Silacyclohex-4-enes: novel silene-cycloadducts for organic synthesis

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Silacyclohex-4-enes: Novel Silene-Cycloadducts for Organic Synthesis

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PhD Thesis

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Abstract

Silenes, compounds containing a Si=C double bond, are highly reactive and are normally observed as transient intermediates which readily dimerise. Evidence for their existence was first reported in 1967 by Gusel'nikov and Flowers.[1] However, since then only minimal effort has been made to exploit their unique reactivity in organic synthesis.

This thesis describes research concerning the chemistry of silenes and more specifically their Diels-Alder adducts, silacyclohex-4-enes. These cycloadducts were utilised as building blocks for organic synthesis, enabling the total synthesis of prelactone B (R = ^{i}Pr) and an analogue (R = Ph) to be achieved in high yields over 5 steps (Figure 1).[2]

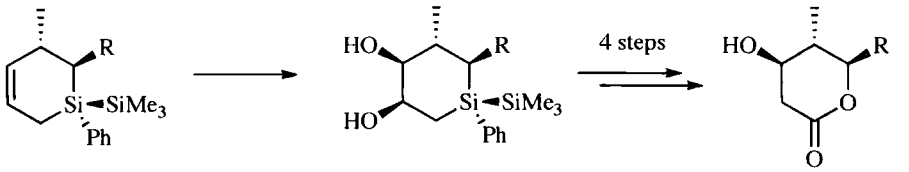


Figure 1

In addition, a unique application of the Hosomi-Sakurai reaction to the cycloadducts provides access to a unique 1,4-monoprotected diol and tetrahydronaphthalene, both possessing four contiguous chiral centres. This methodology was then applied to the total synthesis of the podophyllotoxin analogue, epipicropodophylin (Figure 2).[3-6]

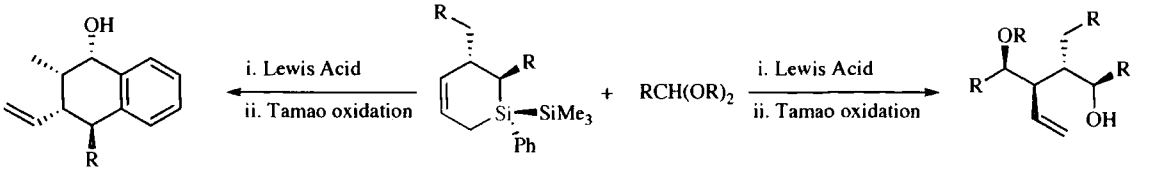


Figure 2

Copyright

Declaration

This work was conducted in the Department of Chemistry at the University of Durham between October 2003 and September 2006. A two month placement was undertaken at Uppsala University, Department of Biochemistry and Organic Chemistry, BMC, Uppsala, Sweden under the supervision of Ass. Prof. Henrik Ottosson. This work has not been submitted in any other university. It is my own work, unless otherwise stated.

Acknowledgments

Firstly, I would like to thank my supervisor Patrick Steel, without whom none of this work would have been possible. His continued support and encouragement were invaluable throughout the three years.

Prof. Henrik Ottosson and the Chemistry department at Uppsala University in Sweden and Dr. Christoph Marschner and the Chemistry department at the Graz University of Technology in Austria, thank you for a warm welcome and much support during my placements in your groups.

The staff at the University of Durham; NMR - Alan, Catherine and Ian; Glassblowers – Peter and Malcolm, everyone at stores and the mass spec department, thank you for all you have done.

The past and present members of CG1/CY1. It has been a pleasure to work with you all through the years. Thank you for making the lab and office an exciting place to be.

Special mentions go to Dr. Liz Grayson (University of Durham) and Dr. John Herbert (Sanofi-Aventis) for proof reading this work.

Finally, the biggest thank you goes to my family and partner Helen. Without their continued support, none of this would have been possible. Thank you for everything!

Abbreviations

b.p.	Boiling point
BF_3•2AcOH	Boron trifluoride diacetic acid complex
BF_3•OEt_2	Boron trifluoride diethyl ether complex
CDI	Carbodiimidazole
CI	Chemical ionization
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAD	Dimethyl acetylenedicarboxylate
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
EDTA	Ethylenediaminetetraacetic acid
EI	Electron impact
eq.	Equivalents
Et_3N	Triethylamine
Et_3SiH	Triethylsilane
GC	Gas chromatography
h	Hours
HF-Py	HF-pyridine complex
Hünigs base	Diisopropylethylamine
Im.	Imidazole
IR	Infra red
kJ	KiloJoule
KO^{t}Bu	Potassium *tert*-butoxide
LDA	Lithium diisopropylamide
LiBr	Lithium bromide
LiHMDS	Lithium hexamethyldisilazane
M	Molar
m	Multiplet
m.p.	Melting point (°C)
mmol	Millimole
MOM	Methoxymethyl
MS	Mass spectroscopy
MTO	Methyltrioxorhenium
n-BuLi	*n*-Butyllithium
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
OsO_4	Osmium tetroxide
PCC	Pyridinium chlorochromate
ppm	Parts per million
PPTS	Pyridinium *p*-toluene sulfonate
q	Quartet
R_f	Retention factor
rt	Room temperature
s	Singlet
t	Triplet
TBAF	Tetra-*N*-butylammonium fluoride

TBAT	*tert*-Butylammonium difluorotriphenylsilicate
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TES	Triethylsilyl
TFA	Trifluoroacetic acid
$TiCl_4$	Titanium tetrachloride
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
p-TSA	*para*-Toluene sulfonic acid
TTBP	2,4,6-Tri-*tert*-butylpyrimidine

1 Introduction

This thesis describes research concerning the chemistry and application of silacyclohex-4-enes in organic chemistry. The following chapter will focus on some selected aspects of organosilicon chemistry, with particular emphasis on silene generation, reactivity and isolation to generate the desired silacyclohex-4-enes. Chapter 2 will present the first total synthesis of Prelactone B and an analogue starting from silacyclohex-4-enes. Chapter 3 focuses on Hosomi-Sakurai methodology applied to elaborate silacyclohex-4-enes to 1,4-monoprotected diols and tetrahydronaphthalenes. Chapter 4 will highlight this methodology by completing the total synthesis of the podophyllotoxin analogue, epipicropodophyllotoxin. Finally, Chapter 5 will conclude the work presented and look at prospects for future work arising from this thesis. Chapter 6 will detail the experimental procedures.

1.1 Selected Aspects of Organosilicon chemistry

1.1.1 General Organosilicon Chemistry

Silicon is a group 14 element positioned directly below carbon. Silicon shares many characteristics with carbon, such as having a valency of 4 and forming tetrahedral compounds.[7] However, silicon has found widespread use in organic synthesis because of its distinct differences when compared to carbon and other elements.[8] This section will briefly outline some of these aspects and give an overview into silicon's reactivity.

1.1.1.1 Bond Length and Strength[8]

A great deal of silicon chemistry is driven by the formation of longer and stronger silicon-oxygen and silicon-fluorine bonds at the expense of others, such as silicon-

carbon (Table 1). Of particular importance is the silicon-fluorine bond, which is longer and almost twice as strong as its carbon equivalent. This key bond is greatly exploited in organic synthesis.

Bond to C	Bond Length[a]	Bond Energy[b]	Bond to Si	Bond Length[a]	Bond Energy[b]
C-C	1.54	334	Si-C	1.89	318
C=C	1.32	620	Si=C	[1.72]	490
C-O	1.41	340	Si-O	1.63	531
C-Cl	1.78	335	Si-Cl	2.05	471
C-F	1.39	**452**	**Si-F**	1.60	**808**

[a.] Bond lengths quoted in angstroms; [b.] Bond energy quoted in kJ mol^{-1}

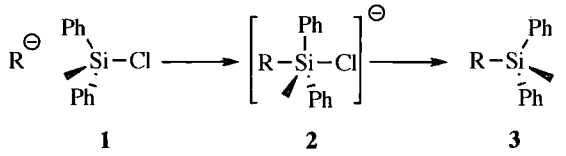
Table 1

1.1.1.2 Inductive Effects

In addition to the physical properties of silicon bonds, the electronic properties also play a crucial role in their chemistry. Silicon is an inductive electron donor to carbon (electronegativities: Si 1.64; C 2.35) leading to a polarised bond, $Si^{\delta+}$-$C^{\delta-}$, which allows for nucleophilic attack at silicon. Moreover, silicon is less electronegative than hydrogen, forming $Si^{\delta+}$-$H^{\delta-}$, allowing Et_3SiH to act as a reducing agent.

1.1.1.3 Nucleophilic Substitution at Silicon

It is the electronic factors outlined above that allow for nucleophilic substitution to occur at silicon by an S_N2-type mechanism. This mechanism is referred to as an S_N2-Si pathway. This pathway proceeds with inversion of stereochemistry *via* a pentacoordinate intermediate **2** (**Scheme 1**).



Scheme 1

In contrast, the S_N2 pathway for that of carbon goes *via* a pentacoordinate transition state. The S_N2-Si mechanism is made possible by the availability of low-lying *d*-orbitals on silicon.

1.1.1.4 α-Carbon-Metal and β-Carbocation Stabilisation

Another useful characteristic of silicon is its ability to stabilise both a carbanion in the α-position and a carbocation in the β-position. This ability to stabilise α-carbanions can be attributed to several factors: 1. Overlap of the α-carbon-metal bond with a silicon *d*-orbital. 2. Overlap of the α-carbon-metal bond with the adjacent σ* antibonding orbital between silicon and carbon. This overlap can occur because the antibonding orbital on silicon is larger than on carbon and silicon is more electropositive (**Figure 3**).

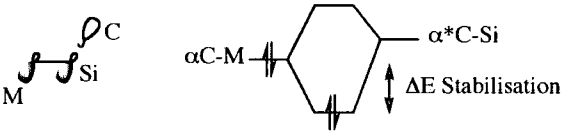


Figure 3

Silicon also stabilises β-carbocations through overlap of the vacant *p* orbital on the β carbon atom and the σ orbital between the silicon atom and the α carbon atom. This effect means that allyl, aryl, vinylsilanes, silyl enol ethers and other such molecules react with electrophiles to place the positive charge β to the silicon (**Figure 4**).

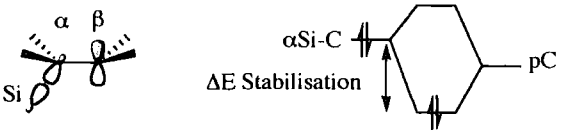


Figure 4

1.1.1.5 Conclusion

In conclusion, silicon possesses four key properties:

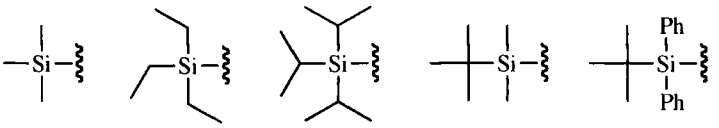
- The ability to form strong silicon-fluorine bonds
- Is an electron donor to carbon and hydrogen
- Undergoes nucleophilic attack *via* an S_N2 mechanism which proceeds through a pentacoordinate intermediate
- Has the ability to stabilise both α-carbanions and β-carbocations

It is these properties that give silicon a unique role in organic synthesis.

1.1.2 Uses of Silicon in organic chemistry

1.1.2.1 Protecting groups [8,9]

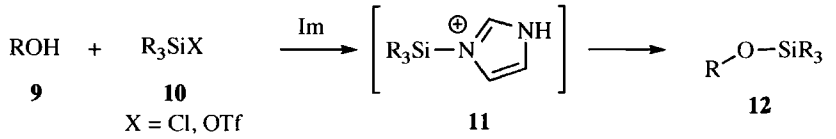
Silicon groups were first employed to increase the volatility and stability of polar compounds during gas chromatography and mass spectrometry. Now silicon groups are primarily used as protecting groups for hydroxyl moieties, but can be used to protect other functional groups such as carboxylic acids, amines and thiols. The most rudimentary silicon protecting group to be employed for hydroxy protection is the trimethysilyl group (TMS) **4**. However, TMS groups are very labile and readily cleaved under acidic and basic conditions. To overcome this problem, a number of bulkier silyl ethers **5-8** have been developed. These are more stable to acidic and basic conditions and as a result have found widespread use in organic synthesis (Figure 5).



TMS **4** TES **5** TIPS **6** TBS **7** TBDPS **8**

Figure 5

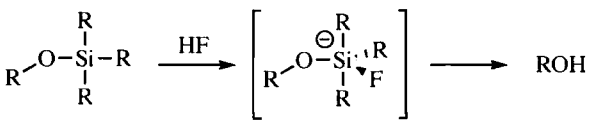
As a direct result of their widespread use, many methods for their introduction and removal have been developed. The most common method utilises the corresponding silyl chloride or the more reactive silyltriflate in the presence of a suitable base such as pyridine, Et_3N, Hünigs base, imidazole or DBU (**Scheme 2**).



ROH **9** + R_3SiX **10** X = Cl, OTf → (Im) → **11** → $R{-}O{-}SiR_3$ **12**

Scheme 2

Cleavage of silicon protecting groups is commonly undertaken utilising a source of fluoride (e.g. TBAF, HF-MeCN, HF-py, $Et_3N.3HF$). Fluoride is employed because of its high affinity for silicon and the strength of a Si-F vs a Si-O bond (*cf.* Section 1.1.1.1) enables a mild and selective cleavage of the protecting group (**Scheme 3**).

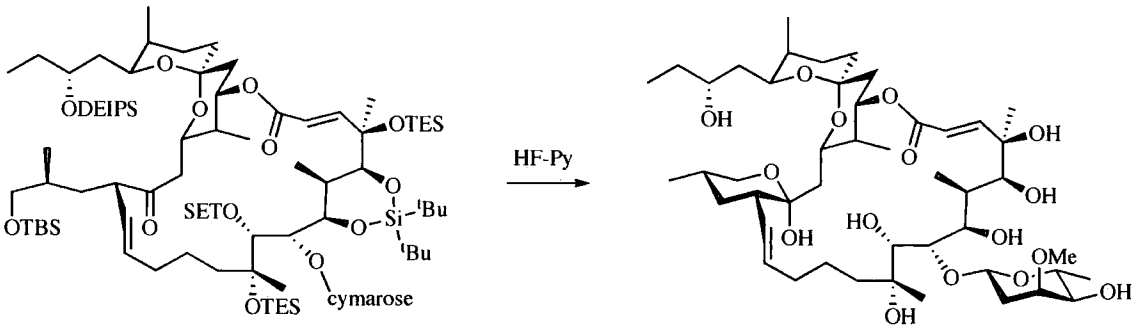


12 → (HF) → **13** → ROH **9**

Scheme 3

Many examples exist in the literature describing the use of silicon as a protecting group. A noteworthy example reported by Evans *et al.*, highlighted the versatility of silicon protecting groups in a total synthesis of Cytovaricin.[10] This synthesis employed a wide range of silicon protecting groups and demonstrated that they would withstand a

phlethora of reactions including Grignard addition, Swern oxidation and Horner-Wittig reactions, until the last step when they were all cleaved with HF-Py (**Scheme 4**).

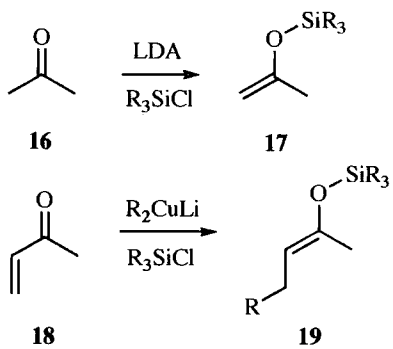


14 **15**

Scheme 4

1.1.2.2 Silyl enol ethers

Despite protecting groups being the most well known function for silicon, other applications have been explored. One such application utilises silicon to trap and stabilise an enolate anion as a silyl enol ether (e.g. **17**), which may be isolated, purified and characterised by analytical methods. Silyl enol ethers are generally prepared from ketones in the presence of a strong base and the corresponding silyl chloride, however, they can also be generated by capturing an enolate anion formed in a nucleophilic addition reaction (e.g. **19**) (**Scheme 5**).



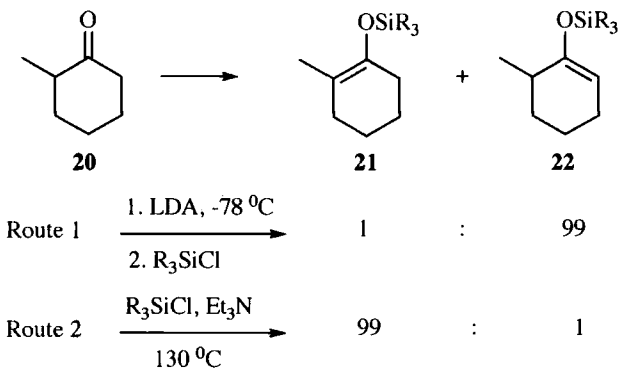
16 **17**

18 **19**

Scheme 5

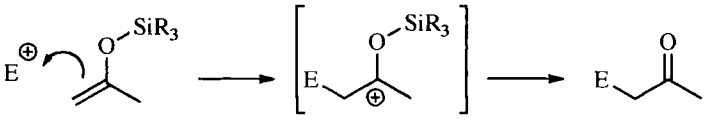
When symmetrical ketones are utilised, only one silyl enol ether can be formed. However, unsymmetrical ketones give rise to selectivity issues. For example, 2-

methylcyclohexanone **20** could give two silyl enol ethers **21** and **22**. However, utilising the correct conditions one silyl enol ether can be formed exclusively in preference to the other. So, under conditions of kinetic control (route 1), deprotonation at the least hindered site is favoured and the enolate anion with the least substituted double bond is formed. However, under conditions of thermodynamic control (route 2), equilibration of the two enolates occurs and eventually gives rise to the enolate containing the most substituted double bond. Therefore, silyl enol ethers can be thought of as synthons for stable regiochemically-pure enolate anions and, as such, they have found widespread application in organic synthesis (**Scheme 6**).



Scheme 6

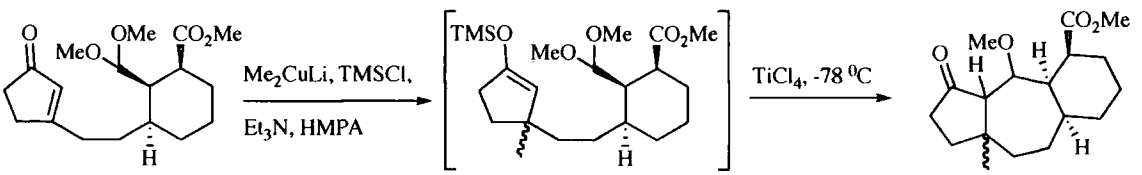
Silyl enol ethers have been utilised in a phlethora of reactions with a range of electrophiles in the presence of a Lewis acid. For example, alkyl halides, aldehydes and ketones react with silyl enol ether **17** to give a stabilised carbocation. Carbocation **23** then collapses with loss of the silicon group to give ketone **24** (**Scheme 7**). Silyl enol ethers react exclusively at the terminal carbon, since any other position would give rise to an unstabilised carbocation. This selectivity, coupled with the regioselective formation of the enolate anion, makes silyl enol ethers very versatile reagents.



17 23 24

Scheme 7

Again, many examples exist in the literature describing the use of silyl enol ethers. The most commonly employed reaction is the Lewis acid-promoted aldol reaction of silyl enol ethers with aldehydes. This reaction has been exploited to great effect in natural product synthesis. An example reported by Kwon *et al.* demonstrates their versatility in a synthesis of the [5-7-6] tricyclic core of Guanacastepene A utilising a silyl enol ether derived from **25**.[11] The silyl enol ether **26** was generated *in situ* by trapping the enolate formed from the conjugate addition of a methyl group to the cyclopentenone. The intramolecular Mukaiyama aldol reaction was then undertaken by reacting **26** with $TiCl_4$ at -78 °C to give the tricyclic core of guanacastepene A **27** in 80% yield (**Scheme 8**).



25 26 27

Scheme 8

1.2 Silene Chemistry

1.2.1 Introduction

As outlined in the previous subsections, silicon-based reagents have found widespread use in organic synthesis. However, multiply-bonded silicon species have found very little. Silenes are molecules that contain a Si=C double bond and are primarily observed as highly reactive transient intermediates. Their high reactivity arises because of a low

Si=C double bond energy (490 kJ mol^{-1}) when compared to C=C (620 kJ mol^{-1}). The low bond energies are rationalised in two ways: firstly the low electronegativity of silicon leads to weak attraction for bonding electron density and secondly there is poor overlap of the Si 3p and carbon 2p orbital. Two contributions to this are the mismatch of energy levels and the diffuse nature of the silicon orbitals at the increased bond length due to the lower effective nuclear charge (**Figure 6**).

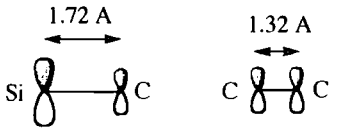


Figure 6

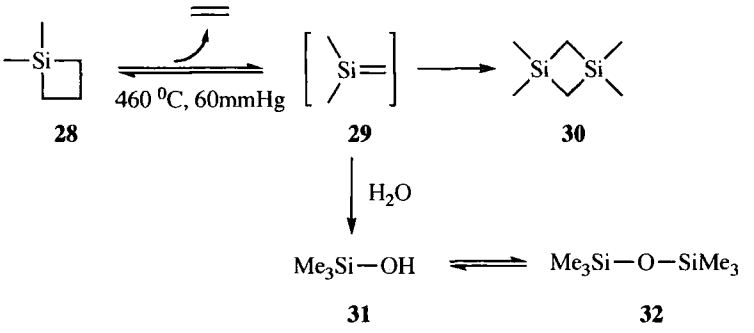
As a direct result of these factors, silenes are primarily generated *in situ* using three key techniques: gas phase pyrolysis, photolysis and a modified Peterson reaction. The following section will examine each technique. However, due to the large amounts of literature available, only a small number of examples for each technique will be described.

1.2.2 Generation of Silenes

1.2.2.1 Gas Phase Pyrolysis

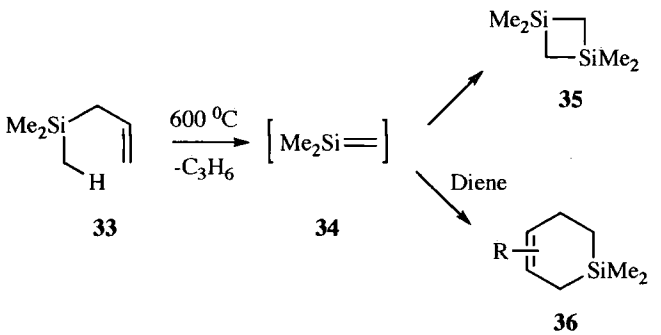
Gas phase pyrolysis is a technique well documented in the literature. However, it is seldom used as it requires very harsh reaction conditions. Despite this, gas phase pyrolysis was utilised to great effect by Gusel'nikov and Flowers.[1] They provided the first evidence for the existence of silenes in 1967 utilising this technique. Their seminal work focused on the pyrolysis of 1,1-dimethylsilacyclobutane **28**. They demonstrated that when pyrolysed, **28** gave rise to ethylene and 1,3-disilacyclobutane **30**. This suggested that silene **29** was formed first by a retro [2+2] cycloaddition followed by

head-to-tail dimerisation. Subsequent studies showed that trimethylsilanol **31** and hexamethyldisiloxane **32** were generated on addition of water to the reaction. This provided further evidence for the intermediacy of silene **29** (**Scheme 9**).



Scheme 9

Following the work of Gusel'nikov and Flowers, other groups began to utilise the pyrolysis technique for silene generation. One distinct approach was reported by Barton *et al.*, which focused on the thermolysis of allylsilane **33**. Barton *et al.* demonstrated that allylsilane **33** underwent a retro-ene fragmentation to give silene **34**. Subsequent dimerisation gave the head-to-tail dimer **35**, identical to that observed by Gusel'nikov and Flowers. Interestingly, in this case, the silene **34** could also be trapped by a diene in a Diels-Alder reaction (**Scheme 10**).[12]

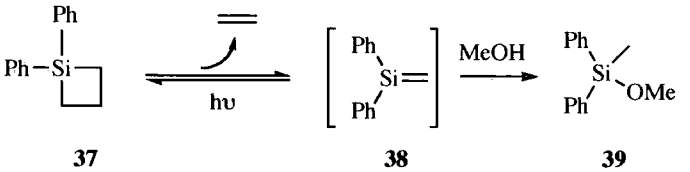


Scheme 10

1.2.2.2 Photolysis

In spite of the reports highlighted in the previous section, pyrolysis was abandoned as a technique for silene generation. Instead photolysis was readily adopted as a mild

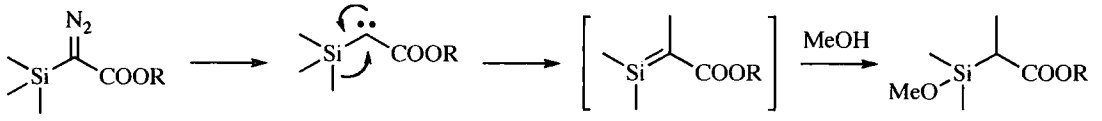
technique when compared to pyrolysis. An early report by Boudjouk and Sommers demonstrated that 1,1-diphenylsilacyclobutane **37** (structurally similar to **28** reported by Gusel'nikov and Flowers) could be photolysed to generate silene **38** under very mild conditions. Silene **38** was subsequently trapped with methanol to give silyl ether **39** (**Scheme 11**).[13]



37 **38** **39**

Scheme 11

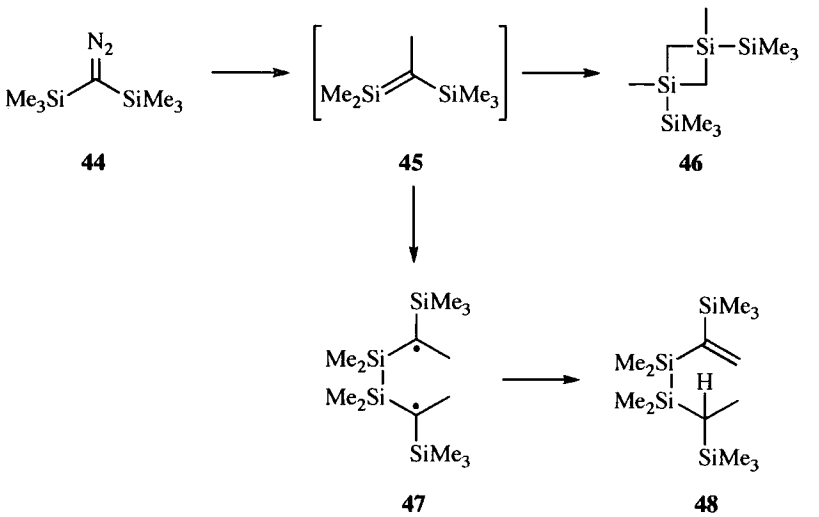
Even though silacyclobutanes are capable of generating silenes, only simple substrates such as 1,1-dimethyl- and 1,1-diphenylsilacyclobutanes have been used. To expand the application of this technique, new substrates were explored. Work by Ando *et al.* highlighted the use of silicon-based diazo compounds,[14] which were examined because carbon-based diazo compounds had been shown to undergo an intramolecular carbon-carbon insertion reaction to yield alkenes. More specifically, these workers reported that trimethylsilylcarboalkoxy diazoacetates **40**, when photolysed, generate silene **42** which was subsequently trapped with methanol to give migrated product **43**. This result suggested that silene **42** was generated from a 1,2 methyl migration in carbene intermediate **41**. Three other products were also isolated, further confirming the intermediacy of carbene **41**. One product arose from the direct reaction of carbene **41** with methanol and the other two from a Wolff rearrangement (**Scheme 12**).



40 **41** **42** **43**

Scheme 12

A similar rationale was employed when Barton and Hoekman reported their work using bis(trimethylsilyl)diazomethane **44**. When photolysed, silene **45** was generated from diazo compound **44** *via* carbene formation and 1,2 methyl migration (as before). Silene **45** was then trapped as its head-to-tail and linear dimerisation products **46** and **48** (**Scheme 13**).[15]



Scheme 13

In spite of their unique reactivity, diazo compounds still provide a limited range of substrates for this technique, due primarily to their unstable nature. Therefore, subsequent investigations explored more stable substrates for photolysis. A report by Ishikawa *et al.*[16] demonstrated that 1-vinyldisilanes are stable substrates, able to generate silenes utilising this technique. Ishikawa *et al.* reported that, when photolysed and quenched with methanol, 1-vinyldisilane **49** generated disilane **51**. Isolation of disilane **51** suggested that the intermediate silene **50** was generated by a 1,3-sigmatropic shift of the silyl group to the terminal vinyl carbon (**Figure 7**).

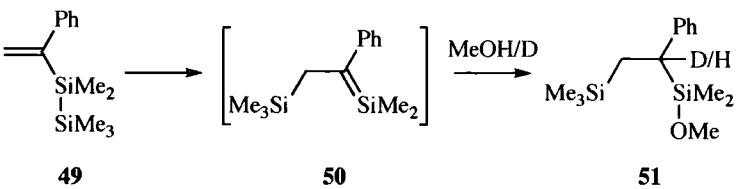
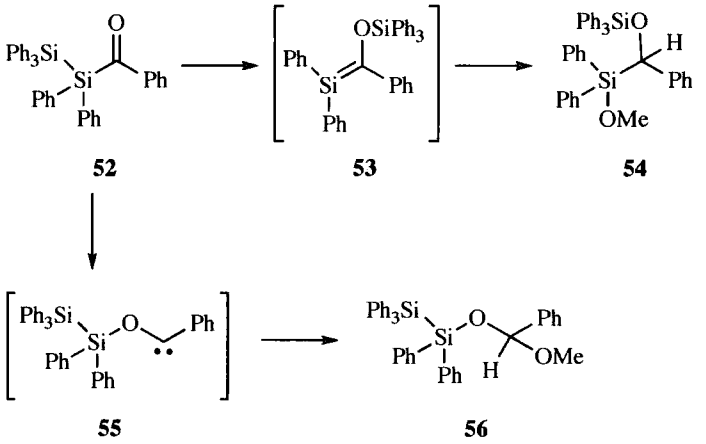


Figure 7

Notwithstanding the substrates discussed so far, the biggest advance for this technique arose through investigations into acylsilanes. A report by Brook *et al.* demonstrated that the stable acyldisilane **52** underwent photolytic activation to generate intermediate silene **53**, which was trapped with methanol to give siloxane **54**, and carbene by-product **55** which underwent attack of methanol to generate the acetal **56** (**Scheme 14**).[17-19]



Scheme 14

Brook *et al.* also demonstrated that a large variety of substrates could be utilised in this process. This variety allowed the same workers to isolate the first crystalline 'stable' silene **58** by photolysis of acyl silane **57**. Silene **58** was isolated as a white crystalline solid. The stability of silene **58** was attributed to the steric bulk imparted by the adamantyl group, blocking its dimerisation. Furthermore, isolation of silene **58** enabled X-ray crystallographic studies to be undertaken to unequivocally prove the existence of silenes (**Figure 8**).[18,20]

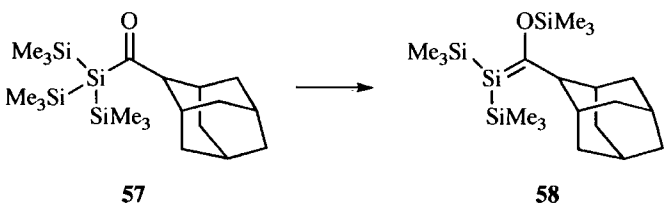
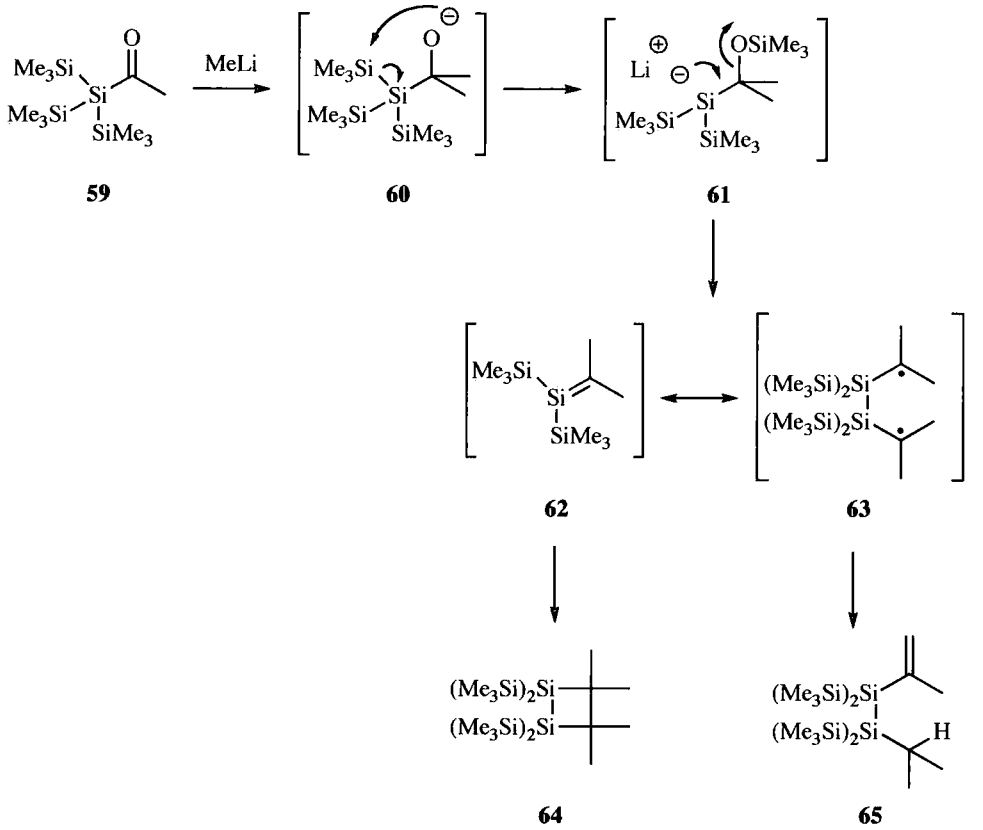


Figure 8

1.2.2.3 Modified Peterson Reaction

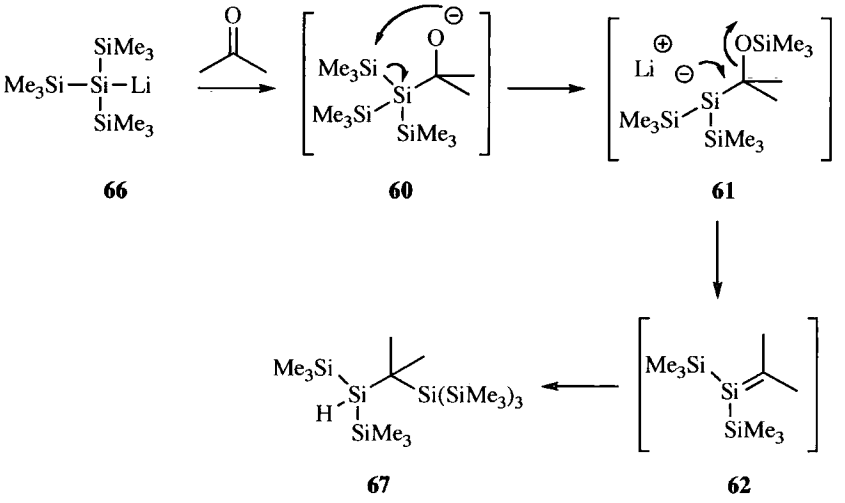
Subsequent to their use in photolysis, acylsilanes were employed in other techniques to generate silenes. One technique that was explored for silene generation was the Peterson reaction. A report by Ishikawa and co workers described this technique for silene generation.[21] They demonstrated that acylsilane **59**, when reacted with methyllithium, generated α-silyl-oxy anion **60**. The anion **60** then underwent a modified Peterson reaction, by first abstracting a trimethylsilyl group intramolecularly. The silyl anion **61** eliminated the trimethylsilanolate to give silene **62**, which subsequently dimerised in a head-to-head fashion to generate dimer **64**. Also, silene **62** reacted as a diradical tautomer **63** to give vinyldisilane **65** (**Scheme 15**).



Scheme 15

As a result of this report, other groups investigated the modified Peterson reaction. Oehme and Wustrack further established this technique by demonstrating that a α-silyl-oxy anion (identical to that reported by Ishikawa, *cf.* **Scheme 15**) could be generated *in*

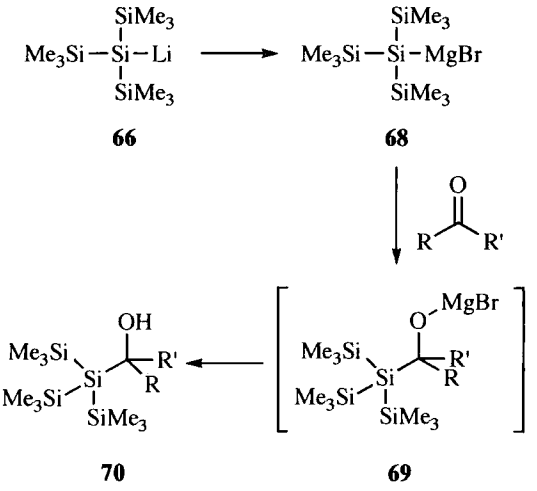
situ from the reaction of silyllithium **66** and acetone.[22] The anion **60** then rearranged (as above) to give silene **62**, which reacted with another equivalent of silyllithium **66** to give a second anion, which was quenched on work-up to give silane **67** (**Scheme 16**). Moreover, being able to generate α-silyl-oxy anions *in situ* by reacting silyllithiums with ketones and aldehydes allowed a large number of substrates to be investigated.[23]



66 **60** **61** **67** **62**

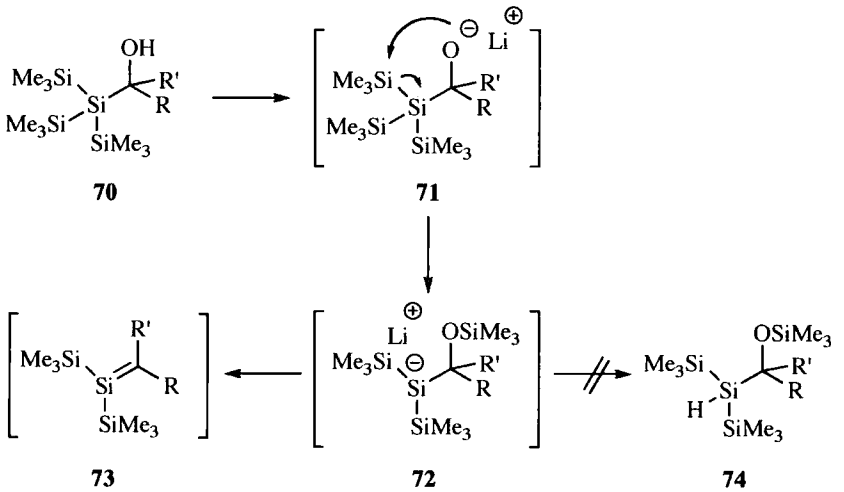
Scheme 16

However, to this point, the modified Peterson reaction had been shown to generate silenes by reaction of an isolated acylsilane with methyllithium or *in situ* by reaction of a silyllithium with a ketone or aldehyde. In an attempt to understand the reaction pathway, it was advantageous to isolate the active α-silyl-oxy anion species before it underwent elimination to form a silene. A report by Oehme provided a procedure for isolating a α-silyl-oxy anion analogue, α-silylalcohol **70**. Oehme demonstrated that by reacting silyl Grignard reagent **68** with carbonyl compounds, an oxy-magnesium bromide **69** was generated. This did not undergo spontaneous migration and elimination to form the corresponding silene (as with the silyllithium species, *cf.* **Scheme 16**) but, upon work-up, yielded α-silylalcohol **70** (**Scheme 17**).[24-29]



Scheme 17

Moreover, the isolation of α-silylalcohol **70** allowed conditions necessary for migration and elimination to be investigated. Another report by Oehme provided conditions that would allow migration and elimination to take place. Oehme demonstrated that on addition of strong base to α-silylalcohol **70**, the α-silyl-oxy anion **71** (*cf.* **Scheme 16**) was generated and underwent spontaneous migration and elimination as observed earlier to give silene **73**, which was isolated as its dimerisation product (**Scheme 18**).



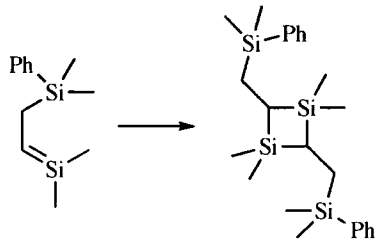
Scheme 18

Now, with mild conditions established for the generation of a variety of α-silylalcohols and conditions for the formation of silenes documented, attention turned to the reactions of silenes utilising these conditions.

1.2.3 Reactions of Silenes

1.2.3.1 Dimerisation Reactions

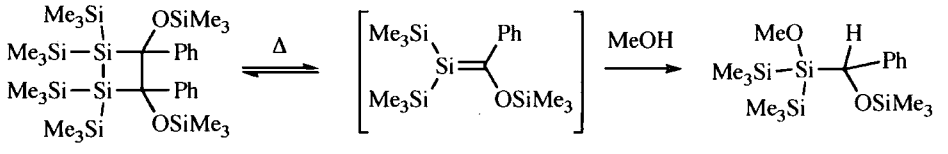
As highlighted in earlier sections, silenes are transient and unstable molecules that, in the absence of any other reagents, dimerise rapidly. It is this reaction mode that facilitated their discovery by pyrolytic formation of a head-to-tail dimer **30** by Gusel'nikov and Flowers.[1] Many of the methods discussed for silene generation relied on the isolation of dimerisation products to prove their existence. One example reported by Ishikawa *et al.* generated a head-to-tail dimer **76** of silene **75** (**Scheme 19**).[16]



75 **76**

Scheme 19

Silene dimerisation was not just used to prove the existence of silenes. A report by Brook *et al.* suggested that silenes were in a dimer-monomer equilibrium. This hypothesis was investigated by refluxing dimer **77** in methanol to isolate silyl ether **79**. This suggested that dimer **77** interconverted to silene **78** *via* a retro [2+2] reaction, and **78** was then trapped by methanol (**Scheme 20**).[18]



77 **78** **79**

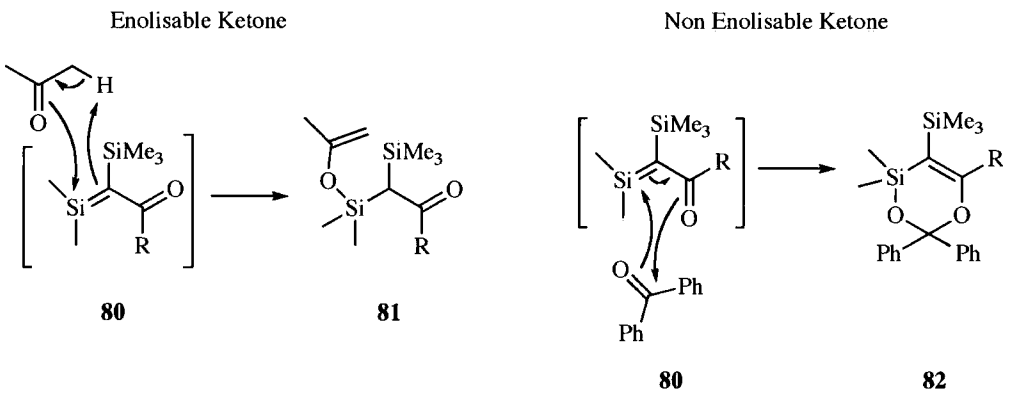
Scheme 20

1.2.3.2 Reactions with Nucleophiles

In addition to dimerisation, silenes were demonstrated to react with alcohols as nucleophiles by oxygen addition to silicon and hydrogen addition to carbon. This reactivity and regioselectivity of addition are attributed to silene's bond polarisation and silicon's affinity for oxygen (*cf.* **Scheme 11**, **Scheme 12**, **Figure 7**). Organometallics have also been shown to react in a similar way, yielding various products after rearrangement. Brook *et al.* published extensive research into the reaction of silenes with Grignard reagents in 1991.[30]

1.2.3.3 Reactions with Carbonyl Compounds and Imines

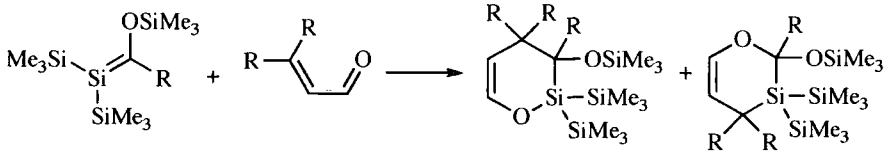
Silenes not only react with nucleophiles, but with carbonyl compounds and imines. A report by Maas *et al.* demonstrated that silenes, generated by photolysis of a diazo silane, would react with carbonyl compounds.[31] Silene **80** was shown to react in an 'ene' manner yielding siloxane **81**, unless the ketone was non-enolisable, in which case a [4+2] cycloaddition was seen, generating siladioxene **82** (**Scheme 21**).



Scheme 21

Interestingly, Brook *et al.* also demonstrated that α,β-unsaturated aldehydes and ketones will undergo [4+2] cycloadditions yielding cyclic silapyran regioisomers **85** and **86**. The

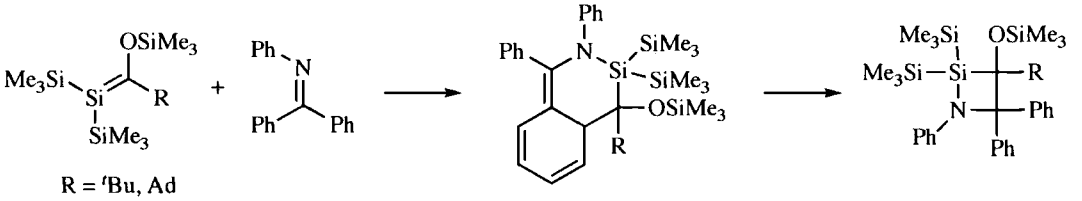
ratio of regioisomers depended on the substituents present in aldehyde **84** (**Scheme 22**).[32]



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

Scheme 22

Another report by Brook *et al.* described the use of imines to trap silenes.[33] Using triphenyl imine **88** and *t*-butyl or adamantyl silene **87**, the [4+2] cycloadduct **89** was initially isolated. Interestingly, on standing in the dark, cycloadduct **89** rearranged to give the [2+2] cycloadduct **90**. It was found that when exposed to light, [4+2] cycloadduct **89** rearranged much faster to the [2+2] cycloadduct **90**, suggesting that a radical rearrangement was taking place (**Scheme 23**).



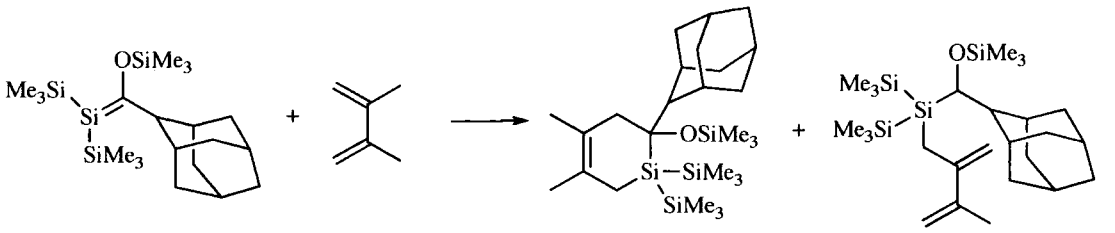
R = ^{t}Bu, Ad

87 **88** **89** **90**

Scheme 23

1.2.3.4 Reactions with Dienes

As well as carbonyl compounds and imines, Brook and co workers examined the use of dienes as trapping agents to prove the existence of silenes. A report by Brook and co workers described the reaction of dienes with silenes in great detail using the stable adamantyl silene **58**. They demonstrated that reactions of dienes with silenes gave mixtures of Diels-Alder product **92** and the 'ene' product **93** (**Scheme 24**).[34]



58 91 92 93

Scheme 24

Other dienes were also utilised in this study. Butadiene and cyclohexadiene reacted with silenes to give [2+2] addition products in a ratio of *ca.* 1:3, besides the expected [4+2] products.

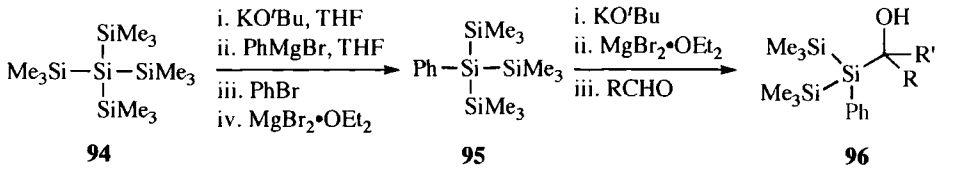
1.2.3.5 Conclusion

In conclusion, three techniques have been utilised to generate silenes. Of these three, photolysis and the modified Peterson olefination have been shown to be mild and reliable techniques. Moreover, they enable the most varied array of precursors to be utilised.

Once generated, silenes have been shown to undergo a variety of reactions. However, particular emphasis was placed on 'trapping' experiments to unambiguously prove their existence. This meant that little effort has been made to exploit their unique reactivity in organic synthesis. Therefore, our intention was to initiate a study to apply this reactivity. The following section will highlight this early work.

1.3 Previous work in the group

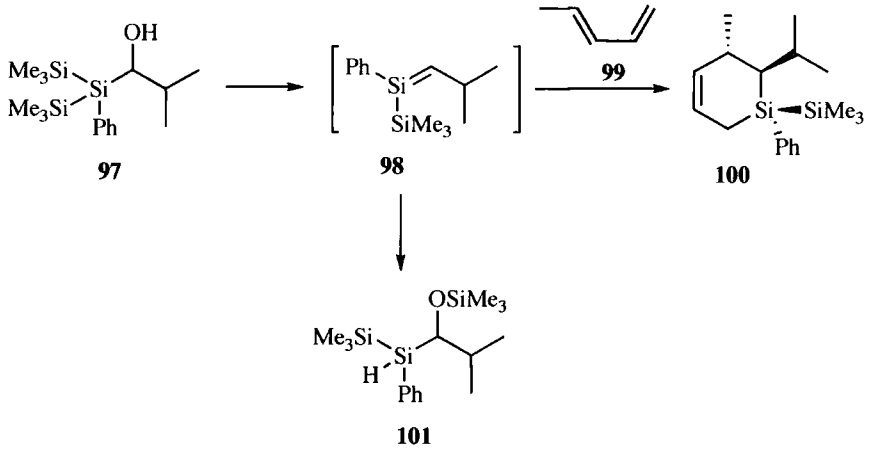
Early work in the group investigated the synthesis of a silene precursor that could be utilised in organic synthesis. Griffiths adapted Oehme's methodology to generate an array of α-silylalcohols **96** possessing a phenyl ring on the silicon atom (**Scheme 25**).[35]



94 **95** **96**

Scheme 25

With the α-silylalcohols in hand, Griffiths then went on to demonstrate that when subjected to the modified Peterson reaction conditions (reported by Oehme), α-silylalcohols **96** underwent migration and elimination to give silenes. More specifically, when α-silylisobutanol **97** was treated with MeLi at -78 °C and warmed to -30 °C, silene **98** was generated. This was then trapped *in situ* with 1,3-pentadiene **99** in a Diels-Alder reaction generating silacyclohex-4-ene **100** in 66% yield (**Scheme 26**).[24-27,36,37]

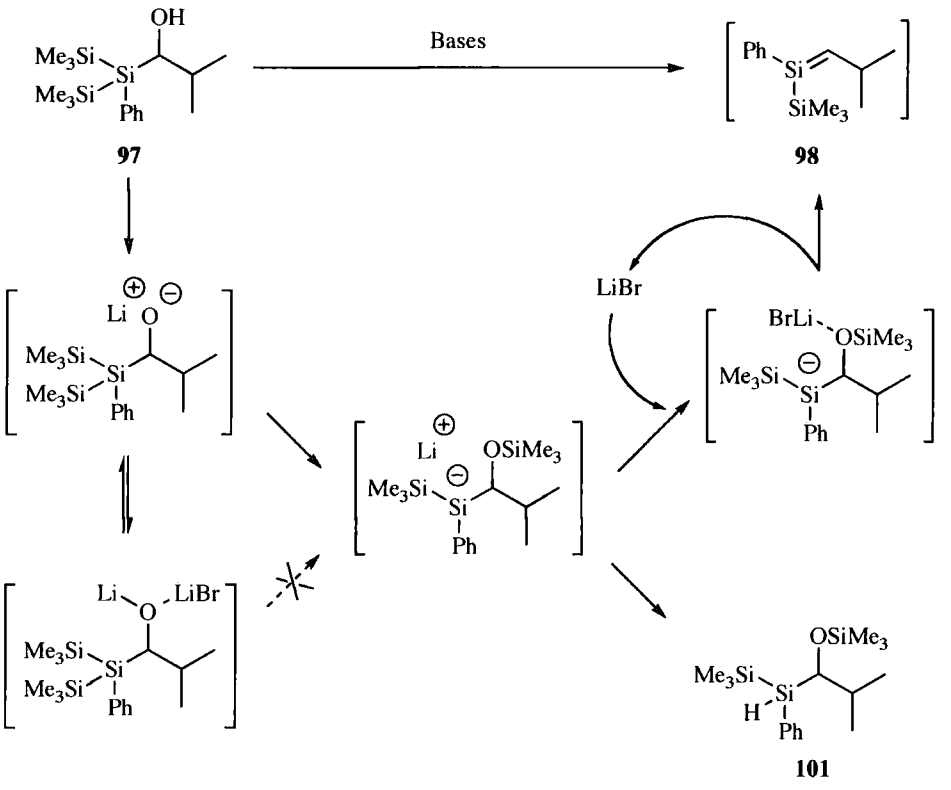


97 **98** **100** **101**

Scheme 26

However, attempts to reproduce the reaction reliably with MeLi failed and the use of other bases, such as *n*-BuLi and LiHMDS led preferentially to the formation of silane **101**. To address this issue of reproducibility, Whelligan implemented a systematic study of bases for silene generation. After extensive research, it was found that treatment of α-silylalcohol **97** with *n*-BuLi in the presence of a catalytic amount of LiBr generated silacyclohex-4-ene **100** reproducibly in 50% yield.[29]

These results were rationalised by analysing the bases used and the mechanism outlined (**Scheme 27**). Commercially available MeLi (1.6M in ether) is described as 'low chloride' and contains approximately 6% LiBr, where as other bases, such as *n*-BuLi (1.6M in hexane) do not. The need for the presence of lithium salts to facilitate the crucial elimination reaction would explain the lack of reproducibility, due to the varying amounts in each commercially available batch of MeLi.



Scheme 27

Following this development of a robust protocol for silene generation, Whelligan was able to demonstrate their versatility in organic synthesis by reaction with a range of simple alkyldienes. This generated a whole variety of silacyclohex-4-enes **102-105** in a reliable manner with reproducible yields and diastereoselectivities. With the silacyclohex-4-enes in hand, attention turned to their elaboration. Subsequent investigations by Whelligan demonstrated that silacyclohex-4-enes **102-105** could be elaborated utilising the Fleming-Tamao reaction (oxidative cleavage of organosilanes

with hydroperoxide). This enabled a series of lactones **106-109** to be prepared in moderate yield (**Table 2**).[38]

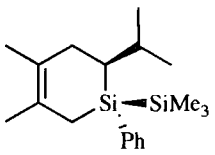
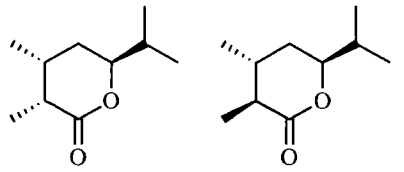
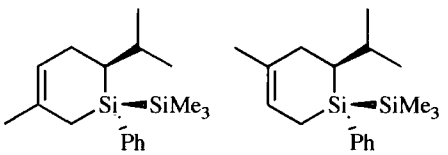
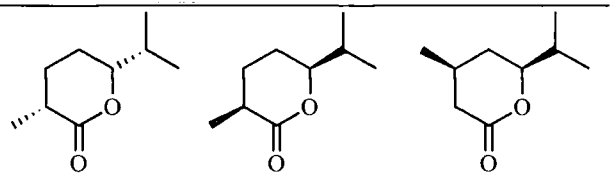
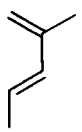
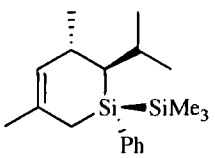
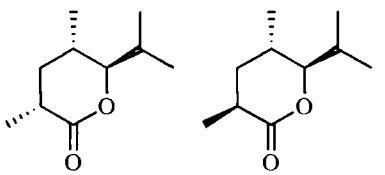
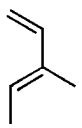
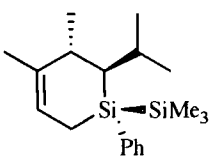
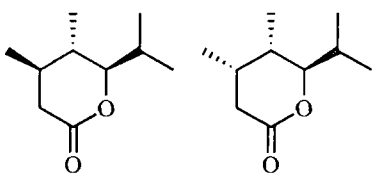
Diene	[4+2] Silacycle	Lactones
	 **102** 42% (83:17)	 **106** 63% 64%
	 **103** 36% (84:16)	 **107** 25% (66:44)
	 **104** 43% (80:14:4)	 **108a** 45% **108b** 26% (79:11:8:2)
	 **105** 38% (86:9:4:1)	 **109a** 13% **109b** 60% (87:10:3)

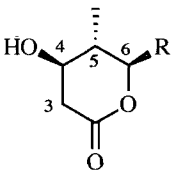
Table 2

Now that a reliable procedure had been established for the generation of silacyclohex-4-enes and their elaboration to lactones, attention turned to utilising these in organic synthesis. More specifically, the intention was to apply silacyclohex-4-enes to the total synthesis of prelactone B, a β-hydroxy-δ-lactone isolated from a bafilomycin-producing *Streptomyces griseus*. The following chapter will report our endeavours towards the first total synthesis of prelactone B, starting from silacyclohex-4-enes.

2 Total synthesis of Prelactone B

2.1 Introduction

δ-Lactones, specifically β-hydroxy-δ-lactones, are found as components of many bioactive natural products. In addition, they also represent useful building blocks for the synthesis of more complex structures. A sub-group of this class of compounds are the prelactones, **110-113** isolated from various polyketide-macrolide-producing microorganisms (**Figure 9**).



Prelactone B, **110**, R = $CH(CH_3)_2$
Prelactone C, **111**, R = $CH{=}CHCH_3$
Prelactone V, **112**, R = CH_3
Prelactone E, **113**, R = C_2H_5

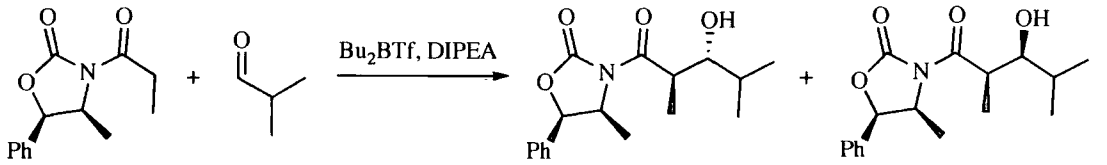
Figure 9

The most widely studied prelactone is prelactone B **110**. First isolated by Bindseil and Zeeck in 1993[39] from the bafilomycin-producing *Streptomyces griseus*, **110** represents an early metabolite in the biosynthesis of polyketide antibiotics. Although a direct product of the polyketide synthase (PKS) enzymes responsible for the synthesis of the macrolide, prelactone B is not incorporated into the natural macrolide and therefore is believed to be a shunt product of the biosynthetic pathway. To investigate this biosynthetic pathway, a number of synthetic routes to prelactone B have been developed. The following section will highlight these routes focusing on key synthetic transformations. Subsequent sections will then describe an alternative approach, discuss the merits and shortcomings of this approach and finally report a total synthesis of prelactone B **110** starting from silacyclohex-4-ene **100**.

2.2 Previous syntheses of Prelactone B

2.2.1 Hanefield route

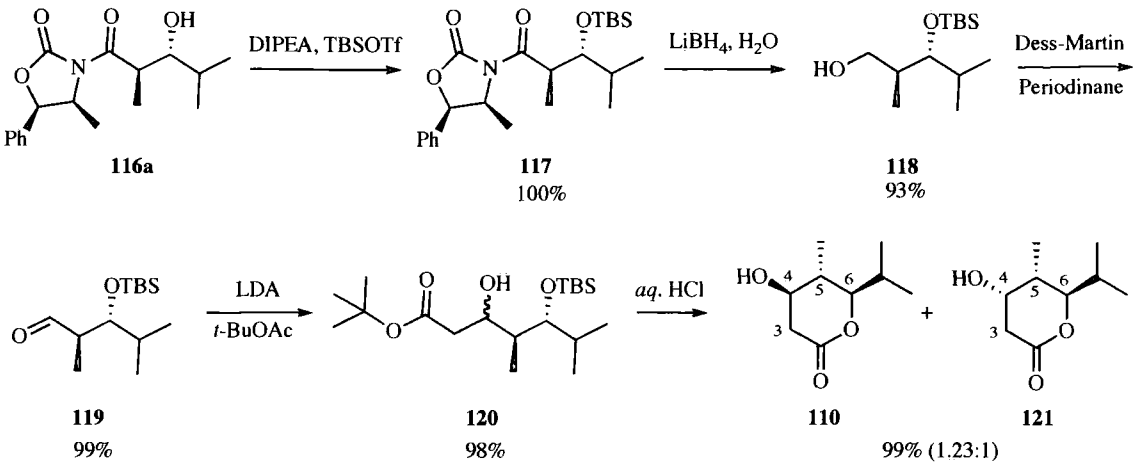
The first synthesis of **110** was reported in 1999 by Hanefield *et al.*, who synthesised both C-4 epimers to make them available as reference compounds.[40] Hanefield *et al.* began their synthesis with the aldol reaction of homochiral amide **114** and isobutyraldehyde to generate a mixture of **116a** and **116b** (Scheme 28).



114 **115** **116a** 63% **116b** 28%

Scheme 28

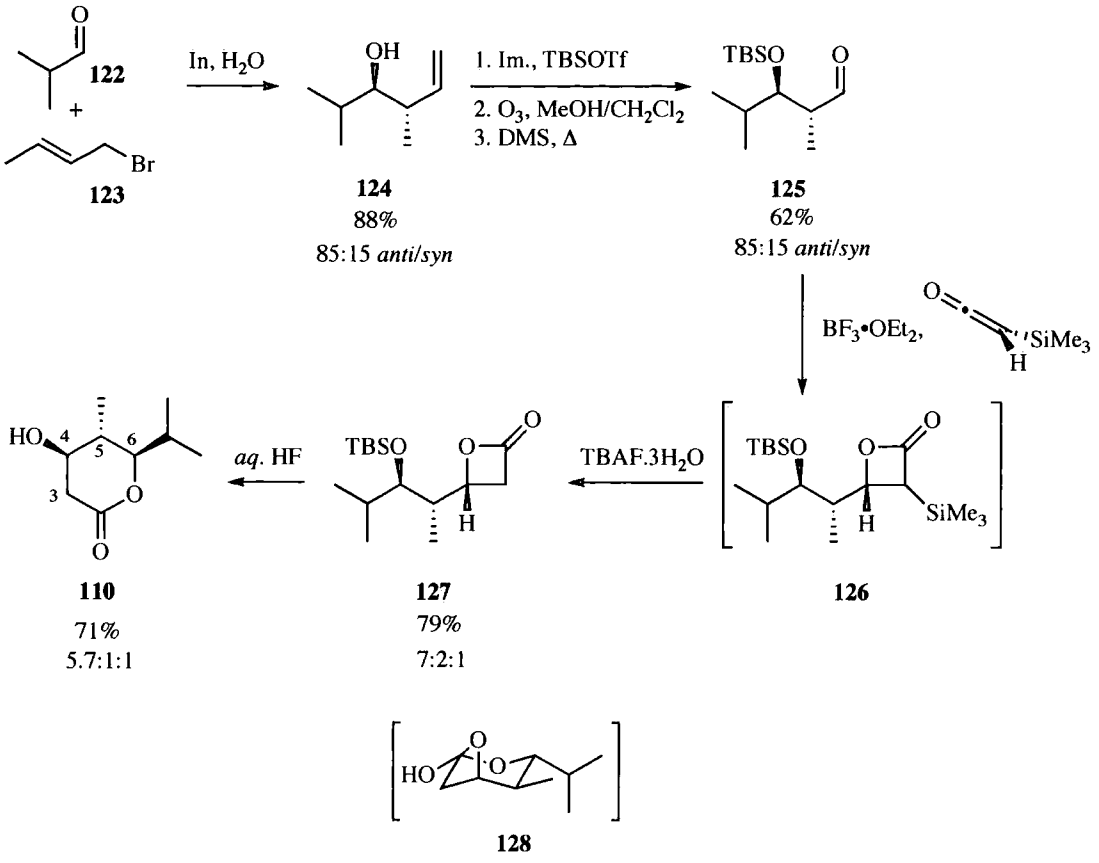
The desired *anti*-aldol isomer **116a** was separated and protected as the TBS ether. Selective reduction of the amide moiety with lithium borohydride in the presence of water produced **118** in good yield. Oxidation of **118** with Dess-Martin periodinane produced the unstable aldehyde **119**, which was treated immediately after purification with lithiated *tert*-butyl acetate. The aldol product **120** was then cyclised with dilute HCl over 7 days to generate a 1.23:1 mixture of **110** and **121**, which were subsequently separated by reverse phase HPLC (Scheme 29).



Scheme 29

2.2.2 Fournier route

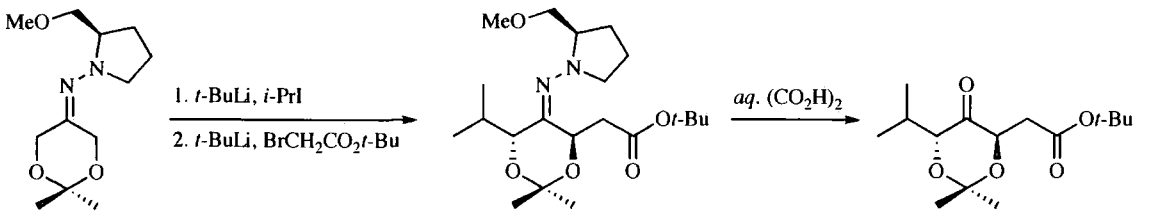
The Fournier approach was a racemic approach utilising a unique aqueous HF-promoted translactonisation process.[41] Fournier *et al.* began their synthesis with the reaction of isobutyraldehyde **122** and crotyl bromide **123** in the presence of indium in water. This gave the homoallylic alcohol **124** as a mixture of diastereoisomers. Homoallylic alcohol **124** was subsequently protected as the TBS ether and the alkene subjected to ozonolysis to yield aldehyde **125**. The aldehyde was then transformed into β-lactone **127** through a two-step sequence involving Lewis-acid-catalysed [2+2] cycloaddition and TBAF-promoted desilylation. Finally translactonisation of **127** with aqueous HF generated **110** as a 5.7:1:1 diastereomeric mixture, arising from a stepwise mechanism involving the intermediate **128** (Scheme 30).



Scheme 30

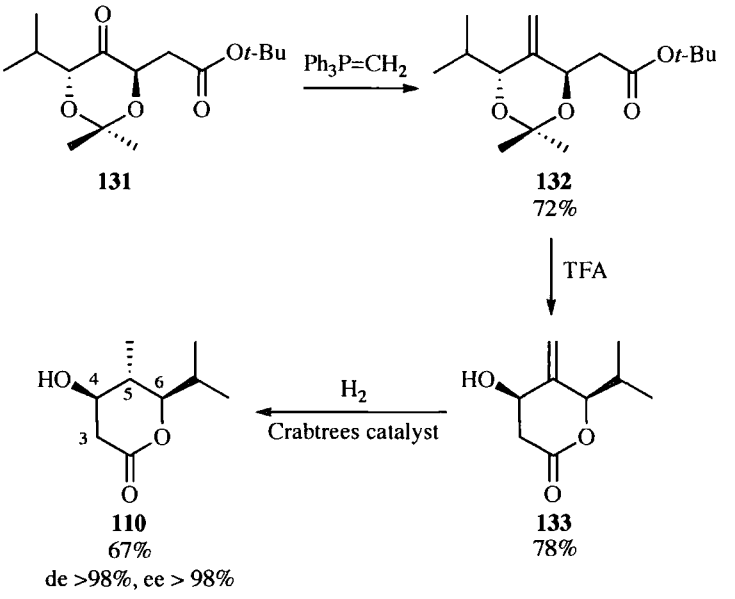
2.2.3 Enders route

The Enders approach synthesised prelactone B **110** asymmetrically utilising a SAMP/RAMP-hydrazone to govern the stereochemistry and a homogenous hydrogenation as a key step.[42] The synthesis began by preparing the (*R*)-1-amino-2-methoxymethylpyrrolidine (RAMP) hydrazone **129** from the condensation of 2,2-dimethyl-1,3-dioxan-5-one and the corresponding hydrazine. Alkylation with isopropyl iodide at the α-position followed after work-up by a second alkylation at the α'-position with *tert*-butyl bromoacetate gave **130** in good yield. Subsequent cleavage of the hydrazone with aqueous oxalic acid led to dioxanone **131** (Scheme 31).



Scheme 31

Wittig methylenation of the dioxanone **131** generated **132** in good yield (80% yield over the three steps). Subsequent removal of the acetonide with TFA and lactonisation provided lactone **133**, which was stereoselectively reduced by hydrogen in the presence of Crabtree's catalyst ([Ir(cod)(PCy_3)(py)]PF_6) to generate prelactone B **110** with high de and ee (Scheme 32).

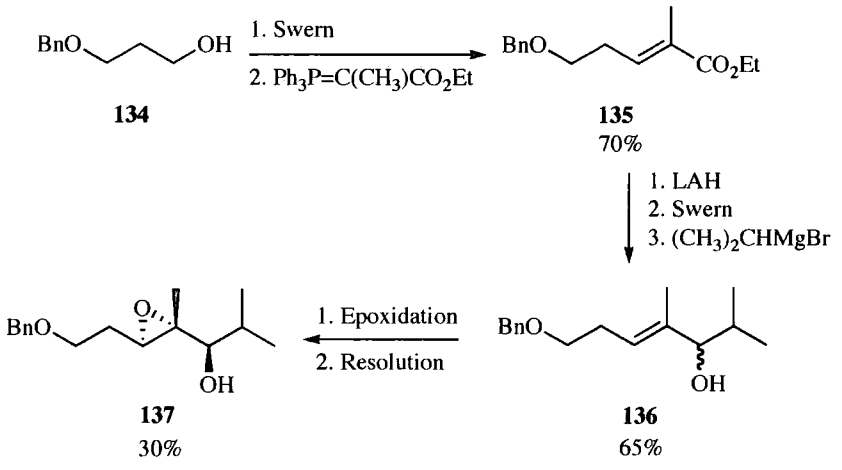


Scheme 32

2.2.4 Chakraborty route

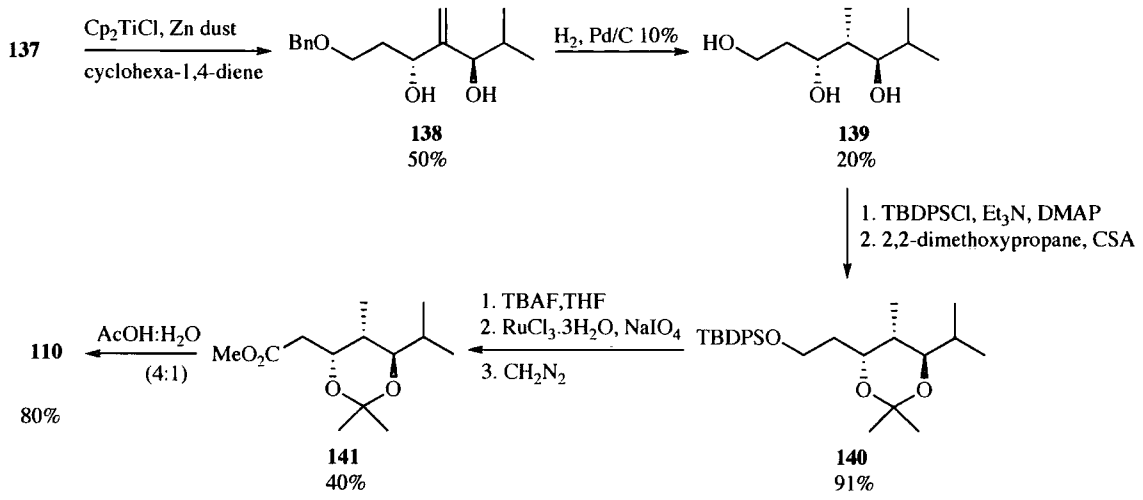
Chakraborty described another asymmetric route to prelactone B **110**, this time by a radical-mediated opening of a trisubstituted epoxy alcohol using Cp_2TiCl.[43] Starting from monoprotected propane-1,3-diol **134** the α,β-unsaturated ester **135** was generated in two steps. Swern oxidation followed by Wittig olefination gave exclusively the *E*-

isomer. Subsequent reduction with LAH, Swern oxidation and Grignard addition generated the allylic alcohol **136** in good overall yield. With the allylic alcohol **136** in hand, Sharpless asymmetric epoxidation and kinetic resolution was undertaken with titanium(IV) isopropoxide and unnatural diethyl D-(-)-tartrate to yield the chiral epoxy alcohol **137** (Scheme 33).



Scheme 33

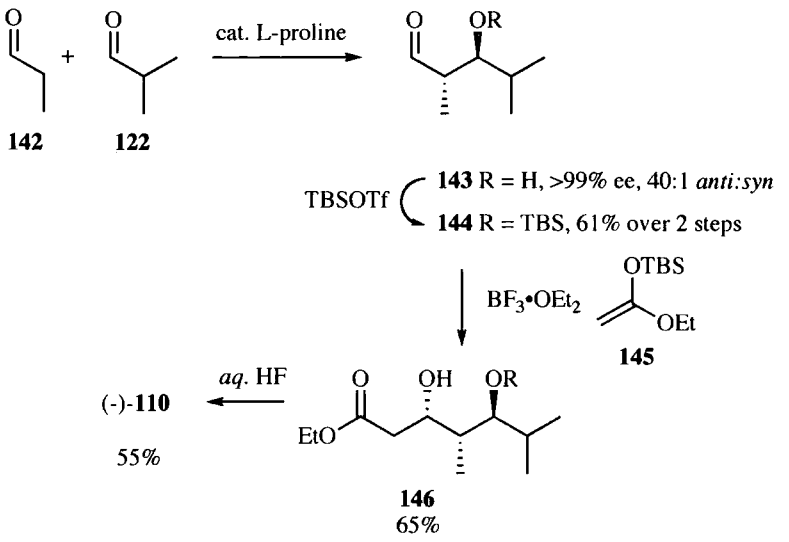
Disappointingly, the desired chiral epoxy alcohol **137** was generated in only 30% yield. Also, the chirality was unable to be confirmed at this juncture. Nevertheless, the stage was now set to carry out the radical-mediated ring opening reaction. Treatment of **137** with Cp_2TiCl did not provide the desired '2-methyl-1,3-diol'; but instead the β-hydride elimination product **138** was generated. Subsequent double bond reduction and debenzylation gave **139** with the correct C-5 stereochemistry (ds 9:1). An ensuing protection/deprotection strategy, followed by oxidation of the primary hydroxy group to the corresponding acid and *O*-methylation with CH_2N_2 provided the acetonide ester **141** in good yield. At this stage the major isomer was separated and the acetonide cleaved with aqueous acetic acid to provide a 1,3-diol that underwent concomitant cyclisation to prelactone B **110** (Scheme 34).



Scheme 34

2.2.5 Pihko route

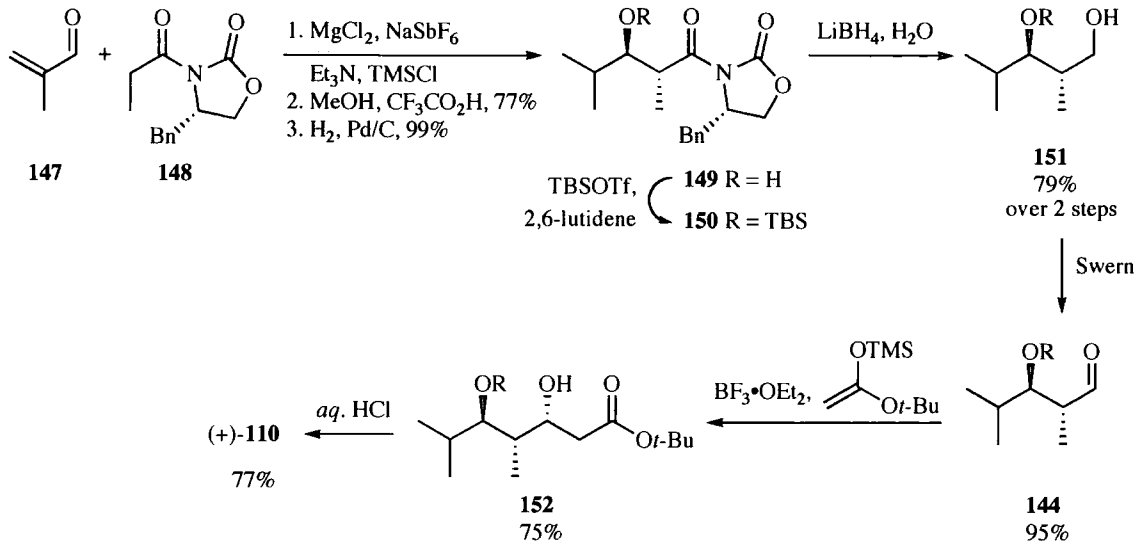
The Pihko approach provided a very short enantioselective approach to prelactone B utilising a unique proline-catalysed crossed-aldol reaction between propionaldehyde **142** and isobutyraldehyde **122**.[44] This reaction gave the aldol product **143** in > 99% ee and 40:1 *anti:syn* diastereoselectivity. Immediate reaction of the unstable aldol product **143** with TBSOTf generated silyl ether **144** in good yield. Subsequent aldol reaction of **144** with silyl enol ether **145** in the presence of $BF_3 \cdot OEt_2$ provided **146** with Felkin-Ahn selectivity. Deprotection and simultaneous lactonisation of **146** with aqueous HF led to (-)-prelactone B **110** (Scheme 35).



Scheme 35

2.2.6 Dias route

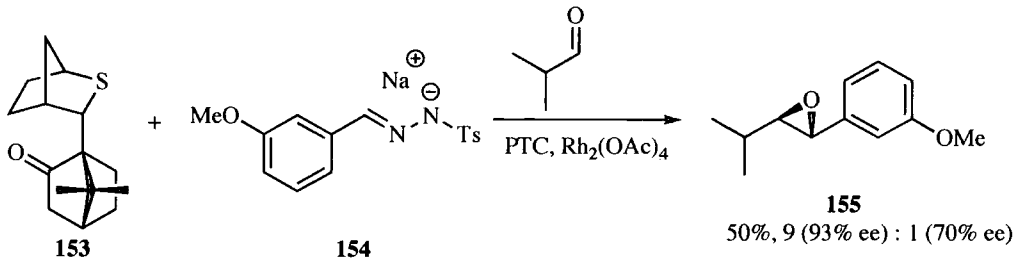
The Dias approach to (+)-prelactone B utilises the same intermediate protected aldehyde **144** described above in the Pihko approach.[45] Dias *et al.* gained access to the protected aldehyde **144** *via* a very efficient Evans oxazolidinone-mediated *anti*-aldol reaction. Reaction of methacrolein **147** and oxazolidinone **148** gave the *anti* aldol product **149** in good yield and 15:1 diastereoselectivity. Intermediate **144** was produced following reduction of the double bond, TBS protection of the free hydroxy group, reductive cleavage of the chiral auxiliary and Swern oxidation of the primary alcohol. Lewis-acid-promoted aldol reaction, as previously described by Pihko *et al.*, then generated **152** with >95:5 diastereoselectivity. Removal of the TBS group and lactonisation with aqueous HCl resulted in the formation of (+)-prelactone B **110** in 77% overall yield (Scheme 36).



Scheme 36

2.2.7 Aggarwal route

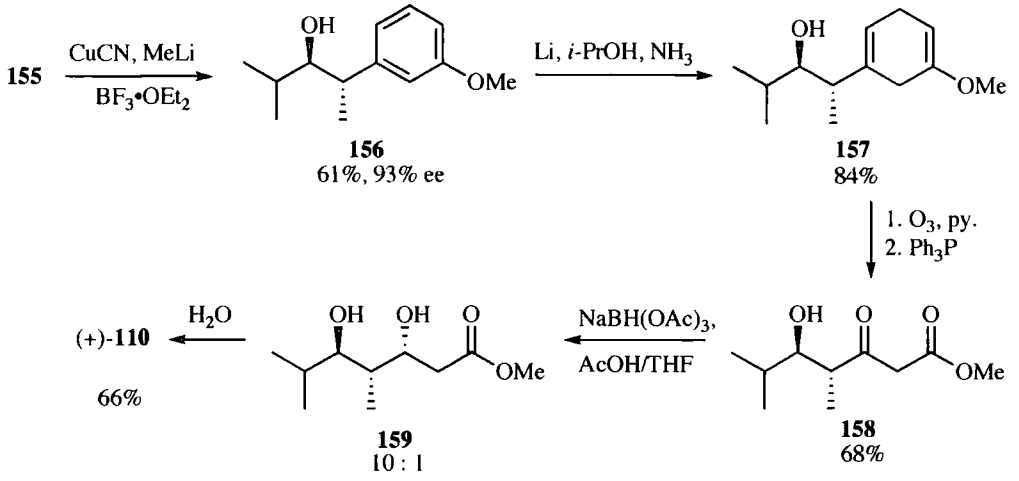
The Aggarwal approach highlighted the application of a unique sulphur-ylide-mediated epoxidation to the asymmetric total synthesis of prelactone B **110**.[46] The synthesis began by treating isobutyraldehyde with a chiral sulphur ylide generated from sulfide **153** and hydrazone **154** to provide epoxide **155** in 50% yield and 9:1 ds. Importantly the major diasereoisomer was generated in >93% ee (Scheme 37).



Scheme 37

With the major epoxide isomer in hand, elaboration towards the target molecule continued with regio- and stereoselective ring opening of the epoxide by a methyl cuprate in the presence of a Lewis acid, followed by Birch reduction of **156** under standard conditions to generate **157** in excellent yield. Ozonolysis of the double bonds provided hydroxy keto ester **158**, which was chemo- and stereoselectively reduced to

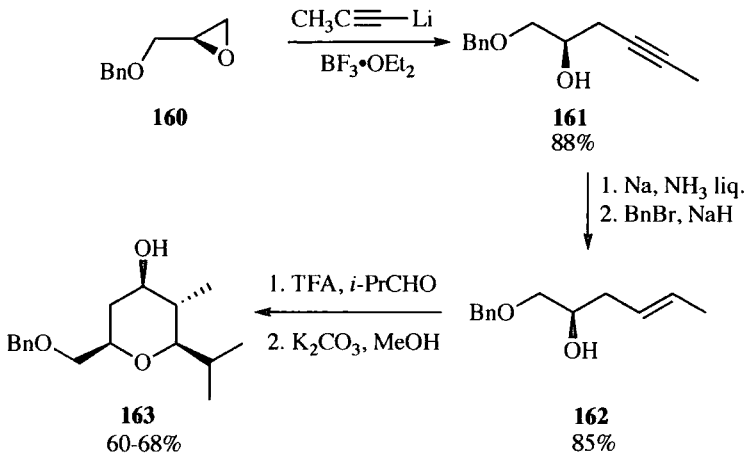
give dihydroxy ester **159**. Lactonisation of **159** with water completed the synthesis of **110** in 66% yield and 93% ee from **158** (Scheme 38).



Scheme 38

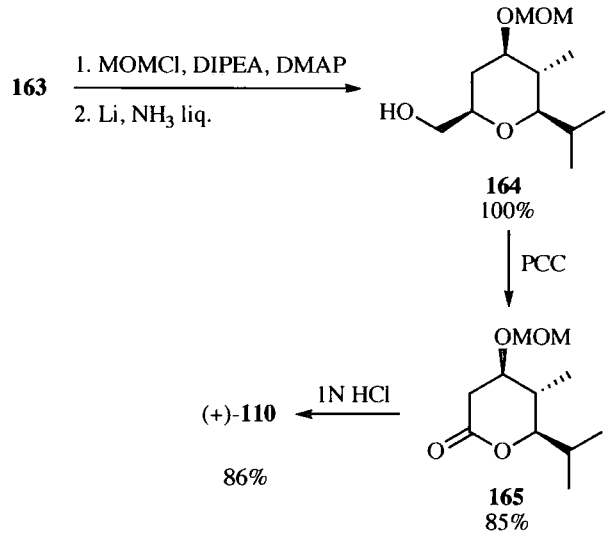
2.2.8 Yadav route

The Yadav approach highlighted a convergent route to prelactone B through Prins cyclisation of a homoallylic alcohol **162**.[47] Yadav *et al.* showed that the key intermediate, homoallylic alcohol **162**, could be prepared from (+)-benzyl glycidyl ether **160** in 3 steps. Starting from **160**, the chiral epoxide was opened with propynyllithium in the presence of $BF_3•OEt_2$ to give **161** in good yield. Birch reduction of the propargylic alcohol **161** led selectively to *trans*-**162**, which was then regioselectively protected as the benzyl ether. With allylic alcohol **162** in hand, the crucial Prins cyclisation was investigated. The results of the investigation revealed that the best conditions for cyclisation were TFA followed by hydrolysis of the esters with potassium carbonate in methanol. These conditions enabled **163** to be generated in 60-68% yield (Scheme 39).



Scheme 39

Substituted tetrahydropyran **163** was transformed rapidly into prelactone B *via* methoxymethyl (MOM) protection of the secondary alcohol and deprotection of the benzyl group by dissolving metal reduction to give **164**. Alcohol **164** was then treated with PCC in refluxing benzene to generate the lactone **165**, which was then MOM deprotected (Scheme 40).

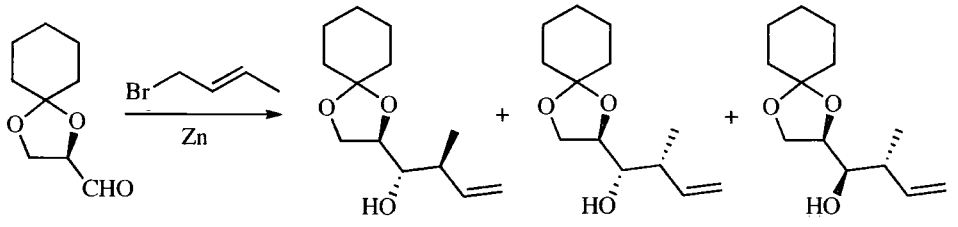


Scheme 40

2.2.9 Salaskar route

The Salaskar approach was developed to take advantage of 1,2-cyclohexylidene glyceraldehydes as chiral templates.[48] The key features of this synthesis were the

stereoselective crotylation of 1,2-cyclohexylidene glyceraldehydes and the enantioselective reduction of a ketone. The synthesis began with a Barbier-type reaction of **166** and crotyl bromide to generate **167** as a mixture of diastereoisomers separable by column chromatography (Scheme 41).

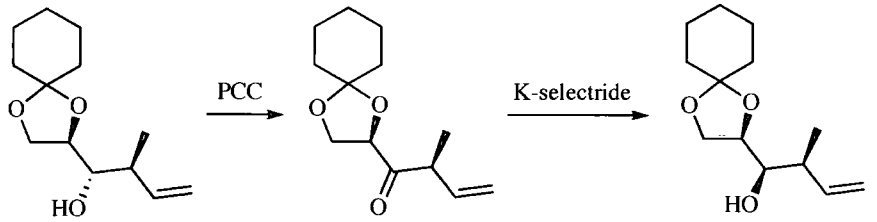


166 **167a** **167b** **167c**

85%, 64 : 34 : trace

Scheme 41

It was noted, however, that the major stereoisomer **167a** possessed the incorrect stereochemistry and therefore a stereoinversion had to be undertaken. This was achieved by oxidation of **167a** with PCC followed by reduction with K-selectride to provide the opposite stereoisomer **169** (Scheme 42).

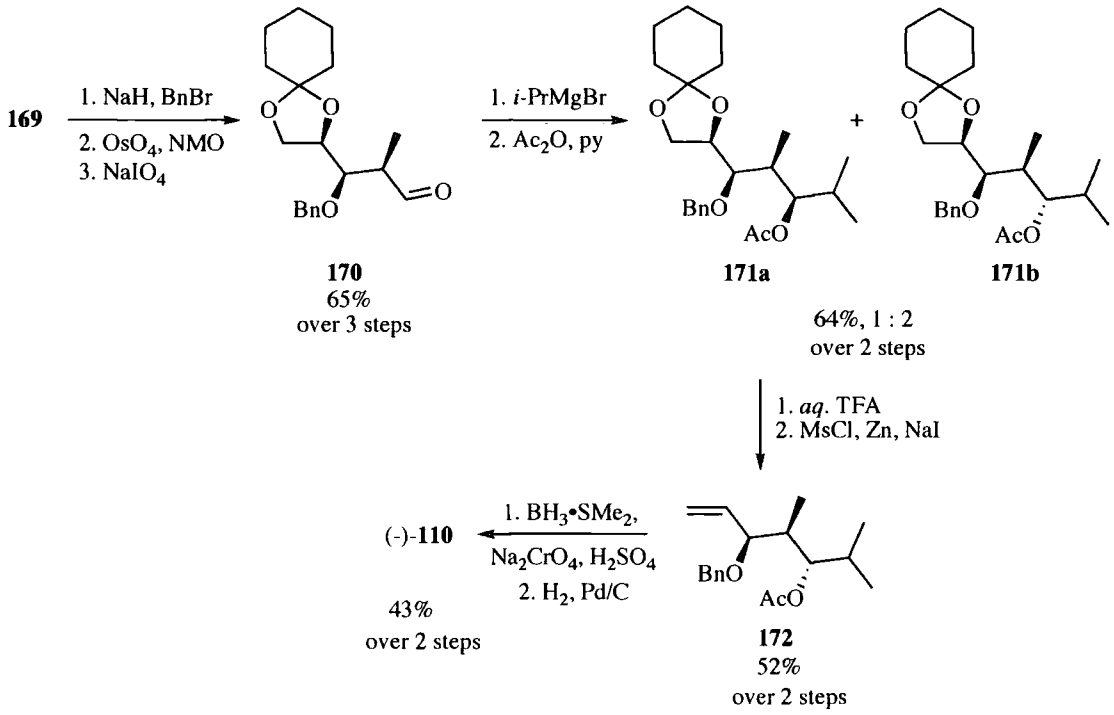


167a **168** 83% **169** 75%

Scheme 42

Alcohol **169** was then benzyl protected, dihydroxylated with osmium tetroxide and oxidised to the aldehyde **170** with sodium periodate. Aldehyde **170** was then reacted with isopropylmagnesium bromide to give an inseparable mixture of mono-protected diols. Fortunately, acylation of the mixture enabled chromatographic separation of the isomers. The desired major isomer **171b** was taken forward and treated with aqueous trifluoroacetic acid to remove the cyclic acetonide. The resultant diol was then

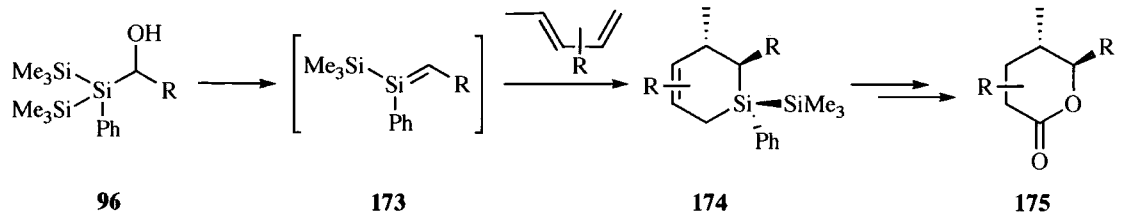
converted to the olefin **172** by mesylation and heating with NaI and zinc dust. Hydroboration of the double bond and *in situ* oxidation with Na_2CrO_4 led directly to the desired lactone. Subsequent debenzylation led to (-)-prelactone B **110** in moderate yield (Scheme 43).



