UNIVERSITY OF SOUTHAMPTON

Lewis acid mediated cyclisations of methylene and alkylidenecyclopropanes

By

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ABSTRACT

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LEWIS ACID MEDIATED CYCLISATIONS OF METHYLENE AND ALKYLIDENECYCLOPROPANES

By Lee Patient

This thesis is concerned with the addition or cyclisation of methylene and alkylidenecyclopropanes to C=X bonds mediated by a Lewis acid in the formation of novel heterocyclic compounds. Various intra- and intermolecular processes are reported including additions to aldehydes, ketones and hydrazones.

Chapter 2 describes the intermolecular addition of silyl methylenecyclopropanes to aldehydes affording tetrahydrofurans and furofurans. The effect on the cyclisation of different silyl groups and additional substituents on the methylenecyclopropane was investigated.

Chapter 3 presents the intramolecular cyclisation of methylenecyclopropylimines to give azabicycles. The effect of different silyl groups on the cyclisation of hydrazones was briefly investigated. Particular attention was paid to a mechanistic study of the cyclisation of methylenecyclopropylhydrazones giving azabicycles.

Chapter 4 details the intramolecular cyclisation of alkylidenecyclopropylcarbonyls to yield chloroalkenols and bicyclic ethers. This methodology could be applied to the synthesis of various natural products.

"I don't wanna come back down from this cloud"

Gavin Rossdale (1967-)

Contents

Preface

The research described in this thesis was carried out under the supervision of professor Jeremy Kilburn at the University of Southampton between October 2000 and October 2003. No part of this thesis has been previously submitted at this or any other University.

Acknowledgements

I would like to thank Professor Jeremy Kilburn for his encouragement and supervision during the course of this research. I also thank Malcolm Berry for his supervision of my time at GSK and continued input throughout the three years.

I would also like to thank the EPSRC and GSK for the funding to support this research.

Many thanks must go to Neil and Jon for taking their time to proof read this thesis. I should also thank all the members of the Kilburn group, past and present that I've worked with.

I am indebted to Neil and Joan for all their work in NMR, John and Julie (Alec at GSK) in mass spec and Mark and Simon for the wonderful crystal structures.

I thank Faye for making my first year so enjoyable and yet surprisingly productive and also for listening to me rant on about all sorts. Jon, cheers for trivia and making me relive the early nineties everyday for my second year and I thank Rich for help in my third year with all the computer related problems related to this thesis.

Thanks goes to all the members of Stanley with whom I played, I'm not a center back and at 5'8 never will be! I thank John Scadden for screwing my ankle back together after I made a mess of it.

I thank all the members of "the Shirley house" past and present for many legendary parties and memorable times.

I thank my parents and sister for all their support and for believing in me to become the first Dr. Patient our family.

Last but not least I thank Rach for all her support throughout my PhD and for putting up with me.

Abbreviations

Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
aq.	aqueous
Ar	aryl
Bn	benzyl
b.p.	boiling point
br	broad
BT-H	benzotriazole
Bu	butyl
Bz	benzoyl
cat.	catalytic
CI	chemical ionization
Δ	heat
d	doublet
dba	*trans,trans*-dibenzylideneacetone
DCM	dichloromethane
DHP	3,4-dihydro-*2H*-pyran
DIBAL-H	diisobutylaluminium hydride
Dil.	dilute
DMF	*N-N*-dimethyl formamide
DMPS	dimethylphenylsilyl
DMSO	dimethyl sulfoxide
EI	electron impact
ES	electrospray
Et	ethyl
ether	diethyl ether
eq.	equivalent
eV	electron volts
GC	gas chromatography

GOESY	1D-gradient nuclear Overhauser spectroscopy
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
hr	hour
Hz	hertz
i	*iso*
IR	infrared spectroscopy
J	coupling constant
LA	Lewis acid
LUMO	lowest unoccupied molecular orbital
LRMS	low resolution mass spectrometry
m	multiplet
m-	*meta*
MCP	methylenecyclopropane
Me	methyl
m.p.	melting point
n	normal
NMR	nuclear magnetic resonance
o-	*ortho*
p-	*para*
petrol	petroleum ether b.p. 40-60°C
ppm	parts per million
PPTS	pyridinium *p*-toluenesulphonate
q	quartet
Ph	phenyl
Pr	propyl
Rac	racemic
R_f	retention factor
RT	room temperature

s	singlet
sat.	saturated solution
t	tertiary
t	triplet
TBDMS	tertiarybutyldimethylsilyl
TBDPS	tertiarybutyldiphenylsilyl
TDA-1	tris(3,6-dioxaheptyl)amide
Tf	triflate
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	trisisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl

Chapter 1

Introduction

1.1 Methylenecyclopropane

1.1.1 Biological Background

Methylenecyclopropane **1** has been found in three naturally occurring amino acids, hypoglycin A[1] **2**, methylenecyclopropylglycine[2] **3** and β-(methylenecyclopropyl)-β-methylalanine[3] **4** (Figure 1).

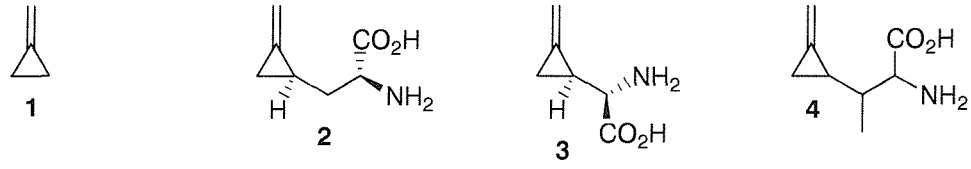


Figure 1 Amino acids containing the methylenecyclopropane structure

Hypoglycin A[1] **2** has been isolated from the unripe fruit of the ackee tree (*blighia sapida*) and has been found to be the cause of Jamaican vomiting sickness.[4] Methylenecyclopropylglycine[2] **3** has been isolated from *billia hippocastanum* and β-(methylenecyclopropyl)-β-methylalanine[3] **4** has been isolated from *aesculus californica*.

The methylenecyclopropane structure also occurs in a recently discovered natural product penitricin D[5] **5**, isolated from *aspergillus niger* (Figure 2). The name comes from the close resemblance to penitricin A **6**.

Figure 2 Penitricin D **5** and pentricin A **6**

1.1.2 Chemical Background

Methylenecyclopropanes are highly strained but stable molecules, which has led to their extensive use in organic synthesis.[6-8] X-ray analysis was carried out on methylenecyclopropane to determine the molecular structure[9] (Figure 3).

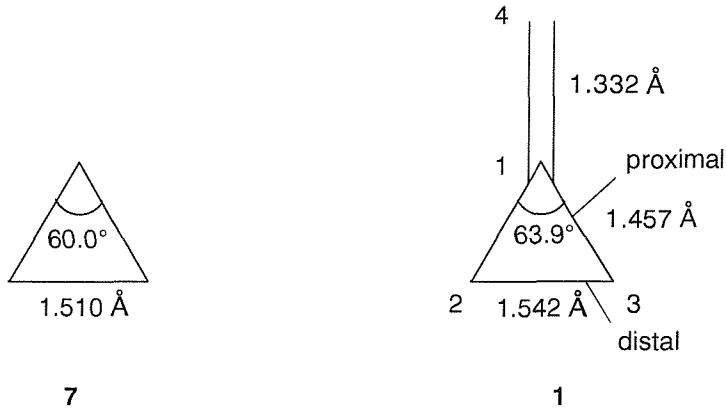


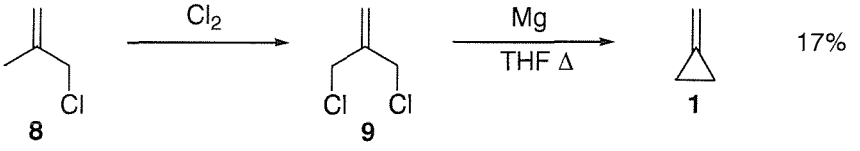
Figure 3 X-ray analysis data of methylenecyclopropane **1**

The exocyclic methylene moiety exerts strain on the cyclopropyl ring, which is reflected in the increase of the C2-C3 bond length and the C2-C1-C3 bond angle in comparison with cyclopropane **7**.

1.2 Synthesis of Methylenecyclopropanes

1.2.1 Synthesis of unsubstituted methylenecyclopropane

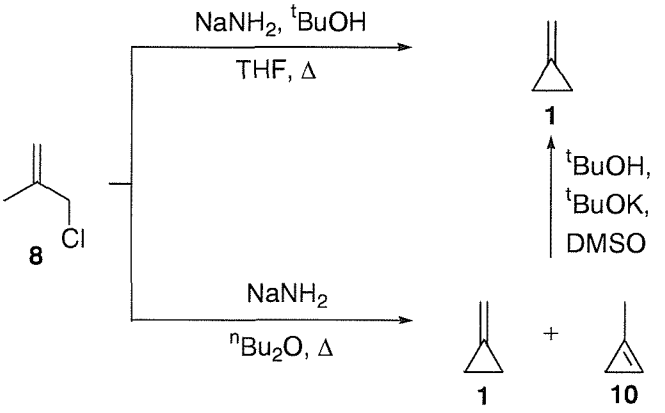
Methylenecyclopropane is commercially available (Fluka), but there are also many reported syntheses.[7]



Scheme 1

In 1953 Gragson *et al.*[10] reported that if dichloride **9** (prepared by chlorination of methylallyl chloride **8**) was treated with magnesium metal in refluxing THF then methylenecyclopropane **1** could be obtained in 17% yield (Scheme 1).

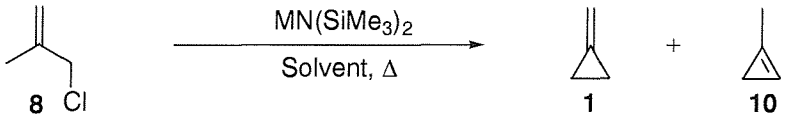
One of the best and most widely used methods for the preparation of methylenecyclopropane **1** was found to be treatment of methallyl chloride **8** with a strong base such as $NaNH_2$, and this method can be used in large-scale production[11,12] (Scheme 2).



Scheme 2

When methallyl chloride **8** is treated with $NaNH_2$ in $^nBu_2O$ at 130°C the reaction proceeds to form a mixture of methylenecyclopropane **1** and methylcyclopropene **10**. This mixture can be readily converted into pure methylenecyclopropane **1** by treatment with ^tBuOK and ^tBuOH in DMSO. However, methylenecyclopropane **1** can be produced directly from methallyl chloride **8** by using $NaNH_2$ and ^tBuOH in THF at 62°C.

Binger *et al.*[13] recently reported detailed results on the effect of the solvent and base on the formation of methylenecyclopropane **1** and methylcyclopropene **10** (Scheme 3).



Scheme 3

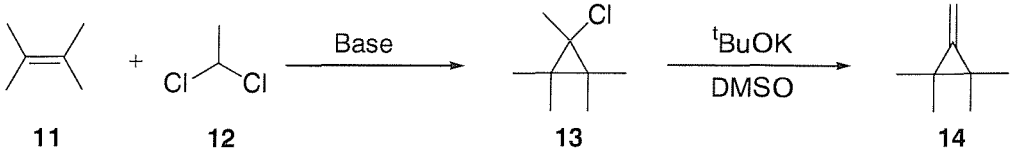
M	Solvent	Reaction temp / °C	Yield / %	Ratio **1**:**10**
Na	THF	65	44	80:20
Na	Toluene	110	72	55:45
Na	*o*-Xylene	140	71	76:24
Na	$^nBu_2O$	130	73	84:16
K	THF	65	6	100:0
K	Toluene	110	70	96:4
K	*o*-Xylene	140	64	96:4
K	$^nBu_2O$	130	76	96:4

Table 1 Treatment of methallyl chloride **8** with various bases and solvents

Various $MN(SiMe_3)_2$ bases were used because they are soluble in organic solvents, whereas MNH_2 bases are not. It was found that methylenecyclopropane could be synthesized cleanly and efficiently using $KN(SiMe_3)_2$. Reactions with $NaN(SiMe_3)_2$ gave a mixture of the two products.

1.2.2 Synthesis of substituted methylenecyclopropanes

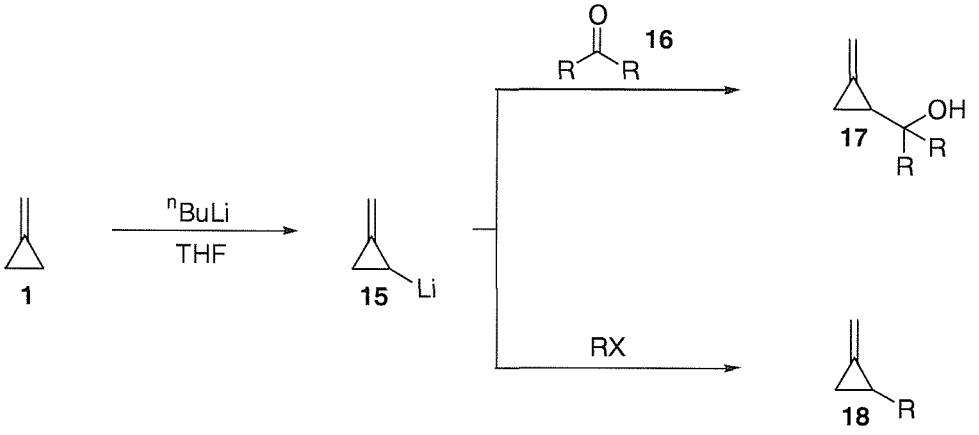
There are two obvious ways to synthesize substituted methylenecyclopropanes: build methylenecyclopropane onto an existing structure or build from methylenecyclopropane. The first of these routes can be achieved by addition of 1,1-dichloroethane **12** to a substituted alkene **11** followed by elimination of HCl (Scheme 4).[14]



Scheme 4

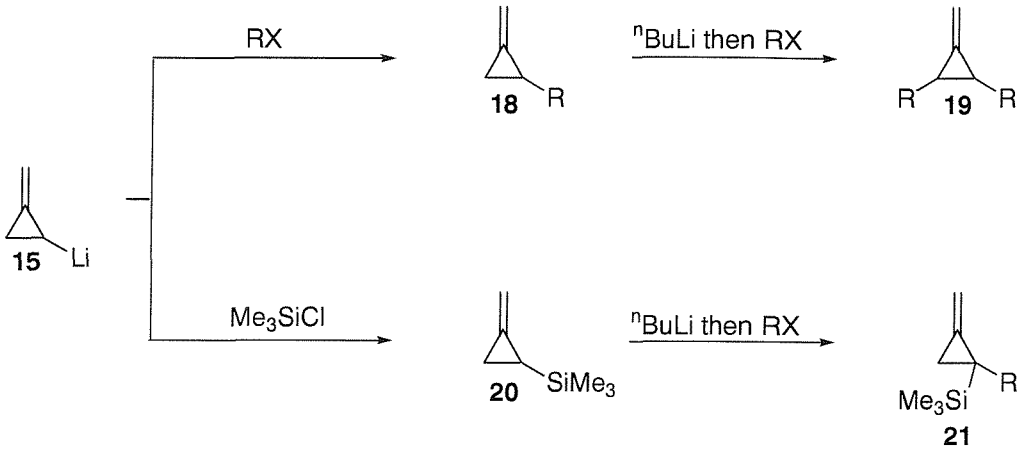
Binger *et al.*[14] reported that deprotonation of 1,1-dichloroethane **12** affords a carbene on loss of chloride. The carbene can add to a substituted alkene **11** to give cyclopropyl chloride **13**, which on treatment with ^{t}BuOK affords substituted methylenecyclopropane **14**.

The second method, building from methylenecyclopropane involves deprotonation with a strong base such as ^{n}BuLi (Scheme 5).[15,16]



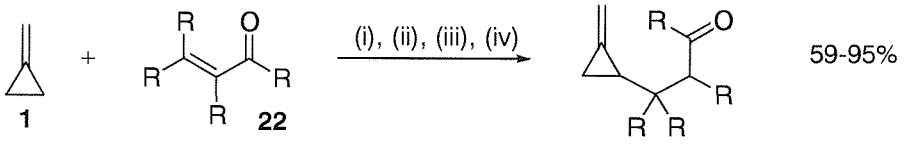
Scheme 5

Thomas[15] reported that when methylenecyclopropane **1** was treated with ^{n}BuLi the subsequent organolithium **15** could be quenched with various electrophiles such as halides, ketones or aldehydes. It was noted that if the first substituent was an alkyl group then the second substitution gave 1,2-disubstituted methylenecyclopropanes **19**. However, if the first substitution was a trimethylsilyl group then the second substitution led to 1,1-disubstituted methylenecyclopropanes **21** (Scheme 6).[16]



Scheme 6

Recently Peron *et al.*[17] reported that methylenecyclopropylcuprate could be utilized in a 1,4-addition to α,β-unsaturated ketones **22** (Scheme 7).



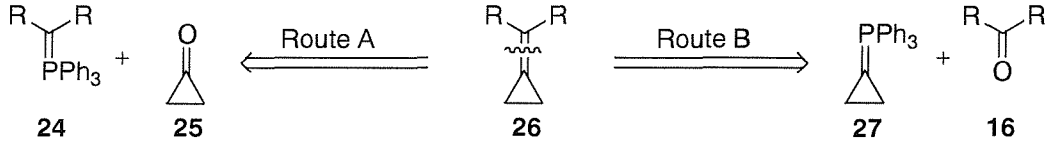
(i) ^{n}BuLi, THF, -78°C
(ii) CuI
(iii) **22**, Me_3SiCl
(iv) Dil. HCl

Scheme 7

Generation of bis(methylenecyclopropyl)cuprate can be achieved by deprotonation of methylenecyclopropane **1** with ^{n}BuLi followed by treatment with copper iodide. The resulting cuprate can then react with an α,β-unsaturated ketone **22** in a Michael addition in the presence of trimethylsilylchloride to trap the formed enolate as a silyl enolether. Acidic work-up then gives the desired methylenecyclopropylketones **23** in good to excellent yields.

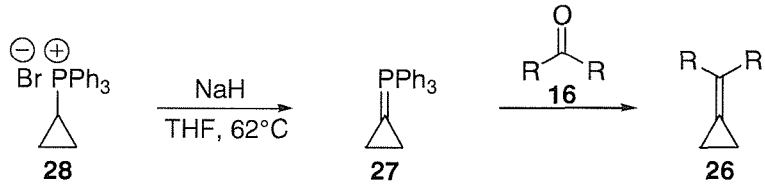
1.2.3 Synthesis of alkylidenecyclopropanes

As with methylenecyclopropanes, there are many reported syntheses of alkylidenecyclopropanes.[7] The most obvious and widely utilized of these methods is the Wittig olefination. There are two possible ways to disconnect alkylidenecyclopropane **26** (Scheme 8).



Scheme 8

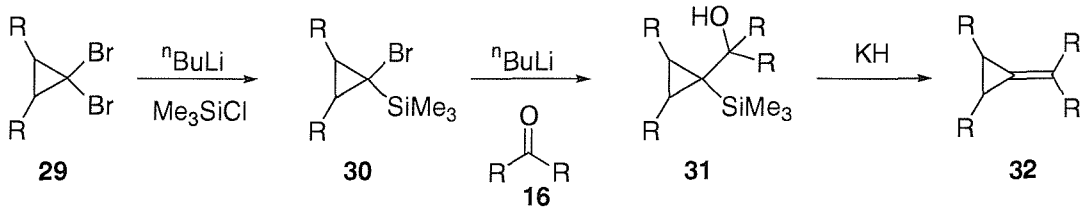
Disconnection *via* route A leads back to phosphonium ylide **24** and cyclopropanone **25**, whereas disconnection *via* route B leads back to cyclopropyl-phosphonium ylide **27** and a carbonyl compound **16**. There are few examples of the forward synthesis using route A[18] due to the instability of cyclopropanones, and route B is therefore used more frequently (Scheme 9).[19]



Scheme 9

Cyclopropyltriphenylphosphonium bromide **28** is commercially available (Lancaster) or can be readily prepared from 1,3-dibromopropane and triphenylphosphine.[20,21] When **28** is treated with NaH it affords cyclopropylphosphonium ylide **27** which reacts with a ketone or aldehyde **16** to give alkylidenecyclopropane **26**. Nemoto *et al.*[22] reported that higher yields could be obtained if the additive TDA-1 was used.

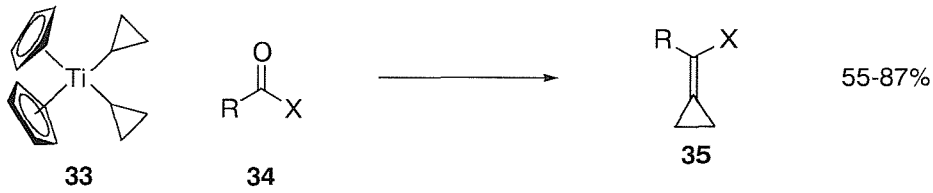
A more versatile method for the formation of alkylidenecyclopropanes is based around the Peterson olefination.[23,24] This method allows the synthesis of derivatives which are substituted on the cyclopropyl ring (Scheme 10).



Scheme 10

Treatment of 1,1-dibromocyclopropanes **29** with ^{n}BuLi followed by trimethylsilylchloride gives trimethylsilylcyclopropanes **30**. Treatment of cyclopropanes **30** with ^{n}BuLi followed by a ketone or aldehyde gives β-silylalcohols **31**, which upon exposure to KH yields alkylidenecyclopropanes **32**.

Another versatile method for the formation of alkylidenecyclopropanes was reported by Petasis *et al.*[25] (Scheme 11).



Scheme 11

Biscyclopropyltitanocene **33** can be coupled with aldehydes, ketones or esters to give cyclopropylidenes **35** in good to excellent yields.

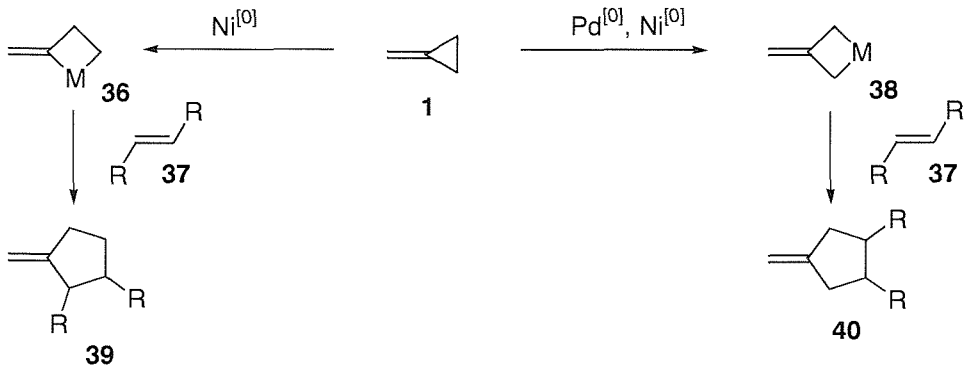
1.3 Methylenecyclopropanes in synthesis

Over the last 25 years the use of methylenecyclopropanes in synthesis has been greatly studied. Many investigations have been carried out including electrophilic additions, Diels-Alder and Pauson-Khand type reactions to name a few.[6,7,26] This section will concentrate on three main classes of reaction: [3+2] cycloadditions, both transition metal catalyzed and thermally induced, 1,3-dipolar cycloadditions and radical based cyclisations.

1.3.1 [3+2] Cycloadditions of methylenecyclopropanes

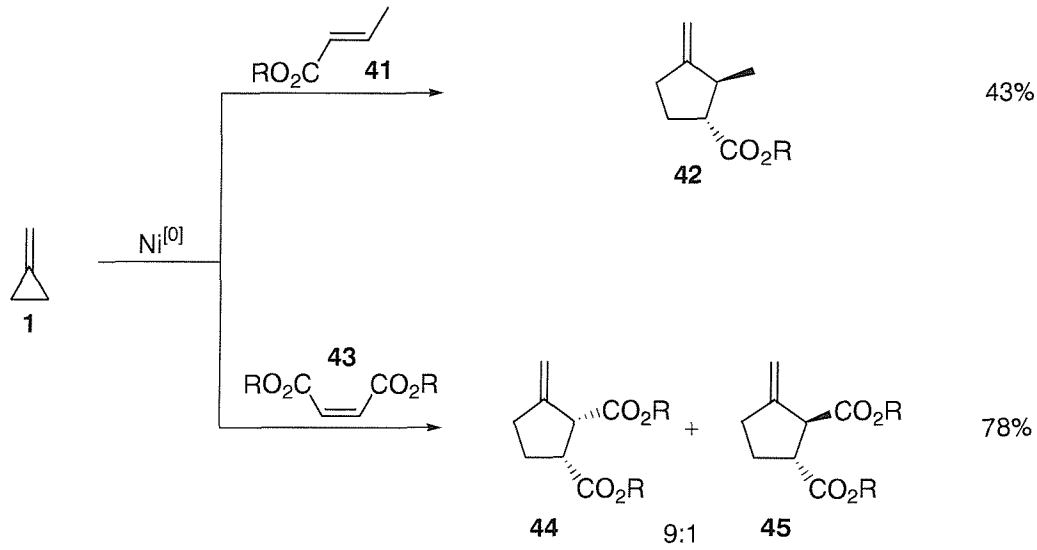
1.3.1.1 Transition metal catalyzed [3+2] cycloadditions

In the past two decades there have been many examples of [3+2] transition metal catalyzed cycloadditions involving methylenecyclopropanes, with methylenecyclopropane providing the three-carbon component. Both inter- and intramolecular versions of this reaction have been investigated and several reviews have been written on the subject.[8,26,27] The transition metals most commonly investigated are nickel, which can lead to either distal or proximal bond cleavage depending on ligands and additives, and palladium, which leads exclusively to distal bond cleavage (Scheme 12).



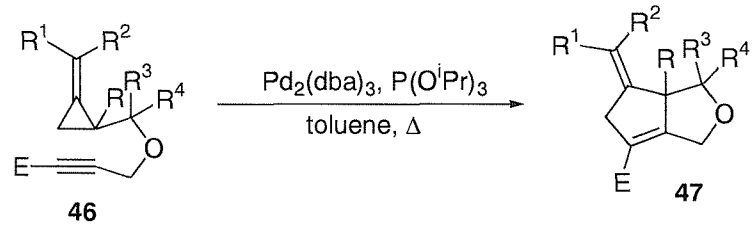
Scheme 12

In the presence of $Ni^{[0]}$ catalyst alkyl crotonates[28] and alkyl maleates[29] undergo [3+2] cycloaddition with methylenecyclopropane *via* cleavage of the proximal bond to give methylenecyclopentane **42** and methylenecyclopentane isomers **44** and **45** respectively (Scheme 13).



Scheme 13

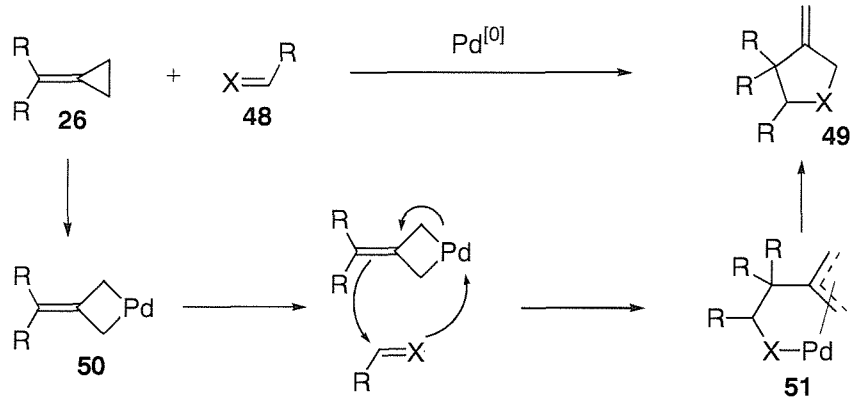
Due to the problems of dimerization in intermolecular reactions, extensive studies of intramolecular reactions of this type have been carried out. One such example was carried out by Lautens *et al.*[30] where $Pd^{[0]}$ was used to catalyze the cyclisation of alkyne **46** and gave the desired bicycle **47** in high yields (Scheme 14).



Scheme 14

Substitution on the carbinol carbon (R^3 and R^4) or on the exocyclic methylene group (R^1 and R^2) had little effect on either the stereoselectivity or the reactivity, whereas substitution on the cyclopropyl carbon had a marked effect. When R=H or OMe the cyclisation proceeded smoothly, but when R=Me the reaction gave a complex mixture of products. Substitution on the acetylenic carbon also had an effect: when E was an electron withdrawing group such as a ketone or ester then the cyclisation proceeded in good yields, however when E was a hydroxymethyl or protected hydroxymethyl group then the cyclisation was effected in excellent yields.

Recently Nakamura *et al.*[31] reported the first intermolecular transition metal catalyzed [3+2] cycloaddition of an alkylidenecyclopropane with a C=X bond (Scheme 15). Aldehydes[31] and imines[32] have both been used to form tetrahydrofurans and pyrolidines respectively.

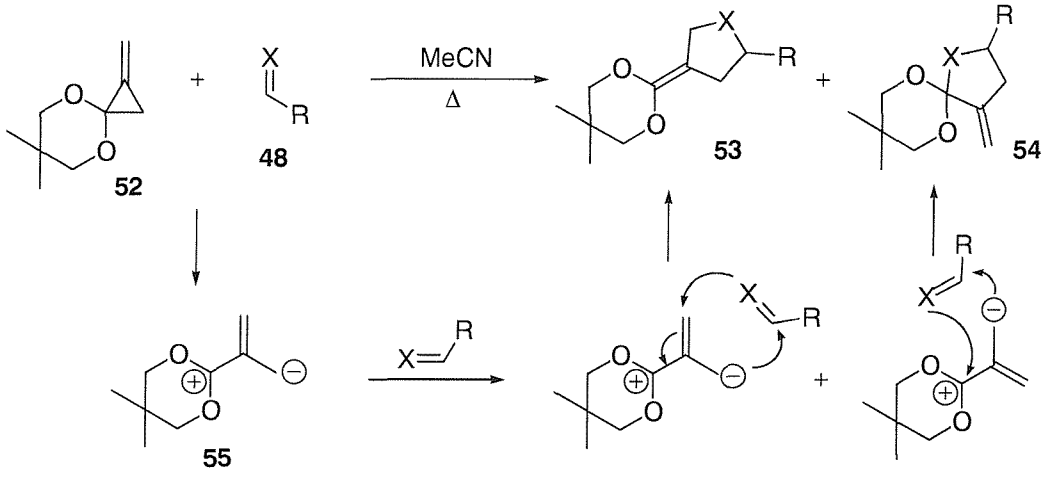


Scheme 15

Following their proposed mechanism, insertion of palladium into the distal bond as expected gives palladacyclobutane complex **50**. Complex **50** can then react with a C=X bond to give π-allyl palladium complex **51**, followed by reductive elimination of palladium to furnish heterocycles **49**.

1.3.1.2 Thermally induced [3+2] cycloadditions

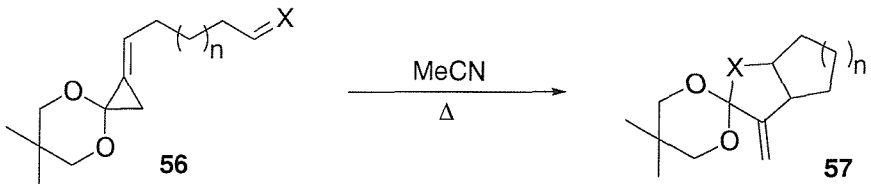
Methylenecyclopropyl ketal **52** can react with a C=X bond when heated in acetonitrile to give functionalized 5-membered ring systems (Scheme 16).[33] This methodology has been performed with electron deficient alkenes,[34-36] alkynes,[33,37] aldehydes[38] and imines.[39,40]



Scheme 16

When methylenecyclopropyl ketal **52** is heated in acetonitrile the cyclopropyl ring can open to form trimethylenemethane intermediate **55**, which is stabilized by the presence of the ketal. Trimethylenemethane **55** can then undergo [3+2] cycloaddition with C=X **48** to give the desired cyclic products **53** and **54**.

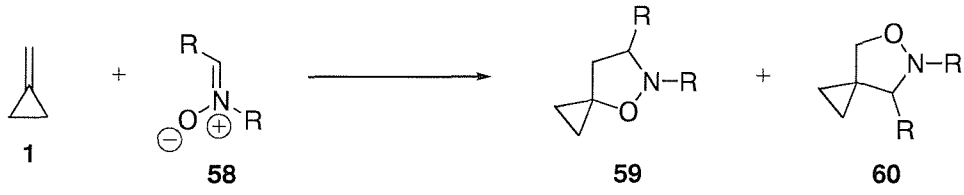
Intramolecular reactions of this nature have been carried out with α,β-unsaturated esters and aldehydes, n=1 and 2 to provide a simple route to 5,5- and 5,6-bicycles and 5,5- and 5,6-bicyclic ethers **57** respectively (Scheme 17).[41]



Scheme 17

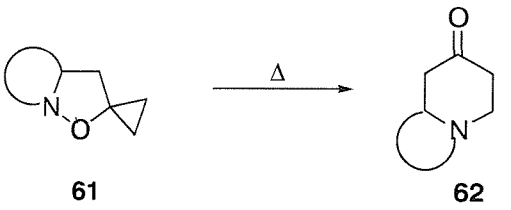
1.3.2 1,3-Dipolar cycloadditions of methylenecyclopropanes

Many [3+2] cycloadditions have been studied with methylenecyclopropane providing the two-carbon component.[42] Additions have been carried out with azides,[43-45] diazoalkanes,[46,47] nitrones[48-50] and nitrile oxides.[51] One of the most extensively studied cycloadditions has been with nitrones (Scheme 18).



Scheme 18

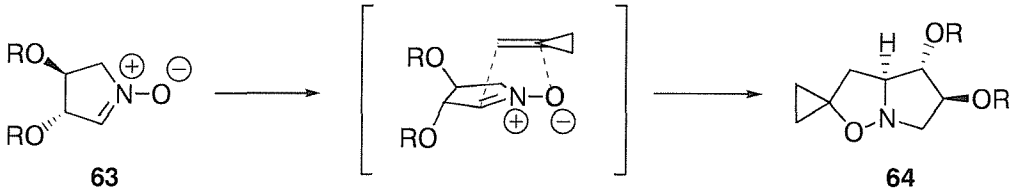
Methylenecyclopropane **1** will react under thermal conditions with nitrones **58** to give 5-spirocyclopropane and 4-spirocyclopropane isoxazolidines **59** and **60** respectively. Unsubstituted methylenecyclopropane generally gives a slight preference for **59** over **60** with product ratios from 2:1 up to 20:1 depending on the substituents on the nitrone.[42] One of the main reasons for the interest in this reaction was the discovery that 5-spirocyclopropane isoxzolidines **61** undergo thermal rearrangement to tetrahydropyridn-4-ones **62**.[48-50] Particular interest was paid to cyclic nitrones, which ultimately provide nitrogen bridgehead bicyclic ketones, the skeleton of many alkaloid natural products (Scheme 19).



61 62

Scheme 19

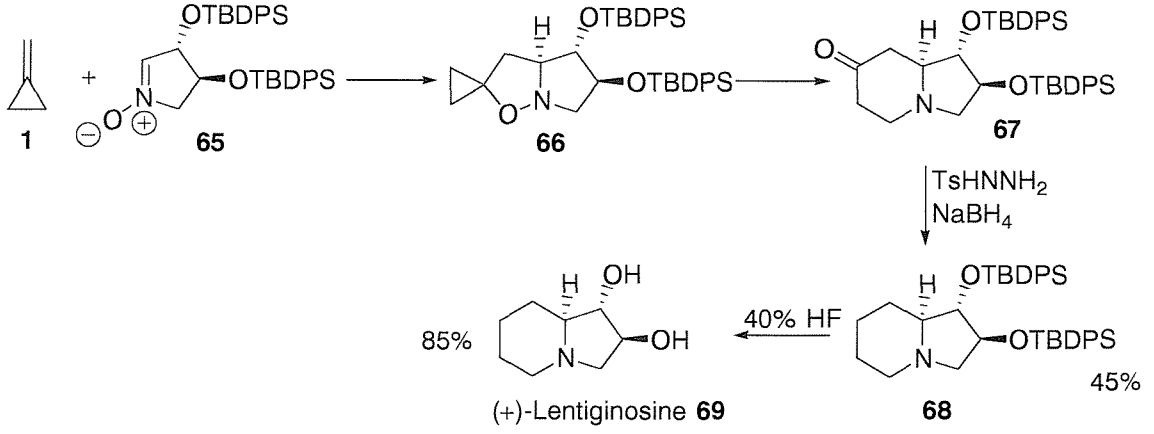
When optically pure nitrones were employed in the cycloaddition, good regio- and diastereoselectivity was observed (Scheme 20).



63 64

Scheme 20

Depending on the alkoxy protecting group used, selectivities from 5:1 up to 12:1 were obtained with good yields of the desired isomer.[42] This methodology has been utilized in the synthesis of natural products, such as the total synthesis of (+)-lentiginosine **69** (Scheme 21).[52,53]

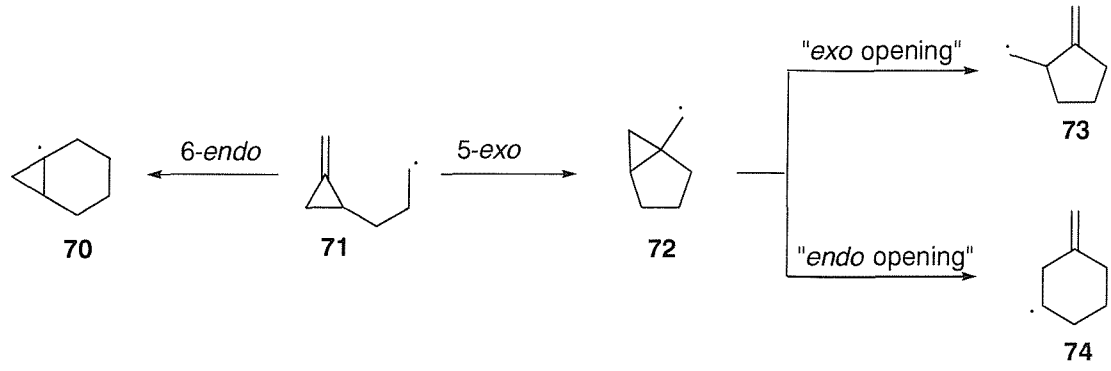


1 65 66 67 (+)-Lentiginosine **69** 68

Scheme 21

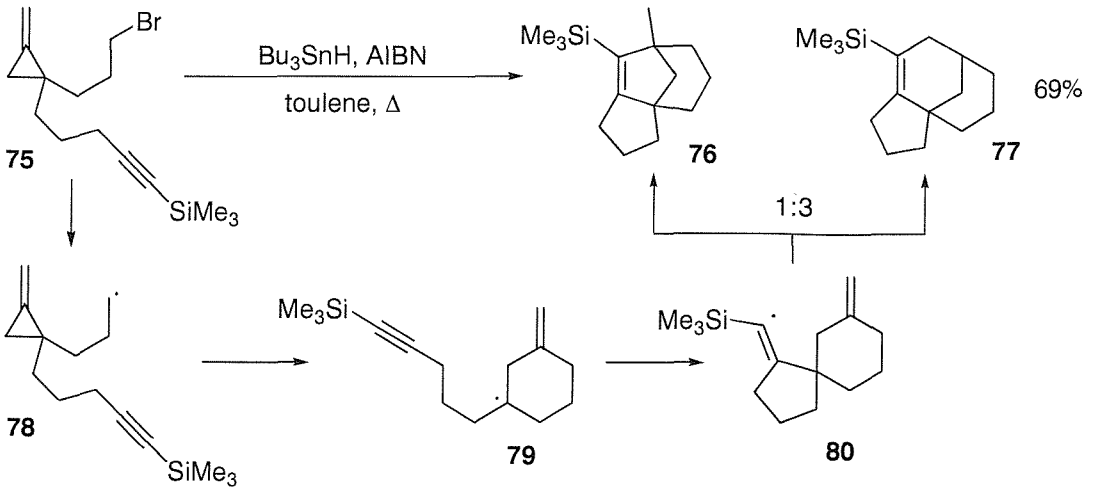
1.3.3 Radical cyclisations of methylenecyclopropane derivatives

Destabel *et al.*[54,55] carried out the first intramolecular cyclisations of methylenecyclopropane derivatives to provide some rules of cyclisation (Scheme 22).



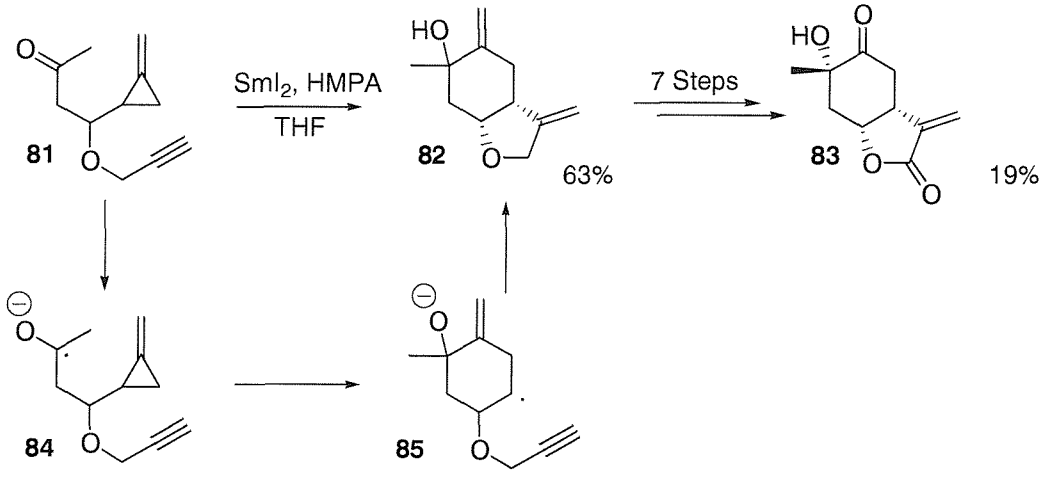
Scheme 22

Methylenecyclopropyl radical **71** can either cyclise *via* 6-*endo* route to give cyclohexyl radical **70**, or *via* 5-*exo* route to give cyclopropylmethyl radical **72**. Cyclopropylradical **72** can then either open "*exo*" fashion to give methylenecyclopentyl radical **73** or "*endo*" fashion to give methylenecyclohexyl radical **74**. Destabel *et al.* discovered that methylenecyclopropyl radical **71** cyclises 5-*exo* trig followed by "*endo* opening" exclusively to give methylenecyclohexyl radical **74**. Such cyclisations have been extended to cascade reactions for the synthesis of various polycyclic compounds. For example, Methylenecyclopropane derivative **75** was treated with tributyltinhydride and AIBN to generate radical **78**, which cyclised to give cyclohexyl radical **79** (Scheme 23).[56,57] Radical **79** cyclised onto the alkyne to give reactive vinyl radical **80**, which in turn cyclised onto methylenecyclohexane to give a 1:3 mixture of the two products **76** and **77** respectively.



Scheme 23

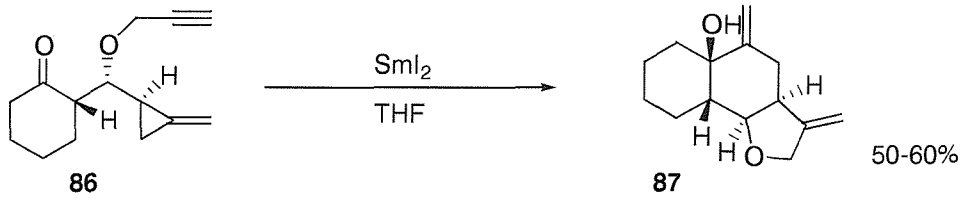
Boffey *et al.*[58-60] used a samarium diiodide mediated cyclisation in the total synthesis of paeonilactone B **83** (Scheme 24).



Scheme 24

Treatment of ketone **81** with samarium diiodide generated ketyl radical **84**, which cyclised to give methylenecyclohexyl radical **85** and further cyclisation onto the propargyl group in 5-*exo* dig fashion gave paeonilactone skeleton **82**. The basic skeleton **82** was elaborated into paeonilactone B **83** in 7 steps in 19% yield.

Watson *et al.*[61] furthered this methodology in the cyclisation of ketone **86** with samarium diiodide to give tricycle **87** in good yields as a single diastereoisomer (Scheme 25).



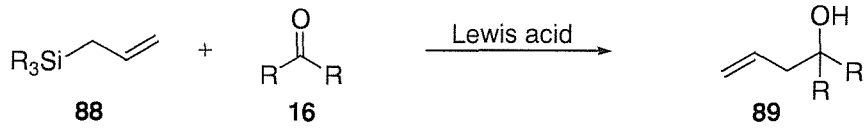
86 **87**

Scheme 25

1.4 Allylsilane chemistry and methylenecyclopropanes

1.4.1 Allyl silane addition to carbonyls

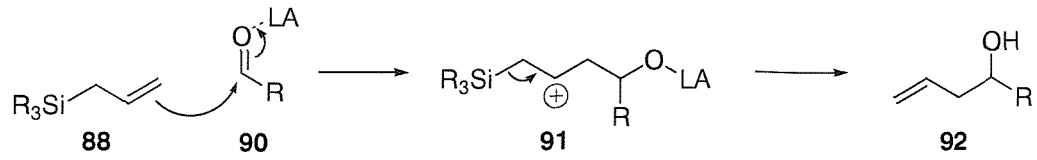
The Lewis acid promoted addition of allyl silanes to ketones and aldehydes is a well established and an important synthetic tool. Carbonyls **16** will react with allyl silanes **88** when promoted by Lewis acids such as $TiCl_4$, $SnCl_4$ or $BF_3{\cdot}Et_2O$ to give homoallylic alcohols **89** (Scheme 26).[62-64]



88 **16** **89**

Scheme 26

This reaction proceeds smoothly due to the ability of silicon to stabilize a β-positive charge **91** (Scheme 27)



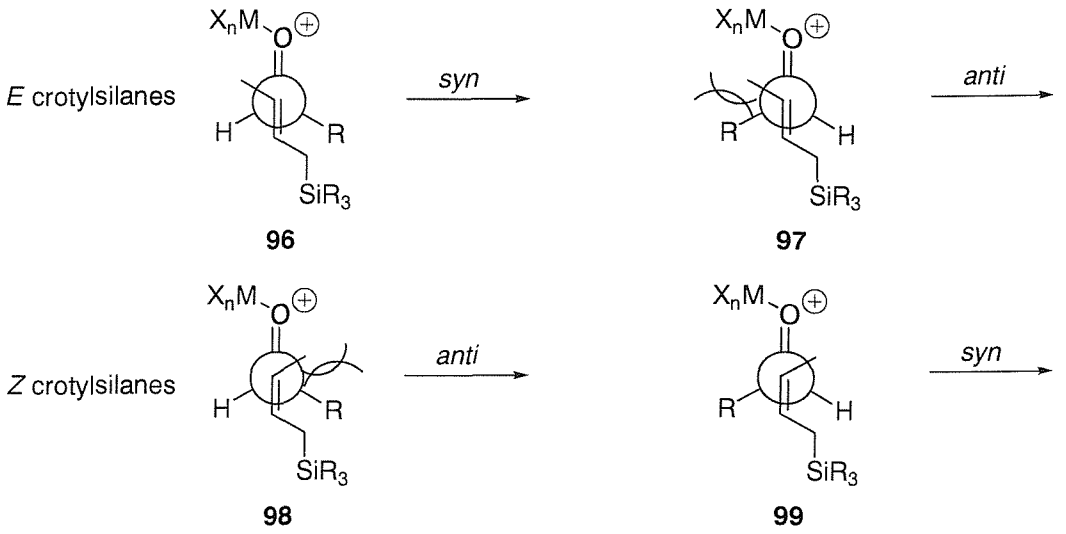
Scheme 27

The carbon-silicon bond is electron rich and can donate electron density to the adjacent positive charge, this often leads to elimination of the silicon group and thus transfer of the allyl group **92**.

When allyl silanes which are substituted on the C-3 carbon are employed in these addition reactions the outcome is selective for the formation of the *syn* isomer regardless of the geometry of the double bond, although better selectivity is observed with *E* crotyl silanes (Scheme 28).[63]

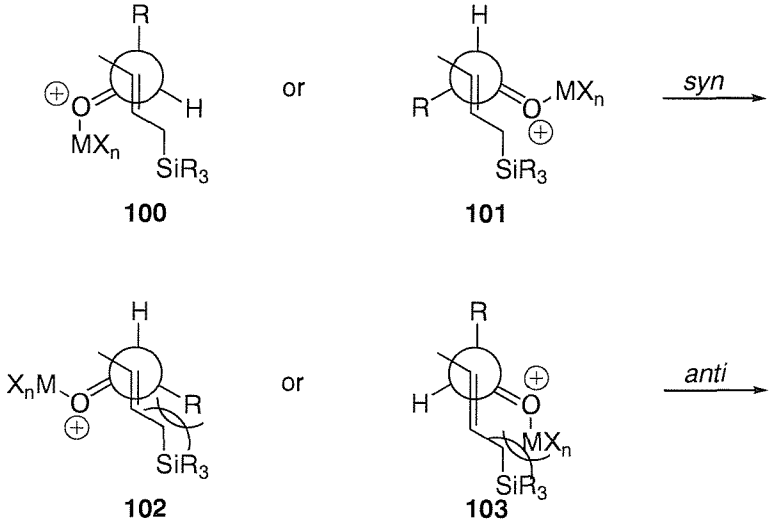
Scheme 28

The selectivity can be explained through an antiperiplanar transition state (Scheme 29) and synclinal transition states (Scheme 30 and Scheme 31).



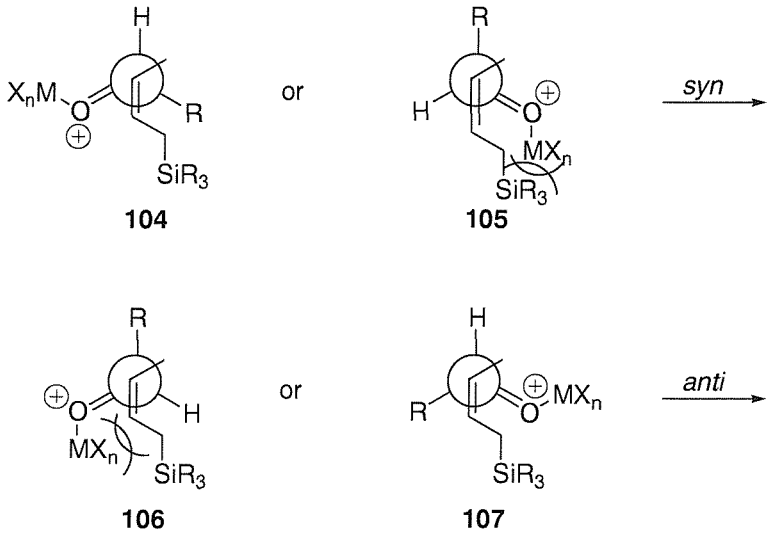
Scheme 29

For addition of the *E* crotyl silane, transition state **97** contains a steric clash between the methyl group and the aldehyde R group, whereas transition state **96** appears to be less sterically demanding and thus *syn* selectivity in preferred. For addition of *Z* crotyl silane the same argument also gives preference for the formation of the *syn* product. In addition a synclinal argument is in agreement with the formation of *syn* selectivity using *E* crotyl silanes (Scheme 30).



Scheme 30

Reactions with *Z* crotyl silanes are less selective and this is reflected in the synclinal argument (Scheme 31).



Scheme 31

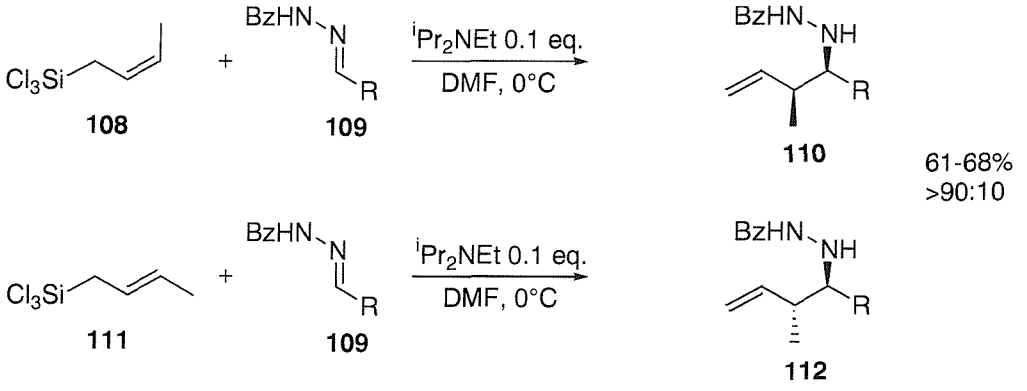
Only one of the transition states which gives rise to *syn* selectivity is favoured on steric grounds, **104**, with transition state **105** having a steric clash between the Lewis acid and the silicon. In transition state **107** there appears to be no unfavourable interactions between the Lewis acid and the crotyl silane thus favouring *anti* selectivity, whereas transition state **106** contains a steric clash between the Lewis acid and the silicon. Denmark *et al.*[65] reported that synclinal transition states could be favoured over antiperiplanar transition states due to secondary orbital interactions between the carbonyl and the crotyl silane, however many other interactions such as substituents on both reagents must also be taken into account.

In the past 10 years significant advances have been made in the field of allyl silane additions, including the use of chiral Lewis acids to promoted enantioselective additions[64] and the use of lanthanide triflates in catalytic quantities.[66,67] Unlike traditional Lewis acids ($TiCl_4$, $SnCl_4$ and $BF_3{\cdot}Et_2O$) which are generally used in stoichiometric quantities, lanthanide Lewis acids have the advantage that they form strong but labile bonds with oxygen donor ligands. These advances have made allyl silane additions to

aldehydes common place and the methodology is regularly utilized in the synthesis of natural products.

1.4.2 Allyl silane addition to imines

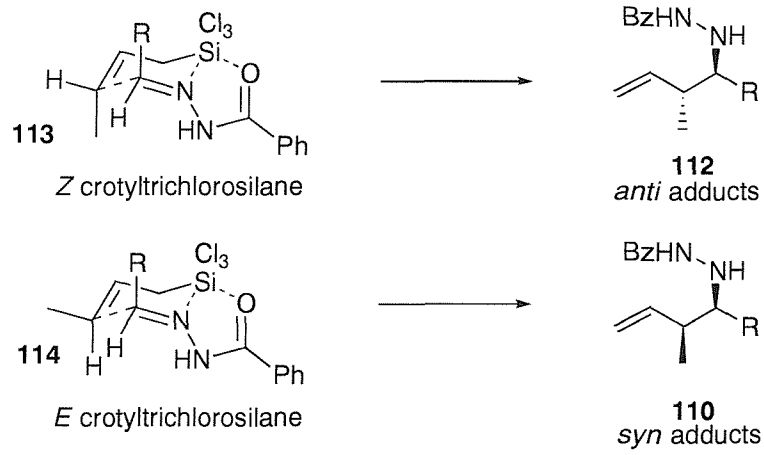
There are reports of Lewis acid promoted additions of allyl stannanes to imines,[64] however this method is less desirable than the equivalent reaction with allyl silanes due to the toxicity of tin. Allyl silane additions to imines can be problematic due to the low nucleophilicity of allyl silanes and the poor electrophilicity of imines. This problem can be overcome in additions to iminium ions and examples have been reported.[68,69] There are reports of Lewis acid promoted additions of allyl silanes to imines but these are generally specific examples.[70-73] In recent years allyltrichlorosilanes have been utilized in addition reactions with benzoylhydrazones in DMF giving excellent yields of homoallylic amines.[74,75] When crotyltrichlorosilanes **111** and **114** were used good stereoselectivity of the formed homoallylic amines was achieved. Both *syn* and *anti* isomers could be accessed selectively by using either *E* or *Z* crotyl silanes respectively. (Scheme 32).



Scheme 32

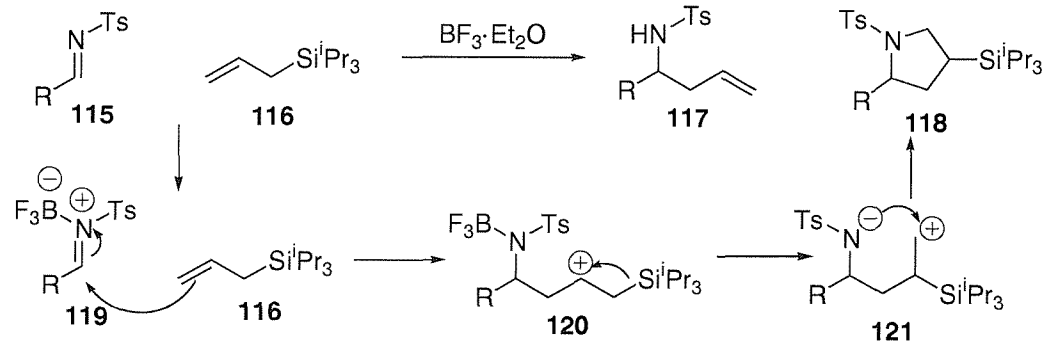
The stereochemical outcome was explained through a chair like transition state where both the imine nitrogen and the carbonyl are chelated to the silicon, and thus

constraining the system and controlling the stereochemistry (Scheme 33).[74] The chelation of the heteroatoms to silicon was enhanced by the fact the silicon is electron deficient due to the electronegative chlorines.



Scheme 33

Trisisopropylallylsilane **116** has been used in conjunction with tosyl imines in the formation of homoallylicamines **117** and pyrolidines **118** (Scheme 34).[76]

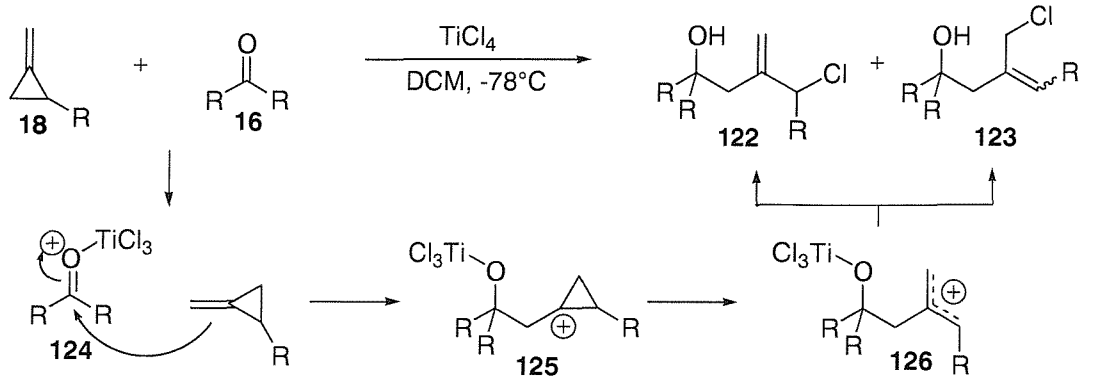


Scheme 34

Allyl silane **116** reacts with imine-BF_3 complex **119** to give β-silyl cation **120**. Elimination of the trisisopropyl group leads to amines **117**, whereas a 1,2-silyl shift can take place followed by quenching of the subsequent cation **121**, by nitrogen to furnish pyrolidines **118**.

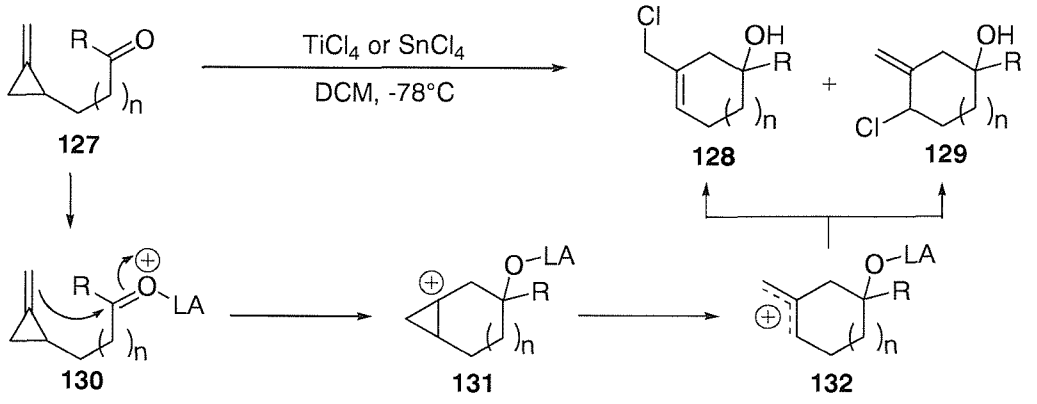
1.4.3 Lewis acids and methylenecyclopropane

Hosomi *et al.*[77] reported that methylenecyclopropane **1** can attack a carbonyl mediated by a Lewis acid, in this case $TiCl_4$ (Scheme 35).



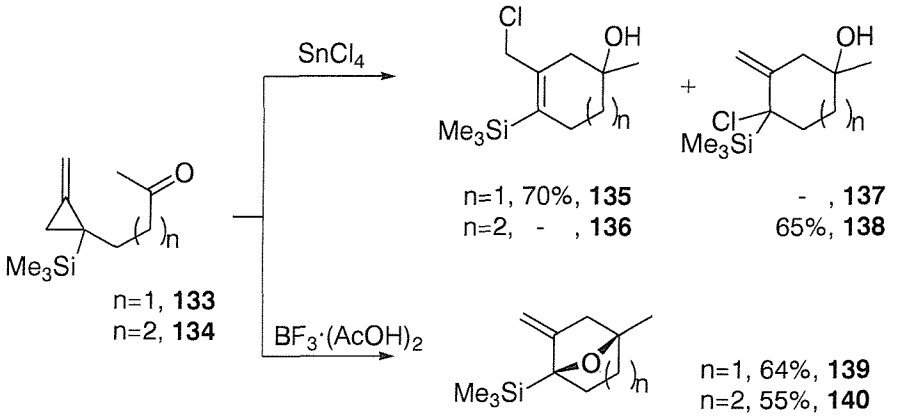
Scheme 35

Following Hosomi's proposed mechanism, $TiCl_4$ chelates to carbonyl **16** giving complex **124**. The olefin of methylenecyclopropane can then attack the carbonyl complex to give cyclopropyl cation **125**, which opens to form π-allyl cation **126**. This allylic cation can then be quenched by chloride to give chloroalkenols **122** and **123**. Hosomi noted that the best results were obtained when carbonyl **16** was an aldehyde and methylenecyclopropane was unsubstituted.



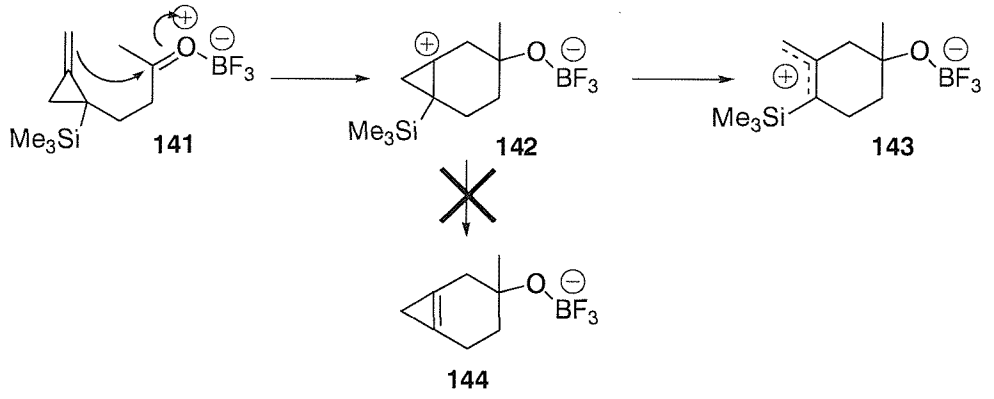
Scheme 36

Peron *et al.*[78] found that methylenecyclopropane would attack both ketones and aldehydes if the reaction was intramolecular to form six and seven membered rings (Scheme 36). The products formed were found to be consistent with Hosomi's proposed mechanism.



Scheme 37

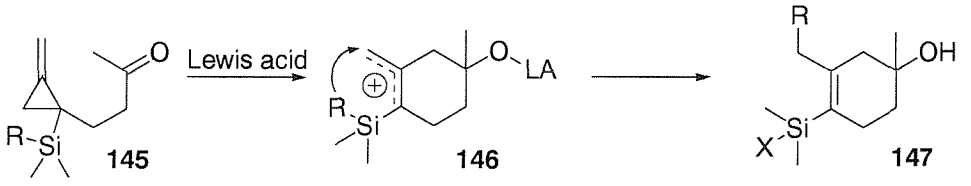
Peron *et al.*[79] reported that trimethylsilyl substituted precursors **133** and **134** cyclised to give higher yields of the desired chloroalkenols **135** and **138** (Scheme 37). In addition it was noted that Lewis acids such as $BF_3{\cdot}(AcOH)_2$ could be used to effect the cyclisation leading to intramolecular trapping of the π-allyl cation by the alkoxide furnishing bicyclic ethers **139** and **140** as the products.



