UNIVERSITY OF SOUTHAMPTON

FACULTY OF SCIENCE

SCHOOL OF CHEMISTRY

Lewis acid mediated reactions of silyl-substituted methylenecyclopropane and *N*-acyliminium ions

Luke Eugene McDonald

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ABSTRACT

FACULTY OF SCIENCE
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Master of Philosophy

LEWIS ACID MEDIATED REACTIONS OF SILYL-SUBSTITUTED METHYLENECYCLOPROPANES AND *N*-ACYLIMINIUM IONS

Luke Eugene McDonald

This thesis is concerned with Lewis acid mediated inter- and intramolecular reactions of silyl-substituted methylenecyclopropane with *N*-acyliminium ions, towards the formation of novel heterocyclic compounds.

Chapter 1 contains background information on synthetic organic chemistry relating to methylenecyclopropane, Lewis acids, *N*-acyliminium ions and related inter- and intramolecular reactions.

Chapter 2 describes the Lewis acid mediated intermolecular additions of silyl-substituted methylenecyclopropane to various substituted pyrrolidinone based *N*-acyliminium ions. The introduction, and subsequent removal, of an *N*-chiral group into the pyrrolidinone moiety is detailed. This *N*-chiral group has the effect of influencing the facial selectivity of the attack of the methylenecyclopropane and hence, the diastereoselectivity of the reaction.

Chapter 3 presents the attempts made to influence the reactivity of the silyl-substituted methylenecyclopropane towards electrophiles by constraining the silicon into a four or five membered ring. The synthesis of a novel silyl-substituted bismethylenecyclopropane compound is described.

Chapter 4 details the synthesis and intramolecular cyclisation studies of silyl-substituted pyrrolidinone precursors to generate novel heterocyclic compounds.

For Dario

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 2005 and October 2009. 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 allowing me the opportunity to work in his group. I would also like to thank Bharti Patel for her support and encouragement particularly during my time at AstraZeneca and Dr. Martin Grossel for his advice and assistance.

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Special gratitude goes to Dr. Sally Dixon for her continuous support, advice, supervision and making the latter part of my research enjoyable.

Also thanks to the residents of St Margaret's care home, who daily provided me with the inspiration and motivation to 'keep calm and carry on'.

Finally, I thank my parents, friends and family for their love and support, without which none of this would have been possible.

Abbreviations

AIBN	2, 2-azobisisobutyronitrile
Ac	acetyl
aq.	aqueous
Ar	aromatic
Bn	benzyl
Boc	tertbutyloxycarbonyl
Bu	butyl
°C	degrees Celsius
CAN	ceric ammonium nitrate
cat.	catalytic
CI	chemical ionisation
Cy	cyclohexyl
Δ	relux
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DMAP	4-(*N*, *N*-dimethylamino)pyridine
DMF	dimethylformamide
DMPS	dimethylphenylsilyl
DMSO	dimethyl sulphoxide
EA	ethyl acetate
EI	electron impact ionisation
equiv.	equivalent
ES	electrospray ionisation
Et	ethyl
ether	diethyl ether
GC	gas chromatography
h	hour (s)
HRMS	high resolution mass spectrometry
Hz	hertz
i	iso
IR	infrared spectroscopy
J	coupling constant
LA	Lewis acid

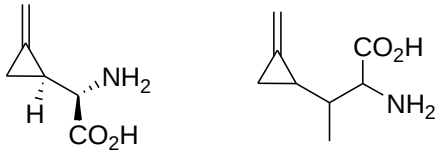
LRMS	low resolution mass spectrometry
LP	light petroleum (40-60)
m	multiplet
m-	meta
MCP	methylenecyclopropane
Me	methyl
MeOH	methanol
min	minute (s)
NMO	*N*-methyl morpholine *N*-oxide
NMR	nuclear magnetic resonance
o-	ortho
p-	para
Ph	phenyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
pr	propyl
q	quartet
quint.	quintuplet
R_f	retention factor
RT	room temperature
s	singlet
sat.	saturated
t	triplet
t	tertiary
TBDMS	tertbutyldimethylsilyl
TBDPS	tertbutyldiphenylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TIPSMCP	triisopropylsilylmethylenecyclopropane
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl, toulenesulphonic
Å	Ångstrom

Chapter 1

1.1 Methylenecyclopropane

1.1.1 General properties of methylenecyclopropane

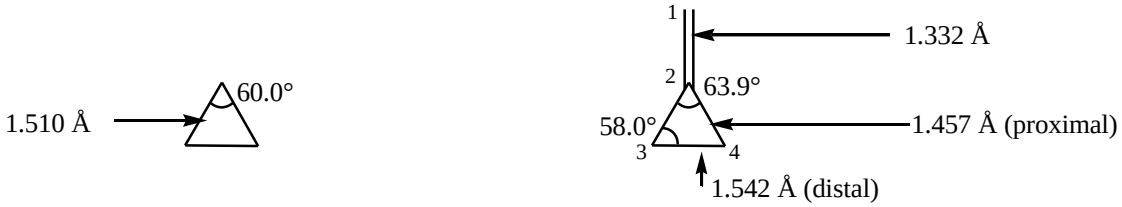
Methylenecyclopropane has been found in naturally occurring amino acids: methylenecyclopropaneglycine **1**[1] and β-(methylenecyclopropyl)-β-methylalanine **2**[2] (Figure 1). Compound **1** is isolated from *billia hippocastanum* and **2** from *aesculus calfornica*.



1 **2**

Figure 1

Methylenecyclopropane is a highly strained, yet stable, molecule. Strain is imposed by the exocyclic double bond, and its affect can be observed by the comparison of the bond angles and lengths in methylenecyclopropane **4** and cyclopropane **3**[3] (Figure 2).



3 **4**

Figure 2

In methylenecyclopropane **4** the proximal bond (C2-C3) is shorter and bond angle C2-C3-C4 is smaller as a result of the inherent ring strain. An indication of the reactivity of methylenecyclopropane **4** can be ascertained by the strain energy relieved upon hydrogenation of the double bond. However, such is the extent of its stability that methylenecyclopropane can be stored for many years without decomposition.[4] Introduction of a trialkylsilyl group at the β-position (C4) of the methylenecyclopropane ring results in stabilisation of a positive charge at the α-position, derived from the ring opened product, by hyperconjugation with the C-Si bond (Figure 3).

This hyperconjugation results from the electronegativity difference between C (2.55) and Si (1.90)[5] and increases the nucleophilicity of the exocyclic double bond towards electrophiles. Silyl-substituted methylenecyclopropanes are in effect highly strained allyl silanes, which can serve as synthetic equivalents for the dipolar reagent **6** (Figure 3).

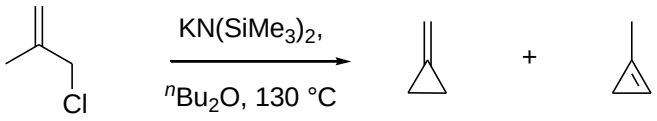
5 **6**

Figure 3

The use of silyl-substituted methylenecyclopropanes is attractive because they are easy to prepare[6] and can be incorporated into complex substrates for intramolecular reactions with relative ease.

1.1.2 Synthesis of unsubstituted methylenecyclopropane

Unsubstituted methylenecyclopropane is commercially available (Fluka), however the first reported synthesis of methylenecyclopropane was in 1953,[7] other syntheses of substituted and unsubstituted methylenecyclopropane have been reported: Brandi and Goti have written a review on this subject.[8] Binger *et al*,[9] improved the original procedure to avoid purification problems and synthesised methylenecyclopropane **4** efficiently (Scheme 1).

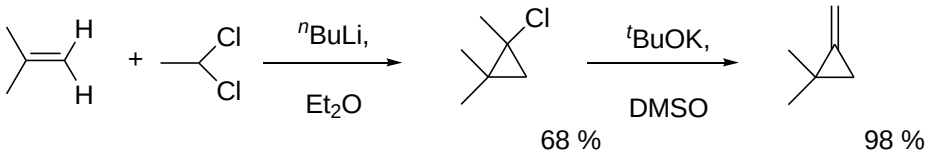


7 **4** **8**

Scheme 1

1.1.3 Synthesis of substituted methylenecyclopropane

The synthesis of substituted methylenecyclopropane has been reported by Binger[10] (Scheme 2).

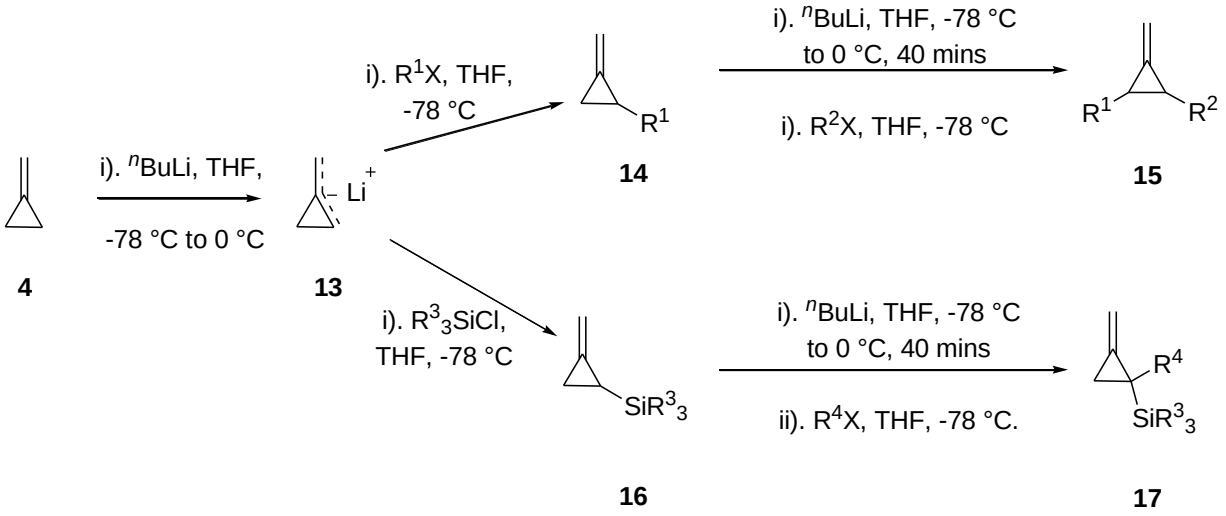


9 **10** **11** **12**

Scheme 2

Addition of dichloroethane **10** to substituted alkene **9** in the presence of a base gives substituted chlorocyclopropane **11** and subsequent elimination of hydrochloric acid gives **12**.

Another method of synthesising substituted methylenecyclopropane utilises the addition of the delocalized anion of methylenecyclopropane **13** to electrophiles (Scheme 3).



4 **13** **14** **15** **16** **17**

Scheme 3

Treatment of methylenecyclopropane **4** with *n*-butyllithium solution generates lithiated methylenecyclopropane **13** which can be quenched with an electrophile; alkylation will always occur first on the ring. The regioselectivity of the second alkylation depends upon the initial substituent. If the first substituent is an alkyl group then the second substitution will occur to give the β-alkylated product **15**.[11-13] However, if the first substituent is an anion stabilising group, such as a trialkylsilyl group, then second substitution will occur at the α-position **17**.[14-18]

This latter methodology provides a wide range of electrophiles that lithiated methylenecyclopropane can be coupled with, for example silyl-substituted methylenecyclopropane with aldehydes[18] or α,β-unsaturated ketones.[19]

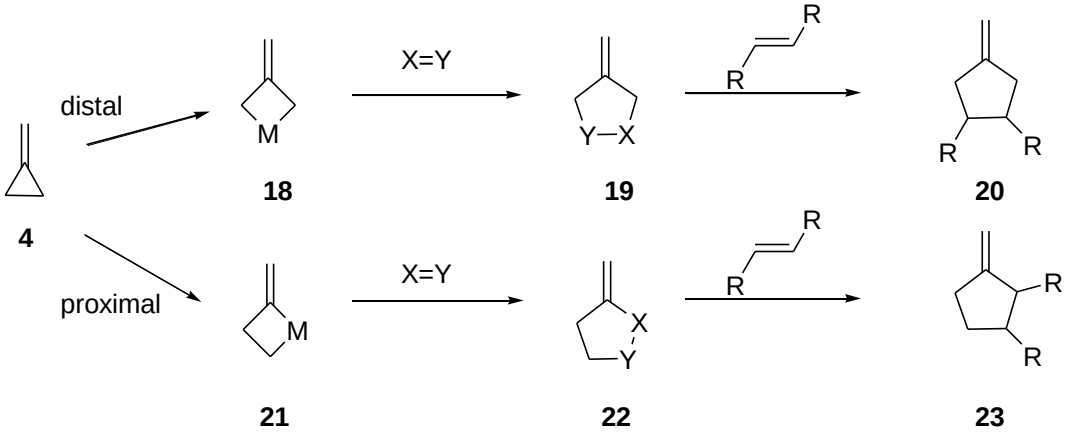
1.2 Methylenecyclopropane in synthesis

Methylenecyclopropane has been used in a variety of synthetic applications, including [3+2] cycloadditions,[20] 1,3 dipolar cycloadditions,[21] Diels-Alder reactions,[6,22] Pauson-Khand reactions[23] and radical based cyclisations.[15,24-27]

1.2.1 Transition metal catalysed [3+2] cycloadditions

[3+2] Cycloaddition reactions between methylenecyclopropane **4** and unsaturated compounds, alkenes, aldehydes and imines to give five membered heterocycles have been reported.[28-31] The role of methylenecyclopropane is to act as the three carbon component.

Metal-catalysed cycloadditions between methylenecyclopropane and a double bond can result in two regioisomeric products **20** and **23** (Scheme 4).



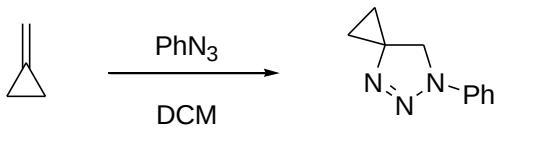
Scheme 4

The cleavage of the cyclopropyl ring and hence the regiochemistry of the product is dependant upon several factors, namely the nature of the metal, the ligands, the substituents on methylenecyclopropane and the unsaturated compound. The most commonly used transition metals are the d^{10} metal species, Pd^0 or Ni^0, an example of the former being palladium catalysed [3 + 2] cycloadditions reported by Motherwell *et al*.[32,33]

1.2.2 1, 3-Dipolar cycloadditions of methylenecyclopropanes

1.2.2.1 Azides

The uses of methylenecyclopropane as the two carbon component in a 1, 3 dipolar cycloaddition are numerous.[21,34] The first reported use in 1974[35] of methylenecyclopropane in this capacity was with an azide. Triazolene **24** is formed in good yield with high regioselectivity, through the coupling of phenyl azide and methylenecyclopropane **4** (Scheme 5).



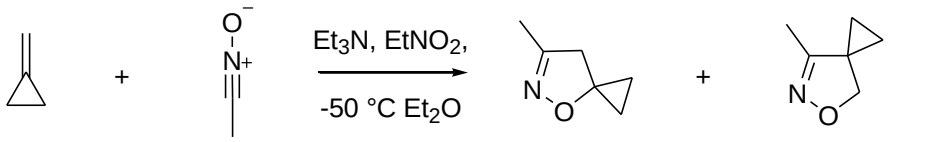
4 **24**

Scheme 5

The cyclopropyl ring aids in directing the addition of the phenyl azide to the methylene moiety.

1.2.2.2 Nitrile oxides

Brandi *et al*[36,37] has shown that the cycloaddition of methylenecyclopropane **4** to a range of nitrile oxides, such as **25** yields the 4-spirocyclopropanes **26** and **27** (Scheme 6). This type of reaction is of synthetic interest because spiro-fused heterocycles can be generated and be utilised in the targeting of natural products.

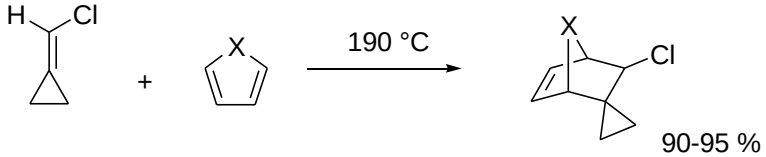


4 **25** **26** **27**

Scheme 6

1.2.3 Diels-Alder reactions

Diels-Alder reactions of halomethylenecyclopropanes with furans have been reported, namely by Bottini[38] who has coupled chloromethylenecyclopropane **28** with furans, cyclopentadienes and 1, 3 dipolarhexadiene to generate **33**, **32** and **34** respectively (Scheme 7).



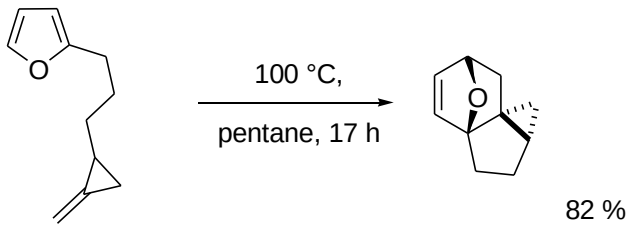
28

29 X= O
30 X= CH_2
31 X= CH_2CH_2

32 X = O
33 X = CH_2
34 X = CH_2CH_2

Scheme 7

De Meijere *et al*[39,40] have demonstrated an intramolecular Diels-Alder reaction of methylenecyclopropane furans of the type **35**, resulting in complex fused ring structures, such as **36**, in good yields (Scheme 8).

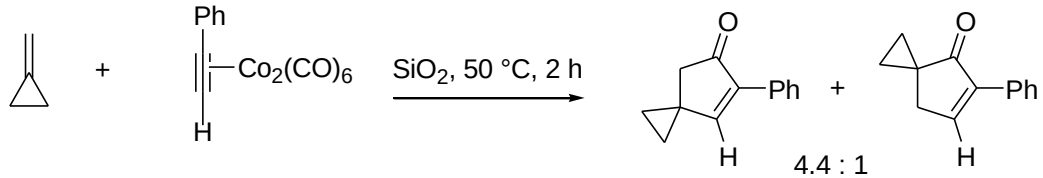


35 **36**

Scheme 8

1.2.4 Pauson-Khand reactions with methylenecyclopropanes

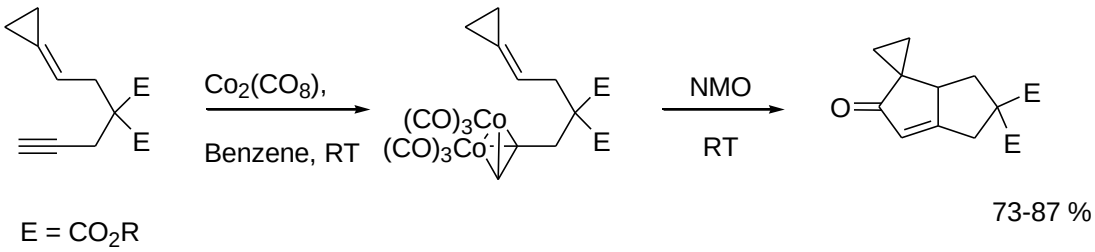
The inherent ring strain in methylenecyclopropane makes Pauson-Khand reactions with dicobalthexacarbonyl alkyne complexes possible.[23,41] Smit *et al*[23] have shown the coupling of methylenecyclopropane **4** with various alkynes utilising solid supports (such as SiO_2), isolating **38** and **39** in good yields (Scheme 9).



4 **37** **38** **39**

Scheme 9

De Meijere *et al*[42,43] have shown intramolecular Pauson-Khand reactions can be utilised to generate bicylic products of the type **42**, highlighting NMO as a suitable reagent for the removal of the cobalt moiety (Scheme 10).

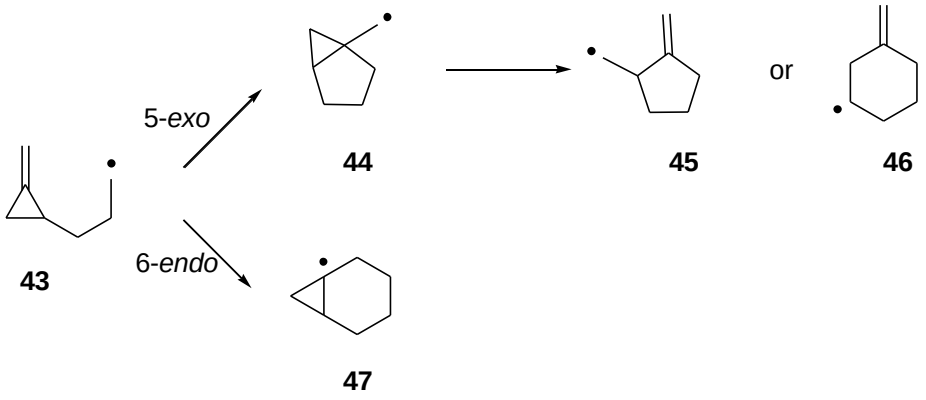


40 **41** **42**

Scheme 10

1.2.5 Radical cyclisations of methylenecyclopropane derivatives

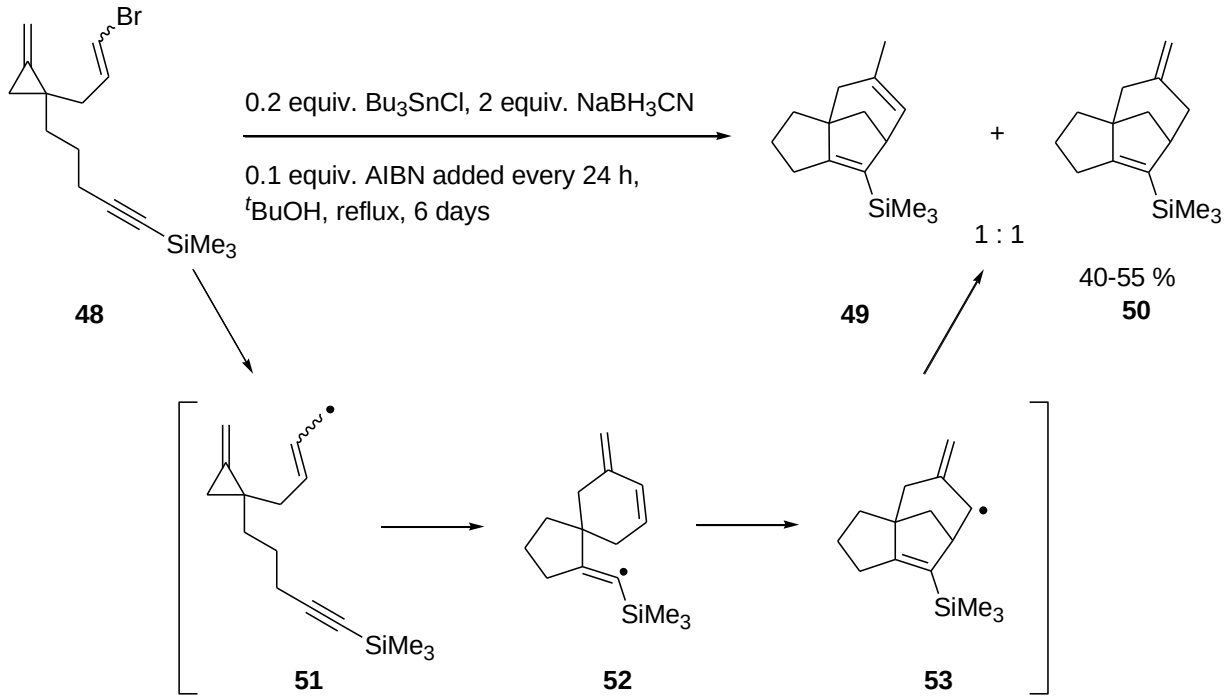
Radical cyclisations of methylenecyclopropane derivatives have been extensively studied.[24-27] Destabel *et al*[15,16,44] carried out the first intramolecular cyclisations of methylenecyclopropane derivatives to provide several rules of radical cyclisation.



43 **44** **45** **46** **47**

Scheme 11

Methylenecyclopropyl radical **43** (Scheme 11) can cyclise via a 6-*endo* route to give a cyclohexyl radical **47**, or via a 5-*exo* route to give a cyclopropylmethyl radical **44**. This latter product can then open in an *exo* fashion to give methylenecyclopentyl radical **45** or in an *endo* fashion to give methylenecyclohexyl radical **46**. Destabel found that cyclisation occurs initially via the 5-*exo* pathway to give the less stable cyclopropyl radical **44**, which then opens via the *endo* pathway to give **46**.[15] This methodology has been extended to cascade radical cyclisations, using tributyltinhydride and AIBN.[17]



Scheme 12

Treatment of **48** with sodium cyanoborohydride and catalytic tributyltin hydride results in a 1 : 1 mixture of geometric isomers **49** : **50**, from the radical species **53** being reduced in a non-selective manner (Scheme 12).

1.3 *N*-Acyliminium ions

Comprehensive reviews of inter and intramolecular cyclisations using *N*-acyliminium ions have been reported.[45-48]

1.3.1 Reactivity of *N*-acyliminium ions

N-Acyliminium ions have highly versatile reaction characteristics and consequently have a wide range of synthetic applications.[45,46,49] They are often compared to the Mannich reagent **54** (Figure 4), however qualitatively it is known[50] that in intermolecular arylation reactions Mannich reagents react extremely poorly with nucleophiles when compared to the more electrophilic *N*-acyliminium ion **55**.

54 **55**

Figure 4

1.3.2 Synthesis of *N*-acyliminium ions

Zaugg and Martin[51] have carried out a detailed account of the formation of *N*-acyliminium ions and the synthesis of their precursors. There are five major synthetic pathways to *N*-acyliminium ions (Figure 5).

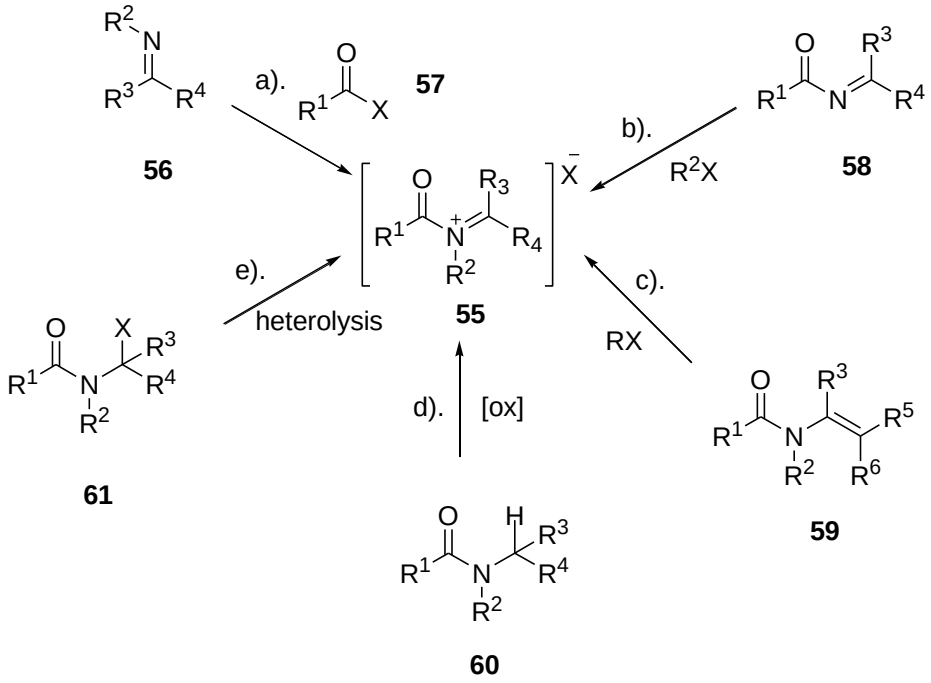


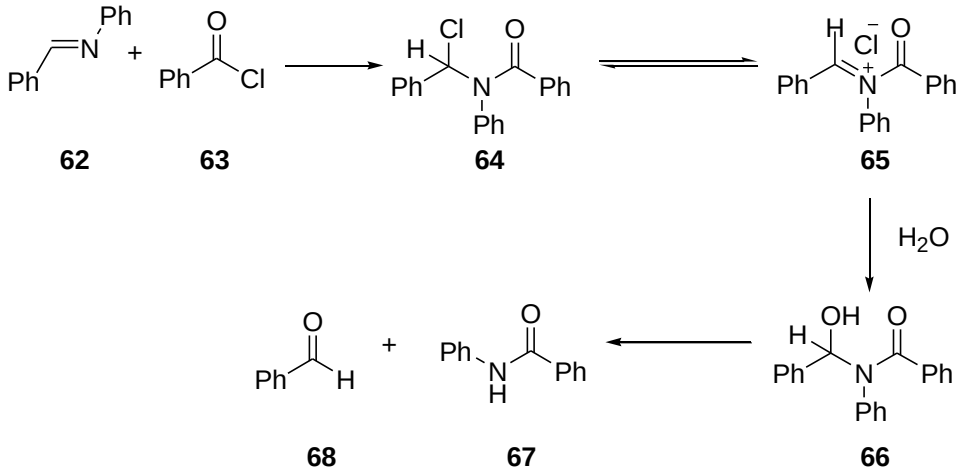
Figure 5

These are: a) the *N*-acylation of imines (see **1.3.2.1**), b) *N*-protonation of *N*-acylimines (when R^2 = H),[52-55] c) electrophilic addition to enamides,[56,57] d) oxidation of amides[57-60] and e) the heterolysis of amides (see **1.3.3**). Of particular relevance is the *N*-acylation of imines and enamide formation.

1.3.2.1 *N*-Acylation of imines

N-Acylation of imines has applications that include enamide formation,[6] β-lactam formation[61] and trapping reactions with carbon and heteroatom nucleophiles.

Imines can be synthesised in high yield by condensation of aldehydes and ketones with primary amines.[62] The subsequent acylation (Scheme 13) with reactive carboxylic acid derivatives like acid chloride or anhydride was first reported in 1914.[63]

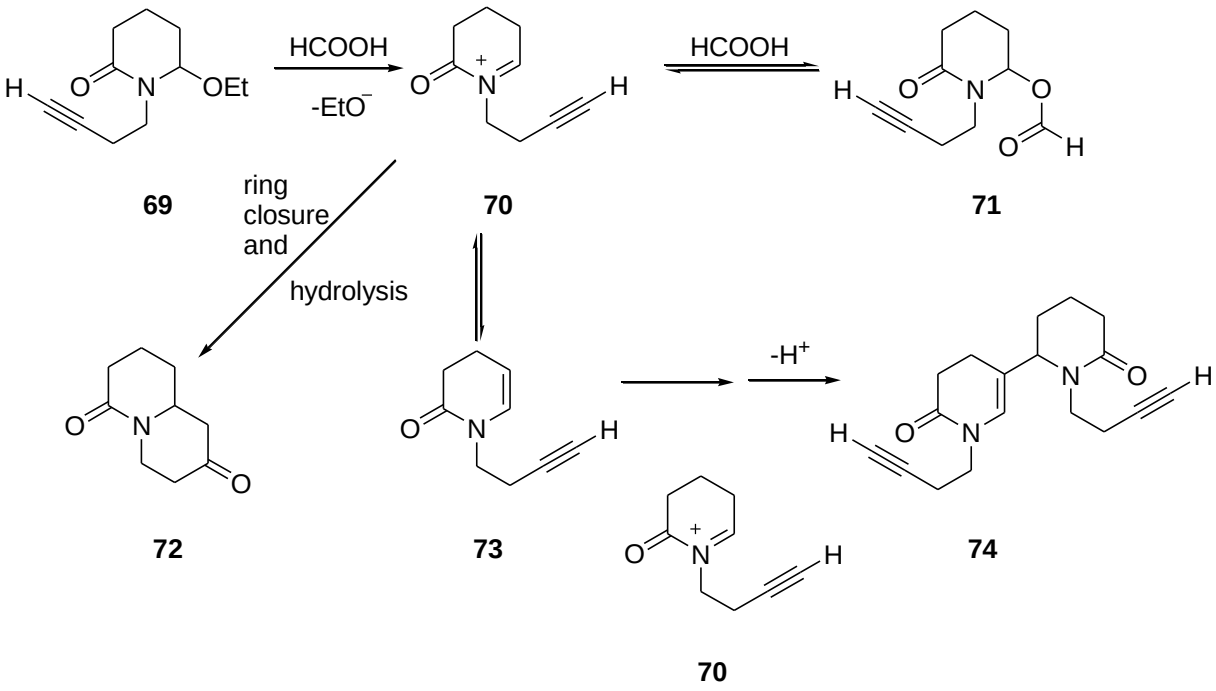


Scheme 13

Acylation of **62** was achieved using the acid chloride **63** and loss of chloride anion from **64** results in formation of *N*-acyliminium ion **65**, which is readily hydrolysed in water to give benzaldehyde **68** and benzanilide **67**. The lability of the carbon-chlorine bond illustrates the propensity of the *N*-acyliminium ion formation.

1.3.2.2 Enamide formation

An important side reaction in *N*-acyliminium ion chemistry is the formation of an enamide via the loss of a proton, a process which may be reversible in acidic media. Enamides can react further, as a nucleophile, with the *N*-acyliminium ion to generate a dimeric species[64] (Scheme 14). This generally occurs if the *N*-acyliminium ion is not trapped fast enough by a nucleophile. It may also occur if: the nucleophile is not very reactive, there is too much steric hindrance or in case of an intramolecular cyclisation, if stereoelectronic factors are unfavourable (anti-Baldwin).

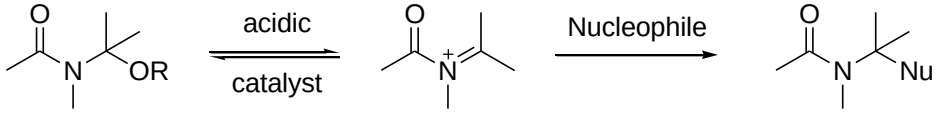


Scheme 14

Treatment of **69** with formic acid results in loss of ethoxide and formation of *N*-acyliminium ion, which can either be quenched by the anion, derived from the formic acid to generate **71**, undergo an intramolecular ring closure and subsequent hydrolysis to give **72** or through formation of the enamide result in a nucleophilic addition to a further equivalent of the *N*-acyliminium ion **70** to yield the dimeric product **74** (Scheme 14). A 5:1 mixture of **72** : **74** is obtained in the reaction using 0.3 mmol of **68** in 3 mL of formic acid. If the reaction is more dilute then **74** is not observed and **72** isolated in high yield. Thus, it appears in this case that the formation of the enamide is reversible, it has been found that the likelihood of a *N*-acyliminium ion forming an enamide depends upon the nature of the acidic catalyst and the solvent.[64]

1.3.3 Heterolysis of amides in the formation of *N*-acyliminium ions

Heterolysis of amides bearing a leaving group 'X' on the α-carbon, with respect to nitrogen, is one of the most common strategies employed in the synthesis of *N*-acyliminium ions. *N*-Acyliminium ions are generally formed *in-situ* due to their limited stability and high reactivity (Scheme 15).



Scheme 15

The mechanistic scheme of most α-amidoalkylations begins with **75** in equilibrium with *N*-acyliminium ion **76** through the influence of an acidic catalyst. Subsequently, a nucleophile reacts in an irreversible process with *N*-acyliminium ion **76** to give the product **77**. This scheme closely resembles the S_N1 process. Generally Brönsted or Lewis acids are used to generate *N*-acyliminium ions from α-oxyalkyl amides. There are three main methods of preparing of α-oxyalkyl amides

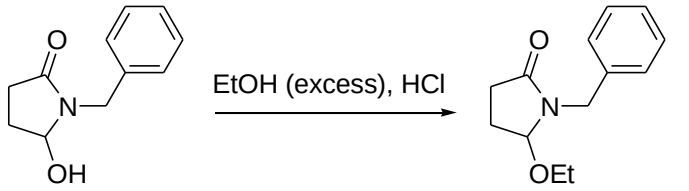
i). Addition of oxygen nucleophiles to *N*-acyliminium ion or *N*-acylimines.

ii). Reaction of primary or secondary amides with aldehydes or ketones.

iii). Partial reduction of cyclic imides.

1.3.3.1 Addition of oxygen nucleophiles to *N*-acyliminium ion or *N*-acylimines.

N-Acyliminium ions generated by any of the five methods outlined in Figure 5 will react with water, alcohol and other oxygen nucleophiles to give α-oxyalkyl amides (carbamates). An example is the conversion of hydroxy lactam **78** to ethoxy lactam **79**[65] (Scheme 16).

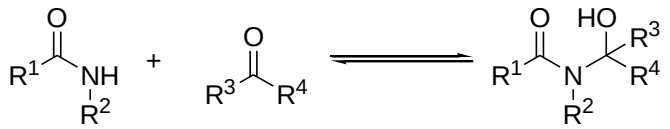


78 **79**

Scheme 16

1.3.3.2 Reaction of primary or secondary amides with aldehydes or ketones

Addition of a primary or secondary amide to carbonyl compounds results in the formation of an equilibrium, and to ensure the formation of the products often a reactive carbonyl or the formation of a favourable five or six-membered ring is required (Scheme 17).



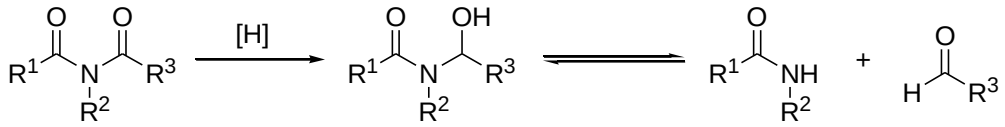
80 **81** **82**

Scheme 17

The use of a five or six membered ring in this capacity requires the partial reduction of cyclic imides.

1.3.3.3 Partial reduction of cyclic imides

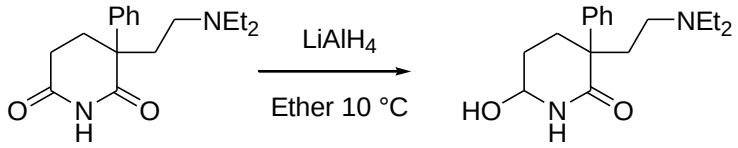
Partial reduction of **83** gives **84** which is in equilibrium with **85** and **86** (Scheme 18). The aldehyde **86** could be further reduced unless the labile C-N bond of **84** is contained within a five or six membered ring: this principle is exploited in the synthesis of five or six membered hydroxy lactams.[66]



83 **84** **85** **86**

Scheme 18

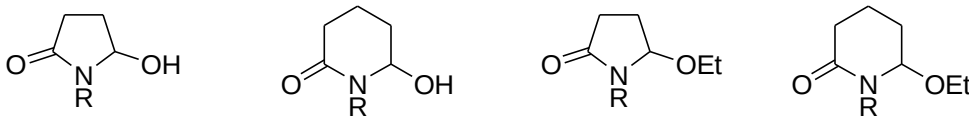
In 1954 it was shown by Tagmann *et al*[67] that lithium aluminium hydride could be utilised to carry out a partial reduction of **87** to yield hydroxy piperidone **88** (Scheme 19).



