The Synthesis and Applications of Cyclic Alkenylsiloxanes

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Abstract: This thesis describes the development of robust methodology to access cyclic alkenylsiloxanes, and their subsequent application in Hiyama-Denmark cross couplings. An early chapter shows the identification of Lindlar reduction conditions capable of generating cyclic alkenylsiloxanes from alkynylsiloxanes in high yields (Scheme 1). The use of such species in Hiyama-Denmark cross coupling is then examined, with particular emphasis on the development of fluoride-free conditions, previously unreported for this class of organosilane.

Scheme 1: Synthesis of cyclic alkenylsiloxanes and their application in cross coupling

A ring-size dependent orthogonality is revealed, where 5-membered cyclic alkenylsiloxanes cross couple under basic conditions, while 6-membered analogues are inert. The origins of this effect are investigated experimentally and theoretically, leading to the proposal of detailed mechanisms for coupling. In the final chapter, the methodology that has been developed is applied to total synthesis. The great potential of the orthogonality uncovered is demonstrated with the highly convergent construction of anti-inflammatory natural product resolin D3 by sequential, one-pot, orthogonal cross couplings (Scheme 2).

Scheme 2: Retrosynthesis of resolin D3 by orthogonal Hiyama-Denmark cross coupling
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And finally, to my wonderful family for their unwavering love and support, and for always being on the other end of a phone.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>CBS</td>
<td>Corey-Bakshi-Shibata</td>
</tr>
<tr>
<td>cod</td>
<td>1,5-cyclooctadiene</td>
</tr>
<tr>
<td>Cp*</td>
<td>pentamethylcyclopentadiene</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicycloundec-7-ene</td>
</tr>
<tr>
<td>DFT</td>
<td>density functional theory</td>
</tr>
<tr>
<td>DIBALH</td>
<td>diisopropylaluminium hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DVDS</td>
<td>1,1-divinyl-1,1,3,3-tetramethyldisiloxane</td>
</tr>
<tr>
<td>EA</td>
<td>elemental analysis</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionisation</td>
</tr>
<tr>
<td>eq</td>
<td>equivalent(s)</td>
</tr>
<tr>
<td>FI</td>
<td>field ionisation</td>
</tr>
<tr>
<td>Grubbs II</td>
<td>(1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichlorophenyl-methylene)(tricyclohexylphosphine)ruthenium</td>
</tr>
<tr>
<td>HKR</td>
<td>hydrolytic kinetic resolution</td>
</tr>
<tr>
<td>HMBC</td>
<td>heteronuclear multiple bond correlation spectroscopy</td>
</tr>
<tr>
<td>HMDS</td>
<td>hexamethyldisilazane</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrum</td>
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<tr>
<td>Abbreviations</td>
<td>Description</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------</td>
</tr>
<tr>
<td>HSQC</td>
<td>heteronuclear single quantum coherence spectroscopy</td>
</tr>
<tr>
<td>IMes</td>
<td>1,3-bis(2,4,6-trimethylphenyl)-imidazolium</td>
</tr>
<tr>
<td>IR</td>
<td>infra-red</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LRMS</td>
<td>low resolution mass spectrum</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl ether</td>
</tr>
<tr>
<td>Ms</td>
<td>methanesulfonyl</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NHC</td>
<td>N-heterocyclic carbene</td>
</tr>
<tr>
<td>NIS</td>
<td>N-iodosuccinimide</td>
</tr>
<tr>
<td>Noyori-Ru</td>
<td>N-tosyl-1,2-diphenylethane-1,2-diamine[η⁶-1-isopropyl-4-methylbenzene]-ruthenium(II)</td>
</tr>
<tr>
<td>PG</td>
<td>protecting group</td>
</tr>
<tr>
<td>PMB</td>
<td>para-methoxybenzyl ether</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium para-toluenesulfonate</td>
</tr>
<tr>
<td>py</td>
<td>pyridine</td>
</tr>
<tr>
<td>RCM</td>
<td>ring-closing metathesis</td>
</tr>
<tr>
<td>RDS</td>
<td>rate-determining step</td>
</tr>
<tr>
<td>RuPhos</td>
<td>2-dicyclocxylphosphino-2',6'-diisopropoxybiphenyl</td>
</tr>
<tr>
<td>Schrock catalyst</td>
<td>2,6-diisopropylphenylimidoneophyldene molybdenum(VI) bis(t-butoxide)</td>
</tr>
<tr>
<td>SMD</td>
<td>steered molecular dynamics</td>
</tr>
<tr>
<td>TASF</td>
<td>tris(dimethylamino)sulfonium difluorotrimethylsilicate</td>
</tr>
<tr>
<td>TBAB</td>
<td>tetrabutylammonium bromide</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBAT</td>
<td>tetrabutylammonium difluorotriphenylsilicate</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>TBDPS</td>
<td><em>tert</em>-butyldiphenylsilane</td>
</tr>
<tr>
<td>TBS</td>
<td><em>tert</em>-butyldimethylsilane</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonate</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydropyranal</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilane</td>
</tr>
<tr>
<td>Ts</td>
<td>4-toluenesulfonate</td>
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1 Introduction

Polyene natural products are isolated from a variety of sources such as fungi, plants, marine organisms and animals.\textsuperscript{1,2} Many of these unsaturated compounds are employed in Nature as chemical defence mechanisms, secreted by the organism which produces them in order to deter predators or competitors. It is therefore unsurprising that many of them exhibit potent biological activity profiles,\textsuperscript{3,4} including antibacterial, antitumour, antifungal and anti-inflammatory properties. This makes them important targets for the synthetic community, due to potential applications in the pharmaceutical and agrochemical industries. Three typical examples of bioactive polyene natural products are shown in Figure 1.1. Pimaricin (1) exhibits antifungal and antiviral activities;\textsuperscript{5} it is marketed worldwide as Natamycin and used to treat fungal infections, and as a common preservative in food.\textsuperscript{6} The strobilurins were first isolated in 1977 from \textit{Strobilurus tenacellus} and were shown to have antifungal activity (one of the family, strobilurin A (2) is shown).\textsuperscript{7} Their structure inspired the development of azoxystrobin (3) by the agrochemical industry; marketed as AMISTAR\textsuperscript{®}, it is the world’s number one fungicide.\textsuperscript{8} Leukotriene B\textsubscript{4}, a derivative of arachidonic acid, has potent anti-inflammatory properties; it induces chemotaxis, chemokinesis, aggregation and degranulation of

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Figure 1.1: Polyene natural products}
\end{figure}
leukocytes implicated in the human immune response.\textsuperscript{9}

The highly conjugated nature of polyenic compounds also leads to use in a range of other applications - for example, they have the potential to conduct charge along their extended $\pi$-orbital networks, and to absorb and emit light.\textsuperscript{10,11} Kwon \textit{et al.} have described the nonlinear optical properties of polyenes such as 5 (Figure 1.2), which are able to form crystalline materials with potential application in integrated photonics and terahertz wave generation and detection (useful for medical and security imaging).\textsuperscript{12} Sklar \textit{et al.} have reported the use of parinaric acid isomers (6 and 7) as fluorescent probes to study \textit{E. coli} membranes.\textsuperscript{13–15} The carotenoids (such as $\beta$-carotene, 8) are a large family of polyenes that are key participants in light harvesting in plants – they absorb energy from sunlight and efficiently transfer it to chlorophyll as the first step in photosynthesis.\textsuperscript{16}

\begin{figure}[h]
\centering
\includegraphics[width=0.7\textwidth]{carotenoids.png}
\caption{Polyenes used in a range of important applications}
\end{figure}

The many uses for complex polyenes demonstrate the importance of finding new solutions to their syntheses. Both $E$- and $Z$-alkene geometries are observed within polyenes in Nature, and hence synthetic methods must offer good control over the stereochemistry of each alkenyl unit in the molecule, as changes to these may affect the biological and physical properties of the polyene. On the other hand, it is desirable if procedures also offer controlled access to other geometrical isomers as these may improve the bioactivity profile of the target compound. Many synthetic strategies have been employed to address these aims,\textsuperscript{1,2} with the use of transition metal catalysed cross coupling being particularly prominent in polyene synthesis. Five decades of work by numerous researchers have led to the introduction of a diverse range
of organometallic coupling partners; this chapter will focus principally on the use of organosilanes in Hiyama-Denmark procedures, considering the preparation of alkenylsilane reagents, the mechanism by which they participate in cross couplings, and examples of their synthetic applications.\textsuperscript{17}

1.1 Introduction to the Hiyama-Denmark Cross Coupling

Hiyama-Denmark cross coupling was one of the last branches of coupling reaction to emerge;\textsuperscript{18} organosilanes were initially overlooked as partners due to the low polarity of the C–Si bond, which renders them inert to cross coupling without an activator. However, the potential for silicon to expand its valence\textsuperscript{19} allows it to be activated to the transmetalation of its substituents by silophilic Lewis bases such as fluoride ions, allowing coupling to proceed. Scheme 1.1 shows how the formation of a pentacoordinate silicate complex 9 (henceforth referred to as an ‘ate’ complex) with an activator such as fluoride, X\textsuperscript{−}, is thought to be necessary for transmetalation to occur.

\textit{Scheme 1.1: Formation of a pentacoordinate silicate species, necessary for transmetalation}

Hiyama-Denmark reactions offer a very attractive alternative to more traditional coupling methods for several reasons.\textsuperscript{18,20} Organosilanes tend to be non-toxic, inexpensive, stable compounds with good oxygen and moisture stability; this allows them to be easily purified, carried through multiple synthetic steps and to tolerate a wide range of functional groups.
Many high-yielding methods are available for the introduction of silicon functionalities, with the resultant organosilanes going on to give good retention of regio- and stereochemistry in couplings. Hiyama-Denmark cross coupling also complies with several of the principles of green chemistry – organosilanes are not harmful to the environment, while their low molecular weight produces low mass by-products that are easily removed. Despite these many advantages, the field has remained somewhat undervalued relative to other branches of coupling – Figure 1.3 shows that while methods such as the Suzuki and Heck reactions have seen enormous uptake in the last decade, Hiyama-Denmark chemistry has been less widely applied. In spite of this, the use of organosilanes in coupling has seen exciting developments over the last decade in particular, with many important applications in both academia and industry, examples of which will be discussed in the following sections.

Figure 1.3: Growth in the number of publications and patents on platinum-group metal-catalysed cross coupling reactions (reproduction)

For many years it was believed that organosilanes were too stable to undergo coupling, and it was only in the 1980s that reports hinting at their potential for cross coupling began to appear. In 1982 Tamao and Kumada utilised pre-formed high-valent alkene pentafluorosilicate salts to form \( \text{E-styrene} \), albeit under harsh conditions (Scheme 1.2). In 1988 Hiyama made the pioneering discovery that it was possible for organosilanes to undergo coupling through \textit{in situ} activation with fluoride; this seminal report enabled the use of more readily accessed tetracoordinate silanes, and thus increased reaction scope (Scheme 1.2). Many early studies
focussed on the use of fluoro- and chlorosilanes, as the resultant polarisation of the C–Si bond facilitates formation of the ‘ate’ complex necessary for transmetalation, allowing coupling with alkenyl, aryl, heteroaryl, allyl and alkyl halides. Unfortunately, many of these halosilanes were moisture sensitive and difficult to handle, hence they have not seen widespread application. To overcome these issues many different, more stable organosilanes have been developed; the focus of this section will be on those with transferable alkene substituents, which represent useful tools in polyene synthesis.

A summary of the range of carbon-substituted organosilanes available for use in Hiyama-Denmark cross couplings is shown in Schemes 1.3. Hiyama’s use of trimethylsilanes, while not commonplace, continues today in various research groups. In 1999 Denmark discovered that siletanes (11) were effective coupling partners; it was initially believed that the silacyclobutane moiety induced ‘strain release Lewis acidity’ which allowed them to easily form ‘ate’ complexes under mild conditions. However, mechanistic studies on these species later revealed that fluoride effected rapid conversion of siletane 14 (Scheme 1.4) to silanol 15 and disiloxane 16; this led Denmark to evaluate the direct use of these more stable species (discussed below). Various researchers have employed aryl, heteroaryl and benzyl substituents on silicon (12 and 13) which represent ‘masked’ silanols, and are especially stable and easy
to work with until activation with a hydrated fluoride source reveals a highly reactive silanol functionality for cross coupling. These are analogous to Denmark’s siletanes but are synthetically more convenient to prepare.\textsuperscript{20,26}

Tamao’s discovery in 1989 that robust and stable mono-, di- or trialkoxysilanes could participate effectively in cross couplings under mild conditions\textsuperscript{27} has led to an enormous diversity of reagents containing Si–O bonds for use in the Hiyama-Denmark reaction (Scheme 1.5). Such species can sometimes be coupled under fluoride free conditions with alkoxide, hydroxide and carbonate bases, where a high concentration of silaphilic oxygen anions increases the proportion of active ‘ate’ complexes (as is observed with fluoride). This represents a significant advantage of the methodology, as common silyl ether protecting groups can be tolerated, and conditions can be employed which are more compatible with industrial processes. This important variant of Hiyama-Denmark coupling will be discussed in more detail in subsequent chapters. Many reports from different researchers have emerged on the use of vinyl alkoxy silanes (17) in couplings with aryl, alkenyl, allyl and alkyl halide partners.\textsuperscript{20}
1. Introduction

Scheme 1.5: Hiyama-Denmark vinyl organosilanes with one or more oxygen substituents

As mentioned above, Denmark has pioneered the use of highly active silanols (18, Scheme 1.5) and their pre-formed silanolate (19) salts to couple a wide range of organometallic and halide partners under both fluoride-promoted and fluoride-free conditions. Silanolate salts offer the advantage that once formed they do not require an additional activator; as such they are useful in couplings requiring the use of halide partners with base- or fluoride-sensitive functionalities (which can include the alkenyl halide itself). Disiloxanes (20) are synthetic equivalents of silanols when activated by fluoride or base; they are more robust than their silanol cousins and hence have also seen wide application. The great diversity of silane reagents available is perhaps an artefact of the high number of researchers in the field, and represents a daunting choice for the non-specialist. Particularly popular and useful species are contained within boxes in Scheme 1.3 and 1.5, chosen for their relative ease of handling and high activity in couplings.

In the following section the synthesis of silanes with vinyl substituents, which are of potential use in polyene synthesis, will be discussed, with a particular focus on methods that install silyl functionality.

1.2 The Synthesis of Vinylsilanes

There are many methods available for the synthesis of alkenylsilanes with diverse geometries and substitution patterns. As the resultant reagents undergo Hiyama-Denmark coupling with a high degree of stereochemical fidelity, it is important that these syntheses proceed with excellent stereo- and regiochemical control. 1,2-Disubstituted vinylsilanes are perhaps the most
useful building blocks in polyene synthesis; Scheme 1.6 shows examples of their preparation. 

_E-Vinyl silanes are most commonly prepared via a syn-hydrosilylation of a terminal alkyne starting material using a hydrosilane and platinum or rhodium catalyst (Eq. 1, Scheme 1.6). A commonly used catalyst is (_t-Bu₃P)PtDVDS, which gives excellent E-selectivities, regioselectivities and high yields across a range of functionalised silanes._**30** This method does however suffer from the drawback that the platinum(0) pre-catalyst and phosphine ligands employed are costly and sensitive to oxygen and moisture. In 1995, Takeuchi revealed that cationic rhodium complexes are also able to catalyse the syn-hydrosilylation of alkynes with excellent stereocontrol. However, only the use of trialkylsilanes was reported, as conditions were not tolerant of siloxane functionality._**31** While many methods for the formation of 1,2-disubstituted vinylsilanes employ terminal alkynes as substrates, there are also techniques available for the direct use of aldehydes. Chromium-mediated Takai olefination has been applied to the synthesis of alkenylsilanes; Anderson and Lim have reported the use of superstoichiometric chromium to generate useful benzylidimethylsilanes _**21**_ (Eq. 2), with boronic esters, ketones and α-stereocentres in the aldehyde component all well tolerated._**32** It is also possible for alkenes to be used as starting materials – they are able to undergo silylative coupling reactions with vinylsilanes mediated by ruthenium hydride catalysts at low loadings to give desired _**22**_ with high _trans_-selectivity (Eq. 3)._**33**

**Scheme 1.6: Selected examples of 1,2-disubstituted E-vinylsilane synthesis**
In contrast to their E-cousins, Z-vinylsilanes are more challenging to access, as the majority of hydro- and silylmetalations occur with syn-stereospecific addition of Si–H across triple bonds (Scheme 1.7). In addition, Z-alkenylsilanes are somewhat vulnerable to light- or heat-mediated isomerism to their more stable E-form. In spite of this, ruthenium and rhodium catalysts have been identified which allow the anti-hydrosilylation of terminal alkynes. While ruthenium catalysts such as [RuCl₂(p-cymene)]₂ are able to generate Z-vinylsilanes in high yields and geometrical purities, they are limited to use of silanes with all-carbon substituents. In contrast, Hiyama has reported that a cationic rhodium complex facilitated the synthesis of more useful mono- and dialkoxy silanes and disiloxanes (Eq. 1, Scheme 1.7). The limitations associated with direct installation of Z-alkenylsilanes have led many researchers to employ an alternative two-step approach, where formation of alkyny silanes such as 23 (Eq. 2) is followed by selective semi-reduction to the Z-alkenylsilane product. While alkyny silanes can be notoriously reluctant to undergo hydrogenation, a few reports have shown successful outcomes with diimide reductions or with syn-hydrometalation followed by protodemetalation using dicyclohexylborane or DIBALH. Notably, the cis-nature of the forming double bond also allows it to exist within a small or medium ring as a cyclic alkenylsiloxane – this will be discussed in the next section.

Scheme 1.7: Selected examples of 1,2-disubstituted Z-vinylsilane synthesis

1.2.1 An Introduction to Cyclic Alkenylsiloxanes and their Preparation

Endocyclic alkenylsiloxanes (24, Scheme 1.8) are vinylsilanes whose cis-geometry allows them to form rings with proximal alcohol functionalities via an Si–O bond. There are several advantages to this structural arrangement. They are easily accessed as the pure Z-isomer, as
any *E*-vinylsilane contaminants are necessarily acyclic, and can be removed by virtue of their differing physical properties. This *cis*-geometry is then protected by the cyclic nature of the silane until the point of use, avoiding the problem of post-synthesis double bond isomerism. These factors ensure that cyclic alkenylsiloxanes are able to perfectly transfer their stereochemistry in cross coupling reactions to give complete control over polyene structure, whilst simultaneously installing allylic or homoallylic alcohol functionality. The motif generated (25) is found in a diverse array of important natural products – some examples will be shown in Section 1.4 and Chapter 5. Once formed, cyclic alkenylsiloxanes are generally considered to be fairly stable to a range of different reaction conditions, and hence can be tolerated in further elaborations before use in coupling; this is an important consideration in total synthesis.

**Scheme 1.8: Cyclic alkenylsiloxanes and their applications**

In addition to their application in Hiyama-Denmark cross couplings, cyclic alkenylsiloxanes can undergo additional transformations. In the presence of fluoride ions and an oxidant such as hydrogen peroxide, the C–Si bond undergoes a Tamao-Fleming oxidation, generating ketones (26) or phenols (depending on the nature of R¹ and R² substituents). It is also possible to perform a protodesilylation to generate useful, geometrically defined alkenes (27). In the presence of an electrophilic iodine source, the silicon atom is replaced with the halide to form vinyliodides with allylic, homoallylic or bis-homoallylic alcohols 28 (for n = 0, 1, 2 respectively), which can be challenging to prepare by other methods. Examples of each mode of reactivity will be presented in Section 1.4.
Despite their great potential in the field of total synthesis, cyclic alkenylsiloxanes have received little attention from the synthetic community, which may be due to perceived difficulties and limitations with their syntheses. However, a variety of methods exist for the preparation of such species with varying substitution patterns. 1,2-Disubstituted vinylsilanes (29, Scheme 1.9) are the simplest of these, and perhaps the most useful due to the prevalence of disubstituted Z-alkenes in natural products. To date, the principle method to access species such as 29 has been ring-closing metathesis of vinylsilanes 30 to form 5-, 6-, and 7-membered rings. The use of this reaction on vinylsilane substrates was first reported by Grubbs in 1997, who noted that the use of the oxygen- and moisture-sensitive molybdenum Schrock catalyst was necessary to overcome the steric hindrance of a bulky silyl substituent.\(^{40,41}\) Denmark has made the most comprehensive study of this process,\(^{42,43}\) and has utilised it in the formation of macrocyclic polyenes;\(^{44,45}\) the application of this strategy to the synthesis of brasilenyne will be discussed below. There are only isolated reports of other methods to access 1,2-disubstituted cyclic alkenylsilanes; in 1994 Salomon reported that Lindlar hydrogenation on alkynylsilane 31 gave 32 in moderate yield,\(^{46}\) while in 2011 Lacôte and co-workers reported that an NHC catalyst could effect trans-hydrosilylation across propargylic alcohol 33 to give cyclic species 34 via the intramolecular hydrosilylation of an alkoxy silane intermediate.\(^{47}\)

\[\text{Scheme 1.9: Synthesis of 1,2-disubstituted cyclic alkenylsiloxanes}\]
A greater diversity of methods are available for the synthesis of cyclic trisubstituted alkenylsilanes,\textsuperscript{29} although these can be reluctant to undergo cross coupling in the presence of sterically encumbering substituents α to silicon;\textsuperscript{48} hence there are many examples of their synthesis but few of their use as coupling partners. The most prevalent technique is Trost’s procedure for hydrosilylation of homopropargylic (or bis-homopropargylic) alcohols (35) by tetramethyldisilazane, followed by ruthenium-catalysed intramolecular endo-anti hydrosilylation to give 36 (Scheme 1.10).\textsuperscript{39} Although a wide range of examples have been reported, propargylic siloxanes are unreactive, (hence 5-membered cyclic silanes are not accessible) and terminal alkynes exhibit exo-dig regioselectivity, thus necessitating the presence of two alkyne substituents. Lee has shown that a complementary potassium tert-

![Scheme 1.10: Synthesis of trisubstituted cyclic vinylsiloxanes](image)

butoxide-mediated hydrosilylation can prepare analogous 5-membered species (37).\textsuperscript{50} Ring closing metathesis again finds application in the synthesis of trisubstituted cyclic silanes: Lee and co-workers have reported many examples of enyne metathesis to generate cyclic alkenylsiloxanes with exocyclic alkene functionalities in the α-position (38) using Grubbs’ second generation catalyst (Grubbs II).\textsuperscript{51,52} This one pot procedure employs alkynylsilane
(39) and (bis-)homoallylic alcohol (40) starting materials which are coupled using \([\text{RuCl}_2(\text{p-cymene})]_2\), before addition of Grubbs II to the same pot. Lee has also described the use of rhenium oxide to drive the rearrangement of strained 8-membered ring siloxanes 41 to more stable 6-membered rings (42).53

Additional methods are available for the synthesis of heavily-substituted cyclic alkenylsiloxanes. Woerpel has developed a three-component procedure where alkyne 43, silacyclopropane 44 and carbonyl 45 give 5-membered siloxanes 46, mediated by silver or copper (Scheme 1.11).54,55 A wide range of substrates are tolerated, giving good control of substituent diversity around the ring. A similar method has been reported by Montgomery which employs dialkylsilane 47 with a nickel-NHC catalytic system; in contrast to Woerpel’s method, the larger alkyne substituent is found next to silicon in 48, providing a complementary substrate scope.56 Although the use of such heavily-substituted cyclic alkenylsiloxanes is rather limited in cross coupling, they are useful for the installation of well-defined trisubstituted alkenes (by protodesilylation), iodides (by iododesilylations) and ketones with two β-substituents (by Tamao oxidation).

The efficient application of Hiyama-Denmark cross coupling in total synthesis is greatly enhanced by an understanding of the underlying mechanisms at play in such reactions. This will be presented in the following section.

Scheme 1.11: Synthesis of heavily-substituted cyclic alkenylsiloxanes
1.3 The Mechanism of the Hiyama-Denmark Cross Coupling

The general catalytic cycle for the Hiyama-Denmark reaction, shown previously in Scheme 1.1, broadly consists of the oxidative addition of an aryl or vinyl halide to palladium, followed by rate determining transmetalation of an activated organosilicon species to install two organic groups on the catalyst; these are then coupled by reductive elimination. The oxidative addition and reductive elimination steps are well understood, as they change little between the various branches of cross coupling. In contrast, the mechanism of the transmetalation step exhibits wide variation across the different organometallic partners that may be involved; indeed, disparity between distinct classes of organosilanes is also observed. An increasingly detailed and sophisticated mechanistic understanding of this process has been built up over the last few decades; new studies are often consistent with previously held ideas, but on occasion contradict them. In these cases, it is not always clear if such contradictions are likely to be general, or if they apply only to the specific cases under investigation. The studies most relevant to the coupling of alkenylsilanes will be presented below as they offer the best insights into the content of this thesis; efforts will be made to highlight where theories support or contradict each other, and to offer a discussion of why any disparity may arise.

Hiyama’s work on fluorosilanes around 20 years ago provided early insight into the mechanism of the reaction which bears his name. While mono- and difluoroalkenylsilanes were able to participate effectively in fluoride-couplings with aryl iodides, trifluorosilanes were found to be inactive. He proposed that the latter must form inactive, coordinatively saturated hexacoordinate species on treatment with fluoride activator; meanwhile the ‘coordinatively unsaturated’ mono- and difluorosilanes were able to undergo transmetalation. It thus seemed reasonable to suggest that formation of a hexacoordinate siliconate species was essential for coupling; this was proposed to correspond to a four-centred hexacoordinate transition state (Scheme 1.12). Silicate (formed by the treatment of a
fluorodimethylvinylsilane with a source of fluoride anions) and the palladium complex resulting from oxidative addition of an aryl halide reacted via 49, where the formation of Si–X and Pd–C(R) bonds was concomitant with the breaking of the Si–C(R) and Pd–X bonds. The species ‘X’ in Scheme 1.12 may be iodide, installed on palladium during oxidative addition, or fluoride, resulting from ligand exchange. A recent study by Hiyama has shown this ligand exchange to have essential implications in the mechanism; this will be discussed in detail later in the section.

\[
\begin{align*}
\text{F}_2\text{Me}_2\text{Si} & \longrightarrow \text{X-Pd} \\
\text{R} & \rightarrow \text{F}_3\text{Me}_2\text{Si} \quad \text{(50)} \\
\text{R} & \rightarrow \text{F}_3\text{Me}_2\text{Si} \quad \text{(49)} \\
\text{Pd} & \rightarrow \text{R} \\
\text{F}_3\text{Me}_2\text{Si} & \longrightarrow \text{Pd} \quad \text{X} \quad \text{R} \\
\end{align*}
\]

*Scheme 1.12: Hiyama’s proposed four-centred transition state*

In 2004 Denmark published seminal work exploring the precise nature of the transmetalating species in the cross couplings of vinyl silanols, disiloxanes, siletanes and fluorosilanes in the presence of TBAF. As has been shown in Scheme 1.4, siletanes are rapidly converted into silanol and disiloxane forms by the action of fluoride, hence they will not be explicitly shown here. Extensive kinetic and spectroscopic data led to the proposal of the equilibrium pathways shown in Scheme 1.13. Denmark and co-workers observed that silanol, disiloxane or fluorosilane starting materials all initially reacted with TBAF to form the same two species in equilibrium (characterised by $^1\text{H}$, $^{19}\text{F}$ and $^{29}\text{Si}$ NMR) – disiloxane 51, and silanol 52, the latter of which is hydrogen bonded to a fluoride anion. The former species then more slowly converts to the siliconate ion 53, which kinetic data suggested to be the active species in
transmetalation. At low fluoride concentrations, increasing the amount of TBAF was found to accelerate the reaction, which is to be expected as fluoride is required to convert disiloxane \(51\) into active \(53\). However, at higher concentrations of fluoride the opposite was observed, and increasing TBAF decreased the rate of coupling. The authors rationalised that high fluoride concentrations would produce more of inactive \(52\), reducing the concentration of \(51\) and therefore active \(53\). Although the findings reported are applicable only to silanes capable of forming disiloxane species such as \(51\), such silanes represent the most popular and widely applied reagents in Hiyama-Denmark coupling;\(^{20}\) hence this work represents a highly significant contribution to the field.

A simultaneous, equally significant report on the mechanism of the base-promoted cross-coupling of organosilanols directly followed the work detailed above.\(^{63}\) Denmark investigated the coupling of a potassium silanolate salt, \(54\), with 2-iodothiophene; as before, detailed kinetic analysis was performed to assess the likely course of the reaction. A key intramolecular transmetalation step was proposed, quite distinct from the fluoride-promoted coupling of similar species (Scheme 1.14). The silanolate oxygen was able to act as a ligand for palladium, forming an Si–O–Pd linkage that renders the transfer of a vinyl group from silicon to palladium intramolecular (\(55\)). The authors noted that this was rather unexpected, and contradicts the previously held dogma that pentacoordinate silicates must be formed for transmetalation to occur; they cite the importance of the Si–O–Pd linkage in rendering such an ‘unactivated’ transmetalation so favourable. It is intriguing that activation by base and fluoride proceed by such dissimilar mechanisms in the case of silanols and related species; it is not clear if this would also be the case for other classes of silanes, such as trimethyl variants. In my opinion it is likely that silane species with an oxygen substituent represent a ‘special’ (if ubiquitous) case that is the exception, rather than the rule.
A DFT computational study on the role of fluoride in the rate enhancement of trimethylvinylsilane coupling was published in 2008 by Hiyama and provides many valuable insights, some of which contradict Denmark’s work.\textsuperscript{61} The geometries and energies of various transition states were analysed for three distinct reaction pathways, each involving a different role of fluoride ions. The pre-formation of a fluorosilicate complex from trimethylvinylsilane was not observed experimentally nor theoretically; hence its contribution was ruled out. Instead, two other roles of fluoride were found to enhance the rate of coupling (Scheme 1.15). Firstly, the exchange of iodide and fluoride ligands on the metal to generate complex 56 was proposed to be crucial; transmetalation proceeded with an activation barrier of 48.7 kcal/mol for the palladium iodide complex, but with a significantly lower barrier of 25.3 kcal/mol for the equivalent fluoride complex (species 57 and 56). The concomitant formation of a very strong Si–F bond (from 58 to 59 to 60) was also an important enthalpic driving force (when compared with the formation of Si–I from an iodide complex). The second accelerating role of fluoride was proposed to be the nucleophilic attack of the anion at the silicon centre (shown in red in Scheme 1.15), which weakens the silicon-vinyl bond, inducing the transfer of the vinyl group to palladium. The authors calculated that the activation barrier for the transmetalation step was lowered to 16.5 kcal/mol when this second role of fluoride was taken into account. Interestingly this makes the preceding ligand exchange the turnover limiting step with an activation barrier of 21.1 kcal/mol. It should be noted that most Hiyama-Denmark cross couplings are in fact performed in the absence of phosphine ligands,\textsuperscript{20,64} which are found to inhibit rate – this seems consistent with Hiyama’s DFT findings. The calculations were repeated with hydroxide in the place of fluoride, which was found to accelerate cross coupling.
via similar interactions, which is in contrast to Denmark’s silanol study which identified distinct mechanistic pathways for fluoride- and base-promoted reactivity. The conclusion that a trimethylfluorovinyl silicate complex is not involved in the reaction pathway as an intermediate that precedes transmetalation directly contradicts Denmark’s earlier findings that fluorosilicate intermediates participate in cross coupling. It may be that Denmark’s kinetic studies were not able to distinguish between the preformation of fluorinated 53 (which could have been observed by NMR as a stable, off-pathway intermediate) and a fluoride-assisted transmetalation as described by Hiyama. Alternatively, the presence of electronegative oxygen substituents in Denmark’s study likely increases the fluorophilicity of silicon, making formation of such complexes more favourable and thus more likely to be important intermediates in that variant of the reaction.

Very recently Jutand published a kinetic study on the mechanism of arylsiloxane coupling.\textsuperscript{65} While not directly relevant to alkenylsilanes, the insights provided were very interesting and merit some discussion. Jutand found three roles of fluoride, which are illustrated in Scheme 1.16. Analogous to Hiyama’s work, it was found that formation of fluoro-palladium complex 61 was crucial as bromo-palladium complex 62 did not react with the arylsiloxane. The fluoride ligand was proposed to interact with the silicon via transition state 63, facilitating transfer of the aryl group to palladium. Interestingly, this Pd–F–Si interaction is analogous to Denmark’s Pd–O–Si in base-promoted coupling. Fluoride was also found to accelerate the rate

![Scheme 1.15: The role of fluoride in accelerating the coupling of trimethylvinylsilane](image-url)
of reductive elimination via the formation of complex 64. However, an antagonistic role of fluoride was uncovered; at high levels it formed silicate 65 with the arylsiloxane, which was found to be unreactive in the catalytic cycle. The same authors have previously revealed similar findings in the Suzuki-Miyaura reactions.\textsuperscript{66} This inhibition of coupling by high concentration of fluoride is again similar to Denmark’s observations in Scheme 1.13.

Unfortunately there are no studies reported on the specific mechanism of cross coupling with endo-cyclic alkenylsiloxane partners. As they are most closely related to alkoxyisilanes, silanols and disiloxanes, it may be that Denmark’s 2004 work bears the most relevance. However, we believe that their unique cyclic nature may have significant mechanistic implications that are not observed in acyclic analogues. This will be investigated in Chapter 4.

1.4 Use of the Hiyama-Denmark Cross Coupling in Total Synthesis

1.4.1 Acyclic Vinylsilanes in Polyene Total Synthesis

The importance of the Hiyama-Denmark reaction as a tool for the preparation of complex polyene targets can be demonstrated by its application in the arena of total synthesis,\textsuperscript{67} where mild reaction conditions and excellent stereochemical retention are highly valued. In 2009 Denmark and co-workers reported the synthesis of isomeric neuroexcitatory agents isodomoic...
acids G and H (66 and 67, Scheme 1.17). Both E- and Z-vinyl iodides (68) coupled with silanol 69 in excellent yields to construct the two diene motifs. Global deprotection produced the natural products.

Scheme 1.17: Synthesis of isodomoic acids G and H

López and co-workers have shown that a diversity of silane coupling partners are well-suited to use in the synthesis of retinoids – Scheme 1.18 shows how both E- and Z-vinylsilanes 70 gave very good yields of both precursors to vitamin A, 71 and 11-cis-retinal 72.69 As the retinoids are a common synthetic target, this study provided the authors with an opportunity to directly compare the performance of Hiyama-Denmark coupling with that of more established methods; López had previously reported use of a vinylboronic acid to construct the C10-C11 bond, forming the tetraene in 83% yield (or 50% with boronic acid and iodide partners swapped), however, the instability of the required vinylboronic acids was identified as a limitation.70 The superior reagent stability and yield of the Hiyama-Denmark strategy (particularly with ethoxysilane and silanol partners) marked it as the superior choice in this case.

Scheme 1.18: Synthesis of retinoids using Hiyama-Denmark coupling

Trost utilised a benzyldimethylsilane coupling partner in a synthesis of dephospho-fostriecin; in the presence of a hydrated fluoride source (TBAF), benzyldimethyl silane 73 is converted to
a silanol, allowing coupling with 74 to occur to give Z,Z,E-triene 75 in moderate yield (Scheme 1.19).37

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{TESO} \\
\text{BnMe3Si} \\
\text{OH} \\
\text{OTBS} \\
\end{array}
\xrightarrow{\text{TBAF (4 eq, slow addition), Pd(dba)2.CHCl3, THF, 0 °C - rt. 54%}}
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{Me2Si} \\
\text{OH} \\
\text{OH} \\
\text{OH} \\
\text{OH} \\
\text{De phospho-fostriecin, 75}
\end{array}
\]

Scheme 1.19: Trost’s synthesis of dephospho-fostriecin

1.4.2 Cyclic Vinylsilanes in Polyene Total Synthesis

The utility of cyclic alkenylsiloxanes has been demonstrated by a number of research groups with their application to total synthesis. In 2004, Denmark and co-workers reported the first enantioselective total synthesis of brasilenyne (76, Scheme 1.20), a halogenated medium-ring ether isolated from Aplysia brasiliana.44 Acyclic vinylsilane 77 was submitted to molybdenum-catalysed RCM, which furnished the 6-membered siloxane 78 in excellent yield, proving the tolerance of the methodology to vinyl iodides. This bifunctional substrate was then able to undergo intramolecular Hiyama-Denmark cross coupling (albeit with high catalyst and fluoride loadings, and extended reaction time) to construct the Z,Z-diene and form the 9-membered ether core of brasilenyne 79 in moderate yield.

\[
\begin{array}{c}
\text{Me2Si} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{OPMBO} \\
\end{array}
\xrightarrow{\text{Schrock’s catalyst, PhH, 92%}}
\begin{array}{c}
\text{Me2Si} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{OPMBO} \\
\end{array}
\]

\[
\begin{array}{c}
\text{HO} \\
\text{OPMBO} \\
\text{79}
\end{array}
\xrightarrow{\text{[allylPdCl2], TBAF (10 eq), THF, 60 h, 61%}}
\begin{array}{c}
\text{HO} \\
\text{OPMBO} \\
\text{Brasilenyne, 76}
\end{array}
\]

Scheme 1.20: Denmark’s total synthesis of brasilenyne

Trost has reported the Tamao oxidation of a cyclic alkenylsiloxane in his total synthesis of spectaline (80, Scheme 1.21), a piperidine alkaloid with potent antifungal properties.71 Homopropargylic alcohol 81 underwent silylation, followed by intramolecular hydrosilylation to generate 6-membered siloxane 82. Treatment of 82 with urea–hydrogen peroxide (UHP)
and fluoride effected Tamao oxidation to give ketone 83, which was transformed into spectaline in two steps.

Scheme 1.21: Trost’s total synthesis of spectaline

Lee has recently published an elegant use of his metathesis methodologies in a total synthesis of (−)-amphidinolide V (84, Scheme 1.22).^{72} Enyne metathesis of 85 gave 6-membered silane 86, which was opened upon treatment with methyllithium. This product was then further

Scheme 1.22: Lee’s total synthesis of (−)-amphidinolide V
elaborated to give 87, which underwent a second metathesis reaction to give the strained 8-membered ring 88, which then rearranged to the more stable 89 under rhenium catalysis. This was later desilylated to reveal the 1,1-disubstituted alkene and homopropargylic alcohol in the final product.

The use of cyclic alkenylsiloxanes in iododesilylations has also found application in total synthesis. Kishi recently published a report on the use of such a technique to efficiently generate the C23-C26 portion of the halichondrin family of natural products (90, Scheme 1.23). These polyether macrocles have extremely potent in vivo and in vitro antitumour activity, where total synthetic efforts have led to the development of the anticancer drug Halaven® (also known as eribulin, 91). 6-Membered siloxane 92 was constructed using Trost’s intramolecular hydrosilylation methodology, and after further elaboration was iododesilylated using iodine monochloride and TBAF to give building block 93.

Scheme 1.23: Synthesis of the C20-C26 building block of halichondrins and eribulin

1.5 Aims of the Project and Thesis Structure

The high value of cyclic alkenylsiloxanes is demonstrated by their utility in synthesis. However, they remain under-used, especially 1,2-disubstituted cyclic vinylsilanes, due to limitations with their synthesis. We postulate that cyclic alkenylsiloxanes might be accessed in
a simpler, more general manner by Lindlar semi-hydrogenation of an alkoxy alkynylsilane (94, Scheme 1.24); the generated Z-vinylsilane 95 might be expected to undergo ring closure with release of an alcohol or water molecule to give cyclic silane 96. As seen in Scheme 1.8, only a single report of this strategy exists in the literature; we propose to develop this process into a general method for the synthesis of compounds such as 96. The development of this robust semi-hydrogenation procedure will be described in Chapter 2 of this thesis.

![Scheme 1.24: Lindlar hydrogenation strategy for the preparation of cyclic alkenylsiloxanes, and their use in Hiyama-Denmark cross coupling](image)

Although Hiyama-Denmark cross couplings of silanes such as 96 have previously been reported, all have employed fluoride as an activator. It would be of significant synthetic value to extend this reaction to fluoride-free couplings, offering tolerance to common silyl protecting groups, and opening up exciting possibilities for orthogonal reactivity. This will be described in Chapters 3 and 4. Although studies have been conducted on the mechanism of the Hiyama-Denmark coupling, significant variations are seen in the exact mechanism of the transmetalation step across different organosilanes studied, and no specific findings for silanes such as 96 are reported. We therefore aspire to shed some light on the exact mode of reaction that such species exhibit and hope to offer some explanation for patterns of reactivity observed experimentally. This is described in Chapter 4.

The principle motivation for developing the synthesis and cross coupling of cyclic alkenylsiloxanes 96 is to apply the methodology to the preparation of complex polyene natural products, as many contain the Z-allylic alcohol motif generated (97, n = 0). Efforts towards this goal are described in Chapter 5.
2 The Development of Hydrogenation Methodology

In the preceding chapter, the importance of polyene motifs in a range of applications was discussed. The Z-alkenyl functionalities commonly required in complex target molecules are often generated by semi-reduction of alkynes via a formal syn-addition of hydrogen across a carbon-carbon triple bond. This chapter will describe the application of this concept to the preparation of cyclic alkenylsiloxanes, a strategy which we believe will allow facile access to these valuable reagents.

2.1 Introduction – the Stereoselective Reduction of Alkynes

Alkynes are a key functional group in synthesis, where versatile chemistry exists for their installation and subsequent transformation into other useful moieties.\(^7^5\) By virtue of the relatively low pK\(_a\) of acetylenic protons,\(^7^6\) nucleophilic metal acetylides are easily formed and react with a range of electrophiles; excellent chemo- and stereoselective control over addition have been reported under finely tuned reaction conditions.\(^7^7\)–\(^7^9\) Alkynes are also useful substrates in Sonogashira couplings and metathesis reactions.\(^8^0\)–\(^8^1\) Many terminal and internal alkynes are commercially available; they can also be generated directly from alkynylation of carbonyls.\(^8^2\)

The breadth of chemistry that generates carbon-carbon triple bonds thus makes them ideal precursors in the synthesis of alkenes. Although many methods are available for the reduction of alkynes to E-vinyl compounds\(^8^3\) the following discussion will focus on the formal syn-addition of hydrogen across triple bonds to generate Z-alkenes. A wide range of processes have been developed for the stereoselective cis-reduction of alkynes,\(^3^6\) and the choice of
available procedures can be daunting to contemplate. Different conditions offer access to complimentary substrate scopes, although some methods have been found to be more general than others. Unsurprisingly these have also proved to be the most popular; a short summary of each will be given below.

Numerous palladium catalysts have been reported to reduce alkynes to Z-alkenes under hydrogen atmospheres; among these, the heterogeneous Lindlar catalyst and its modified cousins are the most often deployed. First reported in 1952, the Lindlar catalyst is formed from palladium metal deposited on calcium carbonate. This is treated with a solution of lead (II) acetate, which has been shown to cause morphological changes to the palladium surface; the proportion of selective terraced sites on the metal surface increases relative to stepped and kinked ones (which can mediate alkene reduction and isomerisation). Quinoline is then added as a poison; this can also independently effect the catalyst modifications described above, and can inhibit alkene surface interactions, further disfavouring overhydrogenation. The Lindlar catalyst (treated with lead) is commercially available, as is Pd/CaCO$_3$ itself and Pd/BaSO$_4$ (Rosenmund catalyst). All three are broadly applied in synthesis, although Maier has noted that the use of quinoline poison alone is as effective as lead acetate treatment at promoting selective catalysis, obviating the need for the use of Lindlar’s original catalyst. It is thus surprising that it continues to enjoy such popularity considering its toxic heavy metal content. All the aforementioned catalysts are stable and easy to handle, which has encouraged widespread uptake of the methodology, as has the excellent scope/functional group tolerance and simple reaction conditions (5–10% catalyst with varying amounts of quinoline (or other poison), stirred with alkyne under an atmospheric pressure of hydrogen). However, for some substrates overreduction and isomerisation can represent significant drawbacks; inconsistent performance between batches of catalyst has also been observed. Nickel catalysis is commonly encountered in the semi-reduction of alkynes, and prevalent in the field is Brown’s catalyst, also known as P2-Ni. This oxygen-sensitive catalyst must be
prepared directly before use from Ni(OAc)$_2$·4H$_2$O and ethanolic NaBH$_4$ under an atmosphere of hydrogen; alkyne substrates are then added directly to the resulting black suspension.$^{88,89}$ Despite this inconvenience, its use is second only to the Lindlar-type catalysts described above, it is tolerant of an enormous range of functionality, and exhibits excellent chemo- and stereoselectivity.$^{36}$

There are many examples of semi-reduction procedures which do not require the use of hydrogen gas itself – these may provide operational advantages in some settings. Diimide is an effective reductant for carbon-carbon triple bonds, although it can also react with alkenes and carbonyls under extended reaction times.$^{90}$ Diimide itself is unstable, and is therefore generated in situ from a more stable precursor, such as an aryl sulfonylhydrazine.$^{91-94}$ Various preparations of activated zinc, in the presence of an alcoholic solvent to act as a hydrogen donor, have also been shown to reduce alkynes to Z-alkenes.$^{36}$ Some zinc reagents are commercially available, while others must be freshly prepared by stirring zinc powder with copper and/or silver salts, or with organic activators such as 1,2-dibromoethane.$^{95,96}$

Another important and widely used class of reduction is a two-step sequence of hydrometalation, followed by protodemetalation.$^{36}$ Sterically hindered boranes are commonly employed for this,$^{97}$ and undergo syn-addition to alkynes (both metal-catalysed and uncatalysed variants have been reported)$^{98,99}$ to generate alkenylboranes. The borane moiety is subsequently removed by protonolysis under acidic$^{100}$ or methanolic$^{101}$ conditions to generate cis-alkene products. This strategy has been employed with a variety of metals, including aluminium,$^{102}$ zinc$^{103}$ and magnesium$^{104}$ which all require the presence of a titanium catalyst; this is reduced in situ to a titanium hydride species which undergoes a hydrotitanation with the alkyne substrate, and is subsequently transmetalated.

The numerous methods described above present a wide choice of options for alkyne semi-reduction. We wish to apply this concept to the formation of cyclic alkenylsiloxanes from
alkynylsilanes (as outlined in the previous chapter, Scheme 1.24); however, the vast majority of substrates feature alkynes with two carbon substituents. In the next section, the specific cases of carbon-carbon triple bonds with a silicon substituent at one end will be examined, with a focus on their use in popular Lindlar-type processes.

2.1.1 The Challenge of Alkynylsilane Reduction

There are a number of reports in the literature of alkynylsilanes in Lindlar-type reductions; however, the outcome observed frequently varies from that expected for non-silylated alkynes. Many exhibit similar behaviour to all-carbon variants, and can be cleanly reduced to Z-alkenes with high yield and stereoselectivity; for example, Fleming has reported the reduction of butynylsilane 98 in excellent yield as a single geometrical isomer (Eq. 1, Scheme 2.1).\textsuperscript{105} Many researchers have found alkynylsilanes to be sluggish substrates in these reductions; Hudson \textit{et al.} struggled with long reaction times and incomplete conversion of substrate 99 (Eq. 2, Scheme 2.1),\textsuperscript{106} and also observed formation of the unwanted E-isomer of 100. The reluctance of alkynylsilanes to undergo hydrogenation can be so profound in some substrates that a silyl group can act as a protecting group for a pseudo-terminal carbon-carbon triple bond: the trimethylsilylalkyne moiety in 101 remains untouched while an internal alkyne is smoothly reduced to 102 (Eq. 3, Scheme 2.1).\textsuperscript{107} Notably, the reaction time in this case is

\begin{equation}
\text{Eq. 1:} \quad \begin{array}{c}
\text{SiMe}_2\text{Ph} \\
\text{H}_2, \text{Pd/BaSO}_4, \text{quinoline, MeOH} \\
3 \text{ h, 80\%}, \text{100\% Z}
\end{array}
\end{equation}

\begin{equation}
\text{Eq. 2:} \quad \begin{array}{c}
\text{TBDPSO} \\
\text{SiMe}_2\text{Ph} \\
\text{H}_2, \text{Pd/BaSO}_4, \text{pyridine} \\
27 \text{ h, 77\% (+16\% 99)} \quad 4:1 Z:E
\end{array}
\end{equation}

\begin{equation}
\text{Eq. 3:} \quad \begin{array}{c}
\text{C}_6\text{H}_9 \\
\text{SiMe}_2\text{Ph} \\
\text{H}_2, \text{Pd/CaCO}_3, \text{quinoline, hexane} \\
30 \text{ min, 70\%}
\end{array}
\end{equation}

\begin{equation}
\text{Eq. 4:} \quad \begin{array}{c}
\text{HO} \\
\text{SiMe}_2\text{Ph} \\
\text{H}_2, \text{Pd/BaSO}_4, \text{quinoline, MeOH} \\
7 \text{ h, 61\%, 19:1 Z:E}
\end{array}
\end{equation}

\text{Scheme 2.1: Varying outcomes in alkynylsilane reduction}
significantly shorter than in the previous examples discussed. Conversely, some alkynylsilanes (such as 103, Eq. 4, Scheme 2.1) are prone to overreduction; a report from Fleming tells of overreduction (104), incomplete conversion and production of the unwanted E-isomer (105).\textsuperscript{108} Similar examples can be found for the alternative methods of semihydrogenation described above, although reports are sparse and successful procedures often require harsh conditions or two-step transformations.\textsuperscript{36} These combined factors make it unsurprising that only a single report exists of the use of alkyne reductions to access cyclic alkenylsiloxanes.\textsuperscript{46}

There may be several factors which give rise to the observed departure from normal alkyne behaviour in the presence of silyl substituents. The atomic radius of silicon is more than twice that of carbon (1.77 Å and 0.77 Å, respectively),\textsuperscript{109} hence a silyl group is often considered a ‘blocking group’ whose large size disfavours the association of alkyne and catalyst. Electronic effects may also play a role in the observed behaviour of alkynylsilanes. A study by Levy and co-workers found significant polarisation in the carbon-carbon triple bond of phenyltrimethylsilylacetylene;\textsuperscript{110} the α-carbon was found to be electronically shielded, while the β-carbon was strongly deshielded (as evidenced by their \textsuperscript{13}C NMR shifts of 92.5 and 101.4 ppm respectively). This was attributed to a significant ground state contribution from resonance form 106 (Scheme 2.2) where electron density from the triple bond was donated to silicon, either via C→Si (p-d)\textsubscript{π} backbonding (107) or hyperconjugation of the C≡C \textπ-bond and Si–C σ* (108). Later studies have shown the latter to be the more plausible explanation.\textsuperscript{111,112} This removal of electron density from the alkyne triple bond may be a factor in its low reactivity toward reduction.

![Scheme 2.2: Resonance forms of phenyltrimethylsilylacetylene](image-url)
Despite the difficulties noted above, we hoped that Lindlar reduction would prove to be a viable route to our desired cyclic alkenylsiloxane species. In the next section previous work on the application of this strategy will be discussed; this will set the scene for development of our own conditions to effect this transformation.

### 2.1.2 Previous Synthesis of Cyclic Alkenylsiloxanes Using Lindlar Hydrogenation

The only previous report of a Lindlar-type reduction employed to access a cyclic alkenylsiloxane species was presented in Chapter 1 (Scheme 1.9, and in Scheme 2.3 reproduced below for convenience). In this work, no comment is made on reaction time, nor geometrical fidelity. The intermediate cis-vinylsilane undergoes palladium-mediated silyl ether formation to give 32; presumably any E-vinylsilane, unable to cyclise in this way, was easily removed after the reaction by virtue of its higher polarity. The moderate yield of 32 may suggest that this E-form of 109 may have been a significant side product, although it should also be noted that the allylic gem-dimethyl and diisopropylsilyl substituents render the alkyne rather sterically hindered.

![Scheme 2.3: Detail of Lindlar reduction reported by Salomon](image)

Preliminary investigations into the use of the Lindlar reduction to access cyclic alkenylsiloxanes had been conducted within our research group prior to the start of the work presented in this thesis. Species 110 was targeted as a key intermediate in the synthesis of

![Scheme 2.4: Application of Lim and Andersons’s cyclic alkenylsiloxane to incednine (unpublished)](image)
the potential chemotherapeutic natural product incednine 111 (Scheme 2.4) which features a polyene motif with a Z-double bond and allylic alcohol (shown in blue in Scheme 2.4). It was envisaged that this fragment could be accessed by the Hiyama-Denmark cross coupling of 110 with an appropriate polyenic halide.

Diane Lim conducted a brief survey of conditions for the semihydrogenation of silylalkyne 112 (Table 2.1). The choice of diethylisopropoxysilyl moiety was judicious; the precise reasons for this will be discussed in the following section. Lead-poisoned and lead-free Lindlar catalysts were investigated in the presence of quinoline poison; Pd/CaCO₃ proved superior (entries 1 and 2). However, reactions times were prohibitively long at these low catalyst loadings, while high loadings led to poor Z-selectivity (entry 4) and overhydrogenation (entry 5). An intermediate loading of 5 mol% of palladium was identified as optimal, under which conditions 110 was produced in good yield and with acceptable Z-selectivity (83:17, entry 3).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Reaction time / h</th>
<th>110 : 113</th>
<th>Yield / %&lt;sup&gt;a&lt;/sup&gt; (conversion / %&lt;sup&gt;b&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd/CaCO₃ (2 mol%)</td>
<td>72</td>
<td>87 : 13</td>
<td>n.d. (50)</td>
</tr>
<tr>
<td>2</td>
<td>Pd/Pb/CaCO₃ (2 mol%)</td>
<td>72</td>
<td>33 : 67</td>
<td>n.d. (29)</td>
</tr>
<tr>
<td>3</td>
<td>Pd/CaCO₃ (5 mol%)</td>
<td>5</td>
<td>83 : 17</td>
<td>84 (100)</td>
</tr>
<tr>
<td>4</td>
<td>Pd/CaCO₃ (10 mol%)</td>
<td>2</td>
<td>75 : 25</td>
<td>33 (100)</td>
</tr>
<tr>
<td>5</td>
<td>Pd/CaCO₃ (20 mol%)</td>
<td>2</td>
<td>91 : 9</td>
<td>15&lt;sup&gt;c&lt;/sup&gt; (100)</td>
</tr>
</tbody>
</table>

n.d. = not determined. <sup>a</sup> Isolated yields of 110 and 113 after chromatography. <sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopic analysis of crude reaction mixtures. <sup>c</sup> Significant overreduction observed.

Table 2.1: Lim’s screen of semihydrogenation conditions (reproduced from thesis)<sup>113</sup>

These results provided a starting point for the development of more general and selective conditions, as will be described below. The initial aim of these studies was to synthesise substrates for this investigation; this will be presented in Section 2.2. Extensive optimisation was then performed to find appropriate hydrogenation conditions, details of which will be
given in Section 2.3. Finally, a range of cyclic alkenylsiloxanes of differing ring sizes, substituents and substitution patterns were synthesised (Section 2.4) and attempts were made to extend the methodology to the generation of larger ring sizes (Section 2.5).

2.2 Synthesis of Substrates for Lindlar Semihydrogenation

The addition of acetylide nucleophiles into a variety of electrophiles offers flexible access to a range of substitution patterns; hence, a terminal alkynylsilane was required that could be used in the synthesis of all substrates. Lim’s previous work had employed a diethylisopropoxysilyl group; this was again selected, due to its favourable compromise of desired characteristics. The diethyl groups had been chosen to provide steric protection for the silicon centre from nucleophilic attack; it was anticipated that dimethylsilanes would be too labile towards desilylation, while diisopropylsilanes might prove too hindered to react in cross coupling applications, a proposal that is in line with Denmark’s studies on exocyclic alkenylsiloxanes. Meanwhile, a secondary alkoxy substituent (isopropoxy) was selected to resist displacement by adventitious nucleophiles, until required during ring closure. Silane 114 was thus identified as our general starting material; it is not commercially available, so was synthesised on multigram scale in two steps from diethyldichlorosilane using Chan’s method (Scheme 2.5).

\[
\begin{align*}
\text{Et}_2\text{SiCl}_2 & \xrightarrow{\text{HNEt}_2, \text{NEt}_3, \text{THF, 0°C} \rightarrow \text{rt}, 16 \text{ h}, 88\%} \text{Et}_2\text{SiCl}(\text{NEt}_3) & \xrightarrow{\text{HCCMeBr, THF, reflux, 5 h; then } \text{i-PrOH, DMAP, 51\%}} \text{i-PrOEt}_2\text{Si}114
\end{align*}
\]

Scheme 2.5: Synthesis of silylalkyne 114

The formation of valuable 5-membered cyclic alkenylsiloxanes required the preparation of propargylic alcohol precursors; their synthesis is shown in Scheme 2.6. The lithium acetylide of 114 was generated and subsequently treated with a range of aldehyde electrophiles, producing 115a-e in good to excellent yields. A range of substituents were introduced to provide diversity in later substrate scope exploration.
The asymmetric synthesis of cyclic alkenylsiloxanes was a key objective of this project, as single enantiomer reagents would be necessary for applications in total synthesis. Several procedures have appeared in the literature that allow direct asymmetric addition of acetylide nucleophiles to aldehydes and ketones. Carreira has reported the use of catalytic zinc triflate, N-methylephedrine and an amine base to prepare propargylic alcohols with high enantiopurity. Unfortunately, when this was applied to the synthesis of (R)-115e none of the desired product was observed, presumably due to the intolerance of the alkoxy alkynylsilane to the Lewis acidic zinc salt. Another widely used strategy in the asymmetric synthesis of propargylic alcohols is the enantioselective reduction of ynones; among these methods, Noyori’s mild ruthenium-catalysed transfer hydrogenation protocol is particularly prominent. Racemic alcohol 115e was thus oxidised cleanly to ketone 116e, which proved highly unstable to silica gel chromatography; the crude material was therefore submitted directly to Noyori’s conditions (Scheme 2.7). To our delight, (R)-115e was produced in excellent yield and enantioselectivity (as determined by chiral HPLC).

Homopropargylic alcohols were expected to give access to 6-membered cyclic alkenylsiloxanes, and were prepared by BF$_3$·OEt$_2$ promoted regioselective opening of various epoxides using the lithium acetylide of 114 to give homopropargylic alcohols 117a-e in...
moderate to quantitative yields (Scheme 2.8). It is interesting to note that the diisopropoxysilane moiety was tolerant of this Lewis acid at low temperature. As previously, a range of substituents were explored; unfortunately it was found that aryl substituents (R = phenyl) could not be introduced by this method, as epoxide opening was non-regioselective and the resulting products too labile to isolate. Substrates could be prepared as single enantiomers via the use of enantioenriched epoxide starting materials. Whilst many are commercially available, the Jacobsen hydrolytic kinetic resolution of terminal epoxides offers an efficient and general route to more complex targets. Using this method epoxide (R)-118e was prepared as a single enantiomer (Scheme 2.8); ring opening gave (R)-117e.

\[
\begin{align*}
\text{Scheme 2.8: Synthesis of homopropargylic alcohol substrates (for 6-membered ring formation)}
\end{align*}
\]

2.3 Optimisation of the Hydrogenation Procedure

With a selection of representative substrates in hand, attention was turned to the identification of conditions to effect our desired transformation – to produce Z-alkenylsilanes that would cyclise in situ to generate valuable cyclic alkenylsiloxanes. This will first be described for the formation of 5-membered silanes (Section 2.3.1); the conclusions from these studies will then be applied to the formation of 6-membered analogues (Section 2.3.2).

2.3.1 Optimisation of the Synthesis of 5-Membered Cyclic Alkenylsiloxanes

Lim’s previous work provided a useful starting point for optimisation studies, hence n-hexyl substituted propargylic alcohol 115a was submitted to her best conditions (Scheme 2.9).
Although the desired cyclic silane 119a was indeed formed, it was a minor component of the crude reaction mixture; E-vinylsilane 120a was the major product, and significant overreduction was also observed. A much shorter reaction time improved Z-selectivity somewhat, but the isolated yield was low (42%). The production of significant amounts of E-isomer is consistent with behaviour seen in Scheme 2.2, although somewhat more severe. A closer examination of the literature revealed that while propargylic alkynylsilanes have previously been reported to participate in Lindlar reductions, the stereochemical outcome is frequently poor; for example, Igawa reported a similar result in 2006 (Scheme 2.10).\textsuperscript{122}

\begin{center}
Scheme 2.9: Initial attempts to reduce alkynylsilane 115a
\end{center}

\begin{center}
Scheme 2.10: Igawa’s semihydrogenation of a propargylic alcohol
\end{center}

Two studies conducted on the mechanism of heterogeneous palladium-mediated hydrogenations prove illuminating in this matter. A report from Maier et al. describes the relative affinity of a series of alkynes and their reduced alkene counterparts for the surface of the Lindlar catalyst (in the absence of quinoline).\textsuperscript{123} Alkyne 121 was found to be almost four times as likely as the reduced alkene to bind to the catalyst surface; in contrast, propargylic alcohol 122 was five times less likely to outcompete the alkene product of its reduction (Scheme 2.11). If the same principle can be applied to our system (albeit tempered by the presence of a quinoline poison), the high affinity of the Lindlar catalyst for reduced 115a disfavours its dissociation from the palladium surface after one equivalent of hydrogen has been absorbed, rendering it vulnerable to the addition of a second equivalent. Another study by Dobson et al. has shown that E-alkene by-products of palladium-mediated semihydrogenation
are a result of post-reduction *cis*-trans isomerisation mediated by the catalyst; crucially this only occurs under an atmosphere of hydrogen.\textsuperscript{124} Therefore the increased association of the reduced form of 115a with the Lindlar catalyst may promote the excessive levels of isomerisation to 120a that were observed.

\begin{align*}
\text{Ulan, Maier and Smith:} & \quad \begin{array}{c}
\text{Ratio of catalyst affinity} \\
\text{for alkyne/alkene:}
\end{array} \\
121 & \quad 3.7 \\
122 & \quad 0.2
\end{align*}

Scheme 2.11: Ulan’s studies on the relative affinity of the Lindlar catalyst for alkynes and alkenes

A footnote in a paper by Panek hinted at a solution to this problem,\textsuperscript{125} where the reduction of dimethylphenylsilyl alkyne 123 with a propargylic acetate group was reported to proceed with superior stereoselectivity relative to the free alcohol (Scheme 2.12). We were delighted to see that when acetate 124a was submitted to Lim’s conditions, very little of undesired 120a was produced (Z:E = 96:4), and after simple treatment of the crude hydrogenation reaction mixture with methanolic potassium carbonate, cyclic alkenylsiloxane 119a was produced in very good yield on both small and multigram scale (entries 1 and 2, Table 2.2). The increased reaction time (relative to the reaction of free alcohol 115a, Scheme 2.9) is a practical advantage as it allows more precise monitoring of conversion by TLC, which avoids overreduction. Other ester protecting groups were investigated to determine whether the formation of 119a could be completely excluded (entries 3-5), but were found to be inferior. A solvent screen was performed to assess the relative suitability of toluene. Benzene proved equally successful, but was discounted due to its toxicity (entry 6). Alcohol solvents (entries 7-9) were found to promote faster reactivity; practically this makes conversion more difficult to follow, and furthermore both overhydrogenation and increased ratios of 120a were observed. Similar

\begin{align*}
\text{Scheme 2.12: Panek’s use of a propargylic acetate to improve Z:E selectivity}
\end{align*}
<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Solvent</th>
<th>Hydrogenation Time</th>
<th>119a : 120a&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ac</td>
<td>toluene</td>
<td>50 min</td>
<td>96 : 4</td>
<td>75%</td>
</tr>
<tr>
<td>2</td>
<td>Ac</td>
<td>toluene</td>
<td>50 min</td>
<td>96 : 4</td>
<td>80%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>COEt</td>
<td>toluene</td>
<td>1 h</td>
<td>95 : 5</td>
<td>73%</td>
</tr>
<tr>
<td>4</td>
<td>COPh</td>
<td>toluene</td>
<td>25 min</td>
<td>96 : 4</td>
<td>20%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>COCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>toluene</td>
<td>5 h</td>
<td>-</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>Ac</td>
<td>benzene</td>
<td>50 min</td>
<td>96 : 4</td>
<td>73%</td>
</tr>
<tr>
<td>7</td>
<td>Ac</td>
<td>MeOH</td>
<td>8 min</td>
<td>89 : 11</td>
<td>72%&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>Ac</td>
<td>EtOH</td>
<td>8 min</td>
<td>95 : 5</td>
<td>75%&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>Ac</td>
<td>i-PrOH</td>
<td>15 min</td>
<td>93 : 7</td>
<td>76%&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>Ac</td>
<td>EtOAc</td>
<td>15 min</td>
<td>87 : 13</td>
<td>66%&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>Ac</td>
<td>THF</td>
<td>1.5 h</td>
<td>95 : 5</td>
<td>76%</td>
</tr>
<tr>
<td>12</td>
<td>Ac</td>
<td>THF</td>
<td>1.5 h</td>
<td>86 : 14</td>
<td>49%&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

All reactions performed with 0.15 mmol of 124, 0.1 M unless otherwise indicated. <sup>a</sup>Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>b</sup>2.2 g of 124a. <sup>c</sup>PhCO<sub>2</sub>Me by-product complicates purification, resulting in lower yield. <sup>d</sup>Overreduction to alkylsilane observed. <sup>e</sup>500 mg of 124a.

Table 2.2: Optimisation of propargylic alcohol hydrogenation conditions

results were obtained with ethyl acetate (entry 10). THF proved to be an effective solvent, producing 119a in high yield and selectivity (entry 11); unfortunately, this result was inconsistent, with varying Z:E ratios observed (entry 12). Despite this, its lower boiling point relative to toluene renders it useful for the preparation of volatile cyclic alkenysiloxanes.

During this work, it became apparent that the isolated yields were consistently lower than predicted from the ratio of products observed in the crude reaction mixtures (Table 2.2). Initial attempts at purifying 119a using standard chromatographic techniques typically resulted in low mass recovery, with at least 50% of material lost during the silica chromatography. We proposed that this might be due to ring strain in 119a; nucleophilic attack by the silanol groups of the stationary phase at silicon may open the ring and sequester the product. Attempts to
buffer the eluent or silica with triethylamine, potassium carbonate or acetic acid proved detrimental, hence it was necessary to limit the time 119a was exposed to silica gel. Thus rapid elution on a short column of untreated silica (4-5 cm, 8-9 g/mmol of crude) was able to provide clean 119a, with an acceptable 70-80% mass recovery; this purification procedure was effective on a variety of scales.

Mild, practical conditions were now in hand to synthesise cyclic alkenylsiloxane 119a in high yield. The next two sections of this chapter will describe the extension of this methodology to the synthesis of 6-membered analogues, followed by an investigation into the scope of the reaction.

2.3.2 Optimisation of the Synthesis of 6-Membered Cyclic Alkenylsiloxanes

The introduction of Z-homoallylic motifs into polyene targets is also an important goal that could be achieved via the cross coupling of 6-membered cyclic alkenylsiloxanes. In order to synthesise these useful reagents we next investigated their formation from homopropargylic alkynylsilanes. Alcohol 117e was submitted to the optimal reaction conditions identified above (entry 1, Table 2.3). In contrast to the result observed with alcohol 115a (entry 1, Table 2.2) this substrate, containing a free alcohol, was reduced with a good Z:E ratio; it seems it is therefore unnecessary to add acetate protection and deprotection steps into the route to 125e.

\[
\begin{align*}
\text{H}_2, \text{Pd/CaCO}_3 (5 \text{ mol}%), \text{ quinoline (see table).} & \quad \text{PhMe; K}_2\text{CO}_3/\text{MeOH filter} \\
\text{117e} & \quad \text{125e} \\
\text{117e} & \quad \text{126e} \\
\text{117e} & \quad \text{127e}
\end{align*}
\]

\[
\begin{array}{|c|c|c|c|c|}
\hline
\text{Entry} & \text{Quinoline Loading} & \text{Reaction Time} & \text{125e : 126e : 127e} & \text{Isolated Yield} \\
\hline
1 & 20 \text{ mol}\% & \text{10 min} & 54 : 6 : 40 & 55\% \\
2 & 50 \text{ mol}\% & \text{10 min} & 92 : 8 : 0 & 79\% \\
3 & 100 \text{ mol}\% & \text{10 min} & 82 : 18 : 0 & 73\% \\
\hline
\end{array}
\]

* Determined by \textsuperscript{1}H NMR spectroscopic analysis of the crude reaction mixture.

Table 2.3: Variation of quinoline loading to minimise overreduction
However, despite the short reaction time a significant amount of overhydrogenation was observed, producing saturated alkoxy silane $127e$. Selectivity for alkyne reduction alone was found to be restored by raising the loading of quinoline poison – 50 mol% was found to be optimal, under which conditions $125e$ was produced in very good yield (entry 2). It is interesting to note that in all cases cyclisation to $125e$ did not occur spontaneously (as was observed with $119a$ in Scheme 2.9); filtration of a methanolic solution of the crude material through a plug of potassium carbonate proved necessary to effect this.

Interestingly, the anticipated (by $^1\text{H}$ NMR analysis) and isolated yields are more consistent for the 6-membered ring product, indicating reduced loss to the chromatographic medium. This is as expected, as 6-membered siloxanes are likely to be less strained. A similar trend can be seen in Denmark’s work with dimethylsilane analogues, where examination of the supporting information reveals that 6-membered silanes were purified by filtration through a short column of silica gel, followed by distillation, whereas the less stable 5-membered rings had to be filtered through celite. Overall, we were pleased to find that the reaction conditions developed in Section 2.2 were so readily applied to another substrate; the generality of the procedure was next investigated with a survey of the scope.