Scheme 38

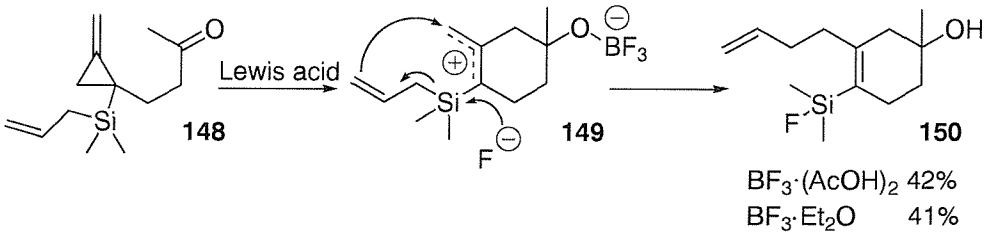
The incorporation of the trimethylsilyl group increases the nucleophilicity of the olefin, thus promoting the desired reaction. Silicon could stabilize β-positive charge **142** which usually leads to elimination of the silicon group **144**. However, in this case the rearrangement of cyclopropyl β-silyl cation **142** to allylic cation **143** proceeds much faster (Scheme 38). Allylic cation **143** is not stabilized by the silicon and trapping of allyl cation **143** is rapid.

Peron[80] also investigated the potential transfer of a group from the silicon to the allyl cation intermediate (Scheme 39).



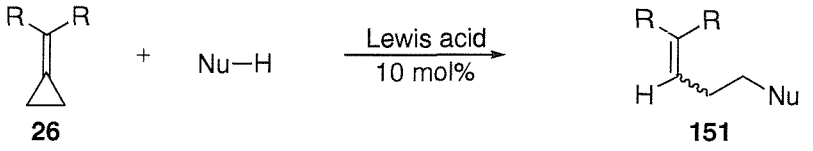
Scheme 39

Allyldimethylsilane **148** was treated with $BF_3{\cdot}(AcOH)_2$ or $BF_3{\cdot}Et_2O$ to give the desired allyl transfer product **150** in moderate yields (Scheme 40).



Scheme 40

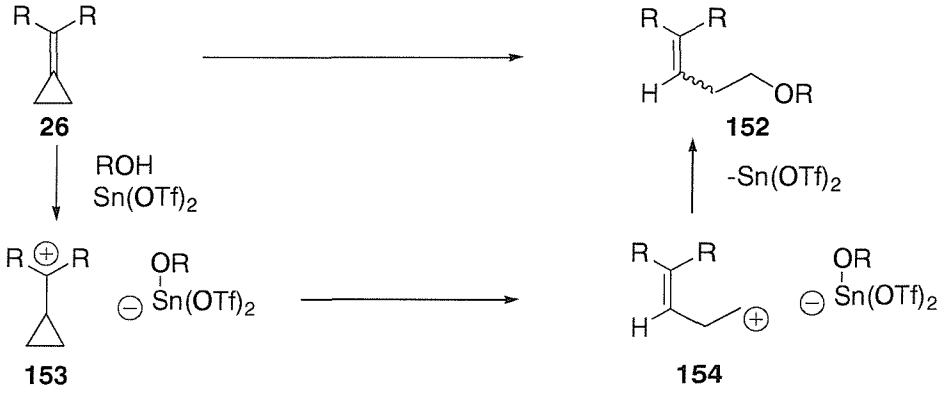
Shi *et al.*[81] reported the Lewis acid catalyzed ring-opening of alkylidenecyclopropanes **26** with alcoholic or acidic nucleophiles (Scheme 41).



26 **151**

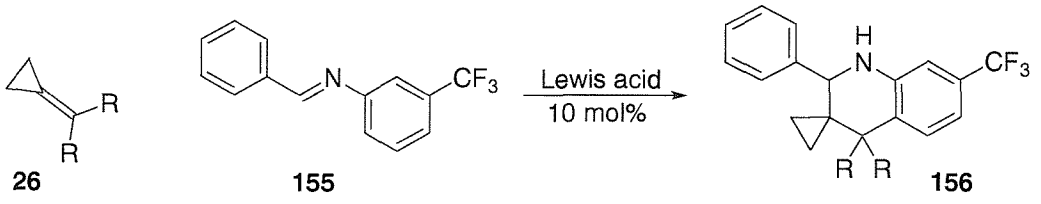
Scheme 41

10 mol% of $Sn(OTf)_2$ was found to be the best Lewis acid for the promotion of this reaction. Various alcohols, carboxylic acids, thiols and even water can act as a nucleophile in the opening of the cyclopropyl ring.



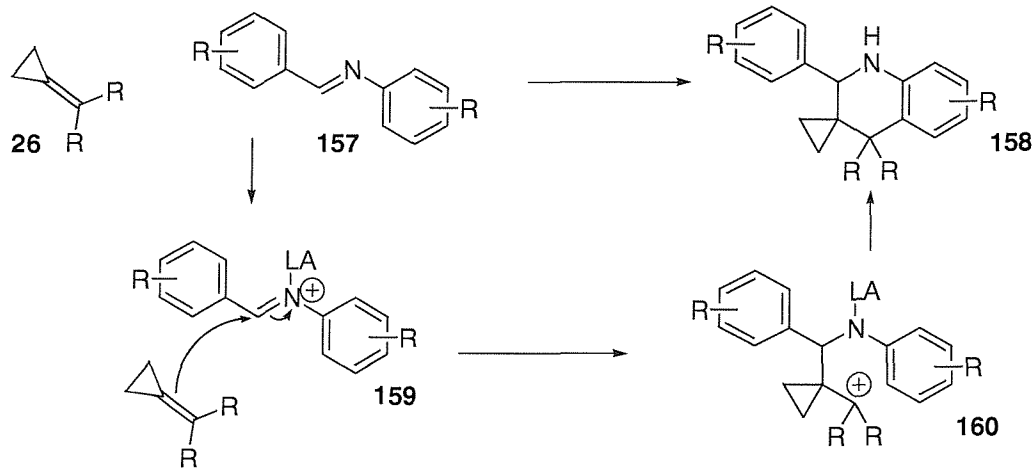
Scheme 42

A mechanism has been proposed for this reaction (Scheme 42). First the alcohol protonates alkylidenecyclopropane **26** in the presence of the Lewis acid giving cation **153**. Cation **153** then rearranges to cation **154** which followed by nucleophilic attack affords the observed products **152**. The tin triflate is consequently recycled to continue the catalytic cycle.



Scheme 43

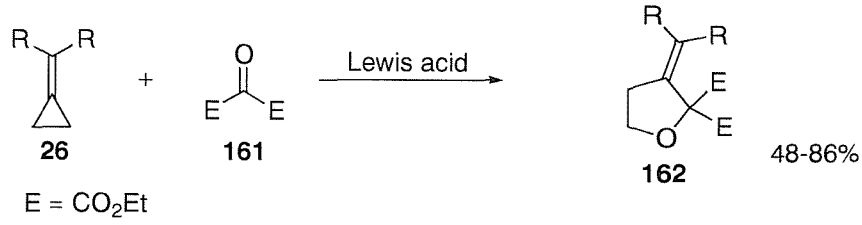
Shi *et al.*[82] furthered their research by reporting that di(*p*-methoxyphenyl) methylenecyclopropane and imine **155**, gave quantitative yields of **156** in an azaDiels-Alder reaction (Scheme 43). Quantative yields of **156** were obtained using 10 mol% of either $Yb(OTf)_3$, $Sc(OTf)_3$ or $Sn(OTf)_2$. The regioselectivity was explained by a non-concerted mechanism (Scheme 44).



Scheme 44

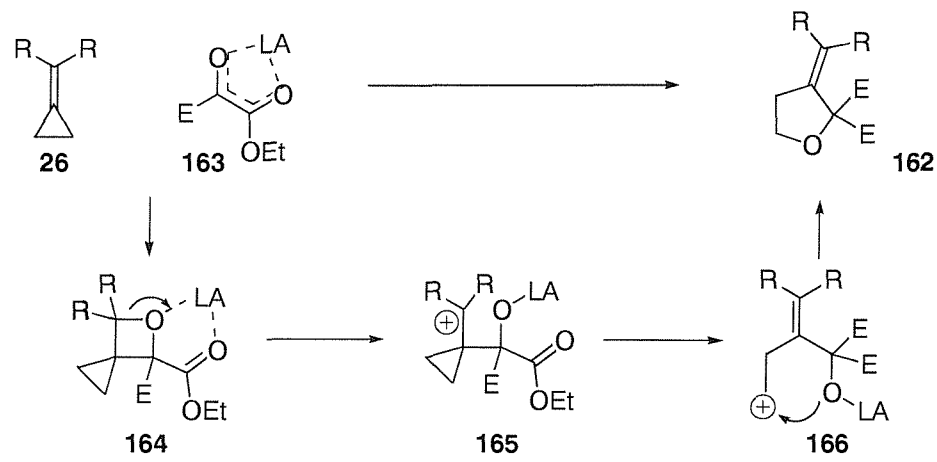
Alkylidenecyclopropane **26** reacts with Lewis acid-imine complex **159** through the cyclopropyl end of the olefin moiety promoted by the formation of the stabilized dibenzylic cation **160**. Intramolecular Friedel-Crafts reaction gives the azaDiels-Alder product **158**, rather than products from the rearrangement of the cyclopropyl methyl cation as seen previously (Scheme 42).

Shi *et al.*[83] recently reported a novel [3+2] cycloaddition of alkylidenecyclo-propanes with activated carbonyls **161** (Scheme 45).



Scheme 45

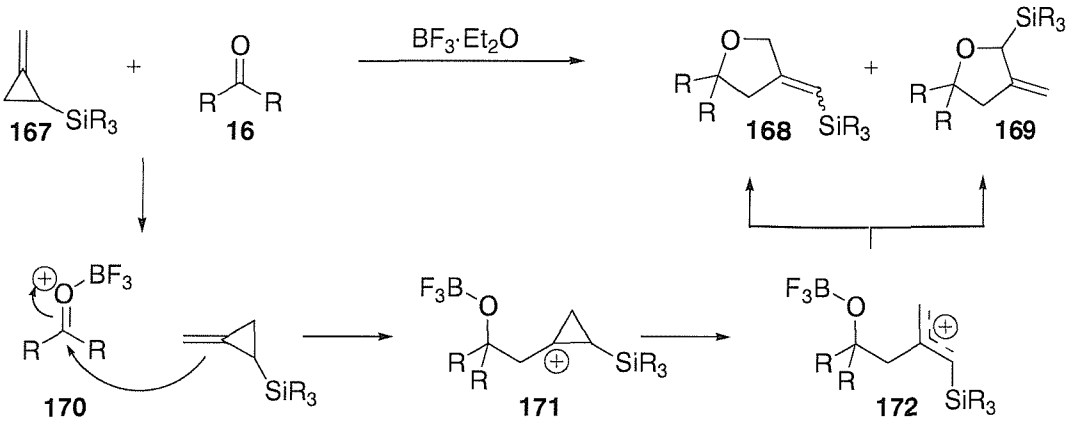
A mechanism has been proposed for this cycloaddition (Scheme 46). Alkylidene-cyclopropane **26** attacks the activated carbonyl mediated by a Lewis acid to give spirocycle **164**. Spirocycle **164** can then open to give stabilized cation **165** which in turn can rearrange to cation **166**. Cation **166** can then be quenched by oxygen to give tetrahydrofuran **162**.



Scheme 46

1.5 Program of work

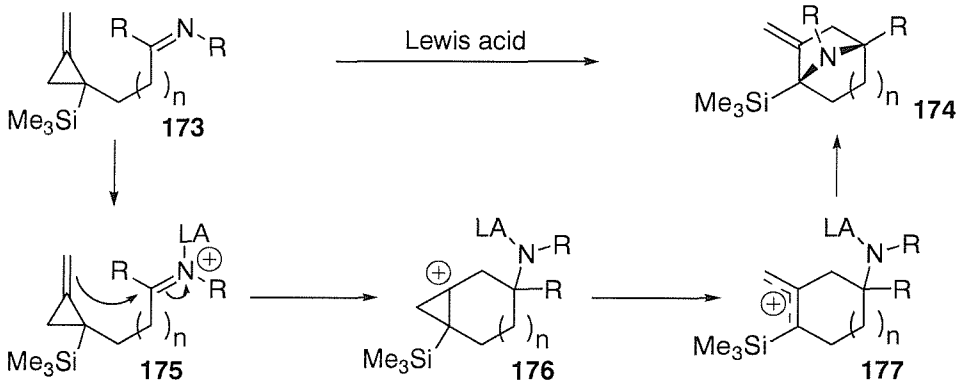
Due to the successful work carried out by Peron *et al.*[79] in cyclising methylenecyclopropylcarbonyls **133** and **134** to yield bicyclic ethers **139** and **140**, it was proposed that an intermolecular version of this reaction could provide a novel route to tetrahydrofurans. Peron reported that the addition of a silyl group enhanced the nucleophilicity of the olefin moiety of methylenecyclopropane so Lewis acids such as $BF_3{\cdot}Et_2O$ and $BF_3{\cdot}(AcOH)_2$ could be used to effect the cyclisation. Therefore the first objective of this project was to investigate whether silylmethylenecyclopropane **167** could react with carbonyls **16** in an intermolecular process to give tetrahydrofurans **168** and **169**, effectively a [3+2] cycloaddition (Scheme 47).



Scheme 47

Silylmethylenecyclopropane **167** should attack Lewis acid carbonyl complex **170** to give cyclopropyl cation **171**, which should open to π-allyl cation **172**. In the absence of a suitable external nucleophile intramolecular trapping of the π-allyl cation should give tetrahydrofurans **168** and **169** as the desired products.

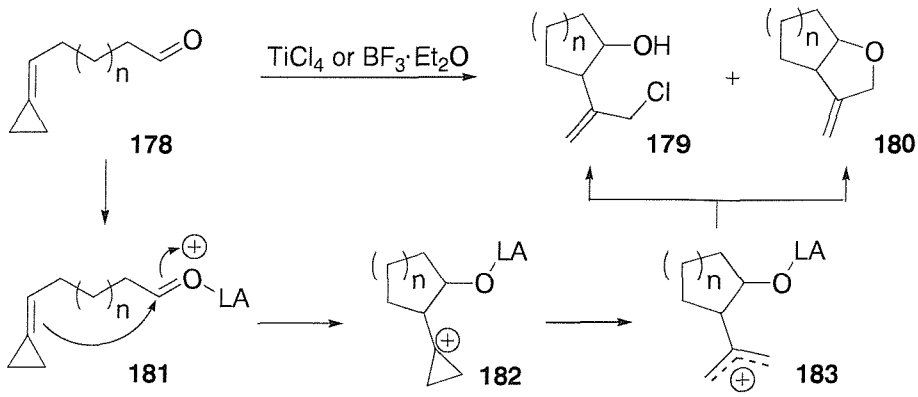
The second objective of this project was to study the cyclisation of methylenecyclopropylimines **173** to form azabicycles **174** (Scheme 48).



Scheme 48

Methylenecyclopropylimines **173** should cyclise to give cyclopropyl cation **176**, which was expected to open to π-allyl cation **177**. π-Allyl cation **177** could then be quenched in an intramolecular fashion by nitrogen to give azabicycle **174**.

Finally an investigation was made into the cyclisation of alkylidenecyclopropyl-carbonyls **178** to give chloroalkenols **179** and bicyclic ethers **180** (Scheme 49).



Scheme 49

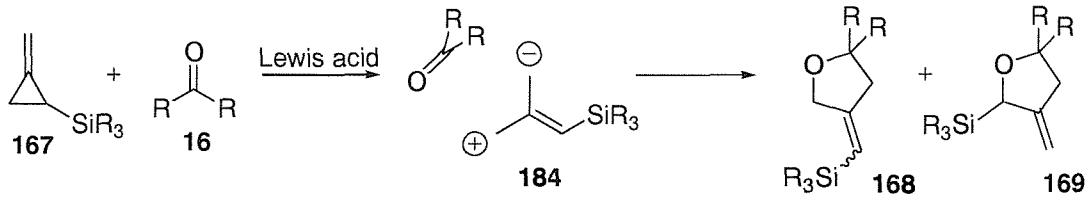
Alkylidenecyclopropanes **178** were expected to cyclise onto the carbonyl mediated by a Lewis acid to give cyclopropyl cation **182** which should open to allyl cation **183**. Cation **183** could then either be quenched by intermolecular addition of chloride or intramolecularly by the alkoxide to give **179** and **180** respectively.

Chapter 2

Intermolecular Additions of Silylmethylenecyclopropanes to Carbonyls

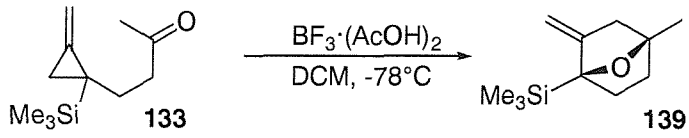
2.1 Introduction

The aim of this research was to investigate whether silylmethylenecyclopropanes **172** could be used as the "three-carbon" component in a [3+2] cycloaddition with aldehydes or ketones mediated by a Lewis acid (Scheme 50).



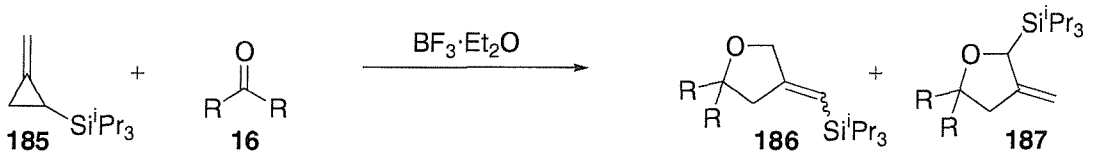
Scheme 50

Hosomi *et al.*[77] reported one example where trimethylsilylmethylenecyclopropane was used to attack an aldehyde mediated by $TiCl_4$ to give a chloroalkenol. Peron *et al.*[79] later reported that when methylenecyclopropane derivatives were substituted with a trimethylsilyl group (effectively an allylsilane), Lewis acids such as $BF_3{\cdot}Et_2O$ and $BF_3{\cdot}(AcOH)_2$ could be used to effect the cyclisation (Scheme 51). The use of these Lewis acids led to intramolecular trapping of the formed π-allyl cation by the alkoxide due to the absence of a suitable intermolecular nucleophile.



Scheme 51

Therefore, intermolecular addition of silylmethylenecyclopropane **185** to an aldehyde or ketone mediated by $BF_3 \cdot Et_2O$ or $BF_3 \cdot (AcOH)_2$ should give rise to tetrahydrofurans **186** and **187** (Scheme 52).

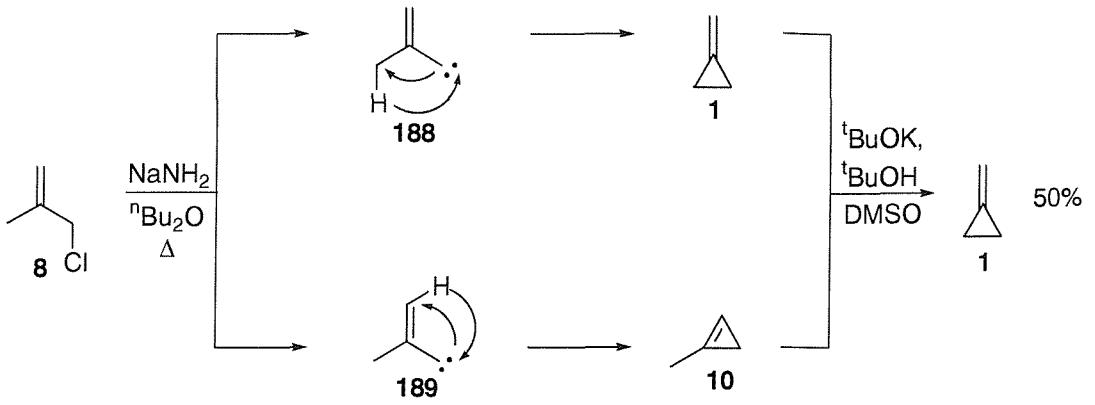


Scheme 52

Trisisopropylsilylmethylenecyclopropane **185** was chosen for initial studies of this reaction because it was found to be easily accessible and non-volatile, unlike trimethylsilylmethylenecyclopropane **20** that could not be easily isolated or utilized.

2.2 Synthesis of precursors

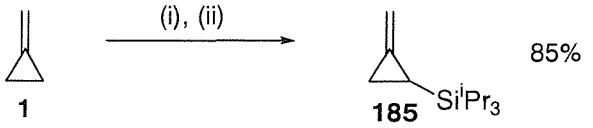
Methylenecyclopropane **1** was synthesized following a procedure reported by Köster *et al.*[12] involving treatment of methylallyl chloride **8** with sodium amide (Scheme 53).



Scheme 53

Sodium amide causes deprotonation α to the chlorine, which in turn leaves to give a carbene. The carbene can insert into either the methyl C-H **188** to give methylenecyclopropane **1** or into the methylene C-H **189** to give methylcyclopropene **10**. A 5:1 mixture of methylenecyclopropane **1** and methylcyclopropene **10** respectively was obtained, and treated with ^{t}BuOK and ^{t}BuOH in DMSO to furnish pure methylenecyclopropane **1** in 50% yield.

Methylenecyclopropane was deprotonated with ^{n}BuLi and then quenched with TIPSCl to give methylenecyclopropane derivative **185** in good 85% yield, following methodology described by Thomas[15] (Scheme 54).



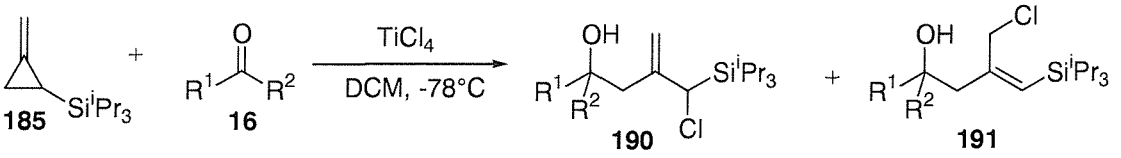
(i) ^{n}BuLi, THF, -78°C, (ii) $^{i}Pr_3SiCl$

Scheme 54

2.3 Cyclisation studies

2.3.1 Studies with $TiCl_4$

Initial studies were carried out using $TiCl_4$ as the Lewis acid to determine whether trisisopropylsilylmethylenecyclopropane **185** would react with aldehydes and ketones in the same fashion as Hosomi *et al.*[77] reported. $TiCl_4$ was added to a mixture of methylenecyclopropane derivative **185** with various aldehydes and ketones (Table 2).

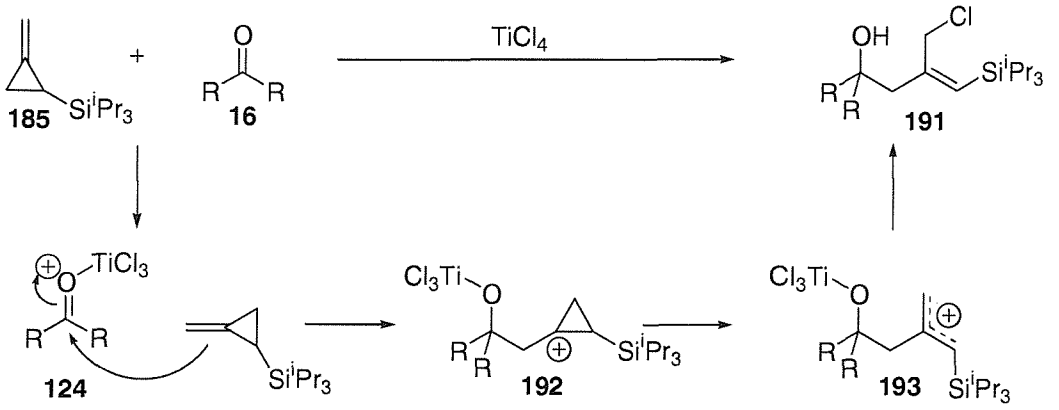


Scheme 55

Entry	R^1	R^2	Conditions	Yield / %	
				190	**191**
a	Ph	Ph	-78°C to RT, 48 hours	-	-
b	Et	Me	-78°C to RT, 48 hours	-	-
c	$-(CH_2)_5-$		-78°C, 3 hours	-	43
d	^{i}Pr	H	-78°C, 1 hour	-	53
e	*p*-O_2NAr	H	-78°C, 1 hour	-	64

Table 2 Reaction of methylenecyclopropane derivative **185** with aldehydes and ketones

No reaction was observed with benzophenone or butanone after 48 hours. The only ketone studied that reacted in the desired fashion was cyclohexanone, which gave **191c** as the only isolated product as a single diastereoisomer in 43% yield. *iso*-Butyraldehyde and *p*-nitrobenzaldehyde also both reacted to give **191d** and **191e** as the only isolated products as single diastereoisomers in 53% and 64% yield respectively.



Scheme 56

Following the proposed mechanism of Hosomi *et al.*[77] the olefin moiety of **185** reacts with Lewis acid-carbonyl complex **124** to give cyclopropyl cation **192**. Cyclopropyl cation **192** rearranges to give π-allyl cation **193**, which is quenched by chloride to give chloroalkenol **191**.

The stereochemistry of **191c** and **191d** was proved by GOESY studies (Figure 4).

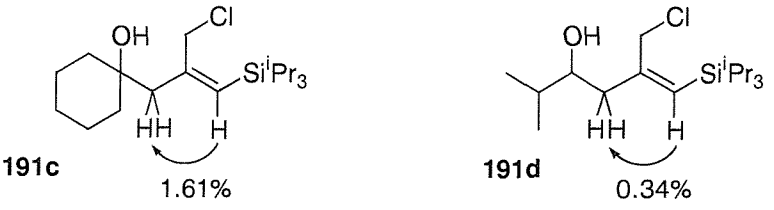


Figure 4 GOESY studies of **191c** and **191d**

In both cases, **191c** and **191d**, the alkene proton was irradiated and each gave enhancement of 1.61% and 0.34% respectively to the methylene adjacent to the alcohol and no enhancement to the chloromethylene group.

The stereochemistry of **191e** was proved by X-ray crystallography (Figure 5).

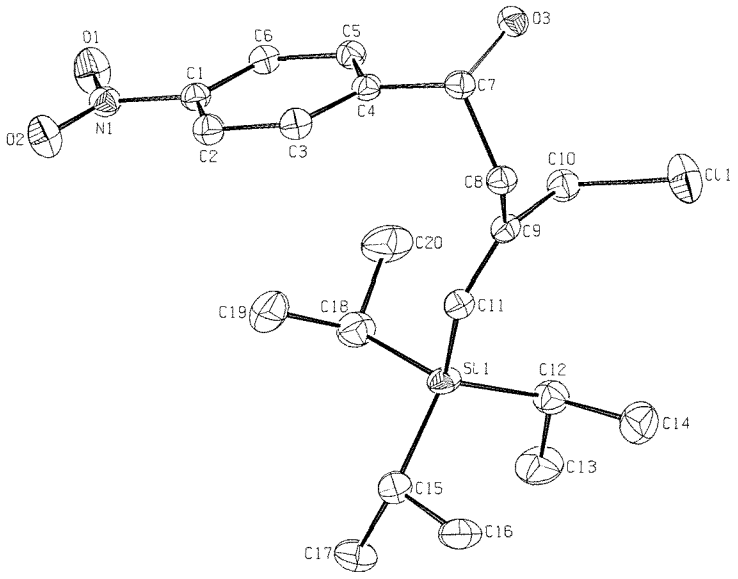


Figure 5 X-ray crystal structure of **191e** (see appendix)

The formation of **191** as the only product as a single isomer could simply be the large steric bulk of the trisisopropylsilyl group preventing chloride addition α to the silyl group **195**. The selective formation of the *Z* isomer of **191c-e** could also be explained by a steric argument since the alkyl chain and the trisisopropylsilyl group presumably prefer a *trans* relationship as in **195** which is less sterically demanding than **194** (Figure 6).

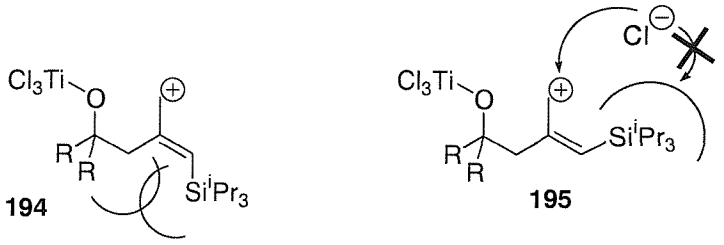
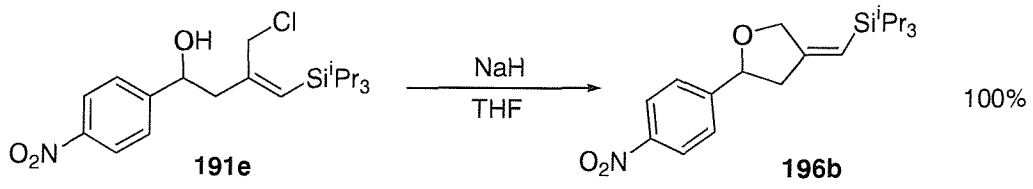


Figure 6 Possible geometries of allylcation **193**

Chloroalkenol **191e** was treated with sodium hydride in THF and gave tetrahydrofuran **196b** in quantitative yield, thus providing an efficient route to such tetrahydrofurans (Scheme 57).

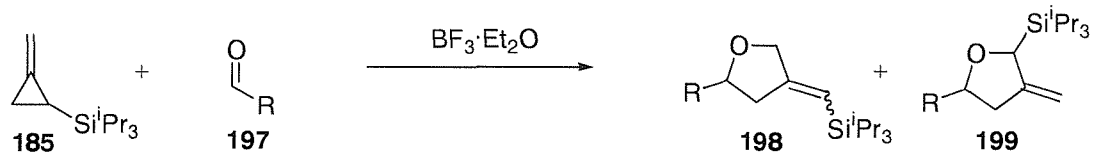


191e **196b**

Scheme 57

2.3.2 Studies with $BF_3{\cdot}Et_2O$

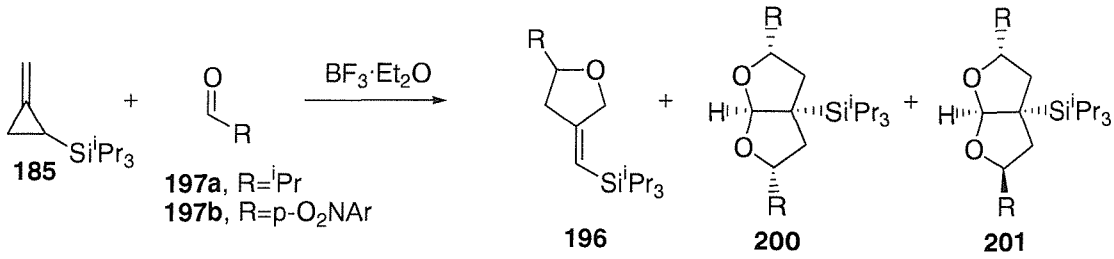
It was hoped that using $BF_3{\cdot}Et_2O$ or $BF_3{\cdot}(AcOH)_2$ as Lewis acids to promote the reaction of methylenecyclopropane derivative **185** with aldehydes would allow the allyl cation to be trapped in an intramolecular fashion by the alkoxide to give tetrahydrofurans **198** and **199** directly (Scheme 58).



185 **197** **198** **199**

Scheme 58

This reaction was investigated initially using aliphatic aldehyde **197a** and aromatic aldehyde **197b** (Scheme 59). Reactions attempted with $BF_3{\cdot}(AcOH)_2$ as the Lewis acid led to decomposition of the starting materials as the reaction was allowed to warm to room temperature from -78°C.

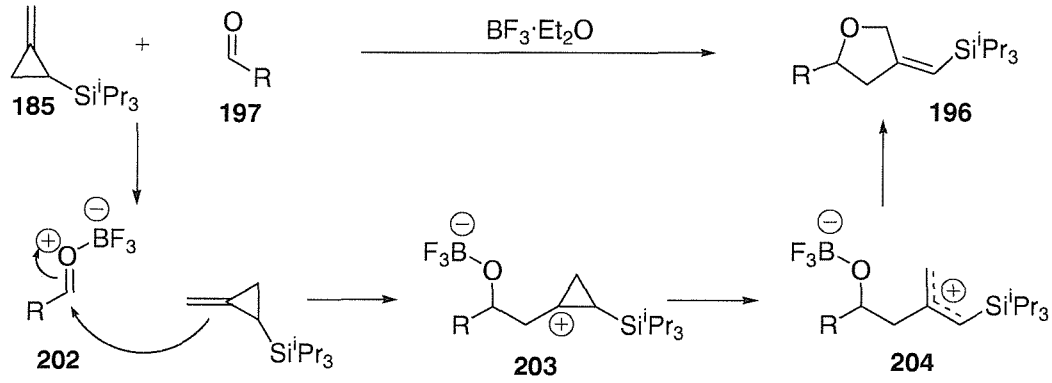


Scheme 59

Entry	R	Solvent	Conditions	Yield / %		
				196	**200**	**201**
a	^{i}Pr	DCM	0°C to RT, 3 hours	30	14	15
b	*p*-O_2NAr	DCM	-78°C to 0°C, 4 hours	32	18	8
c	^{i}Pr	$EtNO_2$	0°C to RT, 4 hours	26	13	13
d	*p*-O_2NAr	$EtNO_2$	-78°C to 0°C, 4 hours	29	16	8

Table 3 Reaction of methylenecyclopropane derivative **185** with aldehydes **197**

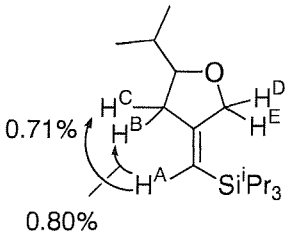
When the reaction was carried out using $BF_3{\cdot}Et_2O$ however, with either *p*-nitrobenzaldehyde or *iso*-butyraldehyde, three products were formed cleanly. The expected tetrahydrofurans **196** and two furofuran isomers **200** and **201**. Tetrahydrofurans **196** were formed following the expected mechanism (Scheme 60).



Scheme 60

Methylenecyclopropane derivative **185** reacts with BF_3-carbonyl complex **202** to give cyclopropyl cation **203** that rearranges to π-allyl cation **204**. Cation **204** is then quenched in an intramolecular fashion by the alkoxide affording tetrahydrofurans **196**.

The stereochemistry of **196a** was proved by GOESY studies (Figure 7).



196a

Figure 7 GOESY studies of **196a**

Irradiation of alkene H^A led to an enhancement of 0.80% and 0.71% of H^B and H^C respectively and no enhancement of H^D or H^E.

The stereochemistry of **196b** was proved by X-ray crystallography (Figure 8).

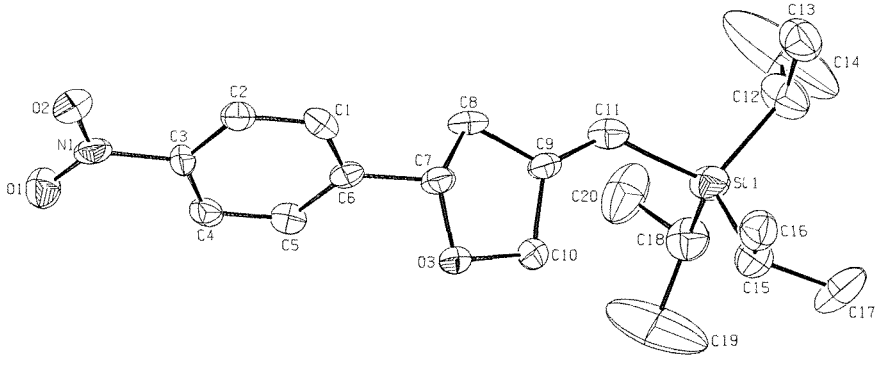
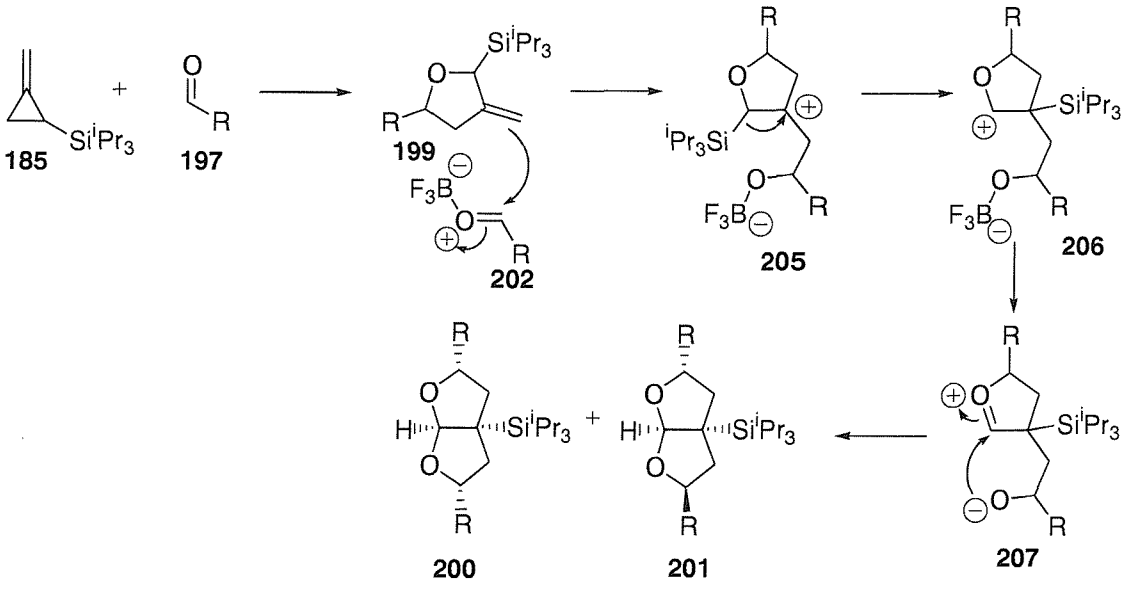


Figure 8 X-ray crystal structure of **196b**[84]



Scheme 61

The formation of furofurans **200** and **201** also follows the proposed mechanism to give tetrahydrofuran **199** as expected (Scheme 61). However, tetrahydrofuran **199** also contains an allylsilane moiety and can react with a second equivalent of BF_3-carbonyl complex **202** to give β-silyl cation **205**. A 1,2-silyl shift can then occur to give cation **206** which is stabilized by the adjacent oxygen to give oxonium ion **207** and then quenched in an intramolecular fashion by the alkoxide to give furofurans **200** and **201**.

The stereochemistry of **200b** and **201b** was proved by X-ray crystallography (Figure 9 **200b** and Figure 10 **201b**).

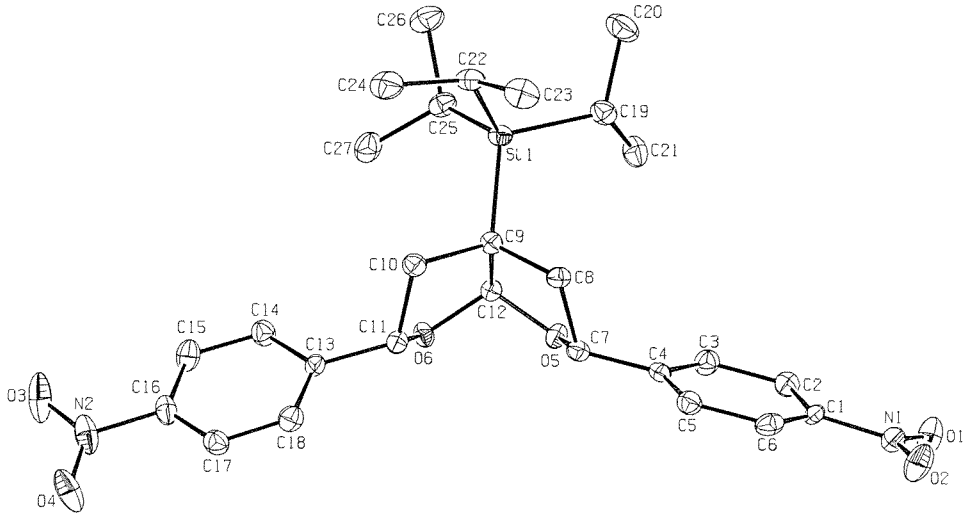


Figure 9 X-ray crystal structure of **200b**[85]

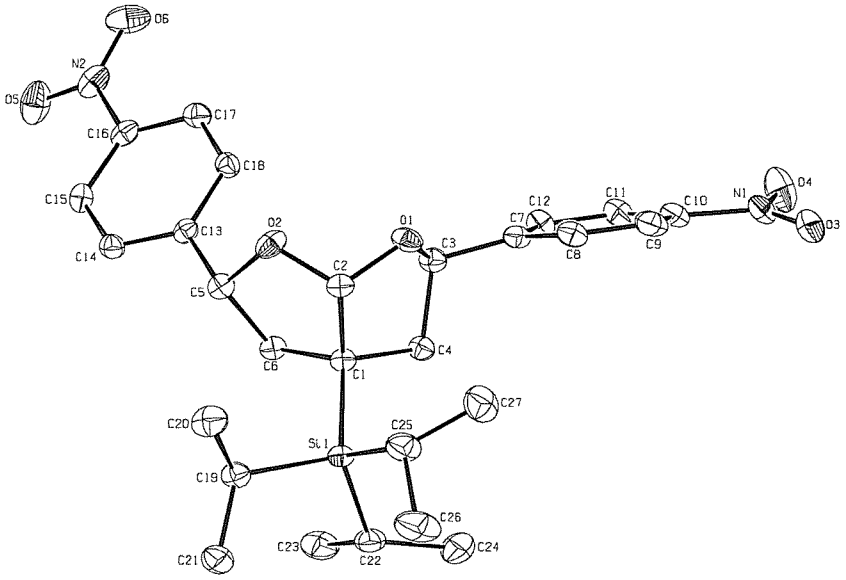


Figure 10 X-ray crystal structure of **201b**[86]

The stereochemistry of **200a** and **201a** was proved by comparison of NMR spectra with those of **200b** and **201b**.

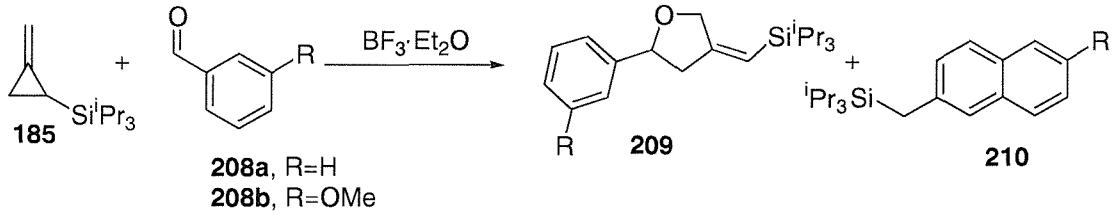
The fact that the formation of furofurans **200** and **201** required two equivalents of aldehyde led to the reactions being repeated using two equivalents of aldehyde (Table 4).

Entry	R	Solvent	Conditions	Yield / %		
				196	**200**	**201**
a	^{i}Pr	DCM	0°C to RT, 3 hours	41	14	28
b	*p*-O_2NAr	DCM	-70°C to -20°C, 2 hours	44	29	16
c	^{i}Pr	$EtNO_2$	0°C to RT, 4 hours	28	12	24
d	*p*-O_2NAr	$EtNO_2$	-70°C to 0°C, 4 hours	40	26	12

Table 4 Reaction of methylenecyclopropane derivative **185** with 2 eq. of aldehydes **197**

Using two equivalents of aldehydes **197** provided tetrahydrofurans **196** and furofurans **200** and **201** in greater yields. Overall yields were between 64 and 89% providing a good mass balance.

Two other aromatic aldehydes **208** were used to investigate this reaction with differing results (Scheme 62).

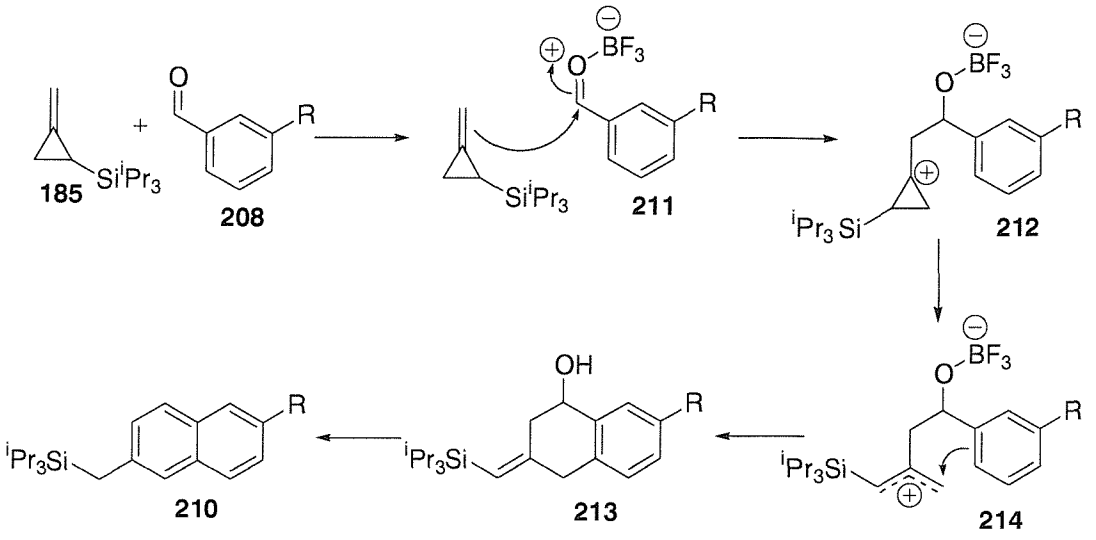


Scheme 62

Entry	R	Solvent	Conditions	Yield / %	
				209	**210**
a	H	DCM	0°C to RT, 4 hours	47	21
b	OMe	DCM	0°C to RT, 2 hours	30	10
c	H	$EtNO_2$	0°C to RT, 4 hours	40	28
d	OMe	$EtNO_2$	0°C to RT, 2 hours	18	16

Table 5 Reaction of methylenecyclopropane derivative **185** with aromatic aldehydes **208**

The formation of tetrahydrofuran **209** followed the same mechanism as before, however, no furofurans were isolated and instead naphthalenes **210** were isolated. The formation of naphthalenes **210** was rationalized by the following mechanism (Scheme 63).



Scheme 63

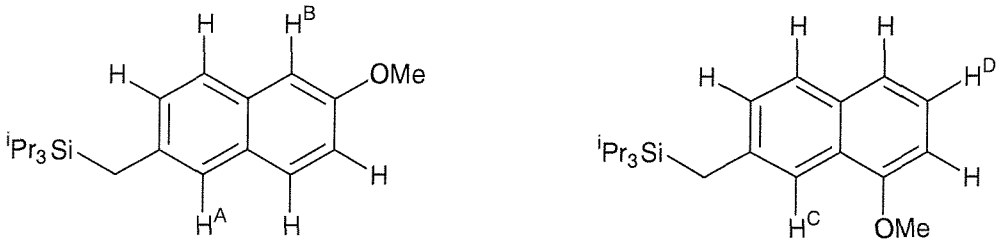
The olefin moiety of **185** reacts with aromatic BF_3-carbonyl complex **211** to give cyclopropylcation **212**, which rearranges to π-allyl cation **214**. Instead of π-allyl cation **214** being quenched by the alkoxide, it can be quenched by the aromatic ring, which can then rearomatize to **213**. It is then easy to envisage dehydration and isomerisation of alcohol **213** to furnish the fully aromatic naphthalene **210**.

Two regioisomeric products of naphthalene **210b** were possible, only one of which was isolated. The formation of **210b** as the only regioisomer could simply be the steric repulsion of the methoxy group and the π-allyl cation favouring *para* substitution relative to the methoxy group.

It was hoped that *m*-methoxybenzaldehyde **208b** would give greater preference to the formation of naphthalene **210b** over that of tetrahydrofuran **209b**, due to the electron donating effect of the methoxy substituent on the aromatic ring. This was found not to be the case, and in fact the yields of methyloxynaphthalene **210b** were found to be lower

that those of naphthalene **210a**. When the reaction was carried out in DCM the ratio of tetrahydrofuran **209b** to naphthalene **210b** was found to be similar to that of tetrahydrofuran **209a** to naphthalene **210a**. However, when the reaction was carried out in $EtNO_2$ the formation of naphthalene **210b** slightly increased relative to that of tetrahydrofuran **209b**.

The stereochemistry of **210b** was elucidated by ^1H NMR coupling patterns (Figure 11).



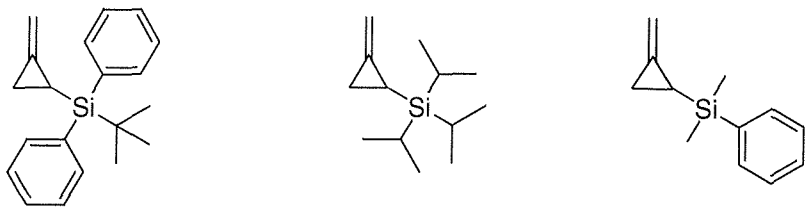
210b **215**

Figure 11 Elucidation of the stereochemistry of **210b**

The ^1H NMR spectrum contains two broad singlets at 7.46 and 7.09 ppm which correspond to protons H^A and H^B. Naphthalene **215** should only contain one singlet corresponding to H^C in the aromatic region. H^D should be a triplet or double doublet with similar coupling constants, however, this coupling pattern was not observed in the ^1H NMR spectrum.

2.4 Other silyl groups

The effect of the substituents of the silyl group were investigated using TBDPS methylenecyclopropane **216** and DMPS methylenecyclopropane **217**. These groups were chosen on the basis of size relative to TIPS methylenecyclopropane **185**, one larger group and one smaller group (Figure 12).

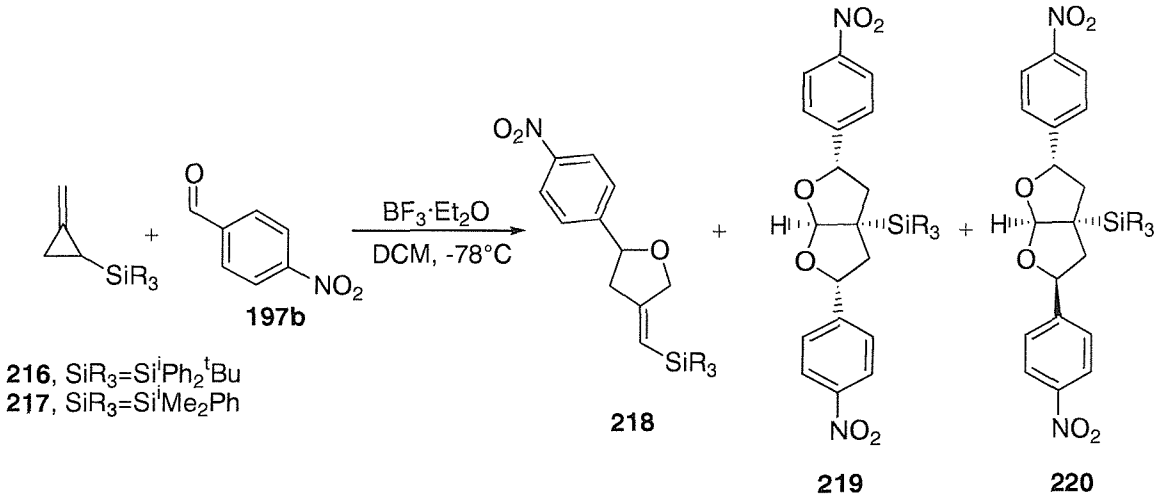


216 **185** **217**

Figure 12 Methylenecyclopropane derivatives **216**, **185** and **217**

The TBDPS and DMPS substituted methylenecyclopropanes **216** and **217** were synthesized in the same manner as TIPS methylenecyclopropane **185** (Scheme 54).[15] TBDPS precursor **216** was only isolated in poor 14% yield, probably due to the large steric bulk of the silyl group hindering the substitution, however enough material was isolated to carry out the investigation. DMPS methylenecyclopropane **217** was synthesized in good 78% yield.

Cyclisations were only carried out with two equivalents of *p*-nitrobenzaldehyde in DCM with $BF_3{\cdot}Et_2O$ as the Lewis acid, because these conditions had given the best overall yields previously (Scheme 64).



Scheme 64

Entry	SiR_3	Conditions	Yield / %		
			218	**219**	**220**
a	$SiPh_2{}^tBu$	-78°C to RT, 4 hours	33	-	20
b	$SiMe_2Ph$	-78°C to 0°C, 3 hours	28	25	-

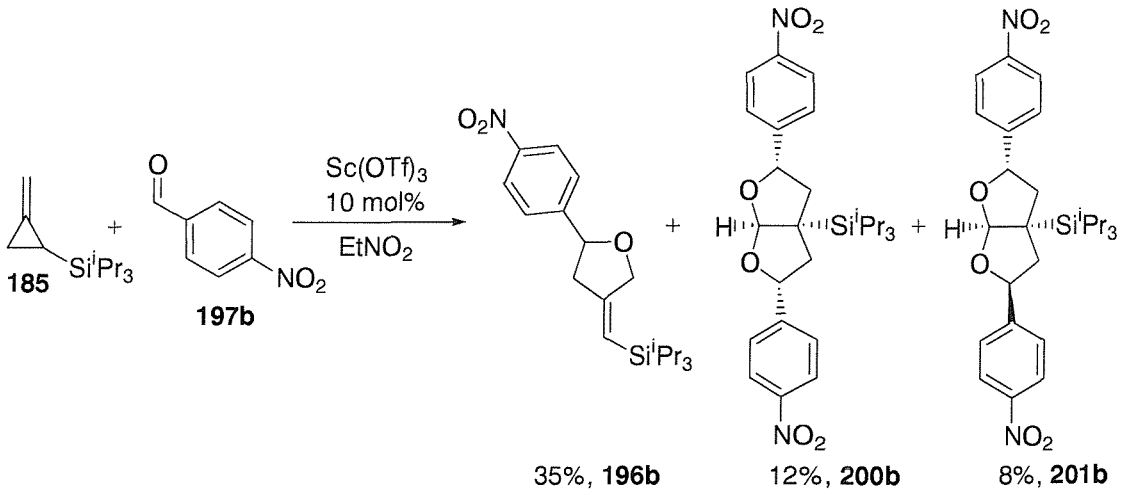
Methylenecyclopropane derivative **185** gave tetrahydrofuran **197b**, 44% and furofurans **200b**, 29% and **201b**, 16%

Table 6 Reaction of methylenecyclopropane derivatives **216** and **217** with aldehyde **197b**

Overall yields of cyclised products using methylenecyclopropyl derivatives **216** or **217** with aldehyde **197b** are lower than for derivative **185**. However, there appears to be some selectivity as to which furofuran isomer is formed and in the case of DMPS precursor **216**, tetrahydrofuran **218b** was formed as a mixture of isomers (5:1 *Z*:*E*). This was attributed to the relatively small steric bulk of the DMPS group having less effect on the stereochemical outcome in comparison with TIPS and TBDPS. Furofuran **219b** was isolated as a single diastereoisomer from reaction of DMPS precursor **216** with aldehyde **197b**, whereas reaction of precursor TBDPS **217** gave only furofuran **220a**. There appeared to be no simple explanation for the stereoselectivity for the formation of furofuran **220a** over furofuran **219a** or for the formation of furofuran **219b** over furofuran **220b**. It may be of some use to know the stereochemistry of the intermediate tetrahydrofuran **199** but this was not isolated on any occasion.

2.5 Other Lewis acids

The effect of using two other Lewis acids was investigated. $Yb(OTf)_3$[67] and $Sc(OTf)_3$[66] were chosen and used in catalytic quantities to promote the cyclisation. Only $Sc(OTf)_3$ in $EtNO_2$ reacted in the desired fashion; there was no observed reaction with $Yb(OTf)_3$ in either DCM or $EtNO_2$ (Scheme 65).



Scheme 65

The cyclisation was successful and gave a similar distribution of products but gave the desired products in lower yields than cyclisation using stoichiometric Lewis acids.

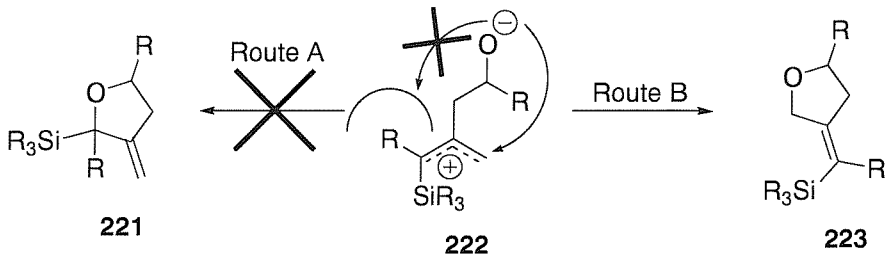
2.6 Disubstituted methylenecyclopropanes

Following the successful work carried out with silyl substituted methylene-cyclopropanes and aldehydes to give tetrahydrofurans and furofurans, the effect on the cyclisation of additional substituents on the silylated methylenecyclopropane was investigated. It was decided that 1,1- and 1,2-disubstituted methylenecyclopropanes would be investigated.

2.6.1 1,1-Disubstituted methylenecyclopropanes

It was hoped that the increased steric hindrance provided by a 1,1-disubstituted methylenecyclopropane would inhibit cyclisation by route A, and thus formation of

tetrahydrofuran **221** and would lead to predominantly tetrahydrofuran **223** *via* route B (Scheme 66).



221 **222** **223**

Scheme 66

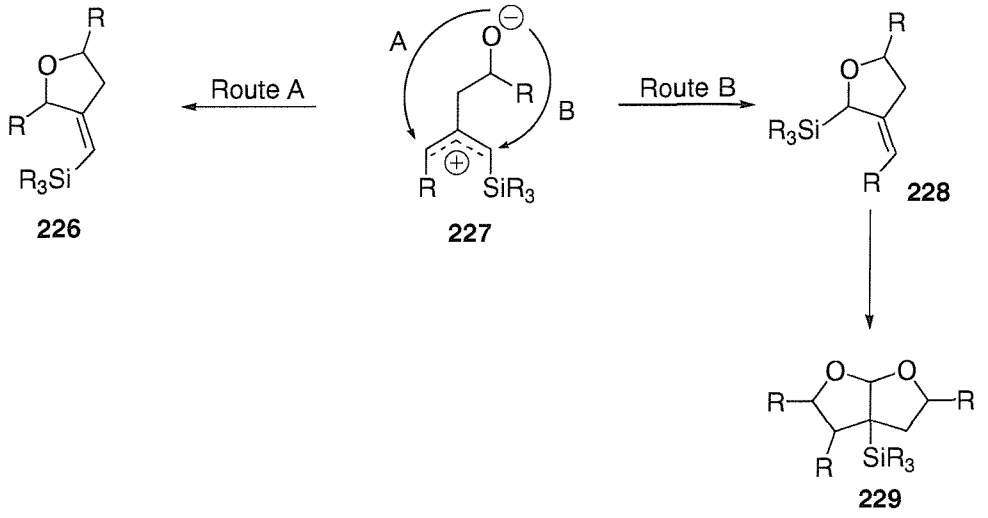
Two precursors were chosen for the study, **224** and **225** (Figure 13). One relatively small (Pr) and one slightly larger (Bn) to investigate what effect if any this would have on the cyclisation.

224 **225**

Figure 13 1,1-Disubstituted methylenecyclopropanes **224** and **225**

2.6.2 1,2-Disubstituted methylenecyclopropanes

By using a 1,2-disubstituted methylenecyclopropane, it was hoped that additional steric hindrance on the alkyl substituted end of allyl cation **227** would suppress cyclisation *via* route A and thus might enhance the yield of furofurans **229** (Scheme 67).



Scheme 67

Only one precursor was chosen for this study **230** (Figure 14).

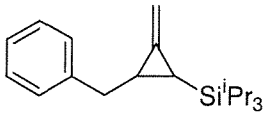
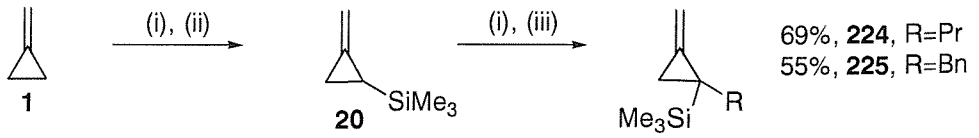


Figure 14 1,2-Disubstituted methylenecyclopropane **230**

2.7 Synthesis of precursors

2.7.1 Synthesis of 1,1-disubstituted methylenecyclopropanes

The synthesis of the 1,1-disubstituted precursors was carried out following a method described by Sternberg *et al.*[16] (Scheme 68).



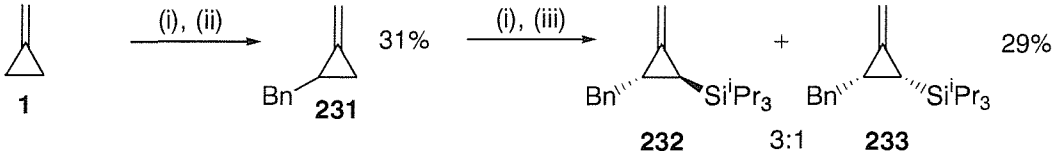
(i) ^{n}BuLi, THF, -78°C
(ii) Me_3SiCl
(iii) RX

Scheme 68

Methylenecyclopropane **1** was treated with ^{n}BuLi and the subsequent anion quenched with TMSCl to give **20**. A second equivalent of ^{n}BuLi was added followed by either iodopropane to give **224** or benzyl bromide to give **225** in 69% and 55% yields respectively.

2.7.2 Synthesis of 1,2-disubstituted methylenecyclopropanes

Synthesis of 1,2-disubstituted precursor **230** was carried out following a method described by Destabel *et al.*[54] (Scheme 69).



(i) ^{n}BuLi, THF, -78°C
(ii) BnBr
(iii) $^{i}Pr_3SiCl$

Scheme 69

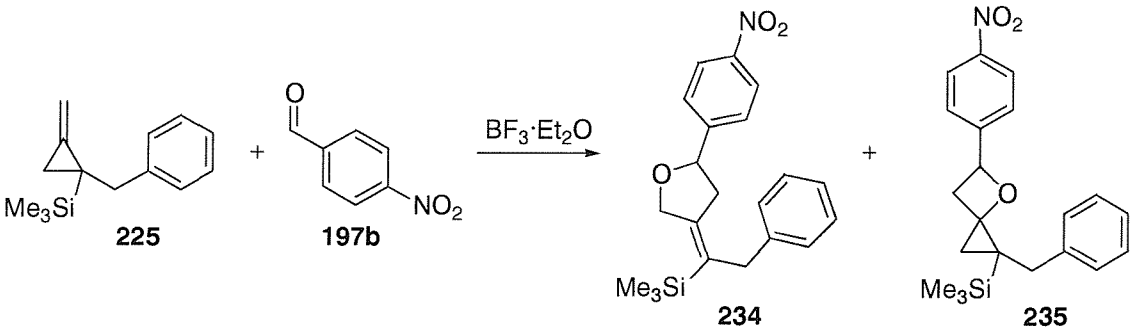
Methylenecyclopropane **1** was treated with ^{n}BuLi then quenched with benzyl bromide to yield **231** in moderate 31% yield. Benzyl methylenecyclopropane **231** was then treated with ^{n}BuLi and quenched with TIPSCl to give **232** and **233** as a 3:1 inseparable mixture of isomers (*trans* was assumed to be the major product based on steric arguments).

With the precursors in hand reactions with *p*-nitrobenzaldehyde using $BF_3{\cdot}Et_2O$ in two different solvents, DCM and $EtNO_2$, were studied since these conditions gave the best results using methylenecyclopropane derivative **185** as described earlier (chapter 2, section 2.3).

2.8 Cyclisation studies with 1,1-disubstituted precursors

2.8.1 Cyclisation studies with benzyl precursor 225

Cyclisation of benzyl substituted methylenecyclopropane **225** with *p*-nitrobenzaldehyde gave the expected tetrahydrofuran **234** and spirocycle **235** as isolated products (Scheme 70).



	234	235
DCM	18%	6%
$EtNO_2$	16%	12%

Scheme 70

The yields shown were the highest isolated yields obtained from the numerous attempts to optimise this reaction. Tetrahydrofuran **234** was formed as a single diastereoisomer, but the stereochemistry of spirocycle **235** could not be determined due to the instability of the compound.

The stereochemistry of tetrahydrofuran **234** was determined by GOESY studies (Figure 15).

