UNIVERSITY OF SOUTHAMPTON

Lewis acid mediated reactions of methylenecyclopropanes and cyclopropenes.

Sarah Margaret Barker

Doctor of Philosophy

FACULTY OF ENGINEERING, SCIENCE & MATHEMATICS
SCHOOL OF CHEMISTRY

November 2004

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF ENGINEERING, SCIENCE & MATHEMATICS

SCHOOL OF CHEMISTRY

Doctor of Philosophy

LEWIS ACID MEDIATED REACTIONS OF METHYLENECYCLOPROPANES AND CYCLOPROPENES.

Sarah Margaret Barker

This thesis is concerned with inter- and intramolecular cyclisation reactions of cyclopropenylsilanes mediated by Lewis acids towards the formation of novel heterocyclic compounds and intermolecular methylenecyclopropane reactions with *N*-acyliminium species in order to form novel bicyclic compounds.

Chapter 1 contains background information on synthetic chemistry involving methylenecyclopropanes. Information on allyl- and vinylsilane chemistry involving Lewis acids is also described.

Chapter 2 discusses synthesis and cyclisation studies of a range of cyclopropenylsilanes with different Lewis acids. Some novel and unexpected cyclisations have been discovered but on the whole these cyclopropenylsilanes were found to be too unreactive for cyclisation to occur in the anticipated manner.

Chapter 3 presents the synthesis and cyclisation studies of methylenecyclopropanes with *N*-acyliminium ions. Various Lewis acids and reaction conditions were studied for optimisation of the cyclisation reactions.

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 2001 and August 2004. 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 supervision and all his encouragement and support during the course of this research. I am really happy that I chose to work in Jeremy's group. I also thank Ian Andrews for his supervision during my time at GlaxoSmithKline.

I would like to thank EPSRC and GSK for funding the project. Thanks to Dr. John Langley, Julie Wright (Southampton) and Alec Simpson (GSK) for their advice with mass spectrometry and Dr. Mark Light and Dr. Simon Coles for the fantastic crystal structures. Acknowledgements also to Joan Street, Neil Wells (Southampton) and Dr. Ben Bardsley (GSK) for NMR experiments. Thank you to Mike Caplin M.B.E., Clive Godden and Melanie Hill who have provided a great glassblowing service. Thanks to Karl Hagon, Ann Caplin and Phil Breach for always supplying the chemicals and equipment I needed. Thank you to Jill Queen and Sue Pipe for their caring advice. Thank you to our tea ladies, especially Pat – I couldn't do without my tea in the morning!

Many thanks go to Jeremy, Allison, Dad and Jon for proofreading and to Andrea, Oscar and Richy for sorting out computer problems.

I thank all of the members of the Kilburn Empire who I have worked with for making my PhD years enjoyable and entertaining. Special thanks to Suvi for being a great friend and to Anawat for maintaining a happy atmosphere in the lab and for being lovely. Thank you Allison and Anaïs for making my third year much less stressful than I expected and for being great friends outside the lab. Thanks to Jon S for being crazy and keeping us all amused. Thanks to 'ever-smiling' Nittaya, Andrea, Lee, Oscar, Sandra, Pla, Suad and Srini for making the lab an enjoyable place to work.

I would like to thank Mum, Dad, Deb and Steve and the rest of my family for their love and support over the years, and special thanks to Dad for giving me the inspiration to study for a PhD in the first place. To my husband Anthony, thank you so much for always being there for me.

Abbreviations.

AIBN	2,2-azobisisobutyronitrile
Ac	acetyl
Ar	aryl
aq.	Aqueous
Å	Ångström
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
°C	degrees centigrade
cat.	catalytic
CI	chemical ionisation
Δ	heat
d	doublet
dba	*trans,trans*-dibenzylidene acetone
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DCM	dichloromethane
DCE	1,2-dichloroethane
DMAP	dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
EI	electron impact
ES	electrospray
Et	ethyl
eq.	equivalent(s)
GC	gas chromatography
GOESY	1D-gradient nuclear Overhauser spectroscopy
h	hour(s)
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectroscopy
Hz	hertz

i	iso
IR	infrared spectroscopy
J	coupling constant
L.A.	Lewis acid
LRMS	low resolution mass spectroscopy
m	multiplet
m-	meta
MCP	methylenecyclopropane
Me	methyl
mol.	molecular
NMO	N-methyl morpholine N-oxide
NOE	nuclear Overhauser effect
NMR	nuclear magnetic reasonance
o-	ortho
p-	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
ppm	parts per million
Pr	propyl
psi	pounds per square inch
q	quartet
quint.	quintuplet
rt	room temperature
rxn	reaction
s	singlet
sat.	saturated
t	triplet
t	tertiary
TBDMS	*t*-butyldimethylsilyl
TDA-1	tris[2-(2-methoxyethoxy)ethyl]amine
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran

TIPS	triisopropylsilyl
TIPSMCP	triisopropylsilylmethylenecyclopropane
TLC	thin layer chromatography
TMM	trimethylene methane
TMS	trimethylsilyl
Ts	tosyl, toluenesulphonic

Chapter 1 Introduction.

1.1 Methylenecyclopropane.

1.1.1 General properties of Methylenecyclopropane.

Methylenecyclopropane is a highly strained but stable molecule. The inherent ring strain on the molecule imposed by a three membered ring is enhanced by the presence of the exocyclic methylene moiety. The structure of methylenecyclopropane has been determined by microwave spectroscopy (**Figure 1**).[1] The ring strain in the molecule is demonstrated by directly comparing bond lengths and angles of methylenecyclopropane **1** with cyclopropane **2.** Due to the strain in the molecule from the exocyclic double bond of methylenecyclopropane, the two proximal bonds are shorter than the distal bond. In addition, the bond angles are significantly different.[2]

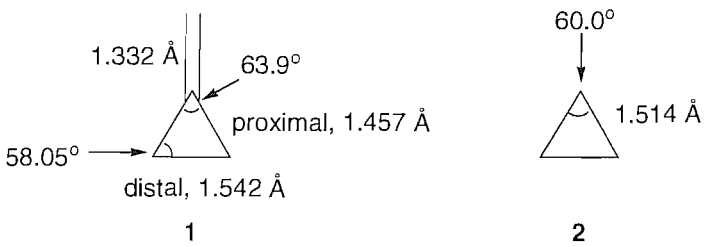
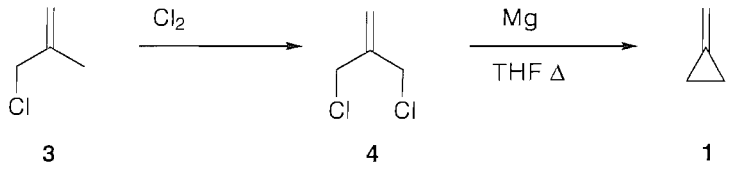


Figure 1 Comparison of methylenecyclopropane **1** and cyclopropane **2** bond lengths and bond angles.

One attractive feature of methylenecyclopropane is that despite the energy associated with this highly strained molecule, it is surprisingly stable and may be stored in sealed containers for several years without decomposition.[3] An example of the stability of the methylenecyclopropane moiety is demonstrated by its presence in a number of natural products.[4, 5] Over recent years methylenecyclopropanes have attracted a lot of scientific interest due to their elevated reactivity and have been used extensively in organic synthesis.[6-8]

1.1.2 Synthesis of unsubstituted methylenecyclopropane.

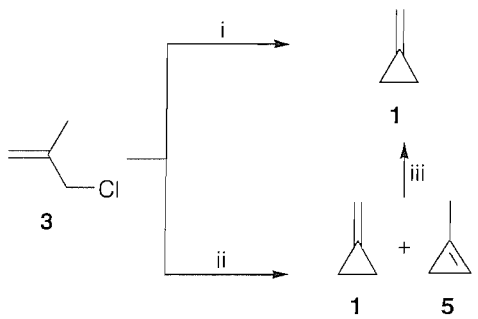
There are many reported syntheses of methylenecyclopropane with the earliest dating back to 1953; Gragson *et al.* reported that when dichloride **4** was treated with Mg in refluxing THF, methylenecyclopropane was obtained in 17% yield (**Scheme 1**).[9]



Scheme 1

Many other syntheses have been developed after this date, for both substituted and unsubstituted methylenecyclopropanes. Brandi and Goti have written an extensive review on the subject.[7] The most commonly used methods will be discussed below.

Methylenecyclopropane can be readily synthesised from methallyl chloride **3** with the use of a strong base such as $NaNH_2$ (**Scheme 2**).

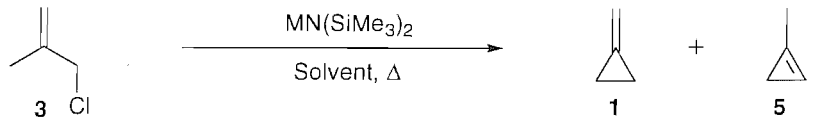


i) $NaNH_2$, ^tBuOH, THF, Δ ii) $NaNH_2$, $^nBu_2O$, Δ iii) ^tBuOK, ^tBuOH, DMSO

Scheme 2

In the one-step synthesis, methallyl chloride **3** is deprotonated with $NaNH_2$. The chloride leaves to give a carbene which, following insertion into a CH bond, gives methylenecyclopropane.[10] This method, however, requires a complicated purification

process. The two step synthesis, where the carbene may insert into either CH bond present in the molecule, produces a mixture of methylenecyclopropane **1** and methylcyclopropene **5**.[11, 12] The mixture is then isomerised fully in the presence of ^{t}BuOK in ^{t}BuOH and DMSO. This method gives good yields of methylenecyclopropane and can be used in large-scale production. More recently Binger *et al.* have introduced modifications to the original synthetic procedure to avoid difficulties in the purification of the product (**Scheme 3**). [13]



Scheme 3

M	Solvent	Reaction temp (°C)	Yield (%)	Ratio of 1:5
Na	THF	65	44	80:20
Na	Toluene	110	72	55:45
Na	*o*-Xylene	140	71	76:24
Na	$^{n}Bu_2O$	130	73	84:16
K	THF	65	6	100:0
K	Toluene	110	70	96:4
K	*o*-Xylene	140	64	96:4
K	$^{n}Bu_2O$	130	76	96:4

Table 1 Treatment of methallyl chloride **3** with different bases and solvents.

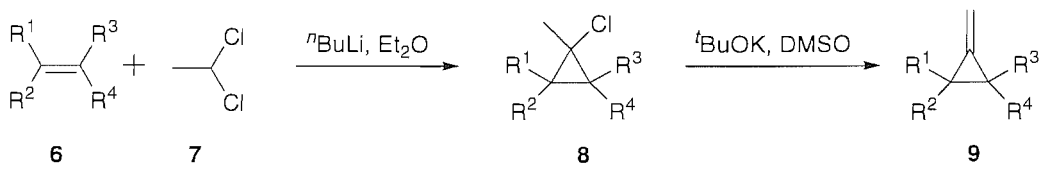
A variety of $MN(SiMe_3)_2$ bases were sampled because of their solubility in organic solvents. $KN(SiMe_3)_2$ gave the best results with methylenecyclopropane being synthesised

cleanly and efficiently. Reactions using $NaN(SiMe_3)_2$ gave similar yields with mixtures of the two products.

1.1.3 Synthesis of substituted methylenecyclopropane.

There are two ways in which functionalised methylenecyclopropanes can be synthesised; either by creating the substituted methylenecyclopropane moiety in one step or by taking methylenecyclopropane and carrying out substitution reactions to it.

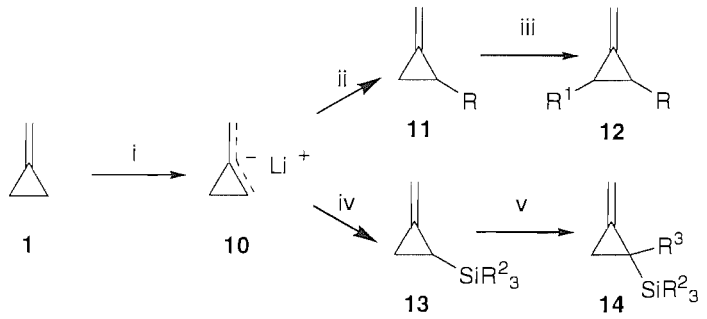
The former method of synthesising substituted methylenecyclopropane was pioneered by Binger.[14] Addition of 1,1-dichloroethane **7** to a substituted alkene **6** in the presence of a strong base gives substituted chlorocyclopropane **8** *via* the chlorocarbene. Elimination of HCl gives substituted methylenecyclopropane **9** (**Scheme 4**).



6 **7** **8** **9**

Scheme 4

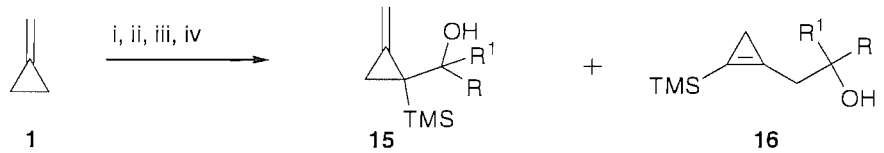
The latter method facilitates addition of electrophiles to the delocalised anion of methylenecyclopropane. It is a straightforward and practical route towards derivatives substituted on the cyclopropane ring. The methylenecyclopropane anion **10**, formed by deprotonation of methylenecyclopropane with ^{n}BuLi, can be alkylated with an electrophile (**Scheme 5**). Alkylation will always occur first on the cyclopropyl ring and, depending on the initial substituent on the methylenecyclopropane formed (**11** or **13**), the second alkylation may occur in two different ways. In general, if R is an alkyl group (**11**) then the second substitution will occur to give β-alkylation products such as **12**.[15-17] If R is an anion stabilising group (e.g. SiR_3, **13**) then the second substitution will be in the α-position.[18-21] Compound **14** may also be synthesised in a one-pot sequence from methylenecyclopropane, in elevated yields without the need for purification of intermediate **13**.[22, 23]



i) ^{n}BuLi, THF -78 °C to 0 °C, ii) RX, THF, -78 °C, iii)1. ^{n}BuLi, THF, -78 °C to 0 °C, 2. R^1X, -78 °C, iv) R^2_3SiCl, THF, -78 °C, v) R^3X, THF, -78 °C.

Scheme 5

Addition of carbonyl compounds to lithiated methylenecyclopropanes has been investigated by Thomas *et al.*[24, 25] and Binger *et al.*[18] In particular, Binger has studied silyl substituted methylenecyclopropanes and found that a mixture of products are formed when lithiated α-silyl methylenecyclopropane is reacted with an aldehyde (**Scheme 6**).



i) ^{n}BuLi, THF,-78 °C to 0 °C, ii) TMSCl, iii) ^{n}BuLi, THF,-78 °C to 0 °C, iv) RR^1CO, THF, -78 °C.

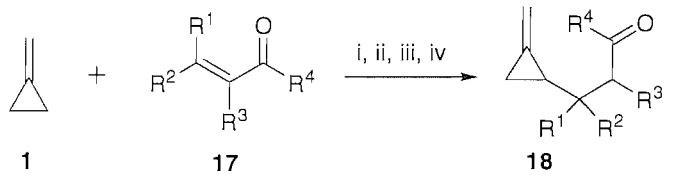
Scheme 6

R	R^1	Yield (%)	Ratio of 15:16
Me	Me	67	59:41
Ph	H	70	0:100

Table 2 Yields and ratios of alkylation products.[18]

Interestingly, it was found that when benzaldehyde was used as the electrophile, the exclusive product formed was the cyclopropene derived from γ-alkylation; this is in concord with similar experiments with lithiated allylsilanes.[26]

Recently, Peron reported that substituted methylenecyclopropanes **18** can be efficiently synthesised by 1,4-addition of lithium *bis*(methylenecyclopropyl) cuprate to a variety of different α,β-unsaturated ketones **17** (**Scheme 7**).[27, 28]



1 **17** **18**

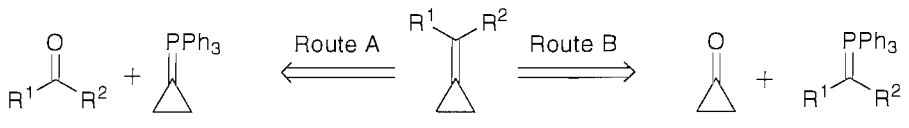
i) ^{n}BuLi, THF, -30°C, ii) CuI, iii) **17**, Me_3SiCl iv) 2M HCl 59-95%

Scheme 7

Bis(methylenecyclopropyl) cuprate is prepared by addition of methylenecyclopropane to a solution of ^{n}BuLi in THF followed by transmetallation of the lithium anion with copper iodide. The resulting cuprate can then react with α,β-unsaturated ketone **17** in a Michael addition reaction using trimethylsilyl chloride to trap the formed enolate as a silyl enolether. Acidic work-up furnishes the desired methylenecyclopropanes in good to excellent yields.

1.1.4 Synthesis of alkylidenecyclopropanes from preformed cyclopropanes.

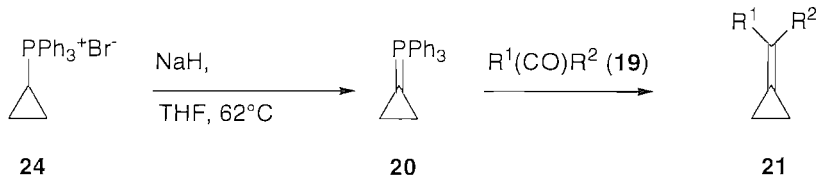
There are many ways of synthesising alkylidenecyclopropanes, with the Wittig olefination method being the most extensively used. Retrosynthetic analysis gives two possible methods for double bond formation (**Scheme 8**).



19 **20** **21** **22** **23**

Scheme 8

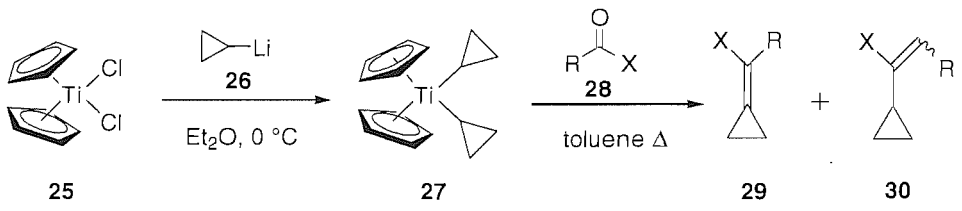
The reaction is normally carried out using Route A, employing carbonyl **19** and cyclopropylidene phosphorane **20**.[29, 30] Route B is not so commonly used because cyclopropanone **22** is labile and polymerises at room temperature.[31] Whilst the hemiacetal of **22** can act as the synthetic equivalent, it displays low reactivity.[32]



Scheme 9

Cyclopropyltriphenylphosphine **24** is commercially available and can be prepared from cyclopropyl bromide and triphenylphosphine.[33, 34] When **24** is treated with NaH, cyclopropylphosphonium ylide **20** is produced (**Scheme 9**). Reaction with aldehyde or ketone **19** gives alkylidenecyclopropane **21**. Nemoto *et al.* reported that addition of the phase transfer catalyst TDA-1 (tris[2-(2-methoxyethoxy)ethyl]-amine) to the reaction mixture helps to solvate counter ions, thus leading to elevated yields.[35]

An alternative method of producing alkylidenecyclopropanes is to apply titanocene chemistry.[36] *Bis*(cyclopropyl)-titanocene **27** readily reacts with aldehydes, ketones and esters *via* a titanacarbene species (**Scheme 10**).

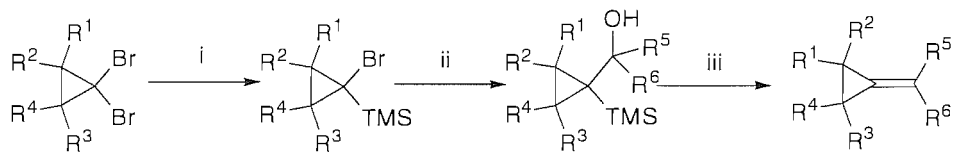


Scheme 10

Bis(cyclopropyl)-titanocene **27** is easily prepared from titanocene dichloride **25** and cyclopropyl lithium **26**, which in turn is generated from cyclopropyl bromide and lithium metal. Heating *bis*(cyclopropyl)-titanocene **27** with carbonyl compounds in toluene affords

the corresponding cyclopropylidenes **29**. In some cases, the cyclopropylidenes isomerise during isolation to give vinyl cyclopropanes **30**. This method may also be used for enolisable carbonyls.[36]

The Peterson olefination also offers a versatile route towards *endo* substituted alkylidenecyclopropanes and has proved to be facile and reliable using a variety of different substrates.[37] It proceeds *via* a base-mediated elimination of Me_3SiOH of silyl substituted cyclopropenes (**Scheme 11**).



31 **32** **33** **34**

i) 1. ^{n}BuLi, THF, -100 °C, 2. TMSCl, THF, -100 °C to -20 °C, ii) 1. ^{n}BuLi, THF, -78 °C, 2. $R^5(CO)R^6$, 3. H_2O, iii) KH, THF, 20 °C

Scheme 11

α-Bromo-α-silylcyclopropane **32** is formed by reaction of 1,1-dibromocyclopropane **31** with ^{n}BuLi followed by a quench of the resulting anion with trimethylsilyl chloride. The α-bromo-α-silylcyclopropane **32** is deprotonated with ^{n}BuLi followed by reaction with an aldehyde or a ketone to give a β-silyl alcohol **33**. Treatment with KH gives alkylidene cyclopropanes **34**.[37]

1.2 Methylenecyclopropane in synthesis.

Over the last few decades there has been a great deal of interest in the use of methylenecyclopropanes and alkylidenecyclopropanes in organic synthesis. Since they are such highly strained molecules, they can be used in a wide range of synthetic applications. Many reactions have been carried out including [3+2] cycloadditions, 1,3-dipolar cycloadditions, Diels-Alder reactions, Pauson-Khand reactions and radical based cyclisations.[2, 6, 7] This section will focus on transition metal catalysed and thermally

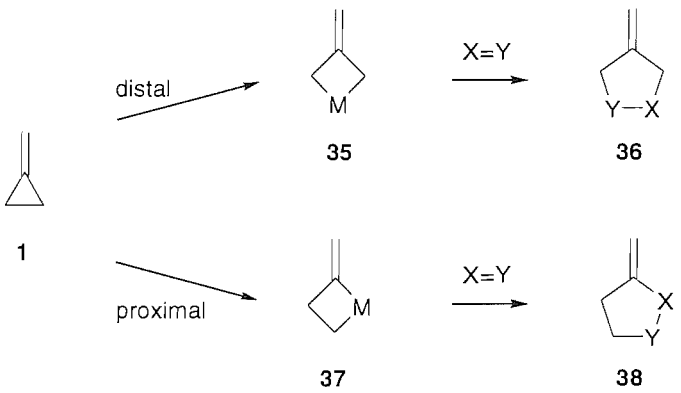
induced [3+2] cycloadditions, 1,3-dipolar cycloadditions, Pauson-Khand reactions and radical based cyclisations.

1.2.1 [3 + 2] Cycloadditions of methylenecyclopropanes.

1.2.1.1 Transition metal catalysed [3 + 2] cycloadditions.

[3 + 2] Cycloaddition reactions between methylenecyclopropanes and unsaturated compounds such as alkenes, aldehydes and imines to give five membered carbocycles or heterocycles, have become increasingly popular over the last decade and have been extensively reviewed.[8, 38, 39]

Metal catalysed cycloaddition between methylenecyclopropane **1** and a double bond can occur *via* two different reaction pathways leading to two regioisomeric products. The regiochemistry of the product is dependant on a variety of aspects; the nature of the metal and the ligands, the presence and type of substituents on the methylenecyclopropane and the nature of the unsaturated compound. Depending on these variants the cleavage of the cyclopropyl ring will either take place at the distal or the proximal bond (**Scheme 12**).

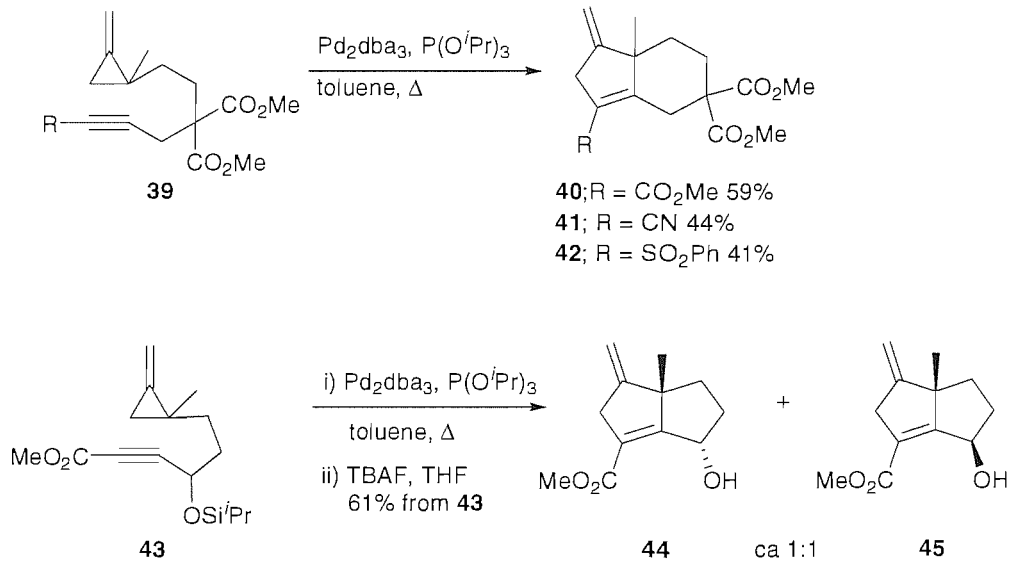


Scheme 12

The transition metal catalysts which are most commonly used are d^{10} metal species; Pd^0 or Ni^0. Depending on the metal and its associated ligands and additives in the reaction, nickel

can lead to either distal or proximal bond cleavage whereas palladium exclusively catalyses the reaction to give distal bond cleavage.

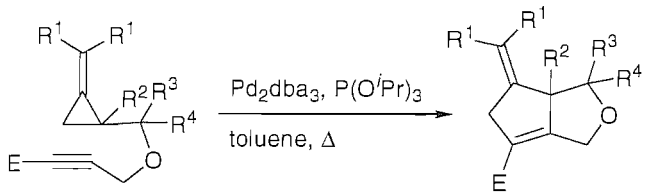
Intermolecular cycloaddition reactions of methylenecyclopropane are hampered by lack of regiochemical control.[40] An intramolecular variant of these reactions in which the reactive intermediates are tethered together, serve to avoid this problem. Motherwell has explored palladium catalysed [3 + 2] cycloadditions using tethered methylenecyclopropanes with acetylenic acceptors such as **39** and **43** (**Scheme 13**).[41, 42]



Scheme 13

Cycloadditions occurred regiospecifically *via* cleavage of the distal bond of the cyclopropyl ring for electron deficient acetylenic ester, nitrile and sulphone systems (**39**). Cyclisation studies with silyl substituted acetylene and terminal alkenes were fruitless showing that the nature of the tethering chain may have a profound effect on the efficiency of these cyclisation reactions.[41] Intramolecular [3 + 2] cycloaddition of methylenecyclopropane **43** gave an inseparable mixture of products **44** and **45** in a 1:1 ratio. The product ratio was found to closely parallel the diastereomeric ratio of the starting material.

Lautens *et al.* have investigated the effect of substitution at different positions in the molecule (**Scheme 14**).[43, 44]

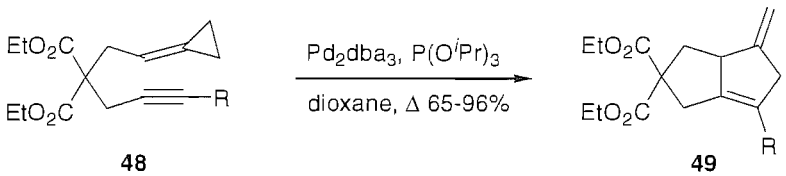


46 **47**

Scheme 14

It was found that substitution on the exocyclic methylene carbon (R^1) and the carbinol carbon (R^3 and R^4) of **46** had little effect on the cyclisation, whereas substitution on the cyclopropyl carbon had a marked effect. When R^2 = Me, the desired product was not formed, however when R^2 = H or OMe, the cyclisation proceeded smoothly. Substitution on the alkyne also had an effect on the cycloaddition success. When E was a strong electron withdrawing group such as an ester or ketone moiety, the reaction proceeded smoothly and gave the cycloadduct in good yield. When E was a weaker electron withdrawing group, such as hydroxymethyl or a protected hydroxymethyl group, the reaction gave excellent cycloaddition yields.[44]

More recently Delgado *et al.* have shown intramolecular cycloaddition reactions of an alkylidenecyclopropane and an alkyne where the reaction occurs at the proximal bond of the methylenecyclopropane to give bicyclo-octene **46** (**Scheme 15**).[45]

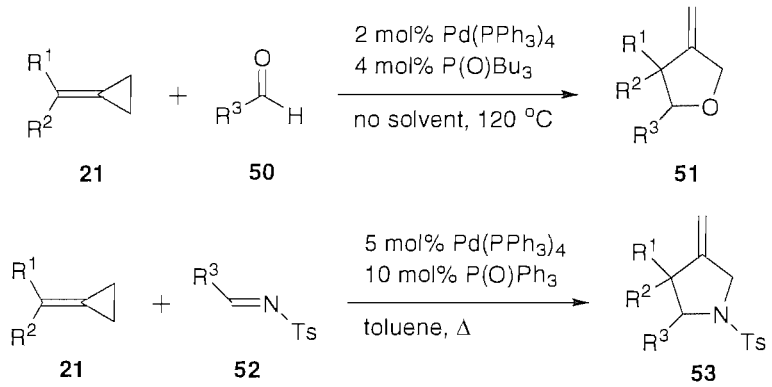


48 **49**

Scheme 15

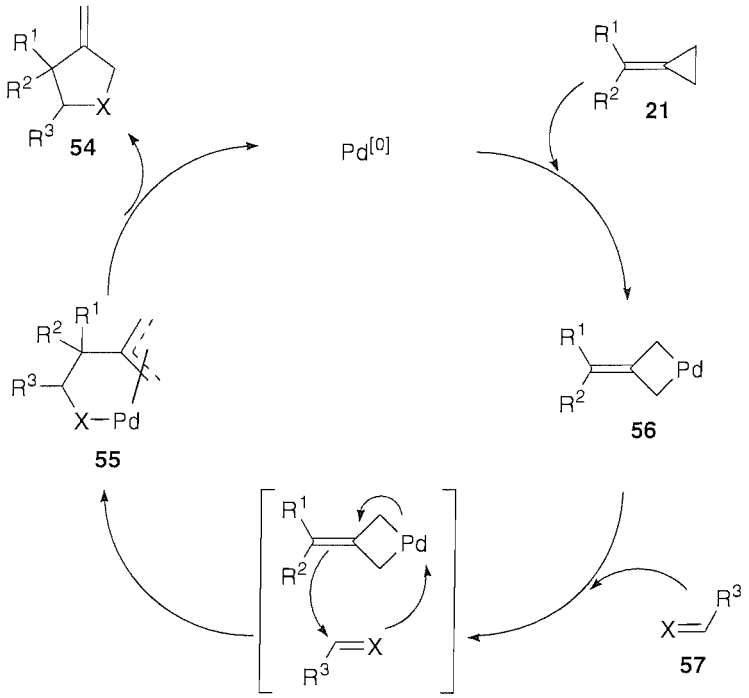
In contrast to the work of Motherwell,[41, 42] this reaction occurs efficiently with non activated alkynes and the presence of a strong electron withdrawing group at the alkyne terminus is detrimental to the cycloaddition.

Recently, alkylidenecyclopropanes **21** have also been shown to react efficiently with aldehydes (**50**)[46] and imines (**52**)[47] to give substituted tetrahydrofurans (**51**) and pyrrolidines (**53**), respectively (**Scheme 16**), thus showing the diversity of this type of reaction.



Scheme 16

The reaction is thought to proceed *via* insertion of Pd^0 into the distal bond of alkylidenecyclopropane **21** to give the palladacyclobutane complex **56** (**Scheme 17**).[46] The reaction of **56** with the C=X bond (**57**) furnishes the π-allylpalladium complex **55**, which undergoes reductive elimination to give heterocycle **54**.

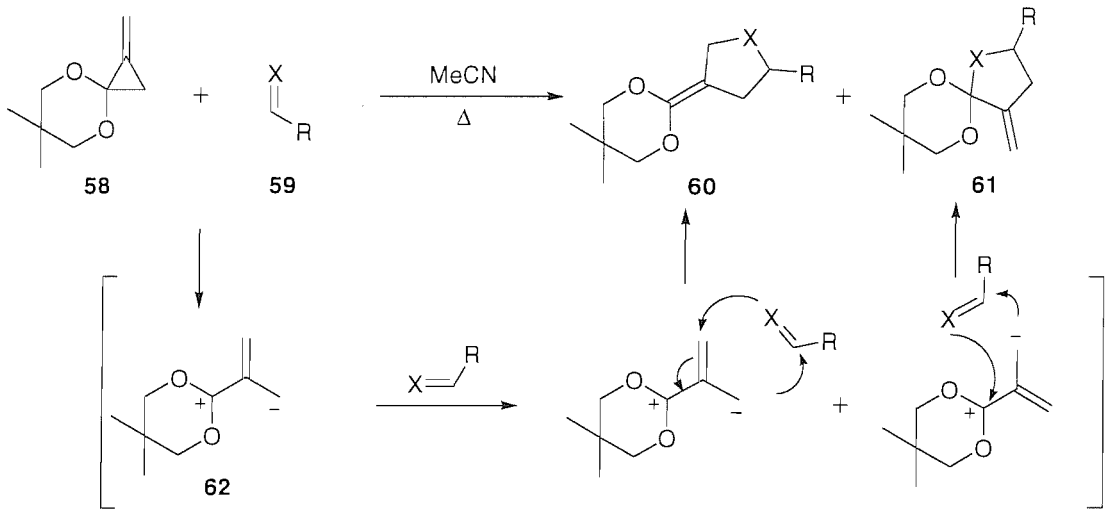


Scheme 17

1.2.1.2 Thermally induced [3 + 2] cycloadditions.

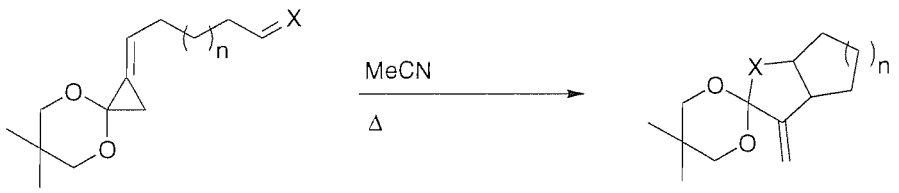
Trimethylenemethane species are short-lived intermediates which can be thermally and reversibly generated from methylenecyclopropanes.[48] Nakamura and Yamago have reported that trimethylenemethanes **62** will react with a C=X bond to give functionalised 5-membered rings (**Scheme 18**).[49] This methodology has been extended to reactions where the C=X species are electron deficient alkenes,[48, 50, 51] alkyloximes[52] and carbonyls,[53-55] and also, analogous reactions with alkynes.[49]

Under simple thermal conditions methylenecyclopropane ketal **58** will give the trimethylenemethane intermediate **62**, which is stabilised by the presence of the ketal.[49] The trimethylenemethane species formed will then undertake cycloaddition reactions with C=X species **59** to give the desired cyclic products **60** and **61**.



Scheme 18

Analogous intramolecular reactions with a methylenecyclopropane ketal and an electron deficient alkene have been studied (**Scheme 19**).[56]



Scheme 19

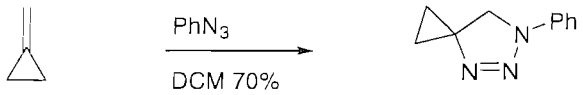
When there is a suitable acetylenic acceptor tethered to the trimethylenemethane species **63** the reaction will occur to form a bicyclo-octane or a bicyclo-nonane compound **64**.

1.2.2 1,3-Dipolar cycloadditions of methylenecyclopropanes.

1.2.2.1 Azides.

Reactions in which the methylenecyclopropane adduct acts as the two carbon component in 1,3-dipolar syntheses are plentiful.[57] Reaction of an azide with the methylenecyclopropane moiety was the first reported 1,3-dipolar cycloaddition reaction of

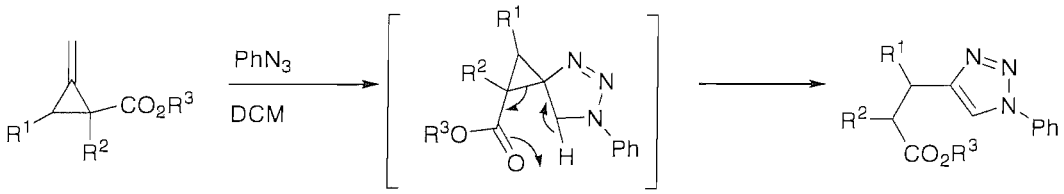
this system.[58] Phenyl azide reacts with methylenecyclopropane **1** to give triazoline **65** (**Scheme 20**).[59, 60] The reaction is highly regioselective because the substituent bearing nitrogen of phenyl azide prefers to bond to the olefinic carbon best able to bear a positive charge. The cyclopropyl ring directs the addition of phenyl azide to the methylene moiety.



1 **65**

Scheme 20

Curiously, when the alkylidenecyclopropane bears an alkoxycarbonyl substituent on the cyclopropyl ring, triazole **68** is formed (**Scheme 21**).[61] The triazoline is formed as an intermediate (**67**), however, it undergoes a rearrangement to the aromatic triazole, presumably *via* a hydrogen transfer assisted by the proximal ester carbonyl.

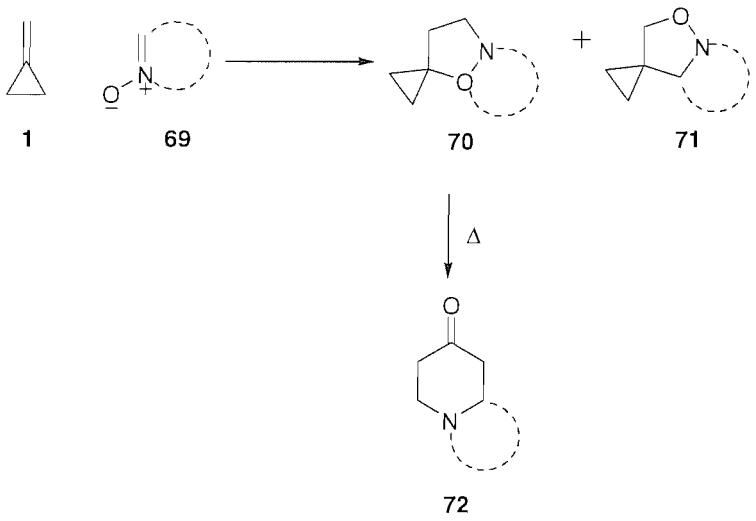


66 **67** **68**

Scheme 21

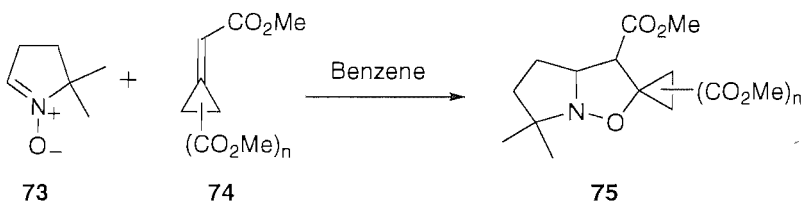
1.2.2.2 Nitrones.

The cycloaddition of nitrones to alkylidenecyclopropanes has been studied extensively.[6] Reactions of this kind are particularly interesting because the spirocyclopropane **70** formed, is able to undergo a thermal rearrangement to substituted indolizidine **72** (**Scheme 22**). When cyclic nitrones are used, N-bridgehead cyclic ketones can be synthesised.[62, 63]



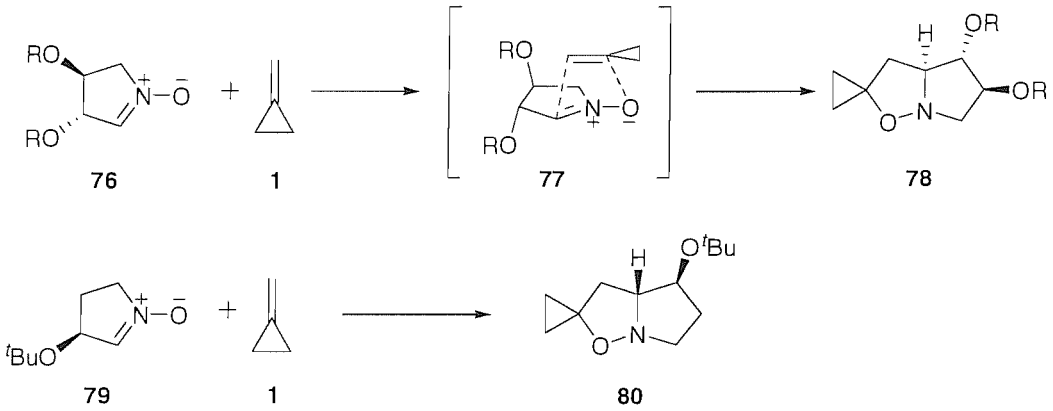
Scheme 22

Interest has been focused in this area because it provides a synthetic route to many naturally occurring alkaloids. In most cases, cycloaddition of nitrones to methylenecyclopropane **1** gives a mixture of regioisomeric products **70** and **71** in ratios ranging from 20:1 to 2:1, respectively. However, it was also noticed that the presence of alkyl or aryl substituents on the exocyclic double bond of methylenecyclopropane directs the reaction towards the formation of the isoxazolidine-4-spirocyclopropane **71**.[64] This is unfavourable because indolizidine **72** cannot be synthesised from this product. On investigation into controlling the regiochemistry of the products formed, it was found that when methoxycarbonyl substituted methylenecyclopropanes **74** were used, a complete reversal of the results was observed with the product being solely the isoxazolidine-5-spirocyclopropane **75** (**Scheme 23**).[64]



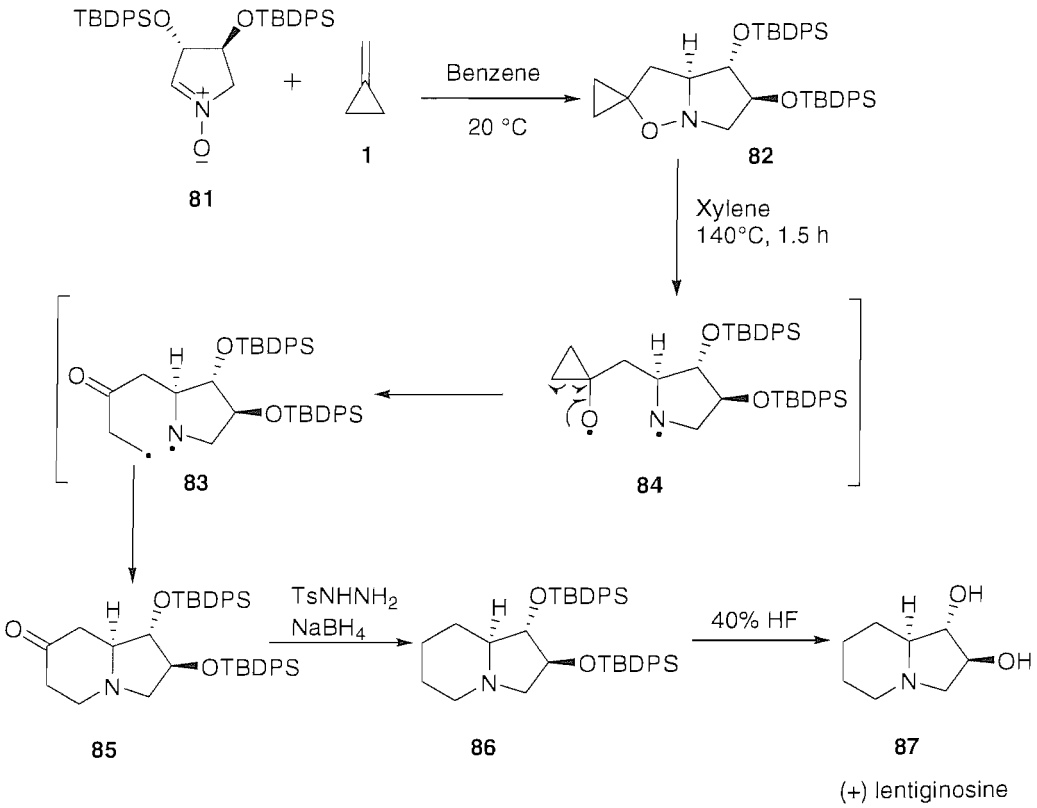
Scheme 23

When chiral nitrones are used in the cycloaddition reaction it gives rise to regio- and diastereoselective addition to methylenecyclopropane in very good yields.[57] Depending on the size of the alkoxy protecting group, the isoxazolidine-5-spirocyclopropane **78** formed from L-tartaric acid derived nitrones **76** are predominantly *anti* (**Scheme 24**). The larger the hydroxyl protecting group, the better the stereoselectivity; on passing from benzyl to TBDPS group the stereoselectivity ranges from 5:1 to 12:1.[65] When a nitrone **79**, derived from L-malic acid was used, the *anti*-product **80** was formed exclusively.[66]



Scheme 24

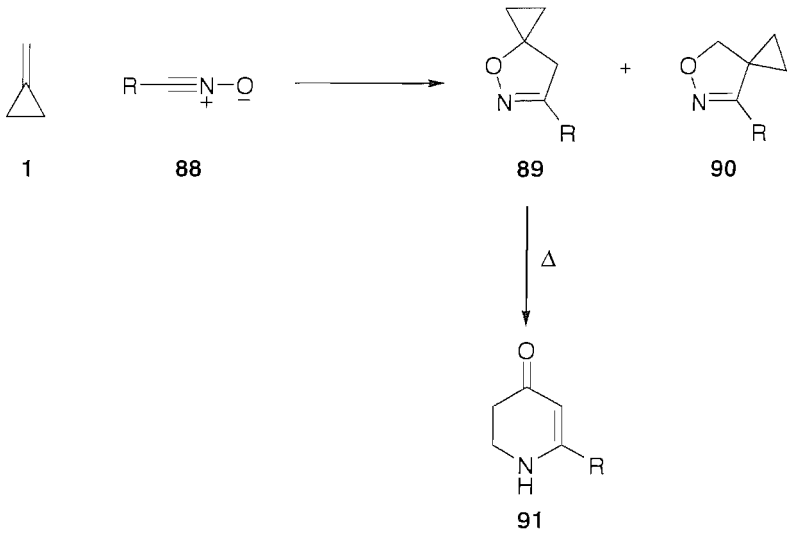
This method had been utilised by Brandi to synthesise (-) and (+)-lentiginosine **87** (**Scheme 25**).[67] Reaction between methylenecyclopropane **1** and nitrone **81** furnished spirocyclopropane **82** which then underwent a thermal rearrangement to give indolizidine **85**. Reduction of the carbonyl group followed by silyl deprotection gave lentiginosine **87** in good yield.



Scheme 25

1.2.2.3 Nitrile oxides.

Nitrile oxides (**88**) are very reactive 1,3-dipolar species and cycloaddition with alkylidenecyclopropanes are of special interest because they have a propensity to undergo a rearrangement towards dihydropyrid-4-ones **91** (**Scheme 26**).[68] Reactions of nitrile oxides with methylenecyclopropane have been found to exhibit better regio- and diastereoselectivity than nitrones. Cycloaddition of unsubstituted methylenecyclopropane to a range of nitrile oxides **88** have primarily given the 4-spirocyclopropane **89** with only traces of 5-spirocyclopropane **90**. In addition, high diastereoselectivity also occurs when there are substituents on the cyclopropane ring. The products formed are *anti* products because the dipole prefers to attack from the less hindered face of the nitrile oxide.[6, 57]

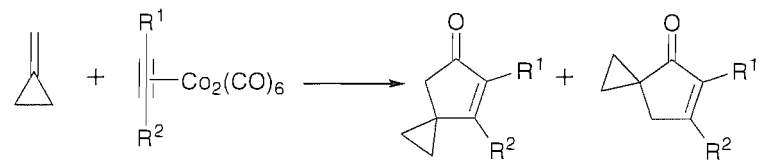


1 88 89 90 91

Scheme 26

1.2.3 Pauson-Khand reactions with methylenecyclopropane.

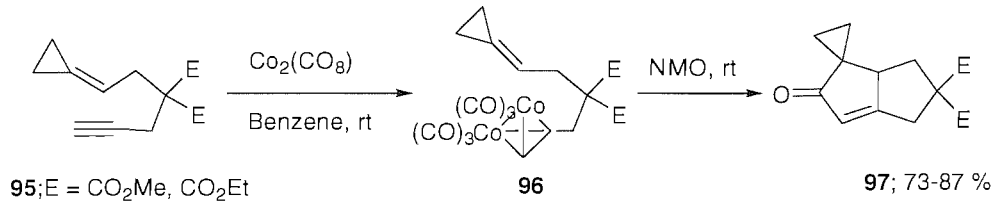
The Pauson-Khand reaction is a $Co_2(CO)_8$ catalysed [2 + 2 + 1] cycloaddition of an alkyne to an alkene with carbon monoxide insertion and can be used as a useful tool towards the synthesis of 5-membered carbocyclic rings. The intermolecular reaction of methylenecyclopropane with several alkyne cobalt complexes **92** was found to give the best results when the reactions were carried out in solvent free conditions after having adsorbed the reagents on SiO_2 or Al_2O_3 (**Scheme 27**).[69] Cyclopentanones **93** and **94** were attained as a mixture, in good to moderate yields with a ratio ranging from 2.5:1 to 6:1, respectively.



1 92 93 94

Scheme 27

De Meijere has found that intramolecular Pauson-Khand reactions proceed well when the double bond is a methylenecyclopropane moiety (**Scheme 28**).[70, 71] NMO removal of the cobalt moiety gives **97** in excellent yields.

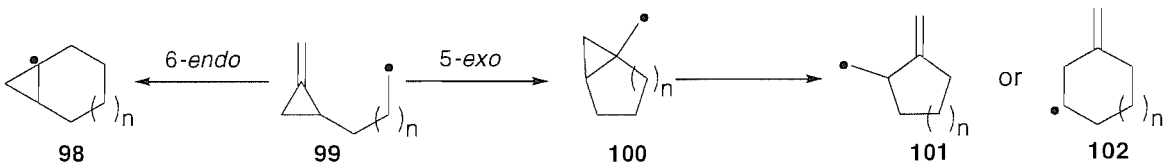


95;E = CO_2Me, CO_2Et **96** **97**; 73-87 %

Scheme 28

1.2.4 Radical cyclisations of methylenecyclopropane derivatives.

Destabel *et al.* pioneered the investigation into cyclisation of the methylenecyclopropane radical in order to establish some rules for cyclisation (**Scheme 29**).[20, 72, 73]

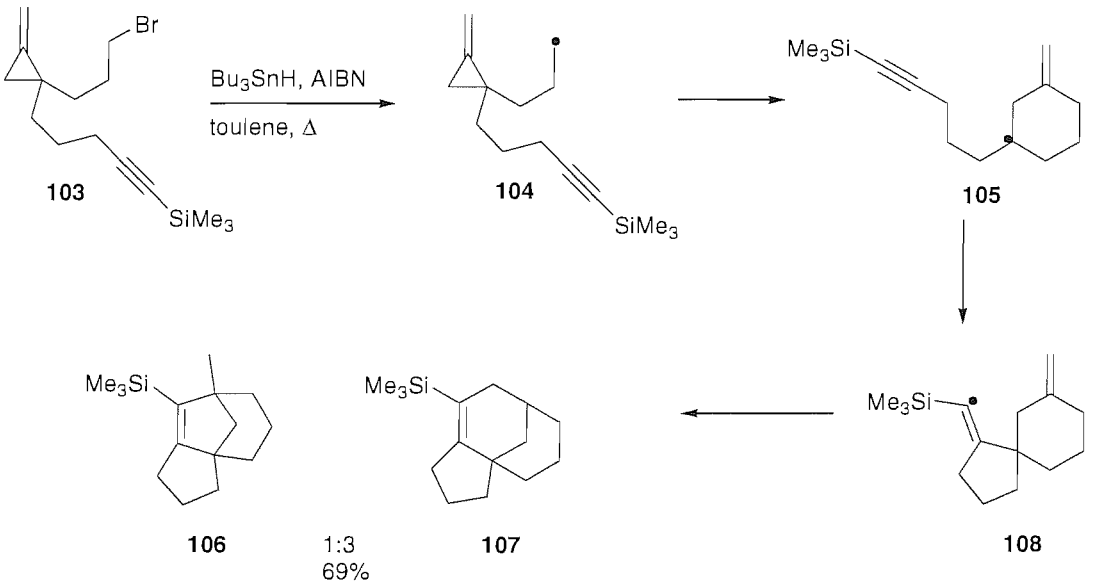


98 **99** **100** **101** **102**

Scheme 29

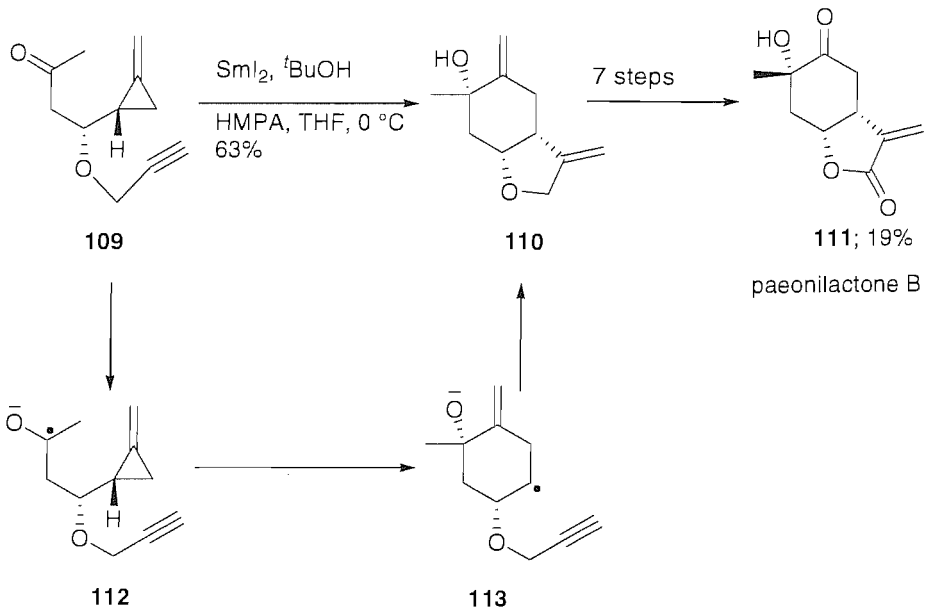
Methylenecyclopropane **99** can either undergo a 6-*endo* cyclisation to give the cyclohexyl radical **98**, or it can cyclise *via* the 5-*exo* route to give a less stable cyclopropyl radical **100**. The 6-*endo* cyclisation would be expected to be the more favoured route since it would suffer less from steric hindrance and would lead to a relatively stable cyclopropyl radical. The 5-*exo* radical formed, may either ring open in an *exo* fashion to give methylenecyclopentyl radical **101** or in an *endo* fashion to give the methylenecyclohexyl radical **102**.

This work was extended to cascade radical cyclisations, using tributyltin hydride and AIBN to generate radical **104**, to give a 1:3 mixture of products **106** and **107** respectively (**Scheme 30**).[21, 74]



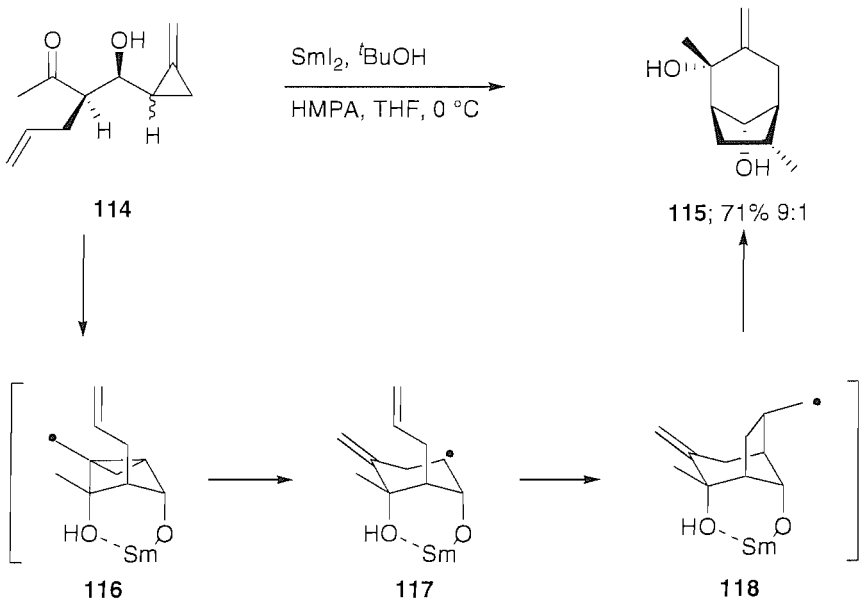
Scheme 30

Boffey *et al.* synthesised the natural product (±)-paenilactone B **111** using a SmI_2 mediated cyclisation (**Scheme 31**).[75-77] Addition of samarium diiodide to methylenecyclopropane **109** gives the ketyl radical **112** which cyclises to form methylenecyclohexyl radical **113**. 5-*Exo* dig cyclisation gives the paeonilactone skeleton, and functional group elaboration furnishes the natural product **111**.



Scheme 31

Recently, Saint-Dizier found that samarium diiodide mediated synthesis provides a simple route to bicycle-[3.2.1]-octanes (**Scheme 32**).[78] Methyl ketone **114** undergoes a radical cyclisation to produce bicyclo-octane **115** with almost complete control of stereochemistry.

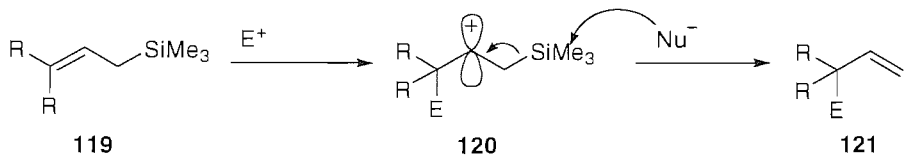


Scheme 32

1.3 Lewis acids and silylated compounds.

Over recent years Lewis acid chemistry has escalated remarkably. Although Lewis acids are used almost routinely in organic synthesis, the choice of Lewis acid can be quite difficult when designing a new reaction. A review by Carlson defining thermodynamic properties of a range of Lewis acids may be used in order to aid the choice of Lewis acid for a new reaction.[79]

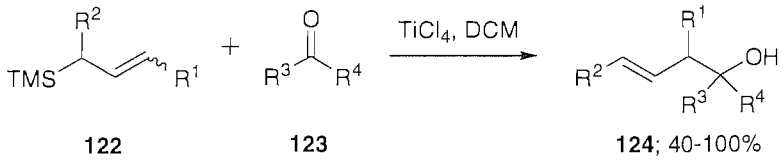
Among the most popular area of reactions with Lewis acids are those with allyl- and vinylsilanes both intra- and intermolecularly.[80] The use of organosilicon reagents has shown to be particularly useful towards the construction of natural products.[81] Allylsilanes are stable nucleophilic π-systems which can undergo reaction with electrophiles in the presence of a Lewis acid. The reaction occurs *via* selective attack of the electrophile allowing the carbon which is β to the silyl group to form cation **120**. The highly polarised C-Si bond stabilises the adjacent positive charge by donating electron density and is known as the β-effect (**Scheme 33**).



Scheme 33

1.3.1 Allylsilanes and carbonyl compounds.

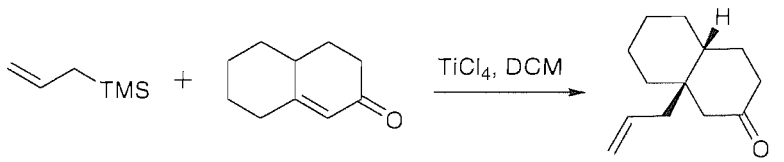
One of the first of these types of reactions was revealed by Hosomi and Sakurai in which allylsilane **122** reacts with carbonyl **123** in the presence of $TiCl_4$ to make homoallylic alcohol **124** (**Scheme 34**).[82]



122 **123** **124**; 40-100%

Scheme 34

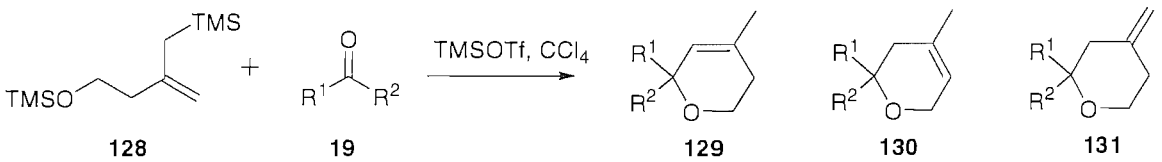
Hosomi furthered the scope of this reaction by using the methodology to furnish bicyclic rings from α,β-unsaturated carbonyls and allylsilanes in the presence of $TiCl_4$ (**Scheme 35**).[83]



125 **126** **127**; 85%

Scheme 35

The Silyl-Modified Sakurai (SMS) reaction is an efficient and versatile one-pot reaction in which homoallylic ethers may be synthesised from trimethylsilyl ethers, homoallylic ethers and allyltrimethylsilane.[84] This method was expanded into the Intramolecular Silyl-Modified Sakurai (ISMS) reaction in order to make monosubstituted- and spiroethers from just two starting materials **128** and **19** (**Scheme 36**).[85]

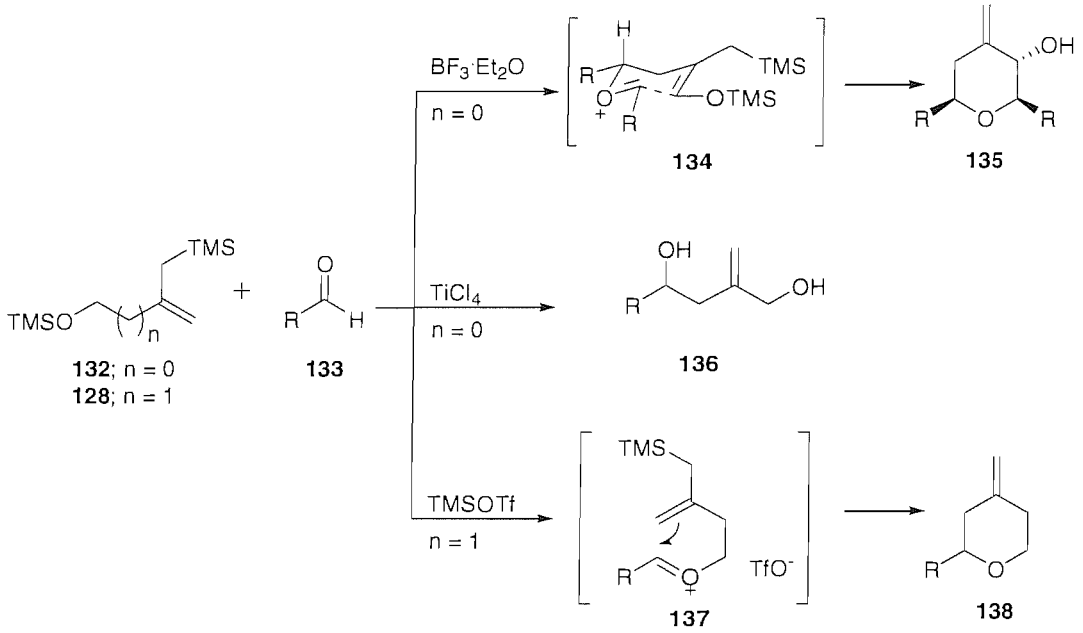


128 **19** **129** **130** **131**

Scheme 36

Markó found that the ISMS condensation of carbonyl **19** and allylsilane **128** gave different products, depending on the Lewis acid used (**Scheme 37**).[86, 87] With $BF_3{\cdot}Et_2O$ as the Lewis acid, tetrahydropyran **135** was synthesised in excellent diastereoselectivity using two

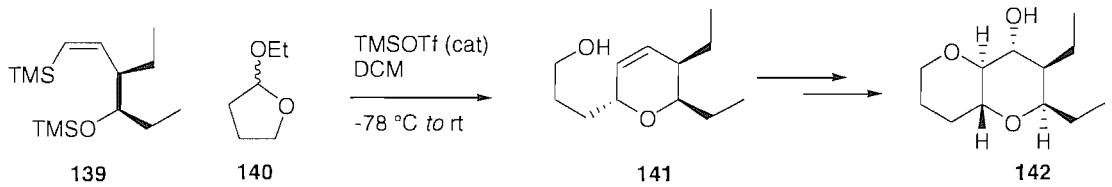
equivalents of aldehyde, whereas $TiCl_4$ furnished allylation product **136**. The use of TMSOTf gave *exo*-methylene tetrahydropyran **138**.



Scheme 37

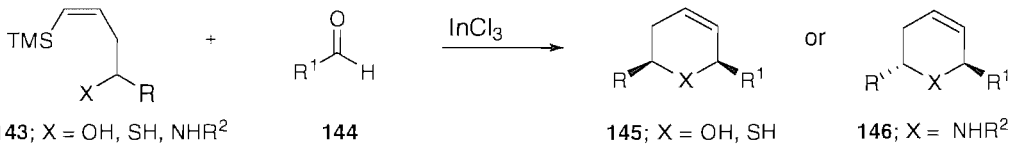
1.3.2 Vinylsilanes and carbonyl compounds.

Stereocontrolled syntheses of 7- and 8-membered rings have been carried out by Overman *et al.* using vinylsilanes with a range of aldehydes and acetals.[88, 89] Markó found that incorporation of 2-ethoxytetrahydrofuran **140** facilitated addition of an unprotected oxygenated side-chain to the formed dihydropyran **141** (**Scheme 38**).[87] This methodology was particularly of interest because *trans*-dioxadecalin **142** is the middle portion subunit of the marine toxin Okadaic acid.[90]



Scheme 38

In order to avoid the synthesis of the *bis*-silylated homoallylic precursor in the approach to the dihydropyran motif in the ISMS reaction, Dobbs has extended Markó's methodology and has introduced the silyl-Prins reaction. The silyl-Prins reaction is a cyclo-condensation reaction of a silylated homoallylic alcohol with an aldehyde or epoxide in the presence of a Lewis acid.[91] Dobbs has found indium trichloride to be the most efficient Lewis acid, and it even catalyses the reaction successfully with mixtures of water and organic solvents. [92] Furthermore, the cyclisation is versatile enough to be extended to the synthesis of heterocycles containing sulphur and nitrogen, as well as oxygen (**Scheme 39**).[93, 94]



143; X = OH, SH, NHR^2 **144** **145**; X = OH, SH **146**; X = NHR^2

Scheme 39

Only a single diastereoisomer was isolated for each case, however, there was complete reversal of diastereocontrol for tetrahydropyridine **146**, presumably due to unfavourable interactions between the N-alkyl group and the R and R^1 groups in the chair-like transition state.

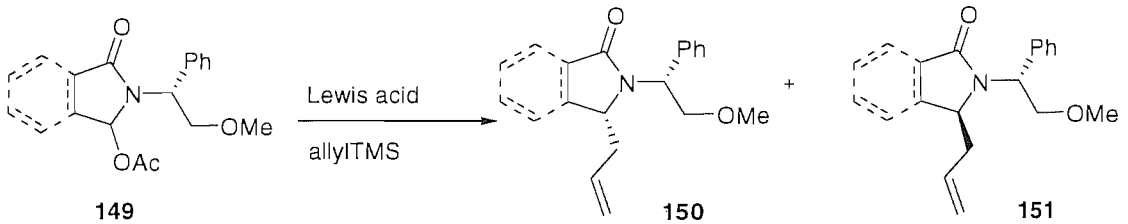
1.3.3 Allylsilanes and *N*-acyliminium ions.

