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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Jonathan D. Sellars
PhD Thesis
Supervisor: Dr. P. G. Steel
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 = 'Pr) and an analogue (R = Ph) to be achieved in high yields over 5 steps (Figure 1).\(^2\)

![Figure 1](image1)

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](image2)
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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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>b.p.</td>
<td>Boiling point</td>
</tr>
<tr>
<td>BF₃•2AcOH</td>
<td>Boron trifluoride diacetic acid complex</td>
</tr>
<tr>
<td>BF₃•OEt₂</td>
<td>Boron trifluoride diethyl ether complex</td>
</tr>
<tr>
<td>CDI</td>
<td>Carbodiimidazole</td>
</tr>
<tr>
<td>CI</td>
<td>Chemical ionization</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-Dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DMAD</td>
<td>Dimethyl acetylenedicarboxylate</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMDO</td>
<td>Dimethyldioxirane</td>
</tr>
<tr>
<td>EDTA</td>
<td>Ethylenediaminetetraacetic acid</td>
</tr>
<tr>
<td>EI</td>
<td>Electron impact</td>
</tr>
<tr>
<td>eq.</td>
<td>Equivalents</td>
</tr>
<tr>
<td>Et₃N</td>
<td>Triethylamine</td>
</tr>
<tr>
<td>Et₃SiH</td>
<td>Triethyilsilane</td>
</tr>
<tr>
<td>GC</td>
<td>Gas chromatography</td>
</tr>
<tr>
<td>h</td>
<td>Hours</td>
</tr>
<tr>
<td>HF-Py</td>
<td>HF-pyridine complex</td>
</tr>
<tr>
<td>Hünig's base</td>
<td>Diisopropylethylamine</td>
</tr>
<tr>
<td>Im.</td>
<td>Imidazole</td>
</tr>
<tr>
<td>IR</td>
<td>Infra red</td>
</tr>
<tr>
<td>kJ</td>
<td>KiloJoule</td>
</tr>
<tr>
<td>KO'Bu</td>
<td>Potassium tert-butoxide</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>LiBr</td>
<td>Lithium bromide</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>Lithium hexamethyldisilazane</td>
</tr>
<tr>
<td>M</td>
<td>Molar</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet</td>
</tr>
<tr>
<td>m.p.</td>
<td>Melting point (°C)</td>
</tr>
<tr>
<td>mmol</td>
<td>Millimole</td>
</tr>
<tr>
<td>MOM</td>
<td>Methoxymethyl</td>
</tr>
<tr>
<td>MS</td>
<td>Mass spectroscopy</td>
</tr>
<tr>
<td>MTO</td>
<td>Methyltrioxorhenium</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>n-Butyllithium</td>
</tr>
<tr>
<td>NMO</td>
<td>N-Methylmorpholine-N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>OsO₄</td>
<td>Osmium tetroxide</td>
</tr>
<tr>
<td>PCC</td>
<td>Pyridinium chlorochromate</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>PPTS</td>
<td>Pyridinium p-toluene sulfonate</td>
</tr>
<tr>
<td>q</td>
<td>Quartet</td>
</tr>
<tr>
<td>Rₐ</td>
<td>Retention factor</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>s</td>
<td>Singlet</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetra-N-butylammonium fluoride</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>TBAT</td>
<td>tert-Butylammonium difluorotriphenylsilylate</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-Butyldiphenylsilyl</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-Butyldimethylsilyl</td>
</tr>
<tr>
<td>TES</td>
<td>Triethylsilyl</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>TiCl₄</td>
<td>Titanium tetrachloride</td>
</tr>
<tr>
<td>TIPS</td>
<td>Triisopropylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>p-TSA</td>
<td>para-Toluene sulfonic acid</td>
</tr>
<tr>
<td>TTBP</td>
<td>2,4,6-Tri-tert-butylpyrimidine</td>
</tr>
</tbody>
</table>
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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.\textsuperscript{7} However, silicon has found widespread use in organic synthesis because of its distinct differences when compared to carbon and other elements.\textsuperscript{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\textsuperscript{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.

<table>
<thead>
<tr>
<th>Bond to C</th>
<th>Bond Length(^a)</th>
<th>Bond Energy(^b)</th>
<th>Bond to Si</th>
<th>Bond Length(^a)</th>
<th>Bond Energy(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-C</td>
<td>1.54</td>
<td>334</td>
<td>Si-C</td>
<td>1.89</td>
<td>318</td>
</tr>
<tr>
<td>C=O</td>
<td>1.32</td>
<td>620</td>
<td>Si=O</td>
<td>[1.72]</td>
<td>490</td>
</tr>
<tr>
<td>C-O</td>
<td>1.41</td>
<td>340</td>
<td>Si-O</td>
<td>1.63</td>
<td>531</td>
</tr>
<tr>
<td>C-Cl</td>
<td>1.78</td>
<td>335</td>
<td>Si-Cl</td>
<td>2.05</td>
<td>471</td>
</tr>
<tr>
<td>C-F</td>
<td>1.39</td>
<td>452</td>
<td>Si-F</td>
<td>1.60</td>
<td>808</td>
</tr>
</tbody>
</table>

\(^a\) 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\(^{6+}\)-C\(^{6-}\), which allows for nucleophilic attack at silicon. Moreover, silicon is less electronegative than hydrogen, forming Si\(^{6+}\)-H\(^{6-}\), allowing Et\(_3\)SiH 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 \textit{via} a pentacoordinate intermediate 2 (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 $\alpha$-Carbon-Metal and $\beta$-Carbocation Stabilisation

Another useful characteristic of silicon is its ability to stabilise both a carbanion in the $\alpha$-position and a carbocation in the $\beta$-position. This ability to stabilise $\alpha$-carbanions can be attributed to several factors: 1. Overlap of the $\alpha$-carbon-metal bond with a silicon $d$-orbital. 2. Overlap of the $\alpha$-carbon-metal bond with the adjacent $\sigma^*$ 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).

Silicon also stabilises $\beta$-carbocations through overlap of the vacant $p$ orbital on the $\beta$ carbon atom and the $\sigma$ orbital between the silicon atom and the $\alpha$ carbon atom. This effect means that allyl, aryl, vinylsilanes, silyl enol ethers and other such molecules react with electrophiles to place the positive charge $\beta$ to the silicon (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 trimethylsilyl 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).
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, Et₃N, Hüning's base, imidazole or DBU (Scheme 2).

$$\text{ROH} + R_3SiX \xrightarrow{\text{Im}} R_3Si\text{NH} \rightarrow R'O-SiR_3$$

Scheme 2

Cleavage of silicon protecting groups is commonly undertaken utilising a source of fluoride (e.g. TBAF, HF-MeCN, HF-py, Et₃N,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).

$$\text{R}^O-Si-R \xrightarrow{\text{HF}} R'O-SiF \rightarrow \text{ROH}$$

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. 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).

![Chemical structures](image)

**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).

![Chemical structures](image)

**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](image)

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.
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. The silyl enol ether 26 was generated \textit{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).

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).

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](image)

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).

![Scheme 10](image)

### 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 Guse'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).\cite{13}

![Scheme 11](image)

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.\cite{14} highlighted the use of silicon-based diazo compounds, 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).

![Scheme 12](image)
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).

\[
\begin{align*}
44 & \rightarrow [\text{Me}_2\text{Si} = \text{SiMe}_3] & 45 & \rightarrow [\text{Si} = \text{SiMe}_3] \\
& \downarrow & & \downarrow \\
47 & \quad & 48
\end{align*}
\]

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.\textsuperscript{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).

\[
\begin{align*}
49 & \rightarrow [\text{Me}_2\text{Si} = \text{SiMe}_3] & 50 & \rightarrow [\text{Si} = \text{SiMe}_3] & \text{MeOH/D} & \rightarrow [\text{Me}_3\text{Si} = \text{SiMe}_2] & 51
\end{align*}
\]

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 acylsilane 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](image)

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](image)
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 \(\alpha\)-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).

As a result of this report, other groups investigated the modified Peterson reaction. Oehme and Wustrack further established this technique by demonstrating that a \(\alpha\)-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. 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.

![Scheme 16](image)

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).
Moreover, the isolation of $\alpha$-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 $\alpha$-silylalcohol 70, the $\alpha$-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).

Now, with mild conditions established for the generation of a variety of $\alpha$-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 \textit{et al.} generated a head-to-tail dimer \( 76 \) of silene \( 75 \) (Scheme 19).\(^{16}\)

![Scheme 19](image)

Silene dimerisation was not just used to prove the existence of silenes. A report by Brook \textit{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).\(^{18}\)

![Scheme 20](image)
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).

Enolisable Ketone

Non Enolisable Ketone

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).\textsuperscript{32}

Another report by Brook et al. described the use of imines to trap silenes.\textsuperscript{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).

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).\textsuperscript{34}
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).\textsuperscript{35}
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 underwent migration and elimination to give silenes. More specifically, when α-silylisobutanol was treated with MeLi at -78 °C and warmed to -30 °C, silene was generated. This was then trapped in situ with 1,3-pentadiene in a Diels-Alder reaction generating silacyclohex-4-ene in 66% yield (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. 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 with n-BuLi in the presence of a catalytic amount of LiBr generated silacyclohex-4-ene reproducibly in 50% yield.
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, whereas 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.

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

<table>
<thead>
<tr>
<th>Diene</th>
<th>[4+2] Silacycle</th>
<th>Lactones</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /> 102</td>
<td><img src="image3.png" alt="Image" /> 106</td>
<td>63% 64%</td>
</tr>
<tr>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /> 103</td>
<td><img src="image6.png" alt="Image" /> 107</td>
<td>25% (66:44)</td>
</tr>
<tr>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /> 104</td>
<td><img src="image9.png" alt="Image" /> 108a 108b</td>
<td>45% 26% (79:11:8:2)</td>
</tr>
<tr>
<td><img src="image10.png" alt="Image" /></td>
<td><img src="image11.png" alt="Image" /> 105</td>
<td><img src="image12.png" alt="Image" /> 109a 109b</td>
<td>13% 60% (87:10:3)</td>
</tr>
</tbody>
</table>

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).

![Figure 9](image)

Prelactone B, 110, \( R = \text{CH(CH}_3)_2 \)
Prelactone C, 111, \( R = \text{CH=CHCH}_3 \)
Prelactone V, 112, \( R = \text{CH}_3 \)
Prelactone E, 113, \( R = \text{C}_2\text{H}_5 \)

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.\textsuperscript{40} Hanefield et al. began their synthesis with the aldol reaction of homochiral amide 114 and isobutyraldehyde to generate a mixture of 116\textsubscript{a} and 116\textsubscript{b} (Scheme 28).

\[ \text{114} + \text{115} \xrightarrow{\text{Bu}_2\text{BTf, DIPEA}} \text{116\textsubscript{a}} + \text{116\textsubscript{b}} \]

\begin{center}
\textbf{Scheme 28}
\end{center}

The desired anti-aldol isomer 116\textsubscript{a} 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 \textit{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).
2.2.2 Fournier route

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

\textbf{Scheme 29}
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 \(\alpha\)-position followed after work-up by a second alkylation at the \(\alpha'\)-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).
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)(PCy3)(py)]PF₆) to generate prelactone B 110 with high de and ee (Scheme 32).

![Scheme 31](image)

**Scheme 31**

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 Cp₂TiCl₄. 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).

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 Cp₂TiCl 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 debenzylolation 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 CH₂N₂ 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).
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. 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 BF₃·OEt₂ provided 146 with Felkin-Ahn selectivity. Deprotection and simultaneous lactonisation of 146 with aqueous HF led to (-)-prelactone B 110 (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. 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).
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 diastereoisomer was generated in >93% ee (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](image)

2.2.8 Yadav route

The Yadav approach highlighted a convergent route to prelactone B through Prins cyclisation of a homoallylic alcohol 162. 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).
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).

2.2.9 Salaskar route

The Salaskar approach was developed to take advantage of 1,2-cyclohexylidene glyceraldehydes as chiral templates. 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).

\[
\begin{align*}
\text{CHO} & \quad \begin{array}{c}
\text{Br} \\
\text{Zn}
\end{array} \\
166 & \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array} \\
& \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array}
\end{align*}
\]

\[
\begin{align*}
167a & \quad 167b \\
& \quad 167c
\end{align*}
\]

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).

\[
\begin{align*}
\text{CHO} & \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array} \\
167a & \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array}
\end{align*}
\]

\[
\begin{align*}
168 & \quad 169
\end{align*}
\]

83%, 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 NaN₅ and zinc dust. Hydroboration of the double bond and in situ oxidation with Na₂CrO₄ 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).
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).

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).
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 \textbf{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 \textbf{100} was produced in good yield and good diastereoselectivity. Silacyclohex-4-ene \textbf{100} was obtained as an inseparable mixture of isomers with the minor components reflecting the presence of small amounts of \textit{exo}-addition products and trace amounts of the adducts of the alternative \textit{E}(Si) silene (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 hydroxy group by means of a hydroboration reaction.

### 2.4.1 Hydroboration

The synthetic utility of the hydroboration reaction in organic chemistry is well known.\textsuperscript{8} To date, many borane and organoborane reagents have been developed.\textsuperscript{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.\textsuperscript{50} They found that when vinylsilanes were treated with borane-THF complex and oxidised, a mixture of $\alpha$- and $\beta$-substituted alcohols were generated. This mixture was attributed to the stabilising effect of silicon with $\beta$-carbocations (discussed in Section 1.1.1.4). However when treated with 9-BBN and oxidised, vinylsilanes produce exclusively the $\beta$-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 $\gamma$-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).

![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. 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). 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.

![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).

![Scheme 50](image)

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).

![Table 3](image)

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 patterns of the regioisomeric carbinol protons (Scheme 51).

**Scheme 51**

Introduction of the hydroxyl group was confirmed by analysis of the IR spectrum, which showed a broad signal at 3368 cm$^{-1}$ 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).

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)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Benzyl bromide, TBAI, NaH</td>
<td>Starting material</td>
</tr>
<tr>
<td>2</td>
<td>Benzyl bromide, Ag_2O</td>
<td>Starting material</td>
</tr>
<tr>
<td>3</td>
<td>Benzyl acetimidate, pTSA</td>
<td>Starting material</td>
</tr>
<tr>
<td>4</td>
<td>PMBCl, DIPEA</td>
<td>Starting material</td>
</tr>
</tbody>
</table>

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 benzyloxymethyl 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).

\[
\begin{align*}
&\text{AcO} & \text{Ac}_2\text{O}, \text{Py} & \text{HO} \\
&\text{190} & & \text{178} & \text{BOMCI, DIPEA} & \text{191} \\
&46\% & & & 50\% \\
\end{align*}
\]

\[\text{i. BF}_3\cdot2\text{AcOH}, \Delta \]
\[\text{ii. aq. } \text{H}_2\text{O}_2, \text{KHCO}_3, \text{THF:MeOH (1:1), } \Delta \]

\[
\begin{align*}
&\text{BOMO} \\
&\text{192} \\
&\text{OH} \\
&\text{OH} \\
\end{align*}
\]

\[\text{Scheme 53}\]

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, 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).
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).

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 (mCPBA) and excess NaHCO₃ 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. Utilising this methodology, entry 3 shows
that when 100 was treated with Jacobsen's 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>mCPBA, NaHCO₃, 0 °C</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2</td>
<td>mCPBA, NaHCO₃, -78 °C</td>
<td>Decomposition</td>
</tr>
<tr>
<td>3</td>
<td>Jacobsen catalyst, NMO, NaOCl, 5NNaOH</td>
<td>Starting material²⁸⁸</td>
</tr>
<tr>
<td>4</td>
<td>MeCN, MeOH, H₂O₂</td>
<td>Starting material</td>
</tr>
</tbody>
</table>

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).
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).

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

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.\textsuperscript{63} Employing the same methodology, silacyclohex-4-ene \textbf{100} was reacted with catalytic MTO and hydrogen peroxide to give access to the silacyclic oxirane \textbf{196}. Interestingly, no reaction was observed and starting material was recovered quantitatively.

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

\textbf{2.4.3 Dihydroxylation}

To advance silacyclohex-4-ene \textbf{100} to prelactone B \textbf{110}, our attention turned to a route involving dihydroxylation. Dihydroxylation is a well-documented transformation for alkenes and has been studied extensively.\textsuperscript{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 \textbf{180}, which would undergo a regioselective silicon directed ring fragmentation, similar to that described for epoxides (\textit{cf. Scheme 55}) when subjected to the Fleming-Tamao oxidation conditions. This would provide access to the dihydroxy compound \textbf{199} (\textit{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).

Then, to our delight when subjected to the Upjohn dihydroxylation conditions (cat. OsO₄, NMO, Acetone:H₂O 20:1) the corresponding diols 207a-c were isolated in 82% yield (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).

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).

To probe this rearrangement, the crude material obtained before oxidation, was analysed by $^1$H (Figure 11) and $^{19}$F NMR. Surprisingly, the $^1$H 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 $^{29}\text{Si}$ NMR and no fluorine signals in the $^{19}\text{F}$ NMR enabled the unknown intermediate to be identified as the cyclic siloxane 212.

![Figure 11](image)

Two possible reaction pathways could account for this observation. The first involves an intramolecular $\text{S_N2}$ 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 $\text{S_N1}$ reaction (Scheme 62).
To explain the stereochemical outcome of the initial rearrangement, pathway 1 may be ruled out because an SN2 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.$^{66-71}$

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\cdot$2AcOH complex to attempt to open the ring, and give access to this species. Interestingly, when analysed by $^1$H 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).

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$_3$•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 $^1$H NMR. Unfortunately, attempts to lactonise triol 218 were unsuccessful, returning only complex mixtures of products (Scheme 65).

![Scheme 65](image)

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 TBSCI and imidazole, a single product possessing only one TBS group by $^1$H 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).

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$_3$•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. $^1$H NMR analysis showed a new signal at 1.26 and 3.99 ppm corresponding to the new methyl group and carbinol proton respectively.

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).
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 $A_{1,3}^{1,3}$ strain. Despite this, the stereochemistry was not fully confirmed
(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).
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 1H NMR analysis of the crude material (Scheme 70).

![Scheme 70](image)

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 1H 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 Et3N.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).

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).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OsO₄, NMO, Acetone:H₂O 20:1</td>
<td>42%</td>
</tr>
<tr>
<td>2</td>
<td>K₂OsO₄.H₂O, K₃Fe(CN)₆, K₂CO₃, Quinuclidine, Methane sulfonamide</td>
<td>46%</td>
</tr>
<tr>
<td>3</td>
<td>OsO₄, TMEDA, Ethylenediamine</td>
<td>37%</td>
</tr>
</tbody>
</table>

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 Et3N.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](image-url)
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).