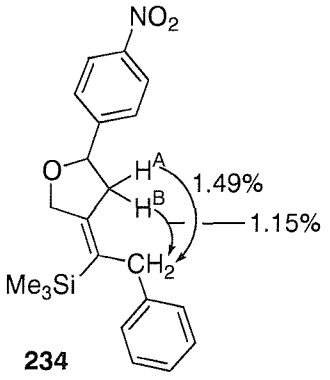
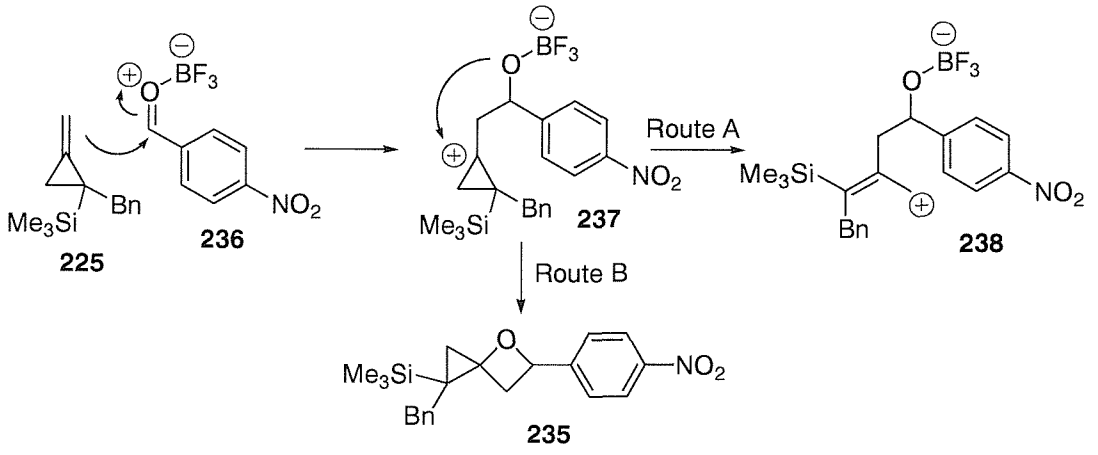


Figure 15 GOESY studies of **234**

Irradiation of H^A and H^B led to a 1.49% and 1.15% enhancement respectively of benzylmethylene CH_2.

The formation of spirocycle **235** presumably arises from addition of methylenecyclopropane derivative **225** to BF_3-carbonyl complex **236** to give cyclopropyl cation **237** (Scheme 71). Opening of cyclopropyl cation **237** would give rise to the formation of a tetra-substituted double bond **238**, route A. The formation of the π-allyl cation must be inhibited sufficiently so that the relatively slow formation of a 4-membered ring competes to give 3,4-spirocycle **235**, route **B**. This result is surprising since cyclopropyl cation rearrangement is known to be very rapid,[87] but the isolation of **235** usefully confirms the intermediacy of the cyclopropyl cation as part of the reaction mechanism.

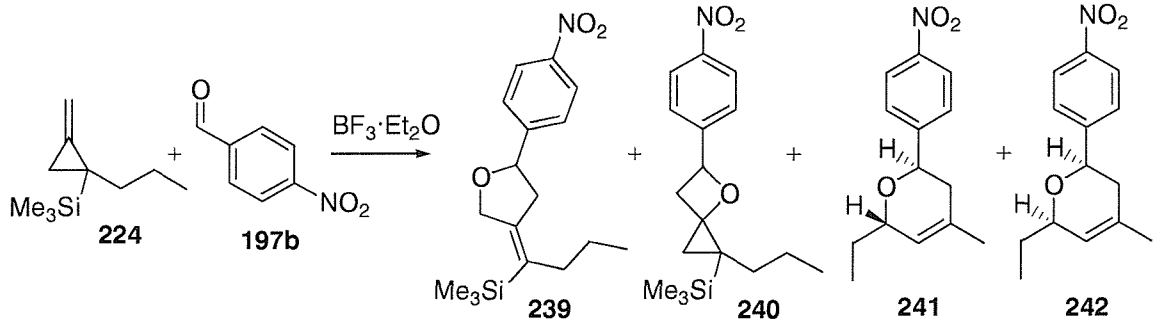


Scheme 71

The overall isolated yields of this reaction were poor, however TLC of the reaction mixture indicated that the reaction was much cleaner and higher yielding than the isolated yields suggest. Both tetrahydrofuran **234** and spirocycle **235** were unstable and it was possible that they decomposed on work-up and/or purification leaving only small quantities as isolated product.

2.8.2 Cyclisation studies with propyi precursor 224

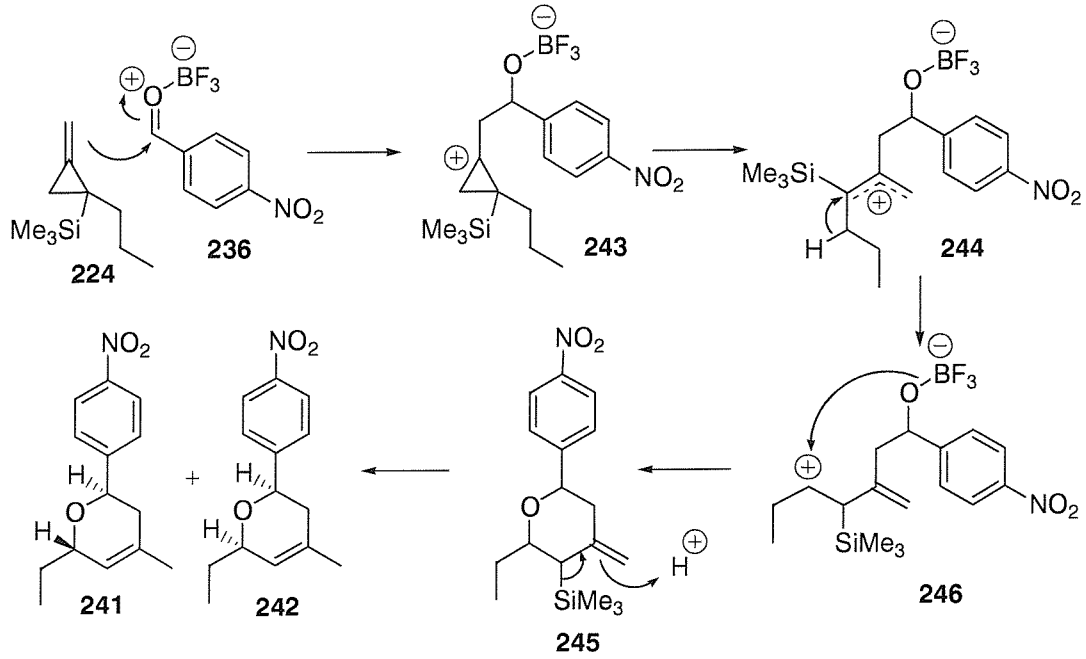
Cyclisation of methylenecyclopropane derivative **224** and *p*-nitrobenzaldehyde in DCM gave a similar result to that observed for methylenecyclopropane derivative **225** (Scheme 72).



DCM	14%	10%	-	-
$EtNO_2$	-	-	17%	7%

Scheme 72

However, cyclisation in $EtNO_2$ gave two addition products, dihydropyrans **241** and **242**. The occurrence of the two dihydropyran isomers was unexpected but rationalized by the following mechanism (Scheme 73).



Scheme 73

Methylenecyclopropyl derivative **224** reacts with BF_3-aldehyde complex **236** to give cyclopropyl cation **243**, which rearranges to allyl cation **244**. A 1,2-hydride shift leads to a stabilized β-silyl cation **246**, which can then be quenched by the alkoxide leading to **245**. Protodesilylation of the allyl silane yields the two dihydropyran isomers **241** and **242**.

The stereochemistry of tetrahydrofuran **239** was determined by GOESY studies (Figure 16).

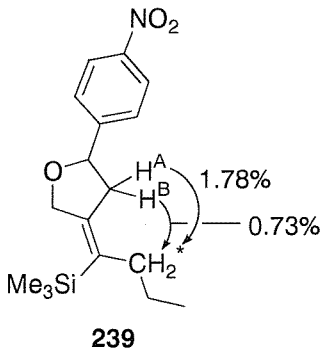


Figure 16 GOESY studies of **239**

Irradiation of H^A and H^B led to a 1.78% and 0.73% enhancement respectively of the propyl CH_2^*. The stereochemistry was found to be consistent with that of the benzyl tetrahydrofuran product **234**. 1,2-Hydride shifts have been noted in the cyclisation of methylenecyclopropane derivatives **288** and **290** that will be discussed in chapter 3, section 3.5.

The stereochemistry of dihydropyrans **241** and **242** was determined by GOESY experiments (Figure 17).

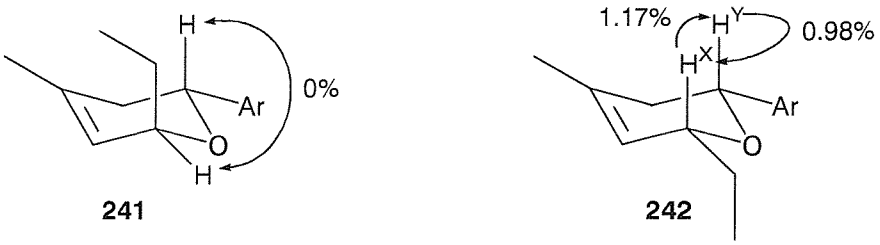
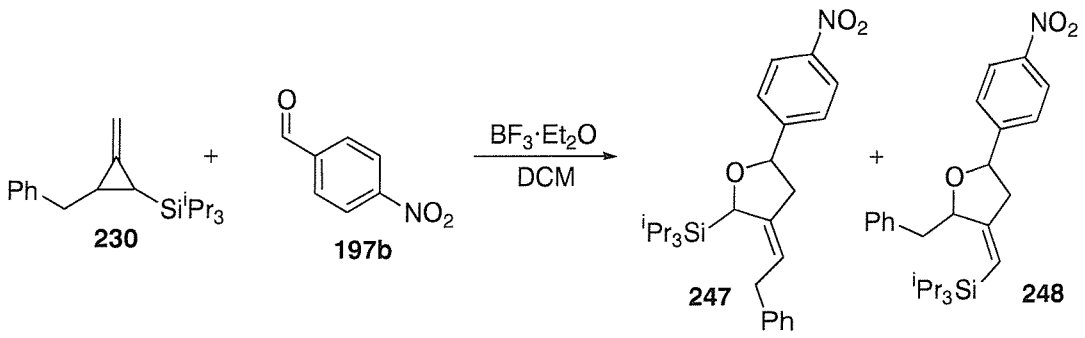


Figure 17 GOESY studies of **241** and **242**

The *cis* isomer **242** showed a distinct enhancement of ~1% between the two protons H^X and H^Y. The *trans* isomer showed no such enhancement in either direction.

2.9 Cyclisation studies with 1,2-disubstituted precursor 230

Cyclisations of methylenecyclopropane derivative **230** were carried out with either propanal or *p*-nitrobenzaldehyde using either $TiCl_4$ or $BF_3{\cdot}Et_2O$ in DCM (Scheme 74). Reactions with $TiCl_4$ as the Lewis acid led to decomposition of the starting materials with both aldehydes at -78°C. Reactions with $BF_3{\cdot}Et_2O$ as the Lewis acid led to only the starting materials being visualized by TLC after 24 hours reaction time at room temperature.



Scheme 74

In the case of the *trans* isomer the lack of reaction could be explained by the two bulky substituents on the cyclopropyl ring preventing the aldehyde from getting close enough to react in the desired manner (Figure 18).

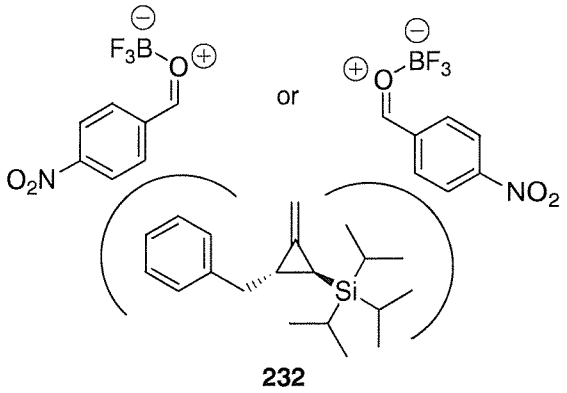


Figure 18 Steric repulsion of *trans* methylenecyclopropyl precursor **232**

The *cis* isomer only constituted 25% of the methylenecyclopropyl cyclisation precursor, therefore if only the *cis* isomer reacted cleanly in the desired manner only small amounts of the tetrahydrofuran products would be present and were possibly not visualized by TLC.

2.10 Conclusions

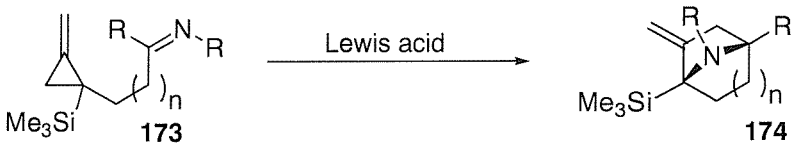
In conclusion, silylmethylenecyclopropanes can be used as allyl silane equivalents to attack aldehydes mediated by various Lewis acids to give tetrahydrofurans **196** and furofurans **200** and **201**.[88] For the formation of tetrahydrofurans **196** the use of $TiCl_4$ to effect the addition then subsequent cyclisation with sodium hydride was found to be the most synthetically useful method. With $BF_3{\cdot}Et_2O$ the overall yields were good to excellent, but the selectivity of the formed products was poor, thus rendering this method less synthetically useful. It has also been shown that catalytic Lewis acids can be used to promote these cycloaddition reactions although to the detriment of the overall yields. Cycloadditions involving disubstituted methylenecyclopropanes proved to be of limited viability in the search for higher yields and selectivity of the desired products. With the yields being poor this was not deemed a synthetically useful method for the preparation of tetrahydrofurans, but the variety of products formed indicated the range of novel mechanistic pathways available in such cyclisations.

Chapter 3

Intramolecular Cyclisation of Methylenecyclopropylimines

3.1 Introduction

The aim of this research was to carry out Lewis acid mediated cyclisations of methylenecyclopropylimines **173** to form azabicycles **174** (Scheme 75).



Scheme 75

Previous studies by Peron *et al.*[17,79] had shown that cyclisation of methylene-cyclopropylketones mediated by Lewis acids gave oxabicycles (Scheme 37). It was discovered that incorporation of a trimethylsilyl group significantly increased the nucleophilicity of the olefin moiety of methylenecyclopropane, effectively an allyl silane. Therefore, for the purposes of this study only the silyl substituted methylenecyclopropylimines were utilized. Various imine derivatives such as hydrazones[72,74,75] **249**, oximes[89,90] **250**, alkyl and aromatic imines[70,71,91] **251** were chosen as suitable cyclisation precursors (Figure 19).

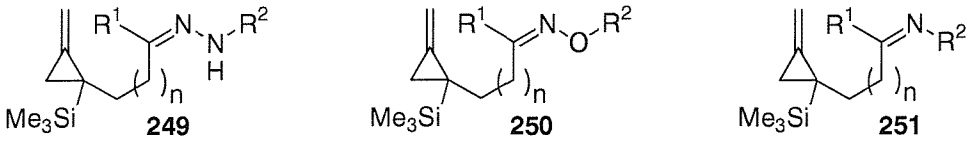
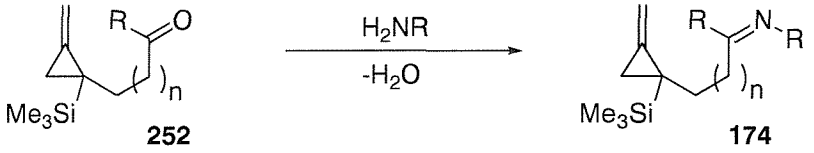


Figure 19 Imine derivatives **249**, **250** and **251**

It was expected that imine derivatives **249-251** could be readily synthesized from the already known carbonyl precursors **252** simply by treatment with the relevant amine under conditions to remove water (Scheme 76).

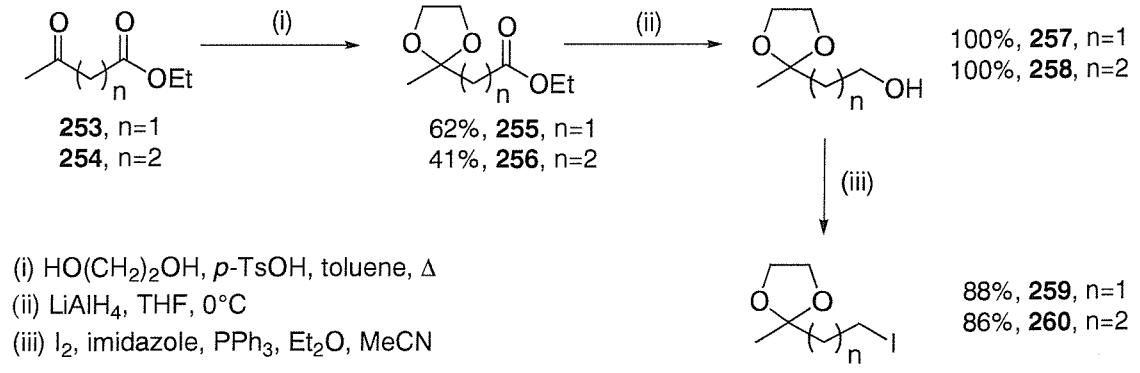


Scheme 76

3.2 Synthesis of precursors

3.2.1 Preparation of ketone precursors 133 and 134

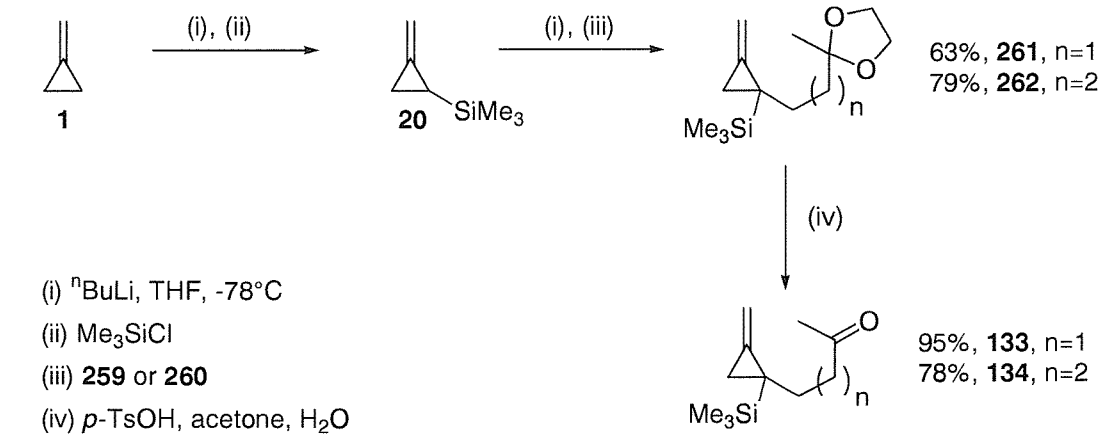
Silyl ketones **133** and **134** were prepared following a procedure reported by Peron *et al.*[79] which initially required the preparation of iodides **259** and **260** (Scheme 77).



Scheme 77

Ketones **253** and **254** were protected with ethylene glycol to give ketals **255** and **256** using Dean-Stark apparatus to remove water from the reaction mixture. The protection was accomplished in yields of 62% and 41% for **255** and **256** respectively. Protected esters **255** and **256** were reduced to alcohols **257** and **258** using $LiAlH_4$, which proceeded in an excellent yield of 100% for both **257** and **258**. Alcohols **257** and **258** were converted into iodides **259** and **260** using PPh_3, imidazole and I_2 in good yields of 88% and 86% for **259** and **260** respectively.

The cyclisation precursors were prepared in a two-step, one-pot synthesis (Scheme 78).

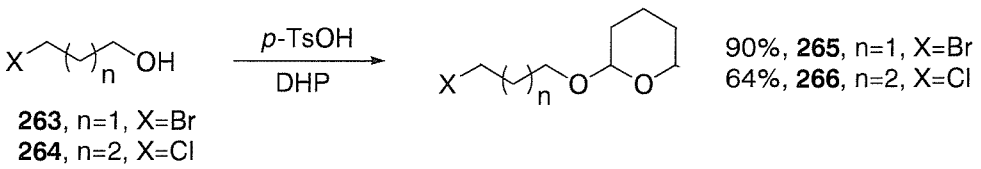


Scheme 78

Methylenecyclopropane **1** was deprotonated using ^{n}BuLi and the subsequent anion quenched with one equivalent of TMSCl. A second equivalent of ^{n}BuLi was added and the resulting anion coupled with iodide **259** or **260**. The two-steps were achieved in good yields of 63% and 79% for **261** and **262** respectively. The ketal group was then removed using *p*-TsOH in wet acetone in 95% and 78% yields to furnish ketones **133** and **134** respectively.

3.2.2 Preparation of aldehyde precursors 271 and 272

Methylenecyclopropylaldehydes **271** and **272** were prepared from the corresponding silyl alcohols **269** and **270** previously reported by Destabel *et al.*[55] (Scheme 79).

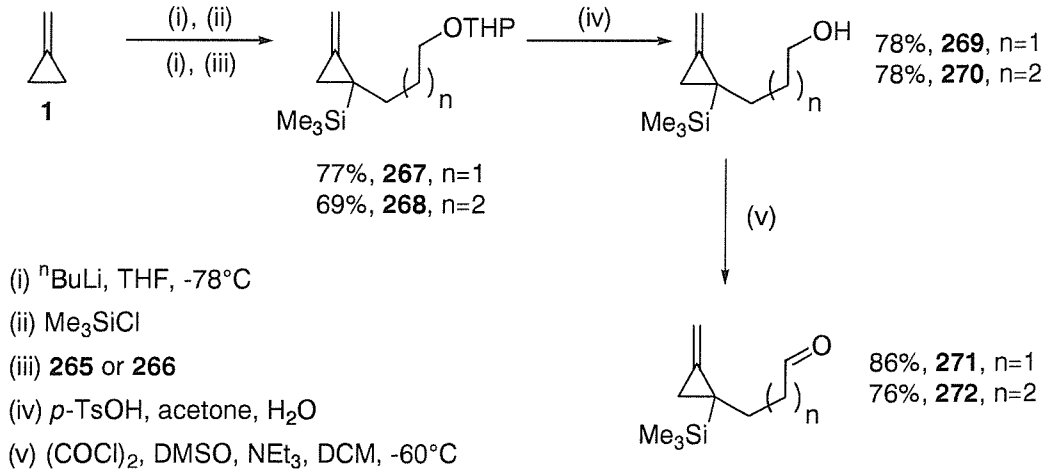


263, n=1, X=Br
264, n=2, X=Cl

Scheme 79

Haloalcohols **263** and **264** were treated with *p*-TsOH in DHP to give the desired tetrahydropyran ethers **265** and **266** in 90% and 64% yields respectively.

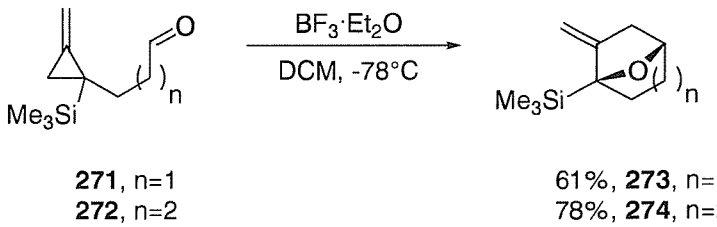
Tetrahydropyran ethers **267** and **268** were synthesized in a two-step, one-pot synthesis analogous to that used for ketones **133** and **134** (Scheme 80).



Scheme 80

Methylenecyclopropane **1** was deprotonated using ^{n}BuLi and the subsequent anion quenched with one equivalent of TMSCl. A second equivalent of ^{n}BuLi was added and the subsequent anion coupled with either bromide **265** or chloride **266**. The two-step synthesis was achieved in good yields of 77% and 69% for **267** and **268** respectively. The tetrahydropyran group was removed using *p*-TsOH in wet acetone to give alcohols **269** and **270** both in 78% yields. Oxidation of alcohols **269** and **270** was carried out using Swern[92] oxidation conditions, which gave the desired aldehydes **271** and **272** in good 86% and 76% yields respectively.

Aldehydes **271** and **272** were not accessed by Peron *et al.* and consequently had not been treated with a Lewis acid to yield bicyclic ethers **273** and **274**. Therefore these aldehydes were treated with $BF_3{\cdot}Et_2O$ to confirm that they would cyclise as described earlier (Scheme 81).

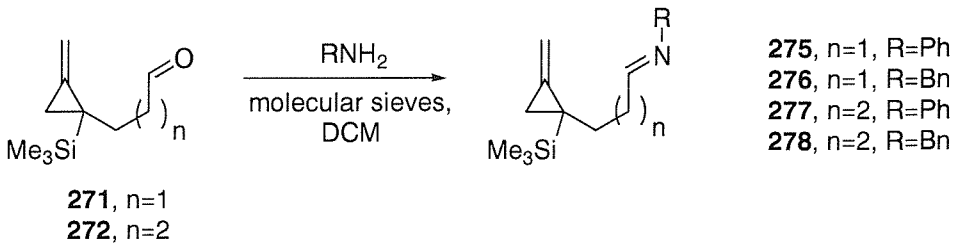


Scheme 81

It was found that both **271** and **272** cyclised to give the desired oxabicycles **273** and **274** in good 61% and 78% yields respectively.

3.2.3 Preparation of alkyl and aromatic imine precursors

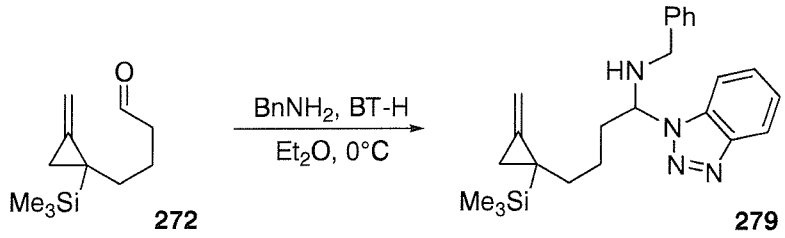
Two amines, aniline and benzylamine, were chosen for the formation of an aryl and an alkyl imine cyclisation precursor (Scheme 82).



Scheme 82

All of the imines **275-278** were prepared in quantitative yields by stirring the relevant amine with the relevant aldehyde in DCM with activated 4Å molecular sieves. The formation of the imines was followed by crude ^{1}H NMR in which the disappearance of the aldehyde peak (~9.75 ppm) was monitored. The rest of the spectrum was mostly unchanged in comparison to the aldehyde starting material except for the additional peaks contributed by the amine. It was found that all the imine derivatives were highly unstable and decomposed even in the NMR tube in $CDCl_3$ and hence full characterization was impossible. Therefore these imine precursors required preparation immediately before use.

Due to the instability of the imine derivatives it was decided to "trap" the imine as a more stable intermediate[93] (Scheme 83).

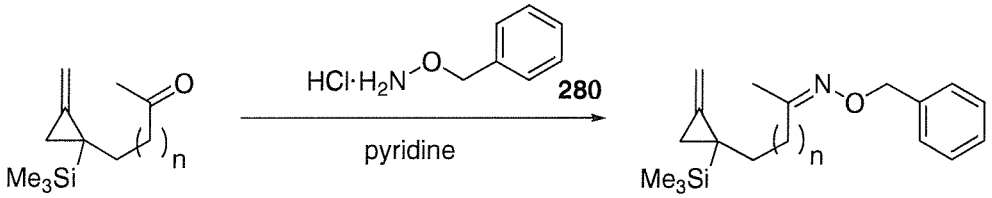


Scheme 83

Only one precursor was chosen for the application of this technique, it was found that benzyl imine **272** could be "trapped" with benzotriazol to give **279**. **279** Proved to be slightly more stable than the corresponding imine, however still required preparation immediately before use. It was expected that on treatment with a Lewis acid the "trapped" imine **279** would collapse to the corresponding imine **278** and react as proposed.

3.2.4 Preparation of oxime precursors

A method for the preparation of oximes was reported by Booth *et al.*[94] (Scheme 84).



133, n=1
134, n=2

76%, **281**, n=1
92%, **282**, n=2

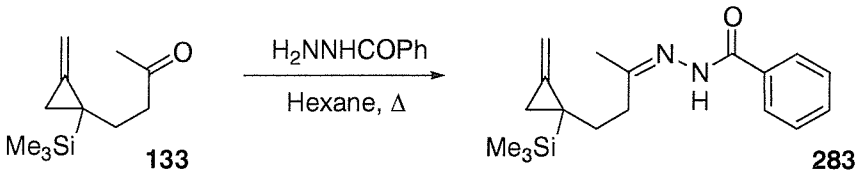
Scheme 84

Treatment of ketones **133** and **134** with *O*-benzylhydroxylamine hydrochloride **280** in pyridine gave the desired oximes **281** and **282** in good 76% and 92% yields respectively, both as a 2:1 mixture of *E*:*Z* isomers. These isomers proved difficult to

separate, however a small quantity of each isomer was obtained for characterization purposes only. The formation of the corresponding aldehyde oximes was not attempted.

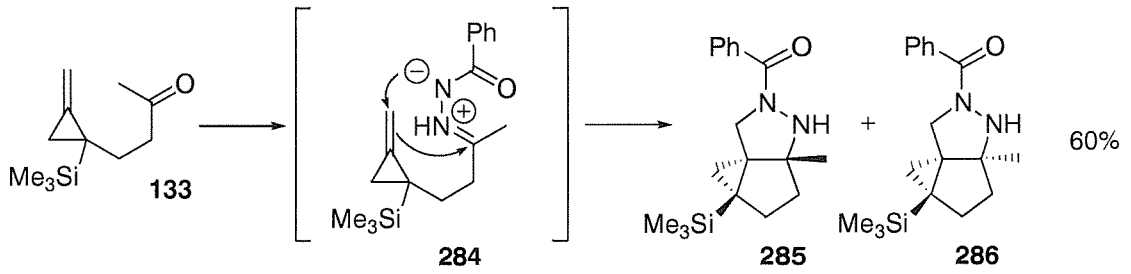
3.2.5 Preparation of hydrazone precursors

A method for the preparation of benzoylhydrazones from the corresponding ketones was reported by Wu *et al.*[95] (Scheme 85).



Scheme 85

Ketone **133** was treated with benzoylhydrazine in refluxing hexane for 48 hours. Unfortunately this method yielded none of the desired hydrazone **283**, but instead gave a good 60% yield of tricyclic isomers **285** and **286** in 1:1 ratio (Scheme 86).



Scheme 86

The formation of tricyclic isomers **285** and **286** was readily explained by thermal rearrangement of the hydrazone to azomethine imine[96] **284** and subsequent [3+2] cycloaddition onto the olefin moiety of the methylenecyclopropane. [3+2]

Cycloadditions onto the olefin moiety of methylenecyclopropanes are well documented in the literature (see chapter 1, section 1.3.1).

The stereochemistry of the isomers was proved by X-ray crystallography of the individual isomers (Figure 20 **285** and Figure 21 **286**).

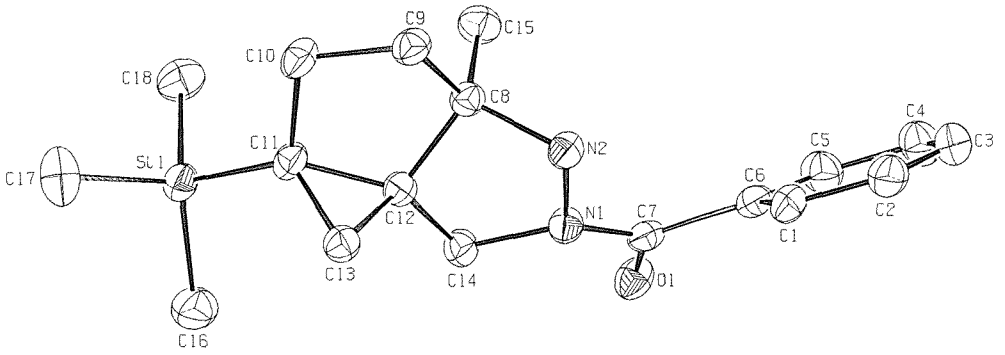


Figure 20 X-ray crystal structure of **285** (see appendix)

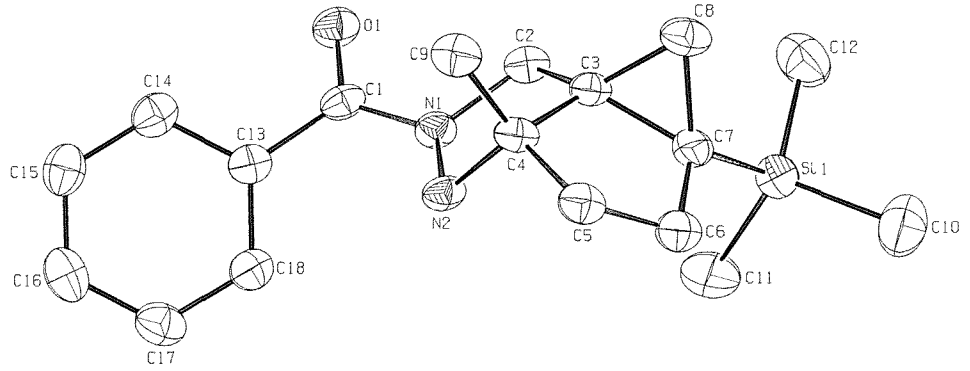
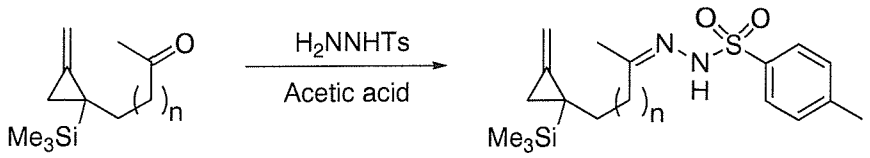


Figure 21 X-ray crystal structure of **286** (see appendix)

Due to the unexpected formation of these tricyclic products another method for the formation of hydrazones was investigated (Scheme 87).



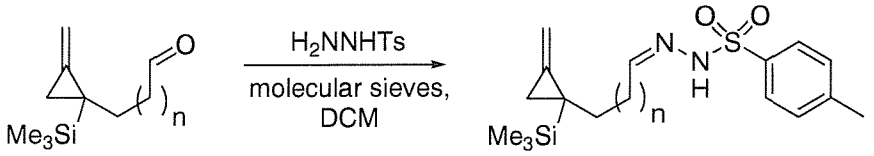
133, n=1
134, n=2

57%, **287**, n=1
50%, **288**, n=2

Scheme 87

Iida *et al.*[97] reported that tosylhydrazones could be prepared by treating a ketone with tosylhydrazine in acetic acid. This method gave the desired tosylhydrazones in 57% and 50% yields for **287** and **288** respectively. Although this reaction did not give high yields of the desired product, significant quantities of the starting ketone were recovered. The hydrazones were formed as 9:1 and 7:1 mixture of *E*:*Z* isomers respectively.

When this method was attempted for the formation of the corresponding aldehydes it was found that the aldehydes decomposed on contact with acetic acid. Therefore a milder method for the formation of the aldehyde hydrazones **289** and **290** was employed (Scheme 88).



271, n=1
272, n=2

100%, **289**, n=1
100%, **290**, n=2

Scheme 88

Simply stirring tosylhydrazine and the relevant aldehyde in DCM with activated 4Å molecular sieves for one hour gave the desired aldehyde hydrazones **289** and **290** in quantitative yields. Again hydrazones **289** and **290** were formed as an inseparable 4:1 and 9:1 mixture of *E*:*Z* isomers respectively. Aldehyde hydrazones **289** and **290** proved to be unstable and required preparation immediately before use.

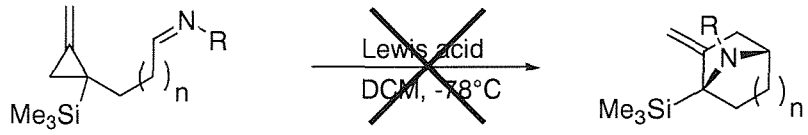
Due to the discovery of this simple method for the formation of aldehyde hydrazones **289** and **290**, it was attempted for the formation of the ketone hydrazones **287**

and **288**. However, reaction at room temperature was unsuccessful but stirring tosylhydrazine in refluxing hexane with the relevant ketone did provided quantitative yields of ketone hydrazones **287** and **288**. Under these reaction conditions with tosylhydrazine there was no observed formation of the tricycles as seen with the corresponding benzoylhydrazines (Scheme 86).

3.3 Cyclisation studies with alkyl and aromatic precursors

3.3.1 Cyclisation studies with crude alkyl and aromatic imines

Cyclisation studies were carried out using $TiCl_4$ and $BF_3 \cdot Et_2O$ as Lewis acids in DCM at -78°C as Peron *et al.*[17,78,79] reported good results in cyclising methylenecyclopropylcarbonyls using these conditions (Scheme 89).



275, n=1, R=Ph
276, n=1, R=Bn
277, n=2, R=Ph
278, n=2, R=Bn

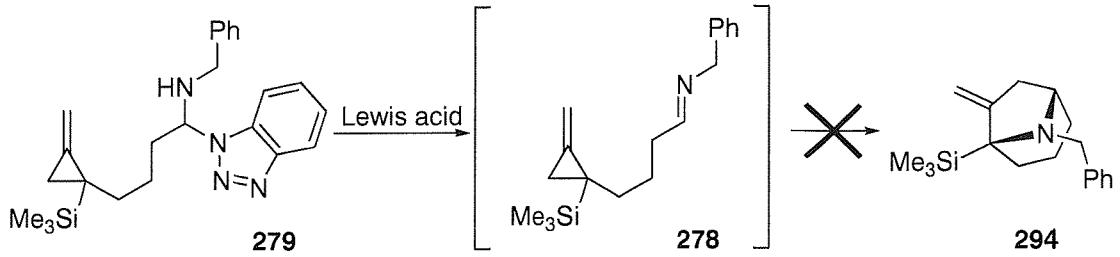
291, n=1, R=Ph
292, n=1, R=Bn
293, n=2, R=Ph
294, n=2, R=Bn

Scheme 89

Unfortunately under all conditions with cyclisation precursors **275-278** led to rapid decomposition of the reaction mixture.

3.3.2 Cyclisation studies with "trapped" precursor 279

The cyclisation of "trapped" precursor **279** was also attempted with $TiCl_4$ or $BF_3{\cdot}Et_2O$ in DCM at -78°C and again led to rapid decomposition of the reaction mixture (Scheme 90).

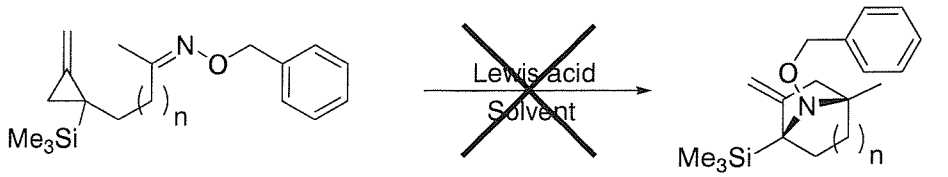


279 **278** **294**

Scheme 90

3.4 Cyclisation studies with oxime precursors

Cyclisation studies were carried out using $TiCl_4$ and $BF_3{\cdot}Et_2O$ as Lewis acids in DCM or $EtNO_2$ at -78°C (Scheme 91).



281, n=1
282, n=2

295, n=1
296, n=2

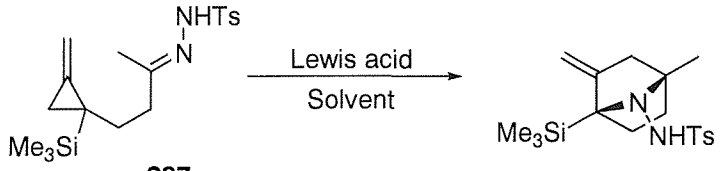
Scheme 91

Reactions carried out with $BF_3{\cdot}Et_2O$ as the Lewis acid yielded no reaction with either **281** or **282** after 24 hours at room temperature. Reactions carried out in $EtNO_2$ with $TiCl_4$ led to slow decomposition, however, reactions in DCM gave a small amount of an unidentified product for both n=1 and 2.

3.5 Cyclisation studies with hydrazone precursors

3.5.1 Cyclisation studies with hydrazone 287

Cyclisations of ketone hydrazone precursor **287** were studied using a variety of Lewis acids and solvents (Table 7).



287 **297**

Scheme 92

Entry	Lewis acid	Solvent	Conditions	Yield / %
a	$BF_3{\cdot}Et_2O$	DCM	-20°C to RT, 3 hrs	20
b	$BF_3{\cdot}(AcOH)_2$	DCM	-20°C to RT, 3 hrs	22
c	$SnCl_4$	DCM	-70°C to RT, 3 hrs	13
d	$TiCl_4$	DCM	-70°C, 2 hrs	-
e	$BF_3{\cdot}Et_2O$	THF	-70°C to RT, 24 hrs	-
f	$TiCl_4$	THF	-70°C to RT, 24 hrs	-
g	$BF_3{\cdot}Et_2O$	$MeNO_2$	-30°C to 0°C, 2 hrs	40
h	$BF_3{\cdot}(AcOH)_2$	$MeNO_2$	-30°C to 0°C, 2 hrs	28
i	$SnCl_4$	$MeNO_2$	-30°C to 10°C, 2 hrs	24
j	$TiCl_4$	$MeNO_2$	-30°C to 0°C, 2 hrs	30
k	$BF_3{\cdot}Et_2O$	$EtNO_2$	-70°C to RT, 5 hrs	48
l	Et_2AlCl	$EtNO_2$	-70°C to RT, 24 hrs	-
m	$EtAlCl_2$	$EtNO_2$	-70°C to RT, 24 hrs	30

Table 7 Reaction of Methylenecyclopropylhydrazone **287** under various conditions

Initial cyclisations were carried out in DCM with four Lewis acids as Peron *et al.*[79] reported that cyclisations with methylenecyclopropylketone **133** under similar conditions gave good results. However, cyclisations of hydrazone **287** in DCM were low yielding and using $TiCl_4$ even led to decomposition. The use of different solvents (THF, $MeNO_2$ and $EtNO_2$) was therefore investigated. Cyclisations attempted in THF gave no reaction, whereas cyclisations in $MeNO_2$ or $EtNO_2$ gave slightly higher yields of the desired azabicycle **298** than the equivalent reaction in DCM, and cyclisation with $BF_3{\cdot}Et_2O$ in $EtNO_2$ giving a best yield of 48%. Two other Lewis acids (Et_2AlCl and $EtAlCl_2$) were used in $EtNO_2$. Cyclisation of hydrazone **287** with Et_2AlCl gave no reaction and cyclisation with $EtAlCl_2$ gave azabicycle **297** in 30% yield.

Peron *et al.*[79] reported that when $TiCl_4$ or $SnCl_4$ were used as Lewis acids the intermediate allyl cation was trapped by chloride and gave chloroalkenols (Scheme 36). Reaction of methylenecyclopropylhydrazone precursor **287** with $TiCl_4$ or $SnCl_4$ furnished no products where the allyl cation was trapped by chloride (Figure 22).

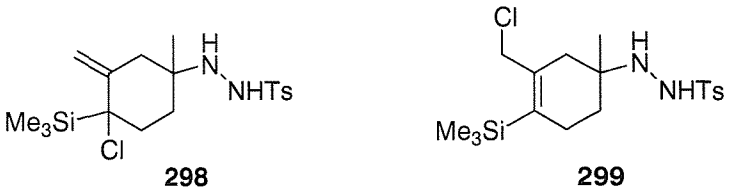


Figure 22 Products expected from chloride trapping of allyl cation

However the isolated yields of azabicycle **297** were low and the reaction was not clean as adjudged by TLC, so it is possible that **298** and **299** were formed in the reaction mixture but either decomposed on work-up or purification and were therefore not isolated.

A crystal structure of azabicycle **297** was obtained (Figure 23).

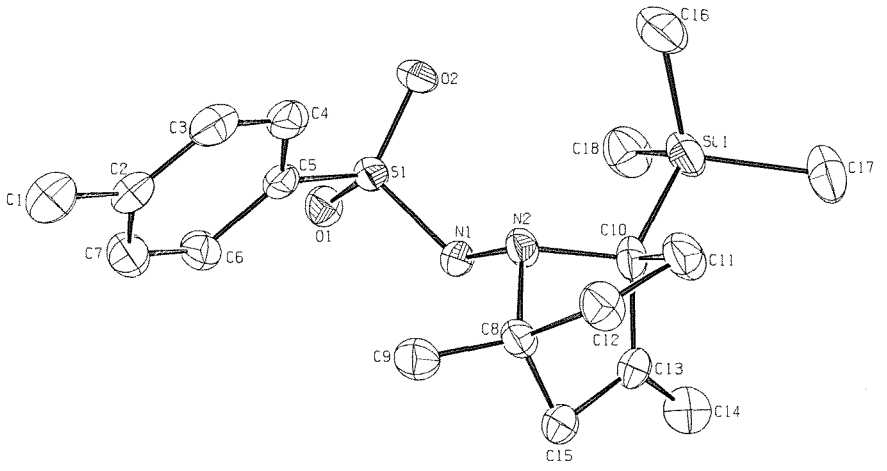
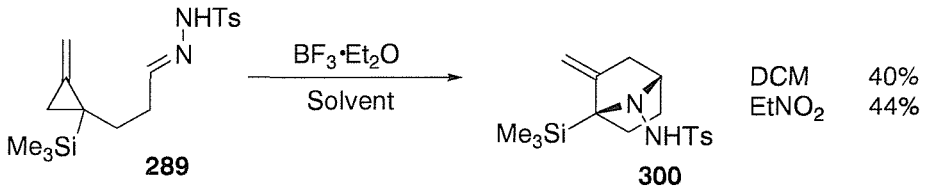


Figure 23 X-ray crystal structure of **297**[98]

3.5.2 Cyclisation studies with hydrazone 289

Cyclisations of aldehyde hydrazone **289** were carried out using $BF_3 \cdot Et_2O$ in either DCM or $EtNO_2$ as solvent because these conditions gave the best results with the corresponding ketone hydrazone **287**.



Scheme 93

In both solvents the desired azabicycle **300** was obtained in moderate 40% and 44% yields. The yields of azabicycle **300** were comparable with the corresponding ketone hydrazone **297**.

A crystal structure of azabicycle **300** was obtained (Figure 24).

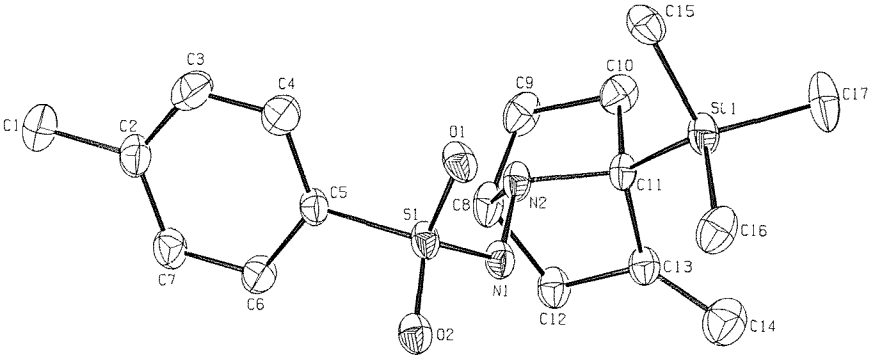
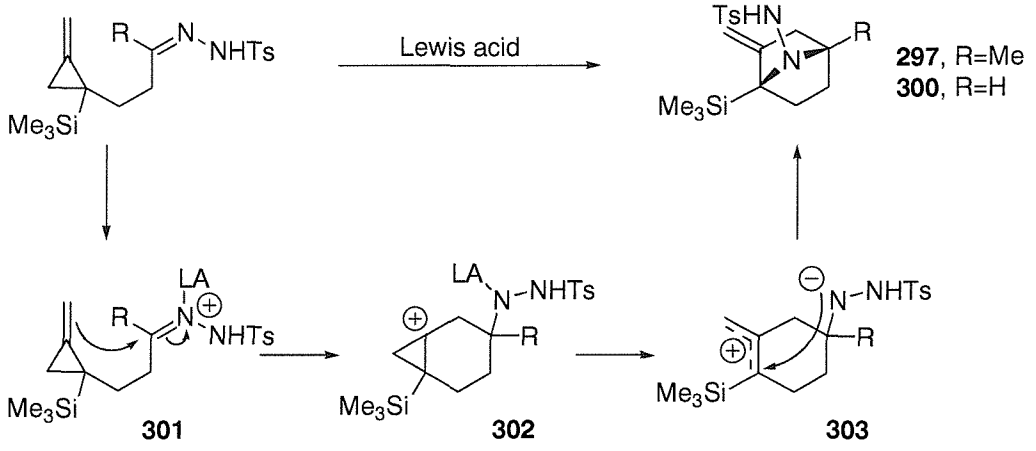


Figure 24 X-ray crystal structure of **300**[98]

The formation of azabicyclic products **297** and **300** presumably followed the mechanism previously reported by Peron *et al.*[79] (Scheme 94).

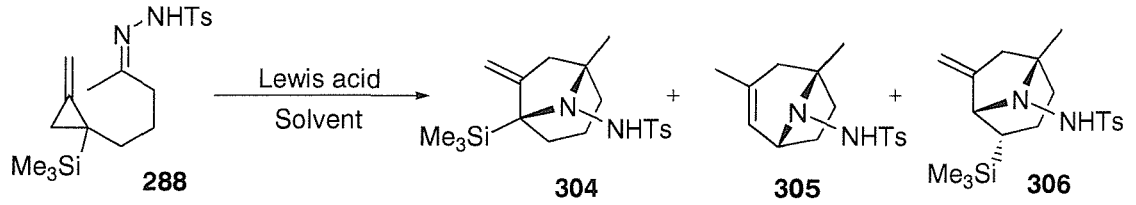


Scheme 94

The Lewis acid chelates to the hydrazone as expected to form complex **301**. The olefin moiety can then attack the Lewis acid-hydrazone complex to give cyclopropyl cation **302**, which rearranges to give π-allyl cation **303**. The allylic cation can then be quenched by the hydrazinyl anion to give azabicycles **297** and **300** as the desired products.

3.5.3 Cyclisation studies with hydrazone 288

Cyclisation of ketone hydrazone **288** was studied using a variety of Lewis acids and solvents (Table 8).



Scheme 95

Entry	Lewis acid	Solvent	Yield / %		
			304	**305**	**306**
a	$BF_3{\cdot}Et_2O$	DCM	-	35	2
b	TMSOTf	DCM	-	32	-
c	$SnCl_4$	DCM	-	-	-
d	$TiCl_4$	DCM	-	-	-
e	Et_2AlCl	DCM	-	-	-
f	$EtAlCl_2$	DCM	-	-	-
g	$BF_3{\cdot}Et_2O$	$EtNO_2$	-	54	-
h	$BF_3{\cdot}(AcOH)_2$	$EtNO_2$	-	42	-

Table 8 Reaction of Methylenecyclopropylhydrazone **288** under various conditions

Employing the best conditions from the earlier cyclisations of **287**, reaction with $BF_3{\cdot}Et_2O$ in DCM or $EtNO_2$ gave none of the expected azabicycle **304** and instead two other products, **305** and **306** were isolated. **305** was isolated in a best yield of 54% using $BF_3{\cdot}Et_2O$ in $EtNO_2$ and azabicycle **306** was only ever isolated as a minor product. The structures of **305** and **306** were proved by X-ray crystallography (Figure 25 **305** and Figure 26 **306**). Other Lewis acids were investigated but none gave better results. **305** was found to be the major product (a, b, g and h) with **306** only being isolated in a small

quantity (a). Using $TiCl_4$ or $SnCl_4$ (c and d) led to decomposition while no reaction was observed with Et_2AlCl or $EtAlCl_2$ (e and f). Five other Lewis acids were used catalytically in an attempt to promote the cyclisation, $InCl_3$, $In(OTf)_3$, $Sc(OTf)_3$, $Y(OTf)_3$ and $Yb(OTf)_3$, however no reaction was observed in any case.

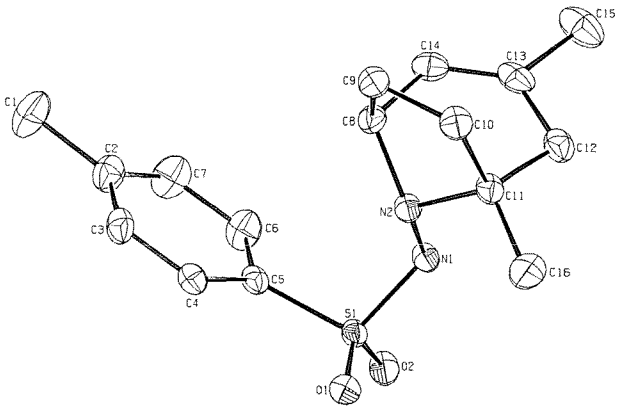


Figure 25 X-ray crystal structure of **305**[98]

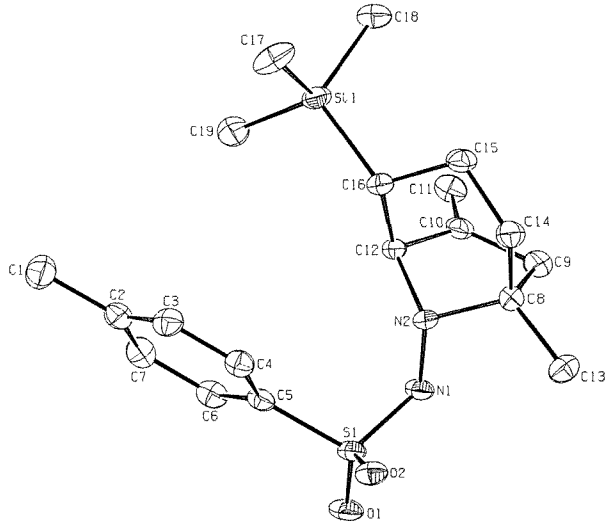
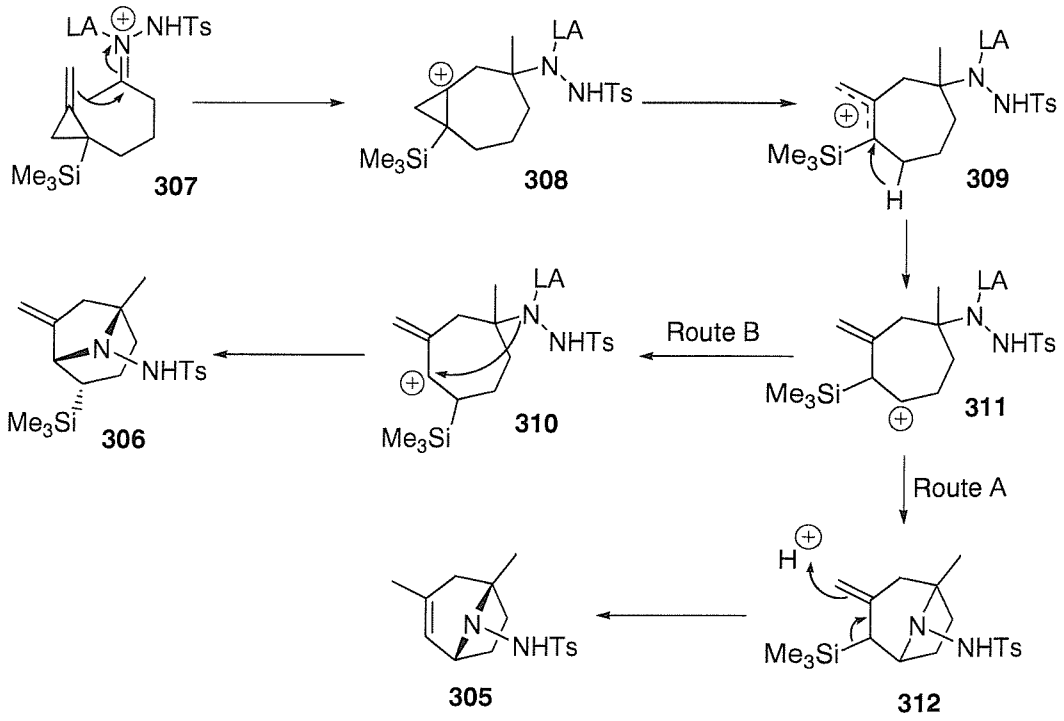


Figure 26 X-ray crystal structure of **306**[98]



Scheme 96

A mechanism has been proposed for the formation of **305** and **306** which initially appeared to follow the mechanism reported by Peron *et al.*[79] up to the formation of π-allyl cation **309** (Scheme 96). Then instead of cation **309** being quenched the hydrazinyl anion, a 1,2-hydride shift can occur to give stabilized β-silyl cation **311**. The β-silyl cation can then either be quenched by nitrogen followed by a protodesilylation step to give **305** (Route A) or a 1,2-silyl shift can occur to give β-silyl π-allyl cation **310** (Route B). Cation **310** can then finally be quenched to give **306** as the product. This proposed mechanism, with a hydride shift in one direction followed by a silyl shift in the opposing direction appears plausible since each subsequent cation appears to be of increasing stability (Figure 27).

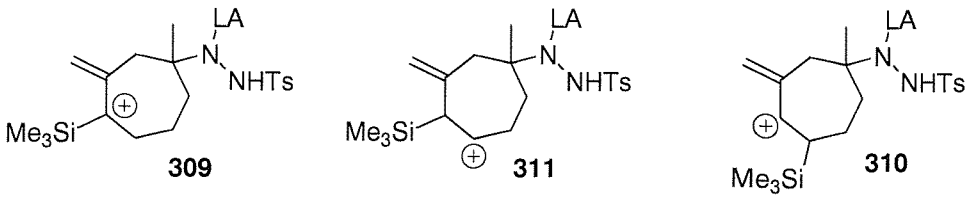


Figure 27 Proposed sequence of cations

Cation **309** is allylic but also α,γ-silyl and hence possibly destabilized.[99] Cation **311**, formed after the 1,2-hydride shift is β-silyl and therefore stabilized by the β-silyl effect. Finally cation **310**, formed after the 1,2-silyl shift is β-silyl and allylic and is therefore the most stable cation in the sequence.

An explanation for the occurrence of the 1,2-hydride shift could be that cation **309** is too sterically hindered for the large *N*-tosyl substituted hydrazinyl species to trap it. Therefore the trapping of the cation by nitrogen is sufficiently slow for a 1,2-hydride shift to take place in preference. No such shifts were reported by Peron *et al.*[79] in the oxygen series of cyclisations, but presumably the alkoxide is a much less sterically hindered nucleophile than an *N*-tosyl substituted hydrazinyl anion (Figure 28).

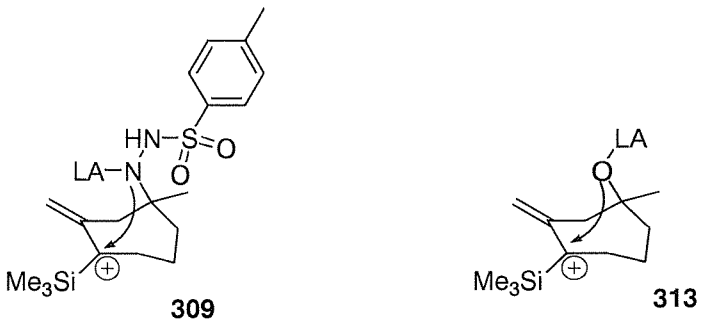
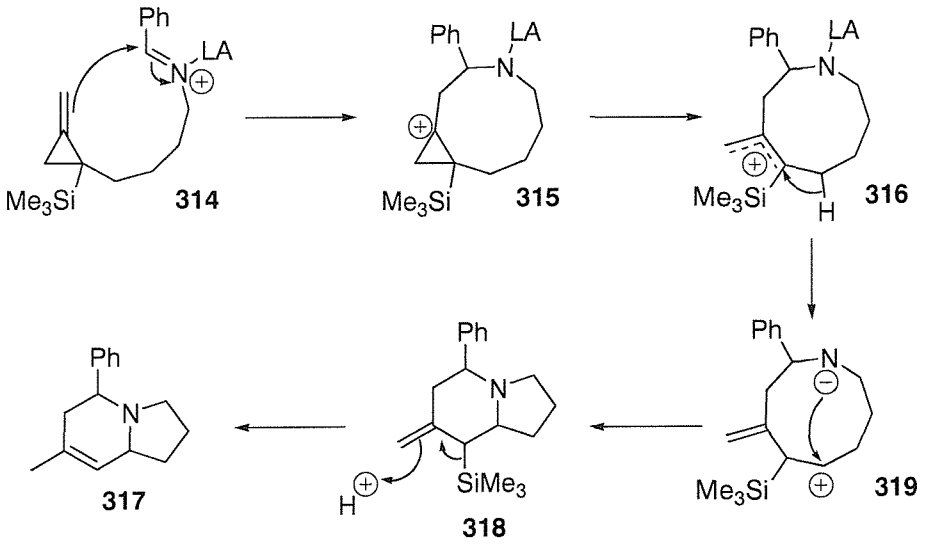


Figure 28 Steric explanation for the 1,2 hydride shift theory

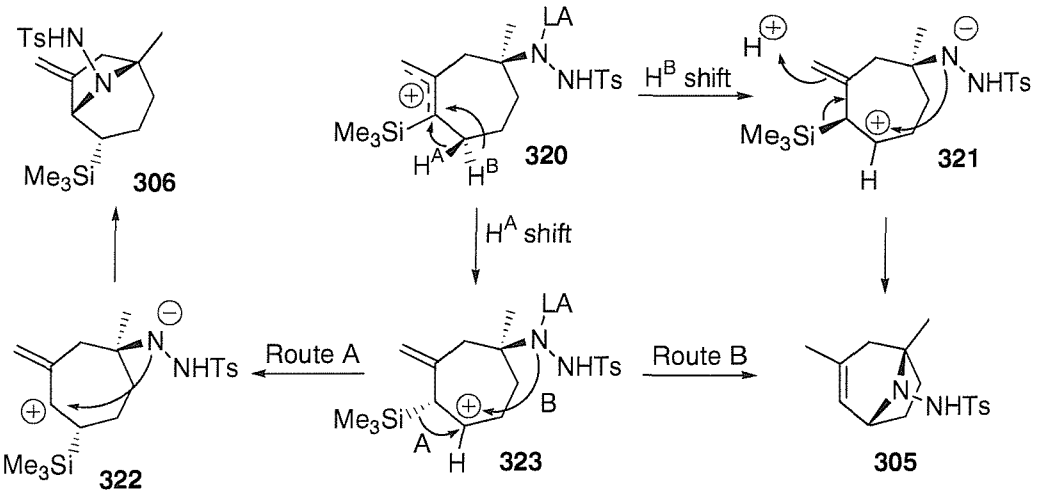
Other work within the group has shown the preference of 1,2-hydrides shifts over trapping of α-silyl cations by nitrogen based anions (Scheme 97).



Scheme 97

Methylenecyclopropylimine **314** reacts with a Lewis acid to give cyclopropyl cation **315**, which rearranges to π-allyl cation **316**. Instead of the nitrogen trapping allyl cation **316** as was expected, a 1,2-hydride shift occurs giving stabilized β-silyl cation **319**. Cation **319** is less sterically congested than cation **316** and is quenched by the nitrogen to give azabicycle **318**. The trimethylsilyl group is then eliminated in a protodesilylation step to give azabicycle **317** as the final product in 30-40 % yields.

The stereochemistry of **306** was proved by X-ray crystallography (Figure 26). Azabicycle **306** can only be formed if H^A is the proton that undergoes the 1,2-hydride shift, whereas azabicycle **305** could be formed if either proton (H^A or H^B) undergoes the 1,2-hydride shift (Scheme 98).



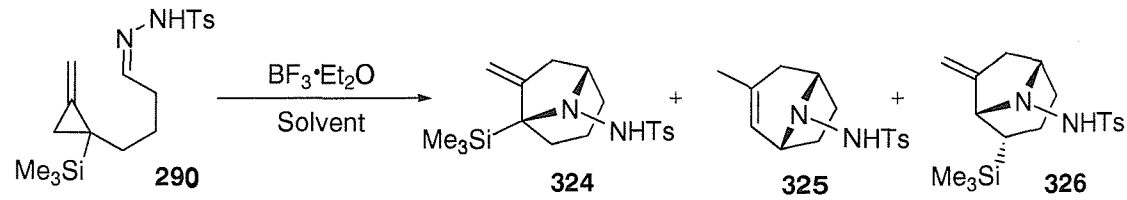
Scheme 98

If H^B is the proton that shifts then the TMS group is on the same face as the *N*-tosyl group **321**, and thus only azabicycle **305** can be formed from the cyclisation. When H^A undergoes the 1,2-hydride shift then cation **323** can either be quenched by the hydrazinyl anion to give **305** (Route B), or a 1,2-silyl shift can occur to give cation **322** (Route A). Cation **322** can then be quenched by the hydrazinyl anion to give **306**.

The preference for the formation of **305** and **306** appeared to be affected very easily by subtle changes in the reaction conditions and a precise ratio could not be consistently obtained on repeating the reaction.

3.5.4 Cyclisation studies with hydrazone 290

Cyclisation of precursor **290** with $BF_3{\cdot}Et_2O$ in either DCM or $EtNO_2$ was expected to give a mixture of azabicyclic products as with the corresponding ketone hydrazone precursor **288** (Scheme 99).



DCM	24%	-	22%
$EtNO_2$	25%	-	20%

Scheme 99

Cyclisation of **290** led to a mixture of **324** and **326** as products in both solvents, but **325** was not isolated as a product at all. In contrast to the corresponding ketone hydrazone **288**, the product from direct trapping of the allyl cation, **324**, was isolated as a significant product of the reaction in 24% and 25% yields. Again the occurrence of **326** as a product would appear to follow the same proposed mechanism for the cyclisation of ketone hydrazone precursor **288**.

Again the structure of both products was proved by X-ray crystallography (Figure 29 **324** and Figure 30 **326**).