Reactions of allylsilanes and imines are not so frequently reported as those with carbonyl compounds. This is presumably because they are more challenging due to the poor electrophilicity of imines and the low nucleophilicity of allylsilanes. If iminium ions are used instead of imines, the reaction rates can be enhanced[95, 96] and *N*-acyliminium ions (**147**) exhibit particularly good addition reactions with allylsilanes.[97] They are very similar to the Mannich reagent **148** (**Figure 2**), however *N*-acyliminium ions **147** are more highly versatile and may be used in many synthetic applications both intramolecularly[98] and intermolecularly. [98, 99]

147 **148**

Figure 2 Comparison of *N*-acyliminium ion to Mannich Reagent.

For application in organic synthesis, *N*-acyliminium ions are almost always generated *in situ,* in view of their limited stability and high reactivity. The use of protic acids in the addition of allylsilanes to *N*-acyliminium ions is more widespread, but Lewis acids have also been used to effect bond formation. For the majority of reactions $BF_3{\cdot}Et_2O$, $TiCl_4$ and $SnCl_4$ are superior in terms of convenience and results.[100] Due to the mechanistic pathway for *N*-acyliminium ion reactions, direct diastereocontrol is difficult to achieve without the presence of a chiral auxiliary on the nitrogen. However, an interesting report by Ukaji *et al.* has shown that by changing the Lewis acid from $SnCl_4$ to $TiCl_4$, the products formed have opposing diastereoselectivities (**Scheme 40**).[101]



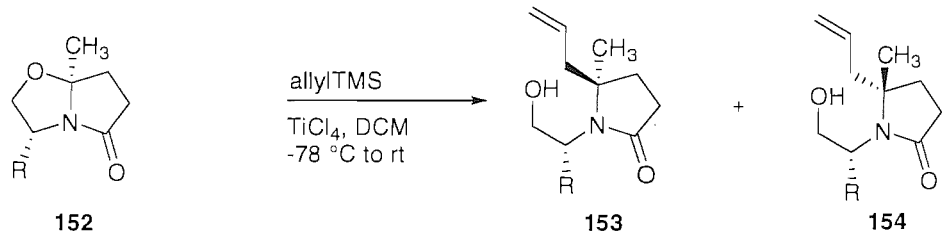
149 **150** **151**

Scheme 40

$TiCl_4$ and $SnCl_4$ gave the diastereomeric ratios of **150:151** as 62:38 and 16:84 respectively. Although the reason for this change is not certain, it is assumed that the stabilising dipole effect in the *N*-acyliminium ion suffers a disruption due to some type of tin-complexation.[100] Other examples of Lewis acid mediated addition of 3-trimethylsilylprop-1-ene (allylTMS) to *N*-acyliminium ions with chiral auxiliaries at the nitrogen position have been published by Meyers *et al.*[102] and Polniaszek *et al.*[103]

Meyers has also studied intermolecular additions of allylTMS/$TiCl_4$ to tertiary cation precursor **152**. The stereochemical outcome of the products is highly sensitive to the size

of the substituent on the nitrogen with the diastereomeric ratio of **153**:**154** ranging from 8:1 for R = Me to 1:11 when R = ^{t}Bu (**Scheme 41**).[104]

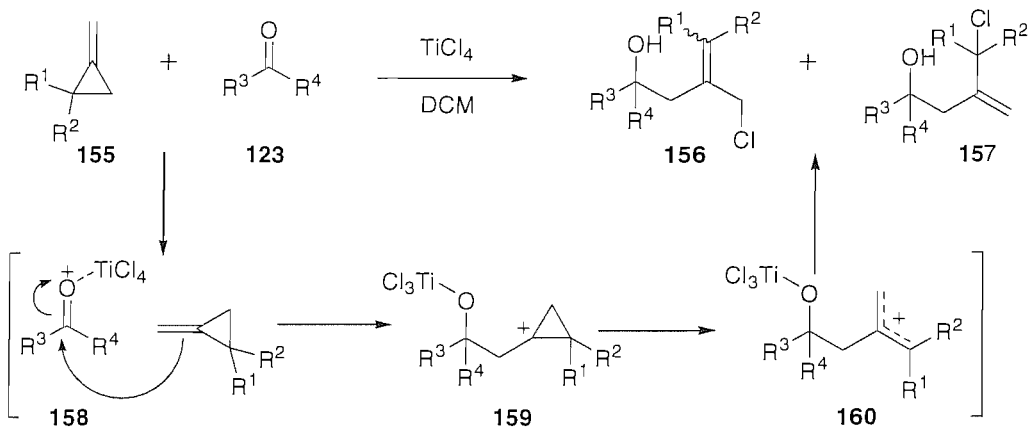


152 **153** **154**

Scheme 41

1.4 Lewis acids and methylenecyclopropane.

To date, little work concerning Lewis acid mediated syntheses with methylenecyclopropane has been carried out. Monti initiated interest in this area with [3 + 2] cycloadditions of methylenecyclopropane and allylsilanes to give methylenecyclopentanes.[105, 106] This was soon followed up by Hosomi in 1997 who demonstrated that substituted methylenecyclopropane **155** could be coupled with carbonyl compounds **123** in the presence of a Lewis acid, such as $TiCl_4$, to furnish alcohols **156** and **157** (**Scheme 42**).[107]



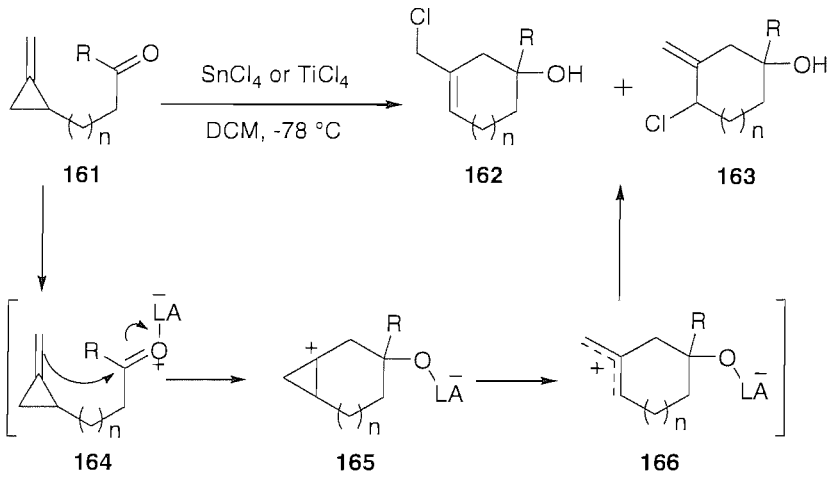
155 **123** **156** **157**

158 **159** **160**

Scheme 42

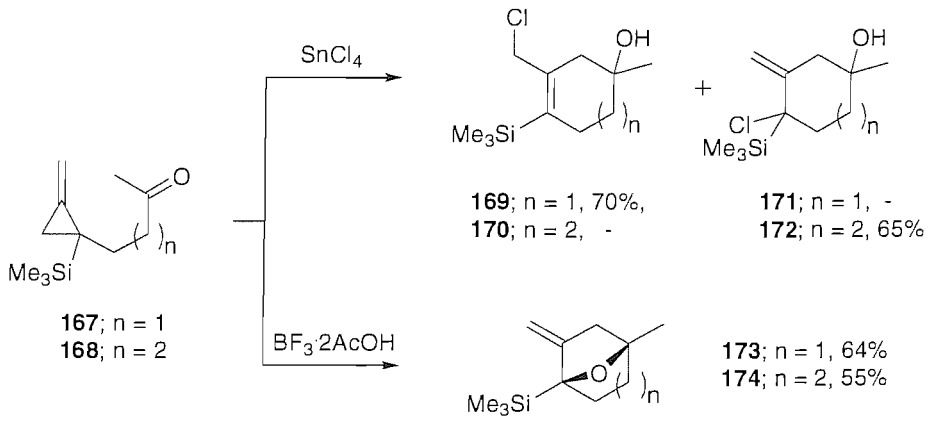
Following Hosomi's proposed mechanism, co-ordination of the carbonyl group to $TiCl_4$ allows nucleophilic addition of methylenecyclopropane **155,** providing cyclopropyl cation **159**. This isomerises to the π-allyl cation intermediate **160** which undergoes a quench by chloride to give homoallylalcohols **156** and **157**.

More recently Peron *et al.* developed this work to an analogous intramolecular cyclisation of methylenecyclopropylketones **161** giving six and seven membered rings (**Scheme 43**).[108, 109] The products formed were consistent with Hosomi's proposed mechanism.



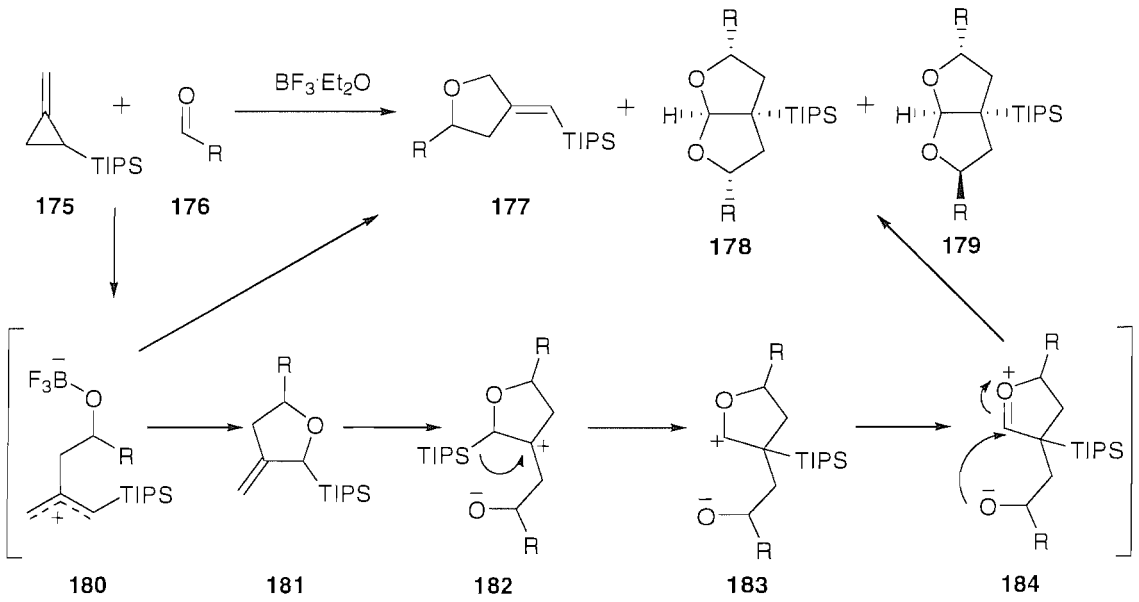
Scheme 43

Moreover, Peron *et al.* showed that incorporation of a trimethylsilyl group on the methylenecyclopropane precursors **167** and **168** enhanced the yields (**Scheme 44**). This is because the presence of the silicon group enhances the nucleophilicity of the methylenecyclopropane double bond and stabilises the intermediate β-silyl cation. Normally silicon elimination from a β-silyl cation is rapid, however, under these circumstances, rearrangement of the cyclopropyl ring to the unstable allyl cation is faster. In addition it was noted that the absence of a sufficiently nucleophilic anion derived from the Lewis acid (e.g. Cl^-) led to intramolecular trapping of the intermediate cation from the alkoxide nucleophile to give bicyclic ethers **173** and **174**.



Scheme 44

Patient *et al.* have investigated intermolecular reactions of methylenecyclopropanes and aldehydes and ketones in the presence of Lewis acids.[22] $BF_3{\cdot}Et_2O$ catalysed reaction of triisopropylmethylenecyclopropane **175** with an aldehyde **176** gave three products; tetrahydrofuran **177** and furofurans **178** and **179** as mixture of diastereoisomers (**Scheme 45**).[23]

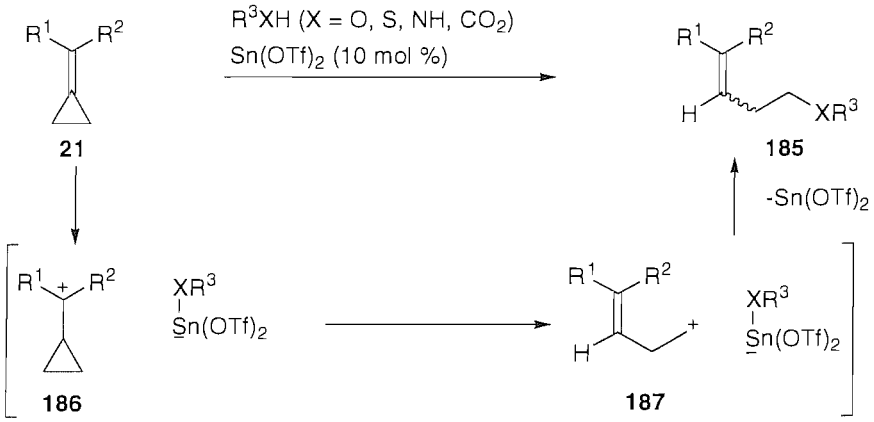


Scheme 45

Addition of triisopropylmethylenecyclopropane **175** to aldehyde **176** is followed by a rearrangement to the allyl cation intermediate **180** which can either be trapped by the

alkoxide to give tetrahydrofuran **177** or the regioisomer **181**. The less stable allylsilane **181** reacts with a further equivalent of the aldehyde and the formed product undergoes a 1,2-silyl shift to give **183**. The second cationic intermediate is trapped intramolecularly by the alkoxide furnishing furofurans **178** and **179**.

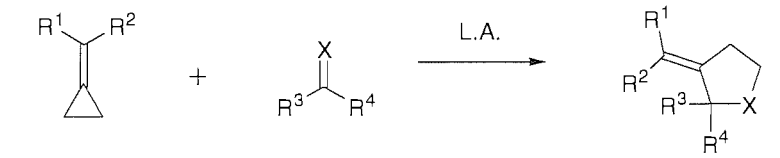
Shi has extensively studied the reaction of alkylidenecyclopropanes with reagents such as alcoholic or acidic nucleophiles,[110] aromatic amines,[111] imines[112] and carbonyl compounds.[113] $Sn(OTf)_2$ was found to be the best Lewis acid to ring-open catalytically the strained three-membered ring (**Scheme 46**).[110]



Scheme 46

The proposed mechanism occurs *via* cation **186**. This rearranges to cation **187** which undergoes nucleophilic attack by the tin species to give alkene **185**.

Shi has also reported a novel [3+2] cycloaddition of an imine or a carbonyl complex to alkylidenecyclopropanes **188** in order to create cyclic compounds **190** and **191** (**Scheme 47**).

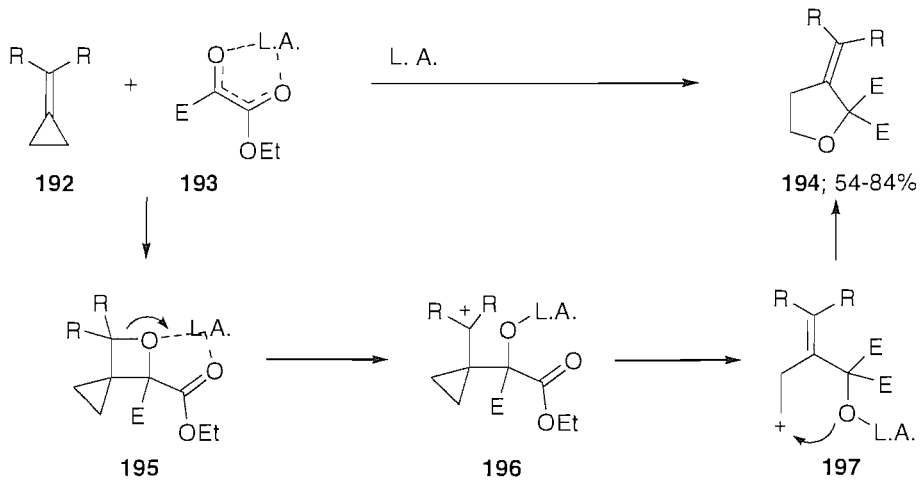


188; R^1, R^2 = Ar **123**; X = O; **189**; X = NTs **190**; X = O; **191**; X = NTs

Scheme 47

For reaction with carbonyl compound **123**, ytterbium triflate was found to be the best Lewis acid, giving excellent isolated yields of tetrahydrofuran **190**, with DCM or DCE as the solvent. For the case of imine **189**, $BF_3{\cdot}Et_2O$ was the preferred Lewis acid.[112] The presence of electron-donating groups in the R^1 and R^2 position of alkylidene **188** gave increased yields.[113]

When electron-withdrawing groups are present on the carbonyl moiety (**193**), the proposed mechanism of reaction with alkylidenecyclopropanes **192** is shown (**Scheme 48**).[113]



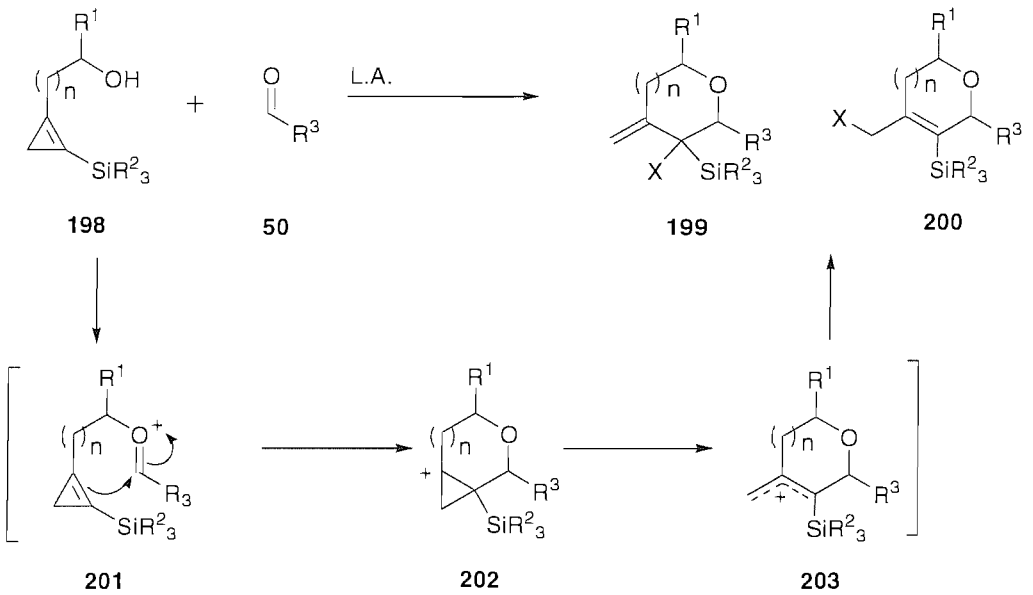
192 **193** **194**; 54-84% **195** **196** **197**

Scheme 48

The Lewis acid activates the carbonyl compound **193** allowing alkylidenecyclopropane **192** to attack more easily. Spirocycle **195** opens up to give the stabilised cation **196**. Following a rearrangement to cation **197**, a quench by the oxygen gives tetrahydrofuran **194**.

1.5 Programme of work.

Following the success of Peron and Patient with inter- and intramolecular cyclisations using silylated methylenecyclopropane and a range of different aldehydes and ketones, it was decided to focus on cyclopropenylsilanes and intermolecular reactions with aldehydes thereof (**Scheme 49**). Markó[86, 90] and Dobbs[91, 93] have extensively studied additions of aldehydes to vinylsilanes. Since vinylsilanes derived from methylenecyclopropanes have an inherent ring strain, this might lead to shorter reaction times and increased yields for analogous studies.

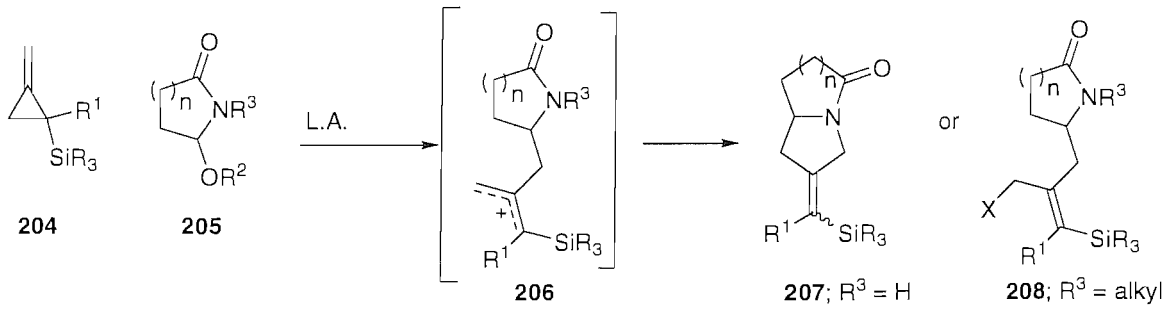


Scheme 49

Aldehyde **50** should react with vinylsilane **198** intermolecularly to create the cyclopropyl unit **202** *via* the oxonium ion **201**. Rearrangement should follow in order to make **203**, which then, following a quench by either the Lewis acid or a proton source, should give **199** and/or **200.** This chemistry may be developed by using a range of Lewis acids to drive the reaction; since $TiCl_4$ and $BF_3{\cdot}Et_2O$ are the most commonly used Lewis acids, it would be interesting to find out whether different Lewis acids are also suitable for this type of

work. This research may also be broadened by investigation into alternative R groups and by perhaps delving into whether different ring sizes may be synthesised.

The second part of this project was concerned with novel addition of a methylenecyclopropyl moiety to an *N*-acyliminium ion. *N*-Acyliminium ions smoothly undergo addition reactions with allylsilanes,[97] thus, since a silylated methylenecyclopropane can be thought of as a highly strained allylsilane, it was of interest to investigate whether addition of a silylated methylenecyclopropane to an *N*-acyliminium ion could be facilitated (**Scheme 50**).



Scheme 50

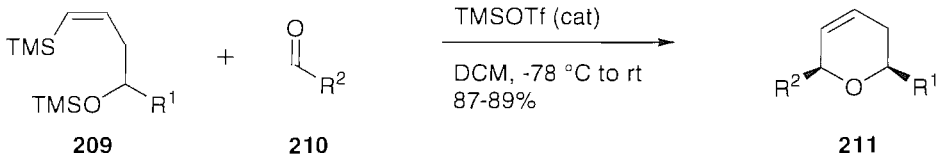
The Lewis acid should co-ordinate to the alkoxy group of **205** facilitating formation of the *N*-acyliminium ion. Attack from the nucleophilic double bond of methylenecyclopropane **204** should lead to the allyl cation intermediate **206**. Trapping of the pendant allyl cation should either occur from the nitrogen or from the Lewis acid to form **207** or **208** respectively.

Research may be directed into variation of the R groups to see how this affects the products formed and their yields. Investigations may be carried out into variation on the size of the ring and also into whether acyclic *N*-acyliminium ions will facilitate this reaction.

Chapter 2 Intermolecular reactions of methylenecyclopropane derived cyclopropenylsilanes.

2.1 Aims.

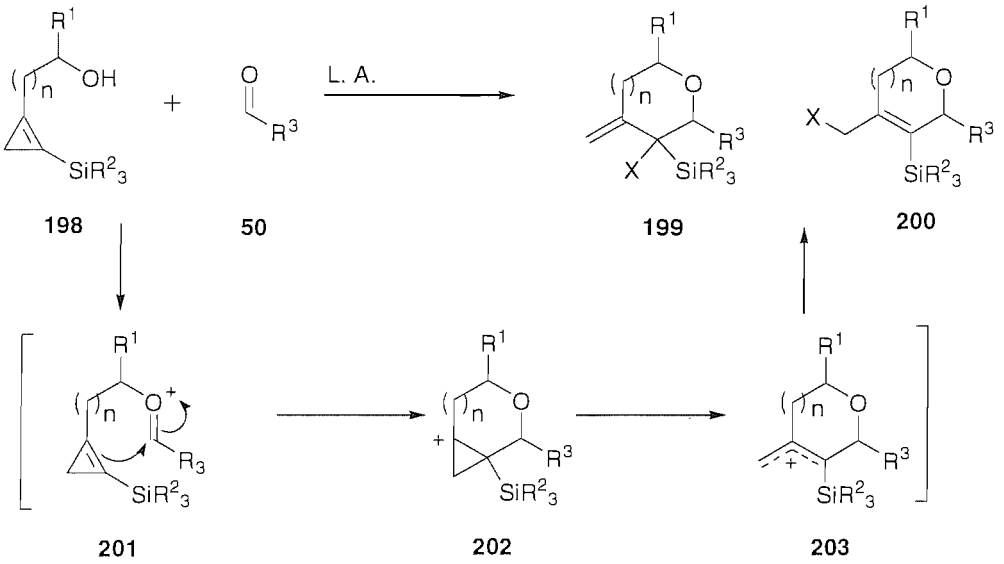
Markó reported that aldehyde addition to vinylsilanes **209** affords dihydropyrans **211** in excellent yields as single diastereoisomers (**Scheme 51**).[87] The reaction proceeds *via* an Intramolecular Silyl-Modified Sakurai reaction.



Scheme 51

Therefore, Lewis acid mediated intermolecular addition of cyclopropenylsilane **198** to aldehyde **50** was expected to give rise to tetrahydropyran **199** and/or dihydropyran **200** (**Scheme 52**). Aldehyde **50** should react with cyclopropenylsilane **198** intermolecularly to create cyclopropyl cation **202** *via* the oxonium ion **201**. Rearrangement should follow in order to make **203**, which then, following a quench from an anion derived from the Lewis acid should give **199** and/or **200.**

The aim of this research was to study the Lewis acid mediated cyclisations of methylenecyclopropane derived cyclopropenylsilanes with a range of different aldehydes to find out whether 6- or 7-membered heterocycles could be synthesised cleanly in one step. Variations can be made on the R groups of cyclopropenylsilane **198**. Initial studies were to be carried out with trimethylsilyl substituted cyclopropenylsilanes.

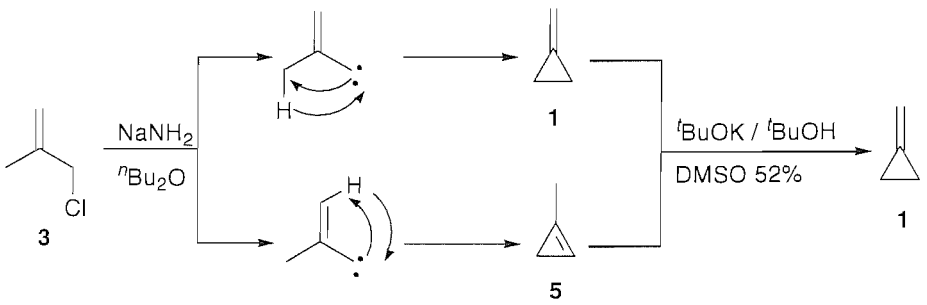


Scheme 52

2.2 Synthesis of precursors.

2.2.1 Synthesis of methylenecyclopropane.

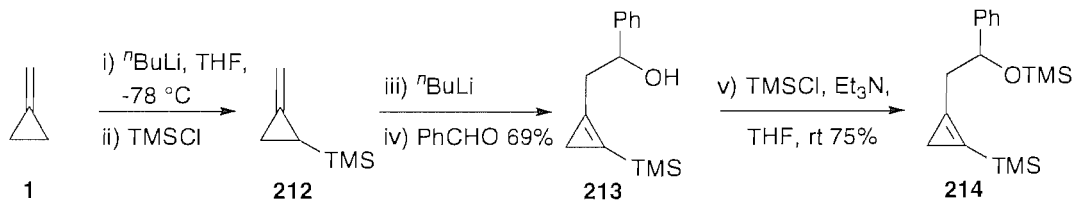
Methylenecyclopropane **1** was synthesised following the procedure reported by Binger *et al.*[11] The carbene, produced from reaction of sodium amide with methallyl chloride (**3**), inserts into either the methyl CH to give methylenecyclopropane **1**, or into the methylene CH to give methylcyclopropene **5**. A 4.7:1 mixture of **1** and **5** respectively, was obtained and fully isomerised by treatment with ^{t}BuOK and ^{t}BuOH in DMSO, giving methylenecyclopropane in 52% yield (**Scheme 53**).



Scheme 53

2.2.2 Synthesis of cyclisation precursors.

Cyclisation precursors **213** and **214** were synthesised in good yield from methylenecyclopropane. Methylenecyclopropane was deprotonated with ^{n}BuLi and the resulting anion was quenched with TMSCl. A further deprotonation was followed by a γ-alkylation with benzaldehyde in a one-pot reaction to give cyclopropenylsilane **213** (**Scheme 54**). Markó has shown that silyl ethers are more reactive than the alcohols.[90] This is presumably because it removes the opportunity for ethanol to be made as a by-product, which could affect the remaining Lewis acid in the reaction mixture. Hence, trimethylsilyl protection of alcohol **213** was completed in excellent yield using an adapted method by Corey.[114]



Scheme 54

2.3 Cyclisation studies with aldehydes.

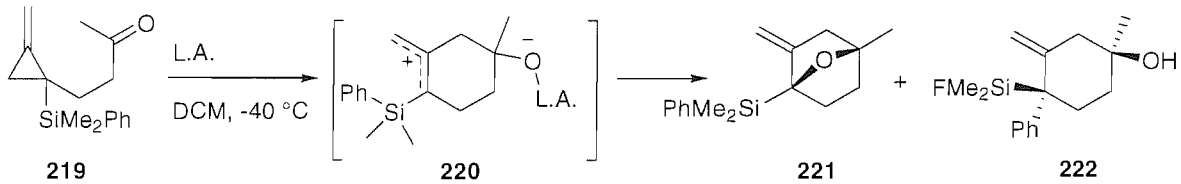
The initial cyclisation studies were carried out using benzaldehyde and isobutraldehyde, as the electrophile, and a range of different Lewis acids with both DCM and $EtNO_2$ as solvents (**Scheme 55**). The Lewis acid was added to the reaction mixture at –78 °C and it was allowed to warm up slowly whilst the reaction was monitored by TLC. Cyclisations were attempted using $BF_3{\cdot}Et_2O$, $Sc(OTf)_3$, $InCl_3$, $In(OTf)_3$, $BF_3{\cdot}2AcOH$, $SnCl_4$ and TMSOTf. With alcohol **213**, either decomposition of starting materials was observed or there was no change to the reaction mixture. For the case of silylether **214**, either the hydrolysed starting material was produced or the reaction products underwent decomposition.

213; R^1 = H **215**; R^2 = ^{i}Pr
214; R^1 = TMS **216**; R^2 = Ph

217 **218**

Scheme 55

The cyclisation was not as facile as expected and this might be due to a problem with the trapping of the allyl cation intermediate. Peron reported that a phenyldimethylsilyl group could be used to quench an analogous allyl cation intermediate **220** in the cyclisation of **219** (**Scheme 56**).[109]



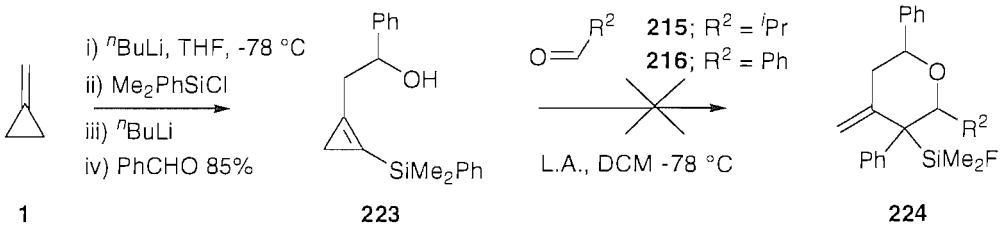
219 **220** **221** **222**

$BF_3{\cdot}Et_2O$, 6h 72%
$BF_3{\cdot}2AcOH$, 45 min 22% 55%

Scheme 56

The allyl cation **220** could either be quenched by the alkoxide nucleophile to make bicyclic ether **221** or by intramolecular addition of the phenyl group to give silylfluoride **222**. With $BF_3{\cdot}2AcOH$ as the Lewis acid the phenyl transfer from the silicon to the allyl cation is able to compete with intramolecular trapping by the alkoxide nucleophile.

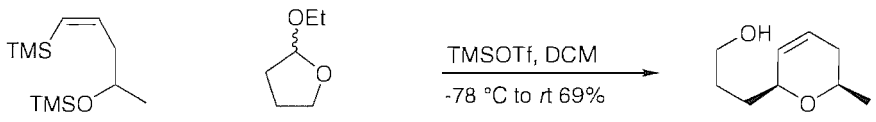
Thus, cyclopropenylsilane **223** was synthesised using the same method as for the analogous trimethylcyclopropenylsilane **213** in 85% yield (**Scheme 57**). Cyclisation reactions were attempted using $BF_3{\cdot}Et_2O$, $Sc(OTf)_3$, $In(OTf)_3$ and $BF_3{\cdot}2AcOH$ as the Lewis acid and DCM as the solvent with two aldehydes **215** and **216**. However, tetrahydropyran **224** was not formed and the reaction products underwent decomposition.



1 223 224

Scheme 57

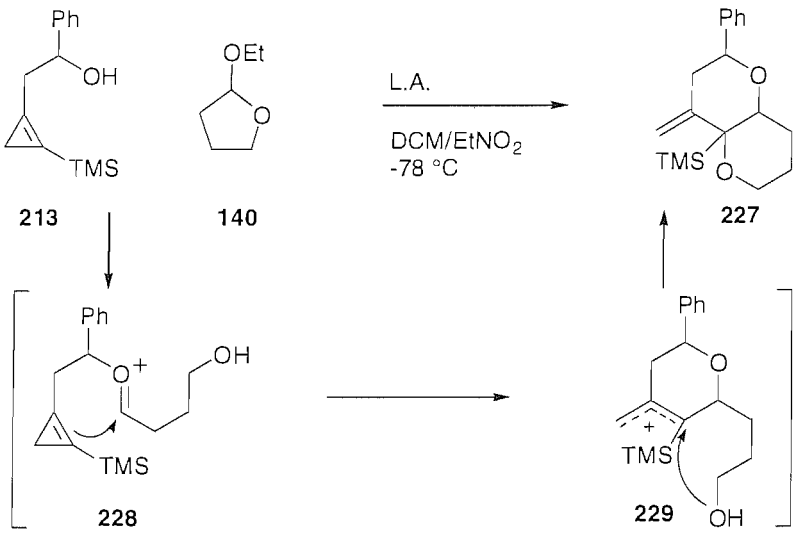
Markó found that addition of vinylsilane **225** to 2-ethoxytetrahydrofuran **140** formed dihydropyran **226**. The dihydropyran had a pendant alcohol side chain present derived from the ring opening of 2-ethoxytetrahydrofuran (**Scheme 58**).[87, 90]



225 140 226

Scheme 58

So, in order to incorporate a pendant nucleophilic moiety into cyclisations of cyclopropene **213**, 2-ethoxytetrahydropyran **140** was used as the electrophile (**Scheme 59**).

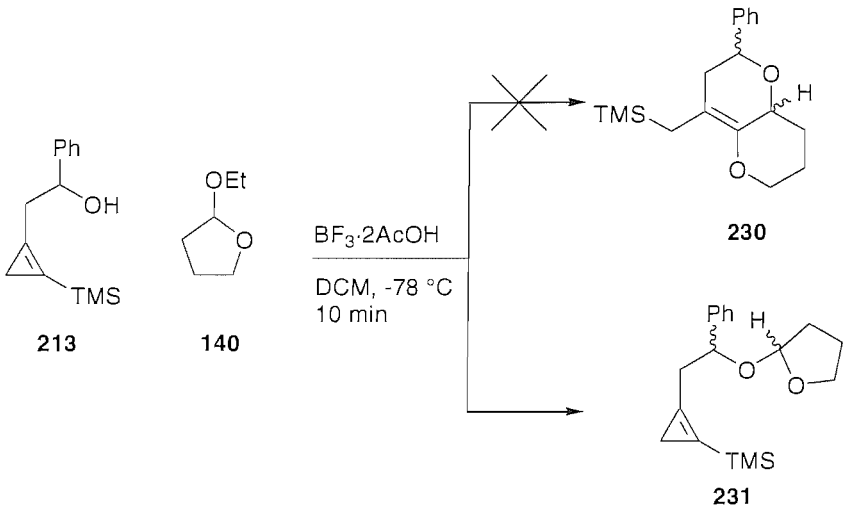


213 140 227 228 229

Scheme 59

The presence of the Lewis acid should allow formation of the oxonium ion **228** which might then undergo attack from the nucleophilic double bond of the cyclopropene. The allyl cation intermediate **229** was expected to undergo a quench from the pendant alcohol group thus forming the bicyclic compound **227**.

Using BF_3·2AcOH as the Lewis acid, cyclopropenylsilane **213** was reacted with 2-ethoxytetrahydrofuran **140** in DCM at –78 °C and gave a new product in 56% yield. Initially it was thought that bicyclic system **230** had been synthesised, but it later became clear that the product was, in fact, acetal **231** (**Scheme 60**).



Scheme 60

Whilst it was surprising that the TMS group should undergo an unprecedented 1,3-migration, the ^1H NMR was consistent with product **230** (**Figure 3**). The upfield CH_AH_B coupling pattern was thought to be the CH_2 next to the TMS group, whereas, it was actually the CH_2 of the cyclopropene moiety. H_CH_D coupled to H_A and there was coupling between H_B and $(CH_2)_3$, all verified by 2D-COSY experiments. The two quaternary carbons (^{13}C NMR; 132.0 and 108.8 ppm) must be attributed to the cyclopropene moiety of the acetal rather than the double bond within the bicyclic structure of **230**. Furthermore, the molecular masses of the two products are identical so mass spectrometry studies did not highlight the difference between the structures.

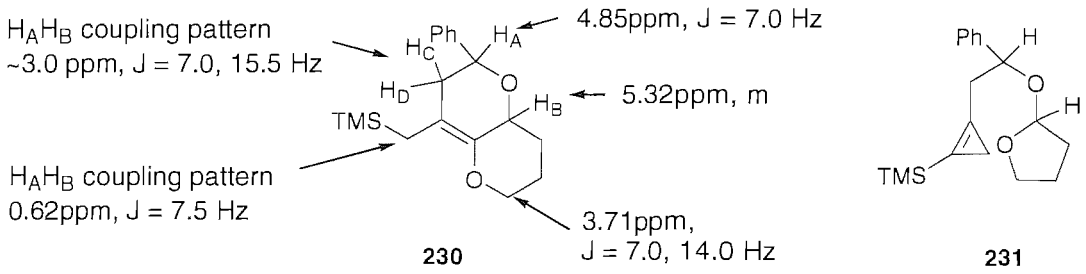
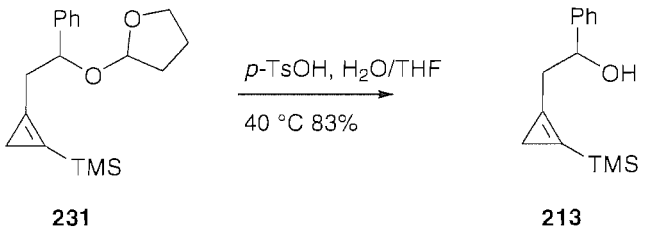


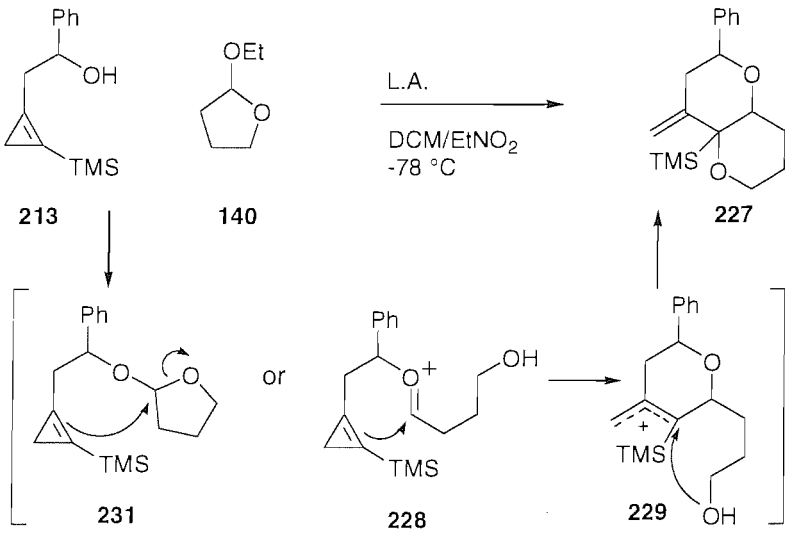
Figure 3: Comparison of **230** to **231**.

It was surprising that the acetal could be isolated because it would not be expected to be very stable in the Lewis acid environment. So, to confirm that acetal **231** had been formed, a decomposition reaction was carried out using *p*-TsOH in wet THF at 40 °C (**Scheme 61**). Under these conditions the isolated product was the alcohol **213**, proving that compound **230** could never have been formed.



Scheme 61

It was curious that acetal **231** (or the oxonium species **228**) did not undergo an intramolecular cyclisation, as it is an intermediate in the proposed mechanism to form **227** (**Scheme 59**).



Scheme 62

In order to try to persuade the acetal, formed as an isolable intermediate, to cyclise towards synthesis of **221**, a range of Lewis acids was added to a stirring solution of cyclopropenylsilane **213** and 2-ethoxytetrahydrofuran **140** in DCM, $EtNO_2$ or MeCN (**Table 3**). The reaction mixtures were allowed to warm up slowly whilst the reaction was monitored by TLC. Lanthanide Lewis acids were among those chosen for these reactions, as recently they have became more common in reactions of allylsilanes and carbonyl compounds alongside the more conventional $TiCl_4$ and $BF_3{\cdot}Et_2O$.[115-117]

However, the only product formed was the acetal **231** with the yields and diastereomeric ratio varying a great deal. It was hoped that with MeCN, the cationic intermediate would be stabilised by the highly polar solvent and facilitate cyclisation, however the acetal was the only product isolated. For experiments with $La(OTf)_3$, the catalyst dissociates more in MeCN than in DCM and should increase the yields.[118] When MeCN was used in conjunction with $Yb(OTf)_3$, the yield was not higher than with DCM or $EtNO_2$. In addition, increasing the quantity of Lewis acid and 2-ethoxytetrahydrofuran **140** in the reaction, did not serve to increase the yield of the acetal and no other products were isolated.

Lewis acid	Solvent	Conditions[a]	Isomer Ratio[b]	Yield of 231[c]
$BF_3{\cdot}Et_2O$[d]	DCM	–78 °C, 1 h	–	Decomposed
	$EtNO_2$	–78 °C → –40 °C, 6 h	4:1	28
$BF_3{\cdot}2AcOH$[d]	DCM	–78 °C, 10 min	8:1	56
	$EtNO_2$	–70 °C, 2 h	20:1	45
	MeCN	–78 °C → –30 °C, 2 h	–	Decomposed
$InCl_3$	DCM	–78 °C → rt, 8 h	3:1	26
	$EtNO_2$	–78 °C → –40 °C, 6 h	2:3	10
$In(OTf)_3$	DCM	–78 °C → –10 °C, 9 h	6:1	42
	$EtNO_2$	–78 °C → –40 °C, 6 h	4:1	26
$Sc(OTf)_3$	DCM	–78 °C → –10 °C, 9 h	6:1	9
	$EtNO_2$	–78 °C → –60 °C, 4 h	4:1	34
$Yb(OTf)_3$	DCM	–78 °C → rt, 8 h	5:1	31
	$EtNO_2$	–78 °C → –40 °C, 6 h	4:1	31
	MeCN	–45 °C → rt, 22h	5:2	24
$SnCl_4$[d]	DCM	–78 °C, 1 h	–	Decomposed
	$EtNO_2$	–78 °C, 15 min	–	Decomposed
$TiCl_4$[d]	DCM	–78 °C, 15 min	–	Decomposed

a) Reactions were carried out with 0.215 mmol of **213**, 0.237 mmol of 2-ethoxytetrahydofuran and 0.022 mmol of Lewis acid in 0.5 mL of solvent. b) Isomer ratio determined by NMR peak integration. c) % yield of purified material after column chromatography. d) 0.237 mmol of Lewis acid.

Table 3

2.4 TMS protection of the alcohol.

Evidence shows that Lewis acids can mediate a reaction between a cyclopropenylsilane **213** and 2-ethoxytetrahydrofuran **140** to give the acetal. However, it was concerning that the reaction would not progress. This was perhaps due to the Lewis acid being affected by ethanol which was made as a by-product. Hence cyclisations were attempted using silylether **214** and 2-ethoxytetrahydrofuran **140** using the method previously described (**Scheme 63**). Once again however, the only product formed was the acetal **231**.

Scheme 63

	Using OTMS[a], 214		Using OH[b], 213	
Lewis acid	**Isomer Ratio[c]**	**Yield[d]**	**Isomer Ratio[c]**	**Yield[d]**
$In(OTf)_3$	4:1	68	6:1	42
$BF_3{\cdot}2AcOH$[e]	6:1	37	8:1	56
$Yb(OTf)_3$	4:1	44	5:1	31

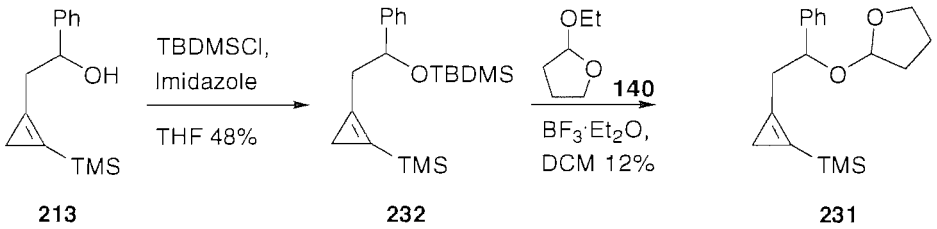
a) Reactions were carried out with 0.092 mmol of **214**, 0.184 mmol of 2-ethoxytetrahydofuran and 0.1 eq. of Lewis acid in 0.5 mL of solvent. b) Reactions were carried out with 0.215 mmol of **213**, 0.237 mmol of 2-ethoxytetrahydofuran and 0.1 eq. of Lewis acid in 0.5 mL of solvent. c) Isomer ratio determined by NMR peak integration. d) % yield of purified material after column chromatography e) 1.1 eq. of Lewis acid.

Table 4

In comparison to reactions with the cyclopropenylsilane **213**, the yields of acetal formation are better overall; the reaction is far cleaner and decomposition occurs far less readily (**Table 4**). The Lewis acid, however, hydrolyses silylether **214** back to the alcohol **213**.

Firstly, this makes it difficult to determine by TLC which species is undergoing the reaction and secondly, the Lewis acid is being used inefficiently.

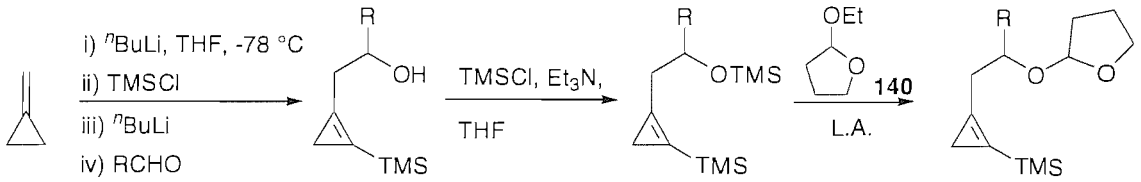
To circumvent the problem of TMS hydrolysis in the cyclisation reaction, TBDMS protection of the alcohol was investigated. Thus *tert*-butyldimethylsilyl protection of alcohol **213** was completed in moderate yield. Reaction with 2-ethoxytetrahydrofuran **140** under standard conditions gave acetal **231** in a low 12% yield when $BF_3{\cdot}Et_2O$ was used (**Scheme 64**). Other reaction conditions led to decomposition.



Scheme 64

2.5 Different R groups on the cyclopropenylsilane.

Three different alkyl groups were chosen to find out whether variation of the size of the alkyl group would allow formation of a cyclisation product rather than the acetal. Thus, methylenecyclopropane was deprotonated with one equivalent of ^{n}BuLi followed by addition of freshly distilled TMSCl. Another equivalent of ^{n}BuLi was added and the resulting anion was coupled with an aldehyde to give cyclopropenylsilanes **233** – **235** in moderate yields (**Scheme 65**). Reactions using alcohols **233** – **235** and 2-ethoxytetrahydrofuran with a range of Lewis acids led to decomposed materials, so trimethylsilyl protection of the alcohols was completed in moderate to quantitative yields using an adapted method of Corey.[114] Cyclisations were then attempted using silylethers **236** – **238** and 2-ethoxytetrahydrofuran in two different solvents. The reactions were tested with Lewis acids $In(OTf)_3$, $Yb(OTf)_3$ and $BF_3{\cdot}2AcOH$ at –78 °C or –40 °C depending on the solvent used (**Table 5**). Once more, the only isolable products were the acetals **239** – **241**.



1

233; R = ^{t}Bu, 44%
234; R = ^{i}Pr, 63%
235; R = Me, 27%

236; R = ^{t}Bu, 98%
237; R = ^{i}Pr, 42%
238; R = Me, 55%

239; R = ^{t}Bu
240; R = ^{i}Pr
241; R = Me

Scheme 65

R	Lewis acid	Solvent	Conditions[a]	Yield[c]
^{t}Bu	$In(OTf)_3$	DCM	–78 °C→ –25 °C, 1½ h	–[c]
		MeCN	–45 °C→–0 °C, 5 h	4
^{t}Bu	BF_3·2AcOH[d]	DCM	–78 °C→ –25 °C, 1½ h	–[c]
		MeCN	–45 °C→ –25 °C, 1½ h	Decomposed
^{i}Pr	$Yb(OTf)_3$	DCM	–78 °C → –10 °C, 7 h	30
		MeCN	–45 °C → rt, 28 h	8
^{i}Pr	BF_3·2AcOH[e]	DCM	–78 °C, ½ h	Decomposed
		MeCN	–45 °C, 5 min	Decomposed
^{i}Pr	$In(OTf)_3$	MeCN	–45 °C → –10 °C, 7½ h	7
Me	$Yb(OTf)_3$	DCM	–78 °C → –10 °C, 7 h	26
Me	$In(OTf)_3$	DCM	–78 °C → –10 °C, 5 h	13

a) Reactions were carried out with 1 eq. of cyclopropenylsilane, 1.1 eq. of 2-ethoxytetrahydofuran and 0.1 eq. of Lewis acid in 0.5 mL of solvent. b) % yield of purified material after column chromatography. c) Hydrolysed starting material. d) 1.1 eq. of Lewis acid.

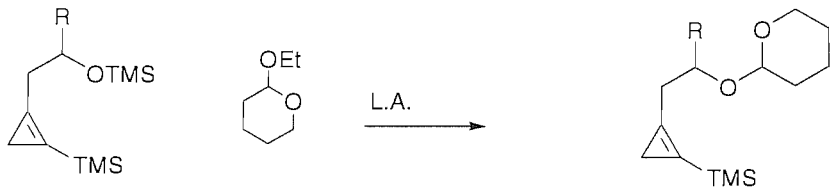
Table 5

Overall the yields of acetal formation are low due to the starting material not being consumed and to the Lewis acid hydrolysing the TMS protection of the alcohol. For

acetal **239** (R = ^{t}Bu), although it was evident from the NMR that the acetal had been formed, it could not be separated from the starting material.

2.6 Reactions using 2-ethoxytetrahydropyran.

It was hoped that by changing the ring-size of the electrophile, a 6,7-bicyclic system could be synthesised. The reactions were varied by using 2-ethoxytetrahydropyran **242** instead of 2-ethoxytetrahydrofuran. No reaction occurred when Lewis acids $BF_3{\cdot}2AcOH$, $BF_3{\cdot}Et_2O$ and $In(OTf)_3$ were used to catalyse the reaction with alcohols **214** and **236** – **238**, so silylethers **243** – **246** were treated with 2-ethoxytetrahydropyran **242** under a range of conditions (**Scheme 66**).



214; R = Ph
236; R = ^{t}Bu
237; R = ^{i}Pr
238; R = Me

242

243; R = Ph
244; R = ^{t}Bu
245; R = ^{i}Pr
246; R = Me

Scheme 66

In each case, the only isolated products were acetals **243** – **246** (**Table 6**). Reactions in MeCN gave the best yields with R = phenyl (**214**) giving the highest yield of the acetal **243** when $Yb(OTf)_3$ was used.

R	Lewis acid	Solvent	Conditions[a]	Yield[b]
Ph	$BF_3{\cdot}2AcOH$[c]	MeCN	–45 °C→ –10 °C, 1¼ h	10
	$Yb(OTf)_3$	MeCN	–45 °C → 0 °C, 5½ h	52
^{t}Bu	$BF_3{\cdot}2AcOH$[c]	MeCN	–45 °C→ –10 °C, 1¼ h	Decomposed
	$In(OTf)_3$	MeCN	–45 °C→ –20 °C, 1½ h	12
^{i}Pr	$Yb(OTf)_3$	DCM	–78 °C → rt, 48 h	No reaction
		MeCN	–45 °C → 0 °C, 6½ h	30
	$In(OTf)_3$	DCM	–78 °C → –10 °C, 5 h	16
		MeCN	–45 °C → –10 °C, 6 h	24
Me	$Yb(OTf)_3$	MeCN	–45 °C → –10 °C, 6 h	25
	$In(OTf)_3$	MeCN	–45 °C, 1 h	32

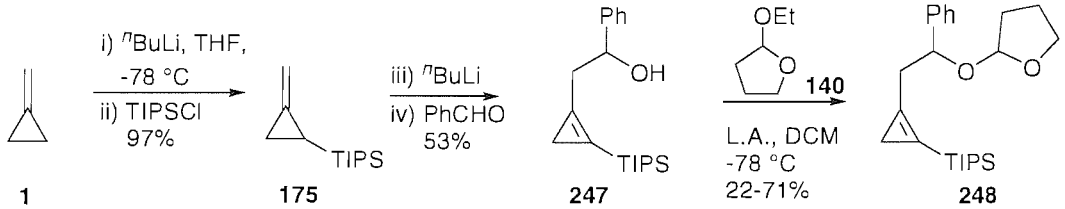
a) Reactions were carried out with 1 eq. of the cyclopropenylsilane, 1.1eq. of 2-ethoxytetrahydofuran and 0.1 eq. of Lewis acid. in 0.5 mL of solvent. b) % yield of purified material after column chromatography. c) 1.1 eq. of Lewis acid.

Table 6

2.7 Variation of the silyl group.

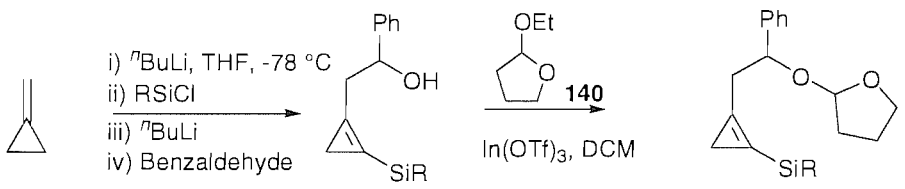
During discussion with Dobbs on silyl-Prins type cyclisation reactions, we were advised to modify the reaction by using a triisopropylsilyl group rather than a trimethylsilyl group, as it could aid cyclisations. The more electron-donating TIPS group is very good at stabilising a β-silyl cation.[119] Furthermore, triisopropylsilyl-methylenecyclopropane (TIPSMCP) is much more convenient to handle than its TMS analogue.[23] Consequently, TIPSMCP **175** was synthesised from methylenecyclopropane **1** in excellent yield using the method of Patient (**Scheme 67**).[23] Deprotonation with ^{n}BuLi followed by reaction with benzaldehyde formed cyclopropenylsilane **247** in moderate yield. Reactions between

cyclopropenylsilane **247** and 2-ethoxytetrahydrofuran **140** were carried out using $Yb(OTf)_3$, $In(OTf)_3$, $BF_3{\cdot}Et_2O$, $BF_3{\cdot}2AcOH$, $TiCl_4$ and $SnCl_4$. The reactions were much cleaner and higher yielding but the product formed was acetal **248** and not the desired cyclic compound. Interestingly, when $BF_3{\cdot}2AcOH$ was used, a dihydrofuran was also formed (**see section 2.11**).



Scheme 67

By varying the silyl group, the electron donating effect on the cation, β to the silyl group will be altered. An increase in the ability of the silyl group to donate will mean that a β-cation or an allylcation, β to the silyl group, will be more stabilised. Thus, deprotonation of methylenecyclopropane **1** with ^{n}BuLi was followed by coupling with R_3SiCl (**Scheme 68**). A further deprotonation with ^{n}BuLi and addition of benzaldehyde gave the desired cyclopropenylsilanes **249** – **252** and **223**. A solution of cyclopropenylsilane **249** – **252** and **223** and 2-ethoxytetrahydrofuran **140** was treated with $In(OTf)_3$ at –78 °C and allowed to warm up slowly (**Scheme 68**). $In(OTf)_3$ was used because it gave the best yield for the TIPSMCP series.



249; R = Et_3, 32%
250; R = ^{i}Pr$(Me)_2$, 43%
251; R = ^{t}Bu$(Me)_2$, 28%
252; R = cyclohexane$(Me)_2$, 51%
223; R = phenyl$(Me)_2$, 85%

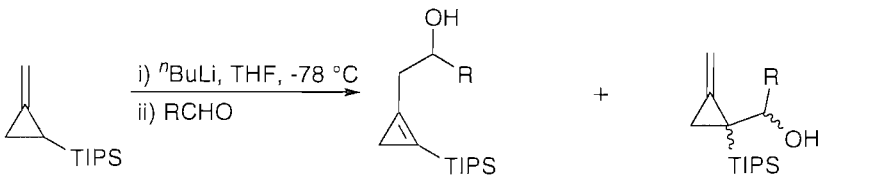
253; R = Et_3, 52%
254; R = ^{i}Pr$(Me)_2$, 47%
255; R = ^{t}Bu$(Me)_2$, 42%
256; R = cyclohexane$(Me)_2$, 33%
257; R = phenyl$(Me)_2$, 38%

Scheme 68

The reactions were closely monitored by TLC but the only products isolated from these reactions were the acetals **253** – **257** and the unused cyclopropenylsilane in good mass balance. Increasing the amount of 2-ethoxytetrahydrofuran in the reaction did not significantly vary the yield.

2.8 Different R group substitution on the cyclopropenylsilane.

The R group was altered to establish whether a product other than the acetal could be formed. Thus, TIPSMCP **175** was deprotonated with ^{n}BuLi and three different aldehydes were added to the resulting anion to give cyclopropenylsilanes **258** – **260** (**Scheme 69**). In contrast to the isopropyl example in the TMSMCP series, where the sole product was a cyclopropene, disubstituted methylenecyclopropane **262** was also created as a 7:5 mixture of diastereoisomers. Similarly, when the methylenecyclopropyl anion was quenched with freshly distilled acetaldehyde, compounds **260** and **263** were the products isolated. 1,1-Disubstituted methylenecyclopropanes were not produced when the silyl group was TMS, so formation of **262** and **263** was not expected to occur due to the steric bulk of the TIPS group.



175

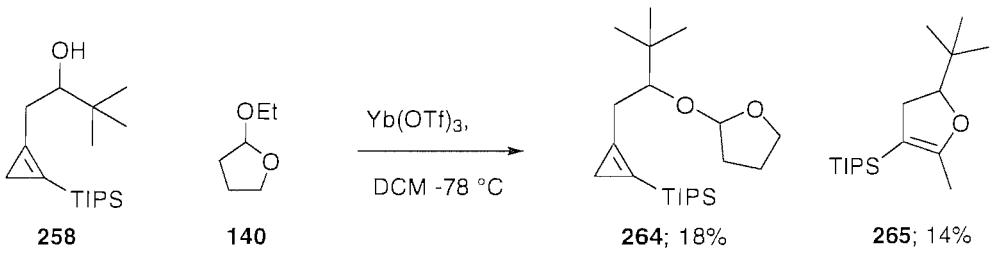
258; R = ^{t}Bu, 44%
259; R = ^{i}Pr, 35%
260; R = Me, 16 %

261; R = ^{t}Bu, 0%
262; R = ^{i}Pr, 12%
263; R = Me, 7%

Scheme 69

Cyclisations were attempted with cyclopropenylsilane **258** (R = ^{t}Bu) using 2-ethoxytetrahydrofuran **140** in DCM and a range of Lewis acids (**Scheme 70**). When using $Yb(OTf)_3$, cyclopropenylsilane **258** reacts with 2-ethoxytetrahydrofuran **140** to give acetal **264**, however, as with the TMS analogue, acetal **264** could not be separated from

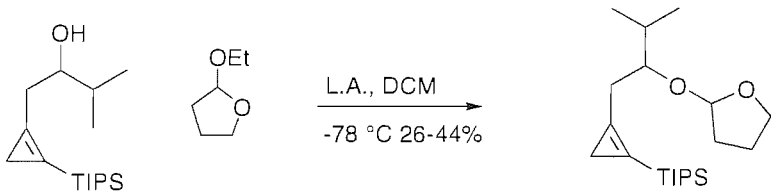
the starting material **258**. Cyclopropenylsilane **258** also cyclises intramolecularly to give dihydrofuran **265** in a similar yield (**see section 2.11**).



258 **140** **264**; 18% **265**; 14%

Scheme 70

Reaction between cyclopropenylsilane **259** with 2-ethoxytetrahydrofuran furnished acetal **266** in 26% and 44% yields with $BF_3{\cdot}Et_2O$ and $In(OTf)_3$ respectively (**Scheme 71**). No intramolecular cyclisation products were isolated.



259 **140** **266**

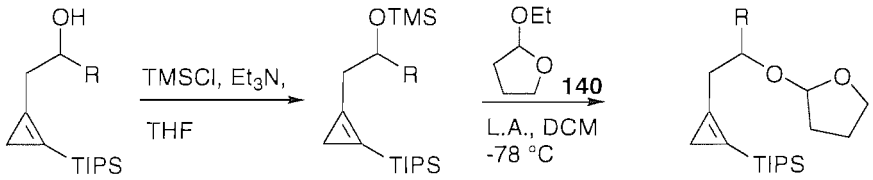
Scheme 71

Attempted reactions of cyclopropenylsilane **260** (R = Me) with 2-ethoxytetrahydrofuran with a range of Lewis acids did not lead to any products and the reaction mixtures decomposed.

2.9 Protection of the alcohol with a TMS group.

Since protection of alcohol **213** with a TMS group gave cleaner reactions for the TMSMCP series of compounds, the alcohols in the TIPSMCP series (**258**, **259** and **247**) were also protected with a TMS group (**267** – **269**) (**Scheme 72**). The yields for TMS protection of the alcohol were low because the reactions did not go to completion and the products were

isolated along with left-over starting material. Reactions of these silylethers **267** – **269** with 2-ethoxytetrahydrofuran were not any cleaner than reactions with alcohols **258**, **259** and **247** and only gave low yields of the undesired acetals **264**, **266** and **248**.



258; R = ^{t}Bu
259; R = ^{i}Pr
247; R = Ph

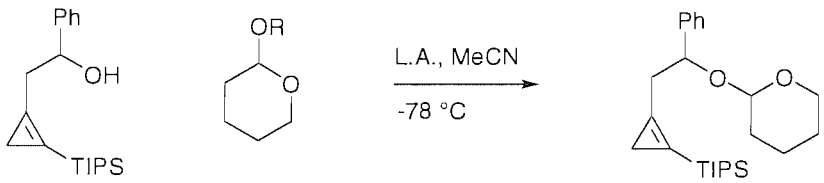
267; R = ^{t}Bu, 53%
268; R = ^{i}Pr, 52%
269; R = Ph, 80%

264; R = ^{t}Bu, 0%
266; R = ^{i}Pr, 9-22%
248; R = Ph, 37-64%

Scheme 72

2.10 Reactions with 2-ethoxytetrahydropyran.

Reactions between alcohol **247** and 2-ethoxytetrahydropyran **242** were carried out to give acetal **271** in yields of 25% and 18% with Lewis acids $Yb(OTf)_3$ and $BF_3{\cdot}2AcOH$ respectively (**Scheme 73**). 2-Methoxytetrahydropyran **270** was also used in attempt to facilitate loss of a better leaving group and make the reaction cleaner and quicker, however, it provided poorer yields of acetal **271**.



247

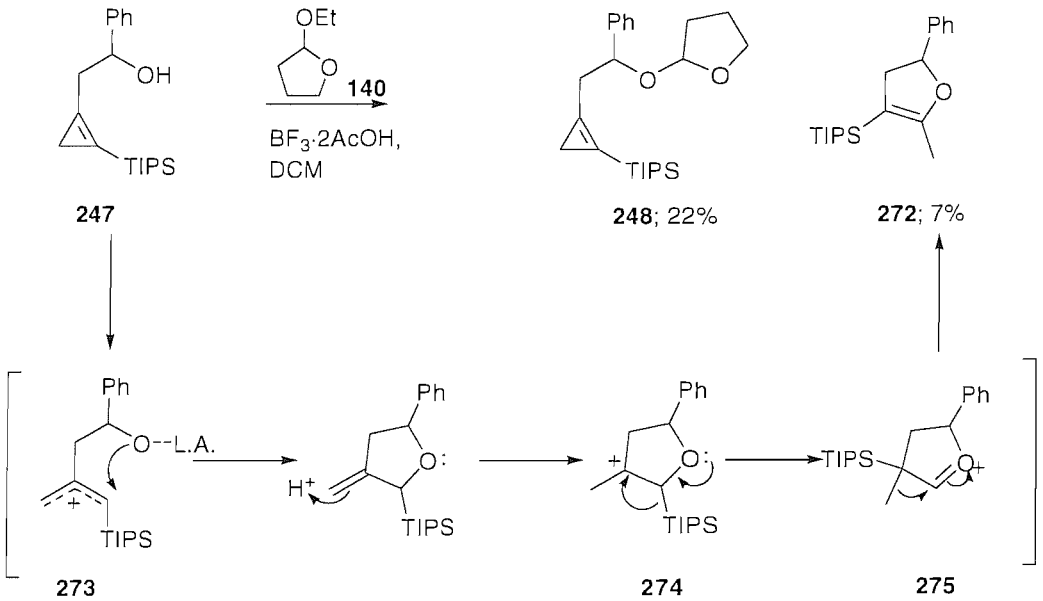
242; R = Et
270; R = Me

271

Scheme 73

2.11 Intramolecular reactions to make dihydrofurans.

Interestingly, when a reaction was carried out between cyclopropenylsilane **247** and 2-ethoxytetrahydrofuran **140** with $BF_3 \cdot 2AcOH$ as the Lewis acid, dihydrofuran **272** was also formed, presumably *via* the mechanism shown (**Scheme 74**).



Scheme 74

The Lewis acid co-ordinates to the alcohol and the formed alkoxide intramolecularly attacks the allyl cation intermediate (**273**) thus giving the β-silyl cation **274** which after quench from a proton gives cation 274. A 1,2-silyl shift can then occur to give oxonium ion **275** followed by a 1,2-alkyl shift to give dihydrofuran **272**.

Supporting evidence for the formation of this dihydrofuran can be shown by comparison of the NMR spectra to a similar compound.[120] In particular, the ^{13}C spectrum illustrates similarities between the unsaturated portion of the dihydrofuran (**Figure 4**).

