative method was investigated.



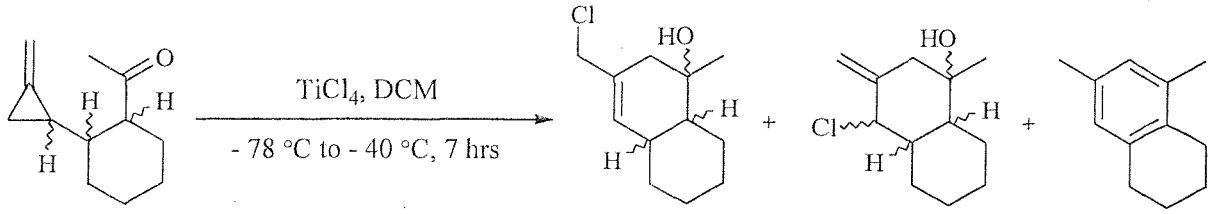
Scheme 70

The unreacted ketone **196** was converted to the corresponding hydrazone **221** following a method described by Wicha[62] (**Scheme 71**). Addition of DBU to ketone **196** followed by addition of an acidified methanolic solution of hydrazine **220** gave hydrazone **221** in 14% yield. However, recrystallisation in ethyl acetate-petroleum ether gave very fragile crystals which failed to provide us with a structure.



Scheme 71

Lewis acid mediated cyclisation of ketone **198** was next investigated. Treatment of ketone **198** with $TiCl_4$ gave a inseparable mixture of regio- and diastereoisomers **222** and **223** in 29% yield, accompanied by aromatic **224** in 38 % yield (**Scheme 72**). However, due to the complexity of the NMR, it was not possible to determine the ratio of each regio- and diastereoisomer.

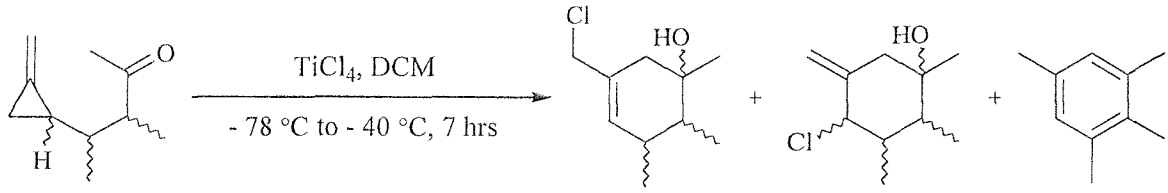


198 **222** **223** **224**

29% 38%

Scheme 72

Ketone **192** gave similar results. Addition of $TiCl_4$ to ketone **192** at - 78 °C, gave a mixture of inseparable regio- and diastereoisomers **225** and **226** in 38% yield, accompanied by tetramethylbenzene **227** in 35% yield (**Scheme 73**). However, as for the cyclisation of ketone **198**, due to the complexity of the NMR, it was not possible to determine the ratio of each regio- and diastereoisomers.

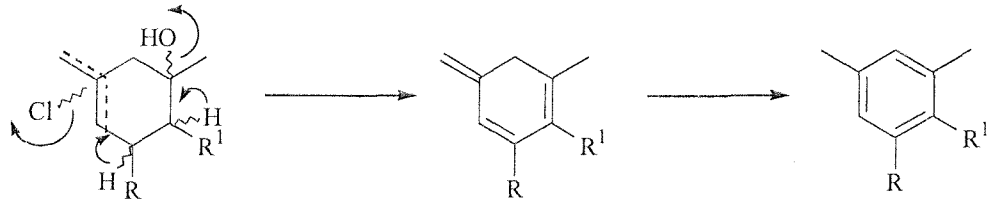


192 **225** **226** **227**

38% 35%

Scheme 73

Aromatics **224** and **227** are presumably derived from the same mechanism, as for the formation of **222** and **225**, requiring only elimination of HCl and H_2O (**Scheme 74**).



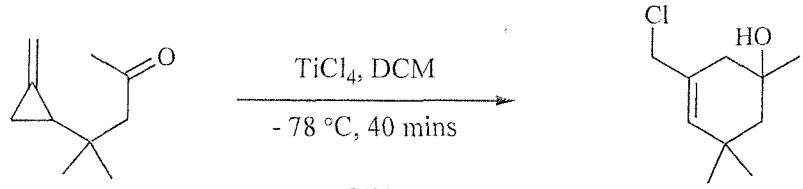
228 **229**

R-R^1 = $(CH_2)_4$, **224**
R = R^1 H CH_3, **227**

Scheme 74

Furthermore, when the cyclised compounds **222** and **223**, and **225** and **226** were treated with 1 equivalent of DBU, aromatics **224** and **227** were formed respectively.

Finally, cyclisation of ketone **194** allowed us to study the effect of gem dimethyl substituents, the Thorpe-Ingold effect.[37] Indeed, when ketone **194** was treated with $TiCl_4$, we observed an acceleration in the rate of the cyclisation, which went to completion after 40 mins instead of the several hours required for ketone **192** and cyclohexene **230** was obtained in a good 65% yield as a single regioisomer (**Scheme 75**).

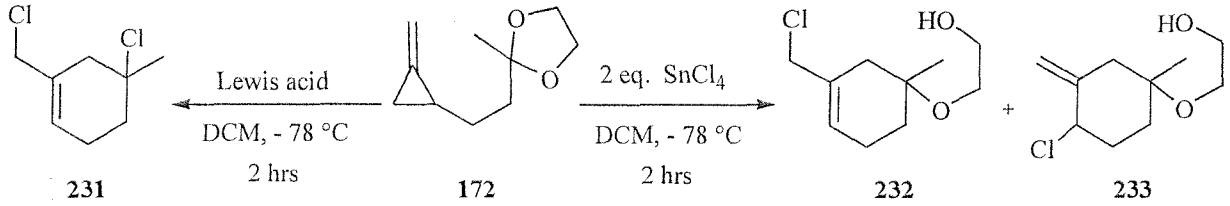


194 **230**

Scheme 75

Cyclisation Study of Methylenecyclopropyl Ketals

Lewis acid mediated cyclisation of ketals **172**, **173** and **179** were also investigated. Ketal **172**, upon treatment with 1.1 equiv. of $TiCl_4$, at - 78 °C, gave dichloride **231** in 37% yield. Using 2 equiv. of $TiCl_4$, a slightly improved yield of **231** was obtained (41%). Using 2 equiv. of $SnCl_4$, cyclohexene **232** and methylenecyclohexane **233**, as a single diastereoisomer, were obtained in 70% yield, as an inseparable mixture of regioisomers, in a 1.6 : 1 ratio (**Scheme 76**).



231 **172** **232** **233**

1.1 eq $TiCl_4$, 37%
2eq $TiCl_4$, 41%

1.6 : 1

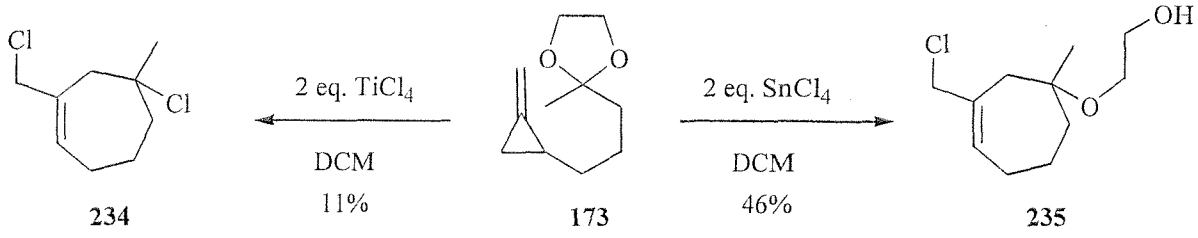
70%

Scheme 76

The same mechanism, as for cyclisation of ketone **166**, is involved in these reactions. However, depending on the Lewis acid used, displacement of the glycol unit occurred or not.

As $TiCl_4$ is a stronger Lewis acid than $SnCl_4$, alkoxyelimination took place, whereas the hydroxy side chain remained with $SnCl_4$. Using $BF_3.Et_2O$ and $BF_3(AcOH)_2$, a complex mixture of products was obtained.

Similar results were obtained with the cyclisation of ketal **173** (**Scheme** 77). As for the cyclisation of **172**, dichloride **234** was obtained in 11% yield when the reaction was carried out with 2 equiv. of $TiCl_4$. Using 2 equiv. of $SnCl_4$, cycloheptene **235** was obtained in 46% yield, as a single regioisomer. A complex mixture of compounds was obtained with $BF_3.Et_2O$ and $BF_3(AcOH)_2$.



234 **173** **235**

Scheme 77

Interestingly, 7-membered rings were obtained with ketal **173**, whereas ketone **167** gave only cyclopentanol **213**.

III-Summary

All attempt to cyclise ketones **127** and **128** and their corresponding protected ketals failed due to chelation in the reaction with Lewis acid, giving ring opened compounds. Deprotected ketones, debenzylation and rearrangement of the cyclopropyl ring into a cyclobutyl ring were also obtained. As no cyclised products were obtained with ketones **127** and **128**, the presence of alkoxy substituents, *alpha* to the cyclopropyl ring is clearly a limitation of this process.

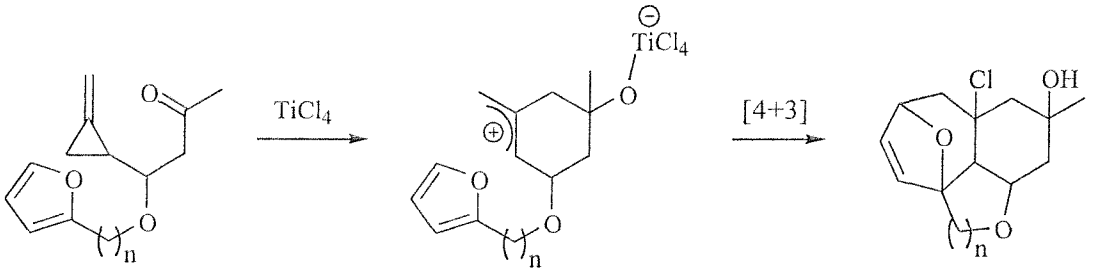
However, removal of the hydroxy function in these precursors avoided the problem of chelation and gave encouraging results. Six and seven membered ring systems were obtained. Furthermore, the efficiency of these cyclisations is sensitive to the Lewis acid used, but under optimum conditions gave reasonable yields of highly functionalised products. Only strong Lewis acids, such as $TiCl_4$ or $SnCl_4$, were efficient. Milder Lewis acids, such as $BF_3.Et_2O$ and $BF_3(AcOH)_2$, failed to give any cyclic compounds.

Finally, a rapid route for the preparation of ketones precursors has been developed with addition of methylenecyclopropylcuprate **183** to conjugated enones.

CHAPTER TWO

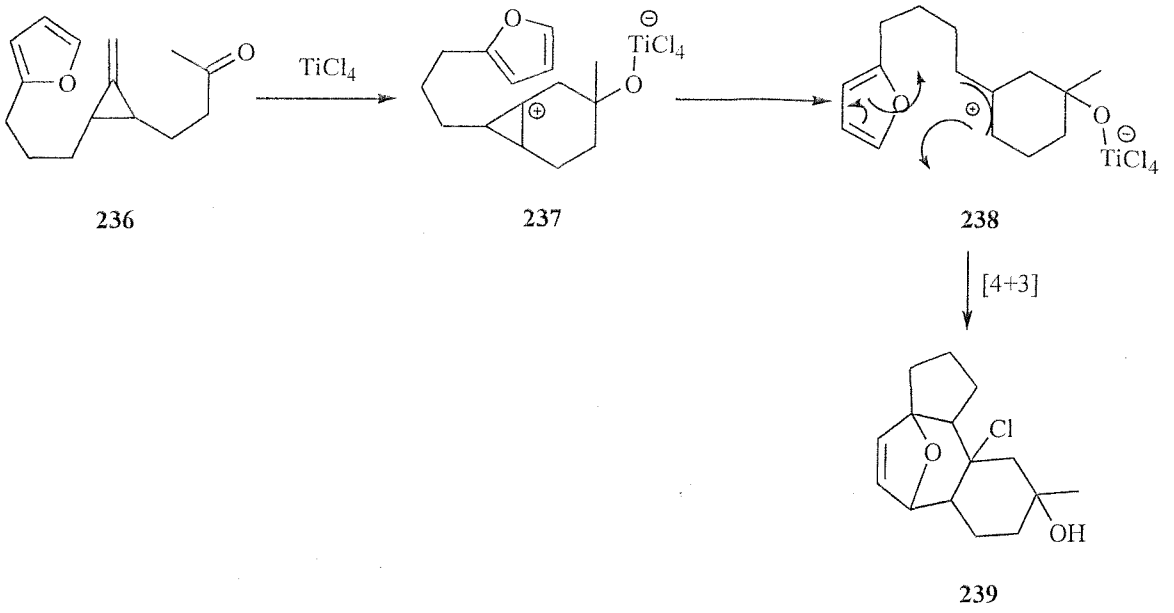
Cyclisation Studies of 1,2-Disubstituted Methylenecyclopropane Derivatives

As the process involves a π-allyl cation intermediate, the aim of the project was to trap the allyl cation in a further reaction to give polycyclic products. For example, the reaction to polycyclic compounds could be extended by using a [4+3] intramolecular cycloaddition as a second step (**Scheme 38**).



Scheme 38

However, methylenecyclopropyl ketones **127** and **128** failed to give cyclic compounds and the synthesis of precursors for possible cascade cyclisation was modified. Attention thus turned to 1,2-disubstituted methylenecyclopropane derivatives. Ketones, such as **236**, were expected to give polycyclic compounds **239** (**Scheme 78**).

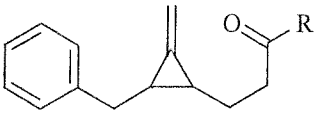


236 **237** **238** **239**

Scheme 78

I-Cyclisation of Methylenecyclopropyl Benzyl Ketone and Aldehyde

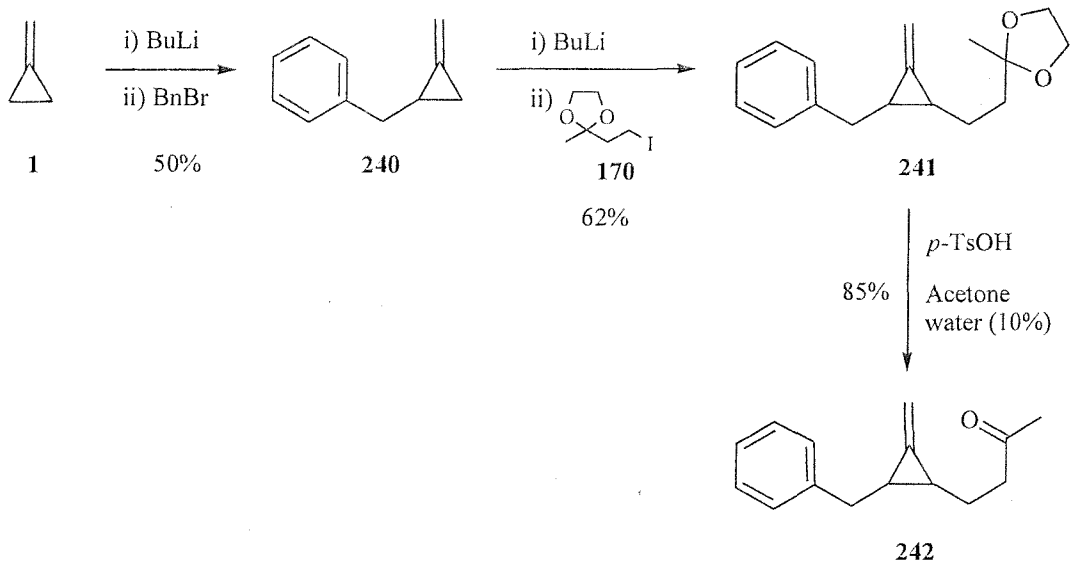
Methylenecyclopropyl benzyl ketone **242** and aldehyde **245** were chosen for the initial cyclisation study of 1,2-disubstituted methylenecyclopropane derivatives.



R = Me, **242**
R = H, **245**

1-Preparation of precursors

Following a procedure described by Destabel,[9] methylenecyclopropane **1** was alkylated with benzyl bromide, to give benzyl-methylenecyclopropane **240** in 50% yield (**Scheme 79**). A second alkylation of **240** with iodide **170** gave 1,2-disubstituted methylenecyclopropyl ketal **241** in 62% yield as a mixture of *cis* and *trans* diastereoisomers. Hydrolysis of the ketal function of **241** gave ketone **242** in 85% yield.

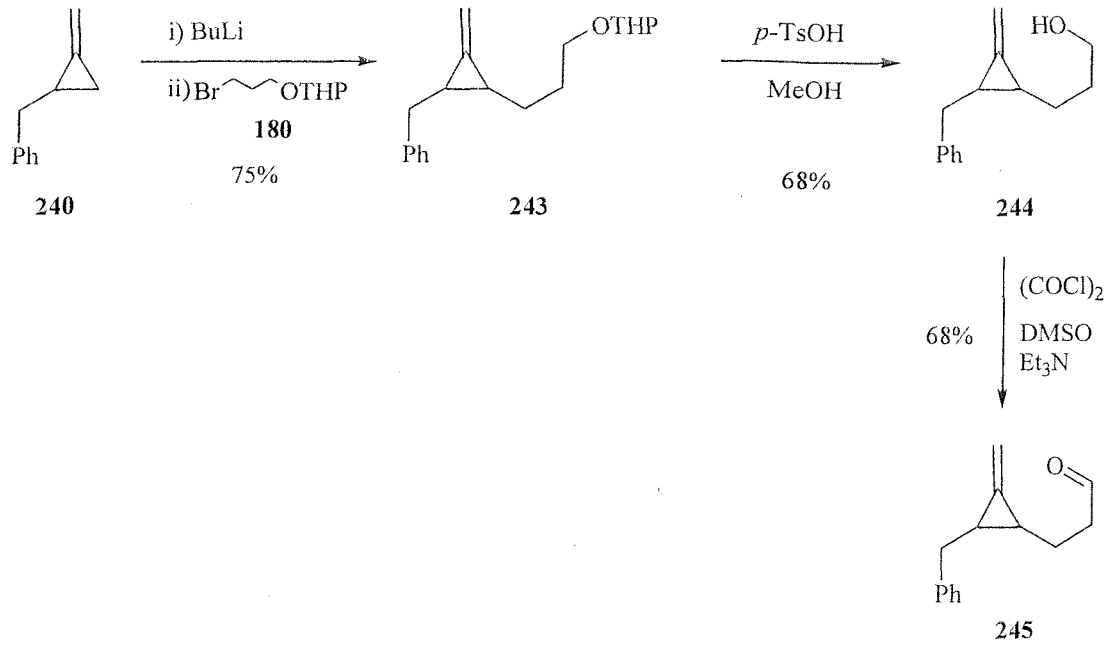


1 240 170 241 242

Scheme 79

However, the second alkylation of lithiated benzyl-methylenecyclopropyl anion with iodide **170**, which gave 1,2-disubstituted methylenecyclopropyl ketal **241**, proved to be problematic. Several experiments were carried out to determine the optimum conditions for this reaction. As the second deprotonation is very slow, the reaction mixture must be warmed very slowly to 0 °C; kept at 0 °C for 1 hour; allowed to warm to room temperature for 30 minutes and then cooled to - 60 °C. Iodide **170** can then be added by cannula at - 60 °C. These results complement those observed by Pike where the reason for the poor second alkylation onto the methylenecyclopropyl ring is the result of poor deprotonation.[10]

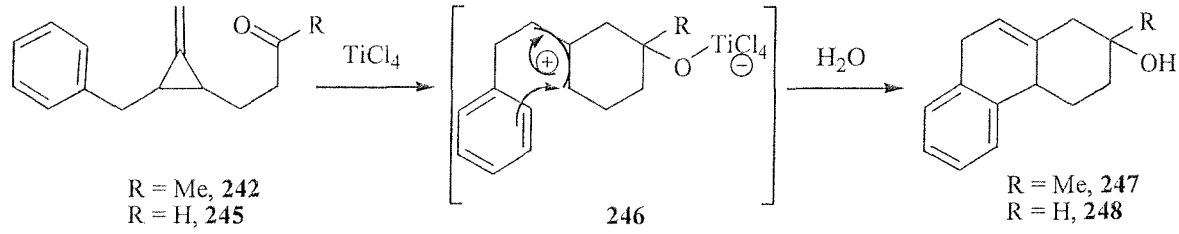
Aldehyde **245** was prepared following the method describe by Boffey[8b] (**Scheme 80**). The second alkylation of benzyl-methylenecyclopropane **240** with THP protected bromo propanol **180** gave THP ether **243** in 75 % yield and as a mixture of diastereoisomers. Hydrolysis of the THP group of **243** gave alcohol **244** in 68% yield and subsequent Swern oxidation afforded 1,2-disubstituted aldehyde **245** in 68% yield.



Scheme 80

2-Cyclisation Studies

1,2-Disubstituted methylenecyclopropyl ketone **242** and aldehyde **245** were expected to give tricycles **247** and **248** respectively, upon treatment with Lewis acid (**Scheme 81**). Activation followed by cyclisation of precursor **242** and **245**, with a suitable Lewis acid such as $TiCl_4$, should give allyl cation intermediate **246**. The allyl cation should be then trapped by the aromatic ring, following a Friedel-Crafts alkylation mechanism, to give tricycles **247** and **248**.



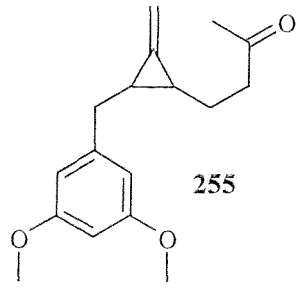
Scheme 81

Unfortunately, none of tricycles **247** or **248** were observed when 1.1 eq. $TiCl_4$ or $SnCl_4$ were added to ketone **242** or aldehyde **245**. A complex mixture of inseparable products

was observed, indicating that the phenyl group is participating in the reaction but without any control.

II-Cyclisation of Methylenecyclopropyl Dimethoxy Phenyl Ketone

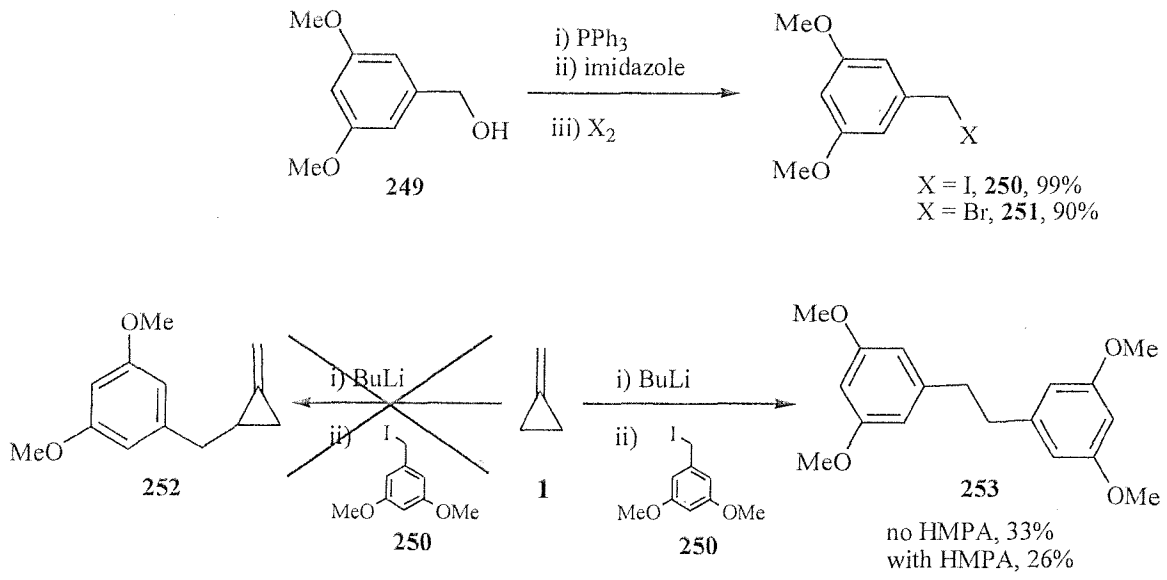
It was assumed that the incorporation of two electron-donating groups on the phenyl ring of the 1,2-disubstituted methylenecyclopropyl ketone **245**, would direct the Friedel-Crafts alkylation in favour of the wanted tricycle product. Ketone **255** was prepared and its cyclisation investigated.



255

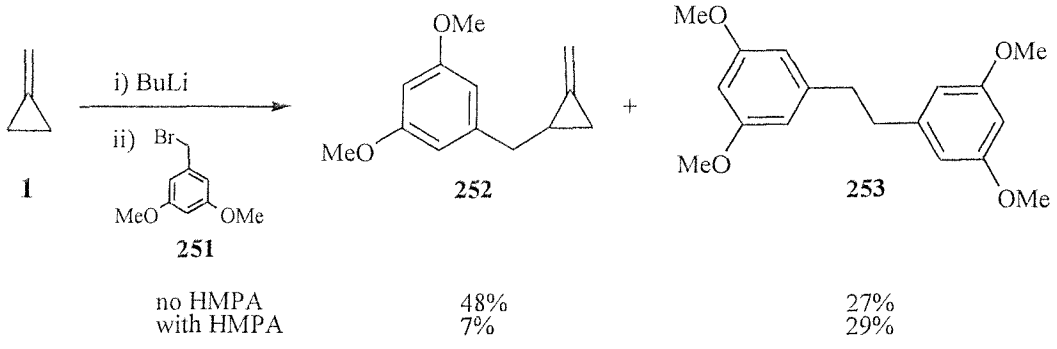
1-Preparation of Precursor

It was anticipated that alkylation of methylenecyclopropane with 3,5-dimethoxybenzyl iodide **250**, obtained in 99% when dimethoxybenzyl alcohol **249** was treated with triphenylphosphine, imidazole and iodine, would give dimethoxy benzyl methylenecyclopropyl **252** (**Scheme 82**). However, only dimer **253** was isolated in 33%, and in 26% yield when HMPA was also used. Dimer **253** is presumably formed due to metal halide exchange.



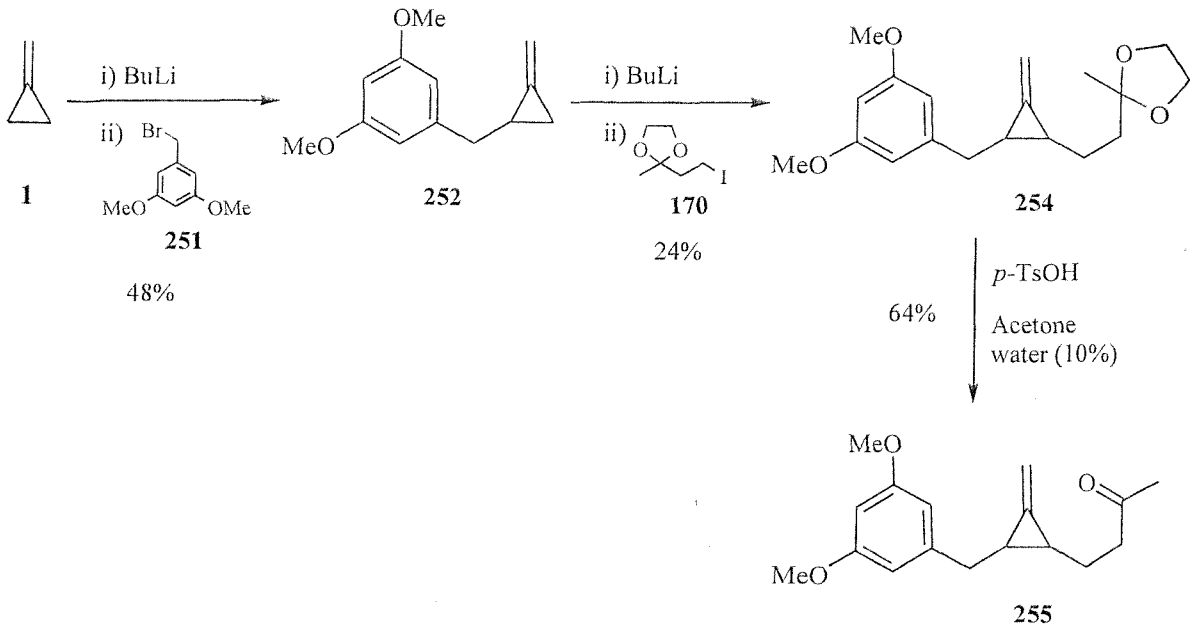
Scheme 82

In order to reduce the metal halide exchange process, iodide **250** was replaced by bromide **251**, obtained in 90% yield in the same way as for iodide **250** (**Scheme 82**). Deprotonation of methylenecyclopropane **1** with BuLi and addition of bromide **251** afforded dimethoxybenzylmethylenecyclopropyl **252** and dimer **253** in 48% and 27% yield respectively. Using HMPA, the yield of **252** dramatically decreased (**Scheme 83**).



Scheme 83

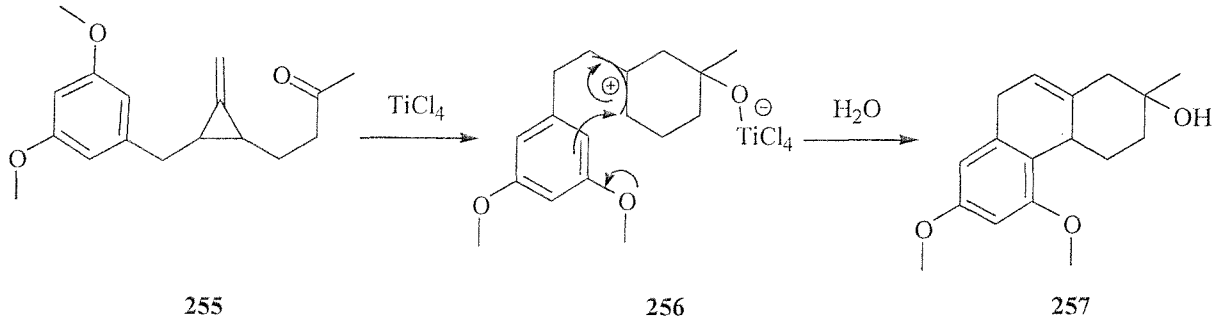
Some of dimer **253** was still obtained, but enough dimethoxybenzylmethylenecyclopropyl **252** was produced to carry on with the synthesis of ketone **255**. A second alkylation of lithiated dimethoxybenzylmethylenecyclopropyl **252** with iodide **170** gave ketal **254**, in a 24% yield. Hydrolysis of the ketal group of **254** afforded ketone **255** (**Scheme 84**).



Scheme 84

2-Cyclisation Studies

With ketone **255** in hand, its cyclisation was investigated. Tricycle **257** was expected to be formed, upon treatment with a Lewis acid (**Scheme 85**).

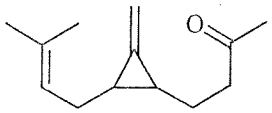


Scheme 85

Unfortunately, all attempts failed to give tricycle **257**. Treatment of ketone **255** with $TiCl_4$ and $SnCl_4$ only ever gave a complex mixture of products.

III-Cyclisation of Methylenecyclopropyl Alkenyl Ketone

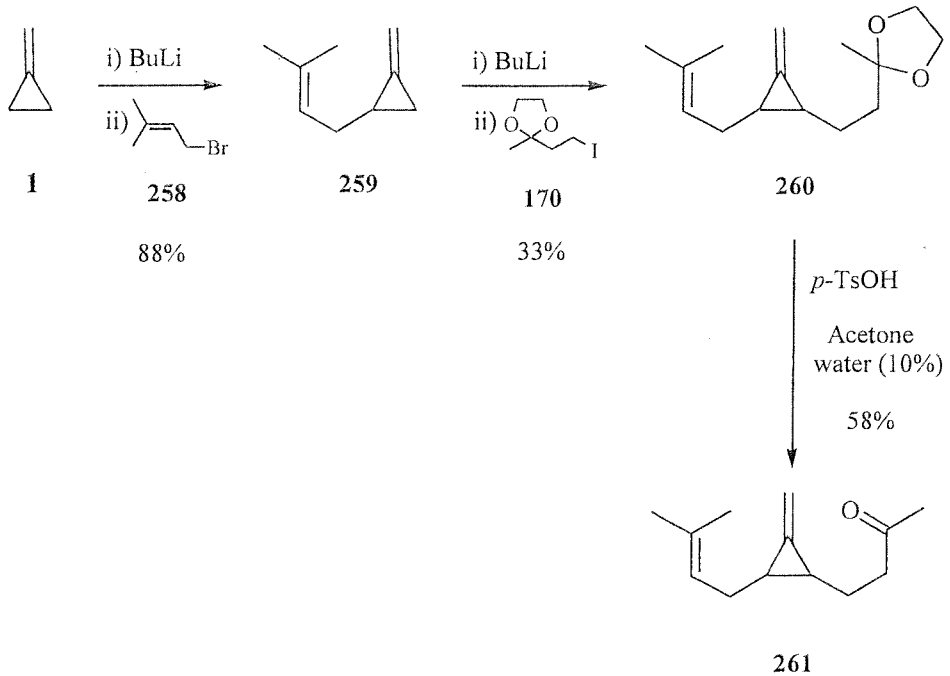
As all attempts to trap the allyl cation in a Friedel Craft reaction failed, it was anticipated that a more simple substrate, such as an alkene, would be able to trap the allyl cation more easily. The synthesis and cyclisation of ketone **261** was therefore investigated.



261

1-Preparation of Precursor

Methylenecyclopropane **1** was first alkylated with 3,3-dimethylallyl bromide **258** to give allylmethylenecyclopropane **259** in 88% yield (**Scheme 86**). A second alkylation with iodide **170** gave ketal **260** in a 33% yield. Deprotection of ketal **260** afforded ketone **261**.



1 **258** **259** **170** **260**

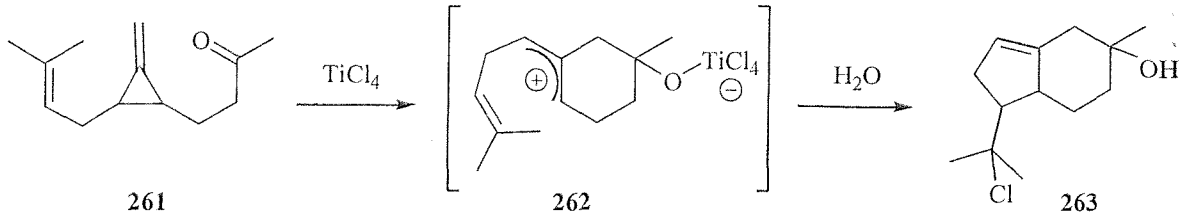
88% 33%

261

Scheme 86

2-Cyclisation Studies

Ketone **261** was expected to give bicycle **263** (**Scheme 87**).



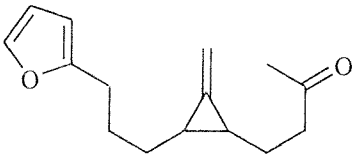
261 **262** **263**

Scheme 87

However, all attempts failed to give bicycle **263**. Treatment of ketone **261** with BF_3,Et_2O, $TiCl_4$ and $SnCl_4$ only ever gave a complex mixture of products, while no reaction was observed with HCl, Et_2AlCl or $EtAlCl_2$.

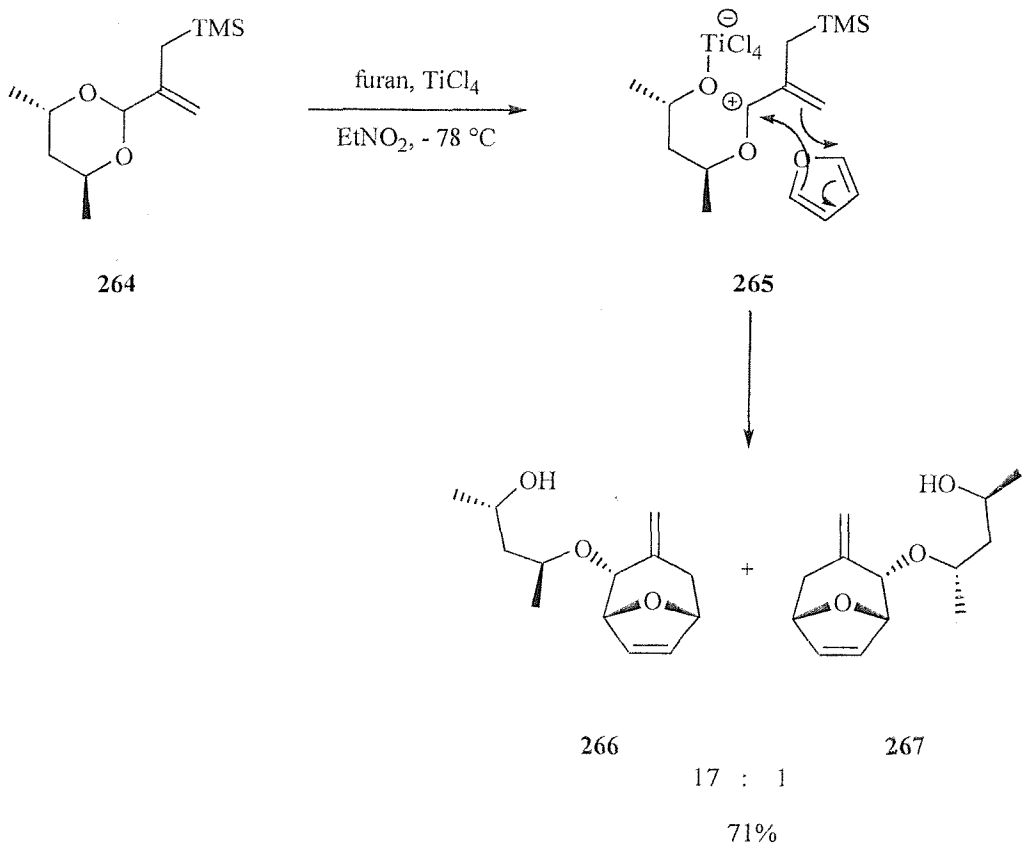
IV-Cyclisation of Methylenecyclopropyl Furyl Ketone

Despite the fact that all attempts to trap the allyl cation intramolecularly had so far failed, cyclisation of methylenecyclopropyl furyl ketone **236** was nevertheless investigated. It was anticipated that a [4+3] cycloaddition might be more appropriate for the trapping of the allyl cation.



236

Indeed, a recent report by Harmata[63] showed that [4+3] cycloaddition can be achieved by generating a π-allyl cation, using $TiCl_4$, and subsequent reaction with furan to give cycloadduct products. Treatment of acetal **264** with $TiCl_4$ in the presence of furan gave intermediate **265** which led to **266** and **267** after Peterson elimination (**Scheme 88**).



264 **265**

266 **267**

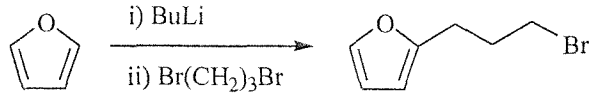
17 : 1

71%

Scheme 88

1-Preparation of Precursor

A convergent strategy was applied for the synthesis of ketone **236**. Bromide **268** was obtained in 78% yield by deprotonation of furan, with BuLi, and alkylation with 1,3-dibromopropane following a procedure described by Padwa[64] (**Scheme 89**).

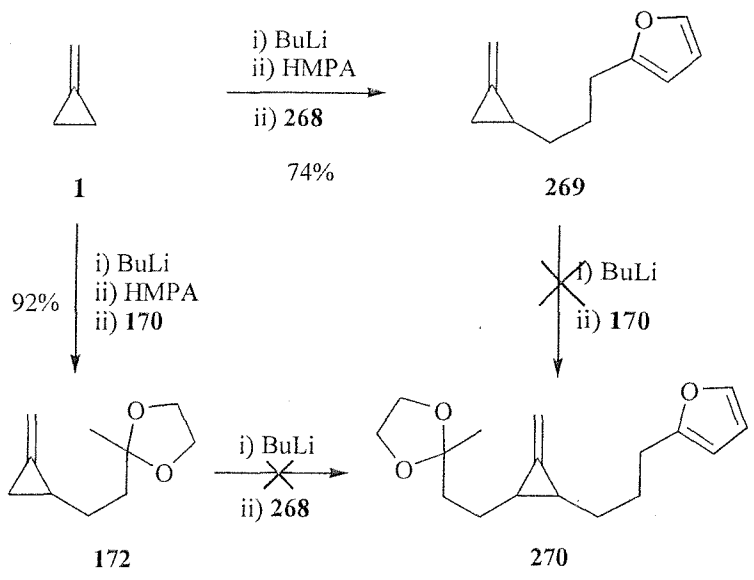


78% **268**

Scheme 89

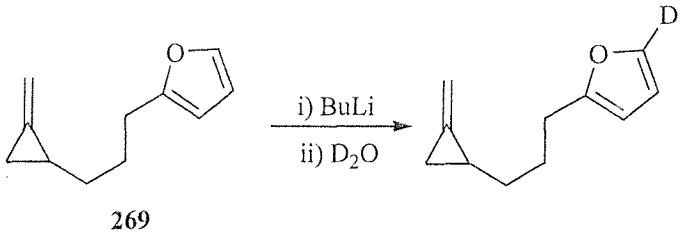
Successive alkylation of methylenecyclopropane **1** first with bromide **268** and second with iodide **170** was then tried (**Scheme 90**). Methylenecyclopropyl furan **269** was obtained in 74% yield from alkylation of lithiated methylenecyclopropane with bromide **268**. However, none of the wanted ketal **270** was obtained after the second alkylation.

Alternatively, the order of alkylation was inverted and gave first ketal **172** in 92% yield. Only starting material was recovered when the second alkylation was tried with bromide **268**.



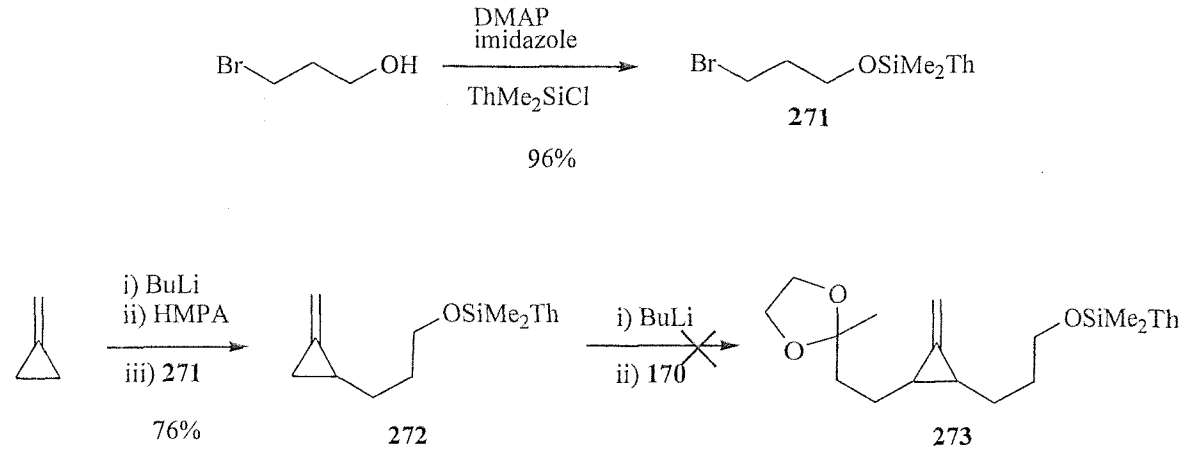
Scheme 90

In fact, quenching the anion generated by addition of BuLi to **269** with D_2O showed, by analysis of the crude NMR, that BuLi deprotonates the furan ring rather than the cyclopropyl ring (**Scheme 91**)



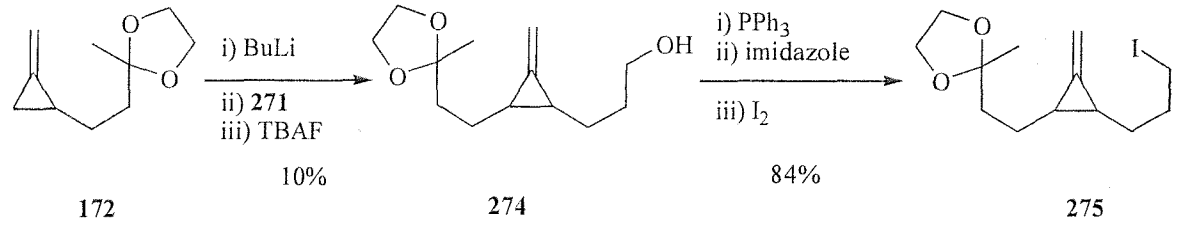
Scheme 91

As no ketal **270** was obtained from the convergent route, an alternative strategy was envisaged. Bromide **271** was obtained in 96% yield by protection of 3-bromopropanol with chlorodimethylthexylsilane in the presence of imidazole and a catalytic amount of DMAP (**Scheme 92**). Alkylation of lithiated methylenecyclopropane with bromide **271** gave silyl ether **272** in 76% yield. However, only starting materials were again recovered when the second alkylation of **272** was tried with iodide **170**.



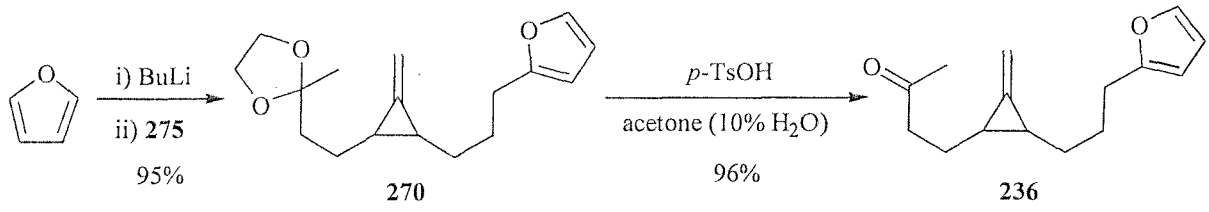
Scheme 92

When the order of alkylation was inverted, silyl ether **273** was obtained and subsequent deprotection of the silyl ether gave alcohol **274** in 10% overall yield (**Scheme 93**). Alcohol **274** was then converted to the corresponding iodide **275** in 84% yield.



Scheme 93

Alkylation of the lithiated furan with iodide **275** gave ketal **270** in 95% yield and deprotection of ketal **270** afforded ketone **236** in 96% yield (**Scheme 94**).



Scheme 94

2-Cyclisation Studies

Ketone **236** was expected to give polycyclic compound **239**, upon treatment with Lewis acid (**Scheme 78**). However, all attempts to obtain compound **239** failed. Decomposition was observed when $TiCl_4$ and $SnCl_4$ were added to either ketal **270** and ketone **236**.

V-Summary

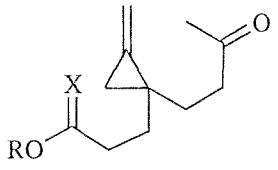
All attempts to obtained polycyclic compounds by intramolecular trapping of the allyl cation failed. Decomposition of the substrate was obtained, indicating that the reaction could not be controlled. The combination of cyclisation and Friedel Craft alkylation was not successful and decomposition of substrates was always observed. The combination of cyclisation and nucleophilic addition of alkene was also unsuccessful with decomposition or no reaction of the substrate. Finally, a combination of cyclisation and cycloaddition was not successful. Decomposition of substrate was observed.

The development of a cascade process initiated by the Lewis acid mediated addition of a methylenecyclopropane to a carbonyl seemed to be much more complex than initially anticipated.

CHAPTER THREE

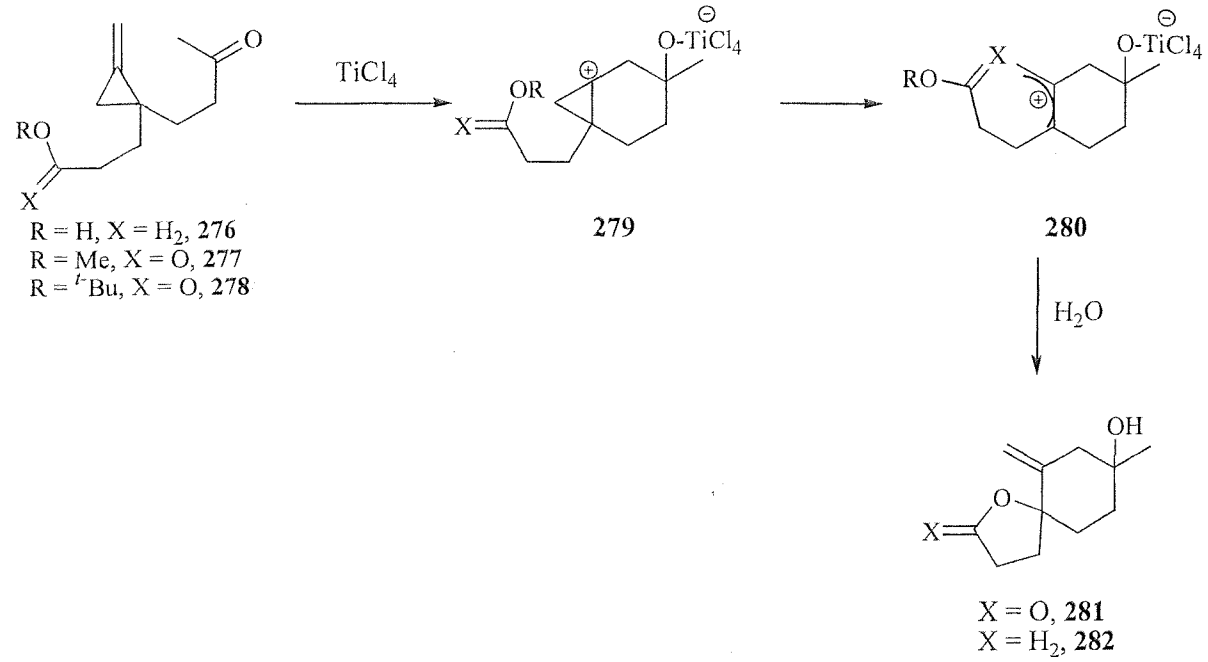
Cyclisation Studies of 1,1-Disubstituted Methylenecyclopropane Derivatives

Cyclisation of 1,2-disubstituted methylenecyclopropanes failed to give the anticipated cascade processes. As an alternative approach, we tried to prepare 1,1-disubstituted methylenecyclopropane derivatives in order to see if the position of substituents on the cyclopropyl ring has an effect on the cascade reaction. To this end, we prepared several precursors and investigated their cyclisations upon treatment with Lewis acid.



R = H, X = H_2, **276**
R = Me, X = O, **277**
R = ^{t}Bu, X = O, **278**

Treatment of precursors **276**, **277** and **278** with a suitable Lewis acid such as $TiCl_4$, should give π-allyl cation intermediate **279**, which could be trapped by the carbonyl or the alkoxide to give spirocycle **281** and **282** after hydrolysis (**Scheme 95**). It was anticipated that with a more simple trapping agent the cyclisation would proceed more smoothly.



R = H, X = H_2, **276**
R = Me, X = O, **277**
R = ^{t}Bu, X = O, **278**

279

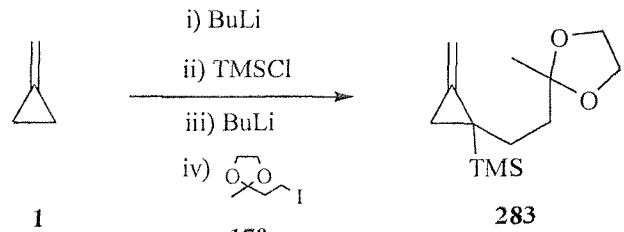
280

X = O, **281**
X = H_2, **282**

Scheme 95

I-Synthesis of 1,1-Disubstitued Methylenecyclopropanes Derivatives

Following the method used by Santagostino,[22] 1,1-disubstituted methylenecyclopropyl ketones were prepared from TMS ketal **283**, easily available following the method described by Binger.[8a] Binger reported that a trimethylsilyl substituent on the cyclopropyl ring of methylenecyclopropane directed the second deprotonation to the silyl bearing carbon, due to the ability of silicon to stabilise an α-carbanion,[65] and that the reaction could be carried out in one pot. Indeed, ketal **283** was obtained in a one pot procedure (**Scheme 96**). Lithiated methylenecyclopropane was first quenched with TMSCl, followed by a second deprotonation with BuLi and quenching with iodide **170** to give silyl ketal **283** in a good 95% yield.



1

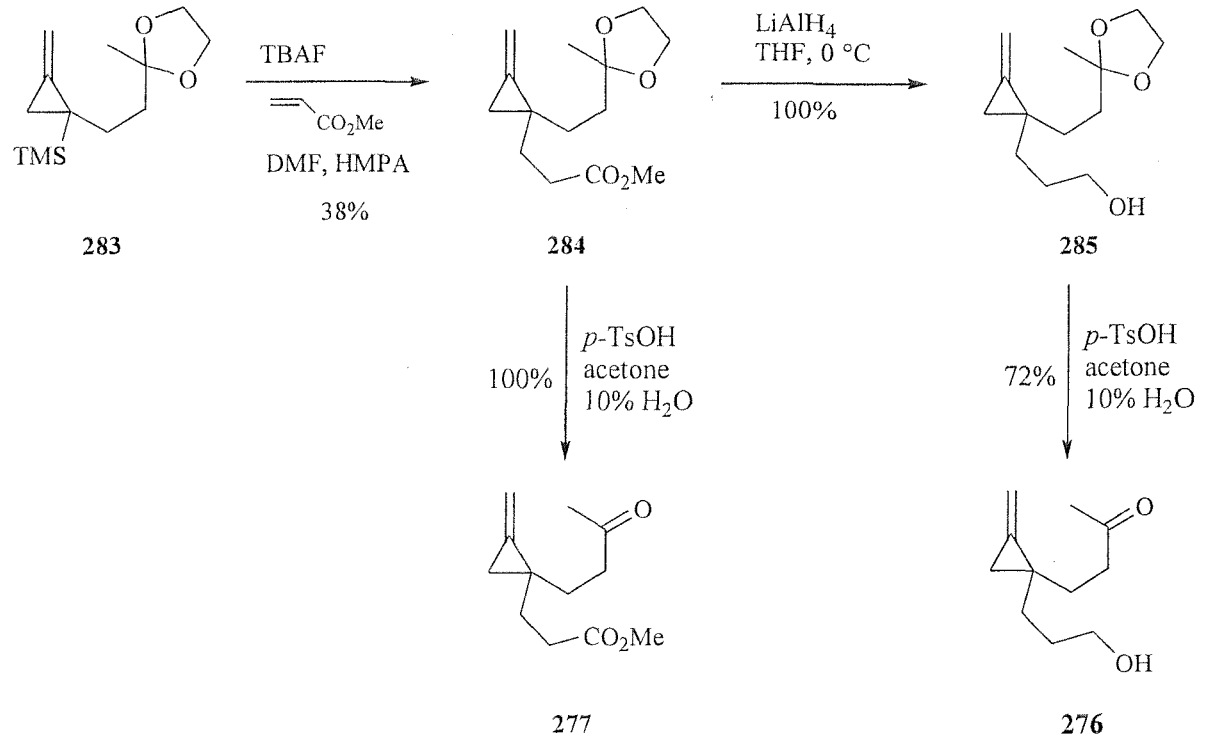
170

95%

283

Scheme 96

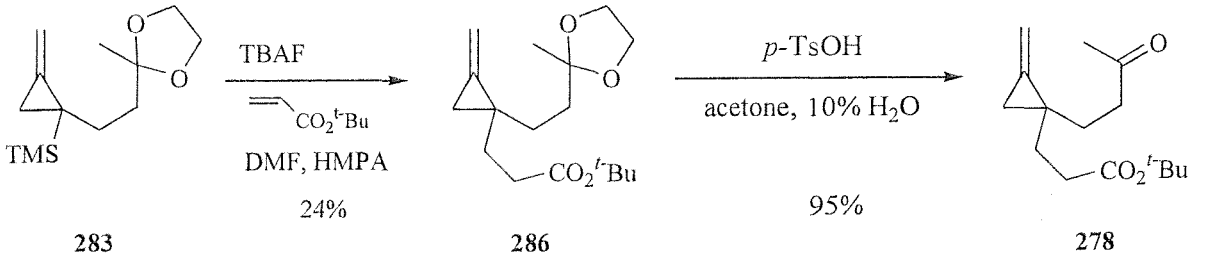
Ketal **283** was next converted to ester **284** following the method used by Santagostino.[22] Desilylation in the presence of TBAF, and Michael addition onto methyl acrylate gave ester **284** in a modest 38% yield. The low yield is attributable to polymerisation of methyl acrylate (**Scheme 97**). Reduction of ester **284** gave alcohol **285** quantitatively. Deprotection of both ester **284** and alcohol **285** afforded ketone precursors **277** and **276** quantitatively and in 72% yield respectively.



283 **284** **285** **277** **276**

Scheme 97

We also prepared *tert*-butyl esters **286** and **278**, as they might give spirolactone products more easily than ester **284** and **277** (**Scheme 98**).



283 **286** **278**

Scheme 98

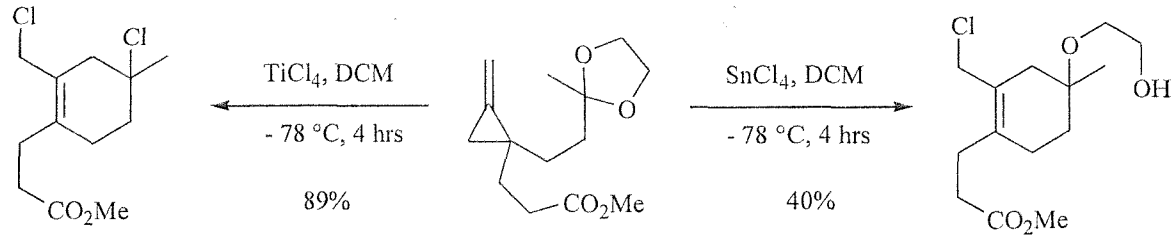
Desilylation of **283** in the presence of TBAF, followed by Michael addition onto *tert*-butyl acrylate, gave ester **286** in a modest 24% yield, again due to polymerisation of *tert*-butyl acrylate. Deprotection of ketal **286** gave keto ester **278** in 95% yield.

II-Cyclisation of 1,1-Disubstituted Methylenecyclopropane Derivatives

1-Cyclisation study of Methylenecyclopropyl Esters

Cyclisation of ketals

Cyclisation of ketal **284** was first investigated. Treatment of ketal **284** with 2 eq. $TiCl_4$ gave dichloride **287** in an excellent 89% yield, whereas addition of $SnCl_4$ gave cyclohexene **288** in 40% yield (**Scheme 99**).



287 **284** **288**

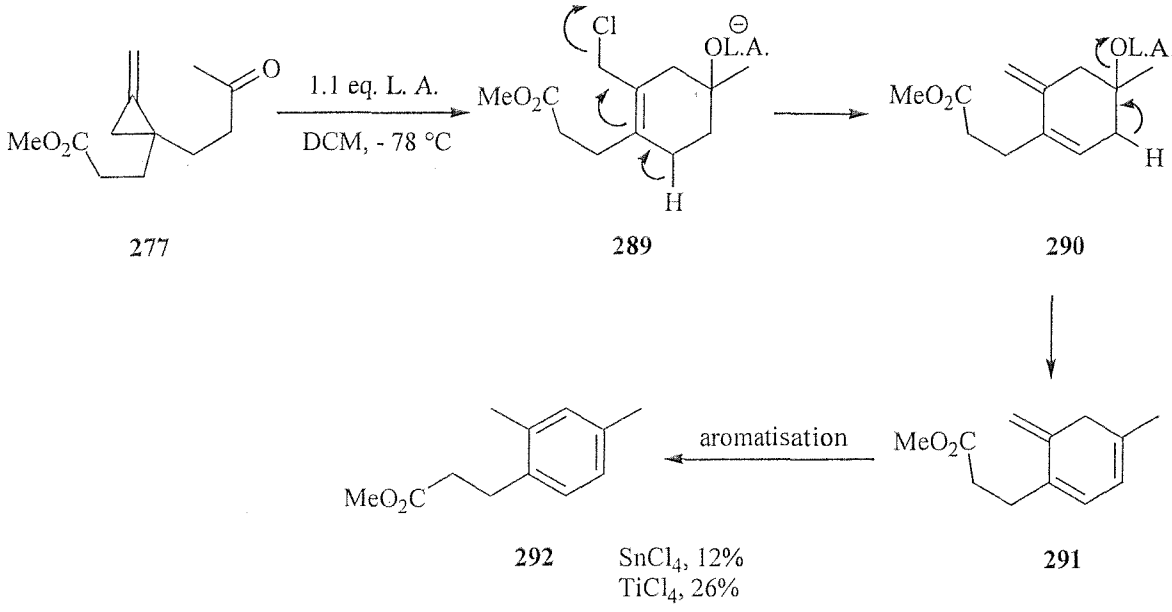
Scheme 99

Unfortunately, no spirolactone was obtained, presumably because the trapping of the allyl cation by the chlorine anion is faster than attack by the carbonyl to give spirolactonisation. In addition, a complex mixture of products was obtained when ketal **284** was treated with softer Lewis acids, $BF_3.Et_2O$ or $BF_3(AcOH)_2$.

tert-Butyl ester **286** was expected to favour this spirolactonisation as a more stable tertiary cation would be formed prior the lactonisation. However, decomposition of the substrates was observed when $TiCl_4$, $SnCl_4$, $BF_3.Et_2O$ and $BF_3(AcOH)_2$ were added to ketal **286**. The *tert*-butyl group is probably a too good leaving group: it may be removed very easily even before the cyclisation starts under Lewis acid conditions thereby giving rise to decomposition of the substrate.

Cyclisation of ketones

Lewis acid mediated cyclisation of ketone **277** was then investigated. Treatment of ketone **277** with either $SnCl_4$ or $TiCl_4$ gave aryl ester **292** in 12% and 26% yield respectively (**Scheme 100**).



Scheme 100

No reaction was observed between - 78 °C and 0 °C, but when the temperature was allowed to come to room temperature, ketone **277** disappeared giving aryl ester **292**. Below 0 °C, the ester function and the ketone function of **277** may be chelated together with the Lewis acid forming a weak 10-membered ring chelate, inhibiting the nucleophilic addition of the methylene unit of **277**.

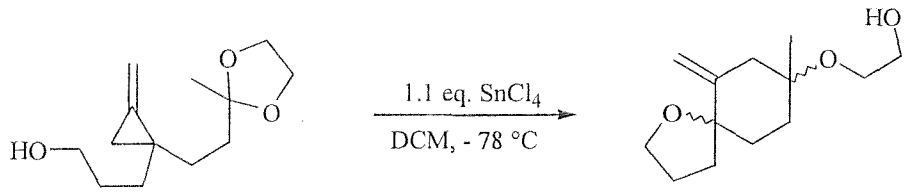
Decomposition of the starting ketone **277**, after 24 hours at ambient temperature, was observed when $BF_3.Et_2O$ and $BF_3(AcOH)_2$ were added. Again, no reaction was observed before the reaction reached room temperature.

Treatment of ketone **278** with $TiCl_4$, $SnCl_4$, $BF_3.Et_2O$ and $BF_3(AcOH)_2$ only ever gave decomposition of the starting material, again presumably due to the facile removal of the *tert*-butyl group leading to decomposition.

2-Cyclisation studies of Methylenecyclopropyl Alcohols

Cyclisation of ketals

Addition of $TiCl_4$ and $BF_3(AcOH)_2$ to ketal **285** gave a complex mixture of inseparable products and there was no reaction with $BF_3.Et_2O$. However, when $SnCl_4$ was added to ketal **285**, the expected spirocycle **293** was isolated in 50% yield, as a 2 : 1 mixture of separable diastereoisomers (**Scheme 101**).

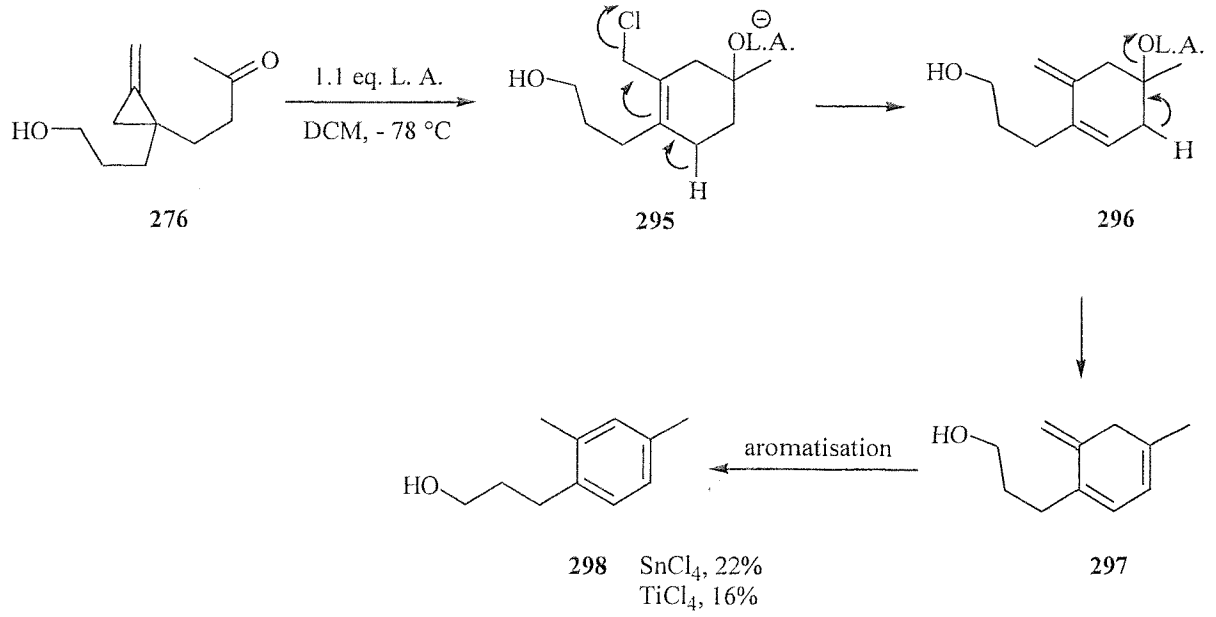


285 → **293**
2 : 1
50%

Scheme 101

Cyclisation of ketones

Ketone **276** was expected to give spirocycle **282** (**Scheme 95**). However, when ketone **276** was subjected to either $BF_3.Et_2O$ and $BF_3(AcOH)_2$, decomposition of the substrate was observed, whereas, treatment with $TiCl_4$ and $SnCl_4$ gave aryl alcohol **298** (**Scheme 102**).



276 295 296

Scheme 102

The mechanism and the reasons for the formation of aryl alcohol **298** follow the same explanations as for the synthesis of aryl ester **292**. The chelate may be broken when the reaction reaches room temperature and cyclisation occurs to give intermediate **295**, which loses a HCl to give **296**. Elimination and aromatisation gives aryl alcohol **298**.

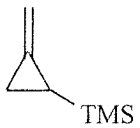
III-Summary

Most of the attempts to trap the allyl cation in further reaction failed, presumably due to rapid trapping of the allyl cation intermediate by a chlorine anion which derived from the Lewis acid, $TiCl_4$ or $SnCl_4$, required for the cyclisation. Indeed, decomposition of substrates was observed when softer Lewis acids, with less nucleophilic ligands, such as $BF_3.Et_2O$ and $BF_3(AcOH)_2$, were used. The only successful example is the synthesis of spirocycle **293** in 50% yield, as a 2 : 1 separable mixture of diastereoisomers. Finally, the cyclisation of 1,1-disubstituted methylenecyclopropyl ketones failed possibly due to chelation of the carbonyl and the alcohol or the ester function with the Lewis acid, giving aromatic rings in poor yield. It appeared that the cyclisation works only if chelation can be avoided and only strong Lewis acids give cyclised products.

CHAPTER FOUR

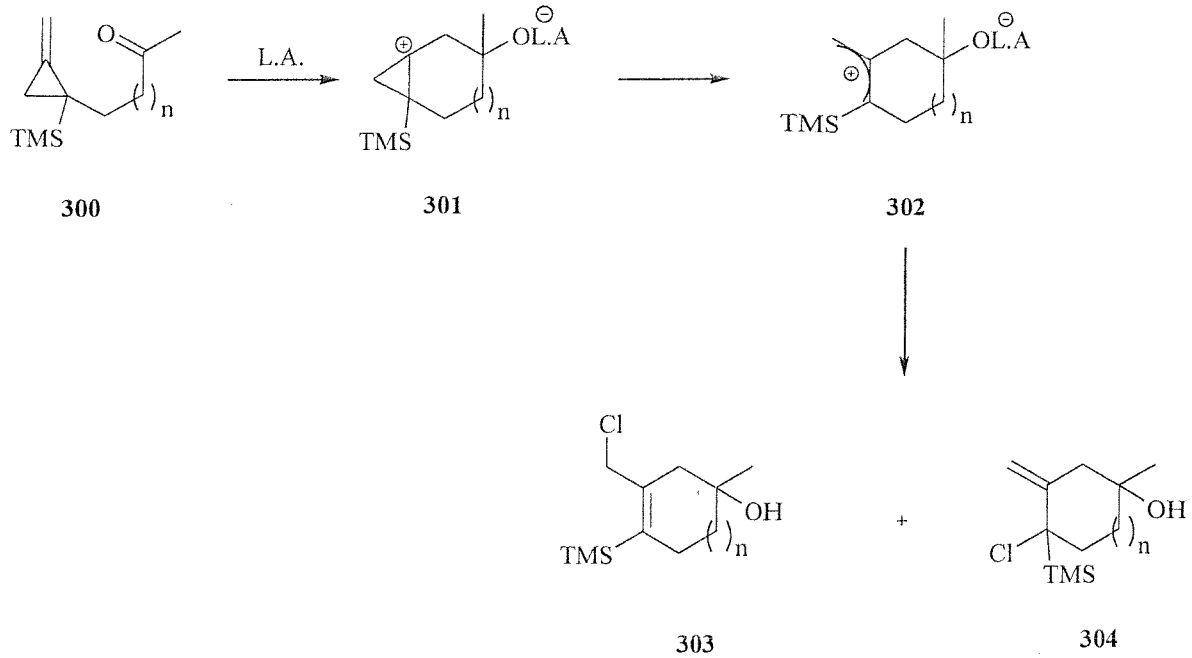
Lewis Acid Mediated Cyclisation of Methylenecyclopropyl Ketones :Effect of a Silyl Group on the Cyclisation

Lewis acid mediated cyclisation of methylenecyclopropyl ketones **166-168** and aldehyde **169** gave encouraging results and prompted us to optimise this reaction. Trimethylsilylmethylenecyclopropane **299** can be considered as an allyl silane and its reactivity is attributed to the electronic effect of the silyl group on the exocyclic methylene carbon. Indeed, its δ ^{13}C value is about 3 ppm more upfield than in methylenecyclopropane **1**. This observation clearly indicates that trimethylsilylmethylenecyclopropane **299** has a higher nucleophilicity than methylenecyclopropane **1**.