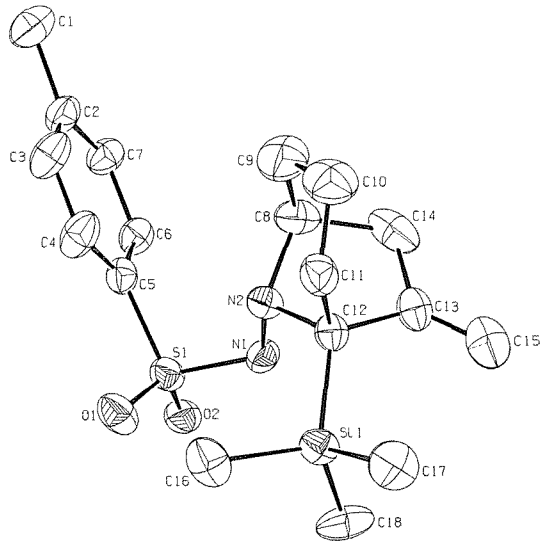


Figure 29 X-ray crystal structure of **324**[98]

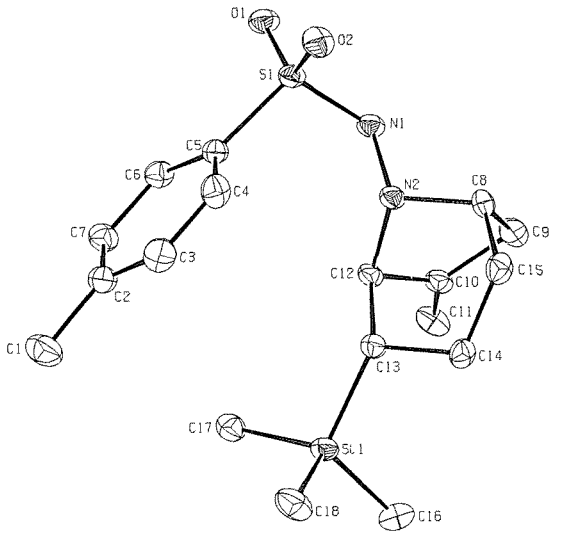
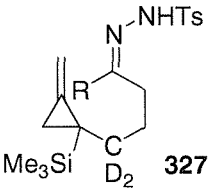


Figure 30 X-ray crystal structure of **326**[98]

3.6 Investigation into the mechanism

3.6.1 Introduction

In the proposed mechanism for the formation of cyclic products **305**, **306** and **326** a 1,2-hydride shift occured. To provide some support for the proposed mechanism it was envisaged that a deuterated precursor could be synthesized (Figure 31). This could then clarify whether a hydride shift was indeed taking place.



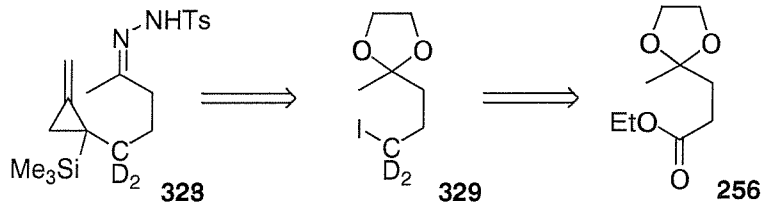
327

Figure 31 Deuterated precursor **327**

In addition the source of the proton in the protodesilylation step giving **305** was in question, and therefore an investigation into the source of the proton was conducted.

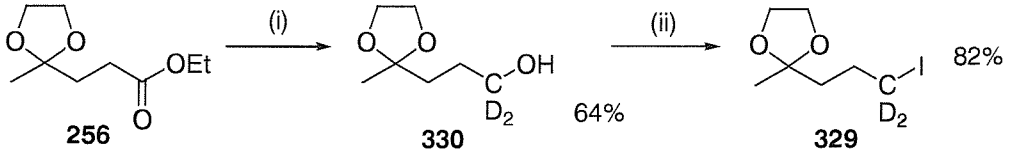
3.6.2 Proof of 1,2-hydride shift theory

It was decided that the route to ketone hydrazone **328** would provide the most accessible route to a deuterated precursor (Scheme 100).



Scheme 100

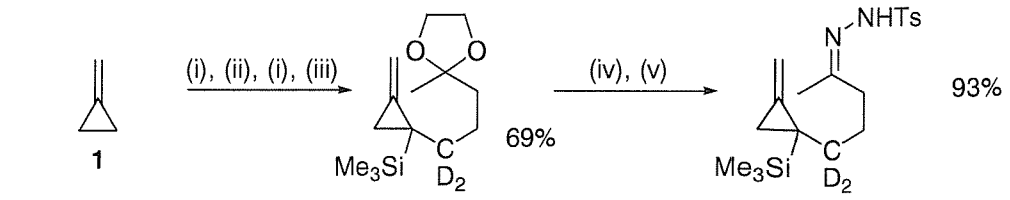
The forward synthesis of **328** was identical to the synthesis of precursor **288** except that reduction of the ester was carried out with $LiAlD_4$ instead of $LiAlH_4$ (Scheme 101).



(i) $LiAlD_4$, THF, 0°C
(ii) I_2, imidazole, PPh_3, Et_2O, MeCN

Scheme 101

Reduction of ester **256** with $LiAlD_4$ to alcohol **330** proceeded in good 64% yield. Alcohol **330** was then converted into iodide **329** in 82% yield. Alkylation of methylenecyclopropane **1** with iodide **329** was carried out in a two-step, one-pot synthesis analogous to that of the non-deuterated precursor **262** (Scheme 102).



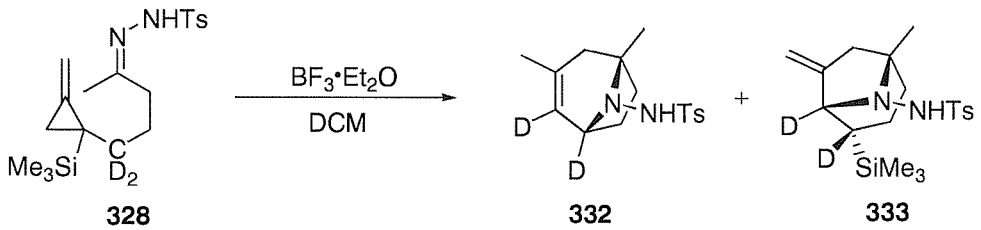
(i) ^{n}BuLi, THF, -78°C
(ii) Me_3SiCl
(iii) **329**
(iv) 2M HCl, acetone, H_2O
(v) $TsHNNH_2$, hexane, Δ

Scheme 102

First methylenecyclopropane **1** was deprotonated using ^{n}BuLi and the subsequent anion quenched with one equivalent of TMSCl, followed by second deprotonated with a second equivalent of ^{n}BuLi and then coupled with iodide **329**. The two-step synthesis was achieved in a good 69% yield. The ketal group was removed using 2 M HCl in wet acetone in good 93% yield. The ketone was refluxed with tosylhydrazine in hexane for one hour to furnish hydrazone **328** quantitatively as a 5:1 mixture of *E*:*Z* isomers.

3.6.3 Cyclisation studies with deuterated precursor 328

It was decided that the cyclisation would be carried out in DCM using $BF_3{\cdot}Et_2O$ as the Lewis acid because these conditions had proved to be most reliable (Scheme 103).



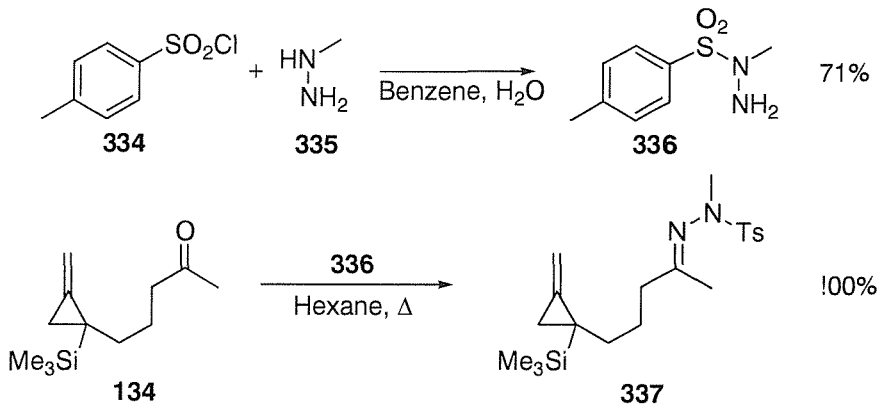
Scheme 103

The cyclisation was initially carried out on small scale (50 mg of the precursor). Unfortunately the reaction proved to be slower and less clean as adjudged by TLC and HPLC than reactions with the equivalent non-deuterated precursor. Therefore the reaction was carried out on larger scale (500 mg of the precursor), which yielded only small quantities of the desired products **332** and **333**. MS analysis showed that the two deuteriums which were present in the cyclisation precursor **328** were also present in the cyclised product. Further, comparison of the ^{1}H NMR spectra of the deuterated and non-deuterated cyclisation products showed that the 1,2-deuteride shift had taken place. The proof of the 1,2-deuteride shift thus verified the occurrence of the 1,2-hydride shift, and hence showed the proposed mechanism to be reasonable up to that point.

3.6.4 Investigation Into the protodesilylation step

An investigation was attempted into the source of the proton in the proposed protodesilylation step to give **305**. At first it was thought that the protodesilylation step might have occurred on work up of the reaction, so the reaction was quenched with D_2O. This experiment led to the cyclised product, however, no deuterium incorporation was observed. Therefore it was assumed that the proton source was in the reaction mixture from the beginning. It was believed that the potential sources were: the hydrazone proton, the α-methyl or methylene groups, residual water in the solvent or even the solvent itself.

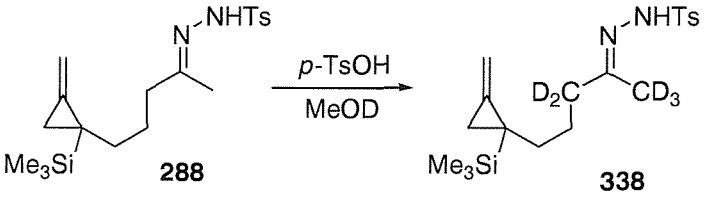
Deuteration of the hydrazone proton proved to be difficult, however >60% deuterium inclusion (adjudged by ^{1}H NMR) was achieved by stirring hydrazone **288** in MeOD for 1 hour. On cyclisation of the precursor it was found that lower yields of the products were formed but no deuterium was present. In addition a precursor was prepared where the hydrazone proton was replaced with a methyl group (Scheme 104).



Scheme 104

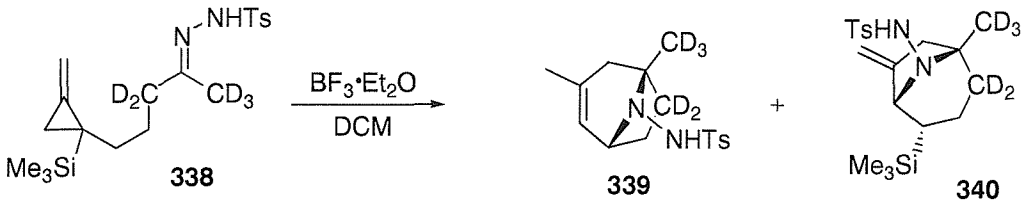
Methyl hydrazine **335** was treated with tosylchloride **334** which gave *N*-methyl-*N*-tosylhydrazine **336** in 71% yield.[100] Ketone **134** and hydrazine **336** were refluxed together in hexane for one hour which furnished hydrazone precursor **337** in quantative yield. Reaction of precursor **337** with $BF_3{\cdot}Et_2O$ in DCM led to decomposition of the reaction mixture.

When hydrazone **288** was stirred in MeOD with a catalytic amount of *p*-TsOH complete deuteration of the methylenes α to the hydrazone was observed **338** (Scheme 105).



Scheme 105

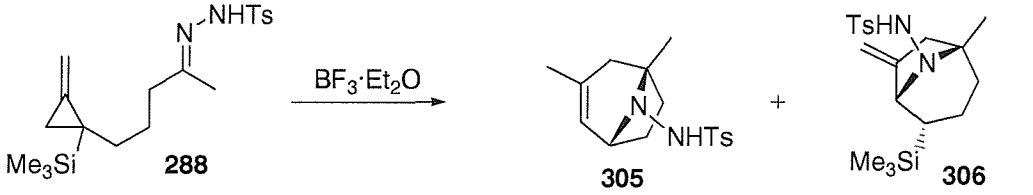
When deuterated hydrazone **338** was treated with $BF_3{\cdot}Et_2O$ in DCM cyclisation took place to form the corresponding deuterated azabicycles **339** and **340** in 30% yield, 1:1 ratio respectively (Scheme 106).



Scheme 106

A cyclisation was also carried out in DCM which had been washed with D_2O to investigate if the proton was coming from residual water in the solvent. This reaction gave a lower yield of the expected products but no deuterium incorporation in the products.

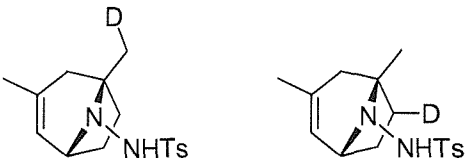
Cyclisations were also carried out in deuterated solvents (Scheme 107).



CD_2Cl_2	10%	24%
$CH_3CD_2NO_2$	40%	-

Scheme 107

The reaction carried out in deuterated DCM gave the cyclised products **305** and **306** with no deuterium inclusion. In the reaction with deuterated $EtNO_2$ some deuterium was present in the cyclised product. A ^2H NMR experiment was carried out and showed the presence of a small amount of deuterium inclusion at two sites in 2.5:1 ratio. From ^1H NMR integrations it was discovered that deuterium was present on the methyl α to the hydrazone in the cyclisation precursor and therefore the other site was assumed to be the methylene α to the hydrazone in the cyclisation precursor (Figure 32).



341 342

Figure 32 Products from cyclisation of ketone hydrazone **288** in deuterated $EtNO_2$

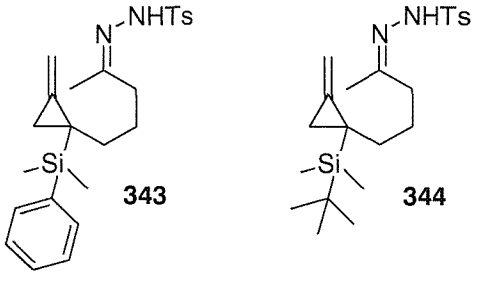
The occurrence of deuterium in these positions (**341** and **342**) was attributed to the formation of an enamine of cyclisation precursor **288** and subsequent quenching with deuterium from the solvent followed by cyclisation.

Unfortunately this investigation did not provide an explanation for the source of the proton in the protodesilylation step in the formation of **305**.

3.7 Other silyl groups

3.7.1 Introduction

Due to the low yielding nature of the cyclisation it was proposed that larger silyl groups might have an effect on the cyclisation. Two different silyl groups were chosen for the study (Figure 33).

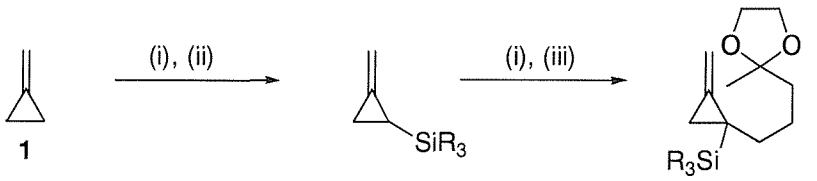


343 344

Figure 33 Hydrazone precursors **343** and **344**

3.7.2 Synthesis of precursors

The synthesis of the precursors was carried out in the same manner as that of the TMS substituted precursor.[79] Iodide **260** was prepared in the same fashion as previously reported (Scheme 77).



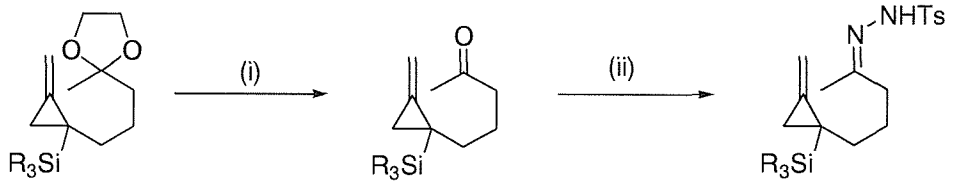
(i) ^{n}BuLi, THF, -78°C
(ii) R_3SiCl
(iii) **260**

78%, **217**, SiR_3=$SiPhMe_2$

71%, **345**, SiR_3=$SiPhMe_2$
36%, **346**, SiR_3=Si^tBuMe_2

Scheme 108

TBDMS ketal **346** was accessed by deprotonation of methylenecyclopropane **1** with ^{n}BuLi followed by quenching with TBDMSCl. A second equivalent of ^{n}BuLi was added and the subsequent anion coupled with iodide **260**. The two-step synthesis was carried out in 36% yield. DMPS ketal **345** was synthesized in 71% yield from the already prepared DMPS methylenecyclopropane **217** (chapter 2, section 2.4) by deprotonation with ^{n}BuLi followed by addition of iodide **260**.



345, SiR_3=$SiPhMe_2$
346, SiR_3=Si^tBuMe_2

84%, **347**, SiR_3=$SiPhMe_2$
91%, **348**, SiR_3=Si^tBuMe_2

100%, **343**, SiR_3=$SiPhMe_2$
100%, **344**, SiR_3=Si^tBuMe_2

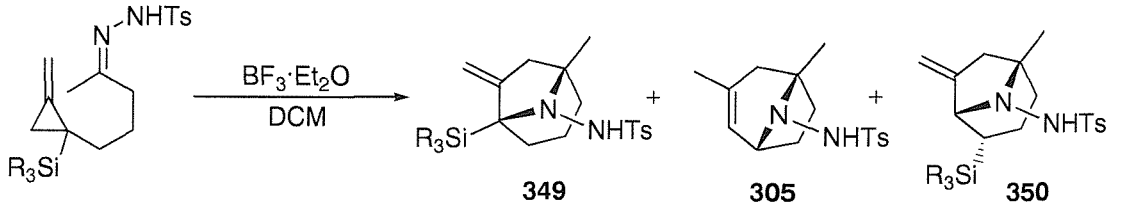
(i) 2 M HCl, acetone, H_2O
(ii) $TsHNNH_2$, hexane, Δ

Scheme 109

Ketals **345** and **346** were deprotected with 2 M HCl in wet acetone in 84% and 91% yields to give ketones **347** and **348** respectively. Ketones **347** and **348** were converted into the corresponding hydrazones **343** and **344** in quantitative yields by refluxing in hexane with tosylhydrazine. Hydrazones **343** and **344** were furnished as inseparable 4:1 and 5:1 mixtures of *E*:*Z* isomers.

3.7.3 Cyclisation of precursors

Cyclisations were carried out in DCM with $BF_3{\cdot}Et_2O$ as these conditions had proved simple and easy to use (Table 9).



349 **305** **350**

343, SiR_3=$SiPhMe_2$
344, SiR_3=Si^tBuMe_2

Scheme 110

Entry	SiR_3	Conditions	Yield / %		
			349	**305**	**350**
a	$SiPhMe_2$	0°C to RT, 18 hours	-	-	27
b	Si^tBuMe_2	0°C to RT, 18 hours	-	29	13

Cyclisation of methylenecyclopropylhydrazone **288** with $BF_3{\cdot}Et_2O$ in DCM gave azabicycles **305**, 35% and **306**, 2%

Table 9 Reaction of hydrazones **343** and **344** with $BF_3{\cdot}Et_2O$ in DCM

Cyclisation of precursor **344** gave bicycle **305** in 29% and bicycle **350b** in 13%, the overall yield was comparable to that of TMS precursor **288**. **305** and **350b** were isolated as an inseparable mixture of the two cyclic products and identified by comparison of ^1H NMR spectra with those of bicycles **305** and **306**. Cyclisation of **343**

appeared to be selective for the formation of **350a**, however the yield was lower, only 27%. In all cases the product resulting from direct quenching of the allyl cation was not observed at all.

3.8 Conclusions

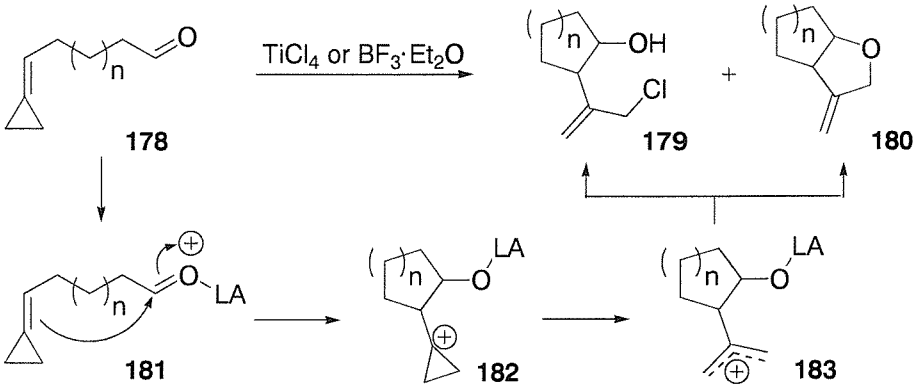
In conclusion, cyclisation of oximes, alkyl and aromatic imines disappointingly gave none of the desired cyclic compounds. Cyclisations of hydrazone precursors **287** and **289** proceeded to give the desired azabicycles **297** and **300** respectively in best yields of 40-50%. Treatment of hydrazone precursors **288** and **290** with Lewis acids also cyclised but gave a mixture of cyclic products in best overall yields of 40-55%. Investigation into the mechanism of the cyclisation proved to be fruitful and deuterated precursor **328** cyclised in the desired fashion to support the 1,2-hydride shift theory. Investigation into the effect of the substituents on the silyl group did not provide higher yields, however DMPS precursor **343** appeared to be selective for the formation of azabicycle **350a** albeit only in 27% yield. Although cyclisations of methylenecyclopropylimines did not provide a synthetically useful method for the formation of azabicyclic compounds, the cyclisation of hydrazone precursors **288** and **290** was mechanistically unusual and interesting.

Chapter 4

Intramolecular Cyclisation of Alkylidenecyclopropylcarbonyls

4.1 Introduction

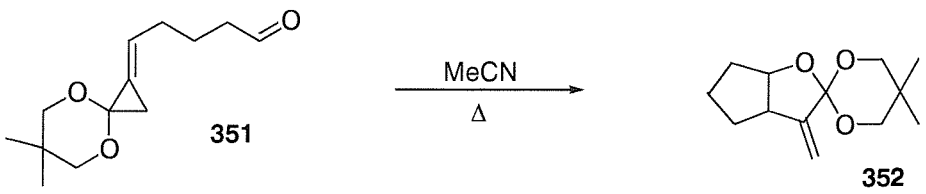
Following the successful work carried out by Peron *et al.*[78] on the cyclisation of methylenecyclopropylcarbonyls **127** yielding chloroalkenols **128** and **129** (Scheme 36), it was proposed that alkylidenecyclopropylcarbonyls **178** would cyclise in a similar manner to give chloroalkenols **179** or bicycles **180** (Scheme 49).



Scheme 49

With the Lewis acid chelated to the carbonyl, the olefin moiety could attack the complex to give cyclopropyl cation **182**. As previously reported the cyclopropyl ring could open to allyl cation **183** which could in turn be quenched by chloride or in an intramolecular fashion by the alkoxide to give **179** and **180** respectively.

Similar work carried out by Nakamura *et al.*[41] gave bicyclic ethers **352** from alkylidenecyclopropanes **351** (Scheme 111).



Scheme 111

Mild thermolysis of alkylidenecyclopropane **351** in acetonitrile leads to the opening of the cyclopropyl ring to give a trimethylenemethane equivalent, which undergoes a [3+2] cycloaddition onto the aldehyde furnishing tricycle **352**. Intermolecular work of this nature has also been carried out with imines[39,40] and olefins.[35,36]

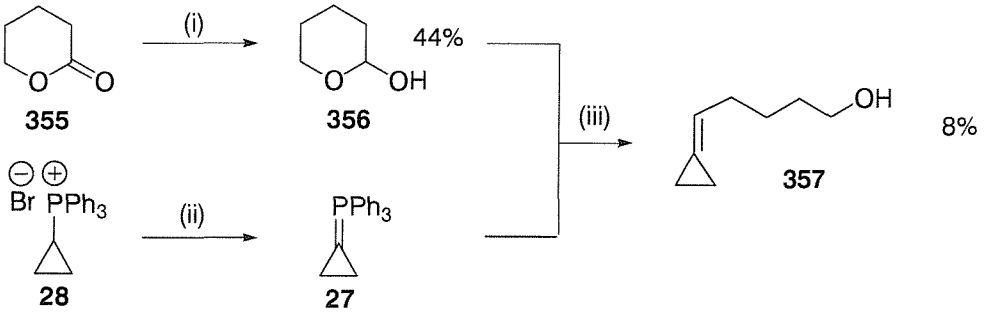
4.2 Synthesis of precursors

One of the most commonly reported syntheses of alkylidenecyclopropanes utilizes the Wittig olefination.[19,101] This method has been carried out with cyclopropyl-triphenylphosphonium ylide **27** and protected alcohols **353** to furnish alkylidene-cyclopropanes **354** (Scheme 112).

Scheme 112

Wittig reactions have also been carried out using lactols as aldehyde equivalents.[102,103] However, this method has not been reported in conjunction with cyclopropyl ylide **27**.

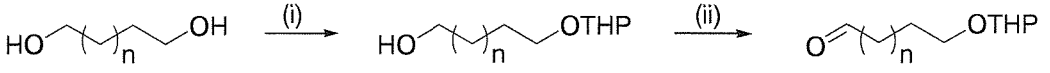
Wittig olefination was attempted with lactol **356** as it required fewer steps to prepare the cyclisation precursor (Scheme 113).



(i) DIBAL-H, -78°C, ether
(ii) NaH, THF, 62°C
(iii) TDA-1

Scheme 113

γ-Valerolactone **355** was treated with DIBAL-H, which gave γ-valerolactol **356** in 44% yield.[104] Preparation of cyclopropyl ylide **27** was achieved by treating cyclopropyltriphenylphosphonium bromide **28** with sodium hydride in THF at 62°C.[22] γ-Valerolactol **356** was then added to cyclopropyl ylide **27** with the additive TDA-1,[22] which furnished alkylidenecyclopropane **357** in poor 8% yield. The poor yield could be explained by the poor quality of the lactol used. However, it was decided that a longer and more reliable route would be employed (Scheme 114).

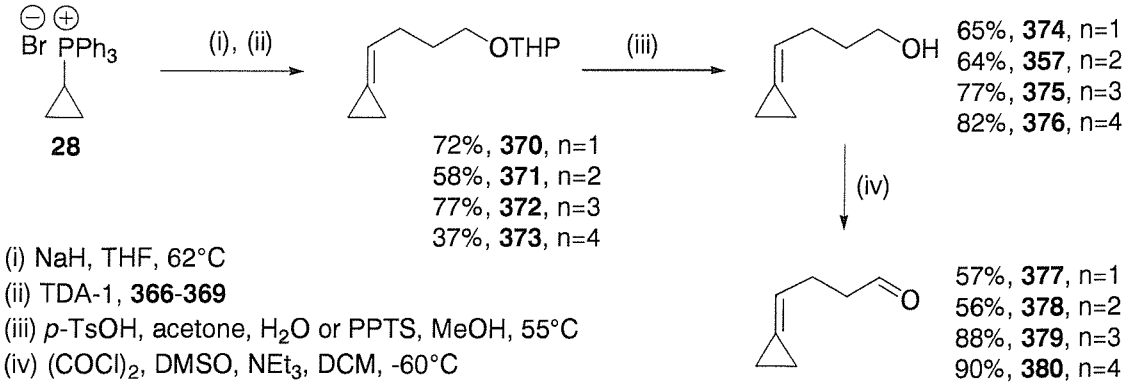


358, n=1	73%, **362**, n=1	62%, **366**, n=1
359, n=2	62%, **363**, n=2	81%, **367**, n=2
360, n=3	71%, **364**, n=3	70%, **368**, n=3
361, n=4	77%, **365**, n=4	56%, **369**, n=4

(i) DHP, dioxane, 0°C
(ii) $(COCl)_2$, DMSO, NEt_3, DCM, -60°C

Scheme 114

Diols **358-361** were treated with DHP and *p*-TsOH to furnish monoprotected diols **362-365** in good 62-77% yields.[105] Alcohols **362-365** were oxidized to aldehydes **366-369** using Swern[92] oxidation conditions in good 56-81% yields.



Scheme 115

Preparation of cyclopropyl ylide **27** was carried out as previously described from cyclopropyltriphenylphosphonium brominde **28**. Aldehydes **366-369** were added to cyclopropyl ylide **27** with TDA-1[22] to give alkylidenecyclopropanes **370-373** in 37-77% yields (Scheme 115). The THP protecting group of alkylidenecyclopropane **370** was removed by treatment with *p*-TsOH in wet acetone to furnish alcohol **374** in 65% yield. The THP protecting groups of **371-373** were removed using PPTS in MeOH at 55°C[106] to give alcohols **357**, **375** and **376** in good 64-82% yields. Oxidation of alcohols **374-376** and **357** to aldehydes **377-380** was carried out using Swern[92] oxidation conditions in 56-90% yields to give the cyclisation precursors.

4.3 Cyclisation of precursors

It was decided that the cyclisations would be carried out in DCM as methylenecyclopropylcarbonyls **127** had given good results as reported by Peron.[80] The Lewis acids selected for these reactions were $TiCl_4$ and $SnCl_4$, which were expected to give chloroalkenols **179**. $BF_3{\cdot}Et_2O$ was used to investigate the relative reactivity of alkylidenecyclopropylcarbonyls **178** compared to methylenecyclopropylcarbonyls **127**. Peron[80] reported that no reaction took place when methylenecyclopropylcarbonyls **127** were treated with either $BF_3{\cdot}Et_2O$ or $BF_3{\cdot}(AcOH)_2$.

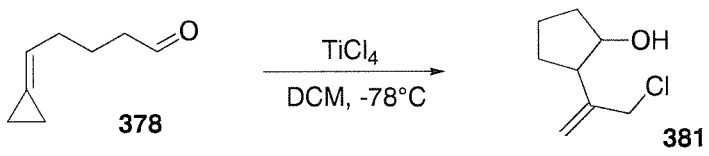
4.3.1 Cyclisation of precursors 377 and 380

When precursor **377** was treated with either $TiCl_4$, $SnCl_4$ or $BF_3{\cdot}Et_2O$ in DCM at -78°C no reaction was observed. As the reaction was allowed to warm to room temperature the starting material slowly decomposed.

When precursor **380** was treated with either $TiCl_4$ or $SnCl_4$ rapid decomposition was observed at -78°C. Treatment of **380** with $BF_3{\cdot}Et_2O$ led to slow decomposition as the reaction mixture was allowed to warm to room temperature.

4.3.2 Cyclisation of precursor 378

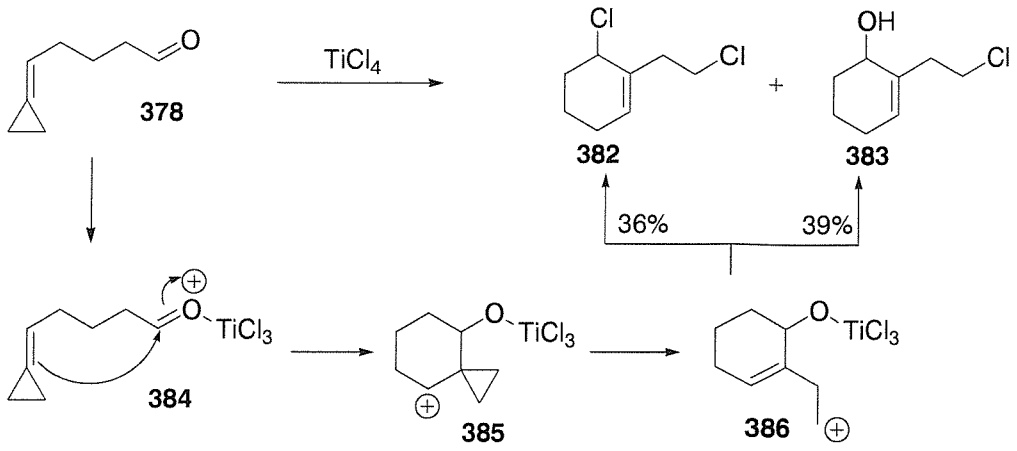
Cyclisation of alkylidenecyclopropane **378** with $TiCl_4$ was expected to give a mixture of cyclopentanol isomers of **381** (Scheme 116).



378 **381**

Scheme 116

The reaction was carried out at -78°C and proceeded quickly and cleanly to form two products in only five minutes. However, the two products formed were not the desired chloroalkenol isomers **381**, but instead cyclohexenes **382** and **383**. A mechanism for the formation of cyclohexenes **382** and **383** was proposed (Scheme 117).



Scheme 117

Instead of the alkyl end of the olefin attacking the Lewis acid-aldehyde complex the cyclopropyl end does. This leads to the formation of spirocycle **385** which can rearrange to cation **386**.[107] Cation **386** can then be simply quenched by chloride leading to cyclohexenol **383**. The occurrence of **382** as a product arises from the oxygen-$TiCl_3$ complex being displaced by chloride and this phenomenon has been reported previously by Peron.[80] Cyclohexenol **383** was isolated in 39% yield and cyclohexene **382** was isolated in 36% yield, the overall yield of the reaction was a good 75%.

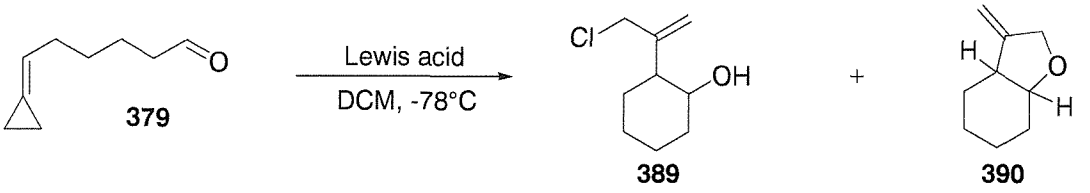
An explanation for the formation of a 6-membered ring in preference to the formation of a 5-membered ring comes from consideration of a chair-like transition state which could give better orbital overlap in this case (Figure 34). Davis *et al.*[108] have noted preference for the formation of 6-membered rings over 5-membered ring promoted by $TiCl_4$ previously.

Figure 34 Possible transition states of **384**

Cyclisation of alkylidenecyclopropane **378** with $BF_3 \cdot Et_2O$ was expected to give a 5,5-bicycle, however with the result of the $TiCl_4$ cyclisation in hand it was not inevitable. The cyclisation was attempted and the starting material was found to decompose rapidly at -78°C.

4.3.3 Cyclisation of precursor 379

Cyclisation of alkylidenecyclopropane **379** with $TiCl_4$ and $SnCl_4$ was expected to give a mixture of cyclohexanol isomers **389** and $BF_3 \cdot Et_2O$ was expected to give bicyclic ethers **390** (Scheme 118).



Scheme 118

Lewis acid	Conditions	Yield / %	
		389	**390**
$TiCl_4$	-78°C, 15 minutes	70	-
$SnCl_4$	-78°C to RT, 6 hours	29	22
$BF_3 \cdot Et_2O$	-78°C to RT, 3 hours	-	85[a]

a) Yield measured by GC

Table 10 Cyclisation of **379**

Reaction of alkylidenecyclopropane **379** with $TiCl_4$ proceeded quickly to furnish the desired chloroalkenol **389** as a 4:1 mixture of *cis*:*trans* isomers. Reaction with $SnCl_4$ proceeded much more slowly and gave a mixture of chloroalcohol **389** (2:1 *cis*:*trans*) and bicycle **390** (2:3 *cis*:*trans*). Reaction with $BF_3 \cdot Et_2O$ proceeded smoothly affording the

expected bicycle **390** as a 2:3 mixture of *cis*:*trans* isomers. The reaction was monitored by GC with tridecane as an internal standard due to the volatility of bicycle **390**.

The ratio of isomers of chloroalkenol **389** was determined by ^{1}H NMR integrations. The assignment of the isomers was elucidated by ^{1}H NMR coupling patterns (Figure 35).

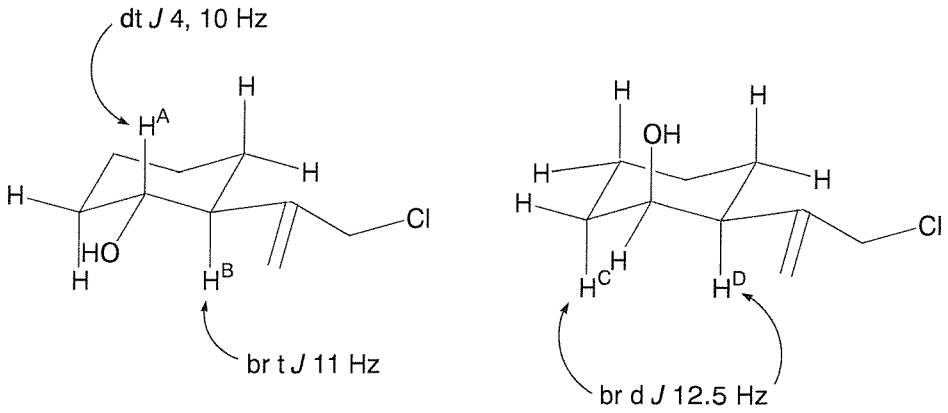


Figure 35 Stereochemical assignment of **389**

A signal at 3.58 ppm attributed to H^A proved to be a double triplet, *J* 4, 10 Hz, which corresponds to having two axial interactions and one equatorial interaction, thus indicating the stereochemistry of the minor isomer to be *trans*. In addition a signal at 2.08 ppm attributed to H^B proved to be a broad triplet, *J* 11 Hz, corresponding to having two axial interactions and an unresolved equatorial interaction. Two signals from the major isomer at 2.35 ppm and 1.95 ppm attributed to H^C and H^D proved to be broad doublets, *J* 12.5 Hz, indicating only one axial interaction and unresolved equatorial interactions leading to the conclusion that the major isomer was *cis*.

The ratio of bicyclic isomers **390** was determined by comparison with literature reported data.[109]

An explanation for the selectivity of the reaction could arise from the relative sizes of the Lewis acids used. The larger $TiCl_4$ leads to greater preference for the *cis* isomer due to a steric clash when both substituents are *pseudo* equatorial **391** (Figure 36). This could force one substituent into a *psuedo* axial position **392** leading to the observed preference for the *cis* isomer.

391 392

Figure 36 Possible transition states **391** and **392**

The smaller BF_3 would provide less steric clash when both substituents are *pseudo* equatorial and therefore leads to a slight preference for the *trans* isomer.

4.4 Synthesis of derivatised precursors

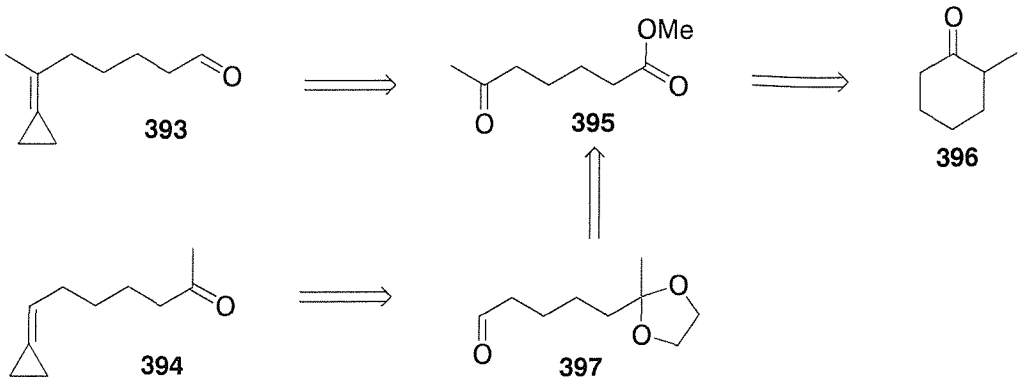
Following the success in the cyclisation of precursor **379** leading to the formation of chloroalkenols **389** and bicyclic ethers **390** it was decided to test the scope of this new methodology. Two other precursors were chosen for cyclisation with substitution on the alkene **393** and the carbonyl **394** (Figure 37).

393 394

Figure 37 Precursors **393** and **394**

4.4.1 Retrosynthesis

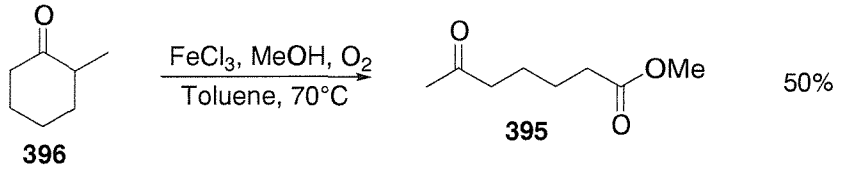
The synthesis of these precursors could be derived from a common ketoester **395** and thus methylcyclohexanone **396** (Scheme 119).



Scheme 119

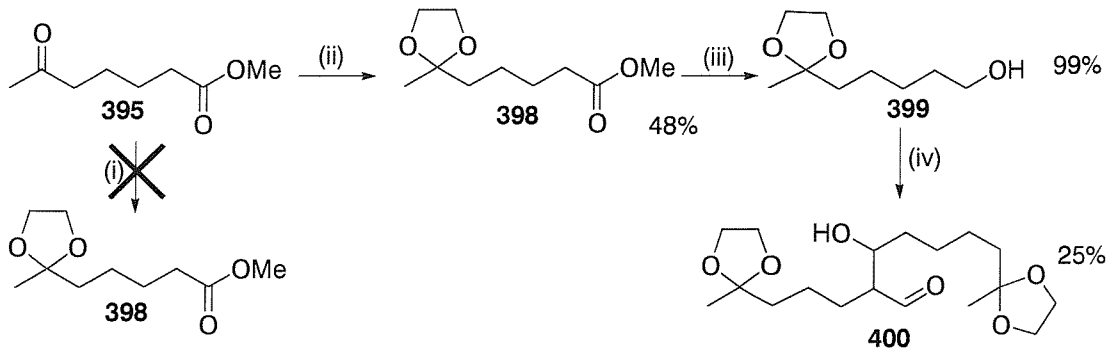
4.4.2 Forward synthesis

2-Methyl cyclohexanone **396** was treated with $FeCl_3$, MeOH in toluene under an oxygen atmosphere to furnish ketoester **395** in 50% yield (Scheme 120).[110]



Scheme 120

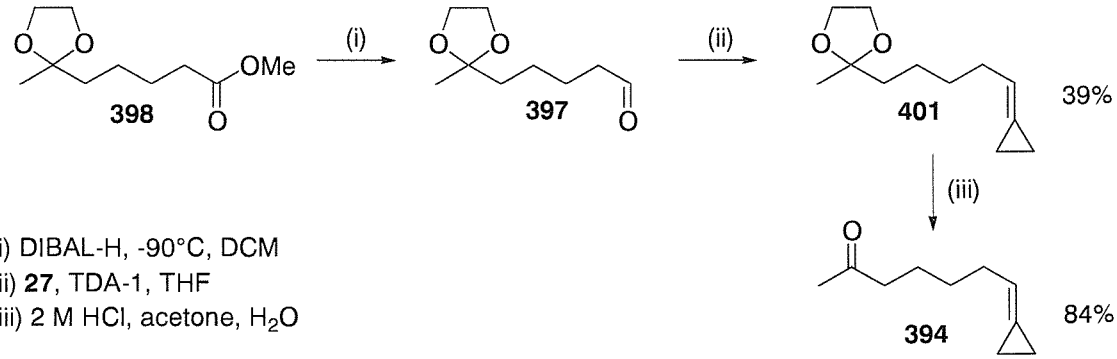
For the formation of precursor **394**, ketoester **395** was treated with ethyleneglycol and *p*-TsOH in refluxing toluene under Dean-Stark apparatus, but unfortunately this led to decomposition of ketoester **395** (Scheme 121).



i) $HO(CH_2)_2OH$, *p*-TsOH, toluene, Δ
ii) $TMSO(CH_2)_2OTMS$, TMSOTf, DCM, -78°C
iii) $LiAlH_4$, THF, 0°C
iv) $(COCl)_2$, DMSO, NEt_3, DCM, -60°C

Scheme 121

A milder method for the ketal protection was utilized in which bisTMS ethyleneglycol was treated with TMSOTf in the presence of ketoester **395** and gave the desired ketal in 48% yield.[111] Ketal **398** was treated with $LiAlH_4$ affording alcohol **399** in excellent 99% yield. When alcohol **399** was subjected to Swern[92] oxidation conditions NMR spectra suggested that an aldol reaction had taken place to give alcohol **400** in 25% yield. Therefore another route to aldehyde **397** was proposed in which a DIBAL-H[104] reduction was performed on ketalester **398** leading directly to aldehyde **397** (Scheme 122).

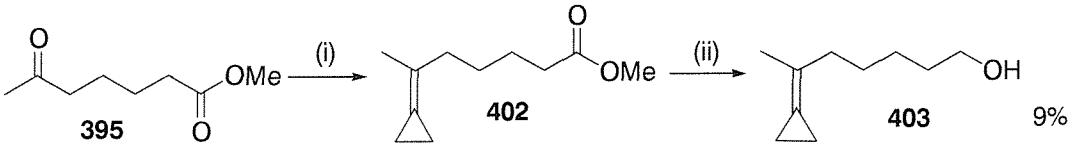


i) DIBAL-H, -90°C, DCM
ii) **27**, TDA-1, THF
iii) 2 M HCl, acetone, H_2O

Scheme 122

DIBAL-H reduction of ester **398** proceeded smoothly to give the desired aldehyde which was treated directly without purification with cyclopropyl ylide **27** affording ketal **401** in 39% yield over the two steps.[22] Ketal **401** was deprotected with aqueous acid to give cyclisation precursor **394**.

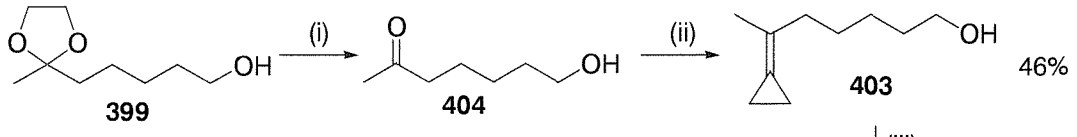
Synthesis of precursor **393** was first attempted by direct Wittig olefination on ketoester **395** followed by immediate reduction of the formed ester to alcohol **403** (Scheme 123).[101]



i) **27**, TDA-1, THF
ii) $LiAlH_4$, THF, 0°C

Scheme 123

However, this reaction only proceed in poor 9% yield so another method was devised (Scheme 124).



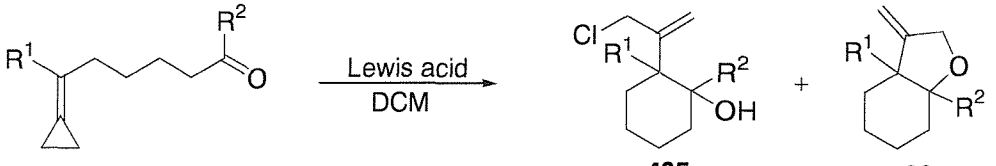
i) *p*-TsOH, acetone, H_2O
ii) **27**, TDA-1, THF
iii) $(COCl)_2$, DMSO, NEt_3, DCM, -60°C

Scheme 124

Ketal **399** was deprotected to ketoalcohol **404** in aqueous acid which was treated crude with cyclopropyl yilde **27** to afford alcohol **403** in 46% overall yield for the two steps.[22] Alcohol **403** was oxidized using Swern[92] oxidation conditions to give cyclisation precursor **393** in excellent 87% yield.

4.5 Cyclisation of precursors 393 and 394

Cyclisations were carried out in DCM using $TiCl_4$ and $BF_3{\cdot}Et_2O$ as Lewis acids because these were found to be the best conditions previously.



393, R^1=Me, R^2=H
394, R^1=H, R^2=Me

405 **406**

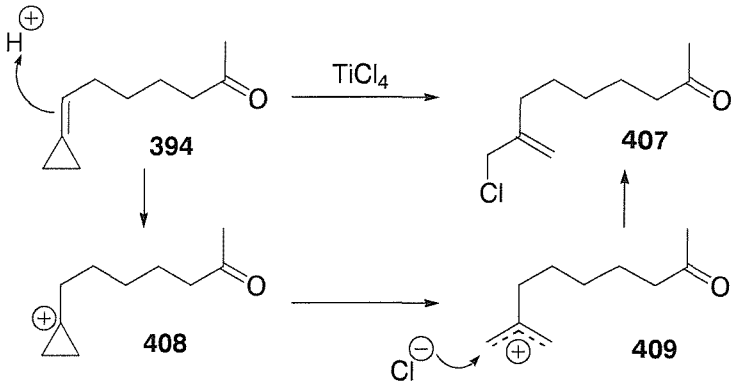
Scheme 125

Entry	R^1	R^2	Lewis acid	Conditions	Yield / %	
					405	**406**
a	H	Me	$TiCl_4$	-78°C, 4 hours	37	30
b	H	Me	$BF_3{\cdot}Et_2O$	RT, 24 hours	-	-
c	Me	H	$TiCl_4$	-78°C, 5 minutes	-	-
d	Me	H	$BF_3{\cdot}Et_2O$	-78°C, 2 hours	-	-

Table 11 Cyclisation of precursors **393** and **394**

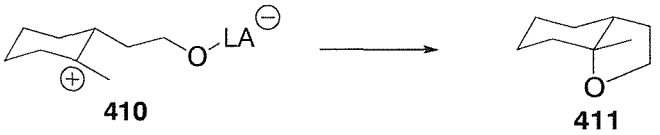
Treatment of precursor **394** with $TiCl_4$ in DCM gave an inseparable mixture of ketone **407** (Scheme 126) and the desired cyclohexanol **405a** as a single diastereoisomer in 9% and 37% yields respectively. Bicycle **406a** was isolated from the reaction mixture in 30% yield as a single diastereoisomer. Reaction of precursor **394** with $BF_3{\cdot}Et_2O$ gave no reaction after 24 hours at room temperature. Precursor **393** was found to decompose when treated with either $TiCl_4$ or $BF_3{\cdot}Et_2O$ in DCM at -78°C.

A possible mechanism for the formation of **407** arises from direct protonation of cyclisation precursor **394**, followed by opening of cyclopropyl cation **408** to π-allyl cation **409**. Cation **409** can then be quenched by chloride to give **407** (Scheme 126).



Scheme 126

The stereochemistry of **405a** and **406a** was assigned based on the preference for formation of *cis* 6,5-systems over *trans* 6,5-systems. Nishizawa *et al.*[112] reported that cation **410** was quenched by the alkoxide providing *cis* 6,5-bicycle **411** exclusively, where either *cis* or *trans* stereochemistry was possible (Scheme 127).



Scheme 127

The stereochemistry of **405a** and **406a** were known to be different because chloroalkenol **405a** was treated with sodium hydride in ether and cyclised to give the opposing stereochemistry to that of **406a**. There appeared to be no great preference for the formation of either *cis* or *trans* stereochemistry in the cyclisation. *Cis* stereochemistry led to intramolecular trapping of the allyl cation, whereas *trans* stereochemistry led to intermolecular trapping by chloride due to the relative rates for the formation of 6,5-bicycles. One substituent, either methyl or carbonyl, must occupy a *psuedo* axial position in the proposed chair transition states **412** and **413** giving rise to a lack of stereoselectivity (Figure 38).

412 413

Figure 38 Possible geometries of chair transition states **412** and **413**

4.6 Conclusions

The formation of 5-membered rings and thus 5,5-bicyclic compounds proved elusive using this methodology. However, it did provide an interesting and novel mechanistic pathway to the formation of cyclohexenes **382** and **383**. Formation of 6-membered rings and thus 6,5-bicyclic compounds was much more fruitful and yielded a successful and novel route to the skeleton of many natural products.

Chapter 5

Experimental

5.1 General Experimental

Whenever possible reagents were purified by standard techniques described in Perrin and Armarego.[113] Solvents were distilled prior to use; THF was distilled from sodium and benzophenone, DCM was distilled from calcium hydride and petrol was distilled from calcium hydride at the fractional boiling point between 40°C and 60°C. Thin layer chromatography was performed on aluminium backed sheets coated with silica gel (0.25 mm) which contained the fluorescent indicator UV_{254}. Flash column chromatography was carried out using Sorbsil C60, 40-60 mesh silica.

5.2 Instrumentation

^{1}H NMR spectra were obtained at 250 MHz on a Bruker DPX 250 spectrometer, 300 MHz on a Bruker AC 300 spectrometer or 400 MHz on a Bruker DPX 400 spectrometer. Peak positions are quoted against the δ scale relative to the residual chloroform signal (δ 7.27), using the following notation; singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). ^{13}C NMR spectra were obtained at 62.5 MHz on a Bruker DPX 250, 75.5 MHz on a Bruker AC 300 or 100 MHz on a Bruker DPX 400 spectrometer. The multiplicities of the signals were determined by DEPT experiment at 135° and are quoted within the brackets using the following notation; quarternary (0), tertiary (1), secondary (2), primary (3).

All infrared spectra were obtained on a Bio-Rad Golden Gate A FT-IR spectrometer. The relative intensity of the peaks are quoted within the brackets using the following notation; broad (br), strong (s), medium, (m), weak (w).

Low resolution EI and CI spectra were obtained on a Thermoquest TraceMS gas chromatography mass spectrometer and ES mass spectra were obtained on a Micromass platform with a quadrapole mass analyser. High resolution EI and CI mass spectra were obtained on a VG 70SE normal geometry double focusing mass spectrometer. High resolution ES were obtained on either a Bruker Apex III FT-ICR mass spectrometer or a Micromass Q-Tof 1 mass spectrometer.

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

5.3 General procedures

5.3.1 Typical intermolecular cyclisation procedure

Lewis acid was added dropwise to a stirred solution of MCP derivative and aldehyde in solvent at specified temperature under an inert atmosphere. The reaction was stirred until no starting material was visualized by TLC. The reaction was quenched with water, extracted with DCM, dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to ether in petrol).

5.3.2 Typical intramolecular cyclisation procedure

Lewis acid was added dropwise to a stirred solution cyclisation precursor in solvent at specified temperature under an inert atmosphere. The reaction was stirred until no starting material was visualized by TLC. The reaction was quenched with water, extracted with DCM, dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to ether in petrol).

5.4 Experimental for chapter 2

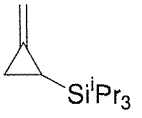
Methylenecyclopropane (1).

Following a method described by Köster *et al.*[12]

In a reaction flask fitted with a cold finger at -40°C with 3 subsequent traps, the first trap at room temperature and the two subsequent traps at -78°C. Methallyl chloride **8** (280 mL, 2.84 mol) was added dropwise over a 9 hour period to a rapidly stirred suspension of sodium amide (139 g, 3.56 mol) in dry ^{n}dibutyl ether (400 mL) at 130-140°C under a slow stream of nitrogen. The reaction mixture was refluxed for a further 10 hours. The cold finger was warmed to 30-40°C for 5 hours and products were collected in the second trap as a mixture of methylenecyclopropane **1**, methylcyclopropene **10** and ammonia. The ammonia layer was allowed to evaporate and the resulting mixture added to a solution of ^{t}BuOH (2.27 mL, 36.0 mmol) in DMSO (50 mL), at 0°C under a slow stream of nitrogen. ^{t}BuOK (1.77 g, 24.0 mmol) in DMSO (30 mL) was added over a 3 hour period. The mixture was warmed to 45°C over a 14 hour period under a cold finger at -60°C. The cold finger was warmed to 35°C over 6 hours and products collected in traps at -78°C to give methylenecyclopropane **1** as a colourless liquid (95 mL, 50%)

δ_H (400 MHz, $CDCl_3$) 5.42 (2H, s, C=CH_2), 1.08 (4H, s, C(CH_2CH_2)); δ_C (100 MHz, $CDCl_3$) 131.43 (0), 103.50 (2), 3.15 (2x2).

Spectroscopic data agrees with Peron.[80]



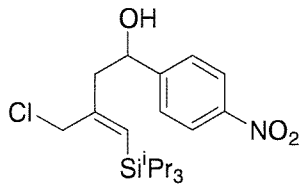
Trisisopropyl(2-methylidenecyclopropyl)silane (185).

Following a method described by Thomas.[15]

^{n}BuLi (30.2 mL, 2.5 M, 74.1 mmol) was added to a stirred solution of methylenecyclopropane **1** (5.0 mL, 74.1 mmol) in THF (100 mL) at -78°C under argon.

The solution was allowed to warm to 0°C over 40 minutes and then up to room temperature over a further 40 minutes. The resulting yellow solution was cooled to -78°C before addition of TIPSCl (15.8 g, 74.1 mmol). The solution turned colourless and was allowed to warm to 0°C and quenched with sat. NH_4Cl (50 mL). The aqueous layer was extracted with ether (3x50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol) to give methylenecyclopropane derivative **185** as a colourless oil (13.2 g, 85%).

R_f 0.76 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2978 (m), 2875 (m), 1382 (w), 1122 (s); δ_H (300 MHz, $CDCl_3$) 5.29 (1H, s, C=CH_AH$_B$), 5.20 (1H, s, C=CH$_A$$H_B$), 1.21 (1H, m, CH_2=CCH_AH$_B$), 1.01 (1H, m, CH_2=CCH$_A$$H_B$), 0.97 (21H, s, Si(CH(C$H_3$)$_2$)$_3$), 0.59 (1H, m, CHSi); δ_C (75 MHz, $CDCl_3$) 135.68 (0), 100.54 (2), 18.53 (6x3), 11.54 (3x1), 6.20 (2), 0.36 (1); LRMS (CI) *m/z* 228 (49%, $[M+NH_4]^+$), 167 (100%, $[M-^iPr]^+$); HRMS (CI) *m/z* 167.1262 ($[M-^iPr]^+$ - $C_{10}H_{19}Si$ requires 167.1256).

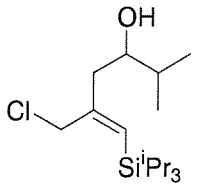


(Z)-3-(Chloromethyl)-1-(4-nitrophenyl)-4-(1,1,1-trisisopropylsilyl)-3-buten-1-ol (191e).

Following the typical intermolecular cyclisation procedure, $TiCl_4$ (1.1 eq.) was added to MCP derivative **185** (100 mg) and *p*-nitrobenzaldehyde (1 eq.) in DCM (4 mL) at -78°C under argon. The reaction was stirred for 1 hour. The crude material was purified by column chromatography (petrol to 7% ether in petrol) to give chloroalkenol **191e** as a white solid (121 mg, 64%).

Found: C, 60.22; H, 7.98; N, 3.43. $C_{20}H_{32}NO_3SiCl$ requires C, 60.35; H, 8.10; N, 3.53%; m.p. 122-124°C; R_f 0.45 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3496 (br), 2942 (w), 2865 (w), 1606 (w), 1515 (m), 1341 (m), 907 (m), 732 (s); δ_H (300 MHz, $CDCl_3$) 8.21 (2H, d, *J* 9 Hz, ArH), 7.58 (2H, d, *J* 9 Hz, ArH), 5.50 (1H, s, C=CHSi), 5.08 (1H, m, C*H*OH), 4.30 (2H, s, CH_2Cl), 2.90 (1H, dd, *J* 5, 14 Hz, CH_AH$_B$CHOH), 2.63 (1H, dd, *J* 9, 14 Hz,

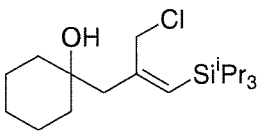
CH_AH_BCHOH), 2.20 (1H, d, *J* 3 Hz, OH), 1.16-1.02 (21H, m, $Si(CH(CH_3)_2)_3$); δ_C (75 MHz, $CDCl_3$) 151.19 (0), 149.64 (0), 147.46 (0), 131.14 (1), 126.79 (2x1), 123.86 (2x1), 71.97 (1), 48.03 (2), 47.63 (2), 18.94 (6x3), 12.16 (3x1); LRMS (CI) *m/z* 415 (22%, $[M+NH_4]^+$).



(*Z*)-5-(Chloromethyl)-2-methyl-6-(1,1,1-trisisopropylsilyl)-5-hexen-3-ol (191d).

Following the typical intermolecular cyclisation procedure, $TiCl_4$ (1.1 eq.) was added to MCP derivative **185** (100 mg) and *iso*-butyraldehyde (1 eq.) in DCM (3 mL) at -78°C under argon. The reaction was stirred for 2 hours. The crude material was purified by column chromatography (petrol to 7% ether in petrol) to give chloroalkenol **191d** as a colourless oil (81 mg, 53%).

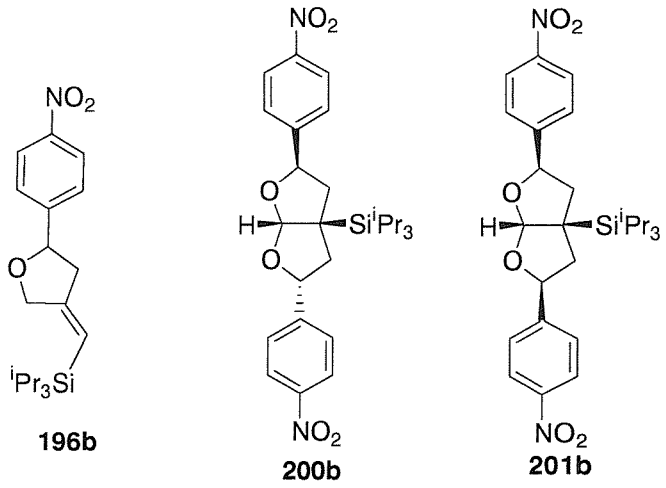
R_f 0.63 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3460 (br), 2942 (s), 2865 (s), 1461 (m), 1253 (w), 997 (m), 880 (s); δ_H (300 MHz, $CDCl_3$) 5.52 (1H, s, CHSi), 4.13 (2H, s, CH_2Cl), 3.55 (1H, ddd, *J* 3, 6, 10 Hz, C*H*OH), 2.70 (1H, dd, *J* 3, 15 Hz, CH_AH_BCHOH), 2.26 (1H, dd, *J* 10, 15 Hz, CH_AH_BCHOH), 1.71 (1H, m, $CH(CH_3)_2$), 1.20-0.99 (21H, m, $Si(CH(CH_3)_2)_3$), 0.97 (3H, d, *J* 7 Hz, CH_3), 0.96 (3H, d, *J* 7 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 152.12 (0), 129.04 (1), 74.51 (1), 47.85 (2), 42.82 (2), 33.83 (1), 19.01 (2x3), 17.68 (6x3), 12.25 (3x1); LRMS (CI) *m/z* 283 (6%, $[M-Cl]^+$), 174 (100%); HRMS (CI) *m/z* 283.2459 ($[M -Cl]^+$- $C_{17}H_{35}OSi$ requires 283.2457).



1-[(*Z*)-2-(Chloromethyl)-3-(1,1,1-trisisopropylsilyl)-2-propenyl]-1-cyclohexanol (191c).

Following the typical intermolecular cyclisation procedure, $TiCl_4$ (1.1 eq.) was added to MCP derivative **185** (100 mg) and cyclohexanone (1 eq.) in DCM (4 mL) at -78°C under argon. The reaction was stirred for 3 hours. The crude material was purified by column chromatography (petrol to 7% ether in petrol) to give chloroalkenol **191c** as a colourless oil (70 mg, 43%).

R_f 0.50 (30:70 ether:petrol); υ_{max} (neat)/cm^{-1} 3461 (br), 2935 (s), 2864 (s), 1604 (w), 1461 (w), 881 (m); δ_H (400 MHz, $CDCl_3$) 5.49 (1H, s, CHSi), 4.28 (2H, s, CH_2Cl), 2.54 (2H, s, CCH_2COH), 1.65-1.46 (10H, m, $(CH_2)_5$), 1.34 (1H, br s, OH), 1.19-1.09 (21H, m, $Si(CH(CH_3)_2)_3$); δ_C (100 MHz, $CDCl_3$) 151.86 (0), 130.67 (1), 72.08 (0), 49.79 (2), 49.16 (2), 38.49 (2x2), s26.02 (2), 22.67 (2x2), 19.12 (6x3), 12.47 (3x1); LRMS (CI) *m/z* 309 (6%, $[M\text{-}Cl]^+$), 98 (100%); HRMS (EI) *m/z* 301.1799 ($[M\text{-}^iPr]^+$ - $C_{16}H_{30}OSi^{35}Cl$ requires 301.1755).



Trisisopropyl[(*Z*)-5-(4-nitrophenyl)tetrahydrofuran-3-yliden]methylsilane (196b).

Rac-[(2*R*,5*R*,)-2,5-Di(4-nitrophenyl)perhydrofuro[2,3-*b*]furan-3-yl](trisisopropyl) silane (200b).

Rac-[(2*S*,3a*r*,5*R*,6a*r*)-2,5-Di(4-nitrophenyl)perhydrofuro[2,3-*b*]furan-3-yl](trisiso propyl)silane (201b).