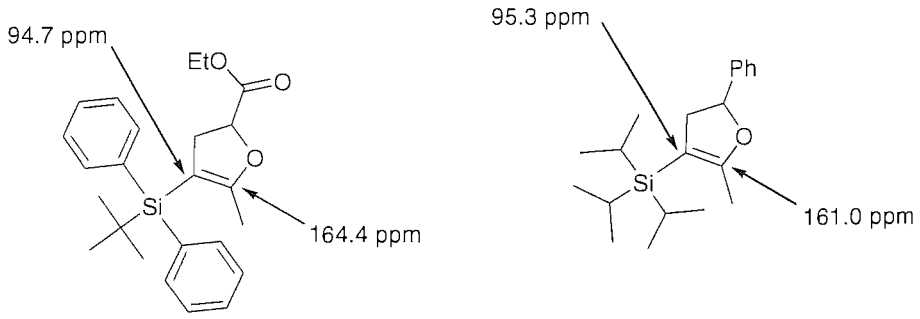


Figure 4 Comparison of ^{13}C NMR peaks.

Coupling patterns between ring protons H_A, H_B and H_C are consistant with the dihydrofuran structure (**Figure 5**). Whilst COSY experiments showed some allylic coupling between H_AH_B and CH_3, NOE studies showed no enhancement in the CH_3 when H_A, H_B or H_C were irradiated. HMQC experiments were also used to confirm the structure of the dihydrofuran.

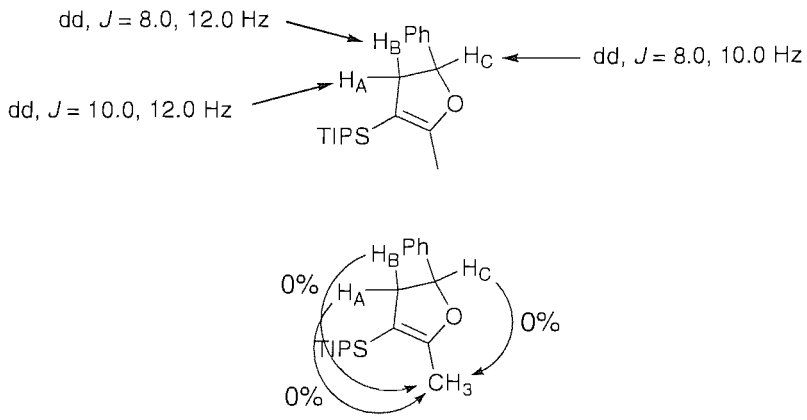
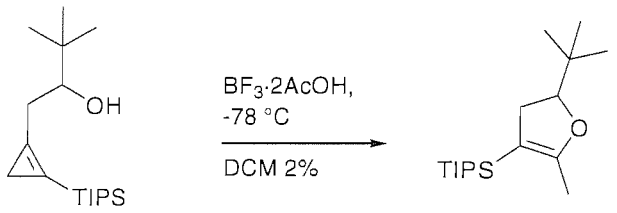


Figure 5 Coupling patterns of dihydrofuran **272**.

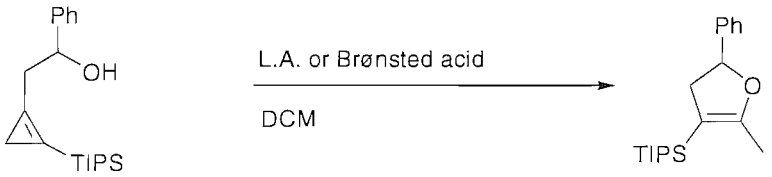
Dihydrofuran **265** (R = ^{t}Bu) was also formed as a side product in the reaction between cyclopropenylsilane **258** and 2-ethoxytetrahydrofuran when $Yb(OTf)_3$ was used to catalyse the reaction (**see section 2.8**). $BF_3{\cdot}2AcOH$ catalysed intramolecular cyclisation of cyclopropenylsilane **258** occurred without 2-ethoxytetrahydrofuran in the reaction mixture, giving dihydrofuran **265** in a very low yield which could not be optimised (**Scheme 75**).



258 **265**

Scheme 75

The formation of dihydrofuran **272** was investigated using cyclopropenylsilane **247** in the presence of a range of Lewis acids and two Brønsted acids (**Scheme 76**). The acid was added to a solution of cyclopropenylsilane **247** in DCM at –78 °C. The reaction mixtures were allowed to warm up slowly whilst the reaction was monitored by TLC.



247 **272**

Scheme 76

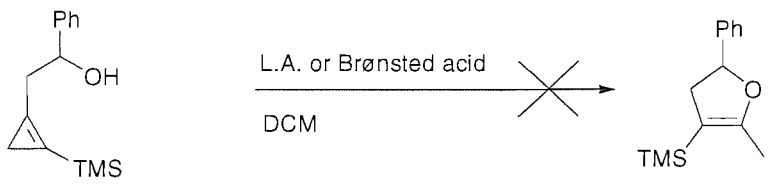
Without the presence of 2-ethoxytetrahydrofuran, and therefore the competing reaction of acetal formation, these reactions proceeded in moderate yields, and with reasonable mass balance of isolated products (**Table 7**). By analogy to Peron's work (**Scheme 43, Introduction**) it could be expected that a quench of the allyl cation **273** (**Scheme 74**) could take place from the nucleophilic Lewis acid $TiCl_4$.[109] It is therefore interesting that intramolecular quench from the alkoxide intermediate **273** is more rapid than intermolecular quench from the Cl^- ion.

Lewis or Brønsted acid	**Conditions**[a]	**Yield** [b]	**Recovered starting material**[c]
$BF_3{\cdot}2AcOH$	–78 °C → –45 °C, 5 h	50	0
$BF_3{\cdot}Et_2O$	–78 °C → –65 °C, 3 h	32	50
$TiCl_4$	–78 °C, ½ h	38	0
$In(OTf)_3$[d]	–78 °C → –60 °C, 5 h	43	18
p-TsOH[e]	rt, 18 h, sieves	No reaction then decomposed	
TFA[e]	rt, 45 h, sieves	27	40

a) Reactions carried out with 0.158 mmol of cyclopropenylsilane **247** and 0.174 mmol of Lewis acid in 1 mL of solvent. b) % yield of purified material after column chromatography. c) % of cyclopropenylsilane **247** isolated. d) 0.174 mmol of Lewis acid. e) 0.016 mmol of Brønsted acid.

Table 7

An analogous reaction was attempted using TMS substituted cyclopropenylsilane **213** with the Lewis acids $BF_3{\cdot}2AcOH$, $BF_3{\cdot}Et_2O$, $TiCl_4$, and $SnCl_4$, in order to establish whether dihydrofuran **276** could be synthesised when there was not the competing acetal formation reaction (**Scheme 77**). The Lewis acid was added to cyclopropenylsilane **213** at –78 °C and the reaction mixture was allowed to warm up slowly whilst the reaction was monitored by TLC. There was no change to the reaction mixture at all until the reaction warmed up, at which point decomposition occurred for each reaction.

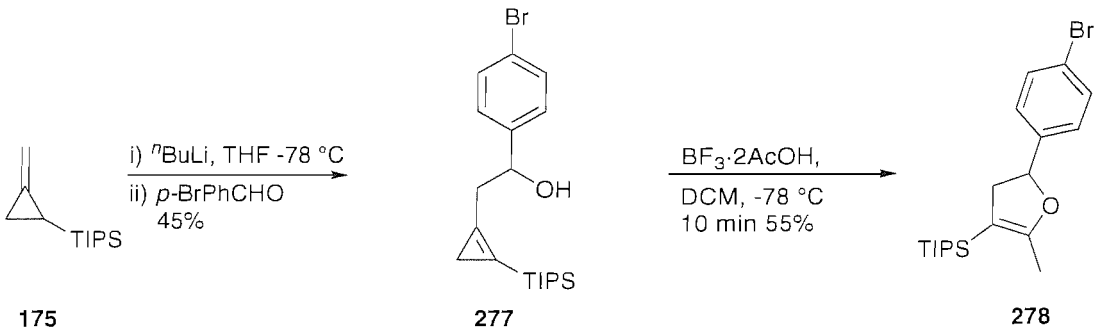


213 **276**

Scheme 77

It is thought that for cyclopropenylsilane **213**, the reaction does not occur because the TMS group is less stabilising towards a β-silyl cation than a TIPS group (e.g. **274 Scheme 74**), therefore this intermediate is less likely to occur.

In endeavouring to synthesise a crystalline dihydrofuran, *p*-bromophenol cyclopropenylsilane **277** was synthesised from TIPSMCP in good yield. BF_3·2AcOH was added to a solution of cyclopropenylsilane **277** in DCM at –78 °C and the reaction mixture was allowed to warm up slowly whilst the reaction was monitored by TLC. Dihydrofuran **278** was obtained in moderate yield but unfortunately the product could not be obtained as a crystalline solid (**Scheme 78**).

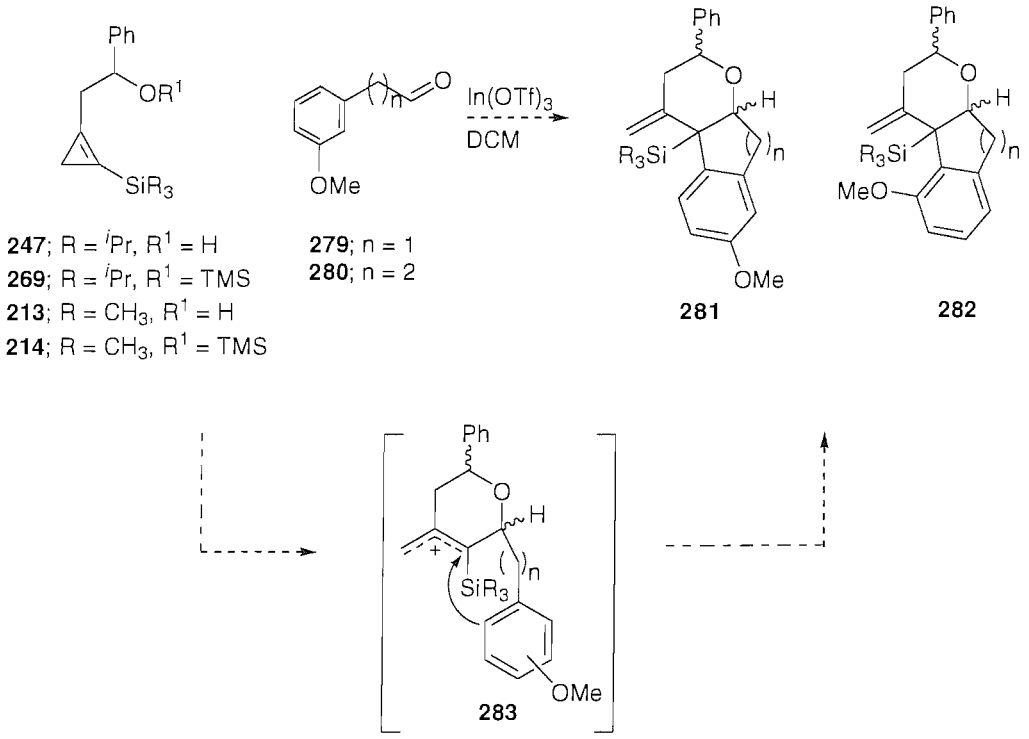


175 277 278

Scheme 78

2.12 Quench from a nucleophilic carbon.

Intermolecular reactions of an aldehyde with a nucleophilic carbon instead of a nucleophilic oxygen were attempted in the hope that successful addition to the allyl cation intermediate **283** could be facilitated (**Scheme 79**).



247; R = ^{i}Pr, R^1 = H
269; R = ^{i}Pr, R^1 = TMS
213; R = CH_3, R^1 = H
214; R = CH_3, R^1 = TMS

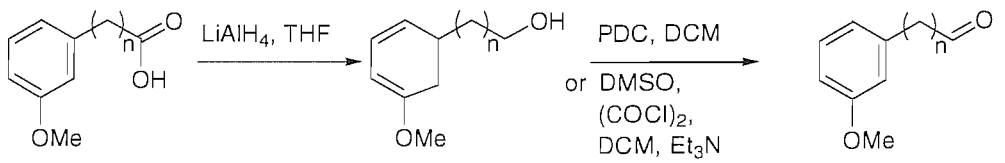
279; n = 1
280; n = 2

281 **282**

283

Scheme 79

Carboxylic acids **284** and **285** were reduced in quantitative yield to the alcohols **286** and **287** using $LiAlH_4$, which were oxidised to the aldehydes **279** and **280** using PDC and Swern methods respectively (**Scheme 80**).



284; n = 1
285; n = 2

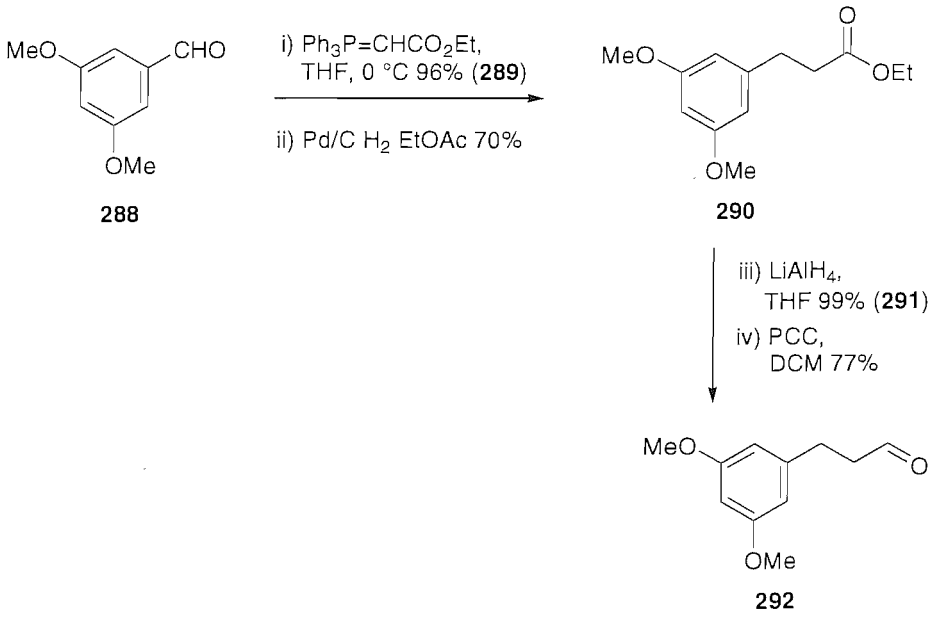
286; n = 1, 98%
287; n = 2, 96%

279; n = 1, 12%
280; n = 2, 43%

Scheme 80

Reactions of aldehydes **279** and **280** with alcohols **247** and **213** and silylethers **269** and **214** in the presence of a range of different Lewis acids were attempted. For silylether **269**, the reaction gave one isolable product in very low yield as a single spot by TLC. This spot, however, proved to be more than one product which could not be separated by HPLC. These products were presumably both diastereoisomers of both **281** and **282**. To

circumvent this problem, aldehyde **292** was synthesised according to the method of Nikas (**Scheme 81**).[121] Using aldehyde **292** there is not the opportunity for two regioisomers (i.e. **281** and **282**) to be formed, only the diastereoisomers, so the spectra should be easier to interpret.



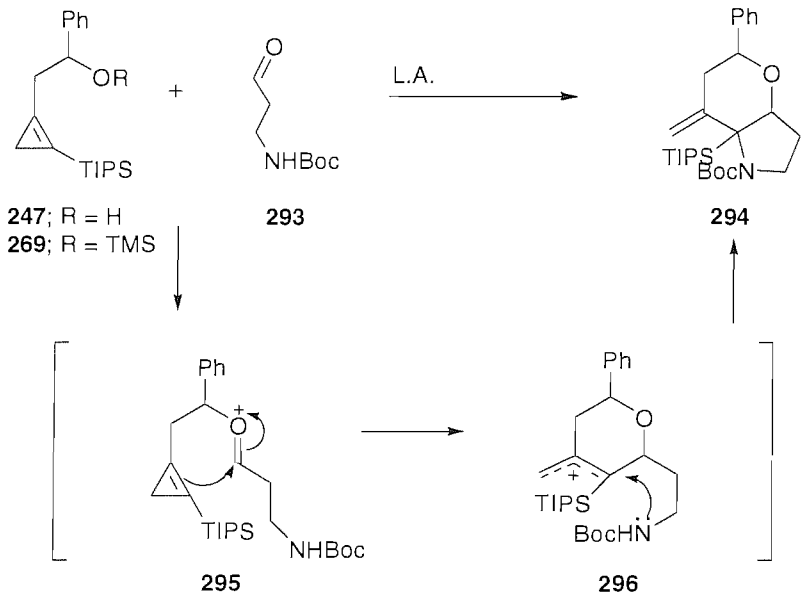
Scheme 81

Aldehyde **288** was coupled to (carbethoxymethylene)triphenylphosphorane in excellent 96% yield followed by hydrogenation of the double bond to give ester **290**. Reduction of the ester to the alcohol with $LiAlH_4$ in 97% was followed by oxidation with PCC to furnish aldehyde **292** in 77% yield.

Cyclisation reactions of alcohol **247** and silylether **269** were attempted with aldehyde **292** under standard conditions. A product was produced which was similar to the product formed when 3-[3-(methoxy)phenyl]propanal **280** was used, as indicated by the virtually identical and very complicated NMR spectra. However, the product from this reaction could not be purified by either HPLC or Mass Directed HPLC and its structure could not be identified unambiguously.

2.13 Nitrogen as a nucleophilic allyl cation quenching agent.

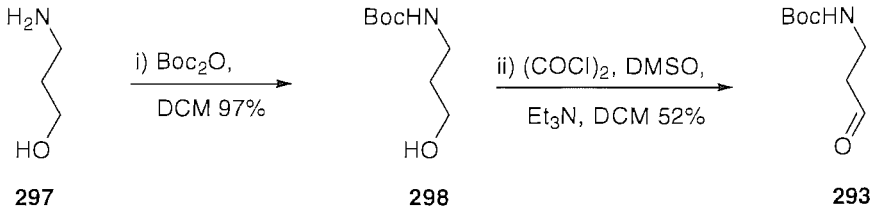
Since nucleophilic quench from an electron-rich phenyl group and from an oxygen proved to be unsuccessful, a pendant nucleophilic nitrogen was incorporated into the molecule instead (**Scheme 82**).



Scheme 82

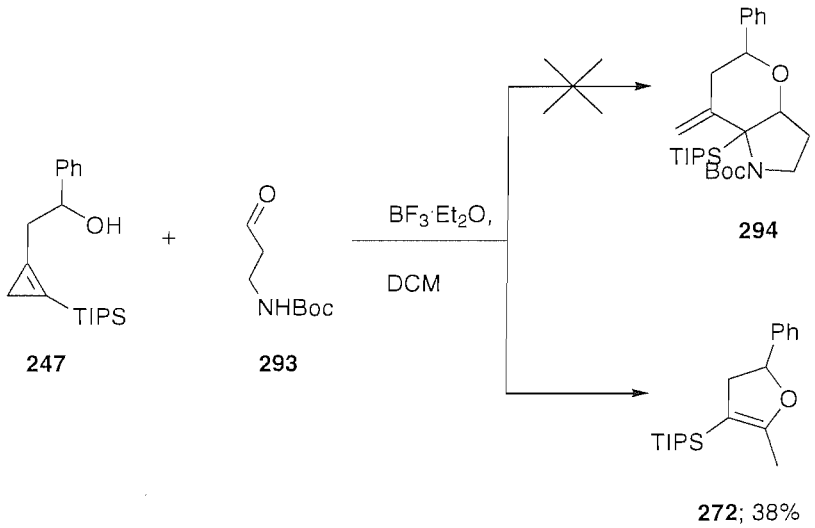
Reaction between alcohol **247** or silylether **269** and aldehyde **293** was expected to give oxonium ion **294**. Attack from the double bond should form allyl cation **296**. Trapping from the *N*-Boc-protected amine intramolecularly should give rise to **294**.

3-Amino-propanol **297** was treated with di-*tert*butyldicarbonate to give the Boc-protected amine **298** in excellent yield which was then oxidised to the aldehyde **293** under Swern conditions (**Scheme 83**).[122]



Scheme 83

Cyclisations were attempted with alcohol **247** and silylether **269** in the presence of different Lewis acids ($In(OTf)_3$, $Sc(OTf)_3$, $BF_3{\cdot}2AcOH$ and $Yb(OTf)_3$) in DCM at – 78 °C. The reaction mixtures were allowed to warm up slowly whilst being monitored by TLC. However, the reaction mixtures underwent decomposition and faint amounts of products that were visible by TLC, decomposed on the column. When $BF_3{\cdot}Et_2O$ was used, the only isolated product was dihydrofuran **272** in 38% yield (**Scheme 84**). This implies that the intramolecular reaction was faster than formation of oxonium ion **295**.

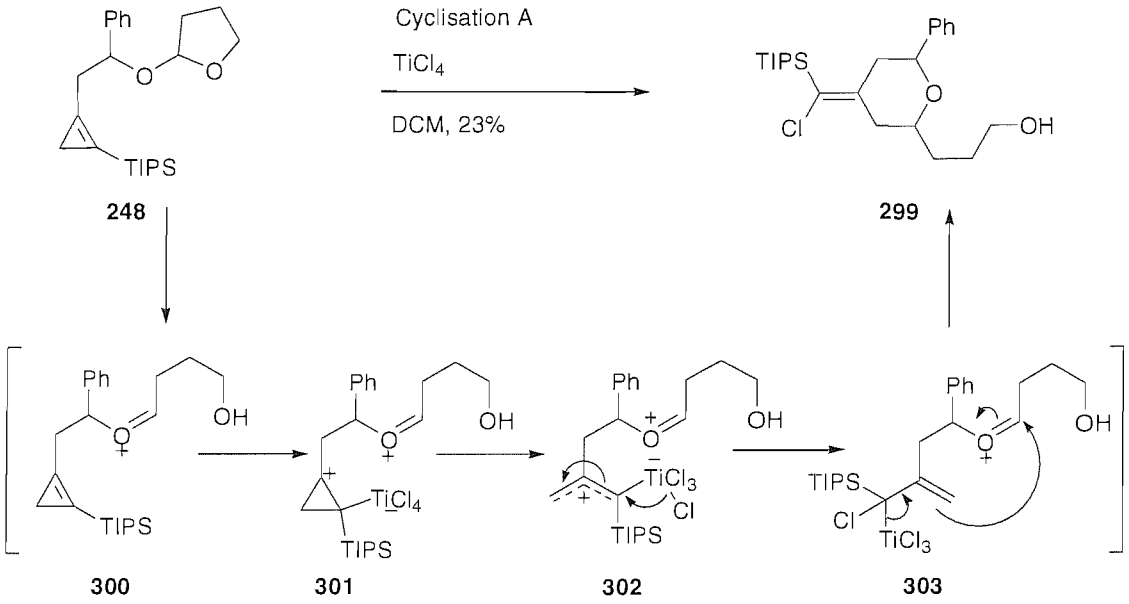


Scheme 84

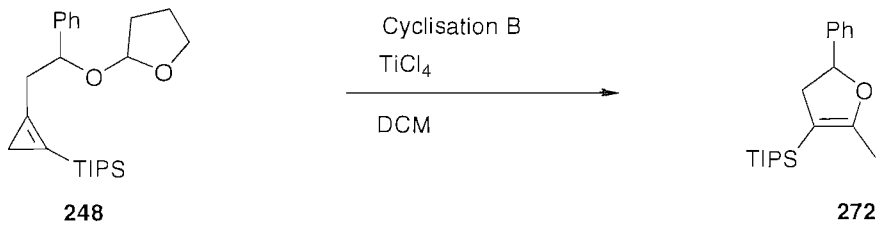
2.14 Cyclisations using an acetal.

It was of interest to see whether intramolecular cyclisations of acetal **248** could be facilitated by a Lewis acid. $TiCl_4$ was added to a solution of acetal **248** in DCM at -78 °C

and the reaction monitored by TLC. One cyclisation occurred to give pyran **299** (**Scheme 85**) and another occurred to give dihydrofuran **272** (**Scheme 86**). A possible mechanism for the formation of pyran **299** involves formation of oxonium ion **300** followed by metallation of the double bond moiety of the cyclopropene (**301**). Ring opening followed by rearrangement to give titanium species **302** followed by loss of $TiCl_3$ facilitates the cyclisation to give tetrahydropyran **299**.



Scheme 85



Scheme 86

The reaction was screened with a range of Lewis acids and two Brønsted acids under the conditions shown. $TiCl_4$ is the only Lewis acid to give compound **299**, albeit very rapidly with a mixture of unidentifiable side products (**Table 8**). Other conditions led to

production of dihydrofuran **272** and isolation of the alcohol **247**, formed *via* hydrolysis of acetal **248**.

Lewis or Brønsted acid	**Conditions**[a]	**Yield of cyclisation A**[b]	**Yield of cyclisation B**[b]	**Recovered alcohol 247**[c]
$TiCl_4$	–78 °C, 10 min, DCM	23	22	6
	–100 °C, 15 min, DCM	22	–	5
	–100 °C, 1 h, $EtNO_2$	–	27	27
$SnCl_4$	–100 °C→ –60 °C, 4 h, DCM	–	53	23
	–100 °C, 4 h, $EtNO_2$	–[d]	–	12
$In(OTf)_3$[e]	–78 °C → –10 °C, 6 h, DCM	No reaction then decomposed		
$BF_3{\cdot}Et_2O$	–78 °C → rt, 24 h, DCM	No reaction then decomposed		
$BF_3{\cdot}2AcOH$	–78 °C → –55 °C, 2 h, DCM	–[f]	37	12
	–78 °C → –60 °C, 3 h, $EtNO_2$	–[d]	45	7
p-TsOH	rt, 72 h, sieves, DCM	–	9	83
TFA	rt, 45 h, sieves, DCM	–[g]	9	37

a) Reactions carried out with 0.129 mmol of acetal **248**, 0.129 mmol of Lewis acid (or 0.013 mmol of *p*-TsOH or TFA) in 1 mL of solvent b) % yield of purified material after column chromatography. c) % of compound **247** isolated. d) 25% starting material **248** recovered. e) 0.013 mmol of Lewis acid f) 27% starting material **248** recovered. g) 40% of starting material **248** recovered.

Table 8

To elucidate stereochemistry of **299**, GOESY experiments were conducted. Irradiation of H_A caused 2.66% enhancement in H_B and only 0.35% enhancement in H_C (**Figure 6**). Irradiation of H_B caused 2.10% enhancement in H_A and no enhancement on the phenyl group. This evidence suggests that H_A and H_B are in close proximity so the relative stereochemistry of **299** can be safely assumed to be the *cis* isomer.

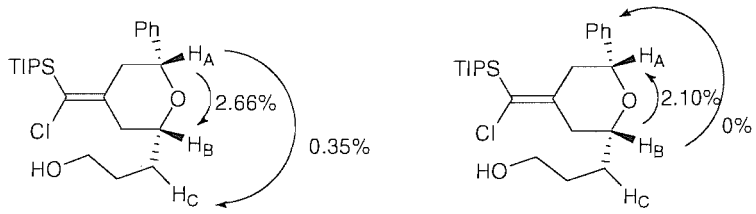


Figure 6 GOESY studies of **299**.

Although irradiation of H_E caused no enhancement in H_H, irradiation of H_D caused 4.93% enhancement in the isopropyl proton H_H (**Figure 7**). Irradiation of H_F and H_G caused no enhancement on the isopropyl proton H_H. This evidence suggests that H_D and the TIPS group are in close proximity so the relative stereochemistry of **299** can be assumed to be as shown.

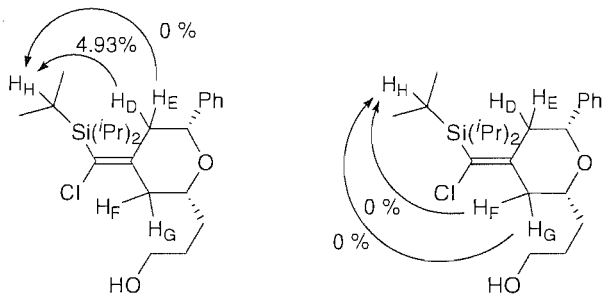


Figure 7 GOESY studies of **299**.

2.15 Conclusions.

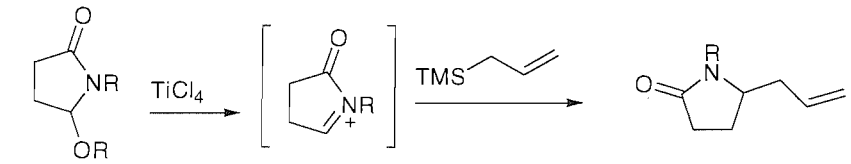
In conclusion, reaction of cyclopropenylsilanes with a range of aldehydes did not lead to formation of a cyclised product. Although it was thought that there were problems associated with the trapping of the allyl cation intermediate, the presence of a pendant alcohol, a Boc-protected amine or an electron rich aromatic group did not lead to cyclised compounds. Reactions of cyclopropenylsilanes with 2-ethoxytetrahydrofuran predominantly furnished acetals, even when the silyl and the R groups were varied. For the TIPSMCP series and using a range of Lewis acids, cyclopropenylsilanes **258**, **247** and **277** were found to undergo a novel intramolecular reaction to give dihydrofurans **265**, **272** and **278**, respectively, in moderate yields. Intermolecular reaction of acetal **248** in the presence of $TiCl_4$ underwent a novel cyclisation to give pyran **299** and dihydrofuran **272** reproducibly. When other Lewis acids were used, dihydrofurans and hydrolysed starting materials were the only observed products.

It was proved that cyclopropenylsilanes can be synthesised in a facile manner with a wide range of different silyl and R groups.

Chapter 3 Intermolecular reactions of methylenecyclopropane and *N*-acyliminium ions.

3.1 Aims.

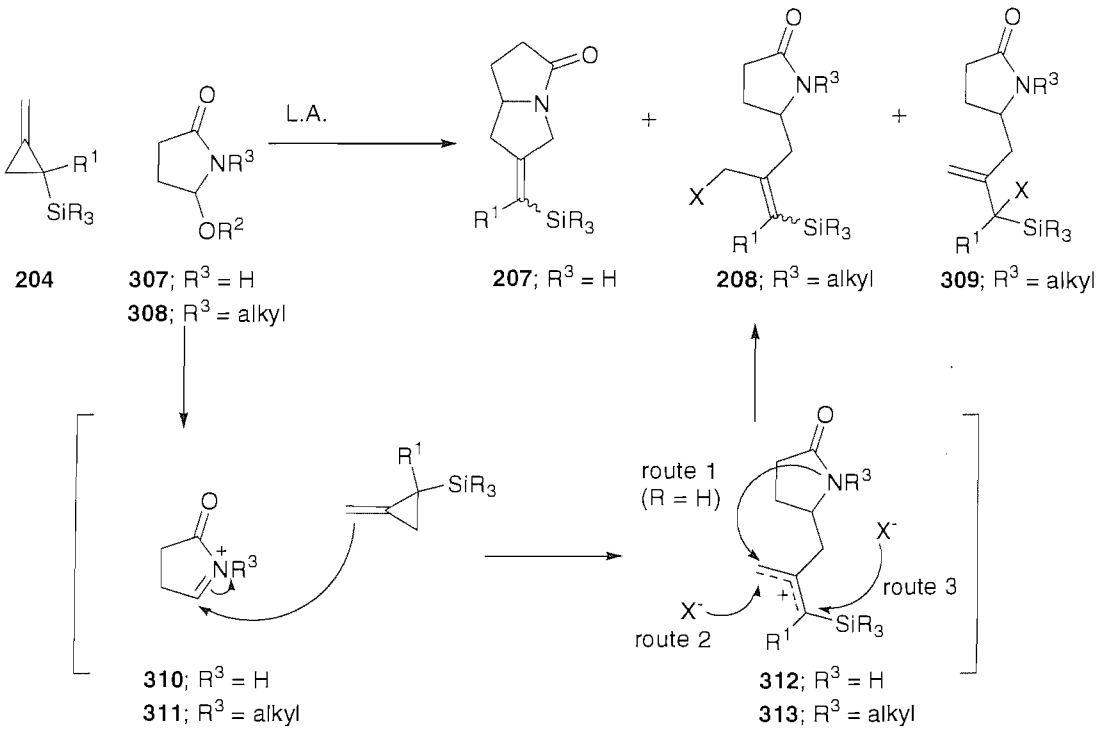
Lewis acid mediated addition of allylsilanes to *N*-acyliminium ions has been researched extensively, both intramolecularly and intermolecularly and the topic is discussed in an excellent review by Maryanoff *et al.*[97] 3-Trimethylsilylprop-1-ene (allylTMS), in particular, in combination with $TiCl_4$, has been used to synthesise various allyl lactams (**306**) from γ-hydroxy- and alkoxylactams (**304**) *via* *N*-acyliminium ions (**305**) (**Scheme 87**)[123-125]



304; R = H, alkyl **305** **306**

Scheme 87

Since silyl substituted methylenecyclopropanes are, in effect, highly strained allylsilane equivalents, the aim of this research was to study addition of methylenecyclopropane to an *N*-acyliminium species to discover whether heterocycles **207**, **208** and **309** can be formed efficiently (**Scheme 88**).



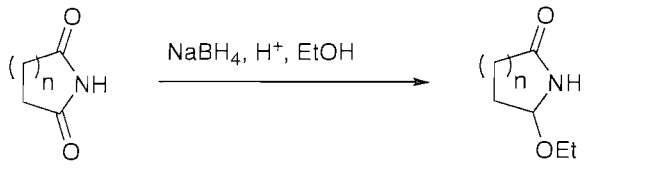
Scheme 88

The presence of the Lewis acid should facilitate formation of *N*-acyliminium ion **310** or **311** which should undergo attack from the nucleophilic double bond of the methylenecyclopropane leading to allyl cations **312** and **313** respectively. Attack from the lone pair of the nitrogen of **312** (route 1) should lead to cyclic system **207** (R = H). For intermediate **313** (R = alkyl), quench from the Lewis acid should lead to lactams **208** and/or **309** (route 2 or 3).

3.2 Synthesis of precursors.

One of the most successful and versatile methods of obtaining *N*-acyliminium ion precursors has been partial reduction of cyclic imides *via* selective addition of hydride to one of the carbonyl components.[98, 126] Various methods are available to perform this conversion and the most commonly described are; sodium borohydride in ethanol with a strong protic acid at 0 °C and sodium borohydride in methanol between –20 °C and 0 °C.[98] The specific reaction conditions are important to ensure that over-reduction, leading to ring

opening of the cyclic imide, does not take place. Thus, ethoxy lactams **316** and **317** were synthesised using the method of Hubert *et al.* in reasonable yields from succinimide **314** and glutarimide **315**, respectively (**Scheme 89**).[126]

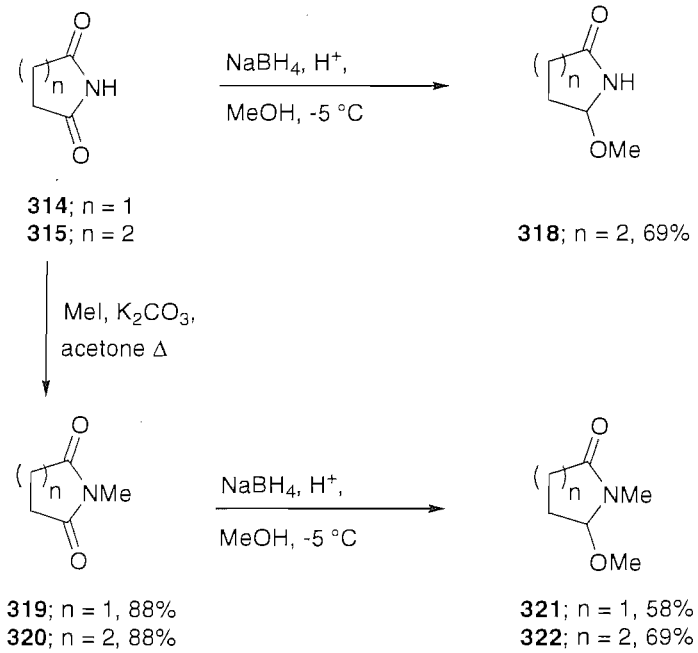


314; n = 1
315; n = 2

316; n = 1, 48%
317; n = 2, 50%

Scheme 89

The yields were lower than desired and these results were difficult to reproduce because the amount of acid used in the reaction was not specified. As a result, another method by Klaver *et al.* was utilised in which the reaction is carried out in MeOH at lower temperatures and a specific amount of HCl is added to the reaction mixture (**Scheme 90**).[127]



314; n = 1
315; n = 2

318; n = 2, 69%

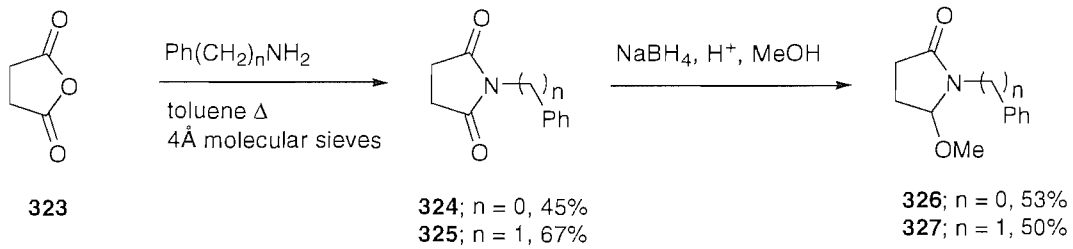
319; n = 1, 88%
320; n = 2, 88%

321; n = 1, 58%
322; n = 2, 69%

Scheme 90

Methylation of succinimide **314** and glutarimide **315** proceeded in excellent yields to give *N*-methylsuccinimide **319** and *N*-methylglutarimide **320**, respectively, using the method of Marson.[128] Imides **315**, **319** and **320** were reduced cleanly using the method of Klaver, to give cyclisation precursors **318**, **321** and **322** in respectable yields (**Scheme 90**).[127]

To investigate the effects of groups with different electron withdrawing properties, phenyl and benzyl analogues **326** and **327** were also synthesised. Using an altered method of Ho and Castagnoli Jr., succinic anhydride **323** was coupled with aniline and benzylamine to give imides **324** and **325,** respectively (**Scheme 91**).[129] $NaBH_4$ reduction using the method of Klaver, furnished the desired cyclisation precursors **326** and **327** in moderate yields.[127]



323

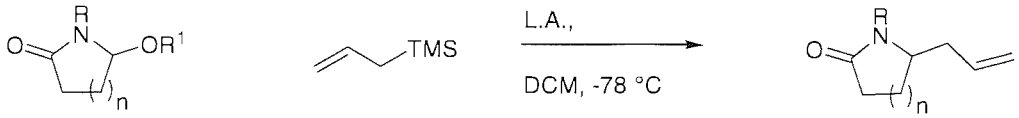
324; n = 0, 45%
325; n = 1, 67%

326; n = 0, 53%
327; n = 1, 50%

Scheme 91

3.3 Intermolecular reactions between *N*-acyliminium ions and allylTMS.

Before the cyclisation reactions were attempted with TIPSMCP, some test reactions were carried out using a range of lactams and allylTMS **125** to see which Lewis acids were best suited to this type of reaction and to determine optimum conditions (**Scheme 92**). Literature searches verified that $BF_3{\cdot}Et_2O$, $SnCl_4$ and $TiCl_4$ were the better Lewis acids for allylTMS addition to *N*-acyliminium species, usually in a two- to fourfold excess using DCM as the solvent.[103, 124, 130, 131] Thus, two equivalents of these Lewis acids in particular, were added to a mixture of the cyclic lactams and three equivalents of allylTMS **125** in DCM at –78 °C in an inert atmosphere using the method of Polniaszek (**Table 9**).[103]



316; R = H, R^1 = Et, n = 1
318; R = H, R^1 = Me, n = 2
325; R = Bn, R^1 = Me, n = 1
321; R = Me, R^1 = Me, n = 1
324; R = Ph, R^1 =Me, n = 1

125

328; R = H, n = 1
329; R = H, n = 2
330; R = Bn, n = 1
331; R = Me, n = 1
332; R = Ph, n = 1

Scheme 92

Lactam used	Lewis acid[a]	Conditions[a]	Yield[b]
316	$TiCl_4$	–78 °C → –10 °C, 8 h	65
	$SnCl_4$	–78 °C → rt, 8 h	42
318	$TiCl_4$	–78 °C → rt	No reaction
	$BF_3{\cdot}Et_2O$	0 °C → rt, 15 h	45[c]
325	$TiCl_4$	–78 °C, 15 min	86
	$SnCl_4$	–78 °C → –60 °C, 1 h	67
321	$TiCl_4$	–78 °C, 10 min	81
	$BF_3{\cdot}Et_2O$	–78 °C → –40 °C, 4 h	76
324	$TiCl_4$	–78 °C → rt, 28 h	94
	$In(OTf)_3$	–78 °C → rt, 48 h	84
	$BF_3{\cdot}Et_2O$	–78 °C → rt, 48 h	79

a) Reactions were carried out with 1 eq. of lactam, 3 eq. of allylTMS and 1.5 eq. of Lewis acid in 5 mL of DCM. b) % yield of purified material after column chromatography. c) Using the method of Ojima; 1 eq. of alcohol, 2 eq. of allylTMS and 1.2 eq. of Lewis acid in 2.5 mL of DCM.[132]

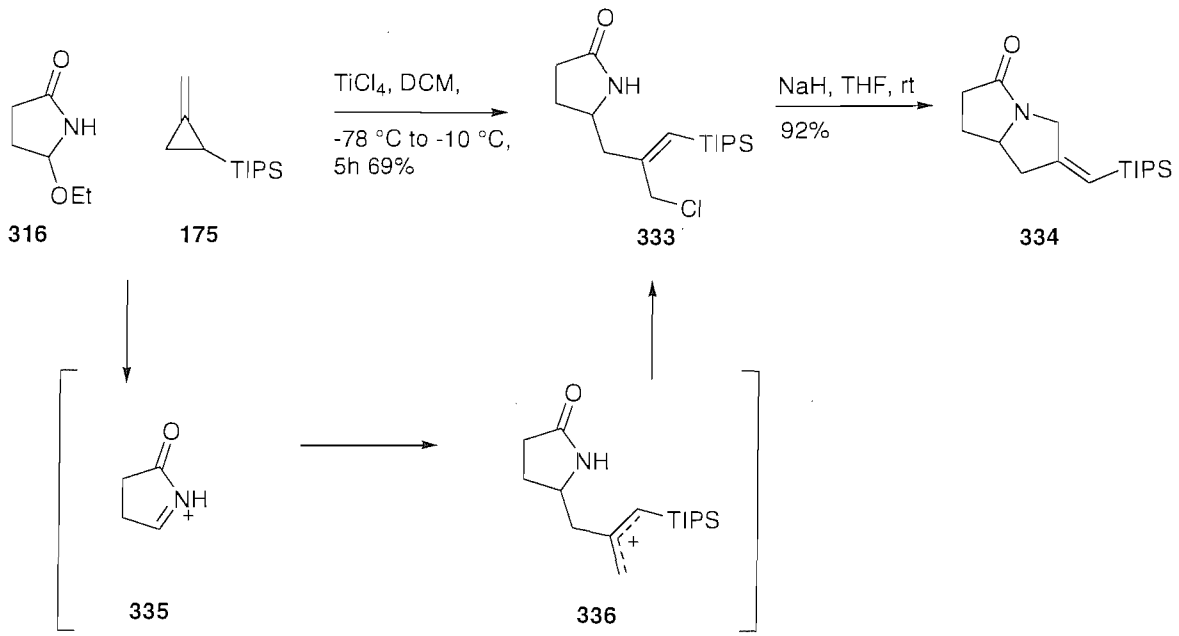
Table 9

When n = 1, $TiCl_4$ was consistently the best Lewis acid, sending the reaction to completion in short reaction times with very good yields. For lactam **318** the desired products were not so forthcoming and the reactions had to be carried out at elevated temperatures using the method of Ojima.[132] Lewis acids $BF_3{\cdot}Et_2O$, $SnCl_4$ and $In(OTf)_3$ gave good to excellent yields with the R = alkyl examples representing the better yields.

3.4 Intermolecular cyclisation reactions between *N*-acyliminium ions and TIPSMCP.

3.4.1 Reactions with 5-ethoxy-pyrrolidin-2-one

Since trial reactions between a range of lactams and allylTMS were very successful with different Lewis acids (**Table 9**), reactions between these lactams and TIPSMCP were attempted. $TiCl_4$ was added to a stirring solution of 5-ethoxy-pyrrolidin-2-one **316** and TIPSMCP **175** in DCM at –78 °C under nitrogen (**Scheme 93**).



Scheme 93

Attack of methylenecyclopropane on the *N*-acyliminium ion **335** facilitates formation of the allyl cation **336** which is then trapped by a chloride ion of the Lewis acid to give **333** in 69% yield. Addition of a strong base in THF at room temperature formed hexahydropyrrolizinone **334** in excellent yield.

Crystal structure determination of lactam **334** confirmed its identity and proved that the *Z*-isomer had been formed (**Figure 8**).

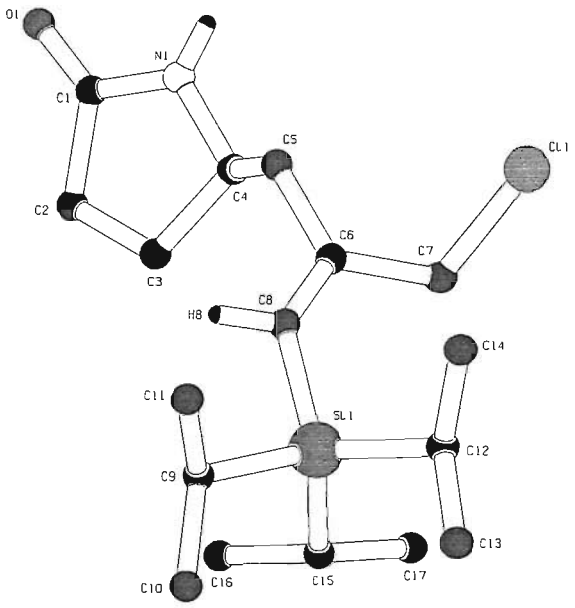


Figure 8 Crystal structure of lactam **333**.

GOESY studies on hexahydropyrrolizinone **334** confirmed the stereochemistry of the double bond (**Figure 9**). Irradiation of H_D caused 2.68% enhancement in H_C protons and no enhancement of H_AH_B. Irradiation of H_A caused 3.03% enhancement in the TIPS protons and no enhancement in H_D. Irradiation of H_B caused 2.61% enhancement in the TIPS protons and no enhancement in H_D. This evidence suggests that H_A and H_B are in close proximity to the TIPS group and that H_D and H_C protons are in close proximity to each other so the stereochemistry of **334** can safely be assumed to be that as shown.

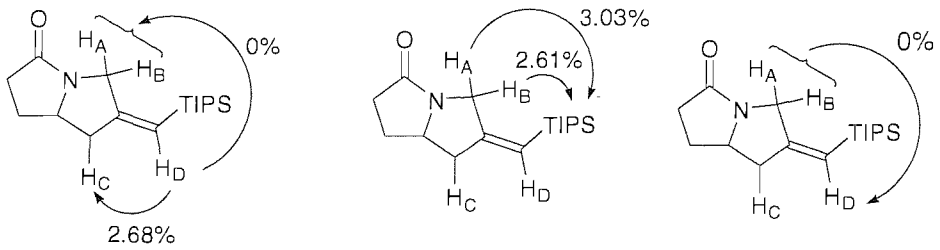


Figure 9 GOESY studies of hexahydropyrrolizinone **334**.

3.4.2 Optimisation of conditions.

Different researchers have reported differing quantities of Lewis acids and starting materials for optimum results which are specific to their chemistry.[103, 124, 125, 130] It was important to optimise this reaction so that these conditions could be applied to future work. Thus, quantities used in the formation of cyclic lactam **333** were varied (**Table 10**).

	Equivalents of TIPSMCP			
Equivalents of $TiCl_4$	**4**	**3**	**2**	**1**
1.5	63	69	59	45
1.2	–	–	–	38
1.0	–	–	–	8

a) % yield of purified material given after column chromatography.

Table 10

It was found that three equivalents of TIPSMCP and one and a half equivalents of $TiCl_4$ gave the best yield so these conditions were used with different Lewis acids and solvents (**Table 11**). $SnCl_4$ was utilised, as it was successful with the allylTMS example. $EtNO_2$, as a more polar solvent, should stabilise the allyl cation **336**.

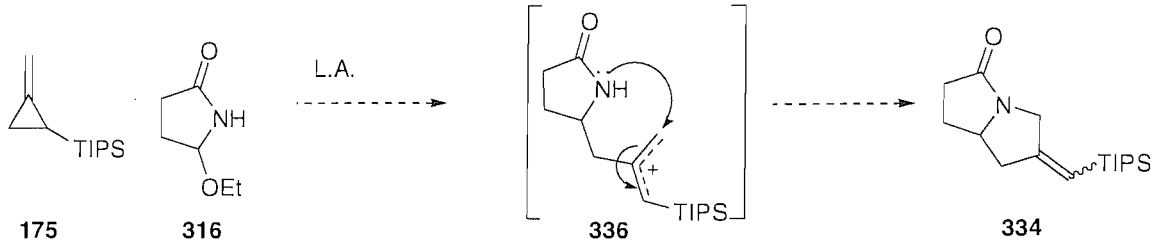
Lewis acid[a]	Solvent	Conditions	Yield of 333[b]
$TiCl_4$	DCM	–78 °C → –10 °C, 5 h	69
	$EtNO_2$	–78 °C → 10 °C, 10 h	78
$SnCl_4$	DCM	–78 °C → rt, then 4 days reflux	44
		rt, 7 h	17
	$EtNO_2$	–78 °C → rt, then 42 h reflux	36

a) Reactions carried out with 0.775 mmol of **316**, 2.323 mmol of TIPSMCP **175** and 1.162 mmol of Lewis acid in 10 mL of solvent. b) % yield of purified material after column chromatography.

Table 11

With $TiCl_4$ the yield was better when $EtNO_2$ was the solvent rather than DCM, however, this was not reflected in the $SnCl_4$ results. Overall, $SnCl_4$ gave lower yields. In addition it was found that even though the reactions with $SnCl_4$ were slower and needed to be refluxed, they still had to be commenced at –78 °C to get a moderate yield.

With reference to Peron's work,[109] in which the use of a non-nucleophilic Lewis acid facilitated intramolecular trapping of the allyl cation intermediate, it was hoped that with such Lewis acids, the nitrogen lone pair would be able to trap the allyl cation intermediate **336** (**Scheme 94**). Cyclisations were attempted with $In(OTf)_3$, $BF_3{\cdot}Et_2O$ and $BF_3{\cdot}2AcOH$ in both DCM and $EtNO_2$ but unfortunately the nitrogen lone pair did not quench the allyl cation intermediate and the reactions underwent decomposition.

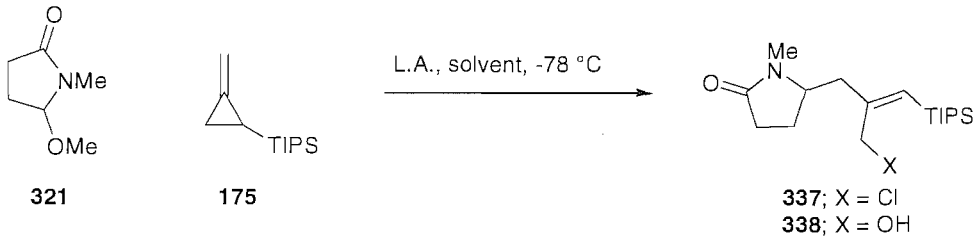


175 **316** **336** **334**

Scheme 94

3.4.3 Reactions with 5-methoxy-1-methyl-pyrrolidin-2-one.

Addition reactions of 5-methoxy-1-methyl-pyrrolidin-2-one **321** and TIPSMCP **175** were attempted with a variety of Lewis acids. The reactions were carried out in either $EtNO_2$ or DCM, adding the Lewis acid into the solution at –78 °C. The reaction was monitored by TLC whilst being allowed to warm up slowly (**Scheme 95**).



321 **175** **337**; X = Cl **338**; X = OH

Scheme 95

Lewis acid[a]	Solvent	Conditions	X	Yield[b]
$TiCl_4$	DCM	–78 °C, 30 min	Cl	64
	$EtNO_2$	–78 °C, 30 min	Cl	28
$SnCl_4$	DCM	–78 °C → rt, then 8 h reflux	Cl	8
$In(OTf)_3$	DCM	–78 °C → –60 °C, 2 h	–	Decomposed
	$EtNO_2$	–78 °C → –60 °C, 3 h	OH	54
$BF_3{\cdot}Et_2O$	DCM	–78 °C → –60 °C, 3 h	–	Decomposed
	$EtNO_2$	–78 °C → –50 °C, 2 h	–	Decomposed

a) Reactions carried out with 0.387 mmol of **321**, 1.162 mmol of TIPSMCP **175** and 0.581 mmol of Lewis acid in 5 mL of solvent. b) % yield of purified material after column chromatography.

Table 12

In the case of $TiCl_4$, the yield is better when DCM is the solvent which surprisingly is opposite to the NH analogue (**Table 11**). $SnCl_4$ gave a very disappointing 8% yield. A

reaction was attempted with $In(OTf)_3$ to see what the outcome would be and interestingly the product formed when $EtNO_2$ was the solvent, was the alcohol **338**. In the absence of a nucleophilic moiety in the lactam, the Lewis acid has quenched the reaction, presumably *via* the triflate species which has been hydrolysed in the work-up to create the alcohol **338**. After this unexpected result, it was of interest to find out whether other Lewis acids without a nucleophilic moiety behaved in the same manner. Reactions with $BF_3{\cdot}Et_2O$ in both DCM and $EtNO_2$ did not produce any interesting products.

GOESY NMR spectroscopy was used in order to confirm the stereochemistry of the double bond of lactam **337** (**Figure 10**).

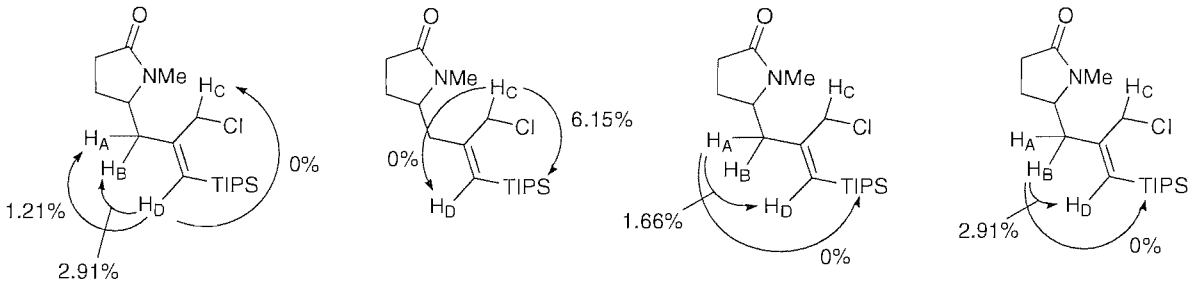


Figure 10 GOESY studies of lactam **337.**

When proton H_D was irradiated it caused a 1.21% and 2.91% enhancement in H_AH_B protons respectively and no enhancement in H_C protons. Irradiation of H_C protons caused a 6.15% enhancement in the TIPS group and no enhancement in H_D. Irradiation of protons H_A and H_B caused 1.66% and 2.91% enhancements in H_D, respectively, and neither caused enhancement to the TIPS group. Therefore the stereochemistry of **337** can be safely assumed to also be the *Z*-isomer, the same as for the NH example **333**.

GOESY studies of the alcohol **338** showed nearly identical enhancements to that of allylchloride **337** thus proving that the isomer formed is also the *Z*-isomer (**Figure 11**).

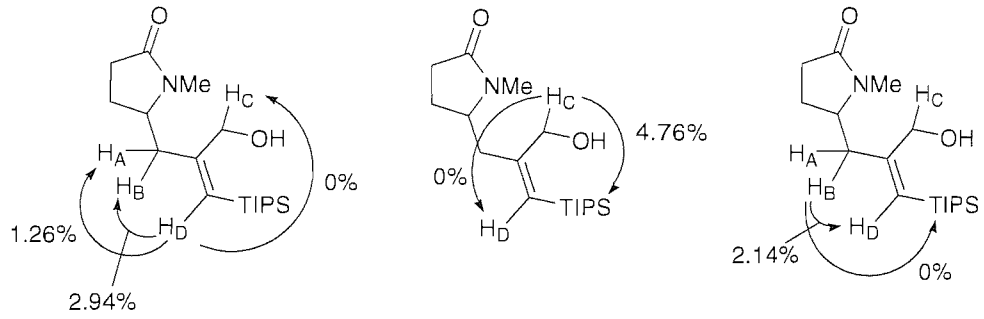
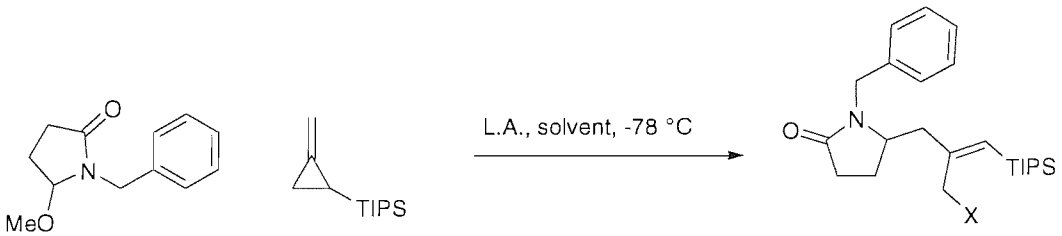


Figure 11 GOESY studies of alcohol **338.**

3.4.4 Reactions with 5-methoxy-1-benzyl-pyrrolidin-2-one.

Addition of TIPSMCP **175** to 5-methoxy-1-benzyl-pyrrolidin-2-one **325** was accomplished with three different Lewis acids (**Scheme 96**). The reactions were carried out in either $EtNO_2$ or DCM, adding the Lewis acid into the stirring solution at –78 °C. The reaction was monitored whilst being allowed to warm up slowly.



325 **175** **339**; X = Cl; **340**; X = F

Scheme 96

Since $TiCl_4$ gave an excellent yield with DCM, this solvent was used for the rest of the reactions (**Table 13**). $SnCl_4$ also gave the desired allylchloride **339** in very good yield. Interestingly, when $BF_3{\cdot}Et_2O$ was used, the fluoride quenched the allylsilane intermediate in an unprecedented fashion and formed allylfluoride **340**. Unlike the methylated example, $In(OTf)_3$ did not furnish the allylalcohol, rather, the reaction underwent decomposition. $InCl_3$ was used because it has been shown to promote allylTMS attack to 3,4-disubstituted analogues of **325.**[133] For allylTMS addition the Lewis acid simply needs to co-ordinate to the methoxy group allowing formation of the *N*-acyliminium species which allylTMS can

then attack. However, with TIPSMCP addition, if the allyl cation intermediate cannot be quenched intramolecularly (route 1, **Scheme 88**), the Lewis acid also has to act as a trapping agent (routes 2 and 3, **Scheme 88**). When $InCl_3$ mediated catalysis was attempted with unsubstituted *N*-benzyl lactam **325** it underwent decomposition, presumably because $InCl_3$ is not nucleophilic enough to quench the allyl cation intermediate. Unlike $BF_3{\cdot}Et_2O$, $BF_3{\cdot}2AcOH$ did not quench the allyl cation intermediate.

Lewis acid[a]	**Solvent**	**Conditions**	**X**	**Yield**[b]
$TiCl_4$	DCM	–78 °C → –30 °C, 4 h	Cl	85
	$EtNO_2$	–78 °C → –20 °C, 6 h	Cl	64
$SnCl_4$	DCM	–78 °C → rt, then 6 h reflux	Cl	74
$BF_3{\cdot}Et_2O$	DCM	–78 °C → rt, then 48 h at rt	F	58
$In(OTf)_3$	DCM	–78 °C → –40 °C, 8 h	–	Decomposed
$InCl_3$	DCM	–78 °C → –20 °C, 4 h	–	Decomposed
$BF_3{\cdot}2AcOH$	DCM	–78 °C → –60 °C, 3 h	–	Decomposed

a) Reactions carried out with 0.244 mmol of compound **324**, 0.732 mmol of TIPSMCP **175** and 0.366 mmol of Lewis acid in 5 mL of solvent. b) % yield of purified material after column chromatography.

Table 13

GOESY experiments prove that the allylchloride **339** was the *Z*-isomer, in accordance with its analogues. The GOESY experiments of allylfluoride **340** also show that the product formed is the *Z*-isomer (**Figure 12**). Irradiation of H_E caused 0.42% and 3.09% enhancements in H_AH_B protons respectively and no enhancement in H_CH_D. Irradiation of H_C and H_D caused 3.90% and 2.73% enhancements in the TIPS group respectively, and both exhibited no enhancement in H_E. As a result, the structure can safely be assumed to be as shown.

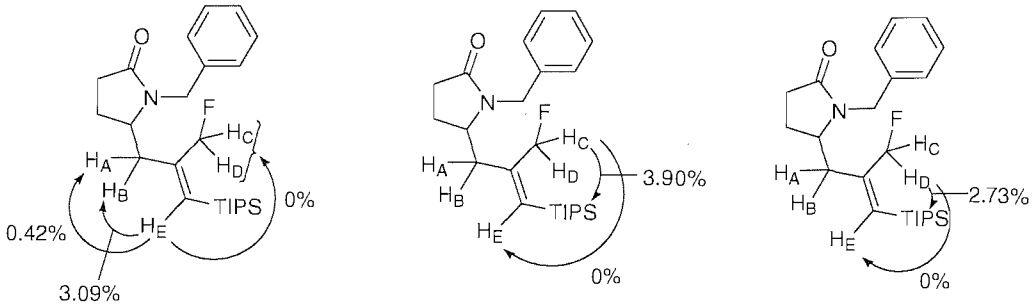
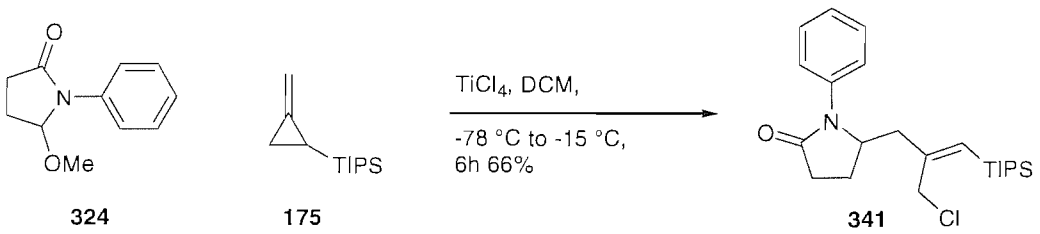


Figure 12 GOESY studies of allylfluoride **340.**

3.4.5 Reactions with 5-methoxy-1-phenyl-pyrrolidin-2-one.

Addition of TIPSMCP **175** to 5-methoxy-1-phenyl-pyrrolidin-2-one **324** in the presence of $TiCl_4$ furnished allylchloride **341** in 66% yield (**Scheme 97**). Reactions were also attempted with $In(OTf)_3$, to find out whether the alcohol could be synthesised, and $BF_3{\cdot}Et_2O$, to see whether the allylfluoride could be made. For both cases, the starting materials decomposed.



324 **175** **341**

Scheme 97

It is not surprising that these reactions were less facile because the nitrogen lone pair is in conjugation with the aromatic system making the formation of the *N*-acyliminium species harder. Once more, GOESY studies confirm that the geometry of the double bond of **341** is *Z* (**Figure 13**).

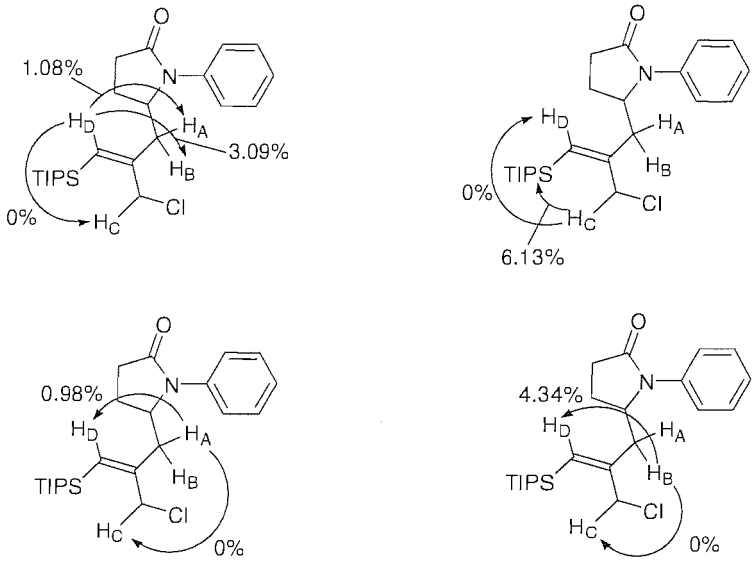
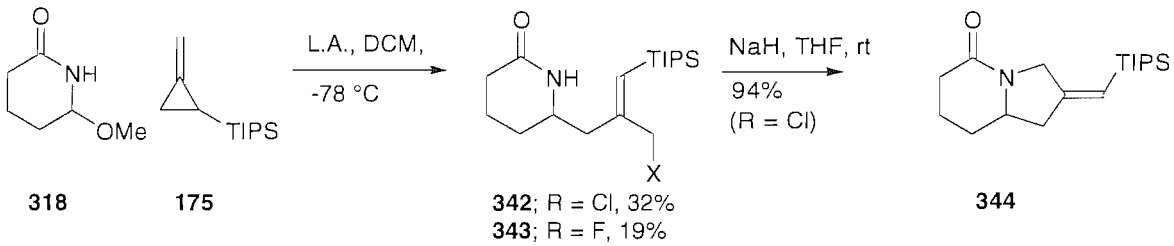


Figure 13 GOESY studies of allylchloride **341.**

3.4.6 Reactions with 6-methoxy-piperidin-2-one.

Since reactions between a range of 5-membered ring lactams and TIPSMCP were successful with different Lewis acids, this methodology was extended to the synthesis of a 5,6-bicyclic lactam. Thus $TiCl_4$ and $BF_3{\cdot}Et_2O$ were added to a stirring solution of methoxylactam **318** and TIPSMCP **175** in DCM at –78 °C under nitrogen (**Scheme 98**).



318 **175** **342**; R = Cl, 32% **343**; R = F, 19% **344**

Scheme 98

The reactions gave lactams **342** and **343** in low yields. Manipulations with reaction temperatures and times for the $TiCl_4$ case, did not serve to increase the yield. Addition of NaH to lactam **342** in THF at room temperature gave the hexahydroindolizinone **344** in excellent yield.

GOESY studies on lactams **342** and **343** show that the geometry of the double bond is *Z* for both compounds. The structure of lactam **344** was proved by X-ray crystallography (**Figure 14**).

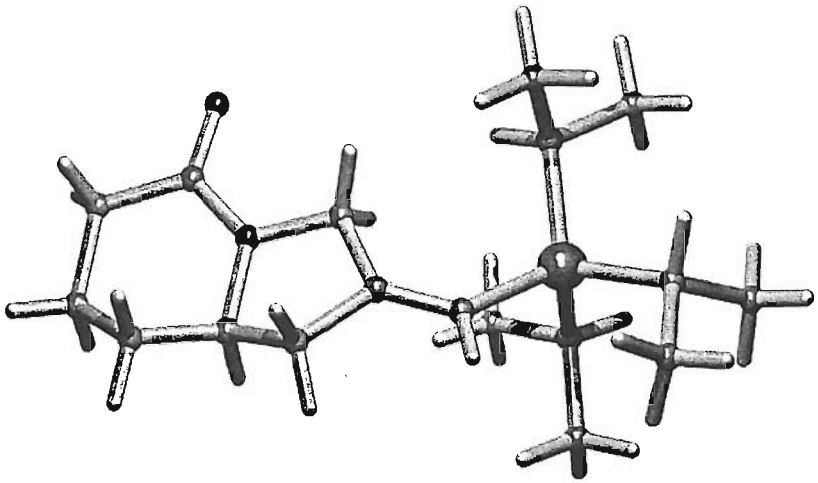
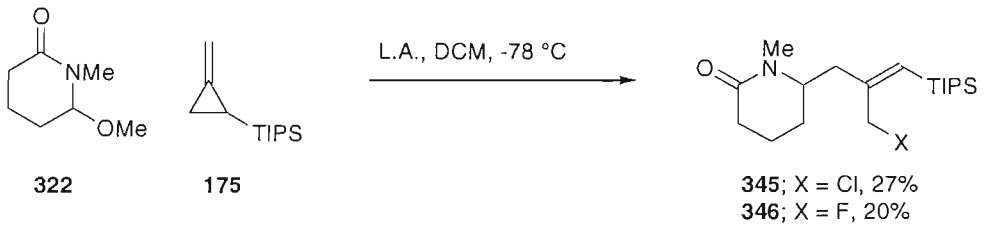


Figure 14 Crystal structure of lactam **344**.