87 **88**

Scheme 19

Speckamp and co-workers developed this partial reduction of cyclic imides to a high yielding procedure by using excess sodium borohydride in ethanol.[68-71] During the reaction a dilute solution of hydrochloric acid in ethanol is slowly added in order to stop the medium from becoming too basic and result in the formation of a ring opened product. The reaction temperature is also kept below 5 °C to prevent this unwanted ring opening. In this way hydroxy lactams **89** and **90** can be obtained (Figure 6).



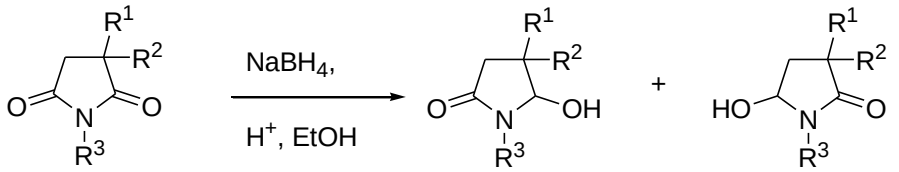
89 **90** **91** **92**

Figure 6

The corresponding ethoxy lactams **91** and **92** are isolated if the reaction medium is made strongly acidic before work up. However, it has been reported that the addition of acid is not necessary for obtaining a good yield of hydroxy lactam if the reaction is carried out at -4 °C in methanol as a solvent.[72] Four and seven membered hydroxy lactams cannot be obtained due to their tautomeric instability.[73]

1.3.3.3.1 Partial reduction of asymmetrically substituted cyclic imides

Asymmetrically substituted cyclic imides pose the problem of regiochemistry of reduction. In the case of geminally disubstituted succinimides it has been found that the carbonyl group adjacent to the quaternary centre (the more sterically hindered one) is preferentially reduced[74] (Scheme 20).

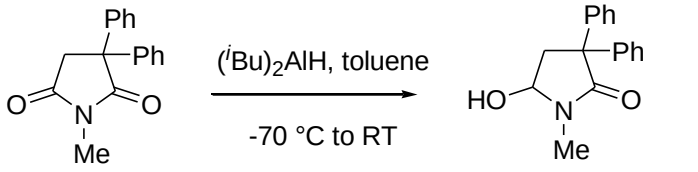


93 $R^1 = R^2 = R^3 = Me$	**94** 79 %	**95** 21%
96 $R^1 = R^2 = Ph$ $R^3 = Me$	**97** > 95 %	**98** < 5 %
99 $R^1 = R^3 = Me$ $R^2 = H$	**100** 59 %	**101** 41 %
102 $R^1 = Ph$ $R^2 = H$ $R^3 = Me$	**103** 40 %	**104** 60 %
105 $R^1 = OAc$ $R^1 = H$ $R^1 = alkyl$	**106** > 95 %	**107** < 5 %

Scheme 20

The phenomenon of preferential reduction of the sterically more hindered carbonyl group of succinimides bears close resemblance to the behaviour of succinic anhydrides toward reducing agents. Various explanations have been proposed[75-77] but the matter is complicated and unlikely that "one soon will be able to make reliable predictions on the regiochemical outcome of more complex imide systems".[46]

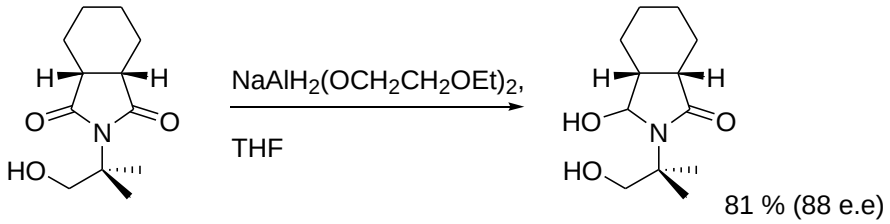
DIBAL-H can also be used to carry out partial reductions but the regiochemical outcome is the opposite[78] (Scheme 21).



96 **98**

Scheme 21

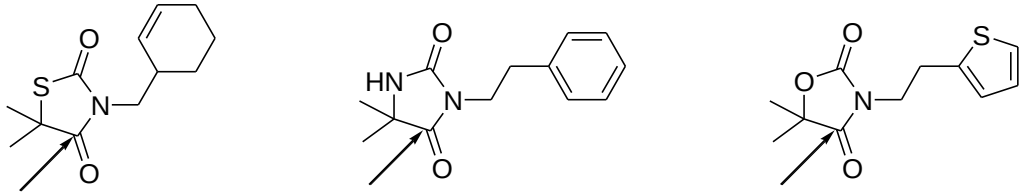
A specific example displaying good stereoselectivity is when using an aluminium hydride reagent that contains two active hydrides, the first connecting the aluminium to the oxygen of the hydroxyl group of **108** allowing reduction of the carbonyl by the second hydride, thus permitting high asymmetric induction[79,80] (Scheme 22).



108 **109**

Scheme 22

Partial reduction of cyclic imides bearing an additional heteroatom can also be carried out using sodium borohydride in ethanol, plus acid or DIBAL-H[81-83] (Figure 7).



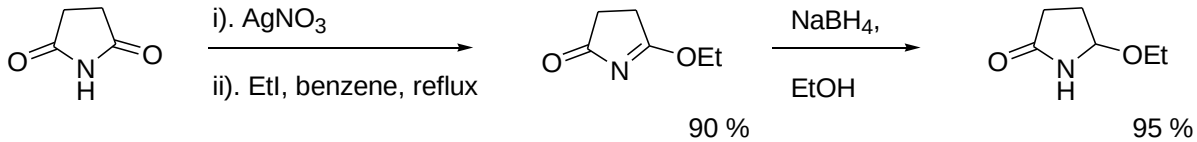
110 **111** **112**

Figure 7

Reduction occurs at the carbonyl indicated with an arrow with complete regioselectivity.

1.3.3.3.2 Reduction of *N*-acylimidates

Cyclic *N*-acylimidates can be prepared from cyclic imides by alkylation of their silver salts with ethyl iodide followed by reduction with sodium borohydride[84] (Scheme 23).

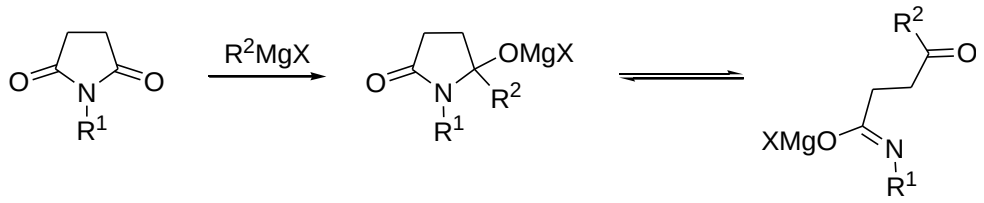


113 **114** **115**

Scheme 23

1.3.3.3.3 Grignard addition to cyclic imides

Hydroxy lactams with a tertiary hydroxyl group, such as **117**, can be prepared by the addition of Grignard reagents to five or six membered cyclic imides.[85,86] A disadvantage of this procedure is that a ring opened product, such as **118**, can be formed from the alkoxide to which further Grignard addition can occur (Scheme 24).



116 **117** **118**

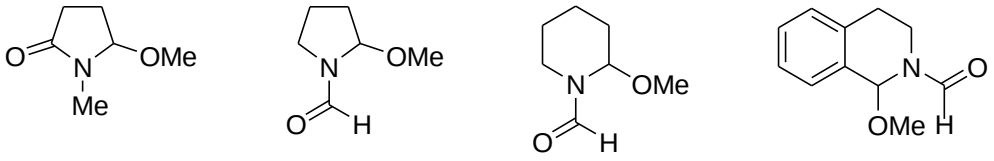
Scheme 24

1.3.4 Nature of the leaving group in the formation of *N*-acyliminium ions

The ease of formation of *N*-acyliminium ions by heterolysis of α-substituted amides depends upon the nature of the leaving group. A study conducted utilising four substituted azetidinones[87] gave the following order of reactivity: $Cl^- > RCOO^- > RSO_2 > N_3 > R\text{-}O > R\text{-}S$ for substitution reactions carried out under non-acidic conditions. However, in an acidic medium this order is likely to differ; the nature of the solvent and structure of the acidic catalyst have a bearing.

1.3.5 Reaction rates of formation of *N*-acyliminium ions

Malmberg and Nyberg[88] have found that reaction rates of the formation of *N*-acyliminium ions depend upon structural variations when utilising methoxy amides **119**, **120**, **121** and **122** (Figure 8). In an alkylation reaction with 1, 3, 5- trimethoxybenzene, catalysed by aluminium trichloride, the order of reactivity of the methoxy amides was shown to be **119**:**120**:**121**:**122** = 30:4.5:1:200.



119 **120** **121** **122**

Figure 8

The order of reaction rates correspond with the order of stability of the *N*-acyliminium ion.

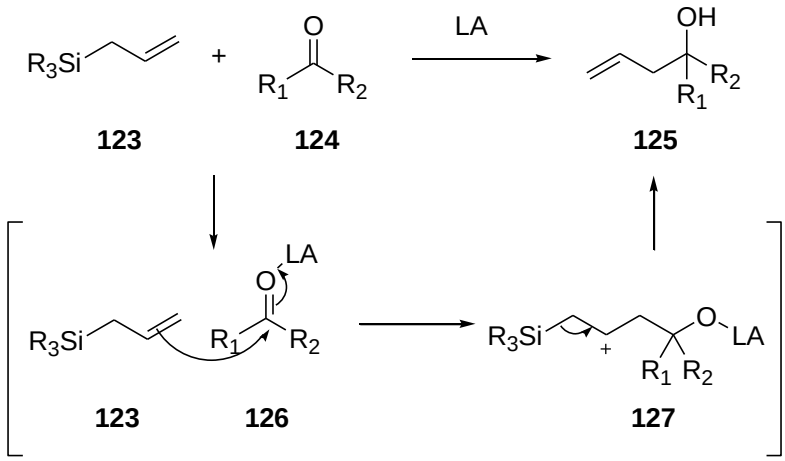
Pyrrolidinone **119** is more stable than **120** since the former is able to conjugate with the carbonyl, as in **120** the conjugation is present in only one of the two carbonyl conformers. **120** is more stable than **121** because of the presence of the double bond which is energetically more favourable in five membered rings than six. **122** is the most stable ion due to conjugation through the aromatic ring.

1.4 Lewis acid catalysed intermolecular addition reactions

In order to utilise the most appropriate Lewis acid for a reaction a comprehensive review has been carried out by Carlson *et al*.[89] One of the most popular areas of reactions involving Lewis acids is that with allyl- and vinylsilanes due to its application towards the construction of natural products,[90] more recently the advance of chiral Lewis acids and use of lanthadide triflates in catalytic quantities has been explored.[91-93]

1.4.1 Lewis acid catalysed allyl silane addition to carbonyl compounds

Hosomi and Sakurai reported some of the first reactions involving allyl silanes and carbonyl groups in the presence of a Lewis acid[94] (Scheme 25).



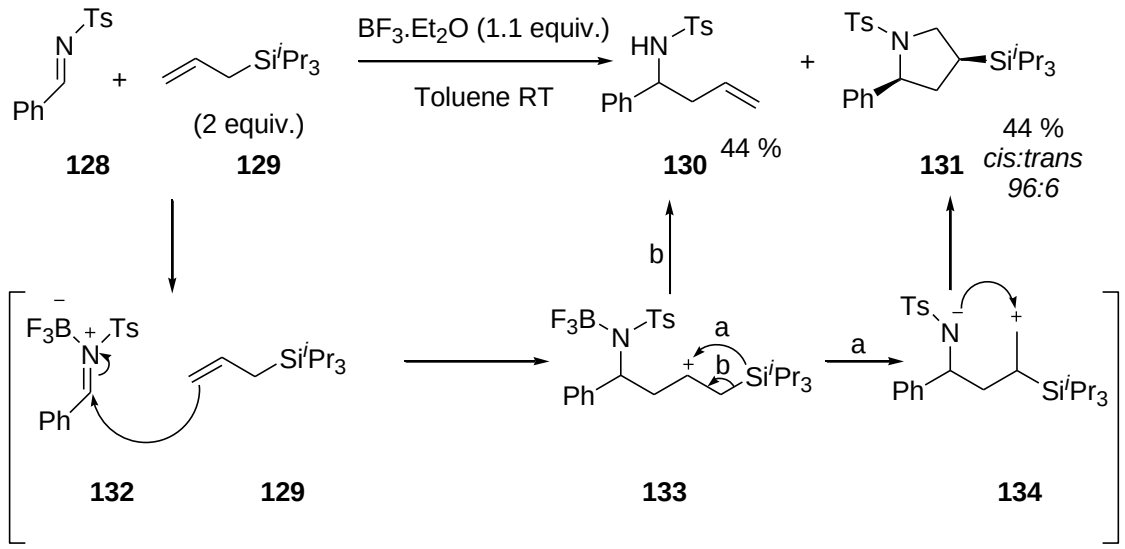
Scheme 25

In the presence of a Lewis acid carbonyl compounds **124** will react with allyl silane **123** to give homoallylic alcohols **125**. The carbon-silicon bond is electron rich and can donate electron density to stabilise the adjacent β-positive charge.

1.4.2 Lewis acid catalysed allyl silane addition to imines

Allyl silane additions to imines are less frequently reported due to the low nucleophilicity of allyl silanes and the poor electrophilicity of imines. The use of iminium ions can overcome this problem.[95,96]

Addition of triisopropylallylsilane **129** to tosyl imine **128** in the presence of boron trifluroetherate gives the homoallylic amine **130** and pyrrolidine **131**[20,97,98] (Scheme 26).

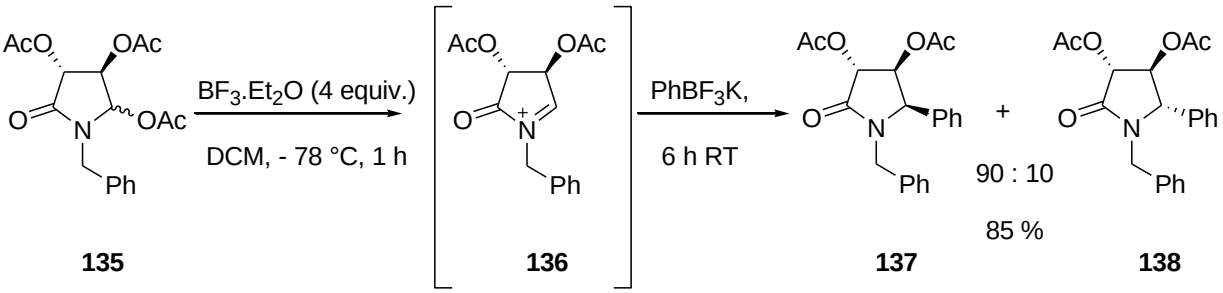


Scheme 26

Allyl silane **129** reacts with the imine-BF_3 complex **130** to give a β-silyl cation **133**. A protodesilylation (route 'b') leads to **130**, but a 1,2-silyl shift (route 'a') followed by quenching of cation **134** by nitrogen gives pyrrolidine **131**.

1.4.3 Lewis acid catalysed addition of nucleophiles to *N*-acyliminium ions

Lewis acid catalysed nucleophilic addition to *N*-acyliminium ions has been reported,[99] most recently by Vieira *et al*[100] who observed the influence of the Lewis acid on the stereoselective addition of their preferred nucleophile phenyltrifluoroborate (Scheme 27).



Scheme 27

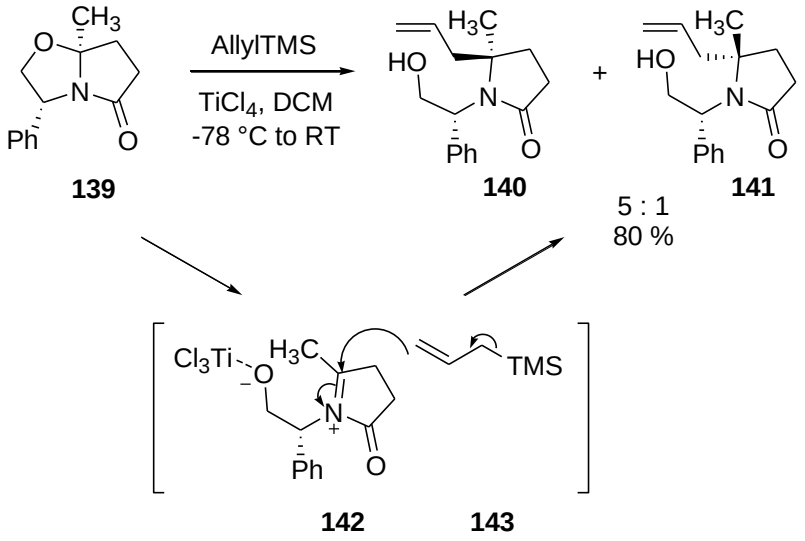
Treatment of **135** with boron trifluoroetherate at -78 °C to ensure *in-situ* formation of the corresponding *N*-acyliminium ion **136** which was formed after one hour. Phenyltrifluoroborate (1.2 equiv.) was added and the reaction allowed to warm to RT allowing the formation of a mixture of *syn* **137** and *anti* **138** products in ratio 90:10.

Cieplak *et al*[101] postulate that the *syn* preference indicates favourable orbital interaction over that of any steric interaction experienced during the *syn* approach of the boron nucleophile to the *N*-acyliminium

ion intermediate **136**: the stereochemical outcome is not ruled by steric effects. It has also been hypothesised that in Lewis acid catalysed processes the stabilising of the emerging σ* orbital interaction with the adjacent σ bonds become critical factors for the *syn* addition.[102,103]

1.4.4 Lewis acid catalysed allyl silane addition to *N*-acyliminium ions

Lewis acids which have been shown to work well with *N*-acyliminium ions are boron trifluoroetherate, titanium(IV) tetrachloride and tin(IV) tetrachloride.[104] An example employing titanium(IV) tetrachloride catalysing allyl silane addition to *N*-acyliminium ion is shown[105] (Scheme 28).

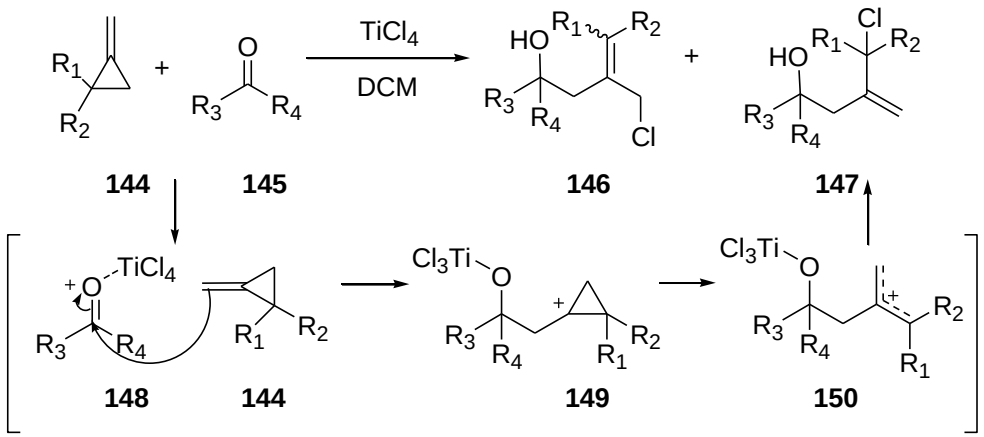


Scheme 28

N-Acyliminium ion **142** (Scheme 28) is generated *in-situ* following reaction of **139** with titanium(IV) tetrachloride, subsequent attack by allyl silane **143** gave **140**:**141** in diastereomeric ratio 5:1 and good yield.

1.4.5 Lewis acid catalysed addition of methylenecyclopropane containing compounds to carbonyl compounds

Hosomi first showed that substituted methylenecyclopropane could be coupled with a carbonyl group[106](Scheme 29).

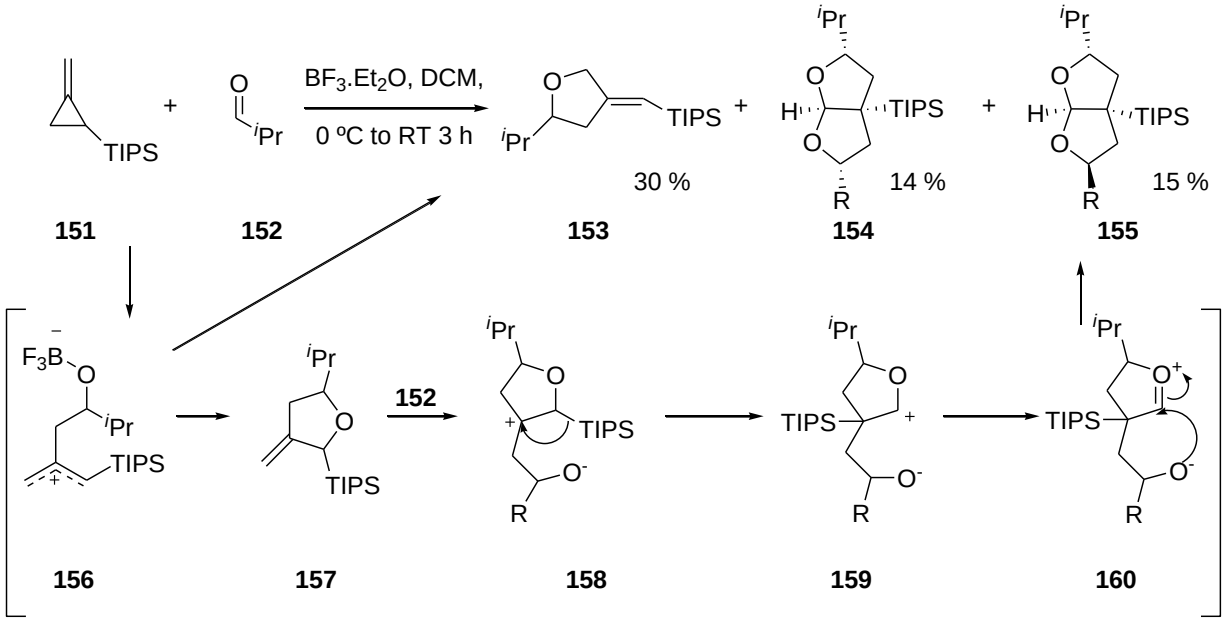


Scheme 29

The nucleophilic exocyclic double bond of the substituted methylenecyclopropane **144** attacks onto the Lewis acid coordinated carbonyl to generate the cyclopropyl cation **148**, which ring-opens to the allyl cation **149**. This is subsequently quenched by the nucleophilic anion, in this case chloride, derived from the Lewis acid to give allyl alcohols **146** and **147**.

1.4.6 Lewis acid catalysed addition of silyl-substituted methylenecyclopropane to carbonyl compounds

Patient *et al*[107,108] investigated intermolecular reactions between methylenecyclopropane and aldehydes or ketones in the presence of a Lewis acid (Scheme 30).

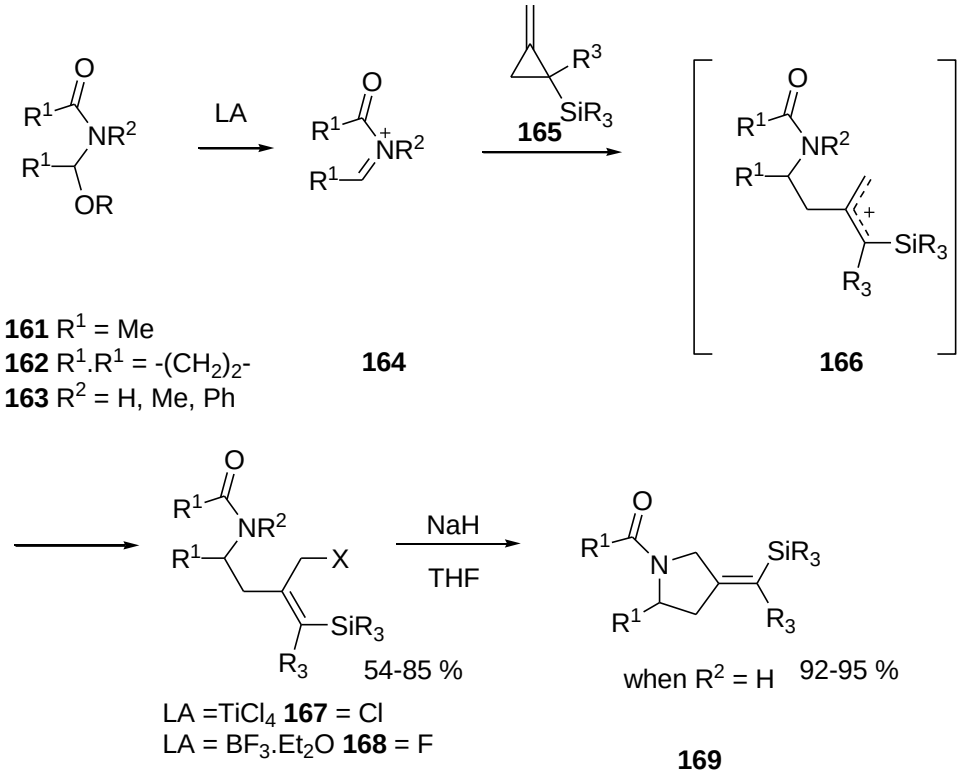


Scheme 30

Addition of triisopropylsilylmethylenecyclopropane **151** to aldehyde **152**, catalysed best by boron trifluoroetherate, is followed by rearrangement to the allyl cation intermediate **156** which can be trapped by the alkoxide to give **153** or regioisomer **157** (Scheme 30). This can then react with a further equivalent of aldehyde **152** and the formed product undergoes a 1,2-silyl shift to furnish **159**. This is then trapped intramolecularly by the alkoxide to give **154** and **155**.

1.4.7 Lewis acid catalysed addition of silyl-substituted methylenecyclopropane to *N*-acyliminum ions

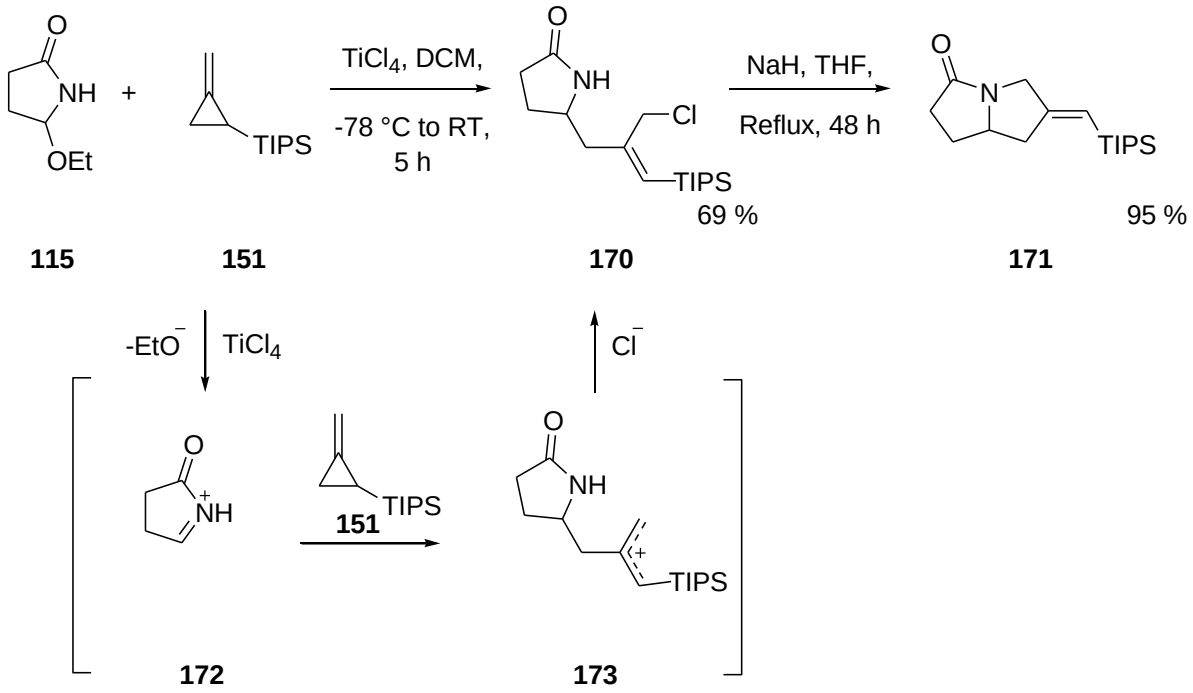
Recently, work by Barker[109] has examined both intermolecular reactions with cyclic and acyclic *N*-acyliminium ions (Scheme 31).



Scheme 31

Adducts **167** and **168** was isolated from the trapping of the cationic intermediate by the chloride or fluoride and was readily cyclised to give natural product-like structures of the type **169**.

One of the most successful reactions by Barker[109] in this series, was that utilising the cyclic imide ethoxypyrrolidinone **115** (Scheme 32).



Scheme 32

The mechanism for the shown example (Scheme 32) is analogous to that by Hosomi[106] (Scheme 29). Under Lewis acid conditions formation of the *N*-acyliminium **172** occurs, via the loss of ethoxide, facilitating the nucleophilic attack of the silyl-substituted methylenecyclopropane **151** resulting in the allyl cation **172** which is quenched by the chloride anion derived from the titanium(IV) tetrachloride. The resultant product **170** can then be converted to the bicyclic product 1**71** via an intramolecular cyclisation under refluxing basic conditions.

1.5 Intramolecular cyclisations to *N*-acyliminium ions

There are three major designs of *N*-acyliminium ions, containing the cyclic imide moiety that are susceptible to intramolecular cyclisation[46,110] (Figure 9).

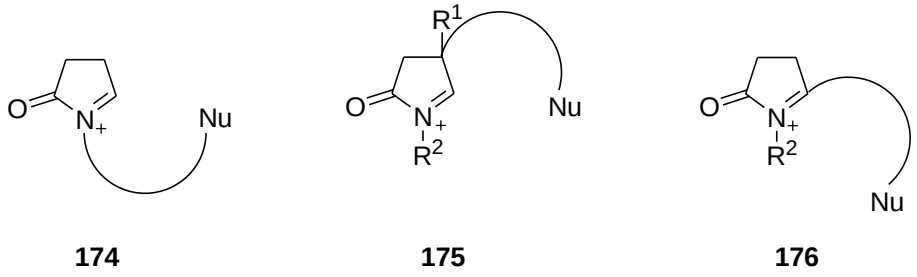


Figure 9

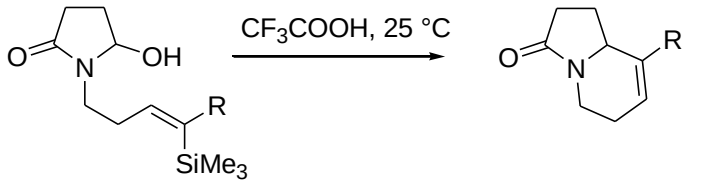
An example utilising the former design (**174**) for intramolecular cyclisation, is that of **177** catalysed by formic acid at room temperature, affording the bicyclic lactams **178** and **179** in high yield[111] (Scheme 33).

Scheme 33

The stereochemistry of the product can be rationalised by envisaging the chair-like transition state **180** with an equatorial orientated R^1 group so that the 1, 3-diaxial interaction between R^1 and H_{ax} is avoided.

1.5.1 Intramolecular cyclisation of allyl silane to *N*-acyliminium ions

Overman *et al*[112] utilised allyl silanes, such as **181**, to cyclise intramolecularly to give the bicyclic product in high yields (Scheme 34).



181

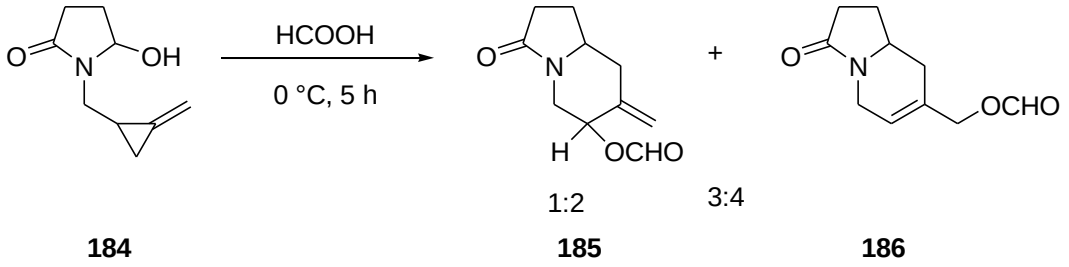
182 R = H, 92 %
183 R = Br, 63 %

Scheme 34

Treatment of **181** with an acidic catalyst results in loss of water and formation of *N*-acyliminium ion which is attacked intramolecularly by the nucleophilic allyl silane to give the bicyclic product **182** or **183** in good yield.

1.5.2 Intramolecular cyclisations of methylenecyclopropane to *N*-acyliminium ions

Similarly, unsubstituted methylenecyclopropane has been used as the nucleophile to cyclise intramolecularly to give **185**, as a 1:2 mixture of epimers, in a 3 : 4 ratio with **186** (Scheme 35).



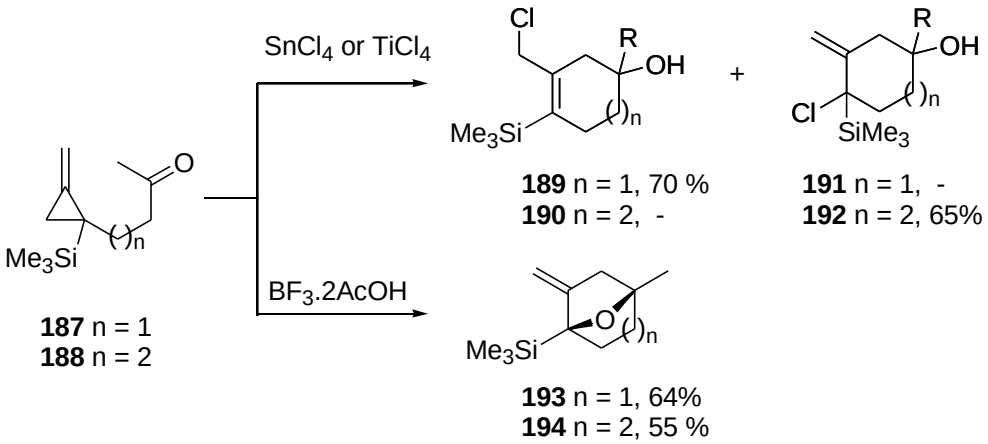
184 **185** **186**

Scheme 35

Bicycle **186** is formed by a disrotatory electrocyclic ring opening of the cyclopropane cationic intermediate, to give the allyl cation which is quenched by the anion derived from formic acid.

1.5.3 Lewis acid catalysed intramolecular cyclisations of silyl-substituted methylenecyclopropane to carbonyl compounds

Peron has reported an intramolecular addition of silyl-substituted methylenecyclopropane to ketones[113,114](Scheme 36).



Scheme 36

Peron noted that using titanium(IV) tetrachloride as the Lewis acid the cationic intermediate is trapped by chloride anion to give allyl chlorides **189** or **190** and **191** or **192**. Using milder Lewis acids such as

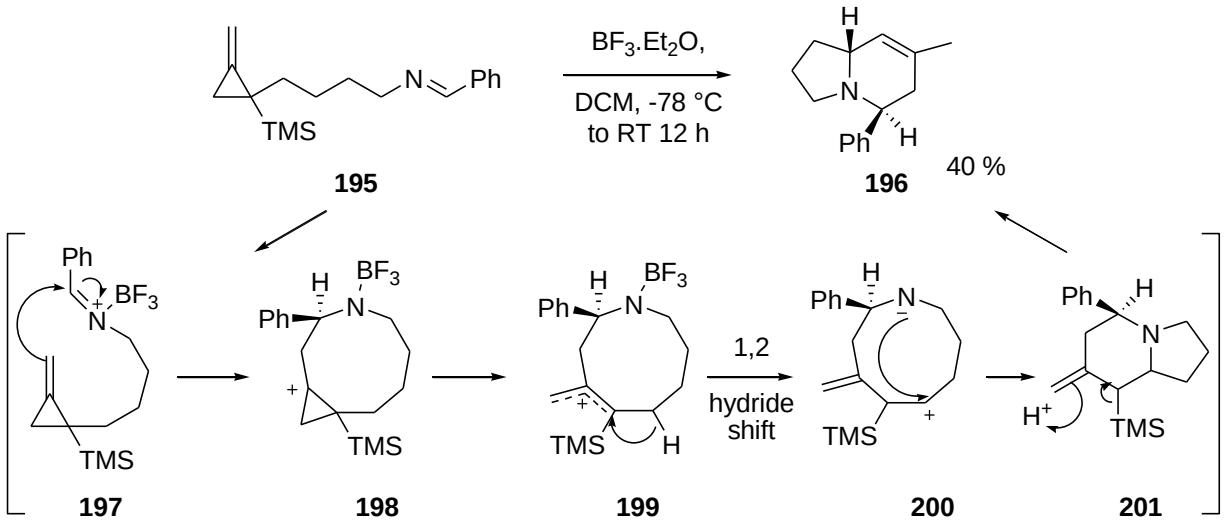
boron trifluoroetherate induced intramolecular trapping of the cationic intermediate by the alkoxide nucleophile to give **193** or **194**.

Importantly, Peron also reported that the introduction of a trimethylsilyl group on the methylenecyclopropane enhanced the nucleophilicity of the methylenecyclopropane double bond.[114] Generally silicon elimination from a β-silyl cation is fast, however under these conditions rearrangement of the cyclopropyl ring to the allyl cation is faster.

1.5.4 Lewis acid catalysed intramolecular cyclisations of silyl-substituted methylenecyclopropane to imines

Extension of Peron's methodology to reactions with imine equivalents has been successfully applied to intramolecular cyclisations with tosylhydrazones[107,115] and to some extent with simple imines.[116]

Work by Rajamaki *et al*[116,117] shows an intramolecular cyclisation of imine **195** to give cationic intermediates **199** and **200** which can be trapped to provide a simple route to bicyclic products **196** (Scheme 37).