299

Considering Hosomi's observations, where the presence of a silyl group on the cyclopropyl ring accelerated the reaction (only one example),[53] we anticipated that the incorporation of a trimethylsilyl group would facilitate the initial addition of the exocyclic double bond of methylenecyclopropane, since the silyl group should stabilised the intermediate cyclopropyl cation **301**. Addition of a suitable Lewis acid, such as $TiCl_4$ should allow initial addition of the double bond of ketone **300** to give a stabilised cyclopropyl cation intermediate **301**. Intermediate **301** should open to the allyl cation intermediate **302**, which in turn, can be trapped by a chlorine anion to give cyclised compounds **303** and **304** (**Scheme 103**).

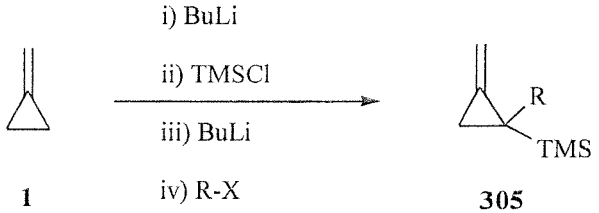


300 **301** **302** **303** **304**

Scheme 103

I-Synthesis of Precursors

Binger[8a] reported that a trimethylsilyl substituent on the cyclopropyl ring of methylenecyclopropane directed the second deprotonation to the silyl bearing carbon, due to the ability of silicon to stabilise an α-carbanion[65] and that the reaction could be carried out in one pot. Addition of TMSCl to lithiated methylenecyclopropane followed by *in-situ* second deprotonation with BuLi and alkylation with alkyl halides gave 1,1disubstituted methylenecyclopropane **305** in moderate to good yields (**Scheme 104**). The yield of alkylation dropped when bromides were replaced by chlorides (**Table 6**).



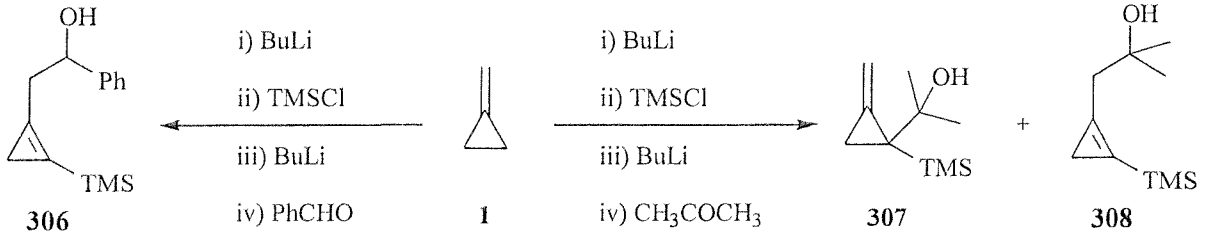
1 **305**

Scheme 104

R	X	Yield
CH_2=$CH(CH_2)_3$-	Br	75%
$O(CH_2)_2O(CH_2)_2$-	Br	54%
$HCC(CH_2)_4$-	Br	65%
$C_6H_5CH_2$-	Cl	46%

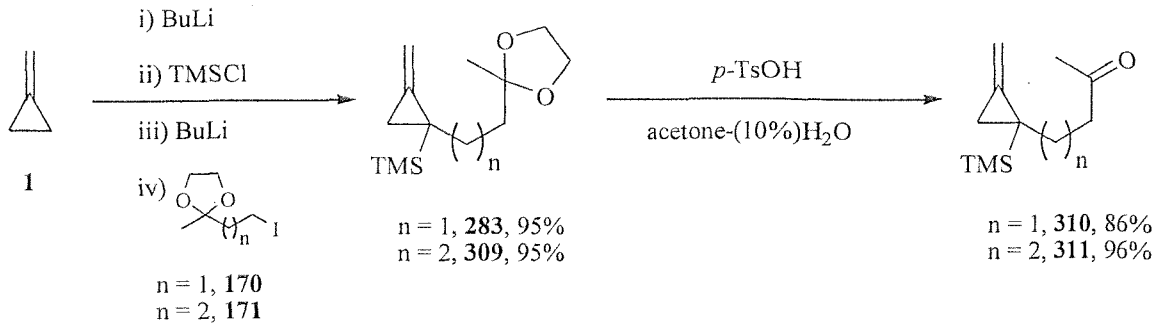
Table 6

Binger anticipated that alkylation with an aldehyde or a ketone would also occur on the cyclopropyl ring. However, benzaldehyde gave exclusively the alkylated cyclopropene **306** which derived from γ-alkylation and acetone gave a mixture of **307** and **308** resulting from α- and γ-alkylation in a 59 : 41 ratio (**Scheme 105**).



Scheme 105

Following the method of Binger, ketals **283** and **309** were obtained in a one pot procedure (**Scheme 106**). Lithiated methylenecyclopropane was first quenched with TMSCl, followed by a second deprotonation with BuLi and quenching with iodide **170** and **171** to give silyl ketals **283** and **309**. In common with Binger, none of the γ-alkylated product was observed with alkyl halides **170** and **171**. In addition, the yield of alkylation was dramatically increased when these iodides were used, the best reported yield by Binger was 75% yield with bromides. Deprotection of each ketal gave ketones **310** and **311** in 86% and 96% yield respectively.



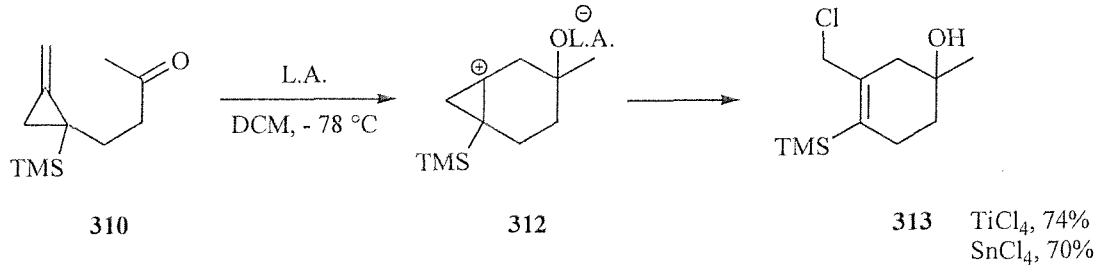
Scheme 106

II-Cyclisation Study of 1,1-Disubstituted Methylenecyclopropanes

Ketones **310** and **311**, as well as ketals **283** and **309**, were expected to give 6- and 7-membered rings under treatment with Lewis acid.

Cyclisation Study of Ketones

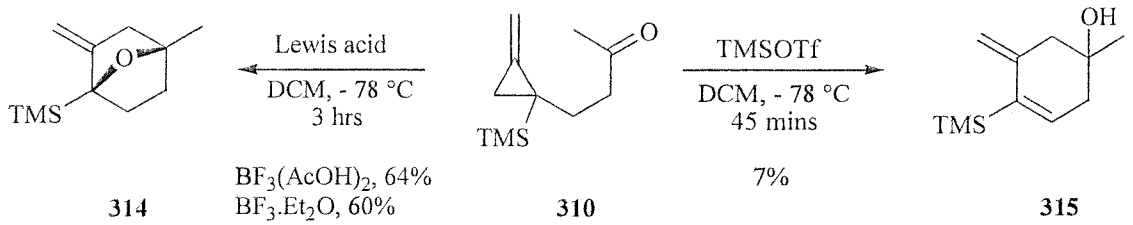
We expected to see an acceleration in the rate of the reaction of ketone **310**, in comparison to the corresponding non-silylated ketone **166**, due to the presence of the silyl group. Indeed, ketone **310** cyclised in one hour at - 78 °C to give cyclohexene **313** in 74% when $TiCl_4$ was used and in 70% with $SnCl_4$ (**Scheme 107**).



Scheme 107

The reaction of the corresponding non-silylated ketone **166** went to completion after 1.5 hours when the reaction was carried out at - 40 °C and cyclohexene **205** was isolated in only 50% yield (**Scheme 64**). From this comparison, we can conclude that the presence of the trimethylsilyl group accelerates the rate of the reaction. The increase in the yield is presumably due to the ability of silicon to stabilise β-cation, since the initial addition of the double bond of methylenecyclopropane generates intermediate **312** with a cation β- to the silicon atom.

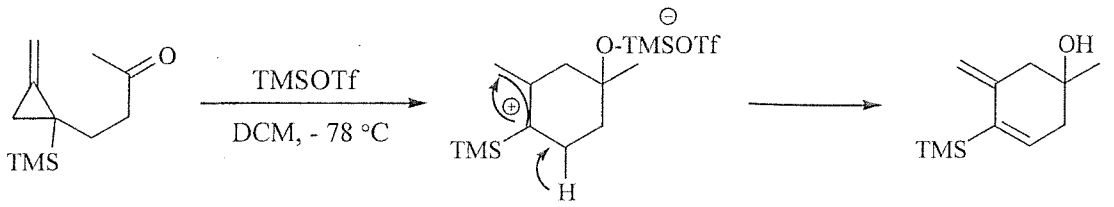
It was also believed that the increased nucleophilicity of the exocyclic double bond of methylenecyclopropane would allow the cyclisation to proceed with softer Lewis acid. Indeed, cyclisation of ketone **310** with $BF_3.Et_2O$ and $BF_3(AcOH)_2$ gave bicyclic ether **314** in 60% and 64% yield respectively (**Scheme 108**).



Scheme 108

Bicyclic ether **314** is presumably obtained by intramolecular trapping of the allyl cation intermediate **302** by the alkoxide, due to the absence of relatively nucleophilic counter anion.

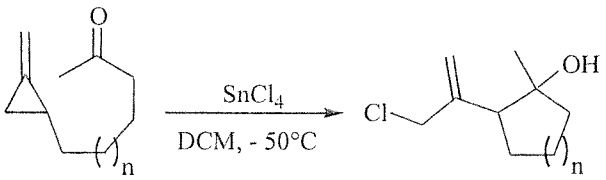
Cyclisation of ketone **310** was also attempted with other Lewis acids. However, treatment of ketone **310** with TMSOTf gave a complex mixture of products with diene **315** isolated in only 7% yield (**Scheme 108**). A possible mechanism for the formation of **315** is outlined in **Scheme 109**. Activation of ketone **310** followed by cyclisation gave intermediate **316**, after ring opening of the cyclopropyl ring, which eliminates a proton to give diene **315**.



310 **316** **315**

Scheme 109

The increased nucleophilicity of the double bond of methylenecyclopropane, due to the presence of the trimethylsilyl group, should allow the formation of 7-membered rings, which failed with the non silylated ketones. Indeed, ketones **167** and **168** gave cyclopentanol **213** and cyclohexanol **214** (**Scheme 67**).

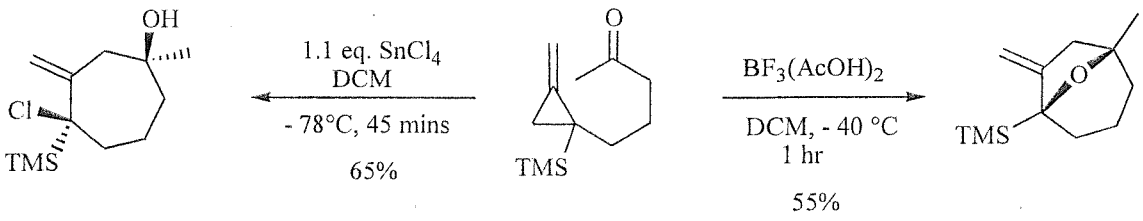


n = 1, **167**
n = 2, **168**

n = 1, **213**, 43%
n = 2, **214**, 40%

Scheme 67

It was thus very encouraging to see that treatment of ketone **311** with $SnCl_4$ gave cleanly the *cis* hydroxychloride **317** in a good 65% yield (**Scheme 110**).



317 **311** **318**

Scheme 110

The stereochemistry of **317** was obtained by crystal structure after recrystallisation from ethanol-water (**Figure 3**). The crystal structure clearly shows the *cis* arrangement of the alcohol function and the chlorine atom.

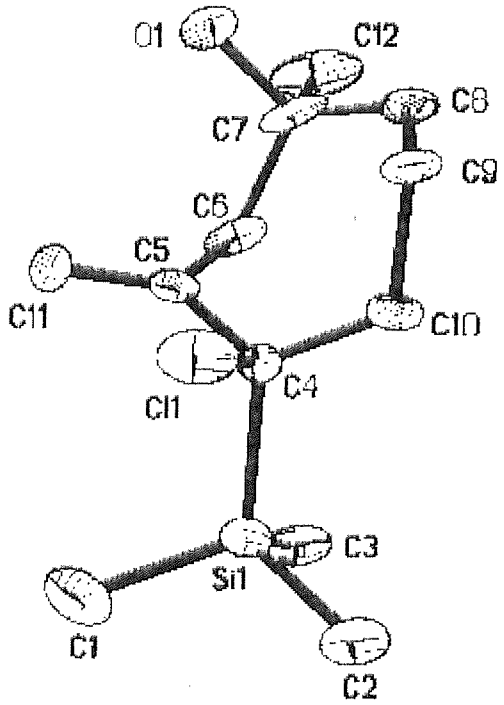
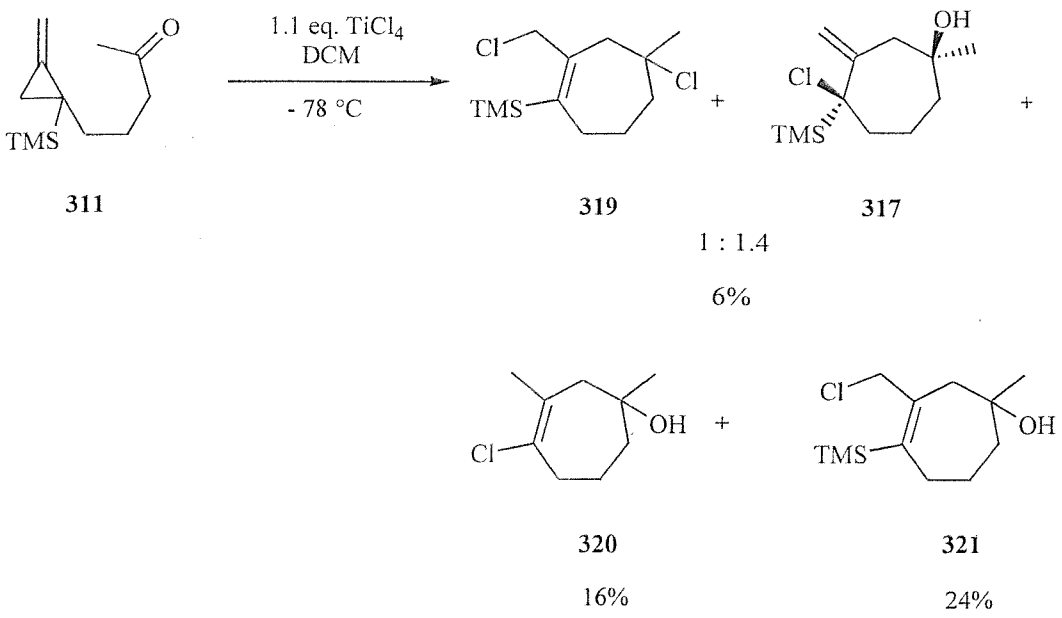


Figure 3 : Crystal structure of **317**

For full details of the X-ray crystallographic data, see appendix B.

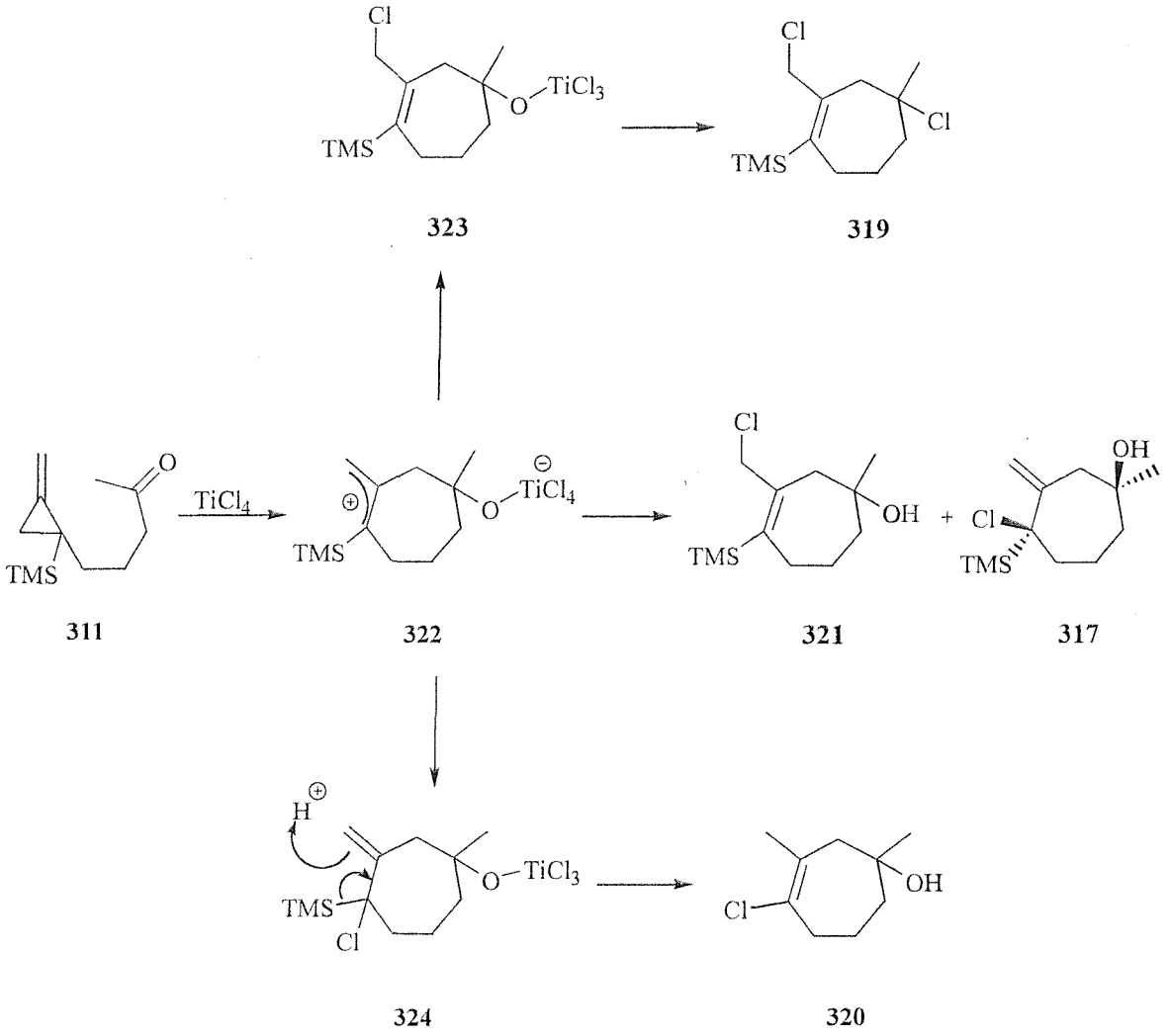
The increased nucleophilicity of the double bond of methylenecyclopropane also allowed the use of milder Lewis acid and bicyclic ether **318** was isolated in a reasonable 55% yield when ketone **311** was treated with $BF_3(AcOH)_2$ (**Scheme 110**). Bicyclic ether **318**, as for bicyclic ether **314**, is presumably obtained by intramolecular trapping of the allyl cation intermediate **302** by the alkoxide, due to the absence of a nucleophilic counter anion. However, a complex mixture of products was obtained when ketone **311** was treated with $BF_3.Et_2O$.

Ketone **311**, upon treatment with $TiCl_4$, gave a mixture of four different 7-membered rings (**Scheme 111**). Dichloride **319** and *cis*-hydroxychloride **317** were isolated as 1 : 1.4 ratio of inseparable compounds in 6% yield. Vinylchloride **320** was also isolated in 16% yield and finally the expected cyclohexene **321** in 24% yield.



Scheme 111

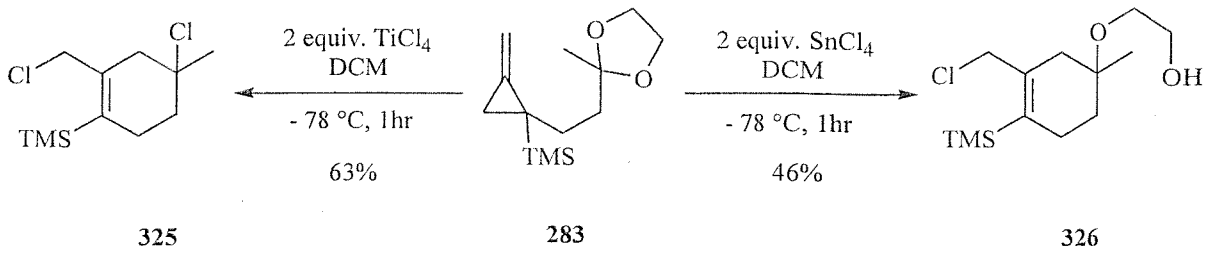
One important point is that all compounds arose from the same intermediate allyl cation **322** (**Scheme 112**). Dichlorides **319** probably came from trapping of the allyl cation intermediate **322** by a chlorine anion, followed by substitution of the alkoxide by a chlorine anion. Vinylchloride **320** presumably arose from trapping of the allyl cation intermediate **322** by a chlorine anion to give intermediate **324** followed by proto-desilylation to give **320**. Finally, cyclohexene **321** and *cis*-hydroxychloride **317** were the expected cyclised products, which arose from quenching of the allyl cation intermediate **322** by a chlorine anion.



Scheme 112

Cyclisation Study of Ketals

It was also anticipated that the presence of the silyl group would accelerate the rate of the reaction with ketals. Indeed, the reaction of ketal **283** with Lewis acid went to completion in an hour and gave dichloride **325** in 63% yield with $TiCl_4$ and cyclohexene **326** was obtained in 46% yield with $SnCl_4$ (**Scheme 113**).



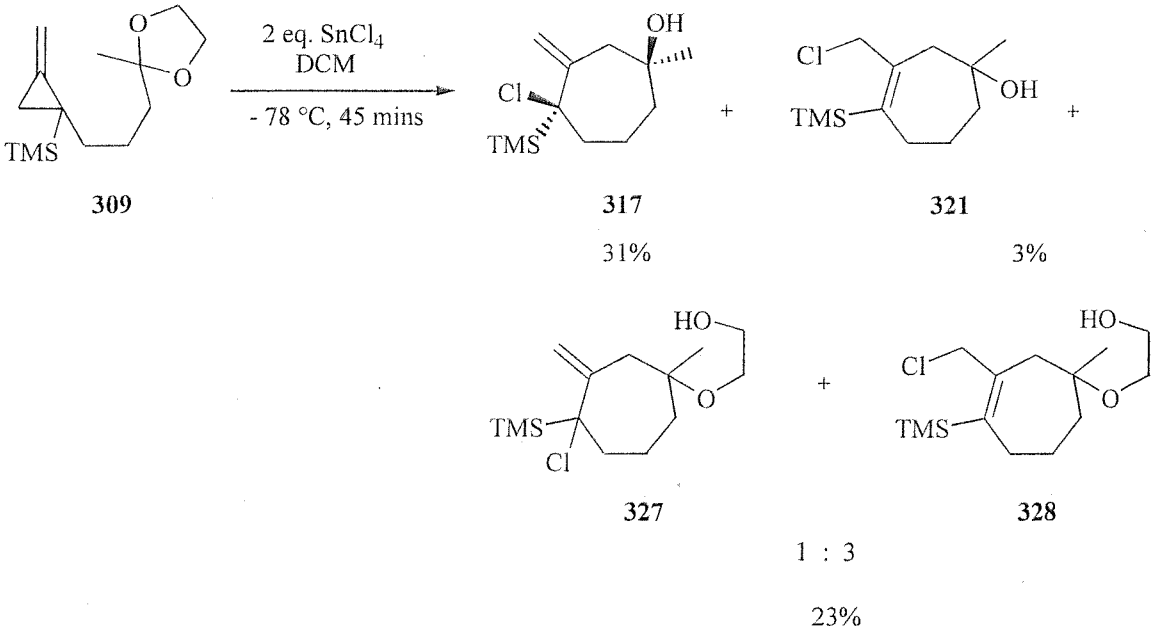
325 283 326

Scheme 113

Cyclisation of the non-silylated equivalent ketal **172** went to completion after 2 hours, indicated that the reaction of trimethylsilylmethylenecyclopropyl ketal is accelerated by the presence of the silyl group, which induced an increase in the nucleophilicity of the exocyclic methylene group. Furthermore, treatment of ketal **172** with $SnCl_4$ gave a mixture of the two possible regioisomers **232** and **233**, whereas ketal **283** gave only cyclohexene **326**, under these conditions. This observation may be attributed to both steric hindrance of the trimethylsilyl group and its stabilising effect on β-carbocations.

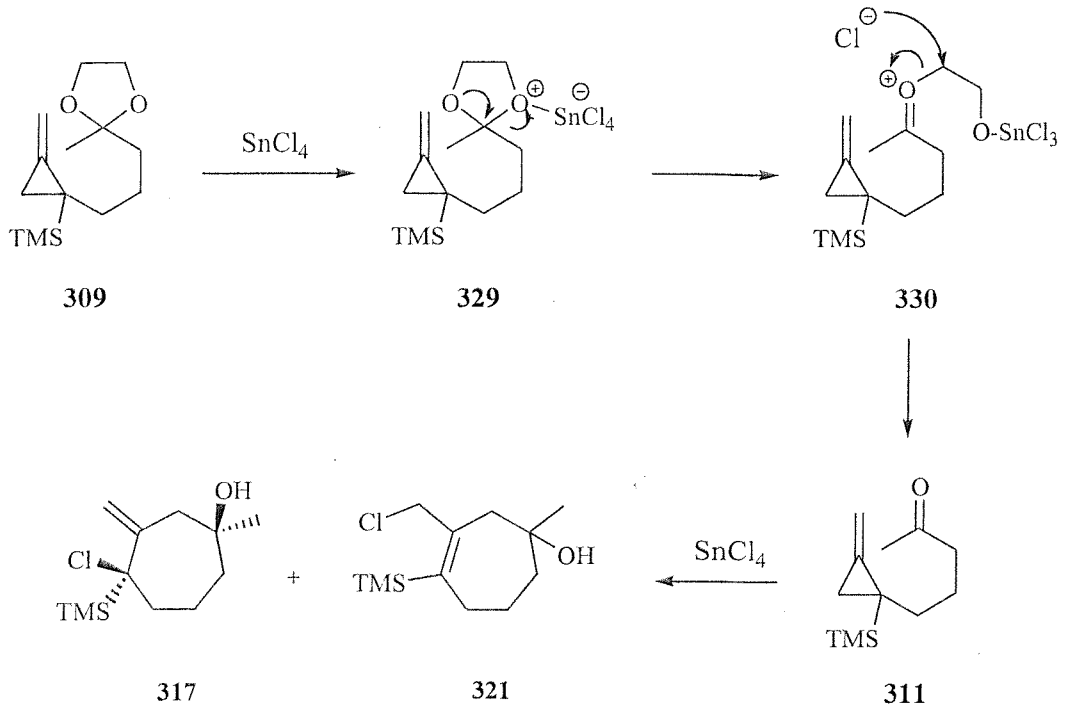
However, treatment of ketal **283** with softer Lewis acids failed to give any cyclic products and decomposition was observed with either $BF_3.Et_2O$ or $BF_3(AcOH)_2$.

Lewis acid mediated cyclisation of ketal **309** was also investigated. Treatment of ketal **309** with $TiCl_4$ gave a complex mixture of products and decomposition of the substrate was observed with $BF_3.Et_2O$ and $BF_3(AcOH)_2$. However, when $SnCl_4$ was added to ketal **309**, *cis*-hydroxychloride **317** and cyclohexene **321** were obtained in 31% and 3% yields respectively. Methylenecycloheptane **327** and cycloheptene **328** were also isolated in 23% yield, as a mixture of inseparable regioisomers, in a 1 : 3 ratio (**Scheme 114**).



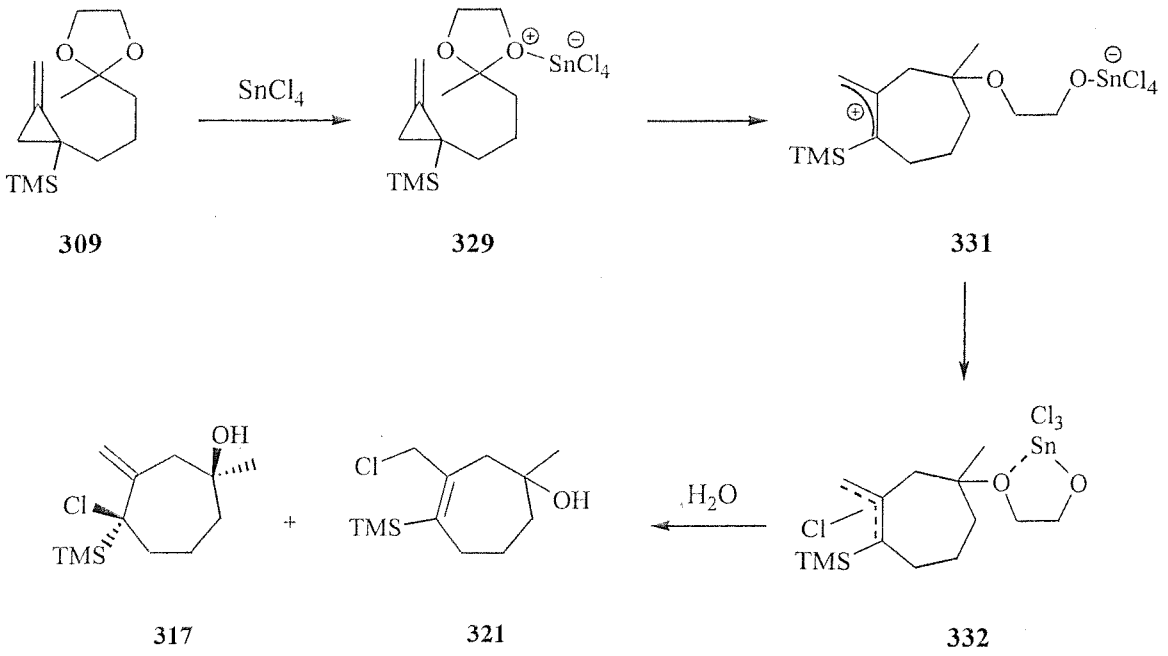
Scheme 114

Methylenecycloheptane **327** and cycloheptene **328** were the expected cyclic products and they presumably arose from trapping of the intermediate allyl cation by a chlorine anion. *cis*-Hydroxychloride **317** and cycloheptene **321** arose from the deprotection of ketal **309** to give ketone **311** under Lewis acid conditions. Cyclisation can then occur and gave *cis*-hydroxychloride **317** and cycloheptene **321**. Jung[54] reported the deprotection of ketals under anhydrous Lewis acid conditions (**Scheme 115**). Activation of ketal **309** gave intermediate **329** which opened to give intermediate **330**. A chlorine anion can then attack the ketal chain to give ketone **311**, which gave *cis*-hydroxychloride **317** and cyclohexene **321** upon treatment with another equivalent of $SnCl_4$, following Hosomi's mechanism.



Scheme 115

Earlier ketone **311** gave only the *cis*-hydroxychloride **317**, upon treatment with $SnCl_4$. Although this course is possible, the reaction of ketal **309** to give *cis*-hydroxychloride **317** and cycloheptene **321** is more likely to proceed *via* the Mukaiyama[48] reaction involving silyl enol ether and acetals (**Scheme 116**). The same intermediate **329** is first formed, followed by intramolecular addition of the double bond to give intermediate **331**. Trapping of the allyl cation by a chlorine anion gave intermediate **332**, which gave *cis*-hydroxychloride **317** and cyclohexene **321** after hydrolysis of the ketal function.



309 **329** **331**

317 **321** **332**

Scheme 116

III-Summary

Lewis acid mediated cyclisation of trimethylsilylmethylenecyclopropyl ketones and ketals gave interesting results. The presence of the silyl group increased the reactivity of such substrates by increasing the nucleophilicity of the exocyclic double bond of methylenecyclopropane, resulting in very fast cyclisation of all precursors.

The reaction is also favoured due to the formation of a β-cyclopropyl cation, stabilised by the silicon atom. The increased nucleophilicity of the double bond of methylenecyclopropane also allowed the use of milder Lewis acids, such as $BF_3.Et_2O$ and $BF_3(AcOH)_2$, and gave bicyclic ether **318** and **314** in reasonable and good yields respectively.

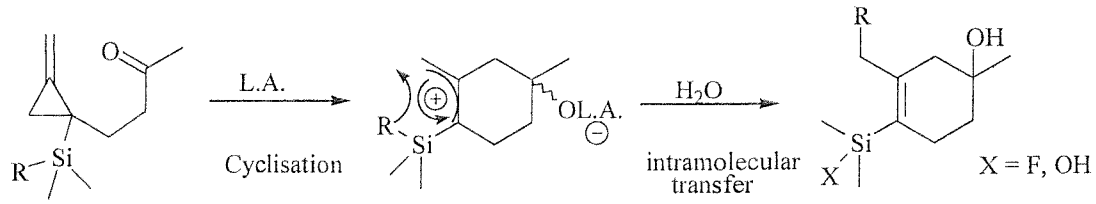
Finally, cyclisation of trimethylsilylmethylenecyclopropyl ketone **311** is in stark contrast with the cyclisation of the non-silylated equivalents, which gave cyclopentanol **213** and cyclohexenol **214**, as 7-membered rings were obtained this time.

CHAPTER FIVE

Lewis Acid Mediated Cascade Reaction of Methylenecyclopropyl Ketones

Earlier we tried to trap the allyl cation, formed as an intermediate in these cyclisations, with a range of nucleophilic groups grafted onto the starting methylenecyclopropyl ketone. However, most of these attempts were thwarted by rapid trapping of the allyl cation by chloride anion derived from the Lewis acid, $TiCl_4$ or $SnCl_4$ which were required for cyclisation. The only successful example is the synthesis of spirocyclic ether **293** in 34% yield, accompanied with bicycle **294** arising from intramolecular trapping of the allyl cation by the alkoxy side chain and by the ketal chain respectively.

The introduction of a silyl substituent, however, allows the cyclisation to be carried out in the absence of a strongly nucleophilic counteranion. So we again thought to exploit the reactivity of the intermediate allyl cation for further reaction. We assumed that the silicon atom could be used as a relay for the trapping of the allyl cation by transferring different groups (**Scheme 117**).



333 **334** **335**

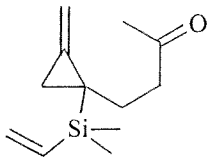
Scheme 117

Treatment of silylated ketone **333** with a suitable Lewis acid, such as $BF_3.Et_2O$ and $BF_3(AcOH)_2$, should first allow the cyclisation to proceed to give allyl cation **334**, after ring

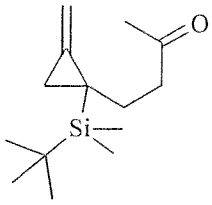
opening of the cyclopropyl intermediate. The allyl cation intermediate **334** should be then trapped intramolecularly by transfer of the R group to give cyclohexene **335**.

I-Preparation of Precursors

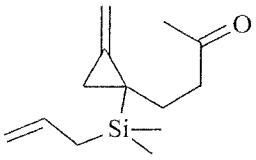
Four substrates were chosen for the study of this cascade process : vinyldimethylsilyl ketone **336**, *t*-butyldimethylsilyl ketone **337**, allyldimethylsilyl ketone **338** and finally phenyldimethylsilyl ketone **339**.



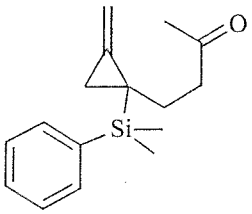
336



337

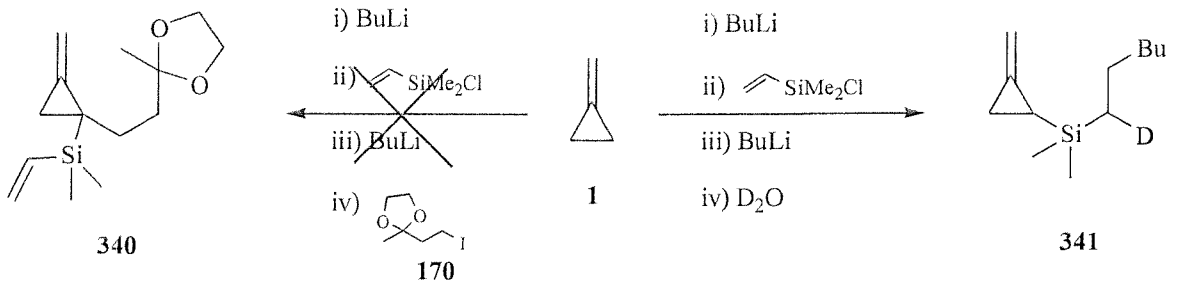


338



339

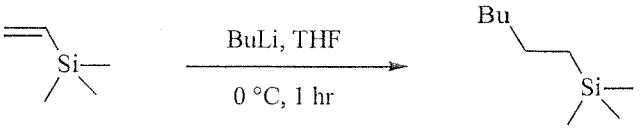
Following the method used by Binger,[8a] synthesis of vinyldimethylsilyl ketone **336** was first attempted. However, none of the expected vinyl silane **340** could be isolated (**Scheme 118**). It was anticipated that the reason for the failure of this reaction was due to side reaction during the second deprotonation. The reaction was repeated, but instead of adding iodide **170**, the second anion expected from the addition of the second equivalent of BuLi was quenched with D_2O. The crude NMR of this reaction showed that BuLi in fact underwent nucleophilic addition onto the vinyl function to give adduct **341**.



340 **170** **1** **341**

Scheme 118

Tamao[66] has reported such addition of BuLi onto vinyl silanes. Addition of Grignard reagents to vinyl silane **342** failed to give any reaction, but organo-lithium reagents, such as BuLi, underwent nucleophilic addition onto vinyl silane **342** to give adduct **343** (**Scheme 119**).

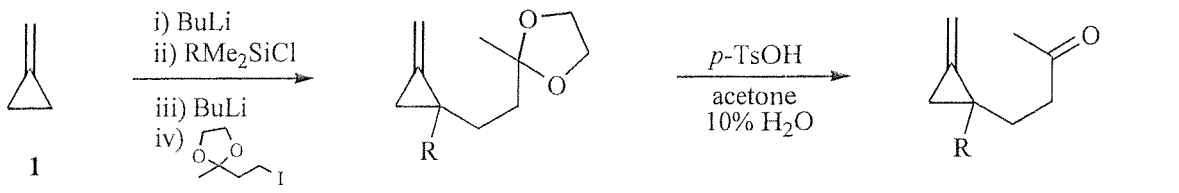


342 **343**

Scheme 119

Preparation of vinyldimethylsilyl ketone **336** proved to be impossible with this method and its synthesis had to be abandoned.

However, preparation of *t*-butyldimethylsilyl ketone **337**, allyldimethylsilyl ketone **338** and phenyldimethylsilyl ketone **339** was not problematic. Lithiated methylenecyclopropane was first quenched with *t*-butyl, allyl, or phenyldimethylsilyl chloride, followed by a second deprotonation with BuLi and quenching with iodide **170** to give ketals **344**, **345** and **346** respectively in very good yields. Deprotection of the resulting ketals afforded ketones **337**, **338** and **339** (**Scheme 120**).



1 **170**

344, R = *t*-$BuMe_2Si$, 87%
345, R = allylMe_2Si, 89%
346, R = $PhMe_2Si$, 81%

337, R = *t*-$BuMe_2Si$, 96%
338, R = allylMe_2Si, 95%
339, R = $PhMe_2Si$, 41%

Scheme 120

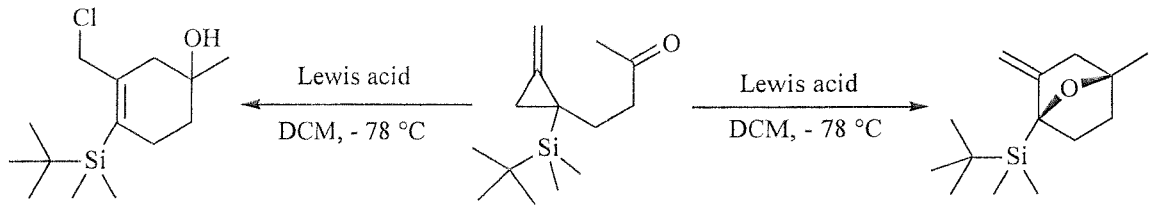
II-Cyclisation study of Lewis Acid mediated Cascade Reaction

1-Cyclisation of *t*-Butyldimethyl silanes

It was anticipated that the *t*-butyldimethyl silanes would give the expected cascade process with trapping of the allyl cation intermediate **334** by intramolecular transfer of the *t*-butyl group.

Cyclisation of Ketone

When ketone **337** was treated with a strong Lewis acid, such as $TiCl_4$ and $SnCl_4$, cyclohexene **347** was obtained in 88% and 82% yield respectively (**Scheme 121**). Addition of the softer Lewis acids, $BF_3.Et_2O$ and $BF_3(AcOH)_2$, gave bicyclo **348** in 70 % and 71% yield respectively.



347 **337** **348**

$TiCl_4$, 30 mins, 88%
$SnCl_4$, 45 mins, 82%

$BF_3(AcOH)_2$, 1 hr, 71%
$BF_3.Et_2O$, 5 hrs, 70%

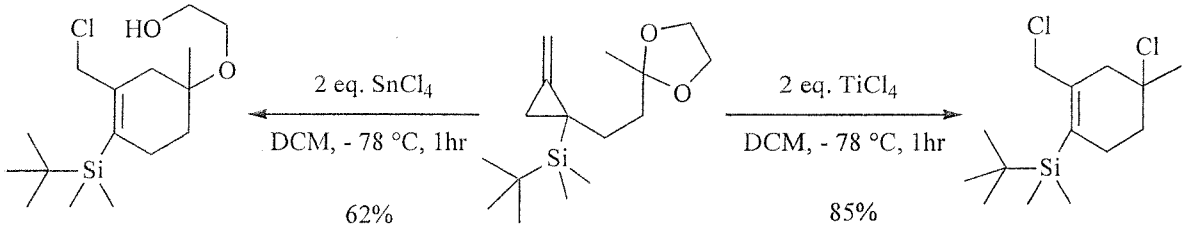
Scheme 121

As observed for the cyclisation of trimethylsilylmethylenecyclopropane derivatives, an increased in the rate of the reaction was observed, in comparison to the corresponding non-silylated ketone **166**, which went to completion in less than an hour for $TiCl_4$ and $SnCl_4$, due to the presence of the silyl group. However, none of the expected compounds were isolated, as a consequence of the rapid trapping of the allyl cation intermediate **334** by the relatively nucleophilic chlorine anion. The same observation can be made with the formation of

bicyclic ether **348**. The allyl cation intermediate **334** is more rapidly quenched by intramolecular trapping by the alkoxide rather than by transfer of the *t*-butyl group from silicon.

Cyclisation of Ketal

Lewis acid mediated cyclisation of ketal **344** also failed to give any of the alkyl transferred compounds. Decomposition of ketal **344** was observed with $BF_3(AcOH)_2$ and there was no reaction with $BF_3.Et_2O$. In addition, treatment of ketal **344** with $SnCl_4$ gave cyclohexene **349** in a good 62% yield and dichloride **350** was obtained with $TiCl_4$ in 85% yield (**Scheme 122**).



349 **344** **350**

Scheme 122

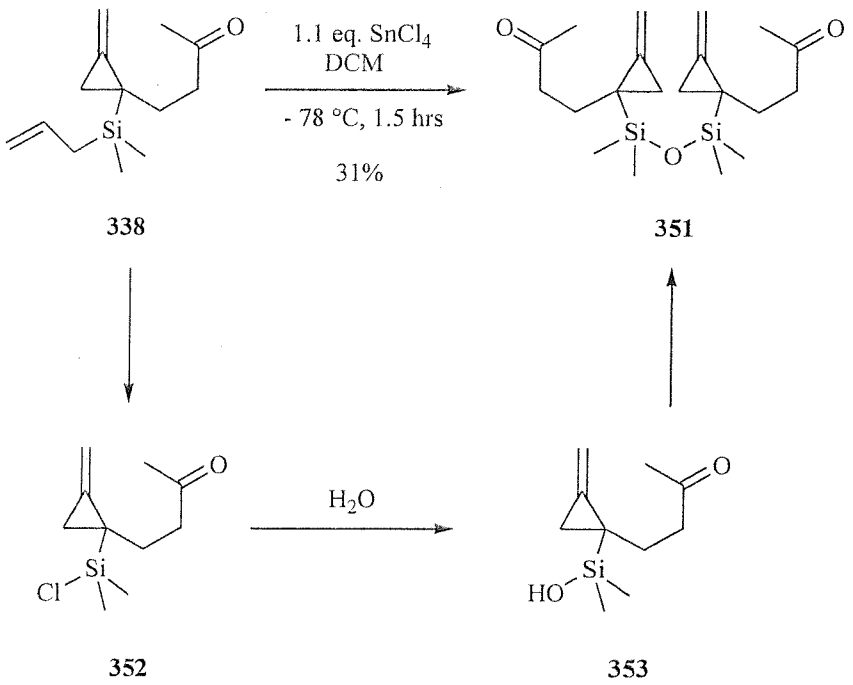
The failure of these cascade processes can again be attributed to the faster trapping of the allyl cation intermediate **334** by the relatively nucleophilic chlorine anion than intramolecular trapping of the allyl cation intermediate **334** by transfer of the *t*-butyl group.

2-Cyclisation of Allyldimethyl silanes

The reaction of allyl silanes has been extensively studied by different groups[46,48,49,67] and it appeared clear that allyl silanes have a great ability to transfer the allyl group in reaction such as the Hosomi-Sakurai[47] reaction. From these results, it was believed that the cascade reaction of the allyl-silanes would be successful.

Cyclisation of Ketone

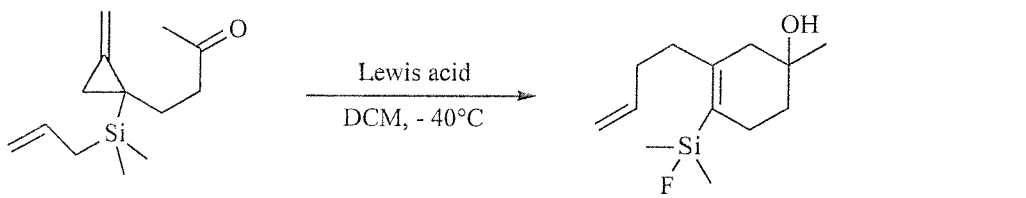
Decomposition of allyldimethylsilyl ketone **338** was observed when $TiCl_4$ was added. Treatment of ketone **338** with $SnCl_4$ gave dimer **351** (**Scheme 123**). Dimer **351** presumably arose from first deallylation resulting from attack of a chlorine anion to give **352**. Intermediate **352** was then hydrolysed, during work up, to silanol **353** and dimerised under acidic condition to give dimer **351**.



338 **351** **352** **353**

Scheme 123

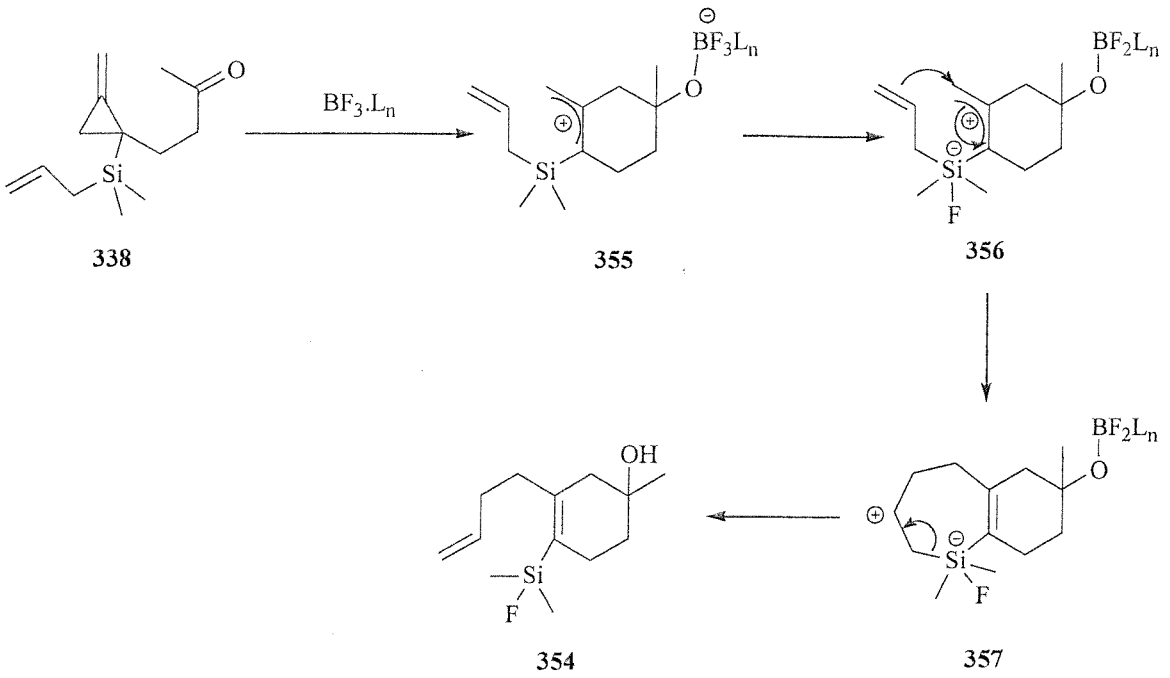
However, when $BF_3.Et_2O$ and $BF_3(AcOH)_2$ were used, cyclohexene **354** was isolated in a modest 41% and 42% yield respectively (**Scheme 124**).



338 **354** $BF_3.Et_2O$, 41%; $BF_3(AcOH)_2$, 42%

Scheme 124

Cyclohexene **354** is presumably formed by the cascade process with initial cyclisation to give allyl cation intermediate **355**, followed by allyl transfer, possibly *via* the ate complex intermediate **356** (**Scheme 125**).

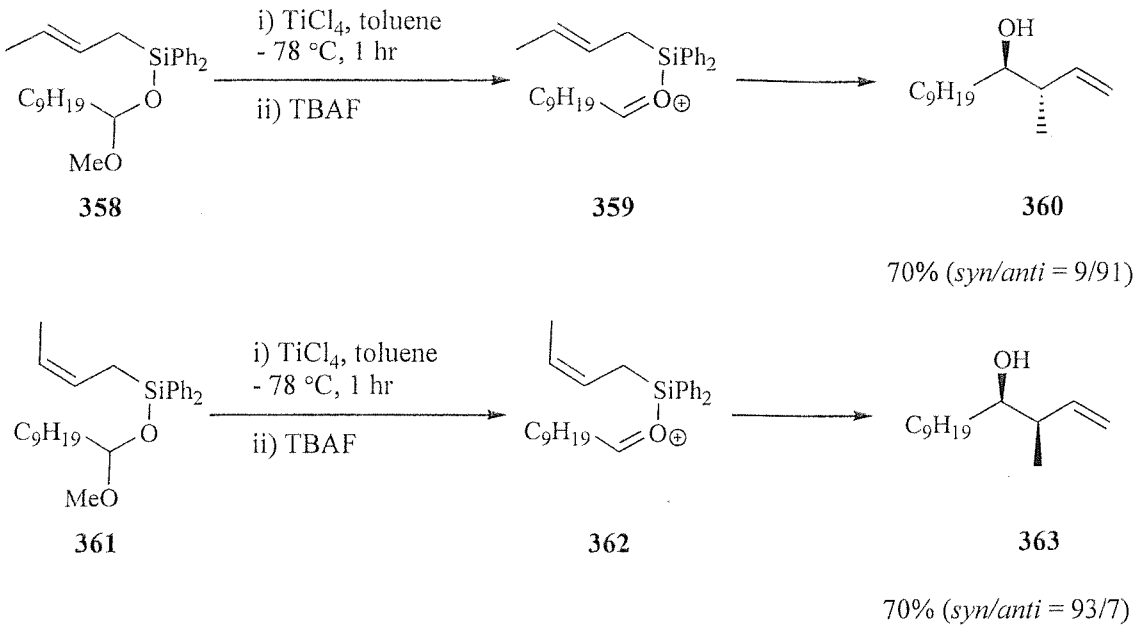


338 **355** **356** **357** **354**

Scheme 125

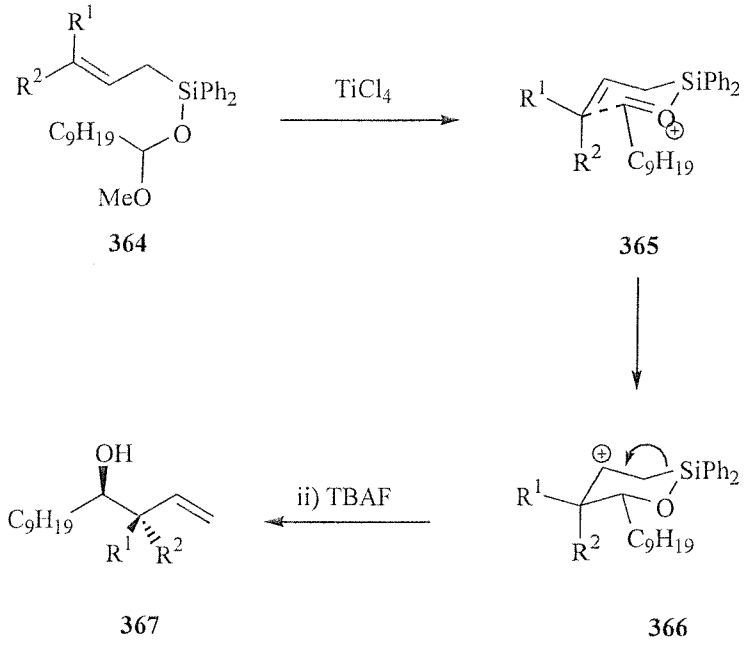
Interestingly, none of the product arising from intramolecular trapping by the alkoxide was isolated, indicating that the transfer of the allyl group is faster than the intramolecular trapping by the alkoxide.

Work by Oshima[68] is in agreement with the proposed mechanism. Addition of $TiCl_4$ to the (*E*)-crotylsilyl acetal **358** gave the *anti*-homoallylic alcohol **360** in 70% yield after desilylation using TBAF (**Scheme 126**). When the (*Z*)-crotylsilyl acetal **361** was treated with $TiCl_4$, the *syn*-homoallylic alcohol **363** was obtained in 70% yield.



Scheme 126

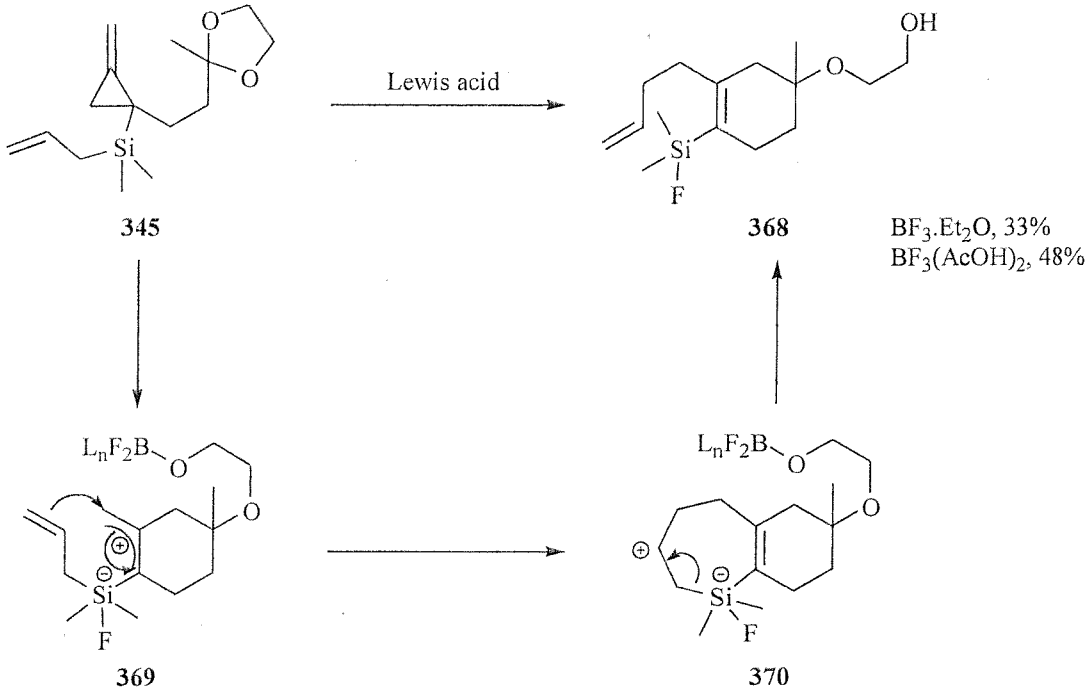
On the basis of these results, it is obvious that the reaction proceeds in a stereoselective manner through a six-membered cyclic transition state such as **365**, which gave cyclohexyl cation intermediate **366**. Elimination and silyl deprotection then afforded the homoallylic alcohol **367** (**Scheme 127**).



Scheme 127

Cyclisation of Ketal

Lewis acid mediated cyclisation of ketal **345** was also investigated. Decomposition of the substrate was observed with $TiCl_4$ and $SnCl_4$. However, when the softer Lewis acids, $BF_3.Et_2O$ and $BF_3(AcOH)_2$, were used, cyclohexene **368** was isolated in a modest 33% and 48% yield respectively (**Scheme 128**).



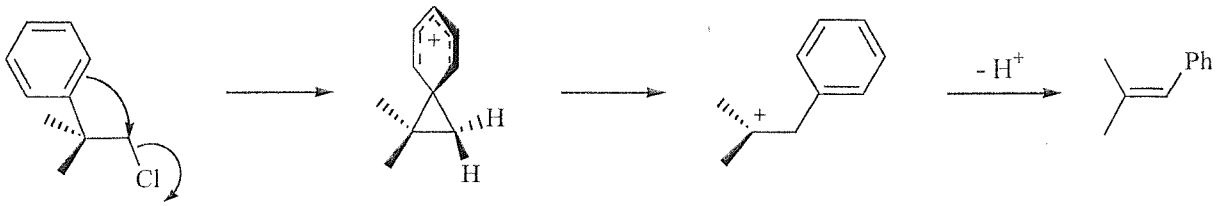
Scheme 128

The same mechanism, as for the cyclisation-intramolecular transfer of ketone **338**, is involved in the formation of **368**.

3-Cyclisation of Phenyldimethyl silanes

The cascade reaction of phenyldimethylsilanes was also investigated. However, it was anticipated that the phenyl group would rather give a 1,2-phenyl shift to trap the allyl cation intermediate α- to the silicon rather than γ- to the silicon.

Indeed, aryl groups have a far greater migratory aptitude than alkyl groups or hydrogen.[69] Solvolysis of chloride **371** is many thousands of times faster than neopentyl chloride **375** in the same conditions. This is ascribed to the fact that, whereas the rate-determining step in the reaction of neopentyl is the formation of the high-energy primary carbocation **376**, in the reaction of the phenyl-substituted chloride the rate-determining step is the formation of a lower-energy bridged phenonium ion **372** and the aryl group is said to provide *anchimeric assistance* to the reaction (**Scheme 129**).



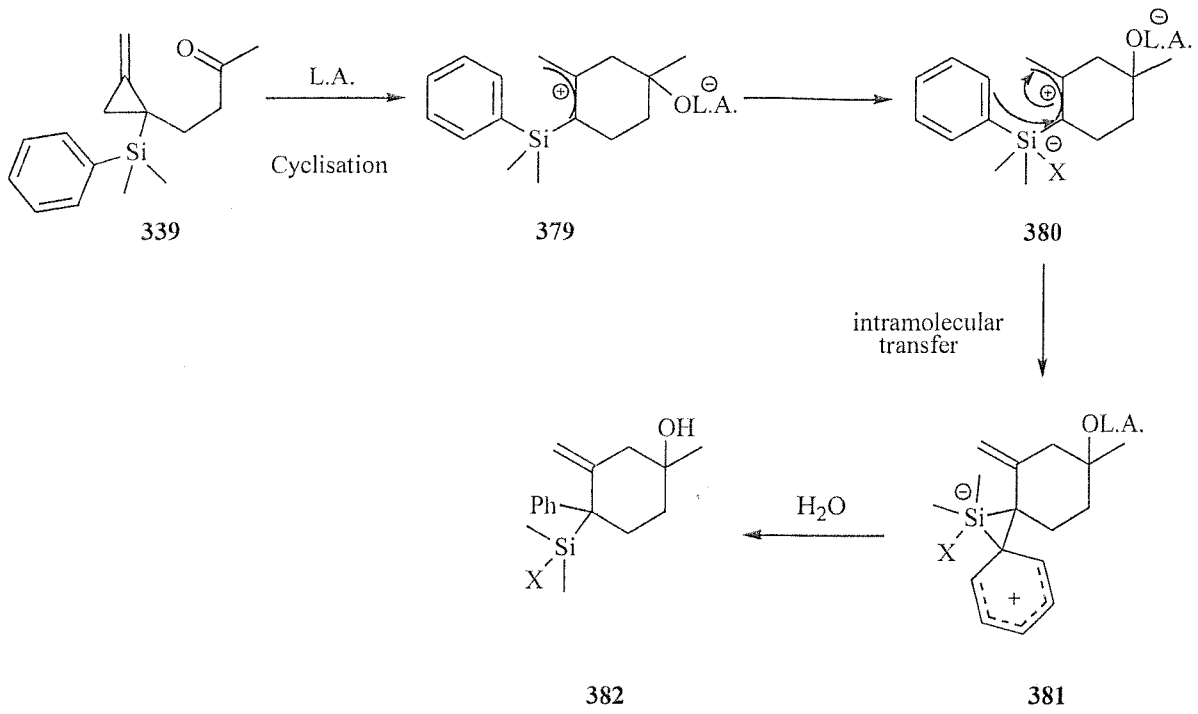
371 **372** **373** **374**

375 **376** **377** **378**

Scheme 129

In addition, the phenonium ion is similar in structure to the intermediate in an electrophilic aromatic substitution and therefore, electron donating group, such as *p*-OMe give rise to greater rates of migration and electron withdrawing groups to lower rates.

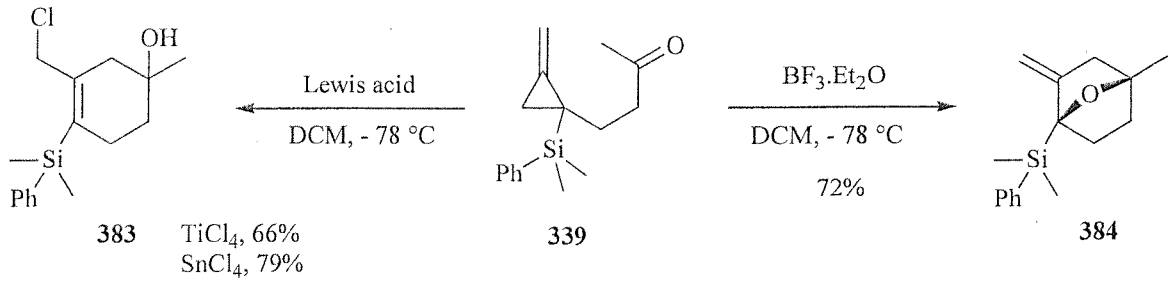
Bearing these observations in mind, activation of ketone **339** with a suitable Lewis acid, such as $BF_3.Et_2O$ or $BF_3(AcOH)_2$, should allow first cyclisation to give intermediate **379**, after ring opening of the cyclopropyl cation. 1,2-Phenyl shift should then occurred, favoured by the formation of the phenonium ion intermediate **381**, to give methylenecyclohexane **382** (**Scheme 130**).



Scheme 130

Cyclisation of Ketone

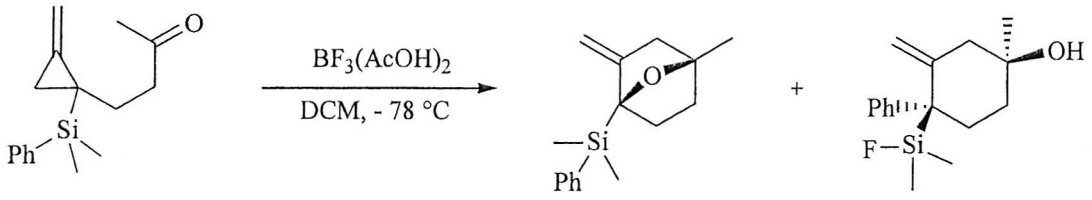
Treatment of ketone **339** with either $TiCl_4$ or $SnCl_4$ gave cyclohexene **383** as the only isolated product in 66% and 79% yield respectively, as a consequence of the rapid trapping of the allyl cation intermediate **379** by the relatively nucleophilic chlorine anion (**Scheme 131**).



Scheme 131

In addition, bicyclic ether **384** was obtained as the only isolated product in 72% yield when ketone **339** was treated with $BF_3.Et_2O$, also as a consequence of the rapid trapping of the allyl cation intermediate **379** by intramolecular quenching by the alkoxide (**Scheme 131**).

However, treatment of ketone **339** with $BF_3(AcOH)_2$ gave bicyclic ether **384** in 22% yield and methylenecyclohexane **385**, as a single diastereoisomer, in 55% yield (**Scheme 132**).



339 **384** **385**

22% 55%

Scheme 132

The stereochemistry of methylenecyclohexane **385** was obtained from X-ray crystallography after recrystallisation in ethanol-water (**Figure 4**).

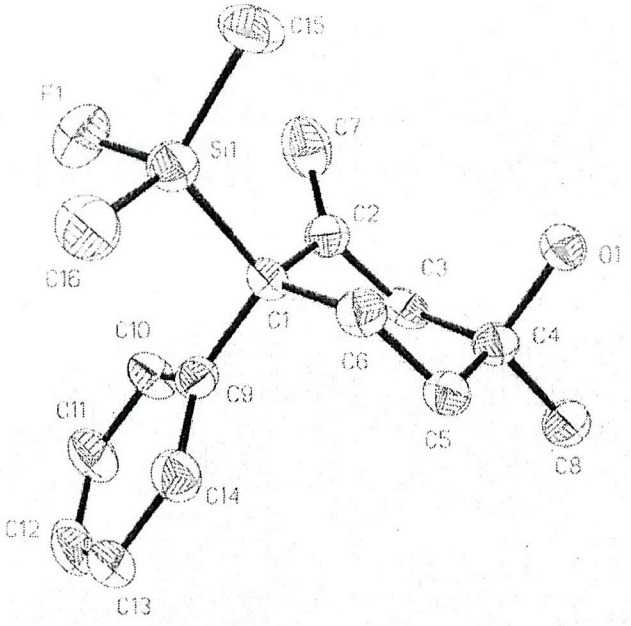


Figure 4 : Crystal Structure of **385**

For full details of the X-ray crystallographic data, see appendix C.

In this case, competition exists between intramolecular trapping of the allyl cation by the alkoxide to give **384** and trapping of the allyl cation intermediate by transfer of the phenyl

group to give **385**. It seems that the rate of the reaction is Lewis acid dependent as no transfer was observed with $BF_3.Et_2O$ and competition occurred when $BF_3(AcOH)_2$ was used. This may be attributed to the ability of $BF_3.Et_2O$ and $BF_3(AcOH)_2$ to deliver a fluorine anion, required for the formation of the ate complex **380**, which may promotes the 1,2-phenyl shift.[65] This observation suggested that $BF_3(AcOH)_2$ is a better fluorine anion donor than $BF_3.Et_2O$.

The stereochemical outcome of this reaction suggests that the reaction proceeds via intermediate **380** with the O-L.A. in the equatorial position and axial attack from the phenyl ring is preferred over equatorial attack for the transfer of the phenyl ring (**Figure 5**). Indeed, axial attack in cyclohexyl ring is usually preferred over equatorial attack.

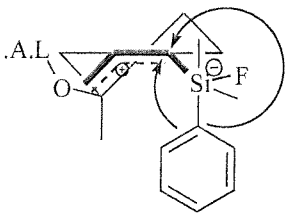
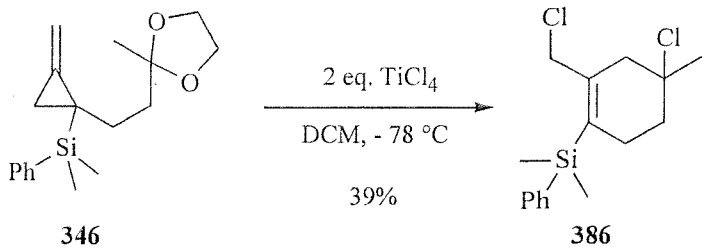


Figure 5 : Geometry of intermediate **380**

Cyclisation of Ketal

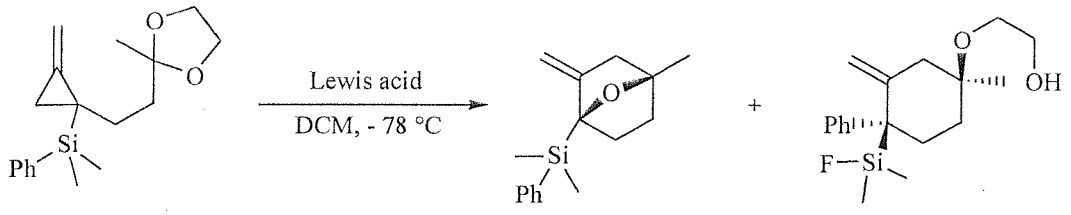
Treatment of ketal **346** with $TiCl_4$ gave dichloride **386** in 39% yield, as a result of the rapid trapping by the chlorine anion (**Scheme 133**).