In 1948 Sommer et al. reported that the allyl-Si σ bond of allylsilanes was easily cleaved by electrophiles and Brønsted acids. Later, Frainnet et al. established that allylsilanes react preferentially at the γ-carbon. 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. 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. Later in the mid 1970s, an independent study by Hosomi et al. reported that carbonyl compounds in the presence of a strong Lewis acid (TiCl₄) underwent smooth allylations with allylsilanes 230 (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).
Subsequent studies by Fleming et al. led to the generally accepted mechanism for this transformation (Scheme 75). 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 \(\beta\)-silicon atom. Such stabilisation is believed to arise from orbital overlap between the empty \(\pi\) orbital on the carbocation and the co-planar C–Si \(\sigma\)-orbital. Subsequent Lewis-acid-catalysed or proto-desilylation of intermediate 240 leads to the allylated product 241.

\[
\begin{array}{c}
\text{R}_3\text{Si} & \text{E}^+ & \text{E}^- \\
\text{230} & \xrightarrow{\text{LA}} & \text{240} \\
\end{array}
\]

\text{SiR}_3 \xrightarrow{\text{LA}} \text{E}

\text{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).

\[
\begin{array}{c}
\text{O} & \text{R}_3\text{Si} & \text{230} & \text{242} & \xrightarrow{\text{Lewis acid, ligand}} & \text{R} & \text{R} & \text{243} \\
\text{R} & \text{R} & \text{O} & \text{O} \\
\end{array}
\]

\text{244} \xrightarrow{\text{Lewis acid}} \text{245} \text{ or } \text{246} \text{ or } \text{247}

\[
\begin{array}{c}
\text{O} & \text{R}_3\text{Si} & \text{230} & \text{248} & \xrightarrow{\text{Lewis acid}} & \text{OH} & \text{249} \\
\text{O} & \text{R} & \text{OR} \\
\end{array}
\]

\text{Scheme 76}

65
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](image)

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). \cite{82,83}

![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).
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. 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).
3.2.1.2 Access to Heterocycles

As described earlier, as well as carbocycles, access to heterocycles through the cycloaddition 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 preceding section. Pathway A affords oxetane 265 and pathway B furnishes tetrahydrofuran 266 (Scheme 81).

![Scheme 81](image)

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 TiCl₄-promoted [2+2] cycloaddition of allylsilane 252 to α-oxo ester 267 (Scheme 82).

![Scheme 82](image)
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

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 allylsilanes 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
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).

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).
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).

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).

\[
\begin{align*}
\text{Ph} & \quad 284 \\
\text{CuCl-(R)-tol-BINAP} & \quad \text{TBAT} \\
\text{H}^+ & \\
\text{tol-BINAP Ar = 4-Me-C}_6\text{H}_4 \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad 285 \\
\text{Ar} & \\
\text{O} & \quad (\text{MeO})_3\text{Si} & \quad \text{OH} \\
\end{align*}
\]

\textbf{Scheme 88}

This was the first example of a catalytic enantioselective allylation of ketones using allylsilanes. Yamamoto \textit{et al.} undertook a similar study, this time utilising a silver-fluoride catalysed process.\textsuperscript{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).

\[
\begin{align*}
\text{R} & \quad 286 \\
\text{AgF-(R)-DIFLUORPHOS (1:1)} & \\
\text{F} & \quad \text{F} & \quad \text{F} \\
\text{O} & \quad \text{O} & \quad \text{PPh}_2 \\
\text{DIFLUORPHOS} & \\
\text{OH} & \quad \text{R}^\prime \\
\end{align*}
\]

\textbf{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 \textit{syn}-products 290a and 290b with high diastereo- and enantioselectivity (Scheme 90).

![Scheme 90](image)

\[\text{Scheme 90}\]

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 \textit{et al.} applied this methodology to synthesise the dihydropyran moiety of the natural product \((-\)-Apicularen A 291 (Figure 18).\(^{91}\)

![Figure 18](image)

\[\text{Figure 18}\]

Panek \textit{et al.} initiated a study concerning the \([4+2]\) annulation of a chiral allylsilane 292 with phenylacetaldehyde. The results demonstrated that the \textit{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 \textit{cis} \((R_3\text{Si}/OSiMe}_3\) relative stereochemistry and (b) the R moiety was \(\text{CH}_2\text{OMe}\) only. Other R moieties (\(\text{CO}_2\text{Me}, \text{CH}_2\text{OAc}\)) gave the pyran products with \textit{cis}- stereochemistry (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).

Substituted pyran units similar to the one described above have also been elegantly synthesised by Marko et al. using an asymmetric Sakurai multicomponent reaction. 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).
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](image)

### 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, allylsilanes 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 p⁻ 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).\textsuperscript{93,94}

![Scheme 95](image)

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).\textsuperscript{95-97}

![Scheme 96](image)

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

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).
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).

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 auxiliary 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).
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. 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).

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).

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).

We proposed that silacyclohex-4-enes 174 would undergo a Hosomi-Sakurai reaction with acetics 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)

\[
\begin{align*}
\text{Scheme 103} \\
\text{An example of this type of reaction was provided earlier (cf. Section 2.4.2, Scheme 56), during epoxidation studies for the synthesis of Prelactone B. It was shown that when epoxidised, silacyclohex-4-enes 174 were ring opened to give the hydroxyl siloxane 200, similar in structure to the desired intermediate 321 described above (Figure 21).}
\end{align*}
\]

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 \textit{exo}-addition products and trace amounts of the adducts of the alternative \(E(Si)\) silene (Scheme 104).

The major diastereomer (boxed in red) is thought to arise from a \(Z(Si)\) silene \(98\) reacting in an \textit{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 \(BF_3\cdot\text{OEt}_2\) 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).
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).

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).

The stereochemistry was ascertained by $^{19}$F NMR integration [$\delta_F$ -184.72 (d, $J = 15.8$ Hz); $\delta_F$ -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).
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 H₂O₂, KHCO₃, Δ) to provide 1,4-monoprotected diol 328 in 80% yield (Scheme 108).

![Scheme 108](image)

Importantly, diol 328 was produced as a 2:1 mixture of diastereoisomers (Figure 23) as confirmed by analysis of the IR and ¹H NMR spectra, which showed a broad signal at 3326 cm⁻¹ corresponding to the hydroxyl groups and peaks at 6.04, 5.09 and 4.76 ppm arising from the allyl group.
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).
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$_3$·OEt$_2$ to the mixture of silacycloclohexene 100 and 4-methoxybenzaldehyde dimethyl acetal led directly to the formation of the non-conjugated diene 329 in 47% yield (Scheme 109).

Importantly, diene 329 was formed as a single diastereoisomer. This suggested that initial addition of the oxonium ion to silacycloclohex-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 109
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 \textit{syn} to the trimethylsilyl group (as highlighted earlier). This requires co-planarity of the C-Si σ bond and alkene π-orbital (\textit{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-\textit{anti}, 3,4-\textit{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 \textit{"exo"} position. Formation of the observed products suggests the former is of lower energy giving rise to the major isomer 337 (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.
\[
\begin{align*}
R, & \text{Si-SiMe}_3, \text{Ph} \\
100 & \text{ (R = } '\text{Pr}) \\
206 & \text{ (R = Ph)}
\end{align*}
\]

\[
\begin{align*}
i. & \text{ R}_1\text{CH(OR}_2\text{I), BF}_3\text{OEt}, \\
& \text{DCM, } 0^\circ\text{C}
\end{align*}
\]

\[
\begin{align*}
\text{ii.} & \text{ KHCO}_3, \text{H}_2\text{O}_2, \\
& \text{THF-MeOH}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Silacycle (R)</th>
<th>Acetal (R(^1))</th>
<th>Si-F Yield (dr)</th>
<th>Alcohol Yield (dr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>C(_6)H(_5)</td>
<td>327 60% (2:1)</td>
<td>328 50% (2:1)</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>4-MeOC(_6)H(_4)</td>
<td>------</td>
<td>329 47% (1:0)</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>4-CF(_3)C(_6)H(_4)</td>
<td>321 Aa 32% (2:1:1)</td>
<td>322 Aa 23% (2:1:1)</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>4-BrC(_6)H(_4)</td>
<td>------</td>
<td>322 Ab 23% (2:1)</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>CH(_3)</td>
<td>321 Ab 45% (2:1)</td>
<td>322 Ac 21% (2:1)</td>
</tr>
<tr>
<td>6</td>
<td>206</td>
<td>C(_6)H(_5)</td>
<td>321 Ac 72% (2:1)</td>
<td>322 Ad 55% (2:1)</td>
</tr>
<tr>
<td>7</td>
<td>206</td>
<td>C(_6)H(_5)</td>
<td>339 72% (2:1)</td>
<td>322 Ae 8% (2:1)</td>
</tr>
<tr>
<td>8</td>
<td>206</td>
<td>4-CF(_3)C(_6)H(_4)</td>
<td>338 50% (8:3:2)</td>
<td>322 Af</td>
</tr>
<tr>
<td>9</td>
<td>206</td>
<td>4-BrC(_6)H(_4)</td>
<td>------</td>
<td>322 Ag 46% (3:1)</td>
</tr>
<tr>
<td>10</td>
<td>206</td>
<td>4-NO(_2)C(_6)H(_4)</td>
<td>340 63% (7:4:2)</td>
<td>322 Ah</td>
</tr>
<tr>
<td>11</td>
<td>206</td>
<td>CH(_3)</td>
<td>321 Ad 38% (2:1)</td>
<td>322 Ai 32% (2:1)</td>
</tr>
<tr>
<td>12</td>
<td>206</td>
<td>c-C(_6)H(_11)</td>
<td>341 36% (1:2)</td>
<td>342</td>
</tr>
<tr>
<td>13</td>
<td>206</td>
<td>C(_6)H(_13)</td>
<td>------</td>
<td>322 Aj 20% (1:1)</td>
</tr>
</tbody>
</table>

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

Table 8
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 11).
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.

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 $^1$H NMR coupling constants (marked in red) and NOESY experiments (Scheme 112)

![Diagram of the reaction pathway.](image)

**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 occurred 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).
The preferential formation of the 1,2 \textit{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 \textbf{345}.

\section*{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 \textit{ortho} or \textit{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.\textsuperscript{100,101} The term lignan was first introduced by Harworth\textsuperscript{102} in 1942 to describe a group of plant phenols whose general structure\textsuperscript{348} was determined by the union of two derivatised cinnamic acid residues linked via the $\beta,\beta'$ bond (Figure 27).

\begin{center}
\includegraphics[width=0.5\textwidth]{figure27.png}
\end{center}

**Figure 27**

Within this large family of lignans are the aryltetralin lignans\textsuperscript{349, 350} and aryltetralin lignan lactones\textsuperscript{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.\textsuperscript{103}
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*).
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 \( \rightarrow \) ABC \( \rightarrow \) ABCD or a convergent AB + D \( \rightarrow \) 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, SnCl₄-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). 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). 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). 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. 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).
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.\textsuperscript{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).\textsuperscript{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).\textsuperscript{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](image)

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$_3$Sn' initiated carbocyclisation of diene 379 afforded a 1:4 *cis/trans* mixture of lactones 380. 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).

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.\textsuperscript{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$_3$N 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).
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 \( \text{387} \) (Scheme 118a),\(^{129}\) C-H insertion of diazoesters \( \text{390} \) (Scheme 118b)\(^{130}\) and enolate alkylation \( \text{392} \) (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-methylxyfuranone proceeded with complete diastereoselectivity (cf. Scheme 114b).
Whilst the majority of syntheses involving C ring formation by aromatic substitution follow an $S_\text{E}Ar$ pathway using a stabilised 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'-demethyleatein $395$ with DDQ in the presence of TFA. This gave rise to the isopodophyllotoxin stereochemistry (Scheme 119).\(^{131}\)
This benzylic oxidation was suggested to be a biomimetic process.\textsuperscript{132} In support of this, Kutney and others have shown that various oxidative enzymes can promote a similar transformation.\textsuperscript{133,134} For example, treatment of the butanolide 398 with a cell-free enzyme preparation derived from \textit{Catharanthus roseus} (AC3 CFE) led directly to a fully substituted C ring lactone possessing the \textit{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-\textit{cis} stereochemistry, albeit as a mixture of lactone stereoisomers 402 and 403 (Scheme 121).\textsuperscript{129}
A similar unsaturated lactone was generated in a novel Heck cyclisation developed by Ishibashi and Ikeda (Scheme 122). In this approach, the stereochemistry of the starting alkene is crucial. Whilst use of the Z-lactone afforded a good yield of apopicrospodophyllin, 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.
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). Treatment of iodide 406, synthesised in four steps from piperonyl 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.
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 oxabicycloaduct 412 derived from isobenzofuran 411 and DMAD contains all the required carbon and oxygen atoms for podophyllotoxin.\cite{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 chemically 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,\cite{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).
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.\textsuperscript{141}Whilst simple reduction of 416 with H\textsubscript{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\textsubscript{4}] afforded enhanced selectivity 20:1 in favour of the former stereochemistry (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.\textsuperscript{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.\textsuperscript{148,149} The particular problems of fumarate cycloadditions are illustrated by the early work of Durst (Scheme 126).\textsuperscript{150} In this an o-quinodimethide was generated and trapped in a photo-enolisation Diels-Alder strategy. Whilst reaction with methyl fumarate established the \textit{syn} C-1 and C-4 arrangement, it also led to the formation of the alternative epiisopodophyllotoxin \textit{trans,trans,cis}-stereochemistry.
Charlton has proposed two solutions to this problem. The first was based on the observation that the fumarates of lactate and mandelate lead preferentially to an exo-adduct\textsuperscript{151}. The reasons for this are not immediately clear but have been exploited to provide a short synthesis of neopodophyllotoxin (Scheme 127a).\textsuperscript{145} The second strategy was to use an α-hydroxy-α-aryl o-quinodimethide in which the hydroxy group would control the regio- and stereochemistry of the cycloaddition. The o-quinodimethane was generated from the corresponding benzocyclobutane 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\textsubscript{3}·OEt\textsubscript{2} and LiAlH\textsubscript{4} proved successful giving a 15:2 mixture of the C-1 α and β isomers with the major isomer being elaborated to deoxypodophyllotoxin (Scheme 127b).\textsuperscript{152}
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
The challenge of controlling the stereo- and regiochemistry of addition to \textit{o-}quinonedimethane-type dienes has also been studied by Jones. In an elegant series of papers using the readily accessible, and sometimes isolable pyrones \textit{433}, he has shown that whilst a C-2 aryl substituent induces an \textit{exo-} orientation for a methoxy carbonyl group at C-2, this directing effect can be overcome using more compact dienophiles.\textsuperscript{156-158} Whilst the lactate fumarate \textit{422a} used by Charlton proved non-selective, the menthylaxy-furanone \textit{434} gave complete selectivity for the \textit{endo-} adduct. Following acid-promoted elimination across the lactone bridge, hydrogenation afforded the podophyllotoxin \textit{1,2-cis 2,3-trans} stereochemistry (\textit{\sim}7:1) with the selectivity directed by the chiral auxiliary. Subsequent C-4 oxidative decarboxylation, hydrolysis of the chiral auxiliary, reduction and lactonisation afforded (\textit{-})-podophyllotoxin \textit{353} in 15\% overall yield from pyrone \textit{433} (\textit{Scheme 129}).\textsuperscript{146}
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).\textsuperscript{159} Alternatively, electrochemical reduction of unsaturated lactone 438 led to the 1,2-trans 2,3-cis picropodophyllin stereochemistry.\textsuperscript{160}
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). However, the drawback to such an approach is the formation of the undesired 1,2-trans- stereochemistry.
In a unique approach to the aryltetralin skeleton, Toste has employed an intramolecular Heck reaction of 1,7-enzyme 445 to construct the C ring in his synthesis of podophyllotoxin (Scheme 132).^{163}

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}
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.\(^\text{112}\)

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 \(^4\)\(^5\)\(^1\) as a key C-ring precursor in an earlier synthesis of picropodophyllin.\(^\text{165,166}\)

Oxo ester \(^4\)\(^5\)\(^1\) was generated in 4 steps from benzophenone derivative \(^4\)\(^5\)\(^0\) through a sequence involving Stobbe condensation, reduction, activation of the carboxylic acid and Friedel-Crafts acylation.\(^\text{167}\) 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 \(\alpha\)-apopodophyllic acid \(^4\)\(^5\)\(^3\), which could be resolved using quinine. Lactonisation and hydration of the alkene then afforded picropodophyllotoxin \(^3\)\(^5\)\(^5\) albeit in low yield (Scheme 134).\(^\text{168}\)
Whilst this established the basic skeleton of aryltetralin lactones, the stereochemistry represented the thermodynamically favoured outcome. However, based on earlier studies exploring the picropodophyllin-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 picropodophyllin. 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. 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](image)

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. 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).
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). 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). 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. The Δ^{1,2} unsaturated skeleton can also be accessed from the C-1 ketone via enol triflate formation and Suzuki-Miyaura cross coupling (Scheme 137c).
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).\textsuperscript{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. Whilst this step proved efficient, the intrinsic diastereoselectivity 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. 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 diastereoselectivity at C-2 (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 139

Scheme 140
Therefore, it was our intention to apply this methodology to the total synthesis of epipicropodophyllin 356. Firstly, a retrosynthetic analysis of epipicropodophyllin 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).

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).
Silyl alcohol 481 was confirmed by analysis of the IR spectrum, which showed a broad signal at 3564 cm\(^{-1}\) coupled with peaks at 5.90 and 5.10 ppm in the \(^1\)H NMR spectrum, corresponding to the dioxolane methylene group and Si-CH 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).\(^{179,180}\)

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).
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-ones (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).
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)

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$_3$·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 hydroxysilacyclohex-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 \(^1\)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).
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 ($m/z = 659$ (M$\text{Na}^+$), 1295 (2M$\text{Na}^+$)). 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).

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 $m/z = 437$ ($M\text{Na}^+$) and $m/z = 851$ ($2M\text{Na}^+$) 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 $^1$H NMR (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).
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).

![Diagram of protecting groups and reaction conditions]

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Me₂)C</td>
<td>(MeO)₂C(CH₃)₂, p-TSA, acetone</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>PhCH</td>
<td>Benzaldehyde, PPTS, DCM</td>
<td>Starting material recovered</td>
</tr>
<tr>
<td>3</td>
<td>'Bu₂Si</td>
<td>('Bu)₂SiCl₂, Im., DCM</td>
<td>Starting material recovered</td>
</tr>
<tr>
<td>4</td>
<td>C=O</td>
<td>CDI, DMAP, DCM</td>
<td>80%</td>
</tr>
</tbody>
</table>

**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, indicating 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).
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.

Scheme 151
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 1731 cm\(^{-1}\) 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 9.03 ppm for the aldehyde proton and a signal at 200 ppm 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. OsO₄ and NaIO₄ 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).

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. 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).
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).
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. 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)dimethylsilane 518. Subsequent ring-closing-metathesis utilising Re$_2$O$_7$-Al$_2$O$_3$ and SnBu$_4$ generated the desired silacyclohex-4-ene 194 in 77% yield (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

Scheme 159
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 1H NMR data with that given in the literature (Figure 35).^56,183

![Figure 35](image)

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, silacyclohex-4-ene 194 was combined with benzaldehyde dimethyl acetal and treated with BF₃•OEt₂ 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).

![Scheme 160](image)

As expected, 1H 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. OsO₄ and NaIO₄ (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'Bu)₃ (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 TBDPSCI 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 '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 NaI$_4$ 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 electrospray ionisation further confirmed the generation of lactol 527 (Scheme 162).

\[ \text{Scheme 162} \]

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 TBDPSCI, despite the low yields. Monoprotected diol 528 would then be subjected to cat. OsO$_4$ and NaI$_4$ (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).

![Figure 36](image)

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 iodoctadiene 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).