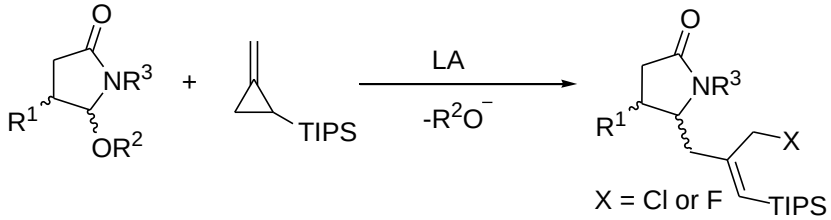


Scheme 37

Lewis acid coordination to the imine facilitates intramolecular cyclisation to form the cyclopropyl cation **198** which ring opens to the allyl cation **199**. After a 1, 2-hydride shift, to give the β-silyl cation **200**, which is quenched by nitrogen to give **201**, a protodesilylation furnishes the bicycle **186**. This mechanism is consistent with that reported by Patient.[107]

1.6 Programme of work

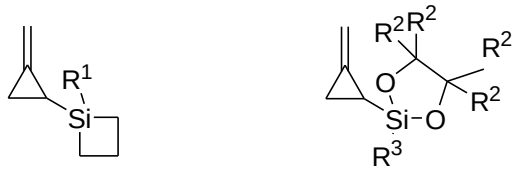
This is a methodology based project with three main areas of focus; the first follows from the work of Barker[109] who coupled silyl-substituted methylenecyclopropane intermolecularly under Lewis acid conditions, with *N*-acyliminium ions (see Scheme 32). It was proposed that by introducing a group at the β-position (R^1 in **202**) the facial selectivity of the attack of the TIPSMCP **151** nucleophile could be influenced and products of the type **203** generated in a diastereoselective fashion (Scheme 38).



202 **151** **203**

Scheme 38

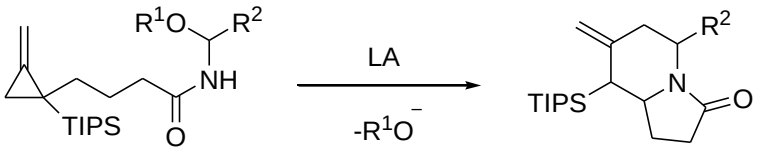
Secondly, it was proposed employing a similar methodology to Denmark[118] and Leighton,[119] constraining silicon into a four or five membered ring, to silyl-substituted methylenecyclopropane would influence its reactivity, with the aim of uncatalaysed reactions with electrophiles . This would result in the synthesis of molecules of the type **204** and **205** (Figure 10).



204 **205**

Figure 10

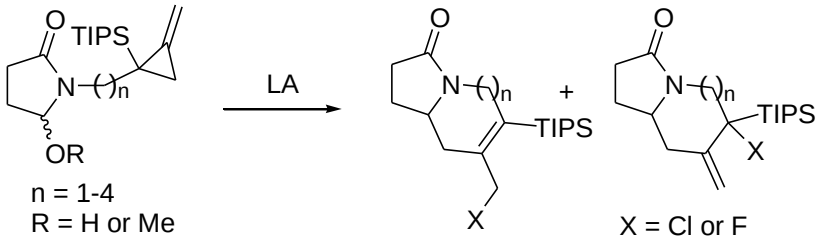
Thirdly, following the work of Rajamaki *et al*[116] who under Lewis acid conditions cyclised intramolecularly silyl-substituted methylenecyclopropane on to imines (see Scheme 37), it was proposed that utilising the more electrophilic *N*-acyliminium ion over imine equivalent would result in higher yields. Following the analogous mechanism laid out by Rajamaki,[116] it was proposed intramolecular cyclisation of **206** would result in formation of natural product-like[90] structures of the type **207** (Scheme 39).



206 **207**

Scheme 39

Also, utilising the work from intermolecular reactions of silyl-substituted methylenecyclopropane to pyrrolidinone based *N*-acyliminium ions[109] it was proposed that incorporating both moieties into one molecule would be suitably poised for intramolecular cyclisation, resulting in a facile route to bicyclic products of the type **209** and **210** (Scheme 40).



208 **209** **210**

Scheme 40

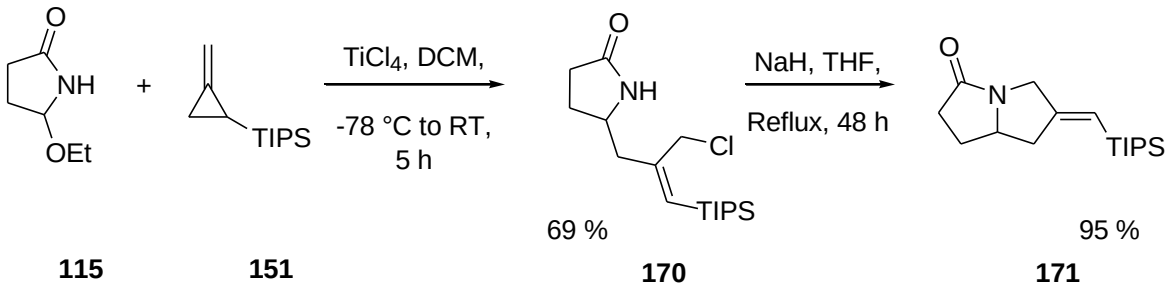
Chapter 2

Intermolecular additions of pyrrolidinones to silyl-substituted methylenecyclopropanes

2.1 Aims

Barker[109] has shown that under Lewis acid conditions ethoxypyrrolidinone **115** can be coupled with TIPSMCP **151** to give **170** in good yield (Scheme 41).

Treatment of ethoxypyrrolidinone **115**[69] with Lewis acid results in loss of the ethoxy group and formation of *N*-acyliminium ion, which facilitates the attack of the TIPSMCP **151** to give the allyl cation, which is quenched by the nucleophilic anion (in this case chloride) derived from the Lewis acid (Scheme 41). Refluxing with sodium hydride generates bicyclic product **171** via a final intramolecular cyclisation.



Scheme 41

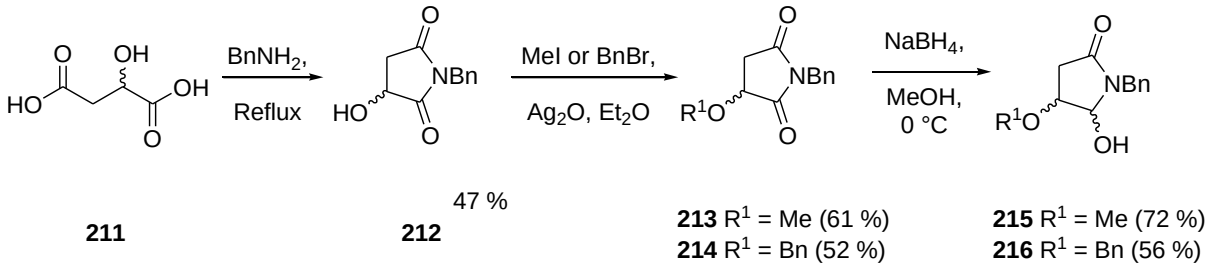
The aim of this research was to influence the diastereoselectivity of this reaction (Scheme 41) by introducing a group at the β–position in the pyrrolidinone moiety in an attempt to influence the facial selectivity of the attack of TIPSMCP **151**. It was proposed that the larger the group at the β–position, the larger the effect upon the attack of **151** and the ratio of diastereoisomers of the products formed.

2.2 Synthesis of precursors

2.2.1 Synthesis of β-substituted pyrrolidinones

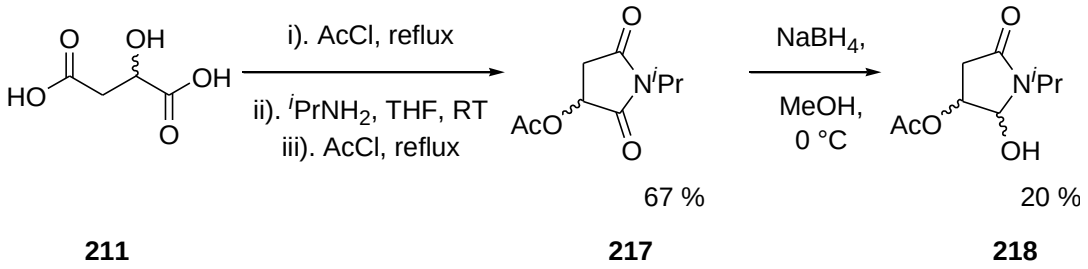
Methyl- **215**, benzyl- **216**, acyl- **218** and phenyl- **221** substituted pyrrolidinones were successfully synthesised (Scheme 42, 43 and 44). Refluxing malic acid **211** in benzylamine[120] generated pyrrolidinedione **212** in moderate yield, which was alkylated at the β–position using methyl iodide, to give the methyl-substituted pyrrolidinedione **213**, or benzyl bromide to yield the benzyl-substituted pyrrolidinedione **214**[121,122] (Scheme 42). This generated pyrrolidinediones **213** and **214** easily and from cheap and readily available starting materials. Using a modified procedure of Speckamp *et al*[69,72] partial

reduction was carried out regiospecifically at the more hindered position, to afford **215** and **216**[123] in good yield (Scheme 42).



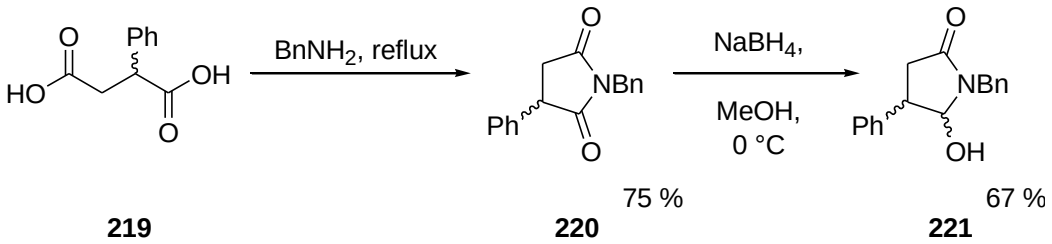
Scheme 42

Introduction of the acyl group at the β–position was achieved by refluxing malic acid in acyl chloride, to give *in-situ* formation of the anhydride, treatment with isopropylamine, to generate *in-situ* the pyrrolidinedione and refluxing with acyl chloride to give **217**[70,71,99,124] in good yield (Scheme 43). This generated pyrrolidinedione **217** with an isopropyl group at the nitrogen position, due to its ease of synthesis. Partial reduction was carried out with sodium borohydride[69] to afford **218** in low yield. Difficulties were encountered resulting from the high polarity of **218** and difficulty of extracting from the aqueous layer (Scheme 43).



Scheme 43

Refluxing phenylsuccinic acid **219** in benzylamine generated **220**,[125] followed by partial reduction[69] to give the hydoxypyrrolidinone **221**, both reactions in good yield (Scheme 44).

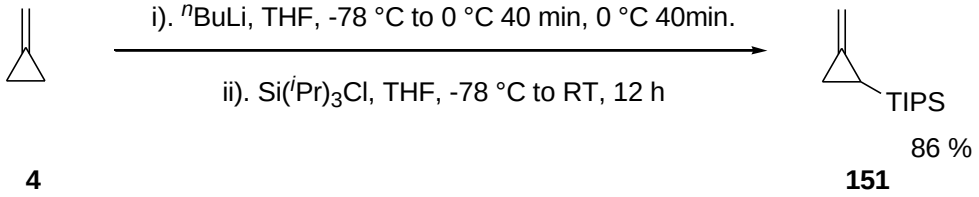


Scheme 44

A range of β–substituted pyrrolidinones **215**, **216**, **218** and **221** have been synthesised all employing a hydroxy leaving group, chosen due to its ease of synthesis from the reduction of the corresponding β–substituted pyrrolidinediones (**213**, **214**, **217** and **220**). It could be rationalised that the resultant leaving hydroxyl group could affect the reactivity or quality of the Lewis acid in a coupling reaction with a nucleophile, however, it has been shown that this is not the case.[126,127]

2.2.2 Synthesis of TIPSMCP

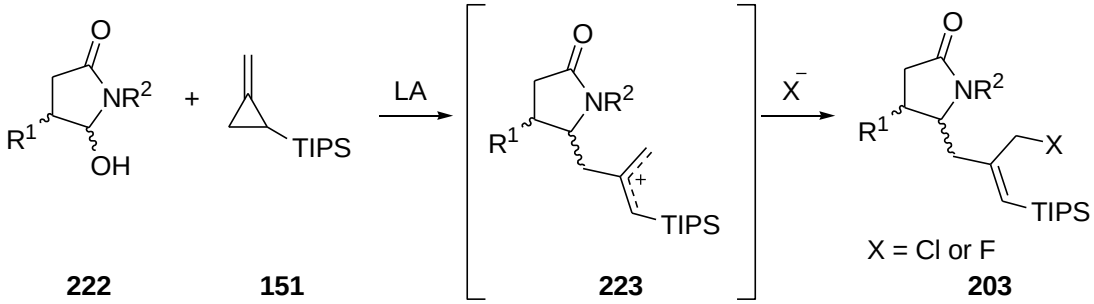
Following the procedure of Patient[107] TIPSMCP **151** was synthesised in good yield (Scheme 45). Deprotonation of methylenecyclopropane **4** with *n*-butyllithium solution (1.6 M in hexanes) generated the lithiated species which was quenched with TIPSCl to give TIPSMCP **151** (Scheme 45).



Scheme 45

2.3 Cyclisation studies with β–substituted pyrrolidinones

A range of β–substituted hydroxypyrrolidinones were coupled with TIPSMCP **151** under Lewis acid conditions* (Scheme 46 and Table 1).



Scheme 46

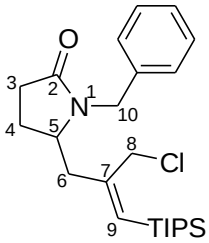
* Results shown in Table 1 are for reactions where products were obtained after purification by flash column chromatography. For each substituent at R^1 tin(IV) tetrachloride, titanium(IV) chloride and boron trifluoroetherate were investigated.

Entry	R^1	R^2	Conditions[a]	Ratio of diastereoisomers of 203[b]	Yield %[c]
1	Ph	Bn	$SnCl_4$, DCM, -20 °C to -10 °C, 2 h	1:5.0	15
2	Ph	Bn	$TiCl_4$, DCM, -20 °C to -10 °C, 1 h	1:7.2	14
3	Ph	Bn	$BF_3.Et_2O$, DCM, -20 °C to R.T, 24 h	1:5.0	4
4	OMe	Bn	$SnCl_4$, DCM, -20 °C to R.T, 72 h	1:3.7	7
5	OMe	Bn	$TiCl_4$, DCM, -20 °C to R.T, 24 h	1:5.3	9
6	OBn	Bn	$TiCl_4$, DCM, -20 °C to R.T, 17 h	1:4.5	6
7	OAc	^{i}Pr	$SnCl_4$, DCM, -20 °C to R.T, 48 h	1:3.3	4
8	OAc	^{i}Pr	$TiCl_4$, DCM, -20 °C to R.T, 48 h	-	4

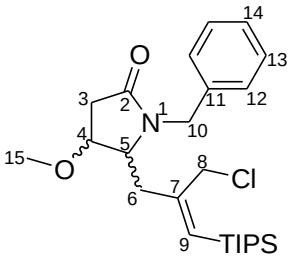
[a]Lewis acid (1.5 equiv) was added dropwise to a stirring solution of **222** and TIPSMCP **151** (3 equiv) in the presence of 4 Å molecular sieves in DCM (0.1 M). [b]Based upon crude ^{1}H NMR (300 MHz $CDCl_3$) integration. [c]Isolated yield.

Table 1

Due to the mixture of diastereoisomers isolated after flash column chromatography, ^{1}H NMR data was difficult to assign. For the cleanest product isolated **225** (Table 1 Entry 5) the key ^{1}H NMR features are highlighted and for comparison **224** reported by Barker[109](Figure 11).



224



225

Reported as a mixture of diastereoisomers in ratio 1:4.3 (^{1}H NMR 300 MHz $CDCl_3$)

^{1}H NMR (300 MHz $CDCl_3$)		
	224 δ_H/ppm (multiplicity/Hz)	**225** δ_H/ppm (multiplicity/Hz)
H(15)	-	3.26 (3H, s, (major)(minor))
Ar	7.40-7.25 (5H, m)	7.27-7.15 (5H, m)
H(10)	5.03 (1H, d, *J* = 15.0 Hz), 4.03 (1H, d, *J* = 15.0 Hz)	5.08-4.97 (1H, m), 4.06-3.97 (1H, m)
H(9)	5.42 (1H, s)	5.68 (1H, m, (minor)), 5.46 (1H, m, (major))
H(8)	4.00 (1H, d, *J* = 11.5 Hz), 3.89 (1H, d, *J* = 11.5 Hz)	4.06-3.97 (2H, m)
H(6)	3.02 (1H, dd, *J* = 13.5, 2.5 Hz), 2.11 (1H, dd, *J* = 13.5, 10.5 Hz)	2.69-2.66 (2H, m)
H(5)	3.61 (1H, m)	3.83-3.82 (1H, m)
H(4)	2.02 (1H, m), 1.78 (1H, m)	3.74-3.68 (1H, m)
H(3)	2.58-2.35 (2H, m)	2.57-2.52 (2H, m)
TIPS	1.10-0.95 (21H, m)	1.01 (21H, m)

^{13}C NMR (75.5 MHz $CDCl_3$)		
	224 δ_H/ppm (Hz)	**225** δ_H/ppm (Hz)
C(15)	-	56.9 (3)
Ar	136.7 (0), 129.9 (1), 128.8 (1), 128.4 (1)	129.9 (1), 129.1 (1), 129.0 (1), 128.3 (1), 128.2 (1), 127.8 (1)
C(11)		136.7 (2x2) (0)
C(10)	40.7 (2)	44.9 (2) (minor), 44.4 (2) (major)
C(9)	127.7 (1)	127.8 (1), 127.6 (1)
C(8)	47.5 (2)	48.5 (2)
C(7)	149.7 (0)	150.6 (0) (major), 150.3 (0) (minor)
C(6)	44.4 (2)	36.4 (2) (minor), 35.8 (major)
C(5)	55.5 (1)	60.4 (1)
C(4)	29.9 (2)	75.0 (1)
C(3)	23.7 (2)	33.7 (2), 32.3 (2)
C(2)	174.9 (0)	173.1 (0)
TIPS	18.9 (3), 12.2 (1)	19.1 (3), 12.5 (1)

Figure 11

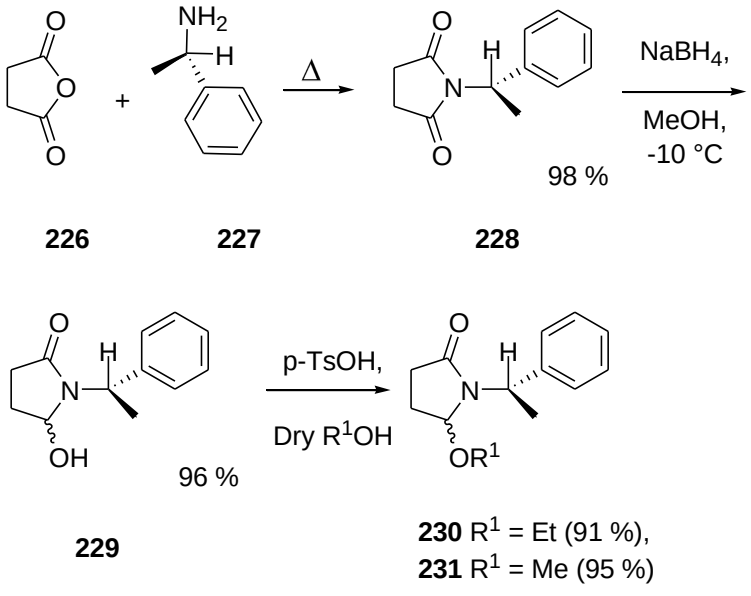
It can be observed (Table 1, Entries 1 and 5) that the introduction of a group at the β–position has a moderate effect upon the facial selectivity of the attack of the TIPSMCP **151**, and that the yields are not comparable to those reported by Barker.[109] It is possible that the *N*-acyliminium ion when formed is too crowded, with large groups at the β– and *N*- position resulting in low yields and, therefore not useful for diastereoselective preparation of target molecules. Under Lewis acid conditions β–elimination of the acetoxy- or methoxy- group is also possible, although this was not observed; β–elimination of the phenyl group is less likely and may explain the difference in yields for these groups.

Redesigning the system to reduce crowding, it was proposed that synthesising a range of *N*-substituted pyrrolidinones would result in higher yields and have an influence on the facial selectivity of the attack of the TIPSMCP **151** onto the *N*-acyliminium ion. It was also proposed that if the *N*-substituted group could be cleaved it would facilitate the synthesis of the bicyclic product **171** (Scheme 41), following deprotection and cyclisation, in an enantiomeric excess.

2.4 Synthesis of precursors

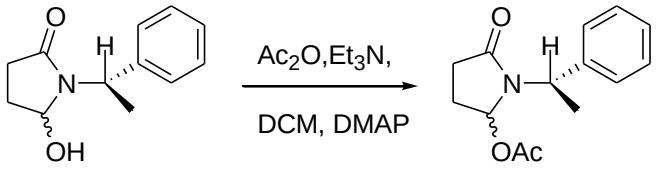
2.4.1 Synthesis of *N*-substituted pyrrolidinones

N-Substituted hydroxypyrrolidinone **229** was synthesised in good yield (Scheme 47). An (*S*)-methylbenzyl group was chosen as a suitable chiral group as it has precedent to be cleaved.[128-131] Utilising the method of Chihab-Eddine *et al* refluxing succinic anhydride **226** and (*S*)-methylbenzylamine **227** gave pyrrolidinedione **228**[80,110,132,133] in good yield (Scheme 47). Partial reduction[69] was carried out to give the hydroxypyrrolidinone **229** (Scheme 47).



Scheme 47

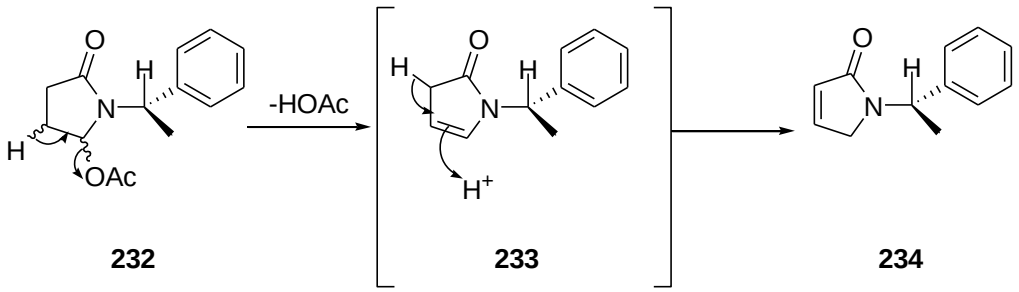
In response to work by Vieria *et al*[100] it was of interest to observe if the leaving group, under Lewis acid conditions had an influence upon the yield. Thus, hydroxy- **229** was converted to ethoxy- **230** and methoxypyrrolidinone **231**[134,135] (Scheme 47). The synthesis of acetoxypyrrolidinone **232** was attempted but not successful (Scheme 48).



229 **232**

Scheme 48

It is proposed that upon work-up loss of acetic acid results in formation of **232** which would tautomerise to the more stable (due to conjugation with the carbonyl) pyrrolone **234** (Scheme 49).

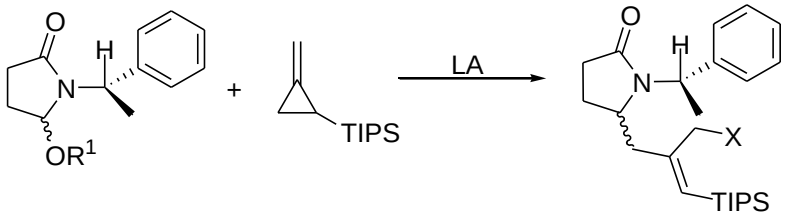


232 **233** **234**

Scheme 49

2.5 Cyclisation studies with *N*–(*S*)-Methylbenzyl substituted pyrrolidinones

Pyrrolidinones **229**, **230** and **231** were coupled with TIPSMCP **151** under various Lewis acid conditions (Scheme 50 and Table 2).



229 R^1 = H
230 R^1 = Et
231 R^1 = Me

151

235a X = Cl
235b X = F

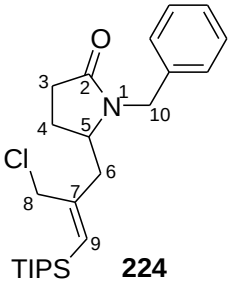
Scheme 50

Entry	R	Solvent	Lewis Acid	Conditions[a]	Ratio of diastereoisomers of 235[b]	Yield %[c]
1	H	$EtNO_2$	$TiCl_4$ (Cl)	-78 °C to RT, 12 h	1:1.7	9
2	H	$EtNO_2$	$BF_3.Et_2O$ (F)	-78 °C to RT, 5 h	-	5
3	Et	$EtNO_2$	$TiCl_4$ (Cl)	-78 °C to -40 °C, 5.5 h	1:1.7	33
4	Et	$EtNO_2$	$BF_3.Et_2O$ (F)	-78 °C to -40 °C, 5 h	-	5
5	Et	$EtNO_2$	$SnCl_4$ (Cl)	-78 °C to -10 °C, 5 h	1:5.5	16
6	H	DCM	$BF_3.Et_2O$ (F)	-78 °C to RT, 5 h	1:2.4	16
7	Et	DCM	$TiCl_4$ (Cl)	-40 °C to RT, 4 h	1:3.1	34
8	Et	DCM	$BF_3.Et_2O$ (F)	-40 °C to 0 °C, 3 h	1:2.4	4
9	Et	DCM	$SnCl_4$ (Cl)	-40 °C to -20 °C, 3 h	1:3.5	52
10	Me	DCM	$TiCl_4$ (Cl)	-40 °C to RT, 4 h	1:1.9	27
11	Me	DCM	$BF_3.Et_2O$ (F)	-40 °C to 0 °C, 3 h	1:1.6	14
12	Me	DCM	$SnCl_4$ (Cl)	-40 °C to -20 °C, 3 h	1:2.7	46

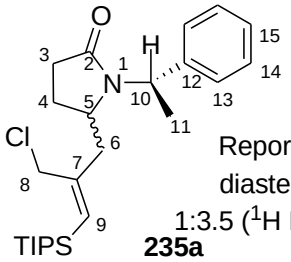
[a]Lewis acid (1.5 equiv) was added dropwise to a stirring solution of appropriate starting material and TIPSMCP **151** (3 equiv) in appropriate solvent (0.1 M). [b]Ratio of diastereoisomers based upon ^{1}H NMR (300MHz $CDCl_3$) integration, ratio supplied where this is possible to do so. [c]Isolated yield of inseparable mixture of isomers.

Table 2

Due to the mixture of diastereoisomers isolated after flash column chromatography, ^{1}H NMR data was difficult to assign. For the cleanest product isolated **235a** (Table 2 Entry 9) the key ^{1}H NMR features are highlighted and for comparison **224** reported by Barker[109] (Figure 12).



224



235a

Reported as a mixture of diastereoisomers in ratio 1:3.5 (^{1}H NMR 300 MHz $CDCl_3$)

^{1}H NMR (300 MHz $CDCl_3$)		
	224 δ_H/ppm (multiplicity/Hz)	**235a** δ_H/ppm (multiplicity/Hz)
Ar	7.40-7.25 (5H, m)	7.41-7.23 (5H, m)
H(11)	-	1.69 (3H, d, *J* = 7.0 Hz (major)), 1.06 (3H, d, *J* = 7.0 Hz (minor))
H(10)	5.03 (1H, d, *J* = 15.0 Hz), 4.03 (1H, d, *J* = 15.0 Hz)	5.41 (1H, q, *J* = 7.0 Hz),
H(9)	5.42 (1H, s)	5.30 (1H, s, (major)), 5.27 (1H, s, (minor))
H(8)	4.00 (1H, d, *J* = 11.5 Hz), 3.89 (1H, d, *J* = 11.5 Hz)	3.97-3.87 (2H, m)
H(6)	3.02 (1H, dd, *J* = 13.5, 2.5 Hz), 2.11 (1H, dd, *J* = 13.5, 10.5 Hz)	2.98-2.92 (1H, m)
H(5)	3.61 (1H, m)	3.72-3.68 (1H, m)
H(4)	2.02 (1H, m), 1.78 (1H, m)	2.10-1.75 (2H, m)
H(3)	2.58-2.35 (2H, m)	2.57-2.27 (2H, m)
TIPS	1.10-0.95 (21H, m)	1.07-0.99 (21 H, m)

^{13}C NMR (75.5 MHz $CDCl_3$)		
	224 δ_H/ppm (Hz)	**235a** δ_H/ppm (Hz)
Ar	136.7 (0), 129.9 (1), 128.8 (1), 128.4 (1)	141.9 (0), 139.3 (0), 129.3 (1), 129.1 (1), 128.5 (1), 128.3 (1), 126.9 (1), 126.7 (1)
C(11)	-	16.2 (3)
C(10)	40.7 (2)	50.7 (1) (minor), 49.4 (1) (minor)
C(9)	127.7 (1)	127.6 (1), 127.5 (1)
C(8)	47.5 (2)	47.3 (2) (major), 47.0 (2) (minor)
C(7)	149.7 (0)	150.0 (0), 150.0 (0)
C(6)	44.4 (2)	42.6 (2) (major), 42.4 (2) (minor)
C(5)	55.5 (1)	55.6 (1)
C(4)	29.9 (2)	30.0 (2), 29.8 (2)
C(3)	23.7 (2)	23.9 (2), 23.7 (2)
C(2)	174.9 (0)	175.0 (0) (major), 174.7 (0) (minor)
TIPS	18.9(3), 12.2 (1)	18.7(3), 12.0 (1)

Figure 12

These results are consistent with those observed when boron trifluoroetherate was used as a Lewis acid and hence the fluorosilane **235b** was isolated (Table 2 Entries 2, 4, 6, 8, 11).

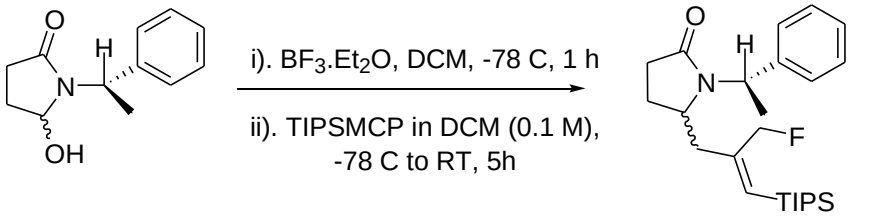
Ethoxy- **230** and methoxy-**231** groups were used predominately as leaving groups due to their ease of synthesis.

It is consistent with Barker[109] to observe that the best yielding Lewis acids are the tin(IV) and titanium(IV) tetrachlorides and the solvent is DCM. Nitroethane was utilised as it was rationalised it would stabilise the allyl cation and result in higher yields, a trend not observed. For instance comparing **Entry 5** and **9** (Table 2) a difference in yield from 16 % when using nitroethane to 52 % using DCM.

Utilising a chiral *N*-substituent (Table 2, Entry 9) does not appear to have as great an influence upon the ratio of diastereoisomers compared to a β-substituent (Table 1, Entry 2). A possible explanation for this is that a group at the *N*-position is further away from the site of nucleophilic attack, and thus less of an effect compared to a group at the β-position; consequently, this approach resulted in higher yields.

2.6 Cyclisation studies with *N*–(*S*)-methylbenzyl substituted pyrrolidinones ; sequential addition of Lewis acid

Following the work of Vieira *et al*[100] it was of interest to observe if the sequential addition of Lewis acid to the cyclic imide would have any effect upon the yield of the reaction. The sequential addition method was employed to observe if there was any improvement in a low yielding reaction (Table 2 Entry 6). Boron trifluoroetherate was added dropwise to **229** and the reaction monitored by TLC, before the addition of a solution of TIPSMCP **151** in DCM (Scheme 51).



Scheme 51

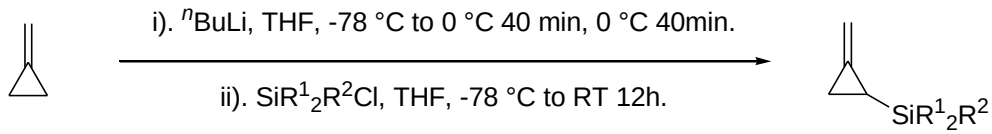
This resulted in the formation of **235b** in 14 % yield compared to 16 % using the non-sequential addition method, thus this method did not appear to have an influence upon the yield.

2.7 Cyclisation studies with *N*–(*S*)-methylbenzyl substituted pyrrolidinones ; use of various silyl-substituted MCP

It was of interest to observe if different groups on the silicon had any influence on the ratio of diastereoisomers of **235** formed.

2.7.1 Synthesis of trialkyl silyl-substituted methylenecyclopropanes

Deprotonation of methylenecyclopropane **4** was carried out with *n*-butyllithium solution (1.6 M in hexanes) and the resultant lithiated methylenecyclopropane quenched with the appropriate trialkylsilyl chloride[107] (Scheme 52).



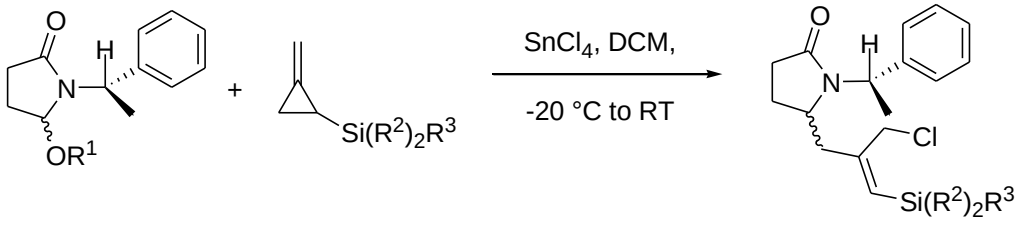
4

236 R^1 = Me and R^2 = Ph, (54 %)
237 R^1 = Me and R^2 = ^{t}Bu, (50 %)
238 R^1 = Ph and R^2 = ^{t}Bu, (13 %)

Scheme 52

2.7.2 Coupling reactions of trialkyl silyl-substituted methylenecyclopropanes to *N*-chiral substituted pyrrolidinones

The three different silyl-substituted methylenecyclopropanes **236**, **237** and **238** were coupled with **229** and **231** using the highest yielding conditions (Table 2, Entry 9) (Scheme 53).



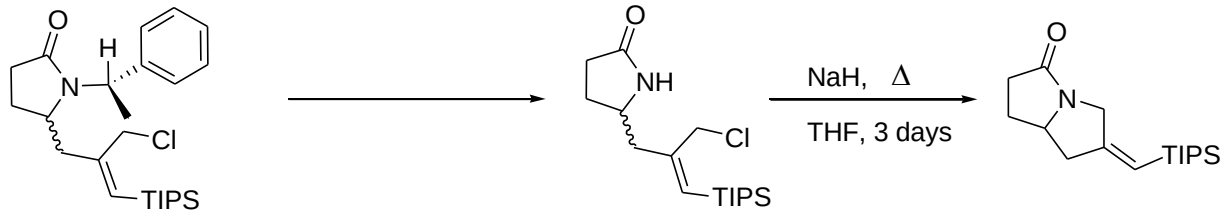
when **229** R^1 = H **238** R^2 = Ph R^3 = ^{t}Bu **239** R^2 = Ph R^3 = ^{t}Bu
231 R^1 = Me **236** R^2 = Me R^3 = Ph **240** R^2 = Me R^3 = Ph
231 R^1 = Me **237** R^2 = Me R^3 = ^{t}Bu **241** R^2 = Me R^3 = ^{t}Bu

Scheme 53

No clean coupled product was isolated after flash column chromatography for any reaction and the majority of starting material was recovered. It is possible that due to the increase in steric bulk around the silicon in **236**, **237** and **238** that the reaction becomes less favoured on steric grounds.

2.8 Removal of the *N*-chiral auxiliary

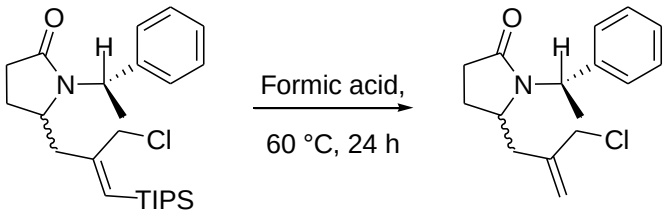
It was of interest to remove the *N*-chiral auxiliary, utilising the known methods[128,129] in order to target the bicylic product **171** (Scheme 54).



235a **170** **171** 90 %

Scheme 54

Deprotection of the benzyl group was not observed using the known methods: Pd/C and H_2,[130,131] Na (s), NH_3(l), -33 °C[128] or formic acid at 60 °C[129] with starting material returned in all except the latter case. Interestingly treatment of **235a** with formic acid and refluxing resulted in protodesilylated product **242**, as indicated by key features in the NMR: the alkene peaks at 5.13 and 4.88 ppm respectively and loss of TIPS group in the ^{1}H NMR (300 MHz, $CDCl_3$) and the terminal CH_2 alkene at 117.3 ppm in the ^{13}C NMR (75 MHz, $CDCl_3$) (Scheme 55).



235a **242**

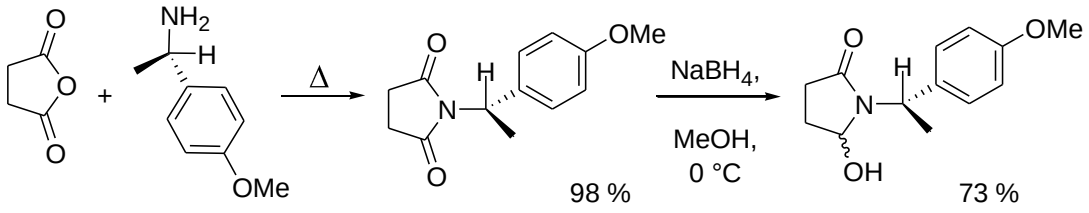
Scheme 55

Consultation of the literature prompted the use of a new modified *N*-chiral auxiliary with the introduction of a *p*-methoxybenzyl group, which also has precedent for cleavage.[136,137]

2.9 Synthesis of precursors

2.9.1 Synthesis of *N*-*p*-methoxybenzyl substituted pyrrolidinone

(*S*)-Hydroxy-*p*-methoxybenzylpyrrolidinone **244** was synthesised in an analogous manner to that of **229** (Scheme 56).

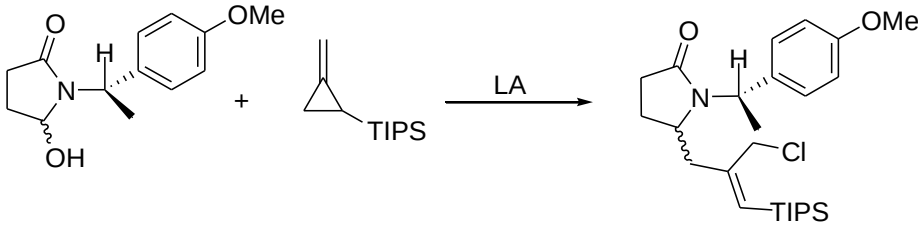


226 **243** **244** **245**

Scheme 56

2.9.2 Cyclisation studies with *N*-*p*-methoxybenzyl substituted pyrrolidinone

Hydroxypyrrolidinone **245** was coupled with TIPSMCP **151** under Lewis acid conditions utilising the most successful conditions previously reported (Table 2, Entry 9 and 12) and hydroxy-substituted compound chosen as a suitable leaving group (Scheme 57).