### 2.4 Investigation of the Scope of Reduction

With conditions now in hand to access both 5- and 6-membered cyclic alkenylsiloxanes, a series of such products were prepared (Scheme 2.13). 5-Membered cyclic siloxanes were obtained in excellent yields; their syntheses show that the methodology is tolerant of straight ($119a$) and branched ($119b$) alkyl chains, as well as the common tert-butyldimethylsilyl ether ($119d$) and para-methoxybenzyl ether protecting groups ($119e$). Substrate $119e$ also demonstrates that the application of Noyori transfer hydrogenation of ynones (as seen in Scheme 2.7) allows access to such species as single enantiomers. The same success across this range of substituents was also observed for their 6-membered cousins ($125a$-$e$); again, the
synthesis of (R)-125e (after Jacobsen HKR on the precursor epoxide) demonstrates the ease with which enantioenriched reagents of this ring size can be generated. It was also possible to vary the pattern of substituents around the cyclic alkenylsiloxane ring – substrate 119f was prepared by addition of lithiated 114 to cyclohexanone, followed by hydrogenation. An acetate precursor to 119f was found to be inert to our reaction conditions, presumably due to increased steric hindrance, thus a free alcohol precursor was employed directly, with high quinoline loading as for a homopropargylic alcohol. Despite the additional poison, overhydrogenation was still observed; however, the use of cyclohexene as a sacrificial co-solvent proved effective in preventing this, and 119f was generated in good yield. The use of disubstituted epoxides led to the production of a fused silane 125g: addition of lithiated 114 into cyclohexene oxide gave the precursor to 125g which underwent reduction in moderate yield.

Scheme 2.13: Cyclic alkenylsiloxanes synthesised by Lindlar reduction (colour indicates reaction conditions employed)

Unfortunately, not all substrates proved successful under the conditions shown above. It was found that aryl sidechains were not well tolerated by the methodology, as shown by the behaviour of 124c under our standard reaction conditions (Scheme 2.14). In addition to desired product 119c, deoxygenation (128c) and further saturation (129c) were also observed in $^1$H
NMR spectra of crude reaction mixtures; presumably the benzylic nature of the C–O bond renders it vulnerable to reductive cleavage. Due to their similar polarity, these products could not be separated from 119c by column chromatography without near complete loss of material. Extensive reoptimisation was undertaken in an effort to find a solution to this problem; catalyst and quinoline loadings were varied, as was concentration. Although variations in the relative proportions of 119c, 128c and 129c were observed, the levels of these unwanted impurities remained significant. A serendipitous discovery by Gudmundsson (another student in the Anderson group) provided an unexpected solution to this issue; the rational exploration and application of this will be discussed in the next section.

2.4.1 The Use of Silanols as Starting Materials

As has previously been implied, the diethylisopropoxysilyl moiety, while stable to a wide range of chemical processes, is found to be labile under certain conditions; on occasion its hydrolysis to the corresponding diethylsilanol, particularly in strong aqueous acid or base, has been observed. Previously this was considered ‘game over’ for the affected material; silanols are too unstable to be purified by column chromatography, and are vulnerable to dimerization to rather inert disiloxanes. In their continuing work towards the synthesis of incednine, Lim, Gudmundsson and Anderson had prepared silylalkyne 130-i-Pr by a titanium-mediated benzoate epoxide opening (Scheme 2.15).113,127 To obtain high yields in this reaction it was necessary to employ work up conditions that hydrolysed 130-i-Pr to its silanol form 130-H. Immediate submission of this crude material to Lindlar conditions heralded a key discovery – not only could alkynylsilanols participate in the reduction, they were found to hydrogenate much faster, and in this case in higher yield than the isopropoxysilane previously employed.
Scheme 2.15: Use of silanol by Gudmundsson towards the synthesis of incednine (unpublished)

The increased rate of alkynylsilanol reduction hinted at a solution to the problem of benzylic C–O cleavage – if the rate of carbon-carbon triple bond reduction could be increased relative to that of the carbon-oxygen bond, perhaps the formation of deoxygenated side products 128c and 129c could be prevented altogether. Alkoxysilane 124c was easily converted to silanol 124c-H, which was used immediately without further purification. Table 2.4 shows the results of these studies; results with isopropoxysilanes 115c and 124c are included for comparison (entries 1 and 3). As expected, acetylated silanol reached full conversion very quickly, although unfortunately little change in the amount of 128c and 129c produced was observed (entry 2). However, we were delighted to find that submission of the silanol as the free alcohol resulted in no traces of 128c or 129c, although significant overreduction lowered the isolated yield (entry 4). Addition of cyclohexene co-solvent tempered this (entry 5).

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Time (min)</th>
<th>Mol % Pd</th>
<th>Additive</th>
<th>Isolated Yield of 119c</th>
<th>128c (%)</th>
<th>129c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ac</td>
<td>i-Pr</td>
<td>180</td>
<td>5</td>
<td>-</td>
<td>&lt;50%</td>
<td>10%</td>
<td>15%</td>
</tr>
<tr>
<td>2</td>
<td>Ac</td>
<td>H</td>
<td>5</td>
<td>5</td>
<td>-</td>
<td>&lt;50%</td>
<td>3%</td>
<td>20%</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>i-Pr</td>
<td>25</td>
<td>5</td>
<td>-</td>
<td>45%</td>
<td>5%</td>
<td>20%</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>H</td>
<td>5</td>
<td>5</td>
<td>cyclohexene c</td>
<td>42%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>H</td>
<td>5</td>
<td>5</td>
<td>cyclohexene c</td>
<td>56%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>H</td>
<td>20</td>
<td>1</td>
<td>cyclohexene c</td>
<td>62%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

a Determined by 1H NMR analysis of the crude reaction mixture. b Overreduction to alkylsilane observed. c Used as a co-solvent, 10:1 toluene:cyclohexene.

Table 2.4: Reoptimisation of synthesis of 119c
catalyst loading to 1 mol% palladium increased the reaction time, allowing more precise monitoring of conversion by TLC; this prevented overreduction, and pure 119c was obtained in good yield. The tolerance of the hydrogenation methodology to silanols is a significant boon; it allows more flexibility when synthesising reduction substrates, meaning that a wider range of reaction and work-up conditions are compatible with routes to synthesise cyclic alkenylsiloxanes. What remains unclear is why silanols behave the way they do – this will be discussed in the following section.

2.4.2 Investigating the Properties of Alkynylsilanols: Applications to Orthogonal Reduction

We postulated that the heightened reactivity of alkynylsilanols could arise for two reasons. The replacement of a large isopropyl group by hydrogen would significantly reduce steric bulk around the carbon-carbon triple bond, potentially allowing better binding to palladium. Alternatively (or additionally) the silanol moiety may act as a ligand for the metal, again favouring its association with the catalyst surface; this has previously been postulated for other types of silanols.63,128,129 In order to investigate this, a series of alkoxysilanes were prepared by substitution of the isopropoxysilane by other alcohols or water with various oxygen substituents on silicon (Scheme 2.16); their behaviour under Lindlar conditions was then studied.

![Scheme 2.16: Preparation of silanes with varied oxygen substituent](image)

It was found that the nature of the oxygen substituent on silicon had a profound effect on the rate of reaction (Table 2.5). Unsurprisingly, the speed of reduction was found to increase as steric bulk was decreased (entries 1-4). It was interesting to note, however, that the
stereoselectivity remained high throughout in acetylated substrates 124a, 124a-Me and 124a-Et. For comparison, silanol 115a-H, with a free alcohol moiety, produced more of unwanted E-120a with significant overreduction (entry 5). From these results it is reasonable to conclude that the rate enhancement observed with silanol substrates is largely due to the reduced steric hindrance around the reacting carbon-carbon triple bond; however this does not preclude the possibility that coordination of the silanol to palladium may also play a role.

Table 2.5: Investigation of the variation of rate of reaction with oxygen substitution

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Hydrogenation Time</th>
<th>119a : 120a</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>i-Pr</td>
<td>Ac</td>
<td>50 min</td>
<td>96 : 4</td>
<td>75%</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>Ac</td>
<td>25 min</td>
<td>96 : 4</td>
<td>71%</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>Ac</td>
<td>15 min</td>
<td>95 : 5</td>
<td>74%</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>Ac</td>
<td>&lt;5 min</td>
<td>95 : 5</td>
<td>62%</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>H</td>
<td>&lt;5 min</td>
<td>80 : 20</td>
<td>41%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

All reactions performed with 0.15 mmol of alkyne, 0.1 M. <sup>a</sup> Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>b</sup> Overreduction to ~ 25% alkylsilane observed.

The significant difference in the relative rates of reduction of isopropoxysilane 124a and silanol 124a-H presents a tantalising opportunity for orthogonal reactivity: would it be possible to reduce an alkynylsilanol in the presence of an isopropoxylalkynylsilane without reduction of the latter? This would not only be interesting from an academic point of view, but could also prove useful in synthetic applications, where orthogonality is highly valued. In order to test this hypothesis, equimolar amounts of silanol 124a-H and isopropoxysilane 124e were submitted to the optimised Lindlar conditions (Scheme 2.17). TLC showed conversion of 124a-H was achieved after 20 minutes, which is slower than was observed for the reduction of 124a-H alone (Table 2.5, entry 4). It is possible that the presence of another alkyne (124e) acts as a mild poison for the catalyst, in a similar manner to quinoline. Nevertheless, we were
delighted to see that silane $119a$ was formed selectively, with only minor conversion of $124e$ leading to trace amounts of $119e$. Meanwhile, alkyne $132e$ (resulting from desilylation of $124e$ under basic methanolic conditions) was recovered in good yield. Overall, this achieves the selective formation of a cyclic alkenylsiloxane in the presence of a masked terminal alkyne, adding this highly valuable group to the list of functionalities that can be accommodated by this methodology.

Scheme 2.17: Orthogonal reduction of silanol $124a$-H in presence of alkoxy silane $124e$

In this section it has been shown that the concept we have developed can be applied to the formation of a range of 5- and 6-membered cyclic alkenylsiloxanes, with various substituents, substitution patterns and protecting groups being well tolerated. The judicious use of silanol substrates also renders the methodology tolerant of hydrogenation-labile benzyl alcohol and alkynyl functionality. In the next section, efforts to extend these findings to the generation of 7-membered analogues will be described.

2.5 Efforts Towards the Synthesis of 7-Membered Cyclic Alkenylsiloxanes

Although polyene motifs with bis-homoallylic alcohols are not as commonplace as their allylic and homoallylic counterparts, examples of natural products containing such structures can be found in the literature – for example, in 1996 Magome et al. identified furanocandin (133, Scheme 2.18), isolated from *Trichlorothecium sp.*, which has been shown to possess antibiotic and antifungal properties. This carbohydrate-based compound has two pendant polyenes, one of which features an E,Z-diene with a bis-homoallylic alcohol functionality (shown in blue
in Scheme 2.18). Motifs such as that shown in Scheme 2.18 could be generated by Hiyama-Denmark cross coupling of appropriate 7-membered cyclic alkenylsiloxanes (such as 134); in order to access these species it would be necessary to prepare a *bis*-homopropargylic alcohol precursor such as 135 for use with the Lindlar reduction conditions developed above.

Scheme 2.18: Furanocandin, a natural product featuring a *bis*-homoallylic diene motif

It was envisaged that this could be achieved *via* propargylic deprotonation of alkynylsilane 136 (prepared in a manner analogous to terminal alkyne 114), followed by addition into an epoxide (Scheme 2.19). Various strong bases were evaluated, with the aim to find a base which could effect propargylic deprotonation, without also undergoing nucleophilic addition to the silane. *n*-Butyllithium did not prove successful, as while it was able to remove the required proton, a relatively high reaction temperature (0 °C) was required to form the lithiate; this promoted nucleophilic displacement of the isopropoxy group to generate a butyldiethylsilane (137a, Scheme 2.19). Lithium diisopropylamide and lithium hexamethyldisilazide were next surveyed; it was anticipated that their non-nucleophilic nature would prevent side reactions at silicon. Unfortunately, they proved unable to deprotonate 136. It was hoped that *s*-butyllithium, as a stronger base, would effect deprotonation at lower temperatures; in addition, its bulky nature might prevent nucleophilic attack at silicon. Although analysis of the $^1$H NMR spectrum of the crude material seemed to show some conversion of starting materials, a complex mixture was observed; attempted purification by column chromatography resulted in complete loss of material.
Unfortunately we were forced to conclude at this point that our methodology may not stretch to the inclusion of silanes such as 134, due to difficulties of substrate preparation. It is likely that different conditions could be found to synthesise 135a – Scheme 2.20 shows several strategies that could be used. Step economy is a concern in all examples, with several protection/deprotection and functional group interconversion processes required which may not be compatible with an alkoxy silane. Late-stage installation of the diethylisopropoxysilyl moiety is possible, but would not represent an efficient route to 7-membered silanes such as 134. Time constraints therefore caused us to abandon our efforts to synthesise 135a, although we remain convinced that 7-membered cyclic alkenylsiloxanes could have an important place in the synthetic chemist’s tool box – particularly if it were possible to generate novel cyclic dienyl silanes. Efforts towards this goal will be described in the following section.
2.5.1 Towards the Synthesis of Cyclic Dienylsiloxanes, Valuable Reagents in Polyene Synthesis

Where cyclic alkenylsiloxanes are valuable as Hiyama-Denmark cross coupling partners that stereospecifically install a Z-double bond, a silane such as 138 (Scheme 2.21), with two endocyclic double bonds, has the potential to selectively introduce a challenging Z,Z-diene motif. Such species would be powerful tools in the synthesis of key natural products such as inthomycin A (139), an antimicrobial, antitumour herbicide;\textsuperscript{131,132} or oximidine II (140), a potent anticancer agent with a novel mode of action that makes it an attractive candidate for chemotherapy.\textsuperscript{133} We propose that 7-membered cyclic dienylsiloxanes could be accessed from the double Lindlar reduction of diynes such as 141; alternatively, enyne substrates such as 142 could be employed, allowing for the incorporation of substituents on the double bond distal to silicon.

Scheme 2.21: Synthesis and application of cyclic dienylsiloxanes

In order to investigate the feasibility of this proposal, the semireduction of enyne 143 (prepared by a Sonogashira cross coupling of 114 with the appropriate vinyl iodide) was attempted; if successful, a very similar species could indeed be applied to the synthesis of the same motif in inthomycin A (Scheme 2.21). Disappointingly the substrate proved inert to optimised Lindlar hydrogenation conditions (Table 2.7, entry 1). The use of different solvents did little to improve this (entries 2 and 3), although faint traces of new vinyl species were observed in the crude \textsuperscript{1}H NMR spectrum when ethanol was employed as a solvent (entry 3). The poor outlook of the Lindlar hydrogenation merited consideration of alternative
semireduction methods.\textsuperscript{36} Zweifel has found that hydroalumination with DIBALH followed by protodealumination is an effective method for reducing silylenynes similar to 143;\textsuperscript{134} however in our hands the procedure proved unsuccessful, and no reaction was observed (entry 4). Hatakeyama and co-workers have reported the successful diimide reduction of a similar enyne;\textsuperscript{135} applying their conditions to our system at last resulted in activity, but unfortunately low conversion was observed, along with complete reduction of the carbon-carbon triple bond to the alkylsilane (entry 5). It was postulated that an acyclic Z,Z-diene must form as an intermediate in this process, and it was hoped that if it could be rapidly cyclised \textit{in situ} it might be protected from the further action of diimide. Potassium carbonate was therefore added to the reaction mixture in an attempt to promote this; however the result was unchanged (entry 6).

Finally, the use of activated zinc was explored, which Solladié \textit{et al.} had reported successful in the reduction of diynes.\textsuperscript{136} Only very faint traces of alkene products were detectable by \textsuperscript{1}H NMR after an extended reaction time (entry 7).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H\textsubscript{2}, Pd/CO\textsubscript{3} (5 mol%), quinoline (20 mol%), toluene, 5 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>As above, in THF, 7 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>As above, in EtOH, 7 h</td>
<td>Traces of new alkene peaks in \textsuperscript{1}H NMR of crude reaction mixture</td>
</tr>
<tr>
<td>4</td>
<td>DIBALH, Et\textsubscript{2}O, 40 °C, 5 h; then NaOH\textsubscript{(aq)}</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>NBSH, Et\textsubscript{3}N, THF/IPA 1/1, 27 h; then MeOH, filter through K\textsubscript{2}CO\textsubscript{3}</td>
<td>Incomplete conversion; no 144 only fully reduced C≡C compound observed</td>
</tr>
<tr>
<td>6</td>
<td>As above, with K\textsubscript{2}CO\textsubscript{3} to promote \textit{in situ} cyclisation</td>
<td>As above</td>
</tr>
<tr>
<td>7</td>
<td>Zn/Cu/Ag, MeOH/H\textsubscript{2}O, 21 h</td>
<td>Traces of new alkene peaks in \textsuperscript{1}H NMR of crude reaction mixture</td>
</tr>
</tbody>
</table>

NBSH = 2-nitrobenzenesulfonylhydrazide (a source of diimide)

\textit{Table 2.7: Attempts to reduce enyne 143}
It is unclear why substrate 143 is so reluctant to undergo semireduction. It may be an electronic effect arising from additional conjugation, or a steric issue with the methyl substituent of the alkene blocking association with the catalyst. Unfortunately time constraints prevented more in-depth investigations that might have found a solution to the problem. These studies were conducted prior to the discovery that silanols are effective participants in hydrogenations – it is possible that conversion of 143 into a silanol prior to reduction could enhance its reactivity and allow 144 to form. The great potential of 7-membered dienyl silanes such as 144 certainly merits further study; it is anticipated that future work within our research group will one day address this.

2.6 Conclusions

This chapter has seen the development of a successful method for the formation of 5- and 6-membered cyclic alkenylsiloxanes under mild reaction conditions from easily prepared propargylic and homopropargylic substrates. A range of examples were prepared using the optimised conditions identified; for some substrates, more specialised conditions were required, and were applied in a logical fashion to improve experimental outcomes.

With a range of silanes in hand our attention next turned to their application as cross coupling partners in the powerful Hiyama-Denmark reaction; this will be discussed in the following chapter.
3  The Use of Cyclic Alkenylsiloxanes in Hiyama-Denmark Cross Couplings and Iododesilylations

The cross coupling of cyclic alkenylsiloxanes allows access to valuable Z-containing polyenes with allylic or homoallylic alcohol substituents, as was seen in Section 1.4.2. This chapter describes the development of fluoride- and base-promoted coupling conditions, and some alternative uses of cyclic alkenylsiloxanes.

3.1  The Synthesis of Vinyl Iodide Coupling Partners

In order to investigate the cross coupling of the cyclic alkenylsiloxanes that were synthesised in Chapter 2, we required vinyl iodide coupling partners that could be used to generate polyene motifs. Only a limited number are commercially available and tend to be prohibitively expensive. However, a wide range of procedures exist for their preparation from various types of starting material. A quick note on compound labelling is necessary at this point: as with the silanes in Chapter 2, which were assigned a letter to denote their differing substituents (while keeping the same number), iodides are also identified by a letter. This is to enable clearer labelling of cross coupled products in later section (of the format 1ab, etc.). Iodostyrene (145a, Scheme 3.1) was to be our ‘standard’ coupling partner for optimisation studies – it was generated in excellent yield from benzyl bromide according to Charette’s one pot homologation/elimination method.\(^\text{137}\) Iodide 145b, featuring a benzylic ether, was synthesised from benzyl propargyl ether via a hydrozirconation with Schwartz’s reagent,\(^\text{138}\) followed by an \textit{in situ} quench of the vinyl zirconium(IV) intermediate with iodine. Finally, Z-vinyl iodides 145c and 145d were prepared using the Stork-Wittig reaction,\(^\text{139}\) which pleasingly generated
exclusively the desired Z-145c in good yield, while Z-145d was prone to minor isomerism. The preparation of further vinyl iodide coupling partners, suitable for use in the total synthesis of polyene natural products, will be discussed in Chapter 5.

3.2 Fluoride-Promoted Cross Coupling

There have been few reports of the cross coupling of cyclic alkenylsiloxanes; Denmark’s 2001 publication features the most relevant examples. While aryl iodides were principally investigated as coupling partners in that work, there is a single use of bromostyrene 146a, which was reacted with 6-membered silane 147 in the presence of TBAF and [allylPdCl]₂ to give diene 148 in high yield (Scheme 3.2).
produced in good yield (entry 3). Pd(dba)$_2$ is also commonly employed in Hiyama-Denmark cross couplings, however it did not improve yields here, and in fact desilylation of 119a was observed, producing terminal alkene 150a (entry 4). Four anhydrous fluoride sources were surveyed (entries 5-8), all of which were found to be inferior to TBAF, with low conversions and protodesilylation reducing the observed yields of diene 149aa. Thus the conditions in entry 3 were identified as optimum in our system. It is noteworthy that our reaction was slower than that reported by Denmark (Scheme 3.2), which is attributed to the increased steric hindrance of the ethyl groups on silicon.

<table>
<thead>
<tr>
<th>Entry</th>
<th>$X$</th>
<th>Catalyst</th>
<th>Conditions</th>
<th>Yield</th>
<th>149aa : 150a $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>[allylPdCl]$_2$</td>
<td>TBAF-3H$_2$O (2 eq), THF, rt</td>
<td>39%</td>
<td>100 : 0 $^b$</td>
</tr>
<tr>
<td>2</td>
<td>I</td>
<td>[allylPdCl]$_2$</td>
<td>TBAF-3H$_2$O (2 eq), THF, rt</td>
<td>66%</td>
<td>100 : 0 $^b$</td>
</tr>
<tr>
<td>3</td>
<td>I</td>
<td>[allylPdCl]$_2$</td>
<td>TBAF-3H$_2$O (3 eq), THF, rt</td>
<td>72%</td>
<td>100 : 0</td>
</tr>
<tr>
<td>4</td>
<td>I</td>
<td>Pd(dba)$_2$</td>
<td>TBAF-3H$_2$O (3 eq), THF, rt</td>
<td>65%</td>
<td>85 : 15 $^b$</td>
</tr>
<tr>
<td>5</td>
<td>I</td>
<td>[allylPdCl]$_2$</td>
<td>TASF (3 eq), THF, rt</td>
<td>44%</td>
<td>99 : 1 $^b$</td>
</tr>
<tr>
<td>6</td>
<td>I</td>
<td>[allylPdCl]$_2$</td>
<td>TBAT (3 eq), THF, rt</td>
<td>0%</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>I</td>
<td>[allylPdCl]$_2$</td>
<td>CsF (3 eq), DMF, 70 °C</td>
<td>47%</td>
<td>87 : 13 $^b$</td>
</tr>
<tr>
<td>8</td>
<td>I</td>
<td>[allylPdCl]$_2$</td>
<td>KF (3 eq), DMF, 70 °C</td>
<td>9%</td>
<td>100 : 0 $^b$</td>
</tr>
</tbody>
</table>

Reactions performed at 0.33 M wrt 119a. $^a$ Determined by $^1$H NMR spectroscopic analysis of the crude reaction mixture. $^b$ Incomplete conversion.

Table 3.1: Screening of reaction conditions for fluoride-promoted cross coupling

We were also keen to investigate whether these conditions could be applied to the cross coupling of 6-membered cyclic alkenylsiloxanes. We were pleased to see that silane 125a and

Scheme 3.3: Cross coupling of a 6-membered cyclic alkenylsiloxane
iodostyrene 145a did indeed give homopropargylic diene 151aa in good yield, although an increased reaction time was necessary to achieve reasonable conversion. It is interesting that ring size affects reactivity in this way; while the effect is minor in this case it was to lead to exciting results later in our studies, as will be described in Chapter 4.

3.3 Base-Promoted Cross Coupling

The use of fluoride as an activator in Hiyama-Denmark cross coupling can be viewed as something of a disadvantage as it renders the methodology intolerant of common silyl ether protecting groups,¹⁴⁰ and requires the use of fluoride sources that may be costly and corrosive on industrial scales. Therefore the development of fluoride-free reaction conditions is an important goal that greatly adds to the synthetic utility of organosilane couplings. It is unsurprising that numerous researchers have worked over the years to achieve this aim, with fluoride-free couplings of a wide range of silanes reported.²⁰ However, to the best of our knowledge, the base-promoted cross coupling of our class of cyclic alkenylsiloxanes had not previously been reported.

3.3.1 Previous Examples of Intramolecular Silane Activation

While the fluoride-free cross coupling of silanes such as 119 is not known in the literature, there are several reports of base-promoted coupling that involve the intramolecular activation of silicon by a neighbouring oxygen species, forming cyclic intermediate ‘ate’ complexes (Scheme 3.4). Shindo has coupled Z-β-trialkylsilylacrylic acids (152) under mildly basic conditions;¹⁴¹,¹⁴² the trimethylsilyl moiety is activated to transmetalation with palladium by intramolecular coordination of the neighbouring carboxylate via pentacoordinate intermediate 153. Nakao and Hiyama have produced a series of studies on the cross coupling of arylsilanes 154.¹⁴³–¹⁴⁷ Under basic conditions, the alcohol functionality in 154 coordinates to silicon to form 155, which activates an exocyclic substituent, R¹, on silicon to transmetalation, allowing it to be cross coupled with an available halide. This concept has been applied to an enormous
range of silane, halide and pseudohalide partners and offers excellent functional group
tolerance. It should also be noted that by-product 156 can be recovered and reused on gram
scale. Takeda has published related work on the interaction of allylic vinylsilanes such as 157
with copper(I) tert-butoxide. The alkoxide moiety in 158 coordinated intramolecularly to
silicon to form intermediate 159, which activated the transmetalation of the C–Si bond to
copper. Vinylcopper species 160 can then go on to transmetalate with palladium, or react
directly in cross coupling reactions.

The examples above are encouraging as the propensity for a proximal oxygen atom to activate
silyl substituents to transmetalation via a 5-membered cyclic intermediate has obvious
analogies to the behaviour of our cyclic alkenylsiloxanes. Our attempts to cross couple silane
119a without the need for fluoride activation will be described below.

### 3.3.2 Identifying Reaction Conditions to Effect Fluoride-Free Coupling of 119a

A wide range of reaction conditions have been used to achieve the base-promoted cross
coupling of alkoxy silanes, silanols and disiloxanes. As these are the closest analogues to
cyclic silane 119a, it was hoped that similar conditions would be effective in the formation of
diene 149aa. A range of bases were screened (Table 3.2, entries 1-5) in the reaction between
silane 119a and iodostyrene 145a. Caesium carbonate was ineffective at promoting the reaction (entry 1); we believe that its low nucleophilicity prevents it from interacting with the silicon centre. Potassium hydroxide has been reported to be an efficient activator by several researchers, while no reaction occurred in aqueous medium (entry 2) we were pleased to observe formation of diene 149aa in methanol, albeit in poor yield (entry 3) and accompanied by significant homocoupling of iodide 145a. Use of the stronger base KOr-Bu (entry 4) exclusively generated alkene 150a, the product of protodesilylation. Potassium trimethylsilanolate (KOSiMe₃) is frequently applied in fluoride-free couplings, and when applied to our system we were delighted to find that diene 149aa was produced in moderate yield (entry 5). Use of commonly employed Pd(dba)₂ significantly improved this, giving 149aa in very good yield (entry 6). Alternative solvents were surveyed (entries 7-9), however

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Activator (eq)</th>
<th>Solvent (Temperature)</th>
<th>Isolated Yield of 149aa</th>
<th>149aa : 150a : 161a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[allylPdCl]₂</td>
<td>Cs₂CO₃ (3.0)</td>
<td>DME (60 °C)</td>
<td>0%</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)₂</td>
<td>KOH (3.0)</td>
<td>H₂O (80 °C)</td>
<td>0%</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>[allylPdCl]₂</td>
<td>KOH (3.0)</td>
<td>MeOH (60 °C)</td>
<td>16%</td>
<td>90 : 10 : 0 b,c</td>
</tr>
<tr>
<td>4</td>
<td>[allylPdCl]₂</td>
<td>KOt-Bu (3.0)</td>
<td>DME (rt)</td>
<td>0%</td>
<td>0 : 100 : 0</td>
</tr>
<tr>
<td>5</td>
<td>[allylPdCl]₂</td>
<td>KOSiMe₃ (3.0)</td>
<td>DME (rt)</td>
<td>52%</td>
<td>87 : 3 : 10</td>
</tr>
<tr>
<td>6</td>
<td>Pd(dba)₂</td>
<td>KOSiMe₃ (3.0)</td>
<td>DME (rt)</td>
<td>79%</td>
<td>89 : 0 : 11</td>
</tr>
<tr>
<td>7</td>
<td>Pd(dba)₂</td>
<td>KOSiMe₃ (3.0)</td>
<td>toluene (rt)</td>
<td>8%</td>
<td>95 : 0 : 5 c</td>
</tr>
<tr>
<td>8</td>
<td>Pd(dba)₂</td>
<td>KOSiMe₃ (3.0)</td>
<td>THF (rt)</td>
<td>0%</td>
<td>* d</td>
</tr>
<tr>
<td>9</td>
<td>Pd(dba)₂</td>
<td>KOSiMe₃ (3.0)</td>
<td>1,4-dioxane (rt)</td>
<td>0%</td>
<td>* d</td>
</tr>
<tr>
<td>10</td>
<td>Pd(dba)₂</td>
<td>KOSiMe₃ (2.0)</td>
<td>DME (rt)</td>
<td>76%</td>
<td>89 : 0 : 11</td>
</tr>
<tr>
<td>11</td>
<td>Pd(dba)₂</td>
<td>KOSiMe₃ (1.0)</td>
<td>DME (rt)</td>
<td>35%</td>
<td>95 : 0 : 5 c</td>
</tr>
<tr>
<td>12</td>
<td>Pd(dba)₂</td>
<td>KOSiMe₃ (2.0)</td>
<td>DME (rt)</td>
<td>41%</td>
<td>57 : 21 : 22</td>
</tr>
</tbody>
</table>

Reactions performed at 0.33 M wrt 119a. a Determined by ¹H NMR spectroscopic analysis of the crude reaction mixture. b Significant iodide homocoupling observed. c Incomplete conversion of 119a. d Decomposition of starting materials. e New batch of KOSiMe₃, several months later.

Table 3.2: Screening of reaction conditions for fluoride-free cross coupling
only DME was found to be effective for the generation of 149aa. It was also possible to lower the equivalents of basic activator from three to two without affecting the yield (entry 10).

With our optimised result in hand (entry 10) we were eager to apply the conditions across a range of silane and halide coupling partners. Unfortunately a serious problem was uncovered – when our best result (entry 10) was repeated several months later with a new batch of KOSiMe₃ (entry 12) a dramatically reduced yield was observed, with a large increase in the formation of deleterious side products 150a and 161a. The homocoupling of silane 119a (to form 161a) was particularly pronounced. The next section will describe our efforts to understand why these side products were formed, and the steps that were taken to minimise their appearance.

3.4 Homocoupling in Base-Promoted Cross Coupling

3.4.1 Possible Mechanisms of Homocoupling

The homocoupling of organometallic reagents in cross coupling reactions is well known in the literature, and several mechanisms have been proposed to account for the formation of such dimers. Transmetalation of silane 119a necessarily occurs with a palladium(II) species; this can occur twice (if such a species has not already undergone oxidative addition with a halide coupling partner) to install two Z-vinyl groups on the catalyst (162, Scheme 3.5). Complex 162 then undergoes reductive elimination to give homocoupled 161a and palladium(0), then oxidation in air regenerates palladium(II). If this mechanism were responsible for the high levels of homocoupled 161a observed in the reactions described above (Table 3.2), it might be expected that performing the same couplings under air would increase the proportion of 161a; experimentally it was found that only a small increase was observed relative to the standard conditions (under argon, with sparged solvent), while more rigorous exclusion of oxygen (freeze-thaw degassing) did not improve matters. Hence we do not
believe that this mechanism is significant in our system as differing levels of oxygen should influence dimer formation.

Several researchers have suggested that the species formed after transmetalation in a normal catalytic cycle (163, Scheme 3.6) may be vulnerable to disproportionation, producing complexes 162 and 164. These would then undergo reductive elimination to form equimolar amounts of silane and iodide homocoupled products 161a and 165 respectively. Under this mechanism, a 1:1 ratio of these dimers would be expected. The 1H NMR spectra of crude coupling reaction mixtures were carefully examined, and while in some cases the ratio of 161a:165 was close to this value, it differed significantly in others. Thus we cannot exclusively invoke this mechanism to explain the formation of 161a, although it may explain some of the homocoupling observed.

Lei and co-workers have observed that homocoupling of organozinc compounds is often accompanied by the dehalogenation of their halide coupling partners; to explain this they have proposed a second transmetalation event which generates a symmetrical palladium species, and effects a halide-zinc switch. Applied to our system, 119a would transmetalate with 163 to produce 162 and vinylsilane 166; these would go on to form homocouple 161a and styrene (from simple protodesilylation), respectively (Scheme 3.7). Due to the relative volatility of styrene we did not expect to observe it in the 1H NMR spectra of previous couplings, hence substituted iodostyrene 145f was instead submitted to our standard fluoride-free reaction.
conditions. Styrene 167 (a known compound) was indeed observed in the $^1$H NMR spectrum of the crude reaction mixture; however, the mechanism described would be expected to generate equimolar amounts of 161a and 167, which was not observed. Therefore, although it seems that this mechanism may be in operation, it does not exclusively account for formation of 161a. We have thus concluded that it is possible that both this and the disproportionation mechanism discussed previously are simultaneously active to varying degrees in some reactions.

Scheme 3.7: Homocoupling via a second transmetalation; observation of styrenyl by-products

While some insight into the mechanism (or mechanisms) of homocoupling had been acquired, we were unfortunately no closer to preventing the formation of 161a. The next section will describe our experimental efforts to achieve this.

3.4.2 Reoptimisation of Conditions to Minimise Homocoupling

The significant difference in reaction outcome using different batches of basic activator at different times in the project (Table 3.2, entries 10 and 12 – further details are included in an Appendix) was rather confusing, hence we set out to ascertain if the decline in reactivity was due to a problem with a specific component of the reaction. Unfortunately, use of ‘fresh’ batches of all reagents (silane, iodide, catalyst, KOSiMe$_3$, solvent) had little effect, and substantial quantities of silane homocoupling product 161a continued to be observed. Variation of reaction stoichiometry and slow addition of silane, iodide, or basic activator were also trialled, but to no avail. This extensive screening ruled out any simple, operational cause
for the problem we faced; hence we sought a deeper understanding of what stage in the reaction 161a was being produced.

To this end, a series of base-promoted cross couplings between 119a and 145a were monitored by $^1$H NMR spectroscopy to assess how the proportion of the different reaction components varied over time. The reaction solvent, 1,2-dimethoxyethane, is not available in deuterated form, hence aliquots were removed at five time points for $^1$H NMR analysis. Graph 3.1 shows a typical reaction profile for a coupling conducted under our standard conditions, where rate of reaction is initially rapid and slows significantly after the first two hours. Silane homocoupling product 161a is generated simultaneously with diene 149aa.

The equivalents of KOSiMe$_3$ were also varied, and here an interesting trend emerged. Graph 3.2 shows how the ratio of desired product 149aa to homocoupled product 161a varies during the course of the reaction, and displays this for different amounts of KOSiMe$_3$. There are two

Production of Diene 149aa and Homocouple 161a Monitored Over Time

Graph 3.1: Following base-activated cross coupling by $^1$H NMR (signals from H were integrated).

Protodesilylation product 150a was present in trace amounts; it has been omitted for clarity.
Graph 3.2: Ratio of diene 149aa / homocouple 161a; effect of time and equivalents of base (signals from H were integrated).

effects to note: firstly, the ratio is more favourable (higher) at the start of reaction, in the first hour after the combination of reagents. Secondly, the amount of homocoupled 161a is significantly reduced when only one equivalent of basic activator is used, although this reaction did not reach completion.

These two key observations show that at low KOSiMe₃ concentrations, and early in the reaction, the production of homocoupled 161a seems disfavoured. We were keen to see if these conditions could somehow be replicated over the whole reaction time, leading to both reduced levels of 161a and complete conversion of starting material. Examination of the aliquot data gathered during the coupling performed with one equivalent of KOSiMe₃ (the black line in Graph 3.2) showed that conversion had stalled after two hours, as expected if all the basic activator were consumed. Hence we anticipated that adding one equivalent of KOSiMe₃ at the start of the reaction would reproduce this result, forming little 161a. After two hours, once all the basic activator had been used up, a second portion could be added,
hopefully again replicating these favourable conditions while effecting further conversion of 119a to 149aa. Various such stepwise addition regimes were trialled, and we were delighted to see a reduction in the amount of homocoupled 161a using the procedure described above. Adding a total of 2.5 equivalents of KOSiMe₃ in portions proved optimal, promoting acceptable conversion. As has previously been stated, addition of base by syringe pump did not induce a positive change in the reaction outcome and it is therefore not clear why addition in discrete portions was able to do so. Increasing the catalyst loading and diluting the reaction mixture stimulated further improvements, and a new set of optimised conditions were identified (Scheme 3.8). We were relieved to see that diene 149aa was at last produced in moderate yield, with much reduced side product formation (only 7% of homocoupled product 161a was produced, compared with 22% in Table 3.2, entry 12).

Scheme 3.8: New optimal conditions, with portionwise addition of KOSiMe₃

Most unfortunately, the reaction conditions shown in Scheme 3.8 again proved inconsistent with repeated use. As the methodology began to be applied to an exploration of substrate scope (Section 3.5), and the synthesis of natural product motifs (Chapter 5), a new problem arose which was more deleterious to yields. The proportion of silane homocouple remained low due to the improved procedure that had been developed; however, protodesilylation to form terminal alkenes (previously produced in only trace amounts in the studies described above) was consuming an increasing percentage of silane starting material – up to 60% in some cases. We began to suspect that minor variations in the amount of water in both the hygroscopic basic activator KOSiMe₃ and/or the (distilled) DME solvent might be affecting the proportion of side products observed in the reaction.
To investigate the validity of this theory, cross couplings were performed with zero, one, three, five or ten equivalents of water added to the reaction; after 24 hours the relative amounts of starting material 119a, desired diene 149aa, homocoupled product 161a and protodesilylation product 150a were established by $^1$H NMR analysis of crude reaction mixtures (Graph 3.3).

The specific reaction conditions employed in this study varied slightly from those found in Scheme 3.8. We chose to undertake this investigation with 2.5 equivalents of basic activator added as a single portion at the start of the reaction, and with lower 5 mol% palladium – we aspired to avoid the need for practically inconvenient multiple additions of base, and high catalyst loadings. Hence, the result under dry conditions in Graph 3.3 does not directly compare with that in Scheme 3.8, but does give a qualitative indication of the devastating extent of protodesilylation that had developed in the intervening period. The trends observed were highly informative. Protodesilylation (producing 150a, the green line in Graph 3.3) was extensive under dry conditions, however addition of five equivalents or more of water completely suppressed this. It was also very interesting to note that the amount of homocoupled product 161a had a strong dependence on water content, with maximum...
amounts produced when the reaction was doped with three equivalents of water (red line). We now believe that this ‘water factor’ is also the cause for the significant but inconsistent degradation in yield described in Table 3.2 – it is likely that the initial result was by chance obtained with an optimally hydrated source of KOSiMe$_3$. We were thrilled to find that when 10 equivalents of water were added to the reaction mixture only 10% of silane 119a was lost to homocoupled 161a, and no protodesilylation was observed. Unfortunately, this came at a price; the high levels of water significantly inhibited conversion. It was found that by increasing reaction temperature to 60 °C, diene 149aa was produced in good yield (Scheme 3.9). The method outlined in the Scheme at last represents a reproducible procedure – by doping the reaction with a relatively large amount of water, the complicated effects and side reactions due to inconsistent hydration are negated, and reliable results are obtained.

We believe that the dramatic differences in reaction outcome observed for very small changes in hydration levels are due to the ability of water to solvate the trimethylsilanolate anion. Similar effects have been previously observed with fluoride ions. A study by Landini et al. showed that the basicity of fluoride was significantly reduced by increasing hydration; meanwhile, nucleophilicity was less affected.$^{157}$ This balance between basicity and nucleophilicity has been shown to have key implications in fluoride-promoted cross couplings, where various researchers have reported that identification of optimal hydration levels was key to controlling side product formation.$^{45,68,158}$ Gordillo and co-workers have reported analogous results using sodium hydroxide as an activator.$^{159}$ It is therefore reasonable to propose that a similar effect may be in operation in our silanolate-promoted system, where moderating basicity relative to nucleophilicity also seems to play an important role, although the exact nature of this is not well understood.
Following the multiple rounds of reoptimisation shown above, conditions were finally in hand to effect both fluoride-promoted and fluoride-free cross couplings of cyclic alkenylsiloxanes. The next section will describe how these were applied to an exploration of substrate scope.

3.5 The Scope of Fluoride-Promoted and Fluoride-Free Cross Couplings of Cyclic Alkenylsiloxanes

As has been emphasized in previous sections of this thesis, the use of 5-membered cyclic alkenylsiloxanes in Hiyama-Denmark cross coupling reactions provides a useful route to the allylic polyene motifs found in a diverse array of natural products. Therefore, we were keen to apply the methodology developed earlier in this chapter to a range of vinyl iodide coupling partners (Scheme 3.10). (A note on labelling: as before, cross coupled product 1xy is formed from silane 2x and iodide 3y.) Cyclic silanes with straight (149aa) and branched (149ba) alkyl chains, and with aromatic substituents (149ca) all coupled well with iodosylene under both

Scheme 3.10: Cross coupling of 5-membered silanes with E-vinyl iodides. \(^a\) 1.5 equivalents of iodide. \(^b\) Fluoride added by syringe pump to minimise protodesilylation.
fluoride-promoted and fluoride-free conditions. Excitingly, the latter allowed diene 149da to be synthesised in good yield, demonstrating that the development of base-promoted reactivity has indeed enabled tolerance of common silyl protecting groups. Gem-disubstituted silane 119f gave poor yields of diene 149fa as exclusively the E,E-isomer, demonstrating that heavier substitution round the silane ring is not well tolerated. 1-Iodohex-1-ene (letter label g) was also found to be an effective coupling partner with silane 119a, producing 149ag in good yield, although similar dienes (149bg-149dg) were produced in mostly poor yields. We believe that the alkyl substituent on this vinyl iodide makes it electron rich; as the ‘electrophilic’ partner in the coupling, this rather disfavours reactivity, and potentially transmetalation. Conversely, vinyl iodide 145b (with an allylic benzyl ether) participated with generally better yields; this is rationalised to be due to the electron withdrawing effect of the oxygen atom.

We were also keen to investigate whether we could employ Z-alkenyl iodide coupling partners to generate challenging Z,Z-diene motifs (Scheme 3.11). Silane 119a was reacted with Z-145c under both fluoride- and base-promoted conditions; the former conditions produced 149ac in low yield, but pleasingly as a single geometrical isomer. Unfortunately KOSiMe₃ proved too basic, and none of the desired 149ac was formed; instead elimination of HI from 145c produced the corresponding alkyne. This elimination was found to be even more pronounced with Z-vinyl styrene (145d) and here was even promoted by fluoride ions; after a brief optimisation, the use of IPA as a co-solvent was found to improve reactivity, presumably via

Scheme 3.11: Cross coupling of 5-membered silanes with Z-vinyl iodides
improved solvation of the fluoride ions, moderating their basicity and reducing elimination.\(^{157}\)

Under these conditions \textit{Z,Z-149ad} was produced in modest yield, but was found to be very vulnerable to light- and heatmediate isomerism to more stable \textit{E,Z-149aa}.

Aryl iodides are perhaps the most commonly employed coupling partner in the HiyamaDenmark reaction, hence their behaviour under our conditions was investigated (Scheme 3.12). We were pleased to see that a good range of silanes coupled with iodobenzene (labelled \textit{e}) to produce alkenes \textit{149ae-149de} in excellent yields; notable again is \textit{149de}, which contains a fluoride-labile \textit{tert}-butyldimethylsilyl protecting group that was well tolerated by the base-promoted coupling conditions.

\[ \text{Scheme 3.12: Cross coupling of 5-membered silanes with iodobenzene} \]

With a large number of allylic dienes and alkenes successfully prepared using our methodology, attention next turned to the use of 6-membered cyclic alkenylsiloxanes as coupling partners (Scheme 3.13). Silanes \textit{125a} and \textit{125e} coupled well with iodostyrene under fluoride-promoted conditions to give homoallylic dienes \textit{151aa} and \textit{151ea} in good yield, albeit with extended reaction times. However, the reagents were recovered unchanged after submission to fluoride-free conditions. The same result was seen when \textit{125e} was coupled with iodobenzene; TBAF-mediation produced \textit{151ee} in near-quantitative yield, while no reaction was observed with KOSiMe\(_3\). This represents a very exciting and significant result – a ring-size dependent orthogonality had been uncovered, where 5-membered cyclic alkenylsiloxanes are activated by base and fluoride, while their 6-membered cousins are inert to the former.

Chapter 4 will be dedicated to the cause and applications of this important effect. As was seen
in Scheme 3.10, branched alkyl side chains were also tolerated (151ba), while iodide 145b coupled in modest yield to give 151eb. Bicyclic silane 125g produced more heavily substituted 151ga only in poor yield, again showing that significant steric hindrance in the silane partner is not well tolerated by the reaction.

While many polyene natural products contain consecutive 1,2-disubstituted alkene units, there are also many examples that contain tri- or tetrasubstituted alkenes. To assess the suitability of this methodology for the generation of such motifs, iodide 145h was coupled with silane 119a (Scheme 3.14); unfortunately the extra methyl substituent was not well tolerated, and diene 149ah was produced in moderate yield under both sets of conditions, and was found to be highly prone to isomerisation.

**Scheme 3.13: Cross coupling of 6-membered cyclic alkenylsiloxanes**

**Scheme 3.14: Cross coupling with trisubstituted vinyl iodide 145h**

In summary, the two sets of reaction conditions that were developed earlier in this Chapter have proven to be effective for the preparation of a range of dienes and alkenes, tolerating a
variety of substituents in both the iodide and silane coupling partners. The limits of the methodology have also been established – cross coupling of Z-vinyl iodides, and substrates with additional steric hindrance proceed in relatively poor yield, although the late stage introduction of the resulting delicate motifs may prove useful in some applications. The substrate scope produced is encouraging for the successful application of the methodology to the synthesis of natural products, which will be described in Chapter 5. As was previously discussed in Section 1.4.2, the use of cyclic alkenylsiloxanes is not limited exclusively to cross coupling, and the next section will discuss alternative ways in which these species can be employed.

### 3.6 Iododesilylation of Cyclic Alkenylsiloxanes – A Useful Route to Allylic Vinyl Iodides

As was described in Section 3.4.2, the loss of silicon from silane starting materials via protodesilylation pathways has at times proved most detrimental to reaction outcomes. The proton source is likely to be adventitious water, and we hypothesised that if another electrophile were present in the mixture, perhaps this could replace silicon instead of a proton, leading to useful, functionalised alkene products. Iododesilylation reactions have been well known in the literature for many years,\textsuperscript{160} and have been applied to numerous total syntheses.\textsuperscript{161–164} Such procedures tend to involve electrophilic iodine sources, with or without a fluoride activator in a range of solvents (Scheme 3.15 shows selected examples). Two geometrical outcomes are possible: iododesilylation can proceed with retention or inversion of configuration, depending on the solvent, iodine source, and substrate employed. Various mechanistic proposals have been offered to explain the differences that may be observed, which will be discussed in due course.

Panek has reported that reaction of vinylsilane \textsuperscript{168} with iodine in DCM produced iodide \textsuperscript{169} in high yield as a single geometrical isomer, with the geometrical configuration of the starting
material maintained in the product.\textsuperscript{165} Kishi transformed vinylsilane 170 into iodide 171, with 90\% retention of configuration.\textsuperscript{166} Zakarian has more recently reported that the use of hexafluoroisopropanol solvent in a related process led to isomerically pure products.\textsuperscript{167} In contrast, Chan has demonstrated that iododesilylation of various insect pheromone precursors proceeds with inversion of configuration; thus E-172 gives Z-173.\textsuperscript{168}

![Scheme 3.15: Examples of iododesilylation reactions](image)

As was previously seen in Section 1.4.2, 6-membered cyclic alkenylsiloxanes have also been employed in iododesilylation reactions to generate homoallylic vinyl iodides (Scheme 1.23). Use of the 5-membered cyclic silanes prepared in Chapter 2 would lead to valuable allylic iodides, which can be difficult to prepare by other methods without use of alkoxide protecting groups – this will be discussed in the context of total synthesis in Chapter 5. In an effort to achieve our desired transformation, a series of conditions were screened (Table 3.2). When silane 119a was stirred with fluoride in the presence of one equivalent of iodine, Z-174a was indeed formed as a single geometrical isomer (entry 1). However, conversion and yield were low; increasing the amount of iodine and heating the reaction (entry 2) led to a minor improvement, and even the use of a large excess of TBAF only converted half of silane 119a (entry 3). Use of KO\textsubscript{SiMe}\textsubscript{3} as identified in the studies above was not effective (entry 4), with the mixed disiloxane (formed from 119a and the trimethylsilylanolate anion) the only product observed. N-iodosuccinimide is also commonly used as an iodine source in iododesilylations;


3. Cyclic Alkenylsiloxanes in Hiyama-Denmark Cross Coupling

![Diagram of the reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Iodine Source (eq)</th>
<th>Activator (eq)</th>
<th>Solvent (Temp)</th>
<th>Conversion</th>
<th>E : Z 174a</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I₂ (1.0)</td>
<td>TBAF (2.0)</td>
<td>THF (rt)</td>
<td>25% b</td>
<td>0 : 100</td>
<td>15%</td>
</tr>
<tr>
<td>2</td>
<td>I₂ (2.0)</td>
<td>TBAF (2.0)</td>
<td>THF (50 °C)</td>
<td>46% b</td>
<td>4 : 96</td>
<td>22%</td>
</tr>
<tr>
<td>3</td>
<td>I₂ (2.0)</td>
<td>TBAF (10.0)</td>
<td>THF (rt)</td>
<td>50%</td>
<td>0 : 100</td>
<td>33%</td>
</tr>
<tr>
<td>4</td>
<td>I₂ (2.0)</td>
<td>KOSiMe₃ (2.0)</td>
<td>DME (rt)</td>
<td>100%</td>
<td>Disiloxane formed</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>NIS (1.0)</td>
<td>TBAF (2.0)</td>
<td>THF (rt)</td>
<td>22% b</td>
<td>0 : 100</td>
<td>19%</td>
</tr>
<tr>
<td>6</td>
<td>NIS (3.0)</td>
<td>TBAF (2.0)</td>
<td>THF (rt)</td>
<td>75%</td>
<td>0 : 100</td>
<td>47%</td>
</tr>
<tr>
<td>7</td>
<td>I₂ (1.0)</td>
<td>-</td>
<td>MeOH</td>
<td>50%</td>
<td>100 : 0</td>
<td>28%</td>
</tr>
<tr>
<td>8</td>
<td>I₂ (5.0)</td>
<td>-</td>
<td>MeOH</td>
<td>100%</td>
<td>94 : 6</td>
<td>45%</td>
</tr>
<tr>
<td>9</td>
<td>I₂ (2.0)</td>
<td>-</td>
<td>DCM</td>
<td>100%</td>
<td>Decomposition</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>NIS (1.0)</td>
<td>-</td>
<td>MeOH</td>
<td>50%</td>
<td>70 : 30</td>
<td>n.r.</td>
</tr>
</tbody>
</table>

* Determined by ¹H NMR spectroscopic analysis of the crude reaction mixture. b Significant amounts of acyclic fluorosilane formed from 119a observed. n.r. = not recorded.

**Table 3.3: Optimisation of iododesilylation procedure**

in the presence of TBAF, it allowed the formation Z-174a as a single isomer, albeit in low yield (entry 5). Use of three equivalents of NIS further improved this to generate Z-174a in moderate yield (entry 6). We were also curious to observe the effect of stirring silane 119a with iodine in the presence of a nucleophilic solvent like methanol, as it was thought that nucleophilic attack of this alcohol at silicon might promote desilylation. To our surprise, stirring 119a with one equivalent of iodine in methanol did indeed effect iododesilylation – but this time with *inversion* of configuration to generate exclusively E-174a in low yield (entry 7). Excess iodine allowed full conversion to give the vinyl iodide in moderate yield (entry 8). Use of DCM as a solvent (as reported by Panek, above) was found to cause complete decomposition of 119a (entry 9). NIS had proved optimal as an iodine source in the presence of an activator, but in this case resulted in poor isomeric ratios of 174a (entry 10).

Although yields from the iododesilylation experiments shown above are not high, the different
geometrical outcome observed in the presence or absence of an activator is rather exciting and represents a usefully divergent method for generating valuable \( E \)- and \( Z \)-vinyl iodides with allylic alcohol functionality from the same silane starting material. Several mechanistic explanations for the invertive and retentive modes of reactivity have been invoked for different substrates under specific reaction conditions.\(^{166,169}\) Tamao and Kumada have published the most relevant study, on the effect of hyperconjugation of silicon on the stereochemical result (Scheme 3.16).\(^{170}\) They found that alkenes with tetracoordinate silanes (such as trimethylsilane) formed unstable \( \text{anti} \)-dihalide intermediates such as 175 on treatment with iodine, as spontaneous cleavage of the \( \text{C–I} \) bond in iodonium intermediate 176 to form a carbocation was slow. Antiperiplanar elimination of \( \text{I–SiR}_3 \) then gave the vinyl iodide with inverted stereochemistry. Conversely, in the presence of a silaphilic nucleophile (or with a preformed pentacoordinate silicate salt), a silicate species underwent iodonium ion formation to generate 177; from this complex, cleavage of the \( \text{C–I} \) bond to generate intermediate 178 was rapid, as the more nucleophilic silicate was better able to stabilise the resultant \( \beta \)-carbocation. At the extreme of this stabilising effect the \( \text{C–Si} \) bond is broken, generating a vinyl iodide with retention of stereochemistry.

\[
\text{Scheme 3.16: Kumada’s mechanism for iodosilylation for [4]-Si and [5]-Si}
\]

Scheme 3.17 shows how such a mechanistic proposal might explain the reactivity observed in our system, although the cyclic nature of silane 119a does complicate matters. Under fluoride-free conditions (entry 8, Table 3.3), it is reasonable to expect that iodonium species 179 is
formed, and then converted to anti-diiodide 180. A ring flip to conformer 181 would then be necessary to align the I–C and C–Si bonds for antiperiplanar elimination, likely promoted by the nucleophilic methanol solvent, and would produce an E-vinyl iodide with an inversion of stereochemistry. The resultant diethylmethoxysilyl substituent on the allylic oxygen would then be cleaved by the action of the generated HI in methanol to give E-174a. The need for a nucleophilic solvent molecule to promote ring opening explains the lack of productive reactivity observed in DCM (entry 9), while the formation of diiodide 180 would be unlikely with a single equivalent of NIS as iodine source (entry 10).

In contrast, in the presence of fluoride ions, a fluorosilicate complex 182 is likely to form rapidly upon addition of TBAF. From this point there are two possible pathways (Scheme 3.17); in the top pathway the molecule remains cyclic, and bicyclic iodonium ion 183 is generated. As suggested by Tamao and Kumada this then forms a carbocation species, two conformers of which exist (184 and 185). Loss of the fluorosilane moiety from 184 would generate Z-174a, while E-174a would be generated from 185. The position of the equilibrium between 184 and 185 would thus determine E:Z ratio, but it is not clear which conformer would be preferred. Interaction of the iodine atom with the vacant p-orbital in 184 would stabilise this species, while in 185 both the ring substituent and large iodine atom would be in
sterically favourable equatorial positions. Therefore, this top pathway does not seem particularly plausible – the energy difference between 184 and 185 is likely to be minor, and would be expected to lead to lower Z:E ratios than were observed (Table 3.3). Additionally, the overlap between the empty p-orbital and filled C–Si σ-orbital in 184 and 185 is rather poor. Therefore, the bottom pathway seems more reasonable, where a second equivalent of fluoride generates acyclic silane 186, which is iodinated (187) and forms carbocation 188, where the acyclic nature of the molecule allows bond rotation to align the C–Si σ orbital more effectively. This intermediate then exclusively generates Z-174a with retention of configuration. Participation from the neighbouring allylic alcohol may also play a role, although the exact nature of this is not clear.

3.7 Conclusions

This chapter has described the development of both the fluoride- and novel base-promoted cross coupling of cyclic alkenylsiloxanes. The latter reaction proved unreliable until it was discovered that side product formation was highly sensitive to water levels; doping the reaction mixture with excess water negated this. The conditions were then applied to produce a range of dienes and alkenes in Hiyama-Denmark couplings, proving the tolerance of the methodology to a variety of substituents. It was also found that 5-membered cyclic alkenylsiloxanes could undergo iododesilylation to generate useful vinyl iodides with allylic alcohol functionality, where geometry was controlled completely by use of different reaction procedures.

A crucial discovery was made in Section 3.4: while 5-membered silanes can be coupled under fluoride-promoted and fluoride-free conditions, 6-membered analogues are inert to the latter. This opens up the possibility for orthogonal, ring-size dependent reactivity which could be highly valuable in synthetic applications. An in depth investigation of this effect will be discussed in the next Chapter.
4 Orthogonality and Insights into the Mechanism of the Coupling Reaction

Orthogonal reactivity is highly valuable in organic synthesis as it allows useful functionalities to be efficiently incorporated into complex molecular targets, and selectively activated under specific reaction conditions. In the previous chapter, it was discovered that 5-membered cyclic alkenylsiloxanes react orthogonally to 6-membered cyclic alkenylsiloxanes in the presence of silanolate base – the former participates in cross coupling reactions, while the latter is inert. This chapter will describe efforts to understand and exploit this ring size dependent reactivity. Later sections will then present how variation of the alkyl substituents on silicon can lead to similar effects.

Few examples of orthogonal Hiyama-Denmark reactivity exist in the literature. This is perhaps unsurprising as diverse silyl functionalities are often activated under similar fluoride- or base-promoted conditions. Denmark has reported an elegant use of such a concept in his total synthesis of the antifungal polyene macrolide RK-397 (189, Scheme 4.1). The C1–C9

Scheme 4.1: Denmark’s use of orthogonal silicon cross coupling in the synthesis of RK-397
tetraene portion (190) was constructed using bis-silane 191, which features both silanol and benzylidimethylsilane (BDMS) functionalities. Under the influence of sodium hydride, 191 coupled selectively with iodide 192 in the presence of the inert BDMS moiety. 193 was subsequently activated by fluoride in the next step to form tetraene 190.

Hiyama has exploited the selective reactivity of silanes such as 154 (as were previously seen in Section 3.2.1) in a series of iterative cross couplings to generate oligoarenes (Scheme 4.2). Activation of 154 under basic conditions forms cyclic silicate 155, which is able to transfer an exocyclic substituent to palladium (194) and therefore participate in cross coupling. However, following protection of the benzylic alcohol functionality, complex 155 can no longer form under basic conditions, hence 195 is inert, or ‘switched off’. This concept was applied to the synthesis of oligoarene 196 by four consecutive couplings. Active silane 197 coupled at the bromine position of arene 198, while its inactive, protected silyl moiety remained inert. Subsequent removal of a THP protecting group ‘switched on’ this coupling handle (199), and further iterations were performed to generate 196.

Scheme 4.2: Hiyama’s iterative cross coupling of arylsilanes

The inert nature of organosilane reagents in the absence of an activator also renders them suitable for orthogonal couplings with other organometallic species. Several examples have been reported of sequential Suzuki-Miyaura and Hiyama-Denmark reactions that generate
asymmetrically substituted alkenes.\textsuperscript{32,174} As many types of silane are inert to the basic conditions required to activate organoboranes to cross coupling, the latter are selectively coupled with aryl and alkenyl halides. Addition of fluoride and a second coupling partner then activates the silane moiety to reaction, installing a second substituent.

In each of the examples discussed above, orthogonal reactivity arose by virtue of different substituents on silicon, or by use of another element altogether. The next section will describe how we have exploited differing ring size, instead of silicon substitution, to achieve selective reactivity.

### 4.1 Orthogonal Cross Coupling of 5- and 6-Membered Cyclic Alkenylsiloxanes

In Section 3.5, the cross coupling of 6-membered silanes with various iodide partners was examined; while they were effective participants under fluoride-promoted conditions, they were inert to basic activation. It was hoped that if equimolar amounts of both \textbf{119e} and \textbf{125e} were stirred with an iodide partner in the presence of a basic activator only \textbf{119e} would react, while \textbf{125e} would be recovered from the reaction mixture. Scheme 4.3 shows the realisation of this strategy. We were delighted to find that under the standard fluoride-free coupling conditions previously developed, iodobenzene reacted selectively with 5-membered silane \textbf{119e} to give allylic \textbf{149ee} in excellent yield. Meanwhile, the equivalent of \textbf{125e} present in the reaction mixture was recovered unchanged and in high yield at the end of the reaction. The same concept could also be demonstrated with iodostyrene \textbf{145a} used as a coupling partner, with diene \textbf{149ea}
the exclusive product of coupling and 125e recovered in very good yield. (Portionwise addition of base under anhydrous conditions was optimal, with only 53% of 149ea produced with our standard procedure).

As was noted in Section 3.2, 6-membered cyclic alkenylsiloxanes were found to react more slowly under fluoride activation than their 5-membered cousins – would this difference in rate be enough to reproduce the results above, allowing additional orthogonal reactivity under fluoride-promoted conditions? To assess this, equimolar amounts of silanes 119e and 125e were stirred with one equivalent of iodobenzene (as before) and TBAF (Scheme 4.4). Unfortunately in this case selectivity for 5-membered 119e was only partial, and a 3:2 ratio of allylic alcohol 149ee and homoallylic alcohol 151ee was observed, in addition to unreacted 119e and 125e. Therefore it seems that ring size dependent orthogonal reactivity is limited to fluoride-free conditions.

Scheme 4.4: Attempted orthogonal cross coupling under fluoride-promoted conditions (from analysis of 1H NMR spectrum of crude reaction mixture)

The competition experiments performed above were a valuable proof of concept in an intermolecular setting; arguably it would be of most use synthetically if a 6-membered silyl moiety remained inert while a halide or 5-membered silane functionality in the same molecule was selectively transformed. Chapter 5 will describe the application of such a strategy towards the efficient synthesis of two anti-inflammatory natural products.

4.2 Mechanistic Insights into the Cross Coupling of Cyclic Silanes

The dissimilar behaviour of 5- and 6-membered cyclic alkenylsiloxanes is synthetically exciting. It is also mechanistically intriguing, as it is not immediately obvious why such an effect has
arisen. This section will present investigations into the mechanism of coupling, and a resultant theory for why the effect is observed.

### 4.2.1 Cross Coupling of Acyclic Vinylsilane Analogue

The cyclic nature of the silanes described seems to be key to explaining their behaviour, therefore it was interesting to investigate how an acyclic analogue would compare. Vinylsilane 199 (Scheme 4.5) was prepared, with a robust PMB protecting group installed on the allylic alcohol to prevent cyclisation. The cross coupling of this species was then attempted with iodostyrene under both fluoride-promoted and fluoride-free conditions. Diene 200 was produced in low yield by the action of TBAF, along with significant amounts of the disiloxane form of 199 and some minor protodesilylation. This was an interesting result, and shows that cyclic alkenylsiloxanes are more activated to cross coupling than equivalent acyclic Z-vinyl silanes under fluoride-promoted conditions.

![Scheme 4.5: Attempted cross coupling of acyclic Z-silane](image)

The experiment above was repeated in the presence of a basic activator; in this reaction, none of diene 200 was formed. Instead, 199 was partially converted into silanol and/or disiloxane species, and experienced minor protodesilylation. This result is analogous to the behaviour of the 6-membered cyclic silane as neither species underwent cross coupling in the absence of fluoride, although the latter, recovered unchanged at the end of the reaction, seemed protected from the hydrolysis, dimerization and protodesilylation of the acyclic species. These observations provide hints of the underlying cause of the orthogonality that had been discovered. The cyclic nature of the 5-membered siloxanes seems crucial, and the above results suggest that this structure is maintained in key reaction intermediates. This is in line with the previous
examples of intramolecular activation of silicon by oxygen substituents described in Section 3.3.1 – all examples featured 5-membered cyclic intermediates, suggesting that this ring size is particularly suited to activation of silyl substituents to transmetalation. In contrast, the behavioural similarities between 6-membered cyclic alkenylsiloxanes and acyclic 199 might suggest that reaction of the former may proceed via acyclic intermediates, which are amenable to fluoride-promotion but do not transmetalate under the influence of base. The next section will describe our attempts to observe some of these key species by $^1$H NMR.

4.2.2 $^1$H NMR Studies

To study the interaction of cyclic alkenylsiloxanes with a nucleophilic activator, which seems key to orthogonality, the behaviour of 5- and 6-membered silanes with three equivalents of activator was observed by $^1$H NMR spectroscopy. As deuterated DME is not available, all experiments were run in d$_8$-THF in an NMR tube, with $^1$H NMR spectra recorded periodically.

When 5-membered 119a was combined with TBAF·3H$_2$O, an equilibrium between silane 119a and an unknown compound was rapidly established. Scheme 4.6 (LHS) shows the alkene region of the $^1$H NMR spectra of the starting material, and the reaction mixture after 5 minutes – a new species, highlighted in blue, has clearly evolved. The data is consistent with two possible structures – cyclic ‘ate’ complex 119a-F, or an open, hydrolysed silanol form 201. The peak at 6.22 ppm appears as a double doublet, split by the neighbouring alkenyl C–H, and one other spin-active nucleus. In ‘ate’ complex 119a-F this would be a $^3$$J_{H-F}$ coupling, of magnitude 8.6 Hz. This assignment would require that the α-C–H and β-C–H had switched their relative positions, potentially a consequence of the reorganisation of charge in the complex upon addition of highly electronegative fluoride.$^{175,176}$ Alternatively, the new species formed could be open form 201, where the additional coupling of 8.6 Hz observed is to the neighbouring allylic proton, which has increased significantly relative to that in 119a due to the change in dihedral angle on moving from cyclic 119a to acyclic 201.
Several NMR experiments were used to distinguish between these two possibilities. A COSY spectrum (not shown) showed a cross-peak between the signal at 6.22 ppm and the allylic proton peak at 4.36 ppm, supporting the assignment of the new species as **201**. $^{19}$F-decoupling resulted in no change to the appearance of the $^1$H NMR spectrum shown, as would be expected if the 8.6 Hz coupling at 6.22 ppm were not due to a $^3J_{H-F}$ interaction, but to a $^3J_{H-H}$ coupling. Therefore the intermediate observed in these studies is likely open form **201**.

A similar phenomenon is observed when silane **119a** and KOSiMe$_3$ are combined in an NMR tube (Scheme 4.6, right hand side). Again, a new species rapidly appeared in the $^1$H NMR spectrum – and, as with the fluoride-promoted case, it is believed that this is acyclic disiloxane **202**, assigned by analogy due to the similar positions of the new peaks in the $^1$H NMR spectrum shown. The signals from starting material **119a** and open form **202** are significantly broadened, hence a new coupling to the allylic proton is not resolved. The broad peaks may imply that **119a** and **202** are interconverting slowly relative to the NMR timescale, while the interconversion of **119a** and **201** is rapid.
Although 201 and 202 are alike, they differ in the substituents on silicon. 201, formed in the presence of TBAF, is thought to be a silanol – adventitious water could hydrolyse the Si–F bond presumed to occur in an intermediate structure. Evidence for this is shown in the multiplicity of the α-C–H signal, which is a doublet showing a coupling only to the neighbouring alkenyl proton (Scheme 4.6). A fluorosilane form of 201 would be expected to show an additional splitting to the 19F nucleus, which is absent. In the corresponding base-promoted reaction, 202 is thought to be a mixed disiloxane, formed by attack of trimethylsilanolate at silicon. The resulting stable species is unlikely to undergo hydrolysis by adventitious water.

The procedure described above was then repeated with 6-membered silane 125a. As before, a new species appeared in each spectrum almost immediately (Scheme 4.7 shows the spectra for both cases). As with 5-membered silane 119a, the species formed under fluoride- or base-activation are distinct, but seem to have structural similarities. They are proposed to be acyclic silanes 203 and 204. In cyclic starting material 125a, the J couplings between the β-C–H and at least one of the allylic protons are characteristically small (2.7 Hz), as restricted bond rotation

Scheme 4.7: Behaviour of 6-membered silane 125a with fluoride or base, observed by 1H NMR

(spectra in d8-THF shown)
maintains an almost orthogonal relationship between them. In contrast, in acyclic 203, coupling to each allylic proton occurs with a larger $J$ value (6.3 and 8.8 Hz, assignment confirmed by strong COSY correlations); a similar splitting pattern is seen in the spectrum of 204.