Scheme 43

2.3 Our approach to Prelactone B

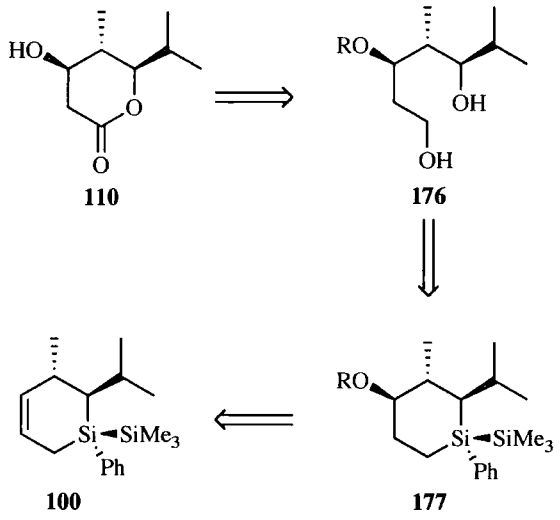
Our interest in prelactone B arose from the development of new synthetic methodology described earlier (*cf.* Section 1.3). The key step involved the novel [4 + 2] cycloaddition of silenes (compounds containing a Si=C double bond) with dienes to yield silacyclohex-4-enes **174** possessing good diastereoselectivity. It was then demonstrated that the cycloadducts could be elaborated to δ-lactones through a sequence involving reduction, Fleming-Tamao oxidation and lactonisation (Scheme 44).



96 **173** **174** **175**

Scheme 44

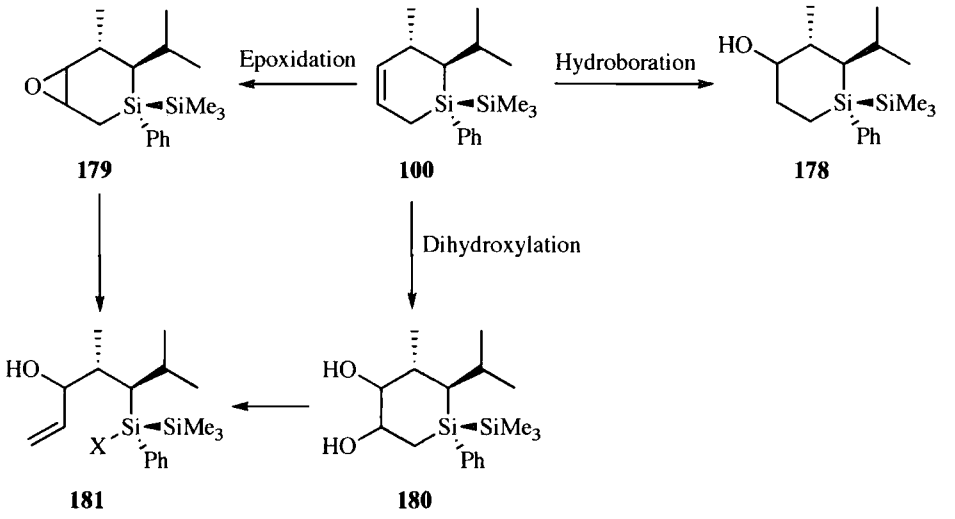
As a result of this preliminary work, a retrosynthetic analysis of prelactone B **110** was undertaken. This revealed that the key step would involve the stereoselective introduction of the C-4 hydroxyl group. The remaining steps would involve protection of the hydroxy group and Fleming-Tamao oxidation to provide diol **176**, which would be lactonised and deprotected to supply the final product (Scheme 45).



110 **176** **100** **177**

Scheme 45

With the analysis in mind, a brief search of the literature suggested that the desired hydroxysilacyclohexane **177** could be accessed in three ways: (i). hydroboration of the silacyclochex-4-ene **100** with the regiochemical outcome directed by the allylsilane unit, (ii). epoxidation of the allylsilane unit followed by silicon-directed fragmentation to give intermediate **181** with the correct regiochemistry, (iii). dihydroxylation of silacyclohex-4-ene **100** followed by silicon-directed fragmentation to give a similar intermediate **181** (Scheme 46).

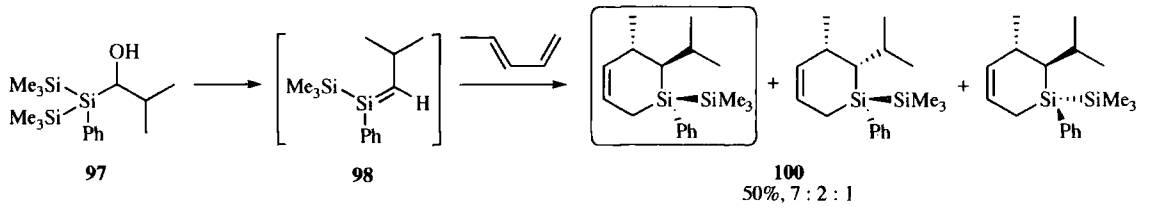


Scheme 46

The following sections will examine each approach individually, discuss the value and limitations of each and ultimately, utilising one approach, report the total synthesis of prelactone B.

2.4 Results and Discussion

As discussed in the previous section, our approach to prelactone B relied on the preparation of silacyclohex-4-ene **100**. Accordingly this became the first objective of the project. It was found that by repeating the silene-diene Diels-Alder reaction, pioneered by Whelligan, the desired silacyclohex-4-ene **100** was produced in good yield and good diastereoselectivity. Silacyclohex-4-ene **100** was obtained as an inseparable mixture of isomers with the minor components reflecting the presence of small amounts of *exo*-addition products and trace amounts of the adducts of the alternative *E*(Si) silene (Scheme 47).



Scheme 47

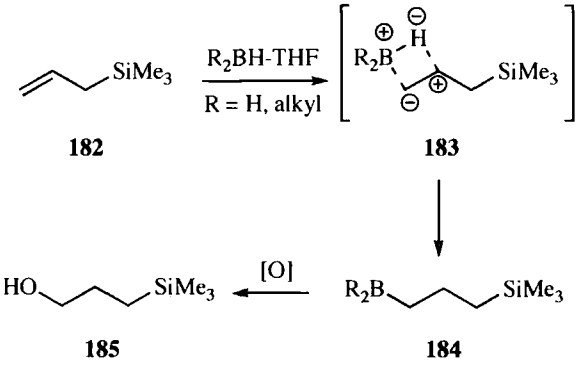
The major diastereomer (boxed in red) is thought to arise from a *Z*(Si) silene **98** reacting in an *endo* Si-Ph orientation. With the silacyclohex-4-ene mixture **100** in hand, attention turned to the introduction of the C-4 hydroxyl group by means of a hydroboration reaction.

2.4.1 Hydroboration

The synthetic utility of the hydroboration reaction in organic chemistry is well known.[8] To date, many borane and organoborane reagents have been developed.[49] In 1980 Brown *et al.* undertook a study to investigate the hydroboration of acyclic vinyl, allyl and butenylsilanes with borane-THF complex and organoboranes.[50] They found that when vinylsilanes were treated with borane-THF complex and oxidised, a mixture of α– and β–substituted alcohols were generated. This mixture was attributed to the stabilising effect of silicon with β-carbocations (discussed in Section 1.1.1.4). However when treated with 9-BBN and oxidised, vinylsilanes produce exclusively the β-product. This switch in selectivity is attributed to the steric interaction between the silicon containing group and bulky alkyl group surrounding the borane, overriding the stabilising effect of silicon.

Following this result, Brown *et al.* went on to investigate the reaction of allylsilanes. When allylsilanes were treated with borane-THF complex and oxidised, the γ-silanol **185** was generated exclusively. This alteration in selectivity is attributed to the

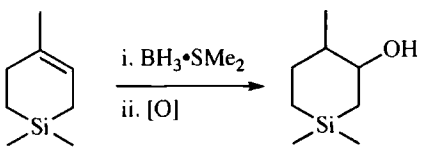
stabilising effect of silicon with β-carbocations. It was also noted that when treated with a bulky alkyl borane the reaction proceeded *via* the same pathway, providing γ-silanol **185** exclusively (Scheme 48).



182 **183** **185** **184**

Scheme 48

Following this, a great number of groups looked at the hydroboration of acyclic allylsilanes, however, very little work was done to investigate the reaction of cyclic allylsilanes.[51-53] Only one publication in 1998 by Soderquist *et al.* looked at the hydroboration of cyclic allylsilane **186**. It was found that treatment of **186** with borane-methylsulfide complex followed by oxidation led to a racemic mixture of alcohols **187** (Scheme 49).[54] In this case the regioselectivity of the reaction was driven by the methyl substituent present on the ring, not the stabilising effect of the silicon.

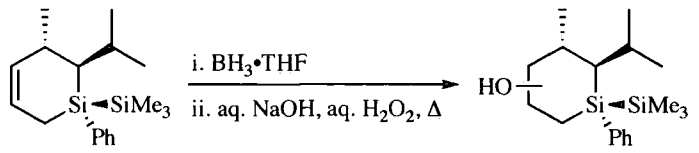


186 **187** 80%

Scheme 49

Consistent with these observations, preliminary work in the group by Whelligan, showed that when a solution of borane-THF complex was treated with a solution of silacyclohex-4-ene **100** in THF at 0 °C and oxidised under standard alkaline conditions, a hydroxyl silacyclohexane **178** was generated in 22% yield and isolated after

chromatography as a single diastereoisomer. Unfortunately the regiochemical outcome of the reaction was not assessed (Scheme 50).

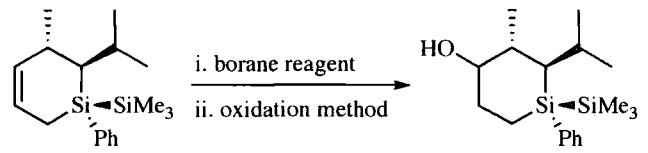


100
ds, 70:20:10

178
22%

Scheme 50

Building on these earlier observations, initial investigations looked to repeat this result in order to improve both the yield and to assess the regiochemical outcome of the reaction (Table 3).



100
ds, 70:20:10

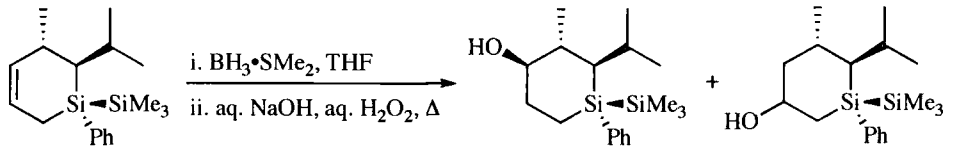
178

Entry	Borane reagent	Oxidation method	Order of addition	Solvent	Yield
1	BH_3•THF	$H_2O/NaOH/H_2O_2$	Alkene to borane	THF	30%
2	BH_3•THF	$H_2O/NaOH/H_2O_2$	Borane to alkene	THF	Starting material
3	BH_3•THF	$NaBO_3.4H_2O$	Alkene to borane	THF	Decomposition
4	BH_3•THF	$NaBO_3.4H_2O$	Alkene to borane	Hexane	Decomposition
5	$BHCl_2$•SMe_2	$NaBO_3.4H_2O$	Alkene to borane	Hexane	Decomposition
6	BH_3•SMe_2	$H_2O/NaOH/H_2O_2$	Alkene to borane	THF	49% (4:1)
7	BH_3•SMe_2	$H_2O/NaOH/H_2O_2$	Alkene to borane	Hexane	26% (4:1)

Table 3

On a larger scale, the Whelligan procedure afforded the hydroxysilacycle in 30% yield (entry 1). However, this yield could not be consistently reproduced as varying amounts of decomposition products were observed. To address this issue the order of reagent

addition was reversed (entry 2). Disappointingly, when the borane reagent was added to the silacyclohex-4-ene, hydroboration did not take place and starting material was recovered unchanged. This suggested that the order of addition was crucial, so subsequent investigations explored changing the oxidation conditions, borane reagent and solvent (entries 3-7). Ultimately, substitution of borane-THF complex with borane-dimethylsulfide complex (as described by Soderquist *et al.*, entry 6) afforded hydroboration of silacyclohex-4-ene **100** with a 49% yield and 4:1 regioselectivity in favour of the correct isomer. The regioselectivity was determined by analysing the ^{1}H NMR splitting paterns of the regioisomeric carbinol protons (Scheme 51).



100
ds, 70:20:10

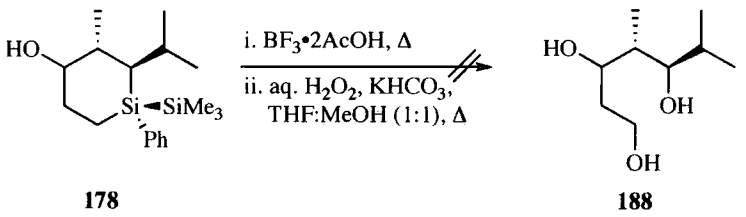
178
49% (4:1)

Scheme 51

Introduction of the hydroxyl group was confirmed by analysis of the IR spectrum, which showed a broad signal at 3368cm^{-1} coupled with a peak at 3.26 ppm in the ^{1}H NMR corresponding to the carbinol proton. The major regioisomer was isolated as a single diastereoisomer by flash column chromatography. Further investigations were undertaken to improve the yield by altering the solvent to hexane (entry 7), but this led to a significant drop in yield. The decision was then taken to curtail further examination of this process and the optimum reaction conditions were set (entry 6).

Initial attempts to carry out the Fleming-Tamao oxidation of hydroxysilacyclohexane **178** were unsuccessful and led to decomposition products. This suggested that the unprotected hydroxyl group interfered with the reaction. Therefore to advance the

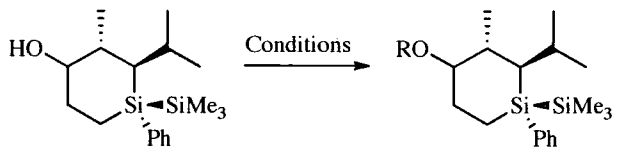
hydroxy substrate to prelactone B, protection of the secondary hydroxy unit was essential (Scheme 52).



178 **188**

Scheme 52

After considering many protecting groups it was decided that a benzyl group would be able to survive both the acidic/basic conditions of the Fleming-Tamao procedure. Consequently, investigations were undertaken to ascertain suitable conditions for benzyl protection of **178** (Table 4)



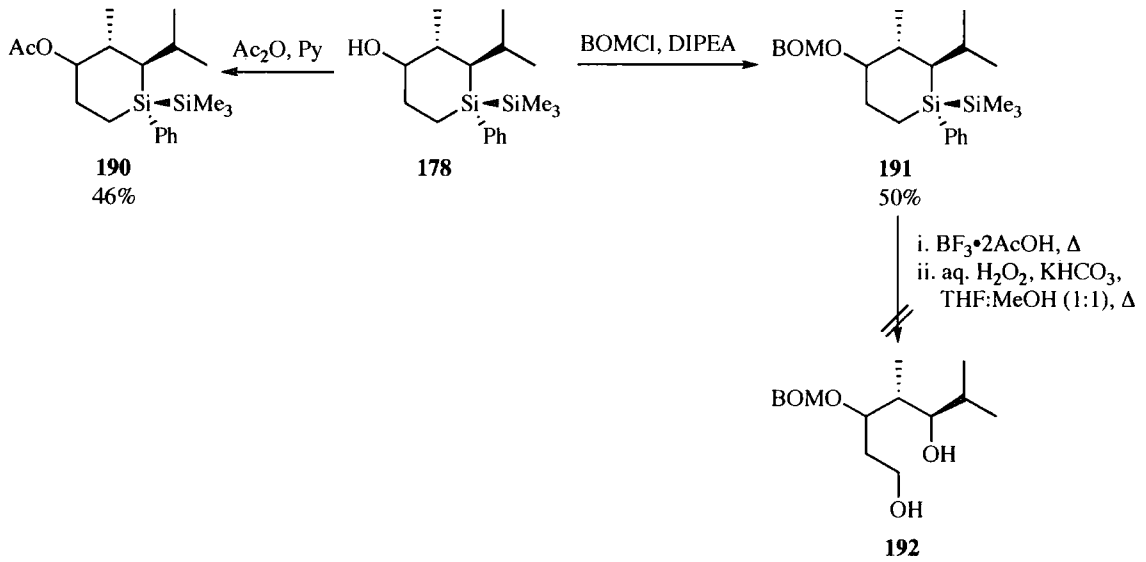
178 **189**

Entry	Conditions	Outcome
1	Benzyl bromide, TBAI, NaH	Starting material
2	Benzyl bromide, Ag_2O	Starting material
3	Benzyl acetimidate, *p*TSA	Starting material
4	PMBCl, DIPEA	Starting material

Table 4

Disappointingly, every effort to introduce a benzyl ether proved unsuccessful. The reason for this failure was not obvious and there was concern that any functionalisation of the hydroxyl group would be difficult. Consequently, other protecting groups were then explored.

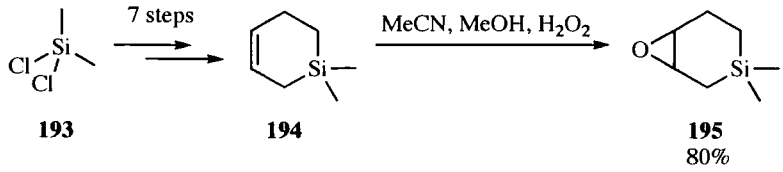
Firstly, acetate protection was attempted. When treated with pyridine and acetic anhydride the desired acetate protected product **190** was generated in 46% yield. In addition to acetate protection, the hydroxyl unit was protected with a benzyloxymethyl (BOM) group. On treatment with benzoxymethyl chloride and DIPEA, the desired protected product **191** was generated in 50% yield. Disappointingly, when **191** was subjected to the Fleming-Tamao conditions, the BOM group did not survive the initial acidic reaction conditions and led to quantitative recovery of the unprotected hydroxysilacyclohexane **178**. As a result, the hydroboration route to prelactone B was abandoned (Scheme 53).



Scheme 53

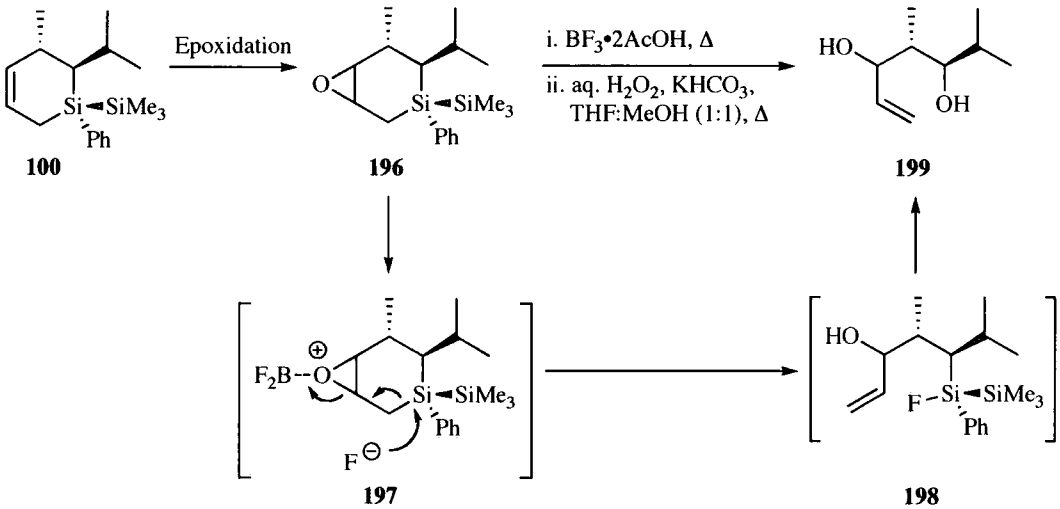
2.4.2 Epoxidation

Disappointed with our initial foray, attention turned to an alternative route involving epoxidation. Epoxidation of alkenes has been utilised extensively in organic synthesis,[55] however to the best of our knowledge, only one example exists in the literature for the epoxidation of silacyclohexenes. This was reported in 1996 by White *et al.* who showed that dimethylsilacyclohexene **194** could be epoxidised to **195** utilising a modified Payne oxidation (**Scheme 54**).[56]



Scheme 54

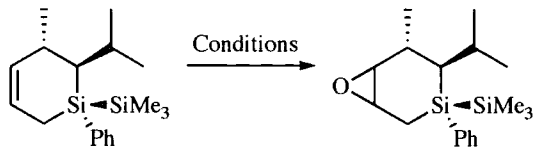
Our intention was to utilise this or other epoxidation reactions to provide access to the silacyclic oxirane **196**. It was hoped that when subjected to the Fleming-Tamao oxidation conditions, **196** would undergo a regioselective ring fragmentation reaction, directed by the silicon atom, to produce the fragmented dihydroxyl product **199** (**Scheme 55**).



Scheme 55

With this hypothesis in mind, epoxidation reactions of silacyclohex-4-ene **100** were investigated (**Table 5**). Entries 1 and 2 highlight our initial attempts at this chemistry. Silacyclohex-4-ene **100** was reacted, under classical epoxidation conditions with *meta*-chloroperbenzoic acid (*m*CPBA) and excess $NaHCO_3$ at various temperatures. Disappointingly, both reactions led to decomposition of the starting material. To address the sensitivity of silacyclohex-4-ene **100** a milder method for epoxidation was investigated. Jacobsen's catalyst has been shown to epoxidise several cyclic and acyclic trisubstituted olefins under mild conditions.[57] Utilising this methodology, entry 3 shows

that when **100** was treated with Jacobsens catalyst, no reaction was observed and the starting material was recovered quantitatively. Subjecting silacyclohex-4-ene **100** to the modified Payne conditions (entry 4) also proved disappointing with starting material being recovered quantitatively.

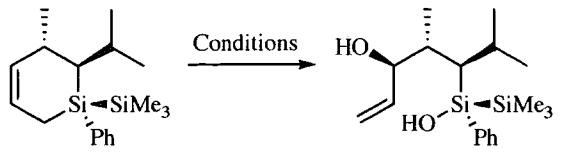


100 **196**

Entry	Conditions	Outcome
1	*m*CPBA, $NaHCO_3$, 0 °C	Decomposition
2	*m*CPBA, $NaHCO_3$, -78 °C	Decomposition
3	Jacobsen catalyst, NMO, NaOCl, 5NNaOH	Starting material[58]
4	MeCN, MeOH, H_2O_2	Starting material

Table 5

A search of the literature was then undertaken to find milder reaction conditions. The results showed that dioxiranes have been utilised as epoxidising agents and first came to prominence in 1985 when Murray *et al.* reported their synthesis and application.[59] Since then they have found much use in organic chemistry, particularly in sugar chemistry because they epoxidise alkenes under neutral conditions. With this promising new method to hand, the reaction of silacyclohex-4-ene **100** was attempted (**Table 6**).

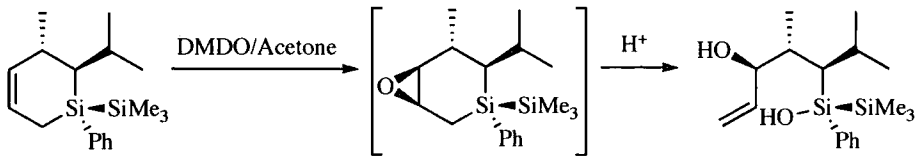


100 **200**

Entry	Conditions	Outcome
1	Oxone, KH_2PO_4, acetone, H_2O, DCM, 18-crown-6	Starting material[60]
2	DMDO, acetone, DCM	20%[61]
3	Oxone, trifluoromethylacetone, aq. EDTA disodium salt, $NaHCO_3$	22%[62]
4	MTO (cat.), TTBP, THF/H_2O_2 (3:1)	Starting material[63]

Table 6

Following the original literature provided by Murray *et al.* a phase transfer reaction (entry 1) was attempted. The reactive dioxirane, dimethyldioxirane (DMDO) is generated *in situ* through the reaction of acetone with oxone. Disappointingly, the reaction provided only starting material after workup. Readdressing the literature it was discovered that DMDO could be generated as a solution in acetone and then used to epoxidise alkenes. Gratifyingly, when silacyclohex-4-ene **100** was treated with an acetone solution of DMDO (entry 2), the compound isolated after chromatography was not the silacyclic oxirane **196** but the dihydroxy compound **200** (Scheme 56).

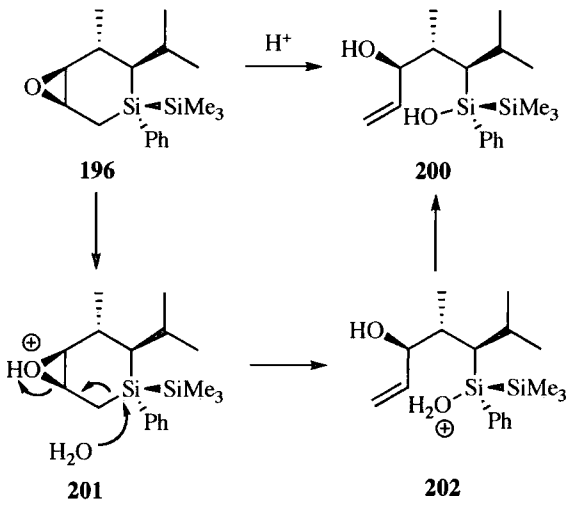


100 **196** **200**
20%

Scheme 56

Fragmentation of the silacyclic oxirane was confirmed by analysis of the IR and ^1H NMR spectra, which showed a broad signal at 3060cm^{-1} for the hydroxyl group coupled with peaks at 5.75, 5.21 and 5.08 ppm in the ^1H NMR for the allyl group. Moreover, the

dihydroxy compound **200** was generated as a single diastereoisomer. Its stereochemistry was assigned by analogy to work described in Chapter 3.4. This would suggest that initial addition of DMDO occurs *syn* to the trimethylsilyl group giving rise to the *anti:anti:anti* stereochemistry. The fragmentation of silacyclic oxirane **196** was believed to arise from an acidic rearrangement mechanism during silica gel chromatography (Scheme 57).



Scheme 57

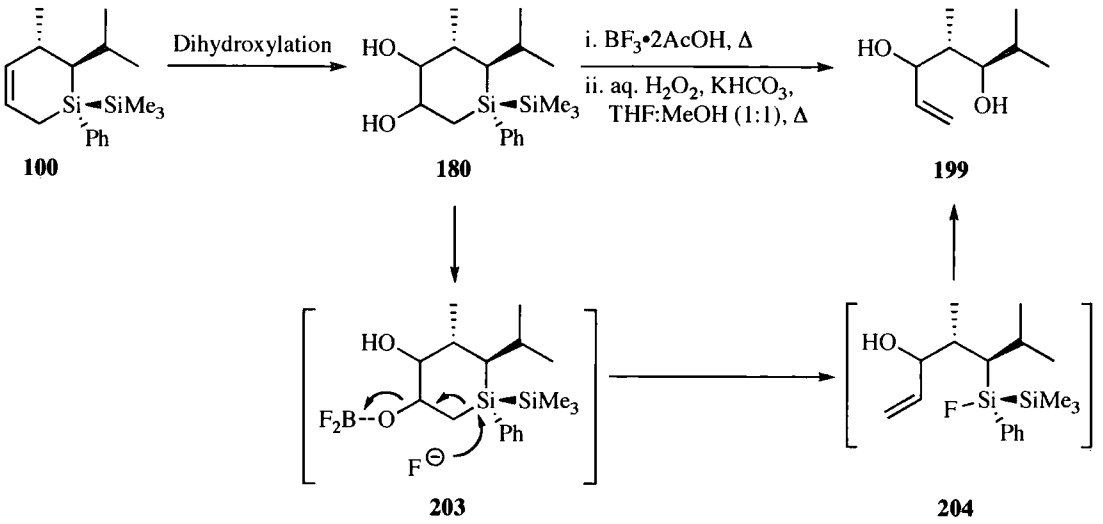
Despite a low yield of 20%, the remaining 80% was recovered as starting material, demonstrating that the reaction is very mild. Subsequently, the low conversion of silacyclohex-4-ene **100** was attributed to the difficulty in isolating the acetone solution of DMDO. To overcome this problem, several groups have reported practical, general and efficient protocols for the *in situ* generation of DMDO and its more reactive substrate methyl(trifluoromethyl)dioxirane.[62] Utilising methyl(trifluoromethyl)dioxirane generated *in situ*, silacyclohex-4-ene **100** was epoxidised to give direct access to the dihydroxyl compound **213** (entry 3) in 22% yield. Attempts to further improve the yield were unsuccessful.

Due to the promising results obtained with dioxiranes, a metal equivalent was investigated. Methyltrioxorhenium (MTO) has been used as an oxidation catalyst in the presence of hydrogen peroxide for the epoxidation of olefins. Their use was first highlighted in 1991 by Herrmann *et al.* who proposed that olefin epoxidation occurred *via* a hydroperoxy complex.[63] Employing the same methodology, silacyclohex-4-ene **100** was reacted with catalytic MTO and hydrogen peroxide to give access to the silacyclic oxirane **196**. Interestingly, no reaction was observed and starting material was recovered quantitatively.

In conclusion, despite epoxidation of silacyclohex-4-ene **100** providing the dihydroxy compound **200** the isolated yield was disappointing. With every effort made to improve the yield exhausted, this route had to be abandoned.

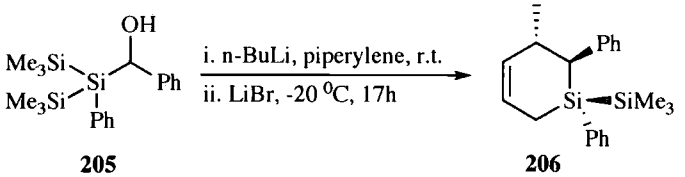
2.4.3 Dihydroxylation

To advance silacyclohex-4-ene **100** to prelactone B **110**, our attention turned to a route involving dihydroxylation. Dihydroxylation is a well-documented transformation for alkenes and has been studied extensively.[64] However, to the best of our knowledge, there are no examples in the literature that employ silacyclohex-4-enes in a dihydroxylation reaction. Therefore, our intention was to utilise this methodology to provide access to dihydroxysilacyclohexane **180**, which would undergo a regioselective silicon directed ring fragmentation, similar to that described for epoxides (*cf.* **Scheme 55**) when subjected to the Fleming-Tamao oxidation conditions. This would provide access to the dihydroxy compound **199** (**Scheme 58**).



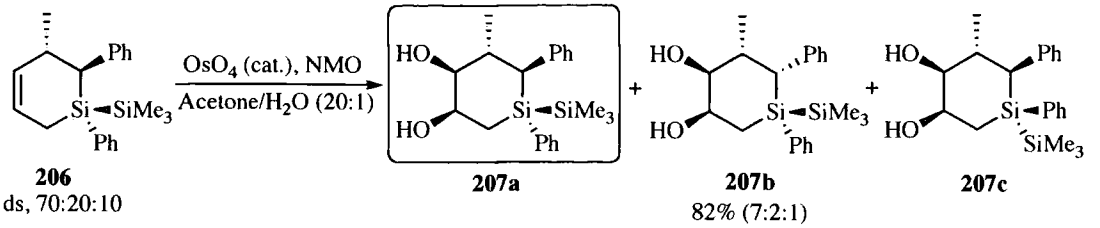
Scheme 58

With this in mind, initial efforts focused on developing methodology for the dihydroxylation of silacyclohex-4-ene **100**. For this, we intended to use a model compound, phenylsilacyclohex-4-ene **206**, as this could be prepared in high yields, identical diastereoselectivity (ds 7:2:1) and possesses a strong chromophore for easy analysis of late stage intermediates. Firstly, phenyl silacyclohex-4-ene **206** was generated by reaction of phenyl silyl alcohol **205** under identical conditions to those outlined in Section 2.3 (**Scheme 59**).



Scheme 59

Then, to our delight when subjected to the Upjohn dihydroxylation conditions (cat. OsO_4, NMO, Acetone:H_2O 20:1) the corresponding diols **207a-c** were isolated in 82% yield (**Scheme 60**).



206
ds, 70:20:10

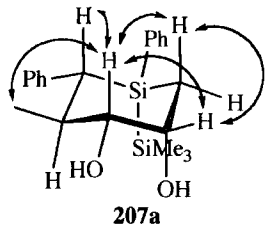
207a

207b
82% (7:2:1)

207c

Scheme 60

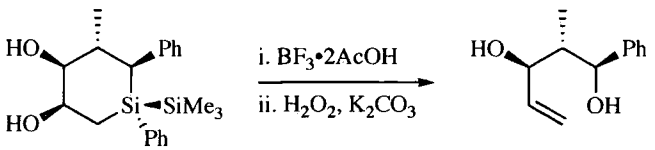
Flash chromatography of the isomeric mixture enabled the major diastereoisomer **207a** to be separated. Importantly, **207a** was shown to possess the 4-hydroxy group *trans* to the methyl group by nOe experiments (Figure 10).



207a

Figure 10

With the 1,2-diol **207a** in hand, the fragmentation reaction was investigated, utilising the Fleming-Tamao conditions. On a small scale, when treated with BF_3•2AcOH complex, followed by hydrogen peroxide oxidation as a one-pot – two-step reaction, diol **208** was generated in 72% yield as a single diastereoisomer (Scheme 61).



207a

208
72%

Scheme 61

To probe this rearrangement, the crude material obtained before oxidation, was analysed by ^1H (**Figure 11**) and ^{19}F NMR. Surprisingly, the ^1H NMR showed that an intermediate was generated as a 1:1 mixture of diastereoisomers and just as surprisingly the ^{19}F NMR showed that no fluorine was present in the molecule.

Puzzled by this result, the reaction was repeated on a larger scale and the unknown intermediate isolated by flash chromatography and fully analysed. Examination of the mass spectrum (obtained by electrospray analysis) showed the molecular ion to have *m/z* = 352. This, coupled with a characteristic peak (-21 ppm) for a siloxane group in the ^{29}Si NMR and no fluorine signals in the ^{19}F NMR enabled the unknown intermediate to be identified as the cyclic siloxane **212**.

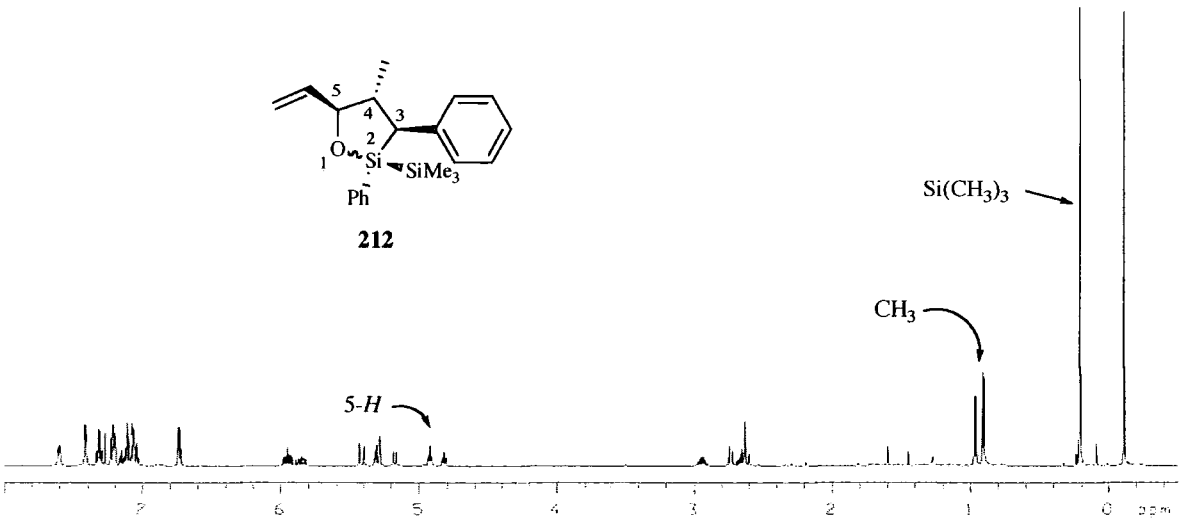
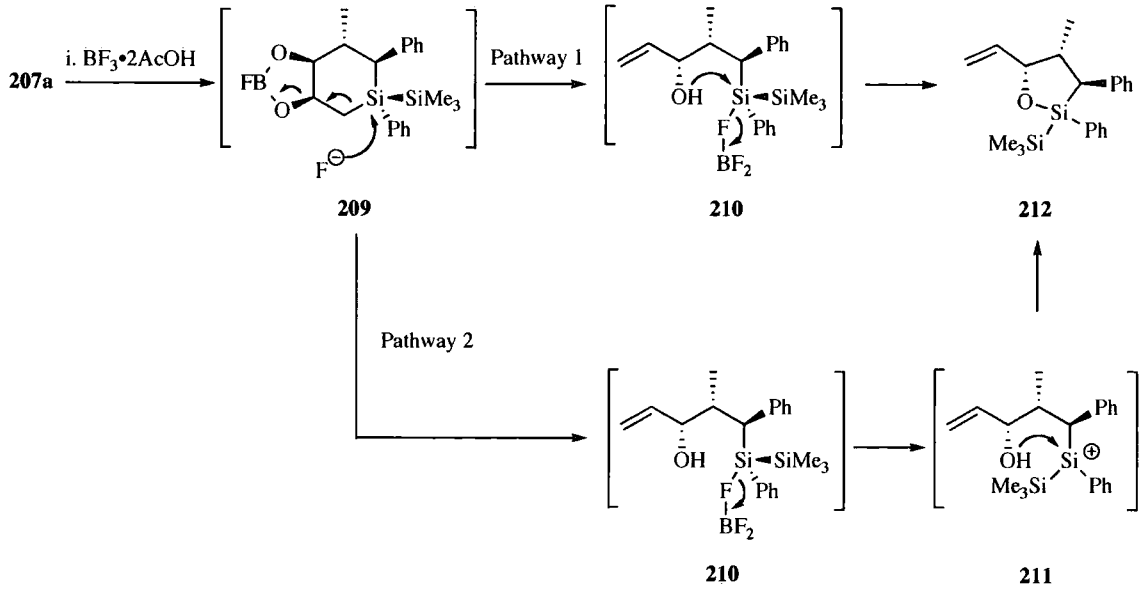


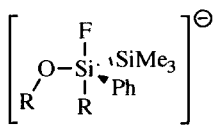
Figure 11

Two possible reaction pathways could account for this observation. The first involves an intramolecular S_N2 reaction of the allylic alcohol with the silyl fluoride species **210**. The second involves the allylic alcohol reacting with a transient silyl cation **211**, generated by an S_N1 reaction (**Scheme 62**).



Scheme 62

To explain the stereochemical outcome of the initial rearrangement, pathway 1 may be ruled out because an S_N2 reaction at the silyl fluoride atom will only give rise to a single diastereoisomer. However, pathway 1 may not be concerted and silicon may enter a pentacoordinate transition state **213** (Figure 12). This might allow the transition state to undergo Berry pseudorotation and scramble the stereochemistry.[65] This would give rise to the observed isomeric product. On the other hand, pathway 2 is rather unlikely as silyl cations are very rare species and highly reactive.[66-71]



213

Figure 12

In order to determine the reaction pathway and a potential mechanism, further experiments were undertaken. Since both pathways require the intermediacy of a ring-opened silyl fluoride species **210**, the cyclic siloxane **212** was treated with BF_3•2AcOH complex to attempt to open the ring, and give access to this species. Interestingly, when analysed by ^1H and ^{19}F NMR, the 1:1 diastereomeric mixture of siloxane **212** had given

rise to a single diastereomeric compound possessing one fluorine atom (Figure 13). This was proposed to be the ring opened silyl fluoride **210** based on the characteristic fluorine doublet observed in the ^{19}F NMR (**Figure 14**).

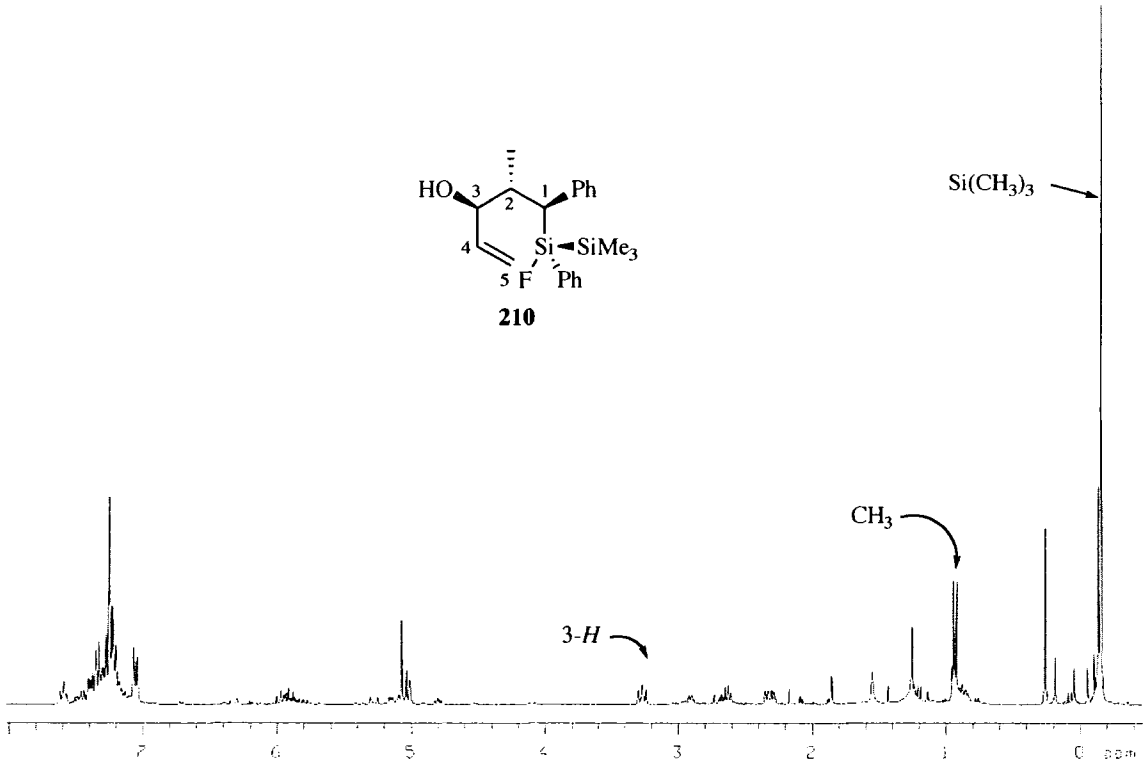


Figure 13

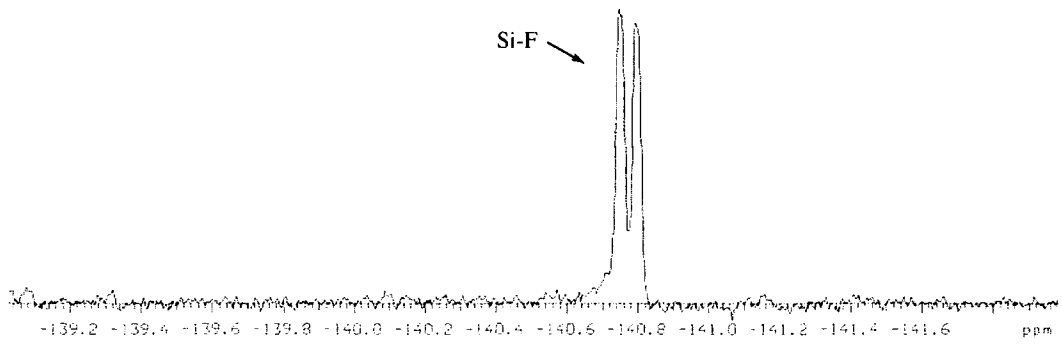
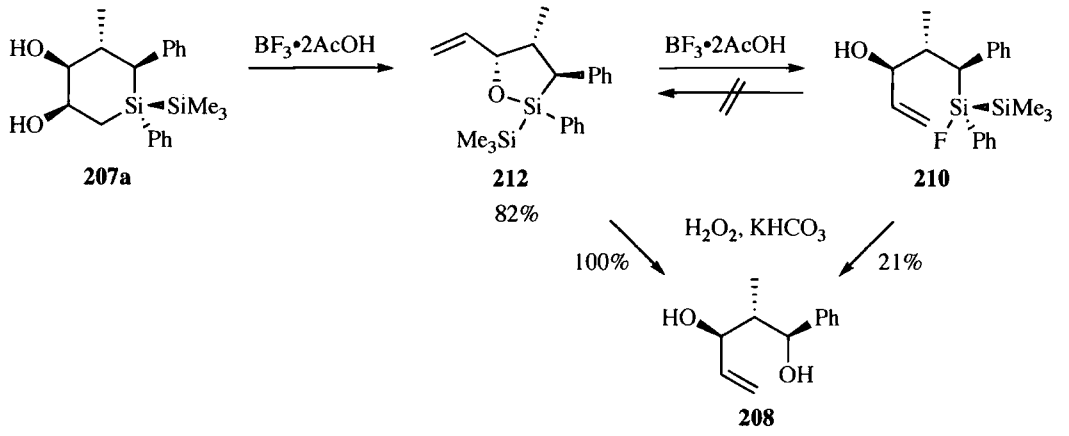


Figure 14

Unfortunately, all attempts to purify and fully characterise this compound were unsuccessful and led to decomposition. Attempts to trap the reactive hydroxyl group as a TBS ether were also unsuccessful, giving only decomposition products. Analogous results were obtained when attempting to cyclise **210** back to the siloxane **212** using a

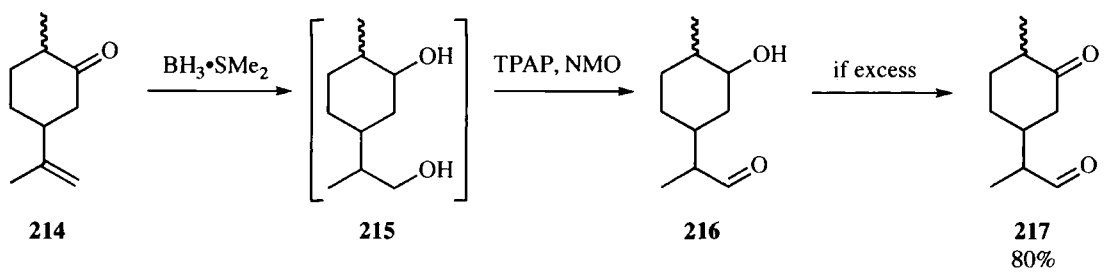
variety of bases. However, oxidation of silyl fluoride **210** using hydrogen peroxide generated the diol **208**, albeit in a low (21%) yield (**Scheme 63**). In conclusion, the silacyclic diol **207a** could be advanced to the 1,3-diol **208** in good yield *via* the intermediacy of cyclic siloxane **212** and in lower yield *via* the proposed silyl fluoride species **210**. Two proposed reaction pathways may account for the formation of cyclic siloxane **212**; however, no evidence exists to support either one.



Scheme 63

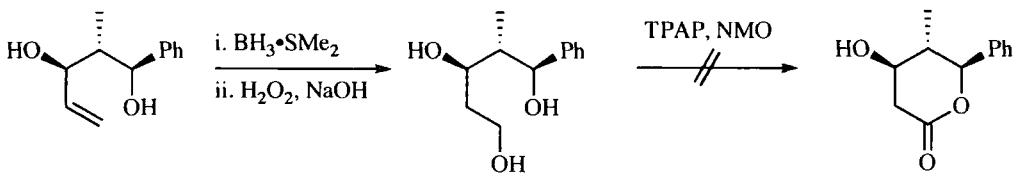
2.4.4 Synthesis of Prelactone B

Despite the interesting reactivity of silacyclic diol **207a**, allylic diol **208** could be synthesised reproducibly in good yield, so attention turned to the synthesis of the prelactones. This required a search of the literature, which revealed a procedure that would enable hydroboration of the double bond in allylic diol **208** followed by oxidation to the lactone in one step (**Scheme 64**).[72]



Scheme 64

However, attempts to replicate this procedure using diol **208** failed to provide the desired product. Therefore, it was decided to split the reactions and attempt to isolate and purify the triol intermediate. So, when **208** was treated with $BH_3 \bullet SMe_2$ complex and oxidised with hydrogen peroxide, the desired triol **218** was generated in 64% yield as a single regioisomer based on the presence of two methylene signals at 3.89 and 1.98 ppm, and the absence of a second signal for the regioisomeric methyl group, in the ^1H NMR. Unfortunately, attempts to lactonise triol **218** were unsuccessful, returning only complex mixtures of products (**Scheme 65**).



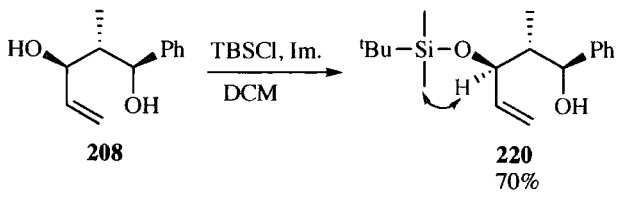
208 **218** 64% **219**

Scheme 65

Disappointed with these results, a new strategy involving protecting groups had to be adopted. It was proposed that to selectively protect the desired allylic hydroxyl group of diol **208** in the presence of a benzylic hydroxyl group would be difficult and would give rise exclusively to the di-protected product. Therefore, the silacyclic diol **207a** had to be protected before the Flaming-Tamao procedure. Attempts to protect both hydroxy units of the silacyclic diol **207a** as a PMB ether or a benzyl ether were unsuccessful.

Frustrated with this string of unsuccessful results, attempts to achieve a selective protection of the diol **208** were investigated. Fortunately, on treatment with a large excess of TBSCl and imidazole, a single product possessing only one TBS group by ^1H NMR was isolated in 70% yield. To ascertain the position of the TBS group, nOe experiments were undertaken. Gratifyingly, a correlation was observed between the methyl group of the TBS unit and the allylic CH, rather than the benzylic CH,

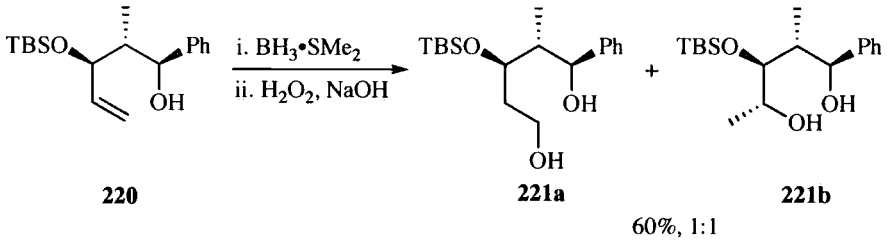
confirming that the protecting group had reacted exclusively with the allylic alcohol. None of the di-protected or benzylic protected product was detected (**Scheme 66**).



208 **220** 70%

Scheme 66

The monoprotected diol **220** could now be advanced to the desired lactone through a sequence involving hydroboration and lactonisation. Initial investigation of the hydroboration reaction began by utilising $BH_3 \bullet SMe_2$ complex followed by hydrogen peroxide oxidation. When subjected to these conditions, monoprotected diol **220** was hydroborated to give a 1:1 regioisomeric mixture of diols **221a** and **221b** in 60% yield (**Scheme 67**). The undesired regioisomer was separated from the desired product by flash chromatography and isolated as a single diastereoisomer. ^1H NMR analysis showed a new signal at 1.26 and 3.99 ppm corresponding to the new methyl group and carbinol proton respectively.



220 **221a** **221b**

60%, 1:1

Scheme 67

This result contrasts that obtained earlier for the hydroboration of diol **208** (*cf.* **Scheme 65**). It was proposed that the TBS group forces the allyl group into close proximity with a co-ordinated borane molecule **222** whereas, in the previous case, the borane molecule co-ordinates both hydroxyl groups **223**, locking the molecule and enabling selective hydroboration (Figure 15).

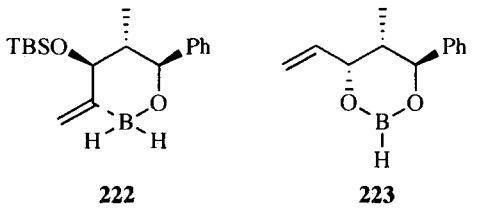
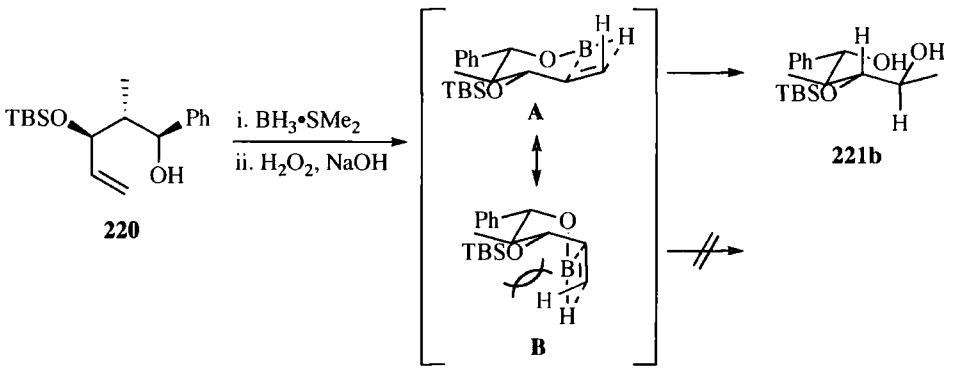


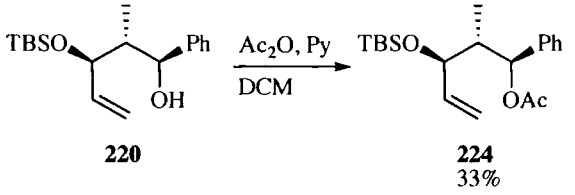
Figure 15

Furthermore, it was found that the regioisomeric diol **221b** was formed as a single diastereoisomer. This selectivity was proposed to arise through an intramolecular hydroboration reaction of the alkene *via* transition state A. Transition state B was discredited due to $A^{1,3}$ strain. Despite this, the stereochemistry was not fully confirmed (**Scheme 68**).



Scheme 68

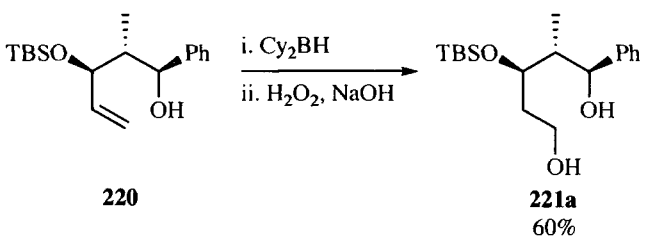
To circumvent this problem, efforts to block the benzylic group were briefly investigated. Treatment of the monoprotected diol **220** with acetic anhydride and pyridine gave the desired di-protected product **224** in low yield, accompanied by starting material and a large amount of decomposition. As a result, alternative solutions were considered (**Scheme 69**).



Scheme 69

Reinvestigation of the literature emphasised that when regioselectivity was an issue, utilising a bulky borane (such as 9-BBN) restored the selectivity of the hydroboration reaction (*cf.* Section 2.4.1). Moreover, these reagents are less likely to bind to the hydroxyl group. With this in mind, attention turned to utilising a bulky borane to hydroborate the alkene of mono-protected diol **220**. Knowing that the product of the reaction would be a diol, it was decided that 9-BBN would not be utilised because the by-product from its oxidation, cyclooctane diol, may hinder purification. Consequently, dicyclohexylborane was selected because the by-product from its oxidation is cyclohexanol, which should not interfere with purification of the diol.

To our satisfaction, when treated with an excess of freshly prepared dicyclohexylborane and oxidised under standard conditions, the desired diol **221a** was generated as the sole product in 60% yield. None of the regioisomeric product was present by TLC or ^{1}H NMR analysis of the crude material (**Scheme 70**).

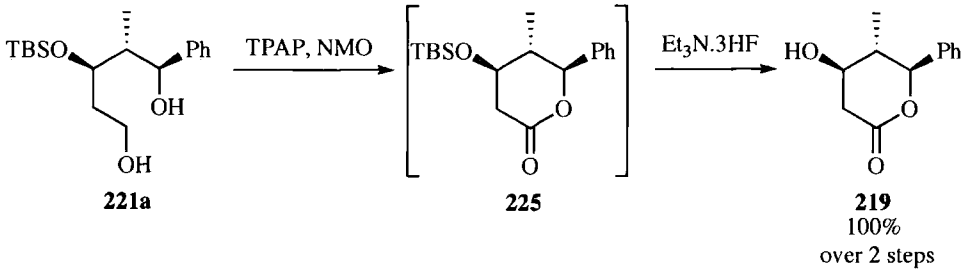


220 **221a** 60%

Scheme 70

With an efficient synthetic strategy in place to gain access to the 1,5-diols, attention turned to the final steps. Lactonisation of diol **221a** was undertaken with TPAP and NMO. Pleasingly, the lactone product **225** was generated in quantitative yield as ascertained by analysis of the ^{1}H NMR. This revealed no signals for the starting material; therefore, no purification was undertaken and the crude lactone product was subjected to mild silicon deprotection utilising $Et_3N.3HF$ in THF. Subsequent overnight

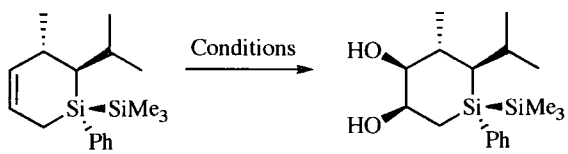
reaction, workup and flash chromatography provided the β-hydroxy-δ-lactone **219** in 100% yield from diol **221a** (**Scheme 71**).



221a **225** **219** 100% over 2 steps

Scheme 71

With the model study completed and a synthetic route defined, attention now turned to the synthesis of prelactone B **110**. Dihydroxylation of silacyclohex-4-ene **100** (ds 4:1) afforded the silacyclic diol **226** in 42% yield (entry 1). Flash chromatography of the diol **226** enabled the major isomer to be isolated as a single diastereoisomer. The stereochemistry was confirmed by nOe experiments as before. Since the yields for the dihydroxylation were lower than those obtained with the phenylsilacyclohex-4-ene, attempts to improve this utilising other dihydroxylation conditions were then undertaken (**Table 7**).

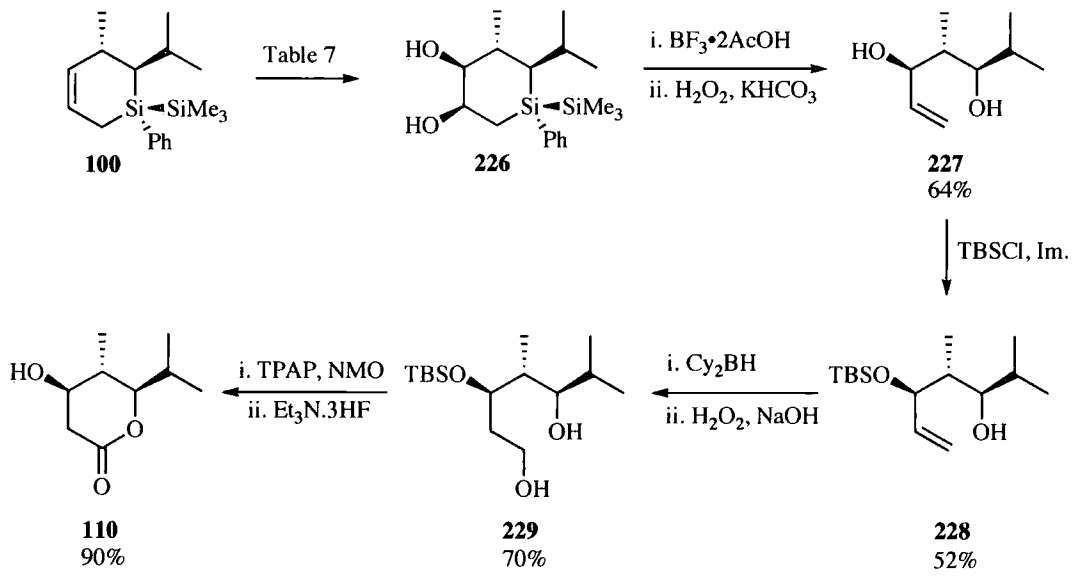


100 **226**

Entry	Conditions	Outcome
1	OsO_4, NMO, Acetone:H_2O 20:1	42%
2	$K_2OsO_4.H_2O$, $K_3Fe(CN)_6$, K_2CO_3, Quinuclidine, Methane sulfonamide	46%
3	OsO_4, TMEDA, Ethylenediamine	37%

Table 7

Unfortunately no significant improvement in yield was observed, and therefore the Upjohn procedure was used for subsequent reactions. With sufficient material in-hand, attention turned to the ring fragmentation reaction. When treated with the Fleming-Tamao conditions silacyclic diol **226** was transformed, *via* the cyclic siloxane, to the corresponding allylic diol **227** in 64% yield. Delighted with this result, protection of the diol was then undertaken utilising TBSCl to give mono-protected diol **228** in 52% yield. As before, the protecting group was shown by nOe experiments to be on the allylic alcohol, analogous to the model study. Hydroboration of the double bond was undertaken with dicyclohexyl borane to give, following oxidation and flash chromatography, the diol **229** as a single regioisomeric product in 70% yield. Cyclisation with TPAP and NMO provided the lactone in quantitative yield, followed by silyl ether cleavage with $Et_3N.3HF$ yielding prelactone B **110** in 90% yield. The spectroscopic data for this compound proved to be identical with those reported in the literature (**Scheme 72**).



Scheme 72

2.5 Conclusion

In conclusion, this work has demonstrated that silacyclohex-4-enes **100** and **206**, derived from silene-diene cycloadditions are viable substrates for the total synthesis of prelactone B **110** and an analogue **219**. The key steps in the synthesis involved the dihydroxylation of the silacyclohex-4-enes to provide the hydroxyl moiety and the selective silicon protection of the diol **227** and **208**. The following chapter focuses on Hosomi-Sakurai methodology applied to elaborate silacyclohex-4-enes to 1,4-monoprotected diols and tetrahydronaphthalenes.

3 Hosomi-Sakurai Chemistry

3.1 Introduction

Allylsilanes are widely used in organic chemistry and have been shown to undergo a plethora of reactions at both the silicon and olefinic moieties (**Figure 16**).[73,74]

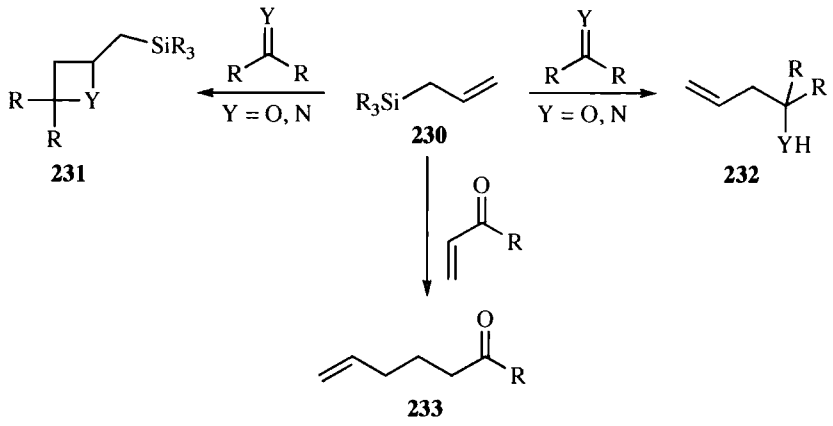
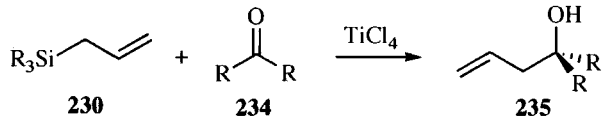


Figure 16

In 1948 Sommer *et al.* reported that the allyl-Si σ bond of allylsilanes was easily cleaved by electrophiles and Brønsted acids.[75] Later, Frainnet *et al.* established that allylsilanes react preferentially at the γ-carbon.[76] Following this early work, increased interest in allylsilanes came about when Hosomi *et al.* reported the first carbon-carbon bond forming reaction in the late 1960s.[77] Then in the 1970s, a flourish of publications by the groups of Abel, Calas and Hosomi highlighted the use of allylsilanes in synthesis. Abel *et al.* and Calas *et al.* both reported that allylsilanes added to activated carbonyl compounds, such as perfluoroacetone.[78,79] Later in the mid 1970s, an independent study by Hosomi *et al.* reported that carbonyl compounds in the presence of a strong Lewis acid ($TiCl_4$) underwent smooth allylations with allylsilanes **230** (Scheme 73).[80]



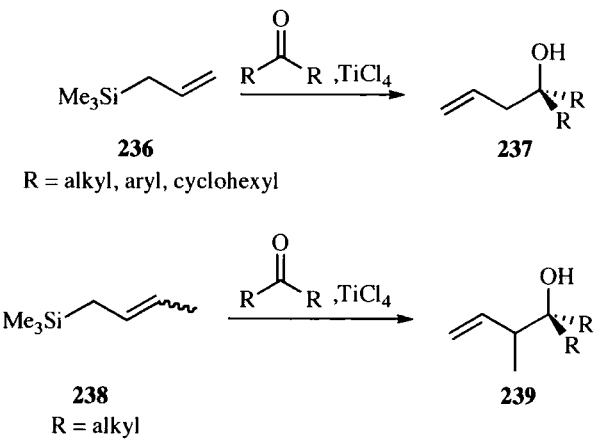
230 **234** **235**

Scheme 73

Since this discovery by Hosomi *et al.*, the Lewis-acid-promoted addition of allylsilanes to carbonyl compounds and related electrophiles (now referred to as the Hosomi-Sakurai reaction) has found considerable use in synthesis. The following section will briefly review this methodology, highlighting its application to organic synthesis. Subsequent sections will then discuss our results obtained by utilising this methodology with silacyclohex-4-enes.

3.2 Hosomi-Sakurai reaction

The Hosomi-Sakurai reaction is the Lewis-acid-promoted addition of allylsilanes to carbonyl compounds and related electrophiles. The simplest allylsilanes, allyltrimethysilane **236** and (E/Z)-crotylsilane **238**, were utilised by Hosomi and Sakurai in their independent studies. Together, they published the reaction of **236** and **238** with a whole variety of ketones and aldehydes to emphasise the usefulness of this transformation in organic synthesis (Scheme 74).



236
R = alkyl, aryl, cyclohexyl

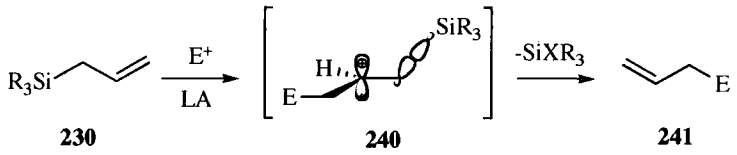
237

238
R = alkyl

239

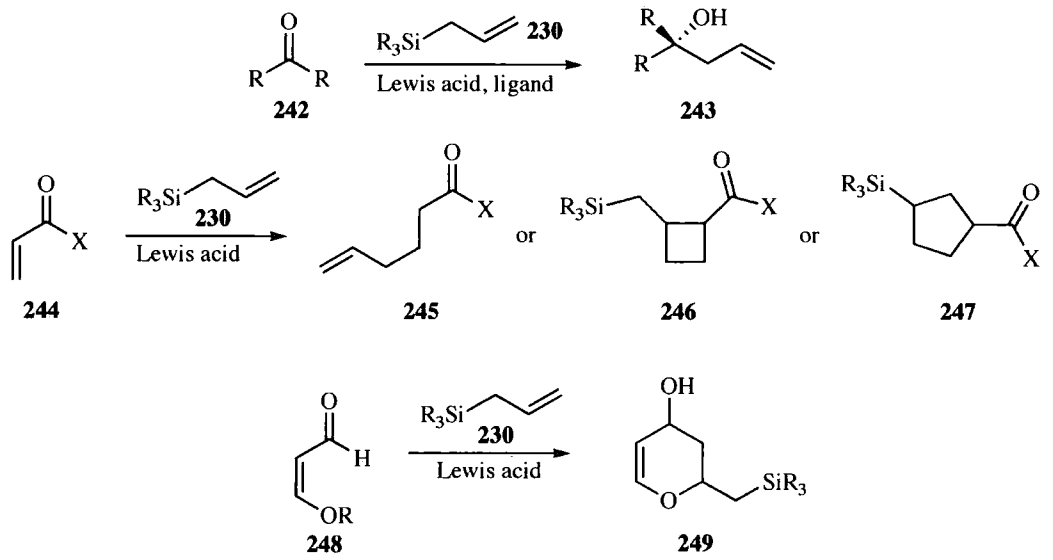
Scheme 74

Subsequent studies by Fleming *et al.* led to the generally accepted mechanism for this transformation (Scheme 75).[81] The mechanism proposed involves initial addition of an electrophile (C^+ or H^+) to an allylsilane leading to the formation of a carbocation intermediate, stabilised by the presence of a β-silicon atom. Such stabilisation is believed to arise from orbital overlap between the empty pπ orbital on the carbocation and the co-planar C–Si σ-orbital. Subsequent Lewis-acid-catalysed or proto-desilylation of intermediate **240** leads to the allylated product **241**.



Scheme 75

Following these early results, many research groups have found numerous applications for this new methodology in stereoselective synthesis. Moreover, this methodology has been further developed to permit cycloaddition reactions with electron-deficient olefins, carbonyl compounds and imines to access carbocycles as well as four-, five-, and six-membered heterocycles (Scheme 76).



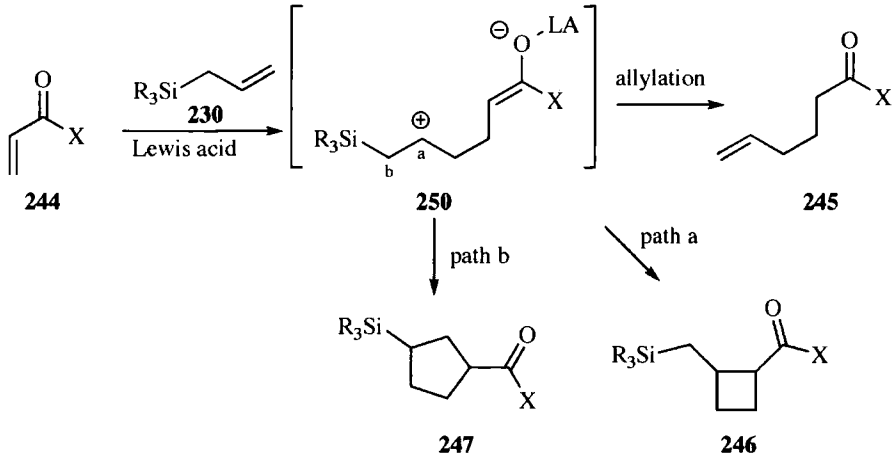
Scheme 76

The following subsections will examine the use of acyclic and cyclic allylsilanes in the Hosomi-Sakurai reaction and demonstrate its application in organic synthesis.

3.2.1 Acyclic allylsilanes

3.2.1.1 Access to Carbocycles

Carbocycles of the type shown in **Scheme 76** are a unique product from the Hosomi-Sakurai reaction. An early report by Knölker *et al.* demonstrated this unique reaction and outlined a mechanism for their formation. Cycloalkanes **246** and **247** were generated by the Lewis-acid-mediated [2+2] or [3+2] annulation reactions of allylsilanes with electron-deficient olefins. These annulation reactions were proposed to involve initial conjugate addition of allylsilane **230** to unsaturated substrates **244** (Scheme 77).



Scheme 77

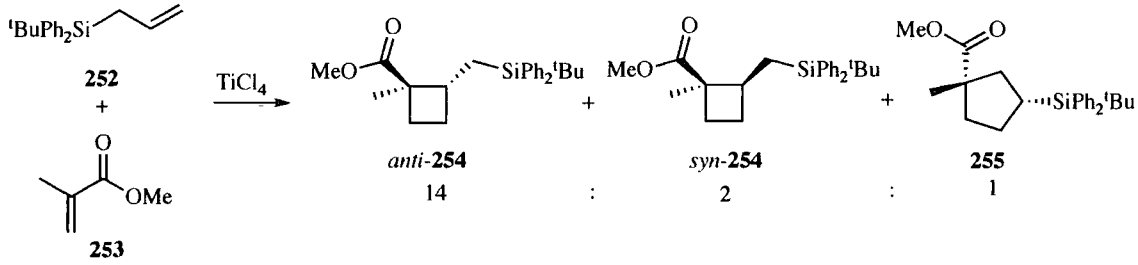
This provides β-silyl cation intermediate **250**, which may collapse through three possible pathways: (i). the silyl group can be displaced with a halide from the Lewis acid to provide the allylated product **245**, (ii). the enolate moiety reacts intramolecularly by a 4-*exo* process with the carbocation (pathway a) to afford cyclobutane **246**, (iii). the enolate moiety reacts through a 5-*endo* process by a sila-Wagner-Meerwein shift

(pathway b) to give cyclopentane **247**. Pathways a and b are dominant pathways when the R groups on silicon are larger than methyl. Knölker *et al.* then applied this methodology to great effect in a stereocontrolled total synthesis of (±)-Fragranol **251** (**Figure 17**).[82,83]

251

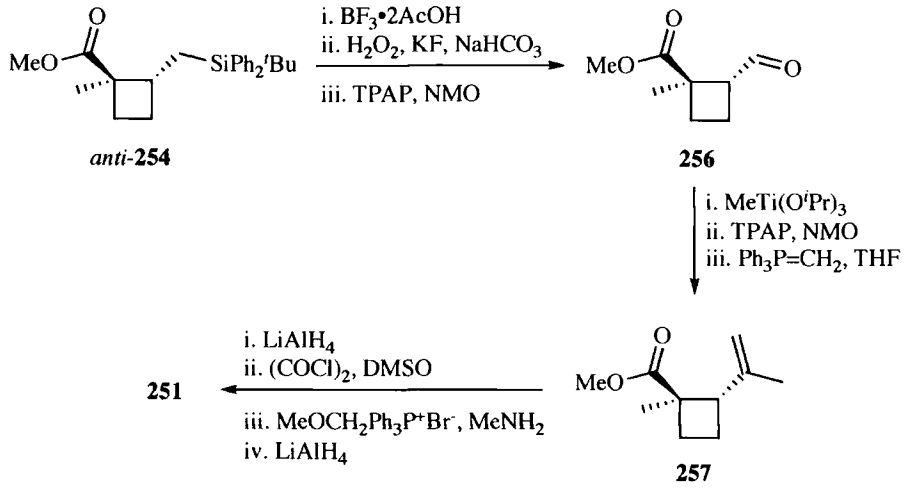
Figure 17

The synthesis began with the reaction of allyl-*tert*-butyldiphenylsilane **252** with methyl methacrylate **253** to afford **254** as two diastereoisomers and the silylcyclopentane **255** in a 14:2:1 ratio (**Scheme 78**).



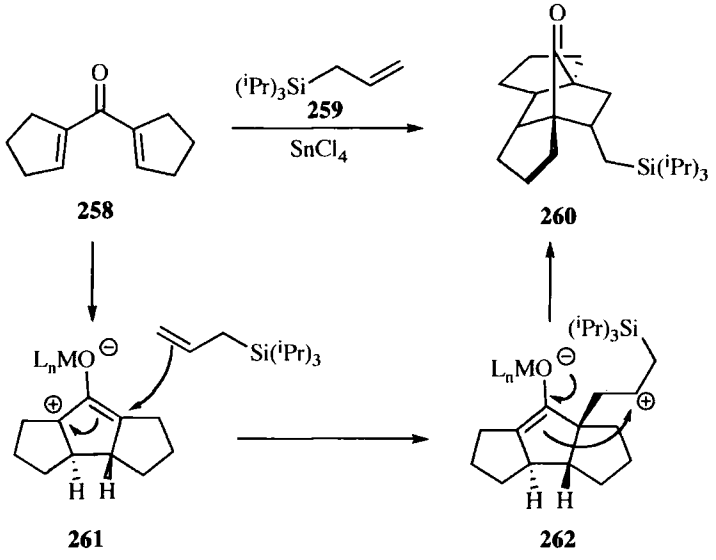
Scheme 78

Anti-cyclobutane **254** was then oxidised under Fleming-Tamao conditions to give the corresponding primary alcohol. This was subsequently oxidised to aldehyde **256**, which was then elaborated to isopropenyl derivative **257**. Methyl ester **257** then underwent a one-carbon homologation in four steps to complete the total synthesis of (±)-Fragranol (Scheme 79).



Scheme 79

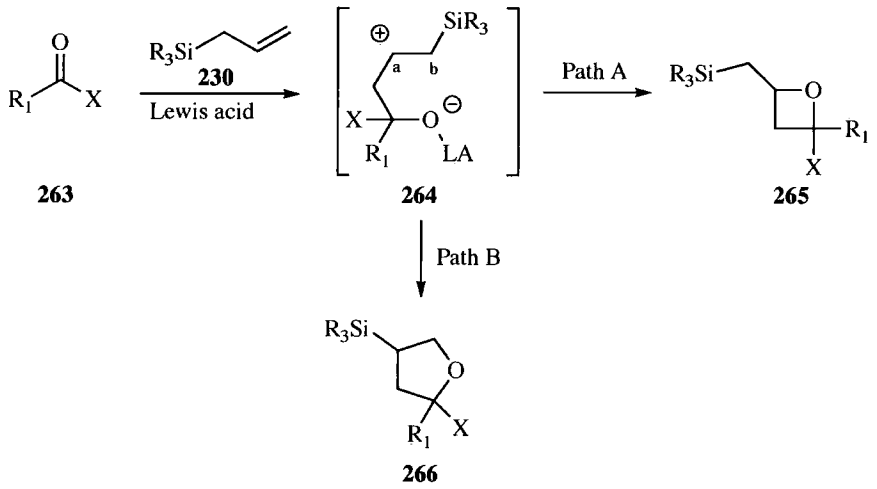
Further application of this methodology to more complex examples was described by Giese *et al.*, who utilised a [3+2] annulation reaction of simple dienone **258** and allylsilane **259** to construct a bicyclo[2.2.1]heptanone **260**.[84] Initial Nazarov electrocyclisation of **258** led to the tricyclic oxyallyl intermediate **261** that was trapped with the allylsilane **259** to provide β-silylcarbocation **262**. Cyclisation of **262** led to the annulated polycyclic system **260** in 91% yield (Scheme 80).



Scheme 80

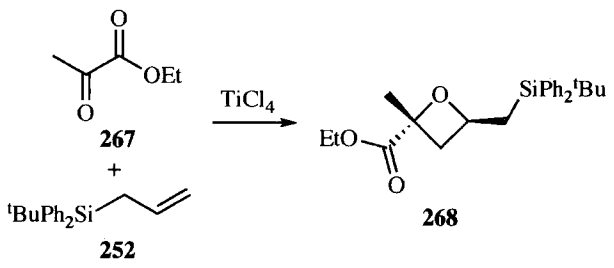
3.2.1.2 Access to Heterocycles

As described earlier, as well as carbocycles, access to heterocycles through the cycloaddtion of allylsilanes with aldehydes and imines has been studied. Mechanistically, allylsilanes **230** react with activated carbonyl compounds to generate a β-silylcarbocation intermediate **264**. The coordinated oxygen atom can then attack the carbocation intermediate through two pathways analogous to those described in the preceeding section. Pathway A affords oxetane **265** and pathway B furnishes tetrahydrofuran **266** (Scheme 81)



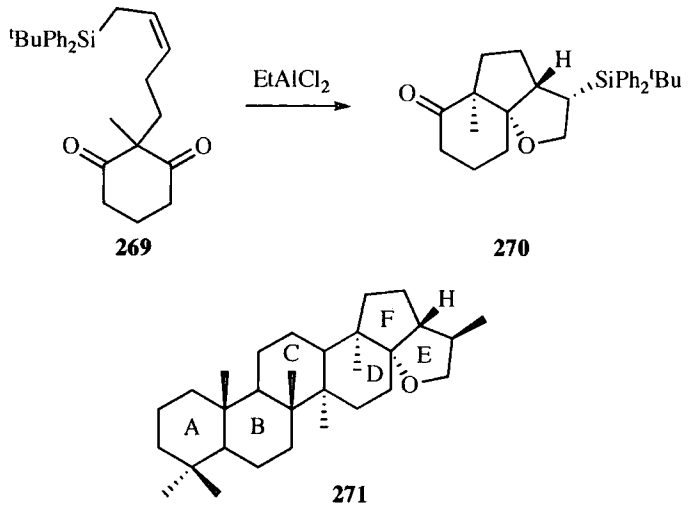
Scheme 81

These two competing pathways have led to some very interesting results. Akiyama *et al.* provided an example of a highly stereoselective construction of oxetanes **268** *via* a $TiCl_4$-promoted [2+2] cycloaddition of allylsilane **252** to α-oxo ester **267** (Scheme 82).[85]



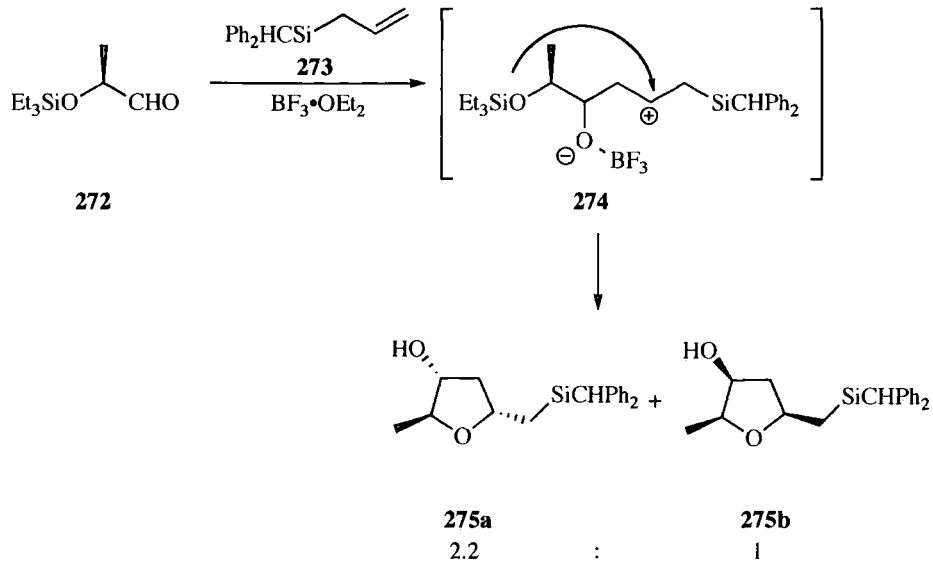
Scheme 82

Also, Schinzer *et al.* went on to provide an example of tetrahydrofuran formation by path B. The methodology was adapted to allow cyclic 1,3-diketone **269** to undergo a novel tandem reaction to provide a tricyclic furan **270**. Compounds of type **270** are a subunit of the triterpenes **271**, present in the hopane family (Scheme 83).[86]



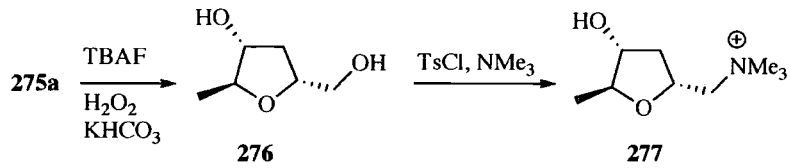
Scheme 83

Mechanistically, the previous two examples require the β-silylcarbocation intermediate to be trapped by the alkoxy anion generated. However, there are some examples where other nucleophiles are used to trap the β-silylcarbocation intermediate. One such example is provided by Angle *et al.* who reported the use of α-triethylsilyloxy-aldehydes with allysilanes in the preparation of tetrahydrofurans. The products **275a** and **275b** of this reaction arose from the formal [3+2] cycloaddition of **272** with allylsilane **273**. Nucleophilic attack of the β-silylcarbocation intermediate occurred with the triethylsilyl ether oxygen and not the Lewis acid complexed alkoxide, as previously described (Scheme 84).[87]



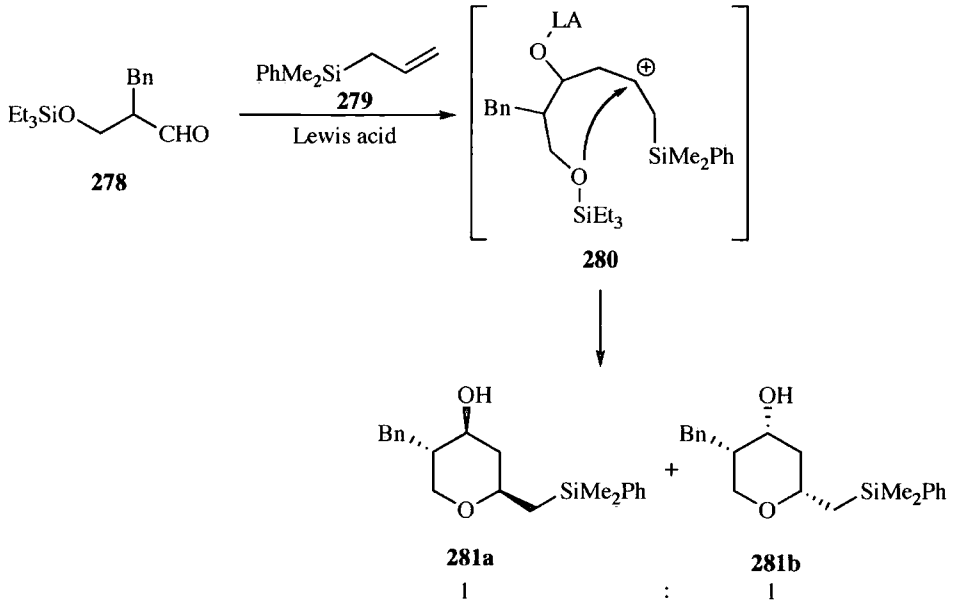
Scheme 84

In addition, Angle *et al.* went on to apply this methodology to the formal synthesis of (-)-*allo*-muscarine **277**. Oxidation of furan **275a** led to the diol **276**, which underwent activation of the primary hydroxy group with tosyl chloride and subsequent displacement with trimethylamine (Scheme 85).



Scheme 85

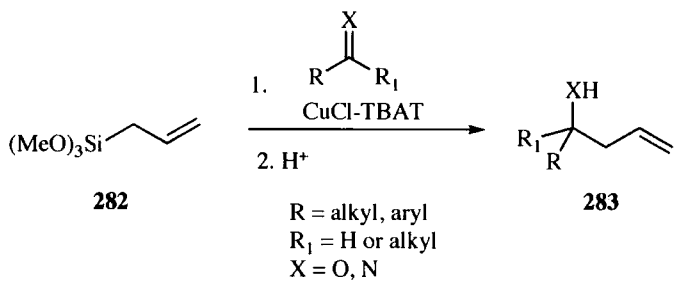
In an extension to this methodology, Angle *et al.* then undertook a series of reactions with β-triethylsilyloxy aldehydes **278**. Their results demonstrated that aldehydes possessing an α-stereocenter react with allylsilanes to provide tetrahydropyrans **281a** and **281b** as an ~1:1 mixture of diastereoisomers (Scheme 86).[88]



Scheme 86

3.2.1.3 Asymmetric allylations and natural product synthesis

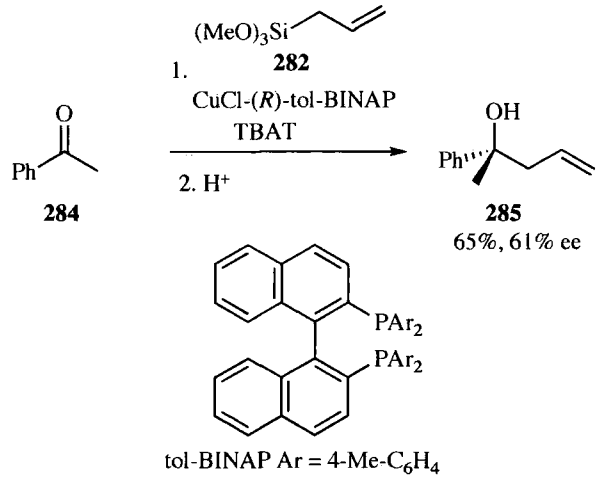
The examples shown so far have utilised the Hosomi-Sakurai reaction to generate a whole variety of highly stereoselective products. However, none of the examples have used this methodology in a catalytic or asymmetric manner. Recently, Shibasaki *et al.* and Yamamoto *et al.* have looked to address this. Shibasaki *et al.* instigated a study of the general catalytic allylation of ketones, aldehydes and imines using allyltrimethoxysilane **282**. After much investigation, a catalytic system (1mol % CuCl-TBAT) was optimised for this process (Scheme 87).[89]



Scheme 87

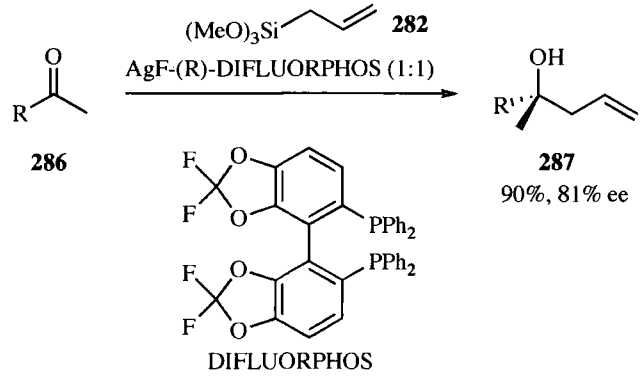
With a catalytic system established, attempts to extend this methodology to a catalytic enantioselective process were undertaken. Results of this investigation showed that by

adding *p*-tol-BINAP to the catalytic system, a moderate 61% enantioselectivity could be obtained (Scheme 88).



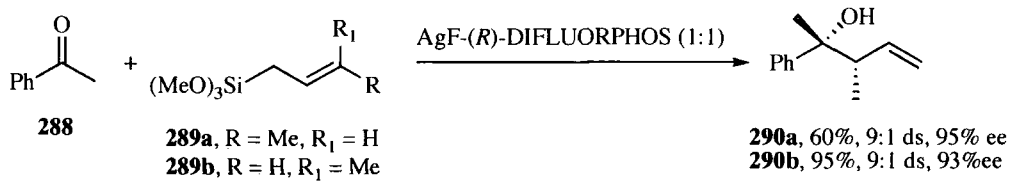
Scheme 88

This was the first example of a catalytic enantioselective allylation of ketones using allylsilanes. Yamamoto *et al.* undertook a similar study, this time utilising a silver-fluoride catalysed process.[90] Indeed, a complex of AgF-(*R*)-BINAP in MeOH provided the tertiary alcohol **287** in 90% yield with a 63% ee. Following this initial result, a survey of ligands and catalyst loadings was undertaken. The results showed that a 1:1 mixture of AgF and (*R*)-DIFLUORPHOS in THF/MeOH provided a significant improvement (>80%) in enantioselectivity using various aromatic and cyclic ketones (Scheme 89).



Scheme 89

Subsequently, investigations of various allyltrimethoxysilanes, such as (*E/Z*)-crotylsilane **289** were undertaken, which demonstrated that both *E*- and *Z*- crotylsilanes **289a** and **289b** when, subjected to the same catalytic system, generated branched *syn*-products **290a** and **290b** with high diastereo- and enantioselectivity (Scheme 90).



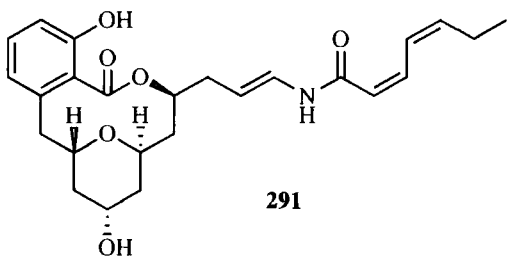
288

289a, R = Me, R_1 = H
289b, R = H, R_1 = Me

290a, 60%, 9:1 ds, 95% ee
290b, 95%, 9:1 ds, 93%ee

Scheme 90

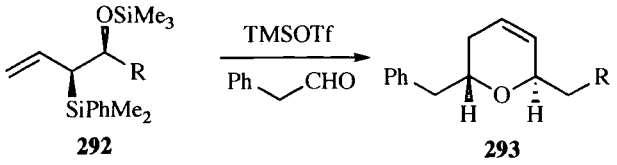
Being able to undertake the Hosomi-Sakurai reaction in a catalytic, diastereoselective and asymmetric fashion has facilitated its application to the synthesis of a variety of complex natural products. Panek *et al.* applied this methodology to synthesise the dihydropyran moiety of the natural product (-)-Apicularen A **291** (**Figure 18**).[91]



291

Figure 18

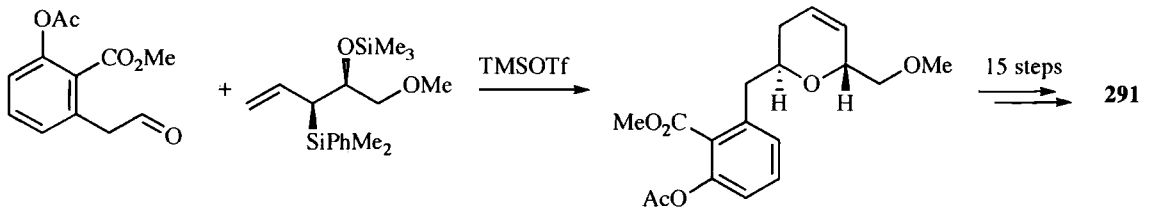
Panek *et al.* initiated a study concerning the [4+2] annulation of a chiral allylsilane **292** with phenylacetaldehyde. The results demonstrated that the *trans*-pyran product **293** could be obtained in good yield and excellent diastereo- and enantioselectivity (91%, >30:1 dr) when (a) the chiral silane possessed the *cis* ($R_3Si/OSiMe_3$) relative stereochemistry and (b) the R moiety was CH_2OMe only. Other R moieties (CO_2Me, CH_2OAc) gave the pyran products with *cis*- stereochemistry (Scheme 91).