245 **151** **246**

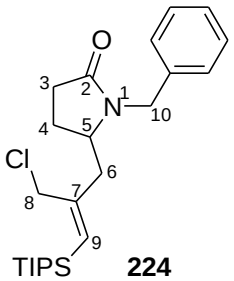
Scheme 57

Entry	**Conditions**[a]	**Ratio of diastereoisomers of 246**[b]	**Yield %** [c]
1	$SnCl_4$, DCM, -20 °C to -10 °C, 10 min	1:2.3	64
2	$TiCl_4$, DCM, -20 °C to -10 °C, 1 hr	1:2.3	54

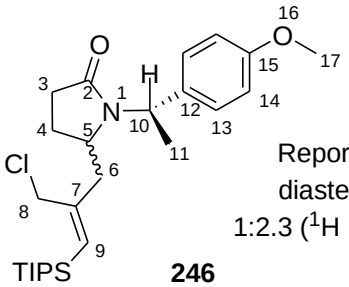
[a]Lewis acid (1.5 equiv) was added dropwise to a stirring solution of **245** and TIPSMCP **151** (3 equiv) in DCM (0.1 M).[b]Based upon ^{1}H NMR (300 MHz $CDCl_3$) integration. [c]Isolated yield.

Table 3

Due to the mixture of diastereoisomers isolated after flash column chromatography, ^{1}H NMR data was difficult to assign. For the cleanest product isolated **246** (Table 3 Entry 1) the key ^{1}H NMR features are shown, with **224** for comparison reported by Barker[109] (Figure 13).



224



246

Reported as a mixture of diastereoisomers in ratio 1:2.3 (^{1}H NMR 300 MHz $CDCl_3$)

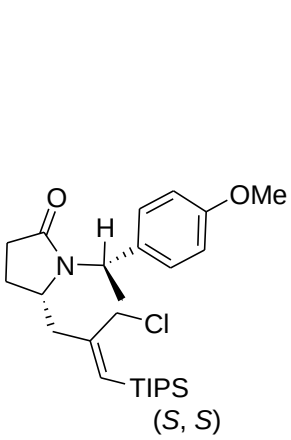
^{1}H NMR (300 MHz $CDCl_3$)		
	224 δ_H/ppm (multiplicity/Hz)	**246** δ_H/ppm (multiplicity/Hz)
H(17)	-	3.79-3.70 (3H, m)
H(11)	-	1.66 (3H, d, *J* = 5.4 Hz (major)), 1.63 (3H, d, *J* = 5.4 Hz, (minor))
Ar	7.40-7.25 (5H, m)	7.34-7.27 (2H, m, (major)(minor)), 6.90-6.81 (2H, m, (major)(minor)
H(10)	5.03 (1H, d, *J* = 15.0 Hz), 4.03 (1H, d, *J* = 15.0 Hz)	5.37 (1H, m),
H(9)	5.42 (1H, s)	5.32 (1H, s, (major)), 5.29 (1H, s, (minor))
H(8)	4.00 (1H, d, *J* = 11.5 Hz), 3.89 (1H, d, *J* = 11.5 Hz)	3.96-3.90 (2H, m, (major)(minor)),
H(6)	3.02 (1H, dd, *J* = 13.5, 2.5 Hz), 2.11 (1H, dd, *J* = 13.5, 10.5 Hz)	2.55-2.44 (2H, m)
H(5)	3.61 (1H, m)	3.79-3.70 (1H, m, (major)(minor))
H(4)	2.02 (1H, m), 1.78 (1H, m)	2.03-1.96 (2H, m)
H(3)	2.58-2.35 (2H, m)	2.35-2.22 (2H, m)
TIPS	1.10-0.95 (21H, m)	1.03-0.99 (21H, m)

^{13}C NMR (75.5 MHz $CDCl_3$)		
	224 δ_H/ppm (Hz)	**246** δ_H/ppm (Hz)
Ar	136.7 (0), 129.9 (1), 128.8 (1), 128.4 (1)	129.6 (1), 129.3 (1), 129.0 (1), 128.6 (1), 114.0 (1), 113.8 (1)
C(12)	-	150.4 (0)
C(11)	-	16.6 (3)
C(10)	40.7 (2)	50.4 (1) (minor), 49.2 (1) (major)
C(9)	127.7 (1)	128.4 (1), 128.1 (1)
C(8)	47.5 (2)	47.6 (2), 47.3 (2)
C(7)	149.7 (0)	150.4 (0)
C(6)	44.4 (2)	42.8 (2), 42.6 (2)
C(5)	55.5 (1)	55.3 (1), 55.1 (1)
C(4)	29.9 (2)	30.2 (2), 30.1 (2)
C(3)	23.7 (2)	24.1 (2), 23.9 (2)
C(2)	174.9 (0)	175.0 (0), 174.8 (0)
TIPS	18.9 (3), 12.2 (1)	19.2 (3), 19.0 (3), 12.4 (1), 12.2 (1)

Figure 13

Similar to coupled product **235** (Table 3) the diastereomeric ratio of **246** was lower than that observed compared to utilising a β-substituent. However, it can be observed (Table 3, Entry 1) the yields have been improved and are now comparable with that previously reported.[109]

A crystal structure of one of the diastereoisomers of **246a** was obtained and X-ray crystallography indicated the (S, S) configuration and *cis* geometry of the double bond, consistent with that reported by Barker.[109] However, crystallisation was difficult and it was not possible to obtain sufficient material for ^{1}H NMR spectroscopy and assignment of the major isomer.



246a

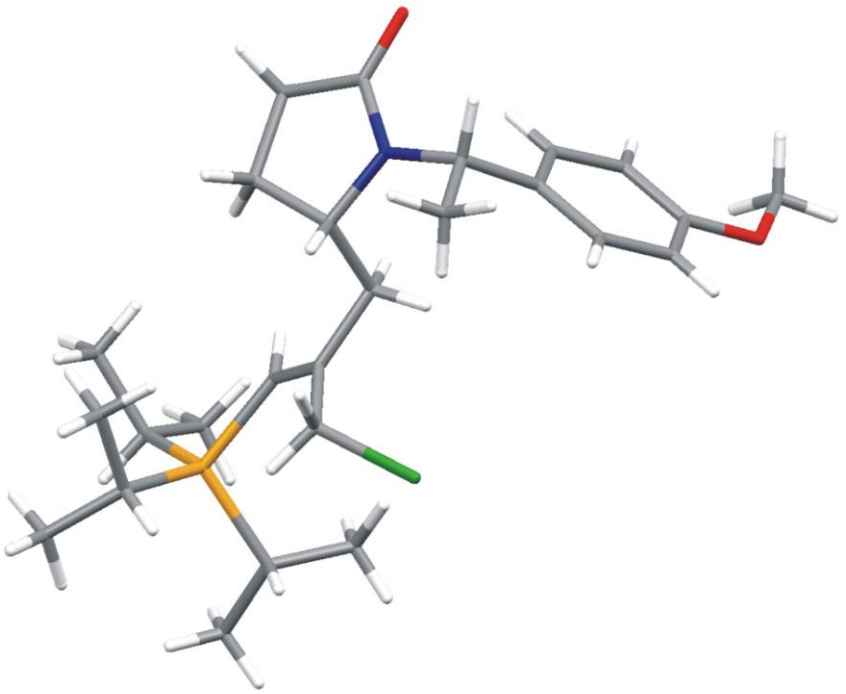
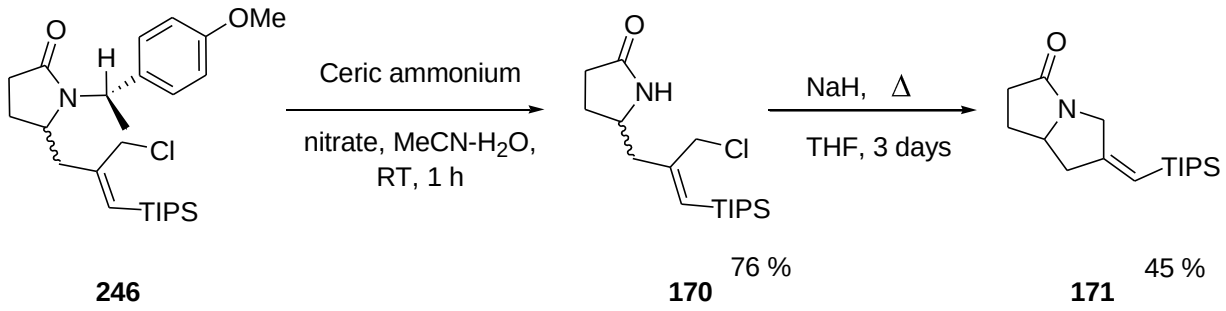


Figure 14 – X-ray crystal strucutre of 246a (see Appendix for full X-ray data)

2.9.3 Removal of the *N*-chiral auxiliary

The mixture of diastereoisomers **246** was treated with cerium(IV) ammonium nitrate utilising a method of Galeazzi *et al*[137] to successfully remove the *N*-chiral group and afford **170** in good yield (Scheme 58), this was then refluxed with sodium hydride to generate the final bicyclic product **171** in moderate yield.



246 **170** 76 % **171** 45 %

Scheme 58

2.10 Conclusions

Initially, it was proposed that a group at the β-position in the pyrrolidinone moiety would have an influence upon the facial selectivity of the attack of the TIPSMCP **151** under Lewis acid conditions, and thus the diastereomeric ratio of the products. This proved to be correct, but the yields obtained were not synthetically viable. It was then devised that an *N*-chiral substitutent would also exhibit an influence upon diastereomeric ratio of the products but result in higher yields. The best example contained a chiral *N*-*p*-methoxybenzyl group, which when coupled TIPSMCP **151** catalysed by tin(IV) tetrachloride formed the coupled product in 64 % yield in a 1:2.3 diastereomeric ratio, a yield more comparable with that previously reported.[109] Although diastereoinduction was disasppointing, a great advantage of this *N*-chiral group was that it was successfully cleaved in excellent yield using CAN, allowing subsequent cyclisation to the bicyclic product **171** (Scheme 58).

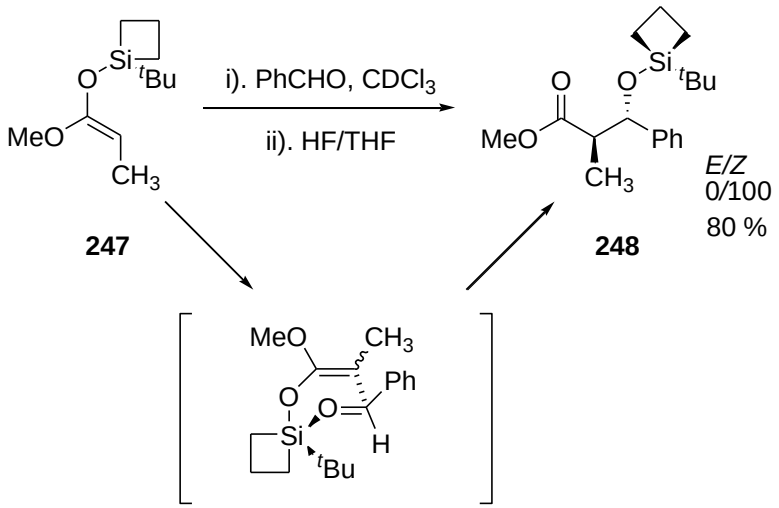
Chapter 3

Influencing the reactivity of silyl-substituted methylenecyclopropane

3.1 Introduction

3.1.1 Enoxysilacyclobutanes

Denmark *et al*[118] has shown that the strain imparted by compressing the tetrahedral silicon atom valencies into a four membered ring is sufficient to promote the coordination of a Lewis basic aldehyde oxygen, such as that shown in **249** (Scheme 59).

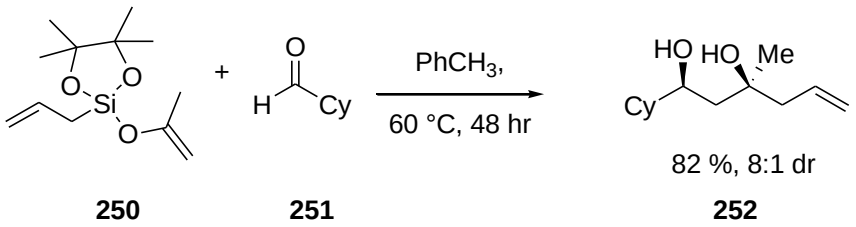


Scheme 59

Denmark exploited this "strain release Lewis acidity" to carry out highly selective aldol reactions of *O*-(silacyclobutyl) ketene acetals, such as **247**, with a variety of aldehydes at room temperature without catalysis (Scheme 59). It was observed that the reaction was dependent on the spectator substituent on the silicon and the geometry of the ketene acetal, also conjugated aldehydes react more rapidly than their aliphatic equivalents. Myers *et al*[138] have also carried out uncatalysed aldol reactions by incorporating silicon into a four-membered ring.

3.1.2 Strained silacycles

Similarly, Leighton *et al*[119,139-142] harnessed the ability of silicon to exhibit Lewis acidity when constrained into a four or five membered ring, for uncatalysed aldol and allylation reactions (Scheme 60).



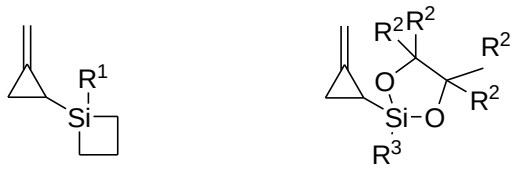
250 **251** **252**

Scheme 60

Leighton showed that ring strain is responsible for reactivity of silacycle **250** as six membered and acyclic equivalents failed to exhibit any reactivity in the same reaction.

3.2 Aims

It was anticipated that applying a similar methodology to Denmark[118] and/or Leighton,[119] to constrain the silicon into a four or five membered ring and synthesising compounds of the type **204** and **205** (Figure 15), would influence the reactivity of the methylenecyclopropane towards electrophiles.

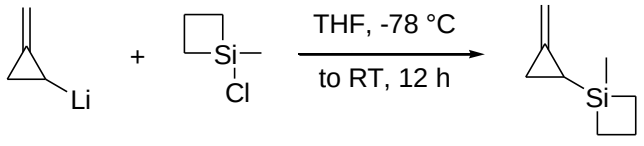


204 **205**

Figure 15

3.3 Synthesis of methylenecyclopropanesilacyclobutane

In an analogous fashion to that shown by Denmark[118] lithiated methylenecyclopropane **13** was coupled with the commercially available methylchlorosilacyclobutane **253** (Scheme 61).



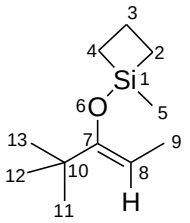
13 **253** **254**

Scheme 61

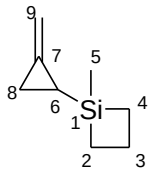
Although evidence from the ^{1}H NMR (300 MHz $CDCl_3$) indicated the coupling had successfully combined the methylenecyclopropane, as indicated by the presence of the MCP alkene peaks at 5.13 and 5.23 ppm in the ^{1}H NMR (300 MHz $CDCl_3$), and silacyclobutane moieties (Figure 16), no clean

compound **254** could be isolated after purification. Several attempts were made at purification by flash column chromatography varying solvent system and preparative thin layer chromatography was also attempted. However, in both instances impurities were too similar in R_f even in the most non-polar solvents to separate from the product.

Shown below is ^{1}H NMR data from the crude product **254** and for comparision a silacyclobutane **255** reported by Denmark[118] (Figure 16).



255



254

^{1}H NMR (300 MHz $CDCl_3$)		
	255 δ_H/ppm (multiplicity/Hz)	**254** δ_H/ppm (multiplicity/Hz)
H(2)	2.00 (2H, m)	1.57-1.39 (2H, m)
H(3)	1.50-1.15 (2H, m)	1.27-1.17 (2H, m)
H(4)	1.50-1.15 (2H, m)	1.00-0.86 (2H, m)
H(5)	0.31 (3H, s)	0.63-0.60 (3H, m)
H(6)	-	2.05 (1H, dd, *J* = 16.4, 7.6 Hz)

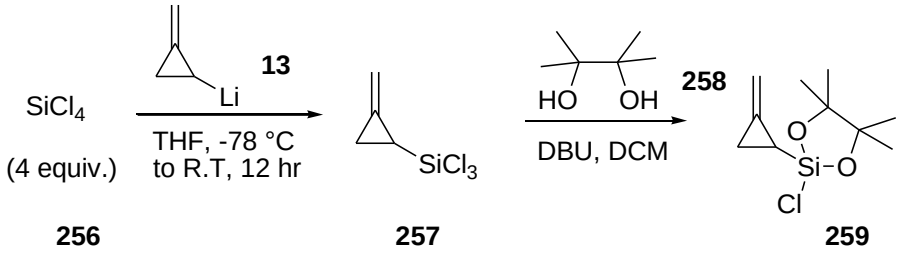
Figure 16

3.4 Synthesis of bis-(methylenecyclopropyl)dioxasila-dispiro[5.0.5.3]pentadecane

Attention was focussed on the work of Leighton *et al*[119] who has shown that the addition of trichloroallylsilane with pinacol in the presence of a base generates allyl pinacolate. This work was of particular appeal due to the known similarities in reactivity of allysilanes and silyl-substituted methylenecyclopropane.[94,106]

Thus, the proposed route, analogous to Leighton,[119] was the cannular dropwise addition of lithiated methylenecyclopropane **13** to an excess (4 equivalents) of silicon tetrachloride **256** to favour, on

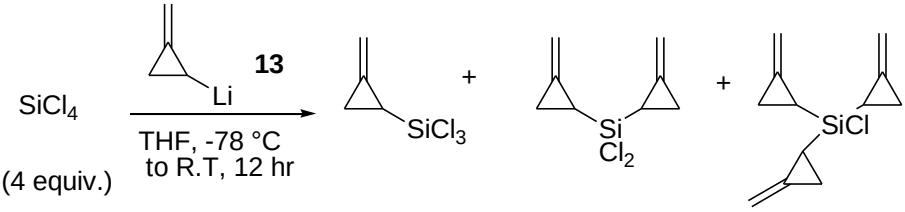
entropic grounds, the mono- product and to generate trichlorosilylmethylenecyclopropane **257**, which upon treatment with pincaol under basic conditions would generate the pinacolate **259** (Scheme 62).



256 **257** **259**

Scheme 62

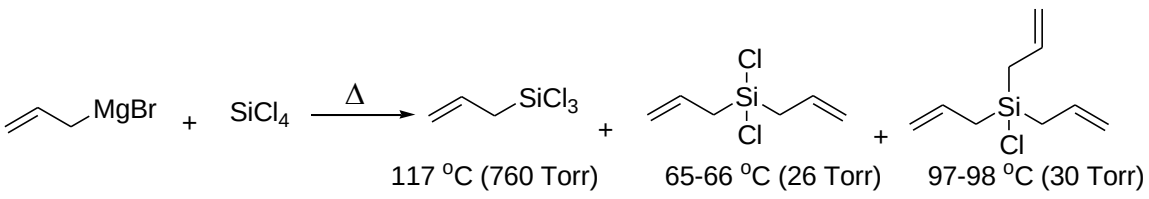
Purification of **257** required distillation to ensure a pure mono methylenecyclopropane product (Scheme 63).



256 **257** **260** **261**

Scheme 63

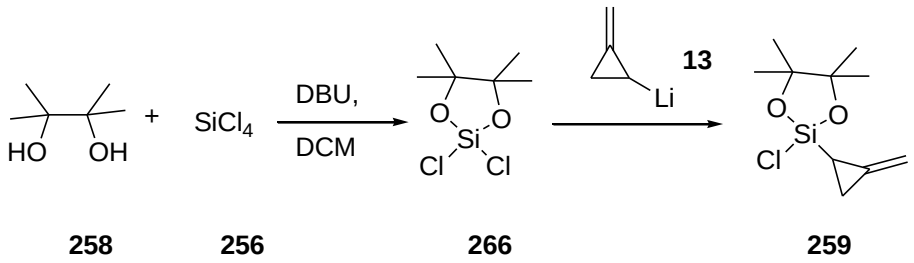
Reverting to the analogous cheaper and more easily synthesised trichloroallylsilane **263**[143-146] allowed the distillation conditions to be optimised without loss of methylenecyclopropane (Scheme 64).



262 **256** **263** **264** **265**

Scheme 64

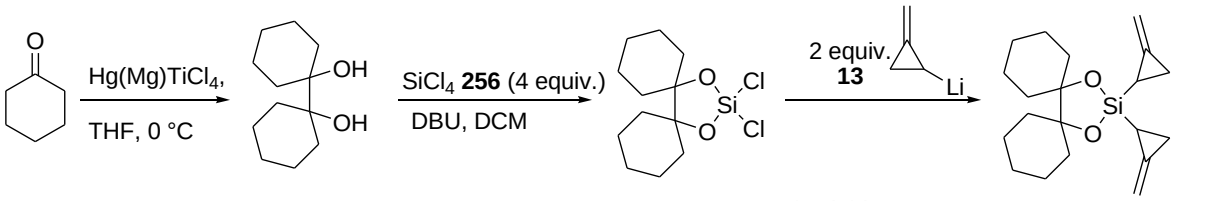
Using these conditions (Scheme 64) for the distillation of **263** resulted in decomposition. Thus, the synthetic route was modified to avoid any distillation. Addition of pinacol to an excess of silicon tetrachloride under basic conditions, followed by the addition of lithiated methylenecyclopropane would avoid the distillation of **263** (Scheme 65).



258 **256** **266** **259**

Scheme 65

Leighton reports[147] that this approach is more successful with the use of bicyclohexyl diol **268**. Accordingly, bicyclohexyl diol **268** was synthesised from the pinacol coupling of cyclohexanone **267**,[148] coupled with an excess of silicon tetrachloride **256** before the dropwise addition of two equivalents of lithiated methylenecyclopropane **13** (Scheme 66). The dichloropinacolate **269** was used without further purification and its formation was inferred from the ^{13}C NMR shift of the quaternary carbons: the quaternary carbon in the dichloro species **269** is 32.4 ppm (75 MHz, $CDCl_3$) compared to 32.2 ppm (75 MHz, $CDCl_3$) in the product **270**.

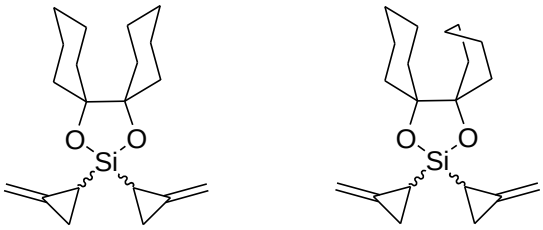


267 **268** **269** **270**

Scheme 66

The purpose of using two equivalents of lithiated methylenecyclopropane was to prevent any easily hydrolysable Si-Cl bonds in the final product and to improve the ease of purification.

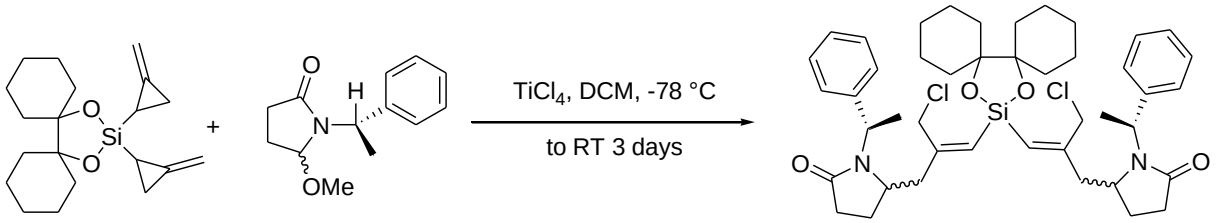
Due to the instability of **270** characterisation proved difficult, it was not possible to obtain HRMS before degradation of the compound. Interpretation of the ^{13}C NMR of **270** can be rationalised by considering, firstly, the different possible conformers of the cyclohexane ring and secondly, that there are a mixture of diastereoisomers. For example, and to illustrate the possibility, shown are two extreme conformers **270a** and **270b**, in reality they may be more complex and their exact conformation is unknown. The two chair conformers adopted in **270a** would result in one set of peaks for the cyclohexyl ring in the ^{13}C NMR, alternatively in **270b** the chair and boat conformers would result in two sets of peaks for the cyclohexyl ring (Figure 7). Indeed, this latter conformation is what is possibly observed (see Chapter 5, page 68-69).



270a **270b**

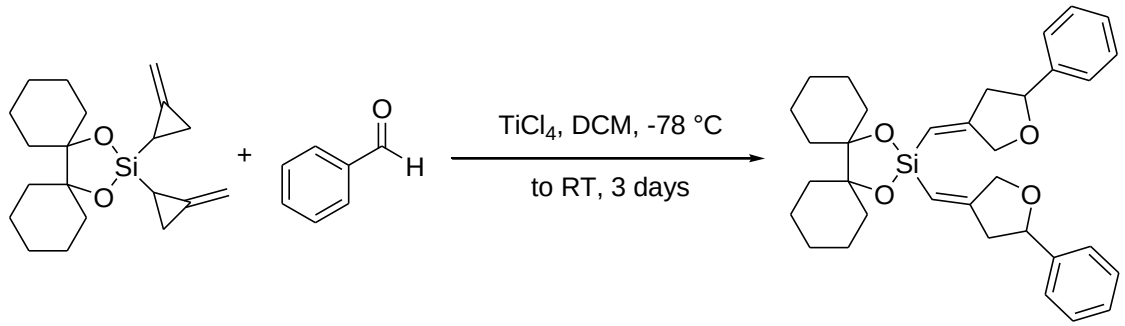
Figure 7

As proof of principle to investigate the reactivity of the novel bis-MCP species, two electrophiles were utilised, methoxypyrrolidinone **231** and benzyaldehyde **68**, in Lewis acid catalysed (Scheme 67 and 68) and uncatalysed reactions.



270 **231** **271**

Scheme 67



270 **68** **272**

Scheme 68

The Lewis acid catalysed reaction (Scheme 67) indicated possible product formation in the crude NMR through the loss of the MCP alkene peaks at 5.30 ppm (^{1}H NMR 300 MHz $CDCl_3$) and formation of alkene peaks at 3.80-3.79 ppm (^{1}H NMR 300 MHz $CDCl_3$) consistent with that shown (Figure 12). However, both uncatalysed reactions returned only starting materials, therefore constraint of silicon in a ring is not a useful strategy in this context and since problems were encountered with purification, this line of investigation was taken no further.

3.5 Conclusions

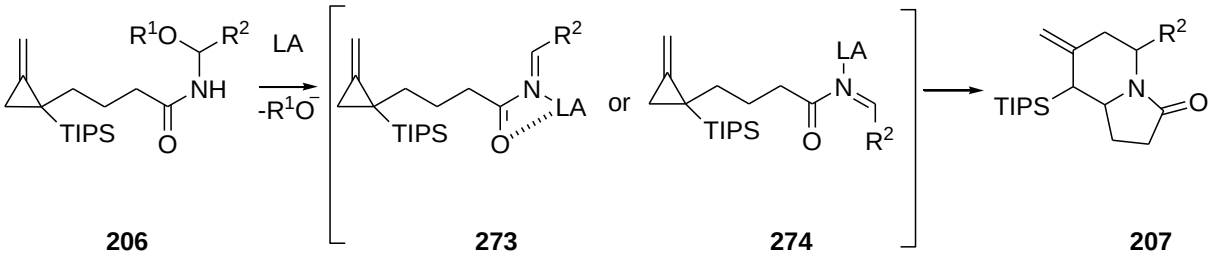
Various strategies to incooperate silicon into a strained system have been attempted, utilising work by Denmark[118] and Leighton.[147] Synthesis of a novel bis- methylenecyclopropane species **270** incorporating the silicon into a strained pinacolate ring has been successfully achieved.

Chapter 4

Intramolecular cyclisations of *N*-acyliminium ions

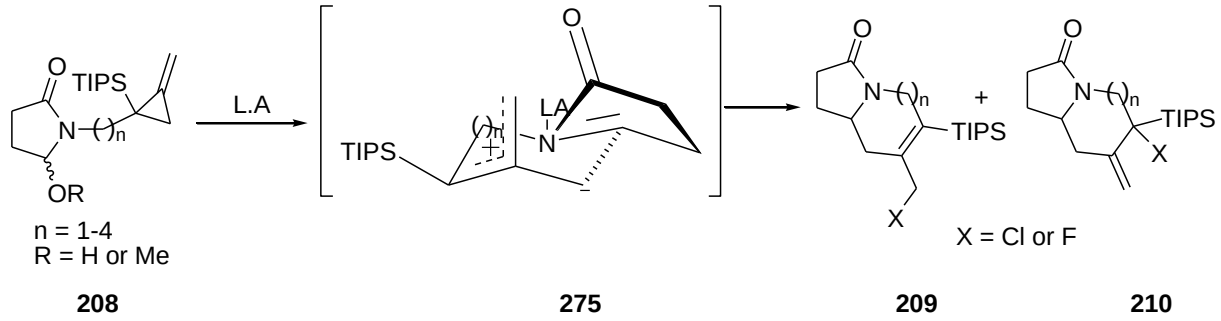
4.1 Aims

It has been shown by the work of Rajamaki[116] that intramolecular cyclisations of silyl-substituted methylenecyclopropane onto imines can be achieved in moderate yield (see Scheme 37). It was the aim of this piece of research to improve the reactivity of such reactions by utilising the more reactive *N*-acyliminium ion over the imine equivalent (of **195** Scheme 37). Under Lewis acid conditions the loss of methoxy group resulting in the formation of *N*-acyliminium ion, which if in the preferred trans-isomer **274** will undergo intramolecular cyclisation to give the bicyclic product **207** (Scheme 69 see also Scheme 37)



Scheme 69

Also on-going was the parallel synthesis of a second precursor for intramolecular cyclisation. Utilising previous work of intermolecular reactions (see Scheme 32), it was envisaged incorporating the silyl-substituted methylenecyclopropane and pyrrolidinone moieties into a single precursor of the type **208** could improve yields the scope of the intermolecular reaction (Scheme 70).



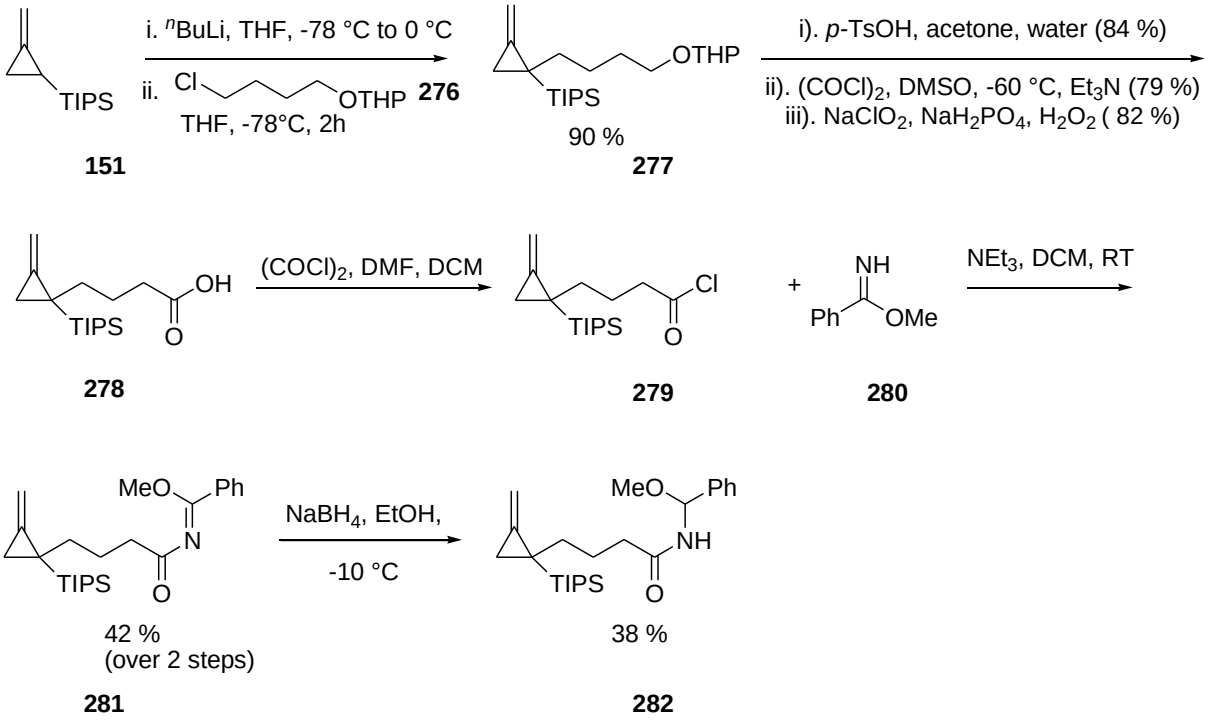
Scheme 70

It was anticipated that under Lewis acid conditions and formation of the *N*-acyliminium ion **275** cyclisation would occur in a favoured endo-trig fashion to give a mixture of isomers **209** and **210** as products (Scheme 70).

Both of these intramolecular cyclisations are of synthetic interest as they generate natural product-like bicyclic structures.

4.2 Synthesis of precursor TIPSMCP-*N*-(methoxy(phenyl)methyl)butanamide

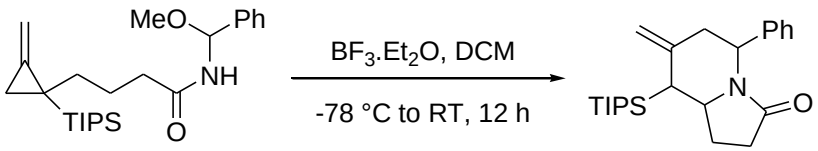
Precursor **282**, analogous to **195** reported by Rajamaki,[117] was successfully sythesised following the described route (Scheme 71). TIPSMCP **151** was lithiated with *n*-butlyllithium solution (1.6 M solution in hexanes) following the procedure of Patient.[107] The lithiated methylenecyclopropane was quenched with the protected alcohol **276**,[149] deprotected to the alcohol, followed by successive oxidations, to the aldehyde,[150] then to the acid **278**,[151] conversion to the acid chloride **279**,[152] coupling with benzyl imidate **280** to give **281**[153] and finally reduction to give **282**[69] (Scheme 71).



Scheme 71

4.3 Intramolecular cyclisation studies with TIPSMCP-*N*-(methoxy(phenyl)methyl)butanamide

The same conditions utilised by Rajamaki[116] were applied but resulted only in decomposition of **282** (Scheme 72).



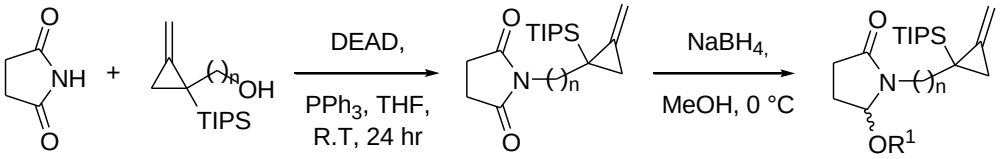
282 **207**

Scheme 72

The reaction was repeated and warmed to +25 °C without formation of the product. The majority of starting material was recovered indicating that possibly for this system a stronger Lewis acid was required to facilitate the desired cyclisation. Due to time constraints various Lewis acids and chain lengths were not fully investigated.

4.4 Synthesis of intramolecular precursors incorporating pyrrolidinone moiety

Precursors incorporating pyrrolidinone and silyl-substituted methylenecyclopropane moieties, suitable for intramolecular cyclisation were successfully synthesised (Scheme 73). Mitsunobu coupling[154] of succinimide **113** and the appropriate alcohol (**286**, **287** or **288**) (synthesised in described manner Scheme 71) afforded the pyrrolidinedione (**286**, **287**, or **288**) followed by partial reduction[69] to give a mixture of hydroxy-(**289**, **291** or **293**) and methoxypyrrolidinones (**290**, **292** or **294**) (Scheme 73).



113

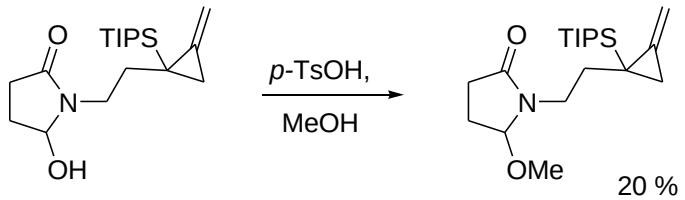
283 n = 2
284 n = 3
285 n = 4

286 n = 2 (88 %)
287 n = 3 (85 %)
288 n = 4 (72 %)

n = 2, R^1 = H (40 %) **289**, Me (39 %) **290**
n = 3, R^1 = H (66 %) **291**, Me (12 %) **292**
n = 4, R^1 = H (69 %) **293**, Me (46 %) **294**

Scheme 73

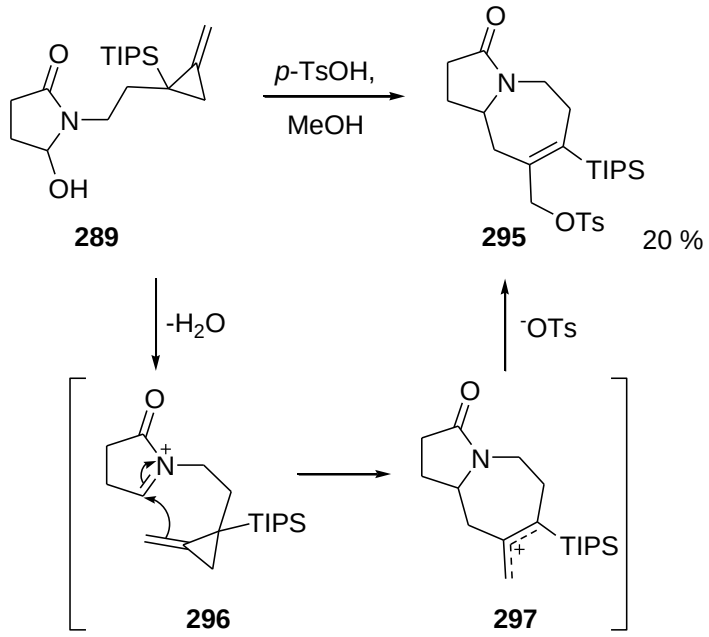
In a similar fashion to the conversion of **279** to **230** or **231** (see Scheme 47) it was of interest to convert hydroxy- **289** to methoxypyrrolidinone **290** utilising the known procedure[134,135] (Scheme 74).