3.4.7 Reactions with 6-methoxy-1-methyl-piperidin-2-one.

Reactions were attempted also with 6-methoxy-1-methyl-piperidin-2-one **322** and TIPSMCP **175** with $TiCl_4$ and $BF_3{\cdot}Et_2O$ in DCM. The Lewis acid was added to the solution at –78 °C, and the reaction was monitored by TLC whilst the reaction mixture was allowed to warm up slowly (**Scheme 99**).



322 **175** **345**; X = Cl, 27%
346; X = F, 20%

Scheme 99

Lactams **345** and **346** were formed with $TiCl_4$ and $BF_3{\cdot}Et_2O$, respectively. Again, the yields were lower than the 5-membered ring analogue.

GOESY NMR spectroscopy was used to confirm the stereochemistry of the double bond of lactams **345** and **346** and one example is shown (**Figure 10**).

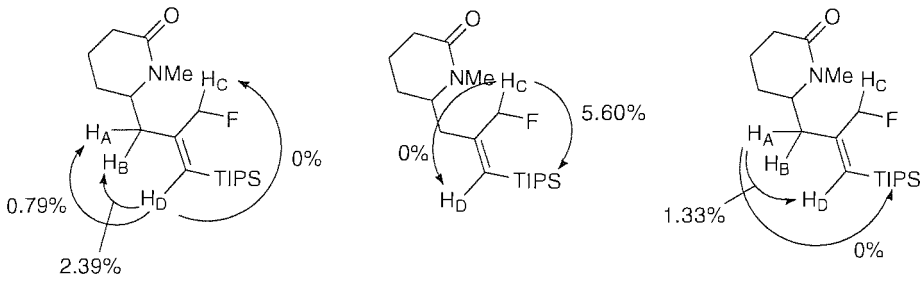
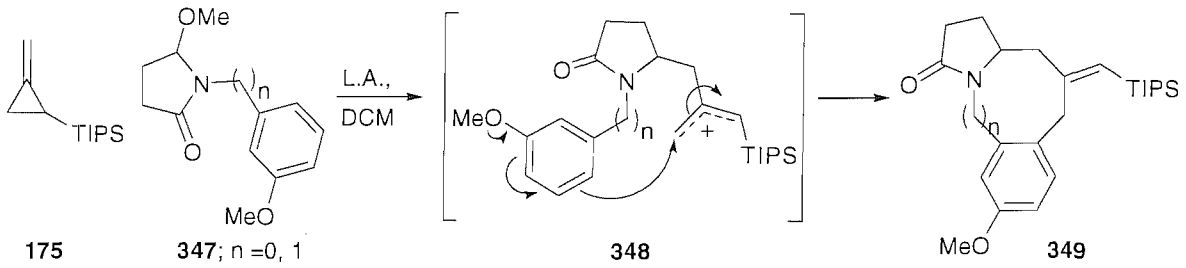


Figure 15 GOESY studies of lactam **346.**

When proton H_D was irradiated it caused a 0.79% and 2.39% enhancement in H_AH_B protons respectively and no enhancement in H_C. Irradiation of H_C caused a 5.60% enhancement in the TIPS group and no enhancement in H_D. Irradiation of proton H_A caused a 1.33% enhancement in H_D and no enhancement to the TIPS group. Therefore the stereochemistry of **346** can be assumed to be the *Z*-isomer.

3.5 Intramolecular trapping of the allyl cation intermediate.

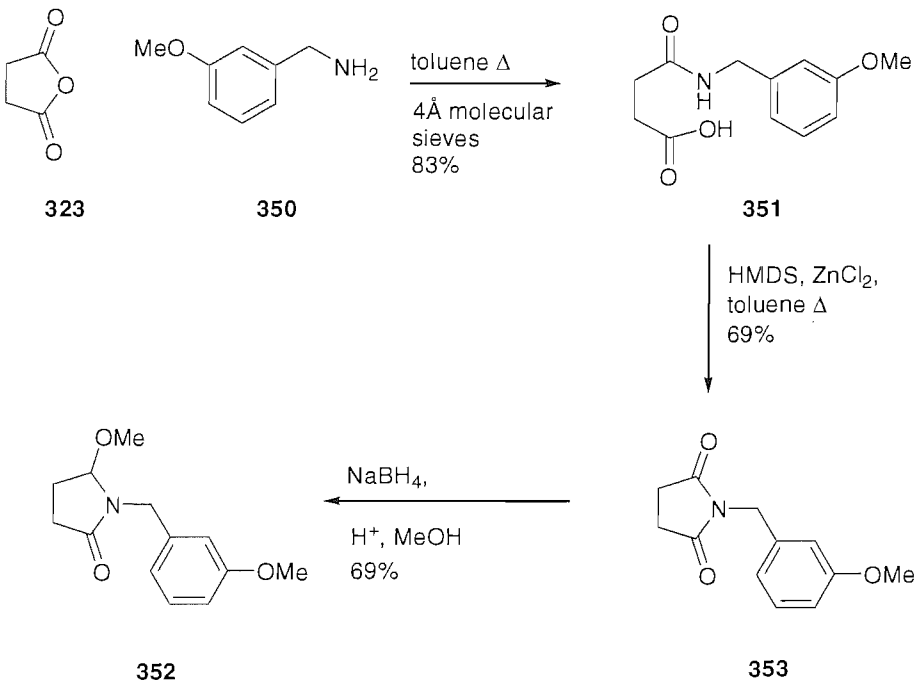
Reactions involving the Lewis acid trapping of the allyl cation intermediates proved to be successful. It was of interest to investigate whether the *N*-acyliminium ion could be trapped intramolecularly from a nucleophilic aromatic ring rather than from the Lewis acid. Since the allyl intermediate **348** forms for the unsubstituted benzyl group, it was of interest to find out whether the reaction can be pushed to proceed *via* the mechanism shown to give 7- or 8-membered rings **349** (**Scheme 100**).



175 **347**; n =0, 1 **348** **349**

Scheme 100

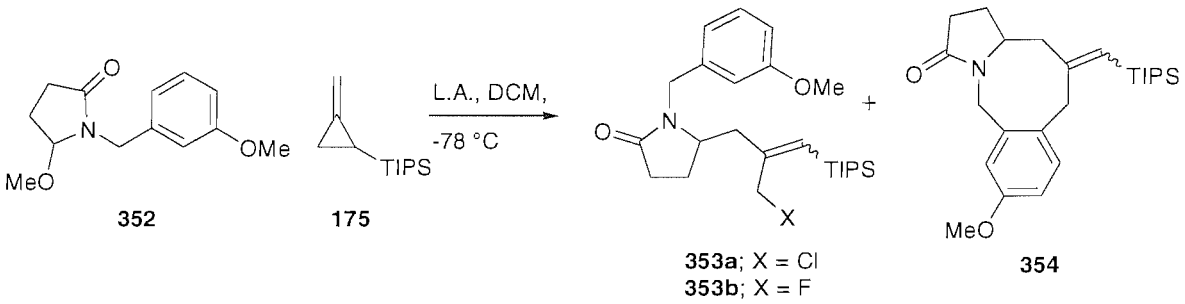
Addition of TIPSMCP **175** to 5-methoxy-1-benzyl-pyrrolidin-2-one **325** proceeded in superior yields to the phenyl analogue **324**, so *m*-methoxy benzyl pyrrolidinone **352** was chosen. Thus, precursor **352** was synthesised in a three step procedure (**Scheme 101**). In attempt to synthesise imide **353**, amic acid **351** was formed which was then cyclised following a method of Reddy *et al* using 1.5 equivalents of HMDS and one equivalent of the Lewis acid $ZnCl_2$ in refluxing toluene.[134] Reduction of imide **353** was carried out using the method of Klaver to give the desired cyclisation precursor in good yield.[127]



323 **350** **351** **352** **353**

Scheme 101

Cyclisations were attempted with $TiCl_4$ and $BF_3{\cdot}Et_2O$ because they should be able to act as a nucleophilic trapping agent for the allyl cation intermediate, and also with $In(OTf)_3$ and $BF_3{\cdot}2AcOH$ because they should promote trapping of the allyl cation intermediate from the electron rich aromatic group. The Lewis acid was added into the stirring solution of lactam **352** and TIPSMCP **175** at –78 °C, and the reaction was monitored by TLC whilst being allowed to warm up slowly (**Scheme 102**).



Scheme 102

Lewis acid[a]	Conditions	X	Yield[b] of 353	Yield[b] of 354
$TiCl_4$	–78 °C → rt, 24 h	Cl	50	–
$BF_3{\cdot}Et_2O$	–78 °C → rt, 26 h	F	49	–
$In(OTf)_3$	–78 °C → –50 °C, 2 h	–	Decomposed	
$BF_3{\cdot}2AcOH$	–78 °C → –40 °C, 2 h	–	Decomposed	

a) Reactions carried out with 0.213 mmol of compound **352**, 0.638 mmol of TIPSMCP **175** and 0.319 mmol of Lewis acid in 5 mL of DCM. b) % yield of purified material after column chromatography.

Table 14

When Lewis acids $TiCl_4$ and $BF_3{\cdot}Et_2O$ were used, as predicted the only products formed were from Lewis acid trapping of the allyl cation intermediate; quench from the Lewis acid was favoured over the 8-endo-trig cyclisation (**Table 14**). When non-nucleophilic $In(OTf)_3$ and $BF_3{\cdot}2AcOH$ were used, it appears as though the 8-membered ring could not

be formed quickly enough and the reaction underwent decomposition. GOESY experiments of compounds **353a** and **353b** proved the stereochemistry of the double bonds to be *Z*. The chloride example is shown (**Figure 16**)

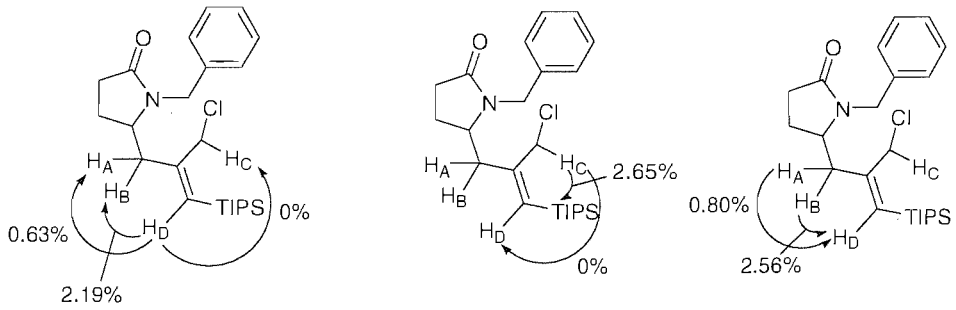
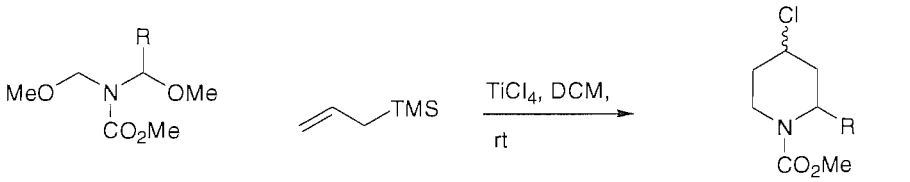


Figure 16 GOESY studies of allylchloride **353a.**

Irradiation of H_D caused 0.63% and 2.19% enhancements in H_AH_B protons respectively and no enhancement in H_C. Irradiation of H_C caused 2.65% enhancement in the TIPS group, and no enhancement in H_D. Irradiation of H_AH_B caused 0.80% and 2.56% enhancement in H_D. As a result, the structure can safely be assumed to be as shown.

3.6 Acyclic *N*-acyliminium ion cyclisations with TIPSMCP.

Whereas cyclisations involving cyclic *N*-acyliminium ions have been extensively studied, reactions involving acyclic *N*-acyliminium ions have been investigated much less.[97] Although certain examples of allylTMS addition to acyclic *N*-acyliminium ions have been shown to exhibit good yields the reactions are few and far between. Shono has shown that addition of allylTMS **125** to *bis*-methoxymethyl-carbamic acid methyl ester **355** in the presence of $TiCl_4$ gives piperidines **357** in 65% yield and the presence of a propyl group (**356**) increases the yield to 75% (**Scheme 103**).[135]



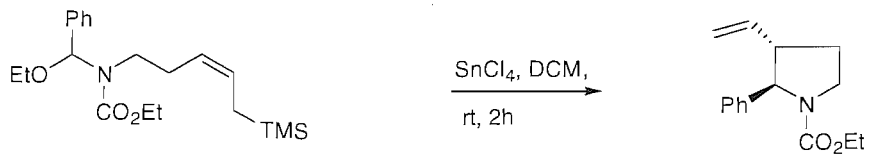
355; R = H
356; R = Pr

125

357; R = H, 65%
358; R = Pr, 75%

Scheme 103

Intramolecular addition reactions of an allylTMS moiety to an acyclic *N*-acyliminium ion has also been shown to proceed with ease (**Scheme 104**).[136]

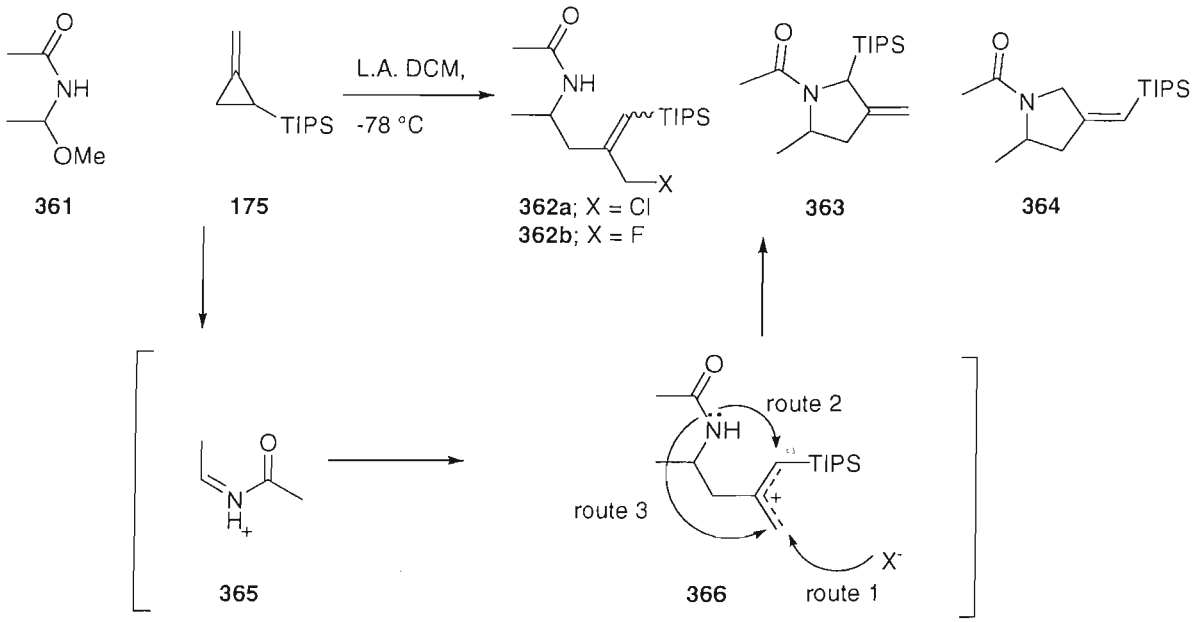


359

360

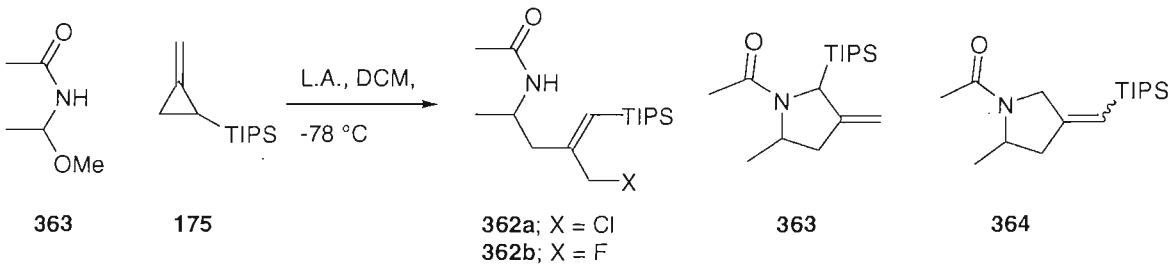
Scheme 104

Hence it was of interest to determine whether acyclic analogues of previous studies described herein would undergo reaction with TIPSMCP (**Scheme 105**). TIPSMCP addition to *N*-(1-methoxy-ethyl)-acetamide **361** should lead to the *N*-acyliminium ion **188** which can then either undergo trapping from the Lewis acid, as previously seen (route 1), or attack from the nitrogen lone pair (routes 2 and 3) to give products **362**, **363** and **364** respectively.



Scheme 105

Consequently, acetamide **363** was formed from reduction of diacetamide using a method of Klaver in a low 23% yield.[127] Four Lewis acids were chosen for the cyclisation step and were added to a stirring mixture of acetamide **363** and TIPSMCP **175** at –78 °C. The reaction was monitored by TLC whilst being allowed to warm up slowly (**Scheme 106**).



Scheme 106

Surprisingly products **362** were not formed (**Table 15**). However, when $BF_3{\cdot}Et_2O$ and $SnCl_4$ were used the products formed were pyrrolidine **363** and pyrrolidines **364** formed as a 1:1 mixture of isomers, thus showing that the intramolecular trapping from the nitrogen lone pair could compete against the quench from the Lewis acid. This reaction was

presumably able to occur because there was no steric constraint in the *N*-acyliminium species. $TiCl_4$ simply caused the reaction to decompose immediately and addition of $In(OTf)_3$ did not bring about a reaction at all and the starting materials underwent decomposition. This work offers an attractive route to the formation of substituted *N*-acylpyrrolidines in reasonable mass balance.

Lewis acid[a]	Conditions	Yield[b] of 362	Yield[b] of 363	Yield[b] of 364
$BF_3{\cdot}Et_2O$	–78 °C → rt, 26 h	–	39	23 (1:1)[c]
$SnCl_4$	–78 °C → rt, 5 h	–	17	11 (1:1)[c]
$TiCl_4$	–78 °C	Decomposed immediately		
$In(OTf)_3$	–78 °C → –50 °C, 7 h	No reaction then decomposed		

a) Reactions carried out with 0.427 mmol of compound **361**, 1.282 mmol of TIPSMCP **175** and 0.641 mmol of Lewis acid in 5 mL of DCM. b) % yield of purified material after column chromatography. c) *E*:*Z* isomer ratio as determined by peak integration of ^{1}H NMR.

Table 15

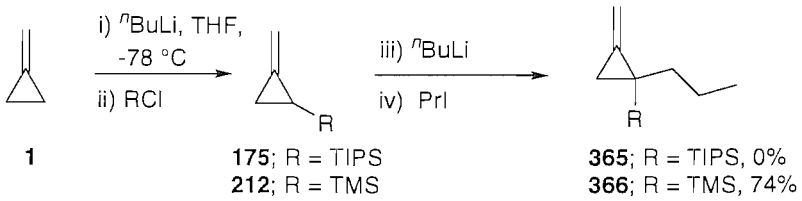
3.7 Reactions using disubstituted methylenecyclopropane.

Addition reactions of TIPSMCP to *N*-acyliminium ions have consistently made the *Z*-isomer. Therefore it was of interest to investigate which isomer would be formed when a 1,1-disubstituted methylenecyclopropane was used.

3.7.1 Synthesis of precursors.

A simple propyl analogue was chosen and synthesised using the method of Patient (**Scheme 107**).[22] Disubstituted methylenecyclopropane **365** could not be synthesised from TIPSMCP, thus methylenecyclopropane **1** was treated with ^{n}BuLi and the subsequent

anion quenched with TMSCl to give **212**. A second equivalent of ^{n}BuLi was added followed by iodopropane to give **366** in 74% yield.

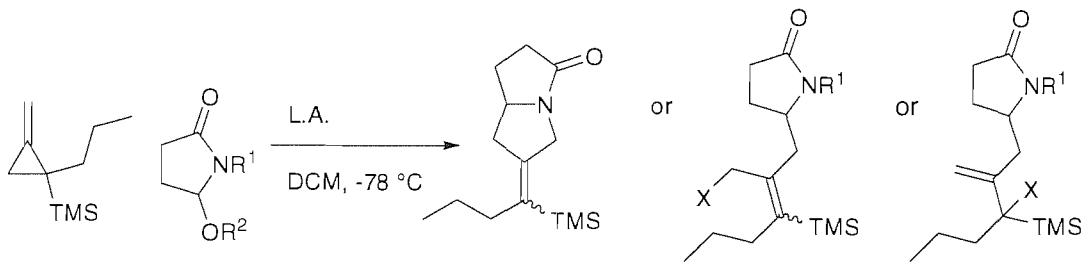


1 **175**; R = TIPS, **212**; R = TMS **365**; R = TIPS, 0%, **366**; R = TMS, 74%

Scheme 107

3.7.2 Cyclisation reactions.

Reactions were carried out with 1,1-disubstituted methylenecyclopropane **366** and lactams **316** and **325** in DCM using $TiCl_4$, $SnCl_4$, $In(OTf)_3$ and $BF_3{\cdot}Et_2O$ since they had displayed good results when TIPSMCP was used. The Lewis acid was added to the reaction mixture at –78 °C and the reaction was allowed to warm up slowly whilst being monitored by TLC (**Scheme 108**).



366 **316**; R^1 = H, R^2 = Et, **325**; R^1 = Bn, R^2 = Me **367**; R^1 = H **368a**; R^1 = H, **368b**; R^1 = Bn **369a**; R^1 = H, **369b**; R^1 = Bn

Scheme 108

Reactions using $TiCl_4$, $SnCl_4$ and $BF_3{\cdot}Et_2O$ with methylenecyclopropane **366** and ethoxy lactam **316** in DCM all decomposed at –78 °C (**Table 16**). Reactions involving methoxy lactam **325** in the presence of $BF_3{\cdot}Et_2O$ and $In(OTf)_3$ were also unsuccessful as the isolated compounds formed were unwanted by-products derived from the methoxy lactam.

However, when $TiCl_4$ was used two products, **368b** and **369b**, were formed as a 3:1 mixture of regioisomers. They were not separable by column chromatography or by HPLC methods and as a result the NMR spectra cannot be conclusively assigned. Distinctive peaks of **368b** can be identified in the ^{13}C NMR spectrum by comparison with its analogues. Similarly, compound **369b** also has distinctive peaks in the alkene region of the ^{13}C NMR.

R^1	R^2	Lewis acid[a]	Conditions	X	Yield of 367	Yield[b] of 368	Yield[b] of 369
H	Et	$TiCl_4$	–78 °C	Cl	Decomposed		
H	Et	$BF_3{\cdot}Et_2O$	–78 °C	F	Decomposed		
H	Et	$SnCl_4$	–78 °C	Cl	Decomposed		
Bn	Me	$TiCl_4$	–78 °C, 2 h	Cl	–	60 (3:1)[c]	
Bn	Me	$BF_3{\cdot}Et_2O$	–78 °C → –10 °C, 6 h	–	By-products		
Bn	Me	$In(OTf)_3$	–78 °C → rt, 6 h	–	By-products		

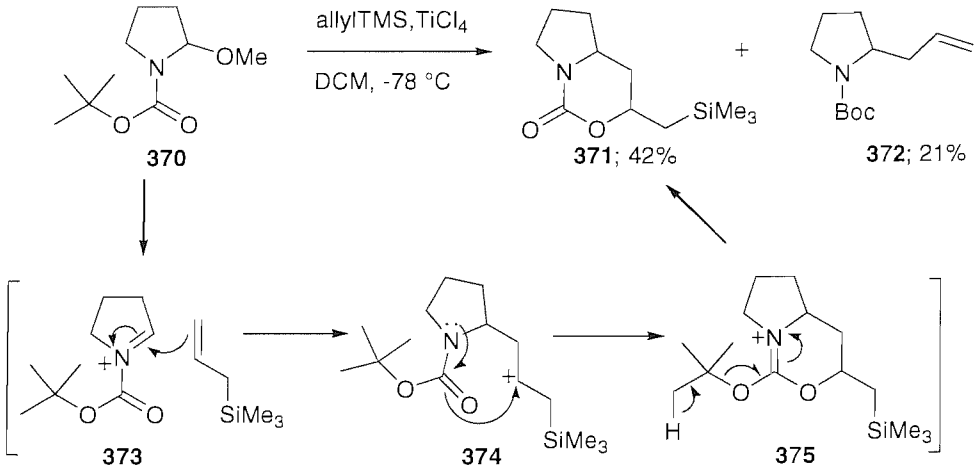
a) Reactions carried out with 1 eq. of lactam, 3 eq. of **366** and 1.5 eq. of Lewis acid in 5 mL of DCM. b) % yield of purified material after column chromatography. c) Regioisomer ratio of **368b**:**369b** as determined by peak integration of ^1H NMR.

Table 16

3.8 Intramolecular Trapping by an *N*-Boc group.

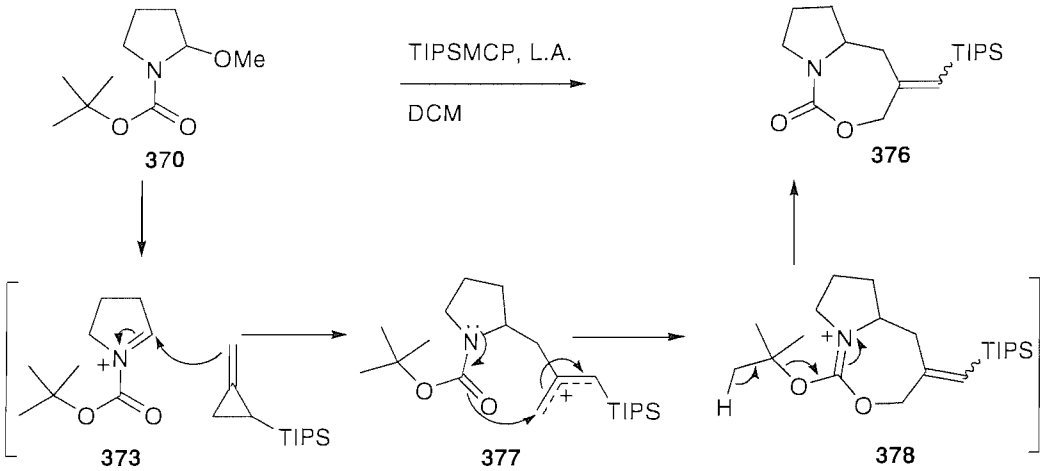
Brocherieux-Lanoy *et al.* have published some interesting work in which they had a surprise result from allylTMS addition to a Boc-protected pyrrolidine (**Scheme 109**).[125] The Lewis acid co-ordinates to the methoxy group of **370**, allowing formation of the *N*-acyliminium ion **373**. Attack from the nucleophilic allylsilane gives the β-silyl carbocation **374** which undergoes intramolecular trapping from the Boc group. Loss of 2-methylpropene leads to formation of silylated oxazinone **371** in moderate yield along

with the expected allylated compound **372**. In addition, when allylTIPS was used, the TIPS-containing oxazinone could be synthesised cleanly in 73% yield with no allylation product formed. This was due to increased stability of the intermediate cation **374** caused by the more electron-donating silicon group.[119]



Scheme 109

Thus it was of interest to determine whether addition of TIPSMCP to an *N*-Boc-protected methoxy lactam **370** could be facilitated (**Scheme 110**).

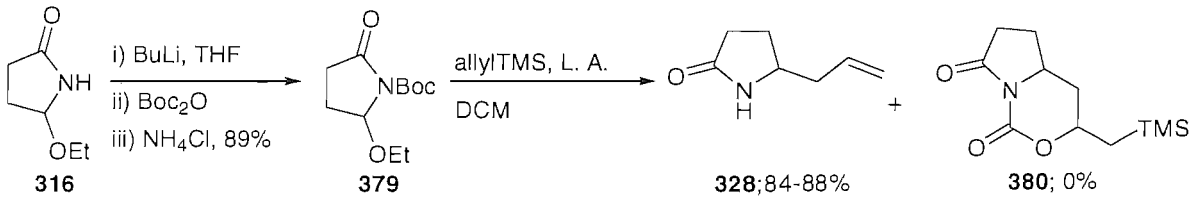


Scheme 110

The Lewis acid should allow formation of *N*-acyliminium ion **373** which should undergo attack from TIPSMCP to give the allyl cation intermediate **377**. Intramolecular trapping from the Boc group followed by loss of 2-methylpropene should lead to formation of 5,7-bicyclic compound **376**. It was hoped that the intramolecular trapping from the Boc-group would be able to compete favourably with trapping of the allyl cation intermediate from the Lewis acid, as seen previously.

3.8.1 Synthesis of precursors and test reactions.

Since an abundance of ethoxylactam **316** was available, it was Boc-protected in excellent yield. Addition reactions of allylTMS with Lewis acids $TiCl_4$, $In(OTf)_3$ and $BF_3{\cdot}Et_2O$ in DCM were carried out at –78 °C (**Scheme 111**). None of the desired silylated oxazinone **380** was produced, presumably due to interference of the carbonyl group; indeed the lone pair of the nitrogen is more inclined to delocalise with the carbonyl of the lactam than facilitate cyclisation towards the ozazinone **380**. Furthermore the Boc-group was not present on the isolated product **328**, again it was assumed that the *N*-Boc bond had been weakened by the presence of the carbonyl group of the lactam.

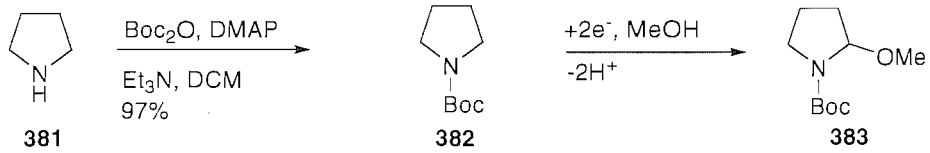


316 **379** **328**;84-88% **380**; 0%

Scheme 111

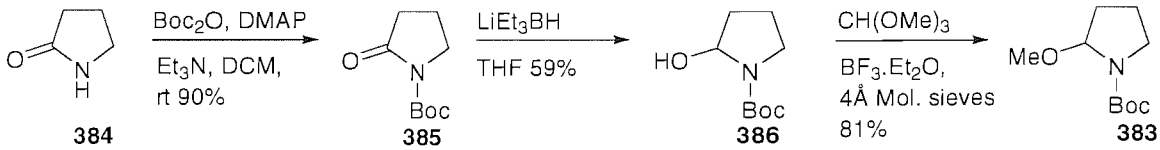
It was considered important to synthesise *N*-Boc protected pyrrolidine **383**. Two methods were attempted. Firstly, anodic α-methoxylation of *N*-Boc-pyrrolidine **383** was conducted in an undivided cell fitted with two graphite electrodes in MeOH (0.5 M) using tetrabutylammonium tetrafluoroborate as a supporting electrolyte for three hours using the method of Shono.[137] During electrolysis the temperature of the reaction was maintained at –10 °C (**Scheme 112**). Initially the reaction was unsuccessful as *N*-Boc-pyrrolidine **382** was being over-methoxylated, even though the reaction was carried out at low temperature

and with low current (10 $mAcm^{-2}$). On repeating the experiment with a lower current (5 $mAcm^{-2}$) and with a shorter reaction time (2 h) the correct product was formed in a yield of less than 1% along with unreacted starting material. The reason for the low yield could be because the conditions described by Shono could not be replicated precisely.



Scheme 112

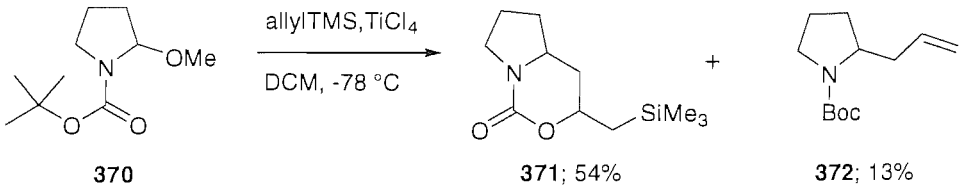
The second method provided *N*-Boc-2-methoxy-pyrrolidine **383** cleanly and efficiently in an overall 43% yield from 2-pyrrolidinone **384** using the method of Rassu *et al.* (**Scheme 113**).[138]



Scheme 113

Boc-protection of 2-pyrrolidinone **384** was carried out in excellent yield followed by reduction of the carbonyl moiety with triethylborohydride (Superhydride®) in 59% yield. Formation of **383** using methylorthoformate also proceeded in excellent yield.

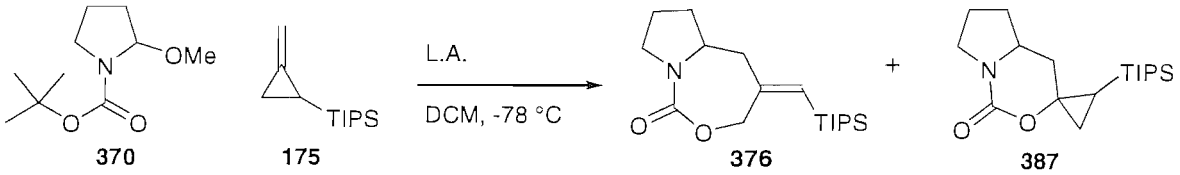
Reaction of allylTMS with *N*-Boc-2-methoxy-pyrrolidine **370** was carried out using the method of Brocherieux-Lanoy *et al.* and the reaction was complete in 5 minutes at –78 °C giving oxazinone **371** and allylated compound **372** in yields comparable to Brocherieux-Lanoy *et al.*[125]



Scheme 114

3.8.2 Reactions with TIPSMCP.

The cyclisation reaction of *N*-Boc-2-methoxy-pyrrolidine **370** and TIPSMCP **175** was carried out using $TiCl_4$ and $BF_3{\cdot}Et_2O$ in DCM at –78 °C under an inert atmosphere and the reactions were allowed to warm slowly as they were monitored by TLC. Two products were formed (**Scheme 115**).



Scheme 115

Lewis acid[a]	Conditions	Yield[b] of 376	Yield[b] of 387
$TiCl_4$	–78 °C → 0 °C, 6 h	11	9
$BF_3{\cdot}Et_2O$	–78 °C → rt, 36 h	40	10

a) Reactions carried out with 0.476 mmol of compound **370**, 1.428 mmol of TIPSMCP **175** and 0.714 mmol of Lewis acid in 5 mL of DCM. b) % yield of purified material after column chromatography.

Table 17

Both Lewis acids gave 5,7-bicycle **376** and 3,6-spirocycle **387** (**Table 17**). $BF_3{\cdot}Et_2O$ catalysed the reaction with much better mass balance, perhaps due to it being a less harsh

Lewis acid. Interestingly, no products were formed from trapping of the allyl cation intermediate by the Lewis acid.

To elucidate the stereochemistry of the double bond of compound **376** GOESY experiments were performed (**Figure 17**).

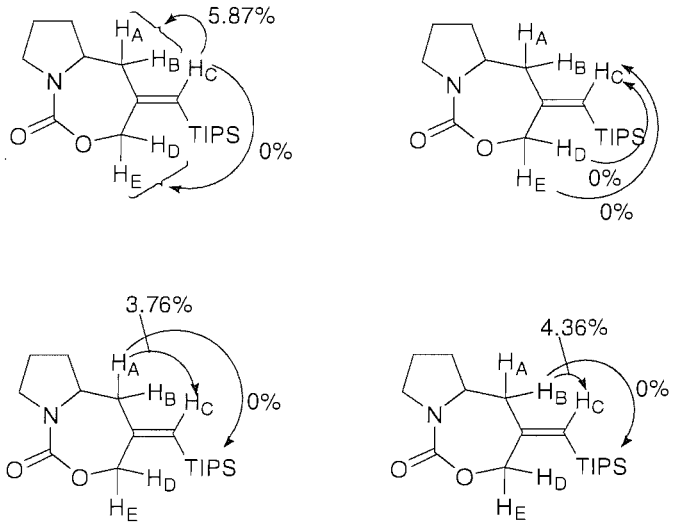
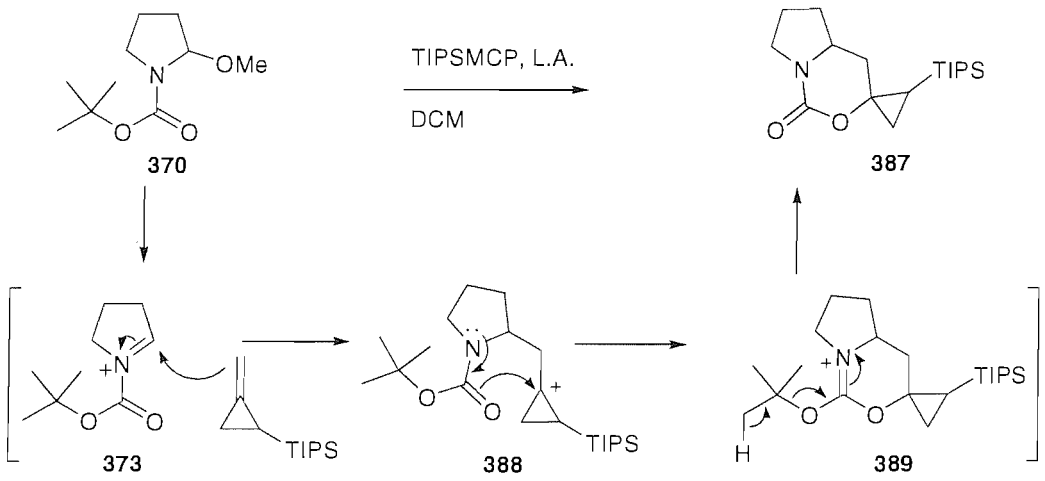


Figure 17 GOESY studies of compound **376.**

When H_C was irradiated it caused a 5.87% enhancement in H_AH_B protons and no enhancement in H_DH_E protons. Irradiation of H_E and H_D both caused no enhancement in H_C. Irradiation of protons H_A and H_B caused 3.76% and 4.36% enhancements in H_C respectively and neither caused enhancement to the TIPS group. Therefore the stereochemistry of the double bond can safely be assumed to be that as shown.

The formation of **387** can be rationalised by the mechanism shown (**Scheme 116**). The Lewis acid allows formation of *N*-acyliminium ion **373** which undergoes attack from TIPSMCP. Rather than the cyclopropene opening to give the allyl cation intermediate, the intramolecular trapping from the Boc group occurs directly onto the cyclopropyl cation **389**. Loss of 2-methylpropene then leads to formation of 3,6-spirocyclic compound **388**. This result is surprising because cyclopropyl cation rearrangement is known to be very

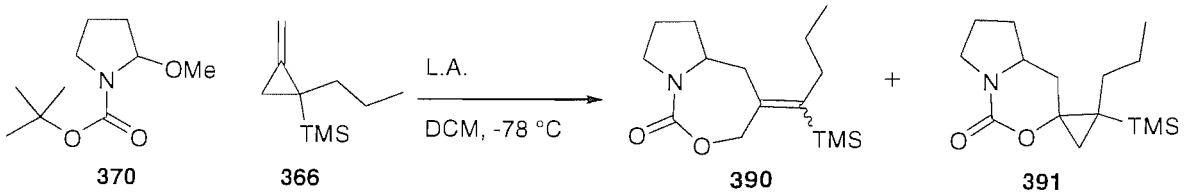
rapid[139] but presumably, the increased stabilisation of the β-cation, owing to the electron-donating TIPS group, permits this route.



Scheme 116

3.8.3 Reactions with 1,1-disubstituted methylenecyclopropane.

By using a 1,1-disubstituted methylenecyclopropane it was hoped that additional steric hindrance on the cyclopropyl ring might aid ring opening to the allyl cation intermediate thus enhancing the yield of 5,7-bicyclic systems. Additionally, the use of a less electron-donating silyl group (e.g. TMS) might encourage the cyclopropyl β-cation to ring-open. Thus two different Lewis acids were added to a stirring solution of 1,1-disubstituted methylenecyclopropane **366** and *N*-Boc-2-methoxy-pyrrolidine **370** –78 °C in DCM. The reactions were allowed to warm slowly as they were monitored by TLC. This time, only one product was formed (**Scheme 117**).



Scheme 117

The yields of **390** are greatly improved when 1,1-disubstituted methylenecyclopropane is used rather than TIPSMCP (**Table 18**). It can be assumed that 3,6-spirocyclic product **391** was not formed for two reasons. Firstly, the β-cation not being stabilised with TMS as much as with a TIPS group. Secondly, the presence of a sterically hindering propyl group may have caused the cyclopropyl ring opening to be more facile.

Lewis acid[a]	**Conditions**	**Yield**[b] **of 390**	**Yield**[b] **of 391**
$TiCl_4$	–78 °C, 30 min	35	0
$BF_3{\cdot}Et_2O$	–78 °C → rt, 24 h	62	0

a) Reactions carried out with 0.238 mmol of compound **370**, 0.714 mmol of **366** and 0.357 mmol of Lewis acid in 5 mL of DCM. b) % yield of purified material after column chromatography.

Table 18

3.9 Conclusions.

Intermolecular reactions of methylenecyclopropane and *N*-acyliminium ions have proved to be successful. A range of 5- and 6-membered rings with different substituents on the nitrogen have undergone reactions with TIPSMCP with good to excellent optimised yields with the allyl cation intermediate undergoing trapping from the Lewis acid. Although it was not possible to facilitate intramolecular cyclisations onto the allyl cation intermediate from either NH systems or from a nucleophilic aromatic ring, bicyclic structures were formed for the NH systems when pushed with a strong base. However, for the acyclic system **361,** $BF_3{\cdot}Et_2O$ and $SnCl_4$ were able to intramolecularly catalyse the formation of pyrrolidines **363** and **364**, thus showing that the intramolecular quench from the nitrogen lone pair could compete with the quench from the Lewis acid.

Reactions of lactams **365** and **366** with 1,1-disubstituted methylenecyclopropane **366** were mostly unsuccessful.

Intermolecular reactions between TIPSMCP and Boc-protected lactam **383** underwent an intramolecular quench by the Boc group to give 5,6-bicyclic compound **376** and 3,6-spirocyclic product **387**. The formation of the 3,6-spirocyclic product could be halted by using a 1,1-disubstituted methylenecyclopropane with TMS substitution due to the intermediate not being as stabilised by the silyl group.

Chapter 4 Experimental.

4.1 General experimental.

Reactions requiring anhydrous conditions were conducted in oven-dried or flame-dried glassware. For reactions at low temperatures acetone-card-ice baths were used. Materials were purchased from commercial sources and used as received. When necessary, solvents and materials were purified prior to use using standard techniques as described by Perrin and Armarego.[140]

All anhydrous solvents were prepared by refluxing with an appropriate drying agent and purified by distillation. THF was refluxed from sodium and benzophenone under argon until a persistent purple colour was maintained. DCM and triethylamine were refluxed from CaH_2. Petroleum ether was distilled at fractional boiling point between 40 °C and 60 °C. Nitroethane was distilled before use. The distilled solvents were taken using the usual syringe techniques. Methylenecyclopropane was handled using the experimental methods as described by Thomas.[24]

Thin layer chromatography was performed on aluminium backed sheets coated with silica gel (0.25 mm) containing the fluorescent indicator UV_{254}. The plates were visualised under UV lamp at 254 nm and/or using $KMnO_4$ or Ceric ammonium molybdate stains. Flash chromatography was performed following the procedure outlined by Still,[141] on Sorbil C_{60}, 40-60 mesh Silica. The eluent solvent ratios are reported by volume prior to mixing.

4.2 Instrumentation.

Infrared spectra were obtained on a Golden Gate Bio-Rad FT-IR spectrometer. Absorptions are given in wavenumbers (cm^{-1}). The relative intensity of the peaks are reported within the brackets using the following abbreviations; broad (b), strong (s), medium (m), weak (w).

^{1}H NMR spectra were recorded at 300 MHz on a Bruker AC 300 spectrometer or 400 MHz on a Bruker DPX 400 spectrometer using the deuterated solvent as the lock and the residual protons as internal standard. Peak positions are quoted against the δ scale relative to the residual chloroform signal (δ = 7.27), using the following abbreviations; singlet (s), doublet (d), triplet (t), quartet (q), quintuplet (quin) and multiplet (m). ^{13}C NMR spectra were obtained at 75.5 MHz on a Bruker AC 300 or at 100 MHz on a Bruker DPX 400 spectrometer using the solvent as lock and internal standard. ^{13}C spectra were proton decoupled and the multiplicities of the signals are quoted within the brackets using the following notation; quarternary (0), tertiary (1), secondary (2), primary (3), as supported by DEPT experiments at 135°. 1D GOESY and 2D correlation NOE, COSY and HMQC were carried out on some compounds to give conclusive assignment of the spectrum. Coupling constants, *J*, are measured in Hertz (Hz).

Low resolution CI and EI spectra were obtained on a Thermoquest TraceMS gas chromatography mass spectrometer, and ES^{+} mass spectra were obtained on a Micromass platform with a quadrupole mass analyser. High resolution CI and EI mass spectra were obtained on a VG 70SE normal geometry double focusing mass spectrometer. High resolution ES mass spectra were obtained on a Bruker Apex III FT-ICR mass spectrometer, or on a Micromass Q-Tof 1 mass spectrometer. M/z signals are reported in atomic mass units followed in brackets by the ion found and peak intensity.

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

4.3 Experimental for Chapter 2.

Methylenecyclopropane 1

Following the method described by Binger *et al.*[11]

Distilled methallyl chloride (280 mL, 2.84 mol) was added drop-wise over a 9 hour period to a rapidly stirred suspension of sodium amide (139 g, 3.56 mol) in dry di^{n}butyl ether (400 mL) at 130 – 140 °C under a slow stream of nitrogen. The reaction flask was fitted with a cold finger condenser (–70 °C) and 3 traps; the first trap was at room temperature and the two subsequent traps at –78 °C. The reaction mixture was refluxed for a further 10 hours after addition. The cold finger condenser was warmed to 30 – 40 °C and products were collected in the second trap. The upper layer of ammonia was allowed to evaporate. The lower layer contained a mixture of methylenecyclopropane **1** and methylcyclopropene **5** (100 mL, 52%) in a 4.7:1 ratio.

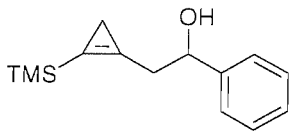
The resulting mixture was added to a solution of ^{t}BuOH (10 g, 0.13 mol) and distilled DMSO (25 mL) at 0 °C under a slow stream of nitrogen. ^{t}BuOK (8 g, 0.07 mol) in DMSO (25 mL) was added over a 3 hour period. The mixture was allowed to warm to 45 °C over a 14 hour period under a cold finger condenser at 60 °C. The cold finger was allowed to warm to 35 °C over 6 hours and methylenecyclopropane **1** (80 g, 100% from the mixture of isomers) was collected in traps at –78 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 5.42 (2H, s, CH_2), 1.08 (4H, s, CH_2CH_2) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 131.2 (0), 103.2 (2), 2.9 (2) ppm.

Spectroscopic data agrees with Binger *et al.*[11]

1-Phenyl-2-[2-trimethylsilyl-1-cyclopropenyl]ethanol 213



Following a method described by Sternberg *et al.*[18]

^{n}Butyllithium (2.37M, 16.0 mL, 25.6 mmol) was added to a stirring solution of methylenecyclopropane (12.9 mL, 25.6 mmol) in dry THF (80 mL) at –70 °C under nitrogen. The reaction mixture was warmed to room temperature over 1¼ hours, stirred at room temperature for 15 minutes and then cooled to –70 °C. Freshly distilled TMSCl (3.25 mL, 25.6 mmol) was added, the reaction mixture warmed to room temperature over 45 minutes, stirred at room temperature for 25 minutes before being cooled to –70 °C. ^{n}Butyllithium (2.37 M, 16.0 mL, 25.6 mmol) was added and the warming process repeated before addition of benzaldehyde (2.86 mL, 28.2 mmol) at –70 °C. The reaction was allowed to warm to room temperature, stirred for 18 hours and was then quenched with saturated ammonium chloride (40 mL). The aqueous layer was extracted with DCM, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material as a yellow oil. The crude material was purified by column chromatography (10% Et_2O–PE) to give the title compound **213** as a yellow oil (4.09 g, 69%).

Rf = 0.73 (3:7 PE–Et_2O).

FT–IR (solution) ν_{max} = 3347 (bw), 2952 (m), 2867 (m), 1790 (m), 1455 (m), 1244 (s), 999 (s), 839 (s) cm^{-1}.

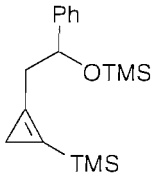
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.30 – 7.11 (5H, m, Ar), 4.85 (1H, t, *J* = 5.5 Hz, C*H*OH), 2.90 (1H, dd, *J* = 5.5, 16.0 Hz, PhCHCH_AH_B), 2.82 (1H, dd, *J* = 5.5, 16.0 Hz, PhCHCH_AH_B), 2.05 (1H, O*H*), 0.66 (1H, d, *J* = 7.5 Hz, CH_AH_BC(TMS)), 0.62 (1H, d, *J* = 7.5 Hz, CH_AH_BC(TMS)), –0.07 (9H, s, Si(CH_3)$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 145.0 (0), 132.6 (0), 129.6 (1), 129.2 (1), 127.3 (1), 110.4 (0), 73.9 (1), 40.0 (2), 7.5 (2), 0.0 (3) ppm.

LRMS (EI) *m/z* = 73 $[Si(CH_3)_3]^+$ 100%, 232 $[M]^+$ 5%.

HRMS (EI) $C_{14}H_{20}OSi$ $[M]^+$ requires 232.1283, found 232.1277.

1-Phenyl-2-[2-trimethylsilyl-1-cyclopropenyl]ethyl (trimethylsilyl) ether 214



Following the method of Corey.[114]

Et_3N (0.23 mL, 1.72 mmol) was added to a stirring solution of 1-phenyl-2-[2-trimethylsilyl-1-cyclopropenyl]ethanol **213** (200 mg, 0.86 mmol) in THF (6 mL) under nitrogen. Freshly distilled TMSCl (0.163 mL, 0.13 mmol) was added and the reaction was monitored by TLC. After 6½ hours the reaction was quenched with water (5 mL). The aqueous layer was extracted with Et_2O, washed with brine, dried ($MgSO_4$) and solvents removed *in vacuo*. The crude liquid was purified by column chromatography (20% Et_2O–PE) to give the title compound **214** as a yellow liquid (197 mg, 75%).

Rf = 0.73 (3:7 EtOAc–PE).

FT–IR (solution) ν_{max} = 2974 (m), 2882 (m), 1795 (m), 1244 (s), 1084 (m), 1069 (m), 904 (s), 834 (s), 729 (s) cm^{-1}.

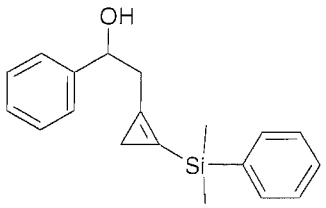
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.30 – 7.18 (5H, m, Ar), 4.90 (1H, t, *J* = 6.5 Hz, C*H*O(TMS)), 3.02 (1H, dd, *J* = 6.5, 14.5 Hz, PhCHCH_AH$_B$), 2.87 (1H, dd, *J* = 6.5, 14.5 Hz, PhCHCH$_A$$H_B$), 0.72 (1H, d, *J* = 7.5 Hz, CH_AH$_B$C(TMS)), 0.67 (1H, d, *J* = 7.5 Hz, CH$_A$$H_B$C(TMS)), 0.05 (9H, s, OSi(CH_3)$_3$), 0.00 (9H, s, Si(CH_3)$_3$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 144.9 (0), 132.0 (0), 128.2 (1), 127.3 (1), 126.1 (1), 108.2 (0), 73.2 (1), 37.9 (2), 6.4 (2), 0.2 (3), –1.4 (3) ppm.

LRMS (EI) *m/z* = 73 $[Si(CH_3)_3]^+$ 100%, 179 $[PhCHOSi(CH_3)_3]^+$ 100%, 231 $[M]^+$ 10%.

HRMS (EI) $C_{17}H_{28}OSi_2$ requires 304.1679, found 304.1681.

2-[2-(Dimethyl-phenyl-silyl)-cycloprop-1-enyl]-1-phenyl-ethanol 223



Following a method described by Sternberg et al.[18]

^{n}Butyllithium (2.31 M, 3.47 mL, 8.0 mmol) was added to a stirring solution of methylenecyclopropane (0.81 mL, 12.0 mmol) in dry THF (20 mL) at –70 °C under nitrogen. The reaction mixture was warmed to room temperature over 1½ hours, stirred at room temperature for 15 minutes and then cooled to –78 °C. Dimethylphenylsilylchloride (1.34 mL, 8.0 mmol) was added, the reaction mixture warmed to room temperature over 2½ hours, stirred at room temperature for 15 minutes before being cooled to –78 °C. ^{n}Butyllithium (2.31 M, 3.47 mL, 8.0 mmol) was added and the warming process repeated before addition of benzaldehyde (0.61 mL, 6.0 mmol) at –78 °C. The reaction was allowed to warm to room temperature and stirred for 17 hours followed by a quench with saturated ammonium chloride (20 mL). The aqueous phase was extracted with diethyl ether, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material as a yellow oil. The crude material was purified by column chromatography (1% Et_2O–PE) to give the title compound **223** as a yellow oil (2.0 g, 85%).

Rf = 0.32 (1:9 Et_2O–PE).

FT–IR (solution) ν_{max} = 3372 (bw), 2956 (m), 2874 (m), 1797 (m), 1247 (m), 1113 (m), 1008 (m), 834 (s), 814 (s) cm^{-1}.

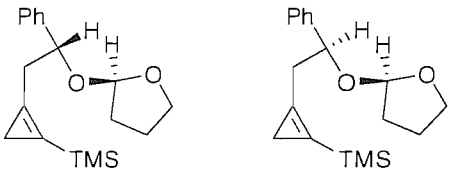
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.48 – 7.18 (10H, m, Ar), 4.78 (1H, t, *J* = 6.5 Hz, C*H*OH), 3.02 (1H, dd, *J* = 6.5, 16.0 Hz, PhCHCH_AH$_B$), 2.95 (1H, dd, *J* = 6.5, 16.0 Hz, PhCHCH$_A$$H_B$), 2.05 (bd, *J* = 3.0 Hz, O*H*), 0.82 (1H, s, CH_2CSi), 0.34 (6H, s, SiPh(CH_3)$_2$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 143.6 (0), 137.7 (0), 133.8 (1), 133.1 (0), 129.4 (1), 128.6 (1), 128.0 (1), 127.8 (1), 125.8 (1), 106.9 (0), 72.4 (1), 38.6 (2), 7.0 (2), –2.4 (3) ppm.

LRMS (EI) *m/z* = 135 $[SiPh(CH_3)_2]^+$ 100%, 294 $[M]^+$ 25%.

HRMS (EI) $C_{19}H_{22}OSi$ $[M]^+$ requires 294.1440, found 294.1429.

Trimethyl-{2-[2-phenyl-2-(tetrahydrofuran-2-yloxy)-ethyl]-cycloprop-1-enyl}-silane 231



A solution of 2-ethoxytetrahydofuran (26 mg, 0.237 mmol) in DCM (0.5 mL) was added to 1-phenyl-2-[2-trimethylsilyl-1-cyclopropenyl]ethanol **213** (50 mg, 0.215 mmol) in DCM (0.5 mL) at –78 °C under nitrogen followed by addition of the Lewis acid. The reaction was monitored by TLC and on completion the reaction mixture was quenched with water (5 mL). The aqueous layer was extracted with DCM, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (1% Et_2O–PE) to give the title compound **231** as a colourless liquid (for yields and conditions see **Table 3**).

Major diastereoisomer

Rf = 0.47 (1:4 Et_2O–PE).

FT–IR (solution) ν_{max} = 2954 (m), 2875 (m), 1799 (m), 1454 (w), 1247 (s), 1024 (s), 918 (m), 838 (s), 755 (m), 699 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.27 – 7.17 (5H, m, Ar), 4.95 – 4.84 (2H, m, OC*H*Ph & OC*H*O), 3.85 – 3.75 (2H, m, OCH_2), 3.02 (1H, dd, *J* = 7.0, 15.0 Hz, $PhCHCH_AH_B$), 2.81 (1H, dd, *J* = 7.0, 15.0 Hz, $PhCHCH_AH_B$), 1.95 – 1.70 (4H, m, OCH_2CH_2 and

$OCH_2CH_2CH_2$), 0.68 (1H, d, J = 7.5 Hz, CH_AH_BC(TMS)), 0.62 (1H, d, J = 7.5 Hz, CH_AH_BC(TMS)), 0.00 (9H, s, $Si(CH_3)_3$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 141.8 (0), 132.0 (0), 128.4 (1), 127.7 (1), 127.2 (1), 108.8 (0), 100.7 (1), 75.1 (1), 67.0 (2), 37.1 (2), 32.4 (2), 23.6 (2), 6.4 (2), −1.4 (3) ppm.

LRMS (CI) *m/z* = 71 $[(CH_2)_3CHO]^+$ 12%.

HRMS (EI) $C_{18}H_{25}O_2Si$ $[M - H]^+$ requires 301.1624, found 301.1612.

Minor diastereoisomer

Rf = 0.41 (1:4 Et_2O–PE).

FT–IR (solution) ν_{max} = 2955 (w), 2875 (w), 1799 (m), 1248 (m), 1035 (m), 839 (m) cm^{-1}.

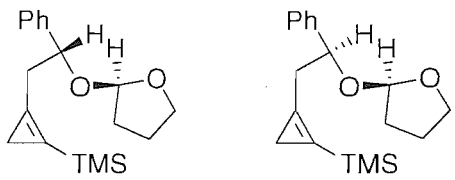
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.35 – 7.20 (5H, m, Ar), 5.32 (1H, m, OC*H*O), 4.85 (1H, t, J = 7.0 Hz, OC*H*Ph), 3.71 (1H, dd, J = 7.0, 14.0 Hz, $OCH_AH_BCH_2$), 3.63 (1H, dd, J = 6.0, 14.0 Hz, OCH_AH_B), 3.11 (1H, dd, J = 7.0, 15.5 Hz, $PhCHCH_AH_B$), 2.95 (1H, dd, J = 7.0, 15.5 Hz, $PhCHCH_AH_B$), 2.05 – 1.78 (4H, m, OCH_2CH_2 & $OCH_2CH_2CH_2$), 0.72 (2H, s, CH_2(TMS)), 0.08 (9H, s, $Si(CH_3)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 143.2 (0), 131.5 (0), 128.2 (1), 127.2 (1), 126.3 (1), 110.0 (0), 103.5 (1), 76.7 (1), 67.0 (2), 37.1 (2), 32.4 (2), 23.6 (2), 6.4 (2), −1.4 (3) ppm.

LRMS (CI) *m/z* = 71 $[(CH_2)_3CHO]^+$ 100.

HRMS (EI) $C_{18}H_{25}O_2Si$ $[M - H]^+$ requires 301.1622, found 301.1624.

Trimethyl-{2-[2-phenyl-2-(tetrahydrofuran-2-yloxy)-ethyl]-cycloprop-1-enyl}-silane 231 from 1-phenyl-2-[2-trimethylsilyl-1-cyclopropenyl]ethyl (trimethylsilyl) ether 214

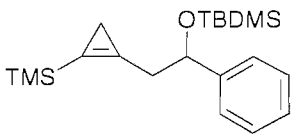


A solution of 2-ethoxytetrahydofuran (21 mg, 0.184 mmol) in DCM (0.5 mL) was added to 1-phenyl-2-[2-trimethylsilyl-1-cyclopropenyl]ethyl (trimethylsilyl) ether **214** (28 mg, 0.092 mmol) in DCM (0.5 mL) at −78 °C under nitrogen followed by addition of the Lewis

acid. The reaction was monitored by TLC and on completion the reaction mixture was quenched with water (5 mL). The aqueous layer was extracted with DCM, washed with brine, dried ($MgSO_4$) and solvents removed *in vacuo*. The crude liquid was purified by column chromatography (1% Et_2O–PE) to give the title compound **231** as a colourless liquid (for yields and conditions see **Table 4**).

Spectroscopic data identical to that previously described.

[2-(2-[1-(*tert*-Butyl)-dimethylsilyl]oxy-2-phenylethyl)-1-cyclopropenyl](triisopropyl)silane 232



Imidazole (0.76 g, 11.2 mmol) was added to a stirring solution of 1-phenyl-2-[2-trimethylsilyl-1-cyclopropenyl] ethanol **213** (1.3 g, 5.6 mmol) in THF (30 mL) at room temperature under nitrogen. TBDMSCl (1.26 g, 3.4 mmol) was added and the reaction was monitored by TLC. After 2 days there was no change to the reaction mixture so it was quenched with water (5 mL) and extracted with Et_2O. The organic layer was washed with brine, dried ($MgSO_4$) and solvents removed *in vacuo*. The liquid was purified by column chromatography (0 – 10% Et_2O–PE) to give the title compound **232** as a yellow liquid (960 mg, 48%).

Rf = 0.95 (1:4 Et_2O–PE).

FT–IR (solution) ν_{max} = 2962 (m), 2859 (m), 1799 (m), 1468 (m), 1241 (s), 1074 (s), 837 (s) cm^{-1}.

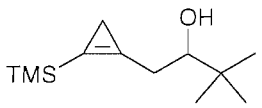
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.30 – 7.20 (5H, m, Ar), 4.42 (1H, t, J = 6.5 Hz, OC*H*Ph), 3.00 (1H, dd, J = 6.5, 14.5 Hz, PhCH_AH$_B$), 2.74 (1H, dd, J = 6.5, 14.5 Hz, PhCH$_A$$H_B$), 0.82 (9H, s, Si(CH$_3$)$_2$(CC$H_3$)$_3$), 0.72 (1H, d, J = 7.5 Hz, CH_AH$_B$C(TMS)), 0.68 (1H, d, J = 7.5 Hz, CH$_A$$H_B$C(TMS)) 0.05 – –0.25 (15H, m, Si(CH_3)$_2$(CCH$_3$)$_3$ & Si(CH_3)$_3$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 145.2 (0), 132.0 (0), 128.1 (1), 127.2 (1), 126.1 (1), 73.3 (1), 40.0 (2), 25.9 (3), 18.3 (0), 6.5 (2), –1.5 (3), –4.5 (3) ppm.

LRMS (EI) *m/z* = 73 $[Si(CH_3)_3]^+$ 100%, 346 $[M]^+$ 3%.

HRMS (EI^+) $C_{20}H_{34}OSi_2$ $[M]^+$ requires 346.2148, found 346.2160.

3,3-Dimethyl-1-[2-trimethylsilyl-1-cyclopropenyl] butan-2-ol 233



Following a method described by Sternberg *et al.*[18]

^{n}Butyllithium (2.32M, 5.17 mL, 12.0 mmol) was added to a stirring solution of methylenecyclopropane (1.22 mL, 18.1 mmol) in dry THF (40 mL) at –70 °C under argon. The reaction mixture was warmed to 0 °C over 1 hour, stirred at 0 °C for 15 minutes and then cooled to –70 °C. Freshly distilled TMSCl (1.52 mL, 12.0 mmol) was added, the reaction mixture warmed to 0 °C over 1 hour, stirred at 0 °C for 10 minutes before being cooled to –70 °C. ^{n}Butyllithium (2.37 M, 5.06 mL, 12.0 mmol) was added and the reaction mixture warmed to 0 °C over 1 hour, stirred at 0 °C for 10 minutes before addition of pivaldehyde (1.30 mL, 12.0 mmol) at –70 °C. The reaction was monitored by TLC. After 30 minutes the reaction mixture was quenched with saturated ammonium chloride (40 mL) and the aqueous phase extracted with diethyl ether. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material as a yellow oil. The crude material was purified by column chromatography (4% Et_2O–PE) to give the title compound **233** as a colourless oil (1.11g, 44%).

Rf = 0.34 (1:5 Et_2O–PE).

FT–IR (neat) ν_{max} = 3495 (b), 2955 (w), 2872 (w), 1795 (m), 1479 (m), 1363 (m), 1247 (m), 994 (m), 834 (s) cm^{-1}.

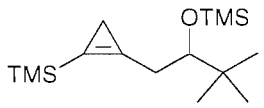
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 3.58 (1H, dd, *J* = 2.5, 10.0 Hz, C*H*OH), 2.79 (1H, dd, *J* = 2.5, 16.0 Hz, CH_AH_BCHOH), 2.60 (1H, dd, *J* = 10.0, 16.0 Hz, CH_AH_BCHOH), 1.85

(bs, O*H*), 0.98 (9H, s, C(CH_3)$_3$), 0.64 (1H, d, J = 7.5 Hz, CH_AH$_B$C(TMS)), 0.56 (1H, d, J = 7.5 Hz, CH$_A$$H_B$C(TMS)), 0.25 – 0.15 (9H, s, Si(CH_3)$_3$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 132.7 (0), 107.4 (0), 77.6 (1), 31.6 (2), 25.8 (3), 25.8 (3), 5.8 (2), –1.3 (3) ppm.

LRMS (CI) m/z = 73 [Si(CH$_3$) + H]$^+$ 100%, 213 [M + H]$^+$ 34%.

(2,2-Dimethyl-1{[2-trimethylsilyl-1-cyclopropenyl]methyl}propoxy)(trimethyl) silane 236



Following a method described by Corey.[114]

Et_3N (0.52 mL, 3.74 mmol) was added to a stirring solution of 3,3-dimethyl-1-[2-trimethylsilyl-1-cyclopropenyl] butan-2-ol **233** (400 mg, 1.87 mmol) in THF (12 mL) under argon. Freshly distilled TMSCl (0.36 mL, 2.86 mmol) was added and the reaction was monitored by TLC. After 3½ hours the reaction was quenched with saturated ammonium chloride (10 mL) and extracted with diethyl ether. The organic layer was washed with brine, dried ($MgSO_4$), solvents removed *in vacuo* and the resulting yellow liquid was purified by column chromatography (10% Et_2O–PE) to give the title compound **236** as a yellow liquid (0.52 g, 98%).

Rf = 0.69 (1:5 Et_2O–PE).

FT–IR (neat) ν_{max} = 2955 (m), 2873 (w), 1797 (w), 1479 (w), 1248 (m), 1095 (m), 832 (s), 751 (m) cm^{-1}.