292 293

Scheme 91

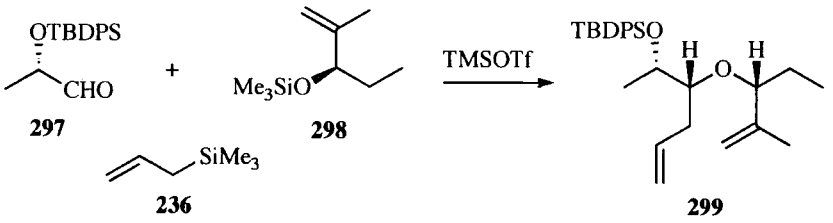
Consequently, the chiral allylsilane was utilised in the total synthesis of (-)-Apicularen A. Functionalised aldehyde **294** was coupled with allylsilane **295** in the presence of TMSOTf to yield *trans*-pyran **296** as a single isomer. Substituted pyran **296** was then elaborated to (-)-Apicularen A **291** in 15 steps (Scheme 92).



294 295 296

Scheme 92

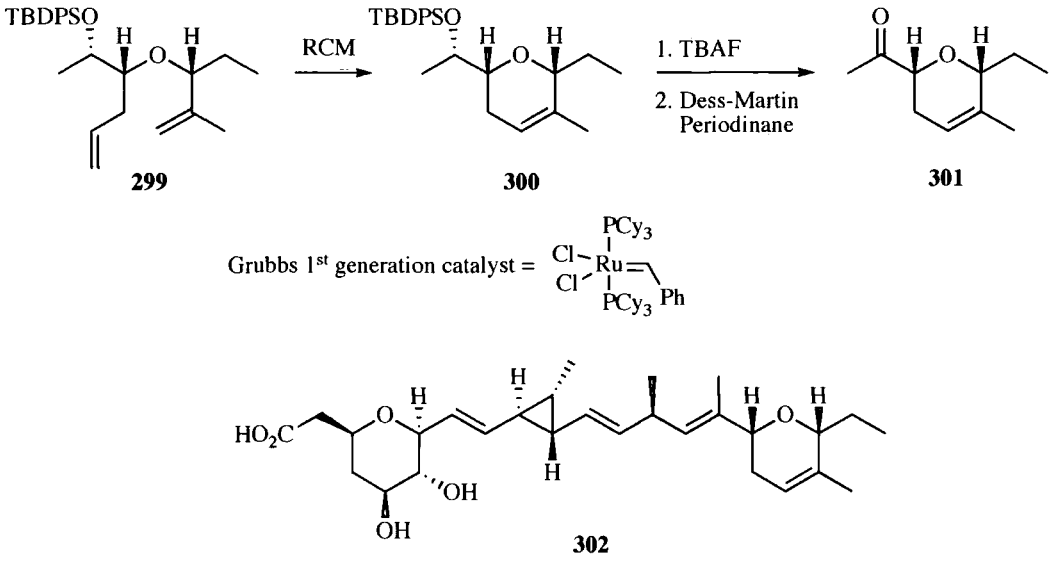
Substituted pyran units similar to the one described above have also been elegantly synthesised by Marko *et al.* using an asymmetric Sakurai multicomponent reaction.[92] Marko *et al.* showed that by mixing chiral aldehyde **297**, allylsilane **236** and chiral allylsiloxane **298** in the presence of a catalytic amount of TMSOTf generated **299** in 81% yield and >95:1 dr (**Scheme 93**).



297 298 236 299

Scheme 93

Subsequent Grubbs metathesis, silicon deprotection and oxidation of the resulting alcohol provided pyran **301**, a fragment of the natural product (+)-Ambruticin **302** (Scheme 94).



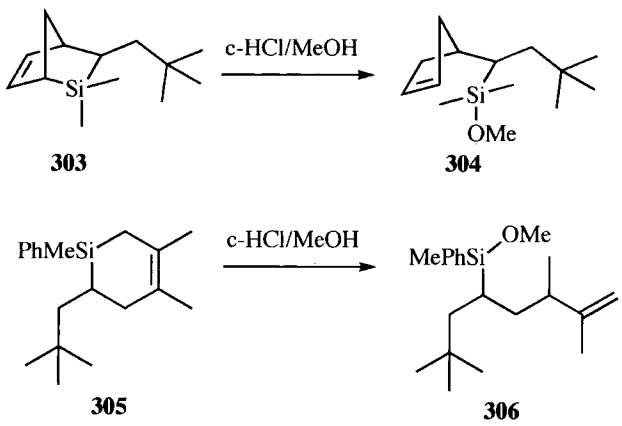
Scheme 94

3.2.2 Cyclic allylsilanes

As shown earlier (*cf.* Section 3.2.1), acyclic allylsilanes undergo a plethora of reactions to yield highly complex products. However, by comparison, cyclic allylsilanes undergo a minuscule number of reactions. This lack of reactivity can be attributed to one factor: the β-silicon effect. As stated earlier, allysilanes react by initial addition of an electrophile (C^+ or H^+) leading to the formation of a carbocation intermediate stabilised by the presence of a β-silicon atom. Such stabilisation is believed to arise from orbital overlap between the empty pπ orbital on the carbocation and the co-planar C–Si σ-orbital. Whilst such an orbital alignment is trivial in acyclic systems, in cyclic systems this is not the case as the correct conformation for orbital alignment is difficult to attain.

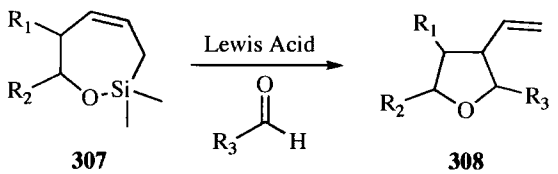
In spite of this, there are some transformations of cyclic and bicyclic substrates. Bicyclonorborn-5-ene **303** and substituted silacyclohex-4-ene **305** have been shown to

undergo acid-promoted cleavage in MeOH to give siloxane **304** and **306** respectively (Scheme 95).[93,94]



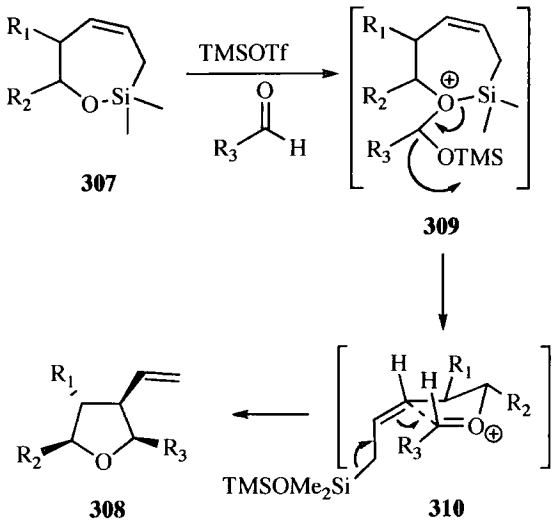
Scheme 95

These transformations validate the ability of cyclic substrates to undergo *pseudo*-Hosomi-Sakurai reactions; however, they only report the use of protons as electrophiles. More recently, several examples utilising carbon electrophiles and cyclic siloxanes **307** have been reported. These examples utilised the Hosomi-Sakurai methodology to synthesise a series of substituted tetrahydrofuran substrates **308** (**Scheme 96**).[95-97]



Scheme 96

Importantly, these cyclic siloxanes do not react by the mechanism outlined in Scheme 75. In this case, initial attack of the oxonium ion is at oxygen and not the allylic double bond, giving rise to acetal **309**, which undergoes rapid ring cleavage to give siloxane **310**. Siloxane **310** then undergoes a typical Hosomi-Sakurai reaction of the allylsilanes with the new oxonium ion to give the tetrahydrofuran **308** (**Scheme 97**).



Scheme 97

Despite this alternative mechanism, Marsden *et al.* has applied this methodology to great effect in the stereocontrolled total synthesis of (+)-Virgatusin **311** (**Figure 19**).[98]

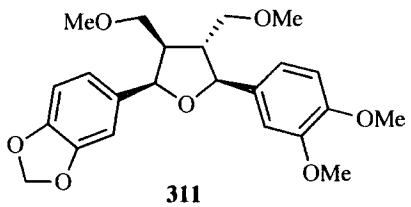
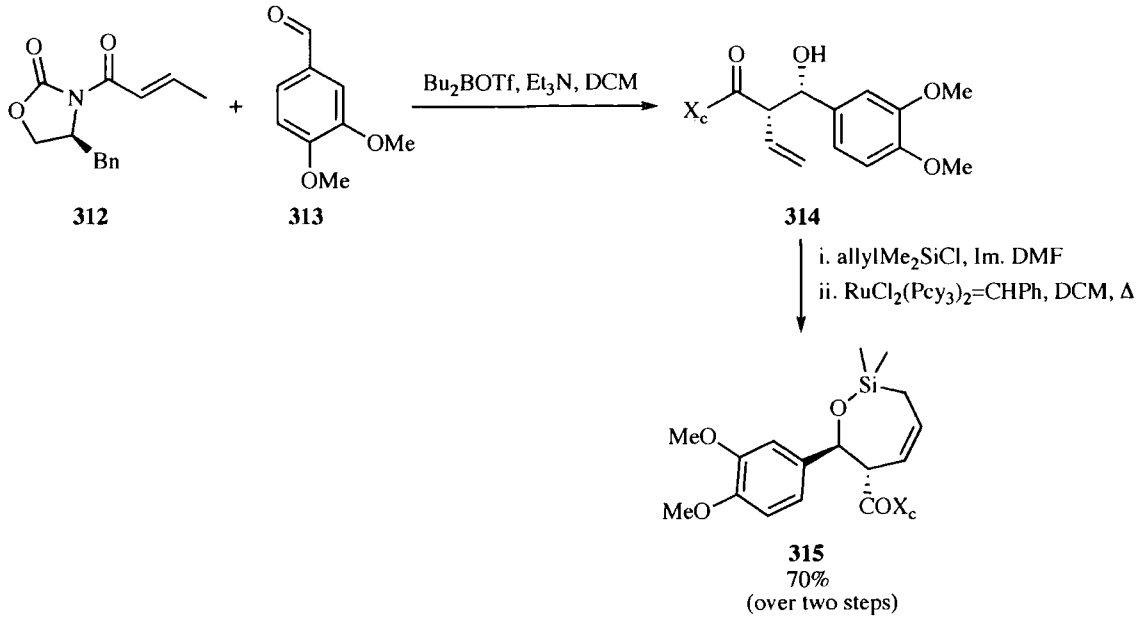


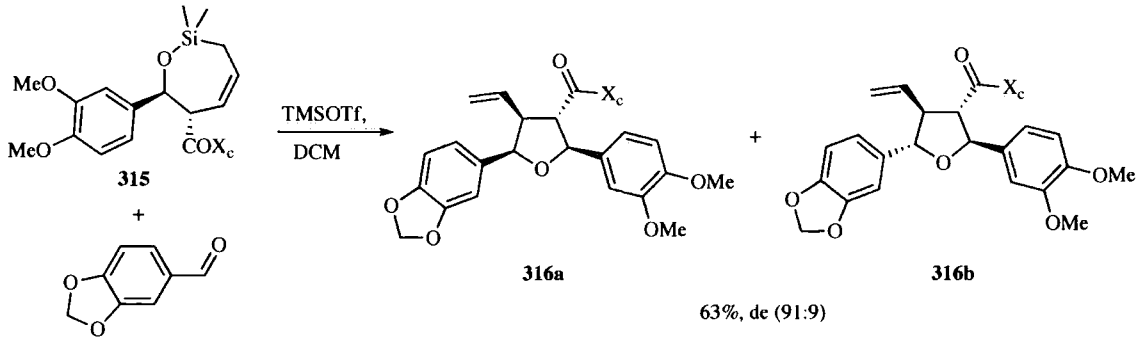
Figure 19

To begin, synthesis of the functionalised enantiomerically enriched allyl siloxane **315** had to be undertaken. This was achieved in three steps from oxazolidinone **312** by deconjugative aldol reaction of **312** with veratraldehyde **313** followed by silylation with allyldimethylsilyl chloride and ring closing metathesis (**Scheme 98**).



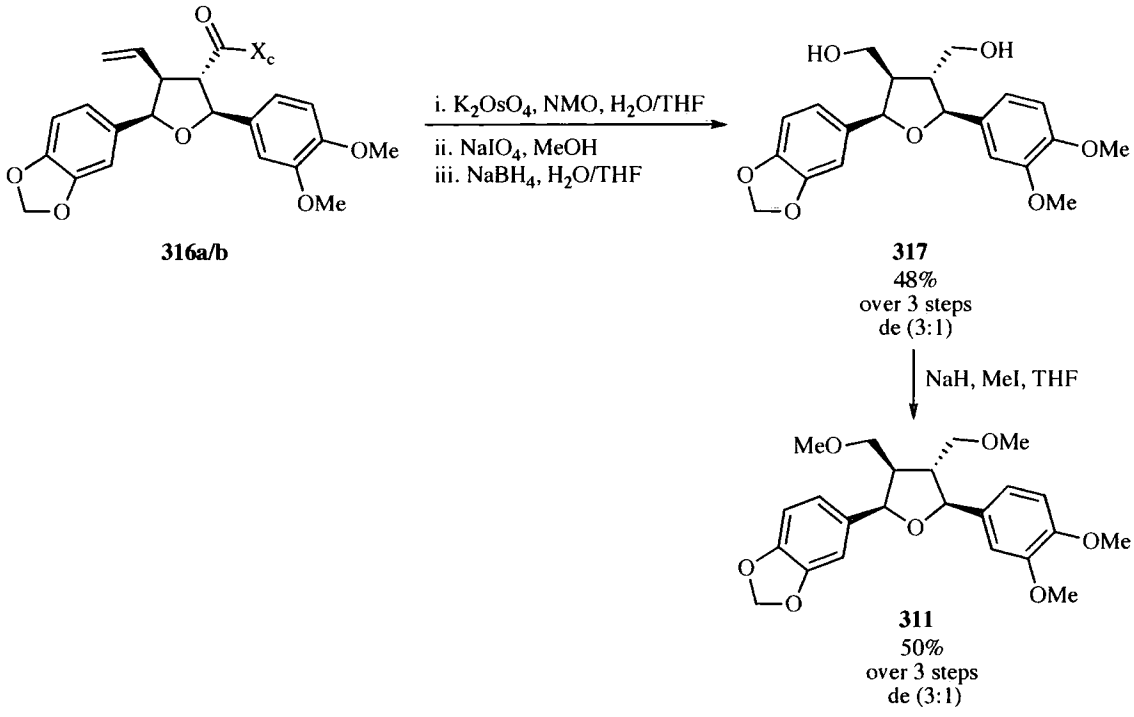
Scheme 98

With the cyclic siloxane **315** in hand, attention turned to the crucial condensation reaction. After much investigation, the reaction of cyclic siloxane **315** was undertaken with TMSOTf and piperonal to yield the desired furan **316a/b** as an inseparable mixture of isomers (**Scheme 99**).



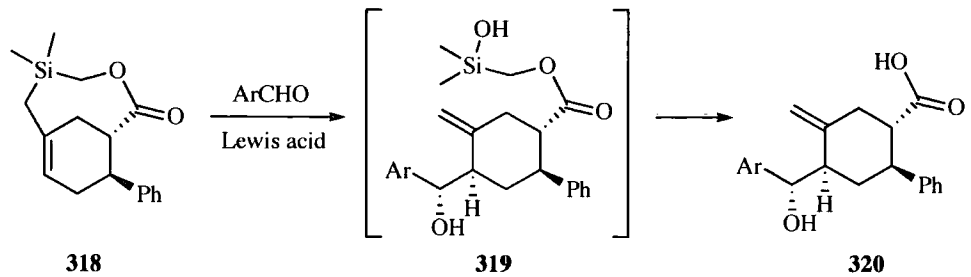
Scheme 99

Finally, to complete the synthesis of Virgatusin, furan **316a/b** was dihydroxylated and oxidised to give the corresponding aldehyde, which was reduced with concomitant removal of the chiral auxillary and reduction to the diol **317**. Finally, methylation of diol **317** returned (+)-Virgatusin **311** in modest yield as an inseparable ca. 3:1 mixture of diastereoisomers (**Scheme 100**).



Scheme 100

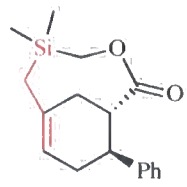
In spite of these elegant examples, there has been only one example describing the use of silacyclic allylsilanes in the Hosomi–Sakurai reaction. This was reported by Shea *et al.* utilising a novel bridgehead allylsilane **318**.[99] Shea *et al.* reported that allylsilane **318** underwent a Hosomi-Sakurai reaction with a variety of electron-deficient aldehydes to give acid **320** (Scheme 101).



Scheme 101

Initially, silanol **319** was isolated at the end of the reaction. However, on stirring the mixture with acid or base, the ester was cleaved to give acid **320** as the sole product. Interestingly, this cyclic allylsilane partakes in the reaction, where others failed, because the silicon atom is locked at a 78° angle to the C=C plane. This is close to the ideal 90°

angle required for stabilisation of carbocations and as such is sufficient to enable the reaction to take place (Figure 20).



318

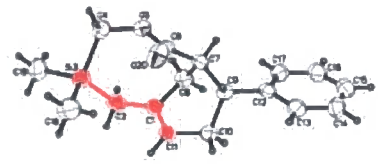
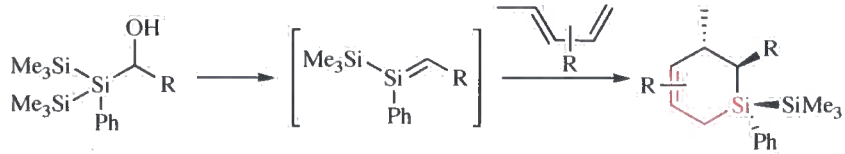


Figure 20

Despite this example, there have been no reports describing the use of silacyclic allylsilanes, where the silicon atom is incorporated into the same ring system as the double bond. The following section will now outline our approach utilising this methodology.

3.3 Our approach utilising this methodology

Our interest in utilising this methodology arose from the development of new synthetic methodology described earlier (*cf.* Section 1.3). This methodology allowed silacyclohex-4-enes **174**, possessing an allylsilane moiety (marked in red) to be generated in good yield and diastereoselectivity (**Scheme 102**).

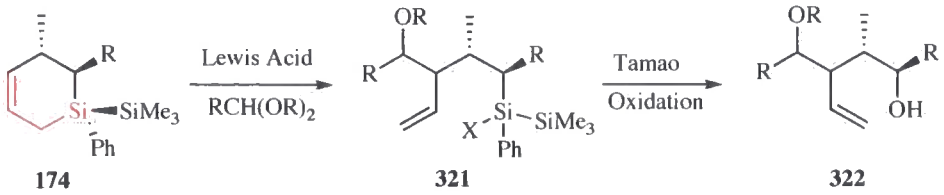


96 **173** **174**

Scheme 102

We proposed that silacyclohex-4-enes **174** would undergo a Hosomi-Sakurai reaction with acetals in the presence of a suitable Lewis acid to give ring-opened disilane **321**. The regiochemistry being consistent with electrophilic addition to the allylsilane, forming a carbocation intermediate stabilised by the β-silicon substituent. The ring

opened disilane **321** would then undergo Fleming-Tamao oxidation of the activated silicon centre to give 1,4-monoprotected diols **322** (**Scheme 103**)



Scheme 103

An example of this type of reaction was provided earlier (*cf.* Section 2.4.2, **Scheme 56**), during epoxidation studies for the synthesis of Prelactone B. It was shown that when epoxidised, silacyclohex-4-enes **174** were ring opened to give the hydroxyl siloxane **200**, similar in structure to the desired intermediate **321** described above (Figure 21).

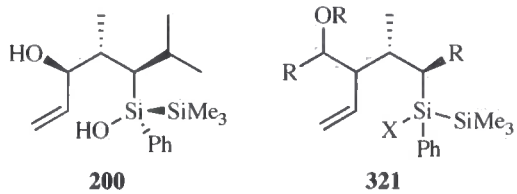


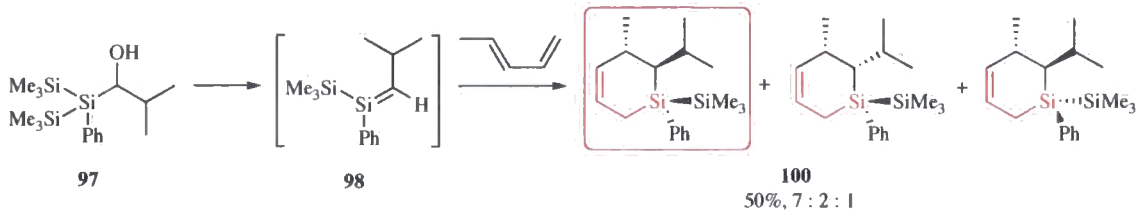
Figure 21

Therefore, the following section will discuss the results of our proposal, providing mechanistic insight into the reaction of silacyclohex-4-enes with acetals and present an array of results demonstrating the versatility of silacyclohex-4-enes in this reaction.

3.4 Results and Discussion

As discussed in previous sections, our proposal relied on the preparation of silacyclohex-4-ene **100**. Accordingly, this became the first objective. It was found that by repeating the silene-diene Diels-Alder reaction, pioneered by Whelligan, the desired silacyclohex-4-ene **100** was produced in good yield and good diastereoselectivity. The silacyclohex-4-ene **100** was obtained as an inseparable mixture of isomers with the

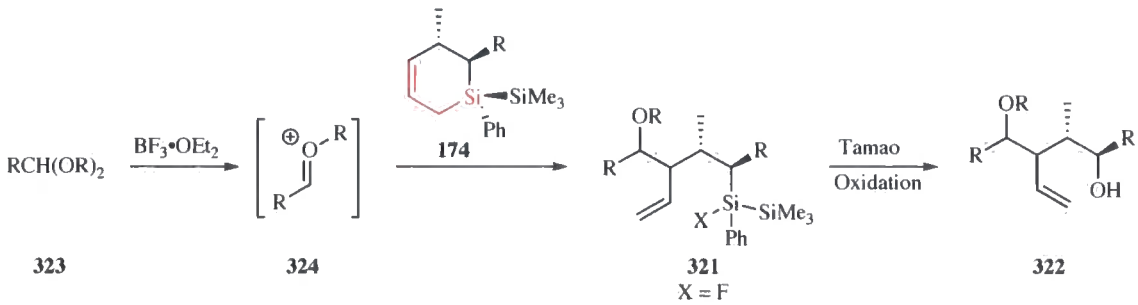
minor components reflecting the presence of small amounts of *exo*-addition products and trace amounts of the adducts of the alternative *E*(Si) silene (Scheme 104).



Scheme 104

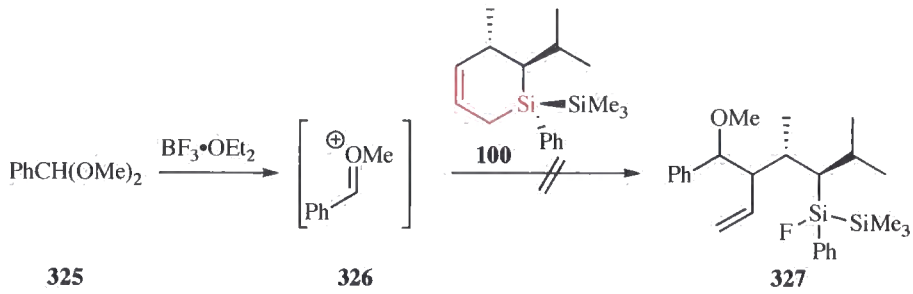
The major diastereomer (boxed in red) is thought to arise from a *Z*(Si) silene **98** reacting in an *endo* Si-Ph orientation. With the silacyclohex-4-ene mixture **100** in hand, attention turned to utilising the allylsilane in the Hosomi-Sakurai reaction.

To begin the investigation an experimental procedure had to be established. Reassessing the literature provided a general experimental procedure commonly used for this reaction. The procedure requires that oxonium ion **324** be generated prior to the addition of the cyclic allylsilane **174**. This would provide the ring opened disilane **321**. However the choice of Lewis acid would be important, as an activated silicon centre was required for the subsequent Tamao oxidation. It was decided that $BF_3{\bullet}OEt_2$ would be used, as this would provide the activated Si-F intermediate **321**, capable of undergoing Tamao oxidation to provide the desired 1,4-monoprotected diols **322** (**Scheme 105**).



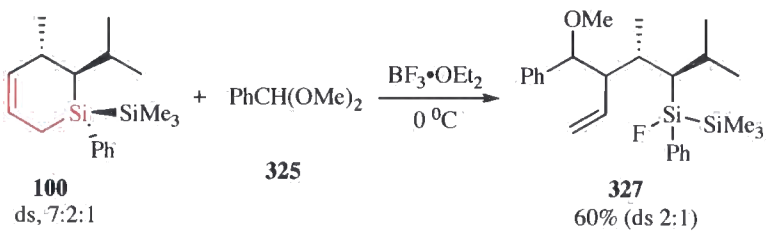
Scheme 105

Initial attempts to generate the ring-fragmented silyl fluoride **327**, following the procedure outlined above were unsuccessful, leading to an intractable mixture of products. It was proposed that the oxonium ion **326** underwent significant decomposition prior to reaction with the silacyclohex-4-ene **100** (**Scheme 106**).



Scheme 106

Undeterred by this initial result, the original procedure was modified to account for this observation by premixing silacyclohex-4-enes with the acetal, prior to the addition of BF_3•OEt_2. Consequently, when silacyclohex-4-ene **100** and benzaldehyde dimethyl acetal **325** were premixed in DCM at 0 °C, then treated with BF_3•OEt_2, the desired silyl fluoride **327** was produced after aqueous work-up and flash chromatography in 60% yield as a 2:1 mixture of stereoisomers (**Scheme 107**).



Scheme 107

The stereochemistry was ascertained by ^{19}F NMR integration [δ_F -184.72 (d, J = 15.8 Hz); δ_F -185.57 (d, J = 17.8 Hz)]. However, at this stage it was not possible to ascertain which of the three new stereocenters was responsible for the relative stereochemistry (**Figure 22**).

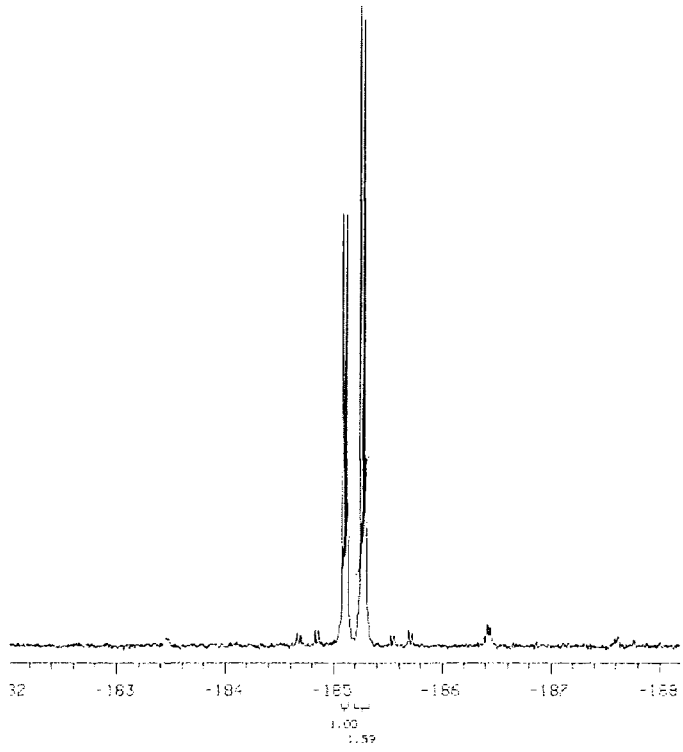
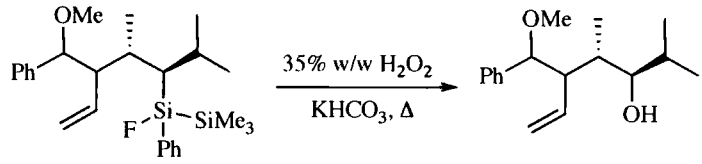


Figure 22

In line with the outlined procedure and to determine which stereocentre gave rise to the overall stereochemistry, the newly generated silyl fluoride **327** was oxidised under Tamao conditions (35% w/w H_2O_2, $KHCO_3$, Δ) to provide 1,4-monoprotected diol **328** in 80% yield (**Scheme 108**).



327
60% (ds 2:1)

328
80% (ds 2:1)

Scheme 108

Importantly, diol **328** was produced as a 2:1 mixture of diastereoisomers (**Figure 23**) as confirmed by analysis of the IR and ^{1}H NMR spectra, which showed a broad signal at 3326cm^{-1} corresponding to the hydroxyl groups and peaks at 6.04, 5.09 and 4.76 ppm arising from the allyl group.

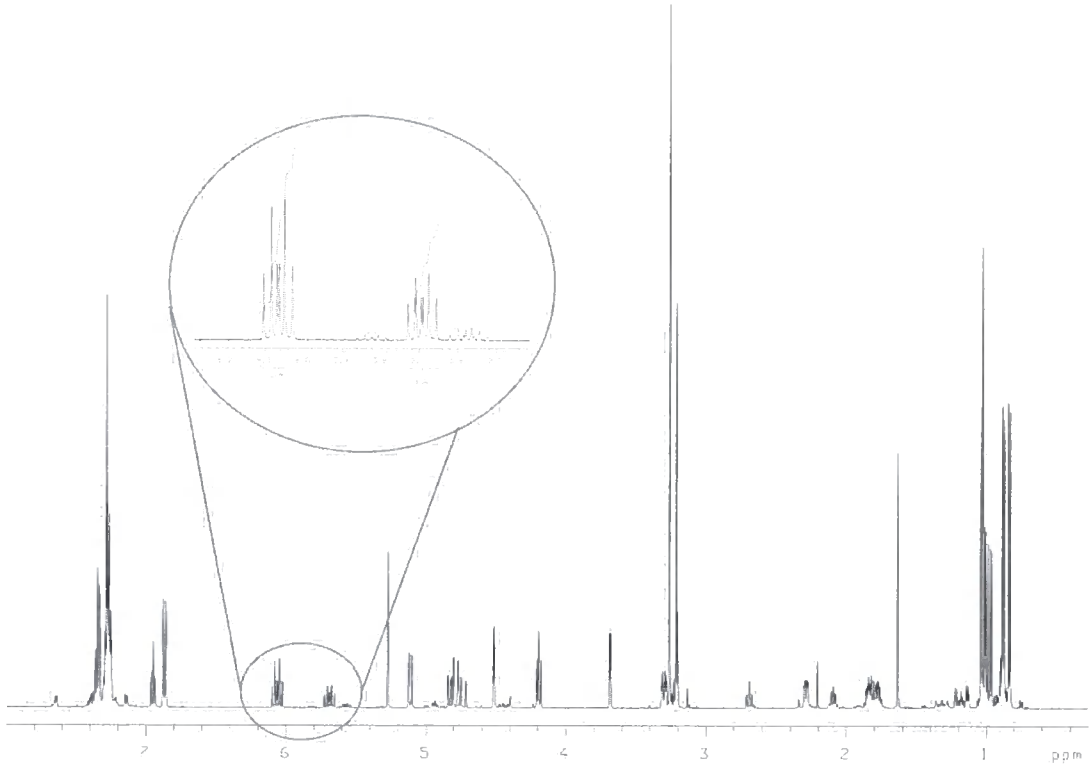
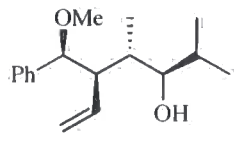


Figure 23

This result implied that the silyl fluoride **327** was formed as a single Si stereoisomer, given that Tamao oxidation is known to proceed with retention of configuration at carbon. Moreover, the major diol isomer provided crystals amenable to single crystal X-ray studies, the results of which confirmed the stereochemistry of the major isomer to be *syn:anti:anti* (Figure 24).



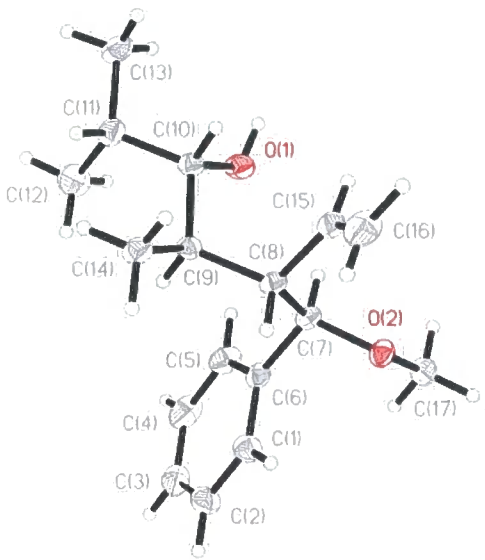
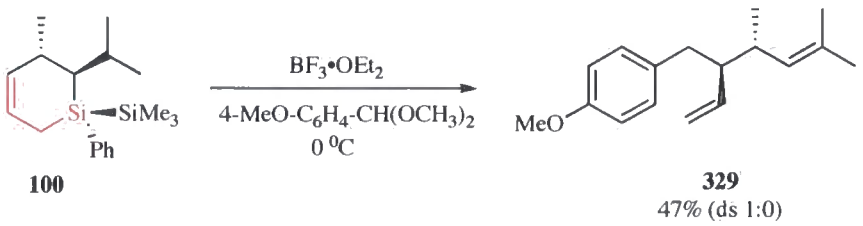


Figure 24: CCDC No.: 298851

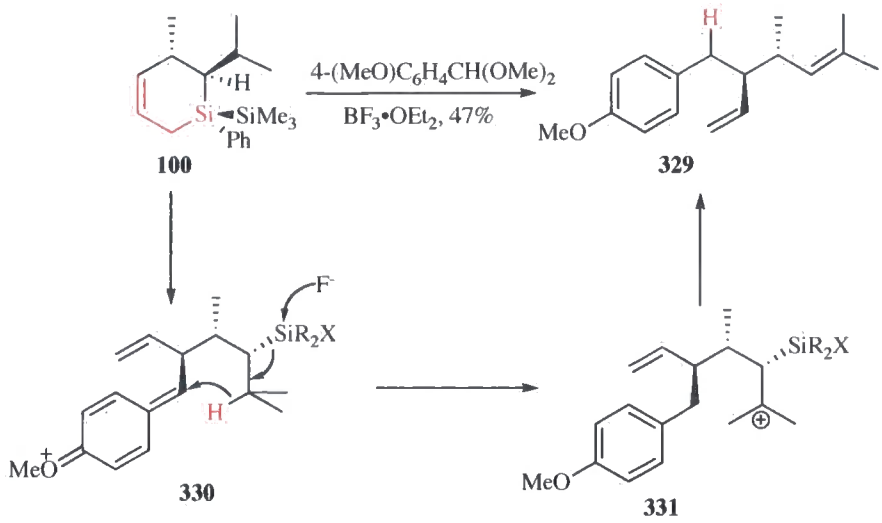
Disappointingly, the minor isomer would not crystallise and so the carbon stereocentre responsible for the mixture of isomers could not be established. Consequently, a second experiment using 4-methoxybenzaldehyde dimethyl acetal was undertaken to ascertain which carbon centre was responsible. In this case, the addition of $BF_3 \bullet OEt_2$ to the mixture of silacyclohexene **100** and 4-methoxybenzaldehyde dimethyl acetal led directly to the formation of the non-conjugated diene **329** in 47% yield (**Scheme 109**).



100 **329**
47% (ds 1:0)

Scheme 109

Importantly, diene **329** was formed as a single diasteroisomer. This suggested that initial addition of the oxonium ion to silacyclohex-4-ene **100** occurred stereoselectively to the face *syn* to the trimethylsilyl group. This would give rise to the correct vinyl stereochemistry observed from the crystal structure above. Subsequent generation of a vinylogous oxacarbenium ion (*p*-quinone methide) **330** followed by an intramolecular hydride transfer affords a silicon-stabilised carbocation **331**. This undergoes rapid fluoride-promoted desilylation to generate the second alkene (**Scheme 110**). As a result of this experiment, it can be unambiguously confirmed that the methoxy- bearing carbon centre is responsible for the mixture of isomers observed with benzaldehyde dimethyl acetal.



Scheme 110

Having established that the methoxy carbon centre was responsible for the observed stereochemistry, a reaction pathway was proposed. To begin, initial addition of the oxonium ion occurs *syn* to the trimethylsilyl group (as highlighted earlier). This requires co-planarity of the C-Si σ bond and alkene π-orbital (*cf.* Section 3.2), which can only be efficiently achieved when the silacyclohex-4-ene adopts a pseudo boat structure. Whilst this is possible for the major silacyclohex-4-ene isomer, the alternative diastereoisomers are inhibited from adopting such a conformation by eclipsing interactions between the Si-Ph and C-2 substituent. Therefore, the observed selectivity is a matter of approach of the oxonium ion to the least hindered (convex) face of the major isomer **333**, i.e that which avoids prow interactions between the methyl group and a C-6 hydrogen. This generates the observed 2,3-*anti*, 3,4-*anti* configuration. The methoxy carbon configuration is then a matter of synclinal or antiperiplanar alignment of the oxonium ion with the allylsilane, such that the aryl group is orientated in an "*exo*" position. Formation of the observed products suggests the former is of lower energy giving rise to the major isomer **337** (Figure 25).

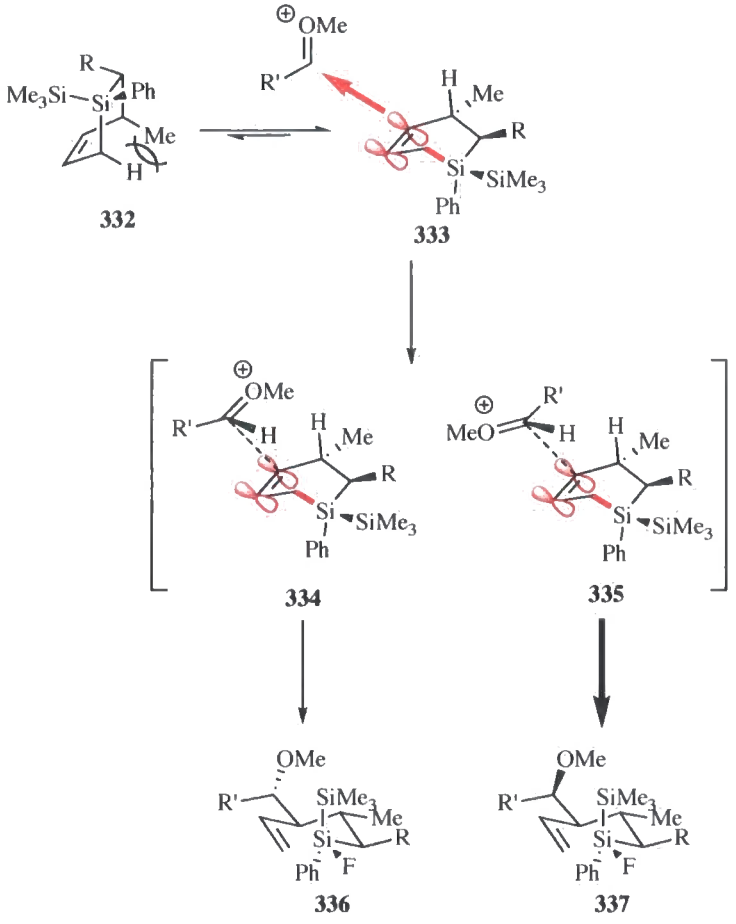
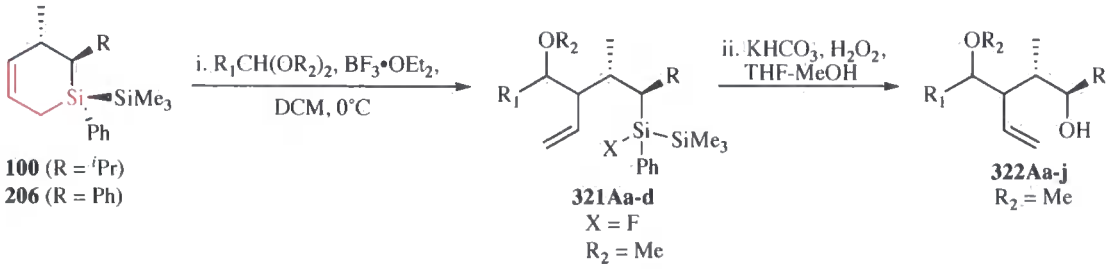


Figure 25

Having established the relative stereochemistry and a robust procedure for the transformation of silacyclohex-4-enes, a series of experiments were undertaken to expand the range of substrates and acetals (**Table 8**). Most of these experiments were undertaken utilising a two-step one-pot procedure. This enabled the desired 1,4-monoprotected diols to be generated directly, without isolation and characterisation of the intermediate silyl fluoride species. However, in some cases, it was necessary to isolate and fully characterise the intermediate, as the yields obtained for the two-step one-pot process were poor.



100 (R = ^{i}Pr)
206 (R = Ph)

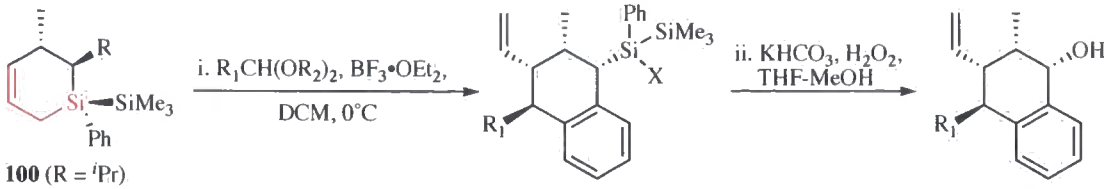
321Aa-d
X = F
R_2 = Me

322Aa-j
R_2 = Me

Entry	Silacycle (R)	Acetal (R^1)	Si-F Yield (dr)	Alcohol Yield (dr)
1	**100**	C_6H_5	**327** 60% (2:1)	**328** 50% (2:1)
2	**100**	4-$MeOC_6H_4$	-----	**329** 47% (1:0)
3	**100**	4-$CF_3C_6H_4$ **338**	**321Aa** 32% (2:1:1)	**322Aa** 23% (2:1:1)
4	**100**	4-BrC_6H_4	-----	**322Ab** 23% (2:1)
5	**100**	CH_3	**321Ab** 45% (2:1)	**322Ac** 21% (2:1)
6	**206**	C_6H_5	**321Ac** 72% (2:1)	**322Ad** 55% (2:1)
7	**206**	C_6H_5[a] **339**	-----	**322Ae** 8% (2:1)
8	**206**	4-$CF_3C_6H_4$ **338**	-----	**322Af** 50% (8:3:2)
9	**206**	4-BrC_6H_4	-----	**322Ag** 46% (3:1)
10	**206**	4-$NO_2C_6H_4$ **340**	-----	**322Ah** 63% (7:4:2)
11	**206**	CH_3	**321Ad** 38% (2:1)	**322Ai** 32% (2:1)
12	**206**	c-C_6H_{11} **341**	-----	**342** 36% (1:2)
13	**206**	C_6H_{13}	-----	**322Aj** 20% (1:1)

a. 2-phenyl dioxane used – product is the 3-hydroxypropylether

Table 8

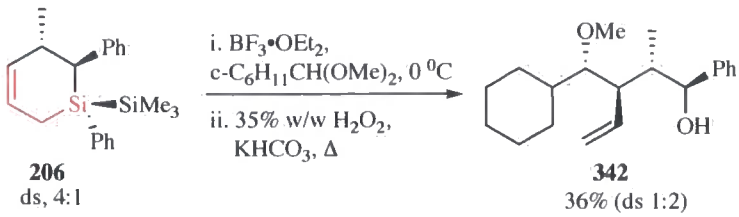


Entry	Silacycle (R)	Acetal (R^1)	Si-F Yield (dr)	Alcohol Yield (dr)
14	**206**	4-$MeOC_6H_4$	**321B** 44% (5:1)	**343** 27% (5:1)
15	**206**	C_6H_4CH=CH **344**	-----	**322B** 44% (7:2)

Table 9

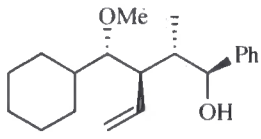
Arising from these experiments were a series of interesting results, beginning with entries 3, 8 and 9 (Table 8). These results demonstrated that when reactive electron deficient oxonium ions were utilised, the 1,4-monoprotected diols were isolated as tri-isomeric mixtures. This contradicts the proposed reaction pathway. However, it was proposed that the third isomer arose from reaction of the minor silacyclohex-4-ene diastereoisomer. Consistent with this proposal, when less reactive acetals were utilised, it was possible to recover small quantities of the starting silacyclohex-4-ene, enriched in the minor isomers. Although these results were interesting, they are only observed with very reactive electron deficient acetals.

Of greater interest was the reaction of cyclohexane carboxaldehyde dimethylacetal with silacyclohex-4-enes (entry 12, Table 8). It was demonstrated that, under the optimised two step – one pot procedure the 1,4-monoprotected diol **342** was generated in good yield as a 1:2 mixture of diastereoisomers. The major isomer, in this case, possessed the *anti:anti:anti* stereochemical arrangement (**Scheme 111**).



Scheme 111

This reversal in stereochemistry was confirmed by X-ray crystallographic studies (Figure 26). However, reasons for the reversal of selectivity are not obvious and cannot be explained by the proposed mechanism.



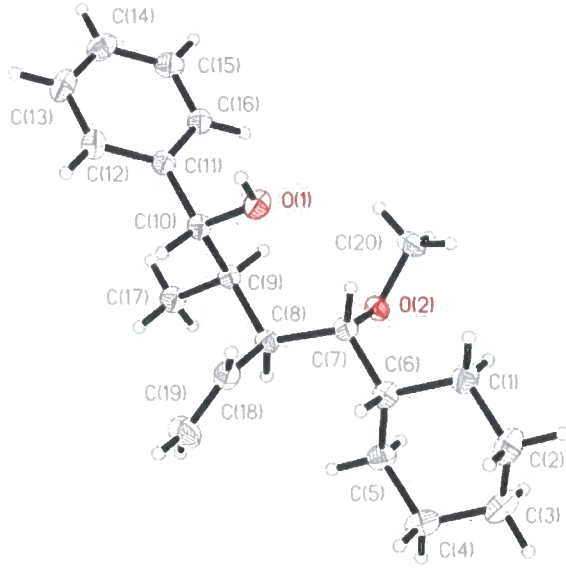
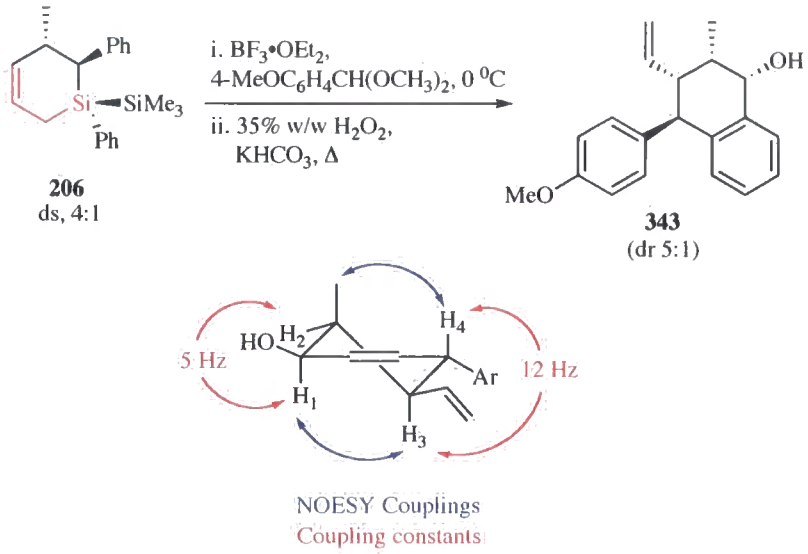


Figure 26: CCDC No.: 298852

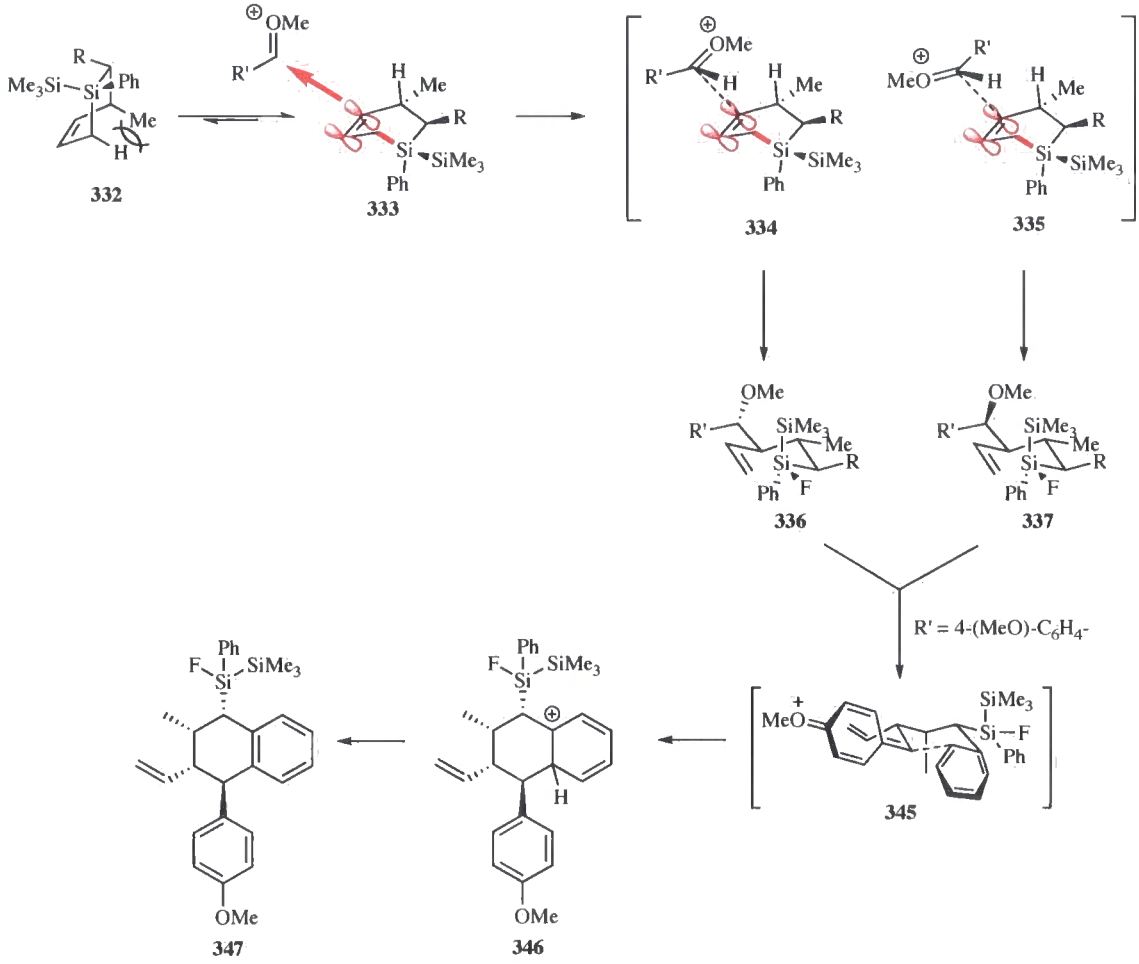
Finally, the most interesting results arising from this series of experiments are highlighted in entries 14 and 15 of Table 9. These results were achieved by adapting methodology, described earlier for the formation of the non-conjugated diene **329** (*cf.* **Scheme 109**). In the formation of **329** it was demonstrated that silacyclohex-4-ene **100** underwent hydride migration to trap a secondary oxonium ion formed from an electron rich acetal. This suggested that further carbon-carbon bond formation could be combined with the Sakurai reaction if a suitable nucleophile could be incorporated into the silacyclohex-4-ene. Gratifyingly, reaction of silacyclohex-4-ene **206**, possessing a phenyl substituent, with 4-methoxybenzaldehyde dimethyl acetal in the presence of

BF_3•OEt_2 at 0 °C afforded, after Tamao oxidation, the tetralol **343** in moderate yield as a 5:1 mixture of stereoisomers. The relative stereochemistry of the major isomer was assigned on the basis of ^1H NMR coupling constants (marked in red) and NOESY experiments (**Scheme 112**)



Scheme 112

Consistent with previous experiments, the diastereomeric ratio was unchanged on oxidation of the silyl fluoride to tetralol **343**, indicating that, as before, the silicon centre was generated as a single stereoisomer and the mixture of diastereoisomers reflects alternative configurations at the benzylic carbon. This suggested that an identical reaction pathway was being followed. As before, initial addition of the oxonium ion occured *syn* to the trimethylsilyl group of the major isomer. This provided the silyl fluoride intermediates **336** and **337**, as a mixture of diastereoisomers at the methoxy carbon centre. The silyl fluoride intermediates **336** and **337** were then able to generate a single vinylogous oxacarbenium intermediate **345**, which underwent carbon-carbon bond formation with the aryl ring to afford a silicon-stabilised carbocation **346**. This then undergoes rapid aromatisation to give the silyl fluoride species **347** (**Scheme 113**).



Scheme 113

The preferential formation of the 1,2 *anti* configuration in the cationic cyclisation has considerable precedent in lignan synthesis literature (*cf.* Chapter 4.1) and is consistent with cyclisation proceeding through a chair-like transition state with all substituents occupying an equatorial position **345**.

3.5 Conclusion

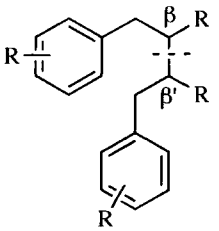
In conclusion, this work has demonstrated that silacyclohex-4-enes, derived from silene-diene cycloadditions are viable substrates for the Hosomi-Sakurai reaction with both aryl and alkyl acetals. Following Tamao oxidation of the resultant silyl fluoride, 1,4-monoprotected diols can be obtained in moderate yield and diastereoselectivity. Moreover, when aryl acetals containing *ortho* or *para* electron-donating substituents are

combined with silacyclohex-4-enes containing an aryl substituent, a further cyclisation occurs to afford the tetralol skeleton found in many lignan natural products. Expanding on this observation, the following chapter will report our results obtained through application of this methodology to the total synthesis of a podophyllotoxin analogue, epipicropodophyllotoxin.

4 Total synthesis of Podophyllotoxin analogue, Epipicropodophyllin

4.1 Introduction

Lignans are a large family of secondary metabolites widely encountered in the plant kingdom.[100,101] The term lignan was first introduced by Harworth[102] in 1942 to describe a group of plant phenols whose general structure **348** was determined by the union of two derivatised cinnamic acid residues linked *via* the β,β' bond (**Figure 27**).



348

Figure 27

Within this large family of lignans are the aryltetralin lignans **349**, **350** and aryltetralin lignan lactones **351**, **352**, which have long been recognised as important natural products (**Figure 28**). To date, several hundred of these lignans have been isolated. Whilst their biological role in plants is unclear and remains to be fully elucidated, they have been shown to display a substantial variety of biological activity and have a long and fascinating medical history that emanates from their use as folk remedies to treat an assortment of conditions.[103]

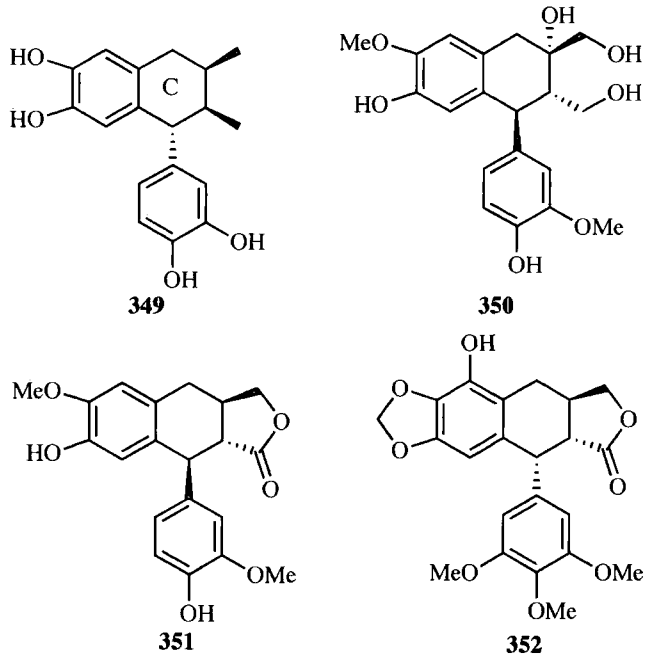
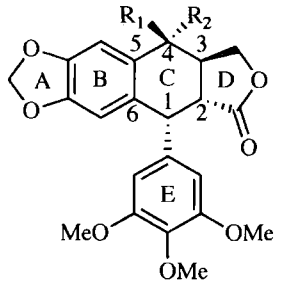
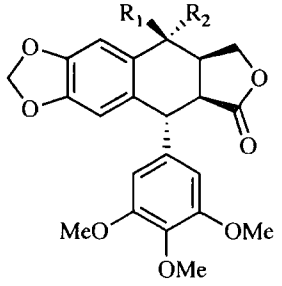


Figure 28

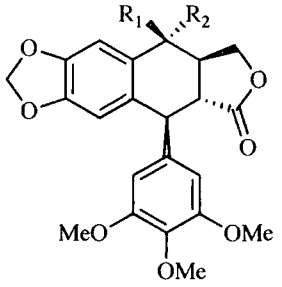
The most prominent member of this group of natural products is podophyllotoxin **353**. This compound, together with analogues **354-358** are aryltetralin lignan lactones isolated from the American Mayapple (*Podophyllum peltatum*) and related Indian species (*Podophyllum emodi*). Structurally these natural products are characterised by a substituted 1,2,3,4-tetrahydronaphthalene core, containing an aryl unit at position 1 and a butyrolactone ring fused to positions 2 and 3 of the C ring. This lactone fusion may have either *cis* or *trans* stereochemistry. Further functionalisation of the C ring occurs at C-4 (**Figure 29**).



Podophyllotoxin **353** $R_1 = H, R_2 = OH$
Epipodophyllotoxin **354** $R_1 = OH, R_2 = H$



Picropodophyllin **355** $R_1 = H, R_2 = OH$
Epipicropodophyllin **356** $R_1 = OH, R_2 = H$



Isopodophyllotoxin **357** $R_1 = H, R_2 = OH$
Epiisopodophyllotoxin **358** $R_1 = OH, R_2 = H$

Figure 29

Since its first isolation in 1953 by Hartwell,[104] podophyllotoxin **353** and its isomers have been the subject of numerous synthetic endeavours, due primarily to their potent activity and stereochemical complexity.[105-111] Moreover, the fact that aryltetralin lignan lactones, such as podophyllotoxin, are still isolated from natural sources in higher yields than achieved through synthesis, renders them a tantalising target for synthetic chemists. Therefore, our attention was drawn to the synthesis of lignan lactones using methodology described in Chapter 3. Consequently, the following section will examine earlier syntheses of podophyllotoxin and its isomers, focusing primarily on the methods employed in the formation of the CD ring moiety. Subsequent sections will then describe an alternative approach to the CD ring moiety of podophyllotoxin, discuss the merits and shortcomings of such an approach, and finally report a total synthesis of epipicropodophyllin **356** starting from silacyclohex-4-enes.

4.2 Synthetic Routes to the CD ring of Podophyllotoxin and its analogues

Synthetic approaches towards the aryl tetralin lactone skeleton follow either a linear AB ↦ ABC ↦ ABCD or a convergent AB + D ↦ ABCD strategy. In both approaches the cyclisation precursor can be either assembled with all the C-ring substituents in place or these can be introduced following completion of the skeleton. In all cases stereochemical issues dominate. The particular challenge when synthesising aryltetralin lactones is in establishing the correct stereochemistry of the lactone moiety. This is highlighted during the synthesis of podophyllotoxin when a *trans*- lactone ring fusion is required. This particular stereochemical combination enforces severe conformational strain on the system and, as such, on mild base treatment the lactone undergoes rapid epimerisation to afford a 97.5:2.5 mixture of picropodophyllin and podophyllotoxin.[112] Consequently, a second challenge associated with the synthesis of aryl tetralin lactones is at what stage the stereochemistry at C-1, C-2 and C-3 should be established. With these issues in mind, the following subsections will outline the linear and convergent approaches to the CD ring moiety, paying particular attention to the stereochemical outcomes.

4.2.1 C-Ring formation by Aryl Substitution

The most common approach to complete the aryl tetralin lactone skeleton has been by electrophilic aromatic substitution forming the C-1 – C-6 bond, simultaneously establishing the stereochemistry at C-1. As indicated above, this can be undertaken using acyclic precursors or with the D ring established. The latter is most attractive and considerable effort has been expended towards this end using a three component coupling procedure involving a benzylic anion **359**, a butenolide Michael acceptor **360** and an aldehyde **361** (**Figure 30**).

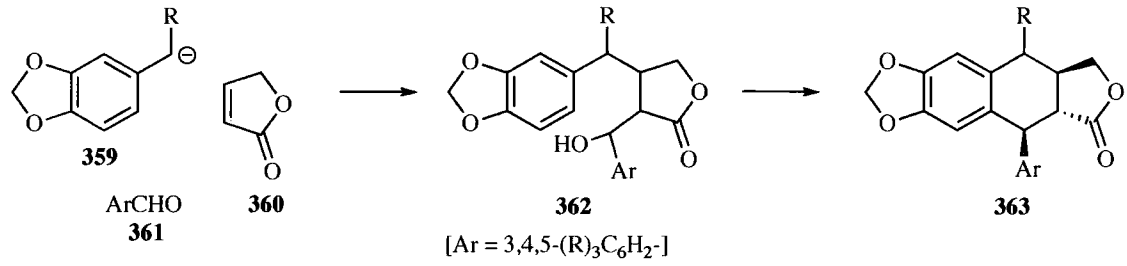
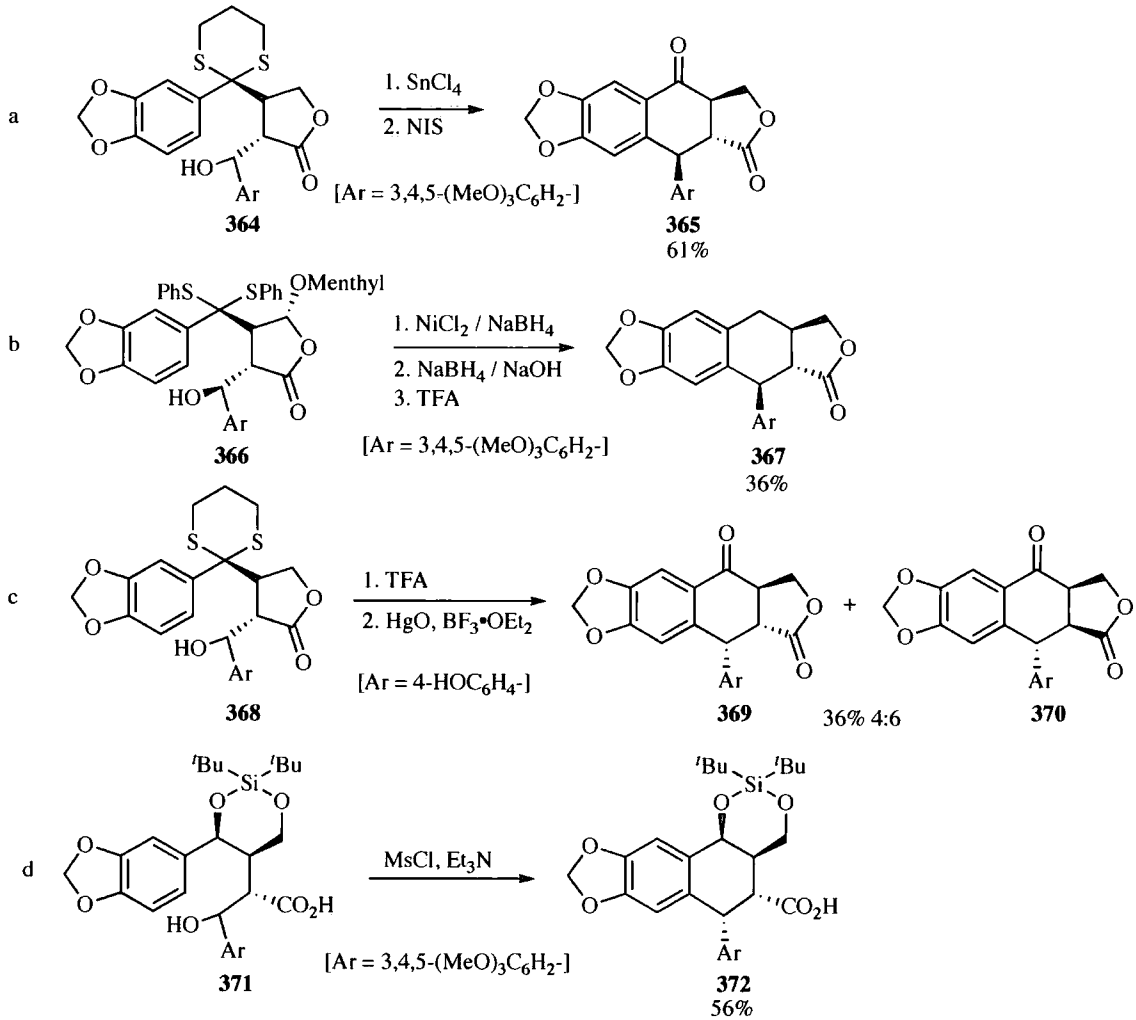


Figure 30

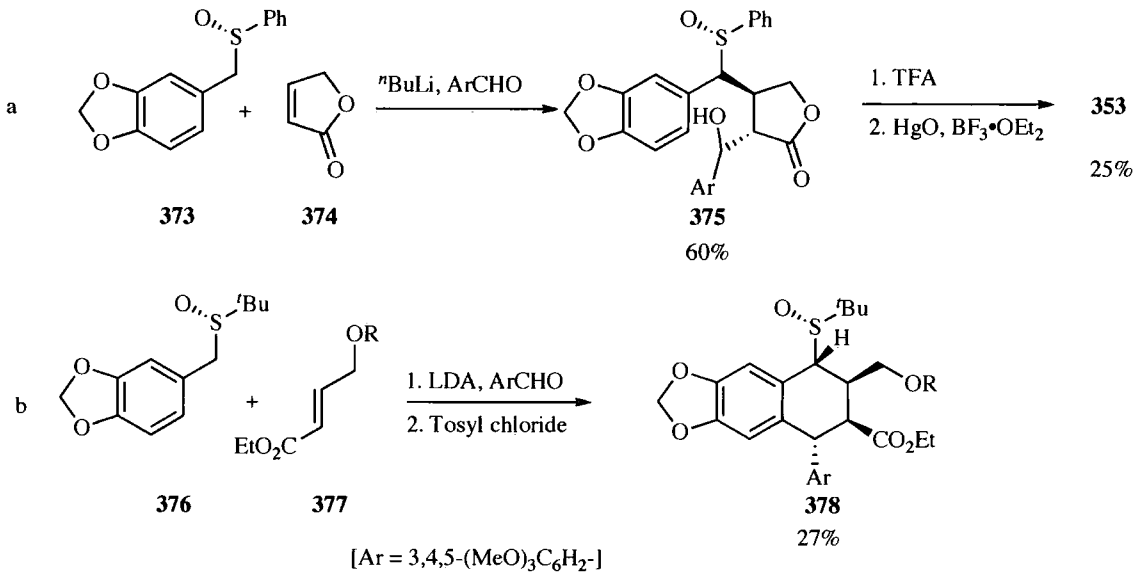
Whilst such an approach leads to the establishment of the *trans*-lactone stereochemistry at an early stage, forming the 1-6 bond in this fashion has a major limitation in the preferential production of the 1-2 *trans*-stereochemistry. This selectivity can be affected by the presence of additional stereochemical elements in the cyclisation process. This is highlighted by the early efforts of Zeigler, Gonzalez, Pelter and Ward who demonstrated that the precise nature of the substituent at C-4 and the cyclisation conditions seem to be crucial. For example, $SnCl_4$-promoted cyclisation of arylcarbinol **364** and subsequent dithiane deprotection afforded a single product **365** with the 1,2-*trans* rather than the desired 1,2-*cis* configuration (**Scheme 114a**).[113] Similarly, when the C-4 dithiane substituent was reductively cleaved, prior to cyclisation with TFA, the lignan lactone **367** was generated with isopodophyllotoxin stereochemistry (**Scheme 114b**).[105,114-116] In contrast to these observations, TFA mediated cyclisation and dithiane hydrolysis of the 4-hydroxyphenyl- containing carbinol **368** afforded a mixture of the podophyllotoxin and picropodophyllin isomers **369** and **370** (**Scheme 114c**).[117] This unusual contrathermodynamic isomerisation has been reinvestigated and it appears that control of the stereochemistry through manipulation of the aryl substituents is unlikely to provide efficient access to the podophyllotoxin series.[118] A highly *cis*- selective cyclisation is observed in the related cyclisation of arylcarbinol **371** which can be attributed to the additional constraints enforced by the fused silacyclic acetal (**Scheme 114d**).[119]



Scheme 114

In a drive for enhanced synthetic efficiency, this highly convergent approach continues to attract significant attention. More recent attempts have explored cyanohydrins and sulfoxides as the acyl anion equivalent.[120-123] Whilst the former are efficient, careful control of pH in the regeneration of the ketone function is necessary to avoid epimerisation at C-3. Application of sulfoxide anions seems to avoid this problem and Bhat has used a chiral sulfoxide in an exceptionally concise asymmetric synthesis of podophyllotoxin (**Scheme 115a**).[124] This synthesis is particularly noteworthy as TFA-mediated cyclisation of aryl carbinol **375** followed by sulfoxide hydrolysis afforded podophyllotoxin albeit in low yield. Formation of the desired *cis* 1-2 stereochemical arrangement in such an acid-catalysed cyclisation is unusual. Casey has subsequently demonstrated that isolation of the aryl carbinol can be avoided (**Scheme 115b**).[125]

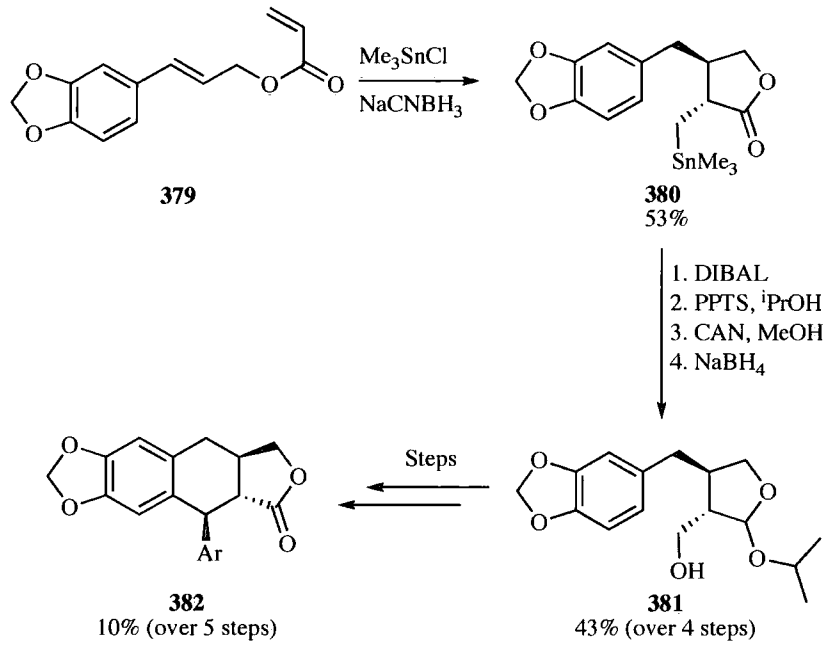
Following tandem conjugate addition - aldol condensation between sulfoxide **376**, crotonate **377** and 3,4,5-trimethoxybenzaldehyde, *in situ* tosylation afforded the tetralin skeleton **378** in a single operation. However, in this case the normal 1,2-*trans*-stereochemistry was produced. Subsequent C-S to C-O conversion and lactonisation of the D ring afforded picropodophyllotoxin. In further contrast to the report by Bhat, attempts to enhance the synthetic efficiency of the process through the use of an intact D ring (butenolide) in the conjugate addition were not successful.



Scheme 115

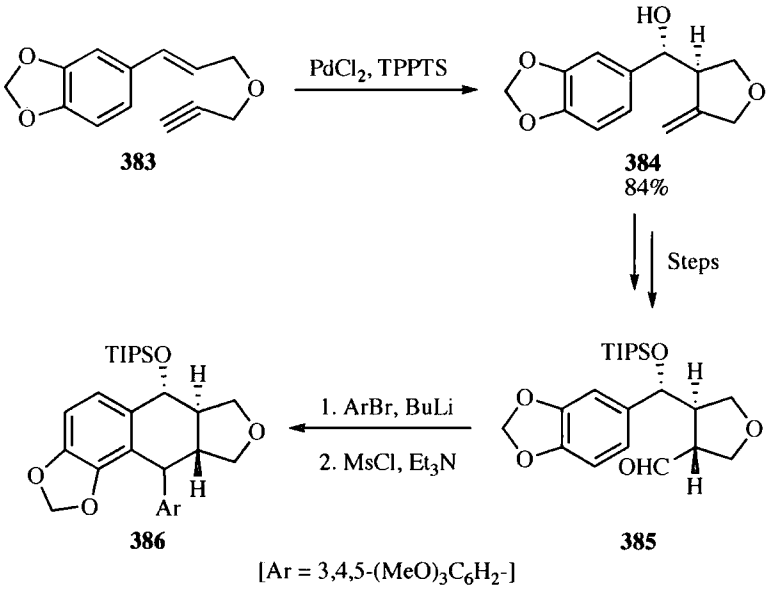
Whilst these highly concise sequences are attractive, considerable effort has also been applied to more stepwise approaches. These involve the initial preparation of a D ring unit, enabling the 2,3-*trans*- stereochemistry to be established at an early stage. For example, $Me_3Sn^{\bullet}$ initiated carbocyclisation of diene **379** afforded a 1:4 *cis/trans* mixture of lactones **380**.[126,127] Protection of the lactone carbonyl group as an acetal, and oxidative cleavage of the C-Sn bond with CAN in MeOH, followed by reduction with $NaBH_4$ then afforded a separable mixture of acetal isomers **381**. Following elaboration to the aryl carbinol, acid-catalysed cyclisation was explored in the hope that the acetal stereocentre would influence the stereochemistry. However, this proved not to be the

case with cyclisation affording deoxyisopodophyllotoxin **382** in moderate yield accompanied by various polycyclic by-products (**Scheme 116**).



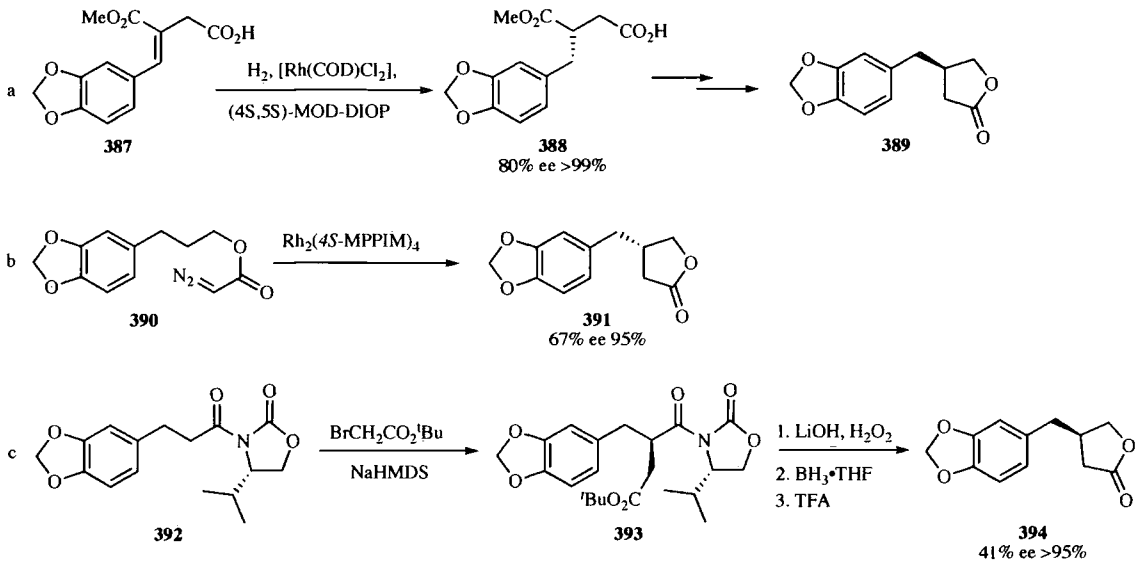
Scheme 116

Another approach by Genet described a method for the production of a D–ring aldehyde **385** using a novel carbohydroxypalladation cycloisomerisation of a 1,6-enyne (**Scheme 117**). Importantly the reaction installs the desired hydroxy function at C-4 with exclusive 3,4-*trans*- selectivity.[128] Whilst this could be elaborated to a cyclisation precursor containing the correct podophyllotoxin stereochemistry at C-2, C-3, and C-4, treatment with MsCl and Et_3N afforded an alternative tetracycle **386**. The reasons for this are not immediately obvious, as many similar examples provide the desired cyclisation products (*cf.* **Scheme 114**).



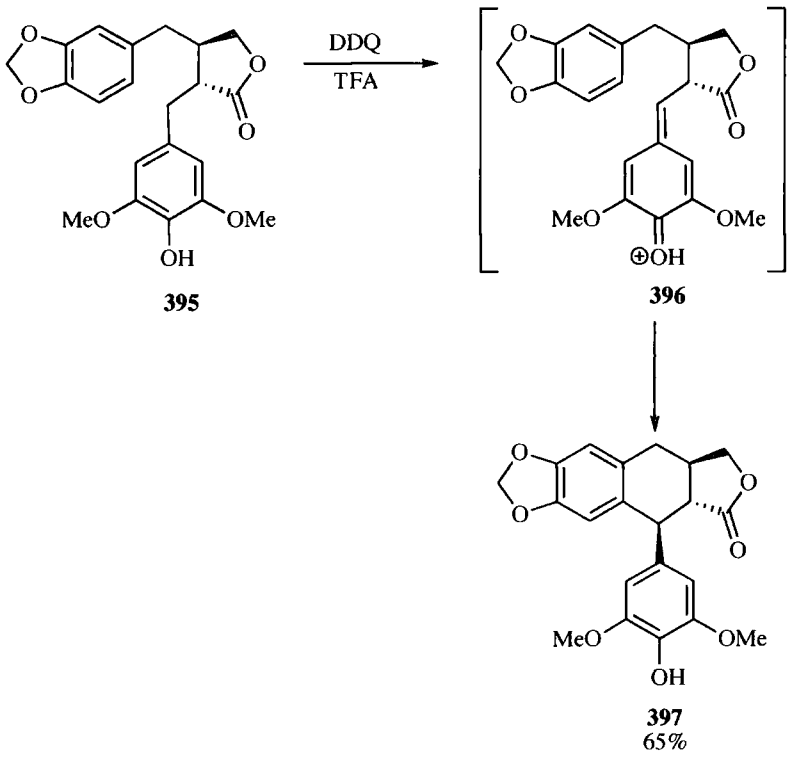
Scheme 117

One challenge in many of these methods, which was not discussed earlier, is in establishing the absolute stereochemistry. Reflecting the control obtained in electrophilic additions to enolates derived from β-substituted butyrolactones, a popular approach has been to develop enantioselective syntheses of these versatile intermediates and then elaborate these to the aryltetralin lactone skeleton. The initial asymmetric centre has been established in a number of ways including asymmetric hydrogenation of succinates **387** (**Scheme 118a**),[129] C-H insertion of diazoesters **390** (**Scheme 118b**)[130] and enolate alkylation **392** (**Scheme 118c**).[131] In this context it is pertinent to note that Pelter has demonstrated that the 3-component coupling reaction of enantiomerically pure 5-menthyloxyfuranone proceeded with complete diastereoselectivity (*cf.* **Scheme 114b**).



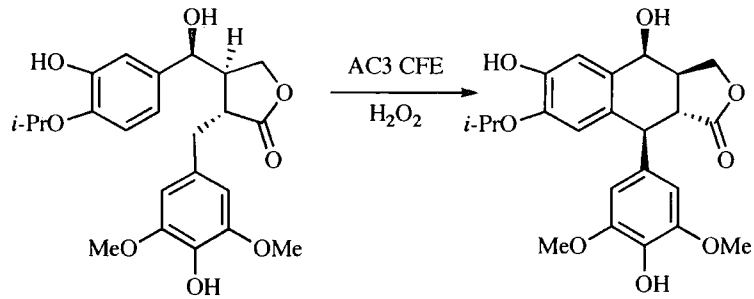
Scheme 118

Whilst the majority of syntheses involving C ring formation by aromatic substitution follow an S_EAr pathway using a stablised cation derived from a C-1 aryl carbinol, other strategies have been explored. Similar cationic intermediates (quinone methides) are probably generated in the oxidation of 4'-demethylyatein **395** with DDQ in the presence of TFA. This gave rise to the isopodophyllotoxin stereochemistry (**Scheme 119**).[131]



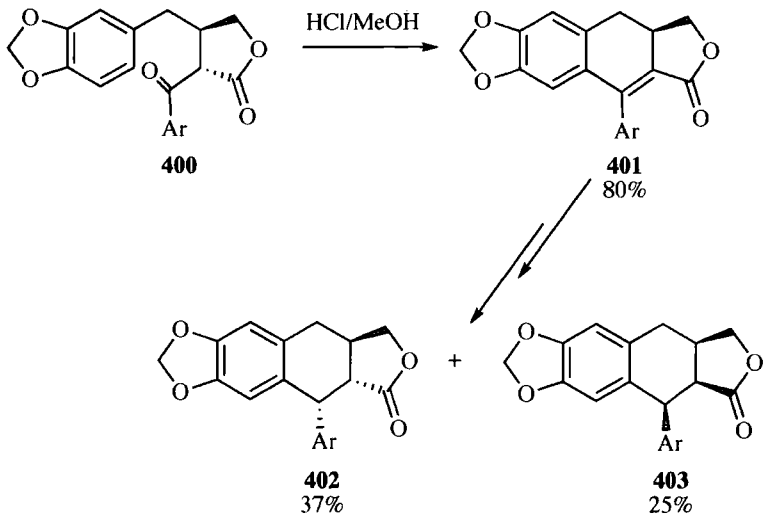
Scheme 119

This benzylic oxidation was suggested to be a biomimetic process.[132] In support of this Kutney and others have shown that various oxidative enzymes can promote a similar transformation.[133,134] For example, treatment of the butanolide **398** with a cell-free enzyme preparation derived from *Catharanthus roseus* (AC3 CFE) led directly to a fully substituted C ring lactone possessing the *cis,trans,trans*- stereochemistry (**Scheme 120**).



Scheme 120

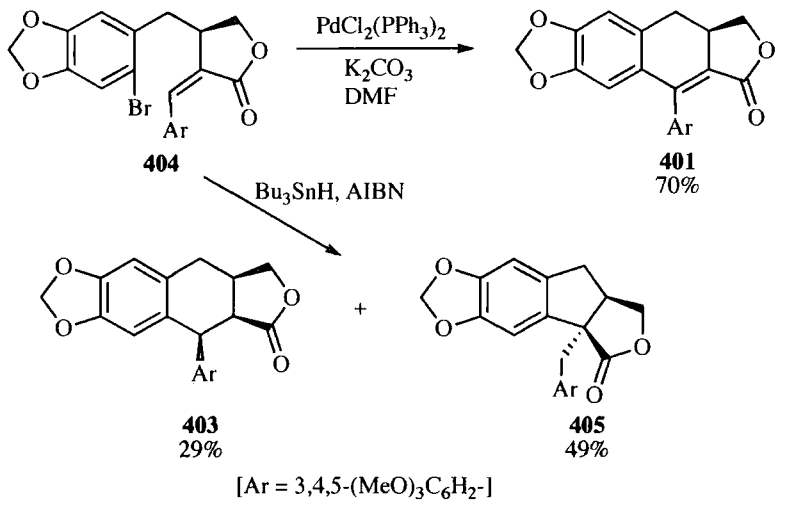
Alternatively, the corresponding C-1 ketone **400** can be used as the cyclisation substrate. This, on acid treatment led to the unsaturated lactone derivative **401**. Saponification of the D ring followed by reduction and re-cyclisation afforded the desired 1,2-*cis* stereochemistry, albeit as a mixture of lactone stereoisomers **402** and **403** (**Scheme 121**).[129]



[Ar = 3,4,5-$(MeO)_3C_6H_2$-]

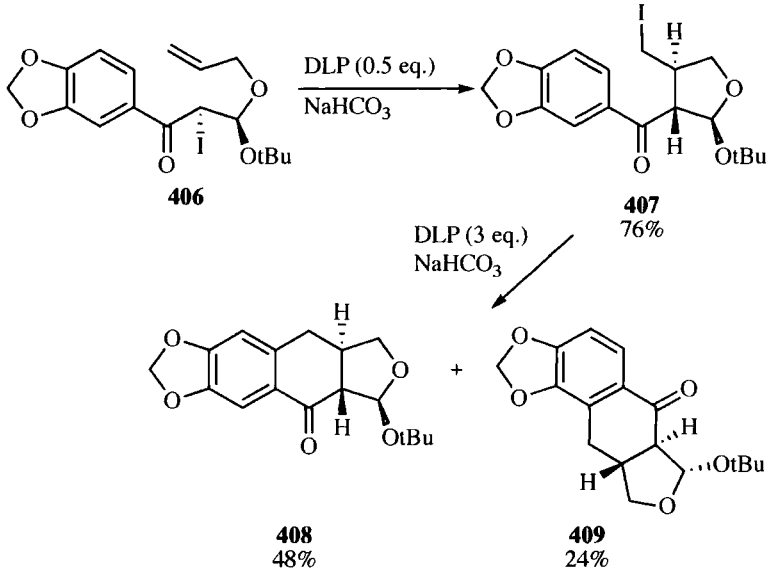
Scheme 121

A similar unsaturated lactone was generated in a novel Heck cyclisation developed by Ishibashi and Ikeda (**Scheme 122**).[135] In this approach, the stereochemistry of the starting alkene is crucial. Whilst use of the *Z*-lactone **404** afforded a good yield of apopicropodophyllin **403**, similar treatment of the *E*-isomer resulted in a complex mixture of products. This is suggested to result from the latter isomer requiring a pseudoaxial aryl group in the transition state, thereby inhibiting the desired cyclisation. Attempts to achieve this ring closure using radical means were less successful with cyclisation of both isomers favouring the 5-*exo* pathway, the *E*-lactone doing so exclusively.



Scheme 122

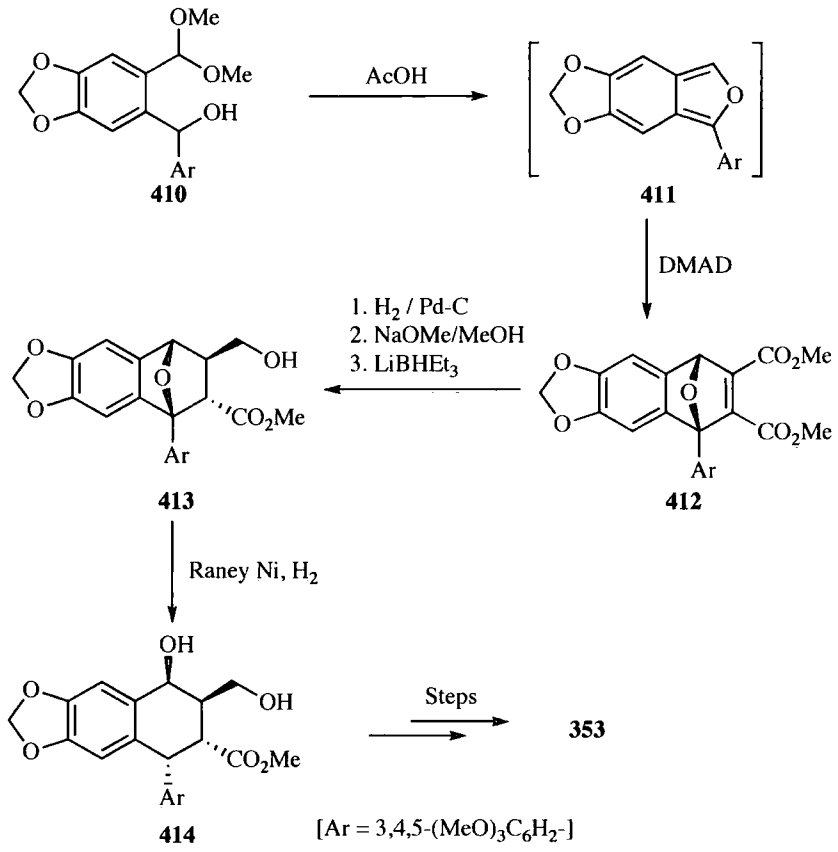
Finally, a conceptually different radical approach to the podophyllotoxin skeleton involving formation of the C-4 – C-5 bond in a cascade cyclisation sequence was reported by Renaud (**Scheme 123**).[136] Treatment of iodide **406**, synthesised in four steps from piperonoyl chloride, with 0.5 equivalents of dilauroyl peroxide (DLP) afforded the D-ring acetal **407** as a single isomer. Subsequent reaction with excess DLP generated the ABCD ring system, albeit accompanied by significant quantities of the regioisomeric tetracycle **409**. Attempts to undertake the cascade in a single process also produced **409** in similar overall yield, but only as a component affording a complex mixture of products that was difficult to separate.



Scheme 123

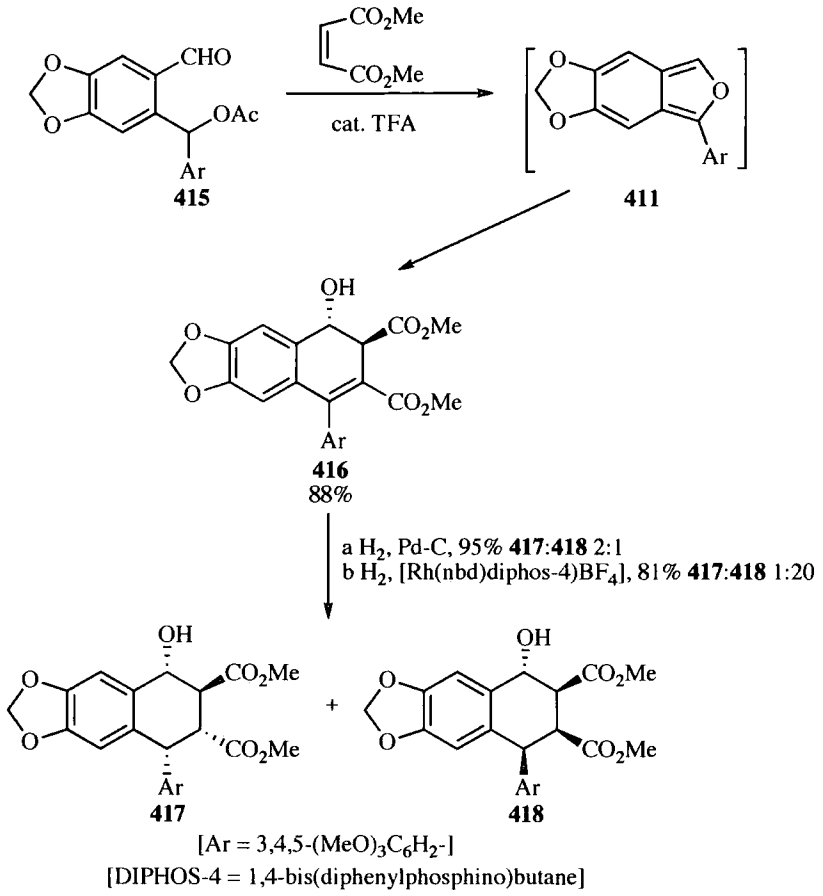
4.2.2 C-Ring Formation *via* Cycloaddition Reactions

The other principal strategy for construction of the C ring has been the Diels-Alder reaction. This has the advantage of installing much of the stereochemistry in a single operation. The challenge for this approach is the generation of a diene component that provides efficient stereocontrol of all centres. This strategy was pioneered by Rodrigo who recognised that the oxabicycloadduct **412** derived from isobenzofuran **411** and DMAD contains all the required carbon and oxygen atoms for podophyllotoxin.[137-139] Whilst the use of DMAD necessitates the additional steps of reduction and C-3 epimerisation, these proceed efficiently and are preferable to a more direct fumarate cycloaddition as the latter leads to a mixture of *endo-* and *exo-* stereoisomers. Importantly, the reductive cleavage of the oxa bridge with Raney nickel occurs chemo- and stereoselectively, with retention of the C-1 stereochemistry, establishing the 1,2-*cis*, 2,3-*trans*- relationship. When combined with the efficient lactonisation procedure developed by Jones,[140] this provided rapid access to epipodophyllotoxin **414** and, after C-4 epimerisation, podophyllotoxin **353** in 19 and 11% yield from piperonal respectively (**Scheme 124**).