289 **290**

Scheme 74

This resulted in intramolecular cyclisation of **289**, quenching of the cation by the tosylate, to give **295** (Scheme 75).



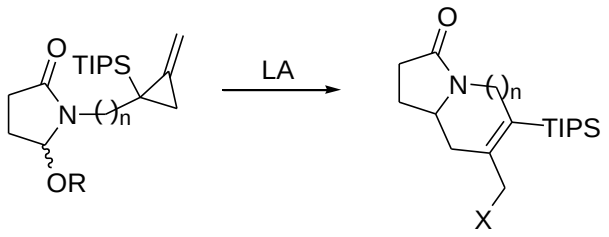
Scheme 75

Formation of the *N*-acyliminium ion **296** is proceeded by the intramolecular cyclisation of the silyl-substituted methylenecyclopropane to give a seven membered ring. The resultant allyl cation **297** is quenched by the tosylate, originating from the acid catalyst to give **295** in modest yield.

4.5 Intramolecular cyclisation studies with precursors incorporating pyrrolidinone moiety

Precursors of the type **208** were placed under Lewis acid conditions[†] and were successfully cyclised intramolecularly in the anticipated fashion (Scheme 76, Table 4).

[†]For R= 4-2 titanium(IV) and tin(IV) tetrachlorides and boron trifluoroetherate were investigated as Lewis acids, only the reactions resulting in clean isolated products have been included in Table 4.



n = 1-4
R = H or Me

209a n = 2 X = Cl
209b n = 2 X = OMe

208 **209**

Scheme 76

Entry	n	R	Conditions[a]	Isolated yield % of 209 (X)[b]
1	3	H	$SnCl_4$, DCM, -78 °C to RT, 12 h	12 (Cl)
2	2	Me	$BF_3.Et_2O$, DCM, -78 °C to RT, 12 h	14 (OMe)
3	2	Me	$SnCl_4$, DCM, -78 °C to RT, 12 h	60 (Cl)
4	2	H	$SnCl_4$, DCM, -78 °C to 5 °C, 3 h	75 (Cl)

[a]Lewis acid (1.5 equiv) was added dropwise to a stirring solution of appropriate starting material in DCM (0.08 M). [b]Product isolated after purification by flash column chromatography.

Table 4

It can be observed that the most favoured cyclisation is the 7-endo-trig, resulting in the cleanest and highest yielding reactions (Table 4 Entries 3 and 4). When n = 4 no product was observed, and starting material was regained; the intramolecular 9-endo-trig cyclisation is less favoured in this case, most likely on entropic and ring strain grounds. The crude yields (Entries 3 and 4) were quantitative, indicated by ^{1}H and ^{13}C NMR, and any loss of yield is a result of the compound's instability on silica during column chromatography. The reaction is best with the stronger Lewis acid tin(IV) chloride and only the most substituted alkene product **209** is observed, both consistent with the intermolecular examples (Scheme 57, Table 3). Also of note is the use of the softer Lewis acid boron trifluoroetherate results in the quenching of the allyl cation by the methoxy leaving group (Table 4 Entry 2): in this case the methoxy group appears to be more nucleophilic and outpace the fluoride anion in attacking the allyl cation. Also the use of leaving group does not appear to influence the yield, comparing (Table 4 Entries 3 and 4). A crystal structure for **209a** was obtained which is consistent with the proposed structure from the NMR data (Figure 18).

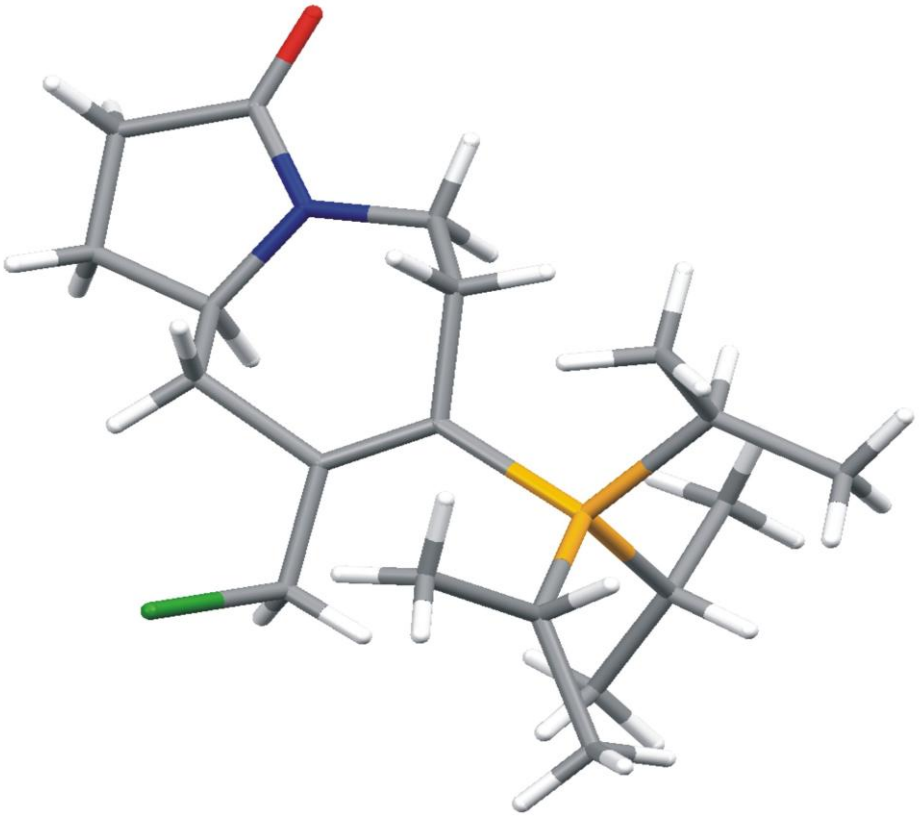


Figure 18 – X-ray crystal structure of 209a (see Appendix for full X-ray data)

4.6 Conclusions

A precusor for intramolecular cyclisation was successfully synthesised, furthering the work of Rajamaki,[116] the scope of this approach was not fully explored. A [5.3.0] bicyclic precursor utilised previous work of intermolecular additions of silyl-substituted methylenecyclopropane to pyrrolidinones and incorporated both moieties into one molecule. This was particularly successful in cyclising in a 7-endo-trig fashion to give a [5.3.0] bicyclic product in high yield and selectivity.

Chapter 5

Experimental

5.1 General experimental

Reactions requiring anhydrous conditions were conducted in oven-dried or flame-dried glassware. For reactions at low temperatures acetone-cardice or liquid nitrogen-ethyl acetate baths were used. Materials were purchased from commercial suppliers. When necessary solvents and materials were purified prior to use, using standard techniques as described by Perrin and Armarego.[155]

All anhydrous solvents were prepared by refluxing with an appropriate drying agent and purification by distillation. THF was distilled from sodium and benzophenone under argon until a persistent purple colour was observed. DCM and triethylamine were distilled from calcium hydride. Petroleum ether was distilled at fractional boiling point between 40 ºC and 60 ºC. Nitroethane was distilled from calcium hydride prior to use. The distilled solvents were taken up using syringe techniques.

Thin layer chromatography was conducted on silica pre-coated plates (Merck silica gel 60 F254, aluminium backed) and the spots were visualised with UV light (254 nm), $KMnO_4$ or phosphomolybdic acid solution. Flash column chromatography was carried out according to the procedure outlined by Still[156] on Sorbil C_{60} 40-60 mesh Silica.

5.2 Instrumentation

Infrared spectra (IR) were obtained on a Mattson Satellite 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) and weak (w). ^1H NMR spectra were recorded on a Bruker AC 300 spectrometer or on a Bruker DPX 400 spectrometer. ^1H NMR peak positions were quoted against the δ scale relative to the residual chloroform singlet (δ 7.26 ppm) using the following abbreviations: singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), quintuplet (quin) and multiplet (m). ^{13}C NMR were obtained on a Bruker AC 300 spectrometer at 75 MHz or Bruker DPX 400 spectrometer at 100 MHz. ^{13}C spectra were proton decoupled and the multiplicities of the signals quoted within the brackets using the following notation: quaternary carbon (0), tertiary (1), secondary (2) and primary (3), as supported by DEPT experiments at 135º. 2D Correleation GOESY, NOE and COSY were carried out on selected compounds to give conclusive assignment of the ^1H and ^{13}C NMR spectra. Coupling constants, *J*, are measured in Hertz (Hz).

Low resolution CI and EI spectra were obtained on a ThermQuest TraceMS gas chromatography mass spectrometer and ES spectra 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 fousing 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 peak intensity and ion found.

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

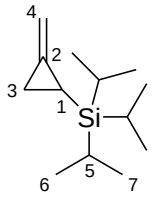
5.3 Experimental for Chapter 2

Compound **113** was synthesised according to the procedure reported by Speckamp *et al*.[69] Compound **212** was synthesised to the procedure reported by Villa *et al*.[120] Compound **214** was synthesised to the procedure reported by Huang *et al*.[121,122] Compound **216** was synthesised to the procedure reported by Yoda *et al*.[123] Compound **217** was synthesised to the procedure reported by Speckamp *et al*.[70,71] Compound **228** was synthesised to the procedure reported by Chihab-Eddine *et al*.[110] Compounds **220** and **221** were synthesised to the procedure reported by Barker *et al*.[125] Compounds **229**, **230** and **231** were synthesised to the procedure reported by Ishibashi *et al*[134]and Arai *et al*.[135]

General procedure **1** ; following that reported by Patient.[107]

To a stirring solution of methylenecyclopropane (1 equiv.) in THF (0.1 M), at -78 °C under a nitrogen atmosphere, was added dropwise *n*-butyllithium solution (1.6 M in hexane) (1 equiv.). The reaction mixture was allowed to warm to 0 °C over 40 min and kept at this temperature for a further 40 min. After cooling to -78 °C the lithiated MCP (yellow solution) was quenched by the dropwise addition of the appropriate trialkyl silyl chloride (1 equiv.). After 5 h at -78 °C and warming to RT over 7 h the reaction mixture was quenched with saturated aqueous ammonium chloride (10 mL required for a 1.0 mmol preparation) and extracted with diethyl ether (3 x 10 mL required for a 1.0 mmol preparation). The combined organic layers were dried with brine (30 mL required for a 1.0 mmol preparation), over magnesium sulfate and concentrated *in vacuo* to give an oil which was purified by flash column chromatography.

Triisopropyl-(2-methylene-cyclopropyl)-silane (**151**):



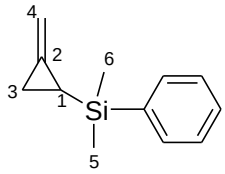
151

Prepared upon 51.86 mmol scale, according to general procedure **1**. Purification by column chromatography (LP) gave the title compound **151** as a colourless oil (9.34 g, 44.43 mmol, 86 %).

FT-IR (oil) ν_{max} = 2941 (b), 2865 (b), 1730 (w), 1463 (m) cm $^{-1}$. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 5.32 (1H, apparent dd, *J* = 2.9, 1.4 Hz, H(4)H_AH_B), 5.22 (1H, apparent dd, *J* = 2.1, 1.1 Hz, H(4)H_AH_B), 1.31-1.24 (2H, m, H(3)H_2), 1.06-0.79 (22H, m, H(1)*H*, H(5)*H*, H(6)H_3, H(7)H_3), 0.64-0.56 (1H, m, H(1)*H*)

ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 134.4 (0), 100.1 (2), 18.4 (3), 11.2 (1), 5.7 (2), 0.01 (1) ppm. **LRMS** (EI): *m/z* (%) = 228.2 (70) $[M+NH_4]^+$.
Data consistent with that reported.[107]

Dimethyl(2-methylenecyclopropyl)phenylsilane (**236**):

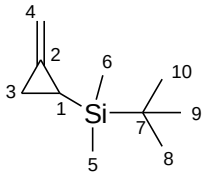


236

Prepared upon 18.48 mmol scale, according to general procedure **1**. Purification by column chromatography (LP) gave the title compound **236** as a colourless oil (1.68 g, 8.93 mmol, 54%). **FT-IR** (oil) ν_{max} = 3069 (w), 2956 (w), 1427 (m), 1113 (m), 831 (s) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 7.49-7.46 (2H, m, Ar), 7.28-7.26 (3H, m, Ar), 5.24-2.23 (1H, m, H(4)H_AH_B), 5.16 – 5.15 (1H, m, H(4)H_AH_B),1.25-1.18 (1H, m, H(3)H_AH_B), 0.87-0.81 (1H, m, H(3)H_AH_B), 0.78-0.68 (1H, m, H(1)*H*), 0.13 (3H, s, H(5)H_3), 0.13 (3H, s, H(6)H_3) ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 138.7 (0), 133.8 (1), 133.7 (1), 129.2 (1), 127.9 (1), 100.8 (2), 5.92 (2), 3.82 (1), -3.86 (3), -4.24 (3) ppm. **LRMS** (EI): *m/z* (%) = 188 (5)$[M]^+$, 173 (50) $[M-CH_3]^+$, 135 (100) $[Si(CH_3)_2Ph]^+$.

Data consistent with that reported.[107]

Tert-butyldimethyl(2-methylenecyclopropyl)silane (**237**):



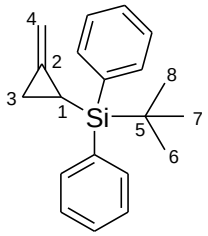
237

Prepared upon 18.48 mmol scale, according to general procedure **1**. Purification by column chromatography (LP) gave the title compound **237** as a colourless oil (1.41g, 8.39 mmol, 50%). **FT-IR** (oil) ν_{max} = 2952 (w), 2928 (w), 2882 (w), 2856 (w), 1780 (w) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 5.31-5.30 (1H, m, H(4)H_AH_B), 5.18-5.17 (1H, m, H(4)H_AH_B), 1.27-1.19 (1H, m, H(3)H_AH_B), 0.94 (10H, m, H(3)H_AH_B, (H(8)H_3)$_3$), 0.67-0.59 (1H, m, H(4)*H*), -0.12 (3H, s, H(5)H_3), -0.14 (3H, s, H(6)H_3)

ppm.**^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 134.3 (0), 100.3 (2), 26.7 (3), 17.2 (0), 5.49 (2), 1.80 (1), -7.56 (3), -7.80 (3) ppm. **LRMS** (EI): *m/z* (%) = 168 (100) $[M]^+$.

Data consistent with that reported.[107]

Tert-butyl(2-methylenecyclopropyl)diphenylsilane (**238**):



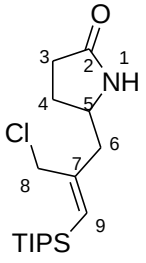
238

Prepared upon 9.24 mmol scale, according to general procedure **1**. Purification by column chromatography (0-10 % of EA in LP) gave the title compound **238** as a colourless oil (510 g, 1.06 mmol, 13%).

FT-IR (oil) ν_{max} = 3071 (w), 2959 (w), 2928 (w), 1109 (m) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H 7.68-7.64 (2H, m, Ar), 7.55-7.34 (2H, m, Ar), 7.33-7.26 (6H, m, Ar), 5.33-5.32 (1H, m, H(1)H_AH_B), 5.30-5.29 (1H, m, H(1)H_AH_B), 1.41-1.34 (1H, m, H(3)H_AH_B), 1.15 (10H, m, H(3)H_AH_B, (H(6)H_3)$_3$), 0.73 (1H, tt, *J* = 7.3, 1.8 Hz, H(4)*H*) ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 136.3 (1), 136.2 (1), 133.9 (0), 133.9 (0), 133.1 (0), 129.3 (1), 129.2 (1), 127.5 (1), 127.4 (1), 101.9 (2), 28.1 (3 x 3), 18.9 (0), 6.24 (2), 0.12 (1) ppm. **LRMS** (EI): *m/z* (%) = 292 (2) $[M]^+$, 235 (100) $[M\text{-}C_4H_9]^+$.

Data consistent with that reported.[107]

5-[(7-Chloromethyl)-3-(1, 1, -triisopropylsilanyl)-2-propenyl]-pyrrolidin-2-one (**170**):



170

Following the method of Galeazzi *et al*.[137]

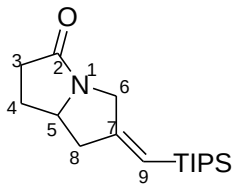
To a stirring solution of pyrrolidinone **246** (30 mg, 0.06 mmol) in acetonitrile (1 mL) was added a solution of CAN (118 mg, 0.21 mmol) in water (1 mL) at RT. After 90 min the reaction mixture was

diluted (5 mL) and extracted (3 x 5 mL) with ethyl acetate. The combined organic layers were washed with brine (30 mL), dried over magnesium sulfate and concentrated *in vacuo* to give an oil which was purified by flash column chromatography (50-100 % of EA in LP) to give the title compound **170** as a colourless oil (15 mg, 0.04 mmol, 73 %).

FT-IR (oil) ν_{max} = 3203 (w), 2942 (m), 2865 (m), 1698 (s), 882 (m) cm^{-1}. **^{1}H NMR** (400 MHz $CDCl_3$) δ_H = 6.04 (1H, brs, N*H*), 5.47 (1H, s, H(9)*H*), 4.04 (2H, d, *J* = 1.0 Hz, H(8)H_AH_B), 3.87 (1H, quin, *J* = 7.0 Hz, H(5)*H*), 2.38-2.32 (2H, m, H(3)H_AH_B), 2.29-2.20 (1H, m, H(4)H_AH_B), 1.83-1.71 (1H, m, H(4)H_AH_B), 1.04-1.02 (21H, m, Si(C*H*(CH_3)$_2$)$_3$) ppm. **^{13}C NMR** (100 MHz $CDCl_3$) δ_C = 177.9 (0), 150.2 (0), 129.1 (1), 52.6 (1), 47.8 (2), 44.4 (2), 30.2 (2), 27.2 (2), 19.0 (6 x 3), 12.1 (1) ppm. **LRMS** (ES+): *m/z* (%) = 681.6 (20) $[2M+Na]^+$, 393.3 (100) $[M+Na+MeCN]^+$.

Data consistent with that reported.[109]

9-[(Triisopropylsilanyl)-methylene]-hexahydropyrrolizin-2-one (**171**):



171

Following the method of Barker.[109]

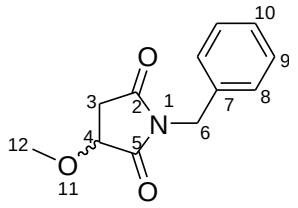
To a stirring solution of sodium hydride (60 % in mineral oil, 12.2 mg, 0.30 mmol) in THF (2.5 mL), at RT under a nitrogen atmosphere, was added dropwise a solution of pyrrolidinone **170** (50 mg, 0.15 mmol) in THF (2.5 mL), which was then set to reflux for 72 h. Upon cooling the reaction mixture was quenched by the slow addition of water (1 mL) and extracted with ether (3 x 10 mL). The aqueous layer was neutralised (2M HCl) and extracted with ether (3 x 10 mL). The combined organic layers were washed with brine (30 mL), dried over magnesium sulfate and concentrated *in vacuo* to give a yellow oil which was purified by flash column chromatography (20-30 % of EA in LP) to give the title compound **171** as a colourless oil (20 mg, 0.06 mmol, 45 %).

FT-IR (oil) ν_{max} = 2940 (m), 2863 (m), 1694 (s), 1298 (m), 881 (m) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 5.52-5.51 (1H, s, C(9)*H*), 4.19 (1H, d, *J* = 16.4 Hz, C(6)H_AH_B), 3.98 (1H, m, C(5)*H*), 3.65-3.59 (1H, m, C(6)H_AH_B), 2.76-2.64 (2H, m, C(8)H_AH_B, C(3)H_AH_B), 2.49-2.29 (3H, m, C(8)H_AH_B, C(3)H_AH_B, C(4)H_AH_B), 1.83-1.72 (1H, m, C(4)H_AH_B), 1.03-1.02 (21H, m, (Si(C*H*(CH_3)$_2$)$_3$)) ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 174.0 (0), 156.0 (0), 118.8 (1), 60.3 (1), 46.3 (2), 44.8 (2), 34.3 (2), 27.3 (2), 18.7

(6x3), 11.6 (1) ppm. **LRMS** (EI): *m/z* (%) = 250 (100)[M-CH(CH_3)$_2$)]$^+$. **LRMS** (ES+): *m/z* (%) = 609 (100) [2M+Na]$^+$, 294 (20) [M+H]$^+$.

Data consistent with that reported.[109]

1-Benzyl-4-methoxy-pyrrolidine-2,5-dione (**213**):



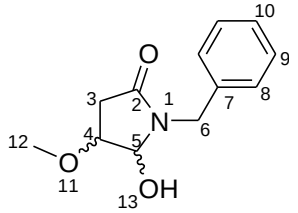
213

Following the modified procedure of Huang.[122]

To a stirring solution of **212** (70.0 mg, 0.82 mmol) in diethyl ether (10 mL), at RT under a nitrogen atmosphere and in dark conditions, was added successively silver oxide (768 mg, 3.31 mmol) and methyl iodide (206 µL, 3.31 mmol). After 72 h the reaction mixture was filtered through celite™, washed with water (10 mL) and brine (20 mL). The combined organic layers were dried over magnesium sulfate, concentrated *in vacuo* and the crude residue purified by flash column chromatography (0-17 % of EA in LP) to give the title compound **213** as an oil (110 mg, 0.50 mmol, 61%).

FT-IR (oil) ν_{max} = 2936 (m), 2831 (m), 1701 (s) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 7.28-7.26 (5H, m, Ar), 4.65 (2H, m, H(6)H_AH_B), 4.19 (1H, dd, *J* = 8.2, 4.2 Hz, H(4)*H*), 3.60 (3H, s, H(12)H_3), 2.99 (1H, dd, *J* =18.1, 8.2 Hz, H(3)H_AH_B), 2.62 (1H, dd, *J* =18.1, 4.2 Hz, H(3)H_AH_B) ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C= 175.6 (0), 174.0 (0), 135.7 (0), 129.0 (1), 129.0 (1), 128.3 (1), 75.1 (3), 59.2 (1), 42.5 (2), 36.2 (2) ppm. **LRMS** (ES+): *m/z* (%) = 242 (100) [M+Na]$^+$. **HRMS** (ES+): *m/z* $C_{12}H_{14}N_1O_3$ [M+H]$^+$ requires 220.0968, found 220.0964.

1-Benzyl-5-hydroxy-4-methoxy-pyrrolidin-2-one (**215**):



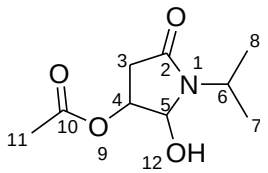
215

Following a modified method of Speckamp *et al*.[69]

To a stirring solution of **213** (110 mg, 0.50 mmol) in methanol (5 mL), at 0 °C under a nitrogen atmosphere, was added sodium borohydride (66.5 mg, 1.75 mmol). After 20 min the reaction mixture was quenched dropwise with saturated aqueous sodium bicarbonate (5 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried over magnesium sulfate, concentrated *in vacuo* and the resultant crude residue was purified by flash column chromatography (40-70 % of EA in LP) to give the title compound **215** as an oil (80 mg, 0.36 mmol, 72 %); reported as a 1 : 2.9 mixture of diastereoisomers (^{1}H NMR 300MHz $CDCl_3$).

FT-IR (oil) ν_{max} = 3350 (m), 2931 (m), 1670 (s) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 7.29-7.27 (5H, m, Ar (major)(minor)), 5.00-4.96 (1H, m, H(5)*H* (major)), 4.92-4.81 (1H, m, H(6)H_AH_B (major)(minor)), 4.23 (1H, d, *J* = 14.6, H(6)H_AH_B (minor)), 4.15 (1H, d, *J* = 14.6, H(6)H_AH_B (major)), 3.88 (1H, dd, *J* = 11.7, 5.1 Hz, H(4)H_AH_B), 3.78-3.75 (1H, m, H(4)H_AH_B), 3.52-3.50 (1H, d, *J* = 8.4 Hz, H(3)H_AH_B (major), 3.41 (3H, s, H(12)H_3 (major)), 3.32 (3H, s, H(12)H_3 (minor)), 2.82 (1H, dd, *J* = 17.5, 6.9 Hz, H(3)H_AH_B (minor)), 2.57-2.53 (1H, m, H(3)H_AH_B (major)(minor)) ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 171.4 (0), 136.7 (0), 129.0 (1), 128.9 (1), 128.8 (1), 128.3 (1), 127.9 (1), 81.3 (1) (major), 81.0 (1) (minor), 74.2 (3), 58.0 (1) (major), 57.2 (1) (minor), 43.7 (2), 36.2 (2) (minor), 35.8 (major) (2) ppm. **LRMS** (ES+): *m/z* (%) = 285.2 (50) $[M+Na+MeCN]^+$, 222.2 (100) $[M+H]^+$. **HRMS** (ES+): *m/z* $C_{12}H_{15}N_1Na_1O_3$ $[M+Na]^+$ requires 244.0944, found 244.0950.

4-Acetoxy-5-hydroxy-1-isopropyl-2-pyrrolidinone (**218**):



218

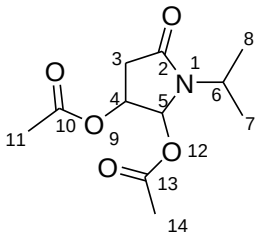
Following the method of Klaver *et al*.[70]

To a stirring solution of **217** (5.00 g, 0.025 mol) in ethanol (250 mL), at 0 °C under a nitrogen atmosphere, was added sodium borohydride (0.95 g, 0.025 mol) in two equal portions over 2 h. After a further 1 h the reaction mixture was cooled to -20 °C, acidified (pH 3) with hydrochloric acid (2 M) and poured into a mixture of saturated aqueous sodium bicarbonate (50 mL) and DCM (130 mL). After extracting with DCM (3 x 200 mL), the combined organic layers were washed with brine (200 mL), dried over magnesium sulfate and concentrated *in vacuo* to give a colourless oil. Purification by flash column chromatography (0-2 % of MeOH in DCM) yielded a white solid (1.66 g, 8.25 mmol) which

was recrystallised (chloroform/hexane) to give the title compound **218** as a white solid (640 mg, 3.18 mmol, 13 %); reported as one diastereoisomer (^{1}H NMR 300MHz $CDCl_3$).

Melting point = 89-94 °C. **FT-IR** (solid) ν_{max} = 3143 (b), 1737(s), 1652 (s) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 5.43-5.39 (1H, m, H(5)*H*), 5.05 (1H, dt, *J* = 8.4, 5.3 Hz, H(4)*H*), 4.22 (1H, septet, *J* = 6.9 Hz, H(6)*H*), 3.30 (1H, d, *J* = 7.3 Hz, O*H*), 2.63 (2H, d, *J* = 8.1 Hz, H(3)H_AH_B), 2.12 (3H, s, H(10)H_3), 1.27 (3H, d, *J* = 6.9 Hz, H(7)H_3), 1.24 (3H, d, *J* = 6.9 Hz, H(8)H_3) ppm.**^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 170.7 (0), 170.6 (0), 80.0 (1), 68.1 (1), 43.8 (1), 34.8 (2), 22.0 (3), 20.8 (3), 19.8 (3) ppm. **LRMS** (ES+): *m/z* (%) = 224.2 (15) $[M+Na]^+$, 202.2 (100) $[M+H]^+$. **HRMS** (ES+): *m/z* $C_9H_{16}N_1O_4$ $[M+H]^+$ requires 202.1074, found 202.1072.

4,5-Bisacetoxy-1-isopropyl-2-pyrrolidinone (**298**):



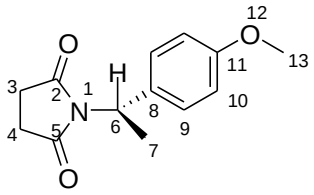
298

Following the method of Kumareswaren *et al*.[124]

To a stirring solution of **218** (300 mg, 1.49 mmol) in DCM (4 mL), at RT under an atmosphere of nitrogen, was successively added pyridine (152 μL, 1.86 mmol), DMAP (18 mg, 0.14 mmol) and acetic anhydride (176 μL, 1.86 mmol). After 2 h the reaction mixture was diluted with DCM (10 mL), washed with water (3 x 4 mL) and then brine (4 mL). The combined organic layers were washed with brine (20 mL), dried over magnesium sulfate and concentrated *in vacuo* to give a white solid which was purified by flash column chromatography (DCM) to give the title compound **298** as a white solid (290 mg, 1.19 mmol, 80 %); reported as one diastereoisomer (^{1}H NMR 300MHz $CDCl_3$).

Melting point = 81-85 °C. **FT-IR** (solid) ν_{max} = 1748 (s), 1702 (s), 2986 (w), 1201 (s), 881 (w) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 6.43 (1H, d, *J* = 5.1 Hz, H(5)*H*), 5.27 (1H, ddd, *J* = 9.5, 8.4, 5.1 Hz, H(4)*H*), 4.25 (1H, septet, *J* = 7.0 Hz, H(6)*H*), 2.68 (1H, dd, *J* = 16.4, 8.4 Hz, H(3)H_AH_B), 2.59 (1H, dd, *J* = 16.4, 9.5 Hz, H(3)H_AH_B), 2.07 (3H, s, H(12)H_3), 2.02 (3H, s, H(10)H_3), 1.18 (3H, d, *J* = 6.8 Hz, H(7)H_3), 1.14 (3H, d, *J* = 6.8 Hz, H(8)H_3) pmm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 171.2 (0), 169.9 (0), 169.7 (0), 85.1 (1), 66.2 (1), 43.6 (1), 34.2 (2), 21.0 (3), 20.9 (3), 20.7 (3), 20.4 (3) ppm. **LRMS** (ES+): *m/z* (%) = 244.2 (100) $[M+H]^+$.

(*S*)-1-[Methoxy-phenyl)-ethyl]-pyrrolidine-2,5-dione (**228**):



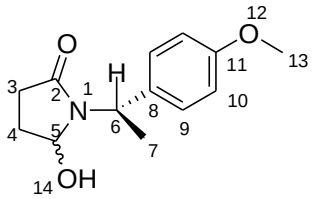
228

Following the method of Chihab-Eddine *et al*.[110]

Succinic anhydride **226** (1.69 g, 16.9 mmol) and (*S*)-(-)-α- methoxymethylbenzyl amine **227** (2.56 g, 16.9 mmol) were refluxed for 12 h. Upon cooling the reaction mixture was dissolved in ether (20 mL) and washed with saturated aqueous sodium bicarbonate (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried over magnesium sulfate and concentrated *in vacuo* to give a white solid which was purified by flash column chromatography (20-60 % of EA in LP) to give the title compound **228** as a white solid (1.94 g, 8.32 mmol, 98 %).

Melting point = 61-63 °C. **FT-IR** (solid) ν_{max} = 2941 (m), 2841(w), 1687 (s) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 7.41-7.38 (2H, m, Ar), 6.85-6.82 (2H, m, Ar), 5.37 (1H, q, *J* = 7.3 Hz, H(6)*H*), 3.78 (3H, s, H(13)H_3), 2.61 (4H, m, H(3)H_AH_B, H(4)H_AH_B), 1.77 (3H, d, *J* = 7.3 Hz, H(7)H_3) ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 177.1 (0), 159.2 (0), 131.9 (0), 129.1 (1), 114.0 (1), 113.7 (1), 55.3 (1), 49.9 (3), 28.1 (2 x 2), 16.8 (3) ppm. **LRMS** (ES+): *m/z* (%) = 256 (100) $[M+Na]^+$. **HRMS** (ES+): *m/z* $C_{12}H_{13}O_1N_1$ $[M+H]^+$ requires 187.9971, found 187.9888.

(*S*)-5-Hydroxy-1-[1-(methoxyphenyl)ethyl]-pyrrolidin-2-one (**229**):



229

Following a modified method of Speckamp *et al*.[69]

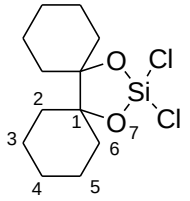
To a stirring solution of pyrrolidinedione **228** (1.84 g, 7.89 mmol) in methanol (80 mL), at 0 °C under a nitrogen atmosphere, was added sodium borohydride (2.24 g, 59.2 mmol). After 1 h the reaction mixture was quenched by the dropwise addition of saturated aqueous sodium bicarbonate (20 mL) and after stirring for 20 min at 0 °C the reaction mixture was extracted with DCM (3 x 100 mL). The combined organic layers were washed with brine (300 mL), dried over magnesium sulfate, concentrated

in vacuo and the crude oil was purified by flash column chromatography (50-75 % of EA in LP) to give the title compound **229** as a white solid (1.36 g, 5.78 mmol, 73 %); reported as a 1: 0.70 mixture of diastereoisomers (^{1}H NMR 300 MHz $CDCl_3$).

Melting point = 72-74 °C. **FT-IR** (solid) ν_{max} = 3275 (w), 2973 (w), 1648 (s) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 7.28-7.16 (2H, m, Ar), 6.76 (2H, m, Ar), 5.27-5.24 (1H, m, H(5)*H* (minor)), 5.22-5.18 (1H, m, H(5)*H* (major)), 4.80 (1H, m, O*H* (major)), 3.68 (3H, s, H(13)H_3 (major or minor)), 3.67 (3H, s, H(13)H_3 (major or minor)), 3.08 (1H, br s, O*H* (minor)), 2.58-2.43 (1H, m, H(6)H_3), 2.20-2.11 (1H, m, H(3)H_AH_B), 2.07-1.92 (1H, m, H(4)H_AH_B), 1.78-1.67 (1H, m, H(4)H_AH_B), 1.53 (3H, d, *J* = 7.0 Hz, H(7)H_3 (major)), 1.49 (3H, d, *J* = 7.0 Hz, H(7)H_3 (minor)) ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 174.9 (0), 174.6 (0), 159.2 (0), 159.1 (0), 133.2 (0), 132.0 (0), 128.9 (1), 128.7 (1), 114.3 (0), 114.0 (0), 82.3 (1) (major), 81.6 (1) (minor), 55.4 (3), 49.9 (1) (major), 49.3 (1) (minor), 29.2 (2), 28.9 (2), 28.4 (2), 19.0 (3), 17.4 (3) ppm. **LRMS** (EI): *m/z* (%) = 187 (40) $[M\text{-}OH]^+$, 105 (100) $[C_8H_9]^+$. **HRMS** (EI): *m/z* $C_{13}H_{15}N_1Na_1O_3$ $[M+Na]^+$ requires 256.0944, found 256.0939.

5.4 Experimental for Chapter 3

Dichloro-13,15-dioxa-14-sila-dispiro[5.0.5.3]pentadecane (**269**):

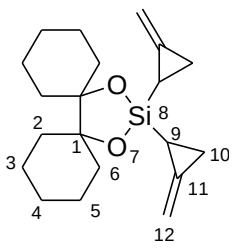


269

Following the method of Leighton *et al*.[147]

To a cooled (0 ºC) solution of silicon tetrachloride **256** (872 μL, 7.62 mmol) in DCM (10 mL) under an atmosphere of nitrogen was added DBU (791 μL, 5.29 mmol). A solution of diol **16** (500 mg, 2.52 mmol) in DCM (5 mL) was added at RT and the reaction mixture allowed to stir for 12 h. The mixture was then concentrated and the remaining residue taken up in ether (20 mL) and allowed to stir at RT under an atmosphere of nitrogen for 2 h. Pentane (30 mL) was then added and the mixture stirred for an additional 2 h. The mixture was then filtered and concentrated *in vacuo* to yield the title compound **269** as an oil (350 mg, 1.18 mmol, 47 %), which was used without further purification.

Bis-(methylenecyclopropyl)dioxasila-dispiro[5.0.5.3]pentadecane (**270**):



270

To a stirring solution of methylenecyclopropane **4** (1.47 M in THF) (4.88 mL, 7.18 mmol) in THF (10 mL) at -78 °C under an atmosphere of nitrogen, was added dropwise *n*-butyllithium solution (1.6 M in hexane) (4.03 mL, 6.46 mmol). The reaction mixture was allowed to warm to 0 °C over a period of 40 min and kept at this temperature for further 40 min. Upon cooling to -78 °C a solution of dichloropinacolate **269** (1.06 g, 3.59 mmol) in THF (9 mL), at -78 °C under an atmosphere of nitrogen, was added dropwise *via* cannular syringe. The reaction mixture was allowed to reach RT over 12 h. The pale yellow reaction mixture was quenched with saturated aqueous ammonium chloride (10 mL), extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried

over magnesium sulfate and concentrating *in vacuo* to give a colourless oil which was purified by flash column chromatography (LP) to give the title compound **270** as a colourless oil (440 mg, 1.33 mmol, 21 %).

FT-IR (oil) ν_{max} = 2927 (m), 2855 (w) cm^{-1}. **^{1}H NMR** (400 MHz $CDCl_3$) δ_H = 5.50-5.22 (4H, m, H(10)H_A*H_B*), 1.67-0.85 (20H, m, H(2, 3, 4, 5, 6)*H_A*H_B*, 0.75-0.61 (2H, m, H(7)*H*), 0.12-0.00 (2H, m, H(8)*H_A*H_B*) ppm. **^{13}C NMR** (100 MHz $CDCl_3$) δ_C = 131.7 (0), 131.4 (0), 101.9 (2), 101.6 (2), 82.8 (0), 82.4 (0), 32.9 (2), 32.8 (2), 32.8 (2), 32.7 (2), 29.8 (2), 26.0 (2), 25.2 (2), 22.2 (2), 22.2 (2), 14.3 (2), 6.71 (2), 6.48 (2), 4.03 (2) 2.71 (1), 2.52 (1) ppm. **LRMS** (EI): *m/z* (%) = 330 (8) $[M+H]^+$, 247 (21) $[M-C_6H_5]^+$.

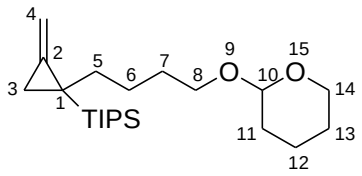
5.5 Experimental for Chapter 4

NMR data for compounds **289**, **290**, **292**, **293** has been included (see Appendix 2 – NMR data) for comparison to the assignments in the ^{1}H and ^{13}C NMR.

General procedure **2**; following that reported by Rajamaki.[117]

To a stirring solution of TIPSMCP **151** (1 equiv.) in THF (0.1 M), at -78 °C under a nitrogen atmosphere, was added dropwise *n*-butyllithium solution (1.6 M in hexane) (1 equiv.). The reaction mixture was allowed to warm to 10 °C over a period of 40 min and kept at this temperature for a further 40 min. After cooling to -78 °C the lithiated MCP **13** was quenched by the dropwise addition of the appropriate protected alcohol (1 equiv.) in THF (0.1 M). After 5 h at -78 °C and warming to RT over 7 h the reaction mixture was quenched with saturated aqueous ammonium chloride (10 mL required for a 1.0 mmol preparation) and extracted with diethyl ether (3 x 10 mL required for a 1.0 mmol preparation). The combined organic layers were dried with brine, over magnesium sulfate and concentrated *in vacuo* to give an oil which was purified by flash column chromatography.