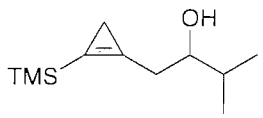
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 3.52 (1H, dd, J = 4.5, 6.5 Hz, C*H*O(TMS)), 2.62 (1H, dd, J = 4.5, 16.0 Hz, CH_AH$_B$CHO(TMS)), 2.44 (1H, dd, J = 6.5, 16.0 Hz, CH$_A$$H_B$CHO(TMS)), 0.62 (9H, s, C(CH_3)$_3$), 0.64 (1H, d, J = 7.5 Hz, CH_AH$_B$C(TMS)), 0.55 (1H, d, J = 7.5 Hz, CH$_A$$H_B$C(TMS)), –0.02 (9H, s, OSi(CH_3)$_3$), –0.12 (9H, s, CHSi(CH_3)$_3$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 133.9 (0), 106.1 (0), 79.0 (1), 35.8 (0), 33.1 (2), 26.1 (3), 26.0 (3), 25.9 (3), 6.5 (2), 0.7 (3), −1.2 (3) ppm.

LRMS (CI) *m/z* = 90 $[OSi(CH_3) + H]^+$ 100%, 285 $[M + H]^+$ 30%.

HRMS (EI) $C_{15}H_{31}OSi_2$ $[M - H]^+$ requires 283.1914, found 283.1929.

3-Methyl-1-[2-trimethylsilyl-1-cyclopropenyl]-butan-2-ol 234



Following a method described by Sternberg *et al.*[18]

^{n}Butyllithium (2.32M, 5.17 mL, 12.0 mmol) was added to a stirring solution of methylenecyclopropane (1.22 mL, 18.1 mmol) in dry THF (40 mL) at −70 °C under argon. The reaction mixture was warmed to 0 °C over 1 hour, stirred at 0 °C for 10 minutes and then cooled to −70 °C. Freshly distilled TMSCl (1.52 mL, 12.0 mmol) was added, the reaction mixture warmed to 0 °C over 1 hour, stirred at 0 °C for 10 minutes before being cooled to −70 °C. ^{n}Butyllithium (2.37 M, 5.06 mL, 12.0 mmol) was added and the reaction mixture warmed to 0 °C over 1 hour, stirred at 0 °C for 10 minutes before addition of isobutraldehyde (0.86 mL, 12.0 mmol) at −70°C. The reaction was monitored by TLC. After 30 minutes the reaction mixture was quenched with saturated ammonium chloride (40 mL) and the aqueous phase extracted with diethyl ether. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material as a yellow oil. The crude material was purified by column chromatography (2% Et_2O–PE) to give the title compound **234** as a yellow oil (1.50g, 63%).

Rf = 0.38 (4:1 PE–Et_2O).

FT–IR (solution) ν_{max} = 3423 (b), 2962 (m), 2875 (m), 1795 (w), 1252 (m), 997 (m), 839 (s), 758 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 3.68 (1H, m, C*H*OH), 2.80 (1H, dd, *J* = 4.0, 16.0 Hz, CH_AH$_B$CHOH), 2.61 (1H, dd, *J* = 8.0, 16.0 Hz, CH$_A$$H_B$CHOH), 1.82 – 1.70 (2H, m, CHC*H*$(CH_3)_2$ and O*H*), 0.98 (3H, d, *J* = 3.0 Hz, CH(CH_3)CH$_3$), 0.96 (3H, d, *J* = 3.5 Hz,

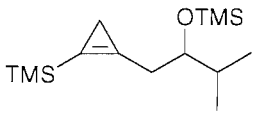
$CH(CH_3)CH_3$), 0.78 (1H, d, J = 7.5 Hz, $CH_AH_BC(TMS)$), 0.75 (1H, d, J = 7.5 Hz, $CH_AH_BC(TMS)$), 0.18 (9H, s, $Si(CH_3)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 131.8 (0), 107.6 (0), 74.9 (1), 33.7 (2), 33.2 (1), 18.9 (3), 17.6 (3), 5.9 (2), –1.3 (3) ppm.

LRMS (CI) m/z = 73 $[Si(CH_3)_3]^+$ 30%, 199 $[M + H]^+$ 100%.

HRMS (EI) $C_{11}H_{21}OSi$ $[M - H]^+$ requires 197.1362, found 197.1359.

2-Methyl-1{[2-trimethylsilyl-1-cyclopropenyl]methyl}propyl)(trimethylsilyl) ether 237



Following a method described by Corey.[114]

Et_3N (1.40 mL, 10.10 mmol) was added to a stirring solution of 3-methyl-1-[2-trimethylsilyl-1-cyclopropenyl]-butan-2-ol **234** (1.0 g, 5.05 mmol) in THF (20 mL) under argon. Freshly distilled TMSCl (0.96 mL, 7.57 mmol) was added and the reaction was monitored by TLC. After 23 hours the reaction was quenched with saturated ammonium chloride (10mL) and exracted with diethyl ether. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless liquid which was purified by column chromatography (2% Et_2O–PE) to give the title compound **237** as a colourless liquid (570 mg, 42%).

Rf = 0.90 (1:4 Et_2O–PE).

FT–IR (neat) ν_{max} = 2956 (m), 2886 (w), 1800 (w), 1152 (m), 1045 (m), 828 (s), 758 (m) cm^{-1}.

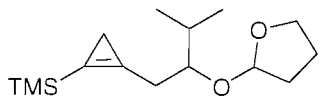
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 3.77 (1H, ddd, J = 4.5, 5.5, 6.5 Hz, $CHO(TMS)$), 2.76 (1H, dd, J = 6.5, 15.5 Hz, $CH_AH_BCHO(TMS)$), 2.69 (1H, dd, J = 5.5, 15.5 Hz, $CH_AH_BCHO(TMS)$), 1.70 (1H, dsept, J = 4.5, 7.0 Hz, $CHCH(CH_3)_2$), 0.92 (3H, d, J = 7.0 Hz, $CH(CH_3)CH_3$), 0.88 (3H, d, J = 7.0 Hz, $CH(CH_3)CH_3$), 0.76 (1H, d, J = 7.5 Hz, $CH_AH_BC(TMS)$), 0.72 (1H, d, J = 7.5 Hz, $CH_AH_BC(TMS)$), 0.18 (9H, s, $OSi(CH_3)_3$), 0.10 (9H, s, $CHSi(CH_3)_3$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 132.4 (0), 106.8 (0), 75.5 (1), 34.3 (2), 32.9 (1), 19.5 (3), 16.8 (3), 6.3 (2), 0.5 (3), −1.3 (3) ppm.

LRMS (CI) *m/z* = 90 $[OSi(CH_3) + H]^+$ 100%, 271 $[M + H]^+$ 38%.

HRMS (EI) $[M]^+ C_{14}H_{30}OSi_2$ requires 270.1835 found 270.1839.

Trimethyl-{2-[3-methyl-2-(tetrahydrofuran-2-yloxy)-butyl]-cycloprop-1-enyl}-silane 240



A solution of 2-ethoxytetrahydrofuran (24 mg, 0.185 mmol) in solvent (0.5 mL) was added to 2-methyl-1{[2-trimethylsilyl-1-cyclopropenyl]methyl}propyl)(trimethylsilyl) ether **237** (50 mg, 0.185 mmol) in solvent (0.5 mL) at −78 °C under argon followed by addition of the Lewis acid. The reaction was monitored by TLC and on completion the reaction mixture was quenched with saturated sodium bicarbonate (5 mL) and the aqueous layer was extracted with DCM. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give a liquid which was purified by column chromatography (0 – 1% Et_2O–PE) to give colourless liquid **240** (for yields and conditions see **Table 5**).

Rf = 0.76 (1:4 Et_2O–PE).

FT–IR ν_{max} = 2960 (m), 2875 (m), 1798 (w), 1248 (m), 1022 (s), 841 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.05 (1H, t, *J* = 3.0 Hz, (^{i}Pr)CHOC*H*O), 3.75 – 3.60 (2H, m, OCH_2CH_2), 3.53 (1H, dd, *J* = 5.5, 11.0 Hz, OC*H*(^{i}Pr)), 2.58 (2H, m, (^{i}Pr)CHCH_2), 1.80 – 1.65 (5H, m, OCH$_2$CH_2, OCH$_2$CH$_2$CH_2 and $(CH_3)_2$C*H*), 0.77 (3H, d, *J* = 6.5 Hz, CH(CH_3)CH$_3$), 0.75 (3H, d, *J* = 6.5 Hz, CH(CH_3)CH_3), 0.58 (2H, s, CH_2(TMS)), 0.00 (9H, s, Si(CH_3)$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 132.6 (0), 107.1 (0), 102.0 (1), 80.7 (1), 66.8 (2), 32.6 (2), 31.0 (1), 30.3 (2), 23.7 (2), 19.1 (3), 19.0 (3), 6.5 (2), −1.2 (3) ppm.

LRMS (CI) *m/z* = 71 $[(CH_2)_3OCH]^+$ 100%, 269 $[M + H]^+$ 50%.

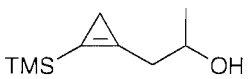
HRMS (ES^+) $[M + Na]^+ C_{15}H_{28}O_2SiNa$ requires 291.17517 found 291.1756.

For the other diastereoisomer the identifiable peaks in the NMR spectra are recorded below:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.02 (1H, t, *J* = 3.0 Hz, (^{i}Pr)CHOC*H*O), 3.49 (1H, dd, *J* = 5.0, 7.0 Hz, OC*H*(*i*-Pr)), 2.71 (1H, dd, *J* = 5.0, 16.0 Hz, (^{i}Pr)CHCH_AH$_B$), 2.62 (1H, dd, *J* = 7.0, 16.0 Hz, (^{i}Pr)CHCH$_A$*H$_B$*), 0.73 (3H, d, *J* = 7.0 Hz, CH(CH_3)CH$_3$), 0.72 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)CH_3), 0.59 (1H, d, J = 8.0 Hz, CH_AH$_B$(TMS)), 0.55 (1H, d, J = 8.0 Hz, CH$_A$*H$_B$*(TMS)) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 132.6 (0), 106.4 (0), 104.8 (1), 78.3 (1), 66.7 (2), 32.3 (2), 23.6 (2), 17.7 (3), 17.2 (3), 6.3 (2) ppm.

1-[2-(Trimethylsilyl)-1-cyclopropenyl] propan-2-ol 235



Following a method described by Sternberg *et al.*[18]

^{n}Butyllithium (2.37M, 5.06 mL, 12.0 mmol) was added to a stirring solution of methylenecyclopropane (1.22 mL, 18.1 mmol) in dry THF (40 mL) at –78 °C under argon. The reaction mixture was warmed to 10 °C over 1 hour, stirred at 10 °C for 15 minutes and then cooled to –70 °C. Freshly distilled TMSCl (1.52 mL, 12.0 mmol) was added, the reaction mixture warmed to 10 °C over 1 hour, stirred at 10 °C for 15 minutes before being cooled to –78 °C. ^{n}Butyllithium (2.37 M, 5.06 mL, 12.0 mmol) was added and the reaction mixture warmed to 0 °C over 1 hour, stirred at 0 °C for 10 minutes before addition of freshly distilled acetaldehyde (0.86 mL, 12.0 mmol) at –70 °C. The reaction was monitored by TLC. After 5 minutes (–78 °C) the reaction mixture was quenched with saturated ammonium chloride (20 mL) and the aqueous phase extracted with diethyl ether. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material as a yellow oil. The crude material was purified by column chromatography (1 – 2% Et_2O–PE) to give the title compound **235** as a yellow oil (38 mg, 27%).

Rf = 0.13 (4:1 PE–Et_2O).

FT–IR (solution) ν_{max} = 3328 (bs), 2963 (m), 2876 (m), 1796 (m), 1411 (w), 1251 (s), 1012 (m), 850 (s) cm^{-1}.

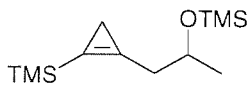
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 4.10 (1H, ddd, *J* = 6.0, 6.0, 6.0 Hz, C*H*OH), 2.75 (1H, dd, *J* = 6.0, 16.5 Hz, CH_AH$_B$CHOH), 2.70 (1H, dd, *J* = 6.0, 16.5 Hz, CH$_A$$H_B$CHOH), 2.10 (bs, O*H*), 1.25 (3H, d, *J* = 6.0 Hz, CH_3), 0.76 (1H, d, *J* = 7.5 Hz, CH_AH$_B$C(TMS)), 0.72 (1H, d, *J* = 7.5 Hz, CH$_A$$H_B$C(TMS)), 0.15 (9H, s, Si(CH_3)$_3$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 131.5 (0), 107.7 (0), 66.5 (1), 38.3 (2), 22.9 (3), 5.9 (2), −1.4 (3) ppm.

LRMS (CI) *m/z* = 155 $[M - CH_3]^+$ 70%, 171 $[M + H]^+$ 100%.

HRMS (CI) $[M - CH_3]^+$ $C_9H_{18}OSi$ requires 170.1127, found 170.1129.

1-Methyl-2-[2-trimethylsilyl-1-cyclopropenyl]ethyl(trimethylsilyl) ether 238



Following a method described by Corey.[114]

Et_3N (0.78 mL, 5.64 mmol) was added to a stirring solution of 1-[2-(trimethylsilyl)-1-cyclopropenyl]-propan-2-ol **235** (480 mg, 2.82 mmol) in THF (10 mL) under argon. Freshly distilled TMSCl (0.54 mL, 4.23 mmol) was added and the reaction was monitored by TLC. After 1¼ hours the reaction was quenched with saturated ammonium chloride (10mL) and extracted with diethyl ether. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material which was purified by column chromatography (PE) to give the title compound **238** as a colourless liquid (376 mg, 55%).

Rf = 0.73 (1:4 Et_2O–PE).

FT–IR (solution) ν_{max} = 2978 (m), 2871 (m), 1382 (m), 1110 (s), 901 (s), 721 (s) cm^{-1}.

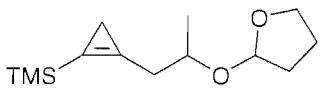
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 4.08 (1H, m, C*H*O(TMS)), 2.78 (1H, dd, *J* = 5.0, 15.5 Hz, CH_AH$_B$CHO(TMS)), 2.64 (1H, dd, *J* = 8.0, 15.5 Hz, CH$_A$$H_B$CHO(TMS)), 1.18 (3H, d, *J* = 6.0 Hz, CH_3), 0.78 (1H, d, *J* = 7.5 Hz, CH_AH$_B$C(TMS)), 0.72 (1H, d, *J* = 7.5 Hz, CH$_A$$H_B$C(TMS)), 0.18 (9H, s, OSi(CH_3)$_3$), 0.12 (9H, s, CHSi(CH_3)$_3$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 132.2 (0), 107.1 (0), 67.2 (1), 38.8 (2), 23.9 (3), 6.2 (2), 0.3 (3), –1.3 (3) ppm.

LRMS (CI) *m/z* = 90 $[OSi(CH_3) + H]^+$ 100%, 243 $[M + H]^+$ 40%.

HRMS (ES^+) $C_{24}H_{52}O_2Si_4Na$ $[2M + Na]^+$ requires 507.2937, found 507.2939.

Trimethyl-{2-[2-(tetrahydrofuran-2-yloxy)-propyl]-cycloprop-1-enyl}-silane 241



A solution of 2-ethoxytetrahydrofuran (24 mg, 0.185 mmol) in solvent (0.5 mL) was added to 1-methyl-2-[2-trimethylsilyl-1-cyclopropenyl]ethyl(trimethylsilyl) ether **238** (50 mg, 0.185 mmol) in solvent (0.5 mL) at –78 °C under argon followed by addition of the Lewis acid. The reaction was monitored by TLC and on completion the reaction mixture was quenched with saturated sodium bicarbonate (5 mL) and the aqueous layer was extracted with DCM. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material which was purified by column chromatography (0 – 1% Et_2O–PE) to give colourless liquid **241** as a 1:1 mixture of diastereoisomers (for yields and conditions see **Table 5**).

Rf = 0.47 (1:4 Et_2O–PE).

FT–IR ν_{max} = 2962 (s), 2881 (s), 1793 (m), 1244 (s), 1001 (s), 852 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.28 (1H, dd, *J* = 1.5, 4.5 Hz, $CH_3CHOCHO$), 4.02 (1H, m, CH_3CH), 3.92 – 3.82 (2H, m, OCH_2CH_2), 2.92 (1H, dd, *J* = 5.0, 15.5 Hz, $CH_3CHCH_AH_B$), 2.66 (1H, dd, *J* = 8.0, 15.5 Hz, $CH_3CHCH_AH_B$), 2.00 – 1.82 (4H, m, $OCH_2(CH_2)_2$), 1.24 (3H, d, *J* = 6.0 Hz, CH_3), 0.75 (1H, d, *J* = 8.0 Hz, $CH_AH_BC(TMS)$), 0.71 (1H, d, *J* = 8.0 Hz, $CH_AH_BC(TMS)$), 0.18 (9H, s, $Si(CH_3)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 133.4 (0), 108.0 (0), 103.3 (1), 71.9 (1), 67.3 (2), 38.0 (2), 34.1 (1), 33.9 (2), 23.3 (3), 7.6 (2), 0.00 (3) ppm.

LRMS (CI) *m/z* = 71 $[(CH_2)_3CHO]^+$ 100%, 241 $[M + H]^+$ 2%.

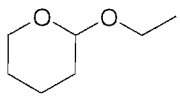
HRMS (ES^+) $C_{26}H_{48}O_4Si_2Na$ $[2M + Na]^+$ requires 503.2983, found 503.2990.

For the other diastereoisomer the identifiable peaks in the NMR spectra are recorded below:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.24 (1H, dd, *J* = 1.5, 4.5 Hz, $CH_3CHOCHO$), 2.85 (1H, dd, *J* = 5.5, 16.0 Hz, $CH_3CHCH_AH_B$), 2.62 (1H, dd, *J* = 7.0, 16.0 Hz, $CH_3CHCH_AH_B$), 1.18 (3H, d, *J* = 6.0 Hz, CH_3), 0.18 (9H, s, $Si(CH_3)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 133.5 (0), 108.5 (0), 104.3 (1), 72.7 (1), 68.1 (2), 36.8 (2), 24.9 (1), 24.8 (2), 21.1 (3), 7.5 (2), 2.5 (3) ppm.

2-Ethoxytetrahydro-2*H*-pyran 242



Follwing the method of Dado and Gellman.[142]

Dihydropyran (8.2 mL, 90 mmol) was added to ethanol (1.72 mL, 30 mmol) and *p*-toluenesulphonic acid (50 mg, 3 mmol) in 1,4-dioxane (50 mL) at room temperature. After 2 hours the solution was neutralised with saturated aqueous $NaHCO_3$ and partitioned between water and EtOAc. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material which was purified by column chromatography (10% Et_2O–PE) to give the title compound **242** as a yellow liquid (2.07 g, 53%).

Rf = 0.43 (1:4 Et_2O–PE).

FT–IR (solution) ν_{max} = 2975 (m), 2881 (w), 1109 (m), 1035 (s) cm^{-1}.

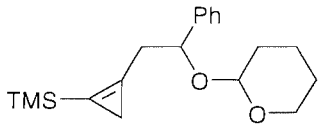
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 4.58 (1H, dd, *J* = 3.0, 4.5 Hz, $CHOC_2H_5$), 3.92 – 3.75 (2H, m, $CHOCH_2CH_2$), 3.52 – 3.40 (2H, m, OCH_2CH_3), 1.90 – 1.45 (6H, m, 3 × CH_2), 0.85 (3H, t, *J* = 7.0 Hz, CH_3) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 98.9 (1), 63.0 (2), 62.2 (2), 30.9 (2), 25.6 (2), 19.9 (2), 15.4 (3) ppm.

LRMS (EI) *m/z* = 85 $[M - OEt]^+$ 100%, 130 $[M]^+$ 4%.

Spectroscopic data agrees with that given by Booth and Readshaw.[143]

Trimethyl-{2-[2-phenyl-2-(tetrahydropyran-2-yloxy)-ethyl]-cycloprop-1-enyl}-silane 243



A solution of 2-ethoxytetrahydopyran (23 mg, 0.180 mmol) in MeCN (0.5 mL) was added to 1-phenyl-2-[2-trimethylsilyl-1-cyclopropenyl]ethanol **214** (50 mg, 0.164 mmol) in MeCN (0.5 mL) at –78 °C under argon followed by addition of the Lewis acid. The reaction was monitored by TLC and on completion the reaction mixture was quenched with saturated sodium bicarbonate (5 mL) and extracted with DCM. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material which was purified by column chromatography (0 – 1% Et_2O–PE) to give the colourless liquid **214** (for yields and conditions see **Table 6**).

Rf = 0.80 (1:4 Et_2O–PE).

FT–IR (solution) ν_{max} = 2956 (m), 2870 (m), 1800 (w), 1257 (m), 1116 (m), 1018 (s), 834 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.30 – 7.15 (5H, m, Ar), 4.92 (1H, t, *J* = 7.0 Hz, PhC*H*), 4.40 (1H, t, *J* = 3.5 Hz, PhCHOC*H*), 3.82 (1H, ddd, *J* = 3.5, 8.5, 11.0 Hz, $OCH_AH_BCH_2$), 3.42 (1H, m, $OCH_AH_BCH_2$), 3.12 (1H, dd, *J* = 7.0, 14.5 Hz, $PhCHCH_AH_B$), 2.91 (1H, dd, *J* = 7.0, 14.5 Hz, $PhCHCH_AH_B$), 1.90 – 1.35 (6H, m, 3 × CH_2), 0.68 (1H, d, *J* = 7.5 Hz, CH_AH_BCTMS)), 0.64 (1H, d, *J* = 7.5 Hz, CH_AH_BCTMS)), 0.00 (9H, s, $Si(CH_3)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 141.8 (0), 131.0 (0), 131.7 (1), 127.3 (1), 126.2 (1), 108.3 (0), 95.2 (1), 75.1 (1), 62.0 (2), 37.1 (2), 30.7 (2), 25.7 (2), 19.3 (2), 6.6 (2), –1.47 (3) ppm.

LRMS (CI) *m/z* = 85 $[(CH_2)_4OCH]^+$ 100%, 317 $[M + H]^+$ 8%.

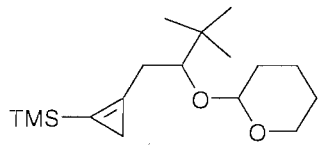
HRMS (ES^+) $[M + Na]^+$ $C_{19}H_{28}O_2SiNa$ requires 339.1751, found 339.1752.

For the other diastereoisomer the identifiable peaks are recorded below:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.85 (1H, t, *J* = 6.5 Hz, PhC*H*), 4.78 (1H, t, *J* = 3.5 Hz, PhCHOC*H*), 3.52 (1H, ddd, *J* = 3.5, 9.5, 11.5 Hz, $OCH_AH_BCH_2$), 3.25 (1H, m, $OCH_AH_BCH_2$), 3.06 (1H, dd, *J* = 6.5, 15.0 Hz, $PhCHCH_AH_B$), 2.92 (1H, dd, *J* = 6.5, 15.0 Hz, $PhCHCH_AH_BH$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 143.1 (0), 131.7 (0), 97.9 (1), 76.5 (1), 61.9 (2), 36.2 (2), 1.2 (3) ppm.

{2-[3,3-Dimethyl-2-(tetrahydropyran-2-yloxy)-butyl]-cycloprop-1-enyl}-trimethylsilane 244



A solution of 2-ethoxytetrahydopyran (24 mg, 0.185 mmol) in MeCN (0.5 mL) was added to (2,2-dimethyl-1{[2-trimethylsilyl-1-cyclopropenyl]methyl}propoxy) (trimethyl) silane **236** (50 mg, 0.168 mmol) in MeCN (0.5 mL) at –78 °C under argon followed by addition of $Yb(OTf)_3$ (12 mg, 0.02 mmol). The reaction was monitored by TLC and on completion the reaction mixture was quenched with saturated sodium bicarbonate (5 mL) and extracted with DCM. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material which was purified by column chromatography (0 – 1% Et_2O–PE) to give the colourless liquid **244** as a 3:1 mixture of diastereoisomers (6 mg, 12%).

Rf = 0.71 (1:4 Et_2O–PE).

FT–IR (solution) ν_{max} = 2955 (w), 2875 (w), 1799 (m), 1248 (m), 1035 (m), 840 (s) cm^{-1}.

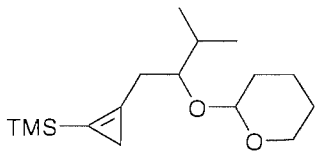
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.38 (1H, dd, *J* = 3.0, 4.5 Hz, OC*H*O), 3.76 (1H, m, $OCH_AH_B(CH_2)_3$), 3.54 (2H, dd, *J* = 4.5, 5.5 Hz, $OCHC(CH_3)_3$), 3.25 (1H, m, $OCH_AH_B(CH_2)_3$), 2.65 (1H, dd, *J* = 4.5, 16.0 Hz, (^{t}Bu)$CHCH_AH_B$), 2.48 (1H, dd, *J* = 5.5, 16.0 Hz, (^{t}Bu)$CHCH_AH_B$), 1.70 – 1.25 (6H, m, $(CH_2)_3$), 0.76 (9H, s, $C(CH_3)_3$), 0.64 (2H, s, CH_2(TMS)), 0.02 (9H, s, $Si(CH_3)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 135.6 (0), 107.5 (0), 98.6 (1), 82.9 (1), 64.5 (2), 36.5 (0), 32.4 (2), 31.6 (2), 27.9 (3), 27.0 (2), 21.6 (2), 8.4 (2), 0.0 (3) ppm.

LRMS (CI) *m/z* = 297 $[M + H]^+$ 100%.

HRMS (EI) $C_{17}H_{32}O_2Si$ $[M]^+$ requires 296.2172 found 296.2161

Trimethyl-{2-[3-methyl-2-(tetrahydropyran-2-yloxy)-butyl]-cycloprop-1-enyl}-silane 245



A solution of 2-ethoxytetrahydopyran (26 mg, 0.203 mmol) in solvent (0.5 mL) was added to 2-methyl-1{[2-trimethylsilyl-1-cyclopropenyl]methyl}propyl(trimethylsilyl) ether **237** (50 mg, 0.185 mmol) in solvent (0.5 mL) at –78 °C under argon followed by addition of the Lewis acid. The reaction was monitored by TLC and on completion the reaction mixture was quenched with saturated sodium bicarbonate (5 mL) and extracted with DCM. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material which was purified by column chromatography (0 – 1% Et_2O–PE) to give the colourless liquid **245** (for yields and conditions see **Table 6**).

Rf = 0.75 (1:4 Et_2O–PE).

FT–IR (solution) ν_{max} = 2960 (m), 2875 (w), 1790 (w), 1253 (m), 1022 (m), 836 (m), 756 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.60 (1H, m, OC*H*O), 3.95 (1H, m, $COCH_AH_BCH_2$), 3.75 (1H, dd, *J* = 5.5, 11.0 Hz, OC*H*(^{i}Pr)), 3.50 (1H, m, $COCH_AH_BCH_2$), 2.78 (2H, d, *J* = 5.5 Hz, (^{i}Pr)CHCH_2), 1.98 – 1.50 (7H, m, 3 × CH_2 and $(CH_3)_2CH$), 0.99 (3H, d, *J* = 6.0 Hz, $CH(CH_3)CH_3$), 0.97 (3H, d, *J* = 6.0 Hz, $CH(CH_3)CH_3$), 0.72 (2H, s, CH_2(TMS)), 0.18 (9H, s, $Si(CH_3)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 133.9 (0), 107.7 (0), 98.2 (1), 80.1 (1), 63.8 (2), 33.4 (2), 31.1 (2), 27.0 (2), 21.2 (2), 20.3 (1), 19.5 (3), 7.6 (2), 0.00 (3) ppm.

LRMS (CI) *m/z* = 85 $[(CH_2)_4OCH]^+$ 100%, 283 $[M + H]^+$ 70%.

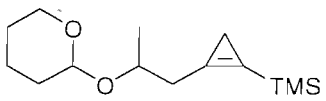
HRMS (ES^+) $C_{16}H_{30}O_2SiNa$ $[M + Na]^+$ requires 305.1907, found 305.1709.

For the other diastereoisomer the identifiable peaks are recorded below:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 3.68 (1H, dd, *J* = 5.0, 7.0 Hz, OC*H*(^{i}Pr)), 2.95 (1H, dd, *J* = 5.0, 16.0 Hz, $(CH_3)_2CHCHCH_AH_B$), 2.85 (1H, dd, *J* = 7.0, 16.0 Hz, (^{i}Pr)$CHCH_AH_B$), 0.91 (3H, d, *J* = 6.5 Hz, $CH(CH_3)CH_3$), 0.72 (3H, d, *J* = 6.5 Hz, $CH(CH_3)CH_3$), 0.08 (9H, s, $Si(CH_3)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 133.8 (0), 108.3 (0), 101.5 (1), 83.2 (1), 63.9 (2), 32.6 (2), 32.4 (2), 21.1 (1), 18.3 (3), 7.6 (2), 2.45 (3) ppm.

Trimethyl-{2-[2-(tetrahydropyran-2-yloxy)-propyl]-cycloprop-1-enyl}-silane 246



A solution of 2-ethoxytetrahydopyran (30 mg, 0.227 mmol) in MeCN (0.5 mL) was added to 1-methyl-2-[2-trimethylsilyl-1-cyclopropenyl]ethyl (trimethylsilyl) ether **238** (50 mg, 0.207 mmol) in MeCN (0.5 mL) at –78 °C under argon followed by addition of the Lewis acid. The reaction was monitored by TLC and on completion the reaction mixture was quenched with saturated sodium bicarbonate (5 mL) and extracted with DCM. The organic layer was washed with brine, dried ($MgSO_4$) and solvents removed *in vacuo* to give a liquid which was purified by column chromatography (0 – 1% Et_2O–PE) to give the colourless liquid **246** (for yields and conditions see **Table 6**).

Rf = 0.60 (1:4 Et_2O–PE).

FT–IR (solution) ν_{max} = 2957 (m), 2870 (m), 1793 (m), 1254 (s), 1020 (s), 827 (s), 990 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.58 (1H, dd, *J* = 3.0, 4.5 Hz, $CH_3CHOCHO$), 3.90 (1H, m, CH_3CH), 3.80 – 3.68 (2H, m, OCH_2CH_2), 3.40 – 3.30 (2H, m, OCH_2CH_2), 2.81 (1H, dd, *J* = 4.5, 15.5 Hz, $CH_3CHCH_AH_B$), 2.55 (1H, dd, *J* = 5.5, 15.5 Hz, $CH_3CHCH_AH_B$),

1.70 – 1.30 (4H, m, OCH(CH_2)$_2$), 1.10 (3H, d, J = 6.0 Hz, CH_3), 0.59 (1H, d, J = 8.0 Hz, CH_AH$_B$C(TMS)), 0.57 (1H, d, J = 8.0 Hz, CH$_A$$H_B$C(TMS)), 0.00 (9H, s, Si(CH_3)$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 133.3 (0), 108.2 (0), 97.9 (1), 71.8 (1), 64.2 (2), 63.7 (2), 38.0 (2), 32.6 (2), 27.0 (2), 23.1 (3), 7.6 (2), 0.00 (3) ppm.

LRMS (CI) m/z = 85 $[(CH_2)_4OCH]^+$ 100%, 255 $[M + H]^+$ 4%.

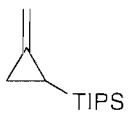
HRMS (ES^+) $C_{28}H_{52}O_4Si_2Na$ $[2M + Na]^+$ requires 531.3296, found 531.3297.

For the other diastereoisomer the identifiable peaks are recorded below:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.50 (1H, dd, J = 3.0, 4.5 Hz, $CH_3CHOCHO$), 2.69 (1H, dd, J = 5.0, 15.5 Hz, $CH_3CHCH_AH_B$), 2.47 (1H, dd, J = 7.5, 15.5 Hz, $CH_3CHCH_AH_B$), 1.02 (3H, d, J = 6.0 Hz, CH_3), 0.57 (2H, s, CH_2C(TMS)) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 133.5 (0), 108.6 (0), 99.2 (1), 72.7 (1), 36.7 (2), 32.5 (2), 26.9 (2), 20.9 (3), 7.5 (2) ppm.

Triisopropylsilane methylenecyclopropane 175



Following the method described by Patient.[22, 23]

^{n}Butyllithium (30.2 mL of 2.5 M, 74.1 mmol in THF) was added to methylenecyclopropane **1** (5 mL, 74.1 mmol) under argon at –78 °C. The reaction was allowed to warm to 0 °C over 40 minutes and kept at room temperature over a further 40 minutes. The resulting yellow solution was cooled to –78 °C before the addition of triisopropylsilyl chloride (15.8 mL, 74.1 mmol). The solution turned colourless and was allowed to warm to room temperature overnight and quenched with saturated ammonium chloride. The aqueous layer was extracted with diethyl ether, washed with brine, dried ($MgSO_4$) and solvents removed *in vacuo*. The crude material was purified by column chromatography (PE) to give the methylenecyclopropane derivative **175** as a colourless liquid (15.1 g, 97%).

Rf = 0.80 (1:1 PE–Et_2O).

FT–IR(solution) ν_{max} = 2941 (m), 2864 (m), 1729 (w), 1468 (m), 881 (s) cm^{-1}.

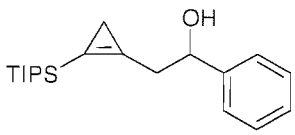
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 5.34 (1H, dt, *J* = 4.5, 2.0 Hz, CCH_AH_B), 5.24 (1H, ddd, *J* = 1.0, 2.0, 4.5 Hz, CCH_AH_B), 1.33 – 1.24 (2H, m, CH_2CH(TIPS)), 1.12 – 1.02 (21H, m, $Si(CH(CH_3)_2)_3$), 0.62 (1H, m, (TIPS)$CH$$CCH_2$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 134.8 (0), 100.5 (2), 18.9 (3), 11.5 (1), 6.2 (2), 0.3 (1) ppm.

LRMS (EI) *m/z* = 167 $[M - {}^{i}Pr]^+$ 34%.

Spectroscopic data agrees with Patient.[22]

1-Phenyl-2-[2-(triisopropylsilyl)-1-cyclopropenyl]ethanol 247



Following a method described by Sternberg *et al.*[18]

^{n}Butyllithium (2.54 M, 4.92 mL, 9.36 mmol) was added to a stirring solution of TIPSMCP **175** (2.00 g, 9.36 mmol) in dry THF (40 mL) at –78 °C under nitrogen. The reaction mixture was warmed to 0 °C over 40 minutes and then cooled to –78 °C before the addition of benzaldehyde (1.00 mL, 9.36 mmol). After 23 hours the reaction mixture was quenched with saturated ammonium chloride (5 mL) and the aqueous phase extracted with diethyl ether. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material as a yellow oil. The crude material was purified by column chromatography (0 – 5% Et_2O–PE) to give the title compound **247** as a yellow oil (1.57g, 53%).

Rf = 0.25 (1:4 Et_2O–PE).

FT–IR (neat) ν_{max} = 3362 (b), 2938 (s), 2862 (s), 1793 (m), 1460 (m), 995 (s), 884 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.42 – 7.25 (5H, m, Ar), 5.08 (1H, dd, *J* = 5.5, 7.5 Hz, CHOH), 3.10 (1H, dd, *J* = 7.5, 15.0 Hz, PhCHCH_AH_B), 3.05 (1H, dd, *J* = 5.5, 15.0 Hz,

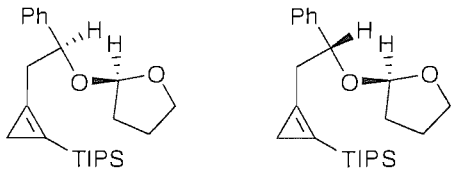
PhCHCH$_A$*H$_B$*), 2.28 (1H, bs, O*H*), 1.20 – 1.02 (21H, m, Si((C*H*(C*H*$_3$)$_2$)$_3$), 0.84 (1H, d, *J* = 7.5 Hz, C*H$_A$*H$_B$C(TIPS)), 0.81 (1H, d, *J* = 7.5 Hz, CH$_A$*H$_B$*C(TIPS)) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 143.7 (0), 131.7 (0), 128.6 (1), 127.8 (1), 125.9 (1), 105.6 (0), 72.5 (1), 38.8 (2), 18.9 (3), 11.5 (1), 6.9 (2) ppm.

LRMS (EI) *m/z* = 273 $[M - {}^{i}Pr]^+$ 65%, 316 $[M]^+$ 6%.

HRMS (EI) $C_{20}H_{31}OSi$ $[M - H]^+$ requires 315.2144, found 315.2136.

Triisopropyl-{2-[2-phenyl-2-(tetrahydrofuran-2-yloxy)-ethyl]-cycloprop-1-enyl}-silane 248



A solution of 2-ethoxytetrahydrofuran (403 mg, 3.481 mmol) in DCM (10 mL) was added to 1-phenyl-2-[2-triisopropylsilyl-1-cyclopropenyl] ethanol **247** (1.00 g, 3.164 mmol) in DCM (10 mL) at –78 °C under nitrogen followed by addition of $In(OTf)_3$ (178 mg, 0.316 mmol). The reaction was monitored by TLC and after 4 hours the reaction mixture was quenched with water (5 mL) and extracted with DCM. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude liquid was purified by column chromatography (2 – 10% Et_2O–PE) to give products **248** as a mixture of diastereoisomers.

Major diastereoisomer (578 mg, 48%).

Rf = 0.67 (1:4 Et_2O–PE).

FT–IR (solution) ν_{max} = 2942 (m), 2865 (m), 1727 (w), 1461 (w), 1019 (w), 905 (s), 729 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.30 – 7.15 (5H, m, Ar), 4.95 (1H, dd, *J* = 6.5, 7.5 Hz, OC*H*Ph), 4.87 (1H, m, OC*H*O), 3.85 – 3.62 (2H, m, OC*H*$_2$), 3.02 (1H, dd, *J* = 7.5, 14.5 Hz, PhCHC*H$_A$*H$_B$), 2.82 (1H, dd, *J* = 6.5, 14.5 Hz, PhCHCH$_A$*H$_B$*), 2.00 – 1.71 (4H, m,

OCH_2CH_2 and $OCH_2CH_2CH_2$), 1.05 – 0.85 (21H, m, Si((C*H*(CH_3)$_2$)$_3$), 0.76 (1H, d, *J* = 7.5 Hz, CH_AH_BC(TIPS)), 0.67 (1H, d, *J* = 7.5 Hz, CH_AH_BC(TIPS)) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 141.8 (0), 133.2 (0), 128.2 (1), 127.8 (1), 127.2 (1), 104.5 (0), 100.6 (1), 75.1 (1), 67.0 (2), 37.6 (2), 32.4 (2), 23.5 (2), 18.8 (3), 11.4 (1), 7.2 (1) ppm.

LRMS (CI) *m/z* = 71 $[(CH_2)_3CHO]^+$ 100%, 343 $[M - {}^iPr]^+$ 8%, 387 $[M + H]^+$ 2%.

Minor diastereoisomer (289 mg, 24%).

Rf = 0.52 (1:4 Et_2O–PE).

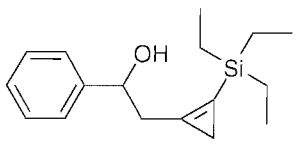
FT–IR (solution) ν_{max} = 2942 (w), 2864 (w), 1461 (w), 1020 (m), 905 (s), 728 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.30 – 7.12 (5H, m, Ar), 5.22 (1H, m, OC*H*O), 4.82 (1H, dd, *J* = 5.5, 7.0 Hz, OC*H*Ph), 3.68 – 3.50 (2H, m, OCH_2CH_2), 3.01 (1H, dd, *J* = 7.5, 14.5 Hz, PhCHCH_AH_B), 2.84 (1H, dd, *J* = 5.5, 14.5 Hz, PhCHCH_AH_B), 1.89 – 1.90 (4H, m, OCH_2CH_2 & $OCH_2CH_2CH_2$), 1.10 – 0.95 (21H, m, Si((C*H*(CH_3)$_2$)$_3$), 0.72 (1H, d, *J* = 7.5 Hz, CH_AH_BC(TIPS)), 0.66 (1H, d, *J* = 7.5 Hz, CH_AH_BC(TIPS)) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 143.6 (0), 132.9 (0), 128.2 (1), 127.2 (1), 126.2 (1), 104.7 (0), 103.3 (1), 76.9 (1), 67.0 (2), 37.2 (2), 32.6 (2), 23.4 (2), 18.8 (3), 11.5 (1), 7.5 (2) ppm.

LRMS (CI) *m/z* = 71 $[(CH_2)_3CHO]^+$ 100, 343 $[M - {}^iPr]^+$ 5%, 387 $[M + H]^+$ 2%.

1-Phenyl-2-(2-triethylsilyl-cycloprop-1-enyl)-ethanol 249



Following a method described by Sternberg *et al.*[18]

^{n}Butyllithium (1.6 M, 6.2 mL, 9.9 mmol) was added to a stirring solution of methylenecyclopropane (1.0 mL, 14.8 mmol) in dry THF (20 mL) at –70 °C under nitrogen. The reaction mixture was warmed to 10 °C over 1 hour and kept at 10 °C for 5 minutes before cooling to –70 °C. Chlorotriethyl silane (1.65 mL, 9.9 mmol) was added,

the reaction mixture warmed to 10 °C over 1 hour and cooled to –70 °C. ^{n}Butyllithium (1.6 M, 6.2 mL, 9.9 mmol) was added and the reaction mixture warmed to room temperature over 1 hour and cooled to –70 °C before addition of benzaldehyde (1.1 mL, 10.9 mmol). The reaction was quenched with saturated ammonium chloride (5 mL) and the aqueous phase washed with ethyl acetate. After a normal workup the organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material as a yellow liquid. The crude material was purified by column chromatography (0 – 10% EtOAc–hexane) to give compound **249** as a colourless oil (863 mg, 32%).

Rf = 0.68 (1:4 EtOAc– hexane).

FT–IR (neat) ν_{max} = 3476 (bw), 2955 (w), 2875 (w), 1738 (s), 1732 (m), 1255 (s), 1044 (m) cm^{-1}.

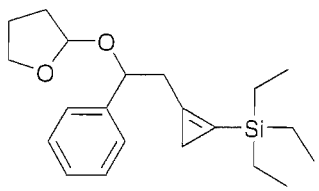
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.40 – 7.46 (5H, m, Ar), 5.03 (1H, m, C*H*OH), 3.07 (1H, dd, *J* = 7.0, 15.5 Hz, CH_AH$_B$CHOH), 3.02 (1H, dd, *J* = 5.0, 15.5 Hz, CH$_A$$H_B$CHOH), 2.22 (1H, bs, *J* = 2.0 Hz, O*H*), 0.93 (6H, t, *J* = 8.0 Hz, Si(CH_2CH$_3$)$_3$), 0.81 (1H, d, *J* = 7.5 Hz, CH_AH$_B$CSi), 0.79 (1H, d, *J* = 7.5 Hz, CH$_A$$H_B$CSi), 0.63 (9H, q, *J* = 8.0 Hz, Si(CH$_2$CH_3)$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 143.5 (0), 131.9 (0), 128.4 (1), 127.6 (1), 125.8 (1), 106.5 (0), 72.3 (1), 38.7 (2), 7.5 (3), 6.2 (2), 3.7 (2) ppm.

LRMS (EI) *m/z* = 245 $[M - Et]^+$ 100%, 274 $[M]^+$ 36%.

HRMS (ES^+) $C_{17}H_{26}OSi$ $[M]^+$ requires 275.1835, found 275.1831.

Triethyl-{2-[2-phenyl-2-(tetrahydrofuran-2-yloxy)-ethyl]-cycloprop-1-enyl}-silane 253



A solution of 2-ethoxytetrahydrofuran (23 mg, 0.201 mmol) in DCM (0.5 mL) was added to 1-phenyl-2-(2-triethylsilyl-cycloprop-1-enyl)-ethanol **249** (50 mg, 0.182 mmol) in DCM (0.5 mL) at –78 °C under nitrogen followed by addition of In(OTf)$_3$ (10 mg, 0.018 mmol).

The reaction was monitored by TLC and after 1 hour at –78 °C it was quenched with water (5 mL) and extracted with DCM. After a normal workup the organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material as a yellow oil. The crude material was purified by column chromatography (0 – 1% EtOAc–hexane) to give colourless oil **253** as a mixture of diastereoisomers (33 mg, 52%).

Rf = 0.38 (1:4 EtOAc– hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.35 – 7.18 (5H, m, Ar), 5.00 – 4.95 (2H, m, PhC*H*OCH and PhCHOC*H*), 3.86 (2H, m, OCH_2CH_2), 3.07 (1H, dd, J = 7.5, 14.5 Hz, PhCHCH_AH_B), 2.88 (1H, dd, J = 6.5, 14.5 Hz, PhCHCH_AH_B), 2.03 – 1.78 (4H, m, OCH_2CH_2 and $OCH_2CH_2CH_2$), 0.88 – 0.80 (9H, m, $Si(CH_2CH_3)_3$), 0.76 (1H, d, J = 8.0 Hz, CH_AH_BCSi), 0.71 (1H, d, J = 8.0 Hz, CH_AH_BCSi), 0.06 – –0.01 (6H, m, $Si(CH_2CH_3)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 141.8 (0), 132.8 (0), 128.4 (1), 127.7 (1), 127.2 (1), 106.4 (0), 100.7 (1), 75.0 (1), 67.0 (2), 37.2 (2), 32.4 (2), 26.5 (3), 23.5 (2), 6.8 (2), –7.0 (2) ppm.

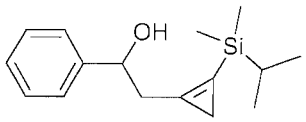
HRMS (ES^+) $C_{21}H_{33}O_2Si$ $[M + H]^+$ requires 345.2250, found 345.2239.

For the minor diastereoisomer the identifiable peaks are recorded below:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.29 (1H, d, J = 4.5 Hz, PhCHOC*H*), 4.86 (1H, t, J = 4.5 Hz, PhC*H*OCH), 3.68 (1H, dd, J = 8.0, 12.0 Hz, $OCH_AH_BCH_2$), 3.61 (1H, dd, J = 6.0, 12.0 Hz, $OCH_AH_BCH_2$), 0.88 – 0.80 (9H, m, $Si(CH_2CH_3)_3$), 0.76 (1H, d, J = 8.0 Hz, $SiCH_AH_B$), 0.71 (1H, d, J = 8.0 Hz, $SiCH_AH_B$), 0.06 – –0.01 (6H, m, $Si(CH_2CH_3)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 103.5 (1), 76.7 (1), 36.7 (2), 32.6 (2), 23.4 (2), 7.0 (2), –6.9 (2) ppm.

2-[2-(Isopropyl-dimethylsilyl)-cycloprop-1-enyl]-1-phenyl-ethanol 250



Following a method described by Sternberg *et al.*[18]

^{n}Butyllithium (1.6 M, 7.71 mL, 12.34 mmol) was added to a stirring solution of methylenecyclopropane (1.25 mL, 18.51 mmol) in dry THF (20 mL) at –70 °C under nitrogen. The reaction mixture was warmed to 10 °C over 1 hour and kept at 10 °C for 5 minutes before cooling to –70 °C. ^{i}Propyldimethylsilylchloride (1.67 g, 12.34 mmol) was added, the reaction mixture warmed to 10 °C over 1 hour and cooled to –70 °C. ^{n}Butyllithium (1.6 M, 7.71 mL, 12.34 mmol) was added and the reaction mixture warmed to room temperature over 1 hour and cooled to –70 °C before addition of benzaldehyde (1.51 mL, 13.57 mmol). After 30 minutes the reaction was quenched with saturated ammonium chloride (5 mL) and the aqueous phase washed with ethyl acetate. After a normal workup the organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material as a yellow oil. The crude material was purified by column chromatography (0.5 – 2% EtOAc–hexane) to give the title compound **250** as a colourless oil (1.37 g, 43%).

Rf = 0.25 (1:4 EtOAc– hexane).

FT–IR (neat) ν_{max} = 3457 (bw), 2954 (m), 2864 (m), 1741 (s), 1454 (m), 1373 (m), 1283 (s), 1045 (s), 1000 (m) cm^{-1}.

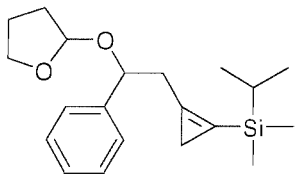
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.31 – 7.17 (5H, m, Ar), 4.93 (1H, ddd, *J* = 2.5, 5.0, 7.5 Hz, C*H*OH), 2.97 (1H, dd, *J* = 7.5, 16.0 Hz, CH_AH_BCHOH), 2.92 (1H, dd, *J* = 5.0, 16.0 Hz, CH_AH_BCHOH), 2.10 (1H, d, *J* = 2.5 Hz, O*H*), 0.86 (6H, d, *J* = 6.5 Hz, $SiCH(CH_3)_2$), 0.81 – 0.75 (1H, m, $SiCH(CH_3)_3$), 0.72 (1H, d, *J* = 7.5 Hz, CH_AH_BCSi), 0.69 (1H, d, *J* = 7.5 Hz, CH_AH_BCSi), 0.00 (6H, s, $Si(CH_3)_2$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 143.6 (0), 131.8 (0), 128.6 (1), 128.0 (1), 125.9 (1), 107.5 (0), 72.4 (1), 38.7 (2), 17.6 (3), 13.9 (1), 6.4 (2), –5.2 (3) ppm.

LRMS (EI) *m/z* = 217 $[M - {}^{i}Pr]^+$ 60%, 260 $[M]^+$ 20%.

HRMS (ES^+) $C_{16}H_{25}OSi$ $[M + H]^+$ requires 261.1675, found 261.1685.

Isopropyl-dimethyl-{2-[2-phenyl-2-(tetrahydrofuran-2-yloxy)-ethyl]-cycloprop-1-enyl}-silane 254



A solution of 2-ethoxytetrahydrofuran (25 mg, 0.216 mmol) in DCM (0.5 mL) was added to 2-[2-(isopropyl-dimethylsilyl)-cycloprop-1-enyl]-1-phenyl-ethanol **250** (50 mg, 0.192 mmol) in DCM (0.5 mL) at −78 °C under nitrogen followed by addition of $In(OTf)_3$ (11 mg, 0.019 mmol). The reaction was monitored by TLC and after 1 hour at −78 °C it was quenched with water (5 mL) and extracted with DCM. After a normal workup the organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material as a colourless oil. The crude material was purified by column chromatography (0 – 1% EtOAc–hexane) to give colourless oil **254** as a mixture of diastereoisomers (30 mg, 47%).

Rf = 0.46 (1:4 EtOAc–hexane).

FT–IR (solution) ν_{max} = 2952 (m), 2863 (m), 1720 (m), 1454 (m), 1363 (m), 1248 (m), 1032 (s), 809 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.35 – 7.18 (5H, m, Ar), 4.96 – 4.93 (2H, m, PhC*H*OCH and PhCHOC*H*), 3.85 (2H, m, OCH_2CH_2), 3.06 (1H, dd, *J* = 7.5, 15.0 Hz, $PhCHCH_AH_B$), 2.87 (1H, dd, *J* = 6.5, 15.0 Hz, $PhCHCH_AH_B$), 2.03 – 1.75 (4H, m, OCH_2CH_2 and $OCH_2CH_2CH_2$), 0.94 – 0.84 (7H, m, $SiCH(CH_3)_2$), 0.73 (1H, d, *J* = 8.0 Hz, CH_AH_BCSi), 0.69 (1H, d, *J* = 8.0 Hz, CH_AH_BCSi), 0.05 – −0.02 (6H, m, $Si(CH_3)_2$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 141.8 (0), 132.7 (0), 128.4 (1), 127.7 (1), 127.1 (1), 106.6 (0), 100.7 (1), 75.1 (1), 67.0 (2), 37.2 (2), 32.4 (2), 23.5 (2), 17.6 (3), 13.9 (1), 6.6 (2), −6.1 (3) ppm.

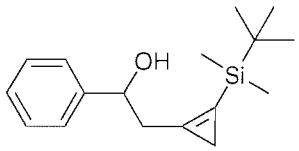
HRMS (ES^+) $C_{20}H_{31}O_2Si$ $[M + H]^+$ requires 331.2093, found 331.2083.

For the minor diastereoisomer the identifiable peaks are recorded below:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.28 (1H, d, *J* = 5.5 Hz, PhCHOC*H*), 4.84 (1H, t, *J* = 6.5 Hz, PhC*H*OCH), 3.67 (1H, dd, *J* = 8.0, 13.5 Hz, $OCH_AH_BCH_2$), 3.59 (1H, dd, *J* = 7.5, 13.5 Hz, $OCH_AH_BCH_2$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 103.6 (1), 76.7 (1), 36.7 (2), 32.6 (2), 23.4 (2), 6.7 (2) ppm.

2-[2-(*tert*-butyl-dimethylsilyl)-cycloprop-1-enyl]-1-phenyl-ethanol 251



Following a method described by Sternberg *et al.*[18]

^{n}Butyllithium (1.6 M, 7.71 mL, 12.34 mmol) was added to a stirring solution of methylenecyclopropane (1.25 mL, 18.51 mmol) in dry THF (20 mL) at −70 °C under nitrogen. The reaction mixture was warmed to 10 °C over 1 hour and kept at 10 °C for 5 minutes before cooling to −70 °C. ^{t}Butyldimethylsilylchloride (1.85 g, 12.34 mmol) was added, the reaction mixture warmed to 10 °C over 1 hour and cooled to −70 °C. ^{n}Butyllithium (1.6 M, 7.71 mL, 12.34 mmol) was added and the reaction mixture warmed to room temperature over 1 hour and cooled to −70 °C before addition of benzaldehyde (1.51 mL, 13.57 mmol). The reaction was quenched with saturated ammonium chloride (5 mL) and the aqueous phase washed with ethyl acetate. After a normal workup the organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material as a yellow oil. The crude material was purified by column chromatography (0.5 – 2% EtOAc–hexane) to give the title compound **251** as a colourless oil (937 mg, 28%).

Rf = 0.30 (1:4 EtOAc– hexane).

FT–IR (neat) ν_{max} = 3440 (bw), 2953 (m), 2856 (m), 1741 (m), 1470 (m), 1373 (m), 1245 (s), 1045 (m), 1007 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.31 – 7.17 (5H, m, Ar), 4.94 (1H, ddd, *J* = 3.0, 5.0, 8.0 Hz, C*H*OH), 2.98 (1H, dd, *J* = 8.0, 16.0 Hz, CH_AH_BCHOH), 2.91 (1H, dd, *J* = 5.0, 16.0 Hz, CH_AH_BCHOH), 2.11 (1H, d, *J* = 3.0 Hz, O*H*), 0.80 (9H, s, $SiC(CH_3)_3$), 0.73 (1H, d, *J* = 8.0 Hz, CH_AH_BCSi), 0.71 (1H, d, *J* = 8.0 Hz, CH_AH_BCSi), 0.00 (6H, s, $Si(CH_3)_2$) ppm.

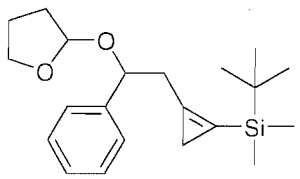
^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 143.4 (0), 131.8 (0), 128.4 (1), 127.6 (1), 125.7 (1), 107.1 (0), 72.3 (1), 38.5 (2), 26.3 (3), 17.1 (0), 6.5 (2), –5.5 (3) ppm.

LRMS (EI) *m/z* = 245 $[M - {}^tBu]^+$ 100%, 274 $[M]^+$ 18%.

HRMS (ES^+) $C_{17}H_{27}OSi$ $[M + H]^+$ requires 275.1835, found 275.1831.

---

tert-Butyl-dimethyl-{2-[2-phenyl-2-(tetrahydrofuran-2-yloxy)-ethyl]-cycloprop-1-enyl}-silane 255



A solution of 2-ethoxytetrahydrofuran (23 mg, 0.201 mmol) in DCM (0.5 mL) was added to 2-[2-(*tert*-butyl-dimethylsilyl)-cycloprop-1-enyl]-1-phenyl-ethanol **251** (50 mg, 0.182 mmol) in DCM (0.5 mL) at –78 °C under nitrogen followed by addition of $In(OTf)_3$ (10 mg, 0.018 mmol). The reaction was monitored by TLC and after 1 hour at –78 °C it was quenched with water (5 mL) and extracted with DCM. After a normal workup the organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material as a yellow oil. The crude material was purified by column chromatography (0 – 1% EtOAc–hexane) to give colourless oil **255** as a mixture of diastereoisomers (27 mg, 42%).

Rf = 0.52 (1:4 EtOAc–hexane).

FT–IR (solution) ν_{max} = 2952 (m), 2874 (m), 1723 (w), 1455 (m), 1185 (s), 1015 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.32 – 7.06 (5H, m, Ar), 4.92 – 4.89 (2H, m, PhC*H*OCH and PhCHOC*H*), 3.80 (2H, m, OCH_2CH_2), 3.01 (1H, dd, *J* = 7.5, 14.5 Hz, $PhCHCH_AH_B$), 2.82 (1H, dd, *J* = 6.5, 14.5 Hz, $PhCHCH_AH_B$), 1.98 – 1.71 (4H, m,

OCH_2CH_2 and $OCH_2CH_2CH_2$), 0.88 – 0.80 (9H, m, $SiC(CH_3)_3$), 0.69 (1H, d, J = 8.0 Hz, CH_AH_BCSi), 0.64 (1H, d, J = 8.0 Hz, CH_AH_BCSi), 0.54 – –0.46 (6H, m, $Si(CH_3)_2$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 141.7 (0), 132.9 (0), 128.4 (1), 128.1 (1), 127.1 (1), 105.6 (0), 100.6 (1), 74.9 (1), 66.9 (2), 37.3 (2), 32.3 (2), 23.4 (2), 7.5 (3), 6.4 (2), 3.8 (3), 1.1 (0) ppm.

LRMS (EI) m/z = 345 $[M + H]^+$ 30%.

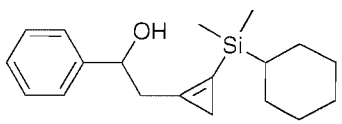
HRMS (ES^+) $C_{21}H_{33}O_2Si$ $[M + H]^+$ requires 345.2250, found 345.2247.

For the minor diastereoisomer the identifiable peaks are recorded below:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.23 (1H, d, J = 4.5 Hz, PhCHOC*H*), 4.80 (1H, t, J = 7.0 Hz, PhC*H*OCH), 3.62 (1H, dd, J = 7.5, 13.5 Hz, $OCH_AH_BCH_2$), 3.53 (1H, dd, J = 7.5, 13.5 Hz, $OCH_AH_BCH_2$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 103.5 (1), 76.7 (1), 36.8 (2), 32.5 (2), 23.4 (2), 6.6 (2), 1.1 (0) ppm.

2-[2-(Cyclohexyl-dimethyl-silyl)-cycloprop-1-enyl]-1-phenyl-ethanol 252



Following a method described by Sternberg *et al.*[18]

^{n}Butyllithium (1.6 M, 7.71 mL, 12.34 mmol) was added to a stirring solution of methylenecyclopropane (1.25 mL, 18.51 mmol) in dry THF (20 mL) at –70 °C under nitrogen. The reaction mixture was warmed to 10 °C over 1 hour and kept at 10 °C for 5 minutes before cooling to –70 °C. Chlorocyclohexyldimethylsilane (2.17 g, 12.34 mmol) was added, the reaction mixture warmed to 10 °C over 1 hour and cooled to –70 °C. ^{n}Butyllithium (1.6 M, 7.71 mL, 12.34 mmol) was added and the reaction mixture warmed to room temperature over 1 hour and cooled to –70 °C before addition of benzaldehyde (1.51 mL, 13.57 mmol). After 30 minutes the reaction was quenched with saturated ammonium chloride (5 mL) and the aqueous phase washed with ethyl acetate. After a

normal workup the organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material as a yellow oil. The crude material was purified by column chromatography (0.5 – 2% EtOAc–hexane) to give the title compound **252** as a viscous yellow oil (1.89 g, 51%).

Rf = 0.25 (1:4 EtOAc– hexane).

FT–IR (neat) ν_{max} = 3343 (bw), 2917 (s), 2845 (m), 1797 (w), 1445 (m), 1245 (m), 1000 (m), 996 (m) cm^{-1}.

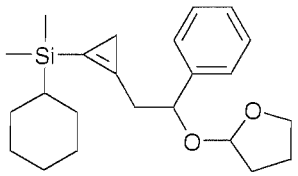
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.32 – 7.19 (5H, m, Ar), 4.95 (1H, t, *J* = 5.0 Hz, C*H*OH), 2.99 (1H, dd, *J* = 7.5, 15.5 Hz, CH_AH$_B$CHOH), 2.93 (1H, dd, *J* = 5.0, 15.5 Hz, CH$_A$$H_B$CHOH), 2.15 (1H, bs, O*H*), 1.63 – 1.50 (6H, m, SiCHCH$_2$CH_2CH_2CH_2), 1.15 – 0.95 (4H, m, 2 × SiCHCH_2), 0.73 (1H, d, *J* = 7.5 Hz, CH_AH$_B$CSi), 0.70 (1H, d, *J* = 7.5 Hz, CH$_A$$H_B$CSi), 0.64 (1H, tt, *J* = 3.0, 12.5 Hz, SiC*H*CH$_2$), 0.00 (6H, s, Si(CH_3)$_2$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 143.6 (0), 131.7 (0), 128.5 (1), 127.8 (1), 125.9 (1), 107.6 (0), 72.4 (1), 38.7 (2), 28.0 (2), 27.5 (2), 27.0 (2), 25.7 (1), 6.4 (2), –5.0 (3) ppm.

LRMS (EI) *m/z* = 217 [M – cyclohexyl]$^+$ 100%, 300 [M]$^+$ 38%.

HRMS (ES$^+$) $C_{19}H_{29}OSi$ [M + H]$^+$ requires 301.1988, found 301.1997.

Cyclohexyl-dimethyl-{2-[2-phenyl-2-(tetrahydrofuran-2-yloxy)-ethyl]-cycloprop-1-enyl}-silane 256



A solution of 2-ethoxytetrahydrofuran (21 mg, 0.183 mmol) in DCM (0.5 mL) was added to 2-[2-(cyclohexyl-dimethyl-silyl)-cycloprop-1-enyl]-1-phenyl-ethanol **252** (50 mg, 0.167 mmol) in DCM (0.5 mL) at –78 °C under nitrogen followed by addition of In(OTf)$_3$ (10 mg, 0.017 mmol). The reaction was monitored by TLC and after 1 hour at –60 °C it was quenched with water (5 mL) and extracted with DCM. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material as a colourless oil. The

crude material was purified by column chromatography (0 – 1% EtOAc–hexane) to give colourless oil **256** as a mixture of diastereoisomers (20 mg, 33%).

Rf = 0.46 (1:4 EtOAc– hexane).

FT–IR (solution) ν_{max} = 2918 (m), 2846 (m), 1718 (m), 1446 (m), 1248 (m), 1025 (s), 835 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.41 – 7.18 (5H, m, Ar), 4.98 – 4.94 (2H, m, PhC*H*OCH and PhCHOC*H*), 3.87 (2H, m, OCH_2CH_2), 3.08 (1H, dd, *J* = 7.5, 14.5 Hz, $PhCHCH_AH_B$), 2.89 (1H, dd, *J* = 6.5, 14.5 Hz, $PhCHCH_AH_B$), 2.15 – 1.77 (4H, m, OCH_2CH_2 and $OCH_2CH_2CH_2$), 1.70 – 1.57 (4H, m, 2 × $SiCHCH_2$), 1.25 – 0.98 (6H, m, $SiCHCH_2CH_2CH_2CH_2$), 0.74 (1H, d, *J* = 6.5 Hz, CH_AH_BCSi), 0.69 (1H, d, *J* = 6.5 Hz, CH_AH_BCSi), 0.10 – –0.03 (7H, m, SiC*H* and $Si(CH_3)_2$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 141.8 (0), 132.4 (0), 128.4 (1), 127.7 (1), 127.2 (1), 106.8 (0), 100.7 (1), 75.1 (1), 70.0 (2), 37.3 (2), 32.4 (2), 27.9 (2), 27.5 (2), 25.7 (2), 23.5 (2), 6.7 (2), 1.0 (1), –6.1 (3) ppm.

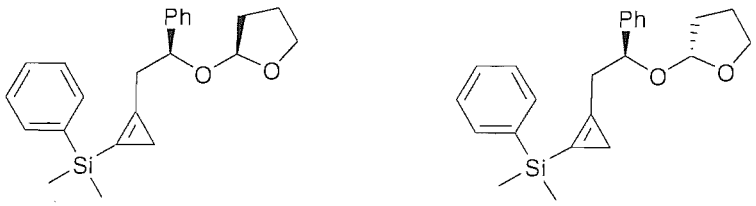
HRMS (ES^+) $C_{23}H_{35}O_2Si$ $[M + H]^+$ requires 371.2406, found 371.2406.

For the minor diastereoisomer the identifiable peaks are recorded below:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.41 – 7.18 (5H, m, Ar), 5.31 (1H, d, *J* = 4.5 Hz, PhCHOC*H*), 4.86 (1H, t, *J* = 7.0 Hz, PhC*H*OCH), 3.69 (1H, dd, *J* = 7.5, 13.5 Hz, $OCH_AH_BCH_2$), 3.61 (1H, dd, *J* = 6.5, 13.5 Hz, $OCH_AH_BCH_2$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 128.2 (1), 127.1 (1), 125.9 (1), 103.5 (1), 76.7 (1), 36.6 (2), 32.6 (2), 23.3 (2), 6.5 (2) ppm.

Dimethyl-phenyl-{2-[2-phenyl-2-(tetrahydrofuran-2-yloxy)-ethyl]-cycloprop-1-enyl}-silane 257



A solution of 2-ethoxytetrahydofuran (32 mg, 0.272 mmol) in DCM (0.5 mL) was added to 2-[2-(dimethylphenylsilyl)-1-cyclopropenyl]-1-phenyl ethanol **223** (40 mg, 0.136 mmol) in DCM (0.5 mL) at –78 °C under nitrogen followed by addition of $BF_3{\cdot}2AcOH$ (20 μL, 0.150 mmol). The reaction was monitored by TLC and after 15 minutes the reaction mixture was quenched with water (5 mL). The aqueous layer was extracted with DCM, washed with brine, dried ($MgSO_4$) and solvents removed *in vacuo* to give a colourless liquid. The crude material was purified by column chromatography (1 – 10% Et_2O–PE) to give the title compounds **257** as colourless oils.

Major diastereoisomer (18 mg, 35%).

Rf = 0.64 (1:4 Et_2O–PE).

FT–IR (solution) ν_{max} = 2956 (m), 2875 (m), 1799 (w), 1428 (w), 1247 (w), 1034 (m), 814 (m), 699 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.50 – 7.28 (10H, m, Ar), 5.05 – 4.95 (2H, m, OC*H*Ph & OC*H*O), 3.91 – 3.80 (2H, m, OCH_2CH_2), 3.14 (1H, dd, J = 7.5, 15.0 Hz, $PhCHCH_AH_B$), 2.94 (1H, dd, J = 6.5, 15.0 Hz, $PhCHCH_AH_B$), 2.04 – 1.76 (4H, m, OCH_2CH_2 and $OCH_2CH_2CH_2$), 0.88 (1H, d, J = 9.0 Hz, $CH_AH_BC(Si)$), 0.82 (1H, d, J = 9.0 Hz, $CH_AH_BC(Si)$), 0.36 (6H, s, $Si(CH_3)_2Ph$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 141.8 (0), 138.0 (0), 134.0 (0), 133.9 (1), 129.2 (1), 128.5 (1), 127.9 (1), 127.8 (1), 127.2 (1), 106.3 (0), 100.8 (1), 75.1 (1), 67.0 (2), 37.4 (2), 32.4 (2), 23.6 (2), 6.8 (2), –2.3 (3) ppm.

LRMS (CI) *m/z* = 135 $[SiMe_2Ph]^+$ 95%, 349 $[M - CH_3]^+$ 6%.

HRMS (EI) $C_{23}H_{27}O_2Si$ $[M - H]^+$ requires 363.1782, found 363.1780.