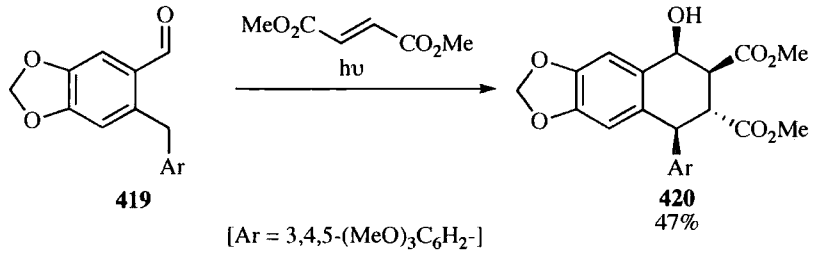
Scheme 124

Alternatively, acid-catalysed elimination of the oxa bridge leads to the dihydronaphthol **416** and catalytic reduction of this leads to the desired 1,2-*cis*- stereochemistry.[141] Whilst simple reduction of **416** with H_2/Pd-C gave a 1:2 mixture of the picropodophyllin : podophyllotoxin isomers, hydroxyl- directed reduction using the cationic rhodium complex [Rh(nbd)(diphos-4)BF_4] afforded enhanced selectivity 20:1 in favour of the former stereochemistry (**Scheme 125**).



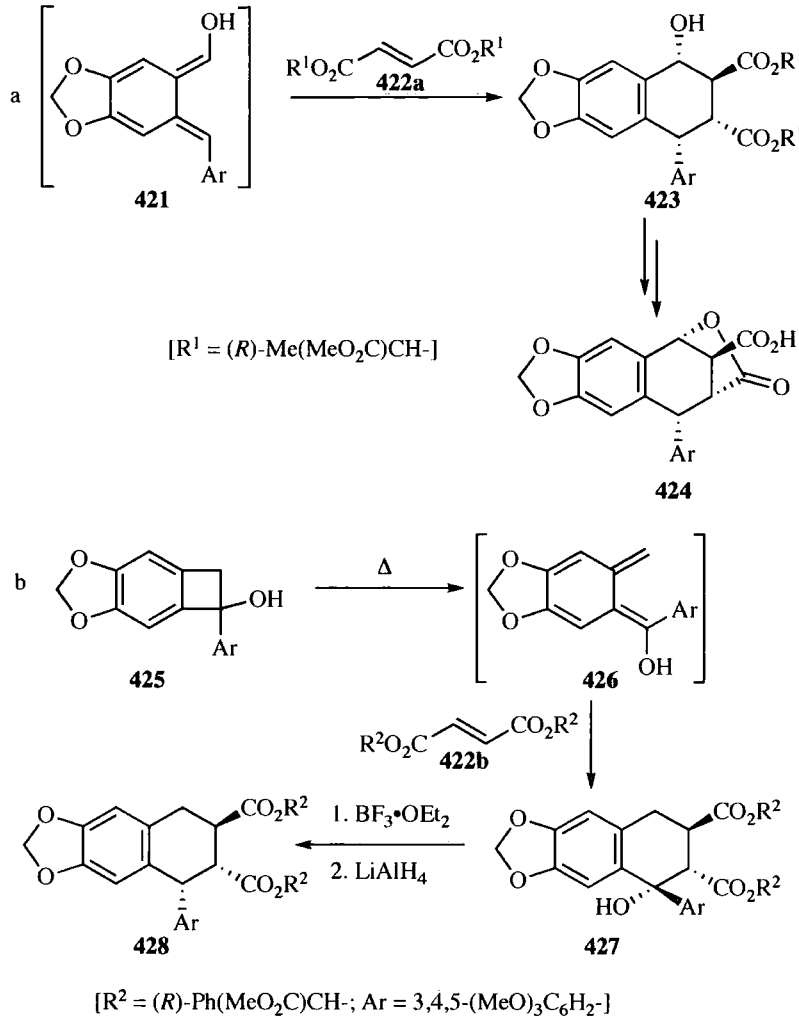
Scheme 125

A range of other dienophiles have been employed in these reactions with *o*-quinodimethane equivalents. However, the regioselectivity observed was frequently only modest when non-symmetrical dienophiles were used.[142-147] For this reason, a number of approaches have used simple symmetrical maleate systems exploiting the greater accessibility of the C-3 carbonyl group for subsequent selective epimerisation and reduction of the cycloadduct.[148,149] The particular problems of fumarate cycloadditions are illustrated by the early work of Durst (**Scheme 126**).[150] In this an *o*-quinodimethide was generated and trapped in a photo-enolisation Diels-Alder strategy. Whilst reaction with methyl fumarate established the *syn* C-1 and C-4 arrangement, it also led to the formation of the alternative epiisopodophyllotoxin *trans,trans,cis*-stereochemistry.



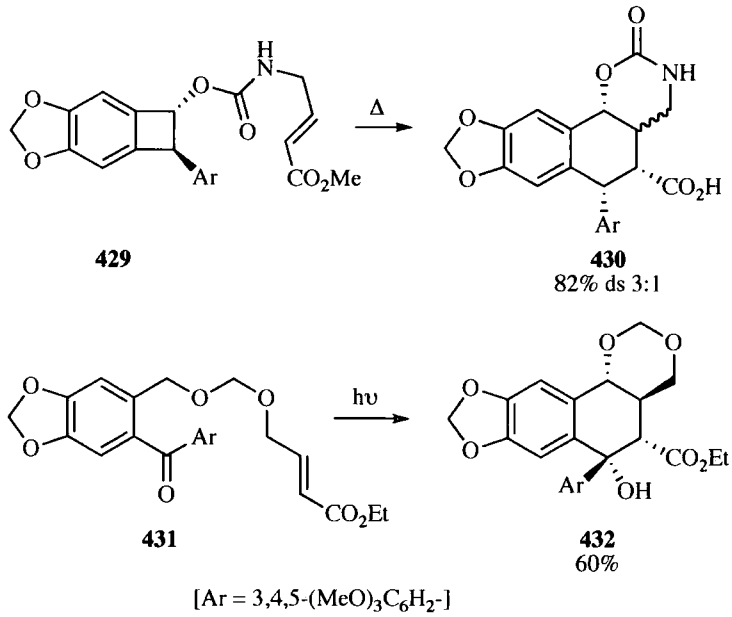
Scheme 126

Charlton has proposed two solutions to this problem. The first was based on the observation that the fumarates of lactate and mandelate **422** lead preferentially to an *exo*- adduct.[151] The reasons for this are not immediately clear but have been exploited to provide a short synthesis of neopodophyllotoxin **424** (**Scheme 127a**).[145] The second strategy was to use an α-hydroxy-α-aryl *o*-quinodimethide **426** in which the hydroxy group would control the regio- and stereochemistry of the cycloaddition. The *o*-quinodimethane was generated from the corresponding benzocyclobutane **425** with the ring opening giving the *E*- 'diene' as predicted by torqueselectivity rules. Whilst this generated the required 2,3-*trans*- stereochemistry, reduction of the C-1 hydroxyl group with inversion proved not to be trivial. After some experimentation a combination of $BF_3 \bullet OEt_2$ and $LiAlH_4$ proved successful giving a 15:2 mixture of the C-1 α and β isomers with the major isomer **428** being elaborated to deoxypodophyllotoxin (**Scheme 127b**).[152]



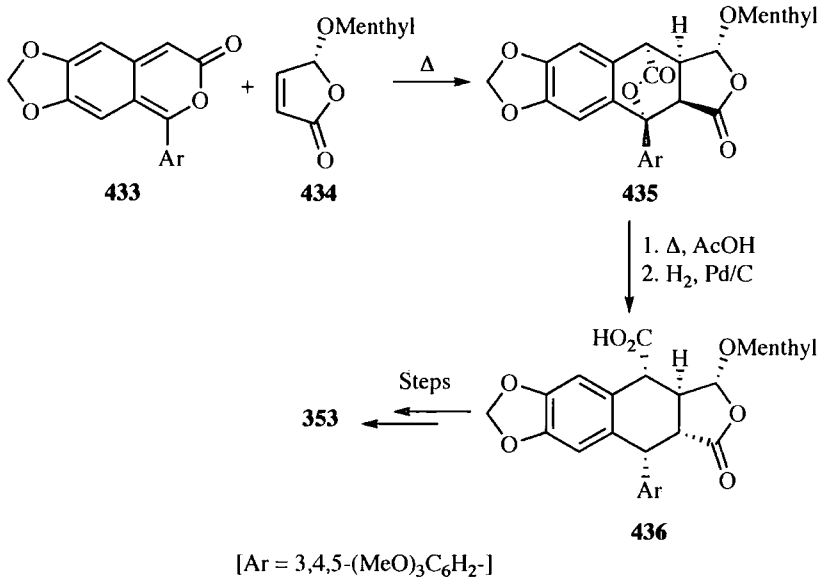
Scheme 127

An alternative solution to the problem of controlling the selectivity of crotonate cycloadditions was to carry out the Diels-Alder reaction in an intramolecular fashion using a C-4 linked tether. In this way, the activating group on the dienophile was forced to occupy the C-2 position and then an *endo*- transition state leads to the desired podophyllotoxin stereochemistry (**Scheme 128**).[153-155]



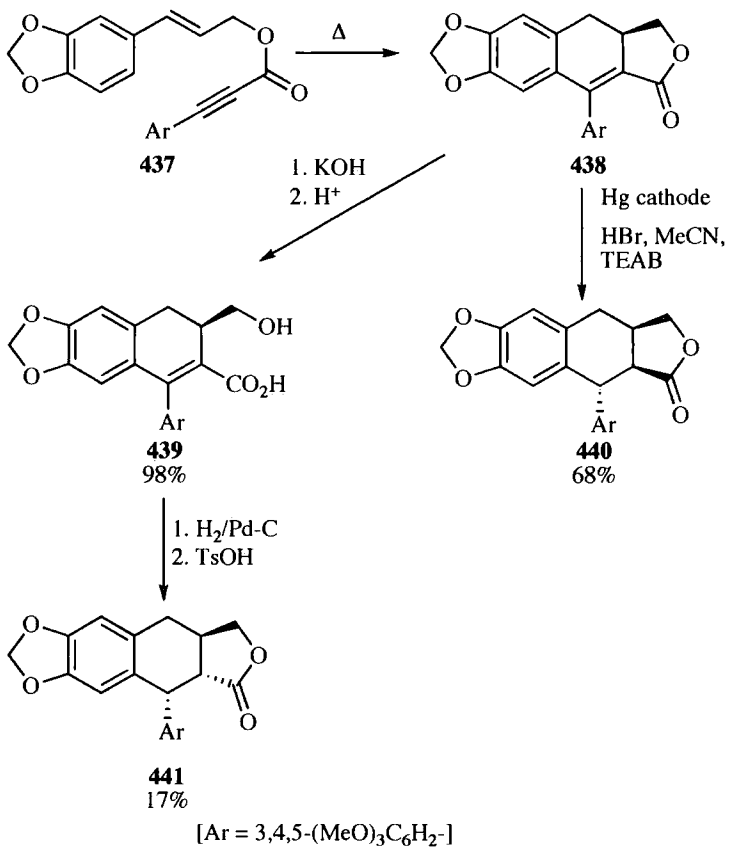
Scheme 128

The challenge of controlling the stereo- and regiochemistry of addition to *o*-quinonedimethane-type dienes has also been studied by Jones. In an elegant series of papers using the readily accessible, and sometimes isolable pyrones **433**, he has shown that whilst a C-2 aryl substituent induces an *exo*- orientation for a methoxy carbonyl group at C-2, this directing effect can be overcome using more compact dienophiles.[156-158] Whilst the lactate fumarate **422a** used by Charlton proved non-selective, the menthyloxy-furanone **434** gave complete selectivity for the *endo*- adduct. Following acid-promoted elimination across the lactone bridge, hydrogenation afforded the podophyllotoxin 1,2-*cis* 2,3-*trans* stereochemistry (~7:1) with the selectivity directed by the chiral auxiliary. Subsequent C-4 oxidative decarboxylation, hydrolysis of the chiral auxiliary, reduction and lactonisation afforded (-)-podophyllotoxin **353** in 15% overall yield from pyrone **433** (**Scheme 129**).[146]



Scheme 129

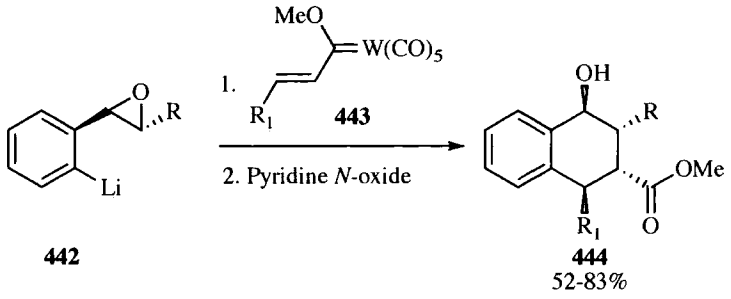
Whilst the Diels-Alder reaction is most commonly undertaken to realise a 1-2, 3-4 disconnection strategy, Klemm and Yamaguchi have reported an alternative 2-3, 1-6 bond construction strategy involving the intramolecular Diels-Alder reaction of propargylic ester **437**. Whilst catalytic reduction of the lactone **438** afforded the all-*cis*-isomer, use of the free hydroxy acid **439** led to the desired 1,2-*cis* 2,3-*trans* stereochemistry, albeit in low yield (**Scheme 130**).[159] Alternatively, electrochemical reduction of unsaturated lactone **438** led to the 1,2-*trans* 2,3-*cis* picropodophyllin stereochemistry.[160]



Scheme 130

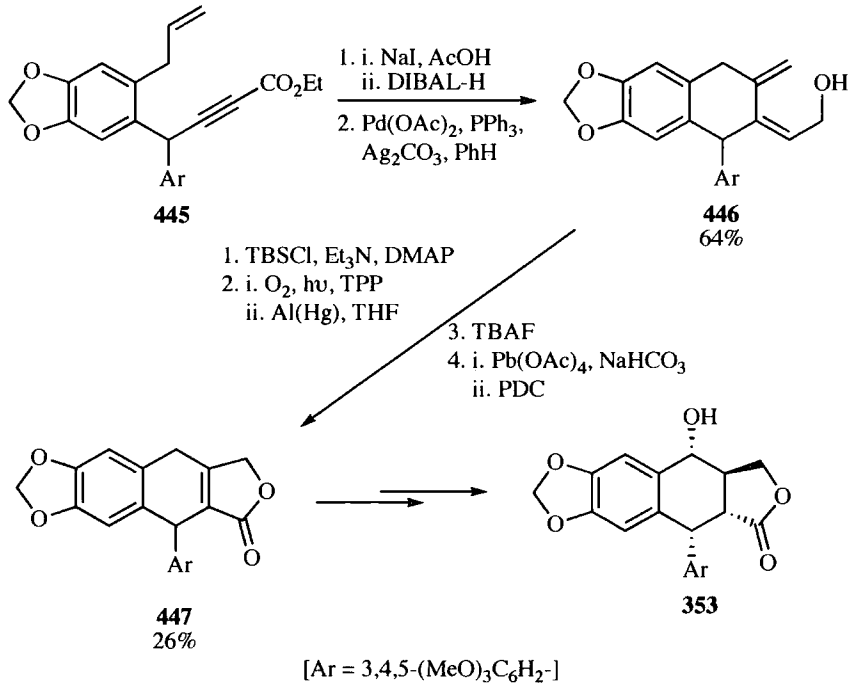
4.2.3 Other modes of C-ring Construction

Whilst the majority of approaches to the CD ring moieties follow one of the two strategies described in previous sections, a few methods have completed the CD rings through the formation of the C-2 – C-3 bond. In the main this reflects the ability to generate an enolate anion at C-2 due to the presence of the future lactone carbonyl group. The process can be rendered very convergent through application of a Michael induced ring closure (MIRC) sequence and can be achieved in a very concise fashion (**Scheme 131**).[161,162] However, the drawback to such an approach is the formation of the undesired 1,2-*trans*- stereochemistry.



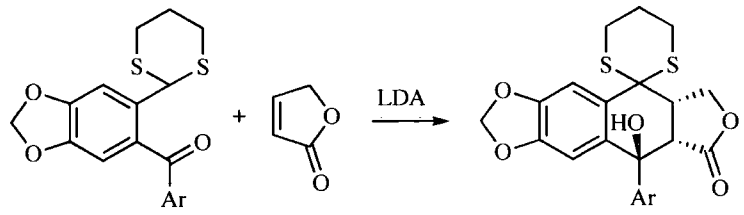
Scheme 131

In a unique approach to the aryltetralin skeleton, Toste has employed an intramolecular Heck reaction of 1,7-enyne **445** to construct the C ring in his synthesis of podophyllotoxin (**Scheme 132**).[163]



Scheme 132

Lastly, in a complementary approach to the tandem conjugate addition strategy described earlier, Harrowven has assembled the C ring *via* construction of the 1,2 and 3,4 bonds through a type II MIRC procedure (**Scheme 133**).[164]



448 **374** **449**
79%

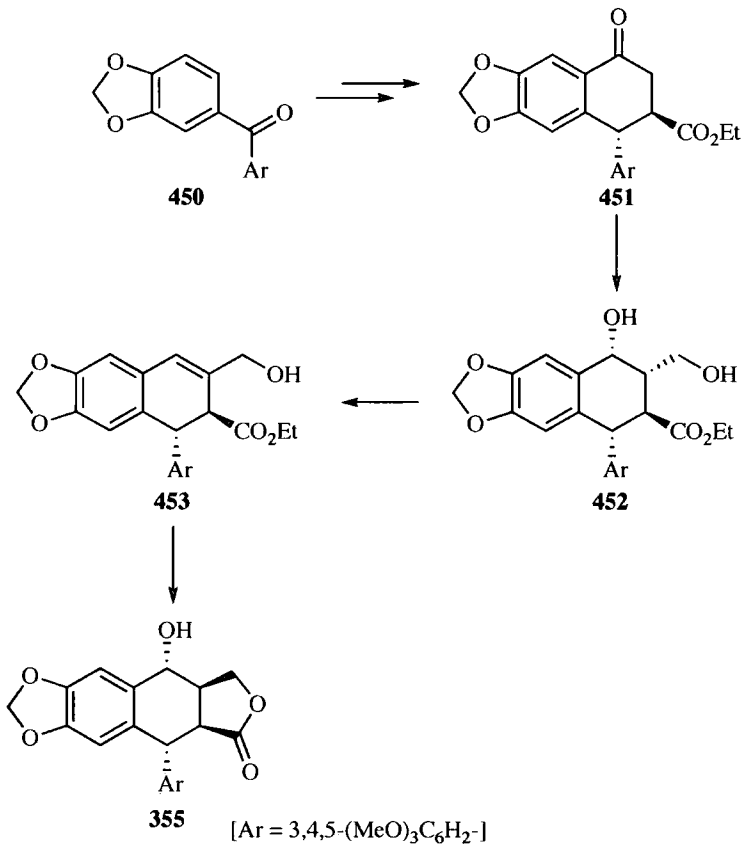
[Ar = 3,4-Methylenedioxy-]

Scheme 133

4.2.4 Functionalisation of Preformed C-Ring

The other principal strategy for the preparation of CD ring moieties relies on an early construction of the C ring and then subsequent introduction of the remaining functionality to provide the D ring. Final manipulation of the stereochemistry is then undertaken to obtain the desired isomeric product. In this respect, it is pertinent to note that conditions for the interconversion of various podophyllotoxin diastereoisomers have been established, notably that of picropodophyllin.[112]

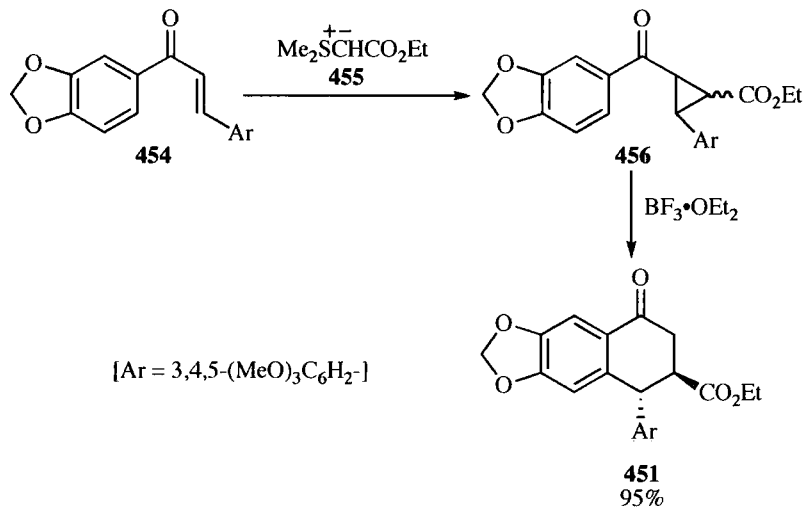
In many cases, the C ring is initially established using methods discussed in the previous section. Gensler, following such an approach, reported the first synthesis of the most prominent aryl tetralin lactone podophyllotoxin in 1962. Gensler had identified the tetralone **451** as a key C-ring precursor in an earlier synthesis of picropodophyllin.[165,166] Oxo ester **451** was generated in 4 steps from benzophenone derivative **450** through a sequence involving Stobbe condensation, reduction, activation of the carboxylic acid and Friedel-Crafts acylation.[167] Functionalisation of the C ring was achieved by Claisen condensation with ethyl formate, followed by reduction to introduce the hydroxymethyl sidechain. Subsequent dehydration and lactone saponification afforded α-apopodophyllic acid **453,** which could be resolved using quinine. Lactonisation and hydration of the alkene then afforded picropodophyllotoxin **355** albeit in low yield (**Scheme 134**).[168]



Scheme 134

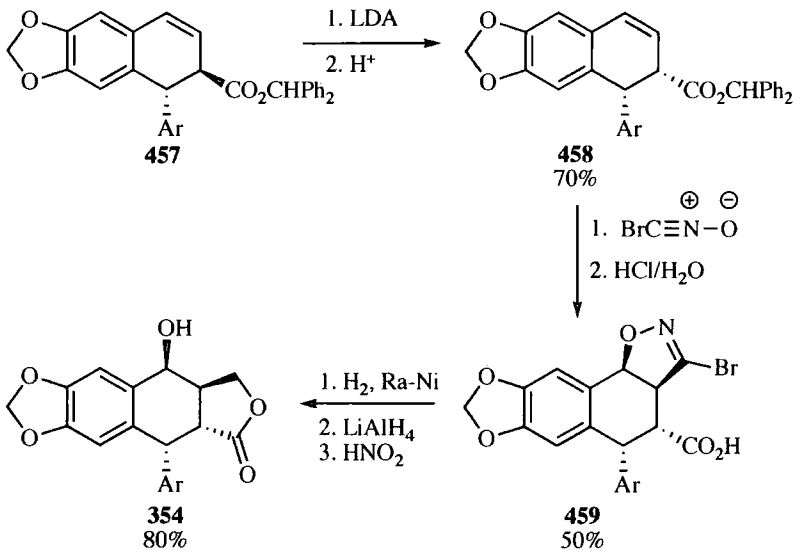
Whilst this established the basic skeleton of aryltetralin lactones, the stereochemistry represented the thermodynamically favoured outcome. However, based on earlier studies exploring the picropodophylin-podophyllotoxin equilibrium, Gensler proposed that kinetic reprotonation of the relatively planar lactone enolate would proceed from the less hindered β-face to afford the desired *trans*- lactone. Importantly, proceeding *via* picropodophyllin establishes the correct stereochemistry at C-3 through preferential formation of a *cis* lactone. Consequently, following alcohol protection as the THP acetal, enolate formation with triphenylmethylsodium and subsequent rapid reprotonation using acetic acid afforded, after deprotection, a separable 45:55 mixture of podophyllotoxin and picropodohyllin.[165] The lower than expected ratio of *trans*- to *cis*- lactones was attributed to a high degree of pyramidalisation of the enolate in the transition state favouring the less strained picropodophyllin geometry.

Following this pioneering synthesis, others have described syntheses of podophyllotoxin and its isomers *via* the same γ-oxo ester intermediate. However, whilst Gensler generated the C ring by a 4,5 bond connection with the C-1, C-2 *trans* stereochemistry established, most subsequent syntheses of this intermediate have completed the C-ring through the 1-6 bond.[169-171] The most concise and efficient of these approaches to the keto-ester **451** is that described by Murphy and Wattanasin involving Lewis-acid-mediated rearrangement of the cyclopropane **456** (**Scheme 135**).



Scheme 135

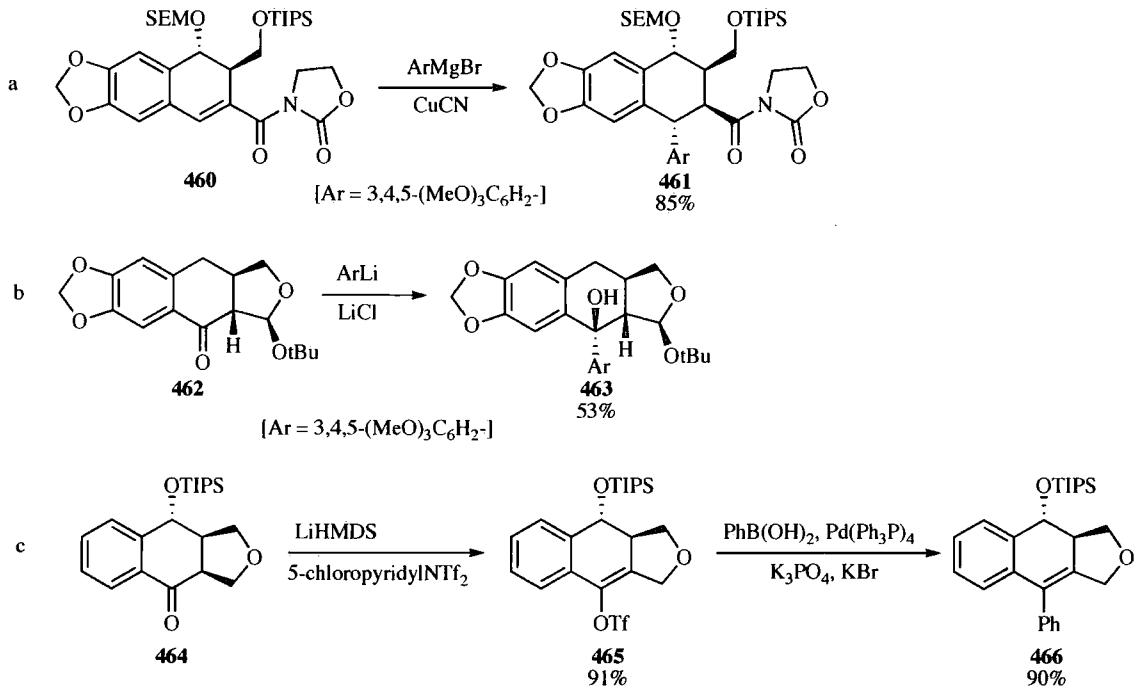
Importantly, as discussed above, in the absence of other stereocontrolling elements, all such approaches produce the 1,2-*trans*- stereochemistry. Consequently, whilst the subsequent steps of the synthesis to picropodophyllone have also been enhanced, the ultimate conversion to podophyllotoxin still requires the unfavourable lactone epimerisation. This challenging transformation can be addressed by carrying out the isomerisation at an earlier stage of the synthesis prior to introduction of the C-3 substituent or following hydrolysis to the keto-acid.[172,173] Importantly, the former approach facilitates the stereocontrolled introduction of the C-3 hydroxymethyl group as seen in the work of Vyas and Wong (**Scheme 136**).



[Ar = 3,4,5-$(MeO)_3C_6H_2$-]

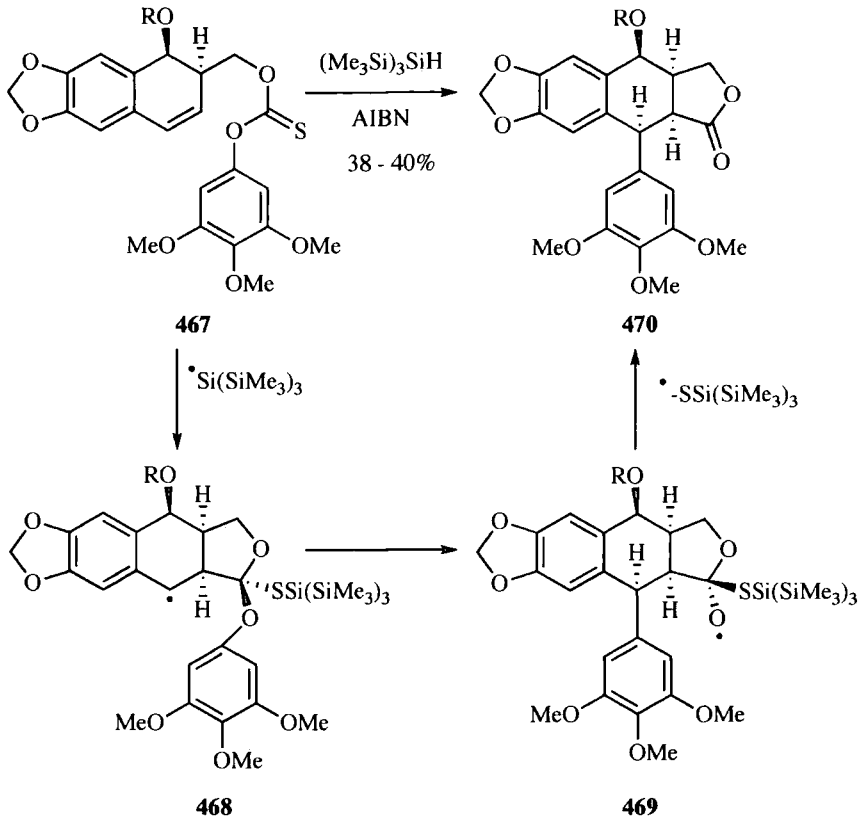
Scheme 136

These approaches have largely established the C-1 stereochemistry early in the synthesis and used this to control the introduction of the remaining stereocentres. However, it is possible to reverse this process, and to introduce the C-1 aryl group and fix the stereochemistry at this centre as part of the end game strategy. The particular attraction for doing so is that it provides easy access to a range of analogues. Conjugate addition to the unsaturated acyl oxazolidinone **460** occurs to give the desired C-1 α-isomer presumably directed by the bulk of the TIPSO group at C-3. Unfortunately protonation of the resultant enolate also occurs from the same face leading to the picropodophyllin stereochemistry (**Scheme 137a**).[174] In the presence of LiCl, addition of an aryllithium to a C-1 keto-lactol **462** occurs stereoselectively to afford tetracyclic aryl carbinol **463**. Unfortunately, conditions for the selective reduction of the tertiary alcohol remain to be identified (**Scheme 137b**).[136] Elimination to apopodophyllotoxin is possible and related reductions in this series have previously been demonstrated to provide the desired 1,2-*cis* 2,3-*trans*- stereochemistry.[129,141,159] The $\Delta^{1,2}$ unsaturated skeleton can also be accessed from the C-1 ketone *via* enol triflate formation and Suzuki-Miyaura cross coupling (**Scheme 137c**).[175]



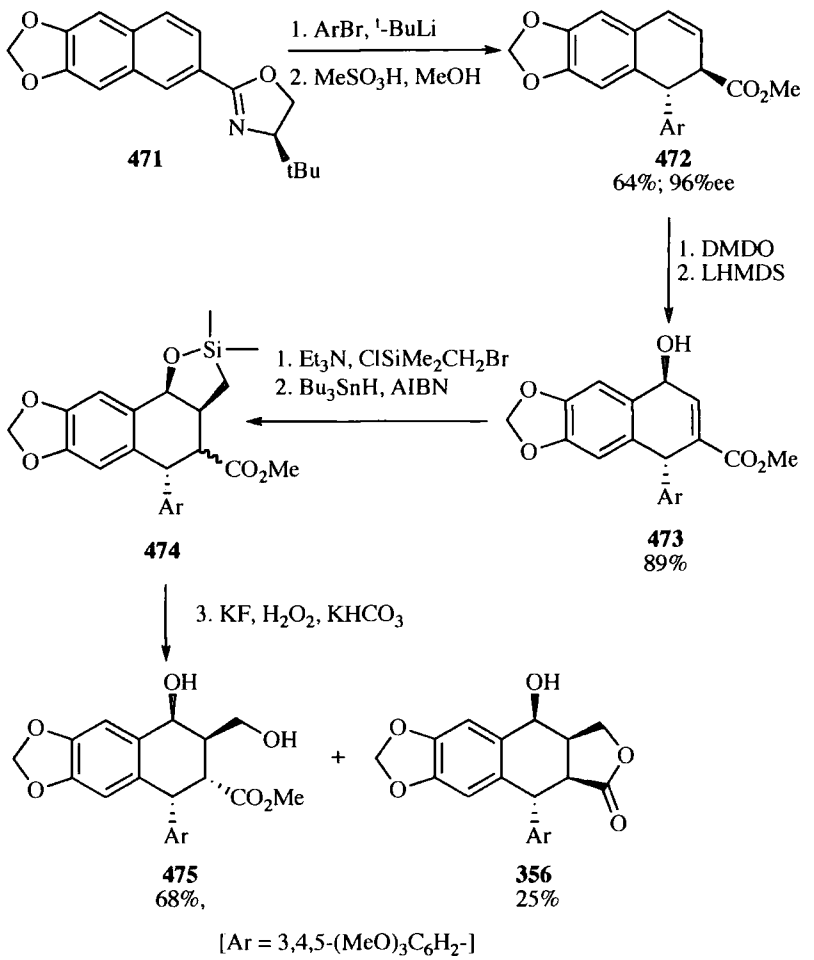
Scheme 137

A particularly elegant approach, which simultaneously establishes the D-ring lactone and introduces the C-1 aryl group, involves a tandem radical cyclisation – radical translocation sequence (**Scheme 138**).[176] Reflecting the tethered nature of each step, high diastereoselectivity was obtained leading to the isopicropodophyllin stereochemistry. The starting thiocarbonates can be prepared in either enantiomeric series using either an Evans' asymmetric aldol-RCM sequence or a Meyers' asymmetric nucleophilic dearomatisation of a naphthalene.



Scheme 138

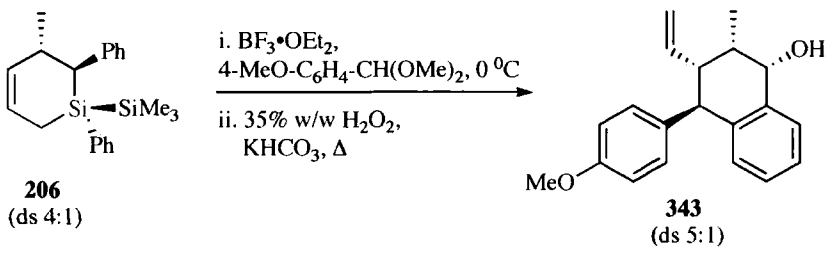
Enantioselective dearomatisation of a naphthalene formed a key step in one of the early syntheses of podophyllotoxin.[177] Whilst this step proved efficient, the intrinsic diasteroselectivity of the process results in the generation of the 1,2-*trans*-stereochemistry which required late stage epimerisation. This synthesis has been refined to provide (-)-epipodophyllotoxin in 96% ee and 30% overall yield from piperonal.[178] In this modification, the key 1,2-*cis*, 2,3-*trans*- stereochemistry is controlled by the C-1 alcohol through a silicon-tethered radical hydroxymethylation, albeit with only moderate diastereoslectivity at C-2 (**Scheme 139**).



Scheme 139

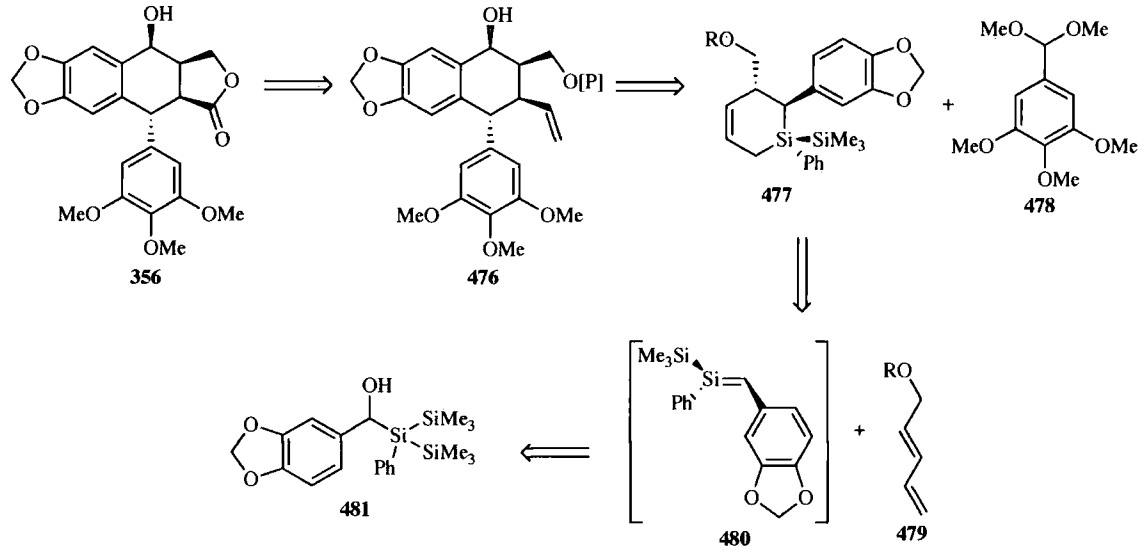
4.3 Our approach to the podophyllotoxin analogue, Epipicropodophyllin

Our approach to the synthesis of the aryl tetralin lactone skeleton arose from the development of new synthetic methodology described earlier (*cf.* Section 3.4). This methodology demonstrated that the Hosomi-Sakurai reaction of silacyclohex-4-enes **206** with electron-rich aromatic acetals generated tetrahydronaphthalenes **343** in good yield and diastereoselectivity (**Scheme 140**).



Scheme 140

Therefore, it was our intention to apply this methodology to the total synthesis of epipicropodophyllin **356**. Firstly, a retrosynthetic analysis of epipicropodophylin was undertaken. This revealed that the key steps would involve the Hosomi-Sakurai reaction of a new, highly functionalised silacyclohex-4-ene **477** with 3,4,5-trimethoxy benzaldehyde dimethyl acetal, to provide the aryl tetralin skeleton **476**. The remaining steps would involve deprotection of the tetrol **476** and introduction of the D ring lactone to supply the final product (**Scheme 141**).

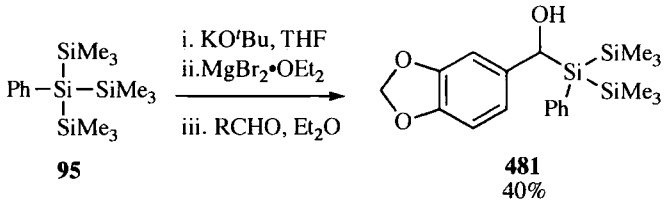


Scheme 141

With this analysis in mind, the following section will discuss the results of our synthetic endeavours, highlighting key issues with this approach and, ultimately, report the total synthesis of epipicropodophyllin.

4.4 Results and Discussion

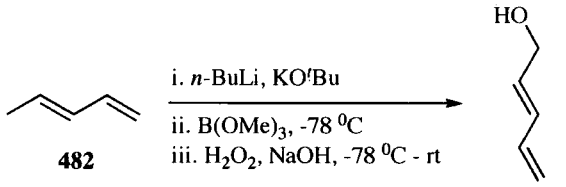
As discussed in the previous section, our approach to epipicropodophyllin relied on the preparation of the highly functionalised silacyclohex-4-ene **477**. Accordingly this became the first objective of the project. To begin, silyl alcohol **481** was synthesised in good yield following the procedure described by Whelligan (**Scheme 142**).



95 **481** 40%

Scheme 142

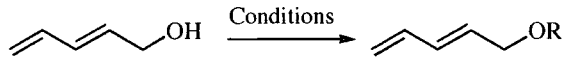
Silyl alcohol **481** was confirmed by analysis of the IR spectrum, which showed a broad signal at 3564cm^{-1} coupled with peaks at 5.90 and 5.10 ppm in the ^{1}H NMR spectrum, corresponding to the dioxolane methylene group and Si-C*H* proton respectively. With the silyl alcohol in hand, attention turned to the synthesis of hydroxydiene **483**. A brief search of the literature revealed that the desired diene **483** could be prepared from piperylene **482** (**Scheme 143**).[179,180]



482 **483** 43% E/Z 9:1

Scheme 143

Treatment of piperylene with Schlosser's base generated a conjugated anion, which was trapped with trimethyl borate. The borate ester was then oxidised with hydrogen peroxide to generate the hydroxy diene **483** in good yield. The structure of diene **483** was confirmed by comparison of ^{1}H NMR data with that given in the literature.[179] Diene **483** was then protected with a variety of protecting groups. This sequence enabled large amounts of diene precursor to be synthesised (**Table 10**).

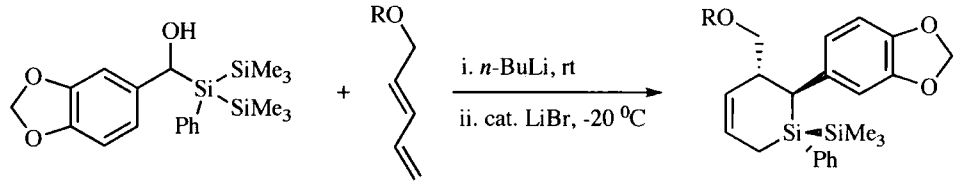


483 **479**

Entry	R group	Conditions	Yield
1	TBS	TBSCl, Im. DCM	95%
2	TBDPS	TBDPSCl, Im. DCM	56%
3	Ac	Ac_2O, DIPEA, DMAP, DCM	32%

Table 10

With three diene substrates in hand, attention turned to their application in the crucial Diels-Alder reaction. Each diene substrate was utilised in the silene-diene Diels-Alder reaction, pioneered by Whelligan to produce the highly functionalised silacyclohex-4-enes (**Table 11**).

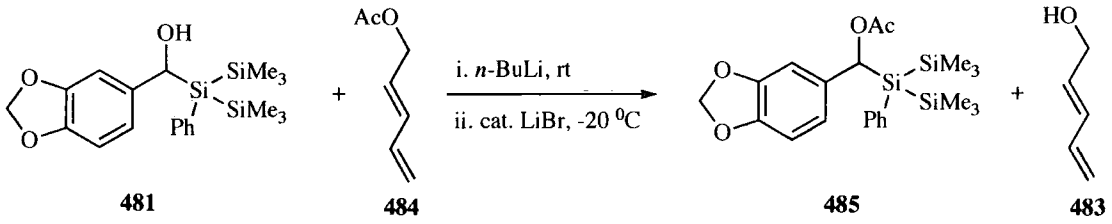


481 **479** **477**

Entry	R group	Yield (ds)
1	Ac	0%
2	TBDPS	55% (complex)
3	TBS	60% (80:13:7)

Table 11

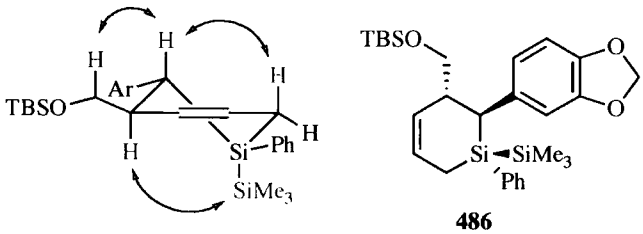
Initially, when diene **483** was protected with an acetate group (entry 1) no product was generated. Instead, the acetate group migrated to the silyl alcohol during the reaction. As a result, acetate-protected silyl alcohol **485** was isolated in a 40% yield, along with the unprotected diene **483** (**Scheme 144**).



481 484 485 483

Scheme 144

Undeterred by this result, when the hydroxydiene was protected as a silyl ether (entries 2 & 3) excellent results were obtained. With the TBDPS ether, silacyclohex-4-ene **477** was generated in modest yield, but as a complex mixture of stereoisomers. However, when the TBS ether was utilised, silacyclohex-4-ene **486** was generated in higher yield and with comparable diastereoselectivity to that obtained with piperylene (*cf.* Section 3.4). Formation of silacyclohex-4-ene **486** was confirmed by analysis of the ^{1}H NMR and MS data, which showed peaks at 6.03 and 5.80ppm characteristic of the two olefinic protons along with a mass spectrum (obtained by electron impact ionisation) showing the molecular ion to have m/z = 510. The stereochemistry of the major isomer was confirmed by nOe experiments to be identical to that obtained with piperylene (*cf.* Section 3.4) (**Figure 31**)

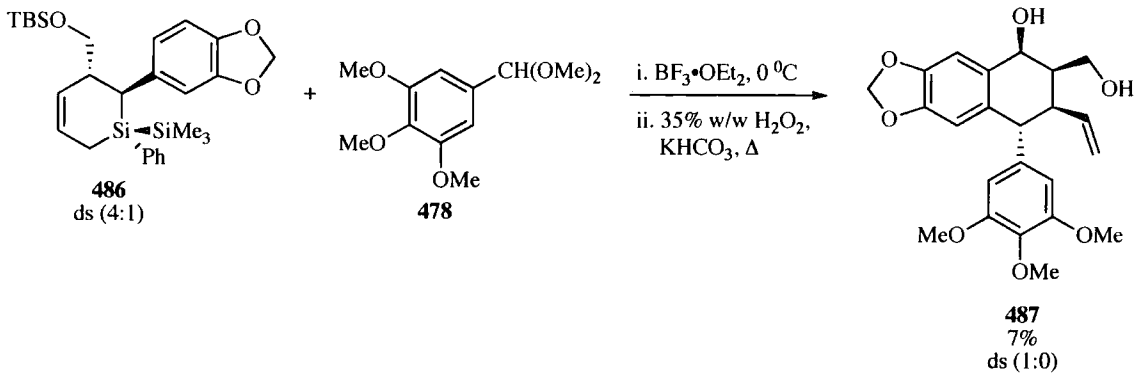


486

Figure 31

With a robust, high yielding procedure established to gain access to the desired silacyclohex-4-ene **486**, subsequent studies focused on its elaboration utilising the Hosomi-Sakurai reaction. Initial reaction of silacyclohex-4-ene **486** with acetal **478**, under the standard conditions, was disappointing generating only trace amounts (7%) of

the unprotected aryltetralindiol **487**. Interestingly, **487** was generated as a single diastereoisomer (**Scheme 145**).



Scheme 145

The low yield was believed to arise from cleavage of the labile TBS group during the cyclisation step with $BF_3 \bullet OEt_2$. Nevertheless, enough of the aryltetralindiol **487** was isolated to determine the relative stereochemistry by nOe experiments (**Figure 32**). Importantly, the single diastereoisomer possesses the same stereochemistry as that observed during earlier experiments (*cf.* Section 3.4).

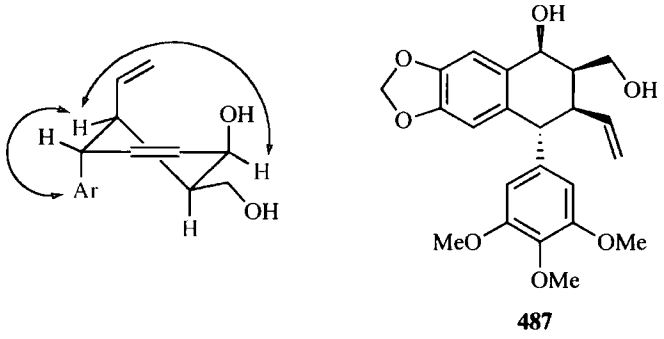
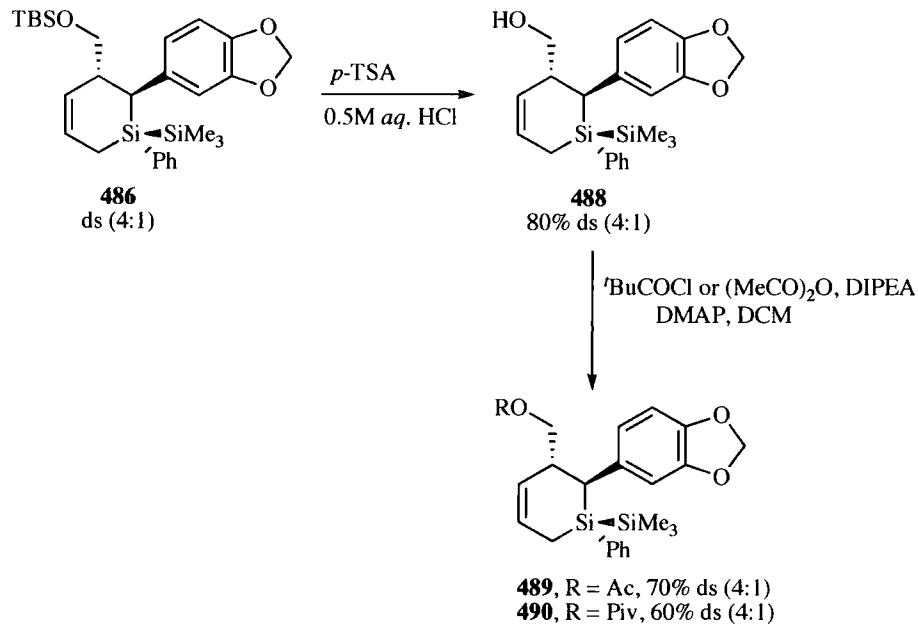


Figure 32

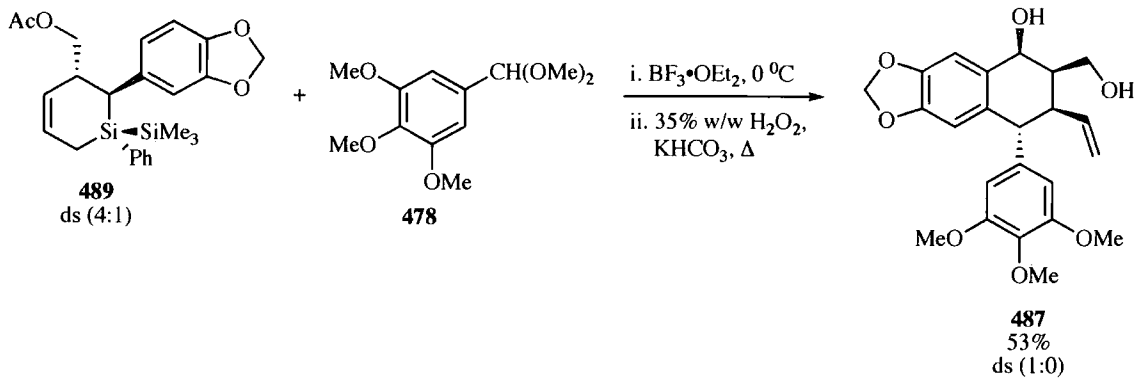
Having shown that aryltetralindiol **487** could be generated, albeit in low yield, attention turned to optimisation of the reaction in an effort to increase the overall yield. Initial studies focused on alteration of the protecting group. The TBS ether of silacyclohex-4-ene **486** was easily cleaved utilising *p*-TSA to give hydroxysilacyclohex-4-ene **488**. Generation of the hydroxylsilacyclohex-4-ene was confirmed by analysis of the IR and

^{1}H NMR spectra, which showed a broad signal at 3500 cm^{-1} for the hydroxyl group coupled with peaks at 3.55 and 3.45 ppm corresponding to the methylene protons. Subsequent protection was then undertaken to provide silacyclohex-4-enes **489** and **490** in good yield (**Scheme 146**).



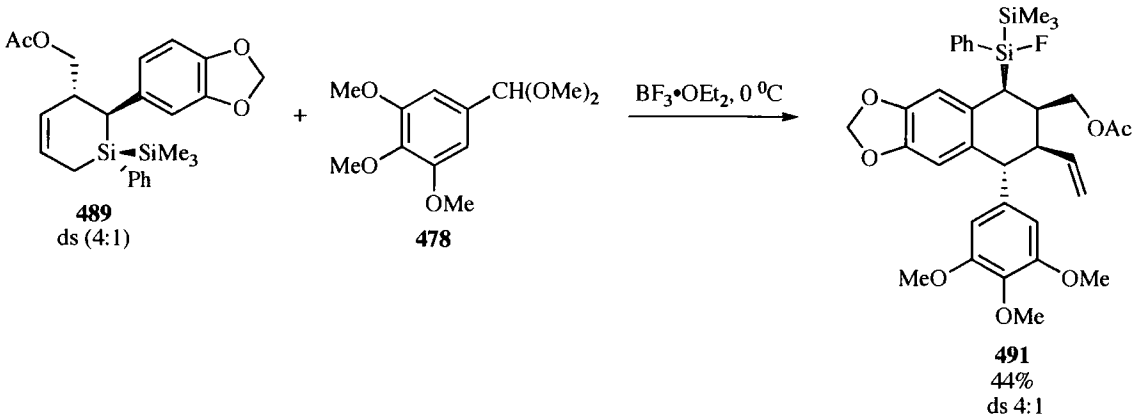
Scheme 146

Confirmation of acetate and pivaloate protection was confirmed by analysis of the ^{1}H and ^{13}C NMR, which showed signals at 1.99 and 1.17 ppm for the acetate methyl and ^{t}Bu protons respectively, coupled with signals at 171 and 178 ppm corresponding to the respective carbonyl carbons. With these two substrates in hand, attention turned to their Hosomi-Sakurai reaction. Gratifyingly, when subjected to the standard conditions outlined above, acetyl-protected silacyclohex-4-ene **489** underwent smooth conversion to the aryltetralindiol **487** as a single diastereoisomer in good yield. Pivaloyl silacyclohex-4-ene **490** also underwent the Hosomi-Sakurai reaction; although a considerable quantity of starting material remained when compared to the former reaction (**Scheme 147**).



Scheme 147

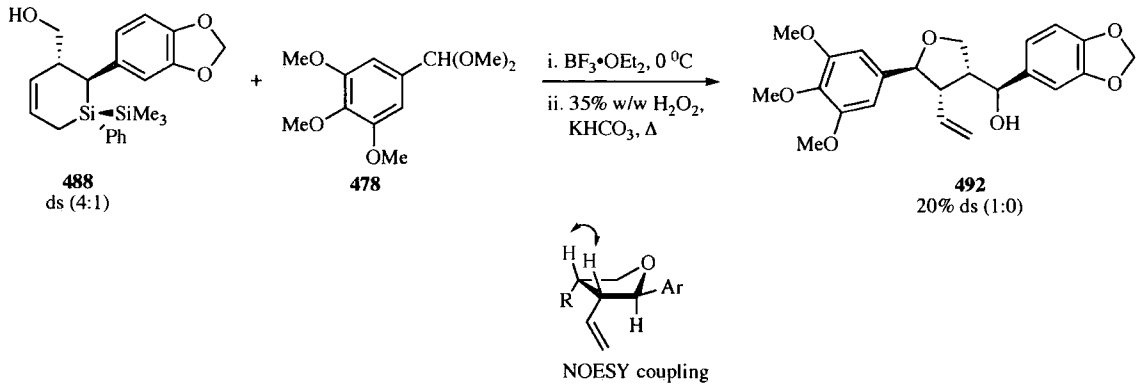
To probe this reaction, the crude material obtained before oxidation was purified by flash chromatography and fully analysed. Interestingly, the isolated product was established as the fully protected silyl fluoride species **491** by examination of the ^{1}H NMR (1.99ppm, acetyl methyl group) and mass spectra (*m/z* = 659 (MNa^{+}), 1295 ($2MNa^{+}$). This demonstrated that protection of the primary hydroxy group during the Hosomi-Sakurai reaction was crucial. Furthermore, examination of the ^{19}F NMR spectrum demonstrated that the fully protected silyl fluoride **491** was generated as a 4:1 mixture of diastereoisomers (**Scheme 148**).



Scheme 148

In addition, to further highlight the necessity for protection of the primary hydroxyl group during the Hosomi-Sakurai reaction, the free hydroxysilacyclohex-4-ene **488** and acetal **478** were treated under the standard conditions. Following oxidation of the

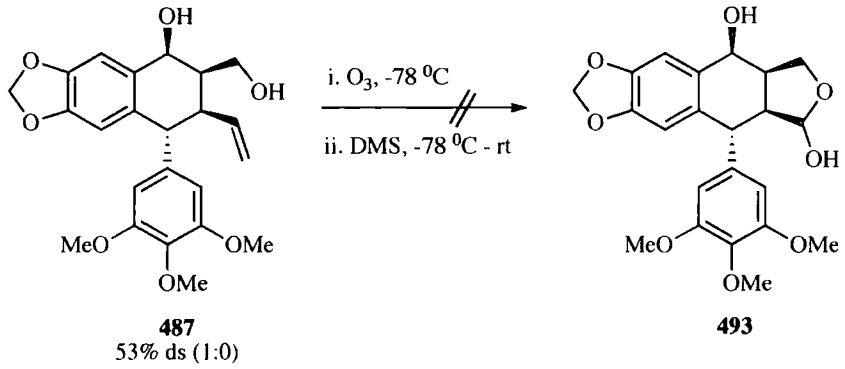
intermediate silyl fluoride, the highly substituted furan **492** (similar to that reported by Marsden *et al.*, *cf.* Section 3.2.2) was generated in modest yield as a single diastereoisomer. Formation of furan **492** was confirmed by analysis of the mass spectrum (obtained by electrospray analysis), showing *m/z* = 437 (MNa^+) and *m/z* = 851 ($2MNa^+$) and the stereochemistry was assigned by nOe experiments (**Scheme 149**).



Scheme 149

4.4.1 Synthesis of Epipicropodophyllin

With a robust procedure established to generate the desired aryltetralindiol **487**, subsequent work focused on elaboration of the aryltetralin **487** towards epipicropodophyllin. Initially it was proposed that elaboration of the double bond *via* ozonolysis would generate an aldehyde diol, which, under the reaction conditions, may generate lactol **493**. Subsequent oxidiation would provide the D ring lactone of epipicropodophyllin. However, attempts to implement this strategy utilising aryltetralin diol **487** failed to provide the desired product, instead an intractable mixture of products was identified by ^1H NMR (**Scheme 150**).



Scheme 150

As a result of this initial study, it was decided that a stepwise approach to the D ring lactone was required. This was to be achieved by first protecting the aryltetralin diol **487**, followed by oxidative cleavage of the alkene to give aldehyde **495**. If possible, over-oxidation to the carboxylic acid **496** was desirable, as concomitant deprotection and lactonisation would then generate epipicropodophyllin in one step. Otherwise, aldehyde **495** would be deprotected and under suitable conditions generate lactol **497**. Subsequent oxidation to the D ring lactone would complete the synthesis of epipicropodophyllin **356** (**Figure 33**).

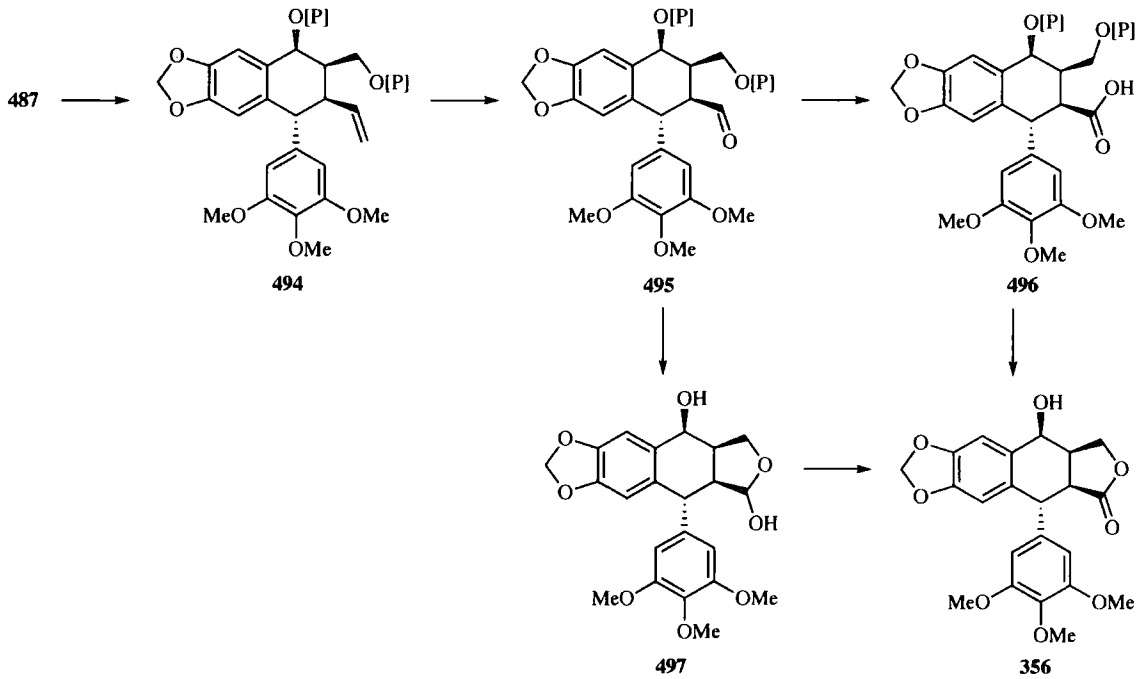
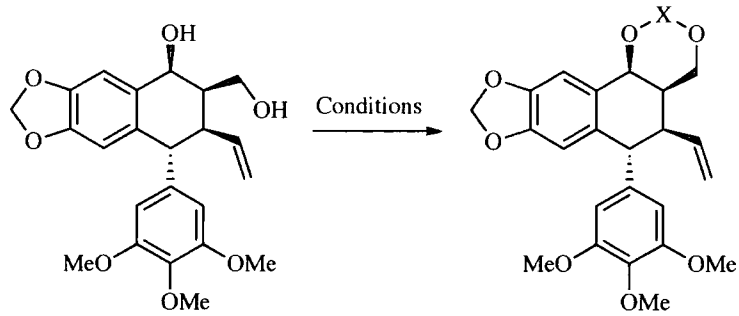


Figure 33

With this in mind, attention turned to the protection of aryltetralindiol **487**. A brief search of the lignan literature revealed that similar diol substrates were typically protected as cyclic acetals. To this end, a series of protecting groups were utilised to protect aryltetralindiol **487** (**Table 12**).

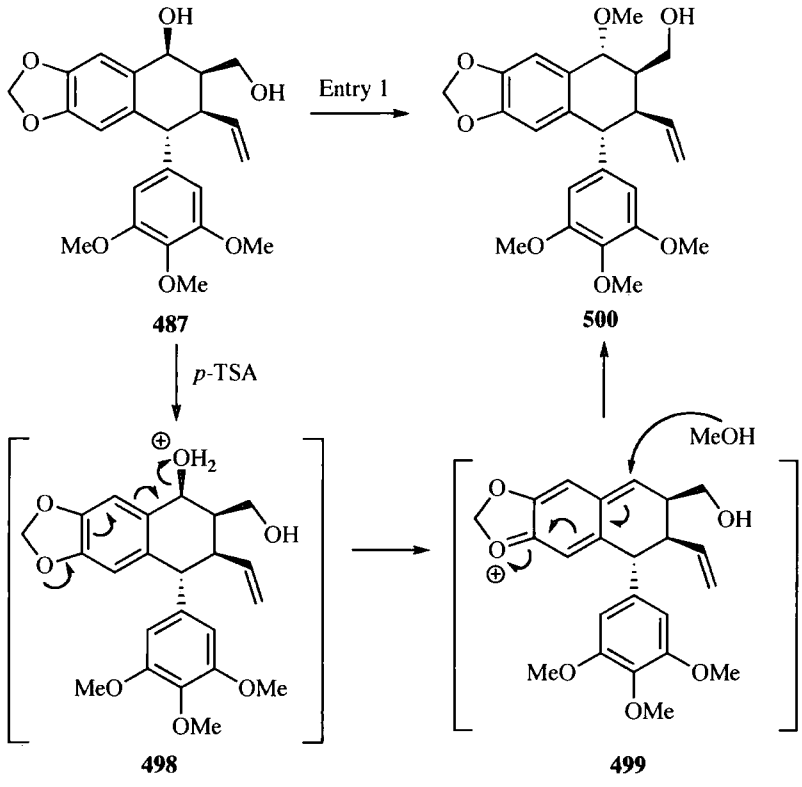


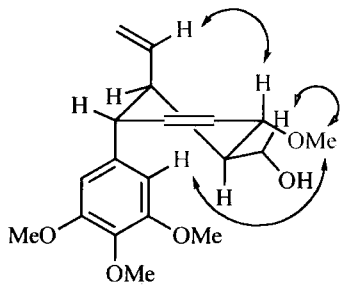
487

Entry	X	Conditions	Result
1	$(Me_2)C$	$(MeO)_2C(CH_3)_2$, *p*-TSA, acetone	decomposition
2	PhCH	Benzaldehyde, PPTS, DCM	Starting material recovered
3	$^tBu_2Si$	$(^tBu)_2SiCl_2$, Im., DCM	Starting material recovered
4	C=O	CDI, DMAP, DCM	80%

Table 12

Initial attempts to protect the aryltetralindiol **487** as an isopropylidene acetal (entry 1) were unsuccessful, leading primarily to decomposition. However, following flash chromatography a new compound was isolated as a single diastereoisomer in 20 % yield. This compound was fully analysed and determined by ^1H NMR (a signal at 3.40 ppm corresponding to a fourth methoxy group) and MS data (obtained by electrospray ionisation, indicationg a pseudomolecular ion at *m/z* = 451) to be the methoxyaryltetralin **500**. It was proposed that methoxyaryltetralin **500** arose from an acidic displacement of the secondary hydroxyl group, giving oxonium ion **499**, which then underwent attack by MeOH, released from 2,2-dimethoxypropane on the least hindered face. The stereochemistry of this isomer was confirmed by nOe experiments (**Scheme 151**).



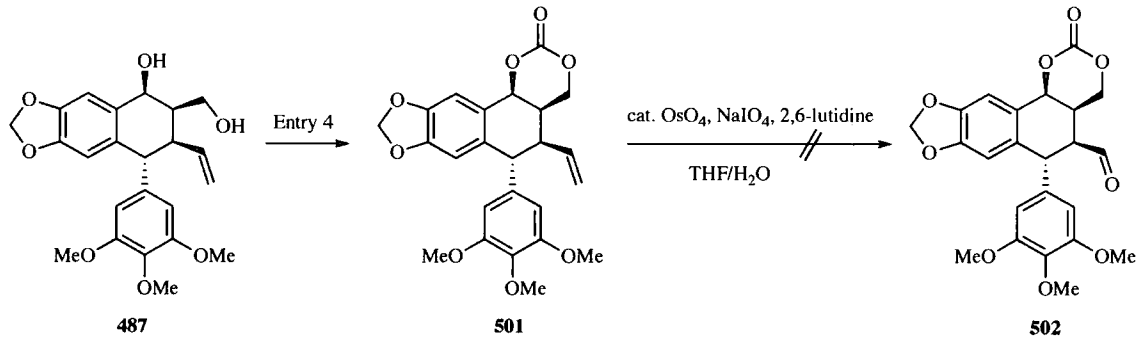


NOESY couplings

Scheme 151

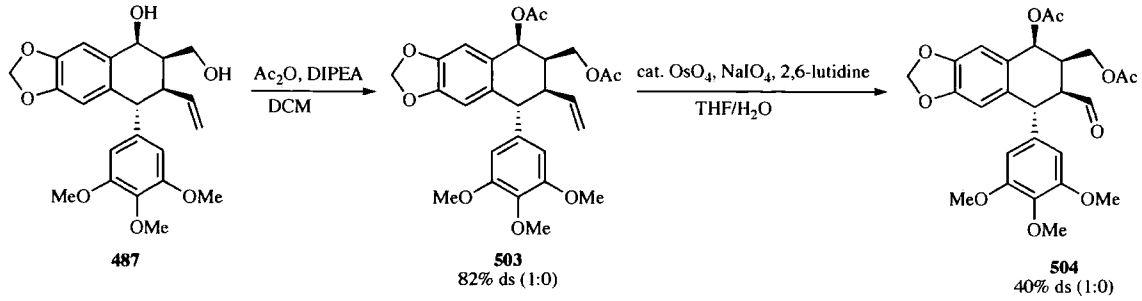
Subsequently, attempts to protect the aryltetralin diol **487** as a cyclic acetal or siloxane were equally unsuccessful, leading primarily to recovered starting material (entry 2 & 3). Despite these results, protection of the aryltetralin diol **487** was achieved in high yield utilising CDI (entry 4). This was confirmed by analysis of the IR and MS data which showed a strong signal at 1748 cm^{-1} corresponding to the carbonyl group coupled with a *m/z* = 451 (MNa^+, obtained by electrospray ionisation). Delighted with this result, attention turned to generating the protected aldehyde **502**. Previous work had shown that ozone was unable to elaborate the aldehyde, and therefore subsequent attempts would need to be undertaken utilising cat. OsO_4, $NaIO_4$ and 2,6-lutidine.

Consequently cyclic carbonate **501** was subjected to the above conditions, however, on work-up and analysis it was discovered that the compound had decomposed (**Scheme 152**).



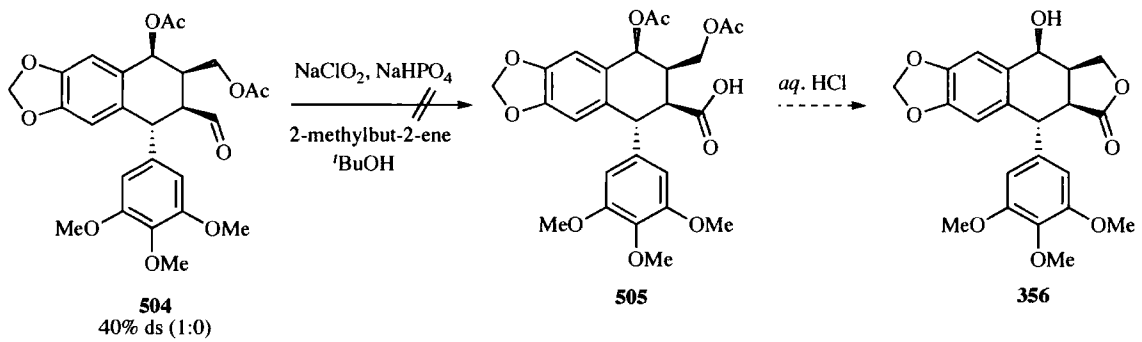
Scheme 152

Frustrated by these results, it was decided that, to advance aryltetralindiol **487** to the desired product, other protecting groups had to be explored. Firstly, acetate protection was attempted. Gratifyingly, when **487** was treated with two equivalents of acetic anhydride and an excess of DIPEA, the desired diacetate aryltetralin **503** was generated in 82% yield. This was confirmed by analysis of the IR spectra, which showed a strong signal at 1731cm^{-1} corresponding to the carbonyl groups, and ^{1}H NMR spectra which contained peaks at 2.08 and 2.00 ppm corresponding to the two acetate methyl groups. Delighted with this result, attention turned to generating the desired aldehyde. Pleasingly, when treated with cat. OsO_4, $NaIO_4$ and 2,6-lutidine, aryltetralindiacetate **503** was converted to the desired diprotected aldehyde **504** in 25% yield. This was confirmed by analysis of the ^{1}H and ^{13}C NMR spectra, which showed a signal at 9.03ppm for the aldehyde proton and a signal at 200ppm corresponding to the aldehyde carbon respectively (**Scheme 153**).



Scheme 153

Importantly, both the diacetate aryltetralin **503** and the diprotected aldehyde **504** were generated as single diastereoisomers. In addition, to increase the yield longer reaction times were employed. However, the maximum yield obtained after 3 h was 40%. The remaining material consisted of starting material and decomposition products (60%). Undeterred by the low yield, elaboration of the diprotected aldehyde **504** to epipicropodophyllin was then undertaken. It was proposed that this could be achieved in two steps by oxidation of the aldehyde to the carboxylic acid, followed by concomitant deprotection of the acetate groups and lactonisation in aqueous acid (**Scheme 154**).

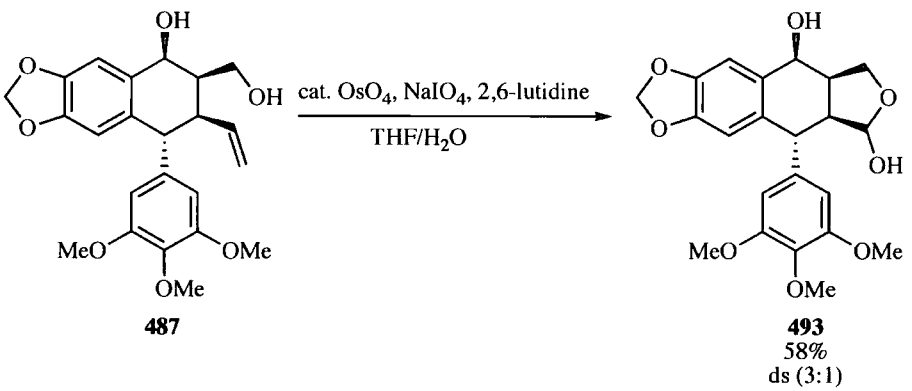


Scheme 154

Disappointingly, efforts to oxidise the aldehyde to the desired carboxylic acid generated complex mixtures of products, none of which corresponded to the desired product. The reason for this failure was not obvious and there was concern that any oxidation of the aldehyde would be difficult.

Consequently, our attention turned back to the direct elaboration of aryltetralindiol **487** to the lactone. As highlighted earlier, aryltetralindiol **487** could not be elaborated to the lactol **493** utilising ozone. However, conditions for the elaboration of the vinyl group to the corresponding aldehyde had been discovered with aryltetralindiacetate **503**. Therefore, it was our intention to employ these conditions with the unprotected aryltetralin diol **487**.

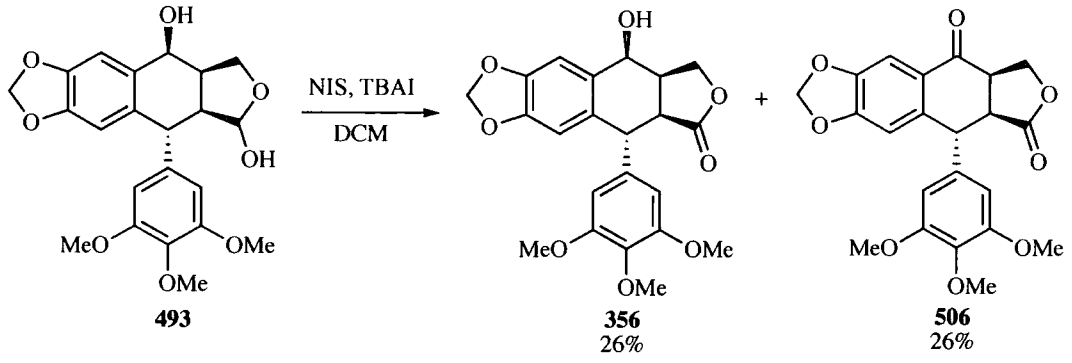
Pleasingly, when treated with cat. OsO_4 and $NaIO_4$ as previously described, aryltetralindiol **487** was converted to the lactol **493** in 58% yield as a 3:1 mixture of diastereoisomers about the new lactol chiral centre. This was confirmed by subsequent oxidation, which gave rise to a product that was isolated as a single diastereoisomer (**Scheme 155**).



Scheme 155

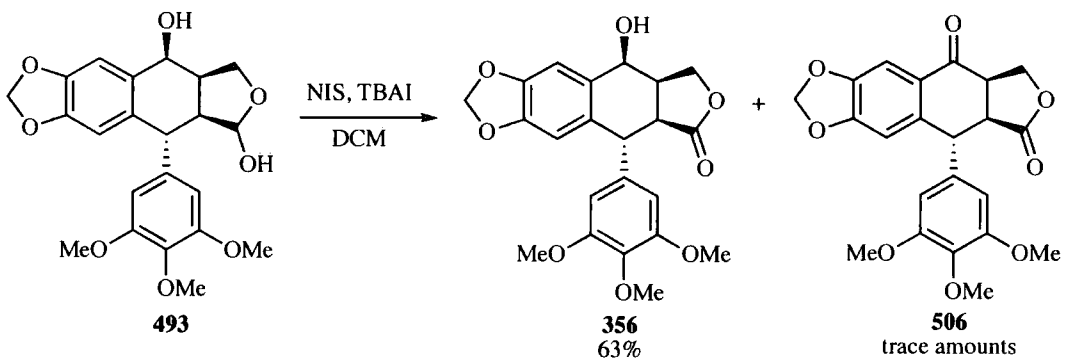
The lactol product was confirmed by analysis of the ^1H NMR spectra which showed a new signal at 4.70ppm corresponding to the lactol CH, and MS data, which gave a pseudomolecular ion at m/z = 855 ($2MNa^+$) by electrospray ionisation. Delighted with this result, attention turned to the oxidation of lactol **493** to the desired lactone. A brief search of the literature revealed that oxidation could be achieved in the presence of a secondary alcohol with NIS and TBAI.[181] Therefore, lactol **493** was subjected to 5eq. NIS and 2eq. of TBAI in DCM. Following isolation and purification by flash

chromatography, the desired product, epipicropodophyllin **356** was generated in 26% yield as a single diastereoisomer. However, a second product was also isolated as a single diastereoisomer in 26% yield. This was determined to be the undesired over oxidation product picropodophyllone **506**. The identities of both products were confirmed by comparison of the ^{1}H NMR with that given in the literature (**Scheme 156**).



Scheme 156

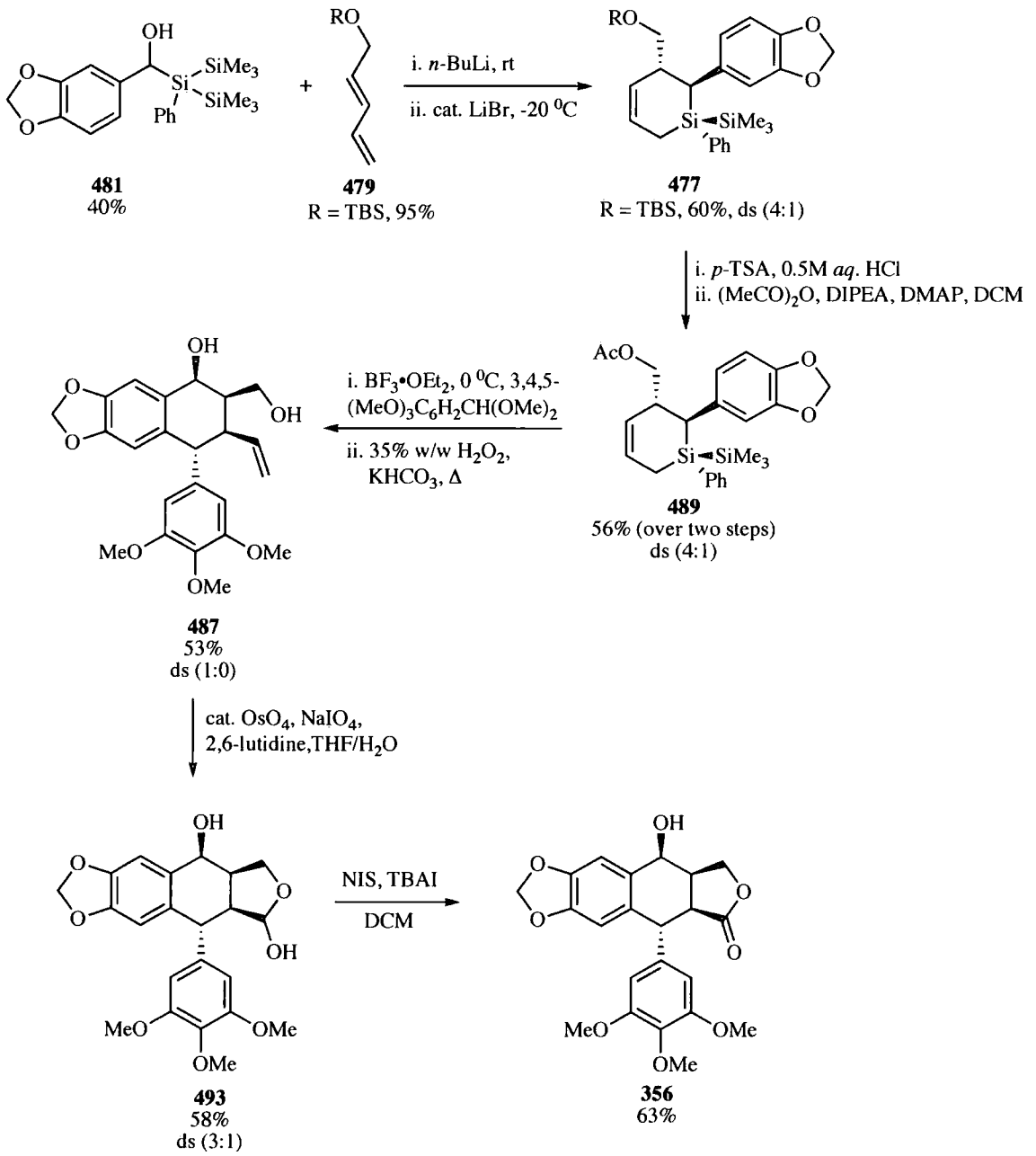
Pleased to have completed the synthesis of epipicropodophyllin, but disappointed with the oxidation yield, a subsequent experiment was undertaken to try to improve this. A further literature search indicated that the reaction could be undertaken with significantly less NIS and TBAI. Therefore, the reaction was repeated with 1eq. NIS and 0.4eq. TBAI. Gratifyingly, when isolated and subjected to flash chromatography epipicropodophyllin **356** was generated in 63% yield with only trace amounts of the over oxidation product **506** (**Scheme 157**).



Scheme 157

4.5 Conclusion

In conclusion, this work has demonstrated that highly functionalised silacyclohex-4-enes, derived from silene-diene cycloaddition reactions of highly functionalised silenes and dienes, are viable substrates for the total synthesis of aryltetralin lignan lactones. The key steps in the synthesis involve the Hosomi-Sakurai reaction of silacyclohex-4-enes with electron rich acetals and elaboration of the vinyl group to the lactone ring **(Scheme 158)**.



Scheme 158

The following chapter will focus on other studies that were undertaken alongside this work, future work related to the studies highlighted in earlier chapters and conclude this thesis.

5 Other Studies and Future Work

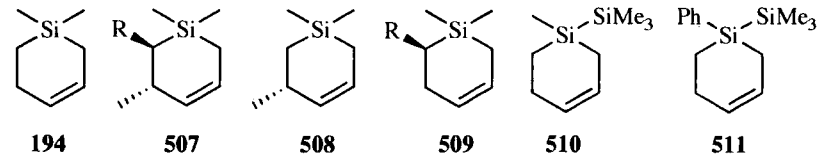
5.1 Future studies with the Hosomi Sakurai reaction

5.1.1 Introduction

It was proposed in Chapter 3 that the stereochemistry of the vinyl group generated during the Hosomi-Sakurai reaction arises from selective approach of the oxonium ion to the least hindered (convex) face of the major silacyclohex-4-ene isomer when it adopts a pseudo-boat conformation. This approach would avoid prow interactions between the methyl group and a C-6 hydrogen. At this stage it is unclear if this is accurate, therefore future work will focus on trying to provide evidence to support this statement.

5.1.2 Strategy

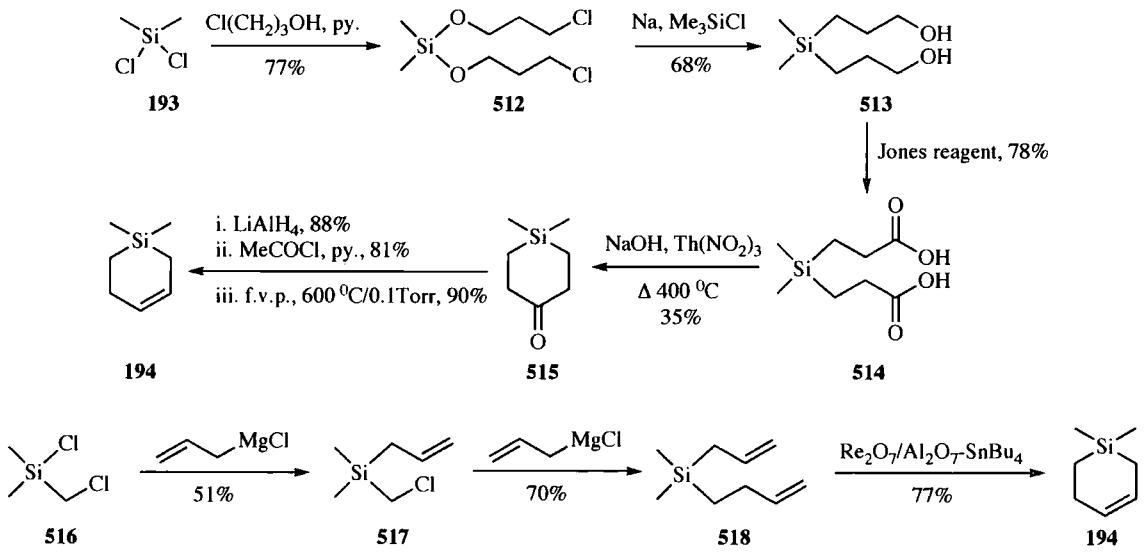
This is to be achieved by generating a series of silacyclohex-4-ene substrates **194, 507-511**, possessing various substituents at different positions around the ring. This means that when silacyclohex-4-enes **194, 507-511** are subjected to the Hosomi-Sakurai reaction, different stereochemistries will be imparted into the final molecule due to the position of the substituent. Ultimately, one position and substituent around the ring will provide the same stereochemical outcome as that observed for the fully substituted silacyclohex-4-ene. Therefore, by inference, the substituent responsible for the stereochemical outcome of the fully substituted silacyclohex-4-ene will have been identified and the above statement proved or disproved (**Figure 34**).



194 507 508 509 510 511

Figure 34

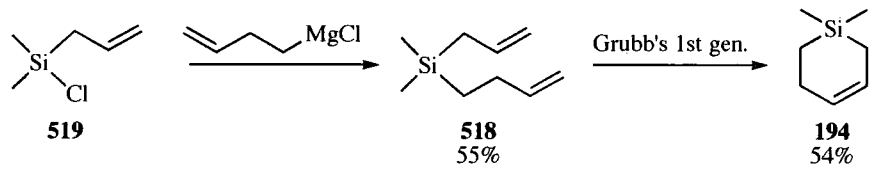
To begin this study, a brief search of the literature was undertaken to provide a synthetic route to the simplest silacyclohex-4-ene **194**. This search revealed very few reports, however silacyclohex-4-ene **194** had previously been synthesised *via* two routes. The first involved a lengthy 7-step synthesis starting from dichlorodimethylsilane **193**.[56] Despite the length, silacyclohex-4-ene **194** was generated in a respectable 10% overall yield. The second route describes the synthesis of silacyclohex-4-ene **194** in 3 steps, starting from chloro(chloromethyl)dimethylsilane **516**. This route involved sequential addition of allylmagnesium chloride to dichlorosilane **516** to generate dimethylallyl(n-butenyl)silane **518**. Subsequent ring-closing-metathesis utilising Re_2O_7-Al_2O_3 and $SnBu_4$ generated the desired silacyclohex-4-ene **194** in 77% yield (**Scheme 159**).[182]



Scheme 159

As a direct result of the literature search, it was our intention to modify the shorter route to incorporate one less step. This is possible by reacting commercially available allylchlorodimethylsilane **519** with but-3-enylmagnesium bromide to generate the same

allyl(butenyl)dimethylsilane precursor **518**. Subsequent ring-closing metathesis with Grubbs 1st generation catalyst would generate the desired silacyclohex-4-ene **194** in only 2 steps. Gratifyingly, when this strategy was implemented, the desired silacyclohex-4-ene **194** was generated in a respectable 25% yield over 2 steps. The two products **518** and **194** were identified by comparing their ^{1}H NMR data with that given in the literature (**Figure 35**).[56,183]

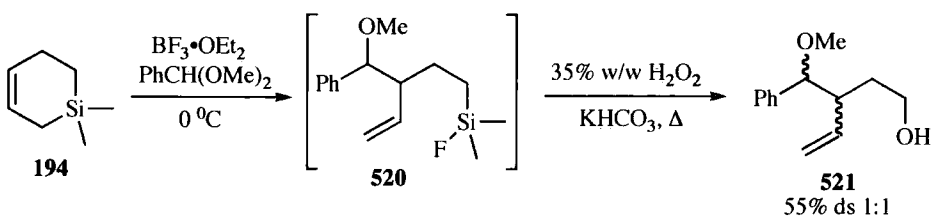


519 **518** 55% **194** 54%

Figure 35

5.1.3 Application in the Hosomi-Sakurai reaction

As described in the previous section, it was now our intention to utilise the silacyclohex-4-ene **194** in the Hosomi-Sakurai reaction. Therefore, silacycohex-4-ene **194** was combined with benzaldehyde dimethyl acetal and treated with $BF_3 \bullet OEt_2$ to give fluorosilane **520**. The intermediate fluorosilane **520** was not purified, but directly subjected to the Tamao oxidation conditions to provide mono-protected diol **521** in 55% yield over the two steps (**Scheme 160**).



194 **520** **521** 55% ds 1:1

Scheme 160

As expected, ^{1}H NMR analysis of the mono-protected diol **521** revealed that the product had been generated as a 1:1 mixture of diastereoisomers. This was in agreement with our proposal, as there is no stereochemistry in the starting silacyclohex-4-ene **194** to be transferred to the final compound, and therefore a 1:1 mixture of diastereoisomers is

expected. Pleased with this initial result, future work will now concentrate on the synthesis of the other substrates **507-511** outlined in **Figure 34**.

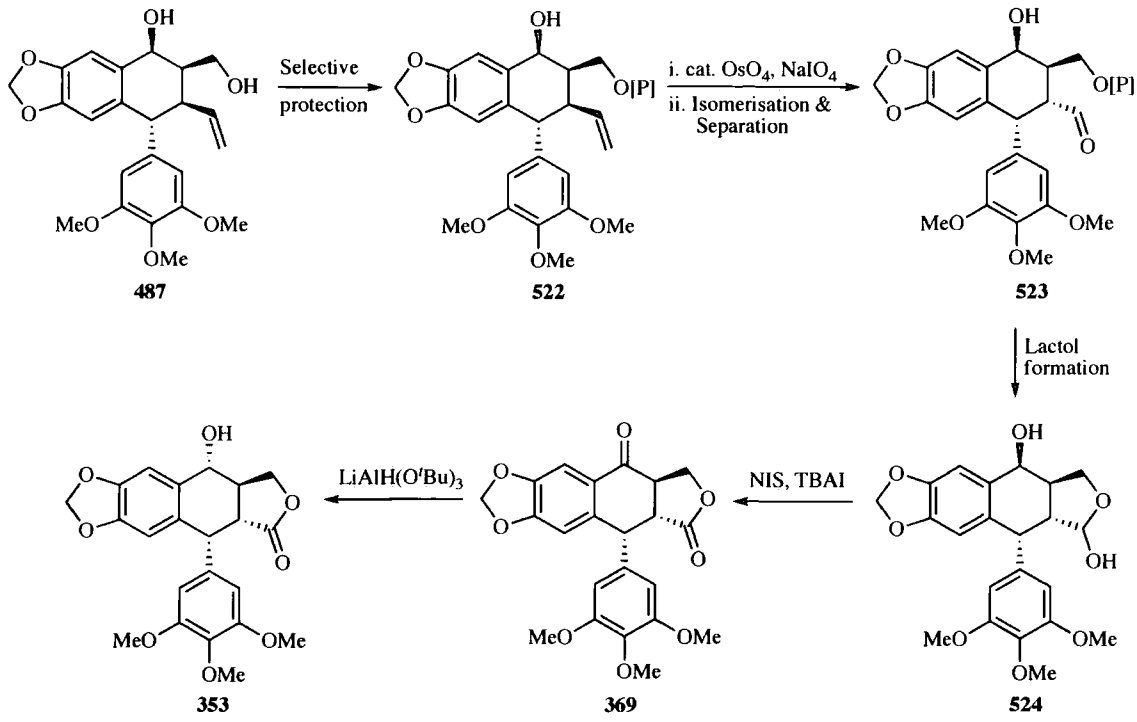
5.2 Future synthesis of Podophyllotoxin

5.2.1 Introduction

Pleased to have completed the synthesis of epipicropodophylin in Chapter 4, our aim was for future work to focus on completing the synthesis of podophyllotoxin and other aryl tetralin lignan lactones, despite the fact that synthesis of epipicropodophyllin can be considered a formal synthesis of podophyllotoxin.

5.2.2 Strategy

Our intention is to utilise the same synthetic strategy outlined in the previous chapter to give access to the aryl tetralin diol **487**. Once synthesised, the lactone ring would not be formed at this stage, as stereochemical manipulations have to be undertaken. Instead, protection of the primary hydroxyl group would stop lactol formation when treated with cat. OsO_4 and $NaIO_4$ (*cf.* **Scheme 155**). Therefore, when subjected to these conditions it was hoped that aldehyde **523** could be generated. At this stage, isomerisation of the aldehyde **523** would be undertaken with thermodynamic control to give a mixture of stereochemistries that could be separated by flash chromatography. Once separated, the primary hydroxyl group of the desired isomer would be deprotected and lactolised *in situ*. Subsequent overoxidation with NIS and TBAI (*cf.* **Scheme 156**) would generate oxo lactone **369** which can be selectively reduced with $LiAlH(O^tBu)_3$ (**Scheme 161**).