Following identification of the species formed almost instantaneously upon combining cyclic silanes with three equivalents of activator, the evolution of each reaction mixture was then observed by $^1$H NMR spectroscopy over a period of 12-14 hours. Graph 4.1 shows the experiments conducted with 5-membered silane 119a, which reveal that the rapidly generated open forms 201 and 202 are both slowly converted to protodesilylation product 150a. Interestingly, with TBAF the ratio of silane 119a and acyclic 201 remains fairly constant throughout (Graph 4.1a); alkene 150a is produced rapidly at first, but conversion slows significantly after the first two hours, perhaps suggesting a sequestering of fluoride. In contrast, acyclic 202 (Graph 4.1b) seems to be present in lower proportions early in the reaction compared to 201. Alkene 150a therefore seems to be produced more slowly at first (compared to Graph 4.1a), although the process experiences less deceleration as the reaction proceeds, perhaps

![Graph 4.1: Reaction of 5-membered 119a with 3.0 equivalents of TBAF (a) or KOSiMe$_3$ (b) in an NMR tube, monitored by periodic $^1$H spectral acquisitions](Image)
suggesting a higher concentration of silanolate compared to fluoride at later stages. Under both sets of conditions conversion to 150a is almost complete after 700 minutes.

The behaviour of 6-membered analogue 125a under the same reaction conditions is markedly different (Graph 4.2). Acyclic forms 203 or 204 are observed in substantial quantities at the first acquisition after mixing (5 minutes); in stark contrast to 119a, no terminal alkene resulting from protodesilylation is formed in either case; indeed protodesilylation of 6-membered rings in cross coupling reactions has never been observed in the course of these studies. In the presence of TBAF, silane 125a and acyclic 203 maintain a constant ratio throughout the time period observed (Graph 4.2a). Meanwhile, the action of KOSiMe₃ seems more sluggish, with the proportion of 204 rising slowly through the reaction, after an initial fast formation (Graph 4.2b).

It is not clear why this is observed.

\[ \text{Graph 4.2: Reaction of 6-membered 125a with 3.0 equivalents of TBAF (a) or KOSiMe}_3 (b) in an NMR tube, monitored by periodic } ^1\text{H spectral acquisitions} \]

It is proposed that the apparent immunity of 6-membered cyclic alkenylsiloxane 125a to protodesilylation arises from its lack of ring strain when compared to its 5-membered cousin 119a (as was implied by their differing stabilities to silica chromatography, discussed in Section 2.3). Conversely, a driving force for protodesilylation in 5-membered 119a may be the release of
this ring strain, implying that although cyclic 119a-F or 119a-OTMS were not directly observed by $^1$H NMR in these studies, they are the key intermediates from which protodesilylation, and indeed transmetalation, occurs. The enhanced reactivity of 5-membered cyclic alkenylsiloxanes in cross-couplings when compared to 6-membered analogues is likely also due to this effect.

As was seen in Chapter 3, the amount of water present in cross couplings has key implications for the outcome observed. Protodesilylation is particularly strongly affected, and is usually totally suppressed by addition of an excess of water to reaction mixtures. It was therefore very interesting to observe the effect of repeating the reactions above in the presence of 10 equivalents of water (the optimal doping level found in Section 3.4). Only traces of 150a were observed when silane 119a was stirred with TBAF and an excess of water (Graph 4.3a); interestingly, the extent of formation of acyclic 201 was also greatly lessened by the increased degree of hydration. This is rather counterintuitive as formation of 201 consumes a molecule of water, and hence would be expected to be favoured. It may be that increased solvation of fluoride allows less of ‘ate’ complex 119a-F to form, and therefore less of acyclic 201 results.

Graph 4.3: Reaction of 5-membered 119a with 3.0 equivalents of TBAF (a) or KOSiMe$_3$ (b) in the presence of water. All $^1$H signals were significantly broadened, reducing the quantitative accuracy of NMR integrations; with KOSiMe$_3$ this was so severe no quantitative data could be extracted. The graph shown (b) is therefore qualitative only, using estimated amounts.
It may also be possible that changes in the solvation of ‘ate’ complex 119a-F and/or acyclic 202 have an effect on the position of the equilibrium observed.

When silane 119a was combined with KOSiMe₃ under these hydrated conditions, similarly miniscule amounts of 150a were generated, but in contrast to the TBAF case none of a 202 could be seen in the ¹H NMR spectra of the reaction mixture (Graph 4.3b). However, the presence of so much water in polar d₆-THF significantly broadened all ¹H signals, making quantitative analysis impossible in this experiment; it is therefore possible that 202 was formed at very low concentrations. The general effect in both these reactions was the same – the amount of acyclic 201 or 202 was dramatically reduced in the presence of water, implying that formation of ‘ate’ complexes 119a-F and 119a-OTMS was also lessened. This likely reduction in the amount of active ‘ate’ species may provide a clue as to the origin of the beneficial role of water in reducing the deleterious formation of protodesilylated and homocoupled side products in the base-promoted cross coupling reaction described in Section 3.4, and also correlates with the reduced reactivity seen in these conditions. This will be discussed in detail in Section 4.2.4.

Graph 4.4: Reaction of 5-membered 119a with 0.1 equivalents of TBAF (a) or 6-membered 125a with 0.1 equivalents TBAF (b) in an NMR tube, monitored by periodic ¹H spectral acquisitions. Dotted lines in graph a) indicate reaction mixture composition after one week.
The effect of using sub-stoichiometric TBAF was also examined (Graph 4.4a). With 5-membered 119a it was unsurprising to see that significantly less of acyclic 201 was formed, and that protodesilylation was also inhibited. It is interesting to note that when the reaction mixture (left to stand in a sealed NMR tube) was re-analysed one week later further desilylation had occurred, with almost 30% of silane 119a converted to 150a. This implies that the action of fluoride can be turned over in this process (only 0.1 equivalents were present), albeit with very slow reaction times. When the experiment was repeated with 6-membered 125a (Graph 4.4b) acyclic 203 was also produced in lower concentrations than previously seen (Graph 4.2a).

Although ‘ate’ complexes were not directly observed in these 1H NMR studies, their key role in the mechanism of cross-coupling seems logical. We next turned to computational studies in an attempt to find evidence to support this concept.

4.2.3 Computational Modelling of ‘Ate’ Complex Geometry

An examination of the bond angles around silicon in both neutral starting materials and negatively charged ‘ate’ complexes sheds some light on the origins of ring-size dependent orthogonality (Scheme 4.9). Computational modelling performed by Dr Rob Paton (University of Oxford) predicted the lowest energy conformations of simplified silanes 207 and 208, and the corresponding ‘ate’ complexes formed via addition of fluoride. In the 5-membered case, the angle within the ring at silicon is 93.1° in 207, which must be slightly compressed to 85.1° upon addition of fluoride in ‘ate’ complex 209. The Gibbs free energy for this transformation was calculated to be -0.3 kcal/mol, showing that the ‘ate’ complex 209 is actually more energetically favourable than neutral 207. In contrast, 6-membered 208 has an angle of 102.9° at silicon which must compress to 92.5° in ‘ate’ complex 210, which is 3.3 kcal/mol higher in energy than neutral 208. It is hoped that further computational work will assess the energetics of forming acyclic silanes such as 201-204 from ‘ate’ species such as those shown in Scheme 4.9, and that such work will allow for a more insightful interpretation of the 1H NMR studies above.
4. Orthogonality and Mechanistic Insights

The lowest energy conformation of ‘ate’ complex 119a-F has electronegative fluoride and oxygen substituents in the apical positions on silicon (Scheme 4.11) – this is as expected, as it is well known that electronegative substituents prefer to occupy apical positions where more electron density is located. The Si–O bond in ‘ate’ complex 209 (Scheme 4.9) is 8% longer than in neutral 207, while the equatorial Si–C(vinyl) bond is only 2% longer. Lengthened bonds are weakened bonds, and it follows that ‘ate’ complex 211 would be more activated to transmetalation with the transferable vinyl group in an apical position (Scheme 4.11). Therefore, although ‘ate’ complex 119a-F may be predominantly formed in the presence of TBAF, its conformational isomer 211 is likely to be the active species in reactions.

Scheme 4.11: Geometry of ‘ate’ complex active in transmetalation

4.2.4 Summary – A Mechanistic Scheme at Last?

The computational work described above allows us to have confidence in invoking the formation of an ‘ate’ complex to explain the mechanism of cross coupling in the 5-membered ring case (Scheme 4.12). Silane 119 rapidly forms ‘ate’ complex 212 in the presence of TBAF or...
KOSiMe$_3$. This stable form probably converts to conformer 213, which places the silicon vinyl substituent in the apical position, weakening the C–Si bond and activating it to transmetalation with a palladium complex (with a fluoro or silanolate ligand). Transmetalation could proceed via transition state 214 – consistent with Hiyama and Jutand’s studies, a Si–X–Pd linkage is formed (where X is fluoride or silanolate) while the silicon centre is hexacoordinate (Section 1.3).$^{51,65}$ Although Hiyama and Jutand discounted the participation of a pre-formed ‘ate’ complex in their studies, the highly favourable formation of 212 renders it a much more feasible intermediate in our system. Transmetalation would provide complex 215, which reductively eliminates to give 216; this is converted to product 149 by further action of activator. This mechanistic scheme also allows us to explain why addition of water to the reaction mixture reduces the formation of protodesilylated and homocoupled side products. As may be implied from the NMR studies described above, formation of ‘ate’ complex 212 is greatly reduced in the presence of water (shown in blue in Scheme 4.12). With less of 212 present in the reaction mixture, less is available to be converted to alkene 150. Possible mechanisms for homocoupling were discussed.

Scheme 4.12: Proposed mechanism for cross coupling of 5-membered cyclic alkenylsiloxanes
in Section 3.4.1 – if intermediate 215 undergoes a second transmetalation with another molecule of ‘ate’ complex 212, complex 217 is formed – this then decays to a homocoupled diene. It is logical that at reduced concentrations of ‘ate’ complex 212 this pathway will be disfavoured. A second mechanism thought to be active involved the bimolecular disproportionation of complex 215, again producing 217 – with less of ‘ate’ complex 212 entering the catalytic cycle it follows that the concentration of intermediate 215 will be lower, and this reaction less likely to occur.

It is also possible to propose a catalytic cycle to account for why homoallylic cross coupled products form under fluoride-promotion but not via the action of KOSiMe₃ (Scheme 4.13). Computational studies have shown that the formation of an ‘ate’ complex such as 218 from neutral 125 is not favourable – instead, acyclic 219 forms. Under the action of TBAF a silanol species is produced, which could react with a further equivalent of TBAF to form acyclic ‘ate’ complex 220. This then participates in transmetalation via transition state 221, which is comparable to that formed in the 5-membered case. It is less clear here whether formation of ‘ate’ complex 220 occurs in advance of palladium coordination, or if it is concomitant with bond migration in 221 (as is proposed by Hiyama and Jutand).61,66 We have chosen not to invoke the

Scheme 4.13: Proposed mechanism for cross coupling of 6-membered cyclic alkenylsiloxanes
involvement of a disiloxane species formed from 219 (as proposed by Denmark in his seminal 2004 paper on fluoride mediated coupling – see Scheme 1.13) due to the high steric hindrance expected in a Z-vinylsiloxane. Examining the reaction in the presence of a basic activator, 219 is a disiloxane formed via the action of KOSiMe$_3$. It is presumed not to go on to form acyclic ‘ate’ complex 222, due to prohibitive steric hindrance, rendering it unable to participate in transmetalation. This could explain the inert nature of 6-membered cyclic alkenylsiloxanes under silanolate-promoted conditions.

A combination of experimental, $^1$H NMR and computational observations have allowed the proposal of two reasonable mechanisms that can explain the behaviour of cyclic alkenylsiloxanes observed over the course of these studies. Very little was known about the specific mechanism of cross coupling of these species at the outset of this project, and it is exciting to have been able to build up such a detailed picture through a combination of experiment and theory.

4.3 Orthogonal Cross Coupling of 5-Membered Cyclic Alkenylsiloxanes by Variation of Silicon Substituent

The development of methodology for the orthogonal cross coupling of 5- and 6-membered cyclic alkenylsiloxanes allows for the selective incorporation of Z-alkenyl units with allylic alcohols in the presence of masked homoallylic moieties. We were keen to see if it would be possible to cross couple one cyclic silane in the presence of another cyclic silane without the need to rely on different ring sizes to control their reactivity. Instead, we anticipated that this could be achieved by varying the alkyl substituents on silicon – dimethylsilanes would be expected to cross couple rapidly, while bulky diisopropylsilanes are likely to be more sluggish, or even inert to the reaction conditions. This section will describe work towards the synthesis of such analogues and their performance in competitive coupling reactions.
4. Orthogonality and Mechanistic Insights

### 4.3.1 Synthesis of Dimethyl- and Diisopropylsilanes

In order to access cyclic silanes with dimethyl- or diisopropylsilyl substituents it was first necessary to synthesise an ethynyl isopropoxysilyl species analogous to that used in the synthesis of diethylsilanes (114, Chapter 2, Section 2.2). Thus, dimethylsilane 223 was required, and could be prepared using Chan’s method (Scheme 4.14). The low molecular weight of 223 renders it highly volatile (bp 98-99 °C), which significantly hampered purification when synthesis directly from chloroaminosilane 224 was attempted. It was not possible to remove THF or i-PrOH impurities, as 223 azeotroped with THF at around 53 °C. A two-step transformation of chloroaminosilane 224 provided a solution (as originally described by Chan). Ethynylaminosilane 225 was isolated following treatment of 224 with a THF solution of Grignard reagent; its higher boiling point (139-140 °C) facilitated the removal of solvent. Reaction of 225 with one equivalent of i-PrOH (neat) then provided 223 in excellent yield, with minor THF and Et₂NH contamination.

With terminal alkynylsilane 223 now in hand, synthesis of 5-membered cyclic alkenylsiloxane 226 was attempted (Scheme 4.15). A benzyl ether side chain was selected for operational reasons: anticipating that analysis of ¹H NMR spectra of competition coupling crude reaction mixtures might involve multiple species, it was chosen for the distinct chemical shift of the benzylic protons. It was also hoped that the ether moiety would alter the polarity of resulting cross coupled products, facilitating their purification from potentially complex crude mixtures. Application of standard alkynylation conditions furnished propargylic alcohol 227, which was found to be highly unstable to silica gel; it was therefore employed crude in subsequent steps. Acetylation of 227 (not shown) preceded Lindlar hydrogenation, however, it was found that
Despite multiple resubmissions of this acetate substrate to palladium, no reduction occurred. Instead, the long reaction times facilitated the cleavage of the alkyne-silane C–Si bond. When free alcohol 227 was utilised, reduction was at last achieved, and silane 226 was produced in moderate yield, albeit with a very long reaction time. As expected, 226 was so unstable to silica gel that it was not even possible to observe its formation by TLC, and hence it could not be further purified. The extended reaction times were rather unexpected - it had been predicted that dimethysiloxane 227 would undergo rapid reduction, due to the reduced steric hindrance around silicon. It is postulated that the benzyl ether may act as an inhibitor, poisoning the catalyst. To confirm this hypothesis alcohol 228, with an alkyl side chain, was prepared; in contrast to 227, hydrogenation was complete after 25 minutes. Silane 229, with a lower molecular weight than 226, could be purified by vacuum distillation, providing a better quality coupling reagent, and was therefore selected as our reagent of choice in the competition coupling experiments described below.

The synthesis of 6-membered 230 (Scheme 4.16) was also attempted (prior to the realisation that the benzyl ether was not an optimal choice of side chain). Unfortunately alkyne-silane 223 was not tolerated by the reaction conditions, which require BF₃·OEt₂ to promote epoxide opening. Only epoxide starting material was isolated from the reaction, while 223 was completely decomposed. It therefore seems that the formation of 6-membered 230 is not possible using this methodology.

**Scheme 4.15: Synthesis of dimethyl-substituted 5-membered cyclic alkenylsiloxanes**

**Scheme 4.16: Attempted synthesis of dimethyl-substituted 6-membered cyclic alkenylsiloxane**
4. Orthogonality and Mechanistic Insights

The synthesis of a diisopropylsilane analogue, in contrast, was more straightforward. Chan’s method was not suitable in this case as the higher molecular weight of the chloroaminosilane required precludes the distillation necessary for purification. Hence ethynylsilane 231 was prepared in excellent yield (Scheme 4.17); treatment with NBS followed by trapping of the resultant bromosilane with i-PrOH gave 232 in moderate yield, after purification via column chromatography. Addition to 3-phenyl propionaldehyde proceeded very well to give 233, the alcohol form of which was reduced with excellent stereoselectivity (98:2 Z:E) without the need for acetate protection. Interestingly the resultant Z-alkenysilane did not spontaneously cyclise with the proximal alcohol moiety; this was achieved as for 6-membered silanes (Section 2.3.2). Cyclic silane 234 was obtained in high yield following purification on silica gel, where as expected the isopropyl substituents on silicon seemed to provide significant stability to the product.

Scheme 4.17: Synthesis of diisopropylsilane 234

4.3.2 Competition Experiments

With dimethylsilane 229 and diisopropylsilane 234 in hand, initial studies sought to ascertain their behaviour in cross coupling reactions (Scheme 4.18). As expected, dimethylsilane 229 reacted rapidly with iodostyrene to give diene 149aa in moderate yield under both fluoride- and base-promoted conditions. Diisopropylsilane 234 was predictably more reluctant to undergo cross couplings, particularly with iodostyrene. Diene 235 was formed in poor yield under both sets of conditions; this was due to low conversion of 234. Use of iodobenzene improved the yield under fluoride promotion, but production of 236 was low when KOSiMe$_3$ was employed.
It was hoped that the rapid reaction of dimethylsilane \( \text{229} \) would allow it to outcompete diethylsilane analogues and cross couple preferentially with a given iodide (silane \( \text{119e} \) was chosen for its distinct \(^1\text{H} \) NMR shifts and increased polarity relative to \( \text{229} \)). Once a single equivalent of each reagent was consumed, it was anticipated that diethylsilane \( \text{119e} \) could then be cross coupled with a second iodide upon addition of more TBAF. Scheme 4.19 shows the results of experiments conducted to test this theory. Dimethylsilane \( \text{229} \) did preferentially react with iodobenzene under TBAF activation to give \( \text{149ea} \) (Eq. 1), however a significant proportion of diethylsilane \( \text{119e} \) also participated in cross coupling, with a roughly 3:2 selectivity in favour of \( \text{229} \). A similar result was seen in the presence of KOSiMe\(_3\), with additional protodesilylation of diethylsilane \( \text{119e} \) observed (Eq. 2). We were pleased to see, however, that 5-membered \( \text{229} \) reacted quickly with iodostyrene in the presence of 6-membered diethylsilane \( \text{125e} \) to give diene \( \text{149aa} \) in good yield, with only 5% of \( \text{125e} \) converted to diene \( \text{151ea} \) (Eq. 3). Following consumption of iodostyrene, an equivalent of iodobenzene was added to the reaction and homoallylic \( \text{151ee} \) was formed in good yield. This is similar to the result shown in the earlier in the chapter (Scheme 4.3); however, in this case a fluoride activator is used, allowing the subsequent coupling of the second silane with a second iodide. While the latter result shows some potential, the poorly selective outcomes with two 5-membered silanes are not promising. Due to this, and the difficulties encountered with the preparation of \( \text{229} \), we believe that cyclic dimethylalkenyldisiloxanes have limited application in orthogonal cross couplings of this type.
Attention next turned to the behaviour of diisopropylsilane \( \text{234} \) in competition with diethylsilane \( \text{119e} \) (Scheme 4.20). As before, equimolar amounts of \( \text{119e}, \text{234} \) and iodostyrene were submitted to TBAF-mediated reaction conditions; after 24 hours iodobenzene was added (Eq. 1).

We were delighted to see that in this case coupling was much more selective, with diene \( \text{149ea} \) produced from \( \text{119e} \) in good yield, and only traces of alternative diene \( \text{236} \) observed. Diisopropylsilane \( \text{234} \) was then able to couple with iodobenzene to produce \( \text{235} \) in excellent yield.

The inert nature of diisopropylsilane \( \text{234} \) to basic activation could also be demonstrated (Eq. 2): 83% was recovered from a reaction that also produced a high yield of \( \text{149ee} \). These results are very promising, and show that orthogonality can be achieved not only between different ring sizes, but also between silanes of the same ring size by variation of silyl substituents. These results encouraged a more ambitious strategy – could 6-membered diethylsilane \( \text{125e} \) be coupled preferentially in the presence of 5-membered diisopropylsilane \( \text{234} \), reversing the selectivity of the previous ring-size dependent reactions? Unfortunately this strategy was not well realised (Eq. 3); while homoallylic diene \( \text{151ee} \) was formed in greater proportion than allylic \( \text{235} \), very little diisopropylsilane \( \text{234} \) was recovered after purification (its significant presence in the \( ^1 \text{H} \) NMR spectrum of the crude mixture suggests that it may have been unexpectedly lost to silica,
and yet merits further investigation). Nevertheless, the previous two experiments had shown that selectivity in cross couplings had again been achieved, a valuable property for applications to the total synthesis of complex targets.

Scheme 4.20: Competition reactions between diethylsilane 119e and diisopropylsilane 234

4.4 Conclusions

In this chapter the orthogonal reactivity of different silanes has been explored under both base- and fluoride-promoted conditions. This can be achieved by simple variation of steric bulk around silicon, or by the use of differing cyclic alkenylsiloxane ring sizes. The latter approach is mechanistically interesting; studies on the origin of this effect have revealed key insights into both the nature of orthogonality, and the mechanistic behaviour of the coupling reactions observed throughout this thesis.
5 Application of Cyclic Alkenylsiloxanes to the Synthesis of Natural Products

Following the development of methodology to prepare and cross couple cyclic alkenylsiloxanes, we were keen to demonstrate the value of such chemistry by applying it to the construction of complex polyene natural products. It was also hoped that total synthesis might showcase the great potential of the 5- vs 6-membered ring orthogonality that had been uncovered – this will be presented in the second section of this chapter.

5.1 Synthesis of Natural Product Fragments

5.1.1 Introduction

The cross coupling of 5-membered cyclic alkenylsiloxanes and vinyl iodides generates Z-allylic diene motifs, which are found in numerous natural products. Three examples are shown below (Scheme 5.1), which have been selected for their diverse diene or triene portions, and potent biological activity.

Scheme 5.1: Natural products featuring a Z-allylic diene motif
Fostriecin (237) was first isolated in 1983 from a culture broth of *Streptomyces pulveraceus*,\(^1\) and has antibiotic and antitumour properties.\(^2\) Its great potential as a chemotherapeutic agent has attracted considerable attention from the synthetic community, and several total syntheses have been reported. Fostriecin features a challenging Z,Z,E-triene segment (C12-C17, highlighted in blue in Scheme 5.1), which has typically been constructed by Stille couplings between C13 and C14,\(^3\) although there are reports of the use of the Suzuki,\(^4\) Sonogashira\(^5\) and Wittig\(^6\) reactions. A single report from Trost describes the use of Hiyama-Denmark coupling to prepare the triene motif — this was discussed in Chapter 1 (Scheme 1.19).\(^7\) In all these syntheses, protection of the allylic alcohols at C11 and C18 was required. Phoslactomycin B (238, Scheme 5.1) is also produced by *Streptomyces* soil bacteria,\(^8\) and exhibits potent antibiotic, antifungal and anticancer activity.\(^9\) It has been synthesised three times, with the Z,Z-diene portion (in blue in Scheme 5.1) accessed by Stille coupling,\(^1\) or by Sonogashira reaction followed by zinc-mediated semireduction.\(^1\)

The bitungolide family of natural products (which are active against dual specificity phosphatase) were first isolated from an Indonesian sea sponge in 2008,\(^1\) and feature an allylic diene motif conjugated to an aromatic ring (Scheme 5.2). Among these, bitungolide C (239, Scheme 5.1 and 5.2) is particularly amenable to the application of our methodology, and has never been prepared by chemical synthesis. Close examination of the literature surrounding this series of compounds reveals some uncertainty as to their absolute stereochemistry. The stereochemistry of bitungolide A (240, Scheme 5.2) was determined based on X-ray data by Tanaka; the rest of the family is assigned by analogy. Comparison of the structure of bitungolide A with that of fostriecin and phoslactomycin B reveals many similarities between their C1–C11 segments, however bitungolide A has the opposite stereochemistry at all common stereocentres (C4, C5, C8, C9 and C11) when compared with 237 and 238. Although there are no reported total syntheses of bitungolide A, two simpler members of the family have been prepared (241 and 242, Scheme 5.2). Bitungolide E was synthesised by Ghosh in 2011,\(^1\) who made the
enantiomer reported in the isolation paper and found its optical rotation to be of opposite sign to that reported for the natural sample. Three total syntheses of bitungolide F have been reported – in each case, although the stereochemistry reported by Tanaka was reproduced, the final products were found to have a specific rotation of equal magnitude but opposite sign when compared with natural material. We conclude that it is highly likely that the stereochemistry of bitungolide A was incorrectly assigned by Tanaka, due to the ambiguity of assigning absolute stereochemistry by X-ray crystallographic analysis. Thus, the structure of bitungolide C (Scheme 5.2) shown is that we believe to be correct, but not as was originally assigned.

Fostriecin, phoslactomycin B and bitungolide C all feature diene or triene portions that could be synthesised by the Hiyama-Denmark cross coupling of an appropriate cyclic alkenylsiloxane and vinyl iodide. In order to demonstrate the feasibility of this approach without incurring significant time and effort on the synthesis of complex silane precursors, we aimed to construct simplified
fragments 243-245 (Scheme 5.3) from a common silane starting material ((R)-119e, the synthesis of which was discussed in Chapter 2). Coupling of (R)-119e with iodide 246 was expected to product the C9-C18 portion of fostriecin, while reaction with 145c would access C9-C21 of phoslactomycin B and 247 would give C9-C21 of bitunoglide C. The latter would represent the first reported synthesis of this portion of the natural product.

5.1.2 Synthesis of Iodide Coupling Partners

The first task in the preparation of natural product fragments 243-245 was the preparation of suitable iodide coupling partners. Iodide 246 is a known compound, and was used by Trost in his formal synthesis of fostriecin; application of this route led to 246 in 37% yield over four steps (Scheme 5.4). The synthesis of cyclohexyl iodide 145c was discussed in Section 3.1 – it is accessed in one step by Stork-Wittig reaction of cyclohexane carboxaldehyde.

Novel iodide 247 was required to prepare bitungolide C fragment 245 – it was envisaged that this could be conveniently accessed by Takai olefination of a corresponding aldehyde (248, Scheme 5.5), in turn synthesised by chlorination of commercially available 3-hydroxybenzaldehyde. Unfortunately, E:Z selectivity was found to be extremely poor, with nearly equimolar amounts of E-247 and unwanted Z-247 formed. An alternative route to E-247 was therefore employed (Scheme 5.6). Stork-Wittig reaction of chlorinated aldehyde 248 gave Z-247 in acceptable yield and excellent dr. Elimination of HI with sodium methoxide provide alkyne 249 in high yield, which was then transformed into desired E-247 via hydrozirconation and subsequent iododemetalation. Negishi’s convenient procedure for the generation of active Cp₂ZrHCl (Schwartz’s reagent) by a simple DIBALH reduction allowed for the use of the cheaper Cp₂ZrCl₂.
5. Applications to Natural Product Synthesis

5.1.3 Cross Coupling to Synthesise Natural Product Fragments

With iodides 145c, 246 and 247 now in hand, their participation in cross couplings with silane (R)-119e was investigated. Dienyl iodide 246 coupled with silane (R)-119e in moderate yield under TBAF-promoted conditions to generate the challenging Z,Z,E-triene motif found in the C9-C18 fragment of fostriecin (243, Scheme 5.7). Pleasingly, this use of a Z-vinyl iodide proceeded smoothly, with no need for protection of the allylic alcohol in 246, as was required in previously reported syntheses. Formation of 243 under basic conditions, however, occurred with only modest yield.

Cross coupling of Z-vinyl iodide 145c and silane (R)-119e provided the C9-C21 portion of phoslactomycin B (Scheme 5.8), but unfortunately significant protodesilylation of (R)-119e was also observed, producing terminal alkene 150e which was inseparable from 244 by column chromatography. Various modifications to the reaction conditions were screened in an attempt to minimise this deleterious side reaction. Slow addition of TBAF reduced formation of 150e but could not prevent it entirely (Eq. 1); likewise, addition of i-PrOH as a cosolvent to help solvate the fluoride ions led only to a reduction in yield (Eq. 2). Addition of water to the reaction...
mixture completely suppressed protodesilylation, although a very long reaction time was required to reach acceptable conversion despite the use of a higher catalyst loading (Eq. 4). Finally, heating the mixture to 50 °C in the presence of water gave diene 244 in moderate yield on a shorter timescale (Eq. 5).

\[
\text{PMBO}_2\text{O}^{-}\text{Si}^+ \text{Et}_2 + \text{145c} \rightarrow \text{TBAF} + 3\text{H}_2\text{O}, [\text{allylPdCl}]_2 \rightarrow \text{THF} \rightarrow \text{PMBO}_2\text{OH} \text{C9-C21 of phoslactomycin B} + \text{PMBO}_2\text{OH} \text{150e}
\]

\[
\begin{align*}
\text{Eq. 1: TBAF} + 3\text{H}_2\text{O}, [\text{allylPdCl}]_2 (2.5 \text{ mol%}), \text{THF, rt, 24 h} & \quad 35\% + 15\% \text{ 150e} \\
\text{Eq. 2: TBAF} + 3\text{H}_2\text{O} \text{ (by pump over 10 h)}, [\text{allylPdCl}]_2 (2.5 \text{ mol%}), \text{THF, rt, 24 h} & \quad 35\% + \text{ trace 150e} \\
\text{Eq. 3: TBAF} + 3\text{H}_2\text{O}, [\text{allylPdCl}]_2 (2.5 \text{ mol%}), \text{THF} + i\text{-PrOH, rt, 24 h} & \quad 19\% + \text{ trace 150e} \\
\text{Eq. 4: TBAF} + 3\text{H}_2\text{O}, [\text{allylPdCl}]_2 (5 \text{ mol%}), \text{THF} + 10 \text{ eq H}_2\text{O, rt, 72 h} & \quad 55\% \text{ with no 150e} \\
\text{Eq. 5: TBAF} + 3\text{H}_2\text{O}, [\text{allylPdCl}]_2 (2.5 \text{ mol%}), \text{THF} + 10 \text{ eq H}_2\text{O, 50 °C, 24 h} & \quad 53\% \text{ with no 150e}
\end{align*}
\]

Scheme 5.8: Optimisation of the synthesis of phoslactomycin B fragment 244

The novel C9-C21 portion of bitungolide C was prepared analogously from silane (R)-119e and iodide E-247, where heat and increased catalyst loading were again applied to increase conversion (Scheme 5.9). We were pleased to see that the free phenol functionality in E-247 was well tolerated by the reaction conditions, with only a minor increase in yield observed when it was protected as a MOM ether group. To the best of our knowledge this represents the first reported synthesis of the C9-C21 portion of bitungolide C.

\[
\text{PMBO}_2\text{O}^{-}\text{Si}^+ \text{Et}_2 + \text{Cl}-\text{E}-247 \rightarrow \text{TBAF} + 3\text{H}_2\text{O}, [\text{allylPdCl}]_2 (5 \text{ mol%}), \text{THF, 50 °C, 24 h} \rightarrow \text{PMBO}_2\text{OH} \text{245, C9-C21 of bitungolide C or 245-MOM}
\]

Scheme 5.9: Synthesis of C9-C21 of bitungolide C

The synthesis of these three natural product fragments 243-245 allowed us to demonstrate the straightforward application of the cross coupling of cyclic alkenylsiloxanes to the efficient synthesis of naturally occurring Z-containing dienes and trienes with allylic alcohol
functionalities. More impressive would be application to complete total synthesis – this will be described in the next section.

5.2 Towards the Syntheses of Resolvins D3 and E1

The resolvin family of natural products are a series of polyene compounds with potent anti-inflammatory and pro-resolving actions that feature both Z-allylic and -homoallylic alcohol motifs (Scheme 5.10). As such they provide an exciting opportunity to demonstrate the power of ring-size dependent orthogonal cross coupling.

5.2.1 Introduction to the Resolvins

Inflammation is a crucial component of the human body’s defence and repair mechanisms in response to tissue injury and infection. An important part of the process is the resolution of inflammation, which terminates the inflammatory response when it is no longer needed and prevents unnecessary damage to surrounding tissue. Failure of these mechanisms to operate results in chronic inflammation, which is the cause of many common health conditions that are difficult to treat – examples include rheumatoid arthritis, cardiovascular disease, diabetes, inflammatory bowel disease, Alzheimer’s and age-related macular degeneration. It has recently been discovered that resolution of inflammation is not a passive process as was previously believed, but an active process regulated by a series of fatty acid metabolites produced in the hours or days following infection or injury. Serhan and Petasis have identified two families of resolvin natural products that act as these regulators, and are potent anti-inflammatory agents at very low concentrations. The D-series are metabolites of the omega-3 fatty acid DHA (Scheme 5.10), produced by enzyme-mediated oxygenation and hydrolysis. Resolvin D3 is shown, and features both diene and triene motifs with Z-allylic or -homoallylic alcohols – as such it could prove amenable to synthesis using our methodology. The E series of resolvins are similarly produced from essential fatty acid EPA. Resolvin E1 is shown, and has
many structural similarities to D3 – the C2-C18 portion of D3 is almost identical to the C3-C19 segment of E1, but with different stereocentres at C17 and C18 respectively.

Scheme 5.10: Biosynthesis of resolvins D3 and E1, potent anti-inflammatory natural products

The resolvin natural products represent promising therapeutic agents for the treatment of a variety of diseases, but are produced in only very small quantities both in vitro and in vivo. They have consequently attracted a considerable amount of attention from the synthetic community, where total synthesis has allowed for the production of sufficient material for clinical evaluation. Serhan and Petasis reported the first total synthesis of resolvin D3 in 2013 (Scheme 5.11). All Z-double bonds were formed by stereoselective reduction of alkyne precursors, which were in turn constructed by Sonogashira couplings and epoxide opening reactions. Numerous protecting groups were required to enact these transformations selectively, giving rise to a high total step count.

Scheme 5.11: Previous synthesis of resolvin D3
Slightly simpler resolvin E1 has been made three times, with the most efficient synthesis registered in a patent by Petasis in 2005 (Scheme 5.12).222 A synthetic strategy similar to that described above is employed; stereoselective reduction produces Z-alkenyl moieties from precursors constructed by Sonogashira couplings. Kobayashi reported a rather lengthy procedure in 2009; numerous protecting groups and functional group interconversions were required.215 Most recently, Schwartz has described the preparation of this important compound via a route very similar to that reported by Petasis, with minor variation in starting materials and some key disconnections.216

The importance of the resolvin natural products is clearly demonstrated by their potent biological properties, and the high levels of interest that they have generated within the scientific community. Efficient routes to access them, and structural analogues which may also prove biologically active, are therefore a challenge worthy of further study. We believe that the orthogonal cross coupling of 5- and 6-membered cyclic alkenylsiloxanes is well suited to this goal.

5.2.2 Retrosynthesis of Resolvins D3 and E1

Resolvin D3 features both allylic and homoallylic Z-alkene motifs which could be installed by cross coupling of 5- and 6-membered cyclic alkenylsiloxanes respectively (Scheme 5.13). We
envisaged that the C14-C15 bond could be constructed by the fluoride-promoted cross coupling of allylic vinyl iodide 254 (a known compound) with 6-membered silane 255. This could in turn be accessed by an orthogonal base-promoted cross coupling between 5-membered silane 256 and vinyl iodide 257. The latter contains the 6-membered ring functionality required for the subsequent fluoride-promoted coupling step, which we hoped would be inert to the preceding KOSiMe₃-mediated coupling.

**Scheme 5.13: Retrosynthetic analysis of resolvin D3**

Resolvin E1 could be synthesised using the same strategy, by fluoride-promoted cross coupling between iodide 258 (also known) and 6-membered silane 259 (Scheme 5.14). The latter could in turn come from the base-promoted cross coupling of 5-membered silane 260, the one-carbon homologue of 256 (Scheme 5.13), and iodide 257, identical to that required for resolvin D3.

**Scheme 5.14: Retrosynthetic analysis of resolvin E1**

The retrosynthetic strategies described above are highly convergent, with the same middle fragment (257) required for both natural products (C7-C14 in D3, C8-C15 in E1). We hoped, therefore, that this would represent an efficient route to these important compounds with lower
step counts than were previously reported, and would also easily allow for analogue synthesis. The consecutive orthogonal cross couplings would also be a powerful demonstration of how valuable this property can be in synthesis.

5.2.3 **Synthesis of the C1-C6 Fragment of Resolvin D3**

It was anticipated that the C1-C6 fragment of resolvin D3 could be synthesised using the Lindlar hydrogenation methodology that we have developed (Scheme 5.15). Propargylic alcohol 261 would thus be required; this could in turn be generated by the asymmetric Noyori reduction of an ynone such as 262, which could be synthesised by addition of lithiated alkynylsilane 114 into acid chloride 263 or succinic anhydride.

Generation of ynone 262 via the one step addition of a silyl acetylide into an appropriate electrophile did not prove trivial. After screening several bases and electrophiles it was found that forming the alkynyl Grignard of alkyne 114 was optimal (Scheme 5.16). This was added by syringe pump to acid chloride 263 at 0 °C to prevent double addition to the ynone product of the reaction. Unfortunately succinic anhydride was not suitable as an electrophile in this process, with complex mixtures resulting from its use. Although this would have allowed direct access to the carboxylic acid functionality at C1 (as is seen in resolvin D3), the use of 263 installs a methyl ester at C1 which could easily be converted to an acid, and has the advantage of easier handling. Ynone 262 was found to be highly unstable to silica gel chromatography (as had previously been observed for silylated ynones, Scheme 2.7), hence it was submitted to Noyori reduction without further purification. This caused some problems with reproducibility, as trace
amounts of terminal alkyne 114 remaining from the previous step could poison the ruthenium catalyst, preventing reduction. This could be minimised by heating the crude mixture of 262 to 50 °C at 2 mBar in a Kugelrohr distillation apparatus, which allowed excess alkyne 114 to be removed. Reduction then proceeded well, giving an acceptable yield of propargylic alcohol 261 over two steps with excellent ee. Cyclisation to lactone 264 was observed to varying degrees.

It was found in Section 2.3.1 that acetylation of propargylic alcohols prior to reduction was necessary to ensure high Z:E selectivity in reduction, hence lactone 264 was in fact the preferred substrate for Lindlar hydrogenation. Mixtures of open chain 261 and cyclic 264 could be converted to lactone 264 by treatment with TFA, although these conditions also caused loss of isopropoxide to generate silanol 265 (Scheme 5.17). Previous work had also shown that silanols are effective substrates in Lindlar reductions (Section 2.4.1), hence 265 was submitted to these optimised conditions. 1H NMR spectroscopic analysis of the crude reaction mixture directly after hydrogenation indicated that Z-alkenylsilane 266 had indeed formed in good yield. However, attempts to convert lactone 266 into cyclic alkenylsiloxane 256 were unsuccessful, with none of desired 256 formed after treatment with methanolic K2CO3, which instead produced a complex mixture of alkenes.
Scheme 5.17: Attempted synthesis of key fragment 256 by silanol reduction

The decomposition of 256 observed after treatment with K$_2$CO$_3$ suggested that acetate deprotection might not be tolerated, hence the reduction of free propargylic alcohol 261 (contaminated with varying amounts of lactone 264) was examined (Table 5.1). Submission of 261 to our standard Lindlar reduction conditions gave 256 in moderate yield, with 4:1 Z:E stereoselectivity (entry 1). Using the conditions identified as optimal for silanol hydrogenation (1 mol% palladium with cyclohexene to prevent overreduction, entry 2) improved Z:E ratio, although in this case more of lactone 264 was present (due to a higher proportion in the starting material). In an attempt to convert lactone 267 to 256 the crude mixture stirred with K$_2$CO$_3$ in methanol, but unfortunately decomposition was again observed, and a reduced yield

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd mol%</th>
<th>Additive</th>
<th>Recyclisation conditions</th>
<th>Reaction time (H$_2$)</th>
<th>Isolated yield of 256</th>
<th>256 : 267 : 268</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>-</td>
<td>none</td>
<td>12 min</td>
<td>50%</td>
<td>80 : 0 : 20</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>cyclohexene</td>
<td>K$_2$CO$_3$, MeOH (whole crude)</td>
<td>40 min</td>
<td>29%</td>
<td>71 : 21 : 8</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>cyclohexene</td>
<td>none</td>
<td>40 min</td>
<td>63%</td>
<td>75 : 17 : 8</td>
</tr>
</tbody>
</table>

20 mol% quinoline employed in each reaction. * Determined by $^1$H NMR spectroscopic analysis of crude reaction mixtures.

Table 5.1: Optimising the reduction of alcohol 261
of 256 isolated. Use of catalytic PPTS or NaOMe in methanol were also ineffective at promoting recyclisation of 267, with decomposition noted. The optimal result was thus to purify crude reaction mixtures with no attempt at conversion of lactone 267 to desired 256 (entry 3), resulting in an improved yield of 63%. Thus the C1-C6 fragment of resolvin D3 was accessed in three steps, although we believe improvements could yet be made to this route.

5.2.4 Synthesis of the C1-C7 Fragment of Resolvin E1

With the C1-C6 fragment of resolvin D3 (256) in hand, attention turned to the preparation of the analogous C1-C7 fragment of resolvin E1 (260). This fragment is simply the one-carbon homologue of 256, hence was prepared via the same route, using acid chloride 269 (Scheme 5.18). Addition of alkynylsilane Grignard to 269 was found to be more sluggish than previously observed (Scheme 5.16) and gave 270 as a mixture of its desired open form and isomeric lactone 271. This isomerisation has been observed by numerous researchers, although is not usually reported in compounds with saturated alkyl chains linking ester and ketone functionalities, and it is unclear if it occurs in the starting material or product under the reaction conditions. Although there are several reports of conditions to interconvert the two forms all attempts to convert the significant quantities of 271 formed to the more useful 270 were unsuccessful (Scheme 5.16).

\[
\text{Scheme 5.18: Synthesis of ynone 270}
\]

Cyclic ketal 271 was found to be unreactive to Noyori or racemic sodium borohydride reduction, hence a method was sought to avoid its formation altogether. It was found that by maintaining the reaction at 0 °C after addition of alkynyl Grignard, the formation of 271 was completely
suppressed, although this was unfortunately accompanied by reduced conversion of <50%. Consequently a large excess of unreacted alkyne 114 remained, and removal by Kugelrohr distillation was ineffective. An extra two steps were therefore necessary to prepare pure ynone 270: reduction with NaBH₄ gave racemic alcohol 272, which could be purified by chromatography, ynone 270 was then regenerated cleanly by γ-MnO₂ oxidation. Noyori reduction conditions afforded (S)-272 in good yield and enantiopurity. Interestingly, the lactone form of 272 was not observed at any point. The C1-C7 fragment of resolvin E1 (260) was then generated in rather low yield by Lindlar reduction – a total of 5 steps. Unfortunately, time constraints prevented further optimisation of this part of the synthesis, although it is hoped that future work within the group will address this.

Scheme 5.19: Synthesis of C1-C7 portion of resolvin E1

5.2.5 Synthesis of the C7-C14 (Resolvin D3)/C8-C15 (Resolvin E1) Fragment

The C7-C14 fragment of resolvin D3 is identical to the C8-C15 portion of resolvin E1, hence one intermediate could be used in both syntheses. Scheme 5.20 shows a retrosynthetic analysis of this key species. The vinyl iodide moiety in 257 could be constructed by Takai olefination of aldehyde 273, which in turn could be synthesised by Wittig reaction of an aldehyde precursor. The 6-membered cyclic alkenylsiloxane in alcohol 274 could be constructed using our Lindlar hydrogenation methodology, requiring 275 as our starting material.
In Section 2.2 epoxide opening with lithiated alkynylsilane 114 gave homoallylic alcohols suitable as precursors for the construction of 6-membered cyclic alkenylsiloxanes. The same strategy was employed here, with enantioenriched epoxide 276 prepared in one step from commercially available (S)-glycidol (Scheme 5.21). Protection of the primary alcohol in this chiral pool starting material was found to be essential, with polymerisation resulting from all attempts to employ glycidol directly in reactions with lithiated 114. The presence of Lewis acidic BF$_3$·OEt$_2$ and the use of a standard NH$_4$Cl$_{aq}$ reaction quench effected partial removal of the TMS protecting group, and also allowed it to migrate to the secondary alcohol in 275. As this functionality was no longer required, a range of work up conditions were trialled to selectively remove the remaining TMS groups without affecting the isopropoxysilane. Eventually it was found that repeated washing with NH$_4$Cl gave the cleanest crude $^1$H NMR spectra, and also the best results in the subsequent hydrogenation step, which generated 274 in moderate yield over two steps (blue text, Scheme 5.21). The latter reduction was performed with crude 275, as this compound was unstable to silica gel chromatography. It was shown in Section 2.4.1 that silanols can also be effective hydrogenation substrates, and by altering the work up conditions, the silanol form of 275 was produced (red text, Scheme 5.21). This proved an inferior reduction substrate, giving 274 in low yield over two steps.
Transformation of alcohol 274 into the C7-C14/C8-C15 portion of resolvin D3/E1 proved fairly straightforward (Scheme 5.22). Alcohol 274 was oxidised to aldehyde 277 in high yield. Submission of 277 to ylide 278 in toluene gave enone 273, with only traces of the dienal product of further Wittig reaction of 273 observed in crude $^1$H NMR spectra. Takai olefination then proceeded smoothly to give 257, our key fragment common to both natural products. The stereoselectivity of this step was moderate, with 14% of unwanted E,Z-257 produced – this is in line with previous reports that the stereoselectivity of Takai reductions is somewhat reduced in $\alpha,\beta$-unsaturated aldehydes. However, this was not anticipated to be problematic in subsequent coupling reactions, as we have observed that Z-vinyl iodides couple more slowly than their E-counterparts.

The route shown above allowed the synthesis of sufficient quantities of key fragment 257 for use in the optimisation of the endgame orthogonal cross couplings. However, the use of 8 equivalents of toxic and expensive CrCl$_2$ in the Takai olefination step was not ideal, and an alternative route was sought. Hydrozirconation of an alkyne, followed by treatment with iodine, is a commonly employed method to generate vinyl iodides, hence an enyne precursor to 257 was required (Scheme 5.23). Wittig reaction of the ylide generated from salt 279 with aldehyde 277 (an intermediate in the route above, Scheme 5.22) gave TMS-protected enyne 280, but unfortunately poor yield and low stereoselectivity were observed, rendering this route unsuitable for the generation of 257. Alternatively, enyne 281 could be made from enone 273 (another intermediate in Scheme 5.22) by a Colvin rearrangement. We were pleased to see that enyne 281 was generated in very good yield as a single isomer via this method, although it was rather unstable to column chromatography and hence was applied crude in the next step. Unfortunately
the presence of crude impurities was not tolerated by Schwartz’s reagent, and no reaction was observed. Snieckus has reported a procedure to generate Schwartz’s reagent in situ from LiAlH(Ot-Bu₃) reduction of cheaper Cp₂ZrCl₂. Applying this method produced traces of 257 as a 1:1 mixture of isomers. Time constraints forced us to abandon the route at this point, although it is hoped that further work in the group may find a method to transform 281 into key fragment 257.

![Scheme 5.23: Alternative routes to key fragment 257 avoiding Takai olefination](image)

A more fundamentally different route to key fragment 257 was also attempted, with the dienyl iodide moiety installed first (Scheme 5.24). Becher has reported the conversion of cheap and readily available SO₃·py complex to glutaconaldehyde salt 282 by treatment with KOH. This can then be transformed into aldehyde 283 using the method reported by Duhamel, which gave 283 as a mixture of geometrical isomers, separable by recrystallization. Epoxide 284 was then accessed by a Corey-Chaykovsky reaction, which proceeded in high yield to give racemic 284 – this could have been obtained in enantioenriched form by application of Jacobsen hydrolytic kinetic resolution. The use of vinyl epoxides in synthesis is well established, thus we were hopeful that 284 could be regioselectively opened by lithiated alkynylsilane 114 to give homopropargylic alcohol 285, which could be transformed into key fragment 257 via a Lindlar reduction/cyclisation sequence. Disappointingly all attempts to realise this strategy failed, with complex mixtures resulting in each case when different bases were screened in the presence of BF₃·OEt₂. We believe that alcohol 285 is extremely acid-sensitive and thus does not tolerate this
Lewis acid, which is required to promote epoxide opening. Therefore the 6 step strategy shown in Scheme 5.22 represents the current best route to key fragment 257.

\[ \text{Scheme 5.24: Attempted synthesis of } 257 \text{ from known aldehyde 282} \]

### 5.2.6 Synthesis of C15-C22 of Resolvin D3

Spur has previously reported the synthesis of iodide 254 in 4 steps in his 2012 synthesis of resolvin D1, hence we chose to employ his procedure (Scheme 5.25).²¹⁰ Commercially available sugar 286 was protected as acetonide 287 and reacted with an unstabilised ylide to generate Z-alkene 288 in high yield as a single geometrical isomer. Iodination proceeded smoothly to give 289, which was treated with an excess of LDA. This eliminated acetone from 289 to give iodide 254 and alkyne 290 (presumably formed from further elimination of HI from the Z-isomer of 254), which were separable by chromatography.

\[ \text{Scheme 5.25: Synthesis of C15-C22 of resolvin D3 from D-deoxyribose using Spur’s strategy} \]

### 5.2.7 Synthesis of C16-C20 of Resolvin E1

The final fragment required was the C16-C20 portion of resolvin E1, which was again a known compound, although previously reported syntheses were rather lengthy.²¹⁶,²²¹,²³⁷–²³⁹ We first envisaged that the C16-C20 portion could be efficiently prepared by treatment of ynone 291
with lithium iodide, followed by asymmetric reduction, and hence methods to access 291 were explored. The high volatility of 291 (bp 110 °C) significantly hampered efforts, and it was generated only in low yield by copper-mediated addition of ethynyl Grignard into propionyl chloride, or by oxidation of commercial available but rather costly alcohol 292. We were delighted to find that iodination proceeded smoothly to give ketone 293 in quantitative yield.241

Schwartz has previously reported the use of Corey-Bakshi-Shibata reduction to generate enantioenriched alcohol 258, but unfortunately in our hands very low conversion and virtually no stereoselectivity were observed. Unfortunately time constraints prevented further optimisation of this potentially efficient route to 258, so instead we turned to a strategy employing our own methodology.

Scheme 5.26: Attempted synthesis of C16-C20 of resolvin via ynone 291

As was previously noted in Section 3.6, iododesilylation of 5-membered cyclic alkenylsiloxanes was able to produce E-vinyl iodides with allylic alcohol groups when stirred with iodine in methanol. Hence, this chemistry was well suited to the synthesis of C16-C20 fragment 258 (Scheme 5.27). Propargylic alcohol 294 was prepared in high yield from propionaldehyde, and subsequently oxidised to give ynone 295. Noyori reduction proceeded in excellent yield and stereoselectivity to give (R)-294, which following acetylation, was transformed into cyclic alkenylsiloxane 297 in good yield. Silane 297 was then simply stirred with iodine in methanol to give 258 in moderate yield as a 9:1 mixture of E:Z isomers. As has previously been discussed, it is expected that E-258 will couple preferential, therefore we were not unduly concerned by the presence of the Z-isomer. In summary, the C16-C20 portion of resolvin E1 was synthesised in 6 steps.
5.2.8 **Endgame – Orthogonal Cross Coupling to Synthesis Resolvins D3**

With five fragments of the two resolvins in hand, work turned to their use in the assembly of the two natural products via orthogonal cross couplings. With limited amounts of each fragment available, cross couplings on two model systems were briefly investigated for orientation purposes. Racemic 256 (C1-C6 of resolvin D3, used in optimisation shown in Table 5.1) was cross coupled with iodostyrene under base-promoted reaction conditions (Scheme 5.28). Notably, the action of KOSiMe$_3$ also converted the ester at C1 to a carboxylic acid – this is unsurprising as silanolate base can be used to deprotect methyl esters.$^{140}$ Addition of four equivalents of base was therefore necessary, and it was found that addition of KOSiMe$_3$ by syringe pump over four hours was optimal. In the real system (for resolvin D3 or E1) fragment 256 (or 260 for E1) would be coupled with a dienyl iodide to give a triene intermediate, which could isomerise with heating, hence these reactions were conducted at room temperature. Diene 298 was generated in 41% yield with 5 mol% palladium catalyst, rising slightly to 48% when 10 mol% catalyst was employed, with the remaining material identified as unreacted silane 256.

Time constraints prevented further optimisation, however it was highly useful to have established how KOSiMe$_3$ would interact with the methyl ester functionality, and to have observed that conversion was rather low, perhaps requiring longer reaction times in the real system.
The second, fluoride-promoted cross coupling of a 6-membered silane moiety was also modelled. Silane 274, an intermediate in the synthesis of the middle fragment of both resolvins (257, Scheme 5.22) was cross coupled with racemic 258 (the C16-C20 fragment of resolvin E1). The standard fluoride-promoted cross coupling conditions developed in Section 3.2 were initially employed (with TBAF added as a single portion) but several attempts resulted in complex mixtures, from which only minor amounts of 299 were isolated (Scheme 5.29). This was accompanied by dienes 300-301, which are produced from the homocoupling of iodide 258. This suggests that cross coupling of 6-membered 274 is slow, allowing competing homocoupling pathways to become more significant. To disfavour this, iodide 258 was added by syringe pump as a THF solution with TBAF over 12 hours – pleasingly this allowed the formation of desired diene 299 in moderate yield, with reduced incidence of dienes 300-302. We were most hopeful that sequential, orthogonal base- and fluoride-promoted cross couplings to construct the resolvins could be performed in one pot, which would require the use of DME solvent in the second, TBAF-mediated coupling. Cross coupling of 274 in DME solvent was therefore also investigated, and found to be as effective as in THF. Time constraints again prevented further optimisation with this system, but it was helpful to have identified iodide homocoupling as a potential problem, and to have identified a solution.
The cross coupling of the C1-C6 and C7-C14 portions (256 and 257) was first examined in isolation (Scheme 5.30). The base loading and addition regime found to be optimal above (Scheme 5.28) were again employed, with a longer reaction time and high catalyst loading to maximise yield of triene 255, C1-C14 of resolvin D3. A very complex mixture resulted, the purification of which was significantly hampered by the high polarity of 255. This resulted in the crude reaction mixture being in contact with the silica chromatographic medium for an extended time, which may be incompatible with the 6-membered ring functionality in 255, hence none of 255 could be isolated. In fact, this suggests that a one-pot procedure in which TBAF and the second vinyl iodide, C15-C22 of resolvin D3, were added after 48 hours might prove a superior strategy. It was interesting to observe that disiloxane 303 could be isolated from the reaction mixture below (and was characterised). It is postulated that this has arisen from a second transmetalation of an intermediate palladium species with silane 256, as was described in Section 3.4.1 (Scheme 3.7) – therefore it is likely that significant homocoupling of 256 had occurred. It is also worth noting that the 6-membered cyclic alkenylsiloxane moiety may have sequestered some silanolate during the reaction by forming an acyclic disiloxane (as was observed in the $^1$H NMR experiments described in Section 4.2.2), although the effect of this on the base-promoted coupling (and any subsequent fluoride-promoted processes, see below) is unclear.

![Scheme 5.30: Base-promoted coupling of C1-C6 and C7-C14 fragments of resolvin D3](image)

After difficulties isolating intermediate 255, the one pot construction of resolvin D3 was attempted (Scheme 5.31). We were hopeful that, if successful, this would be a particularly
powerful demonstration of ring-size dependent orthogonality, and would reduce the step count required to form the resolvin natural products we had targeted. Hence the C1-C6 and C7-C14 fragments were submitted to base-activated coupling conditions as previously described (Scheme 5.30) and after 48 hours, iodide 254 was added as a solution with TBAF in DME, and stirred for a further 48 hours. It was unsurprising to find that the resultant crude reaction mixture again gave rise to a very complex $^1$H NMR spectrum. Purification (which was performed on normal-phase silica with gradient solvent systems) was only partially effective as tetrabutylammonium ions were found to have a similar polarity to many compounds of interest, and significant contamination was present in most fractions, precluding quantitative analysis of the reaction outcome. However, we were delighted to find that the $^1$H NMR spectral data from some fractions closely correlated with that reported for resolvin D3 by Petasis (Figure 5.1 – $^1$H NMR spectra were recorded in different solvents, and our sample contained significant tetrabutylammonium ion contamination, which can affect peak position, hence an exact match was not expected).212 It was thus very exciting and encouraging to see that our target natural product was likely being produced, albeit in modest quantities. Significant amounts of triene 304 were also observed in some fractions, arising from the cross coupling of 5-membered 256 with iodide 254 – this is believed to occur due to the sluggish nature of the desired cross coupling between the 6-membered moiety in 255 and iodide 254.

$\text{Scheme 5.31: Attempted construction of resolvin D3 by orthogonal cross couplings}$
Gently heating the reaction to 40 °C seemed to increase the proportion of 251 formed, but as previously, pure 251 could not be isolated.

The major obstacle to quantitative analysis of reaction outcomes was the enormous excess of tetrabutylammonium cations in each fraction of useful material. To overcome this contamination, the use of ion-exchange resins was explored. Several resins have been reported effective at removing TBAF and its by-products from highly polar compounds,\textsuperscript{242,243} where immobilised sulfonic acid groups exchange a proton for the ammonium cation. Calcium salts are often added to sequester any remaining fluoride anions. Parlow has reported that agitating crude reaction mixtures with a mixture of Amberlite® A-15 / calcium sulfonate resins completely removed traces of TBAF (the latter resin is prepared by flushing Amberlite® with a solution of Ca(OH)\textsubscript{2}).\textsuperscript{242} Application of this method to ammonium-contaminated fractions from above caused only partial removal of these cations. Kishi has described the use of DOWEX 50WX8-400 resin and CaSO\textsubscript{4} to remove TBAF residues from the highly polar natural product

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**Figure 5.1:** Comparison of the alkene region of the $^1$H NMR spectra of resolvin D3 a) as reported by Petasis (CD$_3$OD, 600 MHz);\textsuperscript{212} b) this work (CDCl$_3$, 500 MHz)
halichondrin, but unfortunately use of his procedure caused little reduction in contamination in our hands.

In an attempt to reduce the polarity of resolvin D3, the carboxylic acid moiety at C1 was converted to the methyl ester by treatment of crude material with an excess of trimethylsilyldiazomethane. While this did facilitate TBAF removal, it did not aid overall purification, with the resolvin D3-methyl ester now contaminated with various by-products from the coupling reaction after several rounds of chromatography. Formation of a lactone with the alcohol functionality at C4 further complicated matters. We conclude that the use of a different ester group would be judicious here – for example, an isopropyl ester, installed before cross coupling, would not be deprotected by KOSiMe₃, and would be less vulnerable to lactonisation. It is hoped that future work will address this.

With tetrabutylammonium cation contamination still a significant problem in the construction of resolvin D3, the use of an alternative fluoride source was considered. As was shown in Table 3.1, caesium fluoride was also able to promote simple cross coupling, albeit in reduced yield relative to TBAF. The one-pot procedure outlined above (Scheme 5.31) was therefore repeated with 7 equivalents of caesium fluoride in place of TBAF. Unfortunately, analysis of the crude reaction mixture, and numerous fractions isolated from column chromatography showed no evidence of resolvin D3, although some fractions were so complex it is not possible to rule out its formation. Interestingly, traces of the C1-C14 intermediate 255 were observed here, suggesting that caesium fluoride is not able to promote the cross coupling of the 6-membered ring moiety in 255.

5.2.9 Conclusions and Future Work – Towards the Synthesis of Resolvin E1

In conclusion, the strategy described above has the potential to construct resolvin D3 in a total of 14 steps (using one pot sequential couplings), with a longest linear sequence of just 7 steps – this is considerably lower than reported in Petasis’ 2013 synthesis.²¹² Evidence for the formation
of resolvin D3 in one-pot sequential couplings is therefore highly encouraging. Time constraints have prevented the complete realisation of this strategy, but further work within the group is expected to address deficiencies in the preparation of the three key fragments required, and will further optimise the sequential cross couplings. Purification of this very polar natural product has been rather problematic, and it is likely that future work will seek new solutions to this, such as the application of reverse phase HPLC (as is reported by Petasis),\textsuperscript{212} or the use of different C1 esters.

It is anticipated that the construction of resolvin E1 via sequential base- and fluoride-promoted cross couplings will proceed in a very similar manner to that described above for resolvin D3, hence future work will address the realisation of this strategy. Using the routes described above to access the three key fragments 257, 258 and 260, this would require a total of 18 steps, with a longest linear sequence of 8 steps, although it is hoped that further optimisation of the syntheses of the three key fragments will reduce this step count. It is also anticipated that several unnatural resolvin analogues could be accessed using this highly convergent strategy by variation of the 5-membered cyclic alkenylsiloxane and vinyl iodide (with allylic alcohol) coupling partners, and that such analogues might also exhibit useful biological properties.
6 Conclusions and Future Work

The Hiyama-Denmark cross coupling of organosilanes offers an attractive alternative to more widely used Stille and Suzuki couplings, and cyclic alkenylsiloxanes represent a valuable class of coupling reagents in this reaction. Robust hydrogenation methodology was developed to allow straightforward access to these species, allowing silanes with varying ring sizes, substituents and substitution patterns to be produced in high yields.

The use of cyclic alkenylsiloxanes in Hiyama-Denmark cross coupling was examined next, with fluoride- and base-promoted reactivity achieved. Although the latter produced rather unreliable results in initial studies, addition of water to reaction mixtures allowed access to the desired diene products in good yields. This work, and the development of the hydrogenation methodology described in Chapter 2 formed the basis for a publication in *Chemistry – A European Journal* in 2014.\(^{244}\)

An exciting ring-size dependent orthogonality was discovered in the course of these studies, where 5-membered cyclic alkenylsiloxanes participate in cross couplings orthogonally to 6-membered analogues under fluoride-free conditions. Experimental and theoretical work led to the proposal of detailed mechanisms for the cross coupling of 5- and 6-membered cyclic alkenylsiloxanes which can rationalise the behaviour and trends observed over the course of this thesis. This level of mechanistic understanding is unprecedented for the cross coupling of cyclic alkenylsiloxanes and provides key insights into the process, with many exciting questions remaining unanswered. It is hoped that further collaboration with Dr Rob Paton (University of Oxford) will allow for more computational modelling of additional aspects of the process.
Future work will also examine further the behaviour of such species by $^1$H NMR spectroscopy, and additional evidence will be obtained for the existence of cyclic ‘ate’ complexes.

In the final chapter, the fluoride-promoted cross coupling of 5-membered cyclic alkenylsiloxanes was applied to the synthesis of three natural product fragments – C9-C18 of fostrieacin, C8-C21 of phoslactomycin B and C9-C21 of bitungolide C, demonstrating the suitability of this methodology for use in total synthesis of complex polyene natural products. Work towards the total synthesis of highly bioactive resolvins D3 and E1 was progressed to a very advanced stage. The highly convergent routes developed showcases the power of the ring size dependent orthogonality that has been uncovered, allowing very efficient synthesis of resolvins D3 and E1 and representing an improvement relative to previously reported syntheses. Several key aspects of the above work remain to be addressed, however. Further optimisation of fragment synthesis would allow for the more efficient generation of the starting materials required for the key cross couplings on larger scales. It is also hoped that shorter routes to some fragments could be identified, while the use of toxic and/or expensive reagents could be avoided in others. Initial cross coupling results were highly encouraging, with resolvin D3 likely produced, although purification remains a significant problem. Once this is addressed (potentially by use of reverse phase HPLC or a different ester group at C1), quantitative analysis of reaction outcomes should be possible, allowing the one-pot construction of resolvin D3 by sequential, orthogonal cross couplings to be systematically optimised. It is anticipated that this work will then be applied to the synthesis of resolvin E1, and to unnatural resolvin analogues, further demonstrating the attraction of our highly convergent strategy.
7 Experimental

7.1 General Experimental

Solvents and Reagents. Dichloromethane, tetrahydrofuran, toluene and methanol were obtained anhydrous from solvent dispenser units having been passed through an activated alumina column under argon. Dimethyl sulfoxide, 1,2-dimethoxyethane (DME) and propane-1,3-diol were distilled over calcium hydride under reduced pressure prior to use. Diethylamine was distilled under nitrogen over 3 Å molecular sieves. Benzaldehyde was washed with saturated NaHCO₃ solution and dried (MgSO₄) prior to use. All other reagents were used as received. Tetrabutylammonium fluoride (TBAF) solution was obtained by dissolving tetrabutylammonium fluoride trihydrate in anhydrous THF. TBAF·3H₂O, scandium(III) triflate and potassium trimethylsilanolate were weighed out in a glove box under nitrogen. Potassium trimethylsilanolate was purchased from CombiBlocks. Petrol refers to the fraction of petroleum ether which boils in the range 40-60 ºC. Et₂O refers to diethyl ether. EtOAc refers to ethyl acetate. DCM refers to dichloromethane. Brine refers to a saturated aqueous solution of NaCl. NaHCO₃, K₂CO₃, NH₄Cl and Na₂S₂O₃ solutions refer to saturated aqueous solutions. HCl was also used as an aqueous solution. Silylenyne 143 was given as a gift by Diane Lim. Iodide 145h was given as a gift by Haraldur Gudmundsson. Isolated Noyori catalyst was prepared according a literature procedure and the stereochemistry of the resulting propargylic alcohols assigned by analogy to literature reports.¹¹⁷,²⁴⁵

Reactions. All reactions were carried out under argon or nitrogen unless otherwise stated. Oven-dried glassware was used for reactions requiring anhydrous conditions.

Chromatography. Thin-layer chromatography was performed on Merck aluminium-backed DC 60 F254 0.2 mm precoated plates, which were visualised with UV fluorescence and staining with
potassium(VII) manganate or vanillin. Flash column chromatography was performed on MN Kieselgel 60M (particle size 40-63 μm) with solvent system used in parentheses.

**Melting points.** Melting points were determined using a Griffin melting point apparatus and are uncorrected.

**Infrared Spectroscopy.** Infrared spectra were recorded on a Bruker Tensor 27 Fourier transform spectrometer, as a thin film on a diamond ATR module.

**NMR Spectroscopy.** $^1$H NMR spectra were recorded at 200, 250, 400 or 500 MHz on a Bruker DPX 200, Bruker DPX 250, Bruker DPX 400, Bruker DQX400, Bruker AVN 400, Bruker DRX500 and Bruker AVII 500, respectively. $^{13}$C NMR spectra were recorded at 101 MHz or 125 MHz on a Bruker DQX 400, Bruker AVN 400, Bruker DRX500 or a Bruker ACII 500 with $^{13}$C cryoprobe, respectively. Chemical shifts (δ$_H$ and δ$_C$) are expressed in parts per million (ppm), referenced to the residual solvent peak of CDCl$_3$ or C$_6$D$_6$. Coupling constants (J) are reported to the nearest 0.1 Hz. Spectra are assigned based on chemical shift, coupling constants, COSY, HSQC and HMBC data and comparison with similar compounds. Splitting patterns are described using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), quin. (quintet), sept. (septet).

**Mass spectroscopy.** Low-resolution mass spectra (m/z) were performed on a Micromass LCT Premier Open Access. High-resolution mass spectra were recorded under ESI or EI conditions on a Bruker MicroTOF.

**Elemental Analysis.** Samples were analysed by Mr. Stephen Boyer, Science Centre, London Metropolitan University.
7.2 General Experimental Procedures

7.2.1 General Procedure A: Preparation of Propargylic Alcohols

\( n \)-Butyllithium (2.5 M solution in hexanes, 1.1 eq) was added to a solution of silyl alkyne 114 (1.0 eq) in THF at -78 °C and stirred for one hour. The aldehyde (1.0 eq) was added dropwise at -78 °C and the mixture stirred for a further two - three hours. The reaction was quenched with NH\(_4\)Cl solution, and the aqueous layer extracted three times with Et\(_2\)O and dried (MgSO\(_4\)). The residue was concentrated \textit{in vacuo} and purified \textit{via} flash column chromatography.

7.2.2 General Procedure B: Preparation of Homopropargylic Alcohols

Prepared according to a modified literature procedure.\(^{246}\) \( n \)-Butyllithium (2.5 M solution in hexanes) was added to a solution of silyl alkyne 114 (1.0 eq) in THF and stirred at -78 °C for one hour. Epoxide (1.0 eq) was added, and the mixture stirred for a further 10 minutes before BF\(_3\)·OEt\(_2\) was added. After stirring for the specified time the reaction was quenched with NH\(_4\)Cl solution, extracted with Et\(_2\)O, dried (MgSO\(_4\)) and concentrated \textit{in vacuo}. The crude product was purified \textit{via} flash column chromatography.

7.2.3 General Procedure C: Acetylation of Propargylic Alcohols

Acetic anhydride (2.0 eq) was added dropwise to propargyl alcohol (1.0 eq), one crystal of DMAP and Et\(_3\)N (3.0 eq) in DCM. The mixture was stirred for three hours, and quenched with NaHCO\(_3\) solution. The aqueous layer was extracted three times with DCM and the combined organic layers dried (MgSO\(_4\)) and concentrated to give the acetates as oils that were used in the next step without further purification.