Minor Diastereoisomer (4 mg, 3%).

Rf = 0.55 (1:4 Et_2O–PE).

FT–IR (solution) ν_{max} = 2955 (m), 2876 (m), 1797 (m), 1427 (m), 1248 (m), 1032 (s), 812 (s), 697 (m) cm^{-1}.

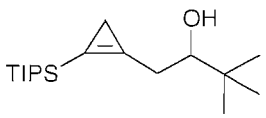
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.40 – 7.18 (10H, m, Ar), 5.27 (1H, d, *J* = 3.5Hz, OC*H*O), 4.85 (1H, t, *J* = 6.5Hz, OC*H*Ph), 3.75 – 3.58 (2H, m, OCH_2CH_2), 3.14 (1H, dd, *J* = 6.5, 15.5 Hz, $PhCHCH_AH_B$), 2.96 (1H, dd, *J* = 6.5, 15.5 Hz, $PhCHCH_AH_B$), 2.02 – 1.75 (4H, m, OCH_2CH_2 and $OCH_2CH_2CH_2$), 0.91 – 0.82 (2H, m, $CH_2C(Si)$), 0.36 (6H, s, $Si(CH_3)_2Ph$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 143.0 (0), 140.4 (0), 133.9 (1), 133.7 (0), 129.2 (1), 128.2 (1), 127.9 (1), 127.2 (1), 126.3 (1), 107.5 (0), 103.5 (1), 76.7 (1), 67.1 (2), 36.5 (2), 32.6 (2), 23.4 (2), 7.0 (2), –2.3 (3) ppm.

LRMS (CI) *m/z* = 135 $[SiMe_2Ph]^+$ 44%, 349 $[M - CH_3]^+$ 4%.

HRMS (CI) $C_{22}H_{25}O_2Si$ $[M - CH_3]^+$ requires 349.1624, found 349.1625.

3,3-Dimethyl-1-[2-triisopropylsilyl-1-cyclopropenyl] butan-2-ol 258



Following a method described by Sternberg *et al.*[18]

^{n}Butyllithium (2.34M, 2.0 mL, 4.67 mmol) was added to a stirring solution of TIPSMCP **175** (1.0 g, 4.67 mmol) in dry THF (25 mL) at –78°C under nitrogen. The reaction mixture was warmed to 10 °C over 1 hour before cooling to –78 °C followed by the addition of pivaldehyde (0.44 mL, 5.13 mmol). The reaction was monitored by TLC and after 1½ hours the reaction mixture was quenched with saturated ammonium chloride (5 mL) and the aqueous phase extracted with diethyl ether. The organic phase was washed

with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material as a yellow oil. The crude material was purified by column chromatography (0 – 2% Et_2O–PE) to give the title compound as a colourless oil **258** (1.00g, 44%).

Rf = 0.65 (1:4 Et_2O–PE).

FT–IR (neat) ν_{max} = 3500 (bs), 2940 (s), 2862 (s), 1789 (m), 1461 (m), 1363 (m), 994 (m), 880 (s) cm^{-1}.

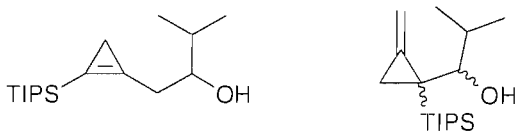
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 3.62 (1H, dt, *J* = 10.0, 2.5 Hz, C*H*OH), 2.83 (1H, dd, *J* = 2.5, 15.0 Hz, C$H_A$$H_B$CHOH), 2.65 (1H, dd, *J* = 10.0, 15.0 Hz, CH$_A$$H_B$CHOH), 1.84 (1H, d, *J* = 2.5 Hz, O*H*), 1.22 – 1.04 (21H, m, Si(C*H*(CH_3)$_2$)$_3$), 0.98 (9H, s, C(CH_3)$_3$), 0.88 (1H, d, *J* = 7.5 Hz, C$H_A$$H_B$C(TIPS)), 0.81 (1H, d, *J* = 7.5 Hz, CH$_A$$H_B$C(TIPS)) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 133.3 (0), 104.9 (0), 77.3 (1), 34.7 (0), 31.6 (2), 25.8 (3), 18.9 (3), 11.5 (1), 6.6 (3) ppm.

LRMS (EI) *m/z* = 253 [M – ^{i}Pr]$^+$ 94%, 296 [M]$^+$ 24%.

HRMS (EI) $C_{18}H_{35}OSi$ [M – H]$^+$ requires 295.2457, found 295.2444.

3-Methyl-1-[2-triisopropylsilyl-1-cyclopropenyl]-butan-2-ol 259 & 2-methyl-1-[2-methylene-1-(triisopropylsilyl)cyclopropyl]propan-1-ol 262



Following a method described by Sternberg *et al.*[18]

^{n}Butyllithium (2.34M, 2.0 mL, 4.67 mmol) was added to a stirring solution of TIPSMCP **175** (1.0 g, 4.67 mmol) in dry THF (25 mL) at –78 °C under nitrogen. The reaction mixture was warmed to 10 °C over 1½ hours, stirred at 10 °C for 10 minutes and then cooled to –78 °C. Isobutraldehyde (0.38 mL, 5.13 mmol) was added and the reaction was monitored by TLC. After 3 hours the reaction mixture was quenched with saturated ammonium chloride (5 mL) and the aqueous phase extracted with diethyl ether. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the

crude material as a yellow oil. The crude material was purified by column chromatography (0 – 2% Et_2O–PE) to give three compounds:

Colourless liquid **259** (462 mg, 35%).

Rf = 0.35 (1:4 Et_2O–PE).

FT–IR (neat) ν_{max} = 3426 (bs), 2939 (m), 2862 (m), 1788 (w), 1461 (m), 1381 (m), 992 (s), 880 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 3.72 (1H, m, C*H*OH), 2.83 (1H, dd, *J* = 4.5, 15.0 Hz, C$H_A$$H_B$CHOH), 2.74 (1H, dd, *J* = 8.0,15.0 Hz, CH$_A$$H_B$CHOH), 1.80 (1H, d, *J* = 4.0 Hz, O*H*), 1.74 (1H, m, C*H*$(CH_3)_2$), 1.20 – 1.12 (21H, m, Si(C*H*$(CH_3)_2)_3$), 0.99 (3H, d, *J* = 4.0 Hz, CH(CH_3)CH_3), 0.97 (3H, d, *J* = 4.0 Hz, CH(CH_3)CH_3), 0.85 (1H, d, *J* = 7.5 Hz, C$H_A$$H_B$C(TIPS)), 0.81 (1H, d, *J* = 7.5 Hz, CH$_A$$H_B$C(TIPS)) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 132.4 (0), 104.9 (0), 74.8 (1), 33.7 (2), 33.3 (3), 18.9 (3), 17.6 (1), 11.5 (1), 6.8 (2) ppm.

LRMS (EI) *m/z* = 239 $[M - {}^iPr]^+$ 100%, 282 $[M]^+$ 32%.

HRMS (EI) $C_{17}H_{34}OSi$ $[M]^+$ requires 282.2378 found 282.2382.

Colourless liquid **262** (49 mg, 5%).

Major diastereoisomer

Rf = 0.63 (1:4 Et_2O–PE).

FT–IR (solution) ν_{max} = 3577 (bw), 2943 (s), 2864 (w), 1726 (w), 1462 (m), 1385 (m), 1132 (m), 985 (m), 882 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.50 (1H, bs, C$H_A$$H_B$CC(TIPS)), 5.32 (1H, dt, *J* = 0.5, 2.0 Hz, CH$_A$$H_B$CC(TIPS)), 3.75 (1H, dd, *J* = 4.5, 5.5 Hz, C*H*$OH_)$, 1.70 (1H, m, C*H*$(CH_3)_2$), 1.38 (2H, t, *J* = 3.5 Hz, CH_2C(TIPS)), 1.20 – 1.00 (21H, m, Si((C*H*$(CH_3)_2)_3$), 1.00 (3H, d, *J* = 6.5 Hz, CH(CH_3)CH_3), 0.95 (3H, d, *J* = 6.5 Hz, CH(CH_3)CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 137.1 (0), 103.3 (2), 74.9 (1), 32.1 (1), 22.0 (3), 19.5 (3), 17.0 (3), 14.1 (0), 12.3 (1), 10.8 (3) ppm.

LRMS (EI) *m/z* = 239 $[M - {}^iPr]^+$ 15%, 282 $[M]^+$ 1%.

HRMS (EI) $C_{16}H_{31}OSi$ $[M - CH_3]^+$ requires 267.2144, found 267.2142.

Colourless liquid **262** (75 mg, 7%).

Minor diastereoisomer

Rf = 0.59 (1:4 Et_2O–PE).

FT–IR (solution) ν_{max} = 3462 (bs), 2943 (m), 2864 (m), 1735 (w), 1462 (m), 1381 (m), 1122 (m), 914 (m), 879 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 5.49 (1H, t, J = 2.0 Hz, $CH_AH_BCC(TIPS)$), 5.33 (1H, t, J = 2.0 Hz, $CH_AH_BCC(TIPS)$), 3.65 (1H, dd, J = 4.5, 8.0 Hz, $CHOH$), 1.73 (1H, m, $CH(CH_3)_2$), 1.28 – 1.18 (2H, m, $CH_2C(TIPS)$), 1.17 – 1.05 (21H, m, $Si((CH(CH_3)_2)_3)$), 0.95 (3H, d, J = 6.5 Hz, $CH(CH_3)CH_3$), 0.87 (3H, d, J = 6.5 Hz, $CH(CH_3)CH_3$) ppm.

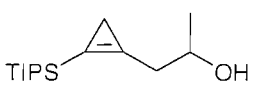
^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 136.7 (0), 104.2 (2), 76.5 (1), 31.6 (1), 22.1 (3), 19.5 (3), 18.9 (0), 16.8 (3), 12.4 (1), 9.5 (2) ppm.

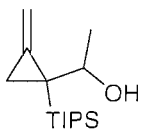
LRMS (EI) m/z = 239 $[M - {}^iPr]^+$ 25%, 282 $[M]^+$ 1%.

HRMS (EI) $C_{14}H_{27}OSi$ $[M - {}^iPr]^+$ requires 239.1831, found 239.1839.

1-[2-Triisopropylsilyl)-1-cyclopropenyl] propan-2-ol 260 &

1-[2-Methylene-1-(triisopropylsilyl)cyclopropyl]ethanol 263





Following a method described by Sternberg *et al.*[18]

^{n}Butyllithium (2.34M, 2.0 mL, 4.67 mmol) was added to a stirring solution of TIPSMCP **175** (1.00 g, 4.67 mmol) in dry THF (25 mL) at –78 °C under nitrogen. The reaction mixture was warmed to 0 °C over 1½ hours, stirred at 0 °C for 10 minutes and then cooled to –78 °C before the addition of freshly distilled acetaldehyde (0.38 mL, 5.13 mmol). The reaction was monitored by TLC and after 3 hours the reaction mixture was quenched with saturated ammonium chloride (5 mL) and the aqueous phase extracted with diethyl ether. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to

give the crude material as a yellow oil. The crude material was purified by column chromatography (0 – 2% Et_2O–PE) to give two compounds:

Yellow oil **260** (188 mg, 16%).

Rf = 0.13 (4:1 PE–Et_2O).

FT–IR (solution) ν_{max} = 3357 (bw), 2939 (s), 2882 (s), 1791 (m), 1461 (m), 993 (m), 890 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 4.16 (1H, ddd, *J* = 6.0, 6.0, 6.0 Hz, C*H*OH), 2.78 (1H, d, *J* = 6.0 Hz, CH_2CHOH), 1.75 (bs, *OH*), 1.27 (3H, d, *J* = 6.0 Hz, CH_3), 0.98 (21H, m, Si((C*H*(CH_3)$_2$)$_3$), 0.84 (1H, d, *J* = 7.5 Hz, CH_AH_BC(TIPS)), 0.81 (1H, d, *J* = 7.5 Hz, CH_AH_BC(TIPS)) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 131.9 (0), 105.1 (0), 66.6 (1), 38.2 (2), 23.1 (3), 18.9 (3), 11.5 (1), 6.7 (2) ppm.

LRMS (EI) *m/z* = 169 (CSi((C*H*(CH_3)$_2$)$_3$)$^+$ 100%, 254 [M]$^+$ 10%.

HRMS (EI) $C_{15}H_{30}OSi$ [M]$^+$ requires 254.2065, found 254.2071.

Colourless liquid **263** (82 mg, 7%).

Rf = 0.32 (1:4 Et_2O–PE).

FT–IR (solution) ν_{max} = 3466 (bs), 2942 (m), 28645 (s), 1728 (m), 1462 (m), 1382 (m), 1255 (m), 1124 (m), 1016 (w), 889 (s) cm^{-1}.

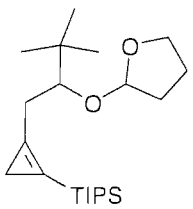
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 5.52 (1H, m, CH_AH_BCC(TIPS)), 5.32 (1H, dt, *J* = 2.5, 8.0 Hz, CH_AH_BCC(TIPS)), 4.18 (1H, m, C*H*OH), 1.52 (1H, d, *J* = 4.0 Hz, O*H*), 1.30 – 1.10 (26H, m, CH_2C(TIPS), CH_3 & Si(C*H*(CH_3)$_2$)$_3$) ppm.

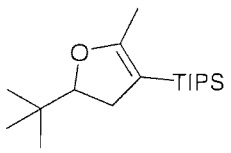
^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 136.7 (0), 103.6 (2), 67.2 (1), 20.5 (3), 20.0 (0), 19.4 (3), 12.3 (1), 9.7 (3) ppm.

LRMS (EI) *m/z* = 157 [Si(^{i}Pr)$_3$]$^+$ 60%, 254 [M]$^+$ 2%.

HRMS (EI) [M – ^{i}Pr]$^+$ $C_{12}H_{23}OSi$ requires 211.1518, found 211.1519.

{2-[3,3-Dimethyl-2-(tetrahydrofuran-2-yloxy)-butyl]-cycloprop-1-enyl}-triisopropylsilane 264 & (5-*tert*-Butyl-2-methyl-4,5-dihydrofuran-3-yl)-triisopropylsilane 265





A solution of 2-ethoxytetrahydrofuran (22 mg, 0.186 mmol) in DCM (0.5 mL) was added to 3,3-dimethyl-1-[2-triisopropylsilyl-1-cyclopropenyl]-butan-2-ol **258** (50 mg, 0.169 mmol) in DCM (0.5 mL) at −78 °C under nitrogen followed by addition of $Yb(OTf)_3$ (10 mg, 0.019 mmol)). The reaction was monitored by TLC and on completion the reaction mixture was quenched with water (5 mL) and extracted with DCM. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (0 – 1% Et_2O–PE) was attempted. Although the presence of the acetal **264** was visible in the NMR spectra, it could not be separated from the starting material.

Furan **265** was isolated as a colourless liquid (7 mg, 14%).

Rf = 0.81 (1:4 Et_2O–PE).

FT–IR (solution) ν_{max} = 2943 (s), 2862 (s), 1736 (w), 1630 (s), 1436 (m), 1379 (m), 1201 (s), 983 (m), 882 (m) cm^{-1}.

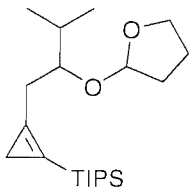
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.12 (1H, dd, *J* = 8.0, 10.0 Hz, C*H*(^{t}Bu)), 2.65-2.40 (2H, m, (^{t}Bu)CHC*H*$_2$), 1.82 (3H, s, C*H*$_3$), 1.10 – 1.05 (21H, m, Si((C*H*(C*H*$_3$)$_2$)$_3$), 0.88 (9H, s, C(C*H*$_3$)$_3$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 160.9 (0), 94.7 (0), 88.3 (1), 37.4 (2), 34.4 (0), 25.2 (3), 18.9 (3), 15.2 (3), 12.2 (1) ppm.

LRMS (EI) *m/z* = 253 [M – ^{i}Pr]$^+$ 100%, 296 [M]$^+$ 10%.

HRMS (EI) $C_{18}H_{36}OSi$ [M]$^+$requires 296.2535, found 296.2542.

Triisopropyl-(2-{3-methyl-2-[(tetrahydrofuran-2-yl)oxy]-butyl}-cycloprop-1-enyl)-silane 266



A solution of 2-ethoxytetrahydrofuran (23 mg, 0.195 mmol) in DCM (0.5 mL) was added to 3-methyl-1-[2-triisopropylsilyl-1-cyclopropenyl]-butan-2-ol **259** (50 mg, 0.177 mmol) in DCM (0.5 mL) at –78 °C under nitrogen, followed by addition of $In(OTf)_3$ (10 mg, 0.02 mmol). The reaction was monitored by TLC and after 2 hours the reaction mixture was quenched with water (5 mL) and extracted with DCM. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material as a liquid. The crude material was purified by column chromatography (0 – 1% Et_2O–PE) to give colourless liquid **266** as mixture of diastereoisomers (27 mg, 44%).

Rf = 0.54 (1:4 Et_2O–PE).

FT–IR (solution) ν_{max} = 2939 (m), 2863 (m), 1790 (m), 1461 (m), 1015 (s), 904 (s), 732 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.24 (1H, t, *J* = 3.0 Hz, OC*H*O), 3.90 – 3.78 (2H, m, OCH_2CH_2), 3.85-3.75 (2H, m, OC*H*(^{i}Pr)), 2.87 (1H, dd, *J* = 6.0, 15.0 Hz, (^{i}Pr)CHCH_AH$_B$), 2.78 (1H, dd, *J* = 7.0, 15.0 Hz, (^{i}Pr)CHCH$_A$*H$_B$*), 2.05 – 1.95 (2H, m, OCH$_2$CH_2) 1.95-1.85 (2H, m, OCH$_2$CH$_2$CH_2), 1.82 (1H, m, *CH*(CH$_3$)$_2$), 1.20-1.05 (21H, m, Si(C*H*(CH_3)$_2$)$_3$), 1.02-0.08 (6H, m, 2 × CH$_3$), 0.82-0.76 (2H, m, CH_2C(TIPS)) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 134.2 (0), 104.8 (1), 104.1 (0), 80.5 (1), 67.1 (2), 32.5 (1), 32.2 (1), 31.0 (2), 24.0 (2), 19.1 (3), 18.0 (3), 17.4 (3), 11.8 (1), 7.8 (2) ppm.

LRMS (EI) *m/z* = 71 $[(CH_2)_3OCH]^+$ 100%, 309 $[M - {}^iPr]^+$ 55%.

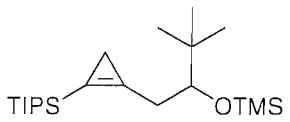
HRMS (EI) $C_{18}H_{33}O_2Si$ requires 309.2250, found 309.2256.

For the other diastereoisomer the identifiable peaks in the NMR spectra are recorded below:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.17 (1H, t, J = 3.0 Hz, OC*H*$(CH_2)_2$), 2.79 (1H, dd, J = 2.0, 15.0 Hz, (^{i}Pr)CHCH_AH$_B$), 2.73 (1H, dd, J = 6.0, 15.0 Hz, (^{i}Pr)CHCH$_A$$H_B$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 103.4 (0), 102.5 (1), 78.7 (1), 67.0 (2), 32.8(2), 31.3 (1), 23.9 (2), 7.6 (2) ppm.

(2-3,3-Dimethyl-2-[(trimethylsilyl)oxy]butyl-1-cyclopropenyl)(triisopropyl)silane 267



Following a method of Corey.[114]

Et_3N (0.65 mL, 4.72 mmol) was added to a stirring solution of 3,3-dimethyl-1-[2-triisopropylsilyl-1-cyclopropenyl]-butan-2-ol **258** (700 mg, 2.36 mmol) in THF (30 mL) under nitrogen. TMSCl (0.45 mL, 3.55 mmol) was added and the reaction was monitored by TLC. A product was formed and TLC analysis showed the concentration to be increasing, with respect to the starting material. After 9 days there was no change to the reaction, so it was quenched with water (5 mL) and extracted with Et_2O. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The liquid was purified by column chromatography (0 – 10% Et_2O–PE) to give the title compound **267** as a yellow liquid (453 mg, 53%).

Rf = 0.89 (1:4 Et_2O–PE).

FT–IR (neat) ν_{max} = 2951 (m), 2863 (m), 1788 (w), 1736 (w), 1462 (m), 1248 (s), 1092 (s), 881 (s) cm^{-1}.

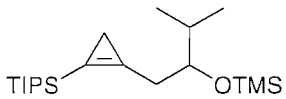
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 3.75 (1H, dd, J = 5.0, 6.0 Hz, C*H*O(TMS)), 2.82 (1H, dd, J = 5.0, 15.5 Hz, CH_AH$_B$CHO(TMS)), 2.60 (1H, dd, J = 6.0,15.0 Hz, CH$_A$$H_B$CHO(TMS)), 1.20 – 1.05 (21H, m, Si((C*H*$(CH_3)_2)_3$), 0.90 (9H, s $(CH_3)_3$), 0.10 (9H, s, OSi$(CH_3)_3$) 0.82 – 0.80 (2H, m, CH_2C(TIPS)) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 135.1 (0), 125.9 (0), 79.1 (1), 35.8 (0), 33.4 (2), 26.2 (3), 18.9 (3), 11.6 (1), 7.6 (2), 0.8 (3) ppm.

LRMS (EI) *m/z* = 73 $[TMS]^+$ 80%, 159 $[C(^tBu)OTMS]^+$ 100%.

HRMS (EI) $C_{21}H_{44}OSi_2$ $[M]^+$ requires 368.2931 found 368.2936.

2-Methyl-1-[2-triisopropylsilyl)-1-cyclopropenyl]methylpropyl (trimethylsilyl) ether 268



Following a method of Corey.[114]

Et_3N (0.62 mL, 4.46 mmol) was added to a stirring solution of 2-methyl-1-[2-methylene-1-triisopropylsilyl)cyclopropyl]-propan-1-ol **259** (600 mg, 2.23 mmol) in THF (25 mL) under nitrogen. TMSCl (0.42 mL, 3.35 mmol) was added and the reaction was monitored by TLC. A product was formed and TLC analysis showed the concentration to be increasing, with respect to the starting material. After 9 days there was no change to the reaction, so it was quenched with water (5 mL) and extracted with Et_2O. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The liquid was purified by column chromatography (10% Et_2O–PE) to give the title compound **268** as a yellow liquid (487 mg, 52%).

Rf = 0.67 (1:4 Et_2O–PE).

FT–IR (solution) ν_{max} = 2954 (m), 2863 (m), 1789 (m), 1462 (m), 1249 (s), 1048 (s), 880 (s), 731 (s) cm^{-1}.

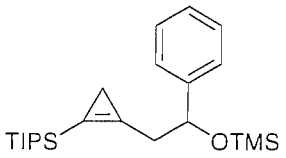
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 3.85 (1H, ddd, *J* = 4.0, 7.0, 6.0 Hz, C*H*O(TMS)), 2.79 (1H, dd, *J* = 7.0, 15.0 Hz, CH_AH$_B$CHO(TMS)), 2.69 (1H, dd, *J* = 6.0, 5.0 Hz, CH$_A$$H_B$CHO(TMS)), 1.68 (1H, m, C*H*$(CH_3)_2$), 1.20 – 1.05 (21H, m, Si((C*H*$(CH_3)_2)_3$), 0.92 (3H, d, *J* = 7.0 Hz, CH(CH_3)CH$_3$), 0.87 (3H, d, *J* = 7.0 Hz, CH(CH$_3$)CH_3), 0.80 (1H, d, *J* = 7.5 Hz, CH_AH$_B$CHO(TMS)), 0.77 (1H, d, *J* = 7.5 Hz, CH$_A$$H_B$CHO(TMS)) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 133.6 (0), 103.7 (0), 75.4 (1), 34.2 (2), 32.9 (1), 19.4 (3), 18.9 (3), 16.6 (3), 11.6 (1), 7.1 (2), 0.5 (3) ppm.

LRMS (EI) *m/z* = 145 $[(CH_3)_2CHCHO(TMS)]^+$ 100%, 354 $[M]^+$ 2%.

HRMS (EI) $[M]^+$ $C_{20}H_{42}OSi_2$ requires 354.2772 found 354.2774.

1-Phenyl-2-[2-triisopropylsilyl-1-cyclopropenyl]ethyl (trimethylsilyl) ether 269



Following a method of Corey.[114]

Et_3N (0.79 mL, 5.69 mmol) was added to a stirring solution of 1-phenyl-2-[2-triisopropylsilyl-1-cyclopropenyl]ethanol **247** (900 mg, 2.84 mmol) in THF (30 mL) under nitrogen. TMSCl (0.54 mL, 4.72 mmol) was added and the reaction was monitored by TLC. A product was formed and TLC analysis showed the concentration to be increasing, with respect to the starting material. After 8 days there was no change to the reaction, so the reaction was quenched with NH_4Cl (5 mL) and extracted with Et_2O. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The liquid was purified by column chromatography (PE) to give the title compound **269** as a yellow liquid (900 mg, 80%).

Rf = 0.73 (1:4 Et_2O–PE).

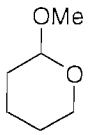
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.35 – 7.20 (5H, m, Ar), 5.02 (1H, t, J = 7.0 Hz, C*H*O(TMS)), 3.08 (1H, dd, J = 7.5, 14.5 Hz, PhCHCH_AH$_B$), 2.92 (1H, dd, J = 6.5, 14.5 Hz, PhCHCH$_A$$H_B$), 1.10 – 0.82 (21H, m, Si((CH(CH_3)$_2$)$_3$), 0.78 (1H, d, J = 7.5 Hz, CH_AH$_B$C(TIPS)), 0.72 (1H, d, J = 7.5 Hz, CH$_A$$H_B$C(TIPS)), 0.01 (9H, s, OSi(CH_3)$_3$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 144.9 (0), 133.1 (0), 128.2 (1), 127.3 (1), 126.1 (1), 104.6 (0), 73.3 (1), 40.3 (2), 18.8 (3), 11.5 (1), 7.3 (2), 0.3 (3) ppm.

LRMS (EI) *m/z* = 73 $[TMS]^+$ 80%, 179 $[CH_2CH(Ph)OTMS]^+$ 100%, 288 $[M]^+$ 1%.

HRMS (EI) $[M]^+$ $C_{23}H_{40}OSi_2$ requires 388.2618, found 388.2611.

2-Methoxytetrahydro-2*H*-pyran 270



Following the method of Dado and Gellman.[142]

Dihydropyran (8.2 mL, 90 mmol) was added to a mixture of MeOH (0.96 g, 30 mmol) and *p*-toluenesulphonic acid (0.57 g, 3.0 mmol) in Et_2O (50 mL) at room temperature. The reaction turned orange and after 1 hour was quenched with NH_4Cl (10mL) extracted with Et_2O. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The liquid was purified by column chromatography (10% Et_2O–PE) to give the title compound **270** as a colourless liquid (487 mg, 47%).

Rf = 0.68 (1:4 Et_2O–PE).

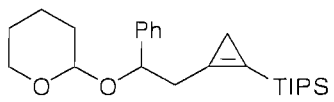
FT–IR (solution) ν_{max} = 2942 (m), 1736 (m), 1364 (w), 1034 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 4.50 (1H, t, J = 3.0 Hz, OC*H*CH_2), 3.90 – 3.80 (1H, m, CHOC$H_A$$H_B$), 3.57 – 3.47 (1H, m, CHOC$H_A$$H_B$), 3.40 (3H, s, CH_3), 1.85 – 1.45 (4H, m, OCHCH_2 & $OCH_2CH_2CH_2$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 99.9 (1), 62.0 (2), 55.1 (3), 30.6 (2), 25.6 (2), 19.5 (2) ppm.

LRMS (EI) *m/z* = 85 $[M - OCH_3]^+$ 100%, 115 $[M - H]^+$ 30%.

Triisopropyl-{2-[2-phenyl-2-(tetrahydropyran-2-yloxy)-ethyl]-cycloprop-1-enyl}-silane 271



A solution of 2-ethoxytetrahydropyran (23 mg, 0.174 mmol) in DCM (0.5 mL) was added to 1-phenyl-2-[2-triisopropylsilyl-1-cyclopropenyl]-ethanol **247** (50 mg, 0.158 mmol) in DCM (0.5 mL) at –78 °C under nitrogen followed by addition of $Yb(OTf)_3$ (10 mg,

0.016 mmol). The reaction was monitored by TLC and after 22 hours the reaction mixture was quenched with saturated ammonium chloride (5 mL) and extracted with DCM. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The liquid was purified by column chromatography (0 – 2% Et_2O–PE) to give **271** as a mixture of two diastereoisomers as a colourless liquid (16 mg, 25%).

Rf = 0.80 (1:4 Et_2O–PE).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.35 – 7.20 (5H, m, Ar), 5.08 (1H, t, J = 7.0 Hz, PhC*H*), 4.48 (1H, t, J = 3.0 Hz, PhCHOC*H*), 3.85 (1H, ddd, J = 3.5, 9.0, 14.5 Hz, $COCH_AH_BCH_2$), 3.50 (1H, m, $COCH_AH_BCH_2$), 3.21 (1H, dd, J = 7.0, 14.5 Hz, $PhCHCH_AH_B$), 2.99 (1H, dd, J = 7.0, 14.5 Hz, $PhCHCH_AH_B$), 1.85 – 1.38 (6H, m, 3 × CH_2), 1.10 – 0.78 (21H, m, $Si(CH(CH_3)_2)_3$), 0.80 (1H, d, J = 7.5 Hz, CH_AH_B(TIPS)), 0.74 (1H, d, J = 7.5 Hz, CH_AH_B(TIPS)) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 141.7 (0), 132.9 (0), 128.4 (1), 127.1 (1), 126.5 (1), 104.8 (0), 95.0 (1), 75.1 (1), 61.9 (2), 37.6 (2), 30.7 (2), 25.7 (2), 29.1 (2), 18.8 (3), 11.4 (1), 7.4 (2) ppm.

LRMS (EI) *m/z* = 85 $[(CH_2)_4OCH]^+$ 100%, 400 $[M]^+$ 8%.

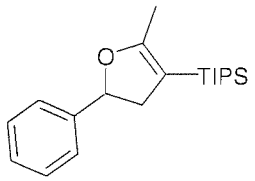
HRMS (EI) $[M - {}^iPr]^+$ $C_{22}H_{33}O_2Si$ requires 357.2250, found 357.2250.

For the other isomer the identifiable peaks in the NMR spectra are recorded below:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.00 (1H, t, J = 6.0 Hz, PhC*H*), 4.88 (1H, t, J = 3.0 Hz, PhCHOC*H*), 3.58 (1H, m, $COCH_AH_BCH_2$), 3.35 (1H, m, $COCH_AH_BCH_2$), 3.15 (1H, dd, J = 7.5, 14.5 Hz, $PhCHCH_AH_B$), 2.95 (1H, dd, J = 5.5, 14.5 Hz, $PhCHCH_AH_B$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 128.2 (1), 127.7 (1), 127.3 (1), 97.9 (1), 76.7 (1), 37.0 (2), 18.8 (3), 11.4 (1) ppm.

Triisopropyl-(2-methyl-5-phenyl-4,5-dihydrofuran-3-yl)-silane 272



The acid was added to 1-phenyl-2-[2-triisopropylsilyl-1-cyclopropenyl]ethanol **247** (50 mg, 0.158 mmol) in DCM (1 mL) at –78 °C under nitrogen. The reaction was monitored by TLC and on completion the reaction mixture was quenched with water (5 mL) and extracted with DCM. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The liquid was purified by column chromatography (0 – 1% Et_2O–PE) to give colourless oil **272** (for yields and conditions see **Table 7**).

Rf = 0.86 (1:4 Et_2O–PE).

FT–IR (solution) ν_{max} = 2939 (s), 2861 (s), 1738 (w), 1629 (s), 1461 (m), 1196 (s), 1379 (m), 881 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.40 – 7.25 (5H, m, Ar), 5.42 (1H, dd with fine splitting, J = 8.0, 10.0 Hz, C*H*Ph), 3.15 (1H, dd with fine splitting, J = 10.0, 12.0 Hz, PhCHCH_AH$_B$), 2.68 (1H, dd, J = 8.0, 12.0 Hz, PhCHCH$_A$*H$_B$*), 1.95 (3H, s, CH_3), 1.32 – 1.00 (21H, m, Si((C*H*(CH_3)$_2$)$_3$) ppm.

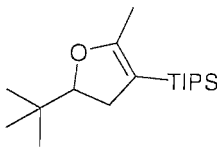
^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 160.9 (0), 144.1 (0), 128.9 (1), 127.8 (1), 125.9 (1), 95.3 (0), 82.1 (5), 45.6 (2), 19.2 (3), 15.5 (3), 12.5 (1) ppm.

LRMS (EI) *m/z* = 2736 [M – ^{i}Pr]$^+$ 100%, 316 [M]$^+$ 10%.

HRMS (EI) $C_{20}H_{32}OSi$ [M]$^+$ requires 316.2222, found 316.2231.

Microanalysis Calculated for $C_{19}H_{32}OSi$: C, 75.88; H, 10.19. Found C, 75.88; H, 75.86.

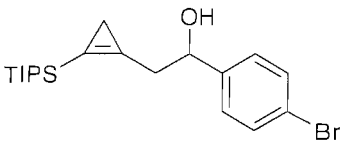
(5-*tert*-Butyl-2-methyl-4,5-dihydrofuran-3-yl)-triisopropylsilane 265



BF_3·AcOH (26 μL, 0.186 mmol) was added to 3,3-dimethyl-1-[2-triisopropylsilyl-1-cyclopropenyl]-butan-2-ol **258** (50 mg, 0.169 mmol) in DCM (1 mL) at –78 °C under nitrogen. The reaction was monitored by TLC and after 5 minutes the reaction mixture was quenched with water (5 mL) and extracted with DCM. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The liquid was purified by column chromatography (0 – 1% Et_2O–PE) to give colourless liquid **265** (1 mg, 2%).

The data agrees with that previously given.

1-(4-Bromophenyl)-2-[2-(triisopropylsilyl)-1-cyclopropenyl] ethanol 277



Following a method described by Sternberg *et al.*[18]

^{n}Butyllithium (2.34M, 1.0 mL, 2.34 mmol) was added to a stirring solution of TIPSMCP (0.50 g, 2.34 mmol) in dry THF (15 mL) at –78°C under nitrogen. The reaction mixture was warmed to 10 °C over 1½ hours and cooled to –78 °C before the addition of *p*-bromobenzaldehyde (0.48 g, 2.57 mmol). The reaction was monitored by TLC and after 1½ hours the reaction mixture was quenched with saturated ammonium chloride (5 mL) and the aqueous phase extracted with diethyl ether. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude material as a yellow oil. The crude material was purified by column chromatography (0 – 2% Et_2O–PE) to give colourless oil **278** (413 mg, 45%).

Rf = 0.25 (1:4 Et_2O–PE).

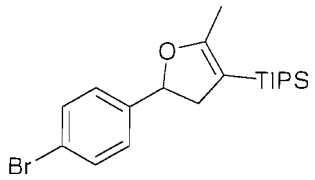
FT–IR (neat) ν_{max} = 3352 (bw), 2938 (m), 2861 (m), 1792 (m), 1461 (m), 1007 (s), 880 (s), 822 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.48 (2H, d, *J* = 8.5 Hz, 2 × C*H*CBr), 7.25 (2H, d, *J* = 8.5 Hz, 2 × C*H*CHCBr), 5.04 (1H, dt, *J* = 7.0, 3.0 Hz, C*H*OH), 3.07 (1H, dd, *J* = 7.0, 15.0 Hz, CH_AH_BCHOH), 3.00 (1H, dd, *J* = 6.0, 15.0 Hz, CH_AH_BCHOH), 2.28 (1H, d, *J* = 3.0 Hz, O*H*), 1.20 – 0.95 (21H, m, $Si(CH(CH_3)_2)_3$), 0.82 (1H, d, *J* = 7.5 Hz, $CH_AH_BC(TIPS)$), 0.77 (1H, d, *J* = 7.5 Hz, $CH_AH_BC(TIPS)$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 142.8 (0), 131.6 (1), 131.2 (0), 127.7 (1), 121.7 (0), 106.7 (0), 71.9 (1), 38.7 (2), 18.8 (3), 11.4 (1), 6.9 (2) ppm.

LRMS (EI) *m/z* = 351 $[M - {}^iPr]^+$ 20%, 394 $[M]^+$ 2%.

[5-(4-Bromophenyl)-2-methyl-4,5-dihydrofuran-3-yl]-triisopropylsilane 278



BF_3·2AcOH (19 μL, 0.139 mmol) was added to a solution of 1-(4-bromophenyl)-2-[2-triisopropylsilyl-1-cyclopropenyl]ethanol **277** (50 mg, 0.127 mmol) in DCM (1 mL) at –78 °C under nitrogen. The reaction was monitored by TLC and after ten minutes the reaction mixture was quenched with water (5 mL) and extracted with DCM. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The liquid was purified twice by column chromatography (0 – 1% Et_2O–PE) to give a colourless oil **278** (28 mg, 55%).

Rf = 0.77 (1:4 Et_2O–PE).

FT–IR (solution) ν_{max} = 2940 (s), 2861 (s), 1630 (s), 1487 (m), 1462 (m), 1379 (m), 1200 (s), 881 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.48 (2H, d, *J* = 8.5 Hz, Ar), 7.21 (2H, d, *J* = 8.5 Hz, Ar) 5.38 (1H, dd, *J* = 7.5, 10.5 Hz, C*H*(Ar)), 3.18 (1H, ddd, *J* = 1.5, 10.5, 14.5 Hz,

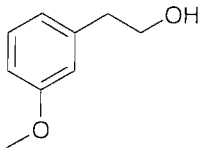
(Ar)CHCH_AH$_B$), 2.60 (1H, ddd, J = 1.5, 7.5, 14.5 Hz, (Ar)CHCH$_A$$H_B$), 1.98 (3H, s, C$H_3$), 1.25 – 1.00 (21H, m, Si((CH(CH_3)$_2$)$_3$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 161.5 (0), 143.9 (0), 132.5 (1), 128.0 (1), 122.0 (0), 95.6 (0), 81.5 (1), 45.6 (2), 18.9 (3), 15.3 (3), 12.3 (1) ppm.

LRMS (EI) m/z = 351 [M – ^{i}Pr]$^+$ 100%, 394 [M]$^+$ 8%.

HRMS (EI) $C_{20}H_{31}OSi^{79}Br$ requires 394.1328, found 394.1329.

3-(3-Methoxyphenyl)-1-propanol 286



A solution of 3-methoxyphenylacetic acid (5.00 g, 30 mmol) in THF (20 mL) was carefully added to a suspension of $LiAlH_4$ (1.72 g, 50 mmol) in THF (30 mL) at 0 °C. After 3 hours the reaction was quenched with 2N sodium hydroxide solution until the excess $LiAlH_4$ turned white. The mixture was washed with brine, dried ($MgSO_4$) and filtered. The solvents were removed *in vacuo* from the filtrate to yield the title compound **286** as a light yellow oil (4.45 g, 98%).

Rf = 0.32 (1:4 Et_2O–PE).

FT–IR (solution) ν_{max} = 3355 (b), 2945 (m), 2838 (m), 1585 (s), 1492 (m), 1264 (s), 1148 (s), 1046 (s), 781 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.30 (1H, t, J = 7.5 Hz, Ar), 6.92 – 6.88 (3H, m, Ar), 3.89 (2H, t, J = 6.5 Hz, CH_2CH$_2$OH), 3.86 (3H, s, OCH_3), 2.90 (2H, t, J = 6.5 Hz, CH_2OH), 2.08 (bs, OH) ppm.

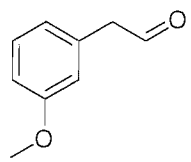
^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 159.7 (0), 140.2 (0), 129.6 (1), 121.4 (1), 114.8 (1), 111.7 (1), 63.6 (2), 55.2 (3), 39.3 (2) ppm.

LRMS (CI) m/z = 153 [M + H]$^+$ 80%, 170 [M + H_2O]$^+$ 100%.

HRMS (EI$^+$) $C_9H_{12}O_2$ [M]$^+$ requires 152.0837, found 152.0830.

This data agrees with Parker and Fokas.[144]

2-(3-Methoxyphenyl)acetaldehyde 279



Pyridinium dichromate (14.8 g, 39.5 mmol) was added to a rapidly stirring solution of 3-(3-methoxyphenyl)-1-propanol **286** (4 g, 26.3 mmol) in DCM (50 mL) at 20 °C under argon. After 24 hours the reaction mixture was quenched with saturated ammonium chloride (50 mL) and extracted with DCM. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The liquid was purified by column chromatography (5% Et_2O–PE) to give colourless liquid **279** (451 mg, 12%).

Rf = 0.60 (1:4 Et_2O–PE).

FT–IR (solution) ν_{max} = 2952 (w), 2835 (w), 1696 (s), 1584 (s), 1483 (m), 1259 (s), 1137 (m), 1036 (m), 746 (m) cm^{-1}.

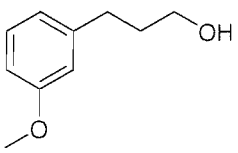
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 9.80 (1H, s, C*H*O), 7.28 – 7.20 (3H, m, Ar), 7.10 – 6.98 (1H, m, Ar), 3.68 (3H, s, OCH_3), 3.61 (2H, s, CH_2) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 192.3 (1), 160.2 (0), 139.1 (0), 130.2 (1), 123.7 (1), 121.7 (1), 114.8 (1), 64.4 (2), 55.6 (3) ppm.

LRMS (CI) *m/z* = 136 $[M - CH_3]^+$ 100%.

This data agrees with Nelson.[145]

3-(3-Methoxyphenyl)-1-propanol 287



A solution of 3-(3-methoxyphenyl)propionic acid (5.00 g, 28 mmol) in THF (20 mL) was carefully added to a suspension of $LiAlH_4$ (1.60 g, 42 mmol) in THF (30 mL) at 0 °C. After 3 hours the reaction was quenched with 2N sodium hydroxide solution until the

excess $LiAlH_4$ turned white. The mixture was washed with brine, dried ($MgSO_4$) and filtered. The solvents were removed *in vacuo* from the filtrate to yield the title compound **287** as a colourless liquid (4.45 g, 96%).

Rf = 0.35 (1:4 Et_2O–PE).

FT–IR (solution) ν_{max} = 3345 (b), 2941 (m), 2866 (m), 1585 (m), 1492 (m), 1269 (s), 1157 (s), 1036 (s), 836 (s) cm^{-1}.

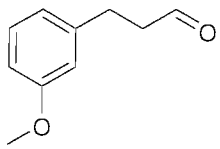
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.71 (1H, t, *J* = 7.5 Hz, Ar), 7.35 – 7.21 (3H, m, Ar), 4.30 (3H, s, OCH_3), 4.18 (2H, t, *J* = 7.0 Hz, CH_2OH), 3.20 (2H, t, *J* = 7.0 Hz, $CH_2CH_2CH_2OH$), 2.52 (bs, O*H*), 2.40 (quin, 2H, *J* = 7.0 Hz, CH_2CH_2OH) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 159.6 (0), 143.6 (0), 129.4 (1), 120.9 (1), 114.3 (1), 111.2 (1), 62.2 (2), 55.2 (3), 34.2 (2), 32.2 (2) ppm.

LRMS (CI) *m/z* = 167 $[M + H]^+$ 100%.

This data agrees with that of Manas and Smith.[146]

3-(3-Methoxyphenyl)propanal 280



Following a method described by Swern.[122]

DMSO (2.79 m, 527 mmol) in DCM (15 mL) was added to a stirring solution of oxalyl chloride (1.79 mL, 263 mmol) in DCM (50 mL) keeping the temperature below –60 °C under nitrogen. This was stirred for 5 minutes before addition of 3-(3-methoxyphenyl)-1-propanol **287** (3.8 g, 229 mmol) in DCM (15 mL) keeping the temperature below –60 °C. The reaction mixture was stirred for 15 minutes before addition of Et_3N (14.6 mL, 0.105 mol) and the reaction was allowed to warm to room temperature over 4 hours. The reaction was quenched with water (10 mL) and extracted with DCM. The organic layer was washed with brine, dried ($MgSO_4$) and solvents removed *in vacuo*. The liquid was purified by column chromatography (10% Et_2O–PE) to give the title compound **280** as a colourless oil (1.60 g, 43%).

Rf = 0.58 (1:4 Et_2O–PE)

FT–IR (solution) ν_{max} = 2936 (w), 2835 (w), 2363 (m), 1722 (s), 1600 (m), 1493 (m), 1254 (s), 1036 (m), 746 (m) cm^{-1}.

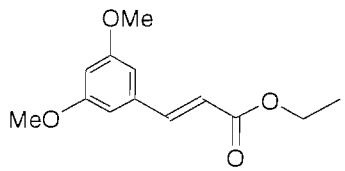
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 9.83 (1H, t, *J* = 1.5 Hz, C*H*O), 7.20 (1H, m, Ar), 6.82 – 6.70 (3H, m, Ar), 3.80 (3H, s, OCH_3), 2.95 (2H, t, *J* = 7.5 Hz, CH_2CHO), 2.87 (2H, t, *J* = 7.5 Hz, CH_2CH_2CHO) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 201.7 (1), 159.9 (0), 142.1 (0), 129.6.(1), 120.9 (1), 114.3 (1), 111.6 (1), 55.3 (3), 45.3 (2), 28.3 (2) ppm.

LRMS (CI) *m/z* = 165 $[M + H]^+$ 40%, 182 $[M + H_2O]^+$ 100%.

This data agrees with that of Manas and Smith.[146]

Ethyl (2*E*)-3-[3,5-*bis*(methyloxy)phenyl]-2-propenoate 287



Following the method of Nikas *et al.* [121]

A solution of 3,5-dimethoxybenzaldehyde (2.5 g, 15.1 mmol) in THF (30 mL) was added over a period of 30 minutes to a stirring solution of (carbethoxymethylene) triphenylphosphorane (7.86 g, 22.6 mmol) in THF (100 mL) at 0 °C under nitrogen. The reaction mixture was allowed to warm to room temperature over 2 hours and quenched with saturated ammonium chloride solution (10 mL). After a normal workup the organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give a white solid. The crude material was purified by column chromatography (10 – 30% EtOAc–hexane) to give **289** as a white crystalline solid as a mixture of *cis* and *trans* isomers in a 3:97 ratio, respectively (3.43 g, 96%).

Rf = 0.50 (1:4 EtOAc–hexane).

Melting point 45 – 46 °C.

FT–IR (solution) ν_{max} = 2970 (w), 2840 (w), 1704 (s), 1591 (s), 1458 (m), 1352 (m), 1279 (s), 1326 (s), 1062 (m), 831 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.60 (1H, d, *J* = 16.0 Hz, Ar), 6.67 (2H, d, *J* = 2.0 Hz, Ar), 6.49 (1H, t, *J* = 2.0 Hz, Ar), 6.41 (1H, d, *J* = 16.0 Hz, Ar), 4.27 (2H, q, *J* = 7.0 Hz, CH_2CH_3), 3.81 (6H, s, 2 × OCH_3), 1.34 (3H, t, *J* = 7.0 Hz, CH_2CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 166.9 (0), 161.0 (0), 144.6 (1), 136.3 (0), 118.8 (1), 105.9 (1), 102.5 (1), 60.6 (2), 55.4 (3) 14.3 (3) ppm.

LRMS (EI) *m/z* = 236 $[M]^+$ 100%.

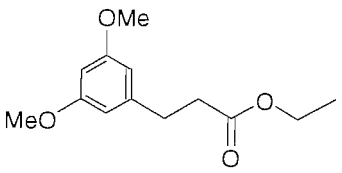
HRMS (ES^+) $C_{13}H_{17}O_4$ $[M + H]^+$ requires 237.1127, found 237.1127.

For the cis isomer the identifiable peaks are recorded below:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 6.84 (1H, d, *J* = 12.5 Hz, Ar), 6.78 (2H, d, *J* = 2.2 Hz, Ar), 6.45 (1H, t, *J* = 2.2 Hz, (OMe)CC*H*C(OMe)), 5.93 (1H, d, *J* = 12.5 Hz, C*H*CHCO$_2$CH$_2$), 4.19 (2H, q, *J* = 7.0 Hz, CH_2CH_3), 3.80 (6H, s, 2 × OCH_3), 1.25 (3H, t, *J* = 7.0 Hz, CH_2CH_3) ppm.

Spectroscopic data agrees with that of Nikas *et al.*[121]

Ethyl 3-[3,5-*bis*(methyloxy)phenyl]propanoate 290



Following a method of Nikas *et al.*[121]

EtOAc (50 mL) was added to a mixture of ethyl (2*E*)-3-[3,5-*bis*(methyloxy)phenyl]-2-propenoate **289** (2.45 g, 10.38 mmol) and 10% Pd/C (834 mg, 50% water, 1.04 mmol). The resulting suspension was stirred vigorously under a hydrogen atmosphere at 50 psi at room temperature. After 12 hours the reaction mixture was filtered through celite and washed with EtOAc. The solvent was removed *in vacuo* to reveal a colourless liquid. The

liquid was purified by column chromatography (10% EtOAc–hexane) to give the title compound **290** as a yellow liquid (1.73 g, 70%).

Rf = 0.43 (1:4 EtOAc–hexane).

FT–IR (solution) ν_{max} = 2937 (w), 2839 (w), 1730 (s), 1595 (s), 1461 (m), 1204 (s), 1148 (s), 1066 (s), 831 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 6.36 (2H, d, *J* = 2.0 Hz, Ar), 6.31 (1H, t, *J* = 2.0 Hz, Ar), 4.14 (1H, d, *J* = 7.0 Hz, $CO_2CH_AH_BCH_3$), 4.12 (1H, d, *J* = 7.0 Hz, $CO_2CH_AH_BCH_3$), 3.77 (6H, s, 2 × OMe), 2.89 (2H, t, *J* = 8.0 Hz, CH_2CO_2Et), 2.61 (2H, t, *J* = 8.0 Hz, $CH_2CH_2CO_2Et$), 1.25 (3H, t, *J* = 7.0 Hz, $CO_2CH_2CH_3$) ppm.

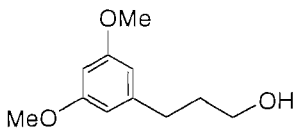
^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 172.9 (0), 160.8 (0), 143.0 (0), 106.3 (1), 98.2 (1), 60.5 (2), 55.3 (3), 35.8 (2), 31.3 (2) 14.3 (3) ppm.

LRMS (EI) *m/z* = 165 $[M - CO_2Et]^+$ 100%, 238 $[M]^+$ 70%.

HRMS (ES^+) $C_{13}H_{19}O_4$ $[M + H]^+$ requires 239.1283, found 239.1276.

Spectroscopic data agrees with that of Nikas *et al.*[121]

3-[3,5-*bis*(Methyloxy)phenyl]-1-propanol 291



Following the method of Nikas *et al.*[121]

To a solution of ethyl 3-[3,5-*bis*(methyloxy)phenyl]propanoate **290** (1.00 g, 4.20 mmol) in THF (20 mL) was added to a stirred suspension of $LiAlH_4$ (333 mg, 5.46 mmol) in THF (30 mL) at 0 °C under nitrogen. The reaction mixture was stirred vigorously for 6 hours at 0 °C before quenching by addition of 2N NaOH and EtOAc. The reaction mixture was dried ($MgSO_4$ and filtered. The filtrate was reduced *in vacuo* to give the crude material as a colourless liquid. The crude material was purified by column chromatography (30% EtOAc–hexane) to give the title compound **291** as a colourless liquid (820 mg, 99%).

Rf = 0.07 (1:4 EtOAc– hexane).

FT–IR (solution) ν_{max} = 3423 (b), 2938 (m), 2840 (m), 1736 (s), 1595 (s), 1461 (m), 1372 (m), 1239 (s), 1149 (s), 1082 (s), 831 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 6.36 (2H, s, Ar), 6.31 (1H, s, Ar), 3.78 (6H, s, 2 × OMe), 3.68 (2H, t, J = 7.0 Hz, CH_2OH), 2.65 (2H, t, J = 7.0 Hz, $CH_2(Ar)$), 1.89 (2H, quin, J = 7.0 Hz, CH_2CH_2OH), 1.34 (1H, bs, O*H*) ppm.

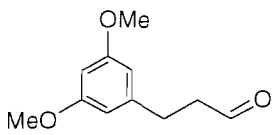
^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 160.8 (0), 143.3 (0), 106.5 (1), 97.8 (1), 62.3 (2), 55.3 (3), 34.0 (2), 32.4 (2) ppm.

LRMS (EI) *m/z* = 152 $[M - (CH_2)_2O]^+$ 100%, 196 $[M]^+$ 32%.

HRMS (ES^+) $C_{11}H_{17}O_3$ $[M + H]^+$ requires 197.1178, found 197.1171.

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

3-[3,5-*bis*(Methyloxy)phenyl]propanal 292



Following the method of Nikas *et al.* [121]

A solution of 3-[3,5-*bis*(methyloxy)phenyl]-1-propanol **291** (600 mg, 3.07 mmol) in DCM (15 mL) was added to a rapidly stirring solution of PCC (1.31 g, 6.06 mmol) in DCM (20 mL) at room temperature under nitrogen. After 4 hours Et_2O was added and the liquid poured away from the black gum. The insoluble residue was washed with Et_2O. The combined organic layers were washed through a pad of silica and solvents were removed *in vacuo* to give the crude material as a colourless liquid. The crude material was purified by column chromatography (10% EtOAc–hexane) to give the title compound **292** as a colourless liquid (360 mg, 77%).

Rf = 0.43 (1:4 EtOAc–hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 9.82 (1H, s, CHO), 6.35 (2H, d, J = 2.0 Hz, Ar), 6.32 (1H, d, J = 2.0 Hz, Ar), 3.78 (6H, s, 2 × OMe), 2.90 (2H, t, J = 7.5 Hz, $CH_2(Ar)$), 2.75 (2H, t, J = 7.5 Hz, CH_2CHO) ppm.

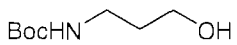
^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 204.5 (1), 160.9 (0), 142.7 (0), 106.4 (1), 98.1 (1), 55.3 (3), 45.1 (2), 28.4 (2) ppm.

LRMS (EI) *m/z* = 194 $[M]^+$ 20%.

HRMS (ES^+) $C_{11}H_{15}O_3$ $[M + H]^+$ requires 195.1021, found 195.1031.

This data agrees with that of Nikas *et al.*[121]

***tert*-Butyl *N*-(3-hydroxypropyl)carbamate 298**



Boc_2O (14.3 g, 0.65 mol) was added to a stirring solution of 3-aminopropan-1-ol **297** (5 mL, 0.65 mol) in DCM (50 mL) at room temperature. After 2 hours the reaction was quenched with saturated $NaHCO_3$ solution (10 mL). The reaction mixture was dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a yellow oil. The oil was purified by column chromatography (30% EtOAc–PE) to give the title compound **298** as a colourless oil (1.03g, 97%).

Rf = 0.22 (Et_2O).

FT–IR (solution) ν_{max} = 3346 (bs), 2976 (m), 2936 (m), 2874 (m), 1682 (s), 1578 (m), 1365 (m), 1257 (m), 1165 (s), 1044 (m) cm^{-1}.

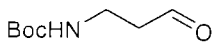
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 4.82 (bs, N*H*), 3.65 (2H, q, *J* = 6.0 Hz, CH_2OH), 3.31 (2H, q, *J* = 6.0 Hz, CH_2NH), 3.12 (1H, t, *J* = 6.0 Hz, O*H*), 1.68 (2H, quin, *J* = 6.0 Hz, CH_2CH_2OH), 1.45 (9H, s, (CH_3)$_3$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 157.4 (0), 79.8 (0), 59.3 (2), 36.9 (2), 33.0 (2), 28.5 (3) ppm.

LRMS (ES^+) *m/z* = 130 $(BocNHCH_2)^+$ 35%, 176 $[M + H]^+$ 10%, 198 $[M + Na)^+$.

Spectroscopic data agrees with that of Lee and Miller.[147]

tert-Butyl *N*-(3-oxopropyl)carbamate 293



Following the method of Swern.[122]

A solution of DMSO (0.372 mL, 7.03 mmol) in DCM (5 mL) was added to a stirring solution of oxalyl chloride (0.209 mL, 3.52 mmol) in DCM (10mL) at –78 °C under argon ensuring that the temperature did not rise above –60 °C. The reaction mixture was stirred for 5 minutes before addition of a solution of *tert*-butyl *N*-(3-hydroxypropyl)carbamate **298** (500 mg, 3.06 mmol) in DCM (5 mL) again ensuring that the temperature did not rise above –60 °C. The reaction mixture was stirred for 45 minutes before addition of triethylamine (1.964 mL, 14.08 mmol) and the reaction was allowed to warm to room temperature overnight. The reaction mixture was quenched with water and after a normal workup it was dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a yellow liquid. The liquid was purified by column chromatography (50% Et_2O–PE) to give the title compound **293** as a yellow oil (275 mg, 52%).

Rf = 0.33 (Et_2O).

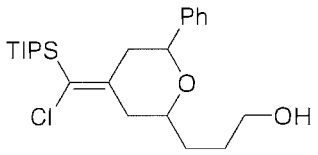
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 9.82 (1H, s, C*H*O), 4.95 (1H, bs, N*H*), 3.42 (2H, q, J = 6.0 Hz, CH_2CHO), 2.72 (2H, t, J = 6.0 Hz, CH_2CH_2CHO), 1.45 (9H, s, $(CH_3)_3$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 201.6 (1), 79.8 (0), 45.8 (0), 44.5 (2), 34.1 (2), 28.5 (3) ppm.

LRMS (ES^+) *m/z* = 175 $[2M + MeOH]^+$ 73%.

Spectroscopic data agrees with that of Blaney *et al.*[148]

3-4-[(*Z*)-1-Chloro-1-(triisopropylsilyl)methylidene]-6-phenyltetrahydro-2*H*-2-pyranyl-1-propanol 299



$TiCl_4$ (14μL, 1.029 mmol) was added to a stirring solution of 1-phenyl-2-[2-triisopropylsilyl-1-cyclopropenyl]ethyl tetrahydro-2-furanyl ether **248** (50 mg, 0.129 mmol) in DCM (1 mL) at –78 °C under N_2. The reaction immediately turned brown and TLC showed decomposition so the reaction was quenched with water and extracted with DCM. The organic layers were dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a brown oil. The oil was purified by column chromatography (0 – 5% Et_2O–PE) to give the title compound **299** as a colourless oil (11 mg, 23%).

Rf = 0.11 (1:4 Et_2O–PE).

FT–IR (solution) ν_{max} = 3411 (b), 2944 (s), 2866 (s), 1738 (m), 1455 (m), 1365 (m), 1216 (m), 1063 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.35 – 7.15 (5H, m, Ar), 4.30 (1H, dd, *J* = 2.0, 13.0 Hz, PhC*H*), 3.59 (2H, t, *J* = 5.5 Hz, CH_2OH), 3.48 (1H, m, PhCHOC*H*), 3.32 (1H, d, *J* = 13.5 Hz, CH_AH$_B$CH(CH$_2$)$_2$), 2.64 (1H, d, *J* = 13.0 Hz, CH_AH$_B$CHPh), 2.17 (1H, t, *J* = 13.0 Hz, CH$_A$H$_B$CHPh), 1.85 (1H, t, *J* = 13.5 Hz, CH$_A$H$_B$CH(CH$_2$)$_2$), 1.72 – 1.61 (4H, m, CH_2CH_2CH$_2$OH), 1.80 – 1.42 (bs, OH – confirmed by D_2O shake), 1.38 – 1.25 (3H, m, Si(C*H*(CH$_3$)$_2$)$_3$), 1.05 – 0.90 (18H, m, Si(CH(CH_3)$_2$)$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 147.6 (0), 142.0 (0), 128.7 (1), 127.9 (1), 127.9 (0), 125.8 (1), 80.3 (1), 78.1 (1), 63.0 (2), 41.9 (2), 37.9 (2), 33.2 (2), 29.2 (2), 18.9 (3), 13.1 (1) ppm.

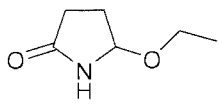
LRMS (ES$^+$) *m/z* = 445 [M + Na]$^+$ 100%.

HRMS (ES$^+$) $C_{24}H_{39}SiO_2ClNa$ [M + Na]$^+$ requires 445.2300, found 445.2306.

Microanalysis Calculated for $C_{24}H_{39}ClO_2Si$: C, 68.13; H, 9.29. Found C, 67.80; H, 9.38.

4.4 Experimental for Chapter 3.

5-Ethoxy-2-pyrrolidinone 316



Following the method described by Hubert *et al.* [126]

Sodium borohydride (2.00 g, 26.10 mmol) was added to a stirring solution of succinimide (1.72 g, 8.69 mmol) in EtOH (50 mL) at 0 °C. The reaction was stirred for four hours with the addition of two drops of concentrated hydrochloric acid every fifteen minutes. The EtOH was removed *in vacuo* and the desired compound was extracted from the residue with DCM. The DCM was removed *in vacuo* to reveal a yellow oil. The solid was purified using column chromatography (0 – 2% MeOH–DCM) to give the title compound **316** as a white solid (539 mg, 48%).

Rf = 0.53 (1:9 MeOH–DCM).

Melting point 48 – 53 °C recrystallised from diiospropyl ether.

FT–IR (solid) ν_{max} = 3259 (m), 2975 (m), 1690 (s), 1454 (w), 1277 (w), 1063 (s), 984 (m) cm^{-1}.

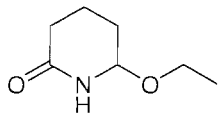
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 8.48 (1H, bs, N*H*), 4.92 (1H, dt, *J* = 6.0, 1.0 Hz, C*H*OCH_2), 3.55 (1H, dq, *J* = 9.0, 7.0 Hz, $OCH_AH_BCH_3$), 3.35 (1H, dq, *J* = 9.0, 7.0 Hz, $OCH_AH_BCH_3$), 2.53 – 1.95 (4H, m, 2 x CH_2), 1.17 (3H, t, *J* = 7.0 Hz, OCH_2CH_3) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 179.1 (0), 85.7 (1), 62.7 (2), 28.5 (2), 28.4 (2), 15.3 (3) ppm.

LRMS (ES^+) *m/z* = 130 $[M + H]^+$ 100%.

Spectroscopic data agrees with that of Hubert *et al.*[126]

6-Ethoxy-2-piperidinone 317



Following the method described by Hubert *et al.*[126]

Sodium borohydride (1.00 g, 26.54 mmol) was added to a stirring solution of glutarimide (1.00 g, 8.85 mmol) in EtOH (25 mL) at 0 °C. The reaction was stirred for four hours with the addition of two drops of concentrated hydrochloric acid every fifteen minutes. The EtOH was removed *in vacuo* and the desired compound was extracted from the residue with DCM. The DCM was removed *in vacuo* to reveal a white solid. The solid was purified using column chromatography (0 – 10% MeOH–DCM) to give the title compound **317** as a white solid (639 mg, 50%).

Rf = 0.36 (1:9 MeOH–DCM).

Melting point 45 °C recrystallised from diethyl ether.

FT–IR (solid) ν_{max} = 3193 (w), 2970 (w), 2897 (w), 1807 (s), 1679 (s), 1496 (w), 1409 (w), 1335 (m) cm^{-1}.

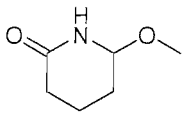
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 6.50 (1H, bs, N*H*), 4.67 (1H, t, *J* = 3.5 Hz, C*H*NH), 3.62 (1H, dq, *J* = 9.0, 7.0 Hz, $OCH_AH_BCH_3$), 3.43 (1H, dq, *J* = 9.0, 7.0 Hz, $OCH_AH_BCH_3$), 2.48 – 1.65 (6H, m, 3 x CH_2), 1.22 (3H, t, *J* = 7.0 Hz, CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 172.6 (0), 82.0 (1), 62.7 (2), 31.8 (2), 28.0 (2), 16.4 (2), 15.4 (3) ppm.

LRMS (ES^+) *m/z* = 144 $[M + H]^+$ 100%, 207 $[M + Na]^+$ MeCN$]^+$ 90%.

Spectroscopic data agrees with that of Hubert *et al.*[126]

6-Methoxy-piperidin-2-one 318



Following a method described by Klaver *et al.*[127]

$NaBH_4$ (3.14 g, 82.7 mmol) was added to a stirring solution of glutarimide **315** (1.50 g, 11.8 mmol) in MeOH (118 mL) at –5 °C under nitrogen. Every fifteen minutes a solution of HCl in MeOH (492 μL, 2M) was added and after one and a half hours the reaction was cooled to –30 °C and acidified (pH 2) with 2M HCl in MeOH. The mixture was stirred for one hour at room temperature before the addition of water and extraction with DCM. The organic layers were combined, dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a yellow oil. The oil was purified by column chromatography (0 – 10% MeOH–DCM) to give the title compound **318** as a colourless oil (1.16 g, 69%).

Rf = 0.67 (1:9 MeOH–DCM).

FT–IR (solution) ν_{max} = 3202 (b), 2946 (w), 1640 (s), 1491 (w), 1308 (m), 1190 (m), 1125 (m), 1063 (s), 835 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.95 (bs, N*H*), 4.52 (1H, m, NHC*H*), 3.32 (3H, s, OCH_3), 2.40 – 1.60 (6H, m, 3 × CH_2) ppm.

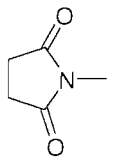
^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 173.5 (0), 82.9 (3), 54.8 (1), 31.5 (2), 27.6 (2), 16.1 (2) ppm.

LRMS (ES^+) *m/z* = 152 $[M + Na]^+$ 100%.

HRMS (ES^+) $C_6H_{11}NO_2Na$ $[M + Na]^+$ requires 152.0682, found 152.0679.

Spectroscopic data agrees with Nishitani *et al.*[149]

1-Methyl-pyrrolidine-2,5-dione 319



Following a method described by Marson *et al.* [128]

A mixture of succinimide (875 mg, 8.84 mmol), methyl iodide (0.66 mL, 10.6 mmol) and potassium carbonate (1.47 g, 10.62 mmol) was heated to reflux in anhydrous acetone (20 mL) for 16 hours. After cooling, more methyl iodide (0.275 mL, 4.42 mmol) and potassium carbonate (0.61 g, 4.42 mmol) were added and the mixture was again heated to reflux for a further 7.5 hours. The reaction mixture was cooled to 0 °C and filtered, with washings of acetone, before removal of solvent *in vacuo* to give a white solid. The solid was recrystallised from EtOH to give the title compound **319** as a white solid (598 mg, 88%).

Rf = 0.32 (1:5 MeOH – DCM).

Melting point 67 – 69 °C recrystallised from EtOH.

FT–IR (solid) ν_{max} = 2940 (w), 1770 (m), 1688 (s), 1427 (m), 1270 (m), 1115 (s), 941 (m), 816 (m), 670 (s) cm^{-1}.

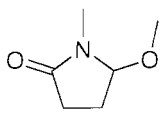
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 2.99 (3H, s, NC*H*$_3$), 2.72 (4H, s, 2 x C*H*$_2$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 177.5 (0), 28.4 (2), 24.9 (3) ppm.

LRMS (ES^+) *m/z* = 113 $[M]^+$ 100%.

Spectroscopic data agrees with that of Hubert *et al*[126]

5-Methoxy-1-methyl-pyrrolidin-2-one 321



Following a method described by Klaver *et al.*[127]

$NaBH_4$ (4.70 g, 123.1 mmol) was added to a stirring solution of 1-methyl-pyrrolidine-2,5-dione **319** (2.00 g, 17.69 mmol) in MeOH (176 mL) at –5 °C under nitrogen. Every fifteen minutes a solution of HCl in MeOH (737 μL, 2M) was added and after one and a half hours the reaction was cooled to –30 °C and acidified (pH 2) with 2M HCl in MeOH. The mixture was stirred for one hour at room temperature before the addition of $NaHCO_3$ and extraction with DCM. The organic layers were combined, dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a yellow oil. The oil was purified by column chromatography (0 – 10% MeOH–DCM) to give the title compound **321** as a colourless oil (1.314 g, 58%).