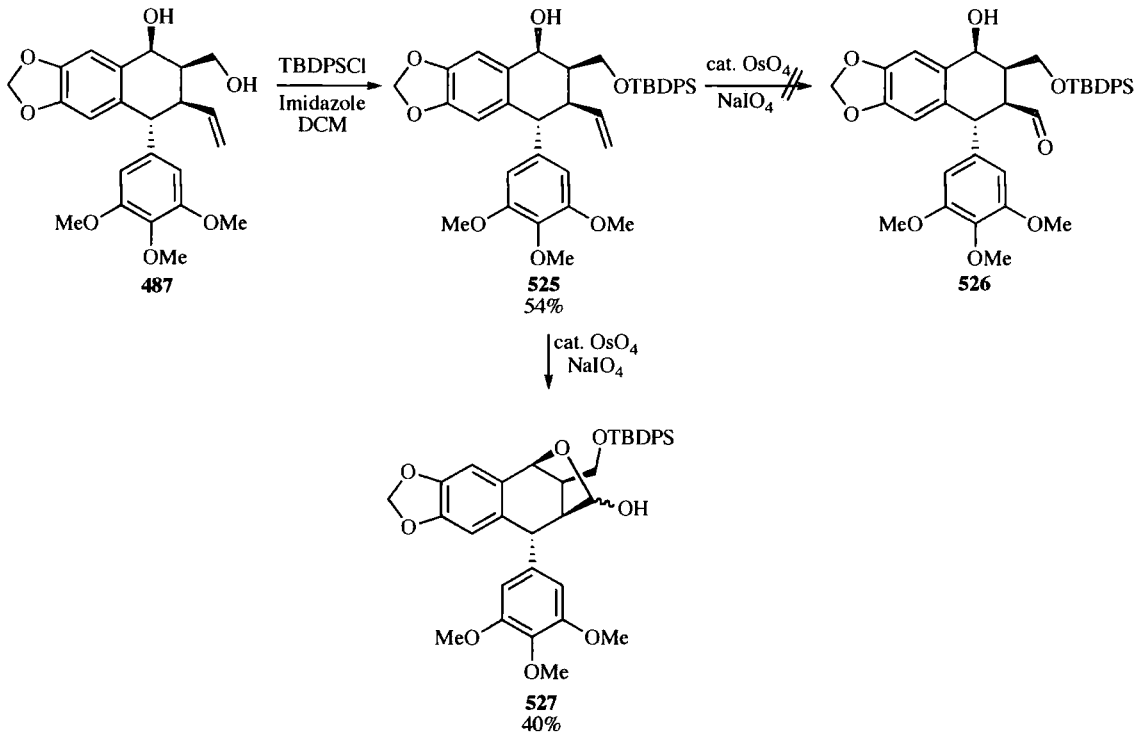
Scheme 161

5.2.3 Synthesis of Podophyllotoxin

With this strategy in mind, a brief investigation of the literature was undertaken to discover a protecting group suitable for this route, given that other protecting groups had been difficult to introduce or were too labile during subsequent reactions (*cf.* Section 4.3.2). Also, selectivity over primary vs secondary alcohol protection maybe an issue. Therefore, it was our intention to use a bulky silicon protecting group such as TBDPS. Gratifyingly, when treated with TBDPSCl and imidazole in DCM at room temperature the monoprotected diol **525** was generated, albeit in a low 54% yield. This was confirmed by analysis of the ^{1}H NMR and MS data which, respectively, revealed a new peak at 0.99 ppm corresponding to the ^{t}Bu group and a pseudomolecular ion at *m/z* = 675 (MNa^+) obtained by electrospray ionisation.

Despite the low yield, protected diol **525** was then subjected to cat. OsO_4 and $NaIO_4$ to generate the desired aldehyde **526**. Surprisingly, the desired aldehyde **526** was not

isolated from the reaction, but instead a cross ring lactol **527** was isolated in 40 % yield. This was confirmed by examination of the ^{1}H NMR, which revealed a new signal at 4.31 ppm corresponding to the lactol CH. This ^{1}H NMR signal corresponds closely to the signal observed for the same proton of lactol **493** (4.70 ppm). Also, MS data (*m/z* = 1331 ($2MNa^+$), obtained by electospray ionisation further confirmed the generation of lactol **527** (**Scheme 162**).



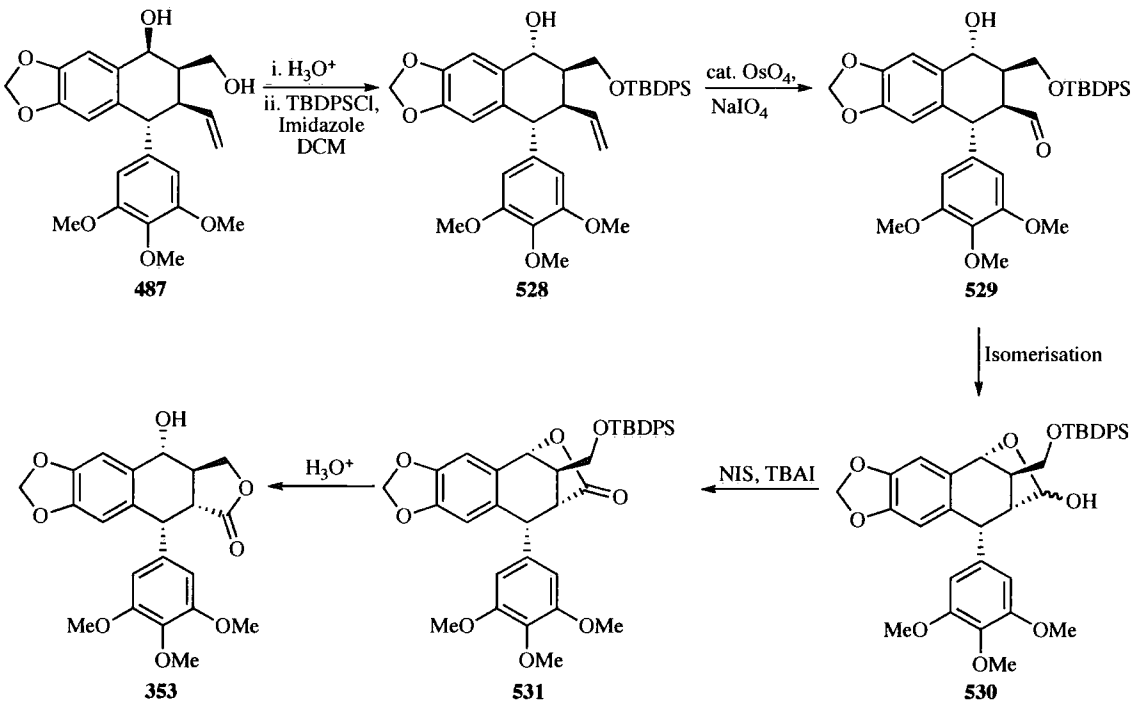
Scheme 162

5.2.4 Future studies

Disappointed by this result and with no time remaining, a new strategy for future studies was proposed. The new strategy begins with an acidic isomerisation of the secondary hydroxyl group utilising aqueous acid. Subsequent selective protection of the primary hydroxyl group would again be undertaken with TBDPSCl, despite the low yields. Monoprotected diol **528** would then be subjected to cat. OsO_4 and $NaIO_4$ (*cf.* **Scheme 155**) to give the desired aldehyde **529**. This time it is hoped that the cross ring lactol

would not form, as the secondary hydroxyl group at C-4 is present on the opposite ring face.

At this stage aldehyde **529** would be isomerised as before. However, in this case it was believed that, when isomerised, the desired aldehyde isomer would lactolise *in situ* (*cf.* **Scheme 162**) with the secondary hydroxyl group and give lactol isomer **530** as the sole product. This process would alleviate issues discussed earlier regarding the difficulty involved in isomerising the C-2 stereocenter (*cf.* Section 4.2.4) If lactol **530** was formed, it could be oxidised with NIS and TBAI to the lactone **531**. Finally hydrolysis, deprotection and cyclisation with aqueous acid would generate podophyllotoxin **353** in one step (**Scheme 163**).

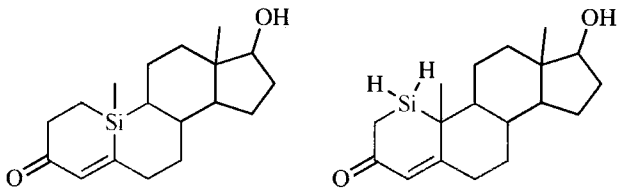


Scheme 163

5.3 Synthesis of Silasteroids

5.3.1 Introduction

Alongside the work described in the proceeding chapters, a collaborative study was initiated with Ass. Prof. Ottosson at Uppsala University in Sweden. This study was undertaken to investigate the synthesis of bicyclic silicon species *via* intramolecular silene Diels-Alder reactions. If successful, this new synthetic methodology will be utilised in the synthesis of complex bicyclic silicon species that may be elaborated to silasteroids similar to **532** and **533** (**Figure 36**).



532 **533**

Figure 36

To begin our collaboration, it was our intention to synthesise simple unsubstituted bicyclic ring systems (marked in red, **Figure 36**), by intramolecular silene Diels-Alder reactions, to locate a silicon group at the bridgehead position and within the six membered ring. To achieve this, suitable substrates for the intramolecular Diels-Alder reaction were required. Consequently, this became the first objective of the project.

5.3.2 Strategy

A retrosynthetic analysis of the two species was undertaken first. This revealed that bicyclic silicon species **534** could be generated from the corresponding silene precursor **535**, which in turn could be generated from the corresponding iodooctadiene **536** and acylpolysilane **537**. The second bicyclic silicon species **538** could be generated from the

corresponding silene precursor **539** which in turn could be generated from nonadienal **540** and tetrakis(trimethylsilyl)silane **94** (**Figure 37**).

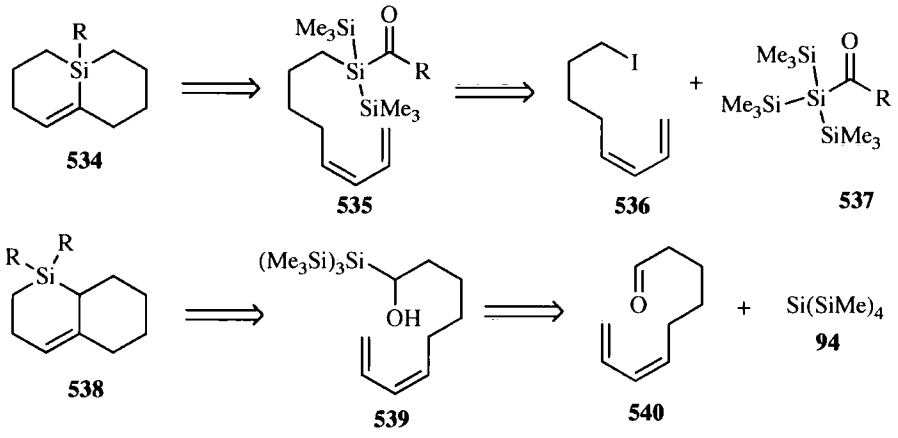
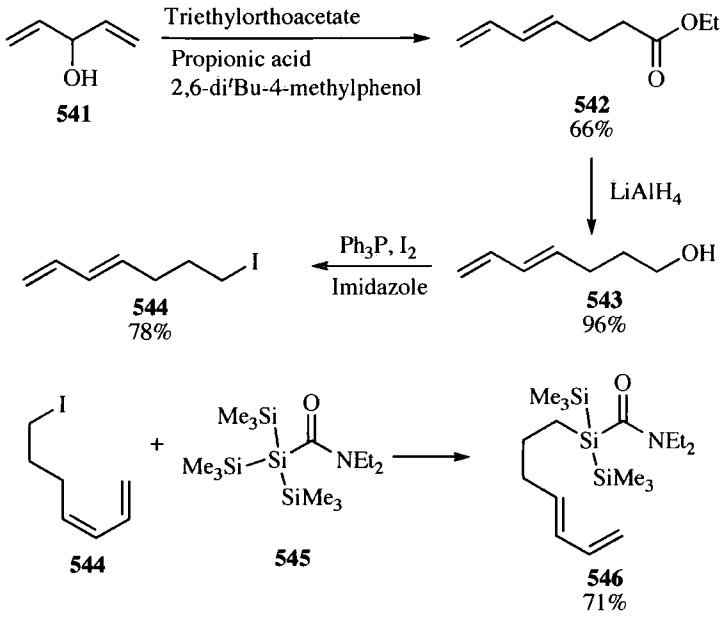


Figure 37

With this strategy in mind, a brief search of the literature revealed that the desired iodooctadiene **536** and nonadienal **540** would require lengthy and difficult synthetic campaigns. Therefore, to aid a more rapid assessment of this methodology, shorter diene precursors, accessible by concise synthetic routes was essential. Pleasingly, previous work in the Ottosson group had demonstrated an elegant and short synthesis of iodoheptadiene **544** starting from penta-1,4-dienol **541**.[184] They went on to couple iodoheptadiene **544** with diethylaminoacylpolysilane **545** to give access to the silene precursor **546** in good yield. If cyclised, silene precursor **546** would have generated a [5,6] fused ring system. However when subjected to sealed tube NMR experiments, silene precursor **546** generated only decomposition products (**Scheme 164**).



Scheme 164

Consequently, it was our intention to utilise this elegant route to generate shorter chain silene precursors **549** and **550**. Firstly, heptadienol **543** would be synthesised on a large scale. A portion would then be taken through to iodoheptadiene **544** and the remainder oxidised to heptadienal **547**. Once synthesised, iodoheptadiene **544** would be coupled with the more stable *t*-butyl acyl polysilane **548** and heptadienal **547** would be coupled with tetrakis(trimethylsilyl)silane **94** (**Figure 38**).

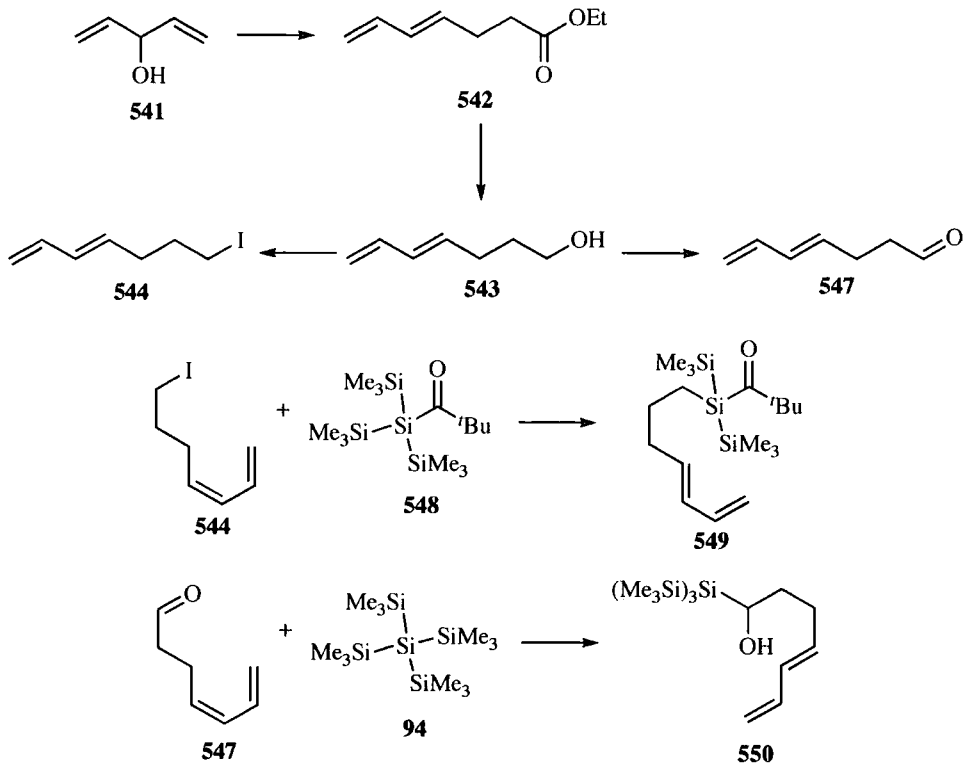
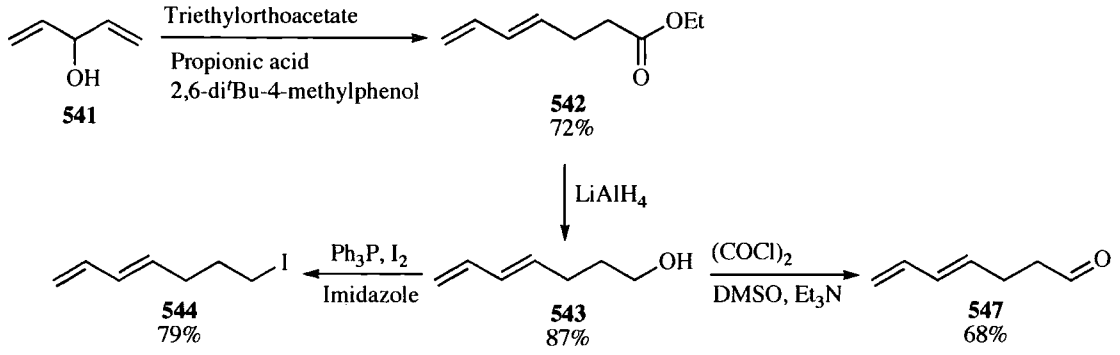


Figure 38

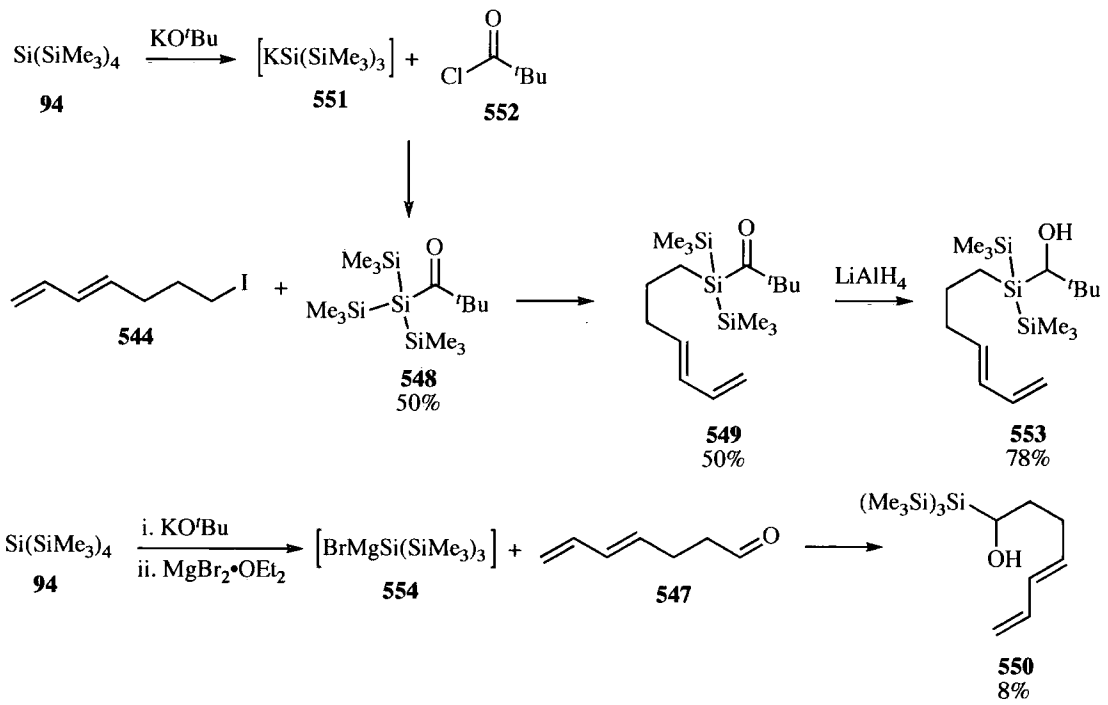
5.3.3 Synthesis of Silene Precursors

Gratifyingly, the synthesis of iodoheptadiene **544** proceded smoothly following the established synthesis. In addition, heptadienal **547** was generated in good yield *via* Swern oxidation of heptadienol **543**. At every stage the products were identified by comparing the ^{1}H NMR data for the synthetic compound with data given in the literature (**Scheme 165**).[184,185]



Scheme 165

With the desired diene moieties in hand, attention turned to their coupling with the silicon moieties **548** and **94**. To begin, *t*-butyl acyl polysilane **548** had to be synthesised. This was achieved in good yield by reacting silylpotassium **551** in toluene with pivaloyl chloride **552**.[186] Subsequently, acylpolysilane **548** was coupled with iodoheptadiene **544** to give the desired silene precursor **549**. Additionally, reduction of silene precursor **549** was effected with $LiAlH_4$ to generate another silene precursor **553**. Finally, heptadienal **547** was coupled with the silyl Grignard reagent **554** from tetrakis(trimethylsilyl)silane **94** to give the desired silene precursor **550**. Each silene precursor **549**, **550** and **553** was identified by comparison of the ^1H NMR data with that obtained by Ottosson *et. al.* for silene precursor **546** (**Scheme 166**).

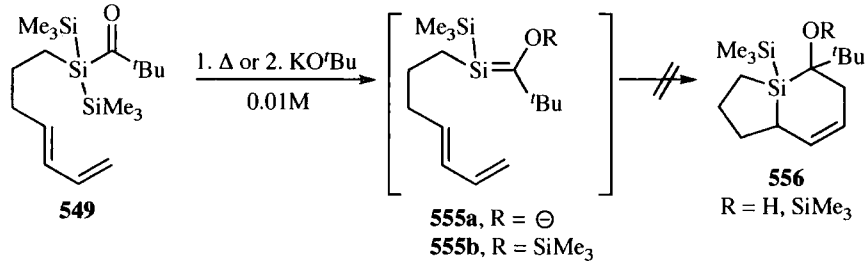


Scheme 166

5.3.4 Synthesis of bicyclic silicon species

With the silene precursors **549**, **550** and **553** in hand, attention turned to their application in the intramolecular silene Diels-Alder reactions. Firstly, silene precursor **549** was investigated utilising two different methods for silene generation. The first

involved heating silene precursor **549** at high dilution in a microwave tube to generate a Brook-type silene **555a** which would be trapped to give a [5,6] fused ring system **556**. The second involved reaction of silene precursor **549** at high dilution with KO^{t}Bu to give a silenolate **555b**, which would be trapped as the [5,6] fused ring system **556** (**Scheme 167**).



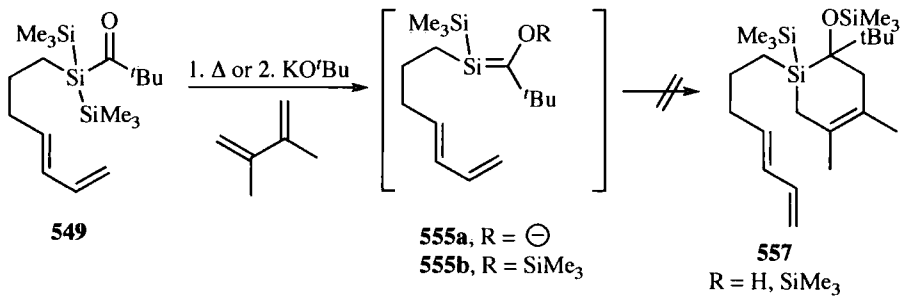
549

555a, R = ⊖
555b, R = $SiMe_3$

556
R = H, $SiMe_3$

Scheme 167

Disappointingly, every effort to generate the desired product failed, returning either unchanged starting material or decomposition products. In an effort to probe these reactions and determine if silenes **555a/b** were being generated, 2,3-dimethylbutadiene was utilised to trap the silene instead of the tethered diene. This would enable an intermolecular reaction to take place, generating silacyclohex-4-ene **557** and confirm the formation of silenes **555a/b**. Unfortunately, utilising either set of conditions, acyl polysilane **549** polymerised (**Scheme 168**).



549

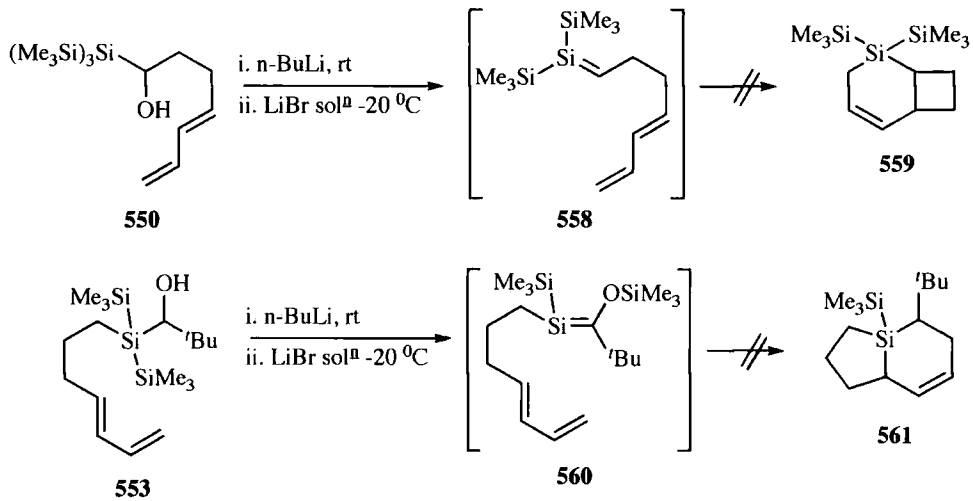
555a, R = ⊖
555b, R = $SiMe_3$

557
R = H, $SiMe_3$

Scheme 168

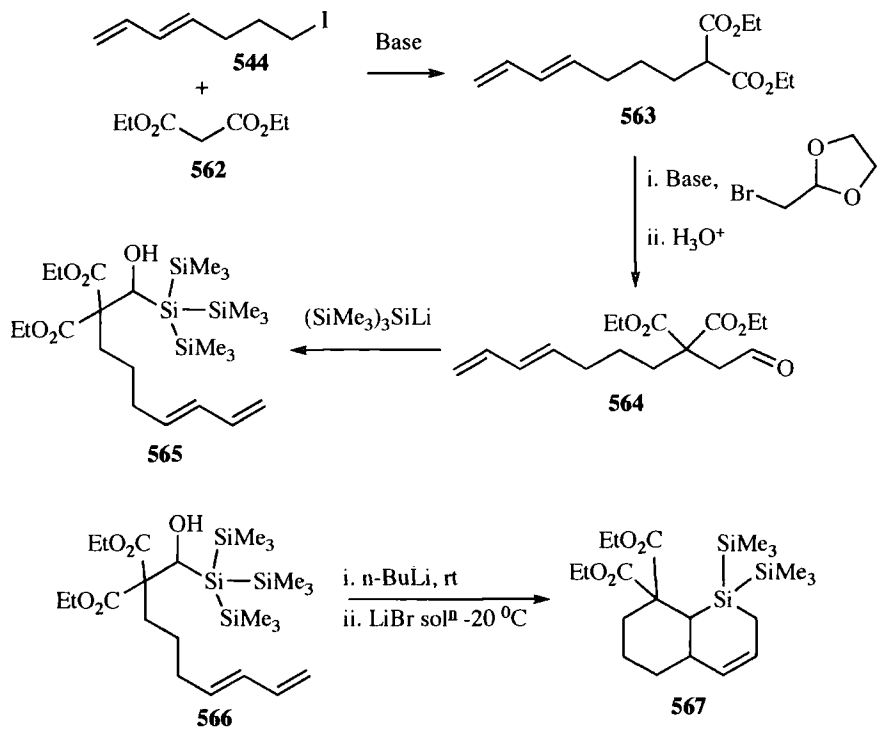
Frustrated by this initial set of results, attention turned to the use of silene precursors **550** and **553**. Our intention was to utilise silene precursors **550** and **553** in a modified

Peterson reaction utilising the conditions developed by Whelligan. Therefore, silene precursors **550** and **553** were treated at high dilution with n-BuLi at room temperature, then cooled to -20 °C and treated with a 0.03M solution of LiBr in ether. Having been left overnight, the reactions were quenched with *aq.* NH_4Cl and extracted with ether. Disappointingly, ^1H NMR analysis of the crude products showed only decomposition products had been generated during these reactions (**Scheme 169**).



Scheme 169

The reasons for this were unclear. However, it was proposed that either the polarity of the silene was incorrect, leading to poor orbital overlap with the diene and a large energy gap or the diene tail was unable to orientate itself towards to silene because of its decreased length. Therefore, future studies will look initially to lengthen the diene chain, then look to orientate the diene towards the silene by introducing geminal substituents to promote a Thorpe-Ingold effect (**Scheme 170**).



Scheme 170

Work currently undertaken within the group has briefly investigated the strategy outlined above. These results will not be presented at this time. Needless to say, bicyclic silicon species are still an elusive target to approach by means of an intramolecular silene Diels-Alder reaction, but work in the group continues towards this goal.

6 Experimental Procedures

6.1 General Procedures

All reactions were carried out under an argon atmosphere in glassware dried under high vacuum by a heat-gun unless otherwise stated.

Solvents

40-60 pet. ether refers to the fraction of petroleum ether boiling between 40 and 60 °C and was redistilled before use. Ether refers to diethyl ether. Solvents were distilled from the following reagents under nitrogen atmosphere: ether and THF (sodium benzophenone ketyl); DCM, xylene and benzene (calcium hydride); chloroform (phosphorus pentoxide) and methanol (sodium methoxide) or obtained from Innovative Technology Solvent Purification System. In cases where mixtures of solvents were utilised, the ratios refer to the volumes used.

Reagents

Reagents were used as supplied unless otherwise stated. Lithium bromide was made anhydrous by heating at 100 °C at 0.06 mmHg for 3 h. Magnesium bromide was synthesised by addition of 1,2-dibromoethane to an equivalent amount of magnesium in ether. Aldehydes and dienes were distilled, immediately prior to use, from anhydrous calcium sulphate and sodium borohydride, respectively.

Chromatography

Flash chromatography was carried out using silica gel 40-63μ 60Å. Analytical thin layer chromatography (TLC) was performed using precoated glass-backed plates (silica

gel 60Å F_{254}) and visualised by UV radiation at 254 nm, or by staining with phosphomolybdic acid in ethanol or potassium permanganate in water.

Melting point

All melting points were determined using a Gallenkamp melting point apparatus and are uncorrected.

Gas chromatography

Gas chromatography was carried out on a Hewlett-Packard 5890 Series II fitted with a 25m column. Detection was by flame ionisation.

IR spectroscopy

Infrared spectra were recorded using a Diamond ATR (attenuated total reflection) accessory (Golden Gate) or as a solution in chloroform *via* transmission IR cells on a Perkin-Elmer FT-IR 1600 spectrometer.

NMR spectroscopy

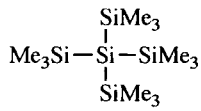
^{1}H NMR spectra were recorded in $CDCl_3$ on Varian Mercury 200, Varian Unity-300, Varian VXR-400 or Varian Inova-500 instruments and are reported as follows; chemical shift δ (ppm) (number of protons, multiplicity, coupling constant *J* (Hz), assignment). Residual protic solvent $CHCl_3$ (δ_H = 7.26) was used as the internal reference. ^{13}C NMR spectra were recorded at 63 MHz or 126 MHz, using the central resonance of $CDCl_3$ (δ_C = 77.0 ppm) as the internal reference. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ_H = 0.00 ppm) and coupling constants are given in Hertz to the nearest 0.5 Hz. Assignment of spectra was carried out using COSY, HSQC, HMBC and NOESY experiments.

Mass spectroscopy

Gas chromatography-mass spectra (EI) were obtained using a Thermo TRACE mass spectrometer. Electrospray mass spectra (ES) were obtained on a Micromass LCT mass spectrometer. High resolution mass spectra were obtained using a Thermo LTQ mass spectrometer (ES) at the University of Durham, or performed by the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea.

6.2 Experimental Details

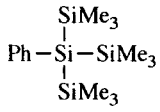
Tetrakis(trimethylsilyl)silane, 94



To a solution of chlorotrimethylsilylsilane (224 ml, 1.8 mol) in THF (400 ml) were added pieces of lithium ribbon (31.0 g, 4.5 mol) and the mixture was stirred for 1h at room temperature. A solution of silicon tetrachloride (43 ml, 0.4 mol) in THF (300 ml) was prepared and 40 ml of this was then added to the stirred TMSCl solution dropwise [CAUTION: Exotherm]. The reaction mixture was stirred for 4 h at room temperature; then the remaining $SiCl_4$ solution was added over 2 h. The reaction was then stirred overnight. The crude reaction mixture was filtered through celite to remove LiCl salts and excess unreacted lithium metal [CAUTION: Fire hazard]. The filter cake was then washed with ether. The filtrate was added to 5M aqueous hydrochloric acid (300 ml). The aqueous layer was separated and extracted with ether (3 x 140 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Recrystallisation of the semi-solid residue from acetone yielded the title compound as a cream crystalline solid (60.4 g, 56%); m.p. 240-242 °C; υ_{max} (thin film) 2951, 2893, 1394, 1243, 818 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.20; δ_C (100 MHz, $CDCl_3$) 2.7; *m/z* (EI)

320 (M^+, 32%), 305 (M^+ -CH_3, 22%), 232 (M^+ -CH_3, -$Si(CH_3)_3$, 84%), 173 (M^+ -$2Si(CH_3)_3$, 72%), 158 (M^+ -$2Si(CH_3)_3$-H, 76%); all data agree with those reported by Whelligan.[35]

Phenyltris(trimethylsilyl)silane, 95



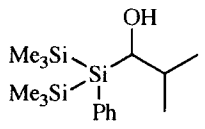
Dry tetrakis(trimethylsilyl)silane **94** (17.5 g, 54.6 mmol) and potassium-*tert*-butoxide (6.4 g, 57.3 mmol) were combined under argon. Dry THF (260 ml) was added and the solution stirred for 2 h, after which time it was dark red. Phenyl magnesium bromide (1.0M, 60 ml, 60 mmol) was added and a white precipitate was formed. The mixture was stirred for 1h and then cooled to -78 °C. Bromobenzene (8.6 ml, 81.9 mmol) was quickly added with rapid stirring, creating an exotherm (observed as effervescence in the dry ice/acetone bath). After stirring for 1 h, the mixture was warmed to room temperature, freshly prepared dry magnesium bromide diethyletherate (1.4 g, 5.5 mmol) was added, and the mixture was refluxed overnight. The reaction was cooled to room temperature and additional phenylmagnesium bromide (1.0M, 60 ml, 60 mmol) was added. Then the reaction was refluxed overnight until NMR showed completion of the reaction. Saturated aq. NH_4Cl (260 ml) was then added. The aqueous layer was separated and extracted with ether (3 x 260 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether) followed by Kugelrohr distillation (100 °C, 2 mbar) afforded the title compound as a grey semi-solid (14.3 g, 80%); R_f 0.74 (*n*-hexane); υ_{max} (thin film) 2950, 2893, 1426, 1243 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.46-7.42 (2H, m, *ortho* Ar-*H*), 7.26-7.23 (3H, m, *meta* and *para* Ar-*H*), 0.22 (27H, s, $Si(Si(CH_3)_3)_3$); δ_C (126 MHz, $CDCl_3$) 136.5 (Ar-*C*), 135.5 (Ar-*C*), 127.7 (Ar-*C*), 127.3 (Ar-*C*), 1.2 ($Si(Si(CH_3)_3)_3$); *m/z* (EI) 324

(M^+, 16%), 309 (M^+ - CH_3, 6%), 251 (M^+ -$Si(CH_3)_3$, 10%), 236 (M^+ - CH_3, -$Si(CH_3)_3$, 14%), 191 (26%), 174 (M^+ -Ph, -$Si(CH_3)_3$, 92%), 159 (M^+ -Ph, -$Si(CH_3)_3$, -CH_3, 42%), 135 (66%), 73 ($(CH_3)_3Si^+$, 100%); all data agree with those reported by Whelligan.[35]

6.2.1 Standard procedure for the preparation of Silyl alcohols

Dry phenyltris(trimethylsilyl)silane **95** (43.0 mmol) and potassium *tert*-butoxide (44.3 mmol) were combined under argon. THF (100 ml) was added and the resulting solution stirred for 2 h after which time it had become bright red. The THF was evaporated directly using a vacuum manifold and ether (100 ml) was added. The resulting solution was added *via* cannula to a suspension of magnesium bromide diethyl etherate (56.0 mmol) in ether (75 ml) [KBr precipitates generating a white suspension]. The reaction mixture was stirred for 1 h and then cooled to -78 °C. Freshly distilled aldehyde (47.3 mmol) was then added and the mixture stirred for 1.5 h. Saturated aq. NH_4Cl was added and the mixture allowed to reach room temperature. The aqueous layer was separated and extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether; pet. ether/ether 39:1, 29:1) afforded the desired silyl alcohols.

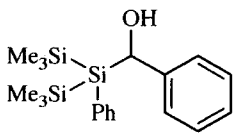
1,1,1,3,3,3-Hexamethyl-2-phenyl-2-(1'-hydroxy-2'-methylpropyl)trisilane, 97



Following the standard procedure outlined on page 161, phenyltris(trimethylsilyl)silane **95** (14.0 g, 43.0 mmol) was combined with isobutryaldehyde to give the title compound as a colourless oil (6.9 g, 49%); R_f 0.57 (pet. ether/ether 9:1); δ_H (200 MHz, $CDCl_3$) 7.54-7.49 (2H, m, Ar-*H*), 7.32-7.28 (3H, m, Ar-*H*), 3.79 (1H, d, *J* 7, SiC*H*), 1.96 (1H,

octet, *J* 7, C*H*(CH_3)$_2$), 0.99 and 0.88 (each 3H, d, *J* 7, CH(C*H*$_3$)$_2$)), 0.24 and 0.2 (each 9H, s, Si(C*H*$_3$)$_3$); δ_C (126 MHz, $CDCl_3$) 136.5 (Ar-*C*), 135.6 (Ar-*C*), 128.1 (Ar-*C*), 127.9 (Ar-*C*), 72.4 (Si*C*H), 34.6 (*C*H(CH_3)$_2$), 21.16 and 19.86 (CH(*C*H$_3$)$_2$), 0.5 (Si(*C*H$_3$)$_3$), 0.2 (Si(*C*H$_3$)$_3$); *m/z* (CI) 342 (MNH_4^+, 10%), 324 (M^+, 36%), 307 (M^+-OH, 100%); all data agree with those reported by Whelligan.[35]

(1,1,1,3,3,3-Hexamethyl-2-phenyl-trisilan-2-yl)-phenyl-methanol, 205



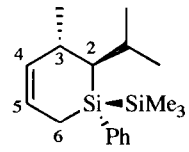
Following the standard procedure outlined on page 161, phenyltris(trimethylsilyl)silane **95** (5.0 g, 15.4 mmol) was combined with benzaldehyde to give the title compound as a yellow solid (1.5 g, 36%); R_f 0.40 (pet. ether/ether 9:1); δ_H (200 MHz, $CDCl_3$) 7.55-7.53 (2H, m, Ar-*H*), 7.34-7.32 (2H, m, Ar-*H*), 7.23-7.14 (6H, m, Ar-*H*), 5.18 (1H, d, *J* 3.5, SiC*H*), 1.75 (1H, d, *J* 4, CHO*H*), 0.14 and 0.10 (each 9H, s, Si(C*H*$_3$)$_3$); *m/z* (CI) 376 (MNH_4^+, 5%), 358 (M^+, 12%), 341 (M^+-OH, 15%); all data agree with those reported by Whelligan.[35]

6.2.2 Standard procedure for the preparation of Silacyclohex-4-enes

n-Butyllithium (1.6M sol. in hexanes, 6.5 mmol) was rapidly added to a stirred solution of silyl alcohol (6.2 mmol) and substituted diene (37.0 mmol) in dry ether (70 ml) at room temperature. The mixture was stirred for 2 h after which time TLC showed complete consumption of starting material. The solution was then cooled to -20 °C and an anhydrous suspension of LiBr in ether (0.31M, 0.3 mmol) was added. The solution was stirred at -20 °C for 19.5 h, after which time saturated aq. NH_4Cl (70 ml) was added and the mixture allowed to reach room temperature. The aqueous layer was separated

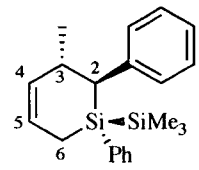
and extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether) afforded the desired silacyclohex-4-ene as an inseperable mixture of isomers

(1*SR*,2*RS*,3*SR*)-1-Phenyl-1-trimethylsilyl-2-(isopropyl)-3-methylsilacyclohex-4-ene, 100



Following the standard procedure for silene generation and cyclisation outlined on page 162, silyl alcohol **97** (2.0 g, 6.2 mmol) was transformed into the title compound which was isolated as a colourless oil (0.8 g, 41%) together with small amounts of isomers in the ratio 86:9:3 by GC; R_f 0.71 (pet. ether); υ_{max} (thin film) 2998, 2950, 2868, 1460, 1426, 1396, 1243, 1100, 830, 733, 696 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.51-7.49 (2H, m, Ar-*H*), 7.31-7.29 (3H, m, Ar-*H*), 5.82 (1H, dtd, *J* 10, 5, 2, 5-*H*), 5.54 (1H, ddt, *J* 10, 5, 2, 4-*H*), 2.36 (1H, m, 3-*H*), 2.10 (1H, d-septet, *J* 7, 4, 2C*H*$(CH_3)_2$), 1.68 (1H, ddd, *J* 17, 5, 2, 6-*H*H), 1.47 (1H, ddt, *J* 17, 5, 2, 6-H*H*), 1.20 (1H, dd, *J* 7, 4, 2-*H*), 1.03 (3H, d, *J* 7, 2-CH(CH_3)$_2$), 0.93 (3H, d, *J* 7, 3-CH_3), 0.88 (3H, d, *J* 7, 2-CH(CH_3)$_2$), 0.14 (9H, s, Si(CH_3)$_3$); δ_C (126 MHz, $CDCl_3$) 139.4 (*ipso*-Ar-*C*), 137.4 (4-*C*), 134.5 (Ar-*C*), 128.2 (Ar-*C*), 127.6 (Ar-*C*), 123.6 (5-*C*), 38.2 (2-*C*), 32.7 (3-*C*), 30.0 (2-*C*H$(CH_3)_2$), 23.5 (3-*C*H_3), 23.0 (2-CH(*C*H_3)$_2$), 22.4 (2-CH(*C*H_3)$_2$), 9.7 (6-*C*), -0.6 (Si(*C*H_3)$_3$); *m/z* (EI) 302 (M^+, 4%), 259 (M^+ -^{i}Pr, 4%), 229 (M^+ -Si$(CH_3)_3$, 32%), 218 (16%), 203 (28%), 173 (22%), 161 (100%), 145 (22%), 135 (52%), 121 (40%); all data agree with those reported by Whelligan.[35]

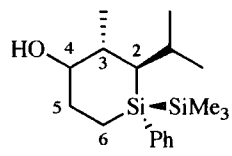
(1*SR*,2*SR*,3*SR*)-3-Methyl-1,2-diphenyl-1-trimethylsilylsilacyclohex-4-ene, 206



Following the standard procedure for silene generation and cyclisation outlined on page 162, phenyl silyl alcohol **205** (0.5 g, 1.4 mmol) was transformed into the title compound which was isolated as a colourless oil (0.2 g, 39%) together with small amounts of isomers in the ratio 70:20:10 by NMR; R_f 0.4 (pet. ether); δ_H (500 MHz, $CDCl_3$) 7.24-7.22 (5H, m, Ar-*H*), 7.05-7.10 (5H, m, Ar-*H*), 6.00 (1H, m, 5-*H*), 5.62 (1H, m, 4-*H*), 2.82 (1H, m, 3-*H*), 2.33 (1H, d, *J* 9, 2-*H*), 1.85 (1H, m, 6-*H*H), 1.65 (1H, m, 6-H*H*), 0.97 (3H, d, *J* 7, 3-CH_3), -0.07 (9H, s, Si(CH_3)$_3$); *m/z* (EI) 336 (M^+, 12%), 321 (M^+ - Me), 268 (80%), 253 (100%), 203 (26%), 183 (24%), 175 (22%), 145 (23%), 135 (64%); all data agree with those reported by Whelligan.[35]

6.3 Total Synthesis of Prelactone B

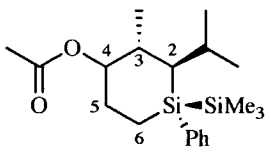
(1*SR*,2*RS*,3SR,4*RS/SR*)-1-Phenyl-1-trimethylsilyl-2-(isopropyl)-3-methyl-4-hydroxysilacyclohexane, 178



Borane dimethyl sulfide complex (0.06 ml, 0.7 mmol) in THF (4 ml) was cooled to 0 °C and treated with a solution of silacyclohex-4-ene **100** (0.2 g, 0.7 mmol) in THF (4 ml). The reaction was stirred for 2 h at 0 °C, then for 1 h at room temperature and treated with water (0.4 ml) (H_2 gas evolved), followed by 3M NaOH (0.2 ml, 0.7 mmol) and a 35% w/w solution of H_2O_2 in water (0.2 ml, 2.2 mmol). The mixture was refluxed at 65 °C for 4 h after which time $Na_2S_2O_3$ (10 ml) was added. The aqueous layer was

separated and extracted with EtOAc (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether, pet. ether/ether [14:1], [9:1], [4:1], [2:1]) afforded the title compound as a white solid (0.07 g, 34%); m.p. 118-120 °C; R_f 0.3 (pet. ether/ether 3:2); υ_{max} (thin film) 3368 (broad-OH), 3067, 2922, 2872, 1726, 1462, 1427, 1244, 1102, 1048, 1019, 852, 833, 735, 700 cm^{-1}; NMR data provided for the major isomer δ_H (300 MHz, $CDCl_3$) 7.55-7.51 (2H, m, Ar-*H*), 7.32-7.29 (3H, m, Ar-*H*), 3.26 (1H, td, *J* 11, 3, 4-*H*), 2.18 (1H, m, 3-*H*), 2.05 (1H, m, 2-C*H*$(CH_3)_2$), 1.65 (2H, m, 6-H_2), 1.45 (1H, m, 2-*H*), 1.26 (2H, m, 5-H_2), 1.14 (3H, d, *J* 7, 2-CH(CH_3)$_2$), 1.00 (3H, d, *J* 7, 3-CH_3), 0.75 (3H, d, *J* 7, 2-CH(CH_3)$_2$), 0.29 (9H, s, Si(CH_3)$_3$); δ_C (126 MHz, $CDCl_3$) 139.9 (*ipso*-Ar-*C*), 134.5 (Ar-*C*), 128.5 (Ar-*C*), 127.9 (Ar-*C*), 77.8 (4-*C*), 41.9 (3-*C*), 38.6 (2-*C*), 35.2 (2-*C*H$(CH_3)_2$), 33.5 (5-*C*), 23.5 (2-CH(*C*H_3)$_2$), 22.1 (2-CH(*C*H_3)$_2$), 18.4 (3-*C*H_3), 9.6 (6-*C*), 0.3 (Si(*C*H_3)$_3$); *m/z* (ES^+) 343 (MNa^+), 303 (M^+ -H_2O); all data agree with those reported by Whelligan.[35]

(1*SR*,2*RS*,3*SR*,4*RS/SR*)-1-Phenyl-1-trimethylsilyl-2-(isopropyl)-3-methyl-4-acetoxysilacyclohexane, 190

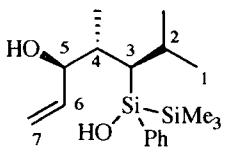


A solution of pyridine (0.02 ml, 0.2 mmol) and acetic anhydride (0.01 ml, 0.1 mmol) in DCM (1 ml) was cooled to 0 °C and treated with silacyclic alcohol **178** (0.03 g, 0.1 mmol) dissolved in DCM (2 ml). The reaction was then warmed to room temperature and reacted for 24 h after which time water was added. The aqueous layer was separated and extracted with ether (3 x 5 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether, pet.

ether/ether [95:5], [9:1]) afforded the title compound as an opaque oil (0.02 g, 46%); R_f 0.2 (pet. ether/ether 95:5); υ_{max} (thin film) 2957, 2872, 1733 (C=O), 1458, 1427, 1368, 1245, 1172, 1142, 1100, 1022, 852, 834, 699 cm^{-1}; partial NMR data δ_H (400 MHz, $CDCl_3$) 7.56-7.51 (2H, m, Ar-*H*), 7.32-7.26 (3H, m, Ar-*H*), 4.56 (1H, td, *J* 10, 3, 4-*H*), 2.18-2.10 (2H, m, 5-H*H*, 2-C*H*$(CH_3)_2$), 2.08 (3H, s, 4-C(O)CH_3), 1.99-1.93 (2H, m, 5-*H*H, 3-*H*), 1.62 (2H, m, 6-H_2), 1.30 (1H, m, 2-*H*), 1.05 (3H, d, *J* 7, 2-CH(CH_3)$_2$), 1.00 (3H, d, *J* 7, 2-CH(CH_3)$_2$), 0.82 (3H, d, *J* 7, 3-CH_3), 0.30 (9H, s, Si(CH_3)$_3$); δ_C (126 MHz, $CDCl_3$) 170.6 (*C*=O), 139.5 (*ipso*-Ar-*C*), 134.5 (Ar-*C*), 128.5 (Ar-*C*), 127.8 (Ar-*C*), 79.7 (4-*C*), 38.7 (2-*C*), 38.6 (5-*C*), 29.6 (3-*C*), 28.1 (2-*C*H$(CH_3)_2$), 23.6 (2-CH(*C*H_3)$_2$), 22.0 (2-CH(*C*H_3)$_2$), 21.4 (4-C(O)*C*H_3), 18.1 (3-*C*H_3), 9.1 (6-*C*), 0.3 (Si(*C*H_3)$_3$); *m/z* (EI) 347 (M^+ -CH_3, 1%), 289 (3%), 229 (10%), 211 (100%), 169 (24%), 135 (33%), 123 (33%).

A high resolution mass spectrum of this compound was unattainable as the molecular ion or adduct was not observed under any form of ionisation

(3*RS*,4*SR*,5*RS*,(*Si*)*RS*/*SR*)-3-(1-Hydroxy-2,2,2-trimethyl-1-phenyldisilanyl)-5-hydroxy-2,4-dimethylhept-6-ene, 200



Method A

A solution of silacyclohex-4-ene **100** (0.14 g, 0.5 mmol) in DCM (2 ml) was cooled to 0 °C and treated with freshly prepared dimethyldioxirane. The reaction was stirred at 0 °C for 1 h, then warmed to room temperature and reacted for a further 1 h. The reaction was evaporated to a crude colourless oil. Flash chromatography (pet. ether, pet.

ether/ether [99:1], [98:2]) afforded the title compound as a colourless oil (0.012 g, 11%).

Method B

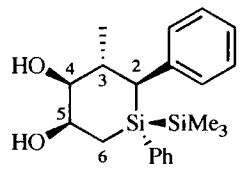
A solution of silacyclohex-4-ene **100** (0.10 g, 0.3 mmol) in acetonitrile (2.5ml) was cooled to 0 °C and treated with EDTA disodium salt (1.7 ml, $4x10^{-4}M$) and trifluoroacetone (0.3 ml, 3.7 mmol). This solution was then treated with a mixture of $NaHCO_3$ (0.2 g, 2.6 mmol) and Oxone (1.0 g, 1.7 mmol) over a period of 1 h and reacted for a further 3 h, after which time the reaction was poured into water and extracted with DCM (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether, pet. ether [99:1], [98:2]) afforded the title compound as a colourless oil (0.025 g, 22%); R_f 0.6 (pet. ether/ether 9:1); υ_{max} (thin film) 3068 (broad-OH), 2956, 2928, 2892, 2870, 1718, 1427, 1244, 1103, 1004, 855, 835, 699 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.58-7.55 (2H, m, Ar-*H*), 7.35-7.34 (3H, m, Ar-*H*), 5.75 (1H, ddd, *J* 17, 10, 7, 6-*H*), 5.21 (1H, d, *J* 17, 7-*H*H), 5.08 (1H, d, *J* 10, 7-H*H*), 4.53 (1H, t, *J* 7, 5-*H*), 2.28 (1H, m, 4-*H*), 1.99 (1H, septet, *J* 6, 2-*H*), 1.26 (1H, m, 3-*H*), 1.09 (3H, d, *J* 6, 1-*H*), 1.07 (3H, d, *J* 6, 2-CH_3), 0.86 (3H, d, *J* 6, 4-CH_3), 0.17 (9H, s, Si(CH_3)$_3$); δ_C (126 MHz, $CDCl_3$) 139.6 (*ipso*-Ar-C), 137.5 (6-*C*), 133.7 (Ar-*C*), 128.9 (Ar-*C*), 127.8 (Ar-*C*), 116.4 (7-*C*), 84.3 (5-*C*), 44.5 (3-*C*), 40.7 (4-*C*), 27.5 (2-*C*), 25.2 (1-*C*), 23.4 (2-*C*H_3), 16.6 (4-*C*H_3), -1.4 (Si(*C*H_3)$_3$); *m/z* (ES^+) 359 (MNa^+); HRMS (ES^+) Found MNa^+, 359.1837 ($C_{18}H_{32}O_2Si_2Na$ requires 359.1833).

6.3.1 Standard procedure for the dihydroxylation of silacycles

A solution of silacyclohex-4-ene (0.15 mmol) in acetone:water (2.1 ml, 20:1) was treated with NMO (0.3 mmol), cooled to 0 °C and treated with a catalytic amount of

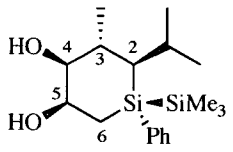
osmium tetroxide (0.007 mmol). After stirring for 45 mins the reaction mixture was treated with aq. $Na_2S_2O_3$ and extracted with EtOAc (3 x 5 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether/ether [1:1], [1:2]) afforded the desired dihydroxyl silacycles.

(1*SR*,2*SR*,3*SR*,4*SR*,5*SR*)-4,5-Dihydroxy-3-methyl-1,2-diphenyl-1-(trimethylsilyl)silacyclohexane, 207



Following the standard procedure outlined on page 167, silacyclohex-4-ene **206** (0.05 g, 0.15 mmol) was transformed into the title compound which was isolated as a colourless gum (0.03 g, 56%); R_f 0.3 (pet. ether/ether 1:1); υ_{max} (thin film) 3631-3579 (broad-OH), 3069, 3026, 2955, 2925, 2895, 2871, 1598, 1426, 1256, 1242, 1049, 1021, 896, 835, 781 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.31-7.21 (5H, m, Ar-*H*), 7.18-7.12 (3H, m, Ar-*H*), 7.08-7.06 (2H, m, Ar-*H*), 4.48 (1H, m, 5-*H*), 3.38 (1H, dd, *J* 10, 3, 4-*H*), 2.57 (1H, m, 3-*H*), 2.15 (1H, d, *J* 12, 2-*H*), 1.63 (1H, dd, *J* 15.5, 6, 6-*H*H), 1.34 (1H, dd, *J* 15.5, 6, 6-H*H*), 0.95 (3H, d, *J* 7, 3-CH_3), 0.03 (9H, s, Si(CH_3)$_3$); δ_C (126 MHz, $CDCl_3$) 143.2 (*ipso*-Ar-*C*), 137.2 (*ipso*-Ar-*C*), 134.9 (Ar-*C*), 128.9 (Ar-*C*), 128.8 (Ar-*C*), 128.6 (Ar-*C*), 127.7 (Ar-*C*), 125.1 (Ar-*C*), 79.8 (4-*C*), 72.2 (5-*C*), 41.0 (2-*C*), 36.1 (3-*C*), 18.1 (3-*C*H_3), 17.5 (6-*C*), -0.7 (Si(*C*H_3)$_3$); δ_{Si} (100 MHz, $CDCl_3$) -18.72, -21.22; *m/z* (ES^+) 393 (MNa^+), 425 (MNa+$MeOH^+$), 763 ($2MNa^+$); HRMS (ES^+) Found MNa^+, 393.1676 ($C_{21}H_{30}O_2Si_2Na$ requires 393.1677).

(1*SR*,2*RS*,3*SR*,4*SR*,5*SR*)-4,5-Dihydroxy-1-Phenyl-1-trimethylsilyl-2-(isopropyl)-3-methylsilacyclohexane, 226



Following the standard procedure outlined on page 167, silacyclohex-4-ene **100** (0.17 g, 0.6 mmol) was transformed into the title compound which was isolated as a yellow oil (0.06 g, 32%); R_f 0.3 (pet. ether/ether 1:1); υ_{max} (thin film) 3498-3211 (broad-OH), 2950, 2932, 2898, 2864, 1426, 1096, 1022, 992, 832, 731, 697 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.53-7.51 (2H, m, Ar-*H*), 7.31-7.30 (3H, m, Ar-*H*), 4.20 (1H, m, 5-*H*), 3.49 (1H, m, 4-*H*), 2.25 (1H, m, 3-*H*), 2.14 (1H, m, 2-C*H*$(CH_3)_2$), 1.36 (1H, dd, *J* 14, 9, 6-*H*H), 1.18 (1H, m, 6-H*H*), 1.08 (1H, dd, *J* 9, 6, 2-*H*), 1.04 (3H, d, *J* 7, 2-CH(C$H_3)_2$), 0.97 (3H, d, *J* 7, 3-CH_3), 0.91 (3H, d, *J* 7, 2-CH(C$H_3)_2$), 0.21 (9H, s, Si(C$H_3)_3$); δ_C (126 MHz, $CDCl_3$) 140.2 (*ipso*-Ar-*C*), 134.4 (Ar-*C*), 128.5 (Ar-*C*), 128.0 (Ar-*C*), 78.8 (4-*C*), 70.2 (5-*C*), 36.8 (2-*C*), 35.8 (3-*C*), 29.1 (2-*C*H$(CH_3)_2$), 23.8 (2-CH(*C*$H_3)_2$), 19.4 (3-*C*H_3), 16.5 (6-*C*), -0.4 (Si(*C*$H_3)_3$); δ_{Si} (100 MHz, $CDCl_3$) -17.90, -23.36; *m/z* (ES^+) 359 (MNa^+); HRMS (ES^+) Found MNa^+, 359.1834 ($C_{18}H_{32}Si_2O_2Na$ requires 359.1833).

6.3.2 Standard procedure for the Fleming-Tamao fragmentation of dihydroxyl silacyclohex-4-enes

Stage 1

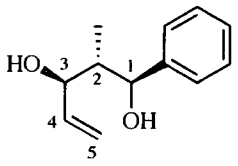
To a solution of silacyclic diol (0.3 mmol) in dry DCM (4 ml) was added trifluoroborane-acetic acid complex (0.6 mmol). The solution was stirred for 15 mins at room temperature then mixed with saturated $NaHCO_3$ solution (5 ml) and extracted with DCM (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered,

concentrated and dried *in vacuo* to give a colourless oil which was used immediately in stage 2.

Stage 2

To the colourless oil was added $KHCO_3$ (1.0 mmol) and KF (0.7 mmol). The mixture was dissolved in methanol:THF solution (1:1, 4 ml) and a 35% w/w solution of H_2O_2 in water (3.9 mmol) was added. The mixture was heated to reflux and stirred for 1 h. The mixture was then allowed to cool to room temperature and saturated $Na_2S_2O_3$ solution (5 ml) was added together with EtOAc (10 ml). The aqueous layer was separated and extracted with EtOAc (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether/ether [9:1], [4:1], [3:2], [1:1], [1:2]) afforded the desired diols.

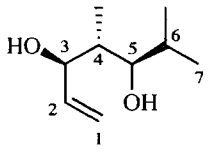
(1*SR*,2*SR*,3*RS*)-2-Methyl-1-phenylpent-4-ene-1,3-diol, 208



Following the standard procedure outlined on page 169, silacyclic diol **207a** (0.12 g, 0.3 mmol) was transformed into the title compound which was isolated as a colourless oil (0.05 g, 72%); R_f 0.3 (pet. ether/ether 1:1); υ_{max} (thin film) 3502-3214 (broad-OH), 3064, 2974, 2886, 1721, 1711, 1690, 1601, 1512, 1450, 1332, 1216, 1128, 1080 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.38-7.36 (4H, m, Ar-*H*), 7.33-7.28 (1H, m, Ar-*H*), 6.00 (1H, ddd, *J* 16, 10, 5, 4-*H*), 5.33 (1H, d, *J* 16, 5-*H*H), 5.26 (1H, d, *J* 10, 5-H*H*), 4.69 (1H, d, *J* 9, 1-*H*), 4.40 (1H, m, 3-*H*), 2.95 (1H, bs, -O*H*), 2.11 (1H, qd, *J* 9, 3, 2-*H*), 0.82 (3H, d, *J* 9, 2-CH_3); δ_C (126 MHz, $CDCl_3$) 143.7 (*ipso*-Ar-*C*), 138.5 (4-*C*), 128.7 (Ar-*C*), 128.0 (Ar-*C*), 126.8 (Ar-*C*), 115.8 (5-*C*), 78.3 (1-*C*), 74.9 (3-*C*), 44.3 (2-*C*), 12.5 (2-CH_3); *m/z*

(ES$^+$) 215 (MNa$^+$); HRMS (ES$^+$) Found MNa$^+$, 215.1043 ($C_{12}H_{16}O_2Na$ requires 215.1043).

(3*RS*,4*RS*,5*RS*)-4,6-Dimethylhept-1-ene-3,5-diol, 227

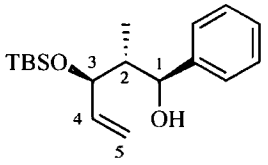


Following the standard procedure outlined on page 169, silacyclic diol **226** (0.06 g, 0.18 mmol) was transformed into the title compound which was isolated as a colourless oil (0.02 g, 64%); R_f 0.3 (pet. ether/ether 1:1); υ_{max} (thin film) 3525-3134 (broad-OH), 2962, 2870, 1459, 1427, 1118, 1081, 974, 919, 844, 697, 639 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 5.94 (1H, ddd, *J* 16, 10, 5, 2-*H*), 5.29 (1H, d, *J* 16, 1-*H*H), 5.19 (1H, d, *J* 10, 1-H*H*), 4.41 (1H, s, 3-*H*), 3.39 (1H, m, 5-*H*), 3.11 (1H, bs, -O*H*), 2.53 (1H, bs, -O*H*), 1.89 (1H, qd, *J* 7, 3, 4-*H*), 1.82 (1H, m, 6-*H*), 0.94 (3H, d, *J* 8, 7-CH_3), 0.92 (3H, d, *J* 8, 6-CH_3), 0.87 (3H, d, *J* 7, 4-CH_3); δ_C (126 MHz, $CDCl_3$) 138.9 (2-*C*), 115.4 (1-*C*), 79.8 (5-*C*), 75.1 (3-*C*), 39.6 (4-*C*), 30.6 (6-*C*), 20.0 (7-*C*H$_3$), 16.0 (6-*C*H$_3$), 12.2 (4-*C*H$_3$); *m/z* (ES$^+$) 181 (MNa$^+$); HRMS (ES$^+$) Found MNa$^+$, 181.1199 ($C_9H_{18}O_2Na$ requires 181.1199).

6.3.3 Standard procedure for the protection of diols

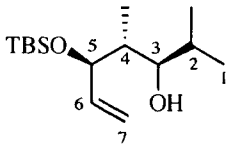
To a solution of diol (0.10 mmol) in dry DCM (2 ml) was added imidazole (0.42 mmol) and *tert*-butylchlorodimethylsilane (0.26 mmol). The solution was stirred for 2 h at room temperature then diluted with EtOAc and washed with water (5 ml) and brine (5 ml). The organic layer was dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether/ether [95:5], [9:1]) afforded the desired mono-protected diols.

(1*SR*,2*RS*,3*RS*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-1-phenylpent-4-en-1-ol, 220



Following the standard procedure outlined on page 171, diol **208** (0.02 g, 0.10 mmol) was transformed into the title compound which was isolated as a colourless oil (0.022 g, 70%); R_f 0.3 (pet. ether/ether 95:5); υ_{max} (thin film) 3572-3286 (broad-OH), 2960, 2932, 2894, 2852, 1468, 1368, 1256, 1026, 926, 832, 770 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.34-7.27 (5H, m, Ar-*H*), 6.05 (1H, ddd, *J* 17, 10, 7, 4-*H*), 5.33-5.27 (2H, dd, *J* 17, 10, 5-H_2), 4.54 (1H, d, *J* 9, 1-*H*), 4.45-4.43 (1H, m, 3-*H*), 2.04 (1H, sd, *J* 9, 3, 2-*H*), 0.99 (9H, s, SiC(CH_3)$_3$), 0.58 (3H, d, *J* 9, 2-CH_3), 0.17 (3H, s, Si(CH_3)$_2$^{t}Bu), 0.12 (3H, s, Si(CH_3)$_2$^{t}Bu); δ_C (126 MHz, $CDCl_3$) 143.9 (*ipso*-Ar-*C*), 137.2 (4-*C*), 128.4 (Ar-*C*), 127.7 (Ar-*C*), 127.3 (Ar-*C*), 116.7 (5-*C*), 78.3 (3-*C*), 77.6 (1-*C*), 45.7 (2-*C*), 26.1 (SiC(CH_3)$_3$), 18.3 (Si*C*(CH_3)$_3$), 13.4 (2-CH_3), -4.2 (Si(CH_3)$_2$^{t}Bu) -4.9 (Si(CH_3)$_2$^{t}Bu); *m/z* (ES^+) 329.3 (MNa^+), 635 ($2MNa^+$); HRMS (ES^+) Found MNa^+, 329.1907 ($C_{18}H_{30}O_2SiNa$ requires 329.1907).

(3*RS*,4*RS*,5*RS*)-5-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylhept-6-en-3-ol, 228



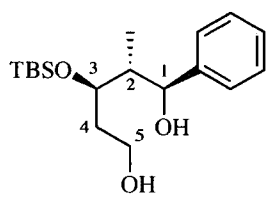
Following the standard procedure outlined on page 171, diol **227** (0.02 g, 0.11 mmol) was transformed into the title compound which was isolated as a colourless oil (0.016 g, 52%); R_f 0.3 (pet. ether/ether 95:5); υ_{max} (thin film) 3630-3130 (broad-OH), 2957, 2930, 2857, 1471, 1384, 1254, 1126, 1022, 996, 835, 776 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 5.93 (1H, ddd, *J* 17, 10, 6, 6-*H*), 5.22 (1H, d, *J* 17, 7-*H*H), 5.19 (1H, d, *J* 10, 7-H*H*),

4.30 (1H, m, 5-*H*), 3.95 (1H, bs, -O*H*), 3.41 (1H, d, *J* 9, 3-*H*), 1.82 (1H, m, 4-*H*), 1.68 (1H, qd, *J* 7, 2, 2-*H*), 0.99 (3H, d, *J* 7, 1-*H*), 0.91 (9H, s, $SiC(CH_3)_3$), 0.86 (3H, d, *J* 7, 2-CH_3), 0.77 (3H, d, *J* 7, 4-CH_3), 0.09 (3H, s, $Si(CH_3)_2{}^tBu$), 0.06 (3H, s, $Si(CH_3)_2{}^tBu$); δ_C (126 MHz, $CDCl_3$) 137.3 (6-*C*), 116.4 (7-*C*), 79.1 (5-*C*), 77.5 (3-*C*), 41.3 (4-*C*), 30.1 (2-*C*), 26.0 ($SiC(CH_3)_3$), 20.4 (1-*C*), 18.4 ($SiC(CH_3)_3$), 14.2 (2-CH_3), 13.1 (4-CH_3), -4.3 ($Si(CH_3)_2{}^tBu$), -5.0 ($Si(CH_3)_2{}^tBu$); *m/z* (ES^+) 295 (MNa^+); HRMS (ES^+) Found MH^+, 273.2245 ($C_{15}H_{33}O_2Si$ requires 273.2244).

6.3.4 Standard procedure for the hydroboration of mono-protected diols

A solution of mono-protected diol (0.07 mmol) in THF (2 ml) was treated with an excess of freshly prepared dicyclohexylborane[187] at 0 °C. The reaction was then warmed to room temperature and reacted for 1 h. The reaction was then treated successively with water (0.5 ml), NaOH (0.14 mmol) and H_2O_2 (0.9 mmol). The mixture was then refluxed for 1 h, then cooled, poured into $Na_2S_2O_3$ and extracted with Et_2O (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether/ether [1:1], [2:3]) afforded the desired mono-protected triols.

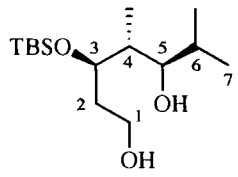
(1*SR*,2*RS*,3*RS*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-1-phenylpentane-1,5-diol, 221a



Following the standard procedure outlined on page 173, mono-protected diol **220** (0.02 g, 0.07 mmol) was transformed into the title compound which was isolated as a

colourless oil (0.012 g, 60%); R_f 0.3 (pet. ether/ether 2:3); υ_{max} (thin film) 3490-3182 (broad-OH), 2956, 2932, 2886, 2860, 1684, 1676, 1560, 1437, 1259, 1202, 1075, 1050, 781 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.34-7.31 (5H, m, Ar-*H*), 4.58 (1H, d, *J* 10, 1-*H*), 4.14 (1H, dt, *J* 10, 3, 3-*H*), 3.85 (1H, m, 5-H*H*), 3.75 (1H, m, 5-*H*H), 2.07-1.96 (2H, m, 2-*H*, 4-*H*H), 1.89 (1H, m, 4-H*H*), 0.97 (9H, s, SiC(CH_3)$_3$), 0.57 (3H, d, *J* 7, 2-CH_3), 0.22 (3H, s, Si(CH_3)$_2$^{t}Bu), 0.16 (3H, s, Si(CH_3)$_2$^{t}Bu); δ_C (126 MHz, $CDCl_3$) 143.9 (*ipso*-Ar-*C*), 128.5 (Ar-*C*), 127.8 (Ar-*C*), 127.3 (Ar-*C*), 77.8 (1-*C*), 74.6 (3-*C*), 60.1 (5-*C*), 45.2 (2-*C*), 34.3 (4-*C*), 26.1 (SiC(CH_3)$_3$), 18.2 (Si*C*(CH_3)$_3$), 14.0 (2-CH_3), -4.1 (Si(CH_3)$_2$^{t}Bu), -4.6 (Si(CH_3)$_2$^{t}Bu); *m/z* (ES^+) 347 (MNa^+); HRMS (ES^+) Found MNa^+, 347.2014 ($C_{18}H_{32}O_3SiNa$ requires 347.2013).

(3*RS*,4*RS*,5*RS*)-3-(*tert*-Butyldimethylsilyloxy)-4,6-dimethylheptane-1,5-diol, 229



Following the standard procedure outlined on page 173, mono-protected diol **228** (0.02 g, 0.06 mmol) was transformed into the title compound which was isolated as a colourless oil (0.012 g, 70%); R_f 0.3 (pet. ether/ether 1:1); υ_{max} (thin film) 3562-3356 (broad-OH), 3005, 2949, 2931, 1713, 1417, 1360, 1223, 1089, 1051, 838, 530 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 4.00 (1H, m, 3-*H*), 3.79 (1H, m, 1-H*H*), 3.70 (1H, m, 1-*H*H), 3.51 (1H, dd, *J* 10, 2, 5-*H*), 1.90-1.83 (2H, m, 4-*H*, 2-*H*H), 1.78 (1H, m, 2-H*H*), 1.68 (1H, m, 6-*H*), 1.00 (3H, d, *J* 6, 7-CH_3), 0.90 (9H, s, SiC(CH_3)$_3$), 0.84 (3H, d, *J* 6, 6-CH_3), 0.76 (3H, d, *J* 7, 4-CH_3), 0.41 (3H, s, Si(CH_3)$_2$^{t}Bu), 0.11 (3H, s, Si(CH_3)$_2$^{t}Bu); δ_C (126 MHz, $CDCl_3$) 75.4 (3-*C*), 60.2 (1-*C*), 40.3 (4-*C*), 34.0 (2-*C*), 30.0 (6-*C*), 26.0 (SiC(CH_3)$_3$), 20.4 (7-CH_3), 18.4 (Si*C*(CH_3)$_3$), 13.83 (6-CH_3), 13.82 (4-CH_3), -4.1 (Si(CH_3)$_2$^{t}Bu), -4.7

($Si(CH_3)_2{}^tBu$); *m/z* (ES^+) 313 (MNa^+), 291 (MH^+); HRMS (ES^+) Found MH^+, 291.2349 ($C_{15}H_{35}O_3Si$ requires 291.2350).

6.3.5 Standard procedure for the lactonisation and deprotection of mono-protected triols

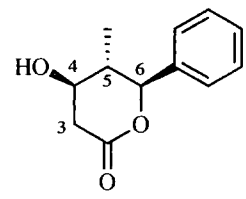
Stage 1

A solution of mono-protected triol (0.04 mmol) in DCM (2 ml) was treated with NMO (0.11 mmol) and 4Å molecular sieves. The mixture was then treated with TPAP (0.002 mmol) at room temperature. After 1 h at room temperature the mixture was filtered through a pad of silica gel (pet.ether/ether 2:3). The filtrate was concentrated and dried *in vacuo* to give a colourless oil which was used immediately in stage 2.

Stage 2

The colourless oil was redissolved in THF (2 ml) and treated with $Et_3N.3HF$ (0.40 mmol) at room temperature. The reaction was left overnight and then mixed with water (2 ml) and extracted with DCM (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (DCM/ether [9:1], [4:1], [7:3]) afforded the desired lactones.

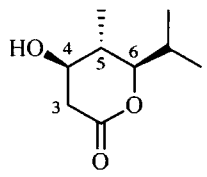
(4*RS*,5*SR*,6*SR*)-4-Hydroxy-5-methyl-6-phenyltetrahydro-2*H*-pyran-2-one, 219



Following the standard procedures outlined on page 175, mono-protected triol **221a** (0.01 g, 0.04 mmol) was converted into the title compound which was isolated as a

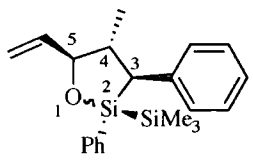
white solid (0.008 g, 100%); R_f 0.3 (DCM/ether 7:3); m.p. 118-120 °C; υ_{max} (thin film) 3530-3190 (broad-OH), 2922, 2852, 2359, 2339, 1736 (C=O), 1654, 1245, 1161, 1056, 1022, 894, 837 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.42-7.38 (3H, m, Ar-*H*), 7.34-7.27 (2H, m, Ar-*H*), 4.77 (1H, d, *J* 11, 6-*H*), 3.95 (1H, m, 4-*H*), 3.09 (1H, dd, *J* 18, 7, 3-*H*H), 2.69 (1H, dd, *J* 18, 7, 3-H*H*), 2.00 (1H, m, 5-*H*), 0.94 (3H, s, 5-CH_3); δ_C (126 MHz, $CDCl_3$) 170.1 (*C*=O), 137.6 (*ipso*-Ar-*C*), 129.2 (Ar-*C*), 128.9 (Ar-*C*), 127.7 (Ar-*C*), 85.2 (6-*C*), 70.1 (4-*C*), 43.5 (5-*C*), 39.5 (3-*C*), 13.9 (5-*C*H_3); *m/z* (ES^+) 261 (MNa+MeOH$^+$); HRMS (ES^+) Found MNa+MeOH$^+$, 261.1098 ($C_{13}H_{18}O_4Na$ requires 261.1097).

(±)-Prelactone B, 110



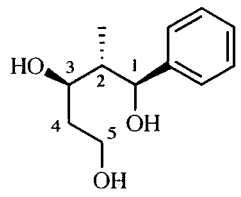
Following the standard procedures outlined on page 175, mono-protected triol **229** (0.01 g, 0.04 mmol) was converted into the title compound which was isolated as a white solid (0.005 g, 90%); R_f 0.3 (DCM/ether 7:3); m.p. 90-92 °C (lit. m.p. 97-98 °C)[40]; υ_{max} (thin film) 3516-3180 (broad-OH), 2967, 2929, 2876, 2260, 2245, 1731 (C=O), 1600, 1253, 1009, 896, 716, 650 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.78-3.76 (2H, m, 6-*H*, 4-*H*), 2.93 (1H, dd, *J* 17, 6, 3-*H*H), 2.48 (1H, dd, *J* 17, 6, 3-H*H*), 2.00 (1H, qd, *J* 7, 2, 6-C*H*(CH_3)$_2$), 1.74 (1H, m, 5-*H*), 1.10 (3H, d, *J* 7, 6-CH(CH_3)$_2$), 1.08 (3H, d, *J* 7, 5-CH_3), 0.92 (3H, d, *J* 7, 6-CH(CH_3)$_2$); δ_C (126 MHz, $CDCl_3$) 170.7 (*C*=O), 86.2 (6-*C*), 69.9 (4-*C*), 39.1 (5-*C*), 39.0 (3-*C*), 28.9 (6-*C*H(CH_3)$_2$), 20.0 (6-CH(*C*H_3)$_2$), 14.0 (5-*C*H_3), 13.5 (6-CH(*C*H_3)$_2$); *m/z* (ES^+) 195 (MNa^+), 227 (MNa+MeOH$^+$); HRMS (ES^+) Found MH^+, 173.1173 ($C_9H_{17}O_3$ requires 173.1172); all data agree with those reported in the literature.[40,43-45,47,48,188]

(2*SR/RS*,3*SR*,4*SR*,5*SR*)-4-Methyl-2,3-diphenyl-2-(trimethylsilyl)-5-vinyl-1,2-oxasilolane, 212



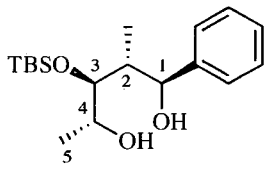
To a solution of silacyclic diol **207a** (0.04 g, 0.1 mmol) in dry DCM (2 ml) was added trifluoroborane-acetic acid complex (0.03 ml, 0.2 mmol). The solution was stirred for 15 mins at room temperature then mixed with saturated $NaHCO_3$ solution (5 ml) and extracted with DCM (3 x 5 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether, pet. ether/ether [98:2]) gave the title compound as an opaque oil (0.03 g, 72%) in a 1:1 isomeric ratio; R_f 0.3 (pet. ether/ether 98:2); υ_{max} (thin film) 2956, 2923, 1650, 1555, 1427, 1244, 1107, 1003, 835, 698 cm^{-1}; NMR data provided for one isomer δ_H (500 MHz, $CDCl_3$) 7.17-7.03 (9H, m, Ar-*H*), 6.74 (1H, d, *J* 8, Ar-*H*), 5.95 (1H, ddd, *J* 17, 9.5, 6.5, 5-C*H*=CH_2), 5.41 (1H, d, *J* 17, 5-CH=C*H*H), 5.31 (1H, d, *J* 9.5, 5-CH=CH*H*), 4.92 (1H, t, *J* 6.5, 5-*H*), 2.69-2.63 (2H, m, 4-*H*, 3-*H*), 0.91 (3H, d, *J* 6, 4-CH_3), 0.21 (9H, s, $Si(CH_3)_3$); δ_C (126 MHz, $CDCl_3$) 139.4 (*ipso*-Ar-C), 138.8 (*ipso*-Ar-C), 137.2 (5-*C*H=CH_2), 133.9 (Ar-*C*), 133.3 (Ar-*C*), 129.0 (Ar-*C*), 128.3 (Ar-*C*), 127.7 (Ar-*C*), 124.7 (Ar-*C*), 116.7 (5-CH=*C*H_2), 83.4 (5-*C*), 40.27 (3-*C*), 40.25 (4-*C*), 15.1 (4-*C*H_3), -1.3 ($Si(CH_3)_3$); δ_{Si} (100 MHz, $CDCl_3$) 19.5, -21.0; *m/z* (ES^+) 353 (MH^+); HRMS (ES^+) Found MH^+, 353.1752 ($C_{21}H_{29}OSi$ requires 353.1752).

(1*SR*,2*SR*,3*RS*)-2-Methyl-1-phenylpentane-1,3,5-triol, 218



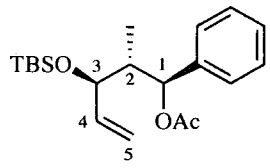
A solution of diol **208** (0.02 g, 0.10 mmol) in THF (1 ml) was treated with borane-dimethylsulfide complex (0.04 ml, 0.37 mmol) at 0 °C. The reaction was then warmed to room temperature and reacted for 1 h. The mixture was then treated successively with water (0.5 ml), NaOH (0.04 ml, 0.10 mmol) and H_2O_2 (0.13 ml, 1.25 mmol). The mixture was then refluxed for 1 h, at which point the mixture was cooled and poured into $Na_2S_2O_3$ and extracted with EtOAc (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (DCM/MeOH [98:2], [95:5], [9:1]) afforded the title compound as a colourless oil (0.015 g, 64%); R_f 0.3 (DCM/MeOH 9:1); υ_{max} (thin film) 3348-3119 (broad-OH), 2962, 2924, 2360, 1684, 1437, 1338, 1223, 1077, 907, 730, 650 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.36-7.34 (4H, m, Ar-*H*), 7.28 (1H, m, Ar-*H*), 4.68 (1H, d, *J* 8, 1-*H*), 4.08 (1H, d, *J* 11, 3-*H*), 3.89-3.82 (3H, m, 5-H_2, -O*H*), 1.98-1.93 (3H, m, 4-*H*H, 2-*H*, -O*H*), 1.55 (1H, d, *J* 11, 4-H*H*), 0.83 (3H, d, *J* 7, 2-CH_3); δ_C (126 MHz, $CDCl_3$) 143.8 (*ipso*-Ar-*C*), 128.7 (Ar-*C*), 127.9 (Ar-*C*), 126.7 (Ar-*C*), 78.5 (1-*C*), 74.7 (3-*C*), 63.0 (5-*C*), 44.4 (2-*C*), 34.4 (4-*C*), 12.8 (2-*C*H_3); *m/z* (ES^+) 233 (MNa^+); HRMS (ES^+) Found MNa^+, 233.1148 ($C_{12}H_{18}O_3Na$ requires 233.1148).

(1*SR*,2*RS*,3*SR*,4*RS*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-1-phenylpentane-1,4-diol, 221b



A solution of mono-protected diol **220** (0.03 g, 0.07 mmol) in THF (1 ml) was treated with borane-dimethylsulfide complex (0.02 ml, 0.18 mmol) at 0 °C. The reaction was then warmed to room temperature and stirred for 1 h. The reaction was then treated successively with water (0.5 ml), NaOH (0.02 ml, 0.07 mmol) and H_2O_2 (0.09 ml, 0.9 mmol). The mixture was then refluxed for 1 h, at which point the mixture was cooled and poured into $Na_2S_2O_3$ and extracted with Et_2O (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether, pet. ether/ether [9:1], [4:1], [1:1], [2:3]) afforded the title compound as a white solid (0.007 g, 30%); R_f 0.4 (pet. ether/ether 2:3); m.p. 120-122 °C; υ_{max} (thin film) 3518-3190 (broad-OH), 3124, 3030, 2962, 2932, 2856, 1606, 1255, 1068, 1024, 896, 835, 716 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.38-7.31 (5H, m, Ar-*H*), 4.46 (1H, d, *J* 9, 1-*H*), 4.11 (1H, dd, *J* 5, 2, 3-*H*), 3.99 (1H, m, 4-*H*), 2.53 (1H, s, -O*H*), 2.19-2.06 (2H, m, 2-*H*, -O*H*), 1.26 (3H, d, *J* 8, 5-*H*), 0.99 (9H, s, $SiC(CH_3)_3$), 0.71 (3H, d, *J* 7, 2-CH_3), 0.22 (3H, s, $Si(CH_3)_2{}^tBu$), 0.17 (3H, s, $Si(CH_3)_2{}^tBu$); δ_C (126 MHz, $CDCl_3$) 143.9 (*ipso*-Ar-*C*), 128.4 (Ar-*C*), 127.7 (Ar-*C*), 126.9 (Ar-*C*), 76.7 (1-*C*), 75.4 (3-*C*), 70.3 (4-*C*), 41.8 (2-*C*), 25.9 ($SiC(CH_3)_3$) 19.1 (5-*C*), 18.3 ($SiC(CH_3)_3$), 12.0 (2-CH_3), -4.2 ($Si(CH_3)_2{}^tBu$), -4.6 ($Si(CH_3)_2{}^tBu$); *m/z* (ES^+) 347 (MNa^+); HRMS (ES^+) Found MNa^+, 347.2011 ($C_{18}H_{32}O_3SiNa$ requires 347.2013).

(1*SR*,2*RS*,3*RS*)-1-Acetoxy-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-1-phenylpent-4-enyl, 224



A solution of TBS protected alcohol **220** (0.02 g, 0.07 mmol) in DCM (1 ml) was treated sequentially with Et_3N (0.06 ml, 0.41 mmol) and acetyl chloride (0.01 ml, 0.14 mmol) at room temperature. The reaction was left for 1 h at which point it was poured into aq. $NaHCO_3$ and extracted with Et_2O (3x5 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether, pet. ether/ether [98:2], [95:5]) afforded the title compound as a colourless oil (0.007 g, 33%); R_f 0.3 (pet. ether/ether 95:5); υ_{max} (thin film) 2929, 2856, 1731 (C=O), 1372, 1251, 1103, 1026, 902, 834, 732, 650 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.31-7.29 (5H, m, Ar-*H*), 5.87 (1H, ddd, *J* 17, 10, 7, 4-*H*), 5.42 (1H, d, *J* 10, 1-*H*), 5.23 (1H, d, *J* 17, 5-*H*H), 5.12 (1H, d, *J* 10, 5-H*H*), 4.51 (1H, m, 3-*H*), 2.02 (3H, s, C(O)CH_3), 1.98 (1H, m, 2-*H*), 0.94 (9H, s, SiC(CH_3)$_3$), 0.58 (3H, d, *J* 7, 2-CH_3), 0.02 (6H, s, Si(CH_3)$_2$^{t}Bu); δ_C (126 MHz, $CDCl_3$) 170.2 (*C*=O), 140.9 (*ipso*-Ar-*C*), 140.4 (4-*C*),128.5 (Ar-*C*), 128.2 (Ar-*C*), 127.8 (Ar-*C*), 114.9 (5-*C*), 78.1 (1-*C*), 72.3 (3-*C*), 44.7 (2-*C*), 26.2 (SiC(*C*H_3)$_3$), 21.6 (C(O)*C*H_3), 18.4 (Si*C*(CH$_3$)$_3$), 10.4 (2-*C*H_3), -3.5 (Si(*C*H_3)$_2$^{t}Bu), -5.1 (Si(*C*H_3)$_2$^{t}Bu); *m/z* (ES^+) 371 (MNa^+); HRMS (ES^+) Found MNa^+, 371.2020 ($C_{20}H_{32}O_3SiNa$ requires 371.2013).

6.4 Application of the Hosomi-Sakurai methodology

6.4.1 Acyclic substrates

6.4.1.1 Standard procedure for the Hosomi-Sakurai reaction of silacycles

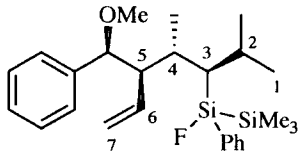
Stage 1

A solution of silacyclohex-4-ene (0.3 mmol) in DCM (5 ml) was treated with aryl or alkyl dimethylacetal (0.6 mmol) and cooled to 0 °C. The solution was then treated with $BF_3 \bullet OEt_2$ ([0.5M] in DCM, 0.3 mmol) and reacted at 0 °C for 6 h. The reaction mixture was then poured into aq. NH_4Cl and extracted with DCM (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. The concentrated organic material could then be utilised directly in the next stage or purified by flash chromatography to afford the silyl fluoride species. These in turn could then be utilised in stage 2.

Stage 2

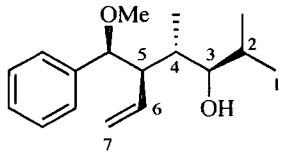
The crude organic material or purified silyl fluoride species was dissolved in methanol:THF (5 ml, 1:1) and treated with $KHCO_3$ (1.0 mmol) and a 35% w/w solution of H_2O_2 (4.0 mmol) at room temperature. The mixture was then heated at reflux over 5 h, at which point the mixture was poured into $Na_2S_2O_3$ and extracted with EtOAc (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether/ether [95:5], [9:1], [4:1]) affords the desired mono-protected 1,4-diols.

(3*RS*,4*SR*,5*RS*,*(Si)RS/SR*)-3-(1-Fluoro-2,2,2-trimethyl-1-phenyldisilyl)-5-((*RS*)-methoxy(phenyl)methyl)-2,4-dimethylhept-6-en-3-yl, 327



Following stage 1 of the standard procedures outlined on page 181, silacyclohex-4-ene **100** (0.35 g, 1.1 mmol) was combined with benzaldehyde dimethylacetal to give the title compound as a pale yellow oil (0.3 g, 60%); R_f 0.6 (pet. ether/ether 95:5) as a mixture of diastereoisomers in the ratio 2:1 by NMR; υ_{max} (thin film) 2926, 2918, 1675, 1651, 1536, 1454, 1428, 1359, 1245, 1189, 1105, 916, 836, 800, 735, 729, 699, 543 cm^{-1}; NMR data given for major isomer δ_H (500 MHz, $CDCl_3$) 7.50-7.49 (2H, m, Ar-*H*), 7.35-7.33 (2H, m, Ar-*H*), 7.32-7.30 (4H, m, Ar-*H*), 7.19-7.17 (2H, m, Ar-*H*), 5.70 (1H, ddd, *J* 17, 10, 10, 6-*H*), 4.95 (1H, d, *J* 10, 7-H*H*), 4.44 (1H, d, *J* 17, 7-*H*H), 3.29 (3H, s, 5-CH(OCH_3)), 2.64 (1H, m, 3-*H*), 2.56 (1H, m, 4-*H*), 2.20 (1H, t, *J* 10, 5-*H*), 1.97 (1H, m, 2-*H*), 1.35 (3H, m, 4-CH_3), 1.14 (1H, m, 5-C*H*(OCH_3)), 1.03 (3H, m, 2-CH_3), 0.62 (3H, d, *J* 7, 1-*H*), 0.13 (9H, s, Si(CH_3)$_3$); δ_C (126 MHz, $CDCl_3$) 141.5 (Ar-*C*), 137.3 (6-*C*), 137.0 (Ar-*C*), 132.7 (Ar-*C*), 132.6 (Ar-*C*), 129.0 (Ar-*C*), 127.7 (Ar-*C*), 127.2 (Ar-*C*), 126.8 (Ar-*C*), 118.5 (7-*C*), 65.9 (5-*C*H(OCH_3)), 57.44 (5-CH(O*C*H_3)), 57.42 (5-*C*), 38.8 (3-*C*), 35.7 (4-*C*), 26.2 (2-*C*), 25.9 (2-*C*H_3), 24.0 (1-*C*), 16.6 (4-*C*H_3), -2.1 (Si(*C*H_3)$_3$); δ_F (300 MHz, $CDCl_3$) -185.6 (1F, d, *J* 18, Si-*F*); *m/z* (CI) 460 (MNH_4^+, 100%), 428 (35%), 411 (M^+ -(OCH_3), 40%); HRMS (CI) Found MNH_4^+, 460.2863 ($C_{26}H_{43}FOSi_2N$ requires 460.2862).

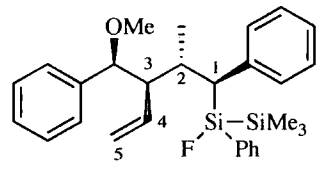
(3*RS*,4*SR*,5*RS*)-5-((*RS*)-Methoxy(phenyl)methyl)-2,4-dimethylhept-6-en-3-ol, 328



Following the standard procedure outlined on page 181, silacyclohex-4-ene **100** (0.1 g, 0.3 mmol) was combined with benzaldehyde dimethyl acetal to give, without purification of the fluorosilane, the title compound isolated as a pale yellow oil (0.04 g, 50%); R_f 0.4 (pet. ether/ether 9:1) as a mixture of diastereoisomers in the ratio 2:1 by NMR.