Triisopropyl-{2-methylene-1-[6-(tetrahydropyran-7-yloxy)-butyl]-cyclopropyl}-silane (**277**):



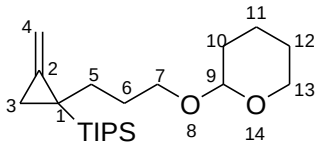
n = 4

277

Prepared upon 8.01 mmol scale, according to general procedure **2**. Purification by column chromatography (0-7 % of EA in LP) gave the title compound **277** as a colourless oil (n = 4, 2.02 g, 5.51 mmol, 69 %); reported as 1 : 0.8 diastereoisomer (^{13}C NMR 300 MHz $CDCl_3$).

FT-IR (oil) ν_{max} = 2940 (b), 2869 (b), 1153 (m), 1075 (m) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 5.32 (1H, m, H(4)H_AH_B), 5.21-5.20 (1H, m, H(4)H_AH_B), 4.56-3.80 (1H, m, H(10)*H*), 3.88-3.80 (1H, m, H(4)H_AH_B), 3.72-3.63 (1H, m, H(8)H_AH_B), 3.50-3.46 (1H, m, H(4)H_AH_B), 3.36-3.29 (1H, m, H(8)H_AH_B), 1.59-1.47 (12H, m, H(5, 6, 7, 11, 12, 13)H_AH_B), 1.23-1.20 (1H, m, H(3)H_AH_B), 1.10 (21H, m, Si(C*H*(CH_3)$_2$)$_3$), 0.91-0.88 (1H, m, H(3)H_AH_B) ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$)δ_C = 139.4 (0), 101.7 (2), 101.7 (2), 98.8 (1), 67.4 (2), 62.2 (2), 34.8 (2), 34.7 (2), 30.8 (2), 30.2 (2), 25.6 (2), 22.4 (2), 22.4 (2), 19.6 (2), 19.4 (6 x 3), 18.0 (0), 12.2 (2), 12.0 (3 x 1) ppm. **LRMS** (ES+): *m/z* (%) = 389 (100) $[M+Na]^+$. **HRMS** (ES+): *m/z* $C_{22}H_{43}O_2Si$ $[M+H]^+$ requires 367.3027, found 367.3032.

Triisopropyl(2-methylene-1-(3-(tetrahydro-2H-pyran-2-yloxy) propyl)cyclopropyl)silane (**299**):

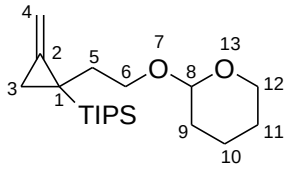


n = 3

299

Prepared upon 13.57 mmol scale, according to general procedure **2**. Purification by column chromatography (0-3.5 % of EA in LP) gave the title compound **299** as a colourless oil (n = 3, 3.82 g, 10.8 mmol, 80 %); reported as a 1 : 0.4 mixture of diastereoisomers (^{1}H NMR 300 MHz $CDCl_3$).
FT-IR (oil) ν_{max} = 2941 (m), 2865 (s), 1464 (s) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H 5.34 (1H, m, H(4)H_AH_B), 5.22 (1H, m, H(4)H_AH_B), 4.55-4.52 (1H, m, H(9)*H*), 3.86-3.79 (1H, m, H(13)H_AH_B), 3.66-3.59 (1H, m, H(7)H_AH_B), 3.52-3.44 (1H, m, H(13)H_AH_B), 3.33-3.26 (1H, m, H(7)H_AH_B), 1.68-1.47 (10H, m, H(5, 6, 10, 11, 12)H_AH_B), 1.23 (1H, m, H(3)H_AH_B), 1.09 (22H, m, H(3)H_AH_B, Si(C*H*(CH_3)$_2$)$_3$) ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 139.1 (0), 139.1 (1), 102.0 (2), 101.9 (1), 98.9 (1), 98.7 (1), 67.9 (2), 67.8 (2), 62.3 (2), 62.3 (2), 33.0 (2), 31.1 (2), 30.8 (2), 28.3 (2), 25.8 (2), 25.6 (2), 23.9 (2), 19.6 (6 x 3), 19.3 (6 x 3), 18.8 (0), 11.9 (3 x 1) ppm. **LRMS** (ES+): *m/z* (%) = 375 (100) $[M+Na]^+$. **HRMS** (ES+): *m/z* $C_{21}H_{41}O_2Si$ $[M+H]^+$ requires 353.2870, found 353.2876.

Triisopropyl(2-methylene-1-(8-(tetrahydropyran-9-yloxy)ethyl)cyclopropyl)silane (**300**):



n = 2

300

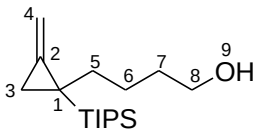
Prepared upon 13.57 mmol scale, according to general procedure **2**. Purification by column chromatography (0-4.5 % of EA in LP) gave the title compound **300** as a colourless oil (n = 2, 3.35 g, 9.90mmol, 73 %); reported as 1 : 0.80 mixture of diastereoisomers (^{13}C NMR 300 MHz $CDCl_3$).
FT-IR (oil) ν_{max} = 2941 (m), 2865 (m), 1464 (s) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 5.36 (1H, m, H(4)H_AH_B), 5.25-5.24 (1H, m, H(4)H_AH_B), 4.50 (1H, m, H(8)*H*), 3.86-3.79 (1H, m, H(12)H_AH_B), 3.72-3.64 (1H, m, H(6)H_AH_B), 3.50-3.43 (1H, m, H(12)H_AH_B), 3.32-3.18 (1H, m, H(6)H_AH_B), 1.51-1.93 (8H, m, H(5, 9, 10, 11) H_AH_B), 1.28-1.25 (1H, H(3)H_AH_B), 1.10 (22H, H(3)H_AH_B, Si(C*H*(CH_3)$_2$)$_3$) ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 138.5 (0), 138.4 (0), 102.4 (2), 102.3 (2), 99.0 (1), 99.0 (1), 65.3 (2), 65.0

(2), 62.4 (2), 62.3 (2), 33.8 (2), 33.7 (2), 30.9 (2), 25.6 (2), 19.7 (2), 19.5 (3), 19.4 (0), 18.0 (0), 12.4 (3), 12.6 (3), 11.5 (1) ppm. **LRMS** (ES+): *m/z* (%) = 361.3 (100) $[M+Na]^+$. **HRMS** (ES+): *m/z* $C_{20}H_{38}Na_1O_2Si$ $[M+Na]^+$ requires 361.2533, found 361.2533.

General procedure **3** ; following that reported by Rajamaki.[117]

A solution of protected alcohol (1 equiv.) in methanol (0.1 M) was refluxed (65 °C) in the presence of amberlite IR-120 (100 % wt). After 48 h the reaction mixture was filtered and concentrated *in vacuo* and the resulting oil purified by flash column chromatography.

4-(1-(Triisopropylsilyl)-2-methylenecyclopropyl)butan-1-ol (**285**):



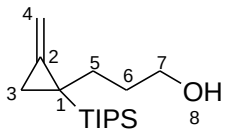
n = 4

285

Prepared upon 5.51 mmol scale, according to general procedure **3**. Purification by column chromatography (5-8 % of EA in LP) gave the title compound **285** as a colourless oil (n = 4, 780 mg, 2.76 mmol, 50 %).

FT-IR (oil) ν_{max} = 3315 (b), 3940 (s), 2864 (s), 1729 (s) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 5.27 (1H, m, H(4)H_AH_B), 5.15 (1H, m, H(4)H_AH_B), 3.52 (2H, t, *J* = 6.6 Hz, H(8)H_2), 1.51-1.45 (2H, m, H(7)H_2), 1.43-1.36 (2H, m, H(6)H_2), 1.19-1.14 (2H, m, H(5)H_2), 1.05-1.10 (21H, m, Si(C*H*(CH_3)$_2$)$_3$), 0.85-0.92 (2H, m, H(3)H_2) ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 138.3 (0), 101.8 (2), 63.0 (2), 34.5 (2), 33.3 (2), 21.8 (2), 19.4 (6 x 3), 18.9 (0), 12.0 (3 x 1), 11.9 (2) ppm. **LRMS** (EI): *m/z* (%) = 239 (20) $[M-(CH(CH_3)_2)]^+$, 197 (40) $[M-(CH(CH_3)_2)_2]^+$, 156 (70) $[M-(CH(CH_3)_3)]^+$. ./**HRMS** (EI): *m/z* $C_{14}H_{25}O_1Si_1$ requires 237.1679 found 237.1674.

3-(1-(Triisopropylsilyl)-2-methylenecyclopropyl)propan-1-ol (**284**):



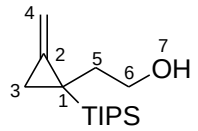
n = 3

284

Prepared upon 2.55 mmol scale, according to general procedure **3**. Purification by column chromatography (5-10 % of EA in LP) gave the title compound **284** as a colourless oil (n = 3, 410 mg, 1.52 mmol, 60 %).

FT-IR (oil) ν_{max} = 3319 (br), 2942 (s), 2865 (s), 1463 (m), 881 (s) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 5.35 (1H, m, C(4)H_AH_B), 5.23-5.22 (1H, m, C(4)H_AH_B), 3.57-3.53 (2H, m, C(7)H_AH_B), 1.66-1.56 (2H, m, C(6)H_AH_B), 1.39 (2H, m, C(5)H_AH_B), 1.24 (1H, dt, *J* = 7.8, 1.8 Hz, C(3)H_AH_B), 1.10 (21H, m, Si(C*H*(CH_3)$_2$)$_3$), 0.90 (1H, dt, *J* = 7.8, 1.8 Hz, C(3)H_AH_B) ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 139.1 (0), 102.1 (2), 63.4 (2), 30.7 (2), 29.2 (2), 19.4 (6x3), 18.8 (0), 11.9 (3x1), 11.6 (2) ppm. **LRMS** (ES+) : *m/z* (%) = 269 (6) $[M+H]^+$.

2-(1-(Triisopropylsilyl)-2-methylenecyclopropyl)ethanol (**283**):



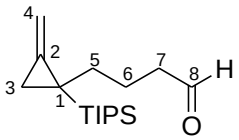
n = 2

283

Prepared upon 3.54 mmol scale, according to general procedure **3**. Purification by column chromatography (5-10 % of EA in LP) gave the title compound **283** as a colourless oil (n = 2, 500 mg, 1.96 mmol, 55%).

FT-IR (oil) ν_{max} = 2943 (w), 2865 (w), 1464 (s) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 5.43 (1H, m, H(4)H_AH_B), 5.33-5.32 (1H, m, H(4)H_AH_B), 3.58-3.46 (2H, m, H(6)H_AH_B), 2.01 (1H, dt, *J* = 13.9, 6.9 H(5)H_AH_B), 1.83-1.74 (1H, m, H(5)H_AH_B), 1.31 (1H, dt, *J* = 8.0, 1.8 Hz, H(3)CH_AH_B), 1.10-1.05 (22H, H(3)H_AH_B + Si(C*H*(CH_3)$_2$)$_3$) ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 139.7 (0), 102.5 (2), 60.6 (2), 36.7 (2), 19.4 (6 x 3), 12.2 (2), 11.7 (3 x 1), 10.0 (0) ppm. **LRMS** (EI): *m/z* (%) = 221 (80) [M-($CH(CH_3)_2$)]$^+$. **HRMS** (EI): $C_{12}H_{21}O_1Si_1$ requires 209.1363 found 209.1361.

4-(1-(Triisopropylsilyl)-2-methylenecyclopropyl)butanal (**301**):



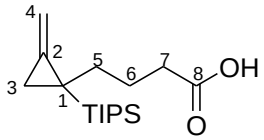
301

To a stirring solution of oxalyl chloride (68.0 µL, 0.78 mmol) in DCM (1.8 mL), at -60 °C under a nitrogen atmosphere, was added dropwise DMSO (127.6 µL, 1.70 mmol) in DCM (0.35 µL).

After 10 min alcohol **285** (200 mg, 0.70mmol) in DCM (0.70 mL) was added dropwise. After 10 min triethylamine (494 µL, 3.54 mmol) was added dropwise. After further 10 min and warming to RT the reaction mixture was quenched with water (3.5 mL) and extracted with DCM (3 x 6 mL). The combined organic layers were washed with brine (20 mL), dried over magnesium sulfate and concentrated *in vacuo* to give a yellow oil which was purified by flash column chromatography (DCM) to give aldehyde **301** as a colourless oil (140 mg, 0.49 mmol, 71 %).

FT-IR (oil) ν_{max} = 2942 (m), 2890 (m), 2865 (m), 1727 (m), 1016 (w), 881 (s) cm^{-1}. **^{1}H NMR**(300 MHz $CDCl_3$) δ_H = 9.70 (1H, t, *J* = 2.0 Hz, H(8)*H*), 5.36 (1H, m, H(4)H_AH_B), 5.24 (1H, m,H(4)H_AH_B), 2.31(2H, dt, *J* = 6.9, 1.8 Hz, H(7)H_AH_B), 1.57-1.54 (2H, m , H(6)H_AH_B), 1.51-1.40 (2H, m, H(3)H_AH_B), 1.25 (1H, dt, *J* = 8.0, 1.8 Hz, H(5)H_AH_B), 1.09 (21H, m, (Si(C*H*(CH_3)$_3$), 0.93 (1H, dt, *J* = 8.0, 1.8 Hz, H(5)H_AH_B) ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 202.5 (1), 138.8 (0), 102.4 (2), 44.3 (2), 34.3 (2), 19.2 (3), 18.2 (2), 17.8 (0), 11.8 (2), 11.8 (1) ppm. **LRMS** (EI): *m/z* (%) = 237 [M-$CH(CH_3)$]$^+$ 44%.

4-(1-(Triisopropylsilyl)-2-methylenecyclopropyl)butanoic acid (**278**):



278

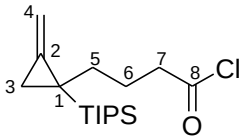
Following the method of Hon *et al*.[151]

To a stirring solution of aldehyde **301** (140 mg, 0.49 mmol) in 2-methyl-2-propanol (1.79 mL) and 2-methyl-2-butene (0.74 µL, 1.49 mmol), at RT and under a nitrogen atmosphere, was successively added (over a period of 5 min) a solution of sodium chlorite (103.8 mg, 1.14 mmol) and dihydrogenphosphate (119.7 mg, 0.99 mmol) in water (0.65 mL). After 4 h the reaction mixture was concentrated *in vacuo.* and the residue washed with water (2 mL) and hexane (3x5 mL). The combined organic layers were washed with brine (20 mL), dried over magnesium sulphate and concentrated *in vacuo* to give a colourless oil which was purified by flash column chromatography (DCM) to give the acid **278** as a colourless oil (160 mg, 0.54 mmol, 69 %).

FT-IR (oil) ν_{max} = 2943 (b), 2865 (s), 1707 (s), 919 (s) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 5.36 (1H, m, H(4)H_AH_B), 5.24 (1H, m, H(4)H_AH_B), 2.26 (2H, t, *J* = 7.1 Hz, H(7)H_AH_B), 1.59-1.56 (2H, m, H(6)H_AH_B), 1.50-1.47 (2H, m, H(3)H_AH_B), 1.25 (1H, dt, *J* = 5.9, 1.7 Hz, H(5)H_AH_B), 1.12-1.07 (21H, m, (Si(C*H*(CH_3)$_2$), 0.93 (1H, m, H(5)H_AH_B) ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 179.5 (0), 138.8 (0), 102.2 (2), 34.4 (2), 34.1 (2), 21.0 (2), 19.4 (6x3), 19.4 (0), 12.0 (1), 11.9 (2) ppm. **LRMS** (EI): *m/z*

(%) = 253.1 (50) $[M\text{-}CH(CH_3)]^+$. **HRMS** (ES+): *m/z* (%) = $C_{14}H_{25}O_2Si_1$ requires 253.1627 found 253.1623.

4-(1-(Triisopropylsilyl)-2-methylenecyclopropyl)butanoyl chloride (**279**):



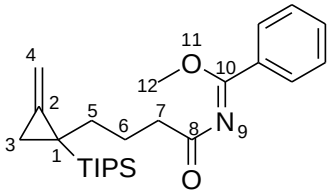
279

Following the method of Quiclet-Sire *et al*.[152]

To a solution of acid **278** (158 mg, 0.53 mmol) in DCM (1.0 mL), at 0 °C under a nitrogen atmosphere, was added dropwise DMF (1-2 drops). After 10 min oxalyl chloride (139 µL, 1.60 mmol) (evolution of gas observed) was added dropwise. After 10 h and warming to RT the reaction mixture was diluted with THF (4 mL) and concentrated *in vacuo*. The resultant oil was dissolved in DCM (10 mL), filtered (cotton wool) and concentrated *in vacuo* to yield the acid chloride **279** as a yellow oil (150 mg, 0.47 mmol, 90 %), which was used without further purification.

FT-IR (oil) ν_{max} = 2944 (b), 2866 (s), 1795 (s) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 5.38 (1H, m, H(4)H_AH_B), 5.25 (1H, m, H(4)H_AH_B), 2.80 (2H, t, *J* = 7.0 Hz, H(7)H_AH_B), 1.66-1.49 (4H, m, H(6)H_AH_B, H(5)H_AH_B), 1.27 (1H, dt, *J* = 8.0, 2.0 Hz, H(3)H_AH_B), 1.12-1.06 (21H, m, (Si(C*H*(CH_3)$_2$), 0.92 (1H, dt, *J* = 8.0, 2.0 Hz, H(3)H_AH_B) ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 173.8 (0), 138.4 (0), 102.7 (2), 47.5 (2), 33.4 (2), 21.5 (2), 19.5 (3), 12.1 (1), 11.9 (0), 11.2 (2) ppm.

***N*-(Methoxyphenylmethylene)-4-(2-methylene-1-triisopropylsilanyl-cyclopropyl)-butyramide** (**281**):



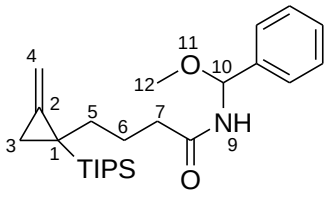
281

Following the method of Alves *et al*.[153]

To a stirring solution of benzylimidate hydrochloride **280** (60.2 mg, 0.35 mmol) in DCM (1 mL), at RT under a nitrogen atmosphere was added dropwise acid chloride **279** (110 mg, 0.35 mmol) and triethylamine (107 µL, 0.76 mmol). After stirring for 10 h the reaction mixture was diluted with dry

light petroleum (5 mL), filtered through celite™ and concentrated *in vacuo* to give the title compound **281** as a colourless oil (60 mg, 0.15 mmol, 42 %) which was used directly without further purification.

***N*-(Methoxy-phenyl-methyl)-4-(2-methylene-1-triisopropylsilanyl-cyclopropyl)-butyramide** (**282**):



282

Following the method of Lokensgard *et al*.[157]

To a stirring suspension of sodium borohydride (10 mg, 0.26 mmol) in ethanol (1 mL), at 0 °C under a nitrogen atmosphere, was added dropwise a solution of **281** (100mg, 0.24 mmol) in diethyl ether (1 mL). After 3 h the reaction mixture was quenched with aqueous sodium carbonate (3 %) (1 mL) and extracted with DCM (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over magnesium sulfate and concentrated *in vacuo* to give an oil which was purified by flash column chromatography (0 - 6 % of EA in LP) to give the title compound as an oil **282** (40 mg, 0.09 mmol, 38 %).

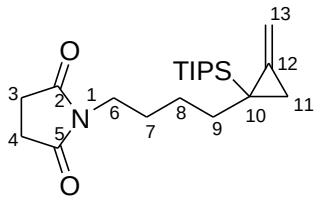
FT-IR (oil) ν_{max} = 3273 (br), 2943 (s), 2865 (s), 1650 (s) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 7.41-7.31 (5H, m Ar), 6.14 (1H, d, *J* = 9.5, C(9)*H*), 5.86 (1H, d, *J* = 9.5, N*H*), 5.34 (1H, m, C(4)H_AH_B), 5.22 (1H, m, C(4)H_AH_B), 3.44 (3H, s, C(10)H_3), 2.16-2.13 (2H, m, C(7)H_AH_B), 1.60-1.51 (4H, m, C(5)H_AH_B, C(6)H_AH_B), 1.25-1.22 (1H, m, C(3)H_AH_B), 1.11-1.05 (21H, m, (Si(C*H*(CH_3)$_2$)), 0.94-0.91 (2H, m, C(3)H_AH_B) ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 173.0 (0), 139.5 (0), 138.7 (0), 128.7 (2x1), 128.6 (2x1), 125.9 (1), 102.2 (2), 81.3 (1), 56.1 (3), 37.2 (2), 34.1 (2), 21.5 (2), 19.4 (6x3), 11.8 (3x1), 11.7 (2) ppm. **LRMS** (EI): *m/z* (%) = 853.4 (40) $[2M+Na]^+$.

General procedure **4**; following that reported by Zonjee.[154]

To a stirring solution of alcohol (1 equiv.) and triphenylphosphine (2 equiv.) in THF (0.1 M), at 0 °C under a nitrogen atmosphere, was added dropwise diethyl azodicarboxylate (2 equiv.) in THF (0.1 M), then after 10 min succinimide (2 equiv.) in THF (0.1 M). After 2 h at 0 °C and warming to RT over 10 h the reaction mixture was concentrated *in vacuo* before partitioning between DCM (10 mL required for a 1.0 mmol preparation) and aqueous potassium hydroxide (5 % by volume) (10 mL required for a 1.0 mmol preparation). The organic layer was washed with hydrochloric acid (2 M) (10 mL required for a 1.0 mmol preparation), then saturated aqueous sodium bicarbonate (10 mL required for a 1.0 mmol preparation). The combined organic layers were washed with brine (10 mL required for a 1.0 mmol

preparation), dried over magnesium sulfate, concentrated *in vacuo* to give an oil which was purified by flash column chromatography.

1-(4-(1-(Triisopropylsilyl)-2-methylenecyclopropyl)butyl)pyrrolidine-2,5-dione (**288**):



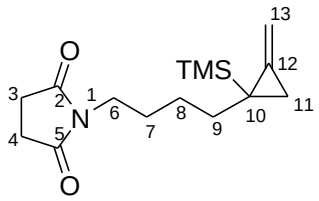
n = 4

288

Prepared upon 2.69 mmol scale, according to general procedure **4**. Purification by column chromatography (10-20 % of EA in LP) gave the title compound **288** as a colourless oil (n = 4, 820 mg, 2.25 mmol, 84%).

FT-IR (oil) ν_{max} = 2941 (m), 2865 (m), 1698 (s), 1400(m) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 5.32 (1H, m, H(13)H_AH_B), 5.20-5.19 (1H, m, H(13)H_AH_B), 3.46-3.41 (2H, m, H(6)H_AH_B), 1.58-1.40 (5H, m, H(7)H_AH_B, H(8)H_AH_B, H(9)H_AH_B), 1.22-1.19 (2H, m, H(9)H_AH_B, H(11)H_AH_B), 1.07 (21H, m, Si(C*H*(CH_3)$_2$)$_3$), 0.87 (1H, dt, *J* = 8.0, 1.8, H(11)H_AH_B) ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 177.3 (0), 139.0 (0), 101.9 (2), 38.8 (2), 34.1 (2), 28.2 (2), 28.1 (2), 22.9 (2), 19.4 (6 x 3), 12.0 (2), 11.9 (3 x 1), 11.9 (0) ppm. **LRMS** (ES+): *m/z* (%) = 363 (5) $[M]^+$, 320 (100) $[M\text{-}CH(CH_3)_3]^+$. **HRMS** (ES+): *m/z* $C_{21}H_{37}N_1Na_1O_2Si_1$ $[M+Na]^+$ requires 386.2486, found 386.2493.

1-(4-(2-Methylene-1-(trimethylsilyl)cyclopropyl)butyl)pyrrolidine-2,5-dione (**302**):



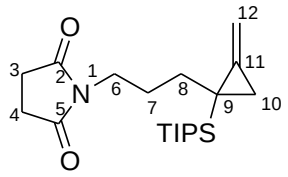
n = 4

302

Prepared upon 0.75 mmol scale, according to general procedure **4**. Purification by column chromatography (10-20 % of EA in LP) gave the title compound **302** as a colourless oil (n = 4, 150 mg, 0.53 mmol, 72 %).

FT-IR (oil) ν_{max} = 2951 (m), 1695 (s), 832 (m) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 5.26 (1H, m, H(13)H_AH_B), 5.20-5.19 (1H, m, H(13)H_AH_B), 3.52-3.47 (1H, m, H(6)H_AH_B), 2.71 (4H, m, H(3)H_AH_B, H(4)H_AH_B), 1.59-1.28 (6H, m, H(7)H_AH_B, H(8)H_AH_B, H(9)H_AH_B), 1.05 (1H, dt, *J* = 7.6, 1.8 Hz, H(11)H_AH_B), 0.81 (1H, dt, *J* = 7.6, 1.8 Hz, H(11)H_AH_B), -0.00 (9H, m, Si(CH_3)$_3$) ppm.**^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 177.2 (0), 139.7 (0), 100.2 (2), 38.7 (2), 35.1 (2), 28.1 (2), 28.0 (2), 25.6 (2), 13.8 (0), 12.5 (2), -2.52 (3 x 3) ppm. **LRMS** (EI): *m/z* (%) = 264 (5) $[M\text{-}CH_3]^+$, 73 (100) $[Si(CH_3)_3]^+$. **HRMS** (ES+): *m/z* $C_{15}H_{25}N_1Na_1O_2Si_1$ $[M+Na]^+$ requires 302.1547, found 302.1544.

1-(3-(1-(Triisopropylsilyl)-2-methylenecyclopropyl)propyl)pyrrolidine-2,5-dione (**287**):



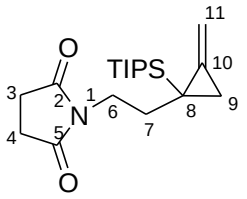
n = 3

287

Prepared upon 1.45 mmol scale, according to general procedure **4**. Purification by column chromatography (0-20 % of EA in LP) gave the title compound **287** as a colourless oil (n = 3, 430 mg, 1.23 mmol, 85%).

FT-IR (oil) ν_{max} = 2942 (m), 2865 (m), 1697 (s), 1400 (m) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 5.33 (1H, m, H(12)H_AH_B), 5.21 (1H, m, H(12)H_AH_B), 3.40 (2H, t, *J* = 6.0 Hz, H(6)H_AH_B), 2.66 (4H, s, H(3)H_AH_B, H(4)H_AH_B), 1.63-1.58 (2H, m, H(7)H_AH_B), 1.51-1.45 (2H, m, H(8)H_AH_B), 1.25-1.19 (1H, m, H(10)H_AH_B), 1.08 (21H, m, Si(CH(CH_3)$_2$)$_3$), 0.09-0.87 (1H, m, H(10)H_AH_B) ppm.**^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 177.2 (0), 138.4 (0), 102.4 (2), 39.1 (2), 31.5 (2), 28.2 (2), 23.7 (2), 19.4 (6 x 3), 11.8 (3 x 1), 11.7 (0) ppm. **LRMS** (EI): *m/z* (%) = 306 $[M\text{-}CH(CH_3)_2]^+$ 100 %. **HRMS** (ES+): *m/z* $C_{20}H_{36}N_1O_2Si_1$ $[M+H]^+$ requires 350.2510, found 350.2506.

1-(2-(1-(Triisopropylsilyl)-2-methylenecyclopropyl)ethyl)pyrrolidine-2,5-dione (**286**):



n = 2

286

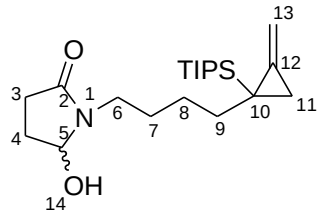
Prepared upon 1.84 mmol scale, according to general procedure **4**. Purification by column chromatography (0-20 % of EA in LP) gave the title compound **286** as a colourless oil (n = 2, 540 mg, 1.61 mmol, 88 %).

FT-IR (oil) ν_{max} = 2944 (w), 2866 (w), 1697 (s), 1401 (m) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 5.40 (1H, m, H(11)H_AH_B), 5.31-5.29 (1H, m, H(11)H_AH_B), 3.47 (1H, ddd, *J* = 12.7, 11.3, 5.6 Hz, C(6)H_AH_B), 3.29 (1H, ddd, *J* = 12.7, 11.3, 5.6 Hz, C(6)H_AH_B), 2.63 (4H, s, C(3)H_AH_B, C(4)H_AH_B), 1.80 (1H, dddd with fine splitting, *J* = 13.0, 11.0, 7.0 Hz, C(7)H_AH_B), 1.71 (1H, ddd, *J* = 13.0, 11.0, 7.0 Hz, C(7)H_AH_B), 1.32 (1H, dt, *J* = 8.0, 2.0 Hz, C(9)H_AH_B), 1.10 (22H, m, C(9)H_AH_B, Si(C*H*$(CH_3)_2)_3$) ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 177.0 (2x0), 137.8 (0), 102.9 (2), 36.3 (2), 31.7 (2), 28.2 (2x2), 19.4 (6x3), 12.2 (2), 11.8 (3x1), 10.0 (0) ppm. **LRMS** (EI): *m/z* (%) = 292 (100) $[M- CH(CH_3)_2]^+$. **HRMS** (ES+): *m/z* $C_{19}H_{34}N_1O_2Si_1$ $[M+H]^+$ requires 336.2353, found 336.2348.

General procedure **5**; following that reported by Speckamp.[69]

To a stirring solution of appropriate pyrrolidinedione (1 equiv.) in methanol (0.04 M), at 0 °C under a nitrogen atmosphere, was added sodium borohydride (3 equiv.). After 30 min the reaction mixture was cooled to -20 °C then quenched by the dropwise addition of saturated aqueous sodium bicarbonate (10 mL required for a 1.0 mmol preparation) and extracted with DCM (3 x 10 mL required for a 1.0 mmol preparation). The combined organic layers were washed with brine (30 mL required for a 1.0 mmol preparation), dried over magnesium sulfate, concentrated *in vacuo* and the crude oil was purified by flash column chromatography.

5-Hydroxy-1-(4-(1-(triisopropylsilyl)-2-methylenecyclopropyl)butyl)pyrrolidin-2-one (**293**):



n = 4

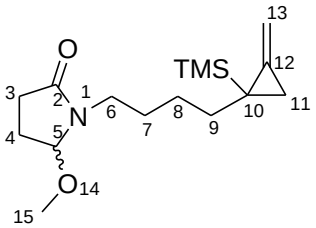
293

Prepared upon 2.14 mmol scale, according to general procedure **5**. Purification by column chromatography (20-80 % of EA in LP) gave the title compound **293** as a colourless oil (n = 4, 560 mg, 1.47 mmol, 69 %), reported as 1 : 0.3 mixture of diastereoisomers (^{1}H NMR 300 MHz $CDCl_3$).

FT-IR (oil) ν_{max} = 3307 (w), 2941 (m), 2864 (m), 1665 (s) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 5.36 (1H, m, H(13)H_AH_B), 5.21-5.21 (1H, m, H(13)H_AH_B), 5.15 (1H, m, H(5)*H*), 3.43-3.32 (1H, m, H(6)H_AH_B), 3.07-2.99 (1H, m, H(6)H_AH_B), 2.53-2.45 (1H, m, H(3)H_AH_B), 2.33-2.22 (1H, m, H(3)H_AH_B,

H(4)H_AH_B), 1.91-1.84 (1H, m, H(4)H_AH_B), 1.79 (1H, m, O*H*), 1.67-1.46 (3H, m, H(7)H_AH_B, H(8)H_AH_B), 1.41-1.32 (1H, m, H(8)H_AH_B), 1.26-1.20 (2H, m, H(9)H_AH_B), 1.08 (22H, m, H(10)H_AH_B, Si(C*H*(CH_3)$_2$)$_3$), 0.89 (1H, m, H(10)H_AH_B) ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 174.7 (0), 174.7 (0), 139.1 (0), 139.1 (0), 101.1 (2), 101.1 (2), 83.3 (1), 40.4 (2), 40.0 (2), 34.4 (2), 34.3 (2), 29.0 (2), 28.7 (2), 28.6 (2), 28.4 (2), 26.8 (2), 26.7 (2), 23.1 (2), 23.0 (2), 19.4 (6 x 3), 12.0 (2), 11.9 (3 x 1), 11.6 (0) ppm. **LRMS** (ES+): *m/z* (%) = 753 (80) $[2M+Na]^+$, 388 (100) $[M+Na]^+$. **HRMS** (ES+): *m/z* $C_{21}H_{39}N_1Na_1O_2Si_1$ $[M+Na]^+$ requires 388.2642, found 388.2640.

5-Methoxy-1-(4-(2-methylene-1-(trimethylsilyl)cyclopropyl)butyl)pyrrolidin-2-one (**303**):



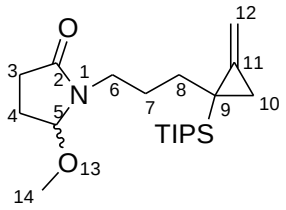
n = 4

303

Prepared upon 2.14 mmol scale, according to general procedure **5**. Purification by column chromatography (20-80 % of EA in LP) gave the title compound **303** as a colourless oil (n = 4, 60 mg, 0.21 mmol, 46 %), reported as one diastereoisomer (^{1}H NMR 300 MHz $CDCl_3$).

FT-IR (oil) ν_{max} = 2941 (m), 2864 (m), 1697 (s), 1461 (m), 1077 (s) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 5.21 (1H, m, H(13)H_AH_B), 5.14-5.14 (1H, m, H(13)H_AH_B), 4.89 (1H, dd, *J* = 6.0, 1.0 Hz, H(5)*H*), 3.43 (1H, ddd, *J* = 14.0, 9.0, 6.4 Hz, H(6)H_AH_B), 3.21 (3H, s, H(12)H_3), 3.04 (1H, ddd, *J* = 19.3, 8.7, 5.5 Hz, H(6)H_AH_B), 2.56-2.41 (1H, m, H(3)H_AH_B), 2.27 (1H, m, ddd, *J* =17.1, 9.6, 3.1 Hz, H(3)H_AH_B), 2.14-2.04 (1H, m, H(9)H_AH_B), 2.00-1.90 (1H, m, H(9)H_AH_B), 1.53-1.41 (3H, m, H(8)H_AH_B, H(4)H_AH_B), 1.35-1.22 (3H, m, H(8)H_AH_B, H(7)H_AH_B), 1.00 (1H, dt, *J* = 7.3, 1.8 Hz, H(11)H_AH_B), 0.75 (1H, dt, *J* = 7.6, 1.8 Hz, H(11)H_AH_B), -0.05 (9H, s, Si(CH_3)$_3$) ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 175.2 (0), 140.1(0), 100.0 (2), 90.2 (1), 83.3 (1), 52.7 (3), 40.7 (2), 35.5 (2), 29.3 (2), 28.6 (2), 28.2 (2), 26.0 (2), 24.0 (2), 14.1 (0), 12.7 (2), -1.90 (3 x 3) ppm.

1-(3-(1-(Triisopropylsilyl)-2-methylenecyclopropyl)propyl)-5-methoxypyrrolidin-2-one (**292**):

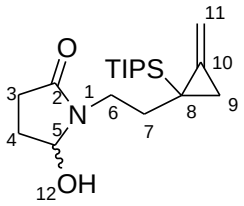


n = 3

292

Prepared upon 1.11 mmol scale, according to general procedure **5**. Purification by column chromatography (20-50 % of EA in LP) gave the title compound **292** as a colourless oil (n = 3, 50 mg, 0.13 mmol, 12 %), reported as a 1 : 0.9 mixture of diastereoisomers (^{13}C NMR 300 MHz $CDCl_3$).
FT-IR (oil) ν_{max} = 2942 (m), 2865 (m), 1663(s) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 5.34 (1H, br s, H(12)H_AH_B), 5.21-5.20 (1H, m, H(12)H_AH_B), 3.44-3.37 (1H, m, H(6)H_AH_B), 3.22 (3H, s, H(14)H_3), 3.02-2.93 (1H, m, H(6)H_AH_B), 2.51-2.42 (1H, m, H(3)H_AH_B), 2.33-2.23 (1H, m, H(3)H_AH_B), 2.15-2.07 (1H, m, H(4)H_AH_B), 2.05-1.96 (1H, m, H(4)H_AH_B), 1.59-1.33 (4H, m, H(7)H_AH_B, H(8)H_AH_B), 1.23-1.19 (1H, m, H(10)H_AH_B), 1.07 (21H, m, Si(CH(CH_3)$_2$)$_3$), 0.91-0.86 (1H, m, H(10)H_AH_B) ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 175.0 (0), 138.8 (0), 138.7 (0), 102.2 (2), 102.1 (2), 89.9 (1), 89.8 (1), 52.6 (3), 40.7 (2), 40.7 (2), 31.6 (2), 31.4 (2), 29.1 (2), 23.8 (2), 23.5 (2), 23.3 (2), 19.3 (3), 18.8 (0), 11.9 (1), 11.7 (0) ppm. **LRMS** (EI): *m/z* (%) = 290 (100) [M-OCH$_3$-CH(CH$_3$)$_2$]$^+$.

5-Hydroxy-1-(2-(1-(triisopropylsilyl)-2-methylenecyclopropyl)ethyl)pyrrolidin-2-one (**289**):



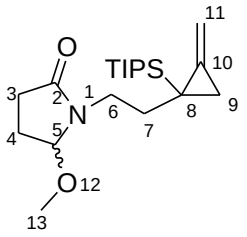
n = 2

289

Prepared upon 1.67 mmol scale, according to general procedure **5**. Purification by column chromatography (20-60 % of EA in LP) gave the title compound **289** as a colourless oil (n = 2, 200 mg, 0.57 mmol, 40 %), reported as a 1 : 0.7 mixture of diastereoisomers (^{13}C NMR 300 MHz $CDCl_3$).
FT-IR (oil) ν_{max} = 3283 (s), 2942 (m), 2864 (m), 1656 (s) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 5.39-5.37 (1H, m, H(11)H_AH_B), 5.29-5.25 (1H, m, H(11)H_AH_B), 5.13-5.11 (1H, m, H(5)H), 3.47-3.22 (1H, m,

H(6)H_AH$_B$ (major)(minor)), 3.13-2.91 (1H, m, H(6)H$_A$$H_B$ (major)(minor)), 2.52-2.43 (1H, m, O*H*), 2.31-2.20 (2H, m, H(7)$H_A$$H_B$), 1.88-1.71 (4H, m, H(2)$H_A$$H_B$, H(3)$H_A$$H_B$), 1.30 (1H, dt, *J* = 8.0, 1.8 Hz, H(9)H_AH$_B$), 1.10 (22H, m, H(9)H$_A$$H_B$, Si(C*H*(C$H_3$)$_2$)$_3$) ppm.**^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 174.4 (0), 138.3 (0), 102.7 (2), 102.6 (2), 83.3 (1), 37.7 (2), 37.5 (2), 32.0 (2 x 2), 28.9 (2), 28.5 (2), 19.4 (6 x 3), 19.2 (6 x 3), 12.8 (2), 12.0 (2), 11.9 (3 x 1), 11.8 (3 x 1), 10.3 (0), 10.2 (0) ppm. **LRMS** (ES+): *m/z* (%) = 697 (80) $[2M+Na]^+$, 360 (100)$[M+Na]^+$. **HRMS** (ES+): *m/z* $C_{19}H_{35}N_1Na_1O_2Si_1$ $[M+Na]^+$ requires 360.2329, found 360.2328.