Rf = 0.68 (1:9 MeOH–DCM).

FT–IR (solution) ν_{max} = 3472 (b), 2940 (m), 2832 (w), 1682 (s), 1447 (m), 1077 (s) cm^{-1}.

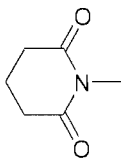
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.80 (1H, dd, *J* = 1.5, 6.5 Hz, NC*H*OMe), 3.22 (3H, s, OCH_3), 2.82 (3H, s, NCH_3), 2.51 – 1.89 (4H, m, 2 × CH_2) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 175.2 (0), 92.0 (3), 53.0 (1), 29.0 (2), 27.9 (3), 24.0 (2) ppm.

LRMS (ES^+) *m/z* = 130 $[M + H]^+$ 25%, 152 $[M + Na]^+$ 100%.

HRMS (ES^+) $C_6H_{11}NO_2Na$ $[M + Na]^+$ requires 152.0683, found 152.0682.

1-Methyl-2,6-piperidinedione 320



Following the method described by Marson *et al.*[128]

A mixture of glutarimide (1.00 g, 8.84 mmol), methyl iodide (0.66 mL, 10.6 mmol) and potassium carbonate (1.47 g, 10.62 mmol) was heated to reflux in anhydrous acetone (20 mL) for 16 hours. After cooling more methyl iodide (0.275 mL, 4.42 mmol) and potassium carbonate (0.61 g, 4.42 mmol) were added and the mixture was again heated to reflux for a further 6 hours. The reaction mixture was cooled to 0 °C and filtered, with washings of acetone, before removal of solvent *in vacuo* to give a white solid. The solid

was purified using column chromatography to give the title compound **320** as a white solid (861 mg, 88%).

Rf = 0.32 (1:5 MeOH – DCM).

Melting point 30 – 31 °C recrystallised from EtOH.

FT–IR (solid) ν_{max} = 2958 (w), 1721 (w), 1695 (s), 1415 (m), 1351 (m), 1293 (s), 1109 (s), 1042 (s) cm^{-1}.

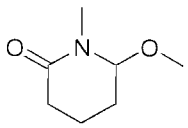
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 3.15 (3H, s, NCH_3), 2.66 (4H, t, J = 6.5 Hz, 2 x CH_2CO), 1.95 (2H, quin, J = 6.5 Hz, CH_2CH_2CO) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 172.9 (0), 32.8 (2), 26.4 (3), 17.2 (2) ppm.

LRMS (ES^+) *m/z* = 128 $[M + H]^+$ 12%, 160 $[M + MeOH + H]^+$ 100%.

Spectroscopic data agrees with that of Marson *et al.*[128]

6-Methoxy-1-methyl-piperidin-2-one 322



Following the method described by Klaver *et al.*[127]

$NaBH_4$ (3.14 g, 82.7 mmol) was added to a stirring solution of 1-methyl-piperidine-2,6-dione **320** (1.50 g, 11.8 mmol) in MeOH (118 mL) at –5 °C under nitrogen. Every fifteen minutes a solution of HCl in MeOH (492 µL, 2M) was added and after one and a half hours the reaction was cooled to –30 °C and acidified (pH 2) with 2M HCl in MeOH. The mixture was stirred for one hour at room temperature before the addition of $NaHCO_3$ and extraction with DCM. The organic layers were combined, dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a colourless oil. The oil was purified by column chromatography (0 – 2% MeOH–DCM) to give the title compound **322** as a colourless oil (1.163 g, 69%).

Rf = 0.67 (1:9 MeOH–DCM).

FT–IR (solution) ν_{max} = 3471 (b), 2945 (m), 2830 (w), 1738 (m), 1646 (s), 1464 (m), 1355 (m), 1021 (m), 1073 (m) cm^{-1}.

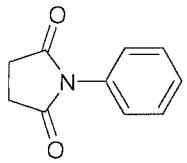
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 4.47 (1H, t, J = 3.0 Hz, NC*H*OMe), 3.32 (3H, s, OCH_3), 2.98 (3H, s, NCH_3), 2.55 – 1.65 (6H, m, 3 × CH_2) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 170.9 (0), 89.8 (3), 55.5 (1), 33.7 (3), 32.3 (2), 26.6 (2), 16.3 (2) ppm.

LRMS (ES^+) *m/z* = 144 $[M + H]^+$ 15%, 166 $[M + Na]^+$ 100%.

HRMS (ES^+) $C_7H_{13}NO_2Na$ $[M + Na]^+$ requires 166.0838, found 166.0837.

1-Phenyl-2,5-pyrrolidinedione 324



Following a method described by Ho and Castagnoli, Jr.[129]

Succinic anhydride (3.00g, 0.03 mmol) and aniline (2.73 mL, 0.03 mmol) were stirred in refluxing toluene (100 mL) in the presence of 4Å molecular sieves for 3 days. The reaction mixture was filtered, solvents removed and the crude solid was recrystallised from chloroform and hexane to give the title compound **324** as white needles (2.37 mg, 45%).

Rf = 0.65 (1:9 MeOH – DCM).

Melting point 156 – 158 °C recrystallised from $CHCl_3$/hexane.

FT–IR (solid) ν_{max} = 2957 (w), 1695 (s), 1499 (m), 1388 (m), 1182 (s), 816 (m), 695 (s), 668 (s) cm^{-1}.

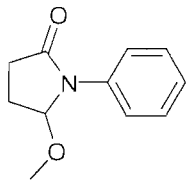
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.55 – 7.26 (5H, m, Ar), 2.91 (4H, s, 2 x CH_2) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 176.3 (0), 131.9 (0), 129.4 (1), 128.8 (1), 126.6 (1), 28.5 (2) ppm.

LRMS (ES^+) *m/z* = 198 $[M + Na]^+$ 57%, 230 $[M + MeOH + Na]^+$ 100%.

Spectroscopic data agrees with that of Reddy *et al.*[134]

5-Methoxy-1-phenyl-pyrrolidin-2-one 326



Following a method described by Klaver *et al.*[127]

$NaBH_4$ (1.00 g, 5.71 mmol) was added to a stirring solution of 1-phenyl-2,5-pyrrolidinedione **324** (2.00 g, 17.69 mmol) in MeOH (115 mL) at –5 °C under nitrogen. Every fifteen minutes a solution of HCl in MeOH (470 μL, 2M) was added and after one and a half hours the reaction was cooled to –30 °C and acidified (pH 2) with 2M HCl in MeOH. The mixture was stirred for one hour at room temperature before the addition of water and extraction with DCM. The organic layers were combined, dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a yellow oil. The oil was purified by column chromatography (0 – 10% MeOH–DCM) to give the title compound **326** as a colourless oil (578 mg, 53%).

Rf = 0.13 (4:1 PE–Et_2O).

FT–IR (neat) ν_{max} = 2940 (w), 1701 (s), 1497 (m), 1395 (m), 1294 (m), 1194 (m), 1068 (s), 885 (m) cm^{-1}.

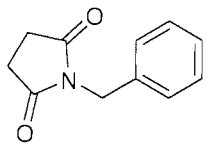
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.60 – 7.21 (5H, m, Ar), 5.37 (1H, dd, *J* = 1.0, 6.0 Hz, NC*H*), 3.32 (3H, s, OCH_3), 2.85 – 2.10 (4H, m, 2 × CH_2) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 174.5 (0), 138.1 (1), 129.2 (1), 126.2 (1), 123.4 (1), 92.2 (1), 53.7 (3), 30.1 (2), 24.6 (2) ppm.

LRMS (ES^+) *m/z* = 214 $[M + Na]^+$ 100%.

HRMS (ES^+) $C_{11}H_{13}NO_2Na$ $[M + Na]^+$ requires 214.0838, found 214.0837.

1-Benzyl-2,5-pyrrolidinedione 325



Following the method described by Ho and Castagnoli, Jr.[129]

Succinic anhydride (5.00g, 0.05 mmol) and benzylamine (5.35 g, 0.05 mmol) were stirred in refluxing toluene (250 mL) in the presence of 4Å molecular sieves for 18 hours. The reaction mixture was filtered, solvents removed and the crude solid was recrystallised from chloroform and hexane to give the title compound **325** as white needles (6.30 g, 67%).

Rf = 0.95 (1:9 MeOH – DCM).

Melting point 102 – 103 °C recrystallised from $CHCl_3$/hexane.

FT–IR (solid) ν_{max} = 2951 (w), 1765 (m), 1691 (s), 1399 (s), 1342 (s), 1163 (s), 1081 (m), 1004 (w), 883 (m), 831 (m) cm^{-1}.

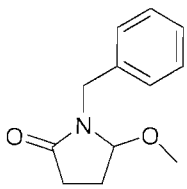
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.45 – 7.28 (5H, m, Ar), 4.67 (2H, s, CH_2Ph), 2.71 (4H, s, 2 x CH_2) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 177.1 (0), 135.9 (0), 129.1 (1), 128.8 (1), 128.1 (1), 42.5 (2), 28.3 (2) ppm.

LRMS (ES^+) *m/z* = 212 $[M + Na]^+$ 100%.

Spectroscopic data agrees with that of Ho and Castagnoli, Jr.[129]

1-Benzyl-5-methoxy-pyrrolidin-2-one 327



Following the method described by Klaver *et al.*[127]

$NaBH_4$ (4.58 g, 121 mmol) was added to a stirring solution of 1-benzyl-pyrrolidine-2,5-dione **325** (3.26 g, 17.24 mmol) in MeOH (172 mL) at –5 °C under nitrogen. Every fifteen minutes a solution of HCl in MeOH (718 μL, 2M) was added and after three hours the reaction was cooled to –30 °C and acidified (pH 3) with 2M HCl in MeOH. The mixture was stirred for one hour at room temperature before the addition of $NaHCO_3$ and extraction with DCM. The organic layers were combined, dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a white solid. The solid was purified by column chromatography (0 – 2% MeOH–DCM) to give the title compound **327** as a white solid (1.62 g, 50%).

Rf = 0.66 (1:9 MeOH–DCM).

Melting point 114 – 115 °C.

FT–IR (solution) ν_{max} = 3151 (b), 2930 (w), 1636 (s), 1440 (m), 1326 (m), 1261 (m), 1076 (s), 948 (m), 696 (s), cm^{-1}.

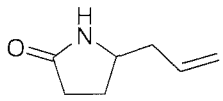
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.40 – 7.26 (5H, m, Ar), 4.98 (1H, d, *J* = 14.5 Hz, NCH_AH_B), 4.74 (1H, dd, *J* = 1.5, 6.5 Hz, $NCHCH_2$), 4.02 (1H, d, *J* = 14.5 Hz, NCH_AH_B), 3.22 (3H, s, OCH_3), 2.60 (1H, dt, *J* = 17.5, 9.0 Hz, $COCH_AH_B$), 2.48 (1H, ddd, *J* = 17.5, 5.5, 9.5 Hz, $COCH_AH_B$), 2.18 – 1.95 (2H, m, $COCH_2CH_2$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 175.1 (0), 136.6 (0), 128.8 (1), 128.6 (1), 127.7 (1), 89.1 (3), 53.0 (1), 43.9 (2), 29.2 (2), 23.9 (2) ppm.

LRMS (ES^+) *m/z* = 206 $[M + H]^+$ 25%, 228 $[M + Na]^+$ 100%.

This data agrees with that of Klaver *et al.*[127]

5-Allyl-pyrrolidin-2-one 328



Following the method described by Polniaszek *et al.* [103]

$TiCl_4$ (127 μL, 1.162 mmol) was added to a stirring solution of 5-ethoxy-2-pyrrolidinone **316** (100 mg, 0.775 mmol) and allylTMS (369 μL, 2.323 mmol) in DCM (10 mL) at –78 °C under N_2 and monitored by TLC. After 8 hours (–10 °C), the reaction was quenched with water and extracted with DCM. The organic layers were dried ($MgSO_4$),

filtered and solvents removed *in vacuo* to give the title compound **328** as a colourless oil (63 mg, 65%).

Rf = 0.51 (1:9 MeOH–DCM).

FT–IR (solution) ν_{max} = 3346 (b), 2974 (m), 2936 (m), 1682 (s), 1517 (m), 1365 (m), 1251 (m), 1165 (s), 1044 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 6.95 (1H, bs, N*H*), 5.74 (1H, ddt, *J* = 17.0, 13.0, 7.0 Hz, NHCHCH$_2$C*H*), 5.14 – 5.06 (2H, m, NHCHCH$_2$CHCH_2), 3.70 (1H, quin, *J* = 6.5 Hz, NHC*H*), 2.45 – 2.15 (5H, m, CH_2CH_AH$_B$CHCH_2), 1.82 – 1.65 (1H, m, CH$_2$CH$_A$$H_B$CHCH$_2$) ppm.

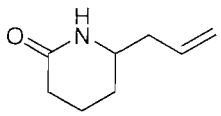
^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 178.5 (0), 133.7 (1), 118.4 (2), 53.9 (1), 41.0 (2), 30.4 (2), 26.6 (2) ppm.

LRMS (ES^+) *m/z* = 126 $[M + H]^+$ 30%, 148 $[M + Na]^+$ 100%, 273 $[2M + Na]^+$ 60%.

HRMS (ES^+) $C_7H_{11}NONa$ $[M + Na]^+$ requires 148.0733, found 148.0732.

This data agrees with that of Boto.[150]

6-Allyl-piperidin-2-one 329



Following the method described by Ojima.[132]

$BF_3{\cdot}Et_2O$ (148 μL, 0.445 mmol) was added to a stirring solution of 6-methoxy-piperidin-2-one **318** (55 mg, 0.370 mmol) and allylTMS (120 mL, 0.740 mmol) in DCM (2.5 mL) at 0 °C under N_2 and monitored by TLC. The reaction mixture was allowed to warm to room temperature and after 15 hours it was quenched with water and extracted with DCM. The organic layers were dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a yellow oil. The oil was purified by column chromatography (2% MeOH–DCM) to give the title compound **329** as a colourless oil (23 mg, 45%).

Rf = 0.13 (4:1 PE–Et_2O).

FT–IR (solution) ν_{max} = 3193 (m), 3077 (w), 2944 (m), 1678 (s), 1637 (m), 1402 (m), 910 (m) cm^{-1}.

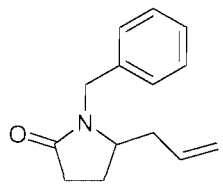
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 5.92 (bs, N*H*), 5.72 (1H, dddd, *J* = 6.0, 8.5, 11.0, 16.5 Hz, NHCHCH$_2$C*H*CH$_2$), 5.20–5.12 (2H, m, NHCHCH$_2$CHC*H*$_2$), 3.39 (1H, dddd, *J* = 4.5, 4.5, 9.0, 9.0 Hz, NHC*H*), 2.45–2.20 (3H, m, COC*H*$_2$ & NHCHC*H*$_A$H$_B$CH), 2.12 (1H, m, NHCHCH$_A$*H*$_B$CH), 1.98 – 1.62 (2H, m, COCH$_2$C*H*$_2$C*H*$_A$H$_B$), 1.45 – 1.30 (1H, m, COCH$_2$CH$_2$CH$_A$*H*$_B$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 172.3 (0), 133.4 (1), 119.4 (2), 52.3 (1), 41.5 (2), 31.4 (2), 28.7 (2), 19.9 (2) ppm.

LRMS (ES^+) *m/z* = 140 $[M + H]^+$ 15%, 162 $[M + Na]^+$ 100%, 301 $[2M + Na]^+$ 10%.

This data agrees with that of Ojima.[132]

5-Allyl-1-benzyl-pyrrolidin-2-one 330



Following the method described by Polniaszek *et al.*[103]

$TiCl_4$ (40 μL, 0.366 mmol) was added to a stirring solution of 1-benzyl-5-methoxy-pyrrolidin-2-one **325** (50 mg, 0.244 mmol) and allylTMS (116 μL, 0.737 mmol) in DCM (5 mL) at –78 °C under N_2 and monitored by TLC. After 15 minutes the reaction was quenched with water and extracted with DCM. The organic layers were dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a yellow oil. The oil was purified by column chromatography (1% MeOH–DCM) to the title compound **330** as a colourless oil (45 mg, 86%).

Rf = 0.58 (1:9 MeOH–DCM).

FT–IR (solution) ν_{max} = 2936 (w), 1690 (s), 1418 (m), 1245 (m), 1171 (m), 1075 (m), 909 (w), 703 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.38 – 7.12 (5H, m, Ar), 5.57 (1H, ddt, *J* = 17.5, 9.5, 7.0 Hz, $NCHCH_2CH$), 5.15 – 4.99 (2H, m, $NCHCH_2CHCH_2$), 4.94 (1H, d, *J* = 15.0 Hz, NCH_AH_B), 3.92 (1H, d, *J* = 15.0 Hz, NCH_AH_B), 3.48 – 3.39 (1H, m, $NCHCH_2$), 2.45 – 2.20 (3H, m, $NCHCH_2CH$ & CH_AH_BCO), 2.15 – 1.89 (2H, CH_AH_BCO & $COCH_2CH_AH_B$), 1.70 (1H, m, $COCH_2CH_AH_B$) ppm.

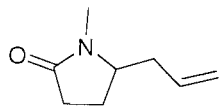
^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 175.3 (0), 136.7 (0), 132.7 (1), 128.7 (1), 128.0 (1), 127.6 (1), 118.9 (2), 56.3 (1), 44.3 (2), 37.2 (2), 30.2 (2), 23.3 (2) ppm.

LRMS (ES^+) *m/z* = 216 $[M + H]^+$ 10%, 238 $[M + Na]^+$ 100%, 453 $[2M + Na]^+$ 30%.

HRMS (ES^+) $C_{14}H_{17}NONa$ $[M + Na]^+$ requires 238.1202, found 238.1199.

Spectroscopic data agrees with Brown.[151]

5-Allyl-1-methyl-pyrrolidin-2-one 331



Following the method described by Polniaszek.[103]

$TiCl_4$ (63 μL, 0.581 mmol) was added to a stirring solution of 5-methoxy-1-methyl-pyrrolidin-2-one **321** (50 mg, 0.387 mmol) and allylTMS (1.84 μL, 1.162 mmol) in DCM (5 mL) at –78 °C under N_2 and monitored by TLC. After 10 minutes the reaction was quenched with water and extracted with DCM. The organic layers were dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a cloudy yellow oil. The oil was purified by column chromatography (2% MeOH–DCM) to give the title compound **331** as a colourless oil (44 mg, 81%).

Rf = 0.47 (1:9 MeOH–DCM).

FT–IR (solution) ν_{max} = 3487 (b), 2974 (m), 2923 (m), 1674 (s), 1398 (m), 1302 (m), 1113 (m), 996 (m), 916 (m) cm^{-1}.

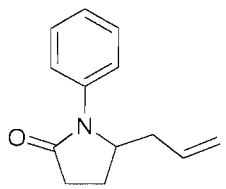
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.64 (1H, ddt, *J* = 17.0, 10.0, 7.5 Hz, $NCHCH_2CH$), 5.11 – 5.05 (1H, m, $NCHCH_2CHCH_2$), 3.52 (1H, quin, *J* = 8.0, 5.0, 3.5 Hz, $N(Me)CH$), 2.78 (3H, s, NCH_3), 2.42 – 2.00 (5H, m, $CH_2CH_2CHCH_AH_B$), 1.73 – 1.64 (1H, m, $CH_2CH_2CHCH_AH_B$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 175.1 (0), 132.7 (1), 118.8 (2), 59.3 (1), 37.5 (2), 30.0 (2), 27.8 (3), 23.2 (2) ppm.

LRMS (ES^+) *m/z* = 140 $[M + H]^+$ 12%, 162 $[M + Na]^+$ 62%.

HRMS (ES^+) $C_{16}H_{26}N_2O_2Na$ $[2M + Na]^+$ requires 301.1886, found 301.1895.

5-Allyl-1-benzyl-pyrrolidin-2-one 332



Following the method described by Polniaszek *et al.* [103]

$TiCl_4$ (43μL, 0.393 mmol) was added to a stirring solution of 5-methoxy-1-phenyl-pyrrolidin-2-one **324** (50 mg, 0.262 mmol) and allylTMS (125 μL, 0.785 mmol) in DCM (5 mL) at –78 °C under N_2 and monitored by TLC. The reaction mixture was allowed to warm to room temperature and after 28 hours it was quenched with water and extracted with DCM. The organic layers were dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give the title compound **332** as a colourless oil (50 mg, 94%).

Rf = 0.43 (1:9 MeOH–DCM).

FT–IR (solution) ν_{max} = 3069 (w), 2975 (w), 2923 (w), 1692 (s), 1498 (m), 1389 (m), 1295 (m), 751 (m) cm^{-1}.

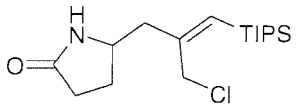
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.32 – 7.15 (5H, m, Ar), 5.57 (1H, ddt, *J* = 17.0, 10.0, 7.0 Hz, $NCHCH_2CHCH_2$), 5.02 – 4.91 (2H, m, $NCHCH_2CHCH_2$), 4.18 (1H, ddt, *J* = 5.0, 3.5, 8.0 Hz, NC*H*), 2.60 – 2.05 (5H, m, $COCH_2CH_AH_BCHCH_2$), 1.82 (1H, m, $COCH_2CH_AH_BCHCH_2$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 174.5 (0), 137.6 (0), 132.7 (1), 129.2 (1), 126.0 (1), 124.3 (1), 119 (2), 52.9 (1), 37.6 (2), 31.4 (2), 23.3 (2) ppm.

LRMS (ES^+) *m/z* = 202 $[M + H]^+$ 5%, 224 $[M + Na]^+$ 100%, 425 $[2M + Na]^+$ 18%.

HRMS (ES^+) $C_{26}H_{30}N_2O_2Na$ $[2M + Na]^+$ requires 224.1046, found 224.1043.

5-[(Z)-2-(Chloromethyl)-3-triisopropylsilyl-2-propenyl]pyrrolidin-2-one 333



$TiCl_4$ (127 μL, 1.162 mmol) was added to a stirring solution of 5-ethoxy-2-pyrrolidinone **316** (100 mg, 0.775 mmol) and TIPSMCP (487 mg, 2.323 mmol) in DCM (10 mL) at –78 °C under N_2 and monitored by TLC. After 5 hours (–10 °C), the reaction was quenched with saturated $NaHCO_3$ and extracted with DCM. The organic layers were dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a yellow oil. The oil was purified by column chromatography (0 – 3% MeOH–DCM) to give the title compound **333** as a colourless oil (81 mg, 69%).

Rf = 0.71 (1:9 MeOH–DCM).

FT–IR (solution) ν_{max} = 3208 (w), 2942 (m), 2804 (m), 1693 (s), 1462 (m), 1255 (w), 881 (m), 731 (m), 661 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.75 (1H, bs, N*H*), 5.41 (1H, s, C*H*(TIPS)), 4.00 (2H, d, *J* = 1.0 Hz, CH_2Cl), 3.88 (1H, quin, *J* = 7.0 Hz, NHC*H*), 2.52 (1H, ddd, *J* = 1.0, 6.0, 14.5 Hz, $CH_AH_BCCH_2Cl$), 2.40 (1H, dd, *J* = 8.0, 14.5 Hz, $NHCHCH_AH_B$), 2.32 – 2.28 (2H, m, CH_2CO), 2.28 – 2.18 (1H, m, $COCH_2CH_AH_B$), 1.80 – 1.68 (1H, m, $COCH_2CH_AH_B$), 1.10 – 0.90 (21H, m, $Si(CH(CH_3)_2)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 177.8 (0), 150.3 (0), 129.2 (1), 52.7 (1), 47.9 (2), 44.6 (2), 30.3 (2), 27.4 (2), 19.1 (3), 12.4 (1) ppm.

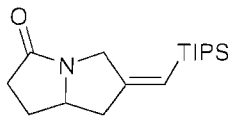
LRMS (ES^+) *m/z* = 352 $[M + Na]^+$ 30%, 681 $[2M + Na]^+$ 100%.

HRMS (ES^+) $C_{17}H_{32}NOSiClNa$ $[M + Na]^+$ requires 352.1834, found 352.1845.

Microanalysis Calculated for $C_{17}H_{32}NOSiCl$: C, 61.88; H, 9.77; N, 4.24. Found C, 61.52; H, 9.83; N, 3.92.

X–ray Crystallography see appendix.

6-[(*Z*)-1-(Triisopropylsilyl)methylidene]perhydro-3-pyrrolizinone 334



5-(2-Chloromethyl-3-triisopropylsilyl-allyl)-pyrrolidin-2-one **333** (50 mg, 0.152 mmol) was added to a stirring mixture of NaH (12.2 mg, 0.304 mmol, 60% in mineral oil) in THF (5 mL) at –30 °C. The reaction mixture was warmed to room temperature and refluxed for three days followed by a quench with water. The reaction mixture was neutralised with 2M HCl and extracted with DCM. The organic layers were dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a yellow oil. The oil was purified by column chromatography (0 – 2% MeOH–DCM) to give the title compound **334** as a colourless oil (41 mg, 92%).

Rf = 0.75 (1:9 MeOH–DCM).

FT–IR (solution) ν_{max} = 2940 (m), 2863 (m), 1963 (s), 1412 (m), 1298 (m), 881 (m), 725 (m), 660 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.55 (1H, s, C*H*(TIPS)), 4.22 (1H, d, *J* = 16.5 Hz, NCH_AH$_B$), 3.99 (1H, m, C*H*N), 3.63 (1H, d, *J* = 16.5 Hz, NCH$_A$$H_B$), 2.72 – 2.68 (2H, m, NCH$_2$CCH_AH$_B$ & COCH_AH$_B$), 2.49 – 2.32 (3H, m, NCH$_2$CCH$_A$$H_B$, COCH$_A$$H_B$, COCH$_2CH_AH_B$), 1.79 (1H, m, COCH$_2CH_A$$H_B$), 1.17 – 0.98 (21H, m, Si(C*H*(CH_3)$_2$)$_3$) ppm.

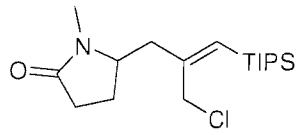
^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 174.1 (0), 156.7 (0), 118.0 (1), 60.4 (1), 46.5 (2), 44.9 (2), 34.9 (2), 27.4 (2), 18.9 (3), 11.8 (1) ppm.

LRMS (ES^+) *m/z* = 294 $[M + H]^+$ 10%, 316 $[M + Na]^+$ 60%, 609 $[2M + Na]^+$ 100%.

HRMS (ES^+) $C_{17}H_{32}NOSi$ $[M + H]^+$ requires 294.2248, found 294.2248.

Microanalysis Calculated for $C_{17}H_{31}NOSi$: C, 69.56; H, 10.64; N, 4.77. Found C, 69.25; H, 10.49; N, 4.52.

5-[(Z)-2-(Chloromethyl)-3-triisopropylsilyl-2-propenyl]-1-methyl-2-pyrrolidinone 337



$TiCl_4$ (63 μL, 0.581 mmol) was added to a stirring solution of 5-methoxy-1-methyl-pyrrolidin-2-one **321** (50 mg, 0.387 mmol) and TIPSMCP (244 mg, 1.162 mmol) in DCM (5 mL) at –78 °C under N_2 and monitored by TLC. After 30 minutes the reaction was quenched with saturated $NaHCO_3$ and extracted with DCM. The organic layers were dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a colourless oil. The oil was purified by column chromatography (0 – 3% MeOH–DCM) to give the title compound **337** as a colourless oil (84 mg, 64%).

Rf = 0.45 (1:9 MeOH–DCM).

FT–IR (solution) ν_{max} = 2942 (m), 2864 (m), 1688 (s), 1461 (m), 1398 (m), 1254 (m), 881 (s), 660 (s) cm^{-1}.

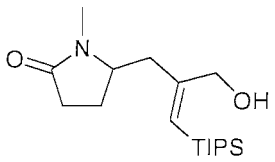
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.53 (1H, s, C*H*(TIPS)), 4.12 (1H, d, *J* = 11.5 Hz, CH_AH_BCl), 4.08 (1H, d, *J* = 11.5 Hz, CH_AH_BCl), 3.79 (1H, m, NMeC*H*), 2.97 (1H, dd, *J* = 4.0, 14.5 Hz, $CHCH_AH_BCC(TIPS)$), 2.87 (3H, s, NCH_3), 2.51 – 2.30 (2H, m, CH_2CO), 2.23 (1H, dd, *J* = 10.0, 14.5 Hz, $CHCH_AH_BCC(TIPS)$), 2.16 – 2.05 (1H, m, $COCH_2CH_AH_B$), 1.82 – 1.70 (1H, m, $COCH_2CH_AH_B$), 1.12 – 0.10 (21H, m, $Si(CH(CH_3)_2)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 174.9 (0), 149.8 (0), 129.5 (1), 58.5 (1), 47.9 (2), 40.9 (2), 29.8 (2), 28.0 (3), 23.8 (2), 18.9 (3), 11.6 (1) ppm.

LRMS (ES^+) *m/z* = 344 $[M + H]^+$ 40%, 366 $[M + Na]^+$ 70%, 709 $[2M + Na]^+$ 100%.

HRMS (ES^+) $C_{18}H_{35}NOSiCl$ $[M + H]^+$ requires 344.2171, found 344.2182.

5-((E)-1-Hydroxymethyl-2-triisopropylsilyl-vinyloxy)-1-methyl-pyrrolidin-2-one 338



$In(OTf)_3$ (326 mg, 0.5801 mmol) was added to a stirring solution of 5-methoxy-1-methyl-pyrrolidin-2-one **321** (50 mg, 0.387 mmol) and TIPSMCP (244 mg, 1.162 mmol) in DCM (5 mL) at –78 °C under N_2 and monitored by TLC. After 3 hours the reaction was quenched with water and extracted with DCM. The organic layers were dried ($MgSO_4$), filtered and solvents removed *in vacuo*. The crude oil was purified by column chromatography (0 – 3% MeOH–DCM) to give the title compound **338** as a colourless oil (67 mg, 54%).

Rf = 0.13 (4:1 PE–Et_2O).

FT–IR (neat) ν_{max} = 3360 (b), 2939 (m), 2863 (m), 1669 (s), 1461 (m), 1400 (m), 882 (m), 727 (s) cm^{-1}.

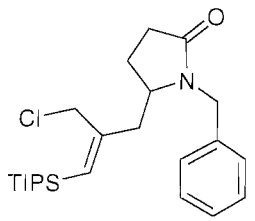
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.38 (1H, s, C*H*(TIPS)), 4.16 (1H, d, *J* = 12.5 Hz, CH_AH_BOH), 4.12 (1H, d, *J* = 12.5 Hz, CH_AH_BOH), 3.79 (1H, m, N(Me)C*H*), 2.95 (1H, dd, *J* = 6.0, 14.5 Hz, $CH_AH_BCCH_2OH$), 2.85 (3H, s, NCH_3), 2.48 – 2.27 (2H, m, CH_2CO), 2.20 – 2.03 (2H, m, $CH_AH_BCCH_2OH$ & $COCH_2CH_AH_B$), 1.78 (1H, m, $COCH_2CH_AH_B$), 1.15 – 0.98 (21H, m, $Si(CH(CH_3)_2)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 175.3 (0), 154.1 (0), 126.1 (1), 65.7 (2), 58.9 (1), 41.1 (2), 29.9 (2), 28.1 (3), 23.8 (2), 19.0(3), 12.5 (1) ppm.

LRMS (ES^+) *m/z* = 348 $[M + Na]^+$ 100%, 673 $[2M + Na]^+$ 22%.

HRMS (ES^+) $C_{18}H_{35}NO_2SiNa$ $[M + Na]^+$ requires 348.2329, found 334.2333.

1-Benzyl-5-((Z)-2-chloromethyl-3-triisopropylsilyl-allyl)-pyrrolidin-2-one 339



$TiCl_4$ (63 μL, 0.581 mmol) was added to a stirring solution of 1-benzyl-5-methoxy-pyrrolidin-2-one **325** (50 mg, 0.387 mmol) and TIPSMCP (244 mL, 1.162 mmol) in DCM (5 mL) at –78 °C under N_2 and monitored by TLC. After 4 hours (–30 °C) the reaction was quenched with saturated $NaHCO_3$ and extracted with DCM. The organic layers were dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a colourless oil. The oil was purified by column chromatography (0 – 3% MeOH–DCM) to give the title compound **339** as a colourless oil (86 mg, 85 %).

Rf = 0.64 (1:9 MeOH–DCM).

FT–IR (solution) ν_{max} = 2941 (m), 2864 (m), 1686 (s), 1416 (m), 1251 (m), 881 (m), 733 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.40 – 7.25 (5H, m, Ar), 5.42 (1H, s, C*H*(TIPS)), 5.03 (1H, d, *J* = 15.0 Hz, C$H_A$$H_B$Ph), 4.03 (1H, d, *J* = 15.0 Hz, CH$_A$$H_B$Ph), 4.00 (1H, d, *J* = 11.5 Hz, C$H_A$$H_B$Cl), 3.89 (1H, d, *J* = 11.5 Hz, CH$_A$$H_B$Cl), 3.61 (1H, m, N(Bn)C*H*), 3.02 (1H, dd, *J* = 2.5, 13.5 Hz, C$H_A$$H_BCCH_2$Cl), 2.58 – 2.35 (2H, m, CH_2CO), 2.11 (1H, dd, *J* = 10.5, 13.5 Hz, CH$_A$$H_BCCH_2$Cl), 2.02 (1H, m, C$H_A$$H_BCH_2$CO), 1.78 (1H, m, CH$_A$$H_BCH_2$CO), 1.10 – 0.95 (21H, m, Si(CH(CH$_3$)$_2$)$_3$) ppm.

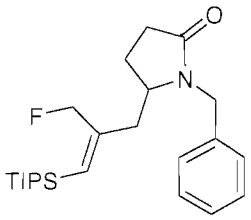
^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 174.9 (0), 149.7 (0), 136.7 (0), 129.9 (1), 128.8 (1), 128.4 (1), 127.7 (1), 55.5 (1), 47.5 (2), 44.4 (2), 40.7 (2), 29.9 (2), 23.7 (2), 18.9 (3), 12.2 (1) ppm.

LRMS (ES$^+$) *m/z* = 420 [M + H]$^+$ 10%, 442 [M + Na]$^+$ 15%, 861 [2M + Na]$^+$ 100%.

HRMS (ES$^+$) $C_{24}H_{38}NOSiClNa$ [M + Na]$^+$ requires 442.2303, found 442.2312.

Microanalysis Calculated for $C_{24}H_{38}NOSiCl$: C, 68.62; H, 9.12; N, 3.33. Found C, 68.35; H, 9.30; N, 3.02.

1-Benzyl-5-((Z)-2-fluoromethyl-3-triisopropylsilyl-allyl)-pyrrolidin-2-one 340



$BF_3{\cdot}Et_2O$ (46 μL, 0.366 mmol) was added to a stirring solution of 1-benzyl-5-methoxy-pyrrolidin-2-one **325** (50 mg, 0.244 mmol) and TIPSMCP (153 mg, 0.732 mmol) in DCM (5 mL) at –78 °C under N_2 and monitored by TLC. After 2 days the reaction was quenched with water and extracted with DCM. The organic layers were dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a colourless oil. The oil was purified by column chromatography (0 – 10% MeOH–DCM) to give the title compound **340** as a colourless oil (58 mg, 58%).

Rf = 0.12 (1:9 MeOH–DCM).

FT–IR (solution) ν_{max} = 2942 (m), 2865 (m), 1688 (s), 1417 (m), 1247 (w), 986 (w), 882 (m) cm^{-1}.

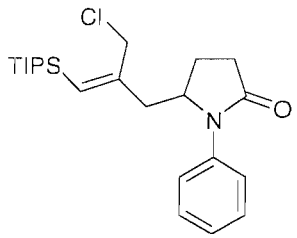
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.35 – 7.20 (5H, m, Ar), 5.47 (1H, s, C*H*(TIPS)), 4.98 (1H, d, *J* = 15.0 Hz, CH_AH$_B$Ph), 4.76 (1H, dd, *J* = 11.0, 47.5 Hz, CH_AH$_B$F), 4.72 (1H, dd, *J* = 11.0, 47.0 Hz, CH$_A$$H_B$F), 4.04 (1H, d, *J* = 15.0 Hz, CH$_A$$H_B$Ph), 3.65 (1H, m, N(Bn)C*H*), 2.87 (1H, dd, *J* = 3.5, 13.5 Hz, CH_AH$_B$CCH$_2$F), 2.56 – 2.35 (2H, m, CH_2CO), 2.11 (1H, dd, *J* = 10.5, 13.5 Hz, CH$_A$$H_BCCH_2$F) 2.06 – 1.70 (2H, m, C$H_2CH_2$CO), 1.10 – 0.85 (21H, m, Si(CH(CH$_3$)$_2$)$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 175.1 (0), 149.8 (0), 136.9 (0), 129.7 (1), 128.3 (1), 128.2 (1), 127.6 (1), 84.8 (d, *J* = 163 Hz, 2), 56.1 (1), 44.5 (2), 40.9 (2), 29.9 (2), 23.7 (2), 18.9 (3), 12.4 (1) ppm.

LRMS (ES$^+$) *m/z* = 404 $[M + H]^+$ 5%, 426 $[M + Na]^+$ 2%, 829 $[2M + Na]^+$ 100%.

HRMS (ES$^+$) $C_{24}H_{39}NOSiF$ $[M + H]^+$ requires 404.2779, found 404.2777.

5-((Z)-2-Chloromethyl-3-triisopropylsilyl-allyl)-1-phenyl-pyrrolidin-2-one 341



$TiCl_4$ (43 μL, 0.393 mmol) was added to a stirring solution of 5-methoxy-1-phenyl-pyrrolidin-2-one **324** (50 mg, 0.262 mmol) and TIPSMCP (154 mg, 0.785 mmol) in DCM (5 mL) at –78 °C under N_2 and monitored by TLC. After 6 hours (–78 °C) the reaction was quenched with water and extracted with DCM. The organic layers were dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a colourless oil. The oil was purified by column chromatography (1 – 103% MeOH–DCM) to give the title compound **341** as a colourless oil (70 mg, 66%).

Rf = 0.46 (1:9 MeOH–DCM).

FT–IR (solution) ν_{max} = 2943 (m), 2864 (m), 1700 (s), 1428 (m), 1389 (m), 1294 (w), 882 (m) cm^{-1}.

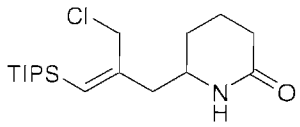
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.40 – 7.10 (5H, m, Ar), 5.40 (1H, s, C*H*(TIPS)), 4.41 (1H, m, N(Ph)C*H*), 3.98 (1H, d, *J* = 11.5 Hz, CH_AH_BCl), 3.93 (1H, d, *J* = 11.5 Hz, CH_AH_BCl), 2.84 (1H, dd, *J* = 3.5, 14.5 Hz, $CH_AH_BCCH_2Cl$), 2.57 (1H, ddd, *J* = 7.0, 9.5, 17.0 Hz, CH_AH_BCO), 2.46 (1H, ddd, *J* = 7.0, 9.5, 17.0 Hz, CH_AH_BCO), 2.19 (1H, m, $CH_AH_BCH_2CO$), 2.10 (1H, m, $CH_AH_BCCH_2Cl$), 1.84 (1H, m, $CH_AH_BCH_2CO$), 1.12 – 0.95 (21H, m, $Si(CH(CH_3)_2)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 174.1 (0), 149.8 (0), 137.5 (0), 129.7 (1), 129.2 (1), 126.0 (1), 123.9 (1), 58.3 (1), 47.9 (2), 41.7 (2), 31.2 (2), 23.8 (2), 19.0 (3), 12.5 (1) ppm.

LRMS (ES^+) *m/z* = 406 $[M + H]^+$ 7%, 428 $[M + Na]^+$ 40%, 833 $[2M + Na]^+$ 100%.

HRMS (ES^+) $C_{23}H_{36}NOSiClNa$ $[M + Na]^+$ requires 428.2142, found 428.2149.

6-((Z)-2-Chloromethyl-3-triisopropylsilyl-allyl)-piperidin-2-one 342



$TiCl_4$ (64 μL, 0.580 mmol) was added to a stirring solution of 6-methoxy-piperidin-2-one **318** (50 mg, 0.387 mmol) and TIPSMCP (284 mg, 1.163 mmol) in DCM (5 mL) at –78 °C under N_2 and monitored by TLC. After 8 hours (0 °C) the reaction was quenched with water and extracted with DCM. The organic layers were dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a yellow oil. The oil was purified by column chromatography (10 – 50% EtOAc–PE) to give the title compound **342** as a colourless oil (44 mg, 32%).

Rf = 0.50 (EtOAc).

FT–IR (neat) ν_{max} = 2942 (m), 2865 (m), 1660 (s), 1462 (m), 1348 (m), 881 (m), 731 (s) cm^{-1}.

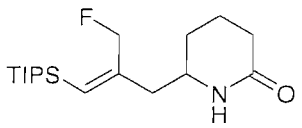
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.71 (1H, bs, N*H*), 5.54 (1H, s, C*H*(TIPS)), 4.07 (2H, s, CH_2Cl), 3.62 (1H, dddd, J = 4.5, 5.0, 9.5, 13.5 Hz, NHC*H*), 2.65 (1H, dd, J = 5.5, 14.5 Hz, $CH_AH_BCCH_2Cl$), 2.47 – 2.27 (3H, m, CH_2CO & $CH_AH_BCCH_2Cl$), 1.95 (1H, m, $COCH_2CH_2CH_AH_B$), 1.79 – 1.68 (2H, m, $COCH_2CH_2CH_2$), 1.30 (1H, m, $COCH_2CH_2CH_AH_B$), 1.18 – 1.05 (21H, m, $Si(CH(CH_3)_2)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 172.1 (0), 149.4 (0), 130.4 (1), 51.0 (1), 47.6 (2), 45.1 (2), 31.5 (2), 28.9 (2), 19.9 (2), 19.0 (3), 12.2 (1) ppm.

LRMS (ES^+) *m/z* = 344 $[M + H]^+$ 18%, 366 $[M + Na]^+$ 18%, 709 $[2M + Na]^+$ 100%.

HRMS (ES^+) $C_{18}H_{35}NOSiCl$ $[M + H]^+$ requires 344.2171, found 344.2179.

6-((Z)-2-Fluoromethyl-3-triisopropylsilyl-allyl)-piperidin-2-one 343



$BF_3{\cdot}Et_2O$ (46 μL, 0.366 mmol) was added to a stirring solution of 6-methoxy-piperidin-2-one **318** (50 mg, 0.357 mmol) and TIPSMCP (244 mg, 1.163 mmol) in DCM (5 mL) at -78 °C under N_2 and monitored by TLC. After 8 hours (0 °C) the reaction was quenched with water and extracted with DCM. The organic layers were dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a yellow oil. The oil was purified by column chromatography (50 – 100% EtOAc–PE) to give the title compound **343** as a colourless oil (24 mg, 19%).

Rf = 0.50 (EtOAc).

FT–IR (solution) ν_{max} = 2942 (m), 2865 (m), 1663 (s), 1463 (m), 983 (w), 882 (m), 729 (m) cm^{-1}.

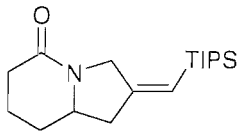
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.75 (1H, bs, N*H*), 5.58 (1H, s, C*H*(TIPS)), 4.46 (2H, d, *J* = 47.0 Hz, CH_2F), 3.60 (1H, m, NHC*H*), 2.56 (1H, dd, *J* = 5.5, 14.5 Hz, $CH_AH_BCCH_2F$), 2.45–2.22 (3H, m, CH_2CO & $CH_AH_BCCH_2F$), 2.10 – 1.30 (4H, m, $CH_2CH_2CH_2CO$), 1.15 – 0.95 (21H, m, $Si(CH(CH_3)_2)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 172.1 (0), 149.4 (0), 130.5 (1), 85.0 (d, *J* = 164.0 Hz, 2), 51.3 (1), 45.4 (2), 31.5 (2), 29.0 (2), 21.0 (2), 20.0 (3), 12.4 (1) ppm.

LRMS (ES^+) *m/z* = 328 $[M + H]^+$ 10%, 350 $[M + Na]^+$ 45%, 677 $[2M + Na]^+$ 100%.

HRMS (ES^+) $C_{18}H_{34}NOSiFNa$ $[M + Na]^+$ requires 350.2286, found 350.2285.

2-[1-Triisopropylsilyl-meth-(Z)-ylidene]-hexahydro-indolizin-5-one 344



6-((Z)-2-Chloromethyl-3-triisopropylsilyl-allyl)-piperidin-2-one **342** (75 mg, 0.219 mmol) was added to a stirring mixture of NaH (17.5 mg, 0.438 mmol, 60% in mineral oil) in THF (5 mL) at 0 °C. The reaction mixture was warmed to room temperature and refluxed for 102 hours followed by a quench with water. The reaction mixture was neutralised with 2M HCl and extracted with DCM. The organic layers were washed, dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a yellow oil. The oil was purified by column chromatography (5 – 30% MeOH–DCM) to give the title compound **344** as a colourless oil (63 mg, 94%).

Rf = 0.72 (EtOAc).

FT–IR (solution) ν_{max} = 2942 (m), 2864 (m), 1643 (s), 1463 (m), 1324 (m), 882 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.51 (1H, s, C*H*(TIPS)), 4.40 (1H, d, *J* = 18.0 Hz, NCH_AH$_B$), 3.88 (1H, d, *J* = 18.0 Hz, NCH$_A$$H_B$), 3.58 (1H, dddd, *J* = 4.0, 4.0, 9.5, 9.5 Hz, C*H*N), 2.73 (1H, dd, *J* = 5.5, 14.5 Hz, NCHCH_AH$_B$CCH$_2$), 2.54 – 2.45 (2H, m, NCHCH$_A$$H_BCCH_2$ & COCH_AH$_B$), 2.30 (1H, ddd, *J* = 7.0, 12.5, 18.5 Hz, COCH$_A$$H_B$), 2.14 (1H, m, COCH$_2CH_2CH_AH_B$), 2.00 – 1.65 (2H, m, COCH$_2$CH$_2$), 1.37 (1H, m, COCH$_2$CH$_2$CH$_A$$H_B$), 1.20 – 0.95 (21H, m, Si(C*H*(CH_3)$_2$)$_3$) ppm.

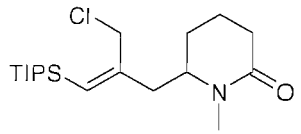
^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 168.9 (0), 152.3 (0), 117.9 (1), 58.6 (1), 49.7 (2), 45.6 (2), 31.1 (2), 29.4 (2), 20.9 (2), 18.9 (3), 11.8 (1) ppm.

LRMS (ES^+) *m/z* = 308 $[M + H]^+$ 25%, 330 $[M + Na]^+$ 40%, 637 $[2M + Na]^+$ 100%.

HRMS (ES^+) $C_{18}H_{33}NOSiNa$ $[M + Na]^+$requires 330.2223, found 330.2228.

X–ray Crystallography see appendix.

6-((Z)-2-Chloromethyl-3-triisopropylsilyl-allyl)-1-methyl-piperidin-2-one 345



$TiCl_4$ (57 μL, 0.524 mmol) was added to a stirring solution of 6-methoxy-1-methyl-piperidin-2-one **322** (50 mg, 0.349 mmol) and TIPSMCP (210 mg, 1.047 mmol) in DCM (5 mL) at –78 °C under N_2 and monitored by TLC. After 2.5 hours (–60 °C) the reaction was quenched with water and extracted with DCM. The organic layers were dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a yellow oil. The oil was purified by column chromatography (1 – 10% EtOAc–PE) to give the title compound **345** as a colourless oil (33 mg, 27%).

Rf = 0.61 (EtOAc).

FT–IR (neat) ν_{max} = 2943 (m), 2865 (m), 1640 (s), 1463 (m), 1332 (m), 882 (m), 732 (s) cm^{-1}.

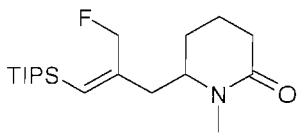
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.49 (1H, s, C*H*(TIPS)), 4.10 (1H, d, *J* = 11.5 Hz, CH_AH_BCl), 4.05 (1H, d, *J* = 11.5 Hz, CH_AH_BCl), 3.58 (1H, m, N(Me)C*H*), 3.02 – 2.95 (4H, m, NCH_3 & $CH_AH_BCCH_2Cl$), 2.48 – 2.30 (3H, m, CH_2CO & $CH_AH_BCCH_2Cl$), 1.95 – 1.65 (4H, m, $COCH_2CH_2CH_2$), 1.18 – 1.01 (21H, m, $Si(CH(CH_3)_2)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 170.3 (0), 150.4 (0), 130.0 (1), 57.3 (1), 51.7 (2), 47.5 (2), 34.0 (3), 32.0 (2), 25.9 (2), 18.9 (3), 17.2 (2), 12.3 (1) ppm.

LRMS (ES^+) *m/z* = 737 $[2M + Na]^+$ 100%.

HRMS (ES^+) $C_{19}H_{37}NOSiCl$ $[M + H]^+$ requires 358.2327, found 358.2333.

6-((Z)-2-Fluoromethyl-3-triisopropylsilyl-allyl)-1-methyl-piperidin-2-one 346



$BF_3{\cdot}Et_2O$ (66 μL, 0.522 mmol) was added to a stirring solution of 6-methoxy-1-methyl-piperidin-2-one **322** (50 mg, 0.349 mmol) and TIPSMCP (210 mg, 1.047 mmol) in DCM (5 mL) at –78 °C under N_2 and monitored by TLC. After 2 hours (–78 °C) the reaction was quenched with water and extracted with DCM. The organic layers were dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a yellow oil. The oil was purified by column chromatography (50 – 100% EtOAc–PE) to give the title compound **346** as a colourless oil (24 mg, 20%).

Rf = 0.31 (EtOAc).

FT–IR (neat) ν_{max} = 2943 (m), 2865 (m), 1639 (s), 1463 (m), 1331 (m), 980 (m), 881 (m) cm^{-1}.

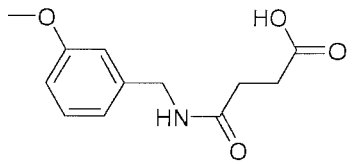
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.53 (1H, s, C*H*(TIPS)), 4.85 (2H, d, *J* = 47.0 Hz, CH_2F), 3.56 (1H, m, N(Me)C*H*), 2.98 (3H, s, NCH_3), 2.86 (1H, dd, *J* = 3.5, 13.5 Hz, $CH_AH_BCCH_2F$), 2.40 – 2.29 (3H, m, CH_2CO & $CH_AH_BCCH_2F$), 1.95 – 1.64 (4H, m, $CH_2CH_2CH_2CO$), 1.18 – 1.02 (21H, m, $Si(CH(CH_3)_2)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 170.3 (0), 150.5 (0), 129.7 (1), 85.1 (d, *J* = 164.0 Hz, 2), 57.7 (1), 40.8 (2), 33.9 (3), 32.0 (2), 25.8 (2), 19.1 (3), 17.2 (2), 12.2 (1) ppm.

LRMS (ES^+) *m/z* = 342 $[M + H]^+$ 2%, 705 $[2M + Na]^+$ 100%.

HRMS (ES^+) $C_{19}H_{37}NOSiF$ $[M + H]^+$ requires 342.2623, found 342.2633.

3-(3-Methoxybenzylamino)-propionic acid 351



Succinic anhydride **323** (1.79g, 17.99 mmol) and 3-methoxybenzylamine **350** (2.30 mL, 17.99 mmol) were stirred in refluxing toluene (100 mL) in the presence of 4Å molecular sieves for 1.5 hours. The reaction mixture was filtered, solvents removed and the orange–brown crude solid was recrystallised from chloroform and hexane to give the title compound **351** as orange crystals (352 mg, 83%).

Rf = 0.54 (1:9 MeOH–DCM).

Melting Point 121 – 123 °C recrystallised from $CHCl_3$/hexane.

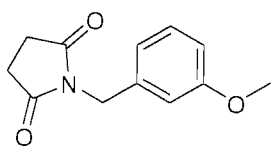
FT–IR (solid) ν_{max} = 3301 (s), 2944 (m), 1696 (s), 1400 (m), 1254 (s), 1154 (m), 1046 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.22 (1H, t, *J* = 8.0 Hz, Ar), 6.85 (bs, N*H*), 6.88 – 6.72 (3H, m, Ar), 6.10 (bs, CO_2H), 4.40 (2H, d, *J* = 4.5 Hz, $NHCH_2$), 3.78 (3H, s, OCH_3), 2.70 – 2.48 (4H, m, $CH_2CH_2CO_2H$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 174.7 (0), 172.0 (0), 159.8 (0), 140.1 (0), 129.5 (1), 119.9 (1), 113.1 (1), 112.8 (1), 55.2 (3), 43.4 (2), 30.9 (2), 29.8 (2) ppm.

LRMS (ES^+) *m/z* = 260 $[M + Na]^+$ 100%.

1-(3-Methoxybenzyl)-pyrrolidine-2,5-dione 353



Following a method described by Reddy *et al.*[134]

A solution of freshly distilled HMDS (3.78 mL, 3.78 mmol) in toluene (75 mL) was added over 30 minutes to a suspension of 3-(3-methoxybenzylamino)-propionic acid **351** (1.50 g,

6.325 mmol) and zinc dichloride (sublimed, 850 mg, 6.325 mmol) in toluene (15 mL) at 80 °C. After reflux at 80 °C for 19 hours the reaction mixture was quenched with HCl (1N, 50 mL) and extracted with EtOAc. The water layer was washed with EtOAc and the organic layers were combined and washed with saturated sodium bicarbonate and brine sequentially. The organic layers were dried and solvents removed *in vacuo* to give a yellow oil. The crude material was purified by column chromatography (10 – 50% EtOAc–PE) to give the title compound **353** as a colourless oil (947 mg, 69%).

Rf = 0.13 (4:1 PE–Et_2O).

FT–IR (neat) ν_{max} = 2942 (w), 2838 (w), 1698 (s), 1398 (m), 1166 (m), 903 (m) cm^{-1}.

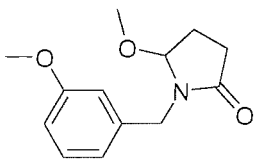
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.21 (1H, t, J = 9.0 Hz, Ar), 6.98 – 6.91 (2H, m, Ar), 6.81 (1H, dd, J = 2.5, 8.0 Hz, Ar), 4.63 (2H, s, CH_2Ph), 3.78 (3H, s, OCH_3), 2.70 (4H, s, 2 × CH_2) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 176.9 (0), 159.8 (0), 137.3 (0), 129.8 (1), 121.2 (1), 114.4 (1), 113.7 (1), 55.3 (3), 42.5 (2), 28.3 (2) ppm.

LRMS (ES^+) m/z = 242 $[M + Na]^+$ 100%.

HRMS (ES^+) $C_{12}H_{13}NO_3Na$ $[M + Na]^+$ requires 242.1787, found 242.0782.

5-Methoxy-1-(3-methoxybenzyl)-pyrrolidin-2-one 352



Following a method described by Klaver *et al.*[127]

$NaBH_4$ (364 mg, 9.60 mmol) was added to a stirring solution of 1-(3-methoxybenzyl)-pyrrolidine-2,5-dione **353** (300 mg, 1.369 mmol) in MeOH (14 mL) at –5 °C under nitrogen. Every fifteen minutes a solution of HCl in MeOH (57 µL, 2M) was added and after 10 minutes the reaction was cooled to –30 °C and acidified (pH 3) with 2M HCl in MeOH. The mixture was stirred for one hour at room temperature before the addition of water and extraction with DCM. The organic layers were combined, dried ($MgSO_4$),

filtered and solvents removed *in vacuo* to give a yellow oil. The oil was purified by column chromatography (30 – 100% EtOAc–PE) to give the title compound **352** as a colourless oil (1.16 g, 69%).

Rf = 0.13 (4:1 PE–Et_2O).

FT–IR (neat) ν_{max} = 2974 (m), 1701 (s), 1389 (s), 1165 (m), 1084 (m), 903 (s), 724 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.25 (1H, t, *J* = 7.0 Hz, Ar), 6.89 – 6.72 (3H, m, Ar), 4.95 (1H, d, *J* = 15.0 Hz, NC*H*$_A$H$_B$), 4.72 (1H, dd, *J* = 6.0, 15.0 Hz, C*H*(OMe)), 3.78 (1H, d, *J* = 15.0 Hz, NCH$_A$*H*$_B$), 3.80 (3H, s, OC*H*$_3$), 3.22 (3H, s, OC*H*$_3$), 2.65 – 1.90 (4H, m, COC*H*$_2$C*H*$_2$) ppm.

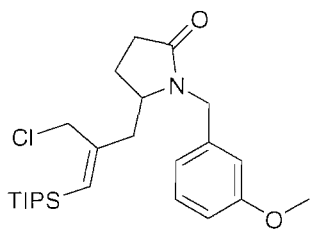
^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 174.9 (0), 160.0 (0), 132.8 (0), 129.8 (1), 120.9 (1), 114.1 (1), 113.2 (1), 89.1 (1), 55.4 (3), 53.1 (3), 43.9 (2), 29.1 (2), 23.9 (2) ppm.

LRMS (ES^+) *m/z* = 258 $[M + Na]^+$ 100%, 493 $[2M + Na]^+$ 5%.

HRMS (ES^+) $C_{13}H_{17}NO_3Na$ $[M + Na]^+$ requires 258.1100, found 258.1098.

5-((Z)-2-Chloromethyl-3-triisopropylsilyl-allyl)-1-(4-methoxybenzyl)-pyrrolidin-2-one 353a

---



$TiCl_4$ (49 µL, 0.319 mmol) was added to a stirring solution of 5-methoxy-1-(3-methoxybenzyl)-pyrrolidin-2-one **352** (70 mg, 0.213 mmol) and TIPSMCP (189 mg, 0.638 mmol) in DCM (7 mL) at –78 °C under N_2 and monitored by TLC. After 24 hours (rt) the reaction was quenched with water and extracted with DCM. The organic layers were dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a yellow oil. The oil was purified by column chromatography (5 – 30% EtOAc–PE) to give the title compound **353a** as a colourless oil (43 mg, 50%).

Rf = 0.77 (EtOAc).

FT–IR (neat) ν_{max} = 2942 (m), 2864 (m), 1688 (s), 1460 (m), 1261 (m), 903 (m), 732 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.25 (1H, m, Ar), 6.90 – 6.80 (3H, m, Ar), 5.43 (1H, s, C*H*(TIPS)), 5.00 (1H, d, *J* = 14.0 Hz, CH_AH$_B$Ph), 4.04 – 3.99 (1H, m, CH$_A$$H_B$Ph & C$H_AH_B$Cl), 3.92 (1H, d, *J* = 11.5 Hz, CH$_A$$H_B$Cl), 3.80 (1H, s, OC$H_3$), 3.64 (1H, m, NC*H*CH$_2$), 3.02 (1H, dd, *J* = 3.0, 14.0 Hz, CH_AH$_B$CCH$_2$Cl), 2.52 (1H, ddd, *J* = 7.0, 9.5, 17.0 Hz, CH_AH$_B$CO), 2.40 (1H, ddd, *J* = 6.0, 10.0, 17.0 Hz, CH$_A$$H_B$CO), 2.12 (1H, dd, *J* = 10.5, 14.0 Hz, CH$_A$$H_BCCH_2$Cl), 2.02 (1H, m, COCH$_2CH_AH_B$), 1.78 (1H, m, COCH$_2CH_A$$H_B$), 1.26 – 0.95 (21H, m, Si(CH(CH$_3$)$_2$)$_3$) ppm.

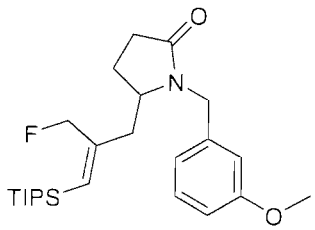
^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 174.9 (0), 160.2 (0), 149.8 (0), 138.4 (0), 130.0 (1), 129.8 (1), 120.7 (1), 113.8 (1), 113.4 (2), 55.7 (1), 55.4 (3), 47.6 (2), 44.5 (2), 40.8 (2), 29.9 (2), 18.9 (3), 12.2 (1) ppm.

LRMS (ES$^+$) *m/z* = 472 $[M + Na]^+$ 100%, 921 $[2M + Na]^+$ 45%.

HRMS (ES$^+$) $C_{25}H_{41}NO_2SiF$ $[M + H]^+$ requires 434.2885, found 434.2889.

5-((Z)-2-Fluoromethyl-3-triisopropylsilyl-allyl)-1-(4-methoxybenzyl)-pyrrolidin-2-one 353b

---



$BF_3{\cdot}Et_2O$ (40 µL, 0.213 mmol) was added to a stirring solution of 5-methoxy-1-(3-methoxybenzyl)-pyrrolidin-2-one **352** (50 mg, 0.213 mmol) and TIPSMCP (134 mg, 0.638 mmol) in DCM (5 mL) at –78 °C under N_2 and monitored by TLC. After 26 hours (rt) the reaction was quenched with water and extracted with DCM. The organic layers were dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a yellow oil. The oil was purified by column chromatography (10% EtOAc–PE) to give the title compound **353b** as a colourless oil (42 mg, 49%).

Rf = 0.13 (4:1 PE–Et_2O).

FT–IR (neat) ν_{max} = 2944 (m), 2866 (m), 1737 (m), 1690 (s), 1460 (m), 1365 (m), 1262 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.22 (1H, m, Ar), 6.88 – 6.78 (3H, m, Ar), 5.48 (1H, s, C*H*(TIPS)), 4.95 (1H, d, *J* = 15.0 Hz, CH_AH_BPh), 4.88 (1H, dd, *J* = 11.5, 47.5 Hz, CH_AH_BF), 4.71 (1H, dd, *J* = 11.5, 47.5 Hz, CH_AH_BF), 4.12 (1H, d, *J* = 15.0 Hz, CH_AH_BPh), 3.88 (1H, s, OCH_3), 3.66 (1H, m, $NCHCH_2$), 2.88 (1H, dd, *J* = 3.0, 13.5 Hz, $CH_AH_BCCH_2F$), 2.55 – 2.35 (2H, m, CH_2CO), 2.08 (1H, dd, *J* = 10.5, 13.5 Hz, $CH_AH_BCCH_2F$), 2.00 – 1.69 (2H, m, CH_2CH_2CO), 1.05 – 0.80 (21H, m, $Si(CH(CH_3)_2)_3$) ppm.

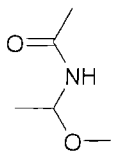
^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 175.0 (0), 160.1 (0), 149.6 (0), 138.5 (0), 129.8 (1), 120.6 (1), 113.8 (1), 113.3 (1), 84.9 (d, *J* = 164.0 Hz, 2), 56.1 (1), 55.4 (3), 44.5 (2), 41.0 (2), 29.9 (2), 23.7 (2), 18.9 (3), 12.1 (1) ppm.

LRMS (ES^+) *m/z* = 456 $[M + Na]^+$ 95%, 890 $[2M + Na]^+$ 100%.

HRMS (ES^+) $C_{25}H_{41}NO_2SiF$ $[M + H]^+$ requires 434.2885, found 434.2889.

Microanalysis Calculated for $C_{25}H_{40}NO_2SiF$: C, 69.24; H, 9.30; N, 3.23. Found C, 68.94; H, 9.24; N, 2.94.

N-(1-Methoxy-ethyl)-acetamide 361



Following a method described by Klaver *et al.*[127]

$NaBH_4$ (2.63 g, 0.069 mol) was added to a stirring solution of diacetamide (1.00 g, 0.010 mol) in MeOH (100 mL) at –5 °C under nitrogen. Every fifteen minutes a solution of HCl in MeOH (416 µL, 2M) was added and after two hours the reaction was cooled to -30 °C and acidified (pH 2) with 2M HCl in MeOH. The mixture was stirred for one hour at room temperature before the addition of water and extraction with DCM. The organic layers were combined, dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a

colourless oil. The oil was purified by column chromatography (1 – 8% MeOH–DCM) to give the title compound **361** as a colourless oil (264 mg, 23%).

Rf = 0.12 (EtOAc).

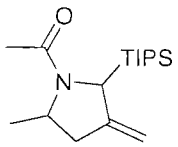
FT–IR (neat) ν_{max} = 3277 (m), 2986 (w), 2936 (w), 1657 (s), 1536 (s), 1374 (m), 1282 (m), 1131 (s), 1090 (s) cm^{-1}.

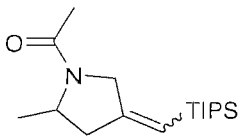
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.80 (1H, bs, N*H*), 5.25 (1H, dq, *J* = 10.0, 6.0 Hz, NHC*H*), 3.32 (3H, s, OCH_3), 2.01 (3H, s, CH_3CO), 1.31 (3H, d, *J* = 6.0 Hz, NHCHCH_3) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 170.5 (0), 77.8 (1), 56.0 (3), 23.8 (3), 21.9 (3) ppm.

1-(5-Methyl-3-methylene-2-triisopropylsilyl-pyrrolidin-1-yl)-ethanone 363 &

1-{2-Methyl-4-[1-triisopropylsilyl-meth-(Z)-ylidene]-pyrrolidin-1-yl}-ethanone 364





$BF_3{\cdot}Et_2O$ (81 µL, 0.641 mmol) was added to a stirring solution of *N*-(1-methoxy-ethyl)-acetamide **361** (50 mg, 0.427 mmol) and TIPSMCP (269 mg, 1.282 mmol) in DCM (5 mL) at –78 °C under N_2 and monitored by TLC. After 3 hours (–10 °C) the reaction was quenched with water and extracted with DCM. The organic layers were dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a yellow oil. The oil was purified by column chromatography (5 – 15% EtOAc–PE) to give two compounds.

Colourless oil **363** (43 mg, 39%).

Rf = 0.13 (4:1 PE–Et_2O).

FT–IR (neat) ν_{max} = 2944 (m), 2867 (s), 1638 (s), 1463 (m), 1400 (m), 1077 (w), 903 (s), 881 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.86 (1H, s, C*H*(TIPS)), 4.77 (2H, s, CH(TIPS)CCH_2), 4.01 (1H, m, NC*H*CH_3), 2.89 (1H, dd, *J* = 8.5, 16.0 Hz, CH_AH_B), 2.47 (1H, m, CH_AH_B),

2.06 (3H, s, CH_3CO), 1.44 (3H, d, J = 6.5 Hz, CH_3CHN), 1.20 – 0.85 (21H, m, $Si(CH(CH_3)_2)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 169.6 (0), 147.5 (0), 104.2 (2), 54.5 (1), 53.9 (1), 42.7 (2), 23.0 (3), 21.9 (3), 19.2 (3), 11.8 (1) ppm.

LRMS (ES^+) *m/z* = 318 $[M + Na]^+$ 100%, 613 $[2M + Na]^+$ 30%.

HRMS (ES^+) $C_{17}H_{33}NOSiNa$ $[M + Na]^+$ requires 318.2223, found 318.2219.

Microanalysis Calculated for $C_{17}H_{33}NOSi$: C, 69.09; H, 11.25; N, 4.74. Found C, 69.13; H, 10.80; N, 4.46.

Colourless oil **364** as a mixture of two diastereoisomers (29 mg, 23%).

Rf = 0.13 (4:1 PE–Et_2O).