![Chemical structures](image)

**Figure 37**

With this strategy in mind, a brief search of the literature revealed that the desired iodoctadiene 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.\textsuperscript{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).
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 $\tau$-butyl acyl polysilane 548 and heptadienal 547 would be coupled with tetrakis(trimethylsilyl)silane 94 (Figure 38).
5.3.3 Synthesis of Silene Precurors

Gratifyingly, the synthesis of iodoheptadiene 544 proceeded 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).\(^{184,185}\)

\[\text{\(\text{OH} \quad \text{Me}_3\text{Si} \quad \text{O} \quad \text{Me} \rightarrow \text{Si} \quad \text{Bu} \)}\]

\[\text{\(\text{Me}_3\text{Si} \quad \text{O} \quad \text{Me} \rightarrow \text{Si} \quad \text{Me}_3 \)}\]

\[\text{\(\text{O} \quad \text{Me}_3\text{Si} \quad \text{SiMe}_3 \quad \text{OH} \)}\]

\[\text{\(\text{Me}_3\text{Si} \quad \text{O} \quad \text{Me} \rightarrow \text{Si} \quad \text{Me}_3 \)}\]

\[\text{\(\text{O} \quad \text{Me}_3\text{Si} \quad \text{SiMe}_3 \quad \text{OH} \)}\]

\[\text{\(\text{Me}_3\text{Si} \quad \text{O} \quad \text{Me} \rightarrow \text{Si} \quad \text{Me}_3 \)}\]

\[\text{\(\text{O} \quad \text{Me}_3\text{Si} \quad \text{SiMe}_3 \quad \text{OH} \)}\]

\[\text{\(\text{Me}_3\text{Si} \quad \text{O} \quad \text{Me} \rightarrow \text{Si} \quad \text{Me}_3 \)}\]

\[\text{\(\text{O} \quad \text{Me}_3\text{Si} \quad \text{SiMe}_3 \quad \text{OH} \)}\]

\[\text{\(\text{Me}_3\text{Si} \quad \text{O} \quad \text{Me} \rightarrow \text{Si} \quad \text{Me}_3 \)}\]

\[\text{\(\text{O} \quad \text{Me}_3\text{Si} \quad \text{SiMe}_3 \quad \text{OH} \)}\]

\[\text{\(\text{Me}_3\text{Si} \quad \text{O} \quad \text{Me} \rightarrow \text{Si} \quad \text{Me}_3 \)}\]

\[\text{\(\text{O} \quad \text{Me}_3\text{Si} \quad \text{SiMe}_3 \quad \text{OH} \)}\]

\[\text{\(\text{Me}_3\text{Si} \quad \text{O} \quad \text{Me} \rightarrow \text{Si} \quad \text{Me}_3 \)}\]

\[\text{\(\text{O} \quad \text{Me}_3\text{Si} \quad \text{SiMe}_3 \quad \text{OH} \)}\]

\[\text{\(\text{Me}_3\text{Si} \quad \text{O} \quad \text{Me} \rightarrow \text{Si} \quad \text{Me}_3 \)}\]

\[\text{\(\text{O} \quad \text{Me}_3\text{Si} \quad \text{SiMe}_3 \quad \text{OH} \)}\]

\[\text{\(\text{Me}_3\text{Si} \quad \text{O} \quad \text{Me} \rightarrow \text{Si} \quad \text{Me}_3 \)}\]

\[\text{\(\text{O} \quad \text{Me}_3\text{Si} \quad \text{SiMe}_3 \quad \text{OH} \)}\]

\[\text{\(\text{Me}_3\text{Si} \quad \text{O} \quad \text{Me} \rightarrow \text{Si} \quad \text{Me}_3 \)}\]

\[\text{\(\text{O} \quad \text{Me}_3\text{Si} \quad \text{SiMe}_3 \quad \text{OH} \)}\]

\[\text{\(\text{Me}_3\text{Si} \quad \text{O} \quad \text{Me} \rightarrow \text{Si} \quad \text{Me}_3 \)}\]

\[\text{\(\text{O} \quad \text{Me}_3\text{Si} \quad \text{SiMe}_3 \quad \text{OH} \)}\]

\[\text{\(\text{Me}_3\text{Si} \quad \text{O} \quad \text{Me} \rightarrow \text{Si} \quad \text{Me}_3 \)}\]

\[\text{\(\text{O} \quad \text{Me}_3\text{Si} \quad \text{SiMe}_3 \quad \text{OH} \)}\]

\[\text{\(\text{Me}_3\text{Si} \quad \text{O} \quad \text{Me} \rightarrow \text{Si} \quad \text{Me}_3 \)}\]

\[\text{\(\text{O} \quad \text{Me}_3\text{Si} \quad \text{SiMe}_3 \quad \text{OH} \)}\]

\[\text{\(\text{Me}_3\text{Si} \quad \text{O} \quad \text{Me} \rightarrow \text{Si} \quad \text{Me}_3 \)}\]

\[\text{\(\text{O} \quad \text{Me}_3\text{Si} \quad \text{SiMe}_3 \quad \text{OH} \)}\]

\[\text{\(\text{Me}_3\text{Si} \quad \text{O} \quad \text{Me} \rightarrow \text{Si} \quad \text{Me}_3 \)}\]

\[\text{\(\text{O} \quad \text{Me}_3\text{Si} \quad \text{SiMe}_3 \quad \text{OH} \)}\]

\[\text{\(\text{Me}_3\text{Si} \quad \text{O} \quad \text{Me} \rightarrow \text{Si} \quad \text{Me}_3 \)}\]

\[\text{\(\text{O} \quad \text{Me}_3\text{Si} \quad \text{SiMe}_3 \quad \text{OH} \)}\]

\[\text{\(\text{Me}_3\text{Si} \quad \text{O} \quad \text{Me} \rightarrow \text{Si} \quad \text{Me}_3 \)}\]

\[\text{\(\text{O} \quad \text{Me}_3\text{Si} \quad \text{SiMe}_3 \quad \text{OH} \)}\]

\[\text{\(\text{Me}_3\text{Si} \quad \text{O} \quad \text{Me} \rightarrow \text{Si} \quad \text{Me}_3 \)}\]

\[\text{\(\text{O} \quad \text{Me}_3\text{Si} \quad \text{SiMe}_3 \quad \text{OH} \)}\]

\[\text{\(\text{Me}_3\text{Si} \quad \text{O} \quad \text{Me} \rightarrow \text{Si} \quad \text{Me}_3 \)}\]

\[\text{\(\text{O} \quad \text{Me}_3\text{Si} \quad \text{SiMe}_3 \quad \text{OH} \)}\]

\[\text{\(\text{Me}_3\text{Si} \quad \text{O} \quad \text{Me} \rightarrow \text{Si} \quad \text{Me}_3 \)}\]
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. Subsequently, acylpolysilane 548 was coupled with iodoheptadiene 544 to give the desired silene precursor 549. Additionally, reduction of silene precursor 549 was effected with LiAlH₄ 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'Bu to give a silenolate 555b, which would be trapped as the [5,6] fused ring system 556 (Scheme 167).

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).

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. NH₄Cl 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 F254) 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 $\delta$ (ppm) (number of protons, multiplicity, coupling constant $J$ (Hz), assignment). Residual protic solvent CHCl$_3$ ($\delta_H = 7.26$) was used as the internal reference. $^{13}$C NMR spectra were recorded at 63 MHz or 126 MHz, using the central resonance of CDCl$_3$ ($\delta_C = 77.0$ ppm) as the internal reference. All chemical shifts are quoted in parts per million relative to tetramethylsilane ($\delta_H = 0.00$ 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

\[
\text{Me}_3\text{Si-Si-SiMe}_3
\]

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 1 h 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 SiCl₄ 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 MgSO₄, 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; \( \nu_{\text{max}} \) (thin film) 2951, 2893, 1394, 1243, 818 cm⁻¹; \( \delta_H \) (300 MHz, CDCl₃) 0.20; \( \delta_C \) (100 MHz, CDCl₃) 2.7; \( m/z \) (EI)
320 (M⁺, 32%), 305 (M⁺ -CH₃, 22%), 232 (M⁺ -CH₃, -Si(CH₃)₃, 84%), 173 (M⁺ -2Si(CH₃)₃, 72%), 158 (M⁺ -2Si(CH₃)₃-H, 76%); all data agree with those reported by Whelligan.³⁵

Phenyltris(trimethylsilyl)silane, 95

\[
\text{Ph-Si-SiMe₃}
\]

Dry tetrakis(trimethylsilyl)silane 94 (17.5 g, 54.6 mmol) and potassium-\textit{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 1 h 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. NH₄Cl (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 MgSO₄, filtered, concentrated and dried \textit{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); \( \nu_{\text{max}} \) (thin film) 2950, 2893, 1426, 1243 cm\(^{-1}\); \( \delta_1 \) (300 MHz, CDCl₃) 7.46-7.42 (2H, m, \text{ortho Ax-H}), 7.26-7.23 (3H, m, meta and para Ax-H), 0.22 (27H, s, Si(Si(CH₃)₃)); \( \delta_C \) (126 MHz, CDCl₃) 136.5 (Ar-C), 135.5 (Ar-C), 127.7 (Ar-C), 127.3 (Ar-C), 1.2 (Si(Si(CH₃)₃)); \( m/z \) (EI) 324
(M⁺, 16%), 309 (M⁺ - CH₃, 6%), 251 (M⁺ -Si(CH₃)₃, 10%), 236 (M⁺ - CH₃, -Si(CH₃)₃, 14%), 191 (26%), 174 (M⁺ -Ph, -Si(CH₃)₃, 92%), 159 (M⁺ -Ph, -Si(CH₃)₃, -CH₃, 42%), 135 (66%), 73 ((CH₃)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. NH₄Cl 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 MgSO₄, 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%); Rf 0.57 (pet. ether/ether 9:1); δH (200 MHz, CDCl₃) 7.54-7.49 (2H, m, Ar-H), 7.32-7.28 (3H, m, Ar-H), 3.79 (1H, d, J 7, SiCH), 1.96 (1H,
octet, \( J 7, \text{CH(CH}_3)_2 \), 0.99 and 0.88 (each 3H, d, \( J 7, \text{CH(CH}_3)_2 \)), 0.24 and 0.2 (each 9H, s, Si(CH\(_3\))\(_3\)); \( \delta_c \) (126 MHz, CDCl\(_3\)) 136.5 (Ar-C), 135.6 (Ar-C), 128.1 (Ar-C), 127.9 (Ar-C), 72.4 (SiCH), 34.6 (CH(CH\(_3\))\(_2\)), 21.16 and 19.86 (CH(CH\(_3\))\(_2\)), 0.5 (Si(CH\(_3\))\(_3\)), 0.2 (Si(CH\(_3\))\(_3\)); \( m/z \) (Cl) 342 (MNH\(_4^+\), 10%), 324 (M\(^+\), 36%), 307 (M\(^+\) - OH, 100%); all data agree with those reported by Whelligan.\(^{35}\)

(1,1,3,3,3-

Hexamethyl-2-phenyl-trisilane-2-yl)-phenyl-methanol, 205

\[
\text{Me}_3\text{Si} - \text{Si} - \text{Me}_3
\]

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); \( \delta_h \) (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, SiCH), 1.75 (1H, d, \( J \) 4, CHO\(_H\)), 0.14 and 0.10 (each 9H, s, Si(CH\(_3\))\(_3\)); \( m/z \) (Cl) 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\(_4\)Cl (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 MgSO₄, filtered, concentrated and dried in vacuo. Flash chromatography (pet. ether) afforded the desired silacyclohex-4-ene as an inseparable mixture of isomers

\[
(1SR,2RS,3SR)-1\text{-Phenyl-1-trimethylsilyl-2-(isopropyl)-3-methylsilacyclohex-4-ene},
\]

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); \( v_{\text{max}} \) (thin film) 2998, 2950, 2868, 1460, 1426, 1396, 1243, 1100, 830, 733, 696 cm\(^{-1}\); \( \delta_H \) (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, 2CH(CH\(_3\))\(_2\)), 1.68 (1H, ddd, \( J \) 17, 5, 2, 6-HH), 1.47 (1H, ddt, \( J \) 17, 5, 2, 6-HH), 1.20 (1H, dd, \( J \) 7, 4, 2-H), 1.03 (3H, dd, \( J \) 7, 5, 2-CH(CH\(_3\))\(_2\)), 0.93 (3H, dd, \( J \) 7, 3-CH\(_3\)), 0.88 (3H, d, \( J \) 7, 2-CH(CH\(_3\))\(_2\)), 0.14 (9H, s, Si(CH\(_3\))\(_3\)); \( \delta_C \) (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-CH(CH\(_3\))\(_2\)), 23.5 (3-CH\(_3\)), 23.0 (2-CH(CH\(_3\))\(_2\)), 22.4 (2-CH(CH\(_3\))\(_2\)), 9.7 (6-C), -0.6 (Si(CH\(_3\))\(_3\)); \( m/z \) (EI) 302 (M\(^+\), 4%), 259 (M\(^+\)-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.\(^{35}\)
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; Rf 0.4 (pet. ether); δH (500 MHz, CDCl3) 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-HH), 1.65 (1H, m, 6-HH), 0.97 (3H, d, J 7, 3-CH3), -0.07 (9H, s, Si(CH3)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

(1SR,2SR,3SR)-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) (H2 gas evolved), followed by 3M NaOH (0.2 ml, 0.7 mmol) and a 35% w/w solution of H2O2 in water (0.2 ml, 2.2 mmol). The mixture was refluxed at 65 °C for 4 h after which time Na2S2O3 (10 ml) was added. The aqueous layer was
separated and extracted with EtOAc (3 x 10 ml). The combined organic layers were
dried over MgSO₄, 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; Rf 0.3 (pet. ether/ether 3:2); vₘₐₓ (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 δH (300 MHz, CDCl₃)
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-CH(CH₃)₂), 1.65 (2H, m, 6-H₂), 1.45 (1H, m, 2-H), 1.26
(2H, m, 5-H₂), 1.14 (3H, d, J 7, 2-CH(CH₃)₂), 1.00 (3H, d, J 7, 3-CH₃), 0.75 (3H, d, J 7,
2-CH(CH₃)₂), 0.29 (9H, s, Si(CH₃)₃); δC (126 MHz, CDCl₃) 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-
CH(CH₃)₂), 33.5 (5-C), 23.5 (2-CH(CH₃)₂), 22.1 (2-CH(CH₃)₂), 18.4 (3-CH₃), 9.6 (6-
C), 0.3 (Si(CH₃)₃); m/z (ES⁺) 343 (MNa⁺), 303 (M⁺-H₂O); all data agree with those
reported by Whelligan.³⁵

**(1SR,2RS,3SR,4RS/ SR)-1-Phenyl-1-trimethylsilyl-2-(isopropyl)-3-methyl-4-
acetoxy silacyclohexane, 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
MgSO₄, 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%); Rf 0.2 (pet. ether/ether 95:5); \( \nu_{\text{max}} \) (thin film) 2957, 2872, 1733 (C=O), 1458, 1427, 1368, 1245, 1172, 1142, 1100, 1022, 852, 834, 699 cm\(^{-1}\); partial NMR data \( \delta \) (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-HH, 2-CH(CH\(_3\))\(_2\)), 2.08 (3H, s, 4-C(O)CH\(_3\)), 1.99-1.93 (2H, m, 5-HH, 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\(_3\))\(_3\)); \( \delta \) (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-CH(CH\(_3\))\(_2\)), 23.6 (2-CH(CH\(_3\))\(_2\)), 22.0 (2-CH(CH\(_3\))\(_2\)), 21.4 (4-C(O)CH\(_3\)), 18.1 (3-CH\(_3\)), 9.1 (6-C), 0.3 (Si(CH\(_3\))\(_3\)); m/z (El) 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

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

\[ \text{Method A} \]

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, 4x10⁻⁴M) and trifluoroacetone (0.3 ml, 3.7 mmol). This solution was then treated with a mixture of NaHCO₃ (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 MgSO₄, 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%); Rf 0.6 (pet. ether/ether 9:1); v_max (thin film) 3068 (broad-OH), 2956, 2892, 2870, 1718, 1427, 1244, 1103, 1004, 855, 835, 699 cm⁻¹; δ_H (500 MHz, CDCl₃) 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-HH), 5.08 (1H, d, J 10, 7-HH), 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-CH₃), 0.86 (3H, d, J 6, 4-CH₃), 0.17 (9H, s, Si(CH₃)₃); δ_C (126 MHz, CDCl₃) 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-CH₃), 16.6 (4-CH₃), -1.4 (Si(CH₃)₃); m/z (ES⁺) 359 (MNa⁺); HRMS (ES⁺) Found MNa⁺, 359.1837 (C₁₈H₃₂O₂Si₂Na 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$_2$S$_2$O$_3$ 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.

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

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); $\nu_{\text{max}}$ (thin film) 3631-3579 (broad-OH), 3069, 3026, 2955, 2925, 2895, 2871, 1598, 1426, 1256, 1242, 1049, 1021, 896, 835, 781 cm$^{-1}$; $\delta$$_H$ (500 MHz, CDCl$_3$) 7.31-7.21 (5H, m, Ar-H), 7.18-7.12 (3H, m, Ar-H), 7.08-7.06 (2H, m, Ar-H), 4.48 (1H, m, 5-H), 3.38 (1H, dd, $J$ 10, 3, 4-H), 2.57 (1H, m, 3-H), 2.15 (1H, d, $J$ 12, 2-H), 1.63 (1H, dd, $J$ 15.5, 6, 6-HH), 1.34 (1H, dd, $J$ 15.5, 6, 6-HH), 0.95 (3H, d, $J$ 7, 3-CH$_3$), 0.03 (9H, s, Si(CH$_3$)$_3$); $\delta$$_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-CH$_3$), 17.5 (6-C), -0.7 (Si(CH$_3$)$_3$); $\delta$$_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$_2$Si$_2$Na requires 393.1677).
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); \( \nu_{\text{max}} \) (thin film) 3498-3211 (broad-OH), 2950, 2932, 2898, 2864, 1426, 1096, 1022, 992, 832, 731, 697 cm\(^{-1}\); \( \delta_H \) (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-CH(CH\(_3\))\(_2\)), 1.36 (1H, dd, J 14, 9, 6-HH), 1.18 (1H, m, 6-HH), 1.08 (1H, dd, J 9, 6, 2-H), 1.04 (3H, d, J 7, 2-CH(CH\(_3\))\(_2\)), 0.97 (3H, d, J 7, 3-CH\(_3\)), 0.91 (3H, d, J 7, 2-CH(CH\(_3\))\(_2\)), 0.21 (9H, s, Si(CH\(_3\))\(_3\)); \( \delta_C \) (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-CH(CH\(_3\))\(_2\)), 23.8 (2-CH(CH\(_3\))\(_2\)), 19.4 (3-CH\(_3\)), 16.5 (6-C), -0.4 (Si(CH\(_3\))\(_3\)); \( \delta_{\text{Si}} \) (100 MHz, CDCl\(_3\)) -17.90, -23.36; \( m/z \) (ES\(^+\)) 359 (MNa\(^+\)); HRMS (ES\(^+\)) Found MNa\(^+\), 359.1834 (C\(_{18}\)H\(_{32}\)Si\(_2\)O\(_2\)Na requires 359.1833).

6.3.2 Standard procedure for the Fleming-Tamao fragmentation of dihydroxy 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 \textit{in vacuo} to give a colourless oil which was used immediately in stage 2.

\textbf{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$_2$O$_2$ 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$_2$S$_2$O$_3$ 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 \textit{in vacuo}. Flash chromatography (pet. ether/ether [9:1], [4:1], [3:2], [1:1], [1:2]) afforded the desired diols.

\textit{(1SR,2SR,3RS)-2-Methyl-1-phenylpent-4-ene-1,3-diol, 208}

\begin{center}
\begin{tikzpicture}
\end{tikzpicture}
\end{center}

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); \textit{v}$_{\text{max}}$ (thin film) 3502-3214 (broad-OH), 3064, 2974, 2886, 1721, 1711, 1690, 1601, 1512, 1450, 1332, 1216, 1128, 1080 cm$^{-1}$; \textit{\delta}$_H$ (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-$HH$), 5.26 (1H, d, $J$ 10, 5-$HH$), 4.69 (1H, d, $J$ 9, 1-$H$), 4.40 (1H, m, 3-$H$), 2.95 (1H, bs, -OH), 2.11 (1H, qd, $J$ 9, 3, 2-$H$), 0.82 (3H, d, $J$ 9, 2-CH$_3$); \textit{\delta}$_C$ (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 (C₁₂H₁₆O₂Na requires 215.1043).