7.2.4 General Procedure D: Preparation of Cyclic 5-membered Alkenylsiloxanes from Acetate Substrates

Palladium on CaCO\(_3\) (5 wt% Pd, 0.05 eq) was added to a stirred solution of acetate (1.0 eq) and quinoline (0.2 eq) in toluene. The resulting solution was stirred under an atmosphere of hydrogen (using a balloon and 19G needle through a rubber septum) until TLC (visualised with vanillin)
showed the reaction was complete. The mixture was then filtered through Celite® and concentrated. The crude mixture was redissolved in methanol, K₂CO₃ (excess) added and stirred vigorously for three hours. The reaction was diluted with Et₂O, washed twice with water, dried (MgSO₄) and concentrated in vacuo. The crude product was purified by rapid flash column chromatography on a short column of silica gel to give oxasiloles as colourless oils which are unstable to silica gel. Typically 4-5 cm of silica gel (or 8-9 g / mmol of crude) was employed, and the crude mixture loaded onto a thick layer of sand (2-3 cm) prior to elution.

7.2.5 General Procedure E: Preparation of Cyclic Alkenylsiloxanes from Alcohol

**Substrates**

Palladium on CaCO₃ (5 wt% Pd, 0.05 eq) was added to a stirred solution of alcohol (1.0 eq) and quinoline (0.2-0.5 eq) in toluene. The resulting solution was stirred under an atmosphere of hydrogen (using a balloon and 19G needle through a rubber septum) until TLC (visualised with vanillin) showed the reaction was complete. The mixture was then filtered through Celite® and concentrated. The crude was redissolved in methanol, and filtered through a plug of K₂CO₃. The mixture was diluted with Et₂O, washed twice with water, dried (MgSO₄) and concentrated in vacuo. The crude was purified by rapid flash column chromatography on a short column of silica gel to give cyclic siloxanes as colourless oils which are unstable to silica gel. Typically 4-5 cm of silica gel (or 8-9 g / mmol of crude) was employed, and the crude mixture loaded onto a thick layer of sand (2-3 cm) prior to elution.

7.2.6 General Procedures for Cross-Coupling of Cyclic Alkenylsiloxanes

**Procedure F:** A degassed solution of TBAF-3H₂O (1.0 M solution in THF, 3.0 eq) and iodide (1.0 eq) was added to the silane (1.0 eq) and allylpalladium chloride dimer (0.025 eq) at room temperature. The mixture was stirred for 24 - 48 hours in the dark, diluted with DCM and filtered through a plug of silica gel. The crude was concentrated and purified by flash column chromatography.

**Procedure G:** A degassed solution of potassium trimethylsilanolate (98 wt%, 0.42 M in DME, 2.5 eq) was added to the silane (1.0 eq), iodide (1.0 eq), water (10.0 eq) and
bis(dibenzylideneacetone)palladium (0.05 eq) at room temperature. The mixture was heated to 60 °C and stirred for 24 hours in the dark, diluted with Et₂O and filtered through a plug of silica gel. The crude was concentrated and purified by flash column chromatography.
7. Experimental

7.3 Synthesis of Substrates for Lindlar Hydrogenation

Diethyl(diethylamino)chlorosilane

\[ \text{CIS} \text{Et}_2(\text{NEt}_2) \]

To a solution of dichlorodiethylsilane (10.0 mL, 67.5 mmol, 1.0 eq) and Et<sub>3</sub>N (10.3 mL, 74.2 mmol, 1.1 eq) in anhydrous THF (10 mL) at 0 °C was added a solution of Et<sub>2</sub>NH (7.1 mL, 67.5 mmol, 1.0 eq) in THF (7 mL) over two hours. The mixture was stirred at room temperature for 16 hours before the solvent was removed \textit{in vacuo} and the crude redissolved in anhydrous pentane, filtered through Celite® under nitrogen, washing with anhydrous pentane and concentrated \textit{in vacuo}. The crude was then distilled under vacuum to afford the title compound as a colourless oil (11.5 g, 59.3 mmol, 88%); \textit{bp} 92-94 °C, 36 mbar (lit.\textsuperscript{247} 104-106 °C, 56 mmHg); \textsuperscript{1}H NMR (CDCl<sub>3</sub>, 200 MHz) \( \delta_H = 2.89 \) (4H, q, \( J = 7.0 \) Hz, N(C\textsubscript{2}H\textsubscript{5}CH\textsubscript{3})\textsubscript{2}), 1.08-0.99 (12H, m, Si(CH\textsubscript{2}C\textsubscript{6}H\textsubscript{5})\textsubscript{2} and N(CH\textsubscript{2}C\textsubscript{6}H\textsubscript{5})\textsubscript{2}), 0.91 (4H, q, \( J = 6.3 \) Hz, Si(CH\textsubscript{2}CH\textsubscript{3})\textsubscript{2}); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 101 MHz) \( \delta_C = 39.5, 15.1, 7.4, 6.9. \)

The physical and spectroscopic data were found to be in agreement with that reported by Cox and co-workers.\textsuperscript{247}

Diethyl(ethynyl)(isopropoxy)silane, 114

\[ \text{Et} \text{C} = \text{CH} \text{Si}(\text{OiPr})_2 \]

Ethynylmagnesium bromide (253 mL of a 0.5 M solution in THF, 127 mmol, 1.1 eq) was added to diethyl(diethylamino)chlorosilane (22.3 g, 115 mmol, 1.0 eq) at -78 °C and warmed to room temperature. The mixture was refluxed for three hours then cooled to room temperature whereupon isopropanol (17.5 mL, 230 mmol, 2.0 eq) and one crystal of DMAP were added and the reaction left to stir at room temperature for 16 hours. The mixture was concentrated \textit{in vacuo}, redissolved in petrol and filtered through Celite®. The filtrate was concentrated \textit{in vacuo} and distilled to afford a 5:1 mixture of the title compound 114: diethyldiisoproxydimethylsilane as a colourless oil (12.1 g, 59.0 mmol, 83% purity by weight, 51%); \( R_f = 0.61 \) (petrol / Et<sub>2</sub>O (9:1)); \textit{bp} 50-52 °C, 20 mbar (lit.\textsuperscript{248} 53 °C, 15 Torr); \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \( \delta_H = 4.18 \) (1H, sept, \( J = 6.1 \) Hz, OCH(CH\textsubscript{3})\textsubscript{2}), 2.43 (1H, s, ...
C≡C, 1.21 (6H, d, J = 6.1 Hz, OCH(CH₃)₂), 1.02 (6H, t, J = 7.8 Hz, Si(CH₂CH₃)₂), 0.68 (4H, q, J = 7.8 Hz, Si(CH₂CH₃)₂); ¹³C NMR (101 MHz, CDCl₃) δC 93.6, 86.5, 66.2, 25.4, 6.6, 6.4.

The physical data were found to be in agreement with that reported by Voronkov and co-workers.²⁴⁸

1-(Diethyl(isopropoxy)silyl)non-1-yn-3-ol, 115a

**Procedure A:** n-Butyllithium (0.96 mL of a 2.5 M solution in hexanes, 2.40 mmol, 1.1 eq), silyl alkyne 114 (450 mg, 83 wt% purity, 2.19 mmol, 1.0 eq) in THF (11 mL) and heptanal (0.31 mL, 2.19 mmol, 1.0 eq) gave, after purification via flash column chromatography (petrol / Et₂O (9:1) + 1% Et₃N), propargylic alcohol 115a as a colourless oil (515 mg, 1.81 mmol, 83%); Rf 0.18 (petrol / Et₂O (9:1)); IR (thin film, ν_max / cm⁻¹) 3353, 2958, 2931, 2876, 2169, 1461, 1380, 1173, 1123, 1032; ¹H NMR (400 MHz, CDCl₃) δH 4.39 (1H, dt, J = 5.8 and 6.4 Hz, H₃), 4.15 (1H, sept, J = 6.1 Hz, OCH(CH₃)₂), 1.75 (1H, d, J = 5.8 Hz, OH), 1.76-1.70 (2H, m H₄), 1.51-1.43 (2H, m, H₅), 1.36-1.27 (6H, m, H₆, H₇ and H₈), 1.20 (6H, d, J = 6.1 Hz, OCH(CH₃)₂), 1.01 (6H, t, J = 7.8 Hz, Si(CH₂CH₃)₂), 0.89 (3H, t, J = 6.7 Hz, H₉), 0.66 (4H, q, J = 7.8 Hz, Si(CH₂CH₃)₂); ¹³C NMR (125 MHz, CDCl₃) δC 107.6, 85.8, 66.1, 62.9, 37.9, 31.7, 31.3, 28.8, 25.4, 24.9, 22.5, 14.0, 6.7, 6.6 (diastereotopic SiCH₂); HRMS (ESI⁺) calc. for C₁₆H₃₂NaO₂Si [M+Na]⁺ 307.2069, found 307.2064; EA calc. for C₁₆H₃₂O₂Si: C, 67.54; H, 11.34. Found: C, 67.64; H, 11.24.

Diethyl(3-hydroxynon-1-yn-1-yl)silanol, 115a-H

A mixture of alcohol 115a (300 mg, 1.05 mmol, 1.0 eq), HCl (3 mL of a 0.1 M solution) and MeOH (3 mL) was stirred for one hour. The mixture was diluted with EtOAc, the aqueous neutralised with
NaHCO$_3$, saturated with NaCl(s), and extracted 4 times with EtOAc. The combined organic layer was
dried (MgSO$_4$) and concentrated to give silanol 115a-H as a colourless, viscous oil, which was
immediately diluted with toluene and used in the next step without further purification (255 mg,
~1.50 mmol, ~99%); $R_f$ 0.25 (Et$_2$O); IR (thin film, $v_{max}$/cm$^{-1}$) 3319, 2956, 2929, 2876, 2859, 2173,
1459, 1412, 1236, 1042; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 4.39 (1H, t, $J$ = 6.7 Hz, H3), 2.29 (2H, br s,
2 $\times$ OCH$_3$), 1.76-1.64 (2H, m H4), 1.50-1.40 (2H, m, H5), 1.33-1.25 (6H, m, H6, H7 and H8),
1.05-0.98 (6H, m, Si(CH$_2$C$_2$H$_3$)$_2$), 0.88 (3H, t, $J$ = 6.7 Hz, H9), 0.72-0.60 (4H, m, Si(CH$_2$C$_2$H$_3$)$_2$);
$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 107.6, 86.4, 62.8, 37.6, 28.9, 25.1, 22.5, 14.1, 7.4, 6.4; HRMS
(ESI+) calc. for C$_{14}$H$_{28}$NaO$_2$Si (MeOH MS sample, -OH exchanged for -OMe) [M+Na]$^+$ 279.1756,
found 279.1746.

1-Cyclohexyl-3-(diethyl(isopropoxy)silyl)prop-2-yn-1-ol, 115b

Procedure A: n-Butyllithium (2.2 mL of a 2.5 M solution in hexanes, 5.50 mmol, 1.1 eq), silyl
alkyne 114 (1.00 g, 85 wt% purity, 4.99 mmol, 1.0 eq) in THF (40 mL) and
cyclohexanecarboxaldehyde (0.60 mL, 4.99 mmol, 1.0 eq) gave, after purification via flash column
chromatography (petrol / Et$_2$O (19:1) + 1% Et$_3$N), propargylic alcohol 115b as a colourless oil (844
mg, 2.99 mmol, 60%); $R_f$ 0.26 (petrol / Et$_2$O (9:1)); IR (thin film, $v_{max}$/cm$^{-1}$) 3385, 2958, 2927,
2854, 2169, 1451, 1381, 1173, 1123, 1084, 1031; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 4.19 (1H, t,
$J$ = 5.8 Hz, CHOH), 4.15 (1H, sept, $J$ = 6.1 Hz, OCH(CH$_3$)$_2$), 1.89-1.65 (7H, m, OH, H3’ and H4’),
1.62-1.53 (1H, m, H1’), 1.32-1.05 (4H, m, H2’), 1.20 (6H, d, $J$ = 6.1 Hz, OCH(CH$_3$)$_2$), 1.01 (6H, t,
$J$ = 7.9 Hz, Si(CH$_2$CH$_3$)$_2$), 0.67 (4H, q, $J$ = 7.9 Hz, Si(CH$_2$CH$_3$)$_2$); $^{13}$C NMR (101 MHz, CDCl$_3$)
$\delta$C 106.5, 86.7, 67.5, 66.1, 44.0, 28.6, 27.9, 26.4, 25.8, 25.8, 25.4, 6.7, 6.6; HRMS (ESI$^+$) calc. for
C$_{16}$H$_{30}$NaO$_2$Si [M+Na]$^+$ 305.1913, found 305.1902; EA calc. for C$_{16}$H$_{30}$O$_2$Si: C, 68.03; H, 10.70.
Found: C, 67.94; H, 10.72.
3-(Diethyl(isoproxy)silyl)-1-phenylprop-2-yn-1-ol, 18, 115c

**Procedure A:** n-Butyllithium (4.4 mL of a 2.5 M solution in hexanes, 11.0 mmol, 1.1 eq), silyl alkyne 114 (2.00 g, 85 wt% purity, 10.0 mmol, 1.0 eq) in THF (40 mL) and benzaldehyde (1.02 mL, 10.0 mmol, 1.0 eq) gave, after purification via flash column chromatography (petrol / EtO (9:1→4:1) + 1% Et3N), propargylic alcohol 115c as a colourless oil (2.73 g, 9.86 mmol, 99%); RF 0.13 (petrol / EtO (9:1)); IR (thin film, v_{max} / cm^{-1}) 3340, 2967, 2878, 2173, 1455, 1381, 1369, 1237, 1173, 1121, 1031; ^1H NMR (500 MHz, CDCl$_3$) δH 7.57 (2H, d, J = 7.4 Hz, o-ArH), 7.40 (2H, app t, J = 7.4 Hz, m-ArH), 7.35 (1H, t, J = 7.4 Hz, p-ArH), 5.50 (1H, s, C_HOH), 4.17 (1H, sept, J = 6.1 Hz, OC$_3$H$_7$CH$_2$), 2.17 (1H, br s, OH), 1.20 (6H, d, J = 6.1 Hz, OCH(CH$_3$)$_2$), 1.02 (6H, t, J = 7.9 Hz, Si(CH$_2$CH$_3$)$_2$), 0.70 (4H, q, J = 7.9 Hz, Si(CH$_2$CH$_3$)$_2$); ^13C NMR (125 MHz, CDCl$_3$) δC 140.2, 128.6, 128.4, 126.7, 105.5, 88.3, 66.2, 65.0, 25.4, 6.7, 6.6; HRMS (ESI') calc. for C$_{16}$H$_{24}$NaO$_2$Si [M+Na]$^+$ 299.1443, found 299.1430.

Diethyl(3-hydroxy-3-phenylprop-1-yn-1-yl)silanol, 115c-H

A mixture of alcohol 115c (96 mg, 0.357 mmol, 1.0 eq), HCl (2 mL of a 0.1 M solution) and MeOH (2 mL) was stirred for 10 minutes. The mixture was aqueous neutralised with NaHCO$_3$, saturated with NaCl$_{aq}$, and extracted 4 times with EtOAc. The combined organic layer was dried (MgSO$_4$) and concentrated to give silanol 115c-H as a colourless, viscous oil, which was immediately diluted with toluene and used in the next step without further purification (77 mg, ~0.329 mmol, ~92%); RF 0.27 (petrol / EtO (1:1)); IR (thin film, v_{max} / cm^{-1}) 3302, 2958, 2914, 2876, 2175, 1494, 1454, 1412, 1238, 1192, 1082, 1039, 1004; ^1H NMR (400 MHz, CDCl$_3$) δH 7.53 (2H, d, J = 7.0 Hz, H4), 7.39-7.29 (3H, m, H5 and H6), 5.44 (1H, s, H3), 3.03 (2H, br s, OH and SiOH), 1.02 (6H, t, J = 7.9 Hz, Si(CH$_2$CH$_3$)$_2$), 0.70 (4H, q, J = 7.9 Hz, Si(CH$_2$CH$_3$)$_2$); ^13C NMR (101 MHz, CDCl$_3$) δC 140.0, 128.6,
128.5, 126.8, 105.6, 88.7, 74, 6.5; HRMS (ESI⁺) calc. for C₁₃H₁₈NaO₂Si [M+Na]⁺ 257.0968, found 257.0970.

3-((Tert-butyldimethylsilyl)oxy)propan-1-ol, S₁

\[
\begin{align*}
\text{Si} & \quad \text{O} \\
& \quad \text{OH}
\end{align*}
\]

Prepared according to a literature procedure. Sodium hydride (1.58 g of a 60 wt% dispersion in mineral oil, 39.4 mmol, 1.0 eq) was taken up in THF (80 mL) and propane-1,3-diol (3.0 g, 39.4 mmol, 1.0 eq) was added dropwise at room temperature. The mixture was stirred for 45 minutes, tert-butyldimethylsilyl chloride (5.94 g, 39.4 mmol, 1.0 eq) added, and stirred for a further 45 minutes. The reaction was then diluted with 500 mL of Et₂O, washed with K₂CO₃ solution and brine, and dried (MgSO₄). The concentrated crude was purified via flash column chromatography (petrol / EtOAc (9:1→1:1)) to give alcohol S₁ as a colourless oil (5.37 g, 28.22 mmol, 72%); \( R_f \) 0.19 (petrol / Et₂O (2:1)); \(^1\text{H NMR} (\text{CDCl}_3, 200 \text{ MHz}) \delta_H 3.88-3.78 (4\text{H, m, H1 and H3}), 2.61 (1\text{H, t, } J = 5.4 \text{ Hz, } \text{OH}), 1.79 (2\text{H, quin, } J = 5.6 \text{ Hz, H2}), 0.91 (9\text{H, s, (CH₃)$_3$Si}), 0.09 (6\text{H, s, 2} \times \text{SiCH₃}); \(^1\text{C NMR} (101 \text{ MHz, CDCl}_3) \delta_C 62.4, 61.8, 34.3, 25.8, 18.1, -5.6; LRMS (ESI⁺) calc. for C₉H₂₂NaO₂Si [M]⁺ 213.1, found 213.1.

The spectroscopic data were found to be in agreement with that reported by Chavan and co-workers.

3-((Tert-butyldimethylsilyl)oxy)propanal, S₂

\[
\begin{align*}
\text{Si} & \quad \text{O} \\
& \quad \text{O}
\end{align*}
\]

Prepared according to a literature procedure. Dimethyl sulfoxide (0.41 mL, 5.78 mmol, 2.2 eq) was added dropwise to oxalyl chloride (0.25 mL, 2.89 mmol, 1.1 eq) in DCM (20 mL) at -78 °C and stirred for 15 minutes before alcohol S₁ (500 mg, 2.63 mmol, 1.0 eq) was cannulated in as a solution in DCM (5 mL). The mixture was stirred for a further 30 minutes at -78 °C, Et₃N (2.2 mL, 15.8
mmol, 6.0 eq) added, and after 10 minutes at -78 °C was warmed to room temperature and stirred for one hour. The mixture was quenched with NaHCO₃ solution, and the aqueous layer extracted three times with DCM. The organic layers were combined, dried (MgSO₄), concentrated and purified via flash column chromatography (petrol / EtOAc (19:1)) to give aldehyde S₂ as a colourless oil (289 mg, 1.83 mmol, 58%); Rₚ 0.50 (petrol / Et₂O (2:1)); ¹H NMR (CDCl₃, 200 MHz) δ_H 9.81 (1H, t, J = 2.1 Hz, H1), 4.00 (2H, t, J = 6.0 Hz, H3), 2.61 (2H, dt, J = 6.0 and 2.1 Hz, H2), 0.89 (9H, s, (CH₃)₃CSi), 0.07 (6H, s, 2×SiC₃H₃); ¹³C NMR (101 MHz, CDCl₃) δ_C 201.9, 57.3, 46.5, 25.8, 18.2, -5.5; LRMS (ESI⁺) calc. for C₉H₂₀NaO₂Si [M+Na]⁺ 211.11, found 211.11.

The spectroscopic data were found to be in agreement with that reported by Gieseler and co-workers.²⁵¹

10,10-Diethyl-2,2,3,3,12-pentamethyl-4,11-dioxo-3,10-disila-8-0yn-7-ol, 115d

Procedure A: n-Butyllithium (0.67 mL of a 2.5 M solution in hexanes, 1.67 mmol, 1.1 eq), silyl alkyne 115 (306 mg, 85 wt% purity, 1.52 mmol, 1.0 eq) in THF (8 mL) and 3-((tert-butylidimethylsilyl)oxy)propanal S₂ (285 mg, 1.52 mmol, 1.0 eq) gave, after purification via flash column chromatography (petrol / Et₂O (9:1) + 1% Et₃N), propargylic alcohol 115d as a colourless oil (495 mg, 1.38 mmol, 91%); Rₚ 0.30 (petrol / Et₂O (4:1)); IR (thin film, ν_max / cm⁻¹) 2957, 2930, 2879, 2172, 1463, 1383, 1255, 1173, 1093, 1032; ¹H NMR (400 MHz, CDCl₃) δ_H 4.65 (1H, dt, J = 6.2 and 4.4 Hz, H7), 4.16 (1H, sept, J = 6.1 Hz, OCH(CH₃)₂), 4.12-4.06 and 3.87-3.82 (2×1H, m, diastereotopic H5), 3.48 (1H, d, J = 4.4 Hz, OH), 2.08-1.99 and 1.91-1.83 (2×1H, m, diastereotopic H6), 1.20 (6H, d, J = 6.1 Hz, OCH(CH₃)₂), 1.01 (6H, t, J = 7.9 Hz, Si(CH₂CH₃)₂), 0.91 (9H, s, Si(CH₃)₂C(CH₃)₃), 0.67 (4H, q, J = 7.9 Hz, Si(CH₂CH₃)₂), 0.10 and 0.09 (2×3H, s, diastereotopic Si(CH₃)₂C(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) 106.9, 85.7, 66.1, 62.3, 61.0, 38.4, 25.8, 25.5, 18.1, 6.7, 6.6, -5.6; HRMS (FI⁺) calc. for C₁₈H₃₄NaO₃Si₂ [M+Na]⁺ 381.2257, found 381.2242.
3-((4-Methoxybenzyl)oxy)propan-1-ol, S3

![Chemical Structure of S3](image)

Prepared according to a literature procedure.\textsuperscript{252} Potassium hydroxide (3.40 g, 60.7 mmol, 2.0 eq) was added portionwise to a solution of propane-1,3-diol (4.4 mL, 60.7 mmol, 2.0 eq) in anhydrous dimethyl sulfoxide (20 mL) at 0 °C. The mixture was warmed to room temperature and stirred for one hour until it became clear, then cooled to 0 °C again and \( p \)-methoxybenzyl chloride (4.1 mL, 30.4 mmol, 1.0 eq) added. The reaction was warmed to room temperature and stirred for three hours, when TLC revealed the starting material had been consumed. It was then diluted with 30 mL of Et\(_2\)O at 0 °C and 15 mL of 4 M HCl was slowly added. The mixture was extracted three times with Et\(_2\)O, dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo. The concentrated crude was purified via flash column chromatography (petrol / EtOAc (5:1→1:1)) to give alcohol S3 as a colourless oil (4.43 g, 22.6 mmol, 74%); \( R_f \) 0.17 (petrol / EtOAc (3:2)); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \)\( H \) 7.26 (2H, d, \( J = 8.8 \) Hz, H6), 6.89 (2H, d, \( J = 8.8 \) Hz, H7), 4.46 (2H, s, H4), 3.81 (3H, s, ArOC\( H_3 \)), 3.81-3.76 (2H, m, H1), 3.64 (2H, t, \( J = 5.9 \) Hz, H3), 2.35 (1H, br, OH), 1.86 (2H, quin, \( J = 5.9 \) Hz, H2); \(^13\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \)\( C \) 159.2, 130.2, 129.3, 113.8, 72.8, 68.8, 61.5, 55.2, 32.1; LRMS (ESI\(^+\)) calc. for C\(_{11}\)H\(_{16}\)NaO\(_3\) [M+Na\(^+\)] 219.1, found 219.1.

The spectroscopic data were found to be in agreement with that reported by Kretschmer and co-workers.\textsuperscript{252}

3-((4-Methoxybenzyl)oxy)propanal, S4

![Chemical Structure of S4](image)

Prepared according to a literature procedure.\textsuperscript{253} Et\(_3\)N (13.5 mL, 97.4 mmol, 5.0 eq), dimethyl sulfoxide (9.7 mL, 137 mmol, 7.0 eq) and SO\(_3\)py (9.23 g, 58.0 mmol, 3.0 eq) were added to a solution of alcohol S3 (3.82 g, 19.5 mmol, 1.0 eq) in DCM (10 mL) at 0 °C and stirred for 30
minutes. The reaction was then quenched with aqueous pH 7 phosphate buffer solution, extracted with EtOAc, washed with brine and dried (Na$_2$SO$_4$). The concentrated crude was purified via flash column chromatography (petrol / EtOAc (9:1→4:1)) to give aldehyde S4 as a colourless oil (2.85 g, 14.7 mmol, 75%); $R_f$ 0.37 (petrol / EtOAc (4:1)); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$H 9.80 (1H, t, $J$ = 1.9 Hz, H1), 7.26 (2H, d, $J$ = 8.7 Hz, H6), 6.89 (2H, d, $J$ = 8.7 Hz, H7), 4.47 (2H, s, H4), 3.81 (3H, s, ArOC$_3$H$_3$), 3.64 (2H, t, $J$ = 5.9 Hz, H3), 2.69 (2H, dt, $J$ = 5.9 and 1.9 Hz, H2); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$C 201.3, 159.3, 129.9, 129.3, 113.8, 72.9, 63.5, 55.2, 43.9; LRMS (ESI$^+$) calc. for C$_{11}$H$_{14}$NaO$_3$ [M+Na]$^+$ 217.1, found 217.1.

The spectroscopic data were found to be in agreement with that reported by Hayashi and co-workers.

1-(Diethyl(isopropoxy)silyl)-5-((4-methoxybenzyl)oxy)pent-1-yn-3-ol, 115e

Procedure A: $n$-Butyllithium (4.5 mL of a 2.5 M solution in hexanes, 11.3 mmol, 1.1 eq), silyl alkyne 114 (2.06 g, 85 wt% purity, 10.3 mmol, 1.0 eq) in THF (50 mL) and 3-((4-methoxybenzyl)oxy)propanal, S4 (2.00 g, 10.3 mmol, 1.0 eq) gave, after purification via flash column chromatography (petrol / EtOAc (9:1) + 1% Et$_3$N), propargylic alcohol 115e as a colourless oil (3.54 g, 9.71 mmol, 94%); $R_f$ 0.23 (petrol / EtOAc (4:1)); IR (thin film, $\nu_{max}$ / cm$^{-1}$) 3426, 2959, 2876, 2170, 1613, 1513, 1412, 1367, 1247, 1173, 1096, 1028; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 7.26 (2H, d, $J$ = 8.7 Hz, H8), 6.89 (2H, d, $J$ = 8.7 Hz, H9), 4.63 (1H, dt, $J$ = 6.5 and 4.5 Hz, H3), 4.48 and 4.45 (2 × 1H, d, $J$ = 11.4 Hz, diastereotopic H6), 4.14 (1H, sept, $J$ = 6.1 Hz, OCH(CH$_3$)$_2$), 3.90-3.84 (1H, m, diastereotopic H5), 3.81 (3H, s, OCH$_3$), 3.70-3.65 (1H, m, diastereotopic H5), 3.08 (1H, d, $J$ = 6.5 Hz, OCH), 2.15-2.07 and 1.99-1.91 (2 × 1H, m, diastereotopic H4), 1.19 (6H, d, $J$ = 6.1 Hz, OCH(CH$_3$)$_2$), 1.00 (6H, t, $J$ = 7.9 Hz, Si(CH$_3$)$_2$), 0.66 (4H, q, $J$ = 7.9 Hz, Si(CH$_2$CH$_3$)$_2$); $^{13}$C NMR (101 MHz, CDCl$_3$) 159.3, 129.9, 129.3, 113.8, 107.0, 85.8, 73.1, 67.3,
66.1, 61.6, 55.2, 36.7, 6.7, 6.6; HRMS (ESI') calc. for C_{20}H_{32}NaO_{4}Si [M+Na]' 387.1968, found 387.1960.

**1-(Diethyl(isopropoxy)silyl)-5-((4-methoxybenzyl)oxy)pent-1-yn-3-one, 116e**

![Chemical Structure](image)

Alcohol 115e (1.17 g, 3.20 mmol, 1.0 eq) was stirred with activated manganese dioxide (5.56 g, 64.0 mmol, 20 eq) and 4 Å molecular sieves in DCM (30 mL) for 4 hours, then filtered through Celite® and concentrated to give ketone 116e as a colourless oil (865 mg, ~2.39 mmol, ~75%); R_f 0.46 (petrol / Et_2O (3:2)); IR (thin film, ν_max / cm⁻¹) 2964, 2936, 2878, 2149, 1681, 1613, 1514, 1248, 1119, 1034; ^1H NMR (400 MHz, CDCl_3) δH 7.24 (2H, d, J = 8.6 Hz, H8), 6.86 (2H, d, J = 8.6 Hz, H9), 4.45 (2H, s, H6), 4.13 (1H, sept, J = 6.1 Hz, OCH(CH_3)_2), 3.81-3.77 (5H, m, H5 and OCH_3), 2.85 (2H, t, J = 6.1 Hz, H4), 1.19 (6H, d, J = 6.1 Hz, OCH(CH_3)_2), 1.01 (6H, t, J = 8.0 Hz, Si(CH_2CH_3)_2), 0.71 (4H, q, J = 8.0 Hz, Si(CH_2CH_3)_2); ^13C NMR (101 MHz, CDCl_3) 185.2, 159.3, 130.0, 129.3, 113.8, 101.8, 94.6, 72.9, 66.7, 64.5, 55.2, 45.7, 25.4, 6.4, 6.4; HRMS (FI') calc. for C_{20}H_{30}O_{4}Si [M]'^+ 362.1913, found 362.1917.

**((R)-1-(Diethyl(isopropoxy)silyl)-5-((4-methoxybenzyl)oxy)pent-1-yn-3-ol, (R)-115e**

![Chemical Structure](image)

A solution of ketone 116e (1.88 g, 5.20 mmol, 1.0 eq) in isopropyl alcohol (10 mL) was degassed with argon for one hour, before the addition of (1R,2R)-(+) N-Tosyl-1,2-diphenylethane-1,2-diamine[η^5-1-isopropyl-4-methylbenzene]-ruthenium(II) (Noyori catalyst^{223}) (74 mg, 0.104 mmol, 0.02 eq) as a solution in DCM (3 mL). The mixture was stirred for 45 minutes before being concentrated under reduced pressure. The crude residue was purified via flash column chromatography (petrol / EtOAc (9:1) + 1% Et_3N) to give propargylic alcohol (R)-115e as a
colourless oil (1.75 g, 4.79 mmol, 92%); ee 97% (CHIRALPAK-IC, 2% IPA/n-Hex, 1.3 mL/min, R - 7.85 min, S - 8.72 min); \[\alpha\]$_D^{25}$ +24.4 (c 1.0, CHCl$_3$). Other data were identical to that reported for (±)-116e.

1-((Diethyl(isopropoxy)silyl)ethynyl)cyclohexan-1-ol, 115f

\[
\text{Procedure A: } n\text{-Butyllithium (0.92 mL of a 2.5 M solution in hexanes, 2.31 mmol, 1.2 eq), silyl alkyne 114 (500 mg, 85 wt% purity, 2.50 mmol, 1.3 eq) in THF (10 mL) and cyclohexanone (0.20 mL, 1.92 mmol, 1.0 eq) gave, after purification via flash column chromatography (petrol / Et$_2$O (9:1) + 1% Et$_3$N), propargylic alcohol 115f as a colourless oil (515 mg, 1.92 mmol, quant.); } R_f 0.18 (petrol / Et$_2$O (4:1)); \text{IR (thin film, } \nu_{\text{max}} / \text{cm}^{-1} \text{)} 3345, 2935, 2877, 2165, 1448, 1340, 1122, 1070, 1008; ^1\text{H NMR (400 MHz, CDCl$_3$)} \delta_{\text{H}} 4.16 (1H, sept, } J = 6.1 \text{ Hz, OCH(CH$_3$)$_2$}, 2.27-2.20 (1H, m, OH), 1.97-1.89 (2H, m, 2 × H3), 1.75-1.67 (2H, m, 2 × H2), 1.63-1.51 (5H, m, 2 × H2, 2 × H3 and 1 × H4), 1.30-1.18 (1H, m, 1 × H4), 1.20 (6H, d, } J = 6.1 \text{ Hz, OCH(CH$_3$)$_2$}, 1.01 (6H, t, } J = 7.8 \text{ Hz, Si(CH$_2$CH$_3$)$_2$}, 0.66 (4H, q, } J = 7.8 \text{ Hz, Si(CH$_2$CH$_3$)$_2$}; ^{13}\text{C NMR (101 MHz, CDCl$_3$)} 110.4, 85.0, 69.0, 66.1, 39.9, 24.5, 25.2, 23.4, 6.8, 6.7; \text{HRMS (ESI$^+$) calc. for } C_{15}H$_{28}$NaO$_2$Si [M+Na]$^+$ 291.1751, found 291.1742.

2-Cyclohexyloxirane, 118b

\[
\text{Prepared according to a modified literature procedure.}^{254} \text{ 3-Chloroperoxybenzoic acid (2.75 g of 77 wt% solid, 8.77 mmol, 1.2 eq) was added to vinylcyclohexane (1.00 mL, 7.30 mmol, 1.0 eq) in DCM (40 mL) at 0 °C, then stirred at room temperature for 16 hours. The mixture was diluted with petrol, washed sequentially with } NaHCO$_3$, Na$_2$S$_2$O$_3$, NaHCO$_3$, and brine solutions, and dried}
(MgSO$_4$). The residue was concentrated \textit{in vacuo} to give epoxide \textbf{118b} as a colourless oil (795 mg, 6.30 mmol, 86%); $R_f$ 0.32 (DCM / petrol (2:3)); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$H 2.65-2.62 (2H, m, H1), 2.46-2.44 (1H, m, H2), 1.83-1.78 (1H, m, H3), 1.70-1.57 (4H, m, H5), 1.22-0.98 (6H, m, H4 and H6); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$C 56.7, 46.0, 40.4, 29.7, 28.8, 26.3, 25.7, 25.5.

The spectroscopic data were found to be in agreement with that reported by Piccinini and co-workers.$^{255}$

\textit{(But-3-en-1-yloxy)(tert-butyl)dimethylsilane, S5}

\begin{center}
\includegraphics[width=0.2\textwidth]{structure_s5.png}
\end{center}

Prepared according to a literature procedure.$^{256}$ Butenol (0.50 mL, 5.80 mmol, 1.0 eq) was added dropwise to a solution of imidazole (435 mg, 6.39 mmol, 1.1 eq) and \textit{tert}-butyldimethylsilyl chloride (963 mg, 6.39 mmol, 1.1 eq) in DCM (15 mL). The reaction was stirred for 2.5 hours, diluted with Et$_2$O, washed three times with water, once with brine, and dried (MgSO$_4$). The crude was concentrated to give alkene \textbf{S5} as a colourless oil used without further purification (940 mg, 5.04 mmol, 87%); $R_f$ 0.70 (petrol / Et$_2$O (2:1)); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$H 5.88-5.77 (1H, m, H3), 5.10-5.01 (2H, m, H4), 3.66 (2H, t, $J = 6.8$ Hz, H1), 2.31-2.26 (2H, m, H2), 0.90 (9H, s, (CH$_3$)$_3$Si), 0.06 (6H, s, 2 x SiCH$_3$); $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$C 135.4, 116.3, 62.8, 37.5, 25.9, 18.3, -5.3; LRMS (ESI$^+$) calc. for C$_{10}$H$_{22}$NaOSi [M+Na]$^+$ 209.13, found 209.13.

The physical and spectroscopic data was found to be in agreement with that reported by Gieseler and co-workers.$^{251}$

\textit{Tert-butyldimethyl(2-oxiran-2-yl)ethoxy)silane, 118d}

\begin{center}
\includegraphics[width=0.2\textwidth]{structure_118d.png}
\end{center}

Prepared according to a modified literature procedure.$^{254}$ 3-chloroperoxybenzoic acid (1.23 g, 5.49 mmol, 1.2 eq) was added to alkene \textbf{S5} (853 mg, 4.58 mmol, 1.0 eq) in DCM (25 mL) at 0 ºC
under argon, then stirred at room temperature for 16 hours. The mixture was diluted with petrol, washed sequentially with NaHCO$_3$, Na$_2$S$_2$O$_3$, NaHCO$_3$, and brine solutions, and dried (MgSO$_4$). The residue was concentrated and purified by column chromatography (petrol / Et$_2$O (9:1)) to give epoxide 118d as a colourless oil (814 mg, 4.02 mmol, 88%); $R_f$ 0.27 (petrol / Et$_2$O (2:1)); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$H 3.78 (2H, t, $J = 5.9$ Hz, H1), 3.08-3.03 (1H, m, H3), 2.79 (1H, t, $J = 4.7$ Hz, 1 x H4), 2.53 (1H, dd, $J = 4.7$ and 2.8 Hz, 1 x H4), 1.83-1.66 (2H, m, H2), 0.90 (9H, s, (CH$_3$)$_3$Si), 0.07 (6H, s, 2 x SiCH$_3$); $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$C 59.9, 50.0, 47.1, 35.9, 25.8, 18.2, -5.4; LRMS (ESI$^+$) calc. for C$_{10}$H$_{22}$NaO$_2$Si [M+Na]$^+$ 225.13, found 225.11.

The physical and spectroscopic data was found to be in agreement with that reported by Tan and co-workers.

1-((But-3-en-1-yloxy)methyl)-4-methoxybenzene, S6

\[ \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \]

$p$-(Methoxybenzyl)-trichloroacetimidate (1.23 g, 4.36 mmol, 1.5 eq) and scandium (III) triflate (71 mg, 0.145 mmol, 0.05 eq) were added to a solution of 3-butyn-1-ol (0.25 mL, 2.91 mmol, 1.0 eq) in toluene (50 mL). The reaction was stirred for 15 minutes, then quenched with NaHCO$_3$ solution, extracted with Et$_2$O, dried (MgSO$_4$) and concentrated in vacuo. The crude was purified by flash column chromatography (petrol / Et$_2$O (19:1)) to give protected alkene S6 as a colourless oil (560 mg, ~2.91 mmol, ~100%); $R_f$ 0.39 (petrol / Et$_2$O (2:1)); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$H 7.27 (2H, d, $J = 8.9$ Hz, H2$'$), 6.89 (2H, d, $J = 8.9$ Hz, H3$'$), 5.89-5.79 (1H, m, H3), 5.10 (1H, d, $J = 17.4$ Hz, H4a), 5.05 (1H, d, $J = 10.3$ Hz, H4b), 4.46 (2H, s, ArCH$_2$O), 3.81 (3H, s, OCH$_3$), 3.50 (2H, t, $J = 6.8$ Hz, H1), 2.37 (2H, q, $J = 6.8$ and 1.7 Hz, H2); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$C 159.1, 135.3, 130.6, 129.3, 116.3, 113.8, 72.6, 69.3, 55.3, 34.3; LRMS (ESI$^+$) calc. for C$_{12}$H$_{16}$NaO$_2$ [M+Na]$^+$ 215.1, found 215.1.

The spectroscopic data were found to be in agreement with that reported by Barbazanges and co-workers.

257
2-(2-((4-Methoxybenzyl)oxy)ethyl)oxirane, 118e

Prepared according to a modified literature procedure. 3-Chloroperoxybenzoic acid, 77% (700 mg, 3.12 mmol, 1.2 eq) was added to alkene S6 (500 mg, 2.60 mmol, 1.0 eq) in DCM (12 mL) at 0 °C, then stirred at room temperature for 16 hours. The mixture was diluted with petrol, washed sequentially with NaHCO₃, Na₂S₂O₃, NaHCO₃, and brine solutions, and dried (MgSO₄). The residue was concentrated in vacuo and purified by column chromatography (petrol / Et₂O (6:1→3:1)) to give epoxide 118e as a colourless oil (455 mg, 2.19 mmol, 84%); \( R_f \) 0.15 (petrol / Et₂O (4:1)); \(^1\)H NMR (CDCl₃, 400 MHz) \( \delta_H \) 7.28 (2H, d, \( J = 8.7 \) Hz, H2'), 6.89 (2H, d, \( J = 8.7 \) Hz, H3'), 4.47 and 4.47 (2 × 1H, d, \( J = 11.7 \) Hz, diastereotopic ArC\( \text{H}_2\)O), 3.82 (3H, s, OC\( \text{H}_3 \)), 3.62-3.58 (2H, m, H1), 3.09-3.05 (1H, m, H3), 2.79 (1H, t, \( J = 4.3 \) Hz, diastereotopic H4), 2.53 (1H, dd, \( J = 4.3 \) and 2.7 Hz, diastereotopic H4), 1.95-1.87 and 1.81-1.73 (2 × 1H, m, diastereotopic H2); \(^{13}\)C NMR (101 MHz, CDCl₃) \( \delta_C \) 159.2, 130.4, 129.2, 113.8, 72.7, 66.7, 55.2, 50.1, 47.1, 33.0; LRMS (ESI⁺) calc. for C₁₂H₁₆O₃ [M+Na]⁺ 231.1, found 231.1.

The spectroscopic data were found to be in agreement with that reported by Dubey and co-workers.

\((R)-2-(2-((4-Methoxybenzyl)oxy)ethyl)oxirane, (R)-118e\)

Prepared according to a modified literature procedure. \((R,R)-(-)-N,N'\)-Bis(3,5-di-tert-butylsalicyclidene)-1,2-cyclohexanediiminocobalt (II) (61 mg, 0.100 mmol, 0.02 eq) was added to neat epoxide (±)-118e (1.04 g, 5.01 mmol, 1.0 eq), followed by acetic acid (23 µL, 0.401 mmol, 0.08 eq). The mixture was cooled to 0 °C, water (50 µL, 2.76 mmol, 0.55 eq) added and left to stir at room temperature for 96 hours. The crude was purified directly via flash column chromatography
Experimental

(.petrol / Et₂O (100:0→99:1) + 1% Et₃N) to give (R)-118e as a pale yellow oil (379 mg, 1.82 mmol, 36%); ee >99% (CHIRALPAK-IC, 1% IPA/n-Hex, 1.3 mL/min, R - 22.10 min, S - 23.79 min); [α]D²⁵ +14.7 (c 1.0, CHCl₃) [lit.²⁶¹ +13.6 (c 3.44, CHCl₃)]. Other data were identical to that reported for (±)-118e.

1-(Diethyl(isopropoxy)silyl)dec-1-yn-4-ol, 117a

Procedure B: n-Butyllithium (2.1 mL of a 2.5 M solution in hexanes, 5.28 mmol, 1.5 eq) and silyl alkyne 114 (1.00 g, 90 wt% purity, 5.28 mmol, 1.5 eq) in THF (20 mL) were stirred at -78 °C for one hour. 1,2-Epoxyoctane (0.54 mL, 3.52 mmol, 1.0 eq) was added, and the mixture stirred for a further 10 minutes before BF₃·OEt₂ (0.65 mL, 5.28 mmol, 1.5 eq) was added. The mixture was stirred for 4.5 hours. The crude was purified via flash column chromatography (petrol / Et₂O (9:1 → 4:1) + 1% Et₃N) to give homopropargylic alcohol 117a as a colourless oil (542 mg, 1.82 mmol, 52%); Rf 0.24 (petrol / Et₂O (9:1)); IR (thin film, νmax / cm⁻¹) 3374, 2958, 2931, 2876, 2174, 1461, 1380, 1236, 1124, 1031; ¹H NMR (400 MHz, CDCl₃) δH 4.07 (1H, sept, J = 6.0 Hz, OCH(CH₃)₂), 3.72-3.65 (1H, m, H4), 2.42 (1H, dd, J = 16.7 and 5.1 Hz, 1 × H3), 2.33 (1H, dd, J = 16.7 and 6.5 Hz, 1 × H3), 1.93 (1H, br s, OH), 1.53-1.19 (10H, m, H5, H6, H7, H8 and H9), 1.12 (6H, d, J = 6.0 Hz, OCH(CH₃)₂), 0.93 (6H, t, J = 7.8 Hz, Si(CH₂CH₃)₂), 0.82 (3H, t, J = 6.6 Hz, H10), 0.58 (4H, q, J = 7.8 Hz, Si(CH₂CH₃)₂); ¹³C NMR (101 MHz, CDCl₃) 104.1, 84.1, 69.9, 66.0, 36.3, 31.8, 29.3, 28.8, 25.5, 25.5, 22.6, 14.1, 6.9, 6.7; HRMS (ESI⁺) calc. for C₁₇H₃₄NaO₂Si [M+Na]⁺ 321.2220, found 321.2221.
1-Cyclohexyl-4-(diethyl(isopropoxy)silyl)but-3-yn-1-ol, 117b

Procedure B: n-Butyllithium (6.6 mL of a 2.0 M solution in hexanes, 13.2 mmol, 2.1 eq) and silyl alkyne 114 (2.52 g, 85 wt% purity, 12.6 mmol, 2.0 eq) in THF (30 mL) were stirred at -78 °C for one hour. Epoxide 118b (795 mg, 6.30 mmol, 1.0 eq) was added, and the mixture stirred for a further 10 minutes before BF₃·OEt₂ (1.55 mL, 12.6 mmol, 2.0 eq) was added. The mixture was stirred for three hours. The crude was purified via flash column chromatography (petrol / Et₂O (19:1) + 1% Et₃N) to give homopropargylic alcohol 117b as a colourless oil (1.24 g, 4.18 mmol, 66%); R_f 0.34 (petrol / Et₂O (19:1)); IR (thin film, v_max / cm⁻¹) 3439, 2927, 2877, 2174, 1451, 1380, 1124, 1031; ¹H NMR (400 MHz, CDCl₃) δ_H 4.07 (1H, sept, J = 6.1 Hz, OC(CH₃)₂), 3.45-3.40 (1H, m, H1), 2.44 (1H, dd, J = 16.9 and 4.6 Hz, 1 × H2), 2.35 (1H, dd, J = 16.9 and 7.2 Hz, 1 × H2), 1.98 (1H, s, OH), 1.88-1.81 (1H, m, 1 × diastereotopic H2'), 1.74-1.67 and 1.63-1.56 (2 × 2H, m, diastereotopic H3'), 1.46-1.37 (1H, m, H1'), 1.21-1.02 (5H, m, 3 × diastereotopic H2' and H4'), 1.12 (6H, d, J = 6.1 Hz, OCH(CH₃)₂), 0.93 (6H, t, J = 7.9 Hz, Si(CH₂CH₃)₂), 0.57 (4H, q, J = 7.9 Hz, Si(CH₂CH₃)₂); ¹³C NMR (101 MHz, CDCl₃) 104.5, 84.0, 73.9, 66.0, 42.7, 29.1, 28.1, 26.4, 26.2, 26.1, 26.0, 25.5, 6.8, 6.7; HRMS (ESI⁺) calc. for C₁₇H₃₂NaO₂Si [M+Na⁺] 319.2064, found 319.2053.

11,11-Diethyl-2,2,3,3,13-pentamethyl-4,12-dioxa-3,11-disilatetradec-9-yn-7-ol, 117d

Procedure B: n-Butyllithium (0.74 mL of a 2.5 M solution in hexanes, 1.86 mmol, 1.6 eq) and silyl alkyne 114 (344 mg, 85 wt% purity, 1.72 mmol, 1.4 eq) in THF (8 mL) were stirred at -78 °C for one hour. Epoxide 118d (243 mg, 1.20 mmol, 1.0 eq) was added, and the mixture stirred for a further 10 minutes before BF₃·OEt₂ (0.21 mL, 1.72 mmol, 1.4 eq) was added. The mixture was stirred for two hours. The crude was purified via flash column chromatography (petrol / Et₂O (9:1) + 1% Et₃N) to give homopropargylic alcohol 117d as a colourless oil (377 mg, 1.19 mmol, 99%); R_f 0.23 (petrol
7. Experimental

\[
\text{IR (thin film, } \nu_{\text{max}} / \text{cm}^{-1} \text{) 3449, 2957, 2931, 2878, 2175, 1471, 1382, 1367, 1120, 1093; } ^1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta_H 4.14 (1H, sept, } J = 6.1 \text{ Hz, OCH(CH}_3\text{)_2} \text{), 4.03-3.97 (1H, m, H3), 3.97-3.91 and 3.86-3.80 (2 } \times \text{ 1H, m, diastereotopic H1), 3.48 (1H, d, } J = 3.1 \text{ Hz, OH), 2.53 (1H, dd, } J = 16.9 \text{ and 5.6 Hz, diastereotopic H4), 2.44 (1H, dd, } J = 16.9 \text{ and 6.9 Hz, diastereotopic H4), 1.92-1.85 and 1.81-1.70 (2 } \times \text{ 1H, m, diastereotopic H2), 1.19 (6H, d, } J = 6.1 \text{ Hz, OCH(CH}_3\text{)_2} \text{), 1.00 (6H, t, } J = 7.8 \text{ Hz, Si(CH}_2\text{CH}_3\text{)_2}, 0.90 (9H, s, SiC(CH}_3\text{)_2} \text{), 0.64 (4H, q, } J = 7.8 \text{ Hz, Si(CH}_2\text{CH}_3\text{)_2}, 0.09 (6H, s, Si(CH}_3\text{)_2}; } ^13\text{C NMR (101 MHz, CDCl}_3\text{)} 104.4, 83.5, 70.4, 66.1, 62.1, 37.3, 28.4, 25.8, 25.4, 18.1, 6.8, 6.6, -5.6; } \text{HRMS (ESI') calc. for C}_{19}\text{H}_{40}\text{NaO}_3\text{Si}_2 [M+Na]^+ 395.2408, found 395.2408.}
\]

(R)-6-(Diethyl(isopropoxy)silyl)-1-((4-methoxybenzyl)oxy)hex-5-yn-3-ol, (R)-117e

\[
\begin{aligned}
\text{(R)-6-(Diethyl(isopropoxy)silyl)-1-((4-methoxybenzyl)oxy)hex-5-yn-3-ol, (R)-117e}
\end{aligned}
\]

**Procedure B:** \( n \)-Butyllithium (0.81 mL of a 2.5 M solution in hexanes, 2.02 mmol, 2.1 eq) and silyl alkyne 114 (385 mg, 85 wt% purity, 1.92 mmol, 2.0 eq) in THF (8 mL) were stirred at -78 °C for one hour. Epoxide (R)-118e (200 mg, 0.961 mmol, 1.0 eq) was added, and the mixture stirred for a further 10 minutes before BF\(_3\cdot\)OEt\(_2\) (0.24 mL, 1.92 mmol, 2.0 eq) was added. The mixture was stirred for 4 hours. The crude was purified via flash column chromatography (petrol / EtOAc (9:1→4:1) + 1% Et\(_3\)N) to give homopropargylic alcohol (R)-117e as a colourless oil (287 mg, 0.758 mmol, 79%); \( \text{ee} >99\% \) (assumed from analysis of (R)-118e); \( \text{Rf} \) 0.20 (petrol / Et\(_2\)O (2:1)); [\( \text{d}_{20}^{19} \) +0.42 (c 0.5, CHCl\(_3\)); \( \text{IR (thin film, } \nu_{\text{max}} / \text{cm}^{-1} \text{) 3452, 2959, 2876, 2173, 1613, 1514, 1248, 1173, 1120, 1096, 1031; } ^1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta_H 7.26 (2H, d, } J = 8.6 \text{ Hz, H2'), 6.88 (2H, d, } J = 8.6 \text{ Hz, H3'), 4.46 (2H, s, H1'), 4.13 (1H, sept, } J = 6.1 \text{ Hz, OCH(CH}_3\text{)_2} \text{), 4.00-3.95 (1H, m, H3), 3.81 (3H, s, OCH}_3\text{), 3.75-3.70 and 3.66-3.60 (2 } \times \text{ 1H, m, diastereotopic H1), 3.08 (1H, br s, OH), 2.50 (1H, dd, } J = 16.8 \text{ and 5.6 Hz, diastereotopic H4), 2.44 (1H, dd, } J = 16.8 \text{ and 6.9 Hz, diastereotopic H4), 1.98-1.91 and 1.88-1.80 (2 } \times \text{ 1H, m, diastereotopic H2), 1.18 (6H, d, } J = 6.1 \text{ Hz,}
\]
OCH(CH\textsubscript{3})\textsubscript{2}, 0.99 (6H, t, \textit{J} = 7.8 Hz, Si(CH\textsubscript{2}CH\textsubscript{3})\textsubscript{2}), 0.64 (4H, q, \textit{J} = 7.8 Hz, Si(CH\textsubscript{2}CH\textsubscript{3})\textsubscript{2}); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) 159.3, 130.0, 129.3, 113.8, 104.2, 83.7, 72.9, 69.6, 68.2, 65.9, 55.2, 35.3, 28.4, 25.6, 6.8, 6.7; HRMS (ESI\textsuperscript{+}) calc. for C\textsubscript{21}H\textsubscript{34}NaO\textsubscript{4}Si [M+Na]\textsuperscript{+} 401.2124, found 401.2114.

2-(((Diethyl(isopropoxy)silyl)ethynyl)cyclohexan-1-ol, 117g

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{structure}
\caption{Structure of 2-(((Diethyl(isopropoxy)silyl)ethynyl)cyclohexan-1-ol}
\end{figure}

**Procedure B:** \textit{n}-Butyllithium (2.7 mL of a 2.5 M solution in hexanes, 6.87 mmol, 1.8 eq) and silyl alkyne 114 (1.30 g, 85 wt% purity, 6.49 mmol, 1.7 eq) in THF (15 mL) were stirred at -78 °C for one hour. Cyclohexene oxide (0.38 mL, 3.74 mmol, 1.0 eq) was added, and the mixture stirred for a further 10 minutes before BF\textsubscript{3}
\cdot OEt\textsubscript{2} (0.80 mL, 6.49 mmol, 1.7 eq) was added. The mixture was stirred for 5 hours. The crude was purified via flash column chromatography (petrol / Et\textsubscript{2}O (9:1) + 1% Et\textsubscript{3}N) to give homopropargylic alcohol 117g as a colourless oil (574 mg, 2.14 mmol, 57%); R\textsubscript{f} 0.17 (petrol / Et\textsubscript{2}O (4:1)); IR (thin film, \textit{v}_{\text{max}} / \text{cm}^{-1}); 3412, 2936, 2877, 2170, 1450, 1366, 1235, 1173, 1124, 1032; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \textit{δ}_{H} 4.14 (1H, sept, \textit{J} = 6.1 Hz, OCH(CH\textsubscript{3})\textsubscript{2}), 3.52-3.45 (1H, m, H1), 2.38 (1H, br s, OH), 2.32-2.26 (1H, m, H2), 2.05-1.98 (2H, m, 1 × H3 and 1 × H6), 1.79-1.74 (1H, m, 1 × H4 or 1 × H5), 1.70-1.64 (1H, m, 1 × H4 or 1 × H5), 1.47-1.14 (4H, m, 1 × H3, 1 × H4, 1 × H5 and 1 × H6), 1.20 (6H, d, \textit{J} = 6.1 Hz, OCH(CH\textsubscript{3})\textsubscript{2}), 1.00 (6H, t, \textit{J} = 7.8 Hz, Si(CH\textsubscript{2}CH\textsubscript{3})\textsubscript{2}), 0.65 (4H, q, \textit{J} = 7.8 Hz, Si(CH\textsubscript{2}CH\textsubscript{3})\textsubscript{2}); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) 109.0, 83.3, 73.3, 66.0, 39.8, 32.8, 30.7, 25.5, 24.7, 24.0, 6.9, 6.7; HRMS (ESI\textsuperscript{+}) calc. for C\textsubscript{15}H\textsubscript{28}NaO\textsubscript{2}Si [M+Na]\textsuperscript{+} 291.1751, found 291.1743.
1-(Diethyl(isopropoxy)silyl)non-1-yn-3-yl acetate, 124a

**Procedure C:** Acetic anhydride (0.20 mL, 2.11 mmol, 2.0 eq), propargyl alcohol 115a (300 mg, 1.05 mmol, 1.0 eq), one crystal of DMAP and Et$_3$N (0.44 mL, 3.16 mmol, 3.0 eq) in DCM (7 mL) gave acetate 124a as a colourless oil that was used in the next step without further purification (324 mg, ~0.990 mmol, ~94%); $R_f$ 0.34 (petrol / Et$_2$O (19:1)); IR (thin film, $\nu_{max}$ / cm$^{-1}$) 2958, 2930, 2876, 2178, 1747, 1461, 1413, 1369, 1293, 1122, 1027; $^1$H NMR (500 MHz, CDCl$_3$) $\delta_H$ 5.39 (1H, t, $J = 6.6$ Hz, H3), 4.13 (1H, sept, $J = 6.0$ Hz, OCH(CH$_3$)$_2$), 2.08 (3H, s, COC$_3$H$_3$), 1.78-1.72 (2H, m, H4), 1.45 (2H, quin, $J = 7.4$ Hz, H5), 1.35-1.26 (6H, m, H6, H7 and H8), 1.19 (6H, d, $J = 6.0$ Hz, OCH(CH$_3$)$_2$), 0.99 (6H, t, $J = 7.7$ Hz, Si(CH$_2$CH$_3$)$_2$), 0.88 (3H, t, $J = 6.7$ Hz, H9), 0.65 (4H, q, $J = 7.7$ Hz, Si(CH$_2$CH$_3$)$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta_C$ 169.8, 103.6, 86.7, 66.7, 64.1, 34.7, 31.6, 28.7, 25.4, 24.9, 22.5, 21.0, 14.0, 6.7, 6.6; HRMS (ESI$^+$) calc. for C$_{18}$H$_{34}$NaO$_3$Si [M+Na]$^+$ 349.2175, found 349.2169.

1-(Diethyl(methoxy)silyl)non-1-yn-3-yl acetate, 124a–Me

Acetate 124a (300 mg, 0.919 mmol, 1.0 eq) and pyridinium $p$-toluenesulfonate (23 mg, 0.092 mmol, 0.1 eq) were stirred in MeOH (5 mL) for three hours, then diluted with Et$_2$O, washed with pH 7 phosphate buffer solution and twice with water. The combined aqueous layers were then reextracted three times with Et$_2$O, and the combine organic layers dried (MgSO$_4$) and concentrated to give 124a–Me as a colourless oil, which was used in the next step without further purification (263 mg, ~0.881 mmol, ~96%); $R_f$ 0.25 (petrol); IR (thin film, $\nu_{max}$ / cm$^{-1}$) 2967, 2933, 2877, 2861, 2179, 1747, 1460, 1371, 1343, 1229, 1089, 1017; $^1$H NMR (400 MHz, CDCl$_3$) $\delta_H$ 5.38 (1H, t, $J = 6.7$ Hz, H3), 3.49
7. Experimental

(3H, s, OCH$_3$), 2.07 (3H, s, COCH$_3$), 1.78-1.71 (2H, m, H4), 1.47-1.39 (2H, m, H5), 1.35-1.25 (6H, m, H6, H7 and H8), 0.99 (6H, t, $J = 7.8$ Hz, Si(CH$_2$CH$_3$)$_2$), 0.87 (3H, t, $J = 6.8$ Hz, H9), 0.66 (4H, q, $J = 7.8$ Hz, Si(CH$_2$CH$_3$)$_2$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$C 169.9, 104.2, 85.7, 64.3, 51.4, 34.7, 31.6, 28.7, 24.9, 22.5, 21.0, 14.0, 6.4, 5.8; HRMS (ESI$^+$) calc. for C$_{16}$H$_{30}$NaO$_3$Si [M+Na]$^+$ 321.18564, found 321.18470.

1-(Diethyl(ethoxy)silyl)non-1-yn-3-yl acetate, 124a-Et

![Chemical structure](image)

Acetate 124a (300 mg, 0.919 mmol, 1.0 eq) and pyridinium $p$-toluenesulfonate (23 mg, 0.092 mmol, 0.1 eq) were stirred in EtOH (5 mL) for three hours, then diluted with Et$_2$O, washed with pH 7 phosphate buffer solution and twice with water. The combined aqueous layers were then reextracted three times with Et$_2$O and the combine organic layers dried (MgSO$_4$) and concentrated to give 124a-Et as a colourless oil, which was used in the next step without further purification (266 mg, ~0.851 mmol, ~93%); $R_f$ 0.23 (petrol); IR (thin film, $\nu_{\text{max}} / \text{cm}^{-1}$) 2957, 2929, 2876, 2179, 1747, 1460, 1371, 1229, 1164, 1106, 1080; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 5.39 (1H, t, $J = 6.7$ Hz, H3), 3.76 (2H, q, $J = 7.0$ Hz, OCH$_2$C$_3$H$_7$), 2.07 (3H, s, COCH$_3$), 1.78-1.72 (2H, m H4), 1.47-1.39 (2H, m, H5), 1.34-1.26 (6H, m, H6, H7 and H8), 1.20 (3H, t, $J = 7.0$ Hz, OCH$_2$CH$_3$), 0.99 (6H, t, $J = 7.8$ Hz, Si(CH$_2$CH$_3$)$_2$), 0.88 (3H, t, $J = 6.8$ Hz, H9), 0.66 (4H, q, $J = 7.8$ Hz, Si(CH$_2$CH$_3$)$_2$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$C 169.9, 103.9, 86.3, 64.3, 59.5, 34.7, 31.6, 28.7, 24.9, 22.5, 21.0, 18.2, 14.0, 6.5, 6.3; HRMS (ESI$^+$) calc. for C$_{17}$H$_{32}$NaO$_3$Si [M+Na]$^+$ 335.20129, found 335.20072.
1-(Diethyl(hydroxy)silyl)non-1-yn-3-yl acetate, 124a-H

A mixture of alcohol 124a (300 mg, 0.919 mmol, 1.0 eq), HCl (3 mL of a 0.1 M aqueous solution) and MeOH (3 mL) was stirred for one hour. The mixture was diluted with EtOAc, the aqueous neutralised with NaHCO₃, saturated with NaCl(aq), and extracted 4 times with EtOAc. The combined organic layer was dried (MgSO₄) and concentrated to give silanol 124a-H as a colourless, viscous oil, which was immediately diluted with toluene and used in the next step without further purification (260 mg, ~0.919 mmol, ~99%); \( R_f \) 0.11 (petrol / Et₂O (4:1)); IR (thin film, \( \nu_{\text{max}} / \text{cm}^{-1} \)) 3435, 2956, 2931, 2876, 2179, 1746, 1460, 1342, 1231, 1017; \(^1\)H NMR (400 MHz, CDCl₃) \( \delta_H \) 5.36 (1H, t, \( J = 6.8 \text{ Hz}, \text{H3} \)), 2.18 (1H, br s, OH), 2.07 (3H, s, CO\text{C\text{H}₃}), 1.79-1.72 (2H, m H4), 1.48-1.38 (2H, m, H5), 1.35-1.25 (6H, m, H6, H7 and H8), 1.00 (6H, t, \( J = 7.8 \text{ Hz}, \text{Si(C\text{H}₂\text{CH}₃)₂} \)), 0.88 (3H, t, \( J = 6.8 \text{ Hz}, \text{H9} \)), 0.66 (4H, q, \( J = 7.8 \text{ Hz}, \text{Si(C\text{H}₂\text{CH}₃)₂} \)); \(^{13}\)C NMR (101 MHz, CDCl₃) \( \delta_C \) 170.0, 103.3, 87.3, 64.3, 34.7, 31.6, 28.7, 24.9, 22.5, 21.0, 14.0, 7.4, 6.4; HRMS (ESI⁺) calc. for C₁₅H₂₈NaO₃Si [M+Na]⁺ 307.16999, found 307.16954.

1-(Diethyl(isopropoxy)silyl)non-1-yn-3-yl acetate, 124x

Propionic anhydride (46 μL, 0.359 mmol, 2.0 eq) was added dropwise to a solution of propargyl alcohol 115a (51 mg, 0.179 mmol, 1.0 eq), one crystal of DMAP and Et₃N (75 μL, 0.538 mmol, 3.0 eq) in DCM (1 mL). The mixture was stirred for three hours, and quenched with NaHCO₃ solution. The aqueous layer was extracted three times with DCM and the combined organic layers dried (MgSO₄) and concentrated to give propionic ester 124x as a colourless oil that was used in the next
7. Experimental

step without further purification (50 mg, ~0.147 mmol, ~82%); \( R_f \) 0.53 (petrol / Et\(_2\)O (9:1)); IR (thin film, \( \nu_{\text{max}} / \text{cm}^{-1} \)) 2958, 2932, 2877, 2179, 1746, 1462, 1380, 1173, 1123, 1031; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta_H \) 5.41 (1H, t, \( J = 6.4 \) Hz, H3), 4.14 (1H, sept, \( J = 6.1 \) Hz, OCH(CH\(_3\))\(_2\)), 2.35 (2H, q, \( J = 7.4 \) Hz, COCH\(_2\)CH\(_3\)), 1.79-1.74 (2H, m, H4), 1.45 (2H, quin, \( J = 7.8 \) Hz, H5), 1.36-1.25 (6H, m, H6, H7 and H8), 1.19 (6H, d, \( J = 6.1 \) Hz, OCH(CH\(_3\))\(_2\)), 0.99 (6H, t, \( J = 7.9 \) Hz, Si(CH\(_2\)CH\(_3\))\(_2\)), 0.89 (3H, t, \( J = 6.9 \) Hz, H9), 0.65 (4H, q, \( J = 7.9 \) Hz, Si(CH\(_2\)CH\(_3\))\(_2\)); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta_C \) 173.2, 103.8, 86.5, 66.1, 64.1, 34.7, 31.6, 28.7, 27.6, 26.2, 25.4, 24.9, 22.5, 14.0, 9.0, 6.6, 6.5 (diastereotopic SiCH\(_3\)); HRMS (ESI\(^+\)) calc. for \( \text{C}_{19}\text{H}_{36}\text{NaO}_3\text{Si} [\text{M+Na}^+] \) \( m/z \) 363.2331, found 363.2326.

1-(Diethyl(isopropoxy)silyl)non-1-yn-3-yl benzoate, 124y

Benzoyl chloride (23 \( \mu \)L, 0.199 mmol, 2.0 eq) was added dropwise to a solution of propargyl alcohol 115a (28 mg, 0.099 mmol, 1.0 eq), DMAP (2.4 mg, 0.020 mmol, 0.2 eq) and Et\(_3\)N (41 \( \mu \)L, 0.298 mmol, 3.0 eq) in DCM (1 mL). The mixture was stirred for 16 hours, and quenched with NaHCO\(_3\) solution. The aqueous layer was extracted three times with DCM and the combined organic layers dried (MgSO\(_4\)) and concentrated to give benzoyl ester 124y as a colourless oil that was used in the next step without further purification (43 mg of crude, ~ 0.099 mmol, ~100%); \( R_f \) 0.50 (petrol / Et\(_2\)O (9:1)); IR (thin film, \( \nu_{\text{max}} / \text{cm}^{-1} \)) 2958, 2831, 2876, 2179, 1726, 1453, 1381, 1265, 1069, 1028; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta_H \) 8.07 (2H, dd, \( J = 7.9 \) and 1.2 Hz, o-PhH), 7.58 (1H, tt, \( J = 7.9 \) and 1.2 Hz, p-PhH), 7.46 (2H, t, \( J = 7.9 \) Hz, m-PhH), 5.66 (1H, t, \( J = 6.6 \) Hz, H3), 4.15 (1H, sept, \( J = 6.1 \) Hz, OCH(CH\(_3\))\(_2\)), 1.97-1.86 (2H, m, H4), 1.55 (2H, quin, \( J = 8.0 \) Hz, H5), 1.41-1.27 (6H, m, H6, H7 and H8), 1.18 (6H, d, \( J = 6.1 \) Hz, OCH(CH\(_3\))\(_2\)), 1.00 (6H, t, \( J = 8.0 \) Hz, Si(CH\(_2\)CH\(_3\))\(_2\)), 0.90 (3H, t, \( J = 7.0 \) Hz, H9), 0.67 (4H, q, \( J = 8.0 \) Hz, Si(CH\(_2\)CH\(_3\))\(_2\)); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta_C \) 165.5, 133.1, 130.1, 129.8, 128.7, 103.6, 87.1, 66.2, 64.5, 34.8, 31.7, 28.8, 25.4, 25.0, 22.6, 22.5, 14.0, 6.6,
6.5 (diastereotopic SiCH₂); HRMS (ESI⁺) calc. for C₂₃H₃₆NaO₃Si [M+Na]⁺ 411.2331, found 411.2326.