1-(2-(1-(Triisopropylsilyl)-2-methylenecyclopropyl)ethyl)-5-methoxypyrrolidin-2-one (**290**):

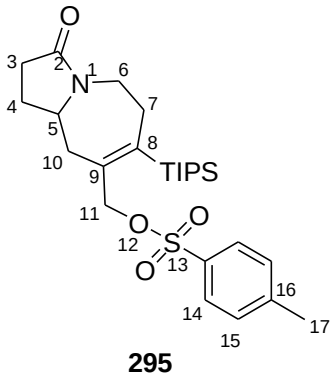


n = 2

290

Prepared upon 1.67 mmol scale, according to general procedure **5**. Purification by column chromatography (20-60 % of EA in LP) gave the title compound **290** as a colourless oil (n = 2, 200 mg, 0.54 mmol, 40 %), reported as a 1 : 0.8 mixture of diastereoisomers (^{13}C NMR 300 MHz $CDCl_3$).
FT-IR (oil) ν_{max} = 2943 (m), 2865 (m), 1671 (s), 1459 (m) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 5.38-5.37 (1H, m, H(11)H_AH$_B$), 5.27-5.27 (1H, m, H(11)H$_A$$H_B$), 4.84-4.83 (1H, d, H(5)*H*), 3.43-3.26 (1H, m, H(6)H_AH$_B$), 3.22 (3H, H(12)H_3), 3.08-2.91 (1H, m, H(6)H$_A$$H_B$), 2.51-2.39 (1H, m, H(3)H_AH$_B$), 2.30-2.19 (1H, m, H(3)H$_A$$H_B$), 2.08-2.00 (1H, m, H(4)H_AH$_B$), 1.97-1.92 (1H, m, H(4)H$_A$$H_B$), 1.83-1.74 (2H, m, H(7)$H_A$$H_B$), 1.30-1.24 (1H, m, H(10)$H_A$$H_B$), 1.10-1.09 (22H, m, H(10)H$_A$$H_B$, Si(C*H*(C$H_3$)$_2$)$_3$) ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C =174.7 (0), 174.7 (0), 138.3 (0), 138.1 (0), 102.7 (2), 102.4 (2), 90.3 (1), 90.1 (1), 52.8 (3), 52.7 (3), 38.4 (2), 38.1 (2), 31.9 (2), 31.8 (2), 29.1 (2), 28.9 (2), 24.0 (2), 23.9 (2), 19.4 (6 x 3), 12.3 (2), 11.9 (3 x 1), 10.3 (0), 10.1 (0) ppm. **LRMS** (ES+): *m/z* (%) = 725 (100) $[2M+Na]^+$, 374 (50) $[M+Na]^+$. **HRMS** (ES+): *m/z* $C_{20}H_{37}N_1Na_1O_2Si_1$ $[M+Na]^+$ requires 374.2486, found 374.2492.

((Z) Hexahydro(triisopropylsilyl)oxopyrroloazepinyl)methylmethylbenzenesulfonate (**295**):

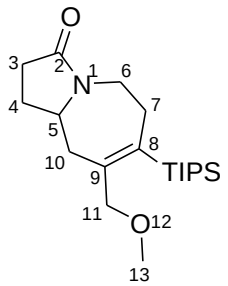


295

To a stirring solution of **289** (36 mg, 0.10 mmol) in methanol (2 mL), at RT under a nitrogen atmosphere, was added dropwise a solution of *p*-toluenesulfonic acid (1.6 mg, 8.41×10^{-3} mmol) in methanol (1 mL). After 3.5 h further *p*-toluenesulfonic acid (1.6 mg, 8.41×10^{-3} mmol) in methanol (1 mL) was added dropwise. After 12 h the reaction mixture was concentrated *in vacuo* to give an oil which was purified by flash column chromatography (10-40 % of EA in LP) to give the title compound **295** as an oil (10 mg, 0.02 mmol, 20 %).

FT-IR (oil) ν_{max} = 2944 (m), 2865 (m), 1670 cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 7.79 (2H, d, *J* = 8.2 Hz, Ar), 7.36 (2H, d, *J* = 8.2 Hz, Ar), 4.45 (2H, m, H(11)H_AH_B), 4.19 (1H, m, H(5)*H*), 3.43-3.33 (1H, m, H(6)H_AH_B), 2.54-2.49 (2H, m, H(6)H_AH_B, H(7)H_AH_B), 2.46-2.44 (3H, m, H(17)H_3), 2.39-2.32 (2H, m, H(7)H_AH_B, H(10)H_AH_B), 2.30-2.23 (2H, m, H(10)H_AH_B, H(3)H_AH_B or H(4)H_AH_B), 1.59-1.53 (1H, m, H(3)H_AH_B or H(4)H_AH_B), 1.07-1.04 (2H, m, H(3)H_AH_B or H(4)H_AH_B), 0.93 (21H, m, (Si(C*H*(CH_3)$_2$) ppm. **^{13}C NMR** (75.5MHz $CDCl_3$) δ_C = 174.6 (0), 145.2 (0), 145.1 (0), 144.8 (0), 132.9 (0), 129.9 (1), 128.1 (1), 74.4 (2), 57.3 (3), 40.9 (2), 40.5 (2), 31.6(2), 30.2 (2), 25.9 (2), 21.8 (1),19.1 (3), 12.8 (1) ppm. **LRMS** (EI): *m/z* (%) = 319 (12) $[M\text{-}C_7H_7O_3S]^+$, 276 (100) $[319\text{-}CH(CH_3)_2]^+$. **LRMS** (ES+): *m/z* (%) = 514 (20) $[M+Na]^+$, 1006 (100) $[2M+Na]^+$. **HRMS** (ES+): *m/z* $C_{26}H_{42}N_1O_4S_1Si_1$ $[M+H]^+$ requires 492.2598, found 492.2601.

(Z)-Hexahydro-(triisopropylsilyl)-8-(methoxymethyl)pyrroloazepin-2-one (209b).

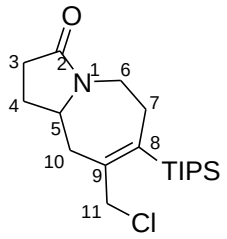


209b

To a stirring solution of **290** (75 mg, 0.21 mmol) in DCM (2.4 mL), at -78 °C under a nitrogen atmosphere, was added boron trifluoroetherate (40 µL, 0.32 mmol). After 2 h at 78 °C and warming to RT over 10 h the reaction mixture was quenched with saturated aqueous ammonium chloride (1.5 mL) and extracted with DCM (3 x 5 mL). The combined organic layers were washed with brine (20 mL), dried over magnesium sulfate and concentrated *in vacuo* to give an oil which was purified by flash column chromatography of (10-70 % of EA in LP) to give the title compound **209b** as a colourless oil (10 mg, 0.02 mmol, 14 %).

FT-IR (oil) ν_{max} = 2943 (m), 2865 (m), 1667 (s) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 4.20 (1H, ddd, *J* = 13.5, 6.6, 1.4 Hz, H(5)*H*), 3.88 (1H, d, *J* = 10.2 Hz, H(11)H_AH_B), 3.79 (1H, d, *J* = 10.2 Hz, H(11)H_AH_B), 3.43-3.37 (1H, m, H(6)H_AH_B), 3.33 (3H, s, H(13)H_3), 2.59-2.40 (2H, m, H(6)H_AH_B, H(7)H_AH_B), 2.37-2.15 (2H, m, H(7)H_AH_B, H(10)H_AH_B), 1.92-1.14 (5H, m, H(3, 4), H(10)H_AH_B), 1.07-1.04 (21H, m, (Si(C*H*(CH_3)$_2$) ppm. **^{13}C NMR** (75.5 MHz $CDCl_3$) δ_C = 174.7 (0), 150.5 (0), 138.8 (0), 76.7(2), 58.7 (1), 57.7 (3), 41.0 (2), 40.6 (2), 31.2 (2), 30.4 (2), 26.1 (2), 19.1 (3), 13.0 (1) ppm. **LRMS** (ES+): *m/z* (%) = 725 (100) $[2M+Na]^+$. **LRMS** (EI): *m/z* (%) = 308 (100) $[M\text{-}CH(CH_3)_2]^+$. **HRMS** (ES+): *m/z* $C_{20}H_{38}N_1O_2Si_1$ $[M+H]^+$ requires 352.2666, found 352.2658.

(Z)(Chloromethyl)hexahydro(triisopropylsilyl)pyrroloazepin-2-one (**209a**):



209a

To a stirring solution of **289** (103 mg, 0.30 mmol) in DCM (3.5 mL) at -78 °C under a nitrogen atmosphere, was added dropwise tin(IV) tetrachloride solution (1M in DCM) (0.45 mL, 0.45 mmol). After 1 h at -78 °C and warming to 5 °C over 2 h the reaction mixture was quenched with saturated aqueous ammonium chloride (1.5 mL) and extracted with DCM (3 x 5 mL). The combined organic layers were washed with brine (20 mL), dried over magnesium sulfate and concentrated *in vacuo* to give an oil which was purified by flash column chromatography (30-50% of EA in LP) to give the title compound **209a** as a white solid (80 mg, 0.22 mmol, 75 %).

Melting point = 67-70 °C. **FT-IR** (solid) ν_{max} = 2946 (m), 2865 (m), 1679(s) cm^{-1}. **^{1}H NMR** (300 MHz $CDCl_3$) δ_H = 4.26 (1H, m, H(5)*H*), 4.20 (1H, d, *J* = 10.9 Hz, H(11)H_AH_B), 4.08 (1H, d, *J* = 10.9 Hz, H(11)H_AH_B), 3.52-3.45 (1H, m, H(6)H_AH_B), 2.63-2.52 (2H, m, H(6)H_AH_B, H(7)H_AH_B), 2.49-2.43 (2H, m, H(7)H_AH_B, H(10)H_AH_B), 2.41-2.32 (1H, m, H(10)H_AH_B), 2.29-2.22 (2H, m, H(3)H_AH_B or H(4)H_AH_B), 1.98-1.58 (2H, m, H(3)H_AH_B or H(4)H_AH_B), 1.09-1.06 (21H, m, (Si(C*H*(CH_3)$_2$) ppm. **^{13}C**

NMR (75.5 MHz $CDCl_3$) δ_C = 174.7 (0), 148.1 (0), 142.2 (0), 58.0 (1), 51.0 (2), 42.1 (2), 40.7 (2), 31.6 (2), 30.3 (2), 25.9 (2), 19.2 (3), 13.0 (1) ppm. **LRMS** (EI): *m/z* (%) = 355 (6) $[M]^+$, 312 (100) $[M-CH(CH_3)_2]^+$. **HRMS** (ES+): *m/z* $C_{19}H_{34}N_1Na_1O_1Si_1$ $[M+Na]^+$ requires 378.1990, found 378.1982.

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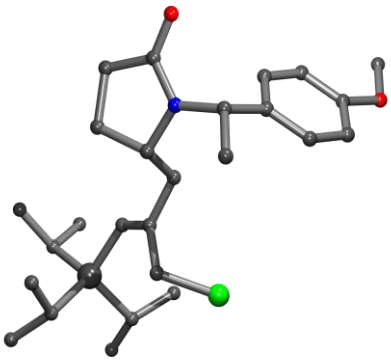
Appendix 1 – X-Ray crystal data

Crystal Structure Data for compound **246a**

Table 1. Crystal data and structure refinement details.

Identification code	**2008sot1073 (LM5192–27 F168+)**
Empirical formula	$C_{26}H_{42}ClNO_2Si$
Formula weight	464.15
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 8.6003(2) Å
	b = 12.2199(3) Å
	c = 24.9458(5) Å
Volume	2621.67(10) Å^3
Z	4
Density (calculated)	1.176 Mg / m^3
Absorption coefficient	0.213 mm^{-1}
F(000)	1008
Crystal	Fragment; Colourless
Crystal size	0.5 × 0.4 × 0.25 mm^3
θ range for data collection	2.96 – 27.48°
Index ranges	$-11 \le h \le 10$, $-15 \le k \le 15$, $-32 \le l \le 31$
Reflections collected	18961
Independent reflections	5979 [R_{int} = 0.0492]
Completeness to θ = 27.48°	99.7 %
Absorption correction	Semi–empirical from equivalents



Max. and min. transmission	0.9486 and 0.9109
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5979 / 0 / 289
Goodness-of-fit on F^2	1.083
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0420, *wR2* = 0.0971
R indices (all data)	*R1* = 0.0542, *wR2* = 0.1026
Absolute structure parameter	**0.08(6) C14 = S, C18 = S**
Extinction coefficient	0.0259(16)
Largest diff. peak and hole	0.444 and –0.410 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 S**tructure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). S**tructure 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.*
C1	2457(3)	5094(2)	–130(1)	43(1)	1
C2	4032(2)	5142(2)	–413(1)	24(1)	1
C3	4128(3)	6190(2)	–748(1)	32(1)	1
C4	5077(3)	2645(2)	–2(1)	30(1)	1
C5	5601(2)	3535(2)	389(1)	21(1)	1
C6	4621(3)	3476(2)	901(1)	32(1)	1
C7	7733(3)	4496(2)	–830(1)	30(1)	1
C8	7652(2)	5087(2)	–286(1)	21(1)	1

C9	8185(3)	6279(2)	−347(1)	33(1)	1
C10	5562(2)	6056(2)	590(1)	17(1)	1
C11	6328(2)	6182(2)	1055(1)	17(1)	1
C12	7500(2)	5364(2)	1245(1)	22(1)	1
C13	6011(2)	7127(2)	1430(1)	18(1)	1
C14	4955(2)	6810(2)	1902(1)	18(1)	1
C15	3254(2)	6566(2)	1743(1)	23(1)	1
C16	2309(2)	7556(2)	1923(1)	26(1)	1
C17	3356(2)	8164(2)	2305(1)	20(1)	1
C18	6076(2)	8147(2)	2613(1)	20(1)	1
C19	7054(2)	7212(2)	2835(1)	26(1)	1
C20	7012(2)	9036(2)	2330(1)	18(1)	1
C21	6262(2)	9834(2)	2025(1)	20(1)	1
C22	7048(2)	10710(2)	1797(1)	22(1)	1
C23	8646(2)	10802(2)	1872(1)	21(1)	1
C24	9429(2)	10013(2)	2168(1)	25(1)	1
C25	8618(2)	9149(2)	2393(1)	23(1)	1
C26	8749(3)	12516(2)	1408(1)	29(1)	1
N1	4792(2)	7725(1)	2283(1)	18(1)	1
O1	2981(2)	8949(1)	2589(1)	27(1)	1
O2	9544(2)	11636(1)	1669(1)	29(1)	1
Si1	5707(1)	4953(1)	67(1)	16(1)	1
Cl1	9437(1)	5941(1)	1260(1)	43(1)	1

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

C1–C2	1.529(3)	C14–C15	1.546(3)
C2–C3	1.531(3)	C15–C16	1.524(3)
C2–Si1	1.8892(19)	C16–C17	1.508(3)
C4–C5	1.528(3)	C17–O1	1.235(2)
C5–C6	1.533(3)	C17–N1	1.348(2)
C5–Si1	1.9112(19)	C18–N1	1.471(2)
C7–C8	1.539(3)	C18–C19	1.523(3)
C8–C9	1.536(3)	C18–C20	1.525(3)
C8–Si1	1.8977(19)	C20–C21	1.396(3)
C10–C11	1.343(2)	C20–C25	1.397(3)
C10–Si1	1.8792(18)	C21–C22	1.387(3)
C11–C12	1.497(3)	C22–C23	1.392(3)
C11–C13	1.510(3)	C23–O2	1.375(2)
C12–Cl1	1.809(2)	C23–C24	1.389(3)
C13–C14	1.537(2)	C24–C25	1.384(3)
C14–N1	1.473(2)	C26–O2	1.431(2)

C1–C2–C3	109.35(19)	C7–C8–Si1	114.15(13)
C1–C2–Si1	112.19(14)	C11–C10–Si1	130.47(15)
C3–C2–Si1	114.03(15)	C10–C11–C12	121.77(17)
C4–C5–C6	109.62(17)	C10–C11–C13	122.29(17)
C4–C5–Si1	113.07(13)	C12–C11–C13	115.88(16)
C6–C5–Si1	114.74(14)	C11–C12–Cl1	111.48(13)
C9–C8–C7	110.06(16)	C11–C13–C14	112.84(15)
C9–C8–Si1	113.02(14)	N1–C14–C13	111.05(14)

N1–C14–C15	102.83(14)	O2–C23–C24	115.96(17)
C13–C14–C15	114.27(15)	O2–C23–C22	124.40(19)
C16–C15–C14	105.98(15)	C24–C23–C22	119.64(19)
C17–C16–C15	105.06(16)	C25–C24–C23	120.06(18)
O1–C17–N1	124.95(18)	C24–C25–C20	121.85(19)
O1–C17–C16	126.13(17)	C17–N1–C18	121.62(16)
N1–C17–C16	108.91(16)	C17–N1–C14	114.61(15)
N1–C18–C19	110.80(16)	C18–N1–C14	123.77(14)
N1–C18–C20	112.76(15)	C23–O2–C26	117.13(16)
C19–C18–C20	114.26(16)	C10–Si1–C2	107.57(9)
C21–C20–C25	116.70(19)	C10–Si1–C8	108.59(9)
C21–C20–C18	120.43(16)	C2–Si1–C8	111.53(9)
C25–C20–C18	122.69(18)	C10–Si1–C5	110.86(8)
C22–C21–C20	122.53(18)	C2–Si1–C5	109.94(9)
C21–C22–C23	119.21(19)	C8–Si1–C5	108.35(9)

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

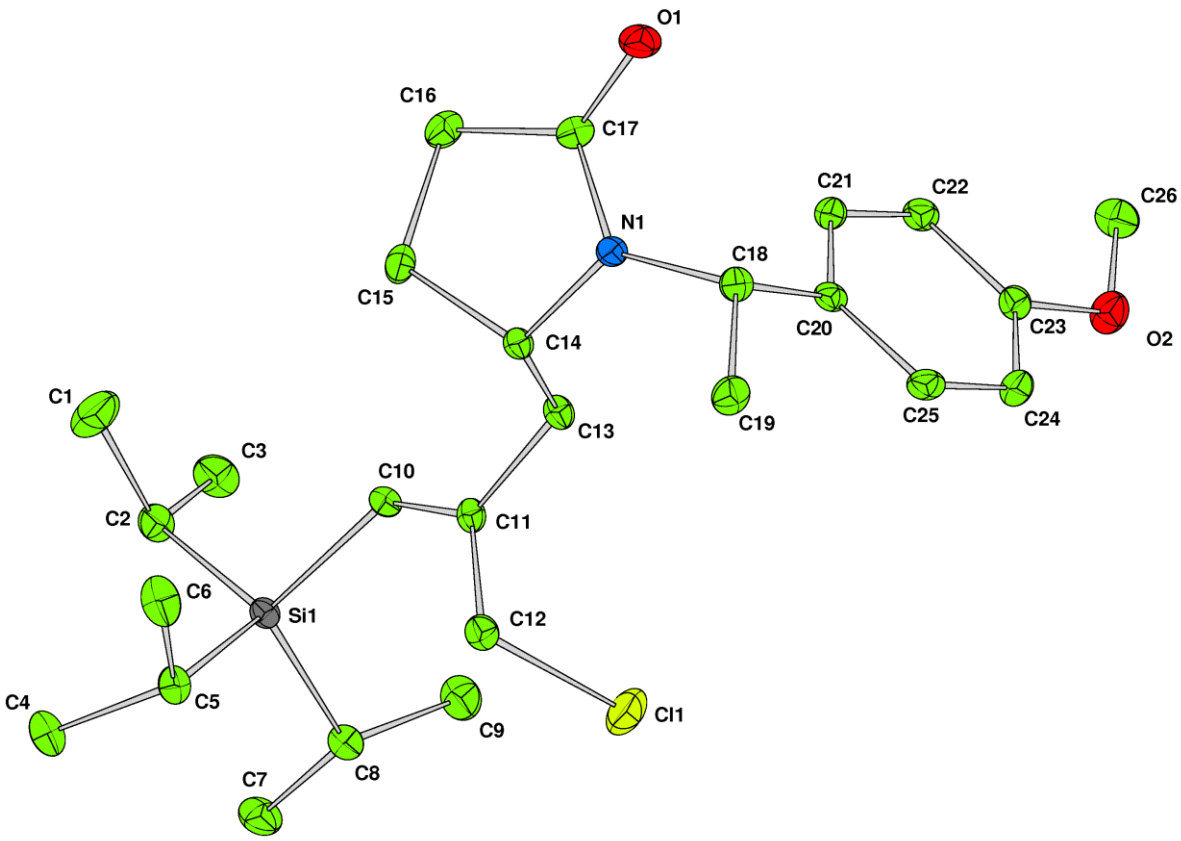
Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	24(1)	50(2)	56(2)	9(1)	–8(1)	2(1)
C2	28(1)	24(1)	21(1)	–2(1)	–8(1)	3(1)
C3	41(1)	28(1)	28(1)	3(1)	–8(1)	7(1)
C4	39(1)	21(1)	29(1)	–2(1)	–1(1)	–5(1)
C5	25(1)	20(1)	19(1)	1(1)	–3(1)	–3(1)
C6	45(1)	28(1)	23(1)	4(1)	2(1)	–10(1)

C7	34(1)	29(1)	26(1)	−5(1)	9(1)	2(1)
C8	25(1)	19(1)	18(1)	1(1)	1(1)	0(1)
C9	35(1)	30(1)	33(1)	−2(1)	11(1)	−8(1)
C10	20(1)	15(1)	17(1)	0(1)	1(1)	1(1)
C11	19(1)	15(1)	16(1)	2(1)	2(1)	−4(1)
C12	23(1)	21(1)	21(1)	−1(1)	−1(1)	0(1)
C13	22(1)	17(1)	16(1)	−1(1)	2(1)	−2(1)
C14	19(1)	18(1)	16(1)	−3(1)	−1(1)	0(1)
C15	20(1)	28(1)	23(1)	−3(1)	0(1)	−6(1)
C16	20(1)	32(1)	26(1)	1(1)	−4(1)	1(1)
C17	19(1)	24(1)	16(1)	4(1)	2(1)	2(1)
C18	22(1)	25(1)	14(1)	−3(1)	−3(1)	1(1)
C19	25(1)	28(1)	25(1)	2(1)	−7(1)	2(1)
C20	20(1)	19(1)	15(1)	−4(1)	−1(1)	4(1)
C21	18(1)	22(1)	20(1)	−4(1)	−3(1)	2(1)
C22	23(1)	21(1)	23(1)	−2(1)	−4(1)	5(1)
C23	21(1)	22(1)	21(1)	−5(1)	0(1)	−1(1)
C24	19(1)	28(1)	27(1)	−3(1)	−5(1)	0(1)
C25	22(1)	24(1)	23(1)	−1(1)	−5(1)	8(1)
C26	34(1)	24(1)	28(1)	5(1)	7(1)	1(1)
N1	17(1)	22(1)	14(1)	−5(1)	0(1)	1(1)
O1	26(1)	32(1)	24(1)	−7(1)	2(1)	6(1)
O2	26(1)	27(1)	35(1)	7(1)	−2(1)	−3(1)
Si1	19(1)	16(1)	14(1)	−1(1)	−1(1)	0(1)
Cl1	23(1)	39(1)	66(1)	4(1)	−13(1)	−3(1)

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1A	2372	5707	122	65	1
H1B	2367	4402	66	65	1
H1C	1622	5144	−397	65	1
H2	4064	4514	−670	29	1
H3A	3230	6230	−989	48	1
H3B	5088	6185	−959	48	1
H3C	4127	6827	−509	48	1
H4A	5120	1931	177	44	1
H4B	5767	2640	−314	44	1
H4C	4009	2793	−117	44	1
H5	6688	3344	496	26	1
H6A	3523	3587	811	47	1
H6B	4959	4048	1151	47	1
H6C	4753	2757	1069	47	1
H7A	7013	4846	−1082	44	1
H7B	7443	3727	−784	44	1
H7C	8794	4541	−971	44	1
H8	8435	4722	−49	25	1
H9A	9217	6297	−514	49	1
H9B	8234	6626	7	49	1
H9C	7444	6676	−574	49	1
H10	4828	6615	512	21	1
H12A	7489	4721	1003	26	1

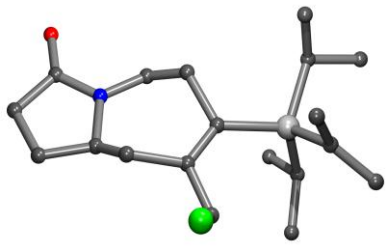
H12B	7214	5111	1609	26	1
H13A	5515	7728	1226	22	1
H13B	7012	7404	1572	22	1
H14	5404	6162	2091	21	1
H15A	3166	6464	1350	28	1
H15B	2880	5894	1923	28	1
H16A	2033	8022	1612	31	1
H16B	1342	7322	2105	31	1
H18	5580	8507	2930	24	1
H19A	6370	6651	2987	39	1
H19B	7747	7492	3115	39	1
H19C	7675	6891	2546	39	1
H21	5172	9775	1970	24	1
H22	6501	11242	1593	27	1
H24	10522	10066	2216	30	1
H25	9169	8617	2596	27	1
H26A	8173	12233	1099	43	1
H26B	9507	13061	1287	43	1
H26C	8021	12858	1660	43	1



Thermal ellipsoids drawn at the 35% probability level

Crystal Structure Data for compound 209a

Table 1. Crystal data and structure refinement details.



Identification code	**2008sot1097**
Empirical formula	$C_{19}H_{34}ClNOSi$
Formula weight	356.01
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 18.327(2) Å
	b = 14.1296(17) Å $\quad \beta$ = 100.800(6)°
	c = 7.9043(8) Å
Volume	2010.6(4) Å^3
Z	4
Density (calculated)	1.176 Mg / m^3
Absorption coefficient	0.255 mm^{-1}
F(000)	776
Crystal	Fragment; Colourless
Crystal size	0.18 × 0.1 × 0.02 mm^3
θ range for data collection	2.99 – 25.02°
Index ranges	$-21 \le h \le 21$, $-15 \le k \le 16$, $-9 \le l \le 9$
Reflections collected	19429
Independent reflections	3533 [R_{int} = 0.1570]
Completeness to θ = 25.02°	99.5 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9949 and 0.9456

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3533 / 222 / 214
Goodness-of-fit on F^2	1.510
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.2175, *wR2* = 0.4672
R indices (all data)	*R1* = 0.3519, *wR2* = 0.5374
Largest diff. peak and hole	1.064 and −0.482 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 S**tructure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). S**tructure 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. The crystals and data quality were poor.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [Å^2 × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
Cl1	1828(1)	3259(1)	4363(1)	120(1)	1
Si1	3199(1)	5165(1)	1565(1)	76(1)	1
O1	453(1)	8239(1)	2725(2)	113(1)	1
N1	858(1)	6763(1)	2422(2)	86(1)	1
C1	359(1)	7398(1)	2730(2)	86(1)	1
C2	−312(1)	6858(1)	3074(1)	107(1)	1
C3	−162(1)	5879(1)	2939(1)	146(1)	1
C4	616(1)	5773(1)	2586(1)	122(1)	1
C5	1071(1)	5177(2)	3481(3)	134(1)	1
C6	1764(1)	4863(1)	2559(3)	109(1)	1
C7	2295(1)	5470(1)	2293(3)	107(1)	1

C8	2163(1)	6515(1)	2706(2)	151(1)	1
C9	1533(1)	7010(1)	1944(2)	118(1)	1
C10	1835(1)	3829(1)	2364(2)	96(1)	1
C11	3042(2)	4876(1)	−793(2)	159(1)	1
C12	2646(2)	3964(1)	−1302(3)	213(2)	1
C13	2697(2)	5724(1)	−1888(3)	220(1)	1
C14	4135(1)	3400(1)	2028(1)	258(2)	1
C15	3724(1)	4251(1)	2866(1)	177(1)	1
C16	3683(1)	4184(1)	4876(1)	163(1)	1
C17	4499(1)	6142(2)	958(3)	172(1)	1
C18	3820(1)	6224(1)	1809(2)	148(1)	1
C19	4055(1)	6504(1)	3684(1)	210(2)	1

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

Cl1–C10	1.7763(18)	C4–C5	1.298(3)
Si1–C15	1.8116(5)	C5–C6	1.639(3)
Si1–C18	1.867(2)	C6–C7	1.343(3)
Si1–C11	1.8768(19)	C6–C10	1.478(2)
Si1–C7	1.903(2)	C7–C8	1.5418(19)
O1–C1	1.202(2)	C8–C9	1.3875(8)
N1–C1	1.335(2)	C11–C12	1.497(3)
N1–C9	1.4038(17)	C11–C13	1.542(3)
N1–C4	1.480(2)	C14–C15	1.6242(4)
C1–C2	1.5147(19)	C15–C16	1.6071(3)
C2–C3	1.4185(3)	C17–C18	1.526(3)
C3–C4	1.5107(4)	C18–C19	1.517(2)

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

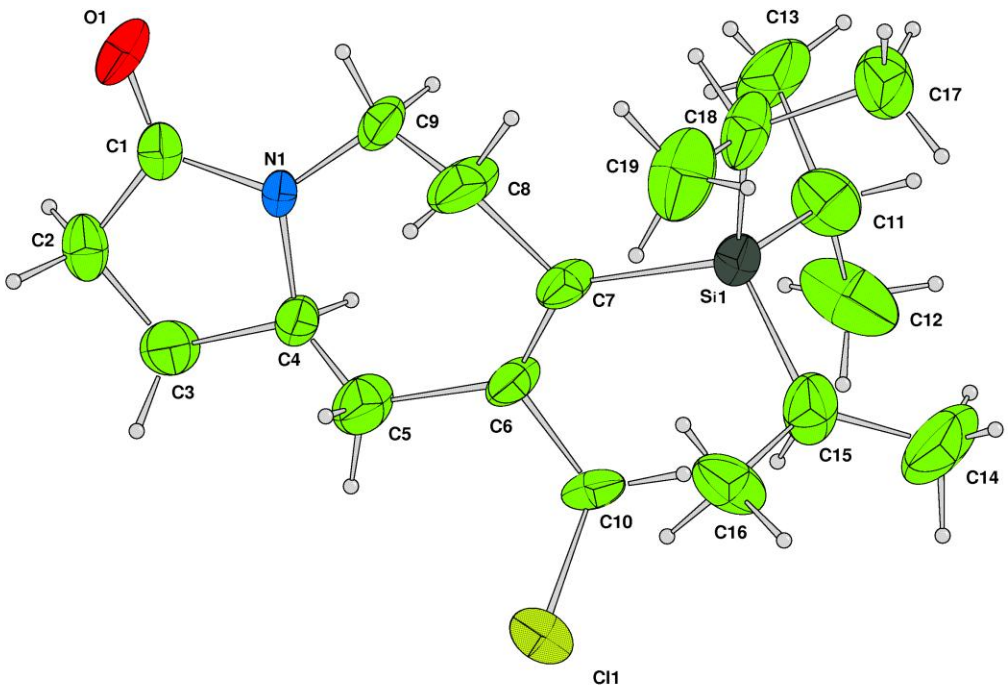
Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl1	110(1)	152(1)	99(1)	16(1)	21(1)	−24(1)
Si1	78(1)	76(1)	73(1)	−8(1)	10(1)	12(1)
O1	99(1)	83(1)	145(1)	−41(1)	−14(1)	27(1)
N1	84(1)	67(1)	122(1)	4(1)	56(1)	9(1)
C1	70(1)	120(1)	62(1)	−9(1)	−1(1)	26(1)
C2	80(1)	149(2)	91(1)	−16(1)	13(1)	23(1)
C3	92(1)	140(2)	219(2)	47(2)	63(1)	16(1)
C4	113(1)	83(1)	189(2)	10(1)	76(1)	11(1)
C5	112(2)	110(1)	181(2)	12(2)	29(1)	−5(1)
C6	79(1)	63(1)	186(2)	19(1)	29(1)	11(1)
C7	72(1)	53(1)	192(2)	4(1)	13(1)	−7(1)
C8	127(2)	85(1)	242(2)	16(2)	36(2)	−7(1)
C9	101(1)	64(1)	195(2)	3(1)	41(1)	17(1)
C10	134(2)	66(1)	78(1)	21(1)	−6(1)	4(1)
C11	191(2)	178(2)	99(1)	3(2)	6(2)	−13(2)
C12	311(3)	215(2)	108(2)	−49(2)	26(2)	−134(2)
C13	303(3)	196(2)	146(2)	71(2)	6(2)	137(2)
C14	307(4)	215(3)	247(3)	72(3)	41(3)	112(3)
C15	149(2)	252(3)	131(2)	45(2)	27(2)	84(2)
C16	111(2)	248(3)	123(2)	74(2)	7(1)	4(2)
C17	127(2)	156(2)	255(2)	−30(2)	91(2)	−21(2)

C18	78(1)	127(2)	238(2)	−75(2)	29(1)	−8(1)
C19	160(2)	195(3)	266(3)	−89(2)	19(2)	−5(2)

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H2A	−403	7007	4240	128	1
H2B	−759	7037	2222	128	1
H3A	−525	5593	1991	175	1
H3B	−204	5552	4025	175	1
H4	541	5520	1384	147	1
H5A	790	4604	3690	161	1
H5B	1274	5464	4614	161	1
H8A	2187	6553	3966	181	1
H8B	2594	6874	2458	181	1
H9A	1473	6933	681	142	1
H9B	1623	7691	2200	142	1
H10A	2306	3684	1972	115	1
H10B	1419	3591	1484	115	1
H11	3549	4795	−1070	190	1
H12A	2109	4062	−1429	320	1
H12B	2808	3487	−411	320	1
H12C	2762	3746	−2399	320	1
H13A	2791	5659	−3063	330	1
H13B	2921	6313	−1380	330	1

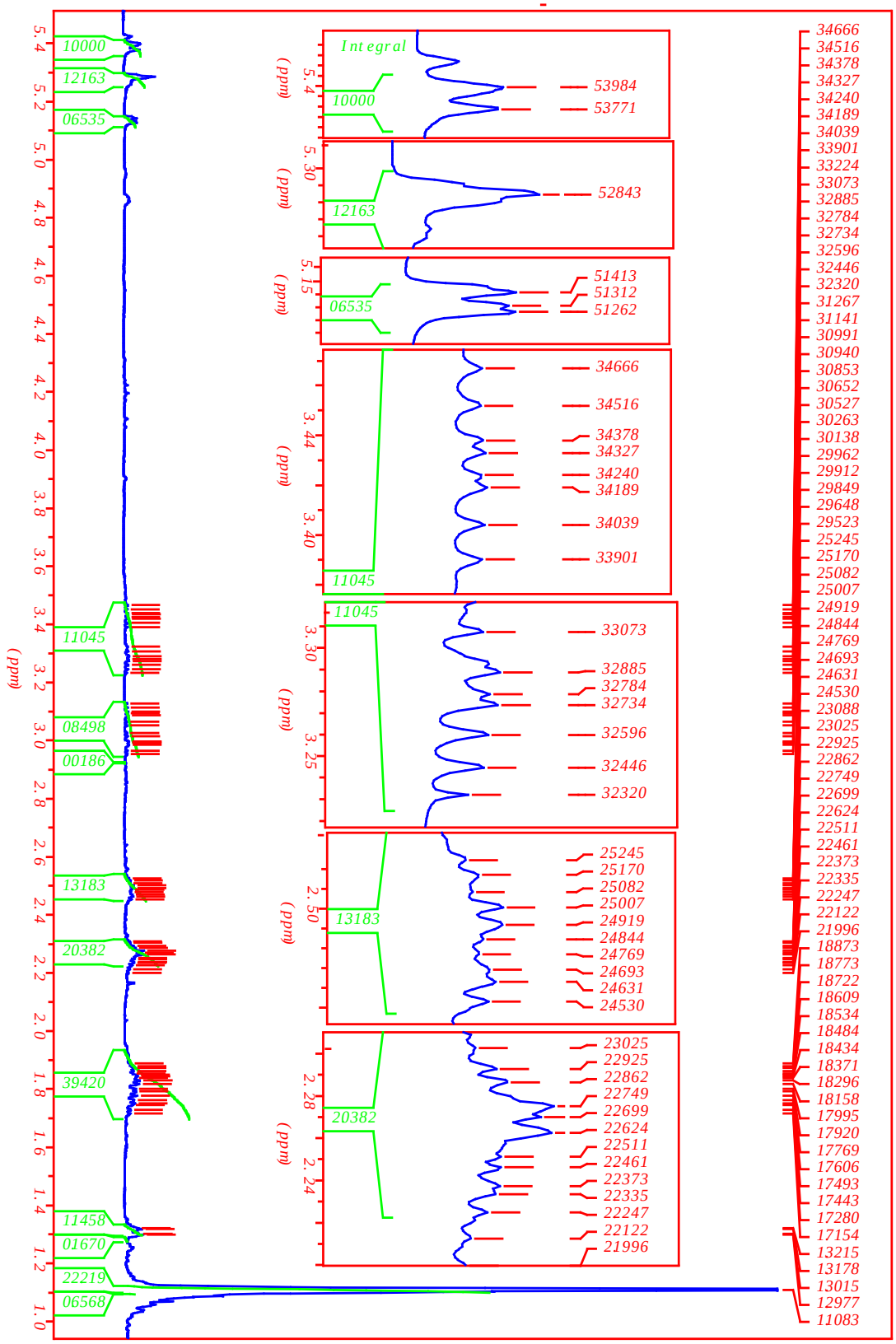
H13C	2160	5738	−1917	330	1
H14A	4642	3323	2680	387	1
H14B	4153	3554	828	387	1
H14C	3858	2810	2071	387	1
H15	4185	4646	3098	212	1
H16A	4044	3716	5436	244	1
H16B	3182	3991	4999	244	1
H16C	3797	4803	5418	244	1
H17A	4794	6724	1165	258	1
H17B	4338	6049	−284	258	1
H17C	4802	5602	1448	258	1
H18	3516	6760	1226	177	1
H19A	4577	6330	4087	314	1
H19B	3744	6175	4377	314	1
H19C	3998	7189	3800	314	1