Following the typical intermolecular cyclisation procedure, $BF_3{\cdot}Et_2O$ (2.5 eq.) was added to MCP derivative **185** (100 mg) and *p*-nitrobenzaldehyde (2 eq.) in DCM (4 mL) at -70°C under argon. The reaction was allowed to warm to -20°C over 2 hours. The crude

material was purified by column chromatography (petrol to 20% ether in petrol) to give tetrahydrofuran **196b** as a white solid (75 mg, 44%), furofuran **200b** as a white solid (40 mg, 16%) and furofuran **201b** as a white solid (70 mg, 29%).

Data for **196b**

Found: C, 66.33; H, 8.88; N, 3.84. $C_{20}H_{31}NO_3Si$ requires C, 66.44; H, 8.64; N, 3.87%; m.p. 67-69°C; R_f 0.66 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2941 (m), 2864 (m), 1630 (w), 1604 (w), 1519 (m), 1345 (m), 733 (s); δ_H (300 MHz, $CDCl_3$) 8.22 (2H, d, *J* 9 Hz, ArH), 7.54 (2H, d, *J* 9 Hz, ArH), 5.54 (1H, t, *J* 1 Hz, CHSi), 5.05 (1H, dd, *J* 7, 8 Hz, OCHAr), 4.61 (1H, d, *J* 14 Hz, OCH_AH_B), 4.43 (1H, d, *J* 14 Hz, OCH_AH_B), 3.13 (1H, ddd, *J* 1, 7, 16 Hz, $OCHCH_AH_B$), 2.63 (1H, br dd, *J* 8, 16 Hz, $OCHCH_AH_B$), 1.18-1.03 (21H, m, $Si(CH(CH_3)_2)_3$); δ_C (75 MHz, $CDCl_3$) 156.56 (0), 149.79 (0), 147.42 (0), 126.64 (2x1), 123.84 (2x1), 115.70 (1), 79.26 (1), 71.60 (2), 45.59 (2), 18.92 (6x3), 11.83 (3x1); LRMS (CI) *m/z* 379 (6%, $[M+NH_4]^+$), 332 (100%).

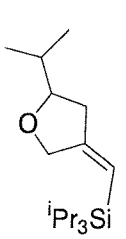
Data for **200b**

Found: C, 62.99; H, 7.25; N, 5.31. $C_{27}H_{36}N_2O_6Si$ requires C, 63.26; H, 7.08; N, 5.46%; m.p. 157-159°C; R_f 0.53 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2947 (w), 2868 (w), 1603 (w), 1520 (s), 1465 (s), 1345 (s); δ_H (300 MHz, $CDCl_3$) 8.24 (2H, d, *J* 9 Hz, ArH), 8.18 (2H, d, *J* 9 Hz, ArH), 7.62 (2H, d, *J* 9 Hz, ArH), 7.48 (2H, d, *J* 9 Hz, ArH), 6.27 (1H, s, OCHO), 5.21 (1H, t, *J* 8 Hz, CHAr), 4.91 (1H, dd, *J* 5, 11 Hz, CHAr), 3.05 (1H, dd, *J* 8, 13 Hz, CH_AH_BCHAr), 2.16 (1H, dd, *J* 5, 13 Hz, CH_AH_BCHAr), 2.00 (1H, dd, *J* 11, 13 Hz, CH_AH_BCHAr), 1.82 (1H, dd, *J* 8, 13 Hz, CH_AH_BCHAr), 1.38-1.15 (21H, m, $Si(CH(CH_3)_2)_3$); δ_C (75 MHz, $CDCl_3$) 150.69 (0), 148.33 (0), 147.51 (0), 147.39 (0), 126.42 (2x1), 125.94 (2x1), 124.00 (4x1), 112.99 (1), 80.07 (1), 76.91 (1), 47.90 (2), 44.93 (2), 43.07 (0), 19.58 (6x3), 11.59 (3x1); LRMS (CI) *m/z* 513 (100%, $[M+H]^+$).

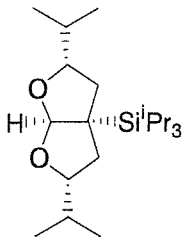
Data for **201b**

Found: C, 63.07; H, 6.97; N, 5.57. $C_{27}H_{36}N_2O_6Si$ requires C, 63.26; H, 7.08; N, 5.46%; m.p. 206-208°C; R_f 0.36 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2947 (w), 2869 (w), 1603 (w), 1519 (s), 1467 (m), 1345 (s); δ_H (300 MHz, $CDCl_3$) 8.24 (4H, d, *J* 9 Hz, ArH), 7.54 (4H, d, *J* 9 Hz, ArH), 6.35 (1H, s, OCHO), 5.36 (2H, dd, *J* 6, 11 Hz, CHAr), 2.48 (2H, dd, *J* 6, 13 Hz, CH_AH_BCHAr), 2.16 (2H, dd, *J* 11, 13 Hz, CH_AH_BCHAr), 1.30-1.15 (21H, m, $Si(CH(CH_3)_2)_3$); δ_C (75 MHz, $CDCl_3$) 148.93 (2x0), 147.46 (2x0), 126.12 (4x1),

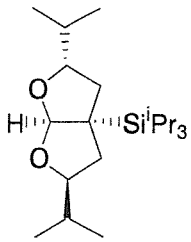
124.04 (4x1), 112.26 (1), 80.46 (2x1), 47.33 (2x2), 42.70 (0), 19.44 (6x3), 11.43 (3x1); LRMS (CI) *m/z* 513 (100%, $[M+H]^+$).



196a



200a



201a

Trisisopropyl[(*Z*)-(5-isopropyltetrahydro-3-furanyliden)methyl]silane (196a).

Rac-[(2*S*,3a*r*,5*R*,6a*r*)-2,5-Diisopropylperhydrofuro[2,3-*b*]furan-3-yl](trisisopropyl) silane (200a).

Rac-[(2*S*,5*S*,)-2,5-Diisopropylperhydrofuro[2,3-*b*]furan-3-yl](trisisopropyl)silane (201a).

Following the typical intermolecular cyclisation procedure, $BF_3{\cdot}Et_2O$ (2.5 eq.) was added to MCP derivative **185** (100 mg) and *iso*-butyraldehyde (2 eq.) in DCM (4 mL) at 0°C under argon. The reaction was allowed to warm to room temperature over 3 hours. The crude material was purified by column chromatography (petrol to 1% ether in petrol) to give tetrahydrofuran **196a** as a colourless oil (55 mg, 41%), furofuran **200a** as a colourless oil (23 mg, 14%) and furofuran **201a** as a colourless oil (47 mg, 28%).

Data for **196a**

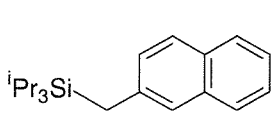
R_f 0.62 (5:95 ether:petrol); υ_{max} (neat)/cm^{-1} 2941 (s), 2864 (s), 1630 (w), 1460 (m), 1063 (m), 880 (s); δ_H (300 MHz, $CDCl_3$) 5.44 (1H, t, *J* 2 Hz, CHSi), 4.38 (1H, br d, *J* 14 Hz, OCH_AH_B), 4.43 (1H, dd, *J* 2, 14 Hz, OCH_AH_B), 3.55 (1H, m, $OCH^{i}Pr$), 2.65 (1H, dd, *J* 6, 16 Hz, $OCHCH_AH_B$), 2.41 (1H, dd, *J* 9, 16 Hz, $OCHCH_AH_B$), 1.71 (1H, m, $CH(CH_3)_2$), 1.20-1.03 (21H, m, $Si(CH(CH_3)_2)_3$), 0.99 (3H, d, *J* 7 Hz, $CH(CH_3)CH_3$), 0.90 (3H, d, *J* 7 Hz, $CH(CH_3)CH_3$); δ_C (75 MHz, $CDCl_3$) 158.99 (0), 113.66 (1), 84.69 (1), 71.24 (2), 41.28 (2), 33.04 (1), 19.40 (3), 18.94 (6x3), 18.78 (3), 11.85 (3x1); LRMS (CI) *m/z* 283 (8%, $[M+H]^+$), 239 (100%, $[M-^{i}Pr]^+$); HRMS (EI) *m/z* 281.2297 ($[M-H]^+$- $C_{17}H_{33}OSi$ requires 281.2301).

Data for **200a**

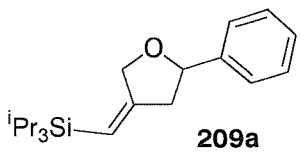
R_f 0.48 (5:95 ether:petrol); υ_{max} (neat)/cm^{-1} 2955 (s), 2868 (s), 1467 (m), 1004 (m), 883 (m); δ_H (400 MHz, $CDCl_3$) 5.81 (1H, s, OCHO), 3.71 (2H, ddd, *J* 6, 8, 10 Hz, OC*H*^{i}Pr), 1.86 (2H, dd, *J* 10, 13 Hz, CH_AH$_B$), 1.80 (2H, dd, *J* 8, 13 Hz, CH$_A$$H_B$), 1.63-1.53 (2H, m, C*H*(CH$_3$)$_2$), 1.30-1.22 (3H, m, Si(C*H*(CH$_3$)$_2$)$_3$), 1.14 (18H, d, *J* 7 Hz, Si(CH(C*H*$_3$)$_2$)$_3$), 1.02 (6H, d, *J* 7 Hz, CH(C*H*$_3$)CH$_3$) 0.86 (6H, d, *J* 7 Hz, CH(CH$_3$)C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 111.64 (1), 85.93 (2x1), 43.34 (2x2), 41.44 (0), 34.34 (2x1), 20.66 (2x3), 19.96 (6x3), 19.06 (2x3), 12.12 (3x1); LRMS (CI) *m/z* 355 (49%, $[M+H]^+$), 311 (34%, $[M-{}^iPr]^+$), 181 (100%); HRMS (CI) *m/z* 355.3023 ($[M+H]^+$- $C_{21}H_{43}O_2Si$ requires 355.3032).

Data for **201a**

R_f 0.46 (5:95 ether:petrol); υ_{max} (neat)/cm^{-1} 2955 (s), 2868 (s), 1467 (m), 902 (s), 776 (s); δ_H (400 MHz, $CDCl_3$) 5.80 (1H, s, OCHO), 3.70 (1H, ddd, *J* 5, 7, 10 Hz, OC*H*^{i}Pr), 3.50 (1H, dt, *J* 10, 7 Hz, OC*H*^{i}Pr), 2.35 (1H, dd, *J* 7, 13 Hz, CH_AH$_B$), 1.77-1.65 (4H, m, CH_AH$_B$, , CH$_A$$H_B$, C*H*(CH$_3$)$_2$), 1.42 (1H, dd, *J* 10, 13 Hz, CH$_A$$H_B$), 1.29-1.20 (3H, m, Si(C*H*(CH$_3$)$_2$)$_3$), 1.15 (18H, d, *J* 7 Hz, Si(CH(C*H*$_3$)$_2$)$_3$), 1.02 (3H, d, *J* 7 Hz, CH(C*H*$_3$)CH$_3$), 1.00 (3H, d, *J* 7 Hz, CH(C*H*$_3$)CH$_3$), 0.88 (3H, d, *J* 7 Hz, CH(CH$_3$)C*H*$_3$), 0.86 (3H, d, *J* 7 Hz, CH(CH$_3$)C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 111.70 (1), 85.80 (1), 81.31 (1), 42.77 (2), 41.55 (0), 40.81 (2), 34.21 (1), 32.60 (1), 20.52 (3), 20.24 (3), 19.99 (6x3), 19.31 (3), 18.81 (3), 11.92 (3x1); LRMS (CI) *m/z* 355 (45%, $[M+H]^+$) 311 (32%, $[M-{}^iPr]^+$), 181 (100%); HRMS (CI) *m/z* 355.3027 ($[M+H]^+$- $C_{21}H_{43}O_2Si$ requires 355.3032).



210a



209a

Trisisopropyl(2-naphthylmethyl)silane (210a).

Trisisopropyl[(5-phenyltetrahydro-3-furanyliden)methyl]silane (209a).

Following the typical intermolecular cyclisation procedure, $BF_3{\cdot}Et_2O$ (1.2 eq.) was added to MCP derivative **185** (100 mg) and benzaldehyde (1 eq.) in DCM (4 mL) at 0°C under argon. The reaction was allowed to warm to room temperature over 4 hours. The crude material was purified by column chromatography (petrol to 1% ether in petrol) to give

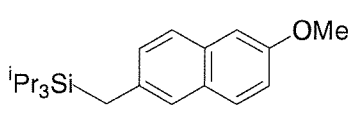
naphthalene **210a** as a colourless oil (30 mg, 21%) and tetrahydrofuran **209a** as a colourless oil (70 mg, 47%).

Data for **210a**

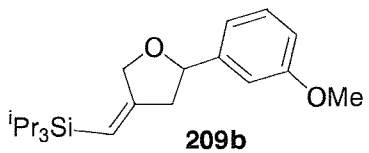
R_f 0.71 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2941 (m), 2864 (m), 1401 (w), 904 (s), 7.31 (s); δ_H (300 MHz, $CDCl_3$) 7.78 (1H, br d, *J* 8 Hz, ArH), 7.71 (1H, d, *J* 8 Hz, ArH), 7.69 (1H, d, *J* 8 Hz, ArH), 7.53 (1H, s, ArH), 7.43 (1H, dt, *J* 1, 7 Hz, ArH), 7.38 (1H, dt, *J* 1, 7 Hz, ArH), 7.28 (1H, dd, *J* 1, 7 Hz, ArH), 2.38 (2H, s, $SiCH_2Ar$), 1.19-1.03 (21H, m, $Si(CH(CH_3)_2)_3$); δ_C (75 MHz, $CDCl_3$) 138.90 (0), 134.15 (0), 131.07 (0), 128.43 (1), 127.69 (1), 127.60 (1), 127.09 (1), 125.95 (1), 125.88 (1), 124.48 (1), 19.51 (2), 18.83 (6x3), 11.22 (3x1); LRMS (CI) *m/z* 299 (100%, $[M+H]^+$); HRMS (EI) *m/z* 298.2111 ($[M]^+$- $C_{20}H_{30}Si$ requires 298.2117).

Data for **209a**

R_f 0.69 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2943 (w), 2865 (w), 905 (m), 729 (s); δ_H (300 MHz, $CDCl_3$) 7.39-7.28 (5H, m, Ph), 5.53 (1H, t, *J* 2 Hz, CHSi), 4.96 (1H, dd, *J* 6, 9 Hz, OCHPh), 4.59 (1H, d, 14 Hz, OCH_AH_B), 4.43 (1H, d, 14 Hz, OCH_AH_B), 3.04 (1H, br dd with fine splitting, *J* 6, 16 Hz, $OCHCH_AH_B$), 2.72 (1H, br dd with fine splitting, *J* 9, 16 Hz, $OCHCH_AH_B$), 1.23-1.09 (21H, m, $Si(CH(CH_3)_2)_3$); δ_C (75 MHz, $CDCl_3$) 158.08 (0), 141.95 (0), 128.55 (2x1), 127.71 (1), 126.13 (2x1), 114.44 (1), 80.74 (1), 71.50 (2), 45.65 (2), 18.97 (6x3), 11.88 (3x1); LRMS (CI) *m/z* 317 (39%, $[M+H]^+$) 273 (95%, $[M-{}^iPr]^+$), 143 (100%); HRMS (EI) *m/z* 316.2217 ($[M]^+$- $C_{20}H_{32}OSi$ requires 316.2222).



210b



209b

Methyl 6-[(1,1,1-trisisopropylsilyl)methyl]-2-naphthyl ether (210b).

Methyl (3-4-[(*Z*)-1-(1,1,1-trisisopropylsilyl)methylidene]tetrahydro-2-furanylphenyl) ether (209b).

Following the typical intermolecular cyclisation procedure, $BF_3{\cdot}Et_2O$ (1.2 eq.) was added to MCP derivative **185** (100 mg) and *m*-methoxybenzaldehyde (1 eq.) in DCM (4 mL) at 0°C under argon. The reaction was allowed to warm to room temperature over 2 hours.

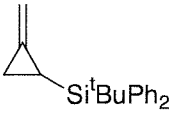
The crude material was purified by column chromatography (petrol to 1% ether in petrol) to give naphthalene **210b** as a colourless oil (15 mg, 10%) and tetrahydrofuran **209b** as a colourless oil (50 mg, 30%).

Data for **210b**

R_f 0.64 (30:70 ether:petrol); υ_{max} (neat)/cm^{-1} 2941 (s), 2864 (s), 1602 (m), 1228 (s), 881 (s); δ_H (300 MHz, $CDCl_3$) 7.65-7.58 (2H, m, ArH), 7.46 (1H, br s, ArH), 7.25 (1H, dd, *J* 2, 8 Hz, ArH), 7.11 (1H, d, *J* 8 Hz, ArH), 7.09 (1H, s, ArH), 3.91 (3H, s, OCH_3), 2.33 (2H, s, $SiCH_2Ar$), 1.19-1.01 (21H, m, $Si(CH(CH_3)_2)_3$); δ_C (75 MHz, $CDCl_3$) 157.03 (0), 136.66 (0), 132.22 (0), 129.72 (0), 129.15 (1), 128.87 (1), 126.76 (1), 126.18 (1), 118.88 (1), 106.08 (1), 55.67 (3), 19.33 (2), 19.17 (6x3), 11.49 (3x1); LRMS (CI) *m/z* 329 (100%, $[M+H]^+$), 285 (69%, $[M-^iPr]^+$); HRMS (EI) *m/z* 328.2218 ($[M]^+$- $C_{21}H_{32}OSi$ requires 328.2222).

Data for **209b**

R_f 0.60 (30:70 ether:petrol); υ_{max} (neat)/cm^{-1} 2942 (w), 2865 (w), 904 (s), 728 (s); δ_H (300 MHz, $CDCl_3$) 7.27 (1H, m, ArH), 6.98-6.94 (2H, m, ArH), 6.85 (1H, m, ArH), 5.51 (1H, br s with fine splitting, CHSi), 4.93 (1H, dd, *J* 6, 9 Hz, OCHAr), 4.58 (1H, br d, *J* 14 Hz, OCH_AH_B), 4.41 (1H, br d, *J* 14 Hz, OCH_AH_B), 3.83 (3H, s, OCH_3), 3.03 (1H, br dd, *J* 6, 16 Hz, $OCHCH_AH_B$), 2.70 (1H, br dd, *J* 9, 16 Hz, $OCHCH_AH_B$), 1.29-1.03 (21H, m, $Si(CH(CH_3)_2)_3$); δ_C (75 MHz, $CDCl_3$) 160.53 (0), 158.57 (0), 144.37 (0), 130.17 (1), 119.04 (1), 115.12 (1), 113.97 (1), 112.05 (1), 80.85 (1), 72.12 (2), 56.00 (3), 46.24 (2), 19.58 (6x3), 12.51 (3x1); LRMS (CI) *m/z* 364 (9%, $[M+NH_4]^+$), 347 (30%, $[M+H]^+$) 173 (100%); HRMS (EI) *m/z* 346.2326 ($[M]^+$- $C_{21}H_{34}O_2Si$ requires 346.2328).



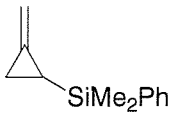
***tert*-Butyl(2-methylidenecyclopropyl)diphenylsilane (216).**

Following a method described by Thomas.[15]

^{n}BuLi (1.80 mL, 2.1 M, 3.70 mmol) was added to a stirred solution of methylenecyclopropane **1** (300 μL, 4.44 mmol), in THF (10 mL) at -70°C under argon.

This was allowed to warm to 10°C over 40 minutes and stirred at 10°C for 40 minutes. The reaction mixture was cooled to -70°C before addition of TBDPSCl (600 μL, 3.70 mmol) and allowed to warm to room temperature overnight. The reaction was quenched with sat. NH_4Cl (7 mL), extracted with ether (3x10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol) to give methylenecyclopropane derivative **216** as a colourless oil (150 mg, 14%).

R_f 0.70 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3071 (w), 2960 (w), 2930 (w), 2957 (w), 1427 (w), 1109 (m), 875 (w); δ_H (300 MHz, $CDCl_3$) 7.69 (2H, dd, *J* 2, 7 Hz, ArH), 7.58 (2H, dd, *J* 2, 7 Hz, ArH), 7.44-7.38 (6H, m, ArH), 5.36 (1H, br s with fine splitting, $C=CH_AH_B$), 5.34 (1H, br s with fine splitting, $C=CH_AH_B$), 1.40 (1H, m, $CH_2=CCH_AH_B$), 1.21-1.17 (10H, m, $CH_2=CCH_AH_B$, $SiC(CH_3)_3$), 0.77 (1H, tt, *J* 2, 7 Hz, CHSi); δ_C (75 MHz, $CDCl_3$) 136.19 (2x1), 136.13 (2x1), 133.85 (0), 133.78 (0), 133.02 (0), 129.22 (1), 129.16 (1), 127.47 (2x1), 127.29 (2x1), 101.83 (2), 28.02 (3x3), 18.82 (0), 6.12 (2), 0.02 (1); LRMS (EI) *m/z* 292 (2%, $[M]^+$), 235 (100%, $[M-^tBu]^+$); HRMS (EI) *m/z* 292.1645 ($[M]^+$ - $C_{20}H_{24}Si$ requires 292.1647).

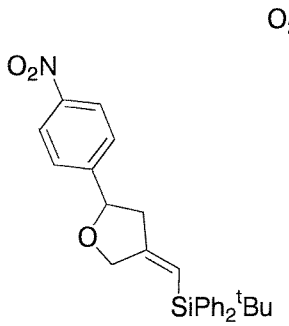


Dimethyl(2-methylenecyclopropyl)phenylsilane (217).

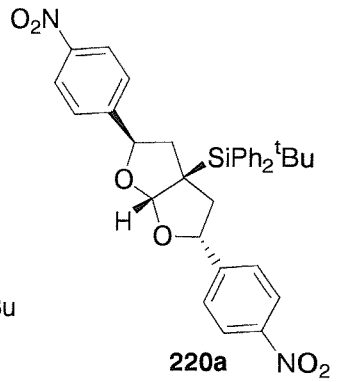
Following a method described by Thomas.[15]

^{n}BuLi (12.8 mL, 2.3 M, 29.6 mmol) was added to a stirred solution methylenecyclopropane **1** (2.0 mL, 29.6 mmol) in THF (70 mL) at -70°C under argon. The reaction was allowed to warm to 0°C over 40 minutes and stirred at 0°C for 1 hour. The reaction was cooled to -70°C and DMPSCl (4.9 mL, 29.6 mmol) added and allowed to warm to room temperature overnight. The reaction was quenched with sat. NH_4Cl (50 mL), extracted with ether (3x50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol) to give methylenecyclopropane derivative **217** as a colourless oil (4.4 g, 78%).

R_f 0.48 (petrol); υ_{max} (neat)/cm^{-1} 3069 (w), 2957 (w), 1427 (m), 1248 (m), 1113 (m), 813 (s); δ_H (400 MHz, $CDCl_3$) 7.63-7.55 (2H, m, Ph), 7.42-7.35 (3H, m, Ph), 5.36 (1H, br s, C=CH_AH$_B$), 5.28 (1H, br s, C=CH$_A$$H_B$), 1.34 (1H, br t with fine splitting, *J* 7.5 Hz, CH_2C=CH_AH$_B$), 0.97 (1H, br t with fine splitting, *J* 7 Hz, CH_2C=CH$_A$$H_B$), 0.89 (1H, m, CHSi), 0.25 (6H, s, Si(CH_3)$_2$Ph); δ_C (100 MHz, $CDCl_3$) 139.31 (0), 134.46 (2x1), 134.32 (0), 129.91 (1), 128.45 (2x1), 101.40 (2), 7.16 (2), 4.47 (1), -3.27 (2x3); LRMS (EI) *m/z* 188 (12%, $[M]^+$), 173 (12%, $[M\text{-}CH_3]^+$), 135 (100%, $[SiMe_2Ph]^+$); HRMS (EI) *m/z* 188.1019 ($[M]^+$ - $C_{12}H_{16}Si$ requires 188.1021).



218a



220a

***tert*-Butyl[(*Z*)-5-(4-nitrophenyl)tetrahydro-3-furanyliden]methyldiphenylsilane (218a).**

Rac-[(2*R*,5*R*)-2,5-Di(4-nitrophenyl)perhydrofuro[2,3-*b*]furan-3-yl](*tert*-butyl) diphenylsilane (220a).

Following the typical intermolecular cyclisation procedure, $BF_3{\cdot}Et_2O$ (2.5 eq.) was added to MCP derivative **216** (50 mg) and *p*-nitrobenzaldehyde (2 eq.) in DCM (4 mL) at -78°C under argon. The reaction was allowed to warm to room temperature over 3 hours. The crude material was purified by column chromatography (petrol to 5% ether in petrol) to give tetrahydrofuran **218a** as a colourless oil (25 mg, 33%) and furofuran **220a** as a white soild (25 mg, 25%).

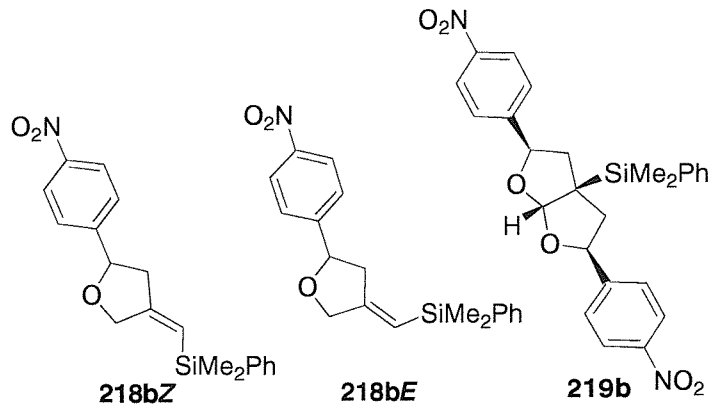
Data for **218a**

R_f 0.51 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3070 (w), 2928 (w), 2856 (w), 1630 (w), 1604 (w), 1519 (m), 1345 (m), 734 (s); δ_H (300 MHz, $CDCl_3$) 8.20 (2H, d, *J* 8 Hz, ArH),

7.70-7.61 (4H, m, PhH), 7.49-7.33 (8H, m, 2xArH, 6xPhH), 6.04 (1H, t, *J* 2 Hz, CHSi), 5.01 (1H, br t, *J* 7.5 Hz, OCHAr), 3.84 (1H, d, *J* 15 Hz, OCH_AH_B), 3.73 (1H, d, *J* 15 Hz, OCH_AH_B), 3.22 (1H, br dd with fine splitting, *J* 7, 16 Hz, $OCHCH_AH_B$), 2.72 (1H, br dd with fine splitting, *J* 8, 16 Hz, $OCHCH_AH_B$), 1.04 (9H, s, $SiC(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 159.91 (0), 149.80 (0), 147.54 (0), 136.14 (4x1), 134.06 (0), 133.96 (0), 129.62 (2x1), 128.01 (4x1), 126.56 (2x1), 123.81 (2x1), 113.93 (1), 78.99 (1), 71.13 (2), 45.44 (2), 27.52 (3x3), 18.38 (0); LRMS (CI) *m/z* 444 (9%, $[M+H]^+$), 414 (100%); HRMS (EI) *m/z* 386.1211 ($[M-^tBu]^+$ - $C_{23}H_{20}NO_3Si$ requires 386.1213).

Data for **220a**

R_f 0.28 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3072 (w), 2964 (w), 2859 (w), 1602 (w), 1519 (s), 1345 (s), 732 (m); δ_H (400 MHz, $CDCl_3$) 8.22 (2H, d, *J* 9 Hz, ArH), 8.12 (2H, d, *J* 9 Hz, ArH), 7.75-7.69 (4H, m, PhH), 7.51-7.43 (8H, m, 2xArH, 6xPhH), 7.35 (2H, d, *J* 9 Hz, ArH), 6.37 (1H, s, OCHO), 5.11 (1H, t, *J* 7 Hz, OCHAr), 3.84 (1H, br t, *J* 8 Hz, OCHAr), 3.01 (1H, dd, *J* 7, 13 Hz, CH_AH_BCHAr), 2.41 (2H, d, *J* 7 Hz, CH_2CHAr), 1.84 (1H, dd, *J* 9, 13 Hz, CH_AH_BCHAr), 1.20 (9H, s, $SiC(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 150.12 (0), 148.24 (0), 147.94 (0), 147.66 (0), 136.89 (2x1), 136.64 (2x1), 133.76 (0), 133.54 (0), 130.40 (2x1), 128.56 (4x1), 126.82 (2x1), 126.11 (2x1), 124.31 (2x1), 124.13 (2x1), 112.93 (1), 79.66 (1), 77.91 (1), 48.58 (2), 46.19 (2), 43.25 (0), 29.79 (3x3), 20.24 (0); LRMS (CI) *m/z* 595 (4%, $[M+H]^+$), 35 (100%).



Dimethyl[(*Z*)-5-(4-nitrophenyl)tetrahydro-3-furanyliden]methylphenylsilane (218b*Z*).

Dimethyl[(*E*)-5-(4-nitrophenyl)tetrahydro-3-furanyliden]methylphenylsilane (218b*E*).

Rac-[(2*S*,3a*r*,5*R*,6a*r*)-2,5-Di(4-nitrophenyl)perhydrofuro[2,3-*b*]furan-3-yl](dimethyl) phenylsilane (219b).

Following the typical intermolecular cyclisation procedure, $BF_3{\cdot}Et_2O$ (2 eq.) was added to MCP derivative **217** (100 mg) and *p*-nitrobenzaldehyde (2 eq.) in DCM (4 mL) at -78°C under argon. The reaction was allowed to warm to 0°C over 3 hours. The crude material was purified by column chromatography (petrol to 20% ether in petrol) to give an inseparable mixture of tetrahydrofurans **218bZ** and **218b*E*** as a colourless oil (50 mg, 28%, 5:1 *Z*:*E*) and furofuran **219b** as a white soild (60 mg, 25%).

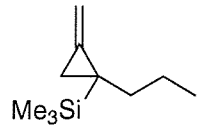
Data for **218b**

R_f 0.60 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3067 (w), 2954 (w), 2850 (w), 1635 (m), 1604 (m), 1518 (s), 1426 (m), 1344 (s), 1248 (m), 1111 (m), 829 (s); δ_H (400 MHz, $CDCl_3$) 8.01 (1.6H, d, *J* 8.5 Hz, ArH), 7.98 (0.4H, d, *J* 8 Hz, ArH), 7.39-7.15 (7H, m, 5xPh, 2xArH), 5.55 (0.8H, s, CHSi), 5.48 (0.2H, s, CHSi), 4.88 (0.2H, br t, 7.5 Hz, CHAr), 4.84 (0.8H, dd, 6.5, 8.5 Hz, CHAr), 4.45 (0.2H, d, *J* 14 Hz, OCH_AH_B), 4.32 (0.2H, d, *J* 14 Hz, OCH_AH_B), 4.24 (0.8H, d, *J* 14 Hz, OCH_AH_B), 4.10 (0.8H, d, *J* 14 Hz, OCH_AH_B), 2.91 (0.8H, dd, *J* 6.5, 16 Hz, $OCHCH_AH_B$), 2.72 (0.2H, dd, *J* 7, 16 Hz, $OCHCH_AH_B$), 2.46 (0.8H, dd, *J* 8.5, 16 Hz, $OCHCH_AH_B$), 2.12 (0.2H, dd, *J* 8, 16 Hz, $OCHCH_AH_B$), 0.22 (6H, s, $Si(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) data for **218bZ** 157.54 (0), 150.26 (0), 148.12 (0), 139.08 (0), 134.47 (1), 130.41 (1), 130.04 (1), 129.94 (1), 128.74 (2x1), 127.24 (2x1), 124.46 (1), 118.83 (1), 79.87 (1), 71.69 (2), 45.71 (2), 0.09 (2x3); LRMS (EI) *m/z* 339 (10%, $[M]^+$), 135 ($[SiMe_2Ph]^+$, 100%); HRMS (EI) *m/z* 339.1289 ($[M]^+$- $C_{19}H_{21}NO_3Si$ requires 339.1291).

Data for **219b**

Found: C, 63.45; H, 5.29; N, 5.46. $C_{26}H_{26}N_2O_6Si$ requires C, 63.66; H, 5.34; N, 5.71%; m.p. 198-200°C; R_f 0.31 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3067 (w), 2957 (w), 1520 (s), 1345 (s), 1089 (w), 984 (w), 844 (w); δ_H (400 MHz, $CDCl_3$) 7.97 (4H, d, *J* 9 Hz, ArH), 7.49-7.25 (5H, m, Ph), 7.13 (4H, d, *J* 9 Hz, ArH), 5.96 (1H, s, OCHO), 5.15 (2H, dd, *J* 6, 10 Hz, CHAr), 2.20 (2H, dd, *J* 6, 13 Hz, CH_AH_BCHAr), 1.83 (2H, dd, *J* 10, 13 Hz, CH_AH_BCHAr), 0.26 (6H, s, $Si(CH_3)_2Ph$); δ_C (100 MHz, $CDCl_3$) 149.83 (2x0), 148.52

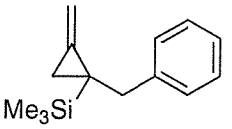
(2x0), 136.09 (0), 135.30 (2x1), 131.10 (1), 129.93 (2x1), 127.62 (4x1), 124.87 (4x1), 113.20 (1), 81.90 (2x1), 46.53 (2x2), 43.23 (0), -4.03 (2x3); LRMS (EI) *m/z* 490 (7%, $[M+H]^+$), 135 ($[SiMe_2Ph]^+$, 100%).



Trimethyl(2-methylene-1-propylcyclopropyl)silane (224).

Following a method described by Sternberg *et al.*[16]

^{n}BuLi (3.09 mL, 2.4 M, 7.41 mmol) was added to a stirred solution of methylenecyclopropane **1** (500 μL, 7.41 mmol) in THF (20 mL) at -70°C under argon. The reaction mixture was allowed to warm to 0°C over 40 minutes and stirred at 0°C for 40 minutes. The reaction was cooled to -70°C and TMSCl (940 μL, 7.41 mmol) added, the reaction was allowed to warm to 0°C over 40 minutes. The reaction mixture was cooled to -70°C before addition of ^{n}BuLi (3.09 mL, 2.4 M, 7.41 mmol) and the warming procedure repeated. The reaction was cooled to -70°C before addition of iodopropane (720 μL, 7.41 mmol) and allowed to warm to room temperature overnight. The reaction was quenched with sat. NH_4Cl (10 mL), extracted with ether (3x15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol) to give methylenecyclopropane derivative **224** as a colourless oil (860 mg, 69%). R_f 0.60 (petrol); υ_{max} (neat)/cm^{-1} 3054 (w), 2959 (w), 1416 (w), 1262 (s), 834 (w); δ_H (400 MHz, $CDCl_3$) 5.24 (1H, br s, C=CH_AH$_B$), 5.19 (1H, br s, C=CH$_A$$H_B$), 1.55-1.23 (4H, m, (C$H_2$)$_2CH_3$), 1.02 (1H, br d, *J* 7 Hz, CH$_2$C=CH_AH$_B$), 0.86 (3H, t, *J* 7 Hz, CH$_3$), 0.81 (1H, br d, *J* 7 Hz, CH$_2$C=CH$_A$$H_B$), -0.01 (9H, s, Si(CH$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 140.83 (0), 100.37 (2), 38.70 (2), 22.14 (2), 15.06 (3), 14.59 (0), 13.07 (2), -0.02 (3x3); LRMS (EI) *m/z* 168 (2%, $[M]^+$), 73 (100%, $[Si(CH_3)_3]^+$).

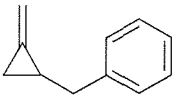


(1-Benzyl-2-methylenecyclopropyl)(trimethyl)silane (225).

Following a method described by Sternberg *et al.*[16]

^{n}BuLi (12.8 mL, 2.3 M, 29.6 mmol) was added to a stirred solution of methylenecyclopropane **1** (2 mL, 29.6 mmol) in THF (60 mL) at -78°C under argon. The reaction mixture was allowed to warm to 0°C over 40 minutes and stirred at 0°C for 40 minutes. The reaction was cooled to -78°C and TMSCl (3.76 mL, 29.6 mmol) added, the reaction was allowed to warm to 10°C over 40 minutes. The reaction mixture was cooled to -78°C before addition of ^{n}BuLi (12.8 mL, 2.3 M, 29.6 mmol) and the warming procedure repeated. The reaction was cooled to -78°C before addition of benzyl bromide (3.52 mL, 29.6 mmol) and allowed to warm to room temperature overnight. The reaction was quenched with sat. NH_4Cl (25 mL), extracted with ether (3x50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol) to give methylenecyclopropane derivative **225** as a colourless oil (3.50 g, 55%).

R_f 0.70 (petrol); υ_{max} (neat)/cm^{-1} 2028 (w), 2954 (w), 2896 (w), 1494 (w), 1453 (w), 1244 (m), 904 (m), 834 (s); δ_H (400 MHz, $CDCl_3$) 7.31-7.21 (5H, m, Ph), 5.36 (2H, s, C=CH_2), 2.89 (1H, d, *J* 14 Hz, CH_AH$_B$Ph), 2.76 (1H, d, *J* 14 Hz, CH$_A$$H_B$Ph), 1.14 (1H, d, *J* 8 Hz, CH_2C=CH_AH$_B$), 0.91 (1H, d, *J* 8 Hz, CH_2C=CH$_A$$H_B$), -0.11 (9H, s, Si$(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 140.77 (0), 139.56 (0), 130.06 (2x1), 128.50 (2x1), 126.74 (1), 140.01 (2), 41.32 (2), 15.47 (0), 13.01 (2), -0.46 (3x3); LRMS (CI) *m/z* 217 (65%, $[M+H]^+$), 73 (100%, $[Si(CH_3)_3]^+$); HRMS (EI) *m/z* 216.1328 ($[M]^+$ - $C_{14}H_{20}Si$ requires 216.1334).



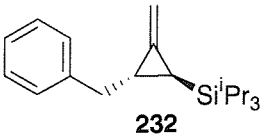
1-[(2-Methylenecyclopropyl)methyl]benzene (231).

Following a method described by Destabel *et al.*[54]

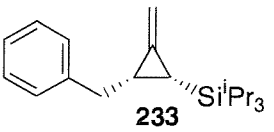
^{n}BuLi (28.0 mL, 2.4 M, 67.2 mmol) was added to a stirred solution of methylenecyclopropane **1** (5.0 mL, 74.1 mmol) in THF (100 mL) at -50°C under argon. The reaction mixture was allowed to warm to 0°C over 30 minutes and stirred at 0°C for 1 hour. The resulting yellow solution was cooled to -70°C before addition of benzyl bromide (8.0 mL, 67.2 mmol) and allowed to warm to room temperature overnight. The reaction was quenched with sat. NH_4Cl (50 mL), extracted with ether (3x50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by distillation, 56-58°C at 1.5 mmHg (lit.[54] 92°C at 15 mmHg) to give benzylmethylenecyclopropane **231** as a colourless oil (3.0 g, 31%).

R_f 0.52 (petrol); δ_H (400 MHz, $CDCl_3$) 7.36-7.22 (5H, m, Ph), 5.47 (1H, br s with fine splitting, C=CH_AH$_B$), 5.43 (1H, br s, C=CH$_A$$H_B$), 2.71 (2H, d, *J* 7 Hz, CH_2Ph), 1.72 (1H, m, CH_2=CCH_AH$_B$), 1.34 (1H, m, CHCH_2Ph), 0.94 (1H, m, CH_2=CCH$_A$$H_B$); δ_C (75 MHz, $CDCl_3$) 141.80 (0), 136.58 (0), 128.77 (2x1), 128.72 (2x1), 126.42 (1), 103.72 (2), 39.34 (2), 16.91 (1), 10.01 (2).

Spectroscopic data agrees with Destabel *et al.*[54]



232



233

Rac-[(1*S*,2*R*)-2-Benzyl-3-methylenecyclopropyl](trisisopropyl)silane (232).

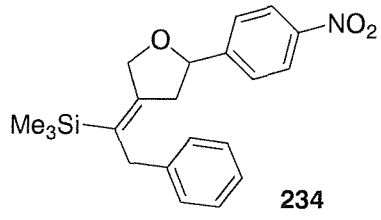
Rac-[(1*R*,2*R*)-2-Benzyl-3-methylenecyclopropyl](trisisopropyl)silane (233).

Following a method described by Destabel *et al.*[54]

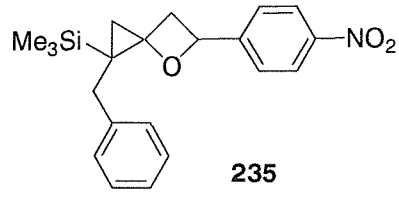
^{n}BuLi (7.61 mL, 2.3 M, 17.4 mmol) was added to a stirred solution of benzyl methylenecyclopropane **231** (2.5 g, 17.4 mmol) in THF (100 mL) at -50°C under argon. The reaction mixture was allowed to warm to 0°C over 30 minutes and stirred at 0°C for 1 hour. The reaction mixture was cooled to -70°C before addition of TIPSCl (3.74 mL, 17.4 mmol) and allowed to warm to room temperature overnight. The reaction was quenched with sat. NH_4Cl (50 mL), extracted with ether (3x50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography

(petrol) to give an inseparable mixture of methylenecyclopropane derivatives **232** and **233** as a colourless oil (1.50 g, 29%, 3:1 trans assumed to be major).

R_f 0.60 (petrol); υ_{max} (neat)/cm^{-1} 2941 (s), 2864 (s), 1462 (m), 881 (m), 737 (m); δ_H (400 MHz, $CDCl_3$) 7.34-7.22 (5H, m, Ph), 5.39 (0.7H, br s, C=CH_AH_B), 5.35 (0.3H, br s, C=CH_AH_B), 5.21 (1H, br s, C=CH_AH_B), 3.14 (0.3H, dd, *J* 4, 14 Hz, CH_AH_BPh), 2.86 (0.7H, dd, *J* 6, 14 Hz, CH_AH_BPh), 2.62 (0.7H, dd, *J* 8, 14 Hz, CH$_A$$H_B$Ph), 2.43 (0.3H, dd, *J* 9, 14 Hz, CH$_A$$H_B$Ph), 1.93 (0.3H, m, C*H*CH$_2$Ph), 1.67 (0.7H, m, C*H*CH$_2$Ph), 1.14-1.02 (21H, m, Si(CH(CH$_3$)$_2$)$_3$), 0.87 (0.3H, m, CHSi), 0.43 (0.7H, dt, *J* 7, 2 Hz, CHSi); δ_C (100 MHz, $CDCl_3$) Data for **232** 141.63 (0), 140.48 (0), 128.83 (2x1), 128.54 (2x1), 126.27 (1), 100.48 (2), 41.27 (2), 20.42 (1), 18.93 (6x3), 11.54 (3x1), 8.12 (1), Data for **233** 142.27 (0), 140.48 (0), 128.68 (2x1), 128.60 (2x1), 126.18 (1), 100.31 (2), 38.07 (2), 20.42 (1), 19.39 (6x3), 12.51 (3x1), 5.29 (1); LRMS (CI) *m/z* 301 (9%, $[M+H]^+$), 257 (88%, $[M-^iPr]^+$), 59 (100%); HRMS (EI) *m/z* 300.2279 ($[M]^+$ - $C_{20}H_{32}Si$ requires 300.2273).



234



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Trimethyl1-[5-(4-nitrophenyl)tetrahydro-3-furanyliden]-2-phenylethylsilane (234). [1-Benzyl-5-(4-nitrophenyl)-4-oxaspiro[2.3]hex-1-yl](trimethyl)silane (235).

Following the typical intermolecular cyclisation procedure, $BF_3 \cdot Et_2O$ (1.5 eq.) was added to MCP derivative **225** (100 mg) and *p*-nitrobenzaldehyde (2 eq.) in $EtNO_2$ (4 mL) at 0°C under argon. The reaction was allowed to warm to room temperature over 24 hours. The crude material was purified by column chromatography (petrol to 1% ether in petrol) to give tetrahydrofuran **234** as a colourless oil (26 mg, 16%) and spirocycle **235** as a pale yellow oil (20 mg, 12%).

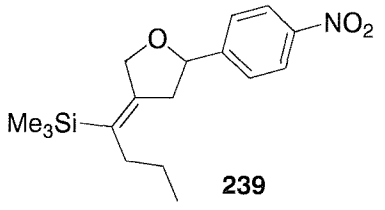
Data for **234**

R_f 0.56 (40:60 ether:petrol); υ_{max} (neat)/cm^{-1} 2954 (w), 2849 (w), 1520 (s), 1346 (s), 853 (m); δ_H (400 MHz, $CDCl_3$) 8.13 (2H, d, *J* 9 Hz, ArH), 7.46 (2H, d, *J* 9 Hz, ArH), 7.20-

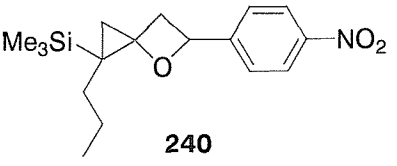
7.10 (3H, m, Ph), 7.03 (2H, d, *J* 6 Hz, Ph), 4.99 (1H, br t, *J* 7.5 Hz, ArCHO), 4.69 (1H, d, *J* 13 Hz, OCH_AH_B), 4.48 (1H, d, *J* 13 Hz, OCH$_A$$H_B$), 3.47 (2H, s, CH_2Ph), 3.03 (1H, dd, *J* 7, 16 Hz, OCHCH_AH_B), 2.41 (1H, dd, *J* 8, 16 Hz, OCHCH$_A$$H_B$), 0.00 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 150.99 (0), 150.08 (0), 147.80 (0), 140.20 (0), 129.65 (0), 128.82 (2x1), 128.54 (2x1), 126.93 (2x1), 126.44 (1), 124.16 (2x1), 79.70 (1), 71.67 (2), 40.73 (2), 40.00 (2), 0.00 (3x3); LRMS (EI) *m/z* 367 (3%, $[M]^+$), 73 (100%, $[Si(CH_3)_3]^+$); HRMS (EI) *m/z* 367.1589 ($[M]^+$ - $C_{21}H_{25}NO_3Si$ requires 367.1604).

Data for **235**

R_f 0.66 (40:60 ether:petrol); υ_{max} (neat)/cm^{-1} 3027 (w), 2952 (w), 1602 (w), 1519 (m), 1345 (m), 1250 (w), 902 (s), 838 (m), 727 (s); δ_H (400 MHz, $CDCl_3$) 8.13 (2H, d, *J* 9 Hz, ArH), 7.44-7.31 (7H, m, 5xPh, 2xArH), 5.41 (1H, br t, *J* 7.5 Hz, ArCHO), 3.20 (1H, d, *J* 15 Hz, CH_AH_BPh), 3.08 (1H, d, *J* 15 Hz, CH$_A$$H_B$Ph), 2.69 (1H, dd, *J* 8.5, 12 Hz, OCHCH_AH_B), 1.98 (1H, dd, *J* 6.5, 12 Hz, OCHCH$_A$$H_B$), 0.84 (1H, d, *J* 5 Hz, SiCCH_AH_BC), 0.82 (1H, d, *J* 5 Hz, SiCCH$_A$$H_B$C), 0.08 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 152.55 (0), 147.02 (0), 141.63 (0), 129.19 (2x1), 128.47 (2x1), 126.49 (1), 126.18 (2x1), 123.82 (2x1), 82.92 (1), 76.35 (0), 42.84 (2), 39.52 (2), 25.49 (2), 19.99 (0), -0.02 (3x3); LRMS (CI) *m/z* 368 (7%, $[M+H]^+$), 73 (100%, $[Si(CH_3)_3]^+$); HRMS (EI) *m/z* 367.1597 ($[M]^+$ - $C_{21}H_{25}NO_3Si$ requires 367.1604).



239



240

TrimethyH-[5-(4-nitrophenyl)tetrahydro-3-furanyliden]butylsilane (239).

Trimethyl[5-(4-nitrophenyl)-1-propyl-4-oxaspiro[2.3]hex-1-yl]silane (240).

Following the typical intermolecular cyclisation procedure, $BF_3{\cdot}Et_2O$ (2 eq.) was added to MCP derivative **224** (120 mg) and *p*-nitrobenzaldehyde (2 eq.) in DCM (7 mL) at room temperature under argon. The reaction was stirred at room temperature for 24 hours. The crude material was purified by column chromatography (hexane to 1% ether

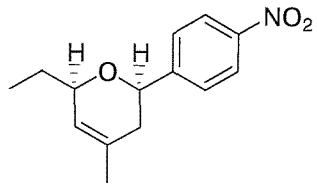
in hexane) to give tetrahydrofuran **239** as a colourless oil (31 mg, 14%) and spirocycle **240** as a pale yellow oil (23 mg, 10%).

Data for **239**

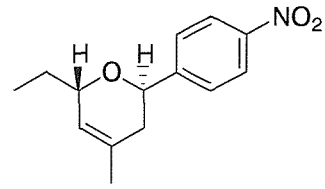
R_f 0.55 (40:60 ether:petrol); υ_{max} (neat)/cm^{-1} 2956 (m), 2868 (w), 1605 (w), 1520 (s), 1345 (s), 1248 (m), 834 (s); δ_H (400 MHz, $CDCl_3$) 8.20 (2H, d, *J* 9 Hz, ArH), 7.54 (2H, d, *J* 9 Hz, ArH), 5.00 (1H, br t, *J* 7.5 Hz, ArCHO), 4.63 (1H, d, *J* 13 Hz, OCH_AH_B), 4.44 (1H, d, *J* 13 Hz, OCH_AH_B), 3.09 (1H, dd, *J* 7, 16 Hz, $OCHCH_AH_B$), 2.44 (1H, dd, *J* 8, 16 Hz, $OCHCH_AH_B$), 2.06 (2H, t, *J* 8 Hz, $SiCCH_2$), 1.38-1.25 (2H, m, CH_2CH_3), 0.90 (3H, t, *J* 7 Hz, CH_2CH_3), 0.14 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 150.32 (0), 148.15 (0), 147.71 (0), 131.73 (0), 126.88 (2x1), 124.09 (2x1), 79.66 (1), 71.69 (2), 40.09 (2), 36.98 (2), 23.14 (2), 14.72 (3), 0.00 (3x3); LRMS (EI) *m/z* 319 (2%, $[M]^+$), 73 (100%, $[Si(CH_3)_3]^+$); HRMS (EI) *m/z* 319.1601 ($[M]^+$ - $C_{17}H_{25}NO_3Si$ requires 319.1604).

Data for **240**

R_f 0.60 (40:60 ether:petrol); υ_{max} (neat)/cm^{-1} 2956 (w), 2871 (w), 1519 (s), 1345 (s), 903 (m), 837 (s), 729 (m); δ_H (400 MHz, $CDCl_3$) 8.16 (2H, d, *J* 9 Hz, ArH), 7.44 (2H, d, *J* 9 Hz, ArH), 5.39 (1H, br t, *J* 7.5 Hz, ArCHO), 2.64 (1H, dd, *J* 8, 13 Hz, $OCHCH_AH_B$), 1.89 (1H, dd, *J* 7, 13 Hz, $OCHCH_AH_B$), 1.79-1.62 (4H, m, $(CH_2)_2CH_3$), 1.02 (3H, t, *J* 7 Hz, CH_3), 0.73 (1H, d, *J* 5 Hz, $SiCCH_AH_BC$), 0.68 (1H, d, *J* 5 Hz, $SiCCH_AH_BC$), 0.08 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 152.44 (0), 147.04 (0), 126.50 (2x1), 124.15 (2x1), 83.51 (1), 76.77 (0), 43.25 (2), 36.09 (2), 26.05 (2), 20.60 (2), 19.56 (0), 14.47 (3), -0.02 (3x3); LRMS EI) *m/z* (319 (6%, $[M]^+$), 73 (100%, $[Si(CH_3)_3]^+$); HRMS (EI) *m/z* 319.1605 ($[M]^+$ - $C_{17}H_{25}NO_3Si$ requires 319.1604).



242



241

Rac-(2*R*,6*R*)-6-Ethyl-4-methyl-2-(4-nitrophenyl)-3,6-dihydro-2*H*-pyran (242).

Rac-(2*R*,6*S*)-6-Ethyl-4-methyl-2-(4-nitrophenyl)-3,6-dihydro-2*H*-pyran (241).

Following the typical intermolecular cyclisation procedure, $BF_3 \cdot Et_2O$ (1.5 eq.) was added to MCP derivative **224** (100 mg) and *p*-nitrobenzaldehyde (1 eq.) in $EtNO_2$ (5 mL) at -78°C under argon. The reaction was allowed to warm to room temperature over 4 hours. The crude material was purified by column chromatography (petrol to 1% ether in petrol) to give dihydropyran **242** as a colourless oil (25 mg, 17%) and dihydropyran **241** as a colourless oil (10 mg, 7%).

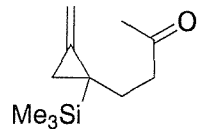
Data for **242**

R_f 0.60 (40:60 ether:petrol); υ_{max} (neat)/cm^{-1} 2962 (w), 2932 (w), 1520 (s), 1345 (s), 1084 (w), 849 (w); δ_H (400 MHz, $CDCl_3$) 8.20 (2H, d, *J* 9 Hz, ArH), 7.56 (2H, d, *J* 9 Hz, ArH), 5.44 (1H, br s, C=CH), 4.69 (1H, t, *J* 6.5 Hz, OCHAr), 4.21 (1H, br s, O*C*$H$$CH_2CH_3$), 2.13 (2H, br d, *J* 6.5 Hz, *C*H_2CHAr), 1.76 (3H, s, CCH_3), 1.69-1.55 (2H, m, *C*H_2CH_3), 1.02 (3H, t, *J* 7 Hz, CH_2C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 151.00 (0), 147.51 (0), 132.25 (0), 126.72 (2x1), 124.38 (1), 123.98 (2x1), 76.72 (1), 75.02 (1), 38.28 (2), 29.10 (2), 23.23 (3), 9.81 (3); LRMS (CI) *m/z* 265 (25%, $[M+NH_4]^+$), 106 (100%); HRMS (EI) *m/z* 247.1208 ($[M]^+$ - $C_{14}H_{17}NO_3$ requires 247.1208).

Data for **241**

R_f 0.57 (40:60 ether:petrol); υ_{max} (neat)/cm^{-1} 2964 (w), 2931 (w), 1519 (s), 1347 (s), 1104 (w), 902 (s), 721 (s); δ_H (400 MHz, $CDCl_3$) 8.20 (2H, d, *J* 9 Hz, ArH), 7.56 (2H, d, *J* 9 Hz, ArH), 5.53 (1H, br s, C=CH), 4.79 (1H, t, *J* 6.5 Hz, OCHAr), 4.16 (1H, br s, O*C*$H$$CH_2CH_3$), 2.18 (2H, br d, *J* 6.5 Hz, *C*H_2CHAr), 1.78 (3H, s, CCH_3), 1.75-1.56 (2H, m, *C*H_2CH_3), 0.99 (3H, t, *J* 7 Hz, CH_2C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 150.65 (0), 147.55 (0), 131.42 (0), 127.21 (2x1), 126.73 (1), 124.05 (2x1), 75.44 (1), 69.26 (1), 37.03 (2), 27.69 (2), 23.46 (3), 10.87 (3); LRMS (CI) *m/z* 265 (10%, $[M+NH_4]^+$), 106 (100%); HRMS (EI) *m/z* 247.1213 ($[M]^+$ - $C_{14}H_{17}NO_3$ requires 247.1208).

5.5 Experimental for chapter 3

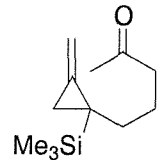


4-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-butanone (133).

Ketal **261** (10.0 g, 41.7 mmol) and *p*-TsOH (9.5 g, 50.0 mmol) were stirred together in acetone (270 mL) and water (30 mL) for 48 hours. The solvent was removed *in vacuo*, replaced with ether (300 mL), washed with sat. $NaHCO_3$ (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 7% ether in petrol) to give ketone **133** as a colourless oil (7.8 g, 95%).

R_f 0.35 (10:90 EtOAc:petrol); δ_H (300 MHz, $CDCl_3$) 5.29 (1H, br s, C=CH_AH$_B$), 5.20 (1H, br s, C=CH$_A$$H_B$), 2.45-2.36 (2H, m, CH_2CO), 2.12 (3H, s, CH_3), 1.87 (1H, ddd, *J* 6, 10, 14 Hz, CH_AH$_B$CH$_2$CO), 1.66 (1H, ddd, *J* 6, 10, 14 Hz, CH$_A$$H_BCH_2$CO), 1.06 (1H, dt, *J* 7, 2 Hz, CH$_2$=CCH_AH$_B$), 0.86 (1H, dt, *J* 7, 2 Hz, CH$_2$=CCH$_A$$H_B$), 0.00 (9H, s, Si$(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 208.97 (0), 138.96 (0), 101.12 (2), 41.84 (2), 30.07 (3), 28.19 (2), 13.07 (0), 12.02 (2), -2.67 (3x3).

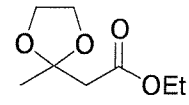
Spectroscopic data agrees with Peron.[80]



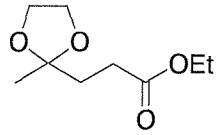
5-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-pentanone (134).

Ketal **262** (14.0 g, 55.1 mmol) and *p*-TsOH (12.6 g, 66.1 mmol) were stirred together in acetone (270 mL) and water (30 mL) for 48 hours. The solvent was removed *in vacuo*, replaced with ether (300 mL), washed with sat. $NaHCO_3$ (2x150 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 10% ether in petrol) to give ketone **134** as a colourless oil (9.0 g, 78%).

R_f 0.42 (30:70 ether:petrol); δ_H (300 MHz, $CDCl_3$) 5.25 (1H, br s, C=CH_AH$_B$), 5.20 (1H, br s, C=CH$_A$$H_B$), 2.37 (2H, t, *J* 7 Hz, CH_2CO), 2.11 (3H, s, CH_3), 1.70-1.28 (4H, m, (CH_2)$_2$$CH_2CO$), 1.03 (1H, dt, *J* 7, 2 Hz, CH_2=CCH_AH$_B$), 0.82 (1H, dt, *J* 7, 2 Hz, CH_2=CCH$_A$$H_B$), -0.01 (9H, s, Si($CH_3$)$_3$); δ_C (75 MHz, $CDCl_3$) 209.01 (0), 139.81 (0), 100.43 (2), 44.04 (2), 35.28 (2), 30.04 (3), 22.71 (2), 13.92 (0), 12.65 (2), -2.44 (3x3).
Spectroscopic data agrees with Peron.[80]



Ethyl-2-(2methyl-1,3-dioxolan-2-yl)acetate (255).
Following a method described by Kelly *et al.*[114]
Ethylacetoacetate **253** (30.0 g, 0.23 mol), ethylene glycol (28.6 g, 0.46 mol) and *p*-TsOH (1.0 g, 10.0 mmol) were refluxed together in toluene (200 ml) for 24 hours using Dean-Stark apparatus to remove water. The reaction mixture was cooled to room temperature and concentrated *in vacuo*, ether (200 mL) was added, washed with sat. $NaHCO_3$ (2x50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by distillation, 63-65°C at 1.5 mmHg (lit.[114] 110°C at 20 mmHg) to give ester **255** as a colourless oil (25.0 g, 62%).
R_f 0.16 (50:50 ether:petrol); δ_H (300 MHz, $CDCl_3$) 4.14 (2H, q, *J* 7 Hz, OCH_2), 3.97 (4H, s, O(CH_2)$_2$O), 2.65 (2H, s, CH_2CO), 1.51 (3H, s, CH_3C), 1.25 (3H, t, *J* 7 Hz, OCH_2CH_3); δ_C (75 MHz, $CDCl_3$) 169.63 (0), 107.76 (0), 64.91 (2x2), 60.69 (2), 44.37 (2), 24.61 (3), 14.31 (3).
Spectroscopic data agrees with Kelly *et al.*[114]

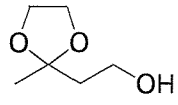


Ethyl-3-(2-methyl-1,3-dioxolan-2-yl)propanoate (256).
Following a method described by Kelly *et al.*[114]

Ethylene glycol (23.2 mL, 0.47 mol), ethyl levulinate **254** (30.0 mL, 0.21 mol) and *p*-TsOH (500 mg, 2.63 mmol) were refluxed together in toluene (100 mL) for 72 hours using Dean-Stark apparatus to remove water. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. Ether (100 ml) was added and washed with sat. $NaHCO_3$ (70 mL). The Organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by distillation, 86-90°C at 1.5 mmHg (lit.[115] 55-56°C at 0.1 mmHg) to give ester **256** as a colourless oil (16.0 g, 41%).

R_f 0.46 (30:70 EtOAc:petrol); υ_{max} (neat)/cm^{-1} 2983 (s), 2884 (s), 1735 (s), 1448 (m), 1376 (s), 1052 (s), 865 (s); δ_H (300 MHz, $CDCl_3$) 4.12 (2H, q, *J* 7 Hz, OCH_2), 3.97-3.90 (4H, m, $O(CH_2)_2O$), 2.38 (2H, t, *J* 7.5 Hz, CH_2CO), 2.01 (2H, t, *J* 7.5 Hz, CH_2CH_2CO) 1.31 (3H, s, CH_3), 1.24 (3H, t, *J* 7 Hz, CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 173.76 (0), 109.30 (0), 64.92 (2x2), 60.47 (2), 34.11 (2), 29.21 (2), 24.13 (3), 14.36 (3).

Spectroscopic data agrees with Dowd *et al.*[115]



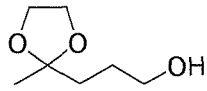
2-(2-Methyl-1,3-dioxolan-2-yl)-1-ethanol (257).

Following a method described by Hitchcock *et al.*[116]

Ester **255** (15.0 g, 86.2 mmol) was added dropwise to a suspension of $LiAlH_4$ (6.5 g, 0.17 mol) in THF (100 mL) at 0°C over 1 hour. The reaction mixture was stirred for 24 hours before addition of ether (200 mL). The reaction was stirred for 5 minutes before being quenched by dropwise addition of NaOH (20 mL, 2 M), filtered and concentrated *in vacuo* to give alcohol **257** as a colourless oil (11.3 g, 100%).

R_f 0.46 (30:70 EtOAc:petrol); δ_H (300 MHz, $CDCl_3$) 3.97 (4H, s, $O(CH_2)_2O$), 3.74 (2H, t, *J* 5 Hz, CH_2OH), 2.70 (1H, br s, OH), 1.93 (2H, t, *J* 5 Hz, CH_2CH_2OH), 1.32 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 110.62 (0), 64.67 (2x2), 59.08 (2), 40.39 (2), 23.99 (3).

Spectroscopic data agrees with Hitchcock *et al.*[116]



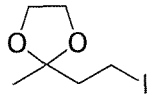
3-(2-Methyl-1,3-dioxolan-2-yl)-propanol (258).

Following a method described by Hitchcock *et al.*[116]

Ester **256** (15.0 g, 79.8 mmol) in THF (10 mL) was added dropwise to a suspension of $LiAlH_4$ (6.1 g, 0.16 mol) in THF (100 ml) at 0°C and stirred 24 hours. Ether (100 ml) was added and stirred for 5 minutes before being quenched by dropwise addition of NaOH (40 ml, 2 M), filtered and concentrated *in vacuo* to give alcohol **258** as a colourless oil (11.6 g, 100%).

R_f 0.15 (30:70 EtOAc:petrol); δ_H (300 MHz, $CDCl_3$) 3.99-3.94 (4H, m, $O(CH_2)_2O$), 3.67-3.63 (2H, m, CH_2OH), 2.18 (1H, br s, OH), 1.79-1.60 (4H, m, $(CH_2)_2CH_2OH$), 1.35 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 110.13 (0), 74.79 (2), 63.16 (2x2), 35.99 (2), 27.30 (2), 23.84 (3).

Spectroscopic data agrees with Peron.[80]



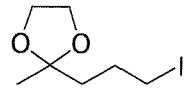
2-(2-Iodoethyl)-2-methyl-1,3-dioxolane (259).

Following a method described by Corlay *et al.*[117]

PPh_3 (29.8 g, 0.11 mol), imidazole (8.8 g, 0.13 mol) and iodine (30.8 g, 0.12 mol) were added in turn to a stirred solution of alcohol **257** (10.0 g, 75.8 mmol) in ether (180 mL) and acetonitrile (60 mL). The resulting red solution was stirred for 20 minutes then diluted with ether (100 mL). The mixture was washed with aq. $Na_2S_2O_3$ until the organic layer was colourless. The organic layer was washed with water (2x100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a white solid. The white solid was triturated in petrol and filtered, the filtrate was concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 5% ether in petrol) to give iodide **259** as a colourless oil (16.0 g, 88%).

R_f 0.53 (50:50 ether:petrol); δ_H (300 MHz, $CDCl_3$) 3.98-3.92 (4H, m, $O(CH_2)_2O$), 3.17 (2H, m, CH_2I), 2.31 (2H, m, CH_2CH_2I), 1.31 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 109.95 (0), 65.01 (2x2), 44.42 (2), 23.94 (3), -2.14 (2).

Spectroscopic data agrees with Trost *et al.*[118]



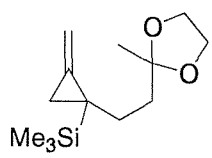
2-(2-Iodopropyl)-2-methyl-1,3-dioxolane (260).