(3RS,4RS,5RS)-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%); Rᵣ 0.3 (pet. ether/ether 1:1); νₘₐₓ (thin film) 3525-3134 (broad-OH), 2962, 2870, 1459, 1427, 1118, 1081, 974, 919, 844, 697, 639 cm⁻¹; δₜ (500 MHz, CDCl₃) 5.94 (1H, ddd, J 16, 10, 5, 2-H), 5.29 (1H, d, J 16, 1-HH), 5.19 (1H, d, J 10, 1-HH), 4.41 (1H, s, 3-H), 3.39 (1H, m, 5-H), 3.11 (1H, bs, -OH), 2.53 (1H, bs, -OH), 1.89 (1H, qd, J 7, 3, 4-H), 1.82 (1H, m, 6-H), 0.94 (3H, d, J 8, 7-CH₃), 0.92 (3H, d, J 8, 6-CH₃), 0.87 (3H, d, J 7, 4-CH₃); δₛ (126 MHz, CDCl₃) 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-CH₃), 16.0 (6-CH₃), 12.2 (4-CH₃); m/z (ES') 181 (MNa'); HRMS (ES') Found MNa', 181.1199 (C₉H₁₈O₂Na 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 MgSO₄, filtered, concentrated and dried in vacuo. Flash chromatography (pet. ether/ether [95:5], [9:1]) afforded the desired mono-protected diols.
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); \( \nu_{\text{max}} \) (thin film) 3572-3286 (broad-OH), 2960, 2932, 2894, 2852, 1468, 1368, 1256, 1026, 926, 832, 770 cm\(^{-1}\); \( \delta_H \) (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, \( \text{SiC(CH}_3\text{)}_3 \)), 0.58 (3H, s, \( \text{Si(CH}_3\text{)}_2\text{Bu} \)), 0.17 (3H, s, \( \text{Si(CH}_3\text{)}_2\text{Bu} \)), 0.12 (3H, s, \( \text{Si(CH}_3\text{)}_2\text{Bu} \)); \( \delta_C \) (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 (SiC(CH\(_3\))\(_3\)), 13.4 (2-CH\(_3\)), -4.2 (Si(CH\(_3\))\(_2\)Bu) -4.9 (Si(CH\(_3\))\(_2\)Bu); \( m/z \) (ES\(^+\)) 329.3 (MNa\(^+\)), 635 (2MNa\(^+\)); HRMS (ES\(^+\)) Found MNa\(^+\), 329.1907 (C\(_{18}\)H\(_{30}\)O\(_2\)SiNa requires 329.1907).

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); \( \nu_{\text{max}} \) (thin film) 3630-3130 (broad-OH), 2957, 2930, 2857, 1471, 1384, 1254, 1126, 1022, 966, 835, 776 cm\(^{-1}\); \( \delta_H \) (500 MHz, CDCl\(_3\)) 5.93 (1H, ddd, \( J \) 17, 10, 6, 6-H), 5.22 (1H, d, \( J \) 17, 7-HH), 5.19 (1H, d, \( J \) 10, 7-HH),
4.30 (1H, m, 5-H), 3.95 (1H, bs, -OH), 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(CH₃)₃), 0.86 (3H, d, J 7, 2-CH₃), 0.77 (3H, d, J 7, 4-CH₃), 0.09 (3H, s, Si(CH₃)₂-Bu), 0.06 (3H, s, Si(CH₃)₂-Bu); δC (126 MHz, CDCl₃) 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(CH₃)₃), 20.4 (1-C), 18.4 (SiC(CH₃)₃), 14.2 (2-CH₃), 13.1 (4-CH₃), -4.3 (Si(CH₃)₂-Bu), -5.0 (Si(CH₃)₂-Bu); m/z (ES⁺) 295 (MNa⁺); HRMS (ES⁺) Found MH⁺, 273.2245 (C₁₅H₃₅O₂Si 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 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 H₂O₂ (0.9 mmol). The mixture was then refluxed for 1 h, then cooled, poured into Na₂S₂O₃ and extracted with Et₂O (3 x 10 ml). The combined organic layers were dried over MgSO₄, filtered, concentrated and dried in vacuo. Flash chromatography (pet. ether/ether [1:1], [2:3]) afforded the desired mono-protected triols.

(1SR,2RS,3RS)-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%); Rf 0.3 (pet. ether/ether 2:3); νmax (thin film) 3490-3182 (broad-OH), 2956, 2932, 2886, 2860, 1684, 1676, 1560, 1437, 1259, 1202, 1075, 1050, 781 cm⁻¹; δH (500 MHz, CDCl₃) 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-HH), 3.75 (1H, m, 5-HH), 2.07-1.96 (2H, m, 2-H, 4-HH), 1.89 (1H, m, 4-HH), 0.97 (9H, s, SiC(CH₃)₃), 0.57 (3H, d, J 7, 2-CH₃), 0.22 (3H, s, Si(CH₃)₂Bu), 0.16 (3H, s, Si(CH₃)₂Bu); δC (126 MHz, CDCl₃) 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(CH₃)₃), 18.2 (Si(CH₃)₂), 14.0 (2-CH₃), -4.1 (Si(CH₃)₂Bu), -4.6 (Si(CH₃)₂Bu); m/z (ES⁺) 347 (MNa⁺); HRMS (ES⁺) Found MNa⁺, 347.2014 (C₁₈H₃₂O₃SiNa requires 347.2013).

(3RS,4RS,5RS)-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%); Rf 0.3 (pet. ether/ether 1:1); νmax (thin film) 3562-3356 (broad-OH), 3005, 2949, 2931, 1713, 1417, 1360, 1223, 1089, 1051, 838, 530 cm⁻¹; δH (500 MHz, CDCl₃) 4.00 (1H, m, 3-H), 3.79 (1H, m, 1-HH), 3.70 (1H, m, 1-HH), 3.51 (1H, dd, J 10, 2, 5-H), 1.90-1.83 (2H, m, 4-H, 2-HH), 1.78 (1H, m, 2-HH), 1.68 (1H, m, 6-H), 1.00 (3H, d, J 6, 7-CH₃), 0.90 (9H, s, SiC(CH₃)₃), 0.84 (3H, d, J 6, 6-CH₃), 0.76 (3H, d, J 7, 4-CH₃), 0.41 (3H, s, Si(CH₃)₂Bu), 0.11 (3H, s, Si(CH₃)₂Bu); δC (126 MHz, CDCl₃) 75.4 (3-C), 60.2 (1-C), 40.3 (4-C), 34.0 (2-C), 30.0 (6-C), 26.0 (SiC(CH₃)₃), 20.4 (7-CH₃), 18.4 (SiC(CH₃)₃), 13.83 (6-CH₃), 13.82 (4-CH₃), -4.1 (Si(CH₃)₂Bu), -4.7
(Si(CH$_3$)$_2$Bu); $m/z$ (ES$^+$) 313 (MNa$^+$), 291 (MH$^+$); HRMS (ES$^+$) Found MH$^+$, 291.2349 (C$_{15}$H$_{35}$O$_3$Si 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$_3$N.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.

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

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; \( \upsilon_{\text{max}}\) (thin film) 3530-3190 (broad-OH), 2922, 2852, 2359, 2339, 1736 (C=O), 1654, 1245, 1161, 1056, 1022, 894, 837 cm\(^{-1}\); \( \delta_H \) (500 MHz, CDCl\(_3\)) 7.42-7.31 (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-HH), 2.69 (1H, dd, J 18, 7, 3-HH), 2.00 (1H, m, 5-H), 0.94 (3H, s, 5-CH\(_3\)); \( \delta_C \) (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-CH\(_3\)); \( m/z \) (ES\(^+\)) 261 (MNa+MeOH\(^+\)); HRMS (ES\(^+\)) Found MNa+MeOH\(^+\), 261.1098 (C\(_{13}\)H\(_{18}\)O\(_4\)Na requires 261.1097).

\((-\text{)}\text{-Prelactone B, 110}\)

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)\(^{40}\); \( \upsilon_{\text{max}}\) (thin film) 3516-3180 (broad-OH), 2967, 2929, 2876, 2260, 2245, 1731 (C=O), 1600, 1253, 1009, 896, 716, 650 cm\(^{-1}\); \( \delta_H \) (500 MHz, CDCl\(_3\)) 3.78-3.76 (2H, m, 6-H, 4-H), 2.93 (1H, dd, J 17, 6, 3-HH), 2.48 (1H, dd, J 17, 6, 3-HH), 2.00 (1H, qd, J 7, 2, 6-CH(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\(_3\))\(_2\)); \( \delta_C \) (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-CH(CH\(_3\))\(_2\)), 20.0 (6-CH(CH\(_3\))\(_2\)), 14.0 (5-CH\(_3\)), 13.5 (6-CH(CH\(_3\))\(_2\)); \( m/z \) (ES\(^+\)) 195 (MNa\(^+\)), 227 (MNa+MeOH\(^+\)); HRMS (ES\(^+\)) Found MH\(^+\), 173.1173 (C\(_9\)H\(_{17}\)O\(_3\) requires 173.1172); all data agree with those reported in the literature.\(^{40,43,45,47,48,188}\)
(2SR/RS,3SR,4SR,5SR)-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 NaHCO₃ solution (5 ml) and extracted with DCM (3 x 5 ml). The combined organic layers were dried over MgSO₄, 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; Rf 0.3 (pet. ether/ether 98:2); \( \nu_{\text{max}} \) (thin film) 2956, 2923, 1650, 1555, 1427, 1244, 1107, 1003, 835, 698 cm⁻¹; NMR data provided for one isomer \( \delta_{\text{H}} \) (500 MHz, CDCl₃) 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-CH=CH₂), 5.41 (1H, d, J 17, 5-CH=CHH), 5.31 (1H, d, J 9.5, 5-CH=CHH), 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-CH₃), 0.21 (9H, s, Si(CH₃)₃); \( \delta_{\text{C}} \) (126 MHz, CDCl₃) 139.4 (ipso-Ar-C), 138.8 (ipso-Ar-C), 137.2 (5-CH=CH₂), 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=CH₂), 83.4 (5-C), 40.27 (3-C), 40.25 (4-C), 15.1 (4-CH₃), -1.3 (Si(CH₃)₃); \( \delta_{\text{Si}} \) (100 MHz, CDCl₃) 19.5, -21.0; \( m/z \) (ES⁺) 353 (MH⁺); HRMS (ES⁺) Found MH⁺, 353.1752 (C₂₁H₂₉OSi requires 353.1752).
(1SR,2SR,3RS)-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 H₂O₂ (0.13 ml, 1.25 mmol). The mixture was then refluxed for 1 h, at which point the mixture was cooled and poured into Na₂S₂O₃ and extracted with EtOAc (3 x 10 ml). The combined organic layers were dried over MgSO₄, 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%); Rf 0.3 (DCM/MeOH 9:1); v_max (thin film) 3348-3119 (broad-OH), 2962, 2924, 2360, 1684, 1437, 1338, 1223, 1077, 907, 730, 650 cm⁻¹; δ_H (500 MHz, CDCl₃) 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-H₂, -OH), 1.98-1.93 (3H, m, 4-HH, 2-H, -OH), 1.55 (1H, d, J 11, 4-HH), 0.83 (3H, d, J 7, 2-CH₃); δ_C (126 MHz, CDCl₃) 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-CH₃); m/z (ES⁺) 233 (MNa⁺); HRMS (ES⁺) Found MNa⁺, 233.1148 (C₁₂H₁₈O₃Na requires 233.1148).
(1SR,2RS,3SR,4RS)-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 H₂O₂ (0.09 ml, 0.9 mmol). The mixture was then refluxed for 1 h, at which point the mixture was cooled and poured into Na₂S₂O₃ and extracted with Et₂O (3 x 10 ml). The combined organic layers were dried over MgSO₄, 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; v_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, CDCl₃) 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, -OH), 2.19-2.06 (2H, m, 2-H, -OH), 1.26 (3H, d, J 8, 5-H), 0.99 (9H, s, SiC(CH₃)₃), 0.71 (3H, d, J 7, 2-CH₃), 0.22 (3H, s, Si(CH₃)₂Bu), 0.17 (3H, s, Si(CH₃)₂Bu); δ_C (126 MHz, CDCl₃) 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(CH₃)₃) 19.1 (5-C), 18.3 (SiC(CH₃)₃), 12.0 (2-CH₃), -4.2 (Si(CH₃)₂Bu), -4.6 (Si(CH₃)₂Bu); m/z (ES⁺) 347 (MNa⁺); HRMS (ES⁺) Found MNa⁺, 347.2011 (C₁₈H₃₂O₂SiNa requires 347.2013).
A solution of TBS protected alcohol 220 (0.02 g, 0.07 mmol) in DCM (1 ml) was treated sequentially with Et$_3$N (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$_2$O (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); $\nu_{max}$ (thin film) 2929, 2856, 1731 (C=O), 1372, 1251, 1103, 1026, 902, 834, 732, 650 cm$^{-1}$; $\delta_H$ (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-HH), 5.12 (1H, d, J 10, 5-HH), 4.51 (1H, m, 3-H), 2.02 (3H, s, C(0)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$_3$)$_2$Bu); $\delta_C$ (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(CH$_3$)$_3$), 21.6 (C(O)CH$_3$), 18.4 (SiC(CH$_3$)$_3$), 10.4 (2-CH$_3$), -3.5 (Si(CH$_3$)$_2$Bu), -5.1 (Si(CH$_3$)$_2$Bu); m/z (ES$^+$) 371 (MNa$^+$); HRMS (ES$^+$) Found MNa$^+$, 371.2020 (C$_{20}$H$_{32}$O$_3$SiNa 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$_3$·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$_4$Cl 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$_2$O$_2$ (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$_2$S$_2$O$_3$ 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.
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; ν_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, CDCl₃) 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-HH), 4.44 (1H, d, J 17, 7-HH), 3.29 (3H, s, 5-CH(OCH₃)), 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-CH₃), 1.14 (1H, m, 5-CH(OCH₃)), 1.03 (3H, m, 2-CH₃), 0.62 (3H, d, J 7, 1-H), 0.13 (9H, s, Si(CH₃)₃); δ_C (126 MHz, CDCl₃) 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-CH(OCH₃)), 57.44 (5-CH(OCH₃)), 57.42 (5-C), 38.8 (3-C), 35.7 (4-C), 26.2 (2-C), 25.9 (2-CH₃), 24.0 (1-C), 16.6 (4-CH₃), -2.1 (Si(CH₃)₃); δ_F (300 MHz, CDCl₃) -185.6 (1F, d, J 18, Si-F); m/z (Cl) 460 (MNH₄⁺, 100%), 428 (35%), 411 (M⁺ -(OCH₃), 40%); HRMS (Cl) Found MNH₄⁺, 460.2863 (C₂₆H₄₃FOSi₂N requires 460.2862).
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<sub>f</sub> 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<sub>f</sub> 0.4 (pet. ether/ether 9:1) as a mixture of diastereoisomers in the ratio 2:1 by NMR; \( \nu_{\text{max}} \) (thin film) 3326 (broad-OH), 2958, 2874, 2834, 1605, 1594, 1498, 1471, 1454, 1363, 1233, 1066, 992, 918, 752, 691 cm<sup>-1</sup>; NMR data given for the major isomer \( \delta_{\text{H}} \) (500 MHz, CDCl<sub>3</sub>) 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-HH), 4.76 (1H, dd, J 17, 2, 7-HH), 4.48 (1H, d, J 4, 5-CH(OCH<sub>3</sub>)), 3.76 (1H, d, J 3, -OH), 3.28 (1H, m, 3-H), 3.23 (3H, s, 5-CH(OCH<sub>3</sub>)), 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-CH<sub>3</sub>), 0.86 (3H, d, J 7, 4-CH<sub>3</sub>), 0.81 (3H, d, J 7, 1-H); \( \delta_{\text{C}} \) (126 MHz, CDCl<sub>3</sub>) 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-CH(OCH<sub>3</sub>)), 76.9 (3-C), 57.8 (5-C), 57.0 (5-CH(OCH<sub>3</sub>)), 40.9 (4-C), 29.6 (2-C), 20.7 (2-CH<sub>3</sub>), 17.4 (4-CH<sub>3</sub>), 13.6 (1-C); \( m/z \) (ES<sup>+</sup>) 285 (MNa<sup>+</sup>); HRMS (ES<sup>+</sup>) Found MNa<sup>+</sup>, 285.1825 (C<sub>17</sub>H<sub>26</sub>O<sub>2</sub>Na requires 285.1825).
Following stage 1 of the standard procedures outlined on page 181, silacyclopent-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%); Rf 0.6 (pet. ether/ether 95:5) as a mixture of diastereoisomers in the ratio 2:1 by NMR; v_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-HH), 4.46 (1H, dd, J 17, 2, 5-HH), 4.37 (1H, d, J 3, 3-CH(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-CH(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\(_2\)Na requires 499.2259).
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%); Rf 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%); Rf 0.3 (pet. ether/ether 9:1) as a mixture of diastereoisomers in the ratio 2:1 by NMR; $\nu_{\text{max}}$ (thin film) 3355 (broad $\text{OH}$), 2362, 2333, 1491, 1452, 1084, 1068, 914, 841, 754, 698 cm$^{-1}$; NMR data given for major isomer $\delta_{\text{H}}$ (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-HH), 4.80 (1H, dd, $J$ 17, 3, 5-HH), 4.55 (1H, m, 3-CH(OCH$_3$)), 4.31 (1H, d, $J$ 10, 1-H), 3.81 (1H, s, -OH), 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$_3$); $\delta_{\text{C}}$ (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-CH(OCH$_3$)), 77.0 (1-C), 57.2 (3-CH(OCH$_3$)), 57.0 (3-C), 43.8 (2-C), 17.2 (2-CH$_3$); $m/z$ (ES$^+$) 319 (MNa$^+$); HRMS (ES$^+$) Found MNa$^+$, 319.1667 (C$_{20}$H$_{24}$O$_2$Na requires 319.1669).
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\textsubscript{f} 0.7 (pet.ether/ether 95:5) as a mixture of diastereoisomers in the ratio 2:1 by mass; v\textsubscript{max} (thin film) 2959, 2887, 2820, 2362, 2341, 1463, 1372, 1245, 1101, 1086, 1005, 913, 835 cm\textsuperscript{-1}; NMR data given for major isomer: δ\textsubscript{H} (500 MHz, CDCl\textsubscript{3}) 7.52-7.50 (2H, m, Ar-H), 7.36-7.35 (3H, m, Ar-H), 5.65 (1H, ddd, J\textsubscript{17}, J\textsubscript{10}, J\textsubscript{10}, 6-H), 5.22 (1H, d, J\textsubscript{10}, 7-H), 4.97 (1H, d, J\textsubscript{17}, 7-H), 3.58 (1H, m, 5-CH(OCH\textsubscript{3})(CH\textsubscript{3})), 3.33 (3H, s, 5-CH(OCH\textsubscript{3})(CH\textsubscript{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\textsubscript{7}, 4-CH\textsubscript{3}), 1.09 (3H, d, J\textsubscript{7}, 5-CH(OCH\textsubscript{3})(CH\textsubscript{3})), 1.01 (3H, d, J\textsubscript{7}, 2-CH\textsubscript{3}), 0.67 (3H, d, J\textsubscript{7}, 1-H), 0.11 (9H, s, (Si(CH\textsubscript{3})\textsubscript{3}); δ\textsubscript{C} (126 MHz, CDCl\textsubscript{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-CH(OCH\textsubscript{3})(CH\textsubscript{3})), 56.7 (5-CH(OCH\textsubscript{3})(CH\textsubscript{3})), 55.6 (5-C), 38.7 (3-C), 35.2 (4-C), 26.2 (2-C), 25.9 (2-CH\textsubscript{3}), 24.0 (1-C), 17.5 (5-CH(OCH\textsubscript{3})(CH\textsubscript{3})), 16.4 (4-CH\textsubscript{3}), -2.1 (Si(CH\textsubscript{3})\textsubscript{3}); δ\textsubscript{F} (300 MHz, CDCl\textsubscript{3}) -185.5 (1F, d, J\textsubscript{16}, Si-F); m/z (ES\textsuperscript{+}) 403 (MNa\textsuperscript{+}); HRMS (ES\textsuperscript{+}) Found MNa\textsuperscript{+}, 403.2268 (C\textsubscript{21}H\textsubscript{37}Si\textsubscript{2}FONa requires 403.2259).