FT–IR (neat) ν_{max} = 2941 (m), 2864 (m), 1639 (s), 1415 (s), 882 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.52 (1H, s, CH(TIPS)), 4.20 (1H, d, J = 17.5 Hz, NCH_AH_B), 4.07 (1H, m, $NCHCH_3$), 3.91 (1H, d, J = 17.5 Hz, NCH_AH_B), 3.03 (1H, ddd, J = 2.0, 8.0, 15.0 Hz, $NCHCH_AH_B$), 2.28 (1H, m $NCHCH_AH_B$), 2.10 (3H, s, CH_3CO), 1.20 – 1.10 (3H, m, CH_3CHN), 1.18 – 0.95 (21H, m, $Si(CH(CH_3)_2)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 168.6 (0), 153.3 (0), 119.0 (1), 53.4 (1), 49.0 (2), 45.1 (2), 21.6 (3), 21.0 (3), 18.9 (3), 11.9 (1) ppm.

LRMS (ES^+) *m/z* = 318 $[M + Na]^+$ 40%, 613 $[2M + Na]^+$ 100%.

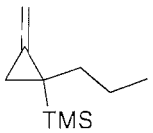
HRMS (ES^+) $C_{17}H_{33}NOSiNa$ $[M + Na]^+$ requires 318.2223, found 318.2219.

For the other diastereoisomer the identifiable peaks in the NMR spectra are recorded below:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.40 (1H, m, NCH_AH_B), 4.02 (1H, m, NCH_AH_B), 2.89 (1H, ddd, J = 2.0, 8.0, 15.5 Hz, $NCHCH_AH_B$), 2.22 (1H, m $NCHCH_AH_B$), 2.01 (3H, s, CH_3CO) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 154.2 (0), 118.7 (1), 51.4 (1), 51.3 (2), 43.8 (2), 22.8 (3), 19.3 (3) ppm.

Trimethyl(2-methylene-1-propylcyclopropyl)silane 366



Following the method described by Patient.[22]

^{n}Butyllithium (16.0 mL, 1.6 M, 25.6 mmol) was added to a stirring solution of methylenecyclopropane **1** (12.8 mL, 25.6 mmol) in THF (80 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 (3.25 mL, 25.6 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}butyllithium (16.0 mL, 1.6 M, 25.6 mmol) and the warming procedure repeated. The reaction was cooled to –70 °C before addition of iodopropane (2.74 mL, 28.2 mmol) and allowed to warm to room temperature overnight. The reaction was quenched with saturated ammonium chloride and extracted with Et_2O. Tthe organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by column chromatography (PE) to give the title compound **366** as a colourless oil (3.21 g, 74%).

Rf = 0.13 (4:1 PE–Et_2O).

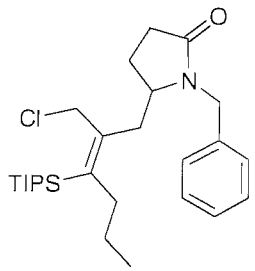
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 5.23 (1H, s, CH_AH$_B$CC(TMS)), 5.18 (1H, s, CH$_A$$H_B$CC(TMS)), 1.52 – 1.23 (4H, m, (CH_2)$_2$CH$_3$), 1.05 (1H, d, J = 7.0 Hz, CH_AH$_B$C(TMS)), 0.90 (3H, t, J = 7.0 Hz, CH_3), 0.81 (1H, d, J = 7.0 Hz, CH$_A$$H_B$C(TMS)), 0.00 (9H, s, Si(CH_3)$_3$) ppm.

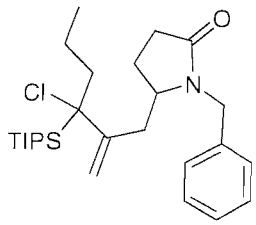
^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 140.2 (0), 101.2 (2), 39.5 (2), 29.5 (2), 14.4 (3), 13.9 (0), 13.8 (2), 0.02 (3) ppm.

LRMS (EI) *m/z* = 73 $[Si(CH_3)_3]^+$ 100%, 168 $[M]^+$ 2%.

Spectroscopic data agrees with Patient.[22]

1-Benzyl-5-(2-chloromethyl-3-triisopropylsilyl-hex-2-enyl)-pyrrolidin-2-one 368b & 1-Benzyl-5-(3-chloro-2-methylene-3-triisopropylsilyl-hexyl)-pyrrolidin-2-one 369b





$TiCl_4$ (80 μL, 0.730 mmol) was added to a stirring solution of 1-benzyl-5-methoxy-pyrrolidin-2-one **325** (100 mg, 0.488 mmol) and trimethyl(2-methylene-1-propylcyclopropyl)silane **366** (246 mg, 1.464 mmol) in DCM (10 mL) at –78 °C under N_2 and monitored by TLC. After 24 hours (–78 °C) the reaction was quenched with water and extracted with DCM. The organic layers were dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a colourless oil. The oil was purified by column chromatography (0 – 5% EtOAc–PE) to give a mixture of the title compounds **368b** and **369b** as a colourless oil (110 mg, 60 %). The compounds were not separable by column chromatography or by using HPLC methods so NMR data cannot be conclusively assigned.

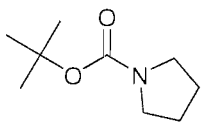
Rf = 0.64 (1:9 MeOH–DCM).

FT–IR (solution) ν_{max} = 2956 (m), 1688 (s), 1418 (m), 1251 (m), 903 (m), 838 (s) cm^{-1}.

LRMS (ES^+) *m/z* = 399 $[M + Na]^+$ 100%, 779 $[2M + Na]^+$ 50%.

HRMS (ES^+) $C_{21}H_{33}NOSiCl$ $[M + H]^+$ requires 400.1834, found 400.1826.

Pyrrolidine-1-carboxylic acid *tert*-butyl ester 382



Following the method described by Dieter and Li.[152]

Pyrrolidine (3.56 g, 50.0 mmol), di^{t}butyldicarbonate (12.15 g, 55.7 mmol), DMAP (6.60 g, 50.0 mmol) and Et_3N (7.5 mL, 50.0 mmol) were stirred in DCM (75 mL) at room temperature under nitrogen. After 21 hours the reaction mixture was diluted with Et_2O (120 mL), washed with 1M HCl and K_2CO_3 and brine sequentially before being dried ($MgSO_4$). Solvents were removed *in vacuo* to give a brown oil which was purified by column chromatography (0 – 3% MeOH–DCM) to give the title compound **382** as a colourless oil (8.28 g, 97%).

Rf = 0.60 (1:91 MeOH – DCM).

FT–IR (neat) ν_{max} = 2972 (m), 2874 (m), 1690 (s), 1396 (s), 1164 (s), 1100 (m), 876 (m), 771 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 3.34 – 3.29 (4H, m, 2 × CH_2N), 1.83 (4H, m, 2 × CH_2CH_2N), 1.48 (9H, s, C(CH_3)$_3$) ppm.

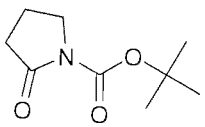
^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 154.8 (0), 78.9 (0), 45.9 (2), 28.7 (3), 25.5 (2) ppm.

LRMS (ES^+) *m/z* = 194 $[M + Na]^+$ 100%, 365 $[2M + Na]^+$ 18%.

HRMS (ES^+) $C_9H_{17}NO_2Na$ $[M + Na]^+$ requires 194.1151, found 194.1153.

Spectroscopic data agrees with Dieter and Li.[152]

Pyrrolidin-2-one-1-carboxylic acid *tert*-butyl ester 385



Following the method of Flynn *et al.*[153]

A solution of 2-pyrrolidinone (3.00 g, 35.3 mmol), di^{t}butyldicarbonate (15.38 g, 70.6 mmol), DMAP (4.30 g, 35.29 mmol) and Et_3N (4.91 mL, 35.29 mmol) in DCM (180 mL) were stirred at room temperature for six hours under N_2. The reaction was quenched with HCl (30 mL, 2M) and extracted with DCM. The organic layer was washed sequentially with saturated sodium bicarbonate and saturated brine solutions before being dried ($MgSO_4$) and solvents removed to give the title compound **385** as a red oil (5.87 g, 90%).

Rf = 0.62 (EtOAc).

FT–IR (neat) ν_{max} = 2979 (m), 1782 (m), 1749 (m), 1712 (m), 1366 (m), 1309 (s), 1149 (s), 1018 (m) cm^{-1}.

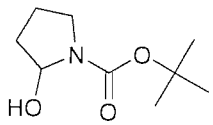
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 3.74 (2H, t, *J* = 7.5 Hz, $COCH_2$), 2.50 (2H, t, *J* = 7.5 Hz, CH_2N), 2.01 (2H, quin, *J* = 7.5 Hz, CH_2CH_2N), 1.52 (9H, s, $C(CH_3)_3$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 174.3 (0), 150.4 (0), 82.9 (0), 46.6 (2), 33.1 (2), 28.1 (3), 17.5 (2) ppm.

LRMS (ES^+) *m/z* = 208 $[M + Na]^+$ 100%, 393 $[2M + Na]^+$ 60%.

Spectroscopic data agrees with Giovannini *et al.*[154]

1-(2-Hydroxypyrrolidin-1-yl)-2,2-dimethylpropan-1-one 386



Following the method of Sato *et al.* [155]

Lithium triethylborohydride (12.2 mL, 12.2 mmol, 1M), was added to a stirring solution of pyrrolidin-2-one-1-carboxylic acid *tert*-butyl ester **385** (1.50 g, 8.10 mmol) in THF (20 mL) at –78 °C under N_2. After 40 minutes at –78 °C the reaction was quenched with $NaHCO_3$. After warming to 0 °C, 30% H_2O_2 (5 drops) was added to the reaction mixture and stirred at 0 °C for 20 minutes. The solvents were removed *in vacuo* and the residue was dissolved in DCM. The solution was dried ($MgSO_4$) and solvents removed *in vacuo* to give a yellow oil. The crude material was purified by column chromatography (1% MeOH–DCM) to give the title compound **386** as a yellow liquid (896 mg, 59%).

Rf = 0.13 (4:1 PE–Et_2O).

FT–IR (neat) ν_{max} = 3421 (b), 3977 (m), 2835 (m), 1677 (s), 1390 (s), 1160 (s), 1100 (s), 905 (m) cm^{-1}.

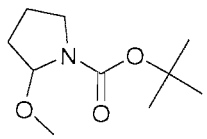
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 5.43 (1H, bd, *J* = 16.0 Hz, O*H*), 3.72 (1H, m, NC*H*OH) 3.58 – 3.20 (2H, m, CH_2N), 2.10 – 1.78 (4H, m, $CH_2CH_2CH_2N$), 1.47 (9H, s, $C(CH_3)_3$) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C = 155.3 (0), 81.8 (1), 46.1 (2), 33.6 (2), 28.6 (3), 23.1 (2) ppm.

LRMS (ES^+) *m/z* = 210 $[M + Na]^+$ 100%.

HRMS (ES^+) $C_9H_{17}NO_3Na$ $[M + Na]^+$ requires 210.1100, found 210.1098.

1-(2-Methoxy-pyrrolidin-1-yl)-2,2-dimethylpropan-1-one 383



Following the method described by Rassu *et al.*[138]

$BF_3{\cdot}Et_2O$ (50 μL, 0.534 mmol) was added to a stirring solution of 1-(2-hydroxypyrrolidin-1-yl)-2,2-dimethylpropan-1-one **386** (0.775 g, 5.34 mmol) and methyl orthoformate (0.44 mL, 5.34 mmol) in Et_2O (37.5 mL) with 4Å molecular sieves at room temperature. After 30 minutes the reaction mixture was filtered and concentrated *in vacuo* followed immediately by purification by column chromatography (10 – 50% EtOAc–PE) to give the title compound **383** as a colourless oil (869 mg, 81%).

Rf = 0.38 (1:1 EtOAc–PE).

FT–IR (solution) ν_{max} = 2937 (m), 1693 (s), 1451 (m), 1261 (m), 1078 (m) cm^{-1}.

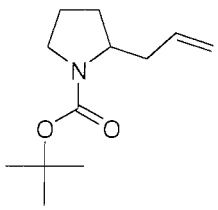
^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 5.13 (1H, bd, *J* = 22.0 Hz, NC*H*OCH_3), 3.55 – 3.35 (2H, m, CH_2N), 3.33 (bs, 3H, OCH_3), 2.10 – 1.76 (4H, m, $CH_2CH_2CH_2N$), 1.50 (9H, s, $C(CH_3)_3$) ppm.

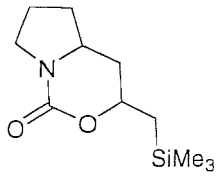
LRMS (ES^+) *m/z* = 224 $[M + Na]^+$ 100%.

HRMS (ES^+) $C_{10}H_{19}NO_3Na$ $[M + Na]^+$ requires 224.1257, found 224.1255.

This data agrees with Shono *et al.*[156]

2-Allyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester 372 and 3-Trimethylsilylmethyl-hexahydro-pyrrolo[1,2-*c*][1,3]oxazin-1-one 371





Following the method described by Brocherieux-Lanoy.[125]

$TiCl_4$ (39 µL, 0.357 mmol) was added to a stirring solution of 1-(2-methoxy-pyrrolidin-1-yl)-2,2-dimethylpropan-1-one **383** (50 mg, 0.238 mmol) and allylTMS (113 µL, 0.714 mmol) in DCM (5 mL) at –78 °C under N_2 and monitored by TLC. After 5 minutes the reaction was quenched with sodium acetate and extracted with DCM. The organic layers were dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a cloudy yellow oil. The oil was purified by column chromatography (5 – 50% EtOAc–PE) to give two compounds.

Compound **372** as a colourless oil (7 mg, 13%).

Rf = 0.89 (EtOAc).

FT–IR (neat) ν_{max} = 2972 (m), 2875 (w), 1692 (s), 1390 (m), 1170 (m), 1108 (m), 911 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.76 (1H, ddt, *J* = 10.0, 17.0, 7.0 Hz, $NCHCH_2CH$), 5.09 – 5.01 (2H, m, $NCHCH_2CHCH_2$), 3.82 (1H, m, $NCHCH_2$), 3.35 (2H, m, NCH_2), 2.50 (1H, m, $NCHCH_AH_BCH$), 2.12 (1H, m, $NCHCH_AH_BCH$), 1.92 – 1.70 (4H, m, $NCH_2CH_2CH_2$), 1.45 (9H, s, $C(CH_3)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 154.7 (0), 135.4 (1), 117.1 (2), 79.2 (0), 56.9 (1), 46.6 (2), 38.8 (2), 29.8 (2), 28.7 (3), 23.4 (2) ppm.

LRMS (ES^+) *m/z* = 234 $[M + Na]^+$ 100%.

HRMS (ES^+) $C_{12}H_{21}NO_2Na$ $[M + Na]^+$ requires 234.1464, found 234.1462.

Compound **371** as a racemic mixture; colourless oil (30 mg, 54%).

Rf = 0.46 (EtOAc).

FT–IR (neat) ν_{max} = 2952 (m), 2889 (w), 1687 (s), 1427 (m), 1128 (m), 842 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.25 (1H, m, OC*H*), 3.55 – 3.28 (3H, m, NCH_2 & NC*H*CH_2), 2.12 – 1.82 (3H, m, $NCH_2CH_AH_B$, $NCHCH_AH_BCHO$ & $NCH_2CH_2CH_AH_B$), 1.35 – 0.95 (4H, m, $NCH_2CH_AH_B$, $NCH_2CH_2CH_AH_B$, $NCHCH_AH_BCHO$ & CH_AH_B(TMS)), 1.90 – 1.81 (1H, m, CH_AH_B(TMS), 0.00 (9H, s, $Si(CH_3)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 154.2 (0), 77.0 (1), 57.4 (2), 47.2 (2), 37.6 (2), 34.2 (2), 34.0 (2), 23.7 (2), 0.00 (3) ppm.

LRMS (ES^+) *m/z* = 250 $[M + Na]^+$ 100%, 477 $[2M + Na]^+$ 75%

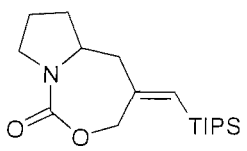
HRMS (ES^+) $C_{11}H_{21}NO_2SiNa$ $[M + Na]^+$ requires 250.1234, found 250.1238.

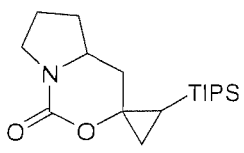
For the other isomer the identifiable peaks are shown below:

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.51 (1H, m, OC*H*), 3.55 – 3.28 (3H, m, NCH_2 & NC*H*CH_2), 2.12 – 1.82 (3H, m, $NCH_2CH_AH_B$, $NCHCH_AH_BCHO$ & $NCH_2CH_2CH_AH_B$), 1.79 – 1.81 (1H, m, $NCHCH_AH_BCHO$), 1.35 – 0.95 (3H, m, $NCH_2CH_AH_B$, $NCH_2CH_2CH_AH_B$ & CH_AH_B(TMS)), 1.90 – 1.81 (1H, m, CH_AH_B(TMS), 0.00 (9H, s, $Si(CH_3)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 153.6 (0), 75.6 (1), 53.1 (2), 47.4 (2), 34.5 (2), 25.2 (2), –0.25 ppm.

4-[1-Triisopropylsilyl-meth-(Z)-ylidene]-hexahydro-pyrrolo[1,2-*c*][1,3]oxazin-1-one 376 & 3,6-spirocycle 387





$BF_3{\cdot}Et_2O$ (90 µL, 0.714 mmol) was added to a stirring solution of 1-(2-methoxy-pyrrolidin-1-yl)-2,2-dimethylpropan-1-one **370** (100 mg, 0.476 mmol) and TIPSMCP (130 mL, 1.428 mmol) in DCM (10 mL) at –78 °C under N_2 and monitored by TLC. After

36 hours the reaction was quenched with sodium acetate and extracted with DCM. The organic layers were washed with brine, dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a yellow oil. The crude material was purified by column chromatography (0 – 10% MeOH–DCM) to give two compounds.

Compound **376** as a colourless oil (16 mg, 11%).

Rf = 0.42 (1:9 EtOAc–PE).

FT–IR (solution) ν_{max} = 2941 (m), 2864 (m), 1659 (s), 1364 (m), 1216 (m), 903 (s), 723 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 5.42 (1H, s, C*H*(TIPS)), 4.72 (1H, d, *J* = 13.5 Hz, OC$H_A$$H_B$), 4.42 (1H, d, *J* = 13.5 Hz, OC$H_A$$H_B$), 3.74 (1H, m, NC*H*$CH_2$), 3.61 (1H, ddd, *J* = 4.0, 8.0, 11.5 Hz, NC$H_A$$H_B$), 3.53 (1H, ddd, *J* = 7.0, 9.5, 11.5 Hz, NC$H_A$$H_B$), 2.62 (2H, m, OCH_2CCH_2), 2.15 (1H, dddd, *J* = 4.0, 6.5, 6.5, 12.5 Hz, $NCH_2CH_2CH_A$$H_B$), 1.95 – 1.72 (2H, m, NCH_2CH_2), 1.60 (1H, m, $NCH_2CH_2CH_A$$H_B$), 1.15 – 0.95 (21H, m, $Si(CH(CH_3)_2)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 157.7 (0), 151.4 (0), 125.2 (1), 71.8 (2), 58.9 (1), 49.2 (2), 45.4 (2), 34.2 (2), 23.5 (2), 20.3 (3), 13.5 (1) ppm.

LRMS (ES^+) *m/z* = 324 $[M + H]^+$ 42%, 346 $[M + Na]^+$ 46%, 669 $[2M + Na]^+$ 100%.

HRMS (ES^+) $C_{18}H_{33}NO_2SiNa$ $[M + Na]^+$ requires 346.2173, found 346.2177.

Compound **387** as a colourless oil (13 mg, 9%).

Rf = 0.36 (1:9 EtOAc–PE).

FT–IR (neat) ν_{max} = 2944 (m), 2866 (m), 1737 (s), 1709 (s), 1420 (m), 1364 (m), 1297 (s), 903 (s), 724 (s) cm^{-1}.

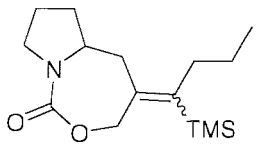
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 3.72 – 3.49 (3H, s, CH_2N & C*H*N), 2.15 (1H, m, NCHC$H_A$$H_B$$CH_2$), 2.01 – 1.76 (4H, m, NCH_2CH_2 & NCHCH_2CO), 1.53 (1H, m, NCHC$H_A$$H_B$$CH_2$), 1.28 (1H, m, C$H_A$$H_B$CH(TIPS)), 1.15 – 0.85 (21H, m, $Si(CH(CH_3)_2)_3$), 0.59 – 0.46 (1H, m, $CH_A$$H_B$CH(TIPS)) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 153.9 (0), 64.2 (0), 56.7 (1), 46.5 (2), 34.1 (2), 33.1 (2), 23.2 (2), 19.2 (2), 15.0 (2), 12.0 (1), 7.1 (1) ppm.

LRMS (ES^+) *m/z* = 346 $[M + Na]^+$ 100%, 669 $[2M + Na]^+$ 65%.

HRMS (ES^+) $C_{18}H_{33}NO_2SiNa$ $[M + Na]^+$ requires 346.2173, found 346.2171.

4-(1-Trimethylsilyl-butylidene)-hexahydro-pyrrolo[1,2-c]oxazepin-1-one 390



$BF_3{\cdot}Et_2O$ (45μL, 0.357 mmol) was added to a stirring solution of 1-(2-methoxy-pyrrolidin-1-yl)-2,2-dimethylpropan-1-one **370** (50 mg, 0.238 mmol) and trimethyl(2-methylene-1-propylcyclopropyl)silane **366** (119 mL, 0.714 mmol) in DCM (5 mL) at –78 °C under N_2 and monitored by TLC. After 24 hours the reaction was quenched with sodium acetate and extracted with DCM. The organic layers were washed with brine, dried ($MgSO_4$), filtered and solvents removed *in vacuo* to give a yellow oil. The crude material was purified by column chromatography (0 – 10% MeOH–DCM) to give the title compound **390** as a colourless oil (43 mg, 62%).

Rf = 0.52 (1:9 EtOAc–PE).

FT–IR (solution) ν_{max} = 2954 (m), 2893 (m), 1690 (s), 1416 (m), 1250 (m), 840 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 4.71 (1H, d, *J* = 13.5 Hz, OCH_AH_B), 4.38 (1H, d, *J* = 13.5 Hz, OCH_AH_B), 3.58 (1H, m, $NCHCH_2$), 3.48 – 3.20 (4H, m, NCH_2 & $C(TMS)CH_2CH_2$), 2.70 (1H, d, *J* = 14.0 Hz, $NCHCH_AH_BCC(TMS)$), 2.12 (1H, dd, *J* = 12.0, 14.0 Hz, $NCHCH_AH_BCC(TMS)$), 1.98 – 1.00 (6H, m, 3 × CH_2), 0.70 (3H, m, CH_2CH_3) , 0.00 (9H, m, $Si(CH_3)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ_C = 156.1 (0), 140.5 (0), 70.4 (2), 67.1 (0), 57.1 (0), 48.4 (2), 45.5 (2), 35.2 (2), 33.6 (2), 33.2 (2), 22.1 (2), 13.3 (3), 0.5 (3) ppm.

LRMS (ES^+) *m/z* = 304 $[M + Na]^+$ 100%.

Microanalysis Calculated for $C_{15}H_{27}NO_2Si$: C, 64.01; H, 9.67; N, 4.98. Found C, 64.21; H, 9.56; N, 4.77.

References.

1. Laurie, V. W.; Stigliani, W. M., *J. Am. Chem. Soc.*, **1970**, *92*, 1485.
2. Binger, P.; Buchi, H. M., *Top. Curr. Chem.*, **1987**, *135*, 77.
3. Anderson, B. C., *J. Org. Chem.*, **1962**, *27*, 2720.
4. Lai, M.; Liu, L.; Liu, H., *J. Am. Chem. Soc.*, **1991**, *113*, 7388.
5. Baldwin, J. E.; Adlington, R. M.; Bebbington, D.; Russell, A. T., *Tetrahedron*, **1994**, *50*, 12015.
6. Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A., *Chem. Rev.*, **2003**, *103*, 1213.
7. Brandi, A.; Goti, A., *Chem. Rev.*, **1998**, *98*, 589.
8. Lautens, M.; Klute, W.; Tam, W., *Chem. Rev.*, **1996**, *96*, 49.
9. Gragson, J. T.; Greenlee, K. W.; Derfer, J. M.; Boord, C. E., *J. Am. Chem. Soc.*, **1953**, *75*, 3344.
10. Salaun, J. R.; Champion, J.; Conia, J. M., *Org. Synth.*, **1977**, *57*, 36.
11. Köster, R.; Arora, S.; Binger, P., *Liebigs Ann. Chem.*, **1973**, 1219.
12. Köster, R.; Arora, S.; Binger, P., *Synthesis*, **1971**, 322.
13. Binger, P.; Brinkmann, A.; Wedemann, P., *Synthesis*, **2002**, *10*, 1344.
14. Arora, S.; Binger, P., *Synthesis*, **1974**, *11*, 801.
15. Destabel, C., *Ph.D. Thesis, University of Southampton*, **1994**.
16. Pike, K., *Ph.D. Thesis, University of Southampton.*, **1997**.
17. Pike, K.; Destabel, C.; Anson, M.; Kilburn, J., *Tetrahedron Lett.*, **1998**, *39*, 5877.
18. Sternberg, E.; Binger, P., *Tetrahedron Lett.*, **1985**, *26*, 301.
19. Destabel, C.; Kilburn, J. D.; Knight, J., *Tetrahedron Lett.*, **1993**, *34*, 3151.
20. Destabel, C.; Kilburn, J. D.; Knight, J., *Tetrahedron*, **1994**, *50*, 11289.
21. Santagostino, M.; Kilburn, J. D., *Tetrahedron Lett.*, **1994**, *35*, 8863.
22. Patient, L., *Ph.D. Thesis, University of Southampton.*, **2003**, 192.
23. Patient, L.; Berry, M. B.; Kilburn, J. D., *Tetrahedron*, **2003**, *44*, 1015.
24. Thomas, E. W., *Tetrahedron Lett.*, **1983**, *42*, 1467.
25. Thomas, E. W.; Szmuszkovicz, J. R., *J. Org. Chem.*, **1990**, *55*, 6054.
26. Lau, P. W. K.; Chan, T. H., *Tetrahedron Lett.*, **1978**, *27*, 2383.
27. Peron, G., *Ph.D. Thesis, University of Southampton*, **2000**, 279.
28. Peron, G.; Norton, D.; Kitteringham, J.; Kilburn, J. D., *Tetrahedron Lett.*, **2001**, *42*, 347.
29. Fournet, G.; Balme, G.; Barieux, J. J.; Gore, J. J., *Tetrahedron*, **1988**, *44*, 5821.
30. Maercker, A.; Daub, V. E. E., *Tetrahedron*, **1994**, *50*, 2439.
31. Salaun, J. R.; Fadel, A., *Tetrahedron Lett.*, **1979**, *45*, 4375.
32. Takanami, T.; Ogawa, A.; Suda, K., *Tetrahedron Lett.*, **2000**, *41*, 3399.
33. Schweizer, E. E.; Berninger, C. J.; Thompson, J. G., *J. Org. Chem.*, **1967**, *33*, 336.
34. Utimoto, K.; Tamura, M.; Sisido, K., *Tetrahedron*, **1973**, *29*, 1169.
35. Nemoto, H.; Shiraki, M.; Fukumoto, K., *J. Org. Chem.*, **1996**, *61*, 1347.
36. Petasis, N. A.; Bzowej, E. I., *Tetrahedron Lett.*, **1993**, *34*, 943.
37. Halazy, S.; Dumont, W.; Krief, A., *Tetrahedron Lett.*, **1981**, *22*, 4737.
38. Nakamura, I.; Yamamoto, Y., *Adv. Synth. Catal.*, **2002**, *344*, 111.

39. Dzhemilev, U. M.; Khusnutsdinov, R. I.; Tolstikov, G. A., *J. Organomet. Chem.*, **1991**, *409*, 15.
40. Binger, P.; Lü, Q.; Wedemann, P., *Angew. Chem., Int. Ed. Engl.*, **1985**, *24*, 316.
41. Corlay, H.; Lewis, R. T.; Motherwell, W. B.; Shipman, M., *Tetrahedron*, **1995**, *51*, 3303.
42. Lewis, R. T.; Motherwell, W. B.; Shipman, M.; Slawin, A. M. Z.; Williams, D. J., *Tetrahedron*, **1995**, *51*, 3289.
43. Lautens, M.; Ren, Y.; Delanghe., P. H. M., *J. Am. Chem. Soc.*, **1994**, *116*, 8821.
44. Lautens, M.; Ren, Y., *J. Am. Chem. Soc.*, **1996**, *118*, 9597.
45. Delgado, A.; Rodriguez, J. R.; Castedo, L.; Mascareñas, J. L., *J. Am. Chem. Soc.*, **2003**, *125*, 9282.
46. Nakamura, I.; Oh, B. H.; Saito, S.; Yamamoto, Y., *Angew. Chem., Int. Ed. Engl.*, **2001**, *40*, 1338.
47. Oh, B. H.; Nakamura, I.; Saito, S.; Yamamoto, Y., *Tetrahedron Lett.*, **2001**, *42*, 6203.
48. Yamago, S.; Ejiri, S.; Nakamura, M.; Nakamura, E., *J. Am. Chem. Soc.*, **1993**, *115*, 5344.
49. Nakamura, E.; Yamago, S., *Acc. Chem. Res.*, **2002**, *35*, 867.
50. Yamago, S.; Nakamura, E., *J. Am. Chem. Soc.*, **1989**, *111*, 7285.
51. Ejiri, S.; Yamago, S.; Nakamura, E., *J. Am. Chem. Soc.*, **1992**, *114*, 8707.
52. Yamago, S.; Nakamura, Y.; Wang, X. Q.; Yanagawa, M.; Tokumitsu, S.; Nakamura, E., *J. Org. Chem.*, **1998**, *63*, 1694.
53. Nakamura, M.; Yoshikai, N.; Toganoh, M.; Wang, X. Q.; Nakamura, E., *Synlett*, **2001**, 1030.
54. Nakamura, M.; Yoshikai, N.; Nakamura, E., *Chem. Lett.*, **2002**, 146.
55. Yamago, S.; Nakamura, E., *J. Org. Chem.*, **1990**, *55*, 5553.
56. Nakamura, M.; Toganoh, M.; Wang, X. Q.; Yamago, S.; Nakamura, E., *Chem. Lett.*, **2000**, 664.
57. Goti, A.; Cordero, F.; Brandi, A., *Top. Curr. Chem.*, **1996**, *178*, 1.
58. Crandall, J. K.; Conover, W. W., *J. Org. Chem.*, **1974**, *39*, 63.
59. Aue, D. H.; Lorens, R. B.; Helwig, G. S., *J. Org. Chem.*, **1979**, *44*, 1202.
60. Aue, D. H.; Lorens, R. B.; Helwig, G. S., *Tetrahedron Lett.*, **1979**, *48*, 4795.
61. Crandall, J. K.; Conover, W. W.; Komin, J. B., *J. Org. Chem.*, **1975**, *40*, 1975.
62. Brandi, A.; Garro, S.; Guarna, A.; Goti, A.; Cordero, F.; De Sarlo, F., *J. Org. Chem.*, **1988**, *53*, 2430.
63. Brandi, A.; Dürüst, Y.; Cordero, F.; De Sarlo, F., *J. Org. Chem.*, **1992**, *57*, 5666.
64. Brandi, A.; Cordero, F. M.; De Sarlo, F.; Gandolfi, R.; Rastelli, A.; Bagatti, M., *Tetrahedron*, **1992**, *48*, 3323.
65. Cordero, F.; Cicchi, S.; Goti, A.; Brandi, A., *Tetrahedron Lett.*, **1994**, *35*, 949.
66. Cicchi, S.; Goti, A.; Brandi, A., *J. Org. Chem.*, **1995**, *60*, 4743.
67. Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, R.; Goti, A.; Picasso, S.; Vogel, P., *J. Org. Chem.*, **1995**, *60*, 6806.
68. Guarna, A.; Brandi, A.; De Sarlo, F.; Goti, A.; Pericciuoli, F., *J. Org. Chem.*, **1988**, *53*, 2426.
69. Smit, W. A.; Kireev, S. L.; Nefedov, O. M.; Tarasov, V. A., *Tetrahedron Lett.*, **1989**, *30*, 4021.

70. Stolle, A.; Becker, H.; Salaün, J.; de Meijere, A., *Tetrahedron Lett.*, **1994**, *35*, 3517.
71. Stolle, A.; Becker, H.; Salaün, J.; de Meijere, A., *Tetrahedron Lett.*, **1994**, *35*, 3521.
72. Destabel, C.; Kilburn, J. D.; Knight, J., *Tetrahedron*, **1994**, *50*, 11267.
73. Destabel, C.; Kilburn, J., *J. Chem. Soc. Chem. Comm.*, **1992**, 596.
74. Santagostino, M.; Kilburn, J. D., *Tetrahedron Lett.*, **1995**, *36*, 1365.
75. Boffey, R. J.; Santagostino, M.; Whittingham, W. G.; Kilburn, J. D., *J. Chem. Soc., Chem. Comm.*, **1998**, 1875.
76. Boffey, R. J.; Whittingham, W. G.; Kilburn, J. D., *Tetrahedron Lett.*, **1999**, *40*, 5625.
77. Boffey, R. J.; Whittingham, W. G.; Kilburn, J. D., *J. Chem. Soc., Perkin Trans. 1*, **2001**, 487.
78. Saint-Dizier, A. C.; Kilburn, J. D., *Tetrahedron Lett.*, **2002**, *43*, 6201.
79. Carlson, R.; Lundstedt, T.; Nordahl, Å.; Prochazka, M., *Acta Chim. Scand.*, **1986**, *40*, 522.
80. Schinzer, D., *Synthesis*, **1988**, 263.
81. Langkopf, E.; Schinzer, D., *Chem. Rev.*, **1995**, *95*, 1375.
82. Hosomi, A.; Sakurai, H., *Tetrahedron Lett.*, **1976**, *17*, 1295.
83. Hosomi, A.; Sakurai, H., *J. Am. Chem. Soc.*, **1977**, *99*, 1673.
84. Mekhalfia, A.; Markó, I. E., *Tetrahedron Lett.*, **1991**, *32*, 4779.
85. Mekhalfia, A.; Markó, I. E.; Adams, H., *Tetrahedron Lett.*, **1991**, *32*, 4783.
86. Markó, I. E.; Bayston, D. J., *Tetrahedron Lett.*, **1993**, *34*, 6595.
87. Markó, I. E.; Bayston, D. J., *Tetrahedron*, **1994**, *50*, 7141.
88. Cantelleda, A.; Kucera, D. J.; Overman, L. E., *J. Org. Chem.*, **1989**, *54*.
89. Blumenkopf, T. A.; Bratz, M.; Casteñeda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S., *J. Am. Chem. Soc*, **1990**, *112*, 4368.
90. Markó, I. E.; Dobbs, A. P.; Scheirmann, V.; Chellé, F.; Bayston, D. J., *Tetrahedron Lett.*, **1997**, *38*, 2899.
91. Dobbs, A. P.; Martinovic, S., *Tetrahedron Lett.*, **2002**, *43*, 7055.
92. Dobbs, A. P., *Personal communication.*
93. Dobbs, A. P.; Guesné, S. J. J.; Hursthouse, M. B.; Coles, S. J., *Synlett*, **2003**, *11*, 1740.
94. Dobbs, A. P.; Guesné, S. J. J.; Martinovic, S.; Coles, S. J.; Hursthouse, M. B., *J. Org. Chem.*, **2003**, *68*, 7880.
95. Panek, J. S.; Jain, N. F., *J. Org. Chem.*, **1993**, *58*, 2345.
96. Larsen, S. D.; Grieco, P. A.; Fobare, W., *J. Am. Chem. Soc.*, **1986**, *108*, 3512.
97. Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A., *Chem. Rev.*, **2004**, *104*, 1431.
98. Speckamp, W. N.; Hiemstra, H., *Tetrahedron*, **1985**, *41*, 4367.
99. Shono, T., *Tetrahedron*, **1984**, *40*, 811.
100. Speckamp, W. N.; Moolenaar, M. J., *Tetrahedron*, **2000**, *56*, 3817.
101. Ukaji, Y.; Tsukamoto, K.; Nasada, Y.; Shimizu, M.; Fujisawa, T., *Chem. Lett.*, **1993**, 221.
102. Meyers, A. I.; Brengel, G. P., *Chem. Commun.*, **1997**, 1.
103. Polniaszek, R. P.; Belmont, S. E.; Alvarez, R., *J. Org. Chem.*, **1990**, 215.

104. Burgess, L. E.; Meyers, A. I., *J. Am. Chem. Soc*, **1991**, *113*, 9858.
105. Monti, H.; Audran, G.; Feraud, M.; Monti, J.-P.; Léandri, G., *Tetrahedron*, **1996**, *52*, 6685.
106. Monti, H.; Rizzotto, D.; Léandri, G., *Tetrahedron*, **1998**, *54*, 6725.
107. Miura, K.; Takasumi, M.; Hondo, T.; Saito, H.; Hosomi, A., *Tetrahedron Lett.*, **1997**, *38*, 4587.
108. Peron, G.; Kitteringham, J.; Kilburn, J. D., *Tetrahedron Lett.*, **1999**, *40*, 3045.
109. Peron, G.; Kitteringham, J.; Kilburn, J. D., *Tetrahedron Lett.*, **2000**, *41*, 1615.
110. Shi, M.; Xu, B., *Org. Lett.*, **2002**, *4*, 2145.
111. Shi, M.; Chen, Y.; Xu, B.; Tang, J., *Tetrahedron Lett.*, **2002**, *43*, 8019.
112. Shi, M.; Xu, B.; Huang, J.-W., *Org. Lett.*, **2004**, *6*, 1175.
113. Shi, M.; Xu, B., *Tetrahedron Lett.*, **2003**, *44*, 3839.
114. Corey, E. J., *J. Am. Chem. Soc.*, **1972**, *94*, 2549.
115. Aspinall, H. C.; Bissett, J. S.; Greeves, N.; Levin, D., *Tetrahedron Lett.*, **2002**, *43*, 319.
116. Aspinall, H. C.; Bissett, J. S.; Greeves, N.; Levin, D., *Tetrahedron Lett.*, **2002**, *43*, 323.
117. Annunziata, R.; Cinquini, M.; Cozzi, F.; Molteni, V.; Schupp, O., *Tetrahedron*, **1996**, *52*, 2573.
118. Bernado, P. D.; Choppin, G. R.; Portanova, R.; Zanonato, P. L., *Inorg. Chim. Acta*, **1993**, *207*, 85.
119. Brengel, G. P.; Meyers, A. I., *J. Org. Chem.*, **1996**, *61*, 3230.
120. Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S., *J. Am. Chem. Soc*, **2001**, *123*, 12095.
121. Nikas, S. P.; Thakur, G. A.; Makriyannis, A., *Synth. Commun.*, **2002**, *32*, 1751.
122. Mancuso, A. J.; Hanug, S.-L.; Swern, D., *J. Org. Chem.*, **1978**, *43*, 2480.
123. Langlois, N.; Choudhury, P. K., *Tetrahedron Lett.*, **1999**, *40*, 2525.
124. Arai, Y.; Matsui, M.; Fujii, A.; Kontani, T.; Ohno, T.; Koizumi, T.; Shiro, M., *J. Chem. Soc., Perkin. Trans. 1*, **1994**, 25.
125. Brocherieux-Lanoy, S.; Dhimane, H.; Poupon, J.-C.; Vanucci, C.; Lhommet, G., *J, Chem. Soc., Perkin. Trans. 1*, **1997**, 2163.
126. Hubert, J. C.; Wunberg, J. P. B. A.; Speckamp, W. N., *Tetrahedron*, **1975**, *31*, 1437.
127. Klaver, W. J.; Moolenaar, M. J.; Hiemstra, H.; Speckamp, W. N., *Tetrahedron*, **1988**, *44*, 3805.
128. Marson, C. M.; Khan, A.; Porter, R. A., *J. Org. Chem.*, **2001**, *66*, 4771.
129. Ho, B.; Castagnoli, N. J., *J. Med. Chem.*, **1980**, *23*, 133.
130. Polniaszek, R. P.; Belmont, S. E., *J. Org. Chem.*, **1990**, *55*, 4688.
131. Kraus, G. A.; Neuenschwander, K., *J, Chem. Soc., Chem. Commun.*, **1982**, 134.
132. Ojima, I.; Zhang, Z., *J. Organomet. Chem.*, **1991**, *417*, 253.
133. Russowsky, D.; Peterson, R. Z.; Godoi, M. N.; Pilli, R. A., *Tetrahedron Lett.*, **2000**, *41*, 9939.
134. Reddy, P. Y.; Kondo, S.; Toru, T.; Ueno, Y., *J. Org. Chem.*, **1997**, *62*, 2652.
135. Shono, T.; Matsumura, Y.; Uchida, K.; Kobayashi, H., *J. Org. Chem.*, **1985**, *50*, 3245.
136. Hiemstra, H.; Fortgens, H. P.; Speckamp, W. N., *J. Org. Chem.*, **1985**, *50*, 4014.

137. Shono, T.; Matsumura, Y.; Tsubata, K., *Org. Synth.*, **1984**, *63*, 206.
138. Rassu, G.; Pinna, L.; Spanu, P.; Ulgheri, F.; Casiraghi, G., *Tetrahedron. Lett*, **1994**, *35*, 4019.
139. Boche, G.; Walborsky, H. M., In *Cyclopropane derived reactive intermediates*, Patai, S.; Rappoport, Z., Eds. Wiley-Interscience: Chichester, 1990; pp 117.
140. Perrin, D. D.; Armarego, W. L. F., *Purification of Laboratory Chemicals*. 3rd ed.; Pergamon Press: 1989.
141. Still, W. C.; Kahn, M.; Mitra, A., *J. Org. Chem.*, **1978**, *43*, 2923.
142. Dado, G. P.; Gellman, S. H., *J. Am. Chem. Soc.*, **1994**, *116*, 1054.
143. Booth, H.; Readshaw, S. A., *Tetrahedron*, **1990**, *46*, 2097.
144. Parker, K. A.; Fokas, D., *J. Org. Chem.*, **1994**, *59*, 3933.
145. Nelson, N. A.; Wollensak, J. C., *J. Am. Chem. Soc*, **1958**, *80*.
146. Manas, A. R.; Smith, R. J., *Tetrahedron*, **1987**, *43*, 1847.
147. Lee, B. H.; Miller, M. J., *J. Org. Chem.*, **1983**, *48*, 24.
148. Blaney, P.; Grigg, R.; Rankovic, Z.; Thornton-Pett, M.; Xu, J., *Tetrahedron*, **2002**, *58*, 1719.
149. Nishitani, T.; Horikawa, H.; Iwasaki, T.; Matsumoto, K.; Inoue, I.; Miyoshi, M., *J. Am. Chem. Soc.*, **1982**, *47*, 1706.
150. Boto, A.; Hernández, R.; Suárez, E., *J. Org. Chem.*, **2000**, *65*, 4930.
151. Brown, D. S.; Charreau, P.; Hansson, T.; Ley, S. V., *Tetrahedron*, **1991**, 1311.
152. Dieter, R. K.; Li, S., *J. Org. Chem.*, **1997**, *62*, 7726.
153. Flynn, D. L.; Zelle, R. E.; Grieco, P. A., *J. Org. Chem.*, **1982**, *48*, 2424.
154. Giovannini, A.; Savoia, D.; Umani-Ronchi, A., *J. Org. Chem.*, **1988**, *54*, 228.
155. Sato, T.; Kugo, Y.; Nakaumi, E.; Ishibashi, H.; Ikeda, M., *J. Chem. Soc., Perkin. Trans.*, **1995**, 1801.
156. Shono, T.; Terauchi, J.; Kitayama, K.; Takeshima, Y.; Matsumura, Y., *Tetrahedron*, **1992**, *48*, 8253.

Appendix.

University of Southampton · Department of Chemistry

EPSRC National Crystallography Service

Table 1. Crystal data and structure refinement.

Identification code	**03sot0154**	
Empirical formula	$C_{17}H_{32}ClNOSi$	
Formula weight	329.98	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 20.667(14) Å	α = 90°
	b = 8.105(4) Å	β = 104.93(5)°
	c = 11.515(7) Å	γ = 90°
Volume	1863.7(19) Å^3	
Z	4	
Density (calculated)	1.176 Mg / m^3	
Absorption coefficient	0.269 mm^{-1}	
F(000)	720	
Crystal	Colourless; block	
Crystal size	0.40 × 0.14 × 0.02 mm^3	
θ range for data collection	3.06 – 24.99°	
Index ranges	$-24 \le h \le 24$, $-9 \le k \le 9$, $-13 \le l \le 13$	
Reflections collected	10846	
Independent reflections	2865 [R_{int} = 0.1602]	
Completeness to θ = 24.99°	87.2 %	
Max. and min. transmission	0.9946 and 0.8999	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2865 / 0 / 199	
Goodness-of-fit on F^2	1.123	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.1250, $wR2$ = 0.1660	
R indices (all data)	$R1$ = 0.2428, $wR2$ = 0.2005	
Extinction coefficient	0.0057(10)	
Largest diff. peak and hole	0.351 and –0.294 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details:

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	4784(4)	3326(9)	11732(9)	42(2)	1
C2	4480(4)	2135(10)	10749(8)	63(3)	1
C3	3995(4)	3107(10)	9841(7)	52(3)	1
C4	4107(6)	4906(12)	10198(9)	89(4)	1
C5	3588(5)	5985(11)	10108(8)	70(3)	1
C6	3080(5)	6141(10)	8914(8)	46(2)	1
C7	3257(4)	7176(10)	7975(8)	50(2)	1
C8	2515(5)	5318(11)	8692(8)	45(3)	1
C9	1211(4)	3728(10)	8026(7)	43(2)	1
C10	639(4)	2888(10)	7123(8)	57(3)	1
C11	943(4)	4612(10)	8961(7)	54(3)	1
C12	1412(4)	7006(10)	6703(7)	41(2)	1
C13	741(4)	6741(11)	5811(8)	57(3)	1
C14	1359(5)	8305(10)	7625(8)	65(3)	1
C15	2027(4)	3755(10)	6216(7)	46(2)	1
C16	2342(4)	2154(10)	6748(8)	60(3)	1
C17	2481(4)	4612(12)	5553(8)	66(3)	1
N1	4558(4)	4801(10)	11377(7)	50(2)	1
O1	5198(3)	3010(7)	12653(5)	58(2)	1
Si1	1788(1)	5018(3)	7373(2)	38(1)	1
Cl1	3489(1)	9213(3)	8510(2)	63(1)	1

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

C1–O1	1.206(9)	C3–C2–H2A	110.6
C1–N1	1.310(10)	C1–C2–H2A	110.6
C1–C2	1.497(11)	C3–C2–H2B	110.6
C2–C3	1.476(10)	C1–C2–H2B	110.6
C2–H2A	0.9900	H2A–C2–H2B	108.8
C2–H2B	0.9900	C2–C3–C4	107.0(7)
C3–C4	1.516(11)	C2–C3–H3A	110.3
C3–H3A	0.9900	C4–C3–H3A	110.3
C3–H3B	0.9900	C2–C3–H3B	110.3
C4–C5	1.367(12)	C4–C3–H3B	110.3
C4–N1	1.438(11)	H3A–C3–H3B	108.6
C4–H4	1.0000	C5–C4–N1	114.5(9)
C5–C6	1.506(11)	C5–C4–C3	122.1(10)
C5–H5A	0.9900	N1–C4–C3	102.4(8)
C5–H5B	0.9900	C5–C4–H4	105.5
C6–C8	1.310(11)	N1–C4–H4	105.5
C6–C7	1.488(11)	C3–C4–H4	105.5
C7–Cl1	1.783(8)	C4–C5–C6	118.2(9)
C7–H7A	0.9900	C4–C5–H5A	107.8
C7–H7B	0.9900	C6–C5–H5A	107.8
C8–Si1	1.857(9)	C4–C5–H5B	107.8
C8–H8	0.90(6)	C6–C5–H5B	107.8
C9–C11	1.512(10)	H5A–C5–H5B	107.1
C9–C10	1.520(10)	C8–C6–C7	121.2(8)
C9–Si1	1.882(8)	C8–C6–C5	120.8(9)
C9–H9	1.0000	C7–C6–C5	117.8(8)
C10–H10A	0.9800	C6–C7–Cl1	111.4(6)
C10–H10B	0.9800	C6–C7–H7A	109.3
C10–H10C	0.9800	Cl1–C7–H7A	109.3
C11–H11A	0.9800	C6–C7–H7B	109.3
C11–H11B	0.9800	Cl1–C7–H7B	109.3
C11–H11C	0.9800	H7A–C7–H7B	108.0
C12–C13	1.514(10)	C6–C8–Si1	136.0(8)
C12–C14	1.519(10)	C6–C8–H8	120(4)
C12–Si1	1.867(8)	Si1–C8–H8	104(4)
C12–H12	1.0000	C11–C9–C10	109.7(7)
C13–H13A	0.9800	C11–C9–Si1	114.0(6)
C13–H13B	0.9800	C10–C9–Si1	115.9(6)
C13–H13C	0.9800	C11–C9–H9	105.4
C14–H14A	0.9800	C10–C9–H9	105.4
C14–H14B	0.9800	Si1–C9–H9	105.4
C14–H14C	0.9800	C9–C10–H10A	109.5
C15–C16	1.509(11)	C9–C10–H10B	109.5
C15–C17	1.521(10)	H10A–C10–H10B	109.5
C15–Si1	1.846(8)	C9–C10–H10C	109.5
C15–H15	1.0000	H10A–C10–H10C	109.5
C16–H16A	0.9800	H10B–C10–H10C	109.5
C16–H16B	0.9800	C9–C11–H11A	109.5
C16–H16C	0.9800	C9–C11–H11B	109.5
C17–H17A	0.9800	H11A–C11–H11B	109.5
C17–H17B	0.9800	C9–C11–H11C	109.5
C17–H17C	0.9800	H11A–C11–H11C	109.5
N1–H1	0.78(10)	H11B–C11–H11C	109.5
		C13–C12–C14	110.7(7)
O1–C1–N1	125.7(8)	C13–C12–Si1	111.7(6)
O1–C1–C2	126.3(7)	C14–C12–Si1	114.0(6)
N1–C1–C2	107.8(8)	C13–C12–H12	106.7
C3–C2–C1	105.5(7)	C14–C12–H12	106.7

Si1–C12–H12	106.7	C15–C16–H16B	109.5
C12–C13–H13A	109.5	H16A–C16–H16B	109.5
C12–C13–H13B	109.5	C15–C16–H16C	109.5
H13A–C13–H13B	109.5	H16A–C16–H16C	109.5
C12–C13–H13C	109.5	H16B–C16–H16C	109.5
H13A–C13–H13C	109.5	C15–C17–H17A	109.5
H13B–C13–H13C	109.5	C15–C17–H17B	109.5
C12–C14–H14A	109.5	H17A–C17–H17B	109.5
C12–C14–H14B	109.5	C15–C17–H17C	109.5
H14A–C14–H14B	109.5	H17A–C17–H17C	109.5
C12–C14–H14C	109.5	H17B–C17–H17C	109.5
H14A–C14–H14C	109.5	C1–N1–C4	116.2(8)
H14B–C14–H14C	109.5	C1–N1–H1	125(8)
C16–C15–C17	109.8(7)	C4–N1–H1	119(8)
C16–C15–Si1	110.6(6)	C15–Si1–C8	110.6(4)
C17–C15–Si1	115.0(6)	C15–Si1–C12	109.9(4)
C16–C15–H15	107.0	C8–Si1–C12	112.8(4)
C17–C15–H15	107.0	C15–Si1–C9	107.2(4)
Si1–C15–H15	107.0	C8–Si1–C9	102.1(4)
C15–C16–H16A	109.5	C12–Si1–C9	113.9(4)

Symmetry transformations used to generate equivalent atoms:

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

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	26(5)	21(5)	73(7)	7(5)	2(5)	9(4)
C2	57(7)	30(5)	79(8)	−14(5)	−21(5)	−3(5)
C3	58(7)	55(6)	36(6)	−12(5)	−3(5)	7(5)
C4	107(9)	41(6)	81(8)	−34(6)	−43(7)	33(6)
C5	71(8)	44(6)	70(8)	0(5)	−26(6)	2(6)
C6	49(6)	31(5)	52(7)	−5(5)	2(5)	5(5)
C7	46(6)	48(6)	52(7)	−3(5)	7(5)	−3(5)
C8	66(7)	29(6)	35(6)	2(5)	6(5)	0(5)
C9	47(6)	40(5)	40(6)	−1(5)	9(5)	5(4)
C10	49(6)	54(6)	69(7)	0(5)	18(5)	−10(5)
C11	69(7)	53(7)	43(6)	3(5)	22(5)	6(5)
C12	46(6)	43(6)	38(6)	14(5)	15(4)	−1(4)
C13	36(6)	64(7)	60(7)	20(5)	−4(5)	−2(5)
C14	73(8)	38(6)	79(8)	10(6)	14(6)	10(5)
C15	42(6)	48(6)	44(6)	−9(5)	4(4)	4(5)
C16	69(7)	52(6)	65(7)	−21(6)	27(5)	6(5)
C17	59(7)	94(8)	49(7)	−10(6)	24(5)	−14(6)
N1	53(5)	32(5)	46(5)	−11(4)	−19(4)	8(4)
O1	58(5)	39(4)	59(5)	11(3)	−19(4)	5(3)
Si1	40(1)	40(1)	32(1)	1(1)	7(1)	4(1)
Cl1	80(2)	43(1)	66(2)	−4(1)	21(1)	−10(1)

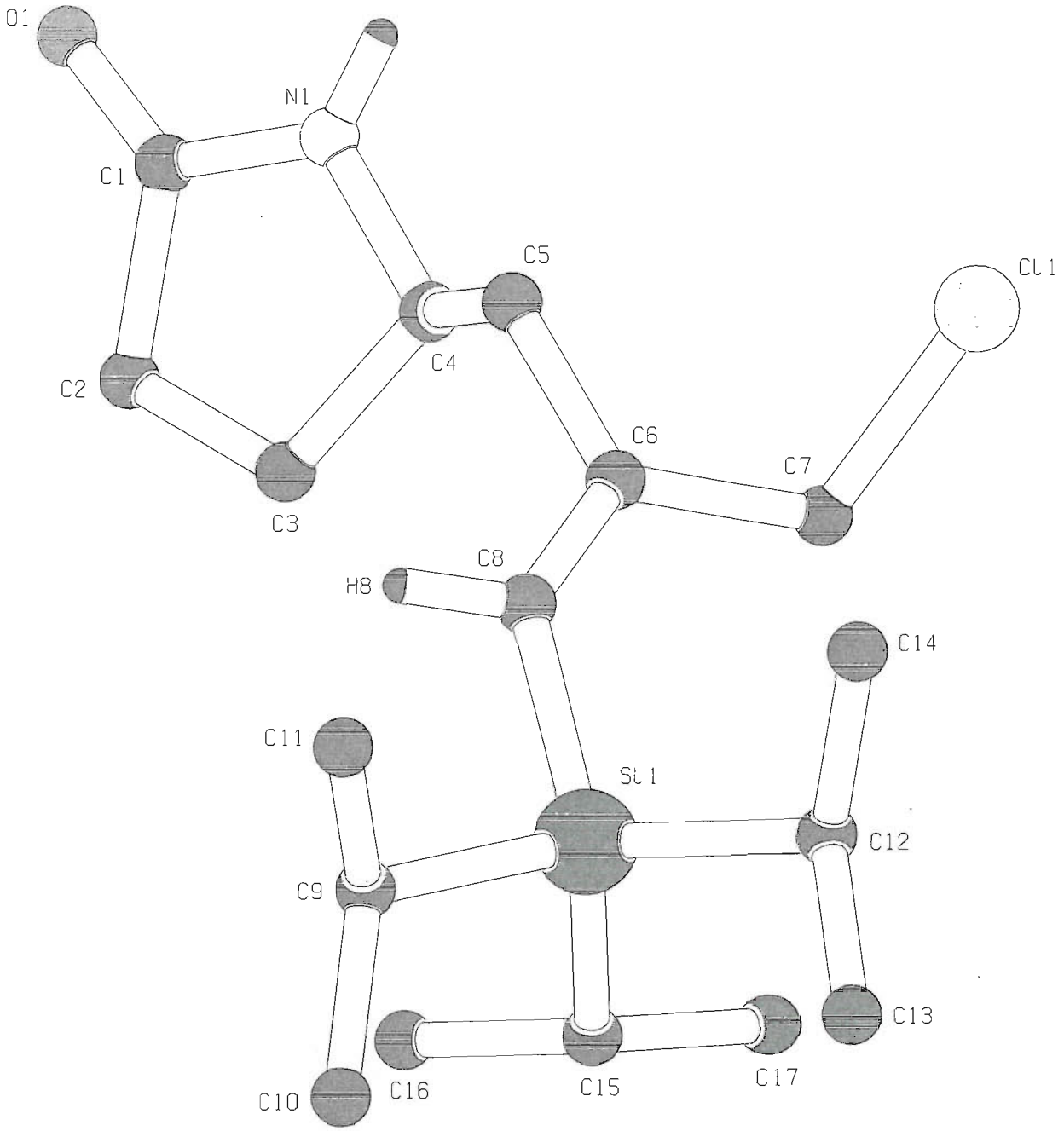

O1
N1
C1
C5
Cl1
C4
C2
C6
C7
C3
C8
H8
C14
C11
Si1
C12
C9
C13
C16
C15
C17
C10

Table 1. Crystal data and structure refinement.

Identification code	**04sot0749**
Empirical formula	$C_{18}H_{33}NOSi$
Formula weight	307.54
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 15.0344(3) Å
	b = 8.0698(2) Å β = 93.8650(10)°
	c = 15.1474(3) Å
Volume	1833.57(7) Å^3
Z	4
Density (calculated)	1.114 Mg / m^3
Absorption coefficient	0.129 mm^{-1}
F(000)	680
Crystal	Colourless Slab
Crystal size	0.60 × 0.25 × 0.08 mm^3
θ range for data collection	2.95 – 25.03°
Index ranges	$-17 \le h \le 17$, $-9 \le k \le 9$, $-18 \le l \le 18$
Reflections collected	29289
Independent reflections	3232 [R_{int} = 0.0462]
Completeness to θ = 25.03°	99.7 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9898 and 0.9268
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3232 / 0 / 196
Goodness-of-fit on F^2	1.202
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0498, $wR2$ = 0.1239
R indices (all data)	$R1$ = 0.0598, $wR2$ = 0.1280
Largest diff. peak and hole	0.482 and –0.277 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement:** *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. 276: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction:** Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution:** *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A46 467–473). **Structure refinement:** *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
Si1	2698(1)	1753(1)	1810(1)	16(1)	1
C2	3850(2)	1247(3)	1447(2)	21(1)	1
C3	4101(2)	−565(3)	1650(2)	24(1)	1
C4	3941(2)	1601(4)	455(2)	26(1)	1
C5	2443(2)	4040(3)	1666(2)	22(1)	1
C6	1516(2)	4466(4)	1982(2)	31(1)	1
C7	3145(2)	5152(4)	2145(2)	32(1)	1
C8	1845(2)	481(3)	1109(2)	19(1)	1
C9	1506(2)	1395(3)	257(2)	24(1)	1
C10	1059(2)	−144(4)	1607(2)	30(1)	1
C11	2617(2)	1300(3)	3014(2)	19(1)	1
C12	3224(2)	1469(3)	3695(2)	18(1)	1
C13	4195(2)	1954(3)	3653(2)	20(1)	1
N14	4478(1)	2392(3)	4567(1)	19(1)	1
C15	3704(2)	2517(3)	5120(2)	20(1)	1
C16	3048(2)	1308(3)	4666(2)	21(1)	1
C17	3992(2)	2216(3)	6083(2)	22(1)	1
C18	4791(2)	3305(3)	6358(2)	24(1)	1
C19	5576(2)	2886(3)	5808(2)	22(1)	1
C20	5345(2)	2544(3)	4833(2)	19(1)	1
O21	5934(1)	2391(2)	4311(1)	25(1)	1

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

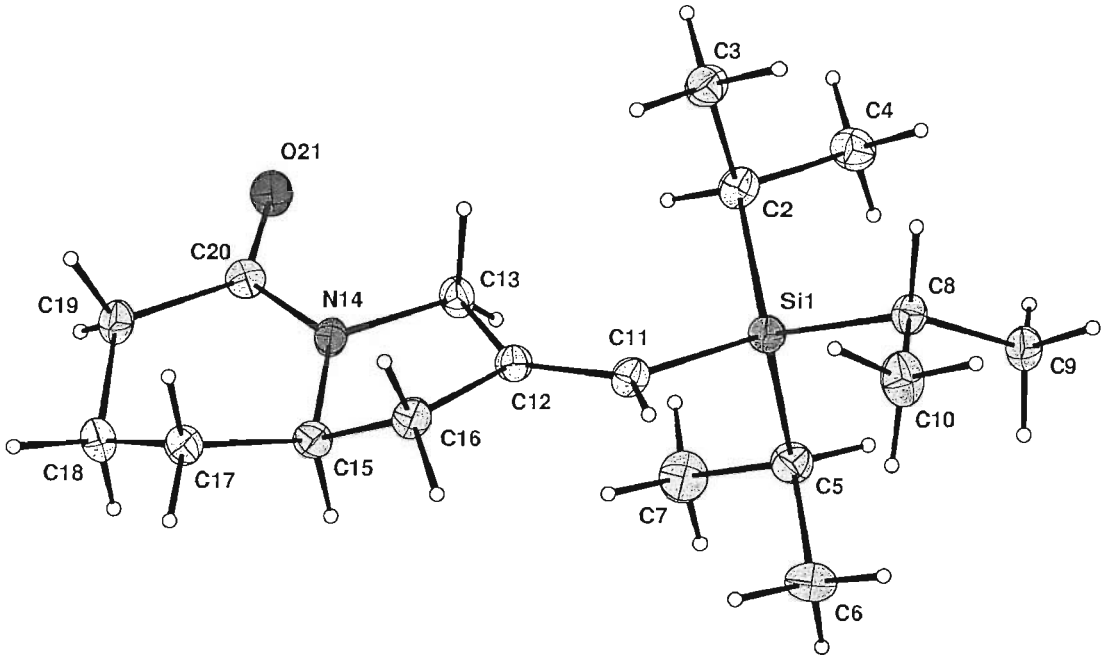
Si1–C11	1.873(3)	C12–C13	1.517(3)
Si1–C5	1.895(3)	C12–C16	1.518(3)
Si1–C2	1.896(3)	C13–N14	1.464(3)
Si1–C8	1.908(3)	N14–C20	1.343(3)
C2–C3	1.536(4)	N14–C15	1.483(3)
C2–C4	1.545(4)	C15–C17	1.513(3)
C5–C7	1.531(4)	C15–C16	1.519(4)
C5–C6	1.541(4)	C17–C18	1.523(4)
C8–C10	1.529(4)	C18–C19	1.527(4)
C8–C9	1.543(3)	C19–C20	1.519(3)
C11–C12	1.336(3)	C20–O21	1.233(3)
C11–Si1–C5	106.01(12)	C11–C12–C16	125.7(2)
C11–Si1–C2	111.17(11)	C13–C12–C16	107.1(2)
C5–Si1–C2	111.01(12)	N14–C13–C12	103.99(19)
C11–Si1–C8	110.58(11)	C20–N14–C13	121.3(2)
C5–Si1–C8	109.65(11)	C20–N14–C15	127.3(2)
C2–Si1–C8	108.42(12)	C13–N14–C15	111.25(19)
C3–C2–C4	109.5(2)	N14–C15–C17	110.4(2)
C3–C2–Si1	111.33(18)	N14–C15–C16	102.2(2)
C4–C2–Si1	112.61(18)	C17–C15–C16	118.0(2)
C7–C5–C6	109.4(2)	C12–C16–C15	103.5(2)
C7–C5–Si1	112.87(18)	C15–C17–C18	109.9(2)
C6–C5–Si1	111.24(19)	C17–C18–C19	110.3(2)
C10–C8–C9	110.3(2)	C20–C19–C18	115.8(2)
C10–C8–Si1	114.61(18)	O21–C20–N14	121.5(2)
C9–C8–Si1	112.32(18)	O21–C20–C19	121.0(2)
C12–C11–Si1	130.2(2)	N14–C20–C19	117.5(2)
C11–C12–C13	127.1(2)		

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

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si1	16(1)	18(1)	15(1)	0(1)	0(1)	−1(1)
C2	18(1)	22(1)	22(1)	2(1)	1(1)	−2(1)
C3	21(1)	24(2)	26(1)	0(1)	0(1)	1(1)
C4	26(1)	28(2)	24(1)	0(1)	6(1)	1(1)
C5	26(1)	20(1)	20(1)	1(1)	0(1)	1(1)
C6	33(2)	28(2)	33(2)	−6(1)	3(1)	8(1)
C7	39(2)	19(2)	36(2)	0(1)	−5(1)	−3(1)
C8	19(1)	20(1)	19(1)	0(1)	−1(1)	−2(1)
C9	25(1)	26(2)	21(1)	−2(1)	−4(1)	1(1)
C10	25(1)	38(2)	28(2)	−1(1)	1(1)	−11(1)
C11	15(1)	22(1)	20(1)	2(1)	2(1)	−2(1)
C12	19(1)	19(1)	17(1)	1(1)	2(1)	1(1)
C13	18(1)	27(1)	15(1)	−1(1)	2(1)	−1(1)
N14	17(1)	24(1)	15(1)	0(1)	−1(1)	1(1)
C15	19(1)	24(1)	17(1)	1(1)	4(1)	2(1)
C16	16(1)	29(2)	18(1)	3(1)	4(1)	0(1)
C17	22(1)	28(2)	16(1)	1(1)	3(1)	3(1)
C18	27(1)	27(2)	17(1)	−2(1)	−1(1)	1(1)
C19	19(1)	26(1)	20(1)	−1(1)	−3(1)	−2(1)
C20	21(1)	14(1)	20(1)	2(1)	2(1)	−2(1)
O21	17(1)	38(1)	22(1)	−1(1)	4(1)	−2(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.*
H2	4288	1968	1793	25	1
H3A	3699	−1300	1296	36	1
H3B	4048	−787	2280	36	1
H3C	4717	−764	1501	36	1
H4A	4560	1422	313	39	1
H4B	3771	2751	323	39	1
H4C	3549	852	98	39	1
H5	2434	4298	1020	26	1
H6A	1495	4165	2607	47	1
H6B	1058	3846	1628	47	1
H6C	1407	5657	1910	47	1
H7A	2985	6317	2043	48	1
H7B	3729	4934	1916	48	1
H7C	3172	4918	2781	48	1
H8	2166	−527	915	23	1
H9A	1130	648	−116	36	1
H9B	2016	1753	−66	36	1
H9C	1157	2366	413	36	1
H10A	737	803	1835	45	1
H10B	1281	−849	2100	45	1
H10C	656	−786	1203	45	1
H11	2056	885	3166	23	1
H13A	4551	1016	3445	24	1
H13B	4258	2910	3252	24	1
H15	3450	3660	5060	24	1
H16A	3161	163	4880	25	1
H16B	2425	1616	4769	25	1
H17A	4154	1035	6172	27	1
H17B	3494	2472	6456	27	1
H18A	4965	3131	6993	28	1
H18B	4627	4485	6272	28	1
H19A	6004	3819	5856	26	1
H19B	5882	1899	6071	26	1



Thermal ellipsoids drawn at the 50% probability level.

Never, never, never give up.
Sir Winston Churchill (1874 – 1965)