Following a method described by Corlay *et al.*[117]

PPh_3 (32.3 g, 0.12 mol), imidazole (9.5 g, 0.14 mol) and iodine (33.4 g, 0.14 mol) were added in turn to a stirred solution of alcohol **258** (12.0 g, 82.2 mmol) in ether (180 mL) and acetonitrile (60 mL). The resulting red solution was stirred for 20 minutes and diluted with ether (100 mL). The mixture was washed with aq. $Na_2S_2O_3$ until the organic layer was colourless. The organic layer was washed with water (2x100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a white solid. The white solid was triturated in petrol and filtered, the filtrate was concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 10% ether in petrol) to give iodide **260** as a colourless oil (18.0 g, 86%).

R_f 0.50 (50:50 ether:petrol); δ_H (300 MHz, $CDCl_3$) 3.99-3.92 (4H, m, $O(CH_2)_2O$), 3.22 (2H, t, *J* 7Hz, CH_2I), 2.02-1.88 (2H, m, CH_2CH_2I), 1.81-1.73 (2H, m, $CH_2(CH_2)_2I$), 1.33 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 109.55 (0), 64.86 (2x2), 40.00 (2), 28.41 (2), 24.15 (3), 7.21 (2).

Spectroscopic data agrees with Wu *et al.*[119]



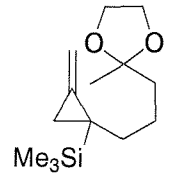
Trimethyl{1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-2-methylidenecyclopropyl} silane (261).

Following a method described by Peron.[80]

^{n}BuLi (27.5 mL, 2.4 M, 66.0 mmol) was added to a stirred solution of methylenecyclopropane **1** (5.3 mL, 79.1 mmol) in THF (200 mL) at -78°C under argon. The solution was allowed to warm to 0°C over 40 minutes and stirred at 0°C for 1 hour. The resulting yellow solution was cooled to -78°C and TMSCl (8.4 mL, 66.0 mmol) added. The solution was allowed to warm to 0°C over 40 minutes before cooling to -78°C and addition of ^{n}BuLi (27.5 mL, 2.4 M, 66.0 mmol) and the warming procedure repeated. The resulting orange solution was cooled to -78°C before addition of iodide **259** (16.0 g, 66.0 mmol) and allowed to warm to room temperature overnight. The reaction mixture was quenched with sat. NH_4Cl (50 mL), extracted with ether (3x75 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 5% ether in petrol) to give ketal **261** as a colourless oil (10.0 g, 63%).

R_f 0.62 (50:50 ether:petrol); δ_H (300 MHz, $CDCl_3$) 5.25 (1H, br s, C=CH_AH$_B$), 5.20 (1H, br s, C=CH$_A$$H_B$), 3.98-3.92 (4H, m, O(CH$_2$)$_2$O), 1.71-1.42 (4H, m, CH$_2$CH$_2$), 1.28 (3H, s, CH$_3$), 1.05 (1H, dt, *J* 7, 2 Hz, CH$_2$=CCH_AH$_B$), 1.03 (1H, dt, *J* 7, 2 Hz, CH$_2$=CCH$_A$$H_B$), 0.00 (9H, s, Si(CH$_3$)$_3$); δ_C (75 MHz, $CDCl_3$) 139.88 (0), 110.01 (0), 100.38 (2), 64.73 (2x2), 37.56 (2), 29.62 (2), 23.82 (3), 13.49 (0), 12.51 (2), -2.47 (3x3).

Spectroscopic data agrees with Peron.[80]



Trimethyl{1-[2-(2-methyl-1,3-dioxolan-2-yl)propyl]-2-methylidenecyclopropyl} silane (262).

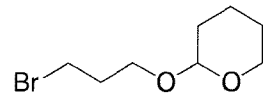
Following a method described by Peron.[80]

^{n}BuLi (29.3 mL, 2.4 M, 70.3 mmol) was added to a stirred solution of methylenecyclopropane **1** (5.7 mL, 84.4 mmol) in THF (200 mL) at -78°C under argon. The solution was allowed to warm to 0°C over 40 minutes and stirred at 0°C for 1 hour.

The resulting yellow solution was cooled to -78°C and TMSCl (8.9 mL, 70.3 mmol) added. The solution was allowed to warm to 0°C over 40 minutes before cooling to -78°C and addition of ^{n}BuLi (29.3 mL, 2.4 M, 70.3 mmol) and the warming procedure repeated. The resulting orange solution was cooled to -78°C before addition of iodide **260** (18.0 g, 70.3 mmol) and allowed to warm to room temperature overnight. The reaction mixture was quenched with sat. NH_4Cl (50 mL), extracted with ether (3x150 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 5% ether in petrol) to give ketal **262** as a colourless oil (14.0 g, 79%).

R_f 0.60 (50:50 ether:petrol); δ_H (300 MHz, $CDCl_3$) 5.25 (1H, br s, C=CH_AH$_B$), 5.20 (1H, br s, C=CH$_A$$H_B$), 3.98-3.51 (4H, m, O(CH$_2$)$_2$O), 1.64-1.34 (6H, m, (CH$_2$)$_3$), 1.31 (3H, s, CH$_3$), 1.03 (1H, dt, *J* 7, 2 Hz, CH$_2$=CCH_AH$_B$), 0.83 (1H, dt, *J* 7, 2 Hz, CH$_2$=CCH$_A$$H_B$), 0.00 (9H, s, Si(CH$_3$)$_3$); δ_C (75 MHz, $CDCl_3$) 140.08 (0), 110.20 (0), 100.21 (2), 64.79 (2x2), 29.61 (2), 35.94 (2), 23.94 (3), 22.96 (2), 14.14 (0), 12.55 (2), -2.41 (3x3).

Spectroscopic data agrees with Peron.[80]



2-(3-Bromopropoxy)tetrahydro-2*H*-pyran (265).

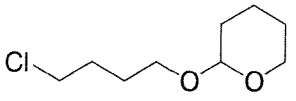
Following a method described by Dado *et al.*[105]

DHP (16.4 mL, 0.18 mol) was added slowly to a stirred solution of 3-bromo-1-propanol **263** (5.4 mL, 60.0 mmol) and *p*-TsOH (1.1 g, 6.0 mmol) in dioxane (80 mL). The reaction mixture was stirred at room temperature for 2 hours and quenched with sat. $NaHCO_3$ (30 mL), extracted with EtOAc (3x50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 10% ether in petrol) to give bromide **265** as a colourless oil (12.0 g, 90%).

R_f 0.50 (50:50 ether:petrol); δ_H (400 MHz, $CDCl_3$) 4.60 (1H, br s with fine splitting, OCHO), 3.89-3.83 (2H, m, OCH_2(CH$_2$)$_3$), 3.52 (2H, t, *J* 6 Hz, BrCH$_2$), 3.50 (2H, t, *J* 6 Hz, Br(CH$_2$)$_2$CH_2O), 2.12 (2H, quintet, *J* 6 Hz, BrCH$_2$CH_2CH$_2$O), 1.85-1.51 (6H, m,

OCH(CH_2)$_3$); δ_C (100 MHz, $CDCl_3$) 99.32 (1), 65.31 (2), 62.68 (2), 33.34 (2), 31.05 (2), 31.02 (2), 25.83 (2), 19.91 (2).

Spectroscopic data agrees with Dado *et al.*[105]



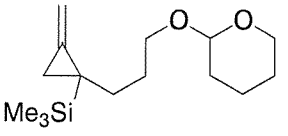
2-(4-Chlorobutoxy)tetrahydro-2*H*-pyran (266).

Following a method described by Dado *et al.*[105]

DHP (12.8 g, 0.15 mol) was added dropwise over 1 hour to a stirred solution of 4-chloro-1-butanol **264** (15.0 g, 0.14 mol) and *p*-TsOH (500 mg) at 50°C under argon. The reaction mixture was stirred at 50°C for 20 hours then allowed to cool to room temperature. The reaction was quenched with sat. $NaHCO_3$ (10 mL), extracted with EtOAc (3x50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 7% ether in petrol) to give chloride **266** as a colourless oil (17.0 g, 64%).

R_f 0.48 (50:50 ether:petrol); δ_H (300 MHz, $CDCl_3$) 4.58 (1H, m, OCHO), 3.89-3.67 (2H, m, CH_2O), 3.58 (2H, t, *J* 6 Hz, CH_2Cl), 3.55-3.39 (2H, m, CH_2O), 1.94-1.54 (10H, m, $ClCH_2(CH_2)_2$, $CH(CH_2)_3$); δ_C (75 MHz, $CDCl_3$) 99.00 (1), 66.75 (2), 62.51 (2), 45.15 (2), 30.85 (2), 29.79 (2), 27.26 (2), 25.60 (2), 19.77 (2).

Spectroscopic data agrees with Dado *et al.*[105]



3-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]propyl tetrahydro-2*H*-2-pyranyl ether (267).

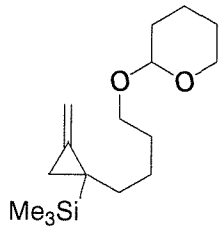
Following a method described by Destabel.[120]

^{n}BuLi (14.1 mL, 2.1 M, 29.6 mmol) was added to a stirred solution of methylenecyclopropane **1** (2.0 mL, 29.6 mmol) in THF (100 mL) at -78°C under argon.

The reaction mixture was allowed to warm to 10°C over 40 minutes and stirred at 10°C for 40 minutes. The resulting yellow solution was cooled to -70°C before addition of TMSCl (3.8 mL, 29.6 mmol). The reaction mixture was allowed to warm to room temperature over 1 hour before cooling to -70°C and addition of ^{n}BuLi (14.1 mL, 2.1 M, 29.6 mmol) and the warming procedure repeated. The reaction mixture was cooled to -70°C before addition of bromide **265** (6.6 g, 29.6 mmol) and allowed to warm to room temperature overnight. The reaction was quenched with sat. NH_4Cl (50 mL), extracted with ether (3x100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 10% ether in petrol) to give methylenecyclopropane derivative **267** as a colourless oil (6.1 g, 77%).

R_f 0.68 (50:50 ether:petrol); δ_H (400 MHz, $CDCl_3$) 5.26 (1H, s, C=CH_AH$_B$), 5.21 (1H, s, C=CH$_A$$H_B$), 4.56 (1H, t, *J* 4 Hz, OCHO), 3.86 (1H, m, OCH_AH$_B$(CH$_2$)$_3$), 3.67 (1H, m, SiC(CH$_2$)$_2$CH_AH$_B$O), 3.51 (1H, m, OCH$_A$$H_B$(CH$_2$)$_3$), 3.34 (1H, m, SiC(CH$_2$)$_2CH_A$$H_B$O), 1.85-1.43 (10H, m, SiC(CH_2)$_2$, OCH(CH_2)$_3$), 1.04 (1H, d, *J* 8 Hz, CH$_2$=CCH_AH$_B$), 0.83 (1H, d, *J* 8 Hz, CH$_2$=CCH$_A$$H_B$), 0.00 (9H, s, Si(CH$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 140.46 (0), 100.76 (2), 99.39 (1), 68.34 (2), 62.93 (2), 32.61 (2), 31.37 (2), 29.07 (2), 26.11 (2), 20.27 (2), 14.27 (0), 13.04 (2), -0.02 (3x3).

Spectroscopic data agrees with Destabel.[120]



4-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]butyl tetrahydro-2*H*-2-pyranyl ether (268).

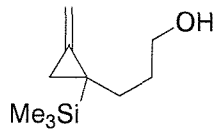
Following a method described by Destabel.[120]

^{n}BuLi (32.0 mL, 2.4 M, 74.1 mmol) was added to a stirred solution of methylenecyclopropane **1** (5.0 mL, 74.1 mmol) in THF (200 mL) at -78°C under argon. The reaction mixture was allowed to warm to 0°C over 40 minutes and stirred at 0°C for

40 minutes. The resulting mixture was cooled to -70°C before addition of TMSCl (9.4 mL, 74.1 mmol). The reaction mixture was allowed to warm to room temperature before cooling to -70°C and addition of ^{n}BuLi (32.0 mL, 2.4 M, 74.1 mmol) and the warming procedure repeated. The reaction mixture was cooled to -70°C before addition of chloride **266** (14.3 g, 74.1 mmol) and allowed to warm to room temperature overnight. The reaction was quenched with sat. NH_4Cl (50 mL), extracted with ether (3x100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 5% ether in petrol) to give methylenecyclopropane derivative **268** as a colourless oil (14.5 g, 69%).

R_f 0.73 (50:50 ether:petrol); δ_H (400 MHz, $CDCl_3$) 5.24 (1H, s, C=CH_AH$_B$), 5.19 (1H, s, C=CH$_A$$H_B$), 4.58 (1H, br s with fine splitting, OCHO), 3.87 (1H, m, OCH_AH$_B$(CH$_2$)$_3$CH), 3.70 (1H, dt, *J* 9.5, 7 Hz, SiC(CH$_2$)$_3$CH_AH$_B$O), 3.50 (1H, m, OCH$_A$$H_B$(CH$_2$)$_3$CH), 3.37 (1H, dt, *J* 9.5, 7 Hz, SiC(CH$_2$)$_3$CH$_A$$H_B$O), 1.88-1.31 (12H, m, (CH_2)$_3$CH$_2$O, CH(CH_2)$_3$), 1.03 (1H, d, *J* 8 Hz, CH$_2$=CCH_AH$_B$), 0.81 (1H, d, *J* 8 Hz, CH$_2$=CCH$_A$$H_B$), -0.01 (9H, s, Si(CH$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 140.64 (0), 100.53 (2), 99.30 (1), 67.92 (2), 62.76 (2), 36.08 (2), 31.31 (2), 30.58 (2), 26.09 (2), 25.53 (2), 20.15 (2), 14.59 (0), 13.06 (2), -0.02 (3x3).

Spectroscopic data agrees with Destabel.[120]

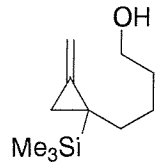


3-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-1-propanol (269).

Methylenecyclopropane derivative **267** (200 mg, 0.75 mmol) and *p*-TsOH (170 mg, 0.90 mmol) were stirred together in acetone (9 mL) and water (1 mL) at room temperature for 24 hours. The solvent was removed *in vacuo*, replaced with ether (10 mL), washed sat. $NaHCO_3$ (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 15% ether in petrol) to give alcohol **269** as a colourless oil (110 mg, 80%).

R_f 0.35 (50:50 ether:petrol); δ_H (400 MHz, $CDCl_3$) 5.27 (1H, br s, C=CH_AH$_B$), 5.21 (1H, br s, C=CH$_A$$H_B$), 3.60 (2H, t, *J* 6 Hz, CH_2OH), 1.64-1.41 (5H, m, (CH_2)$_2$CH$_2$O*H*), 1.06 (1H, dt, *J* 8, 2 Hz, CH$_2$=CCH_AH$_B$), 0.81 (1H, dt, *J* 8, 2 Hz, CH$_2$=CCH$_A$$H_B$), 0.00 (9H, s, Si(CH$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 140.40 (0), 100.90 (2), 63.67 (2), 32.18 (2), 31.96 (2), 14.14 (0), 13.06 (2), -0.02 (3x3).

Spectroscopic data agrees with Destabel.[120]

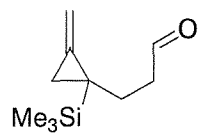


4-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-1-butanol (270).

Methylenecyclopropane derivative **268** (100 mg, 0.36 mmol) and HCl (200 μL, 2 M, 0.39 mmol) were stirred together in acetone (9 mL) and water (1 mL) at room temperature for 24 hours. The solvent was removed *in vacuo* and the crude material was dissolved in ether (15 mL), washed with sat. $NaHCO_3$ (2x7 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 20% ether in petrol) to give alcohol **270** as a colourless oil (55 mg, 78%).

R_f 0.36 (50:50 ether:petrol); δ_H (400 MHz, $CDCl_3$) 5.26 (1H, s, C=CH_AH$_B$), 5.20 (1H, s, C=CH$_A$$H_B$), 3.63 (2H, t, *J* 7 Hz, CH_2OH), 1.55-1.35 (7H, m, (CH_2)$_3$CH$_2$O*H*), 1.04 (1H, d, *J* 8 Hz, CH$_2$=CCH_AH$_B$), 0.83 (1H, d, *J* 8 Hz, CH$_2$=CCH$_A$$H_B$), 0.00 (9H, s, Si(CH$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 140.54 (0), 100.66 (2), 63.45 (2), 35.98 (2), 33.69 (2), 24.99 (2), 14.56 (0), 13.03 (2), -0.02 (3x3).

Spectroscopic data agrees with Destabel.[120]

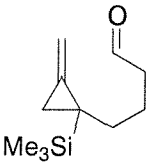


3-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]propanal (271).

Following a method described by Swern *et al.*[92]

DMSO (1.32 mL, 25.0 mmol) in DCM (10 mL) was added to a stirred solution of oxalyl chloride (850 μL, 13.0 mmol) in DCM (30 mL) keeping the temperature below -60°C under argon. The reaction was stirred for 2 minutes before addition of alcohol **269** (2.0 g, 11.0 mmol) in DCM (15 mL) within 5 minutes also keeping the temperature below -60°C. After 15 minutes NEt_3 (6.98 mL, 50.0 mmol) was added and the reaction allowed to warm to 10°C over 2 hours. The reaction was quenched with water (25 mL), extracted with DCM (3x30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 5% ether in petrol) to give aldehyde **271** as a colourless oil (1.70 g, 86%).

R_f 0.51 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2957 (w), 2818 (w), 1726 (s), 1249 (m), 838 (s); δ_H (400 MHz, $CDCl_3$) 9.73 (1H, t, *J* 2 Hz, CHO), 5.31 (1H, s, C=CH_AH$_B$), 5.21 (1H, s, C=CH$_A$$H_B$), 2.44-2.36 (2H, m, C$H_2$CHO), 1.93 (1H, ddd, *J* 6, 9, 14 Hz, CH_AH$_B$CH$_2$CHO), 1.74 (1H, ddd, *J* 6, 9, 14 Hz, CH$_A$$H_BCH_2$CHO), 1.07 (1H, dt, *J* 8, 2 Hz, CH$_2$=CCH_AH$_B$), 0.84 (1H, dt, *J* 8, 2 Hz, CH$_2$=CCH$_A$$H_B$), 0.01 (9H, s, Si(CH$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 203.16 (1), 139.41 (0), 102.20 (2), 42.89 (2), 27.49 (2), 13.72 (0), 12.83 (2), -0.02 (3x3); LRMS (CI) *m/z* 183 (7%, $[M+H]^+$), 73 (100%, $[SiMe_3]^+$); HRMS (CI) *m/z* 183.1204 ($[M+H]^+$ - $C_{10}H_{19}OSi$ requires 183.1205).



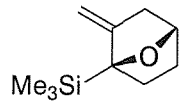
4-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]butanal (272).

Following a method described by Swern *et al.*[92]

DMSO (3.3 mL, 62.2 mmol) in DCM (20 mL) was added to a stirred solution of oxalyl chloride (2.1 mL, 31.1 mmol) in DCM (60 mL) keeping the temperature below -60°C under argon. The reaction was stirred for 2 minutes before addition of alcohol **270** (5.3 g, 27.0 mmol) in DCM (30 mL) within 5 minutes keeping the temperature below -60°C. After 15 minutes NEt_3 (17.2 mL, 0.12 mol) was added and the reaction allowed to warm to 10°C over 2 hours. The reaction was quenched with water (50 mL), extracted with

DCM (3x75 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 5% ether in petrol) to give aldehyde **272** as a colourless oil (4.0 g, 76%).

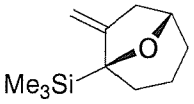
R_f 0.50 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2954 (w), 2896 (w), 1726 (m), 1249 (m), 904 (s), 837 (s), 729 (s); δ_H (400 MHz, $CDCl_3$) 9.74 (1H, br s, CHO), 5.27 (1H, s, C=C$H_A$$H_B$), 5.21 (1H, s, C=C$H_A$$H_B$), 2.39 (2H, dt, *J* 1, 7 Hz, CH_2CHO), 1.76-1.50 (3H, m, CH_2C$H_A$$H_B$), 1.39 (1H, m, $CH_2CH_A$$H_B$) 1.06 (1H, d, *J* 8 Hz, CH_2=CC$H_A$$H_B$), 0.83 (1H, d, *J* 8 Hz, CH_2=C$CH_A$$H_B$), 0.00 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 202.96 (1), 140.06 (0), 101.08 (2), 44.67 (2), 35.71 (2), 21.45 (2), 14.39 (0), 13.14 (2), -0.02 (3x3); LRMS (CI) *m/z* 197 (15%, $[M+H]^+$), 73 (100%, $[Si(CH_3)_3]^+$); HRMS (CI) *m/z* 195.1208 ($[M-H]^+$ - $C_{11}H_{19}OSi$ requires 195.1205).



Rac-Trimethyl(2-methylene-7-oxabicyclo[2.2.1]hept-1-yl)silane (273).

Following the typical intramolecular cyclisation procedure, $BF_3 \cdot Et_2O$ (1.2 eq.) was added to cyclisation precursor **271** (100 mg) in DCM (4 mL) at -78°C under argon. The reaction was stirred at -78°C for 1 hour. The crude material was purified by column chromatography (petrol to 3% ether in petrol) to give bicycle **273** as a colourless oil (61 mg, 61%).

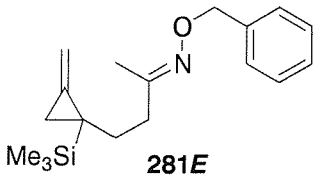
R_f 0.61 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2955 (w), 1249 (m), 904 (s), 837 (m), 728 (s); δ_H (400 MHz, $CDCl_3$) 4.80 (1H, s, C=C$H_A$$H_B$), 4.75 (1H, t, *J* 2 Hz, C=$CH_A$$H_B$), 4.64 (1H, m, OCH), 2.40 (1H, br d with fine splitting, *J* 15 Hz, CH_2=CC$H_A$$H_B$), 2.17 (1H, dt, *J* 15, 2 Hz, CH_2=C$CH_A$$H_B$), 1.77-1.71 (2H, m, $SiCCH_2CH_2$), 1.59-1.51 (2H, m, $SiCCH_2$), 0.18 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 155.35 (0), 102.27 (2), 81.67 (0), 78.66 (1), 42.22 (2), 34.33 (2), 30.80 (2), -2.46 (3x3); LRMS (CI) *m/z* 183 (36%, $[M+H]^+$), 73 (100%, $[SiMe_3]^+$); HRMS (CI) *m/z* 183.1202 ($[M+H]^+$ - $C_{10}H_{19}OSi$ requires 183.1205).



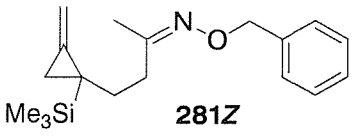
Rac-Trimethyl(7-methylene-8-oxabicyclo[3.2.1]oct-1-yl)silane (274).

Following the typical intramolecular cyclisation procedure, $BF_3{\cdot}Et_2O$ (1.2 eq.) was added to cyclisation precursor **272** (50 mg) in DCM (4 mL) at -78°C under nitrogen. The reaction was stirred at -78°C for 1 hour. The crude material was purified by column chromatography (petrol to 2% ether in petrol) to give bicycle **274** as a colourless oil (39 mg, 78%).

R_f 0.68 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2940 (m), 1650 (w), 1429 (w), 1245 (m), 837 (s); δ_H (400 MHz, $CDCl_3$) 4.94 (1H, s, C=CH_AH$_B$), 4.72 (1H, s, C=CH$_A$$H_B$), 4.32 (1H, br d, *J* 7 Hz, OCH), 2.68 (1H, m, CH_2=CCH_AH$_B$), 2.52 (1H, d, *J* 16 Hz, CH_2=CCH$_A$$H_B$), 1.94-1.79 (3H, m, C$H_2CH_AH_B$), 1.59-1.37 (3H, m, CH$_A$$H_BCH_2$), 0.09 (9H, s, $Si(CH_3)_3$);); δ_C (100 MHz, $CDCl_3$) 156.59 (0), 102.10 (2), 80.14 (0), 75.75 (1), 41.02 (2), 34.43 (2), 31.30 (2), 17.49 (2), -2.77 (3x3); LRMS (CI) *m/z* 197 (82%, $[M+H]^+$), 73 (100%, $[Si(CH_3)_3]^+$); HRMS (EI) *m/z* 196.1278 ($[M]^+$ - $C_{11}H_{20}OSi$ requires 195.1283).



281*E*



281*Z*

4-[(*E*)-2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-butanone *O*2-benzyloxime (281*E*).

4-[(*Z*)-2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-butanone *O*2-benzyloxime (281*Z*).

Following a method described by Booth *et al.*[94]

Ketone **133** (500 mg, 2.55 mmol) and benzylhydroxylamine hydrochloride (489 mg, 3.06 mmol) were stirred together in pyridine (12 mL) for 24 hours at room temperature. The solvent was removed *in vacuo*, replaced with ether (15 mL), washed with water (2x10

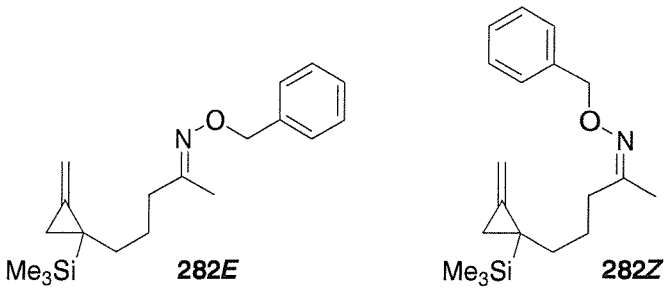
mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 2% ether in petrol) to give a mixture of oximes **281*E*** and **281*Z*** as a colourless oil (580 mg, 76%, 2:1, *E*:*Z*).

Data for **281*E***

R_f 0.68 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2954 (w), 2918 (w), 1730 (w), 1453 (w), 1366 (m), 1248 (m), 1042 (m), 834 (s); δ_H (300 MHz, $CDCl_3$) 7.40-7.28 (5H, m, Ph), 5.30 (1H, s, C=CH_AH$_B$), 5.23 (1H, s, C=CH$_A$$H_B$), 5.09 (2H, s, OCH_2Ph), 2.25-2.15 (2H, m, CH_2CN), 1.85 (3H, s, CH_3), 1.75 (1H, ddd, *J* 6.5, 10, 13 Hz, CH_AH$_B$$CH_2CN$), 1.64 (1H, ddd, *J* 6.5, 10.5, 13 Hz, CH$_A$$H_B$$CH_2CN$), 1.07 (1H, br d, *J* 7.5 Hz, CH_2=CCH_AH$_B$), 0.88 (1H, br d, *J* 7.5 Hz, CH_2=CCH$_A$$H_B$), 0.03 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 158.22 (0), 139.27 (0), 138.45 (0), 128.43 (2x1), 128.21 (2x1), 127.74 (1), 100.88 (2), 75.44 (2), 34.69 (2), 32.10 (2), 14.58 (3), 13.69 (0), 12.46 (2), -2.43 (3x3); LRMS (CI) *m/z* 302 (100%, $[M+H]^+$), 194 (72%, $[M-OBn]^+$); HRMS (ES+) *m/z* 324.1754 ($[M+Na]^+$ - $C_{18}H_{27}NOSiNa$ requires 324.1754).

Data for **281*Z***

R_f 0.64 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2954 (w), 2955 (w), 1731 (w), 1453 (w), 1366 (w), 1249 (m), 1043 (w), 837 (s), 732 (s); δ_H (300 MHz, $CDCl_3$) 7.39-7.27 (5H, m, Ph), 5.27 (1H, s, C=CH_AH$_B$), 5.22 (1H, s, C=CH$_A$$H_B$), 5.06 (2H, s, OCH_2Ph), 2.45-2.24 (2H, m, CH_2CN), 1.82 (3H, s, CH_3), 1.69-1.47 (2H, m, CH_2CH_2CN), 1.06 (1H, br d, *J* 7.5 Hz, CH_2=CCH_AH$_B$), 0.86 (1H, br d, *J* 7.5 Hz, CH_2=CCH$_A$$H_B$), -0.02 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 158.90 (0), 139.51 (0), 138.41 (0), 128.39 (2x1), 128.03 (2x1), 127.68 (1), 100.62 (2), 75.35 (2), 31.27 (2), 28.90 (2), 20.18 (3), 14.01 (0), 12.60 (2), -2.49 (3x3); LRMS (CI) *m/z* 302 (100%, $[M+H]^+$), 194 (86%, $[M-OBn]^+$); HRMS (ES+) *m/z* 302.1936 ($[M+H]^+$ - $C_{18}H_{28}NOSi$ requires 302.1935).



5-[(*E*)-2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-pentanone *O*2-benzyl oxime (282*E*).

5-[(*Z*)-2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-pentanone *O*2-benzyl oxime (282*Z*).

Following a method described by Booth *et al.*[94]

Ketone **134** (500 mg, 2.38 mmol) and benzylhydroxylamine hydrochloride (456 mg, 2.86 mmol) were stirred together in pyridine (12 mL) for 24 hours at room temperature. The solvent was removed *in vacuo*, replaced with ether (15 mL), washed with water (2x10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 2% ether in petrol) to give a mixture of oximes **282*E*** and **282*Z*** as a colourless oil (690 mg, 92%, 2:1, *E*:*Z*).

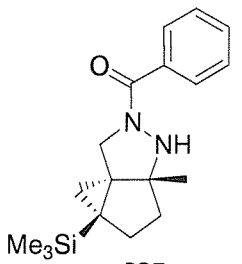
Data for **282*E***

R_f 0.65 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3032 (w), 2951 (w), 1730 (w), 1453 (w), 1365 (w), 1248 (m), 1018 (w), 839 (s); δ_H (300 MHz, $CDCl_3$) 7.40-7.28 (5H, m, Ph), 5.27 (1H, s, C=CH_AH_B), 5.21 (1H, s, C=CH_AH_B), 5.09 (2H, s, OCH_2Ph), 2.14 (2H, t, *J* 7 Hz, CH_2CN), 1.87 (3H, s, CH_3), 1.65-1.30 (4H, m, $(CH_2)_2CH_2CN$), 1.05 (1H, br d, *J* 7.5 Hz, CH_2=CCH_AH_B), 0.82 (1H, br d, *J* 7.5 Hz, CH_2=CCH_AH_B), 0.00 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 158.23 (0), 139.93 (0), 138.52 (0), 128.44 (2x1), 128.05 (2x1), 127.71 (1), 100.34 (2), 75.40 (2), 36.20 (2), 35.30 (2), 25.34 (2), 14.29 (3), 13.93 (0), 12.70 (2), -2.38 (3x3); LRMS (CI) *m/z* 316 (100%, $[M+H]^+$), 210 (66%, $[M-OBn]^+$); HRMS (ES+) *m/z* 316.2091 ($[M+H]^+$ - $C_{19}H_{30}NOSi$ requires 316.2091).

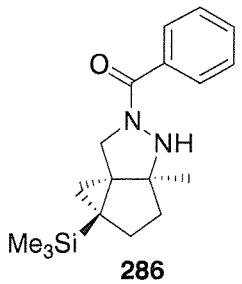
Data for **282*Z***

R_f 0.61 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3033 (w), 2953 (w), 1731 (w), 1454 (w), 1366 (w), 1249 (m), 1047 (w), 837 (s); δ_H (300 MHz, $CDCl_3$) 7.40-7.28 (5H, m, Ph), 5.26

(1H, s, C=CH_AH$_B$), 5.20 (1H, s, C=CH$_A$$H_B$), 5.06 (2H, s, OCH$_2$Ph), 2.35-2.27 (2H, m, CH$_2$CN), 1.85 (3H, s, CH$_3$), 1.61-1.31 (4H, m, (CH_2)$_2$CH$_2$CN), 1.03 (1H, br d, *J* 7.5 Hz, CH$_2$=CCH_AH$_B$), 0.81 (1H, br d, *J* 7.5 Hz, CH$_2$=CCH$_A$$H_B$), -0.02 (9H, s, Si(CH$_3$)$_3$); δ_C (75 MHz, CDCl$_3$) 158.81 (0), 139.85 (0), 138.69 (0), 128.42 (2x1), 128.00 (2x1), 127.69 (1), 100.38 (2), 75.34 (2), 35.74 (2), 29.94 (2), 24.50 (2), 20.18 (3), 13.96 (0), 12.67 (2), -2.42 (3x3); LRMS (CI) *m/z* 316 (31%, [M+H]$^+$), 210 (100%, [M-OBn]$^+$); HRMS (ES+) *m/z* 316.2091 ([M+H]$^+$ - $C_{19}H_{30}NOSi$ requires 316.2091).



285



286

Rac-[(3a*S*,4a*S*,6a*R*)-6a-Methyl-4a-(1,1,1-trimethylsilyl)perhydrocyclopropa[2,3] cyclopenta[*c*]pyrazol-2-yl](phenyl)methanone (285).

Rac-[(3a*S*,4a*S*,6a*S*)-6a-Methyl-4a-(1,1,1-trimethylsilyl)perhydrocyclopropa[2,3] cyclopenta[*c*]pyrazol-2-yl](phenyl)methanone (286).

Following a method described by Wu *et al.*[Peilinwu, 1995 #96]

Ketone **133** (200 mg, 1.02 mmol) and benzoyl hydrazine (139 mg, 1.02 mmol) were refluxed together in hexane (10 mL) for 48 hours. The reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. The crude material was purified by column chromatography (petrol to 50% ether in petrol) to give tricycle **285** as a white solid (100 mg, 31%) and tricycle **286** as a white solid (100 mg, 31%).

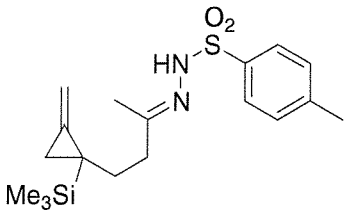
Data for **285**

Found: C, 68.41; H, 8.56; N, 8.75. $C_{18}H_{26}N_2OSi$ requires C, 68.74; H, 8.33; N, 8.90%; m.p. 206-208°C; R_f 0.38 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3217 (w), 3049 (br), 2949 (w), 1608 (m), 1246 (m), 832 (s); δ_H (400 MHz, CDCl$_3$) 7.68-7.64 (2H, m, PhH), 7.38-7.33 (3H, m, PhH), 4.09 (1H, br s, NH), 4.05 (1H, d, *J* 8 Hz, NCH_AH$_B$), 3.37 (1H, d, *J* 8 Hz, NCH$_A$$H_B$), 2.11 (1H, m, CH$_2CH_AH_B$), 1.94 (1H, m, C$H_AH_BCH_2$), 1.28-1.14 (2H, m,

$CH_AH_BCH_AH_B$) 1.03 (3H, s, CH_3), 0.88 (1H, d, *J* 5 Hz, $NCH_2CCH_AH_B$), 0.17 (1H, d, *J* 5 Hz, $NCH_2CCH_AH_B$), 0.00 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 174.11 (0), 138.96 (0), 132.90 (1), 131.22 (2x1), 130.57 (2x1), 73.95 (0), 51.86 (2), 50.40 (0), 37.90 (2), 27.69 (2), 23.90 (0), 19.82 (3), 18.16 (2), 0.18 (3x3); LRMS (ES+) *m/z* 315 (52%, $[M+H]^+$), 145 (100%).

Data for **286**

Found: C, 68.56; H, 8.27; N, 8.69. $C_{18}H_{26}N_2OSi$ requires C, 68.74; H, 8.33; N, 8.90%; m.p. 162-164°C; R_f 0.44 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3235 (br), 3049 (br), 2950 (m), 2869 (m), 1249 (m), 834 (s); δ_H (400 MHz, $CDCl_3$) 7.67 (2H, d, *J* 7.5 Hz, PhH), 7.38-7.34 (3H, m, PhH), 4.07 (1H, d, *J* 8 Hz, NCH_AH_B), 3.78 (1H, br s, NH), 3.57 (1H, d, *J* 8 Hz, NCH_AH_B), 1.85-1.65 (3H, m, $CH_AH_BCH_2$), 1.34 (1H, m, $CH_AH_BCH_2$), 1.06 (3H, s, CH_3), 0.99 (1H, d, *J* 5 Hz, $NCH_2CCH_AH_B$), 0.63 (1H, d, *J* 5 Hz, $NCH_2CCH_AH_B$), 0.00 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 173.19 (0), 138.44 (0), 132.60 (1), 131.20 (2x1), 130.22 (2x1), 75.03 (0), 51.06 (2), 48.35 (0), 33.33 (2), 30.74 (2), 23.07 (0), 21.67 (3), 14.99 (2), 0.00 (3x3); LRMS (ES+) *m/z* 315 (12%, $[M+H]^+$), 145 (100%).

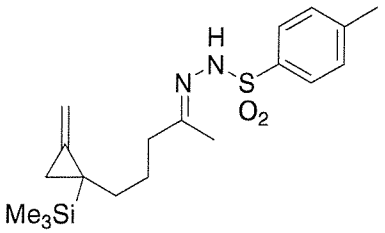


***N*1-{(*E*)-1-Methyl-3-[2-methylidene-1-(1,1,1,-trimethylsilyl)cyclopropyl] propylidene}-4-methylbenzene-1-sulfonohydrazide (287).**

Following a method described by Iida *et al.*[97]

Ketone **133** (400 mg, 2.04 mmol) and tosylhydrazine (380 mg, 2.04 mmol), were stirred together in acetic acid (10 mL) at room temperature for 48 hours. The reaction mixture was diluted with water (15 mL) and extracted with DCM (3x20 mL). The organic layer was washed with sat. $NaHCO_3$ (3x15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 20% ether in petrol) to give hydrazone **287** as a white solid (420 mg, 57%, 9:1 mixture of isomers *E*:*Z*).

M.p. 108-110°C; R_f 0.17 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3231 (br), 2954 (w), 1598 (w), 1334 (w), 1166 (s), 838 (s), 666 (m); δ_H (300 MHz, $CDCl_3$) 7.84 (2H, d, *J* 8 Hz, ArH), 7.35 (1H, br s, NH), 7.29 (2H, d, *J* 8 Hz, ArH), 5.21 (1H, br s, C=CH_AH_B), 5.11 (1H, br s, C=CH_AH_B), 2.42 (3H, s, $ArCH_3$), 2.21-2.14 (2H, m, CH_2CN), 1.71 (3H, s, $CNCH_3$), 1.66 (1H, m, C$H_AH_BCH_2CN$), 1.50 (1H, ddd, *J* 7, 11, 14 Hz, $CH_AH_BCH_2CN$), 0.99 (1H, dt, *J* 8, 2 Hz, CH_2=CCH_AH_B), 0.76 (1H, dt, *J* 8, 2 Hz, CH_2=CCH_AH_B), -0.04 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 158.40 (0), 144.08 (0), 139.11 (0), 135.48 (0), 129.56 (2x1), 128.31 (2x1), 100.85 (2), 37.20 (2), 31.10 (2), 21.75 (3), 15.91 (3), 13.42 (0), 12.27 (2), -2.58 (3x3); LRMS (ES+) *m/z* 365 (17%, $[M+H]^+$), 146 (100%); HRMS (ES+) *m/z* 365.1731 ($[M+H]^+$ - $C_{18}H_{29}N_2O_2SSi$ requires 365.1714).

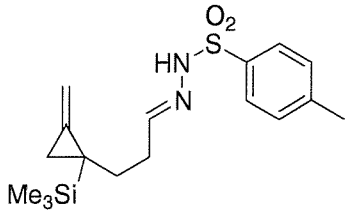


N1-{(*E*)-1-Methyl-4-[2-methylidene-1-(1,1,1,trimethylsilyl)cyclopropyl] butylidene}-4-methylbenzene-1-sulfonohydrazide (288).

Ketone **134** (100 mg, 0.47 mmol) and tosylhydrazine (88 mg, 0.47 mmol) were refluxed together in hexane (2 mL) for 1 hour. The solvent was removed *in vacuo* to give hydrazone **288** as a white solid (179 mg, 100%, 6:1 mixture of isomers *E*:*Z*).

M.p. 92-94°C; R_f 0.20 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3220 (br), 2953 (w), 2894 (w), 1402 (w), 1336 (m), 1165 (s), 857 (s); δ_H (300 MHz, $CDCl_3$) 7.85 (2H, d, *J* 8 Hz, ArH), 7.67 (1H, br s, NH), 7.30 (2H, d, *J* 8 Hz, ArH), 5.23 (1H, br s, C=CH_AH_B), 5.16 (1H, br s, C=CH_AH_B), 2.44 (3H, s, $ArCH_3$), 2.14 (2H, t, *J* 7 Hz, CH_2CN), 1.75 (3H, s, $CNCH_3$), 1.54-1.16 (4H, m, $(CH_2)_2CH_2CN$), 1.02 (1H, dt, *J* 8, 2 Hz, CH_2=CCH_AH_B), 0.72 (1H, dt, *J* 8, 2 Hz, CH_2=CCH_AH_B), -0.04 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 158.47 (0), 144.00 (0), 139.86 (0), 135.54 (0), 129.69 (1), 129.63 (1), 128.23 (1), 128.14 (1), 100.33 (2), 39.12 (2), 35.18 (2) 24.85 (2), 21.78 (3), 15.82 (3), 13.86 (0), 12.71 (2),

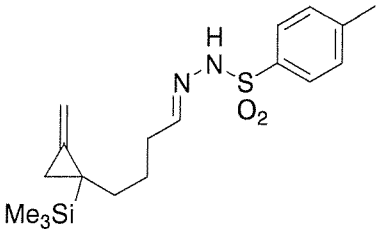
-2.42 (3x3); HRMS (ES+) *m/z* 401.1694 ($[M+Na]^+$ - $C_{19}H_{30}N_2O_2SSiNa$ requires 401.1689).



***N*'1-(*E*)-3-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]propylidene-4-methyl-1-benzenesulfonohydrazide (289).**

Aldehyde **271** (25 mg, 0.14 mmol) and tosylhydrazine (25 mg, 0.14 mmol) were stirred together in DCM (5 mL) with 4Å molecular sieves at room temperature under argon. The reaction mixture was stirred for 2 hours, the sieves were removed and the solvent removed *in vacuo* to give hydrazone **289** as a viscous colourless oil (50 mg, 100%, 4:1 mixture of isomers *E*:*Z*).

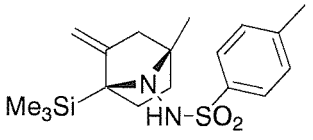
R_f 0.24 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3202 (br), 2954 (w), 2851 (w), 1598 (w), 1449 (w), 1320 (w), 1249 (w), 1164 (m), 1093 (w), 904 (s); δ_H (400 MHz, $CDCl_3$) 7.80 (2H, d, *J* 8 Hz, ArH), 7.78 (1H, s, NH), 7.32 (2H, d, *J* 8 Hz, ArH), 7.11 (1H, t, *J* 5 Hz, CHN), 5.23 (1H, s, C=CH_AH_B), 5.11 (1H, s, C=CH_AH_B), 2.43 (3H, s, CH_3), 2.43-2.02 (2H, m, CH_2CHN), 1.80-1.43 (2H, m, CH_2CH_2CHN), 1.00 (1H, dt, *J* 8, 2 Hz, CH_2=CCH_AH_B), 0.76 (1H, dt, *J* 8, 2 Hz, CH_2=CCH_AH_B), -0.04 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 153.44 (1), 144.84 (0), 139.59 (0), 136.10 (0), 130.43 (2x1), 128.79 (2x1), 101.72 (2), 32.07 (2), 31.62 (2), 22.35 (3), 14.01 (0), 12.97 (2), -0.29 (3x3); HRMS (ES+) *m/z* 373.1380 ($[M+Na]^+$ - $C_{17}H_{26}N_2O_2SSiNa$ requires 373.1376).



N'1-(E)-4-[2-Methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]butylidene-4-methyl-1-benzenesulfonohydrazide (290).

Aldehyde **272** (100 mg, 0.51 mmol) and tosylhydrazine (95 mg, 0.51 mmol) were stirred together in DCM (8 mL) with 4Å molecular sieves at room temperature under argon. The reaction mixture was stirred for 1 hour, the sieves were removed and the solvent removed *in vacuo* to give hydrazone **290** as a viscous oil (194mg, 100%, 9:1 mixture of isomers *E*:*Z*).

R_f 0.29 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3201 (br), 2952 (w), 2895 (w), 1325 (w), 1248 (m), 1163 (s), 1093 (w), 836 (s); δ_H (400 MHz, $CDCl_3$) 7.86 (2H, d, *J* 8 Hz, ArH), 7.37 (2H, d, *J* 8 Hz, ArH), 7.19 (1H, t, *J* 6 Hz, CHN), 5.28 (1H, s, C=CH_AH$_B$), 5.20 (1H, s, C=CH$_A$$H_B$), 2.48 (3H, s, $ArCH_3$), 2.24-2.15 (2H, m, CH_2CHN), 1.57-1.41 (4H, m, (CH_2)$_2$CH$_2$CHN), 1.06 (1H, d, *J* 8 Hz, CH$_2$=CCH_AH$_B$), 0.76 (1H, d, *J* 8 Hz, CH$_2$=CCH$_A$$H_B$), 0.00 (9H, s, Si(CH$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 153.21 (1), 144.83 (0), 140.17 (0), 135.86 (0), 130.29 (2x1), 128.54 (2x1), 100.90 (2), 35.65 (2), 33.14 (2), 25.52 (2), 22.21 (3), 14.14 (0), 13.09 (2), -0.02 (3x3); HRMS (ES+) *m/z* 387.1540 ([M+Na]$^+$ - $C_{18}H_{28}N_2O_2SSiNa$ requires 387.1533).

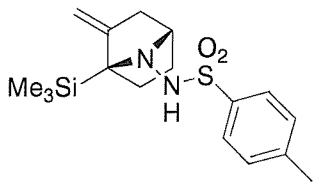


Rac-N1-[4-Methyl-2-methylidene-1-(1,1,1,-trimethylsilyl)-7-azabicyclo(2.2.1]hept-7-yl]-4-methylbenzene-1-sulfonamide (297).

Following the typical intramolecular cyclisation procedure, $BF_3{\cdot}Et_2O$ (1.1 eq.) was added to cyclisation precursor **287** (50 mg) in DCM (4 mL) at -30°C under argon. The reaction

was allowed to warm to room temperature over 5 hours. The crude material was purified by column chromatography (petrol to 7% ether in petrol) to give bicycle **297** as a white solid (24 mg, 48%).

M.p. 109-111°C; R_f 0.46 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3231 (br), 2962 (w), 2948 (w), 1334 (m), 1247 (m), 1161 (s), 1094 (m), 841 (m); δ_H (300 MHz, $CDCl_3$) 7.81 (2H, d, *J* 8 Hz, ArH), 7.28 (2H, d, *J* 8 Hz, ArH), 5.30 (1H, br s, NH), 5.03 (1H, br s, C=CH_AH$_B$), 4.98 (1H, br s, C=CH$_A$$H_B$), 2.43 (3H, s, $ArCH_3$), 2.11 (2H, s, CH_2=CCH_2), 1.48-1.19 (4H, m, CH_2CH_2), 0.51 (3H, s, $NCCH_3$), 0.25 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 153.16 (0), 143.67 (0), 136.90 (0), 129.28 (2x1), 128.78 (2x1), 108.17 (2), 70.54 (0), 68.45 (0), 40.97 (2), 34.36 (2), 29.71 (2), 21.75 (3), 18.02 (3), -1.94 (3x3); LRMS (ES+) *m/z* 365 (37%, $[M+H]^+$), 145 (100%); HRMS (ES+) *m/z* 365.1722 ($[M+H]^+$ - $C_{18}H_{29}N_2O_2SSi$ requires 365.1719).

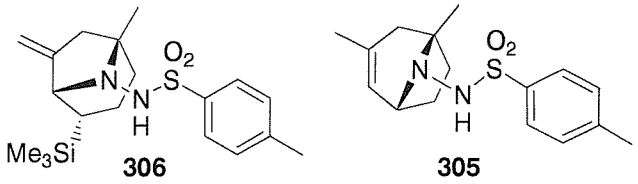


Rac-4-Methyl-*N*-(2-methylene-1-trimethylsilanyl-7-aza-bicyclo[2.2.1]hept-7-yl)-benzenesulfonamide (300).

Following the typical intramolecular cyclisation procedure, $BF_3 \cdot Et_2O$ (1.2 eq.) was added to cyclisation precursor **289** (50 mg) in $EtNO_2$ (4 mL) at -70°C under argon. The reaction was stirred at -70°C for 1 hour. The crude material was purified by column chromatography (petrol to 20% ether in petrol) to give bicycle **300** as a white solid (22 mg, 44%).

M.p. 146-148°C; R_f 0.30 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3220 (w), 2953 (w), 2901 (w), 1598 (w), 1452 (w), 1335 (w), 1249 (w), 1167 (m), 1094 (w); δ_H (400 MHz, $CDCl_3$) 7.81 (2H, d, *J* 8 Hz, ArH), 7.30 (2H, d, *J* 8 Hz, ArH), 5.13 (1H, s, C=CH_AH$_B$), 4.99-4.95 (2H, m, N*H*, C=CH$_A$$H_B$),2.93 (1H, br s, NCH), 2.45-2.36 (4H, m, CH_2=CCH_AH$_B$, CH_3), 2.04 (1H, br d, *J* 15 Hz, CH_2=CCH$_A$$H_B$), 1.81 (1H, dt, *J* 3, 11 Hz, $SiCCH_2CH_AH_B$), 1.59 (1H, m, $SiCCH_2CH_AH_B$), 1.32-1.15 (2H, m, $SiCCH_2$), 0.09 (9H, s, $Si(CH_3)_3$); δ_C (100

MHz, $CDCl_3$) 152.66 (0), 144.25 (0), 136.58 (0), 129.88 (2x1), 128.87 (2x1), 107.86 (2), 66.34 (0), 63.76 (1), 34.88 (2), 31.12 (2), 28.21 (2), 22.08 (3), -2.00 (3x3); LRMS (ES+) *m/z* 351 (13%, $[M+H]^+$), 540 (100%); HRMS (ES+) *m/z* 373.1380 ($[M+Na]^+$ - $C_{17}H_{26}N_2O_2SSiNa$ requires 373.1376).



Rac-4-Methyl-*N*-(1-methyl-6-methylene-4-trimethylsilanyl-8-aza-bicyclo[3.2.1]oct-8-yl)-benzenesulfonamide (306).

Rac-*N*1-(3,5-Dimethyl-8-azabicyclo[3.2.1]oct-2-en-8-yl)-4-methyl-benzene-1-sulfonamide (305).

Following the typical intramolecular cyclisation procedure, $BF_3{\cdot}Et_2O$ (2 eq.) was added to cyclisation precursor **288** (70 mg) in DCM (5 mL) at 0°C under nitrogen. The reaction was allowed to warm to room temperature over 18 hours. The crude material was purified by column chromatography (petrol to 15% ether in petrol) to give bicycle **306** as a white solid (21 mg, 30%) and bicycle **305** as a white solid (4 mg, 7%).

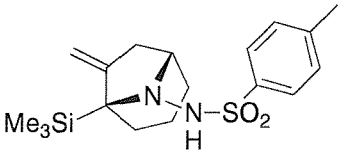
Data for **306**

M.p. 128-130°C; R_f 0.30 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3214 (br), 2928 (m), 1599 (w), 1539 (w), 1458 (m), 1403 (m), 1331 (m), 1248 (m), 1164 (s), 1094 (m), 905 (s); δ_H (400 MHz, $CDCl_3$) 7.83 (2H, d, *J* 8 Hz, ArH), 7.32 (2H, d, *J* 8 Hz, ArH), 5.18 (1H, br s, NH), 5.03 (1H, s, C=CH_AH_B), 4.80 (1H, s, C=CH_AH_B), 2.83 (1H, br s, NCH), 2.44 (3H, s, $ArCH_3$), 2.28 (1H, d, *J* 17 Hz, CH_2=CCH_AH_B), 2.16 (1H, d, *J* 17 Hz, CH_2=CCH_AH_B), 1.69-1.26 (4H, m, CH_2CH_2), 1.13 (3H, s, CH_3), 0.97 (1H, m, CHSi), -0.19 (9H, s, $Si(CH_3)_3$); LRMS (ES+) *m/z* 379 (100%, $[M+H]^+$); HRMS (ES+) *m/z* 379.1857 ($[M+H]^+$ - $C_{19}H_{31}N_2O_2SSi$ requires 379.1876).

Data for **305**

Found: C, 62.60; H, 7.25; N, 8.91. $C_{16}H_{22}N_2O_2S$ requires C, 62.72; H, 7.24; N, 9.14%; m.p. 169-171°C; R_f 0.40 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3203 (br), 2963 (w), 2925

(w), 1442 (w), 1332 (w), 1163 (s), 1094 (m), 811 (m); δ_H (400 MHz, $CDCl_3$) 7.82 (2H, d, *J* 8 Hz, ArH), 7.29 (2H, d, *J* 8 Hz, ArH), 5.57 (1H, s, NH), 5.25 (1H, br s with fine splitting, C=CH), 2.93 (1H, t, *J* 5 Hz, HCN), 2.44 (3H, s, $ArCH_3$), 2.15 (1H, d, *J* 8 Hz, $CH{=}CC\mathit{H}_A H_B$), 1.63 (3H, s, $CH{=}CC\mathit{H}_3$), 1.76-1.38 (5H, m, $(CH_2)_2$, $CH{=}CCH_A\mathit{H}_B$), 0.97 (3H, s, $NCCH_3$); δ_C (100 MHz, $CDCl_3$) 143.75 (0), 136.07 (0), 135.63 (0), 129.40 (2x1), 128.48 (2x1), 121.32 (1), 60.19 (0), 60.05 (1), 41.53 (2), 35.16 (2), 30.37 (2), 24.87 (3), 22.40 (3), 21.79 (3); LRMS (ES+) *m/z* 307 (25%, $[M+H]^+$), 130 (100%).



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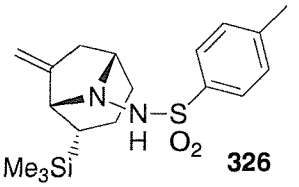


326

Rac-*N*-(7-Methylene-1-trimethylsilanyl-8-aza-bicyclo[3.2.1]oct-8-yl)- 4-methyl benzenesulfonamide (324).

Rac-*N*-(7-Methylene-2-trimethylsilanyl-8-aza-bicyclo[3.2.1]oct-8-yl)- 4-methyl benzenesulfonamide (326).

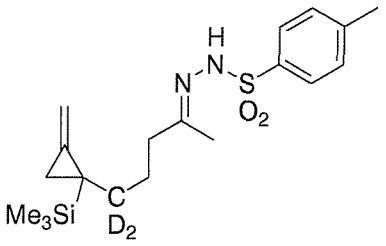
Following the typical intramolecular cyclisation procedure, $BF_3{\cdot}Et_2O$ (1 eq.) was added to cyclisation precursor **290** (194 mg) in DCM (8 mL) at -30°C under nitrogen. The reaction was allowed to warm to 0°C over 3 hours. The crude material was purified by column chromatography (petrol to 15% ether in petrol) to give bicycle **324** as a white solid (47 mg, 24%) and bicycle **326** as a white solid (42 mg, 22%).

Data for **324**

M.p. 133-135°C; R_f 0.39 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3220 (w), 2927 (m), 1998 (w), 1449 (w), 1403 (w), 1336 (m), 1247 (m), 1164 (s), 1086 (w), 841 (m); δ_H (400 MHz, $CDCl_3$) 7.82 (2H, d, *J* 8 Hz, ArH), 7.32 (2H, d, *J* 8 Hz, ArH), 5.31 (1H, br s, NH), 5.05 (1H, s ,$C{=}C\mathit{H}_A H_B$), 4.93 (1H, s ,$C{=}CH_A\mathit{H}_B$), 2.65-2.52 (2H, m, $CH_2{=}CC\mathit{H}_A H_B$, $NC\mathit{H}$), 2.44 (3H, s, $ArCH_3$), 2.29 (1H, d, *J* 16 Hz, $CH_2{=}CCH_A\mathit{H}_B$), 1.88 (1H, dt, *J* 13, 6 Hz, $C\mathit{H}_A H_B$), 1.71-1.16 (5H, m, $(C\mathit{H}_2)_2$, $CH_A\mathit{H}_B$), 0.15 (9H, s, $Si(CH_3)_3$); LRMS (ES+) *m/z* 365 (100%, $[M+H]^+$); HRMS (ES+) *m/z* (387.1543 ($[M+Na]^+$ - $C_{18}H_{28}N_2O_2SSiNa$ requires 387.1533).

Data for **326**

M.p. 92-94°C; R_f 0.39 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3215 (br), 2926 (w), 2857 (w), 1401 (w), 1334 (m), 1247 (m), 1161 (s), 1093 (m), 883 (s); δ_H (400 MHz, $CDCl_3$) 7.85 (2H, d, *J* 8 Hz, ArH), 7.31 (2H, d, *J* 8 Hz, ArH), 5.32 (1H, br s, NH), 5.32 (1H, s, C=C$H_A$$H_B$), 4.91 (1H, s, C=C$H_A$$H_B$), 3.40 (1H, m, NC*H*$CH_2$), 2.85 (1H, br s, CH_2=CC*H*N), 2.50 (1H, dd, *J* 7, 17 Hz, CH_2=CC$H_A$$H_B$), 2.44 (3H, s, CH_3), 2.25 (1H, d, *J* 17 Hz, CH_2=CC$H_A$$H_B$), 1.89 (1H, m, NCHC$H_A$$H_B$$CH_2$), 1.49 (1H, m, NCHC$H_A$$H_B$$CH_2$), 1.36-1.19 (2H, m, SiCHCH_2), 1.05 (1H, m, SiC*H*CH_2), -0.18 (9H, s, $Si(CH_3)_3$); LRMS (ES+) *m/z* 365 (100%, $[M+H]^+$); HRMS (ES+) *m/z* 365.1712 ($[M+H]^+$ - $C_{18}H_{29}N_2O_2SSi$ requires 365.1714).

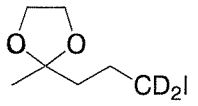


***N*'1-(*E*)-4,4-Dideutero-1-methyl-4-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl] butylidene-4-methyl-1-benzenesulfonohydrazide (328).**

Ketone **414** (100 mg, 0.47 mmol) and tosylhydrazine (88 mg, 0.47 mmol) were refluxed together in hexane (2 mL) for 1 hour. The solvent was removed *in vacuo* to give hydrazone **328** as a white solid (179 mg, 100%, 6:1 mixture of isomers *E*:*Z*).

M.p. 79-81°C; R_f 0.25 (50:50 ether:hexane); υ_{max} (neat)/cm^{-1} 3216 (br), 2956 (w), 1592 (w), 1332 (m), 1246 (m), 1165 (s), 834 (s); δ_H (250 MHz, $CDCl_3$) 7.89 (2H, d, *J* 9 Hz, ArH), 7.35 (2H, d, *J* 9 Hz, ArH), 5.29 (1H, br s, C=C$H_A$$H_B$), 5.20 (1H, br s, C=C$H_A$$H_B$), 2.48 (3H, s, $ArCH_3$), 2.19 (2H, t, *J* 7 Hz, CH_2CN), 1.78 (3H, s, $CNCH_3$), 1.54-1.43 (2H, m, CD_2CH_2), 1.07 (1H, dt, *J* 8, 2 Hz, CH_2=CC$H_A$$H_B$), 0.77 (1H, dt, *J* 8, 2 Hz, CH_2=CC$H_A$$H_B$), 0.00 (9H, s, $Si(CH_3)_3$); δ_C (62.5 MHz, $CDCl_3$) 158.92 (0), 144.45 (0), 140.29 (0), 136.11 (0), 130.53 (2x1), 128.59 (2x1), 100.86 (2), 39.51 (2), 34.78 (quintet, *J* 18.9 Hz), 25.09 (2), 22.18 (3), 16.26 (3), 14.20 (0), 13.06 (2), -2.00 (3x3); LRMS (ES+)

m/z 381 (100%, $[M+H]^+$); HRMS (ES+) *m/z* 381.1995 ($[M+H]^+$ - $C_{19}H_{29}{}^2H_2N_2O_2SSi$ requires 381.2001).

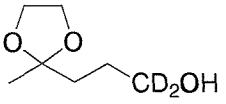


2-(3,3-Dideutero-3-iodopropyl)-2-methyl-1,3-dioxolane (329).

Following a method described by Corlay *et al.*[117]

PPh_3 (19.9 g, 76.0 mmol), imidazole (5.9 g, 86.2 mmol) and iodine (20.6 g, 81.1 mmol) were added in turn to a stirred solution of alcohol **330** (7.5 g, 50.7 mmol) in ether (90 mL) and acetonitrile (30 mL). The resulting red solution was stirred for 20 minutes then diluted with ether (50 mL). The mixture was washed with aq. $Na_2S_2O_3$ until the organic layer was colourless. The organic layer was washed with water (2x50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a white solid. The white solid was triturated in hexane and filtered, the filtrate was concentrated *in vacuo*. The crude material was purified by column chromatography (hexane to 7% ether in hexane) to give iodide **329** as a colourless oil (10.6 g, 82%).

R_f 0.50 (50:50 ether:hexane); δ_H (250 MHz, $CDCl_3$) 3.98-3.91 (4H, m, $O(CH_2)_2O$), 1.97-1.89 (2H, m, CH_2), 1.87-1.71 (2H, m, CH_2), 1.33 (3H, s, CH_3); δ_C (62.5 MHz, $CDCl_3$) 110.79 (0), 66.08 (2x2), 41.17 (2), 29.43 (2), 25.37 (3), 8.12 (quintet, *J* 22.7 Hz).



1,1-Dideutero-3-(2-methyl-1,3-dioxolan-2-yl)-1-propanol (330).

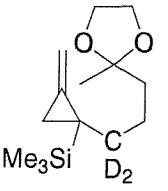
Following a method described by Dowd *et al.*[115]

Ester **256** (15.0 g, 79.8 mmol) in THF (20 mL) was added dropwise to a suspension of $LiAlD_4$ (5.0 g, 0.12 mol) in THF (100 mL) at 0°C. The reaction was stirred for 4 hours before addition of ether (100 mL). The reaction was stirred for 5 minutes before being quenched by dropwise addition of NaOH (20 mL, 2 M), filtered and concentrated *in*

vacuo. The crude material was purified by column chromatography (50:50 EtOAc:hexane) to give alcohol **330** as a colourless oil (7.5 g, 64%).

R_f 0.33 (EtOAc); δ_H (250 MHz, $CDCl_3$) 3.99-3.95 (4H, m, $O(CH_2)_2O$), 2.02 (1H, br s, OH), 1.82-1.64 (4H, m, $(CH_2)_2CD_2I$), 1.35 (3H, s, CH_3); δ_C (62.5 MHz, $CDCl_3$) 110.37 (0), 65.01 (2x2), 62.55 (quintet, *J* 21.3 Hz), 36.16 (2), 27.35 (2), 24.06 (3), LRMS (ES+) *m/z* 133 (12%, $[M-CH_3]^+$), 105 (100%, $[M+H-C_2H_4]^+$).

Spectroscopic data agrees with Dowd *et al.*[115]



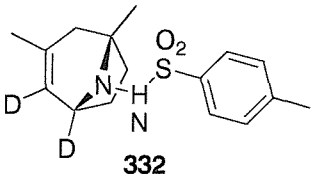
1-[1,1-Dideutero-3-(2-methyl-1,3-dioxolan-2-yl)propyl]-2-methylenecyclopropyl (trimethyl)silane (331).

Following a method described by Peron.[80]

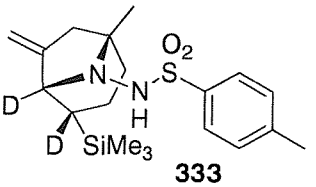
^{n}BuLi (25.4 mL, 1.6 M, 40.7 mmol) was added to a stirred solution of methylenecyclopropane **1** (3.3 mL, 48.8 mmol) in THF (100 mL) at -70°C under argon. The solution was allowed to warm to 0°C over 40 minutes and stirred at 0°C for 40 minutes. The resulting yellow solution was cooled to -70°C and TMSCl (5.2 mL, 40.7 mmol) added. The solution was allowed to warm to 0°C over 40 minutes before cooling to -70°C and addition of ^{n}BuLi (25.4 mL, 1.6 M, 40.7 mmol) and the warming procedure repeated. The resulting orange solution was cooled to -70°C before addition of iodide **329** (10.5 g, 40.7 mmol) in THF (7 mL) and allowed to warm to room temperature overnight. The reaction mixture was quenched with sat. NH_4Cl (50 mL), extracted with ether (3x100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (hexane to 3% ether in hexane) to give ketal **331** as a colourless oil (7.1 g, 69%).