346 **386**

Scheme 133

However, addition of $BF_3.Et_2O$ and $BF_3(AcOH)_2$ gave bicyclic ether **384** and the desired product from the cascade reaction, **387**, as a single diastereoisomer (**Scheme 134**). $BF_3.Et_2O$ gave **384** and **387** in 12% and 30% yield respectively. $BF_3(AcOH)_2$ gave **384** and **387** in 21% and 39% yield respectively.

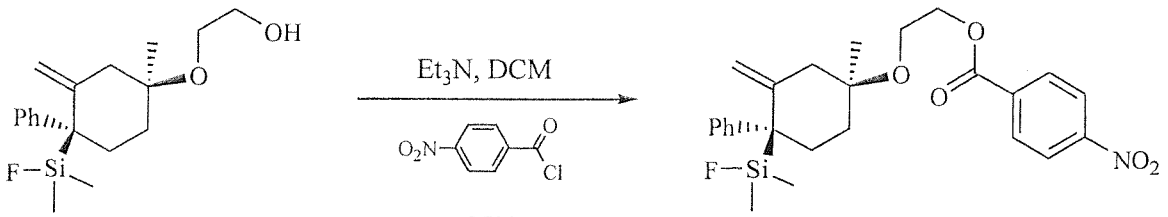


346 **384** **387**

$BF_3.Et_2O$	12%	30%
$BF_3(AcOH)_2$	21%	39%

Scheme 134

The stereochemistry of **387** was determined by the synthesis of its *p*-nitro-benzoate derivative. Treatment of methylenecyclohexane **387** with Et_3N in the presence of *p*-nitro-benzoyl chloride gave *p*-nitro-benzoate derivative **388** in 95% yield (**Scheme 135**).



387 **388**

Scheme 135

The stereochemistry of benzoate **388** was obtained by X-ray diffraction after recrystallisation in ethanol-water (**Figure 6**).

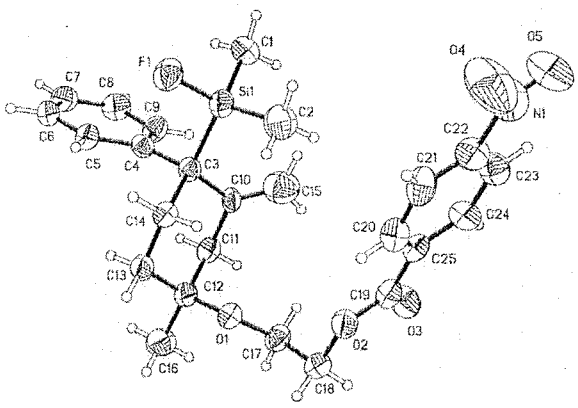
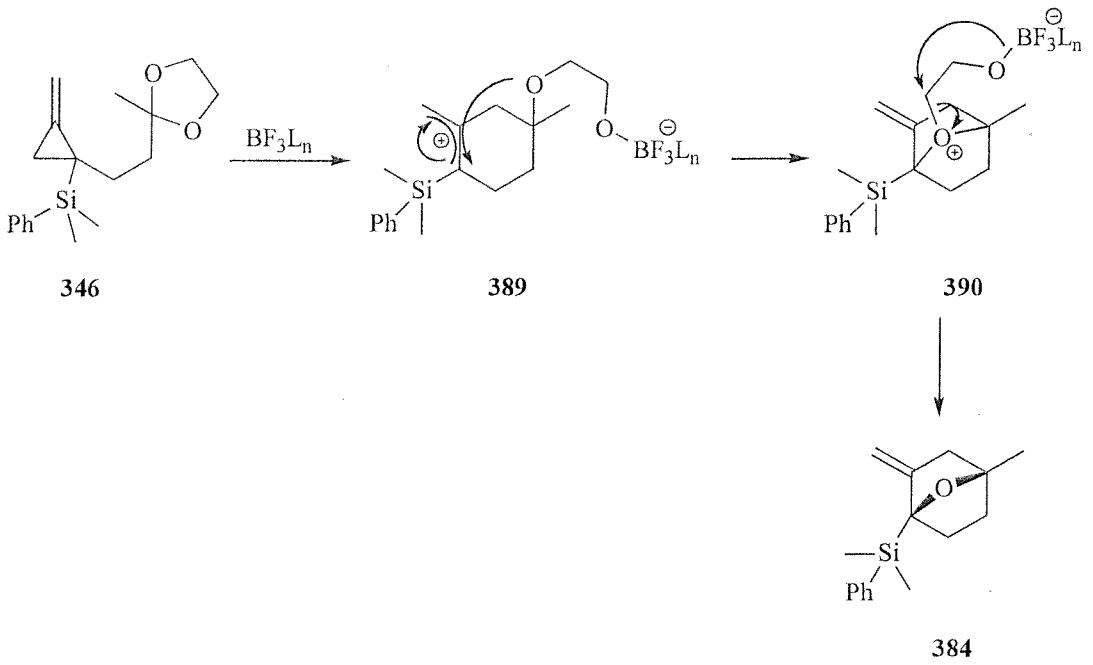


Figure 6 : Crystal structure of Benzoate **388**

For full details of the X-ray crystallographic data, see appendix D.

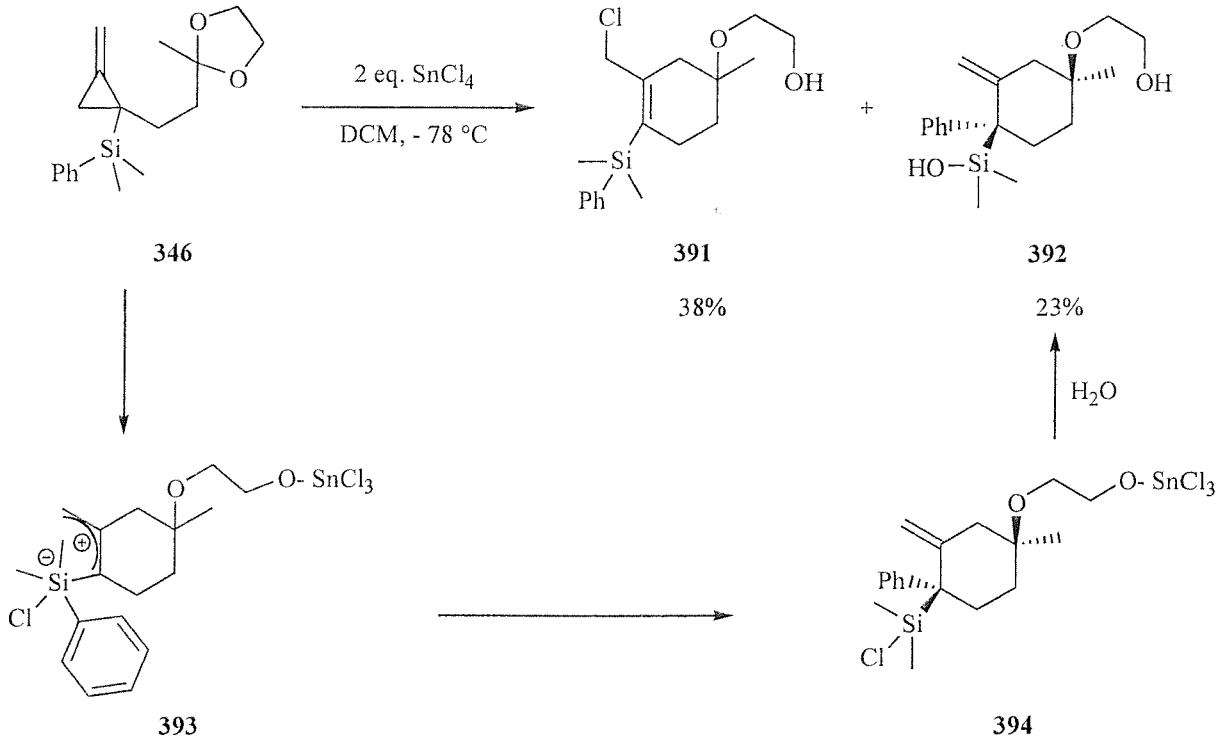
Methylenecyclohexane **387** has the same relative stereochemistry as methylenecyclohexane **385**. As a consequence, identical argument can be given for the stereochemical outcome of this reaction.

The formation of bicyclic ether **384** is presumably due to trapping of the allyl cation intermediate **389** by the alkoxy function α- to the quaternary carbon to give intermediate **390**, which loses ethylene oxide to give bicyclic ether **384** (**Scheme 136**).



Scheme 136

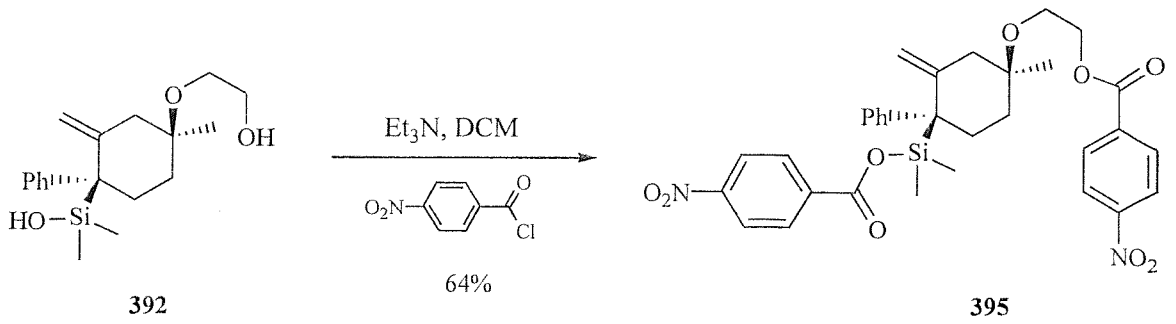
Finally, ketal **346**, upon treatment with $SnCl_4$, gave cyclohexene **391** and diol **392**, as a single diastereoisomer, in 38% and 23% yield respectively (**Scheme 137**). In this case competition occurred between rapid trapping of the allyl cation intermediate by the relatively nucleophilic chlorine anion and by 1,2-phenyl shift.



Scheme 137

The mechanism involved in the formation of **392** is similar to the one proposed for **385** and **387**. However, the ate complex **393** is formed by addition of a chlorine anion onto the silicon atom, which resulted in chlorosilane **394** after 1,2-phenyl shift. This chloro-silane **394** is presumably hydrolysed to silanol **392** during work up (**Scheme 137**).

A benzoate derivative of diol **392** was obtained by treating diol **392** with Et_3N in the presence of *p*-nitro-benzoyl chloride and the *bis*-benzoate **395** was isolated in 64% yield (**Scheme 138**).



392 395

Scheme 138

However, X-ray quality crystals could not be obtained, but the stereochemistry of diol **392** is assumed to be *cis*, based on the previous observation for methylenecyclohexane **385** and **387**.

III-Summary

The cascade process with a *t*-butyl group failed. The reason for the failure can be attributed to a faster trapping of the allyl cation intermediate **334** by either the relatively nucleophilic chlorine anion or the alkoxide function than intramolecular trapping by transfer of the *t*-butyl group. However, as described in **Chapter 4**, the presence of the silyl group increased the rate of the reaction due to either an increased nucleophilicity of the exocyclic double bond of methylenecyclopropane or the ability of silicon to stabilise *β*-carbocations.

The cascade reaction of allylsilanes was successful giving reasonable yield of the allyl transferred compounds. The reaction is believed to proceed through an ate complex followed by the formation of a 7-membered intermediate. Furthermore, none of the products resulting from trapping of the allyl cation intermediate by the alkoxide were obtained, indicating that the transfer of the allyl group is faster than the trapping of the allyl cation intermediate by the alkoxide.

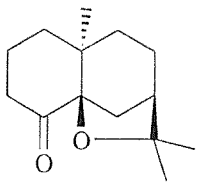
The cascade reaction of phenyl silanes was also successful. However, in this case competition occurred between trapping of the allyl cation intermediate by the relatively nucleophilic chlorine anion or by intramolecular addition of the alkoxide and intramolecular trapping of the allyl cation intermediate by 1,2-phenyl shift. However, the cascade process with phenyl silanes is stereoselective, giving a single diastereoisomer for every reaction.

Regarding all these results, it can be proposed that the transfer ability is as follow : allylsilane > phenylsilane > alkylsilane.

CHAPTER SIX

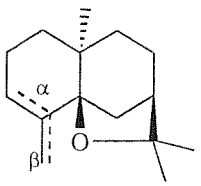
Towards the synthesis of Norketoagarofuran

With the conditions set up for good cyclisation, it was the final aim of this project to apply this methodology in the synthesis of a natural product. Norketoagarofuran **396** was chosen as a suitable target.

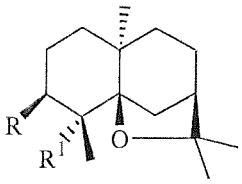


396, Norketoagarofuran

Norketoagarofuran **396** is a sequiterpene found in Agar-wood oil isolated from fungus-infected *Aquillaria Agallocha Roxb*[70] along with five closely related decalinic sequiterpenes **397-401**.



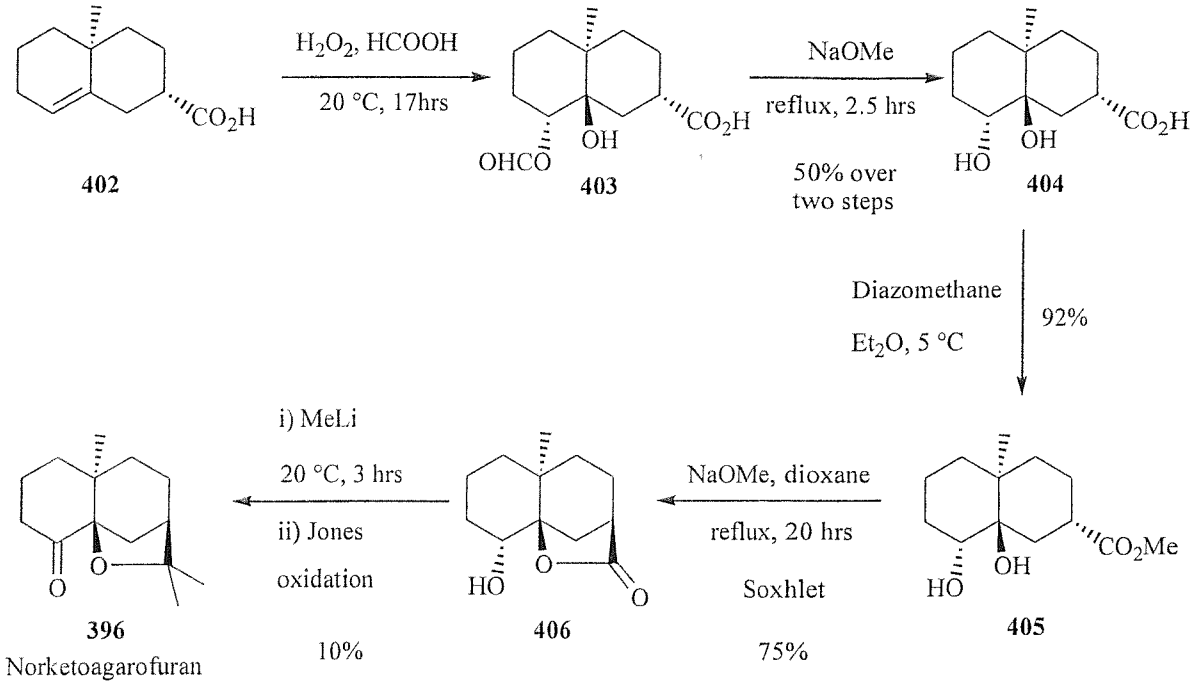
397, α-Agarofuran
398, β-Agarofuran



399, R = R^1 = H, Dihydroagarofuran
400, R = H, R^1 = OH, 4-Hydroxyagarofuran
401, R = R^1 = OH, 3,4-Dihydroxyagarofuran

These compounds have attracted a great deal of interest on account of their cytotoxic,[71] antitumor,[72] immunosuppresive[73] and insect antifeedant activities.[74] However, very few synthesis of Norketoagarofuran **396** has been reported.[75]

The latest synthesis of Norketoagarofuran **396** was reported by Kelly,[76] starting from unsaturated acid **402** (**Scheme 139**).

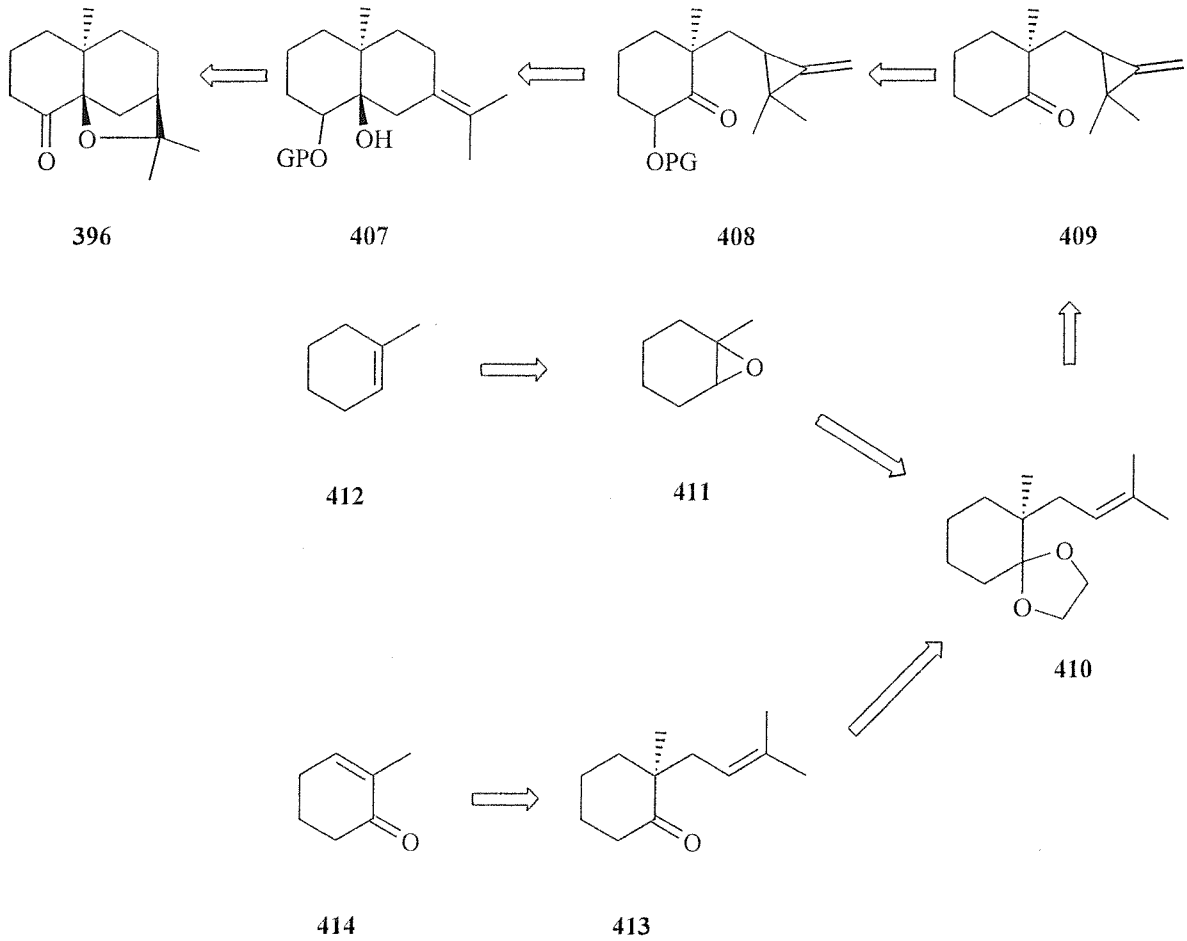


Scheme 139

Treatment of **402** with performic acid, formed *in-situ* from reaction of formic acid with hydrogen peroxide, gave diol acid monoformate **403**. Saponification of diol acid monoformate **403** with sodium methoxide gave diol **404**, which afforded ester **405** upon treatment with diazomethane in ether. Ester **405** was then treated with sodium methoxide in dioxane and gave lactone **406**, after epimerisation and lactonisation. Lactone **406** was finally subjected successively to MeLi and Jones reagent to give Norketoagarofuran **396**.

I-Retrosynthetic Study

Our retrosynthetic approach to the total synthesis of Norketoagarofuran **396** is shown in **Scheme 140**. Norketoagarofuran **396** would arise from etherification of alcohol **407**, followed by deprotection of the secondary alcohol and subsequent oxidation. Alcohol **407** should come from cyclisation of ketone **408** mediated by Lewis acid, as the key step in the synthesis, after α-hydroxylation of ketone **409**. Ketone **409** should come from methylenecyclopropanation of alkene **410**, following the method of Binger.[6] Finally, alkene **410** should arise from either ring opening of epoxide **411** at the most substituted centre, following a method developed by Iwata,[77] or Birch reduction-alkylation with prenyl bromide of conjugated ketone **414**.



396 **407** **408** **409**

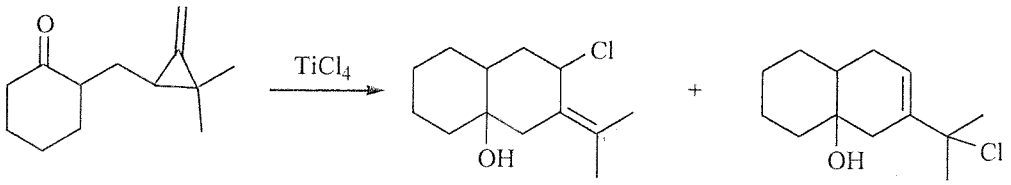
412 **411** **410**

414 **413**

Scheme 140

II-Model Study

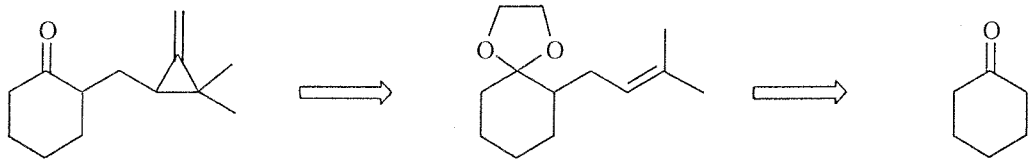
Methylene cyclopropyl ketone **415** was chosen as the lead compound for the initial cyclisation study. It was anticipated that **415** would give decaline **416** and **417**, upon treatment with a suitable Lewis acid, such as $TiCl_4$ (**Scheme 141**).



415 **416** **417**

Scheme 141

A retrosynthetic analysis for the preparation of methylenecyclopropyl ketone **415** is shown in **Scheme 142**.

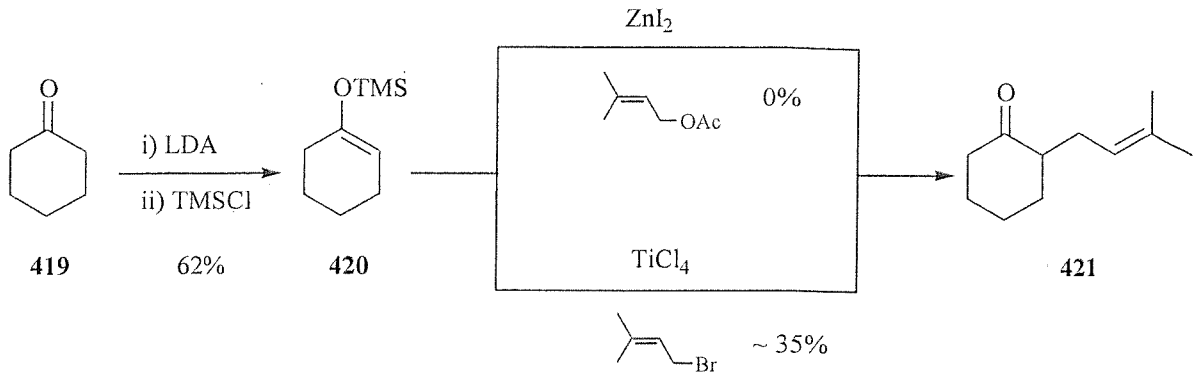


415 **418** **419**

Scheme 142

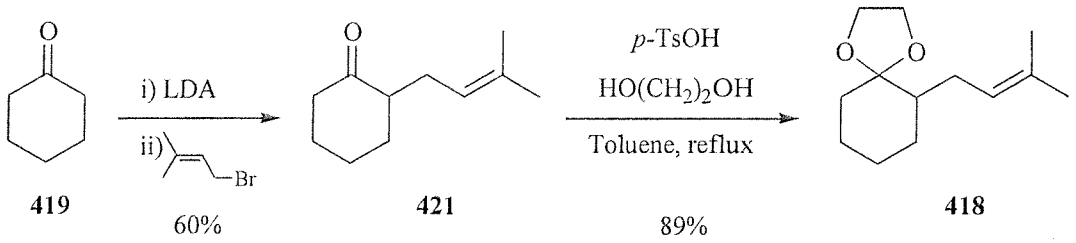
Methylenecyclopropyl ketone **415** should come from methylenecyclopropanation of alkene **418**, using the method of Binger.[6] Alkene **418** should arise from protection of the α-alkylated ketone resulting from α-alkylation of cyclohexanone **419**.

Most of the reported methods used for the preparation of α-substituted ketones require the use of silyl enol ether.[78] So silyl enol ether **420** was prepared following Fleming and Paterson method.[79] The method of Reetz[79a] , for the synthesis of α-substituted ketone **421**, was first tried. Addition of silyl enol ether **420** and prenyl acetate to a suspension of ZnI_2 in dichloromethane gave a mixture of compounds impossible to separate. The method of House[79b] also gave disappointing results. When $TiCl_4$ was added to a solution of silyl enol ether **420** and prenyl bromide, ketone **421** was obtained, not pure, in only 35% yield (**Scheme 143**).



Scheme 143

Direct alkylation of the cyclohexanone enolate with prenyl bromide was then tried, and ketone **421** was obtained in 60% yield. However, when the reaction was scaled up, none of the wanted ketone **421** could be isolated, presumably because of polymerisation of reagents. However, enough material was obtained to carry on with the synthesis. Ketone **421** was then easily protected to give ketal **418** in 89 % yield (**Scheme 144**).

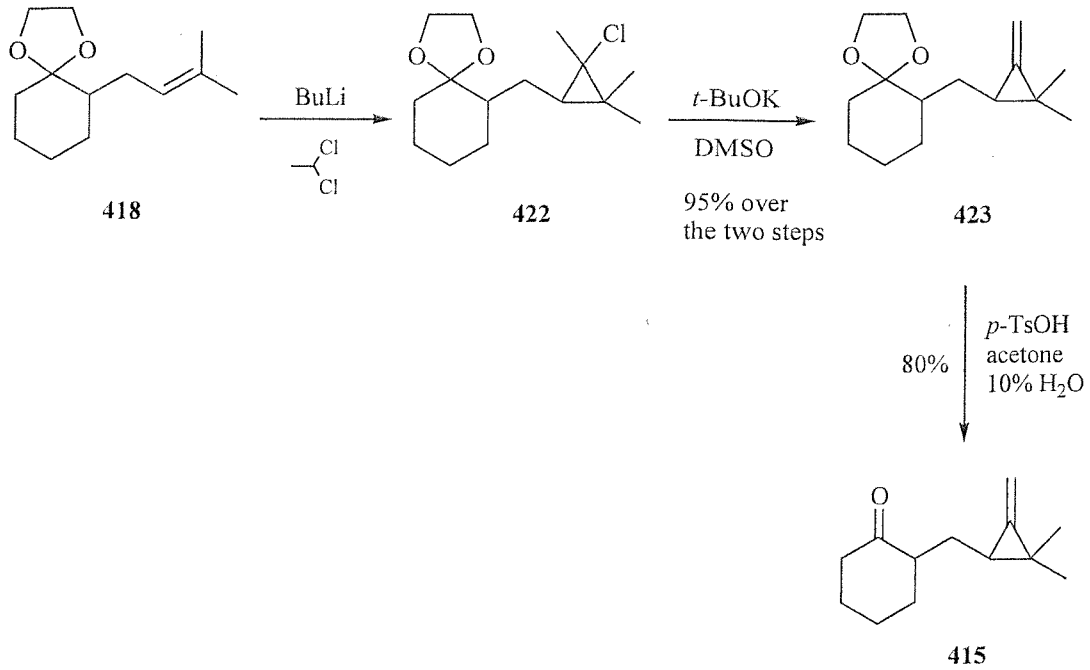


Scheme 144

Attention was next turned onto the cyclopropanation of alkene **418** in order to obtain methylenecyclopropyl ketone **415** and this reaction proved to be problematic. Different conditions were tried.

When BuLi was added over two hours at - 35 °C, very small amounts of chlorocyclopropane **422** was formed even when the reaction was repeated twice. A decent amount was obtained when the addition was extended to 9 hrs. However, when the addition was carried out at - 25 °C, chlorocyclopropane **422** was obtained in an excellent yield, as a mixture of diastereoisomer, with no further purification needed. The crude reaction was then added to a suspension of *t*-BuOK for elimination and the methylenecyclopropyl ketal **423** was obtained in 95% yield over the two steps, as a 2 : 1 mixture of diastereoisomer. Finally,

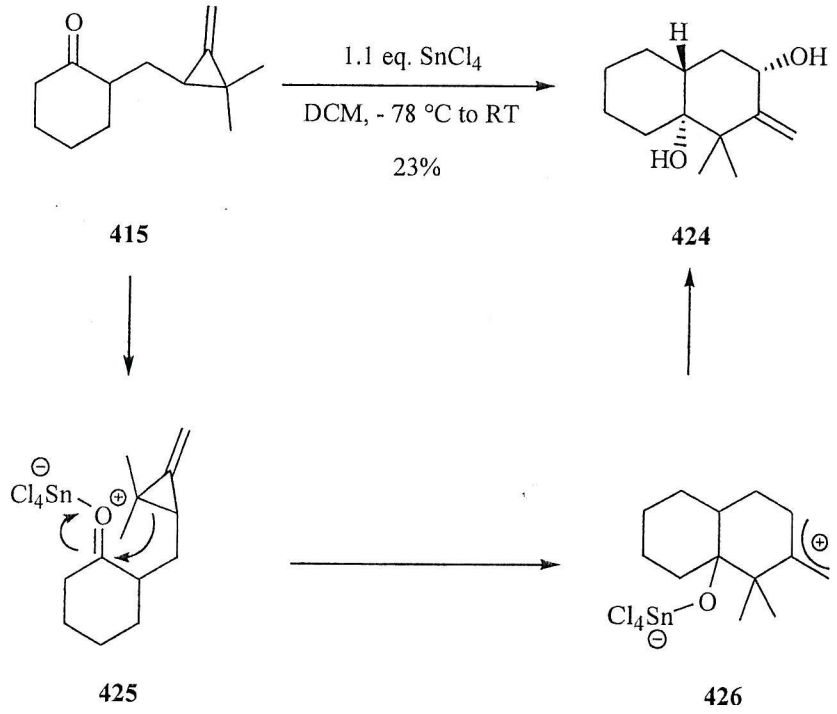
deprotection to the expected ketone precursor **415** was obtained in 80% yield, as a 2 : 1 mixture of diastereoisomer, using *p*-TsOH in wet acetone (**Scheme 145**).



Scheme 145

With ketone **415** in hand, it was then possible to study its cyclisation. Unfortunately, this reaction was again problematic. $TiCl_4$ gave a complex mixture of products. There was no reaction with $BF_3.Et_2O$ and decomposition of the substrate was observed with $BF_3(AcOH)_2$. Treatment of ketone **415** with $ZrCl_4$ in DCM gave a complex mixture of products. Similar results were obtained when the solvent was changed for EDC and the presence or not of molecular sieves had no effect on the reaction.

However, treatment of ketone **415** with $SnCl_4$ did give diol **424** in 23% yield, as a single diastereoisomer **(Scheme 146)**. Diol **424** is presumably obtained by nucleophilic addition of the distal cyclopropyl sigma bond on the activated carbonyl intermediate **425**, due probably to favourable overlapping of the sigma orbital of the cyclopropyl ring and the π^* orbital of the carbonyl. The allyl cation intermediate **426** formed was then probably hydrolysed to give diol **424**.



Scheme 146

The stereochemistry of diol **424** was determined by X-ray diffraction after recrystallisation in ethanol-water (**Figure 7**).

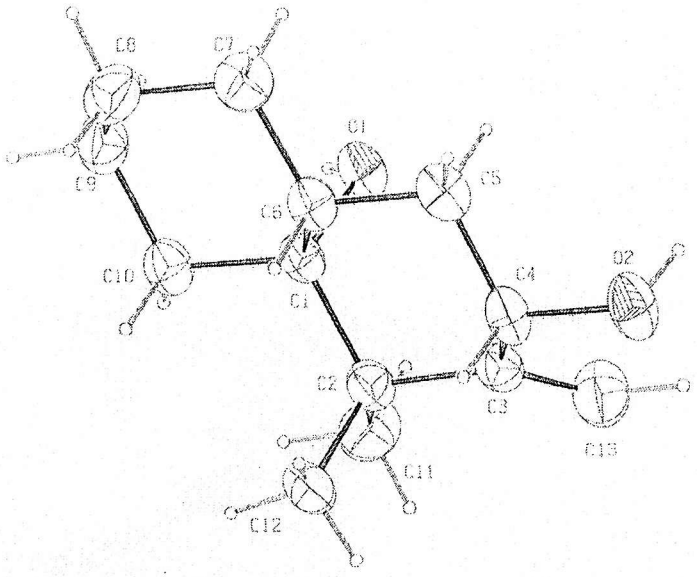


Figure 7 : Crystal Structure of diol **424**

For full details of the X-ray crystallographic data, see appendix E.

The ring junction has a *trans* configuration with the two alcohol function *cis*. In order to try to obtain the expected cyclised products, it was anticipated that the corresponding ketal **423** may provide us with the wanted skeleton.

However, all attempts failed. Ketal **423**, upon treatment with $TiCl_4$, $BF_3(AcOH)_2$ and $ZrCl_4$ gave decomposition of the substrate. There was no reaction, when ketal **423** was treated with $BF_3.Et_2O$ and a complex mixture of product was obtained with $SnCl_4$.

From these results, it appeared that the presence of the two methyl on the cyclopropyl ring has a dramatic effect on the reaction with Lewis acid. Methylenecyclopropyl ketone **415** and ketal **423** are obviously not good substrates for the formation of the wanted decalinic rings. A different route for the total synthesis of Norketoagarofuran **396** may have to be envisaged.

III-Summary

The total synthesis of Norketoagarofuran **396** was unsuccessful as the model study compounds proved to be sensitive to Lewis acid. None of the wanted decalin was obtained. Only diol **424** could be isolated in a poor 23% yield, due to addition of the σ-bond of the cyclopropyl ring onto the carbonyl function of ketone **415**. As a consequence, a different approach may have to be consider for the total synthesis of Norketoagarofuran **396**.

EXPERIMENTAL

I-General Experimental

All reactions requiring anhydrous conditions were conducted in flame dried glassware under a static, inert atmosphere unless otherwise stated. Stirring was magnetic unless otherwise stated. Where degassed solvents were used, a stream of Ar has been passed through them immediately prior to use. All stereogenic centres are relative, i.e. racemic products.

Solvents were of commercial grade and were used without further purification unless otherwise stated. In particular THF, and toluene were distilled from benzophenone ketal,[80] DCM was distilled from calcium hydride and petrol was also distilled from calcium hydride and the fraction boiling between 40 °C and 60 °C was used throughout. Diethyl ether was distilled from sodium.

Thin layer chromatography (T. L. C.) was performed on plastic backed sheets (Camlab) coated with silica gel (SiO_2 : 0.25mm) containing fluorescent indicator UV_{254}. Flash column chromatography was performed according to the procedure outlined by Still,[81] on Sorbil C_{60}, 40-60 mesh silica.

Methylenecyclopropane **1** was handled using the experimental methods as described by Thomas.[7]

II-Instrumentation

Infrared spectra were recorded on a Perkin-Elmer series FT-IR spectrometer. Sample films supported on sodium chloride plates.

Proton NMR spectra were obtained at 300 MHz on a Bruker AC 300, at 300 MHz on a Bruker AM 300 and at 400 MHz on a Bruker DPX or courtesy of SmithKline Beecham, Harlow. Samples were dissolved in the solvents stated and peak positions are quoted on the δ scale. Spectra were referenced with respect to the solvent peak for the deuterated solvent concerned, or to an internal standard of tetramethylsilane (δ = 0.00). The following

abbreviations are used : (s) singlet, (d) doublet, (t) triplet, (m) multiplet, (p) pentet, (q) quartet and (br) broad. Coupling constants are reported in hertz (Hz).

Carbon-13 were obtained at 75 MHz on a Bruker AC 300 and at 100 MHz on a Bruker DPX. The multiplicities of the signals were determined using the Distortionless Enhancement by Phase Transfer (DEPT) spectral editing techniques with second pulse at 135° and 90° or courtesy of SmithKline Beecham, Harlow.

COSY spectra and ^{1}H-^{13}C correlation spectra were performed on a Bruker AC 300 and on a Bruker DPX 400 and nOe data was recorded on the Bruker DPX 400.

Mass spectra were obtained on a VG analytical 70-250-SE normal geometry double focusing mass spectrometer. All EI data were acquired at 70 eV, with the source temperature at 200 °C and with an accelerating voltage of 6 kV. All CI data were obtained using ammonia reagent gas, the source temperature being 200 °C and with an emission current of 0.5mA or courtesy of SmithKline Beecham, Harlow.

X-ray diffraction data were obtained from an *Enraf Nonius KappaCCD* diffractometer, the structure determined by direct methods using the program *SHELXS97*[82] and refined using *SHELXL97*.[83]

EXPERIMENTAL FOR CHAPTER ONE

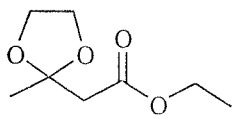
1

Methylenecyclopropane 1

Using a modification of the method of Binger,[84] methallyl chloride **5** (280 ml, 2.84 mol) was added dropwise over 9 hours to a rapidly stirred suspension of sodium amide (139 g, 3.56 mol) in dry *n*-Bu_2O (400 ml) at 130-140 °C under a slow stream of nitrogen. The reaction mixture was refluxed for a further 10 hours using a cold finger condenser at - 40 °C. The products were collected in vessels at - 78 °C. The upper layer of NH_3 was allowed to evaporate and the lower layer contained a mixture of methylenecyclopropane **1** and methylcyclopropene **6** (100 ml, 52%) in a 1 : 4.7 ratio.

The mixture was added to a solution of ^{t}BuOH (10 g, 0.13 mol) and DMSO (25 ml) at 0 °C under a slow stream of nitrogen, and ^{t}BuOK (8 g, 0.07 mol) in DMSO (25 ml) was added over 3 hours. The reaction was allowed to warm to 45 °C over 14 hours under a cold finger condenser at - 60 °C. The cold finger was allowed to warm to 35 °C over 6 hours. Methylenecyclopropane **1** (80 g, 100%) was trapped in vessels at - 78 °C δ_H (300 MHz; $CDCl_3$) 5.43 (2H, quintet, *J* 2, =CH_2) and 1.09 (4H, t, *J* 2, 2 x CH_2 cyclopropyl); δ_C (75 MHz; $CDCl_3$) 130.90 (0), 103.08 (2) and 2.69 (2 x 2).

All data agrees with data reported by Binger.[5b]



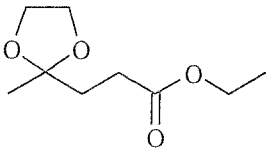
134

Ethyl-2-(2-methyl-dioxolanyl)-acetate 134

Following the method of Kelly *et al.*,[85] ethylene glycol (55 ml, 1 mol), ethylacetoacetate **132** (63 ml, 0.49 mol) and *p*-TsOH (1 g, 5 mmol) were refluxed together in toluene (200 ml) for 20 hours using a Dean Stark apparatus to remove water. The reaction mixture was cooled and concentrated *in vacuo*. Ether (200 ml) was added and washed once

with aq. $NaHCO_3$ (5%, 100 ml). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil which was distilled (98-106 °C/10 mm Hg ; lit.[86] bp. 99.5-101 °C/17-18 mm Hg) to give **134** as a colourless oil (63 g, 74%) δ_H (300 MHz; $CDCl_3$) 4.15 (2H, q, *J* 7, OCH_2CH_3), 3.89 (4H, s, $O(CH_2)_2O$), 2.60 (2H, s, CH_2COOEt), 1.45 (3H, s, CH_3) and 1.28 (3H, t, *J* 7, OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 169.46 (0), 107.64 (0), 64.80 (2 x 2), 60.51 (2), 44.23(2), 24.49 (2) and 14.20 (3).

All data agrees with data reported by Kelly *et al.*[85]

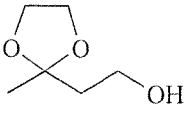


135

Ethyl-3-(2-methyl-1,3-dioxolan-2-yl)propanoate 135

Following the method of Kelly *et al.*,[85] ethylene glycol (8.7 g, 140 mmol), ethyl levulinate **133** (10 g, 69 mmol) and *p*-TsOH (0.13 g, 0.7 mmol) were refluxed together in toluene (70 ml) for 20 hours using a Dean Stark apparatus to remove water. The reaction mixture was cooled and concentrated *in vacuo*. Ether (50 ml) was added and washed once with aq. $NaHCO_3$ (5%, 50ml). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give **135** as a colourless oil (12.3 g, 95%) δ_H (300 MHz; $CDCl_3$) 4.12 (2H, q, *J* 7, OCH_2CH_3), 3.99-3.88 (4H, m, $O(CH_2)_2O$), 2.36 (2H, t, *J* 8, CH_2COOEt), 1.99 (2H, t, *J* 8, CH_2CH_2COOEt), 1.30 (3H, s, CH_3) and 1.23 (3H, t, *J* 7, OCH_2CH_3); δ_C (75 MHz; $CDCl_3$) 173.70 (0), 109.27 (0), 64.90 (2 x 2), 60.43 (2), 34.10 (2), 29.20 (2), 24.11 (3) and 14.34 (3).

All data agrees with data reported by Trivedi.[87]



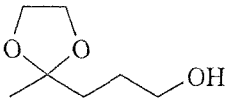
136

2-(2-Methyl-dioxolanyl)-hydroxyethyl 136

Following the method of Albizati *et al.*,[88] ester **134** (10 g, 57.5 mmol) was added dropwise to a suspension of $LiAlH_4$ (2.4 g, 63.2 mmol) in THF (300 ml) at 0 °C and stirred for 1 hour. Ether (200 ml) was added and the solution was stirred at 0 °C for 5 minutes.

NaOH (40 ml, 4 M) was added and the mixture stirred until a white heavy precipitate was observed. The mixture was filtered and washed with ether (300 ml) and concentrated *in vacuo* to give **136** as a colourless oil (7.6 g, 100%) R_f = 0.33 (50/50 ether/petrol); δ_H (300 MHz; $CDCl_3$) 3.97 (4H, s, $O(CH_2)_2O$), 3.76 (2H, t, *J* 5, CH_2OH), 2.80 (1H, br s, OH), 1.95 (2H, t, *J* 5, CH_2CH_2OH) and 1.36 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 110.50 (0), 64.64 (2 x 2), 58.98 (2), 40.44 (2) and 23.97 (3).

All data agrees with data reported by Albizati *et al.*[88]

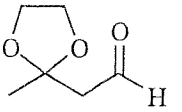


137

3-(2-Methyl-1,3-dioxolan-2-yl)-1-propanol 137

Following the method of Albizati *et al.*,[88] ester **135** (8.4 g, 44.8 mmol) was added dropwise to a suspension of $LiAlH_4$ (1.9 g, 49.3 mmol) in THF (70 ml) at 0 °C and stirred for 1 hour. Ether (50 ml) was added and the solution was stirred at 0 °C for 5 minutes. NaOH (10 ml, 4 M) was added and the mixture stirred until a white heavy precipitate was observed. The mixture was filtered and washed with ether (200 ml) and concentrated *in vacuo* to give **137** as a colourless oil (6.55 g, 100%) R_f = 0.08 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3418, 2953, 1450, 1378, 1254, 1144 and 1066; δ_H (300 MHz; $CDCl_3$) 3.97-3.92 (4H, m, $O(CH_2)_2O$), 3.63 (2H, t, *J* 6, CH_2OH), 2.45 (1H, s, OH), 1.81-1.59 (4H, m, CH_2CH_2OH and $CH_2(CH_2)_2OH$) and 1.32 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 110.13 (0), 64.75 (2 x 2), 63.01 (2), 35.90 (2), 27.27 (2) and 23.83 (3); m/z (EI+) 145 ($[M]^+$, 10%) and 131 (100%).

All data agrees with data reported by Joshi Navalkishore.[89]



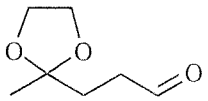
138

2-(2-Methyl-2-dioxolanyl)-ethanal 138

Following the method of Swern,[90] DMSO (22.8 ml, 290 mmol), in dichloromethane (50 ml), was added to a solution of oxalyl chloride (13.3 ml, 141 mmol), in dichloromethane (150 ml), keeping the mixture below - 50 °C. The mixture was stirred for 2 minutes at - 60

°C. Alcohol **136** (16.9 g, 128 mmol), in dichloromethane (150 ml), was then added within 5 minutes, again keeping the temperature below - 50 °C. The solution was stirred for 15 minutes and triethylamine (82.7 ml, 590 mmol) was added and stirred for 5 minutes. The solution was allowed to warm to room temperature. The mixture was quenched with water (500 ml) and extracted with dichloromethane (3 x 150 ml). The organic phase was dried over $MgSO_4$, concentrated *in vacuo* and distilled (54-56 °C/10 mm Hg) to give **138** as a colourless oil (10.17 g, 61%) R_f = 0.3 (50/50 ether/petrol); δ_H (300 MHz; $CDCl_3$) 9.75 (1H, t, *J* 2, CHO), 4.12-3.86 (4H, m, $O(CH_2)_2O$), 2.72 (2H, d, *J* 2, CH_2CHO) and 1.43 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 200.10 (1), 107.59 (0), 64.77 (2 x 2), 52.20 (2) and 24.89 (3).

All data agrees with data reported by Kelly *et al.*[85]

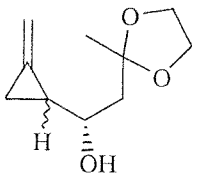


139

3-(2-Methyl-1,3-dioxolan-2-yl)propanal 139

Following the method of Swern,[90] DMSO (4.33 ml, 55.1 mmol), in dichloromethane (5 ml), was added to a solution of oxalyl chloride (2.5 ml, 26.4 mmol), in dichloromethane (50 ml), keeping the mixture below - 50 °C. The mixture was stirred for 2 minutes at - 60 °C. Alcohol **137** (3.5 g, 24 mmol), in dichloromethane (10 ml), was then added within 5 minutes, again keeping the temperature below - 50 °C. The solution was stirred for 15 minutes and triethylamine (15.5 ml, 110 mmol) was added and stirred for 5 minutes. The solution was allowed to warm to room temperature. The mixture was quenched with water (50 ml) and extracted with dichloromethane (3 x 50 ml). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/ether ; 100 to 60/40) to give **139** (2.4 g, 69%) as a colourless oil R_f = 0.41 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2885, 1719, 1376, 1054 and 900; δ_H (300 MHz; $CDCl_3$) 9.69 (1H, t, *J* 2, CHO), 4.05-3.81 (4H, m, $O(CH_2)_2O$), 2.45 (2H, dt, *J* 2 and 7, CH_2CHO), 2.05 (2H, t, *J* 7, CH_2CH_2CHO) and 1.31 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 202.06 (1), 109.23 (0), 61.87 (2 x 2), 38.59 (2), 31.96 (2) and 24.27 (3); m/z (CI) 145 ($[M + H]^+$, 17%) and 87 (100%).

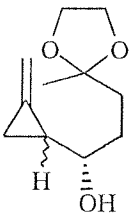
All data agrees with data reported by Siek *et al.*[91]



140

2-Methyl-[1'-[(2'-hydroxyethyl)-(1''-methylenecyclopropyl)]]-1,3-dioxolane 140

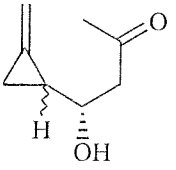
BuLi (5 ml of 2.01 M in hexane, 12.3 mmol) was added to methylenecyclopropane **1** (1 ml, 13.4 mmol) in THF (100 ml) at - 30 °C. The temperature was allowed to rise to 0 °C over 1 hour, and held at 0 °C for 1 hour. Then the solution was raised to room temperature for 10 minutes before cooling to - 78 °C. Aldehyde **138** (1.45 g, 11.2 mmol) in THF (50 ml) was then added to methylenecyclopropane anion via canula (the aldehyde was at - 78 °C). The solution was allowed to warm to - 20 °C. The reaction mixture was quenched with sat. NH_4Cl (50 ml) and extracted with ether (3 x 50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was then purified by flash column chromatography (ether/petrol : 0/100 to 40/60), to give **140** ***syn*** and **140** ***anti*** (1.26 g, 61%) as a colourless oil and as a 1 : 1 mixture of diastereoisomers (Found: C, 64.87; H, 8.87. $C_{10}H_{16}O_3$ requires C, 65.19; H, 8.75%); ν_{max} (film)/cm^{-1} 3475, 2984, 2884, 1380, 1256, 1220, 1109 and 1051; m/z (CI) 185 ($[M + H]^+$, 5%) and 167 ($[M - OH]^+$, 10%); the two diastereoisomers were separated by flash column chromatography eluting with petrol, gradually increasing the polarity to 15% ether-petrol to give **140** ***anti*** (0.63 g) R_f = 0.3 (50/50 ether/petrol); δ_H (300 MHz, $CDCl_3$) 5.53 (1H, s, C=CH_AH$_B$), 5.41 (1H, s, C=CH$_A$$H_B$), 3.97 (4H, s, O($CH_2$)$_2$O), 3.63-3.50 (2H, m, OH and C*H*OH), 2.08-1.91 (2H, m, CH_2CHOH), 1.64 (1H, m, C*H*C=CH_2), 1.34 (3H, s, CH_3), 1.18 (1H, m, CH_AH$_B$C=CH_2) and 0.96 (1H, m, CH$_A$$H_B$C=$CH_2$); δ_C (75 MHz, $CDCl_3$) 133.71 (0), 110.26 (0), 103.98 (2), 70.54 (1), 64.85 (2), 64.43 (2), 44.24 (2), 24.26 (3), 21.39 (1) and 6.81 (2); and **140** ***syn*** (0.63 g) R_f = 0.25 (50/50 ether/petrol); δ_H (300 MHz; $CDCl_3$) 5.39 (2H, s, fine coupling =CH_2), 3.97 (4H, s, O(CH_2)$_2$O), 3.63 (1H, br s, OH), 3.38 (1H, dt, *J* 8 and 4, C*H*OH), 2.01-1.93 (2H, m, CH_2CHOH), 1.62 (1H, m, C*H*C=CH_2), 1.33 (3H, s, CH_3), 1.25 (1H, m, CH_AH$_B$C=CH_2) and 1.08-1.02 (1H, m, CH$_A$$H_B$C=$CH_2$); δ_C (75 MHz; $CDCl_3$) 132.85 (0), 110.24 (0), 104.08 (2), 71.18 (1), 64.85 (2), 64.38 (2), 44.97 (1), 24.16 (3), 21.89 (1) and 8.60 (2).



141

3-(2-Methyl-1,3-dioxolan-2-yl)-1-(2-methylenecyclopropyl)-1-propanol 141

BuLi (6.8 ml of 2.26 M in hexane, 15.3 mmol) was added to methylenecyclopropane **1** (21.69 ml of 1 M in THF, 16.7 mmol) in THF (50 ml) at - 30 °C. The temperature was allowed to come to 0 °C over 30 mins, and held at 0 °C for 30 mins. Then the solution was raised to room temperature for 10 minutes before cooling to - 78 °C. Aldehyde **139** (2 g, 13.9 mmol) in THF (10 ml) was then added to methylenecyclopropyl anion at -78 °C *via* canula. The solution was allowed to warm to - 20 °C. The reaction mixture was quenched with aq. NH_4Cl (10 ml) and extracted with ether (3 x 50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/ether ; 100 to 50/50) to give **141** (1.86 g, 67%) as a colourless oil and as a 1 : 1 mixture of diastereoisomers R_f = 0.15 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3423, 2981, 1376, 1218, 1060 and 889; δ_H (300 MHz; $CDCl_3$) 5.51 (0.5 x 1H, s, =CH_AH$_B$), 5.40 (0.5 x 3H, s, =CH_2 and =C$H_A$$H_B$), 3.94 (4H, s, O$(CH_2)_2$O), 3.23 (0.5 x 1H, m, C*H*OH), 3.14 (0.5 x 1H, m, C*H*OH), 1.97-1.51 (6H, m, 2 x CH_2 and C*H*C=CH_2 and OH), 1.33 (3H, s, CH_3), 1.25 (1H, m, CH_AH$_B$C=CH_2) and 1.01 (1H, m, C$H_A$$H_B$C=$CH_2$); δ_C (75 MHz; $CDCl_3$) 133.26 (0), 132.90 (0), 109.98 (0), 104.07 (2), 103.98 (2), 100.11 (0), 74.14 (1), 70.05 (1), 64.63 (4 x 2), 35.25 (2), 35.11 (2), 31.39 (2), 31.32 (2), 23.76 (3), 23.71 (3), 22.40 (1), 21.74 (1), 7.74 (2) and 7.41 (2); m/z (CI) 181 ([M - H_2O]$^+$, 75%) and 87 (100%).

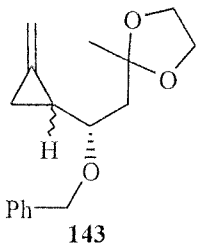


142

1'-(1-Methylenecyclopropyl)butan-3'-one-1'ol 142

2-Methyl-[1'-[(2'-hydroxyethyl)-(1''-methylenecyclopropyl)]]-1,3-dioxolane **140** (0.5 g, 2.71 mmol) was stirred with *p*-toluenesulfonic acid (0.13 g, 0.68 mmol) in a mixture of acetone (45 ml) and 10% water (5 ml) for 24 hours. The mixture was concentrated *in vacuo*.

Ether (50 ml) was added. The mixture was then washed once with 10% aq. $NaHCO_3$ (100 ml) and extracted with ether (3 x 75 ml). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give **142** as a colourless oil (0.11 g, 28%) and as a 1 : 1 mixture of diastereoisomers R_f = 0.13 (50/50 ether/petrol); (Found: C, 66.04; H, 8.70. $C_{10}H_{16}O_3$ requires C, 65.55; H, 8.63%); ν_{max} (film)/cm^{-1} 3410, 2889, 1710, 1362, 1072 and 893; δ_H (300 MHz; $CDCl_3$) 5.51 (0.5 x 1H, s, =CH_AH$_B$), 5.40 (0.5 x 3H, s, =CH_2 and =CH$_A$$H_B$), 3.73 (0.5 x 1H, ddd, *J* 8 and 8 and 4, C*H*OH), 3.53 (0.5 x 1H, m, C*H*OH), 3.05 (1H, br s, OH), 2.85 (1H, dd, *J* 16 and 7, CH_AH$_B$CHOH), 2.63 (1H, dd, *J* 16 and 4, CH$_A$$H_B$CHOH), 2.18 (3H, s, CH_3), 1.66 (1H, m, CHC=CH_2), 1.07 (1H, m, CH_AH$_B$C=CH_2) and 0.98 (1H, m, CH$_A$$H_B$C=$CH_2$); δ_C (75 MHz; $CDCl_3$) 209.46 (0), 209.29 (0), 132.84 (0), 132.38 (0), 104.47 (2), 70.56 (1), 69.95 (1), 49.87 (2), 49.24 (2), 30.95 (3), 30.88 (3), 21.16 (1), 20.71 (1), 8.77 (2) and 7.01 (2); m/z (CI) 158 ([M + NH_4^+]$^+$, 20%), 140 ([M]$^+$, 30%) and 123 ([M - OH]$^+$, 100%).



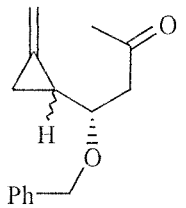
143

2-Methyl-[1'-[(2'-benzylethylether)-(1''-methylenecyclopropyl)]]-1,3-dioxolane 143

2-Methyl-[1'-[(2'-hydroxyethyl)-(1''-methylenecyclopropyl)]]-1,3-dioxolane **140** (0.36 g, 2 mmol) in THF (5 ml) was added to a suspension of sodium hydride (0.12 g, 4.8 mmol) in THF (15 ml) under N_2 at 0 °C. The mixture was allowed to warm to room temperature and stirred for 30 minutes. The solution was cooled to 0 °C and DMPU (0.62 g, 4.8 mmol) was then added and stirred for 10 minutes. Benzyl bromide (1.3 g, 7.6 mmol) was added and the mixture was allowed to warm to room temperature overnight. The solution was quenched with a 2 M solution NaOH (20 ml) and the aqueous phase was extracted with ether (3 x 50 ml). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The mixture was then purified by flash column chromatography (petrol/ether ; 100/0 to 50/50) to give **143** as a colourless oil (0.50 g, 91%) and as a 1 : 1 mixture of diastereoisomers R_f = 0.71 (50/50 Petrol/ether); ν_{max} (film)/cm^{-1} 3030, 2983, 2879, 1454, 1376, 1106, 1057 and 697; δ_H (300 MHz; $CDCl_3$) 7.45-7.23 (5H, m, Ar*H*), 5.60-5.41 (2H, m, =CH_2), 4.85 + 4.79 (1H, d, *J* 11, OCH_AH$_B$Bz), 4.57 + 4.48 (1H, d, *J* 11, OCH$_A$$H_B$Bz), 4.06-3.85 (4H, m, O(CH_2)$_2$O), 3.24

(1H, m, C*H*OCH$_2$Bz), 2.14-1.93 (2H, m, C*H*$_2$CHOCH$_2$Bz), 1.66 (1H, m, cyclopropyl CH), 1.48-1.36 (0.5 x 1H, m, cyclopropyl CH), 1.43 (0.5 x 3H, s, CH$_3$), 1.41 (0.5 x 3H, s, CH$_3$), 1.15 (0.5 x 1H, m, cyclopropyl CH) and 0.90 (0.5 x 1H, m, cyclopropyl CH); δ_C (75 MHz; CDCl$_3$) 139.06 (0), 135.11 (0), 132.14 (0), 128.44 (2 x 1), 127.89 (1), 127.81 (1), 127.52 (1), 109.39 (0), 104.49 (2), 104.34 (2), 79.03 (2), 78.62 (1), 71.25 (2), 71.12 (2), 64.57 (2 x 2), 64.49 (2 x 2), 44.41 (2), 44.08 (2), 24.82 (3), 24.66 (3), 21.01 (1), 20.55 (1), 10.11 (2) and 6.92 (2); m/z (CI) 275 ([M + H]$^+$, 10%) and 167 ([M - OC$_7$H$_7$]$^+$, 30%).

All data agrees with data reported by Boffey.[26]

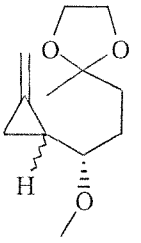


145

Benzyl(1-methylenecyclopropylbutyl-3-one)ether 145

2-Methyl-[1'-[(2'-benzylethylether)-(1''-methylenecyclopropyl)]]-1,3-dioxolane **143** (0.18 g, 0.66 mmol) was stirred with *p*-toluenesulfonic acid (0.15 g, 0.79 mmol) in a mixture of acetone (18 ml) and 10% water (2 ml) for 2 days. The mixture was concentrated *in vacuo*. Ether (50 ml) was added. The mixture was then washed once with 10% solution NaHCO$_3$ (20 ml) and extracted with ether (3 x 30 ml). The organic phase was dried over MgSO$_4$ and concentrated *in vacuo* to give **145** as a colourless oil (0.15 g, 100 %) and as a 1 : 1 mixture of diastereoisomers R_f = 0.68 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3065, 2990, 2870, 1717, 1358, 1073, 893 and 738; δ_H (300 MHz; CDCl$_3$) 7.45-7.23 (5H, m, Ar*H*), 5.60-5.41 (2H, m, =CH$_2$), 4.86 + 4.76 (1H, d, *J* 8, OC*H*$_2$Bz), 4.54 + 4.45 (1H, d, *J* 11, OC*H*$_2$Bz), 3.55 (1H, ddd, *J* 9 and 9 and 4, C*H*OCH$_2$Bz), 2.89 (1H, dd, *J* 15 and 9, C*H*$_A$H$_B$CHOCH$_2$Bz), 2.63 (0.5H, dd, *J* 15 and 4, CH$_A$*H*$_B$CHOCH$_2$Bz), 2.58 (0.5H, dd, *J* 15 and 4, CH$_A$*H*$_B$CHOCH$_2$Bz), 2.18 (3H, s, CH$_3$), 1.65 (1H, m, CH cyclopropyl), 1.45 (0.5H, m, CH cyclopropyl), 1.32 (0.5H, m, CH cyclopropyl), 1.14 (0.5H, m, CH cyclopropyl) and 0.93 (0.5H, m, CH cyclopropyl); δ_C (75 MHz; CDCl$_3$) 207.34 (0), 207.11 (0), 138.62 (0), 133.91 (0), 131.21 (0), 128.50 (2 x 1), 127.90 (1), 127.86 (1), 127.72 (1), 127.57 (1) 104.96 (2), 104.82 (2), 78.36 (1), 78.10 (1), 71.80 (2), 71.60 (2), 49.69 (2), 48.87 (2), 31.33 (3), 31.26 (3), 19.77 (1), 19.62 (1), 10.05 (2)

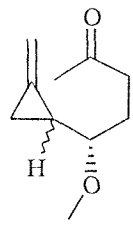
and 6.74 (2); m/z (CI) 229.1194 ($[M - H]^+$. $C_{15}H_{17}O_2$ requires 229.1229), 248 ($[M + NH_4^+]^+$, 100%) and 231 ($[M + H]^+$, 70%).



144

2-[3-Methoxy-3-(2-methylenecyclopropyl)propyl]-2-methyl-1,3-dioxolane 144

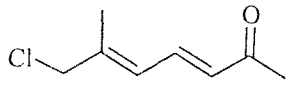
3-(2-Methyl-1,3-dioxolan-2-yl)-1-(2-methylenecyclopropyl)-1-propanol **141** (0.55 g, 2.78 mmol) in THF (5 ml) was added to a suspension of sodium hydride (0.17 g, 7.27 mmol) in THF (20 ml) under N_2 at 0 °C. The mixture was allowed to come to room temperature and stirred for 30 minutes. The solution was cooled again to 0 °C. DMPU (0.88 ml, 7.27 mmol) was added and stirred for 10 minutes. Methyl iodide (0.72 g, 11.5 mmol) was added and the mixture was allowed to warm to room temperature. The solution was stirred overnight and quenched with a 2 M solution of NaOH (10 ml). The aqueous phase was extracted with ether (3 x 50 ml). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The mixture was then purified by flash column chromatography (petrol/ether ; 100/0 to 80/20) to give **144** as a colourless oil (0.55 g, 95%) and as a 1 : 1 mixture of inseparable diastereoisomers R_f = 0.52 (50/50 Petrol/ether); ν_{max} (film)/cm^{-1} 2878, 1375, 1218, 1064 and 888; δ_H (300 MHz; $CDCl_3$) 5.43 (2H, s, $=CH_2$), 3.93 (4H, s, $O(CH_2)_2O$), 3.40 (0.5 x 3H, s, CH_3O), 3.37 (0.5 x 3H, s, CH_3O), 2.69 (1H, m, $CHOCH_3$), 1.97-1.59 (4H, m, 2 x CH_2), 1.49 (1H, m, $CHC{=}CH_2$), 1.31 (3H, s, CH_3), 1.08 (1H, m, $CH_AH_BC{=}CH_2$) and 0.83 (1H, m, $CH_AH_BC{=}CH_2$); δ_C (75 MHz; $CDCl_3$) 134.25 (0), 131.99 (0), 110.05 (0), 104.27 (2), 104.07 (2), 100.11 (0), 83.42 (3), 83.20 (3), 64.61 (4 x 2), 56.87 (1), 56.78 (1), 34.96 (2), 34.49 (2), 29.34 (2), 29.28 (2), 23.80 (3), 19.586 (1), 19.51 (1), 9.48 (2) and 6.59 (2); m/z (EI+) 212.1418 (M^+. $C_{12}H_{20}O_3$ requires 212.1412), m/z (CI) 213 ($[M + H]^+$, 6%) and 87 (100%).



146

5-Methoxy-5-(2-methylenecyclopropyl)-2-pentanone 146

2-[3-Methoxy-3-(2-methylenecyclopropyl)propyl]-2-methyl-1,3-dioxolane **144** (0.37 g, 1.74 mmol) was stirred with *p*-toluenesulfonic acid (0.33 g, 1.74 mmol) in a mixture of acetone (90 ml) and 10% water (10 ml) for 24 hours. The mixture was concentrated *in vacuo*. Ether (50 ml) was added. The mixture was then washed once with 10% aq. $NaHCO_3$ (100 ml) and extracted with ether (3 x 75 ml). The organic phase was dried over $MgSO_4$, concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/ether ; 100/0 to 80/20) to give **146** as a colourless oil (0.19 g, 65%) and as a 1 : 1 mixture of inseparable diastereoisomers R_f = 0.48 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2929, 1714, 1357, 1090 and 886; δ_H (300 MHz; $CDCl_3$) 5.43 (2H, s, $=CH_2$), 3.39 (0.5 x 3H, s, CH_3O), 3.36 (0.5 x 3H, s, CH_3O), 2.71-2.44 (3H, m, $CHOCH_3$ and CH_2CO), 2.13 (3H, s, CH_3), 2.01-1.71 (5H, m, $CHC{=}CH_2$ and 2 x CH_2), 1.47 (1H, m, $CH_AH_BC{=}CH_2$) and 0.83 (1H, m, $CH_AH_BC{=}CH_2$); δ_C (75 MHz; $CDCl_3$) 209.06 (0), 134.24 (0), 131.48 (0), 104.72 (2), 104.43 (2), 82.78 (3), 82.60 (3), 57.05 (1), 39.82 (2), 39.64 (2), 30.13 (3), 29.08 (2), 28.96 (2), 19.47 (1), 19.29 (1), 9.84 (2) and 6.54 (2); m/z (EI+) 168.1151 (M^+. $C_{10}H_{16}O_2$ requires 168.1150), m/z (CI) 169 ($[M + H]^+$, 19%) and 137 (100%).

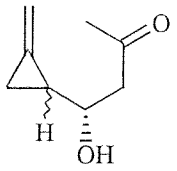


147

(*3E*, *5E*)-7-Chloro-6-methyl-3,5-heptadien-2-one 147

$TiCl_4$ (0.72 ml of 1 M in DCM, 0.72 mmol) was added to 1'-(1-methylenecyclopropyl)butan-3'-one-1'ol **142** (0.1 g, 0.71 mmol) in dichloromethane (20 ml), at - 78 °C under Ar. The solution was stirred for two hours. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100

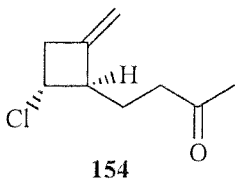
to 60/40) to give diene **147** (0.011g, 20%) as a pale yellow oil R_f = 0.51 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2974, 1712, 1356, 1255, 1087, 909 and 804; δ_H (300 MHz; $CDCl_3$) 7.26 (1H, dd, *J* 10 and 14, C*H*=CHCOCH$_3$), 6.22 (1H, d, *J* 10, C*H*=C(CH$_3$)CH$_2$Cl), 6.11 (1H, d, *J* 14, =C*H*COCH$_3$), 4.02 (2H, s, C*H*$_2$Cl), 2.21 (3H, s, C*H*$_3$CO) and 1.94 (3H, s, C*H*$_3$C=); δ_C (75 MHz; $CDCl_3$) 199.21 (0), 143.7 (0), 137.89 (1), 131.62 (1), 127.33 (1), 50.91 (2), 27.97 (3) and 15.71 (3); m/z (CI) 176 ([M + NH_4^+]$^+$, 11%), 159 ([M + H]$^+$, 60%), 125 ([M - Cl]$^+$, 100%).



142

1'-(1-Methylenecyclopropyl)butan-3'-one-1'ol 142

$TiCl_4$ (0.08 ml, 0.73 mmol) was added to benzyl(1-methylenecyclopropylbutyl-3-one)ether **145** (0.16 g, 0.69 mmol) in dichloromethane (10 ml), at - 78 °C under Ar. The solution was stirred for two hours. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100 to 60/40) to give ketone **142** (0.065 g, 67%) as a colourless oil and as a 1 : 1 mixture of diastereoisomer.

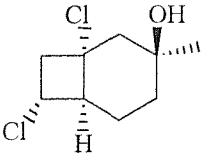


154

***(2R,4R)*-4-(2-Chloro-4-methylenecyclobutyl)-2-butanone 154**

$SnCl_4$ (0.038 ml, 0.33 mmol) was added to 5-methoxy-5-(2-methylene cyclopropyl)-2-pentanone **146** (0.05 g, 0.29 mmol), in dichloromethane (10 ml), at - 78 °C under Ar. The solution was allowed to come to room temperature overnight. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated

in vacuo. The crude mixture was purified by flash column chromatography (petrol/ether ; 100/0 to 90/10) to give ketone **154** (0.035 g, 68%) as a pale yellow oil and as a single diastereoisomer R_f = 0.64 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2925, 1714, 1357, 1160 and 880; δ_H (300 MHz; $CDCl_3$) 4.84 (2H, s, $=CH_2$), 3.90 (1H, m, CHCl), 3.12-3.01 (2H, m, CH_2CH_2CH), 2.86 (1H, m, $CHCH_2$), 2.57 (2H, t, *J* 8, CH_2CO), 2.17 (3H, s, CH_3), 1.96 (1H, m, CH_AH_B cyclobutyl) and 1.71 (1H, m, CH_AH_B cyclobutyl); δ_C (75 MHz; $CDCl_3$) 208.16 (0), 144.87 (0), 105.65 (2), 56.27 (1), 52.87 (1), 42.24 (2), 40.09 (2), 30.27 (3) and 25.21 (2); m/z (EI+) 172.0651 (M^+. $C_9H_{13}ClO$ requires 172.0655), m/z (CI) 173 ($[M + H]^+$, 12%) and 43 (100%).