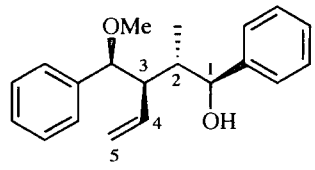
Following stage 2 of the standard procedures outlined on page 181, fluorosilane **327** (0.3 g, 0.6 mmol) was transformed into the title compound which was isolated as a colourless oil (0.1 g, 80%); R_f 0.4 (pet. ether/ether 9:1) as a mixture of diastereoisomers in the ratio 2:1 by NMR; υ_{max} (thin film) 3326 (broad-OH), 2958, 2874, 2834, 1605, 1594, 1498, 1471, 1454, 1363, 1233, 1066, 992, 918, 752, 691 cm^{-1}; NMR data given for the major isomer δ_H (500 MHz, $CDCl_3$) 7.34-7.31 (2H, m, Ar-*H*), 7.27-7.23 (3H, m, Ar-*H*), 6.04 (1H, ddd, *J* 17, 10, 10, 6-*H*), 5.09 (1H, dd, *J* 10, 2, 7-*H*H), 4.76 (1H, dd, *J* 17, 2, 7-H*H*), 4.48 (1H, d, *J* 4, 5-C*H*(OCH_3)), 3.76 (1H, d, *J* 3, -O*H*), 3.28 (1H, m, 3-*H*), 3.23 (3H, s, 5-CH(OC*H*$_3$)), 2.26 (1H, m, 5-*H*), 1.82 (1H, m, 4-*H*), 1.74 (1H, m, 2-*H*), 1.00 (3H, d, *J* 7, 2-C*H*$_3$), 0.86 (3H, d, *J* 7, 4-C*H*$_3$), 0.81 (3H, d, *J* 7, 1-*H*); δ_C (126 MHz, $CDCl_3$) 140.7 (*ipso*-Ar-*C*), 134.3 (6-*C*), 128.0 (Ar-*C*), 127.4 (Ar-*C*), 127.3 (Ar-*C*), 118.8 (7-*C*), 86.9 (5-*C*H(OCH$_3$)), 76.9 (3-*C*), 57.8 (5-*C*), 57.0 (5-CH(O*C*H$_3$)), 40.9 (4-*C*), 29.6 (2-*C*), 20.7 (2-*C*H$_3$), 17.4 (4-*C*H$_3$), 13.6 (1-*C*); *m/z* (ES^+) 285 (MNa^+); HRMS (ES^+) Found MNa^+, 285.1825 ($C_{17}H_{26}O_2Na$ requires 285.1825).

(1*SR*,2*SR*,3*RS*,*(Si)RS/SR*)-1-(1-Fluoro-2,2,2-trimethyl-1-phenyldisilyl)-3-((*RS*)-methoxy(phenyl)methyl)-2-methyl-1-phenylpent-4-enyl, 321Ac



Following stage 1 of the standard procedures outlined on page 181, silacyclohex-4-ene **206** (0.2 g, 0.6 mmol) was combined with benzaldehyde dimethylacetal to give the title compound as a pale yellow oil (0.2 g, 72%); R_f 0.6 (pet. ether/ether 95:5) as a mixture of diastereoisomers in the ratio 2:1 by NMR; υ_{max} (thin film) 1491, 1449, 1427, 1245, 1103, 915, 834, 798, 734, 697 cm^{-1}; NMR data given for major isomer δ_H (500 MHz, $CDCl_3$) 7.43-7.06 (15H, m, Ar-*H*), 5.76 (1H, ddd, *J* 17, 10, 10, 4-*H*), 5.02 (1H, dd, *J* 10, 2, 5-*H*H), 4.46 (1H, dd, *J* 17, 2, 5-H*H*), 4.37 (1H, d, *J* 3, 3-C*H*(OCH_3)), 3.24 (3H, s, 3-CH(OCH_3)), 2.59 (1H, m, 2-*H*), 2.00 (1H, m, 3-*H*), 1.20 (3H, d, *J* 7, 2-CH_3), 1.05 (1H, m, 1-*H*), 0.09 (9H, s, $Si(CH_3)_3$); δ_C (126 MHz, $CDCl_3$) 141.2 (*ipso*-Ar-*C*), 137.3 (4-*C*), 133.2 (Ar-*C*), 131.2 (*ipso*-Ar-*C*), 130.9 (*ipso*-Ar-*C*), 129.4 (Ar-*C*), 128.9 (Ar-*C*), 127.8 (Ar-*C*), 127.7 (Ar-*C*), 127.6 (Ar-*C*), 127.2 (Ar-*C*), 126.7 (Ar-*C*), 125.4 (Ar-*C*), 118.8 (5-*C*), 83.2 (3-*C*H(OCH_3)), 57.1 (3-CH(OCH_3)), 55.8 (3-*C*), 35.9 (2-*C*), 16.7 (1-*C*), 16.7 (2-CH_3), -2.0 ($Si(CH_3)_3$); δ_F (300 MHz, $CDCl_3$) -184.6 (1F, d, *J* 11, Si-*F*); *m/z* (ES^+) 513 (MK^+), 499 (MNa^+); HRMS (ES^+) Found MNa^+, 499.2271 ($C_{29}H_{37}FOSi_2Na$ requires 499.2259).

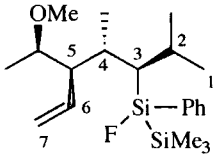
(1*SR*,2*SR*,3*RS*)-3-((*RS*)-Methoxy(phenyl)methyl)-2-methyl-1-phenylpent-4-en-1-ol, 322Ad



Following the standard procedure outlined on page 181, silacyclohex-4-ene **206** (0.1 g, 0.3 mmol) was combined with benzaldehyde dimethyl acetal to give, without purification of the fluorosilane, the title compound isolated as a pale yellow oil (0.05 g, 55%); R_f 0.3 (pet. ether/ether 9:1) as a mixture of diastereoisomers in the ratio 2:1 by NMR.

Following stage 2 of the standard procedures outlined on page 181, fluorosilane **321Ac** (0.17 g, 0.4 mmol) was transformed into the title compound which was isolated as a colourless oil (0.04 g, 55%); R_f 0.3 (pet. ether/ether 9:1) as a mixture of diastereoisomers in the ratio 2:1 by NMR; υ_{max} (thin film) 3355 (broad –OH), 2362, 2333, 1491, 1452, 1084, 1068, 914, 841, 754, 698 cm^{-1}; NMR data given for major isomer δ_H (500 MHz, $CDCl_3$) 7.30-7.16 (10H, m, Ar-*H*), 6.05 (1H, ddd, *J* 17, 10, 10, 4-*H*), 5.14 (1H, dd *J* 10, 3, 5-H*H*), 4.80 (1H, dd, *J* 17, 3, 5-*H*H), 4.55 (1H, m, 3-C*H*(OCH_3)), 4.31 (1H, d, *J* 10, 1-*H*), 3.81 (1H, s, -O*H*), 3.26 (3H, s, 3-CH(OCH_3)), 2.29 (1H, m, 3-*H*), 1.98 (1H, m, 2-*H*), 0.55 (3H, d, *J* 7, 2-CH_3); δ_C (126 MHz, $CDCl_3$) 144.1 (Ar-*C*), 140.8 (*ipso*-Ar-*C*), 134.6 (4-*C*), 128.2 (Ar-*C*), 128.1 (Ar-*C*), 127.6 (Ar-*C*), 127.4 (Ar-*C*), 127.2 (Ar-*C*), 126.6 (Ar-*C*), 119.2 (5-*C*), 86.6 (3-*C*H(OCH_3)), 77.0 (1-*C*), 57.2 (3-CH(O*C*H_3)), 57.0 (3-*C*), 43.8 (2-*C*), 17.2 (2-*C*H_3); *m/z* (ES^+) 319 (MNa^+); HRMS (ES^+) Found MNa^+, 319.1667 ($C_{20}H_{24}O_2Na$ requires 319.1669).

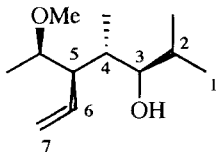
(3*RS*,4*SR*,5*RS*,(*Si*)*RS*/*SR*)-3-(1-Fluoro-2,2,2-trimethyl-1-phenyldisilyl)-5-((*R*)-1-methoxyethyl)-2,4-dimethylhept-6-en-3-yl, 321Ab



Following stage 1 of the standard procedures outlined on page 181, silacyclohex-4-ene **100** (0.1 g, 0.3 mmol) was combined with acetaldehyde dimethylacetal to give the title compound as a colourless oil (0.034 g, 30%); R_f 0.7 (pet.ether/ether 95:5) as a mixture of diastereoisomers in the ratio 2:1 by mass; υ_{max} (thin film) 2959, 2887, 2820, 2362, 2341, 1463, 1372, 1245, 1101, 1086, 1005, 913, 835 cm^{-1}; NMR data given for major isomer δ_H (500 MHz, $CDCl_3$) 7.52-7.50 (2H, m, Ar-*H*), 7.36-7.35 (3H, m, Ar-*H*), 5.65 (1H, ddd, *J* 17, 10, 10, 6-*H*), 5.22 (1H, d, *J* 10, 7-H*H*), 4.97 (1H, d, *J* 17, 7-*H*H), 3.58 (1H, m, 5-C*H*(OCH_3)(CH_3)), 3.33 (3H, s, 5-CH(OCH_3)(CH_3)), 2.45 (1H, m, 4-*H*), 2.02-1.90 (2H, m, 5-*H*, 2-*H*), 1.40 (1H, m, 3-*H*), 1.19 (3H, d, *J* 7, 4-CH_3), 1.09 (3H, d, *J* 7, 5-CH(OCH_3)(CH_3)), 1.01 (3H, d, *J* 7, 2-CH_3), 0.67 (3H, d, *J* 7, 1-*H*), 0.11 (9H, s, (Si(CH_3)$_3$); δ_C (126 MHz, $CDCl_3$) 138.6 (6-*C*), 138.2 (*ipso*-Ar-*C*), 132.7 (Ar-*C*), 128.9 (Ar-*C*), 127.8 (Ar-*C*), 118.3 (7-*C*), 75.6 (5-*C*H(OCH_3)(CH_3)), 56.7 (5-CH(O*C*H_3)(CH_3)), 55.6 (5-*C*), 38.7 (3-*C*), 35.2 (4-*C*), 26.2 (2-*C*), 25.9 (2-*C*H_3), 24.0 (1-*C*), 17.5 (5-CH(OCH_3)(*C*H_3)), 16.4 (4-*C*H_3), -2.1 (Si(CH_3)$_3$); δ_F (300 MHz, $CDCl_3$) -185.5 (1F, d, *J* 16, Si-*F*); *m/z* (ES^+) 403 (MNa^+); HRMS (ES^+) Found MNa^+, 403.2268 ($C_{21}H_{37}Si_2FONa$ requires 403.2259).

Further elution gave the minor diastereoisomer as a colourless oil (0.017 g, 15%).

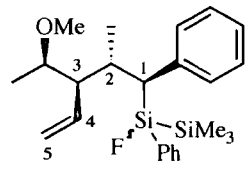
(3*RS*,4*SR*,5*RS*)-5-((*R*)-1-Methoxyethyl)-2,4-dimethylhept-6-en-3-ol, 322Ac



Following stage 2 of the standard procedures outlined on page 181, major fluorosilane isomer **321Ab** (0.04 g, 0.1 mmol) was transformed into the title compound which was isolated as a colourless oil (0.007 g, 35%); R_f 0.2 (pet. ether/ether 9:1); υ_{max} (thin film) 3374 (broad-OH), 2960, 2928, 2878, 1737, 1678, 1600, 1520, 1468, 1428, 1364, 1256, 1232, 1120, 1072, 1042; cm^{-1}; δ_H (500 MHz, $CDCl_3$) 5.93 (1H, ddd, *J* 17, 10, 10, 6-*H*), 5.19 (1H, dd, *J* 10, 2, 7-*H*H), 5.03 (1H, m, 7-H*H*), 4.42 (1H, s, -O*H*), 3.52 (1H, m, 5-C*H*(OCH_3)(CH_3)), 3.34 (3H, s, 5-CH(OCH_3)(CH_3)), 3.21 (1H, m, 3-*H*), 2.02 (1H, d, *J* 10, 5-*H*), 1.80-1.68 (2H, m, 4-*H*, 2-*H*), 1.12 (3H, m, 5-CH(OCH_3)(CH_3)), 0.92 (3H, m, 2-CH_3), 0.87 (3H, d, *J* 7, 4-CH_3), 0.83 (3H, d, *J* 7, 1-*H*); δ_C (126 MHz, $CDCl_3$) 137.2 (6-*C*), 119.1 (7-*C*), 80.2 (5-*C*H(OCH_3)(CH_3)), 76.0 (3-*C*), 57.3 (5-*C*), 56.6 (5-CH(OCH_3)(CH_3)), 42.0 (4-*C*), 30.0 (2-*C*), 20.4 (2-*C*H_3), 18.0 (4-*C*H_3), 17.4 (5-C*H*(OCH_3)(*C*H_3)), 14.0 (1-*C*); *m/z* (ES^+) 223 (MNa^+); HRMS (ES^+) Found MNa^+, 223.1669 ($C_{12}H_{24}O_2Na$ requires 223.1668).

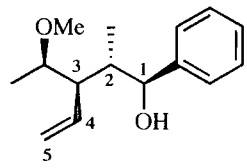
Oxidation of the minor fluorosilane isomer afforded the title isomeric compound as a colourless oil (0.005 g, 53%).

(1*SR*,2*SR*,3*RS*,*(Si)RS/SR*)-1-(1-Fluoro-2,2,2-trimethyl-1-phenyldisilyl)-3-((*RS*)-1-methoxyethyl)-2-methyl-1-phenylpent-4-enyl, 321Ad



Following stage 1 of the standard procedures outlined on page 181, silacyclohex-4-ene **206** (0.3 g, 0.9 mmol) was combined with acetaldehyde dimethylacetal to give the title compound as a colourless oil (0.13 g, 38%); R_f 0.6 (pet. ether/ether 95:5) as a mixture of diastereoisomers in the ratio 2:1 by NMR; υ_{max} (thin film) 2971, 2957, 1493, 1427, 1374, 1244, 1108, 998, 913, 855, 834, 800, 741, 696 cm^{-1}; NMR data given for major isomer δ_H (500 MHz, $CDCl_3$) 7.32-7.24 (5H, m, Ar-*H*), 7.17-7.07 (5H, m, Ar-*H*), 5.76 (1H, ddd, *J* 17, 10, 10, 4-*H*), 5.30 (1H, dd, *J* 10, 2, 5-*H*H), 4.97 (1H, m, 5-H*H*), 3.29 (3H, s, 3-CH(OCH_3)(CH_3)), 2.80 (1H, dd, *J* 12, 4, 1-*H*), 2.49 (1H, m, 2-*H*), 2.28 (1H, m, 3-C*H*(OCH_3)(CH_3)), 1.74 (1H, m, 3-*H*), 1.10 (3H, m, 2-CH_3), 1.01 (3H, m, 3-CH(OCH_3)(CH_3)), 0.10 (9H, s, Si(CH_3)$_3$); δ_C (126 MHz, $CDCl_3$) 140.7 (*ipso*-Ar-*C*), 140.4 (*ipso*-Ar-*C*), 140.2 (*ipso*-Ar-*C*), 137.6 (4-*C*), 133.1 (Ar-*C*), 131.3 (Ar-*C*), 127.7 (Ar-*C*), 127.7 (Ar-*C*), 125.4 (Ar-*C*), 118.8 (5-*C*), 79.8 (1-*C*), 77.5 (3-*C*H(OCH_3)(CH_3)), 56.3 (3-CH(OCH_3)(CH_3)), 54.1 (3-*C*), 41.5 (2-*C*), 17.2 (3-CH(OCH_3)(*C*H_3)), 14.9 (2-*C*H_3), -2.0 (Si(*C*H_3)$_3$); δ_F (300 MHz, $CDCl_3$) -185.3 (1F, d, *J* 14, Si-*F*); *m/z* (ES^+) 437 (MNa^+); HRMS (ES^+) Found MNa^+, 437.2101 ($C_{24}H_{35}OFSi_2Na$ requires 437.2103).

(1*SR*,2*SR*,3*RS*)-3-((*RS*)-1-Methoxyethyl)-2-methyl-1-phenylpent-4-en-1-ol, 322Ai

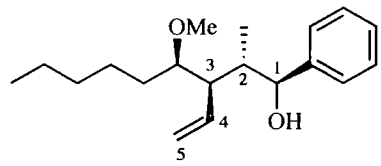


Following stage 2 of the standard procedures outlined on page 181, fluorosilane **321Ad** (0.15 g, 0.4 mmol) was transformed into the title compound which was isolated as a white solid (0.034 g, 40%); R_f 0.2 (pet. ether/ether 9:1) as a mixture of diastereoisomers in the ratio 2:1 by NMR.

Also, following the standard procedure outlined on page 181, silacyclohex-4-ene **206** (0.2 g, 0.6 mmol) was combined with acetaldehyde dimethylacetal to give, without purification of the fluorosilane, the title compound as a colourless oil (0.011 g, 8%); R_f 0.2 (pet. ether/ether 9:1); υ_{max} (thin film) 3332 (broad-OH), 3071, 3027, 2974, 2930, 2831, 2359, 2338, 1716, 1683, 1652, 1558, 1540, 1455, 1260, 1197, 1119, 1074, 843 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.33-7.32 (5H, m, Ar-*H*), 5.80 (1H, ddd, *J* 17, 11, 10, 4-*H*), 5.04 (1H, dd, *J* 10, 2, 5-*H*H), 4.91 (1H, dd, *J* 17, 2, 5-H*H*), 4.50 (1H, m, 1-*H*), 3.46 (1H, m, 3-C*H*(OCH_3)(CH_3)), 3.42 (3H, s, 3-CH(OCH_3)(CH_3)), 2.24 (1H, m, 3-*H*), 2.18 (1H, m, 2-*H*), 1.13 (3H, d, *J* 6, 3-CH(OCH_3)(CH_3)), 0.83 (3H, d, *J* 7, 2-CH_3); δ_C (126 MHz, $CDCl_3$) 144.5 (*ipso*-Ar-*C*), 138.3 (4-*C*), 128.1 (Ar-*C*), 126.9 (Ar-*C*), 126.7 (Ar-*C*), 118.7 (5-*C*), 79.5 (1-*C*), 76.5 (3-*C*H(OCH_3)(CH_3)), 56.1 (3-CH(OCH_3)(CH_3)), 52.0 (3-*C*), 42.8 (2-*C*), 17.2 (3-CH(OCH_3)(*C*H_3)), 14.8 (2-*C*H_3); *m/z* (ES^+) 257 (MNa^+); HRMS (ES^+) Found MNa^+, 257.1510 ($C_{15}H_{22}O_2Na$ requires 257.1512).

Further elution gave a mixture of diastereoisomers as a pale yellow oil (0.033 g, 24%); all data for the major isomer agreeing with that given above.

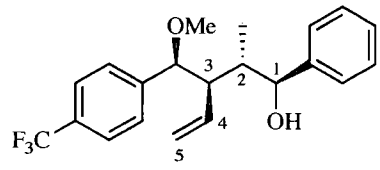
(1*SR*,2*SR*,3*RS*)-3-((*RS*)-1-Methoxyhexyl)-2-methyl-1-phenylpent-4-en-1-ol, 322Aj



Following the standard procedure outlined on page 181, silacyclohex-4-ene **206** (0.1 g, 0.3 mmol) was combined with hexanal dimethylacetal to give, without purification of the fluorosilane, the title compound as a yellow oil (0.08 g, 10%); R_f 0.3 (pet. ether/ether 9:1); υ_{max} (thin film) 3689, 3602, 3343 (broad –OH), 2958, 2831, 2872, 2860, 2243, 1681, 1600, 1493, 1455, 1378, 1260, 1197, 1111, 1081, 1011 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.32-7.14 (5H, m, Ar-*H*), 5.90 (1H, ddd, *J* 17, 11, 10, 4-*H*), 5.08 (1H, dd, *J* 10, 2, 5-*H*H), 4.96 (1H, dd, *J* 17, 2, 5-H*H*), 4.63 (1H, s, -O*H*), 4.44 (1H, d, *J* 8, 1-*H*), 3.43 (3H, s, 3-CH(OCH_3)(CH_2)$_4CH_3$)), 3.37 (1H, m, 3-C*H*(OCH_3)(CH_2)$_4CH_3$)), 2.37 (1H, m, 3-*H*), 2.14 (1H, m, 2-*H*), 1.66-1.25 (8H, m, 3-CH(OCH_3)(CH_2)$_4CH_3$)), 0.87 (3H, m, 3-CH(OCH_3)(CH_2)$_4$CH_3)), 0.76 (3H, d, *J* 7, 2-CH_3); δ_C (126 MHz, $CDCl_3$) 144.6 (*ipso*-Ar-*C*), 138.0 (4-*C*), 128.0 (Ar-*C*), 127.0 (Ar-*C*), 126.9 (Ar-*C*), 116.8 (5-*C*), 81.7 (3-*C*H(OCH_3)(CH_2)$_4CH_3$)), 76.6 (1-*C*), 57.1 (3-CH(O*C*H_3)(CH_2)$_4CH_3$)), 49.7 (3-*C*), 42.0 (2-*C*), 32.1, 30.4, 23.7, 22.6 (3-CH(OCH_3)(*C*H_2)$_4CH_3$), 15.6 (2-*C*H_3), 14.0 (3-CH(OCH_3)(CH_2)$_4$*C*H_3)); *m/z* (ES^+) 313 (MNa^+), 603 ($2MNa^+$); HRMS (ES^+) Found MNa^+, 313.2138 ($C_{19}H_{30}O_2Na$ requires 313.2138).

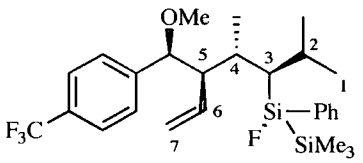
Further elution gave the minor diastereoisomer as a colourless oil (0.08 g, 10%).

(1*SR*,2*SR*,3*RS*)-3-((*RS*)-Methoxy(4-(trifluoromethyl)phenyl)methyl)-2-methyl-1-phenylpent-4-en-1-ol, 322Af



Following the standard procedure outlined on page 181, silacyclohex-4-ene **206** (0.1 g, 0.3 mmol) was combined with trifluoromethylbenzaldehyde dimethylacetal **338** to give, without purification of the fluorosilane, the title compound as a colourless oil (0.05 g, 50%); R_f 0.3 (pet. ether/ether 9:1) as a mixture of diastereoisomers in the ratio 4:1.5:1 by NMR; υ_{max} (thin film) 3370 (broad-OH), 2960, 2931, 2876, 1736, 1618, 1599, 1417, 1325, 1167, 1129 cm^{-1}; NMR data given for the major isomer δ_H (500 MHz, $CDCl_3$) 7.62 (2H, d, *J* 9, Ar-*H*), 7.45 (2H, d, *J* 9, Ar-*H*), 7.33-7.26 (5H, m, Ar-*H*), 6.09 (1H, ddd, *J* 17, 11, 10, 4-*H*), 5.21 (1H, dd, *J* 10, 2, 5-*H*H), 4.86 (1H, dd, *J* 17, 2, 5-H*H*), 4.70 (1H, d, *J* 6, 3-C*H*(OCH_3)), 4.43 (1H, d, *J* 9, 1-*H*), 3.34 (1H, s, -O*H*), 3.27 (3H, s, 3-CH(OCH_3)), 2.30 (1H, m, 3-*H*), 2.04 (1H, m, 2-*H*), 0.65 (3H, d, *J* 7, 2-CH_3); δ_C (126 MHz, $CDCl_3$) 143.8 (*ipso*-Ar-*C*), 140.6 (*ipso*-Ar-*C*), 134.6 (4-*C*), 128.3 (Ar-*C*), 127.9 (*ipso*-Ar-*C*CF_3), 127.8 (Ar-*C*), 127.6 (Ar-*C*), 127.1 (Ar-*C*), 125.0 (Ar-*C*), 124.5 (*p*-CF_3, q, *J* 271), 119.5 (5-*C*), 85.6 (3-*C*H(OCH_3)), 57.2 (3-CH(OCH_3)), 56.7 (3-*C*), 43.1 (1-*C*), 43.0 (2-*C*), 16.7 (2-CH_3); δ_F (300 MHz, $CDCl_3$) -62.72 (3F, m, Ar-CF_3); *m/z* (CI) 382 (MNH_4^+); HRMS (CI) Found MNH_4^+, 382.1985 ($C_{21}H_{27}O_2NF_3$ requires 382.1988).

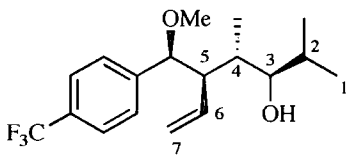
(3*RS*,4*SR*,5*RS*,(*Si*)*RS*/*SR*)-3-(1-Fluoro-2,2,2-trimethyl-1-phenyldisilyl)-5-((*S*)-methoxy(4-(trifluoromethyl)phenyl)methyl)-2,4-dimethylhept-6-en-3-yl, 321Aa



Following stage 1 of the standard procedures outlined on page 181, silacyclohex-4-ene **100** (0.1 g, 0.3 mmol) was combined with trifluoromethylbenzaldehyde dimethylacetal **338** to give the title compound as a colourless oil (0.031 g, 20%); R_f 0.7 (pet. ether/ether 95:5); υ_{max} (thin film) 2981, 2940, 1466, 1411, 1355, 1235, 1100, 967, 908, 845 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.56 (2H, d, *J* 8, Ar-*H*), 7.51-7.49 (2H, m, Ar-*H*), 7.37-7.35 (3H, m, Ar-*H*), 7.29 (2H, d, *J* 8, Ar-*H*), 5.68 (1H, ddd, *J* 17, 10, 10, 6-*H*), 4.95 (1H, dd, *J* 10, 2, 7-H*H*), 4.56 (1H, s, 5-C*H*(OCH_3)), 4.41 (1H, dd, *J* 17, 2, 7-*H*H), 3.29 (3H, s, 5-CH(OCH_3)), 2.58 (1H, m, 4-*H*), 2.18 (1H, dt, *J* 10, 2, 5-*H*), 1.90 (1H, m, 2-*H*), 1.40 (1H, d, *J* 17, 3-*H*), 1.36 (3H, d, *J* 7, 4-CH_3), 1.03 (3H, d, *J* 7, 2-CH_3), 0.62 (3H, d, *J* 7, 1-*H*), 0.14 (9H, s, ($Si(CH_3)_3$); δ_C (126 MHz, $CDCl_3$) 145.8 (Ar-*C*), 140.3 (*ipso*-Ar-*C*), 138.4 (*ipso*-Ar-*C*), 136.3 (6-*C*), 132.7 (Ar-*C*), 130.8 (*ipso*-Ar-*C*CF_3, q, *J* 33), 129.1 (Ar-*C*), 127.8 (Ar-*C*), 127.1 (Ar-*C*), 124.7 (Ar-*C*), 124.3 (*p*-*C*F_3, q, *J* 272), 119.1 (7-*C*), 83.1 (5-*C*H(OCH_3)), 57.6 (5-CH(OCH_3)), 57.3 (5-*C*), 38.8 (3-*C*), 35.7 (4-*C*), 26.2 (2-*C*H_3), 25.8 (2-*C*), 24.0 (1-*C*), 16.6 (4-*C*H_3), -2.1 ($Si(CH_3)_3$); δ_F (300 MHz, $CDCl_3$) -62.8 (-C*F*$_3$), -185.5 (Si-*F*); *m/z* (ES^+) 533 (MNa^+); HRMS (ES^+) Found MNa^+, 533.2289 ($C_{27}H_{38}OF_4Si_2Na$ requires 533.2289).

Further elution gave a mixture of diastereoisomers as a colourless oil (0.022 g, 12%); all data for the major isomer agreeing with that given above.

(3*RS*,4*SR*,5*RS*)-5-((*S*)-Methoxy(4-(trifluoromethyl)phenyl)methyl)-2,4-dimethylhept-6-en-3-ol, 322Aa

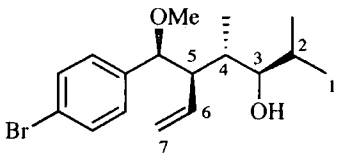


Following the standard procedure outlined on page 181, silacyclohex-4-ene **100** (0.1 g, 0.3 mmol) was combined with trifluoromethylbenzaldehyde dimethylacetal **338** to give, without purification of the fluorosilane, the title compound as a colourless oil (0.012 g, 11%).

Also, following stage 2 of the standard procedures outlined on page 181, fluorosilane **321Aa** (0.03 g, 0.07 mmol) was transformed into the title compound which was isolated as a colourless oil (0.012 g, 56%); R_f 0.3 (pet. ether/ether 9:1); υ_{max} (thin film) 3386 (broad-OH), 2960, 2931, 2872, 1736, 1600, 1517, 1416, 1364, 1325, 1256, 1228, 1128 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.58 (2H, d, *J* 8, Ar-*H*), 7.38 (2H, d, *J* 8, Ar-*H*), 6.01 (1H, ddd, *J* 17, 11, 10, 6-*H*), 5.09 (1H, dd, *J* 10, 2, 7-*H*H), 4.77 (1H, dd, *J* 17, 2, 7-H*H*), 4.59 (1H, d, *J* 4, 5-C*H*(OCH_3)), 3.30 (1H, m, 3-*H*), 3.23 (3H, s, 5-CH(OC*H*$_3$)), 3.08 (1H, d, *J* 4, -O*H*), 2.24 (1H, m, 5-*H*), 1.79-1.73 (2H, m, 4-*H* & 2-*H*), 1.00 (3H, d, *J* 7, 2-C*H*$_3$), 0.85 (3H, d, *J* 7, 4-C*H*$_3$), 0.80 (3H, d, *J* 7, 1-*H*); δ_C (126 MHz, $CDCl_3$) 145.6 (*ipso*-Ar-*C*), 134.7 (6-*C*), 128.3 (Ar-*C*), 127.9 (*ipso*-Ar-*C*CF_3, q, *J* 33), 125.2 (Ar-*C*), 124.5 (*p*-*C*F_3, q, *J* 271), 119.1 (7-*C*), 86.2 (5-*C*H(OCH_3)), 78.8 (3-*C*), 57.5 (5-*C*), 57.4 (5-CH(O*C*H_3)), 40.5 (4-*C*), 29.8 (2-*C*), 20.8 (2-*C*H_3), 17.2 (4-*C*H_3), 14.0 (1-*C*); δ_F (300 MHz, $CDCl_3$) -62.73 (3F, m, C*F*$_3$); *m/z* (ES^+) 353 (MNa^+); HRMS (ES^+) Found MNa^+, 353.1700 ($C_{18}H_{25}O_2F_3Na$ requires 353.1699).

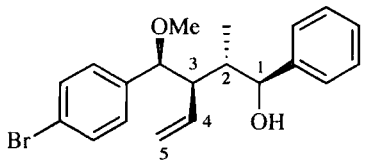
Oxidation of the fluorosilane mixture afforded a diastereomeric mixture of the title compound as a colourless oil (0.09 g, 70%), all data for the major isomer agreeing with that given above.

(3*RS*,4*SR*,5*RS*)-5-((*RS*)-(4-Bromophenyl)(methoxy)methyl)-2,4-dimethylhept-6-en-3-ol, 322Ab



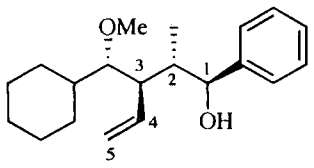
Following the standard procedure outlined on page 181, silacyclohex-4-ene **100** (0.1 g, 0.3 mmol) was combined with bromobenzaldehyde dimethylacetal to give, without purification of the fluorosilane, the title compound as a colourless oil (0.026 g, 23%); R_f 0.3 (pet. ether/ether 9:1) as a mixture of diastereoisomers in the ratio 2:1 by NMR; υ_{max} (thin film) 3391 (broad –OH), 2961, 2932, 2875, 2241, 1737, 1486, 1463, 1405, 1364, 1259, 1072, 1011, 840, 821 cm^{-1}; NMR data given for major isomer δ_H (500 MHz, $CDCl_3$) 7.47 (2H, d, *J* 9, Ar-*H*), 7.16 (2H, d, *J* 9, Ar-*H*), 6.01 (1H, ddd, *J* 17, 11, 10, 6-*H*), 5.12 (1H, dd, *J* 10, 2, 7-*H*H), 4.81 (1H, dd, *J* 17, 2, 7-H*H*), 4.50 (1H, d, *J* 4, 5-C*H*(OCH_3)), 3.76 (1H, d, *J* 6, -O*H*), 3.30 (1H, m, 3-*H*), 3.23 (3H, s, 5-CH(OCH_3)), 2.22 (1H, m, 5-*H*), 1.80-1.74 (2H, m, 4-*H*, 2-*H*), 1.02 (3H, d, *J* 7, 1-*H*), 0.87 (3H, d, *J* 7, 4-CH_3), 0.82 (3H, d, *J* 7, 2-CH_3); δ_C (126 MHz, $CDCl_3$) 139.5 (*ipso*-Ar-*C*), 135.4 (*ipso*-Ar-*C*), 134.5 (6-*C*), 131.1 (Ar-*C*), 129.1 (Ar-*C*), 118.8 (7-*C*), 86.0 (5-*C*H(OCH_3)), 76.6 (3-*C*), 57.5 (5-*C*), 57.0 (5-CH(OCH_3)), 40.3 (4-*C*), 29.6 (2-*C*), 20.6 (1-*C*), 17.1 (4-*C*H_3), 13.7 (2-*C*H_3); *m/z* (ES^+) 363 ([^{79}Br]MNa^+); HRMS (ES^+) Found [^{79}Br]MNa^+, 363.0931 ($C_{17}H_{25}O_2{}^{79}BrNa$ requires 363.0930).

(1*SR*,2*SR*,3*RS*)-3-((*RS*)-(4-Bromophenyl)(methoxy)methyl)-2-methyl-1-phenylpent-4-en-1-ol, 322Ag



Following the standard procedure outlined on page 181, silacyclohex-4-ene **206** (0.1 g, 0.3 mmol) was combined with bromobenzaldehyde dimethylacetal to give, without purification of the fluorosilane, the title compound as a yellow oil (0.051 g, 46%); R_f 0.3 (pet. ether/ether 9:1) as a mixture of diastereoisomers in the ratio 3:1 by NMR; υ_{max} (thin film) 3605, 3362 (broad-OH), 2960, 2929, 2243, 1719, 1591, 1487, 1453, 1405, 1269, 1081, 1072, 1011, 839, 818 cm^{-1}; NMR data given for major isomer δ_H (500 MHz, $CDCl_3$) 7.49 (2H, d, *J* 9, Ar-*H*), 7.40-7.25 (5H, m, Ar-*H*), 7.21 (2H, d, *J* 9, Ar-*H*), 6.07 (1H, ddd, *J* 17, 10, 10, 4-*H*), 5.21 (1H, dd, *J* 10, 2, 5-*H*H), 4.88 (1H, dd, *J* 17, 2, 5-H*H*), 4.60 (1H, d, *J* 4, 3-C*H*(OCH_3)), 4.40 (1H, d, *J* 9, 1-*H*), 3.45 (1H, s, -O*H*), 3.25 (3H, s, 3-CH(OCH_3)), 2.26 (1H, m, 3-*H*), 1.99 (1H, m, 2-*H*), 0.61 (3H, d, *J* 7, 2-CH_3); δ_C (126 MHz, $CDCl_3$) 144.2 (*ipso*-Ar-*C*), 140.4 (*ipso*-Ar-*C*), 135.0 (4-*C*), 132.1 (Ar-*C*), 131.5 (Ar-*C*), 129.6 (Ar-*C*), 128.5 (Ar-*C*), 127.4 (Ar-*C*), 121.5 (*ipso*-Ar-*C*), 119.6 (5-*C*), 86.0 (3-*C*H(OCH_3)), 77.0 (1-*C*), 57.3 (3-CH(OCH_3)), 57.2 (3-*C*), 43.4 (2-*C*), 17.2 (2-CH_3); *m/z* (ES^+) 397 ([^{79}Br]MNa^+); HRMS (ES^+) Found [^{79}Br]MNa^+, 397.0775 ($C_{20}H_{23}O_2{}^{79}BrNa$ requires 397.0775).

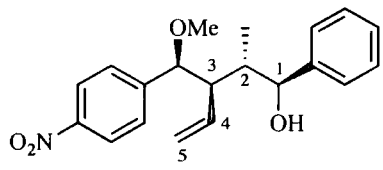
(1*SR*,2*SR*,3*RS*)-3-((*S*)-Cyclohexyl(methoxy)methyl)-2-methyl-1-phenylpent-4-en-1-ol, 342



Following the standard procedure outlined on page 181, silacyclohex-4-ene **206** (0.2 g, 0.7 mmol) was combined with cyclohexane dimethylacetal **341** to give, without purification of the fluorosilane, the title compound as a white solid (0.031 g, 16%); m.p. 106-108 °C; R_f 0.3 (pet. ether/ether 9:1); υ_{max} (thin film) 3324 (broad-OH), 3068, 3038, 2930, 2853, 2358, 2241, 1716, 1602, 1540, 1455, 1078, 1010, 834 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.32-7.30 (5H, m, Ar-*H*), 6.10 (1H, ddd, *J* 17, 10, 10, 4-*H*), 5.19 (1H, d, *J* 10, 5-H*H*), 5.10 (1H, d, *J* 17, 5-*H*H), 4.32 (1H, d, *J* 10, 1-*H*), 3.58 (3H, s, 3-CH(OCH_3)), 3.06 (1H, t, *J* 6, 3-C*H*(OCH_3)), 2.45 (1H, m, 3-*H*), 2.14 (1H, m, 2-*H*), 1.98 (1H, d, *J* 14, (CH*H*)$_5$), 1.80-1.69 (3H, m, (CH_2)$_5$), 1.62-1.59 (1H, d, *J* 14, (C*H*H)$_5$), 1.31-1.16 (4H, m, (CH_2)$_5$), 1.10-1.01 (2H, m, (CH_2)$_5$), 0.65 (3H, d, *J* 7, 2-CH_3); δ_C (126 MHz, $CDCl_3$) 144.7 (*ipso*-Ar-*C*), 137.3 (4-*C*), 128.1 (Ar-*C*), 127.1 (Ar-*C*), 126.8 (Ar-*C*), 117.5 (5-*C*), 89.5 (3-*C*H(OCH_3)), 76.0 (1-*C*), 61.6 (3-CH(OCH_3)), 51.0 (3-*C*), 41.0 (CH_2CHCH_2), 40.3 (2-*C*), 30.0, 29.6, 26.5, 26.3, 26.0 ((CH_2)$_5$), 17.7 (2-CH_3); *m/z* (ES^+) 325 (MNa^+), 627 ($2MNa^+$); HRMS (ES^+) Found 325.2137 ($C_{20}H_{30}O_2Na$ requires 325.2138).

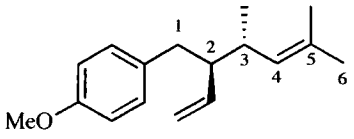
Further elution yielded the title compound (0.04 g, 20%) as a mixture of diastereoisomers by NMR.

(1*SR*,2*SR*,3*RS*)-3-((*RS*)-Methoxy(4-nitrophenyl)methyl)-2-methyl-1-phenylpent-4-en-1-ol, 322Ah



Following the standard procedure outlined on page 181, silacyclohex-4-ene **206** (0.05 g, 0.15 mmol) was combined with 4-nitrobenzaldehyde dimethylacetal **340** to give, without purification of the fluorosilane, the title compound as a pale yellow oil (0.032 g, 63%); R_f 0.3 (pet. ether/ether 9:1) as a mixture of diastereoisomer in the ratio 3.5:2:1 by NMR; υ_{max} (thin film) 3474-3228 (broad-OH), 3079, 2932, 2884, 2361, 2244, 1600, 1522, 1346, 1107, 1084 cm^{-1}; NMR data given for major isomer δ_H (500 MHz, $CDCl_3$) 8.23 (2H, d, *J* 8, Ar-*H*), 7.52 (2H, d, *J* 8, Ar-*H*), 7.36-7.24 (5H, m, Ar-*H*), 6.06 (1H, ddd, *J* 17, 10, 10, 4-*H*), 5.21 (1H, dd, *J* 10, 2, 5-*H*H), 4.86 (1H, dd, *J* 17, 2, 5-H*H*), 4.77 (1H, d, *J* 6, 3-C*H*(OCH_3)), 4.47 (1H, d, *J* 8, 1-*H*), 3.28 (3H, s, 3-CH(OCH_3)), 2.29 (1H, m, 3-*H*), 1.96 (1H, m, 2-*H*), 0.66 (3H, d, *J* 8, 2-CH_3); δ_C (126 MHz, $CDCl_3$) 149.4 (*ipso*-Ar-*C*), 147.6 (*ipso*-Ar-*C*), 143.8 (*ipso*-Ar-*C*), 134.9 (4-*C*), 128.5 (Ar-*C*), 128.0 (Ar-*C*), 127.3 (Ar-*C*), 125.8 (Ar-*C*), 123.6 (Ar-*C*), 119.8 (5-*C*), 85.3 (3-*C*H(OCH_3)), 77.1 (1-*C*), 57.6 (3-CH(OCH_3)), 56.7 (3-*C*), 42.9 (2-*C*), 16.5 (2-CH_3); *m/z* (ES^+) 364 (MNa^+); HRMS (ES^+) Found MNa^+, 364.1519 ($C_{20}H_{23}NO_4Na$ requires 364.1519).

1-((2*RS*,3*SR*)-3,5-Dimethyl-2-vinylhex-4-enyl)-4-methoxybenzene, 329



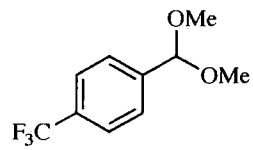
A solution of silacyclohex-4-ene **100** (0.05 g, 0.2 mmol) in DCM (5 ml) was cooled to -78 °C and treated with 4-methoxybenzaldehyde dimethylacetal (0.1 ml, 0.3 mmol), then BF_3•OEt_2 (0.03 ml, 0.2 mmol). The reaction mixture was then warmed to room temperature and stirred overnight. The reaction was poured into aq. NH_4Cl and extracted with DCM (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether, pet. ether [98:2], [95:5], [9:1]) afforded the title compound as a colourless oil (0.02 g, 47%); R_f 0.7 (pet. ether/ether 9:1); υ_{max} (thin film) 2955, 2927, 2871, 2833, 2362, 2337, 1510, 1440, 1299, 1243, 1175, 1038, 910, 834 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.02 (2H, d, *J* 9, Ar-*H*), 6.80 (2H, d, *J* 9, Ar-*H*), 5.68 (1H, ddd, *J* 17, 11, 10, 2-C*H*=CH_2), 5.00 (1H, d, *J* 11, 4-*H*), 4.85 (1H, d, *J* 11, 2-CH=C*H*H), 4.82 (1H, d, *J* 17, 2-CH=CH*H*), 3.78 (3H, s, -OCH_3), 2.55 (2H, dd, *J* 14, 6, 1-H_2), 2.44 (1H, m, 2-*H*), 2.24 (1H, m, 3-*H*), 1.73 (3H, s, 6-*H*), 1.57 (3H, s, 5-CH_3), 0.92 (3H, d, *J* 7, 3-CH_3); δ_C (126 MHz, $CDCl_3$) 157.5 (CH_3O-Ar-*C*), 139.4 (2-*C*H=CH_2), 133.2 (*ipso*-Ar-*C*), 131.2 (5-*C*), 130.0 (Ar-*C*), 127.3 (4-*C*), 115.9 (2-CH=*C*H_2), 113.4 (Ar-*C*), 55.2 (O*C*H_3), 51.9 (2-*C*), 38.2 (1-*C*), 35.3 (3-*C*), 26.0 (6-*C*), 19.5 (3-*C*H_3), 18.1 (5-*C*H_3); *m/z* (CI) 262 (MNH_4^+, 15%), 245 (M^+, 65%), 161 (10%), 121 (100%); HRMS (ES^+) Found M^+, 245.1896 ($C_{17}H_{24}O$ requires 245.1900).

6.4.1.2 Standard procedure for the formation of dimethyl acetals

Trimethylorthoformate (109.8 mmol) was added to a solution of aldehyde (36.6 mmol), p-toluenesulfonic acid (3.7 mmol) and methanol (98.9 mmol) at room temperature and

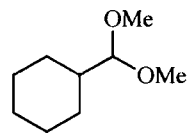
under argon. The solution was stirred for 15 h. An excess of sodium bisulfite was then added and the mixture stirred for 45 mins. The mixture was then filtered through celite, washed with ether, concentrated and dried *in vacuo* to afford the desired dimethyl acetals.

4-Trifluoromethylbenzaldehyde dimethyl acetal, 338



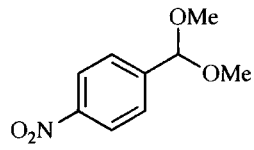
Following the standard procedure outlined on page 198, trifluoromethylbenzaldehyde (5 ml, 36.6 mmol) was transformed into the title compound which was isolated as a pale yellow oil (6.9 g, 85%); δ_H (500 MHz, $CDCl_3$) 7.65-7.56 (4H, m, Ar-*H*), 5.44 (1H, s, C*H*$(OCH_3)_2$), 3.33 (6H, s, CH$(OCH_3)_2$); δ_F (300 MHz, $CDCl_3$) -63.0 (3F, s, Ar-CF_3); all data agree with those reported in the literature.[189]

Dimethoxymethylcyclohexane, 341



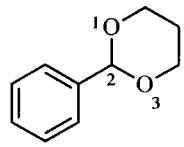
Following the standard procedure outlined on page 198, 4-cyclohexane-carboxaldehyde (2.2 ml, 112.2 mmol) was transformed into the title compound which was isolated as a semi solid (2.0 g, 71%); δ_H (500 MHz, $CDCl_3$) 3.98 (1H, d, *J* 7, C*H*$(OCH_3)_2$), 3.33 (6H, s, CH$(OCH_3)_2$), 1.75-1.58 (6H, m, C_6H_{11}), 1.25-0.95 (5H, m, C_6H_{11}); δ_C (126 MHz, $CDCl_3$) 108.8 (*C*H$(OCH_3)_2$), 53.8 (CH$(OCH_3)_2$), 40.3, 28.3, 26.6, 26.0 (C_6H_{11}); all data agree with those reported in the literature.[190]

1-(Dimethoxymethyl)-4-nitrobenzene, 340



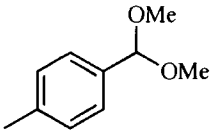
Following the standard procedure outlined on page 198, 4-nitrobenzaldehyde (1.0 g, 6.6 mmol) was transformed into the title compound which was isolated as a yellow oil (1.3 g, 62%); υ_{max} (thin film) 1519 (NO_2 stretch), 1340 (NO_2 stretch), 1204, 1098, 1051, 985, 897, 852, 828 cm^{-1}; δ_H (500 MHz, $CDCl_3$), 8.22 (2H, d, *J* 9, Ar-*H*), 7.64 (2H, d, *J* 9, Ar-*H*), 5.48 (1H, s, C*H*(OCH_3)$_2$)), 3.34 (6H, s, CH(OCH_3)$_2$); δ_C (126 MHz, $CDCl_3$) 147.9 (*ipso*-Ar-*C*), 145.0 (*ipso*-Ar-*C*), 127.8 (Ar-*C*), 123.4 (Ar-*C*), 101.5 (*C*H(OCH_3)$_2$), 52.7 (CH(OCH_3)$_2$); all data agree with those reported in the literature.[191]

2-Phenyl-1,3-dioxane, 339



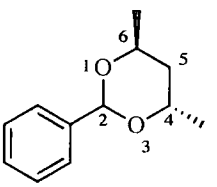
Following the standard procedure outlined on page 198, benzaldehyde (5.0 ml, 49.1 mmol) was transformed into the title compound which was isolated as a colourless oil (2.9 g, 36%); δ_H (500 MHz, $CDCl_3$) 7.49-7.46 (2H, m, Ar-*H*), 7.37-7.34 (3H, m, Ar-*H*), 5.51 (1H, s, 2-*H*), 4.30-4.25 (2H, m, O-$CH_2CH_2CH_2$-O), 4.02-3.99 (2H, m, O-$CH_2CH_2CH_2$-O), 2.22 (1H, m, O-CH_2CHHCH_2-O), 1.45 (1H, m, O-CH_2CHHCH_2-O); δ_C (126 MHz, $CDCl_3$) 138.7 (*ipso*-Ar-*C*), 128.8 (Ar-*C*), 128.2 (Ar-*C*), 126.0 (Ar-*C*), 101.7 (2-*C*), 67.4 (O-$CH_2CH_2CH_2$-O), 25.8 (O-$CH_2CH_2CH_2$-O); all data agree with those reported in the literature.[192]

1-Dimethoxymethyl-4-methylbenzene



Following the standard procedure outlined on page 198, 4-tolualdehyde (4.9 ml, 41.6 mmol) was transformed into the title compound which was isolated as a orange oil (7.1 g, 99%); δ_H (500 MHz, $CDCl_3$) 7.35 (2H, d, *J* 9, Ar-*H*), 7.19 (2H, d, *J* 9, Ar-*H*), 5.38 (1H, s, C*H*$(OCH_3)_2$), 3.33 (6H, s, CH$(OCH_3)_2$), 2.36 (3H, s, Ar-CH_3); δ_C (126 MHz, $CDCl_3$) 138.1 (*ipso*-Ar-*C*), 135.1 (*ipso*-Ar-*C*), 128.8 (Ar-*C*), 126.5 (Ar-*C*), 103.1 (*C*H$(OCH_3)_2$), 52.5 (CH$(OCH_3)_2$), 21.1 (Ar-*C*H_3); all data agree with those reported in the literature.[189]

4,6-Dimethyl-2-phenyl-1,3-dioxane

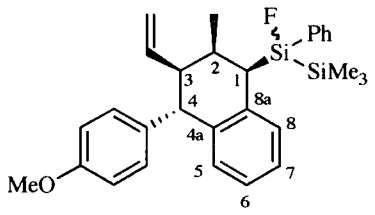


Benzaldehyde (0.5 ml, 4.8 mmol) and (*R*,*R*)-(-)-2,4-pentanediol (0.5 g, 4.8 mmol) were dissolved in benzene (5 ml). *p*-Toluenesulfonic acid (0.01 g, 0.05 mmol) was added and the solution refluxed using a Dean-Stark apparatus for 8.5 h. The solution was diluted with ether (3 x 10 ml) and washed with aq. $NaHCO_3$ and brine. The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether/ethyl acetate 20:1, 10:1) followed by Kugelrohr distillation gave the title compound as a colourless oil (0.7 g, 75%); R_f 0.5 (pet. ether/ethyl acetate 10:1); δ_H (300 MHz, $CDCl_3$) 7.52-7.50 (2H, m, Ar-*H*), 7.37-7.34 (3H, m, Ar-*H*), 5.84 (1H, s, 2-*H*), 4.51 (1H, m, 5-H*H*), 4.22 (1H, m, 5-*H*H), 2.05 (1H, m, 6-*H*), 1.50 (3H, d, *J* 7, 6-CH_3), 1.47 (1H, m, 4-*H*), 1.30 (3H, d, *J* 7, 4-CH_3); δ_C (126 MHz, $CDCl_3$) 139.4

(*ipso*-Ar-*C*), 128.9 (Ar-*C*), 128.5 (Ar-*C*), 126.5 (Ar-*C*), 94.3 (2-*C*), 68.9 (6-*C*), 68.4 (4-*C*), 37.0 (5-*C*), 22.2 (6-CH_3), 17.5 (4-CH_3); all data agree with those reported in the literature.[193]

6.4.2 Cyclic substrates

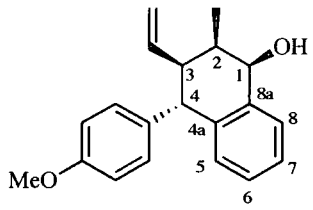
(1*RS*,2*RS*,3*RS*,4*SR*,*(Si)RS/SR*)-1-(1-Fluoro-2,2,2-trimethyl-1-phenyldisilyl)-4-(4-methoxyphenyl)-2-methyl-3-vinyl-1,2,3,4-tetrahydronaphthalen-1-yl, 321B



Following stage 1 of the standard procedures outlined on page 181, silacyclohex-4-ene **206** (0.6 g, 1.8 mmol) was combined with 4-methoxybenzaldehyde dimethylacetal to give the title compound as a colourless gum (0.4 g, 44%); R_f 0.3 (pet. ether/ether 95:5) as a mixture of diastereoisomers in the ratio 5:1 by NMR; υ_{max} (thin film) 1609, 1509, 1487, 1442, 1427, 1301, 1243, 1175, 1105, 1036, 912, 835 cm^{-1}; NMR data given for major isomer δ_H (500 MHz, $CDCl_3$) 7.66-7.64 (2H, m, Ar-*H*), 7.44-7.42 (3H, m, Ar-*H*), 7.38 (1H, m, Ar-*H*), 7.25 (1H, m, Ar-*H*), 6.98-6.96 (3H, m, Ar-*H*), 6.80-6.77 (3H, m, Ar-*H*), 5.71 (1H, m, 3-C*H*=CH_2), 4.87 (1H, d, *J* 10, 3-CH=C*H*H), 4.76 (1H, d, *J* 17, 3-CH=CH*H*), 3.87 (1H, d, *J* 11, 4-*H*), 3.78 (3H, s, Ar-(OCH_3)), 3.25 (1H, m, 1-*H*), 2.62 (1H, m, 3-*H*), 2.31 (1H, m, 2-*H*), 1.05 (3H, d, *J* 7, 2-CH_3), 0.14 (9H, s, Si(CH_3)$_3$); δ_C (126 MHz, $CDCl_3$) 157.8 (*ipso*-Ar-*C*), 140.2 (3-*C*H=CH_2), 139.9 (*ipso*-Ar-*C*), 138.0 (*ipso*-Ar-*C*), 136.8 (Ar-*C*), 136.4 (Ar-*C*), 135.2 (*ipso*-Ar-*C*), 133.2 (Ar-*C*), 130.9 (Ar-*C*), 130.4 (Ar-*C*), 129.7 (Ar-*C*), 128.2 (Ar-*C*), 125.9 (Ar-*C*), 125.5 (Ar-*C*), 116.0 (3-CH=*C*H_2), 113.5 (Ar-*C*), 55.1 (Ar-(OCH_3)), 52.7 (3-*C*), 46.3 (4-*C*), 38.7 (1-*C*), 34.4 (2-*C*), 12.8 (2-CH_3), -1.4 (Si(CH_3)$_3$); δ_F (300 MHz, $CDCl_3$) -183.5 (1F, d, *J* 7, Si-*F*); *m/z*

(ES$^+$) 497 (MNa$^+$), 971 (2M$^+$ -2OCH$_3$); HRMS (ES$^+$) Found 497.2107 ($C_{29}H_{35}Si_2OFNa$ requires 497.2103).

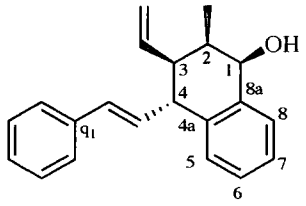
(1*RS*,2*RS*,3*RS*,4*SR*)-4-(4-Methoxy-phenyl)-2-methyl-3-vinyl-1,2,3,4-tetrahydronaphthalen-1-ol, 343



Following stage 2 of the standard procedures outlined on page 181, fluorosilane **321Ba** (0.37 g, 0.7 mmol) was transformed into the title compound which was isolated as a white solid (0.085 g, 36%); R_f 0.1 (pet. ether/ether 9:1); m.p. 122-124 °C; υ_{max} (thin film) 3350 (broad – OH), 2961, 2907, 1611, 1511, 1451, 1301, 1261, 1245, 1177, 1115, 1026, 913 cm^{-1}; δ_H (500 MHz, CD_3COCD_3) 7.68 (1H, d, *J* 10, 8-*H*), 7.20 (1H, m, 7-*H*), 7.09-7.04 (3H, m, 6-*H*, Ar-*H*), 6.86 (2H, d, *J* 11, Ar-*H*), 6.75 (1H, d, *J* 10, 5-*H*), 5.96 (1H, ddd, *J* 20, 11, 9, 3-C*H*=CH$_2$), 5.14 (1H, m, 1-*H*), 4.91 (2H, m, 3-CH=C*H*$_2$), 4.41 (1H, d, *J* 8, -O*H*), 3.99 (1H, d, *J* 12, 4-*H*), 3.79 (3H, s, Ar-OC*H*$_3$), 2.82 (1H, m, 3-*H*), 2.35 (1H, m, 2-*H*), 0.94 (3H, d, *J* 9, 2-C*H*$_3$); δ_C (126 MHz, CD_3COCD_3) 159.7 (*ipso*-Ar-*C*), 142.0 (3-*C*H=CH$_2$), 140.8 (Ar-*C*), 140.5 (Ar-*C*), 139.6 (*ipso*-Ar-*C*), 136.7 (Ar-*C*), 136.3 (Ar-*C*), 131.9 (Ar-*C*), 128.1 (8-*C*), 128.0 (7-*C*), 116.5 (3-CH=*C*H$_2$), 115.1 (Ar-*C*), 72.8 (1-*C*), 56.1 (Ar-OCH$_3$), 51.9 (3-*C*), 48.3 (4-*C*), 41.0 (2-*C*), 8.7 (2-*C*H$_3$); *m/z* (ES$^+$) 317 (MNa$^+$); Elemental analysis [Found C, 81.15 %; H, 7.59 %; required for $C_{20}H_{22}O_2$: C, 81.59 %; H, 7.53 %].

Further elution gave a mixture of diastereoisomers as a colourless oil (0.059 g, 25%); all data for the major isomer agree with that given above.

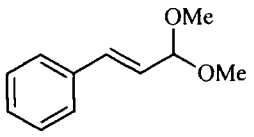
(1*RS*,2*RS*,3*RS*,4*RS*)-2-Methyl-4-(2-phenylethenyl)-3-ethenyl-1,2,3,4-tetrahydronaphthalen-1-ol, 322B



Following the standard procedure outlined on page 181, silacyclohex-4-ene **206** (0.1 g, 0.3 mmol) was combined with cinnemaldehyde dimethylacetal **344** to give, without purification of the fluorosilane, the title compound as a white solid (0.016 g, 19%); m.p. 119-121 °C; R_f 0.3 (pet. ether/ether 9:1); υ_{max} (thin film) 3428 (broad-OH), 2958, 2365, 2357, 1599, 1493, 1448, 1384, 1259, 1091, 1029, 964, 915, 795, 759, 692 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.67 (1H, d, *J* 7, Ar-*H*), 7.44 (1H, d, *J* 7, Ar-*H*), 7.32 (1H, t, *J* 7, Ar-*H*), 7.25-7.19 (6H, m, Ar-*H*), 6.56 (1H, d *J* 16, 4-CH=C*H*Ar), 6.14 (1H, dd, *J* 16, 10, 4-C*H*=CHAr), 6.00 (1H, ddd, *J* 17, 10, 8, 3-C*H*=CH_2), 5.14 (1H, d, *J* 17, 3-CH=CH*H*), 5.07 (1H, d, *J* 8, 3-CH=C*H*H), 4.98 (1H, t, *J* 5, 1-*H*), 4.36 (1H, d, *J* 5, -O*H*), 3.60 (1H, t, *J* 9, 4-*H*), 2.64 (1H, m, 3-*H*), 2.36 (1H, m, 2-*H*), 0.92 (3H, d, *J* 7, 2-CH_3); δ_C (126 MHz, $CDCl_3$) 140.2 (4a-*C*), 139.2 (8a-*C*), 137.9 (Ar-*C*), 136.6 (Ar-*C*), 133.8 (3-*C*H=CH_2), 131.9 (4-CH=*C*HAr), 129.0 (4-*C*H=CHAr), 128.7 (Ar-*C*), 127.3 (Ar-*C*), 126.7 (Ar-*C*), 126.5 (Ar-*C*), 126.4 (Ar-*C*), 126.1 (Ar-*C*), 115.1 (3-CH=*C*H_2), 71.2 (1-*C*), 47.5 (3-*C*), 45.2 (4-*C*), 38.9 (2-*C*), 7.6 (2-CH_3); *m/z* (EI) 290 (M^+); HRMS (EI) Found M^+, 290.1663 ($C_{21}H_{22}O$ requires 290.1665).

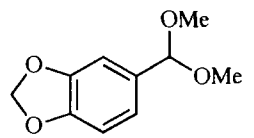
Further elution gave a mixture of diastereoisomers as a white solid (0.022 g, 25%); all data for the major isomer agree with that given above.

(3,3-Dimethoxy-propenyl)-benzene, 344



Following the standard procedure outlined on page 198, *trans*-cinnamaldehyde (5.0 ml, 39.7 mmol) was transformed into the title compound which was isolated as a yellow oil (6.7 g, 95%); δ_H (500 MHz, $CDCl_3$) 7.51-7.49 (2H, m, Ar-*H*), 7.38-7.34 (2H, m, Ar-*H*), 7.29 (1H, m, Ar-*H*), 6.74 (1H, d, *J* 16, Ar-C*H*=CH), 6.22 (1H, dd, *J* 16, 5, Ar-CH=C*H*), 4.95 (1H, d, *J* 5, C*H*$(OCH_3)_2$), 3.31 (6H, s, CH$(OCH_3)_2$); δ_C (126 MHz, $CDCl_3$) 136.6 (*ipso*-Ar-*C*), 133.1 (*C*H$(OCH_3)_2$), 128.8 (Ar-*C*), 128.2 (Ar-*C*), 126.9 (Ar-*C*), 126.5 (Ar-CH=*C*H), 103.1 (Ar-*C*H=CH), 52.1 CH$(OCH_3)_2$); all data agree with those reported in the literature.[194]

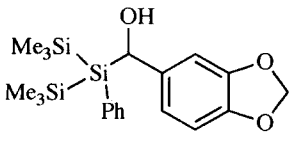
Piperonal dimethyl acetal



Following the standard procedure outlined on page 198, piperonal (5.00 g, 33.30 mmol) was transformed into the title compound which was isolated as a blue oil (5.92 g, 91%); δ_H (500 MHz, $CDCl_3$) 6.94-6.92 (2H, m, Ar-*H*), 6.79 (1H, m Ar-*H*), 5.96 (2H, s, O-CH_2-O), 5.28 (1H, s, C*H*$(OCH_3)_2$), 3.31 (6H, s, CH$(OCH_3)_2$); all data agree with those reported in the literature.[195]

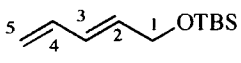
6.5 Total Synthesis of Epipicropodophyllotoxin

Benzo[*d*][1,3]dioxol-5-yl(1,1,1,3,3,3-hexamethyl-2-phenyltrisilan-2-yl)methanol, 481



Following the standard procedure outlined on page 161, phenyltris(trimethylsilyl)silane **95** (13.0 g, 40.0 mmol) was combined with piperonal to give the title compound as a yellow solid (6.5 g, 40%); m.p. 80-82 °C; R_f 0.3 (pet. ether/ether 9:1); υ_{max} (thin film) 3564 (broad-OH), 2952, 2898, 1499, 1482, 1244, 1095, 1036, 1012, 929, 912, 834, 810, 692 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.57-7.53 (2H, m, Ar-*H*), 7.39-7.30 (3H, m, Ar-*H*), 6.70-6.61 (3H, m, Ar-*H*), 5.90 (2H, s, -OCH_2O-), 5.10 (1H, s, SiC*H*), 0.16 and 0.13 (each 9H, s, Si(CH_3)$_3$); δ_C (126 MHz, $CDCl_3$) 147.5 (Ar-*C*), 145.7 (Ar-*C*), 139.6 (Ar-*C*), 136.1 (Ar-*C*), 135.1 (Ar-*C*), 128.4 (Ar-*C*), 127.9 (Ar-*C*), 118.1 (Ar-*C*), 107.9 (Ar-*C*), 106.3 (Ar-*C*), 100.7 (-OCH_2O-), 69.6 (SiCH), 0.1 (Si(CH_3)$_3$) 0.07 (Si(CH_3)$_3$); *m/z* (ES^+) 425 (MNa^+); HRMS (ES^+) Found MNa^+, 425.1390 ($C_{20}H_{30}Si_3Na$ requires 425.1395); all data agree with those reported by Pullin.[180]

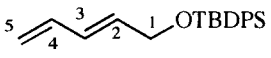
(*E*)-*tert*-Butyldimethyl(penta-2,4-dienyloxy)silane, Table 9, entry 1



To a solution of 2,4-pentadien-1-ol **483** (2.2 g, 26 mmol) in dry DCM (15 ml) was added imidazole (7 g, 104 mmol) and *tert*-butylchlorodimethylsilane (5.9 g, 39 mmol). The solution was stirred for 2 h at room temperature then diluted with Et_2O and washed with water (15 ml) and brine (15 ml). The organic layer was dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether/ether [9:1], [4:1]) gave the title compound as a colourless oil (5.0 g, 95%); R_f 0.4 (pet. ether/ether 9:1); δ_H

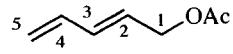
(500 MHz, $CDCl_3$) 6.36 (1H, ddd, *J* 16, 10, 9, 4-*H*), 6.25 (1H, m, 3-*H*), 5.79 (1H, dt, *J* 15, 10, 5, 2-*H*), 5.20 (1H, d, *J* 16, 5-*H*H), 5.07 (1H, d, *J* 10, 5-H*H*), 4.23 (2H, d, *J* 5, 1-CH_2), 0.93 (9H, s, SiC(CH_3)$_3$), 0.10 (6H, s, Si(CH_3)$_2$^{t}Bu); δ_C (126 MHz, $CDCl_3$) 136.8 (4-*C*), 133.4 (2-*C*), 130.6 (3-*C*), 116.9 (5-*C*), 63.6 (1-*C*), 26.2 (SiC(*C*H_3)$_3$), 18.7 (Si*C*(CH$_3$)$_3$), -5.0 (Si(*C*H$_3$)$_2$^{t}Bu); all data agree with those reported by Pullin.[180]

(*E*)-*tert*-Butyl(penta-2,4-dienyloxy)diphenylsilane, Table 9, entry 2



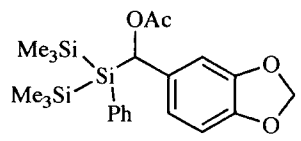
To a solution of 2,4-pentadien-1-ol **483** (2.2 g, 26 mmol) in dry DCM (15 ml) was added imidazole (7 g, 104 mmol) and *tert*-butylchlorodiphenylsilane (5.9 g, 39 mmol). The solution was stirred for 2 h at room temperature then diluted with Et_2O and washed with water (15 ml) and brine (15 ml). The organic layer was dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether/ether [9:1], [4:1]) gave the title compound as a colourless oil (4.7 g, 56%); R_f 0.3 (pet. ether/ether 9:1); υ_{max} (thin film) 3070, 2957, 2930, 2856, 1427, 1112, 1003, 822, 701 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.75-7.73 (4H, m, Ar-*H*), 7.49-7.42 (6H, m, Ar-*H*), 6.45-6.34 (2H, m, 3-*H*, 4-*H*), 5.84 (1H, dt, *J* 13, 10, 5, 2-*H*), 5.23 (1H, d, *J* 17, 5-*H*H), 5.12 (1H, d, *J* 10, 5-H*H*), 4.30 (2H, d, *J* 4, 1-CH_2), 1.13 (9H, s, SiC(CH_3)$_3$); δ_C (126 MHz, $CDCl_3$) 136.9 (4-*C*), 135.8 (Ar-*C*), 133.0 (2-*C*), 130.5 (3-*C*), 129.9 (Ar-*C*), 128.0 (Ar-*C*), 127.9 (Ar-*C*), 116.9 (5-*C*), 64.2 (1-*C*), 27.1 (SiC(*C*H$_3$)$_3$), 19.5 (Si*C*(CH$_3$)$_3$); *m/z* (ES$^+$) 345 (MNa$^+$); HRMS (ES$^+$) Found MNa$^+$, 345.1647 ($C_{21}H_{26}SiONa$ requires 345.1645).

(*E*)-Penta-2,4-dienyl ethanoate, 484



A solution of 2,4-pentadien-1-ol **483** (0.4 g, 5 mmol) in DCM (5 ml) was treated consecutively with DIPEA (3.2 ml, 19.0 mmol), acetic anhydride (0.9 ml, 9.5 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 45min after which time aq. NH_4Cl (10 ml) was added. The aqueous layer was separated and extracted with DCM (3 x 20 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether; pet. ether/ether [95:5], [9:1]) afforded the title compound as a colourless oil (0.2 g, 32%); R_f 0.3 (pet. ether/ether 9:1); υ_{max} (thin film) 3090, 3020, 2954, 2928, 1735 (C=O), 1248, 1025, 1005, 955 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.40-6.33 (2H, m, 3-*H*, 4-*H*), 5.78 (1H, m, 2-*H*), 5.24 (1H, d, *J* 17, 5-*H*H), 5.17 (1H, d, *J* 10, 5-H*H*), 4.60 (2H, d, *J* 6, 1-CH_2), 2.08 (3H, s, -(C=O)CH_3); δ_C (126 MHz, $CDCl_3$) 170.5 (C=O), 136.4 (4-*C*), 135.5 (2-*C*), 127.4 (3-*C*), 119.3 (5-*C*), 64.1 (1-*C*), 20.5 ((C=O)CH_3); all data agree with those reported in the literature.[196]

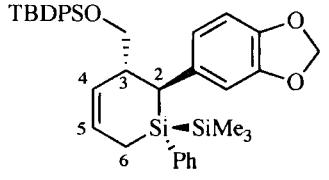
Benzo[*d*][1,3]dioxol-5-yl(1,1,1,3,3,3-hexamethyl-2-phenyltrisilan-2-yl)methyl ethanoate, 485



n-Butyl lithium (1.6M sol. in hexanes, 1.5 ml, 1.8 mmol) was added to a stirred solution of silyl alcohol **481** (0.3 g, 0.7 mmol) and diene **484** (0.2 g, 1.4 mmol) in dry ether (7 ml) at room temperature. The mixture was stirred for 2 h after which time aq. NH_4Cl (20 ml) was added. The aqueous layer was separated and extracted with ether (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and

dried *in vacuo*. Flash chromatography (pet. ether; pet. ether/ether [95:5], [9:1]) afforded the title compound as a colourless oil (0.1 g, 40%); R_f 0.3 (pet. ether/ether 9:1); υ_{max} (thin film) 3069, 2954, 2893, 1733 (C=O), 1503, 1488, 1442, 1367, 1245, 1041, 836 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.58-7.53 (2H, m, Ar-*H*), 7.39-7.30 (3H, m, Ar-*H*), 6.70-6.61 (3H, m, Ar-*H*), 6.15 (1H, s, SiC*H*), 5.87 (2H, s, -OCH_2O-), 2.09 (3H, s, -(C=O)CH_3) 0.16 and 0.13 (each 9H, s, Si(CH_3)$_3$); δ_C (126 MHz, $CDCl_3$) 170.5 (C=O), 147.4 (Ar-*C*), 146.0 (Ar-*C*), 136.0 (Ar-*C*), 135.4 (Ar-*C*), 134.2 (Ar-*C*), 128.6 (Ar-*C*), 127.9 (Ar-*C*), 119.3 (Ar-*C*), 108.0 (Ar-*C*), 106.9 (Ar-*C*), 100.8 (-O*C*H_2O-), 70.6 (Si*C*H), 21.3 ((C=O)*C*H_3), -0.05 (Si(*C*H_3)$_3$) -0.2 (Si(*C*H_3)$_3$); Elemental analysis [Found C, 58.94 %; H, 7.44 %; required for $C_{22}H_{32}O_4Si_3$: C, 59.41 %; H, 7.25 %]

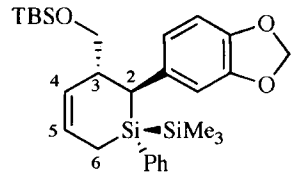
(1*SR*,2*SR*,3*RS*)-2-(Benzo[*d*][1,3]dioxol-5-yl)-3-((*tert*-butyldiphenylsilyloxy)methyl)-1-phenyl-1-(trimethylsilyl)-silacyclohex-4-ene, Table 10, entry 2



Following the standard procedure for silene generation and cyclisation outlined on page 162, silyl alcohol **481** (1.0 g, 2.5 mmol) was transformed into the title compound which was isolated as a colourless oil (0.9 g, 55%), as a complex mixture of diastereoisomers; R_f 0.2 (pet. ether); υ_{max} (thin film) 3070, 3018, 2955, 2896, 2858, 2098, 1602, 1503, 1485, 1427, 1246, 1111, 1041, 837, 699 cm^{-1}; NMR data given for major isomer δ_H (500 MHz, $CDCl_3$) 7.57-7.50 (5H, m, Ar-*H*), 7.43-7.24 (10H, m, Ar-*H*), 6.64 (1H, m, Ar-*H*), 6.56 (1H, s, Ar-*H*), 6.48 (1H, d, *J* 6, Ar-*H*), 6.10 (1H, m, 5-*H*), 5.93 (2H, s, -OCH_2O-), 5.88 (1H, m, 4-*H*), 3.51 (1H, dd, *J* 10, 5, 3-C*H*HOSi(Ph)$_2$^{t}Bu), 3.44 (1H, dd, *J* 10, 5, 3-CH*H*OSi(Ph)$_2$^{t}Bu), 2.81 (1H, m, 3-*H*), 2.72 (1H, d, *J* 9, 2-*H*), 1.84 (1H, m, 6-*H*H), 1.67 (1H, m, 6-H*H*), 1.01 (9H, s, SiC(CH_3)$_3$), -0.04 (9H, s, Si(CH_3)$_3$); δ_C (126

MHz, $CDCl_3$) 147.8 (Ar-*C*), 147.5 (Ar-*C*), 145.8 (Ar-*C*), 144.9 (Ar-*C*), 144.9 (Ar-*C*), 138.4 (*ipso*-Ar-*C*), 136.4 (Ar-*C*), 135.8 (Ar-*C*), 134.7 (Ar-*C*), 132.7 (4-*C*), 129.7 (Ar-*C*), 128.8 (Ar-*C*), 127.9 (5-*C*), 126.3 (Ar-*C*), 120.9 (Ar-*C*), 118.6 (Ar-*C*), 108.8 (Ar-*C*), 108.4 (Ar-*C*), 107.9 (Ar-*C*), 106.8 (Ar-*C*), 100.9 (-O*C*H_2O-), 66.6 (3-*C*H_2OSi(Ph)$_2$^{t}Bu), 44.9 (3-*C*), 33.4 (2-*C*), 27.1 (SiC(*C*H_3)$_3$), 19.5 (Si*C*(CH$_3$)$_3$), 9.5 (6-*C*), -1.5 (Si(*C*H_3)$_3$); *m/z* (ES^+) 657 (MNa^+); HRMS (ES^+) Found MNa^+, 657.2655 ($C_{38}H_{46}Si_3O_3Na$ requires 657.2647).

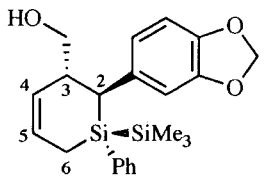
(1*SR*,2*SR*,3*RS*)-2-(Benzo[*d*][1,3]dioxol-5-yl)-3-((*tert*-butyldimethylsilyloxy)methyl)-1-phenyl-1-(trimethylsilyl)-silacyclohex-4-ene, 486



Following the standard procedure for silene generation and cyclisation outlined on page 162, silyl alcohol **481** (1.0 g, 2.5 mmol) was transformed into the title compound which was isolated as a colourless oil (0.8 g, 60%), along with small amounts of isomers in the ratio 80:13:3:4 by GCMS; R_f 0.2 (pet. ether); NMR data given for major isomer δ_H (500 MHz, $CDCl_3$) 7.27-7.26 (5H, m, Ar-*H*), 6.70 (1H, m, Ar-*H*), 6.63 (1H, d, *J* 2, Ar-*H*), 6.55 (1H, m, Ar-*H*), 6.03 (1H, m, 5-*H*), 5.92 (2H, s, -OC*H*$_2$O-), 5.80 (1H, m, 4-*H*), 3.42 (1H, dd, *J* 10, 5, 3-C*H*HOSi(CH$_3$)$_2$^{t}Bu), 3.25 (1H, dd, *J* 10, 5, 3-CH*H*OSi(CH$_3$)$_2$^{t}Bu), 2.73 (1H, m, 3-*H*), 2.54 (1H, d, *J* 9, 2-*H*), 1.80 (1H, m, 6-*H*H), 1.64 (1H, m, 6-H*H*), 0.83 (9H, s, SiC(C*H*$_3$)$_3$), -0.05 (9H, s, Si(C*H*$_3$)$_3$), -0.1 (6H, s, Si(C*H*$_3$)$_2$); δ_C (126 MHz, $CDCl_3$) 147.9 (Ar-*C*), 144.9 (Ar-*C*), 138.7 (*ipso*-Ar-*C*), 136.7 (Ar-*C*), 134.6 (Ar-*C*), 132.6 (4-*C*), 128.8 (Ar-*C*), 127.9 (Ar-*C*), 125.9 (5-*C*), 120.9 (Ar-*C*), 108.6 (Ar-*C*), 108.2 (Ar-*C*), 100.8 (-O*C*H_2O-), 65.6 (3-*C*H_2OSi(CH$_3$)$_2$^{t}Bu), 45.0 (3-*C*), 33.5 (2-*C*), 26.1 (SiC(*C*H_3)$_3$), 18.5 (Si*C*(CH$_3$)$_3$), 9.4 (6-*C*), -1.0 (Si(*C*H_3)$_3$), -5.2 (Si(*C*H_3)$_2$); *m/z* (EI)

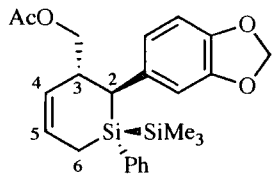
510 (M^+, < 1 %), 437 (M^+ -$Si(CH_3)_3$, 45%) 135 (90%), 73 ($Si(CH_3)_3$, 100%); all data agree with those reported by Pullin.[180]

(1*SR*,2*SR*,3*RS*)-2-(Benzo[*d*][1,3]dioxol-5-yl)-1-phenyl-1-(trimethylsilyl)-3-(hydroxymethyl)-silacyclohex-4-ene, 488



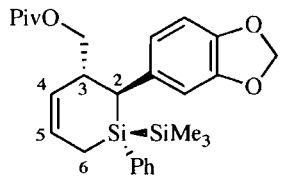
To a solution of hydroxyl protected silacycle **486** (0.2 g, 0.4 mmol) in THF:MeOH (1:1, 2 ml) was added a catalytic amount of *p*-toluenesulfonic acid and 0.5M aq. HCl. The solution was stirred for 1 h at room temperature then diluted with Et_2O and washed with water (5 ml). The organic layer was dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether/ether [9:1], [4:1], [7:3]) gave the title compound as a colourless oil (0.1 g, 64%); R_f 0.3 (pet. ether/ether 7:3); υ_{max} (thin film) 3508-3192 (broad-OH), 3016, 2950, 2882, 1606, 1502, 1484, 1246, 1041, 835 cm^{-1}; NMR data given for major isomer δ_H (500 MHz, $CDCl_3$) 7.29-7.28 (5H, m, Ar-*H*), 6.72 (1H, d, *J* 8, Ar-*H*), 6.65 (1H, s, Ar-*H*), 6.57 (1H, d, *J* 8, Ar-*H*), 6.15 (1H, m, 5-*H*), 5.95 (2H, s, -OC*H*$_2$O-), 5.76 (1H, m, 4-*H*), 3.55 (1H, dd, *J* 10, 5, 3-C*H*HOH), 3.45 (1H, dd, *J* 10, 5, 3-CH*H*OH), 2.82 (1H, m, 3-*H*), 2.63 (1H, d, *J* 9, 2-*H*), 1.87 (1H, m, 6-*H*H), 1.68 (1H, m, 6-H*H*), -0.02 (9H, s, Si(C*H*$_3$)$_3$); δ_C (126 MHz, $CDCl_3$) 148.0 (Ar-*C*), 145.2 (Ar-*C*), 137.9 (*ipso*-Ar-*C*), 134.6 (Ar-*C*), 134.2 (Ar-*C*), 131.6 (4-*C*), 128.9 (Ar-*C*), 128.1 (Ar-*C*), 127.9 (5-*C*), 121.1 (Ar-*C*), 108.8 (Ar-*C*), 108.6 (Ar-*C*), 101.0 (-O*C*H$_2$O-), 65.6 (3-*C*H$_2$OH), 45.4 (3-*C*), 38.8 (2-*C*), 9.8 (6-*C*), -0.9 (Si(*C*H$_3$)$_3$); δ_{Si} (100 MHz, $CDCl_3$) -18.96, -22.60; *m/z* (ES^+) 419 (MNa^+); HRMS (ES^+) Found MNa^+, 419.1473 ($C_{22}H_{28}Si_2O_3Na$ requires 419.1469).

(1*SR*,2*SR*,3*RS*)-2-(Benzo[*d*][1,3]dioxol-5-yl)-1-phenyl-1-(trimethylsilyl)-3-(acetoxymethyl)-silacyclohex-4-ene, 489



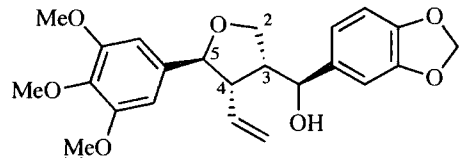
A solution of hydroxysilacycle **488** (0.1 g, 0.3 mmol) in DCM (3 ml) was treated consecutively with DIPEA (0.18 ml, 1.0 mmol), acetic anhydride (0.05 ml, 0.5 mmol) and a catalytic amount of DMAP. The reaction was stirred at room temperature for 45min after which time aq. NH_4Cl (10 ml) was added. The aqueous layer was separated and extracted with DCM (3 x 20 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether; pet. ether/ether [9:1], [4:1]) afforded the title compound as a colourless oil (0.08 g, 70%); R_f 0.5 (pet. ether/ether 7:3); υ_{max} (thin film) 2955, 2884, 1720 (C=O), 1502, 1484, 1439, 1285, 1246, 1160, 1041, 896, 835 cm^{-1}; NMR data given for major isomer δ_H (500 MHz, $CDCl_3$) 7.30-7.25 (5H, m, Ar-*H*), 6.71 (1H, d, *J* 8, Ar-*H*), 6.62 (1H, s, Ar-*H*), 6.55 (1H, d, *J* 8, Ar-*H*), 6.11 (1H, m, 5-*H*), 5.94 (2H, s, -OC*H*$_2$O-), 5.71 (1H, m, 4-*H*), 4.00 (1H, dd, *J* 10, 5, 3-C*H*HO(C=O)CH_3), 3.81 (1H, dd, *J* 10, 5, 3-CH*H*O(C=O)CH_3), 2.93 (1H, m, 3-*H*), 2.48 (1H, d, *J* 9, 2-*H*), 1.99 (3H, s, 3-CH_2O(C=O)C*H*$_3$), 1.87 (1H, m, 6-*H*H), 1.69 (1H, m, 6-H*H*), -0.01 (9H, s, Si(C*H*$_3$)$_3$); δ_C (126 MHz, $CDCl_3$) 171.1 (3-CH_2O(*C*=O)CH_3), 147.8 (Ar-*C*), 145.0 (Ar-*C*), 137.1 (*ipso*-Ar-*C*), 136.4 (Ar-*C*), 134.3 (Ar-*C*), 133.9 (Ar-*C*), 130.8 (4-*C*), 129.8 (Ar-*C*), 127.8 (Ar-*C*), 127.2 (5-*C*), 120.7 (Ar-*C*), 108.4 (Ar-*C*), 100.8 (-O*C*H$_2$O-), 67.1 (3-*C*H$_2$O(C=O)CH_3), 41.2 (3-*C*), 34.4 (2-*C*), 20.9 (3-CH_2O(C=O)*C*H$_3$), 9.5 (6-*C*), -1.3 (Si(*C*H$_3$)$_3$); *m/z* (ES^+) 461 (MNa^+); HRMS (ES^+) Found MH^+, 439.1758 ($C_{24}H_{31}Si_2O_4$ requires 439.1755).

(1*SR*,2*SR*,3*RS*)-2-(Benzo[*d*][1,3]dioxol-5-yl)-1-phenyl-1-(trimethylsilyl)-3-(methyl 2,2-dimethylpropanoate)-silacyclohex-4-ene, 490



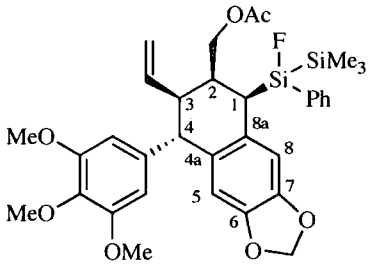
A solution of hydroxysilacycle **488** (0.1 g, 0.3 mmol) in DCM (3 ml) was treated consecutively with DIPEA (0.18 ml, 1.0 mmol), pivaloyl chloride (0.06 ml, 0.5 mmol) and a catalytic amount of DMAP. The reaction was stirred at room temperature for 1 h, after which time aq. NH_4Cl (10 ml) was added. The aqueous layer was separated and extracted with DCM (3 x 20 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether; pet. ether/ether [9:1], [4:1]) afforded the title compound as a colourless oil (0.07 g, 60%); R_f 0.8 (pet. ether/ether 7:3); υ_{max} (thin film) 2958, 2928, 2882, 1724 (C=O), 1612, 1501, 1426, 1246, 1185, 1128, 1040, 905, 836 cm^{-1}; NMR data given for major isomer δ_H (500 MHz, $CDCl_3$) 7.28-7.21 (5H, m, Ar-*H*), 6.72 (1H, d, *J* 6, Ar-*H*), 6.63 (1H, s, Ar-*H*), 6.55 (1H, d, *J* 6, Ar-*H*), 6.09 (1H, m, 5-*H*), 5.94 (2H, s, -OC*H*$_2$O-), 5.66 (1H, m, 4-*H*), 4.00 (1H, dd, *J* 10, 5, 3-C*H*HO(C=O)C(CH$_3$)$_3$), 3.78 (1H, dd, *J* 10, 5, 3-CH*H*O(C=O)C(CH$_3$)$_3$), 2.92 (1H, m, 3-*H*), 2.53 (1H, d, *J* 10, 2-*H*), 1.86 (1H, m, 6-*H*H), 1.69 (1H, m, 6-H*H*), 1.17 (9H, s, 3-CH$_2$O(C=O)C(C*H*$_3$)$_3$), -0.01 (9H, s, Si(C*H*$_3$)$_3$); δ_C (126 MHz, $CDCl_3$) 178.4 (3-CH$_2$O(*C*=O)C(CH$_3$)$_3$), 147.8 (Ar-*C*), 145.0 (Ar-*C*), 137.2 (*ipso*-Ar-*C*), 136.5 (Ar-*C*), 134.3 (Ar-*C*), 133.9 (Ar-*C*), 130.9 (4-*C*), 128.7 (Ar-*C*), 127.7 (Ar-*C*), 127.1 (5-*C*), 120.7 (Ar-*C*), 108.5 (Ar-*C*), 100.8 (-O*C*H$_2$O-), 66.5 (3-*C*H$_2$O(C=O)C(CH$_3$)$_3$), 41.7 (3-*C*), 38.8 (3-CH$_2$O(C=O)*C*(CH$_3$)$_3$), 34.3 (2-*C*), 27.2 (3-CH$_2$O(C=O)C(*C*H$_3$)$_3$), 9.5 (6-*C*), -1.3 (Si(*C*H$_3$)$_3$); *m/z* (ES$^+$) 503 (MNa$^+$); HRMS (ES$^+$) Found MH$^+$, 481.2228 ($C_{27}H_{37}Si_2O_4$ requires 481.2225).

(3*RS*,4*SR*,5*SR*)-3-((*RS*)-Benzo[*d*][1,3]dioxol-5-yl)-5-(3,4,5-trimethoxyphenyl)-4-vinyltetrahydrofuran, 492



Following the standard procedure outlined on page 181, hydroxysilacycle **488** (0.1 g, 0.3 mmol) was combined with 3,4,5-trimethoxybenzaldehyde dimethylacetal **478** to give, without purification of the fluorosilane, the title compound as a white solid (0.02 g, 20%); R_f 0.2 (pet. ether/ether 1:1); m.p. 140-142 °C; υ_{max} (thin film) 3500-3184 (broad-OH), 3006, 2983, 2884, 2361, 2245, 1592, 1504, 1488, 1418, 1357, 1247, 1129, 1041, 1001 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.89 (1H, s, Ar-*H*), 6.77 (2H, s, Ar-*H*), 6.48 (2H, s, Ar-*H*), 5.97 (2H, s, -OC*H*$_2$O-), 5.69 (1H, ddd, *J* 17, 10, 10, 4-C*H*=CH$_2$), 5.11-5.06 (3H, m, 4-CH=C*H*$_2$, 5-*H*), 4.47 (1H, dd, *J* 10, 2, 3-C*H*(OH)Ar), 3.84 (6H, s, Ar-OC*H*$_3$), 3.82 (3H, s, Ar-OC*H*$_3$), 3.63 (2H, m, 2-*H*), 3.21 (1H, m, 4-*H*), 3.00 (1H, m, 3-*H*), 2.10 (1H, d, *J* 2, 3-CH(O*H*)Ar); δ_C (126 MHz, $CDCl_3$) 153.0 (*q*-Ar-*C*), 147.7 (*q*-Ar-*C*), 136.9 (*q*-Ar-*C*), 135.1 (*q*-Ar-*C*), 134.6 (Ar-*C*), 133.4 (4-*C*H=CH$_2$), 128.2 (*q*-Ar-*C*), 120.0 (Ar-C), 119.1 (4-CH=*C*H$_2$), 108.5 (Ar-*C*), 106.9 (Ar-*C*), 103.1 (Ar-*C*), 101.4 (-O*C*H$_2$O-), 84.7 (5-*C*), 73.7 (3-*C*H(OH)Ar), 68.5 (2-*C*), 61.1 (Ar-O*C*H$_3$), 56.3 (Ar-O*C*H$_3$), 52.5 (3-*C*), 51.8 (4-*C*); *m/z* (ES^+) 437 (MNa^+), 851 ($2MNa^+$); HRMS (ES^+) Found MNa^+, 437.1573 ($C_{23}H_{26}O_7Na$ requires 437.1571).

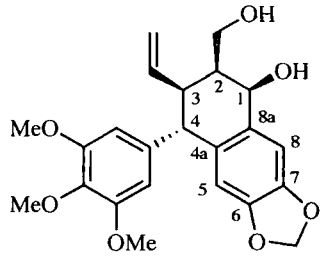
(1*RS*,2*SR*,3*RS*,4*SR*,(*Si*)*RS*/*SR*)-1-(1-Fluoro-2,2,2-trimethyl-1-phenyldisilyl)-2-(acetoxymethyl)-6,7-methylenedioxy-4-(3,4,5-trimethoxyphenyl)-3-vinyl-1,2,3,4-tetrahydronaphthalene, 491



Following stage 1 of the standard procedures outlined on page 181, acetyl-protected hydroxysilacycle **489** (0.1 g, 0.2 mmol) was combined with 3,4,5-trimethoxybenzaldehyde dimethylacetal **478** to give the title compound as a colourless oil (0.06 g, 44%); R_f 0.1 (pet.ether/ether 7:3) as a mixture of diastereoisomers in the ratio 5:1 by NMR; υ_{max} (thin film) 3071, 3006, 2956, 2940, 2891, 2839, 2245, 1731 (C=O), 1591, 1504, 1484, 1422, 1329, 1236, 1129, 1041, 1002, 838 cm^{-1}; NMR data given for major isomer δ_H (500 MHz, $CDCl_3$) 7.47-7.36 (5H, m, Ar-*H*), 6.73 (1H, s, Ar-*H*), 6.24 (1H, s, Ar-*H*), 6.13 (2H, s, Ar-*H*), 5.87 (1H, d, *J* 1.2, -OCH*H*O-), 5.85 (1H, d, *J* 1.2, -OC*H*HO-), 5.77 (1H, ddd, *J* 17, 10, 10, 3-C*H*=CH_2), 4.98 (1H, d, *J* 10, 3-CH=C*H*H), 4.90 (1H, d, *J* 17, 3-CH=CH*H*), 4.24 (1H, dd, *J* 11, 6, 2-C*H*HOAc), 4.09 (1H, dd, *J* 11, 6, 2-CH*H*OAc), 3.83 (3H, s, Ar-OCH_3), 3.80 (6H, s, Ar-OCH_3), 3.55 (1H, d, *J* 8, 4-*H*), 3.21 (1H, m, 1-*H*), 2.75 (1H, m, 3-*H*), 2.68 (1H, m, 2-*H*), 1.99 (3H, s, 2-CH_2O(C=O)CH_3), 0.18 (9H, s, Si(CH_3)$_3$); δ_C (126 MHz, $CDCl_3$) 170.8 (*C*=O), 153.0 (*q*-Ar-*C*), 145.73 (*q*-Ar-*C*), 145.70 (*q*-Ar-*C*), 140.4 (*ipso*-Ar-*C*), 138.6 (3-*C*H=CH_2), 136.5 (*q*-Ar-*C*), 133.0 (Ar-*C*), 132.9 (Ar-*C*), 132.3 (*q*-Ar-*C*), 129.7 (*q*-Ar-*C*), 128.7 (Ar-*C*), 128.1 (Ar-*C*), 117.1 (3-CH=*C*H_2), 110.2 (Ar-*C*), 108.2 (Ar-*C*), 106.0 (Ar-*C*), 100.7 (-O*C*H_2O-), 64.4 (2-*C*H_2OAc), 60.8 (Ar-OCH$_3$), 56.1 (Ar-OCH$_3$), 50.4 (3-*C*), 49.6 (4-*C*), 39.7 (2-*C*), 35.6 (1-*C*), 20.9 (2-CH_2O(C=O)CH_3), -1.7 (Si(CH_3)$_3$); δ_F (300 MHz, $CDCl_3$) -182.5 (1F, d, *J* 8, Si-*F*); δ_{Si} (100 MHz, $CDCl_3$) 15.90, -19.33; *m/z* (ES^+) 659

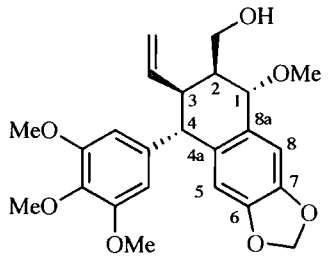
(MNa^+), 1295 ($2MNa^+$); HRMS (ES^+) Found MH^+, 637.2455 ($C_{34}H_{42}O_7FSi_2$ requires 637.2448).