1-(Diethyl(isopropoxy)silyl)non-1-yn-3-yl 2,2,2-trichloroacetate, 124z

Trichloroacetyl chloride (32 μL, 0.287 mmol, 2.0 eq) was added dropwise to a solution of propargyl alcohol 115a (41 mg, 0.143 mmol, 1.0 eq), and Et₃N (60 μL, 0.429 mmol, 3.0 eq) in THF (1 mL) at 0 °C. The mixture was stirred for one hour, and quenched with NaHCO₃ solution. The aqueous layer was extracted three times with Et₂O and the combined organic layers washed (1 M HCl, water, 1 M HCl), dried (MgSO₄) and concentrated to give ester 124z as a colourless oil that was used in the next step without further purification (60 mg, ~0.140 mmol, ~98%); Rf 0.68 (petrol / Et₂O (9:1)); IR (thin film, ν_max / cm⁻¹) 2958, 2931, 2876, 2181, 1767, 1412, 1369, 1233, 1173, 1122, 1032; ¹H NMR (500 MHz, CDCl₃) δH 5.46 (1H, t, J = 6.6 Hz, H₃), 4.14 (1H, sept, J = 6.2 Hz, OCH(CH₃)₂), 1.98 - 1.87 (2H, m, H₄), 1.55-1.48 (2H, m, H₅), 1.40-1.26 (6H, m, H₆, H₇ and H₈), 1.19 (6H, d, J = 6.2 Hz, OCH(CH₃)₂), 0.99 (6H, t, J = 7.7 Hz, Si(CH₂CH₃)₂), 0.90 (3H, t, J = 7.0 Hz, H₉), 0.67 (4H, q, J = 7.7 Hz, Si(CH₂CH₃)₂); ¹³C NMR (125 MHz, CDCl₃) δC 160.9, 100.7, 89.4, 81.1, 69.9, 66.3, 34.2, 31.6, 28.5, 25.0, 24.7, 22.5, 22.4, 14.0, 6.5, 6.4 (diastereotopic SiCH₂); HRMS (FI⁺) calc. for C₁₈H₃₁Cl₂O₃Si [M]⁺ 428.1108, found 428.1101.
1-Cyclohexyl-3-(diethyl(isopropoxy)silyl)prop-2-yn-1-yl acetate, 124b

Procedure C: Acetic anhydride (0.56 mL, 5.95 mmol, 2.0 eq), propargyl alcohol 115b (840 mg, 2.97 mmol, 1.0 eq), one crystal of DMAP and Et$_3$N (1.2 mL, 8.92 mmol, 3.0 eq) in DCM gave acetate 124b as a colourless oil that was used in the next step without further purification (968 mg, ~2.97 mmol, ~100%); $R_f$ 0.42 (petrol / Et$_2$O (9:1)); IR (thin film, $\nu_{\text{max}}$ / cm$^{-1}$) 2960, 2931, 2878, 2856, 2176, 1746, 1452, 1370, 1228, 1173, 1122, 1082, 1032; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 5.26 (1H, d, $J$ = 6.0 Hz, C$_{\text{H}}$OAc), 4.15 (1H, sept, $J$ = 6.1 Hz, OCH(CH$_3$)$_2$), 2.09 (3H, s, COC$_{\text{H}}$$_3$), 1.88-1.61 (7H, m, H1', H3' and H4'), 1.30-1.10 (7H, m, H2'), 1.20 (6H, d, $J$ = 6.1 Hz, OCH(CH$_3$)$_2$), 1.00 (6H, t, $J$ = 8.0 Hz, Si(CH$_2$CH$_3$)$_2$), 0.66 (4H, q, $J$ = 8.0 Hz, Si(C$_{\text{H}}$$_2$CH$_3$)$_2$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$C 169.9, 102.5, 87.4, 68.5, 66.1, 41.7, 28.5, 27.9, 26.4, 25.7, 25.6, 25.4, 20.9, 6.7, 6.5; HRMS (ESI$^+$) calc. for C$_{18}$H$_{32}$NaO$_3$Si [M+Na]$^+$ 347.2018, found 347.2002.

3-(Diethyl(isopropoxy)silyl)-1-phenylprop-2-yn-1-yl acetate, 124c

Procedure C: Acetic anhydride (0.38 mL, 4.06 mmol, 2.0 eq), propargyl alcohol 115a (562 mg, 2.03 mmol, 1.0 eq), one crystal of DMAP and Et$_3$N (0.84 mL, 6.09 mmol, 3.0 eq) in DCM gave acetate 124c as a colourless oil that was used in the next step without further purification (651 mg, ~2.03 mmol, ~100%); $R_f$ 0.25 (petrol / Et$_2$O (9:1)); IR (thin film, $\nu_{\text{max}}$ / cm$^{-1}$) 2961, 2931, 2878, 2856, 2181, 1745, 1496, 1457, 1369, 1223, 1122, 1028; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 7.54 (2H, dd, $J$ = 7.8, 2.0 Hz, o-ArH), 7.42-7.36 (3H, m, m-ArH and p-ArH), 6.50 (1H, s, CHOAc), 4.15 (1H, sept, $J$ = 6.0, OCH(CH$_3$)$_2$), 2.11 (3H, s, COCH$_3$), 1.18 (6H, d, $J$ = 6.0, OCH(CH$_3$)$_2$), 1.01 (6H, t, $J$ = 8.0 Hz, Si(CH$_2$CH$_3$)$_2$), 0.69 (4H, q, $J$ = 8.0 Hz, Si(CH$_2$CH$_3$)$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$C
169.6, 136.7, 128.9, 128.6, 127.8, 102.1, 89.1, 66.2, 65.8, 25.4, 21.0, 6.6, 6.5; HRMS (ESI\(^+\)) calc. for C\(_{18}\)H\(_{26}\)NaO\(_3\)Si [M+Na]\(^+\) 341.1549, found 341.1542.

10,10-Diethyl-2,2,3,3,12-pentamethyl-4,11-dioxa-3,10-disilatridec-8-yn-7-yl acetate, 124d

Procedure C: Acetic anhydride (0.22 mL, 2.30 mmol, 2.0 eq), propargyl alcohol 115d (412 mg, 1.15 mmol, 1.0 eq), one crystal of DMAP and Et\(_3\)N (0.48 mL, 3.45 mmol, 3.0 eq) in DCM gave acetate 124d as a colourless oil that was used in the next step without further purification (462 mg, ~1.15 mmol, ~100%); \(R_f\) 0.28 (petrol / Et\(_2\)O (19:1)); IR (thin film, \(\nu_{\text{max}}\) / cm\(^{-1}\)) 2958, 2878, 2178, 1750, 1463, 1370, 1229, 1120, 1032; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.52 (1H, t, \(J = 6.9\) Hz, H7), 4.13 (1H, sept, \(J = 6.0\) Hz, OCH(CH\(_3\))\(_2\)), 3.79-3.71 (2H, m, H5), 2.07 (3H, s, COCH\(_3\)), 2.04-1.94 (2H, m, H6), 1.18 (6H, d, \(J = 6.0\) Hz, OCH(CH\(_3\))\(_2\)), 0.99 (6H, t, \(J = 7.9\) Hz, Si(CH\(_2\)CH\(_3\))\(_2\)), 0.89 (9H, s, Si(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)), 0.65 (4H, q, \(J = 7.9\) Hz, Si(CH\(_2\)CH\(_3\))\(_2\)), 0.05 and 0.05 (2 \(\times\) 3H, s, diastereotopic Si(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)); \(^13\)C NMR (125 MHz, CDCl\(_3\)) 169.5, 103.3, 86.9, 66.1, 61.5, 58.7, 37.7, 25.8, 25.4, 20.9, 18.2, 7.8, 6.6, 6.5, -5.5, -5.5; HRMS (ESI\(^+\)) calc. for C\(_{20}\)H\(_{40}\)NaO\(_4\)Si\(_2\) [M+Na]\(^+\) 423.2363, found 423.2365.

(R)-1-(Diethyl(isopropoxy)silyl)-5-((4-methoxybenzyl)oxy)pent-1-yn-3-yl, (R)-124e

Procedure C: Acetic anhydride (0.20 mL, 2.11 mmol, 2.0 eq), propargyl alcohol (R)-115e (300 mg, 1.05 mmol, 1.0 eq), one crystal of DMAP and Et\(_3\)N (0.44 mL, 3.16 mmol, 3.0 eq) in DCM (7 mL) gave acetate (R)-115e as a colourless oil that was used in the next step without further purification.
7. Experimental

(324 mg, ~0.990 mmol, ~94%); ee 97% (assumed from analysis of (R)-115e); \( R_f \) 0.34 (petrol / Et₂O (19:1)); \([\alpha]^{25}_{D} +56.6 \) (c 1.0, CHCl₃); \( \text{IR} \) (thin film, \( \nu_{\text{max}} / \text{cm}^{-1} \)) 2963, 2936, 2877, 2179, 1747, 1613, 1587, 1514, 1463, 1369, 1302, 1173, 1120, 1099, 1030; \( ^{1}H \text{NMR} \) (400 MHz, CDCl₃) \( \delta \) H 7.25 (2H, d, \( J = 8.7 \) Hz, H₈), 6.88 (2H, d, \( J = 8.7 \) Hz, H₉), 5.57 (1H, t, \( J = 6.7 \) Hz, H₃), 4.43 and 4.42 (2 × 1H, d, \( J = 11.5 \) Hz, diastereotopic H₆), 4.11 (1H, sept, \( J = 6.0 \) Hz, OCH(CH₃)₂), 3.81 (3H, s, OCH₃), 3.63-3.52 (2H, m, diastereotopic H₅), 2.14-2.01 (2H, m, diastereotopic H₄), 2.05 (3H, s, COCH₃), 1.18 (6H, d, \( J = 6.0 \) Hz, OCH(CH₃)₂), 0.98 (6H, t, \( J = 7.8 \) Hz, Si(CH₂CH₃)₂), 0.64 (4H, q, \( J = 7.8 \) Hz, Si(CH₂CH₃)₂); \( ^{13}C \text{NMR} \) (400 MHz, CDCl₃) 169.6, 159.2, 130.2, 129.3, 113.7, 103.2, 86.9, 72.7, 66.1, 65.4, 61.7, 55.2, 35.1, 25.4, 20.9, 6.6, 6.5; \( \text{HRMS} \) (FT) calc. for C₂₂H₃₄O₅Si [M]+ 406.2176, found 406.2187.

7.4 Synthesis of Cyclic Alkenylsiloxanes via Lindlar Hydrogenation

2,2-Diethyl-5-hexyl-2,5-dihydro-1,2-oxasilole, 119a

\[
\text{Et}_2\text{Si} \quad \text{O} \quad \text{Si} \quad \text{Et}_2
\]

Procedure D: Palladium on CaCO₃ (722 mg, 5 wt % Pd, 0.339 mmol, 0.05 eq), acetate 124a (2.21 g, 6.78 mmol, 1.0 eq) and quinoline (0.16 mL, 1.36 mmol, 0.2 eq) in toluene (20 mL) were stirred under a hydrogen atmosphere for two hours and gave, after purification by rapid flash column chromatography (petrol / Et₂O (19:1)), oxasilole 119a as a colourless oil which was unstable to silica gel (1.23 g, 5.43 mmol, 80% isolated); \( R_f \) 0.57 (petrol / Et₂O (19:1)); \( \text{IR} \) (thin film, \( \nu_{\text{max}} / \text{cm}^{-1} \)) 2957, 2930, 2875, 2858, 1740, 1558, 1460, 1236, 1133, 1021; \( ^{1}H \text{NMR} \) (500 MHz, CDCl₃) \( \delta \) H 6.91 (1H, dd, \( J = 10.5 \) and 1.5 Hz, H₄), 5.96 (1H, dd, \( J = 10.5 \) and 2.0 Hz, H₃), 4.67 (1H, tdd, \( J = 5.2 \), 2.0 and 1.5 Hz, H₅), 1.51-1.24 (10H, m, H₆-H₁₀), 0.95 and 0.92 (2 × 3H, t, \( J = 7.8 \) Hz, 2 × diastereotopic Si(CH₂CH₃)), 0.89 (3H, t, \( J = 7.1 \) Hz, H₁₁), 0.76-0.59 (4H, m, Si(CH₂CH₃)₂); \( ^{13}C \text{NMR} \) (125 MHz,
CDCl₃) δC 154.6, 124.1, 83.3, 37.7, 31.8, 29.4, 25.4, 22.6, 14.0, 7.2, 7.1, 6.8, 6.5; HRMS (F1⁺) calc. for C₁₃H₂₆O₆Si [M]+ 226.1753, found 226.1760.

**5-Cyclohexyl-2,2-diethyl-2,5-dihydro-1,2-oxasilole, 119b**

![Image of 5-Cyclohexyl-2,2-diethyl-2,5-dihydro-1,2-oxasilole, 119b](image)

**Procedure D:** Palladium on CaCO₃ (53 mg, 5 wt % Pd, 0.025 mmol, 0.05 eq), acetate 124b (160 mg, 0.493 mmol, 1.0 eq) and quinoline (12 μL, 0.099 mmol, 0.2 eq) in toluene (6 mL) were stirred under a hydrogen atmosphere for two hours and gave, after purification by rapid flash column chromatography (petrol / Et₂O (19:1)), oxasilole 119b as a colourless oil which was unstable to silica gel (89 mg, 0.397 mmol, 80% isolated); Rf 0.67 (petrol / Et₂O (4:1)); IR (thin film, νmax / cm⁻¹) 2955, 2926, 2875, 1557, 1450, 1376, 1261, 1231, 1134, 1022; ¹H NMR (400 MHz, CDCl₃) δH 6.95 (1H, dd, J = 10.7 and 1.4 Hz, H₄), 6.01 (1H, dd, J = 10.7 and 2.2 Hz, H₃), 4.48 (1H, m, H₅), 1.79-1.65 (6H, m, H₈ and H₉), 1.44 (1H, m, H₆), 1.29-1.02 (4H, m, H₇), 0.97 and 0.91 (2 × 3H, t, J = 8.0 Hz, diastereotopic Si(CH₂CH₃)), 0.77-0.57 (4H, m, Si(CH₂CH₃)₂); ¹³C NMR (125 MHz, CDCl₃) δC 153.0, 125.0, 87.7, 44.2, 29.0, 28.5, 26.6, 26.3, 7.2, 6.9, 6.9, 6.5; HRMS (F1⁺) calc. for C₁₃H₂₆O₆Si [M]+ 224.1596 found 224.1591.

**2,2,2-Diethyl-5-phenyl-2,5-dihydro-1,2-oxasilole, 124c**

![Image of 2,2,2-Diethyl-5-phenyl-2,5-dihydro-1,2-oxasilole, 124c](image)

**Procedure E** (modified): Palladium on CaCO₃ (90 mg, 5 wt % Pd, 0.04 mmol, 0.01 eq) was added to a stirred solution of silanol 115c-H (990 mg, 4.22 mmol, 1.0 eq) and quinoline (0.25 mL, 0.211 mmol, 0.5 eq) in toluene (20 mL) and cyclohexene (2 mL). The solution was stirred under a hydrogen atmosphere for 40 minutes, then filtered through Celite® and concentrated as the cyclic product. The crude was purified by rapid flash column chromatography (petrol / Et₂O (19:1)) to give
oxasilole 119c as a colourless oil which was unstable to silica gel (569 g, 2.61 mmol, 62%); \( R_f \) 0.55 (petrol / Et\(_2\)O (19:1)); \( \text{IR} \) (thin film, \( v_{\text{max}} / \text{cm}^{-1} \)) 2956, 2876, 1556, 1455, 1234, 1090, 1021; \( ^1\text{H NMR} \) (500 MHz, CDCl\(_3\)) \( \delta_H \) 7.37-7.25 (5H, m, Ar\( H \)), 6.99 (1H, dd, \( J = 10.6 \) and 1.6 Hz, H4), 6.11 (1H, dd, \( J = 10.6 \) and 2.5 Hz, H3), 5.71 (1H, m, H5), 1.02 and 1.00 (2 \( \times \) 3H, t, \( J = 7.9 \) Hz, diastereotopic Si(CH\(_2\)CH\(_3\)))
0.86-0.68 (4H, m, Si(CH\(_2\)CH\(_3\))\(_2\))
HRMS (ESI\(^+\)) calc. for C\(_{13}\)H\(_{18}\)NaOSi [M+Na]\(^+\) 241.1025, found 241.1028.

5-(2-((Tert-butyldimethylsilyl)oxy)ethyl)-2,2-diethyl-2,5-dihydro-1,2-oxasilole, 119d

Procedure D: Palladium on CaCO\(_3\) (240 mg, 5 wt % Pd, 0.112 mmol, 0.05 eq), acetate 124d (900 mg, 2.25 mmol, 1.0 eq) and quinoline (53 \( \mu \)L, 0.45 mmol, 0.2 eq) in toluene (15 mL) were stirred under a hydrogen atmosphere for three hours and gave, after purification by rapid flash column chromatography (petrol / Et\(_2\)O (50:1)), oxasilole 119d as a colourless oil which was unstable to silica gel (540 mg, 1.80 mmol, 80% isolated); \( R_f \) 0.70 (petrol / Et\(_2\)O (4:1)); \( \text{IR} \) (thin film, \( v_{\text{max}} / \text{cm}^{-1} \)) 2956, 2931, 2876, 2858, 1740, 1558, 1463, 1255, 1093; \( ^1\text{H NMR} \) (400 MHz, CDCl\(_3\)) \( \delta_H \) 6.93 (1H, dd, \( J = 10.6 \) and 1.5 Hz, H4), 5.95 (1H, dd, \( J = 10.6 \) and 2.2 Hz, H3), 4.79-4.75 (1H, m, H5), 3.82-3.78 (2H, m, H7), 1.87-1.79 and 1.66-1.57 (2 \( \times \) 1H, m, diastereotopic H6), 0.95-0.90 (6H, m, diastereotopic Si(CH\(_2\)CH\(_3\))\(_2\)), 0.90 (9H, s, SiC(CH\(_3\))\(_3\)), 0.76-0.57 (4H, m, diastereotopic Si(CH\(_2\)CH\(_3\))\(_2\)), 0.07 (6H, s, Si(CH\(_3\))\(_3\)); \( ^{13}\text{C NMR} \) (101 MHz, CDCl\(_3\)) \( \delta_C \) 154.7, 123.9, 80.4, 60.2, 40.7, 25.9, 18.3, 7.2, 7.1, 6.8, 6.5, -5.4; HRMS (ESI\(^+\)) calc. for C\(_{15}\)H\(_{32}\)NaO\(_2\)Si\(_2\) [M+Na]\(^+\) 323.1839, found 323.1830.
(R)-2,2-Diethyl-5-((2-((4-methoxybenzyl)oxy)ethyl)-2,5-dihydro-1,2-oxasilole, (R)-119e

Procedure D: Palladium on CaCO₃ (440 mg, 5 wt % Pd, 0.207 mmol, 0.05 eq), acetate 124e (1.68 g, 4.13 mmol, 1.0 eq) and quinoline (101 μL, 0.826 mmol, 0.2 eq) in toluene (25 mL) were stirred under a hydrogen atmosphere for one hour and gave, after purification by rapid flash column chromatography (petrol / Et₂O (19:1)), oxasilole 119e as a colourless oil which was unstable to silica gel (925 mg, 3.02 mmol, 73% isolated); ee 97% (assumed from analysis of (R)-115e); Rf 0.55 (petrol / EtOAc (4:1)); [α]D₂⁵ −40.9 (c 1.0, CHCl₃); IR (thin film, νmax / cm⁻¹) 2955, 2875, 1613, 1248, 1095, 1038; ¹H NMR (400 MHz, CDCl₃) δH 7.28 (2H, d, J = 8.7 Hz, H10), 6.91 (1H, dd, J = 10.5 and 1.5 Hz, H4), 6.88 (2H, d, J = 8.7 Hz, H11), 5.96 (1H, dd, J = 10.5 and 2.2 Hz, H3), 4.82-4.79 (1H, m, H5), 4.47 and 4.45 (2 × 1H, d, J = 11.6 Hz, diastereotopic H8), 3.81 (3H, s, OC₆H₃), 3.68-3.59 (2H, m, H7), 1.97-1.89 and 1.74-1.66 (2 × 1H, m, diastereotopic H6), 0.93 and 0.92 (2 × 3H, t, J = 7.9 Hz, diastereotopic Si(CH₂CH₃)), 0.76-0.58 (4H, m, Si(CH₂CH₃)₂); ¹³C NMR (101 MHz, CDCl₃) δC 159.1, 154.5, 130.7, 129.3, 124.1, 113.7, 80.7, 72.7, 67.0, 55.2, 37.7, 7.2, 7.1, 6.8, 6.5; HRMS (ESI⁺) calc. for C₁₇H₂₆NaO₃Si [M+Na]⁺ 329.1543, found 329.1536.

2,2-Diethyl-1-oxa-2-silaspiro[4.5]dec-3-ene, 119f

Procedure E (modified): Palladium on CaCO₃ (78 mg, 5 wt% Pd, 0.037 mmol, 0.05 eq), 115f (196 mg, 0.730 mmol, 1.0 eq) and quinoline (17 μL, 0.146 mmol, 0.2 eq) in toluene (7 mL) and cyclohexene (0.7 mL) were stirred under an atmosphere of hydrogen for two hours. The reaction mixture was filtered through Celite® and concentrated (cyclisation occurred in situ). The crude was purified by rapid flash column chromatography (petrol / Et₂O (19:1)) to give silaspiro 119f as a colourless oil (116 mg, 0.551 mmol, 76%); Rf 0.15 (petrol); IR (thin film, νmax / cm⁻¹) 2931, 2875,
1558, 1458, 1099, 1031; $^1$H NMR (400 MHz, CDCl$_3$) 6.94 (1H, d, $J = 10.5$ Hz, H4), 5.84 (1H, d, $J = 10.5$ Hz, H3), 1.74-1.65 (2H, m, 2 × H7), 1.57-1.48 (7H, m, 4 × H6, 2 × H7 and 1 × H8), 1.38-1.31 (1H, m, 1 × H8), 0.91 (2 × 3H, t, $J = 8.0$ Hz, diastereotopic Si(CH$_2$CH$_3$)); $^{13}$C NMR (101 MHz, CDCl$_3$) δ$_C$ 159.0, 122.7, 85.4, 38.5, 25.5, 22.7, 7.5, 7.0; HRMS (FI$^+$) calc. for C$_{12}$H$_{22}$OSi [M]$^+$ 210.1440, found 210.1445.

2,2-Diethyl-6-hexyl-5,6-dihydro-2H-1,2-oxasiline, 125a

![Structure of 125a](image)

**Procedure E:** Palladium on CaCO$_3$ (108 mg, 5 wt% Pd, 0.050 mmol, 0.05 eq), 117a (303 mg, 1.01 mmol, 1.0 eq) and quinoline (60 μL, 0.507 mmol, 0.5 eq) in toluene (10 mL) were stirred under an atmosphere of hydrogen for 55 minutes. The crude was purified by flash column chromatography (petrol / Et$_2$O (19:1)) to give oxasiline 125a as a colourless oil (173 mg, 0.720 mmol, 71%); $R_f$ 0.26 (petrol / Et$_2$O (99:1)); IR (thin film, $\nu_{\text{max}}$ / cm$^{-1}$) 2956, 2927, 2875, 1588, 1460, 1353, 1234, 1085, 1005; $^1$H NMR (400 MHz, CDCl$_3$) δ$_H$ 6.85 (1H, ddd, $J = 14.1$, 5.4 and 2.9 Hz, H4), 5.72 (1H, ddd, $J = 14.1$, 2.5 and 1.2 Hz, H3), 3.92-3.86 (1H, m, H6), 2.17-2.04 (2H, m, H5), 1.58-1.50 (1H, m, 1 × H7), 1.47-1.37 (2H, m, 1 × H7 and 1 × H8), 1.34-1.23 (7H, m, 1 × H8, H9, H10 and H11), 0.98 and 0.93 (2 × 3H, t, $J = 7.9$ Hz, diastereotopic Si(CH$_2$CH$_3$)); $^{13}$C NMR (101 MHz, CDCl$_3$) δ$_C$ 148.5, 124.9, 71.8, 38.0, 36.6, 31.9, 29.3, 25.5, 22.7, 14.1, 6.8, 6.7, 6.5, 5.9; HRMS (FI$^+$) calc. for C$_{14}$H$_{30}$OSi [M]$^+$ 240.1909, found 240.1903.
6-Cyclohexyl-2,2-diethyl-5,6-dihydro-2H-1,2-oxasiline, 125b

![Chemical Structure](attachment:image.png)

**Procedure E** (modified): Palladium on CaCO₃ (300 mg of a 5 wt% solid, 0.141 mmol, 0.05 eq), 117b (837 mg, 2.82 mmol, 1.0 eq) and quinoline (170 μL, 0.141 mmol, 0.5 eq) in THF (30 mL) were stirred under an atmosphere of hydrogen for one hour. The crude was purified by flash column chromatography (petrol / Et₂O (19:1)) to give oxasiline 125b as a colourless oil (447 mg, 1.88 mmol, 66%); R_f 0.45 (petrol / Et₂O (99:1)); IR (thin film, ν_max / cm⁻¹) 2954, 2853, 1588, 1450, 1351, 1234, 1048; ^1H NMR (400 MHz, CDCl₃) δ_H 6.81 (1H, dt, J = 14.0 and 4.2 Hz, H4), 5.65 (1H, dt, J = 14.0 and 1.8 Hz, H3), 3.58-3.51 (1H, m, H6), 2.07-2.04 (2H, m, H8), 1.89-1.83 (1H, m, 1 × H9), 1.69-1.64 and 1.61-1.55 (2 × 1H, m, H10), 1.34-1.25 (1H, m, H7), 1.24-0.84 (11H, m, 3 × H9, H8 and Si(CH₂CH₃)₂), 0.60-0.46 (4H, m, Si(CH₂CH₃)₂); ^13C NMR (400 MHz, CDCl₃) δ_C 148.9, 124.9, 76.0, 44.2, 33.4, 28.8, 28.8, 26.7, 26.3, 26.2, 6.9, 6.7, 6.5, 5.9; HRMS (FT) calc. for C₁₄H₂₆OSi [M]^+ 238.1753, found 238.1758.

6-(2-((Tert-butyldimethylsilyl)oxy)ethyl)-2,2-diethyl-5,6-dihydro-2H-1,2-oxasiline, 125d

![Chemical Structure](attachment:image.png)

**Procedure E** (modified): Palladium on CaCO₃ (12 mg of a 5 wt% solid, 0.005 mmol, 0.05 eq), 117d (34 mg, 0.091 mmol, 1.0 eq) and quinoline (2.1 μL, 0.018 mmol, 0.2 eq) in toluene (1 mL) were stirred under an atmosphere of hydrogen for 15 minutes. The crude was purified by flash column chromatography (petrol / Et₂O (19:1)) to give oxasiline 125d as a colourless oil (21 mg, 0.067 mmol, 73%); R_f 0.25 (petrol / Et₂O (99:1)); IR (thin film, ν_max / cm⁻¹) 2987, 2955, 2877, 1588, 1471, 1463, 1255, 1092; ^1H NMR (400 MHz, CDCl₃) δ_H 6.86 (1H, dt, J = 14.0 and 4.0 Hz, H4), 5.74 (1H, dt, J = 14.0 and 2.0 Hz, H3), 4.14-4.07 (1H, m, H6), 3.81-3.75 and 3.73-3.68 (2 × 1H, m, diastereotopic H8), 2.16-2.12 (2H, m, H5), 1.76-1.62 (2H, m, H7), 0.98 and 0.94 (2 × 3H, t, J = 8.0 Hz,
diastereotopic $\text{Si(CH}_2\text{CH}_3)$), 0.89 (9H, s, $\text{SiC(CH}_2\text{H}_3)$), 0.69-0.52 (4H, m, $\text{Si(CH}_2\text{CH}_3)_2$), 0.05 (6H, s, $\text{Si(CH}_3)_2$); $^{13}$C NMR (101 MHz, CDCl$_3$) δ$_C$ 148.5, 124.9, 68.4, 59.5, 41.1, 36.8, 26.0, 18.3, 6.8, 6.7, 6.4, 5.9, -5.4; HRMS (ESI⁺) calc. for $\text{C}_{16}\text{H}_{34}\text{NaO}_2\text{Si}_2$ [M+Na]$^+$ 337.1990, found 337.1983.

$(R)$-2,2-Diethyl-6-((4-methoxybenzyl)oxy)ethyl)-5,6-dihydro-2H-1,2-oxasiline, $(R)$-125e

Procedure E: Palladium on CaCO$_3$ (14 mg, 5 wt% Pd, 0.007 mmol, 0.05 eq), $(R)$-117e (50 mg, 0.132 mmol, 1.0 eq) and quinoline (8 μL, 0.066 mmol, 0.5 eq) in toluene (1.3 mL) were stirred under an atmosphere of hydrogen for 10 minutes. The crude was purified by flash column chromatography (petrol / Et$_2$O (19:1)) to give oxasiline $(R)$-125e as a colourless oil (34 mg, 0.106 mmol, 79%); ee >99% (assumed from analysis of $(R)$-118e); $R_f$ 0.52 (petrol / Et$_2$O (2:1)); $[\alpha]_D^{25}$ +23.9 (c 1.0, CHCl$_3$); IR (thin film, $\nu_{\text{max}}$ / cm$^{-1}$) 2986, 2875, 1613, 1587, 1513, 1248, 1094, 1037; $^1$H NMR (400 MHz, CDCl$_3$) δ$_H$ 7.27 (2H, d, $J$ = 8.8 Hz, H3), 6.90-6.82 (3H, m, H2 and H10), 5.73 (1H, dt, $J$ = 14.3 and 1.8 Hz, H11), 4.45 and 4.43 (2 × 1H, d, $J$ = 11.7 Hz, diastereotopic H5), 4.15-4.09 (1H, m, H8), 3.81 (3H, s, OCH$_3$), 3.67-3.54 (2H, m, H6), 2.15-2.12 (2H, m, H9), 1.81-1.75 (2H, m, H7), 0.99 and 0.94 (2 × 3H, t, $J$ = 7.8 Hz, diastereotopic $\text{Si(CH}_2\text{CH}_3)$), 0.69-0.54 (4H, m, $\text{Si(CH}_2\text{CH}_3)_2$); $^{13}$C NMR (101 MHz, CDCl$_3$) δ$_C$ 159.1, 148.4, 130.7, 129.3, 124.8, 113.7, 72.8, 68.7, 66.6, 55.3, 38.0, 36.8, 6.8, 6.7, 6.4, 5.9; HRMS (ESI⁺) calc. for $\text{C}_{18}\text{H}_{30}\text{NaO}_3\text{Si}_2$ [M+Na]$^+$ 343.1705, found 343.1695.

2,2-Diethyl-4a,5,6,7,8a-hexahydro-2H-benzo[e][1,2]oxasiline, 125g

Procedure E: Palladium on CaCO$_3$ (176 mg, 5 wt% Pd, 0.083 mmol, 0.05 eq), 117g (444 mg, 1.65 mmol, 1.0 eq) and quinoline (39 μL, 0.830 mmol, 0.5 eq) in toluene (17 mL) was stirred under an atmosphere of hydrogen for 50 minutes. The crude was purified by flash column chromatography
(petrol / Et$_2$O (19:1)) to give oxasilane 125g as a colourless oil (278 mg, 1.07 mmol, 65%); $R_f$ 0.31 (petrol / Et$_2$O (99:1)); IR (thin film, $\nu_{max}$ / cm$^{-1}$) 2930, 2875, 2856, 1584, 1449, 1130, 1073, 1004; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 6.56 (1H, d, $J = 14.1$ Hz, H4), 5.71 (1H, dd, $J = 14.1$ and 3.5 Hz, H3), 3.50-3.45 (1H, m, H10), 2.00-1.93 (2H, m, H5, 1 × H9), 1.86-1.75 (2H, m, 1 × H6 and 1 × H8), 1.70-1.65 (1H, m, 1 × H7), 1.42-1.21 (3H, m, 1 × H7, 1 × H8 and 1 × H9), 1.13-1.04 (1H, m, 1 × H6), 0.99 and 0.94 (2 × 3H, t, $J = 8.0$ Hz, diastereotopic Si(CH$_2$CH$_3$)$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 155.0, 124.2, 76.3, 45.3, 35.3, 31.7, 25.9, 25.0, 6.7, 6.8, 6.8, 6.4; HRMS (FI$^+$) calc. for C$_{12}$H$_{22}$O$_3$Si [M]$^+$ 210.1440, found 210.1446.

5-((4-Methoxybenzyl)oxy)pent-1-yn-3-ol, 132e and 119a

**Procedure D** (modified): Palladium on CaCO$_3$ (16 mg, 5 wt % Pd, 0.008 mmol, 0.05 eq), silanol 124a-H (1.5 mL of a 0.1 M solution in toluene, 0.150 mmol, 1.0 eq), acetate 124e (61 mg, 0.150 mmol, 1.0 eq) and quinoline (3.5 μL, 0.030 mmol, 0.2 eq) were stirred under a hydrogen atmosphere for 20 minutes and gave, after purification by rapid flash column chromatography (petrol / Et$_2$O (19:1—0:100)), oxasilole 119a as a colourless oil which was unstable to silica gel (19 mg, 0.084 mmol, 56% isolated; characterised above) and alkyne 32e as a colourless oil (23 mg, 0.104 mmol, 71%); $R_f$ 0.07 (petrol / Et$_2$O (7:3)); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 7.27 (2H, d, $J = 8.5$ Hz, H8), 6.90 (2H, d, $J = 8.5$ Hz, H9), 4.64-4.59 (1H, m, H3), 4.49 and 4.47 (2 × 1H, d, $J = 11.4$ Hz, diastereotopic H6), 3.88-3.82 (1H, m, H5), 3.82 (3H, s, OCH$_3$), 3.70-3.65 (1H, m, H5), 3.32 (1H, br d, $J = 5.6$ Hz, OH), 2.47 (1H, d, $J = 2.2$ Hz, H1), 2.14-2.06 and 2.00-1.92 (2 × 1H, m, diastereotopic H4); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$C 159.3, 129.8, 129.4, 113.9, 84.3, 73.1, 72.9, 67.3, 61.4, 55.3, 36.5; LRMS (ESI$^+$) calc. for C$_{13}$H$_{16}$O$_3$Si [M+Na]$^+$ 243.1 found 243.1.

The spectroscopic data was found to be in agreement with that reported by Ting and co-workers.
Diethyl(prop-1-yn-1-yl)(isopropoxy)silane, S7

Propynylmagnesium bromide (54 mL of a 0.5 M solution in THF, 27.0 mmol, 1.1 eq) was added to diethyl(diethylamino)chlorosilane (4.75 g, 24.5 mmol, 1.0 eq) at -78 °C and warmed to room temperature. The mixture was refluxed for 6 hours then cooled to room temperature whereupon isopropanol (3.7 mL, 49.0 mmol, 2.0 eq) and one crystal of DMAP were added and the reaction left to stir at room temperature for 16 hours. The mixture was concentrated in vacuo, redissolved in petrol and filtered through Celite®. The filtrate was concentrated in vacuo and distilled to afford the title compound as a colourless oil (3.43 g, 18.6 mmol, 76%); \( R_f \) 0.19 (petrol); \( \text{bp} \) 85-87 °C, 28 mbar; \( \text{IR} \) (thin film, \( \nu_{\text{max}} / \text{cm}^{-1} \)) 2963, 2918, 2878, 2181, 1461, 1381, 1124, 1027; \( ^{1} \text{H NMR} \) (CDCl\(_3\), 400 MHz) \( \delta \)H 4.15 (1H, sept, \( J = 6.1 \) Hz, OCH(CH\(_3\))\(_2\)), 1.93 (3H, s, C≡CC\(_3\)), 1.20 (6H, d, \( J = 6.1 \) Hz, OCH(CH\(_3\))\(_2\)), 1.01 (6H, t, \( J = 7.8 \) Hz, Si(CH\(_2\)CH\(_3\))\(_2\)), 0.64 (4H, q, \( J = 7.8 \) Hz, Si(CH\(_2\)CH\(_3\))\(_2\)); \( ^{13} \text{C NMR} \) (101 MHz, CDCl\(_3\)) \( \delta \)C 103.6, 80.4, 65.8, 25.5, 6.93, 6.65, 4.82; \( \text{HRMS} \) (FI\(^{+}\)) calc. for C\(_{10}\)H\(_{20}\)OSi [M]+ 184.1283, found 184.1292.

7.5 Synthesis of Iodide Coupling Partners (Chapter 3)

E-Iodostyrene, 145a

Prepared according to a literature procedure.\(^{137}\) Diiodomethane (2.0 mL, 24.8 mmol, 1.5 eq) in THF (6 mL) was added over 30 minutes in the dark to a solution of sodium bis(trimethylsilyl)amide (25 mL of a 2.0 M solution in THF, 49.7 mmol, 3.0 eq) in Et\(_2\)O (15 mL) at -78 °C and stirred for 20 minutes before benzyl bromide (1.97 mL, 16.6 mmol, 1.0 eq) in THF (10 mL) was added over 15 minutes. The mixture was stirred for a further 90 minutes in the dark at -78 °C, before warming to room temperature over 30 minutes. 1,8-Diazabicycloundec-7-ene (2.5 mL, 16.6 mmol, 1.0 eq) was added dropwise and the reaction stirred at room temperature for two hours. The mixture was then diluted with Et\(_2\)O (100 mL) and filtered through a plug of Celite® over silica gel and concentrated in
vacuo. The crude was purified by flash column chromatography (petrol) to give iodostyrene, 145a as a yellow oil (3.56 g, 15.5 mmol, 93%); \( R_f \) 0.40 (petrol); \(^1\)H NMR (CDCl\(_3\), 250 MHz) \( \delta \)H 7.45 (1H, d, \( J = 14.9 \) Hz, C=CH\( \text{I} \)), 7.37-7.27 (5H, m, ArH), 6.83 (1H, d, \( J = 14.9 \) Hz, C=CHAr); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \)C 145.0, 137.7, 128.8, 128.4, 126.1, 76.9.

The spectroscopic data were found to be in agreement with that reported by Charette and co-workers.\(^{137}\)

\(((\text{Prop-2-yn-1-yl oxy})\text{methyl})\text{benzene, S8}\)

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Prepared according to a literature procedure.\(^{263}\) Benzyl alcohol (1.00 mL, 9.66 mmol, 1.0 eq) was added slowly to a suspension of sodium hydride (464 mg, 60 wt% dispersion in mineral oil, 11.6 mmol, 1.2 eq) in THF (10 mL) at 0 °C. The reaction was stirred until the evolution of hydrogen gas subsided, then propargyl bromide (1.1 mL, 80% in toluene, 11.6 mmol, 1.2 eq) was added and the mixture warmed slowly to room temperature and stirred for 24 hours. Water was added, the mixture separated and the aqueous layer extracted twice with Et\(_2\)O. The combined organic phase was dried (MgSO\(_4\)), concentrated and purified \textit{via} flash column chromatography (petrol / Et\(_2\)O (100:0→99:1)) to give propargylic S8 as a colourless oil (1.12 g, 7.68 mmol, 80%); \( R_f \) 0.26 (petrol);

\(^1\)H NMR (CDCl\(_3\), 250 MHz) \( \delta \)H 7.38-7.27 (5H, m, H5, H6 and H7), 4.62 (2H, s, H4), 4.18 (2H, d, \( J = 2.4 \) Hz, H3), 2.47 (1H, t, \( J = 2.4 \) Hz, H1); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \)C 137.4, 128.5, 128.2, 128.0, 79.7, 74.7, 71.6, 57.1. \textbf{LRMS} (ESI\(^+\)) calc. for C\(_{10}\)H\(_{10}\)NaO [M+Na]\(^+\) 169.1, found 169.1.

The spectroscopic data were found to be in agreement with that reported by Li and co-workers.\(^{263}\)
(E)-(((3-Iodoallyl)oxy)methyl)benzene, 145b

Prepared according to a modified literature procedure.\textsuperscript{264} Alkyne S8 (0.50 mL, 3.46 mmol, 1.0 eq) was added to a suspension of Cp\textsubscript{2}ZrHCl (936 mg, 3.63 mmol, 1.05 eq) in THF (20 mL) at room temperature and stirred for 15 minutes until the solution became clear. The reaction was cooled to 0 °C, iodine added (1.05 g, 4.15 mmol, 1.2 eq) and the mixture stirred at 0 °C for two hours, then room temperature for 4 hours. The reaction was diluted with wet Et\textsubscript{2}O (10 mL), Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} (30 mL) added, and stirred for one hour, then separated, the aqueous extracted with Et\textsubscript{2}O and the combined organic phase dried (MgSO\textsubscript{4}) and concentrated. The crude residue was purified via flash column chromatography (petrol / Et\textsubscript{2}O (100:0→99:1)) to give iodide 145b as a pale yellow oil (720 mg, 2.63 mmol, 76%); \textit{R}_{f} 0.11 (petrol / Et\textsubscript{2}O (99:1)); \textit{^1H NMR} (CDCl\textsubscript{3}, 400 MHz) \(\delta\)H 7.40-7.30 (5H, m, H5, H6 and H7), 6.66 (1H, dt, \(J = 14.4\) and \(5.6\) Hz, H2), 4.43 (1H, d, \(J = 14.4\) Hz, H1), 4.53 (2H, s, H4), 3.97 (2H, d, \(J = 5.6\) Hz, H3); \textit{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}) \(\delta\)C 142.2, 137.8, 128.5, 127.8, 78.9, 72.4, 71.8. \textit{LRMS} (ESI\textsuperscript{+}) calc. for C\textsubscript{10}H\textsubscript{11}ILiO [M+Li]\textsuperscript{+} 281.0, found 281.0.

The spectroscopic data were found to be in agreement with that reported by Hu and co-workers.\textsuperscript{265}

(Z)-(2-Iodovinyl)cyclohexane, 145c

Prepared according to a modified literature procedure.\textsuperscript{266} Sodium bis(trimethylsilyl)amide (0.91 mL of a 2.0 M solution in THF, 1.82 mmol, 1.1 eq) was added dropwise at room temperature to a suspension of Stork-Wittig reagent [Ph\textsubscript{3}PCH\textsubscript{2}I]\textsuperscript{+}[I]\textsuperscript{−} (960 mg, 1.82 mmol, 1.1 eq) in THF (8 mL) and stirred for 10 minutes. This solution was then cooled to -78 °C, and cyclohexanecarboxaldehyde (0.20 mL, 1.65 mmol, 1.0 eq) added dropwise. The mixture was stirred at -78 °C in the dark for 4 hours, then quenched with NaHCO\textsubscript{3} solution, diluted with petrol, and filtered through a pad of Celite©. The biphasic mixture was separated and the organic phase dried (MgSO\textsubscript{4}) and concentrated.
in vacuo. The crude was purified by flash column chromatography (petrol) to give vinyl iodide 145c as a colourless oil (230 mg, 0.974 mmol, 59%, >99:1 Z:E); \( R_f \) 0.64 (petrol); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta_H \) 6.07 (1H, d, \( J = 7.4 \) Hz, H2), 5.99 (1H, dd, \( J = 8.4 \) and 7.4 Hz, H1), 2.37-2.28 (1H, m, H1’), 1.75-1.70 (4H, m, H2’), 1.39-1.29 (2H, m, H4’), 1.24-1.09 (4H, m, H3’); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta_C \) 146.3, 79.6, 43.6, 31.1, 25.9, 25.5.

The spectroscopic data were found to be in agreement with that reported by Beshai and co-workers.\(^{266}\)

\((Z)-(2-Iodovinyl)benzene, 145d\)

\[
\begin{center}
\text{\includegraphics[width=0.2\textwidth]{image}}
\end{center}
\]

Prepared according to a modified literature procedure.\(^{266}\) Sodium bis(trimethylsilyl)amide (1.08 mL of a 2.0 M solution in THF, 2.16 mmol, 1.1 eq) was added dropwise at room temperature to a solution of Stork-Wittig reagent \([\text{Ph}_3\text{PCH}_2\text{I}]^+\)[I]\(^-\) (1.15 g, 2.16 mmol, 1.1 eq) in THF (10 mL) and stirred for 10 minutes. This solution was then cooled to -78 °C, and benzaldehyde (0.20 mL, 1.96 mmol, 1.0 eq) added dropwise. The mixture was stirred at -78 °C in the dark for 4 hours, then quenched with NaHCO\(_3\) solution, diluted with petrol, and filtered through a pad of Celite\(^\circledR\). The biphasic mixture was separated and the organic phase dried (MgSO\(_4\)) and concentrated. The crude was purified by flash column chromatography (petrol) to give vinyl iodide 145d as a colourless oil (282 mg, 1.23 mmol, 62%, 96:4 Z:E); \( R_f \) 0.40 (petrol); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta_H \) 7.65-7.63 (2H, m, p-ArH, ArCH=CHI), 7.42-7.32 (4H, m, m-ArH, o-ArH), 6.59 (1H, \( J = 8.4 \) Hz, ArCH=CHI); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta_C \) 138.6, 136.7, 128.4, 128.4, 128.2, 79.4.

The spectroscopic data was found to be in agreement with that reported by Carpita and co-workers.\(^{267}\)
(E)-3-(2-Iodovinyl)phenol, 145f

Prepared according to a modified literature procedure. A solution of 3-hydroxybenzaldehyde (500 mg, 4.09 mmol, 1.0 eq) and iodoform (3.22 g, 8.19 mmol, 2.0 eq) in THF (10 mL) was added via cannula to a suspension of chromium (II) chloride (3.00 g, 24.6 mmol, 6.0 eq) in THF (50 mL) at 0 °C. The mixture was stirred for 6 hours, before it was poured into brine (50 mL), extracted with EtOAc (3 × 40 mL) and dried (MgSO₄). The concentrated crude was purified via flash column chromatography (petrol / EtOAc (9:1→4:1)) to give iodide 145f as a salmon-coloured solid (846 mg, 3.44 mmol, 84%, E:Z 10:1); Rf 0.36 (petrol / Et₂O (4:1)); IR (thin film, νmax / cm⁻¹) 3315, 1599, 1575, 1490, 1446, 1259, 1155; mp 61–63 ºC; ¹H NMR (400 MHz, CDCl₃) δH 7.26 (1H, dd, J = 15.1 and 3.0 Hz, ArC=CHI), 7.10 (1H, app t, J = 7.7 Hz, H5), 6.78 (1H, d, J = 7.7 Hz, H4), 6.73-6.65 (3H, m, H2, H6 and ArCH=CHI), 5.20 (1H, br s, OH); ¹³C NMR (101 MHz, CDCl₃) δC 155.5, 144.5, 139.4, 130.1, 119.1, 115.5, 112.6, 77.6; HRMS (ESI) calc. for C₈H₆IO [M-H] 244.9469, found 244.9475.

7.6 Cross Coupling of 5-Membered Cyclic Alkenylsiloxanes

(1E,3Z)-1-Phenylundeca-1,3-dien-5-ol, 149aa

**Procedure F:** A solution of TBAF•3H₂O (0.66 mL of a 1.0 M solution in THF, 0.660 mmol, 3.0 eq) was added to silane 119a (50 mg, 0.221 mmol, 1.0 eq), E-iodostyrene 145a (51 mg, 0.221 mmol, 1.0 eq) and allylpalladium chloride dimer (1.8 mg, 0.005 mmol, 0.025 eq) at room temperature and stirred for 24 hours. The concentrated crude was purified by flash column chromatography (petrol /
Et₂O (9:1→4:1) + 1% Et₃N) to give diene 149aa as a yellow solid (39 mg, 0.159 mmol, 72%; isomerized to minor amounts of E,E-149aa on exposure to light).

**Procedure G:** A solution of potassium trimethylsilanolate (1.32 mL of a 0.42 M solution in DME, 0.552 mmol, 2.5 eq) was added to silane 119a (50 mg, 0.221 mmol, 1.0 eq), E-iodostyrene 145a (51 mg, 0.221 mmol, 1.0 eq), water (40 µL, 2.21 mmol, 10 eq) and bis(dibenzylideneacetone)palladium (6.3 mg, 0.011 mmol, 0.05 eq) at room temperature and stirred at 60 °C for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et₂O (9:1→17:3) + 1% Et₃N) to give alkene 149aa as a yellow solid (35 mg, 0.143 mmol, 65%; isomerized to minor amounts of E,E-149aa on exposure to light); Rf 0.16 (petrol / Et₂O (19:1)); mp 50-51 °C, IR (thin film, ν_max / cm⁻¹) 3352, 3080, 2955, 2927, 2856, 1637, 1494, 1465, 1449, 1378, 1030; ¹H NMR (400 MHz, C₆D₆) δ_H 7.27 (2H, d, J = 7.8 Hz, o-ArH), 7.17-7.09 (3H, m, m-ArH and H2), 7.03 (1H, t, J = 7.8 Hz, p-ArH), 6.43 (1H, d, J = 15.5 Hz, H1), 6.10 (1H, app t, J = 11.1 Hz, H3), 5.44 (1H, app t, J = 11.1 Hz, H4), 4.59-4.52 (1H, m, H5), 1.66-1.57 (1H, m, 1 × H6), 1.50-1.17 (9H, m, 1 × H6, H7, H8, H9 and H10), 1.11 (1H, s, OH), 0.85 (3H, t, J = 6.8 Hz, H11); ¹³C NMR (101 MHz, C₆D₆) δ_C 137.6, 135.6, 134.3, 129.9, 128.9, 128.3, 126.9, 124.4, 68.1, 38.1, 32.2, 29.7, 25.7, 23.0, 14.3; HRMS (ESI⁺) calc. for C₁₇H₂₄NaO [M+Na]⁺ 267.1725, found 267.1725.

Non-1-en-3-ol, 150a

Isolated as a side product from the above reaction. Rf 0.31 (petrol / Et₂O (7:3)); ¹H NMR (400 MHz, C₆D₆) δ_H 5.80-5.71 (1H, m, H2), 5.13 (1H, dt, J = 17.2 and 1.4 Hz, trans H1), 4.96 (1H, dt, J = 10.5 and 1.4 Hz, cis H1), 3.91-3.86 (1H, m, H3), 1.47-1.34 (3H, m, H4 and OH), 1.30-1.18 (8H, m, H5, H6, H7 and H8), 0.88 (3H, t, J = 7.0 Hz, H9); ¹³C NMR (101 MHz, C₆D₆) δ_C 141.9, 113.3, 72.6, 37.2, 31.9, 29.3, 25.3, 22.7, 14.0; HRMS (ESI⁺) calc. for C₉H₂₂NO [M+NH₄]⁺ 160.1696, found 160.1688.
All spectroscopic data were found to be in agreement with that reported by Bourland and co-workers.\textsuperscript{269}

(8Z,10Z)-Octadeca-8,10-diene-7,12-diol, 161a

\begin{center}
\includegraphics[width=0.3\textwidth]{diene_161a}
\end{center}

Isolated as a side product from the above reaction. \(R_f\) 0.24 (petrol / Et\(_2\)O (7:3)); mp 79-82 °C; IR (thin film, \(\nu_{\text{max}}\) / cm\(^{-1}\)) 3336, 2959, 2930, 2858, 1461, 1041, 1009; \(^1\)H NMR (400 MHz, C\(_{6}\)D\(_6\)) \(\delta_H\) 6.41-6.33 (2H, m, H9 and H10), 5.58-5.49 (2H, m, H8 and H11), 4.57-4.51 (2H, m, H7 and H12), 1.74-1.64 (2H, m, 1 × diastereotopic H6 and 1 × diastereotopic H13), 1.58-1.30 (18H, m, H2, H3, H4, H5, 1 × diastereotopic H6, 1 × diastereotopic H13, H14, H15, H16 and H17), 1.09 (2H, br s, 2 × OH), 1.00 (6H, t, \(J = 7.2\) Hz, H1 and H18); \(^{13}\)C NMR (101 MHz, C\(_{6}\)D\(_6\)) \(\delta_C\) 136.5, 123.9, 67.5, 38.0, 32.2, 29.7, 25.6, 23.0, 14.3; HRMS (ESI\(^+\)) calc. for C\(_{18}\)H\(_{34}\)NaO\(_2\) [M+Na]\(^+\) 305.2451, found 305.2450.

(2E,4Z)-1-(Benzyloxy)dodeca-2,4-dien-6-ol, 149ab

\begin{center}
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\end{center}

\textbf{Procedure F:} A solution of TBAF•3H\(_2\)O (0.53 mL of a 1.0 M solution in THF, 0.530 mmol, 3.0 eq) was added to silane 119a (40 mg, 0.177 mmol, 1.0 eq), iodide 145b (48 mg, 0.177 mmol, 1.0 eq) and allylpalladium chloride dimer (1.4 mg, 0.004 mmol, 0.025 eq) at room temperature and stirred for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et\(_2\)O (9:1→17:3) + 1% Et\(_3\)N) to give diene 149ab as a pale yellow oil (35 mg, 0.128 mmol, 72%; isomerized to minor amounts of \(E,E\)-149ab on exposure to light).

\textbf{Procedure G:} A solution of potassium trimethylsilanolate (0.93 mL of a 0.42 M solution in DME, 0.386 mmol, 2.5 eq) was added to silane 119a (35 mg, 0.155 mmol, 1.0 eq), iodide 145b (42 mg,
0.155 mmol, 1.0 eq), water (28 µL, 1.55 mmol, 10 eq) and bis(dibenzylideneacetone)palladium (4.4 mg, 0.008 mmol, 0.05 eq) at room temperature and stirred at 60 °C for 24 hours. The concentrated crude was purified by flash column chromatography (petrol/ Et₂O (9:1) + 1% Et₃N) to give diene 149ab as a pale yellow oil (22 mg, 0.076 mmol, 49%); R_f 0.18 (petrol / Et₂O (4:1)); IR (thin film, ν_max / cm⁻¹) 3400, 2957, 2929, 2855, 1496, 1359, 1114, 1095, 1065, 1028; ¹H NMR (500 MHz, C₆D₆) δ_H 7.29 (2H, d, J = 7.7 Hz, o-ArH), 7.17 (1H, t, J = 7.7 Hz, m-ArH), 7.08 (1H, t, J = 7.7 Hz, p-ArH), 6.64 (1H, dd, J = 14.8 and 11.4 Hz, H3), 5.95 (1H, app t, J = 11.4 Hz, H4), 5.68 (1H, dt, J = 14.8 and 5.6 Hz, H2), 5.35 (1H, app t, J = 11.4 Hz, H5), 4.47-4.37 (1H, m, H6), 4.33 (2H, s, ArCH₂O), 3.86 (2H, d, J = 5.6 Hz, H1), 1.59-1.52 (1H, m, 1 × H7), 1.43-1.12 (10H, m, 1 × H7, H8, H9, H10, H11 and O-H), 0.75 (3H, t, J = 7.0 Hz, H12); ¹³C NMR (125 MHz, C₆D₆) δ_C 139.0, 135.3, 131.9, 128.9, 128.6, 128.3, 127.7, 127.2, 72.4, 70.3, 67.9, 38.1, 32.2, 29.7, 25.7, 23.0, 14.3; HRMS (ESI⁺) calc. for C₁₉H₂₈NaO₂ [M+Na]⁺ 311.1982, found 311.1970.

(1Z,3Z)-1-Cyclohexylundeca-1,3-dien-5-ol, 149ac

Procedure F: A solution of TBAF•3H₂O (0.25 mL of a 1.0 M solution in THF, 0.250 mmol, 3.0 eq) was added to silane 119a (19 mg, 0.083 mmol, 1.0 eq), iodide 145c (20 mg, 0.084 mmol, 1.0 eq) and allylpalladium chloride dimer (1.4 mg, 0.004 mmol, 0.025 eq) at room temperature and stirred for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et₂O (19:1→9:1) + 1% Et₃N) to give diene 149ac as a colourless oil (6 mg, 0.024 mmol, 29%); R_f 0.26 (petrol / Et₂O (4:1)); IR (thin film, ν_max / cm⁻¹) 3329, 2926, 1743, 1449, 1029; ¹H NMR (400 MHz, C₆D₆) δ_H 6.33 (1H, app t, J = 11.3 Hz, H2), 6.24 (1H, app t, J = 11.3 Hz, H3), 5.42 (1H, app t, J = 11.3, H1), 5.35 (1H, app t, J = 11.3 Hz, H4), 4.52-4.46 (1H, m, H5), 2.48-2.38 (1H, m, H1’), 1.69-1.54 (7H, m, H2’, H6 and O-H), 1.44-1.20 (14H, m, H3’, H4’, H7, H8, H9 and H10), 0.90 (3H, t, J = 7.1 Hz, H11); ¹³C NMR (125 MHz, C₆D₆) δ_C 139.6, 134.3, 124.6, 121.5, 67.4, 37.6, 36.4, 33.1,
31.8, 29.3, 25.9, 25.8, 25.3, 22.6, 14.0; HRMS (ESI\(^+\)) calc. for C\(_{17}\)H\(_{30}\)NaO [M+Na\(^+\)] 273.2194, found 273.2187.

\((1Z,3Z)-1\text{-Phenylundeca}-1,3\text{-dien}-5\text{-ol}, 149\text{ad}\)

![Chemical structure of 149ad](image)

**Procedure F** (modified): A solution of TBAF•3H\(_2\)O (0.66 mL of a 1.0 M solution in THF, 0.660 mmol, 3.0 eq) and \(i\)-PrOH (66 μl) was added to silane 119a (50 mg, 0.221 mmol, 1.0 eq), iodide 145d (51 mg, 0.221 mmol, 1.0 eq) and allylpalladium chloride dimer (8 mg, 0.022 mmol, 0.10 eq) at room temperature and stirred for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et\(_2\)O (93:7→4:1) + 1% Et\(_3\)N) with lights in the vicinity switched off, to give diene 149ad (which isomerises to produce inseparable \(E,Z\)-diene 149aa) as a yellow oil (19 mg, 0.078 mmol, 35%, 96:4 Z,Z:E,E); \(R_f\) 0.16 (petrol / Et\(_2\)O (20:1)); IR (thin film, \(v_{\text{max}}\) / cm\(^{-1}\)) 3358, 2927, 2856, 1493, 1449, 1315, 1029; \(^1\text{H NMR}\) (400 MHz, C\(_6\)D\(_6\)) \(\delta_{\text{H}}\) 7.28 (2H, d, \(J = 7.7\) Hz, \(\text{o-Ar}\)H), 7.20-7.10 (2H, m, \text{m-ArH}), 7.07-7.02 (1H, m, \text{p-ArH}), 6.58 (1H, app t, \(J = 11.3\) Hz, H3), 6.48 (1H, app t, \(J = 11.3\) Hz, H2), 6.41 (1H, d, \(J = 11.3\) Hz, H1), 5.45-5.40 (1H, m, H4), 4.57-4.47 (1H, m, H5), 1.65-1.20 (11H, m, H6, H7, H8, H9, H10 and OH), 0.88 (3H, t, \(J = 6.8\) Hz, H11); \(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta_{\text{C}}\) 137.5, 137.5, 131.5, 129.5, 128.5, 127.4, 125.4, 125.2, 67.8, 38.0, 32.2, 29.7, 25.7, 23.0, 14.3; HRMS (ESI\(^+\)) calc. for C\(_{17}\)H\(_{32}\)NaO [M+Na\(^+\)] 267.1719, found 267.1718.

\((Z)-1\text{-Phenylnon}-1\text{-en}-3\text{-ol}, 149\text{ae}\)

![Chemical structure of 149ae](image)

**Procedure F**: A solution of TBAF•3H\(_2\)O (0.32 mL of a 1.0 M solution in THF, 0.320 mmol, 3.0 eq) was added to silane 119a (24 mg, 0.106 mmol, 1.0 eq), iodobenzene (12 μL, 0.106 mmol, 1.0 eq)
and allylpalladium chloride dimer (1.1 mg, 0.003 mmol, 0.025 eq) at room temperature and the mixture was stirred for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et$_2$O (19:1→9:1) + 1% Et$_3$N) to give alkene 149ae as a yellow oil (18 mg, 0.084 mmol, 80%).

**Procedure G:** A solution of potassium trimethylsilanolate (1.32 mL of a 0.42 M solution in DME, 0.552 mmol, 2.5 eq) was added to silane 119a (50 mg, 0.221 mmol, 1.0 eq), iodobenzene (25 µL, 0.221 mmol, 1.0 eq), water (40 µL, 2.21 mmol, 10 eq) and bis(dibenzylideneacetone)palladium (6.3 mg, 0.011 mmol, 0.05 eq) at room temperature and stirred at 60 °C for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et$_2$O (9:1→17:3) + 1% Et$_3$N) to give alkene 149ae as a yellow oil (42 mg, 0.192 mmol, 87%); $R_f$ 0.20 (petrol / Et$_2$O (4:1)); **IR** (thin film, $v_{max}$ / cm$^{-1}$) 3332, 3010, 2955, 2927, 2856, 1736, 1494, 1459, 1377, 1232, 1040, 1012; **$^1$H NMR** (400 MHz, CDCl$_3$) δH 7.38-7.25 (5H, m, ArH), 6.57 (1H, d, $J = 11.5$ Hz, H1), 5.68 (1H, dd, $J = 11.5$ and 9.2 Hz, H2), 4.61-4.55 (1H, m, H3), 1.71-1.53 (2H, m, H4), 1.43-1.24 (8H, m, H5, H6, H7, H8 and OMe), 0.88 (3H, t, $J = 6.8$ Hz, H9); **$^{13}$C NMR** (101 MHz, CDCl$_3$) δC 136.7, 134.7, 131.0, 128.7, 128.3, 127.2, 67.9, 37.6, 31.8, 29.2, 25.3, 22.6, 14.1; **HRMS** (ESI$^+$) calc. for C$_{15}$H$_{22}$NaO [M+Na]$^+$ 241.1568, found 241.1567.

(8Z,10E)-Pentadeca-8,10-dien-7-ol, 149ag

![structure](image)

**Procedure F:** A solution of TBAF•3H$_2$O (0.68 mL of a 1.0 M solution in THF, 0.675 mmol, 3.0 eq) was added to silane 119a (51 mg, 0.225 mmol, 1.0 eq), (E)-1-iodohex-1-ene (47 mg, 0.225 mmol, 1.0 eq) and allylpalladium chloride dimer (2.2 mg, 0.006 mmol, 0.025 eq) at room temperature and stirred for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et$_2$O (9:1) + 1% Et$_3$N) to give diene 149ag as a colourless oil (31 mg, 0.138 mmol, 62%).

**Procedure G:** A solution of potassium trimethylsilanolate (1.32 mL of a 0.42 M solution in DME, 0.552 mmol, 2.5 eq) was added to silane 119a (50 mg, 0.221 mmol, 1.0 eq), (E)-1-iodohex-1-ene (70
mg, 0.331 mmol, 1.5 eq), water (40 µL, 2.21 mmol, 10 eq) and bis(dibenzylideneacetone)palladium (6.3 mg, 0.011 mmol, 0.05 eq) at room temperature and stirred at 60 °C for 24 hours. The concentrated crude was purified by flash column chromatography (petrol/ EtOAc (9:1) + 1% Et3N) to give diene 149ag as a colourless oil (28 mg, 0.125 mmol, 57%); Rf 0.22 (petrol / Et2O (4:1)); IR (thin film, νmax / cm⁻¹) 3348, 3021, 2957, 2927, 2872, 2857, 1654, 1466, 1378, 1123, 1060, 1034, 1006; ¹H NMR (500 MHz, C₆D₆) δH 6.53 (1H, dd, J = 15.0 and 11.2 Hz, H10), 6.13 (1H, app t, J = 11.2 Hz, H9), 5.72 (1H, dt, J = 15.0 and 7.0, H11), 5.42 (1H, t, J = 11.2 Hz, H8), 4.64-4.60 (1H, m, H7), 2.11 (2H, q, J = 7.0 Hz, H12), 1.76-1.69 (1H, m, OH), 1.61-1.32 (14H, m, H2, H3, H4, H5, H6, H13 and H14), 0.98 (3H, t, J = 7.0 Hz, H1 or H15), 0.96 (3H, t, J = 7.2 Hz, H1 or H15); ¹³C NMR (125 MHz, C₆D₆) δC 136.4, 132.9, 130.0, 126.0, 68.0, 38.2, 32.8, 32.2, 31.7, 29.7, 25.7, 23.0, 22.6, 14.3, 14.1; HRMS (ESI’) calc. for C₁₅H₂₈NaO [M+Na]+ 247.2038, found 247.2039.

(2E,4Z)-2-Methyldodeca-2,4-diene-1,6-diol, 149ah

Procedure F: A solution of TBAF·3H₂O (0.66 mL of a 1.0 M solution in THF, 0.660 mmol, 3.0 eq) was added to silane 119a (50 mg, 0.221 mmol, 1.0 eq), iodide 145h (66 mg, 0.331 mmol, 1.5 eq) and allylpalladium chloride dimer (2.2 mg, 0.006 mmol, 0.025 eq) at room temperature and stirred for 24 hours. The concentrated crude (which was very sensitive to light) was purified by flash column chromatography (petrol / EtOAc (7:3→3:2) + 1% Et₃N) to give diene 149ah as a pale yellow oil (15 mg, 0.071 mmol, 32%).

Procedure G (modified): A solution of potassium trimethylsilanolate (0.66 mL of a 0.74 M solution in DME, 0.486 mmol, 2.2 eq), silane 119a (50 mg, 0.221 mmol, 1.0 eq), iodide 145h (66 mg, 0.331 mmol, 1.5 eq) and bis(dibenzylideneacetone)palladium (6.3 mg, 0.011 mmol, 0.05 eq) were stirred at room temperature and stirred for 24 hours. The concentrated crude (which was very sensitive to light) was purified by flash column chromatography (petrol / EtOAc (7:3→3:2) + 1% Et₃N) to give
alkene 149ah as a pale yellow oil (10 mg, 0.047 mmol, 22%); \( R_f \) 0.28 (petrol / EtOAc (1:1)); \text{IR} (thin film, \( \nu_{\text{max}} / \text{cm}^{-1} \)) 3339, 2956, 2928, 2857, 1656, 1457, 1379, 1132, 1067, 1012; \text{\( ^1 \)H NMR} (500 MHz, \( \text{C}_6\text{D}_6 \)) \( \delta \) H 6.57-6.54 (1H, m, H3), 6.34 (1H, app t, \( J = 11.3 \) Hz, H4), 5.57-5.53 (1H, m, H5), 4.72-4.67 (1H, m, H6), 3.85 (2H, s, H1), 1.77-1.70 (1H, m, \( 1 \times \text{diastereotopic H7} \)), 1.64 (3H, s, H2), 1.62-1.29 (11H, m, \( 1 \times \text{diastereotopic H7, H8, H9, H10, H11, 2 \times \text{OH} \)), \( 0.98 \) (3H, t, \( J = 7.1 \) Hz, H12); \text{\( ^{13} \)C NMR} (125 MHz, \( \text{C}_6\text{D}_6 \)) \( \delta \) C 139.3, 134.5, 125.1, 119.2, 68.0, 67.8, 38.2, 32.2, 29.7, 25.7, 23.0, 14.3, 13.7; \text{HRMS} (ESI') calc. for C_{13}H_{24}NaO_2 [M+Na]'^+ 235.1669, found 235.1667.

\( (2Z,4E) \)-1-Cyclohexyl-5-phenylpenta-2,4-dien-1-ol, 149ba

\[ \begin{align*}
\text{Procedure F:} & \quad \text{A solution of TBAF•3H}_2\text{O (0.69 mL of a 1.0 M solution in THF, 0.690 mmol, 3.0 eq) was added to silane 119b (50 mg, 0.228 mmol, 1.0 eq), E-iodostyrene 145a (51 mg, 0.228 mmol, 1.0 eq) and allylpalladium chloride dimer (2.0 mg, 0.005 mmol, 0.025 eq) at room temperature and stirred for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / \text{Et}_2\text{O (19:1) + 1% Et}_3\text{N}) to give diene 149ba as a yellow oil (33 mg, 0.135 mmol, 60%).} \\
\text{Procedure G:} & \quad \text{A solution of potassium trimethylsilanolate (1.32 mL of a 0.42 M solution in DME, 0.570 mmol, 2.5 eq) was added to silane 119b (50 mg, 0.228 mmol, 1.0 eq), E-iodostyrene 145a (51 mg, 0.228 mmol, 1.0 eq), water (40 µL, 2.28 mmol, 10 eq) and bis(dibenzylideneacetone) palladium (6.3 mg, 0.010 mmol, 0.05 eq) at room temperature and stirred at 60 °C for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / \text{Et}_2\text{O (19:1) + 1% Et}_3\text{N}) to give alkene 149ba as a yellow oil (29 mg, 0.120 mmol, 54%); \( R_f \) 0.24 (petrol / \text{Et}_2\text{O (2:1)}); \text{IR} (\text{thin film, } \nu_{\text{max}} / \text{cm}^{-1} ) 3357, 3027, 2923, 2852, 1492, 1449, 1261, 1080, 1017; \text{\( ^1 \)H NMR} (400 MHz, \( \text{C}_6\text{D}_6 \)) \( \delta \) H 7.28 (2H, d, \( J = 7.6 \) Hz, o-ArH), 7.15-7.09 (3H, m, m-ArH and p-ArH), 7.07-7.01 (1H, m, H4), 6.44 (1H, d, \( J = 15.6 \) Hz, H5), 6.14 (1H, app t, \( J = 11.2 \) Hz, H3), 5.41 (1H, dd, \( J = 11.2 \) and 9.3 Hz, H2), 4.27 (1H, dd, \( J = 9.3 \) and 7.2 Hz, H1), 2.01 (1H, d, \( J = 11.7 \) Hz, OH), 1.73-1.56 (4H, m, H2'), 1.41-} \]
1.32 (1H, m, H1’), 1.22-0.90 (6H, m, H3’ and H4’); $^{13}$C NMR (125 MHz, C$_6$D$_6$) δ$_C$ 137.7, 128.3, 134.3, 134.1, 130.7, 129.0, 126.9, 124.6, 72.3, 44.6, 29.1 and 29.0 (conformationally isomeric H3’ or H4’), 27.0 and 26.6 (conformationally isomeric H3’ or H4’), 26.5; HRMS (ESI’) calc. for C$_{17}$H$_{22}$NaO [M+Na]$^+$ 265.1568, found 265.1563.