Further elution gave the minor diastereoisomer as a colourless oil (0.017 g, 15%).
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%); Rf 0.2 (pet. ether/ether 9:1); νmax (thin film) 3374 (broad-OH), 2960, 2928, 2878, 1737, 1678, 1600, 1520, 1468, 1428, 1364, 1256, 1232, 1120, 1072, 1042; cm⁻¹; δH (500 MHz, CDCl3) 5.93 (1H, ddd, J 17, 10, 10, 6-H), 5.19 (1H, dd, J 10, 2, 7-HH), 5.03 (1H, m, 7-HH), 4.42 (1H, s, -OH), 3.52 (1H, m, 5-CH(OCH3)(CH3)), 3.34 (3H, s, 5-CH(OCH3)(CH3)), 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(OCH3)(CH3)), 0.92 (3H, m, 2-CH3), 0.87 (3H, d, J 7, 4-CH3), 0.83 (3H, d, J 7, 1-H); δC (126 MHz, CDCl3) 137.2 (6-C), 119.1 (7-C), 80.2 (5-CH(OCH3)(CH3)), 76.0 (3-C), 57.3 (5-C), 56.6 (5-CH(OCH3)(CH3)), 42.0 (4-C), 30.0 (2-C), 20.4 (2-CH3), 18.0 (4-CH3), 17.4 (5-CH(OCH3)(CH3)), 14.0 (1-C); m/z (ES⁺) 223 (MNa⁺); HRMS (ES⁺) Found MNa⁺, 223.1669 (C12H24O2Na requires 223.1668).

Oxidation of the minor fluorosilane isomer afforded the title isomeric compound as a colourless oil (0.005 g, 53%).
(1R,2SR,3RS,(Si)RS/RS)-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%); Rf 0.6 (pet. ether/ether 95:5) as a mixture of diastereoisomers in the ratio 2:1 by NMR; νmax (thin film) 2971, 2957, 1493, 1427, 1374, 1244, 998, 913, 855, 834, 800, 741, 696 cm⁻¹; NMR data given for major isomer δH (500 MHz, CDCl₃) 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-HH), 4.97 (1H, m, 5-HH), 3.29 (3H, s, 3-CH(CH₃)(CH₃)), 2.80 (1H, dd, J 12, 4, 1-H), 2.49 (1H, m, 2-H), 2.28 (1H, m, 3-CH(CH₃)(CH₃)), 1.74 (1H, m, 3-H), 1.10 (3H, m, 2-CH₃), 1.01 (3H, m, 3-CH(CH₃)(CH₃)), 0.10 (9H, s, Si(CH₃)₃); δC (126 MHz, CDCl₃) 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-CH(OCH₃)(CH₃)), 56.3 (3-CH(OCH₃)(CH₃)), 54.1 (3-C), 41.5 (2-C), 17.2 (3-CH(OCH₃)(CH₃)), 14.9 (2-CH₃), -2.0 (Si(CH₃)₃); δF (300 MHz, CDCl₃) -185.3 (1F, d, J 14, Si-F); m/z (ES⁺) 437 (MNa⁺); HRMS (ES⁺) Found MNa⁺, 437.2101 (C₂₄H₃₅OFSi₂Na requires 437.2103).
Following stage 2 of the standard procedures outlined on page 181, fluorosilane \(321\text{Ad}\) (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); \(v_{\text{max}}\) (thin film) 3332 (broad-OH), 3071, 3027, 2974, 2930, 2831, 2359, 2338, 1716, 1683, 1652, 1558, 1540, 1455, 1260, 1197, 1119, 1074, 843 cm\(^{-1}\); \(\delta_h\) (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-HH), 4.91 (1H, dd, J 17, 2, 5-HH), 4.50 (1H, m, 1-H), 3.46 (1H, m, 3-CH(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\(_3\)); \(\delta_c\) (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-CH(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\(_3\))(CH\(_3\))), 14.8 (2-CH\(_3\)); \(m/z\) (ES\(^+\)) 257 (MNa\(^+\))\(^{\text{a}}\); HRMS (ES\(^+\)) Found MNa\(^+\), 257.1510 (C\(_{18}\)H\(_{22}\)O\(_2\)Na 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.
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%); Rf 0.3 (pet. ether/ether 9:1); \( \nu_{\text{max}} \) (thin film) 3689, 3602, 3343 (broad –OH), 2958, 2831, 2872, 2860, 2243, 1681, 1600, 1493, 1455, 1378, 1260, 1197, 1111, 1081, 1011 cm\(^{-1}\); \( \delta_{\text{H}} \) (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-HH), 4.96 (1H, dd, \( J \) 17, 2, 5-HH), 4.63 (1H, s, -OH), 4.44 (1H, d, \( J \) 8, 1-H), 3.43 (3H, s, 3-CH(OCH\(_3\))(CH\(_2\))\(_4\)CH\(_3\)), 3.37 (1H, m, 3-CH(OCH\(_3\))(CH\(_2\))\(_4\)CH\(_3\)), 2.37 (1H, m, 3-H), 2.14 (1H, m, 2-H), 1.66-1.25 (8H, m, 3-CH(OCH\(_3\))(CH\(_2\))\(_4\)CH\(_3\)), 0.87 (3H, d, \( J \) 7, 2-CH\(_3\)); \( \delta_{\text{C}} \) (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-CH(OCH\(_3\))(CH\(_2\))\(_4\)CH\(_3\)), 76.6 (1-C), 57.1 (3-CH(OCH\(_3\))(CH\(_2\))\(_4\)CH\(_3\)), 49.7 (3-C), 42.0 (2-C), 32.1, 30.4, 23.7, 22.6 (3-CH(OCH\(_3\))(CH\(_2\))\(_4\)CH\(_3\)), 15.6 (2-CH\(_3\)), 14.0 (3-CH(OCH\(_3\))(CH\(_2\))\(_4\)CH\(_3\)); \( m/z \) (ES\(^{+}\)) 313 (MNa\(^{+}\)), 603 (2MNa\(^{+}\); HRMS (ES\(^{+}\)) Found MNa\(^{+}\), 313.2138 (C\(_{19}\)H\(_{30}\)O\(_2\)Na requires 313.2138).

Further elution gave the minor diastereoisomer as a colourless oil (0.08 g, 10%).
(1SR,2SR,3RS)-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%); Rf 0.3 (pet. ether/ether 9:1) as a mixture of diastereoisomers in the ratio 4:1.5:1 by NMR; \( \nu_{\text{max}} \) (thin film) 3370 (broad-OH), 2960, 2931, 2876, 1736, 1618, 1599, 1417, 1325, 1167, 1129 cm\(^{-1}\); NMR data given for the major isomer \( \delta_H \) (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, \( J_{17}, J_{11}, J_4 \)), 5.21 (1H, dd, \( J_{10}, J_2, J_{5-H} \)), 4.86 (1H, dd, \( J_{17}, J_2, J_{5-H} \)), 4.70 (1H, d, \( J_6 \), 3-CH(OCH\(_3\))), 4.43 (1H, d, \( J_9 \), 1-H), 3.34 (1H, s, -OH), 3.27 (3H, s, 3-CH(OCH\(_3\))), 2.30 (1H, m, 3-H), 2.04 (1H, m, 2-H), 0.65 (3H, d, \( J_2 \), 2-CH\(_3\)); \( \delta_C \) (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-CCF\(_3\)), 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-CH(OCH\(_3\))), 57.2 (3-CH(OCH\(_3\))), 56.7 (3-C), 43.1 (1-C), 43.0 (2-C), 16.7 (2-CH\(_3\)); \( \delta_F \) (300 MHz, CDCl\(_3\)) -62.72 (3F, m, Ar-CCF\(_3\)); \( m/z \) (CI) 382 (MNH\(_4^+\)); HRMS (CI) Found MNH\(_4^+\), 382.1985 (C\(_{21}\)H\(_{27}\)O\(_2\)NF\(_3\) requires 382.1988).
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%); Rf 0.7 (pet. ether/ether 95:5); \( \nu_{\text{max}} \) (thin film) 2981, 2940, 1466, 1411, 1355, 1235, 1100, 967, 908, 845 cm\(^{-1}\);
\( \delta_H \) (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-HH), 4.56 (1H, s, 5-CH(OCH\(_3\))), 4.41 (1H, dd, \( J \) 17, 2, 7-HH), 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\(_3\))\(_3\)); \( \delta_C \) (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-CCF\(_3\), q, \( J \) 33), 129.1 (Ar-C), 127.8 (Ar-C), 127.1 (Ar-C), 124.7 (Ar-C), 124.3 (p-CF\(_3\), q, \( J \) 272), 119.1 (7-C), 83.1 (5-CH(OCH\(_3\))), 57.6 (5-CH(OCH\(_3\))), 57.3 (5-C), 38.8 (3-C), 35.7 (4-C), 26.2 (2-CH\(_3\)), 25.8 (2-C), 24.0 (1-C), 16.6 (4-CH\(_3\)), -2.1 (Si(CH\(_3\))\(_3\)); \( \delta_F \) (300 MHz, CDCl\(_3\)) -62.8 (-CF\(_3\)), -185.5 (Si-F); \( m/z \) (ES\(^+\)) 533 (MNa\(^+\)); HRMS (ES\(^+\)) Found MNa\(^+\), 533.2289 (C\(_27\)H\(_{38}\)OF\(_4\)Si\(_2\)Na 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.
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<sub>f</sub> 0.3 (pet. ether/ether 9:1); ν<sub>max</sub> (thin film) 3386 (broad-OH), 2960, 2931, 2872, 1736, 1600, 1517, 1416, 1364, 1325, 1256, 1228, 1128 cm<sup>-1</sup>; δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 7.58 (2H, d, <i>J</i> 8, Ar-H), 7.38 (2H, d, <i>J</i> 8, Ar-H), 6.01 (1H, ddd, <i>J</i> 17, 11, 10, 6-H), 5.09 (1H, dd, <i>J</i> 10, 2, 7-HH), 4.77 (1H, dd, <i>J</i> 17, 2, 7-HH), 4.59 (1H, d, <i>J</i> 4, 5-CH(OCH<sub>3</sub>)), 3.30 (1H, m, 3-H), 3.23 (3H, s, 5-CH(OCH<sub>3</sub>)), 3.08 (1H, d, <i>J</i> 4, -OH), 2.24 (1H, m, 5-H), 1.79-1.73 (2H, m, 4-H & 2-H), 1.00 (3H, d, <i>J</i> 7, 2-CH<sub>3</sub>), 0.85 (3H, d, <i>J</i> 7, 4-CH<sub>3</sub>), 0.80 (3H, d, <i>J</i> 7, 1-H); δ<sub>C</sub> (126 MHz, CDCl<sub>3</sub>) 145.6 (ipso-Ar-C), 134.7 (6-C), 128.3 (Ar-C), 127.9 (ipso-Ar-CF<sub>3</sub>, q, <i>J</i> 33), 125.2 (Ar-C), 124.5 (<i>p</i>-CF<sub>3</sub>, q, <i>J</i> 271), 119.1 (7-C), 86.2 (5-CH(OCH<sub>3</sub>)), 78.8 (3-C), 57.5 (5-C), 57.4 (5-CH(OCH<sub>3</sub>)), 40.5 (4-C), 29.8 (2-C), 20.8 (2-CH<sub>3</sub>), 17.2 (4-CH<sub>3</sub>), 14.0 (1-C); δ<sub>F</sub> (300 MHz, CDCl<sub>3</sub>) -62.73 (3F, m, CF<sub>3</sub>); <i>m/z</i> (ES<sup>+</sup>) 353 (MNa<sup>+</sup>); HRMS (ES<sup>+</sup>) Found MNa<sup>+</sup>, 353.1700 (C<sub>18</sub>H<sub>25</sub>O<sub>2</sub>F<sub>3</sub>Na 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.

**3RS,4SR,5RS**-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; \( \nu_{\text{max}} \) (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 \( \delta_H \) (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-HH), 4.81 (1H, dd, J 17, 2, 7-HH), 4.50 (1H, d, J 5, 5-CH(OCH\(_3\))), 3.76 (1H, d, J 6, -OH), 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\(_3\)); \( \delta_C \) (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-CH(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-CH\(_3\)), 13.7 (2-CH\(_3\)); \( m/z \) (ES\(^+\)) 363 ([\(^{79}\text{Br}\)MNa\(^+\)]; HRMS (ES\(^+\)) Found \([^{79}\text{Br}]\text{MNa}^+\), 363.0931 (C\(_{17}\)H\(_{25}\)O\(_2\)){\(^{79}\text{Br}\)Na requires 363.0930).
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%); Rf 0.3 (pet. ether/ether 9:1) as a mixture of diastereoisomers in the ratio 3:1 by NMR; \( \nu_{\text{max}} \) (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 \( \delta_{\text{H}} \) (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-HH), 4.88 (1H, dd, J 17, 2, 5-HH), 4.60 (1H, d, J 4, 3-CH(OCH\(_3\))), 4.40 (1H, d, J 9, 1-H), 3.45 (1H, s, -OH), 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\(_3\)); \( \delta_{\text{C}} \) (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-CH(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]M\(\text{Na}^{+}\)); HRMS (ES\(^{+}\)) Found [\(^{79}\)Br]M\(\text{Na}^{+}\), 397.0775 (C\(_{20}\)H\(_{23}\)O\(_{2}\)\(^{79}\)BrNa requires 397.0775).
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; Rf 0.3 (pet. ether/ether 9:1); $\nu_{\text{max}}$ (thin film) 3324 (broad-OH), 3068, 3038, 2930, 2853, 2358, 2241, 1716, 1602, 1540, 1455, 1078, 1010, 834 cm$^{-1}$; $\delta_{\text{H}}$ (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-HH), 5.10 (1H, d, $J$ 17, 5-HH), 4.32 (1H, d, $J$ 10, 1-H), 3.58 (3H, s, 3-CH(OCH$_3$)), 3.06 (1H, t, $J$ 6, 3-CH(OCH$_3$)), 2.45 (1H, m, 3-H), 2.14 (1H, m, 2-H), 1.98 (1H, d, $J$ 14, (CHH)$_3$), 1.80-1.69 (3H, m, (CH$_2$)$_3$), 1.62-1.59 (1H, d, $J$ 14, (CHH)$_3$), 1.31-1.16 (4H, m, (CH$_2$)$_3$), 1.10-1.01 (2H, m, (CH$_2$)$_3$), 0.65 (3H, d, $J$ 7, 2-CH$_3$); $\delta_{\text{C}}$ (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-CH(OCH$_3$)), 76.0 (1-C), 61.6 (3-CH(OCH$_3$)), 51.0 (3-C), 41.0 (CH$_2$CHCH$_2$), 40.3 (2-C), 30.0, 29.6, 26.5, 26.3, 26.0 ((CH$_2$)$_3$), 17.7 (2-CH$_3$); m/z (ES$^+$) 325 (MNa$^+$), 627 (2MNa$^+$); HRMS (ES$^+$) Found 325.2137 (C$_{20}$H$_{30}$O$_2$Na requires 325.2138).

Further elution yielded the title compound (0.04 g, 20%) as a mixture of diastereoisomers by NMR.
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%); Rf 0.3 (pet. ether/ether 9:1) as a mixture of diastereoisomer in the ratio 3.5:2:1 by NMR; \( \nu_{\text{max}} \) (thin film) 3474-3228 (broad-OH), 3079, 2932, 2884, 2361, 2244, 1600, 1522, 1346, 1107, 1084 cm\(^{-1}\); NMR data given for major isomer \( \delta_1 \) (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-CH(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\(_3\)); \( \delta_\text{C} \) (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-CH(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\(_4\)Na requires 364.1519).
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 BF₃•OEt₂ (0.03 ml, 0.2 mmol). The reaction mixture was then warmed to room temperature and stirred overnight. The reaction was poured into aq. NH₄Cl and extracted with DCM (3 x 10 ml). The combined organic layers were dried over MgSO₄, 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%); Rₓ 0.7 (pet. ether/ether 9:1); uy max (thin film) 2955, 2927, 2871, 2833, 2362, 2337, 1510, 1440, 1299, 1243, 1175, 1038, 910, 834 cm⁻¹; δH (500 MHz, CDCl₃) 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-CH=CH₂), 5.00 (1H, d, J 11, 4-H), 4.85 (1H, d, J 11, 2-CH=CH₂), 4.82 (1H, d, J 17, 2-CH=CH₂), 3.78 (3H, s, -OCH₃), 2.55 (2H, dd, J 14, 6, 1-H₂), 2.44 (1H, m, 2-H), 2.24 (1H, m, 3-H), 1.73 (3H, s, 6-H), 1.57 (3H, s, 5-CH₃), 0.92 (3H, d, J 7, 3-CH₃); δC (126 MHz, CDCl₃) 157.5 (CH₃O-Ar-C), 139.4 (2-CH=CH₂), 133.2 (ipso-Ar-C), 131.2 (5-C), 130.0 (Ar-C), 127.3 (4-C), 115.9 (2-CH=CH₂), 113.4 (Ar-C), 55.2 (OCH₃), 51.9 (2-C), 38.2 (1-C), 35.3 (3-C), 26.0 (6-C), 19.5 (3-CH₃), 18.1 (5-CH₃); m/z (CI) 262 (MNH₄⁺, 15%), 245 (M⁺, 65%), 161 (10%), 121 (100%); HRMS (ES⁺) Found M⁺, 245.1896 (C₁₇H₂₄O 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%); δH (500 MHz, CDCl₃) 7.65-7.56 (4H, m, Ar-H), 5.44 (1H, s, CH(OCH₃)₂), 3.33 (6H, s, CH(OCH₃)₂); δF (300 MHz, CDCl₃) -63.0 (3F, s, Ar-CF₃); 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%); δH (500 MHz, CDCl₃) 3.98 (1H, d, J 7, CH(OCH₃)₂), 3.33 (6H, s, CH(OCH₃)₂), 1.75-1.58 (6H, m, C₆H₁₁), 1.25-0.95 (5H, m, C₆H₁₁); δC (126 MHz, CDCl₃) 108.8 (CH(OCH₃)₂), 53.8 (CH(OCH₃)₂), 40.3, 28.3, 26.6, 26.0 (C₆H₁₁); 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%); $\nu_{\text{max}}$ (thin film) 1519 (NO$_2$ stretch), 1340 (NO$_2$ stretch), 1204, 1098, 1051, 985, 897, 852, 828 cm$^{-1}$; $\delta$$_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(//OCH$_3$)$_2$)), 3.34 (6H, s, CH(OC(//OCH$_3$)$_2$)); $\delta$C (126 MHz, CDCl$_3$) 147.9 (ipso-Ar-Q, 145.0 (ipso-Ar-C), 127.8 (Ar-C), 123.4 (Ar-C), 101.5 (CH(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%); $\delta$$_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$_2$CH$_2$CH$_2$-O), 4.02-3.99 (2H, m, O-CH$_2$CH$_2$CH$_2$-O), 2.22 (1H, m, O-CH$_2$CHHCH$_2$-O), 1.45 (1H, m, O-CH$_2$CHHCH$_2$-O); $\delta$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$_2$CH$_2$CH$_2$-O), 25.8 (O-CH$_2$CH$_2$CH$_2$-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%); $\delta_H$ (500 MHz, CDCl$_3$) 7.35 (2H, d, $J$ 9, Ar-H), 7.19 (2H, d, $J$ 9, Ar-H), 5.38 (1H, s, CH(OCH$_3$)$_2$), 3.33 (6H, s, CH(OCH$_3$)$_2$), 2.36 (3H, s, Ar-CH$_3$); $\delta_C$ (126 MHz, CDCl$_3$) 138.1 (ipso-Ar-Q, 135.1 (ipso-Ar-Q, 128.8 (Ar-Q, 126.5 (Ar-Q, 103.1 (CH(OCH$_3$)$_2$), 52.5 (CH(OCH$_3$)$_2$), 21.1 (Ar-CH$_3$); 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). $p$-Toluenesulfonylic 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); $\delta_H$ (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-HH), 4.22 (1H, m, 5-HH), 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$_3$); $\delta_C$ (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-CH₃), 17.5 (4-CH₃); all data agree with those reported in the literature.