(1*RS*,2*SR*,3*RS*,4*SR*)-2-(Hydroxymethyl)-6,7-methylenedioxy-4-(3,4,5-trimethoxyphenyl)-3-vinyl-1,2,3,4-tetrahydronaphthalen-1-ol, 487



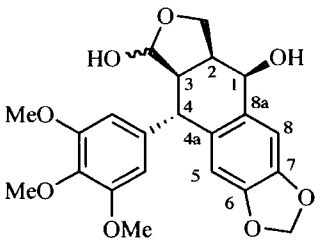
Following the standard procedure outlined on page 181, acetyl-protected hydroxysilacycle **489** (2.0 g, 4.6 mmol) was combined with 3,4,5-trimethoxybenzaldehyde dimethylacetal **478** to give, without purification of the fluorosilane, the title compound as a white solid (1.0 g, 53%); R_f 0.7 (ether); m.p. 177-179 °C; δ_H (500 MHz, $CDCl_3$) 7.11 (1H, s, Ar-*H*), 6.40 (1H, s, Ar-*H*), 6.17 (2H, s, Ar-*H*), 6.01 (1H, m, 3-C*H*=CH_2), 5.95 (1H, d, *J* 1.4, -OCH*H*O-), 5.94 (1H, d, *J* 1.4, -OC*H*HO-), 5.09 (1H, d, *J* 18, 3-CH=C*H*H), 5.05 (1H, d, *J* 7, 3-CH=CH*H*), 5.02 (1H, m, 1-*H*), 3.97 (1H, m, 2-C*H*HOH), 3.90-3.89 (2H, m, 2-CH*H*OH, 4-*H*), 3.83 (3H, s, Ar-OCH_3), 3.76 (6H, s, Ar-OCH_3), 2.89 (1H, m, 1-O*H*), 2.70 (1H, m, 3-*H*), 2.47 (1H, m, 2-*H*); δ_C (126 MHz, $CDCl_3$) 153.0 (*q*-Ar-*C*), 147.4 (*q*-Ar-*C*), 146.9 (*q*-Ar-*C*), 140.7 (*ipso*-Ar-*C*), 139.4 (3-*C*H=CH_2), 136.5 (*q*-Ar-*C*), 131.9 (*q*-Ar-*C*), 130.2 (*q*-Ar-*C*), 116.3 (3-CH=*C*H_2), 109.4 (Ar-*C*), 107.7 (Ar-*C*), 105.9 (Ar-*C*), 101.0 (-O*C*H_2O-), 70.4 (1-*C*), 62.0 (2-*C*H_2OH), 60.8 (Ar-OCH_3), 56.1 (Ar-OCH_3), 49.5 (4-*C*), 47.0 (3-*C*), 42.0 (2-*C*); all data agree with those reported by Pullin.[180]

(1*SR*,2*SR*,3*RS*,4*SR*)-2-(Hydroxymethyl)-6,7-methylenedioxy-1-methoxy-4-(3,4,5-trimethoxyphenyl)-3-vinyl-1,2,3,4-tetrahydronaphthalene, 500



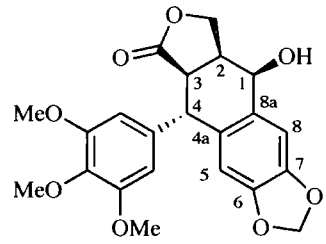
A solution of naphthalenediol **487** (0.05 g, 0.1 mmol) in acetone (2 ml) was treated with *p*-toluenesulfonic acid (0.002 g, 0.01 mmol) and molecular sieves at room temperature. The solution was then treated with 2,2-dimethoxypropane (0.1 ml, 1 mmol) and reacted for 1 h. The reaction mixture was then poured into H_2O and extracted with Et_2O (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether/ether [3:2], [1:1], [1:2], [2:3], [1:4], ether) afforded the title compound as a colourless oil (0.011 g, 20%); R_f 0.8 (ether); υ_{max} (thin film) 3420 (broad-OH), 3082, 3010, 2935, 2836, 1718, 1590, 1504, 1483, 1419, 1329, 1234, 1129, 1041 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.87 (1H, s, Ar-*H*), 6.39 (1H, s, Ar-*H*), 6.27 (2H, s, Ar-*H*), 5.94 (1H, d, *J* 1.5, -OCH*H*O-), 5.93 (1H, d, *J* 1.5, -OC*H*HO-), 5.80 (1H, ddd, *J* 17, 10, 8, 3-C*H*=CH_2), 5.11 (1H, d, *J* 17, 3-CH=C*H*H), 5.06 (1H, d, *J* 10, 3-CH=CH*H*), 4.48 (1H, d, *J* 7, 1-*H*), 3.82 (3H, s, Ar-OCH_3), 3.78-3.73 (9H, s, 2-C*H*HOH, 4-*H*, Ar-OCH_3), 3.64 (1H, m, 2-C*H*HOH), 3.40 (3H, s, 1-OCH_3), 2.97 (1H, m, 3-*H*), 2.44 (1H, m, 2-*H*); δ_C (126 MHz, $CDCl_3$) 153.2 (*q*-Ar-*C*), 147.9 (*q*-Ar-*C*), 146.9 (*q*-Ar-*C*), 141.1 (*ipso*-Ar-*C*), 138.7 (3-*C*H=CH_2), 136.7 (*q*-Ar-*C*), 132.6 (*q*-Ar-*C*), 128.3 (*q*-Ar-*C*), 117.2 (3-CH=CH_2), 110.1 (Ar-*C*), 108.6 (Ar-*C*), 106.4 (Ar-*C*), 101.3 (-OCH_2O-), 78.6 (1-*C*), 63.1 (2-CH_2OH), 61.1 (1-OCH_3), 56.3 (Ar-OCH_3), 54.5 (Ar-OCH_3), 49.5 (4-*C*), 45.9 (3-*C*), 40.3 (2-*C*); *m/z* (ES^+) 451 (MNa^+), 879 ($2MNa^+$); HRMS (ES^+) Found MNa^+, 451.1731 ($C_{24}H_{28}O_7Na$ requires 451.1727).

(1*SR*,2*SR*,3*RS*,4*SR*)-6,7-(Methylenedioxy)-4-(3,4,5-trimethoxyphenyl)-1,2,2',3,3',4-hexahydro-naptho[2,2'-c]furan-1,3'-diol, 493



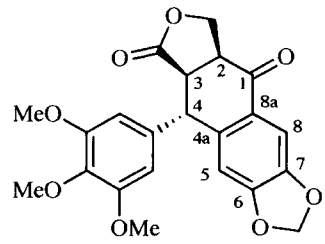
A solution of naphthalenediol **487** (0.03 g, 0.06 mmol) in THF:H_2O (1:1, 3 ml) was treated with 2,6-lutidine (0.01 ml, 0.1 mmol), osmium tetroxide (0.002 g, 0.006 mmol) and sodium periodate (0.05 g, 0.2 mmol) at room temperature. The solution was stirred for 1 h then poured into H_2O and extracted with DCM (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash column chromatography (ether) afforded the title compound as a light brown oil (0.014 g, 58%); R_f 0.3 (ether) as a mixture of diastereoisomers in the ratio 3:1 by NMR; υ_{max} (thin film) 3155 (broad-OH), 2982, 2901, 1793, 1591, 1482, 1382, 1238, 1130, 913, 731 cm^{-1}; NMR data given for major isomer δ_H (500 MHz, $CDCl_3$) 6.74 (1H, s, Ar-*H*), 6.48 (2H, s, Ar-*H*), 6.31 (1H, s, Ar-*H*), 5.91 (1H, s, -OCH*H*O-), 5.89 (1H, s, -*OCH*HO-), 5.19 (1H, m, 2-C*H*HO), 4.97 (1H, m, 2-CH*H*O), 4.70 (1H, s, 3-C*H*OH), 4.24-4.15 (2H, m, 1-*H*, 4-*H*), 3.88 (3H, s, Ar-OCH_3), 3.83 (6H, s, Ar-OCH_3), 3.03 (1H, s, 3-CHO*H*), 2.87 (1H, m, 2-*H*), 2.73 (1H, m, 3-*H*); δ_C (126 MHz, $CDCl_3$) 153.8 (*q*-Ar-*C*), 148.1 (*q*-Ar-*C*), 145.8 (*q*-Ar-*C*), 140.0 (*ipso*-Ar-*C*), 135.6 (*q*-Ar-*C*), 132.0 (*q*-Ar-*C*), 109.3 (Ar-*C*), 108.6 (Ar-*C*), 106.3 (Ar-*C*), 106.1 (Ar-*C*), 101.4 (-O*C*H_2O-), 97.4 (2-*C*H_2O), 70.3 (3-*C*HOH), 67.2 (1-*C*), 61.2 (Ar-OCH_3), 56.4 (Ar-OCH_3), 50.1 (2-*C*), 43.7 (4-*C*), 42.0 (3-*C*); *m/z* (ES^+) 855 ($2MNa^+$); HRMS (ES^+) Found $2MNa^+$, 855.2845 ($C_{44}H_{48}O_{16}Na$ requires 855.2835).

(±)-Epipicropodophyllin, 356



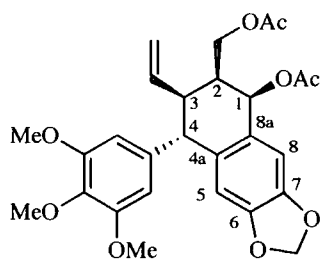
A solution of lactol **493** (0.01 g, 0.04 mmol) in DCM (2 ml) was treated with NIS (0.02 g, 0.08 mmol) and TBAI (0.01 g, 0.02 mmol) at room temperature. The solution was stirred for 1 h then poured into $Na_2S_2O_3$ and extracted with DCM (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash column chromatography (pet. ether/ether [2:3], [3:7], [1:4], [1:9], ether) afforded the title compound as a semi solid (0.009 g, 63%); R_f 0.3 (ether); m.p. 185-188 °C (lit. m.p. 190-192 °C)[139]; υ_{max} (thin film) 3155 (broad-OH), 2903, 1765 (C=O), 1483, 1383, 1246, 1130, 1095, 927, 732 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.01 (1H, s, Ar-*H*), 6.60 (1H, s, Ar-*H*), 6.35 (2H, s, Ar-*H*), 5.98 (1H, d, *J* 1.0, -OCH*H*O-), 5.95 (1H, d, *J* 1.0, -OC*H*HO-), 4.82 (1H, m, 1-*H*), 4.45 (1H, d, *J* 4, 4-*H*), 4.35 (2H, m, 2-CH_2O), 3.82 (3H, s, Ar-OCH_3), 3.78 (6H, s, Ar-OCH_3), 3.44 (1H, dd, *J* 10, 4, 3-*H*), 3.16 (1H, m, 2-*H*), 2.08 (1H, d, *J* 5, 1-O*H*); δ_C (126 MHz, $CDCl_3$) 178.8 (*C*=O), 153.3 (*q*-Ar-*C*), 147.5 (*q*-Ar-*C*), 147.1 (*q*-Ar-*C*), 137.6 (*ipso*-Ar-*C*), 136.8 (Ar-*C*), 131.1 (*q*-Ar-*C*), 130.1 (*q*-Ar-*C*), 109.8 (Ar-*C*), 106.3 (Ar-*C*), 104.9 (Ar-*C*), 101.2 (-O*C*H_2O-), 68.1 (2-*C*H_2O), 67.9 (1-*C*), 60.9 (Ar-O*C*H_3), 56.2 (Ar-O*C*H_3), 45.2 (4-*C*), 44.4 (3-*C*), 39.5 (2-*C*); *m/z* (ES^+) 415 (MH^+); all data agree with those reported in the literature.[139]

(±)-Picropodophyllone, 506



Overoxidation of lactol **493** utilising an excess of NIS and TBAI, yielded after chromatography picropodophyllone as a white solid (0.012, 26%); R_f 0.5 (ether); m.p. 146-148 °C (lit. m.p. 152-158 °C)[174]; υ_{max} (thin film) 2982, 1780 (C=O), 1722 (C=O), 1479, 1383, 1343, 1257, 1161, 1130, 1097, 899, 751 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.50 (1H, s, Ar-*H*), 6.70 (1H, s, Ar-*H*), 6.23 (2H, s, Ar-*H*), 6.06 (1H, d, *J* 1.2, -OCH*H*O-), 6.04 (1H, d, *J* 1.2, -OC*H*HO-), 4.76 (1H, d, *J* 9, 4-*H*), 4.69 (1H, s, 3-*H*), 4.35 (1H, m, 2-*H*), 3.79 (3H, s, Ar-OCH_3), 3.75 (6H, s, Ar-OCH_3), 3.31 (2H, m, 2-CH_2O); δ_C (126 MHz, $CDCl_3$) 177.5 (*C*=O), 175.9 (*C*=O), 154.0 (Ar-*C*), 153.9 (*q*-Ar-*C*), 148.7 (*q*-Ar-*C*), 139.8 (*ipso*-Ar-*C*), 138.2 (*q*-Ar-*C*), 137.4, 127.4 (*q*-Ar-C), 109.7 (Ar-*C*), 106.3 (Ar-*C*), 104.8 (Ar-*C*), 102.5 (-OCH_2O-), 70.8 (3-*C*), 66.1 (2-*C*H_2O), 61.1 (Ar-OCH_3), 56.4 (Ar-OCH_3), 46.9 (4-*C*), 43.6 (2-*C*); *m/z* (ES^+) 413 (MH^+), 454 ($MMeCN^+$); all data agree with those reported in the literature.[177,197]

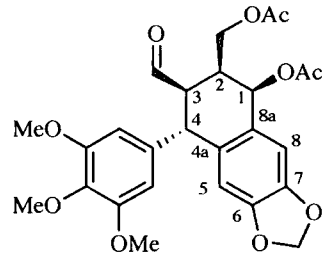
(1*RS*,2*SR*,3*RS*,4*SR*)-1-Acetoxy-2-(acetoxymethyl)-6,7-methylenedioxy-4-(3,4,5-trimethoxyphenyl)-3-vinyl-1,2,3,4-tetrahydronaphthalene, 503



A solution of naphthalenediol **487** (0.05 g, 0.1 mmol) in DCM (2 ml) was treated consecutively with DIPEA (0.08 ml, 0.5 mmol), acetic anhydride (0.03 ml, 0.3 mmol)

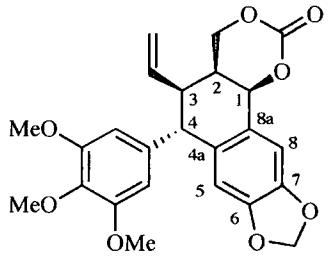
and a catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 10min after which time aq. NH_4Cl (10 ml) was added. The aqueous layer was separated and extracted with DCM (3 x 20 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether/ether [3:7], [2:3], [1:4]) afforded the title compound as a colourless oil (0.05 g, 82%); R_f 0.5 (pet. ether/ether 2:3); υ_{max} (thin film) 3074, 2960, 2890, 1731 (C=O), 1590, 1504, 1485, 1418, 1369, 1239, 1129, 1041 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.88 (1H, s, Ar-*H*), 6.41 (1H, s, Ar-*H*), 6.24 (1H, d, *J* 5, 1-*H*), 6.13 (2H, s, Ar-*H*), 6.00 (1H, m, 3-C*H*=CH_2), 5.95 (1H, d, *J* 1.3, -OCH*H*O-), 5.93 (1H, d, *J* 1.3, -OC*H*HO-), 5.07 (2H, m, 3-CH=CH_2), 4.20 (1H, dd, *J* 11, 9, 2-C*H*HOAc), 4.00 (1H, d, *J* 4, 4-*H*), 3.91 (1H, d, *J* 11, 9, 2-C*H*HOAc), 3.82 (3H, s, Ar-OCH_3), 3.76 (6H, s, Ar-OCH_3), 2.66-2.55 (2H, m, 2-*H*, 3-*H*), 2.08 (3H, s, 2-CH_2O(C=O)CH_3), 2.00 (3H, s, 1-O(C=O)CH_3); δ_C (126 MHz, $CDCl_3$) 171.2 (*C*=O), 171.1 (*C*=O), 153.3 (*q*-Ar-*C*), 148.3 (*q*-Ar-*C*), 147.2 (*q*-Ar-*C*), 140.6 (*ipso*-Ar-*C*), 138.8 (3-*C*H=CH_2), 136.9 (*q*-Ar-*C*), 130.9 (*q*-Ar-*C*), 128.2 (*q*-Ar-C), 116.5 (3-CH=*C*H_2), 110.1 (Ar-*C*), 108.5 (Ar-*C*), 106.1 (Ar-*C*), 101.6 (-O*C*H_2O-), 68.4 (1-*C*), 63.2 (2-*C*H_2O), 61.1 (Ar-O*C*H_3), 56.4 (Ar-O*C*H_3), 50.7 (4-*C*), 47.5 (3-*C*), 36.2 (2-*C*), 21.4 (2-CH_2O(C=O)*C*H_3), 21.1 (1-O(C=O)*C*H_3); *m/z* (ES^+) 521 (MNa^+), 1018 ($2MNa^+$); HRMS (ES^+) Found MNa^+, 521.1785 ($C_{27}H_{30}O_9Na$ requires 521.1782).

(1*RS*,2*SR*,3*RS*,4*SR*)-1-Aceoxy-3-formyl-2-(acetoxymethyl)-6,7-methylenedioxy-4-(3,4,5-trimethoxyphenyl)-3-vinyl-1,2,3,4-tetrahydronaphthalen-1-ethanoate, 504



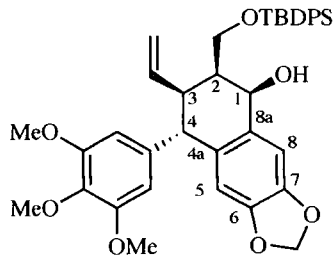
A solution of naphthalene acetate **503** (0.03 g, 0.06 mmol) in THF:H_2O (1:1, 3 ml) was treated with 2,6-lutidine (0.01 ml, 0.1 mmol), osmium tetroxide (0.001 g, 0.006 mmol) and sodium periodate (0.05 g, 0.3 mmol) at room temperature. The solution was stirred for 3 h then poured into H_2O and extracted with DCM (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash column chromatography (pet. ether/ether [3:7], [2:3], [1:4]) afforded the title compound as a white gum (0.012 g, 39%); R_f 0.3 (pet. ether/ether 3:7); υ_{max} (thin film) 2962, 2938, 1736 (C=O), 1591 (C=O), 1505, 1485, 1419, 1371, 1238, 1130, 1041 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.83 (1H, s, 3-C*H*O), 6.87 (1H, s, Ar-*H*), 6.48 (1H, s, Ar-*H*), 6.21 (1H, d, *J* 4, 1-*H*), 6.17 (2H, s, Ar-*H*), 5.98 (1H, d, *J* 1.2, -OCH*H*O-), 5.95 (1H, d, *J* 1.2, -OC*H*HO-), 4.64 (1H, d, *J* 5, 4-*H*), 4.41 (1H, d, *J* 11, 8, 2-C*H*HOAc), 4.10 (1H, d, *J* 11, 8, 2-CH*H*OAc), 3.82 (3H, s, Ar-OCH_3), 3.77 (6H, s, Ar-OCH_3), 2.92 (1H, m, 2-*H*), 2.79 (1H, m, 3-*H*), 2.08 (3H, s, 2-CH_2O(C=O)CH_3), 2.03 (3H, s, 1-O(C=O)CH_3); δ_C (126 MHz, $CDCl_3$) 200.8 (3-*C*HO), 170.9 (*C*=O), 170.5 (*C*=O), 153.6 (*q*-Ar-*C*), 148.7 (*q*-Ar-*C*), 147.4 (*q*-Ar-*C*), 139.8 (*ipso*-Ar-*C*), 137.2 (*q*-Ar-*C*), 130.5 (*q*-Ar-*C*),127.6 (*q*-Ar-C), 110.1 (Ar-*C*), 108.5 (Ar-*C*), 106.1 (Ar-*C*), 101.6 (-O*C*H_2O-), 68.7 (1-*C*), 61.8 (2-*C*H_2O), 61.0 (Ar-O*C*H_3), 56.5 (Ar-O*C*H_3), 54.7 (3-*C*), 43.2 (4-*C*), 36.3 (2-*C*), 21.3 (2-CH_2O(C=O)*C*H_3), 21.0 (1-O(C=O)*C*H_3); *m/z* (ES^+) 523 (MNa^+); HRMS (ES^+) Found MNa^+, 523.1580 ($C_{26}H_{28}O_{10}Na$ requires 523.1575).

(1*RS*,2*SR*,3*RS*,4*SR*)-1,2*H*-(benzo[*d*][1,3]dioxin-2-one)-6,7-methylenedioxy-4-(3,4,5-trimethoxyphenyl)-3-vinyl-1,2,3,4-tetrahydronaphthalene, 501



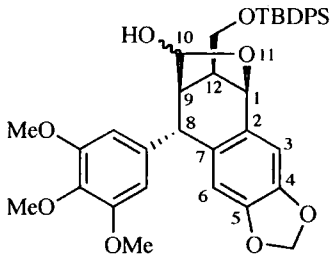
A solution of naphthalene diol **487** (0.02 g, 0.05 mmol) in DCM (2 ml) was treated consecutively with carbonyldiimidazole (0.008 g, 0.05 mmol) and a catalytic amount of DMAP. The reaction was stirred at room temperature for 2 h after which time aq. NH_4Cl (10 ml) was added. The aqueous layer was separated and extracted with DCM (3 x 20 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (ether) afforded the title compound as a cream gum (0.017 g, 80%); R_f 0.4 (ether); υ_{max} (thin film) 2966, 2934, 2246, 1748 (C=O), 1591, 1505, 1485, 1464, 1421, 1242, 1129, 1041 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.06 (1H, s, Ar-*H*), 6.36 (1H, s, Ar-*H*), 6.16 (2H, s, Ar-*H*), 5.97 (1H, s, -OCH*H*O-), 5.95 (1H, s, -OC*H*HO-), 5.78 (1H, m, 3-C*H*=CH_2), 5.65 (1H, d, *J* 5, 1-*H*), 5.14 (2H, m, 3-CH=CH_2), 4.55 (1H, dd, *J* 11, 5, 2-C*H*HO), 4.33 (1H, d, *J* 11, 5, 2-C*H*HO), 3.84-3.82 (1H, m, 4-*H*), 3.82 (3H, s, Ar-OCH_3), 3.77 (6H, s, Ar-OCH_3), 2.82 (1H, m, 3-*H*), 2.77 (1H, m, 2-*H*); δ_C (126 MHz, $CDCl_3$) 153.3 (*q*-Ar-*C*), 148.6 (*q*-Ar-*C*), 148.4 (C=O), 147.4 (*q*-Ar-*C*), 139.0 (3-*C*H=CH_2), 136.9 (*q*-Ar-*C*), 136.9 (*q*-Ar-*C*), 130.5 (*q*-Ar-*C*), 125.5 (*q*-Ar-C), 118.1 (3-CH=*C*H_2), 109.5 (Ar-*C*), 107.7 (Ar-*C*), 105.9 (Ar-*C*), 101.4 (-O*C*H_2O-), 77.0 (1-*C*), 67.4 (2-*C*H_2O), 60.8 (Ar-OCH_3), 56.2 (Ar-OCH_3), 48.8 (4-*C*), 46.8 (3-*C*), 32.5 (2-*C*); *m/z* (ES^+) 504 ($MMeCNNa^+$), 903 ($2MNa^+$); HRMS (ES^+) Found $MMeCNNa^+$, 504.1632 ($C_{26}H_{27}O_8NNa$ requires 504.1629).

(1*RS*,2*SR*,3*RS*,4*SR*)-2-((*tert*-butyldiphenylsilyloxy)methyl)-6,7-methylenedioxy-4-(3,4,5-trimethoxyphenyl)-3-vinyl-1,2,3,4-tetrahydronaphthalen-1-ol, 525



To a solution of naphthalene diol **487** (0.1 g, 0.2 mmol) in dry DCM (3 ml) was added imidazole (0.03 g, 0.5 mmol) and *tert*-butylchlorodiphenylsilane (0.07 ml, 0.3 mmol). The solution was stirred for 2 h at room temperature then diluted with DCM and washed with NH_4Cl (10 ml) and brine (10 ml). The organic layer was separated, dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether/ether [1:1]) gave the title compound as a white solid (0.09 g, 54%); R_f 0.4 (pet. ether/ether 1:1); mp 68-70 °C; υ_{max} (thin film) 3459 (broad-OH), 3073, 2962, 2933, 2246, 1590, 1504, 1481, 1427, 1363, 1236, 1224, 1130, 1113 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.63-7.32 (10H, m, Ar-*H*), 7.20 (1H, s, Ar-*H*), 6.34 (1H, s, Ar-*H*), 6.12 (2H, s, Ar-*H*), 5.97 (1H, d, *J* 1.3, -OCH*H*O-), 5.95 (1H, d, *J* 1.3, -OC*H*HO-), 5.74 (1H, ddd, *J* 17, 9, 7, 3-C*H*=CH_2), 4.94-4.90 (3H, m, 3-CH=CH_2, 1-*H*), 3.94 (2H, m, 2-CH_2O), 3.81 (3H, s, Ar-OCH_3), 3.73 (7H, s, Ar-OCH_3, 4-*H*), 3.53 (1H, d, *J* 8, 1-O*H*), 2.75 (1H, m, 3-*H*), 2.51 (1H, m, 2-*H*) 0.99 (9H, s, SiC(CH_3)$_3$); δ_C (126 MHz, $CDCl_3$) 153.2 (*q*-Ar-*C*), 147.3 (*q*-Ar-*C*), 146.9 (*q*-Ar-*C*), 141.1 (*ipso*-Ar-*C*), 139.1 (3-*C*H=CH_2), 136.6 (*q*-Ar-*C*), 135.8 (Ar-*C*), 133.1 (Ar-*C*), 130.4 (*q*-Ar-*C*), 130.1 (*q*-Ar-*C*), 128.0 (Ar-*C*), 116.5 (3-CH=CH_2), 109.5 (Ar-*C*), 107.8 (Ar-*C*), 106.2 (Ar-*C*), 106.1 (Ar-*C*), 101.2 (-OCH_2O-), 71.5 (1-*C*), 62.9 (2-CH_2O), 61.1 (Ar-OCH_3), 56.3 (Ar-OCH_3), 49.5 (4-*C*), 47.1 (3-*C*), 42.7 (2-*C*) 26.9 (SiC(CH_3)$_3$), 19.2 (Si*C*(CH_3)$_3$); *m/z* (ES^+) 675 (MNa^+), 1327 ($2MNa^+$); HRMS (ES^+) Found $2MNa^+$, 1327.5645 ($C_{78}H_{88}Si_2O_{14}Na$ requires 1327.5605).

(1*RS*,8*SR*,9*RS*,10*RS/SR*,12*SR*)-12-((*tert*-butyldiphenylsilyloxy)methyl)-4,5-methylenedioxy-8-(3,4,5-trimethoxyphenyl)-10-hydroxy-11-oxatricyclo[7.2.1]dodeca-2,4,6-triene, 527

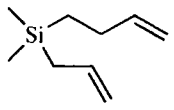


A solution of protected naphthalene **525** (0.08 g, 0.1 mmol) in THF:H_2O (1:1, 3 ml) was treated with 2,6-lutidine (0.03 ml, 0.2 mmol), osmium tetroxide (0.003 g, 0.01 mmol) and sodium periodate (0.1 g, 0.5 mmol) at room temperature. The solution was stirred for 1 h then poured into H_2O and extracted with DCM (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash column chromatography (pet. ether/ether [1:1], [3:7]) afforded the title compound as a colourless gum (0.03 g, 40%); R_f 0.5 (pet. ether/ether 3:7) as a mixture of diastereoisomers in the ratio 2:1 by NMR; υ_{max} (thin film) 3691 (broad-OH), 3155, 2900, 2859, 2253, 1793, 1590, 1483, 1464, 1381, 1246, 1129, 1106 cm^{-1}; NMR data given for major isomer δ_H (500 MHz, $CDCl_3$) 7.61-7.27 (12H, m, Ar-*H*), 6.66 (1H, s, Ar-*H*), 6.50 (1H, s, Ar-*H*), 6.25 (2H, s, Ar-*H*), 5.91 (2H, s, -OC*H*$_2$O-), 5.33 (1H, d, *J* 5, 1-*H*), 4.76 (1H, s, 8-*H*), 4.31 (1H, s, 10-*H*), 3.94 (1H, dd, *J* 10, 7, 12-CH*H*O), 3.84 (3H, s, -OC*H*$_3$), 3.74 (7H, s, -OC*H*$_3$, 12-C*H*HO), 2.70 (1H, m, 9-*H*), 2.51 (1H, t, *J* 10, 12-*H*), 0.98 (9H, s, SiC((C*H*$_3$)$_3$); δ_C (126 MHz, $CDCl_3$) 153.4 (*q*-Ar-*C*), 147.9 (*q*-Ar-*C*), 146.5 (*q*-Ar-*C*), 140.6 (*q*-Ar-*C*), 135.6 (*q*-Ar-*C*), 135.0 (*q*-Ar-*C*), 133.4 (*q*-Ar-*C*), 133.1 (*q*-Ar-*C*), 129.9 (Ar-*C*), 128.3 (*q*-Ar-*C*), 127.9 (Ar-*C*), 111.2 (Ar-*C*), 107.5 (Ar-*C*), 106.2 (Ar-*C*), 102.7 (1-*C*), 101.3 (O*C*H$_2$O), 81.0 (8-*C*), 64.1 (12-*C*H$_2$O), 61.1 (O*C*H$_3$), 56.8 (O*C*H$_3$), 53.2 (9-*C*), 49.9 (10-*C*), 42.7 (12-*C*), 26.9 (SiC((*C*H$_3$)$_3$), 19.4 (Si*C*((CH$_3$)$_3$);

m/z (ES^+) 1331 ($2MNa^+$); HRMS (ES^+) Found $2MNa^+$, 1331.5228 ($C_{76}H_{84}O_{16}Si_2Na$ requires 1331.5190).

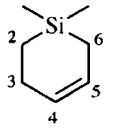
6.6 Other studies

Allyl(but-3-enyl)dimethylsilane, 518



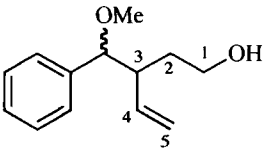
4-Bromo-1-butene (7.3 ml, 74.0 mmol) was added dropwise to a suspension of magnesium turnings (3.6 g, 148 mmol) in ether (25 ml) and stirred for 30 mins [CAUTION: Exothermic]. The supernatant was then added *via* cannula to a solution of allyl(chloro)dimethylsilane **519** (5.0 ml, 37.0 mmol) in ether (25 ml) and the resulting mixture refluxed overnight. The solution was then cooled, quenched with NH_4Cl and extracted with ether (3 x 15 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Fractional distillation afforded the title compound as a colourless oil (3.1 g, 55%); b.p. 160-164 °C, 760 mmHg; δ_H (500 MHz, $CDCl_3$) 5.94-5.76 (2H, m, $CH_2CH{=}CH_2$), 5.04-4.84 (4H, m, $CH_2CH{=}CH_2$), 2.11 (2H, m, $CH_2CH{=}CH_2$), 1.56-1.54 (2H, d, *J* 8, $CH_2CH{=}CH_2$), 0.67-0.64 (2H, m, $CH_2CH{=}CH_2$), 0.02 (6H, s, $Si(CH_3)_2$); δ_C (126 MHz, $CDCl_3$) 141.8, 135.3 ($CH_2CH{=}CH_2$), 113.03, 112.99 ($CH_2CH{=}CH_2$), 28.1, 23.5, 14.2 ($CH_2CH{=}CH_2$), -3.5 ($Si(CH_3)_2$); *m/z* (EI) 154 (M^+, 25%), 139 (M^+ -CH_3, 25%), 125 (M^+ -CH_2CH_3, 100%); all data agree with those reported in the literature.[183]

1,1-Dimethyl-1,2,3,6-tetrahydrosiline, 194



A solution of allylbutenylsilane **518** (2.5 g, 16 mmol) in DCM (32 ml, 0.5M) was treated with Grubbs 1st generation catalyst (0.10 g, 0.16 mmol) at room temperature. The solution was then refluxed for 2 h, cooled to room temperature and filtered through silica gel. Fractional distillation afforded the title compound as a colourless oil (1.1 g, 54%); b.p. 125-130 °C, 760 mmHg; δ_H (500 MHz, $CDCl_3$) 5.74 (1H, m, 4-*H*), 5.63 (1H, m, 5-*H*), 2.22 (2H, m, 3-H_2), 1.20 (2H, m, 6-H_2), 0.66 (2H, t, *J* 7, 2-H_2), 0.07 (3H, s, $Si(CH_3)_2$), 0.05 (3H, s, $Si(CH_3)_2$); δ_C (126 MHz, $CDCl_3$) 130.2 (4-*C*), 126.0 (5-*C*), 22.8 (3-*C*), 13.2 (6-*C*), 10.1 (2-*C*), -2.5 ($Si(CH_3)_2$); *m/z* (EI) 126 (M^+, 45%), 111 (M^+ -CH_3, 50%); all data agree with those reported in the literature.[56]

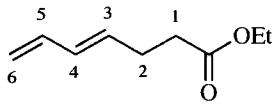
(3RS/RS)-3-((*RS/SR*)Methoxy(phenyl)methyl)pent-4-en-1-ol, 521



Following the standard procedure outlined on page 181, dimethylsilacyclohex-4-ene **194** (0.25 g, 2.0 mmol) was combined with benzaldehyde dimethylacetal to give, without purification of the fluorosilane, the title compound as a pale yellow oil (0.23 g, 55%); R_f 0.3 (pet. ether/ether 1:1) as a mixture of diastereoisomers in the ratio 1:1 by NMR; υ_{max} (thin film) 3516-3186 (broad-OH), 2942, 2880, 2820, 1458, 1100, 1068, 990, 914 cm^{-1}; NMR data given for one isomer δ_H (500 MHz, $CDCl_3$) 7.37-7.33 (5H, m, Ar-*H*), 5.69 (1H, ddd, *J* 16, 10, 9, 4-*H*), 5.11 (1H, dd, *J* 10, 2, 5-*H*H), 5.02 (1H, dd, *J* 16, 2, 5-H*H*), 4.11 (1H, d, *J* 6, 3-C*H*(OCH_3)), 3.69 (2H, m, 1-H_2), 3.23 (3H, s, 3-

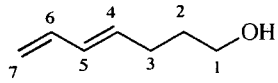
CH(OCH_3)), 2.55 (1H, m, 3-*H*), 1.64 (1H, m, 2-*H*H), 1.48 (1H, m, 2-H*H*); δ_C (126 MHz, $CDCl_3$) 140.1 (*ipso*-Ar-*C*), 139.1 (4-*C*), 128.4 (Ar-*C*), 127.9 (Ar-*C*), 127.8 (Ar-*C*), 117.1 (5-*C*), 87.2 (3-*C*H(OCH$_3$)), 61.4 (1-*C*), 57.3 (3-CH(O*C*H$_3$)), 48.5 (3-*C*), 33.8 (2-*C*); *m/z* (ES^+) 207 (MH^+); HRMS (ES^+) Found MH^+, 207.1379 ($C_{13}H_{19}O_2$ requires 207.1380).

Ethylhepta-3,5-dienoate, 542



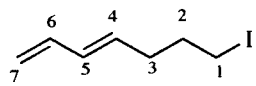
A solution of penta-1,4-dien-3-ol **541** (5 ml, 51.5 mmol) and propionic acid (0.4 ml, 5.2 mmol) in triethyl orthoacetate (71 ml) was heated to reflux for 1 h. The mixture was cooled and ethanol was removed by distillation. The mixture was heated to reflux for 2 h, cooled and ethanol was again removed by distillation. 2,6-Di-*tert*-butyl-4-methylphenol (0.2 g, 1.0 mmol) was added and triethyl orthoacetate was removed *in vacuo*. The residue was subjected to flash chromatography (pentane/ether 4:1) to afford the title compound as a colourless oil (5.7 g, 72%); R_f 0.8 (pentane/ether 4:1); δ_H (300 MHz, $CDCl_3$) 6.28 (1H, ddd, *J* 16, 11, 10, 5-*H*), 6.09 (1H, dd, *J* 11, 10, 4-*H*), 5.72 (1H, m, 3-*H*), 5.11 (1H, d, *J* 16, 6-*H*H), 4.99 (1H, d, *J* 10, 6-H*H*), 4.14 (2H, m, OCH_2CH$_3$), 2.40 (4H, m, 1-H_2, 2-H_2), 1.25 (3H, t, *J* 7, OCH$_2$CH_3); δ_C (126 MHz, $CDCl_3$) 172.9 (*C*=O), 136.9 (5-*C*), 132.7 (4-*C*), 131.9 (3-*C*), 115.7 (6-*C*), 60.4 (O*C*H$_2$CH$_3$), 33.8 (2-*C*), 27.8 (1-*C*), 14.2 (OCH$_2$*C*H$_3$); all data agree with those reported in the literature.[184]

Hepta-4,6-dienol, 543



To a suspension of lithium aluminium hydride (2.8 g, 74.0 mmol) in ether (80 ml) at 0 °C was added ethyl hepta-4,6-dienoate **542** (5.7 g, 37.0 mmol) dropwise. The mixture was allowed to warm to room temperature and stirred for 1 h. The excess lithium aluminium hydride was cautiously quenched sequentially with ethyl acetate, methanol and water. 1M aq. HCl was added to break up any solid material and the mixture was extracted with ether (3 x 20 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pentane/ether 4:1, 1:2) afforded the title compound as a colourless oil (3.59 g, 87%); R_f 0.7 (pentane/ether 1:2); δ_H (300 MHz, $CDCl_3$) 6.31 (1H, ddd, *J* 16, 10, 10, 6-*H*), 6.10 (1H, dd, *J* 16, 10, 5-*H*), 5.73 (1H, m, 4-*H*), 5.13 (1H, d, *J* 16, 7-*H*H), 4.99 (1H, d, *J* 10, 7-H*H*), 3.68 (2H, t, *J* 7, 1-H_2), 2.20 (2H, m, 3-H_2), 1.70 (2H, m, 2-H_2); δ_C (126 MHz, $CDCl_3$) 137.0 (6-*C*), 134.3 (5-*C*), 131.5 (4-*C*), 115.1 (7-*C*), 62.4 (1-*C*), 32.0 (3-*C*), 28.8 (2-*C*); all data agree with those reported in the literature.[184]

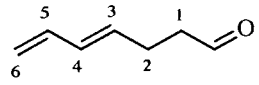
1-Iodohepta-4,6-diene, 544



To a solution of triphenylphosphine (2.8 g, 11.0 mmol) and imidazole (0.7 g, 11.0 mmol) in acetonitrile (40 ml) at room temperature under argon was added iodine (2.7 g, 11 mmol). The solution turned yellow and a white precipitate was observed. Hepta-4,6-dienol **543** (1.0 g, 9.0 mmol) in acetonitrile was added dropwise. The mixture was stirred for 4 h, diluted with ethyl acetate (50 ml) and washed with aq. $Na_2S_2O_3$ and aq. $CuSO_4$. The organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in*

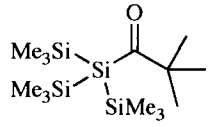
vacuo. Flash chromatography (pentane/ether 4:1) afforded the title compound as a colourless oil (1.57 g, 79%); R_f 0.8 (pentane/ether 4:1); δ_H (300 MHz, $CDCl_3$) 6.29 (1H, ddd, *J* 16, 11, 10, 6-*H*), 6.07 (1H, dd, *J* 16, 11, 5-*H*), 5.63 (1H, m, 4-*H*), 5.13 (1H, d, *J* 16, 7-*H*H), 5.00 (1H, d, *J* 10, 7-H*H*), 3.19 (2H, t, *J* 7, 1-H_2), 2.19 (2H, m, 3-H_2), 1.93 (2H, m, 2-H_2); δ_C (126 MHz, $CDCl_3$) 136.9 (6-*C*), 132.5 (5-*C*), 132.3 (4-*C*), 115.6 (7-*C*), 33.1 (3-*C*), 32.7 (2-*C*), 6.3 (1-*C*); all data agree with those reported in the literature.[184]

Hepta-4,6-dienal, 547



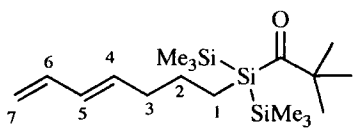
A solution of dimethyl sulfoxide (1.0 ml, 13.4 mmol) in DCM (40 ml) was treated with oxalyl chloride (1.2 ml, 13.4 mmol) at -78 °C. The solution was stirred for 15 mins and then treated with a solution of hepta-4,6-dienol **543** (1.0 g, 9.0 mmol) in DCM (5 ml). After 30 mins the solution was then treated with triethylamine (6.3 ml, 44.6 mmol) and stirred for 10 mins. The reaction was then warmed to room temperature and reacted for a further 1.5 h. After this time the reaction was quenched with water, neutralised with 1N aq. HCl and extracted with DCM (3 x 15 ml). The organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pentane/ether 9:1, 4:1) afforded the title compound as a yellow oil (0.673 g, 68%); R_f 0.4 (pentane/ether 4:1); δ_H (300 MHz, $CDCl_3$) 9.80 (1H, t, *J* 2, C*H*O), 6.30 (1H, ddd, *J* 17, 11, 10, 5-*H*), 6.10 (1H, m, 4-*H*), 5.71 (1H, m, 3-*H*), 5.14 (1H, d, *J* 17, 6-*H*H), 5.02 (1H, d, *J* 10, 6-H*H*), 2.57 (2H, m, 1-H_2), 2.48 (2H, m, 2-H_2); δ_C (126 MHz, $CDCl_3$) 201.7 (*C*=O), 136.7 (5-*C*), 132.3 (4-*C*), 132.1 (3-*C*), 115.9 (6-*C*), 43.1 (1-*C*), 25.0 (2-*C*); all data agree with those reported in the literature.[185]

Tris(trimethylsilyl)silyl pivaloate, 548



Dry tetrakis(trimethylsilyl)silane **94** (3.0 g, 9.4 mmol) and potassium *tert*-butoxide (1.1 g, 9.9 mmol) were combined under argon. Dry THF (5 ml) was added and the solution stirred for 2 h after which time it was dark red. After removal of the solvent, toluene (10 ml) was added and the solution was added dropwise to a solution of pivaloyl chloride (1.3 ml, 10.4 mmol) in toluene (10 ml) at 0 °C. The mixture was stirred for 1.5 h then poured into an ice/H_2SO_4 mixture (10%). The aqueous layer was extracted with ether (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (toluene/pentane 9:1) afforded the title compound as a semi solid (1.5 g, 50%); R_f 0.7 (toluene/pentane 9:1); δ_H (300 MHz, $CDCl_3$) 1.02 (9H, s, $C(CH_3)_3$), 0.23 (27H, s, $(Si(CH_3)_3)_3$); δ_C (126 MHz, $CDCl_3$) 248.3 (C=O), 49.2 ($C(CH_3)_3$), 24.7 ($C(CH_3)_3$), 1.6 ($(Si(CH_3)_3)_3$); all data agree with those reported in the literature.[186]

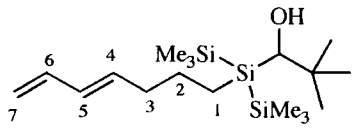
Bis(trimethylsilyl)hepta-4,6-dienylsilylpivaloate, 549



A solution of tris(trimethylsilyl)silyl pivaloate **548** (1.0 g, 3.0 mmol) in THF (3 ml) was treated with potassium *tert*-butoxide (0.37 g, 3.3 mmol). The resultant solution was stirred for 1 h after which time the solution was a deep orange colour. The THF solution was then added, dropwise to a solution of 1-iodohepta-4,6-diene **544** (0.7 g, 3.0 mmol) in ether (5 ml) at room temperature. The reaction was stirred for 10 mins, quenched with water and extracted with ether (3 x 15 ml). The combined organic layers were

dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pentane; pentane/ether 95:5) afforded the title compound as a colourless oil (0.525 g, 50%); R_f 0.4 (pentane/ether 9:1); υ_{max} (thin film) 2964, 2900, 1626 (C=O), 1476, 1448, 1364, 1238, 1056, 1000, 934, 830 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.32 (1H, ddd, *J* 16, 11, 10, 6-*H*), 6.06 (1H, dd, *J* 10, 9, 5-*H*), 5.69 (1H, m, 4-*H*), 5.10 (1H, d, *J* 16, 7-*H*H), 4.97 (1H, d, *J* 11, 7-H*H*), 2.15 (2H, q, *J* 7, 2-H_2), 1.48 (2H, m, 3-H_2), 1.33 (2H, s, 1-H_2), 1.03 (9H, s, -C(CH_3)$_3$), 0.17 (18H, s, (Si(CH_3)$_3$)$_2$); δ_C (126 MHz, $CDCl_3$) 240.3 (*C*=O), 137.5 (6-*C*), 134.9 (4-*C*), 131.7 (5-*C*), 115.1 (7-*C*), 37.1 (3-*C*), 32.0 (1-*C*), 27.1 (2-*C*), 25.0 (C(*C*H_3)$_3$), 12.4 (*C*(CH$_3$)$_3$), 0.5 (Si(*C*H_3)$_3$)$_2$); *m/z* (EI) 354 (M^+, 10%), 339 (M^+ -CH_3, 70%), 281 (M^+ -$SiMe_3$, 100%).

1-(2-Hepta-4,6-dienyl-1,1,1,3,3,3-hexamethyltrisilan-2-yl)-2,2-dimethylpropan-1-ol, 553

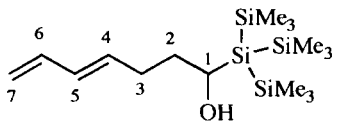


To a suspension of lithium aluminium hydride (0.2 g, 5.7 mmol) in ether (10 ml) at 0 °C was added bis(trimethylsilyl)hepta-4,6-dienylsilyl pivaloate **549** (0.3 g, 2.8 mmol) dropwise. The mixture was allowed to warm to room temperature and stirred for 1 h. The excess lithium aluminium hydride was cautiously quenched sequentially with ethyl acetate, methanol and water. 1M aq. HCl was added to break up any solid material and the mixture was extracted with ether (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pentane, pentane/ether 98:2) afforded the title compound as a colourless oil (0.21 g, 78%); R_f 0.8 (pentane/ether 98:2); υ_{max} (thin film) 3068 (broad-OH), 2954, 2900, 1366, 1248, 1060, 1006, 966, 900, 832 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.31 (1H, ddd, *J* 16, 10, 10, 6-*H*), 6.06 (1H, dd, *J* 10, 10, 5-*H*), 5.70 (1H, m, 4-*H*), 5.09 (1H, d, *J* 16, 7-*H*H), 4.96

(1H, d, *J* 10, 7-H*H*), 3.54 (1H, d, *J* 8, C*H*(OH)), 2.12 (2H, q, *J* 7, 2-H_2), 1.51 (2H, m, 3-H_2), 1.30 (2H, m, 1-H_2), 1.19 (1H, d, *J* 8, CH(O*H*)), 0.97 (9H, s, -C(CH_3)$_3$), 0.18 (18H, s, (Si(CH_3)$_3$)$_2$); δ_C (126 MHz, $CDCl_3$) 137.3 (6-*C*), 135.0 (4-*C*), 131.3 (5-*C*), 114.7 (7-*C*), 76.1 (*C*H(OH)), 37.1 (3-*C*), 36.3 (1-*C*), 27.7 (C(*C*H$_3$)$_3$)), 26.8 (2-*C*), 11.7 (*C*(CH$_3$)$_3$), 0.7 ((Si(*C*H$_3$)$_3$)$_2$), 0.6 ((Si(*C*H$_3$)$_3$)$_2$).

A mass spectrum of this compound was unattainable due to rapid decomposition under all forms of ionisation.

1-Tris(trimethylsilyl)-hepta-4,6-dien-1-ol, 550

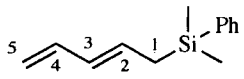


Dry tetrakis(trimethylsilyl)silane **94** (2.0 g, 6.3 mmol) and potassium-*tert*-butoxide (0.8 g, 6.9 mmol) were combined under argon. Dry THF (14 ml) was added and the solution stirred for 2 h after which time it was dark red. The solution was then treated directly with magnesium bromide diethyl etherate (2.1 g, 8.1 mmol). The reaction mixture was stirred for 1 h and then cooled to -78 °C. Aldehyde **547** (0.8 g, 6.9 mmol) was then added and the mixture stirred for 1.5 h. Saturated aq. NH_4Cl was added and the mixture allowed to reach room temperature. The aqueous layer was separated and extracted with ether (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pentane; pentane/ether 98:2, 95:5, 9:1) followed by Kugelrohr distillation (90 °C, 2mbar) afforded the title compound as a colourless oil (0.18 g, 8%); R_f 0.5 (pet. ether/ether 9:1); υ_{max} (thin film) 3624 (broad-OH), 2948, 2902, 1440, 1400, 1242, 1008, 950, 900, 834, 822 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.32 (1H, ddd, *J* 16, 11, 10, 6-*H*), 6.08 (1H, dd, *J* 10, 10, 5-*H*), 5.71 (1H, m, 4-*H*), 5.10 (1H, d, *J* 16, 7-*H*H), 4.97 (1H, d, *J* 11, 7-H*H*), 3.89 (1H, d, *J* 10, 1-*H*), 2.40 (1H, m, 3-H*H*), 2.16 (1H, m, 3-*H*H), 1.81 (1H, m, 2-H*H*), 1.68 (1H, m, 2-*H*H),

0.21 (27H, s, ($Si(CH_3)_3)_3$); δ_C (126 MHz, $CDCl_3$) 137.4 (6-*C*), 134.9 (4-*C*), 131.8 (5-*C*), 115.3 (7-*C*), 65.2 (1-*C*), 39.0 (3-*C*), 31.0 (2-*C*), 1.8 (($Si(CH_3)_3)_3$).

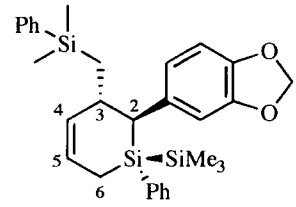
A mass spectrum of this compound was unattainable due to rapid decomposition under all forms of ionisation.

(*E*)-Dimethyl(penta-2,4-dienyl)(phenyl)silane, 568



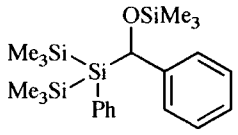
n-Butyllithium (34 ml, 1.6 M, 54 mmol) was added to a stirred solution of piperylene (5 ml, 54 mmol) in hexanes (40 ml). The resultant mixture was added to a stirred slurry of potassium-*tert*-butoxide (6.1 g, 54 mmol) in hexanes (38 ml) at 0 °C. After 20 mins the reaction mixture was cooled to -78 °C and treated with a solution of dimethyl(phenyl)chlorosilane (10 ml, 60 mmol) in diethyl ether (18 ml) and stirred for a further 20 mins. Water (100 ml) was added and the biphasic mixture stirred vigorously whilst warming to room temperature. The aqueous layer was separated and extracted with diethyl ether. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a yellow oil. Flash column chromatography and distillation of the residue afforded the title compound as colourless oil (3.3 g, 30 %); b.p. 90-100°C/0.8 mbar; υ_{max} (thin film) 2954, 1641, 1427, 1249, 1147, 1114, 1000, 826, 786, 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.39-7.35 (5H, m, Ar-*H*), 6.34 (1H, ddd, *J* 15, 10, 9, 4-*H*), 5.96 (1H, dd, *J* 16, 10, 3-*H*), 5.71 (1H, m, 2-*H*), 5.00 (1H, d, *J* 17, 5-H*H*), 4.88 (1H, d, *J* 9, 5-*H*H), 1.78 (2H, d, *J* 8, 1-H_2), 0.29 (6H, s, $Si(CH_3)_2Ph$); δ_C (126 MHz, $CDCl_3$) 139.0 (*ipso*-Ar-*C*), 138.3 (4-*C*), 134.3 (Ar-*C*), 131.8 (2-*C*), 131.5 (3-*C*), 129.9 (Ar-*C*), 128.6 (Ar-*C*), 113.9 (5-*C*), 23.4 (1-*C*), -2.6 ($Si(CH_3)_2Ph$); δ_{Si} (100 MHz, $CDCl_3$) -3.8; *m/z* (EI) 202 (M^+).

(1*SR*,2*SR*,3*RS*)-2-(Benzo[*d*][1,3]dioxol-5-yl)-3-((dimethyl(phenyl)silyl)methyl)-1-phenyl-1-(trimethylsilyl)-silacyclohex-4-ene, 569



Following the standard procedure for silene generation and cyclisation outlined on page 162, silyl alcohol **481** (0.5 g, 1.2 mmol) was transformed into the title compound which was isolated as a colourless oil (0.3 g, 54%) as a mixture of isomers in the ratio 1:1 by NMR; R_f 0.5 (pet. ether/ether 9:1); υ_{max} (thin film) 3008, 2947, 2886, 1486, 1440, 1246, 1108, 1036, 827, 730, 699 cm^{-1}; NMR data given for one isomer δ_H (500 MHz, $CDCl_3$) 7.45-7.41 (5H m, Ar-*H*), 7.36-7.28 (5H, m, Ar-*H*), 6.69-6.66 (3H, m, Ar-*H*), 5.94-5.89 (3H, m, -OC*H*$_2$O-, 5-*H*), 5.60 (1H, m, 4-*H*), 4.92 (1H, dd, *J* 10, 5, 3-C*H*HSi$(CH_3)_2$Ph), 4.20 (1H, dd, *J* 10, 5, 3-CH*H*Si$(CH_3)_2$Ph), 2.71 (1H, m, 3-*H*), 2.34 (1H, d, *J* 10, 2-*H*), 1.81 (1H, m, 6-*H*H), 1.62 (1H, m, 6-H*H*), 0.25 & 0.22 (each 6H, s, Si(C*H*$_3)_2$), -0.03 (9H, s, Si(C*H*$_3)_3$); δ_C (126 MHz, $CDCl_3$) 147.8 (Ar-*C*), 145.8 (Ar-*C*), 139.8 (Ar-*C*), 138.8 (*ipso*-Ar-*C*), 137.6 (*ipso*-Ar-*C*), 136.7 (4-*C*), 134.6 (Ar-*C*), 133.9 (Ar-*C*), 129.2 (Ar-*C*), 128.8 (Ar-*C*), 124.9 (5-*C*), 121.1 (Ar-*C*), 118.6 (Ar-C), 108.9 (Ar-*C*), 108.4 (Ar-*C*), 100.9 (-O*C*H$_2$O-), 68.8 (3-*C*H$_2$Si$(CH_3)_2$Ph), 45.0 (3-*C*), 33.5 (2-*C*), 26.1 (SiC(*C*H$_3)_3$), 18.5 (Si*C*$(CH_3)_3$), 9.4 (6-*C*), -1.2 (Si(*C*H$_3)_3$), -1.6 (Si(*C*H$_3)_2$), -2.1 (Si(*C*H$_3)_2$); δ_{Si} (100 MHz, $CDCl_3$) -19.0, -20.94, -25.0; *m/z* (EI) 514 (M^+, 2%), 312 (50%) 135 (100%), 73 (Si$(CH_3)_3$, 32%); HRMS (CI) Found MNH_4^+, 532.2516 ($C_{30}H_{42}Si_3O_2N$ requires 532.2518).

1,1,1-Trimethyl-2-phenyl-2-(phenyl-trimethylsilanyloxy-methyl)-2-trimethylsilanylmethyl-disilane, 570



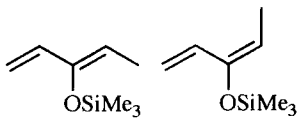
Triethylamine (0.2 ml, 1.8 mmol) and chlorotrimethylsilane (0.1 ml, 0.84 mmol) in DCM (3 ml) were treated with a solution of silyl alcohol **205** (0.25 g, 0.7 mmol) in DCM (2 ml) at room temperature. The solution was stirred overnight, then poured into water and extracted with pet. ether (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether) afforded the title compound as a colourless oil (0.22 g, 72%); R_f 0.6 (pet. ether); υ_{max} (thin film) 2954, 2891, 1600, 1486, 1449, 1426, 1244, 1038, 1024, 828, 743, 696 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.51-7.49 (2H, m, Ar-*H*), 7.29-7.27 (2H, m, Ar-*H*), 7.16-7.09 (6H, m, Ar-*H*), 5.09 (1H, s, C*H*OSi$(CH_3)_3$), 0.15 (9H, s, Si(C*H*$_3)_3$), 0.05 (9H, s, Si(C*H*$_3)_3$), -0.08 (9H, s, (Si(C*H*$_3)_3$); δ_C (126 MHz, $CDCl_3$) 145.4 (Ar-*C*), 136.3 (Ar-*C*), 136.1 (Ar-*C*), 128.1 (Ar-*C*), 127.8 (Ar-*C*), 127.5 (Ar-*C*), 125.9 (Ar-*C*), 125.7 (Ar-*C*), 71.2 (*C*HOSi$(CH_3)_3$), 0.4 (Si(*C*H$_3)_3$), 0.34 (Si(*C*H$_3)_3$), 0.15 (Si(*C*H$_3)_3$); *m/z* (CI) 448 (MNH_4^+, 2%), 431 (M^+, 5%), 415 (M^+ -CH_3, 10%), 358 (M^+ -Si$(CH_3)_3$, 100%); HRMS (CI) Found MNH_4^+, 448.2337 ($C_{22}H_{42}Si_4ON$ requires 448.2338).

Dimethyldioxirane, 571

Water (11 ml), acetone (7 ml, 94.0 mmol) and $NaHCO_3$ (13 g) were added to a 3-necked round bottomed flask equipped with a pressure equalising dropping funnel containing acetone (8.4 ml, 114.0 mmol) and water (8.4 ml), an air cooled condenser fitted with a acetone/dry ice cold finger dewar and finally a solid addition funnel

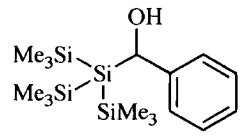
containing oxone (25 g, 40.7 mmol). The oxone was then added portionwise (2-5 g) to the reaction vessel, whilst adding the acetone/water mixture simultaneously to the vigorously stirred mixture. The mixture was reacted for 30 mins at room temperature, after which time a slight pressure (30 mmHg) was added to finish the reaction off. The isolated pale yellow solution was used directly in the following epoxidation reaction.

(*E/Z*)-Trimethyl(penta-1,3-dien-3-yloxy)silane, 572



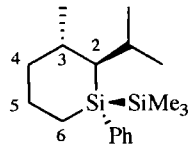
Ethyl vinyl ketone (2.6 ml, 25 mmol), triethylamine (4.4 ml, 31 mmol) and chlorotrimethylsilane (4.0 ml, 31 mmol) were mixed and cooled to 0 °C. Sodium iodide (4.7 g, 31 mmol) in acetonitrile (31 ml) was added dropwise to the stirred solution. Immediately after addition the onium salt formed quantitatively and the reaction was then warmed to 80 °C for 10 h after which time the reaction was poured onto ice/water. The aqueous phase was separated and extracted with pet. ether (3 x 50 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Kugelrohr distillation (50 °C, 6 mbar) afforded the title compound as a colourless oil (0.8 g, 21%); all data given for the major *Z* isomer; υ_{max} (thin film) 2960, 1649, 1605, 1339, 1252, 1052, 900, 842 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.17 (1H, d, *J* 10, CC*H*=CH_2), 5.23 (1H, d, *J* 15, CCH=C*H*H), 4.95-4.87 (2H, m, CCH=CH*H*, C=C*H*CH_3), 1.64 (3H, d, *J* 6, C=CHCH_3), 0.22 (9H, s, Si(CH_3)$_3$); δ_C (126 MHz, $CDCl_3$) 135.5 (C*C*H=CH_2), 111.4 (CCH=*C*H_2), 110.3 (C=*C*HCH_3), 11.6 (C=CH*C*H_3), 0.6 (Si(*C*H_3)$_3$); *m/z* (EI) 156 (M^+, 84%), 141 (M^+ -Me, 88%), 127 (M^+ -Me, -CH_2, 96%); all data agree with those reported in the literature.[198]

(1,1,1,3,3,3-Hexamethyl-2-(trimethylsilyl)trisilan-2-yl)(phenyl)methanol, 573



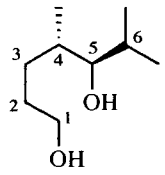
Dry tetrakis(trimethylsilyl)silane (10.0 g, 31.0 mmol) and potassium *tert*-butoxide (3.6 g, 32.2 mmol) were combined under argon. THF (40 ml) was added and the resulting solution stirred for 2 h after which time it had become bright red. The THF was evaporated directly using a vacuum manifold and ether (40 ml) was added. The resulting solution was added *via* canula to a suspension of magnesium bromide diethyl etherate (10.5 g, 40.6 mmol) in ether (40 ml). The reaction mixture was stirred for 1h and then cooled to -78 °C. Freshly distilled benzaldehyde (1.0 ml, 34.4 mmol) was added and the mixture stirred for 1.5 h. Saturated aq. NH_4Cl was added and the mixture allowed to reach room temperature. The aqueous layer was separated and extracted with ether (3 x 30 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether; pet. ether/ether 39:1, 29:1) afforded the title compound as a yellow solid (2.6 g, 24%); R_f 0.3 (pet. ether/ether 9:1); m.p. 100-102 °C; υ_{max} (thin film) 3696 (broad-OH), 2950, 2892, 1600, 1245, 838 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.29-7.27 (3H, m, Ar-*H*), 7.16-7.14 (2H, m, Ar-*H*), 5.04 (1H, s, SiC*H*), 0.14 (27H, s, $Si(Si(CH_3)_3)_3$); δ_C (126 MHz, $CDCl_3$) 147.3 (*ipso*-Ar-*C*), 128.3 (Ar-*C*), 126.1 (Ar-*C*), 125.4 (Ar-*C*), 69.4 (Si*C*H), 1.5 ($Si(Si(CH_3)_3)_3$); *m/z* (ES^+) 377 (MNa^+).

(1*SR*,2*RS*,3*SR*)-1-Phenyl-1-trimethylsilyl-2-(prop-2'-yl)-3-methylsilacyclohexane, 574



A mixture of silacycle **100** (0.1 g, 0.3 mmol) and Pd/C (10% Pd approx. 0.001 g) in dry toluene (2 ml) was repeatedly evacuated and flushed with hydrogen from a balloon. The mixture was then stirred under a hydrogen atmosphere for 8 h. It was then filtered through a celite pad and the pad washed with ether. The filtrate was concentrated and dried *in vacuo*. Flash chromatography (hexane) gave the title compound as a colourless oil (0.06 g, 55%); R_f 0.9 (pet. ether); δ_H (300 MHz, $CDCl_3$) 7.54-7.52 (2H, m, Ar-*H*), 7.33-7.30 (3H, m, Ar-*H*), 2.16 (1H, septet d, *J* 7, 4, 2-C*H*$(CH_3)_2$), 1.95 (1H, dm, *J* 13, 5-H*H*), 1.81 (1H, m, 3-*H*), 1.74 (1H, dm, *J* 13, 4-H*H*), 1.50 (1H, qt, *J* 13, 3, 5-*H*H), 1.19 (1H, m, 4-*H*H), 1.11 (1H, dd, *J* 10, 4, 2-*H*), 1.07 (1H, m, 6-H*H*), 1.05 (1H, m, 6-H*H*), 1.02 (3H, d, *J* 7, 2-CH(CH_3)$_2$), 0.97 (3H, d, *J* 7, 3-CH_3), 0.79 (3H, d, *J* 7, 2-CH(CH_3)$_2$), 0.27 (9H, s, Si(CH_3)$_3$); *m/z* (EI) 304 (M^+, 12%), 289 (M^+-Me, 1%), 231 (M^+-Si$(CH_3)_3$, 76%), 187 (10%), 175 (34%), 161 (56%), 153 (44%), 147 (28%), 135 (70%), 121 (100%), 107 (38%), 105 (52%); all data agree with those reported by Whelligan.[35]

(4*SR*,5*RS*)-4,6-Dimethylheptane-1,5-diol, 575



Stage 1

To a solution of (1*SR*,2*RS*,3*SR*)-1-Phenyl-1-trimethylsilyl-2-(prop-2'-yl)-3-methylsilacyclohexane (0.06 g, 0.2 mmol) in dry chloroform (4 ml) was added

trifluoroborane-acetic acid complex (0.5 ml, 3.6 mmol). The mixture was then heated to reflux and stirred for 18 h. The solution was then allowed to cool to room temperature and saturated $NaHCO_3$ solution (5 ml) was added. The aqueous layer was separated and extracted with DCM (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo* to give a dark orange oil which was used immediately in stage 2.

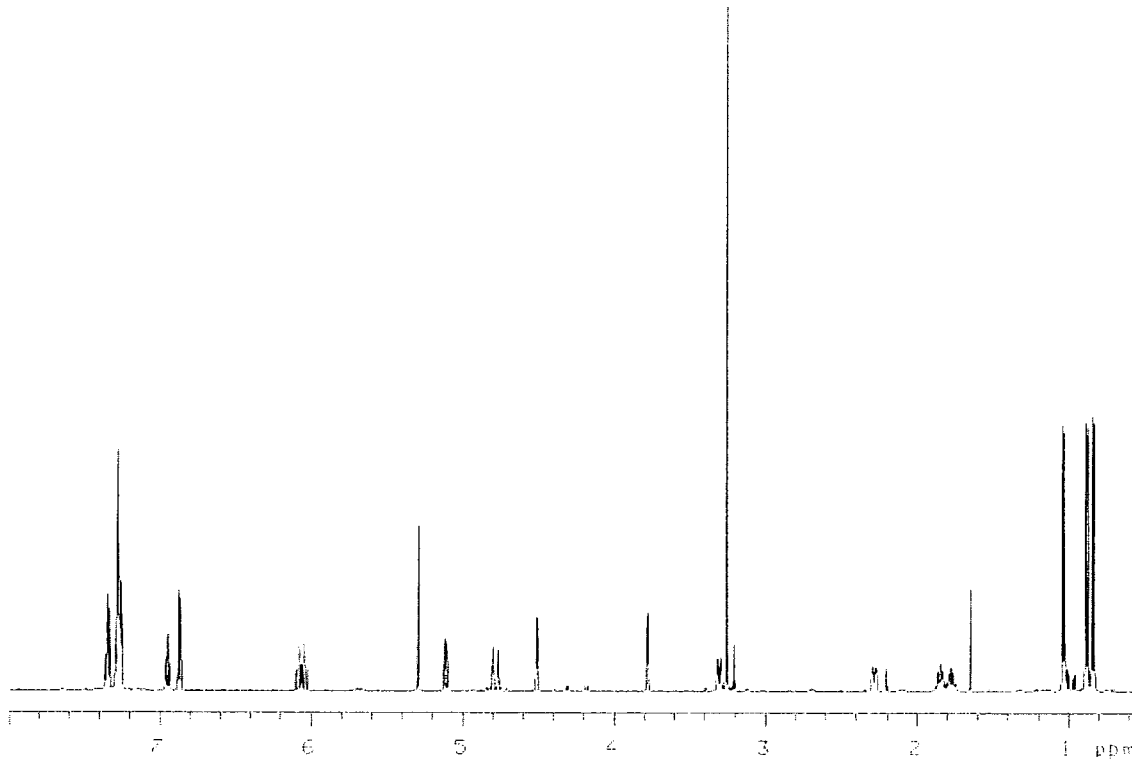
Stage 2

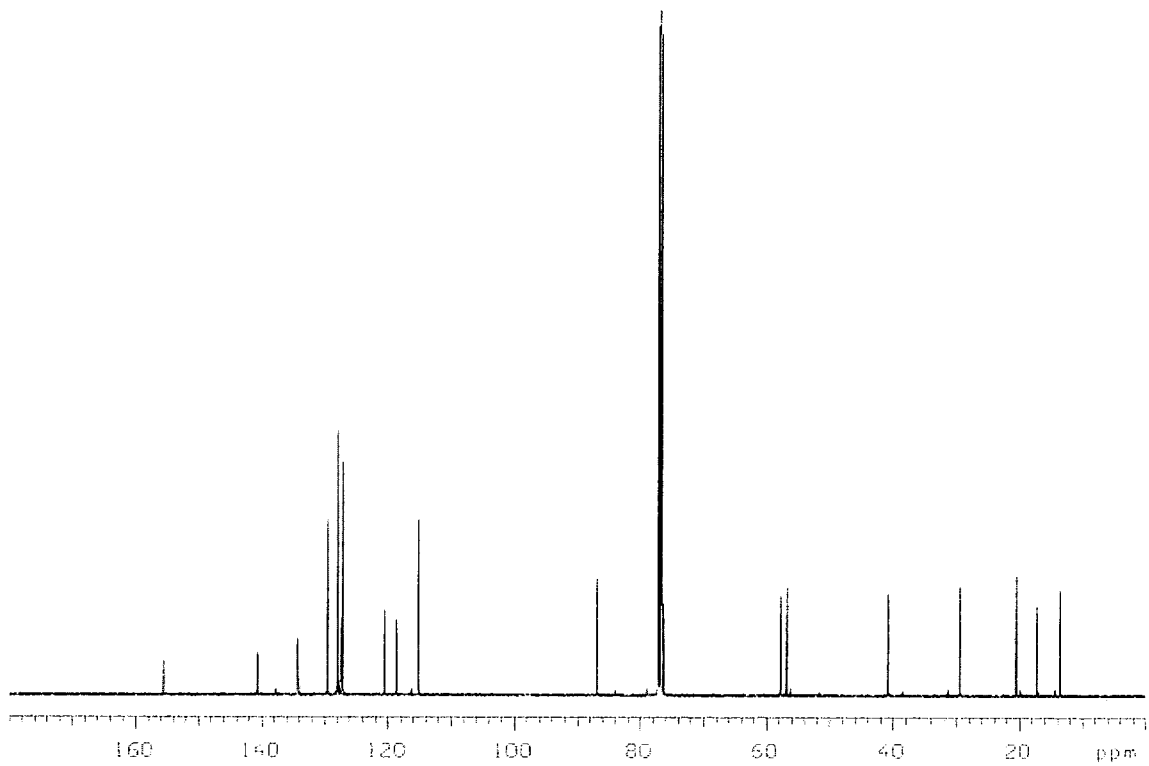
To the dark orange oil was added $KHCO_3$ (0.07 g, 0.7 mmol) and KF (0.04 g, 0.7 mmol). The mixture was dissolved in methanol:THF solution (1:1, 4 ml) and a 35% w/w solution of H_2O_2 in water (0.4 ml, 4.3 mmol) was added. The mixture was heated to reflux and stirred for 19 h. The mixture was then allowed to cool to room temperature and saturated $Na_2S_2O_3$ solution (5 ml) was added together with EtOAc (10 ml). The aqueous layer was separated and extracted with EtOAc (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and dried *in vacuo*. Flash chromatography (pet. ether/ethyl acetate 1:1) gave the title compound as a colourless oil (0.004 g, 14%); R_f 0.2 (pet. ether/ethyl acetate 1:1); δ_H (300 MHz, $CDCl_3$) 3.65 (2H, t, *J* 6, 1-*H*$_2$), 3.09 (1H, t, *J* 7, 5-*H*), 1.82 (1H, octet, *J* 7, 6-*H*), 1.69 (2H, m, 3-H*H*, 2-H*H*), 1.60 (1H, m, 4-*H*), 1.50 (1H, m, 2-*H*H), 1.18 (1H, q, *J* 9, 3-*H*H), 0.93 (3H, d, *J* 7, 6-C*H*$_3$), 0.90 (3H, d, *J* 7, 4-C*H*$_3$), 0.89 (3H, d, *J* 7, 6-C*H*$_3$); all data agree with those reported by Whelligan.[35]

7 Appendix

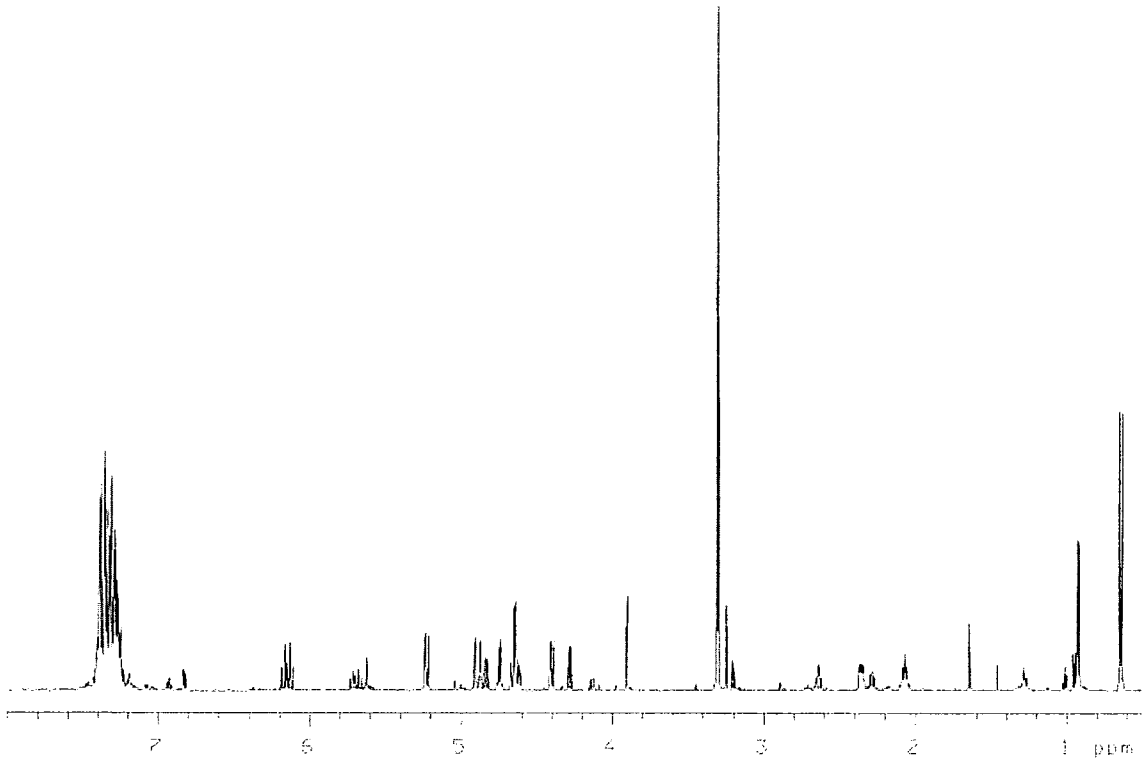
This appendix presents ^{1}H and ^{13}C NMR spectra to make available evidence for the minor diastereoisomers obtained from the Hosomi-Sakurai and other reactions.