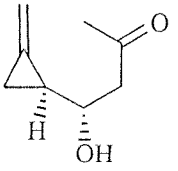
153

(*1S,3R,6S,7R*)-1,7-Dichloro-3-methylbicyclo[4.2.0]octan-3-ol 153

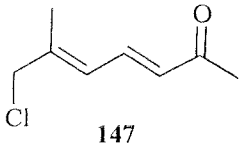
$TiCl_4$ (0.33 ml of 1 M in DCM, 0.33 mmol) was added to 5-methoxy-5-(2-methylenecyclopropyl)-2-pentanone **146** (0.05 g, 0.30 mmol) in dichloromethane (10 ml), at -78 °C under Ar. The solution was allowed to come to room temperature and stirred overnight. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100 to 60/40) to give bicycle **153** (0.022 g, 36%) as a pale yellow crystalline solid and as a single diastereoisomer, which was recrystallised from ethanol-water.

Alternatively, $TiCl_4$ (0.083 ml of 1 M in DCM, 0.083 mmol) was added to 4-(2-chloro-4-methylenecyclobutyl)-2-butanone **154** (0.013 g, 0.075 mmol) in dichloromethane (10 ml), at - 78 °C under Ar. The solution was allowed to come to room temperature and stirred overnight. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100 to 60/40) to give bicycle **153** (0.003 g, 19%) as a pale yellow crystalline and as a single diastereoisomer R_f = 0.17 (50/50

ether/petrol); ν_{max} (film)/cm^{-1} 3367, 2935, 1707, 1378, 1204, 1122 and 914; δ_H (300 MHz; $CDCl_3$) 3.97 (1H, m, CHCl), 2.96 (1H, m, C*H*CH_2CH_2), 2.86 (1H, dd, *J* 8 and 11, CHClC*H*$_A$H$_B$CCl), 2.64 (1H, dd, *J* 8 and 11, CHClCH$_A$*H*$_B$CCl), 2.30 (1H, d, *J* 14, CClC*H*$_A$H$_B$COH), 1.92-1.71 (3H, m, CClCH$_A$*H*$_B$COH and C*H*$_2$CH$_2$C(OH)), 1.70-1.48 (3H, m, C(OH)C*H*$_2$CH$_2$ and OH) and 1.37 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 69.82 (0), 59.65 (0), 55.83 (1), 50.96 (2), 50.84 (2), 47.62 (1), 34.94 (2), 26.52 (3) and 21.09 (2); m/z (EI+) 208.0416 (M^+. $C_9H_{14}Cl_2O$ requires 208.0422), 208 ($[M]^+$, 5%) and 35 (100%); structure and stereochemistry confirmed by X-ray diffraction.



142 *syn*

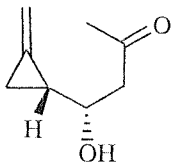


147

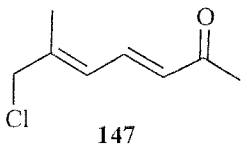
1'-(1-Methylenecyclopropyl)butan-3'-one-1'ol 142 ***syn***

(3E, 5E)-7-Chloro-6-methyl-3,5-heptadien-2-one 147

$TiCl_4$ (0.041 ml, 0.37 mmol) was added to 2-methyl-[1'-[(2'-hydroxyethyl)-(1''-methylenecyclopropyl)]]-1,3-dioxolane **140** *syn* (0.065 g, 0.35 mmol) in dichloromethane (10 ml), at - 78 °C under Ar. The solution was stirred for two hours. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100 to 60/40) to give ketone **142** *syn* (0.018 g, 30%) as a colourless oil and diene **147** (0.019 g, 20%) as a pale yellow oil.



142 *anti*

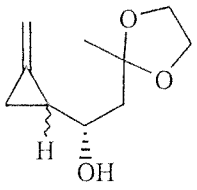


147

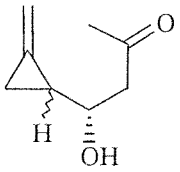
1'-(1-Methylenecyclopropyl)butan-3'-one-1'ol 142 ***anti***

(3E, 5E)-7-Chloro-6-methyl-3,5-heptadien-2-one 147

$TiCl_4$ (0.041 ml, 0.37 mmol) was added to 2-methyl-[1'-[(2'-hydroxyethyl)-(1''-methylenecyclopropyl)]]-1,3-dioxolane **140** *anti* (0.065 g, 0.35 mmol) in dichloromethane (10 ml), at - 78 °C under Ar. The solution was stirred for two hours. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100 to 60/40) to give ketone **142** *anti* (0.018 g, 30%) as a colourless oil and diene **147** (0.019 g, 20%) as a pale yellow oil.



140

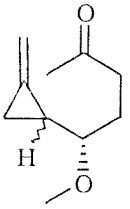


142

2-Methyl-[1'-[(2'-hydroxyethyl)-(1''-methylenecyclopropyl)]]-1,3-dioxolane 140

1'-(1-Methylenecyclopropyl)butan-3'-one-1'ol 142

$TiCl_4$ (0. 05 ml, 0.41 mmol) was added to 2-methyl-[1'-[(2'-benzylethylether)-(1''-methylenecyclopropyl)]]-1,3-dioxolane **143** (0.11 g, 0.39 mmol) in dichloromethane (10 ml), at - 78 °C under Ar. The solution was stirred for two hours. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100 to 60/40) to give ketal **140** (0.015 g, 21%) as a colourless oil and as a 1 : 1 mixture of diastereoisomers and ketone **142** (0.020 g, 37%) as a colourless oil and as a 1 : 1 mixture of diastereoisomers.

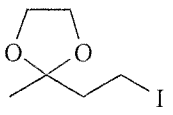


146

5-Methoxy-5-(2-methylenecyclopropyl)-2-pentanone 146

2-[3-Methoxy-3-(2-methylenecyclopropyl)propyl]-2-methyl-1,3-dioxolane **144** (0.05 g, 0.23 mmol) in dichloromethane (5 ml) was added over 45 mins, using syringe pump, to a solution of $SnCl_4$ (0.055 ml, 0.47 mmol) in dichloromethane (10 ml) at - 78 °C under Ar. The solution was stirred for 1 hour at - 78 °C. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100/0 to 80/20) to give ketone **146** (0.028 g, 71%) as a colourless oil and as a 1 : 1 mixture of inseparable diastereoisomer;

2-[3-Methoxy-3-(2-methylenecyclopropyl)propyl]-2-methyl-1,3-dioxolane **144** (0.05 g, 0.23 mmol) in dichloromethane (5 ml) was added over 45 mins, using syringe pump, to a solution of $TiCl_4$ (0.47 ml of 1 M in DCM, 0.47 mmol) in dichloromethane (10 ml) at - 78 °C under Ar. The solution was stirred for 1 hour at - 78 °C. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100/0 to 80/20) to give ketone **146** (0.022 g, 55%) as a colourless oil and as a 1 : 1 mixture of inseparable diastereoisomer.



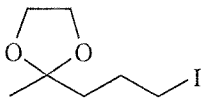
170

2-(2-Methyl-dioxolanyl)-iodoethane 170

Following the method of Motherwell,[17b] triphenylphosphine (8.9 g, 34.1 mmol), imidazole (2.63 g, 38.6 mmol) and finally iodine (9.23 g, 36.3 mmol) were added to a stirred solution of alcohol **136** (3 g, 22.7 mmol) in ether (60 ml) and acetonitrile (20 ml). The solution was stirred for 15 minutes. The resulting red solution was diluted in ether (100 ml),

washed with aq. $Na_2S_2O_3$ (5%, 100 ml), then water (50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with petrol (5 x 20 ml), filtered, concentrated *in vacuo* and purified by flash column chromatography (ether/petrol ; 0/100 to 10/90) to give **170** (4.99 g, 91%) R_f = 0.58 (50/50 ether/petrol); δ_H (300 MHz; $CDCl_3$) 3.99-3.87 (4H, m, $O(CH_2)_2O$), 3.15 (2H, t, *J* 8, CH_2I), 2.29 (2H, t, *J* 8, CH_2CH_2I) and 1.30 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 109.94 (0), 65.01 (2 x 2), 44.42 (2), 23.94 (3) and -2.12 (2); m/z (CI) 243 ($[M + H]^+$, 25%) and 87 (100%).

All data agrees with data reported by Trost.[92]

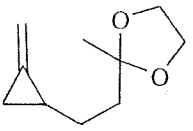


171

2-(3-Iodopropyl)-2-methyl-1,3-dioxolane 171

Following the method of Motherwell,[17b] triphenylphosphine (2.69 g, 10.3 mmol), imidazole (0.79 g, 11.6 mmol) and finally iodine (2.78 g, 10.9 mmol) were added to a stirred solution of 3-(2-methyl-1,3-dioxolan-2-yl)-1-propanol **137** (1 g, 6.85 mmol) in ether (60 ml) and acetonitrile (20 ml). The solution was stirred for 15 minutes. The resulting red solution was diluted in ether (100 ml), washed with aq. $Na_2S_2O_3$ (5%, 100 ml), then water (50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with petrol (5 x 20 ml), filtered, concentrated *in vacuo* and purified by flash column chromatography (ether/petrol ; 0/100 to 10/90) to give **171** (1.71 g, 98%) R_f = 0.60 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2879, 1448, 1376, 1252, 1044 and 862; δ_H (300 MHz; $CDCl_3$) 4.01-3.90 (4H, m, $O(CH_2)_2O$), 3.21 (2H, t, *J* 7, CH_2I), 2.00-1.91 (2H, m, $CH_2CH_2CH_2I$), 1.78 (2H, t, *J* 7, $CH_2(CH_2)_2I$) and 1.32 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 109.53 (0), 64.85 (2 x 2), 39.99 (2), 28.40 (2), 24.15 (3) and 7.22 (2); m/z (CI) 257 ([M + H]+, 27%) and 87 (100%).

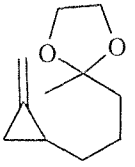
All data agrees with data reported by Ahlberg.[93]



172

2-Methyl-[(2'-ethyl)-(1''-methylenecyclopropyl)]-1,3-dioxolane 172

BuLi (4 ml of 2.01 M in hexane, 7.94 mmol) was added to methylenecyclopropane **1** (15.9 ml of 1 M in THF, 15.9 mmol) in THF (30 ml) at - 30 °C, and allowed to warm to 0 °C over 30 minutes. The reaction mixture was cooled to - 60 °C and HMPA (2.14 ml, 11.9 mmol) was added followed immediately by the dropwise addition of iodide **170** (1.5 g, 6.2 mmol). The reaction mixture was allowed to come to room temperature overnight. The reaction was quenched with saturated aq. NH_4Cl (40 ml) and extracted with ether (3 x 150 ml). The combined organic phases were washed once with brine (100 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/ether ; 100/0 to 70/30) to give **172** (1.38 g, 92%) as a colourless oil R_f = 0.72 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3068, 3066, 2982, 1744, 1717, 1454, 1376, 1221, 1132, 1065, 947, 889 and 859; δ_H (300 MHz; $CDCl_3$) 5.39 (1H, s, =CH_AH$_B$), 5.32 (1H, s, =CH$_A$$H_B$), 3.97-3.86 (4H, m, O($CH_2$)$_2$O), 1.81-1.71 (2H, m, C$H_2$CO($CH_2$)$_2$O), 1.49-1.35 (3H, m, C$H_2$ and CH cyclopropyl), 1.29 (3H, s, CH_3), 1.19 (1H, m, CH_AH$_B$ cyclopropyl) and 0.72 (1H, m, CH$_A$$H_B$ cyclopropyl); δ_C (75 MHz; $CDCl_3$) 136.97 (0), 109.96 (0), 102.71 (2), 64.76 (2 x2), 38.84 (2), 27.69 (2), 23.96 (3), 15.71 (1) and 9.50 (2); m/z (EI+) 168.1154 (M^+. $C_{10}H_{16}O_2$ requires 168.1150), m/z (CI) 169 ($[M + H]^+$, 14%) and 87 (100%).

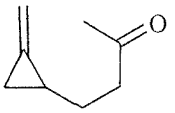


173

2-Methyl-2-[3-(2-methylenecyclopropyl)propyl]-1,3-dioxolane 173

BuLi (4.19 ml of 2.04 M in hexane, 8.55 mmol) was added to methylenecyclopropane **1** (1.15 ml, 17.1 mmol) in THF (50 ml) at - 30 °C, and allowed to warm to 0 °C over 30 minutes. The reaction mixture was cooled to - 60 °C and HMPA (2.3 ml, 12.8 mmol) was added followed immediately by the dropwise addition of 2-(3-iodopropyl)-2-methyl-1,3-dioxolane **171**. The reaction was allowed to come to room temperature overnight. The

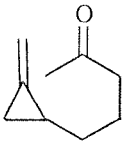
reaction mixture was quenched with saturated aq. NH_4Cl (20 ml) and extracted with ether (3 x 100 ml). The combined organic phases were washed once with brine (100 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/ether ; 100/0 to 90/10) to give **173** (1.12 g, 88%) as a colourless oil R_f = 0.66 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3067, 3042, 2943, 1745, 1461, 1376, 1312, 1252, 1136, 1069, 947 and 885; δ_H (300 MHz; $CDCl_3$) 5.39 (1H, s, =C*H*$_A$H$_B$), 5.33 (1H, s, =CH$_A$*H*$_B$), 3.97-3.89 (4H, m, O(CH$_2$)$_2$O), 1.70-1.34 (7H, m, 3 x CH_2 and C*H*(CH$_2$)$_3$), 1.32 (3H, s, CH_3), 1.21 (1H, m, C*H*$_A$H$_B$ cyclopropyl) and 0.73 (1H, m, CH$_A$*H*$_B$ cyclopropyl); δ_C (75 MHz; $CDCl_3$) 137.12 (0), 110.26 (0), 102.61 (2), 64.77 (2 x 2), 39.02 (2), 33.40 (2), 24.10 (2), 23.90 (3), 15.81 (1) and 9.57 (2); m/z (EI+) 182.1305 (M^+. $C_{11}H_{18}O_2$ requires 182.1307), m/z (CI) 183 ($[M + H]^+$, 7%) and 87 (100%).



166

4-Methylenecyclopropylbutan-2-one 166

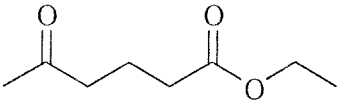
2-Methyl-[(2'-ethyl)-(1''-methylenecyclopropyl)]-1,3-dioxolane **172** (1.17 g, 6.96 mmol) was stirred with *p*-toluenesulfonic acid (2.65 g, 13.9 mmol) in a mixture of acetone (90 ml) and 10% water (10 ml) for 48 hours. The mixture was concentrated *in vacuo*. Ether (50 ml) was added. The mixture was then washed once with 10% $NaHCO_3$ (100 ml) and extracted with ether (3 x 75 ml). The organic phase was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (petrol/ether ; 100/0 to 80/20) to give **166** as a colourless oil (0.67 g, 78%) R_f = 0.59 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2974, 2342, 1717, 1409, 1365 and 1152; δ_H (300 MHz; $CDCl_3$) 5.39 (1H, s, =C*H*$_A$H$_B$), 5.34 (1H, s, =CH$_A$*H*$_B$), 2.53 (2H, t, *J* 8, C*H*$_2$CO), 2.15 (3H, s, CH_3), 1.75-1.51 (2H, m, C*H*$_2$CH$_2$CO), 1.42 (1H, m, CH cyclopropyl), 1.21 (1H, m, C*H*$_A$H$_B$ cyclopropyl), and 0.74 (1H, m, CH$_A$*H*$_B$ cyclopropyl); δ_C (75 MHz; $CDCl_3$) 208.87 (0), 136.23 (0), 103.16 (2), 43.34 (2), 30.11 (2), 27.29 (3), 15.04 (1) and 9.47 (2); m/z (CI) 125.0957 ($[M + H]^+$. $C_8H_{13}O$ requires 125.0966), 142 ($[M + NH_4^+]^+$, 8%), 125 ($[M + H]^+$, 25%) and 42 (100%).



167

5-(2-Methylenecyclopropyl)-2-pentanone 167

2-Methyl-2-[3-(2-methylenecyclopropyl)propyl]-1,3-dioxolane **173** (0.99 g, 5.44 mmol) was stirred with *p*-toluenesulfonic acid (2 g, 10.9 mmol) in a mixture of acetone (180 ml) and 10% water (20 ml) for 24 hours. The mixture was concentrated *in vacuo*. Ether (50 ml) was added. The mixture was then washed once with 10% $NaHCO_3$ (100 ml) and extracted with ether (3 x 75 ml). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/ether ; 100/0 to 90/10) to give **167** as a colourless oil (0.49 g, 65%) R_f = 0.58 (40/60 ether/petrol); ν_{max} (film)/cm^{-1} 3068, 3044, 2974, 1715, 1409, 1360, 1226, 1163 and 890; δ_H (300 MHz; $CDCl_3$) 5.37 (1H, s, $=CH_AH_B$), 5.31 (1H, s, $=CH_AH_B$), 2.44 (2H, t, *J* 8 Hz, CH_2CO), 2.12 (3H, s, CH_3), 1.76-1.62 (2H, m, $CH_2CH_2COCH_3$), 1.42-1.29 (3H, m, $CH_2(CH_2)_2COCH_3$ and $CHC=CH_2$), 1.23 (1H, m, $CH_AH_BC=CH_2$) and 0.73 (1H, m, $CH_AH_BC=CH_2$); δ_C (75 MHz; $CDCl_3$) 209.19 (0), 136.72 (0), 102.83 (2), 43.47 (2), 32.62 (2), 30.03 (3), 23.76 (2), 15.50 (1) and 9.54 (2); m/z (CI) 138.1043 (M^+. $C_9H_{14}O$ requires 138.1047), 119 ($[M - H_2O]^+$, 25%) and 95 (100%).

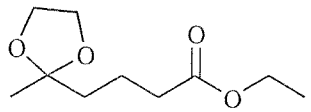


175

Ethyl-5-oxohexanoate 175

Following the method of Rychnovsky *et al.*[94], ethanol (50 ml), 4-acetylbutyric acid **174** (7 g, 69.3 mmol) and 3 drops of concentrated sulfuric acid in toluene (100 ml) were refluxed together for 8 hrs using a Dean-Stark apparatus to remove water. The reaction mixture was then cooled, concentrated *in vacuo* and distilled under reduced pressure (bp. 78-80 °C/0.5 mm Hg) to give ester **175** (7.86g, 72%) as a colourless oil δ_H (300 MHz; $CDCl_3$) 4.10 (2H, q, *J* 7, OCH_2CH_3), 2.49 (2H, t, *J* 7, CH_2CO), 2.30 (2H, t, *J* 7, CH_3COCH_2), 2.12 (3H, s, CH_3), 1.87 (2H, p, *J* 7, $CH_2CH_2CH_2$) and 1.23 (3H, t, *J* 7, CH_3CH_2O); δ_C (75 MHz; $CDCl_3$) 208.17 (0), 173.28 (0), 60.47 (2), 42.59 (2), 33.35 (2), 30.06 (3), 18.99 (2) and 14.35 (3).

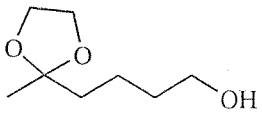
All data agrees with data reported by Rychnovsky.[94]



176

Ethyl-4-(2-methyl-1,3-dioxolan-2-yl)butanoate 176

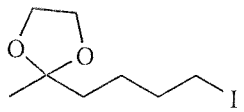
Following the method of Kelly *et al.*,[85] ethylene glycol (6.13 g, 98.7 mmol), ethyl-5-oxohexanoate **175** (7.8 g, 49.4 mmol) and *p*-TsOH (0.1 g, 0.49 mmol) were refluxed together in toluene (100 ml) for 20 hours using a Dean Stark apparatus to remove water. The reaction mixture was cooled and concentrated *in vacuo*. Ether (50 ml) was added and washed once with aq. $NaHCO_3$ (5%, 50 ml). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was distilled under reduced pressure (bp. 92-96 °C/0.5 mm Hg) to give ester **176** (8.34 g, 84%) as a colourless oil δ_H (300 MHz; $CDCl_3$) 4.11 (2H, q, *J* 7, OCH_2CH_3), 3.98-3.84 (4H, m, $O(CH_2)_2O$), 2.31 (2H, t, *J* 7, CH_2CO_2Et), 1.81-1.58 (4H, m, 2 x CH_2), 1.31 (3H, s, CH_3) and 1.24 (3H, t, *J* 7, CH_3CH_2O); δ_C (75 MHz; $CDCl_3$) 173.65 (0), 109.87 (0), 64.77 (2 x 2), 60.35 (2), 38.46 (2), 34.42 (2), 23.90 (3), 19.72 (2) and 14.38 (3).
All data agrees with data reported by Rychnovsky.[94]



177

4-(2-Methyl-1,3-dioxolan-2-yl)-1-butanol 177

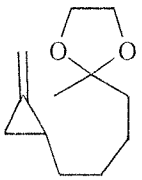
Following the method of Albizati *et al.*,[88] ethyl-4-(2-methyl-1,3-dioxolan-2-yl)butanoate **176** (8 g, 39.6 mmol) was added dropwise to a suspension of $LiAlH_4$ (1.65 g, 43.5 mmol) in THF (60 ml) at 0 °C and stirred for 1 hour. Ether (40 ml) was added and the solution was stirred at 0 °C for 5 minutes. NaOH (15 ml, 4 M) was added and the mixture stirred until a white heavy precipitate was observed. The mixture was filtered and washed with ether (200 ml) and concentrated *in vacuo* to give **177** as a colourless oil (6.34 g, 100%) R_f = 0.07 (50/50 ether/petrol); δ_H (300 MHz; $CDCl_3$) 3.96-3.86 (4H, m, $O(CH_2)_2O$), 3.61 (2H, t, *J* 7, CH_2OH), 2.05 (1H, br s, OH), 1.71-1.48 (6H, m, 3 x CH_2) and 1.29 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 110.18 (0), 64.75 (2 x 2), 62.72 (2), 38.95 (2), 32.91 (2), 23.87 (3) and 20.35 (2).
All data agreed with data reported by Rychnovsky.[94]



178

2-(4-Iodobutyl)-2-methyl-1,3-dioxolane 178

Following the method of Motherwell,[17b] triphenylphosphine (7.35 g, 28.1 mmol), imidazole (2.17 g, 31.9 mmol) and finally iodine (7.62 g, 30 mmol) were added to a stirred solution of alcohol **177** (3 g, 18.7 mmol) in ether (120 ml) and acetonitrile (40 ml). The solution was stirred for 15 minutes. The resulting red solution was diluted in ether (50 ml), washed with aq. $Na_2S_2O_3$ (5%, 20 ml), then water (50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with petrol (5 x 20 ml), filtered, concentrated *in vacuo* and purified by flash column chromatography (ether/petrol ; 5/95 to 20/80) to give **178** (4.03 g, 80%) as a colourless oil R_f = 0.42 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2945, 1427, 1189, 1044 and 730; δ_H (300 MHz; $CDCl_3$) 4.04-3.89 (4H, m, $O(CH_2)_2O$), 3.21 (2H, t, *J* 7, CH_2I), 1.87 (2H, p, *J* 7, CH_2CH_2I), 1.75-1.62 (2H, m, $CH_2CO(CH_2)_2O$), 1.60-1.43 (2H, m, $CH_2(CH_2)_2I$) and 1.34 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 109.94 (0), 64.81 (2 x 2), 38.10 (2), 33.74 (2), 25.22 (2), 23.95 (3) and 6.94 (2); m/z (CI) 271 ($[M + H]^+$, 100%).

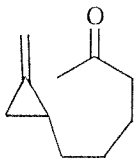


179

2-Methyl-2-[4-(2-methylenecyclopropyl)butyl]-1,3dioxolane 179

BuLi (9.27 ml of 1.79 M in hexane, 16.6 mmol) was added to methylenecyclopropane **1** (2.24 ml, 33.2 mmol) in THF (50 ml) at - 30 °C, and allowed to warm to 0 °C over 30 minutes. The reaction mixture was cooled to - 60 °C and HMPA (4.46 ml, 24.9 mmol) was added followed immediately by the dropwise addition of iodide **178** (3.5 g, 12.9 mmol). The reaction was allowed to come to room temperature overnight. The reaction mixture was quenched with aq. NH_4Cl (50 ml) and extracted with ether (3 x 50 ml). The combined organic phases were washed once with brine (50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/ether ; 95/5) to give

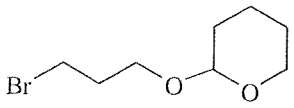
179 (2.24 g, 88%) as a colourless oil R_f = 0.66 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2936, 1374, 1220, 1069 and 883; δ_H (300 MHz; $CDCl_3$) 5.38 (1H, s, $=CH_AH_B$), 5.32 (1H, s, $=CH_AH_B$), 4.01-3.84 (4H, m, $O(CH_2)_2O$), 1.71-1.56 (2H, m, $CH_2C(CH_3)O$), 1.52-1.27 (7H, m, 3 x CH_2 and $CHC=CH_2$), 1.31 (3H, s, CH_3), 1.20 (1H, m, $CH_AH_BC=CH_2$) and 0.70 (1H, m, $CH_AH_BC=CH_2$); δ_C (100 MHz; $CDCl_3$) 138.36 (0), 111.33 (0), 103.52 (2), 65.80 (2 x 2), 40.81 (2), 34.24 (2), 30.84 (2), 30.62 (2), 24.93 (3), 16.87 (1) and 10.56 (2); m/z (CI) 197.1554 ($[M + H]^+$. $C_{12}H_{21}O_2$ requires 197.1541) and 197 ($[M + H]^+$, 100%).



168

6-(2-Methylenecyclopropyl)-2-hexanone 168

2-Methyl-2-[4-(2-methylenecyclopropyl)butyl]-1,3dioxolane **179** (1 g, 5.1 mmol) was stirred with *p*-TsOH (0.97 g, 5.1 mmol) in a mixture of acetone (180 ml) and 10% water (20 ml) for 48 hours. The mixture was concentrated *in vacuo*. Ether (50 ml) was added. The mixture was then washed once with 10% $NaHCO_3$ (100 ml) and extracted with ether (3 x 75 ml). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/ether ; 100/0 to 80/20) to give **168** as a colourless oil (0.66 g, 86%) R_f = 0.51 (40/60 ether/petrol); ν_{max} (film)/cm^{-1} 2929, 1715, 1357, 1160 and 884; δ_H (300 MHz; $CDCl_3$) 5.38 (1H, s, $=CH_AH_B$), 5.32 (1H, s, $=CH_AH_B$), 2.43 (2H, t, *J* 7, CH_2COCH_3), 2.13 (3H, s, CH_3), 1.79-0.84 (8H, 3 x CH_2 and $CHC=CH_2$ and $CH_AH_BC=CH_2$) and 0.71 (1H, m, $CH_AH_BC=CH_2$); δ_C (100 MHz; $CDCl_3$) 209.16 (0), 137.03 (0), 102.60 (2), 43.82 (2), 32.93 (2), 29.97 (3), 29.07 (2), 23.62 (2), 15.64 (1) and 9.50 (2); m/z (EI+) 152.1201 (M^+. $C_{10}H_{16}O$ requires 152.1201), m/z (CI) 170 ($[M + NH_4^+]^+$, 100%) and 153($[M + H]^+$, 35%).

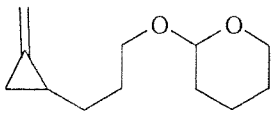


180

2-(3-Bromopropoxy)tetrahydropyran 180

Following the method of Anderson,[95] dihydropyran (24.7 ml, 270 mmol) was added dropwise over 1 hour to a mixture of 3-bromopropan-1-ol (25 g, 180 mmol) and *p*-TsOH (0.041 g, 0.22 mmol) at 55 °C. The mixture was kept at 55 °C for 1 hour before being cooled to room temperature and $NaHCO_3$ (0.031 g, 0.36 mmol) added. After 30 minutes, the reaction mixture was distilled under reduced pressure (bp. 70-72 °C/0.7 mmHg) to give the protected alcohol **180** as a colourless oil (29.15 g, 73%) R_f = 0.62 (50/50 ether/petrol); δ_H (300 MHz; $CDCl_3$) 4.57 (1H, t, *J* 3, OCHO), 3.89 (1H, m, CH_AH_BO), 3.74 (2H, t, *J* 6, CH_2Br), 3.61-3.41 (3H, m, CH_AH_BO and CH_2O), 2.10 (2H, tt, *J* 6 and 6, CH_2CH_2Br) and 1.79-1.42 (6H, m, 3 x CH_2); δ_C (75 MHz; $CDCl_3$) 99.04 (1), 65.03 (2), 62.42 (2), 33.03 (2), 30.85 (2), 30.74 (2), 25.55 (2) and 19.62 (2).

All data agrees with data reported by Maskill.[96]



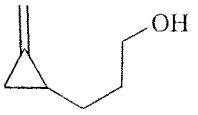
181

2-(3-Methylenecyclopropylpropoxy)tetrahydropyran 181

BuLi (19.7 ml of 2.01 M in hexane, 39.4 mmol) was added to methylenecyclopropane **1** (5.32 ml, 78.9 mmol) in THF (60 ml) at - 30 °C, and allowed to warm to 0 °C over 30 minutes. The reaction mixture was cooled to - 60 °C and HMPA (10.6 ml, 59.1 mmol) added followed immediately by the dropwise addition of bromide **180**. The reaction mixture was allowed to come to room temperature overnight. The reaction was quenched with aq. NH_4Cl (10%, 50 ml) and extracted with ether (3 x 150 ml). The combined organic phases were washed once with brine (100 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/ether ; 100/0 to 95/5) to give **181** (4.52 g, 75%) as colourless oil R_f = 0.69 (50/50 ether/petrol); δ_H (300 MHz; $CDCl_3$) 5.40 (1H, s, $=CH_AH_B$), 5.34 (1H, s, $=CH_AH_B$), 4.58 (1H, t, *J* 3, OCHO), 3.87 (1H, m, CH_AH_BO), 3.76 (1H, m, CH_AH_BO), 3.52 (1H, m, CH_AH_BO), 3.38 (1H, m, CH_AH_BO), 2.00-1.00 (12H, m,

5 x CH_2 and $CHC{=}CH_2$ and $CH_AH_BC{=}CH_2$) and 0.73 (1H, m, $CH_AH_BC{=}CH_2$); δ_C (75 MHz; $CDCl_3$) 137.04 (0), 102.68 (2), 98.97 (1), 67.34 (2), 62.47 (2), 30.91 (2), 29.88 (2), 29.66 (2), 25.64 (2), 19.81 (2), 15.59 (1) and 9.55 (2).

All data agrees with data reported by Destabel.[9]

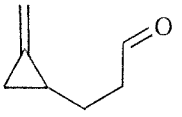


182

3-Methylenecyclopropylpropan-1-ol 182

2-(3-Methylenecyclopropylpropoxy)tetrahydropyran **181** (1 g, 5.1 mmol) was stirred with *p*-TsOH (1.17 g, 6.12 mmol) in a mixture of acetone (90 ml) and 10% water (10 ml) for 48 hours. The mixture was concentrated *in vacuo*. Ether (50 ml) was added. The mixture was then washed once with aq. $NaHCO_3$ (10%, 25 ml) and extracted with ether (3 x 75 ml). The organic phase was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (petrol/ether ; 100/0 to 70/30) to give **182** as a colourless oil (0.21 g, 65%) R_f = 0.29 (50/50 ether/petrol); δ_H (300 MHz; $CDCl_3$) 5.40 (1H, s, $=CH_AH_B$), 5.35 (1H, s, $=CH_AH_B$), 3.68 (2H, t, *J* 3, CH_2OH), 2.00-1.56 (5H, m, 2 x CH_2 and OH), 1.41 (1H, m, $CHC{=}CH_2$), 1.23 (1H, m, $CH_AH_BC{=}CH_2$) and 0.75 (1H, m, $CH_AH_BC{=}CH_2$); δ_C (75 MHz; $CDCl_3$) 136.93 (0), 102.79 (2), 62.66 (2), 32.54 (2), 29.40 (2), 15.46 (1) and 9.54 (2).

All data agrees with data reported by Destabel.[9]



169

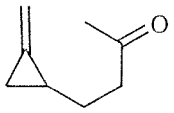
3-Methylenecyclopropylpropanal 169

Following the method of Swern,[87] DMSO (0.33 ml, 4.25 mmol), in dichloromethane (10 ml), was added to a solution of oxalyl chloride (0.2 ml, 2.15 mmol), in dichloromethane (10 ml), keeping the mixture below - 50 °C. The mixture was stirred for 2 minutes at - 60 °C. Alcohol **182** (0.21 g, 1.87 mmol), in dichloromethane (20 ml), was then added within 5 minutes, again keeping the temperature below - 50 °C. The solution was stirred for 15

minutes and triethylamine (1.19 ml, 8.5 mmol) was added and stirred for 5 minutes. The solution was allowed to warm to room temperature. The mixture was quenched with water (100 ml) and extracted with dichloromethane (3 x 50 ml). The organic phase was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (petrol/ether ; 100/0 to 80/20) to give **169** as a colourless oil (0.11 g, 55%) R_f = 0.70 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2928, 1725 and 888; δ_H (300 MHz; $CDCl_3$) 9.80 (1H, t, *J* 2, CHO), 5.41 (1H, s, =CH_AH$_B$), 5.37 (1H, s, =CH$_A$$H_B$), 2.61 (2H, dt, *J* 2 and 7, CH_2CHO), 1.83-1.58 (2H, m, CH_2CH$_2$CHO), 1.36 (1H, m, C*H*C=CH$_2$), 1.19 (1H, m, CH_AH$_B$C=CH$_2$) and 0.70 (1H, m, CH$_A$$H_B$C=CH$_2$); δ_C (100 MHz; $CDCl_3$) 202.67 (0), 136.16 (0), 103.74 (2), 43.93 (2), 26.04 (2), 15.27 (1) and 9.85 (2); m/z (EI+) 110.0732 (M^+. $C_7H_{10}O$ requires 110.0732) and m/z (CI) 118 ([M + NH_4^+]$^+$, 48%).

General procedure for the addition of conjugated ketones onto methylenecyclopropyl cuprate

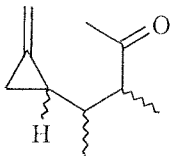
BuLi (4.37 ml of 2.40 M in hexane, 10.5 mmol) was added to methylenecyclopropane **1** (0.71 ml, 10.5 mmol) in THF (10 ml) at - 30 °C, and allowed to warm to 0 °C over 30 minutes. The reaction mixture was kept at 0 °C for 1 hour and then allowed to warm to room temperature over 15 mins. The reaction was cooled to - 25 °C and cannulated to a rapidly stirred suspension of CuI (1 g, 5.25 mmol) in THF (20 ml) at - 25 °C. The mixture turned black. The black solution was stirred for 30 mins before cooling to - 78 °C. A solution of TMSCl (1.33 ml, 10.5 mmol) and the electrophile (3.93 mmol) in THF (5 ml) was added over 30 mins to the rapidly stirred organocuprate. The temperature was allowed to come to room temperature overnight and quenched with aq. NH_4Cl (50 ml). The aqueous layer was extracted with ether (3 x 25 ml). The combined organic phases were washed once with brine (10 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was dissolved in Et_2O (20 ml) and a solution of HCl was added (20 ml, 2 M). the reaction was vigorously stirred for 2 days. The crude reaction was transferred in a separating funnel and extracted with Et_2O (3 x 30 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography to give the Michael adduct.



166

4-Methylenecyclopropylbutan-2-one 166

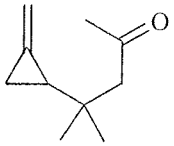
Following the general procedure for addition of conjugated ketones to methylenecyclopropyl cuprate, methyl vinyl ketone **190** (0.33 ml, 3.93 mmol) was added with TMSCl in THF. After work up and desilylation, the crude product was purified by flash column chromatography (petrol/ether ; 100/0 to 90/10) to give ketone **166** (0.39 g, 79%).



192

3-Methyl-4-(2-methylenecyclopropyl)-2-pentanone 192

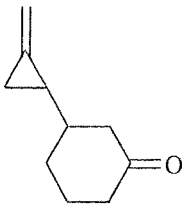
Following the general procedure for addition of conjugated ketones to methylenecyclopropyl cuprate, 3-methyl-3-penten-2-one **191** (0.44 ml, 3.93 mmol) was added with TMSCl in THF. After work up and desilylation, the crude product was purified by flash column chromatography (petrol/ether ; 100/0 to 90/10) to give ketone **192** (0.35 g, 59%) and as a 3 : 3 : 2 : 1 mixture of inseparable diastereoisomers R_f = 0.34 (10/90 ethyl acetate/petrol); ν_{max} (film)/cm^{-1} 2967, 2869, 1708, 1453, 1353, 1235, 1180, 1073 and 730; δ_H (300 MHz; $CDCl_3$) 5.47-5.22 (2H, m, $=CH_2$), 2.75-2.42 (4H, m, 2 x C*H*CH_3), 2.30-2.09 (4H, m, 2 x C*H*CH_3), 2.16 (3H, s, CH_3CO), 2.15 (3H, s, CH_3CO), 2.13 (3H, s, CH_3CO), 2.12 (3H, s, CH_3CO) and 1.54-0.57 (36 H, m, 8 x C*H*$_3$CH and 4 x C*H*C=CH_2 and 4 x C*H*$_2$C=CH_2); δ_C (75 MHz; $CDCl_3$) 212.81 (0), 135.87 (0), 135.72 (0), 134.77 (0), 103.94 (2), 103.44 (2), 103.11 (2), 53.66 (1), 53.33 (1), 52.38 (1), 51.99 (1), 39.62 (1), 39.34 (1), 29.37 (3), 29.11 (3), 20.83 (3), 19.97 (3), 19.16 (3), 18.40 (3), 18.24 (3), 15.77 (1), 15.09 (1), 13.84 (3), 12.15 (1), 11.85 (1), 10.12 (2), 9.60 (2), 8.98 (2) and 8.19 (2); m/z (CI) 170.1534 ($[M + NH_4^+]^+$. $C_{10}H_{20}ON$ requires 170.1545), 170 ($[M + NH_4^+]^+$, 33%), 153 ($[M + H]^+$, 97%) and 109 (100%).



194

4-Methyl-4-(2-methylenecyclopropyl)-2-pentanone 194

Following the general procedure for addition of conjugated ketones to methylenecyclopropyl cuprate, mesityl oxide **193** (0.45 ml, 3.93 mmol) was added with TMSCl in THF. After work up and desilylation, the crude product was purified by flash column chromatography (petrol/ether ; 100/0 to 90/10) to give ketone **194** (0.42 g, 71%) R_f = 0.35 (10/90 ethyl acetate/petrol); ν_{max} (film)/cm^{-1} 3046, 2960, 2873, 1715, 1467, 1359, 1159, 1138 and 885; δ_H (300 MHz; $CDCl_3$) 5.39 (1H, s with fine splitting, =CH_AH$_B$), 5.37 (1H, s with fine splitting, =CH$_A$$H_B$), 2.45 (1H, d, *J* 14, CH_AH$_B$CO), 2.37 (1H, d, *J* 14, CH$_A$$H_B$CO), 2.18 (3H, s, CH_3CO), 1.59 (1H, m, C*H*C=CH_2), 1.04 (1H, m, CH_AH$_B$C=CH_2), 0.96 (3H, s, CH_3), 0.93 (3H, s, CH_3) and 0.92 (1H, m, CH$_A$$H_B$C=$CH_2$); δ_C (100 MHz; $CDCl_3$) 209.28 (0), 134.38 (0), 104.04 (2), 55.02 (2), 33.83 (0), 33.06 (3), 26.47 (1), 25.96 (3), 24.92 (3) and 5.86 (2); m/z (CI) 170.1548 ([M + NH_4^+]$^+$. $C_{10}H_{20}ON$ requires 170.1545), 170 ([M + NH_4^+]$^+$, 24%), 153 ([M + H]$^+$, 94%) and 135 (100%).

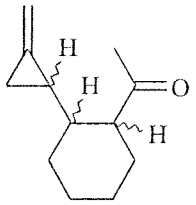


196

3-(2-Methylenecyclopropyl)-1-cyclohexanone 196

Following the general procedure for addition of conjugated ketones to methylenecyclopropyl cuprate, cyclohexenone **195** (0.38 ml, 3.93 mmol) was added with TMSCl in THF. After work up and desilylation, the crude product was purified by flash column chromatography (petrol/ether ; 100/0 to 90/10) to give ketone **196** (0.56 g, 95%) and as a 1 : 1 mixture of inseparable diastereoisomers R_f = 0.63 (30/70 ethyl acetate/petrol); ν_{max} (film)/cm^{-1} 2932, 1708, 1310, 1024 and 885; δ_H (400 MHz; $CDCl_3$) 5.45 (0.5H, s with fine splitting, =CH_AH$_B$), 5.38 (0.5 x 3H, s, =CH$_A$$H_B$ and =CH_2), 2.60-1.85 (6H, m, C*H*CH_2CO and 2 x CH_2 and CH_AH$_B$), 1.71-1.18 (5H, m, CH_2 and CH$_A$$H_B$ and C*H*C=CH_2 and CH_AH$_B$C=CH_2) and 0.84 (1H, m, CH_AH$_B$C=CH_2); δ_C (100 MHz; $CDCl_3$) 211.74 (0), 135.08

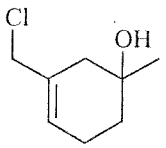
(0), 134.71 (0), 103.96 (2), 103.73 (2), 47.70 (2), 43.11 (1), 42.75 (1), 41.74 (2), 41.64 (2), 31.32 (2), 30.98 (2), 25.46 (2), 25.37 (2), 21.27 (1), 8.62 (2) and 8.47 (2); m/z (CI) 151.1126 ($[M + H]^+$. $C_{10}H_{15}O$ requires 151.1123) 151 ($[M + H]^+$, 36%) and 168 ($[M + NH_4^+]^+$, 100%).



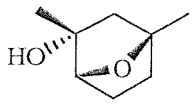
198

1-[2-(2-Methylenecyclopropyl)cyclohexyl]-1-ethanone 198

Following the general procedure for addition of conjugated ketones to methylenecyclopropyl cuprate, cyclohexene **197** (0.49 g, 3.93 mmol) was added with TMSCl in THF. After work up and desilylation, the crude product was purified by flash column chromatography (petrol/ether ; 100/0 to 90/10) to give ketone **198** (0.53 g, 76%) and as a 5 : 5 : 3 : 2 mixture of inseparable diastereoisomers R_f = 0.32 (10/90 ethyl acetate/petrol); ν_{max} (film)/cm^{-1} 3069, 2933, 2854, 1712, 1449, 1351, 1309, 1173, 1124, 1030, 891 and 844; δ_H (300 MHz; $CDCl_3$) 5.35-5.02 (2H, m, $=CH_2$), 2.68 (1H, dt, *J* 10 and 4, C*H*CO), 2.32-1.90 (3H, m, 3 x CHCO), 2.11 (3H, s, CH_3), 2.08 (3H, s, CH_3), 2.02 (3H, s, CH_3), 1.97 (3H, s, CH_3), 1.82-0.86 (11H, 4 x CH_2 and 2 x CH and $CH_AH_BC=CH_2$) and 0.55 (1H, m, $CH_AH_BC=CH_2$); δ_C (75 MHz; $CDCl_3$) 212.05 (0), 136.21 (0), 135.68 (0), 135.08(0), 104.22 (2), 104.04 (2), 103.65 (2), 103.46 (2), 58.27 (1), 57.64 (1), 53.79 (1), 53.30 (1), 42.88 (1), 42.79 (1), 42.43 (1), 42.24 (1), 31.98 (3), 31.55 (3), 31.35 (3), 30.86 (3), 30.11 (2), 29.72 (2), 29.58 (2), 29.52 (2), 25.93 (2), 25.91 (2), 25.71 (2), 25.62 (2), 24.81 (2), 24.65 (2), 24.45 (2), 22.69 (2), 21.11 (1), 20.81 (1), 16.20 (1), 15.87 (1), 10.66 (2), 9.90 (2), 9.43 (2) and 7.93 (2); m/z (CI) 179.1436 ($[M + H]^+$. $C_{12}H_{19}O$ requires 179.1436), 196 ($[M + NH_4^+]^+$, 15%) and 179 ($[M + H]^+$, 100%).



205

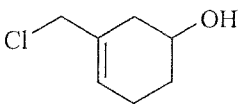


207

3-Chloromethyl-1-methylcyclohex-3-en-1-ol 205

(*1R,2S,4S*)-2,4-Dimethyl-7-oxabicyclo[2.2.1]heptan-2-ol 207

$TiCl_4$ (0.15 ml, 1.33 mmol) was added to 4-methylenecyclopropylbutan-2-one **166** (0.15 g, 1.21 mmol), in dichloromethane (6 ml), at - 40 °C under Ar. The solution was stirred for 1.5 hours. The reaction mixture was quenched with water (15 ml) and extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100/0 to 70/30) to give cyclohexene **205** (0.097 g, 50%) as a pale yellow oil R_f = 0.29 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3386, 2926, 1708, 1667, 1436, 1373, 1259, 1102 and 683; δ_H (300 MHz; $CDCl_3$) 5.84 (1H, br s, =CH), 4.01 (2H, s, CH_2Cl), 2.28-2.11 (4H, m, =CCH_2COH and CH_2), 1.71-1.50 (3H, m, CH_2COH and OH) and 1.29 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 132.39 (0), 126.49 (1), 68.89 (0), 50.20 (2), 40.47 (2), 34.53 (2), 28.80 (3) and 23.17 (2); m/z (CI) 160.0689 (M^+. $C_8H_{13}ClO$ requires 160.0655), 160 ($[M]^+$, 16%) and 178 ($[M + NH_4^+]^+$, 100%); and bicyclic ether **207** (0.010 g, 9%) as a pale yellow oil and as a single diastereoisomer R_f = 0.51 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3581, 3448, 2968, 1718, 1444, 1377, 1194, 1120, 969 and 913; δ_H (300 MHz; $CDCl_3$) 4.35 (1H, br s, CHO), 3.24 (1H, br s, OH), 2.64 (1H, m, C$H_A$$H_B$$CH_2$), 2.18-1.84 (3H, m, $CH_A$$H_B$$CH_2$ and CCH_2C(OH)Me), 1.73 (3H, s, CH_3), 1.71-1.59 (2H, m, C$H_2$$CH_A$$H_B$) and 1.24 (3H, s, C$H_3$COH); δ_C (75 MHz; $CDCl_3$) 72.21 (0), 69.21 (0), 64.80 (1), 45.14 (2), 32.57 (3), 31.77 (2), 31.10 (3) and 26.35 (2); m/z (EI+) 142.0995 (M^+. $C_8H_{14}O_2$ requires 142.0994), m/z (CI) 143 ($[M + H]^+$, 19%) and 125 ($[M - H_2O]^+$, 100%).

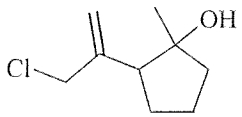


211

3-Chloromethylcyclohex-3-en-1-ol 211

$TiCl_4$ (0.11 ml, 0.99 mmol) was added to 3-methylenecyclopropylpropanal **169** (0.1 g, 0.91 mmol), in dichloromethane (4 ml), at 0 °C under Ar. The solution was stirred for 1

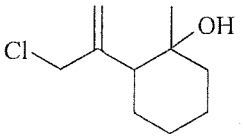
hours. The reaction mixture was quenched with water (10 ml) and extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100/0 to 60/40) to give cyclohexene **211** (0.065 g, 50%) as a pale yellow oil R_f = 0.24 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3346, 2926, 1706, 1666, 1438, 1359, 1259, 1066, 905 and 683; δ_H (400 MHz; $CDCl_3$) 5.80 (1H, br s, =CH), 4.05 (1H, m, C*H*OH), 4.00 (2H, s, CH_2Cl), 2.46 (1H, dd, *J* 4 and 14, =CCH_AH$_B$CHOH), 2.35-2.03 (3H, m, C=CHCH_2 and OH), 1.92-1.79 (2H, m, =CCH$_A$$H_B$CHOH and CH$_2CH_AH_B$CHOH) and 1.60 (1H, m, CH$_2$CH$_A$$H_B$CHOH); δ_C (100 MHz; $CDCl_3$) 132.15 (0), 127.15 (1), 67.42 (1), 50.31 (2), 35.40 (2), 30.05 (2) and 23.49 (2); m/z (CI) 164.0825 ([M + NH_4^+]$^+$. $C_7H_{15}ClNO$ requires 164.0842), 146 ([M]$^+$, 16%), 128 ([M - H_2O] $^+$, 16%) and 164 ([M + NH_4^+]$^+$, 100%).



213

2-[1-(Chloromethyl)-1-ethenyl]-1-methyl-1-cyclopentanol 213

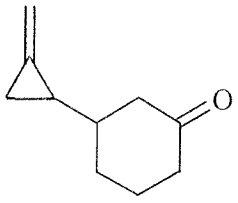
$SnCl_4$ (0.093 ml, 0.79 mmol) was added dropwise to 5-(2-methylenecyclopropyl)-2-pentanone **167** (0.1 g, 0.72 mmol) in dichloromethane (10 ml) at - 55 °C under Ar. The solution was stirred for 6 hours at - 55 °C. The reaction mixture was quenched with water (15 ml) and extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100/0 to 70/30) to give cyclopentanol **213** (0.054 g, 43%) as a colourless oil and as a single diastereoisomer R_f = 0.43 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3460, 3090, 2928, 1639, 1447, 1375, 1260, 1122, 1048, 936, 849 and 736; δ_H (300 MHz; $CDCl_3$) 5.42 (1H, s, =CH_AH$_B$), 5.20 (1H, s, =CH$_A$$H_B$), 4.14 (2H, s, CH_2Cl), 2.47 (1H, t, *J* 9, C*H*C(CH_2Cl)=CH_2), 2.00-1.50 (6H, m, 3 x CH_2), 1.40 (1H, br s, OH) and 1.31 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 144.75 (0), 117.12 (2), 79.44 (0), 53.21 (1), 49.20 (2), 41.20 (2), 30.48 (2), 27.49 (3) and 21.37 (2); m/z (EI+) 174.0806 (M^+. $C_9H_{15}ClO$ requires 174.0811), 123 ([M - 51]$^+$, 15%) and 28 (100%).



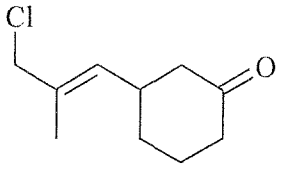
214

2-[1-(Chloromethyl)vinyl]-1-methylcyclohexan-1-ol 214

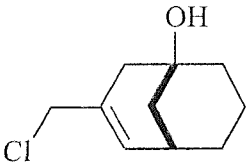
$SnCl_4$ (0.085 ml, 0.72 mmol) was added to 6-(2-methylenecyclopropyl)-2-hexanone **168** (0.1 g, 0.66 mmol), in dichloromethane (20 ml), at - 78 °C under Ar. The solution was stirred for 8 hrs at - 78 °C. The reaction mixture was quenched with water (20 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 30 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 95/5 to 90/10) to give cyclohexanol **214** (0.051 g, 40%) as a pale yellow oil and as a single diastereoisomer R_f = 0.51 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3469, 2929, 1373, 1098 and 917; δ_H (400 MHz; $CDCl_3$) 5.26 (1H, s, $=CH_AH_B$), 5.11 (1H, $=CH_AH_B$), 4.05 (2H, s, CH_2Cl), 2.04 (1H, dd, *J* 4 and 13, $CH{=}CH_2$), 1.83-1.39 (6H, m, $CHCH_2$ and 2 x CH_2), 1.38-1.27 (2H, m, $CHCH_2CH_2$), 1.21 (1H, m, OH) and 1.08 (3H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 147.69 (0), 116.98 (2), 70.85 (0), 50.94 (1), 49.95 (2), 40.56 (2), 30.08 (3), 29.18 (2), 26.59 (2) and 22.03 (2); m/z (EI+) 188.0973 (M^+. $C_{10}H_{17}ClO$ requires 188.0968), m/z (CI) 188 ($[M]^+$, 14%) and 206 ($[M + NH_4^+]^+$, 100%).



196



217



218

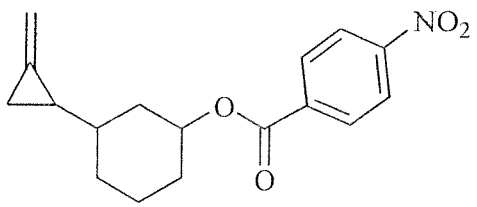
3-(2-Methylenecyclopropyl)-1-cyclohexanone 196

3-[(E/Z)-3-Chloro-2-methyl-1-propenyl]-1-cyclohexanone 217

3-(Chloromethyl)bicyclo[3.3.1]non-3-en-1-ol 218

$TiCl_4$ (0.73 ml of 1 M solution in DCM, 0.73 mmol) was added to 3-(2-methylenecyclopropyl)-1-cyclohexanone **196** (0.1 g, 0.68 mmol) in dichloromethane (20 ml), at - 78 °C, under Ar. The solution was allowed to come to 0 °C over 8 hours. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with

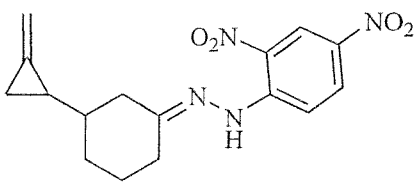
dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether; 95/5 to 70/30) to give cyclohexanone **196**, as a single diastereoisomer, (0.043 g, 43%) and as a colourless oil R_f = 0.56 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2932, 1708, 1310, 1024 and 885; δ_H (400 MHz; $CDCl_3$) 5.44 (1H, s, =C*H*$_A$H$_B$), 5.37 (1H, s, =CH$_A$*H*$_B$), 2.53 (1H, m, CHC*H*$_A$H$_B$CO), 2.39-2.13 (3H, m, CHCH$_A$*H*$_B$CO and C*H*CH$_A$H$_B$CO and CH$_2$C*H*$_A$H$_B$CO), 2.06 (1H, m, CH$_2$CH$_A$*H*$_B$CO), 1.96 (1H, m, C*H*$_A$H$_B$), 1.70-1.48 (3H, m, CH$_A$*H*$_B$ and CH$_2$), 1.37 (1H, m, C*H*C=CH$_2$), 1.24 (1H, m, C*H*$_A$H$_B$C=CH$_2$) and 0.82 (1H, m, CH$_A$*H*$_B$C=CH$_2$); δ_C (100 MHz; $CDCl_3$) 211.74 (0), 135.09 (0), 103.73 (2), 47.71 (2), 43.11 (1), 41.75 (2), 31.33 (2), 25.46 (2), 21.28 (1) and 8.63 (2); m/z (CI) 151.1126 ([M + H]$^+$. $C_{10}H_{15}O$ requires 151.1123) 151 ([M + H]$^+$, 36%) and 168 ([M + NH_4^+]$^+$, 100%); cyclohexanone **217** (0.018 g, 15%) as a colourless oil R_f = 0.46 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2937, 1709, 1346, 1222, 914 and 686; δ_H (400 MHz; $CDCl_3$) 5.41 (1H, d, *J* 9, =CH), 4.00 (2H, s, CH_2Cl), 2.72 (1H, m, =CHC*H*), 2.44-2.25 (2H, m, CHC*H*$_2$CO), 2.19-2.06 (2H, m, (CH$_2$)$_2$C*H*$_2$CO), 1.91-1.67 (2H, m CH$_2$C*H*$_2$CH$_2$), 1.76 (3H, s, CH_3) and 1.58-1.44 (2H, m, CHC*H*$_2$(CH$_2$)$_2$CO); δ_C (100 MHz; $CDCl_3$) 210.94 (0), 133.31 (1), 132.41 (0), 52.20 (2), 47.67 (2), 41.58 (2), 38.47 (1), 31.56 (2), 25.62 (2) and 14.72 (3); m/z (EI+) 186.0812 ([M]$^+$. $C_{10}H_{15}OCl$ requires 186.0811) m/z (CI) 204 ([M + NH_4^+]$^+$, 13%) and 170 (100%); and bicyclo [3.3.1] **218** (0.043 g, 35%) as a yellow oil R_f = 0.25 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3368, 2931, 1352, 1259, 1071, 898 and 734; δ_H (400 MHz; $CDCl_3$) 5.75 (1H, d, *J* 6, =C*H*CH), 4.07 (1H, d, *J* 11, C*H*$_A$H$_B$Cl), 4.00 (1H, d, *J* 11, CH$_A$*H*$_B$Cl), 2.67 (1H, br s, =CHC*H*), 2.36 (1H, d, *J* 18, =CC*H*$_A$H$_B$COH), 2.30 (1H, d, *J* 18, =CCH$_A$*H*$_B$COH), 1.80 (2H, d, *J* 11, CHC*H*$_2$COH) and 1.63-1.35 (7H, m, 3 x CH_2 and OH); δ_C (100 MHz; $CDCl_3$) 135.54 (0), 130.09 (1), 69.46 (0), 49.15 (2), 42.06 (2), 41.84 (2), 40.54 (2), 33.97 (1), 28.24 (2) and 19.75 (2); m/z (EI+) 186.0812 ([M]$^+$. $C_{10}H_{15}OCl$ requires 186.0811) m/z (CI) 204 ([M + NH_4^+]$^+$, 6%) and 186 ([M]$^+$, 100%).



219

3-(Methylenecyclopropyl)cyclohexyl 4-nitrobenzoate 219

Following the method used by Albizati *et al.*,[85] ketone **196** (0.020 g, 0.13 mmol) in THF (1 ml) was added dropwise to a suspension of $LiAlH_4$ (0.010 g, 0.26 mmol) in THF (4 ml) at 0 °C and stirred for 1 hour. Ether (2 ml) was added and the solution was stirred at 0 °C for 5 minutes. NaOH (0.5 ml, 4 M) was added and the mixture stirred until a white heavy precipitate was observed. The mixture was filtered and washed with ether (20 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil, which was used without further purification. The crude product was added to a suspension of NaH (0.010 g, 0.39 mmol) in THF (2 ml) under Ar at 0 °C. The mixture was allowed to come to room temperature and stirred for 30 minutes. DMPU (0.047 ml, 0.39 mmol) was added and stirred for 10 minutes. *p*-Nitrobenzoyl chloride (0.12 g, 0.65 mmol) was added and the mixture was allowed to warm to room temperature. The solution was stirred overnight and quenched with NaOH (2 ml, 2 M). The aqueous phase was extracted with ether (3 x 10 ml). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The mixture was purified by flash column chromatography (petrol/ether ; 100/0 to 50/50) to give **219** as a pale yellow solid (0.009 g, 23%) and as a single diastereoisomer R_f = 0.72 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2866, 1719, 1527, 1278, 898 and 718; δ_H (400 MHz; $CDCl_3$) 8.28 (2H, d, *J* 9, C*H*=CHCNO$_2$), 8.20 (2H, d, *J* 9, CH=C*H*CNO$_2$), 5.43 (1H, s, =CH_AH$_B$), 5.37 (1H, s, =CH$_A$$H_B$), 4.95 (1H, m, CHO), 2.27 (1H, m, CH_AH$_B$CHO), 2.10 (1H, m, CH$_A$$H_B$CHO), 1.89 (1H, m, C$H_AH_B$CHO), 1.82 (1H, m, CH$_A$$H_B$CHO), 1.50-1.02 (7H, m, 3 x CH_2 and CH) and 0.85 (1H, m, CHC=CH_2); δ_C (100 MHz; $CDCl_3$) 164.86 (0), 151.23 (0), 137.01 (0), 136.02 (0), 131.40 (2 x 1), 124.21 (2 x 1), 103.70 (2), 75.63 (1), 40.66 (1), 38.32 (2), 32.37 (2), 32.01 (2), 24.39 (2), 22.03 (1) and 8.73 (2); m/z (CI) 153 ([M - 148]$^+$, 4%) and 135 (100%).

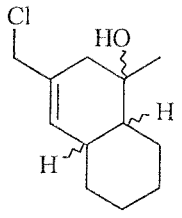


221

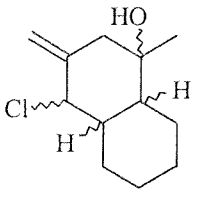
3-(2-Methylenecyclopropyl)-1-cyclohexanone 1-(2,4-dinitrophenyl)hydrazone 221

Ketone **196** (0.045 g, 0.3 mmol) was dissolved in Et_2O-DCM (0.4 : 0.2 ml) to yield a 0.5 M solution and 1 mol equivalent DBU (0.045 ml, 0.3 mmol) was added. The solution was

left for 1 hour and an excess of methanolic hydrazine **220** acidified with H_2SO_4 was added. The mixture was concentrated in vacuo, redissolved in Et_2O (5 ml) and washed once with diluted HCl (10 ml). The organic layer was dried over $MgSO_4$, concentrated in vacuo and purified by flash column chromatography (petrol/ether ; 95/5) to give **221** as an orange solid (0.014 g, 14%) and as a single diastereoisomer, mp. 105-107 (from chloroform) R_f = 0.67 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3318, 2933, 1616, 1584, 1519, 1423, 1334, 1304, 1066, 921, 893, 832, 743 and 724; δ_H (400 MHz; $CDCl_3$) 11.24 (1H, d, *J* 19, N*H*), 9.13 (1H, t, *J* 3, CH Ar), 8.28 (1H, dd, *J* 10 and 3, *H*C=CH Ar), 7.98 (1H, dd, *J* 10 and 6, HC=C*H* Ar), 5.47 (1H, s, =CH_AH$_B$), 5.41 (1H, s, =CH$_A$$H_B$), 3.00-2.65 (2H, m, C$H_2$C=N), 2.54 (1H, C$H_AH_B$C=N), 2.33 (1H, m, CH$_A$$H_B$C=N), 2.25-1.87 (3H, m, CH and CH_2), 1.75-1.10 (4H, m, CH_2 and C*H*C=CH_2 and CH_AH$_B$C=CH_2) and 0.91 (1H, m, CH$_A$$H_B$C=$CH_2$); δ_C (100 MHz; $CDCl_3$) 161.11 (0), 160.99 (0), 145.71 (0), 137.92 (0), 135.20 (0), 130.39 (1), 124.04 (1), 116.69 (1), 103.75 (2), 42.78 (1), 41.48 (2), 35.79 (2), 27.16 (2), 25.07 (2), 20.97 (1) and 8.69 (1); m/z (CI) 331 ([M + H]+, 34%) and 35 (100%).



222



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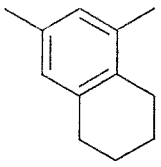


224

3-(Chloromethyl)-1-methyl-1,2,4a,5,6,7,8,8a-octahydro-1-naphthalenol 222

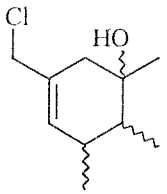
4-Chloro-1-methyl-3-methyleneperhydro-1-naphthlenol 223

5,7-Dimethyl-1,2,3,4-tetrahydronaphthalene 224

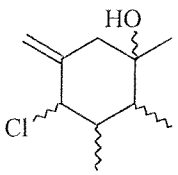
$TiCl_4$ (0.62 ml, 0.62 mmol) was added to 1-[2-(2-methylenecyclopropyl)cyclohexyl]-1-ethanone **198** (0.1 g, 0.56 mmol), in dichloromethane (20 ml), at - 78 °C under Ar. The solution was allowed to come to - 40 °C over 7 hours. The reaction mixture was quenched

with water (10 ml) and extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100/0 to 70/30) to give naphthalenol **222** and **223** (0.035 g, 29%) as a yellow oil and as a inseparable mixture of regio- and diastereoisomers R_f = 0.24 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3416, 2919, 2852, 1443, 1373, 1258, 804 and 732; δ_H (300 MHz; $CDCl_3$) 5.64 (1H, br s, =CH), 5.51 (1H, br s, =CH), 5.09-4.80 (2H, m, $=CH_2$), 4.11-3.89 (3H, m, CHCl and CH_2Cl), 2.50 (1H, br s, OH) and 2.43-0.79 (31H, m, 10 x CH_2 and 4 x CH and OH and 2 x CH_3); δ_C (75 MHz; $CDCl_3$) 134.26 (0), 132.47 (1), 131.08 (0), 130.57 (1), 113.54 (2), 72.46. (0), 70.27 (0), 50.10 (2), 49.76 (2), 48.06 (1), 45.23 (1), 44.29 (2), 42.34 (2), 37.79 (2), 37.65 (1), 35.46 (1), 32.89 (2), 31.42 (2), 27.86 (3), 27.00 (3), 26.76 (2), 26.55 (2), 26.06 (3), 25.57 (2), 24.82 (2), 22.51 (2) and 22.33 (2); m/z (CI) 232.1475 ($[M + NH_4^+]^+$. $C_{12}H_{23}ONCl$ requires 232.1468), 232 ($[M + NH_4^+]^+$, 60%), 214 ($[M]^+$, 10%) and 179 (100%); and tetrahydronaphthalene **224** (0.034 g, 38%) as a yellowish oil R_f = 0.75 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2922, 2855, 1612, 1480, 1436, 1375, 1030, 984, 846, 822 and 722; δ_H (300 MHz; $CDCl_3$) 6.85 (1H, s, H Ar), 6.80 (1H, s, H Ar), 2.77 (2H, t, *J* 6, $=CCH_2CH_2$), 2.62 (2H, t, *J* 6, $=CCH_2CH_2$), 2.29 (3H, s, CH_3), 2.21 (3H, s, CH_3) and 1-95-1.74 (4H, m, 2 x CH_2); δ_C (75 MHz; $CDCl_3$) 137.14 (0), 136.64 (0), 134.62 (0), 132.58 (0), 128.12 (1), 127.59 (1), 30.22 (2), 26.53 (2), 23.72 (2), 23.17 (2), 20.97 (3) and 19.56 (3); m/z (EI+) 160 ($[M]^+$, 72%) and 145 (100%).

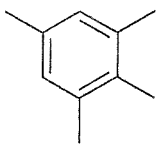
All data for **224** agrees with data reported by Marson.[97]



225



226



227

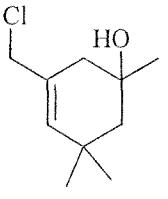
3-(Chloromethyl)-1,5,6-trimethyl-3-cyclohexen-1-ol 225

4-Chloro-1,2,3-trimethyl-5-methylene-1-cyclohexanol 226

1,2,3,5-Tetramethylbenzene 227

$TiCl_4$ (0.72 ml of 1 M in DCM, 0.72 mmol) was added to 3-methyl-4-(2-methylenecyclopropyl)-2-pentanone **192** (0.1 g, 0.66 mmol), in dichloromethane (20 ml), at -78 °C under Ar. The solution was allowed to come to - 20 °C over 7 hours. The reaction

mixture was quenched with water (10 ml) and extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100/0 to 70/30) to give cyclohexenol **225** and methylenecyclohexane **226** (0.040 g, 38%) as a yellow oil and as a inseparable mixture of regio- and diastereoisomers R_f = 0.35 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3411, 2962, 2875, 1375, 1256, 1032, 881 and 731; δ_H (400 MHz; $CDCl_3$) 5.64 (1H, br s, =CH), 5.50 (1H, br s, =CH), 5.42 (1H, br s, =CH), 4.91 (1H, s, =C$H_A$$H_B$), 4.84 (1H, s, =C$H_A$$H_B$), 4.03-4.82 (3 H, m, CH_2Cl and CHCl), 2.41 (1H, br s, OH) and 2.31-0.74 (27H, m, 6 x CH_3 and 4 x C*H*CH_3 and 2 x CH_2 and OH); δ_C (100 MHz; $CDCl_3$) 144.70 (0), 133.55 (1), 132.73 (1), 132.19 (0), 132.07 (0), 131.04 (1), 130.89 (0), 113.75 (2), 113.50 (2), 90.11 (1), 72.60 (0), 72.45 (0), 71.28 (0), 70.96 (0), 50.77 (1), 50.28 (2), 50.03 (2), 49.96 (2), 45.83 (1), 44.05 (1), 42.90 (2), 42.71 (1), 42.54 (1), 41.94 (2), 37.51 (2), 35.11 (1), 34.02 (1), 28.24 (3), 27.58 (3), 26.54 (3), 21.02 (3), 20.06 (3), 17.68 (3), 17.43 (3), 14.95 (3) and 12.21 (3); m/z (CI) 206.1317 ([M + NH_4^+]$^+$. $C_{10}H_{21}ONCl$ requires 206.1312), 206 ([M + NH_4^+]$^+$, 87%), 188 ([M]$^+$, 12%) and 153 (100%); and benzene **227** (0.031 g, 35%) as a yellowish oil R_f = 0.75 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2913, 2869, 1484, 1375, 1012, 893, 847 and 704; δ_H (400 MHz; $CDCl_3$) 6.75 (2H, s, H Ar) and 2.20 (12H, s, 4 x CH_3); δ_C (100 MHz; $CDCl_3$) 135.22 (4 x 0), 127.30 (2 x 1) and 19.40 (4 x 3); m/z (EI+) 134 ([M]$^+$, 95%) and 119 (100%).

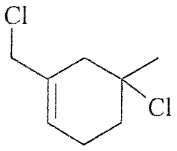


230

3-(Chloromethyl)-1,5,5-trimethyl-3-cyclohexen-1-ol 230

$TiCl_4$ (0.72 ml of 1 M in DCM, 0.72 mmol) was added to 4-methyl-4-(2-methylenecyclopropyl)-2-pentanone **194** (0.1 g, 0.66 mmol), in dichloromethane (20 ml), at - 78 °C under Ar. The reaction mixture was stirred for 40 mins at - 78 °C. The reaction mixture was quenched with water (10 ml) and extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100/0 to 70/30) to

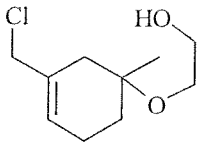
give cyclohexenol **230** (0.080 g, 65%) as a pale yellow oil R_f = 0.33 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3451, 2957, 2864, 1455, 1375, 1212, 1158, 1096, 1067, 903 and 681; δ_H (300 MHz; $CDCl_3$) 5.60 (1H, br s, =CH), 4.06 (1H, d, *J* 11, CH_AH_BCl), 4.01 (1H, d, *J* 11, CH_AH_BCl), 2.23 (1H, d, *J* 17, $=CCH_AH_BCOH$), 2.11 (1H, d, *J* 17, $=CCH_AH_BCOH$), 1.68 (1H, d, *J* 14, $(CH_3)_2CCH_AH_BCOH$), 1.59 (1H, br s, OH), 1.47 (1H, d, *J* 14, $(CH_3)_2CCH_AH_BCOH$), 1.31 (3H, s, CH_3) and 1.14 (3H, s, CH_3), 1.01 (3H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 137.20 (1), 129.27 (0), 70.50 (0), 50.78 (2), 48.64 (2), 40.39 (2), 33.52 (0), 31.99 (3), 30.71 (3) and 30.55 (3); m/z (CI) 206.1322 ($[M + NH_4^+]^+$. $C_{10}H_{21}ONCl$ requires 206.1312) 188 ($[M]^+$, 11%) and 206 ($[M + NH_4^+]^+$, 100%).