(2Z,4E)-6-(Benzyloxy)-1-cyclohexylhexa-2,4-dien-1-ol, 149bb

**Procedure F:** A solution of TBAF·3H$_2$O (0.53 mL of a 1.0 M solution in THF, 0.530 mmol, 3.0 eq) was added to silane 119b (40 mg, 0.178 mmol, 1.0 eq), iodide 145b (49 mg, 0.178 mmol, 1.0 eq) and allylpalladium chloride dimer (1.4 mg, 0.004 mmol, 0.025 eq) at room temperature and stirred for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et$_2$O (9:1) + 1% Et$_3$N) to give diene 149bb as a yellow oil (16 mg, 0.059 mmol, 34%).

**Procedure G** (modified): A solution of potassium trimethylsilanolate (0.53 mL of a 0.74 M solution in DME, 0.392 mmol, 2.2 eq) was added to silane 119b (40 mg, 0.178 mmol, 1.0 eq), iodide 145b (49 mg, 0.178 mmol, 1.0 eq) and bis(dibenzylideneacetone)palladium (5.2 mg, 0.009 mmol, 0.05 eq) at room temperature and stirred for 15 hours. The concentrated crude was purified by flash column chromatography (petrol / Et$_2$O (9:1) + 1% Et$_3$N) to give alkene 149bb as a yellow oil (23 mg, 0.084 mmol, 46%); $R_f$ 0.18 (petrol / Et$_2$O (4:1)); IR (thin film, 10000/cm) 3426, 3029, 2922, 2851, 1496, 1451, 1359, 1306, 1205, 1098, 1056, 1027; $^1$H NMR (500 MHz, C$_6$D$_6$) δ$_H$ 7.30 (2H, d, $J = 7.5$ Hz, H8), 7.17 (1H, t, $J = 7.5$ Hz, H9), 7.09 (1H, t, $J = 7.5$ Hz, H10), 6.63 (1H, dd, $J = 15.3$ and 11.4 Hz, H4), 6.00 (1H, app t, $J = 11.4$ Hz, H3), 5.70 (1H, dt, $J = 15.3$ and 5.8 Hz, H5), 5.33 (1H, app t, $J = 11.4$ Hz, H2), 4.35 (2H, s, H7), 4.17-4.13 (1H, m, H1), 3.88 (2H, d, $J = 5.8$ Hz, H6), 1.98-1.94 (1H, m, 1 × H3’), 1.71-1.61 (3H, m, 2 × H2’ and 1 × H3’), 1.59-1.55 (1H, m, 1 × H4’), 1.36-1.28 (1H, m, 1 × H1’), 1.20-0.88 (6H, m, 2 × H2’, 2 × H3’, 1 × H4’ and OH); $^{13}$C NMR (125 MHz, C$_6$D$_6$)
δ_C 139.3, 134.1, 132.2, 130.0, 129.9, 128.6, 128.0, 127.7, 72.6, 72.3, 70.6, 44.8, 29.3, 29.2, 27.2, 26.8, 26.7; HRMS (ESI⁺) calc. for C_{15}H_{26}NaO₂ [M+Na]⁺ 309.1825, found 309.1825.

(Z)-1-Cyclohexyl-3-phenylprop-2-en-1-ol, 149be

Procedure F: A solution of TBAF·3H₂O (0.64 mL of a 1.0 M solution in THF, 0.640 mmol, 3.0 eq) was added to silane 119b (48 mg, 0.214 mmol, 1.0 eq), iodobenzene (24 μL, 0.214 mmol, 1.0 eq) and allylpalladium chloride dimer (1.8 mg, 0.005 mmol, 0.025 eq) at room temperature and the mixture was stirred for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et₂O (9:1) + 1% Et₃N) to give alkene 149be as a colourless solid (42 mg, 0.196 mmol, 92%).

Procedure G: A solution of potassium trimethylsilanolate (1.32 mL of a 0.42 M solution in DME, 0.552 mmol, 2.5 eq) was added to silane 119b (50 mg, 0.221 mmol, 1.0 eq), iodobenzene (25 μL, 0.221 mmol, 1.0 eq), water (40 μL, 2.21 mmol, 10 eq) and bis(dibenzylideneacetone)palladium (6.3 mg, 0.011 mmol, 0.05 eq) at room temperature and stirred at 60 °C for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et₂O (9:1→17:3) + 1% Et₃N) to give alkene 149be as a colourless solid (38 mg, 0.176 mmol, 80%); R_f 0.31 (petrol / Et₂O (2:1)); mp 77-78 °C; IR (thin film, ν_max / cm⁻¹) 3393, 3023, 2920, 2849, 1494, 1306, 1239, 1209, 1140, 1094, 1081, 1005; ¹H NMR (400 MHz, C₆D₆) δ_H 7.32 (2H, d, J = 7.5 Hz, o-ArH), 7.15 (2H, t, J = 7.5 Hz, m-ArH), 7.04 (1H, t, J = 7.5 Hz, p-ArH), 6.46 (1H, d, J = 11.8 Hz, H3), 5.55 (1H, dd, J = 11.8 and 9.6 Hz, H2), 4.24 (1H, dd, J = 9.6 and 7.2 Hz, H1), 1.97-1.91 (1H, m, O_H), 1.68-1.54 (4H, m, H2’), 1.35-1.26 (1H, m, H1’), 1.16-0.86 (6H, m, H3’ and H4’); ¹³C NMR (101 MHz, C₆D₆) δ_C 137.4, 134.3, 131.6, 129.2, 128.5, 127.3, 71.8, 44.7, 29.2, 28.7, 26.8, 26.5, 26.4; HRMS (ESI⁺) calc. for C_{15}H_{26}NaO [M+Na]⁺ 239.1412, found 239.1416.
Procedure F: A solution of TBAF•3H₂O (0.66 mL of a 1.0 M solution in THF, 0.660 mmol, 3.0 eq) was added to silane 119b (49 mg, 0.218 mmol, 1.0 eq), (E)-1-iodohex-1-ene (55 mg, 0.262 mmol, 1.2 eq) and allylpalladium chloride dimer (2.2 mg, 0.005 mmol, 0.025 eq) at room temperature and stirred for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et₂O (19:1) + 1% Et₃N) to give diene 149bg as a colourless oil (19 mg, 0.085 mmol, 39%).

Procedure G: A solution of potassium trimethylsilanolate (1.32 mL of a 0.42 M solution in DME, 0.570 mmol, 2.5 eq) was added to silane 119b (50 mg, 0.228 mmol, 1.0 eq), (E)-1-iodohex-1-ene (94 mg, 0.446 mmol, 1.0 eq), water (40 µL, 2.28 mmol, 10 eq) and bis(dibenzylideneacetone) palladium (6.3 mg, 0.010 mmol, 0.05 eq) at room temperature and stirred at 60 °C for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et₂O (9:1) + 1% Et₃N) to give diene 149bg as a colourless oil (15 mg, 0.067 mmol, 30%); \( R_f \) 0.39 (petrol / Et₂O (2:1)); IR (thin film, \( \nu_{\text{max}} / \text{cm}^{-1} \)) 3368, 2924, 2853, 1653, 1378, 1232, 1081, 1017; \(^1\text{H NMR} \) (400 MHz, \( \text{C}_6\text{D}_6 \)) \( \delta \)H 6.52 (1H, dd, \( J = 15.1 \) and 11.3 Hz, H4), 6.16 (1H, app t, \( J = 11.3 \) Hz, H3), 5.72 (1H, dt, \( J = 15.1 \) and 7.1 Hz, H5), 5.41-5.36 (1H, m, H2), 4.35-4.31 (1H, m, H1), 2.14-2.08 (2H, m, H6), 1.84-1.67 (4H, m, H3’), 1.49-1.01 (11H, m, H7, H8, H2’, H4’ and OH), 0.95 (3H, t, \( J = 7.1 \) Hz, H9); \(^{13}\text{C NMR} \) (101 MHz, \( \text{C}_6\text{D}_6 \)) \( \delta \)C 136.6, 131.5, 130.8, 126.2, 72.1, 44.6, 32.8, 31.7, 29.1 and 29.0 (conformationally isomeric C3’ or C4’), 26.9, 26.5 and 26.4 (conformationally isomeric C3’ or C4’), 22.5, 14.0; HRMS (FI⁺) calc. for \( \text{C}_{15}\text{H}_{26}\text{O} \) [M⁺] 222.1984, found 222.1981.
(2Z,4E)-1,5-Diphenylpenta-2,4-dien-1-ol, 149ca

**Procedure F:** A solution of TBAF•3H2O (0.69 mL of a 1.0 M solution in THF, 0.690 mmol, 3.0 eq) was added to silane 119c (50 mg, 0.230 mmol, 1.0 eq), E-iodostyrene 145a (53 μL, 0.230 mmol, 1.0 eq) and allylpalladium chloride dimer (2.0 mg, 0.006 mmol, 0.025 eq) at room temperature and the mixture was stirred for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et2O (7:3) + 1% Et3N) to give alkene 149ca as a yellow oil (35 mg, 0.148 mmol, 64%).

**Procedure G:** A solution of potassium trimethylsilanolate ((1.32 mL of a 0.42 M solution in DME, 0.553 mmol, 2.5 eq) was added to silane 119c (48 mg, 0.221 mmol, 1.0 eq), E-iodostyrene 145a (51 μL, 0.221 mmol, 1.0 eq), water (40 μL, 2.21 mmol, 10 eq) and bis(dibenzylideneacetone)palladium (6.3 mg, 0.011 mmol, 0.05 eq) at room temperature and stirred at 60 °C for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et2O (9:1→4:1) + 1% Et3N) to give alkene 149ca as a yellow oil (26 mg, 0.110 mmol, 50%); Rf 0.30 (petrol / Et2O (2:1)); IR (thin film, νmax / cm−1) 3356, 3027, 2920, 1575, 1492, 1449, 1026; 1H NMR (400 MHz, C6D6) δH 7.41 (2H, d, J = 7.5 Hz, o-ArA'H), 7.37 (2H, d, J = 7.4 Hz, o-ArB'H), 7.32-7.15 (7H, m, m-ArA'H, p-ArA'H, m-ArB'H and p-ArB'H, H4), 6.54 (1H, d, J = 15.6, H5), 6.19 (1H, app t, J = 10.3 Hz, H3), 5.73– 5.67 (2H, m, H1 and H2), 1.49 (1H, br, OH); 13C NMR (125 MHz, C6D6) δC 144.0, 137.5, 135.1, 134.1, 129.9, 128.9, 128.7, 128.3, 127.5, 127.0, 126.3, 124.0, 70.1; HRMS (ESI+) calc. for C17H16NaO [M+Na]+ 259.1099, found 259.1086.
**Procedure F:** A solution of TBAF·3H2O (0.47 mL of a 1.0 M solution in THF, 0.470 mmol, 3.0 eq) was added to silane 119c (34 mg, .0155 mmol, 1.0 eq), iodide 145b (42 mg, 0.155 mmol, 1.0 eq) and allylpalladium chloride dimer (1.4 mg, 0.004 mmol, 0.025 eq) at room temperature and stirred for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et2O (9:1→4:1) + 1% Et3N) to give diene 149cb as a yellow oil (22 mg, 0.076 mmol, 52%).

**Procedure G:** A solution of potassium trimethylsilanolate (0.93 mL of a 0.42 M solution in DME, 0.388 mmol, 2.5 eq) was added to silane 119c (34 mg, 0.155 mmol, 1.0 eq), iodide 145b (64 mg, 0.233 mmol, 1.5 eq), water (28 µL, 1.55 mmol, 10 eq) and bis(dibenzylideneacetone)palladium (4.4 mg, 0.008 mmol, 0.05 eq) at room temperature and stirred at 60 °C for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et2O (9:1→4:1) + 1% Et3N) to give alkene 149cb as a yellow oil (22 mg, 0.076 mmol, 52%); Rf 0.12 (petrol / Et2O (4:1)); IR (thin film, νmax / cm⁻¹) 3400, 3062, 3029, 2852, 1603, 1494, 1452, 1359, 1104, 1027; ¹H NMR (500 MHz, C6D6) δH 7.36 (2H, d, J = 7.6 Hz, o-ArH), 7.29 (2H, d, J = 7.6 Hz, o-ArH), 7.19-7.13 (4H, m, 2 × m-ArH), 7.09 (1H, t, J = 7.6 Hz, p-ArH), 7.05 (1H, t, J = 7.6 Hz, p-ArH), 6.71 (1H, dd, J = 14.9 and 11.3 Hz, H4), 5.93 (1H, app t, J = 11.4 Hz, H3), 5.68 (1H, dt, J = 14.9 and 5.5 Hz, H5), 5.53-5.47 (2H, m, H1 and H5), 4.33 (2H, s, ArCH2O), 3.85 (2H, d, J = 5.5 Hz, H6), 1.58 (1H, br s, OH); ¹³C NMR (125 MHz, C6D6) δC 144.1, 139.0, 134.1, 132.7, 128.9, 128.6, 128.6, 128.3, 127.8, 127.5, 126.9, 126.3, 72.4, 70.2, 69.9; HRMS (ESI⁺) calc. for C19H20NaO2 [M+Na⁺] 303.1356, found 303.1352.
(Z)-1,3-Diphenylprop-2-en-1-ol, 149ce

Procedure F: A solution of TBAF•3H2O (0.69 mL of a 1.0 M solution in THF, 0.690 mmol, 3.0 eq) was added to silane 119c (50 mg, 0.230 mmol, 1.0 eq), iodobenzene (26 μL, 0.230 mmol, 1.0 eq) and allylpalladium chloride dimer (2.2 mg, 0.006 mmol, 0.025 eq) at room temperature and the mixture was stirred for a further 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et2O (9:1→3:1) + 1% Et3N) to give alkene 149ce as a colourless oil (42 mg, 0.200 mmol, 87%).

Procedure G: A solution of potassium trimethylsilanolate (1.32 mL of a 0.42 M solution in DME, 0.552 mmol, 2.5 eq) was added to silane 119c (48 mg, 0.221 mmol, 1.0 eq), iodobenzene (25 μL, 0.221 mmol, 1.0 eq), water (40 μL, 2.21 mmol, 10 eq) and bis(dibenzylideneacetone)palladium (6.3 mg, 0.011 mmol, 0.05 eq) at room temperature and stirred at 60 °C for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et2O (9:1→17:3) + 1% Et3N) to give alkene 149ce as a colourless oil (41 mg, 0.195 mmol, 88%); Rf 0.26 (petrol / Et2O (2:1)); 1H NMR (500 MHz, C6D6) δH 7.47 (2H, d, J = 7.6 Hz, o-ArH), 7.39 (2H, d, J = 7.6 Hz, o-ArH), 7.28-7.15 (6H, m, m-ArH, p-ArH and p-ArH), 6.55 (1H, d, J = 11.6 Hz, H3), 5.91 (1H, dd, J = 11.6 and 9.4 Hz, H2), 5.68 (1H, d, J = 9.4 Hz, H1), 1.84 (1H, br, OH); 13C NMR (125 MHz, C6D6) δC 144.1, 137.0, 134.4, 130.9, 129.2, 128.7, 128.6, 127.7, 127.6, 126.6, 70.0; LRMS (ESI+) calc. for C15H14NaO [M+Na]+ 233.1, found 233.1.

The spectroscopic data were found to be in agreement with that reported by Silva and co-workers.270
(2Z,4E)-1-Phenylnona-2,4-dien-1-ol, 149cg

**Procedure F:** A solution of TBAF•3H2O (0.47 mL of a 1.0 M solution in THF, 0.470 mmol, 3.0 eq) was added to silane 119c (34 mg, 0.156 mmol, 1.0 eq), (E)-1-iodohex-1-ene (49 mg, 0.234 mmol, 1.5 eq) and allylpalladium chloride dimer (1.4 mg, 0.004 mmol, 0.025 eq) at room temperature and the mixture was stirred for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et2O (19:1→9:1) + 1% Et3N) to give alkene 149cg as a colourless oil (19 mg, 0.090 mmol, 57%).

**Procedure G:** A solution of potassium trimethylsilanolate (1.32 mL of a 0.42 M solution in DME, 0.552 mmol, 2.5 eq) was added to silane 119c (48 mg, 0.221 mmol, 1.0 eq), (E)-1-iodohex-1-ene (70 mg, 0.331 mmol, 1.5 eq), water (40 µL, 2.21 mmol, 10 eq) and bis(dibenzylideneacetone)palladium (6.3 mg, 0.011 mmol, 0.05 eq) at room temperature and stirred at 60 °C for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et2O (9:1→17:3) + 1% Et3N) to give alkene 149cg as a colourless oil (28 mg, 0.125 mmol, 57%); Rf 0.40 (petrol / Et2O (2:1)); IR (thin film, νmax / cm⁻¹) 3338, 2957, 2926, 2872, 1652, 1493, 1452, 1024; ¹H NMR (500 MHz, C₆D₆) δH 7.41 (2H, d, J = 7.7 Hz, o-ArH), 7.17 (2H, t, J = 7.7 Hz, m-ArH), 7.07 (1H, t, J = 7.7 Hz, p-ArH), 6.47 (1H, dd, J = 14.8 and 11.4 Hz, H4), 5.99 (1H, app t, J = 11.4 Hz, H3), 5.60 (1H, dt, J = 14.8 and 7.2 Hz, H5), 5.55 (1H, d, J = 9.3 Hz, H1), 5.45 (1H, m, H2), 1.98 (2H, q, J = 7.2 Hz, H6), 1.36-1.18 (5H, m, H7, H8 and OAr), 0.84 (3H, t, J = 7.0 Hz, H9); ¹³C NMR (125 MHz, C₆D₆) δc 144.6, 137.8, 132.1, 130.4, 128.9, 127.7, 126.5, 126.0, 70.2, 33.1, 31.9, 22.9, 14.4; HRMS (ESI⁺) calc. for C₁₅H₂₀NaO [M+Na]⁺ 239.1412, found 239.1408.
(4Z,6E)-1-((Tert-butyldimethylsilyl)oxy)-7-phenylhepta-4,6-dien-3-ol, 149da

Procedure G: A solution of potassium trimethylsilanolate (1.32 mL of a 0.42 M solution in DME, 0.552 mmol, 2.5 eq) was added to silane 119d (50 mg, 0.221 mmol, 1.0 eq), iodide 145a (76 mg, 0.332 mmol, 1.5 eq), water (40 µL, 2.21 mmol, 10 eq) and bis(dibenzylideneacetone)palladium (6.3 mg, 0.011 mmol, 0.05 eq) at room temperature and stirred at 60 °C for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et₂O (9:1→17:3) + 1% Et₃N) to give alkene 149da as a pale yellow oil (39 mg, 0.128 mmol, 58%); Rf 0.15 (petrol / Et₂O (2:1)); IR (thin film, νmax / cm⁻¹) 3417, 2954, 2929, 2857, 1471, 1256, 1086; ¹H NMR (500 MHz, C₆D₆) δH 7.29 (2H, d, J = 7.3 Hz, H9), 7.23 (1H, dd, J = 15.5 and 11.2 Hz, H6), 7.11 (2H, t, J = 7.3 Hz, H10), 7.01 (1H, t, J = 7.3 Hz, H11), 6.41 (1H, d, J = 15.5 Hz, H7), 6.09 (1H, app t, J = 11.2 Hz, H5), 5.54 (1H, dd, J = 11.2 and 8.7 Hz, H4), 4.96-4.92 (1H, m, H3), 3.71-3.67 and 3.60-3.55 (2 × 1H, m, diastereotopic H1), 2.28 (1H, br, OH), 1.81-1.74 and 1.64-1.58 (2 × 1H, m, diastereotopic H2), 0.92 (9H, s, SiC(CH₃)_3), 0.00 and -0.02 (2 × 3H, s, diastereotopic Si(CH₃)_2); ¹³C NMR (125 MHz, C₆D₆) δC 138.0, 135.6, 134.5, 129.8, 129.2, 128.2, 127.2, 124.8, 67.2, 61.3, 40.5, 26.4, 18.6, -5.1, -5.2; HRMS (ESI⁺) calc. for C₁₉H₃₀NaO₂Si [M+Na]+ 341.1913, found 341.1900.

(4Z,6E)-8-(Benzyloxy)-1-((tert-butyldimethylsilyl)oxy)octa-4,6-dien-3-ol, 149db

Procedure (modified): A solution of potassium trimethylsilanolate (0.50 mL of a 0.74 M solution in DME, 0.366 mmol, 2.2 eq) was added to silane 119d (50 mg, 0.166 mmol, 1.0 eq), iodide 145b (46 mg, 0.166 mmol, 1.0 eq) and bis(dibenzylideneacetone)palladium (4.6 mg, 0.008 mmol, 0.05 eq) at room temperature and stirred for 15 hours. The concentrated crude was purified by flash column chromatography (petrol / Et₂O (9:1→17:3) + 1% Et₃N) to give alkene 149db as a pale yellow oil (39 mg, 0.128 mmol, 58%); Rf 0.15 (petrol / Et₂O (2:1)); IR (thin film, νmax / cm⁻¹) 3417, 2954, 2929, 2857, 1471, 1256, 1086; ¹H NMR (500 MHz, C₆D₆) δH 7.29 (2H, d, J = 7.3 Hz, H9), 7.23 (1H, dd, J = 15.5 and 11.2 Hz, H6), 7.11 (2H, t, J = 7.3 Hz, H10), 7.01 (1H, t, J = 7.3 Hz, H11), 6.41 (1H, d, J = 15.5 Hz, H7), 6.09 (1H, app t, J = 11.2 Hz, H5), 5.54 (1H, dd, J = 11.2 and 8.7 Hz, H4), 4.96-4.92 (1H, m, H3), 3.71-3.67 and 3.60-3.55 (2 × 1H, m, diastereotopic H1), 2.28 (1H, br, OH), 1.81-1.74 and 1.64-1.58 (2 × 1H, m, diastereotopic H2), 0.92 (9H, s, SiC(CH₃)_3), 0.00 and -0.02 (2 × 3H, s, diastereotopic Si(CH₃)_2); ¹³C NMR (125 MHz, C₆D₆) δC 138.0, 135.6, 134.5, 129.8, 129.2, 128.2, 127.2, 124.8, 67.2, 61.3, 40.5, 26.4, 18.6, -5.1, -5.2; HRMS (ESI⁺) calc. for C₁₉H₃₀NaO₂Si [M+Na]+ 341.1913, found 341.1900.
chromatography (petrol / EtO (9:1) + 1% Et3N) to give alkene **149db** as a pale yellow oil (20 mg, 0.057 mmol, 35%); \( R_f \) 0.21 (petrol / EtO (4:1)); **IR** (thin film, \( \nu_{max} / \text{cm}^{-1} \)) 3435, 2955, 2928, 2855, 1471, 1388, 12541092, 1058; **\( ^1H \) NMR** (500 MHz, \( \text{C}_6\text{D}_6 \)) \( \delta_H \) 7.29 (2H, d, \( J = 7.7 \text{ Hz, H10} \)), 7.17 (1H, t, \( J = 7.7 \text{ Hz, H11} \)), 7.08 (1H, t, \( J = 7.7 \text{ Hz, H12} \)), 6.72 (1H, dd, \( J = 15.1 \text{ and 11.5 Hz, H6} \)), 5.95 (1H, app t, \( J = 11.5 \text{ Hz, H5} \)), 5.69 (1H, dt, \( J = 15.1 \text{ and 5.5 Hz, H7} \)), 5.47 (1H, app t, \( J = 11.5 \text{ Hz, H4} \)), 4.85-4.78 (1H, m, H3), 4.33 (2H, s, H9), 3.88 (2H, d, \( J = 5.5 \text{ Hz, H8} \)), 3.67-3.63 and 3.56-3.51 (2 × 1H, m, diaste\( \text{reotopic H1} \)), 2.25 (1H, br s, O\( \text{H} \)), 1.78-1.70 and 1.59-1.53 (2 × 1H, m, diastereotopic H2), 0.92 (9H, s, Si(CH\( \text{3} \))\( \text{2} \)C(CH\( \text{3} \))\( \text{3} \)), 0.00 and -0.01 (2 × 3H, s, diastereotopic Si(CH\( \text{3} \))\( \text{2} \)C(CH\( \text{3} \)))\( \text{3} \)); **\( ^{13}C \) NMR** (125 MHz, \( \text{C}_6\text{D}_6 \)) \( \delta_C \) 139.1, 135.0, 131.9, 128.6, 128.6, 128.3, 127.7, 127.4, 72.3, 70.4, 66.9, 61.2, 40.1, 26.1, 18.3, -5.4, -5.4; **HRMS** (ESI\( ^+ \)) calc. for \( \text{C}_{21}\text{H}_{34}\text{NaO}_{3}\text{Si} [\text{M+Na}]^+ 385.2169, \text{found} 385.2169.

**(Z)-5-((Tert-butyltrimethylsilyl)oxy)-1-phenylpent-1-en-3-ol, 149de**

**Procedure G:** A solution of potassium trimethylsilanolate (1.32 mL of a 0.42 M solution in DME), 0.552 mmol, 2.5 eq) was added to silane **119d** (66 mg, 0.221 mmol, 1.0 eq), iodobenzene (25 \( \mu \text{L}, 0.221 \text{ mmol, 1.0 eq}), water (40 \( \mu \text{L}, 2.2 \text{ mmol, 10 eq}) and bis(dibenzylideneacetone)palladium (6.3 mg, 0.011 mmol, 0.05 eq) at room temperature and stirred at 60 °C for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / EtO (9:1→17:3) + 1% Et\( \text{3} \)N) to give alkene **149de** as a pale yellow oil (46 mg, 0.165 mmol, 75%); \( R_f \) 0.33 (petrol / EtO (2:1)); **IR** (thin film, \( \nu_{max} / \text{cm}^{-1} \)) 3429, 2954, 2929, 2857, 1471, 1255, 1085, 1006; **\( ^1H \) NMR** (500 MHz, \( \text{C}_6\text{D}_6 \)) \( \delta_H \) 7.39 (2H, d, \( J = 7.5 \text{ Hz, H7} \)), 7.21 (2H, t, \( J = 7.5 \text{ Hz, H8} \)), 7.08 (1H, t, \( J = 7.5 \text{ Hz, H9} \)), 6.41 (1H, d, \( J = 11.7 \text{ Hz, H5} \)), 5.72 (1H, dd, \( J = 11.7 \text{ and 9.1 Hz, H4} \)), 4.93 (1H, dt, \( J = 9.1 \text{ and 3.4 Hz, H3} \)), 3.74-3.70 and 3.59-3.55 (2 × 1H, m, diastereotopic H1), 2.38 (1H, br, OH), 1.81-1.75 and 1.71-1.65 (2 × 1H, m, diastereotopic H2), 0.93 (9H, s, Si(CH\( \text{3} \))\( \text{3} \)), 0.01 and 0.00 (2 × 3H, s, diastereotopic Si(CH\( \text{3} \))\( \text{2} \)); **\( ^{13}C \) NMR** (125 MHz, \( \text{C}_6\text{D}_6 \)) \( \delta_C \) 137.6, 135.9, 130.4, 129.6,
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128.9, 127.6, 66.7, 61.3, 40.1, 26.3, 18.6, -5.2; **HRMS** (ESI+) calc. for C_{17}H_{28}NaO_{2}Si [M+Na]^+ 315.1756, found 315.1745.

**(4Z,6E)-1-((Tert-butyl(dimethyl)silyl)oxy)undeca-4,6-dien-3-ol, 149dg**

![Structural diagram](image)

**Procedure G** (modified): A solution of potassium trimethylsilanolate (0.50 mL of a 0.78 M solution in DME, 0.390 mmol, 2.5 eq) was added to silane **119d** (47 mg, 0.156 mmol, 1.0 eq), (E)-1-iodohex-1-ene (49 mg, 0.235 mmol, 1.5 eq), water (28 µL, 1.56 mmol, 10 eq) and bis(dibenzylideneacetone)palladium (4.5 mg, 0.008 mmol, 0.05 eq) at room temperature and stirred at 60 °C for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et_{2}O (9:1) + 1% Et_{3}N) to give alkene 149dg as a colourless oil (9 mg, 0.027 mmol, 19%); **R_{f} 0.30** (petrol / Et_{2}O (2:1)); **IR** (thin film, ν_{max} / cm⁻¹) 3364, 2956, 2858, 1470, 1257, 1096; **^1H NMR** (400 MHz, C_{6}D_{6}) δ_H 6.62 (1H, dd, J = 15.1 and 11.3 Hz, H6), 6.12 (1H, t, J = 1.3 Hz, H5), 5.71 (1H, dt, J = 15.1 and 7.1 Hz, H7), 5.53 (1H, dd, J = 11.3 and 8.6 Hz, H4), 5.03-4.97 (1H, m, H3), 3.84-3.74 and 3.72-3.63 (2 x 1H, m, diastereotopic H1), 2.13 (2H, t, J = 7.1 Hz, H8), 1.95-1.86 and 1.78-1.71 (2 x 1H, m, diastereotopic H2), 1.44-1.32 (5H, m, H9, H10 and OHi), 1.07 (9H, s, Si(CH_{3})_{2}C(CH_{3})_{3}), 0.96 (3H, t, J = 7.2 Hz, H11), 0.13 and 0.13 (2 x 3H, s, diastereotopic Si(CH_{3})_{2}C(CH_{3})_{3}); **^13C NMR** (101 MHz, C_{6}D_{6}) δ_C 136.5, 132.7, 129.6, 126.1, 66.7, 61.2, 40.3, 32.9, 31.7, 26.0, 22.6, 18.3, 14.2, -5.4; **HRMS** (FI+) calc. for C_{17}H_{30}O_{2}Si [M]⁺ 298.2328, found 298.2325.
(4Z,6E)-1-((4-Methoxybenzyl)oxy)-7-phenylhepta-4,6-dien-3-ol, 149ea

A solution of potassium trimethylsilanolate was added portionwise at 0 h, 2 h and 6 h (3 × 75 µL of a 1.0 M solution in DME, 3 × 0.075 mmol, 3 × 1.0 eq) to silane 119e (23 mg, 0.075 mmol, 1.0 eq), silane 125e (24 mg, 0.075 mmol, 1.0 eq), iodide 145a (17 mg, 0.075 mmol, 1.0 eq), and bis(dibenzylideneacetone)palladium (4.6 mg, 0.008 mmol, 0.10 eq) at room temperature and stirred for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / EtOAc (100:0→4:1) + 1% Et3N) to give silane 125e (19 mg, 0.059 mmol, 79% recovered) and alkene 149ea as a yellow oil (17 mg, 0.052 mmol, 70%); Rf 0.25 (petrol / EtOAc (7:3)); IR (thin film, νmax / cm−1) 3407, 3035, 2934, 2861, 2839, 1613, 1513, 1248, 1095, 1034; 1H NMR (500 MHz, C6D6) δ 7.28-7.22 (3H, m, H6 and H2'), 7.19-7.15 (2H, m, H8), 7.11 (2H, t, J = 7.7 Hz, H9), 7.03 (1H, t, J = 7.7 Hz, H10), 6.77 (2H, d, J = 8.4 Hz, H3'), 6.44 (1H, d, J = 15.6 Hz, H7), 6.13 (1H, app t, J = 11.0 Hz, H5), 5.53 (1H, dd, J = 11.0 and 8.4 Hz, H4), 5.01-4.96 (1H, m, H3), 4.25 (2H, s, H1'), 3.51-3.47 and 3.41-3.36 (2 × 1H, m, diastereotopic H1), 3.31 (3H, s, OCH3), 2.34 (1H, br s, OH), 2.00-1.93 and 1.72-1.66 (2 × 1H, m, diastereotopic H2); 13C NMR (125 MHz, C6D6) δc 160.0, 138.0, 135.4, 134.5, 131.1, 130.1, 129.7, 129.2, 128.6, 127.2, 124.9, 114.4, 73.3, 68.0, 67.3, 55.0, 38.1; HRMS (ESI+) calc. for C21H24NaO3 [M+Na]+ 347.1618, found 347.1621.

(Z)-5-((4-Methoxybenzyl)oxy)-1-phenylpent-1-en-3-ol, 149ee

Procedure G: A solution of potassium trimethylsilanolate (0.98 mL of a 0.42 M solution in DME, 0.408 mmol, 2.5 eq) was added to silane 119e (50 mg, 0.163 mmol, 1.0 eq), silane 125e (52 mg, 0.163 mmol, 1.0 eq), iodobenzene (18 µL, 0.163 mmol, 1.0 eq), water (29 µL, 1.63 mmol, 10.0 eq) and bis(dibenzylideneacetone)palladium (4.6 mg, 0.008 mmol, 0.05 eq) at room temperature and
stirred at 60 °C for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / EtOAc (19:1→3:1)) to give silane 125e (45 mg, 0.140 mmol, 86% recovered) and alkene 149ee as a pale yellow oil (44 mg, 0.147 mmol, 90%); \( R_f \) 0.17 (petrol / EtOAc (7:3)); IR (thin film, \( v_{\text{max}} \) / cm\(^{-1}\)) 3413, 2937, 2913, 2861, 1613, 1513, 1463, 1362, 1302, 1247, 1174, 1090, 1033; \(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)) \( \delta \) 7.39 (2H, d, \( J = 8.7 \) Hz, H2’), 7.19-7.13 (4H, m, H6 and H7), 7.06 (1H, t, \( J = 7.4 \) Hz, H8), 6.79 (2H, d, \( J = 8.7 \) Hz, H3’), 6.42 (1H, d, \( J = 11.7 \) Hz, H5), 5.72 (1H, dd, \( J = 11.7 \) and 9.2 Hz, H4), 4.97-4.91 (1H, m, H3), 4.24-4.17 (2H, m, H1’), 3.53-3.46 and 3.40-3.35 (2 \( \times \) 1H, m, diastereotopic H1), 3.33 (3H, s, OCH\(_3\)), 2.55 (1H, br s, O\( H \)), 1.95-1.87 and 1.79-1.71 (2 \( \times \) 1H, m, diastereotopic H2); \(^{13}\)C NMR (101 MHz, C\(_6\)D\(_6\)) \( \delta \) C 159.4, 137.0, 135.0, 130.5, 130.0, 129.0, 129.0, 128.2, 127.0, 113.8, 72.6, 67.6, 66.5, 54.4, 37.6; HRMS (ESI\(^+\)) calc. for C\(_{19}\)H\(_{22}\)NaO\(_3\) [M+Na]\(^+\) 321.1461, found 321.1460.

1-((1\(E\),3\(E\))-4-Phenylbuta-1,3-dien-1-yl)cyclohexan-1-ol, 149fa

**Procedure F:** A solution of TBAF·3H\(_2\)O (0.71 mL of a 1.0 M solution in THF, 0.710 mmol, 3.0 eq) was added tosilane 119f (50 mg, 0.238 mmol, 1.0 eq), iodide 145a (55 mg, 0.238 mmol, 1.0 eq) and allylpalladium chloride dimer (2.2 mg, 0.006 mmol, 0.025 eq) at room temperature and stirred for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et\(_2\)O (9:1→17:3) + 1% Et\(_3\)N) to give diene 145fa as a yellow oil which had completely isomerised on purification to the \( E,E \)-isomer (15 mg, 0.062 mmol, 25%).

**Procedure G** (modified): A solution of potassium trimethylsilanolate (0.52 mL of a 1.0 M solution in DME, 0.520 mmol, 2.2 eq) was added to silane 119f (50 mg, 0.238 mmol, 1.0 eq), iodide 145a (50 mg, 0.238 mmol, 1.0 eq) and bis(dibenzylideneacetone)palladium (6.9 mg, 0.012 mmol, 0.05 eq) at room temperature and stirred for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et\(_2\)O (19:1→9:1) + 1% Et\(_3\)N) to give alkene 145fa as a yellow oil which
7. Experimental

had completely isomerised on purification to the E,E-isomer (2 mg, 0.008 mmol, 3%); $R_f$ 0.10 (petrol / Et$_2$O (4:1)); IR (thin film, $\nu_{\text{max}}$ / cm$^{-1}$) 3380, 3025, 2931, 2855, 1491, 1447, 1263, 1074; $^1$H NMR (500 MHz, C$_6$D$_6$) $\delta$H 7.29 (2H, d, $J = 7.8$ Hz, H10), 7.14 (2H, t, $J = 7.8$ Hz, H11), 7.04 (1H, t, $J = 7.8$ Hz, H12), 6.72 (1H, dd, $J = 15.5$ and 10.5 Hz, H5), 6.45 (1H, d, $J = 15.5$ Hz, H6), 6.40 (1H,dd, $J = 15.3$ and 10.7 Hz, H7), 7.75 (1H, d, $J = 15.3$ Hz, H8), 1.71-1.62 (2H, m, 2 × H3), 1.53-1.46 (3H, m, 1 × H1 and 2 × H2), 1.44-1.35 (4H, m, 2 × H2 and 2 × H3), 1.19-1.10 (1H, m, H1), 0.82 (1H, br s, OH); $^{13}$C NMR (125 MHz, C$_6$D$_6$) $\delta$C 142.8, 138.0, 132.2, 129.5, 128.9, 128.3, 127.6, 126.7, 71.2, 38.2, 25.9, 22.3; HRMS (FI') calc. for C$_{16}$H$_{20}$O [M] $^+$ 228.1514, found 228.1528.

7.7 Cross Coupling of 6-Membered Cyclic Alkenylsiloxanes

(1E,3Z)-1-Phenyldec-1,3-dien-6-ol, 151aa

Procedure F: A solution of TBAF·3H$_2$O (0.62 mL of a 1.0 M solution in THF, 0.620 mmol, 3.0 eq) was added to silane 125a (50 mg, 0.208 mmol, 1.0 eq), iodide 145a (48 mg, 0.208 mmol, 1.0 eq) and allylpalladium chloride dimer (1.8 mg, 0.005 mmol, 0.025 eq) at room temperature and stirred for 48 hours. The concentrated crude was purified by flash column chromatography (petrol / Et$_2$O (9:1) + 1% Et$_3$N) to give diene 151aa as a yellow oil (32 mg, 0.124 mmol, 60%); $R_f$ 0.09 (petrol / Et$_2$O (4:1)); IR (thin film, $\nu_{\text{max}}$ / cm$^{-1}$) 3359, 3027, 2954, 2927, 2856, 1595, 1493, 1450, 1409, 1377, 1124, 1071, 1045; $^1$H NMR (500 MHz, C$_6$D$_6$) $\delta$H 7.31 (2H, d, $J = 7.7$ Hz, H1'), 7.21-7.11 (3H, m, H2' and H2), 7.05 (1H, t, $J = 7.7$Hz, H3'), 6.49 (1H, d, $J = 15.5$ Hz, H1), 6.28 (1H, app t, $J = 11.0$ Hz, H3), 5.53 (1H, dt, $J = 11.0$ and 7.7 Hz, H4), 3.52-3.47 (1H, m, H6), 2.49-2.28 (2H, m, H5), 1.45-1.37 (3H, m, 1 × H7 and H8), 1.32-1.23 (7H, m, 1 × H7, H9, H10 and H11), 1.10-1.08 (1H, m, OH), 0.90 (3H, t, $J = 7.0$ Hz, H12); $^{13}$C NMR (125 MHz, C$_6$D$_6$) $\delta$C 137.9, 133.5, 131.6, 128.9, 128.8, 128.3, 126.8,
124.6, 71.4, 37.4, 36.6, 32.3, 29.8, 26.1, 23.1, 14.4; \textbf{HRMS} (ESI\textsuperscript{+}) calc. for C\(_{18}\)H\(_{26}\)NaO [M+Na]\textsuperscript{+} 281.1876, found 281.1870.

\textbf{(3Z,5E)-1-Cyclohexyl-6-phenylhexa-3,5-dien-1-ol, 151ba}

\textbf{Procedure F:} A solution of TBAF-3H\(_2\)O (0.63 mL of a 1.0 M solution in THF, 0.630 mmol, 3.0 eq) was added to silane 125b (50 mg, 0.210 mmol, 1.0 eq), \textit{E}-iodostyrene 145a (48 mg, 0.210 mmol, 1.0 eq) and allylpalladium chloride dimer (1.8 mg, 0.005 mmol, 0.025 eq) at room temperature and the mixture stirred for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et\(_2\)O (4:1 + 1% Et\(_3\)N) to give diene 151ba as a yellow oil (29 mg, 0.113 mmol, 54%); \(R_f\) 0.12 (petrol / Et\(_2\)O (4:1)); \textbf{IR} (thin film, \(\nu_{\text{max}} / \text{cm}^{-1}\)) 3378, 3027, 2924, 2852, 1493, 1449, 1085, 1036; \(\textsf{\textbf{1H NMR}}\) (500 MHz, C\(_6\)D\(_6\)) \(\delta_H\) 7.43 (2H, d, \(J = 7.8\) Hz, H7), 7.29 (1H, dd, \(J = 15.8\) and 11.4 Hz, H5), 7.23 (2H, t, \(J = 7.8\) Hz, H8), 7.15 (1H, t, \(J = 7.8\) Hz, H9), 6.60 (1H, d, \(J = 15.8\) Hz, H6), 6.39 (1H, app t, \(J = 11.4\) Hz, H4), 5.69-5.63 (1H, m, H3), 3.39-3.34 (1H, m, H1), 2.51-2.41 (2H, m, H2), 1.98 (1H, d, \(J = 12.7\) Hz, OH), 1.86-1.77 and 1.74-1.67 (2 \(\times\) 2H, m, diastereotopic H3\textsuperscript{\*}); \(\textsf{\textbf{13C NMR}}\) (125 MHz, CDCl\(_3\)) \(\delta_C\) 138.0, 133.5, 131.6, 129.4, 128.9, 127.8, 126.8, 124.6, 75.5, 43.6, 33.5, 29.7, 28.2, 26.9, 26.7, 26.6; \textbf{HRMS} (ESI\textsuperscript{+}) calc. for C\(_{18}\)H\(_{24}\)NaO [M+Na]\textsuperscript{+} 279.1719, found 279.1723.
Procedure F: A solution of TBAF•3H2O (0.46 mL of a 1.0 M solution in THF, 0.460 mmol, 3.0 eq) was added to silane 125e (49 mg, 0.153 mmol, 1.0 eq), E-iodostyrene 145a (35 mg, 0.153 mmol, 1.0 eq) and allylpalladium chloride dimer (1.4 mg, 0.004 mmol, 0.025 eq) at room temperature and the mixture was stirred for 48 hours. The concentrated crude was purified by flash column chromatography (petrol / EtOAc (4:1) + 1% Et3N) to give alkene 151ea as a yellow oil (37 mg, 0.109 mmol, 71%); Rf 0.24 (petrol / EtOAc (4:1)); IR (thin film, νmax / cm⁻¹) 3458, 3026, 2934, 2861, 1612, 1513, 1248, 1089; ¹H NMR (400 MHz, C6D6) δH 7.39 (2H, d, J = 7.5 Hz, H9), 7.30-7.21 (5H, m, H7, H10 and H2'), 7.14 (1H, t, J = 7.5 Hz, H11), 6.88 (2H, d, J = 8.4 Hz, H3'), 6.57 (1H, d, J = 15.5 Hz, H8), 6.36 (1H, app t, J = 11.0 Hz, H6), 5.75-5.68 (1H, m, H5), 4.32 (2H, s, H1'), 4.01-3.94 (1H, m, H3), 3.59-3.54 and 3.51-3.45 (2 × 1H, m, diastereotopic H1), 3.39 (3H, s, OCH3), 2.89 (1H, br s, OH), 2.65-2.58 and 2.56-2.49 (2 × 1H, m, diastereotopic H4), 1.86-1.77 and 1.74-1.67 (2 × 1H, m, diastereotopic H2); ¹³C NMR (101 MHz, C6D6) δC 159.8, 138.0, 133.3, 131.2, 130.6, 129.4, 129.0, 128.9, 127.7, 126.8, 124.7, 114.1, 73.1, 71.1, 68.8, 54.8, 36.5, 36.5; HRMS (ESI⁺) calc. for C22H26NaO3 [M+Na]⁺ 361.1774, found 361.1764.

Procedure F: A solution of TBAF•3H2O (0.47 mL of a 1.0 M solution in THF, 0.470 mmol, 3.0 eq) was added to silane 125e (50 mg, 0.156 mmol, 1.0 eq), iodobenzene (32 mg, 0.156 mmol, 1.0 eq), and allylpalladium chloride dimer (1.4 mg, 0.004 mmol, 0.025 eq) at room temperature and the mixture was stirred for 48 hours. The concentrated crude was purified by flash column
chromatography (petrol / EtOAc (17:3) + 1% Et₃N) to give alkene 151ee as a colourless oil (46 mg, 0.147 mmol, 94%); \( R_f \) 0.18 (petrol / EtOAc (4:1)); \( \text{IR} \) (thin film, \( \nu_{\text{max}}/ \text{cm}^{-1} \)) 3435, 3012, 2935, 2861, 1612, 1513, 1248, 1087, 1034; \( ^1H \text{NMR} \) (400 MHz, \( \text{C}_6\text{D}_6 \)) \( \delta_H \) 7.41 (2H, d, \( J = 7.6 \) Hz, H7), 7.29-7.22 (4H, m, H8 and H2'), 7.16 (1H, t, \( J = 7.6 \) Hz, H9), 6.87 (2H, d, \( J = 8.6 \) Hz, H3'), 6.62 (1H, d, \( J = 12.3 \) Hz, H6), 5.93 (1H, dt, \( J = 12.3 \) and 7.3 Hz, H5), 4.16 and 4.15 (2 × 1H, d, \( J = 11.9 \) Hz, diastereotopic H1'), 3.98-3.92 (1H, m, H3), 3.52-3.47 and 3.44-3.40 (2 × 1H, m, diastereotopic H1), 3.40 (3H, s, OC\( \text{H}_3 \)), 2.93 (1H, br s, OH), 2.71-2.63 and 2.61-2.54 (2 × 1H, m, diastereotopic H4), 1.77-1.68 and 1.62-1.55 (2 × 1H, m, diastereotopic H2); \( ^{13}C \text{NMR} \) (101 MHz, \( \text{C}_6\text{D}_6 \)) \( \delta_C \) 159.8, 138.0, 130.9, 130.6, 129.4, 129.3, 129.2, 128.6, 126.9, 114.1, 73.0, 71.1, 68.7, 54.8, 37.0, 36.6; \( \text{HRMS} \) (ESI') calc. for C\( _{20} \)H\( _{24} \)NaO\( _3 \) [M+Na]⁺ 335.1618, found 335.1618.

(5Z,7E)-9-(Benzyloxy)-1-((4-methoxybenzyl)oxy)nona-5,7-dien-3-ol, 151eb

**Procedure F:** A solution of TBAF·3H\( \text{O} \) (0.51 mL of a 1.0 M solution in THF, 0.510 mmol, 3.0 eq) was added to silane 125e (54 mg, 0.169 mmol, 1.0 eq), iodide 151eb (46 mg, 0.169 mmol, 1.0 eq) and allylpalladium chloride dimer (1.4 mg, 0.004 mmol, 0.025 eq) at room temperature and stirred for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et\( _2 \)O (4:1) + 1% Et\( _3 \)N) to give diene 151eb as a pale yellow oil (26 mg, 0.071 mmol, 43%); \( R_f \) 0.23 (petrol / EtOAc (7:3)); \( \text{IR} \) (thin film, \( \nu_{\text{max}}/ \text{cm}^{-1} \)) 3031, 2920, 2858, 1616, 1466, 1330, 1248, 1175, 1096; \( ^1H \text{NMR} \) (500 MHz, \( \text{C}_6\text{D}_6 \)) \( \delta_H \) 7.30 (2H, d, \( J = 7.5 \) Hz, H11), 7.18-7.12 (4H, m, H14 and H2'), 7.08 (1H, t, \( J = 7.5 \) Hz, H13), 6.75 (2H, d, \( J = 8.4 \) Hz, H3'), 6.66-6.61 (1H, m, H7), 6.11 (1H, app t, \( J = 11.1 \) Hz, H6), 5.72 (1H, dt, \( J = 15.0 \) and 5.9 Hz, H8), 5.54-5.48 (1H, m, H5), 4.34 (2H, s, H10), 4.20 and 4.19 (2 × 1H, d, \( J = 11.6 \) Hz, diastereotopic H1'), 3.89 (2H, d, \( J = 5.9 \) Hz, H9), 3.81-3.76 (1H, m, H3), 3.44-3.41 and 3.36-3.32 (2 × 1H, m, diastereoptic H1), 3.28 (3H, s, ArOC\( \text{H}_3 \)), 2.60 (1H, d, \( J = 3.2 \) Hz, OH), 2.40-2.33 and 2.32-2.56 (2 × 1H, m, diastereotropic H4), 1.67-1.60 (2 × 1H,
m, diastereotopic H2); $^{13}$C NMR (125 MHz, C$_6$D$_6$) δ$_C$ 159.6, 139.0, 130.7, 130.5, 130.2, 129.2, 128.4, 128.3, 128.1, 127.5, 127.4, 113.9, 72.8, 72.0, 70.7, 70.4, 68.5, 54.5, 36.3, 36.1; HRMS (ESI') calc. for C$_{24}$H$_{30}$NaO$_4$ [M+Na]' 405.2036, found 405.2020.

2-((1Z,3E)-4-Phenylbuta-1,3-dien-1-yl)cyclohexan-1-ol, 151ba

![Structure of 151ba]

**Procedure F:** A solution of TBAF·3H$_2$O (0.74 mL of a 1.0 M solution in THF, 0.740 mmol, 3.0 eq) was added to silane 125b (52 mg, 0.248 mmol, 1.0 eq), iodide 145a (57 mg, 0.248 mmol, 1.0 eq) and allylpalladium chloride dimer (2.2 mg, 0.006 mmol, 0.025 eq) at room temperature and stirred for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et$_2$O (9:1→4:1) + 1% Et$_3$N) to give diene 151ba as a yellow oil (15 mg, 0.062 mmol, 25%); $R_f$ 0.10 (petrol / Et$_2$O (4:1)); IR (thin film, $\nu_{max}$/ cm$^{-1}$) 3419, 3026, 3002, 2929, 2855, 1595, 1494, 1449, 1411, 1330, 1267, 1234, 1061, 1016; $^1$H NMR (500 MHz, C$_6$D$_6$) δ$_H$ 7.27 (2H, d, $J = 7.6$ Hz, H11), 7.22 (1H, dd, $J = 15.5$ and 11.0 Hz, H9), 7.08 (2H, t, $J = 7.6$ Hz, H12), 7.01 (1H, t, $J = 7.6$ Hz, H13), 6.47 (1H, d, $J = 15.5$ Hz, H10), 6.22 (1H, app t, $J = 11.0$ Hz, H8), 5.14 (1H, app t, $J = 11.0$ Hz, H7), 3.09-3.03 (1H, m, H1), 2.54-2.47 (1H, m, H6), 2.05-2.00 (1H, m, 1 × H2), 1.64-1.55 (2H, m, 1 × H3 and 1 × H5), 1.47-1.41 (1H, m, 1 × H4), 1.38-1.30 (2H, m, 1 × H2 and 1 × H3), 1.13-0.92 (3H, m, 1 × H4, 1 × H5 and OH); $^{13}$C NMR (125 MHz, C$_6$D$_6$) δ$_C$ 137.8, 134.9, 134.0, 131.6, 128.9, 128.3, 126.9, 124.8, 73.8, 46.0, 34.2, 31.7, 25.4, 25.0; HRMS (FI') calc. for C$_{16}$H$_{20}$O [M]+ 228.1514, found 228.1566.
7.8 Iododesilylation Reactions (Chapter 3)

\((E)-1\text{-iodonor-1-en-3-ol, (E)-174a}\)

\[
\begin{array}{c}
\text{1} \\
\text{3} \\
\text{1}\text{HO}
\end{array}
\]

A solution of silane 119a (30 mg, 0.132 mmol, 1.0 eq) and iodine (170 mg, 0.670 mmol, 5.0 eq) in MeOH (0.26 mL) was stirred at room temperature for 24 hours. The mixture was then diluted with Et₂O, washed with Na₂S₂O₃ solution and brine, and dried (MgSO₄). The crude was purified by flash column chromatography (petrol / Et₂O (9:1) to give vinyl iodide \((E)-174a\) as a colourless oil (16 mg, 0.060 mmol, 45%), \(R_f\) 0.17 (petrol / Et₂O (4:1)); IR (thin film, \(\nu_{\text{max}} / \text{cm}^{-1}\)) 3314, 2955, 2926, 2856, 1607, 1465, 1168, 1041; \(^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3) \delta \ H \ 6.57 \ (1H, \text{dd, } J = 14.5 \text{ and } 6.4 \text{ Hz, H2}), \ 6.34 \ (1H, \text{dd, } J = 14.5 \text{ and } 1.1 \text{ Hz, H1}), \ 4.12-4.05 \ (1H, \text{m, H3}), \ 1.64 \ (1H, \text{ d, } J = 4.2 \text{ Hz, OH}), \ 1.56-1.49 \ (2H, \text{ m, H4}), \ 1.39-1.23 \ (8H, \text{ m, H5, H6, H7 and H8}), \ 0.88 \ (3H, \text{ t, } J = 6.8 \text{ Hz, H9}); \ \text{IRMS (Ft')} \text{ calc. for C}_9\text{H}_{17}\text{OI [M]}^+ 268.0324 \text{ found} 268.0323.

\((Z)-1\text{-iodonor-1-en-3-ol, (Z)-174a}\)

\[
\begin{array}{c}
\text{1} \\
\text{3} \\
\text{1}\text{HO}
\end{array}
\]

A solution of silane 119a (20 mg, 0.088 mmol, 1.0 eq), \(N\)-iodosuccinimide (60 mg, 0.264 mmol, 1.0 eq) and TBAF·3H₂O (0.18 mL of a 1.0 M solution in THF, 0.180 mmol, 2.0 eq) was stirred at room temperature for 24 hours. The mixture was then diluted with Et₂O, washed with Na₂S₂O₃ solution and brine, and dried (MgSO₄). The crude was purified by flash column chromatography (petrol / Et₂O (9:1) to give vinyl iodide \((E)-174a\) as a colourless oil (11 mg, 0.041 mmol, 47%); \(R_f\) 0.19 (petrol / Et₂O (4:1)); IR (thin film, \(\nu_{\text{max}} / \text{cm}^{-1}\)) 2956, 2929, 1459, 1252, 1055; \(^1\text{H NMR} \ (500 \text{ MHz, CDCl}_3) \delta \ H \ 6.34 \ (1H, \text{dd, } J = 7.7 \text{ and } 0.8 \text{ Hz, H1}), \ 6.24 \ (1H, \text{app t, } J = 7.7 \text{ Hz, H2}), \ 4.42-4.37 \ (1H, \text{ m,}}
7. Experimental

H3), 1.71 (1H, d, J = 3.6 Hz, OH), 1.66-1.52 (2H, m, H4), 1.39-1.25 (8H, m, H5, H6, H7 and H8), 0.88 (3H, t, J = 7.1 Hz, H9); 13C NMR (125 MHz, CDCl3) δC 143.5, 82.3, 74.5, 35.9, 31.8, 29.2, 25.0, 22.6, 14.1; HRMS (ESI+) calc. for C9H17INaO [M+Na]+ 291.0216 found 291.0220.

7.9 Cross Coupling of Acyclic Alkenylsiloxane

Diethyl(isopropoxy)(3-((4-methoxybenzyl)oxy)non-1-yn-1-yl)silane, S9

\[
\text{\begin{center}
\includegraphics[width=0.2\textwidth]{diagram.png}
\end{center}}
\]

p-(Methoxybenzyl)-trichloroacetimidate (1.38 g, 4.87 mmol, 1.5 eq) and scandium (III) triflate (240 mg, 0.487 mmol, 0.15 eq) were added to a solution of alcohol 115a (924 mg, 3.25 mmol, 1.0 eq) in toluene (20 mL). The reaction was stirred for 45 minutes, then quenched with NaHCO3 solution, extracted with Et2O, dried (MgSO4) and concentrated in vacuo. The crude was purified by flash column chromatography (petrol + 1% Et3N) to give S9 as a colourless oil (1.21 g, 3.00 mmol, 92%); Rf 0.29 (petrol / Et2O (19:1)); IR (thin film, νmax / cm⁻¹) 2956, 2932, 2875, 2167, 1613, 1587, 1513, 1463, 1381, 1368, 1332, 1248, 1173, 1083; 1H NMR (400 MHz, CDCl3) δH 7.29 (2H, d, J = 8.5 Hz, H12), 6.88 (2H, d, J = 8.5 Hz, H13), 4.75 and 4.45 (2 × 1H, d, J = 11.2 Hz, diastereotopic H11), 4.19 (1H, sept, J = 6.0 Hz, OCH(CH3)2), 4.08 (1H, t, J = 6.7 Hz, H3), 3.81 (3H, s, OCH3), 1.82-1.68 (2H, m, H4), 1.52-1.42 (2H, m, H5), 1.36-1.25 (6H, m, H6, H7 and H8), 1.23 (6H, d, J = 6.0 Hz, OCH(CH3)2), 1.05 (6H, t, J = 7.7 Hz, Si(CH2CH3)2), 0.89 (3H, t, J = 6.2 Hz, H9), 0.70 (4H, q, J = 7.7 Hz, Si(CH2CH3)2); 13C NMR (101 MHz, CDCl3) δC 159.4, 130.1, 129.7, 113.8, 106.0, 86.9, 70.1, 68.7, 66.2, 55.3, 35.7, 31.8, 29.0, 25.5, 25.3, 22.6, 14.1, 6.9, 6.7; HRMS (ESI+) calc. for C24H46NaO3Si [M+Na]+ 427.2639, found 427.2645.
(Z)-Diethyl(isopropoxy)(3-((4-methoxybenzyl)oxy)non-1-en-1-yl)silane, 199

Palladium on CaCO$_3$ (139 mg, 5 wt % Pd, 0.066 mmol, 0.05 eq), S9 (530 mg, 1.31 mmol, 1.0 eq) and quinoline (31 μL, 0.262 mmol, 0.2 eq) in toluene (7 mL) were stirred under an atmosphere of hydrogen for three hours before the reaction mixture was filtered through Celite$^\text{®}$ and concentrate. The crude (92:8 Z:E) was purified by flash column chromatography (petrol + 1% Et$_3$N) to give 199 as a colourless oil (458 mg, 1.13 mmol, 86%, 93:7 Z:E (up to 97% Z in some fractions)); $R_f$ 0.33 (petrol / Et$_2$O (19:1)); IR (thin film, $\nu_{\text{max}}$ / cm$^{-1}$) 2956, 2931, 2874, 1613, 1513, 1463, 1368, 1301, 1246, 1172, 1123, 1081, 1026; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 7.26 (2H, d, $J = 8.5$ Hz, H12), 6.87 (2H, d, $J = 8.5$ Hz, H13), 6.33 (1H, dd, $J = 14.7$ and 9.1 Hz, H2), 5.63 (1H, d, $J = 14.7$ Hz, H1), 4.52 \text{ and } 4.33 (2 \times 1H, d, J = 11.3 Hz, diastereotopic H11), 4.32-4.18 (1H, m, H3), 4.04 (1H, sept, $J = 6.0$ Hz, OCH(CH$_3$)$_2$), 3.80 (3H, s, OCH$_3$), 1.68-1.59 (1H, m, 1 × H4 and 1 × H5), 1.40-1.26 (7H, m, 1 × H5, H6, H7 and H8), 1.18-1.15 (6H, m, OCH(CH$_3$)$_2$), 0.99 and 0.98 (2 × 3H, t, $J = 7.6$ Hz, diastereotopic Si(CH$_2$CH$_3$)$_2$), 0.89 (3H, t, $J = 7.2$ Hz, H9), 0.67 (4H, q, $J = 7.6$ Hz, Si(CH$_2$CH$_3$)$_2$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$C 159.0, 152.1, 131.4, 129.2, 127.5, 113.7, 79.3, 70.1, 65.3, 55.3, 36.0, 31.9, 29.5, 25.9, 25.5, 22.7, 14.1, 7.0, 6.9; HRMS (ESI$^+$) calcd. for C$_{23}$H$_{42}$NaO$_3$Si [M+Na]$^+$ 429.2795, found 429.2780.
1-Methoxy-4-(((1E,3Z)-1-phenylundeca-1,3-dien-5-yl)oxy)methyl)benzene, 200

![Chemical Structure](image)

**Procedure F:** A solution of TBAF·3H₂O (0.37 mL of a 1.0 M solution in THF, 0.370 mmol, 3.0 eq) was added to acyclic silane 199 (50 mg, 0.123 mmol, 1.0 eq, 94:6 Z:E), iodide 145a (28 mg, 0.123 mmol, 1.0 eq) and allylpalladium chloride dimer (1.1 mg, 0.003 mmol, 0.025 eq) at room temperature and stirred for 24 hours. The concentrated crude was purified by flash column chromatography (petrol) to give diene 200 as a yellow oil (8 mg, 0.022 mmol, 18%, 85:15 Z,E:E,E);

- **R_f** 0.24 (petrol / Et₂O (19:1)); **IR** (thin film, ν max / cm⁻¹) 2929, 2857, 1612, 1511, 1464, 1301, 1246, 1173, 1072, 1037; **¹H NMR** (500 MHz, C₆D₆) δH 7.32 (2H, d, J = 7.8 Hz, H13), 7.28 (2H, d, J = 7.2 Hz, o-Ar H), 7.15-7.10 (3H, m, m-Ar H and H2), 7.04 (1H, t, J = 7.2 Hz, p-Ar H), 6.82 (2H, d, J = 7.8 Hz, H14), 6.47 (1H, d, J = 15.6 Hz, H1), 6.32 (1H, app t, J = 10.5 Hz, H3), 5.52 (1H, app t, J = 10.5 Hz, H4), 4.69 and 4.39 (2 × 1H, d, J = 11.4 Hz, diastereotopic H12), 4.47-4.43 (1H, m, H5), 3.31 (3H, s, OCH₃), 1.92-1.83 and 1.68-1.61 (2 × 1H, m, diastereotopic H6), 1.57-1.40 (2H, m, H7), 1.32-1.21 (6H, m, H8, H9 and H10), 0.86 (3H, t, J = 7.0 Hz, H11); **¹³C NMR** (125 MHz, C₆D₆) δC 159.7, 137.6, 134.4, 133.7, 132.0, 131.6, 129.8, 129.4, 128.9, 126.9, 124.4, 114.1, 73.7, 69.7, 54.7, 35.2, 32.2, 29.8, 25.8, 23.0, 14.3; **HRMS** (ESI⁺) calc. for C₂₅H₃₂NaO₂ [M+Na]⁺ 387.2295, found 387.2286.

### 7.10 ¹H NMR Protodesilylation Experiments

¹H NMR spectroscopic studies of protodesilylation were conducted on a Bruker AVB400. Silane (0.25 mmol, 1.0 eq) was added to an NMR tube, followed by d₈-THF (0.75 mL), and water (22.5 μL, 2.50 mmol, 10 eq) added as appropriate. TBAF·3H₂O or KOSiMe₃ (see main text for eq) was weighed out in a small vial. ¹H NMR spectra were recorded of mixtures in the absence of activator before the start of each experiment. The contents of the NMR tube (silane, THF, water) were tipped...
into the vial containing the activator and then transferred back into the NMR tube immediately by pipette. The sample was then submitted for $^1$H NMR spectral acquisitions at 5, 10, 15, 20, 25, 30, 40, 50, and 60 minutes, with additional spectra recorded approximately every 30 minutes after this time. Spectra were automatically phased by the Topspin programme and manually integrated as described below.

119a: peak at 6.88 ppm (H’) integrated. 201: peak at 6.22 ppm (H’) integrated. 150a: peaks overlapped with those of 119a and 201, hence peak at 5.87 ppm, which contained 1H from 119a (H) and 1H from 150a (H’) was integrated, and the value subtracted from that obtained from the peak at 6.88 ppm.

119a: peak at 6.88 ppm (H’) integrated. 202: peak at 6.33 ppm (H’) integrated. 150a: peaks overlapped with those of 119a and 202, hence peak at 5.87 ppm, which contained 1H from 119a (H) and 1H from 150a (H’) was integrated, and the value subtracted from that obtained from the peak at 6.88 ppm.

125a: peak at 6.74 ppm (H’) integrated. 203: peak at 6.23 ppm (H’) integrated.

125a: peak at 6.74 ppm (H’) integrated. 204: peak at 6.22 ppm (H’) integrated.
7.11 Synthesis and Use of Cyclic Dimethyl- and Diisopropylsiloxanes

**Dimethyl(diethylamino)chlorosilane, 224**

\[ \text{Me}_2\text{SiCl(NEt}_2\text{)} \]

To a solution of dichlorodimethylsilane (10.0 mL, 82.9 mmol, 1.0 eq) and Et\(_3\)N (12.6 mL, 91.2 mmol, 1.1 eq) in anhydrous THF (10 mL) at 0 ºC was added a solution of Et\(_2\)NH (8.7 mL, 82.9 mmol, 1.0 eq) in THF (10 mL) over two hours. The mixture was stirred at room temperature for 18 hours before the solvent was removed *in vacuo* and the crude redissolved in anhydrous pentane, filtered through Celite\textsuperscript{®} under nitrogen, washing with anhydrous pentane and concentrated *in vacuo*. The crude was then distilled under vacuum to afford the title compound as a colourless oil (6.33 g, 38.2 mmol, 46%); bp 78-86 ºC, 110 mbar (lit.\textsuperscript{247} 82-85 ºC, 90 mmHg); \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta_H 0.90 (4\text{H, q, } J = 7.0 \text{ Hz, N(CH}_2\text{CH}_3\text{)}_2\), 1.05 (6\text{H, t, } J = 7.0 \text{ Hz, N(CH}_2\text{CH}_3\text{)}_2\), 0.47 (6\text{H, s, Si(CH}_3\text{)}_2\); \(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta_C 37.9, 13.3, 0.0\).

The spectroscopic data were found to be in agreement with that reported by Beignet and co-workers.\textsuperscript{247}

**Dimethyl(diethylamino)ethynylsilane, 225**

![Chemical structure](image)

Ethynylmagnesium bromide (223 mL of a 0.5 M solution in THF, 111 mmol, 1.1 eq) was added dropwise to dimethyl(diethylamino)chlorosilane (16.8 g, 101 mmol, 1.0 eq) at -78 ºC, then stirred at room temperature for three hours, and refluxed for three hours. A mini distillation head was connected to the reaction vessel, and THF removed by distillation. The crude redissolved in anhydrous pentane, filtered through Celite\textsuperscript{®} under nitrogen, washing with anhydrous pentane and concentrated *in vacuo*. The crude oil was then distilled under at 500 mbar to produced two fractions.
containing silane 225 (1st fraction: bp 70-108 °C, 3.53 g, 45 wt% 225 with THF, 10.2 mmol, 10%. 2nd fraction: bp 110-120 °C, 8.32 g, 85 wt% 225 with THF, 45.5 mmol, 45%; lit.115 139-140 °C, 750 mmHg); \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta_H 2.85 (4H, q, J = 7.0 \text{ Hz}, \text{N(CH}_2\text{CH}_3)_2), 2.35 (1H, s, \text{CCCH}), 1.01 (6H, t, J = 7.0 \text{ Hz}, \text{N(CH}_2\text{CH}_3)_2), 0.23 (6H, s, \text{Si(CH}_3)_2); \( ^{13}C \) NMR (101 MHz, CDCl\(_3\)) \( \delta_C 91.5, 90.2, 40.1, 15.5, 0.0. \) The spectroscopic data were found to be in agreement with that reported by Chan and co-workers.115

**Ethynyl(isopropoxy)dimethylsilane, 223**

![Ethynyl(isopropoxy)dimethylsilane, 223](image)

Prepared according to a modified literature procedure.115 Silane 225 (11.9 g, 73 wt%, 55.8 mmol, 1.0 eq) and isopropyl alcohol (4.2 mL, 55.8 mmol, 1.0 eq) were stirred in a round bottomed flask with a distillation head attached at 80 °C for 24 hours. The temperature was then increased to 100 °C and the mixture was heated for another 96 hours. The distillate was collected and analyzed.