6.4.2 Cyclic substrates

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

Following stage 1 of the standard procedures outlined on page 181, silacyclohex-4-ene (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; \(\nu_{max}\) (thin film) 1609, 1509, 1487, 1442, 1427, 1301, 1243, 1175, 1105, 1036, 912, 835 cm\(^{-1}\); NMR data given for major isomer 5

\[\begin{align*}
\text{H} & (500 \text{ MHz, CDCl}_3) 7.66-7.64 (2\text{H, m, Ar-H}), 7.44-7.42 (3\text{H, m, Ar-H}), 7.38 (1\text{H, m, Ar-H}), 7.25 (1\text{H, m, Ar-H}), 6.98-6.96 (3\text{H, m, Ar-H}), 6.80-6.77 (3\text{H, m, Ar-H}), 5.71 (1\text{H, m, 3-CH=CH}_2), 4.87 (1\text{H, d, J 10, 3-CH=CHH}), 4.76 (1\text{H, d, J 17, 3-CH=CHH}), 3.87 (1\text{H, d, J 11, 4-H}), 3.78 (3\text{H, s, Ar-(OCH}_3)), 3.25 (1\text{H, m, 1-H}), 2.62 (1\text{H, m, 3-H}), 2.31 (1\text{H, m, 2-H}), 1.05 (3\text{H, d, J 7, 2-CH}_3), 0.14 (9\text{H, s, Si(CH}_3)) ; \\
\delta_C & (126 \text{ MHz, CDCl}_3) 157.8 (ipso-Ar-C), 140.2 (3-CH=CH_2), 139.9 (ipso-Ar-C), 138.0 (ipso-Ar-C), 136.8 (Ar-C), 136.4 (Ar-C), 135.2 (ipso-Ar-C), 133.2 (Ar-C), 130.9 (Ar-C), 130.4 (Ar-C), 129.7 (Ar-C), 128.2 (Ar-C), 125.9 (Ar-C), 125.5 (Ar-C), 116.0 (3-CH=CH_2), 113.5 (Ar-C), 55.1 (Ar-(OCH_3)), 52.7 (3-C), 46.3 (4-C), 38.7 (1-C), 34.4 (2-C), 12.8 (2-CH_3), -1.4 (Si(CH_3)_3); \\
\delta_F & (300 \text{ MHz, CDCl}_3) -183.5 (1\text{F, d, J 7, Si-F}); \\
m/z & 
\end{align*}\]
Following stage 2 of the standard procedures outlined on page 181, fluorosilane $321\text{Ba}$ (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; $\nu_{\text{max}}$ (thin film) 3350 (broad – OH), 2961, 2907, 1611, 1511, 1451, 1301, 1261, 1245, 1177, 1115, 1026, 913 cm$^{-1}$; $\delta_H$ (500 MHz, CD$_3$COCD$_3$) 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-CH=CH$_2$), 5.14 (1H, m, 1-H), 4.91 (2H, m, 3-CH=CH$_2$), 4.41 (1H, d, $J$ 8, -OH), 3.99 (1H, d, $J$ 12, 4-H), 3.79 (3H, s, Ar-OC$_3$), 2.82 (1H, m, 3-H), 2.35 (1H, m, 2-H), 0.94 (3H, d, $J$ 9, 2-CH$_3$); $\delta_C$ (126 MHz, CD$_3$COCD$_3$) 159.7 (ipso-Ar-C), 142.0 (3-CH=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=CH$_2$), 115.1 (Ar-C), 72.8 (1-C), 56.1 (Ar-OC$_3$), 51.9 (3-C), 48.3 (4-C), 41.0 (2-C), 8.7 (2-CH$_3$); $m/z$ (ES$^+$) 317 (MNa$^+$); Elemental analysis [Found C, 81.15 %; H, 7.59 %; required for C$_{39}$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.
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; Rf 0.3 (pet. ether/ether 9:1); $\nu_{\text{max}}$ (thin film) 3428 (broad-OH), 2958, 2365, 2357, 1599, 1493, 1448, 1384, 1259, 1091, 1029, 964, 915, 795, 759, 692 cm$^{-1}$; $\delta_H$ (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=CHAr), 6.14 (1H, dd, $J_{16}$, 10, 4-CH=CHAr), 6.00 (1H, ddd, $J_{17}$, 10, 8, 3-CH=CH$_2$), 5.14 (1H, d, $J_{17}$, 3-CH=CH$_2$), 5.07 (1H, d, $J_8$, 3-CH=CH$_2$), 4.98 (1H, t, $J_5$, 1-H), 4.36 (1H, d, $J_5$, -OH), 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$_3$); $\delta_C$ (126 MHz, CDCl$_3$) 140.2 (4a-C), 139.2 (8a-C), 137.9 (Ar-C), 136.6 (Ar-C), 133.8 (3-CH=CH$_2$), 131.9 (4-CH=CHAr), 129.0 (4-CH=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=CH$_2$), 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, CDCl₃) 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-CH=CH), 6.22 (1H, dd, J 16, 5, Ar-CH=CH), 4.95 (1H, d, J 5, CH(OCH₃)₂), 3.31 (6H, s, CH(OCH₃)₂); δ_C (126 MHz, CDCl₃) 136.6 (ipso-Ar-C), 133.1 (CH(OCH₃)₂), 128.8 (Ar-C), 128.2 (Ar-C), 126.9 (Ar-C), 126.5 (Ar-CH=CH), 103.1 (Ar-CH=CH), 52.1 CH(OCH₃)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, CDCl₃) 6.94-6.92 (2H, m, Ar-H), 6.79 (1H, m Ar-H), 5.96 (2H, s, O-CH₂-O), 5.28 (1H, s, CH(OCH₃)₂), 3.31 (6H, s, CH(OCH₃)₂); all data agree with those reported in the literature.¹⁹⁵
6.5 Total Synthesis of Epipicropodophyllotoxin
Benzo[d][1,3]dioxol-5-yl(1,1,3,3,3-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; Rf 0.3 (pet. ether/ether 9:1); v_max (thin film) 3564 (broad-OH), 2952, 2898, 1499, 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, SiCH), 0.16 and 0.13 (each 9H, s, Si(CH_3)_3); δ_C (126 MHz, CDCl_3) 147.5 (Ar-Q), 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_20H_30Si_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-butyldimethylsilylchloride (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%); Rf 0.4 (pet. ether/ether 9:1); δ_H
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 Et2O and washed with water (15 ml) and brine (15 ml). The organic layer was dried over MgSO4, 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%); Rf 0.3 (pet. ether/ether 9:1); \( \nu \text{max} \) (thin film) 3070, 2957, 2930, 2856, 1427, 1112, 1003, 822, 701 cm\(^{-1}\); \( \delta \)H (500 MHz, CDCl3) 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-HH), 5.12 (1H, d, J 10, 5-HH), 4.30 (2H, d, J 4, 1-CH\(_2\)), 1.13 (9H, s, SiC(CH\(_3\))\(_3\)); \( \delta \)C (126 MHz, CDCl3) 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(CH\(_3\))\(_3\)), 19.5 (SiC(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 45 min after which time aq. NH₄Cl (10 ml) was added. The aqueous layer was separated and extracted with DCM (3 x 20 ml). The combined organic layers were dried over MgSO₄, 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%); Rf 0.3 (pet. ether/ether 9:1); νmax (thin film) 3090, 3020, 2954, 2928, 1735 (C=O), 1248, 1025, 1005, 955 cm⁻¹; δH (500 MHz, CDCl₃) 6.40-6.33 (2H, m, 3-H, 4-H), 5.78 (1H, m, 2-H), 5.24 (1H, d, J 17, 5-H), 5.17 (1H, d, J 10, 5-HH), 4.60 (2H, d, J 6, 1-CH₂), 2.08 (3H, s, -(C=O)CH₃); δC (126 MHz, CDCl₃) 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)CH₃); 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. NH₄Cl (20 ml) was added. The aqueous layer was separated and extracted with ether (3 x 10 ml). The combined organic layers were dried over MgSO₄, 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); ν_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, SiCH), 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 (-OCH_2O-), 70.6 (SiCH), 21.3 ((C=O)CH_3), -0.05 (Si(CH_3)_3) -0.2 (Si(CH_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 %]

(1SR,2SR,3RS)-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); ν_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-CHHOSi(Ph)_2Bu), 3.44 (1H, dd, J 10, 5, 3-CHHOSi(Ph)_2Bu), 2.81 (1H, m, 3-H), 2.72 (1H, d, J 9, 2-H), 1.84 (1H, m, 6-HH), 1.67 (1H, m, 6-HH), 1.01 (9H, s, SiC(CH_3)_3), -0.04 (9H, s, Si(CH_3)_3); δ_C (126
MHz, CDCl₃) 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 (-OCH₂O-), 66.6 (3-CH₂OSi(Ph)₂(Bu), 44.9 (3-C), 33.4 (2-C), 27.1 (SiC(CH₃)₃), 19.5 (SiC(CH₃)₃), 9.5 (6-C), -1.5 (Si(CH₃)₃); m/z (ES⁺) 657 (MNa⁺); HRMS (ES⁺) Found MNa⁺, 657.2655 (C₃₈H₄₆Si₃O₃Na requires 657.2647).

(1SR,2SR,3RS)-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; Rₜ 0.2 (pet. ether); NMR data given for major isomer δ_H (500 MHz, CDCl₃) 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, -OCH₂O-), 5.80 (1H, m, 4-H), 3.42 (1H, dd, J 10, 5, 3-CHHOSi(CH₃)₂(Bu)), 3.25 (1H, dd, J 10, 5, 3-CHHOSi(CH₃)₂(Bu)), 2.73 (1H, m, 3-H), 2.54 (1H, d, J 9, 2-H), 1.80 (1H, m, 6-HH), 1.64 (1H, m, 6-HH), 0.83 (9H, s, SiC(CH₃)₃), -0.05 (9H, s, SiC(CH₃)₃), -0.1 (6H, s, Si(CH₃)₂); δ_C (126 MHz, CDCl₃) 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 (-OCH₂O-), 65.6 (3-CH₂OSi(CH₃)₂(Bu), 45.0 (3-C), 33.5 (2-C), 26.1 (SiC(CH₃)₃), 18.5 (SiC(CH₃)₃), 9.4 (6-C), -1.0 (Si(CH₃)₃), -5.2 (Si(CH₃)₂); m/z (EI)
510 (M⁺, < 1 %), 437 (M⁺ -Si(CH₃)₃, 45%) 135 (90%), 73 (Si(CH₃)₃, 100%); all data agree with those reported by Pullin.¹⁸⁰

(1SR,2SR,3RS)-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-toluensulfonic acid and 0.5M aq. HCl. The solution was stirred for 1 h at room temperature then diluted with Et₂O and washed with water (5 ml). The organic layer was dried over MgSO₄, 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%); Rₚ 0.3 (pet. ether/ether 7:3); νmax (thin film) 3508-3192 (broad-OH), 3016, 2950, 2882, 1606, 1502, 1484, 1246, 1041, 835 cm⁻¹; NMR data given for major isomer δH (500 MHz, CDCl₃) 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, -OCH₂O-), 5.76 (1H, m, 4-H), 3.55 (1H, dd, J 10, 5, 3-CHHOH), 3.45 (1H, dd, J 10, 5, 3-CHHOH), 2.82 (1H, m, 3-H), 2.63 (1H, d, J 9, 2-H), 1.87 (1H, m, 6-HH), 1.68 (1H, m, 6-HH), -0.02 (9H, s, Si(CH₃)₃); δC (126 MHz, CDCl₃) 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 (-OCH₂O-), 65.6 (3-CH₂OH), 45.4 (3-C), 38.8 (2-C), 9.8 (6-C), -0.9 (Si(CH₃)₃); δSi (100 MHz, CDCl₃) -18.96, -22.60; m/z (ES⁺) 419 (MNa⁺); HRMS (ES⁺) Found MNa⁺, 419.1473 (C₂₂H₂₈Si₂O₃Na requires 419.1469).
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 45 min after which time aq. \( \text{NH}_4\text{Cl} \) (10 ml) was added. The aqueous layer was separated and extracted with DCM (3 x 20 ml). The combined organic layers were dried over \( \text{MgSO}_4 \), 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); \( v_{\text{max}} \) (thin film) 2955, 2884, 1720 (C=O), 1502, 1484, 1439, 1285, 1246, 1160, 1041, 896, 835 cm\(^{-1}\); NMR data given for major isomer:

\[
\begin{align*}
\delta_H (500 \text{ MHz, CDCl}_3) & \quad 7.30-7.25 (5H, m, \text{Ar-}H), 6.71 (1H, d, J 8, \text{Ar-}H), 6.62 (1H, s, \text{Ar-}H), 6.55 (1H, d, J 8, \text{Ar-}H), 6.11 (1H, m, 5-H), 5.94 (2H, s, -OCH_2O-), 5.71 (1H, m, 4-H), 4.00 (1H, dd, J 10, 5, 3-CHHO(C=O)CH_3), 3.81 (1H, dd, J 10, 5, 3-CHM)(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)CH_3), 1.87 (1H, m, 6-HH), 1.69 (1H, m, 6-HH), -0.01 (9H, s, Si(CH_3)_3); \\
\delta_C (126 \text{ MHz, CDCl}_3) & \quad 171.1 (3-CH_2O(C=O)CH_3), 147.8 (\text{Ar-}C), 145.0 (\text{Ar-}C), 137.1 (ipso-\text{Ar-}C), 136.4 (\text{Ar-}C), 134.3 (\text{Ar-}C), 133.9 (\text{Ar-}C), 130.8 (4-\text{C}), 129.8 (\text{Ar-}C), 127.8 (\text{Ar-}C), 127.2 (5-\text{C}), 120.7 (\text{Ar-}C), 108.4 (\text{Ar-}C), 100.8 (-OCH_2O-), 67.1 (3-CH_2O(C=O)CH_3), 41.2 (3-C), 34.4 (2-C), 20.9 (3-CH_2O(C=O)CH_3), 9.5 (6-C), -1.3 (Si(CH_3)_3); m/z (ES\(^+\)) 461 (MNa\(^+\)); HRMS (ES\(^+\)) Found MH\(^+\), 439.1758 (C_{24}H_{31}Si_2O_4 requires 439.1755).}
\]
(1SR,2SR,3RS)-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. NH₄Cl (10 ml) was added. The aqueous layer was separated and extracted with DCM (3 x 20 ml). The combined organic layers were dried over MgSO₄, 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%); Rf 0.8 (pet. ether/ether 7:3); νₚₓₚₓ (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 δₜₜ (500 MHz, CDCl₃) 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, -OCH₂O-), 5.66 (1H, m, 4-H), 4.00 (1H, dd, J 10, 5, 3-CHHO(C=O)C(CH₃)₃), 3.78 (1H, dd, J 10, 5, 3-CHHO(C=O)C(CH₃)₃), 2.92 (1H, m, 3-H), 2.53 (1H, d, J 10, 2-H), 1.86 (1H, m, 6-HH), 1.69 (1H, m, 6-HH), 1.17 (9H, s, 3-CH₂O(C=O)C(CH₃)₃), -0.01 (9H, s, Si(CH₃)₃); δC (126 MHz, CDCl₃) 178.4 (3-CH₂O(C=O)C(CH₃)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 (-OCH₂O-), 66.5 (3-CH₂O(C=O)C(CH₃)₃), 41.7 (3-C), 38.8 (3-CH₂O(C=O)C(CH₃)₃), 34.3 (2-C), 27.2 (3-CH₂O(C=O)C(CH₃)₃), 9.5 (6-C), -1.3 (Si(CH₃)₃); m/z (ES⁺) 503 (MNa⁺); HRMS (ES⁺) Found MH⁺, 481.2228 (C₂₇H₃₇Si₂O₄ requires 481.2225).
(3RS,4SR,5SR)-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%); Rf 0.2 (pet. ether/ether 1:1); m.p. 140-142 °C; νmax (thin film) 3500-3184 (broad-OH), 3006, 2984, 2884, 2361, 2245, 1592, 1504, 1488, 1418, 1357, 1247, 1129, 1041, 1001 cm⁻¹; δH (500 MHz, CDCl₃) 6.89 (1H, s, Ar-H), 6.77 (2H, s, Ar-H), 6.48 (2H, s, Ar-H), 5.97 (2H, s, -OCH₂O-), 5.69 (1H, ddd, J 17, 10, 10, 4-CH=CH₂), 5.11-5.06 (3H, m, 4-CH=CH₂, 5-H), 4.47 (1H, dd, J 10, 2, 3-CH(OH)Ar), 3.84 (6H, s, Ar-OCH₃), 3.82 (3H, s, Ar-OCH₃), 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(OH)Ar); δC (126 MHz, CDCl₃) 153.0 (q-Ar-C), 135.1 (q-Ar-C), 134.6 (Ar-C), 133.4 (4-CH=CH₂), 128.2 (q-Ar-C), 120.0 (Ar-C), 119.1 (4-CH=CH₂), 108.5 (Ar-C), 106.9 (Ar-C), 103.1 (Ar-C), 101.4 (-OCH₂O-), 84.7 (5-C), 73.7 (3-CH(OH)Ar), 68.5 (2-C), 61.1 (Ar-OCH₃), 56.3 (Ar-OCH₃), 52.5 (3-C), 51.8 (4-C); m/z (ES⁺) 437 (MNa⁺), 851 (2MNa⁺); HRMS (ES⁺) Found MNa⁺, 437.1573 (C₂₃H₂₆O₇Na requires 437.1571).
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%); Rf 0.1 (pet.ether/ether 7:3) as a mixture of diastereoisomers in the ratio 5:1 by NMR; \( \nu_{\text{max}} \) (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 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, -OCHHO-), 5.85 (1H, d, J 1.2, -OCHHO-), 5.77 (1H, ddd, J 17, 10, 10, 3-CH=CH\(_2\)), 4.98 (1H, d, J 10, 3-CH=CH\(_2\)), 4.90 (1H, d, J 17, 3-CH=CH\(_2\)), 4.24 (1H, dd, J 11, 6, 2-CHHOAc), 4.09 (1H, dd, J 11, 6, 2-CHHOAc), 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\(_2\)O(C=O)CH\(_3\)), 0.18 (9H, s, Si(CH\(_3\))\(_3\)); \( \delta_C \) (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-CH=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=CH\(_2\)), 110.2 (Ar-C), 108.2 (Ar-C), 106.0 (Ar-C), 100.7 (-OCH\(_3\)O-), 64.4 (2-CH\(_2\)OAc), 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\(_2\)O(C=O)CH\(_3\)), -1.7 (Si(CH\(_3\))\(_3\)); \( \delta_Si \) (300 MHz, CDCl\(_3\)) -182.5 (1F, d, J 8, Si-F); \( m/z \) (ES\(^+\)) 659
(MNa\(^+\)), 1295 (2MNa\(^+\)); HRMS (ES\(^+\)) Found MH\(^+\), 637.2455 (C\(_{34}\)H\(_{42}\)O\(_7\)Si\(_2\) requires 637.2448).