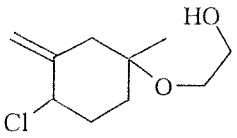
231

5-Chloro-1-(chloromethyl)-5-methyl-1-cyclohexene 231

$TiCl_4$ (0.60 ml of 1 M in DCM, 0.60 mmol) was added to 2-methyl-[(2'-ethyl)-(1''-methylenecyclopropyl)]-1,3-dioxolane **172** (0.05 g, 0.3 mmol) in dichloromethane (10 ml), at - 78 °C under Ar. The solution was stirred for 2 hours. The reaction mixture was quenched with water (15 ml) and extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (100% petrol) to give dichloride **231** (0.022 g, 41%) as a pale yellow oil R_f = 0.62 (10/90 ether/petrol); ν_{max} (film)/cm^{-1} 3051, 2924, 1670, 1429, 1378, 1261, 1208, 1113, 1073, 776, 680 and 572; δ_H (300 MHz; $CDCl_3$) 5.86 (1H, br s, =CH), 4.01 (2H, s, CH_2Cl), 2.57 (2H, d, *J* 11, $=CCH_AH_BC(CH_3)Cl$), 2.46 (2H, d, *J* 11, $=CCH_AH_BC(CH_3)Cl$), 2.36 (1H, m, $C=CHCH_AH_B$), 2.18 (1H, m, $C=CHCH_AH_B$), 2.00 (1H, m, $CH_2CH_AH_BC(CH_3)Cl$), 1.77 (1H, m, $CH_2CH_AH_BC(CH_3)Cl$) and 1.68 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 131.45 (0), 126.15 (1), 68.25 (0), 49.91 (2), 42.45 (2), 36.85 (2), 32.41 (3) and 23.79 (2); m/z (EI+) 178.0321 (M^+. $C_8H_{12}Cl_2$ requires 178.0316), 142 ($[M - Cl]^+$, 3%) and 41 (100%).



232

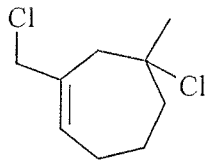


233

2-{[3-(Chloromethyl)-1-methyl-3-cyclohexenyl]oxy}-1-ethanol 232

2-[(4-Chloro-1-methyl-3-methylenecyclohexyl)oxy]-1-ethanol 233

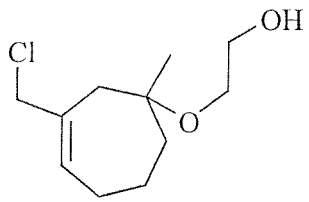
$SnCl_4$ (0.14 ml, 1.19 mmol) was added dropwise to 2-methyl-[(2'-ethyl)-(1''-methylenecyclopropyl)]-1,3-dioxolane **172** (0.1 g, 0.59 mmol) in dichloromethane (10 ml) at - 78 °C under Ar. The solution was stirred for 2 hours. The reaction mixture was quenched with water (15 ml) and extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100/0 to 70/30) to give an inseparable mixture of cyclohexene **232** and methylenecyclohexane **233** (0.085 g, 70%) in a 1.6 : 1 ratio, as a pale yellow oil R_f = 0.14 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3418, 3074, 2928, 1433, 1376, 1260, 1111, 1052, 967, 911 and 682; m/z (EI+) 204.0917 (M^+. $C_{10}H_{17}ClO_2$ requires 204.0917), 169 ($[M - Cl]^+$, 10%) and 59 (100%); data for **232** δ_H (300 MHz; $CDCl_3$) 5.81 (1H, br s, =CH), 4.01 (2H, s, CH_2Cl), 3.70-3.62 (2H, m, CH_2OH), 3.48 (1H, m, $OCH_AH_BCH_2OH$), 3.38 (1H, m, $OCH_AH_BCH_2OH$), 2.31-2.00 (4H, m, $CH_2CH_2C(CH_3)O$ and $=CCH_2C(CH_3)O$), 1.98-1.49 (3H, m, $CH_2CH_2C(CH_3)O$ and OH) and 1.23 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 132.07 (0), 126.73 (1), 73.02 (0), 68.84 (2), 62.22 (2), 50.32 (2), 37.21 (2), 32.15 (2), 23.84 (3) and 23.26 (2); data for **233** δ_H (300 MHz; $CDCl_3$) 5.03 (1H, s, $=CH_AH_B$), 4.98 (1H, s, $=CH_AH_B$), 3.84 (1H, br s, CHCl), 3.70-3.62 (2H, m, CH_2OH), 3.52-3.45 (2H, m, OCH_2CH_2OH), 2.50 (1H, d, *J* 14, $=CCH_AH_BC(CH_3)O$), 2.39 (1H, d, *J* 14, $=CCH_AH_BC(CH_3)O$), 2.13-1.71 (5H, m, $CH_2CH_2C(CH_3)O$ and $CH_2CH_2C(CH_3)O$ and OH) and 1.66 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 142.79 (0), 114.60 (2), 78.21 (1), 72.07 (0), 62.34 (2), 62.04 (2), 45.95 (2), 36.02 (2), 33.43 (3) and 29.28 (2).



234

6-Cloro-1-(chloromethyl)-6-methyl-1-cycloheptene 234

$TiCl_4$ (1.1 ml of 1 M in DCM, 1.1 mmol) was added dropwise to 2-methyl-2-[3-(2-methylenecyclopropyl)propyl]-1,3-dioxolane **173** (0.1 g, 0.55 mmol) in dichloromethane (10 ml) at - 78 °C under Ar. The solution was stirred for 2 hours. The reaction mixture was quenched with water (15 ml) and extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (100% petrol) to give cycloheptene **234** (0.012 g, 11%) as a pale yellow oil R_f = 0.65 (10/90 ether/petrol); ν_{max} (film)/cm^{-1} 2935, 1442, 1377, 1257, 1186, 1116, 1067, 1020, 912, 734 and 684; δ_H (300 MHz; $CDCl_3$) 6.09 (1H, t, *J* 7, =CH), 4.09 (1H, d, *J* 11, CH_AH_BCl), 4.02 (1H, d, *J* 11, CH_AH_BCl), 2.77 (1H, d, *J* 14, $=CCH_AH_BC(CH_3)Cl$), 2.70 (1H, d, *J* 14, $=CCH_AH_BC(CH_3)Cl$), 2.30-1.99 (6H, m, 3 x CH_2) and 1.67 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 135.74 (0), 133.46 (1), 70.42 (0), 52.63 (2), 48.41 (2), 45.13 (2), 33.14 (3), 27.75 (2) and 22.94 (2); m/z (EI+) 192.0475 (M^+. $C_9H_{14}Cl_2$ requires 192.0473), 192 ($[M]^+$, 12%), 156 ($[M - HCl]^+$, 51%), 121 ($[M - 2 \times HCl]^+$, 87%) and 107 (100%).



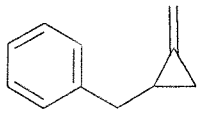
235

2-{[3-(Chloromethyl)-1-methyl-3-cycloheptenyl]oxy}-1-ethanol 235

2-Methyl-2-[3-(2-methylenecyclopropyl)propyl]-1,3-dioxolane **173** (0.1 g, 0.55 mmol) in dichloromethane (5 ml) was added over 45 mins, using a syringe pump, to a solution of $SnCl_4$ (0.13 ml, 1.1 mmol) in dichloromethane (10 ml) at - 78 °C under Ar. The solution was stirred for 6 hours at - 78 °C. The reaction mixture was quenched with water (15 ml) and extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column

chromatography (petrol/ether ; 100/0 to 70/30) to give cycloheptene **235** (0.055 g, 46%) as a colourless oil R_f = 0.20 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3418, 2932, 1442, 1375, 1279, 1258, 1209, 1086, 935 and 681; δ_H (300 MHz; $CDCl_3$) 6.00 (1H, t, *J* 7, =CH), 4.06 (2H, d, *J* 11, CH_AH_BCl), 4.00 (2H, d, *J* 11, CH_AH_BCl), 3.68 (2H, dt, *J* 9 and 5, CH_2OH), 3.48 (2H, t, *J* 5, CH_2CH_2OH), 2.53 (1H, d, *J* 15, $=CCH_AH_BC(CH_3)O$), 2.39 (1H, d, *J* 15, $=CCH_AH_BC(CH_3)O$), 2.20-2.10 (2H, m, $=CHCH_2(CH_2)_2$), 1.95 (1H, m, $CH_2CH_2CH_AH_BC(CH_3)O$), 1.80-1.67 (2H, m, OH and $CH_2CH_2CH_AH_BC(CH_3)O$), 1.60 (1H, m, $CH_2CH_AH_BCH_2$), 1.45 (1H, m, $CH_2CH_AH_BCH_2$) and 1.21 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 135.03 (0), 132.57 (1), 74.25 (0), 62.29 (2), 61.91 (2), 52.88 (2), 41.75 (2), 40.63 (2), 28.17 (2), 24.66 (3) and 21.99 (2); m/z (EI+) 218.1070 (M^+. $C_{11}H_{19}ClO_2$ requires 218.1074), 217 ($[M - H]^+$, 7%) and 57 (100%).

EXPERIMENTAL FOR CHAPTER TWO

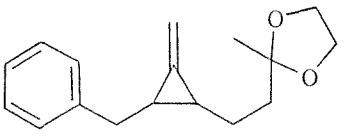


240

2-Benzyl-methylenecyclopropyl 240

BuLi (23.97 ml of 2.5 M in hexane, 59.9 mmol) was added to methylenecyclopropane **1** (4.67 ml, 69.2 mmol) in THF (100 ml) at - 30 °C, and allowed to warm to 0 °C over 30 minutes. The reaction mixture was cooled to - 60 °C and benzylbromide (5.49 ml, 46.1 mmol) was added dropwise. The mixture was allowed to come to room temperature overnight. The reaction was then distilled under reduced pressure (bp. 56-58 °C/0.7 mm Hg) to give **240** (3.33 g, 50%) as a colourless oil R_f = 0.74 (50/50 ether/petrol); δ_H (300 MHz; $CDCl_3$) 7.41-7.15 (5H, m, H Ar), 5.50 (1H, s, $=CH_AH_B$), 5.45 (1H, s, $=CH_AH_B$), 2.73 (2H, d, *J* 7, CH_2Ph), 1.74 (1H, m, $CHCH_2Ph$), 1.36 (1H, m, $CH_AH_BC=CH_2$) and 0.91 (1H, m, $CH_AH_BC=CH_2$); δ_C (75 MHz; $CDCl_3$) 141.57 (0), 136.35 (0), 128.54 (2 x 1), 128.49 (2 x 1), 126.19 (1), 103.52 (2), 39.10 (2), 16.67 (1) and 9.78 (2).

All data agrees with data reported by Destabel.[9]

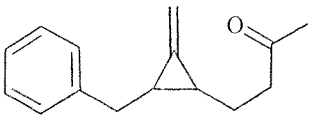


241

2-Methyl-2-(2-[methylene-3-(phenylmethyl)cyclopropyl]ethyl)-1.3-dioxolane 241

BuLi (3.26 ml of 2.34 M in hexane, 7.63 mmol) was added to 2-benzyl-methylenecyclopropyl **240** (1.11 g, 7.71 mmol) in THF (15 ml) at - 40 °C, and allowed to warm slowly to 0 °C over 30 minutes. The temperature was kept at 0 °C for 1 hour and then warmed to room temperature over 20 minutes. The reaction mixture was cooled to - 60 °C and iodide **170** (0.93 g, 3.86 mmol) was cannulated. The reaction mixture was allowed to come to room temperature overnight. The reaction was quenched with aq. NH_4Cl (50 ml) and extracted with ether (3 x 50 ml). The combined organic phases were washed once with brine (50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by

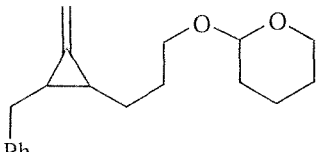
flash column chromatography (petrol/ethyl acetate ; 100/0 to 95/5) to give **241** (0.62 g, 62%) as a colourless oil and as an inseparable mixture of diastereoisomers (trans assumed to be major) R_f = 0.39 (90/10 petrol/ethyl acetate); ν_{max} (film)/cm^{-1} 3062, 3026, 2945, 1602, 1496, 1453, 1376, 1220, 1139, 1065 and 947; δ_H (300 MHz; $CDCl_3$) 7.39-7.15 (5H, m, H Ar), 5.43 (1H, s, =C$H_A$$H_B$), 5.41 (1H, s, =C$H_A$$H_B$), 4.05-3.85 (4H, m, O($CH_2$)$_2$O), 2.71 (2H, d, *J* 7, CH_2Ph) and 1.89-1.09 (6H, m, 2 x CH_2 and C*H*CH_2Ph and C*H*C=CH_2) and 1.30 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 141.95 (0), 141.69 (0), 128.45 (4 x 1), 126.08 (1), 109.95 (0), 103.07 (2 trans), 102.13 (2 cis), 64.77 (2 x 2), 38.84 (2 trans), 38.72 (2 cis), 29.22 (2 trans), 28.75 (2 cis), 27.84 (2 cis), 27.25 (2 trans), 23.98 (3 trans), 23.63 (3 cis), 22.80 (1 trans), 22.49 (1 cis) and 11.60 (1); m/z (CI) 259.1684 ([M + H]$^+$. $C_{17}H_{23}O_2$ requires 259.1698).



242

4-[2-Methylene-3-(phenylmethyl)cyclopropyl]-2-butanone 242

2-Methyl-2-(2-[methylene-3-(phenylmethyl)cyclopropyl]ethyl)-1.3-dioxolane **241** (0.88 g, 3.40 mmol) was stirred with *p*-TsOH (1.3 g, 6.81 mmol) in a mixture of acetone (90 ml) and 10% water (10 ml) for 48 hours. The mixture was concentrated *in vacuo*. Ether (50 ml) was added. The mixture was then washed once with 10% $NaHCO_3$ (50 ml) and extracted with ether (3 x 75 ml). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give **242** (0.62 g, 85%) as a colourless oil and as an inseparable mixture of diastereoisomers (trans assumed to be major) R_f = 0.34 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3062, 3026, 2922, 1716, 1602, 1496, 1453, 1364, 1163, 1030, 890, 747 and 700; δ_H (300 MHz; $CDCl_3$) 7.35-7.19 (5H, m, H Ar), 5.43 (1H, s, =C$H_A$$H_B$), 5.39 (1H, s, =C$H_A$$H_B$), 2.64 (2H, d, *J* 7, C$H_2$Ph), 2.43 (2H, t, *J* 7, CH_2CO), 2.07 (3H, s, CH_3), 1.83 (1H, m, C*H*CH_2Ph), 1.65 (2H, dt, *J* 7 and 7, C$H_2$$CH_2CO$) and 1.35 (1H, m, C*H*$CH_2CH_2CO$); δ_C (75 MHz; $CDCl_3$) 208.77 (0), 141.61 (0), 141.32 (0), 128.50 (2 x 1), 128.45 (2 x 1), 126.16 (1), 103.47 (2 trans), 102.50 (2 cis), 44.00 (2 cis), 43.24 (2 trans), 38.63 (2), 30.47 (2 cis), 30.09 (2 trans), 26.67 (2), 23.80 (3), 22.16 (1 cis), 22.08 (1 trans) and 15.45 (1); m/z (CI) 215.1445 ([M + H]$^+$. $C_{15}H_{19}O$ requires 215.1436).

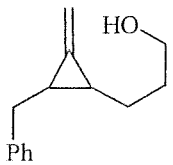


243

2-({3-[2-Methylene-3-(phenylmethyl)cyclopropyl]propyl}oxy)tetrahydro-2H-pyran 243

BuLi (2.94 ml of 2.34 M in hexane, 6.88 mmol) was added to 2-benzyl-methylenecyclopropyl **240** (1 g, 6.94 mmol) in THF (15 ml) at - 40 °C, and allowed to warm slowly to 0 °C over 30 minutes. The temperature was kept at 0 °C for 1 hour and then warmed to room temperature over 20 minutes. The reaction mixture was cooled to - 60 °C and bromide **180** (0.77 g, 3.47 mmol) was cannulated. The reaction mixture was allowed to come to room temperature overnight. The reaction was quenched with aq. NH_4Cl (50 ml) and extracted with ether (3 x 50 ml). The combined organic phases were washed once with brine (100 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/ethyl acetate ; 100/0 to 95/5) to give **243** (0.74 g, 75%) as a colourless oil and as an inseparable mixture of diastereoisomers (trans assumed to be major) R_f = 0.43 (90/10 petrol/ethyl acetate); ν_{max} (film)/cm^{-1} 3062, 3026, 2990, 1602, 1496, 1453, 1352, 1261, 1200, 1121, 1077, 1032, 988, 886 and 815; δ_H (300 MHz; $CDCl_3$) 7.34-7.19 (5H, m, H Ar), 5.41 (1H, s, =CH_AH$_B$), 5.37 (1H, s, =CH$_A$$H_B$), 4.59 (1H, t, *J* 4, OCHO cis), 4.56 (1H, t, *J* 4, OCHO trans), 3.86 (1H, m, CH_AH$_B$O), 3.77 (1H, m, CH$_A$$H_B$O), 3.49 (1H, m, C$H_AH_B$O), 3.36 (1H, m, CH$_A$$H_B$O), 2.72 (2H, d, *J* 7, CH_2Ph cis), 2.70 (2H, d, *J* 7, CH_2Ph trans), 1.90-1.42 (10H, m, 5 x CH_2), 1.36 (1H, m, CHCH$_2$Ph) and 1.25 (1H, m, CH(CH$_2$)$_3$); δ_C (75 MHz; $CDCl_3$) 142.02 (0), 141.70 (0), 128.48 (2 x 1), 128.44 (2 x 1), 126.08 (1), 103.03 (2 trans), 102.12 (2 cis), 98.99 (1), 67.30 (2), 62.50 (2), 38.78 (2 trans), 33.52 (2 cis), 30.92 (2 trans), 30.26 (2 cis), 29.67 (2), 29.42 (2), 25.66 (2 trans), 24.59 (2 cis), 23.62 (1 trans), 22.68 (1 trans), 22.50 (1 cis), 20.46 (1 cis) and 19.84 (2).

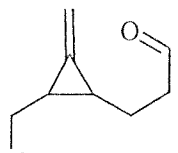
All data agrees with data reported by Destabel.[9]



244

3-[2-methylene-3-(phenylmethyl)cyclopropyl]-1-propanol 244

To a stirred solution of **243** (0.32 g, 1.13 mmol) in MeOH (50 ml) was added *p*-TsOH (0.43 g, 2.26 mmol). The solution was stirred for 2 days. K_2CO_3 (0.5 g, 3.62 mmol) was added and the reaction was concentrate *in vacuo*. Water (10 ml) was added and extracted with ether (3 x 50 ml). The organic layer was dried over $MgSO_4$ and concentrate *in vacuo*. The crude product was purified by flash column chromatography (petrol/ethyl acetate ; 100/0 to 80/20) to give **244** (0.16 g, 68%) as a colourless oil and as an inseparable mixture of diastereoisomers (trans assumed to be major) R_f = 0.23 (80/20 petrol/ethyl acetate); ν_{max} (film)/cm^{-1} 3346, 3062, 3026, 2932, 2854, 1602, 1496, 1453, 1140, 1059, 1030 and 888; δ_H (300 MHz; $CDCl_3$) 7.34-7.19 (5H, m, H Ar), 5.43 (2H, s, $=CH_2$), 3.71 (2H, t, *J* 6, CH_2OH trans), 3.62 (2H, t, *J* 6, CH_2OH cis), 2.70 (2H, d, *J* 7, CH_2Ph) and 1.76-1.19 (7H, m, 2 x CH_2 and OH and $CHCH_2Ph$ and $CH(CH_2)_3$); δ_C (75 MHz; $CDCl_3$) 141.92 (0), 141.65 (0), 128.46 (4 x 1), 126.12 (1), 103.12 (2 trans), 102.19 (2 cis), 62.76 (2 cis), 62.59 (2 trans), 38.71 (2 trans), 33.50 (2 cis), 33.14 (2 cis), 32.54 (2 trans), 28.88 (2 trans), 24.10 (2 cis), 23.64 (2 trans), 22.51 (1 trans), 21.22 (1 cis), 20.39 (1 trans) and 19.75 (1 cis).
All data agrees with data reported by Destabel.[9]

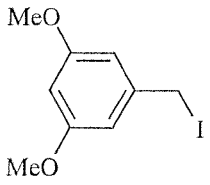


245

3-[Methylene-3-(phenylmethyl)cyclopropyl]propanal 245

Following the method of Swern,[90] DMSO (0.31 ml, 4.04 mmol), in dichloromethane (4 ml), was added to a solution of oxalyl chloride (0.19 ml, 2.05 mmol), in dichloromethane (15 ml), keeping the mixture below - 50 °C. The mixture was stirred for 2 minutes at - 60 °C. Alcohol **244** (0.36 g, 1.78 mmol), in dichloromethane (5 ml), was then added within 5 minutes, again keeping the temperature below - 50 °C. The solution was stirred for 15 minutes and triethylamine (1.12 ml, 8.06 mmol) was added and stirred for 5 minutes. The

solution was allowed to warm to room temperature. The mixture was quenched with water (50 ml) and extracted with dichloromethane (3 x 50 ml). The organic phase was dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (petrol/ethyl acetate : 100/0 to 90/10) to give **245** (0.24 g, 68%) as a colourless oil and as an inseparable mixture of diastereoisomers (trans assumed to be major) R_f = 0.49 (80/20 petrol/ethyl acetate); ν_{max} (film)/cm^{-1} 3062, 3027, 2920, 2721, 1721, 1602, 1496, 1453, 1242, 1074, 890 and 700; δ_H (300 MHz; $CDCl_3$) 9.80 (1H, t, *J* 2, CHO cis), 9.72 (1H, t, *J* 2, CHO trans), 7.39-7.20 (5H, m, H Ar), 5.44 (2H, s, $=CH_2$ trans), 5.43 (2H, s, $=CH_2$ cis), 2.71 (2H, d, *J* 7, CH_2Ph cis), 2.67 (2H, d, *J* 7, CH_2Ph trans), 2.57 (2H, dt, *J* 2 and 8 CH_2CHO cis), 2.46 (2H, dt, *J* 2 and 8 CH_2CHO trans), 1.86-1.61 (2H, m, CH_2CH_2CHO), 1.38 (1H, m, CHCH$_2$Ph) and 1.26 (1H, m, $CH(CH_2)_2$); δ_C (75 MHz; $CDCl_3$) 202.46 (1), 141.45 (0), 140.95 (0 trans), 140.67 (0 cis), 128.51 (2 x 1), 128.44 (2 x 1), 126.22 (1), 103.83 (2 trans), 102.79 (2 cis), 44.33 (2 cis), 43.69 (2 trans), 38.55 (2 trans), 33.42 (2 cis), 25.26 (2 trans), 23.93 (1 trans), 21.94 (1 trans), 20.64 (2 cis), 20.53 (1 cis) and 19.20 (1 cis); m/z (CI) 218.1548 ([M + NH_4^+]$^+$. $C_{14}H_{20}NO$ requires 218.1545).

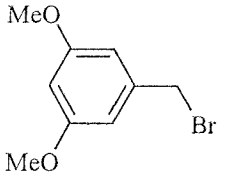


250

1-(Iodomethyl)-3,5-di(methoxy)benzene 250

Following the method of Motherwell,[17b] triphenylphosphine (2.33 g, 8.91 mmol), imidazole (0.69 g, 10 mmol) and finally iodine (2.41 g, 9.5 mmol) were added to a stirred solution of alcohol **249** (1 g, 5.94 mmol) in ether (60 ml) and acetonitrile (20 ml). The solution was stirred for 15 minutes. The resulting red solution was diluted in ether (100 ml), washed with 5% $Na_2S_2O_3$ (100 ml), then water (50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with petrol (5 x 20 ml), filtered and concentrated *in vacuo* to give **250** (1.63 g, 99%) as a pale yellow solid (mp. : 76-78 °C) R_f = 0.64 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2930, 2833, 1591, 1475, 1327, 1150, 1051 and 940; δ_H (300 MHz; $CDCl_3$) 6.54 (2H, d, *J* 2, Ar H), 6.36 (1H, t, *J* 2, Ar H), 4.39 (2H, s, CH_2I) and 3.79

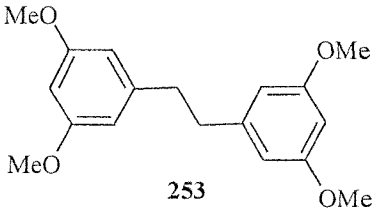
(6H, s, 2 x CH_3O); δ_C (75 MHz; $CDCl_3$) 160.80 (2 x 0), 141.21 (0), 106.69 (2 x 1), 100.16 (1), 55.38 (2 x 3) and 5.68 (2); m/z (EI+) 277 ($[M - H]^+$, 42%) and 151 (100%).



251

1-(Bromomethyl)-3,5-di(methoxy)benzene 251

Following the method of Motherwell,[17b] triphenylphosphine (2.33 g, 8.91 mmol), imidazole (0.69 g, 10 mmol) and finally bromine (0.49 g, 9.5 mmol) were added to a stirred solution of alcohol **249** (1 g, 5.94 mmol) in ether (60 ml) and acetonitrile (20 ml). The solution was stirred for 15 minutes. The resulting solution was diluted in ether (100 ml), washed with 5% $Na_2S_2O_3$ (100 ml), then water (50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with petrol (5 x 20 ml), filtered, concentrated *in vacuo* and purified by flash column chromatography (ether/petrol ; 0/100 to 5/95) to give **251** (1.23 g, 90%) as a white solid (mp. : 53-55 °C) R_f = 0.67 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2925, 2833, 1592, 1425, 1317, 1200, 1167 and 1058; δ_H (300 MHz; $CDCl_3$) 6.55 (2H, d, *J* 2, Ar H), 6.41 (1H, t, *J* 2, Ar H), 4.44 (2H, s, CH_2Br) and 3.81 (6H, s, 2 x CH_3O); δ_C (75 MHz; $CDCl_3$) 161.05 (2 x 0), 139.89 (0), 107.10 (2 x 1), 100.74 (1), 55.55 (2 x 3) and 33.80 (2); m/z (EI+) 231 ($[M]^+$, 100%).

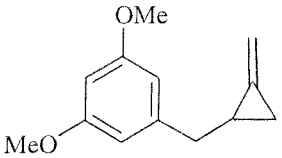


253

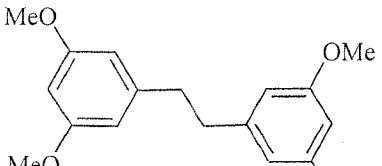
1-{2-[3,5-Di(methoxy)phenyl]ethyl}-3,5-di(methoxy)benzene 253

BuLi (1.38 ml of 2.34 M in hexane, 3.24 mmol) was added to methylenecyclopropane **1** (0.24 ml, 3.6 mmol) in THF (10 ml) at - 30 °C, and allowed to warm to 0 °C over 30 minutes. The reaction mixture was cooled to - 60 °C and iodide **250** (0.5 g, 1.8 mmol) in THF (2 ml) was added dropwise. The mixture was allowed to come to room temperature

overnight. The reaction was quenched with aq. NH_4Cl (10%, 50 ml) and extracted with ether (3 x 50 ml). The combined organic phases were washed once with brine (100 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/ether : 100/0 to 70/30) to give **253** (0.18 g, 33%) as a white solid (mp. : 91-93 °C) R_f = 0.48 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2930, 2832, 1596, 1455, 1313, 1205, 1141 and 1067; δ_H (300 MHz; $CDCl_3$) 6.38 (4H, d, *J* 2, Ar H), 6.34 (2H, t, *J* 2, Ar H), 3.79 (12H, s, 4 x CH_3O) and 2.87 (4H, s, 2 x CH_2); δ_C (75 MHz; $CDCl_3$) 160.77 (4 x 0), 144.14 (2 x 0), 106.53 (4 x 1), 98 (2 x 1), 55.28 (4 x 3) and 38.02 (2 x 2); m/z (EI+) 302 ($[M]^+$, 85%) and 151 (100%).



252



253

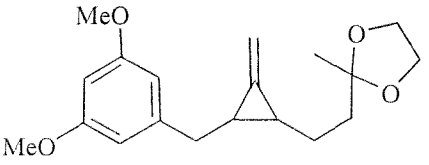
1-[(2-Methylenecyclopropyl)methyl]-3,5-di(methoxy)benzene 252

1-{2-[3,5-Di(methoxy)phenyl]ethyl}-3,5-di(methoxy)benzene 253

BuLi (6 ml of 2.34 M in hexane, 14.1 mmol) was added to methylenecyclopropane **1** (1.1 ml, 16.2 mmol) in THF (50 ml) at - 30 °C, and allowed to warm to 0 °C over 30 minutes. The reaction mixture was cooled to - 60 °C and bromide **251** (2.5 g, 10.8 mmol) in THF (10 ml) was added dropwise. The mixture was allowed to come to room temperature overnight. The reaction was quenched with aq. NH_4Cl (10%, 50 ml) and extracted with ether (3 x 50 ml). The combined organic phases were washed once with brine (100 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/ether : 100/0 to 95/5) to give **252** (1.05 g, 48%) as a colourless oil and dimer **253** (0.17 g, 27%) as a white solid;

BuLi (6 ml of 2.34 M in hexane, 14.1 mmol) was added to methylenecyclopropane **1** (1.1 ml, 16.2 mmol) in THF (50 ml) at - 30 °C, and allowed to warm to 0 °C over 30 minutes. The reaction mixture was cooled to - 60 °C and HMPA (0.74 ml, 4.15 mmol) was added followed by the dropwise addition of bromide **251** (2.5 g, 10.8 mmol) in THF (10 ml). The mixture was allowed to come to room temperature overnight. The reaction was quenched with aq. NH_4Cl (10%, 50 ml) and extracted with ether (3 x 50

ml). The combined organic phases were washed once with brine (100 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/ether : 100/0 to 95/5) to give **252** (0.03 g, 7%) as a colourless oil R_f = 0.75 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2936, 1596, 1461, 1429, 1319, 1206, 1155, 1068 and 888; δ_H (300 MHz; $CDCl_3$) 6.45 (2H, d, *J* 2, Ar H), 6.35 (1H, t, *J* 2, Ar H), 5.49 (1H, s, $=CH_AH_B$), 5.43 (1H, s, $=CH_AH_B$), 3.81 (6H, s, 2 x CH_3O), 2.67-2.63 (2H, m, CH_2Ar), 1.63 (1H, m, $CHCH_2Ar$), 1.35 (1H, m, $CH_AH_BC{=}CH_2$) and 0.93 (1H, m, $CH_AH_BC{=}CH_2$); δ_C (75 MHz; $CDCl_3$) 160.87 (2 x 0), 143.99 (0), 136.29 (0), 106.55 (2 x 1), 103.52 (2), 98.08 (1), 55.41 (2 x 3), 39.37 (2), 15.44 (1) and 9.77 (2); m/z (EI+) 204 ($[M]^+$, 79%) and 151 (100%); and dimmer **253** (0.19 g, 29%) as a white solid.

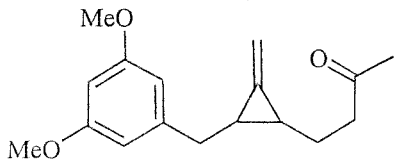


254

2-[2-(2-{[3,5-Di(methoxy)phenyl]methyl}-3-methylenecyclopropyl)ethyl]-2-methyl-1,3-dioxolane 254

BuLi (1.04 ml of 2.34 M in hexane, 2.43 mmol) was added to 1-[(2-methylenecyclopropyl)methyl]-3,5-di(methoxy)benzene **252** (0.5 g, 2.45 mmol) in THF (5 ml) at - 40 °C, and allowed to warm slowly to 0 °C over 30 minutes. The temperature was kept at 0 °C for 1 hour and then warmed to room temperature over 20 minutes. The reaction mixture was cooled to -60 °C and iodide **170** (0.3 g, 1.22 mmol) was added dropwise. The reaction mixture was allowed to come to room temperature overnight. The reaction was quenched with aq. NH_4Cl (20 ml) and extracted with ether (3 x 50 ml). The combined organic phases were washed once with brine (50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/ether : 100/0 to 80/20) to give **254** (0.093 g, 24%) as a colourless oil and as a mixture of diastereoisomers (trans assumed to be major) R_f = 0.54 (50/50 petrol/ether); ν_{max} (film)/cm^{-1} 2943, 2834, 1593, 1458, 1420, 1374, 1204, 1147, 1055, 884, 829 and 736; δ_H (300 MHz; $CDCl_3$) 6.55-6.26 (3H, m, Ar H), 5.49 (2H, s, $=CH_2$ cis), 5.43 (2H, s, $=CH_2$ trans), 4.09-3.89 (4H, m, $O(CH_2)_2O$), 3.83 (6H, s, 2 x CH_3O cis), 3.81 (6H, s, 2 x CH_3O trans), 2.78-2.68 (2H, m, CH_2Ar trans),

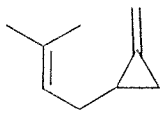
2.68-2.55 (2H, m, C*H*$_2$Ar cis), 1.79-1.74 (2H, m, C*H*$_2$CHCHCH$_2$Ar), 1.43 (3H, s, CH$_3$), 1.40-1.28 (3H, m, CH$_2$CO and C*H*CH$_2$Ar) and 0.89 (1H, m, C*H*(CH$_2$)$_2$); δ_C (75 MHz; CDCl$_3$) 144.11 (0), 141.90 (0), 140.43 (0), 136.53 (0), 110.34 (0 trans), 109.94 (0 cis), 106.47 (2 x 1), 103.95 (2 trans), 103.44 (2 cis), 98.32 (1), 64.78 (2 x 2 cis), 64.74 (2 x 2 trans), 55.39 (2 x 3), 39.65 (2 trans), 39.03 (2 cis), 38.86 (2 cis), 37.88 (2 trans),27.23 (2 trans), 23.99 (3 trans), 23.80 (3 cis), 23.38 (2 cis), 22.83 (1 cis),17.75 (1 cis), 16.69 (1 trans) and 9.77 (1 trans); m/z (CI) 319.1910 ([M + H]$^+$. $C_{19}H_{27}O_4$ requires 319.1909).



255

4-(2-{[3,5-Di(methoxy)phenyl]methyl}-3-methylenecyclopropyl)-2-butanone 255

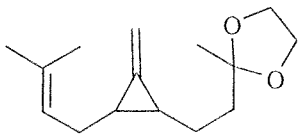
2-[2-(2-{[3,5-Di(methoxy)phenyl]methyl}-3-methylenecyclopropyl)ethyl]-2-methyl-1,3-dioxolane **254** (0.19 g, 0.59 mmol) was stirred with *p*-TsOH (0.23 g, 1.19 mmol) in a mixture of acetone (90 ml) and 10% water (10 ml) for 48 hours. The mixture was concentrated *in vacuo*. Ether (50 ml) was added. The mixture was then washed once with 10% NaHCO$_3$ (50 ml) and extracted with ether (3 x 75 ml). The organic phase was dried over MgSO$_4$, concentrated *in vacuo* to give **255** (0.1 g, 64%) as a colourless oil and as an inseparable mixture of diastereoisomers R_f = 0.35 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2935, 1713, 1600, 1462, 1321, 1155 and 1063; δ_H (300 MHz; CDCl$_3$) 6.48-6.29 (3H, m, Ar H), 5.43 (2H, s, =CH$_2$ trans), 5.41 (2H, s, =CH$_2$ cis), 3.80 (6H, s, 2 x CH$_3$O), 2.61-2.56 (2H, m, C*H*$_2$Ar trans), 2.51-2.41 (2H, m, C*H*$_2$Ar cis), 2.14 (2H, t, *J* 7, C*H*$_2$CO), 2.09 (3H, s, CH$_3$), 1.64 (1H, m, C*H*CH$_2$Ar), 1.34-1.26 (2H, m, CH$_2$C*H*$_2$CHC=CH$_2$) and 0.88 (1H, m, C*H*(CH$_2$)$_2$); δ_C (75 MHz; CDCl$_3$) 208.77 (0), 160.88 (2 x 0), 144.02 (0), 141.28 (0), 106.46 (2 x 1), 103.51 (2 trans), 102.55 (2 cis), 98.11 (1), 55.40 (2 x 3), 43.99 (2 cis), 43.23 (2 trans), 38.94 (2), 33.68 (2 cis), 30.07 (2 trans), 26.66 (3), 23.56 (1 trans), 22.09 (1 trans), 20.30 (1 cis) and 19.21 (1 cis); m/z (CI) 275.1647 ([M + H]$^+$. $C_{17}H_{23}O_3$ requires 275.1647).



259

3-Methyl-1-(2-methylenecyclopropyl)-2-butene 259

BuLi (8.6 ml of 2.04 M in hexane, 17.5 mmol) was added to methylenecyclopropane **1** (1.35 ml, 20.1 mmol) in THF (10 ml) at - 30 °C, and allowed to warm to 0 °C over 30 minutes. The reaction mixture was cooled to - 60 °C and allyl bromide **258** (1.55 ml, 13.4 mmol) was added dropwise. The mixture was allowed to come to room temperature overnight. The reaction was then distilled under reduced pressure (bp. 119-121 °C/60 mm Hg) to give **259** (1.43 g, 88%) as a colourless oil R_f = 0.77 (80/20 ether/petrol); ν_{max} (film)/cm^{-1} 2972, 1446, 1109 and 886; δ_H (300 MHz; $CDCl_3$) 5.43 (1H, s, =CH_AH$_B$), 5.36 (1H, s, =CH$_A$$H_B$), 5.22 (1H, t with fine coupling, *J* 6, =CH), 2.09-2.05 (2H, m, CH_2CH=), 1.73 (3H, s, CH_3), 1.62 (3H, s, CH_3), 1.44 (1H, m, C*H*CH$_2$CH=), 1.31 (1H, m, CH_AH$_B$CHCH$_2$CH=) and 0.89 (1H, m, CH$_A$$H_B$CHCH$_2$CH); δ_C (75 MHz; $CDCl_3$) 136.81 (0), 132.32 (0), 123.06 (1), 102.77 (2), 31.36 (2), 25.89 (1), 17.92 (3), 15.89 (3) and 9.15 (2); m/z (EI+) 107 ([M - CH_3]$^+$, 30%) and 87 (100%).

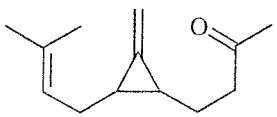


260

2-Ethyl-2-{2-[2-(3-methyl-2-butyl)-3-methylenecyclopropyl]ethyl}-1,3-dioxolane 260

BuLi (2.5 ml of 2.04 M in hexane, 5.11 mmol) was added to 3-methyl-1-(2-methylenecyclopropyl)-2-butene **259** (0.63 g, 5.16 mmol) in THF (10 ml) at - 40 °C, and allowed to warm slowly to 0 °C over 30 minutes. The temperature was kept at 0 °C for 1 hour and then warmed to room temperature over 20 minutes. The reaction mixture was cooled to - 60 °C and iodide **170** (1 g, 9.38 mmol) was added dropwise. The reaction mixture was allowed to come to room temperature overnight. The reaction was quenched with aq. NH_4Cl (10%, 100 ml) and extracted with ether (3 x 50 ml). The combined organic phases were washed once with brine (50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/ether : 100/0 to 95/5) to give **260** (0.32 g, 33%) as a colourless oil and as an inseparable mixture of diastereoisomers (trans

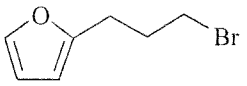
assumed to be major) R_f = 0.56 (80/20 petrol/ether); ν_{max} (film)/cm^{-1} 2929, 1449, 1376, 1218, 1112, 1065 and 887; δ_H (300 MHz; $CDCl_3$) 5.36 (2H, s, =CH_2 trans), 5.31 (2H, s, =CH_2 cis), 5.18 (1H, t with fine coupling, *J* 6, =CH), 4.05-3.85 (4H, m, O(CH_2)$_2$O), 2.19-1.90 (2H, m, CH_2CH=), 1.86-1.69 (2H, m, CHCH_2CH_2), 1.71 (3H, s, CH_3C=), 1.60 (3H, s, CH_3C=), 1.54-1.29 (3H, m, CHCH_2CH_2 and C*H*CH_2CH=), 1.31 (3H, s, CH_3) and 1.07 (1H, m, C*H*(CH_2)$_2$); δ_C (75 MHz; $CDCl_3$) 142.46 (0), 132.06 (0), 123.26 (1 trans), 122.64 (1 cis), 110.00 (0), 102.34 (2 trans), 101.42 (2 cis), 64.77 (2 x 2), 38.97 (2 trans), 38.51 (2 cis), 33.02 (2 cis), 30.99 (2 trans), 28.79 (2 cis), 27.29 (2 trans), 25.89 (3), 23.97 (3), 22.85 (1 trans), 22.31 (1trans), 20.01 (1 cis), 19.76 (1 cis) and 17.95 (3); m/z (CI) 237.1844 ([M + H]$^+$. $C_{15}H_{25}O_2$ requires 237.1854), 175 ([M - O(CH_2)$_2$O]$^+$, 20%) and 87 (100%).



261

4-[2-(3-Methyl-2-butyl)-3-methylenecyclopropyl]-2-butanone 261

2-Ethyl-2-{2-[2-(3-methyl-2-butyl)-3-methylenecyclopropyl]ethyl}-1,3-dioxolane **260** (0.32 g, 1.35 mmol) was stirred with *p*-TsOH (0.52 g, 2.71 mmol) in a mixture of acetone (45 ml) and 10% water (5 ml) for 48 hours. The mixture was concentrated *in vacuo*. Ether (50 ml) was added. The mixture was then washed once with 10% $NaHCO_3$ (50 ml) and extracted with ether (3 x 75 ml). The organic phase was dried over $MgSO_4$, concentrated *in vacuo* to give **261** (0.15 g, 58%) as a colourless oil and as a mixture of diastereoisomers R_f = 0.35 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3063, 2928, 1718, 1438, 1364, 1162 and 887; δ_H (300 MHz; $CDCl_3$) 5.32 (1H, s, =CH_AH$_B$), 5.30 (1H, s, =CH$_A$$H_B$), 5.11 (1H, t with fine coupling, *J* 6, =CH), 2.47 (2H, t, *J* 7, CH_2COCH_3), 2.10 (3H, s, COCH_3), 2.06-1.90 (2H, m, =CHCH_2CH), 1.66 (3H, s, CH_3C=), 1.71-1.50 (3H, m, CHCH_2CH_2COMe and =CHCH_2C*H*), 1.54 (3H,s, CH_3C=) and 1.03 (1H, m, C*H*(CH_2)$_2$COMe); δ_C (75 MHz; $CDCl_3$) 208.92 (0), 141.72 (0), 132.27 (0), 123.05 (1 trans), 122.40 (1 cis), 102.81 (2 trans), 101.82 (2 cis), 43.48 (2 trans), 43.02 (2 cis), 33.00 (2 cis), 30.85 (2 trans), 30.14 (2 trans), 28.23 (2 cis), 26.89 (3), 25.89 (3), 22.86 (1 trans), 22.04 (1 cis), 21.58 (1 trans), 20.07 (1 cis), 19.00 (3 cis) and 17.93 (3 trans); m/z (CI) 193.1242 ([M + H]$^+$. $C_{13}H_{21}O$ requires 193.3083), 210 ([M + NH_4^+]$^+$, 4%), 193 ([M + H]$^+$, 6%) and 180 (100%).

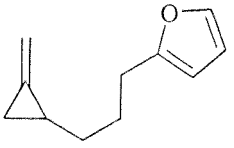


268

2-(3-Bromopropyl)furan 268

Following the method of Padwa,[64] BuLi (32.24 ml, 73.4 mmol) was added to a stirred solution of furan (5.34 ml, 73.4 mmol) in THF (50 ml) at 0 °C. The mixture was stirred at 0 °C for 1 hr. A solution of 1,3-dibromopropane (9.69 ml, 95.4 mmol) in THF (5 ml) was rapidly added. The mixture was allowed to warm to room temperature overnight. The solution was quenched with sat. NH_4Cl (50 ml) and extracted with ether (3 x 50 ml). The combined organic layers were washed with brine (50 ml), dried over $MgSO_4$ and concentrated *in vacuo* to form a colourless oil, which was distilled (89-91 °C/10 mm Hg ; lit. bp.[63] 100-103 °C/20 mm Hg) to give **268** as a colourless oil (6.08 g, 78%) R_f = 0.68 (95/5 petrol/ether); δ_H (300 MHz; $CDCl_3$) 7.33 (1H, dd, *J* 0.7 and 0.7, OHC=C*H*-CH=), 6.30 (1H, d, *J* = 0.7, O*H*C=CH), 6.07 (1H, d, *J* 0.7, C*H*=CCH_2), 3.44 (2H, t, *J* 7, CH_2Br), 2.83 (2H, t, *J* 7, =CCH_2), 2.20 (2H, p, *J* 7, $CH_2CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 154.32 (0), 141.39 (1), 110.33 (1), 105.88 (1), 33.03 (2), 31.17 (2) and 26.52 (2).

All data agrees with data reported by Padwa.[64]

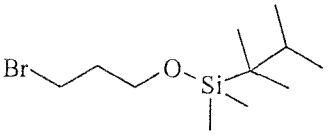


269

2-[3-(2-Methylenecyclopropyl)propyl]furan 269

BuLi (1.1 ml of 2.28 M in hexane, 2.5 mmol) was added to methylenecyclopropane **1** (5 ml of 1 M in THF, 4.99 mmol) in THF (15 ml) at - 30 °C, and allowed to warm to 0 °C over 30 minutes. The reaction mixture was cooled to - 60 °C and HMPA (0.67 ml, 3.74 mmol) added followed immediately by the dropwise addition of 2-(3-bromopropyl)furan **268** (0.36 g, 1.95 mmol). The reaction was allowed to come to room temperature overnight. The reaction mixture was quenched with aq. NH_4Cl (10%, 20 ml) and extracted with ether (3 x 50 ml). The combined organic phases were washed once with brine (50 ml), dried over $MgSO_4$

and concentrated *in vacuo*. The crude product was purified by flash column chromatography (100% petrol) to give **269** (0.23 g, 74%) as a colourless oil R_f = 0.73 (5/95 ether/petrol); ν_{max} (film)/cm^{-1} 3067, 3042, 2932, 1596, 1507, 1146, 1007 and 886; δ_H (300 MHz; $CDCl_3$) 7.31 (1H, dd, *J* 0.7 and 0.7, OHC=C*H*-CH=), 6.29 (1H, d, *J* 0.7, O*H*C=CH), 6.00 (1H, d, *J* 0.7, C*H*=CCH$_2$), 5.42 (1H, s, =CH_AH$_B$), 5.36 (1H, s, =CH$_A$$H_B$), 2.68 (2H, t, *J* 7, (CH$_2$)$_2$CH_2furan), 1.79 (2H, p, *J* 7, CH$_2$CH_2CH$_2$), 1.55-1.31 (3H, m, CH_2CHC=CH$_2$ and C*H*C=CH$_2$), 1.24 (1H, m, CH_AH$_B$C=CH$_2$) and 0.76 (1H, m, CH$_A$$H_B$C=CH$_2$); δ_C (75 MHz; $CDCl_3$) 156.31 (0), 140.70 (1), 136.81 (0), 110.03 (1), 104.05 (1), 102.57 (2), 32.54 (2), 27.82 (2), 27.64 (2), 15.44 (1) and 9.40 (2); m/z (EI+) 162 ([M]$^+$, 3%) and 81 (100%).

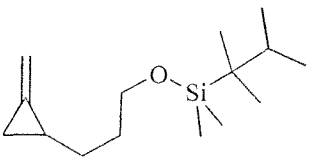


271

3-Bromopropyl[1,1-dimethyl-1-(1,1,2-trimethylpropyl)silyl]ether 271

Dimethylthexylsilyl chloride (17 ml, 86.3 mmol) was added dropwise to a stirred solution of 3-bromopropanol (10 g, 71.9 mmol), imidazole (19.6 g, 288 mmol) and a catalytic amount of DMAP, in DCM (60 ml) at 0 °C. The mixture was allowed to come to room temperature over 2 hrs. The mixture was poured into ice-cooled water and the organic layer separated, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (petrol/ethyl acetate ; 100 to 95/5) to give **271** (19.43 g, 96%) as a colourless oil R_f = 0.79 (70/30 petrol/ethyl acetate); δ_H (300 MHz; $CDCl_3$) 3.72 (2H, t, *J* 5, CH_2O), 3.52 (2H, t, *J* 6, CH_2Br), 2.03 (2H, tt, *J* 6 and 5, CH_2), 1.63 (1H, septet, *J* 7, CH), 0.89 (6H, d, *J* 7, 2 x CH_3), 0.85 (6H, s, 2 x CH_3) and 0.11 (6H, s, Si$(CH_3)_2$); δ_C (75 MHz; $CDCl_3$) 60.16 (2), 35.57 (2), 34.24 (1), 30.76 (2), 25.13 (0), 20.32 (2 x 3), 18.49 (2 x 3), -3.50 (2 x 3).

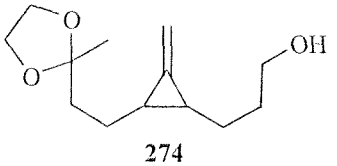
All data agreed with data reported by Pike.[10]



272

1,1-Dimethyl-1-(1,1,2-trimethylpropyl)silyl[3-(2-methylenecyclopropyl)propyl] ether 272

BuLi (10.68 ml of 1.57 M in hexane, 16.8 mmol) was added to methylenecyclopropane **1** (43.64 ml of 1 M in THF, 33.6 mmol) in THF (100 ml) at - 30 °C, and allowed to warm to 0 °C over 30 minutes. The reaction mixture was cooled to - 60 °C and HMPA (4.51 ml, 25.1 mmol) added followed immediately by the dropwise addition of silylbromide **271** (3.69 g, 13.1 mmol). The reaction was allowed to come to room temperature overnight. The reaction mixture was quenched with aq. NH_4Cl (10%, 50 ml) and extracted with ether (3 x 100 ml). The combined organic phases were washed once with brine (100 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (100% petrol) to give **272** (2.79 g, 76%) as a colourless oil R_f = 0.69 (5/95 ether/petrol); ν_{max} (film)/cm^{-1} 2957, 1464, 1379, 1251, 1094 and 826; δ_H (300 MHz; $CDCl_3$) 5.40 (1H, s, =C*H*$_A$H$_B$), 5.34 (1H, s, =CH$_A$*H*$_B$), 3.63 (2H, t, *J* 8, CH_2O), 1.73-1.58 (3H, m, $CH_2CH_2CH_2$ and $CH(CH_3)_2$), 1.49-1.35 (2H, m, $CH_2CH_2CH_2O$), 1.23 (1H, m, $CHC=CH_2$), 0.89 (6H, d, *J* 7, 2 x CH_3), 0.87 (1H, m, C*H*$_A$H$_B$C=CH2), 0.85 (6H, s, 2 x CH_3), 0.76 (1H, m, CH$_A$*H*$_B$C=CH_2) and 0.09 (6H, s, $Si(CH_3)_2$); δ_C (75 MHz; $CDCl_3$) 137.06 (0), 102.37 (2), 62.56 (2), 34.23 (2), 32.57 (1), 29.47 (2), 25.14 (0), 20.37 (2 x 3), 18.50 (2 x 3), 15.51 (1), 9.40 (2) and -3.38 (2 x 3); m/z (CI) 255 ([M + H]$^+$, 4%) and 95 (100%).

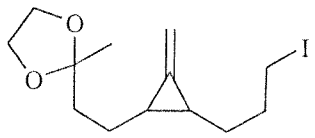


274

3-{2-[2-52-Methyl-1,3-dioxolan-2-yl)ethyl]-3-methylenecyclopropyl}-1-propanol 274

BuLi (2 ml of 1.48 M in hexane, 2.95 mmol) was added to 2-methyl-[(2'-ethyl)-(1''-methylenecyclopropyl)]-1,3-dioxolane **172** (0.5 g, 2.98 mmol) in THF (10 ml) at - 40 °C, and allowed to warm slowly to 0 °C over 30 minutes. The temperature was kept at 0 °C for 1 hour and then warmed to room temperature over 20 minutes. The reaction mixture was cooled to -

60 °C and silylbromide **271** (0.42 g, 1.49 mmol) was added dropwise. The reaction mixture was allowed to come to room temperature overnight. The reaction was quenched with aq. NH_4Cl (10%, 50 ml) and extracted with ether (3 x 50 ml). The combined organic phases were washed once with brine (50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction was dissolved in THF (10 ml) and TBAF (1.49 ml of 1 M in THF, 1.49 mmol) was added to the solution at 0 °C and stirred for 30 mins.. The mixture was allowed to come to room temperature and left overnight. The solution was concentrated *in vacuo* and purified by flash column chromatography (petrol/ether : 100/0 to 30/70) to give **274** (0.023 g, 10%) as a colourless oil and as an inseparable mixture of diastereoisomers (trans assumed to be major) R_f = 0.09 (50/50 petrol/ether); ν_{max} (film)/cm^{-1} 3378, 2931, 1451, 1376, 1060 and 885; δ_H (300 MHz; $CDCl_3$) 5.36 (2H, s, $=CH_2$ trans), 5.33 (2H, s, $=CH_2$ cis), 4.05-3.85 (4H, m, $O(CH_2)_2O$), 3.68 (2H, t, *J* 7, CH_2OH), 2.34 (1H, br s, OH), 1.82-1.61 (4H, m, 2 x CH_2), 1.53-1.49 (5H, m, 2 x CH_2 and $CHC=CH_2$), 1.30 (3H, s, CH_3) and 1.05 (1H, m, $CHC=CH_2$); δ_C (75 MHz; $CDCl_3$) 142.56 (0 trans), 142.23 (0 cis), 109.97 (0), 102.40 (2 trans), 101.50 (2 cis), 64.86 (2 x 2 cis), 64.78 (2 x 2 trans), 62.75 (2 cis), 62.68 (2 trans), 39.54 (2 cis), 39.00 (2 trans), 33.20 (2 cis), 32.70 (2 trans), 31.71 (2 cis), 28.96 (2 trans), 28.74 (2 cis), 27.29 (2 trans), 23.97 (3 trans), 23.61 (3 cis), 22.70 (1 trans), 22.46 (1 trans), 19.65 (1 cis) and 19.47 (1 cis); m/z (CI) 244 ($[M + NH_4^+]^+$, 2%) and 165 (100%).

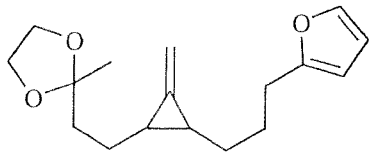


275

2-{2-[2-(3-Iodopropyl)-3-methylenecyclopropyl]ethyl}-2-methyl-1,3-dioxolane 275

Following the method of Motherwell,[17b] triphenylphosphine (0.68 g, 2.59 mmol), imidazole (0.2 g, 2.93 mmol) and finally iodine (0.7 g, 2.76 mmol) were added to a stirred solution of alcohol **274** (0.39 g, 1.72 mmol) in ether (60 ml) and acetonitrile (20 ml). The solution was stirred for 15 minutes. The resulting red solution was diluted in ether (50 ml), washed with 5% $Na_2S_2O_3$ (20 ml), then water (50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with petrol (5 x 20 ml), filtered, concentrated *in vacuo* and purified by flash column chromatography (ether/petrol ; 0/100 to 10/90) to give **275** (0.49 g, 84%) as a colourless oil and as an inseparable mixture of diastereoisomers (trans assumed to

be major) R_f = 0.48 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2980, 1749, 1374, 1218, 1058 and 885; δ_H (300 MHz; $CDCl_3$) 5.37 (1H, s, =C*H*$_A$H$_B$), 5.34 (2H, s, =CH$_A$*H*$_B$), 4.01-3.85 (4H, m, O(CH$_2$)$_2$O), 3.32-3.12 (2H, m, CH$_2$I), 2.16-1.85 (2H, m, C*H*$_2$CH$_2$I), 1.81-1.68 (2H, m, C*H*$_2$CO(CH$_2$)$_2$O), 1.64-1.44 (4H, m, C*H*$_2$(CH$_2$)$_2$I and C*H*$_2$CH$_2$), 1.29 (3H, s, CH$_3$), 1.07 (1H, m, (CH$_2$)$_3$C*H*C=CH$_2$), 0.86 (1H, m, C*H*C=CH$_2$); δ_C (75 MHz; $CDCl_3$) 141.49 (0 trans), 141.60 (0 cis), 109.93 (0), 102.75 (2 trans), 101.87 (2 cis), 64.88 (2 x 2 cis), 64.80 (2 x 2 trans), 39.51 (2 cis), 38.96 (2 trans), 34.84 (2 cis), 34.06 (2 cis), 33.62 (2 trans), 33.45 (2 trans), 28.32 (2 cis), 27.26 (2 trans), 23.98 (3), 22.70 (1 trans), 22.22 (1 trans), 19.70 (1 cis), 18.64 (1 cis), 7.04 (2 cis) and 6.74 (2 trans); m/z (CI) 337 ([M + H]$^+$, 20%) and 275 (100%).

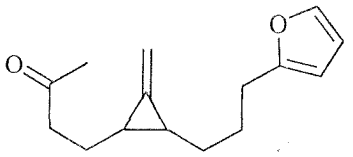


270

2-(2-{2-[3-(2-Furyl)propyl]-3-methylenecyclopropyl}ethyl)-2-methyl-1,3-dioxolane 270

Following Padwa *et al.* method,[64] BuLi (0.56 ml of 2.22 M in hexane, 1.24 mmol) was added to a stirred solution of furan (0.1 ml, 1.43 mmol) in THF (5 ml) at 0 °C. The mixture was stirred at 0 °C for 1 hr. A solution of 2-{2-[2-(3-iodopropyl)-3-methylenecyclopropyl]ethyl}-2-methyl-1,3-dioxolane **275** (0.32 g, 0.95 mmol) in THF (2 ml) was added dropwise. The mixture was allowed to warm to room temperature overnight. The solution was quenched with sat. NH_4Cl (5 ml) and extracted with ether (3 x 20 ml). The combined organic layers were washed with brine (10 ml), dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (ether/petrol ; 0/100 to 10/90) to give **270** as a colourless oil (0.25 g, 95%) and as an inseparable mixture of diastereoisomers (trans assumed to be major) R_f = 0.55 (50/50 petrol/ether); ν_{max} (film)/cm^{-1} 2934, 1595, 1507, 1453, 1374, 1210, 1145, 1058 and 884; δ_H (300 MHz; $CDCl_3$) 7.30 (1H, dd, *J* 0.7 and 0.7, Furan H), 6.28 (1H, br s, Furan H), 5.98 (1H, br s, Furan H), 5.36 (2H, s, =CH$_2$ trans), 5.32 (2H, s, =CH$_2$ cis), 4.01-3.86 (4H, m, O(CH$_2$)$_2$O), 2.65 (2H, t, *J* 7, C*H*$_2$furan), 1.89-1.68 (4H, m, C*H*$_2$CO(CH$_2$)$_2$O and CH=CCH$_2$C*H*$_2$), 1.57-1.34 (4H, m, 2 x CH$_2$), 1.31 (3H, s, CH$_3$), 1.05 (1H, m, (CH$_2$)$_3$C*H*C=CH$_2$) and 0.86 (1H, m, C*H*C=CH$_2$); δ_C (100 MHz; $CDCl_3$) 155.95 (0), 142.16 (0 trans), 141.83 (0 cis), 140.36 (1), 109.57 (1), 109.50 (0), 104.32 (1), 101.81 (2 trans), 100.96 (2 cis), 64.37 (2 x 2 cis), 64.28 (2 x 2 trans), 39.04 (2 cis), 38.53 (2 trans),

33.22 (2 cis), 31.78 (2 trans), 28.06 (2 cis), 27.62 (2 trans), 27.45 (2 trans), 27.31 (2 cis), 26.87 (2 trans), 26.47 (2 cis), 23.47 (3 trans), 23.39 (3 cis), 22.26 (1 trans), 22.13 (1 trans), 19.24 (1 cis) and 19.09 (1 cis); m/z (EI+) 276.1776 ($[M]^+$. $C_{17}H_{24}O_3$ requires 276.1726) m/z (CI) 277 ($[M + H]^+$, 7%) and 215 (100%).

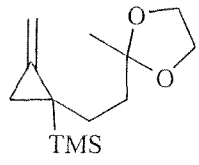


236

4-{2-[3-(2-Furyl)propyl]-3-methylenecyclopropyl}-2-butanone 236

2-(2-{2-[3-(2-Furyl)propyl]-3-methylenecyclopropyl}ethyl)-2-methyl-1,3-dioxolane **270** (0.31 g, 1.11 mmol) was stirred with *p*-TsOH (0.21 g, 1.11 mmol) in a mixture of acetone (90 ml) and 10% water (10 ml) for 48 hours. The mixture was concentrated *in vacuo*. Ether (50 ml) was added. The mixture was then washed once with 10% $NaHCO_3$ (100 ml) and extracted with ether (3 x 75 ml). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/ether ; 100/0 to 90/10) to give **236** as a colourless oil (0.25 g, 96%) and as an inseparable mixture of diastereoisomers (trans assumed to be major) R_f = 0.57 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2927, 1714, 1434, 1162, 884 and 727; δ_H (300 MHz; $CDCl_3$) 7.30 (1H, dd, *J* 0.7 and 0.7, Furan H), 6.28 (1H, s, Furan H), 5.98 (1H, s, Furan H), 5.36 (2H, s, $=CH_2$ trans), 5.34 (2H, s, $=CH_2$ cis), 2.64 (2H, t, *J* 7, $CH{=}CC\mathit{H}_2(CH_2)_2$), 2.52 (2H, t, *J* 7, $C\mathit{H}_2COCH_3$), 2.15 (3H, s, CH_3) and 1.91-0.81 (5H, m, 3 x CH_2, $C\mathit{H}(CH_2)_2$ and $C\mathit{H}(CH_2)_3$); δ_C (75 MHz; $CDCl_3$) 209.98 (0), 156.58 (0), 142.15 (0 trans), 141.91 (0 cis), 141.14 (1), 110.46 (1), 105.13 (1), 103.06 (2 trans), 102.11 (2 cis), 33.93 (2 cis), 32.42 (2 trans), 30.37 (2 trans), 28.76 (2 cis), 28.47 (2 trans), 28.32 (2 cis), 28.16 (2 cis), 28.03 (2 trans), 27.34 (2 cis), 27.24 (2 trans), 23.03 (3 cis), 22.27 (3 trans), 19.92 (1 trans), 19.22 (1 trans), 14.73 (1 cis) and 11.84 (1 trans); m/z (EI+) 232.1463 ($[M]^+$. $C_{15}H_{20}O_2$ requires 2232.1463) and m/z (CI) 233 ($[M + H]^+$, 100%).

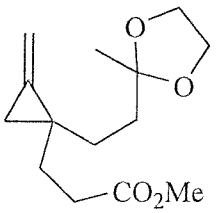
EXPERIMENTAL FOR CHAPTER THREE



283

Trimethyl{1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-2-methylenecyclopropyl} silane 283

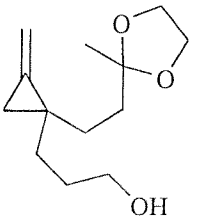
BuLi (12 ml of 1.48 M in hexane, 17.7 mmol) was added to methylenecyclopropane **1** (1.56 ml, 23 mmol) in THF (50 ml) at - 30 °C under N_2. The solution was allowed to warm to 0 °C over 30 mins and kept at 0 °C for 1 hr. After cooling at - 55 °C, TMSCl (2.12 ml, 16.7 mmol) was added to the orange solution, which became colourless. The solution was warmed to 0 °C over 30 mins and kept at 0 °C for 30 mins. After cooling again at - 60 °C, n-BuLi (12 ml of 1.48 M in hexane, 17.7 mmol) was added and the warming procedure repeated. The orange solution was cooled to - 78 °C and iodide **170** (4 g, 16.5 mmol) was added dropwise. The temperature was allowed to warm to room temperature over 5 hrs. The reaction was quenched with saturated NH_4Cl (50 ml), extracted with ether (3 x 50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ethyl acetate ; 95/5) to give silyl ketal **283** (3.78 g, 95%) as a pale yellow oil $R_f = 0.52$ (90/10 petrol/ ethyl acetate); ν_{max} (film)/cm^{-1} 2952, 1375, 1247, 1053, 869 and 732; δ_H (300 MHz; $CDCl_3$) 5.25 (1H, s, $=CH_AH_B$), 5.19 (1H, s, $=CH_AH_B$), 3.99-3.87 (4H, m, $O(CH_2)_2O$), 1.72-1.42 (4H, m, 2 x CH_2), 1.28 (3H, s, CH_3), 1.02 (1H, dt, *J* 7 and 2, $CH_AH_BC=CH_2$), 0.82 (1H, dt, *J* 7 and 2, $CH_AH_BC=CH_2$) and - 0.01 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz; $CDCl_3$) 140.17 (0), 110.29 (0), 100.63 (2), 65.08 (2 x 2), 37.83 (2), 29.89 (2), 24.07 (3), 13.80 (0), 12.77 (2) and - 2.17 (3 x 3); m/z (EI+) 240.1541 (M^+. $C_{13}H_{24}O_2Si$ requires 240.1545), m/z (CI) 241 ($[M + H]^+$, 4%) and 87 (100%).



284

Methyl3-{1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-2-methylenecyclopropyl} propanoate 284

Trimethyl{1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-2-methylenecyclopropyl}silane **283** (1.75 g, 7.29 mmol) was added to a stirred solution of methyl acrylate (4.5 ml, 50 mmol) and TBAF (0.5 ml of 1 M in THF, 0.5 mmol), in dry DMF (20 ml) and HMPA (1.5 ml, 8.33 mmol) under N_2. The yellow solution was then put in an oil bath at 95 °C and stirred under N_2 for 15 mins. The solution was transferred to a separating funnel, diluted with water (20 ml) and extracted with ether (3 x 50 ml). The combined organic layers were dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (petrol/ethyl acetate ; 95/5 to 80/20) to give **284** (0.70 g, 38%) as a colourless oil R_f = 0.51 (20/80 ether/petrol); ν_{max} (film)/cm^{-1} 2983, 1736, 1436, 1374, 1196, 1055 and 857; δ_H (400 MHz; $CDCl_3$) 5.36 (1H, s, $=CH_AH_B$), 5.30 (1H, s, $=CH_AH_B$), 3.99-3.82 (4H, m, $O(CH_2)_2O$), 3.65 (3H, s, CH_3O), 2.34 (2H, ddd, *J* 4 and 7 and 10, $CH_2CO_2CH_3$), 1.85-1.62 (4H, m, 2 x CH_2), 1.47 (2H, ddd, *J* 4 and 7 and 10, $CH_2CH_2CO_2CH_3$), 1.28 (3H, s, CH_3) and 0.93 (2H, s, $CH_2C=CH_2$); δ_C (100 MHz; $CDCl_3$) 174.38 (0), 141.12 (0), 110.16 (0), 102.94 (2), 65.02 (2 x 2), 51.90 (3), 36.24 (2), 31.78 (2), 30.31 (2), 29.18 (2), 23.29 (3), 21.36 (0) and 15.68 (2); m/z (EI+) 254.1515 (M^+. $C_{14}H_{22}O_4$ requires 254.1518), m/z (CI) 255 ($[M + H]^+$, 43.2%) and 87 (100%).

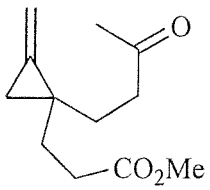


285

3-{1-[2-(2-Methyl-1,3-dioxolan-2-yl)ethyl]-2-methylenecyclopropyl}propan-1-ol 285

Following the method used by Albizati,[88] methyl 3-{1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-2-methylenecyclopropyl}propanoate **284** (0.27 g, 1.06 mmol) was added dropwise

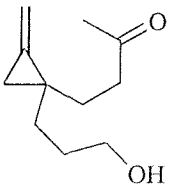
to a suspension of $LiAlH_4$ (0.044 g, 1.17 mmol) in THF (4 ml) at 0 °C and stirred for 1 hour. Ether (10 ml) was added and the solution was stirred at 0 °C for 5 minutes. A 4 M solution NaOH (1 ml) was added and the mixture stirred until a white heavy precipitate was observed. The mixture was filtered and washed with ether (50 ml) and concentrated *in vacuo* to give **285** (0.24 g, 100%) as a colourless oil R_f = 0.25 (80/20 ether/petrol); ν_{max} (film)/cm^{-1} 3388, 2935, 1376, 1054 and 884; δ_H (300 MHz; $CDCl_3$) 5.36 (1H, s, $=CH_AH_B$), 5.29 (1H, s, $=CH_AH_B$), 4.02-3.84 (4H, m, $O(CH_2)_2O$), 3.70-3.63 (2H, m, CH_2OH), 1.78-1.47 (9H, m, 4 x CH_2 and OH), 1.29 (3H, s, CH_3) and 0.93 (2H, s, $CH_2C=CH_2$); δ_C (100 MHz; $CDCl_3$) 142.23 (0), 110.29 (0), 102.38 (2), 65.15 (2 x 2), 63.26 (2), 36.25 (2), 32.86 (2), 31.30 (2), 30.04 (2), 24.23 (3), 23.49 (0) and 15.89 (2); m/z (CI) 227.1638 ($[M + H]^+$. $C_{13}H_{23}O_3$ requires 227.1647), 227 ($[M + H]^+$, 7.3%) and 147 (100%).