2nd fraction: bp 84-110 °C, 9.34 g, 80 wt% 223 with Et\(_2\)NH, THF, 52.5 mmol, 94%); \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta_H 4.03 (1H, \text{sept}, J = 6.1 \text{ Hz}, \text{OCH(CH}_3)_2), 2.29 (1H, s, \text{CCCH}), 1.08 (6H, d, J = 6.1 \text{ Hz}, \text{OCH(CH}_3)_2), 0.15 (6H, s, \text{Si(CH}_3)_2); \( ^{13}C \) NMR (101 MHz, CDCl\(_3\)) \( \delta_C 92.3, 87.8, 65.7, 24.9, 0.0. \) The spectroscopic data were found to be in agreement with that reported by Kinoshita and co-workers.271

**3-(Benzzyloxy)propan-1-ol, S10**

![3-(Benzzyloxy)propan-1-ol, S10](image)

1,3-Propanediol (1.0 mL, 13.8 mmol, 1.0 eq) was added dropwise to a suspension of sodium hydride (610 mg, 60 wt% in mineral oil, 15.2 mmol, 1.1 eq) and tetrabutylammonium iodide (25 mg, 0.069 mol) in THF (50 mL). The mixture was stirred for 2 hours at 80 °C, then cooled to room temperature and the solvent was evaporated. The residue was purified by column chromatography.
mmol, 0.005 eq) in THF (50 mL) at 0°C and stirred for 30 minutes. Benzyl bromide (1.8 mL, 15.2 mmol, 1.1 eq) was added, the mixture warmed to room temperature and stirred for 48 hours before it was quenched with water, extracted three times with Et₂O, dried (Na₂SO₄) and concentrated. The crude was purified via flash column chromatography (petrol / EtOAc (4:1 → 1:1)) to give S10 as a colourless oil (1.10 g, 6.62 mmol, 48%); Rf 0.36 (Et₂O); ¹H NMR (400 MHz, CDCl₃) δH 7.41-7.29 (5H, m, H₅, H₆ and H₇), 4.56 (2H, s, H₄), 3.84-3.78 (2H, m, H₁), 3.69 (2H, t, J = 5.8 Hz, H₃), 2.52 (1H, br s, OH), 1.90 (2H, quin, J = 5.8 Hz, H₂); ¹³C NMR (101 MHz, CDCl₃) δC 138.1, 128.5, 127.7, 127.7, 73.3, 69.3, 61.8, 32.2; LRMS (ESI⁺) calc. for C₁₀H₁₄O₂Na [M+Na]⁺ 189.1 found 189.1.

The spectroscopic data was found to be in agreement with that reported by Chouhan and co-workers.²⁷²

3-(Benzyloxy)propanal, S11

Dimethylsulfoxide (3.2 mL, 45.1 mmol, 7.0 eq) was added to SO₃·pyridine (3.07 g, 19.3 mmol, 3.0 eq) in DCM (30 mL) and stirred for 20 minutes before diethylisopropyl amine (5.6 mL, 32.1 mmol, 5.0 eq) and alcohol S10 (1.07 g, 6.44 mmol, 1.0 eq) were added via cannula in DCM (2 mL). The mixture was stirred for three hours, quenched with NH₄Cl solution, extracted three times with DCM, dried (Na₂SO₄) and concentrated. The crude was purified via flash column chromatography (petrol / Et₂O (7:3)) to give S11 as a colourless oil (856 mg, 5.21 mmol, 81%); Rf 0.31 (petrol / Et₂O (7:3)); ¹H NMR (400 MHz, CDCl₃) δH 9.84 (1H, t, J = 1.8 Hz, H₁), 7.42-7.31 (5H, m, H₅, H₆ and H₇), 4.57 (2H, s, H₄), 3.85 (2H, t, J = 6.0 Hz, H₃), 2.74 (2H, dd, J = 6.0 and 1.8 Hz, H₂); ¹³C NMR (101 MHz, CDCl₃) δC 201.2, 137.9, 128.4, 127.8, 127.7, 73.3, 63.9, 43.9.

The spectroscopic data was found to be in agreement with that reported by Willwacher and co-workers.²⁷³
5-(Benzyloxy)-1-(isopropoxydimethylsilyl)pent-1-yn-3-ol, 227

Procedure A (modified): n-Butyllithium (2.0 mL of a 2.5 M solution in hexanes, 5.00 mmol, 1.1 eq), silyl alkyne 223 (894 mg, 80 wt%, 5.00 mmol, 1.1 eq) in THF (20 mL) and aldehyde S10 (750 mg, 4.57 mmol, 1.0 eq) were stirred at -78 °C for 24 hours. The reaction was quenched with pH 7 phosphate buffer solution, extracted three times with Et₂O, dried (Na₂SO₄) and concentrated to give 227 as a colourless oil that was unstable to silica and was used without further purification (840 mg, ~2.74 mmol, ~60%); a sample was purified via flash column chromatography (petrol / EtOAc (4:1→3:2) + 1% Et₃N); R_f 0.30 (petrol / Et₂O (3:2)); IR (thin film, ν<sub>max</sub>/ cm⁻¹) 3420, 2969, 2929, 2869, 2171, 1496, 1454, 1381, 1254, 1027; ^1H NMR (400 MHz, CDCl₃) δ_H 7.38-7.27 (5H, m, H7, H8 and H9), 4.65-4.60 (1H, m, H3), 4.57-4.49 (2H, m, H6), 4.13 (1H, sept, J = 6.1 Hz, OCH(CH₃)₂), 3.91-3.84 and 3.72-3.66 (2 × 1H, m, diastereotopic H5), 3.06 (1H, d, J = 6.4 Hz, OCH(CH₃)₂), 2.15-2.06 and 2.00-1.92 (2 × 1H, m, diastereotopic H4), 1.19 (6H, d, J = 6.1 Hz, OCH(CH₃)₂), 0.25 (9H, s, Si(CH₃)₃); ^13C NMR (101 MHz, CDCl₃) δ_C 137.2, 127.9, 127.2, 127.0, 105.2, 87.1, 72.8, 67.1, 65.4, 61.1, 36.0, 24.8, 0.0; HRMS (ESI⁺) calc. for C₁₇H₂₆O₃NaSi [M+Na]⁺ 329.1549, found 329.1539.

5-(Benzyloxy)-1-(isopropoxydimethylsilyl)pent-1-yn-3-ol, 226

Procedure E (modified): Palladium on CaCO₃ (17 mg, 5 wt % Pd, 0.008 mmol, 0.05 eq), silane 227 (50 mg, 0.163 mmol, 1.0 eq) and quinoline (3.8 μL, 0.033 mmol, 0.2 eq) in toluene (1.6 mL) were stirred under a hydrogen atmosphere for 12 hours, followed by filtration and concentration in vacuo. The crude was redissolved in Et₂O, washed three times with 1 M HCl, once with 1 M NaOH, dried (MgSO₄) and concentrated to give oxasilole 226 as a colourless oil that was extremely unstable to silica gel (22 mg, ~0.105 mmol, ~64%, 4:1 Z:E); IR (thin film, ν<sub>max</sub>/ cm⁻¹) 2957, 2928, 2858, 1466,
1379, 1338, 1252, 1172, 1122, 1023; \textit{^1}H NMR (400 MHz, CDCl$_3$) $\delta$H 7.38-7.27 (5H, m, H9, H10 and H11), 6.86 (1H, dd, $J = 10.5$ and 1.3 Hz, H4), 6.02 (1H, dd, $J = 10.5$ and 2.1 Hz, H3), 4.85-4.81 (1H, m, H5), 4.56-4.49 (2H, m, H8), 3.76-3.58 (2H, m, H7), 2.00-1.92 and 1.76-1.66 (2 × 1H, m, diastereotopic H4), 0.24 (6H, s, Si(CH$_3$)$_2$); \textit{^13}C NMR (101 MHz, CDCl$_3$) $\delta$C 152.9, 137.9, 127.9, 127.8, 127.1, 126.1, 79.7, 72.4, 66.6, 37.0, 0.0; HRMS (ESI$^+$) calc. for C$_{14}$H$_{20}$O$_2$NaSi [M+Na]$^+$ 271.11248, found 271.11192.

1-(Isopropoxydimethylsilyl)non-1-yn-3-ol, 228

\begin{center}
\includegraphics[width=0.5\textwidth]{figure}
\end{center}

**Procedure A** (modified): \textit{n}-Butyllithium (2.2 mL of a 2.5 M solution in hexanes, 5.50 mmol, 1.1 eq), silyl alkyne 114 (1.00 g, 80 wt%, 5.00 mmol, 1.1 eq) in THF (15 mL) and heptaldehyde (0.71 mL, 5.00 mmol, 1.0 eq) were stirred at -78 °C for 5 hours. The reaction was quenched with pH 7 phosphate buffer solution, extracted three times with Et$_2$O, dried (Na$_2$SO$_4$) and concentrated to give 228 as a pale yellow oil that was unstable to silica and was used without further purification (887 mg, ~3.46 mmol, ~69%); a sample was purified via flash column chromatography (petrol / Et$_2$O (9:1→4:1) + 1% Et$_3$N); $R_f$ 0.23 (petrol / Et$_2$O (4:1)); IR (thin film, $\nu_{\text{max}}$ cm$^{-1}$) 3366, 2958, 2929, 2859, 2171, 1465, 1380, 1369, 1334, 1254, 1173, 1121, 1031; \textit{^1}H NMR (400 MHz, CDCl$_3$) $\delta$H 4.36 (1H, t, $J = 6.6$ Hz, H3), 4.13 (1H, sept, $J = 6.1$ Hz, OCH(CH$_3$)$_2$), 2.08 (1H, br s, OH), 1.73-1.65 (2H, m, H4), 1.49-1.39 (2H, m, H5), 1.36-1.25 (6H, m, H6, H7 and H8), 1.19 (6H, d, $J = 6.1$ Hz, OCH(CH$_3$)$_2$), 0.88 (3H, t, $J = 6.9$ Hz, H9), 0.25 (9H, s, Si(CH$_3$)$_3$); \textit{^13}C NMR (101 MHz, CDCl$_3$) $\delta$C 106.0, 87.0, 65.4, 63.2, 37.0, 31.1, 28.2, 24.8, 24.4, 21.9, 13.5, 0.0; HRMS (ESI$^+$) calc. for C$_{14}$H$_{28}$O$_2$NaSi [M+Na]$^+$ 279.17508, found 279.17462.
5-Hexyl-2,2-dimethyl-2,5-dihydro-1,2-oxasilole, 229

Procedure E (modified): Palladium on CaCO₃ (210 mg, 5 wt % Pd, 0.097 mmol, 0.05 eq), silane 228 (500 mg, 1.94 mmol, 1.0 eq) and quinoline (46 μL, 0.390 mmol, 0.2 eq) in THF (19 mL) were stirred under a hydrogen atmosphere for 25 minutes, followed by filtration and concentration in vacuo. The crude was redissolved in Et₂O, washed three times with 1 M HCl, once with 1 M NaOH, dried (MgSO₄) and concentrated. The crude was purified by Kugelrohr distillation (140 °C, 20 mbar) to give oxasilole 229 as a pale yellow oil that was extremely unstable to silica gel (180 mg, 0.907 mmol, 48%); IR (thin film, ν / cm⁻¹) 2956, 2922, 2861, 1496, 1454, 1410, 1365, 1316, 1253, 1206, 1094; ᵃH NMR (400 MHz, CDCl₃) δ(H) 6.81 (1H, d, J = 10.5 Hz, H4), 6.00 (1H, dd, J = 10.5 and 2.0 Hz, H3), 4.70-4.66 (1H, m, H5), 1.64-1.52 (2H, m, H6), 1.49-1.24 (8H, m, H7, H8, H9 and H10), 0.89-0.85 (3H, m, H11), 0.24 and 0.22 (2 × 3H, s, Si(CH₃)₂); ᵃC NMR (101 MHz, CDCl₃) δ(C) 153.0, 126.0, 82.4, 36.7, 31.2, 28.8, 24.6, 21.9, 13.5, 0.0; HRMS (FT⁺) calc. for C₁₁H₂₂OSi [M]⁺ 198.1440, found 198.1500.

(But-3-en-1-yloxy)methyl)benzene, S12

3-Buten-1-ol (1.0 mL, 11.6 mmol, 1.0 eq) was added dropwise to a suspension of sodium hydride (556 mg, 60 wt% in mineral oil, 13.9 mmol, 1.1 eq) in THF (50 mL) at 0°C and stirred for 30 minutes. Benzyl bromide (1.7 mL, 13.9 mmol, 1.1 eq) was added, the mixture warmed to room temperature and stirred for 48 hours before it was quenched with water, extracted three times with Et₂O, dried (Na₂SO₄) and concentrated. The crude was purified via flash column chromatography (petrol / Et₂O (100:1 → 19:1)) to give S12 as a colourless oil (872 mg, 5.38 mmol, 46%); Rf 0.41 (petrol / Et₂O (9:1)); ᵃH NMR (400 MHz, CDCl₃) δ(H) 7.39-7.28 (5H, m, ArH), 5.92-5.81 (1H, m,
7. Experimental

H3), 5.16-5.05 (2H, m, H4 and H5), 4.54 (2H, s, OCH2Ar), 3.57-3.53 (2H, m, H1), 2.44-2.38 (2H, m, H2); 13C NMR (101 MHz, CDCl3) δc 138.5, 135.3, 128.4, 127.7, 127.6, 116.4, 72.9, 69.6, 34.3; LRMS (ESI+) calc. for C11H14ONa [M+Na]+ 185.1 found 185.1.

The spectroscopic data was found to be in agreement with that reported by Yabe and co-workers.274

2-(2-(Benzyloxy)ethyl)oxirane, S13

\[
\begin{align*}
&\text{m-Chloroperbenzoic acid (1.59 g, 70 wt \%, 6.44 mmol, 1.2 \text{ eq}) was added to a solution of alkene S12} \\
&(870 mg, 5.36 mmol, 1.0 \text{ eq}) in DCM (15 mL) at 0 °C, warmed to room temperature and stirred for} \\
&16 \text{ hours. The mixture was then washed sequentially with NaHCO}_3, \text{ Na}_2\text{S}_2\text{O}_3, \text{ NaHCO}_3, \text{ brine and} \\
dried (\text{Na}_2\text{SO}_4). \text{ The concentrated crude was purified via flash column chromatography (petrol / Et}_2\text{O} \\
(4:1)) to give S13 as a colourless oil (776 mg, 4.35 mmol, 81%); R_f 0.37 (petrol / EtOAc (4:1));}
\end{align*}
\]

1H NMR (400 MHz, CDCl3) δh 7.38-7.27 (5H, m, H6, H7 and H8), 4.54 (2H, s, H5), 3.68-3.60 (2H, m, H3), 3.11-3.06 (1H, m, H2), 2.82-2.78 and 2.56-2.52 (2 × 1H, m, H1), 1.98-1.89 and 1.83-1.75 (2 × 1H, m, H3); 13C NMR (101 MHz, CDCl3) δc 138.3, 128.4, 127.7, 127.7, 73.1, 67.1, 50.1, 47.1, 33.0; LRMS (ESI+) calc. for C11H14O2Na [M+Na]+ 201.1, found 201.1.

The spectroscopic data was found to be in agreement with that reported by Taber and co-workers.275

Ethynylidiisopropylsilane, 231

\[
\begin{align*}
&\text{Ethynylmagnesium bromide (13.0 mL of a 0.5 M solution in THF, 6.44 mmol, 1.1 \text{ eq}) was added} \\
&\text{slowly to diisopropylchlorosilane (1.0 mL, 5.86 mmol, 1.0 \text{ eq}) at -78 °C before warming to room} \\
temperature and stirring for 20 hours. The mixture was then quenched with water, extracted three} \\
\end{align*}
\]
times with Et₂O, dried (Na₂SO₄) and concentrated to give silane 231 as a colourless oil that was used without further purification (1.02 g, 72 wt% with THF, ~5.23 mmol, ~89%); ¹H NMR (400 MHz, CDCl₃) δ_H 3.70 (1H, br s, SiH), 2.40 (1H, s, CCH), 1.11-1.00 (14H, m, Si(CH(CH₃)₂)₂); ¹³C NMR (101 MHz, CDCl₃) δ_C 95.7, 83.8, 18.3, 18.1, 10.5.

The spectroscopic data were found to be in agreement with that reported by Sharma and co-workers.²⁷⁶

**Ethynyl(isopropoxy)diisopropylsilane, 232**

\[
\text{\begin{center}
\includegraphics[width=0.2\textwidth]{image}
\end{center}}
\]

\_N-Bromosuccinimide (812 mmol, 4.56 mmol, 1.0 eq) was slowly added portionwise to a solution of silane 231 (1.00 g, 4.56 mmol, 1.0 eq) in DCM (4.5 mL) at 0 °C, then warmed to room temperature over 20 minutes. A solution of isopropyl alcohol (0.35 mL, 4.56 mmol, 1.0 eq), Et₃N (0.38 mL, 4.56 mmol, 1.0 eq) and DMAP (1 crystal) in DCM (4.5 mL) was added via cannula and the mixture stirred for 16 hours. The crude was concentrated and purified via flash column chromatography (petrol + 1% Et₃N) to give silane 232 as a colourless oil (515 mg, 2.60 mmol, 57%) R_f 0.26 (petrol); IR (thin film, ν_max / cm⁻¹) 3295, 2956, 2868, 2037, 1465, 1386, 1008; ¹H NMR (400 MHz, CDCl₃) δ_H 4.21 (1H, sept, J = 6.1 Hz, OCH(CH₃)₂), 2.41 (1H, s, CCH), 1.21 (6H, d, J = 6.1 Hz, OCH(CH₃)₂), 1.10-1.00 (14H, m, Si(CH(CH₃)₂)₂); ¹³C NMR (101 MHz, CDCl₃) δ_C 94.3, 85.1, 66.7, 25.4, 17.0, 16.9, 13.0; HRMS (FI⁺) calc. for C₁₁H₂₂OSi [M⁺] 198.1440, found 198.1445.
1-(Isopropoxydiisopropylsilyl)-5-phenylpent-1-yn-3-ol, 233

![Chemical structure of 1-(Isopropoxydiisopropylsilyl)-5-phenylpent-1-yn-3-ol, 233](image)

**Procedure A** (modified): *n*-Butyllithium (1.0 mL of a 2.5 M solution in hexanes, 2.50 mmol, 1.1 eq), silyl alkyne 232 (500 mg, 2.50 mmol, 1.1 eq) in THF (25 mL) and 3-phenyl propanal (0.30 mL, 2.27 mmol, 1.0 eq) gave, after purification via flash column chromatography (petrol / Et₂O (9:1→4:1) + 1% Et₃N), propargylic alcohol 233 as a colourless oil (689 mg, 2.07 mmol, 91%); $R_f$ 0.32 (petrol / Et₂O (4:1)); IR (thin film, $\nu_{\text{max}}$ / cm⁻¹) 3463, 2944, 2888, 2866, 2166, 1496, 1463, 1381, 1333, 1242, 1172, 1123, 1031; $^1$H NMR (400 MHz, CDCl₃) $\delta$H 7.33 (2H, m, H7), 7.24 - 7.19 (3H, m, H6 and H8), 4.41 (1H, t, $J = 6.6$ Hz, H3), 4.20 (1H, sept, $J = 6.2$ Hz, OCH(CH₃)₂), 2.83 (2H, t, $J = 7.6$ Hz, H5), 2.12-1.98 (2H, m, H4), 1.88 (1H, br s, OH), 1.21 (6H, d, $J = 6.2$ Hz, OCH(CH₃)₂), 1.06 (12H, d, $J = 5.8$ Hz, Si(CH(CH₃)₂)₂), 1.03-0.91 (2H, m, Si(CH(CH₃)₂)₂); $^{13}$C NMR (101 MHz, CDCl₃) $\delta$C 141.3, 128.5, 128.5, 126.1, 107.9, 85.1, 66.6, 62.2, 39.4, 31.4, 25.5, 17.2, 17.1, 13.1; HRMS (ESI⁺) calc. for C₂₀H₃₂O₂NaSi [M+Na]⁺ 355.20638, found 355.20547.

2,2-Diisopropyl-5-phenethyl-2,5-dihydro-1,2-oxasilole, 234

![Chemical structure of 2,2-Diisopropyl-5-phenethyl-2,5-dihydro-1,2-oxasilole, 234](image)

**Procedure E** (modified): Palladium on CaCO₃ (243 mg, 5 wt % Pd, 0.114 mmol, 0.05 eq), silane 233 (760 mg, 2.29 mmol, 1.0 eq) and quinoline (44 μL, 0.457 mmol, 0.2 eq) in toluene (23 mL) were stirred under a hydrogen atmosphere for 20 minutes, followed by filtration and concentration in vacuo. The crude was redissolved in MeOH and filtered through a plug of K₂CO₃, diluted with Et₂O, washed with water 3 times, dried (MgSO₄) and concentrated. The crude was purified via rapid flash column chromatography (petrol / Et₂O (19:1)) to give oxasilole 234 as a colourless oil (508 mg, 1.85 mmol, 81%); $R_f$ 0.41 (petrol / Et₂O (19:1)); IR (thin film, $\nu_{\text{max}}$ / cm⁻¹) 2941, 2863, 1556, 1496, 1462, 1122, 1030; $^1$H NMR (400 MHz, CDCl₃) $\delta$H 7.32 (2H, m, H9), 7.25-7.18 (3H, m, H8 and...
H10), 6.94 (1H, d, J = 10.4 Hz, H4), 5.97 (1H, dd, J = 14.4 and 2.0 Hz, H3), 4.70-4.65 (1H, m, H5),
2.89-2.82 and 2.80-2.71 (2 × 1H, m, H7), 1.95-1.86 and 1.81-1.72 (2 × 1H, m, H6), 1.09-0.97 (14H,
m, Si(CH(CH₃)₂)₂ and Si(CH(CH₃)₂)₂); ¹³C NMR (101 MHz, CDCl₃) δC 154.5, 142.4, 128.5, 128.4,
125.7, 122.9, 82.9, 39.3, 32.2, 17.6, 17.5, 17.1, 17.1, 13.1, 12.4; HRMS (ESI⁺) calc. for C₁₇H₂₇OSi
[M+H]⁺ 275.18257, found 275.18208.

(4Z,6E)-1,7-Diphenylocta-4,6-dien-3-ol, 235

Procedure F: A solution of TBAF•3H₂O (0.45 mL of a 1.0 M solution in THF, 0.450 mmol, 3.0 eq)
was added to silane 234 (41 mg, 0.151 mmol, 1.0 eq), E-iodostyrene 145a (35 mg, 0.151 mmol, 1.0
eq) and allylpalladium chloride dimer (1.4 mg, 0.004 mmol, 0.025 eq) at room temperature and
stirred for 24 hours. The concentrated crude was purified by flash column chromatography (petrol /
Et₂O (1:0→17:3) + 1% Et₃N) to give alkene 235 as a yellow oil (13 mg, 0.049 mmol, 33%).

Procedure G: A solution of potassium trimethylsilanolate (0.90 mL of a 0.42 M solution in DME,
0.378 mmol, 2.5 eq) was added to silane 234 (41 mg, 0.151 mmol, 1.0 eq), E-iodostyrene 145a (35
mg, 0.151 mmol, 1.0 eq), water (27 μL, 1.51 mmol, 10 eq) and bis(dibenzylideneacetone)palladium
(4.6 mg, 0.008 mmol, 0.05 eq) at room temperature and stirred at 60 °C for 24 hours. The
concentrated crude was purified by flash column chromatography (petrol / Et₂O (9:1→17:3) + 1%
Et₃N) to give alkene 235 as a yellow oil (10 mg, 0.038 mmol, 25%); Rf 0.13 (petrol / Et₂O (4:1)); IR
(thin film, νmax / cm⁻¹) 3360, 3081, 3060, 3026, 2932, 2855, 1602, 1494, 1452, 1382, 1304, 1155,
1043; ¹H NMR (500 MHz, C₆D₆) δH 7.29-7.05 (10H, m, ArH), 6.95 (1H, ddd, J = 15.5, 11.1 and 1.1
Hz, H6), 6.42 (1H, d, J = 15.5 Hz, H7), 6.07 (1H, app t, J = 11.1 Hz, H5), 5.42-5.38 (1H, m, H4),
4.58-4.50 and 4.50-4.45 (1H, m, H3), 2.67-2.63 (2H, m, H1), 1.94-1.85 and 1.82-1.73 (2 × 1H, m,
diastereotopic H2), 1.32 (1H, br s, OH); ¹³C NMR (125 MHz, C₆D₆) δC 141.8, 137.2, 137.2, 134.8,
(Z)-1,5-Diphenylpent-1-en-3-ol, 236

Procedure F: A solution of TBAF•3H₂O (0.33 mL of a 1.0 M solution in THF, 0.330 mmol, 3.0 eq) was added to silane 234 (30 mg, 0.109 mmol, 1.0 eq), iodobenzene (12 µL, 0.109 mmol, 1.0 eq) and allylpalladium chloride dimer (1.1 mg, 0.003 mmol, 0.025 eq) at room temperature and stirred for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et₂O (9:1→17:3) + 1% Et₃N) to give alkene 236 as a yellow oil (14 mg, 0.059 mmol, 54%).

Procedure G: A solution of potassium trimethylsilanolate (0.66 mL of a 0.42 M solution in DME, 0.273 mmol, 2.5 eq) was added to silane 234 (30 mg, 0.109 mmol, 1.0 eq), iodobenzene (12 µL, 0.109 mmol, 1.0 eq), water (20 µL, 1.09 mmol, 10 eq) and bis(dibenzylideneacetone)palladium (3.5 mg, 0.006 mmol, 0.05 eq) at room temperature and stirred at 60 °C for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / Et₂O (9:1→17:3) + 1% Et₃N) to give alkene 236 as a yellow oil (10 mg, 0.041 mmol, 38%); Rf 0.19 (petrol / Et₂O (4:1)); IR (thin film, \( \nu_{\text{max}} / \text{cm}^{-1} \) ) 3342, 3060, 3026, 2928, 2863, 1494, 1454, 1029; \(^1\)H NMR (400 MHz, C₆D₆) δH 7.24-7.07 (10H, m, ArH), 6.40 (1H, d, \( J = 11.5 \text{ Hz}, \text{H1} \)), 5.62 (1H, dd, \( J = 11.5 \text{ and } 9.2 \text{ Hz}, \text{H2} \)), 4.58-4.51 (1H, m, H3), 2.70-2.66 (2H, m, H5), 1.94-1.85 and 1.82-1.73 (2 × 1H, m, diastereotopic H4), 1.23-1.13 (1H, m, OH); \(^{13}\)C NMR (101 MHz, C₆D₆) δC 141.9, 136.8, 135.3, 130.1, 128.9, 128.6, 128.3, 128.2, 127.0, 125.7, 66.5, 39.2, 31.6; HRMS (ESI⁺) calc. for C₁₇H₁₈ONa [M+Na]⁺ 261.12499 found 261.12462.
7.12 Synthesis of Natural Product Fragments

7.12.1 Synthesis of Iodide Coupling Partners

(Z)-Methyl 3-iodoacrylate, S13

\[
\begin{align*}
\text{O} & \quad \text{I} \\
\end{align*}
\]

Prepared according to a literature procedure.\(^{277}\) Sodium iodide (1.68 g, 11.2 mmol, 2.0 eq) was added to a solution of methyl propiolate (0.50 mL, 5.62 mmol, 1.0 eq) in acetic acid (3 mL) and stirred at 70 °C for 16 hours. The reaction was then diluted with Et\(_2\)O and 1 M NaOH (aq) was added (3 mL). The aqueous layer was extracted with Et\(_2\)O, and the combined organic layers washed with K\(_2\)CO\(_3\) and NaHCO\(_3\) solutions, then dried (MgSO\(_4\)) and concentrated in vacuo to give iodide S13 as a brown oil (1.20 g, ~5.62 mmol, ~100%); \(R_f\) 0.31 (petrol / Et\(_2\)O (9:1)); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta_H\) 7.49 (1H, d, J = 8.9 Hz, CHI=CHCO\(_2\)CH\(_3\)), 6.93 (1H, d, J = 8.9 Hz, CHI=CHCO\(_2\)CH\(_3\)), 3.80 (3H, s, CHI=CHCO\(_2\)CH\(_3\)); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta_C\) 165.0, 129.5, 95.2, 51.7; LRMS (ESI\(^+\)) calc. for C\(_4\)H\(_5\)INaO\(_2\) [M+Na\(^+\)] 234.9, found 234.9.

The spectroscopic data were found to be in agreement with that reported by Spino and co-workers.\(^{277}\)

(2\(E,4\)Z)-Ethyl 5-iodopenta-2,4-dienoate, S14

\[
\begin{align*}
\text{O} & \quad \text{I} \\
\end{align*}
\]

Prepared according to a literature procedure.\(^{37}\) Diisobutylaluminium hydride (6.6 mL of a 1.0 M solution in hexanes, 6.60 mmol, 1.1 eq) was added slowly over 10 minutes to a solution of iodide S13 (1.27 g, 6.00 mmol, 1.0 eq) in DCM (12 mL) at -78 °C and stirred for a further 5 minutes. Methanol (1.00 mL) was added, followed by aqueous sodium/potassium tartrate solution (24 mL)
and the mixture was warmed to room temperature. Et₂O (12 mL) was added and the reaction stirred in the dark for one hour, before being diluted with Et₂O and water, and the aqueous layer extracted with Et₂O. The combined organic extracts were washed with brine, dried (K₂CO₃) and concentrated *in vacuo*. The aldehyde obtained was used immediately in the next step without further purification.

*n*-Butyllithium (2.5 mL of a 2.5 M solution in hexanes, 6.30 mmol, 1.05 eq) was added to a solution of triethylphosphonoacetate (1.25 mL, 6.30 mmol, 1.05 eq) in THF (10 mL) at -78 °C and stirred for 30 minutes, before a THF solution of the intermediate aldehyde previously prepared was added via cannula. The mixture was stirred in the dark for two hours while warming to room temperature, and then a further hour once this had been reached. Et₂O and water were added, the aqueous phase extracted with Et₂O and the combined organic extracts washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The crude was purified by flash column chromatography (petrol / EtOAc (97:3)) to give vinyl iodide S14 as a pale orange oil (789 mg, 3.13 mmol, 52%, 99:1 *E,Z,E*; *R*₁ 0.31 (petrol / Et₂O (9:1)); \(^1\)H NMR (400 MHz, CDCl₃) \(\delta_H\) 7.41 (1H, dd, \(J = 15.3\) and 10.3 Hz, H3), 6.91 (1H, dd, \(J = 10.3\) and 7.9 Hz, H4), 6.84 (1H, d, \(J = 7.9\) Hz, H5), 6.14 (1H, d, \(J = 15.3\) Hz, H2), 4.25 (2H, q, \(J = 7.1\) Hz, \(\text{CH}_2\text{CH}_3\)), 1.33 (3H, t, \(J = 7.1\) Hz, \(\text{CH}_2\text{CH}_3\)); \(^13\)C NMR (101 MHz, CDCl₃) \(\delta_C\) 166.4, 143.0, 136.6, 125.8, 92.0, 60.7, 14.3; HRMS (FI⁺) calc. for C₇H₉IO₂ [M⁺] 251.9647, found 251.9649.

The spectroscopic data were found to be in agreement with that reported by Trost and co-workers.³⁷

\((2E, AZ)-5\text{-Iodopenta-2,4-dien-1-ol}, 246\)

Prepared according to a literature procedure.³⁷ Diisobutylaluminium hydride (7.7 mL of a 1.0 M solution in hexanes, 7.70 mmol, 2.5 eq) was added dropwise to a solution of ester S14 (780 mg, 3.10 mmol, 1.0 eq) in DCM (8 mL) at 0 °C and stirred for 50 minutes in the dark. The reaction was then quenched with aqueous sodium/potassium tartrate solution (8 mL), stirred for 5 minutes, the aqueous phase extracted with Et₂O, and the combined organic extracts dried (MgSO₄) and
concentrated in vacuo. The crude was purified by flash column chromatography (petrol / EtOAc (3:1)) to give vinyl iodide 246 as a pale yellow oil (470 mg, 2.24 mmol, 72%, 99:1 E,Z:E,E); \( R_f \) 0.10 (petrol / EtO (9:1)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta_H \) 6.76 (1H, dd, \( J = 10.3 \) and 7.4 Hz, H4), 6.44 (1H, dd, \( J = 15.3 \) and 10.3 Hz, H3), 6.29 (1H, d, \( J = 7.4 \) Hz, H5), 6.12 (1H, dt, \( J = 15.3 \) and 5.1 Hz, H2), 4.26-4.22 (2H, m, H1); \(^13\)C NMR (101 MHz, CDCl\(_3\)) \( \delta_C \) 137.6, 137.1, 130.7, 82.8, 63.1; HRMS (FI\(^+\)) calc. for C\(_5\)H\(_7\)IO [M]\(^+\) 209.9542, found 209.9542.

The spectroscopic data were found to be in agreement with that reported by Trost and co-workers.\(^{37}\)

2-Chloro-3-hydroxybenzaldehyde, 248

Prepared according to a literature procedure.\(^{204}\) Freshly prepared \( t \)-butyl hypochlorite\(^{278}\) (4.9 mL, 43 mmol, 1.05 eq) was added dropwise in the dark to 3-hydroxybenzaldehyde (5.00 g, 41 mmol, 1.0 eq) in 90% aqueous acetic acid (20 mL). The mixture was stirred for three hours, before a colourless precipitate was removed by filtration and recrystallised from a hot solution of 50% acetic acid/water to give the chlorinated product as tan-coloured crystals (2.52 g, 16.1 mmol, 39%); \( R_f \) 0.32 (petrol / EtO (1:1)); mp 136-137 °C (lit.\(^{204}\) 137-138 °C); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta_H \) 10.41 (1H, s, CHO), 7.53 (1H, dd, \( J = 7.5 \) and 1.9 Hz, H6), 7.34 (1H, t, \( J = 7.5 \) Hz, H5), 7.30 (1H, dd, \( J = 7.5 \) and 1.9 Hz, H4), 5.82 (1H, br s, OH); \(^13\)C NMR (101 MHz, CDCl\(_3\)) \( \delta_C \) 189.3, 152.1, 132.7, 128.1, 122.8, 122.1, 121.8; LRMS (ESI) calc. for C\(_7\)H\(_4\)ClO\(_2\) [\(^{35}\)ClM-H] \(^+\) 154.99, found 154.99.

The physical and spectroscopic data were found to be in agreement with that reported by Giles and co-workers.\(^{204}\)
(Z)-2-Chloro-3-(2-iodovinyl)phenol, (Z)-247

Prepared according to a modified literature procedure. Sodium bis(trimethylsilyl)amide (1.9 mL of a 2.0 M solution in THF, 3.80 mmol, 1.2 eq) was added dropwise to a solution of aldehyde 248 (500 mg, 3.19 mmol, 1.0 eq) in THF (5 mL) at -78 ºC and stirred at that temperature for 20 minutes. Meanwhile, sodium bis(trimethylsilyl)amide (1.8 mL of a 2.0 M solution in THF, 3.60 mmol, 1.1 eq) was added dropwise to a suspension of Stork-Wittig reagent [Ph₃PCH₂I⁺][I⁻] (1.86 g, 3.51 mmol, 1.1 eq) in THF (20 mL) at room temperature and stirred for 15 minutes. This solution was then cooled to -78 ºC, and the solution of deprotonated aldehyde added via cannula. The mixture was stirred at -78 ºC in the dark for 5 hours, then quenched with NaHCO₃ solution, diluted with Et₂O, and filtered through a pad of Celite®. The biphasic mixture was separated and the organic phase dried (MgSO₄) and concentrated in vacuo. The crude was purified by flash column chromatography (petrol / Et₂O (19:1)) to give vinyl iodide (Z)-247 as a yellow oil (444 mg, 1.59 mmol, 50%, >99:1 Z:E); Rf 0.23 (petrol / EtOAc (4:1)); IR (thin film, νmax / cm⁻¹) 3512, 1594, 1578, 1474, 1466, 1435, 1300, 1262, 1198, 1166, 1099, 1042; ¹H NMR (400 MHz, CDCl₃) δH 7.35 (1H, d, J = 8.6 Hz, ArCH=C,H), 7.27-7.21 (2H, m, H4 and H5), 7.04 (1H, dd, J = 6.8 and 3.0 Hz, H6), 6.79 (1H, d, J = 8.6 Hz, ArCH=CHI), 5.61 (1H, br s, OH); ¹³C NMR (101 MHz, CDCl₃) δC 151.6, 136.5, 136.4, 127.3, 121.7, 119.0, 115.8, 84.3; HRMS (ESI) calc. for C₈H₅ClIO [M-H]- 278.9079, found 278.9086.

2-Chloro-3-ethynylphenol, 249

Prepared according to a modified literature procedure. Freshly prepared sodium methoxide solution (1.8 mL of a 1.0 M solution in MeOH, 1.80 mmol, 2.5 eq) was added to iodide (Z)-247 (200
mg, 0.715 mmol, 1.0 eq) and heated to 70 ºC for 24 hours. The mixture was then quenched with NH₄Cl solution and extracted with DCM, dried (MgSO₄) and concentrated in vacuo. The crude was used in the next step without further purification as a brown oil (96 mg, ~0.629 mmol, ~88%); \( R_f \) 0.23 (petrol / EtOAc (4:1)); \( \text{IR} \) (thin film, \( \nu_{\text{max}} / \text{cm}^{-1} \)) 3510, 3293, 2103, 1578, 1462, 1439, 1288, 1251, 1188; \( \text{\^H NMR} \) (400 MHz, CDCl₃) \( \delta \)H 7.18-7.13 (2H, m, H4 and H5), 7.07-7.02 (1H, m, H6), 5.62 (1H, br s, O\( \text{H} \)), 3.38 (1H, s, C\( \equiv\text{C} \)H); \( \text{\^C NMR} \) (101 MHz, CDCl₃) \( \delta \)C 151.6, 127.7, 126.0, 122.4, 122.0, 116.9, 82.5, 79.9; \( \text{HRMS} \) (ESI) calc. for C₈H₄ClO [\(^{35}\text{Cl-M-H}\)]\(^-\) 150.9956, found 150.9955.

\( (E)\)-2-Chloro-3-(2-iodovinyl)phenol, \( (E)\)-247

\[ \text{\begin{center} \includegraphics[width=0.2\textwidth]{image.png} \end{center}} \]

Prepared according to a literature procedure.²⁰⁸ Diisobutylaluminium hydride (0.69 mL of a 1.0 M solution in hexanes, 0.690 mmol, 1.1 eq) was added dropwise to zirconocenedichloride (202 mg, 0.692 mmol, 1.1 eq), in THF (2 mL) at 0 ºC and stirred for 30 minutes before a solution of alkyne 249 (96 mg, 0.629 mmol, 1.0 eq) in THF (1.5 mL) was added via cannula. The mixture was stirred at that temperature for a further 40 minutes before cooling to -78 ºC. A solution of iodine (208 mg, 0.818 mmol, 1.3 eq) in THF (1 mL) was added via cannula and the mixture stirred for two hours, then quenched with 1 M HCl, extracted with Et₂O and washed sequentially with Na₂S₂O₃, NaHCO₃ and brine solutions. The organic layer was then dried (MgSO₄) and concentrated in vacuo. The crude was purified by flash column chromatography (petrol / Et₂O (19:1)) to give iodide \( (E)\)-247 as a colourless solid (62 mg, 0.222 mmol, 35%); \( R_f \) 0.23 (petrol / EtOAc (4:1)); \( \text{mp} \) 91-93 ºC; \( \text{IR} \) (thin film, \( \nu_{\text{max}} / \text{cm}^{-1} \)) 3339, 3056, 2921, 2850, 1571, 1463, 1356, 1288, 1181; \( \text{\^H NMR} \) (400 MHz, CDCl₃) \( \delta \)H 7.72 (1H, d, \( J = 14.8 \) Hz, Ar\( \text{CH}=\text{CHI} \)), 7.16 (2H, t, \( J = 7.9 \) Hz, H5), 7.00 (2H, m, H4 and H6), 6.93 (1H, d, \( J = 14.8 \) Hz, Ar\( \text{CH}=\text{CHI} \)), 5.66 (1H, br s, \( \text{OH} \)); \( \text{\^C NMR} \) (101 MHz, CDCl₃) \( \delta \)C 151.6, 141.0, 136.3, 127.8, 118.7, 118.1, 115.7, 80.5; \( \text{HRMS} \) (ESI) calc. for C₈H₃ClO [\(^{35}\text{Cl-M-H}\)]\(^-\) 278.9079, found 278.9086.
(E)-2-Chloro-1-(2-iodovinyl)-3-(methoxymethoxy)benzene, (E)-247-MOM

Prepared according to a modified literature procedure. Chloromethyl methyl ether (0.25 mL, 3.26 mmol, 1.5 eq) was added dropwise to a solution of phenol (E)-247 (610 mg, 2.17 mmol, 1.0 eq) and diisopropylethylamine (1.14 mL, 6.52 mmol, 3.0 eq) in DCM and the mixture stirred at room temperature for one hour. Water (15 mL) was added, and the aqueous layer extracted with DCM three times, the combined organic layers washed with 1M NaOH solution, dried (MgSO₄) and concentrated. The crude was purified by flash column chromatography (petrol / Et₂O (1:0→96:4)) to give iodide (E)-247-MOM as a pale yellow solid (603 mg, 1.97 mmol, 91%); R_f 0.30 (petrol / EtOAc (9:1)); mp 68–70 ºC; IR (thin film, ν_max / cm⁻¹) 3060, 2957, 2826, 1594, 1566, 1466, 1427, 1404, 1264, 1206, 1154, 1087, 1049, 1020; ¹H NMR (400 MHz, CDCl₃) δH 7.84 (1H, d, J = 14.3 Hz, ArCH=CHI), 7.22-7.08 (3H, m, H4, H5 and H6), 6.90 (1H, d, J = 14.3 Hz, ArCH=CHI), 5.26 (2H, s, ArOC₂H₂OCH₃), 3.53 (3H, s, ArOCH₂OCH₃); ¹³C NMR (101 MHz, CDCl₃) δC 153.1, 141.5, 137.3, 127.2, 121.9, 120.1, 115.8, 95.3, 80.3, 56.5; HRMS (FI⁺) calc. for C₁₀H₁₀ClIO₂ [³⁵ClM]⁺ 323.9414, found 323.9417.

7.12.2 Cross Coupling to Generate Natural Product Fragments

(2E,4Z,6Z)-10-((4-Methoxybenzyl)oxy)deca-2,4,6-triene-1,8-diol, 243

Procedure F (modified): TBAF•3H₂O (0.49 mL of a 1.0 M solution in THF, 0.490 mmol, 3.0 eq) was added to silane (R)-119e (50 mg, 0.163 mmol, 1.0 eq), iodide 246 (45 mg, 0.212 mmol, 1.3 eq), and allylpalladium chloride dimer (2.8 mg, 0.008 mmol, 0.05 eq) and stirred at room temperature for 48 hours. The reaction mixture was diluted with EtOAc, washed with water three times and dried
(Na₂SO₄). The concentrated crude, which was kept in the dark and not heated above 20 °C, was purified by flash column chromatography (DCM / methanol (100:0→99.75:0.25) + 1% Et₃N) to give triene 243 as a pale yellow oil (34 mg, 0.107 mmol, 66%).

**Method B:** A solution of potassium trimethylsilanolate (74 mg, 1.0 M in DME, 0.522 mmol, 3.0 eq) was added to silane (R)-119e (50 mg, 0.163 mmol, 1.0 eq), iodide 246 (34 mg, 0.163 mmol, 1.0 eq) and bis(dibenzylideneacetone)palladium (4.7 mg, 0.008 mmol, 0.05 eq) over 10 hours by syringe pump stirred for a further 14 hours. The crude, which was kept in the dark and not heated, was purified by flash column chromatography (petroleum ether / ethyl acetate / methanol (49:50:1) + 1% triethylamine) to give triene 243 as a pale yellow oil (21 mg, 0.069 mmol, 43%); ee 97% ; Rf 0.16 (petrol / EtOAc / methanol (49:50:1)); [α]D²⁰ -70.1 (c 0.5, CHCl₃); IR (thin film, νmax / cm⁻¹) 3375, 2920, 2853, 1612, 1512, 1246, 1088; ¹H NMR (400 MHz, CDCl₃) δH 7.26 (2H, d, J = 8.5 Hz, H12), 6.89 (2H, d, J = 8.5 Hz, H13), 6.73 (1H, dd, J = 15.0 and 11.3 Hz, H3), 6.50 (1H, t, J = 11.3 Hz, H6), 6.27 (1H, t, J = 11.3 Hz, H5), 6.06 (1H, t, J = 11.3 Hz, H4), 5.91 (1H, dt, J = 15.0 and 5.7 Hz, H2), 5.56-5.50 (1H, m, H7), 4.89-4.81 (1H, m, H8), 4.44 (2H, s, H11), 4.24 (2H, d, J = 5.7 Hz, H1), 3.81 (3H, s, OCH₃), 3.70-3.65 and 3.61-3.56 (2 × 1H, m, diastereotopic H10), 2.80 (1H, br s, OH), 1.97-1.88 and 1.80-1.73 (2 × 1H, m, diastereotopic H9), 1.64 (1H, br s, OH); ¹³C NMR (101 MHz, CDCl₃) δC 159.4, 134.5, 134.1, 130.0, 129.9, 129.4, 125.8, 124.2, 124.1, 113.8, 73.0, 67.9, 67.0, 63.3, 55.3, 36.8; HRMS (ESI⁺) calc. for C₁₉H₂₅NaO₄ [M+Na]+ 327.1567, found 327.1563.

**(4Z,6Z)-7-Cyclohexyl-1-((4-methoxybenzyl)oxy)hepta-4,6-dien-3-ol, 244**

**Procedure F** (modified): TBAF•3H₂O (0.50 mL of a 1.0 M solution in THF, 0.500 mmol, 3.0 eq) was added to silane (R)-119e (50 mg, 0.163 mmol, 1.0 eq), iodide 145c (77 mg, 0.326 mmol, 2.0 eq), water (29 µL, 1.63 mmol, 10 eq) and allylpalladium chloride dimer (2.8 mg, 0.008 mmol, 0.05 eq) and the mixture stirred at 50 °C for a 24 hours. The concentrated crude was purified by flash column chromatography (petrol / EtOAc (100:0→9:1) + 1% Et₃N) to give diene 244 as a pale yellow oil.
Experimental

(28 mg, 0.085 mmol, 53%; isomerized to minor amounts of E,Z- and E,E-244 on exposure to light);

$\text{ee } 97\%$ (assumed from analysis of $(R)$-115e); $R_f$ 0.26 (petrol / EtOAc (4:1)); $[\alpha]_D^{25}$ -43.6 (c 1.0, CHCl$_3$); IR (thin film, $\nu_{\text{max}} / \text{cm}^{-1}$) 3415, 2924, 2851, 1613, 1513, 1248, 1094, 1036; $^1$H NMR (500 MHz, C$_6$D$_6$) $\delta$ 7.17 (2H, d, $J = 8.8$ Hz, H2'), 6.77 (2H, d, $J = 8.8$ Hz, H3'), 6.34 - 6.26 (2H, m, H5 and H6), 5.55 - 5.51 (1H, m, H4), 5.34 - 5.30 (1H, m, H7), 4.90 - 4.86 (1H, m, H3), 4.24 (2H, s, H1'), 3.49 - 3.45 and 3.40 - 3.35 (2 × 1H, m, diastereotopic H1), 3.29 (3H, s, OC$_3$H$_3$), 2.46 - 2.31 (2H, m, H8 and O'H), 1.94 - 1.87 and 1.72 - 1.68 (2 × 1H, m, diastereotopic H2), 1.67 - 1.53 (4H, m, H10), 1.23 - 1.15 (2H, m, H11), 1.12 - 0.97 (4H, m, H9); $^{13}$C NMR (125 MHz, C$_6$D$_6$) $\delta$ 159.8, 139.5, 134.8, 128.3, 124.4, 122.2, 114.1, 73.0, 67.9, 66.8, 54.8, 37.8, 36.8, 33.5, 26.3, 26.1; HRMS (ESI$^+$) calc. for C$_{21}$H$_{30}$NaO$_3$ [M+Na]$^+$ 353.2087, found 353.2076.

2-Chloro-3-((1E,3Z)-5-hydroxy-7-((4-methoxybenzyl)oxy)hepta-1,3-dien-1-yl)phenol, 245

**Procedure F** (modified): TBAF•3H$_2$O (0.39 mL of a 1.0 M solution in THF, 0.390 mmol, 3.0 eq) was added to silane (R)-119e (40 mg, 0.129 mmol, 1.0 eq), E-iodide (E)-247 (47 mg, 0.214 mmol, 1.3 eq) and allylpalladium chloride dimer (2.2 mg, 0.006 mmol, 0.05 eq) and the mixture stirred at 50 °C for a 24 hours. The mixture was filtered through a plug of SiO$_2$ eluting with EtOAc, then DCM, diluted with Et$_2$O, washed 5 times with water and dried (Na$_2$SO$_4$). The concentrated crude was purified by flash column chromatography (DCM / MeOH (100:0→99.6:0.4) + 1% Et$_3$N) to give diene 245 as a pale yellow oil (33 mg, 97 wt% with Et$_3$N, 0.085 mmol, 66%, 98:2 Z:E:E); ee 97% (assumed from analysis of (R)-115e); $R_f$ 0.09 (petrol / EtOAc (1:1)); $[\alpha]_D^{20}$ -76.8 (c 0.5, CHCl$_3$); IR (thin film, $\nu_{\text{max}} / \text{cm}^{-1}$) 3374, 2924, 2862, 1612, 1513, 1465, 1245, 1035; $^1$H NMR (400 MHz, C$_6$D$_6$) $\delta$ 7.23 - 7.12 (3H, m, H2 and H9), 6.96 (1H, d, $J = 15.5$ Hz, H10), 6.94 (1H, dd, $J = 7.6$ and 1.4 Hz, H11), 6.84 (1H, dd, $J = 7.9$ and 1.4 Hz, H13), 6.77 - 6.73 (3H, m, H1 and H12), 6.08 (1H, t, $J = 11.1$ Hz, H8), 5.49 (1H, dd, $J = 11.1$ and 8.6 Hz, H7), 4.93 - 4.87 (1H, m, H6), 4.26 (1H, s, ArOH), 4.23-
4.16 (2H, m, H3), 3.47-3.40 and 3.35-3.28 (2 × 1H, m, diastereotopic H4), 3.29 (3H, s, OCH₃), 1.94-1.86 and 1.65-1.57 (2 × 1H, m, diastereotopic H5), 1.36 (1H, br s, 2º OH); ¹³C NMR (125 MHz, C₆D₆) δC 160.0, 152.5, 136.4, 130.7, 129.5, 129.5, 129.4, 129.4, 128.5, 127.7, 119.7, 118.6, 115.3, 114.1, 73.0, 67.7, 67.2, 54.8, 37.7; HRMS (ESI⁺) calc. for C₂₁H₂₃ClNaO₄ [¹³ClM+Na⁺] 397.1177, found 397.1165.

(4Z,6E)-7-(2-Chloro-3-(methoxymethoxy)phenyl)-1-((4-methoxybenzyl)oxy) hepta-4,6-dien-3-ol, 245-MOM

Procedure F (modified): TBAF·3H₂O (0.49 mL of a 1.0 M solution in THF, 0.490 mmol, 3.0 eq) was added to silane (R)-119e (50 mg, 0.163 mmol, 1.0 eq), E-iodide (E)-147-MOM (69 mg, 0.214 mmol, 1.3 eq) and allylpalladium chloride dimer (2.8 mg, 0.008 mmol, 0.05 eq) and the mixture stirred at 50 °C for 24 hours. The concentrated crude was purified by flash column chromatography (petrol / EtOAc (7:3) + 1% Et₃N) to give diene 245-MOM as a pale yellow oil (48 mg, 0.115 mmol, 70%, 96:4 Z,E:E,E; ee 97% (assumed from analysis of (R)-115e); Rf 0.35 (petrol / EtOAc (1:1)); [α]D²⁰ -53.1 (c 1, CHCl₃); IR (thin film, v max / cm⁻¹) 3420, 2934, 2908, 2860, 1612, 1567, 1513, 1467, 1248, 1154, 1087, 1023; ¹H NMR (500 MHz, C₆D₆) δH 7.21 (2H, d, J = 8.6 Hz, H2), 7.18-7.12 (2H, m, H9 and H10), 7.09 (1H, d, J = 7.8 Hz, H11), 6.92 (1H, d, J = 7.8 Hz, H13), 6.82 (1H, t, J = 7.8 Hz, H12), 6.76 (2H, d, J = 8.6 Hz, H1), 6.41-6.10 (1H, m, H8), 5.48 (1H, dd, J = 10.6 and 8.7 Hz, H7), 4.95-4.90 (1H, m, H6), 4.81 (2H, s, ArOCH₂OCH₃) 4.24-4.18 (2H, m, H3), 3.46-3.43 and 3.35-3.29 (2 × 1H, m, diastereotopic H4), 3.30 (3H, s, ArOCH₃), 3.09 (3H, s, ArOCH₂OCH₃), 2.17 (1H, br s, OH), 1.94-1.87 and 1.65-1.59 (2 × 1H, m, diastereotopic H5); ¹³C NMR (125 MHz, C₆D₆) δC 159.8, 154.0, 137.4, 136.2, 130.8, 130.1, 129.7, 129.4, 128.3, 127.6, 127.2, 123.3, 120.1, 115.1, 114.2, 95.1, 73.0, 67.7, 67.1, 55.9, 54.8, 37.7; HRMS (ESI⁺) calc. for C₂₁H₂₃ClNaO₄ [¹³ClM+Na⁺] 397.1177, found 397.1165.
7.13 Synthesis of Resolins D3 and E1

7.13.1 Synthesis of C1-C4 of Resolvin D3

Methyl 6-(diethyl(isopropoxy)silyl)-4-oxohex-5-ynoate, 262

Methylmagnesium bromide (0.78 mL of a 3.0 M solution in Et₂O, 2.33 mmol, 1.0 eq) was added to a solution of alkyne 115 (410 mg, 2.33 mmol, 1.0 eq) in THF (5.8 mL) at 0 °C and stirred for two hours at room temperature to form a 0.33 M solution of alkynyl Grignard that was used immediately. The alkynyl Grignard (6.0 mL of the 0.33 M solution prepared above, 2.00 mmol, 1.0 eq) was added over three hours at 0 °C to a solution of methyl-4-chloro-4-oxybutyrate (0.25 mL, 2.00 mmol, 1.0 eq) in THF (8 mL). The reaction was warmed to room temperature and stirred for a further 4 hours, then quenched with NH₄Cl solution, extracted with Et₂O and the combined organic phase dried (Na₂SO₄) and concentrated to give ynone 262 as a colourless oil that was unstable to silica gel and hence was used without further purification (394 mg, 80 wt% with dimethylsuccinate, ~1.30 mmol, ~65%); Rᵢ 0.26 (petrol / Et₂O (4:1)); IR (thin film, νmax / cm⁻¹) 2961, 2879, 2147, 1740, 1683, 1647, 1438, 1413, 1369, 1172, 1112, 1032; ¹H NMR (400 MHz, CDCl₃) δH 4.14 (1H, sept, J = 6.1 Hz, OCH(CH₃)₂), 3.69 (3H, s, OC₂H₃), 2.93 (2H, t, J = 6.7 Hz, H3), 2.65 (2H, t, J = 6.7 Hz), 1.20 (6H, d, J = 6.1 Hz, OCH(CH₃)₂), 1.01 (6H, t, J = 7.9 Hz, Si(CH₂CH₃)₂), 0.72 (4H, q, J = 7.9 Hz, Si(CH₂CH₃)₂); ¹³C NMR (101 MHz, CDCl₃) δC 185.0, 172.5, 101.4, 95.0, 66.7, 51.9, 40.0, 27.7, 25.4, 6.4, 6.3; HRMS (FI⁺) calc. for C₁₄H₂₄O₄Si [M]⁺ 285.1469 found 285.1470.
Methyl (S)-6-(diethyl(isoproxy)silyl)-4-hydroxyhex-5-ynoate, 261

A solution of crude ynone 262 (193 mg, <0.679 mmol, <1.0 eq) in isopropyl alcohol (7 mL) was degassed with argon for one hour, before the addition of (1S,2S)-(+)N-Tosyl-1,2-diphenylethane-1,2-diamine[η⁶-1-isopropyl-4-methylbenzene]-ruthenium(II) (Noyori catalyst) (24 mg, 0.034 mmol, 0.05 eq) as a solution in DCM (0.7 mL) and degassed for a further 15 minutes. The mixture was stirred for 30 minutes before being concentrated under reduced pressure. The crude residue was purified via flash column chromatography (petrol / EtOAc (4:1→1:1) + 1% Et₃N) to give alcohol 261 as a colourless oil (80 mg, 0.279 mmol, 38% over two steps); ee 99% (assumed from analysis of S15); Rf 0.26 (petrol / EtOAc (1:1)); [α]_D^{20} -9.1 (c 1.0, CHCl₃); IR (thin film, νmax/cm⁻¹) 3424, 2960, 2937, 2878, 2172, 1740, 1439, 1172, 1029; ¹H NMR (400 MHz, CDCl₃) δH 4.50 (1H, q, J = 6.0, H₄), 4.12 (1H, sept, J = 6.1 Hz, OC(H(CH₃)₂)), 3.69 (3H, s, OCH₃), 2.65-2.48 (2H, m, H₃), 2.24 (1H, d, J = 6.0 Hz, OH), 2.08-2.02 (2H, m, H2), 1.19 (6H, d, J = 6.1 Hz, OCH(CH₃)₂), 0.99(6H, t, J = 7.6 Hz, Si(CH₂CH₃)₂); ¹³C NMR (101 MHz, CDCl₃) δC 174.1, 106.3, 86.6, 66.2, 61.8, 51.8, 32.3, 29.7, 25.5, 6.7, 6.6; HRMS (ESI⁺) calc. for C₁₄H₂₆O₄NaSi [M+Na]⁺ 309.14926 found 309.14868.

(S)-1-(Diethyl(isoproxy)silyl)-6-methoxy-6-oxohex-1-yn-3-yl benzoate, S15

Benzoyl chloride (24 μL, 0.209 mmol, 2.0 eq) was added dropwise to alcohol 261 (30 mg, 0.105 mmol, 1.0 eq), DMAP (3 mg, 0.021 mmol, 0.2 eq) and Et₃N (44 μL, 0.314 mmol, 3.0 eq) in DCM (0.5 mL). The mixture was stirred for three hours, and quenched with NaHCO₃ solution. The
aqueous layer was extracted with DCM and the combined organic layers dried (MgSO₄) and concentrated. The crude was purified \textit{via} flash column chromatography (petrol / Et₂O (19:1) + 1% Et₃N) to give S15 as a pale yellow oil (12 mg, 0.031 mmol, 29%); \textit{ee} 98% (CHIRALPAK-IB, 0.7% IPA/n-Hex, 1.3 mL/min, \(R - 5.0\) min, \(S - 5.9\) min); \(|\alpha|_{D}^{20}\) 0.37 (petrol / Et₂O (4:1)); \([\alpha]_{D}^{20}\) -20.6 (c 1.0, CHCl₃); IR (thin film, \(\nu_{\text{max}}\) / cm\(^{-1}\)) 2960, 2878, 2179, 1727, 1452, 1264, 1027; \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\)H 8.05 (2H, d, \(J = 8.3\) Hz, o-ArH), 7.58 (1H, t, \(J = 8.3\) Hz, p-ArH), 7.45 (2H, t, \(J = 8.3\) Hz, m-ArH), 5.73 (1H, t, \(J = 6.2\), H₃), 4.14 (1H, sept, \(J = 6.2\) Hz, OC₃H(CH₃)₂), 3.66 (3H, s, OC₃H₃), 2.60 (2H, t, \(J = 7.5\) Hz, H₅), 2.30-2.23 (2H, m, H₄), 1.17 (6H, d, \(J = 6.2\) Hz, OCH(C(CH₃)₂), 0.99 (6H, t, \(J = 7.8\) Hz, Si(CH₂CH₃)₂), 0.66 (4H, q, \(J = 7.8\) Hz, Si(CH₂CH₃)₂); \(^{13}\)C NMR (101 MHz, CDCl₃) \(\delta\)C 172.9, 165.2, 133.2, 129.8, 129.8, 128.4, 102.3, 88.0, 66.2, 63.8, 51.7, 30.0, 29.6, 25.4, 21.8, 6.6, 6.5; HRMS (FI') calc. for C₂₁H₃₀O₅Si [M]’ 390.1862 found 390.1872.

Methyl (S)-3-(2,2-diethyl-2,5-dihydro-1,2-oxasilol-5-yl)propanoate, 256

\[
\text{Si} \quad \text{O} \\
\text{Et}_2 \\
\text{O} \\
\text{Et}_2 \\
\text{O}
\]

\textbf{Procedure E} (modified): Palladium on CaCO₃ (4 mg, 5 wt % Pd, 0.002 mmol, 0.01 eq), silane 261 (50 mg, 0.175 mmol, 1.0 eq) and quinoline (4.0 μL, 0.035 mmol, 0.2 eq) in toluene (2 mL) and cyclohexene (0.2 mL) were stirred under a hydrogen atmosphere for 40 minutes, followed by filtration and concentration \textit{in vacuo}. The crude was purified \textit{via} rapid flash column chromatography (petrol / Et₂O (4:1)) to give oxasilole 256 as a colourless oil which was unstable to silica gel (25 mg, 0.110 mmol, 63% isolated); \textit{ee} 99% (assumed from analysis of S15); \(R_f\) 0.15 (petrol / Et₂O (9:1)); \(|\alpha|_{D}^{20}\) +72.5 (c 1.0, CHCl₃); IR (thin film, \(\nu_{\text{max}}\) / cm\(^{-1}\)) 2956, 2877, 1741, 1558, 1438, 1124, 1037; \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\)H 6.85 (1H, dd, \(J = 10.6\) and 1.3 Hz, H₅), 6.00 (1H, dd, \(J = 10.6\) and 2.4 Hz, H₆), 4.72-4.67 (1H, m, H₄), 3.66 (3H, s, OCH₃), 2.48-2.43 (2H, m, H₂), 2.05-1.96 (1H, m, 1 × H₃), 1.73-1.64 (1H, m, 1 × 3), 0.94 and 0.90 (2 × 3H, t, \(J = 7.9\) Hz, Si(CH₂CH₃)₂), 0.75-0.58 (4H, m, Si(CH₂CH₃)₂); \(^{13}\)C NMR (101 MHz, CDCl₃) \(\delta\)C 174.2, 153.6,
125.4, 82.1, 51.6, 32.1, 30.0, 7.1, 7.0, 6.8, 6.4; **HRMS (ESI')** calc. for C\textsubscript{11}H\textsubscript{20}O\textsubscript{3}NaSi [M+Na]\textsuperscript{+}

251.10739 found 251.10690.

7.13.2 Synthesis of C1-C5 of Resolvin E1

Methyl 7-(diethyl(isopropoxy)silyl)-5-oxohept-6-ynoate, 270 and 6-(diethyl(isopropoxy)silyl)-ethynyl)-6-methoxytetrahydro-2H-pyran-2-one, 271

Methylmagnesium bromide (1.56 mL of a 3.0 M solution in Et\textsubscript{2}O, 4.66 mmol, 1.0 eq) was added to a solution of alkyne 114 (820 mg, 4.66 mmol, 1.0 eq) in THF (11.6 mL) at 0 °C and stirred for two hours at room temperature to form a 0.33 M solution of alkyne Grignard that was used immediately. The alkyne Grignard (12 mL of the 0.33 M solution prepared above, 4.00 mmol, 1.2 eq) was added over three hours at 0 °C to a solution of glutaric acid monomethyl ester chloride (0.46 mL, 3.33 mmol, 1.0 eq) in THF (12 mL). The reaction was then warmed to room temperature and stirred for a further 20 hours, then quenched with NH\textsubscript{4}Cl solution, extracted with Et\textsubscript{2}O and the combined organic phase dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated to give 270 as a colourless oil that was unstable to silica gel and hence was used without further purification (910 mg, as a 1:2 mixture of 270:271 (which was found to vary by experiment), 3.05 mmol, 92%). A small sample of 270 and 271 could be separated by column chromatography with significant loss of 270 (petrol / Et\textsubscript{2}O (9:1) + 1% Et\textsubscript{3}N).

Pure 270 could be prepared by the following two-step procedure. Sodium borohydride (157 mg, 4.15 mmol, 3.0 eq) was added to a solution of 270 (1.24 g, ~30 wt% with 271, 1.38 mmol, 1.0 eq) in THF (20 mL) at 0 °C and stirred for three hours, then quenched cautiously at 0 °C with NH\textsubscript{4}Cl solution, extracted three times with Et\textsubscript{2}O, dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated. The crude was purified by flash column chromatography (petrol / Et\textsubscript{2}O (4:1→7:3) + Et\textsubscript{3}N) to give alcohol 272 as a
colourless oil (232 mg, 0.773 mmol, 56%). Alcohol 272 (232 mg, 0.773 mmol, 1.0 eq) was dissolved in DCM and 4 Å molecular sieves and γ-MnO₂ (1.34 g, 15.4 mmol, 20.0 eq) were added. The mixture was stirred for 1.5 hours, then filtered through Celite® and concentrated to give pure ketone 270 (178 mg, 0.596 mmol, 77%).

270; Rᵣ 0.22 (petrol / Et₂O (19:1)); IR (thin film, ν max / cm⁻¹) 2963, 2879, 2149, 1740, 1680, 1459, 1437, 1370, 1117, 1033; ¹H NMR (500 MHz, CDCl₃) δH 4.15 (1H, sept, J = 6.1 Hz, OCH(CH₃)₂), 3.68 (3H, s, OCH₃), 2.68 (2H, t, J = 7.3 Hz, H4), 2.38 (2H, t, J = 7.3 Hz, H2), 1.99 (2H, quin, J = 7.3 Hz, H3), 1.20 (6H, d, J = 6.1 Hz, OCH(C₂H₃)₂), 0.72 (4H, q, J = 8.0 Hz, Si(C₂H₃CH₃)₂); ¹³C NMR (125 MHz, CDCl₃) δC 186.6, 173.3, 101.8, 94.5, 66.7, 51.6, 44.3, 32.8, 25.4, 19.0, 6.4, 6.4; HRMS (ESI⁺) calc. for C₁₅H₂₆O₄Si [M]⁺ 298.1600 found 298.1594.

271 (which exists as a ~1:1 mixture of conformers); Rᵣ 0.18 (petrol / Et₂O (19:1)); IR (thin film, ν max / cm⁻¹) 2961, 2878, 2175, 1741, 1460, 1437, 1381, 1369, 1194, 1121, 1029; ¹H NMR (400 MHz, CDCl₃) δH 4.15 (1H, sept, J = 6.2 Hz, OCH(CH₃)₂), 3.68 and 3.67 (3H, s, OCH₃ of two conformers), 2.42-2.34 (3H, m, H3 and 1 × H5), 2.12-2.07 (1H, m, 1 × H5), 2.00-1.91 (2H, m, H4); 1.18 (6H, d, J = 6.2 Hz, OCH(CH₃)₂), 1.02-0.95 (6H, m, Si(CH₂CH₃)₂), 0.68-0.61 (4H, m, Si(CH₂CH₃)₂); ¹³C NMR (101 MHz, CDCl₃) δC 186.6, 173.3, 169.4, 101.7, 87.1, 67.2, 66.4, 51.6, 41.4, 33.5, 33.4, 32.8, 25.4, 20.1, 20.0, 6.6, 6.5; LRMS (ESI⁺) calc. for C₃₀H₅₂O₈Na₂Si₂ [2M+Na]⁺ 619.3 found 619.2.

**Methyl (S)-7-(diethyl(isopropoxy)silyl)-5-hydroxyhept-6-ynoate, (S)-272**

![Chemical structure](image)

A solution of pure ynone 270 (177 mg, 0.600 mmol, 1.0 eq) in isopropyl alcohol (6 mL) was degassed with argon for one hour, before the addition of (1S,2S)-(+)-N-Tosyl-1,2-diphenylethane-1,2-diamine[η⁶-1-isopropyl-4-methylbenzene]-ruthenium(II) (Noyori catalyst²²) (13 mg, 0.018 mmol, 0.03 eq) as a solution in DCM (0.6mL) and degassed for a further 15 minutes. The mixture
was stirred for 30 minutes before being concentrated under reduced pressure. The crude residue was purified via flash column chromatography (petrol / Et₂O (4:1→7:3) + 1% Et₃N) to give alcohol (S)-272 as a colourless oil (137 mg, 0.456 mmol, 76%); ee 92% (assumed from analysis of S16); Rf 0.18 (petrol / Et₂O (3:2)); [α]D²⁰ -2.4 (c 0.5, CHCl₃); IR (thin film, νmax / cm⁻¹) 3442, 2960, 2878, 2170, 1741, 1438, 1369, 1172, 1122; ¹H NMR (400 MHz, CDCl₃) δH 4.43-4.39 (1H, m, H₅), 4.12 (1H, sept, J = 6.1 Hz, OC₃H(CH₃)₂), 3.67 (3H, s, OC₃H₃), 2.34 (1H, t, J = 6.9 Hz, H₂), 2.04 (1H, d, J = 3.6 Hz, OH), 1.85-1.71 (4H, m, H₃ and H₄), 1.18 (6H, d, J = 6.0 Hz, OCH(C₂H₃)₂), 0.99 (6H, t, J = 8.0 Hz, Si(CH₂CH₃)₂), 0.65 (4H, q, J = 8.0 Hz, Si(CH₂CH₃)₂); ¹³C NMR (101 MHz, CDCl₃) δC 173.8, 107.0, 86.2, 66.1, 62.3, 51.6, 36.9, 33.5, 25.5, 20.5, 6.7, 6.6; HRMS (ESI⁺) calc. for C₁₅H₂₈O₄NaSi [M+Na]⁺ 323.16491 found 323.16405.