\((1RS,2SR,3RS,4SR)-2-(\text{Hydroxymethyl})-6,7\text{-methyleneedioxy-4-(3,4,5-\text{trimethoxyphenyl})-3-vinyl-1,2,3,4-tetrahydronaphthalen-1-ol, 487}\)

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; \(\delta_H\) (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-CH=CH\(_2\)), 5.95 (1H, d, J 1.4, -OCH\(_2\)OH), 5.94 (1H, d, J 1.4, -OCH\(_2\)OH), 5.09 (1H, d, J 18, 3-CH=CHH), 5.05 (1H, d, J 7, 3-CH=CHH), 5.02 (1H, m, 1-H), 3.97 (1H, m, 2-CH\(_2\)OH), 3.90-3.89 (2H, m, 2-CH\(_2\)OH, 4-H), 3.83 (3H, s, Ar-OC\(_3\)H), 3.76 (6H, s, Ar-OC\(_3\)H), 2.89 (1H, m, 1-OH), 2.70 (1H, m, 3-H), 2.47 (1H, m, 2-H); \(\delta_C\) (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-CH=CH\(_2\)), 136.5 (q-Ar-C), 131.9 (q-Ar-C), 130.2 (q-Ar-C), 116.3 (3-CH=CH\(_2\)), 109.4 (Ar-C), 107.7 (Ar-C), 105.9 (Ar-C), 101.0 (-OCH\(_2\)OH-), 70.4 (1-C), 62.0 (2-CH\(_2\)OH), 60.8 (Ar-OC\(_3\)H), 56.1 (Ar-OC\(_3\)H), 49.5 (4-C), 47.0 (3-C), 42.0 (2-C); all data agree with those reported by Pullin.\(^{180}\)
(1SR,2SR,3RS,4SR)-2-(Hydroxymethyl)-6,7-methylenedioxy-1-methoxy-4-(3,4,5-
trimethoxyphenyl)-3-vinyl-1,2,3,4-tetrahydronaphthalene, 500

A solution of naphthalediol 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 H2O and extracted with Et2O (3 x 10
ml). The combined organic layers were dried over MgSO4, 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%); Rf 0.8 (ether);
υmax (thin film) 3420 (broad-OH), 3082, 3010, 2935, 2836, 1718, 1590, 1504, 1483,
1419, 1329, 1234, 1129, 1041 cm⁻¹; δH (500 MHz, CDCl3) 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, -OCH3/O-), 5.93 (1H, d, J 1.5, -
OCH3O-), 5.80 (1H, ddd, J 17, 10, 8, 3-CH=CH2), 5.11 (1H, d, J 17, 3-CH=CHH),
5.06 (1H, d, J 10, 3-CH=CHH), 4.48 (1H, d, J 7, 1-H), 3.82 (3H, s, Ar-OCH3), 3.78-
3.73 (9H, s, 2-CH3OH, 4-H, Ar-OCH3), 3.64 (1H, m, 2-CH2OH), 3.40 (3H, s, 1-
OCH3), 2.97 (1H, m, 3-H), 2.44 (1H, m, 2-H); δC (126 MHz, CDCl3) 153.2 (q-Ar-C),
147.9 (q-Ar-C), 146.9 (q-Ar-C), 141.1 (ipso-Ar-C), 138.7 (3-CH=CH2), 136.7 (q-Ar-C),
132.6 (q-Ar-C), 128.3 (q-Ar-C), 117.2 (3-CH=CH2), 110.1 (Ar-C), 108.6 (Ar-C), 106.4
(Ar-C), 101.3 (-OCH2O-), 78.6 (1-C), 63.1 (2-CH2OH), 61.1 (1-OCH3), 56.3 (Ar-
OCH3), 54.5 (Ar-OCH3), 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 (C24H28O7Na requires 451.1727).
(1SR,2SR,3RS,4SR)-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:H2O (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 H2O and extracted with DCM (3 x 10 ml). The combined
organic layers were dried over MgSO4, filtered, concentrated and dried in vacuo. Flash
column chromatography (ether) afforded the title compound as a light brown oil (0.014
g, 58%); Rf 0.3 (ether) as a mixture of diastereoisomers in the ratio 3:1 by NMR; \(v_{\text{max}}\)
(thin film) 3155 (broad-OH), 2982, 2901, 1793, 1591, 1482, 1382, 1238, 1130, 913, 731
\(\text{cm}^{-1}\); NMR data given for major isomer \(\delta\) (500 MHz, CDCl3) 6.74 (1H, s, Ar-H), 6.48
(2H, s, Ar-H), 6.31 (1H, s, Ar-H), 5.91 (1H, s, -OCHHO-), 5.89 (1H, s, -OCHHO-),
5.19 (1H, m, 2-CHHO), 4.97 (1H, m, 2-CHHO), 4.70 (1H, s, 3-CHOH), 4.24-4.15 (2H,
m, 1-H, 4-H), 3.88 (3H, s, Ar-OCH3), 3.83 (6H, s, Ar-OCH3), 3.03 (1H, s, 3-CHOH),
2.87 (1H, m, 2-H), 2.73 (1H, m, 3-H); \(\delta\)C (126 MHz, CDCl3) 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 (-OCH2O-), 97.4 (2-CH2O), 70.3
(3-CHOH), 67.2 (1-C), 61.2 (Ar-OCH3), 56.4 (Ar-OCH3), 50.1 (2-C), 43.7 (4-C), 42.0
(3-C); \(m/z\) (ES+) 855 (2MNa+); HRMS (ES+) Found 2MNa+, 855.2845 (C44H48O16Na
requires 855.2835).
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 Na₂S₂O₃ and extracted with DCM (3 x 10 ml). The combined organic layers were dried over MgSO₄, 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%); Rf 0.3 (ether); m.p. 185-188 °C (lit. m.p. 190-192 °C); υmax (thin film) 3155 (broad-OH), 2903, 1765 (C=O), 1483, 1383, 1246, 1130, 1095, 927, 732 cm⁻¹; δH (500 MHz, CDCl₃) 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/HO-), 5.95 (1H, d, J 1.0, -OCH/HO-), 4.82 (1H, m, 1-H), 4.45 (1H, d, J 4, 4-H), 4.35 (2H, m, 2-CH₂O), 3.82 (3H, s, Ar-OC/H), 3.78 (6H, s, Ar-OC/H), 3.44 (1H, dd, J 10, 4, 3-H), 3.16 (1H, m, 2-H), 2.08 (1H, d, J 5, 1-OH); δC (126 MHz, CDCl₃) 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 (-OCH₂O-), 68.1 (2-CH₂O), 67.9 (1-C), 60.9 (Ar-OC/H), 56.2 (Ar-OC/H), 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.
(±)-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\text{f} 0.5 (ether); m.p. 146-148 °C (lit. m.p. 152-158 °C)\textsuperscript{174}; \nu_{\text{max}} \text{ (thin film)} 2982, 1780 (C=O), 1722 (C=O), 1479, 1383, 1343, 1257, 1161, 1130, 1097, 899, 751 cm\textsuperscript{-1}; \delta_H (500 MHz, CDCl\textsubscript{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\textsubscript{2}HO-), 6.04 (1H, d, J 1.2, -OCH\textsubscript{2}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-OC\textsubscript{3}H\textsubscript{3}), 3.75 (6H, s, Ar-OC\textsubscript{3}H\textsubscript{3}), 3.31 (2H, m, 2-CH\textsubscript{2}O); \delta_C (126 MHz, CDCl\textsubscript{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\textsubscript{2}O-), 70.8 (3-C), 66.1 (2-CH\textsubscript{2}O), 61.1 (Ar-OC\textsubscript{3}H\textsubscript{3}), 56.4 (Ar-OC\textsubscript{3}H\textsubscript{3}), 46.9 (4-C), 43.6 (2-C); m/z (ES\textsuperscript{+}) 413 (MH\textsuperscript{+}), 454 (MMeCN\textsuperscript{+}); all data agree with those reported in the literature.\textsuperscript{177,197}

(1\text{RS},2\text{SR},3\text{RS},4\text{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 10 min after which time aq. NH₄Cl (10 ml) was added. The aqueous layer was separated and extracted with DCM (3 x 20 ml). The combined organic layers were dried over MgSO₄, 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%); Rf 0.5 (pet. ether/ether 2:3); \( \nu_{\text{max}} \) (thin film) 3074, 2960, 2890, 1731 (C=O), 1590, 1504, 1485, 1418, 1369, 1239, 1129, 1041 cm\(^{-1} \); \( \delta_H \) (500 MHz, CDCl₃) 6.88 (1H, s, Ar-H), 6.41 (1H, s, Ar-H), 6.24 (1H, d, \( J \approx 5 \), 1-H), 6.13 (2H, s, Ar-H), 6.00 (1H, m, 3-CH=CH₂), 5.95 (1H, d, \( J \approx 1.3 \), -OCH₃O-), 5.93 (1H, d, \( J \approx 1.3 \), -OCH₃O-), 5.07 (2H, m, 3-CH=CH₂), 4.20 (1H, dd, \( J \approx 11, 9 \), 2-CH₂OAc), 4.00 (1H, d, \( J \approx 4 \), 4-H), 3.91 (1H, d, \( J \approx 11, 9 \), 2-CH₂OAc), 3.82 (3H, s, Ar-OCH₃), 3.76 (6H, s, Ar-OCH₃), 2.66-2.55 (2H, m, 2-H, 3-H), 2.08 (3H, s, 2-CH₂O(C=O)CH₃), 2.00 (3H, s, 1-O(C=O)CH₃); \( \delta_C \) (126 MHz, CDCl₃) 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-CH=CH₂), 136.9 (q-Ar-C), 130.9 (q-Ar-C), 128.2 (q-Ar-C), 116.5 (3-CH=CH₂), 110.1 (Ar-C), 108.5 (Ar-C), 106.1 (Ar-C), 101.6 (-OCH₃O-), 68.4 (1-C), 63.2 (2-CH₂O), 61.1 (Ar-OCH₃), 56.4 (Ar-OCH₃), 50.7 (4-C), 47.5 (3-C), 36.2 (2-C), 21.4 (2-CH₂O(C=O)CH₃), 21.1 (1-O(C=O)CH₃); m/z (ES⁺) 521 (MNa⁺), 1018 (2MNa⁺); HRMS (ES⁺) Found MNa⁺, 521.1785 (C₂₇H₃₀O₉Na requires 521.1782).
(1RS,2SR,3RS,4SR)-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:H₂O (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 H₂O and extracted with DCM (3 x 10 ml). The combined organic layers were dried over MgSO₄, 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%); Rf 0.3 (pet. ether/ether 3:7); νmax (thin film) 2962, 2938, 1736 (C=O), 1591 (C=O), 1505, 1485, 1419, 1371, 1238, 1130, 1041 cm⁻¹; δH (500 MHz, CDCl₃) 9.83 (1H, s, 3-CM)), 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, -OCHHO-), 5.95 (1H, d, J 1.2, -OCHHO-), 4.64 (1H, d, J 5, 4-H), 4.41 (1H, d, J 11, 8, 2-CHHOAc), 4.10 (1H, d, J 11, 8, 2-CHHOAc), 3.82 (3H, s, Ar-OCH₃), 3.77 (6H, s, Ar-OCH₃), 2.92 (1H, m, 2-H), 2.79 (1H, m, 3-H), 2.08 (3H, s, 2-CH₂O(C=O)CH₃), 2.03 (3H, s, 1-O(C=O)CH₃); δC (126 MHz, CDCl₃) 200.8 (3-CHO), 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 (ips-o-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 (-OCH₂O-), 68.7 (1-C), 61.8 (2-CH₂O), 61.0 (Ar-OCH₃), 56.5 (Ar-OCH₃), 54.7 (3-C), 43.2 (4-C), 36.3 (2-C), 21.3 (2-CH₂O(C=O)CH₃), 21.0 (1-O(C=O)CH₃); m/z (ES⁺) 523 (MNa⁺); HRMS (ES⁺) Found MNa⁺, 523.1580 (C₂₆H₂₈O₁₀Na requires 523.1575).
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. NH₄Cl (10 ml) was added. The aqueous layer was separated and extracted with DCM (3 x 20 ml). The combined organic layers were dried over MgSO₄, filtered, concentrated and dried in vacuo. Flash chromatography (ether) afforded the title compound as a cream gum (0.017 g, 80%); Rₓ 0.4 (ether); νₓ max (thin film) 2966, 2934, 2246, 1748 (C=O), 1591, 1505, 1485, 1464, 1421, 1242, 1129, 1041 cm⁻¹; δH (500 MHz, CDCl₃) 7.06 (1H, s, Ar-H), 6.36 (1H, s, Ar-H), 6.16 (2H, s, Ar-H), 5.97 (1H, s, -OCH₂O-), 5.95 (1H, s, -OCH₂O-), 5.78 (1H, m, 3-CH=CH₂), 5.65 (1H, d, J 5, 1-H), 5.14 (2H, m, 3-CH=CH₂), 4.55 (1H, dd, J 11, 5, 2-CH₂O), 4.33 (1H, d, J 11, 5, 2-CH₂O), 3.84-3.82 (1H, m, 4-H), 3.82 (3H, s, Ar-OCH₃), 3.77 (6H, s, Ar-OCH₃), 2.82 (1H, m, 3-H), 2.77 (1H, m, 2-H); δC (126 MHz, CDCl₃) 153.3 (q-Ar-C), 148.6 (q-Ar-C), 148.4 (C=O), 147.4 (q-Ar-C), 139.0 (3-CH=CH₂), 136.9 (q-Ar-C), 136.9 (q-Ar-C), 130.5 (q-Ar-C), 125.5 (q-Ar-C), 118.1 (3-CH=CH₂), 109.5 (Ar-C), 107.7 (Ar-C), 105.9 (Ar-C), 101.4 (-OCH₂O-), 74.3 (1-C), 67.4 (2-CH₂O), 60.8 (Ar-OCH₃), 56.2 (Ar-OCH₃), 48.8 (4-C), 46.8 (3-C), 32.5 (2-C); m/z (ES⁺) 504 (MMeCNa⁺), 903 (2MNa⁺); HRMS (ES⁺) Found MMeCNa⁺, 504.1632 (C₂₆H₂₇O₈NNa requires 504.1629).
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 NH₄Cl (10 ml) and brine (10 ml). The organic layer was separated, dried over MgSO₄, 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%); Rf 0.4 (pet. ether/ether 1:1); mp 68-70 °C; v 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, CDCl₃) 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, -OCHHO-), 5.95 (1H, d, J 1.3, -OCHHO-), 5.74 (1H, ddd, J 17, 9, 7, 3-CH=CH₂), 4.94-4.90 (3H, m, 3-CH=CH₂, 1-H), 3.94 (2H, m, 2-CH₂O), 3.81 (3H, s, Ar-OCH₃), 3.73 (7H, s, Ar-OCH₃, 4-H), 3.53 (1H, d, J 8, 1-OH), 2.75 (1H, m, 3-H), 2.51 (1H, m, 2-H) 0.99 (9H, s, SiC(CH₃)₃); δ C (126 MHz, CDCl₃) 153.2 (q-Ar-C), 147.3 (q-Ar-C), 146.9 (q-Ar-C), 141.1 (ipso-Ar-C), 139.1 (3-CH=CH₂), 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=CH₂), 109.5 (Ar-C), 107.8 (Ar-C), 106.2 (Ar-C), 106.1 (Ar-C), 101.2 (-OCH₂O-), 71.5 (1-C), 62.9 (2-CH₂O), 61.1 (Ar-OCH₃), 56.3 (Ar-OCH₃), 49.5 (4-C), 47.1 (3-C), 42.7 (2-C) 26.9 (SiC(CH₃)₃), 19.2 (SiC(CH₃)₃); m/z (ES⁺) 675 (MNa⁺), 1327 (2MNa⁺); HRMS (ES⁺) Found 2MNa⁺, 1327.5645 (C₇₈H₈₈Si₂O₁₄Na requires 1327.5605).
(1RS,8SR,9RS,10RS/8R,12SR)-12-((tert-butylidiphenylsilyloxy)methyl)-4,5-methylenedioxo-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:H₂O (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 H₂O and extracted with DCM (3 x 10 ml). The combined organic layers were dried over MgSO₄, filtered, concentrated and dried \textit{in vacuo}. Flash column chromatography (pet. ether/ether [1:1], [3:7]) afforded the title compound as a colourless gum (0.03 g, 40%); Rₚ 0.5 (pet. ether/ether 3:7) as a mixture of diastereoisomers in the ratio 2:1 by NMR; \( \nu_{\text{max}} \) (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 5

\[
\begin{align*}
\delta_H & (500 \text{ MHz, CDCl}_3) \quad 7.61-7.27 (12\text{H}, \text{Ar-H}), \\
& 6.66 (1\text{H}, \text{s, Ar-H}), \\
& 6.50 (1\text{H}, \text{s, Ar-H}), \\
& 6.25 (2\text{H}, \text{s, Ar-H}), \\
& 5.91 (2\text{H}, \text{s, -OCH}_2\text{O-}), \\
& 5.33 (1\text{H}, \text{d, J 5, 1-H}), \\
& 4.76 (1\text{H}, \text{s, 8-H}), \\
& 4.31 (1\text{H}, \text{s, 10-H}), \\
& 3.94 (1\text{H}, \text{dd, J 10, 7, 12-CHHO}), \\
& 3.84 (3\text{H}, \text{s, -OCH}_3), \\
& 3.74 (7\text{H}, \text{s, -OCH}_3, 12-\text{CHHO}), \\
& 2.70 (1\text{H}, \text{m, 9-H}), \\
& 2.51 (1\text{H}, \text{t, J 10, 12-H}), \\
& 0.98 (9\text{H}, \text{s, SiC(\text{CH}_3)}_3); \\
\delta_C & (126 \text{ MHz, CDCl}_3) \quad 153.4 (q-\text{Ar-C}), 147.9 (q-\text{Ar-C}), 146.5 (q-\text{Ar-C}), 140.6 (q-\text{Ar-C}), 135.6 (q-\text{Ar-C}), 135.0 (q-\text{Ar-C}), 133.4 (q-\text{Ar-C}), 133.1 (q-\text{Ar-C}), 129.9 (Ar-C), 128.3 (q-\text{Ar-C}), 127.9 (Ar-C), 111.2 (Ar-C), 107.5 (Ar-C), 106.2 (Ar-C), 102.7 (1-C), 101.3 (OCH_2O), 81.0 (8-C), 64.1 (12-CH_2O), 61.1 (OCH_3), 56.8 (OCH_3), 53.2 (9-C), 49.9 (10-C), 42.7 (12-C), 26.9 (SiC(\text{CH}_3)_3), 19.4 (SiC(\text{CH}_3)_3); \\
\end{align*}
\]
m/z (ES⁺) 1331 (2MNa⁺); HRMS (ES⁺) Found 2MNa⁺, 1331.5228 (C₇₆H₈₄O₁₆Si₂Na 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 NH₄Cl and extracted with ether (3 x 15 ml). The combined organic layers were dried over MgSO₄, 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; δₜ (500 MHz, CDCl₃) 5.94-5.76 (2H, m, CH₂CH=CH₂), 5.04-4.84 (4H, m, CH₂CH=CH₂), 2.11 (2H, m, CH₂CH=CH₂), 1.56-1.54 (2H, d, J 8, CH₂CH=CH₂), 0.67-0.64 (2H, m, CH₂CH=CH₂), 0.02 (6H, s, Si(CH₃)₂); δc (126 MHz, CDCl₃) 141.8, 135.3 (CH₂CH=CH₂), 113.03, 112.99 (CH₂CH=CH₂), 28.1, 23.5, 14.2 (CH₂CH=CH₂), -3.5 (Si(CH₃)₂); m/z (EI) 154 (M⁺, 25%), 139 (M⁺ -CH₃, 25%), 125 (M⁺ -CH₂CH₃, 100%); all data agree with those reported in the literature.¹⁸³
1,1-Dimethyl-1,2,3,6-tetrahydrosilane, 194