277

Methyl 3-[2-methylene-1-(3-oxobutyl)cyclopropyl]propanoate 277

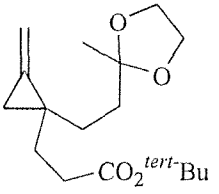
Methyl 3-{1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-2-methylenecyclopropyl} propanoate **284** (0.15 g, 0.59 mmol) was stirred with *p*-toluene sulfonic acid (0.11 g, 0.59 mmol) in a mixture of acetone (90 ml) and 10% water (10 ml) for 48 hours. The mixture was concentrated *in vacuo*. Ether (50 ml) was added. The mixture was then washed once with 10% $NaHCO_3$ (100 ml) and extracted with ether (3 x 75 ml). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/ether ; 95/5 to 70/30) to give **277** (0.11 g, 100%) as a colourless oil R_f = 0.32 (60/40 ether/petrol); ν_{max} (film)/cm^{-1} 2950, 1734, 1713, 1162 and 888; δ_H (300 MHz; $CDCl_3$) 5.35 (1H, s, $=CH_AH_B$), 5.32 (1H, s, $=CH_AH_B$), 3.65 (3H, s, CH_3O), 2.51-2.41 (2H, m, CH_2CO_2Me), 2.36-2.30 (2H, m, CH_2COCH_3), 1.85-1.55 (4H, m, 2 x CH_2) and 0.94 (2H, s, $CH_2C=CH_2$); δ_C (100 MHz; $CDCl_3$) 208.37 (0), 173.88 (0), 139.92 (0), 103.21 (2), 51.56 (3), 40.60 (2), 31.37 (2), 31.24 (2), 29.93 (3), 28.32 (2), 22.55 (0) and 15.11 (2); m/z (EI+) 210.1260 (M^+. $C_{12}H_{18}O_3$ requires 210.1256), m/z (CI) 228 ($[M + NH_4^+]^+$, 47%) and 211 ($[M + H]^+$, 100%).



276

4-[1-(3-Hydroxypropyl)-2-methylenecyclorpopyl]-2-butanone 276

3-{1-[2-(2-Methyl-1,3-dioxolan-2-yl)ethyl]-2-methylenecyclopropyl}propan-1-ol **285** (0.67 g, 2.96 mmol) was stirred with *p*-TsOH (0.56 g, 2.96 mmol) in a mixture of acetone (180 ml) and 10% water (20 ml) for 48 hours. The mixture was concentrated *in vacuo*. Ether (50 ml) was added. The mixture was then washed once with 10% $NaHCO_3$ (100 ml) and extracted with ether (3 x 75 ml). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/ether ; 50/50 to 40/60) to give **276** as a colourless oil (0.38 g, 71%) R_f = 0.46 (95/5 ethyl acetate/petrol); ν_{max} (film)/cm^{-1} 3500, 2934, 1713, 1417, 1264 and 735; δ_H (400 MHz; $CDCl_3$) 5.34 (1H, s with fine splitting, $=CH_AH_B$), 5.30 (1H, s, $=CH_AH_B$), 3.61 (2H, t, *J* 7, CH_2OH), 2.51-2.37 (2H, m, CH_2CO), 2.12 (3H, s, CH_3), 1.86-1.29 (7H, m, 3 x CH_2 and OH) and 0.92 (2H, s, $CH_2C=CH_2$); δ_C (100 MHz; $CDCl_3$) 209.28 (0), 141.38 (0), 103.00 (2), 63.07 (2), 41.14 (2), 31.53 (2), 30.32 (3), 29.93 (2), 28.83 (2), 23.25 (0) and 15.68 (2); m/z (CI) 183.1382 ($[M + H]^+$. $C_{11}H_{19}O_2$ requires 183.1385), 183 ($[M + H]^+$, 70%) and 165 (100%).

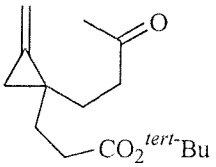


286

***tert*-Butyl 3-{1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-2-methylenecyclo propyl} propanoate 286**

Trimethyl{1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-2-methylenecyclopropyl}silane **283** (2 g, 8.33 mmol) was added to a stirred solution of *tert*-butyl acrylate (7.32 ml, 50 mmol) and TBAF (0.5 ml of 1 M in THF, 0.5 mmol), in dry DMF (20 ml) and HMPA (1.5 ml, 8.33 mmol) under N_2. The yellow solution was then put in an oil bath at 95 °C and stirred under N_2 for 15 mins. The solution was transferred to a separating funnel, diluted with water (20 ml) and extracted with ether (3 x 50 ml). The combined organic layers were dried over

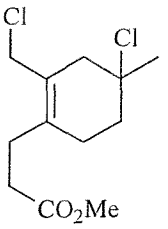
$MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (petrol/ethyl acetate ; 95/5 to 70/30) to give **286** (0.59 g, 24%) as a colourless oil R_f = 0.58 (70/30 petrol/ethyl acetate); ν_{max} (film)/cm^{-1} 2931, 1727, 1452, 1367, 1145, 1057 and 885; δ_H (400 MHz; $CDCl_3$) 5.29 (1H, s with fine splitting, $=CH_AH_B$), 5.22 (1H, s, $=CH_AH_B$), 3.93-3.77 (4H, m, $O(CH_2)_2O$), 2.26-2.07 (2H, m, $CH_2CO_2C(CH_3)_3$), 1.72-1.37 (6H, m, 3 x CH_2), 1.36 (9H, s, $CO_2C(CH_3)_3$), 1.22 (3H, s, CH_3) and 0.86 (2H, s, $CH_2C=CH_2$); δ_C (75 MHz; $CDCl_3$) 173.11 (0), 141.07 (0), 109.96 (0), 102.60 (2), 80.26 (0), 64.78 (2 x 2), 35.98 (2), 32.92 (2), 30.00 (2), 29.04 (2), 28.23 (3 x 3), 24.00 (3), 23.06 (0) and 15.44 (2); m/z (CI) 314.2315 ([M + NH_4^+]$^+$. $C_{17}H_{32}NO_4$ requires 314.2331), 314 ([M+ NH_4^+]$^+$, 16%) and 161 (100%).



278

tert-Butyl 3-[2-methylene-1-(3-oxobutyl)cyclopropyl]propanoate 278

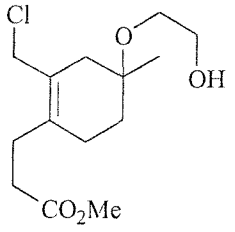
tert-Butyl 3-{1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-2-methylenecyclopropyl} propanoate **286** (0.5 g, 1.69 mmol) was stirred with *p*-TsOH (0.32 g, 1.69 mmol) in a mixture of acetone (180 ml) and 10% water (20 ml) for two days. The mixture was concentrated *in vacuo*. Ether (50 ml) was added. The mixture was then washed once with 10% $NaHCO_3$ (100 ml) and extracted with ether (3 x 75 ml). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/ether ; 100/0 to 70/30) to give **278** (0.40 g, 95%) as a colourless oil R_f = 0.58 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2976, 1717, 1365, 1148 and 886; δ_H (400 MHz; $CDCl_3$) 5.34 (1H, s, $=CH_AH_B$), 5.30 (1H, s, $=CH_AH_B$), 2.53-2.36 (2H, m, $CH_2CO_2C(CH_3)_3$), 2.29-2.14 (2H, m, CH_2COCH_3), 2.11 (3H, s, CH_3), 1.79-1.55 (4H, m, 2 x CH_2), 1.41 (9H, s, $(CH_3)_3CO$), 0.95 (1H, dt, *J* 9 and 2, $CH_AH_BC=CH_2$) and 0.91 (1H, dt, *J* 9 and 2, $CH_AH_BC=CH_2$); δ_C (100 MHz; $CDCl_3$) 208.81 (0), 173.20 (0), 140.55 (0), 103.44 (2), 80.58 (0), 41.05 (2), 33.05 (2), 30.30 (2), 30.25 (3), 28.90 (2), 28.45 (3 x 3), 23.02 (0) and 15.54 (2); m/z (CI) 253.1791 ([M + H]$^+$. $C_{15}H_{25}O_3$ requires 253.1803), 270 ([M + NH_4^+]$^+$, 14%), 253 ([M + H]$^+$, 5%) and 214 (100%).



287

Methyl 3-[4-chloro-2-(chloromethyl)-4-methyl-1-cyclohexenyl]propanoate 287

$TiCl_4$ (0.47 ml of 1 M in DCM, 0.47 mmol) was added to methyl-3-{1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-2-methylenecyclopropyl}propanoate **284** (0.06 g, 0.24 mmol) in dichloromethane (10 ml), at - 78 °C under Ar. The solution was stirred for 4 hours. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 80/20 to 60/40) to give cyclohexene **287** (0.055 g, 89%) as a pale yellow oil R_f = 0.47 (70/30 ether/petrol); ν_{max} (film)/cm^{-1} 2950, 1734, 1195, 910 and 730; δ_H (300 MHz; $CDCl_3$) 4.15 (1H, d, *J* 11, CH_AH_BCl), 4.02 (1H, d, *J* 11, CH_AH_BCl), 3.67 (3H, s, CH_3O), 2.54 (1H, d, *J* 14, $=CCH_AH_BC(CH_3)Cl$), 2.50 (1H, d, *J* 14, $=CCH_AH_BC(CH_3)Cl$), 2.68-2.29 (5H, m, $CH_2CH_2CO_2Me$, $CH_2CH_2CO_2Me$ and $=CCH_2CH_AH_B$), 2.13 (1H, m, $=CCH_2CH_AH_B$), 1.98 (1H, m, $=CCH_AH_BCH_2$), 1.77 (1H, m, $=CCH_AH_BCH_2$) and 1.64 (3H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 172.21 (0), 137.81 (0), 124.75 (0), 67.03 (0), 50.71 (3), 43.62 (2), 42.97 (2), 36.34 (2), 31.73 (2), 30.96 (3), 26.87 (2) and 26.85 (2); m/z (CI) 282.1033 ($[M + NH_4^+]^+$. $C_{12}H_{22}NCl_2O_2$ requires 282.1027), 229 ($[M - Cl]^+$, 40%) and 282 ($[M + NH_4^+]^+$, 100%).

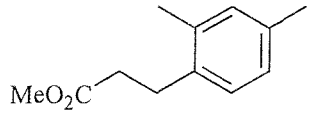


288

Methyl-3-[2-(chloromethyl)-4-(2-hydroxyethoxy)-4-methyl-1-cyclohexenyl] propanoate 288

$SnCl_4$ (0.046 ml, 0.39 mmol) was added to methyl-3-{1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-2-methylenecyclopropyl}propanoate **284** (0.05 g, 0.2 mmol), in dichloromethane

(10 ml), at - 78 °C under Ar. The solution was stirred for 4 hrs. The reaction mixture was quenched with water (20 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 30 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 95/5 to 60/40) to give cyclohexene **288** (0.023 g, 40%) as a colourless oil R_f = 0.13 (80/20 ether/petrol); ν_{max} (film)/cm^{-1} 2922, 1733, 1373, 1109, 908 and 728; δ_H (300 MHz; $CDCl_3$) 4.14 (1H, d, *J* 11, CH_AH_BCl), 4.02 (1H, d, *J* 11, CH_AH_BCl), 3.67 (3H, s, CH_3O), 3.67 (2H, t, *J* 7, CH_2OH), 3.47 (2H, t, *J* 7, CH_2CH_2OH), 2.56-2.37 (2H, m, CH_2CO_2Me), 2.43 (2H, t, *J* 5, $CH_2CH_2CO_2Me$), 2.34-2.11 (4H, m, $=CCH_2C(CH_3)O$ and $CH_2CH_2C(CH_3)O$), 2.02 (1H, br s, OH), 1.89-1.52 (2H, m, $CH_2CH_2C(CH_3)O$) and 1.20 (3H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 173.78 (0), 135.57 (0), 126.64 (0), 72.96 (0), 62.66 (2), 62.63 (2), 52.16 (3), 45.55 (2), 39.28 (2), 33.26 (2), 33.02 (2), 28.45 (2), 27.72 (2) and 24.07 (3); m/z (CI) 308.1641 ($[M + NH_4^+]^+$. $C_{14}H_{27}NClO_4$ requires 308.1628), 258 ($[M - MeOH]^+$, 69%) and 210 (100%).



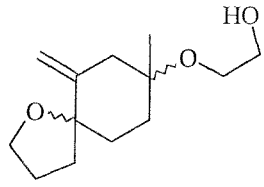
292

Methyl 3-(2,4-dimethylphenyl)propanoate 292

$SnCl_4$ (0.05 ml, 0.43 mmol) was added to methyl 3-[2-methylene-1-(3-oxobutyl)cyclopropyl]propanoate **277** (0.045 g, 0.21 mmol) in dichloromethane (10 ml), at - 78 °C under Ar. The solution was allowed to come to room temperature and stirred overnight. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 95/5 to 60/40) to give aromatic ester **292** as a colourless oil (0.005 g, 12%);

$TiCl_4$ (0.47 ml of 1 M in DCM, 0.47 mmol) was added to methyl 3-[2-methylene-1-(3-oxobutyl)cyclopropyl]propanoate **277** (0.05 g, 0.24 mmol) in dichloromethane (10 ml), at - 78 °C under Ar. The solution was allowed to come to room temperature and stirred overnight. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried

over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 95/5 to 60/40) to give aromatic ester **292** (0.012 g, 26%) as a colourless oil R_f = 0.70 (80/20 ether/petrol); ν_{max} (film)/cm^{-1} 2950, 1736, 1435, 1153 and 817; δ_H (300 MHz; $CDCl_3$) 7.04 (1H, d, *J* 8, C*H*=CHCCH$_3$), 6.99 (1H, d, *J* 8, CH=C*H*CCH$_3$), 6.98 (1H, s, CH$_3$C=C*H*CCH$_3$), 3.70 (3H, s, CH$_3$O), 2.89 (2H, t, *J* 8, C*H*$_2$CO$_2$Me), 2.58 (2H, t, *J* 8, C*H*$_2$CH$_2$CO$_2$Me) and 2.30 (6H, s, 2 x CH$_3$); δ_C (100 MHz; $CDCl_3$) 173.98 (0), 136.33 (0), 136.19 (0), 135.95 (0), 131.55 (1), 128.88 (1), 127.17 (1), 52.06 (3), 35.01 (2), 28.37 (2), 21.32 (3) and 19.58 (3); m/z (EI+) 192.1150 (M^+. $C_{12}H_{16}O_2$ requires 192.1150), m/z (CI) 210 ([M + NH_4^+]$^+$, 85%) and 192 ([M]$^+$, 100%).

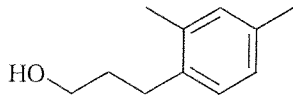


293

2-[(8-Metthyl-6-methylene-1-oxaspiro[4.5]dec-8-yl)oxy]-1-ethanol 293

$SnCl_4$ (0.052 ml, 0.44 mmol) was added to 3-{1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-2-methylenecyclopropyl}propan-1-ol **285** (0.05 g, 0.22 mmol), in dichloromethane (10 ml), at - 78 °C under Ar. The solution was stirred for 4 hrs. The reaction mixture was quenched with water (20 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 30 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 95/5 to 60/40) to give spirocyclic ether **293** (0.025 g, 50%) as a pale yellow oil and as a 2 : 1 mixture of separable diastereoisomers ν_{max} (film)/cm^{-1} 3416, 2935, 1437, 1046, 898 and 729; m/z (EI+) 226.1564 (M^+. $C_{13}H_{22}O_3$ requires 226.1569), m/z (CI) 244 ([M + NH_4^+]$^+$, 7%), 227 ([M + H]$^+$, 5%) and 165 (100%); the two diastereoisomers were separated by flash column chromatography (petrol/ether ; 95/5 to 60/40) to give isomer A (0.017g) R_f = 0.23 (90/10 ether/petrol; δ_H (300 MHz; $CDCl_3$) 4.95 (1H, s, =C*H*$_A$H$_B$), 4.76 (1H, s, =CH$_A$*H*$_B$), 3.84 (2H, ddd, *J* 19 and 15 and 7, (CH$_2$)$_2$C*H*$_2$OC), 3.68 (2H, t, *J* 5, C*H*$_2$OH), 3.49 (2H, t, *J* 5, OC*H*$_2$CH$_2$OH), 2.44 (1H, d, *J* 14, =CC*H*$_A$H$_B$C(CH$_3$)O), 2.35 (1H, d, *J* 14, =CCH$_A$*H*$_B$C(CH$_3$)O), 2.04 (1H, m, C*H*$_A$H$_B$CH$_2$C(CH$_3$)O), 2.01-1.80 (2H, m, CH$_2$C*H*$_2$C(CH$_3$)O), 1.77 (1H, m, CH$_A$*H*$_B$CH$_2$C(CH$_3$)O), 1.69-1.50 (5H, m, 2 x CH$_2$ and OH)

and 1.18 (3H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 148.17 (0), 108.92 (2), 84.49 (0), 75.69 (0), 67.43 (2), 62.67 (2), 62.44 (2), 44.36 (2), 35.26 (2), 35.06 (2), 34.42 (2), 25.79 (2) and 22.94 (3); and isomer B (0.008 g) R_f = 0.13 (90/10 ether/petrol); δ_H (400 MHz; $CDCl_3$) 5.01 (1H, s, $=CH_AH_B$), 4.73 (1H, s, $=CH_AH_B$), 3.92 (2H, t, *J* 7, $(CH_2)_2CH_2OC$), 3.70-3.62 (2H, m, OCH_2CH_2OH), 3.54-3.38 (2H, m, OCH_2CH_2OH), 2.17-2.02 (2H, m, $=CCH_2C(CH_3)O$), 2.00-1.86 (5H, m, 2 x CH_2 and OH), 1.80-1.59 (2H, m, $CH_2CH_2C(CH_3)O$), 1.57-1.48 (2H, m, $CH_2CH_2C(CH_3)O$) and 1.19 (3H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 148.97 (0), 108.36 (2), 84.89 (0), 74.49 (0), 67.92 (2), 62.63 (2), 62.36 (2), 43.49 (2), 35.99 (2), 35.07 (2), 34.99 (2), 25.89 (2) and 24.92 (3).



298

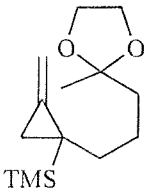
3-(2,4-Dimethylphenyl)-1-propanol 298

$TiCl_4$ (0.30 ml of 1 M in DCM, 0.30 mmol) was added to 4-[1-(3-hydroxypropyl)-2-methylenecyclorpopyl]-2-butanone **276** (0.05 g, 0.27 mmol) in dichloromethane (10 ml), at -78 °C under Ar. The solution was allowed to come to room temperature and stirred overnight. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 95/5 to 80/20) to give aromatic alcohol **298** as a pale yellow oil (0.007 g, 16%);

$SnCl_4$ (0.30 ml of 1 M in DCM, 0.30 mmol) was added to 4-[1-(3-hydroxypropyl)-2-methylenecyclorpopyl]-2-butanone **276** (0.05 g, 0.27mmol) in dichloromethane (10 ml), at -78 °C under Ar. The solution was allowed to come to room temperature and stirred overnight. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 95/5 to 80/20) to give aromatic alcohol **298** (0.010 g, 22%) as a pale yellow oil R_f = 0.57 (95/5 ethyl acetate/petrol); ν_{max} (film)/cm^{-1} 3338, 2932, 1453, 1900 and 819; δ_H (300 MHz; $CDCl_3$) 7.05 (1H, d, *J* 8, CH=$CHCCH_3$), 6.98 (1H, s,

$CH_3C{=}CHCCH_3$), 6.96 (1H, d, *J* 8, $CH{=}CHCCH_3$), 3.72 (2H, t, *J* 7, CH_2OH), 2.64 (2H, t, *J* 7, $CH_2(CH_2)_2OH$), 2.29 (6H, s, 2 x CH_3) 1.91-1.79 (2H, m, $CH_2CH_2CH_2$) and 1.45 (1H,br s, OH); δ_C (100 MHz; $CDCl_3$) 137.29 (0), 136.15 (0), 135.85 (0), 131.47 (1), 129.17 (1), 127.02 (1), 63.04 (2), 33.61 (2), 29.44 (2), 21.27 (3) and 19.59 (3); m/z (EI+) 164.2448 (M^+. $C_{11}H_{16}O$ requires 164.2468), m/z (CI) 164 ($[M]^+$, 35%) and 182 ($[M + NH_4^+]^+$, 100%).

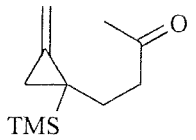
EXPERIMENTAL FOR CHAPTER FOUR



309

Trimethyl{1-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]-2-methylenecyclopropyl} silane 309

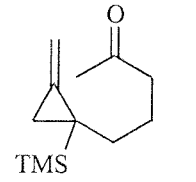
BuLi (7.95 ml of 2.22 M in hexane, 17.6 mmol) was added to methylenecyclopropane **1** (9.24 ml of 2.5 M in THF, 23.1 mmol) in THF (30 ml) at - 30 °C under N_2. The solution was allowed to warm to 0 °C over 30 mins and kept at 0 °C for 1 hr. After cooling at - 55 °C, TMSCl (2.11 ml, 16.7 mmol) was added to the orange solution which became colourless. The solution was warmed to 0 °C over 30 mins and kept at 0 °C for 30 mins. After cooling again at - 60 °C, BuLi (7.95 ml, 17.6 mmol) was added and the warming procedure repeated. The orange solution was cooled to - 78 °C and iodide **171** (4.22 g, 16.5 mmol) was added dropwise. The temperature was allowed to warm to room temperature over 5 hrs. The reaction was quenched with saturated NH_4Cl (50 ml), extracted with ether (3 x 50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ethyl acetate ; 95/5) to give silyl ketal **309** (3.99 g, 95%) as a pale yellow oil R_f = 0.43 (90/10 petrol/ ethyl acetate); ν_{max} (film)/cm^{-1} 3064, 3034, 2950, 1729, 1374, 1247, 1068 and 869; δ_H (300 MHz; $CDCl_3$) 5.25 (1H, s, $=CH_AH_B$), 5.21 (1H, s, $=CH_AH_B$), 3.99-3.85 (4H, m, $O(CH_2)_2O$), 1.65-1.35 (6H, m, 3 x CH_2), 1.31 (3H, s, CH_3), 1.02 (1H, dt, *J* 7 and 2, $CH_AH_BC=CH_2$), 0.82 (1H, dt, *J* 7 and 2, $CH_AH_BC=CH_2$) and - 0.02 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz; $CDCl_3$) 139.93 (0), 110.06 (0), 100.04 (2), 64.61 (2 x 2), 39.48 (2), 35.79 (2), 23.78 (3), 23.79 (2), 14.03 (0), 12.40 (2) and - 2.59 (3 x 3); m/z (EI+) 254.1702 (M^+. $C_{14}H_{26}O_2Si$ requires 254.1702), 254 ($[M]^+$, 45%) and 239 (100%).



310

4-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-butanone 310

Trimethyl{1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-2-methylenecyclopropyl}silane **283** (0.5 g, 2.08 mmol) was stirred with *p*-TsOH (0.4 g, 2.08 mmol) in a mixture of acetone (180 ml) and 10% water (20 ml) for 48 hours. The mixture was concentrated *in vacuo*. Ether (100 ml) was added. The mixture was then washed once with 10% $NaHCO_3$ (100 ml) and extracted with ether (3 x 75 ml). The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (petrol/ether ; 100/0 to 98/2) to give **310** (0.35 g, 86%) as a colourless oil R_f = 0.46 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3065, 3045, 2954, 1718, 1248 and 833; δ_H (300 MHz; $CDCl_3$) 5.28 (1H, s, $=CH_AH_B$), 5.18 (1H, s, $=CH_AH_B$), 2.44-2.33 (2H, m, CH_2CO), 2.11 (3H, s, CH_3), 1.87 (1H, ddd, *J* 6 and 10 and 14, $CH_AH_BCH_2CO$), 1.66 (1H, ddd, *J* 6 and 10 and 14, $CH_AH_BCH_2CO$), 1.04 (1H, dt, *J* 8 and 2, $CH_AH_BC=CH_2$), 0.80 (1H, dt, *J* 8 and 2, $CH_AH_BC=CH_2$) and 0.00 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz; $CDCl_3$) 208.94 (0), 138.95 (0), 101.12 (2), 41.82 (2), 30.05 (3), 28.17 (2), 1306 (0), 12.00 (2) and - 2.68 (3 x 3); m/z (EI+) 196.1279 (M^+. $C_{11}H_{20}OSi$ requires 196.1283) and m/z (CI) 197 ($[M + H]^+$, 100%).

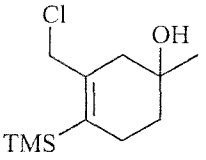


311

5-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-pentanone 311

Trimethyl{1-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]-2-methylenecyclopropyl}silane **309** (1 g, 3.9 mmol) was stirred with *p*-TsOH (0.74 g, 3.9 mmol) in a mixture of acetone (180 ml) and 10% water (20 ml) for 48 hours. The mixture was concentrated *in vacuo*. Ether (50 ml) was added. The mixture was then washed once with 10% $NaHCO_3$ (100 ml) and extracted with ether (3 x 75 ml). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/ether ; 100/0 to 90/10) to give **311** (0.80 g, 96%) as a colourless oil R_f = 0.56 (40/60 ether/petrol);

ν_{max} (film)/cm^{-1} 2952, 1716, 1406, 1356, 1248 and 833; δ_H (400 MHz; $CDCl_3$) 5.25 (1H, s, =C*H*$_A$H$_B$), 5.19 (1H, s, =CH$_A$*H*$_B$), 2.39 (2H, t, *J* 7, C*H*$_2$COCH$_3$), 2.12 (3H, s, CH$_3$), 1.70-1.55 (2H, m, CH$_2$), 1.49 (1H, m, C*H*$_A$H$_B$(CH$_2$)$_2$), 1.35 (1H, m, CH$_A$*H*$_B$(CH$_2$)$_2$), 1.05 (1H, dt, *J* 8 and 2, C*H*$_A$H$_B$C=CH$_2$), 0.82 (1H, dt, *J* 8 and 2, CH$_A$*H*$_B$C=CH$_2$) and 0.00 (9H, s, Si(CH$_3$)$_3$); δ_C (100 MHz; $CDCl_3$) 208.96 (0), 139.80 (0), 100.42 (2), 44.02 (2), 35.27 (2), 30.02 (3), 22.69 (2), 13.91 (0), 12.64 (2) and - 2.45 (3 x 3); m/z (EI+) 210.1444 (M^+. $C_{12}H_{22}OSi$ requires 210.1440), m/z (CI) 211 ($[M + H]^+$, 96%) and 121 (100%).



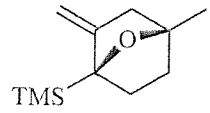
313

3-(Chloromethyl)-1-methyl-4-(1,1,1-trimethylsilyl)-3-cyclohexen-1-ol 313

$TiCl_4$ (0.28 ml of 1 M in DCM, 0.28 mmol) was added to 4-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-butanone **310** (0.050 g, 0.25 mmol) in dichloromethane (10 ml), at - 78 °C, under Ar. The solution was stirred for 1 hour. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 95/5 to 80/20) to give cyclohexene **313** (0.044 g, 74%) as a pale yellow oil;

$SnCl_4$ (0.28 ml of 1 M in DCM, 0.28 mmol) was added to 4-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-butanone **310** (0.050 g, 0.25 mmol) in dichloromethane (10 ml), at - 78 °C, under Ar. The solution was stirred for 1 hour. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 95/5 to 80/20) to give cyclohexene **313** (0.041 g, 70%) as a pale yellow oil R_f = 0.29 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3373, 2955, 1372, 1249 and 833; δ_H (400 MHz; $CDCl_3$) 4.09 (1H, d, *J* 11, C*H*$_A$H$_B$Cl), 4.06 (1H, d, *J* 11, CH$_A$*H*$_B$Cl), 2.39-2.05 (4H, m, =CC*H*$_2$C(CH$_3$)OH and C*H*$_2$CH$_2$), 1.74-1.41 (3H, m, CH$_2$C*H*$_2$ and OH), 1.26 (3H, s, CH$_3$) and 0.20 (9H, s, Si(CH$_3$)$_3$); δ_C (100 MHz; $CDCl_3$) 140.26 (0), 137.44 (0), 68.32 (0), 48.74 (2), 42.96 (2),

35.04 (0), 28.40 (3), 27.71 (2) and 0.00 (3 x 3); m/z (EI+) 232.1046 (M^+. $C_{11}H_{21}ClOSi$ requires 232.1050), m/z (CI) 232 ($[M]^+$, 16%), 215 ($[M - H_2O]^+$, 45%) and 107 (100%).

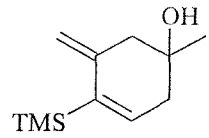


314

Trimethyl(4-methyl-2-methylene-7-oxabicyclo[2.2.1]hept-1-yl)silane 314

$BF_3(AcOH)_2$ (0.078 ml, 0.56 mmol) was added to 4-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-butanone **310** (0.1 g, 0.51 mmol) in dichloromethane (20 ml), at - 78 °C, under Ar. The solution was stirred for 3 hours. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 95/5 to 60/40) to give bicyclic ether **314** (0.064 g, 64%) as a pale yellow oil;

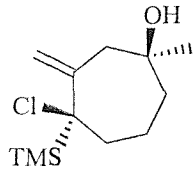
$BF_3.Et_2O$ (0.070 ml, 0.56 mmol) was added to 4-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-butanone **310** (0.1 g, 0.51 mmol) in dichloromethane (20 ml), at - 78 °C, under Ar. The solution was stirred for 3 hours. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 95/5 to 60/40) to give bicyclic ether **314** (0.06 g, 60%) as a pale yellow oil R_f = 0.68 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2966, 1452, 1248, 1073 and 836; δ_H (400 MHz; $CDCl_3$) 4.56 (1H, t, *J* 2, $=CH_AH_B$), 4.52 (1H, t, *J* 2, $=CH_AH_B$), 2.10 (1H, dt, *J* 15 and 2, $CH_2=CCH_AH_BCCH_3$), 2.03 (1H, ddd, *J* 2 and 5 and 15, $CH_2=CCH_AH_BCCH_3$), 1.70 (1H, dt, *J* 11 and 4, $CH_AH_BCH_2$), 1.53-1.37 (2H, m, $CH_2CH_AH_B$), 1.33 (3H, s, CH_3), 1.30 (1H, m, $CH_AH_BCH_2$) and 0.00 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz; $CDCl_3$) 156.96 (0), 101.46 (2), 85.76 (0), 82.95 (0), 47.51 (2), 36.56 (2), 35.77 (2), 21.03 (3) and - 2.61 (3 x 3); m/z (CI) 197.1369 ($[M + H]^+$. $C_{11}H_{21}OSi$ requires 197.1362), 214 ($[M + NH_4^+]^+$, 15%), 197 ($[M + H]^+$, 49%) and 90 (100%).



315

1-Methyl-5-methylene-4-(1,1,1-trimethylsilyl)-3-cyclohexen-1-ol 315

TMSOTf (0.05 ml, 0.28 mmol) was added to 4-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-butanone **310** (0.045 g, 0.23 mmol) in dichloromethane (10 ml), at - 78 °C under Ar. The solution was stirred for 45 mins. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 95/5 to 70/30) to give diene **315** (0.003 g, 7%) as a pale yellow oil R_f = 0.31 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3372, 2953, 1248 and 835; δ_H (400 MHz; $CDCl_3$) 6.04 (1H, br s, =CH), 5.09 (1H, s, =CH_AH$_B$), 4.98 (1H, s, =CH$_A$$H_B$), 2.34 (2H, s, CH_2=CCH_2), 2.28 (2H, d, *J* 3, =CHCH_2), 1.66 (1H, br s, OH), 1.25 (3H, s, CH_3) and 0.18 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz; $CDCl_3$) 143.57 (0), 138.54 (0), 138.27 (1), 115.41 (2), 69.33 (0), 47.17 (2), 42.45 (2), 28.50 (3) and 0.00 (3 x 3); m/z (EI+) 196.1287 (M^+. $C_{11}H_{20}OSi$ requires 196.1283) and m/z (CI) 197 ($[M + H]^+$, 100%).

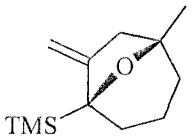


317

(*1R,4S*)-4-Chloro-1-methyl-3-methylene-4-(1,1,1-trimethylsilyl)cycloheptan-1-ol 317

$SnCl_4$ (0.061 ml of 1 M in DCM, 0.52 mmol) was added to 5-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-pentanone **311** (0.1 g, 0.47 mmol) in dichloromethane (20 ml), at - 78 °C under Ar. The solution was stirred for 1 hour. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 95/5 to 60/40) to give methylenecycloheptane **317** (0.069 g, 65%) as a single diastereoisomer and as a white solid mp 42-44 °C (from EtOH-H_2O) R_f = 0.45 (40/60 ether/petrol).; ν_{max}

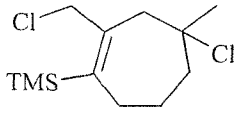
(film)/cm^{-1} 3450, 3092, 2928, 1616, 1431, 1247, 1069 and 831; δ_H (400 MHz; $CDCl_3$) 5.45 (1H, s, =C*H*$_A$H$_B$), 5.16 (1H, s, =CH$_A$*H*$_B$), 2.49 (1H, br s, OH), 2.30 (1H, d, *J* 14, =CC*H*$_A$H$_B$C(CH$_3$)OH),), 2.24 (1H, d, *J* 14, =CCH$_A$*H*$_B$C(CH$_3$)OH), 2.14 (1H, ddd, *J* 4 and 10 and 16, (CH$_2$)$_2$C*H*$_A$H$_B$C(CH$_3$)OH), 1.95 (1H, ddd, *J* 4 and 10 and 16, (CH$_2$)$_2$CH$_A$*H*$_B$C(CH$_3$)OH), 1.81 (1H, m, TMS(Cl)CC*H*$_A$H$_B$), 1.74-1.51 (2H, m, CH$_2$C*H*$_2$CH$_2$), 1.30 (1H, m, TMS(Cl)CCH$_A$*H*$_B$), 1.26 (3H, s, CH$_3$) and 0.12 (9H, s, Si(CH$_3$)$_3$); δ_C (75 MHz; $CDCl_3$) 146.45 (0), 120.32 (2), 69.97 (0), 69.16 (0), 47.74 (2), 44.29 (2), 38.09 (2), 31.12 (3), 18.75 (2) and - 3.59 (3 x 3); m/z (CI) 264.1544 ([M + NH_4^+]$^+$. $C_{12}H_{27}ONSiCl$ requires 264.1550), m/z (EI+) 246 ([M]$^+$, 20%) and 73 (100); structure and stereochemistry confirmed by X-ray diffraction.



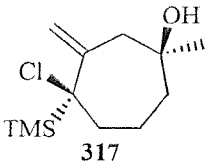
318

Trimethyl(5-methyl-7-methylene-8-oxabicyclo[3.2.1]oct-1-yl)silane 318

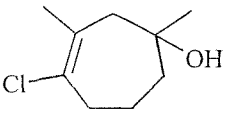
$BF_3(AcOH)_2$ (0.036 ml, 0.26 mmol) was added to 5-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-pentanone **311** (0.05 g, 0.24 mmol) in dichloromethane (10 ml), at - 78 °C, under Ar. The solution was stirred for 3 hours. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 95/5 to 60/40) to give bicyclic ether **318** (0.028 g, 55%) as a pale yellow oil R_f = 0.75 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2932, 1245, 1035 and 834; δ_H (400 MHz; $CDCl_3$) 4.77 (1H, s with fine splitting, =C*H*$_A$H$_B$), 4.57 (1H, s with fine splitting, =CH$_A$*H*$_B$), 2.46 (1H, d, *J* 16, CH$_2$=CC*H*$_A$H$_B$CCH$_3$), 2.22 (1H, d, *J* 16, CH$_2$=CCH$_A$*H*$_B$CCH$_3$), 1.84-1.61 (2H, m, C*H*$_2$(CH$_2$)$_2$CCH$_3$), 1.56-1.43 (2H, m, CH$_2$C*H*$_2$CH$_2$), 1.39 (1H, m, C*H*$_A$H$_B$CH$_2$), 1.32 (1H, m, CH$_A$*H*$_B$CH$_2$), 1.16 (3H, s, CH$_3$) and 0.00 (9H, s, Si(CH$_3$)$_3$); δ_C (100 MHz; $CDCl_3$) 157.40 (0), 100.91 (2), 80.73 (0), 79.17 (0), 46.64 (2), 36.48 (2), 32.86 (2), 26.99 (3), 18.29 (2) and - 3.46 (3 x 3); m/z (EI+) 210.1433 (M$^+$. $C_{12}H_{22}OSi$ requires 210.1439) and m/z (CI) 211 ([M + H]$^+$, 100%).



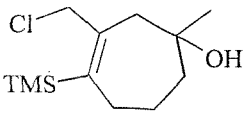
319



317



320



321

[(4-Chloro-2-(chloromethyl)-4-methyl-1-cycloheptenyl](trimethyl)silane 319

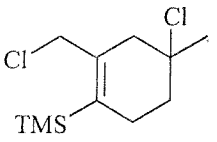
(*1R,4S*)-4-Chloro-1-methyl-3-methylene-4-(1,1,1-trimethylsilyl)cycloheptan-1-ol 317

4-Chloro-1,3-dimethyl-3-cyclohepten-1-ol 320

3-(Chloromethyl)-1-methyl-4-(1,1,1-trimethhylsilyl)-3-cyclohepten-1-ol 321

$TiCl_4$ (0.52 ml of 1 M in DCM, 0.52 mmol) was added to 5-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-pentanone **311** (0.1 g, 0.47 mmol) in dichloromethane (20 ml), at - 78 °C under Ar. The solution was stirred for 1 hour. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 95/5 to 60/40) to give cycloheptene **319** and methylenecycloheptane **317**, as a 1 : 1.4 mixture of inseparable compounds and as a pale yellow oil (0.007g, 7%) R_f = 0.45 (40/60 ether/petrol); ν_{max} (film)/cm^{-1} 3450, 3092, 2928, 1616, 1431, 1247, 1069 and 831; m/z (CI) 264 ($[M]^+$, 35%), 211($[M - 2\ Cl]^+$, 45%) and 121 (100%) for **319**; 247 ($[M + H]^+$, 8%), 231 ($[M - H_2O]^+$, 5%) and 121 (100%) for **317**; data for **319** δ_H (300 MHz; $CDCl_3$) 4.14 (2H, s, CH_2Cl), 2.52-2.38 (2H, m, $(CH_2)_2CH_2C(CH_3)Cl$), 2.28 (2H, s, $=CCH_2C(CH_3)Cl$), 2.15 (3H, s, CH_3), 1.91-1.48 (4H, m, 2 x CH_2) and 0.20 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz; $CDCl_3$) 141.82 (0), 140.31 (0), 69.07 (0), 49.59 (2), 42.74 (2), 41.44 (2), 33.45 (2), 29.21 (3), 22.84 (2) and 0.02 (3 x 3); cycloheptene **320** (0.013 g, 16%) as a pale yellow oil R_f = 0.38 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3402, 2927, 1374, 1103 and 838; δ_H (300 MHz; $CDCl_3$) 2.62-2.52 (2H, m, $(CH_2)_2CH_2C(CH_3)OH$), 2.44 (1H, d, *J* 14, $=CCH_AH_BC(CH_3)OH$), 2.35 (1H, d, *J* 14, $=CH_AH_BC(CH_3)OH$), 2.14 (1H, br s, OH), 1.87 (3H, s, $CH_3C=C$), 1.82-1.47 (4H, m, 2 x CH_2) and 1.23 (3H, s, CH_3COH); δ_C (100 MHz; $CDCl_3$) 130.76 (0), 129.52 (0), 69.88 (0), 47.60 (2), 45.22 (2), 38.36 (2), 28.71 (3), 24.29 (3) and 22.26 (2); m/z (EI+) 174.0809 (M^+. $C_9H_{15}ClO$ requires 174.0811), m/z (CI) 192 ($[M + NH4^+]^+$, 17%), 174 ($[M]^+$, 55%) and 157 (100%); and cycloheptene **321** (0.028 g, 27%) as a pale yellow oil R_f = 0.22 (40/60 ether/petrol); ν_{max} (film)/cm^{-1} 3392, 2922, 1244, 1109, 1024 and 829; δ_H (300 MHz; $CDCl_3$) 4.17 (1H, d, *J* 11, CH_AH_BCl), 4.13 (1H, d, *J* 11, CH_AH_BCl), 2.64 (1H, d, *J* 14,

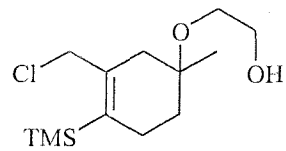
=CCH_AH$_B$C(CH$_3$)OH), 2.51 (1H, d, *J* 14, =CCH$_A$$H_B$C(CH$_3$)OH), 2.29-2.12 (2H, m, =C(TMS)CH_2(CH$_2$)$_2$), 1.89-1.61 (2H, m, (CH$_2$)$_2$CH_2C(CH$_3$)OH), 1.52-1.41 (2H, m, CH$_2$CH_2CH$_2$), 1.26 (3H, s, CH$_3$) and 0.20 (9H, s, Si(CH$_3$)$_3$); δ_C (100 MHz; CDCl$_3$) 146.77 (0), 143.72 (0), 68.48 (0), 50.58 (2), 46.18 (2), 45.19 (2), 31.06 (2), 29.65 (3), 21.92 (2) and 0.00 (3 x 3); m/z (EI+) 246.1203 (M^+. $C_{12}H_{23}ClOSi$ requires 246.1207), m/z (CI) 264 ([M + NH4$^+$]$^+$, 15%), 246 ([M]$^+$, 17%) and 121 (100%).



325

[4-Chloro-2-(chloromethyl)-4-methyl-1-cyclohexyl](trimethyl)silane 325

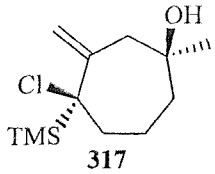
TiCl$_4$ (0.42 ml of 1 M in DCM, 0.42 mmol) was added to trimethyl{1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-2-methylenecyclopropyl}silane **283** (0.05 g, 0.21 mmol) in dichloromethane (10 ml), at - 78 °C under Ar. The solution was stirred for 1 hr. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over MgSO$_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100 to 80/20) to give dichloride **325** (0.033 g, 63%) as a pale yellow oil R_f = 0.66 (20/80 ether/petrol); ν_{max} (film)/cm^{-1} 2923, 1377, 1250, 1075, 834 and 689; δ_H (300 MHz; CDCl$_3$) 4.14 (1H, d, *J* 11, CH_AH$_B$Cl), 4.05 (1H, d, *J* 11, CH$_A$$H_B$Cl), 2.60 (1H, d, *J* 17, =CCH_AH$_B$C(CH$_3$)Cl), 2.52 (1H, d, *J* 17, =CCH$_A$$H_B$C(CH$_3$)Cl), 2.41 (1H, m, CH$_2CH_AH_B$C(CH$_3$)Cl), 2.29 (1H, m, CH$_2CH_A$$H_B$C(CH$_3$)Cl), 1.97 (1H, m, C$H_AH_BCH_2$C(CH$_3$)Cl), 1.70 (1H, m, CH$_A$$H_BCH_2$C(CH$_3$)Cl), 1.64 (3H, s, CH$_3$) and 0.22 (9H, s, Si(CH$_3$)$_3$); δ_C (75 MHz; CDCl$_3$) 138.99 (0), 137.07 (0), 68.14 (0), 48.55 (2), 44.69 (2), 37.28 (2), 31.95 (3), 28.26 (2) and 0.00 (3 x 3); m/z (EI+) 250.0712 (M^+. $C_{11}H_{20}Cl_2Si$ requires 250.0711) and m/z (CI) 250 ([M]$^+$, 100%).



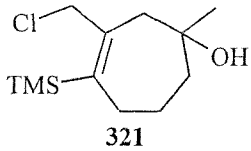
326

2-{[3-(Chloromethyl)-1-methyl-4-(1,1,1-trimethylsilyl)-3-cyclohexenyl]oxy}-1-ethanol 326

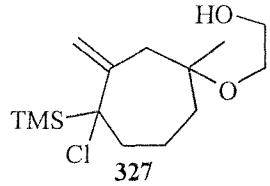
$SnCl_4$ (0.097 ml, 0.83 mmol) was added to trimethyl{1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-2-methylenecyclopropyl}silane **283** (0.1 g, 0.42 mmol), in dichloromethane (20 ml), at - 78 °C under Ar. The solution was stirred for 1 hr. The reaction mixture was quenched with water (30 ml) and the aqueous phase was extracted with dichloromethane (2 x 40 ml) and ether (2 x 50 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100/0 to 70/30) to give cyclohexene **326** (0.053 g, 46%) as a pale yellow oil R_f = 0.32 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3398, 2929, 1615, 1372, 1249, 1050 and 833; δ_H (300 MHz; $CDCl_3$) 4.11 (1H, d, *J* 11, CH_AH_BCl), 4.05 (1H, d, *J* 11, CH_AH_BCl), 3.69-3.61 (2H, m, CH_2CH_2OH), 3.48 (2H, t, *J* 5, CH_2OH), 2.38-2.02 (5H, m, $=CCH_2C(CH_3)O$, OH and $CH_2CH_2C(CH_3)O$), 1.68 (1H, m, $CH_AH_BCH_2C(CH_3)O$), 1.54 (1H, m, $CH_AH_BCH_2C(CH_3)O$), 1.18 (3H, s, CH_3) and 0.18 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz; $CDCl_3$) 140.06 (0), 137.67 (0), 72.50 (0), 62.24 (2), 61.90 (2), 48.90 (2), 39.68 (2), 32.71 (2), 27.84 (2), 23.48 (3) and 0.00 (3 x 3); m/z (EI+) 276.1309 (M^+. $C_{13}H_{25}ClO_2Si$ requires 276.1312), m/z (CI) 294 ($[M + NH_4^+]^+$, 93%) and 215 (100%).



317



321



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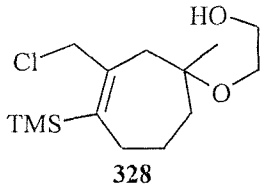


328

(*1R,4S*)-4-Chloro-1-methyl-3-methylene-4-(1,1,1-trimethylsilyl)cycloheptan-1-ol 317

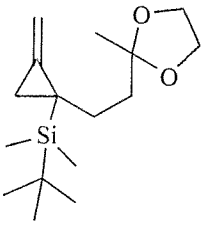
3-(Chloromethyl)-1-methyl-4-(1,1,1-trimethhylsilyl)-3-cyclllohepten-1-ol 321

2-{[4-Chloro-1-methyl-3-methylene-4-(1,1,1-trimethylsilyl)cycloheptyl]oxy}-1-ethanol 327

2-{[3-(Chloromethyl)-1-methyl-4-(1,1,1-trimethylsilyl)-3-cycloheptenyl]oxy}-1-ethanol 328

$SnCl_4$ (0.091 ml, 0.78 mmol) was added to trimethyl{1-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]-2-methylenecyclopropyl}silane **309** (0.1 g, 0.39 mmol), in dichloromethane (20 ml), at - 78 °C under Ar. The solution was stirred for 45 mins. The reaction mixture was quenched with water (30 ml) and the aqueous phase was extracted with dichloromethane (2 x 40 ml) and ether (2 x 50 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100/0 to 80/20) to give methylenecycloheptanol **317** (0.03 g, 31%) as a white solid and as a single diastereoisomer; cycloheptene **321** as a pale yellow oil (0.003 g, 3%); and methylenecycloheptane **327** and cycloheptene **328** (0.026 g, 23%), as a 1 : 2.9 ratio of inseparable regioisomers and as a pale yellow oil R_f = 0.15 (40/60 ether/petrol); ν_{max} (film)/cm^{-1} 3443, 2930, 1448, 1249, 1116 and 837; m/z (EI+) 290.1460 (M^+. $C_{14}H_{27}ClO_2Si$ requires 290.1469), m/z (CI) 255 ($[M - Cl]^+$, 54%) and 121 (100%); data for **327** δ_H (300 MHz; $CDCl_3$) 4.94 (1H, s, $=CH_AH_B$), 4.86 (1H, d, *J* 2, $=CH_AH_B$), 3.75-3.64 (2H, m, CH_2CH_2OH), 3.55-3.43 (2H, m, CH_2CH_2OH), 2.01-1.91 (2H, m, $CH_2=CCH_2C(CH_3)O$), 1.80-1.32 (7H, m, 3 x CH_2 and OH) 1.24 (3H, s, CH_3) and 0.11 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz; $CDCl_3$) 145.06 (0), 119.23 (2), 74.26 (0), 68.48 (0), 61.71 (2), 61.62 (2), 48.19 (2), 46.39 (2), 36.40 (2), 25.89 (2), 23.50 (3) and - 0.95 (3 x 3); data for **328** δ_H (300 MHz; $CDCl_3$) 4.17 (2H, s, CH_2Cl), 3.75-3.64 (2H, m, CH_2CH_2OH), 3.55-3.43 (2H, m, CH_2CH_2OH), 2.62 (1H, d, *J* 14, $=CCH_AH_BC(CH_3)OH$), 2.51 (1H, d, *J* 14, $=CCH_AH_BC(CH_3)OH$), 2.31-2.21 (3H, m, $=C(TMS)CH_2(CH_2)_2$ and OH), 2.02-1.89 (2H, m, $(CH_2)_2CH_2C(CH_3)O$), 1.52-1.41 (2H, m, $CH_2CH_2CH_2$), 1.19 (3H, s, CH_3) and 0.20 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz; $CDCl_3$) 144.26 (0), 141.28 (0), 73.29 (0), 62.10 (2), 62.05 (2), 50.54 (2), 43.60 (2), 40.89 (2), 30.90 (2), 24.46 (3), 21.99 (2) and 0.00 (3 x 3).

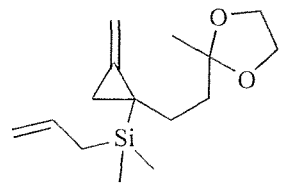
EXPERIMENTAL FOR CHAPTER FIVE



344

***tert*-Butyl(dimethyl)-{1-[2-(2-methyl-1,3dioxolan-2-yl)ethyl]-2-methylene cyclopropyl}silane 344**

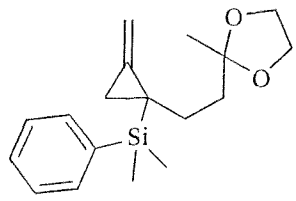
BuLi (5.56 ml of 2.39 M in hexane, 13.3 mmol) was added to methylenecyclopropane **1** (1.2 ml, 17.3 mmol) in THF (40 ml) at - 30 °C under N_2. The solution was allowed to warm to 0 °C over 30 mins and kept at 0 °C for 1 hr. After cooling at - 55 °C, *t*-butyldimethylchlorosilane (1.89 g, 12.5 mmol) was added to the orange solution which became colourless. The solution was warmed to 0 °C over 30 mins and kept at 0 °C for 30 mins. After cooling again at - 60 °C, BuLi (5.56 ml of 2.39 M in hexane, 13.3 mmol) was added and the warming procedure repeated. The orange solution was cooled to - 78 °C and iodide **170** (3 g, 12.4 mmol) was added dropwise. The temperature was allowed to warm to room temperature over 5 hrs. The reaction was quenched with saturated NH_4Cl (50 ml), extracted with ether (3 x 50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ethyl acetate ; 99/1) to give silyl ketal **344** (3.05 g, 87%) as a colourless oil R_f = 0.52 (90/10 petrol/ ethyl acetate); ν_{max} (film)/cm^{-1} 2953, 1469, 1375, 1251, 1053 and 832; δ_H (400 MHz; $CDCl_3$) 5.28 (1 H, s, $=CH_AH_B$), 5.21 (1 H, s, $=CH_AH_B$), 3.99-3.83 (4H, m, $O(CH_2)_2O$), 1.72-1.53 (4H, m, 2 x CH_2), 1.27 (3H, s, CH_3), 1.08 (1H, dt, *J* 7 and 2, $CH_AH_BC=CH_2$), 0.97 (9H, s, 3 x CH_3 *t*-butyl), 0.81 (1H, dt, *J* 7 and 2, $CH_AH_BC=CH_2$), - 0.09 (3H, s, $SiCH_3$) and - 0.10 (3H, s, $SiCH_3$); δ_C (100 MHz; $CDCl_3$) 140.04 (0), 110.30 (0), 101.37 (2), 64.97 (2 x 2), 37.33 (2), 30.59 (2), 27.81 (3 x3), 24.10 (3), 18.67 (0), 13.05 (2), - 5.79 (3) and - 6.12 (3); m/z (CI) 283.1951 (M^+. $C_{17}H_{31}O_2Si$ requires 283.5052), 284 ($[M + H]^+$, 4%) and 87 (100%).



345

Allyl(dimethyl)-{1-[2-(methyl-1,3dioxolan-2-yl)ethyl]-2-methylenecyclopropyl}silane 345

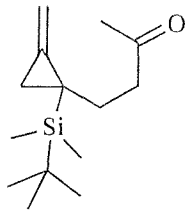
BuLi (3.49 ml of 2.53 M in hexane, 8.84 mmol) was added to methylenecyclopropane **1** (0.78 ml, 11.5 mmol) in THF (40 ml) at - 30 °C under N_2. The solution was allowed to warm to 0 °C over 30 mins and kept at 0 °C for 1 hr. After cooling at - 55 °C, allyldimethylchlorosilane (1.22 ml, 8.34 mmol) was added to the orange solution which became colourless. The solution was warmed to 0 °C over 30 mins and kept at 0 °C for 30 mins. After cooling again at - 60 °C, BuLi (3.49 ml of 2.53 M in hexane, 8.84 mmol) was added and the warming procedure repeated. The orange solution was cooled to - 78 °C and iodide **170** (2 g, 8.26 mmol) was added dropwise. The temperature was allowed to warm to room temperature over 5 hrs. The reaction was quenched with saturated NH_4Cl (50 ml), extracted with ether (3 x 50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ethyl acetate ; 95/5) to give silyl ketal **345** (1.97 g, 89%) as a pale yellow oil R_f = 0.41 (90/10 petrol/ ethyl acetate); ν_{max} (film)/cm^{-1} 2954, 1451, 1375, 1042 and 832; δ_H (400 MHz; $CDCl_3$) 5.79 (1H, ddt, *J* 8 and 10 and 16, H_2C=C*H*CH_2Si), 5.29 (1 H, s with fine splitting, =CH_AH_B), 5.23 (1 H, s with fine splitting, =CH_AH_B), 4.92-4.82 (2H, m, H_2C=CHCH_2Si), 3.99-3.88 (4H, m, $O(CH_2)_2O$), 1.74-1.47 (6H, m, 3 x CH_2), 1.29 (3H, s, CH_3), 1.08 (1H, dt, *J* 2 and 7, CH_AH_BC=CH_2), 0.86 (1H, dt, *J* 2 and 7, CH_AH_BC=CH_2), - 0.00 (3H, s, $SiCH_3$) and -0.007 (3H, s, $SiCH_3$); δ_C (100 MHz; $CDCl_3$) 140.73 (0), 136.50 (1), 114.71 (2), 111.42 (0), 102.45 (2), 66.18 (2 x 2), 38.83 (2), 30.95 (2), 25.27 (3), 23.85 (2), 14.41 (0), 13.97 (2), - 3.09 (3) and - 3.17 (3); m/z (EI+) 266.1706 (M^+. $C_{15}H_{26}O_2Si$ requires 266.1702), m/z (CI) 284 ([M + NH_4^+]$^+$, 5%) and 35 (100%).



346

Dimethyl{1-[2-(2-methyl-1,3dioxolan-2-yl)ethyl]-2-methylenecyclopropyl}phenylsilane 346

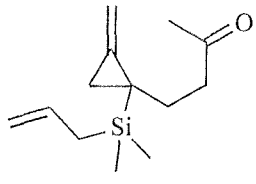
BuLi (3.41 ml of 2.59 M in hexane, 8.84 mmol) was added to methylenecyclopropane **1** (0.78 ml, 11.5 mmol) in THF (40 ml) at - 30 °C under N_2. The solution was allowed to warm to 0 °C over 30 mins and kept at 0 °C for 1 hr. After cooling at - 55 °C, phenyldimethylchlorosilane (1.40 ml, 8.35 mmol) was added to the orange solution which became colourless. The solution was warmed to 0 °C over 30 mins and kept at 0 °C for 30 mins. After cooling again at - 60 °C, BuLi (3.41 ml of 2.59 M in hexane, 8.84 mmol) was added and the warming procedure repeated. The orange solution was cooled to - 78 °C and iodide **170** (2 g, 8.26 mmol) was added dropwise. The temperature was allowed to warm to room temperature over 5 hrs. The reaction was quenched with saturated NH_4Cl (50 ml), extracted with ether (3 x 50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ethyl acetate ; 98/2) to give silyl ketal **346** (2.02 g, 81%) as a colourless oil R_f = 0.52 (80/20 petrol/ ethyl acetate); ν_{max} (film)/cm^{-1} 2954, 1427, 1248, 1111, 1052, 812 and 699; δ_H (400 MHz; $CDCl_3$) 7.47 (2H, m, Ar *H*), 7.28 (3H, m, Ar *H*), 5.23 (1H, s, $=CH_AH_B$), 5.21 (1H, s with fine splitting, $=CH_AH_B$), 3.81-3.66 (4H, m, $O(CH_2)_2O$), 1.57-1.31 (4H, m 2 x CH_2), 1.09 (3H, s, CH_3), 1.01 (1H, dt, *J* 8 and 2, $CH_AH_BC{=}CH_2$), 0.79 (1H, dt, *J* 8 and 2, $CH_AH_BC{=}CH_2$) and 0.19 (6H, s, $Si(CH_3)_2$); δ_C (100 MHz; $CDCl_3$) 141.46 (0), 140.34 (0), 136.40 (2 x 1), 131.48 (1), 130.07 (2 x 1), 112.20 (0), 103.58 (2), 66.87 (2 x 2), 39.46 (2), 31.94 (2), 25.93 (3), 15.37 (0), 15.17 (2), - 1.75 (3) and - 1.77 (3); m/z (EI+) 302.1707 (M^+. $C_{18}H_{26}O_2Si$ requires 302.1702), 302 ($[M]^+$, 7%), 135 ($[M - 167]^+$, 92%) and 35 (100%).



337

4-{1-[1-(*tert*-Butyl)-1,1-dimethylsilyl]-2-methylenecyclopropyl}-2-butanone 337

tert-Butyl(dimethyl)-{1-[2-(2-methyl-1,3dioxolan-2-yl)ethyl]-2-methylenecyclopropyl} silane **344** (0.58 g, 2.05 mmol) was stirred with *p*-TsOH (0.39 g, 2.05 mmol) in a mixture of acetone (180 ml) and 10% water (20 ml) for 48 hours. The mixture was concentrated *in vacuo*. Ether (50 ml) was added. The mixture was then washed once with 10% $NaHCO_3$ (100 ml) and extracted with ether (3 x 75 ml). The organic phase was dried over $MgSO_4$, concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/ether ; 100/0 to 95/5) to give **337** (0.47 g, 96%) as a colourless oil R_f = 0.53 (20/80 ether/petrol); ν_{max} (film)/cm^{-1} 2929, 1718, 1361, 1252 and 831; δ_H (400 MHz; $CDCl_3$) 5.33 (1H, s, $=CH_AH_B$), 5.20 (1 H, s, $=CH_AH_B$), 2.45-2.24 (2H, m, CH_2CO), 2.11 (3H, s, CH_3), 1.98 (1H, ddd, *J* 5 and 10 and 14, $CH_AH_BCH_2CO$), 1.78 (1H, ddd, *J* 5 and 10 and 14, $CH_AH_BCH_2CO$), 1.10 (1H, dt, *J* 7 and 2, $CH_AH_BC=CH_2$), 0.98 (9H, s, 3 x CH_3 *t*-butyl), 0.82 (1H, dt, *J* 7 and 2, $CH_AH_BC=CH_2$), - 0.06 (3H, s, $SiCH_3$) and - 0.08 (3H, s, $SiCH_3$); δ_C (100 MHz; $CDCl_3$) 208.99 (0), 138.97 (0), 102.26 (2), 41.30 (2), 30.29 (3), 28.75 (2), 27.84 (3 x 3), 18.72 (0), 12.26 (2), - 6.08 (3) and - 6.52 (3); m/z (CI) 239.1835 ($[M + H]^+$. $C_{14}H_{27}OSi$ requires 239.1831), 256 ($[M + NH_4^+]^+$, 2%), 239 ($[M + H]^+$, 70%) and 135 (100%).

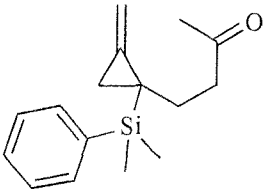


338

4-[1-(1-Allyl-1,1-dimethylsilyl)-2-methylenecyclopropyl]-2-butanone 338

Allyl(dimethyl)-{1-[2-(methyl-1,3dioxolan-2-yl)ethyl]-2-methylenecyclopropyl}silane **345** (1 g, 3.76 mmol) was stirred with *p*-toluenesulfonic acid (0.71 g, 3.76 mmol) in a mixture of acetone (180 ml) and 10% water (20 ml) for 48 hours. The mixture was concentrated *in vacuo*. Ether (50 ml) was added. The mixture was then washed once with 10% $NaHCO_3$ (100 ml) and extracted with ether (3 x 75 ml). The organic phase was dried

over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/ether ; 100/0 to 95/5) to give **338** (0.79 g, 95%) as a colourless oil R_f = 0.50 (30/70 ether/petrol); ν_{max} (film)/cm^{-1} 2961, 1716, 1361, 1155 and 832; δ_H (400 MHz; $CDCl_3$) 5.79 (1H, tdd, *J* 8 and 10 and 17, H_2C=C*H*CH_2Si), 5.33 (1H, s, =CH_AH_B), 5.22 (1H, s with fine splitting, =CH_AH_B), 4.89 (1H, dd, *J* 2 and 17, CH_AH_B=$CHCH_2$), 4.85 (1H, dd, *J* 2 and 10, CH_AH_B=$CHCH_2$), 2.48-2.30 (2H, m, CH_2COCH_3), 2.13 (3H, s, CH_3), 1.90 (1H, ddd, *J* 6 and 10 and 14, C$H_AH_BCH_2CO$), 1.71 (1H, ddd, *J* 6 and 10 and 14, $CH_AH_BCH_2CO$), 1.59 (2H, dd, *J* 1 and 8, $SiCH_2CH$=CH_2), 1.09 (1H, dt, *J* 2 and 7, CH_AH_BC=CH_2), 0.85 (1H, dt, *J* 2 and 7, CH_AH_BC=CH_2), - 0.00 (3H, s, $SiCH_3$) and - 0.004 (3H, s, $SiCH_3$); δ_C (100 MHz; $CDCl_3$) 208.95 (0), 138.66 (0), 135.11 (1), 113.76 (2), 102.09 (2), 41.83 (2), 30.33 (3), 28.28 (2), 22.50 (2), 12.84 (0), 12.3 (2), - 4.47 (3) and - 4.57 (3); m/z (EI+) 222.1427 (M^+. $C_{13}H_{22}OSi$ requires 222.1440), m/z (CI) 240 ([M + NH_4^+]$^+$, 35%), 223 ([M + H]$^+$, 50%) and 181 (100%).

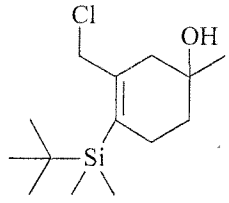


339

4-[1-(1,1Dimethyl-1-phenylsilyl)-2-methylenecyclopropyl]-2-butanone 339

Dimethyl{1-[2-(2-methyl-1,3dioxolan-2-yl)ethyl]-2-methylenecyclopropyl}phenyl silane **346** (1.6 g, 5.3 mmol) was stirred with *p*-toluenesulfonic acid (1 g, 5.3 mmol) in a mixture of acetone (90 ml) and 10% water (10 ml) for 48 hours. The mixture was concentrated *in vacuo*. Ether (50 ml) was added. The mixture was then washed once with 10% $NaHCO_3$ (100 ml) and extracted with ether (3 x 75 ml). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/ether ; 100/0 to 97/3) to give **339** (0.56 g, 41%) as a colourless oil R_f = 0.50 (70/30 ether/petrol); ν_{max} (film)/cm^{-1} 2956, 1716, 1362, 1112, 811 and 699; δ_H (400 MHz; $CDCl_3$) 7.42 (2H, m, H aromatics), 7.25 (3H, m, H aromatics), 5.23 (1H, s, =CH_AH_B), 5.17 (1H, s with fine splitting, =CH_AH_B), 2.18-2.01 (2H, m, CH_2CO), 1.84 (3H, s, CH_3), 1.73 (1H, ddd, *J* 17 and 10 and 9, C$H_AH_BCH_2CO$), 1.50 (1H, ddd, *J* 17 and 10 and 9, $CH_AH_BCH_2CO$), 1.01 (1H, dt, *J* 8 and 2, CH_AH_BC=CH_2), 0.76 (1H, dt, *J* 8 and 2,

$CH_AH_BC{=}CH_2$) and 0.15 (6H, s, $(CH_3)_2Si$); δ_C (100 MHz; $CDCl_3$) 210.99(0), 140.58 (0), 140.03 (0), 136.27(2 x 1), 131.56 (1), 130.13 (2 x 1), 104.16 (2), 43.85 (2), 32.06 (3), 30.49 (2), 14.95 (0), 14.63 (2), - 2.16 (3) and - 2.25 (3); m/z (EI+) 258.1444 (M^+. $C_{16}H_{22}OSi$ requires 258.1440), 258 ($[M]^+$, 2%) and 135 (100%).



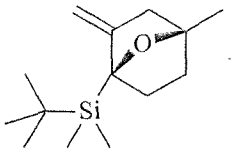
347

4-[1-(*tert*-Butyl) 1,1-dimethylsilyl]-3-(chloromethyl)-1-methyl-3-cyclohexen-1-ol 347

$TiCl_4$ (0.14 ml of 1 M solution in DCM, 0.14 mmol) was added to 4-{1-[1-(*tert*-butyl)-1,1-dimethylsilyl]-2-methylenecyclopropyl}-2-butanone **337** (0.03 g, 0.12 mmol) in dichloromethane (10 ml), at - 78 °C, under Ar. The solution was stirred for 0.5 hr. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 80/20 to 40/60) to give cyclohexenol **347** (0.030 g, 88%) as a colourless oil;

$SnCl_4$ (0.14 ml of 1 M solution in DCM, 0.14 mmol) was added to 4-{1-[1-(*tert*-butyl)-1,1-dimethylsilyl]-2-methylenecyclopropyl}-2-butanone **337** (0.03 g, 0.12 mmol) in dichloromethane (10 ml), at - 78 °C, under Ar. The solution was stirred for 45 mins. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 80/20 to 40/60) to give cyclohexenol **347** (0.028 g, 82%) as a colourless oil R_f = 0.32 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3353, 2962, 1471, 1252, 832 and 770; δ_H (400 MHz; $CDCl_3$) 4.10 (1H, d, *J* 11, CH_AH_BCl), 4.04 (1H, d, *J* 11, CH_AH_BCl), 2.41-2.13 (4H, m, $=CCH_2C(CH_3)OH$ and $=CCH_2CH_2C(CH_3)OH$), 1.68-1.45 (3H, m, $CH_2CH_2C(CH_3)OH$ and OH), 1.26 (3H, s, CH_3), 0.90 (9H, s, 3 x CH_3 *t*-butyl), 0.21 (3H, s, CH_3Si) and 0.19 (3H, s, CH_3Si); δ_C (100 MHz; $CDCl_3$) 142.01 (0), 135.74 (0), 68.95 (0), 50.39 (2), 43.73 (2), 35.80 (2), 29.97 (2), 29.17 (3), 27.66 (3 x 3), 18.78 (0), - 2.72 (3) and -

3.21 (3); m/z (CI) 292.1850 ([M + NH_4^+]$^+$. $C_{14}H_{31}NOClSi$ requires 292.1863), 274 ([M]$^+$, 20%), 256 ([M - H_2O]$^+$, 24%) and 292 ([M + NH_4^+]$^+$, 100%).

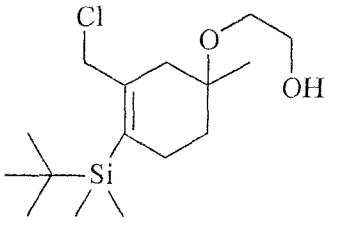


348

***tert*-Butyl(dimethyl)(4-methyl-2-methylene-7-oxabicyclo[2.2.1]hept-1-yl)silane 348**

$BF_3.Et_2O$ (0.035 ml, 0.28 mmol) was added to 4-{1-[1-(*tert*-butyl)-1,1-dimethylsilyl]-2-methylenecyclopropyl}-2-butanone **337** (0.06 g, 0.25 mmol) in dichloromethane (20 ml), at - 78 °C, under Ar. The solution was stirred for 5 hours. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (neat petrol) to give bicyclic ether **348** (0.042 g, 70%) as a pale yellow oil;

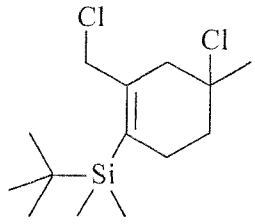
$BF_3(AcOH)_2$ (0.045 ml, 0.32 mmol) was added to 4-{1-[1-(*tert*-butyl)-1,1-dimethylsilyl]-2-methylenecyclopropyl}-2-butanone **337** (0.07 g, 0.29 mmol) in dichloromethane (20 ml), at - 78 °C, under Ar. The solution was stirred for 1 hour. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (neat petrol) to give bicyclic ether **348** (0.05 g, 71%) as a pale yellow oil R_f = 0.72 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2929, 1361, 1249, 1112, 832 and 731; δ_H (400 MHz; $CDCl_3$) 4.76 (1H, s with fine splitting, =CH_AH$_B$), 4.71 (1H, s with fine splitting, =CH$_A$$H_B$), 2.30-2.15 (2H, m, CH$_AH_BCH_2$), 1.98 (1H, m, C$H_AH_BCH_2$), 1.66-1.53 (1H, m, =CC$H_2$C(CH$_3$)O), 1.48 (3H, s, CH$_3$), 1.40 (1H, m, CH$_A$$H_BCH_2$), 0.99 (9H, s, 3 x CH$_3$), 0.15 (3H, s, CH$_3$Si) and 0.12 (3H, s, CH$_3$Si); δ_C (100 MHz; $CDCl_3$) 158.28 (0), 102.32 (0), 85.81 (0), 83.99 (0), 48.24 (2), 37.95 (2), 36.49 (2), 28.59 (3 x 3), 21.41 (3), 18.99 (0), - 5.19 (3) and - 5.32 (3); m/z (CI) 239.1835 ([M + H]$^+$. $C_{14}H_{27}OSi$ requires 239.1831), 239 ([M + H]$^+$, 24%), 221 ([M - H_2O]$^+$, 15%) and 107 (100%).