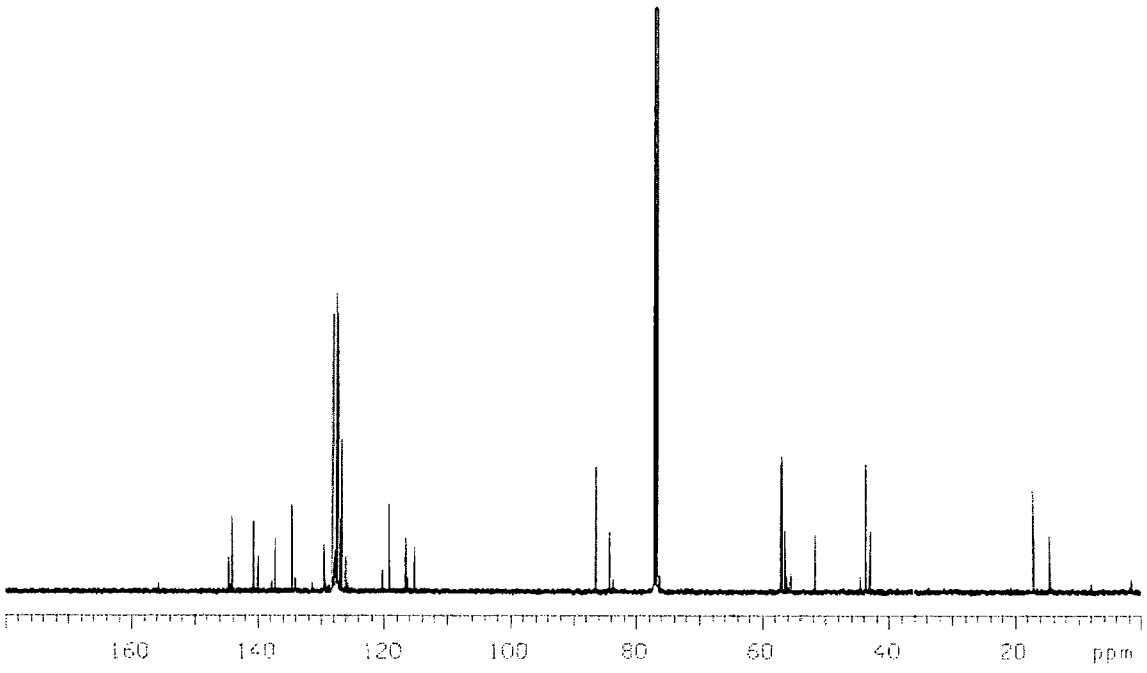
^{1}H and ^{13}C NMR for **328**



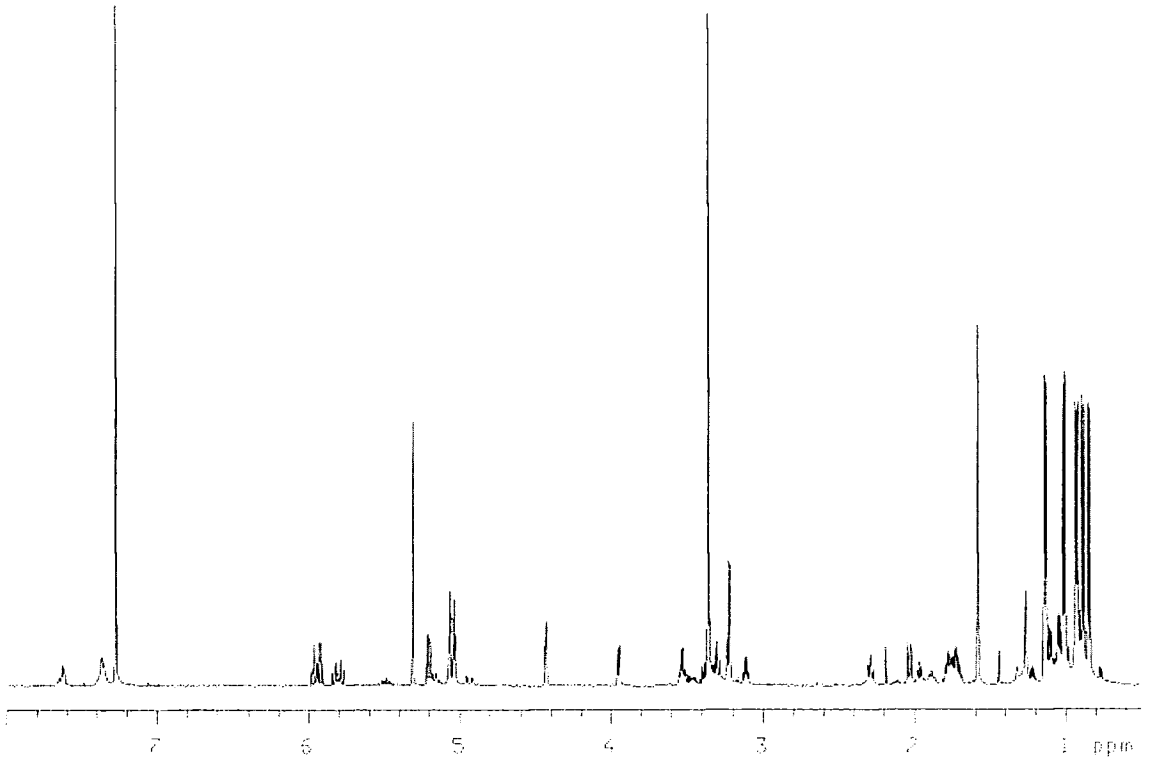


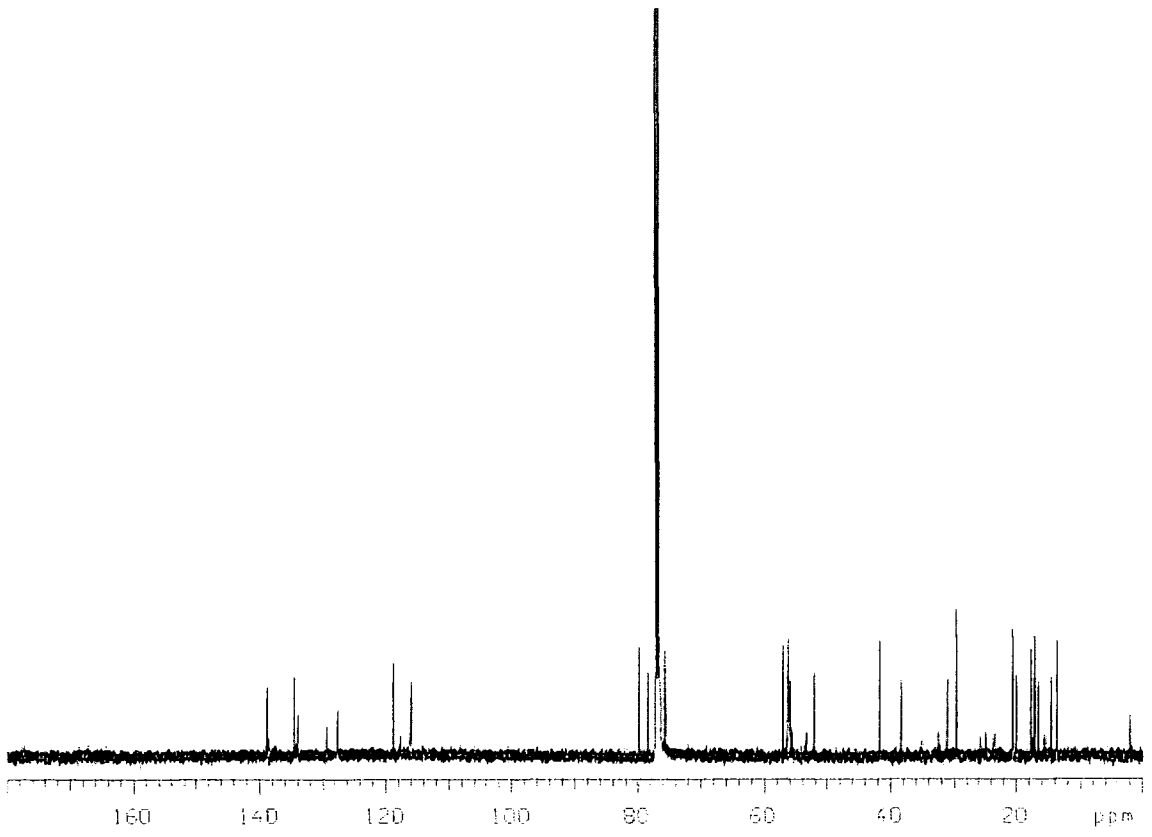
^{1}H and ^{13}C NMR for **322Ad**



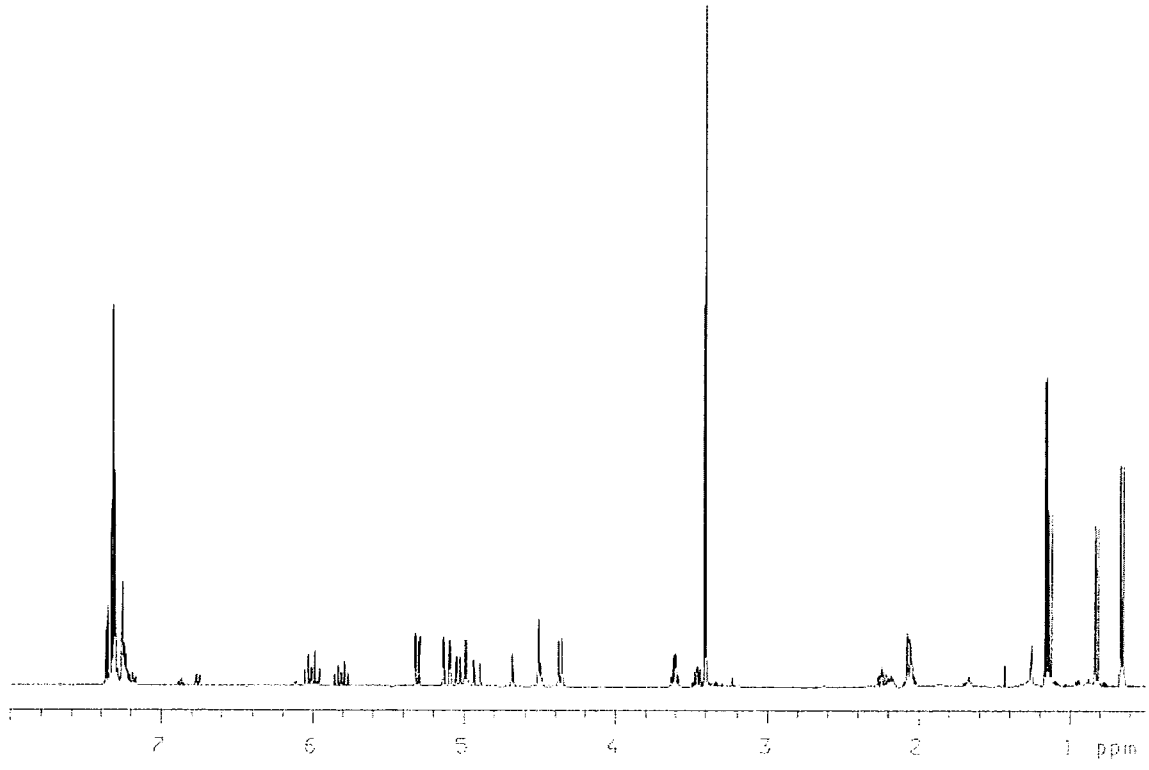


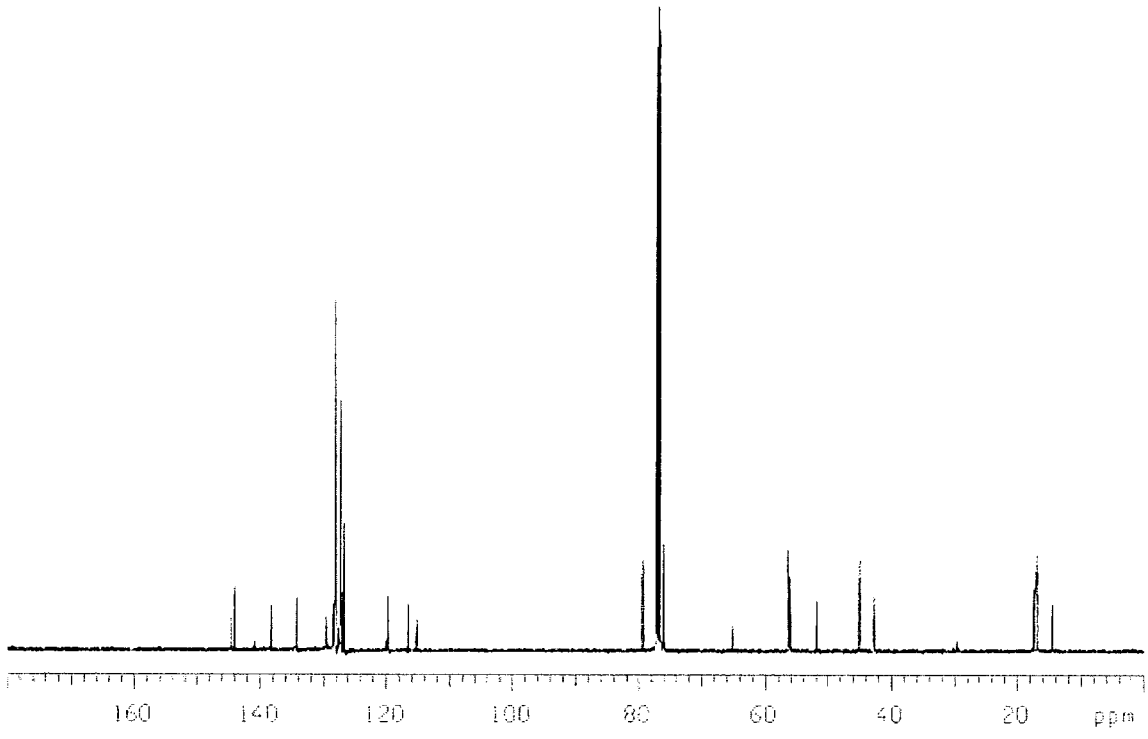
^{1}H and ^{13}C NMR for **322Ac**



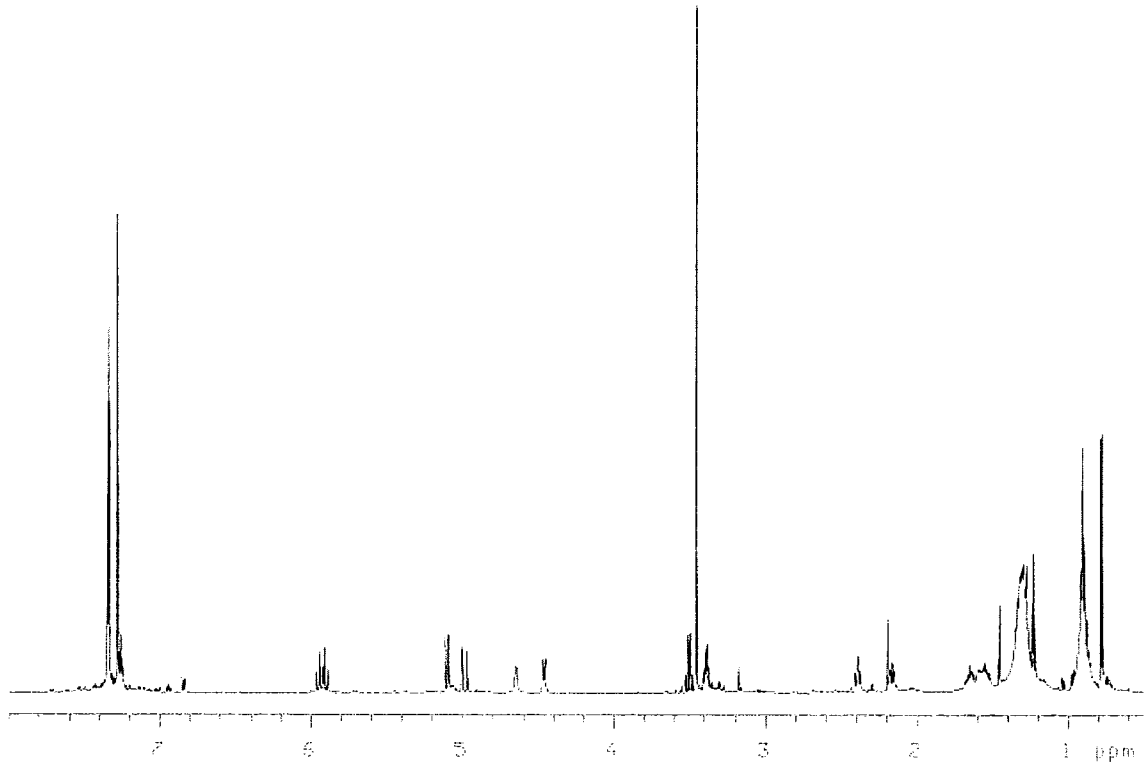


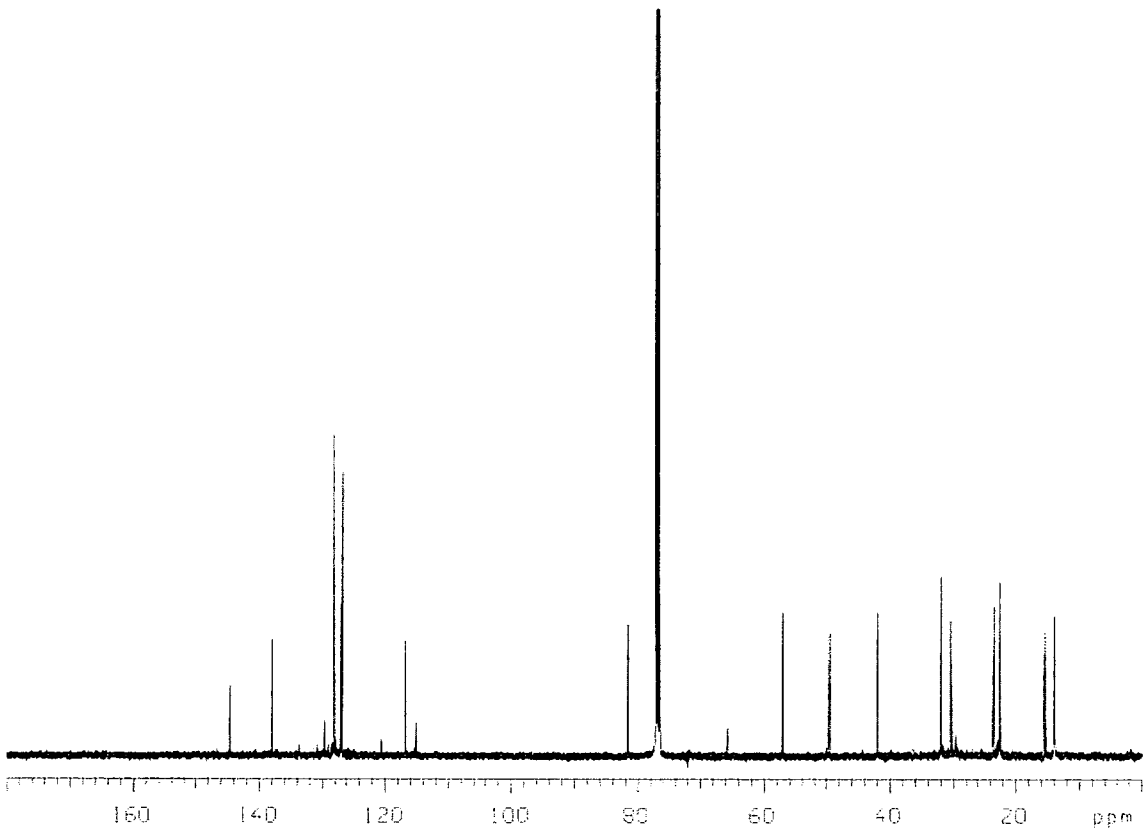
^{1}H and ^{13}C NMR for **322Ai**



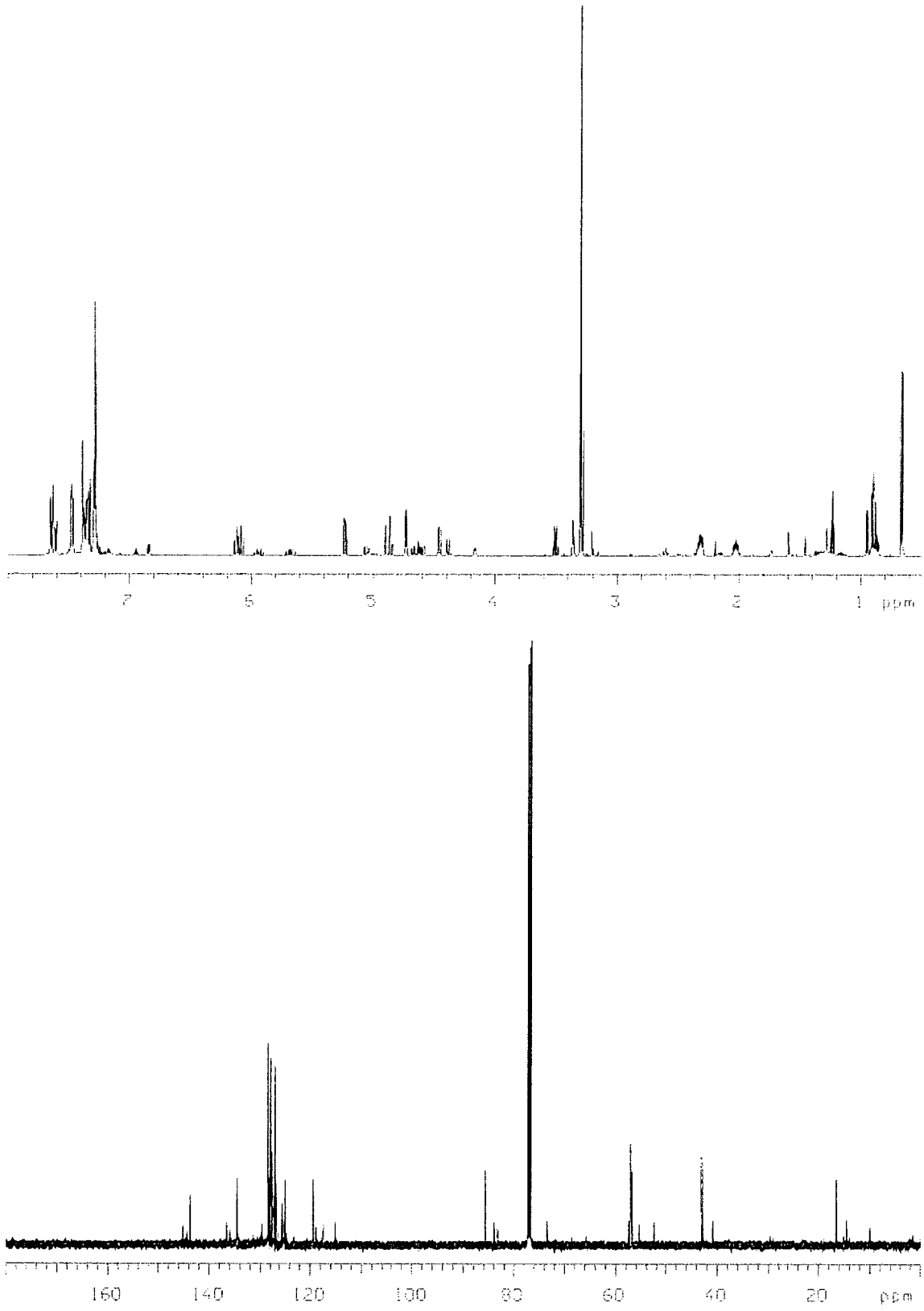


^{1}H and ^{13}C NMR for **322Aj**

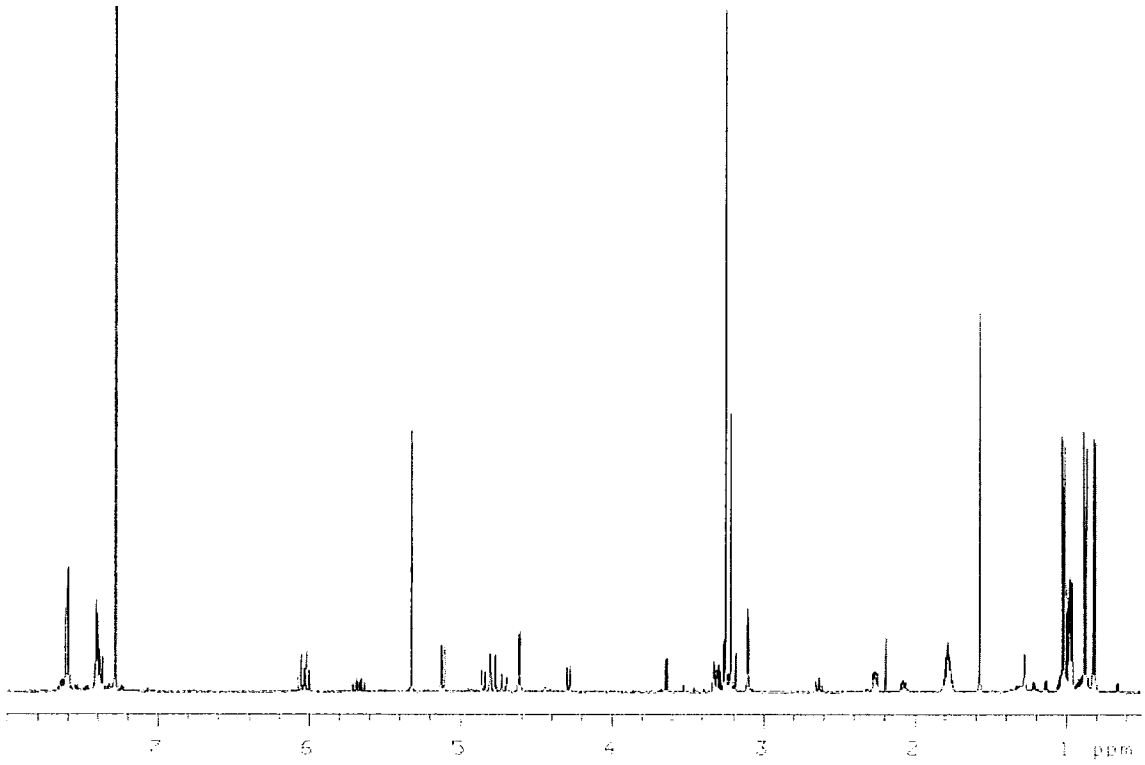


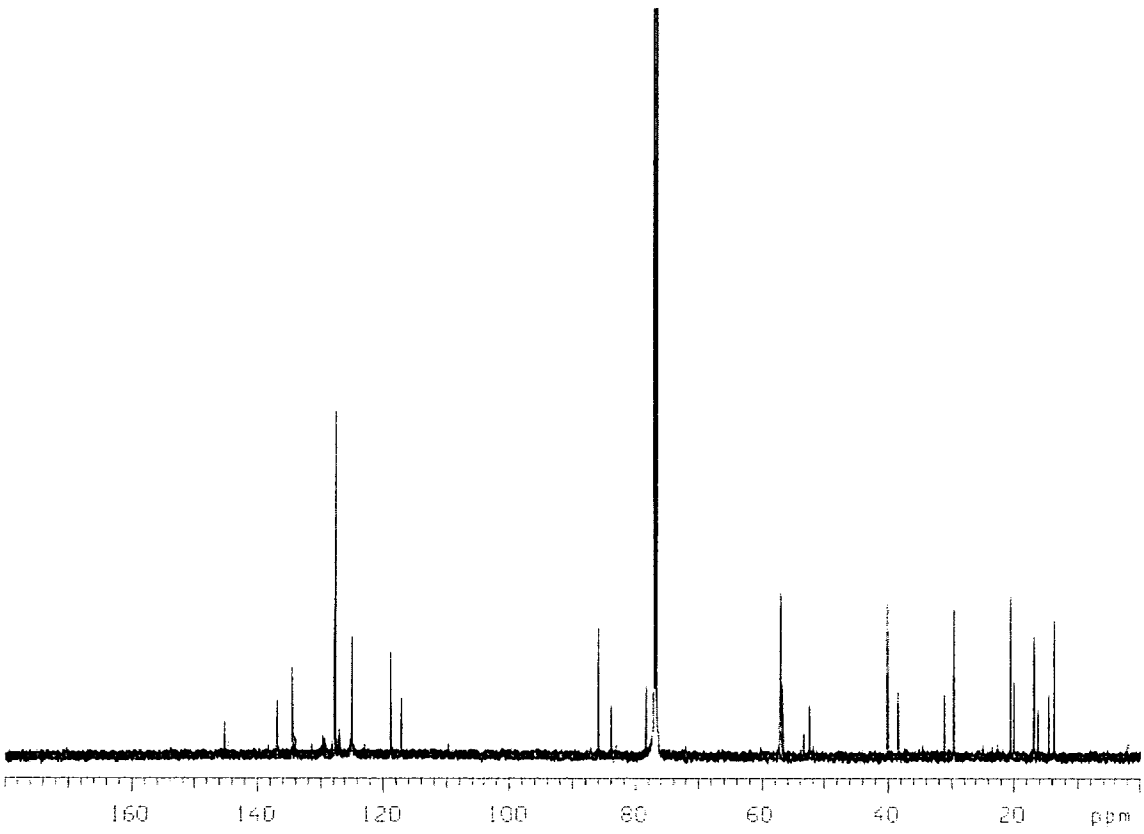


^{1}H and ^{13}C NMR for **322Af**

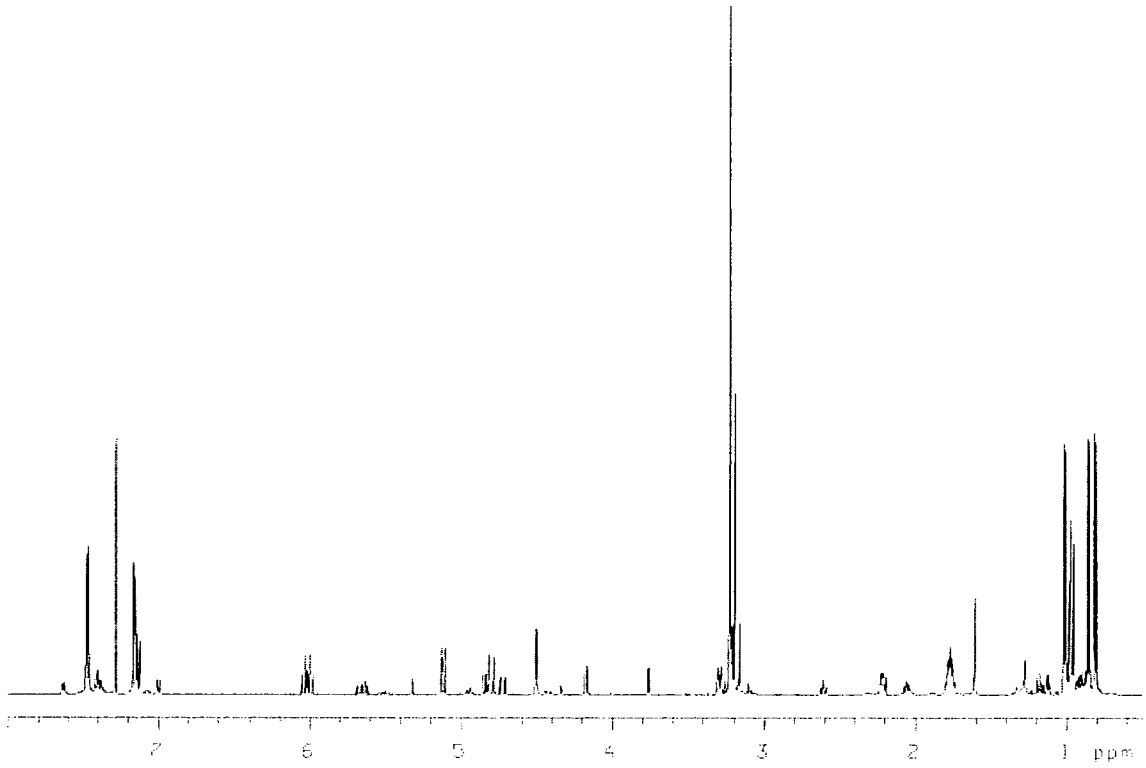


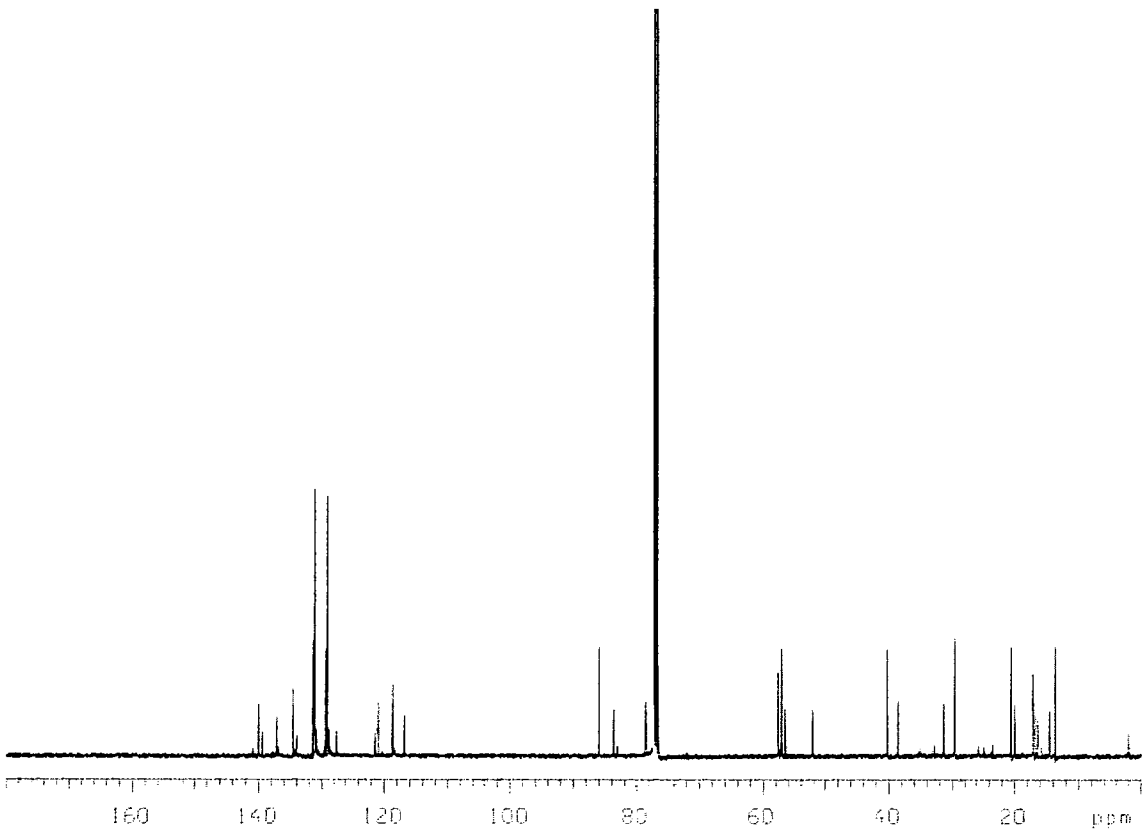
^{1}H and ^{13}C NMR for **322Aa**



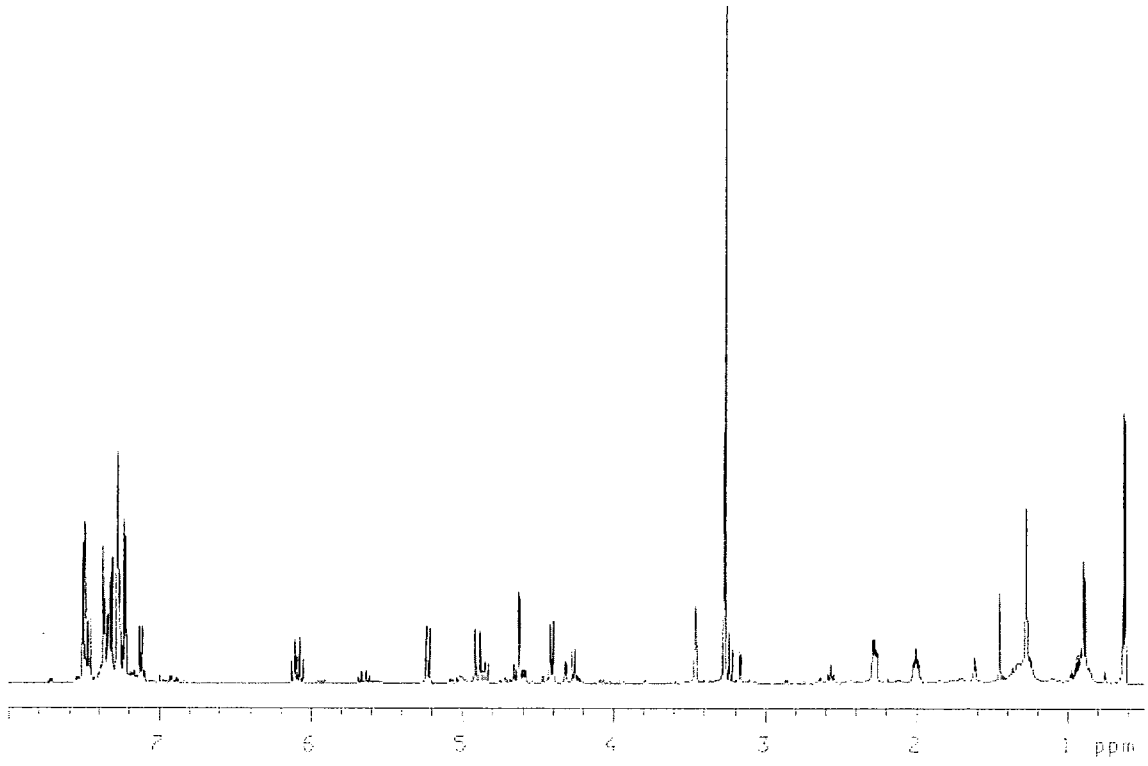


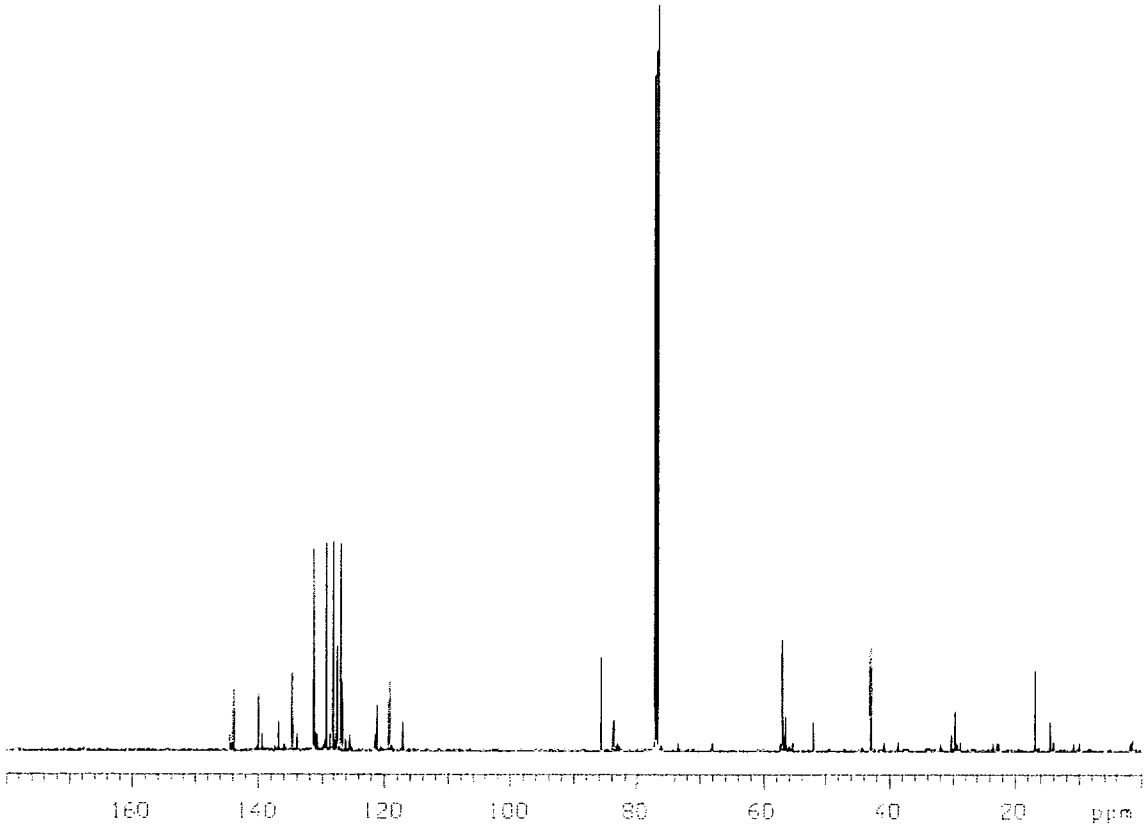
^{1}H and ^{13}C NMR for **322Ab**



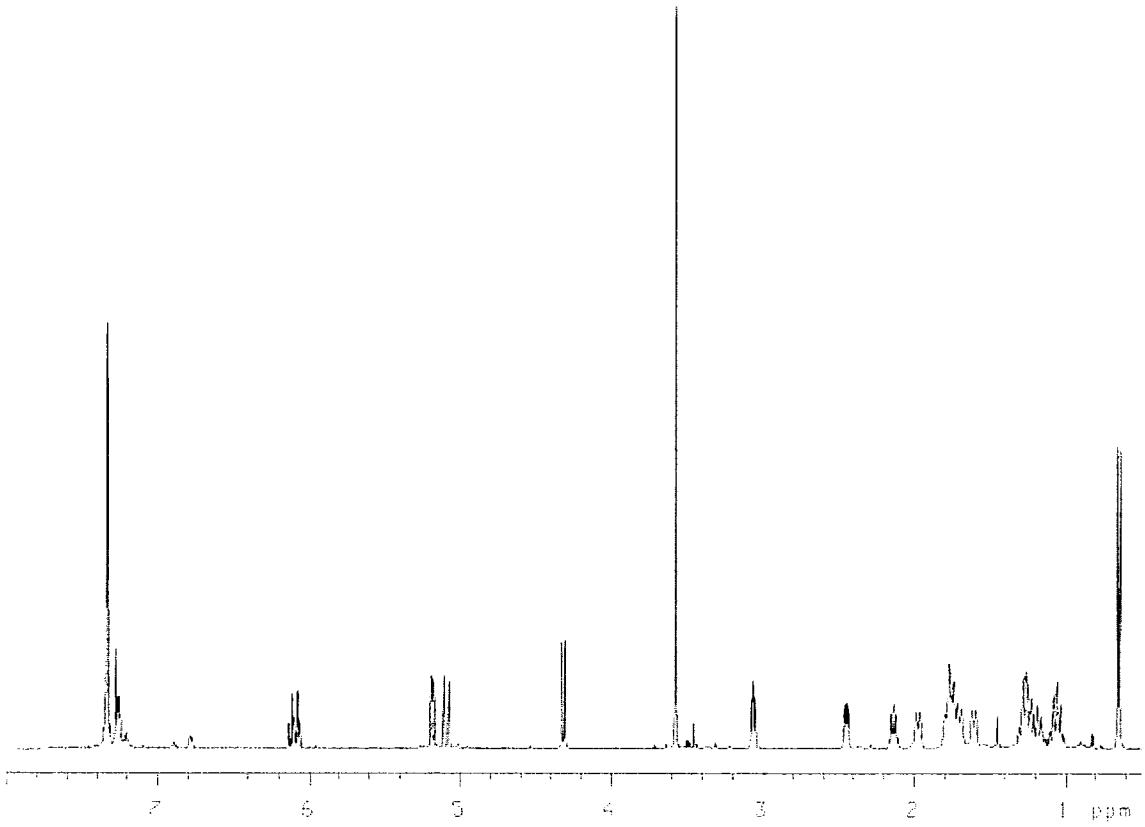


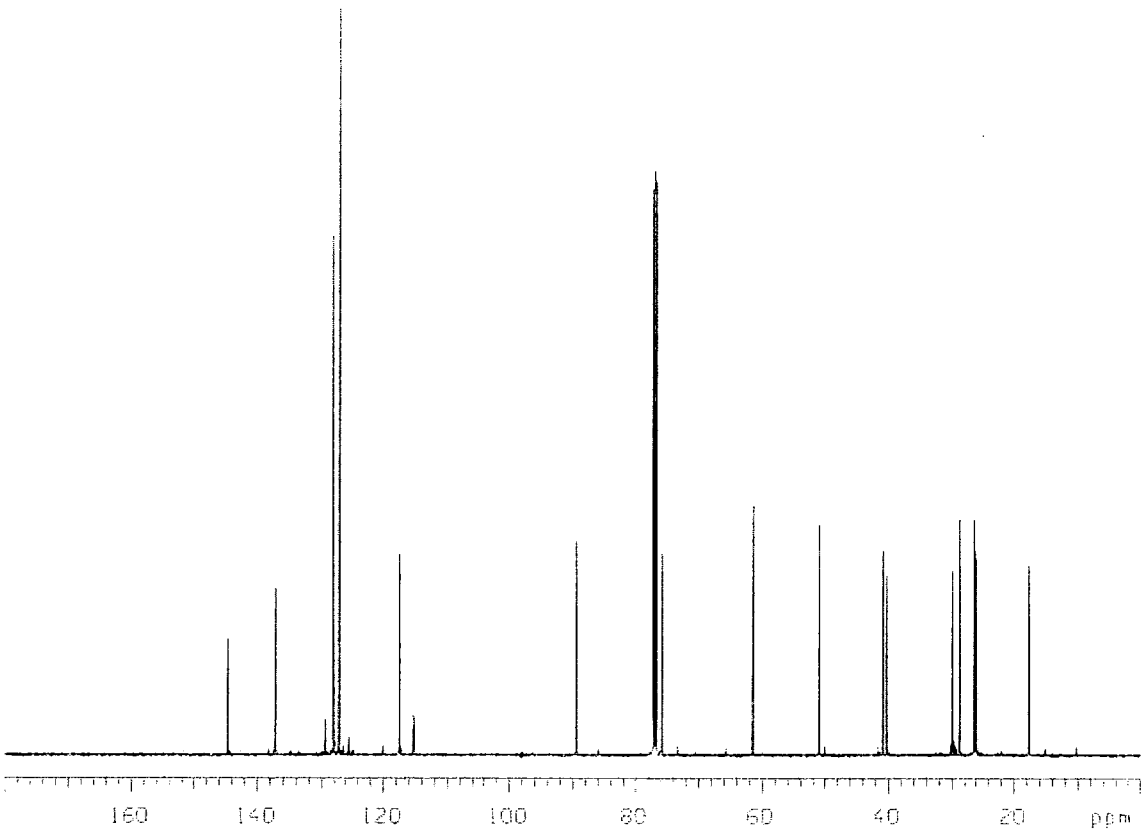
^{1}H and ^{13}C NMR for **322Ag**



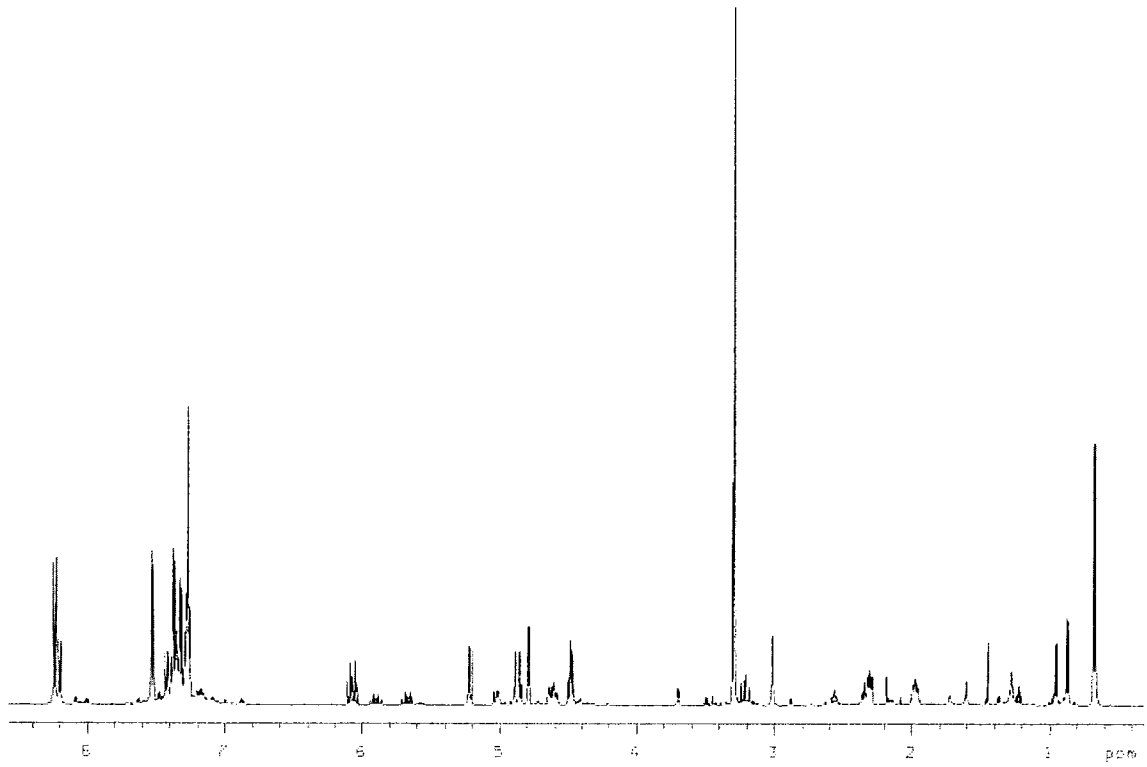


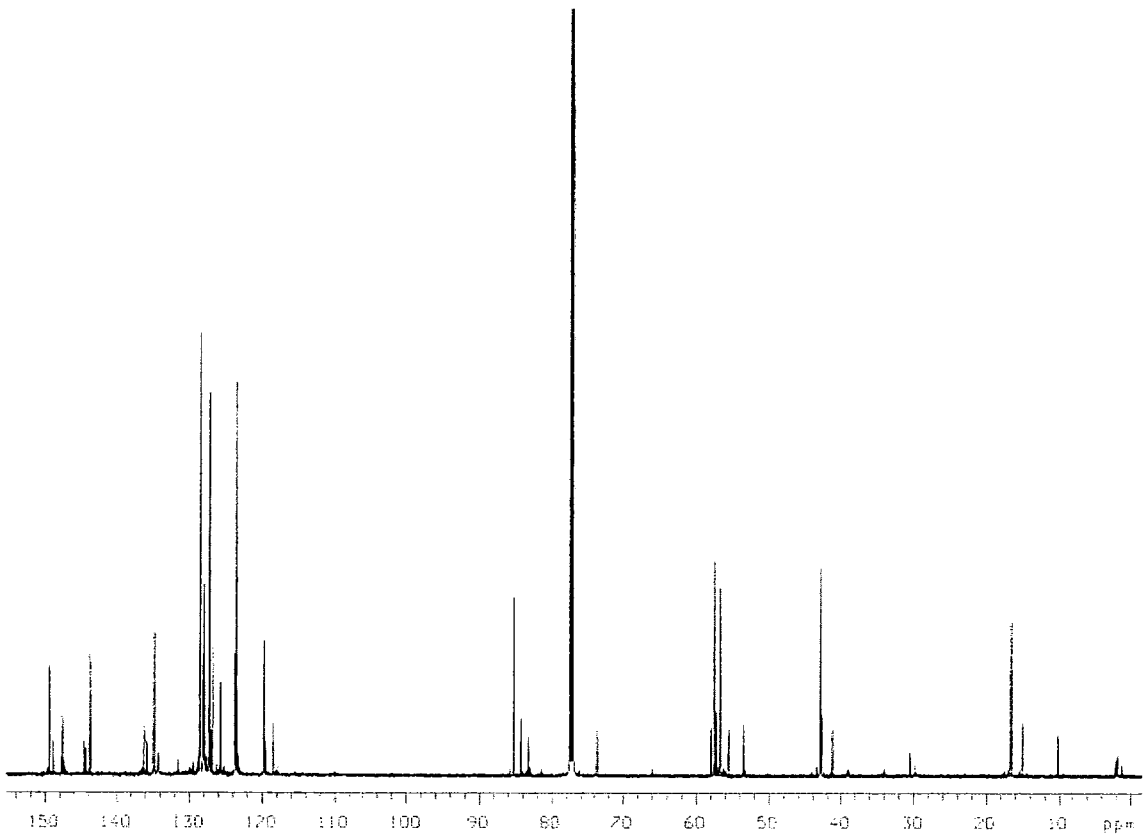
^{1}H and ^{13}C NMR for **342**



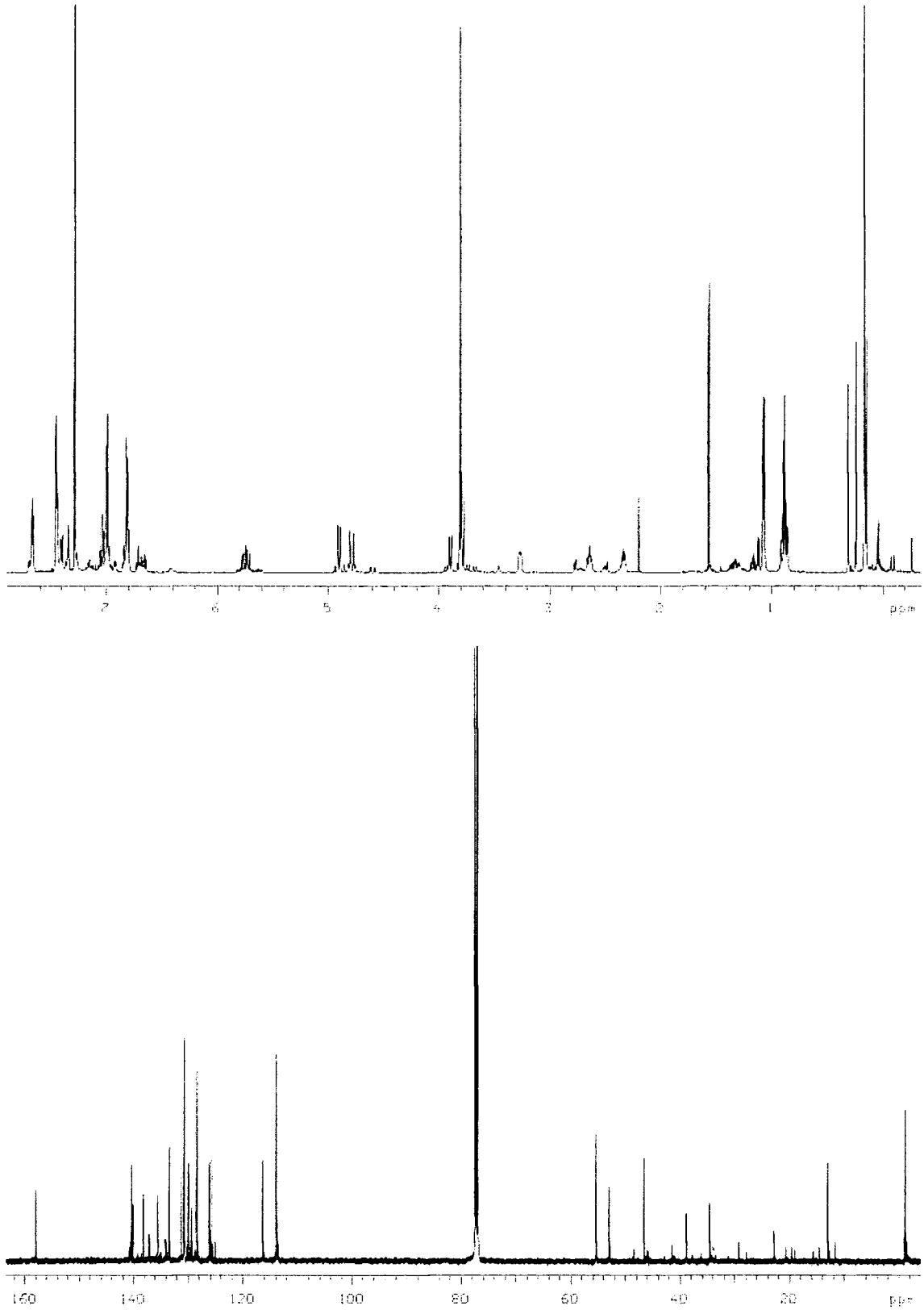


^{1}H and ^{13}C NMR for **322Ah**

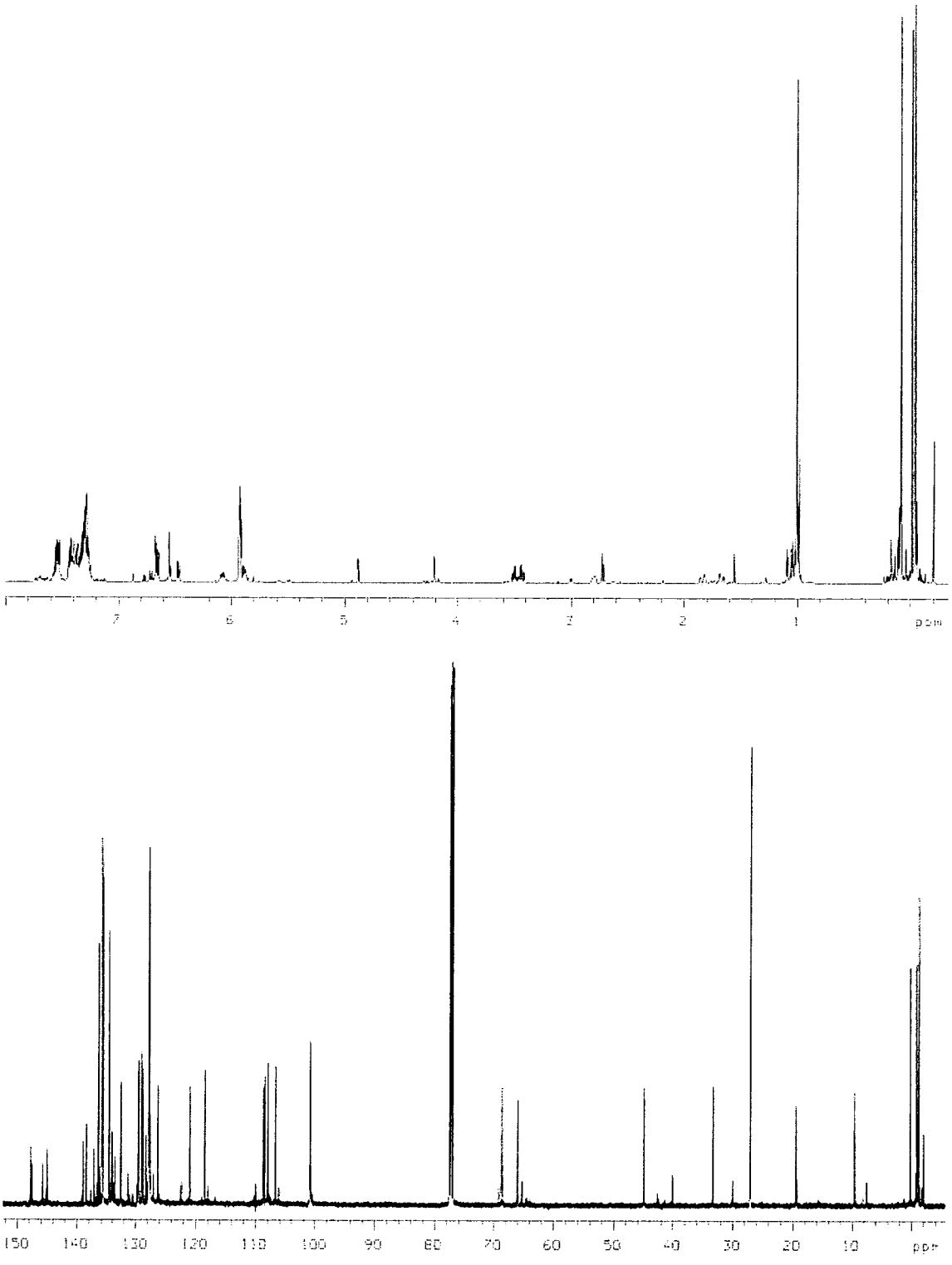




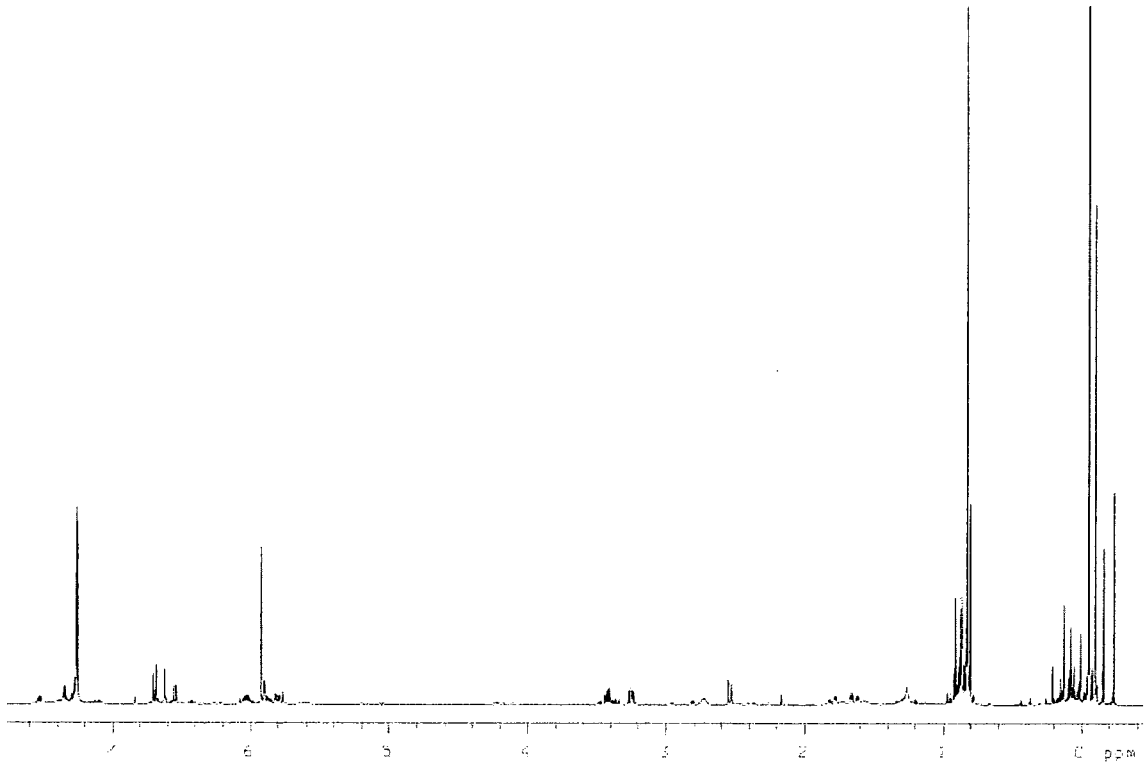
^{1}H and ^{13}C NMR for **321B**

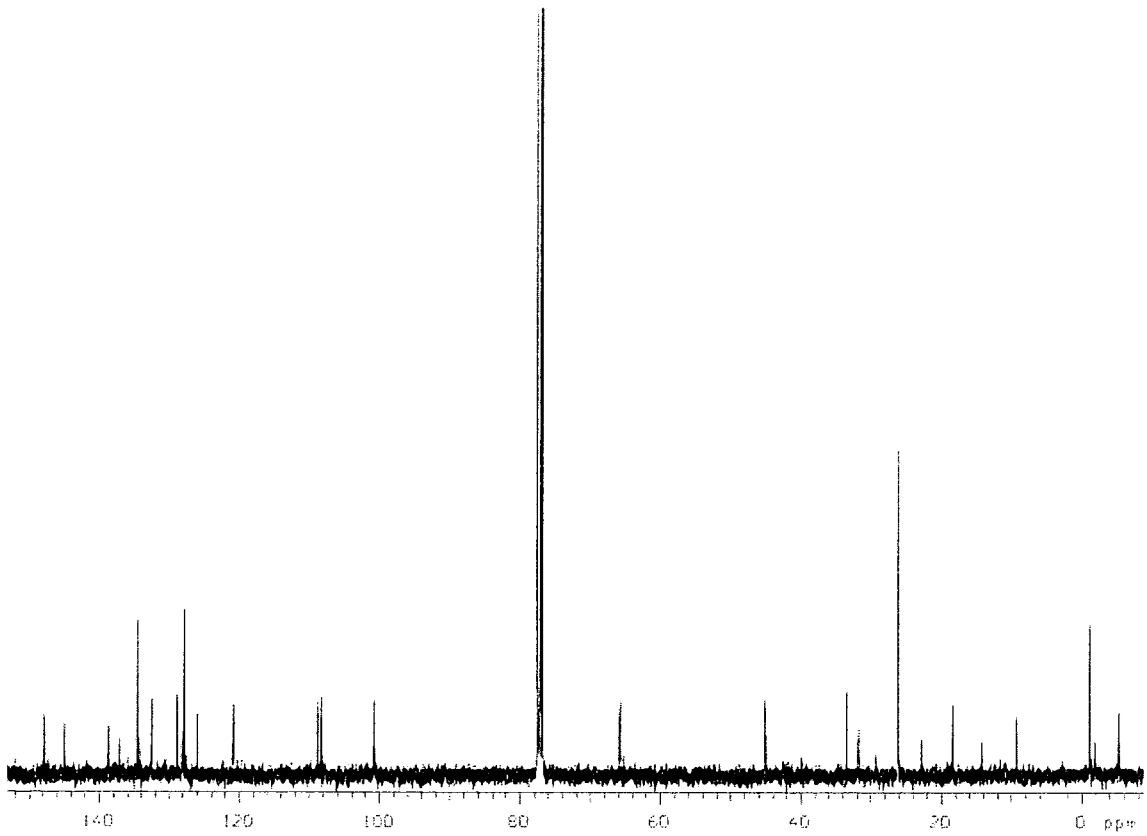


^{1}H and ^{13}C NMR for **Table 10, entry 2**

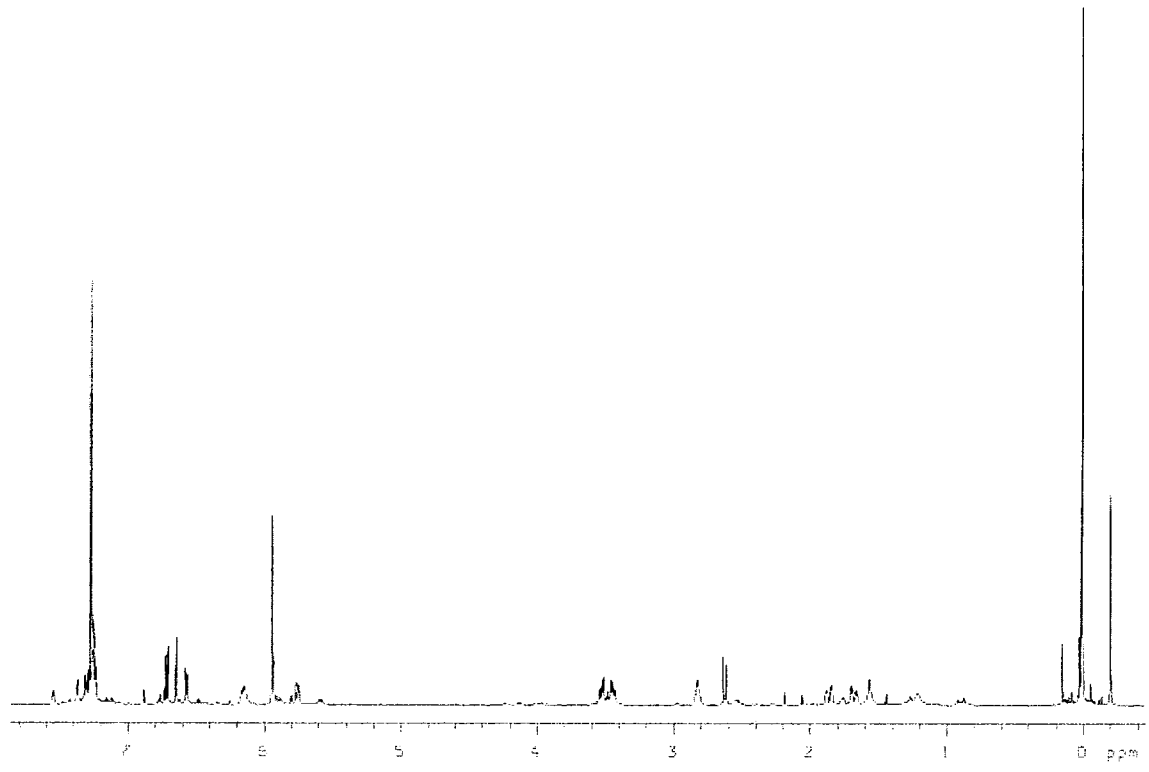


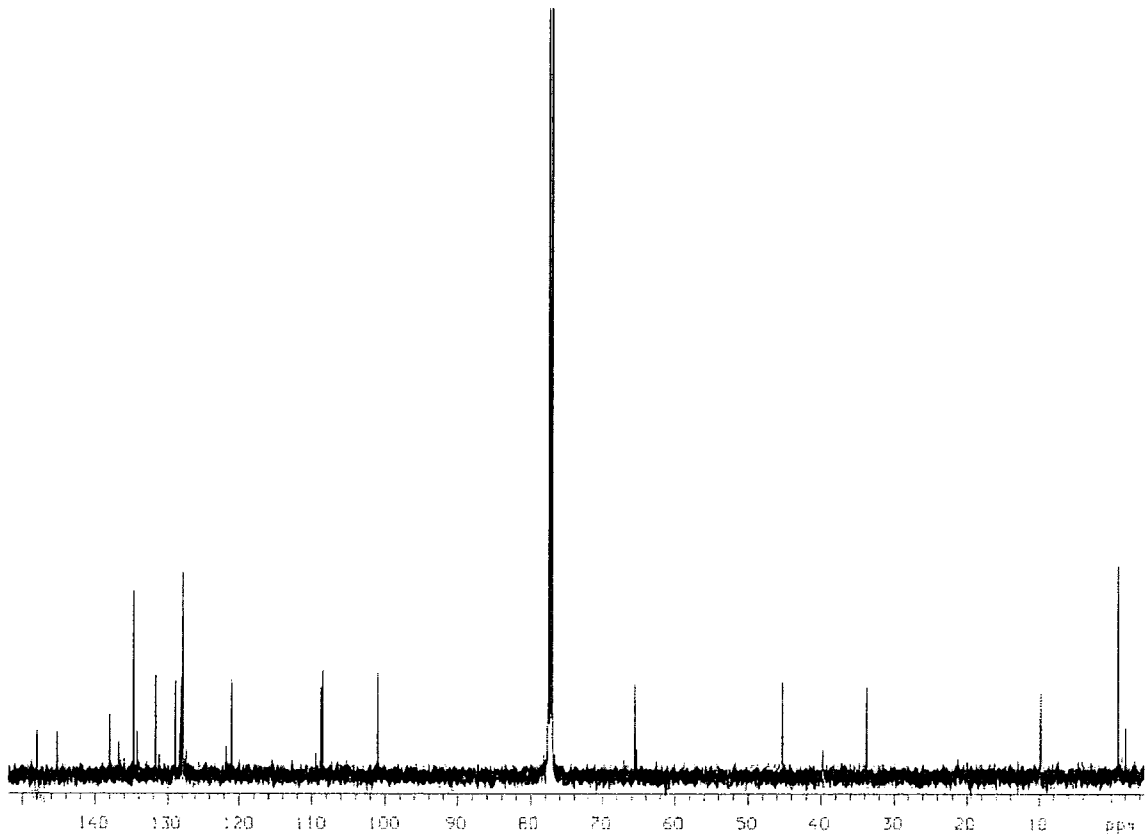
^{1}H and ^{13}C NMR for **486**



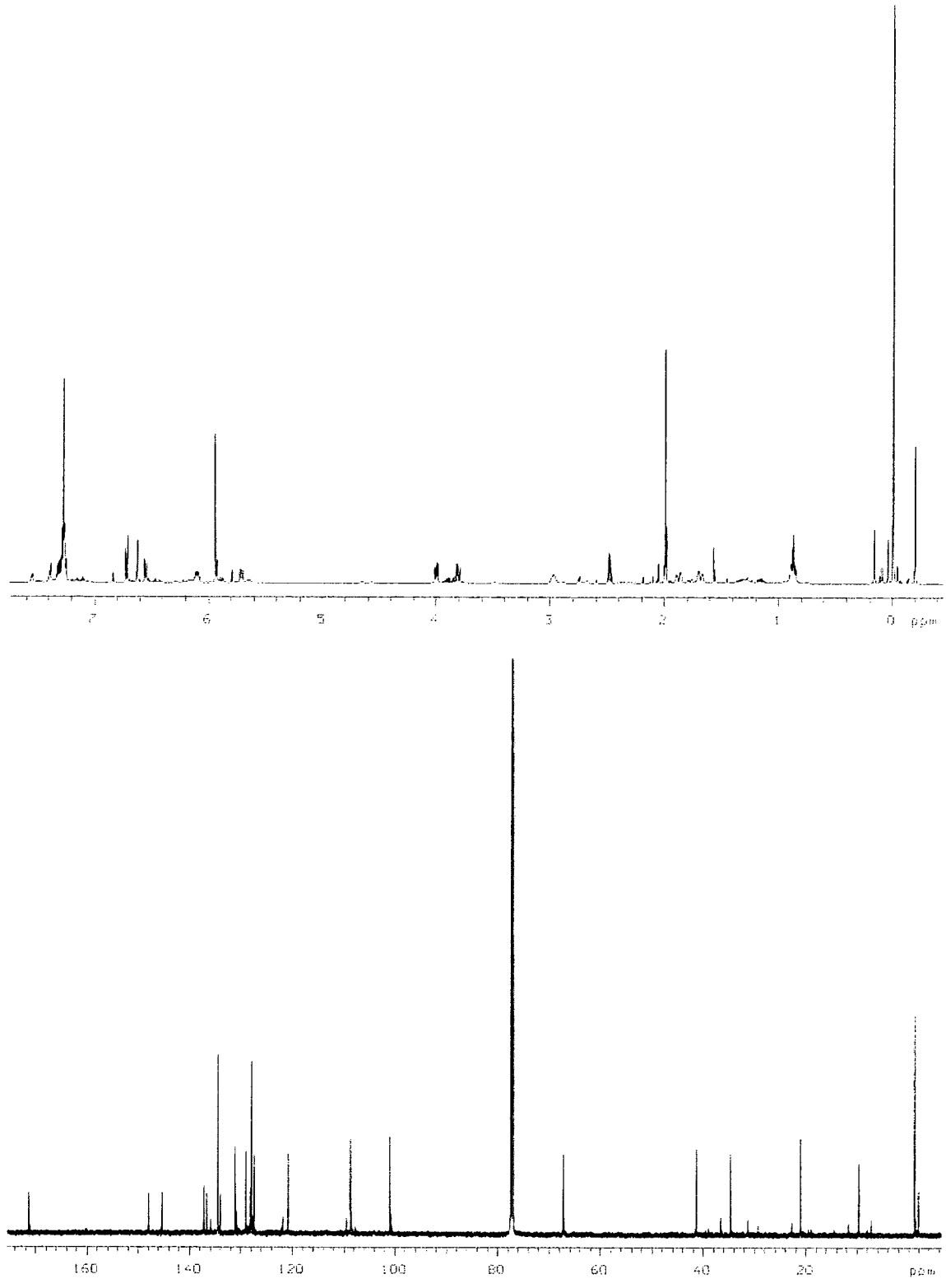


^{1}H and ^{13}C NMR for **488**

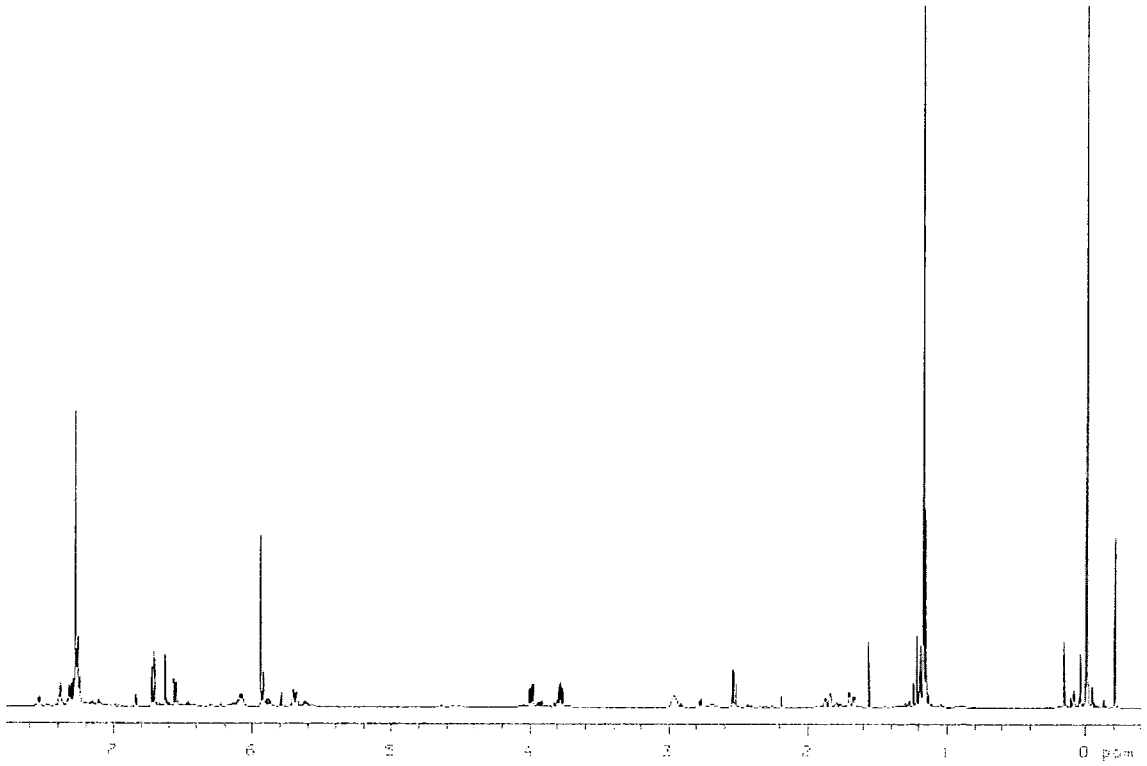


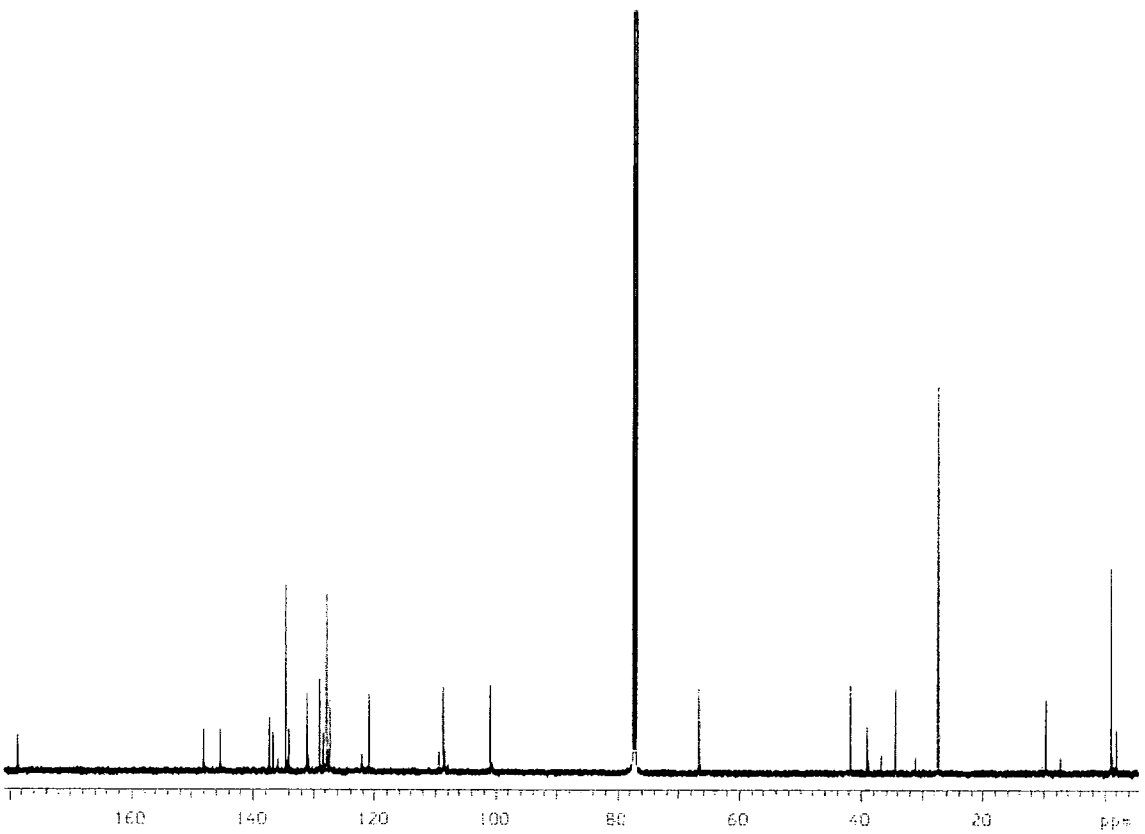


^{1}H and ^{13}C NMR for **489**

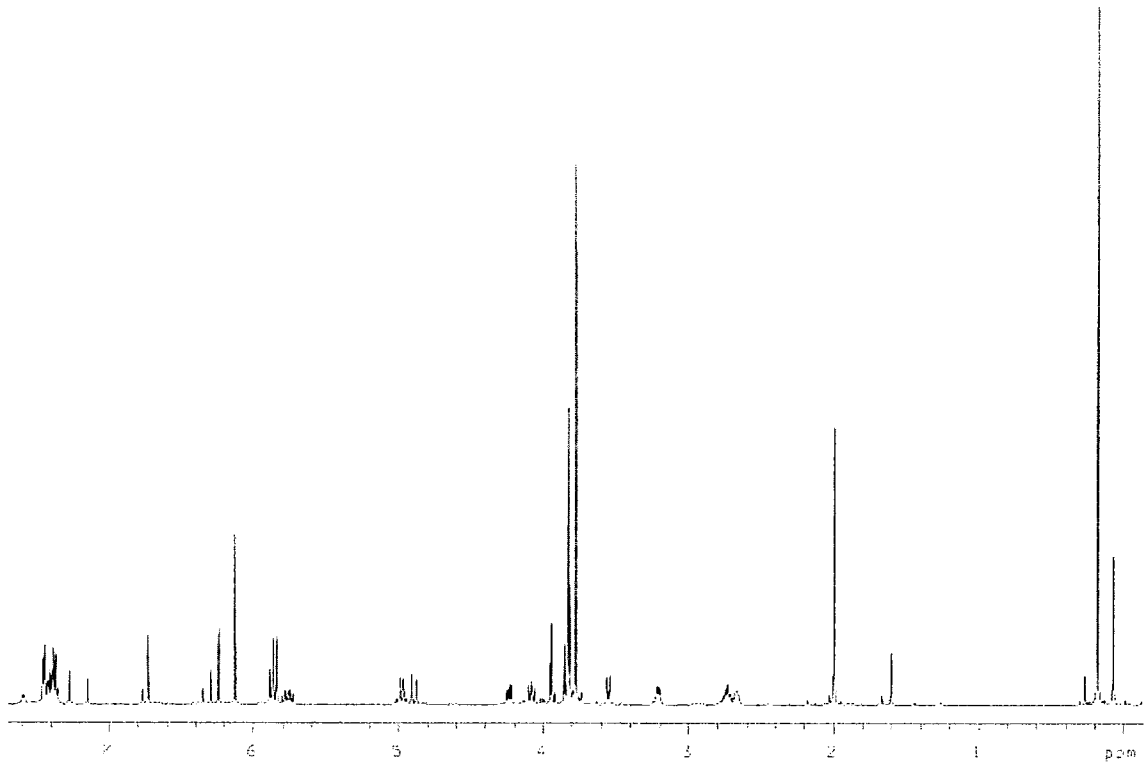


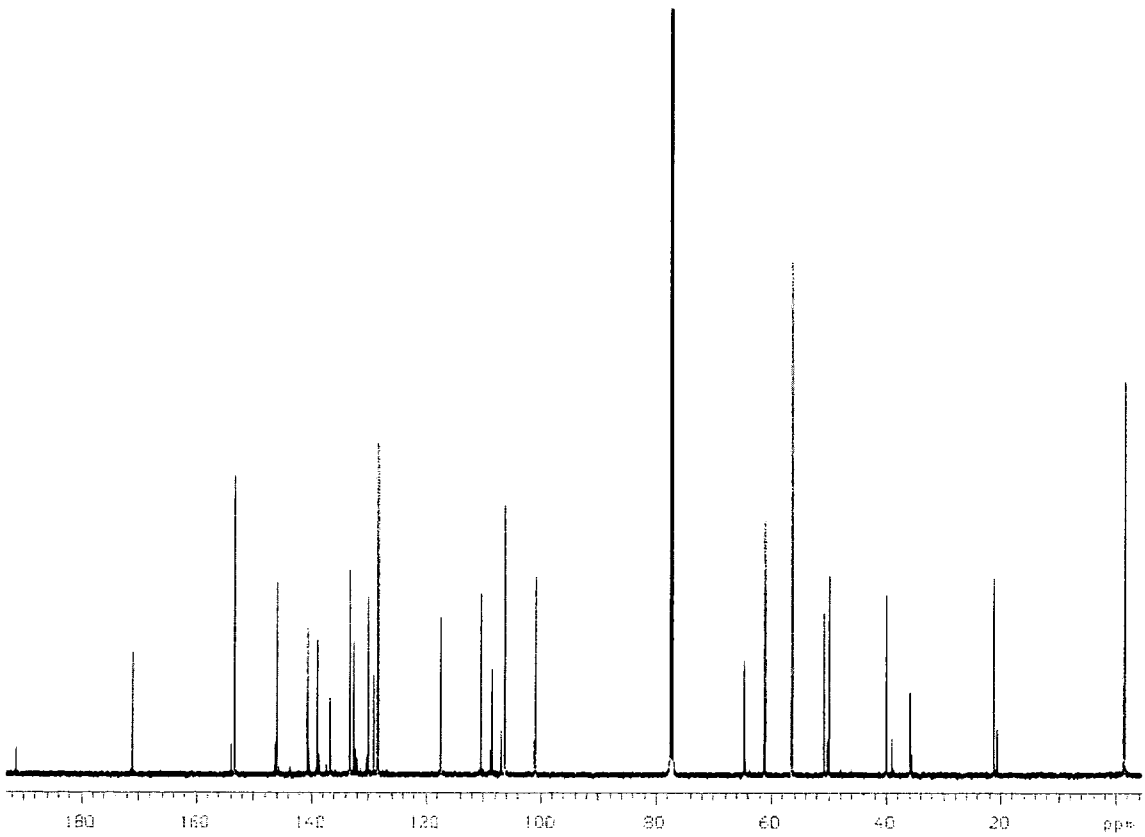
^{1}H and ^{13}C NMR for **490**



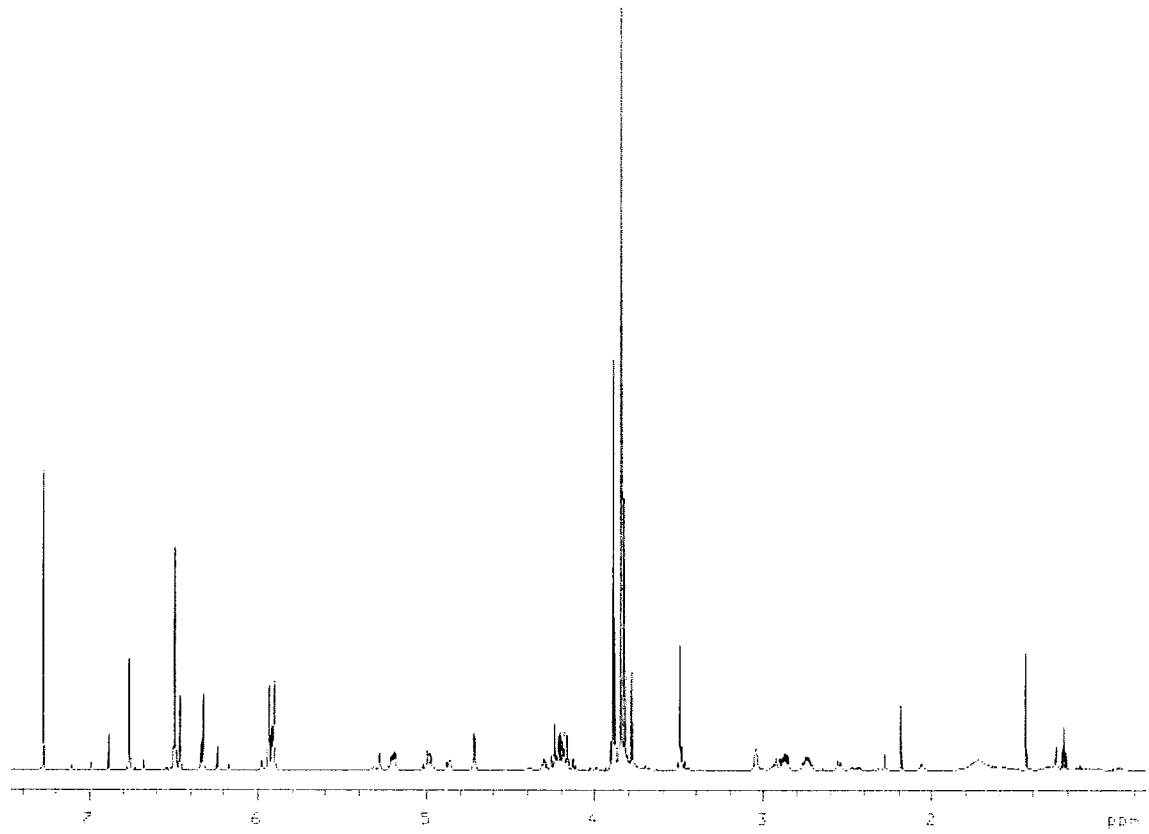


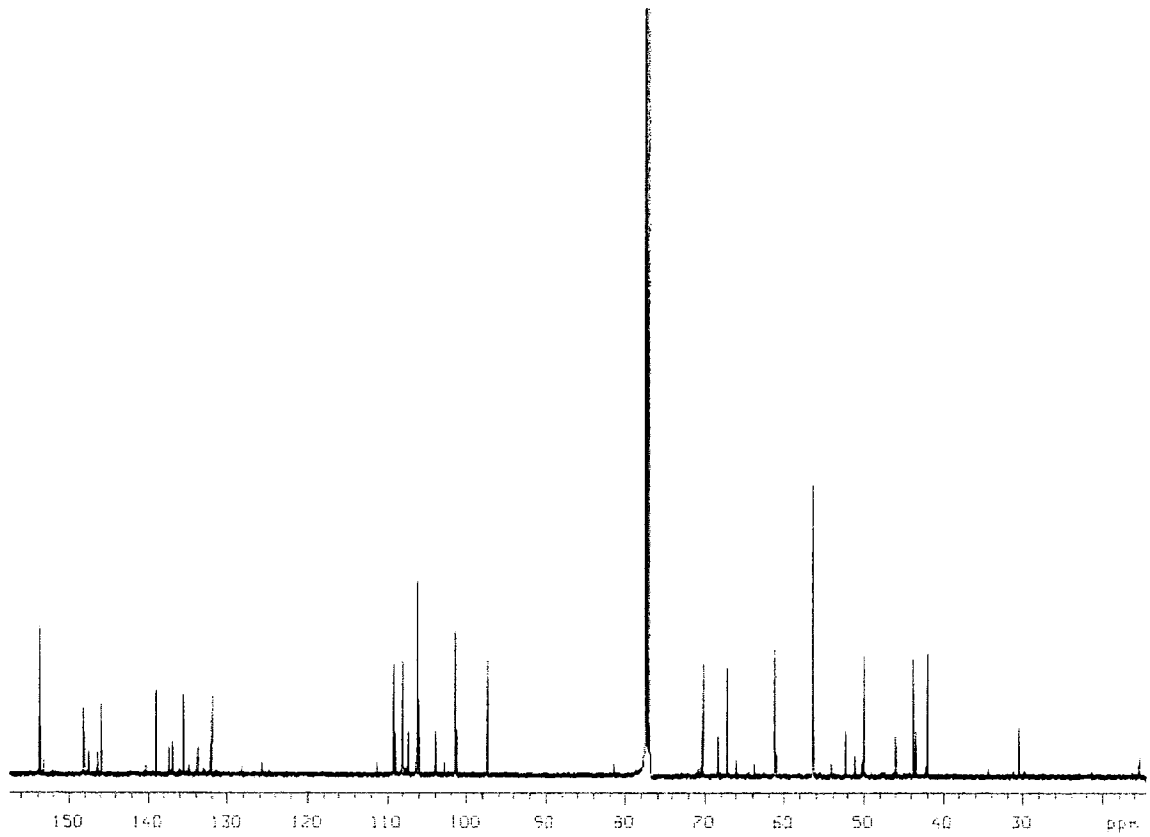
^{1}H and ^{13}C NMR for **491**



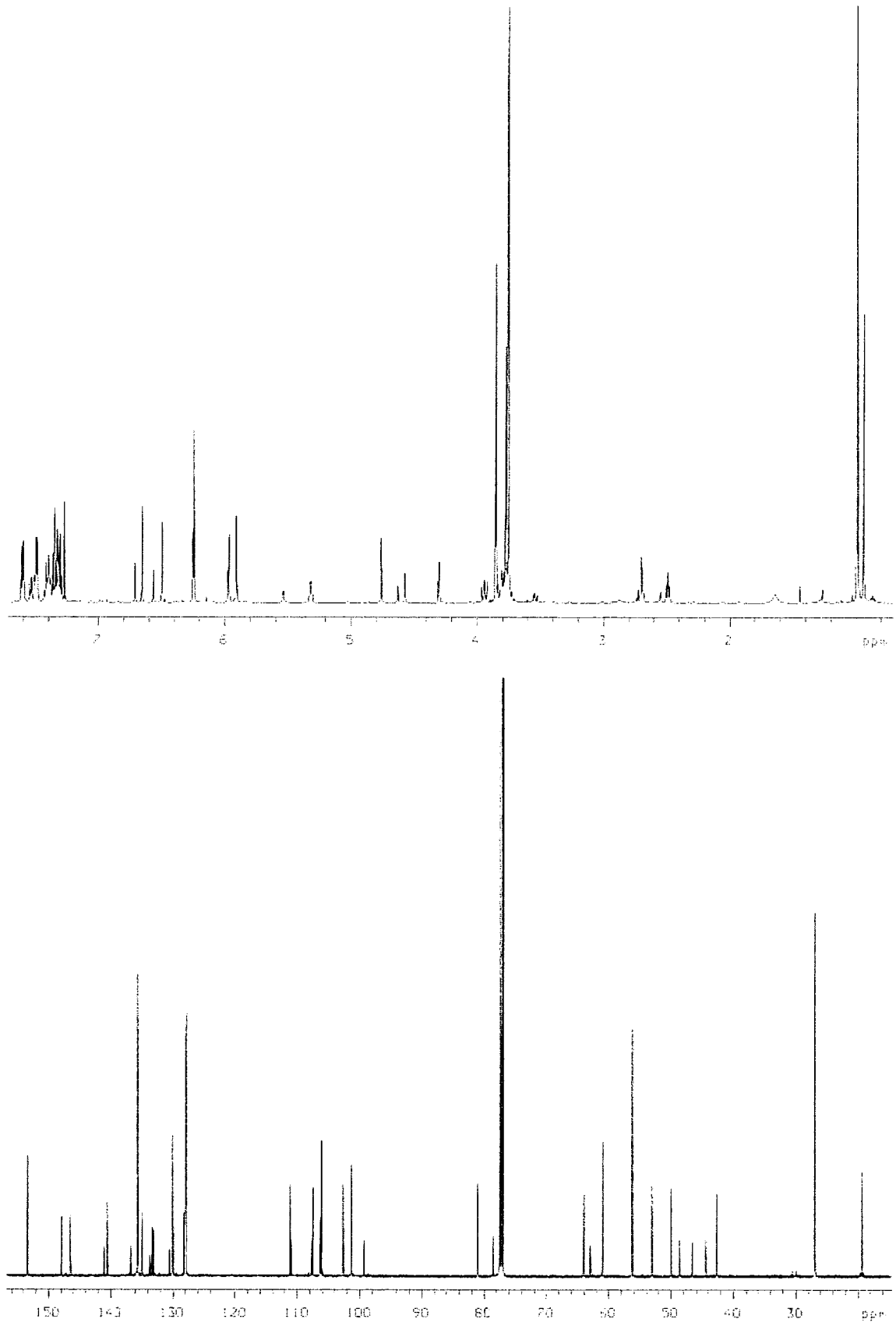


^{1}H and ^{13}C NMR for **493**

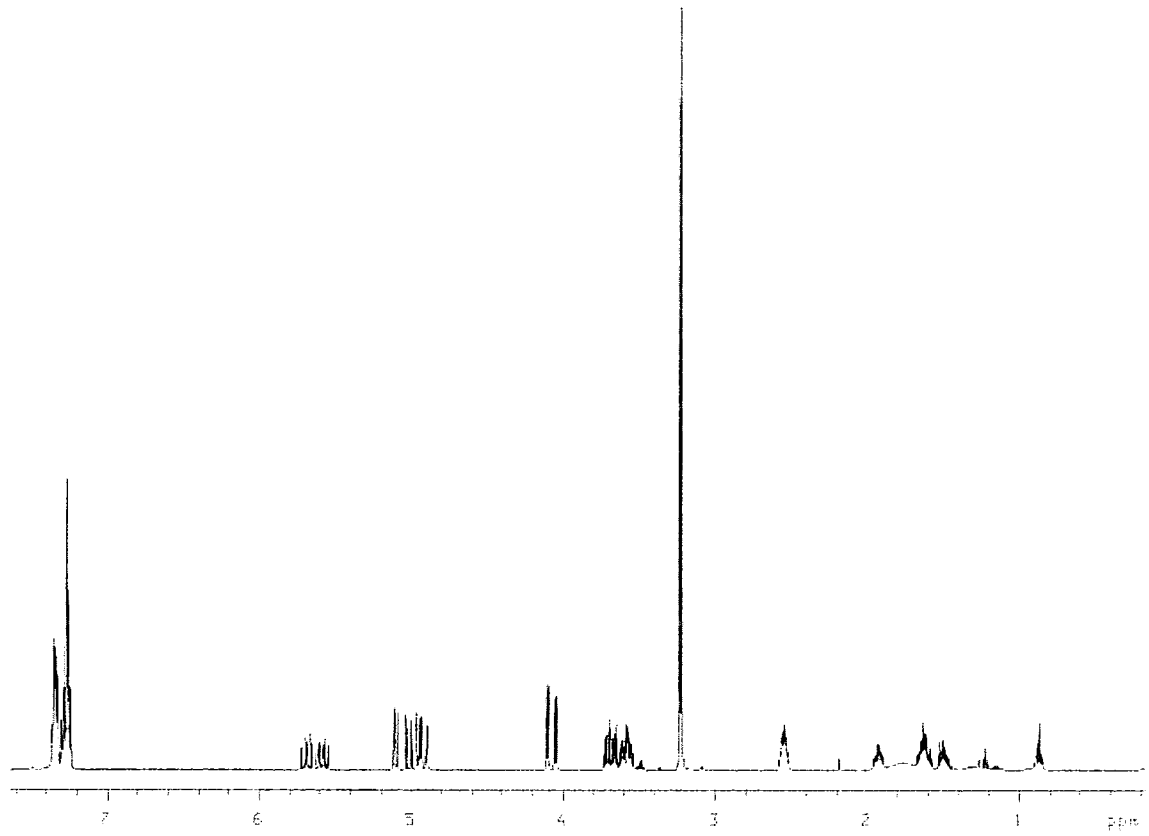


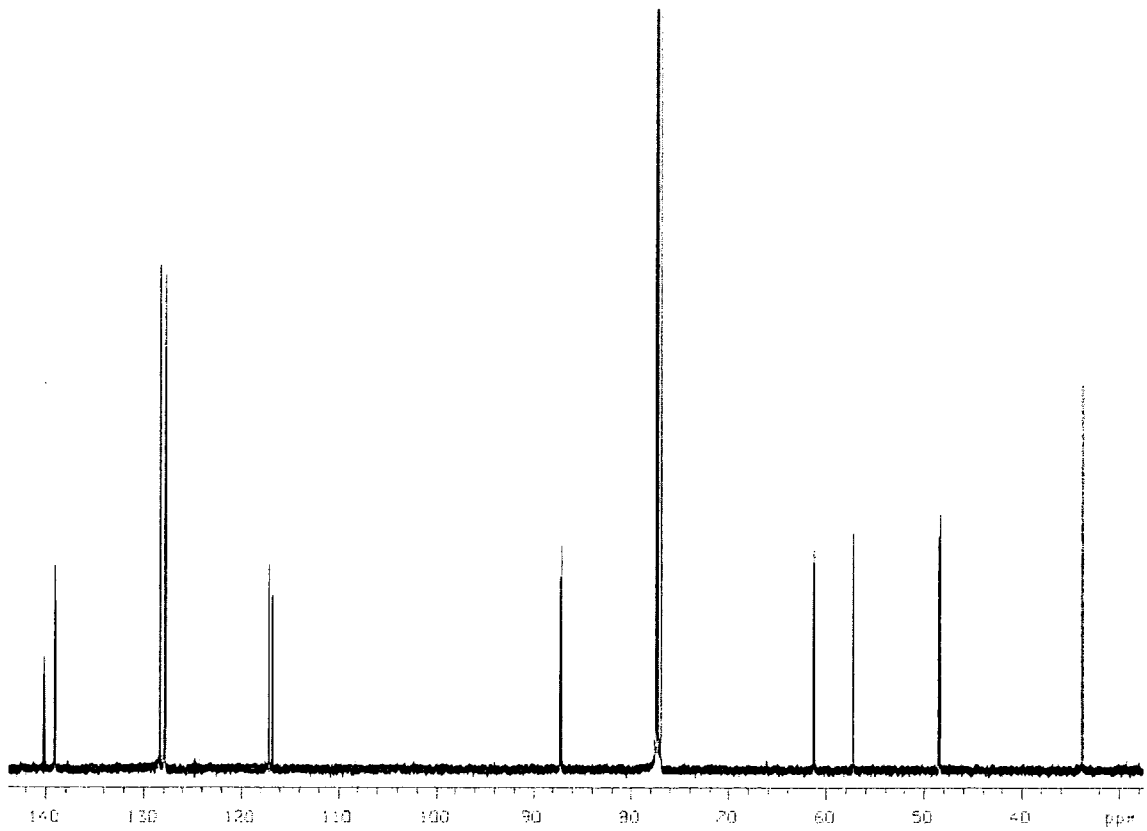


^{1}H and ^{13}C NMR for **527**

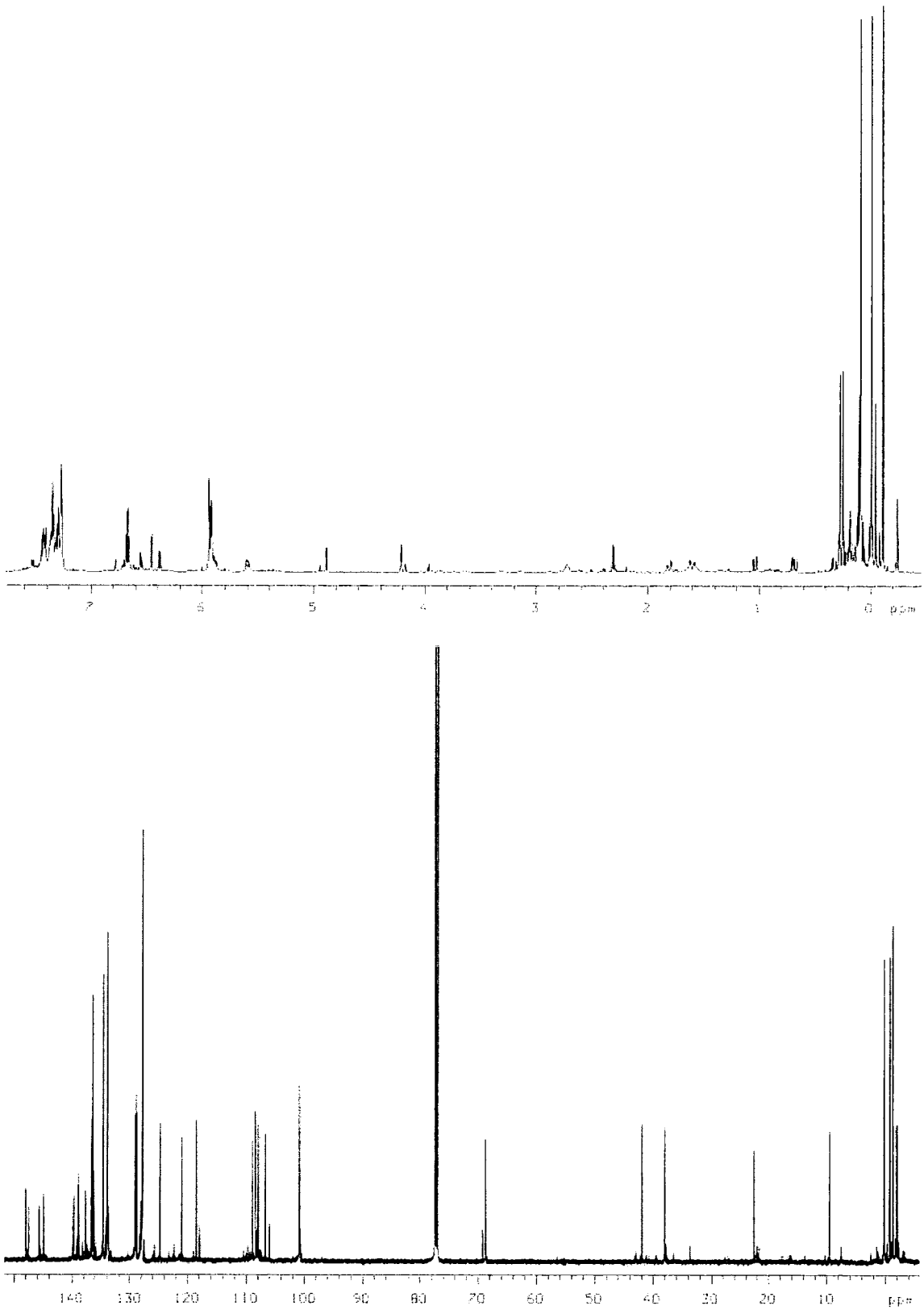


^{1}H and ^{13}C NMR for **521**

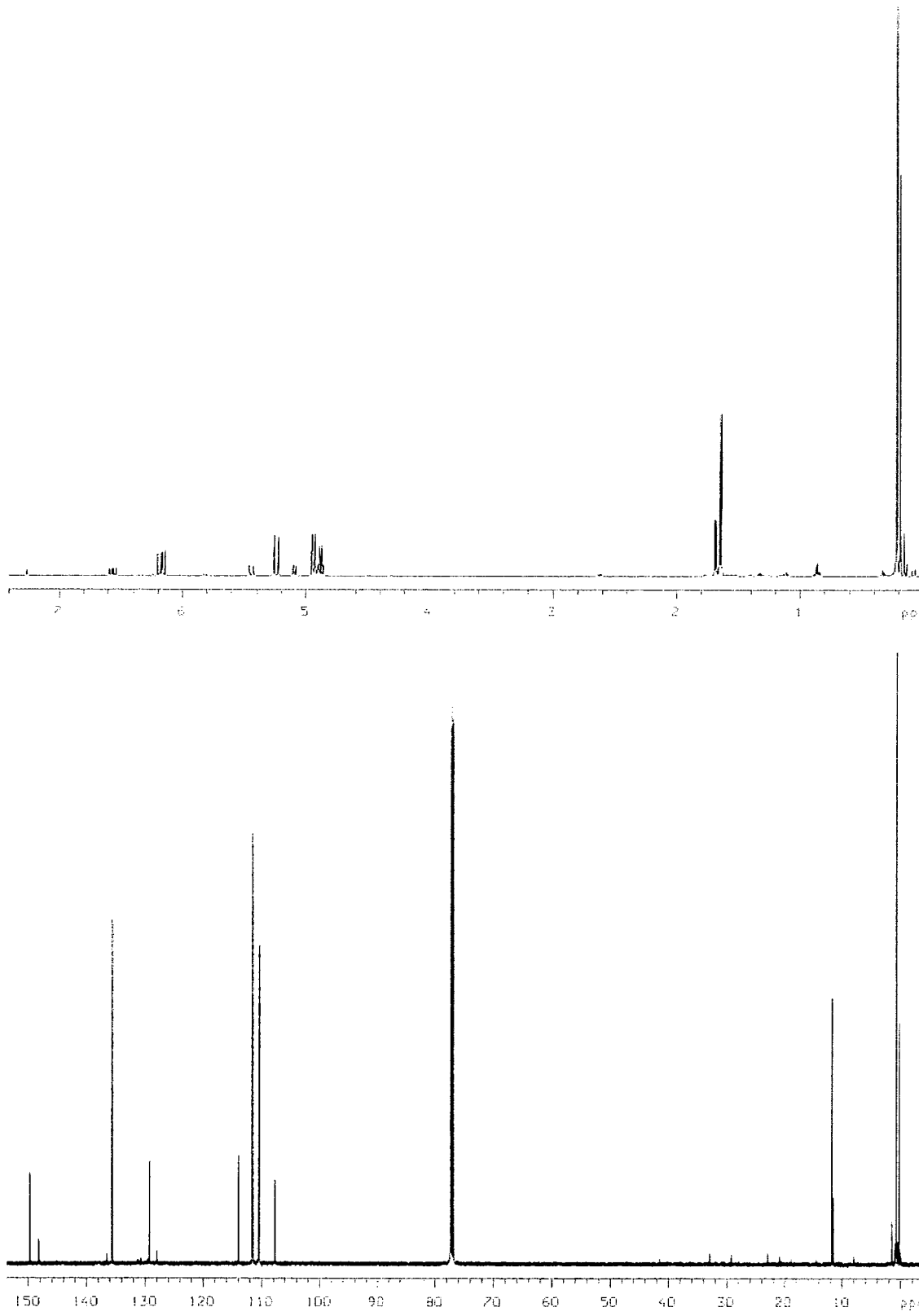




^{1}H and ^{13}C NMR for **569**



^{1}H and ^{13}C NMR for **572**



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