R_f 0.60 (50:50 ether:hexane); υ_{max} (neat)/cm^{-1} 2954 (w), 2870 (w), 1376 (w), 1245 (m), 1065 (m), 832 (s), 747 (m); δ_H (250 MHz, $CDCl_3$) 5.26 (1H, br s, $C=CH_AH_B$), 5.20 (1H, br s, $C=CH_AH_B$), 3.98-3.91 (4H, m, $O(CH_2)_2O$), 1.64-1.55 (2H, m, $CD_2CH_2CH_2$),1.46-

1.35 (2H, m, CD_2CH_2), 1.32 (3H, s, CH_3), 1.05 (1H, dt, *J* 8, 2 Hz, CH_2=CC*H*$_A$H$_B$), 0.83 (1H, dt, *J* 8, 2 Hz, CH_2=CCH$_A$*H*$_B$), 0.00 (9H, s, $Si(CH_3)_3$); δ_C (62.5 MHz, $CDCl_3$) 140.50 (0), 110.60 (0), 100.63 (2), 65.20 (2x2), 40.00 (2), 38.54 (quintet, *J* 19.2 Hz), 24.36 (3), 23.18 (2), 14.44 (0), 12.91 (2), -2.00 (3x3); LRMS (ES+) *m/z* 257 (6%, $[M+H]^+$), 186 (100%); HRMS (ES+) *m/z* 257.1907 ($[M+H]^+$ - $C_{14}H_{25}{}^2H_2O_2Si$ requires 257.1906).



332



333

Rac-*N*1-(6,7-Dideutero-3,5-dimethyl-8-azabicyclo[3.2.1]oct-2-en-8-yl)-4-methyl-benzene-1-sulfonamide (332).

Rac-4-Methyl-*N*-(4,5-dideutero-1-methyl-6-methylene-4-trimethylsilanyl-8-aza-bicyclo[3.2.1]oct-8-yl)-benzenesulfonamide (333).

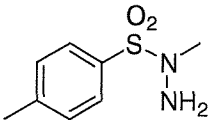
Following the typical intramolecular cyclisation procedure, $BF_3{\cdot}Et_2O$ (1.2 eq.) was added to cyclisation precursor **328** (900 mg) in DCM (40 mL) at room temperature under nitrogen. The reaction was stirred at room temperature for 18 hours. The crude material was purified column chromatography (petrol to 20% ether in petrol) to give bicycle **332** as a white solid (50 mg, 10%) and bicycle **333** as a white solid (10 mg, 1%).

Data for **332**

M.p. 150-152°C; R_f 0.40 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3206 (br), 2966 (w), 1597 (m), 1443 (w), 1329 (m), 1159 (s), 1092 (m), 1812 (m); δ_H (250 MHz, $CDCl_3$) 7.81 (2H, d, *J* 8 Hz, ArH), 7.29 (2H, d, *J* 8 Hz, ArH), 5.54 (1H, br s, NH), 2.43 (3H, s, $ArCH_3$), 2.14 (1H, d, *J* 13 Hz, CD=CC*H*$_A$H$_B$), 1.79-1.43 (5H, m, CD=CCH$_A$*H*$_B$, C*H*$_2$C*H*$_2$), 1.62 (3H, s, $CD{=}CCH_3$), 0.96 (3H, s, $NCCH_3$); δ_C (62.5 MHz, $CDCl_3$) 143.95 (0), 136.35 (0), 135.78 (0), 129.60 (2x1), 128.74 (2x1), 120.80 (t, *J* 24.7 Hz), 60.44 (0), 59.48 (t, *J* 21.8 Hz), 41.75 (2), 35.42 (2), 30.53 (2), 25.08 (3), 22.54 (3), 21.98 (3); LRMS (ES+) *m/z* 309 (100%, $[M+H]^+$), 153 (18%, $[M-CH_3ArSO_2]^+$); HRMS (ES+) *m/z* 309.1614 ($[M+H]^+$ - $C_{16}H_{21}{}^2H_2N_2O_2S$ requires 309.1606).

Data for **333**

M.p. 158-160°C; R_f 0.30 (50:50 ether:petrol); δ_H (250 MHz, $CDCl_3$) 7.83 (2H, d, *J* 8 Hz, ArH), 7.31 (2H, d, *J* 8 Hz, ArH), 5.16 (1H, br, s, HN), 5.03 (1H, br s, C=CH_AH_B), 4.80 (1H, t, *J* 2.5 Hz, C=CH_AH_B), 2.44 (3H, s, $ArCH_3$), 2.31 (1H, dt, *J* 16, 2.5 Hz, CH_2=CCH_AH_B), 2.13 (1H, d, *J* 16 Hz, CH_2=CCH_AH_B), 1.88-1.25 (4H, m, CH_2CH_2), 1.12 (3H, s, CH_3), -0.20 (9H, s, $Si(CH_3)_3$); LRMS (ES+) *m/z* 381 (7%, $[M+H]^+$), 129 (100%); HRMS (ES+) *m/z* 381.1988 ($[M+H]^+$ - $C_{16}H_{21}{}^2H_2N_2O_2S$ requires 381.1996).



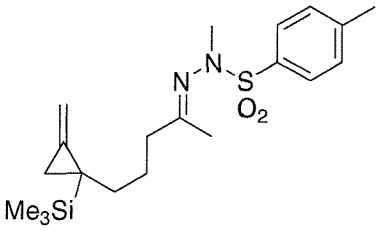
***N*1,4-Dimethyl-1-benzenesulfonohydrazide (336).**

Following a method described by Han *et al.*[100]

Tosyl chloride **334** (6.1 g, 31.9 mmol) in benzene (10 mL) was added dropwise to a stirred solution of methyl hydrazine **335** (5.0 mL, 94.1 mmol) in water (25 mL) at room temperature. The reaction was stirred for 30 minutes and the solvent removed *in vacuo* to give a white solid suspended in water. The solid was filtered and washed with cold water (3x20 mL), dissolved in DCM (30 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give hydrazine **336** as a white solid (4.5 g, 71%).

M.p. 80-82°C; δ_H (400 MHz, $CDCl_3$) 7.73 (2H, d, *J* 8 Hz, ArH), 7.38 (2H, d, *J* 8 Hz, ArH), 3.94 (2H, br s, NH_2), 2.84 (3H, s, NCH_3), 2.46 (3H, s, $ArCH_3$); δ_C (100 MHz, $CDCl_3$) 145.01 (0), 130.27 (2x1), 129.75 (0), 129.29 (2x1), 40.52 (3), 22.00 (3).

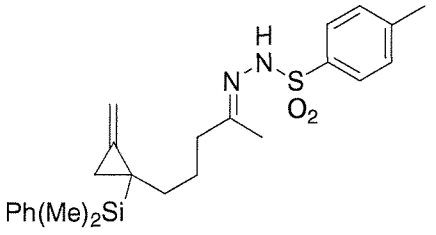
Spectroscopic data agrees with Hrubiec *et al.*[121]



***N*1,4-Dimethyl-*N*'1-(*E*)-1-methyl-4-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl] butylidene-1-benzenesulfonohydrazide (337).**

Ketone **134** (100 mg, 0.48 nmmol) and *N*-methyl tosylhydrazine **336** (94 mg, 0.48 mmol) were refluxed together in hexane (3 mL) for 1 hour. The solvent was removed *in vacuo* to give hydrazone **337** as a colourless oil (179 mg, 96%, 6:1 mixture of isomers *E*:*Z*).

R_f 0.41 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2950 (w), 2890 (w), 1632 (w), 1598 (w), 1444 (s), 1245 (m), 1162 (s), 1089 (m), 834 (s); δ_H (400 MHz, $CDCl_3$) 7.72 (2H, d, *J* 8 Hz, ArH), 7.73 (2H, d, *J* 8 Hz, ArH), 5.28 (1H, s, C=C*H*$_A$H$_B$), 5.21 (1H, s, C=CH$_A$*H*$_B$), 2.69 (3H, s, NCH_3), 2.44 (3H, s, $ArCH_3$), 2.28 (2H, t, *J* 7 Hz, CH_2CN), 2.15 (3H, s, $CNCH_3$), 1.66-1.37 (4H, m, (C*H*$_2$)$_2$CH$_2$CN), 1.05 (1H, d, *J* 7 Hz, CH$_2$=CC*H*$_A$H$_B$), 0.83 (1H, d, *J* 7 Hz, CH$_2$=CCH$_A$*H*$_B$), 0.00 (9H, s, Si(CH$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 181.39 (0), 144.47 (0), 140.25 (0), 131.64 (0), 130.03 (2x1), 129.80 (2x1), 100.88 (2), 39.72 (2), 39.52 (3), 35.58 (2), 25.41 (2), 22.20 (3), 19.40 (3), 14.41 (0), 13.06 (2), -2.00 (3x3); LRMS (ES+) *m/z* 415 (45%, $[M+Na]^+$), 393 (63%, $[M+H]^+$), 130 (100%); HRMS (ES+) *m/z* 393.2039 ($[M+H]^+$ - $C_{20}H_{33}N_2O_2SSi$ requires 393.2027).

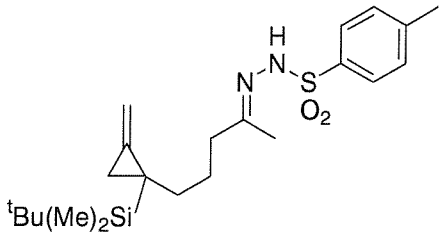


***N*'1-(*E*)-4-[1-(1,1-Dimethyl-1-phenylsilyl)-2-methylenecyclopropyl]-1-methyl-butylidene-4-methyl-1-benzenesulfonohydrazide (343).**

Ketone **347** (100 mg, 0.37 nmmol) and tosylhydrazine (68 mg, 0.37 mmol) were refluxed together in hexane (3 mL) for 1 hour. The solvent was removed *in vacuo* to give hydrazone **343** as a yellow solid (160 mg, 100%, 6:1 mixture of isomers *E*:*Z*).

M.p. 82-84°C; R_f 0.20 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3223 (br), 3064 (w), 2951 (w), 1247 (w), 1160 (s), 808 (s); δ_H (400 MHz, $CDCl_3$) 7.86 (2H, d, *J* 8 Hz, ArH), 7.54 (2H, d, *J* 8 Hz, ArH), 7.39-7.30 (5H, m, Ph), 5.35 (1H, s, C=C*H*$_A$H$_B$), 5.30 (1H, s, C=CH$_A$*H*$_B$), 2.48 (3H, s, $ArCH_3$), 2.07 (2H, t, *J* 7 Hz, CH_2CN), 1.62 (3H, s, $CNCH_3$), 1.51-1.21 (4H, m, (C*H*$_2$)$_2$CH$_2$CN), 1.15 (1H, d, *J* 8 Hz, CH$_2$=CC*H*$_A$H$_B$), 0.86 (1H, d, *J* 8 Hz, CH$_2$=CCH$_A$*H*$_B$), 0.27 (6H, s, Si(C*H*$_3$)$_2$Ph); δ_C (100 MHz, $CDCl_3$) 158.50 (0), 143.87

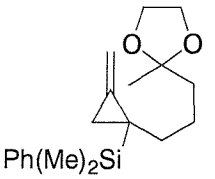
(0), 138.99 (0), 137.98 (0), 135.54 (0), 133.95 (2x1), 129.54 (1), 129.49 (1), 129.16 (1), 128.16 (2x1), 127.74 (2x1), 101.19 (2), 38.79 (2), 34.88 (2), 24.47 (2), 21.65 (3), 15.31 (3), 13.29 (0), 12.86 (2), -3.76 (3), -3.82 (3); LRMS (ES+) *m/z* 463 (11%, $[M+Na]^+$), 441 (16%, $[M+H]^+$), 294 (100%); HRMS (ES+) *m/z* 441.2036 ($[M+H]^+$ - $C_{24}H_{33}N_2O_2SSi$ requires 441.2027).



***N*'1-((*E*)-4-1-[1-(*tert*-Butyl)-1,1-dimethylsilyl]-2-methylenecyclopropyl-1-methyl-butylidene)-4-methyl-1-benzenesulfonohydrazide (344).**

Ketone **348** (100 mg, 0.40 nmmol) and tosylhydrazine (74 mg, 0.40 mmol) were refluxed together in hexane (5 mL) for 1 hour. The solvent was removed *in vacuo* to give hydrazone **344** as a white solid (166 mg, 100%, 5:1 mixture of isomers *E*:*Z*).

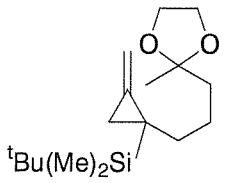
R_f 0.20 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3222 (br), 2927 (w), 2852 (w), 1456 (w), 1397 (w), 1250 (w), 1166 (s), 905 (m), 809 (m); δ_H(400 MHz, $CDCl_3$) 7.83 (2H, d, *J* 8 Hz, ArH), 7.31 (2H, d, *J* 8 Hz, ArH), 5.28 (1H, s, C=CH_AH_B), 5.17 (1H, s, C=CH_AH_B), 2.43 (3H, s, $ArCH_3$), 2.13 (2H, t, *J* 7 Hz, CH_2CN), 1.73 (3H, s, $CNCH_3$), 1.49-1.25 (4H, m, $(CH_2)_2CH_2CN$), 1.07 (1H, d, *J* 7 Hz, CH_2=CCH_AH_B), 0.93 (9H, s, $C(CH_3)_3$), 0.75 (1H, d, *J* 7 Hz, CH_2=CCH_AH_B), -0.12 (6H, s, $Si(CH_3)_2{}^tBu$); δ_C(100 MHz, $CDCl_3$) 158.54 (0), 144.24 (0), 139.94 (0), 135.87 (0), 129.93 (2x1), 128.52 (2x1), 101.33 (2), 39.40 (2), 35.92 (2), 27.80 (3x3), 24.58 (2), 22.02 (3), 18.70 (0), 15.76 (3), 14.52 (0), 13.17 (2), -5.78 (3), -6.18 (3); LRMS (ES+) *m/z* 421 (72%, $[M+H]^+$), 153 (100%); HRMS (ES+) *m/z* 421.2337 ($[M+H]^+$ - $C_{22}H_{37}N_2O_2SSi$ requires 421.2340).



Dimethyl1-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]-2-methylenecyclopropyl-phenyl silane (345).

^{n}BuLi (1.4 mL, 2.3 M, 3.32 mmol) was added to a stirred solution of dimethylphenyl-silylmethylenecyclopropane **217** (620 mg, 3.32 mmol) in THF (10 mL) at -78°C under argon. The solution was allowed to warm to room temperature over 1 hour and stirred at room temperature for 1 hour. The resulting orange solution was cooled to -78°C before addition of iodide **260** (850 mg, 3.32 mmol) and allowed to warm to room temperature over 4 hours. The reaction mixture was quenched with sat. NH_4Cl (5 mL), extracted with ether (3x15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 5% ether in petrol) to give ketal **345** as a colourless oil (750 mg, 71%).

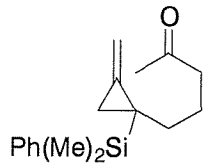
R_f 0.54 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2951 (w), 2878 (w), 1245 (m), 1108 (m), 1066 (m), 811 (m); δ_H (400 MHz, $CDCl_3$) 7.57-7.54 (2H, m, Ph), 7.36-7.35 (3H, m, Ph), 5.32 (1H, s, C=CH_AH$_B$), 5.30 (1H, s, C=CH$_A$$H_B$), 3.96-3.78 (4H, m, O(CH$_2$)$_2$O), 1.47 (2H, t, *J* 8 Hz, SiC(CH$_2$)$_2$CH_2), 1.39-1.22 (4H, m, SiC(CH_2)$_2$CH$_2$), 1.20 (3H, s, CH$_3$), 1.10 (1H, d, *J* 8 Hz, CH$_2$=CCH_AH$_B$), 0.90 (1H, d, *J* 8 Hz, CH$_2$=CCH$_A$$H_B$), 0.27 (6H, s, Si(C$H_3$)$_2$Ph); δ_C (100 MHz, $CDCl_3$) 139.56 (0), 138.62 (0), 134.38 (2x1), 129.37 (1), 128.03 (2x1), 110.39 (0), 101.42 (2), 65.11 (2), 64.98 (2), 39.76 (2), 35.99 (2), 24.17 (3), 22.92 (2), 14.06 (0), 13.01 (2), -3.80 (2x3); LRMS (CI) *m/z* 317 (3%, [M+H]$^+$), 255 (100%), 135 (92%, [Si(CH$_3$)$_2$)Ph]$^+$); HRMS (EI) *m/z* 316.1837 ([M]$^+$ - $C_{19}H_{28}O_2Si$ requires 316.1859).



***tert*-Butyl(dimethyl)1-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]-2-methylenecyclopropylsilane (346).**

^{n}BuLi (1.38 mL, 2.4 M, 3.32 mmol) was added to a stirred solution of methylenecyclopropane **1** (250 μL, 3.32 mmol) in THF (10 mL) at -60°C under argon. The solution was allowed to warm to 0°C over 40 minutes and stirred at 0°C for 40 minutes. The resulting yellow solution was cooled to -70°C and TBDMSCl (500 mg, 3.32 mmol) in THF (2 mL) added. The solution was allowed to warm to 0°C over 1 hour before cooling to -70°C and addition of ^{n}BuLi (1.38 mL, 2.4 M, 3.32 mmol) and the warming procedure repeated. The resulting orange solution was cooled to -70°C before addition of iodide **260** (850 mg, 3.32 mmol) in THF (1 mL) and allowed to warm to room temperature overnight. The reaction mixture was quenched with sat. NH_4Cl (10 mL), extracted with ether (3x15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 3% ether in petrol) to give ketal **346** as a colourless oil (350 mg, 36%).

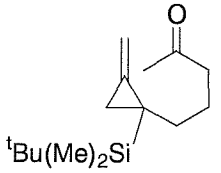
R_f 0.63 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2956 (m), 2855 (m), 1467 (w), 1249 (m), 1072 (m), 829 (m); δ_H (400 MHz, $CDCl_3$) 5.28 (1H, s, C=CH_AH$_B$), 5.21 (1H, s, C=CH$_A$$H_B$), 3.94-3.91 (4H, m, O(CH$_2$)$_2$O), 1.56-1.33 (6H, m, (CH$_2$)$_3$), 1.30 (3H, s, CH$_3$), 1.08 (1H, d, *J* 8 Hz, CH$_2$=CCH_AH$_B$), 0.97 (9H, s, C(CH$_3$)$_3$), 0.83 (1H, d, *J* 8 Hz, CH$_2$=CCH$_A$$H_B$), -0.08 (3H, s, Si(C$H_3$)CH$_3$), -0.09 (3H, s, Si(CH$_3$)C$H_3$); δ_C (100 MHz, $CDCl_3$) 140.11 (0), 110.46 (0), 101.21 (2), 65.02 (2x2), 39.87 (2), 36.58 (2), 27.84 (3x3), 24.19 (3), 22.54 (2), 18.72 (0), 13.61 (0), 12.91 (2), -5.87 (3), -6.16 (3); LRMS (CI) *m/z* 297 (2%, [M+H]$^+$), 253 (6%, [M+H-(CH$_2$)$_2$O), 73 (100%); HRMS (EI) *m/z* 296.2162 ([M]$^+$ - $C_{17}H_{32}O_2Si$ requires 296.2172).



5-[1-(1,1-Dimethyl-1-phenylsilyl)-2-methylenecyclopropyl]-2-pentanone (347).

Ketal **345** (730 mg, 2.31 mmol) and HCl (1.40 mL, 2 M, 2.77 mmol) were stirred together in acetone (18 mL) and water (2 mL) for 24 hours. The solvent was removed *in vacuo*, replaced with ether (20 mL), washed with sat. $NaHCO_3$ (2x10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 5% ether in petrol) to give ketone **347** as a colourless oil (530 mg, 84%).

R_f 0.51 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2954 (w), 2893 (w), 1721 (s), 1428 (m), 1359 (m), 1249 (m), 1161 (m), 1108 (m), 811 (s); δ_H (400 MHz, $CDCl_3$) 7.57-7.55 (2H, m, Ph), 7.36-7.32 (3H, m, Ph), 5.34 (1H, s, C=C$H_A$$H_B$), 5.30 (1H, s, C=C$H_A$$H_B$), 2.25 (2H, t, *J* 8 Hz, CH_2CO), 2.01 (3H, s, $COCH_3$), 1.53-1.30 (4H, m, (CH_2)$_2$$CH_2CO$), 1.12 (1H, d, *J* 8 Hz, CH_2=CC$H_A$$H_B$), 0.91 (1H, d, *J* 8 Hz, CH_2=CC$H_A$$H_B$), 0.28 (6H, s, Si($CH_3$)$_2$Ph); δ_C (100 MHz, $CDCl_3$) 209.11 (0), 139.25 (0), 138.34 (0), 134.32 (2x1), 129.46 (1), 128.06 (2x1), 101.63 (2), 44.14 (2), 35.29 (2), 30.01 (3), 22.70 (2), 13.74 (0), 13.09 (2), -3.82 (2x3); LRMS (CI) *m/z* 291 (22%, $[M+Na]^+$), 273 (44%, $[M+H]^+$), 135 (100%, $[Si(CH_3)_2)Ph]^+$); HRMS (EI) *m/z* 272.1591 ($[M]^+$ - $C_{17}H_{24}OSi$ requires 272.1596).

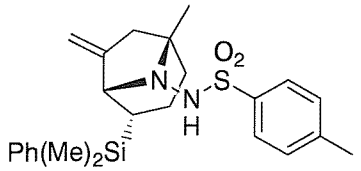


5-1-[1-(*tert*-Butyl)-1,1-dimethylsilyl]-2-methylenecyclopropyl-2-pentanone (348).

Ketal **346** (330 mg, 1.11 mmol) and HCl (670 μL, 2 M, 1.34 mmol) were stirred together in acetone (9 mL) and water (1 mL) for 4 hours. The solvent was removed *in vacuo*, replaced with ether (20 mL), washed with sat $NaHCO_3$ (2x10 mL), dried ($MgSO_4$) and

concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 5% ether in petrol) to give ketone **348** as a colourless oil (260 mg, 91%).

R_f 0.36 (20:80 ether:petrol); υ_{max} (neat)/cm^{-1} 2928 (m), 2853 (m), 1716 (m), 1465 (w), 1357 (w), 1249 (m), 1162 (w), 821 (m); δ_H (400 MHz, $CDCl_3$) 5.30 (1H, s, C=CH_AH$_B$), 5.22 (1H, s, C=CH$_A$$H_B$), 2.36 (2H, t, *J* 7 Hz, CH_2CO), 2.11 (3H, s, $COCH_3$), 1.55-1.44 (4H, m, (CH_2)$_2$$CH_2CO$), 1.09 (1H, d, *J* 7 Hz, CH_2=CCH_AH$_B$), 0.97 (9H, s, C(CH_3)$_3$), 0.83 (1H, d, *J* 7 Hz, CH_2=CCH$_A$$H_B$), -0.09 (6H, s, Si($CH_3$)$_2$^{t}Bu); δ_C (100 MHz, $CDCl_3$) 209.10 (0), 139.85 (0), 101.46 (2), 44.39 (2), 35.96 (2), 30.22 (3), 27.84 (3x3), 22.40 (2), 18.71 (0), 13.37 (0), 13.03 (2), -5.85 (3), -6.20 (3); LRMS (CI) *m/z* 253 (30%, [M+H]$^+$), 195 (36%, [M-^{t}Bu]$^+$), 121 (100%); HRMS (EI) *m/z* 252.1908 ([M]$^+$ - $C_{15}H_{28}OSi$ requires 252.1909).

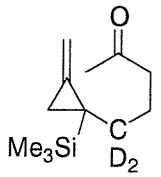


Rac-*N*-[4-(Dimethyl-phenyl-silanyl)-1-methyl-6-methylene-8-aza-bicyclo[3.2.1]oct-8-yl]-4-methyl-benzenesulfonamide (350a).

Following the typical intramolecular cyclisation procedure, BF_3·Et_2O (1.2 eq.) was added to cyclisation precursor **343** (85 mg) in DCM (5 mL) at room temperature under nitrogen. The reaction was stirred at room temperature for 18 hours. The crude material was purified by column chromatography (petrol to 40% ether in petrol) to give bicycle **350a** as a colourless oil (25 mg, 29%).

R_f 0.41 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3229 (br), 2925 (w), 2860 (w), 1427 (w), 1336 (m), 1249 (w), 1162 (s), 1092 (w), 810 (m); δ_H (400 MHz, $CDCl_3$) 7.82 (2H, d, *J* 8 Hz, ArH), 7.40-7.28 (7H, m, 5xPh, 2xArH), 5.15 (1H, br s, NH), 5.00 (1H, s, C=CH_AH$_B$), 4.76 (1H, s, C=CH$_A$$H_B$), 2.89 (1H, br s, CH_2=CCH), 2.47 (3H, s, $ArCH_3$), 2.28 (1H, d, *J* 17 Hz, CH_2=CCH_AH$_B$), 2.16 (1H, d, *J* 17 Hz, CH_2=CCH$_A$$H_B$), 1.46-1.09 (7H, m, $CH_2CH_2CCH_3$), 0.88 (1H, m, CHSi), 0.14 (3H, s, Si(CH_3)CH_3), 0.05 (3H, s,

$Si(CH_3)CH_3$); LRMS (ES+) *m/z* 441 (100%, $[M+H]^+$); HRMS (ES+) *m/z* 441.2033 ($[M+H]^+$ - $C_{24}H_{33}N_2O_2SSi$ requires 441.2027).

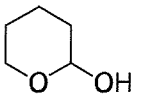


5,5-Dideutero-5-[2-methylene-1-(1,1,1-trimethylsilyl)cyclopropyl]-2-pentanone (414).

Ketal **331** (7.1 g, 27.7 mmol) and *p*-TsOH (6.3 g, 33.2 mmol) were stirred together in acetone (135 mL) and water (15 mL) for 5 hours. The solvent was removed *in vacuo*, replaced with ether (100 mL), washed with sat. $NaHCO_3$ (2x50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (hexane to 2% ether in hexane) to give ketone **414** as a colourless oil (5.5 g, 93%).

R_f 0.47 (30:70 ether:hexane); υ_{max} (neat)/cm^{-1} 2956 (w), 2892 (w), 1715 (m), 1407 (m), 1358 (w), 1245 (m), 1163 (w), 836 (s), 753 (w); δ_H (250 MHz, $CDCl_3$) 5.27 (1H, br s, $C=CH_AH_B$), 5.21 (1H, br s, $C=CH_AH_B$), 2.39 (2H, t, *J* 7 Hz, CH_2CO), 2.13 (3H, s, $COCH_3$), 1.60 (2H, br t, *J* 7 Hz, CD_2CH_2), 1.06 (1H, dt, *J* 8, 2 Hz, $CH_2=CCH_AH_B$), 0.81 (1H, dt, *J* 8, 2 Hz, $CH_2=CCH_AH_B$), 0.00 (9H, s, $Si(CH_3)_3$); δ_C (62.5 MHz, $CDCl_3$) 209.34 (0), 140.26 (0), 100.88 (2), 44.45 (2), 35.92 (quintet, *J* 19.3 Hz), 30.44 (3), 22.98 (2), 14.26 (0), 13.02 (2), -2.00 (3x3); LRMS (ES+) *m/z* 213 (100%, $[M+H]^+$); HRMS (ES+) *m/z* 213.1645 ($[M+H]^+$ - $C_{12}H_{21}{}^2H_2OSi$ requires 213.1644).

5.6 Experimental for chapter 4



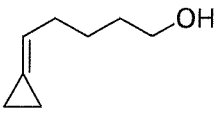
Tetrahydro-2*H*-2-pyranol (356).

Following a method described by Van Hijfte *et al.*[104]

DIBAL-H (20 mL, 1.0 M, 0.02 mol) was added dropwise to a stirred solution of tetrahydro-2*H*-2-pyranone **355** (2.0 g, 0.02 mol) in ether (70 mL) at -78°C under argon. The reaction mixture was stirred for 45 minutes, MeOH (10 mL) was added and the reaction allowed to warm to room temperature. Brine (30 mL) was added and stirred for 30 minutes before filtration through celite. The aqueous layer was extracted with EtOAc (3x25 mL), the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 40% ether in petrol) to give lactol **356** as a colourless oil (900 mg, 44%).

R_f 0.14 (50:50 ether:petrol); δ_H (300 MHz, $CDCl_3$) 4.89 (1H, br s, OCHO), 4.00 (1H, m, CH_AH_BO), 3.68 (1H, d, *J* 5 Hz, OH), 3.56 (1H, dt, *J* 11, 5.5 Hz, CH_AH_BO), 1.94-1.76 (2H, m, CH_2), 1.61-1.45 (4H, m, CH_2CH_2); δ_C (75 MHz, $CDCl_3$) 94.63 (1), 64.05 (2), 32.05 (2), 25.35 (2), 20.44 (2).

Spectroscopic data agrees with Jones *et al.*[122]



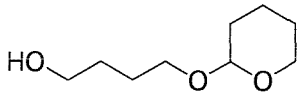
5-Cyclopropyliden-1-pentanol (357).

Following a method described by Miyashita *et al.*[106]

Alkylidenecyclopropane **371** (330 mg, 1.55 mmol) and PPTS (39 mg, 0.16 mmol) were stirred together in methanol (10 mL) at 55°C for 24 hours. The reaction mixture was allowed to cool then concentrated *in vacuo*. The crude material was purified by column

chromatography (petrol to 20% ether in petrol) to give alcohol **357** as a colourless oil (130 mg, 64%).

R_f 0.32 (60:40 ether:petrol); υ_{max} (neat)/cm^{-1} 3338 (br), 2977 (m), 2932 (s), 2860 (m), 1439 (w), 1060 (m), 1033 (m), 986 (w); δ_H (400 MHz, $CDCl_3$) 5.76 (1H, m, C=CH), 3.66 (2H, t, *J* 6 Hz, CH_2OH), 2.20 (2H, br q, *J* 7 Hz, C=CHCH_2), 1.65-1.42 (5H, m, $(CH_2)_2CH_2OH$), 1.02 (4H, s, CH=C(CH_2CH_2)); δ_C (100 MHz, $CDCl_3$) 121.58 (0), 118.06 (1), 63.06 (2), 32.50 (2), 31.66 (2), 25.60 (2), 2.52 (2), 2.00 (2); LRMS (CI) *m/z* 127 (11%, $[M+H]^+$), 109 (17%, $[M+H-H_2O]^+$), 71 (100%, $[C_4H_5+NH_4]^+$).



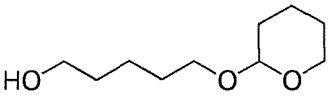
4-(Tetrahydro-2*H*-2-pyranyloxy)-1-butanol (362).

Following a method described by Dado *et al.*[105]

DHP (4.9 g, 55.5 mmol) was added dropwise to a stirred solution of 1, 4 butanediol **358** (10.0 g, 0.11 mol) and *p*-TsOH (1.1 g, 5.56 mmol) in dioxane (40 mL). The reaction mixture was stirred for 1 hour and quenched with sat. $NaHCO_3$ (20 mL), extracted with EtOAc (3x50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 50% ether in petrol) to give alcohol **362** as a colourless oil (7.0 g, 73%).

R_f 0.39 (ether); δ_H (400 MHz, $CDCl_3$) 4.61 (1H, m, OCHO), 3.91-3.77 (2H, m, OCH_AH_B, OCH_AH_B), 3.68 (2H, t, *J* 6 Hz, CH_2OH), 3.56-3.39 (2H, m, OCH_AH_B, OCH_AH_B), 1.94 (1H, br s, OH), 1.88-1.49 (10H, m, $(CH_2)_3$, $(CH_2)_2CH_2OH$); δ_C (100 MHz, $CDCl_3$) 99.20 (1), 67.94 (2), 63.17 (2), 62.77 (2), 31.15 (2), 30.57 (2), 26.99 (2), 25.91 (2), 19.98 (2).

Spectroscopic data agrees with Clasby *et al.*[123]



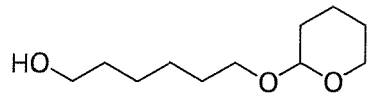
5-(Tetrahydro-2*H*-2-pyranyloxy)-1-pentanol (363).

Following a method described by Dado *et al.*[105]

DHP (4.3 g, 48.1 mmol) was added dropwise to a stirred solution of 1, 5 pentanediol **359** (10.0 g, 96.1 mmol) and *p*-TsOH (900 mg, 4.8 mmol) in dioxane (40 mL). The reaction mixture was stirred for 1 hour then quenched with sat. $NaHCO_3$ (20 mL), extracted with EtOAc (2x25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 50% ether in petrol) to give alcohol **363** as a colourless oil (5.6 g, 62%).

R_f 0.18 (70:30 ether:petrol); δ_H (400 MHz, $CDCl_3$) 4.57 (1H, m, OCHO), 3.86 (1H, m, OCH_AH_B), 3.74 (1H, dt, *J* 10, 7 Hz, CH_AH_BOTHP), 3.65 (2H, t, *J* 6.5 Hz, CH_2OH), 3.50 (1H, m, OCH_AH_B), 3.39 (1H, dt, *J* 10, 7 Hz, CH_AH_BOTHP), 1.87-1.41 (13H, m, OH, $(CH_2)_3$, $(CH_2)_3$); δ_C (100 MHz, $CDCl_3$) 99.33 (1), 67.91 (2), 63.21 (2), 62.79 (2), 32.93 (2), 31.16 (2), 29.98 (2), 25.88 (2), 22.89 (2), 20.09 (2).

Spectroscopic data agrees with Clasby *et al.*[123]



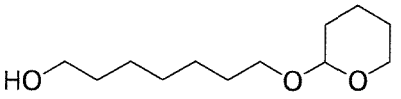
6-(Tetrahydro-2*H*-2-pyranyloxy)-1-hexanol (364).

Following a method described by Dado *et al.*[105]

DHP (3.77 g, 0.042 mol) was added dropwise to a stirred solution of 1, 6 hexanediol **360** (10.0 g, 0.085 mol) and *p*-TsOH (805 mg, 4.23 mmol) in dioxane (40 mL). The reaction mixture was stirred for 1.5 hours then quenched with sat. $NaHCO_3$ (20 mL), extracted with EtOAc (3x50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (10% ether in petrol to 50% ether in petrol) to give alcohol **364** as a colourless oil (6.0 g, 71%).

R_f 0.27 (70:30 ether:petrol); δ_H (400 MHz, $CDCl_3$) 4.57 (1H, br s with fine splitting, OCHO), 3.86 (1H, m, OCH_AH_B), 3.72 (1H, dt, *J* 10, 7 Hz, CH_AH_BOTHP), 3.63 (2H, t, *J* 7 Hz, CH_2OH), 3.51 (1H, m, OCH_AH_B), 3.38 (1H, dt, *J* 10, 7 Hz, CH_AH_BOTHP), 1.89-1.35 (15H, m, $(CH_2)_4CH_2OH$, $(CH_2)_3$); δ_C (100 MHz, $CDCl_3$) 98.92 (1), 67.66 (2), 62.96 (2), 62.41 (2), 32.80 (2), 30.87 (2), 29.77 (2), 26.22 (2), 25.64 (2), 25.59 (2), 19.80 (2).

Spectroscopic data agrees with Clasby *et al.*[123]

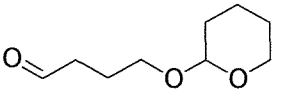


7-(Tetrahydro-2*H*-2-pyranyloxy)-1-heptanol (365).

Following a method described by Dado *et al.*[105]

DHP (1.68 g, 18.9 mmol) was added dropwise to a stirred solution of 1, 7 heptanediol **361** (5.0 g, 37.8 mmol) and *p*-TsOH (360 mg, 1.89 mmol) in dioxane (20 mL). The reaction mixture was stirred for 2 hours then quenched with sat. $NaHCO_3$ (20 mL), extracted with EtOAc (3x50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 50% ether in petrol) to give alcohol **365** as a colourless oil (3.15 g, 77%).

R_f 0.28 (70:30 ether:petrol); δ_H (400 MHz, $CDCl_3$) 4.58 (1H, m, OCHO), 3.88 (1H, m, OCH_AH_B), 3.73 (1H, dt, *J* 9, 7 Hz, CH_AH_BOTHP), 3.65 (2H, t, *J* 6.5 Hz, CH_2OH), 3.49 (1H, m, OCH_AH_B), 3.39 (1H, dt, *J* 9, 7 Hz, CH_AH_BOTHP), 1.88-1.10 (15H, m, $(CH_2)_2CH_2(CH_2)_2CH_2OH$, $(CH_2)_3$), 0.90-0.83 (2H, m, $(CH_2)_2CH_2(CH_2)_2$); δ_C (100 MHz, $CDCl_3$) 99.29 (1), 68.02 (2), 63.45 (2), 92.78 (2), 33.14 (2), 31.20 (2), 30.09 (2), 29.65 (2), 26.62 (2), 26.09 (2), 25.92 (2), 20.12 (2).



4-(Tetrahydro-2*H*-2-pyranyloxy)butanal (366).

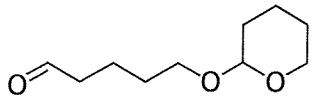
Following a method described by Swern *et al.*[92]

DMSO (2.10 mL, 40.0 mmol) in DCM (20 mL) was added to a stirred solution of oxalyl chloride (1.35 mL, 20.0 mmol) in DCM (30 mL) under nitrogen keeping the temperature below -60°C. The reaction was stirred for 5 minutes before addition of alcohol **362** (3.0 g, 17.0 mmol) in DCM (15 mL) within 5 minutes also keeping the temperature below -60°C. After 30 minutes NEt_3 (11.1 mL, 79.0 mmol) was added and the reaction allowed to warm to room temperature over 2 hours. The reaction was quenched with water (30 mL), extracted with DCM (3x30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The

crude material was purified by column chromatography (petrol to 20% ether in petrol) to give aldehyde **366** as a colourless oil (1.80 g, 62%).

R_f 0.30 (60:40 ether:petrol); δ_H (300 MHz, $CDCl_3$) 9.79 (1H, t, *J* 1.5 Hz, CHO), 4.57 (1H, t, *J* 2.5 Hz, OCHO), 3.89-3.74 (2H, m, OCH_AH_B, OCH_AH_B), 3.51 (1H, m, OCH_AH_B), 3.42 (1H, dt, *J* 10, 6 Hz, OCH_AH_B), 2.54 (2H, br t, *J* 7 Hz, CH_2CHO), 2.01-1.46 (8H, m, CH_2CH_2CHO, $(CH_2)_3$); δ_C (75 MHz, $CDCl_3$) 202.63 (1), 99.01 (1), 66.55 (2), 62.46 (2), 41.28 (2), 30.72 (2), 25.56 (2), 22.79 (2), 19.63 (2).

Spectroscopic data agrees with Clasby *et al.*[123]



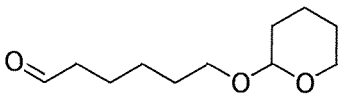
5-(Tetrahydro-2*H*-2-pyranyloxy)pentanal (367).

Following a method described by Swern *et al.*[92]

DMSO (1.30 mL, 24.5 mmol) in DCM (10 mL) was added to a stirred solution of oxalyl chloride (830 μL, 12.2 mmol) in DCM (20 mL) under nitrogen keeping the temperature below -60°C. The reaction was stirred for 2 minutes before addition of alcohol **363** (2.00 g, 10.6 mmol) in DCM (15 mL) within 5 minutes keeping the temperature below -60°C. After 25 minutes NEt_3 (6.83 mL, 48.9 mmol) was added and the reaction allowed to warm to room temperature over 2 hours. The reaction was quenched with water (30 mL), extracted with DCM (3x30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 10% ether in petrol) to give aldehyde **367** as a colourless oil (1.60 g, 81%).

R_f 0.28 (50:50 ether:petrol); δ_H (300 MHz, $CDCl_3$) 9.78 (1H, s, CHO), 4.57 (1H, m, OCHO), 3.86 (1H, m, OCH_AH_B), 3.75 (1H, dt, *J* 9.5, 6 Hz, CH_AH_BOTHP), 3.52 (1H, m, OCH_AH_B), 3.41 (1H, dt, *J* 9.5, 6 Hz, CH_AH_BOTHP), 2.49 (2H, t, *J* 7 Hz, CH_2CHO), 1.89-1.45 (10H, m, $(CH_2)_2CH_2CHO$, $(CH_2)_3$); δ_C (75 MHz, $CDCl_3$) 202.77 (1), 99.06 (1), 67.13 (2), 62.54 (2), 43.81 (2), 30.85 (2), 29.29 (2), 25.59 (2), 19.80 (2), 19.17 (2).

Spectroscopic data agrees with Clasby *et al.*[123]



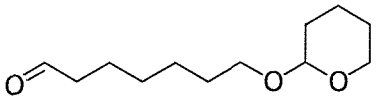
6-(Tetrahydro-2*H*-2-pyranyloxy)hexanal (368).

Following a method described by Swern *et al.*[92]

DMSO (1.21 mL, 22.7 mmol) in DCM (10 mL) was added to a stirred solution of oxalyl chloride (0.78 mL, 11.4 mmol) in DCM (20 mL) under nitrogen keeping the temperature below -60°C. The reaction was stirred for 2 minutes before addition of alcohol **364** (2.0 g, 9.90 mmol) in DCM (15 mL) within 5 minutes keeping the temperature below -60°C. After 25 minutes NEt_3 (6.36 mL, 45.5 mmol) was added and the reaction allowed to warm to 25°C over 2 hours. The reaction was quenched with water (25 mL), extracted with DCM (3x50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 20% ether in petrol) to give aldehyde **368** as a colourless oil (1.39 g, 70%).

R_f 0.49 (70:30 ether:petrol); δ_H (300 MHz, $CDCl_3$) 9.77 (1H, s, CHO), 4.56 (1H, m, OCHO), 3.85 (1H, m, OCH_AH_B), 3.72 (1H, dt, *J* 10, 6.5 Hz, CH_AH_BOTHP), 3.51 (1H, m, OCH_AH_B), 3.38 (1H, dt, *J* 10, 6.5 Hz, CH_AH_BOTHP), 2.45 (2H, t, *J* 7 Hz, CH_2CHO), 1.91-1.35 (12H, m, $(CH_2)_3CH_2CHO$, $(CH_2)_3$); δ_C (75 MHz, $CDCl_3$) 202.89 (1), 99.08 (1), 67.41 (2), 62.57 (2), 43.99 (2), 30.89 (2), 29.64 (2), 26.03 (2), 25.61 (2), 22.06 (2), 19.86 (2).

Spectroscopic data agrees with Clasby *et al.*[123]



7-(Tetrahydro-2*H*-2-pyranyloxy)heptanal (369).

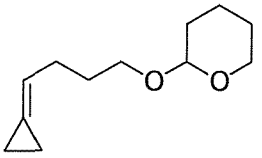
Following a method described by Swern *et al.*[92]

DMSO (1.78 mL, 34.0 mmol) in DCM (10 mL) was added to a stirred solution of oxalyl chloride (1.14 mL, 18.0 mmol) in DCM (20 mL) under nitrogen keeping the temperature below -60°C. The reaction was stirred for 5 minutes before addition of alcohol **365** (3.15 g, 15.0 mmol) in DCM (15 mL) within 5 minutes keeping the temperature below -60°C.

After 35 minutes NEt_3 (9.36 mL, 67.0 mmol) was added and the reaction allowed to warm to 25°C over 3 hours. The reaction was quenched with water (30 mL), extracted with DCM (3x50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 10% ether in petrol) to give aldehyde **369** as a colourless oil (1.80 g, 56%).

R_f 0.38 (60:40 ether:petrol); δ_H (300 MHz, $CDCl_3$) 9.77 (1H, t, *J* 2 Hz, CHO), 4.57 (1H, m, OCHO), 3.87 (1H, m, OCH_AH_B), 3.72 (1H, dt, *J* 9.5, 7 Hz, CH_AH_BOTHP), 3.52 (1H, m, OCH_AH_B), 3.40 (1H, dt, *J* 9.5, 7 Hz, CH_AH_BOTHP), 2.44 (2H, dt, *J* 2, 7 Hz, CH_2CHO), 1.91-1.31 (14H, m, $(CH_2)_4CH_2CHO$, $(CH_2)_3$); δ_C (75 MHz, $CDCl_3$) 203.04 (1), 99.06 (1), 67.62 (2), 62.56 (2), 44.00 (2), 30.92 (2), 29.69 (2), 29.14 (2), 26.19 (2), 25.63 (2), 22.17 (2), 19.87 (2).

Spectroscopic data agrees with Yamagiwa *et al.*[124]



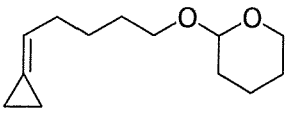
2-[(4-Cyclopropylidenbutyl)oxy]tetrahydro-2*H*-pyran (370).

Following a method described by Nemoto *et al.*[22]

Cyclopropyltriphenylphosphoniumbromide **28** (7.58 g, 19.8 mmol) and NaH (470 mg, 19.8 mmol) in THF (25 mL) were heated to 62°C under nitrogen for 5 hours. Aldehyde **366** (1.70 g, 9.88 mmol) and TDA-1 (320 mg, 0.99 mmol) in THF (5 mL) was added to the reaction mixture and heated at 62°C for 18 hours. The reaction was allowed to cool to room temperature and then quenched dropwise with water (15 mL), extracted with ether (3x25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 5% ether in petrol) to give alkylidenecyclopropane **370** as a colourless oil (1.40 g, 72%).

R_f 0.65 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2939 (w), 2867 (w), 1479 (w), 1434 (w), 1120 (w), 1033 (w), 903 (s); δ_H (400 MHz, $CDCl_3$) 5.78 (1H, m, C=CH), 4.58 (1H, t, *J* 3 Hz, OCHO), 3.86 (1H, m, OCH_AH_B), 3.77 (1H, dt, *J* 9.5, 7 Hz, CH_AH_BOTHP), 3.52 (1H, m, OCH_AH_B), 3.40 (1H, dt, *J* 9.5, 7 Hz, CH_AH_BOTHP), 2.30-2.23 (2H, m, $C=CHCH_2$),

1.89-1.48 (8H, m, CH_2CH$_2$OTHP, (CH_2)$_3$), 1.03 (4H, s, CH=C(CH_2CH_2)); δ_C (100 MHz, $CDCl_3$) 121.39 (0), 117.79 (1), 99.01 (1), 67.38 (2), 62.45 (2), 30.92 (2), 29.51 (2), 28.68 (2), 25.66 (2), 19.81 (2), 2.27 (2), 2.08 (2); LRMS (CI) *m/z* 197 (13%, $[M+H]^+$), 85 (100%, $[C_5H_9O]^+$); HRMS (EI) *m/z* 195.1390 ($[M-H]^+$ - $C_{12}H_{19}O_2$ requires 195.1385).



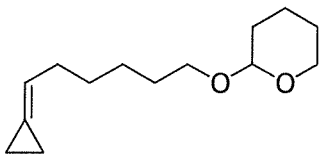
2-[(5-Cyclopropylidenpentyl)oxy]tetrahydro-2*H*-pyran (371).

Following a method described by Nemoto *et al.*[22]

Cyclopropyltriphenylphosphoniumbromide **28** (6.59 g, 17.2 mmol) and NaH (0.41 g, 17.2 mmol) in THF (20 mL) were heated to 62°C under nitrogen for 8 hours. Aldehyde **367** (1.60 g, 8.60 mmol) and TDA-1 (280 mg, 0.9 mmol) in THF (5 mL) was added to the reaction mixture and heated at 62°C for 18 hours. The reaction was allowed to cool to room temperature and then quenched dropwise with water (15 mL), extracted with ether (3x25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 10% ether in petrol) to give alkylidenecyclopropane **371** as a colourless oil (1.09 g, 58%).

R_f 0.60 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2939 (s), 2868 (m), 1440 (w), 1121 (m), 1077 (m), 1033 (s), 988 (w); δ_H (400 MHz, $CDCl_3$) 5.77 (1H, m, C=CH), 4.59 (1H, m, OCHO), 3.88 (1H, m, OCH_AH$_B$), 3.75 (1H, dt, *J* 9.5, 7 Hz, CH_AH$_B$OTHP), 3.50 (1H, m, OCH$_A$$H_B$), 3.40 (1H, dt, *J* 9.5, 7 Hz, CH$_A$$H_B$OTHP), 2.22 (2H, q, *J* 7 Hz, C=CHCH_2), 1.89-1.46 (10H, m, (CH_2)$_2$CH$_2$OTHP, (CH_2)$_3$), 1.02 (4H, s, CH=C(CH_2CH_2)); δ_C (100 MHz, $CDCl_3$) 121.40 (0), 118.23 (1), 98.97 (1), 67.67 (2), 62.43 (2), 31.77 (2), 30.94 (2), 29.52 (2), 26.16 (2), 25.69 (2), 19.82 (2), 2.32 (2), 2.00 (2); LRMS (CI) *m/z* 211 (2%, $[M+H]^+$), 85 (100%, $[C_5H_9O]^+$); HRMS (EI) *m/z* 210.1619 ($[M]^+$ - $C_{13}H_{22}O_2$ requires 210.1620).

Spectroscopic data agrees with Fournet *et al.*[19]

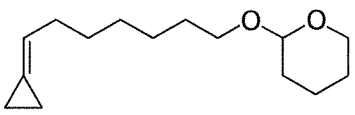


2-[(6-Cyclopropylidenhexyl)oxy]tetrahydro-2*H*-pyran (372).

Following a method described by Nemoto *et al.*[22]

Cyclopropyltriphenylphosphoniumbromide **28** (5.86 g, 15.3 mmol) and NaH (367 mg, 15.3 mmol) in THF (20 mL) were heated to 62°C under nitrogen for 8 hours. Aldehyde **368** (1.39 g, 6.95 mmol) and TDA-1 (225 mg, 0.70 mmol) in THF (5 mL) was added to the reaction mixture and heated at 62°C for 18 hours. The reaction was allowed to cool to room temperature and then quenched dropwise with water (15 mL), extracted with ether (3x30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 10% ether in petrol) to give alkylidenecyclopropane **372** as a colourless oil (1.20 g, 77%).

R_f 0.60 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2935 (s), 2856 (m), 1453 (w), 1352 (w), 1121 (s), 1077 (s), 1034 (s); δ_H (400 MHz, $CDCl_3$) 5.75 (1H, m, C=CH), 4.58 (1H, m, OCHO), 3.88 (1H, m, OCH_AH_B), 3.73 (1H, dt, *J* 10, 7 Hz, CH_AH_BOTHP), 3.52 (1H, m, OCH_AH_B), 3.40 (1H, dt, *J* 10, 7 Hz, CH_AH_BOTHP), 2.18 (2H, br q, *J* 7 Hz, $C=CHCH_2$), 1.90-1.33 (12H, m, $(CH_2)_3CH_2OTHP$, $(CH_2)_3$), 1.02 (4H, s, $CH=C(CH_2CH_2)$); δ_C (100 MHz, $CDCl_3$) 121.22 (0), 118.40 (1), 99.01 (1), 67.81 (2), 62.50 (2), 31.92 (2), 30.96 (2), 29.80 (2), 29.39 (2), 26.03 (2), 25.69 (2), 19.87 (2), 2.33 (2), 2.00 (2); LRMS (CI) *m/z* 225 (2%, $[M+H]^+$), 85 (100%, $[C_5H_9O]^+$); HRMS (EI) *m/z* 224.1782 ($[M]^+$ - $C_{14}H_{24}O_2$ requires 224.1776).

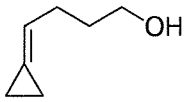


2-[(7-Cyclopropylidenheptyl)oxy]tetrahydro-2*H*-pyran (373).

Following a method described by Nemoto *et al.*[22]

Cyclopropyltriphenylphosphoniumbromide **28** (6.45 g, 16.8 mmol) and NaH (404 mg, 16.8 mmol) in THF (22 mL) were heated to 62°C under nitrogen for 8 hours. Aldehyde **369** (1.80 g, 8.41 mmol) and TDA-1 (272 mg, 0.84 mmol) in THF (5 mL) was added to the reaction mixture and heated at 62°C for 18 hours. The reaction was allowed to cool to room temperature and then quenched dropwise with water (15 mL), extracted with ether (3x25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 5% ether in petrol) to give alkylidenecyclopropane **373** as a colourless oil (750 mg, 37%).

R_f 0.60 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2930 (s), 2854 (m), 1436 (w), 1351 (w), 1120 (m), 1032 (s), 904 (s), 723 (s); δ_H (400 MHz, $CDCl_3$) 5.76 (1H, m, C=CH), 4.59 (1H, m, OCHO), 3.88 (1H, m, OCH_AH_B), 3.73 (1H, dt, *J* 9.5, 7 Hz, CH_AH_BOTHP), 3.52 (1H, m, OCH_AH_B), 3.41 (1H, dt, *J* 9.5, 7 Hz, CH_AH_BOTHP), 2.17 (2H, br q, *J* 7 Hz, $C=CHCH_2$), 1.90-1.39 (14H, m, $(CH_2)_4CH_2OTHP$, $(CH_2)_3$), 1.02 (4H, s, $CH=C(CH_2CH_2)$); δ_C (100 MHz, $CDCl_3$) 121.11 (0), 118.52 (1), 99.03 (1), 67.85 (2), 62.52 (2), 31.93 (2), 30.98 (2), 29.93 (2), 29.48 (2), 29.28 (2), 26.30 (2), 25.70 (2), 19.88 (2), 2.31 (2), 2.00 (2); LRMS (EI) *m/z* 238 (1%, $[M]^+$), 85 (100%, $[C_5H_9O]^+$); HRMS (CI) *m/z* 239.2015 ($[M+H]^+$ - $C_{15}H_{27}O_2$ requires 239.2011).



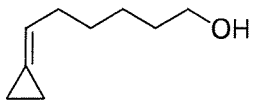
4-Cyclopropyliden-1-butanol (374).

Alkylidenecyclopropane **366** (1.30 g, 6.63 mmol) and *p*-TsOH (1.51 g, 7.96 mmol) were stirred together in acetone (45 mL) and water (5 mL) for 4 days. The solvent was removed *in vacuo*, replaced with ether (50 mL), washed with sat. $NaHCO_3$ (2x25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 15% ether in petrol) to give alcohol **374** as a colourless oil (840 mg, 65%).

R_f 0.27 (50:50 ether:petrol); δ_H (400 MHz, $CDCl_3$) 5.79 (1H, m, C=CH), 3.67 (2H, t, *J* 7 Hz, CH_2OH), 2.26 (2H, br q, *J* 7 Hz, $C=CHCH_2$), 1.74 (2H, quintet, *J* 7 Hz, CH_2CH_2OH),

1.49 (1H, br s, OH), 1.03 (4H, s, CH=C(CH_2CH_2)); δ_C (100 MHz, $CDCl_3$) 121.94 (0), 117.59 (1), 62.58 (2), 32.36 (2), 28.27 (2), 2.31 (2), 2.00 (2).

Spectroscopic data agrees with Fournet *et al.*[19]

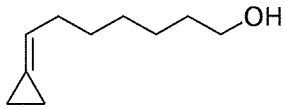


6-Cyclopropyliden-1-hexanol (375).

Following a method described by Miyashita *et al.*[106]

Alkylidenecyclopropane **372** (440 mg, 1.96 mmol) and PPTS (49 mg, 0.20 mmol) were stirred together in methanol (10 mL) at 55°C for 18 hours. The reaction mixture was allowed to cool then concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 20% ether in petrol) to give alcohol **375** as a colourless oil (210 mg, 77%).

R_f 0.23 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3320 (br), 2930 (s), 2856 (m), 1460 (w), 1051 (m), 904 (s), 728 (s); δ_H (400 MHz, $CDCl_3$) 5.76 (1H, m, C=CH), 3.65 (2H, t, *J* 7 Hz, CH_2OH), 2.19 (2H, br q, *J* 7 Hz, C=CHCH_2), 1.59 (2H, quintet, *J* 7 Hz, CH_2CH_2OH), 1.48 (2H, quintet, *J* 7 Hz, $CHCH_2CH_2$), 1.43-1.36 (2H, m, $CH_2(CH_2)_2OH$), 1.32 (1H, br s, OH), 1.02 (4H, s, CH=C(CH_2CH_2)); δ_C (100 MHz, $CDCl_3$) 121.34 (0), 118.28 (1), 63.21 (2), 32.86 (2), 31.91 (2), 29.30 (2), 25.51 (2), 2.33 (2), 2.00 (2); LRMS (CI) *m/z* 158 (5%, $[M+NH_4]^+$), 123 (25%, $[M+H-H_2O]^+$), 81 (100%, $[M-C_3H_7O]^+$); HRMS (EI) *m/z* 140.1201 ($[M]^+$ - $C_9H_{16}O$ requires 140.1201).



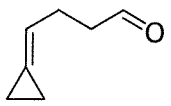
7-Cyclopropyliden-1-heptanol (376).

Following a method described by Miyashita *et al.*[106]

Alkylidenecyclopropane **373** (750 mg, 3.15 mmol) and PPTS (79 mg, 0.32 mmol) were stirred together in methanol (20 mL) at 55°C for 24 hours. The reaction mixture was

allowed to cool then concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 20% ether in petrol) to give alcohol **376** as a colourless oil (400 mg, 82%).

R_f 0.33 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3316 (br), 2926 (w), 2854 (w), 1459 (w), 1054 (w), 887 (s); δ_H (400 MHz, $CDCl_3$) 5.76 (1H, m, C=CH), 3.65 (2H, t, *J* 6.5 Hz, CH_2OH), 2.18 (2H, q, *J* 6.5 Hz, C=CHCH_2), 1.58 (2H, quintet, *J* 6.5 Hz, CH_2CH_2OH), 1.47 (2H, quintet, *J* 6.5 Hz, $CHCH_2CH_2$), 1.40-1.32 (4H, m, $(CH_2)_2(CH_2)_2OH$), 1.03 (4H, s, CH=C(CH_2CH_2)); δ_C (100 MHz, $CDCl_3$) 121.18 (0), 118.44 (1), 63.25 (2), 32.96 (2), 31.90 (2), 29.48 (2), 29.20 (2), 25.78 (2), 2.32 (2), 2.00 (2); LRMS (EI) *m/z* 154 (1%, $[M]^+$), 41 (100%); HRMS (EI) *m/z* 121.1020 ($[M-CH_3-H_2O]^+$ - C_9H_{13} requires 121.1020).

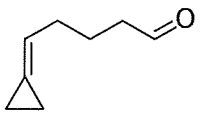


4-Cyclopropylidenbutanal (377).

Following a method described by Swern *et al.*[92]

DMSO (490 μL, 9.24 mmol) in DCM (4 mL) was added to a stirred solution of oxalyl chloride (314 μL, 4.62 mmol) in DCM (10 mL) under nitrogen keeping the temperature below -60°C. The reaction was stirred for 5 minutes before addition of alcohol **374** (450 mg, 4.02 mmol) in DCM (6 mL) within 5 minutes keeping the temperature below -60°C. After 45 minutes NEt_3 (2.58 mL, 18.92 mmol) was added and the reaction allowed to warm to 20°C over 2 hours. The reaction was quenched with water (10 mL), extracted with DCM (3x15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 5% ether in petrol) to give aldehyde **377** as a colourless oil (250 mg, 57%).

R_f 0.58 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 1733 (m), 1374 (w), 1216 (w), 904 (s); δ_H (400 MHz, $CDCl_3$) 9.79 (1H, s, CHO), 5.79 (1H, m, C=CH), 2.66-2.49 (4H, m, $(CH_2)_2CHO$), 1.04 (4H, s, CH=C(CH_2CH_2)); δ_C (100 MHz, $CDCl_3$) 202.61 (1), 122.70 (0), 115.88 (1), 43.04 (2), 24.56 (2), 2.16 (2), 2.00 (2); LRMS (CI) *m/z* 128 (4%, $[M+NH_4]^+$) 81 (100%); HRMS (EI) *m/z* 109.0655 ($[M-H]^+$ - C_7H_9O requires 109.0653).

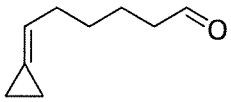


5-Cyclopropylidenpentanal (378).

Following a method described by Swern *et al.*[92]

DMSO (240 μL, 4.44 mmol) in DCM (2 mL) was added to a stirred solution of oxalyl chloride (150 μL, 2.22 mmol) in DCM (5 mL) under nitrogen keeping the temperature below -60°C. The reaction was stirred for 3 minutes before addition of alcohol **357** (200 mg, 1.59 mmol) in DCM (3 mL) within 5 minutes keeping the temperature below -60°C. After 30 minutes NEt_3 (1.26 mL, 9.05 mmol) was added and the reaction stirred at -70°C for 1 hour. The reaction was quenched with water (5 mL), extracted with DCM (3x10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 5% ether in petrol) to give aldehyde **378** as a colourless oil (110 mg, 56%).

R_f 0.48 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2980 (w), 2944 (w), 1723 (s), 905 (s); δ_H (400 MHz, $CDCl_3$) 9.77 (1H, t, *J* 2 Hz, CHO), 5.73 (1H, m, C=CH), 2.43 (2H, dt, *J* 2, 7 Hz, CH_2CHO), 2.23 (2H, q, *J* 7 Hz, C=CHCH_2), 1.81 (2H, quintet, *J* 7 Hz, CH_2CH_2CHO), 1.03 (4H, s, CH=C(CH_2CH_2)); δ_C (100 MHz, $CDCl_3$) 202.81 (1), 122.71 (0), 116.99 (1), 43.43 (2), 31.22 (2), 21.88 (2), 2.32 (2), 2.00 (2); LRMS (CI) *m/z* 142 (14%, $[M+NH_4]^+$), 125 (76%, $[M+H]^+$), 95 (100%, $[M-CHO]^+$); HRMS (EI) *m/z* 109.0653 ($[M-CH_3]^+$ - C_7H_9O requires 109.0653).



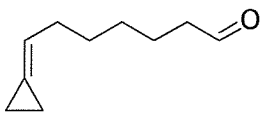
6-Cyclopropylidenhexanal (379).

Following a method described by Swern *et al.*[92]

DMSO (194 μL, 3.65 mmol) in DCM (2 mL) was added to a stirred solution of oxalyl chloride (124 μL, 1.85 mmol) in DCM (5 mL) under nitrogen keeping the temperature below -60°C. The reaction was stirred for 5 minutes before addition of alcohol **375** (180

mg, 1.29 mmol) in DCM (3 mL) within 5 minutes keeping the temperature below -60°C. After 30 minutes NEt_3 (1.02 mL, 7.30 mmol) was added and the reaction allowed to warm to 25°C over 2 hours. The reaction was quenched with water (10 mL), extracted with DCM 3x15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 7% ether in petrol) to give aldehyde **379** as a colourless oil (154 mg, 88%).

R_f 0.43 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2930 (m), 2856 (w), 1725 (m), 1084 (w), 904 (s), 727 (s); δ_H (400 MHz, $CDCl_3$) 9.78 (1H, t, *J* 2 Hz, CHO), 5.74 (1H, m, C=CH), 2.44 (2H, dt, *J* 2, 7 Hz, CH_2CHO), 2.20 (2H, br q, *J* 7 Hz, C=CHCH_2), 1.67 (2H, quintet, *J* 7 Hz, CH_2CH_2CHO), 1.50 (2H, quintet, *J* 7 Hz, C=CHCH_2CH_2), 1.03 (4H, s, CH=C(CH_2CH_2)); δ_C (100 MHz, $CDCl_3$) 202.89 (1), 121.81 (0), 117.69 (1), 43.92 (2), 31.58 (2), 26.93 (2), 21.80 (2), 2.33 (2), 2.00 (2); LRMS (CI) *m/z* 156 (3%, $[M+NH_4]^+$) 79 (100%); HRMS (EI) *m/z* 137.0971 ($[M-H]^+$ - $C_9H_{13}O$ requires 137.0966).



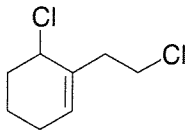
7-Cyclopropylidenheptanal (380).

Following a method described by Swern *et al.*[92]

DMSO (337 μL, 6.36 mmol) in DCM (3 mL) was added to a stirred solution of oxalyl chloride (216 μL, 3.18 mmol) in DCM (7 mL) under nitrogen keeping the temperature below -60°C. The reaction was stirred for 5 minutes before addition of alcohol **376** (350 mg, 2.27 mmol) in DCM (4 mL) within 5 minutes keeping the temperature below -60°C. After 40 minutes NEt_3 (1.81 mL, 13.0 mmol) was added and the reaction allowed to warm to 15°C over 30 minutes. The reaction was quenched with water (10 mL), extracted with DCM (3x15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 5% ether in petrol) to give aldehyde **380** as a colourless oil (310 mg, 90%).

R_f 0.61 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2978 (w), 2929 (w), 2855 (w), 1723 (m), 1461 (w), 1410 (w), 1091 (w), 903 (s); δ_H (400 MHz, $CDCl_3$) 9.77 (1H, t, *J* 1.5 Hz,

CHO), 5.74 (1H, m, C=CH), 2.42 (2H, dt, 1.5, 7 Hz, CH_2CHO), 2.17 (2H, br q, J 7 Hz, C=CHCH_2), 1.65 (2H, quintet, J 7 Hz, CH_2CH$_2$CHO), 1.47 (2H, quintet, J 7 Hz, CHCH$_2$CH_2), 1.39-1.22 (2H, m, CH_2(CH$_2$)$_2$CHO); δ_C (100 MHz, $CDCl_3$) 202.97 (1), 121.45 (0), 118.13 (1), 44.05 (2), 31.71 (2), 29.20 (2), 28.91 (2), 22.13 (2), 2.32 (2), 2.00 (2); LRMS (EI) m/z 152 (2%, $[M]^+$), 41 (100%); HRMS (EI) m/z 151.1122 ($[M-H]^+$ - $C_{10}H_{15}O$ requires 151.1123).