349

2-{[4-[1-(*tert*-Butyl)-1,1-dimethylsilyl]-3-(chloromethyl)-1-methyl-3-cyclohexenyl]oxy}-1-ethanol 349

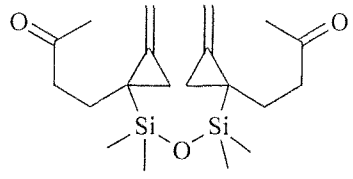
$SnCl_4$ (0.041 ml, 0.35 mmol) was added to *tert*-butyl(dimethyl)-{1-[2-(2-methyl-1,3dioxolan-2-yl)ethyl]-2-methylenecyclopropyl}silane **344** (0.05 g, 0.18 mmol) in dichloromethane (10 ml), at -78 °C, under Ar. The solution was stirred for 1 hour. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100/0 to 80/20) to give cyclohexene **349** (0.035 g, 62%) as a yellow oil R_f = 0.24 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3440, 2926, 1427, 1253, 1103, 834 and 731; δ_H (400 MHz; $CDCl_3$) 4.11 (1H, d, *J* 11, C*H*$_A$H$_B$Cl), 4.04 (1H, d, *J* 11, CH$_A$*H*$_B$Cl), 3.67 (2H, t, *J* 5, C*H*$_2$OH), 3.50 (2H, t, *J* 5, C*H*$_2$CH$_2$OH), 2.39 (1H, d, *J* 18, =CC*H*$_A$H$_B$C(CH$_3$)O), 2.27 (1H, m, CH$_2$C*H*$_A$H$_B$C(CH$_3$)O), 2.24 (1H, d, *J* 18, =CCH$_A$*H*$_B$C(CH$_3$)O), 2.14 (1H, m, CH$_2$CH$_A$*H*$_B$C(CH$_3$)O), 1.97 (1H, br s, OH), 1.69 (1H, m, C*H*$_A$H$_B$CH$_2$), 1.53 (1H, m, CH$_A$*H*$_B$CH$_2$), 1.20 (3H, s, CH$_3$), 0.89 (9H, s, 3 x CH$_3$), 0.20 (3H, s, SiCH$_3$) and 0.19 (3H, s, SiCH$_3$); δ_C (100 MHz; $CDCl_3$) 141.55 (0), 135.68 (0), 72.87 (0), 62.66 (2), 62.35 (2), 50.32 (2), 40.27 (2), 33.18 (2), 29.74 (2), 27.41 (3 x 3), 23.99 (3), 18.50 (0), - 3.11 (3) and - 3.23 (3); m/z (CI) 336.2129 ([M + NH_4^+]$^+$. $C_{16}H_{35}ClNO_2Si$ requires 336.2125), 336 ([M + NH_4^+]$^+$, 54%), 300 ([M - H_2O]$^+$, 15%) and 132 (100%).



350

***tert*-Butyl[4-chloro-2-(chloromethyl)-4-methyl-1-cyclohexenyl]dimethylsilane 350**

$TiCl_4$ (0.28 ml of 1 M solution in DCM, 0.28 mmol) was added to *tert*-butyl(dimethyl)-{1-[2-(2-methyl-1,3dioxolan-2-yl)ethyl]-2-methylenecyclopropyl}silane **344** (0.04 g, 0.14 mmol) in dichloromethane (10 ml), at - 78 °C, under Ar. The solution was stirred for 1 hr. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (neat petrol) to give dichloride **350** (0.032 g, 85%) as a pale yellow oil R_f = 0.73 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2956, 1427, 1252, 1075, 904 and 728 δ_H (400 MHz; $CDCl_3$) 4.15 (1H, d, *J* 11, CH_AH_BCl), 4.03 (1H, d, *J* 11, CH_AH_BCl), 2.65 (1H, d, *J* 18, $=CCH_AH_BC(CH_3)Cl$), 2.57 (1H, d, *J* 18, $=CCH_AH_BC(CH_3)Cl$), 2.43 (1H, m, $CH_AH_BCH_2C=$), 2.28 (1H, m, $CH_AH_BCH_2C=$), 1.97 (1H, m, $CH_AH_BC=$), 1.70 (1H, m, $CH_AH_BC=$), 1.65 (3H, s, CH_3), 0.92 (9H, s, 3 x CH_3), 0.23 (3H, s, CH_3Si) and 0.21 (3H, s, CH_3Si); δ_C (100 MHz; $CDCl_3$) 140.48 (0), 135.10 (0), 68.52 (0), 50.02 (2), 45.28 (2), 37.71 (2), 32.49 (3), 30.18 (2), 27.40 (3 x 3), 18.58 (0), - 3.08 (3) and - 3.27 (3); m/z (CI) 310 ([M + NH_4^+]$^+$, 8%), 274 ([M - H_2O]$^+$, 15%) and 132 (100%).

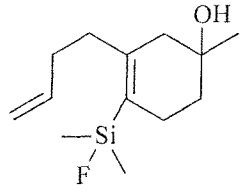


351

4-{1-[1-({1,1-Dimethyl-1-[2-methylene-1-(3-oxobutyl)cyclopropyl]silyl}oxy)-1,1-dimethylsilyl]-2-methylenecyclopropyl}-2-butanone 351

$SnCl_4$ (0.03 ml, 0.25 mmol) was added to 4-[1-(1-allyl-1,1-dimethylsilyl)-2-methylenecyclopropyl]-2-butanone **338** (0.05 g, 0.22 mmol) in dichloromethane (10 ml), at - 40 °C, under Ar. The solution was stirred for 40 mins. The reaction mixture was quenched

with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100/0 to 50/50) to give dimer **351** (0.026 g, 31%) as a pale yellow oil and as a single diastereoisomer R_f = 0.44 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2959, 1715, 1361, 1254, 1045 and 829; δ_H (400 MHz; $CDCl_3$) 5.23 (2H, s, 2 x $=CH_AH_B$), 5.15 (2H, s with fine splitting, 2 x $=CH_AH_B$), 2.46-2.29 (4H, m, 2 x CH_2CO), 2.06 (6H, s, 2 x CH_3), 1.81 (2H, ddd, *J* 6 and 10 and 14, 2 x $CH_AH_BCH_2CO$), 1.58 (2H, ddd, *J* 6 and 10 and 14, 2 x $CH_AH_BCH_2CO$), 1.07 (2H, dt, *J* 2 and 8, 2 x $CH_AH_BC{=}CH_2$), 0.76 (2H, dt, *J* 2 and 8, 2 x $CH_AH_BC{=}CH_2$), 0.01 (6H, d, *J* 2, 2 x $SiCH_3$) and 0.00 (6H, d, *J* 2, 2 x $SiCH_3$); δ_C (100 MHz; $CDCl_3$) 209.00 (0), 138.53 (0), 101.73 (2), 42.26 (2), 30.28 (3), 28.24 (2), 14.91 (0), 12.26 (2), - 0.62 (3) and - 0.91 (3); m/z (CI) 396.2420 ($[M + NH_4^+]^+$. $C_{20}H_{38}Si_2NO_3$ requires 396.2390), m/z (EI+) 378 ($[M]^+$, 6%) and 181 (100%).



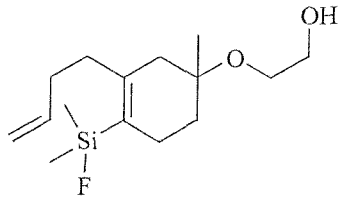
354

3-(3-Butenyl)-4-(1-fluoro-1,1-dimethylsilyl)-1-methyl-3-cyclohexen-1-ol 354

$BF_3(AcOH)_2$ (0.034 ml, 0.25 mmol) was added to 4-[1-(1-allyl-1,1-dimethylsilyl)-2-methylenecyclopropyl]-2-butanone **338** (0.05 g, 0.22 mmol) in dichloromethane (10 ml), at -40 °C, under Ar. The solution was stirred for 40 mins. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100/0 to 70/30) to give alcohol **354** (0.023 g, 42%) as a pale yellow oil;

$BF_3.Et_2O$ (0.031 ml, 0.25 mmol) was added to 4-[1-(1-allyl-1,1-dimethylsilyl)-2-methylenecyclopropyl]-2-butanone **338** (0.05 g, 0.22 mmol) in dichloromethane (10 ml), at -40 °C, under Ar. The solution was stirred for 3 hours. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in*

vacuo. The crude mixture was purified by flash column chromatography (petrol/ether ; 95/5 to 70/30) to give alcohol **354** (0.022 g, 41%) as a pale yellow oil R_f = 0.28 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3351, 2973, 1259, 1099, 974 and 866; δ_H (400 MHz; $CDCl_3$) 5.79 (1H, ddt, *J* 16 and 10 and 6, CH_2CH=CH_2), 5.02 (1H, dd, *J* 2 and 17, CH_AH_B=$CHCH_2$), 4.95 (1H, dd, *J* 2 and 11, CH_AH_B=$CHCH_2$), 2.40-2.01 (7H, m, 3 x CH_2 and OH), 1.70-1.39 (4H, m, 2 x CH_2), 1.24 (3H, s, CH_3), 0.34 (3H, d, *J* 2, $SiCH_3$) and 0.32 (3H, d, *J* 2, $SiCH_3$); δ_C (100 MHz; $CDCl_3$) 148.14 (0), 138.39 (1), 127.36 (d, 0), 115.24 (2), 68.99 (0), 44.88 (2), 37.60 (2), 35.48 (2), 33.41 (2), 28.65 (3), 26.24 (2), 0.63 (d, 3) and 0.75 (d, 3); m/z (CI) 260.1854 ($[M + NH_4^+]^+$. $C_{13}H_{27}NOSiF$ requires 260.1846), 243 ($[M + H]^+$, 36%), 224 ($[M - H_2O]^+$, 70%) and 260 ($[M + NH_4^+]^+$, 100%).



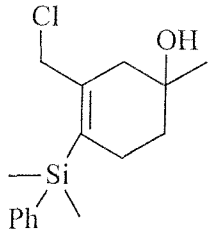
368

2-{[3-(3-Butenyl)-4-(1-fluoro-1,1-dimethylsilyl)-1-methyl-3-cyclohexenyl]oxy}-1-ethanol 368

$BF_3(AcOH)_2$ (0.052 ml, 0.37 mmol) was added to allyl(dimethyl)-{1-[2-(methyl-1,3dioxolan-2-yl)ethyl]-2-methylenecyclopropyl}silane **345** (0.05 g, 0.19 mmol) in dichloromethane (10 ml), at - 78 °C, under Ar. The solution was stirred for 3 hours. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 95/5 to 70/30) to give alcohol **368** (0.026 g, 48%) as a pale yellow oil;

$BF_3.Et_2O$ (0.048 ml, 0.37 mmol) was added to allyl(dimethyl)-{1-[2-(methyl-1,3dioxolan-2-yl)ethyl]-2-methylenecyclopropyl}silane **345** (0.05 g, 0.19 mmol) in dichloromethane (10 ml), at - 78 °C, under Ar. The solution was stirred for 3 hours. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column

chromatography (petrol/ether ; 95/5 to 70/30) to give alcohol **368** (0.018 g, 33%) as a pale yellow oil R_f = 0.28 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3452, 2927, 1372, 1255, 1053, 862, 827 and 785; δ_H (400 MHz; $CDCl_3$) 5.80 (1H, ddt, *J* 17 and 11 and 6, $CH_2CH{=}CH_2$), 5.03 (1H, dd, *J* 2 and 17, $CH_AH_B{=}CHCH_2$), 4.96 (1H, dd, *J* 2 and 11, $CH_AH_B{=}CHCH_2$), 3.71-3.63 (2H, m, OCH_2CH_2OH), 3.54-3.43 (2H, m, OCH_2CH_2OH), 2.31-2.11 (7H, m, 3 x CH_2 and OH), 2.11-1.99 (2H, m, $CH_2CH{=}CH_2$), 1.65 (1H, dt, *J* 12 and 6, $CH_AH_BC(CH_3)O$), 1.56 (1H, dt, *J* 12 and 6, $CH_AH_BC(CH_3)O$), 1.16 (3H, s, CH_3), 0.32 (3H, d, *J* 2, CH_3Si) and 0.30 (3H, d, *J* 2, CH_3Si); δ_C (100 MHz; $CDCl_3$) 147.89 (0), 138.39 (1), 127.50 (d, 0), 115.16 (2), 73.27 (0), 62.61 (2), 62.23 (2), 41.96 (2), 37.66 (2), 33.50 (2), 32.76 (2), 26.40 (2), 23.86 (3), 0.60 (d, 3) and 0.54 (d, 3); m/z (CI) 304.2109 ($[M + NH_4^+]^+$. $C_{15}H_{31}NO_2FSi$ requires 304.2108), 304 ($[M + NH_4^+]^+$, 49%) and 225 (100%).



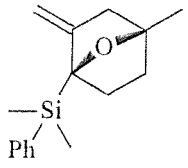
383

3-(Chloromethyl)-4-(1,1-dimethyl-1-phenylsilyl)-1-methyl-3-cyclohexen-1-ol 383

$TiCl_4$ (0.21 ml of 1 M solution in DCM, 0.21 mmol) was added to 4-[1-(1,1dimethyl-1-phenylsilyl)-2-methylenecyclopropyl]-2-butanone **339** (0.05 g, 0.20 mmol) in dichloromethane (10 ml), at - 78 °C, under Ar. The solution was stirred for 1 hr. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 80/20 to 40/60) to give cyclohexenol **383** (0.038 g, 66%) as a yellow oil;

$SnCl_4$ (0.025 ml, 0.21 mmol) was added to 4-[1-(1,1dimethyl-1-phenylsilyl)-2-methylenecyclopropyl]-2-butanone **339** (0.05 g, 0.20 mmol) in dichloromethane (10 ml), at - 78 °C, under Ar. The solution was stirred for 6 hrs. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*.

The crude mixture was purified by flash column chromatography (petrol/ether; 80/20 to 40/60) to give cyclohexenol **383** (0.046 g, 79%) as a yellow oil R_f = 0.25 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3376, 2962, 1427, 1252, 810 and 697; δ_H (400 MHz; $CDCl_3$) 7.51 (2H, m, H aromatics), 7.37 (3H, m, H aromatics), 3.99 (1H, d, *J* 11, C*H*$_A$H$_B$Cl), 3.94 (1H, d, *J* 11, CH$_A$*H*$_B$Cl), 2.44-2.12 (4H, m, =CC*H*$_2$C(CH$_3$)OH and =CC*H*$_2$CH$_2$C(CH$_3$)OH), 1.73-1.44 (3H, m, CH$_2$C*H*$_2$C(CH$_3$)OH and OH), 1.28 (3H, s, CH$_3$), 0.47 (3H, s, CH$_3$Si) and 0.46 (3H, s, CH$_3$Si); δ_C (100 MHz; $CDCl_3$) 143.06 (0), 139.78 (0), 136.28 (0), 134.72 (2 x 1), 130.27 (1), 129.10 (2 x 1), 69.47 (0), 49.96 (2), 44.20 (2), 36.22 (2), 29.54 (2), 29.49 (3), 0.00 (3) and -0.21 (3); m/z (CI) 312.1541 ([M + NH_4^+]$^+$. $C_{16}H_{27}NOSiCl$ requires 312.1550), m/z (EI+) 294 ([M]$^+$, 0.5%), 135 ([PhMe$_2$Si]$^+$, 93%) and 43 (100%).

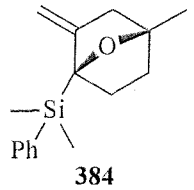


384

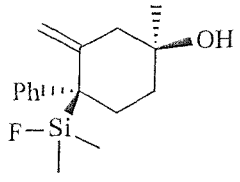
Dimethyl(4-methyl-2-methylene-7-oxabicyclo[2.2.1]hept-1-yl)phenylsilane 384

$BF_3.Et_2O$ (0.027 ml, 0.21 mmol) was added to 4-[1-(1,1dimethyl-1-phenylsilyl)-2-methylenecyclopropyl]-2-butanone **339** (0.05 g, 0.20 mmol) in dichloromethane (10 ml), at -40 °C, under Ar. The solution was stirred for 6 hours. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether; 100/0 to 90/10) to give bicyclic ether **384** (0.036 g, 72%) as a pale yellow oil R_f = 0.71 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3071, 2970, 1381, 1247, 1112, 832 and 699; δ_H (400 MHz; $CDCl_3$) 7.67 (2H, m, H aromatics), 7.38 (3H, m, H aromatics), 4.63 (1H, t, *J* 2, =C*H*$_A$H$_B$), 4.61 (1H, t, *J* 2, =CH$_A$*H*$_B$), 2.31-2.19 (2H, m, CH$_A$H$_B$C*H*$_2$), 2.01 (1H, m, C*H*$_A$H$_B$CH$_2$), 1.67 (1H, d, *J* 10, =CC*H*$_A$H$_B$C(CH$_3$)O), 1.65 (1H, d, *J* 10, =CCH$_A$*H*$_B$C(CH$_3$)O), 1.53 (3H, s, CH$_3$), 1.51 (1H, m, CH$_A$*H*$_B$CH$_2$), 0.47 (3H, s, CH$_3$Si) and 0.44 (3H, s, CH$_3$Si); δ_C (100 MHz; $CDCl_3$) 156.14 (0), 137.23 (0), 134.46 (2 x 1), 129.05 (1), 127.62 (2 x 1), 101.83 (2), 85.30 (0), 82.17 (0), 47.07 (2), 36.11 (2), 35.79 (2), 20.62 (3), - 4.02 (3) and - 4.67 (3); m/z (CI)

259.1526 ([M + H]$^+$. $C_{16}H_{23}SiO$ requires 259.1518), m/z (EI+) 258 ([M]$^+$, 23%) and 135 ([$PhMe_2Si$]$^+$, 100%).



384

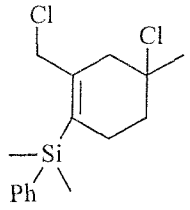


385

Dimethyl(4-methyl-2-methylene-7-oxabicyclo[2.2.1]hept-1-yl)phenylsilane 384

(*1R,4R*)-4-(1-Fluoro-1,1-dimethylsilyl)-1-methyl-3-methylene-4-phenyl-1-cyclohexanol 385

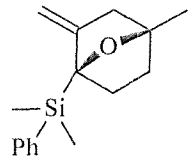
$BF_3(AcOH)_2$ (0.03 ml, 0.21 mmol) was added to 4-[1-(1,1dimethyl-1-phenylsilyl)-2-methylenecyclopropyl]-2-butanone **339** (0.05 g, 0.20 mmol) in dichloromethane (10 ml), at -40 °C, under Ar. The solution was stirred for 45 mins. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100/0 to 50/50) to give bicyclic ether **384** (0.011 g, 22%) as a pale yellow oil and methylenecyclohexane **385** (0.030 g, 55%) as a white solid and as a single diastereoisomer mp 44-46 °C (from EtOH-H_2O) R_f = 0.31 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3452, 2932, 1445, 1257, 864 and 700; δ_H (400 MHz; $CDCl_3$) 7.26 (4H, m, H aromatics), 7.16 (1H, m, H aromatics), 5.21 (1H, s, $=CH_AH_B$), 5.17 (1H, s, $=CH_AH_B$), 2.41 (1H, dt, *J* 14 and 4, $CH_AH_BCH_AH_B$), 2.13 (1H, d, *J* 14, $=CCH_AH_BC(CH_3)OH$), 2.08 (1H, ddd, *J* 14 and 11 and 7, $CH_AH_BCH_AH_B$), 1.98 (1H, d, *J* 14, $=CCH_AH_BC(CH_3)OH$), 1.82 (1H, br s, OH), 1.58-1.50 (2H, m, $CH_AH_BCH_AH_B$ and $CH_AH_BCH_AH_B$), 1.08 (3H, s, CH_3), 0.18 (3H, d, *J* 7, CH_3SiF) and 0.15 (3H, d, *J* 7, CH_3SiF); δ_C (100 MHz; $CDCl_3$) 148.41 (0), 140.09 (0), 129.11 (2 x 1), 128.60 (2 x 1), 126.18 (1), 116.84 (2), 71.58 (0), 47.73 (2), 43.33 (d, 0), 33.92 (2), 30.53 (3), 26.00 (2), - 2.00 (d, 3) and - 2.05 (d, 3); m/z (EI+) 278.1492 ([M]$^+$. $C_{16}H_{23}OSiF$ requires 278.1502), 278 ([M]$^+$, 16%), 77 ([FMe_2Si]$^+$, 95%) and 169 (100%); structure and stereochemistry confirmed by X-ray diffraction.



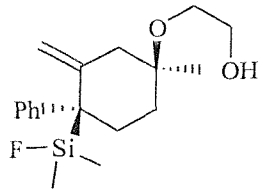
386

[4-Chloro-2-(chloromethyl)-4-methhyl-1-cyclohexenyl](dimethyl)phenylsilane 386

$TiCl_4$ (0.33 ml of 1 M solution in DCM, 0.33 mmol) was added to dimethyl{1-[2-(2-methyl-1,3dioxolan-2-yl)ethyl]-2-methylenecyclopropyl}phenyl silane **346** (0.05 g, 0.16 mmol) in dichloromethane (10 ml), at - 78 °C, under Ar. The solution was stirred for 1 hr. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100/0 to 90/10) to give dichloride **386** (0.019 g, 39%) as a pale yellow oil R_f = 0.75 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3068, 2955, 1427, 1252, 1112, 1076, 811 and 667; δ_H (400 MHz; $CDCl_3$) 7.51 (2H, m, H aromatics), 7.37 (3H, m, H aromatics), 4.02 (1H, d, *J* 11, CH_AH_BCl), 3.89 (1H, d, *J* 11, CH_AH_BCl), 2.63 (1H, d, *J* 18, $=CCH_AH_BC(CH_3)Cl$), 2.57 (1H, d, *J* 18, $=CCH_AH_BC(CH_3)Cl$), 2.49 (1H, m, $CH_AH_BCH_2C=$), 2.29 (1H, m, $CH_AH_BCH_2C=$), 1.99 (1H, m, $CH_AH_BC=$), 1.71 (1H, ddd, *J* 11 and 9 and 5, $CH_AH_BC=$), 1.66 (3H, s, CH_3), 0.47 (3H, s, CH_3Si) and 0.44 (3H, s, CH_3Si); δ_C (100 MHz; $CDCl_3$) 141.45 (0), 139.36 (0), 135.58 (0), 134.43 (2 x1), 130.00 (1), 128.82 (2 x 1), 68.85 (0), 49.51 (2), 45.60 (2), 38.02 (2), 33.85 (3), 29.65 (2), - 0.30 (3) and - 0.61 (3); m/z (CI) 330.1218 ($[M + NH_4^+]^+$. $C_{16}H_{26}NCl_2Si$ requires 330.1211), m/z (EI+) 312 ($[M]^+$, 4%), 135 ($[Ph\ (CH_3)_2Si]^+$, 27%) and 107 (100%).



384



387

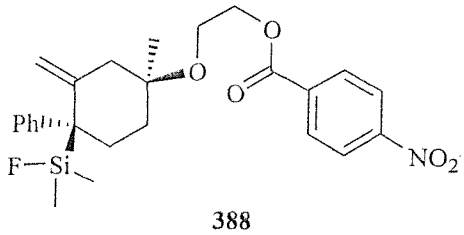
Dimethyl(4-methyl-2-methylene-7-oxabicyclo[2.2.1]hept-1-yl)phenylsilane 384

2-{[(*1R,4S*)-4-(1-Fluoro-1,1-dimethylsilyl)-1-methyl-3-methylene-4-phenylcyclohexyl] oxy}-1-ethanol 387

$BF_3.Et_2O$ (0.042 ml, 0.33 mmol) was added to dimethyl{1-[2-(2-methyl-1,3dioxolan-2-yl)ethyl]-2-methylenecyclopropyl}phenylsilane **346** (0.05 g, 0.16 mmol) in dichloromethane (10 ml), at - 78 °C, under Ar. The solution was stirred for 6 hours. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100/0 to 50/50) to give bicyclic ether **384** (0.005 g, 12%) as a pale yellow oil and methylenecyclohexane **387** (0.016 g, 30%) as a yellow oil and as a single diastereoisomer;

$BF_3(AcOH)_2$ (0.046 ml, 0.33 mmol) was added to dimethyl{1-[2-(2-methyl-1,3dioxolan-2-yl)ethyl]-2-methylenecyclopropyl}phenylsilane **346** (0.05 g, 0.16 mmol) in dichloromethane (10 ml), at - 78 °C, under Ar. The solution was stirred for 5 hours. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100/0 to 50/50) to give bicyclic ether **384** (0.009 g, 21%) as a pale yellow oil and methylenecyclohexane **387** (0.021 g, 39%) as a yellow oil and as a single diastereoisomer R_f = 0.26 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3405, 2933, 1445, 1257, 1086, 869, 730 and 699; δ_H (400 MHz; $CDCl_3$) 7.31 (4H, m, H aromatics), 7.18 (1H, m, H aromatics), 5.18 (1H, s, $=CH_AH_B$), 5.08 (1H, s, $=CH_AH_B$), 3.72 (2H, t, *J* 5, CH_2OH), 3.48 (1H, m, $CH_2CH_AH_BOH$), 3.44 (1H, m, $CH_2CH_AH_BOH$), 2.32 (1H, d, *J* 14, $=CCH_AH_BC(CH_3)O$), 2.29 (1H, m, $CH_AH_BCH_AH_B$), 2.18 (1H, dt, *J* 3 and 13, $CH_AH_BCH_AH_B$), 1.90 (1H, d, *J* 14, $=CCH_AH_BC(CH_3)O$), 1.76 (1H, m, $CH_AH_BCH_AH_B$), 1.62 (1H, br s, OH), 1.48 (1H, dt, *J* 3 and 13, $CH_AH_BCH_AH_B$), 1.02 (3H, s, CH_3), 0.19 (3H, d, *J* 8, $FSiCH_3$) and 0.17 (3H, d, *J* 8, $FSiCH_3$); δ_C (100 MHz; $CDCl_3$) 148.02 (0), 140.44 (0), 128.91

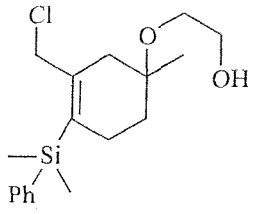
(2 x 1), 128.20 (2 x 1), 125.85 (1), 115.73 (2), 74.97 (0), 62.92 (2), 62.21 (2), 43.29 (2), 42.70 (d, 0), 32.01 (2), 25.76 (3), 24.87 (2), - 2.05 (d, 3) and - 2.21 (d, 3); m/z (CI) 340.2104 ([M + NH_4^+]$^+$. $C_{18}H_{31}NO_2SiF$ requires 340.2108), m/z (EI+) 322 ([M]$^+$, 1%) and 77 ([FMe_2Si]$^+$, 56%) and 260 (100%).



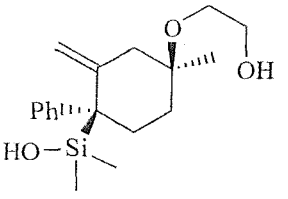
388

2-{[(*1R,4S*)-4-(1-Fluoro-1,1-dimethylsilyl)-1-methyl-3-methylene-4-phenylcyclohexyl] oxy}ethyl 4-nitrobenzoate 388

Et_3N (0.037 ml, 0.27 mmol) was added to a solution of alcohol **387** (0.029 g, 0.09 mmol) in DCM (5 ml) at 0 °C under Ar, followed by the rapid addition of *p*-nitrobenzoyl chloride (0.083 g, 0.45 mmol). The reaction mixture was stirred for 30 mins at 0 °C and allowed to come to room temperature overnight. The crude reaction was directly purified on a flash column chromatography (petrol/ether ; 90/10 to 70/30) to give benzoate **388** (0.040 g, 95%) as a pale yellow solid, mp. 65-67°C (from ethanol-water) and as a single diastereoisomer R_f = 0.55 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2933, 1719, 1525, 1347, 1086, 871, 828, 749 and 720; δ_H (300 MHz; $CDCl_3$) 8.32-8.22 (4H, m, H Ar), 7.31-7.25 (4H, m, H Ar), 7.17 (1H, m, H Ar), 5.15 (1H, s, =CH_AH$_B$), 5.04 (1H, s, =CH$_A$$H_B$), 4.50 (2H, t, *J* 5, C$H_2$OCO), 3.75 (1H, m, COOCH$_2CH_AH_B$O), 3.67 (1H, m, COOCH$_2CH_A$$H_B$O), 2.40-2.15 (2H, m, C$H_2CH_AH_B$), 2.33 (1H, d, *J* 14, =CCH_AH$_B$C(CH$_3$)O), 1.91 (1H, d, *J* 14, =CCH$_A$$H_B$C(CH$_3$)O), 1.68 (1H, m, CH$_2CH_AH_B$), 1.48 (1H, m, CH$_2CH_A$$H_B$), 1.03 (3H, s, CH$_3$), 0.11 (3H, d, *J* 8, FSiCH$_3$) and 0.10 (3H, d, *J* 8, FSiCH$_3$); δ_C (75 MHz; $CDCl_3$) 164.95 (0), 150.69 (0), 147.26 (0), 139.95 (0), 135.82 (0), 131.02 (2 x 1), 128.48 (2 x 1), 127.82 (2 x 1), 125.42 (1), 123.67 (2 x 1), 114.93 (2), 75.11 (0), 65.88 (2), 58.97 (2), 42.68 (2), 42.31 (d 0), 31.67 (2), 25.19 (3), 24.51 (2), - 2.44 (d 3) and - 2.63 (d 3); m/z (CI) 489 ([M + NH_4^+]$^+$, 38%) and 182 (100%); structure and stereochemistry confirmed by X-ray diffraction.



391



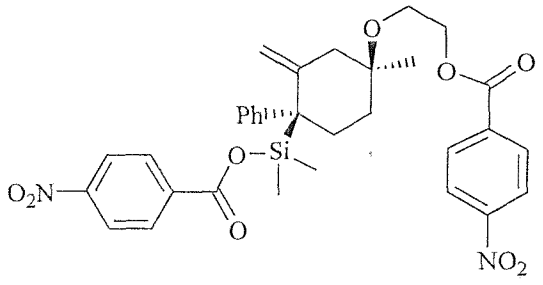
392

2-{[3-(Chloromethyl)-4-(1,1-dimethyl-1-phenylsilyl)-1-methyl-3-cyclohexenyl]oxy}-1-ethanol 391

2-{[(*1R,4S*)-4-(1-Hydroxy-1,1-dimethylsilyl)-1-methyl-3-methylene-4-phenylcyclohexyl] oxy}-1-ethanol 392

$SnCl_4$ (0.038 ml, 0.33 mmol) was added to dimethyl{1-[2-(2-methyl-1,3dioxolan-2-yl)ethyl]-2-methylenecyclopropyl}phenylsilane **346** (0.05 g, 0.16 mmol) in dichloromethane (10 ml), at - 78 °C, under Ar. The solution was stirred for 1 hour. The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x 20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100/0 to 0/100) to give cyclohexene **391** (0.021 g, 38%) as a yellow oil R_f = 0.22 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3452, 2928, 1427, 1251, 1107, 810 and 660; δ_H (400 MHz; $CDCl_3$) 7.51 (2H, m, H aromatics), 7.38 (3H, m, H aromatics), 4.02 (1H, d, *J* 11, CH_AH_BCl), 3.95 (1H, d, *J* 11, CH_AH_BCl), 3.71 (2H, t, *J* 5, CH_2OH), 3.52 (2H, t, *J* 5, CH_2CH_2OH), 2.40 (1H, d, *J* 14, $=CCH_AH_BC(CH_3)O$), 2.26 (1H, d, *J* 14, $=CCH_AH_BC(CH_3)O$), 2.40-2.01 (3H, m, $CH_2C(CH_3)O$ and OH), 1.75 (1H, m, $CH_AH_BCH_2$), 1.58 (1H, m, $CH_AH_BCH_2$), 1.24 (3H, s, CH_3), 0.47 (3H, s, $SiCH_3$) and 0.36 (3H, s, $SiCH_3$); δ_C (100 MHz; $CDCl_3$) 142.53 (0), 139.64 (0), 136.27 (0), 134.45 (2 x 1), 130.01 (1), 129.86 (2 x 1), 73.32 (0), 63.13 (2), 62.82 (2), 49.87 (2), 40.73 (2), 33.50 (2), 29.16 (2), 24.45 (3), 0.04 (3) and - 0.40 (3); m/z (CI) 356.1812 ($[M + NH_4^+]^+$. $C_{18}H_{31}NO_2SiCl$ requires 356.1812), 320 ($[M - H_2O]^+$, 7%) and 356 ($[M + NH_4^+]^+$, 100%); and diol **392** (0.012 g, 23%) as a yellow oil and as a single diastereoisomer R_f = 0.04 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3380, 2932, 1253, 1055 and 867; δ_H (400 MHz; $CDCl_3$) 7.29 (4H, m, H aromatics), 7.12 (1H, m, H aromatics), 5.19 (1H, s, $=CH_AH_B$), 5.14 (1H, s, $=CH_AH_B$), 3.67 (2H, t, *J* 5, CH_2CH_2OH), 3.45 (1H, m, $HOCH_2CH_AH_BO$), 3.38 (1H, m, $HOCH_2CH_AH_BO$), 2.26 (1H, m, $CH_AH_BCH_AH_B$), 2.21 (1H, d, *J* 14, $=CCH_AH_BC$), 2.12 (1H, dt, *J* 3 and 13, $CH_AH_BCH_AH_B$), 1.90-1.60 (3H, m, $CH_AH_BCH_AH_B$ and 2 x OH), 1.82 (1H, d, *J* 14, $=CCH_AH_BC$), 1.44 (1H, dt, *J* 3 and 13, $CH_AH_BCH_AH_B$), 0.97 (3H, s, CH_3), 0.10 (3H, s, $SiCH_3$) and 0.05 (3H, s, $SiCH_3$); δ_C (100

MHz; $CDCl_3$) 148.80 (0), 141.74 (0), 129.10 (2 x 1), 128.12 (2 x 1), 125.67 (1), 116.09 (2), 75.24 (0), 63.06 (2), 62.34 (2), 43.82 (2), 43.37 (0), 32.30 (2), 25.92 (3), 25.31 (2), - 1.00 (3) and - 1.03 (3); m/z (CI) 338.2162 ($[M + NH_4^+]^+$. $C_{18}H_{32}NO_3Si$ requires 338.2151), m/z (EI+) 320 ($[M]^+$, 1%) and 75 ($[HOSiMe_2]^+$, 100%).

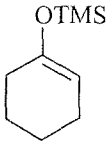


395

1,1-Dimethyl-1-((*1S,4R*)-4-methyl-2-methylene-4-{2-[(4-nitrobenzoyl)oxy]ethoxy}-1-phenylcyclohexyl)silyl 4-nitrobenzoate 395

Et_3N (0.007 ml, 0.06 mmol) was added to a solution of alcohol **392** (0.006 g, 0.02 mmol) in DCM (2 ml) at 0 °C under Ar, followed by the rapid addition of *p*-nitrobenzoyl chloride (0.017 g, 0.09 mmol). The reaction mixture was stirred for 30 mins at 0 °C and allowed to come to room temperature overnight. The crude reaction was directly purified on a flash column chromatography (petrol/ether ; 90/10 to 70/30) to give dibenzoate **395** (0.007 g, 64%) as a pale yellow solid, mp. 65-67°C (from ethanol-water) and as a single diastereoisomer R_f = 0.43 (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 2933, 1719, 1525, 1347, 1086, 871, 828, 749 and 720; δ_H (400 MHz; CD_3OD) 8.42-8.18 (8H, m, H Ar), 7.37-7.20 (4H, m, H Ar), 7.11 (1H, m, H Ar), 5.14 (2H, s, $=CH_2$), 4.56-4.41 (2H, m, CH_2OCO), 3.78 (1H, m, $OCH_AH_BCH_2OCO$), 3.69 (1H, m, $OCH_AH_BCH_2OCO$), 2.33 (1H, m, $CH_AH_BCH_AH_B$), 2.32 (1H, d, *J* 14, $=CCH_AH_BC(CH_3)O$), 2.20 (1H, m, $CH_AH_BCH_AH_B$), 1.87 (1H, d, *J* 14, $=CCH_AH_BC(CH_3)O$), 1.71 (1H, m, $CH_AH_BCH_AH_B$), 1.48 (1H, m, $CH_AH_BCH_AH_B$), 1.01 (3H, s, CH_3), 0.03 (3H, s, $SiCH_3$) and - 0.02 (3H, s, $SiCH_3$); δ_C (100 MHz; $CDCl_3$) 169.09 (0), 167.70 (0), 153.59 (0), 153.48 (0), 151.04 (0), 143.97 (0), 139.13 (0), 138.48 (0), 133.43 (4 x 1), 130.50 (4 x 1), 127.23 (1), 126.12 (2 x 1), 126.03 (2 x 1), 117.02 (2), 77.93 (0), 68.39 (2), 61.64 (2), 45.50 (0), 45.45 (2), 34.14 (2), 27.29 (2), 27.07 (3), 0.19 (3) and 0.00 (3); m/z (CI) 652 ($[M + NH_4^+]^+$, 47%) and 75 (100%).

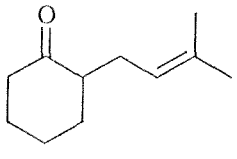
EXPERIMENTAL FOR CHAPTER SIX



420

(1-cyclohexanyloxy)(trimethyl)silane 420

Following the method used by Fleming[79] cyclohexanone **419** (1.83 ml, 17.6 mmol) in THF (2 ml) is added to a stirred solution of LDA [prepared in situ by addition of n-BuLi (7.8 ml, 18.7 mmol) to diisopropylamine (2.97 ml, 21.2 mmol) in THF (40 ml) at - 78 °C] under Ar at - 78 °C over 5 mins. The solution was stirred for a further hour and then TMSCl (3.81 ml, 31 mmol) was added over 5 mins. The reaction was allowed to come to room temperature and after stirring for 1 hour, the solvent was evaporated *in vacuo*. Dry pentane (50 ml) was added and the LiCl was removed by filtration. Distillation under vacuum (bp. 72-74 °C/40 mmHg) gave silyl enol ether **420** (1.87 g, 62%) as a colourless oil ν_{max} (film)/cm^{-1} 2928, 1366, 1250, 1184 and 838; δ_H (300 MHz; $CDCl_3$) 4.87 (1H, br s, =CH), 2.07-1.92 (4H, m, CH_2C=CH and CH_2CH=), 1.72-1.59 (2H, m, CH_2), 1.57-1.46 (2H, m, CH_2) and 0.18 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz; $CDCl_3$) 150.43 (0), 104.40 (1), 30.03 (2), 23.95 (2), 23.30 (2), 22.48 (2) and 0.49 (3 x 3); m/z (CI) 171 ($[M + H]^+$, 100%).

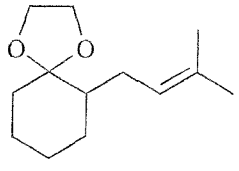


421

2-(3-Methyl-2-butenyl)-1-cyclohexanone 421

Following the method used by Fleming[79] cyclohexanone **419** (0.62 ml, 6.02 mmol) in THF (2 ml) is added to a stirred solution of LDA [prepared in situ by addition of BuLi (2.66 ml, 6.38 mmol) to diisopropylamine (1.01 ml, 7.23 mmol) in THF (15 ml) at - 78 °C] under Ar at - 78 °C over 5 mins. The solution was stirred for a further hour and then prenyl bromide (1.04 ml, 9.04 mmol) was added over 5 mins. The reaction was allowed to come to room temperature and after stirring for 1 hour, the solvent was evaporated *in vacuo*. Dry pentane

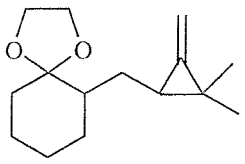
(50 ml) was added and the LiCl was removed by filtration. Distillation under vacuum (bp. 118-120 °C/40 mmHg) gave cyclohexanone **421** (0.6 g, 60%) as a colourless oil ν_{max} (film)/cm^{-1} 2927, 1708, 1446, 1126 and 837; δ_H (400 MHz; $CDCl_3$) 5.07 (1H, t, *J* 7, CH_2CH=$C(CH_3)_2$), 2.46-2.34 (2H, m, CH_2), 2.34-2.22 (2H, m, CH_2), 2.11 (1H, m, CHCO), 2.07-1.91 (2H, m, CH_2), 1.85 (1H, m, CH_AH_BCH), 1.68 (3H, s, CH_3C=), 1.66 (1H, m, CH_AH_BCH), 1.60 (3H, s, CH_3C=) and 1.41-1.29 (2H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 213.49 (0), 133.31 (0), 122.46 (1), 51.55 (1), 42.41 (2), 33.79 (2), 28.40 (2), 28.29 (2), 26.18 (3), 25.38 (2) and 18.18 (3); m/z (CI) 167 ([M + H]$^+$, 100%).



418

6-(3-Methyl-2-butenyl)-1,4-dioxaspiro[4.5]decane 418

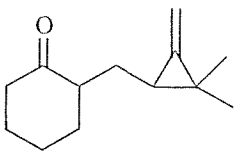
Following the method of Kelly,[85] ethylene glycol (0.34 ml, 6.02 mmol), 2-(3-methyl-2-butenyl)-1-cyclohexanone **421** (0.5 g, 3.01 mmol) and *p*-TsOH (0.006 g, 0.03 mmol) were refluxed together in toluene (50 ml) for 20 hours using a Dean Stark apparatus to remove water. The reaction mixture was cooled and concentrated *in vacuo*. Ether (50 ml) was added and washed once with aq. $NaHCO_3$ (5%, 50 ml). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (100/0 to 98/2 petrol/ethyl acetate) to give ketal **418** (0.56 g, 89%) as a colourless oil R_f = 0.48 (90/10 petrol/ethyl acetate); ν_{max} (film)/cm^{-1} 2930, 1442, 1086 and 924; δ_H (400 MHz; $CDCl_3$) 5.10 (1H, t, *J* 7, =CH), 4.01-3.89 (4H, m, $O(CH_2)_2O$), 2.21 (1H, m, CH_AH_BCH=), 1.89-1.42 (13H, m, 2 x CH_3 and $CHCH_AH_BCH$= and CH_AH_BCH= and $CH_AH_BCHCH_2CH$= and 2 x CH_2), 1.35 (1H, m, $CH_AH_BCHCH_2CH$=) and 1.27-1.14 (2H, m CH_2); δ_C (100 MHz; $CDCl_3$) 132.41 (0), 123.94 (1), 111.20 (0), 65.23 (2 x 2), 45.79 (1), 35.28 (2), 29.37 (2), 27.18 (2), 26.22 (3), 25.09 (2), 24.44 (2) and 18.19 (3); m/z (EI+) 210.1612 (M^+. $C_{13}H_{22}O_2$ requires 210.1619), m/z (CI) 211 ([M + H]$^+$, 11%) and 149 (100%).



423

6-[(2,2-Dimethyl-3-methylenecyclopropyl)methyl]-1,4-dioxaspiro[4.5]decane 423

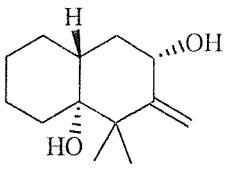
BuLi (10.42 ml of 2.40 M in hexane, 25 mmol) was added to a mixture of 6-(3-methyl-2-butenyl)-1,4-dioxaspiro[4.5]decane **418** (1.5 g, 7.14 mmol) and 1,1-dichloroethane (0.70 ml, 8.3 mmol) in ether (12 ml, 0.6 M solution) at - 25 °C over 6 hrs. Further portion of 1,1-dichloroethane (8 x 0.25 ml, 23.8 mmol) were added after 30 mins and then every 45 mins. The mixture was allowed to come to room temperature overnight. The mixture was quenched with water (15 ml), extracted with ether (3 x 20 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give a colourless oil which was used without further purification. The crude mixture in DMSO (5 ml) was added dropwise to a suspension of ^{t}BuOK (1.6 g, 1.43 mmol) in DMSO (15 ml) at 70 °C under Ar. The mixture turned dark brown and was stirred overnight. The mixture was allowed to cool to room temperature and transferred on a silica gel column chromatography eluting with a 95/5 solution of petrol/ethyl acetate for purification to give acetal **423** (1.59 g, 95%) as a yellow oil and as a 2 : 1 mixture of diastereoisomer R_f = 0.51 (90/10 petrol/ethyl acetate); ν_{max} (film)/cm^{-1} 2933, 1445, 1160 and 889; δ_H (400 MHz; $CDCl_3$) 5.25 (1H, s, =C*H*$_A$H$_B$), 5.21 (0.5H, s, =CH$_A$*H*$_B$), 5.19 (0.5H, s, =CH$_A$*H*$_B$), 3.99-3.85 (4H, m, O(CH$_2$)$_2$O), 1.90 (1H, m, C*H*CO(CH$_2$)$_2$O), 1.81-1.57 (6H, m, 3 x CH$_2$), 1.49 (1H, m, C*H*C=CH$_2$), 1.41-0.96 (4H, m, 2 x CH$_2$), 1.16 (0.5 x 3H, s, CH$_3$), 1.15 (0.5 x 3H, s, CH$_3$), 1.08 (0.5 x 3H, s, CH$_3$) and 1.06 (0.5 x 3H, s, CH$_3$); δ_C (100 MHz; $CDCl_3$) 150.04 (0), 149.25 (0), 111.15 (0), 100.06 (2), 65.15 (2 x 2), 45.72 (1), 45.49 (1), 35.17 (2), 34.95 (2), 29.32 (2), 29.19 (2), 27.41 (2), 26.56 (3), 26.47 (3), 25.97 (2), 25.12 (2), 24.79 (2), 24.36 (2), 24.32 (2), 19.86 (1), 19.39 (0) and 18.88 (1); m/z (CI) 237.1865 ([M + H]$^+$. $C_{15}H_{25}O_2$ requires 237.1855), 237 ([M + H]$^+$, 8%) and 175 (100%).



415

2-[(2,2-Dimethhyl-3-methylenecyclopropyl)methyl]-1-cyclohexanone 415

6-[(2,2-Dimethyl-3-methylenecyclopropyl)methyl]-1,4-dioxaspiro[4.5]decane **423** (1.5 g, 6.35 mmol) was stirred with *p*-TsOH (1.21 g, 6.35 mmol) in a mixture of acetone (270 ml) and 10% water (30 ml) for 48 hours. The mixture was concentrated *in vacuo*. Ether (50 ml) was added. The mixture was then washed once with 10% $NaHCO_3$ (100 ml) and extracted with ether (3 x 75 ml). The organic phase was dried over $MgSO_4$, concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol/ether ; 100/0 to 95/5) to give cyclohexanone **415** as a pale yellow oil and as a 2 : 1 mixture of diastereoisomer (0.98 g, 80%) R_f = 0.68 (20/80 ethyl acetate/petrol); ν_{max} (film)/cm^{-1} 2931, 1707, 1448, 1128 and 881; δ_H (400 MHz; $CDCl_3$) 5.29 (1H, s with fine splitting, =CH_AH$_B$), 5.23 (1H, s, =CH$_A$$H_B$), 2.52-2.30 (3H, m, CH_2CO and CHCO), 2.24 (1H, m, CH_AH$_B$CHCO), 2.08 (1H, m, CH$_A$$H_B$CHCO), 1.98-1.79 (2H, m, CH_2CHC=CH$_2$), 1.78-1.65 (2H, m, CH_2), 1.53-1.40 (2H, m, CH_2), 1.19 (3H, s, CH_3), 1.18 (1H, m, C*H*C=CH$_2$) and 1.11 (3H, s, CH_3); δ_C (100 MHz; $CDCl_3$) 213.59 (0), 213.51 (0), 149.29 (0), 148.70 (0), 100.49 (2), 100.32 (2), 51.49 (1), 51.10 (1), 42.47 (2), 42.36 (2), 34.13 (2), 33.85 (2), 28.41 (2), 28.34 (2), 28.23 (2), 26.43 (3), 26.39 (3), 25.44 (3), 25.39 (3), 25.35 (2), 25.31 (2), 25.22 (2), 19.73 (0), 19.39 (0), 19.14 (1) and 18.99 (1); m/z (CI) 193.1604 ($[M + H]^+$. $C_{13}H_{21}O$ requires 193.1592), 193 ($[M + H]^+$, 4%) and 149 (100%).



424

(2R,4aS,8aR)-4,4-Dimethyl-3-methyleneperhydro-2,4a-naphthalenediol 424

$SnCl_4$ (0.013 ml, 0.11 mmol) was added to 2-[(2,2-dimethhyl-3-methylenecyclopropyl) methyl]-1-cyclohexanone **415** (0.02 g, 0.10 mmol) in dichloromethane (10 ml), at - 78 °C, under Ar. The solution was allowed to warm slowly over 8 hours . The reaction mixture was quenched with water (15 ml) and the aqueous phase was extracted with dichloromethane (2 x

20 ml) and ether (2 x 20 ml). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petrol/ether ; 100/0 to 50/50) to give diol **424** (0.005 g, 23%) as a white solid and as a single diastereoisomer $R_f = 0.11$ (50/50 ether/petrol); ν_{max} (film)/cm^{-1} 3421, 2932, 1214 and 750; δ_H (400 MHz; $CDCl_3$) 5.28 (1H, s, $=CH_AH_B$), 4.99 (1H, s, $=CH_AH_B$), 4.38 (1H, ddt, *J* 12 and 6 and 2, C*H*OH), 1.92-1.80 (3H, m, CH_2CHOH and OH), 1.78-1.66 (2H, m, CH_2), 1.62-1.50 (3H, m, CH_2 and OH), 1.43-1.24 (3H, m, CH_2CH and CH_AH_BCOH), 1.19 (1H, m, $CHCH_2CHOH$), 1.14 (3H, s, CH_3), 1.12 (3H, s, CH_3) and 0.91 (1H, m, CH_AH_BCOH); δ_C (100 MHz; $CDCl_3$) 157.19 (0), 106.31 (2), 75.13 (0), 68.96 (1), 45.81 (0), 40.84 (2), 37.97 (1), 31.09 (2), 29.41 (2), 26.31 (2), 24.62 (3), 22.18 (2) and 21.17 (3); m/z (EI+) 210.1612 (M^+. $C_{13}H_{22}O_2$ requires 210.1620), 210 ($[M]^+$, 6%), 192 ($[M - H_2O]^+$, 30%) and 175 (100%); structure and stereochemistry confirmed by X-ray diffraction.

Appendix A

X-ray crystallographic data for **153**

Table 1. Crystal data and structure refinement.

Identification code	**00sot063**	
Empirical formula	$C_9H_{14}Cl_2O$	
Formula weight	209.10	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	a = 10.7087(10) Å	α = 110.139(4)°
	b = 11.4437(13) Å	β = 91.011(4)°
	c = 13.7080(15) Å	γ = 96.298(4)°
Volume	1564.9(3) Å^3	
Z	6	
Density (calculated)	1.331 Mg / m^3	
Absorption coefficient	0.575 mm^{-1}	
F(000)	660	
Crystal	Block; colourless	
Crystal size	0.10 × 0.08 × 0.08 mm^3	
θ range for data collection	3.08 – 24.50°	
Index ranges	$-12 \le h \le 11$, $-13 \le k \le 13$, $-14 \le l \le 15$	
Reflections collected	10719	
Independent reflections	5102 [R_{int} = 0.0580]	
Completeness to θ = 24.50°	98.0 %	
Max. and min. transmission	0.9554 and 0.9447	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5102 / 0 / 367	
Goodness-of-fit on F^2	1.083	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0594, $wR2$ = 0.1179	
R indices (all data)	$R1$ = 0.1171, $wR2$ = 0.1289	
Largest diff. peak and hole	0.506 and −0.281 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:
Asymmetric unit contains 3 molecules
Hydrogen bonds (Table 6) ⇒ ring system built up by six molecules

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.*
Cl1	1524(1)	270(1)	798(1)	66(1)	1
Cl2	4252(1)	−867(1)	−2221(1)	87(1)	1
O1	2047(2)	4281(2)	394(2)	56(1)	1
C1	2125(3)	782(3)	−229(3)	47(1)	1
C2	1947(4)	−210(4)	−1318(3)	57(1)	1
C3	3283(4)	267(4)	−1487(3)	56(1)	1
C4	3558(3)	808(3)	−307(3)	47(1)	1
C5	2521(3)	3197(3)	513(3)	44(1)	1
C6	1659(3)	2034(3)	−158(3)	44(1)	1
C7	4429(4)	1994(3)	213(3)	57(1)	1
C8	3838(4)	3121(4)	127(3)	55(1)	1
C9	2502(5)	3417(4)	1676(3)	66(1)	1
Cl1'	1294(1)	6030(1)	5912(1)	59(1)	1
Cl2'	4142(1)	2837(1)	4086(1)	60(1)	1
O1'	1457(2)	3862(2)	8348(2)	45(1)	1
C1'	1846(3)	4576(3)	5867(3)	41(1)	1
C2'	1772(3)	3566(3)	4772(3)	48(1)	1
C3'	3060(3)	3290(3)	5080(3)	44(1)	1
C4'	3302(3)	4612(3)	5878(3)	43(1)	1
C5'	1979(3)	4611(3)	7758(3)	39(1)	1
C6'	1262(3)	4126(3)	6693(3)	40(1)	1
C7'	4026(3)	4916(4)	6906(3)	48(1)	1
C8'	3341(3)	4330(3)	7615(3)	43(1)	1
C9'	1898(4)	5989(3)	8356(3)	53(1)	1
Cl1"	4900(1)	8435(1)	3646(1)	50(1)	1
Cl2"	1741(1)	10573(1)	6126(1)	55(1)	1
O1"	1069(2)	6275(2)	1663(2)	52(1)	1
C1"	3260(3)	8343(3)	3953(3)	38(1)	1
C2"	3057(3)	8486(3)	5088(3)	45(1)	1
C3"	2005(4)	9264(3)	4994(3)	45(1)	1
C4"	2653(3)	9546(3)	4116(3)	38(1)	1
C5"	1954(3)	7375(3)	2197(3)	42(1)	1
C6"	2517(3)	7187(3)	3158(3)	42(1)	1
C7"	1928(3)	9679(3)	3222(3)	42(1)	1
C8"	1160(3)	8447(3)	2538(3)	44(1)	1
C9"	2924(3)	7545(3)	1462(3)	51(1)	1

Table 3. Bond lengths [Å] and angles [°].

Cl1–C1	1.805(4)
Cl2–C3	1.790(4)
O1–C5	1.449(4)
O1–H1	0.8400
C1–C2	1.527(5)
C1–C4	1.538(5)
C1–C6	1.541(5)
C2–C3	1.525(5)
C2–H2A	0.9900
C2–H2B	0.9900
C3–C4	1.530(5)
C3–H3	1.0000
C4–C7	1.500(5)
C4–H4	1.0000
C5–C8	1.517(5)
C5–C6	1.525(5)
C5–C9	1.526(5)
C6–H6A	0.9900
C6–H6B	0.9900
C7–C8	1.536(5)
C7–H7A	0.9900
C7–H7B	0.9900
C8–H8A	0.9900
C8–H8B	0.9900
C9–H9A	0.9800
C9–H9B	0.9800
C9–H9C	0.9800
Cl1'–C1'	1.808(4)
Cl2'–C3'	1.780(3)
O1'–C5'	1.446(4)
O1'–H1'	0.8400
C1'–C6'	1.515(5)
C1'–C2'	1.541(5)
C1'–C4'	1.554(5)
C2'–C3'	1.532(5)
C2'–H2'1	0.9900
C2'–H2'2	0.9900
C3'–C4'	1.522(5)
C3'–H3'	1.0000
C4'–C7'	1.507(5)
C4'–H4'	1.0000
C5'–C9'	1.520(5)
C5'–C8'	1.529(5)
C5'–C6'	1.529(5)
C6'–H6'1	0.9900
C6'–H6'2	0.9900
C7'–C8'	1.516(5)
C7'–H7'1	0.9900
C7'–H7'2	0.9900
C8'–H8'1	0.9900
C8'–H8'2	0.9900
C9'–H9'1	0.9800
C9'–H9'2	0.9800
C9'–H9'3	0.9800
Cl1"–C1"	1.813(3)
Cl2"–C3"	1.799(3)
O1"–C5"	1.448(4)
O1"–H1"	0.8400
C1"–C6"	1.522(4)

C1"–C2"	1.530(5)
C1"–C4"	1.536(4)
C2"–C3"	1.540(5)
C2"–H2"1	0.9900
C2"–H2"2	0.9900
C3"–C4"	1.510(5)
C3"–H3"	1.0000
C4"–C7"	1.500(5)
C4"–H4"	1.0000
C5"–C9"	1.503(5)
C5"–C8"	1.514(5)
C5"–C6"	1.530(5)
C6"–H6"1	0.9900
C6"–H6"2	0.9900
C7"–C8"	1.533(4)
C7"–H7"1	0.9900
C7"–H7"2	0.9900
C8"–H8"1	0.9900
C8"–H8"2	0.9900
C9"–H9"1	0.9800
C9"–H9"2	0.9800
C9"–H9"3	0.9800

C5–O1–H1	109.5
C2–C1–C4	89.1(3)
C2–C1–C6	113.8(3)
C4–C1–C6	113.0(3)
C2–C1–Cl1	115.1(3)
C4–C1–Cl1	114.0(3)
C6–C1–Cl1	110.5(3)
C3–C2–C1	86.8(3)
C3–C2–H2A	114.2
C1–C2–H2A	114.2
C3–C2–H2B	114.2
C1–C2–H2B	114.2
H2A–C2–H2B	111.3
C2–C3–C4	89.4(3)
C2–C3–Cl2	117.6(3)
C4–C3–Cl2	116.9(3)
C2–C3–H3	110.4
C4–C3–H3	110.4
Cl2–C3–H3	110.4
C7–C4–C3	122.2(4)
C7–C4–C1	121.0(3)
C3–C4–C1	86.2(3)
C7–C4–H4	108.5
C3–C4–H4	108.5
C1–C4–H4	108.5
O1–C5–C8	108.9(3)
O1–C5–C6	107.7(3)
C8–C5–C6	109.1(3)
O1–C5–C9	105.0(3)
C8–C5–C9	112.3(3)
C6–C5–C9	113.4(3)
C5–C6–C1	114.4(3)
C5–C6–H6A	108.7
C1–C6–H6A	108.7
C5–C6–H6B	108.7
C1–C6–H6B	108.7
H6A–C6–H6B	107.6
C4–C7–C8	110.0(3)

C4–C7–H7A	109.7
C8–C7–H7A	109.7
C4–C7–H7B	109.7
C8–C7–H7B	109.7
H7A–C7–H7B	108.2
C5–C8–C7	113.2(3)
C5–C8–H8A	108.9
C7–C8–H8A	108.9
C5–C8–H8B	108.9
C7–C8–H8B	108.9
H8A–C8–H8B	107.7
C5–C9–H9A	109.5
C5–C9–H9B	109.5
H9A–C9–H9B	109.5
C5–C9–H9C	109.5
H9A–C9–H9C	109.5
H9B–C9–H9C	109.5
C5'–O1'–H1'	109.5
C6'–C1'–C2'	114.5(3)
C6'–C1'–C4'	113.3(3)
C2'–C1'–C4'	88.3(3)
C6'–C1'–Cl1'	110.5(2)
C2'–C1'–Cl1'	114.6(3)
C4'–C1'–Cl1'	114.0(2)
C3'–C2'–C1'	86.0(3)
C3'–C2'–H2'1	114.3
C1'–C2'–H2'1	114.3
C3'–C2'–H2'2	114.3
C1'–C2'–H2'2	114.3
H2'1–C2'–H2'2	111.5
C4'–C3'–C2'	89.8(3)
C4'–C3'–Cl2'	117.8(2)
C2'–C3'–Cl2'	117.4(3)
C4'–C3'–H3'	110.1
C2'–C3'–H3'	110.1
Cl2'–C3'–H3'	110.1
C7'–C4'–C3'	122.8(3)
C7'–C4'–C1'	118.6(3)
C3'–C4'–C1'	85.9(2)
C7'–C4'–H4'	109.1
C3'–C4'–H4'	109.1
C1'–C4'–H4'	109.1
O1'–C5'–C9'	109.6(3)
O1'–C5'–C8'	105.0(3)
C9'–C5'–C8'	112.1(3)
O1'–C5'–C6'	107.4(3)
C9'–C5'–C6'	113.4(3)
C8'–C5'–C6'	108.9(3)
C1'–C6'–C5'	115.9(3)
C1'–C6'–H6'1	108.3
C5'–C6'–H6'1	108.3
C1'–C6'–H6'2	108.3
C5'–C6'–H6'2	108.3
H6'1–C6'–H6'2	107.4
C4'–C7'–C8'	112.3(3)
C4'–C7'–H7'1	109.1
C8'–C7'–H7'1	109.1
C4'–C7'–H7'2	109.1
C8'–C7'–H7'2	109.1
H7'1–C7'–H7'2	107.9
C7'–C8'–C5'	113.6(3)

C7'–C8'–H8'1	108.8
C5'–C8'–H8'1	108.8
C7'–C8'–H8'2	108.8
C5'–C8'–H8'2	108.8
H8'1–C8'–H8'2	107.7
C5'–C9'–H9'1	109.5
C5'–C9'–H9'2	109.5
H9'1–C9'–H9'2	109.5
C5'–C9'–H9'3	109.5
H9'1–C9'–H9'3	109.5
H9'2–C9'–H9'3	109.5
C5"–O1"–H1"	109.5
C6"–C1"–C2"	114.6(3)
C6"–C1"–C4"	113.0(3)
C2"–C1"–C4"	89.3(3)
C6"–C1"–Cl1"	109.9(2)
C2"–C1"–Cl1"	114.1(2)
C4"–C1"–Cl1"	114.8(2)
C1"–C2"–C3"	85.0(3)
C1"–C2"–H2"1	114.5
C3"–C2"–H2"1	114.5
C1"–C2"–H2"2	114.5
C3"–C2"–H2"2	114.5
H2"1–C2"–H2"2	111.6
C4"–C3"–C2"	89.9(3)
C4"–C3"–Cl2"	117.6(2)
C2"–C3"–Cl2"	117.7(3)
C4"–C3"–H3"	110.1
C2"–C3"–H3"	110.1
Cl2"–C3"–H3"	110.1
C7"–C4"–C3"	122.0(3)
C7"–C4"–C1"	119.3(3)
C3"–C4"–C1"	85.8(3)
C7"–C4"–H4"	109.2
C3"–C4"–H4"	109.2
C1"–C4"–H4"	109.2
O1"–C5"–C9"	109.3(3)
O1"–C5"–C8"	104.8(3)
C9"–C5"–C8"	112.4(3)
O1"–C5"–C6"	107.2(3)
C9"–C5"–C6"	113.3(3)
C8"–C5"–C6"	109.4(3)
C1"–C6"–C5"	115.7(3)
C1"–C6"–H6"1	108.3
C5"–C6"–H6"1	108.3
C1"–C6"–H6"2	108.3
C5"–C6"–H6"2	108.3
H6"1–C6"–H6"2	107.4
C4"–C7"–C8"	112.8(3)
C4"–C7"–H7"1	109.0
C8"–C7"–H7"1	109.0
C4"–C7"–H7"2	109.0
C8"–C7"–H7"2	109.0
H7"1–C7"–H7"2	107.8
C5"–C8"–C7"	112.1(3)
C5"–C8"–H8"1	109.2
C7"–C8"–H8"1	109.2
C5"–C8"–H8"2	109.2
C7"–C8"–H8"2	109.2
H8"1–C8"–H8"2	107.9
C5"–C9"–H9"1	109.5

C5"–C9"–H9"2	109.5
H9"1–C9"–H9"2	109.5
C5"–C9"–H9"3	109.5
H9"1–C9"–H9"3	109.5
H9"2–C9"–H9"3	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}
Cl1	59(1)	81(1)	70(1)	42(1)	9(1)	4(1)
Cl2	117(1)	93(1)	61(1)	24(1)	26(1)	66(1)
O1	72(2)	50(2)	45(2)	11(1)	−1(1)	22(1)
C1	45(3)	45(2)	56(3)	24(2)	4(2)	6(2)
C2	68(3)	48(3)	54(3)	16(2)	−7(2)	13(2)
C3	64(3)	55(2)	51(3)	15(2)	11(2)	31(2)
C4	46(3)	55(2)	46(3)	21(2)	4(2)	21(2)
C5	48(3)	46(2)	39(2)	14(2)	1(2)	13(2)
C6	32(2)	57(2)	43(3)	17(2)	4(2)	8(2)
C7	41(3)	69(3)	61(3)	20(2)	12(2)	13(2)
C8	50(3)	55(3)	58(3)	19(2)	3(2)	2(2)
C9	75(4)	69(3)	51(3)	13(2)	−4(3)	23(3)
Cl1'	49(1)	57(1)	80(1)	33(1)	2(1)	14(1)
Cl2'	47(1)	75(1)	58(1)	22(1)	19(1)	12(1)
O1'	38(2)	54(2)	47(2)	21(1)	8(1)	9(1)
C1'	32(2)	42(2)	50(2)	16(2)	−2(2)	7(2)
C2'	34(2)	58(2)	56(3)	26(2)	−5(2)	6(2)
C3'	40(2)	59(2)	44(2)	27(2)	16(2)	14(2)
C4'	32(2)	48(2)	49(3)	21(2)	4(2)	−1(2)
C5'	32(2)	42(2)	45(2)	16(2)	3(2)	8(2)
C6'	26(2)	47(2)	49(2)	17(2)	3(2)	4(2)
C7'	32(2)	59(3)	55(3)	22(2)	−1(2)	4(2)
C8'	35(2)	51(2)	42(2)	16(2)	−2(2)	9(2)
C9'	48(3)	55(3)	47(3)	6(2)	0(2)	8(2)
Cl1"	29(1)	59(1)	59(1)	14(1)	6(1)	11(1)
Cl2"	48(1)	63(1)	50(1)	10(1)	17(1)	17(1)
O1"	32(2)	45(2)	64(2)	−1(1)	3(1)	4(1)
C1"	23(2)	45(2)	49(2)	17(2)	8(2)	8(2)
C2"	38(2)	55(2)	49(3)	27(2)	2(2)	8(2)
C3"	38(2)	49(2)	45(2)	11(2)	8(2)	5(2)
C4"	30(2)	37(2)	44(2)	10(2)	2(2)	6(2)
C5"	30(2)	43(2)	43(2)	4(2)	6(2)	4(2)
C6"	28(2)	40(2)	52(3)	10(2)	8(2)	7(2)
C7"	41(2)	39(2)	45(2)	11(2)	4(2)	12(2)
C8"	36(2)	51(2)	46(3)	15(2)	2(2)	11(2)
C9"	40(2)	57(3)	47(3)	8(2)	7(2)	4(2)

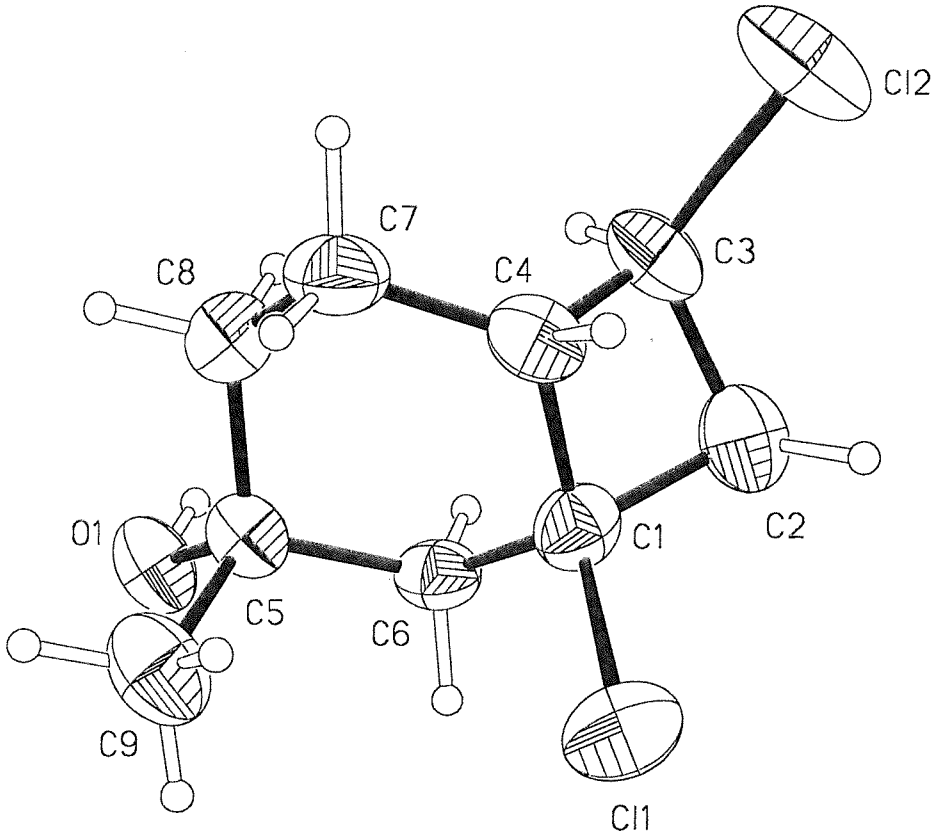
Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

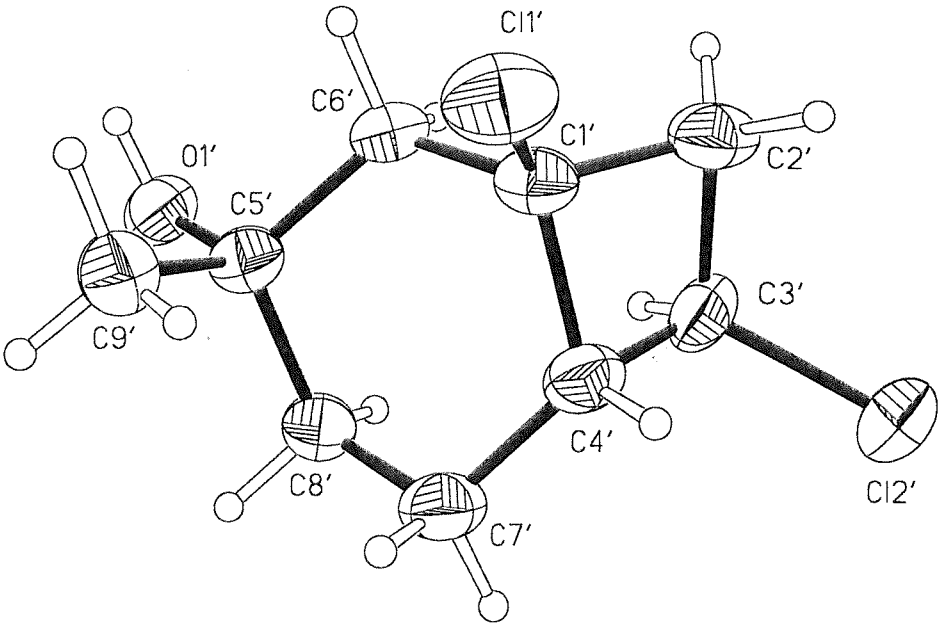
Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	2031	4211	−237	52(13)	1
H2A	1842	−1085	−1327	62(12)	1
H2B	1290	−76	−1772	79(14)	1
H3	3273	957	−1777	58(12)	1
H4	3835	135	−73	51(11)	1
H6A	1565	2061	−869	59(12)	1
H6B	816	2062	129	63(12)	1
H7A	5242	1936	−121	81(14)	1
H7B	4591	2108	956	61(13)	1
H8A	4382	3902	534	60(12)	1
H8B	3808	3065	−610	42(10)	1
H9A	1632	3438	1886	94(17)	1
H9B	3003	4218	2068	70(13)	1
H9C	2858	2736	1820	78(14)	1
H1'	703	3979	8453	106(19)	1
H2'1	1087	2868	4653	50(10)	1
H2'2	1780	3902	4196	48(11)	1
H3'	2952	2663	5440	24(8)	1
H4'	3655	5200	5527	41(10)	1
H6'1	1176	3198	6433	41(9)	1
H6'2	403	4376	6786	62(11)	1
H7'1	4168	5838	7257	39(9)	1
H7'2	4858	4610	6778	42(10)	1
H8'1	3803	4642	8305	43(10)	1
H8'2	3346	3410	7324	32(9)	1
H9'1	1013	6131	8420	48(10)	1
H9'2	2317	6500	7983	42(10)	1
H9'3	2313	6225	9052	28(9)	1
H1"	1456	5642	1455	85(16)	1
H2"1	3771	8968	5583	48(10)	1
H2"2	2759	7694	5199	48(10)	1
H3"	1199	8702	4723	15(7)	1
H4"	3306	10290	4413	35(9)	1
H6"1	1823	6879	3510	33(9)	1
H6"2	3077	6522	2924	50(10)	1
H7"1	2523	9977	2789	49(10)	1
H7"2	1351	10321	3497	30(8)	1
H8"1	459	8231	2931	39(9)	1
H8"2	792	8562	1915	39(10)	1
H9"1	3426	6843	1277	77(13)	1
H9"2	3475	8333	1800	53(11)	1
H9"3	2502	7572	832	54(12)	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
O1–H1···O1^{i}	0.84	1.92	2.728(4)	162.0
O1'–H1'···O1"^{ii}	0.84	1.88	2.692(3)	161.2
O1"–H1"···O1	0.84	1.91	2.681(3)	152.9

Symmetry transformations used to generate equivalent atoms:
(i) x,y,z–1 (ii) –x,–y+1,–z+1


Cl2
C7
C3
C8
C4
O1
C1
C2
C5
C6
C9
Cl1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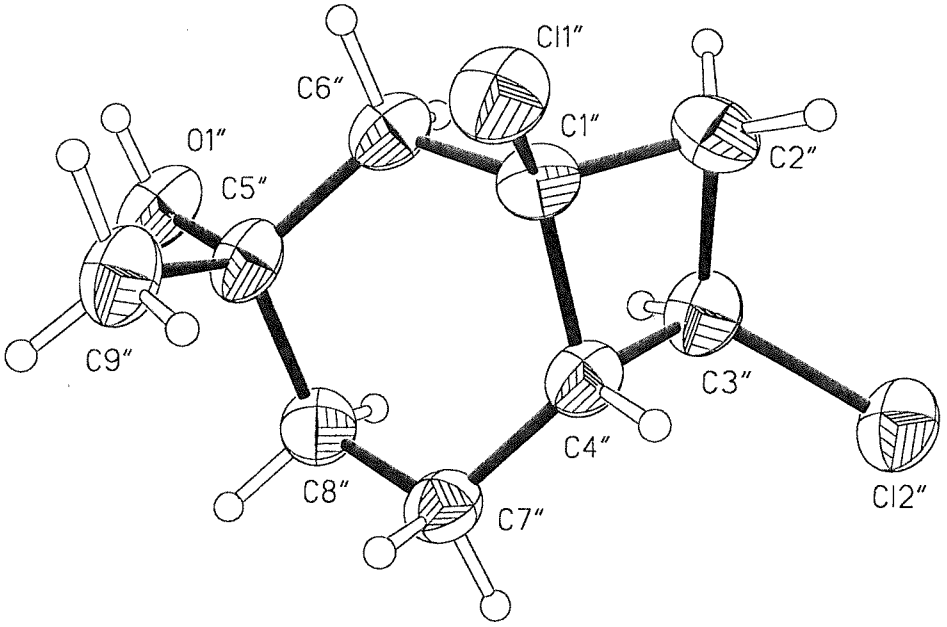
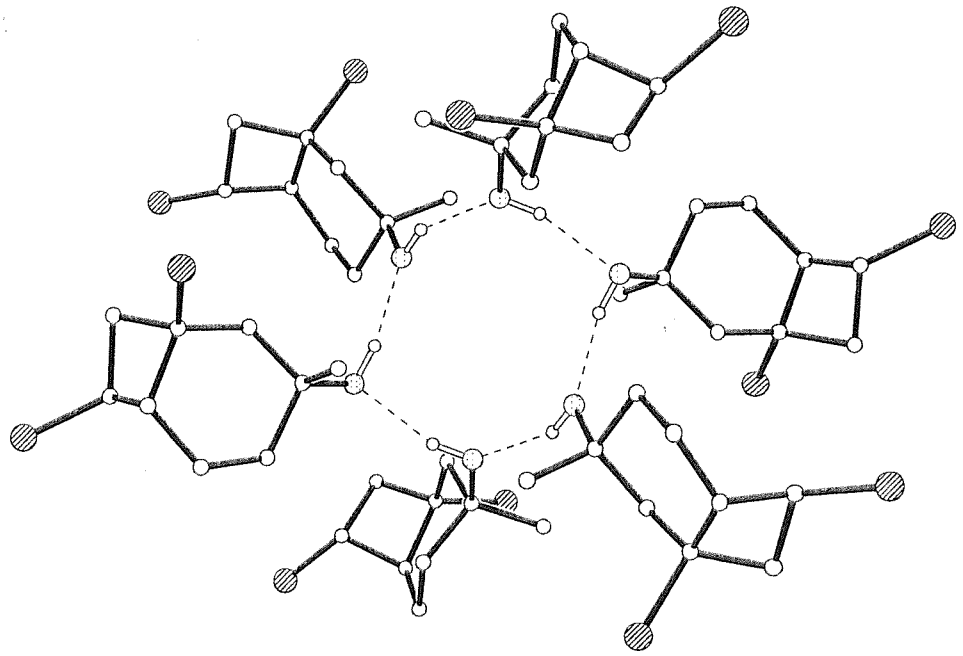
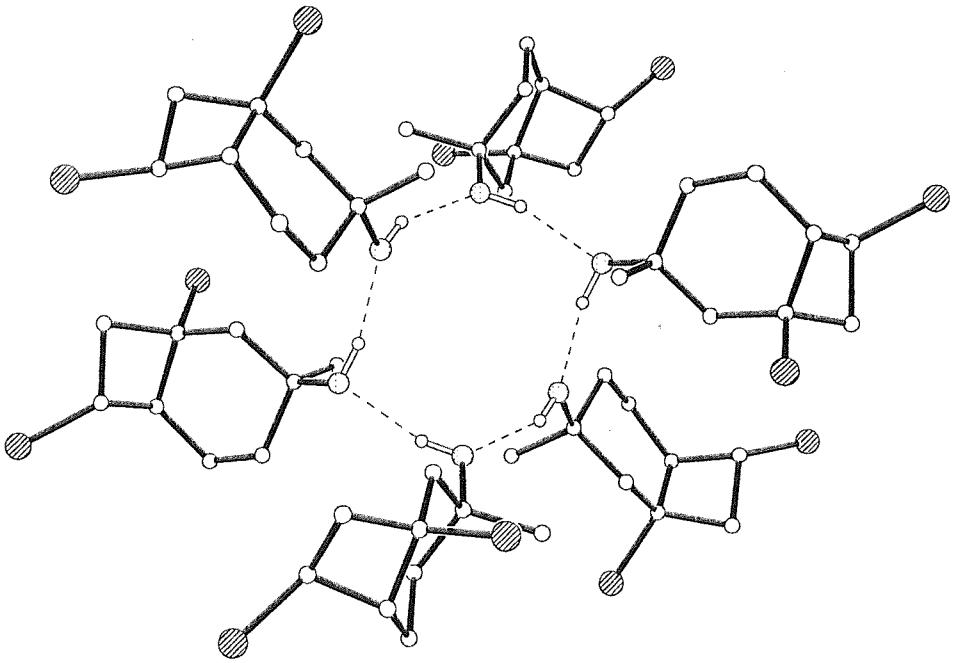
C6′
C1′
C2′
O1′
C5′
C3′
C9′
C4′
C8′
Cl2′
C7′


Cl1″
C6″
C1″
O1″
C5″
C2″
C9″
C3″
C4″
C8″
C7″
Cl2″





Appendix B

X-ray crystallographic data for **317**

Table 1. Crystal data and structure refinement.