(S)-1-(Diethyl(isopropoxy)silyl)-7-methoxy-7-oxohept-1-yn-3-yl benzoate, S16

Benzoyl chloride (4.6 μL, 0.040 mmol, 2.0 eq) was added dropwise to alcohol (S)-272 (6 mg, 0.020 mmol, 1.0 eq), DMAP (0.5 mg, 0.004 mmol, 0.2 eq) and Et₃N (8.3 μL, 0.060 mmol, 3.0 eq) in DCM (0.2 mL). The mixture was stirred for three hours, and quenched with NaHCO₃ solution. The aqueous layer was extracted with DCM and the combined organic layers dried (MgSO₄) and concentrated. The crude was purified via flash column chromatography (petrol + 1% Et₃N) to give S16 as a colourless oil (7 mg, 0.017 mmol, 87%); ee 92% (CHIRALPAK-IB, 0.3% IPA/n-Hex, 1.3 mL/min, R = 5.4 min, S = 5.8 min); Rf 0.13 (petrol / Et₂O (19:1)); [α]D²⁰ -16.2 (c 0.5, CHCl₃); IR (thin film, νmax / cm⁻¹) 2962, 2878, 2177, 1727, 1602, 1491, 1452, 1437, 1264, 1199, 1173, 1096; ¹H NMR (500 MHz, CDCl₃) δH 8.07 (2H, d, J = 8.4 Hz, o-ArH), 7.57 (1H, t, J = 8.4 Hz, p-ArH), 7.45 (2H, t, J = 8.4 Hz, m-ArH), 5.67 (1H, t, J = 5.9, H3), 4.13 (1H, sept, J = 6.0 Hz, OCH(CH₃)₂), 3.67 (3H, s, OCH₃), 2.41 (2H, t, J = 7.3 Hz, H6), 1.98-1.85 (4H, m, H4 and H5), 1.17 (6H, d, J = 6.0 Hz,
OCH(CH$_3$)$_2$, 0.99 (6H, t, $J = 7.7$ Hz, Si(CH$_2$CH$_3$)$_2$), 0.65 (4H, q, $J = 7.7$ Hz, Si(CH$_2$CH$_3$)$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta_C$ 173.5, 165.3, 133.2, 129.9, 129.8, 128.4, 102.9, 87.6, 66.2, 64.3, 51.6, 34.1, 33.5, 25.4, 20.5, 6.6, 6.5; HRMS (ESI$^+$) calc. for $\text{C}_{22}\text{H}_{32}$O$_5$Si $[\text{M+Na}]^+$ 427.19112 found 427.19050.

**Methyl (S)-4-(2,2-diethyl-2,5-dihydro-1,2-oxasilol-5-yl)butanoate, 260**

![Methyl (S)-4-(2,2-diethyl-2,5-dihydro-1,2-oxasilol-5-yl)butanoate](image)

**Procedure E** (modified): Palladium on CaCO$_3$ (7 mg, 5 wt % Pd, 0.03 mmol, 0.01 eq), silane (S)-272 (101 mg, 0.336 mmol, 1.0 eq) and quinoline (8 $\mu$L, 0.067 mmol, 0.2 eq) in toluene (3.4 mL) and cyclohexene (0.34 mL) were stirred under a hydrogen atmosphere for 1.5 hours, followed by filtration and concentration *in vacuo*. The crude was purified via rapid flash column chromatography (petrol / Et$_2$O (4:1)) to give oxasilole 260 as a colourless oil which was unstable to silica gel (26 mg, 0.107 mmol, 32% isolated); ee 99% (assumed from analysis of S16); $R_f$ 0.20 (petrol / Et$_2$O (9:1)); [$\alpha$]$_D^{20}$ +76.5 (c 0.67, CHCl$_3$); IR thin film, $\nu_{\max}$ / cm$^{-1}$) 2955, 2876, 1741, 1558, 1436, 1160, 1123, 1019; $^1$H NMR (400 MHz, CDCl$_3$) $\delta_H$ 6.85 (1H, dd, $J = 10.6$ and 1.5 Hz, H6), 5.98 (1H, dd, $J = 10.6$ and 2.2 Hz, H7), 4.68-4.64 (1H, m, H5), 3.66 (3H, s, OCH$_3$), 2.36 (2H, t, $J = 7.5$ Hz, H2), 1.86-1.58 (3H, m, 1 × H4, H3), 1.49-1.40 (1H, m, 1 × H4), 0.95-0.89 (6H, m, Si(CH$_2$CH$_3$)$_2$), 0.75-0.56 (4H, m, Si(CH$_2$CH$_3$)$_2$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta_C$ 174.0, 154.0, 124.6, 82.8, 51.4, 36.7, 36.7, 34.0, 30.3, 21.1, 7.2, 7.1, 6.8, 6.5; HRMS (ESI$^+$) calc. for $\text{C}_{12}\text{H}_{22}$O$_3$NaSi $[\text{M+Na}]^+$ 265.12304 found 265.12244.
7.13.3 Synthesis of Central Fragment Common to Resolvins D3 and E1

(R)-Trimethyl(oxiran-2-ylmethoxy)silane, 276

Trimethylsilyl chloride (2.1 mL, 16.6 mmol, 1.1 eq) was added dropwise to a solution of (S)-glycidol (1.0 mL, 15.1 mmol, 1.0 eq) and Et₃N (2.5 mL, 18.1 mmol, 1.2 eq) in DCM (10 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 24 hours, then quenched with cold NaHCO₃ solution, separated, and the organic phase washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure. The crude mixture was purified by Kuhgelrohr distillation (70-91 °C, 49-51 mbar; lit. 281 80 °C, 9 mmHg) to give epoxide 276 as a colourless oil (1.81 g, 12.4 mmol, 82%); Rᵣ 0.38 (petrol / Et₂O (4:1)); [α]D₂₀ -0.7 (c 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δH 3.78 (1H, dd, J = 12.0 and 3.3 Hz, 1 × diastereotopic H1), 3.56 (1H, dd, J = 12.0 and 5.1 Hz, 1 × diastereotopic H1), 3.07-3.03 (1H, m, H2), 2.74 (1H, dd, J = 5.0 and 4.0 Hz, 1 × diastereotopic H3), 2.58 (1H, dd, J = 5.0 and 2.6 Hz, 1 × diastereotopic H3), 0.10 (9H, s, Si(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δC 63.4, 52.2, 44.5, -0.6; HRMS (ESI⁺) calc. for C₆H₁₅O₂Si [M+H]⁺ 147.0836, found 147.0829.

All spectroscopic data were found to be in agreement with that reported by Davies and co-workers. 281

(R)-(2,2-Diethyl-5,6-dihydro-2H-1,2-oxasilin-6-yl)methanol, 274

n-Butyllithium (3.3 mL of a 2.5 M solution in hexane, 8.13 mmol, 1.5 eq) and silyl alkyne 114 (1.43 g, 8.13 mmol, 1.5 eq) in THF (25 mL) were stirred at -78 °C for one hour. BF₃·OEt₂ (1.00 mL,
Experimental

8.13 mmol, 1.5 eq) was added, and the mixture stirred for a further 10 minutes before epoxide 276 (793 mg, 5.42 mmol, 1.0 eq) was added. The mixture was stirred for 5 hours, quenched with NH₄Cl solution and the aqueous phase extracted three times with EtOAc. The combined organic phase was washed with brine, dried (Na₂SO₄) and concentrated. The crude residue was then redissolved in EtOAc and washed three times with NH₄Cl, dried (Na₂SO₄) and concentrated. The residue was then dissolved in THF (25 mL), and quinoline (0.32 mL, 2.71 mmol, 0.5 eq), cyclohexene (2.5 mL) and palladium on CaCO₃ (577 mg, 5 wt% Pd, 0.271 mmol, 0.05 eq) were added. The mixture was stirred under hydrogen for one hour and 40 minutes, before being filtered through Celite® and concentrated. The residue was redissolved in MeOH (10 mL), pyridinium p-toluenesulfonate (136 mg, 0.542 mmol, 0.1 eq) added, and the reaction stirred for three hours. The mixture was diluted with Et₂O, washed three times with water, the aqueous reextracted with Et₂O and the combined organic phase dried (Na₂SO₄) and concentrated. The crude was purified by flash column chromatography (petrol / Et₂O (9:1)) to give 274 as a pale yellow oil (384 mg, 2.06 mmol, 38%); Rf 0.26 (petrol / Et₂O (7:3)); [α]D²⁰ +16.9 (c 2.0, CHCl₃); IR (thin film, νmax / cm⁻¹) 3424, 2954, 2915, 1589, 1460, 1407, 1242, 1164, 1102, 1055; ¹H NMR (400 MHz, CDCl₃) δH 6.80 (1H, ddd, J = 14.2, 6.2 and 2.6 Hz, H4), 5.68 (1H, ddd, J = 14.2, 2.6 and 0.6 Hz, H3), 4.00-3.95 (1H, m, H6), 3.53 (1H, dd, J = 10.9 and 2.9 Hz, 1 × H7), 3.41 (1H, dd, J = 10.9 and 6.5 Hz, 1 × H7), 2.35 (1H, br s, OH), 2.16-2.11 (1H, ddt, J = 17.8, 10.5 and 2.6 Hz, 1 × H5), 2.00 (1H, dddd, J = 17.8, 6.2, 2.6 and 0.6 Hz, 1 × H5), 0.92 and 0.87 (2 × 3H, t, J = 7.9 Hz, diastereotopic Si(CH₂CH₃)₂), 0.64-0.46 (4H, m, Si(CH₂CH₃)₂); ¹³C NMR (101 MHz, CDCl₃) δC 147.9, 124.7, 72.1, 66.9, 32.3, 6.8, 6.8, 3.4, 5.9; HRMS (ESI⁺) calc. for C₅H₁₂NaO₂Si [M+Na]+ 209.0968, found 209.0962.

(R)-2,2-Diethyl-5,6-dihydro-2H-1,2-oxasiline-6-carbaldehyde, 277

![](image)

Dimethylsulfoxide (0.40 mL, 5.64 mmol, 10.5 eq) was added to a solution of SO₃·py (265 mg, 3.10 mmol, 3.1 eq) in DCM (2 mL) and stirred for 20 minutes before a solution of
diisopropylethylamine (0.49 mL, 2.79 mmol, 5.2 eq) and alcohol 274 (100 mg, 0.537 mmol, 1.0 eq) in DCM (2 mL) was added via cannula. After 90 minutes the reaction was quenched with NH₄Cl solution, extracted with DCM, dried (Na₂SO₄) and concentrated to give aldehyde 277 as a colourless oil which was used in the next step without further purification (133 mg, 56 wt% with pyridine, ~0.405 mmol, ~75%). An analytical sample was purified by flash column chromatography (petrol / Et₂O (4:1→2:1)); Rf 0.28 (petrol / Et₂O (7:3)); [α]D²³ +30.0 (c 0.67, CHCl₃); IR (thin film, νmax / cm⁻¹) 2957, 2914, 2877, 1738, 1588, 1460, 1422, 1354, 1237, 1203, 1161, 1111; ¹H NMR (400 MHz, CDCl₃) δ H 9.66 (1H, br s, H7), 6.87 (1H, ddd, J = 14.2, 5.7 and 2.7 Hz, H4), 5.80 (1H, ddd, J = 14.2, 2.6 and 0.8 Hz, H3), 4.32 (1H, dd, J = 6.5 and 3.7 Hz, H6), 2.46-2.37 (1H, m, 1 × H5), 2.32-2.26 (1H, m, 1 × H5), 1.01-0.93 (6H, m, Si(CH₂CH₃)₂), 0.77-0.62 (4H, m, Si(CH₂CH₃)₂); ¹³C NMR (101 MHz, CDCl₃) δC 203.3, 146.3, 125.9, 76.4, 30.7, 6.7, 6.6, 6.2, 6.0; HRMS (F) calc. for C₃H₁₆O₂Si [M]+ 184.0920 found 184.0916.

(R,E)-3-(2,2-Diethyl-5,6-dihydro-2H-1,2-oxasilin-6-yl)acrylaldehyde, 273

2-(Triphenylphosphoranylidene)acetaldehyde (125 mg, 0.411 mmol, 1.0 eq) was added to a solution of aldehyde 274 (76 mg, 0.411 mmol, 1.0 eq) in toluene (4 mL) and stirred at room temperature in the dark for 16 h. The reaction mixture was concentrated and purified by flash column chromatography (petrol / Et₂O (9:1) + 1% Et₃N) to give acrylaldehyde 273 as a pale yellow oil (54 mg, 0.257 mmol, 62%); Rf 0.21 (petrol / Et₂O (9:1)); [α]D²⁰ +45.0 (c 1.0, CHCl₃); IR (thin film, νmax / cm⁻¹) 2957, 2877, 1693, 1588, 1460, 1133, 1102; ¹H NMR (400 MHz, CDCl₃) δH 9.58 (1H, d, J = 8.1 Hz, H9), 6.87 (1H, ddd, J = 14.2, 6.2 and 2.4 Hz, H4), 6.80 (1H, dd, J = 15.5 and 3.8 Hz, H7), 6.38 (1H, ddd, J = 15.5, 8.1 and 1.6 Hz, H8), 5.81 (1H, dd, J = 14.2 and 2.4 Hz, H3), 4.74-4.68 (1H, m, H6), 2.35-2.15 (2H, m, H5), 0.97 and 0.96 (2 × 3H, t, J = 7.9 Hz, diastereotopic Si(CH₂CH₃)₂), 0.72-0.56 (4H, m, Si(CH₂CH₃)₂); ¹³C NMR (101 MHz, CDCl₃) δC 196.4, 158.3.
147.0, 130.6, 125.6, 70.5, 35.4, 6.7, 6.7, 6.3, 5.9; HRMS (F1) calc. for C₁₁H₁₇O₂Si [M⁺] 209.1003 found 209.1013.

(R)-2,2-Diethyl-6-((1E,3E)-4-iodobuta-1,3-dien-1-yl)-5,6-dihydro-2H-1,2-oxasiline, 257

![Chemical Structure](image)

Chromium (II) chloride (771 mg, 6.28 mmol, 8.0 eq) was dried by heating under high vacuum. Once cooled to room temperature THF (4 mL) was added to form a grey suspension which was stirred for 10 minutes then cooled to 0 °C. A solution of iodoform (618 mg, 1.57 mmol, 2.0 eq) in THF (0.5 mL) was added via cannula and stirred for 20 minutes. A solution of aldehyde 273 (165 mg, 0.784 mmol, 1.0 eq) in THF (0.5 mL) was added via cannula and the reaction stirred in the dark at 0 °C for 3.5 hours. The mixture was then diluted with Et₂O, washed three times with brine, dried (MgSO₄) and concentrated. The crude was purified by flash column chromatography (petrol / Et₂O (1:0→19:1) + 1% Et₃N) to give vinyl iodide 257 as a pale yellow oil (157 mg, 0.470 mmol, 60%, 84:16 7E,9E:7E,9Z; Rf 0.63 (petrol / Et₂O (9:1)); [α]D²⁰ +35.6 (c 0.25, CHCl₃); IR (thin film, ν_max / cm⁻¹) 2955, 2912, 2875, 1587, 1459, 1364, 1254, 1200, 1167, 1104, 1060; ¹H NMR (500 MHz, CDCl₃) δ_H 7.03 (1H, dd, J = 14.4 and 10.7 Hz, H9), 6.89-6.84 (1H, m, H4), 6.33 (1H, d, J = 14.4 Hz, H10), 6.23 (1H, ddd, J = 15.2, 10.7 and 1.3 Hz, H8), 5.81-5.76 (2H, m, H3 and H7), 4.48-4.43 (1H, m, H6), 2.25-2.14 (2H, m, H5), 0.99 and 0.96 (2 × 3H, t, J = 7.9 Hz, diastereotopic Si(CH₂CH₃)₂), 0.72-0.56 (4H, m, Si(CH₂CH₃)₂); ¹³C NMR (125 MHz, CDCl₃) δ_C 147.7, 144.8, 136.7, 129.2, 125.2, 78.9, 71.3, 36.5, 6.8, 6.4, 6.0; HRMS (ESI⁺) calc. for C₁₂H₁₉NaOŠi [M+Na]+ 357.0142 found 357.0149.
(3-Trimethylsilyl-2-propynyl)triphenylphosphonium bromide, 279

Prepared according to a modified literature procedure.\textsuperscript{230} 3-(Trimethylsilyl)propargyl bromide (0.50 mL, 3.06 mmol, 1.0 eq) was added dropwise to a solution of triphenylphosphine (803 mg, 3.06 mmol, 1.0 eq) in toluene (3 mL) and stirred in the dark for 19 hours. The resulting precipitate was collected by suction filtration, washed with petrol and dried under high vacuum to give salt 279 as yellow solid (835 mg, 1.84 mmol, 60%); mp 159-163 °C (lit.\textsuperscript{282} 159-161 °C); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 7.96-7.88 (6H, m, o-ArH), 7.83-7.78 (3H, m, p-ArH), 7.71-7.65 (6H, m, m-ArH), 5.23 (2H, d, $J$ = 15.3 Hz, CH$_2$), -0.04 (9H, s, Si(CH$_3$)$_3$), $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$C 136.1 (d, $^1$J(C-P) = 3.1 Hz), 134.7 (d, $^3$J(C-P) = 10.1 Hz), 131.1 (d, $^2$J(C-P) = 13.0 Hz), 118.2 (d, $^1$J(C-P) = 87.8 Hz), 95.5 (d, $^3$J(C-P) = 8.3 Hz), 93.6 (d, $^2$J(C-P) = 13.2 Hz), 20.3 (d, $^1$J(C-P) = 55.0 Hz), 0.0; LRMS (ESI$^+$) calc. for C$_{28}$H$_{13}$IONa [M+Na]$^+$ 275.0 found 275.0.

The spectroscopic data were found to be in agreement with that reported by Zürcher and co-workers.\textsuperscript{283}

(R,E)-2,2-Diethyl-6-(4-(trimethylsilyl)but-1-en-3-yn-1-yl)-5,6-dihydro-2H-1,2-oxasiline, 280

Prepared according to a modified literature procedure. D n-Butyllithium (0.11 mL of a 2.5 M solution in hexanes, 0.285 mmol, 1.5 eq) was added to a solution of salt 279 (133 mg, 0.294 mmol, 1.55 eq) in THF (1 mL) at -78 °C and stirred for one hour. Crude aldehyde 277 (250 mg, 14 wt%, 0.190 mmol, 1.0 eq) in THF (0.5 mL) was added via cannula and the mixture stirred for 4 hours at -78 °C, two hours at 0 °C and 16 hours at room temperature. The reaction was then quenched with NH$_4$Cl
solution, extracted three times with Et₂O, dried (MgSO₄) and concentrated. The crude was purified by flash column chromatography (petrol + Et₃N) to give enyne 280 as a pale yellow oil (14 mg, 0.050 mmol, 26%, 2:1 Z:E); \( R_f \) 0.26 (Z), 0.40 (E) (petrol / Et₂O (99:1)); \([\alpha]_D^{20} \) -66.0 (c 1.0, CHCl₃); 

**IR** (thin film, \( \nu_{\text{max}} / \text{cm}^{-1} \)) 2957, 2879, 2149, 1587, 1460, 1250, 1159, 1066; **\(^1\)H NMR** (500 MHz, CDCl₃) \( \delta \) E-280: 6.84 (1H, ddd, \( J = 14.3, 5.9 \) and 2.3 Hz, H4), 6.23 (1H, dd, \( J = 15.7 \) and 4.7 Hz, H7), 5.84 (1H, dd, \( J = 15.7 \) and 1.8 Hz, H8), 5.77 (1H, dd, \( J = 14.3 \) and 2.4 Hz, H3), 4.49-4.45 (1H, m, H6), 2.36-2.11 (2H, m, H5), 1.05-0.92 (6H, m, Si(CH₂CH₃)₂), 0.17 (9H, s, Si(CH₃)₃); Z-280: 6.89 (ddd, \( J = 14.3, 5.7 \) and 2.4 Hz, H4), 6.00 (1H, dd, \( J = 10.9 \) and 8.7 Hz, H7), 5.77 (1H, dd, \( J = 14.3 \) and 2.4 Hz, H3), 5.52 (1H, dd, \( J = 10.9 \) and 1.0 Hz, H8), 5.03-4.98 (1H, m, H6), 2.36-2.11 (2H, m, H5), 1.05-0.92 (6H, m, Si(CH₂CH₃)₂), 0.73-0.54 (4H, m, Si(CH₂CH₃)₂), 0.17 (9H, s, Si(CH₃)₃); 

**\(^{13}\)C NMR** (125 MHz, CDCl₃) \( \delta_C \) E-280: 148.1, 146.4, 125.1, 109.2, 100.4, 93.0, 71.3, 36.4, 6.9, 6.9, 6.5, 6.1, 0.1); Z-280: 147.7, 146.4, 125.1, 109.6, 100.9, 95.2, 70.3, 35.6, 7.1, 7.1, 6.6, 6.2, 0.0; **HRMS** (FI⁺) calc. for C₁₅H₂₆O₅Si [M]+ 278.1522 found 278.1530.

\((R,E)\)-6-(But-1-en-3-yn-1-yl)-2,2-diethyl-5,6-dihydro-2H-1,2-oxasiline, 281

(Trimethylsilane)diazomethane (157 \( \mu \)L of a 2.0 M solution in hexane, 0.313 mmol, 1.1 eq) was added to a lithium diisopropylamide (1.9 mL of a freshly prepared 0.164 M solution in THF, 0.313 mmol, 1.1 eq) at -78 °C and stirred for one hour. Aldehyde 273 (60 mg, 0.285 mmol, 1.0 eq) in THF (0.5 mL) was added dropwise via cannula and the mixture stirred for three hours at -78 °C and two at 0 °C. The mixture was then diluted with Et₂O, washed three times with 1 M HCl, dried (MgSO₄) and concentrated to give volatile enyne 281 as a pale yellow oil that was unstable to silica gel and used without further purification (129 mg, 42 wt% with THF, ~0.261 mmol, 83%); \( R_f \) 0.15
Experimental

Glutaconaldehyde potassium salt, 282

prepared according to a literature procedure.\textsuperscript{233} \(\text{SO}_3\cdot\text{py} (10.0 \text{ g, 62.8 mmol, 1.0 eq})\) was added to a solution of powdered KOH (18.6 g, 331 mmol, 5.7 eq) in water (50 mL) at -20 °C and stirred at this temperature for one hour, before being allowed to warm slowly to room temperature over 4 hours. The reaction was then heated to 40 °C for 30 minutes, cooled to 5 °C and left to stand for 30 minutes. The crystals that had formed were collected by suction filtration and dried under air (30 minutes) and high vacuum (30 minutes) to give salt 282 as a yellow-green solid (7.83 g, 57.5 mmol, 92\%); \(\text{mp} >350 ^\circ\text{C} \text{ (lit.}^{233} 350 ^\circ\text{C)}\); \(\text{H NMR (400 MHz, (CD}_3\text{)_2SO)} \delta_H 8.68 (2H, d, J = 9.1 \text{ Hz, H1 and H5}), 7.05 (1H, t, J = 13.2, H3), 5.11 (2H, dd, J = 13.2 and 9.1 Hz, H2 and H4); \(\text{C NMR (101 MHz, CDCl}_3\text{)} \delta_C 184.4, 160.3, 106.6; \text{LRMS (ESI')} \text{ calc. for C}_3\text{H}_7\text{KNaO}_2 [\text{M+Na}'] 159.0, \text{ found 159.0.} \)

The physical and spectroscopic data were found to be in agreement with that reported by Becher and co-workers.\textsuperscript{233}
Experimental

(2E,4E)-5-Iodopenta-2,4-dienal, 283

\[
\text{\textcolor{red}{\text{\(\text{\(2\text{E,4E}\)}\)-5-Iodopenta-2,4-dienal, 283}}}}
\]

Prepared according to a literature procedure. Powdered iodine (14.8 g, 58.3 mmol, 1.1 eq) was added to a solution of triphenylphosphine (15.3 g, 58.3 mmol, 1.1 eq) in DCM (75 mL) at 0 °C, followed by salt 282 (7.20 g, 52.9 mmol, 1.0 eq). The mixture was stirred for 72 hours at room temperature in the dark, then was quenched with NaHCO₃ solution, extracted with DCM, dried (MgSO₄) and concentrated. The crude residue was purified via flash column chromatography (petrol / Et₂O (7:3)) to give iodide 283 as a yellow solid (6.02 g, 28.9 mmol, 55%, 62:38 2E,4E:2E,4Z). The solid was then recrystallized from petrol to give isomerically enriched 283 (3.50 g, 16.8 mmol, 32%, 93:7 2E:4E:2E:4Z); \(R_f\) 0.25 (petrol / Et₂O (4:1)); mp 64-65 °C (lit.²³⁴ 58-62 °C); \(^1\text{H NMR}\) (400 MHz, C₆D₆) \(\delta\)H 9.18 (1H, d, \(J = 7.8\) Hz, H1), 6.48 (1H, dd, \(J = 14.4\) and 10.4 Hz, H4), 6.14 (1H, d, \(J = 14.4\) Hz, H5), 5.83 (1H, dd, \(J = 15.2\) and 10.4 Hz, H3), 5.58 (1H, dd, \(J = 15.2\) and 7.8 Hz, H2); \(^{13}\text{C NMR}\) (101 MHz, C₆D₆) \(\delta\)C 191.7, 148.0, 142.9, 131.1, 90.6; \(^{13}\text{C NMR}\) (ESI⁺) calc. for C₅H₅IINO [M+Na]⁺ 230.9, found 230.9.

The physical and spectroscopic data were found to be in agreement with that reported by Soullez and co-workers.²³⁴

2-((1E,3E)-4-Iodobuta-1,3-dien-1-yl)oxirane, 284

\[
\text{\textcolor{red}{\text{\(\text{\(2\text{-}\((1\text{E,3E}\)}\)-4-Iodobuta-1,3-dien-1-yl)oxirane, 284}}}}}
\]

Prepared according to a modified literature procedure.²⁸⁴ To a solution of aldehyde 283 (1.00 g, 4.81 mmol, 1.0 eq) in DCM (20 mL) was added trimethylsulfonium iodide (1.96 g, 9.62 mmol, 2.0 eq), TBAB (15 mg, 0.048 mmol, 0.01 eq) and NaOH (4 mL of a 50 wt% aq. solution). The reaction was heated at 45 °C for 66 h, before it was diluted with water, extracted with DCM, and the combined organic phase washed with brine, dried (MgSO₄) and concentrated to give epoxide 284 as
7. Experimental

A brown oil that was used without further purification (923 mg, ~4.16 mmol, ~86%); Rf 0.38 (petrol/EtO (4:1)); IR (thin film, νmax/cm⁻¹) 3048, 2985, 2911, 1678, 1571, 1472, 1388, 1288, 1246, 1193, 1131; ¹H NMR (400 MHz, CDCl₃) δH 7.03 (1H, dd, J = 14.5 and 10.9 Hz, H5), 6.42 (1H, d, J = 14.5 Hz, H6), 6.35 (1H, dd, J = 15.2 and 10.9 Hz, H4), 5.40 (1H, dd, J = 15.2 and 7.8 Hz, H3), 3.34-3.34 (1H, m, H2), 2.98 (1H, dd, J = 5.3 and 4.2 Hz, 1 × H1), 2.66 (1H, dd, J = 5.3 and 2.6 Hz, 1 × H1); ¹³C NMR (101 MHz, CDCl₃) δC 143.9, 134.0, 131.4, 80.9, 51.6, 49.2; HRMS (F⁻) calc. for C₆H₇IO [M]⁻ 221.9542, found 221.9544.

7.13.4 Synthesis of C15-C22 of Resolvin D3

D-Deoxyribose dimethylacetal, 287

Prepared according to a modified literature procedure.²⁸⁵ 2-Methoxypropene (0.71 mL, 7.46 mmol, 2.0 eq) was added to a solution of D-deoxyribose (500 mg, 3.73 mmol, 1.0 eq), pyridinium p-toluenesulfonate (19 mg, 0.075 mmol, 0.02 eq) and 4 Å molecular sieves in EtOAc (15 mL) and the reaction stirred for 5 hours when TLC revealed remaining starting material. A further portion of 2-methoxypropene (0.18 mL, 1.87 mmol, 0.5 eq) was added and the mixture stirred for a further three hours before it was filtered and concentrated. The crude was purified via flash column chromatography (petrol/Et₂O (4:1 → 1:1) + 1% Et₃N) to give 287 as a colourless, viscous oil (340 mg, 1.95 mmol, 52%); Rf 0.36 (petrol/EtOAc (1:1)); [α]D²⁰ -21.4 (c 1.0, CHCl₃) [lit.²⁸⁵ -18.5 (c 4.2, CHCl₃)]; ¹H NMR (400 MHz, CDCl₃) δH 5.26 (0.8H, dt, J = 7.1 and 4.3 Hz, H1), 5.08 (0.2H, dt, J = 9.2 and 3.4 Hz, H1), 4.48 (0.8H, dt, J = 6.6 and 4.3 Hz, H4), 4.44-4.40 (0.2H, m, H4), 4.21-4.09 (1H, m, H3), 3.93 (1H, dd, J = 12.7 and 3.5 Hz, H5), 3.70 (1H, dd, J = 12.7 and 3.3 Hz, H5'), 2.65 (1H, s, OH), 2.24 (0.8H, dt, J = 14.8 and 4.3 Hz, H2), 2.11-2.08 (0.2H, m, H2), 1.81-1.74 (1H, m, H2').
1.57 (2.4H, s, CH₃), 1.36 (0.6H, s, CH₃), 1.35 (3H, s, CH₃); \(^{13}\)C NMR (101 MHz, CDCl₃) δC [109.4, 108.8, [91.4], 91.0, 71.6, [71.2], [70.7], 70.4, 62.1, [60.6], [32.4], 32.1, [28.0], 27.2 (square brackets indicate minor isomer); LRMS (ESI\(^+\)) calc. for C₈H₁₄O₄Na [M+Na]\(^+\) 197.1 found 197.1.

The spectroscopic data was found to be in agreement with that reported by Jogireddy and co-workers.\(^{286}\)

\(((4R,5S)-2,2-Dimethyl-5-((Z)-pent-2-en-1-yl)-1,3-dioxolan-4-yl)methanol, 288\)

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\text{HO} \quad 4 \quad 7
\]

Prepared according to a modified literature procedure.\(^{211}\) NaHMDS (0.69 mL of a 1.86 M solution in THF, 1.29 mmol, 2.5 eq) was added to a solution of (1-propyl)triphenylphosphonium bromide (498 mg, 1.29 mmol, 2.5 eq) in Et₂O (10 mL) at 0°C and stirred for 20 minutes, before stirring at room temperature for a further 20 minutes. The mixture was cooled to -78 °C and a solution of protected sugar 287 (90 mg, 0.517 mmol, 1.0 eq) in Et₂O (1 mL) added via cannula. The reaction was warmed to 0 °C over 5 hours, quenched with a pH 7 phosphate buffer solution, extracted three times with Et₂O, dried (Na₂SO₄) and concentrated. The crude was purified via flash column chromatography (petrol / Et₂O (3:2)) to give 288 as a colourless oil (86 mg, 0.429 mmol, 83%); \(R_f\) 0.10 (petrol / Et₂O (7:3)); \([\alpha]_{D}^{20}\) +17.7 (c 1.0, CHCl₃); \(^{1}H\) NMR (400 MHz, CDCl₃) δH 5.53-5.45 (1H, m, H6), 5.37-5.29 (1H, m, H5), 4.21-4.13 (2H, m, H2 and H3), 3.66-3.59 (2H, m, H1), 2.41-2.11 (3H, m, H4 and OH), 2.09-1.99 (2H, m, H7), 1.46 (3H, s, CH₃), 1.34 (3H, s, CH₃), 0.96 (3H, t, \(J = 7.5\ Hz, H8\)); \(^{13}\)C NMR (101 MHz, CDCl₃) δC 134.4, 123.8, 123.8, 108.8, 77.9, 76.7, 61.6, 28.1, 27.3, 25.4, 20.8, 14.0; LRMS (ESI\(^+\)) calc. for C₁₁H₂₀O₃Na [M+Na]\(^+\) 223.1 found 223.1.

The spectroscopic data was found to be in agreement with that reported by Rodríguez and co-workers.\(^{211}\)
(4S,5S)-4-(Iodomethyl)-2,2-dimethyl-5-((Z)-pent-2-en-1-yl)-1,3-dioxolane, 289

Prepared according to a modified literature procedure.\textsuperscript{210} Triphenylphosphine (1.85 g, 7.05 mmol, 1.2 eq), imidazole (1.20 g, 17.6 mmol, 3.0 eq) and iodine (1.94 g, 7.64 mmol, 1.3 eq) were added sequentially to a solution of alcohol 288 (1.18 g, 5.89 mmol, 1.0 eq) in toluene (25 mL) at 60 °C and stirred for 50 minutes. The mixture was cooled to room temperature, quenched with Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} solution, extracted three times with Et\textsubscript{2}O, dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated. The crude was purified \textit{via} flash column chromatography (petrol / Et\textsubscript{2}O (19:1)) to give 289 as a colourless oil (1.28 g, 4.13 mmol, 70%); \(R_f\) 0.10 (petrol / Et\textsubscript{2}O (99:1)); \([\alpha]_D^{20} +1.3\) (c 2.0, CHCl\textsubscript{3}); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 5.58-5.50 (1H, m, H\textsubscript{6}), 5.41-5.37 (1H, m, H5), 4.38-4.31 (1H, m, H2), 4.19-4.13 (1H, m, H3), 3.21-3.17 (2H, m, H1), 2.36-2.32 (2H, m, H4), 2.11-2.01 (2H, m, H7), 1.48 (3H, s, CH\textsubscript{3}), 1.36 (3H, s, CH\textsubscript{3}), 0.99 (3H, t, \(J = 7.5\) Hz, H8); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) 134.5, 123.5, 108.5, 78.3, 77.6, 28.4, 27.4, 25.7, 20.9, 14.0, 3.8.

The spectroscopic data was found to be in agreement with that reported by Rodríguez and co-workers.\textsuperscript{210}

\((S,1E,5Z)-1-Iodo-oct-1,5-dien-3-ol, 254\) and \((S,Z)-oct-5-en-1-yn-3-ol, 290)\n
Prepared according to a modified literature procedure.\textsuperscript{210} n-Butyllithium (2.6 mL of a 2.5 M solution in hexanes, 6.44 mmol, 4.0 eq) was added to diisopropylamine (0.99 mL, 7.09 mmol, 4.4 eq) in THF (16 mL) at 0 °C and stirred for 30 minutes. The mixture was then cooled to -78 °C, iodide 289 (500 mg, 1.61 mmol, 1.0 eq) was added \textit{via} cannula and the reaction stirred for 20 hours. The mixture was then warmed to room temperature, quenched with NH\textsubscript{4}Cl solution, extracted three times
with Et₂O, dried (Na₂SO₄) and concentrated. The crude was purified via flash column chromatography (petrol / EtOAc (97:3)) to give 254 as a light yellow oil (133 mg, 0.528 mmol, 33%) and 290 as a colourless, volatile oil (8 mg, 0.064 mmol, 4%).

**254**: \( R_f \) 0.39 (petrol / EtOAc (4:1)); \([\alpha]_{D}^{20}\) -20.7 (c 2.0, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃) \( \delta_H \) 6.59 (1H, d, \( J = 14.4 \) and 5.9 Hz, H2), 6.37 (1H, dd, \( J = 14.4 \) and 1.4 Hz, H1), 5.64-5.57 (1H, m, H6), 5.36-5.29 (1H, m, H5), 4.17-4.10 (1H, m, H3), 2.31 (2H, t, \( J = 6.8 \) Hz, H4), 2.10-2.02 (2H, m, H7), 1.71 (1H, d, \( J = 4.3 \) Hz, OH), 0.98 (3H, t, \( J = 7.5 \) Hz, H8); \(^{13}\)C NMR (101 MHz, CDCl₃) \( \delta_C \) 147.8, 136.2, 122.7, 77.3, 73.9, 34.5, 20.8, 14.2; LRMS (ESI⁺) calc. for \( \text{C}_8\text{H}_{13}\text{ONa}[\text{M+Na}]^+ \) 275.0 found 275.0.

**290**: \( R_f \) 0.29 (petrol / EtOAc (4:1)); \([\alpha]_{D}^{20}\) -27.6 (c 1.0, CHCl₃) [lit.\(^{287}\) -28.3 (c 1.5, CHCl₃)]; \(^1\)H NMR (400 MHz, CDCl₃) \( \delta_H \) 5.66-5.57 (1H, m, H6), 5.45-5.39 (1H, m, H5), 4.40-4.35 (1H, m, H3), 2.51-2.45 (2H, m, H4), 2.45 (1H, d, \( J = 2.1 \) Hz, H1), 2.16 (1H, br s, OH), 2.07 (2H, quin, \( J = 7.6 \) Hz, H7), 0.96 (3H, t, \( J = 7.6 \) Hz, H8); \(^{13}\)C NMR (101 MHz, CDCl₃) \( \delta_C \) 136.1, 122.4, 84.5, 73.0, 61.8, 35.4, 20.8, 14.2; LRMS (ESI⁺) calc. for \( \text{C}_8\text{H}_{13}\text{ONa}[\text{M+Na}]^+ \) 147.1 found 147.1

The spectroscopic data were found to be in agreement with that reported by Rodríguez and co-workers.\(^{210}\)

### 7.13.5 Synthesis of C16-C20 of Resolvin E1

Pent-1-yn-3-one, 291

\[ \text{C}_5\text{H}_8\text{O} \]

\( \gamma\)-MnO₂ (6.00 g, 69.5 mmol, 20.0 eq) was added to a solution of 1-pentyn-3-ol (0.30 mL, 3.48 mmol, 1.0 eq) and 4 Å molecular sieves in DCM (20 mL) and the reaction stirred for 4 hours. The mixture was then filtered through Celite\(^\circledR\) and concentrated cautiously under reduced pressure to give ynone
291 as a volatile, colourless oil which was used without further purification (133 mg, 61 wt% with DCM and unreacted 1-pentyn-3-ol, ~0.981 mmol, ~28%); $^1$H NMR (400 MHz, CDCl$_3$) δ$_H$ 3.20 (1H, s, H1), 2.62 (2H, q, $J$ = 7.4 Hz, H4), 1.16 (3H, t, $J$ = 7.4 Hz, H5).

The spectroscopic data was found to be in agreement with that reported by Lockhart and co-workers.

(E)-1-Iodopent-1-en-3-one, 293

![Image of (E)-1-Iodopent-1-en-3-one](image)

Prepared according to a modified literature procedure. A solution of ynone 291 (62 mg, 63 wt%, 0.476 mmol, 1.0 eq), lithium iodide (76 mg, 0.599 mmol, 1.2 eq) and acetic acid (0.5 mL) was stirred for three hours. The mixture was diluted with Et$_2$O and water, separated, and the aqueous phase extracted twice with Et$_2$O. The combined organic phase was washed 6 times with NaHCO$_3$, dried (Na$_2$SO$_4$) and concentrated to give vinyl iodide 293 as a yellow oil which was used without further purification (100 mg, ~0.476 mmol, ~100%); $R_f$ 0.21 (petrol / Et$_2$O (19:1)); $^1$H NMR (400 MHz, CDCl$_3$) δ$_H$ 7.81 (1H, d, $J$ = 14.9 Hz, H1), 7.17 (1H, d, $J$ = 14.9 Hz, H2), 2.54 (2H, q, $J$ = 7.3 Hz, H4), 1.11 (3H, t, $J$ = 7.3 Hz, H5); $^{13}$C NMR (101 MHz, CDCl$_3$) δ$_C$ 197.9, 144.4, 95.6, 33.7, 7.7.

The spectroscopic data were found to be in agreement with that reported by Amin and co-workers.

1-(Diethyl(isopropoxy)silyl)pent-1-yn-3-ol, 294

![Image of 1-(Diethyl(isopropoxy)silyl)pent-1-yn-3-ol](image)

**Procedure A:** n-Butyllithium (2.1 mL of a 2.5 M solution in hexanes, 5.25 mmol, 1.1 eq), silyl alkyne 114 (1.00 g, 94 wt% purity, 5.25 mmol, 1.1 eq) in THF (20 mL) and propionaldehyde (0.35 mL, 4.77 mmol, 1.0 eq) gave, after purification via flash column chromatography (petrol / Et$_2$O (9:1) + 1% Et$_3$N), propargylic alcohol 294 as a colourless oil (805 mg, 3.52 mmol, 74%); $R_f$ 0.27 (petrol /
Et₂O (4:1); IR (thin film, ν<sub>max</sub> / cm<sup>-1</sup>) 3398, 2968, 2879, 2170, 1462, 1381, 1237, 1173, 1122;

<sup>1</sup>H MR (400 MHz, CDCl<sub>3</sub>) δₜ 4.34 (1H, t, J = 6.4 Hz, H3), 4.14 (1H, sept, J = 6.0 Hz, OCH(CH₃)₂), 1.90 (1H, br s, OH), 1.79-1.69 (2H, m, H4), 1.19 (6H, d, J = 6.0 Hz, OCH(CH₃)₂), 1.02 (3H, t, J = 7.4 Hz, H5), 0.99 (6H, t, J = 7.8 Hz, Si(CH₂CH₃)₂), 0.65 (4H, q, J = 7.8 Hz, Si(C₂H₄CH₃)₂);

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ<sub>c</sub> 107.3, 85.9, 66.1, 64.1, 30.8, 25.5, 9.3, 6.7, 6.6; HRMS (ESI<sup>+</sup>) calc. for C₁₂H₂₄O₂NaSi [M+Na]<sup>+</sup> 251.14378 found 251.14338.

1-(Diethyl(isopropoxy)silyl)pent-1-yn-3-one, 295

[Chemical structure image]

γ-MnO₂ (5.72 g, 65.8 mmol, 20.0 eq) was added to a solution of alcohol 294 (749 mg, 3.29 mmol, 1.0 eq) and 4 Å molecular sieves in DCM (10 mL) and the reaction stirred for 4 hours. The mixture was then filtered through Celite<sup>®</sup> and concentrated to give ketone 295 as a yellow oil that was unstable to silica gel and used without further purification (530 mg, ~2.34 mmol, ~71%); R<sub>f</sub> 0.18 (petrol / Et₂O (49:1)); IR (thin film, ν<sub>max</sub> / cm<sup>-1</sup>) 2970, 2939, 2916, 2879, 2150, 1684, 1460, 1411, 1382, 1174, 1130; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δₜ 4.15 (1H, sept, J = 6.1 Hz, OCH(CH₃)₂), 2.60 (1H, q, J = 7.4 Hz, H4), 1.20 (6H, d, J = 6.1 Hz, OCH(CH₃)₂), 1.16 (3H, t, J = 7.4 Hz, H5), 1.02 (6H, t, J = 7.8 Hz, Si(CH₂CH₃)₂), 0.72 (4H, q, J = 7.8 Hz, Si(C₂H₄CH₃)₂); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ<sub>c</sub> 188.2, 101.9, 94.0, 66.7, 38.8, 25.4, 7.8, 6.4, 6.4; HRMS (FI<sup>+</sup>) calc. for C₁₂H₂₄O₂Si [M]<sup>+</sup> 226.1389 found 226.1387.
(R)-1-(Diethyl(isopropoxy)silyl)pent-1-yn-3-ol, (R)-294

A solution of crude ynone 295 (480 mg, 2.10 mmol, 1.0 eq) in isopropyl alcohol (15 mL) was degassed with argon for one hour, before the addition of (1R,2R)-(+)−N-Tosyl-1,2-diphenylethane-1,2-diamine[η⁶-1-isopropyl-4-methylbenzene]-ruthenium(II) (Noyori catalyst²²) (36 mg, 0.050 mmol, 0.025 eq) as a solution in DCM (1 mL) and degassed for a further 15 minutes. The mixture was stirred for 1.5 hours before being concentrated under reduced pressure. The crude residue was purified via flash column chromatography (petrol / Et₂O (4:1) + 1% Et₃N) to give alcohol (R)-294 as a colourless oil (443 mg, 1.94 mmol, 92%); ee 97% (assumed from analysis of S17); [α]̲D²⁰ +4.8 (c 1.0, CHCl₃). Other data were identical to that reported for (±)-294.

(R)-1-(Diethyl(isopropoxy)silyl)pent-1-yn-3-yl acetate, 296

Procedure C: Acetic anhydride (0.38 mL, 4.03 mmol, 2.0 eq), propargyl alcohol 294 (460 mg, 2.01 mmol, 1.0 eq), one crystal of DMAP and Et₃N (0.84 mL, 6.04 mmol, 3.0 eq) in DCM (10 mL) gave acetate 296 as a pale yellow oil that was used in the next step without further purification (540 mg, ~2.00 mmol, ~quant.); ee 97% (assumed from analysis of S17); Rf 0.16 (petrol / Et₂O (19:1)); [α]̲D²⁰ +90.9 (c 1.0, CHCl₃). IR (thin film, νmax / cm⁻¹) 2972, 2879, 2179, 1748, 1459, 1370, 1231, 1173, 1130, 1031; ¹H NMR (400 MHz, CDCl₃) δH 5.34 (1H, t, J = 6.5 Hz, H3), 4.12 (1H, sept, J = 6.0 Hz, OC₂H₂), 2.07 (3H, s, OCOC₂H₃), 1.78 (2H, quin, J = 6.5 Hz, H4), 1.79-1.69 (2H, m, H4), 1.18 (6H, d, J = 6.0 Hz, OCH(CH₃)₂), 1.01 (3H, t, J = 6.5 Hz, H5), 0.98 (6H, t, J = 7.9 Hz, Si(CH₂CH₃)₂), 0.64 (4H, q, J = 7.9 Hz, Si(CH₂CH₃)₂); ¹³C NMR (101 MHz, CDCl₃) δC 169.9, 103.3,
7. Experimental

| 86.8, 66.2, 65.4, 28.0, 25.4, 21.0, 9.3, 6.6, 6.5; HRMS (ESI+) calc. for C_{14}H_{26}O_{3}NaSi [M+Na]^+ 293.15379 found 293.15434. |

(R)-1-(Diethyl(isopropoxy)silyl)pent-1-yn-3-yl benzoate, S17

![Structure of (R)-1-(Diethyl(isopropoxy)silyl)pent-1-yn-3-yl benzoate, S17]

Benzoyl chloride (16 μL, 0.014 mmol, 2.0 eq) was added dropwise to alcohol (R)-294 (20 mg, 0.070 mmol, 1.0 eq), DMAP (2 mg, 0.014 mmol, 0.2 eq) and Et$_3$N (29 μL, 0.210 mmol, 3.0 eq) in DCM (0.7 mL). The mixture was stirred for three hours, and quenched with NaHCO$_3$ solution. The aqueous layer was extracted with DCM and the combined organic layers dried (MgSO$_4$) and concentrated. The crude was purified via flash column chromatography (petrol / Et$_2$O (1:0→19:1) + 1% Et$_3$N) to give S17 as a colourless oil (23 mg, ~0.070 mmol, quant); ee 97% (CHIRALPAK-IA, 0.05% IPA/n-Hex, 1.0 mL/min, S – 7.8 min, R – 8.3 min); $R_f$ 0.22 (petrol / Et$_2$O (49:1)); $[\alpha]_D^{20}$ +22.6 (c 1.0, CHCl$_3$); IR thin film, $\nu_{max}$ / cm$^{-1}$ 2971, 2937, 2878, 2178, 1725, 1453, 1382, 1265, 1094, 1069, 1026; $^1$H NMR (400 MHz, CDCl$_3$) $\delta_H$ 8.08 (2H, m, o-ArH), 7.59-7.54 (1H, m, p-ArH), 7.47-7.43 (2H, m, m-ArH), 5.62 (1H, t, $J$ = 6.4 Hz, H3), 4.15 (1H, sept, $J$ = 6.0 Hz, OCH(CH$_3$)$_2$), 1.94 (2H, quin, $J$ = 6.4 Hz, H4), 1.79-1.69 (2H, m, H4), 1.18 (6H, d, $J$ = 6.0 Hz, OCH(CH$_3$)$_2$), 1.10 (3H, t, $J$ = 6.4 Hz, H5), 1.00 (6H, t, $J$ = 7.8 Hz, Si(CH$_3$)$_2$), 0.66 (4H, q, $J$ = 7.8 Hz, Si(CH$_2$CH$_3$)$_2$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta_C$ 165.4, 133.1, 130.1, 129.8, 128.4, 103.3, 87.1, 66.2, 65.9, 28.2, 25.4, 9.4, 6.7, 6.6; HRMS (ESI+) calc. for C$_{19}$H$_{26}$O$_3$NaSi [M+Na]$^+$ 355.16934, found 355.16999.
(R)-2,2,5-Triethyl-2,5-dihydro-1,2-oxasilole, 297

Procedure D: Palladium on CaCO3 (214 mg, 5 wt % Pd, 0.010 mmol, 0.05 eq), acetate 296 (540 mg, 2.00 mmol, 1.0 eq) and quinoline (47 μL, 0.400 mmol, 0.2 eq) in THF (20 mL) were stirred under a hydrogen atmosphere for three hours and gave, after purification by rapid flash column chromatography (petrol / Et2O (19:1)), oxasilole 297 a pale yellow oil which was unstable to silica gel (200 mg, 1.17 mmol, 59% isolated); ee 97% (assumed from analysis of S17); Rf 0.21 (petrol); [α]D20 -89.1 (c 1.0, CHCl3); IR (thin film, νmax / cm⁻¹) 2958, 2936, 2915, 2877, 1557, 1461, 1412, 1237, 1099, 1019, 1006; ¹H NMR (400 MHz, CDCl3) δH 6.89 (1H, dd, J = 10.5 and 1.4 Hz, H4), 5.97 (1H, dd, J = 10.5 and 2.2 Hz, H3), 4.64-4.60 (1H, m, H5), 1.68-1.47 (2H, m, H6), 0.98-0.89 (9H, m, H7 and Si(CH2CH3)2), 0.76-0.58 (4H, m, Si(CH2CH3)2); ¹³C NMR (101 MHz, CDCl3) δC 154.4, 124.4, 84.4, 30.2, 9.6, 7.2, 7.1, 6.8, 6.5; HRMS (FI⁺) calc. for C₉H₁₈OSi [M]+ 170.1127 found 170.1128.

(R,E)-1-Iodopent-1-en-3-ol, 258

A solution of silane 297 (96 mg, 0.564 mmol, 1.0 eq) and iodine (715 mg, 2.82 mmol, 5.0 eq) in MeOH (1.5 mL) was stirred in the dark for two hours before the reaction was quenched with Na₂S₂O₃ solution, extracted three times with Et₂O and dried (MgSO₄) and concentrated. The crude was purified via flash column chromatography (petrol / Et₂O (9:1→7:3)) to give iodide 258 as a yellow oil (66 mg, 0.311 mmol, 55%, 9:1 E:Z); ee 96% (CHIRALPAK-IA, 1% IPA/n-Hex, 1.3 mL/min, R – 15.4 min, S - 16.5 min); Rf 0.23 (petrol / Et₂O (7:3)); [α]D20 0.00 (c 1.0, CHCl3); ¹H NMR (400 MHz, CDCl3) δH 6.57 (1H, dd, J = 14.3 and 6.4 Hz, H2), 6.34 (1H, d, J = 14.3 Hz, H1), 4.03 (1H, m, H3), 1.71 (1H, m, OH), 1.56 (2H, quin, J = 7.1 Hz, H4), 0.93 (3H, t, J = 7.1 Hz, H5); ¹³C NMR (101 MHz, CDCl3) δC 148.4, 77.3, 76.0, 29.5, 9.5.
7. Experimental

The spectroscopic data were found to be in agreement with that reported by Amin and co-workers.\textsuperscript{221}

7.13.6 Endgame Cross Couplings To Construct Resolvin Natural Products

(5Z,7E)-4-Hydroxy-8-phenylocta-5,7-dienoic acid, 298

A degassed solution of potassium trimethylsilanolate (46 mg of a 98 wt% solid in 0.33 mL of DME, 0.350 mmol, 4.0 eq) was added over 4 hours by syringe pump to silane 256 (20 mg, 0.088 mmol, 1.0 eq), E-iodostyrene 145a (20 mg, 0.088 mmol, 1.0 eq), water (16 μL, 0.880 mmol, 10 eq) and bis(dibenzylideneacetone)palladium (4.6 mg, 0.008 mmol, 0.10 eq) in degassed DME (0.2 mL) and stirred at room temperature for 24 hours. The mixture was then quenched with 1M HCl, extracted 4 times with EtOAc, dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated \textit{in vacuo}. The crude was purified by flash column chromatography (DCM / MeOH (1:0→9:1)) to give alkene 298 as a yellow oil (11 mg, 89 wt% with Et\textsubscript{2}Si(OH)\textsubscript{2}, 0.042 mmol, 48%; isomerized to minor amounts of \textit{E,E}-298 on exposure to light); \textit{Rf} 0.23 (DCM / MeOH (9:1)); \textbf{IR} (thin film, \nu\textsubscript{max} / cm\textsuperscript{-1}) 3385, 3027, 2958, 1709, 1639, 1494, 1449, 1414, 1184, 1058; \textbf{\textbf{1H NMR}} (500 MHz, C\textsubscript{6}D\textsubscript{6}) \delta\textsubscript{H} 7.35 (2H, d, \textit{J} = 7.36 Hz, H9), 7.20-7.12 (2H, m, H10), 7.10-7.05 (2H, m, H7 and H11), 6.42 (1H, d, \textit{J} = 15.6 Hz, H8), 6.03 (1H, app t, \textit{J} = 11.1 Hz, H6), 5.32-5.28 (1H, m, H5), 4.54-4.49 (1H, m, H4), 3.48 (2H, br s, OH and CO\textsubscript{2}H), 2.37-2.22 (2H, m, H2), 1.77-1.69 (2H, m, H3); \textbf{\textbf{13C NMR}} (125 MHz, C\textsubscript{6}D\textsubscript{6}) \delta\textsubscript{C} 178.6, 137.3, 134.4, 133.9, 129.9, 128.6, 126.7, 123.8, 122.9, 67.0, 32.1, 29.6; \textbf{HRMS} (ESI\textsuperscript{+}) calc. for C\textsubscript{14}H\textsubscript{16}O\textsubscript{3}Na [M+Na]\textsuperscript{+} 255.09917 found 255.09896.
(2R,AZ,6E)-Deca-4,6-diene-1,2,8-triol, 299

A degassed solution of TBAF·3H₂O (0.24 mL of a 1.0 M solution in DME, 0.240 mmol, 3.0 eq) was added over 12 hours by syringe pump to silane 274 (15 mg, 0.081 mmol, 1.0 eq), iodide 258 (26 mg, 0.121 mmol, 1.5 eq), and allylpalladiumchloride dimer (1.4 mg, 0.004 mmol, 0.05 eq) in degassed DME (0.1 mL) and stirred at room temperature for a further 12 hours. The unconcentrated reaction mixture (applied directly to silica) was purified by flash column chromatography (petrol / Et₂O (1:0→0:1; then DCM / MeOH (1:0→9:1)) to give alkene 299 as a pale yellow oil (9 mg, 73 wt% with DCM, 0.035 mmol, 43%); Rₓ 0.19 (DCM / MeOH (9:1)); IR (thin film, νmax / cm⁻¹) 3343, 2962, 2929, 2875, 1684, 1457, 1413, 1379, 1341, 1233; ¹H NMR (500 MHz, CDCl₃) δH 6.51 (1H, ddq, J = 15.2 Hz, 11.0 and 1.0 Hz, H₆), 6.16 (1H, app t, J = 11.0 Hz, H₅), 5.73 (1H, dd., J = 15.2 and 6.6 Hz, H₇), 5.50-5.44 (1H, m, H₄), 4.13-4.09 (1H, m, H₈), 3.81-3.76 (1H, m, H₂), 3.71-3.66 and 3.53-3.46 (2 × 1H, m, diastereotopic H₁), 2.47-2.15 (4H, m, H₃ and 2 × OH), 1.82 (1H, br s, OH), 1.62-1.55 (2H, m, H₉), 0.95-0.91 (3H, m, H₁₀); ¹³C NMR (125 MHz, CDCl₃) δC 137.2, 131.0, 126.6, 125.2, 73.9, 71.8, 66.1, 31.7, 30.2, 9.7; HRMS (ESI⁺) calc. for C₁₀H₁₈O₃Na [M+Na]⁺ 209.11482 found 209.11465.

(4E,6E)-8-Hydroxydeca-4,6-dien-3-one, 301

Isolated as a side product of the above reaction. Yellow oil; Rₓ 0.24 (petrol / EtOAc (7:3)); IR (thin film, νmax / cm⁻¹) 3404, 2965, 2936, 2877, 1662, 1638, 1598, 1459, 1413, 1377, 1211, 1117, 1002; ¹H NMR (500 MHz, CDCl₃) δH 7.16 (1H, dd., J = 15.3 and 10.8 Hz, H₇), 6.37 (1H, dd., J = 15.2 and 10.8 Hz, H₅), 6.18 (1H, d, J = 15.2 Hz, H₄), 6.15 (1H, dd., J = 15.3 and 5.8 Hz, H₆), 4.22-4.17 (1H,
m, H8), 2.59 (2H, q, $J = 7.2$ Hz, H2), 1.64-1.58 (2H, m, H9), 1.57 (1H, br s, OH), 1.12 (3H, t, $J = 7.2$ Hz, H1), 0.95 (3H, t, $J = 7.2$ Hz, H10); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 201.2, 145.3, 141.4, 129.6, 128.1, 73.3, 33.8, 30.0, 9.5, 8.2; LRMS (ESI$^+$) calc. for C$_{10}$H$_{16}$O$_2$Na [M+Na]$^+$ 191.1 found 191.1.

(4Z,6E)-Deca-4,6-diene-3,8-diol, 302

Isolated as a side product of the above reaction. Yellow oil; $R_f$ 0.35 (petrol / EtOAc (1:1)); IR (thin film, $\nu_{\text{max}}$ / cm$^{-1}$) 3394, 2960, 2934, 2877, 1660, 1638, 1596, 1459, 1412, 1377, 1328, 1240, 1160; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 6.53 (1H, dd, $J = 15.0$ and 11.2 Hz, H6), 6.07 (1H, app t, $J = 11.2$ Hz, H5), 5.74 (1H, dd, $J = 15.0$ and 6.0 Hz, H7), 5.40 (1H, app t, $J = 11.2$ Hz, H4), 4.54-4.50 (1H, m, H3), 4.13-4.06 (1H, m, H8), 3.67 (1H, d, $J = 2.4$ Hz, OH), 1.68-1.47 (5H, m, H2, H9 and OH), 0.95-0.90 (6H, m, H1 and H10); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 138.2, 133.8, 129.9, 125.3, 73.9, 69.3, 30.4, 30.2, 9.7, 9.7; HRMS (ESI$^+$) calc. for C$_{10}$H$_{18}$O$_2$Na [M+Na]$^+$ 193.11990 found 193.11982.

Attempting to Synthesis Resolvin D3:

A degassed solution of potassium trimethylsilanolate (31 mg of a 98 wt% solid in 0.20 mL of DME, 0.239 mmol, 4.0 eq) was added over 4 hours by syringe pump to silane 256 (14 mg, 0.060 mmol, 1.0 eq), silane 257 (20 mg, 0.060 mmol, 1.0 eq), water (11 $\mu$L, 0.600 mmol, 10 eq) and bis(dibenzylideneacetone)palladium (3.5 mg, 0.006 mmol, 0.1 eq) in degassed DME (0.16 mL) and stirred at 60 °C for 24 hours. The mixture was degassed with argon for 5 minutes, before the addition of a further portion of bis(dibenzylideneacetone)palladium (3.5 mg, 0.006 mmol, 0.1 eq). The reaction was stirred a further 24 hours at 60 °C, then cooled to room temperature and degassed again for 5 minutes. Allylpalladiumchloride dimer (2.2 mg, 0.006 mmol, 0.1 eq) was added, followed by a solution of degassed TBAF·3H$_2$O (0.42 mL of a 1.0 M solution in DME, 0.420 mmol, 7.0 eq) and iodide 254 (30 mg, 0.120 mmol, 2.0 eq) by syringe pump over 12 hours. After a further 12 hours, the
solution was degassed for 5 minutes, and a further portion of allylpalladiumchloride dimer (2.2 mg, 0.006 mmol, 0.1 eq) added. The mixture was stirred for a further 24 hours before it was loaded directly onto a column of silica gel. The crude was purified by flash column chromatography (petrol / Et₂O (1:0→0:1; then DCM / MeOH (1:0→9:1)) to give a series of compounds; all available data is given below.

**Resolvin D3, 251**

Yellow oil. $^1$H NMR (500 MHz, CDCl₃) δH 6.57-6.45 (2H, m), 6.34-6.19 (2H, m), 6.10-6.01 (2H, m), 5.83-5.74 (2H, m), 5.59-5.47 (2H, m), 5.44-5.31 (2H, m), 5.17-5.12 (2H, m), 4.71-4.68 (1H, m), 4.27-4.19 (2H, m), 2.49-2.10 (9H, m, H12, H18 and 3 × OH), 2.05 (2H, t, J = 7.0 Hz, H2), 1.92-1.75 (2H, m, H3), 0.96 (3H, t, J = 7.3 Hz, H22).

**(R)-6-((1E,3E)-4-(1,1-Diethyl-3,3,3-trimethylsiloxanyl)buta-1,3-dien-1-yl)-2,2-diethyl-5,6-dihydro-2H-1,2-oxasiline, 303**

Yellow oil. R$_f$ 0.18 (petrol); IR (thin film, ν$_{max}$ / cm$^{-1}$) 2956, 2879, 1586, 1260, 1060, 1017, 1004; $^1$H NMR (500 MHz, CDCl₃) δH 6.87 (1H, ddd, J = 14.2, 5.5 and 4.0 Hz, H4), 6.56 (1H, dd, J = 18.5 and 10.1 Hz, H9), 6.28 (1H, dd, J = 15.6 and 10.1 Hz, H8), 5.82-5.73 (3H, m, H3, H7 and H10), 4.51-4.47 (1H, m, H6), 2.23-2.20 (2H, m, H5), 1.01-0.91 (12H, m, 2 × Si(CH$_2$CH$_3$)$_2$), 0.70-0.53 (8H, m, 2 × Si(CH$_2$CH$_3$)$_2$), 0.08 (9H, s, Si(CH$_3$)$_3$); $^{13}$C NMR (125 MHz, CDCl₃) δC 146.0,
142.8, 134.7, 130.5, 129.0, 123.1, 69.8, 34.6, 5.1, 4.9, 4.7, 4.4, 4.0, 0.0; **HRMS** (FI) calc. for C_{19}H_{38}O_{2}Si_{3} [M]^{+} 382.2180 found 382.2190.

**Methyl (4S,5Z,7E,9S,11Z)-4,9-dihydroxytetradeca-5,7,11-trienoate, 304**

Yellow oil. **R**_{f} 0.28 (DCM / MeOH (17:3)); **IR** (thin film, ν_{max} / cm\(^{-1}\)) 3402, 2959, 2874, 2854, 1736, 1438, 1261, 1174, 1058, 1014; **\(^{1}\)H NMR** (500 MHz, CDCl\(_3\)) δ\(_{H}\) 6.59 (1H, dd, J = 14.9 and 11.0 Hz, H7), 6.12 (1H, app t, J = 11.0 Hz, H6), 5.84 (1H, dd, J = 14.9 and 6.2 Hz, H8), 5.68-5.61 (1H, m, H12), 5.47 (dd, J = 11.0 and 8.8 Hz, H5), 5.44-5.38 (1H, m, H11), 4.74-4.69 (1H, m, H4), 4.31-4.26 (1H, m, H9), 3.75 (3H, s, OCH\(_3\)), 2.52-2.48 (2H, m, H10), 2.42-2.36 (2H, m, H13), 2.13 (2H, t, J = 7.0 Hz, H2), 2.01-1.87 (2H, m, H3), 1.31 (2H, br s, OH), 1.03 (3H, t, J = 7.4 Hz); **\(^{13}\)C NMR** (125 MHz, MeOH) δ\(_{C}\) 177.1, 137.8, 133.3, 133.3, 128.2, 124.6, 123.9, 71.4, 65.9, 54.1, 34.6, 32.6, 30.4, 20.0, 12.7.
Appendix: Further Details of Potassium Trimethylsilanolate

Batch Dependence and Water Screening

(Please note that this section is primarily included to aid future research in our group.)

In an effort to reduce the amount of deleterious silane homocoupling (to form $161a$) and protodesilylation (to form $150a$) in the cross coupling of silane $119a$ with iodostyrene ($145a$) the effect of different batches of activator, under wet and dry conditions, was examined (Table 1). Wide variation was observed between different batches of KOSiMe$_3$ purchased from the same supplier at different times (entries 1-3). It was intriguing that use of wet DME almost completely suppressed protodesilylation, while significantly increasing the proportion of homocouple $161a$ produced (entry 4, compared to entry 1). Conversely, use of KOSiMe$_3$ that

$$\text{Et}_3\text{Si} + \text{I}-\text{Ph} \xrightarrow{2.5 \text{ eq activator} (\text{see table})} \text{Ph} - \text{I}-\text{Ph} + \text{OH}-\text{n-Hex} + \text{OH}-\text{n-Hex}$$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Activator (purchased)</th>
<th>Wet or Dry DME $^a$</th>
<th>$119a : 149aa : 150a : 161a$ $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KOSiMe$_3$, 90 wt%, Sigma Aldrich (pre-2011)</td>
<td>Dry</td>
<td>$0 : 60 : 21 : 19$</td>
</tr>
<tr>
<td>2</td>
<td>KOSiMe$_3$, 90 wt%, Sigma Aldrich (6/2013)</td>
<td>Dry</td>
<td>$0 : 57 : 21 : 22$</td>
</tr>
<tr>
<td>3</td>
<td>KOSiMe$_3$, 90 wt%, Sigma Aldrich (11/2013)</td>
<td>Dry</td>
<td>$0 : 37 : 50 : 13$</td>
</tr>
<tr>
<td>4</td>
<td>KOSiMe$_3$, 90 wt%, Sigma Aldrich (pre-2011) dried at 100 °C under HV for 24 h</td>
<td>Wet</td>
<td>$0 : 55 : 4 : 41$</td>
</tr>
<tr>
<td>5</td>
<td>KOSiMe$_3$, 90 wt%, Sigma Aldrich (pre-2011) dried at 100 °C under HV for 24 h</td>
<td>Dry</td>
<td>$24 : 29 : 47 : 0$</td>
</tr>
<tr>
<td>6</td>
<td>NaOSiMe$_3$, 95 wt%, Sigma Aldrich (11/2013)</td>
<td>Dry</td>
<td>$0 : 62 : 0 : 38$</td>
</tr>
<tr>
<td>7</td>
<td>KOSiMe$_3$, 98 wt%, CombiBlocks (11/2013)</td>
<td>Dry</td>
<td>$0 : 34 : 59 : 7$</td>
</tr>
</tbody>
</table>

Reactions performed at 0.16 M wrt $119a$. $^a$ Wet DME refers to solvent taken directly from a Winchester. Dry DME refers to DME distilled from CaH$_2$ and stored over 4Å molecular sieves. $^b$ Determined by $^1$H NMR spectroscopic analysis of the crude reaction mixture.

Table 1: Comparison of different batches of activator under wet and dry conditions
was dried under high vacuum prior to reaction resulted in greatly increased protodesilylation and no homocoupling (entry 5). It was also interesting that related silanolate base NaOSiMe₃ was able to promote the reaction with no protodesilylation observed at all, although a high proportion of homocouple 161a was produced (entry 6). Finally, KOSiMe₃ of a higher purity showed extensive protodesilylation but a much reduced quantity of homocoupled 161a (entry 7).

The complete suppression of homocoupling when a dried batch of KOSiMe₃ was employed was very promising (entry 5), hence the effect of water on the reaction was investigated (Graph 1). The trends observed are similar to those seen with the KOSiMe₃ of higher purity, as discussed in Section 3.4.2 of the main text (entry 7 in Table 1, and Graph 3.3 in the main thesis text), hence the use of the dried batch was abandoned in favour of the higher purity material which produced less of homocoupled silane 161a.

Water screening experiments were conducted with NaOSiMe₃ as an activator, which also seemed promising due to the suppression of protodesilylation that was observed under dry conditions (Table 1, entry 6). It was hoped that water doping would reduce the high levels of homocoupling that were observed. Unfortunately, the ratio of desired diene 149aa to unwanted homocouple 161a remained almost constant throughout (Graph 2). The use of this activator was therefore also abandoned.

It should be noted that impurities present in commercial KOSiMe₃ may play a role in determining the proportion of side products produced by these reactions. Silanolate base purchased from Sigma Aldrich is of technical grade, with the identity of the remaining 10 % of material undisclosed. Several methods have been reported for the synthesis of KOSiMe₃ which may give rise to different impurities, but unfortunately Sigma Aldrich were unwilling to reveal which process they employ when contacted. There was insufficient time available to pursue this line of enquiry further.
Investigating the Effect of $H_2O$ on Base-Activated Cross Coupling with Old Batch of KOSiMe$_3$, dried

Graph 1: Water screening to investigate the effect of water in cross coupling with old batch of KOSiMe$_3$ (pre-2011) that was dried under high vacuum (see Table 1, entry 5)

Investigating the Effect of $H_2O$ on Base-Activated Cross Coupling with

Graph 2: Water screening to investigate the effect of water in cross coupling with NaOSiMe$_3$
9 References


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9. References