![Structure of 1,1-Dimethyl-1,2,3,6-tetrahydrosilane]

A solution of allylbutenylsilane 518 (2.5 g, 16 mmol) in DCM (32 ml, 0.5M) was treated with Grubbs 1\textsuperscript{st} 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\textsubscript{H} (500 MHz, CDCl\textsubscript{3}) 5.74 (1H, m, 4-H), 5.63 (1H, m, 5-H), 2.22 (2H, m, 3-H\textsubscript{2}), 1.20 (2H, m, 6-H\textsubscript{2}), 0.66 (2H, t, J 7, 2-H\textsubscript{2}), 0.07 (3H, s, Si(CH\textsubscript{3})\textsubscript{2}), 0.05 (3H, s, Si(CH\textsubscript{3})\textsubscript{2}); δ\textsubscript{C} (126 MHz, CDCl\textsubscript{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\textsubscript{3})\textsubscript{2}); m/z (El) 126 (M\textsuperscript{+}, 45\%), 111 (M\textsuperscript{+} -CH\textsubscript{3}, 50\%); all data agree with those reported in the literature.\textsuperscript{56}

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

![Structure of (3RS/RS)-3-((RS/RS)Methoxy(phenyl)methyl)pent-4-en-1-ol]

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\textsubscript{f} 0.3 (pet. ether/ether 1:1) as a mixture of diastereoisomers in the ratio 1:1 by NMR; δ\textsubscript{max} (thin film) 3516-3186 (broad-OH), 2942, 2880, 2820, 1458, 1100, 1068, 990, 914 cm\textsuperscript{-1}; NMR data given for one isomer δ\textsubscript{H} (500 MHz, CDCl\textsubscript{3}) 7.37-7.33 (5H, m, Ar-H\textsubscript{5}), 5.69 (1H, ddd, J 16, 10, 9, 4-H\textsubscript{1}), 5.11 (1H, dd, J 10, 2, 5-HH\textsubscript{1}), 5.02 (1H, dd, J 16, 2, 5-HH\textsubscript{2}), 4.11 (1H, d, J 6, 3-CH(OCH\textsubscript{3})), 3.69 (2H, m, 1-H\textsubscript{2}), 3.23 (3H, s, 3-
CH(OCH₃)), 2.55 (1H, m, 3-H), 1.64 (1H, m, 2-HH), 1.48 (1H, m, 2-HH); δC (126 MHz, CDCl₃) 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-CH(OCH₃)), 61.4 (1-C), 57.3 (3-CH(OCH₃)), 48.5 (3-C), 33.8 (2-C); m/z (ES⁺) 207 (MH⁺); HRMS (ES⁺) Found MH⁺, 207.1379 (C₁₃H₁₉O₂ 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%); Rf 0.8 (pentane/ether 4:1); δH (300 MHz, CDCl₃) 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-HH), 4.99 (1H, d, J 10, 6-HH), 4.14 (2H, m, OCH₂CH₃), 2.40 (4H, m, 1-H2, 2-H2), 1.25 (3H, t, J 7, OCH₂CH₃); δC (126 MHz, CDCl₃) 172.9 (C=O), 136.9 (5-C), 132.7 (4-C), 131.9 (3-C), 115.7 (6-C), 60.4 (OCH₂CH₃), 33.8 (2-C), 27.8 (1-C), 14.2 (OCH₂CH₃); all data agree with those reported in the literature.¹⁸⁴
Hepta-4,6-dienol, 543

![Hepta-4,6-dienol structure]

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 MgSO₄, 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%); Rf 0.7 (pentane/ether 1:2); δ_H (300 MHz, CDCl₃) 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-HH), 4.99 (1H, d, J 10, 7-HH), 3.68 (2H, t, J 7, 1-H₂), 2.20 (2H, m, 3-H₂), 1.70 (2H, m, 2-H₂); δ_C (126 MHz, CDCl₃) 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

![1-Iodohepta-4,6-diene structure]

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. Na₂S₂O₃ and aq. CuSO₄. The organic layers were dried over MgSO₄, filtered, concentrated and dried in...
Flash chromatography (pentane/ether 4:1) afforded the title compound as a colourless oil (1.57 g, 79%); Rf 0.8 (pentane/ether 4:1); δH (300 MHz, CDCl₃) 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), 5.00 (1H, d, J 10, 7-HH), 3.19 (2H, t, J 7, 1-H), 2.19 (2H, m, 3-H), 1.93 (2H, m, 2-H); δC (126 MHz, CDCl₃) 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**

![Hepta-4,6-dienal](image)

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 MgSO₄, 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%); Rf 0.4 (pentane/ether 4:1); δH (300 MHz, CDCl₃) 9.80 (1H, t, J 2, CHO), 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-HH), 5.02 (1H, d, J 10, 6-HH), 2.57 (2H, m, 1-H), 2.48 (2H, m, 2-H); δC (126 MHz, CDCl₃) 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

![structure](image_url)

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$_2$SO$_4$ 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); $\delta$$_H$ (300 MHz, CDCl$_3$) 1.02 (9H, s, C(C$_3$H$_3$)$_3$), 0.23 (27H, s, (Si(C$_3$H$_3$)$_3$)$_3$); $\delta$$_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

![structure](image_url)

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 MgSO₄, 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%); Rf 0.4 (pentane/ether 9:1); \( \nu_{\text{max}} \) (thin film) 2964, 2900, 1626 (C=O), 1476, 1448, 1364, 1238, 1056, 1000, 934, 830 cm⁻¹; \( \delta_H \) (300 MHz, CDCl₃) 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-HH), 4.97 (1H, d, J 11, 7-HH), 2.15 (2H, q, J 7, 2-H₂), 1.48 (2H, m, 3-H₂), 1.33 (2H, s, 1-H₂), 1.03 (9H, s, -C(CH₃)₃), 0.17 (18H, s, (Si(CH₃)₃)₂); \( \delta_C \) (126 MHz, CDCl₃) 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(CH₃)₃), 12.4 (C(CH₃)₃), 0.5 (Si(CH₃)₃)₂; m/z (EI) 354 (M⁺, 10%), 339 (M⁺ -CH₃, 70%), 281 (M⁺ -SiMe₃, 100%).

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

![Chemical structure](attachment:structure.png)

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-dienysilyl 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 MgSO₄, 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%); Rf 0.8 (pentane/ether 98:2); \( \nu_{\text{max}} \) (thin film) 3068 (broad-OH), 2954, 2900, 1366, 1248, 1060, 1006, 966, 900, 832 cm⁻¹; \( \delta_H \) (300 MHz, CDCl₃) 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-HH), 4.96
(1H, d, J 10, 7-HH), 3.54 (1H, d, J 8, CH(OH)), 2.12 (2H, q, J 7, 2-H2), 1.51 (2H, m, 3-H2), 1.30 (2H, m, 1-H2), 1.19 (1H, d, J 8, CH(OH)), 0.97 (9H, s, -C(CH3)3), 0.18 (18H, s, (Si(CH3)3)2); δC (126 MHz, CDCl3) 137.3 (6-Q), 135.0 (4-Q), 131.3 (5-Q), 114.7 (7-Q), 76.1 (CH(OH)), 37.1 (3-C), 36.3 (1-C), 27.7 (C(CH3)3), 26.8 (2-C), 11.7 (C(CH3)3), 0.7 ((Si(CH3)3)2), 0.6 ((Si(CH3)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. NH4Cl 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 MgSO4, 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%); Rf 0.5 (pet. ether/ether 9:1); v max (thin film) 3624 (broad-OH), 2948, 2902, 1440, 1400, 1242, 1008, 950, 834, 822 cm⁻¹; δH (300 MHz, CDCl3) 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-HH), 4.97 (1H, d, J 11, 7-HH), 3.89 (1H, d, J 10, 1-H), 2.40 (1H, m, 3-HH), 2.16 (1H, m, 3-HH), 1.81 (1H, m, 2-HH), 1.68 (1H, m, 2-HH),

233
0.21 (27H, s, (Si(CH₃)₃)₃); δ₁ (126 MHz, CDCl₃) 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(CH₃)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

\[
\begin{align*}
\text{n-Butyllithium (34 ml, 1.6 M, 54 mmol) was added to a stirred solution of piperylene (5 ml, 54 mmol) in hexanes (40 ml). The resultant mixture was added to a stirred slurry of potassium-tert-butoxide (6.1 g, 54 mmol) in hexanes (38 ml) at 0 °C. After 20 mins the reaction mixture was cooled to -78 °C and treated with a solution of dimethyl(phenyl)chlorosilane (10 ml, 60 mmol) in diethyl ether (18 ml) and stirred for a further 20 mins. Water (100 ml) was added and the biphasic mixture stirred vigorously whilst warming to room temperature. The aqueous layer was separated and extracted with diethyl ether. The combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo to afford a yellow oil. Flash column chromatography and distillation of the residue afforded the title compound as colourless oil (3.3 g, 30 %); b.p. 90-100°C/0.8 mbar; ν_max (thin film) 2954, 1641, 1427, 1249, 1147, 1114, 1000, 826, 786, 697 cm⁻¹; δ₁ (400 MHz, CDCl₃) 7.39-7.35 (5H, m, Ar-H), 6.34 (1H, ddd, J 15, 10, 9, 4-H), 5.96 (1H, dd, J 16, 10, 3-H), 5.71 (1H, m, 2-H), 5.00 (1H, d, J 17, 5-HH), 4.88 (1H, d, J 9, 5-HH), 1.78 (2H, d, J 8, 1-H₂), 0.29 (6H, s, Si(CH₃)₂Ph); δ₁ (126 MHz, CDCl₃) 139.0 (ipso-Ar-C), 138.3 (4-C), 134.3 (Ar-C), 131.8 (2-C), 131.5 (3-C), 129.9 (Ar-C), 128.6 (Ar-C), 113.9 (5-C), 23.4 (1-C), -2.6 (Si(CH₃)₂Ph); δ₁ (100 MHz, CDCl₃) -3.8; m/z (EI) 202 (M⁺).}
\]
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; Rf 0.5 (pet. ether/ether 9:1); v<sub>max</sub> (thin film) 3008, 2947, 2886, 1486, 1440, 1246, 1108, 1036, 827, 730, 699 cm<sup>-1</sup>; NMR data given for one isomer δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 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, -OCH<sub>2</sub>O-, 5-H), 5.60 (1H, m, 4-H), 4.92 (1H, dd, J 10, 5, 3-CHHSi(CH<sub>3</sub>)<sub>2</sub>Ph), 4.20 (1H, dd, J 10, 5, 3-CHHSi(CH<sub>3</sub>)<sub>2</sub>Ph), 2.71 (1H, m, 3-H), 2.34 (1H, d, J 10, 2-H), 1.81 (1H, m, 6-HH), 1.62 (1H, m, 6-HH), 0.25 & 0.22 (each 6H, s, Si(CH<sub>3</sub>)<sub>2</sub>), -0.03 (9H, s, Si(CH<sub>3</sub>)<sub>3</sub>); δ<sub>C</sub> (126 MHz, CDCl<sub>3</sub>) 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 (-OCH<sub>2</sub>O-), 68.8 (3-CH<sub>2</sub>Si(CH<sub>3</sub>)<sub>2</sub>Ph), 45.0 (3-C), 33.5 (2-C), 26.1 (SiC(CH<sub>3</sub>)<sub>3</sub>), 18.5 (SiC(CH<sub>3</sub>)<sub>3</sub>), 9.4 (6-C), -1.2 (Si(CH<sub>3</sub>)<sub>2</sub>), -1.6 (Si(CH<sub>3</sub>)<sub>2</sub>), -2.1 (Si(CH<sub>3</sub>)<sub>2</sub>); δ<sub>Si</sub> (100 MHz, CDCl<sub>3</sub>) -19.0, -20.94, -25.0; m/z (EI) 514 (M<sup>+</sup>, 2%), 312 (50%) 135 (100%), 73 (Si(CH<sub>3</sub>)<sub>3</sub>, 32%); HRMS (Cl) Found MNH<sub>4</sub><sup>+</sup>, 532.2516 (C<sub>30</sub>H<sub>42</sub>Si<sub>3</sub>O<sub>2</sub>N requires 532.2518).
1,1,1-Trimethyl-2-phenyl-2-(phenyl-trimethylsilyloxy-methyl)-2-trimethylsilylmethyl-disilane, 570

\[
\begin{array}{c}
\text{Me}_3\text{Si} \\
\text{Me}_3\text{Si} \\
\text{Ph}
\end{array}
\begin{array}{c}
\text{OSiMe}_3 \\
\text{Me}_3\text{Si}
\end{array}
\]

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 MgSO₄, 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); \( \nu_{\text{max}} \) (thin film) 2954, 2891, 1600, 1486, 1449, 1426, 1244, 1038, 1024, 828, 743, 696 cm⁻¹; \( \delta_H \) (300 MHz, CDCl₃) 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, CHOSi(CH₃)₃), 0.15 (9H, s, Si(CH₃)₃), 0.05 (9H, s, Si(CH₃)₃), -0.08 (9H, s, (Si(CH₃)₃); \( \delta_C \) (126 MHz, CDCl₃) 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 (CHOSi(CH₃)₃), 0.4 (Si(CH₃)₃), 0.34 (Si(CH₃)₃), 0.15 (Si(CH₃)₃); \( m/z \) (CI) 448 (MNH₄⁺, 2%), 431 (M⁺, 5%), 415 (M⁺-CH₃, 10%), 358 (M⁺-Si(CH₃)₃, 100%); HRMS (CI) Found MNH₄⁺, 448.2337 (C₂₂H₄₂Si₄ON requires 448.2338).

Dimethyldioxirane, 571

\[
\begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\]

Water (11 ml), acetone (7 ml, 94.0 mmol) and NaHCO₃ (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.

\((E/Z)-\text{Trimethyl(penta-1,3-dien-3-yloxy)silane, 572}\)

\[
\begin{align*}
\text{OSiMe}_3 & \quad \text{OSiMe}_3 \\
\end{align*}
\]

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 MgSO₄, 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; \(\nu_{\text{max}}\) (thin film) 2960, 1649, 1605, 1339, 1252, 1052, 900, 842 cm⁻¹; \(\delta_H\) (300 MHz, CDCl₃) 6.17 (1H, d, \(J 10, CC\cong CH_2\)), 5.23 (1H, d, \(J 15, CCH=CHH\)), 4.95-4.87 (2H, m, CCH=CHH, C=CHCH₃), 1.64 (3H, d, \(J 6, C=CHCH₃\)), 0.22 (9H, s, Si(CH₃)₃); \(\delta_C\) (126 MHz, CDCl₃) 135.5 (CCH=CH₂), 111.4 (CCH=CH₂), 110.3 (C=CHCH₃), 11.6 (C=CHCH₃), 0.6 (Si(CH₃)₃); \(m/z\) (EI) 156 (M⁺, 84%), 141 (M⁺ -Me, 88%), 127 (M⁺ -Me, -CH₂, 96%); all data agree with those reported in the literature.¹⁹⁸
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 1 h 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. NH₄Cl 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 MgSO₄, 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%); Rf 0.3 (pet. ether/ether 9:1); m.p. 100-102 °C; \( \nu_{\text{max}} \) (thin film) 3696 (broad-OH), 2950, 2892, 1600, 1245, 838 cm\(^{-1}\); \( \delta_H \) (500 MHz, CDCl₃) 7.29-7.27 (3H, m, Ar-H), 7.16-7.14 (2H, m, Ar-H), 5.04 (1H, s, SiCH), 0.14 (27H, s, Si(Si(CH₃)₃)₃); \( \delta_C \) (126 MHz, CDCl₃) 147.3 (ipso-Ar-C), 128.3 (Ar-C), 126.1 (Ar-C), 125.4 (Ar-C), 69.4 (SiCH), 1.5 (Si(Si(CH₃)₃)₃); m/z (ES\(^{+}\)) 377 (MNa\(^{+}\)).
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<sub>f</sub> 0.9 (pet. ether); δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 7.54-7.52 (2H, m, Ar-H), 7.33-7.30 (3H, m, Ar-H), 2.16 (1H, septet d, <i>J</i> 7, 4, 2-CH(CH<sub>3</sub>)<sub>2</sub>), 1.95 (1H, dm, <i>J</i> 13, 5-HH), 1.81 (1H, m, 3-H), 1.74 (1H, dm, <i>J</i> 13, 4-HH), 1.50 (1H, qt, <i>J</i> 13, 3, 5-HH), 1.19 (1H, m, 4-HH), 1.11 (1H, dd, <i>J</i> 10, 4, 2-H), 1.07 (1H, m, 6-HH), 1.05 (1H, m, 6-HH), 1.02 (3H, d, <i>J</i> 7, 2-CH(CH<sub>3</sub>)<sub>2</sub>), 0.97 (3H, d, <i>J</i> 7, 3-CH<sub>3</sub>), 0.79 (3H, d, <i>J</i> 7, 2-CH(CH<sub>3</sub>)<sub>2</sub>), 0.27 (9H, s, Si(CH<sub>3</sub>)<sub>3</sub>); m/z (El) 304 (M<sup>+</sup>, 12%), 289 (M<sup>+</sup>-Me, 1%), 231 (M<sup>+</sup>-Si(CH<sub>3</sub>)<sub>3</sub>, 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.\textsuperscript{35}

**Stage 1**

To a solution of (1SR,2RS,3SR)-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 NaHCO₃ 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 MgSO₄, 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 KHCO₃ (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 H₂O₂ 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 Na₂S₂O₃ 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 MgSO₄, 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%); Rf 0.2 (pet. ether/ethyl acetate 1:1); δH (300 MHz, CDCl₃) 3.65 (2H, t, J 6, 1-H₂), 3.09 (1H, t, J 7, 5-H), 1.82 (1H, octet, J 7, 6-H), 1.69 (2H, m, 3-HH, 2-HH), 1.60 (1H, m, 4-H), 1.50 (1H, m, 2-HH), 1.18 (1H, q, J 9, 3-HH), 0.93 (3H, d, J 7, 6-CH₃), 0.90 (3H, d, J 7, 4-CH₃), 0.89 (3H, d, J 7, 6-CH₃); 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
$^{1}\text{H}$ and $^{13}\text{C}$ NMR for 322Ad
$^1$H and $^{13}$C NMR for 322Ac
$^1$H and $^{13}$C NMR for $^{322}$Ai
$^1$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 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
8 Bibliography