Identification code	**00sot013** (= 99sot042)	
Empirical formula	$C_{12}H_{21}ClOSi$	
Formula weight	244.83	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	$a = 6.8053(5)$ Å	$\alpha = 96.225(3)°$
	$b = 9.2212(6)$ Å	$\beta = 90.765(3)°$
	$c = 22.718(2)$ Å	$\gamma = 94.491(4)°$
Volume	1412.52(19) Å^3	
Z	4	
Density (calculated)	1.151 Mg / m^3	
Absorption coefficient	0.332 mm^{-1}	
F(000)	528	
Crystal	Needle; colourless	
Crystal size	0.20 × 0.05 × 0.05 mm^3	
θ range for data collection	3.00 – 24.75°	
Index ranges	$-8 \le h \le 8$, $-10 \le k \le 10$, $-25 \le l \le 26$	
Reflections collected	7818	
Independent reflections	4149 [$R_{int} = 0.1049$]	
Completeness to $\theta = 24.75°$	86.5 %	
Max. and min. transmission	0.9836 and 0.9366	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4149 / 12 / 271	
Goodness-of-fit on F^2	0.935	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0945$, $wR2 = 0.1307$	
R indices (all data)	$R1 = 0.2615$, $wR2 = 0.1610$	
Largest diff. peak and hole	0.476 and −0.371 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. **A51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) 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:

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.*
Si1	6761(3)	1071(2)	6345(1)	29(1)	1
Cl1	9648(2)	−1077(2)	6521(1)	50(1)	1
O1	5211(6)	−4962(5)	5686(2)	38(2)	1
C1	8313(10)	1688(8)	5743(3)	50(3)	1
C2	7520(9)	2130(7)	7067(3)	46(3)	1
C3	4118(8)	1338(7)	6193(3)	44(3)	1
C4	6981(8)	−973(7)	6388(3)	22(2)	1
C5	6396(10)	−1865(7)	5798(4)	26(2)	1
C6	4273(9)	−2481(8)	5752(3)	39(2)	1
C7	3812(10)	−3996(9)	5953(4)	43(3)	1
C8	4046(10)	−4022(8)	6620(4)	46(2)	1
C9	5867(10)	−3225(7)	6921(3)	43(2)	1
C10	5995(10)	−1556(7)	6916(3)	36(2)	1
C11	7606(12)	−2072(9)	5350(4)	54(3)	1
C12	1757(9)	−4608(8)	5740(4)	76(4)	1
Si1'	1563(3)	344(2)	8670(1)	32(1)	1
Cl1'	4391(2)	−1917(2)	8469(1)	51(1)	1
O1'	57(6)	−5368(5)	9304(2)	41(2)	1
C1'	2325(9)	1049(8)	7963(3)	35(2)	1
C2'	3186(9)	1265(7)	9276(3)	41(2)	1
C3'	−1047(8)	698(8)	8822(4)	52(3)	1
C4'	1757(8)	−1718(8)	8615(3)	26(2)	1
C5'	1248(9)	−2314(7)	9194(3)	24(2)	1
C6'	−890(9)	−2893(8)	9245(3)	40(2)	1
C7'	−1297(10)	−4513(8)	9050(4)	35(2)	1
C9'	540(11)	−4252(8)	8046(3)	46(2)	1
C8'	−1272(11)	−4903(8)	8378(4)	50(3)	1
C10'	640(10)	−2566(8)	8077(3)	42(2)	1
C12'	−3333(9)	−5051(8)	9250(4)	61(3)	1
C11'	2533(11)	−2300(8)	9643(4)	53(3)	1

Table 3. Bond lengths [Å] and angles [°].

Si1–C1	1.850(8)
Si1–C2	1.860(7)
Si1–C3	1.867(6)
Si1–C4	1.915(7)
Cl1–C4	1.848(6)
O1–C7	1.449(8)
O1–H1	0.8400
C1–H1A	0.9800
C1–H1B	0.9800
C1–H1C	0.9800
C2–H2A	0.9800
C2–H2B	0.9800
C2–H2C	0.9800
C3–H3A	0.9800
C3–H3B	0.9800
C3–H3C	0.9800
C4–C10	1.512(9)
C4–C5	1.525(9)
C5–C11	1.325(10)
C5–C6	1.509(8)
C6–C7	1.527(10)
C6–H6A	0.9900
C6–H6B	0.9900
C7–C12	1.519(8)
C7–C8	1.523(10)
C8–C9	1.507(8)
C8–H8A	0.9900
C8–H8B	0.9900
C9–C10	1.536(9)
C9–H9A	0.9900
C9–H9B	0.9900
C10–H10A	0.9900
C10–H10B	0.9900
C12–H12A	0.9800
C12–H12B	0.9800
C12–H12C	0.9800
Si1'–C2'	1.843(6)
Si1'–C3'	1.861(7)
Si1'–C1'	1.862(7)
Si1'–C4'	1.907(7)
Cl1'–C4'	1.847(6)
O1'–C7'	1.415(7)
O1'–H1'	0.8400
C1'–H1'1	0.9800
C1'–H1'2	0.9800
C1'–H1'3	0.9800
C2'–H2'1	0.9800
C2'–H2'2	0.9800
C2'–H2'3	0.9800
C3'–H3'1	0.9800
C3'–H3'2	0.9800
C3'–H3'3	0.9800
C4'–C5'	1.515(9)
C4'–C10'	1.534(8)
C5'–C11'	1.333(8)
C5'–C6'	1.521(8)
C6'–C7'	1.515(9)
C6'–H6'1	0.9900
C6'–H6'2	0.9900

C7'–C12'	1.527(9)
C7'–C8'	1.531(10)
C9'–C10'	1.545(9)
C9'–C8'	1.567(9)
C9'–H9'1	0.9900
C9'–H9'2	0.9900
C8'–H8'1	0.9900
C8'–H8'2	0.9900
C10'–H10C	0.9900
C10'–H10D	0.9900
C12'–H12D	0.9800
C12'–H12E	0.9800
C12'–H12F	0.9800

C1–Si1–C2	110.7(3)
C1–Si1–C3	110.3(3)
C2–Si1–C3	108.3(3)
C1–Si1–C4	109.5(3)
C2–Si1–C4	110.0(3)
C3–Si1–C4	108.0(3)
C7–O1–H1	109.5
Si1–C1–H1A	109.5
Si1–C1–H1B	109.5
H1A–C1–H1B	109.5
Si1–C1–H1C	109.5
H1A–C1–H1C	109.5
H1B–C1–H1C	109.5
Si1–C2–H2A	109.5
Si1–C2–H2B	109.5
H2A–C2–H2B	109.5
Si1–C2–H2C	109.5
H2A–C2–H2C	109.5
H2B–C2–H2C	109.5
Si1–C3–H3A	109.5
Si1–C3–H3B	109.5
H3A–C3–H3B	109.5
Si1–C3–H3C	109.5
H3A–C3–H3C	109.5
H3B–C3–H3C	109.5
C10–C4–C5	113.9(5)
C10–C4–Cl1	105.0(4)
C5–C4–Cl1	108.4(5)
C10–C4–Si1	114.2(5)
C5–C4–Si1	111.1(4)
Cl1–C4–Si1	103.3(3)
C11–C5–C6	121.5(7)
C11–C5–C4	124.0(6)
C6–C5–C4	114.5(7)
C5–C6–C7	117.1(6)
C5–C6–H6A	108.0
C7–C6–H6A	108.0
C5–C6–H6B	108.0
C7–C6–H6B	108.0
H6A–C6–H6B	107.3
O1–C7–C12	108.0(6)
O1–C7–C8	106.0(6)
C12–C7–C8	110.7(7)
O1–C7–C6	108.3(7)
C12–C7–C6	110.2(6)
C8–C7–C6	113.5(6)
C9–C8–C7	117.6(6)

C9–C8–H8A	107.9
C7–C8–H8A	107.9
C9–C8–H8B	107.9
C7–C8–H8B	107.9
H8A–C8–H8B	107.2
C8–C9–C10	114.6(6)
C8–C9–H9A	108.6
C10–C9–H9A	108.6
C8–C9–H9B	108.6
C10–C9–H9B	108.6
H9A–C9–H9B	107.6
C4–C10–C9	115.9(7)
C4–C10–H10A	108.3
C9–C10–H10A	108.3
C4–C10–H10B	108.3
C9–C10–H10B	108.3
H10A–C10–H10B	107.4
C7–C12–H12A	109.5
C7–C12–H12B	109.5
H12A–C12–H12B	109.5
C7–C12–H12C	109.5
H12A–C12–H12C	109.5
H12B–C12–H12C	109.5
C2'–Si1'–C3'	110.0(4)
C2'–Si1'–C1'	108.9(3)
C3'–Si1'–C1'	110.1(3)
C2'–Si1'–C4'	109.8(3)
C3'–Si1'–C4'	108.0(3)
C1'–Si1'–C4'	110.0(3)
C7'–O1'–H1'	109.5
Si1'–C1'–H1'1	109.5
Si1'–C1'–H1'2	109.5
H1'1–C1'–H1'2	109.5
Si1'–C1'–H1'3	109.5
H1'1–C1'–H1'3	109.5
H1'2–C1'–H1'3	109.5
Si1'–C2'–H2'1	109.5
Si1'–C2'–H2'2	109.5
H2'1–C2'–H2'2	109.5
Si1'–C2'–H2'3	109.5
H2'1–C2'–H2'3	109.5
H2'2–C2'–H2'3	109.5
Si1'–C3'–H3'1	109.5
Si1'–C3'–H3'2	109.5
H3'1–C3'–H3'2	109.5
Si1'–C3'–H3'3	109.5
H3'1–C3'–H3'3	109.5
H3'2–C3'–H3'3	109.5
C5'–C4'–C10'	113.4(5)
C5'–C4'–Cl1'	109.0(4)
C10'–C4'–Cl1'	105.2(5)
C5'–C4'–Si1'	111.3(5)
C10'–C4'–Si1'	113.6(5)
Cl1'–C4'–Si1'	103.6(3)
C11'–C5'–C4'	123.7(6)
C11'–C5'–C6'	121.0(7)
C4'–C5'–C6'	115.2(6)
C7'–C6'–C5'	114.4(6)
C7'–C6'–H6'1	108.7
C5'–C6'–H6'1	108.7
C7'–C6'–H6'2	108.7

C5'–C6'–H6'2	108.7
H6'1–C6'–H6'2	107.6
O1'–C7'–C6'	112.5(6)
O1'–C7'–C12'	106.1(6)
C6'–C7'–C12'	110.0(7)
O1'–C7'–C8'	107.3(7)
C6'–C7'–C8'	113.8(6)
C12'–C7'–C8'	106.7(6)
C10'–C9'–C8'	112.7(7)
C10'–C9'–H9'1	109.1
C8'–C9'–H9'1	109.1
C10'–C9'–H9'2	109.1
C8'–C9'–H9'2	109.1
H9'1–C9'–H9'2	107.8
C7'–C8'–C9'	116.9(6)
C7'–C8'–H8'1	108.1
C9'–C8'–H8'1	108.1
C7'–C8'–H8'2	108.1
C9'–C8'–H8'2	108.1
H8'1–C8'–H8'2	107.3
C4'–C10'–C9'	116.1(6)
C4'–C10'–H10C	108.3
C9'–C10'–H10C	108.3
C4'–C10'–H10D	108.3
C9'–C10'–H10D	108.3
H10C–C10'–H10D	107.4
C7'–C12'–H12D	109.5
C7'–C12'–H12E	109.5
H12D–C12'–H12E	109.5
C7'–C12'–H12F	109.5
H12D–C12'–H12F	109.5
H12E–C12'–H12F	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}
Si1	27(1)	22(2)	36(2)	4(1)	−5(1)	−2(1)
Cl1	32(1)	36(2)	83(2)	8(1)	−14(1)	6(1)
O1	45(3)	27(4)	40(4)	−6(3)	−4(3)	5(3)
C1	57(5)	46(6)	48(7)	19(5)	−13(5)	−14(4)
C2	42(5)	28(6)	66(7)	−4(5)	−4(5)	1(4)
C3	38(5)	23(5)	71(7)	−1(5)	−18(5)	10(4)
C4	17(4)	20(5)	29(6)	2(4)	−1(4)	1(3)
C5	34(4)	15(4)	29(4)	6(3)	−8(3)	1(3)
C6	44(5)	23(5)	49(7)	−11(4)	−13(4)	14(4)
C7	31(5)	19(6)	75(8)	−22(5)	−5(5)	8(4)
C8	51(5)	15(5)	67(8)	−5(5)	22(5)	−11(4)
C9	78(6)	15(5)	35(6)	−4(4)	−4(5)	6(4)
C10	52(5)	18(5)	35(6)	0(4)	−8(5)	−11(4)
C11	90(6)	32(6)	44(7)	9(5)	39(5)	19(5)
C12	37(5)	34(6)	150(11)	−16(6)	−31(6)	−2(4)
Si1'	29(1)	28(2)	39(2)	8(1)	1(1)	1(1)
Cl1'	36(1)	40(2)	79(2)	16(1)	21(1)	11(1)
O1'	32(3)	28(3)	65(4)	16(3)	4(3)	1(2)
C1'	30(4)	32(5)	45(6)	16(4)	5(4)	−2(4)
C2'	52(5)	27(5)	42(6)	0(5)	0(4)	−5(4)
C3'	33(5)	27(6)	99(8)	6(5)	11(5)	13(4)
C4'	18(4)	40(6)	19(5)	2(4)	−1(4)	1(3)
C5'	28(3)	19(4)	25(4)	3(3)	6(3)	7(3)
C6'	52(5)	33(6)	34(6)	4(5)	13(4)	7(4)
C7'	34(5)	23(6)	53(7)	19(5)	9(5)	7(4)
C9'	87(6)	23(6)	24(6)	−5(4)	0(5)	−6(5)
C8'	66(6)	20(6)	65(8)	15(5)	−8(6)	−9(4)
C10'	72(6)	29(6)	25(6)	7(4)	−4(5)	0(4)
C12'	42(5)	36(6)	111(9)	34(6)	12(5)	4(4)
C11'	86(6)	28(6)	46(7)	15(5)	−28(6)	−9(4)

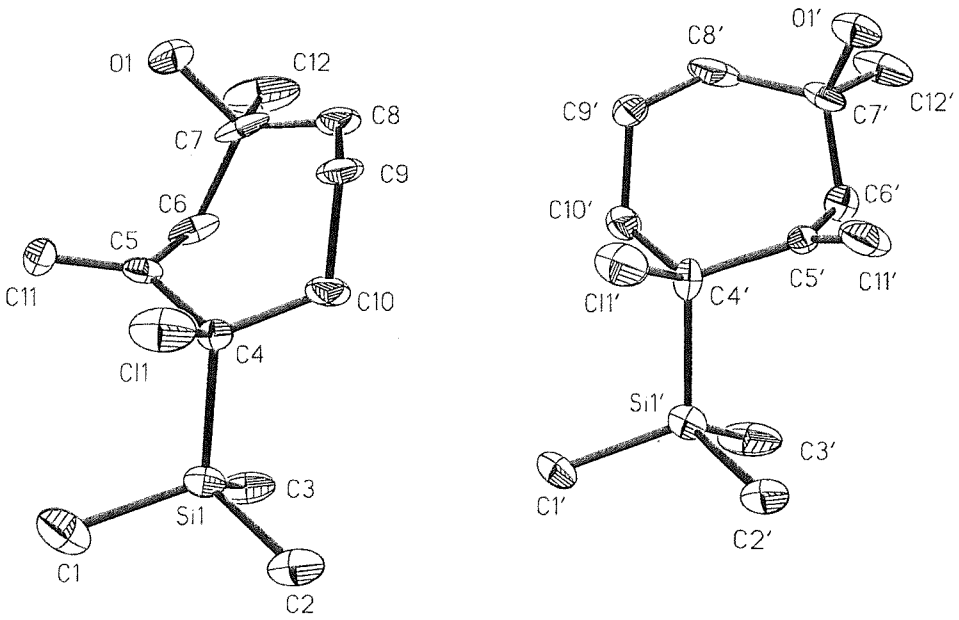
Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	4989	−5113	5319	57	1
H1A	7884	1124	5366	76	1
H1B	9694	1536	5826	76	1
H1C	8183	2730	5716	76	1
H2A	6682	1788	7379	69	1
H2B	7379	3172	7044	69	1
H2C	8899	1987	7158	69	1
H3A	3312	995	6513	66	1
H3B	3688	780	5816	66	1
H3C	3968	2379	6172	66	1
H6A	3827	−2519	5334	47	1
H6B	3476	−1786	5989	47	1
H8A	2883	−3605	6809	55	1
H8B	4012	−5058	6700	55	1
H9A	7041	−3606	6724	52	1
H9B	5913	−3449	7337	52	1
H10A	4641	−1234	6937	43	1
H10B	6721	−1103	7279	43	1
H12A	1473	−5576	5874	114	1
H12B	1686	−4694	5306	114	1
H12C	787	−3949	5902	114	1
H1'	1188	−4929	9317	61	1
H1'1	1477	559	7637	53	1
H1'2	3699	853	7887	53	1
H1'3	2201	2106	7993	53	1
H2'1	4555	1065	9195	62	1
H2'2	2798	898	9650	62	1
H2'3	3068	2323	9305	62	1
H3'1	−1900	207	8497	79	1
H3'2	−1182	1754	8854	79	1
H3'3	−1434	321	9194	79	1
H6'1	−1281	−2697	9663	47	1
H6'2	−1728	−2344	9003	47	1
H9'1	1767	−4543	8223	55	1
H9'2	461	−4672	7626	55	1
H8'1	−2483	−4575	8205	61	1
H8'2	−1339	−5983	8295	61	1
H10C	1271	−2270	7714	50	1
H10D	−724	−2265	8075	50	1
H12D	−3600	−6093	9111	92	1
H12E	−4335	−4494	9084	92	1
H12F	−3372	−4911	9683	92	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
O1–H1···O1^{i}	0.84	2.29	3.119(9)	167.2

Symmetry transformations used to generate equivalent atoms:
(i) –x+1,–y–1,–z+1


O1
C12
C8
C7
C9
C6
C5
C11
C10
Cl1
C4
Si1
C3
C1
C2
O1′
C8′
C9′
C7′
C12′
C10′
C6′
C5′
C11′
Cl1′
C4′
Si1′
C3′
C1′
C2′

Appendix C

X-ray crystallographic data for **385**

Table 1. Crystal data and structure refinement.

Identification code	**99sot064**	
Empirical formula	$C_{16}H_{23}FOSi$	
Formula weight	278.43	
Temperature	193(2) K	
Wavelength	0.71073 Å	
Crystal system	Tetragonal	
Space group	$P\bar{4}2_1c$	
Unit cell dimensions	a = 14.1637(6) Å	α = 90°
	b = 14.1637(6) Å	β = 90°
	c = 16.4308(9) Å	γ = 90°
Volume	3296.2(3) Å^3	
Z	8	
Density (calculated)	1.122 Mg / m^3	
Absorption coefficient	0.144 mm^{-1}	
F(000)	1200	
Crystal	Plate; colourless	
Crystal size	0.07 × 0.05 × 0.05 mm^3	
θ range for data collection	1.90 – 23.50°	
Index ranges	$-15 \le h \le 15$, $-15 \le k \le 15$, $-13 \le l \le 18$	
Reflections collected	5499	
Independent reflections	2155 [R_{int} = 0.1012]	
Completeness to θ = 23.50°	94.8 %	
Max. and min. transmission	0.9928 and 0.9900	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2155 / 0 / 191	
Goodness-of-fit on F^2	0.876	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0582, $wR2$ = 0.1024	
R indices (all data)	$R1$ = 0.1586, $wR2$ = 0.1219	
Absolute structure parameter	0.0(2)	
Extinction coefficient	0.0033(8)	
Largest diff. peak and hole	0.179 and −0.125 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:
Hydrogen bonds (Table 6)

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.*
Si1	15944(1)	12376(1)	19188(1)	79(1)	1
O1	18697(3)	10498(3)	20055(3)	69(1)	1
F1	14882(2)	11983(2)	19098(2)	119(1)	1
C1	16500(3)	11804(3)	20104(3)	51(1)	1
C2	16622(4)	10742(4)	20032(4)	61(2)	1
C3	17190(4)	10289(3)	20684(4)	62(2)	1
C4	18173(4)	10706(3)	20784(4)	62(1)	1
C5	18081(4)	11767(3)	20855(4)	69(2)	1
C6	17511(4)	12211(4)	20172(4)	65(2)	1
C7	16234(5)	10238(5)	19464(6)	100(2)	1
C8	18676(5)	10289(5)	21509(4)	88(2)	1
C9	15893(4)	12036(4)	20845(4)	60(2)	1
C10	15147(4)	11463(4)	21066(4)	76(2)	1
C11	14581(5)	11647(6)	21723(5)	101(2)	1
C12	14756(6)	12420(7)	22192(5)	102(2)	1
C13	15479(6)	13030(6)	22004(5)	93(2)	1
C14	16042(5)	12817(4)	21333(4)	79(2)	1
C16	15845(4)	13656(4)	19331(4)	105(2)	1
C15	16590(4)	12127(4)	18248(4)	115(3)	1

Table 3. Bond lengths [Å] and angles [°].

Si1–F1	1.610(4)
Si1–C15	1.831(6)
Si1–C16	1.833(5)
Si1–C1	1.881(6)
O1–C4	1.440(6)
C1–C2	1.518(7)
C1–C9	1.527(8)
C1–C6	1.548(6)
C2–C7	1.298(8)
C2–C3	1.485(7)
C3–C4	1.521(6)
C4–C8	1.508(8)
C4–C5	1.513(6)
C5–C6	1.518(7)
C9–C10	1.381(7)
C9–C14	1.383(7)
C10–C11	1.370(8)
C11–C12	1.362(8)
C12–C13	1.376(8)
C13–C14	1.394(8)
F1–Si1–C15	108.8(3)
F1–Si1–C16	106.4(2)
C15–Si1–C16	109.7(3)
F1–Si1–C1	108.4(2)
C15–Si1–C1	112.5(2)
C16–Si1–C1	110.9(3)
C2–C1–C9	109.8(4)
C2–C1–C6	105.6(4)
C9–C1–C6	112.5(5)
C2–C1–Si1	114.4(4)
C9–C1–Si1	108.0(3)
C6–C1–Si1	106.6(4)
C7–C2–C3	120.7(6)
C7–C2–C1	123.5(6)
C3–C2–C1	115.7(5)
C2–C3–C4	113.9(5)
O1–C4–C8	109.5(5)
O1–C4–C5	108.1(5)
C8–C4–C5	111.6(6)
O1–C4–C3	107.6(5)
C8–C4–C3	111.5(5)
C5–C4–C3	108.4(4)
C4–C5–C6	113.6(5)
C5–C6–C1	113.1(4)
C10–C9–C14	115.8(6)
C10–C9–C1	120.9(5)
C14–C9–C1	123.3(5)
C11–C10–C9	122.9(6)
C12–C11–C10	119.6(8)
C11–C12–C13	120.9(8)
C12–C13–C14	117.8(8)
C9–C14–C13	123.0(7)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si1	91(1)	83(1)	62(1)	6(1)	0(1)	14(1)
O1	58(3)	88(3)	61(3)	−5(2)	10(2)	−4(2)
F1	96(2)	145(3)	116(4)	2(3)	−30(3)	8(2)
C1	51(4)	49(4)	52(4)	−5(3)	9(3)	0(3)
C2	62(4)	66(5)	56(5)	−3(4)	0(4)	−4(3)
C3	80(4)	50(4)	56(5)	0(3)	22(4)	0(3)
C4	66(4)	66(4)	54(4)	3(4)	1(4)	1(3)
C5	65(4)	76(4)	65(5)	−17(4)	3(4)	−1(3)
C6	72(4)	53(4)	69(5)	−5(3)	−2(4)	−4(3)
C7	93(5)	73(6)	132(8)	−14(5)	9(5)	7(4)
C8	90(6)	113(7)	62(6)	2(4)	−12(4)	32(5)
C9	64(4)	59(4)	56(4)	−1(4)	−9(4)	4(3)
C10	81(5)	67(4)	81(6)	−18(4)	19(4)	−2(4)
C11	88(6)	122(7)	92(7)	−13(5)	34(5)	15(5)
C12	87(6)	140(8)	79(6)	1(6)	27(5)	45(6)
C13	93(6)	115(7)	69(6)	−22(5)	2(5)	36(5)
C14	74(5)	71(5)	90(6)	−15(4)	1(4)	2(4)
C16	142(5)	93(5)	81(6)	23(4)	11(5)	33(4)
C15	149(6)	144(6)	54(6)	6(4)	25(4)	44(5)

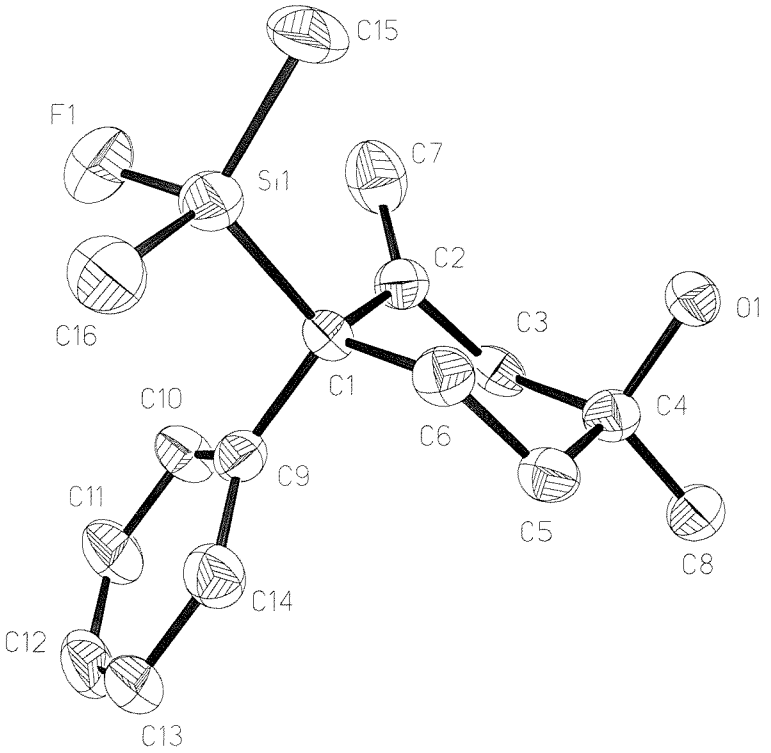
Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

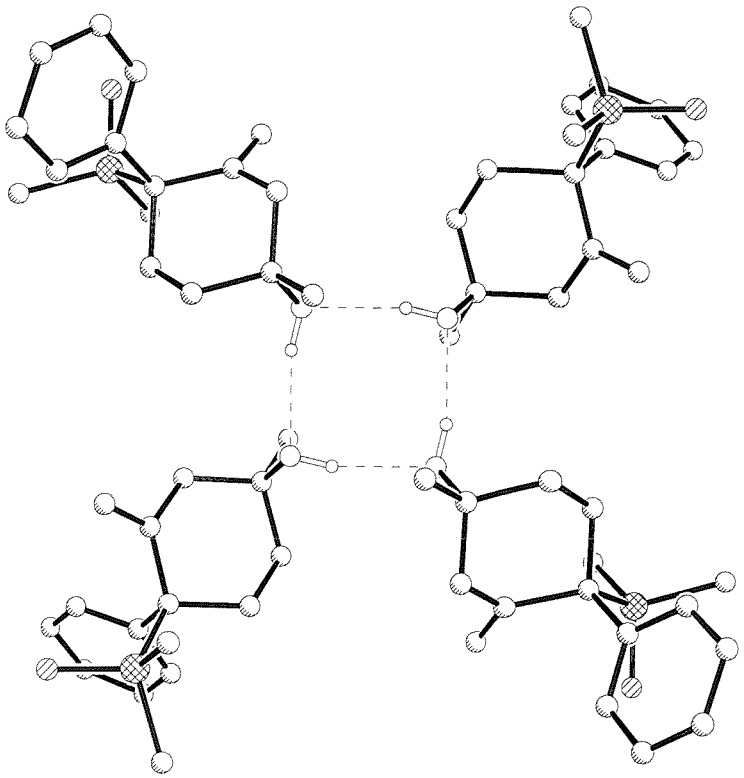
Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1O	19180	10817	20046	80(20)	1
H3A	17248	9621	20565	54(14)	1
H3B	16854	10350	21196	44(13)	1
H5A	18708	12043	20858	50(13)	1
H5B	17784	11918	21371	66(19)	1
H6A	17839	12112	19661	100(20)	1
H6B	17472	12887	20264	31(12)	1
H7A	16310	9586	19462	75(19)	1
H7B	15880	10529	19058	210(50)	1
H8A	18739	9619	21437	100(20)	1
H8B	18319	10414	21993	150(30)	1
H8C	19291	10569	21558	66(19)	1
H10	15024	10928	20755	36(13)	1
H11	14081	11247	21848	150(30)	1
H12	14382	12536	22646	130(30)	1
H13	15589	13568	22315	170(40)	1
H14	16541	13218	21208	31(13)	1
H16A	15523	13784	19833	158	1
H16B	15495	13924	18887	158	1
H16C	16464	13930	19347	158	1
H15A	16620	11456	18164	173	1
H15B	17219	12376	18289	173	1
H15C	16271	12416	17797	173	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
O1–H1O···O1^{i}	0.82	2.00	2.801(5)	166.4

Symmetry transformations used to generate equivalent atoms:
(i) y+1,–x+3,–z+4


C15
F1
C7
Si1
C2
C16
C3
O1
C1
C10
C6
C4
C9
C11
C5
C8
C14
C12
C13



Appendix D

X-ray crystallographic data for **388**

Table 1. Crystal data and structure refinement.

Identification code	**00sot065**	
Empirical formula	$C_{25}H_{30}FNO_5Si$	
Formula weight	471.59	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	a = 7.9022(3) Å	α = 104.3760(17)°
	b = 10.6116(4) Å	β = 91.5070(15)°
	c = 15.3911(8) Å	γ = 90.616(2)°
Volume	1249.58(9) Å^3	
Z	2	
Density (calculated)	1.253 Mg / m^3	
Absorption coefficient	0.136 mm^{-1}	
$F(000)$	500	
Crystal	Needle; colourless	
Crystal size	0.10 × 0.05 × 0.05 mm^3	
θ range for data collection	2.88 – 24.24°	
Index ranges	$-9 \le h \le 9$, $-12 \le k \le 12$, $-17 \le l \le 17$	
Reflections collected	9210	
Independent reflections	3852 [R_{int} = 0.0655]	
Completeness to θ = 24.24°	95.5 %	
Max. and min. transmission	0.9932 and 0.9865	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3852 / 6 / 327	
Goodness-of-fit on F^2	1.182	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0681, $wR2$ = 0.1042	
R indices (all data)	$R1$ = 0.1784, $wR2$ = 0.1173	
Extinction coefficient	0.0063(12)	
Largest diff. peak and hole	0.542 and –0.178 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:

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.*
Si1	4713(1)	3753(1)	2821(1)	69(1)	1
F1	5751(2)	2864(2)	3337(2)	90(1)	1
O1	7652(3)	7546(3)	2197(2)	63(1)	1
O2	5242(4)	9306(2)	3254(2)	72(1)	1
O3	3028(3)	9462(3)	2368(2)	93(1)	1
O4	−82(6)	7579(5)	6185(4)	190(2)	1
O5	−2201(5)	7667(4)	5359(3)	145(2)	1
N1	−697(7)	7745(5)	5515(3)	119(2)	1
C1	2997(5)	2720(5)	2176(4)	95(2)	1
C2	3896(8)	5114(5)	3691(4)	107(2)	1
C3	6304(4)	4272(4)	2071(3)	53(1)	1
C4	6950(4)	3019(4)	1466(3)	54(1)	1
C5	8263(5)	2319(4)	1714(3)	59(1)	1
C6	8771(5)	1148(5)	1170(4)	73(1)	1
C7	7962(6)	636(5)	370(4)	74(1)	1
C8	6658(6)	1291(5)	95(3)	80(1)	1
C9	6151(5)	2476(5)	646(3)	71(1)	1
C10	5574(5)	5164(3)	1542(3)	56(1)	1
C11	6826(5)	5657(4)	972(3)	64(1)	1
C12	8280(5)	6429(4)	1546(3)	67(1)	1
C13	9054(4)	5587(4)	2098(3)	68(1)	1
C14	7780(4)	5080(4)	2686(3)	71(1)	1
C15	4028(7)	5514(5)	1493(3)	124(2)	1
C16	9589(6)	6865(5)	954(3)	89(1)	1
C17	6698(5)	8456(4)	1843(3)	71(1)	1
C18	6340(5)	9611(4)	2600(3)	76(1)	1
C19	3602(6)	9249(4)	3040(3)	69(1)	1
C20	3207(6)	8607(4)	4486(3)	76(1)	1
C21	2175(7)	8235(4)	5090(3)	84(1)	1
C22	478(7)	8138(4)	4891(3)	78(1)	1
C23	−246(6)	8418(4)	4158(4)	81(1)	1
C24	805(5)	8801(4)	3547(3)	72(1)	1
C25	2529(5)	8903(3)	3732(3)	62(1)	1

Table 3. Bond lengths [Å] and angles [°].

Si1–F1	1.597(2)
Si1–C1	1.839(4)
Si1–C2	1.845(4)
Si1–C3	1.895(3)
O1–C17	1.433(4)
O1–C12	1.451(4)
O2–C19	1.326(4)
O2–C18	1.439(4)
O3–C19	1.192(4)
O4–N1	1.182(5)
O5–N1	1.204(5)
N1–C22	1.482(6)
C1–H1A	0.9600
C1–H1B	0.9600
C1–H1C	0.9600
C2–H2A	0.9600
C2–H2B	0.9600
C2–H2C	0.9600
C3–C10	1.504(5)
C3–C4	1.523(5)
C3–C14	1.584(4)
C4–C9	1.383(5)
C4–C5	1.383(5)
C5–C6	1.385(5)
C5–H5	0.9300
C6–C7	1.356(5)
C6–H6	0.9300
C7–C8	1.365(5)
C7–H7	0.9300
C8–C9	1.400(5)
C8–H8	0.9300
C9–H9	0.9300
C10–C15	1.286(5)
C10–C11	1.512(5)
C11–C12	1.528(5)
C11–H11A	0.9700
C11–H11B	0.9700
C12–C13	1.502(5)
C12–C16	1.537(5)
C13–C14	1.550(5)
C13–H13A	0.9700
C13–H13B	0.9700
C14–H14A	0.9700
C14–H14B	0.9700
C15–H15A	0.9300
C15–H15B	0.9300
C16–H16A	0.9600
C16–H16B	0.9600
C16–H16C	0.9600
C17–C18	1.502(5)
C17–H17A	0.9700
C17–H17B	0.9700
C18–H18A	0.9700
C18–H18B	0.9700
C19–C25	1.492(5)
C20–C25	1.371(5)
C20–C21	1.379(5)
C20–H20	0.9300
C21–C22	1.365(5)

C21–H21	0.9300
C22–C23	1.351(5)
C23–C24	1.400(5)
C23–H23	0.9300
C24–C25	1.382(5)
C24–H24	0.9300

F1–Si1–C1	106.6(2)
F1–Si1–C2	106.5(2)
C1–Si1–C2	112.0(3)
F1–Si1–C3	104.89(14)
C1–Si1–C3	112.4(2)
C2–Si1–C3	113.7(2)
C17–O1–C12	116.3(3)
C19–O2–C18	115.6(3)
O4–N1–O5	122.6(6)
O4–N1–C22	116.3(5)
O5–N1–C22	121.0(5)
Si1–C1–H1A	109.5
Si1–C1–H1B	109.5
H1A–C1–H1B	109.5
Si1–C1–H1C	109.5
H1A–C1–H1C	109.5
H1B–C1–H1C	109.5
Si1–C2–H2A	109.5
Si1–C2–H2B	109.5
H2A–C2–H2B	109.5
Si1–C2–H2C	109.5
H2A–C2–H2C	109.5
H2B–C2–H2C	109.5
C10–C3–C4	112.1(3)
C10–C3–C14	105.8(3)
C4–C3–C14	111.6(3)
C10–C3–Si1	113.1(2)
C4–C3–Si1	105.9(2)
C14–C3–Si1	108.5(3)
C9–C4–C5	116.2(4)
C9–C4–C3	120.4(4)
C5–C4–C3	123.3(4)
C4–C5–C6	122.1(4)
C4–C5–H5	118.9
C6–C5–H5	118.9
C7–C6–C5	120.4(5)
C7–C6–H6	119.8
C5–C6–H6	119.8
C6–C7–C8	119.7(5)
C6–C7–H7	120.2
C8–C7–H7	120.2
C7–C8–C9	119.7(5)
C7–C8–H8	120.1
C9–C8–H8	120.1
C4–C9–C8	121.8(4)
C4–C9–H9	119.1
C8–C9–H9	119.1
C15–C10–C3	128.2(4)
C15–C10–C11	117.0(4)
C3–C10–C11	114.8(3)
C10–C11–C12	111.4(3)
C10–C11–H11A	109.3
C12–C11–H11A	109.3
C10–C11–H11B	109.3

C12–C11–H11B	109.3
H11A–C11–H11B	108.0
O1–C12–C13	104.8(3)
O1–C12–C11	111.0(3)
C13–C12–C11	108.0(3)
O1–C12–C16	110.3(3)
C13–C12–C16	111.7(4)
C11–C12–C16	110.9(4)
C12–C13–C14	114.1(3)
C12–C13–H13A	108.7
C14–C13–H13A	108.7
C12–C13–H13B	108.7
C14–C13–H13B	108.7
H13A–C13–H13B	107.6
C13–C14–C3	109.8(3)
C13–C14–H14A	109.7
C3–C14–H14A	109.7
C13–C14–H14B	109.7
C3–C14–H14B	109.7
H14A–C14–H14B	108.2
C10–C15–H15A	120.0
C10–C15–H15B	120.0
H15A–C15–H15B	120.0
C12–C16–H16A	109.5
C12–C16–H16B	109.5
H16A–C16–H16B	109.5
C12–C16–H16C	109.5
H16A–C16–H16C	109.5
H16B–C16–H16C	109.5
O1–C17–C18	108.4(4)
O1–C17–H17A	110.0
C18–C17–H17A	110.0
O1–C17–H17B	110.0
C18–C17–H17B	110.0
H17A–C17–H17B	108.4
O2–C18–C17	113.2(3)
O2–C18–H18A	108.9
C17–C18–H18A	108.9
O2–C18–H18B	108.9
C17–C18–H18B	108.9
H18A–C18–H18B	107.7
O3–C19–O2	123.8(4)
O3–C19–C25	122.9(4)
O2–C19–C25	113.3(4)
C25–C20–C21	120.6(4)
C25–C20–H20	119.7
C21–C20–H20	119.7
C22–C21–C20	117.3(5)
C22–C21–H21	121.3
C20–C21–H21	121.3
C23–C22–C21	124.1(5)
C23–C22–N1	116.0(5)
C21–C22–N1	119.9(5)
C22–C23–C24	118.4(4)
C22–C23–H23	120.8
C24–C23–H23	120.8
C25–C24–C23	118.5(4)
C25–C24–H24	120.7
C23–C24–H24	120.7
C20–C25–C24	121.0(4)
C20–C25–C19	122.3(4)

C24–C25–C19	116.5(4)

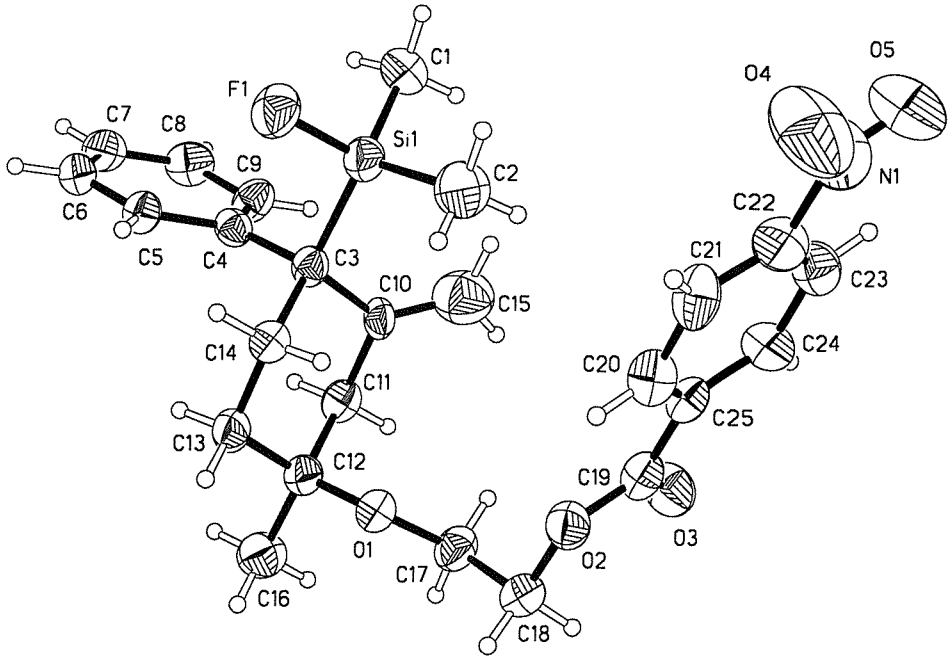
Symmetry transformations used to generate equivalent atoms:

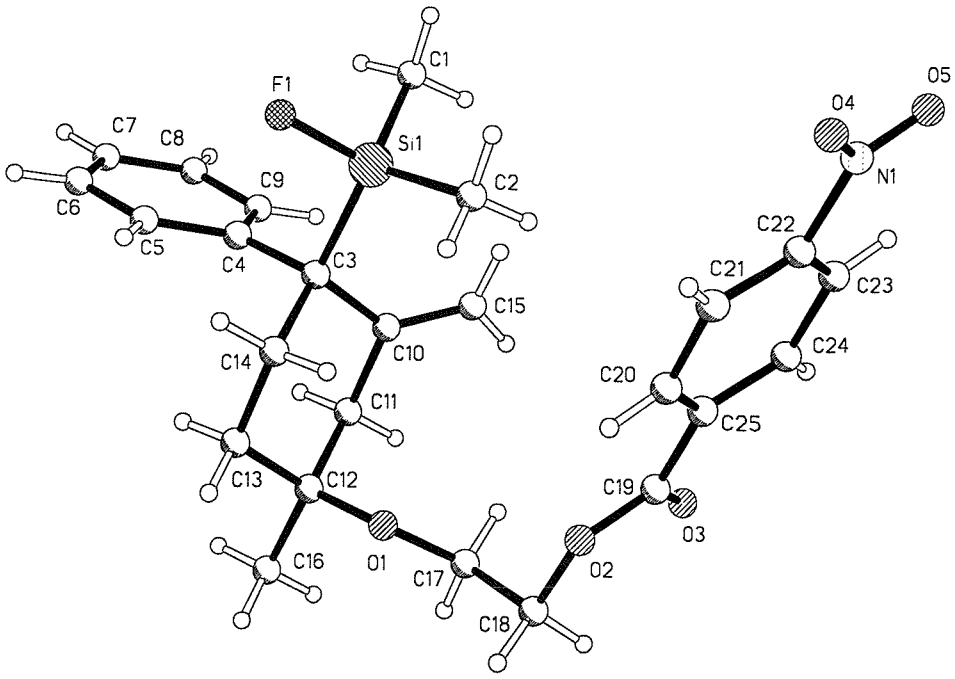
Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\ h\ k\ a^*\ b^*\ U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si1	67(1)	68(1)	75(1)	22(1)	15(1)	12(1)
F1	97(2)	99(2)	87(2)	45(2)	13(1)	23(1)
O1	63(2)	56(2)	72(2)	17(2)	3(1)	6(1)
O2	67(2)	68(2)	78(2)	11(2)	2(2)	5(1)
O3	81(2)	118(3)	90(3)	44(2)	−4(2)	2(2)
O4	148(3)	313(5)	148(4)	127(4)	41(3)	29(3)
O5	115(3)	194(4)	134(4)	60(3)	14(3)	−30(3)
N1	129(4)	165(4)	75(4)	52(3)	8(4)	19(4)
C1	66(3)	97(4)	126(4)	36(4)	6(3)	−4(3)
C2	118(4)	94(4)	104(4)	10(4)	47(4)	11(4)
C3	50(2)	52(3)	56(3)	11(2)	−8(2)	3(2)
C4	49(2)	63(3)	51(3)	19(3)	2(2)	0(2)
C5	61(3)	56(3)	60(3)	11(3)	3(3)	7(2)
C6	56(3)	68(4)	99(5)	30(3)	15(3)	11(3)
C7	78(3)	62(4)	77(4)	5(3)	17(3)	1(3)
C8	89(3)	80(4)	66(4)	10(3)	−12(3)	−11(3)
C9	83(3)	58(3)	69(4)	13(3)	−16(3)	4(3)
C10	40(2)	57(3)	70(3)	14(2)	−8(2)	10(2)
C11	72(3)	60(3)	60(3)	15(3)	−2(3)	8(3)
C12	62(3)	58(3)	84(4)	22(3)	18(3)	7(2)
C13	56(2)	53(3)	89(3)	4(3)	−4(3)	6(2)
C14	61(2)	57(3)	98(4)	23(3)	−1(3)	3(2)
C15	129(4)	130(5)	124(5)	51(4)	−3(4)	−13(4)
C16	96(3)	79(4)	92(4)	17(4)	36(3)	0(4)
C17	82(3)	62(3)	73(4)	26(3)	14(3)	11(3)
C18	77(3)	57(3)	96(4)	20(3)	11(3)	2(3)
C19	76(4)	59(3)	68(4)	10(3)	−6(3)	10(2)
C20	80(4)	81(3)	60(4)	9(3)	−5(3)	9(2)
C21	93(4)	97(4)	63(4)	21(3)	−7(3)	31(3)
C22	92(4)	86(3)	59(4)	22(3)	12(3)	7(3)
C23	72(4)	90(4)	76(4)	11(3)	1(3)	3(2)
C24	69(3)	83(3)	66(4)	21(3)	−1(3)	−3(2)
C25	75(3)	49(3)	60(3)	8(2)	−1(3)	7(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	3472	2023	1733	140(20)	1
H1B	2293	3232	1883	119(18)	1
H1C	2329	2367	2574	170(20)	1
H2A	4827	5630	4010	160(30)	1
H2B	3241	4777	4102	210(30)	1
H2C	3194	5645	3413	210(30)	1
H5	8824	2644	2265	38(10)	1
H6	9671	710	1354	75(13)	1
H7	8295	−156	10	99(17)	1
H8	6107	952	−457	67(12)	1
H9	5253	2910	456	73(13)	1
H11A	6249	6208	646	61(11)	1
H11B	7280	4925	537	63(12)	1
H13A	9946	6082	2484	55(10)	1
H13B	9571	4848	1698	57(11)	1
H14A	7311	5809	3118	210(30)	1
H14B	8359	4533	3014	57(11)	1
H15A	3204	5204	1812	187	1
H15B	3734	6076	1139	187	1
H16A	10484	7354	1327	114(18)	1
H16B	9052	7400	612	140(20)	1
H16C	10049	6114	553	112(18)	1
H17A	5644	8054	1567	66(12)	1
H17B	7338	8729	1390	73(12)	1
H18A	7403	9963	2896	96(15)	1
H18B	5823	10279	2356	82(13)	1
H20	4374	8658	4590	150(20)	1
H21	2618	8058	5612	80(13)	1
H23	−1413	8358	4061	49(10)	1
H24	352	8983	3029	114(18)	1


C1
F1
Si1
C2
C7
C8
C9
C6
C5
C4
C3
C10
C15
C14
C11
C13
C12
O1
C16
C17
O2
C18
C19
O3
C20
C25
C21
C22
C23
C24
O4
O5
N1


C1
F1
Si1
C2
C7
C8
C9
C6
C5
C4
C3
C15
C14
C10
C11
C13
C12
C16
O1
C17
C18
O2
C19
O3
C20
C25
C21
C23
C24
C22
N1
O4
O5

Appendix E

X-ray crystallographic data for **424**

Table 1. Crystal data and structure refinement.

Identification code	**00sot037**	
Empirical formula	$C_{13}H_{22}O_2$	
Formula weight	210.31	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 8.9541(2) Å	α = 90°
	b = 7.1843(2) Å	β = 98.162(1)°
	c = 19.1662(2) Å	γ = 90°
Volume	1220.45(5) Å^3	
Z	4	
Density (calculated)	1.145 Mg / m^3	
Absorption coefficient	0.075 mm^{-1}	
F(000)	464	
Crystal	Needle; colourless	
Crystal size	0.20 × 0.04 × 0.04 mm^3	
θ range for data collection	3.03 – 25.50°	
Index ranges	$-10 \le h \le 10$, $-8 \le k \le 8$, $-14 \le l \le 23$	
Reflections collected	4854	
Independent reflections	2160 [R_{int} = 0.0571]	
Completeness to θ = 25.50°	95.2 %	
Max. and min. transmission	0.9970 and 0.9852	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2160 / 0 / 225	
Goodness-of-fit on F^2	0.913	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0469, $wR2$ = 0.0955	
R indices (all data)	$R1$ = 0.0978, $wR2$ = 0.1078	
Extinction coefficient	0.007(3)	
Largest diff. peak and hole	0.178 and –0.137 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:

Hydrogen bonds (Table 6)

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	3452(1)	6738(2)	1895(1)	40(1)	1
O2	2539(2)	13003(2)	1868(1)	53(1)	1
C1	3853(2)	7527(2)	1255(1)	34(1)	1
C2	2395(2)	8420(2)	839(1)	40(1)	1
C3	1872(2)	10011(2)	1273(1)	38(1)	1
C4	3063(2)	11470(2)	1496(1)	41(1)	1
C5	4443(2)	10561(2)	1910(1)	42(1)	1
C6	5059(2)	9016(2)	1492(1)	39(1)	1
C7	6502(2)	8166(3)	1884(1)	52(1)	1
C8	7142(2)	6662(3)	1456(1)	56(1)	1
C9	5966(2)	5171(3)	1246(1)	54(1)	1
C10	4544(2)	6019(3)	839(1)	44(1)	1
C11	1164(3)	6932(3)	675(2)	62(1)	1
C12	2693(3)	9227(4)	125(1)	58(1)	1
C13	511(3)	10150(3)	1457(1)	59(1)	1

Table 3. Bond lengths [Å] and angles [°].

O1–C1	1.4410(18)
O1–H1O	0.91(2)
O2–C4	1.427(2)
O2–H2O	0.87(3)
C1–C10	1.527(2)
C1–C6	1.542(2)
C1–C2	1.568(2)
C2–C3	1.526(2)
C2–C11	1.536(3)
C2–C12	1.544(3)
C3–C13	1.319(3)
C3–C4	1.514(2)
C4–C5	1.518(3)
C4–H4	1.042(16)
C5–C6	1.518(2)
C5–H5A	0.990(18)
C5–H5B	0.987(19)
C6–C7	1.527(3)
C6–H6	0.993(18)
C7–C8	1.517(3)
C7–H7A	0.97(2)
C7–H7B	0.984(19)
C8–C9	1.515(3)
C8–H8A	0.98(2)
C8–H8B	0.99(2)
C9–C10	1.523(3)
C9–H9A	1.03(2)
C9–H9B	0.99(2)
C10–H10A	0.994(16)
C10–H10B	1.016(19)
C11–H11A	1.01(2)
C11–H11B	0.95(2)
C11–H11C	0.97(2)
C12–H12A	0.98(2)
C12–H12B	1.01(2)
C12–H12C	0.95(2)
C13–H13B	0.970(19)
C13–H13A	0.970(19)

C1–O1–H1O	111.2(16)
C4–O2–H2O	114.1(16)
O1–C1–C10	109.47(13)
O1–C1–C6	105.74(13)
C10–C1–C6	109.08(14)
O1–C1–C2	107.71(12)
C10–C1–C2	113.22(15)
C6–C1–C2	111.33(13)
C3–C2–C11	111.44(16)
C3–C2–C12	107.92(15)
C11–C2–C12	106.83(19)
C3–C2–C1	109.06(13)
C11–C2–C1	109.93(16)
C12–C2–C1	111.65(16)
C13–C3–C4	120.87(18)
C13–C3–C2	124.69(18)
C4–C3–C2	114.44(15)
O2–C4–C3	114.02(15)
O2–C4–C5	111.86(16)
C3–C4–C5	109.75(14)

O2–C4–H4	105.1(8)
C3–C4–H4	108.4(9)
C5–C4–H4	107.3(8)
C4–C5–C6	111.62(16)
C4–C5–H5A	110.3(10)
C6–C5–H5A	110.1(10)
C4–C5–H5B	110.3(9)
C6–C5–H5B	110.0(9)
H5A–C5–H5B	104.4(14)
C5–C6–C7	112.21(16)
C5–C6–C1	111.75(14)
C7–C6–C1	112.07(15)
C5–C6–H6	106.4(9)
C7–C6–H6	109.8(9)
C1–C6–H6	104.2(9)
C8–C7–C6	112.13(19)
C8–C7–H7A	112.4(12)
C6–C7–H7A	108.7(11)
C8–C7–H7B	109.2(10)
C6–C7–H7B	111.8(11)
H7A–C7–H7B	102.3(16)
C9–C8–C7	110.20(18)
C9–C8–H8A	111.3(11)
C7–C8–H8A	109.4(11)
C9–C8–H8B	111.0(11)
C7–C8–H8B	109.3(11)
H8A–C8–H8B	105.4(15)
C8–C9–C10	110.60(17)
C8–C9–H9A	110.8(10)
C10–C9–H9A	108.4(11)
C8–C9–H9B	108.2(11)
C10–C9–H9B	110.6(11)
H9A–C9–H9B	108.2(14)
C9–C10–C1	112.80(17)
C9–C10–H10A	112.6(9)
C1–C10–H10A	108.2(9)
C9–C10–H10B	107.1(10)
C1–C10–H10B	109.7(9)
H10A–C10–H10B	106.2(14)
C2–C11–H11A	110.0(11)
C2–C11–H11B	110.8(11)
H11A–C11–H11B	107.5(17)
C2–C11–H11C	110.3(12)
H11A–C11–H11C	106.3(16)
H11B–C11–H11C	111.8(17)
C2–C12–H12A	111.9(11)
C2–C12–H12B	113.1(15)
H12A–C12–H12B	110.1(18)
C2–C12–H12C	110.1(15)
H12A–C12–H12C	104.8(19)
H12B–C12–H12C	106.5(19)
C3–C13–H13B	121.1(11)
C3–C13–H13A	120.8(11)
H13B–C13–H13A	118.1(16)

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}
O1	58(1)	30(1)	36(1)	1(1)	17(1)	−7(1)
O2	85(1)	28(1)	52(1)	−2(1)	30(1)	2(1)
C1	45(1)	29(1)	30(1)	0(1)	11(1)	−4(1)
C2	47(1)	39(1)	35(1)	−3(1)	6(1)	0(1)
C3	47(1)	37(1)	31(1)	3(1)	8(1)	1(1)
C4	61(1)	28(1)	39(1)	−1(1)	22(1)	−3(1)
C5	51(1)	35(1)	42(1)	−4(1)	11(1)	−14(1)
C6	46(1)	34(1)	38(1)	2(1)	12(1)	−6(1)
C7	47(1)	54(1)	54(2)	−2(1)	6(1)	−9(1)
C8	44(1)	62(1)	64(2)	7(1)	11(1)	6(1)
C9	66(2)	45(1)	54(2)	1(1)	19(1)	11(1)
C10	54(1)	38(1)	42(1)	−4(1)	12(1)	−2(1)
C11	54(2)	53(1)	74(2)	−15(2)	−6(1)	−2(1)
C12	82(2)	61(2)	33(1)	−2(1)	7(1)	19(2)
C13	56(2)	60(2)	62(2)	−12(1)	13(1)	1(1)

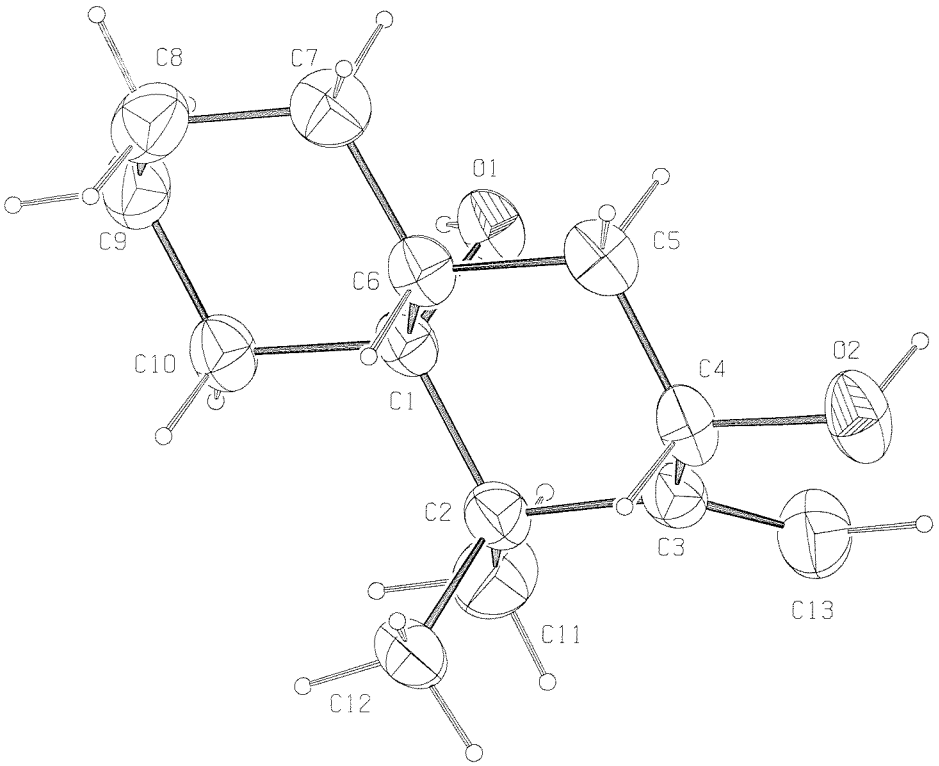
Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

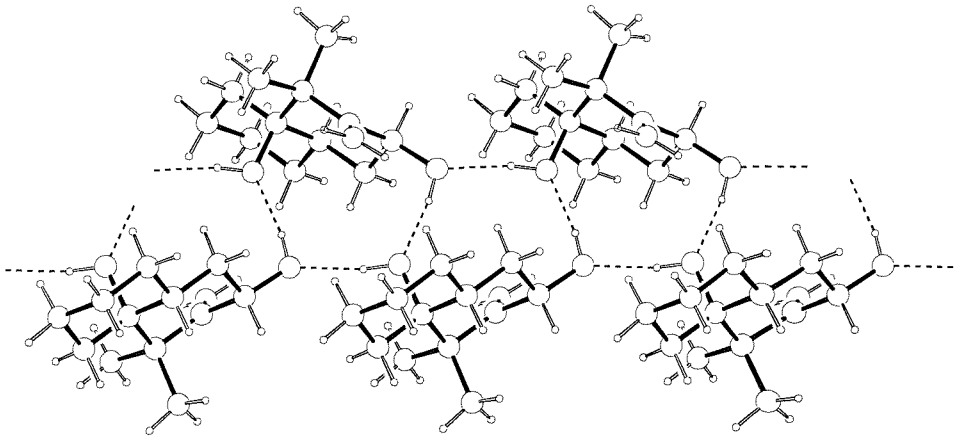
Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1O	3190(20)	5520(30)	1835(13)	93(8)	1
H2O	2350(30)	12730(30)	2287(14)	103(10)	1
H4	3398(16)	12050(20)	1044(9)	42(5)	1
H5A	5236(19)	11500(20)	2051(10)	53(5)	1
H5B	4197(18)	10070(20)	2361(10)	39(5)	1
H6	5271(18)	9590(20)	1044(10)	38(5)	1
H7A	7220(20)	9150(30)	2019(10)	66(6)	1
H7B	6340(20)	7650(20)	2343(10)	48(5)	1
H8A	8050(20)	6140(20)	1732(10)	59(6)	1
H8B	7480(20)	7230(30)	1036(11)	66(6)	1
H9A	6370(20)	4180(30)	933(11)	65(6)	1
H9B	5740(20)	4550(20)	1683(11)	57(6)	1
H10A	3754(18)	5070(20)	688(9)	38(4)	1
H10B	4836(19)	6570(20)	390(11)	51(5)	1
H11A	1530(20)	5910(30)	379(11)	62(6)	1
H11B	280(20)	7450(30)	413(11)	61(6)	1
H11C	950(20)	6350(30)	1108(12)	69(8)	1
H12A	2860(20)	8250(30)	−210(11)	74(7)	1
H12B	3550(30)	10150(30)	172(14)	95(9)	1
H12C	1830(30)	9870(30)	−95(14)	92(8)	1
H13B	−230(20)	9170(30)	1346(11)	65(6)	1
H13A	228(19)	11230(30)	1711(10)	58(6)	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
O1–H1O···O2^{i}	0.91(2)	1.90(2)	2.8034(16)	170(2)
O2–H2O···O1^{ii}	0.87(3)	1.95(3)	2.8000(18)	166(2)

Symmetry transformations used to generate equivalent atoms:
(i) x,y–1,z (ii) –x+1/2,y+1/2,–z+1/2


C8
C7
O1
C9
C5
C6
C10
C1
C4
O2
C2
C3
C13
C11
C12



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