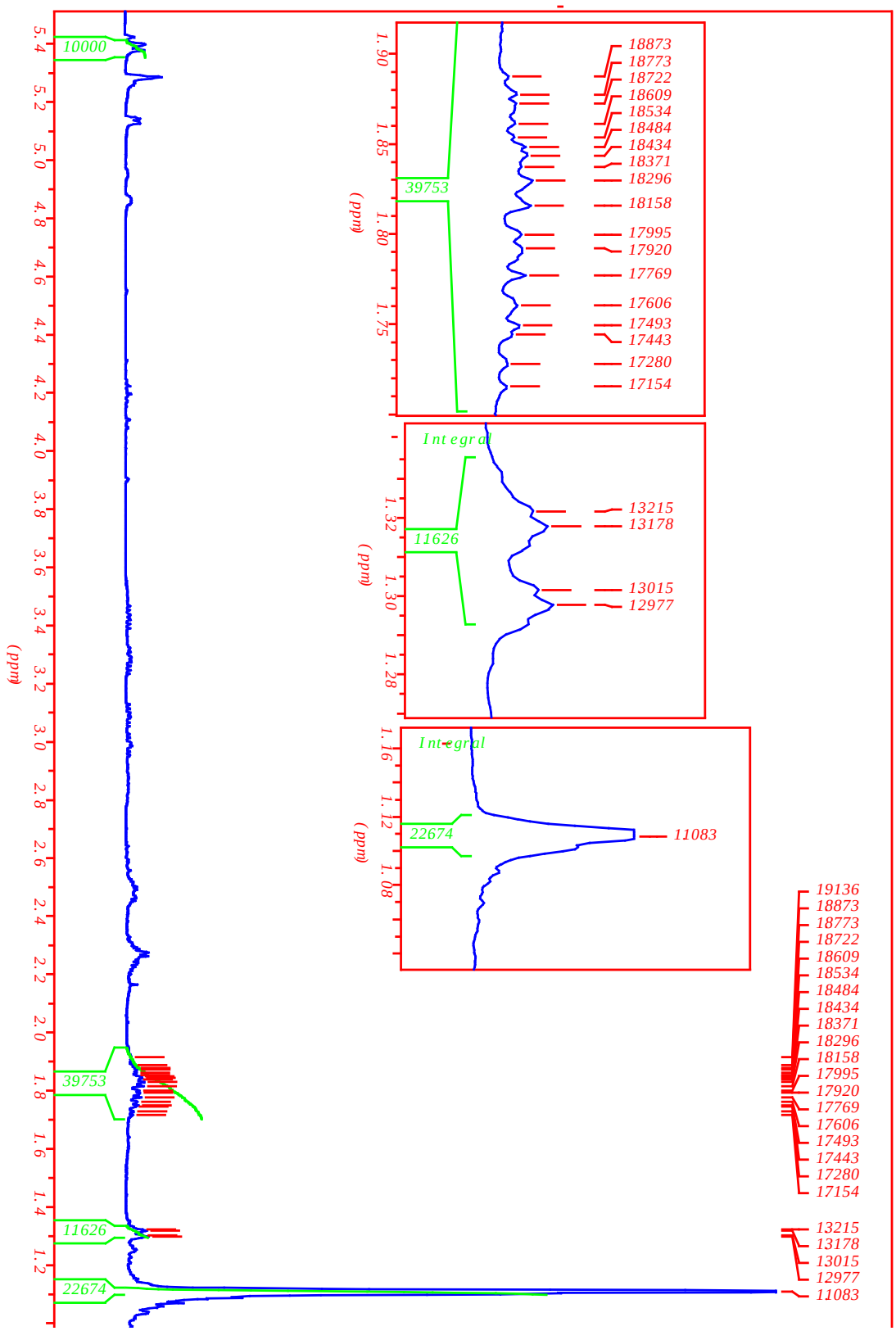
Thermal ellipsoids drawn at the 20% probability level

Appendix 2 – NMR data

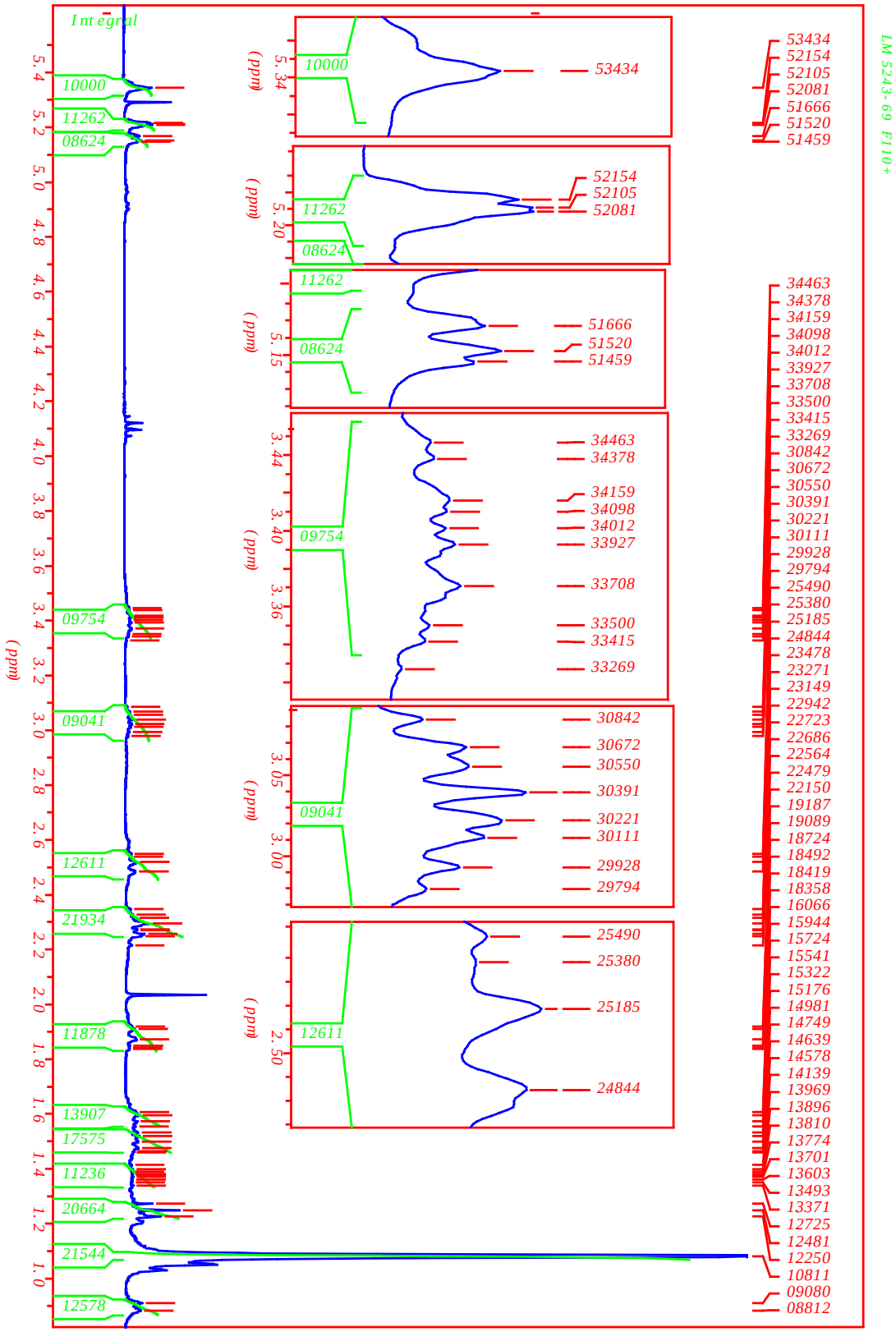
^{1}H NMR (300 MHz $CDCl_3$) data for compound **289**



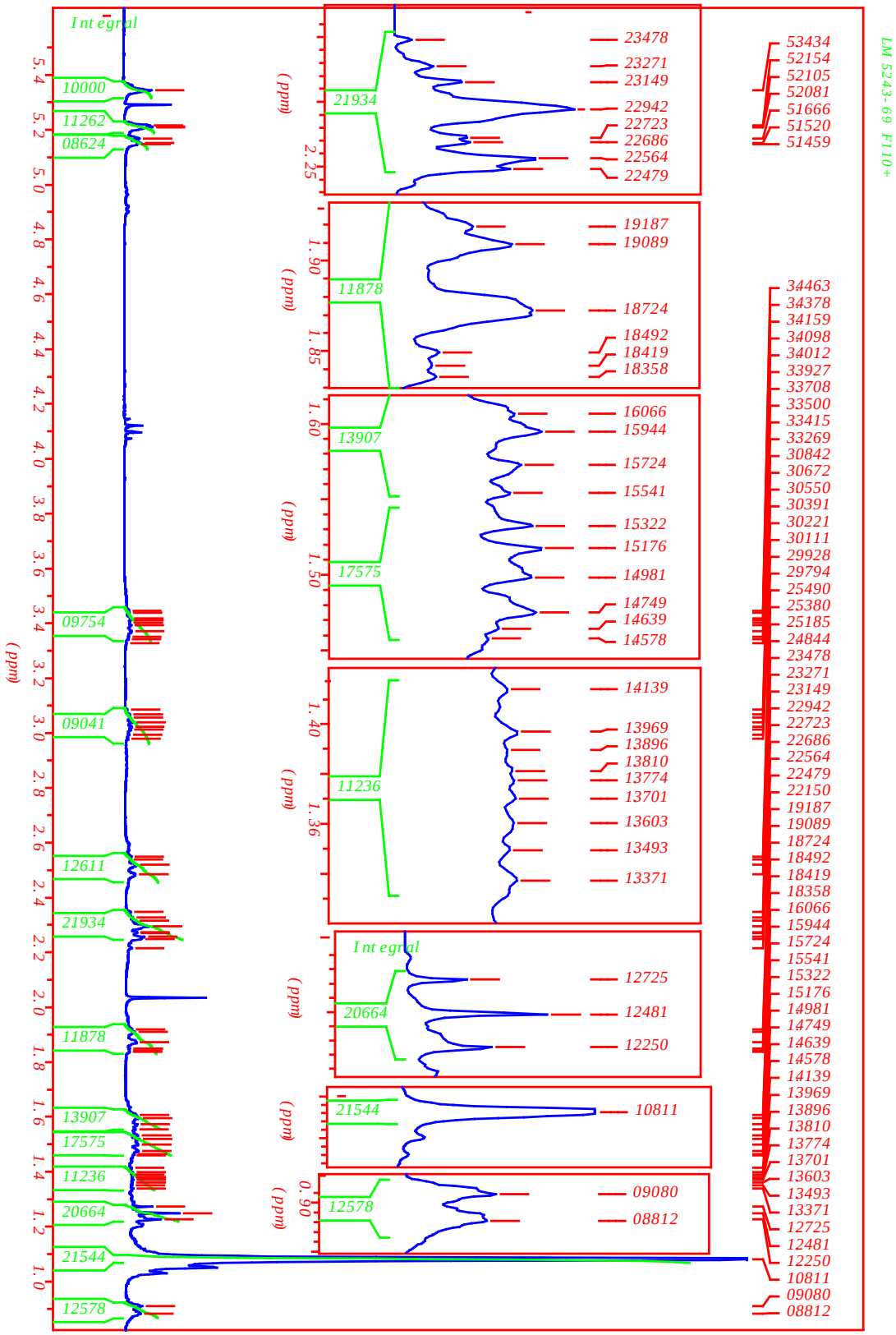
^{1}H NMR (300 MHz $CDCl_3$) data for compound **289**



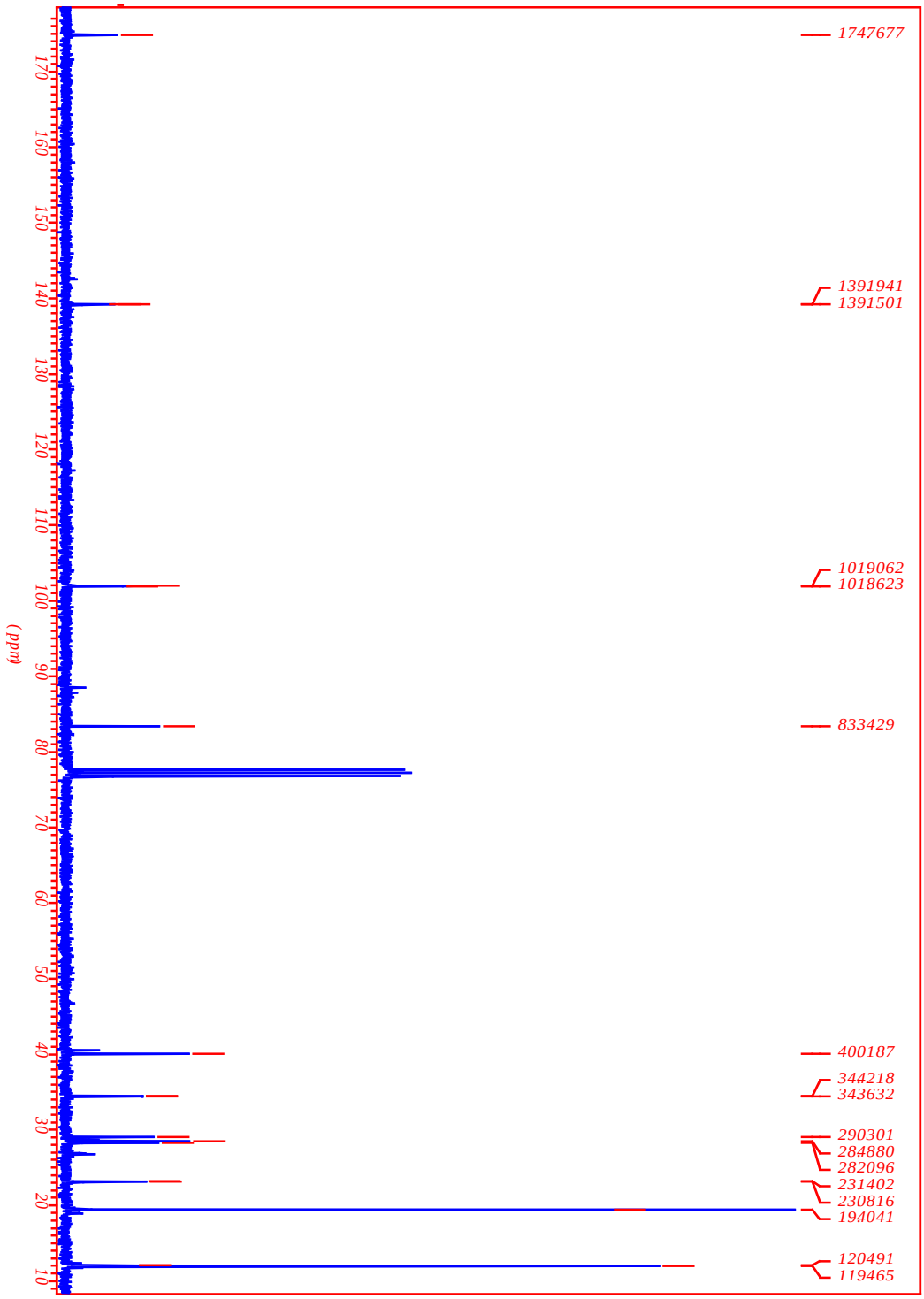
^{1}H NMR (300 MHz $CDCl_3$) data for compound **293**



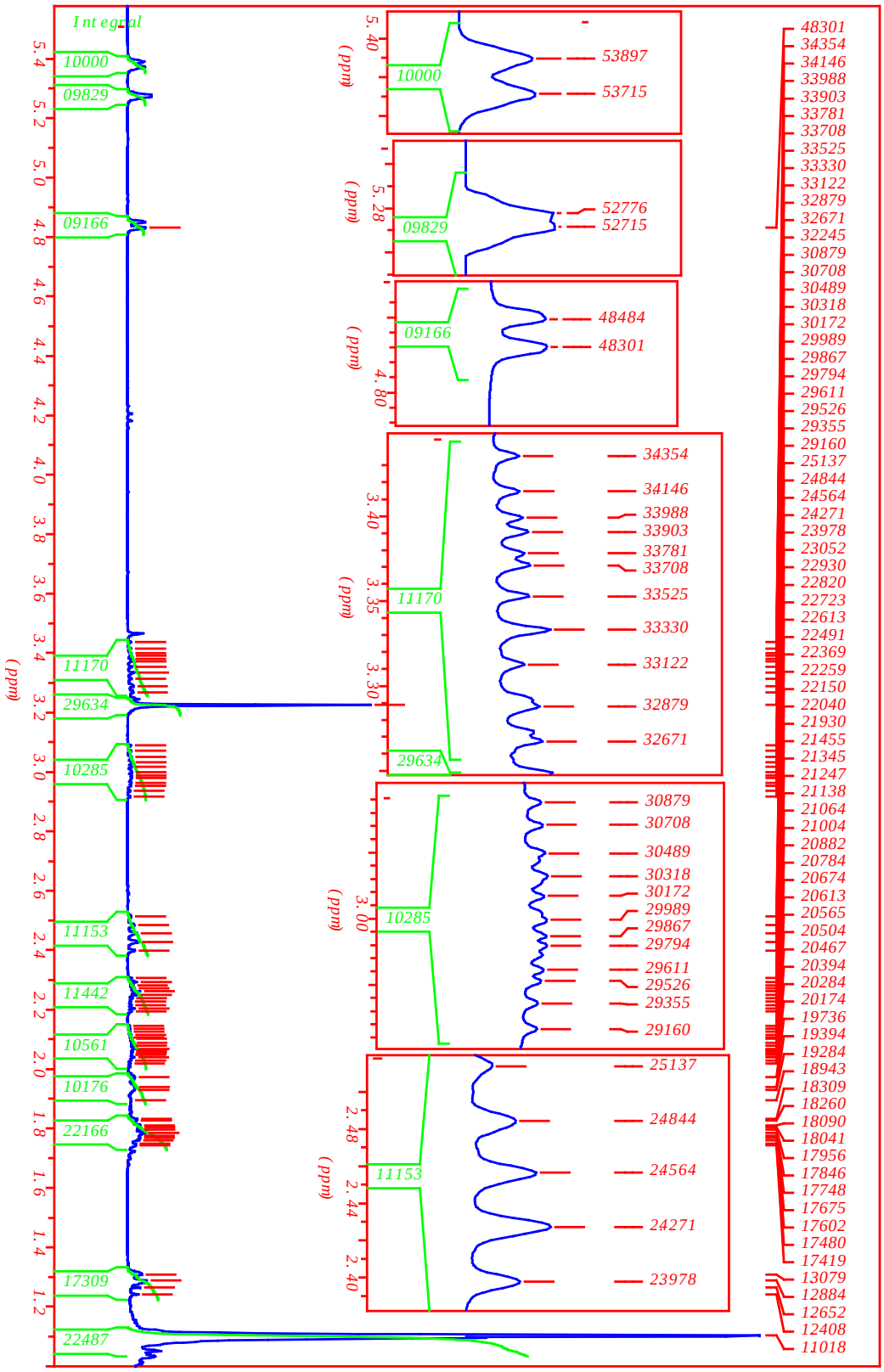
^{1}H NMR (300 MHz $CDCl_3$) data for compound **293**



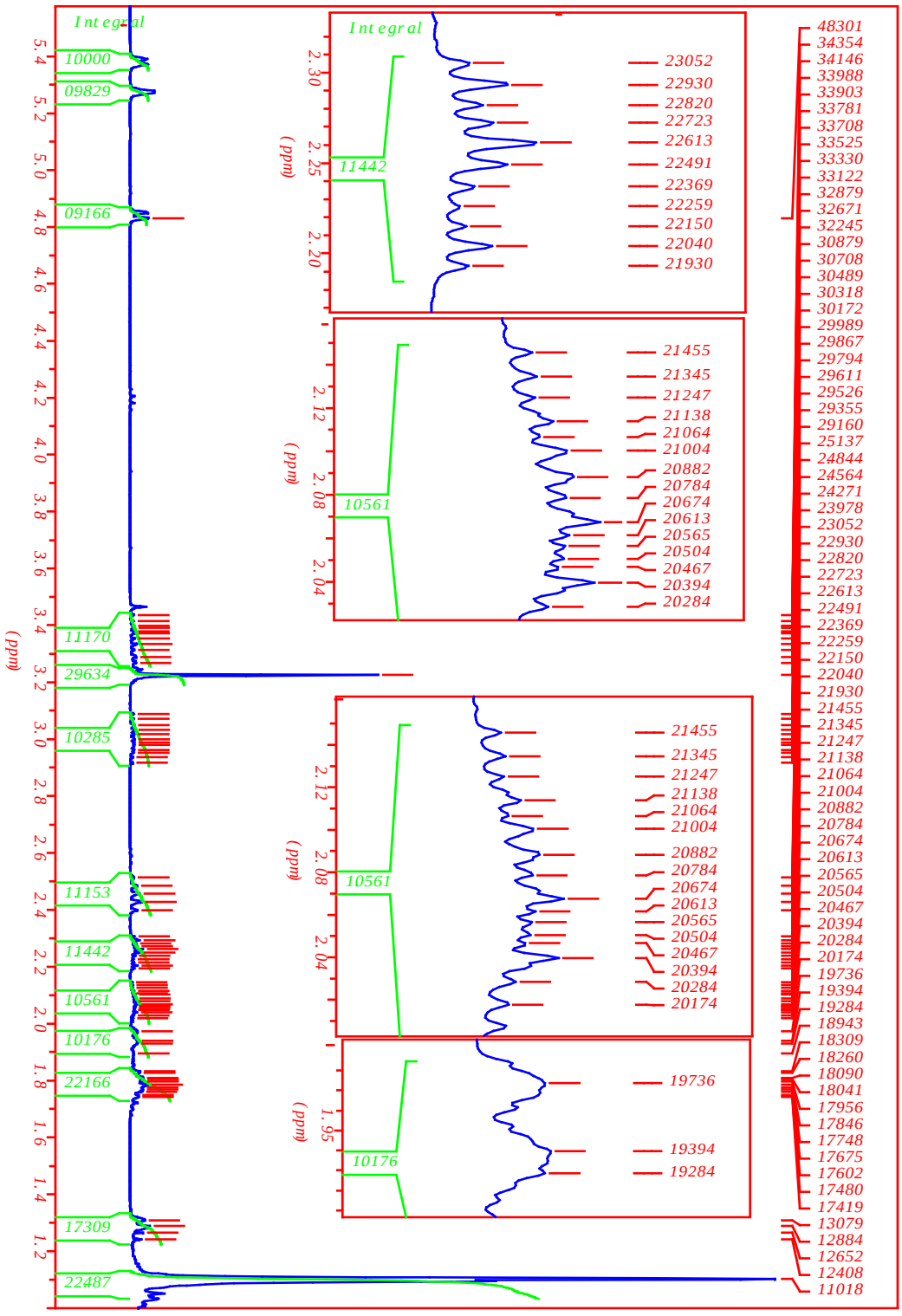
^{13}C NMR (75 MHz $CDCl_3$) data for compound **293**



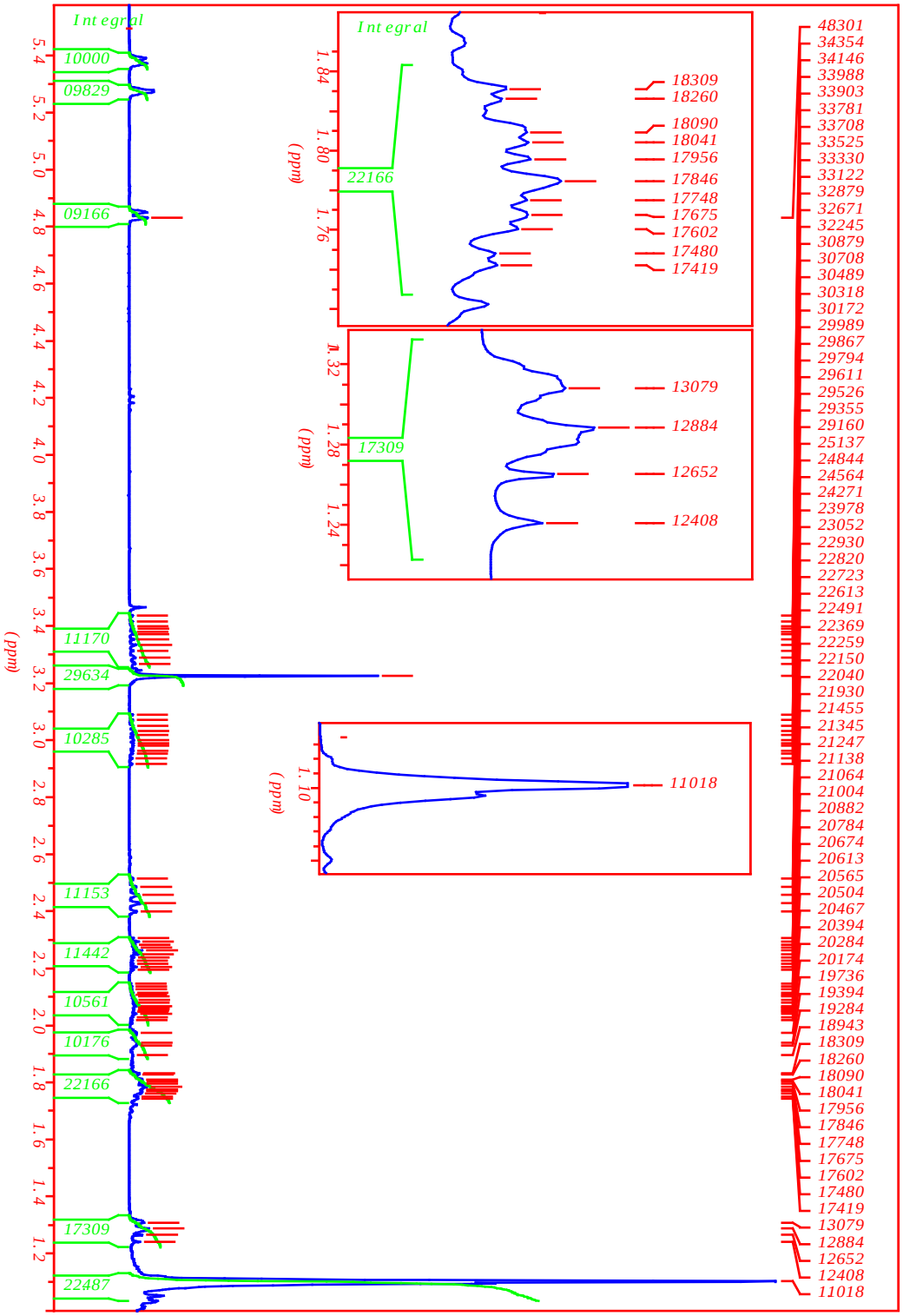
^{1}H NMR (300 MHz $CDCl_3$) data for compound **290**



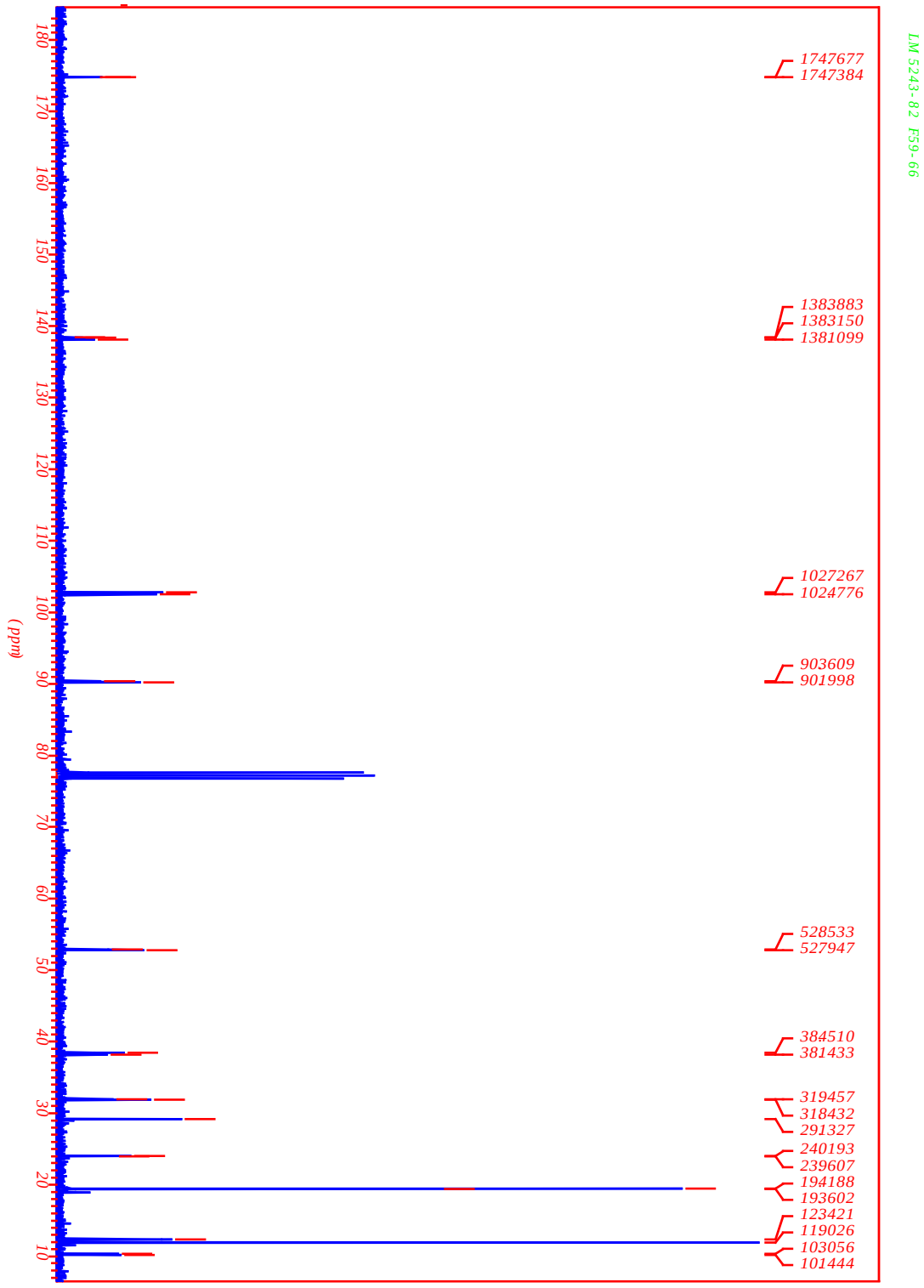
^{1}H NMR (300 MHz $CDCl_3$) data for compound **290**



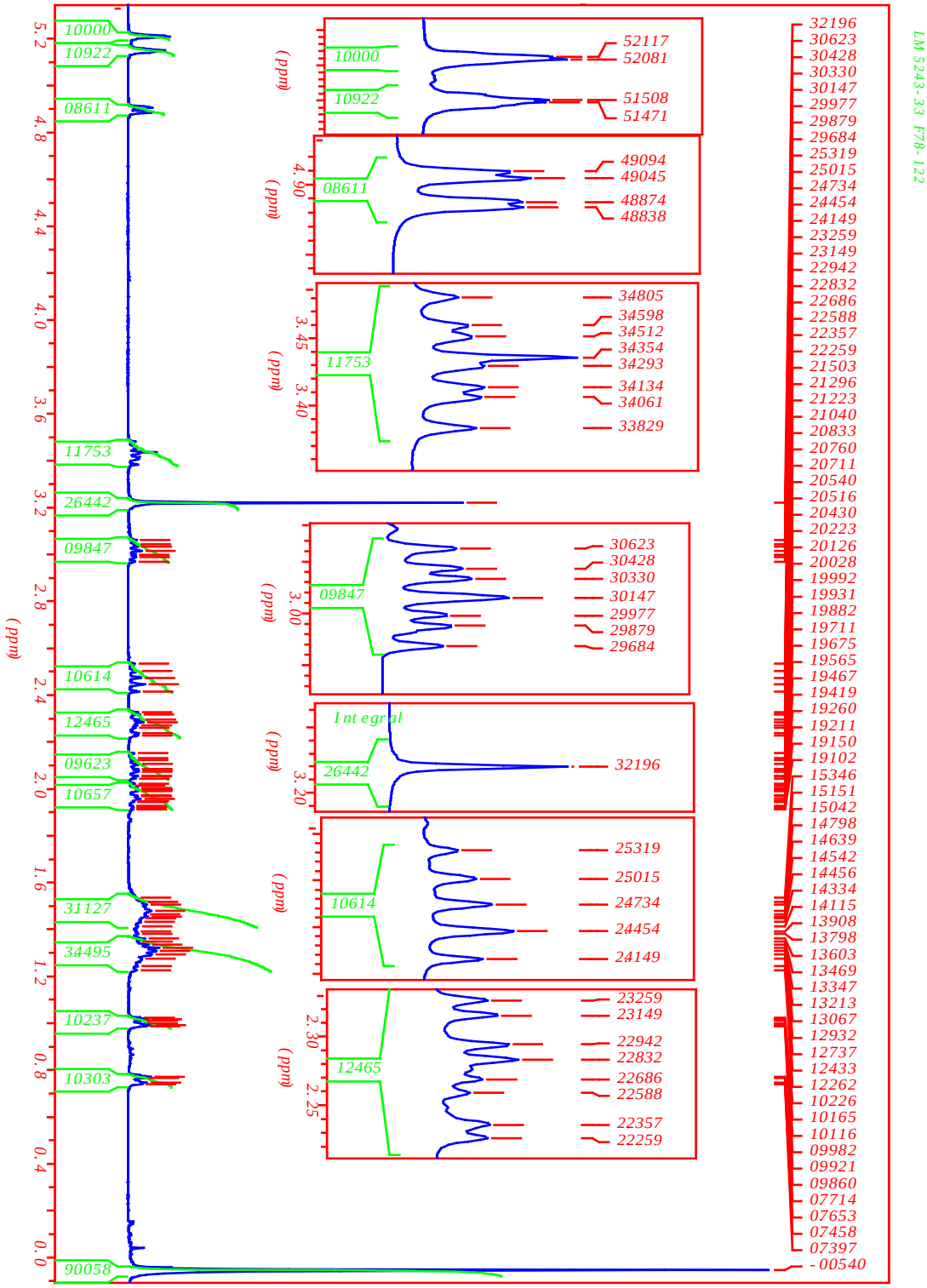
^{1}H NMR (300 MHz $CDCl_3$) data for compound **290**



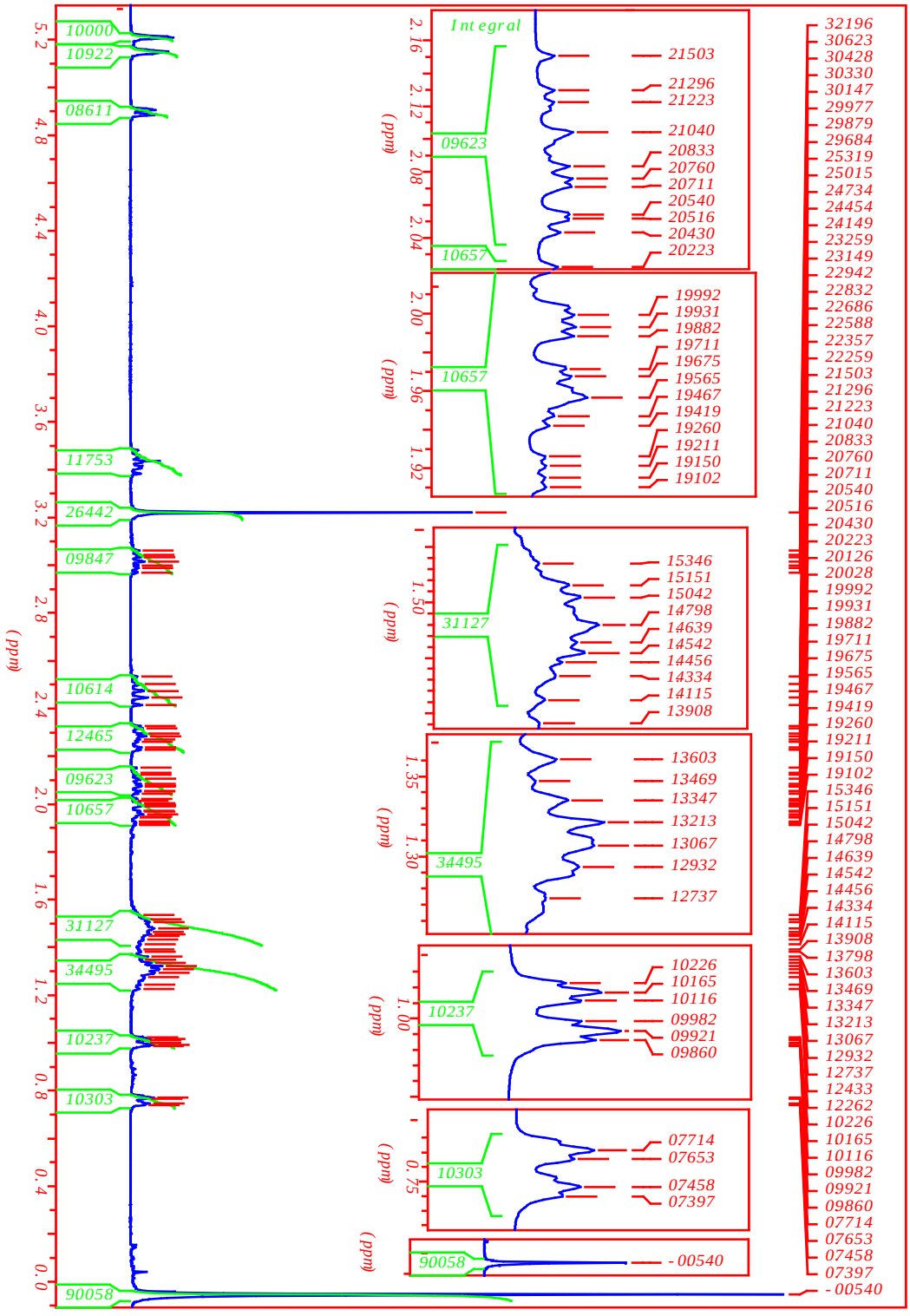
^{13}C NMR (75 MHz $CDCl_3$) data for compound **290**



^{1}H NMR (300 MHz $CDCl_3$) data for compound **292**



^{1}H NMR (300 MHz $CDCl_3$) data for compound **292**



^{13}C NMR (75 MHz $CDCl_3$) data for compound **292**