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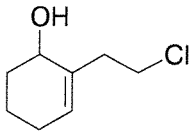


383

6-Chloro-1-(2-chloroethyl)-1-cyclohexene (382).

2-(2-Chloroethyl)-2-cyclohexen-1-ol (383).

Following the typical intramolecular cyclisation procedure, $TiCl_4$ (1.2 eq.) was added to MCP derivative **378** (40 mg) in DCM (4 mL) at -78°C under nitrogen. The reaction was stirred at -78°C for 10 minutes. The crude material was purified by column chromatography (petrol to 20% ether in petrol) to give dichloride **382** as a colourless oil (21 mg, 36%) and alcohol **383** as a colourless oil (20 mg, 39%).

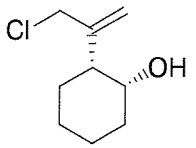
Data for **382**

R_f 0.74 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2947 (s), 2867 (m), 1437 (m), 1222 (m), 1138 (w), 964 (w), 898 (s); δ_H (400 MHz, $CDCl_3$) 5.74 (1H, br s, C=CH), 4.53 (1H, br s, CHCl), 3.66 (2H, m, CH_2Cl), 2.66 (1H, dt, J 15, 6.5 Hz, CH_AH$_B$CH$_2$Cl), 2.53 (1H, dt, J 15, 7 Hz, CH$_A$$H_BCH_2$Cl), 2.23-1.62 (6H, m, (CH$_2$)$_3$); δ_C (100 MHz, $CDCl_3$) 134.26 (0), 130.35 (1), 58.47 (1), 43.35 (2), 38.18 (2), 32.97 (2), 25.54 (2), 17.46 (2); LRMS (CI) m/z 143 (100%, $[M-Cl]^+$); HRMS (EI) m/z 178.0312 ($[M]^+$ - $C_8H_{12}{}^{35}Cl_2$ requires 178.0316).

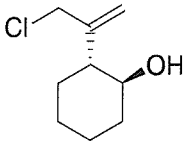
Data for **383**

R_f 0.29 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3357 (br), 2934 (m), 2860 (w), 1446 (w), 1309 (w), 905 (s); δ_H (400 MHz, $CDCl_3$) 5.68 (1H, br s, C=CH), 4.09 (1H, br s, CHOH) 3.68 (2H, m, CH_2Cl), 2.66 (1H, dt, J 14, 7 Hz, CH_AH$_B$CH$_2$Cl), 2.50 (1H, dt, J 14, 7 Hz, CH$_A$$H_BCH_2$Cl), 2.13-1.42 (7H, m, (CH$_2$)$_3$, OH); δ_C (100 MHz, $CDCl_3$) 136.14 (0), 128.82

(1), 67.30 (1), 44.09 (2), 38.12 (2), 32.76 (2), 25.82 (2), 18.35 (2); LRMS (CI) *m/z* 160 (42%, $[M+NH_4-H_2O]^+$), 143 (44%, $[M+H-H_2O]^+$), 125 (100%, $[M-Cl]^+$); HRMS (EI) *m/z* 160.0659 ($[M]^+$ - $C_8H_{13}O^{35}Cl$ requires 160.0655).



389*cis*



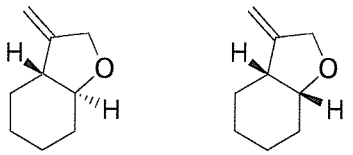
389*trans*

Rac-(1*R*,2*R*)-2-[1-(Chloromethyl)vinyl]cyclohexan-1-ol (389*cis*).

Rac-(1*S*,2*R*)-2-[1-(Chloromethyl)vinyl]cyclohexan-1-ol (389*trans*).

Following the typical intramolecular cyclisation procedure, $TiCl_4$ (1.2 eq.) was added to MCP derivative **379** (50 mg) in DCM (4 mL) at -78°C under nitrogen. The reaction was stirred at -78°C for 15 minutes. The crude material was purified by column chromatography (petrol to 15% ether in petrol) to give an inseparable mixture of alcohols **389*cis*** and **389*trans*** as a colourless oil (44 mg, 70%, 4:1 *cis*:*trans*).

R_f 0.30 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3435 (br), 2931 (s), 2857 (m), 1446 (m), 1262 (w), 1110 (w), 1056 (w), 973 (s), 907 (m); δ_H (400 MHz, $CDCl_3$) 5.34 (1H, s, C=CH_AH$_B$), 5.15 (0.2H, s, C=CH$_A$$H_B$), 5.10 (0.8H, s, C=CH$_A$$H_B$), 4.14 (1H, d, *J* 12 Hz, CH_AH$_B$Cl), 4.12-4.07 (1.8H, m, CH$_A$$H_B$Cl, C*H*OH), 3.58 (0.2H, dt, *J* 4, 10 Hz, C*H*OH), 2.35 (0.8H, br d, *J* 12.5 Hz, C*H*CHOH), 2.08 (0.2H, br t, *J* 11 Hz, C*H*CHOH), 1.95 (0.8H, br d, *J* 12.5 Hz, CH_AH$_B$CHOH), 1.85-1.24 (8.2H, m, (CH_2)$_3$CH$_A$$H_B$CHO*H*, C$H_AH_B$CHOH); δ_C (100 MHz, $CDCl_3$) data for **389*cis*** 147.43 (0), 116.51 (2), 66.67 (1), 48.13 (2), 45.10 (1), 32.95 (2), 26.32 (2), 24.60 (2), 19.93 (2), data for **389*trans*** 147.67 (0), 116.26 (2), 73.33 (1), 51.30 (1), 48.13 (2), 35.14 (2), 32.30 (2), 26.20 (2), 25.24 (2); LRMS (CI) *m/z* 192 (28%, $[M+NH_4]^+$) 139 (100%, $[M-Cl]^+$); HRMS (EI) *m/z* 156.0712 ($[M-H_2O]^+$ - $C_9H_{13}{}^{35}Cl$ requires 156.0706).



390*trans* **390*cis***

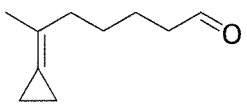
Rac-(3a*R*,7a*S*)-3-methyleneperhydrobenzo[*b*]furan (390*trans*).

Rac-(3a*R*,7a*R*)-3-methyleneperhydrobenzo[*b*]furan (390*cis*).

Following the typical intramolecular cyclisation procedure, $SnCl_4$ (1.2 eq.) was added to MCP derivative **379** (50 mg) in DCM (4 mL) at -78°C under nitrogen. The reaction was allowed to warm to room temperature over 6 hours. The crude material was purified by column chromatography (petrol to 20% ether in petrol) to give an inseparable mixture of bicycles **390*trans*** and **390*cis*** as a colourless oil (11 mg, 22%).

R_f 0.45 (50:50 ether:petrol); δ_H (400 MHz, $CDCl_3$) 4.91 (0.4H, s, C=CH_AH_B), 4.85 (1H, br s, C=CH_AH_B), 4.80 (0.6H, s, C=CH_AH_B), 4.48 (1H, m, OCH_AH_B), 4.28 (1H, m, OCH_AH_B), 3.98 (0.4H, br q, *J* 4 Hz, OCH), 3.06 (0.6H, dt, *J* 4, 11 Hz, OCH), 2.53 (0.4H, br, s, with fine splitting, CH_2=CC*H*), 2.18-1.05 (8.6H, m, CH_2=CC*H*, $(CH_2)_4$); δ_C (100 MHz, $CDCl_3$) data for **390*trans*** 151.10 (0), 101.03 (2), 83.79 (1), 70.89 (2), 49.56 (1), 31.54 (2), 26.10 (2), 25.14 (2), 24.13 (2); data for **390*cis*** 152.69 (0), 102.49 (2), 77.92 (1), 69.78 (2), 43.36 (1), 27.77 (2), 27.11 (2), 23.05 (2), 21.30 (2).

Spectroscopic data agrees with Trost *et al.*[109]



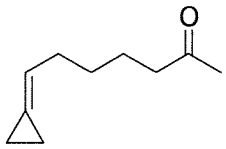
6-Cyclopropylidenheptanal (393).

Following a method described by Swern *et al.*[92]

DMSO (67 μL, 1.27 mmol) in DCM (1 mL) was added to a stirred solution of oxalyl chloride (43 μL, 0.64 mmol) in DCM (3 mL) under nitrogen keeping the temperature below -60°C. The reaction was stirred for 2 minutes before addition of alcohol **403** (70 mg, 0.46 mmol) in DCM (1 mL) within 5 minutes keeping the temperature below -60°C. After 30 minutes NEt_3 (362 μL, 2.59 mmol) was added and the reaction allowed to warm

to 10°C over 45 minutes. The reaction was quenched with water (10 mL), extracted with DCM (3x15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 5% ether in petrol) to give aldehyde **393** as a colourless oil (60 g, 87%).

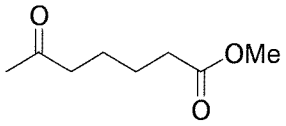
R_f 0.55 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2976 (w), 2932 (m), 2858 (w), 1722 (s), 1446 (w), 1373 (w); δ_H (300 MHz, $CDCl_3$) 9.78 (1H, s, CHO), 2.45 (2H, t, *J* 7 Hz, CH_2CHO), 2.19 (2H, t, *J* 7 Hz, $C=C(CH_3)CH_2$), 1.80 (3H, s, CH_3), 1.66-1.52 (4H, m, $(CH_2)_2CH_2CHO$), 1.08 (4H, m, $C=C(CH_2CH_2)$); δ_C (100 MHz, $CDCl_3$) 203.27 (1), 124.07 (0), 116.10 (0), 44.28 (2), 36.63 (2), 27.43 (2), 22.27 (2), 20.96 (3), 3.34 (2), 2.00 (2); LRMS (EI) *m/z* 152 (12%, $[M]^+$), 41 (100%); HRMS (CI) *m/z* 153.1278 ($[M+H]^+$ - $C_{10}H_{17}O$ requires 153.1279).



7-Cyclopropyliden-2-heptanone (394).

Ketal **401** (100 mg, 0.51 mmol) and HCl (306 μL, 2 M, 0.61 mmol) were stirred together in acetone (9 mL) and water (1 mL) for 5 hours. The solvent was removed *in vacuo*, replaced with ether (10 mL), washed with sat. $NaHCO_3$ (2x5 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give ketone **394** as a colourless oil (65 mg, 84%).

R_f 0.40 (40:60 ether:petrol); υ_{max} (neat)/cm^{-1} 2978 (w), 2929 (w), 2857 (w), 1713 (m), 1410 (w), 1358 (w), 1159 (w), 903 (s), 724 (s); δ_H (400 MHz, $CDCl_3$) 5.74 (1H, br s with fine splitting, C=CH), 2.43 (2H, t, *J* 7 Hz, CH_2CO), 2.20 (2H, br q, *J* 7 Hz, $C=CHCH_2$), 2.14 (3H, s, $COCH_3$), 1.61 (2H, quintet, *J* 7 Hz, CH_2CH_2CO), 1.46 (2H, quintet, *J* 7 Hz, $CHCH_2CH_2$), 1.02 (4H, s, $CH=C(CH_2CH_2)$); δ_C (100 MHz, $CDCl_3$) 209.34 (0), 121.61 (0), 117.92 (1), 43.82 (2), 31.68 (2), 30.00 (3), 29.01 (2), 23.63 (2), 2.33 (2), 2.00 (2); LRMS (CI) *m/z* 170 (6%, $[M+NH_4]^+$), 153 (11%, $[M+H]^+$), 43 (100%, $[COCH_3]^+$); HRMS (EI) *m/z* 152.1205 ($[M]^+$ - $C_{10}H_{16}O$ requires 152.1201).



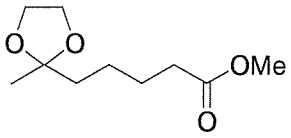
Methyl 6-oxoheptanoate (395).

Following a method described by Ito *et al.*[110]

2-Methyl cyclohexanone **396** (10.0 g, 89.2 mmol), $FeCl_3$ (1.0 g) and MeOH (50 mL) were stirred in toluene (250 mL) at 70°C under O_2 for 72 hours. The reaction was allowed to cool then the solvent removed *in vacuo*. Ether (200 mL) was added and the organic layer washed with water (3x100 mL). The organic layer was dried ($MgSO_4$), concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 25% ether in petrol) to give ketoester **395** as a yellow oil (7.0 g, 50%).

R_f 0.30 (60:40 ether:petrol); δ_H (400 MHz, $CDCl_3$) 3.66 (3H, s, OCH_3), 2.45 (2H, t, *J* 6.5 Hz, CH_2CO_2), 2.33 (2H, t, *J* 7 Hz, $COCH_2$), 2.14 (3H, s, CH_3CO), 1.65-1.56 (4H, m, $(CH_2)_2CH_2CO_2$); δ_C (100 MHz, $CDCl_3$) 208.88 (0), 174.23 (0), 51.92 (3), 43.65 (2), 34.20 (2), 30.27 (3), 24.78 (2), 23.58 (2).

Spectroscopic data agrees with Ito *et al.*[110]

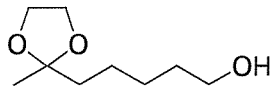


Methyl 5-(2-methyl-1,3-dioxolan-2-yl)pentanoate (398).

Following a method described by Tsunoda *et al.*[111]

TMSOTf (172 uL, 0.95 mmol) was added to a stirred solution of ketoester **395** (1.5 g, 9.49 mmol) and bis(trimethylsilyloxy)ethane (3.92 g, 18.9 mmol) in DCM (20 mL) at -78°C under nitrogen. The reaction was allowed to warm to room temperature over 18 hours and then quenched with sat. $NaHCO_3$ (10 mL), extracted with DCM (3x20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 15% ether in petrol) to give ketal **398** as a yellow oil (920 mg, 48%).

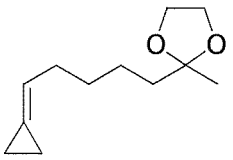
R_f 0.49 (70:30 ether:petrol); δ_H (400 MHz, $CDCl_3$) 3.97-3.92 (4H, m, $O(CH_2)_2O$), 3.67 (3H, s, OCH_3), 2.32 (2H, t, *J* 7.5 Hz, CH_2CO_2), 1.71-1.59 (4H, m, CH_2CH_2), 1.52-1.39 (2H, m, CH_2), 1.31 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 174.18 (0), 110.03 (0), 64.73 (2x2), 51.36 (3), 38.91 (2), 34.17 (2), 25.24 (2), 23.86 (3), 23.76 (2).
Spectroscopic data agrees with Oppolzer *et al.*[125]



5-(2-Methyl-1,3-dioxolan-2-yl)-1-pentanol (399).

Ketal **398** (900 mg, 4.46 mmol) in THF (5 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (338 mg, 8.91 mmol) in THF (10 mL) at 0°C under nitrogen. The reaction mixture was stirred for 2 hours at 0°C then ether (15 mL) added. The reaction was quenched by dropwise addition of NaOH (4 mL, 2 M), extracted with ether (3x25 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give alcohol **399** as a yellow oil (770 mg, 99%).

R_f 0.46 (ether); δ_H (400 MHz, $CDCl_3$) 3.96-3.88 (4H, m, $O(CH_2)_2O$), 3.64 (2H, t, *J* 6.5 Hz, CH_2OH), 1.69-1.53 (4H, m, CH_2CH_2), 1.48-1.34 (4H, m, CH_2CH_2), 1.31 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 110.50 (0), 65.00 (2x2), 63.28 (2), 39.54 (2), 33.11 (2), 26.35 (2), 24.25 (3), 24.11 (2).
Spectroscopic data agrees with Cavallaro *et al.*[126]

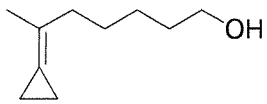


2-(5-Cyclopropylidenpentyl)-2-methyl-1,3-dioxolane (401).

DIBAL-H (4.31 mL, 1.0M, 4.31 mmol) was added dropwise over 1 hour *via* syringe pump to a stirred solution of ester **398** (290 mg, 1.44 mmol) in DCM (15 mL) at -90°C under nitrogen. The reaction was stirred at -90°C for 30 minutes then MeOH (4 mL) added. Brine (10 mL) was added and the reaction allowed to warm to room temperature.

The reaction mixture was filtered, extracted (DCM 3x15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give aldehyde **397** crude as a colourless oil (230 mg). Cyclopropyltriphenylphosphoniumbromide **28** (1.28 g, 3.34 mmol) and NaH (80 mg, 3.34 mmol) in THF (10 mL) were heated to 62°C under nitrogen for 8 hours. Aldehyde **397** (230 mg, 1.34 mmol) and TDA-1 (43 mg, 0.13 mmol) in THF (3 mL) was added to the reaction mixture and heated at 62°C for 18 hours. The reaction was allowed to cool to room temperature and then quenched dropwise (water 5 mL), extracted (ether 3x10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 5% ether in petrol) to give ketal **401** as a colourless oil (110 mg, 39%).

R_f 0.52 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 2939 (w), 2869 (w), 1458 (w), 1377 (w), 1219 (w), 1069 (w), 903 (s); δ_H (300 MHz, $CDCl_3$) 5.75 (1H, br s with fine splitting, C=CH), 3.97-3.87 (4H, m, $O(CH_2)_2O$), 2.23-2.15 (2H, m, $C=CHCH_2$), 1.69-1.59 (2H, m, CH_2CCH_3), 1.50-1.36 (4H, m, $CHCH_2(CH_2)_2$), 1.31 (3H, s, CH_3), 1.01 (4H, s, $CH=C(CH_2CH_2)$); δ_C (100 MHz, $CDCl_3$) 121.25 (0), 118.29 (1), 110.33 (0), 64.76 (2x2), 39.24 (2), 31.93 (2), 29.76 (2), 23.92 (3), 23.86 (2), 2.32 (2), 1.96 (2); LRMS (CI) *m/z* 197 (8%, $[M+H]^+$), 181 (9%, $[M-CH_3]^+$), 87 (100%, $[C_4H_7O_2]^+$); HRMS (EI) *m/z* 196.1468 ($[M]^+$ - $C_{12}H_{20}O_2$ requires 196.1463).

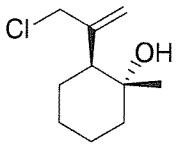


6-Cyclopropyliden-1-heptanol (403).

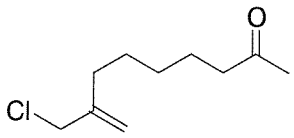
Alcohol **399** (730 mg, 4.20 mmol) and HCl (2.5 mL, 2 M, 5.03 mmol) were stirred together in acetone (18 mL) and water (2 mL) at room temperature for 24 hours. The reaction mixture was concentrated *in vacuo*, replaced with ether (20 mL), washed with sat. $NaHCO_3$ (2x10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give alcohol **404** as a colourless oil (400 mg, 3.08 mmol). Cyclopropyltriphenylphosphonium bromide **28** (4.72 g, 12.3 mmol) and NaH (295 mg, 12.3 mmol) in THF (20 mL) were heated to 62°C under nitrogen for 5 hours. Alcohol **404** (400 mg, 3.08 mmol) and TDA-1 (100 mg, 0.31 mmol) in THF (3 mL) was added and the reaction stirred at 62°C for 18 hours. The

reaction was quenched by dropwise addition of water (10 mL), extracted with ether (3x25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (petrol to 25% ether in petrol) to give alcohol **403** as a colourless oil (370 mg, 46%).

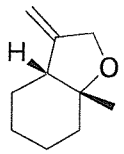
R_f 0.27 (50:50 ether:petrol); υ_{max} (neat)/cm^{-1} 3315 (br), 2973 (w), 2931 (m), 2857 (w), 1053 (w), 992 (w), 904 (s); δ_H (300 MHz, $CDCl_3$) 3.64 (2H, t, *J* 7 Hz, CH_2OH), 2.17 (2H, t, *J* 7.5 Hz, $C=C(CH_3)CH_2$), 1.80 (3H, s, CH_3), 1.64-1.48 (4H, m, CCH_2CH_2, CH_2CH_2OH), 1.46 (1H, br s, OH), 1.38-1.31 (2H, m, $CH_2(CH_2)_2OH$), 1.06-0.92 (4H, m, $C=C(CH_2CH_2)$); δ_C (100 MHz, $CDCl_3$) 124.65 (0), 115.69 (0), 63.55 (2), 36.99 (2), 33.22 (2), 27.82 (2), 26.02 (2), 21.04 (3), 3.34 (2), 2.00 (2); LRMS (EI) *m/z* 154 (3%, $[M]^+$), 41 (100%); HRMS (EI) *m/z* 154.1357 ($[M]^+$ - $C_{10}H_{18}O$ requires 154.1358).



405a



407



406a

Rac-(1*R*,2*S*)-2-[1-(Chloromethyl)vinyl]-1-methylcyclohexan-1-ol (405a).

8-(Chloromethyl)-8-nonen-2-one (407).

Rac-(3a*R*,7a*R*)-7a-Methyl-3-methyleneperhydrobenzo[*b*]furan (406a).

Following the typical intramolecular cyclisation procedure, $TiCl_4$ (1.2 eq.) was added to MCP derivative **394** (30 mg) in DCM (3 mL) at -78°C under nitrogen. The reaction was stirred at -78°C for 4 hours. The crude material was purified by column chromatography (petrol to 10% ether in petrol) to give an inseparable mixture of chloride **405a** and chloroalkenol **407** as a colourless oil (17 mg, 46%, 4:1, **405a**:**407**) and bicycle **406a** as a colourless oil (9 mg, 30%).

Data for **405a** and **407**

R_f 0.36 (40:60 ether:petrol); υ_{max} (neat)/cm^{-1} 3486 (br), 2931 (m), 2859 (w), 1445 (w), 1373 (w), 903 (s), 724 (s); δ_H (400 MHz, $CDCl_3$) 5.34 (0.8H, s, $C=CH_AH_B$), 5.20 (0.8H, s, $C=CH_AH_B$), 5.13 (0.2H, s, $C=CH_AH_B$), 4.96 (0.2H, s, $C=CH_AH_B$), 4.13 (1.6H, s, CH_2Cl), 4.04 (0.4H, s, CH_2Cl), 2.44 (0.4H, t, *J* 7.5 Hz, CH_2CO), 2.22-2.08 (1.8H, m,

C*H*C=CH_2, CH_2C=CH_2, COCH_3), 1.51-1.23 (7.6H, m, (CH_2)$_4$, (CH_2)$_3$CH_2CO), 1.16 (2.4H, s, CH_3); δ_C (100 MHz, $CDCl_3$) data for **405a** 147.70 (0), 116.97 (2), 70.86 (0), 51.01 (1), 49.87 (2), 40.61 (2), 30.06 (3), 29.19 (2), 26.59 (2), 22.03 (2); LRMS (CI) *m/z* 153 (67%, $[M-Cl]^+$), 137 (100%, M-HCl-CH_3).

Spectroscopic data for **405a** agrees with Peron.[80]

Data for **406a**

R_f 0.34 (40:60 ether:petrol); υ_{max} (neat)/cm^{-1} 2932 (s), 2861 (m), 1445 (m), 1374 (w), 1125 (m), 903 (s), 727 (s); δ_H (400 MHz, $CDCl_3$) 5.37 (1H, s, C=C$H_A$$H_B$), 4.97 (1H, s, C=C$H_A$$H_B$), 4.41 (1H, d, *J* 11.5 Hz, OC$H_A$$H_B$), 4.18 (1H, d, *J* 11.5 Hz, OC$H_A$$H_B$), 2.34 (1H, dd, *J* 3, 12.5 Hz, C*H*C=CH_2), 1.83-1.23 (8H, m, (CH_2)$_4$), 1.12 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 147.94 (0), 116.55 (2), 73.98 (0), 51.44 (1), 50.59 (2), 43.60 (2), 30.14 (2), 26.58 (2), 24.51 (2), 21.53 (3); LRMS (CI) *m/z* 153 (34%, $[M+H]^+$), 137 (100%, M-CH_3); HRMS (EI) *m/z* 152.1203 ($[M]^+$ - $C_{10}H_{16}O$ requires 152.1201).

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Appendix

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EPSRC National Crystallography Service

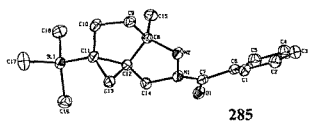

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Table 1. Crystal data and structure refinement.

Identification code	**00sot123**	
Empirical formula	$C_{18}H_{26}N_2OSi$	
Formula weight	314.50	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*Cc*	
Unit cell dimensions	a = 6.3132(13) Å	α = 90°
	b = 36.675(7) Å	β = 105.57(3)°
	c = 7.8489(16) Å	γ = 90°
Volume	1750.6(6) Å^3	
Z	4	
Density (calculated)	1.193 Mg / m^3	
Absorption coefficient	0.138 mm^{-1}	
F(000)	680	
Crystal	Plate; colourless	
Crystal size	0.30 × 0.25 × 0.06 mm^3	
θ range for data collection	2.91 – 27.47°	
Index ranges	$-7 \le h \le 7, -47 \le k \le 47, -10 \le l \le 10$	
Reflections collected	6359	
Independent reflections	3114 [R_{int} = 0.0469]	
Completeness to θ = 27.47°	89.4 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9918 and 0.9597	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3114 / 2 / 204	
Goodness-of-fit on F^2	1.022	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0387, *wR2* = 0.0948	
R indices (all data)	*R1* = 0.0433, *wR2* = 0.0978	
Absolute structure parameter	–0.03(12)	
Extinction coefficient	0.013(2)	
Largest diff. peak and hole	0.377 and –0.415 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. **A51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) **A46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Further information: http://www.soton.ac.uk/~xservice/strat.htm
Special details:

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	10827(4)	1925(1)	12378(3)	28(1)	1
C2	11132(4)	2239(1)	13399(3)	34(1)	1
C3	12925(5)	2462(1)	13499(3)	38(1)	1
C4	14451(4)	2365(1)	12611(4)	38(1)	1
C5	14173(4)	2052(1)	11601(3)	32(1)	1
C6	12351(4)	1832(1)	11462(3)	23(1)	1
C7	12228(4)	1485(1)	10421(3)	23(1)	1
C8	7376(4)	1452(1)	7252(3)	23(1)	1
C9	4918(4)	1477(1)	6366(3)	27(1)	1
C10	4595(4)	1174(1)	4942(3)	29(1)	1
C11	6280(4)	868(1)	5709(3)	25(1)	1
C12	7854(4)	1047(1)	7289(3)	21(1)	1
C13	6172(4)	781(1)	7582(3)	25(1)	1
C14	10200(4)	1021(1)	8375(3)	25(1)	1
C15	8636(4)	1660(1)	6146(3)	29(1)	1
C16	9170(5)	218(1)	5512(4)	38(1)	1
C17	4517(5)	281(1)	2995(4)	45(1)	1
C18	8177(5)	786(1)	2584(3)	35(1)	1
N1	10273(3)	1338(1)	9599(3)	23(1)	1
N2	8264(3)	1554(1)	9129(2)	24(1)	1
O1	13942(3)	1327(1)	10364(2)	29(1)	1
Si1	7037(1)	534(1)	4197(1)	26(1)	1

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

C1–C2	1.385(3)
C1–C6	1.389(3)
C2–C3	1.382(4)
C3–C4	1.378(4)
C4–C5	1.379(4)
C5–C6	1.385(3)
C6–C7	1.502(3)
C7–O1	1.239(3)
C7–N1	1.343(3)
C8–N2	1.476(3)
C8–C12	1.514(3)
C8–C9	1.524(3)
C8–C15	1.529(3)
C9–C10	1.549(3)
C10–C11	1.554(3)
C11–C12	1.516(3)
C11–C13	1.523(3)
C11–Si1	1.855(2)
C12–C14	1.501(3)
C12–C13	1.503(3)
C14–N1	1.503(3)
C16–Si1	1.863(3)
C17–Si1	1.863(3)
C18–Si1	1.862(3)
N1–N2	1.455(3)

C2–C1–C6	119.7(2)
C3–C2–C1	120.6(2)
C4–C3–C2	119.5(2)
C3–C4–C5	120.4(2)
C4–C5–C6	120.4(2)
C5–C6–C1	119.4(2)
C5–C6–C7	117.2(2)
C1–C6–C7	123.2(2)
O1–C7–N1	119.60(19)
O1–C7–C6	119.9(2)
N1–C7–C6	120.5(2)
N2–C8–C12	102.02(18)
N2–C8–C9	120.50(18)
C12–C8–C9	103.90(19)
N2–C8–C15	108.98(19)
C12–C8–C15	111.63(17)
C9–C8–C15	109.40(19)
C8–C9–C10	101.97(18)
C9–C10–C11	107.18(19)
C12–C11–C13	59.30(14)
C12–C11–C10	103.42(18)
C13–C11–C10	108.68(19)
C12–C11–Si1	125.84(17)
C13–C11–Si1	124.53(16)
C10–C11–Si1	119.83(16)
C14–C12–C13	120.04(19)
C14–C12–C8	103.62(18)
C13–C12–C8	119.58(18)
C14–C12–C11	140.05(19)
C13–C12–C11	60.59(15)
C8–C12–C11	109.12(19)
C12–C13–C11	60.11(15)
C12–C14–N1	99.72(17)
C7–N1–N2	122.07(17)
C7–N1–C14	118.99(18)
N2–N1–C14	112.56(17)
N1–N2–C8	100.79(16)
C11–Si1–C18	108.61(12)
C11–Si1–C17	108.67(12)
C18–Si1–C17	109.65(14)
C11–Si1–C16	109.13(11)
C18–Si1–C16	109.38(13)
C17–Si1–C16	111.36(14)

Symmetry transformations used to generate equivalent atoms:

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

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	35(1)	29(1)	20(1)	−1(1)	6(1)	−2(1)
C2	42(2)	33(1)	26(1)	−2(1)	10(1)	4(1)
C3	51(2)	27(1)	31(1)	−5(1)	3(1)	1(1)
C4	35(2)	30(1)	44(2)	1(1)	5(1)	−8(1)
C5	30(2)	31(1)	35(1)	1(1)	8(1)	−3(1)
C6	26(1)	24(1)	18(1)	2(1)	3(1)	3(1)
C7	25(1)	25(1)	17(1)	4(1)	5(1)	4(1)
C8	25(1)	23(1)	21(1)	1(1)	7(1)	1(1)
C9	26(1)	29(1)	25(1)	1(1)	3(1)	4(1)
C10	24(1)	36(1)	22(1)	−2(1)	−1(1)	3(1)
C11	23(1)	30(1)	20(1)	−1(1)	0(1)	−2(1)
C12	23(1)	22(1)	20(1)	−1(1)	8(1)	0(1)
C13	27(1)	26(1)	23(1)	0(1)	8(1)	−1(1)
C14	27(1)	23(1)	24(1)	−3(1)	6(1)	2(1)
C15	32(1)	28(1)	30(1)	4(1)	12(1)	0(1)
C16	46(2)	35(1)	33(1)	1(1)	10(1)	9(1)
C17	41(2)	45(2)	49(2)	−18(1)	12(1)	−9(1)
C18	35(2)	42(1)	30(1)	5(1)	11(1)	4(1)
N1	20(1)	24(1)	24(1)	−2(1)	3(1)	4(1)
N2	23(1)	26(1)	22(1)	−3(1)	5(1)	6(1)
O1	24(1)	36(1)	25(1)	−3(1)	4(1)	4(1)
Si1	29(1)	27(1)	21(1)	−2(1)	5(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.*
H1	9582	1774	12304	34	1
H2	10099	2301	14036	40	1
H3	13104	2680	14175	46	1
H4	15701	2515	12695	45	1
H5	15236	1987	10998	38	1
H9A	4512	1719	5824	33	1
H9B	4045	1427	7217	33	1
H10A	4853	1273	3842	34	1
H10B	3077	1077	4667	34	1
H13A	4916	880	7967	30	1
H13B	6697	539	8074	30	1
H14A	11243	1051	7643	30	1
H14B	10498	787	9028	30	1
H15A	8240	1919	6107	44	1
H15B	8254	1561	4941	44	1
H15C	10220	1633	6679	44	1
H16A	10449	359	6166	57	1
H16B	9620	47	4714	57	1
H16C	8565	82	6347	57	1
H17A	3917	150	3847	68	1
H17B	4890	107	2173	68	1
H17C	3419	454	2333	68	1
H18A	7032	943	1848	53	1
H18B	8682	612	1831	53	1
H18C	9417	937	3225	53	1
H2A	7725	1703	9784	28	1

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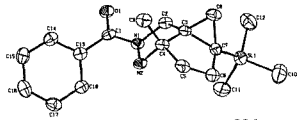

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Table 1. Crystal data and structure refinement.

Identification code	**00sot134**	
Empirical formula	$C_{18}H_{26}N_2OSi$	
Formula weight	314.50	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 21.2704(8) Å	α = 90°
	b = 7.5887(2) Å	β = 102.2340(10)°
	c = 11.2915(3) Å	γ = 90°
Volume	1781.22(9) Å^3	
Z	4	
Density (calculated)	1.173 Mg / m^3	
Absorption coefficient	0.136 mm^{-1}	
F(000)	680	
Crystal	Colourless plate	
Crystal size	0.25 × 0.20 × 0.08 mm^3	
θ range for data collection	2.94 – 25.09°	
Index ranges	$-25 \le h \le 25$, $-9 \le k \le 8$, $-13 \le l \le 13$	
Reflections collected	10582	
Independent reflections	3150 [R_{int} = 0.0729]	
Completeness to θ = 25.09°	99.5 %	
Max. and min. transmission	0.9899 and 0.9668	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3150 / 0 / 229	
Goodness-of-fit on F^2	0.951	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0493, $wR2$ = 0.1034	
R indices (all data)	$R1$ = 0.0894, $wR2$ = 0.1151	
Extinction coefficient	0.0029(13)	
Largest diff. peak and hole	0.305 and –0.269 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:

Intermolecular H-bonds (Table 6) > infinite 1D chains parallel to the c-axis

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
Si1	1071(1)	5846(1)	2951(1)	36(1)	1
O1	2906(1)	6193(2)	–478(1)	33(1)	1
N1	2845(1)	6000(2)	1476(1)	27(1)	1
N2	3182(1)	5686(2)	2709(1)	28(1)	1
C1	3171(1)	6393(3)	604(2)	27(1)	1
C2	2220(1)	5082(3)	1177(2)	31(1)	1
C3	2223(1)	4077(3)	2327(2)	27(1)	1
C4	2919(1)	3961(3)	2995(2)	29(1)	1
C5	2901(1)	3790(3)	4333(2)	33(1)	1
C6	2255(1)	4540(3)	4480(2)	34(1)	1
C7	1800(1)	4435(3)	3233(2)	30(1)	1
C8	1780(1)	2663(3)	2569(2)	35(1)	1
C9	3291(1)	2501(3)	2545(2)	38(1)	1
C10	657(1)	5456(4)	4221(2)	60(1)	1
C11	1301(1)	8201(3)	2914(2)	46(1)	1
C12	510(1)	5262(4)	1506(2)	53(1)	1
C13	3825(1)	7157(3)	942(2)	27(1)	1
C14	4261(1)	6787(3)	218(2)	34(1)	1
C15	4853(1)	7599(3)	418(2)	38(1)	1
C16	5017(1)	8826(3)	1338(2)	39(1)	1
C17	4586(1)	9200(3)	2063(2)	39(1)	1
C18	3997(1)	8377(3)	1874(2)	31(1)	1

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

Si1–C7	1.855(2)
Si1–C11	1.856(2)
Si1–C10	1.858(2)
Si1–C12	1.860(2)
O1–C1	1.241(2)
N1–C1	1.353(2)
N1–N2	1.445(2)
N1–C2	1.474(2)
N2–C4	1.486(3)
N2–H2N	0.89(2)
C1–C13	1.480(3)
C2–C3	1.505(3)
C2–H2A	0.9900
C2–H2B	0.9900
C3–C8	1.492(3)
C3–C4	1.514(3)
C3–C7	1.524(3)
C4–C9	1.511(3)
C4–C5	1.525(3)
C5–C6	1.529(3)
C5–H5A	0.9900
C5–H5B	0.9900
C6–C7	1.533(3)

C6–H6A	0.9900
C6–H6B	0.9900
C7–C8	1.536(3)
C8–H8A	0.9900
C8–H8B	0.9900
C9–H9A	0.9800
C9–H9B	0.9800
C9–H9C	0.9800
C10–H10A	0.9800
C10–H10B	0.9800
C10–H10C	0.9800
C11–H11A	0.9800
C11–H11B	0.9800
C11–H11C	0.9800
C12–H12A	0.9800
C12–H12B	0.9800
C12–H12C	0.9800
C13–C14	1.389(3)
C13–C18	1.392(3)
C14–C15	1.376(3)
C14–H14	0.9500
C15–C16	1.384(3)
C15–H15	0.9500
C16–C17	1.383(3)
C16–H16	0.9500
C17–C18	1.374(3)
C17–H17	0.9500
C18–H18	0.9500

C7–Si1–C11	110.19(11)
C7–Si1–C10	106.94(12)
C11–Si1–C10	109.97(13)
C7–Si1–C12	111.75(11)
C11–Si1–C12	109.43(12)
C10–Si1–C12	108.52(13)
C1–N1–N2	120.75(17)
C1–N1–C2	120.88(15)
N2–N1–C2	112.48(14)
N1–N2–C4	102.77(14)
N1–N2–H2N	106.1(12)
C4–N2–H2N	107.3(13)
O1–C1–N1	119.61(19)
O1–C1–C13	120.48(17)
N1–C1–C13	119.81(16)
N1–C2–C3	101.74(15)
N1–C2–H2A	111.4
C3–C2–H2A	111.4
N1–C2–H2B	111.4
C3–C2–H2B	111.4
H2A–C2–H2B	109.3
C8–C3–C2	129.46(17)
C8–C3–C4	117.15(17)
C2–C3–C4	106.49(17)

C8–C3–C7	61.23(13)
C2–C3–C7	126.45(18)
C4–C3–C7	109.27(15)
N2–C4–C9	108.91(17)
N2–C4–C3	102.40(16)
C9–C4–C3	113.67(16)
N2–C4–C5	112.29(16)
C9–C4–C5	113.30(18)
C3–C4–C5	105.79(17)
C4–C5–C6	106.70(17)
C4–C5–H5A	110.4
C6–C5–H5A	110.4
C4–C5–H5B	110.4
C6–C5–H5B	110.4
H5A–C5–H5B	108.6
C5–C6–C7	106.75(15)
C5–C6–H6A	110.4
C7–C6–H6A	110.4
C5–C6–H6B	110.4
C7–C6–H6B	110.4
H6A–C6–H6B	108.6
C3–C7–C6	106.14(17)
C3–C7–C8	58.36(12)
C6–C7–C8	116.18(18)
C3–C7–Si1	125.39(14)
C6–C7–Si1	118.00(14)
C8–C7–Si1	119.07(15)
C3–C8–C7	60.41(13)
C3–C8–H8A	117.7
C7–C8–H8A	117.7
C3–C8–H8B	117.7
C7–C8–H8B	117.7
H8A–C8–H8B	114.9
C4–C9–H9A	109.5
C4–C9–H9B	109.5
H9A–C9–H9B	109.5
C4–C9–H9C	109.5
H9A–C9–H9C	109.5
H9B–C9–H9C	109.5
Si1–C10–H10A	109.5
Si1–C10–H10B	109.5
H10A–C10–H10B	109.5
Si1–C10–H10C	109.5
H10A–C10–H10C	109.5
H10B–C10–H10C	109.5
Si1–C11–H11A	109.5
Si1–C11–H11B	109.5
H11A–C11–H11B	109.5
Si1–C11–H11C	109.5
H11A–C11–H11C	109.5
H11B–C11–H11C	109.5
Si1–C12–H12A	109.5

Si1–C12–H12B	109.5
H12A–C12–H12B	109.5
Si1–C12–H12C	109.5
H12A–C12–H12C	109.5
H12B–C12–H12C	109.5
C14–C13–C18	118.5(2)
C14–C13–C1	118.53(18)
C18–C13–C1	122.56(18)
C15–C14–C13	121.0(2)
C15–C14–H14	119.5
C13–C14–H14	119.5
C14–C15–C16	120.1(2)
C14–C15–H15	120.0
C16–C15–H15	120.0
C17–C16–C15	119.3(2)
C17–C16–H16	120.4
C15–C16–H16	120.4
C18–C17–C16	120.8(2)
C18–C17–H17	119.6
C16–C17–H17	119.6
C17–C18–C13	120.3(2)
C17–C18–H18	119.8
C13–C18–H18	119.8

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

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si1	37(1)	36(1)	38(1)	−2(1)	11(1)	−5(1)
O1	39(1)	34(1)	23(1)	1(1)	4(1)	0(1)
N1	30(1)	30(1)	18(1)	0(1)	2(1)	−1(1)
N2	38(1)	29(1)	17(1)	−1(1)	4(1)	−1(1)
C1	38(1)	20(1)	23(1)	0(1)	7(1)	6(1)
C2	36(2)	30(1)	26(1)	−4(1)	4(1)	0(1)
C3	34(1)	23(1)	24(1)	−3(1)	5(1)	−4(1)
C4	36(1)	23(1)	25(1)	−2(1)	3(1)	−2(1)
C5	43(2)	27(1)	28(1)	5(1)	5(1)	−4(1)
C6	47(2)	30(2)	27(1)	3(1)	9(1)	−7(1)
C7	35(1)	27(1)	30(1)	−2(1)	11(1)	−9(1)
C8	45(2)	25(1)	34(1)	−2(1)	5(1)	−5(1)
C9	38(2)	33(2)	38(1)	−2(1)	1(1)	3(1)
C10	58(2)	66(2)	64(2)	3(1)	30(2)	1(2)
C11	50(2)	36(2)	49(2)	−3(1)	4(1)	−1(1)
C12	40(2)	52(2)	62(2)	−3(1)	2(1)	−5(2)
C13	35(1)	22(1)	23(1)	6(1)	4(1)	3(1)
C14	44(2)	32(1)	28(1)	5(1)	10(1)	3(1)
C15	39(2)	39(2)	38(1)	9(1)	14(1)	4(1)
C16	33(2)	35(2)	47(1)	16(1)	4(1)	−2(1)
C17	47(2)	30(2)	38(1)	0(1)	6(1)	−6(1)
C18	38(2)	27(1)	30(1)	2(1)	9(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}	$S.o.f.$
H2N	3041(9)	6500(30)	3159(16)	24(6)	1
H2A	2197	4278	479	23(5)	1
H2B	1858	5926	998	41(6)	1
H5A	3260	4459	4837	51(7)	1
H5B	2940	2539	4585	30(6)	1
H6A	2306	5778	4761	28(5)	1
H6B	2083	3844	5081	40(6)	1
H8A	1972	1627	3043	36(6)	1
H8B	1395	2403	1927	44(6)	1
H9A	3736	2506	3008	32(6)	1
H9B	3287	2685	1684	56(7)	1
H9C	3092	1364	2650	75(9)	1
H10A	267	6181	4105	110(12)	1
H10B	945	5772	4989	73(9)	1
H10C	540	4209	4238	66(9)	1
H11A	913	8933	2767	97(11)	1
H11B	1534	8386	2263	69(8)	1
H11C	1578	8526	3692	66(8)	1
H12A	131	6030	1389	85(10)	1
H12B	375	4031	1537	91(10)	1
H12C	727	5418	830	68(8)	1
H14	4149	5962	−425	36(6)	1
H15	5149	7316	−76	45(6)	1
H16	5422	9404	1470	47(7)	1
H17	4697	10036	2700	40(6)	1
H18	3706	8643	2382	33(6)	1

Table 6. Hydrogen bonds [Å and °].

D–H···A	$d(D$–H)	d(H···A)	$d(D\cdots A)$	$\angle(DHA)$
N2–H2N···O1^{i}	0.89(2)	2.39(2)	3.264(2)	167.5(16)

Symmetry transformations used to generate equivalent atoms:
(i) x,−y+3/2,z+1/2

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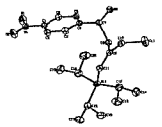

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Table 1. Crystal data and structure refinement.

Identification code	**01sot090**	
Empirical formula	$C_{20}H_{32}ClNO_3Si$	
Formula weight	398.01	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P*–1	
Unit cell dimensions	a = 9.793(2) Å	α = 104.98(3)°
	b = 10.982(2) Å	β = 94.20(3)°
	c = 21.013(4) Å	γ = 94.27(3)°
Volume	2167.1(8) Å^3	
Z	4	
Density (calculated)	1.220 Mg / m^3	
Absorption coefficient	0.250 mm^{-1}	
F(000)	856	
Crystal	Plate; yellow	
Crystal size	0.20 × 0.16 × 0.05 mm^3	
θ range for data collection	2.91 – 27.45°	
Index ranges	$-12 \le h \le 12$, $-13 \le k \le 14$, $-27 \le l \le 27$	
Reflections collected	30399	
Independent reflections	9651 [R_{int} = 0.0937]	
Completeness to θ = 27.45°	97.3 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9876 and 0.9517	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9651 / 324 / 505	
Goodness-of-fit on F^2	0.996	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0640, *wR2* = 0.1520	
R indices (all data)	*R1* = 0.1122, *wR2* = 0.1763	
Largest diff. peak and hole	0.618 and –0.507 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:
Two molecules in asymmetric unit, -only one shown in figure.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	2903(2)	4001(2)	4235(1)	20(1)	1
C2	3433(2)	2873(2)	4255(1)	23(1)	1
C3	4835(2)	2813(2)	4214(1)	23(1)	1
C4	5682(2)	3841(2)	4153(1)	19(1)	1
C5	5120(2)	4956(2)	4139(1)	20(1)	1
C6	3717(2)	5042(2)	4181(1)	20(1)	1
C7	7208(2)	3707(2)	4101(1)	20(1)	1
C8	7460(2)	2874(2)	3413(1)	21(1)	1
C9	6864(2)	3292(2)	2828(1)	20(1)	1
C10	7433(2)	4563(2)	2766(1)	25(1)	1
C11	5858(2)	2581(2)	2396(1)	21(1)	1
C12	5918(3)	3554(2)	1112(1)	29(1)	1
C13	5098(3)	3631(3)	468(1)	42(1)	1
C14	7282(3)	2979(3)	955(1)	40(1)	1
C15	4057(3)	1115(2)	1212(1)	27(1)	1
C16	5138(3)	206(3)	976(1)	36(1)	1
C17	2902(3)	1019(3)	657(1)	37(1)	1
C18	3399(3)	3773(2)	1925(1)	32(1)	1
C19	2556(3)	3195(3)	2382(2)	49(1)	1
C20	3879(3)	5173(3)	2257(2)	46(1)	1
N1	1424(2)	4079(2)	4278(1)	22(1)	1
O1	951(2)	5079(2)	4278(1)	36(1)	1
O2	708(2)	3144(2)	4313(1)	34(1)	1
O3	7929(2)	4920(2)	4259(1)	23(1)	0.882(4)
O3'	7820(14)	3328(13)	4594(6)	22(4)	0.118(4)
Si1	4841(1)	2785(1)	1641(1)	22(1)	1
Cl1	9257(1)	4602(1)	2685(1)	42(1)	1
C21	–2113(2)	8994(2)	4230(1)	20(1)	1
C22	–1321(2)	10015(2)	4137(1)	22(1)	1
C23	82(2)	9940(2)	4105(1)	21(1)	1
C24	676(2)	8862(2)	4168(1)	19(1)	1
C25	–159(2)	7852(2)	4262(1)	24(1)	1
C26	–1560(2)	7902(2)	4293(1)	23(1)	1
C27	2198(2)	8741(2)	4126(1)	20(1)	1
C28	2462(2)	7889(2)	3444(1)	21(1)	1
C29	1959(2)	8339(2)	2855(1)	20(1)	1
C30	2741(2)	9493(2)	2756(1)	28(1)	1
C31	859(2)	7748(2)	2448(1)	23(1)	1
C32	–24(3)	9621(2)	1602(1)	29(1)	1
C33	–583(3)	10533(3)	2187(2)	43(1)	1
C34	–729(3)	9742(3)	945(1)	42(1)	1
C35	–1844(3)	7130(3)	1671(1)	33(1)	1
C36	–2524(3)	7694(3)	2302(2)	52(1)	1
C37	–2831(3)	7023(3)	1054(2)	58(1)	1
C38	801(3)	6959(3)	952(1)	35(1)	1
C39	2314(3)	7469(3)	983(2)	49(1)	1
C40	718(3)	5545(3)	927(2)	47(1)	1
N2	–3597(2)	9064(2)	4280(1)	23(1)	1
O4	–4303(2)	8132(2)	4326(1)	33(1)	1
O5	–4076(2)	10056(2)	4278(1)	39(1)	1
O6	2913(2)	9949(2)	4269(1)	22(1)	0.838(4)

O6'	2818(11)	8347(10)	4624(4)	24(3)	0.162(4)
Si2	−65(1)	7921(1)	1663(1)	25(1)	1
Cl2	4523(1)	9250(1)	2651(1)	46(1)	1

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

C1–C6	1.379(3)
C1–C2	1.387(3)
C1–N1	1.465(3)
C2–C3	1.387(3)
C2–H2	0.9500
C3–C4	1.389(3)
C3–H3	0.9500
C4–C5	1.386(3)
C4–C7	1.521(3)
C5–C6	1.392(3)
C5–H5	0.9500
C6–H6	0.9500
C7–O3'	1.333(12)
C7–O3	1.407(3)
C7–C8	1.547(3)
C7–H7	1.0000
C8–C9	1.513(3)
C8–H8A	0.9900
C8–H8B	0.9900
C9–C11	1.339(3)
C9–C10	1.505(3)
C10–Cl1	1.805(2)
C10–H10A	0.9900
C10–H10B	0.9900
C11–Si1	1.882(2)
C11–H11	0.9500
C12–C14	1.541(4)
C12–C13	1.547(3)
C12–Si1	1.893(3)
C12–H12	1.0000
C13–H13A	0.9800
C13–H13B	0.9800
C13–H13C	0.9800
C14–H14A	0.9800
C14–H14B	0.9800
C14–H14C	0.9800
C15–C16	1.529(3)
C15–C17	1.541(3)
C15–Si1	1.898(3)
C15–H15	1.0000
C16–H16A	0.9800
C16–H16B	0.9800
C16–H16C	0.9800
C17–H17A	0.9800
C17–H17B	0.9800
C17–H17C	0.9800
C18–C19	1.535(4)
C18–C20	1.537(4)
C18–Si1	1.883(3)
C18–H18	1.0000
C19–H19A	0.9800
C19–H19B	0.9800
C19–H19C	0.9800
C20–H20A	0.9800
C20–H20B	0.9800
C20–H20C	0.9800
N1–O2	1.221(3)
N1–O1	1.224(2)
O3–H3A	0.8400
O3'–H3'	0.8400
C21–C22	1.380(3)
C21–C26	1.385(3)
C21–N2	1.471(3)
C22–C23	1.388(3)
C22–H22	0.9500
C23–C24	1.390(3)
C23–H23	0.9500
C24–C25	1.393(3)
C24–C27	1.514(3)
C25–C26	1.382(3)
C25–H25	0.9500
C26–H26	0.9500
C27–O6'	1.353(9)
C27–O6	1.402(3)
C27–C28	1.546(3)
C27–H27	1.0000
C28–C29	1.511(3)
C28–H28A	0.9900
C28–H28B	0.9900
C29–C31	1.336(3)
C29–C30	1.500(3)
C30–Cl2	1.806(2)
C30–H30A	0.9900
C30–H30B	0.9900
C31–Si2	1.883(2)
C31–H31	0.9500
C32–C33	1.535(4)
C32–C34	1.540(3)
C32–Si2	1.902(3)
C32–H32	1.0000
C33–H33A	0.9800
C33–H33B	0.9800
C33–H33C	0.9800
C34–H34A	0.9800
C34–H34B	0.9800
C34–H34C	0.9800
C35–C37	1.532(4)
C35–C36	1.534(4)
C35–Si2	1.891(3)

C35–H35	1.0000
C36–H36A	0.9800
C36–H36B	0.9800
C36–H36C	0.9800
C37–H37A	0.9800
C37–H37B	0.9800
C37–H37C	0.9800
C38–C39	1.535(4)
C38–C40	1.536(4)
C38–Si2	1.890(3)
C38–H38	1.0000
C39–H39A	0.9800
C39–H39B	0.9800
C39–H39C	0.9800
C40–H40A	0.9800
C40–H40B	0.9800
C40–H40C	0.9800
N2–O5	1.218(2)
N2–O4	1.221(3)
O6–H6A	0.8400
O6'–H6'	0.8400

C6–C1–C2	122.4(2)
C6–C1–N1	119.34(19)
C2–C1–N1	118.3(2)
C1–C2–C3	117.6(2)
C1–C2–H2	121.2
C3–C2–H2	121.2
C2–C3–C4	121.5(2)
C2–C3–H3	119.2
C4–C3–H3	119.2
C5–C4–C3	119.4(2)
C5–C4–C7	121.8(2)
C3–C4–C7	118.85(19)
C4–C5–C6	120.3(2)
C4–C5–H5	119.9
C6–C5–H5	119.9
C1–C6–C5	118.9(2)
C1–C6–H6	120.6
C5–C6–H6	120.6
O3'–C7–O3	96.6(6)
O3'–C7–C4	113.7(7)
O3–C7–C4	109.14(17)
O3'–C7–C8	112.5(6)
O3–C7–C8	113.1(2)
C4–C7–C8	111.06(19)
O3'–C7–H7	11.3
O3–C7–H7	107.8
C4–C7–H7	107.8
C8–C7–H7	107.8
C9–C8–C7	115.47(18)
C9–C8–H8A	108.4
C7–C8–H8A	108.4

C9–C8–H8B	108.4
C7–C8–H8B	108.4
H8A–C8–H8B	107.5
C11–C9–C10	121.6(2)
C11–C9–C8	121.7(2)
C10–C9–C8	116.6(2)
C9–C10–C11	111.04(16)
C9–C10–H10A	109.4
C11–C10–H10A	109.4
C9–C10–H10B	109.4
C11–C10–H10B	109.4
H10A–C10–H10B	108.0
C9–C11–Si1	134.20(19)
C9–C11–H11	112.9
Si1–C11–H11	112.9
C14–C12–C13	110.3(2)
C14–C12–Si1	114.96(18)
C13–C12–Si1	112.75(19)
C14–C12–H12	106.0
C13–C12–H12	106.0
Si1–C12–H12	106.0
C12–C13–H13A	109.5
C12–C13–H13B	109.5
H13A–C13–H13B	109.5
C12–C13–H13C	109.5
H13A–C13–H13C	109.5
H13B–C13–H13C	109.5
C12–C14–H14A	109.5
C12–C14–H14B	109.5
H14A–C14–H14B	109.5
C12–C14–H14C	109.5
H14A–C14–H14C	109.5
H14B–C14–H14C	109.5
C16–C15–C17	111.3(2)
C16–C15–Si1	112.80(18)
C17–C15–Si1	114.97(17)
C16–C15–H15	105.6
C17–C15–H15	105.6
Si1–C15–H15	105.6
C15–C16–H16A	109.5
C15–C16–H16B	109.5
H16A–C16–H16B	109.5
C15–C16–H16C	109.5
H16A–C16–H16C	109.5
H16B–C16–H16C	109.5
C15–C17–H17A	109.5
C15–C17–H17B	109.5
H17A–C17–H17B	109.5
C15–C17–H17C	109.5
H17A–C17–H17C	109.5
H17B–C17–H17C	109.5
C19–C18–C20	110.7(2)

C19–C18–Si1	110.56(18)
C20–C18–Si1	113.72(19)
C19–C18–H18	107.2
C20–C18–H18	107.2
Si1–C18–H18	107.2
C18–C19–H19A	109.5
C18–C19–H19B	109.5
H19A–C19–H19B	109.5
C18–C19–H19C	109.5
H19A–C19–H19C	109.5
H19B–C19–H19C	109.5
C18–C20–H20A	109.5
C18–C20–H20B	109.5
H20A–C20–H20B	109.5
C18–C20–H20C	109.5
H20A–C20–H20C	109.5
H20B–C20–H20C	109.5
O2–N1–O1	122.4(2)
O2–N1–C1	118.84(18)
O1–N1–C1	118.8(2)
C7–O3–H3A	109.5
C7–O3'–H3'	109.5
C11–Si1–C18	108.02(11)
C11–Si1–C12	113.13(11)
C18–Si1–C12	109.91(12)
C11–Si1–C15	103.05(11)
C18–Si1–C15	107.88(12)
C12–Si1–C15	114.42(12)
C22–C21–C26	122.4(2)
C22–C21–N2	119.43(19)
C26–C21–N2	118.1(2)
C21–C22–C23	118.6(2)
C21–C22–H22	120.7
C23–C22–H22	120.7
C22–C23–C24	120.6(2)
C22–C23–H23	119.7
C24–C23–H23	119.7
C23–C24–C25	119.0(2)
C23–C24–C27	122.0(2)
C25–C24–C27	118.95(19)
C26–C25–C24	121.4(2)
C26–C25–H25	119.3
C24–C25–H25	119.3
C25–C26–C21	117.9(2)
C25–C26–H26	121.0
C21–C26–H26	121.0
O6'–C27–O6	98.1(5)
O6'–C27–C24	114.1(5)
O6–C27–C24	109.61(18)
O6'–C27–C28	111.0(4)
O6–C27–C28	112.7(2)
C24–C27–C28	110.77(19)

O6'–C27–H27	10.0
O6–C27–H27	107.9
C24–C27–H27	107.9
C28–C27–H27	107.9
C29–C28–C27	115.21(18)
C29–C28–H28A	108.5
C27–C28–H28A	108.5
C29–C28–H28B	108.5
C27–C28–H28B	108.5
H28A–C28–H28B	107.5
C31–C29–C30	121.7(2)
C31–C29–C28	121.6(2)
C30–C29–C28	116.7(2)
C29–C30–Cl2	111.52(16)
C29–C30–H30A	109.3
Cl2–C30–H30A	109.3
C29–C30–H30B	109.3
Cl2–C30–H30B	109.3
H30A–C30–H30B	108.0
C29–C31–Si2	136.0(2)
C29–C31–H31	112.0
Si2–C31–H31	112.0
C33–C32–C34	110.0(2)
C33–C32–Si2	114.12(19)
C34–C32–Si2	113.42(18)
C33–C32–H32	106.2
C34–C32–H32	106.2
Si2–C32–H32	106.2
C32–C33–H33A	109.5
C32–C33–H33B	109.5
H33A–C33–H33B	109.5
C32–C33–H33C	109.5
H33A–C33–H33C	109.5
H33B–C33–H33C	109.5
C32–C34–H34A	109.5
C32–C34–H34B	109.5
H34A–C34–H34B	109.5
C32–C34–H34C	109.5
H34A–C34–H34C	109.5
H34B–C34–H34C	109.5
C37–C35–C36	110.7(3)
C37–C35–Si2	115.2(2)
C36–C35–Si2	113.27(19)
C37–C35–H35	105.6
C36–C35–H35	105.6
Si2–C35–H35	105.6
C35–C36–H36A	109.5
C35–C36–H36B	109.5
H36A–C36–H36B	109.5
C35–C36–H36C	109.5
H36A–C36–H36C	109.5
H36B–C36–H36C	109.5

C35–C37–H37A	109.5
C35–C37–H37B	109.5
H37A–C37–H37B	109.5
C35–C37–H37C	109.5
H37A–C37–H37C	109.5
H37B–C37–H37C	109.5
C39–C38–C40	109.3(2)
C39–C38–Si2	111.04(19)
C40–C38–Si2	112.8(2)
C39–C38–H38	107.8
C40–C38–H38	107.8
Si2–C38–H38	107.8
C38–C39–H39A	109.5
C38–C39–H39B	109.5
H39A–C39–H39B	109.5
C38–C39–H39C	109.5
H39A–C39–H39C	109.5
H39B–C39–H39C	109.5
C38–C40–H40A	109.5
C38–C40–H40B	109.5
H40A–C40–H40B	109.5
C38–C40–H40C	109.5
H40A–C40–H40C	109.5
H40B–C40–H40C	109.5
O5–N2–O4	122.4(2)
O5–N2–C21	118.7(2)
O4–N2–C21	118.95(18)
C27–O6–H6A	109.5
C27–O6'–H6'	109.5
C31–Si2–C38	106.98(11)
C31–Si2–C35	102.52(12)
C38–Si2–C35	109.41(13)
C31–Si2–C32	113.99(11)
C38–Si2–C32	108.87(12)
C35–Si2–C32	114.67(12)

Symmetry transformations used to generate equivalent atoms:

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

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	20(1)	21(1)	17(1)	4(1)	1(1)	3(1)
C2	24(1)	21(1)	22(1)	6(1)	2(1)	2(1)
C3	24(1)	21(1)	23(1)	7(1)	2(1)	4(1)
C4	20(1)	21(1)	15(1)	4(1)	0(1)	2(1)
C5	21(1)	20(1)	18(1)	5(1)	1(1)	1(1)
C6	22(1)	20(1)	19(1)	5(1)	1(1)	4(1)
C7	21(1)	20(1)	19(1)	5(1)	0(1)	2(1)
C8	22(1)	22(1)	19(1)	5(1)	1(1)	2(1)
C9	21(1)	21(1)	18(1)	4(1)	3(1)	5(1)
C10	25(1)	26(1)	23(1)	7(1)	1(1)	2(1)
C11	22(1)	22(1)	20(1)	5(1)	2(1)	3(1)
C12	33(1)	30(1)	25(1)	8(1)	1(1)	1(1)
C13	56(2)	52(2)	21(2)	14(1)	−4(1)	2(2)
C14	37(2)	53(2)	32(2)	15(1)	7(1)	−2(2)
C15	28(1)	29(1)	23(1)	6(1)	2(1)	2(1)
C16	42(2)	33(2)	26(2)	−2(1)	−1(1)	2(1)
C17	37(2)	42(2)	25(2)	3(1)	−7(1)	−2(1)
C18	31(1)	34(1)	29(1)	5(1)	1(1)	7(1)
C19	34(2)	63(2)	44(2)	−3(2)	12(1)	11(2)
C20	48(2)	40(2)	43(2)	−4(1)	−2(2)	22(2)
N1	22(1)	24(1)	20(1)	6(1)	1(1)	3(1)
O1	26(1)	31(1)	54(1)	18(1)	5(1)	11(1)
O2	25(1)	32(1)	45(1)	13(1)	2(1)	−2(1)
O3	19(1)	24(1)	24(1)	3(1)	0(1)	2(1)
O3'	28(8)	30(8)	6(7)	5(6)	−10(6)	4(7)
Si1	25(1)	26(1)	14(1)	4(1)	−1(1)	5(1)
Cl1	29(1)	49(1)	53(1)	23(1)	3(1)	−5(1)
C21	20(1)	21(1)	18(1)	4(1)	1(1)	2(1)
C22	24(1)	22(1)	22(1)	6(1)	1(1)	4(1)
C23	22(1)	21(1)	21(1)	6(1)	2(1)	0(1)
C24	20(1)	20(1)	16(1)	3(1)	1(1)	2(1)
C25	25(1)	23(1)	24(1)	6(1)	2(1)	4(1)
C26	24(1)	22(1)	22(1)	7(1)	3(1)	1(1)
C27	20(1)	21(1)	19(1)	5(1)	0(1)	2(1)
C28	21(1)	22(1)	19(1)	5(1)	2(1)	3(1)
C29	20(1)	21(1)	19(1)	4(1)	3(1)	5(1)
C30	27(1)	29(1)	26(1)	8(1)	2(1)	2(1)
C31	23(1)	24(1)	21(1)	6(1)	3(1)	3(1)
C32	29(1)	32(1)	28(1)	9(1)	1(1)	4(1)
C33	50(2)	33(2)	47(2)	10(1)	7(2)	12(1)
C34	41(2)	50(2)	38(2)	24(1)	−7(1)	6(2)
C35	32(1)	33(1)	33(1)	9(1)	−3(1)	2(1)
C36	31(2)	50(2)	74(2)	13(2)	13(2)	0(2)
C37	48(2)	56(2)	68(2)	30(2)	−34(2)	−15(2)
C38	39(1)	37(1)	30(1)	9(1)	2(1)	6(1)
C39	57(2)	53(2)	38(2)	7(2)	21(2)	11(2)
C40	54(2)	38(2)	40(2)	−6(1)	−1(2)	13(2)
N2	22(1)	24(1)	21(1)	6(1)	1(1)	3(1)
O4	23(1)	35(1)	45(1)	15(1)	4(1)	−1(1)
O5	25(1)	33(1)	64(1)	20(1)	6(1)	12(1)
O6	18(1)	24(1)	23(1)	3(1)	2(1)	1(1)
O6'	31(6)	40(6)	2(5)	8(4)	0(4)	12(5)
Si2	27(1)	29(1)	17(1)	5(1)	−2(1)	4(1)
Cl2	28(1)	62(1)	56(1)	29(1)	8(1)	−2(1)

"Its taken me all this time to find out what I need"

Gavin Rossdale (1967-)